# STRUCTURE ACTIVITY RELATIONSHIPS

# IN ONE-RING PSYCHOTOMIMETICS

by

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This dissertation is dedicated to:

My parents, who awaited its outcome for so long with such unbridled enthusiasm,

Peter, Neil, and Gene, who supported these almost endless undertaking,

My classmates, especially Tariq, Woody, Bob and Mike,
And of course to Shasha who provided more than enought spiritual motivation.

University of California, San Francisco

ABSTRACT

# STRUCTURE ACTIVITY RELATIONSHIPS IN ONE-RING PSYCHOTOMIMETICS

by

GEORGE M. ANDERSON, III

UNDER THE SUPERVISION OF PROFESSOR PETER KOLLMAN
AND PROFESSOR NEAL CASTAGNOLI, JR.

Phenylalkylamines comprise an important group of compounds having a diverse spectrum of pharmacological actions which range from neuroregulatory, in the case of dopamine and norephinephrine, to stimulant/psychotomimetic in the case of amphetamine (1-phenyl-2-aminopropane), and DOM (1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane). The present thesis details the synthesis, pharmacology, physicochemical properties, and Structure Activity Relationships of ring-substituted derivatives of amphetamine.

The synthetic route leading to the racemic analogues involved condensation of the appropriate benzaldehydes with

nitroethane and subsequent reduction of the resulting nitropenes with $LiAlH_4$. Enantiomeric derivatives were prepared by reductive amination of the substituted phenylacetones with (+) or (-)-α-methylbenzylamine followed by hydrogenation with Raney Nickel and subsequent hydrogenolysis with Pd/C. The racemates of the substituted congeners of methamphetamine were prepared by reductive amination of the substituted phenylacetones with $CH_3NH_3Cl$ and $NaCNBH_3$. The enantiomeric compounds were obtained in good yields by reaction of the optically active primary amines with ethylchloroformate and reduction of the resulting carbamates with $LiAlH_4$.

Pharmacological evaluation was made using rabbit hyperthermia as a measure of potency. Available evidence suggests that the hyperthermia induced by psychotomimetics results from interactions of these compounds with serotonergic and/or dopaminergic innervations in the anterior and posterior hypothalmus. Regardless of the mechanism, a good correlation (n=18, r=0.89) was found to exist between the Hyperthermic Potency (HP) in the rabbit and psychotomimetic potency in man. Of these compounds, the most potent were 1-(2,5-dimethoxy-4-X-phenyl)-2-aminopropanes, in which the potency increased as follows: $H<OCH_3<OCH_2CH_3<SCH_3<CH_3<Br$. Similar ordering of activity does not occur in the 1-(2,4-dimethoxy-5-X-phenyl)-2-aminopropanes which have comparably low potency. In the 1-(4,5-dimethoxy-2-X-phenyl)-2-aminopropane series, replacement of the 2-H substituent with any other

group increases potency. The data also indicated that for the most potent derivatives of amphetamine the corresponding N-methyl analogues are greatly diminished in activity by comparison. In contrast, the N-methyl counterparts of weakly potent primary amines are almost equiactive. Whereas the (R) enantiomer has greater HP than the (S) isomer of substituted derivatives of amphetamine, this trend was reversed in the case of the N-methyl compounds where the most potent enantiomer was the (S). These data are consistent with the conclusion that the CNS activity of these derivatives of methamphetamine resembles the stimulant action of amphetamine rather than the psychotomimetic activity of DOM.

Analyses of the physico-chemical properties, such as conformation, ionization potential (IP) and distribution constant (Log P) were made. The PCILO molecular orbital method was used to calculate the conformational structure of a series of 1-(2-X-phenyl)-2-aminoethanes (+), but those studied indicated no straightforward explanation of the SAR. CNDO/2 calculations of Frontier Orbital Energies demonstrated a dependence upon the conformation of the substituents. An unusual finding was that the preferred conformation for ortho-dimethoxybenzene consisted of a planar and a perpendicular methoxy group. For the minimum energy conformations, the IP's were ordered as follows: 4-X<5-X<2-X. Consideration of the derived and measured Log P's shows that the 4-X and 5-X compounds are nearly isolipophilic but members of the 2-X series were uniformly much less. Furthermore, these

Log P's can be satisfactorily expressed as the sum of substituent group contributions ($\pi$ values) and an interaction correction which accounts for the mutual pertubation of two groups ortho to one another.

Reasonable SAR's were obtained for the 1-(2,5-dimethoxy-4-X-phenyl)-2-aminopropanes: Log HP=2.49($\pm$0.71)Log P - 0.46($\pm$0.13)Log $P^2$ - 1.31; n=13, r=0.74. By comparison, the HP of the remaining compounds were not significantly related to either Log P or IP. While the activities of these analogues were poorly predicted by overall molecular parameters, HP's could be related to regiospecific properties such as local group lipophilicity or potential metabolic conversion into reactive intermediates.

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# CHEMISTRY

# INTRODUCTION

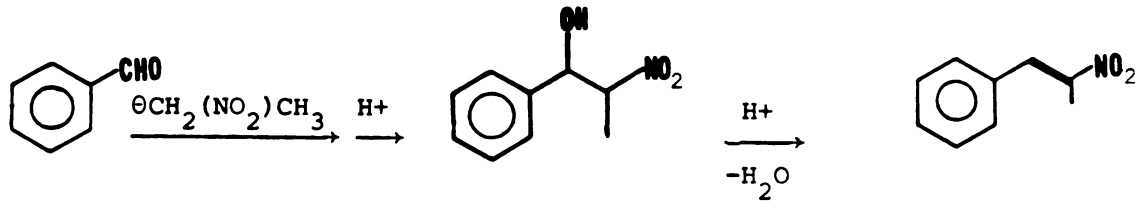
The reaction sequence employed in the synthesis of various derivatives of 1-phenyl-2-aminopropane is outlined in Figure 1. Synthetic proceduresand data are collectively presented in the Experimental Section and discussions of the reactions and mechanisms are detailed below.

Synthesis of 1-Phenyl-2-nitroprop-1-enes

Knoevenagel and Walters[1] first reported that the condensation of benzaldehyde with nitromethane or nitroethane under basic conditions afforded 1-phenyl-2-nitroalkenes in good yields. Following this initial report, many nitro compounds have been prepared by this route[2a,b] using a remarkable variety of experimental conditions. For example, this reaction proceeds readily in solvents which range in polarity from $EtOH/H_2O$[1,3a,b] to nitroethane[3c,d] and toluene[2b]. Similarly, a diversity of bases such as NaOH[1,3a,b], NaCN[3f], $NH_2CH_3$[3a], $NH_2C_4H_9$[2b], and $NH_4OAc$[3c,d] have been successfully employed, as have reaction timesranging from 30 seconds[3a,b] to five hours.[3c] Comparison of these experimental data shows that, in many cases, both the rates and products of these reactions were different[3a] depending upon the base used.

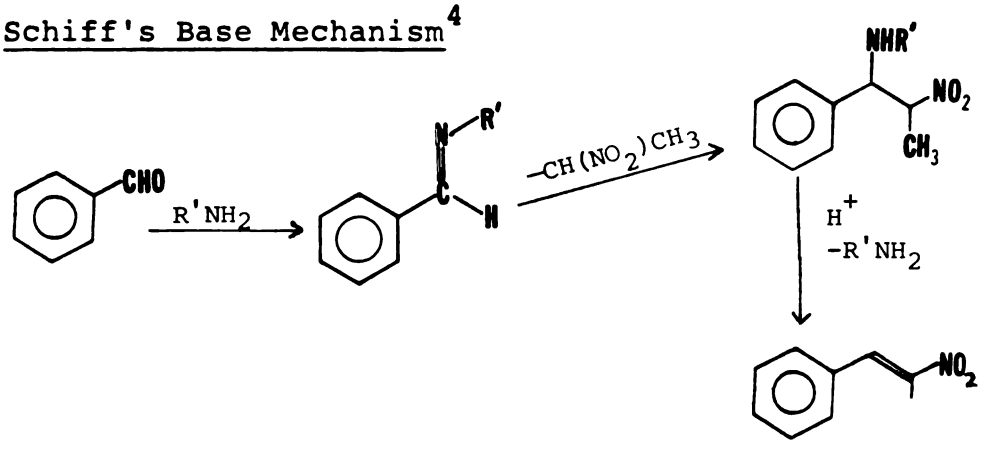
These data have been explained by Worrall [4a] in terms of the presence of two distinct reaction mechanisms outlined on the page following:

Knoevenagel Mechanism




Applicable where B=NaOH, NaCN, $NHR_1R_2$, $NR_1R_2R_3$ (R=alkyl).

Schiff's Base Mechanism[4]




Applicable where $B=NH_2R$ (R=alkyl).

In support of the Knoevenagel Mechanism is the observation that rapid neutralization of reaction mixtures catalyzed by strong bases with one equivalent of $CH_3COOH$ often resulted in the formation of the nitroalcohol[3a,b,f]. Similar results were obtained with secondary and tertiary amines[4a]. In contrast, when the reaction is catalyzed by a primary amine, the nitroalcohol is not found[4a]. Support for the conclusion that the nitrostyrenes obtained in these cases result from attack of the nitroalkane on the Schiff's base according to the second mechanism is provided by the successful condensation of several Schiff bases with nitromethane under

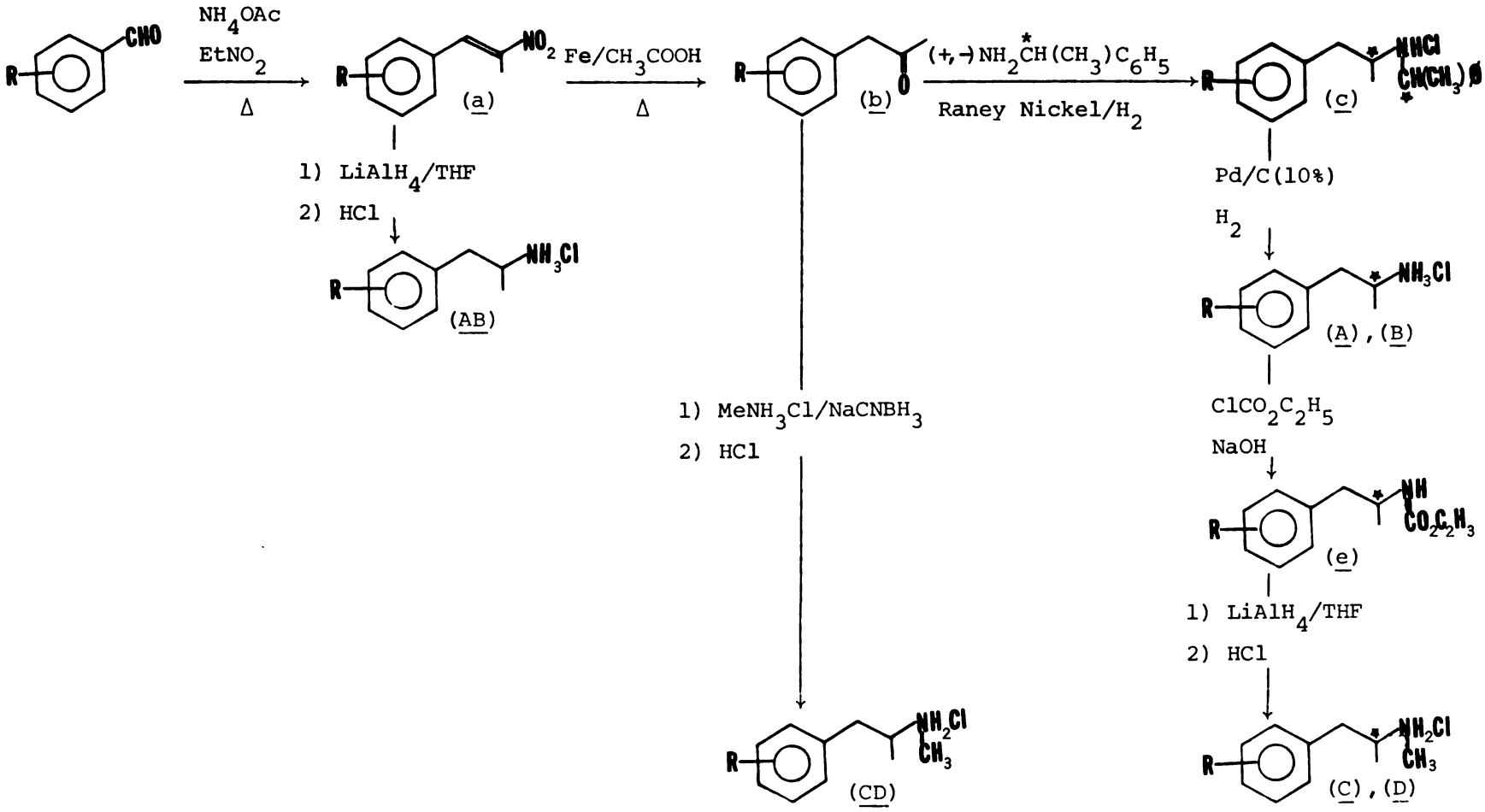



FIGURE 1. Synthetic Route Employed in the Preparation of Derivatives of 1-Phenyl-2-aminopropane.

neutral conditions[5a]. Furthermore, reports of Hurd and Strong[5b], as well as Leonard et al.[5c], show that in ethanol, the intermediate addition product ( I ) can be isolated from the neutral condensation of nitromethane with the Schiff base. Additionally, the second mechanism explains the anamolously slow reaction rate of meta-nitrobenzaldehyde and nitromethane when $NH_2Me$ is used as a base[5d]. It is not clear which mechanism is followed in reactions catalysed by $NH_4OAc$. Knoevenagel condensation between the 20 ring-substituted benzaldehydes and nitroethane was used to prepare the substituted 1-phenyl-2-nitroprop-1-enes in yields ranging from 38 - 73% (see Table I). Generally, yields were lowest for the nitropenes with the lowest melting points, indicating that in these cases, product was lost in the recrystallization step.

Synthesis of 1-Phenyl-2-aminopropanes

In the early days of phenethylamine research, it was widely recognized that 1-phenyl-2-nitroethenes were reduced in good yields by the action of Adams catalyst (Pd/C) and $H_2$ under acidic conditions[3a,f]. Ramirez and Burger[6a] were the first to report that $LiAlH_4$ was also capable of effecting the eight electron reduction of nitrostyrenes to the corresponding phenethylamines, with yields comparable to the catalytic hydrogenation route. Other modifications of this reagent have also proved useful, for example, Jacobs[6b] has shown that $AlH_3$ can be used in the reduction of phenylnitroalkenes containing base labile groups such as aromatic bromo substituents.

Alternately, exotic catalysts[6c] as well as electrochemical methods[6d] have been infrequently employed. Due to the ease and efficiency of the $LiAlH_4$ reduction, this procedure has been used almost exclusively[6f]. Of the 21 compounds reduced by the author, the yields were typically good, ranging from 55-87%. The postulated mechanism proceeds as follows:

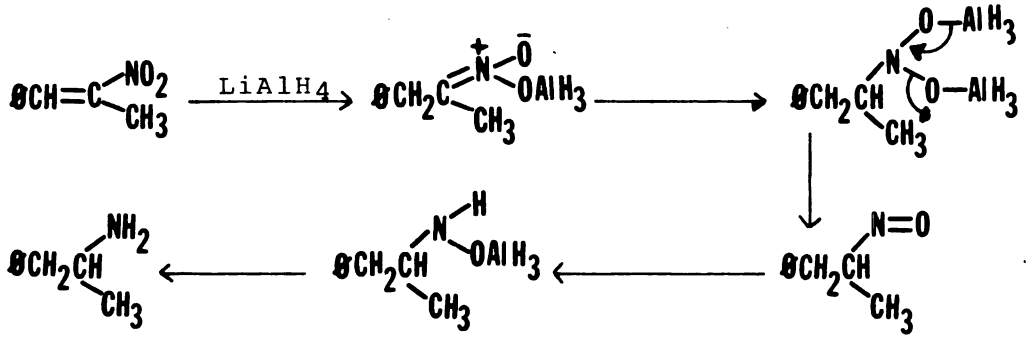
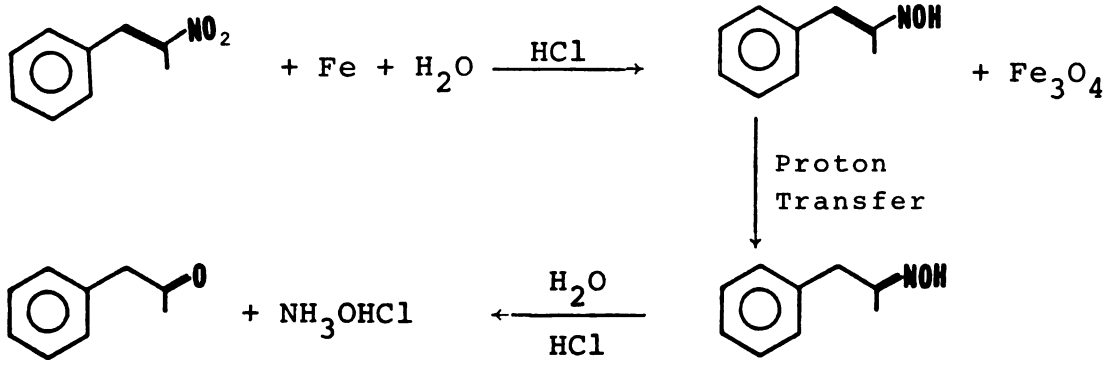



Figure 2. Reduction of a Phenylnitropropene with $LiAlH_4$.

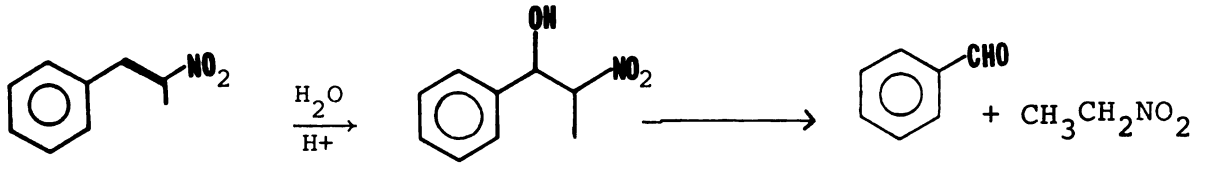
Synthesis of 1-Phenyl-2-propanone

Hass et al.[7a] first reported that reduction of 1-phenyl-2-nitroprop-1-ene with Fe/HCl rendered 1-phenyl-2-propanone in moderate yields. These authors suggested the following mechanism for this reduction:




As can be seen, depending on the amount of acid used, either the propanone or the ketoxime can be isolated. Caution must

be exercized, since the nitrostyrenes themselves are unstable to strong acids, decomposing back to the benzaldehydes from which they came according to the following steps[7a]:




Other modifications of this reaction have been introduced by Heinzelman[7b] which consist of addition of benzene to the reaction mixture which facilitates the reduction of nitrostyrenes which are not particularly soluble in boiling $H_2O$. Alternately, Ames[7c] has shown that $CH_3COOH$ is also capable of effecting this reaction and this procedure has the dual advantage of both dissolving the nitrostyrenes and also providing a buffered reaction mixture. Of the 13 ring-substituted phenylacetones prepared by this reaction (Table 3) the yields ranged from 21-74%. There was no apparent connection between the aromatic substitution pattern and the percent yield . The by-products of the reaction consisted of highly colored intractable tars having boiling points much higher than the desired products.

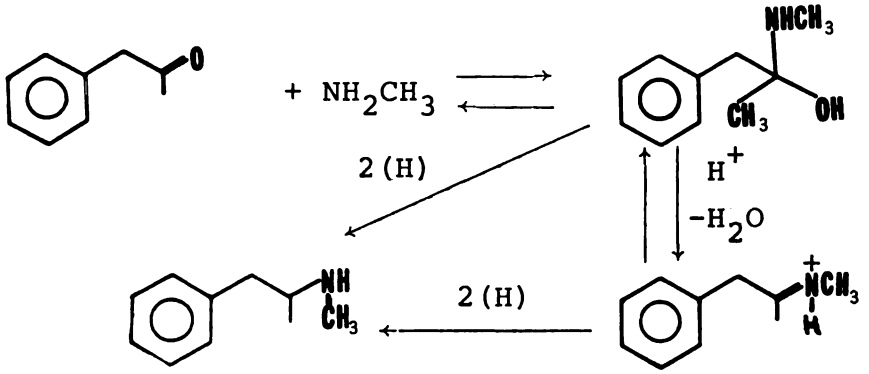
Synthesis of 1-Phenyl-2-methylaminopropanes

Many methods have been devised for the synthesis of secondary amines and the subject has received considerable attention in the literature[8a]. Perhaps the oldest and most straightforward approach for preparing 1-phenyl-2-methylaminopropanes consists of addition of MeI or MeBr to

1-phenyl-2-aminopropane. This method, however, is almost never used since it is well established that mixtures of unreacted, mono-, di-, and even trimethyl-substituted amines are produced, and generally these mixtures are very difficult or impossible to separate via distillation due to the similarity in the boiling points[8b]. Accordingly, alternate routes have been devised. For example, Ho et al.[3c] have prepared 1-(2, 5-dimethoxy-4-methylphenyl)-2-methylaminopropane by methylation of the Schiff's base adduct of the primary amine and benzaldehyde with $Me_2SO_4$. Shulgin et al.[8c,d] have also synthesized this compound and several other derivatives by formylation of the primary amine with ethyl formate and reduction of the resulting amide with $LiAlH_4$ in THF.

Two routes were used to prepare the N-methyl derivatives. In the first method, condensation of the appropriately substituted 1-phenylpropan-2-one with $NH_2Me$ results in the formation of the Schiff's base which can be reduced in situ to the desired product with $NaCNBH_3$. This method is representative of numerous reductive amination procedures[8e] which differ principally by the type of reducing agents employed. Previous to the introduction of $NaCNBH_3$ by Borch et al.[9a,b], the reducing agent most commonly employed was either Raney Nickel/$H_2$[9c] or Pd/$H_2$[9d] and occasionally Zn/HCl[9e]. However, reductions catalyzed by the neutral agents often require elevated $H_2$ pressures and result in yields ranging from 33-63%[8e]. Furthermore, Raney Nickel often leads to unwanted by-products when aliphatic amines are used[9f]. Similarly, Pd/$H_2$

effects dehalogenation of compounds containing aromatic bromo groups. Use of Zn/HCl often requires elevated reaction temperature, conditions known to lead to polymerization of the Schiff's base[9g], and hence often leads to variable yields[8e]. Reductions effected by $NaCNBH_3$ suffer none of these disadvantages and the required reaction conditions are very mild by comparison (see the preparation of Compound (16CD). The remarkable stability of this reducing agent to pH's as low as three allows rapid reduction of the Schiff's base (generated in situ) while minimizing the reduction of the 1-phenylpropan-2-one[9a]. For these reasons, this reducing agent is currently finding numerous applications for reactions of this type[9h,i]. The proposed mechanism for reductive aminations of 1-phenylpropan-2-one is detailed below.




A survey of the 14 compounds prepared in this manner is contained in Table 4. As can be seen, the yields vary from 49-87% and the reaction mixtures consisted mainly of the desired products and starting materials which are readily separated by distillation.

Clearly, the reductive amination procedure (Method 1) used in the synthesis of the racemic N-methyl derivative is

unsuitable for the preparation of enantiomeric analogues. Consequently, methylation of the enantiomers of 1-phenyl-2-aminopropanes was achieved by reacting these primary amines with $ClCO_2C_2H_5$ and reduction of the corresponding carbamates with $LiAlH_4$ (see the preparation of Compound 16e) according to the methods reported by Hartman et al.[10a], and Gutsche et al.[10b]. While similar to the amide route used by Shulgin et al.[8b], this procedure avoids many of the pitfalls in that approach since the carbamate route requires neither long reaction times nor elevated temperatures and provides, in very good yields (68-95%), the required products as nearly pure crystalline solids (see Table 5). Reduction of the carbamates with $LiAlH_4$ rendered the enantiomeric N-methyl analogues in good yields (66-91%, see Table 6) with little or no apparent racemization of the chiral center.

Synthesis of the Enantiomers of the 1-Phenyl-2-aminopropanes

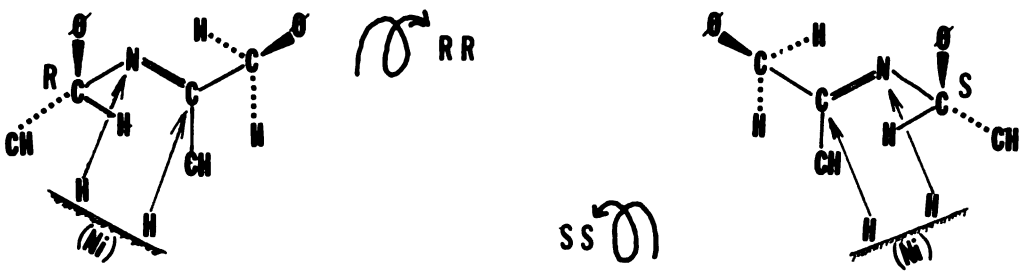
Two main routes have been utilized in the preparation of enantiomeric 1-phenyl-2-aminopropanes. The first method consists of resolution of a diasteromeric salt formed form the racemic primary amine and a chiral acid. Repeated recrystallizations of this salt often results in at least partial separation of the optical isomers[11a]. Alternately, asymmetric syntheses have been devised using chiral reagents to effect preferential formation of diasteromeric intermediates which in turn can be reacted to yield the desired enantiomers[11b].

Classical resolution of 1-(3,4-methylenedioxyphenyl)-2-methylaminopropane (5CD) with (+)- and

(-)-di-p-toluoyl-tartaric acid provides an example of the first method (see the Experimental Section for details). While this route does in fact give the required enantiomers, it suffers from numerous problems: (1) An appropriate chiral acid must be found which yields a crystalline solid that is easily recrystallized. Typically, different amines will require different chiral acids and only experimentation is capable of determining which acid is appropriate (for 5CD , eight chiral acid salts were investigated), (2) numerous recrystallizations are often needed to obtain enantiomeric purity (in the case of 5CD , three recrystallizations were made for each enantiomer) and even then, complete resolution is not assured, (3) generally, the resultant yields are quite low (for 5C the overall yield was 9.1%, for 5D the yield was 11%). In light of these observations, it is fair to describe the classical resolution route as a tedious, time-consuming operation which, at least in many cases, seldom provides very much product considering the effort involved.

Asymmetric synthetic routes leading to the preparation of enantiomeric derivatives of 1-phenyl-2-aminopropane have been reported by two groups. In the route employed by Aldous et al.,[11c] the racemic primary amines are reacted with N-benzyloxycarbonyl-L- (or D-) phenylalanine p-nitrophenyl ester and the resulting amides subjected to fractional recrystallization. Recovery of the enantiomeric compounds was effected by catalytic hydrogenation followed by Edman degradation. Yields obtained from this route were quite

variable ranging from 9-75%. Alternately, the reaction sequence reported by Nichols et al.[11d] involves condensation of the appropriately substituted 1-phenylpropan-2-one with either (+)- or (-)-α-methylbenzylamine and this adduct is then reduced with Raney Nickel. The asymmetric induction results from the preferential introduction of the two reducing hydrides from the sterically less-hindered face of the Schiff's base as shown below:




Since the necessary 1-phenylpropan-2-ones were readily available, the synthesis employed by Nichols et al. was used to prepare the nine enantiomeric compounds whose physical properties are detailed in Table 7. In the author's hands, the yields of the α-methylbenzylamine adducts ( II )were considerably less than the literature values, however, this may be due to the three additional recrystallization steps which were not performed in Nichols' procedure. These additional purifications were necessary in order to remove the highly-colored by-products resulting from addition of HCl to intermediate II . These impurities probably arise from aldol condensations of the Schiff's base I [9g] . Further, our experience has been that after only one recrystallization, the

Schiff's base adduct (II) was contaminated by about 30% with the HCl salt of unreacted α-methylbenzylamine. Hence, it appears that the factor limiting the overall yields in this reaction sequence is the condensation of the 1-phenylpropan-2-one with the α-methylbenzylamine. Yields in the catalytic hydrogenation step were all typically high (79-96%, see Table 8).

Synthesis of 1-(2,5-Dihydroxy-4-methylphenyl)-2-aminopropane (32AB).

The usual synthetic route employed in the preparation of methoxy-substituted phenylalkylamines involves the condensation reaction of the benzaldehyde and subsequent reduction of the nitropene. While this sequence works well in most cases, the presence of hydroxy groups in the benzaldehyde often leads to problems. Hahn and Stiehl[3a], in an early report on Knoevenagel condensations, have carefully examined the reactions between $MeNO_2$ and 2-, 3-, and 4-hydroxybenzaldehydes using both NaOH and $NH_2Me$. Under these experimental conditions, the 4-hydroxybenzaldehyde failed to undergo condensation using either base. In contrast, the 3-hydroxybenzaldehyde reacted to give the nitropene in 80% yield with NaOH but no reaction was observed with $NH_2Me$. Both bases gave comparable yields (28-35%) of the 2-hydroxynitropene. Clearly, abstraction of the p-phenolic proton by the base retards the condensation by increasing the charge on the aldehyde carbon via electron donation. Such interference does not occur in the m-hydroxy compound and consequently the reaction is

successful. In the o-hydroxybenzaldehyde, the higher $pK_a$ of the phenol relative to the p compound probably accounts for the observed condensation. In any case, hydroxy-substituted-phenylalkylamines are seldom prepared by condensations with the unprotected hydroxybenzaldehydes. Instead, the phenols have been transformed into either acetoxy[3b] or benzyloxy groups[3e] and Knoevenagel condensation of these benzaldehydes can be routinely effected. Subsequently, cleavage of these groups yields the hydroxyphenylalkylamines.

Alternately, demethylation of methoxy-substituted aromatics can be achieved, often in very good yields, with a variety of acids or bases and these procedures have found much application.[12a,b] The most commonly employed bases are KSCN/DMF[13a], K/liq. ammonium[13b], and LiI/alkylpyridines[13c].

Examples of acid catalysis are HBr[13d,e], $BBr_3$[13f] and $Me_3SiI$[13g]. Generally, these agents are not discriminating enough to allow selective demethylation of multi-methoxy substituted aromatics (although several notable exceptions have been reported[13e]). Regardless, when exhaustive demethylation yields the desired compound, this route is clearly the method of choice. Considerable experience indicates that the acidic catalysts are superior to the basic agents when the reaction leads to the formation of either an o- or p-hydroquinone since under basic conditions these compounds undergo numerous oxidative and polymerization side reactions[14a].

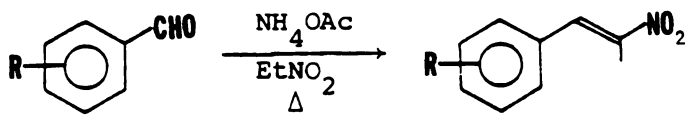
Successful demethylation of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (16AB) with $BBr_3$ rendered 1-(2,5-dihydroxy-4-methylphenyl)-2-aminopropane in moderately good yields (see the Experimental Section for details). The dihydroxy compound, after purification by ion exchange chromatography, was obtained as a white solid. However, even when stored under $N_2$ and refrigerated at $0^{\circ}$ C, decomposition becomes noticeable. During a period from four to six months the hydroquinone turned red and this color change was concomitant with the formation of water insoluble by-products whose constitution has been established by Castagnoli et al.[14 b,c].

Synthesis of 1-(2,5-Diacetoxy-4-methylphenyl)-2-aminopropane (34AB).

Preparation of the diacetoxy derivative of 1-(2,5-dihydroxy-4-methylphenyl)-2-aminopropane poses the synthetic challenge of achieving acetylation of the phenol ($pK_a$=10 ) without concomitant reaction with the amine which is considerably more basic ($pK_a$= 9 ). In this regard, two routes have been reported. The first method involves formation of the carbobenzyloxy derivative of the amine, acetylation of the phenolic groups, followed by hydrogenolysis of the protecting group. In this manner, Borgman et al.[15a] have successfully prepared 1-(3,4-diacetoxyphenyl)-2-aminopropane and Glennon and Lieborwitz[15b] have synthesized 1-(2-acetoxy-5-methoxyphenyl)-2-aminopropane. However, during the hydrogenolysis reaction, O---N acetyl migration was observed and the reported yields were quite low. These difficulties are

circumvented in the second procedure which involves selective acetylation of the phenol with $CH_3COOH$ and $CF_3COOH$. Previero was the first to develop this method which he used in the preparation of O-acetoxy derivatives of a variety of hydroxyamino acids[15c]. This procedure yielded the di-O-acetoxy derivative of 1-(2,5-dihydroxy-4-methylphenyl)-2-aminopropane HCl in modest yields. This compound was obtained, only with great difficulty, as a white solid with a sharp melting point and consistent NMR, IR and mass spectra (See Experimental Section). All of these analyses indicated that the acetylation was selectively O rather than N. However, the elemental analysis was not within acceptable limits. After storage ($0^{o}$ C) for about four months, the white color gradually gave way to red, and the elemental analysis continued to deteriorate. The colored by-product(s) were distinctly less water soluble than the desired compound, and probably result from a slow O→N acetyl migration occuring even in the solid state. Such migrations are known to occur in the somewhat analogous O→N acetyl migration in pseudoephedrine[15d,e,f].

Table 1. Synthetic Data on Ring-Substituted Analogues of 1-Phenyl-2-nitroprop-1-enes.




| Compound | Aromatic Sub. Pattern $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | % Yield | Melting Point C° | Melting Point (Lit.) |
|---|---|---|---|---|---|---|---|---|
| (1a) | H | H | H | H | H | 40% | 63-64 | 64-65[a] |
| (2a) | H | H | $OCH_3$ | H | H | 66% | 45-46 | 46-47[b] |
| (3a) | H | $OCH_3$ | H | H | H | 38% | 43-45 | 44.5-45.5[b] |
| (4a) | $OCH_3$ | H | H | H | H | 29% | 46-47.5 | 46.5-47.0[b] |
| (5a) | H | H | O—$CH_2$—O | | H | 54% | 96-97 | 97-98[c] |
| (6a) | $OCH_3$ | $OCH_3$ | H | H | H | 67% | 75-76 | 78-79[a] |
| (7a) | $OCH_3$ | H | $OCH_3$ | H | H | 58% | 76.5-77.5 | 77-78[b], 78[d] |
| (8a) | $OCH_3$ | H | H | $OCH_3$ | H | 73% | 73-74.5 | 74-75[b] |
| (9a) | $OCH_3$ | H | H | H | $OCH_3$ | 52% | 97-98.5 | ——— |
| (10a) | H | $OCH_3$ | H | $OCH_3$ | H | 57% | 81-82 | 87.5-88.5[e] |
| (11a) | H | H | $OCH_3$ | $OCH_3$ | H | 44% | 71.5-72.5 | 67-68[a], 71[c] |
| (12a) | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | 54% | 58-59 | 57[f] |
| (13a) | $OCH_3$ | H | $OCH_3$ | $OCH_3$ | H | 65% | 96.5-97 | 102[f] |
| (14a) | $OCH_3$ | H | $OCH_3$ | H | $OCH_3$ | 47% | 144.5-145 | 148[f] |
| (15a) | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | 69% | 93.5-94.5 | 94[f] |
| (16a) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 49% | 90-90.5 | 86.5-88[g] |
| (18a) | $OCH_2CH_3$ | H | $OCH_3$ | $OCH_3$ | H | 55% | 74.5-75.5 | 76[h] |
| (19a) | $OCH_3$ | H | $OCH_2CH_3$ | $OCH_3$ | H | 63% | 127-128 | 129[h] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (20a) | $OCH_3$ | H | $OCH_3$ | $OCH_2CH_3$ | H | 42% | 95.5-96.5 | 97[h] |
| (21a) | $CH_3$ | H | $OCH_3$ | H | $OCH_3$ | 39% | 85-86 | ——— |

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[c] I. A. Pearl and D. L. Beyer, J. Org. Chem., 18, 1, 1953.

[d] T. A. Govindarchari and M. V. Lakshmikantham, Proc. Indian Acad. Sci., 46A, 407 (1957).

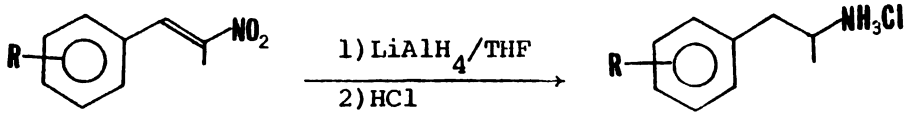
[e] B. T. Ho, W. M. McIsaac, R. An, L. W. Tansey, K.E. Walker, L. F. Englert, Jr. and M. B. Noel, J. Org. Chem., 13, 26 (1970).

[f] A. T. Shulgin, J. Med. Chem., 9, 445 (1966).

[g] U. S. Patent 3547999 (1970).

[h] A. T. Shulgin, J. Med. Chem., 11, 196 (1968).

Table 2. Synthetic Data on Ring-Substituted Analogues of 1-Phenyl-2-aminopropanes HCL.




| Compound | Aromatic Sub. Pattern $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | % Yield | Melting Point (Lit.) °C | NMR Characterization[a] |
|---|---|---|---|---|---|---|---|---|
| (1AB) | H | H | H | H | H | 72% | 144.5-146 (147)[b] | δ=1.35 (d, J=7 Hz, 3H, $CCH_3$), δ=2.95, (d, J=7 Hz, 2H, $CH_2$), δ=3.1-3.8 (m, 1H, CH), δ=7.4 (s, 5H, Ar H). |
| (2AB) | H | H | $OCH_3$ | H | H | 79% | 207-208 (206-207)[c] | δ=1.3 (d, J=7 Hz, 3H, $CCH_3$), δ=2.9 (d, J=8 Hz, 2H, $CH_2$), δ=3.2-3.9 (m, 4H, CH, $OCH_3$), δ=6.85-7.4 (m, 4H, Ar H). |
| (3AB) | H | $OCH_3$ | H | H | H | 55% | 113-115 (115-116)[c] | δ=1.37 (d, J=7 Hz, 3H, $CCH_3$), δ=3.0 (d, J=8 Hz, 2H, $CH_2$), δ=3.5-4.0 (m, 4H, $OCH_3$, CH), δ=6.8-7.6 (m, 4H, Ar H). |
| (4AB) | $OCH_3$ | H | H | H | H | 67% | 114-115.5 (108-110)[c] | δ=1.36 (d, J=7 Hz, 3H, $CCH_3$), δ=3.05 (d, J=7 Hz, 2H, $CH_2$), δ=3.4-4.0 (m, 4H, $OCH_3$, CH), δ=6.9-7.5 (m, 4H, Ar H). |
| (5AB) | H | H | O--$CH_2$--O | | H | 88% | 178-179 (181)[d] | δ=1.38 (d, J=6 Hz, 3H, $CCH_3$), δ=2.8-3.1 (m, 2H, $CH_2$), δ=3.35-3.95 (m, 1H, CH), δ=6.1 (s, 2H, $OCH_2O$), δ=6.89 (s, 3H, Ar H). |
| (6AB) | $OCH_3$ | $OCH_3$ | H | H | H | 84% | 142-143.5 (154-156)[d] (154-155)[e] | δ=1.37 (d, J=6 Hz, 3H, $CCH_3$), δ=2.95-3.15 (m, 2H, $CH_2$), δ=3.2-3.6 (m, 1H, CH), δ=3.82 (s, 3H, $OCH_3$), δ=3.95 (s, 3H, $OCH_3$). |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (7AB) | $OCH_3$ | H | $OCH_3$ | H | H | 73% | 147.5-149 (149-150)[e] | δ=1.31 (d, J=7 Hz, 3H, $CCH_3$), δ=2.92 (d, J=7 Hz, 2H, $CH_2$), δ=3.5-4.0 (m, 7H, $OCH_3$), CH), δ=6.52-6.75 (m, 2H, Ar H), δ=7.1-7.4 (m, 1H, Ar H). |
| (8AB) | $OCH_3$ | H | H | $OCH_3$ | H | 66% | 109-110.5 (111.5-112)[d] (105-106)[e] | δ=1.3 (d, J=7 Hz, 3H, $CCH_3$), δ=2.96 (d, J=7 Hz, 2H, $CH_2$), δ=3.55-3.9 (m, 7 H, CH, $OCH_3$), δ=6.8-7.05 (m, 3H, Ar H). |
| (9AB) | $OCH_3$ | H | H | H | $OCH_3$ | 75% | 186.5-188 (185-186)[e] | δ=1.28 (d, J=7 Hz, 3H, $CCH_3$), δ=2.92 (d, J=7 Hz, 2H, $CH_2$), δ=3.5-4.9 (m, 7H, $OCH_3$, CH), δ=6.75-6.91 (m, 2H, Ar H), δ=3.2-3.6 (m, 1H, Ar H). |
| (10AB) | H | $OCH_3$ | H | $OCH_3$ | H | 61% | 146-147.5 (160-161)[d] (161-162)[e] (147)[f] | δ=1.35 (d, J=7 Hz, 3H, $CCH_3$), δ=2.93 (d, J=7 Hz, 2H, $CH_2$), δ=3.5-3.8 (m, 7H, $OCH_3$, CH), δ=7.02 (d, J=63 Hz, 3H, Ar H). |
| (11AB) | H | H | $OCH_3$ | $OCH_3$ | H | 70% | 129-131.5 (147.5-148)[d] (145-146)[e] | δ=1.36 (d, J=6 Hz, 3H, $CCH_3$), δ=2.95 (d, J=7 Hz, 2H, $CH_2$), δ=3.5-4.0 (m, 7 H, $OCH_3$), CH), δ=7.02 (s, 3H, Ar H). |
| (12AB) | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | 55% | 146-147 (149)[g] | δ=1.37 (d, J=7 Hz, 3H, $CCH_3$), δ=2.98 (d, J=7 Hz, 2H, $CH_2$), δ=3.4-4.0 (m, 10H, $OCH_3$, CH), δ=6.85-7.25 (m, 2H, Ar H). |
| (13AB) | $OCH_3$ | H | $OCH_3$ | $OCH_3$ | H | 87% | 188-189.5 (187)[g] | δ=1.34 (d, J=7 Hz, 3H, $CCH_3$), δ=2.9 (d, J=7 Hz, 2H, $CH_2$), δ=3.4-3.95 (m, 10 H, $OCH_3$, CH), δ=6.88 (d, J=7 Hz, 2H, Ar H). |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (14AB) | $OCH_3$ | H | $OCH_3$ | H | $OCH_3$ | 63% | 208-210 (214)[g] | δ=1.29 (d, J=7 Hz, 3H, $CCH_3$), δ=2.86 (d, J=6 Hz, 2H, $CH_2$), δ=3.4-3.9 (m, 10 H, $OCH_3$), CH), δ=6.35 (s, 2H, Ar H). |
| (15AB) | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | 91% | 215-217 (209)[g] | δ=1.33 (d, J=7 Hz, 3H, $CCH_3$), δ=2.94 (d, J=7 Hz, 2H, $CH_2$), δ=3.45-3.8 (m, 4H, $OCH_3$, CH), δ=3.96 (s, 3H, $OCH_3$), δ =6.76 (s, 2H, Ar H). |
| (16AB) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 74% | 186.5-187 (189-189.5)[h] | δ=1.11 (d, J=7 Hz, 3H, $CCH_3$), δ=2.19 (s, 3H, Ar $CH_3$), δ=2.35-2.82 (m, 2H, $CCH_2$), δ=2.88-3.52 (m, 1H, CH), δ= 3.74 (s, 3H, $OCH_3$), δ=3.78 (s, 3H, $OCH_3$), δ=6.67 (s, 1H, Ar H), δ=6.72 (s, 1H, Ar H). |
| (17AB) | $OCH_3$ | H | Br | $OCH_3$ | H | 49% | 196-197 (195-196)[i] | δ=1.32 (d, J=7 Hz, 3H, $CCH_3$), δ=2.98 (d, J=7 Hz, 2H, $CCH_2$), δ=3.4-4.1 (m, 7H, CH, $OCH_3$), δ=7.11 (s, 1H, Ar H), δ=7.16 (s, 1H, Ar H). |
| (18AB) | $OCH_2CH_3$ | H | $OCH_3$ | $OCH_3$ | H | 78% | 171.5-172.5 (172)[j] | δ=1.2-1.6 (m, 6H, $CCH_3$, $OCCH_3$), δ= 2.86 (d, J=7 Hz, 2H, $CH_2$), δ=3.4-3.95 (m, 7H, CH, $OCH_3$), δ=4.1 (q, J=7 Hz, 2H, $OCH_2$), δ=6.81 (d, J=11 Hz, 2H, Ar H). |
| (19AB) | $OCH_3$ | H | $OCH_2CH_3$ | $OCH_3$ | H | 66% | 176-177 (172)[j] | δ=1.2,1.6 (m, 6H, $CCH_3$, $OCCH_3$), δ= 2.89 (d, J=7 Hz, 2H, $CH_2$), δ=3.4-4.0 (m, 7H, CH, $OCH_3$), δ=4.15 (q, J=7 Hz, 2H, $OCH_2$), δ=6.89 (d, J=8 Hz, 2H, Ar H). |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (20AB) | $OCH_3$ | H | $OCH_3$ | $OCH_2CH_3$ | H | 85% | 170-171 (172)[j] | δ=1.2-1.6 (m, 6H, $CCH_3$, $OCH_3$), δ=2.93 (d, J=7 Hz, 2H, $CH_2$), δ=3.4-3.9 (m, 7H, CH, $OCH_3$), δ=4.15 (q, J=7 Hz, 2H, $OCH_2$), δ=6.84 (d, J=8 Hz, 2H, Ar H). |
| (21AB) | $CH_3$ | H | $OCH_3$ | H | $OCH_3$ | 85% | 186-188 ——— | δ=1.32 (d, J=7 Hz, 3H, $CCH_3$), δ=2.25 (s, 3H, Ar $CH_3$), δ=2.9 (d, J=6 Hz, 2H, $CH_2$), δ=3.3-3.9 (m, 7H, $OCH_3$), CH), δ= 6.49 (s, 2H, Ar H). |

[a] NMR's run in $D_2O$ with DSS as internal calibrant.

[b] H. Hartung, T. Munch, J. Am. Chem. Soc., 53, 1875 (1931).

[c] K. Bailey, H. D. Beckstead, D. Legault, and D. Verner, J.A.O.A.C., 57, 1134 (1974).

[d] B. T. Ho, W. M. McIsaac, R. An, W. Tansey, K. E. Walker, L. F. Englert, and M. B. Noel, J. Med. Chem, 13, 26 (1970).

[e] K. Bailey, D. Legault, and D. Verner, J.A.O.A.C., 57, 70 (1974).

[f] T. A. Gorindachari and M. V. Lakshmikantham, Proc. Indian Acad. Sci., 46A, 406 (1957).

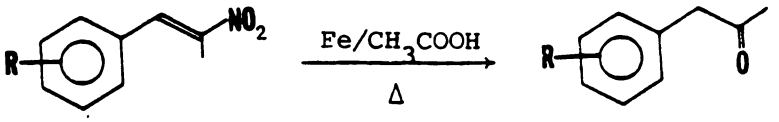
[g] A. T. Shulgin, J. Pharm. Pharmacol., 25, 271 (1973).

[h] A. T. Shulgin and D. C. Dyer, J. Med. Chem., 18, 1201 (1975).

[i] R. T. Coutts and J. L. Malicky, Can. J. Chem. Soc., 51, 1402 (1973).

[j] A. T. Shulgin, J. Med. Chem., 11, 186 (1968).

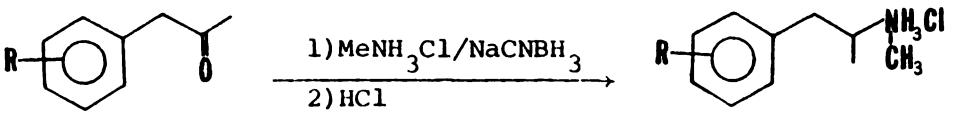
Table 3. Synthetic Data on Ring-Substituted Analogues of 1-Phenyl-2-propanone.




| Compound | Aromatic Sub. Pattern $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | % Yield | M. P. or B. P. Point °C | M.P. or B.P. (Lit.) |
|---|---|---|---|---|---|---|---|---|
| (1b) | H | H | H | H | H | 46% | 60-75/2.4mm | 216/760mm.[a] |
| (2b) | H | H | $OCH_3$ | H | H | 38% | 162-165 | 163-164[a] |
| (5b) | H | H | O--$CH_2$--O | | H | 47% | 100-120/1.3mm | |
| (6b) | $OCH_3$ | $OCH_3$ | H | H | H | 32% | 115-125/5mm | |
| (7b) | $OCH_3$ | H | $OCH_3$ | H | H | 55% | 120-130/3mm | |
| (8b) | $OCH_3$ | H | H | $OCH_3$ | H | 51% | 120-130/3mm | |
| (10b) | H | $OCH_3$ | H | $OCH_3$ | H | 65% | 145-155/10mm | |
| (11b) | H | H | $OCH_3$ | $OCH_3$ | H | 33% | 110-125/5mm | 59/0.3[a] |
| (12b) | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | 21% | 120-135/1mm | |
| (13b) | $OCH_3$ | H | $OCH_3$ | $OCH_3$ | H | 74% | 130-150/4mm | |
| (14b) | $OCH_3$ | H | $OCH_3$ | H | $OCH_3$ | 59% | 120-140/4mm | |
| (15b) | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | 69% | 65-66 | 65-67[a] |
| (16b) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 45% | 59.5-60.5 | |

[a] H. B. Hass et al. ref 7a.

Table 4. Synthetic Data on Ring-Substituted Analogues of 1-Phenyl-2-methylaminopropane




| Compound | Aromatic Sub. Pattern $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | % Yield | Melting Point °C (Lit.) | Ob. & Cal. Elemental Analysis | NMR Characterization[a] |
|---|---|---|---|---|---|---|---|---|---|
| (1CD) | H | H | H | H | H | 87% | 127.5-129.0 (129-130)[b] | ——— | δ=1.32 (d, J=7 Hz, 3H, $CCH_3$), δ=2.95 (s, 3H, $NCH_3$), δ=3.21 (d, J=7 Hz, 2H, $CH_2$), δ=3.5-3.9 (m, H. CH), δ=7.52 (s, 5H, Ar H). |
| (2CD) | H | H | $OCH_3$ | H | H | 72% | 175.5-176.5 (177-178)[b] | C 61.24 61.25<br>H 8.31 8.41<br>N 6.37 6.49<br>Cl 16.50 16.43 | δ=1.32 (d, J-7 Hz, 3H, $CCH_3$), δ=2.81 (s, $NCH_3$), δ=3.12 (d, J=7 Hz, 2H, $CH_2$), δ=3.6-3.9 (m, 1H, CH), δ=3.88 (s, 3H, $OCH_3$), δ=7.22 (m, 4H, Ar H). |
| (5CD) | H | H | O--$CH_2$--O | | H | 65% | 148-149 (149-150)[c] | C 57.59 57.52<br>H 6.95 7.02<br>N 6.07 6.10<br>Cl 15.58 15.44 | δ=1.41 (d, J=7 Hz, 3H, $CCH_3$), δ=2.89 (s, $NCH_3$), δ=3.14 (d, J=7 Hz, 2H, $CH_2$), δ=3.6-3.9 (m, 1H, CH), δ=6.2 (s, 2H, $CH_2$), δ=6.84 (s, 3H, Ar H). |
| (6CD) | $OCH_3$ | $OCH_3$ | H | H | H | 52% | 94.5-96 ——— | C 58.87 58.65<br>H 8.17 8.20<br>N 5.75 5.70<br>Cl 14.51 14.43 | δ=1.30 (d, J=7 Hz, 3H, $CCH_3$), δ=2.95 (s, 3H, $NCH_3$), δ=3.18 (d, J=7 Hz, 2H, $CH_2$), δ=3.6-4.0 (m, 7H, CH, $OCH_3$), δ=6.8-7.5 (m, 3H, Ar H). |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (7CD) | $OCH_3$ | H | $OCH_3$ | H | H | 57% | 124.0-125.5 | C | 58.48 | 58.65 |
| | | | | | | | | H | 8.13 | 8.20 |
| | | | | | | | | N | 5.74 | 5.70 |
| | | | | | | | | Cl | 14.36 | 14.43 |

δ=1.33 (d, J=7 Hz, 3H, $C\underline{H}_3$), δ=2.84 (s, 3H, $NC\underline{H}_3$), δ=3.04 (d, J=7 Hz, 2H, $C\underline{H}_2$), δ=3.4-3.8 (m, 1H, C<u>H</u>), δ=3.94 (s, 6H, $OC\underline{H}_3$), δ=6.5-7.4 (m, 3H, Ar <u>H</u>).

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (8CD) | $OCH_3$ | H | H | $OCH_3$ | H | 75% | 115.5-116.0 | C | 58.48 | 58.65 |
| | | | | | | | | H | 8.13 | 8.20 |
| | | | | | | | | N | 5.74 | 5.70 |
| | | | | | | | | Cl | 14.36 | 14.43 |

δ=1.35 (d, J=7 Hz, 3H, $CC\underline{H}_3$), δ=2.94 (s, 3H, $NC\underline{H}_3$), δ=3.11 (d, J=7 Hz, 2H, $C\underline{H}_2$), δ=3.7-3.9 (m, 1H, C<u>H</u>), δ=3.83 (s, 3H, $OC\underline{H}_3$), δ=3.87 (s, 3H, $OC\underline{H}_3$).

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (10CD) | H | $OCH_3$ | H | $OCH_3$ | H | 51% | 126.5-127.0 | C | 58.44 | 58.65 |
| | | | | | | | | H | 8.11 | 8.20 |
| | | | | | | | | N | 5.68 | 5.70 |
| | | | | | | | | Cl | 14.60 | 14.43 |

δ=1.39 (d, J=7 Hz, 3H, $CC\underline{H}_3$), δ=2.95 (s, 3H, $NC\underline{H}_3$), δ=3.17 (d, J=7 Hz, 2H, $C\underline{H}_2$), δ=3.7-4.1 (m, 7H, $OC\underline{H}_3$, C<u>H</u>), δ=6.51 (s, 1H, Ar <u>H</u>), δ=6.68 (s, 2H, Ar <u>H</u>).

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (11CD) | H | H | $OCH_3$ | $OCH_3$ | H | 49% | 119-120 | C | 38.56 | 58.65 |
| | | | | | | | | H | 8.16 | 8.20 |
| | | | | | | | | N | 5.67 | 5.70 |
| | | | | | | | | Cl | 14.51 | 14.43 |

δ=1.38 (d, J=7 Hz, 3H, $CC\underline{H}_3$), δ=2.91 (s, $NC\underline{H}_3$), δ=3.15 (d, J=7 Hz, 2H, $C\underline{H}_2$), δ=3.5-4.1 (m, C<u>H</u>), δ=3.91 (s, 3H, $OC\underline{H}_3$), δ=3.98 (s, 3H, $OC\underline{H}_3$), δ=7.0 (s, 3H, Ar <u>H</u>).

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (12CD) | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | 45% | 106.0-107.0 | C | 56.34 | 56.62 |
| | | | | | | | | H | 7.83 | 8.04 |
| | | | | | | | | N | 5.08 | 5.08 |
| | | | | | | | | Cl | 12.94 | 12.86 |

δ=1.41 (d, J=7 Hz, 3H, $CC\underline{H}_3$), δ=2.98 (s, 3H, $NC\underline{H}_3$), δ=3.17 (d, J=7 Hz, 2H, $CC\underline{H}_2$), δ=3.2-3.7 (m, 1H, C<u>H</u>), δ=3.95 (s, 3H, $OC\underline{H}_3$), δ=4.08 (s, 6H, $OC\underline{H}_3$) δ=6.95 (m, 2H, Ar <u>H</u>).

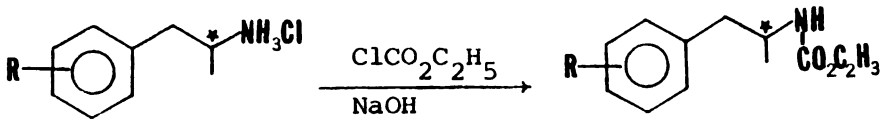
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (13CD) | $OCH_3$ | H | $OCH_3$ | $OCH_3$ | H | 68% | 185.5-186.5 | C 56.59 56.62<br>H 7.92 8.04<br>N 5.12 5.08<br>Cl 12.91 12.86 | δ=1.41 (d, J=7 Hz, 3H, $CCH_3$), δ=3.9-3.2 (m, 5H, $NCH_3$, $CCH_2$), δ=3.3-3.8 (m, 1H, CH), δ=3.88 (s, 9H, $OCH_3$), δ=6.72 (s, 1H, Ar H), δ=6.95 (s, 1H, Ar H). |
| (14CD) | $OCH_3$ | H | $OCH_3$ | H | $OCH_3$ | 83% | 158-159 | C 56.41 56.62<br>H 7.83 8.04<br>N 5.06 5.08<br>Cl 13.06 12.86 | δ=1.33 (d, J=7 Hz, 3H, $CCH_3$), δ=2.8-3.2 (m, 5H, $NCH_3$, $CH_2$), δ=3.4-3.8 (m, 1H, CH), δ=3.95 (s, 9H, $OCH_3$), δ=6.37 (s, 2H, Ar H). |
| (15CD) | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | 61% | 157-158 | C 56.53 56.62<br>H 7.96 8.04<br>N 5.06 5.08<br>Cl 13.02 12.86 | δ=1.42 (d, J=7 Hz, 3H, $CCH_3$), δ=2.9-3.8 (m, 6H, $NCH_3$, CH), $CH_2$), δ=3.84 (s, 3H, $OCH_3$), δ=4.02 (s, 6H, $OCH_3$), δ=6.78 (s, 2H, Ar H). |
| (16CD) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 54% | 129-130.5 | C 60.06 60.11<br>H 8.69 8.54<br>N 5.43 5.39<br>Cl 13.47 13.65 | δ=1.37 (d, J=7 Hz, 3H, $CCH_3$), δ=2.12 (s, 3H, Ar $CH_3$), δ=2.6-3.4 (m, 6H, $NCH_3$, $CH_2$, CH), δ=3.65 (s, 6H, $OCH_3$), δ=6.81 (s, 1H, Ar H), δ=6.9 (s, 1H, Ar H). |
| (17CD) | $OCH_3$ | H | Br | $OCH_3$ | H | 46% | 145-146 | C 44.41 44.40<br>H 5.92 5.89<br>N 4.18 4.31<br>Br 24.86 24.64<br>Cl 11.03 10.92 | δ=1.30 (d, J=7 Hz, 3H, $CCH_3$), δ=2.7-3.2 (m, 5H, $NCH_3$, $CCH_2$), δ=3.4-4.0 (m, 7H, CH, $OCH_3$), δ=7.04 (s, 1H, Ar H), δ=7.13 (s, 1H, Ar H). |

[a] NMR's run in $D_2O$ with DSS as internal calibrant.

[b] K. Bailey, A. W. By, D. Legault, and D. Vernier, J.A.O.A.C., 58, 62 (1975).

[c] U. Braun, A. T. Shulgin, and G. Braun, J. Pharm. Sci., 69, 192 (1980).

Table 5. Synthetic Data on Ring-Substituted Enantiomers of Ethyl-N-(1-phenyl-2-propyl)-carbamate

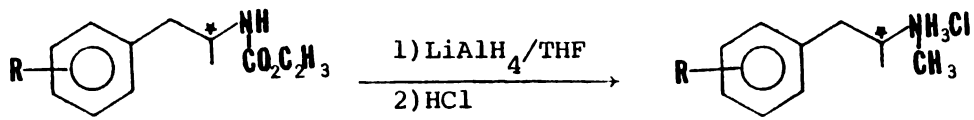



| Compound | Aromatic Sub. Pattern $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Configuration | Melting Point C° | % Yield | NMR Characterization[a] |
|---|---|---|---|---|---|---|---|---|---|
| (1f) | H | H | H | H | H | S | 49-49.5 | 72% | δ=1.05-1.38 (m, 6H, $CCH_3$, $OCCH_3$), δ=1.9-3.1 (br m, 3H, $CH_2$, CH), δ= 3.7-4.25 (m, 2H, $OCH_2$), δ=7.39 (m, 5H, Ar H). |
| (2e) | H | H | $OCH_3$ | H | H | R | 50-51.5 | 92% | δ=1.08-1.35 (m, 6H, $CCH_3$, $OCCH_3$), δ=1.9-3.2 (m, 3H, $CH_2$, CH), δ= 3.68-4.2 (m, 5H, $OCH_2$, $OCH_3$), δ= 6.65-7.32 (m, 4H, Ar H). |
| (2f) | H | H | $OCH_3$ | H | H | S | 50.5-51.5 | 87% | δ=0.97-1.31 (m, 6H, $CCH_3$, $OCCH_3$), δ=2.0-3.1 (br m, 3H, $CH_2$, CH), δ= 3.73-4.25 (m, 5H, $OCH_2$, $OCH_3$), δ= 6.7-7.3 (m, 4H, Ar H). |
| (5e) | H | H | O--$CH_2$--O | | H | R | 51-52 | 95% | δ=1.0-1.3 (m, 6H, $CCH_3$, $OCCH_3$), δ=1.9-3.2 (br m, 3H, $CH_2$, CH), δ= 3.75-4.24 (m, 5H, $OCH_2$), δ=5.97 (s, 2H, $OCH_2O$), δ=6.76 (s, 4H, Ar H). |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (5f) | H | H | O--$CH_2$--O | | H | S | 50.5-51 | 79% | δ=0.97-1.34 (m, 6H, $CCH_3$, $OCCH_3$), δ=1.9-3.1 (br m, 3H, $CH_2$, CH), δ=3.72-4.25 (m, 5H, $OCH_2$), δ=5.04 (s, 2H, $OCH_2O$), δ=6.81 (s, 4H, Ar H). |
| (8e) | $OCH_3$ | H | H | $OCH_3$ | H | R | 74.5-75.5 | 68% | δ=0.95-1.32 (m, 6H, $CCH_3$, $OCCH_3$), δ=1.9-3.1 (br m, 3H, $CH_2$, CH), δ=3.76-4.17 (m, 8H, $OCH_3$, $OCH_2$), δ=6.82 (s, 3H, Ar H). |
| (8f) | $OCH_3$ | H | H | $OCH_3$ | H | S | 75-75.5 | 84% | δ=0.9-1.3 (m, 6H, $CCH_3$, $OCCH_3$), δ=1.9-3.0 (br m, 3H, $CH_2$, CH), δ=3.6-4.2 (m, 8H, $OCH_3$, $OCH_2$), δ=6.79 (s, 3H, Ar H). |
| (16e) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | R | 124-124.5 | 82% | δ=0.95-1.30 (m, 6H, $CCH_3$, $OCCH_3$), δ=1.9-3.2 (m, 6H, Ar $CH_3$, $CH_2$, CH), δ=3.6-4.2 (m, 8H, $OCH_3$, $OCH_2$), δ=6.79 (s, 2H, Ar H). |
| (16f) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | S | 124.5-125 | 89% | δ=0.97-1.28 (m, 6H, $CCH_3$, $OCCH_3$), δ=1.9-3.2 (m, 6H, Ar $CH_3$, $CH_2$, CH), δ=3.65-4.23 (m, 8H, $OCH_3$, $OCH_2$), δ=6.82 (s, 2H, Ar H). |

[a]NMR's run in $d_6$-acetone with TMS as an internal calibrant.

Table 6. Synthetic Data on Ring-Substituted Enantiomers of 1-Phenyl-2-methylaminopropane (HCl).




| Compound | Aromatic Sub. Pattern $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | % Yield | Melting Point (Lit.) °C | Configuration | $\{\alpha\}^d$ (Lit.)[a] | NMR Characterization[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| (1D) | H | H | H | H | H | 66% | 169.5-170.5<br>170-175[c] | S | +16.9<br>(+17.5)[d] | δ=1.29 (d, J=7 Hz, 3H, $CCH_3$), δ=2.75-3.2(m, 5H, $NCH_3$, $CH_2$), δ=3.28-3.75 (m, 1H, CH), δ=7.38 (s, 5H, Ar H). |
| (2C) | H | H | $OCH_3$ | H | H | 73% | 196.5-198 | R | -17.1 | δ=1.32 (d, J=7 Hz, 3H, $CCH_3$), δ=2.93 (d, J=7 Hz, 2H, $CH_2$), δ=3.2-3.9 (m, 4H, CH, $OCH_3$), δ=6.9-7.4 (m, 4H, Ar H). |
| (2D) | H | H | $OCH_3$ | H | H | 85% | 197-198 | S | +17.2 | δ=1.30 (d, J=7 Hz, 3H, $CCH_3$), δ=2.91 (d, J=7 Hz, 2H, $CH_2$), δ=3.15-3.85 (m, 4H, CH, $OCH_3$), δ=6.9-7.4 (m, 4H, Ar H). |
| (5C) | H | H | O--$CH_2$--O | H | H | 80% | 179.0-180.5<br>(181-183)[d] | R | -17.7<br>(-18.2)[d] | δ=1.30 (d, J=7 Hz, 3H, $CCH_3$), δ=2.75 (s, 3H, $NCH_3$), δ=2.80-3.07 (m, 2H, $CCH_2$), δ=3.15-3.82 (m, 1H, CH), δ=6.0 (s, 2H, $OCH_2O$), δ=6.78 (s, 3H, Ar H). |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (5D) | H | H | O--$CH_2$--O | H | 77% | 180.0-181.5 (184-185)[d] | S | +17.9 (+17.2)[d] | δ=1.31 (d, J=7 Hz, 3H, $CCH_3$), δ=2.74 (s, 3H, $NCH_3$), δ=2.8-3.5 (m, 2H, $CH_2$) δ=3.2-3.8 (m, 1H, CH), δ=6.06 (s, 2H, $OCH_2O$), δ=6.9 (s, 3H, Ar H). |
| (8C) | $OCH_3$ | H | H | $OCH_3$ | H | 91% | 123.5-124.5 | R | -18.10 | δ=1.30 (d, J=7 Hz, 3H, $CCH_3$), δ=2.76 (s, 3H, $NCH_3$), δ=2.83-3.14 (m, 2H, $CH_2$), δ=3.2-3.8 (m, 1H, CH), δ=3.78 (s, 3H, $OCH_3$), δ=3.86 (s, 3H, $OCH_3$), δ=6.8-7.05 (m, 3H, Ar H). |
| (8D) | $OCH_3$ | H | H | $OCH_3$ | H | 87% | 123.0-124.5 | S | +18.6 | δ=1.26 (d, J=7 Hz, 3H, $CCH_3$), δ=2.73 (s, 3H, $NCH_3$), δ=2.85-3.12 (m, 2H, $CH_2$), δ=3.2-3.8 (m, 1H, CH), δ=3.83 (s, 3H, $OCH_3$), δ=3.89 (s, 3H, $OCH_3$), δ=6.84-7.1 (m, 3H, Ar H). |
| (16C) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 84% | 162.0-163.0 | R | -21.1 | δ=1.29 (d, J=7 Hz, 3H, $CCH_3$), δ=2.23 (s, 3H, $NCH_3$), δ=2.82-3.10 (m, 2H, $CH_2$), δ=3.15-3.75 (m, 1H, CH), δ=3.87 (s, 6H, $OCH_3$), δ=6.89-7.04 (m, 2H, Ar H). |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (16D) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 69% | 170.0-171.5 | S | +20.9 | $\delta$=1.27 (d, J=7 Hz, 3H, $CCH_3$), $\delta$=2.21 (s, 3H, $NCH_3$), $\delta$=2.8-3.1 (m, 2H, $CH_2$) $\delta$=3.15-3.8 (m, 1H, CH), $\delta$=3.87 (s, 6H, $OCH_3$), $\delta$=6.87-7.06 (m, 2H, (Ar H). |

[a] $\{\alpha\}^d$ values are given in (c 1.0, $H_2O$) and represent the average of 3 determinations.

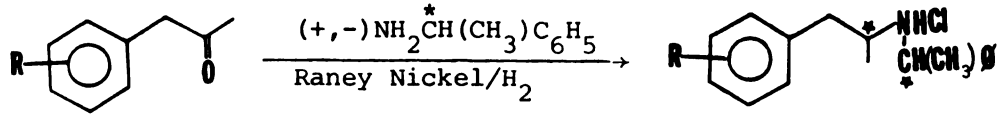
[b] NMR's run in $D_2O$ with DSS as calibrant standard.

[c] Value from "Merck Index," 9th Ed., Merck Co., Rahway, N.J., 1976, pp. 5807.

[d] Values from J. C. Craig, R. P. K. Chan, and S. K. Roy, Tetrahedron, 23, 3573 (1967).

[e] G. M. Anderson III, G. Braun, U. Braun, D. E. Nichols, and A. T. Shulgin in QuaSAR Research Monograph #22, G. Barnett, M. Trsic, and R. Willette, eds., 1978, pp. 8-15.

Table 7. Synthetic Data on Ring-Substituted Analogues of 1-Phenyl-2-(R,S)-(R,S-1-methyl-2-phenylethane)-aminopropane HCl.



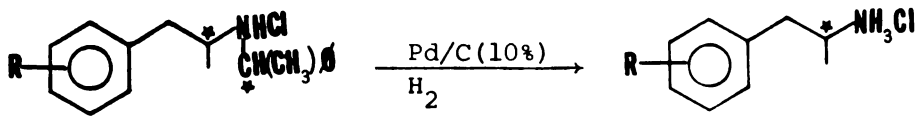

| Compound | Aromatic Sub. Pattern $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | % Yield | Melting Point C° (Lit.) | Configuration | $\{\alpha\}^d$ (Lit.)[a] |
|---|---|---|---|---|---|---|---|---|---|
| (1d) | H | H | H | H | H | 29% | 226-228 | SS | -20.6 |
| (2c) | H | H | $OCH_3$ | H | H | 34% | 191-192.5 (195-197)[b] | RR | +34.8 (+36.1)[b] |
| (2d) | H | H | $OCH_3$ | H | H | 41% | 191.5-192.5 (195-197)[b] | SS | -34.1 (-36.1)[b] |
| (5c) | H | H | O--$CH_2$--O | | H | 46% | 184-185 | RR | +16.1 |
| (5d) | H | H | O--$CH_2$--O | | H | 38% | 185-186 | SS | -17.4 |
| (8c) | $OCH_3$ | H | H | $OCH_3$ | H | 47% | 221-222 (227-228)[b] | RR | +7.9 (+7.5)[b] |
| (8d) | $OCH_3$ | H | H | $OCH_3$ | H | 32% | 223-224 (227-228)[b] | SS | -7.6 (-7.8)[b] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (16c) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 36% | 198.5-200 (198-199)[b] | RR | +6.9 (+7.4)[b] |
| (16d) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 44% | 199-201 (195-196.5)[b] | SS | -7.9 (-7.4)[b] |

[a] $\{\alpha\}^d$ values are given for (c 1.0, $H_2O$) and represent the average of 3 determinations.

[b] D. E. Nichols, C. F. Barfknecht, D. B. Rusterhols, F. Benington, and R. D. Morin, J. Med. Chem., 16, 480 (1973).

Table 8. Synthetic Data on Ring Substituted Enantiomers of 1-Phenyl-2-aminopropane HCl.




| Compound | Aromatic Sub. Pattern $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | % Yield | Melting Point (Lit.) °C | Configuration | $\{\alpha\}^d$ (Lit.)[a] | NMR Characterization[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| (1B) | H | H | H | H | H | 96% | 154-155 | S | | δ=1.28 (d, J=6 Hz, 3H, $CCH_3$), δ=2.96 (d, J=7 Hz, 2H, $CH_2$), δ=3.3-3.95 (m, 1H, CH), δ=7.45 (s, 5H, Ar H). |
| (2A) | H | H | $OCH_3$ | H | H | 90% | 247.5-249 (251-253)[d] | R | -22.7 (-22.5)[d] | δ=1.32 (d, J=7 Hz, 3H, $CCH_3$), δ=2.94 (d, J=7 Hz, 2H, $CH_2$), δ=3.34-3.9 (m, 4H, CH, $OCH_3$), δ=6.8-7.5 (m, 4H, Ar H). |
| (2B) | H | H | $OCH_3$ | H | H | 89% | 248.0-249 (250.5-251.5)[d] | S | +22.1 (+22.4)[d] | δ=1.31 (d, J=7 Hz, 3H, $CCH_3$), δ=2.93 (d, J=7 Hz, 2H, $CH_2$), δ=3.4-3.9 (m, 4H, CH, $OCH_3$), δ=6.9-7.45 (m, 4H, Ar H). |
| (5A) | H | H | O--$CH_2$--O | H | H | 85% | 194.5-195.5 | R | -24.8 (-24.7)[e] | δ=1.32 (d, J=7 Hz, 3H, $CCH_3$), δ=2.92 (d, J=7 Hz, 2H, $CH_2$), δ=3.3-3.9 (m, 1H, CH), δ=6.3 (s, 2H, $OCH_2O$), δ=6.87 (s, 4H, Ar H). |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (5B) | H | H | O--$CH_2$--O | H | 79% | 193.0-194.5 ——— | S | +24.1 (+25.3)[e] | δ=1.33 (d, J=7 Hz, 3H, $CCH_3$), δ=2.91 (d, J=6Hz, 2H, $CH_2$), δ=6.1 (s, 2H, $OCH_2O$), δ=6.89 (s, 4H, Ar H). |
| (8A) | $OCH_3$ | H | H | $OCH_3$ | H | 83% | 143.5-145.0 (145-146)[d] | R | -18.5 (-18.7)[d] | δ=1.35 (d, J=7 Hz, 3H, $CCH_3$), δ=2.94 (d, J=7 Hz, 2H, $CH_2$), δ=3.4-3.9 (m, 7H, CH, $OCH_3$), δ=6.8-7.1 (m, 3H, Ar H). |
| (8B) | $OCH_3$ | H | H | $OCH_3$ | H | 79% | 142-143 (144-145)[d] | S | +18.6 (+18.7)[d] | δ=1.34 (d, J=7 Hz, 3H, $CCH_3$), δ=2.91 (d, J=7 Hz, 2H, $CH_2$), δ=3.4-3.9 (m, 7H, CH. $OCH_3$), δ=6.8-7.1 (m, 4H, Ar H). |
| (16A) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 91% | 201-202 (204-205)[d] | R | -16.7 (-17.2)[d] | δ=1.31 (d, J=7 Hz, 3H, $CCH_3$), δ=2.25 (s, 3H, Ar $CH_3$) δ=2.91 (d, J=7 Hz, 2H, $CH_2$), δ=3.4-3.9 (m, 7H, CH, $OCH_3$), δ=6.81 (s, 1H, Ar H), δ=6.98 (s, 1H, Ar H). |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (16B) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 88% | 201.5-202.5 (204-205)[d] | S | +17.3 (+17.7)[d] | $\delta$=1.34 (d, J=7 Hz, 3H, $CCH_3$), $\delta$=2.23 (s, 3H, Ar $CH_3$), $\delta$=2.91 (d, J=7 Hz, 2H, $CH_2$), $\delta$=3.45-3.9 (m, 7H, CH, $OCH_3$), $\delta$=6.81 (s, 1H, Ar H), $\delta$=7.1 (s, 1H, Ar H). |

[a] $\{\alpha\}^d$ values are given for (c 1.0, $H_2O$) and represent the average of 3 determinations.

[b] NMR's were run in $D_2O$ with DSS and an internal calibrant.

[c] W. Leithe, Chem. Ber., 65, 664 (1932).

[d] D. E. Nichols, C. F. Barfknecht, D. B. Rusterholz, F. Benington, and R. D. Morin, J. Med. Chem., 16, 480 (1973).

[e] G. M. Anderson III, G. Braun, U. Braun, D. E. Nichols, and A. T. Shulgin in "QuaSAR: Research Monograph #22," G. Barnett, M. Trsic, and R. Willette, NIDA (1978), pp. 8-15.

# EXPERIMENTAL SECTION

Solvents were removed by means of a rotary evaporator under vacuum. Melting points were taken on a Thomas-Hoover apparatus and reported uncorrected. IR spectra were recorded using a Perkin-Elmer Model 337 grating spectrometer. NMR spectra were taken on either a Varian A-60A or Varian 80 spectrometer. Chemical ionization mass spectra were taken on an AEI MS 902 double docusing mass spectrometer equipped with a direct inlet system modified for chemical ionization mass spectrometry using isobutane (0.5 Torr) as reagent gas. Elemental analyses were performed by the Microanalytical Laboratory of the University of California, Berkeley.

When a series of analogues were prepared by a common reaction sequence, these reactions have been reported in detail as a transformation of a derivative of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane. The synthetic data on the remaining compounds were summarized into Tables.

1-(2,5-Dimethoxy-4-methylphenyl)-2-nitroprop-1-ene (16a). A solution of 10 g (0.067 mol) of 2,5-dimethoxy-4-methylbenzaldehyde, 2.3 g (0.030 mol) of $NH_4OAc$, and 100 ml of $EtNO_2$ was heated at reflux for six hours during which time a bright yellow color developed. Evaporation of excess nitroethane resulted in the formation of a yellow solid which was dissolved in 50 ml of ethanol and 10 ml of $H_2O$, 2 g of activated charcoal were added, and the solution was filtered hot. The filtrate was chilled and drop-wise addition of $H_2O$ resulted in the formation of 7.2 g (0.03 mol; 45% yield) of yellow needles having a melting point of 90-90.5° C (Lit.=86.5-88) [16a]; nmr ($CHCl_3$/TMS) $\delta$=2.32 (s, 3H, $ArC\underline{H}_3$), $\delta$=2.45 (s, 3H, $CC\underline{H}_3$), $\delta$=3.85 (s, 6H, $OC\underline{H}_3$), $\delta$=6.81 (s, 1H, Ar $\underline{H}$), $\delta$=6.87 (s, 1H, Ar $\underline{H}$), $\delta$=8.4-8.6 (s, 1H, Ar $C\underline{H}$).

1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane HCl (16AB). Under an atmosphere of $N_2$, a solution of 6.5 g (0.027 mol) of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroprop-1-ene dissolved in 75 ml of dry THF was added dropwise to an ice-cooled, stirred solution of 5.1 g (0.135 mol) of $LiAlH_4$ in 100 ml of dry THF. After the addition was completed, the reaction mixture was heated to reflux and held at that temperature for 24 hours. Workup followed the procedure of House: The reaction mixture was allowed to return to room temperature, 5 ml of $H_2O$ in 20 ml of THF was added dropwise over a 30 minute period with efficient stirring, after which 5 ml of a 20% NaOH solution was added, followed by addition of 15 ml of $H_2O$. A

filterable, granular filter cake results which is filtered with suction and washed 4 times with 50 ml portions of ether, the organics combined, and removed to give a pale yellow oil. This oil was taken up in 100 ml of anhydrous ether and dried with 2 g of $Na_2CO_3$ overnight; the drying agent filtered off, solvents removed and the resulting oil subjected to Kuglerohr distillation at 135-145° C/ 0.4 mm. The distillate consisted of a clear viscous oil which solidified in the bulb giving 4.2 g (0.020 mol; 74% yield) of a white solid having a melting point of 105-106° C (Lit.=104.5-105.5) [16a]. The HCl salt of the amine was made by dissolving 3.5 g (0.007 mol) of 1-(2,5- dimethoxy-4-methylphenyl)-2-aminopropane in 50 ml of dry ether and cooling to 4° C; dropwise addition of etheral HCl resulted in the formation of 3.9 g of a clean white solid having a melting point of 186.5-187° C (Lit.=189-189.5)[16b]; nmr ($D_2O$/DSS) δ=1.11 (d, J=7 Hz, 3H, $C\underline{H}_3$), δ=2.19 (s, 3H, Ar $C\underline{H}_3$), δ=2.35-2.82 (m, 2H, $CC\underline{H}_2$), δ=2.88-3.52 (m, 1H, C<u>H</u>), δ=3.74 (s, 3H, $OC\underline{H}_3$), δ=3.78 (s, 3H, $OC\underline{H}_3$), δ=6.67 (s, 1H, Ar <u>H</u>), δ=6.72 (s, 1H, Ar <u>H</u>).

<u>1-(2,5-Dimethoxy-4-methylphenyl)-2-propanone (16b)</u>. 56 g (1 mol) of Fe powder (200 mesh; purified by hydrogen) was added to a 1000 ml three neck roundbottom flask containing 200 ml of glacial acetic acid and equipped with a mechanical stirrer, an addition funnel, and two parallel condensers. The Fe/acid mixture was heated to reflux and stirred vigorously for 30-45 minutes during which time, the

Fe assumes a lusterous silvery appearance. At this point the reduction was begun by the dropwise addition of a solution of 14 g (0.059 mol) of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroprop-1-ene, 100 ml of glacial acetic acid, and 5 ml of concentrated HCl (36%) to the reaction flask over a 30 minute period. Heating and stirring were continued for another three hours, then the reaction mixture was filtered hot through Filter Aid, the filter cake washed with three 100 ml portions of $CH_2Cl_2$, the organics combined and evaporated under reduced pressure to give a viscous dark red oil which was taken up into 200 ml of $CH_2Cl_2$ and extracted with three portions of 50 ml of saturated $NaHCO_3$ solution, and the organic phase dried with $Na_2CO_3$ overnight. The drying agent was filtered off, the solvent was evaporated and the resulting oil subjected to distillation via Kuglerohr giving a pale yellow oil which solidified in the bulb to give 5.9 g (0.028 mol; 48% yield) of solid having a melting point of 54-55.5° C; nmr ($CDCl_3$/TMS) $\delta$=2.10 (s, 3H, $C\underline{H}_3$), $\delta$=2.21 (s, 3H, Ar $C\underline{H}_3$), $\delta$=3.65 (s, 2H, $C\underline{H}_2$), $\delta$=3.79 (s, 6H, $OC\underline{H}_3$), $\delta$=6.66 (s, 1H, Ar $\underline{H}$), $\delta$=6.75 (s, 1H, Ar $\underline{H}$).

1-(2,5-Dimethoxy-4-methylphenyl)-2-methylaminopropane (16CD). A solution of 7.5 g (0.036 mol.) of 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone, 2.8 g (0.045 mol.) $NaBH_3CN$, 6.9 g (0.108 mol.) of methylamine HCl, and 75 ml of anhydrous methanol was stirred at room temperature for eight days. Twice each day, the pH of the reaction mixture was checked with wet litmus paper and adjusted to a pH range of

4 to 5 by dropwise addition of concentrated HCl (36%). Workup involved first the elimination of the excess $NaBH_3CN$, followed by removal of the excess $NH_2CH_3$. The pH of the reaction mixture was adjusted to 2 by drop-wise addition of concentrated HCl to the stirred solution. This must be done in an efficient hood since copious amounts of HCN gas are liberated. Inorganic salts are filtered off, and the solvent removed to give a clear, slightly yellow oil which was taken up in 10 ml of water and the pH adjusted to 11 by the dropwise addition of a 40% NaOH solution, and the aqueous solution evaporated to give a viscous slightly yellow oil. 100 ml of anhydrous ether was added along with 2 g of $Na_2CO_3$ and the resulting solution was allowed to dry overnight. The drying agent was filtered off, the solvent removed, and the oil subjected to Kuglerohr distillation at 70-80° C at 0.3-0.4 mm. The distillate consisted of a clear oil which solidified in the bulb yielding 4.3 g (0.019 mol; 54% yield) of a white solid. The HCl salt was prepared as described previously and characterized as a white flaky solid having a melting point of 129-130.5° C; nmr ($D_2O$/DSS), $\delta$ =1.17 (d, J=7 Hz, 3H, $CC\underline{H}_3$), $\delta$=2.12 (s, 3H, Ar $C\underline{H}_3$), $\delta$=2.6-3.0 (m, 6H, $NC\underline{H}_3$, $C\underline{H}_2$, $C\underline{H}$), $\delta$=3.65 (s, 6H, $OC\underline{H}_3$), $\delta$=6.81 (s, 1H, Ar $\underline{H}$), $\delta$=6.9 (s, 1H, Ar $\underline{H}$). Anal. Calc'd for C H N Cl; C, 60.11; H, 8.54; N, 5.39; Cl, 13.65. Found C, 60.06; H, 8.69; N, 5.43; Cl, 13.47.

1-(2,5-Dimethoxy-4-methylphenyl)-2-R-(R-1-methyl-2-phenylethane)-aminopropane HCl (16c). A solution composed

of 21.5 g (0.13 mol) of 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone, 15.7 g (0.13 mol) of R-α-methylbenzylamine (Aldrich; $\{\alpha\}_d^{d\,23}$=+38) and 100 ml of anhydrous benzene was heated at reflux for two days and the $H_2O$ produced was removed via a Dean Stark trap. The solvent was removed leaving a semisolid residue which was dissolved in 70 ml of EtOH, transferred to a waiting hydrogenation bottle containing 5 g of Raney Nickel (Grace Co, W-2 activity) and hydrogenated on a Parr apparatus at 50 psi of $H_2$ for three days. Then the reaction mixture was filtered, the catalyst washed twice with 50 ml of EtOH. (Caution, the Raney nickel catalyst is still very pyrophoric when allowed to dry in air.) The organics were combined and evaporated to give an orange viscous residue which was dissolved in 70 ml of ether/30 ml of EtOH and cooled to $0^{o}$ C. Careful addition of etheral HCl resulted in the formation of a dark red solution containing a highly colored red solid which was filtered, and air-dried. Recrystallization was effected by dissolving the solid in a minimum volume of a boiling mixture of MeOH and acetonitrile (70/30) and 3 g decolorizing charcoal. After hot filtration, the solution was cooled to $0^{o}$ C and crystal formation was encouraged by addition of ether, resulting in an off-colored amorphous mass with a slight reddish hue. This solid was recrystallized from EtOH/$H_2O$ to give a clean white solid of semiamorphous composition (23.5 g; m.p. =185-187$^{o}$ C) which was recrystallized again from EtOH/$H_2O$ to finally give 19.9 g (0.057 mol; 36% yield) of white

flake crystals having a melting point of 198.5-200° C (Lit. m.p. 198-199° C)[11d] and an $\{\alpha\}^d$ of -7.5 (Lit. $\{\alpha\}^d$= -7.38)[11d]; nmr: δ=1.20 (d, J=6 Hz, 3H, $C\underline{H}_3$), δ=1.72 (d, J=7 Hz, 3H, $C\underline{H}_3$), δ=2.20 (s, 3H, Ar $C\underline{H}_3$), δ=2.20 (s, 3H, Ar $C\underline{H}_3$), δ=2.4-3.2 (m, 10H, Ar $OC\underline{H}_3$, $C\underline{H}$, $C\underline{H}$, $C\underline{H}_2$), δ=6.71 (s, 1H, Ar $\underline{H}$), δ=6.83 (s, 1H, Ar $\underline{H}$), δ=7.35 (s, 5H, Ar $\underline{H}$).

1-(2,5-Dimethoxy-4-methylphenyl)-2-R-aminopropane HCl (16A). A solution of 17 g (0.049 mol) of 1-(2,5-dimethoxy-4-methylphenyl)-2-R-(R-1-methyl-2-phenylethane)-aminopropane HCl and 150 ml MeOH was transferred to a hydrogenation bottle containing 3 grams of Pd/C (made from a slurry with 0.5 ml of $H_2O$) and placed on a Parr hydrogenator under 50 psi of $H_2$ for three days. The charcoal was filtered off, solvent evaporated to give a glassy amorphous residue. Recrystallization from a 50/50 mixture of isopropanol/ethanol with ether encouragement afforded 10.9 g (0.045 mol; 91% yield) of clean white plates having a melting point of 201-202° C (Lit. m.p. 204-205° C)[11d] and an $\{\alpha\}^d$ of -16.7 (Lit. $\{\alpha\}^d$ =-17.2)[11d]; nmr ($D_2O$/DSS): δ=1.22 (d, J=7 Hz, 3H, $CC\underline{H}_3$), δ=2.1 (s, 3H, Ar $C\underline{H}_3$), δ=2.5-3.3 (m, 3H, $C\underline{H}_2$, $C\underline{H}$), δ=3.72 (s, 6H, $OC\underline{H}_3$), δ=6.75 (s, 1H, Ar $\underline{H}$), δ=6.82 (s, 1H, Ar $\underline{H}$).

N-Ethyl-(1-(2,5-dimethoxy-4-methylphenyl)-2-R-propyl)--carbamate (16e). A 100 ml three neck flask equipped with a magnetic stirrer and two 10 ml addition funnels and a thermometer was immersed in an ice bath and charged with 3.19 g (0.013 mol) of 1-(2,5-dimethoxy-4-methylphenyl)-2-R-amino-

propane HCl dissolved in a solution of 10 ml of $H_2O$ and 5 g of crushed ice. The pH of the solution was adjusted to 8 by dropwise addition of a 20% solution of NaOH followed by dropwise addition of 1.82 g (0.018 mol) of ethyl chloroformate at a rate which was consistent with a reaction mixture temperature of $< 10^{\circ}$ C. After this initial addition was complete, another portion of 1.82 g of ethyl chloroformate was added slowly in concert with an ice-cooled solution of 4 g (0.01 mol) of NaOH in 5 ml of $H_2O$ at a rate so that the reaction temperature did not exceed $10^{\circ}$ C. Stirring was continued for an additional 30 minutes, after which the reaction mixture was filtered, and the solid precipitate washed with 100 ml cold $H_2O$. The air-dried product amounted to 2.7 g (0.009 mol, 71.9% yield) of amorphous white solid having a melting point of 124-125.5° C; nmr ($d_6$ Acetone/TMS) $\delta$=0.95-1.30 (m, 6H, $CC\underline{H}_3$, $OCCH_3$), $\delta$=1.9-3.2 (m, 6H, Ar $C\underline{H}_3$, $CH_2$, $C\underline{H}$), $\delta$=3.6-4.2 (m, 8H, $OC\underline{H}_3$, $OC\underline{H}_2$), $\delta$=6.79 (s, 2H, Ar $\underline{H}$).

1-(2,5-Dimethoxy-4-methylphenyl-2-(R)-methylaminopropane HCl (16C). Under an atmosphere of $N_2$, a solution consisting of 2.1 g (0.007 mol) of N-ethyl-(1-(2,5-dimethoxy-4-methylphenyl)-2-R-propyl)-carbamate dissolved in 20 ml of anhydrous THF was added dropwise with efficient stirring to an ice-cooled solution of 3 g of $LiAlH_4$ in 50 ml of THF. Upon completion of addition, the reaction mixture was heated at reflux in a water bath for 48 hours, at which time the reaction was terminated according to House's procedure as

described previously. The organic phase was evaporated yielding light yellow oil which was taken up in 75 ml of dry ether and dried overnight with 2 g of $Na_2CO_3$. The drying agent was then filtered off. Addition of ethereal HCl resulted in the formation of a white solid. Recrystallized from EtOH/ether to yield 1.6 g (0.005 mol; 84% yield) of a clean white flake having a melting point of 161-162.5° C $\{\alpha\}^d$ -21.1; nmr ($D_2O$/DSS) $\delta$=1.29 (d, J=7 Hz, 3H, $CC\underline{H}_3$), $\delta$=2.23 (s, 3H, $NC\underline{H}_3$), $\delta$=2.82-3.10 (m, 2H, $C\underline{H}_2$), $\delta$=3.15-3.75 (m, 1H, C$\underline{H}$), =3.87 (s, 6H, $OC\underline{H}_3$), $\delta$=6.89-7.04 (m, 2H, Ar $\underline{H}$).

Resolution of 1-(3,4-Methylenedioxyphenyl)-2-methylaminopropane (5CD). Classical resolution of compound (5CD) was attempted via formation of a diasteromeric salt between the secondary amine and a chiral acid, followed by repeated recrystallizations. Since the resolution of (5CD) was not reported in literature, it was necessary to find a suitably crystalline salt. Towards this end, salts of the following acids were explored: a). (+)-d-10-camphorsulfonic acid (Aldrich; $\{\alpha\}^d$=+19.9), b). d-tartaric acid (Aldrich; $\{\alpha\}^d$ =12), c). (+)-d-malic acid (Aldrich; $\{\alpha\}^d$=24.9), d). (+)-3-methyladipic acid (Aldrich; $\{\alpha\}^d$=8), e). l-orthonitrotartanilic acid (N. P. McGraw), f). (-)-l-menthoxyacetic acid (Aldrich; $\{\alpha\}^d$=-88), g). (-)-l-2-pyrrolidone-5-carboxylic acid (Aldrich; $\{\alpha\}^d$=-8.7), and h). (+)-di-p-toluoyl-l-tartaric acid monohydrate (Aldrich; $\{\alpha\}^d$=132). Formation of the diasteromeric salt was afforded by dissolving the respective acids in a minimum amount of

anhydrous ethanol, addition of an equimolar quantity of the freshly distilled racemic amine (0.2 g) and refrigeration of the ethanolic solutions. Only the di-p-toluoyl-l-tartaric acid yielded a manageable salt.

Resolution of (5CD) was achieved by dissolving 12.9 g (0.032 mol) of di-p-toluoyl-l-tartaric acid in a minimum volume of a mixture of 30/70% MeOH/isopropanol, followed by addition of 6.5 g (0.032 mol) of RS-l-(3,4-methylenedioxyphenyl)-2-methylaminopropane. Evaporation of the solvent yielded 18.6 g of a white powdery solid having a melting point of 156-159.5° C. This salt was recrystallized from EtOH/Ether to give 11.2 g of a white solid with a melting point of 172-173.5° C. The second recrystallization was made from ethanol and acetonitrile (70/30%) to give 5.4 g of a white flaky crystalline solid having a melting point of 193-194.5° C. A third recrystallization was made from a minimum amount of a mixture of EtOH/MeOH, which with ether encouragement yielded 4.3 g of a clean white flaky solid having a melting point of 195.5-196.5° C, and an $\{\alpha\}^d$ of -250.7 (C 1.0, MeOH). Further recrystallization resulted in no further increases in melting point or $\{\alpha\}^d$. The resolved amine was recovered by dissolving the diastereomeric salt in 50 ml of $H_2O$, adjusting the pH of the solution to 9-10 and extracting with three 100 ml portions of ether. The water layer was discarded, and the ether phase was dried over 2 g of $Na_2CO_3$ overnight. The drying agent was filtered off and the ether solution cooled to 4° C. Addition of an

etheral HCl solution (4° C) resulted in formation of 1.1 g of a white solid having a melting point of 178-180° C. Recrystallization of the resolved HCl salt of (5D) from ethanol gave 0.71 g (0.03 mol; 9.1% yield) of a beautiful white flaky solid having a melting point of 182-182.5° C and an $\{\alpha\}^d$=+(17.4)(c 1.0, $H_2O$), (Lit. $\{\alpha\}^d$=17.2)[16c].

The mother liquors from the various recrystallizations of the l-diasteromeric salt were combined, the solvents evaporated, and the free amine extracted into ether and dried as described previously and the corresponding d-tartaric acid salt was prepared. Recrystallization of this salt was made in a manner exactly as that used for the l-salt and the physical data characterizing compound (5C) is summarized below:

From 5.4 g of the amine and 10.71 g of (-)-di-p-toluoyl-d-tartaric acid (Aldrich: $\{\alpha\}^d$=-126).

| Recrystallization | Yield | Melting Point |
|---|---|---|
| 1st | 3.8 g | 171.5-175° |
| 2nd | 1.7 g | 174-175.5° |
| 3rd | 0.87 g | 182-183.5° |
| 4th | 0.32 g | 192.5-193° |

The diasteromeric salt was decomposed with base, the free amine was then extracted into ether, and salted as described for the other enantiomer. Compound (5C) was recrystallized from EtOH yielding 0.77 g (0.0032 mol; 11% yield) of a white flaky solid with a melting point of 183-184° (Lit. = 181-183)[16c] and an $\{\alpha\}^d$ of -15.1 (Lit. $\{\alpha\}^d$= -18.2 )[16c].

1-(2,5-Dihydroxy-4-methylphenyl)-2-aminopropane HCl (16EF). Under an atmosphere of $N_2$, 23.8 g (0.095 mol) of $BBr_3$ was added dropwise over a 45 minute period to a stirred solution containing 9.8 g (0.040 mol) of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane HCl and 35 ml of dry dichloromethane which was cooled in a dry ice/acetone bath. After addition of the $BBr_3$ was complete, the reaction mixture was removed from external cooling and allowed to stir at room temperature for an additional eight hours. Then 100 ml of MeOH was added cautiously with stirring and the solution evaporated (water bath temperature $<55^{\circ}$ C) and this procedure repeated three more times until final evaporation yielded a glass of slightly orangish color. This semisolid was dissolved in 75 ml $H_2O$ and immediately placed on a column composed of 85 g of Dowex-W4 cation exchange resin previously activated by the following procedure: The resin was first washed twice with 1000 ml of 4N HCl followed by 3000 ml of distilled $H_2O$. After application of the amine /water solution, the column was washed with copious amounts $H_2O$ until free of $Cl^-$ ions by $AgNO_3$ test; and (16EF) was eluded with 1000 ml of 6N HCl. Evaporation of this solution resulted in the formation of a glass having a slightly yellow color, which was taken up with a minimum volume of warm MeOH and cooled to $4^{\circ}$ C. Addition of 200 ml of dichloromethane produced a turbid solution which solidified upon addition of ether to give 5.1 g (0.024 mol; 59% yield) of a clean white solid having a melting point of 224-225$^{\circ}$ C;

nmr ($D_2O$/DSS) $\delta$=1.37 (d, J=7 Hz, 3H, $CC\underline{H}_3$), $\delta$=2.19 (s, 3H, Ar $C\underline{H}_3$), $\delta$=2.88 (d, J=7 Hz, $C\underline{H}_2$), $\delta$=3.4-3.9 (m, 1$\underline{H}$, C$\underline{H}$), $\delta$=6.75 (s, 1H, Ar $\underline{H}$), $\delta$=6.82 (s, 1H, Ar $\underline{H}$).

1-(2,5-Diacetoxy-4-methylphenyl)-2-aminopropane HCl (16GH). 2.7 g (0.034 mol) of freshly distilled acetyl chloride was added dropwise over a 10 minute period to a stirred solution containing 10 ml of freshly distilled trifluoroacetic acid and 3 g (0.014 mol) of 1-(2,5-dihydroxy-4-methylphenyl)-2-aminopropane HCl. The reaction mixture was stirred at room temperature for an additional 20 minutes after which 30 ml of wet MeOH was added. Evaporation of solvent was made on a rotovap (water bath temperature must not exceed 40° C) yielded an amorphous glass with a faint orange color. This semisolid was washed three times with 50 ml portions of a cold (4° C) solution of ether/hexane (50/50%) and then dissolved in 5 ml of warm MeOH. This solution was cooled to 4° C and 2 ml of dry dichloromethane was added producing a turbid white solution which, with the addition of ether and further cooling, resulted in 1.2 g (0.004 mol; 28% yield) of a white solid having a melting point of 209-210.5° C. Anal.(performed shortly after synthesis) for C H N Cl; C, 55.72; H, 6.68; N, 4.64; Cl, 11.75. Found: C, 55.13; H, 6.92; N, 4.76; Cl, 16.53. Sample was resubmitted for analysis about six months later at which time the following analysis was obtained: C, 52.49; H, 7.22; N, 5.92; Cl, 16.53. Mass spectroscopy on the

initial reaction product indicated a small amount (less than 2%) of impurity having masses of 322, 308, and 304, however, the parent mass was 266, in accordance with the desired compound. NMR ($D_2O$/DSS) on the initial product rendered the following information: $\delta$ = 1.16 (d, J= 6.55 Hz., 3H, $CC\underline{H}_3$), $\delta$ = 2.12 (s,3H, $ArCH_3$), $\delta$= 2.15 (d, J= 29 Hz., $C\underline{H}_2$), $\delta$ = 3.37 (s, 6H, $OCOC\underline{H}_3$), $\delta$ = 6.82 (s, 1H, Ar$\underline{H}$), $\delta$ =6.9 (s, 1H, Ar$\underline{H}$). IR analysis of the starting material (15GH) was obtained in Nujol and showed prominent absorptions at 3220 and 3430 $cm^{-1}$ due to the phenolic groups. These peaks were absent in the diacetoxy compound whose spectrum showed absorptions at 1850 and 1220 $cm^{-1}$, characteristic of an acetyl ester group.

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# PHARMACOLOGY

# INTRODUCTION

The pharmacology of psychoactive drugs encompasses a broad field of investigation which seeks to define and quantify the actions of substances upon the complex operations of the central nervous system. Usually, pharmacological evaluation of these agents involves measurement of overt behavioral changes produced in an intact animal. Interractions of these drugs with endogenous neurotransmitters and their receptors also provide useful information. Unfortunately, attempts to relate these two areas of study are faced with numerous difficulties. For example, it is quite unclear how the binding of a particular agent alters the normal functioning of a receptor site, and an equally formidable question concerns the manner in which drug induced neuroreceptor changes are incorporated on a macro level into alterations in behavior. Underlying these difficulties is the lack of basic understanding of the mechanisms responsible for the normal operation of the brain.

Extensive experience has shown that psychoactive compounds derived from 1-phenyl-2-aminopropane (amphetamine) possess a diverse spectrum of pharmacological actions. In this regard, amphetamine illustrates this remarkable diversity. Inital studies in 1930 by Alles's group were directed towards development of the bronchodilator properties and while conducting human testing of the compound, the

psychogenic stimulant effects were discovered[1a,b]. With the advent of World War II, these stimulant properties were much exploited by members of the fighting forces on both sides, who consumed hundreds of pounds of amphetamine[1c]. Following this, numerous psychologists were prescribing amphetamine as a tool for controlling incipient depression[1b,d] and later, paradoxically, this compound was found to be beneficial in the treatment of hyperactive children[1e]. In the period between 1950-1970, obese people were taking amphetamines for the anorexic effects[1f] and athletes were improving their performances with amphetamine[1g]. Of course, throughout its history there have been abusers who have taken amphetamine for reasons not well understood[1i]. Yet despite the orchestrated hue and cry of drug abuse which emerged in the mid-sixties and seventies, the amount of amphetamine consumed by "addicts" represented only a tiny fraction of that consumed legitimately[1c].

Aside from the clinical diversity already noted, amphetamine has been shown to be an inhibitor of the release and reuptake of norepinepherine[2a,b] (NE) and the reuptake of dopamine[2c,d] (DA) as well as a weak serotonin (S) depleator[2e,f] and an inhibitor of Monamine Oxidase[2g,h]. However, the relationships between these various neurochemical effects to the observed behavioral changes remain highly controversial with respect to both the autonomic and central nervous systems. In general, two schools of thought have been advanced: a) amphetamine acts directly on central receptors, and conversely,

b) amphetamine acts indirectly via release or inhibition of reuptake of central endogenous amines. Advocates of the direct agonistic actions of amphetamine[2i-k] have pointed to the fact that the behavioral effects of amphetamine are still manifest even after pretreatment with reserpine, which is known to produce large reductions in the brain concentrations of NE, DA and S[21,m]. But the importance of such data is compromised both by the complex actions produced by reserpine as well as the recent observations which indicate that normal CNS functioning is really dependent upon a small "functional" pool of neurotransmitters (10-20% of the total brain levels), and hence disruption or reduction of the "spare" pools are behaviorally unimportant. Evidence supporting this conclusion is obtained from the studies of the effects of 6-hydroxydopamine, which upon intracisternal or intraventricular injection, reduce brain NE and DA by 80% and 75% respectively, with no observable innate behavioral changes (after a seven day recovery period)[2n,p]. In light of these discoveries, theories of direct action of amphetamine lose credibility. On the other hand, theories of indirect action are generally based on the observation that amphetamine is capable of dislocating NE, DA and S[2q-w] from brain binding sites either in the whole brain or in synaptisomal preparations. These effects are strongly regionally dependent as shown by Raiteri et al[2u] who report that d-amphetamine caused release of DA and NE in the corpus striatum but caused no disruption of

these amines in either the hypothalmus, cerebellum or pons-medulla. Others have demonstrated biphasic effects of amphetamine on striatal DA levels[2w]. Further support for the indirect mode of action is found in the observation that pretreatment with L-dopa, which is known to increase brain DA levels[3a,b], potentiates the locomotor stimulant properties of amphetamine in rats[3a,d]. However, these studies have recently been somewhat discredited by the observation that under the loading doses (often 1,000 mg/kg) of L-dopa used, DA began appearing in sites in which it is not normally found[3e], presumably due to the fact that the enzyme L-aromatic acid decarboxylase, which is responsible for the transformation of L-dopa into DA, is the same enzyme catalyzing the conversion of 5-OH tryptophan into serotonin and apparently unusual concentrations of DA were being stored in S sites[3f]. Hence, it was difficult to assign the locomotor potentiation which was seen on the action of amphetamine on DA sites. Even if consistent effects of amphetamine on monamines could be demonstrated, that which is observed may reflect irrelevant changes in the "spare" nonfunctional pools. Indeed, subcellular studies show that amphetamine is capable of effecting release of NE mainly from nonspecific cytoplasmic rather than granular storage sites[3g,i].

The variations in the monamine levels in the CNS produced by amphetamine may result from its presynaptic actions as a direct releaser of cathecolamines[2r-t, 3j,k] or from its

ability to disrupt reuptake[3l]. Both sides seem equally populated with ardent believers armed with irrefutable evidence, but one often comes away from these discussions feeling like Alice when she remarked, "It seems very pretty, it fills my head with ideas only I don't know what they are[3p]."

Physiologically, amphetamine elicits vasoconstriction in the periphery[3q], increased blood pressure[3r] and elevation of the body temperature[3s-v]. Amphetamine in low doses (<7mg/kg) facilitates innate and operant animal behaviors related to motor functioning, such as locomotor activity[4a,b], avoidance response[4c,d], and self stimulation[4e]. However, at much higher dosages (>25mg/kg) depression is uniformly observed[4f]. In man, studies have demonstrated that amphetamine in low doses (<25mg) induces a psychological state characterized by hyperactivity, euphoria, and a sense of well-being[4g,h]; but with increasing dosages (>300 mg) the euphoriant effects gradually give way to anxiety associated with ideas of reference, paranoid delusions, and occasionally auditory hallucinations[4i-k].

Considerably less is known concerning the pharmacological actions of ring-substituted amphetamines such as 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), first synthesized by Shulgin et al.[4l,m]. In animals, DOM has proved a potent agent in disrupting conditioned avoidance response[4n,o] and also in eliciting hyperthermia[4p-r].

In man, DOM in low doses (2-5 mg) results in significant increases in anxiety and obsessive-compulsive symptoms, as well as both euphoria and dysphoria, rapid mood shifts, and slight perceptional changes[4s,t]. At higher dosages (>14mg) visual hallucination, loss of reality, depersonalization, and distortions of the time sense emerge[4u,v] and persist for about eight hours. The neurochemical actions in the CNS produced by DOM (2-~20mg/kg) include facilitation of release and inhibition of uptake of norepinephrine[5a,b], as well as normetanephrine[5c], and an increased turnover of dopamine[5d] in the rat brain. However, the importance of such effects appears highly questionable given the near lethal doses required to obtain measurable changes. By contrast, studies in isolated peripheral serotonergic receptor preparations such as the sheep umbilical artery[5e,f] and the rat stomach fundus[5g,h] have demonstrated that DOM possesses a high binding affinity for serotonergic receptors and appears to act at these sites mainly as an antagonist. These data engendered the hypothesis that the behavioral effects elicited by a diversity of psychotomimetic substances such as LSD and tryptamine derivatives[5i,j] were due to this disruption of serotonergic mechanisms. But simple explanations such as these became untenable when compounds such as BOL were discovered which had extremely high binding affinities[5i] but whose CNS actions were not psychotomimetic[5k,l]. Another counterexample is serotonin, which despite having very high binding affinity, has no pronounced CNS activity

upon i.v. injection[4y], presumably due to poor penetration of the blood brain barrier.

Following these nearly insurmountable objections, the advocates of the "serotonin hypothesis" advanced the theory that the actions of these compounds were related to their agonistic[5m] rather than antagonistic properties, even though the former were orders of magnitude less than the latter. At present, no conclusive evidence based on binding of these amphetamine derivatives to any receptor is capable of describing the behavioral potencies of more than a select few compounds. Considering the inconclusive state of development, it seems premature to incorporate any hypothesis involving a particular receptor into explanations aimed at explaining the structure-activity-relationships (SAR) resulting from studies of behavioral potencies. Furthermore, the multiplicity of neuroreceptor interactions demonstrated by either amphetamine or DOM makes simple explanations unworkable, since the effects of drug-induced activation/deactivation of any group of neuroreceptors in one region of the CNS affects the behavior of identical/different neuroreceptors in other areas. For example, while serotonin neurons exhibit inhibitory actions in certain areas of the brain, activation of serotonergic pathways in other areas are facilitory[5n]. Consequently, knowledge of binding affinities holds little promise of explaining behavioral potencies without

detailed knowledge of the "hard wiring" of the various CNS receptor systems.

# PSYCHOPHARMACOLOGICAL ACTIVITY OF DERIVATIVES OF AMPHETAMINE

Perhaps the simplest assay of psychopharmacological evaluation consists of observing the innate behavior of an animal both before and after administration of an unknown agent. While crude, the lack of any observable changes in behavior, even when large doses are used, is usually strong evidence for a lack of pharmacological efficacy. On the other hand, observation of distinct behavioral changes seldom reveals much information concerning the mechanism of action of a compound. Indeed, specific quantitation of potency according to these measures is often at variance with potencies typically found in human studies. For example, in an early study by Smythies et al.[50,p], the potencies of a series of amphetamine derivatives led to the conclusion that 1-(4-methoxyphenyl)-2-aminopropane was a potent disruptor of rat behavior and suggested that it would have powerful effects in humans. However, Shulgin et al.[41,m] have clearly demonstrated that this is not the case. In fact, this compound proved to be among the least active of all the derivatives tested. Another extreme example is that of LSD and Psylocibin, synthesized and tested by Hofman et al.[5q] In both cases, while the compounds involved were known to be powerful psychogenics in man, animal studies initially conducted by Rothlin were at variance with those findings.

Another widely used assay for biological activity consists of determining the dose needed to kill half of a

given colony of rats ($LD_{50}$). While dose-mortality studies are apparently simple experiments, the results of these studies are often very difficult to interpret. For example, amphetamine toxicity in isolated rats is greatly increased when the animals are aggregated (∿2 fold) and in both cases, plots of percentage killed vs. dose are triphasic[5r-t]. Similar results concerning non-linear mortality-dose relationships and environmental influences have been reported for 1-(2,5-dimethoxyphenyl)-2-aminopropane, 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane, and 1-(2-methoxy-4,5-methylenedioxyphenyl)-2-aminopropane[5u]. Causal explanations of these effects have not been forthcoming.

Harris et al.[3d] have reported the potencies of several methoxy-substitutes amphetamine derivatives as determined by the ability of these agents to disrupt responding in rats trained to fixed ratio (FR 30) and fixed interval (FI 2 minutes) schedules of food presentation. While potencies according to either schedule were not grossly different than those reported in humans, the strict numerical correlation between these measures was not impressive. Similarly, Smythies et al.[5v] has reported the relative potencies of several methoxy-substituted derivatives in disrupting performance maintained by a shock avoidance schedule in the rat. Yet again, the values obtained from the Bovet-Gatti profiles of these drugs were not well correlated to the human potencies ($n= 6$, $r= 0.64$).

In an early study, Jacob and Leville[6a] reported that mescaline and LSD as well as amphetamine were capable of producing hyperthermia in the rabbit. Furthermore, the hyperthermic potencies of these compounds were highly correlated to the effective potencies in man. More recently, Aldous et al.[4q] have reported detailed hyperthermic data on an extensive series of amphetamine derivatives and have reported a remarkable correlation between these values and those obtained in humans (n= 9 , r=0.95). Accordingly, investigations in our group have obtained results presented graphically in Figure 3, which are also well correlated with the human data (n= 14 , r= 0.94)[6b,c]. In spite of the good correlation, compounds possing thermogenic activity do not necessarily produce the same CNS and behavioral actions. For example, while DOM is a potent psychotomimetic agent, amphetamine is usually classified as a stimulant. Hence it is apparent that a strict extrapolation of psychotomimetic potencies in man from hypertermic data in rabbits may be misleading. In distinct contrast to DOM, amphetamine is only weakly potent, has a more rapid onset, and much shorter duration of action. Comparison of the rabbit hyperthermic potencies of the enantiomers of amphetamine and DOM shows that the (S)/(R) potency ratios are 3.1 and 0.1, respectively. Studies in man report a range of values for the (S)/(R) ratio for amphetamine 1-4[6d-f]. On the other hand, only the (R) enantiomer of DOM has been reported to be psychotomimetic in man[41,m]. Similar results are obtained in studies of the thermogenic properties of

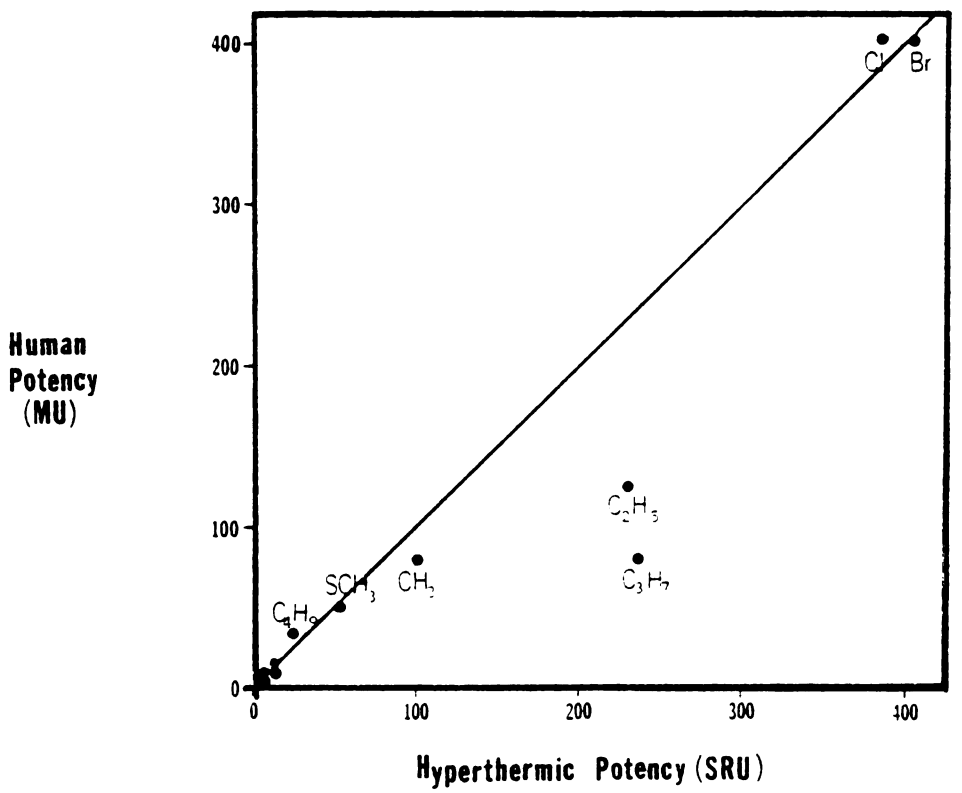


FIGURE 3. Correlation Between Hyperthermic Potency in the Rabbit (SRU; Method A) and Psychotomimetic Potency in the Human (MU) for 14 Ring-substituted Derivatives of 1-Phenyl-2-aminopropane.

amphetamine and DOM in the rat[6g,h]. In this species, the doses of amphetamine and DOM required to produce a 1° C increase in body temperature were 20.4 mmol/kg and 0.3 mmol/kg respectively. Both of these doses are considerably less than those required to produce measurable differences in either norepinepherine, dopamine, or serotonin brain levels[2u,v] and yet the involvement of these neurotransmitters is clearly evidenced in the experiments of Horita and others[3s, 4p] who have shown that prior administration of pimozide, a known CNS dopamine antagonist[6i], almost completely attenuates the hypertermia induced by amphetamine, but yet even in massive dosages, has little effect on the pyrexic actions of DOM[4p]. Conversely, these workers have shown that cinanserin, a compound having known antiserotonergic properties in the periphery[6j], and suspected activity in the CNS[6k], was capable of blocking the hyperthermia elicited in response to DOM but was ineffective against amphetamine[4p]. Almost identical results have been reported from studies of thermogenesis in rats[6g,h]. Taken as a whole, this body of data points to a catecholaminergic link in the thermic effects due to amphetamine and in contrast, the involvement of a serotonergic pathway in the pyrexic effects of DOM. Further, since activation of serotonergic neurons by intraventricular administration of serotonin produces a precipitous temperature decrease[6i-n], it appears that potent psychotomimetic agents such as DOM probably act in an antagonistic fashion at these receptors. Alternately, it appears feasible that less highly

substituted compounds may also possess agonistic actions such as amphetamine on either N.E. or D.A. in the CNS since activation of these neurotransmitters leads to increases in body temperature in the rabbit and to some extent in the rat[6n] . Supporting evidence is also obtained from the use of antagonist and inhibitors which either increase or decrease the central levels of these neurotransmitters. However, it appears difficult to attribute hyperthermia caused by any agent solely on one neurotransmitter since these systems do not exist in isolation from one another. Indeed, recent investigations by Horita and Quock into the hyperthermic actions of apomorphine (a dopamine agonist) suggest that while this agent acts mainly on dopamergic receptors, an intact serotonin system is necessary for the expression of the thermogenic effects[6u] .

# STRUCTURE ACTIVITY RELATIONSHIPS IN A SERIES OF AMPHETAMINE DERIVATIVES

Detailed hyperthermia data on various ring-substituted and N-substituted derivatives of amphetamine are contained in Tables 10 and 11 and graphic presentation of the time-temperature plots are shown in Figures 4-40. Inspection of these results shows that the nine most potent analogues are 2,5-dimethoxy-substituted compounds which differ with respect to the identity of the four substituents. Maximum potency is achieved in the 4-Br and 4-Cl analogues. Of the 4-alkyl homologues, the 4-ethyl and 4-propyl congeners are about half as active as the 4-halo compounds, and the 4-methyl, 4-thiomethyl, and higher alkyl analogues are all of decreasing potency.

With reference to the time-temperature characteristics, all of the potent derivatives produced profiles in which the temperature maximum occured between 165-210 min. In contrast, both amphetamine and 1-(3,4-methylenedioxyphenyl)-2-amino-propane (MDA) had much steeper curves, shorter duration, and temperature maxima between 45 - 90 min.

Remarkably, compounds not having the <u>para</u>-oxo pattern uniformly possessed much less activity than the corresponding 2,5-dimethoxy compounds. Alternately the variations in potency caused by the introduction of the X-substituent into a position either <u>ortho</u> or <u>meta</u>, can be analyzed by comparison with 2,4,5-trimethoxyamphetamine. When viewed

from this perspective, the following trends become evident: a) All of the 4-X-substituted derivatives of the 2,5-dimethoxy series possess greater potency than the 2,4,5-trimethoxy analogue except for the OEt compound; b) In the 4,5-dimethoxy-2-X series, replacement of a 2-OMe group with any other group results in a decrease in compound potency; and similarly, c) Substitution of a 5-OMe group in the 2,4-dimethoxy-5-X series uniformly results in a decrease in activity. Of the N-methyl-substituted compounds, the most potent racemates were derivatives of DOM>MDA>amphetamine. However, in contrast to the enantiomeric specificity found in the $1^{o}$ amino compounds, the most potent enantiomers of this series all contained an "S" configuration about the chiral carbon. These results were remarkable and unprecedented in the literature.

Comparison of the hyperthermic and human potencies (see Figure 3) reveals a very satisfactory correlation (n=14; r= 0.94) which indicates that about 88% of the variation in the human potencies (accurate to about ±25%) is reproduced by the hyperthermic activities. However, the values assigned in the rabbit assay for the 4-$C_2H_5$, 4-$C_3H_7$ and 4-$OCH_2CH_3$ compounds differed from the human potencies by more than 100%.

# EXPERIMENTAL SECTION

## PHARMACOLOGY

Experiments were performed on male New Zealand white rabbits (Big Pine, 3.0-3.4 kg) housed in a constant temperature room maintained at 20.0±0.7°C. Rectal temperatures were measured with Yellow Springs (YSI 701) probes and recorded on a Honeywell-Brown 12 channel recorder (see Appendix I). Solutions of drug were prepared by dissolution of the HCl salts in pyrogen-free isotonic saline, filtration through 0.22μ Millipore Filters, and sealed into ampules sterilized previously by heating in a hot flame. The experimental procedure used was very similar to that of Aldous, et al.[4q] Groups of four rabbits, previously drug-free for a period of six days, were lightly restrained in stocks, temperature probes were inserted 8 cm into the rectum, and basal temperatures (38.0-39.0°C) were determined over a 30 minute period. Injection of the drug, according to the weight of each rabbit, was then made into the marginal ear vein, and the temperature followed at 15 minute intervals over a six hour period. Each drug was administered at three concentrations, and the hyperthermic potency determined from the Log Dose procedures of Aldous, et al.[4q] In Method A, the drug response was defined as the maximum temperature reached at a given dose level; in Method B, the potency was defined in terms of the integrated area under the time-temperature curve. The potencies are reported relative to DOM (2) which is assigned a value of 100 Standard Rabbit Units (SRU). Rabbits used in this assay were trained according to the

following procedure:

a) introduction to the stocks over four sessions lasting about two hours each;

b) light confinement under constant supervision for two sessions of three hours duration;

c) confinement in stocks and insertion of rectal probes for twelve sessions of four hours duration; and

d) confinement, insertion of rectal probes, and injection of saline (two sessions of six hours duration).

Using these procedures, the "trained" rabbits were both well-behaved and also showed only small deviations in body temperature ($\pm 0.3^{o}C$) over the experimental period of six hours.

Since the rabbits were used in successive experiments, the following criterion for rejection of an animal were adopted to insure reproducability of the results:

1) Basal temperatures must fall within $38.9\text{-}39.8^{o}C$ range.

2) Mean maximum temperature increase elicited by a challenging dose of 0.50μ mol/kg. of DOM (administered every six experiments) must not deviate from $1.98^{o}C$ by more than 40%; nor fall below 30% on two consecutive calibration doses of DOM.

DATA

Table 9. Comparison of Rabbit Hyperthermic Potencies (SRU) with Human Psychotomimetic Potencies (MU).

| Compound | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Method A | Method B | Human Potency (MU) |
|---|---|---|---|---|---|---|---|---|
| (1AB) | H | H | H | H | H | 1.3(∿1)[a] | 1.0(∿1)[a] | —— |
| (5AB) | H | H | O - $CH_2$ -O | | H | 2.46 | 1.51 | 3[b] |
| (7AB) | $OCH_3$ | H | $OCH_3$ | H | H | 2.5 | 3.1 | 5[b] |
| (8AB) | $OCH_3$ | H | H | $OCH_3$ | H | 2.7(3)[a] | 3.2(2.5)[a] | 8[b] |
| (11AB) | H | H | $OCH_3$ | $OCH_3$ | H | 0.3 | 0.2 | 1[b] |
| (12AB) | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | <<0.3 | <<0.3 | <2[b] |
| (13AB) | $OCH_3$ | H | $OCH_3$ | $OCH_3$ | H | 11.8(10)[a] | 15.1(9.2)[a] | 17[b] |
| (14AB) | $OCH_3$ | H | $OCH_3$ | H | $OCH_3$ | 3.1 | 3.3 | 10[b], 12[c] |
| (15AB) | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | 3.6[a] | 3.0[a] | 2.2[b] |
| (16AB) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 100 | 100 | 80[b] |
| (17AB) | $OCH_3$ | H | Br | $OCH_3$ | H | 405 | 301 | 400[d] |
| (18AB) | $OCH_2CH_3$ | H | $OCH_3$ | $OCH_3$ | H | 0.7 | 0.8 | <7[b] |
| (19AB) | $OCH_3$ | H | $OCH_2CH_3$ | $OCH_3$ | H | 3.4 | 3.7 | 15[b] |
| (20AB) | $OCH_3$ | H | $OCH_3$ | $OCH_2CH_3$ | H | 1.3 | 1.3 | <7[b] |
| (22AB) | $OCH_3$ | H | $CH_3$ | H | $OCH_3$ | 5.4 | 5.4 | —— |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (24AB) | $OCH_3$ | H | $SCH_3$ | $OCH_3$ | H | 53.9 | 63.9 | 50[e] |
| (29AB) | $OCH_3$ | H | $OCH_3$ | Br | H | 2.3 | 3.2 | 4[f] |
| (30AB) | $OCH_3$ | H | $C_4H_9$ | $OCH_3$ | H | 25.7 | 38.4 | 36[g] |
| (31AB) | $OCH_3$ | H | $C_5H_{11}$ | $OCH_3$ | H | 5.6 | 6.8 | 10[g] |
| (34AB) | $OCH_3$ | H | $C_2H_5$ | $OCH_3$ | H | 229[a] | 222[a] | 125[g] |
| (35AB) | $OCH_3$ | H | $C_3H_7$ | $OCH_3$ | H | 237[a] | 244[a] | 80[g] |
| (36AB) | $OCH_3$ | H | $i\text{-}C_3H_7$ | $OCH_3$ | H | 16[a] | 8[a] | —— |
| (37AB) | $OCH_3$ | H | $t\text{-}C_4H_9$ | $OCH_3$ | H | 14.2[a] | 13[a] | <4[h] |


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Table 10. Detailed Hyperthermia Data for Derivatives of 1-Phenyl-2-aminopropane.

| Compound | Dose (umoles/kg) | Period of Peak Effect (min.) | Mean Maximum Temp. Rise (Method A) | Integration of Time-Temp. Curve (0-300 min.) (Method B) | Approximate Dose for 1° C Temp. Rise (umoles/kg) | Potency Relative to DOM Method A | Potency Relative to DOM Method B |
|---|---|---|---|---|---|---|---|
| (1AB) | 47.60 | 60-90 | 2.28±0.25 | 0.960±0.126 | 20.42 | 1.3 | 1.0 |
| | 27.19 | 60-90 | 1.38±0.09 | 0.505±0.090 | | | |
| | 15.56 | 60-90 | 1.58±0.06 | 0.221±0.066 | | | |
| (1A) | 58.48 | 45-75 | 1.53±0.10 | 0.581±0.091 | 33.88 | 0.79 | 0.54 |
| | 35.09 | 30-60 | 1.08±0.11 | 0.326±0.085 | | | |
| (1B) | 22.19 | 45-75 | 1.82±0.15 | 0.621±0.103 | 10.96 | 2.46 | 1.55 |
| | 13.45 | 45-75 | 1.23±0.20 | 0.389±0.129 | | | |
| | 8.15 | 45-75 | 0.57±0.02 | 0.156±0.041 | | | |
| (5AB) | 28.42 | 45-75 | 2.17±0.18 | 0.829±0.071 | 10.97 | 2.46 | 1.51 |
| | 16.24 | 45-75 | 1.41±0.04 | 0.418±0.087 | | | |
| | 9.30 | 30-60 | 0.87±0.04 | 0.309±0.092 | | | |
| (5A) | 16.24 | 45-75 | 1.65±0.11 | 0.627±0.107 | 7.76 | 3.48 | 2.29 |
| | 9.56 | 30-60 | 1.10±0.06 | 0.404±0.097 | | | |
| | 5.30 | 45-75 | 0.67±0.10 | 0.226±0.071 | | | |
| (5B) | 16.71 | 30-60 | 1.02±0.14 | 0.394±0.077 | 9.23 | 2.93 | 0.91 |
| | 9.56 | 30-60 | 1.02±0.11 | 0.213±0.047 | | | |
| | 5.48 | 30-60 | 0.57±0.04 | 0.125±0.044 | | | |
| (7AB) | 25.97 | 135-165 | 1.61±0.10 | 0.974±0.085 | 10.97 | 2.5 | 3.1 |
| | 12.98 | 150-180 | 1.07±0.15 | 0.631±0.013 | | | |
| | 6.49 | 150-180 | 0.64±0.08 | 0.368±0.054 | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (8AB) | 25.97 | 115-145 | 1.71±0.18 | 1.053±0.160 | 10.03 | 2.7 | 3.2 |
| | 12.99 | 150-180 | 1.24±0.17 | 0.672±0.128 | | | |
| | 6.49 | 120-150 | 0.67±0.06 | 0.357±0.085 | | | |
| (11AB) | 108.20 | 135-165 | 1.01±0.14 | 0.631±0.133 | 108 | 0.3 | 0.2 |
| | 54.10 | 135-165 | 0.63±0.04 | 0.394±0.065 | | | |
| (12AB) | 90.91 | ——— | ±0.2° | ——— | >90 | <<0.3 | <<0.3 |
| (13AB) | 7.66 | 165-195 | 1.83±0.14 | 1.154±0.169 | 2.29 | 11.8 | 15.1 |
| | 3.83 | 150-180 | 1.32±0.11 | 0.799±0.061 | | | |
| | 1.92 | 135-165 | 0.85±0.05 | 0.529±0.054 | | | |
| (14AB) | 19.16 | 165=195 | 1.65±0.18 | 1.071±0.088 | 8.71 | 3.1 | 3.3 |
| | 9.58 | 150-180 | 1.15±0.15 | 0.669±0.073 | | | |
| | 4.79 | 105-135 | 0.70±0.03 | 0.377±0.053 | | | |
| (16AB) | 1.00 | 165-210 | 2.85±0.35 | 1.631±0.291 | 0.27 | 100.0 | 100.0 |
| | 0.50 | 195-225 | 1.98±0.14 | 1.121±0.115 | | | |
| | 0.25 | 135-165 | 0.80±0.11 | 0.489±0.043 | | | |
| (18AB) | 43.64 | 135-165 | 1.07±0.03 | 0.640±0.077 | 40.74 | 0.7 | 0.8 |
| | 27.27 | 135-165 | 0.60±0.04 | 0.304±0.064 | | | |
| (19AB) | 15.71 | 150-180 | 1.56±0.08 | 0.861±0.092 | 8.04 | 3.4 | 3.7 |
| | 8.73 | 120-150 | 1.09±0.12 | 0.620±0.108 | | | |
| | 4.84 | 135-180 | 0.55±0.07 | 0.254±0.049 | | | |
| (20AB) | 27.24 | 120-150 | 1.13±0.08 | 0.575±0.091 | 21.13 | 1.3 | 1.3 |
| | 14.55 | 120-150 | 0.73±0.05 | 0.365±0.052 | | | |
| (21AB) | 61.73 | 120-180 | 0.78±0.17 | 0.528±0.066 | 102 | 2.6 | 4.8 |
| | 30.86 | 150-180 | 0.43±0.05 | 0.247±0.042 | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (22AB) | 32.92 | 180-210 | 1.94±0.13 | 1.294±0.181 | 5.01 | 5.4 | 5.4 |
| | 8.23 | 135-165 | 1.40±0.06 | 0.593±0.081 | | | |
| | 2.06 | 105-135 | 0.49±0.04 | 0.288±0.037 | | | |
| (23AB) | 14.00 | 75-105 | 1.01±0.13 | 0.543±0.039 | 14 | 2 | 2 |
| | 7.10 | 105-135 | 0.82±0.06 | 0.448±0.037 | | | |
| (24AB) | 1.96 | 195-225 | 2.31±0.51 | 1.384±0.292 | 0.50 | 53.9 | 63.9 |
| | 0.67 | 165-195 | 1.15±0.22 | 0.731±0.113 | | | |
| | 0.22 | 120-135 | 0.60±0.16 | 0.343±0.013 | | | |
| (25AB) | 21.30 | 180-210 | 1.62±0.06 | 1.070±0.060 | 9.77 | 2.8 | 3.9 |
| | 10.60 | 135-165 | 1.09±0.07 | 0.683±0.050 | | | |
| | 5.30 | 120-165 | 0.60±0.07 | 0.451±0.015 | | | |
| (26AB) | 61.73 | 120-180 | 0.78±0.17 | 0.528±0.066 | 102 | 2.6 | 4.8 |
| | 30.86 | 150-180 | 0.43±0.05 | 0.247±0.042 | | | |
| (27AB) | 57.62 | 135-165 | 1.83±0.17 | 1.161±0.171 | 29.51 | 0.9 | 1.3 |
| | 28.81 | 105-135 | 0.90±0.19 | 0.550±0.128 | | | |
| | 13.37 | 90-120 | 0.62±0.03 | 0.347±0.057 | | | |
| (28AB) | 24.30 | 105-135 | 1.47±0.11 | 0.952±0.057 | 8 | 3 | 3 |
| | 12.15 | 60-105 | 1.15±0.05 | 0.639±0.027 | | | |
| (29AB) | 24.30 | 135-165 | 1.49±0.16 | 0.926±0.109 | 11.61 | 2.3 | 3.2 |
| | 12.10 | 135-165 | 0.99±0.08 | 0.601±0.028 | | | |
| | 6.10 | 90-120 | 0.62±0.05 | 0.349±0.009 | | | |
| (30AB) | 4.36 | 180-210 | 1.91±0.12 | 1.206±0.072 | 1.05 | 25.7 | 38.4 |
| | 2.18 | 180-210 | 1.43±0.09 | 0.875±0.042 | | | |
| | 1.09 | 165-195 | 1.08±0.07 | 0.673±0.098 | | | |
| (31AB) | 13.29 | 180-210 | 1.73±0.16 | 0.985±0.045 | 4.79 | 5.6 | 6.8 |
| | 6.65 | 165-195 | 1.18±0.06 | 0.683±0.105 | | | |
| | 3.32 | 165-195 | 0.72±0.05 | 0.402±0.045 | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (32AB) | 78.34 | 210-240 | 1.47±0.06 | 0.756±0.088 | 45.08 | 0.6 | 0.6 |
| | 36.87 | 195-225 | 0.78±0.07 | 0.359±0.080 | | | |
| (33AB) | 46.59 | 165-195 | 1.34±0.21 | 0.717±0.102 | 35.50 | 0.8 | 0.8 |
| | 24.85 | 150-180 | 0.68±0.04 | 0.309±0.057 | | | |

Table 11. Detailed Hyperthermia Data for Derivatives of 1-Phenyl-2-methylaminopropane.

| Compound | Dose (umoles/kg) | Period of Peak Effect (min.) | Mean Minimum Temp. Rise (Method A) | Integration of Time-Temp. Curve (0-300 min.) (Method B) | Approximate Dose for 1° C Temp. Rise (umoles/kg) | Potency Relative to DOM Method A | Potency Relative to DOM Method B |
|---|---|---|---|---|---|---|---|
| (1CD) | 48.16 | 45-75 | 1.78±0.17 | 0.638±0.099 | 20.89 | 1.29 | 0.91 |
| | 25.76 | 45-75 | 1.27±0.16 | 0.534±0.097 | | | |
| | 14.86 | 60-90 | 0.65±0.06 | 0.263±0.080 | | | |
| (1C) | 108.10 | —— | ±0.2 | ———— | >>108 | <<0.3 | <<0.3 |
| (1D) | 24.11 | 45-75 | 1.92±0.09 | 0.589±0.080 | 8.71 | 3.10 | 1.41 |
| | 13.41 | 30-60 | 1.40±0.04 | 0.381±0.060 | | | |
| | 7.46 | 30-60 | 0.82±0.01 | 0.219±0.057 | | | |
| (5CD) | 30.50 | 60-90 | 2.02±0.17 | 0.690±0.137 | 13.80 | 1.96 | 1.15 |
| | 17.43 | 30-60 | 1.27±0.10 | 0.339±0.055 | | | |
| | 9.93 | 30-60 | 0.78±0.08 | 0.239±0.064 | | | |
| (5C) | 41.39 | 45-90 | 1.08±0.08 | 0.372±0.051 | 38.02 | 0.7 | 0.5 |
| | 24.36 | 60-90 | 0.61±0.04 | 0.219±0.070 | | | |
| (5D) | 13.07 | 30-60 | 1.78±0.21 | 0.428±0.085 | 5.61 | 4.81 | 1.30 |
| | 7.06 | 15-45 | 1.13±0.09 | 0.229±0.056 | | | |
| | 3.82 | 15-45 | 0.75±0.04 | 0.154±0.046 | | | |
| (11CD) | 102.04 | 135-165 | 0.85±0.09 | 0.440±0.063 | 102.04 | ∿0.2 | ∿0.2 |
| (12CD) | 95.79 | ——— | ±0.2 | ———— | >95.8 | <<0.3 | <<0.3 |
| (13CD) | 41.81 | 75-105 | 1.31±0.11 | 0.551±0.068 | 33.11 | 0.8 | 0.71 |
| | 25.45 | 75-105 | 0.67±0.03 | 0.294±0.058 | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (15CD) | 72.7 | 150-180 | 0.97±0.03 | 0.505±0.050 | | | |
| | 6.35 | 135-165 | 0.51±0.06 | 0.361±0.065 | | | |
| (16CD) | 16.41 | 120-150 | 1.44±0.11 | 0.743±0.095 | 10.96 | 2.46 | 2.45 |
| | 9.65 | 105-135 | 0.83±0.07 | 0.387±0.073 | | | |
| | 5.68 | 105-135 | 0.43±0.04 | 0.164±0.076 | | | |
| (16C) | 9.65 | ——— | ±0.02 | ——— | | | |
| (16D) | 9.65 | 135-165 | 1.55±0.09 | 0.761±0.087 | 5.92 | 4.56 | 5.12 |
| | 5.68 | 120-150 | 0.92±0.06 | 0.395±0.067 | | | |

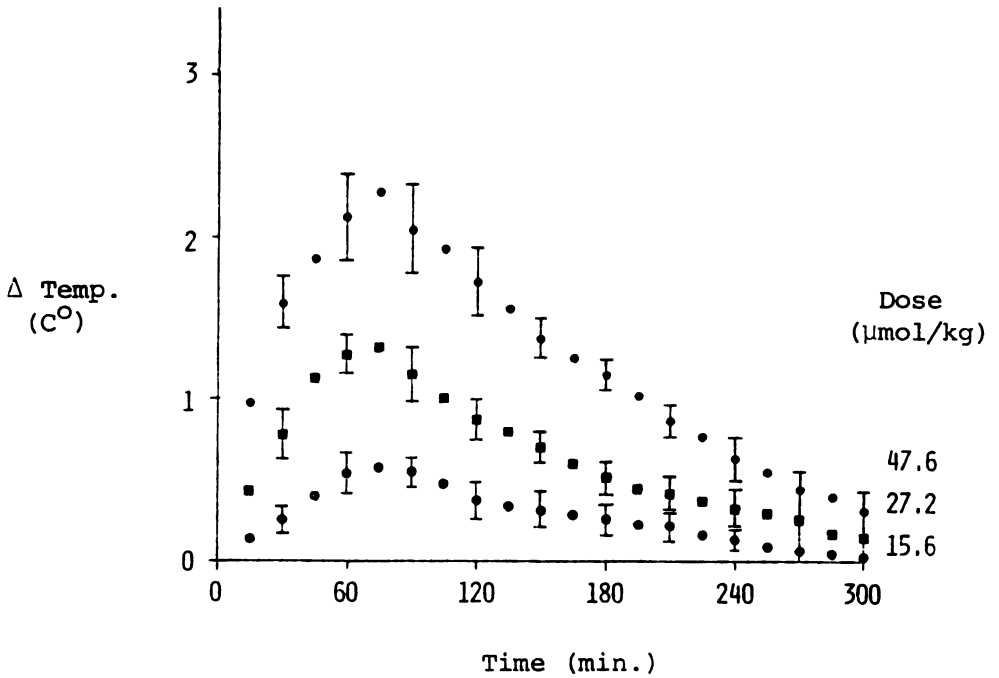


FIGURE 4. Hyperthermia elicited in the Rabbit by (RS)-1-Phenyl-2-aminopropane HCl (1AB).

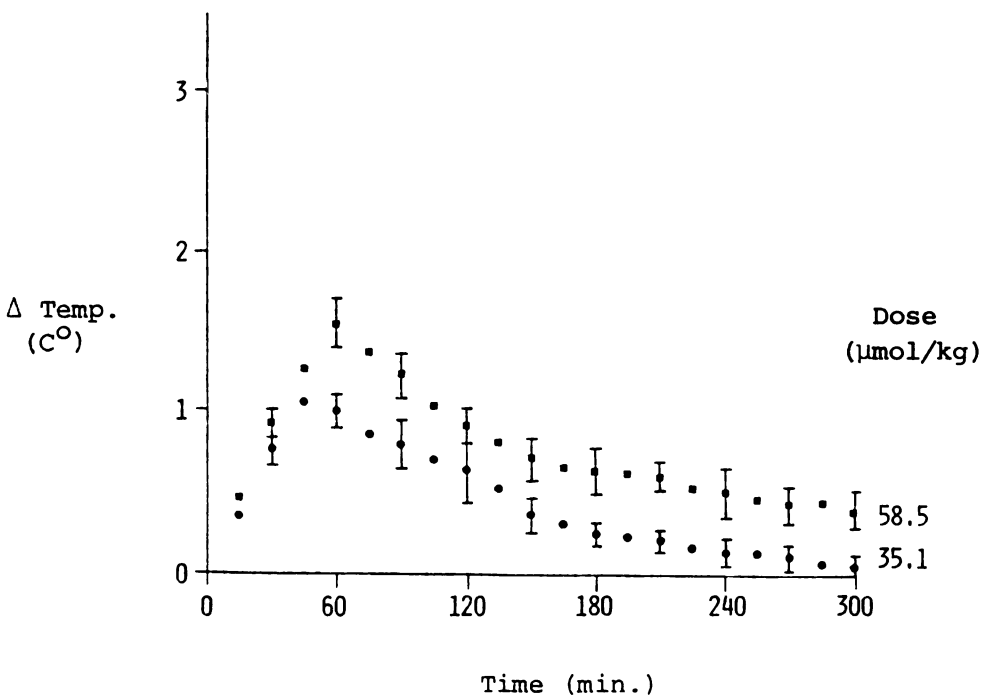


FIGURE 5. Hyperthermia elicited in the Rabbit by (R)-1-Phenyl-2-aminopropane HCl (1A).

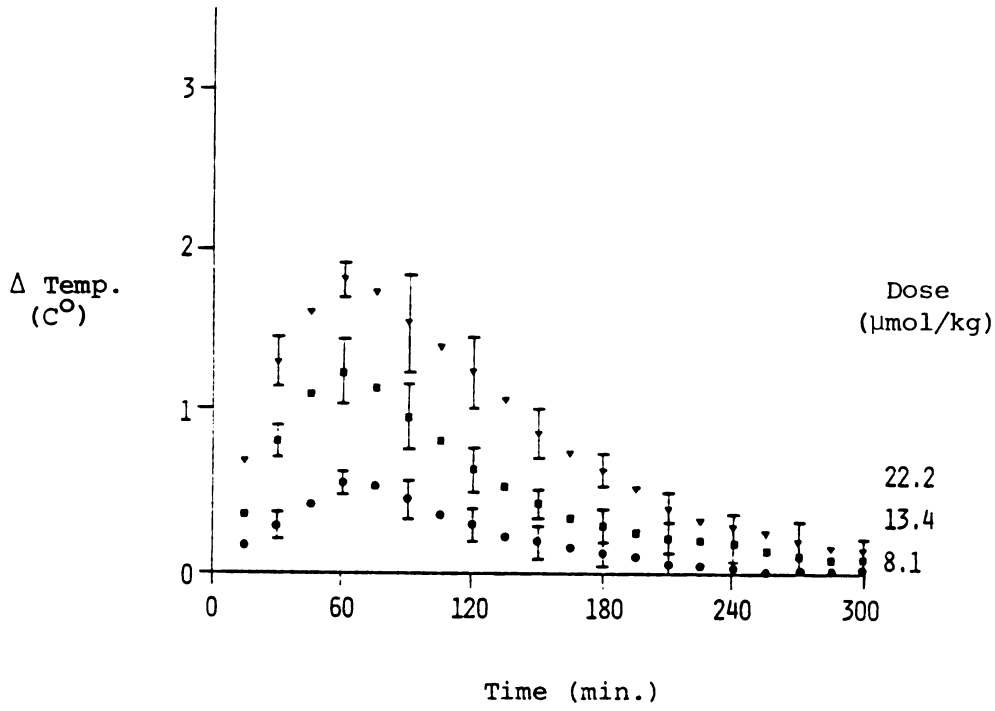


FIGURE 6. Hyperthermia elicited in the Rabbit by (S)-1-Phenyl-2-aminopropane HCl (1B).

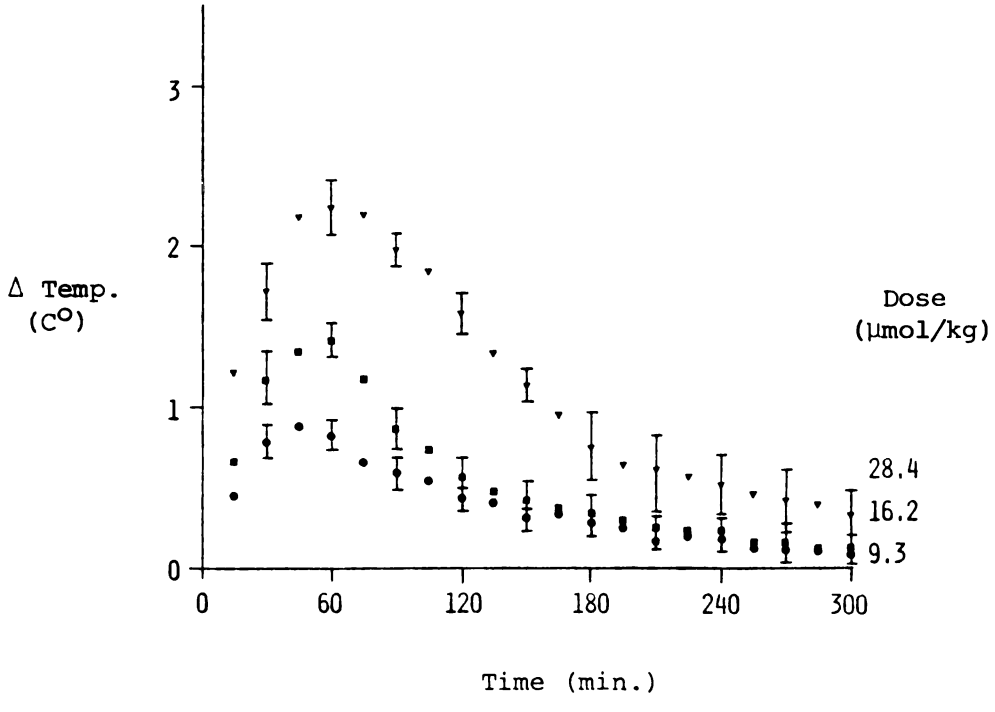


FIGURE 7. Hyperthermia elicited in the Rabbit by (RS)-1-(3,4-Methylenedioxyphenyl)-2-aminopropane HCl (5AB).

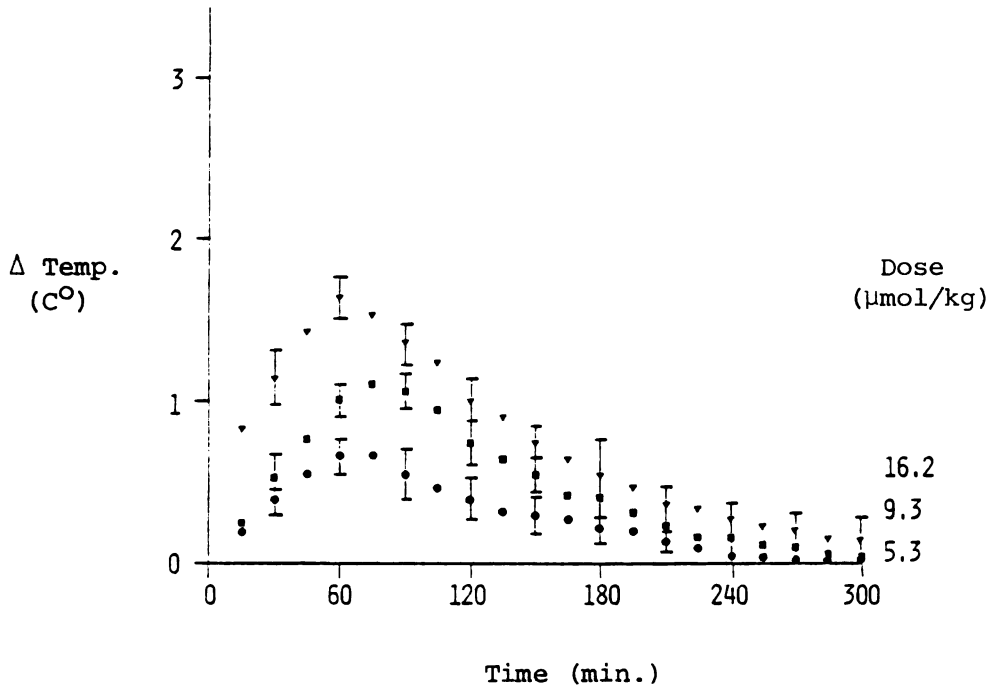


FIGURE 8. Hyperthermia elicited in the Rabbit by (R)-1-(3,4-Methylenedioxyphenyl)-2-aminopropane HCl (5A).

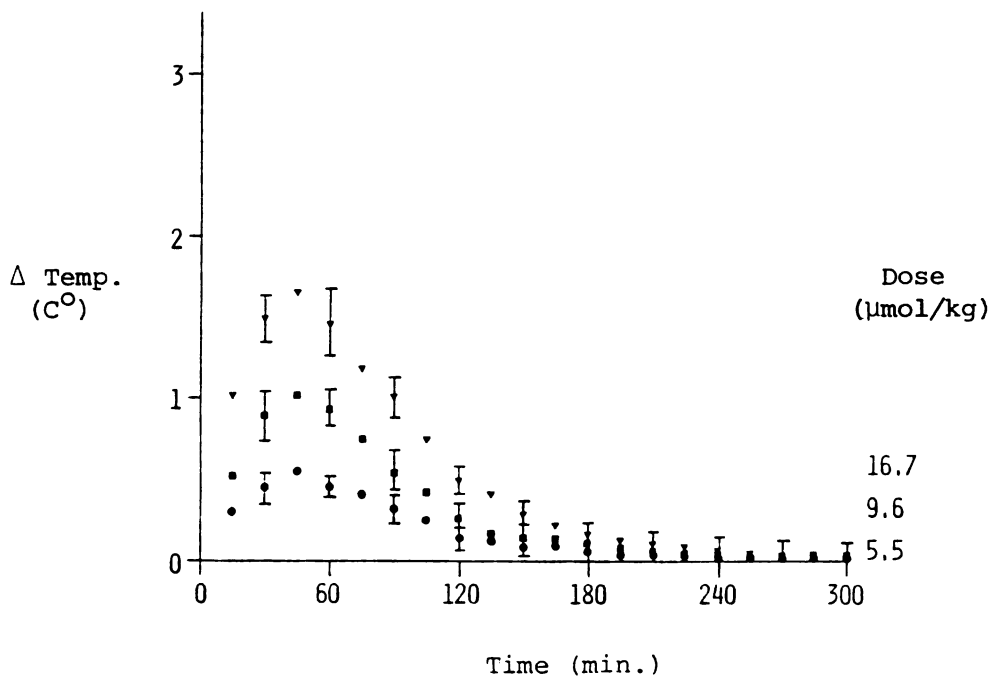


FIGURE 9. Hyperthermia elicited in the Rabbit by (S)-1-(3,4-Methylenedioxyphenyl)-2-aminopropane HCl (5B).

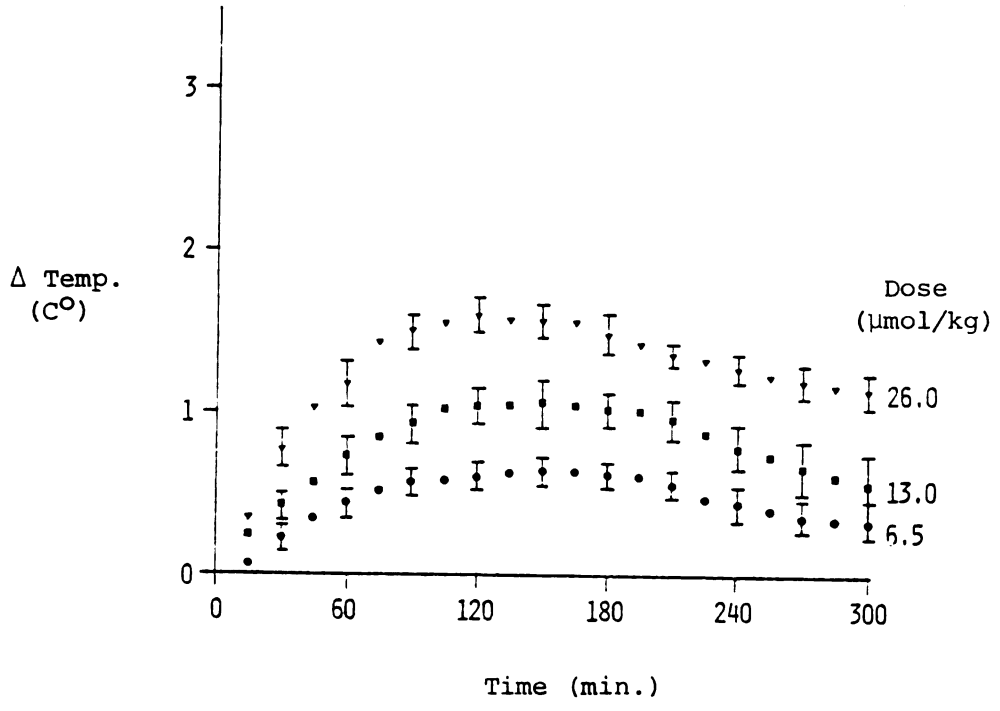


FIGURE 10. Hyperthermia elicited in the Rabbit by (RS)-1-(2,4-Dimethoxyphenyl)-2-aminopropane HCl (7AB).

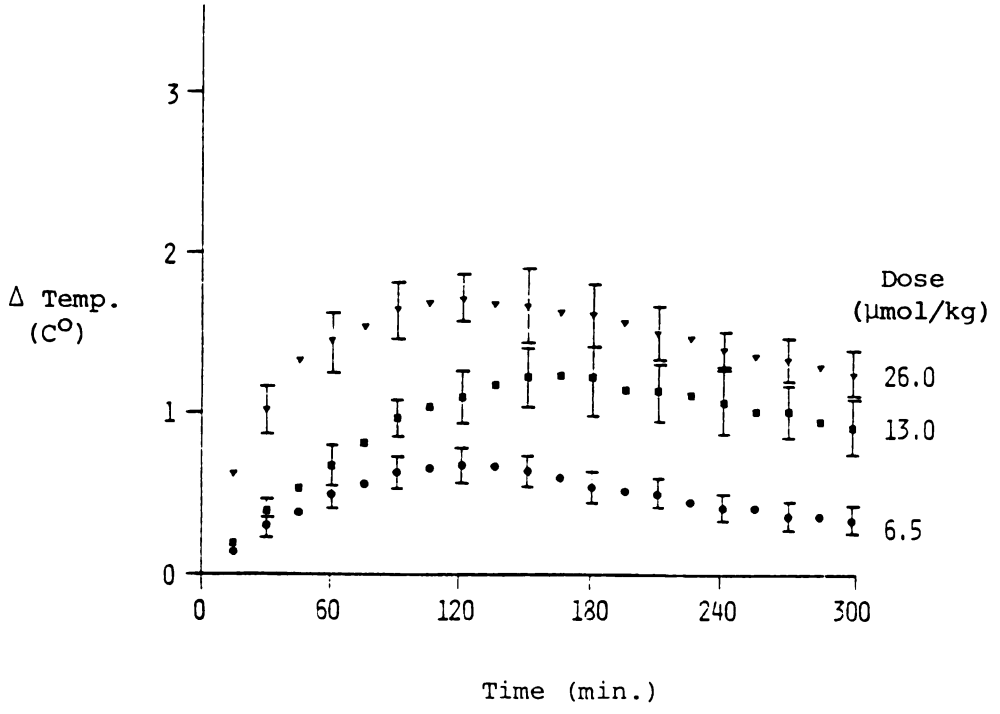


FIGURE 11. Hyperthermia elicited in the Rabbit by (RS)-1-(2,5-Dimethoxyphenyl)-2-aminopropane HCl (8AB).

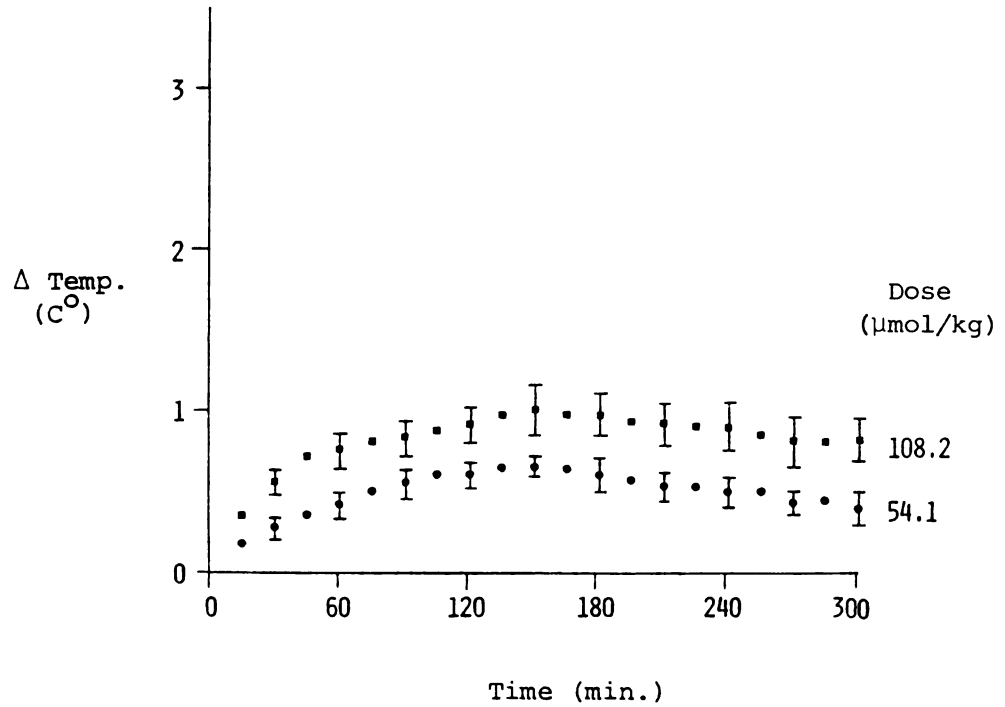


FIGURE 12. Hyperthermia elicited in the Rabbit by (RS)-1-(3,4-Dimethoxyphenyl)-2-aminopropane HCl (11AB).

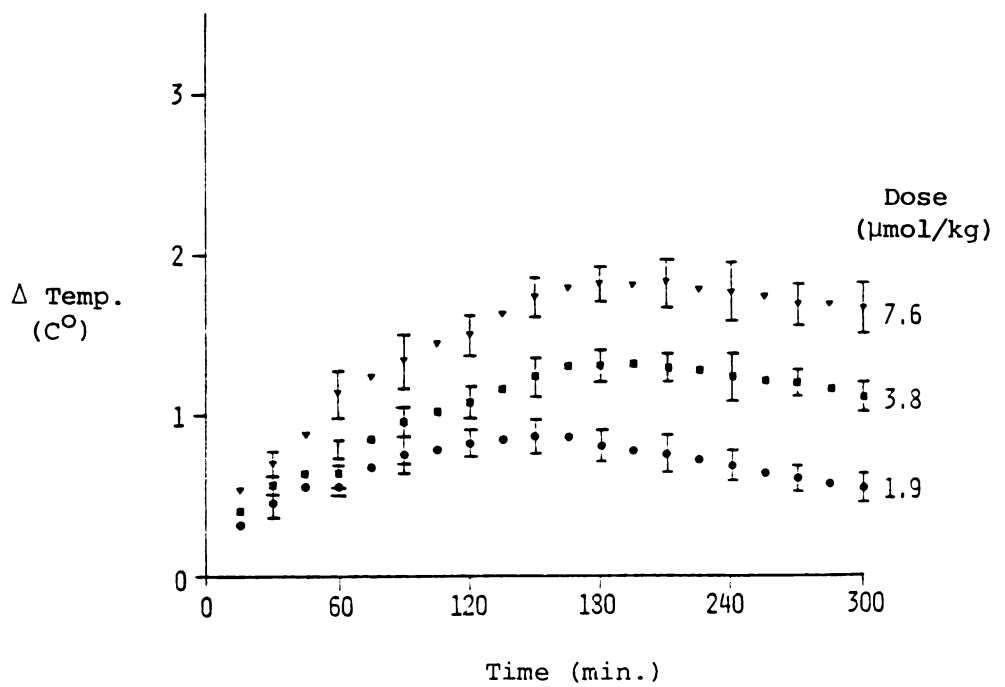


FIGURE 13. Hyperthermia elicited in the Rabbit by (RS)-1-(2,4,5-Trimethoxyphenyl)-2-aminopropane HCL (13AB).

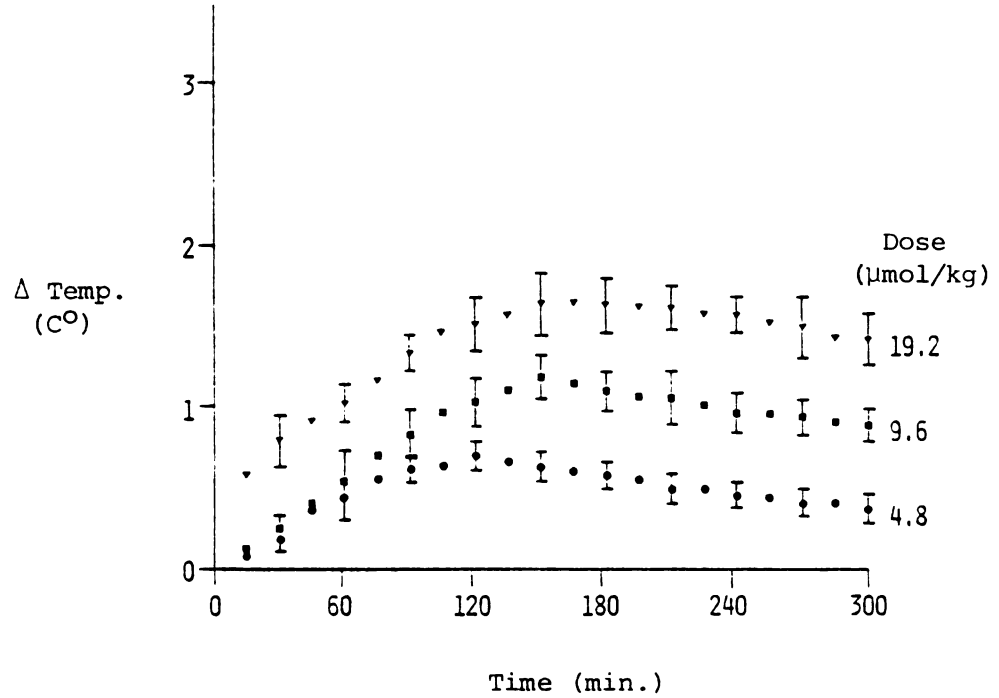


FIGURE 14. Hyperthermia elicited in the Rabbit by (RS)-1-(2,4,6-Trimethoxyphenyl)-2-aminopropane HCl (14AB).

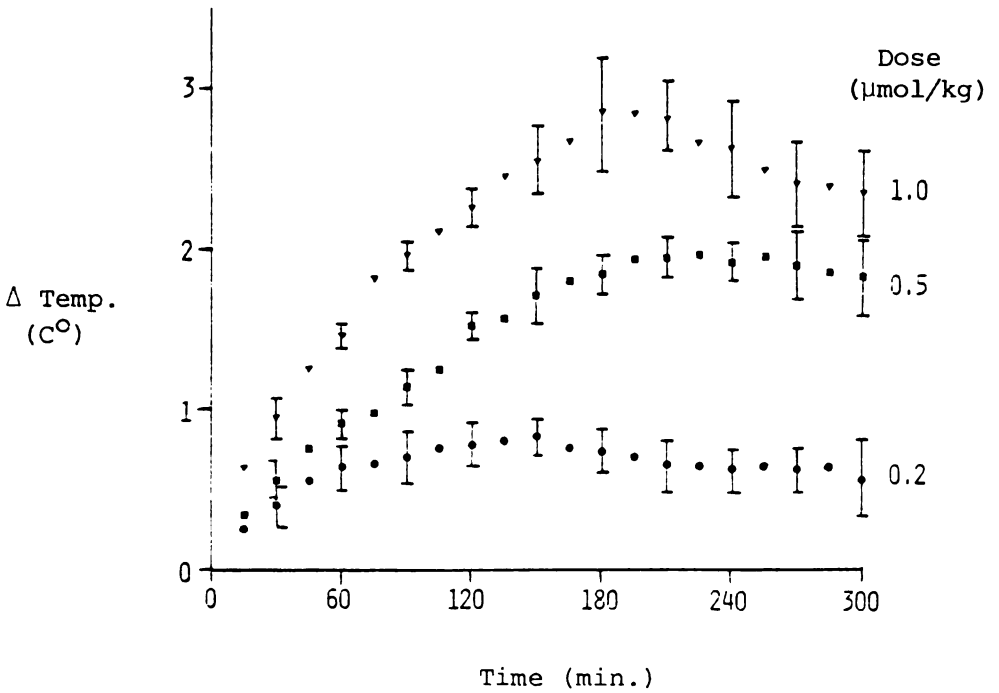


FIGURE 15. Hyperthermia elicited in the Rabbit by (RS)-1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane HCl (16AB).

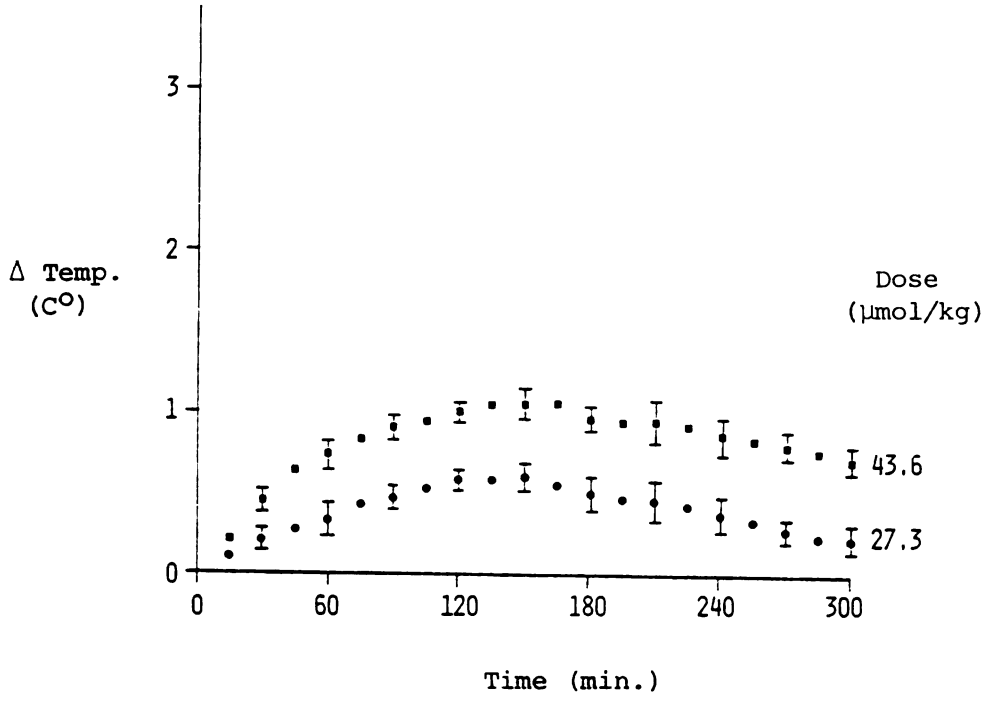


FIGURE 16. Hyperthermia elicited in the Rabbit by (RS)-1-(2-Ethoxy-4,5-dimethoxyphenyl)-2-aminopropane HCl (18AB).

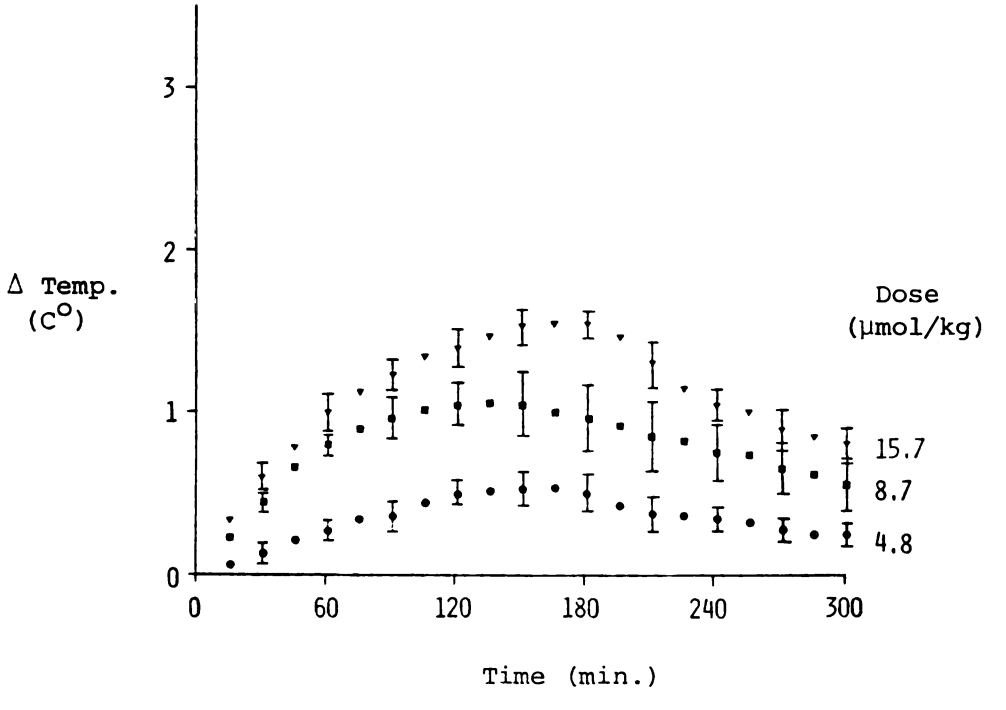


FIGURE 17. Hyperthermia elicited in the Rabbit by (RS)-1-(2,5-Dimethoxy-4-ethoxyphenyl)-2-aminopropane HCl (19AB).

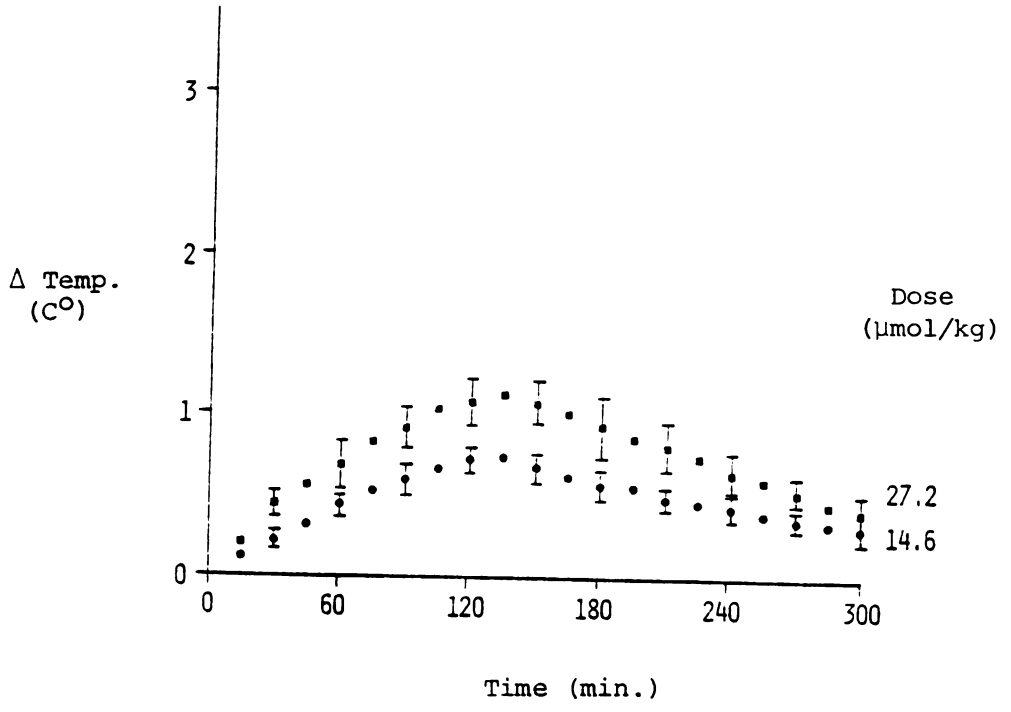


FIGURE 18. Hyperthermia elicited in the Rabbit by (RS)-1-(2,4-Dimethoxy-5-ethoxyphenyl)-2-aminopropane HCl (20AB).

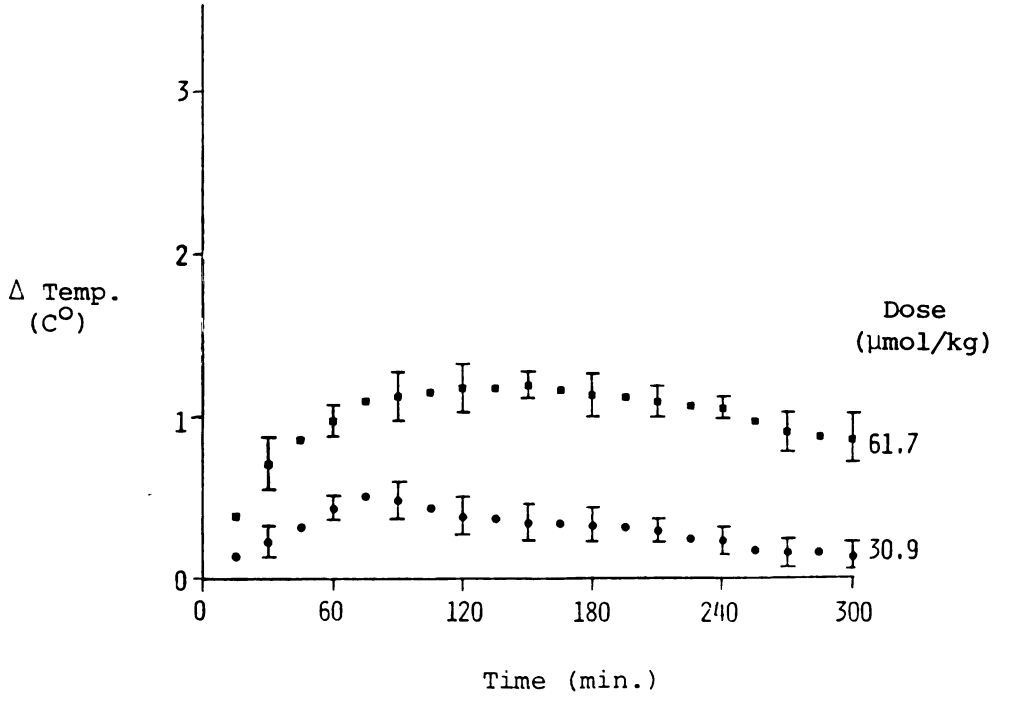


FIGURE 19. Hyperthermia elicited in the Rabbit by (RS)-1-(2-Methyl-4,6-dimethoxyphenyl)-2-aminopropane HCl (21AB).

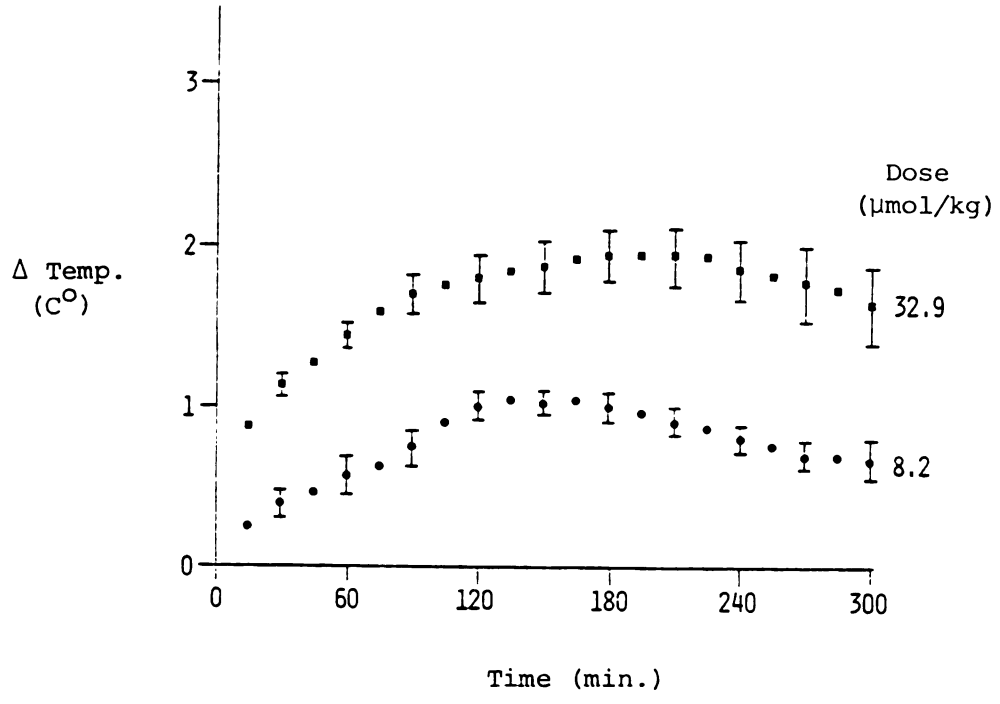


FIGURE 20. Hyperthermia elicited in the Rabbit by (RS)-1-(2,6-Dimethoxy-4-methylphenyl)-2-aminopropane HCl (22AB).

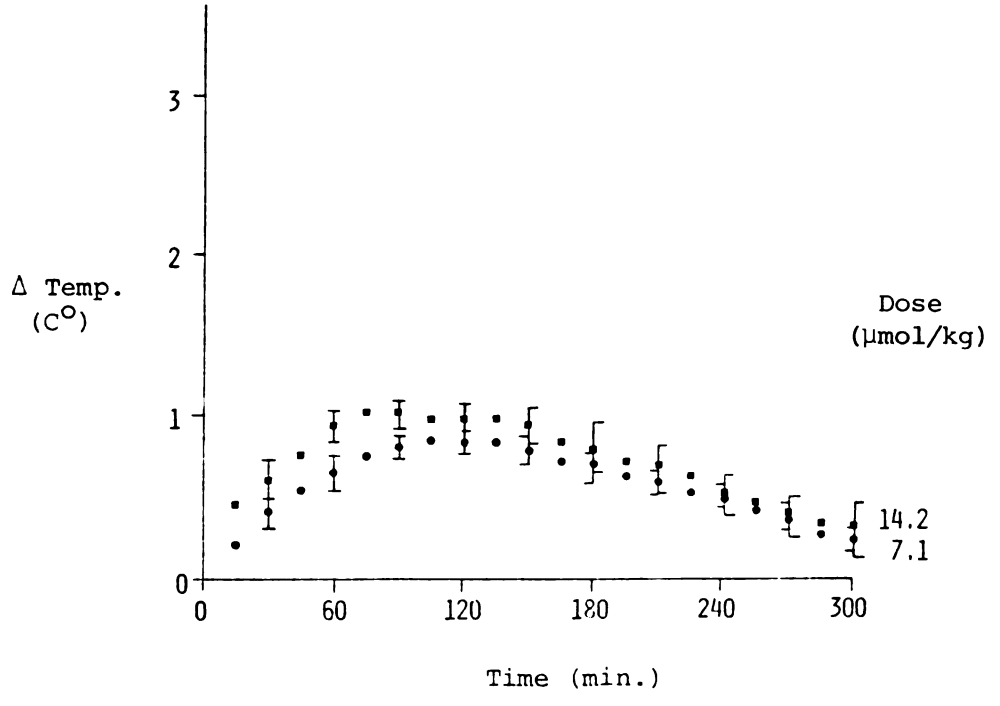


FIGURE 21. Hyperthermia elicited in the Rabbit by (RS)-1-(2,-Thiomethyl-4,5-dimethoxyphenyl)-2-aminopropane HCl (23AB).

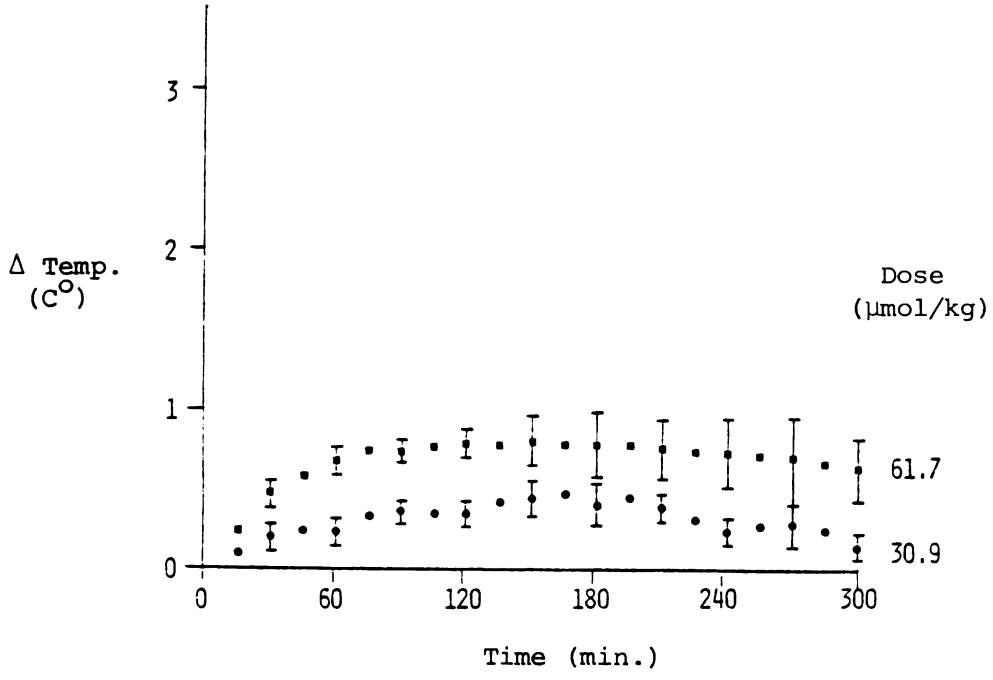


FIGURE 22. Hyperthermia elicited in the Rabbit by (RS)-1-(2-Methyl-4,5-dimethoxyphenyl)-2-aminopropane HCl (26AB)

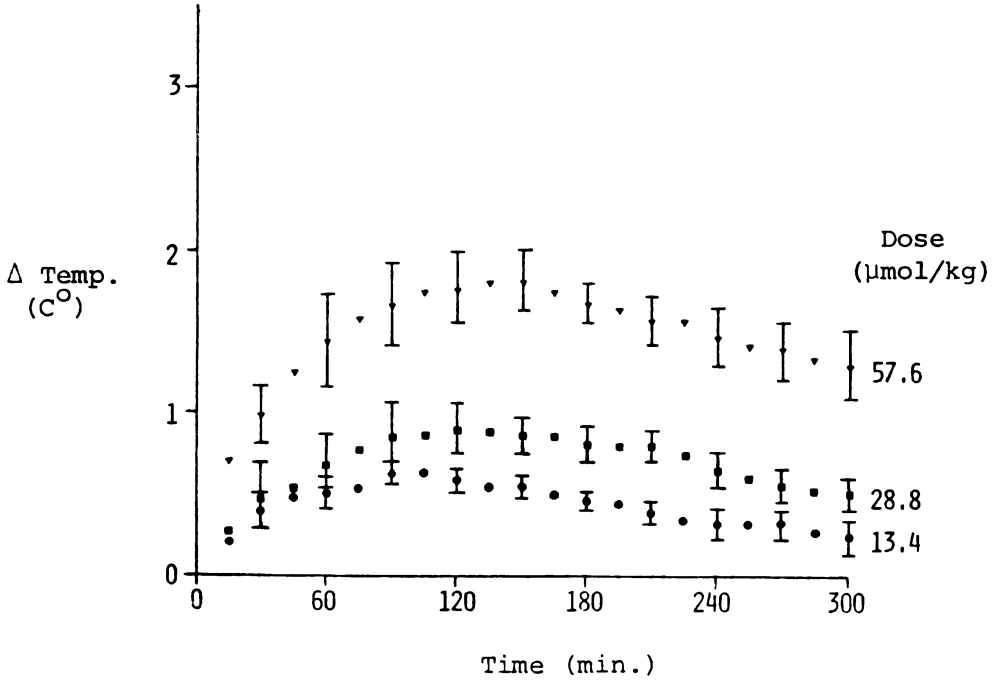


FIGURE 23. Hyperthermia elicited in the Rabbit by (RS)-1-(2,4-Dimethoxy-5-methylphenyl)-2-aminopropane HCl (27AB).

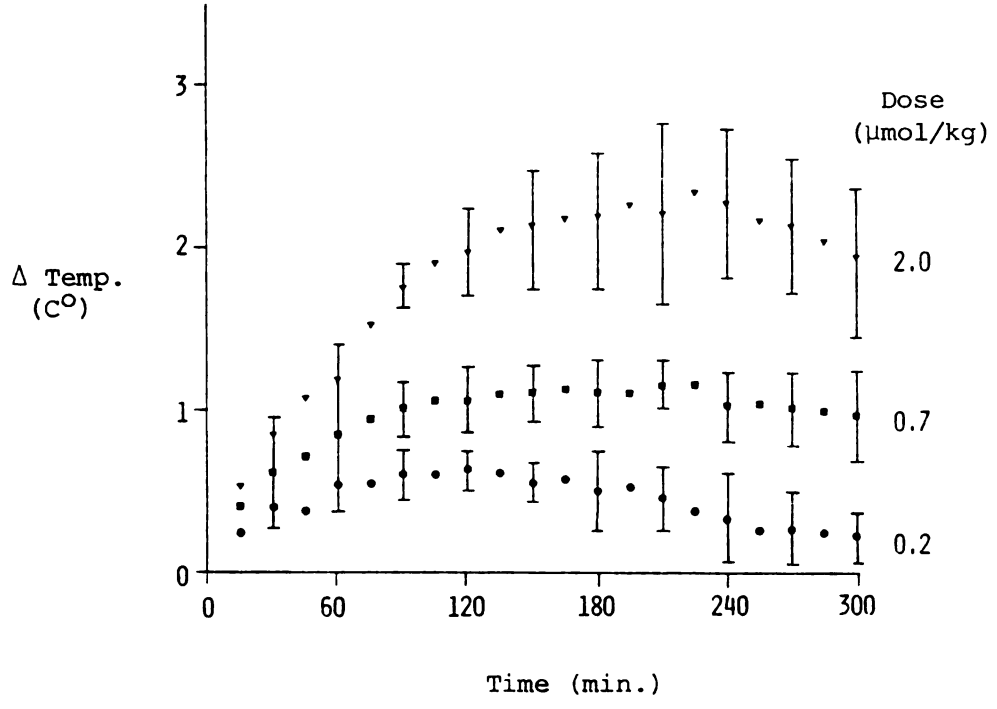


FIGURE 24. Hyperthermia elicited in the Rabbit by (RS)-1-(2,5-Dimethoxy-4-thiomethylphenyl)-2-aminopropane HCl (24AB).

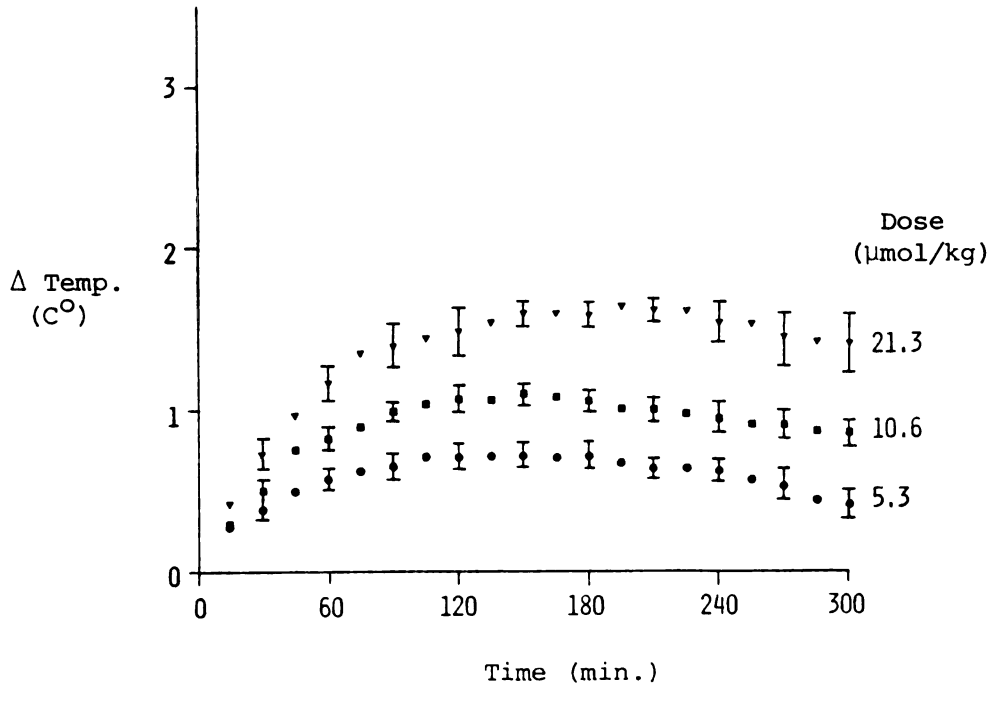


FIGURE 25. Hyperthermia elicited in the Rabbit by (RS)-1-(2,4-Dimethoxy-5-thiomethylphenyl)-2-aminopropane HCl (25AB).

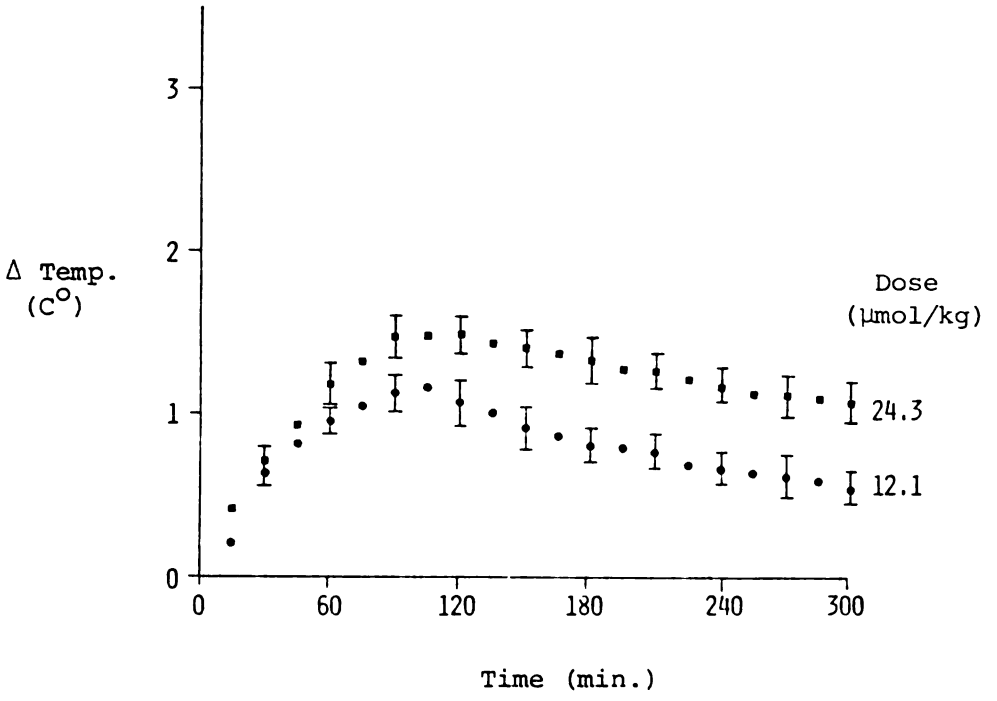


FIGURE 26. Hyperthermia elicited in the Rabbit by (RS)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-aminopropane HCl (28AB).

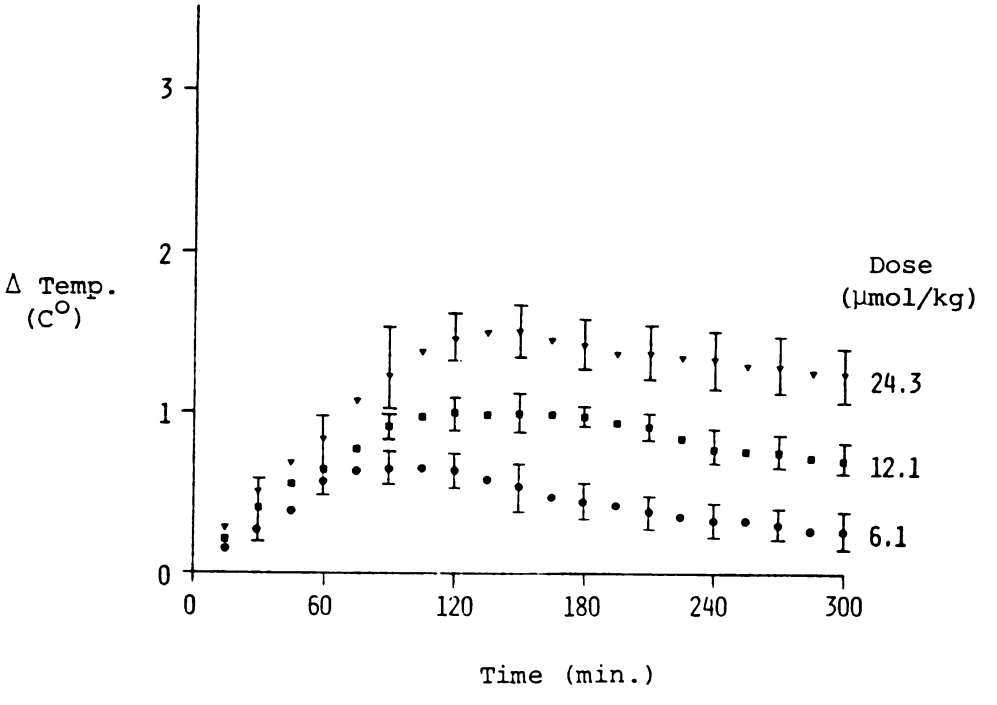


FIGURE 27. Hyperthermia elicited in the Rabbit by (RS)-1-(2,4-Dimethoxy-5-bromophenyl)-2-aminopropane HCl (29AB)

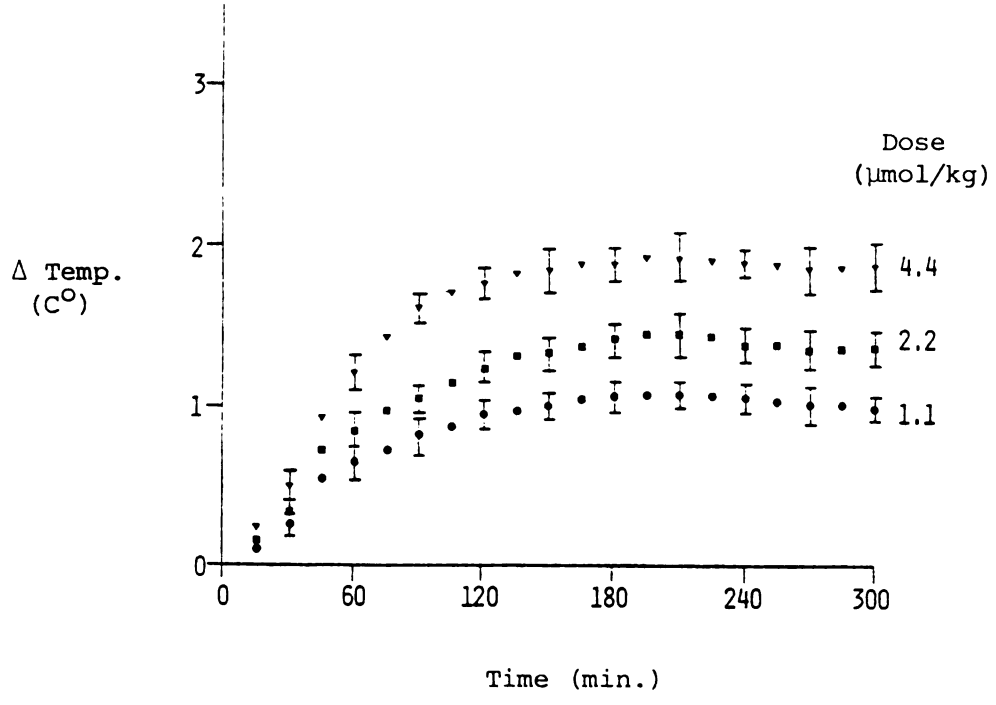


FIGURE 28. Hyperthermia elicited in the Rabbit by (RS)-1-(2,5-Dimethoxy-4-n-butylphenyl)-2-aminopropane HCl (30AB).

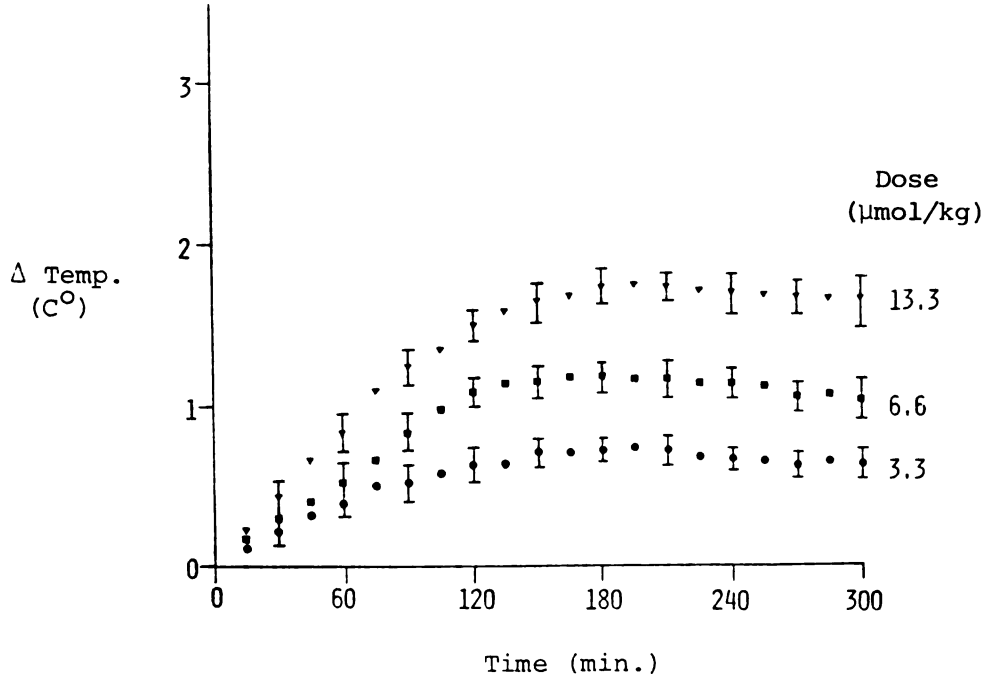


FIGURE 29. Hyperthermia elicited in the Rabbit by (RS)-1-(2,5-Dimethoxy-4-n-amylphenyl)-2-aminopropane HCl (31AB).

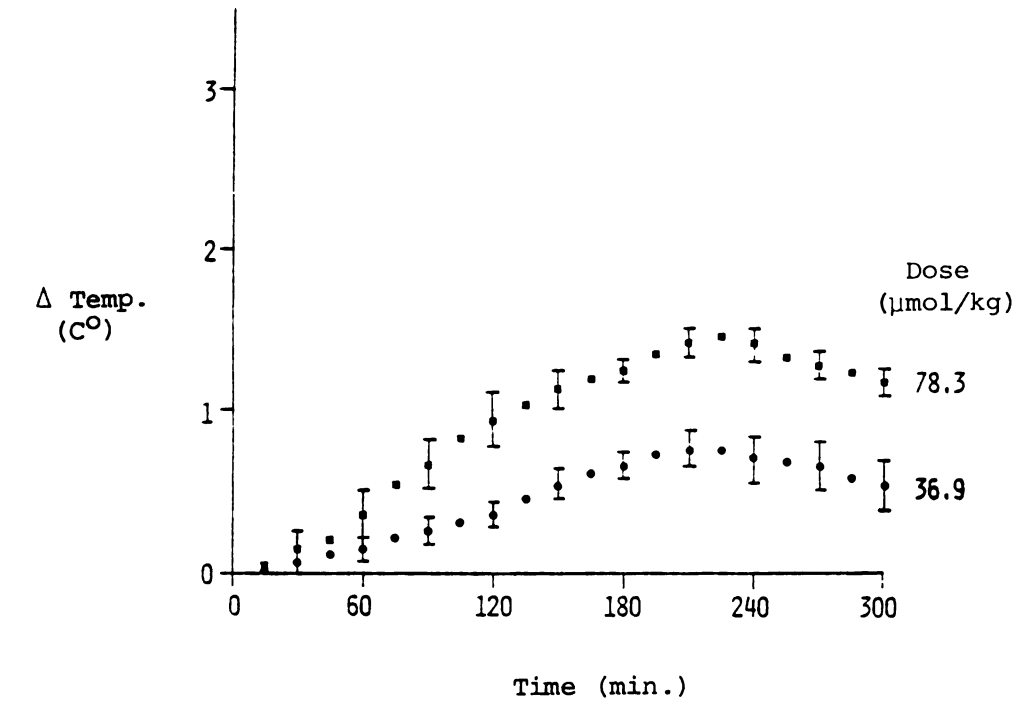


FIGURE 30. Hyperthermia elicited in the Rabbit by (RS)-1-(2,5-Dihydroxy-4-methylphenyl)-2-aminopropane HCl (32AB).

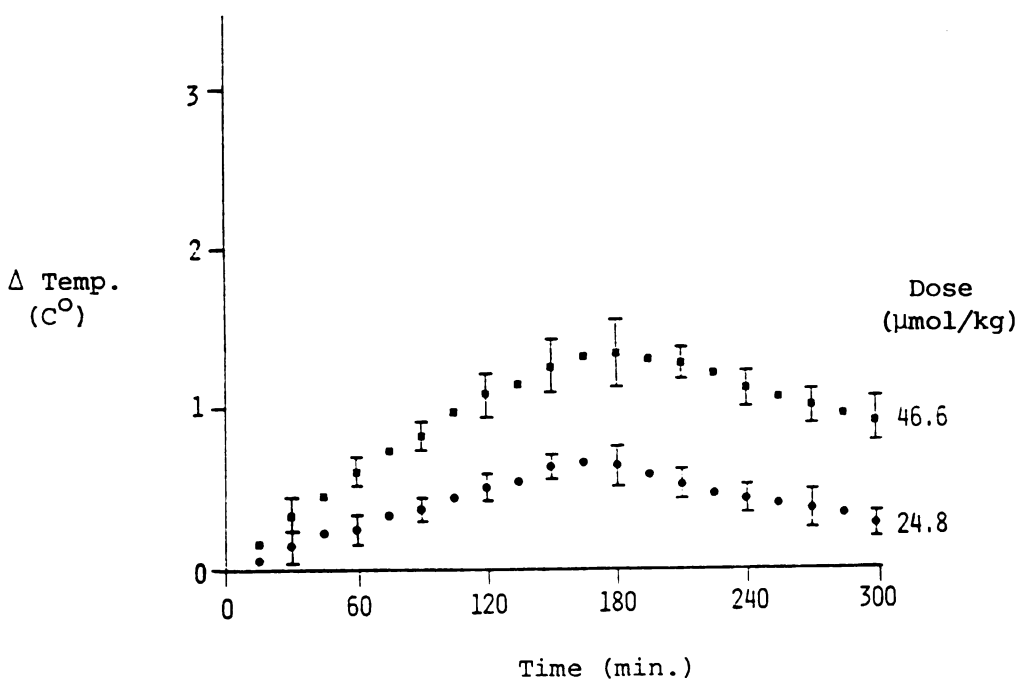


FIGURE 31. Hyperthermia elicited in the Rabbit by the Imminoquinone of (RS)-1-(2,5-Dihydroxy-4-methylphenyl)-2-aminopropane (33AB).

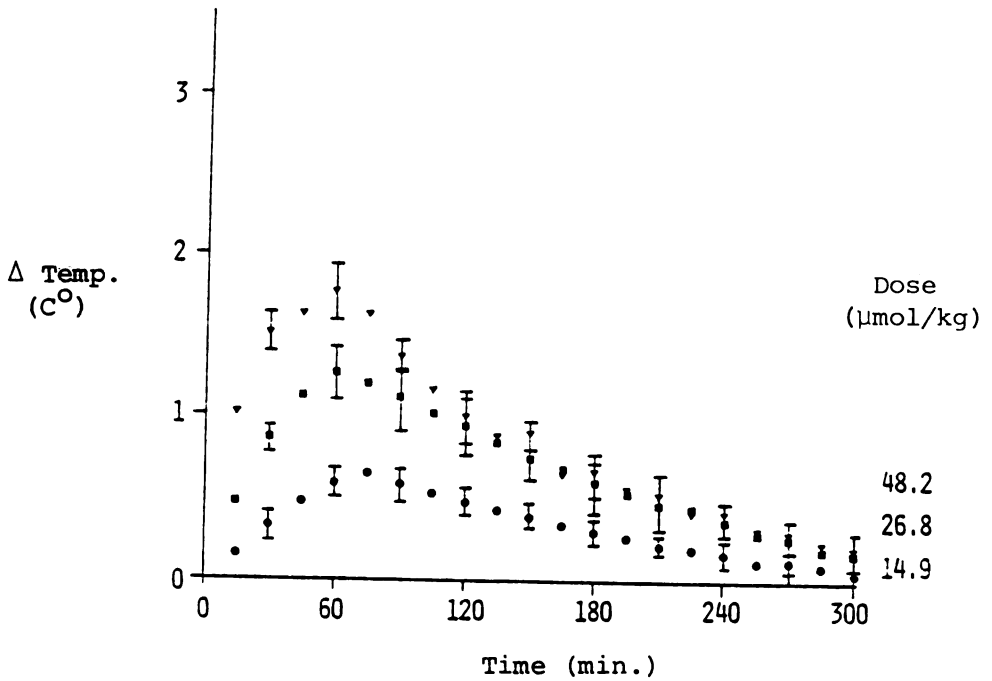


FIGURE 32. Hyperthermia elicited in the Rabbit by (RS)-1-Phenyl-2-methylaminopropane HCl (1CD).

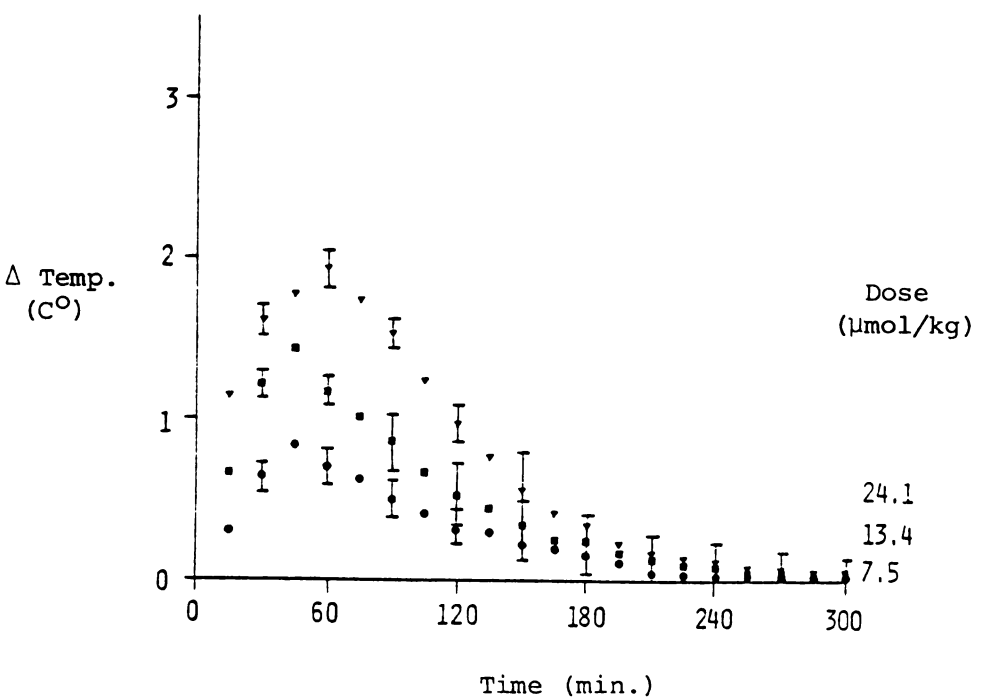


FIGURE 33. Hyperthermia elicited in the Rabbit by (S)-1-Phenyl-methylaminopropane HCl (1D).

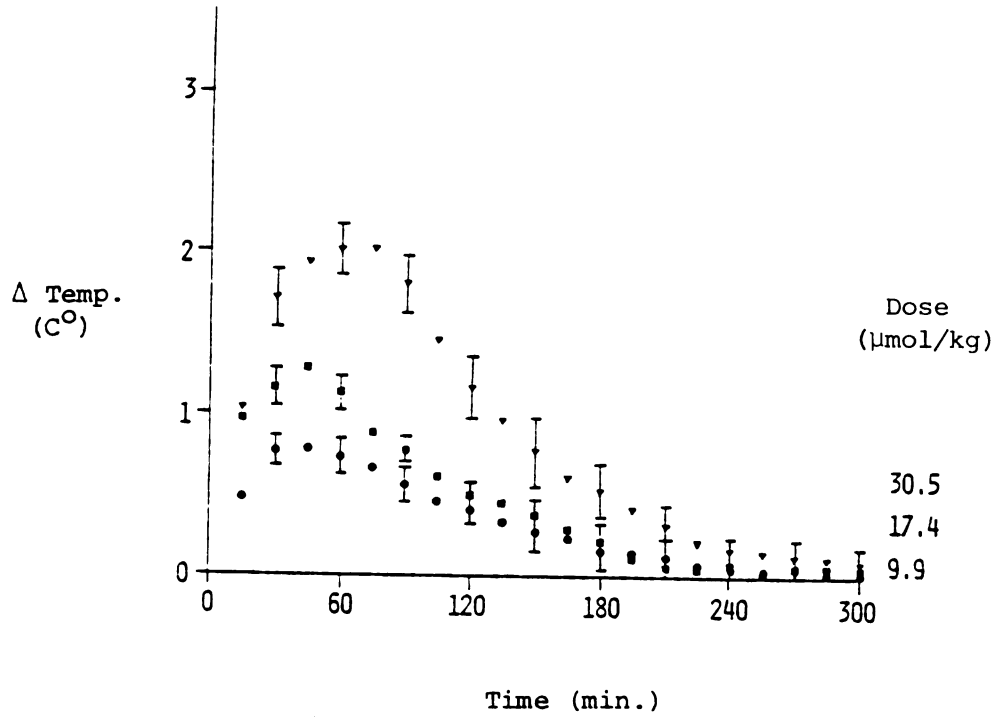


FIGURE 34. Hyperthermia elicited in the Rabbit by (RS)-1-(3,4-Methylenedioxyphenyl)-2-methyl-aminopropane HCl (5CD).

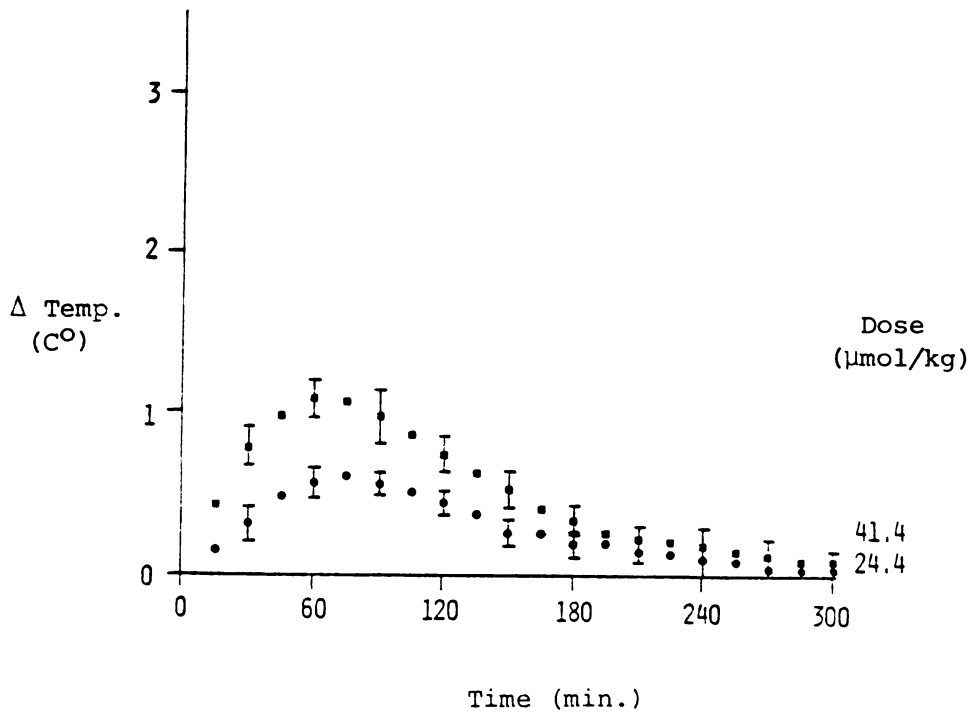


FIGURE 35. Hyperthermia elicited in the Rabbit by (R)-1-(3,4-Methylenedioxyphenyl)-2-methyl-aminopropane HCl (5C).

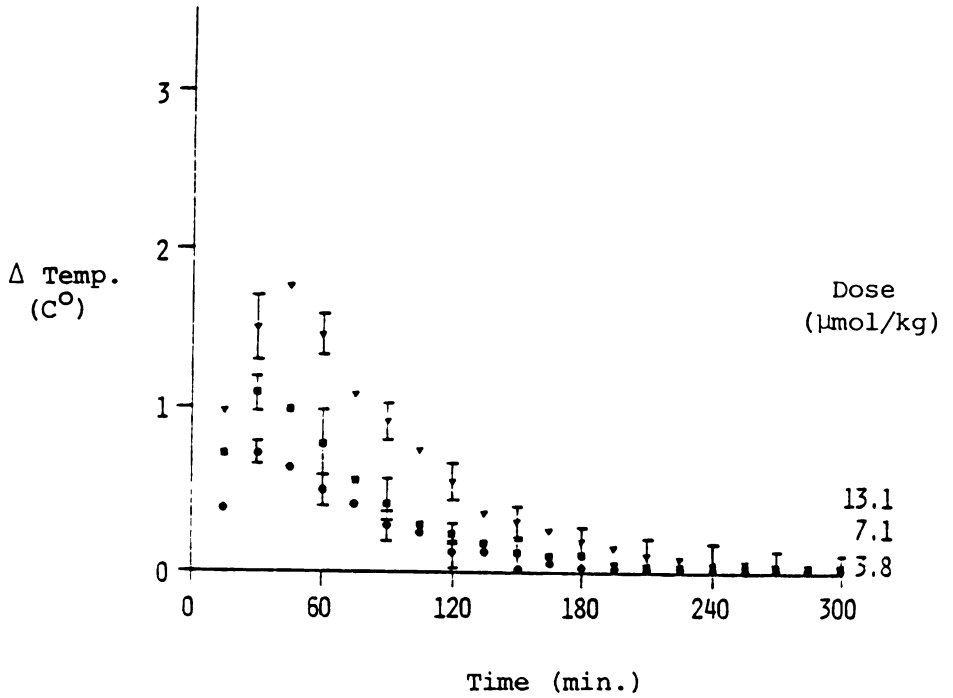


FIGURE 36. Hyperthermia elicited in the Rabbit by (S)-1-(3,4-Methylenedioxyphenyl)-2-methyl-aminopropane HCl (5D).

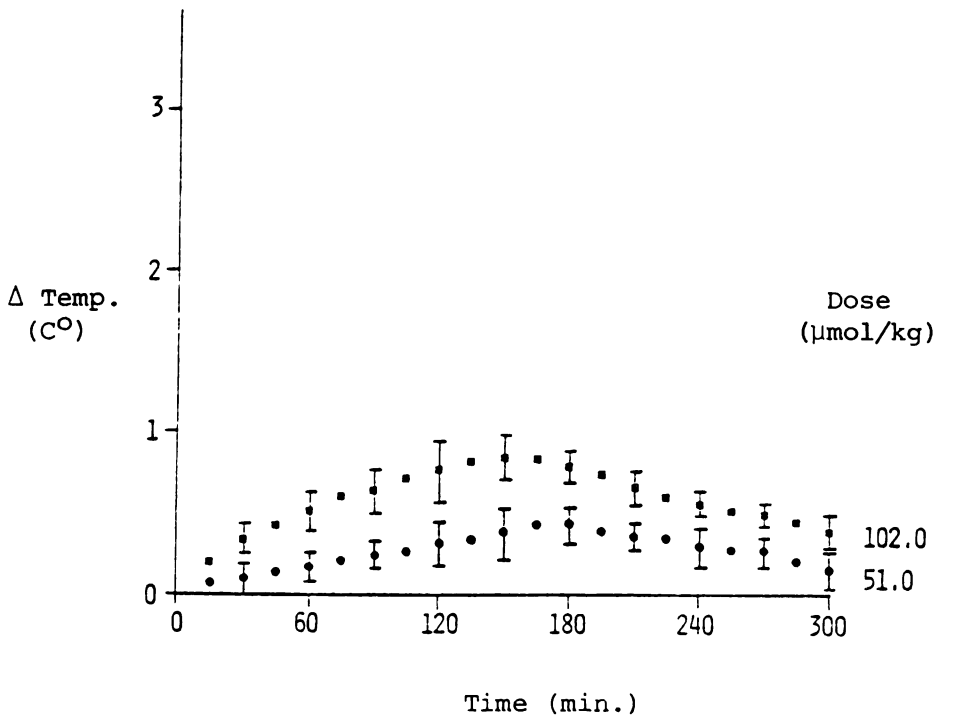


FIGURE 37. Hyperthermia elicited in the Rabbit by (RS)-1-(3,4-Dimethoxyphenyl)-2-methyl-aminopropane HCl (11CD).

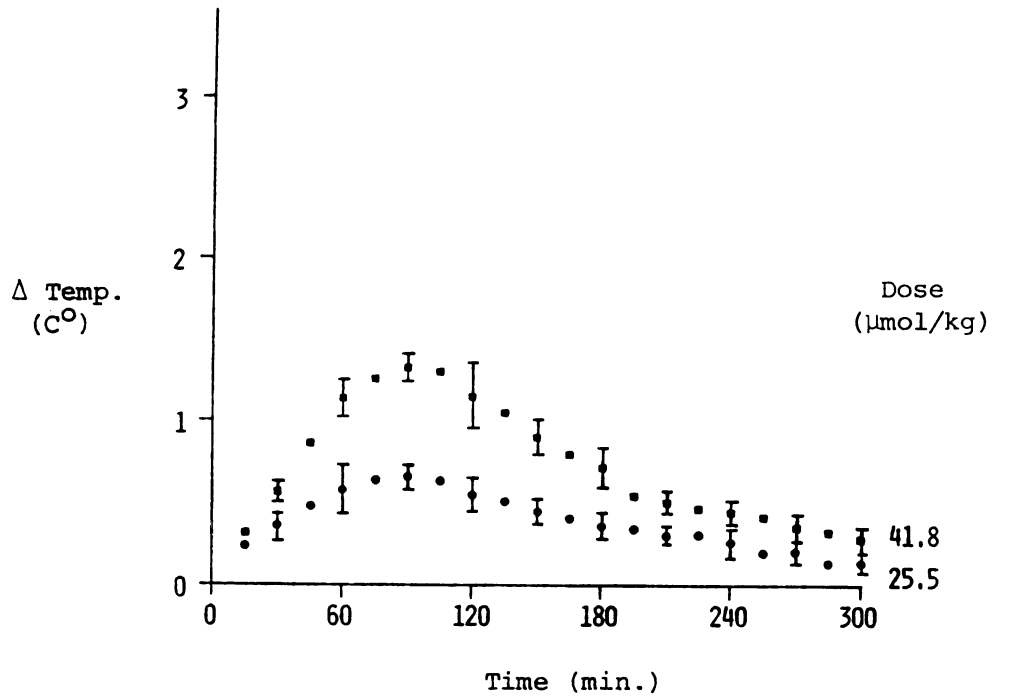


FIGURE 38. Hyperthermia elicited in the Rabbit by (RS)-1-(2,4,5-Trimethoxyphenyl)-2-aminopropane HCl (13CD).

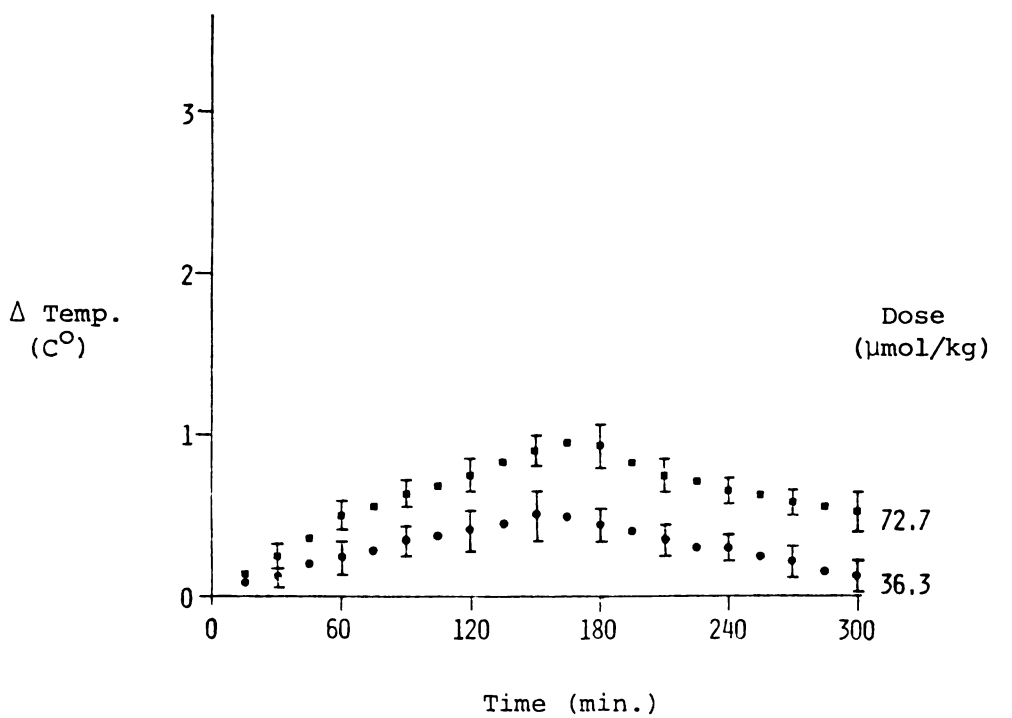


FIGURE 39. Hyperthermia elicited in the Rabbit by (RS)-1-(3,4,5-Trimethoxyphenyl)-2-aminopropane HCl (15CD).

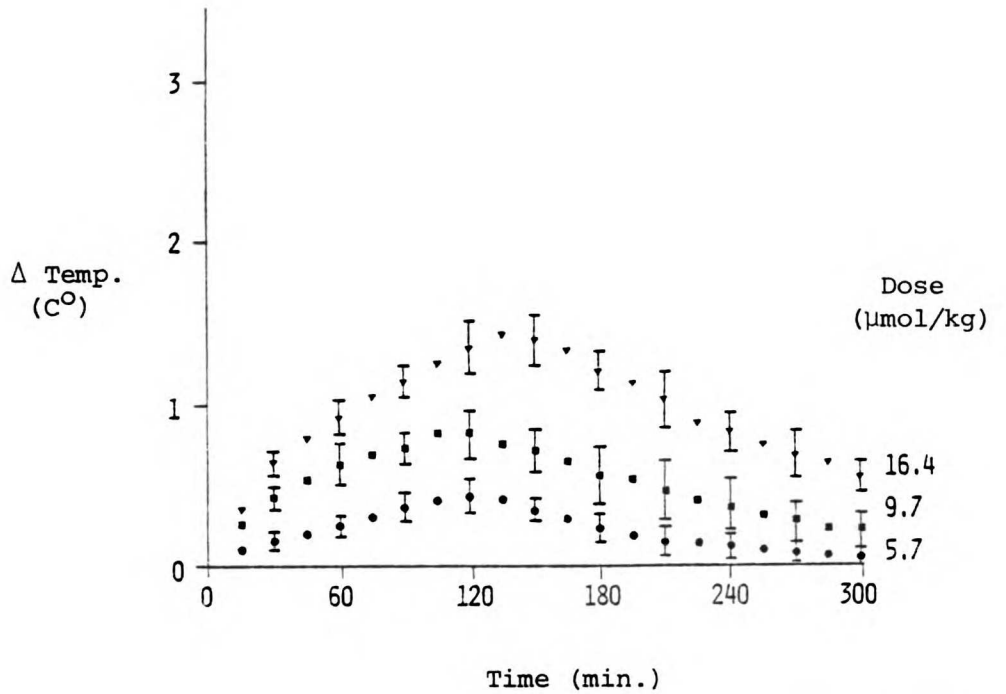


FIGURE 40. Hyperthermia elicited in the Rabbit by (RS)-1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane HCl (16CD).

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# CONFORMATIONAL PROPERTIES

# CONFORMATION OF PHENALKYLAMINES

Extensive pharmacological evaluations of compounds bearing the phenylalkylamine moiety have clearly demonstrated the remarkable diversity of CNS actions produced by these agents. For example, this pharmacophore is present in narcotic analagesics (i.e. morphine), dopamine agonists (apomorphine), stimulants (amphetamine), and psychotomimetics (DOM). Clearly, other structural features of these analogues account for the differences in the biological response elicited, still analysis of the conformational properties of the phenethylamine functionality is of widespread importance in rationalizing the Structure Activity Relationships (SAR). Snyder et al.[1a] was the first to suggest that the potencies of a variety of psychotomimetics were related to the ability of the phenethylamine to mimic certain structural features of the very potent compound, LSD. Following this initial report, numerous other conformational theories have been proposed and these mimic conformers are illustrated in Figures 41-49. As can be seen, these conformational arguments differ not only with respect to the rotational angles ($T_1$ and $T_2$) assumed by the ethylamine side chain, but also with regard to the counterparts of LSD to which they are related. In the Snyder model, the B and C rings of LSD are assumed to be topologically equivalent to certain folded conformations of phenethylamine. Alternately, Kang et al.[1b] have proposed an important role for the extended trans conformation which results from a direct superposition of the phenethylamine moiety in both the substituted phenethylamine and LSD. Glennon et al.[1c] have

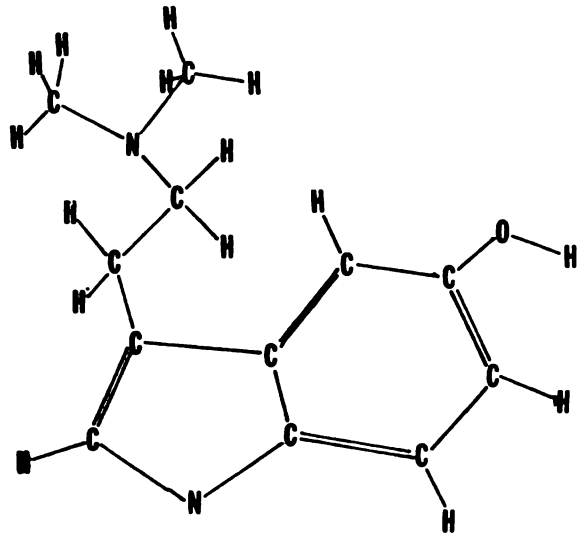


Figure 41. Molecular Structure of N,N-Dimethyl-5-hydroxy-tryptamine in the "LSD" Conformation.

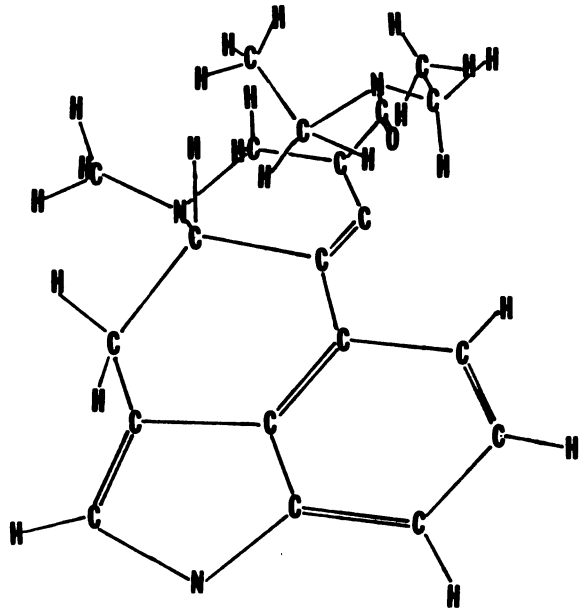


Figure 42. X-ray Crystalographic Structure of LSD.

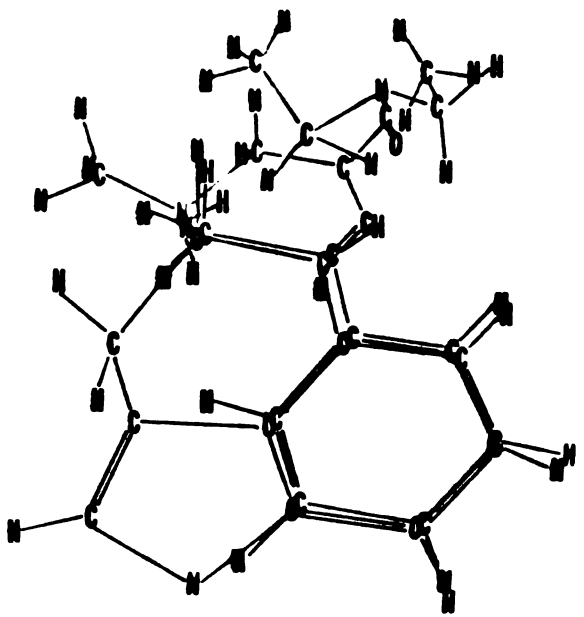


Figure 43. Superposition of Phenethylamine and LSD According to the Conformational Mimic Proposed by Kang et al. (Ref. 1b)($T_1$=150°; $T_2$=170°)

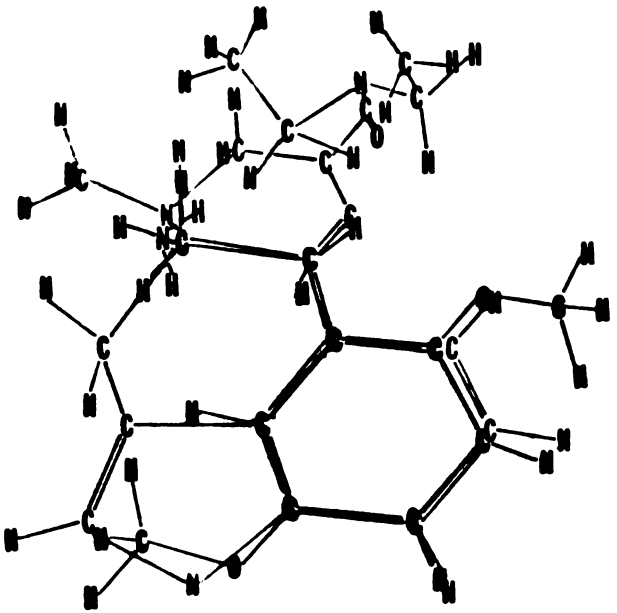


Figure 44. Superposition of 1-(2,5-Dimethoxyphenyl)-2-aminoethane and LSD According to the Conformational Mimic proposed by Kier et al. (Ref. 1c)($T_1$=150°; $T_2$=170°)

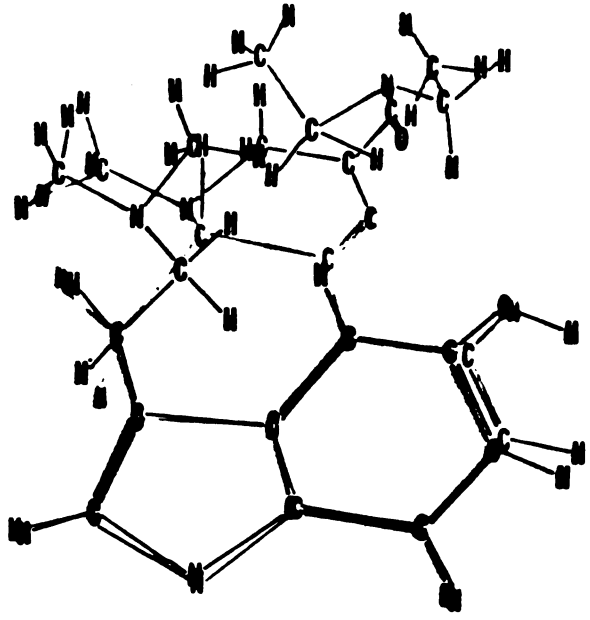


Figure 45. Superposition of Serotonin ($T_1$= 140°, $T_2$= 180°) on LSD

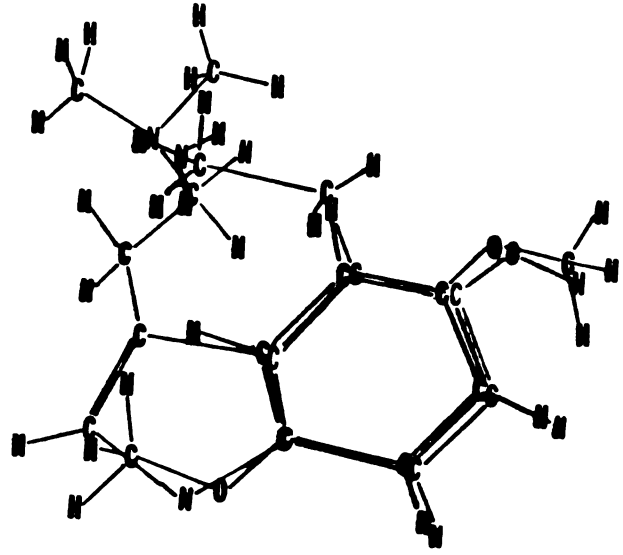


Figure 46. Superposition of 1-(2,5-Dimethoxyphenyl)-2-aminoethane and Serotonin ($T_1$= 140°, $T_2$=180°) According to the Conformational Mimic Proposed by Kier et al. (Ref. 1c)

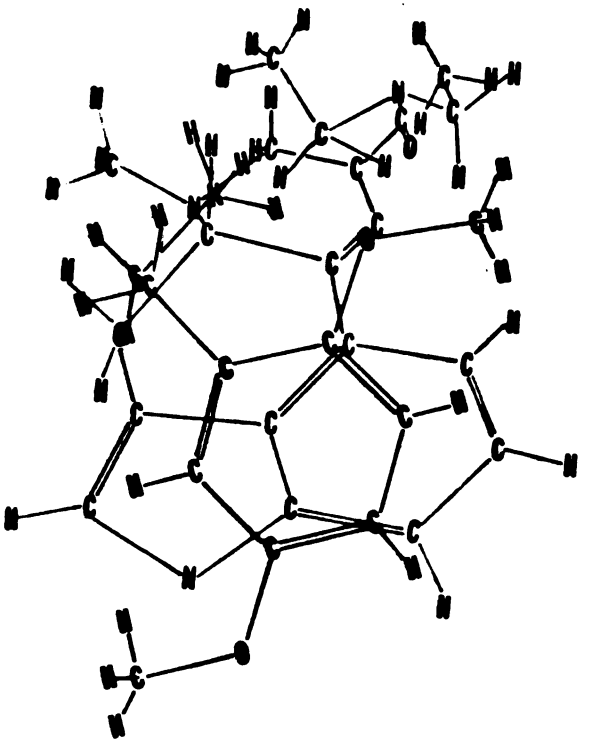


Figure 47. Superposition of 1-(2,5-Dimethoxyphenyl)-2-aminoethane and LSD According to the Conformational Mimic Proposed by Baker et al. (Ref. 1e)($T_1$=40°; $T_2$=240°)

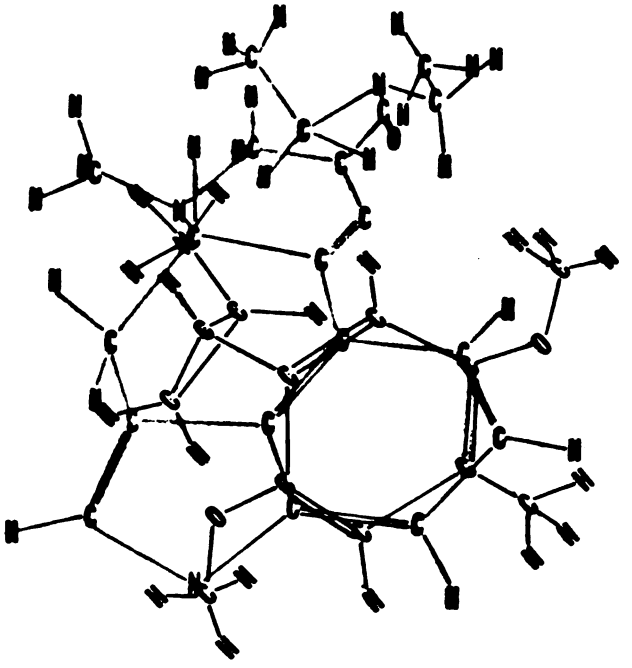


Figure 48. Superposition of Trans-1-(2,5-dimethoxy-4-methylphenyl)-2-cyclopropylamine and LSD According to the Conformational Mimic Proposed by Nichols et al. (Ref. 1d)($T_1$= 205°; $T_2$=32°)

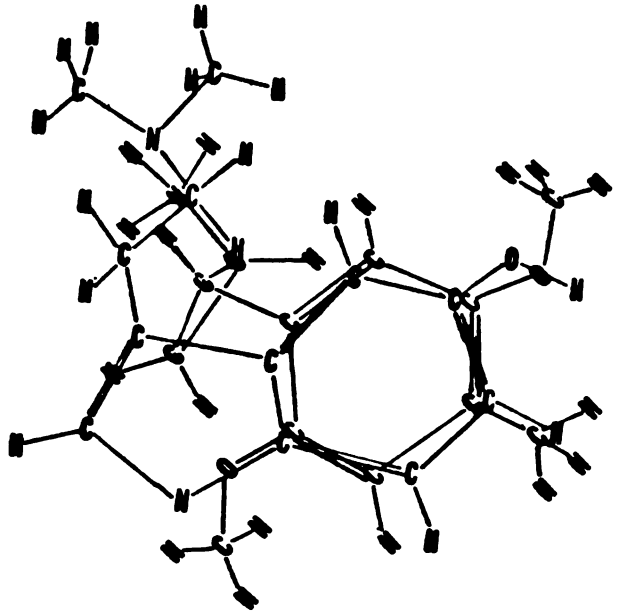


Figure 49. Superposition of Trans-1-(2,5-Dimethoxy-4-methylphenyl)-2-cyclopropylamine on Serotonin ($T_1$= -20°, $T_2$= 40°) According to the Conformational Mimic Proposed by Nichols et al. (Ref. 1d)

offered a further elaboration of the model of Kang *et al.* by stipulating that a *meta*-methoxy substituent, present in many phenylalkylamines be superimposed on the indolic nitrogen of LSD and various psychotomimetic tryptamines. In contrast, Nichols *et al.*[1d] have proposed that the *ortho*- rather than the *meta*-methoxy groups are congruent with the indolic nitrogen. Even more demanding is the model of Baker *et al.*[1e] which maintains a folded (*gauche*) orientation of the ethylamine side chain and a superimposition of 2- and 5-methoxy groups with the 9-10 double bond in LSD and the indolic nitrogen, respectively.

While these conformational arguments differ considerably, most ascribe an important conformational role for *ortho*-methoxy-phenylalkylamines and hence the conformational properties of these compounds have been studied using a variety of techniques. In the present chapter, analysis is made of the conformational profiles of derivatives of 1-phenyl-2-aminoethane bearing X-substitutents (where X=H, OH, $OCH_3$, $SCH_3$, $CH_3$, and Br) in the 2 position of the aromatic ring. The influence of these groups on the side chain conformation are evaluated using the semiempirical PCILO method[2a] and, to a limited extent, using the "*ab initio*" (STO-3G)[2b] formalism. An attempt is made to relate the conformational preferences of the substituted model compounds with the pharmacological potencies of a series of 1-(2-X-4,5-dimethoxyphenyl)-2-aminopropanes. Additionally, these "gas phase" conformations are compared to the "liquid phase" conformations determined via

NMR and the "solid state" conformations derived from X-ray crystal structure data.

Although the conformational properties of phenylalkylamines have often been explored, little attention has been directed towards the conformational characteristics of the aromatic substituents. Accordingly, the conformational profiles of various methoxy-substituted aromatics were studied using the semi-empirical CNDO/2[2c] and "ab initio" (STO-3G) methods. Comparison is made between the conformations of these groups and several experimentally measurable physical properties such as dipole moment, ionization potential, and octanol/water solubilities.

# MOLECULAR ORBITAL CALCULATION OF THE PREFERRED CONFORMATION OF 2-X-SUBSTITUTED PHENETHYLAMINES

The conformational energy profile of phenylethane calculated according to the PCILO method is presented in Figure 50. As can be seen, the trans conformation ($T_1$=90°) is preferred over the gauche ($T_1$=0°, 180°) by 2.2 kcal/mol. Undoubtedly, the higher energy of the gauche forms results from steric repulsions between the terminal methyl hydrogens and the neighboring ortho hydrogens on the aromatic ring.

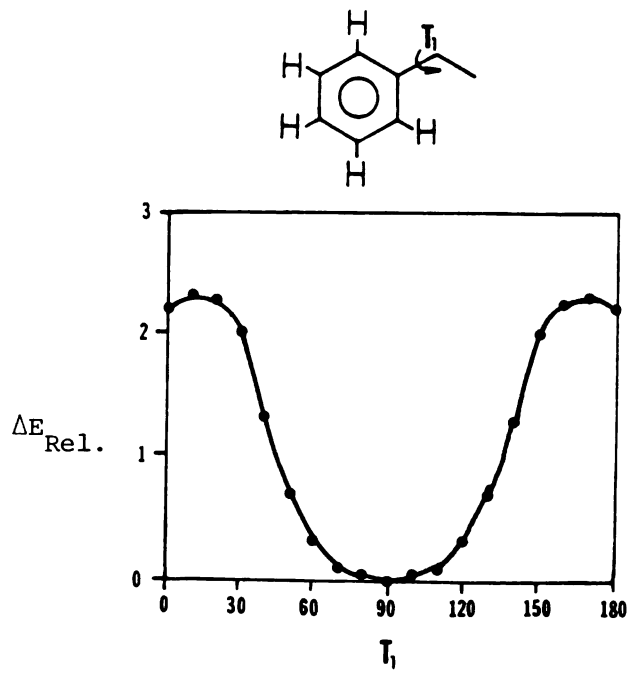
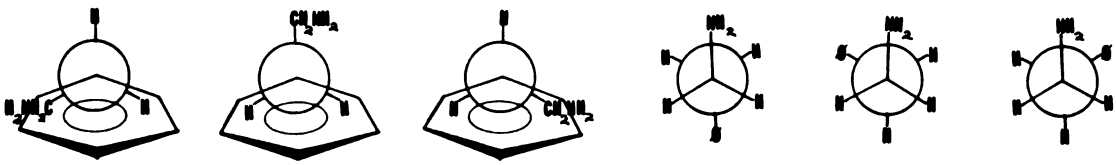



FIGURE 50. PCILO Conformational Energy Profile of Phenylethane.

The conformational energy maps of phenethylamine (Figure 51) and phenethylammonium (Figure 52) are more complex than phenylethane in that specification of two rotational axes ($T_1$ and $T_2$) are required to completely describe the orientation of the side chain. Rotations about these

axes may be conviently decomposed into two sets of Newman projections as shown below:

$T_1$ Projections $T_2$ Projections



In both the protonated and unprotonated forms of phenethylamine, the gauche configurations are found to be slightly more stable than the trans conformers indicating the presence of favorable, albeit weak interactions between the amine moiety and the aromatic ring. In the neutral forms, the gauche ($T_1$=90°, $T_2$=60°) preference ($E_T$-$E_G$=0.2 kcal/mol.) can be rationalized in terms of weak attractions between the Ar-H...$NH_2$ groups. In the protonated form of phenethylammonium, interaction between the $NH_3$(+)...$\pi$ electrons result in a slight reorganization of the gauche global minima ($T_1$=60°, $T_2$=60°) and further stabilization of the folded forms ($E_T$-$E_G$=0.4 kcal/mol.). Consistent with this argument is the observation that upon introduction of electron donating groups such as methoxy into the para position, even greater stabilization of the gauche conformers occurs ($E_T$-$E_G$= 1.1kcal/mol.). "Ab initio" (STO-3G) calculations on phenethylammonium also predict the gauche orientation to be more stable than the trans by 2.2 kcal/mol. By comparison, Martin et al.[3a] have reported the $E_T$-$E_G$ difference in

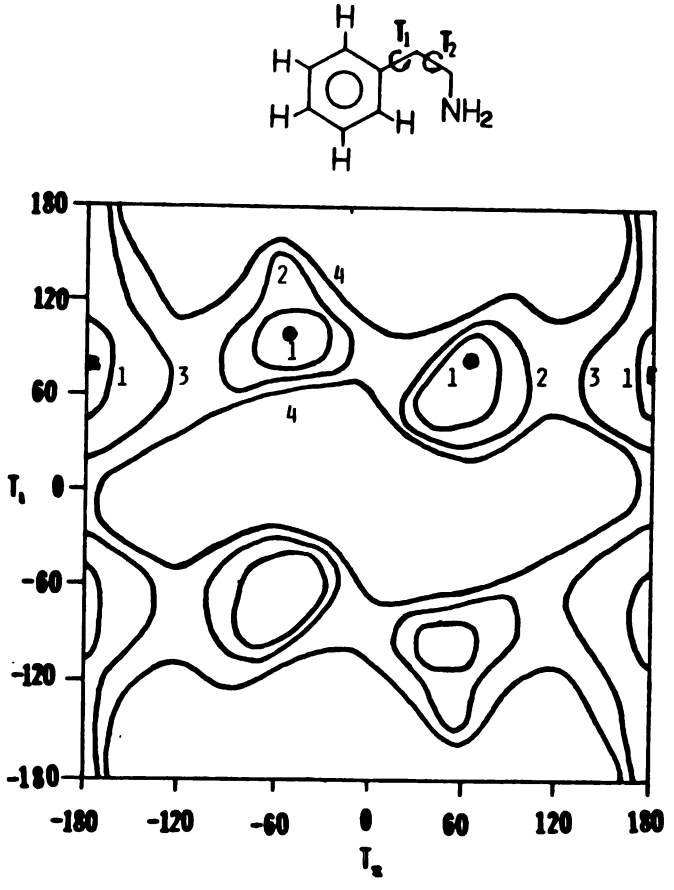



FIGURE 52. PCILO Conformational Energy Map of Phenethylamine. (● =Global Minimum; E(■)= 0.2 kcal/mol).

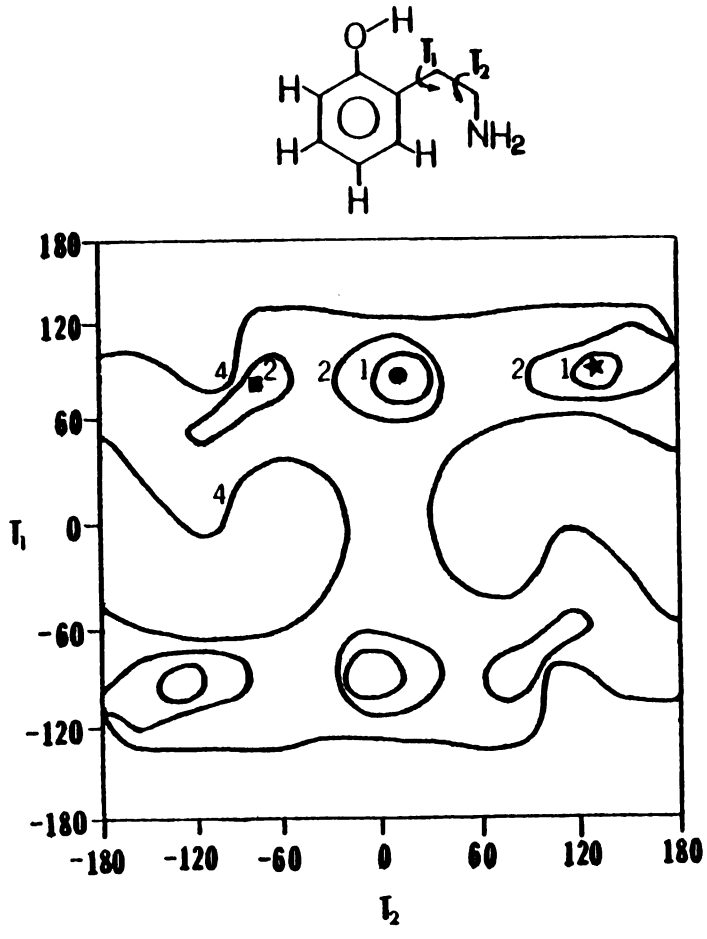



FIGURE 53. PCILO Conformational Energy Map of 2-OH-Phenethylamine ($T_S=0^o$). (★=Global Minimum; $\Delta E$(■)=1.4; $\Delta E$(●)=0.8 kcal/mol.).

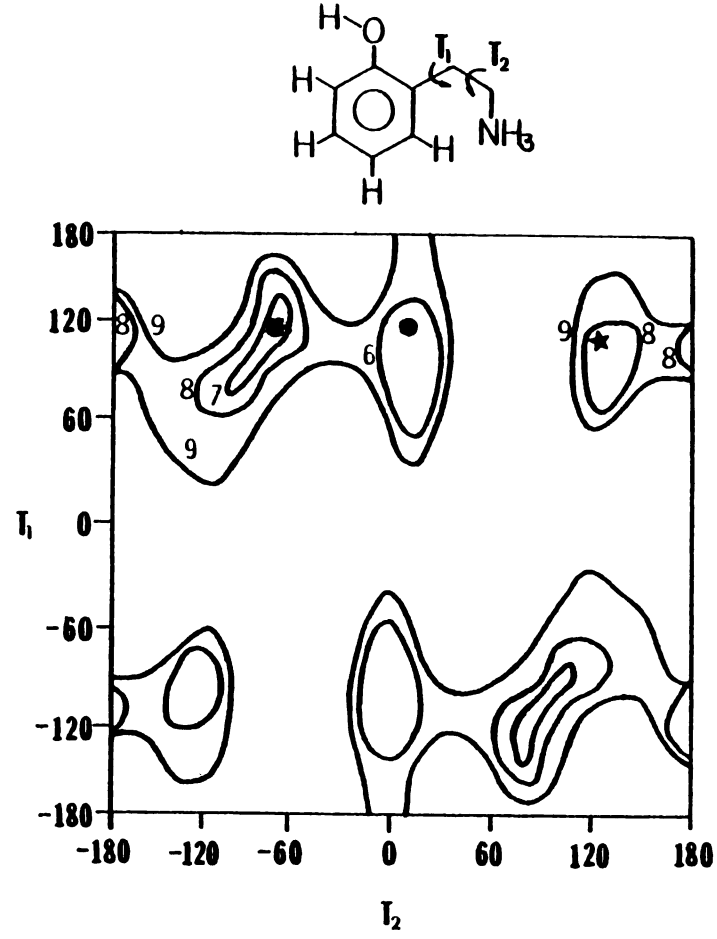



FIGURE 54. PCILO Conformational Energy Map of 2-OH-Phenethylammonium(+) ($T_S=180^o$). (★=Global Minimum; $\Delta E$(■)=7.6; $\Delta E$(●)=7.1 kcal/mol.).

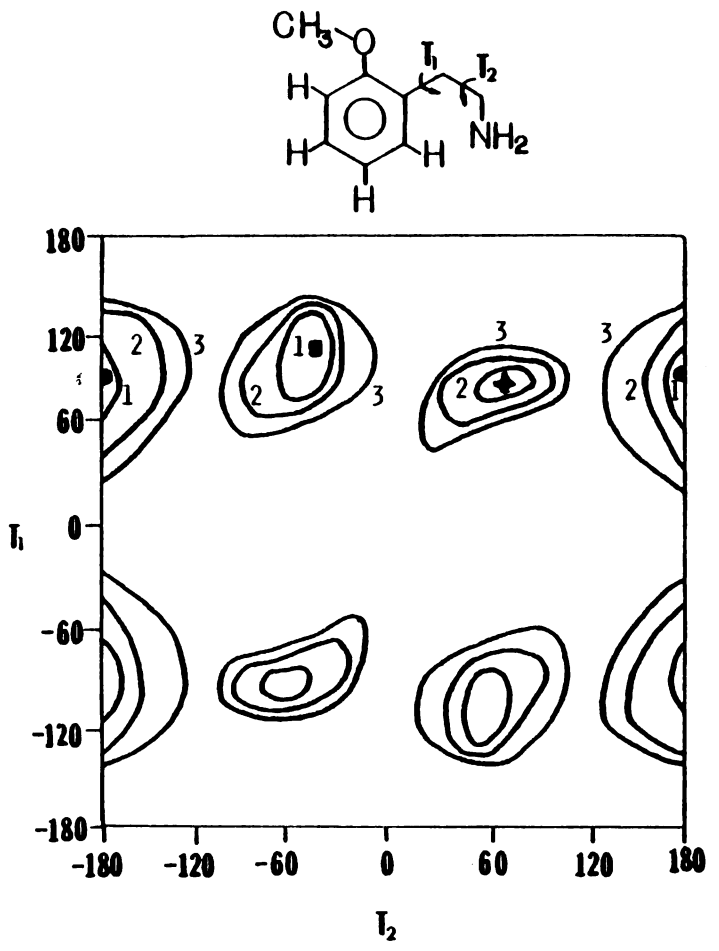



FIGURE 55. PCILO Conformational Energy Map of 2-$OCH_3$-Phenethylamine ($T_S$=180°). (✱=Global Minimum; ΔE(■)=0.4; ΔE(●)= 1.0 kcal/mol.).

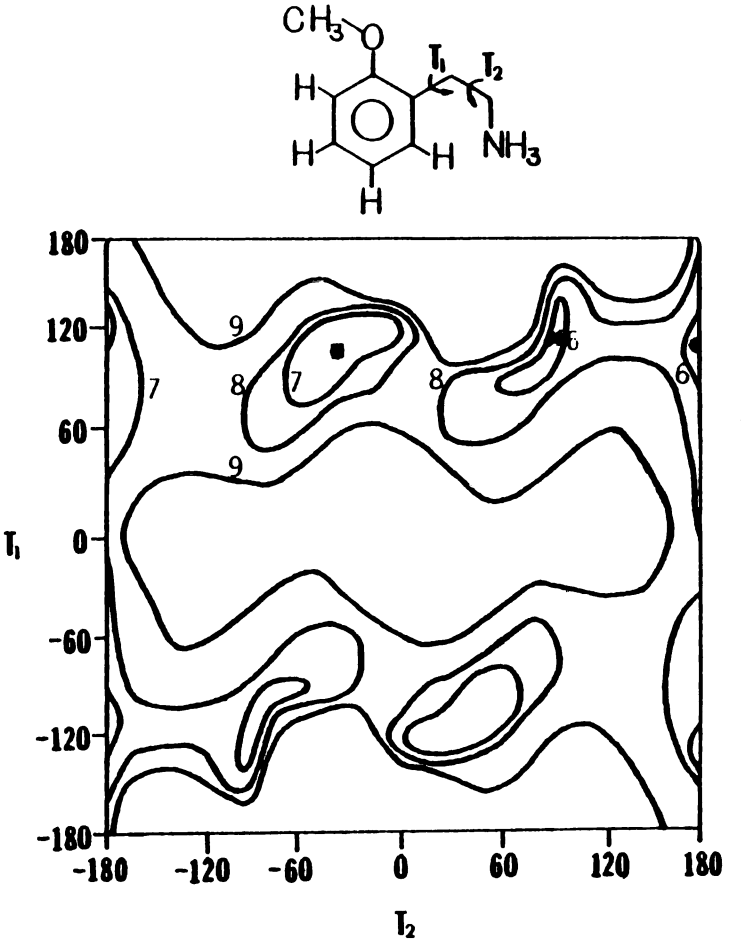



FIGURE 56. PCILO Conformational Energy Map of 2-$OCH_3$-Phenethylammonium(+) ($T_S$=180°). (✱=Global Minimum; ΔE(■)=6.8; ΔE(●)=6.5 kcal/mol.).

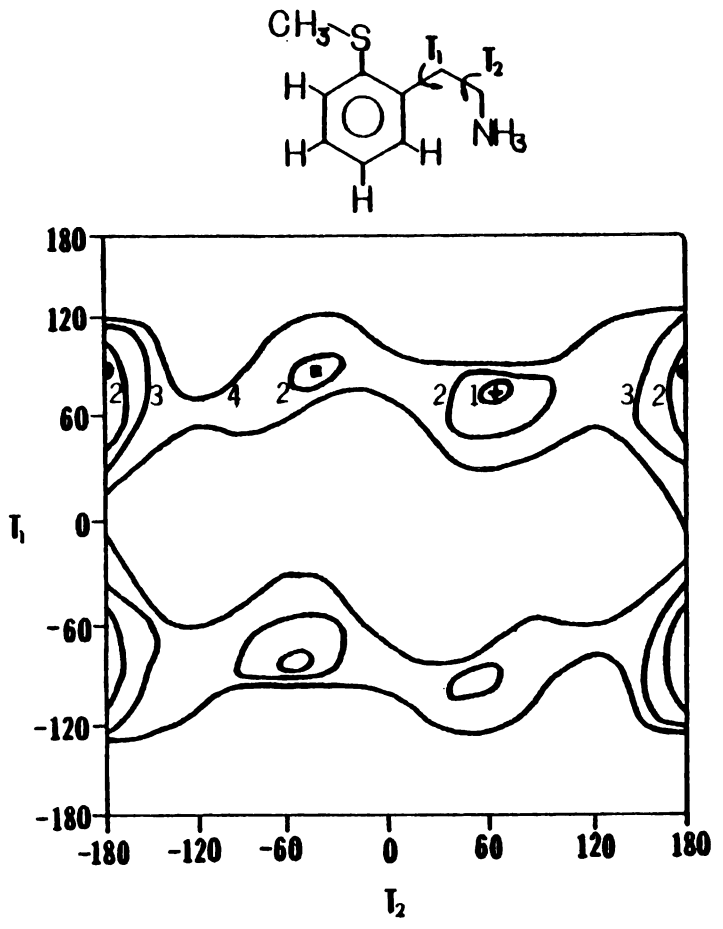



FIGURE 57. PCILO Conformational Energy Map of 2-$SCH_3$-Phenethylammonium(+) ($T_S$=180°). (★=Global Minimum; ΔE(■)=1.7; ΔE(●)=0.9 kcal/mol.).

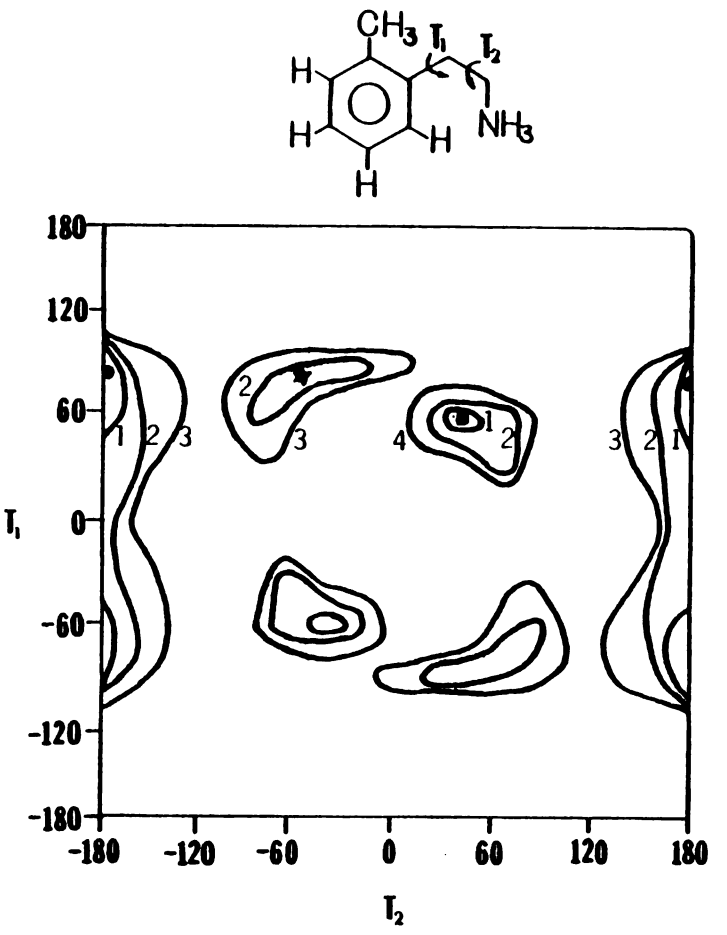



FIGURE 58. PCILO Conformational Energy Map of 2-$CH_3$-Phenethylammonium(+) (★=Global Minimum; ΔE(■)=0.6; ΔE(●)=1.1 kcal/mol.).

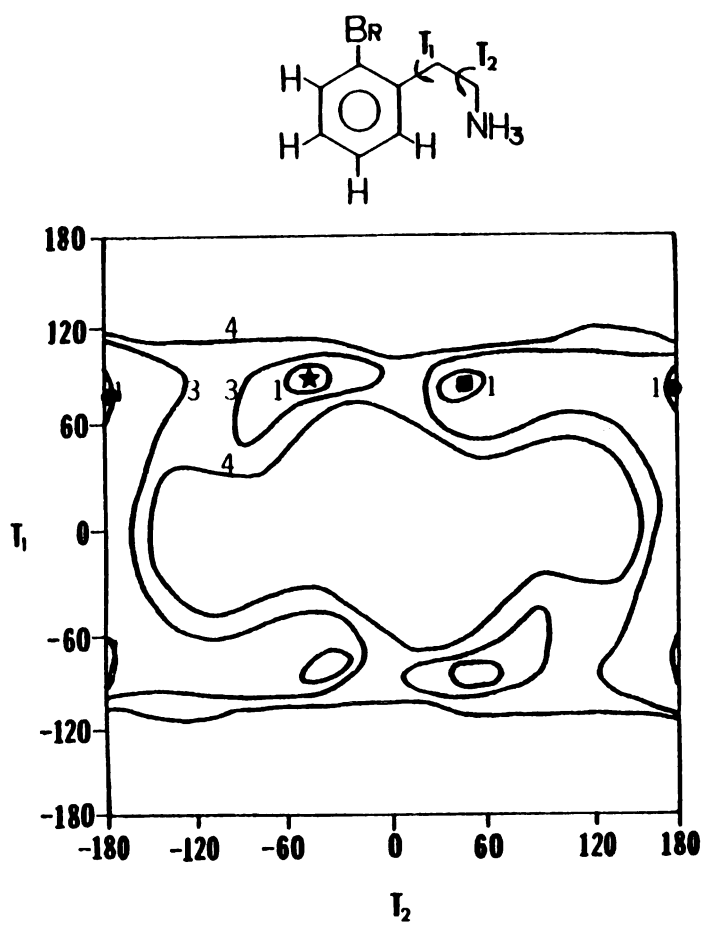



FIGURE 59. PCILO Conformational Energy Map of 2-Br-Phenethylammonium(+). (★=Global Minimum; ΔE(■)=0.5; ΔE(●)=0.4 kcal/mol.).

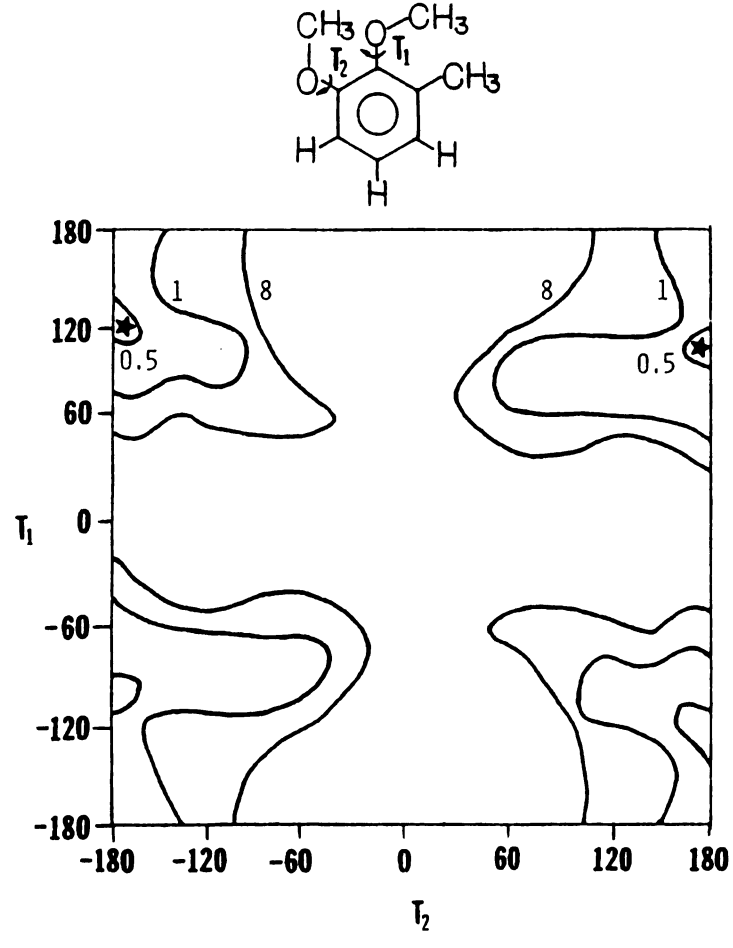



FIGURE 60. CNDO/2 Conformational Energy Map of 2,3-Dimethoxytoluene. (★=Global Minimum in kcal/mol.)

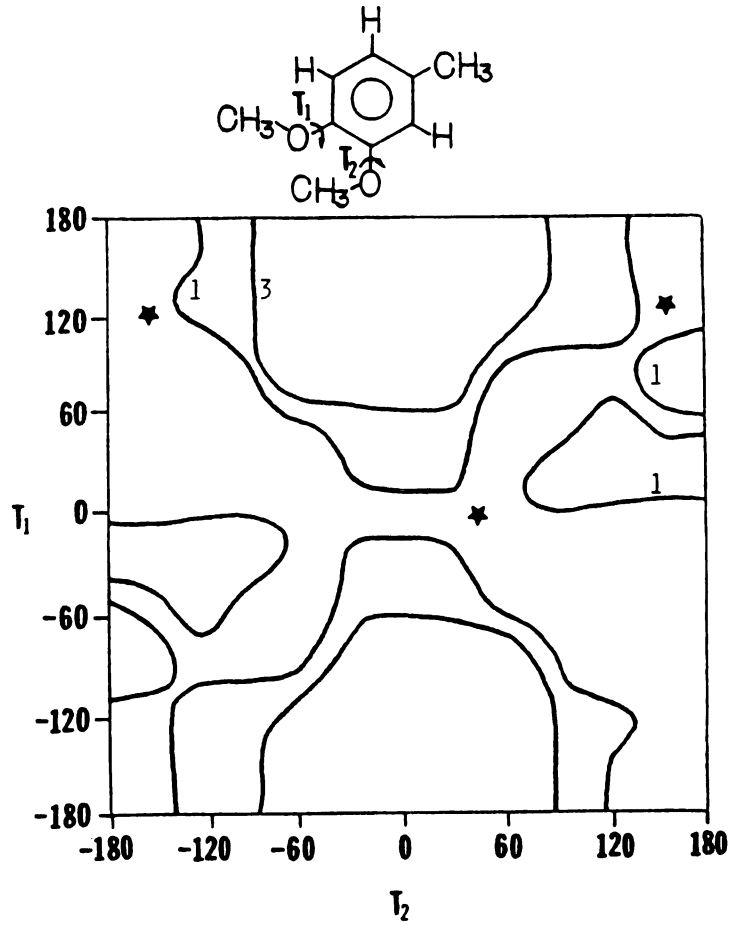



FIGURE 61. CNDO/2 Conformational Energy Map of 3,4-Dimethoxytoluene. (★=Global Minimum in kcal.mol.)

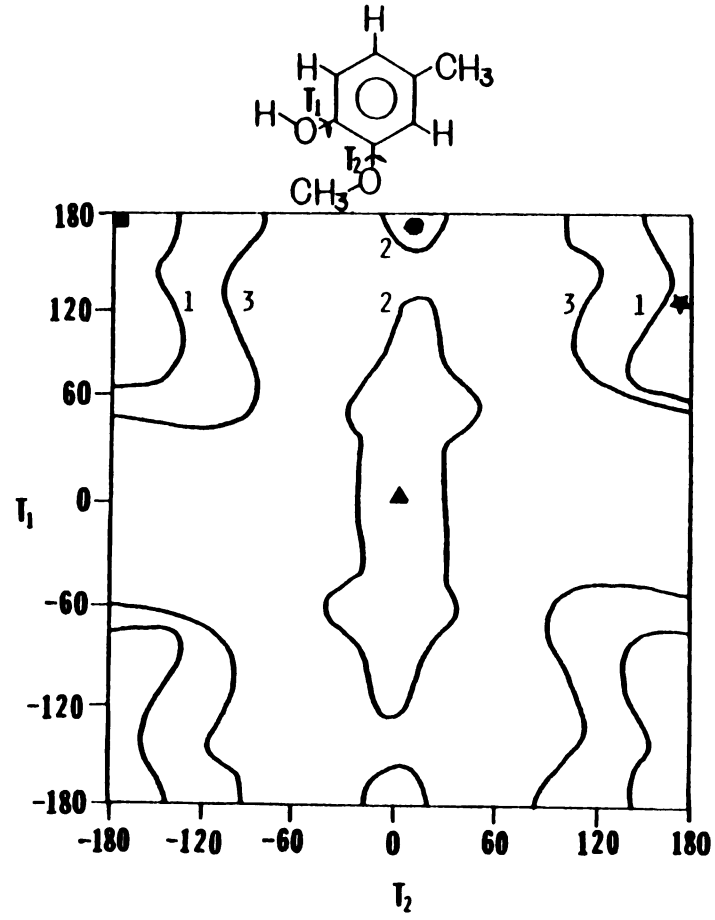



FIGURE 62. CNDO/2 Conformational Energy Map of 3-Hydroxy-4-methoxytoluene. (★=Global Minimum; ΔE(■)=0.2; ΔE(●)=1.5; ΔE(▲)=0.8 kcal/mol.)

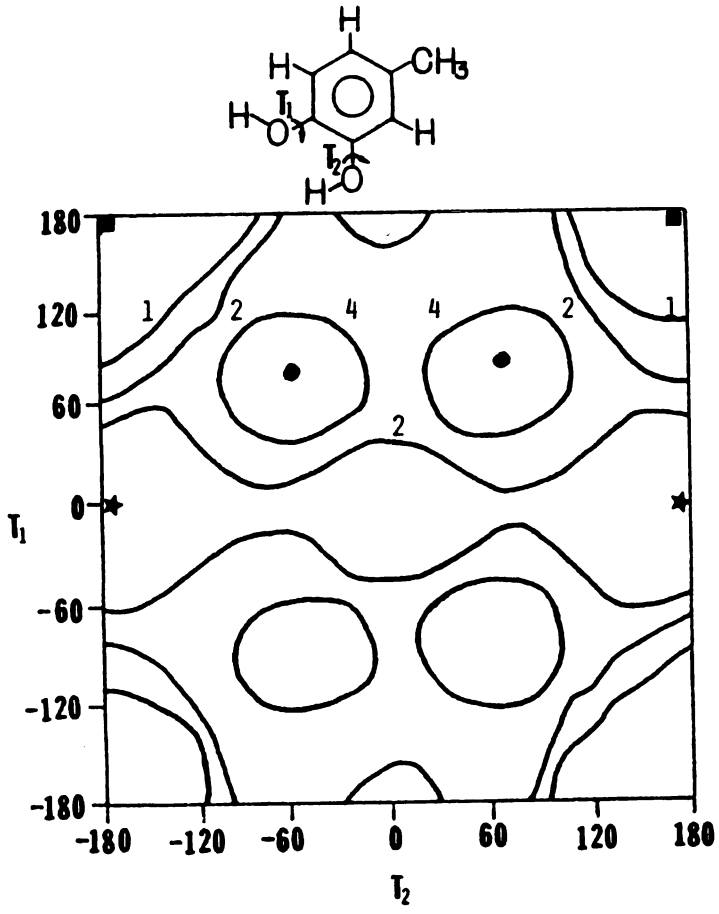



FIGURE 63. CNDO/2 Conformational Energy Map of 3,4-Dihydroxytoluene. (★=Global Minimum; ΔE(■)=0.1; ΔE(●)=1.4 kcal/mol.).

phenethylammonium obtained from "ab initio" (STO-3G), PCILO, and CNDO/2 to be 1.1, 0.2, and 5.9 kcal/mol., respectively. "Ab initio" calculations performed by Hall et al.[3b] using combinations of spherical gaussian wave functions indicate a $E_T$-$E_G$ difference of about 5 kcal/mol. In contrast, Pullman et al.[3c], using the PCILO formalism, have reported nearly equivalent trans and gauche energies. From an early conformational study of a series of phenylalkylammoniums using empirical potential functions, Weintraub et al.[3d] report the gauche conformation of phenethylammonium to be preferred over the trans by about 5 kcal/mol., regardless of whether this molecule is solvated or not. Recently, these functions have been modified and the "improved" results[3e] predict the gauche orientation to be about 2 kcal/mol. more stable than the trans in the gas phase and in the solvated state, these conformations were energetically equivalent.

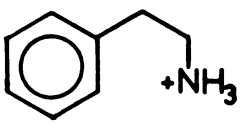
The presence of an ortho hydroxy substituent dramatically perturbs the conformation of the ethylamine side chain and leads to a preponderance of gauche conformers. In the neutral amino state, the global minima (Figure 53) arises from the formation of a weak hydrogen bond between the $NH_2$ group and the OH substitutent ($T_1$=60°, $T_2$=90°). By comparison, in the protinated species (Figure 54), much stronger hydrogen bonding occurs between the $NH_3(+)$...OH groups producing an even greater reduction in the energy of the gauche conformation ($T_1$=120°, $T_2$=90°) relative to the trans local minima ($E_T$-$E_G$= 0.8 kcal/mol.

Both ortho methoxy and thiomethyl substituents affect the conformational profiles in a manner similar to that found in the ortho hydroxy compound. While the gauche conformations of these analogues are slightly more stable than the extended trans conformers, the minimum energy folded forms of the methoxy and thiomethyl substituted phenethylamines are those in which the substituent methyl groups are oriented away from the side chain ($T_3$=180°). Similarly, the attractions found in the ortho hydroxy phenethylammonium(-) are also present in the ortho-methoxy (Figure 56) and thiomethyl (Figure 57) analogues and, as expected, the global minima in these cases are gauche ($T_1$=120°, $T_2$=90°; $T_1$=90°, $T_2$=60°). But, unlike the ortho-hydroxy compound, the ortho-methoxy analogue obtains a large stabilization ($E_T$-$E_G$= 6.5 kcal/mol.) due to the hydrogen bond formation, whereas, much smaller attraction is seen in the ortho-thiomethyl case ($E_T$-$E_G$=1.6 kcal/mol.).

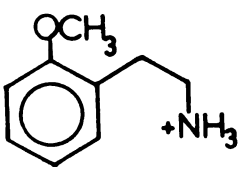
Calculations of the stabilities of trans and gauche conformations of ortho-methoxyphenethylammonium according to the "ab initio" (STO-3G) method (Table 12) using the optimum PCILO geometries yield results which were qualitatively similar to the PCILO computations in that the gauche conformer was considerably preferred over trans ($E_T$-$E_G$=10.6 kcal/mol.). Pullman et al.[3f], using the PCILO methodology, have reported that the gauche conformation of 2,4,5-trimethoxyamphetamine to be more stable than the trans by about 1 kcal/mol.[3f].

In both ortho-methylphenethylammonium(+) (Figure 58)

Table 12. Conformational Energies Obtained from "ab initio" (STO-3G) and PCILO Calculations on Phenethylammonium and 2-Methoxyphenethylammonium.




| Conformation | ($T_1^o$, $T_2^o$) | ΔE (STO-3G) | ΔE(PCILO) |
|---|---|---|---|
| TRANS | (70, 180) | 2.2 | 0.4 |
| | (100, 180) | 2.0 | 0.3 |
| GAUCHE | (90, 60) | 0[a] | 0 |
| KG[b] | (150, 160) | 9.1 | 1.3 |



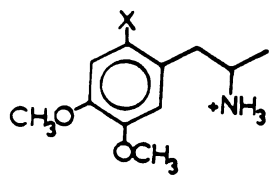

| Conformation | ($T_1^o$, $T_2^o$) | ΔE (STO-3G) | ΔE(PCILO) |
|---|---|---|---|
| TRANS | (70, 180) | 10.6 | 7.4 |
| GAUCHE | (120, 90) | 0[c] | 0 |
| KG[b] | (150, 160) | 16.2 | 9.1 |

[a]E= 225.777611 kcal/mol. [b]Conformational mimic proposed by Kang and Green (ref. 1b). [c]E= 296.3189134 kcal/mol.

and ortho-bromophenethylammonium(+) (Figure 59), favorable attractions cannot occur between the ortho substituents and the ammonium group and hence the preferred gauche conformer found in the previous examples is not the minimum energy conformation. Instead, the complimentary gauche conformation ($T_1$=90°, $T_2$=60°; $T_1$=90°, $T_2$=-30°) is the global minima in these cases and is only slightly more stable than the trans orientation ($E_T$-$E_G$=0.6 kcal/mol.; $E_T$-$E_G$=0.5 kcal/mol.).

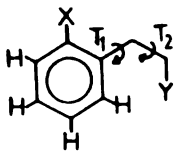
Table 13 consists of the PCILO calculated energies of the five LSD mimic conformations of a series of 2-X-substituted phenethylammoniums. As can be seen, the planar gauche conformations proposed by Snyder are energetically impossible. On the other hand, the remaining mimic conformers are quite reasonable, since if the phenethylammonium binds to the receptor 1,000 times weaker than LSD and has the same total intrinsic attraction at its LSD mimic conformation, one would expect that a reasonable upper bound for the conformational energy would be about 4 kcal/mol. relative to the global minimum ($\Delta G$=-2.3 RT log ($10^3$)). Conversely, if LSD has a greater intrinsic affinity for the receptor than the LSD mimic conformation of the analogue, then the upper bound of the conformational energy must be correspondingly less in order to compensate for this. While most of the energies of the mimics (except for Snyder's) are within this range, comparison of stabilities of the ortho-H and -$OCH_3$ analogues predicts that the binding of the latter

derivative should be correspondingly weaker than the former. Furthermore, the conformational energies of the ortho-$SCH_3$, -$CH_3$, and -Br derivatives are less than those obtained by the ortho-$OCH_3$ analogue, and therefore these compounds would be expected to be correspondingly more potent than the ortho-$OCH_3$ phenethylammonium. These results are not supported by the hyperthermic potencies of a series of 1-(2-X-4,5-dimethoxyphenyl-2-aminopropanes)(Table 10 ).




Hence, there appears to be no straightforward explanation of the potencies of these compounds based solely on conformational arguments[3f]. Neverless, compounds bearing ortho-substituents which tend to favor gauche conformations ($CH_3$,Br) in which the ethylammonium side chain is oriented away from the ortho group are typically less potent by comparson with ortho-substituted compounds which are capable of favorable interraction with the side chain ammonium group ($OCH_3$, $SCH_3$). At least to this extent, a relationship between conformation and biological potency appears to exist.

Table 13. PCILO Conformational Analysis of a Series of Substituted Phenethylamines




| | | | | Energy (Kcal/mole)[b] | | | | |
|---|---|---|---|---|---|---|---|---|
| X= | Y= | Global Minimum[a] | Local Minimum[a] | S I[c] | S II[d] | KG[e] | B[f] | N[g] |
| -H | $NH_3(+)$ | G I=G II | T (0.9) | 253 | 480 | 1.3 | 5.5 | 1.4 |
| $-OCH_3$ | $NH_3(+)$ | G I | G II (6.9)<br>T (6.5) | 260 | 278 | 8.5 | 15.3 | 8.7 |
| -OH[h] | $NH_3(+)$ | G I | G II (7.6)<br>T (7.1) | 1705 | 474 | 9.6 | 12.3 | 13.4 |
| -OH[i] | $NH_2$ | G I | G II (1.4)<br>T (0.8) | 10088 | 21.7 | 90.4 | 4.5 | 36.6 |
| $-SCH_3$ | $NH_3(+)$ | G I | G II (0.9)<br>T (1.7) | 256 | 981 | 3.5 | 5.7 | 4.0 |
| $-CH_3$ | $NH_3(+)$ | G II | G I (1.1)<br>T (0.7) | 251 | 2117 | 1.6 | 5.5 | 4.9 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| -Br | $NH_3(+)$ | G II | G I (0.3)<br>T (0.5) | 253 | 1061 | 2.2 | 5.4 | 4.3 |

[a]G I=gauche conformation with $NH_3(+)$ group toward X ($T_2$ 0), G II=gauche conformation with $NH_3(+)$ group away from X ($T_2$ 0); T=trans conformation.

[b]Energy above the conformational minimum.

[c]"B ring mimic" of Snyder[1a].

[d]"C ring mimic" of Snyder[1a].

[e]LSD mimic of Kang and Green[1b].

[f]LSD mimic of Baker[1e].

[g]LSD mimic of Nichols[1d].

[h]-OH pointed away from side chain.

[i]-OH pointed toward side chain

# CONFORMATION OF PHENALKYLAMINES IN SOLUTION

Early valence bond calculations performed by M. Karplus[4a] demonstrated that the approximate relationship between the dihderal angle θ and the magnitude of the vicinal proton coupling constant $J_{H-C-C-H}$, has the following form:

$$J=J^{o} \cos^{2} \theta - C \quad (0^{o} \leq \theta \leq 90^{o})$$

$$J=J^{180} \cos^{2} \theta - C \quad (90^{o} \leq \theta \leq 180^{o})$$

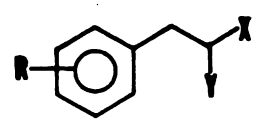
where $J^{o}$, $J^{180}$, and C are constants. Experimental verification was soon obtained via determination of the vicinal coupling constants measured in several rigid ring systems, such as camphane-2, 3-diols[5a], various sugar derivatives[5b], and adamantane compounds[5c], whose molecular structures were known by other methods. Subsequently, it was shown that these coupling constants were also dependent upon electronegativities and orientation of the substituents as well as bond lengths and angles of these groups[5d]. While these factors affect the magnitude of $J_{vic}$, the angular dependence specified by the Karplus equation remains unchanged by these pertubations. Extensions of this approach have been reported, and this NMR method has often been used to ascertain the rotomeric populations of many flexible compounds which can exist as mixtures of several conformations[5e].

Using these formulations, several groups have applied the Karplus relationship to NMR data in order to ascertain the conformational preferences of various phenylalkylamines in solution and these results have been condensed in Table 14. The NMR spectral features of the side chain hydrogens in

$ArCH_AH_BCH_C(NH_X)Y$ (where X=2 or 3 and Y=H or $CH_3$) constitute an ABC spin system[5f]. Analysis of this pattern, typically by computer simulation methods[5g], allows delineation of the vicinal proton coupling constants $\bar{J}_{AC}$ and $\bar{J}_{BC}$. If estimates of the vicinal coupling constants $J_T$, $J_{GI}$, and $J_{GII}$ for the three $T_2$ rotamers (see $T_2$ Newman projections illustrated previously) are made, then the relative populations of these conformers can be easily calculated. Usually, estimates of the rotameric coupling constants are taken from analogous rigid ring analogues of known geometry such as 2-phenylmorpholine, and, while these values differ ($J_T$=11.0-13.11 Hz, $J_{GI}=J_{GII}$=2.0-3.6 Hz), the respective rotamer populations vary accordingly by less than 6%. The $T_1$ rotamers are not given to such analysis due to the very small vicinal coupling between the $H_A$ or $H_B$ protons with the ortho Ar H's (<<2 Hz)[5d].

Scrutiny of Table 14 shows that in the simplest compound, phenethylammonium, the trans rotamers are slightly favored over the equivalent gauche rotamers ($P_T$=56%, $P_G$=44%). These results are in contrast to the previously reported PCILO calculations on the gas phase conformational profile which predicted the gauche to be slightly more stable than the trans. This discrepancy probably results from the influence of solvation of the protonated specie and in fact evidence for this effect has been reported by Pullman[5h] from their explicit solvation calculations using the supermolecule approach which indicate that trans conformers are more stable than the

Table 14. Conformation of Several Derivatives of Phenalkylamines Found in Solution by NMR Methods.



| Aromatic Sub. Pattern | | | | | | | | Rotomer Pop. % | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | X | Y | Sol. | $G_1$ | $G_2$ | T | Ref. |
| H | H | H | H | H | H | $NH_3Cl$ | $D_2O$ | - 44 - | | 56[a] | 6a |
| H | OH | OH | H | H | H | $NH_3Cl$ | $D_2O$ | - 57 - | | 43[b] | 6b |
| H | H | $OCH_3$ | H | H | H | $NH_3Cl$ | $D_2O$ | - 58 - | | 42[c] | 6c |
| H | H | H | H | H | $CH_3$ | $NH_2$ | $D_2O$ | 39 | 11 | 50[b] | 6d |
| H | H | H | H | H | $CH_3$ | $NH_3Cl$ | $D_2O$ | 45 | 5 | 50[b] | 6d |
| $OCH_3$ | H | H | H | H | $CH_3$ | $NH_2$ | $CDCl_3$ | 24 | 12 | 64[e] | 6e |
| H | $OCH_3$ | H | H | H | $CH_3$ | $NH_2$ | $CDCl_3$ | 25 | 12 | 63[e] | 6e |
| H | H | $OCH_3$ | H | H | $CH_3$ | $NH_2$ | $CHCl_3$ | 24 | 12 | 64[e] | 6e |
| H | H | $OCH_3$ | H | H | $CH_3$ | $NH_3Cl$ | $D_2O$ | 47 | 6 | 47[d] | 6c |
| $OCH_3$ | $OCH_3$ | H | H | H | $CH_3$ | $NH_2$ | $CDCl_3$ | 21 | 12 | 67[e] | 6e |
| $OCH_3$ | $OCH_3$ | H | H | H | $CH_3$ | $NH_3Cl$ | $CDCl_3$ | 32 | 0 | 68[e] | 6e |
| $OCH_3$ | H | $OCH_3$ | H | H | $CH_3$ | $NH_2$ | $CDCl_3$ | 26 | 12 | 62[e] | 6e |
| $OCH_3$ | H | $OCH_3$ | H | H | $CH_3$ | $NH_3Cl$ | $CDCl_3$ | 33.5 | 0 | 66.5[e] | 6e |
| $OCH_3$ | H | H | $OCH_3$ | H | $CH_3$ | $NH_2$ | $CDCl_3$ | 24 | 12 | 64[e] | 6e |
| $OCH_3$ | H | H | $OCH_3$ | H | $CH_3$ | $NH_3Cl$ | $CDCl_3$ | 35 | 0 | 65[e] | 6e |
| H | H | $OCH_3$ | $OCH_3$ | H | $CH_3$ | $NH_2$ | $CDCl_3$ | 25 | 11 | 64[e] | 6e |
| H | H | $OCH_3$ | $OCH_3$ | H | $CH_3$ | $NH_3Cl$ | $CDCl_3$ | 23 | 1 | 76[e] | 6e |
| H | $OCH_3$ | H | $OCH_3$ | H | $CH_3$ | $NH_2$ | $CDCl_3$ | 23 | 12 | 65[e] | 6e |
| H | $OCH_3$ | H | $OCH_3$ | H | $CH_3$ | $NH_3Cl$ | $CDCl_3$ | 25 | 0 | 75[e] | 6e |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | H | H | $CH_3$ | $N(CH_3)_2HCl$ | $D_2O$ | 39 | 6 | 55[e] | 6d |
| $OCH_3$ | H | H | H | H | $CH_3$ | $N(CH_3)_2HCl$ | $D_2O$ | 36 | 17 | 47[e] | 6d |

Rotamer populations computed from Karplus equation using the following vicinal coupling constants:

[a] $J_T$=13.1, $J_G$=3.6 Hz.

[b] $J_T$=13.0, $J_G$=2.0 Hz.

[c] $J_T$=11.0, $J_G$=3.5 Hz.

[d] $J_T$=13.11, $J_G$=$J_G'$=3.63 Hz.

[e] $J_T$=12.0, $J_G$=$J_G'$=2.0 Hz.

gauche forms.

However, substitution of electron donating groups such as hydroxys or methoxys on the aromatic ring clearly results in an increase in the population of the gauche rotamers ($P_T$=42-43%, $P_G$=57-58%). This conformational shift from trans to gauche forms was correctly predicted by the gas phase PCILO calculations (although the presence of the solvent clearly attenuates the intermolecular stabilization).

The equivalence of the gauche rotamers in the phenethylamines is destroyed by the introduction of an α-methyl group as occurs in amphetamine. In these cases, the gauche orientation in which the phenyl group is flanked by the adjacent α-$CH_3$ and $NH_X$ groups is decidedly less favorable than its $60^o$ counterpart due to greater steric repulsions. None the less, in both the protonated and unprotonated forms of amphetamine (in $D_2O$), the sum of the populations of gauche rotamers are equivalent to the trans. By comparison, substitution of methoxy groups at various positions on the aromatic ring in the unprotonated species results in slight variation of the rotameric proportions ($P_{G_{tot}}$=33-36%, $P_T$=62-67%) in $CDCl_3$. In contrast, in the protonated species compound bearing ortho methoxy groups have uniformly higher combined gauche populations ($P_{G_{tot.}}$=32-35%) than those without such groups ($P_{G_{tot.}}$ = 24-25%). Once again, these observations are qualitatively consistent with the PCILO predictions but the gauche stabilization found in the gas phase are considerably reduced by inter molecular attractions of the ammonium group with solvent

molecules rather than intramolecular interaction with the ortho methoxy group. Consistent with this interpretation are the reported findings of Neville et al.[6d] that addition of increasing amounts of DMSO-$d_6$ to solutions of amphetamine HCl in $D_2O$ resulted in a uniform increase in the trans rotomer at the expense of the gauche conformers.

# CONFORMATION OF PHENYLALKYLAMINES IN THE CRYSTALLINE STATE

Recent progress in computers and methodology have allowed tremendous advances in the field of X-ray crystallography. Consequently, an extensive number of X-ray structure determinations relevant to the constitution of molecules in the crystalline state are now available. With regard to psychotomimetics, the structures of 11 CNS active phenylalkylamines [7a-k] and 10 tryptamines [8a-h] have been reported. In the present section, only the conformation of the phenylalkylamines will be considered in detail and these data have been condensed into Table 15.

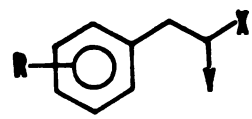
Phenethylamine HCl typifies the orientation of most reported phenylalkylamines in that the side chain exists in an extended configuration with the $T_1$ angles ranging from 58-88° and the $T_2$ angles varying from 171-189°. An interesting exception is the structure of mescaline HBr, which unlike mescaline HCl, exists in a folded gauche conformation. By comparison, amphetamines exist in the trans orientation ($T_1$= 75-78°, $T_2$=172-174°) except when ortho methoxy substituents are present. Two such cases are known and in each, the experimental conformation is gauche regardless of whether the amine is protonated or not.

It is difficult to formulate any uniform conclusions concerning the variety of conformations exhibited by these derivatives since many forces are present in crystals which are absent in the gas phase and attenuated in solution. For example, inter- and intra-molecular hydrogen bonds as well as ionic

(dipole-dipole) interactions comprise the major attractive forces in crystals containing groups capable of this behavior. Additionally, dispersion and induced multipole forces provide weaker stabilization, conversely, van der Waal repulsions limit the molecular density[9a]. In flexible molecules, the crystalline conformations tend to be those in which the repulsive forces are minimized while the attractive forces are maximized. Hence, it appears quite difficult to compare crystalline conformations to those in gas or solution state. Consider, for example, one apparent anomaly between the PCILO conformations of ortho-hydroxy- and methoxy-substituted phenethylammoniums and the crystal conformation of the two derivatives containing these groups. While both groups provide an almost identical gauche stabilization in the gas phase, in the crystal, only the ortho methoxy derivative exist in a gauche orientation.

The answer to this apparent inconsistency is revealed by scrutiny of the molecules in the unit cell. In 6-hydroxy dopamine[7d], the ammonium group in one molecule is hydrogen bonded to 4,5-dihydroxy groups in its nearest neighbor, and the 2-hydroxy group is similarly hydrogen bonded to the chlorine counterion. Clearly, the orientation of the side chain in this instance is governed by this recurrent hydrogen bonding network which is obviously a more stable configuration than that obtained by a single intramolecular hydrogen bond, and hence the trans orientation[7d]. Such a hydrogen bonding pattern is not possible in 2,4,5-trimethoxy amphetamine.

Table 15. Conformation of Several Derivatives of Phenalkylamines Found in the Crystalline State by X-Ray Structure Analysis.



| Aromatic Sub. Pattern | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | X | Y | $T_1{}^{o}$ [a] | $T_2{}^{o}$ | Ref. |
| H | H | H | H | H | H | $NH_3Cl$ | 70 | 171 | 7a |
| H | H | OH | OH | H | H | $NH_3Cl$ | 80 | 174 | 7b |
| H | OH | OH | OH | H | H | $NH_3Cl$ | 58 | 189 | 7c |
| OH | H | OH | OH | H | H | $NH_3Cl$ | 85 | 175 | 7d |
| H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | $NH_3Cl$ | 88(83) | 176 | 7e |
| H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | $NH_3Br$ | 88(80) | -55 | 7f |
| H | H | H | H | H | $CH_3$ | $NH_3SO_4^-$ | 75 | 172 | 7g |
| H | H | H | H | H | $CH_3$ | $NH_3PO_4^-$ | -78 | 174 | 7h |
| $OCH_3$ | H | $OCH_3$ | $OCH_3$ | H | $CH_3$ | $NH_3Cl$ | 70 | 50 | 7i |
| $OCH_3$ | H | $C_2H_5$ | $OCH_3$ | H | $CH_3$ | $NH_2$ | -75 | -61 | 7j |
| | | | | | | | 111 | ±139 | 7k |

[a] $T_1$ angles are taken as (+) if the side chain is directed towards an ortho substituent and (-) if not.

Instead, it appears that the ammonium group in this compound undergoes hydrogen bonding to both the ortho-methoxy group and the 5-methoxy group in its nearest neighbor, and hence, in this case, an unusual gauche conformation is achieved[7i]. Alternately, the gauche orientation in 1-(2,5-dimethoxy-4-ethylphenyl)-2-aminopropane(O)(DOET) is not dissimilar to the preferred conformation of ortho-methoxy phenethylamine(O) predicted by the PCILO calculations and in DOET, the amine group shows no evidence of hydrogen bonding.

In the much simpler cases of phenethylammonium or amphetamine(+), the orientation of the ammonium/chloride ions is very simlar to that found in $NH_4Cl$ where each nitrogen has eight chloride ions surrounding it at corners of a cube with four hydrogens randomized along alternate N---Cl diagonals.[9b] Since this configuration requires steric freedom about the ammonium group, a trans conformation is clearly favorable. However, the shift from trans to gauche orientations in mescaline, depending on whether the HCl or HBr salt is studied, remains a strange anomaly without explanation.

# CONFORMATION OF AROMATIC SUBSTITUENT GROUPS

# INTRODUCTION

The conformation of substituents, usually various combinations of methoxy groups located on the aromatic ring of amphetamine derivatives have received almost vanishing attention in the chemical literature. And yet, the importance of this aspect of molecular structure has recently become apparent due to the emergence of inconsistencies found in studies of the ionization potentials and partition coefficients of these compounds. For these, and other reasons related to attempts to formulate SAR, a detailed study was made of the conformational profiles of substituents in the gas phase using the CNDO/2 and "ab initio" molecular orbital technique. Information concerning the conformation in solution was obtained from studies of partition coefficients, dipole moments, dielectric relaxation times, NMR and UV spectral data. And finally, the preferred conformation in the crystalline state of a variety of aromatic groups has been determined from compilations of X-ray structural data on derivatives bearing these substituents.

# MOLECULAR ORBITAL CALCULATION OF THE PREFERRED CONFORMATION OF AROMATIC SUBSTITUENT GROUPS

CNDO/2 calculations of the rotational energy barriers of ortho-, meta-, and para-methoxytoluene are presented in Figures 64-66. As can be seen, in these simple molecules, the planar orientation is found to be minimum energy conformation in each case and the energy differences between the planar and perpendicular conformations were $\Delta E_{para}$=0.37, $\Delta E_{meta}$=0.59, and $\Delta E_{ortho}$=0.40 kcal/mol. This planar preference is generally thought to arise from favorable delocalization of an oxygen lone pair into the aromatic ring which is possible only in the planar forms. The differences between the $0^{o}$ and $90^{o}$ conformations of the ortho-, meta-, and para-methoxys can be attributed to the presence of the $ArCH_3$ group which by itself is a weak electron donor and hence, slightly diminishes electron donation by methoxy groups located at positions of conjugation, and thereby reduces the stability of the planar conformation in the ortho and para cases. Closer scrutiny of Figures 64-66 shows that the barriers to rotation are considerably higher than the $E_{90^o} - E_{0^o}$ differences since the height of the barrier is steepest, in each case, at the $30^{o}$ conformation. This arises from the unfavorable steric repulsions between the ortho-aromatic H and the methoxy-methyl H (which are bifurcated in the planar conformation) that occurs in this conformation. While the $0\text{-}90^{o}$ and $180\text{-}90^{o}$ regions of the rotational profiles are the same for the meta- and para-methoxytoluenes, the presence of the

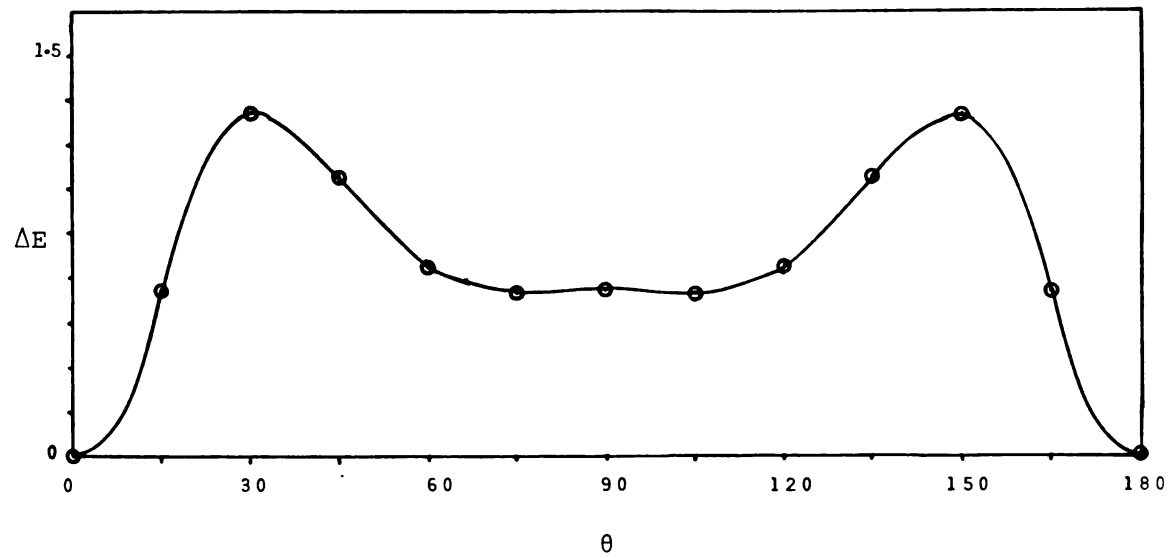



FIGURE 64. CNDO/2 Calculated Rotational Barrier in Para-methoxytoluene in kcal/mol.

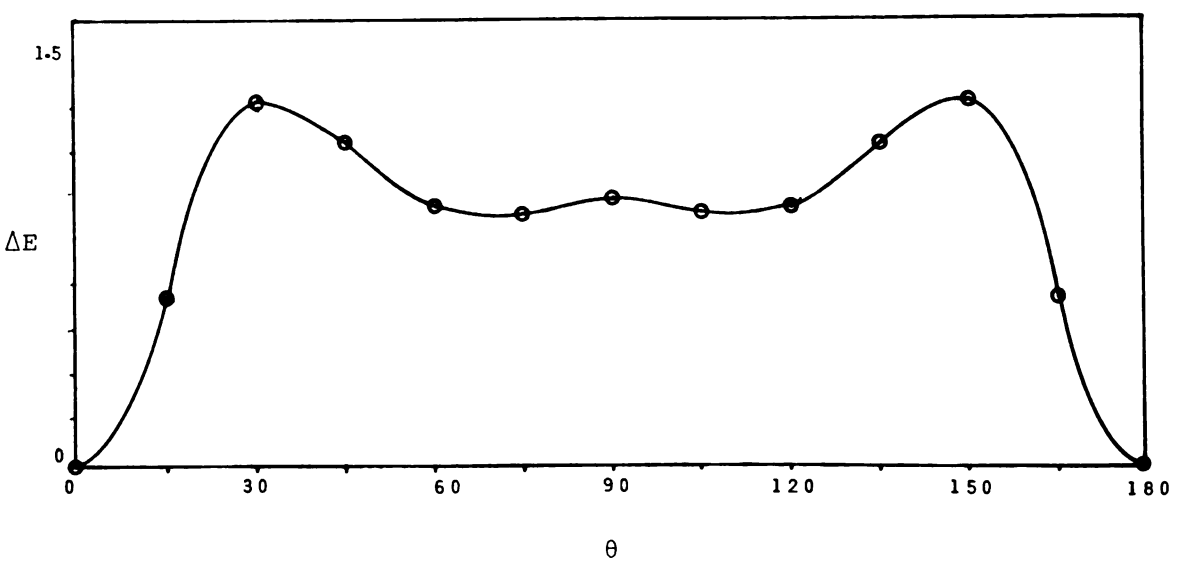



FIGURE 65. CNDO/2 Calculated Rotational Barrier in Meta-methoxytoluene in kcal/mol.

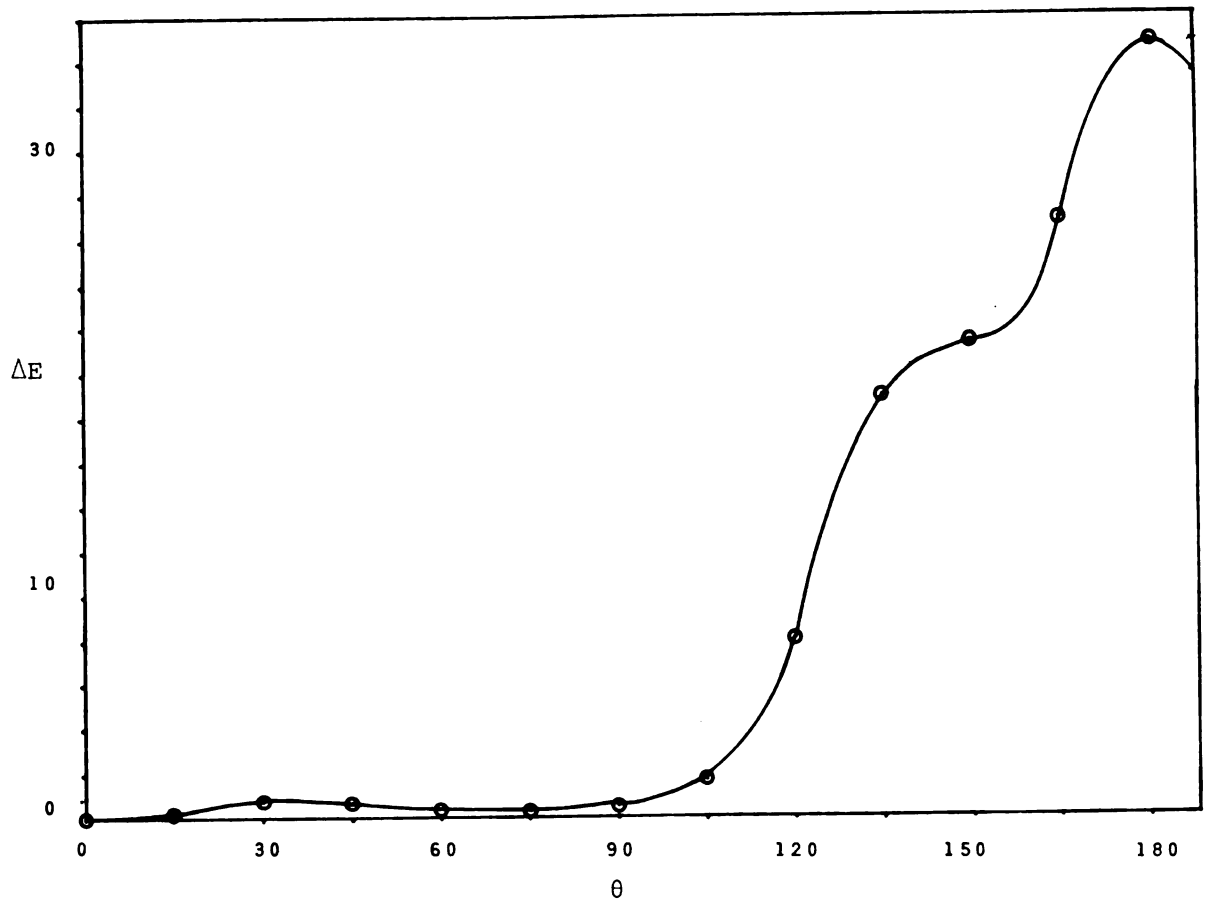



FIGURE 66. CNDO/2 Calculated Rotational Barrier in Ortho-methoxytoluene in kcal/mol.

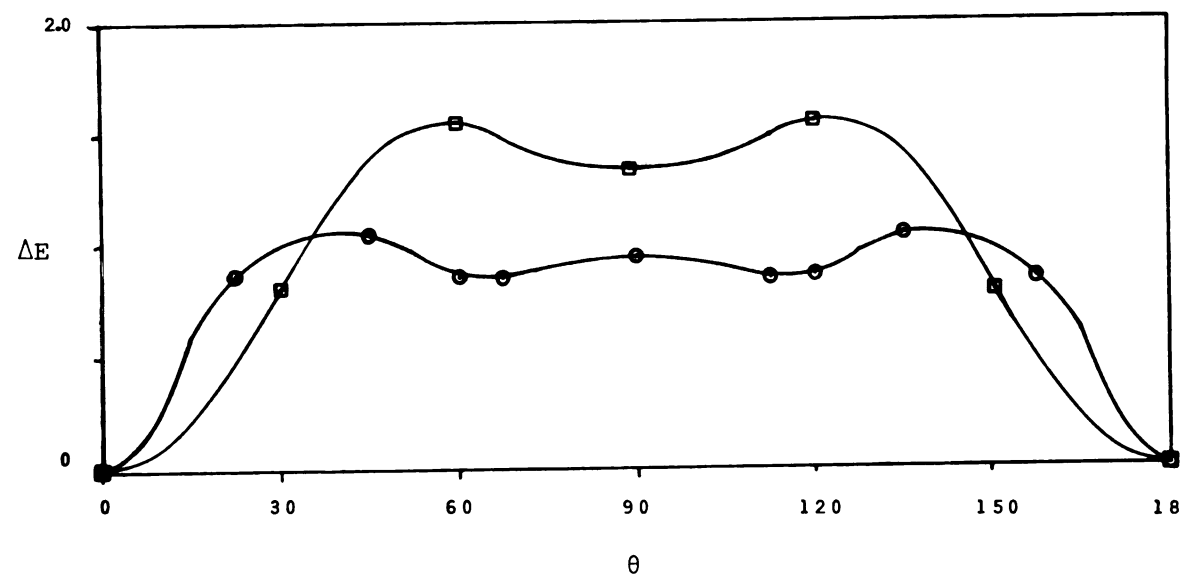



FIGURE 67. "Ab Initio" (STO-3G) Calculated Rotational Barriers in Anisole in kcal/mol. (Standard Geometry Calculation is Represented by Circles; Optimized Geometries by Squares).

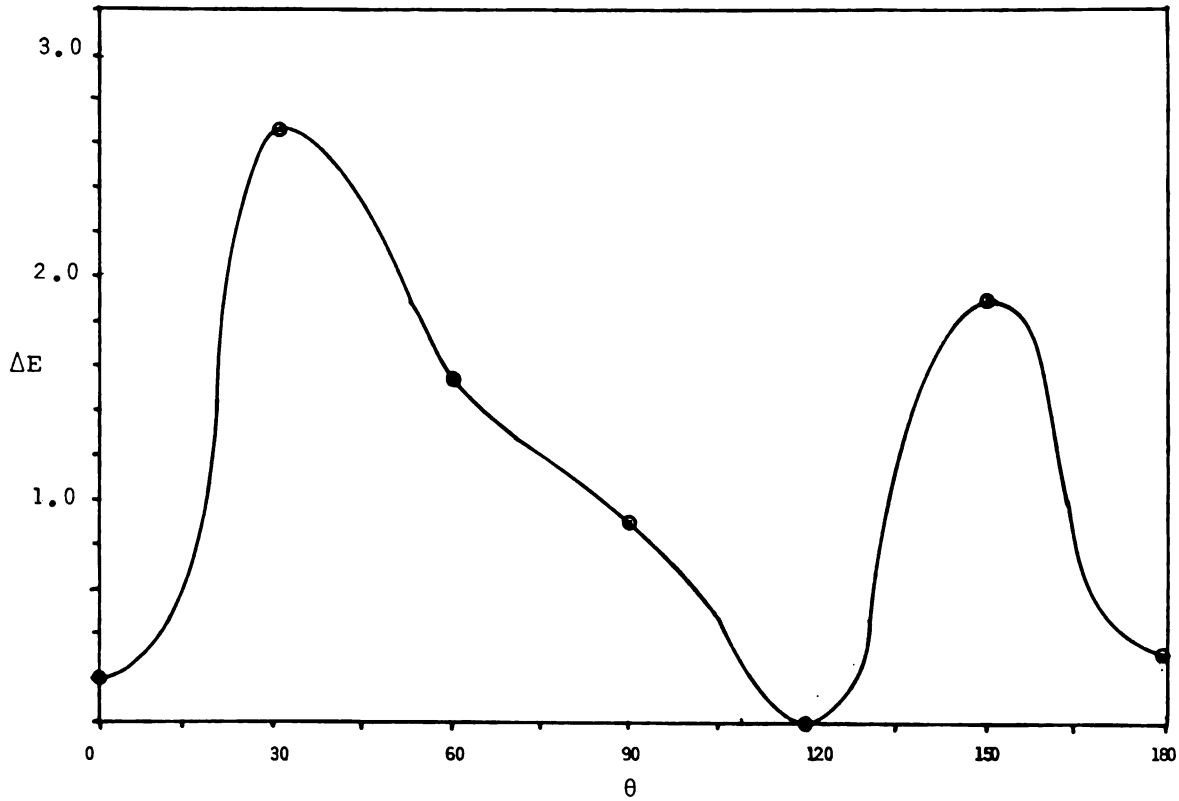



FIGURE 68. CNDO/2 Calculated Rotational Barrier in 3,4-Dimethoxytoluene in kcal/mol.

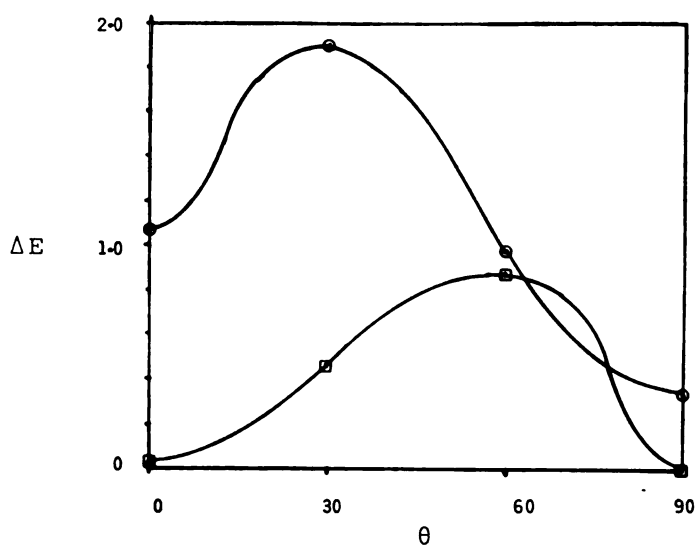



FIGURE 69. "Ab Initio" (STO-3G) Calculated Rotational Barriers in Ortho-dimethoxybenzene in kcal/mol. (Standard Geometry Calculation is Represented by Circles; Optimized Geometries by Squares.

nearby methyl group presents considerable steric repulsions in ortho-methoxytoluene and thereby greatly raises the 90-180° barrier.

"Ab initio" calculation of the rotational energy barrier in anisole (methoxybenzene) using standard and partially optimized geometries are presented in Figure 67 and Table 16. The standard geometry calculations predict the $E_{90°} - E_{0°}$ energy difference to be 0.94 kcal/mol., and the shape of this energy barrier is similar to those of the methoxytoluenes discussed previously. However, interpretation of the far-infrared spectra of anisole in the gas phase indicates that the planar conformation was preferred over the perpendicular by about 3.6 kcal/mol.[10a]. This value, which is subject to some experimental uncertainty, seems too high compared to the barrier in phenol (3.3[10b] to 3.6[10c] kcal/mol.). Furthermore, results similar to ours have been reported by Hofer[10d] from MINDO/3 calculations ($E_{90°} - E_{0°}$ =4.2 kcal/mol.) and by Hehre et al.[10e] from STO-3G calculations ($E_{90°} - E_{0°}$ =5.5 kcal/mol.). From this data, it appears that the CNDO/2 method definitely underestimates the energy barrier in anisole, as does the STO-3G method, but to a smaller extent.[10f] In contrast, calculations carried out on anisole using optimized $r_{O-C(aromatic)}$, C-C-O angle and C-O-$CH_3$ angle (Figure 67) yield very different results. As can be seen, the rotational barrier in the optimized geometry (1.5 kcal/mole) is greater than the corresponding barrier in the standard geometry. Both, however, show four local minima, and, the planar

conformations ($0^{\circ}$ and $180^{\circ}$) are preferred over the perpendicular ($90^{\circ}$ and $270^{\circ}$) orientations.[10e] Hehre et al. have shown that optimization on only the C-O-$CH_3$ angle caused the planar conformation of anisole to remain 0.06 kcal/mol. more stable than the perpendicular. In our studies, the largest stabilization due to geometry optimization occurred in the C-C-O bond angle (optimum=$125.5^{\circ}$, standard=$120^{\circ}$) of planar anisole; the optimum angle for the perpendicular conformation was $120^{\circ}$. Comparison of the conformational perferences of phenol, ethylbenzene, and anisole yields insight into the origins of the rotational barrier in methoxybenzenes. In phenol, the planar conformation is preferred owing to favorable conjugation between the p-type lone-pair electrons and the aromatic ring.[10g] Theoretical and experimental data indicate that the perpendicular conformation of ethylbenzene is preferred over the planar by 2.2[10e] and 1.3[10h] kcal/mol, respectively. Undoubtedly, the perpendicular preference in ethylbenzene results from unfavorable steric interactions between the methyl group and the ortho-hydrogens in the planar arrangement. The conformation of anisole is a compromise between attractive (conjugative) and repulsive (steric) influences, but, since both theoretical and experimental evidence show that the planar conformation is preferred, clearly the conjugative interactions dominate (even though the C-O bond length in anisole is shorter than the corresponding C-C bond in ethylbenzene, and consequently repulsions in methoxybenzenes would be expected to be larger

than in ethylbenzene for the planar conformations). A simple calculation employing empirical non-bonded potential functions[10i] indicates that steric repulsion in the planar orientation of anisole arises almost exclusively from $CH_3$, ortho-hydroxy interactions, which are 2.2 kcal/mol. higher in the planar conformation than the perpendicular. Consistent with this calculation is the observation that the energetic preferences for planarity in the methoxybenzenes are 2.7-3.8 kcal/mol. less than in the analogous hydroxybenzenes. Furthermore, scrutiny of the optimum geometries illustrates how anisole relieves steric repulsions in the planar conformation: The internal C-C-O angle increases from 120° (optimum in the perpendicular conformation) to 125.5°. This distortion increases the distance between the methyl hydrogens and ortho hydrogens, thereby decreasing the repulsion. Similar angle distortions are found in the X-ray structures of the planar and nonplanar methoxybenzenes (see conformation of aromatic substituents in the crystalline state).

In more highly substituted compounds, the "ab initio" calculations (Table 17) show that addition of a methoxy group at the meta position of anisole (resulting in meta-dimethoxybenzene) provides more stabilization than substitution of a methoxy group on benzene, as judged by the isodesmic comparison, and the barrier to rotation of the methoxy group in meta-dimethoxybenzene is correspondingly higher. By contrast, the barrier in para-dimethoxybenzene

is almost zero, while ortho-dimethoxybenzene has lower rotational barriers and a preferred nonplanar conformation. These trends are consistent with the smaller stabilizing effect of the second methoxy group than the first in para-dimethoxybenzene and the even smaller effect in ortho-dimethoxybenzene. The parallel between the relatively high barriers to rotation and large stabilization energy was noted earlier by Pople and co-workers [9c] in their study of the rotational barriers in para- substituted phenols. These calculations indicate a strong preference for rotation of one or both methoxys out of planarity as long as the methyl groups in ortho-dimethoxybenzene are rotated away from each other.

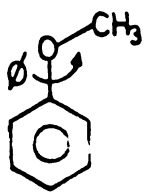
The calculations for the hydroxybenzenes (Table 18) show entirely analogous trends. That is, the barrier to rotation is highest for meta-dihydroxybenzene (resorcinol), and decreases along the series phenol, para-dihydroxybenzene (hydroquinone), ortho-dihydroxybenzene (pyrocatechol). As noted previously by Pople, the calculated barrier for phenol (5.16 or 4.7 kcal/mol. calculated here) is higher than the experimental values (3.3 to 3.6 kcal/mol.), but the change in rotational barrier upon para substitution is predicted quite accurately (±0.08 kcal/mol.) except for para-hydroxybenzaldehyde, where the increase in the C-O rotational barrier is underestimated by 0.4 kcal/mol. If the changes in the barriers calculated here are accurate, the $0^{o}$, $90^{o}$ conformation of ortho-dihydroxybenzene is only 1.2-1.5 kcal/mol. higher in energy than the planar conformation.

Table 16. STO-3G Energies (kcal/mol) and Dipole Moments (D) for Anisole and *o*-DMB Using Partially Optimized Geometries[a]

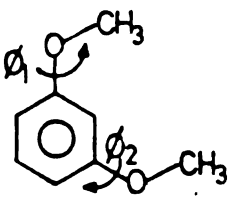
| anisole | | | *o*-dimethoxybenzene | | | |
|---|---|---|---|---|---|---|
| $\phi$, deg | $E_{rel}$ | $\mu$ | $\phi_1$, deg | $\phi_2$, deg | $E_{rel}$ | $\mu$ |
| 0 | 0[b] | 1.16 | 0 | 0 | 0.03[c] | 0.96 |
| 30 | 0.70 | 1.21 | 0 | 30 | 0.46 | 1.29 |
| 60 | 1.55 | 1.28 | 0 | 60 | 0.88 | 1.72 |
| 90 | 1.34 | 1.35 | 0 | 90 | 0 | 2.06 |
| | | | 90 | 90 | 0.22 | 0.43 |

[a]The values of $r_{o-c(aromatic)}$, C-C-O, and C-O-$CH_3$ angles were optimized for anisole at $\phi$=0 and 90°. For $\phi$=0°, these values were 1.401 Å, 125.5°, and 117.28°, respectively; at $\phi$=90°, these values were 1.403 Å, 120°, and 110.23°. These values were used for as well. For the $\phi$=30 and 60° geometries of anisole and *o*-DMB, the bond lengths and angles were linearly interpolated from the 0 and 90° geometries and the C-O-C-H dihedral angles were optimized to minimize $CH_3$-*o*-H repulsions. These angles were found to be $\phi'$=43, 163 and 283° for $\phi$=30° and $\phi'$=58, 178 and 298° for $\phi$=60°. [b]Total energy is -340.3089 au. [c]Total energy is -452.7224 au.

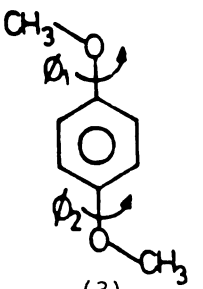
Table 17. STO-3G Energies (kcal/mol) for Methoxybenzenes in Standard Geometries[a]



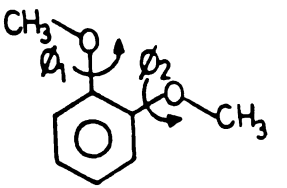
(1)



(2)



(3)



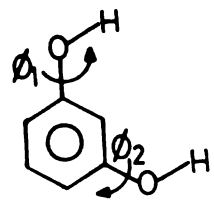
(4)

| anisole(1) | | *m*-dimethoxybenzene(2) | | | *p*-dimethoxybenzene(3) | | | *o*-dimethoxybenzene(4) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $E$(stab)[b] | 10.0(5.5) | | 11.0 | | | 8.5 | | | 6.7 | |
| $\phi$, deg | $E_{rel}$ | $\phi_1$, deg | $\phi_2$, deg | $E_{rel}$[c] | $\phi_1$, deg | $\phi_2$, deg | $E_{rel}$[c] | $\phi_1$, deg | $\phi_2$, deg | $E_{rel}$ |
| 0 | 0[d] | 0 | 0 | 0[e] | 0 | 0 | 0[f] | 0 | 0 | 1.07[g] |
| 22.5 | 0.87 | 90 | 0 | 2.25 | 90 | 0 | 0.16 | 30 | 0 | 1.90 |
| 45 | 1.05 | | | | | | | 60 | 0 | 0.98 |
| 60 | 0.86 | | | | | | | 90 | 0 | 0.34 |
| 67.5 | 0.85 | | | | | | | 180 | 0 | 10.14 |
| 90 | 0.94 | | | | | | | 60 | 60 | 0.96 |
| | | | | | | | | 90 | 90 | 0 |
| | | | | | | | | 90 | 270 | 5.64 |

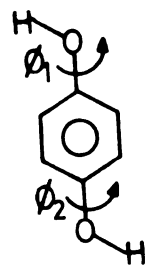
[a]See footnote a above. [b]Defined as the energy of the isodesmic reaction: ArH+MeOMe → ArOMe+MeH. Methane and dimethyl ether energies are from ref.10e. [c]We expect that for *m*- and *p*-dimethoxy isomers the energy of $\phi_1=0^o$, $\phi_2=0^o$ will be approximately identical with that of $\phi_1=0^o$, $\phi_2=180^o$; i.e., the methyls are too far apart to interact significantly. [d]Total energy is -340.3042 au. [e]Total energy is -452.7192 au. [f]Total energy is -452.7164 au. [g]Total energy is -452.7124 au.

Table 18. STO-3G Energies (kcal/mol) for Hydroxybenzenes in Standard Geometries[a]

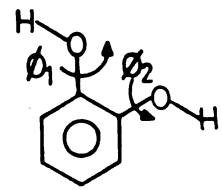
(1)



(2)



(3)



(4)

| phenol(1) | | *m*-dihydroxybenzene(2) | | | *p*-dihydroxybenzene(3) | | | *o*-dihydroxybenzene(4) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $E$(stab)[b] 8.8(12.4) | | | 9.3 | | | 7.4 | | | 4.6 | |
| $\phi$, deg | $E_{rel}$ | $\phi_1$, deg | $\phi_2$, deg | $E_{rel}$ | $\phi_1$, deg | $\phi_2$, deg | $E_{rel}$ | $\phi_1$, deg | $\phi_2$, deg | $E_{rel}$ |
| 0 | 0[c] | 0 | 0 | 0[d] | 0 | 0 | 0[e] | 0 | 0 | 0[f] |
| 90 | 4.71(5.16) | 90 | 0 | 4.94 | 90 | 0 | 3.81(4.21) | 90 | 0 | 2.60 |

[a]Drawings show geometries for $\phi$=0. [b]Defined as the energy of the isodesmic reaction: ArH+MeOH → ArOH+MeH. Methane and methanol energies are from ref.10e. [c]Total energy is -301.7237 au. [d]Total Energy is -375.5573 au. [e]Total energy is -375.5543 au. [f]Total energy is -375.5499 au.

When ortho-dimethoxybenzene calculations were carried out using the optimum anisole geometries for the methoxy group, the planar conformation is stabilized so that the nonplanar conformation ($0^{o}$, $90^{o}$), is only 0.03 kcal/mol. more stable than the planar conformation. Nevertheless, as compared to anisole, the rotational barrier in ortho-dimethoxybenzene is anomalously low. For example, in the standard geometry, the $90^{o}$ conformation of anisole is 0.94 kcal/mol. above the planar. If the rotational barriers were the same in ortho-dimethoxybenzene, the $90^{o}$, $90^{o}$ conformation should be 1.9 kcal/mol. above the $0^{o}$, $0^{o}$, whereas the calculations suggest that the $90^{o}$, $90^{o}$ conformation is actually 1.1 kcal/mol. more stable than the planar. Using optimized geometries and assuming no interaction between the methoxy groups, the anisole barrier implies that the $90^{o}$, $90^{o}$ conformation should be 2.7 kcal/mol. less stable than the $0^{o}$, $0^{o}$ orientation; the calculated difference is only 0.2 kcal/mol. Hence, using either geometry, the $90^{o}$, $90^{o}$ conformation of ortho-dimethoxybenzene is 2.5-3.0 kcal/mol. more stable relative to the planar conformation than expected from additivity of the barriers in anisole.

While the calculated difference in the energies of the nonplanar and planar conformations in ortho-dimethoxybenzene in the partially optimized geometry is small, the predominant conformation in the gas phase is almost certainly nonplanar for the following reasons: (1) Conformational degeneracy predicts that the nonplanar forms would be favored four to

one over the unique planar conformation, assuming that the energy of both were equal. (2) The experimental gas-phase barrier to rotation in phenol is 3.3-3.6 kcal/mol., whereas the calculated value is 4.7 kcal/mol. This suggests that at this level of theory (STO-3G) the stabilities of the planar conformations are slightly overestimated with respect to the nonplanar structures. (3) There is a strong experimental evidence, detailed in the remaining chapters, which indicates that in both gas phase and in solution the conformation of ortho-dimethoxybenzene is predominantly nonplanar.

Complete rotational maps for a variety of methoxy- and hydroxy-toluenes (Figures 60 - 63 ) have been obtained from CNDO/2 computations using standard geometries (see Experimental Section for details). Scrutiny of the energy profile of 2,3-dimethoxytoluene (Figure 60) shows that the most stable conformation is that in which the meta-methoxy group is rotated $180^{o}$ away from the ortho-methoxy substituent which itself assumes an angle of $120^{0}$ with respect to the toluene methyl group. Interestingly, the entirely planar orientation ($T_1$=$180^{o}$, $T_2$=$180^{o}$) is also of low energy (within 1 kcal/mol. of the global minimum). In this conformation, the ortho-methoxy-methyl is well within the van der Waals radius of the meta-methoxy-oxygen and hence it is not immediately obvious why an unusual conformation of this kind would have such stability. Rather than revealing some subtle information inaccesible to intuition, it appears that this prediction is an artifact of the CNDO/2 method's rather ineffectual way of

dealing with non-bonded interactions[10f]. Indeed, erroneous results, similar to ours, have been reported by Tylli[11o], who unlike the author, chose to believe in the reality of the result. However, the "ab initio" calculations (Table 17) clearly indicate that this planar conformation is certainly much higher in energy than the planar-nonplanar orientation.

Comparison of the rotational map of 4,5-dimethoxytoluene with that of 2,3-isomer reveals some similarity between the two, in that, of the three global minima, two consist of the planar-nonplanar orientations of the methoxy groups. Unlike the previous case, both methoxys are allowed access to this conformation since both are flanked by ortho-hydrogens. Further, the near planar orientation, which arises when both methoxy-methyls are pointed away from one another also emerges as one of the global minima. Hence, the main features of the "ab initio" results are also present in the CNDO/2 calculations.

In the 4-hydroxy-5-methoxytoluene, the minimum energy orientation results from the weak hydrogen bonding conformation in which the 4-hydroxy-H is oriented toward the 5-methoxy group whose methyl is directed away. One would expect that in the planar orientation in which the phenolic-H and the methoxy-$CH_3$ were directed away from one another would be more stable than in the 4,5-dimethoxy case since phenol prefers planarity more than does anisole. While this is undoubtedly the case, the energy of this conformation is, in fact, greater for the hydroxy-methoxy case due to the

formation of the intra-molecular hydrogen bond that occurs in the other planar orientation. In other words, the hydrogen bond strength, based on these simple considerations should be about 1 kcal/mol. which is consistent with the experimental results.

# CONFORMATION OF AROMATIC SUBSTITUENT GROUPS IN THE SOLUTION PHASE

Analysis of the vibrational spectra of liquid anisole suggests planarity of the methoxy group and a barrier to rotation about the aryl C-O bond of 6 kcal/mol.[11a] Kerr constant[11b] measurements performed on dilute solutions of anisole indicate a nonplanar minimum energy conformation in which $\phi=20^{o}$. The rotational barrier in the neat liquid is significantly higher than the gas-phase value, but the Kerr constant measurements are in accord with our calculations if they are interpreted to result from a mixture of planar and perpendicular conformations of anisole with the latter 0.9 kcal/mol. higher in energy.

In solution, evidence for the presence of nonplanar methoxy groups in ortho-dimethoxybenzene is found in the measurement of the partition coefficient, dipole moment, and dielectric relaxation time.

The partition coefficient (log P), a distribution constant defined by the partitioning of a compound between octanol and water, is usually well represented as the sum of group contributions ($\pi$ values)[11c] of the substituent parts of a molecule. However, dramatic deviations from this additivity rule occur when strong interactions between neighboring groups cause conformational or electronic pertubations which alter the solvation of the substituents. For example, Leo et al.[11c] have noted that the measured log P of 1,2,3-trimethoxybenzene (1.53) is anomalously low in comparison

with the expected additive value of 2.07. Furthermore, the $\pi$ group value for the central nonplanar methoxy, derived by subtracting the partition coefficients of meta-dimethoxybenzene from trimethoxybenzene (1.53-2.09=-0.56), resembles the $\pi$ value of an aliphatic methoxy (-0.47) more than an aromatic methoxy substituent (-0.02), as does the hybridization of the oxygen lone pairs. A similar effect occurs in ortho-dimethoxybenzene and in 3,4-dimethoxyamphetamine; the $\pi$ values of the second methoxy in these compounds are -0.85 and -0.77 respectively. The same trend was found in several other ortho-disubstituted aromatics such as methoxyethoxy and methoxythiomethoxy, where, in the absence of steric hindrance, the derived $\pi$ value of the methoxy group is consistently lower than expected, implicating the existence of nonplanar conformations of the methoxy substituents in these compounds.[11d] In contrast, the unusually high $\pi$ value of the 1,3-dioxo group (-0.02 as compared with the expected additivity value of -0.50) supports the conclusion that in solution the predominant conformation of ortho-dimethoxybenzene and derivatives is nonplanar.

Naggy and Hencsei[11e] have reported that the experimentally measured dipole moments[11f] of anisole (1.25 D), para-dimethoxybenzene (1.70 D), and meta-dimethoxybenzene (1.59 D) can be accurately calculated by assuming free rotation about the Ar-O-$CH_3$ bond and averaging the conformational moments. in ortho-dimethoxybenzene, however, the experimental dipole moment (1.31 D) is dramatically different from the calculated

moment of 2.09 D. These results have been interpreted to imply that free rotation ($0^{o}$ to $180^{o}$) does not occur in ortho-dimethoxybenzene and that the conformational moments must be weighted by the energies of the respective conformers.[11g] Consistent with these considerations is the finding by DiBello and others[11h] that the dipole moment of ortho-dimethoxybenzene, unlike anisole, meta-dimethoxybenzene, or para-dimethoxybenzene, is temperature dependent in a number of solvents. If the three lowest energy conformations of ortho-dimethoxybenzene (with the optimum geometry) are weighted by their energies and degeneracies, our calculations predict a dipole moment of 1.54 D at $0^{o}$C. Attempts, using our calculated energies and dipole moments, to reproduce the temperature dependence reported by DiBello were unsuccessful, probably owing to an incomplete knowledge of the conformational surface. Still, the increase in dipole moment with increasing temperature may result from population of high-energy conformations such as $90^{o}$, $270^{o}$ which have large dipole moments (2.60 D).

Dielectric relaxation of methoxybenzenes, as measured in solution by microwave dispersion, is dependent upon both internal rotations and molecular motions. Application of these methods to a series of methyl- and methoxy-substituted aromatics has been made by Roberti and Smith and others[11i] with the consistent finding that the relaxation times of the methoxy compounds are slightly shorter than those of the corresponding methyl analogues; however, in

ortho-dimethoxybenzene, the much lower relaxation time indicates that the internal methoxy rotations contribute significantly to the overall molecular relaxation processes. These observations are consistent with the predictions of a low rotational barrier in ortho-dimethoxybenzene reported from microwave studies conducted by Klages and Zentek[11j] as compared to other methoxybenzenes.

NMR measurements have also shown anomalous results for ortho-dimethoxybenzene. Martin and Dailey have shown that the chemical shifts of protons ortho to the methoxy substituents in ortho-dimethoxybenzene are not well expressed as a sum of the group shielding constants.[11k] Further, a study of methoxybenzenes showed that in ortho-dimethoxybenzene the long-range spin-spin coupling between the $OCH_3$ and ortho protons is much smaller than usual for ortho-substituted anisoles.[111] Similarly, Dhami and Stothers[11m] have studied the $^{13}C$ chemical shifts of a series of ortho-substituted anisoles and concluded that for ortho-dimethoxybenzene the magnitude of the chemical shift was poorly expressed as the sum of substitutent contributions. These data are consistent with the presence of nonplanar methoxy substituents and low rotational barriers in ortho-dimethoxybenzene.

Additionally, Zweig[11n] has found that the transition energies for charge-transfer complexes of many ortho-dimethoxybenzenes are at a higher energy than expected on the basis of Hückel calculations and charge-transfer transition energies of other methoxybenzenes.[11e] Naggy and Hencsei

have also found that PPP calculations of the UV transition energies for planar arrangements of anisole, meta-dimethoxybenezene, and para-dimethoxybenzene were in good agreement with experimental values, but the high singlet energy of ortho-dimethoxybenzene was poorly predicted by calculations performed on the planar structure.

# CONFORMATION OF AROMATIC SUBSTITUENT GROUPS IN THE CRYSTALLINE STATE

The X-ray crystal structures of numerous methoxy-substituted aromatics were examined in order to determine the preferred conformations of unhindered monomethoxy, ortho-dimethoxy, and ortho-trimethoxy substituents in the solid state. These data are summarized in Table 19. Scrutiny of 30 examples of unhindered monomethoxy derivatives show the methoxy groups to be nearly planar.[12a] The C-C-O angle distortion observed in the optimized anisole geometry calculations was also present in the X-ray structures (anisole optimum= 125.5°, compared to 124.5° found in crystals). A planar orientation of methoxy groups was found in 30 of the 32 unhindered ortho-dimethoxy derivatives.[12b] However, for no obvious reason, the crystal structures of two unhindered ortho-dimethoxy compounds contained both a planar and a perpendicular methoxy group.[12c] In these derivatives, the nonplanar methoxy groups reside in a void in the crystal, have unusually large thermal parameters, and have significantly lower C-C-O angles (119.5±0.7°) than the planar value of 125°. In the ortho-trimethoxy substituted compounds, the outer methoxys are nearly planar whereas the central methoxy is almost perpendicular.[12d] Both calculations and X-ray structures indicate that nonplanar methoxys have a significantly smaller C-O-C angle (110°, calculated; 115°, X-ray) than planar methoxys (117-118° calculated and X-ray). A common feature found in this substitution pattern is the expansion

Table 19. Summary of Physical Data Derived from the X-ray Structures of Monomethoxy-, ortho-Dimethoxy-, and ortho-Trimethoxy-Substituted Aromatics

| Aromatic Substitution Pattern | Number of Groups Examined | Bond Lengths (std dev), Å | | Bond Angles[a] (std dev), deg | | Dihedral Angles[a] (std dev), deg |
|---|---|---|---|---|---|---|
| | | C-O | O-$CH_3$ | C-C-O | C-O-$CH_3$ | C-C-O-$CH_3$ |
| Monomethoxy | 30 | 1.37 (±0.02) | 1.43 (±0.02) | 124 (±1.1) | 117.7 (±0.9) | 6 (±6) |
| Planar *o*-dimethoxy | 58 | 1.37 (±0.02) | 1.43 (±0.03) | 125 (±2) | 117 (±2) | 7 (±6) |
| Nonplanar *o*-dimethoxy | 2 | 1.377 (±0.003) | 1.41 (±0.03) | 119.5 (±0.7) | 115 (±1) | 110 (±14) |
| *o*-trimethoxy outer methoxy[b] | 6 | 1.37 (±0.01) | 1.42 (±0.02) | 124.8 (±0.7) | 118 (±1) | 5 (±4) |
| inner methoxy | 6 | 1.37 (±0.01) | 1.43 (±0.01) | 122 (±2) | 115.2 (±0.7) | 98.1 (±6.5) |
| outer methoxy[c] | 6 | 1.371 (±0.006) | 1.42 (±0.01) | 117 (±4) | 117.7 (±1) | 5.2 (±1.9) |

[a]Angles defined along the side of the aromatic ring bearing the methoxymethyl group. [b]Methoxy substituent furthest removed from the methyl group of the central methoxy. [c]Methoxy substitutent nearest to the methyl group of the central methoxy.

of the C-C-O angle of one of the outer methoxys and the contraction of the other.

In contrast to the gaseous and liquid phases, the preferred orientation of ortho-dimethoxybenzenes is clearly planar in the crystalline state. While many forces are known to affect conformations in crystals, planarity here probably results from staking forces, which clearly favor the planar forms. Indeed, the 2.4 kcal/mol. higher rotational barrier found for anisole in the neat liquid as compared with the gas-phase value is probably a manifestation of these stacking forces, even in solution.[10a] Analysis of the immediate environment of the methoxy group in a manner similar to that proposed by Kitaigorodsky[9a,b] reveals that the space surrounding the two nonplanar ortho-dimethoxybenzenes is 37% freer than that in the corresponding planar structures; hence the favored planarity in the crystal structure is apparently associated with favorable crystal packing[9b].

# ORIGIN OF VARIABLE BARRIERS TO ROTATION OF AROMATIC HYDROXY AND METHOXY GROUPS

The trend in barriers to rotation observed for both hydroxybenzenes and methoxybenzenes can be explained by resonance arguments such as those used by Radom et al.[10g] or by more detailed frontier orbital interaction arguments. Both of these approaches will be discussed here.

Correlations Between π Charge Densities and Rotational Barriers.

The ring carbon π charge densities from STO-3G calculations on phenol, anisole, and ortho-, meta-, and para-dimethoxybenzenes are shown in Figure 70. For anisole, the net π charges (relative to benzene) are negative at the ortho and para positions and positive at the meta position. Methoxy or hydroxy are strong donors and polarizers when planar, and the planar conformation is most strongly favored when a second methoxy group is attached at the meta position. However, when attached para to a second methoxy, the planar conformation is destabilized somewhat, since rotation from planarity relieves electron donation to an already electron-rich carbon. Attachment at the ortho position is even less favorable owing to the larger negative charge at carbons ortho to a methoxy group.

This argument is of practical value, since the π charges of ortho-, meta-, and para-dimethoxybenzenes can be easily calculated from the π charges of anisole (Figure 70). For example, the π charge on the carbon between the methoxys in meta-dimethoxybenzene would be predicted to be

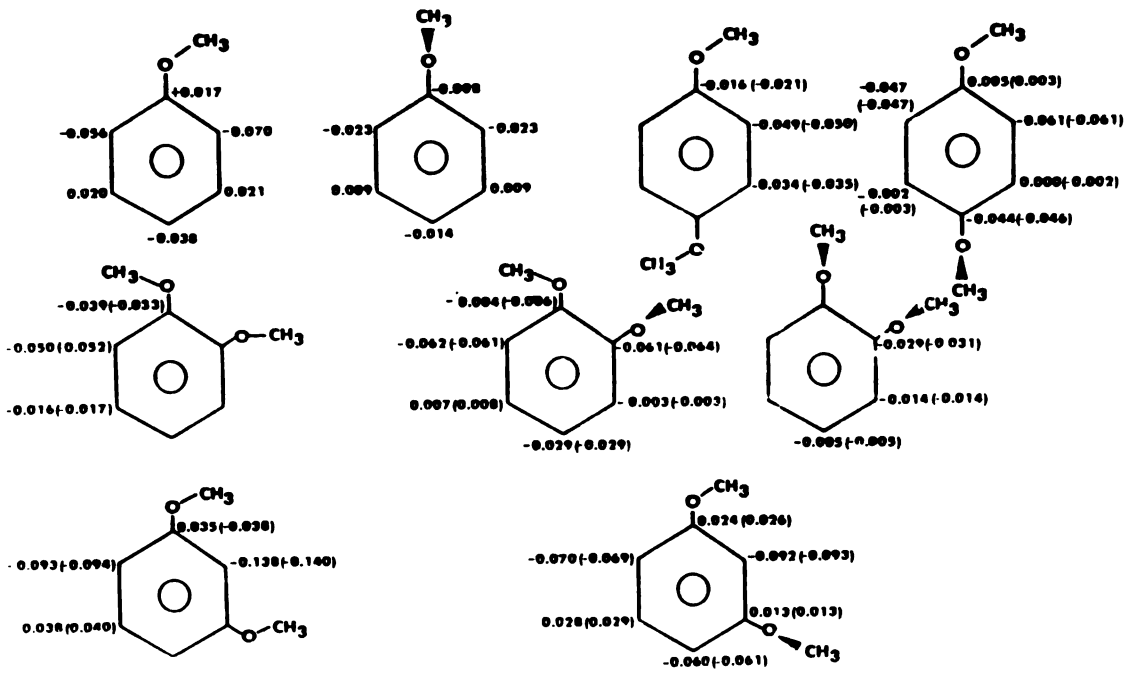


FIGURE 70. Carbon π charges in anisole and the dimethoxybenzenes in both planar and perpendicular conformations. For the dimethoxybenzenes, the charges in parentheses are those predicted by adding the appropriate anisole charges.

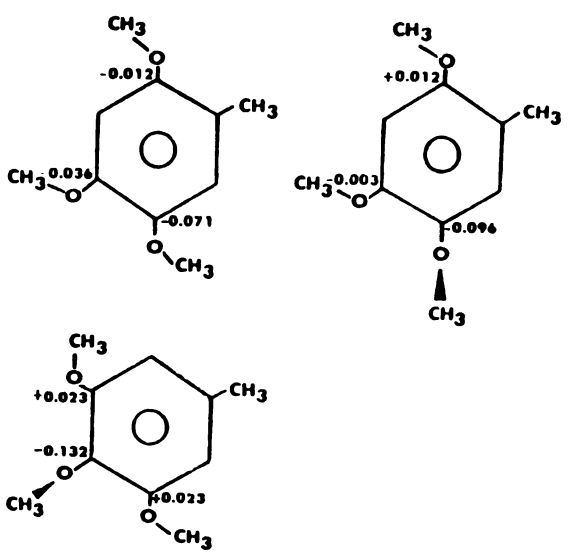


FIGURE 71. Predicted π charges at the methoxy positions for 2,4,5- and 3,4,5-trimethoxytoluene.

-0.070+-0.070=-0.140, and the STO-3G calculated π charge is -0.138. The π charges of the other dimethoxybenzenes can be estimated simply by adding appropriate charges from the anisole calculation. The agreement with the STO-3G calculated π charges is very good (average error=0.002, largest error=0.006) not only for all planar conformations, but for conformations involving planar and perpendicular methoxy groups in the same molecule (using anisole, $\phi=90^{o}$, to derive the charges for dimethoxybenzenes with perpendicular methoxys). The reason this additivity works so well is that the perturbations of the benzene π electron distribution induced by the methoxy groups are relatively small, as noted by Hehre et al.[10e] The net π charge transferred to the benzene ring in anisole is only -0.1 e, and the polarization of the π charges in the ring is at least as important as charge transfer in determining charge distributions[13b].

The predicted π charges on the carbon to which the methoxy is bonded correlate well with the rotational barrier; π charges of 0.0035, 0.017, -0.016, and -0.039 for meta-dimethoxybenzene, anisole, para- dimethoxy benzene, and ortho-dimethoxybenzene correspond to STO-3G calculated rotational barriers of 2.2, 0.9, 0.2, and -0.7 kcal/mol.[13c]. Focusing on the change in the π charge of the carbon to which the hydroxy is attached for the para-substituted phenols analyzed by Radom et al.[10g] gives an excellent correlation with the calculated rotational barriers of para-substituted phenols. For X=OH, F, $CH_3$, H, CHO, CN, and $NO_2$, the π charges are

-0.039, -0.021, -0.012, 0, 0.018, 0.028, and 0.043; the π charges in the rotational barriers (relative to phenol) are -0.05, -0.53, -0.28, 0, 0.47, 0.66, and 1.02 kcal/mol., respectively[13d].

The good correlations between the calculated barriers and the π charges allows one to qualitatively predict rotational barriers in any polysubstituted benzene, for substituents for which the π charges in the monosubstituted species are available. Hehre, et al.[10e] have reported STO-3G calculations for 32 monosubstituted benzenes, so that rotational barriers may be easily predicted for most ordinary substituted aromatics.

Because of our interest in the properties of psychotomimetic phenylisopropylamines, one example will be discussed, that of 2,4,5-trimethoxyphenylisopropylamine, a particularly potent hallucinogen[13e]. Photoelectron spectra reported earlier indicate that the influence of the aminopropyl side chain upon the electronic structure of the aromatic ring is essentially identical with that of a methyl group[13f]. For that reason, 2,4,5-trimethoxytoluene is a reasonable model for this psychotomimetic. The additively predicted π charges for the molecule given in Figure suggest that the 5-methoxy group will be in a perpendicular conformation. Adjusting the charges accordingly, one predicts that the 2 and 4 methoxy groups may prefer planarity, but not by as much as the methoxy group in anisole. Put another way, the methoxy group ortho to one and para to another methoxy has a greater

preference for nonplanarity than a methoxy ortho to one and meta to another.

This prediction allows the rationalization of the fact that substitution of the 4-methoxy by 4-ethoxy in 3,4,5-trimethoxyphenylisopropylamine increases psychotomimetic potency by ∿10, whereas the same substitution in the 2,4,5 compound has no effect on the potency[13e]. In the 3,4,5-trimethoxy compound, the 4-methoxy group is forced out of the ring plane by the steric and electronic effects of the neighboring 3- and 5-methoxys, while the 3- and 5-methoxys remain planar; in 2,4,5 trimethoxyamphetamine, the 5-methoxy has the largest tendency for nonplanarity and the 4-methoxy prefers planarity. Thus, one expects the ethoxy group in 4-ethoxy-3,5-dimethoxyphenylisopropylamine to interact significantly with the receptor surface[13e], since the 4-ethoxy group extends out of the plane of the aromatic ring. However, the 4-ethoxy, like the 4-methoxy, of 2,4,5-trimethoxyamphetamine is planar, and neither methyl or ethyl groups can interact with the same hydrophobic part of the receptor surface.

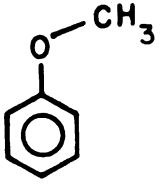
The application of π charges to rationalize and predict rotational barriers is a simple and useful method which should be applicable to systems other than substituted benzenes such as alkoxyheteroaromatics and vinyl ethers. Steric effects can also play a role, but these are not necessarily large, even when groups are in close proximity; for example, ortho-methylphenol and ortho-methylanisole are planar[13g].

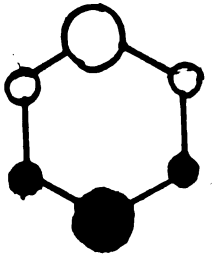
# A FRONTIER ORBITAL MODEL FOR ROTATIONAL BARRIERS

A more detailed rationalization of the variable rotational barriers can be constructed with the aid of the high-lying filled and low-lying vacant Molecular Orbitals (MO) of anisole, shown in Figure 72. As described in detail elsewhere, the degeneracies of the HighestOccupied Molecular Orbitals (HOMO) and Lowest Unoccupied Molecular Orbitals (LUMO) of benzene are not only split by donor substitution, but significant polarization of these orbitals occurs as well, so that the HOMO has coefficients para > ortho > meta and the Second Lowest Unoccupied Molecular Orbital (SLUMO) has coefficients para > meta > ortho [13b, 14a].

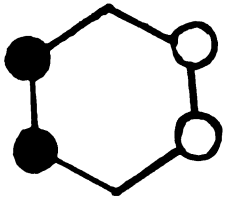
It has been shown in many previous investigations that the preferred conformations of molecules are those which maximize overlap between the high-lying filled orbitals of one fragment and the low-lying vacant orbitals of the other fragment (which leads to stabilizing two-electron interactions) and minimize overlap of the high-lying filled orbitals of the two fragments (which leads to destabilizing four-electron interactions) [14b]. Such arguments, along with the anisole MO's (which are very similar to those of phenol), can be used to rationalize the trends found here.

In benzene, the HOMO and Second Highest Occupied Molecular Orbital (SHOMO) are degenerate, as are the LUMO and SLUMO. Attachment of a planar methoxy at any carbon results in four-electron closed-shell repulsion due to overlap of the filled methoxy $\pi_o$ orbital with one of the filled aromatic



a.



b.

FIGURE 72. $\pi$ Molecular Orbitals of Anisole (a. Shape of the HOMO, b. Shape of the SHOMO).

HOMO's, and a stabilizing two-electron interaction of the filled $\pi_o$ orbital with one of the aromatic LUMO's. In anisole, the six carbons are no longer equivalent owing both to the split in degeneracy and to the coefficient polarization. The HOMO is polarized away from the meta position, so that attachment of methoxy here results in less closed-shell repulsion than upon attachment of a methoxy to benzene[13b]. At the same time, the SLUMO is polarized toward the meta carbon, and a larger $\pi_o$-SLUMO stabilizing interaction will result than when a methoxy is attached to benzene. Both of these effects increase the stabilizing effect of the second methoxy group and favor the planar conformation of meta-dimethoxybenzene more than in anisole.

However, the HOMO has increased coefficients at the ortho and para positions relative to benzene. Similarly, the SLUMO is polarized away from the ortho and para positions. Less stabilization occurs upon attachment of a methoxy at these carbons, and barriers to rotation decrease (Figure 73).

The SHOMO and LUMO are essentially unaffected by the methoxy substituent, so that the influence of these orbitals on barriers to rotation of the second methoxy group is identical with the influence of these orbitals on the anisole barrier.

The parallelism of closed-shell repulsion between $\pi_o$, and HOMO and stabilizing $\pi_o$-SLUMO interaction is no accident. In fact, much of the polarization of the anisole HOMO and SLUMO arises from admixture of the corresponding benzene

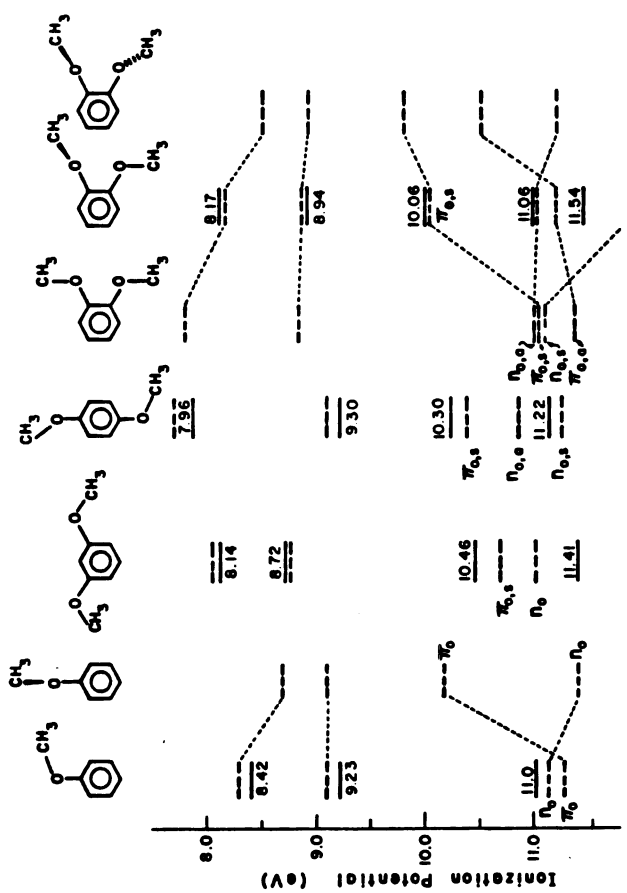



FIGURE 73. Experimentally Determined Ionization Potentials (PES) and Calculated Ionization Potentials (STO-3G) for Anisole and the Dimethoxybenzenes. (The dashed lines represent the calculated values, and the solid lines represent the experimental values).

orbitals in a negative fashion at the site of methoxy substitution in the HOMO and in a positive fashion in the LUMO[14b]. The orbital polarizations which result also force electron density onto the ortho and para positions at the expense of the meta positions.

Further insight can be obtained by comparing the rotational barriers in methoxybenzenes to the corresponding barriers in $H_2N\text{-}CH_2^+$ and $HO\text{-}CH_2^+$. In contrast to anisole or phenol, the rotational barriers in these carbonium ions increase as the charge residing in the carbon p-π orbital increases[14c]. The dissimilar rotational barriers result from differences in the nature of the substituent perturbations; in the carbonium ions, only a bonding interaction occurs between the substituent orbital (filled) and the empty carbonium p orbital, whereas in methoxybenzene both stabilizing and destabilizing interactions result from substituent perturbations. As discussed previously, the preferred planarity of methoxybenzene or hydroxybenzene implies that the destabilizing influences are outweighed by the stabilizing influences. However, the relationship between the changes in the rotational barriers for methoxy-substituted benzenes and the carbon p-π population ipso to the methoxy group suggests that these barrier differences are dominated by the antibonding interactions illustrated by the HOMO shapes in Figure 72. Thus a decrease in the π charge on the ipso carbon is indicative of a reduction in the magnitude of the antibonding interactions.

Both of these qualitative explanations are quite general. For π systems with significant polarization, such as nonalternant hydrocarbons and heterocycles, hydroxy or methoxy groups attached to sites of plus charge or sites with small HOMO coefficients and large LUMO coefficients will have high rotational barriers. Conversely, attachment of a hydroxy or methoxy at a site of negative charge, or a site with large HOMO coefficient and small LUMO coefficient, will result in low rotational barriers or even nonplanarity. Interestingly, this is not a steric effect at all, but instead a pure electronic effect.

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b) The packing coefficients of the ortho-dimethoxy-substituted aromatics showed no consistent difference between the planar and nonplanar structures, probably owing to the size of the alkaloids to which these

groups are attached. Our procedure is more selective since the immediate environment of the methoxy substiuent can be studied; however, unlike the packing coefficient defined by Kitaigorodsky, which is dependent only on the unit cell volume, our results vary with the unit cell geometries. In our work, the unit spherical volume was centered 2.5 Å along the $C_{aromatic}$-O axis and having a radius of 5.0 Å. The Bondi intersection volume of neighboring molecules was then computed in a manner similar to Kitaigorodsky's method.


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d) $\Delta E(\text{barrier}) = 24.17q_{\pi} - 0.003$, $r = 0.999$.

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# DISTRIBUTIONAL PROPERTIES

Meyer[1a,b] and Overton[1c] were the first to consider the role of distributional properties on the biological potencies of a series of sedatives and hypnotics. These scientists postulated that, for a series of derivatives, the maximum potency would correspond to that compound whose lipid solubility was optimum with regard to its site of action. These early ideas were later quantified and systemized, and extensively developed by Hansch and co-workers[1d-f]. In the Hansch method, the lipid solubility of a compound is measured in terms of the log of its octanol/water equilibrium coefficient (Log P), and a regression relation is sought between the log of the biological activities (B.A.) and the Log P's. The forms of relationship (EQ(1) and EQ((2) ) using Log P as the dependent variable have commonly been employed:

$$\log \text{B.A.} = a \log P + b \qquad \text{EQ(1)}$$

$$\log \text{B.A.} = a \log P + b \log P^2 + c \qquad \text{EQ(2)}$$

where a, b, and c are constants. The log $P^2$ term in EQ has been employed on empirical grounds to account for the notion that an optimum Log $P_o$ (d(log B.A.)/d Log P =0) exist for each receptor site and that compounds with Log P's radically different from Log $P_o$ might well be concentrated at sites other than the receptor, and hence be biologically ineffective. Later, a certain degree of theoretical justification of the physical validity for EQ(2) has been reported by both Hansch et al.[1g] and McFarland[1h]. From analysis of the concentration dependence of drug when distributed, under

non-steady state conditions, in a bi-layer (lipid/water) multicompartmental diffusional model.

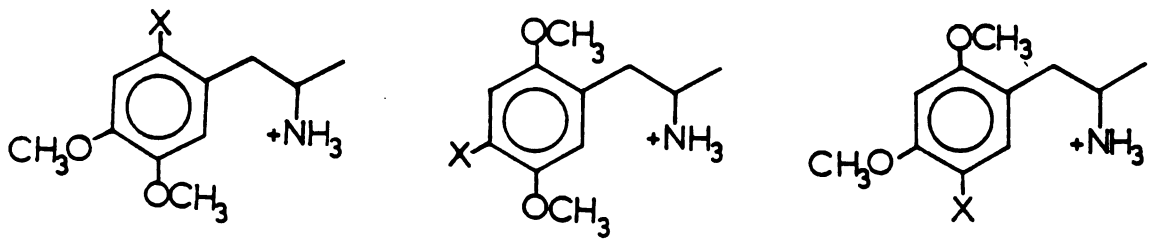
Measurement of the Log P's of an extensive number of compounds has led Hansch et al.[1i-j] to postulate that compared to a model compound, the Log P of a substituted derivative were typically well predicted by the summation of the Log P of the parent and the π values of respective substituents. Although exceptions to the utility of this additive principle have been reported[1k], generally these cases occur when interactions between the substitutent moieties are present. If correction factors accounting for these effects are introduced, then Log P values can be accurately predicted.

In spite of excellent statistical regression between the B.A.'s and Log P's for a variety of antifungal[1l], antibacterostatic[1m], hypnotics[1n] and other classes of compounds, the exact physical meaning of the Log P terms is still far from settled. Two possibilities seem most appealing: 1) the optimum Log P results from the most favorable bulk distribution[1g,h] or, 2) the optimum Log P results from the most favorable hydrophobic/hydrophilic binding to the receptor site[1o].

Barfknecht et al.[1p] in an early publication have reported a satisfactory regression relationship between the human potencies and Log P's of a series of methoxy-substituted and 1-(2,5-dimethoxy-4-X-phenyl)-2-aminopropanes (EQ(3) ). More recently, Nichols et al.[1q] have reached similar conclusions regarding the role of distributional factors (EQ(4) ).

However, none of the above-mentioned studies have included compounds bearing non-methoxy substituents located at positions ortho or meta to the isopropylamine side chain.

In the present chapter, investigation is made of the regression relationships present in both the methoxy-substituted 1-phenyl-2-aminopropanes as well as the three sets of "rearranged" 2,4,5-substituted derivatives detailed below:




Factors such as substituent group conformation which govern the Log P's of these compounds will be discussed in detail. And finally, regression relations involving sets comprised of regiospecific $\pi$ values and the biological activities are also explored.

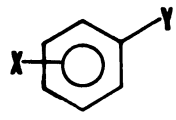
Origins of the Neighboring Group Effect on Log P.

The conformational dependence of the lipid solubility of methoxy-substituted aromatics was first noted by Leo et al.[1f], who pointed out that the $\pi$ value of the central methoxy group in 1,2,3-trimethoxybenzene was derived (using the additivity principle) to be -0.56, a number which is much closer to the $\pi$ value of an aliphatic methoxy group (-0.47) than that of an aromatic methoxy group (-0.02). Pointing to X-ray crystal structure data, these workers observed that the central methoxy group in this compound was nonplanar, making the hybridization of the oxygen more "$sp^3$" and hence

resembling the electronic structure present in an aliphatic methoxy group, which is capable of greater solvation by water. The π values for various mono-, di-, and trimethoxy substituted model compounds have been selected from the extensive compilation of measured Log P's reported in Leo et al.'s review article and substituent π methoxy values have been calculated in the usual manner ($\pi_{methoxy(Y)}$ = Log $P_{Y-Ar-X}$ - Log $P_{Ar-X}$), and this data is contained in Table 20. As can be seen, the positional monomethoxy isomers had almost equivalent π values (π = 0.03 - 0.09) and were reasonably close to the traditional value of -0.02. Similar results were obtained for the 2,3-, 2,4-, and 2,5-dimethoxy orientations. However, in the case of the 3,4-dimethoxy grouping, a very large neighboring group interaction substantially lowered the π substituent value. In the trimethoxy arrangements, the 2,4,6- pattern appears to have a normal π value, whereas the 2,4,5-trimethoxy π value derived from Nichols et al.'s measurement resembles the 3,4-dimethoxy π value in that it is considerably more hydrophilic than expected. The 2,3,4- and 3,4,5-trimethoxy π values are very similar (π =-0.20) and somewhat less lipophilic than expected.

These results are very similar to those reported by Currie et al.[2a] in their investigations into the Log P of a large series of methoxy-substituted β-nitroalkenylbenzenes. Of the 96 various derivatives studied, the largest deviations were found to occur in 3,4-dimethoxy substituted aromatics.

Table 20. Model Compound Study of the Positional Monomethoxy Π Substituent Values, and also the Positional Di- and Trimethoxy Π Multisubstituent Values.

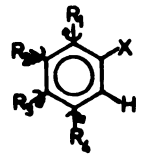



| X=Monomethoxy | $\Pi_{4\text{-}OCH_3}$ | $\Pi_{3\text{-}OCH_3}$ | $\Pi_{2\text{-}OCH_3}$ |
|---|---|---|---|
| Y=-COOH | 0.09 | 0.15 | ——— |
| -CHCHNO$_2$ | -0.06 | 0.09 | 0.33 |
| -CHC(CH$_3$)NO$_2$ | -0.34 | -0.06 | -0.07 |
| -CH$_2$COOH | 0.01 | 0.09 | ——— |
| -OCH$_2$COOH | 0.12 | -0.03 | -0.33 |
| -OH | -0.12 | 0.12 | ——— |
| -NH$_2$ | 0.05 | 0.05 | 0.03 |
| -CONH$_2$ | 0.22 | 0.30 | 0.23 |
| -CH$_2$CH(CH$_3$)NH$_2$ | 0.14 | ——— | ——— |
| -CH$_2$CH(CH$_3$)NH$_2$ | 0.15 | ——— | ——— |
| Average = | 0.03 | 0.09 | 0.04 |
| (Stand. Dev.) | ±0.19 | ±0.10 | ±0.25 |

| X=Dimethoxy | $\Pi_{2,3\text{-}(OCH_3)_2}$ | $\Pi_{2,4\text{-}(OCH_3)_2}$ | $\Pi_{2,5\text{-}(OCH_3)_2}$ | $\Pi_{3,4\text{-}(OCH_3)_2}$ |
|---|---|---|---|---|
| Y=-CHCHNO$_2$ | 0.13 | 0.23 | -0.01 | -0.86 |
| -CHC(CH$_3$)NH$_2$ | -0.11 | -0.14 | -0.19 | -0.92 |
| -CH$_2$CH(CH$_3$)NH$_2$ | ——— | 0.12 | 0.25 | -0.43 |
| -CH$_2$CH(CH$_3$)NH$_2$ | ——— | ——— | 0.07 | -0.75 |
| Average = | 0.01 | 0.07 | 0.03 | -0.74 |
| (Stand. Dev.) | ±0.12 | ±0.15 | ±0.16 | ±0.19 |

| X=Trimethoxy | $\Pi_{2,3,4\text{-}(OCH_3)_3}$ | $\Pi_{2,4,5\text{-}(OCH_3)_3}$ | $\Pi_{2,4,6\text{-}(OCH_3)_3}$ | $\Pi_{3,4,5\text{-}(OCH_3)_3}$ |
|---|---|---|---|---|
| Y=-CH$_2$CH(CH$_3$)NH$_2$ | -0.27 | (0.11) | -0.06 | -0.34 |
| -CH$_2$CH(CH$_3$)NH$_2$ | -0.12 | -0.53 | ——— | -0.12 |
| Average = | -0.19 | ? | (-0.06) | -0.23 |
| (Stand. Dev.) | ±0.07 | ——— | ——— | ±0.11 |

Table 21. Model System Study of the π Substituent Values and the CNDO/2 Calculated Conformational Structure of Various ortho-Oxygen Substituted Groups.




| Aromatic Sub. Pattern | | | | | | | CNDO/2 Minima[c] | |
|---|---|---|---|---|---|---|---|---|
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $\pi_{add.}$[a] | $\pi_{obs.}$[b] | $\pi_{add.}-\pi_{obs.}$ | Global | Local |
| $OCH_3$ | $OCH_3$ | H | H | -0.04 | 0.01 (±0.12) | -0.05 | NP[d] | P[e] (ΔE=78) |
| H | H | $OCH_3$ | $OCH_3$ | -0.04 | -0.74 (±0.19) | 0.70 | NP[d] | P[e] (ΔE=0.65) |
| H | H | $OCH_3$ | $OCH_3$ | 0.59 | 0.37 (±0.12) | 0.22 | NP[d] | P[e] (ΔE=1.06) |
| H | H | $OCH_2CH_3$ | $OCH_3$ | 0.36 | -0.65 (±0.17) | 1.01 | | |
| H | H | OH | $OCH_3$ | -0.69 | -0.31 (±0.07) | -0.38 | NP[f] | P[g] (ΔE=0.23) |
| H | H | O--$CH_2$--O | | -0.50 | -0.02 (±0.03) | -0.48 | --------P------- | |
| H | H | OH | OH | -1.34 | -1.42 (±0.10) | 0.08 | P[h] | NP[d] (ΔE=2.50) |
| $OCH_3$ | $OCH_3$ | $OCH_3$ | H | -0.06 | -0.19 (±0.07) | 0.04 | NP[i] | P[j] (ΔE=15.94) |
| H | $OCH_3$ | $OCH_3$ | $OCH_3$ | -0.06 | -0.23 (±0.11) | 0.17 | NP[k] | P[m] (ΔE=0.02) |

[a] Substituent π values taken from Hansch et al. (ref. 1d). [b] Determined from measured Log P of model compounds. [c] Energy in kcal/mole and X=$CH_3$; NP=nonplanar, P=planar. [d] $T_a=120^\circ$, $T_b=180^\circ$ (a < b). [e] $T_a=0^\circ$, $T_b=180^\circ$ (a < b). [f] $T_3=180^\circ$, $T_4=90^\circ$. [g] $T_a=180^\circ$, $T_b=180^\circ$ (a < b). [h] $T_3=0^\circ$, $T_4=0^\circ$. [i] $T_1=225^\circ$, $T_2=135^\circ$, $T_3=180^\circ$. [j] $T_1=90^\circ$, $T_2=0^\circ$, $T_3=180^\circ$. [k] $T_2=135^\circ$, $T_3=45^\circ$, $T_4=180^\circ$. [m] $T_2=0^\circ$, $T_3=0^\circ$, $T_4=180^\circ$.

The validity of this conclusion has been further augmented by the extensive Log P measurements in a variety of other derivatives reported by H. L. Holms [2b].

Having noticed the unusual distributional properties of the 3,4-dimethoxy configuration, an exploration of other ortho oxygen substituted compounds was undertaken and the $\pi$ substituent values as well as the CNDO/2 minimum energy conformations (see Conformation of Aromatic Substituents) are summarized in Table 21. As can be seen from the table, the minimum energy conformation of both 2,3- and 3,4-dimethoxytoluene and also 3-methoxy-4-thiomethyltoluene was predicted by CNDO/2 to be nonplanar; however, in the latter two substitution patterns, a low-lying planar conformation similar to the conformational minima of 3,4-dimethoxytoluene was computed to be slightly more stable than the planar form which differs from the dimethoxy case in that the hydrogen of the phenol is directed toward a methoxy group whose methyl substituent is pointed away. A planar global minima was found in 3,4-dihydroxytoluene whereas nonplanar conformations were favored in both 2,3,4- and 3,4,5-trimethoxytoluene. The hydrophilicity of the 3,4-dimethoxy grouping can be explained in one of two ways: 1) lone pair-lone pair repulsions in adjacent methoxy groups favor nonplanar conformations which are more strongly solvated than the planar structures, or 2) the planar orientation which exists as a low-lying local minima results in the buildup of electron density between the methoxy substituents, and this region provides a good site of

solvation. It is difficult to rule out either one of these explanations. Since both the 2,3- and 3,4-dimethoxytoluenes exist in nonplanar forms and yet only the latter has an abnormal $\pi$ value, one might conclude that a specific solvation site is implicated. However, the differences between the $\pi$ values in these two cases could also be explained by steric inhibition of solvation in the 2,3-dimethoxy compounds by the ortho substituent (such as an ethylamine side chain). Conversely, the methylenedioxy grouping, which is more lipophilic than the component substituents would suggest that both the planar and the specific solvation sites are blocked by the methylene moiety. Similarly, the 3-methoxy-4-hydroxy pattern is more lipophilic than expected, probably due to intermolecular hydrogen bonding in the low-lying planar conformational minima.

Analysis of Regression Relationships between Log P and Biological Activities.

Table 22 contains a compilation of measured and derived Log P's for a series of 31 ring-substituted 1-phenyl-2-aminopropanes for which biological potencies are available. Of these analogues, 1-(3,4-dimethoxyphenyl)-2-aminopropane is clearly the most hydrophilic of the analogues for which Log P have been measured. Only the 3-methoxy-4-ethoxyphenyl grouping may be more hydrophilic, but this is difficult to judge due to the extreme range of variations encountered in model compounds containing this grouping. The regression relation (EQ 5 ) between the Log P's and the Log B.A. for a series of

methoxy-substituted 1-phenyl-2-aminopropanes is graphically presented in Figure 74.

Log B.A.(MU)= 1.133 Log P- 1.130 EQ(5)

n=8, r= 0.56

While this compound set is limited and the variation in Log P and Log M.U. is small, still the regression is capable of describing 31% of the variation between these variables. Consideration of the six compounds which comprise the 1-(2-X, 4,5-dimethoxyphenyl)-2-aminopropane series leads to the regression relation (EQ(6) ) which is graphically presented in Figure 75. As can be seen, a fairly linear relationship occurs in this series, except for the 2-$OCH_3$ analogue in which the hyperthermic potency is considerably higher than expected on the basis of its lipid solubility.

Log B.A.(SRU)= 0.903 Log P- 1.140 EQ(6)

n=6, r=0.48

Analysis of the regression relations in the largest and most studied series, 1-(2,5-dimethoxy-4-X-phenyl)-2-aminopropanes, yields regression equations EQ(7) and EQ(8) . It is clear from Figure 76 and the statistical data that the hyperbolic form of EQ(8) best describes the variation in the hyperthermic potencies.

Log B.A.(SRU)= 0.097 Log P- 1.203 EQ(7)

n=12, r=0.14

EQ(8)

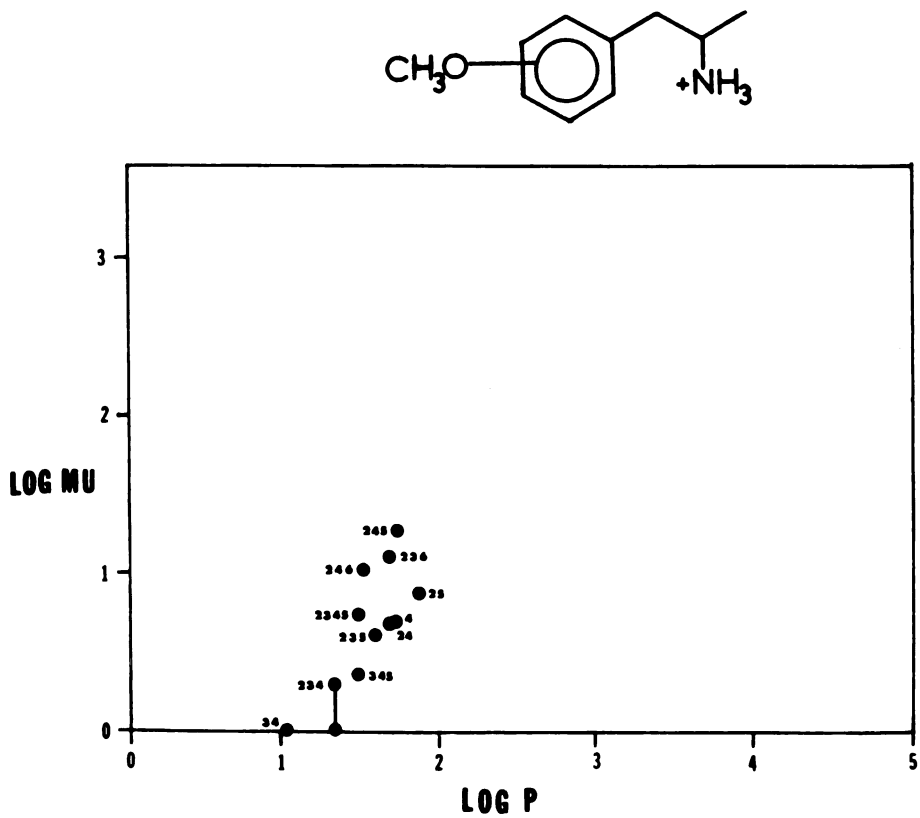



FIGURE 74. Relationship Between the Psychotomimetic Potencies (MU) and the Partition Coefficients (Log P's) for a Series of Methoxy-substituted 1-Phenyl-2-aminopropanes.

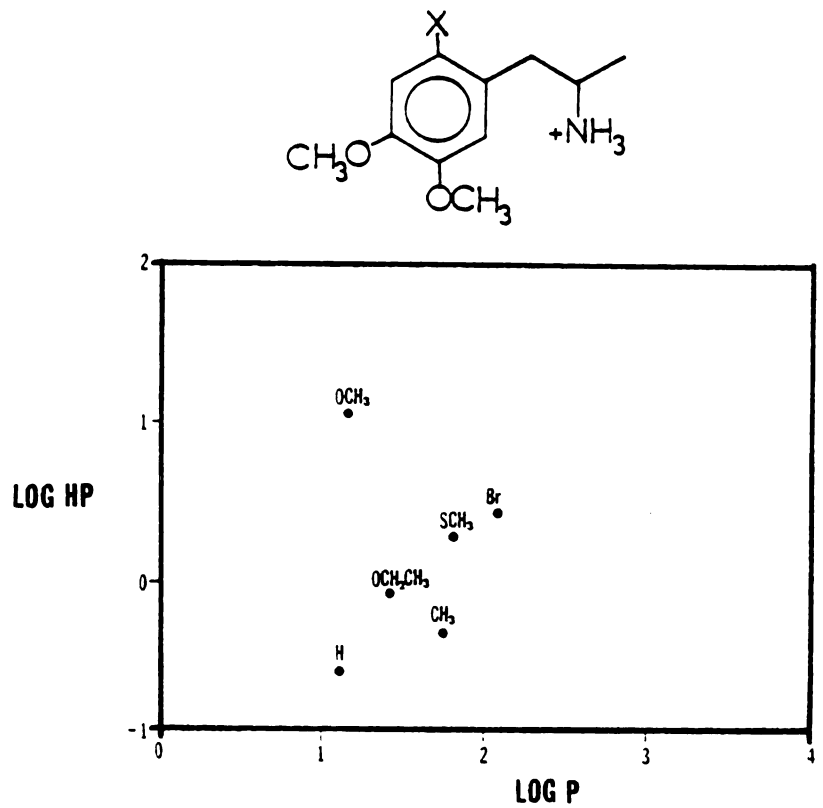



FIGURE 75. Relationship Between the Hyperthermic Potencies (SRU; Method A) and the Partition Coefficients (Log P's) for a Series of 1-(2-X-4,5-Dimethoxyphenyl)-2-aminopropanes.

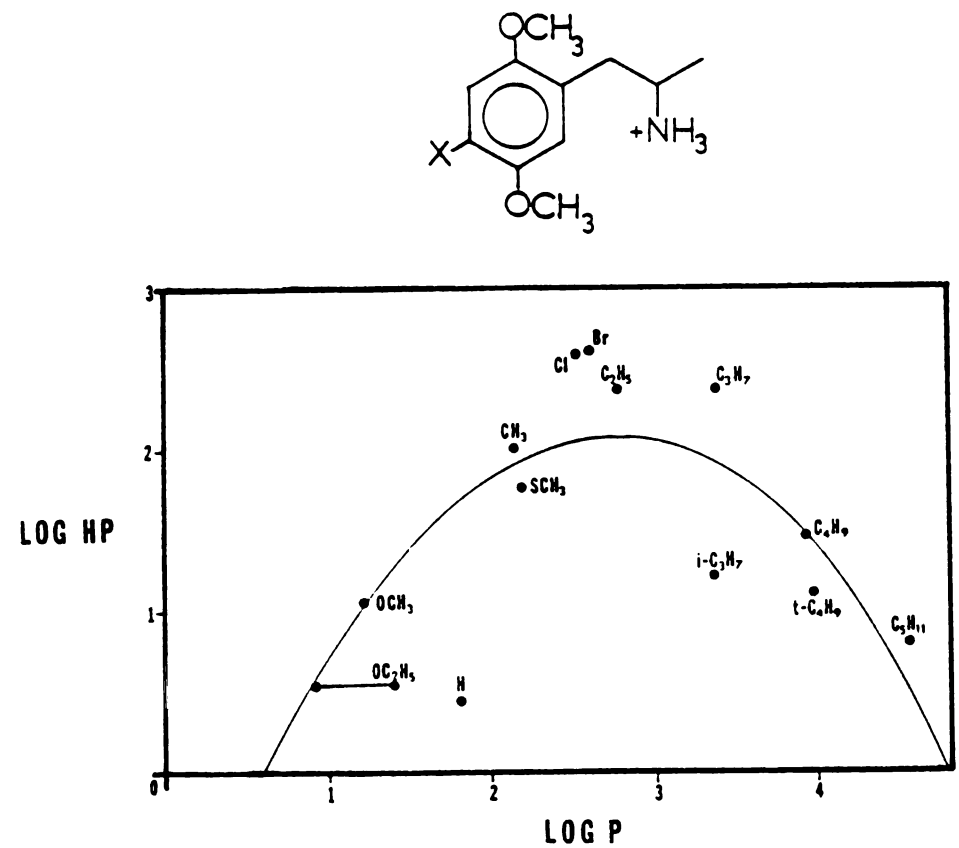



FIGURE 76. Relationship Between the Hyperthermic Potencies (SRU; Method A) and the Partition Coefficients (Log P's) for a Series of 1-(2,5-Dimethoxy-4-X-phenyl)-2-aminopropanes.

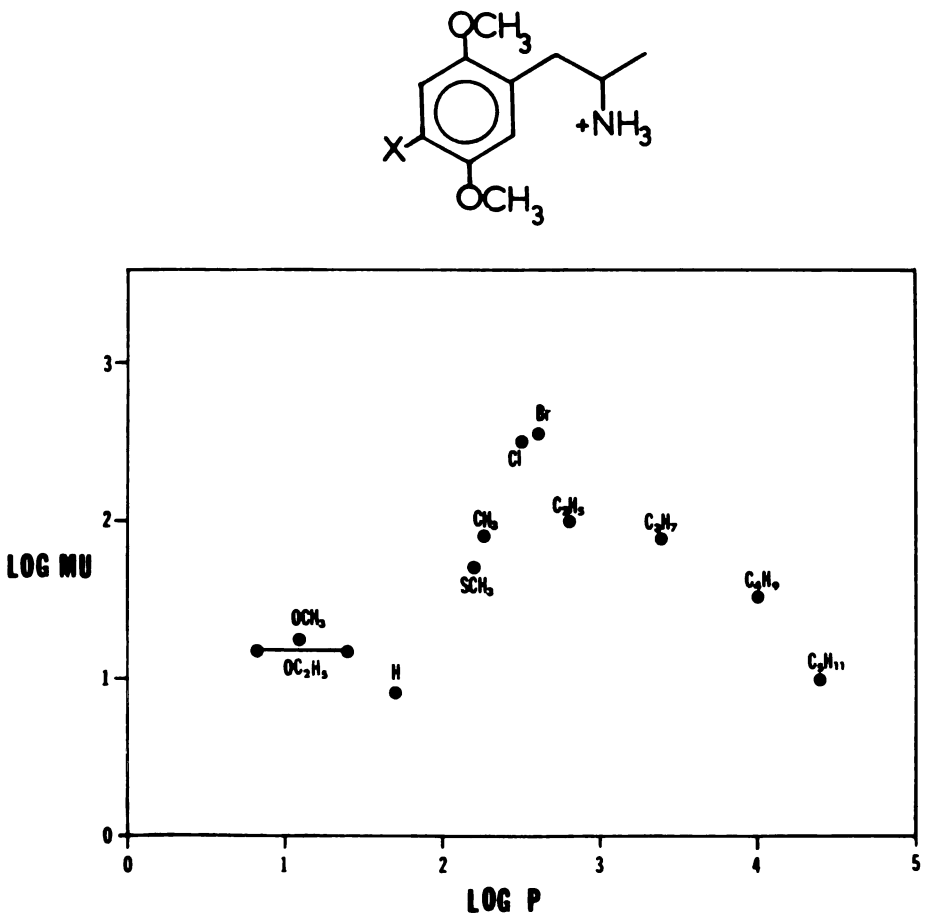



FIGURE 77. Relationship Between the Psychotomimetic Potencies (MU) and the Partition Coefficients (Log P's) for a Series of 1-(2,5-Dimethoxy-4-X-phenyl)-2-aminopropanes.

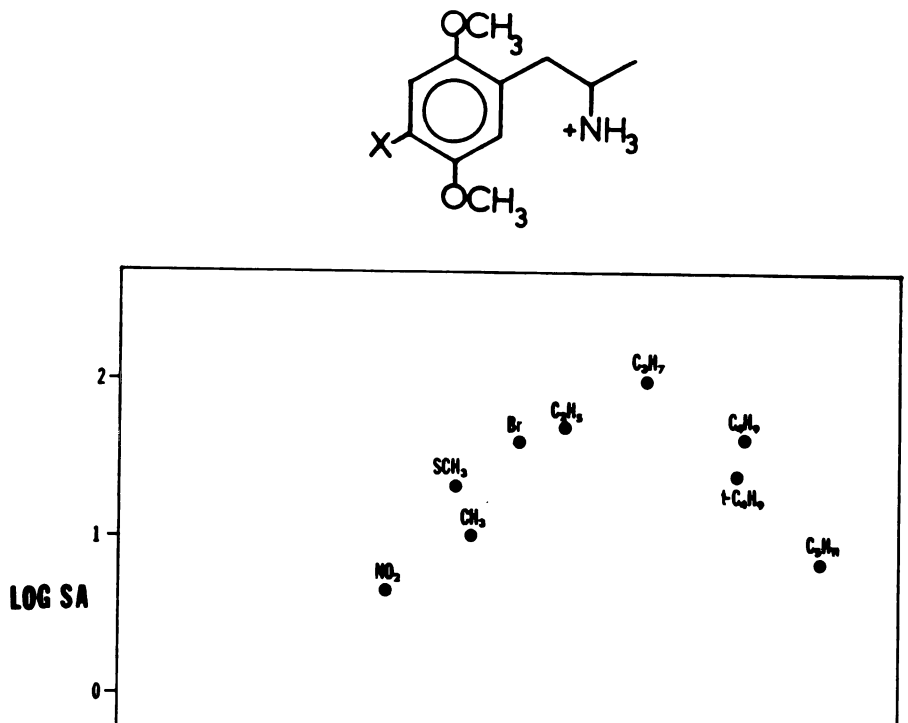



FIGURE 78. Relationship Between Serotonin Agonism and the Partition Coefficients (Log P's) for a Series of 1-(2,5-Dimethoxy-4-X-phenyl)-2-aminopropanes.

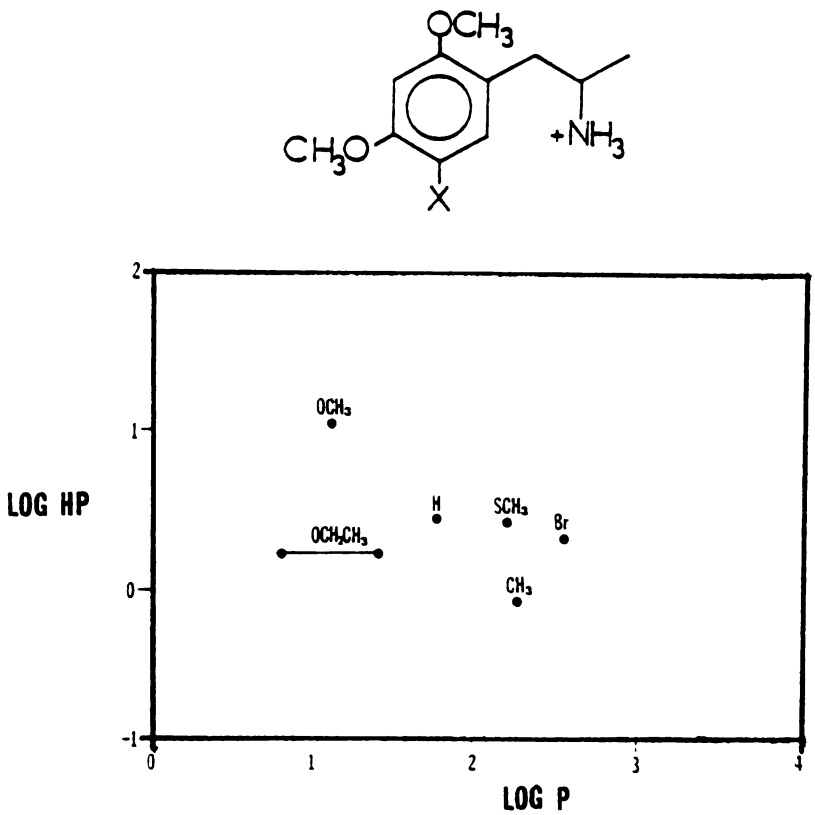



FIGURE 79. Relationship Between the Hyperthermic Potencies (SRU; Method A) and the Partition Coefficients (Log P's) for a Series of 1-(2,4-Dimethoxy-5-X-phenyl)-2-aminopropanes.

Furthermore, the data suggest that branching of the 4-alkyl chain tends to diminish the potency of these derivatives in a manner which appears to be unrelated to the π values of these substituent groups. Comparison of Figure 76 with 77 , and EQ(8) to EQ(3) shows that the SAR's obtained from the hyperthermic potencies are very similar to those obtained by Barfknecht et al. from analysis of human potencies. But this is not surprising given the good correlation between these biological measures (r= 0.94 ). Furthermore, Nichols et al. have reported serotonin antagonistic potencies for 10 of these 2,5-dimethoxy-4-X compounds and this data is illustrated in Figure 78 and the regression equation corresponds to EQ(9) . Clearly, in these data, a parabolic relationship is repeatedly obtained between the Log of the B.A.'s and the Log P.

$$\text{Log B. A.} = 3.63\text{Log P} - 0.57\text{Log P}^2 - 3.98 \qquad \text{(EQ 9)}$$

$$n=10,\ r=0.76$$

$$\text{Log B.A.(SRU)} = -0.180\ \text{Log P} + 0.733 \qquad \text{(EQ10)}$$

$$n=6,\ r= -0.27$$

In contrast to the preceding series, the log of the hyperthermic potencies of the 2,4-dimethoxy-5-X compounds (Figure 79) shows very little dependence on equations employing Log P as a descriptor (EQ 10 ).

Intercomparison of the SAR's found for these sets of compounds shows that for the methoxy-, 2,5-dimethoxy-4-X- and 4,5-dimethoxy-2-X-substituted analogues, the potency increases

Table 22. Compilation of Measured and Derived Partition Coefficients (Log P's) for Derivatives of 1-Phenyl-2-aminopropane.

| | Aromatic Sub. Pattern | | | | | |
|---|---|---|---|---|---|---|
| Compound | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Log P |
| (1AB) | H | H | H | H | H | 1.63[a] |
| (2AB) | H | H | $OCH_3$ | H | H | 1.77[b] |
| (5AB) | H | H | O - $CH_2$ - O | | H | 1.64[b] |
| (7AB) | $OCH_3$ | H | $OCH_3$ | H | H | 1.75[b] |
| (8AB) | $OCH_3$ | H | H | $OCH_3$ | H | 1.88[b], 1.72[c] |
| (11AB) | H | H | $OCH_3$ | $OCH_3$ | H | 1.00[b], 1.20[c] |
| (12AB) | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | 1.36[b] |
| (13AB) | $OCH_3$ | H | $OCH_3$ | $OCH_3$ | H | 1.74[b], 1.10[c] |
| (14AB) | $OCH_3$ | H | $OCH_3$ | H | $OCH_3$ | 1.57[b] |
| (15AB) | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | 1.48[b] |
| (16AB) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 2.08[b], 2.24[c] |
| (17AB) | $OCH_3$ | H | Br | $OCH_3$ | H | 2.58[b], 2.54[c] |
| (18AB) | $OCH_2CH_3$ | H | $OCH_3$ | $OCH_3$ | H | 1.48[d1] |
| (19AB) | $OCH_3$ | H | $OCH_2CH_3$ | $OCH_3$ | H | 0.79-1.43[d2] |
| (20AB) | $OCH_3$ | H | $OCH_3$ | $OCH_2CH_3$ | H | 1.12[d3] |
| (21AB) | $CH_3$ | H | $OCH_3$ | H | $OCH_3$ | 2.31[d4] |
| (22AB) | $OCH_3$ | H | $CH_3$ | H | $OCH_3$ | 2.27[d5] |
| (23AB) | $SCH_3$ | H | $OCH_3$ | $OCH_3$ | H | 1.71[d6] |
| (24AB) | $OCH_3$ | H | $SCH_3$ | $OCH_3$ | H | 2.17[c] |
| (25AB) | $OCH_3$ | H | $OCH_3$ | $SCH_3$ | H | 2.22[d7] |
| (26AB) | $CH_3$ | H | $OCH_3$ | $OCH_3$ | H | 1.66[d8] |
| (27AB) | $OCH_3$ | H | $OCH_3$ | $CH_3$ | H | 2.31[d9] |
| (28AB) | Br | H | $OCH_3$ | $OCH_3$ | H | 1.96[d10] |
| (29AB) | $OCH_3$ | H | $OCH_3$ | Br | H | 2.61[d11] |

| | | | | | | |
|---|---|---|---|---|---|---|
| (30AB) | $OCH_3$ | H | $n\text{-}C_4H_9$ | $OCH_3$ | H | 3.81[b], 4.00[c] |
| (31AB) | $OCH_3$ | H | $n\text{-}C_5H_{12}$ | $OCH_3$ | H | 4.31[b], 4.43[c] |
| (32AB) | OH | H | $CH_3$ | OH | H | 1.04[d12] |
| (34AB) | $OCH_3$ | H | $C_2H_5$ | $OCH_3$ | H | 2.81[b], 2.76[c] |
| (35AB) | $OCH_3$ | H | $n\text{-}C_3H_7$ | $OCH_3$ | H | 3.37[c], 3.31[b] |
| (36AB) | $OCH_3$ | H | $t\text{-}C_4H_9$ | $OCH_3$ | H | 3.91[b] |
| (37AB) | $OCH_3$ | H | $i\text{-}C_3H_7$ | $OCH_3$ | H | 3.33[d13] |

[a]Values taken from T. B. Vree, A. Muskens, and J. M. Van Rossum, J. Pharm. Pharmacol., 21, 774 (1969).
[b]Values taken from C. F. Barfknecht, D. E. Nichols, and W. J. Dunn III, J. Med. Chem., 18, 208 (1975).
[c]Values taken from D. E. Nichols, A. T. Shulgin, and D. C. Dyer, Life Sciences, 21, 569 (1977).
[d]Values estimated according to the following equations:

(d1) $\text{Log P}=\text{Log P}_{3,4\text{-diOMe}}+\pi_{OC_2H_5}=1.10+0.38=1.48.$

(d2) $\text{Log P}=\text{Log P}_{2,5\text{-diOMe}}+\pi_{OC_2H_5}+\pi_{\text{int.}}=1.80+0.38-1.01=1.17.$

(d3) $\text{Log P}=\text{Log P}_{2,4\text{-diOMe}}+\pi_{OC_2H_5}+\pi_{\text{int.}}=1.75+0.38-1.01=1.12.$

(d4) $\text{Log P}=\text{Log P}_{2,4\text{-diOMe}}+\pi_{CH_3}=1.75+0.56=2.31.$

(d5) $\text{Log P}=\text{Log P}_{2,6\text{-diOMe}}+\pi_{CH_3}=1.71+0.56=2.27.$

(d6) $\text{Log P}=\text{Log P}_{3,4\text{-diOMe}}+\pi_{SCH_3}=1.10-0.61=1.71.$

(d7) $\text{Log P}=\text{Log P}_{2,4\text{-diOMe}}+\pi_{SCH_3}+\pi_{\text{int.}}=1.75+0.61-0.16=2.20.$

(d8) $\text{Log P}=\text{Log P}_{3,4\text{-diOMe}}+\pi_{CH_3}=1.10+0.56=1.66.$

(d9) $\text{Log P}=\text{Log P}_{2,4\text{-diOMe}}+\pi_{CH_3}=1.75+0.56=2.31.$

(d10) $\text{Log P}=\text{Log P}_{3,4\text{-diOMe}}+\pi_{Br}=1.10+0.86=1.96.$

(d11) $\text{Log P}=\text{Log P}_{2,4\text{-diOMe}}+\pi_{Br}=1.75+0.86=2.61.$

(d12) $\text{Log P}=\text{Log P}_{2,5\text{-diOMe-4-Me}}-2(\pi_{CH_3})=2.16-1.12=1.04.$

(d13) $\text{Log P}=\text{Log P}_{2,5\text{-diOMe}}+\pi_{\text{ipropyl}}=1.80+1.53=3.32.$

with increasing Log P for values between 0 and 3. In contrast, the potencies of the 2,4-dimethoxy-4-X- compounds are not significantly related to Log P. The differences in the potencies of the 2,4,5-substituted compounds may arise from the different orientations of the methoxy groups or from the location and nature of the X substitutent. In any case, it is clear that the B.A.'s of these compounds are dependent on "regiospecific" factors rather than overall lipid solubility. An alternate way of arriving at this conclusion involves formulating regression relationships between the log of the hyperthermic potencies and the combined $\pi$ substiurent constants for the ortho, meta, and para groups (for example $\pi_{ortho} = \Sigma\pi$(ortho groups). The pertinent data included in this analysis for the 2,4,5-substituted compounds is presented in Table 23. Relationships between these regiospecific values and Log B. A.(SRU) are demonstrated in Equations 11-13.

$$\text{Log B. A.(SRU)} = -0.046\,\Sigma\pi_{ortho} + 0.590 \qquad \text{EQ(11)}$$

$$n = 16,\ r = -0.033$$

$$\text{Log B. A.(SRU)} = -0.677\,\Sigma\pi_{meta} + 0.687 \qquad \text{EQ(12)}$$

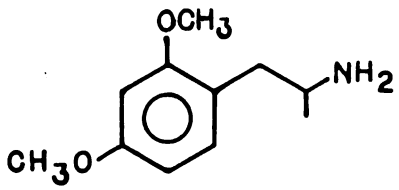
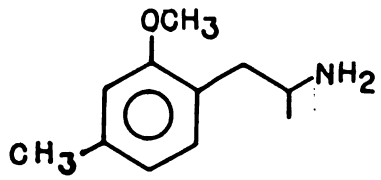
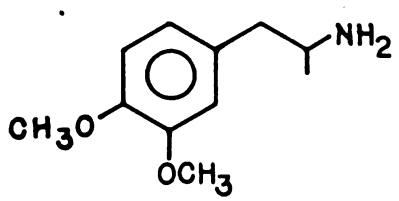
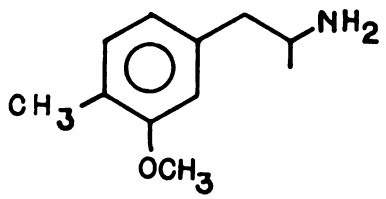
$$n = 16,\ r = -0.237$$

$$\text{Log B. A.(SRU)} = 2.425\,\Sigma\pi_{para} + 0.237 \qquad \text{EQ(13)}$$

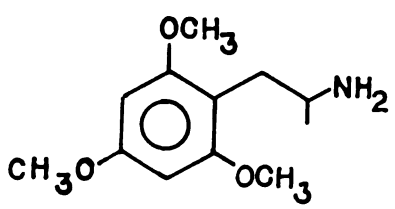
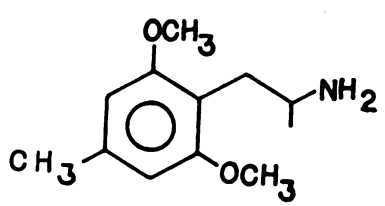
$$n = 16,\ r = 0.860$$

As can be seen, the B. A's of these 2,4,5-substituted compounds are significantly related to the lipophilic character of the para substituent. Furthermore, addition

of either the $\Sigma\pi_{\underline{meta}}$ or the $\Sigma\pi_{\underline{ortho}}$ variables to EQ(13) results in no enchancement in significance. Similar increases in potency occur in the disubstituted compounds diagramed below:

However, comparison of the potency of compound (14AB) with compound (22AB) shows that at least in these 2,4,6-trisubstituted derivatives, dramatic increases in activity are apparently not achieved by increasing the lipophilicity of the para-substituent. This data may indicate that the potency of these 1-phenyl-2-aminopropanes may result from an interplay between the location of methoxy substituent(s) and the position of the lipophilic group.

The variations in the potencies of the ring substituted 1-phenyl-2-aminopropanes are quite dissimilar to those found in the corresponding 1-phenyl-2-N-methylaminopropanes as demonstrated below:

| Derivatives of 1-Phenyl-2-aminopropanes | Potencies (SRU) | Ratio of Potencies ($1^{o}/2^{o}$) | Potencies (SRU) | Derivatives of 1-Phenyl-2-methylamino-propanes |
|---|---|---|---|---|
| (1AB) | 1.30 | 1.00 | 1.29 | (1CD) |
| (5AB) | 1.25 | 1.25 | 1.96 | (5CD) |
| (11AB) | 0.3 | 1.50 | 0.2 | (11CD) |
| (13AB) | 11.8 | 14.75 | 0.8 | (13AB) |
| (15AB) | 3.6 | 2.12 | 1.7 | (15CD) |
| (16AB) | 100 | 40.65 | 2.46 | (16CD) |

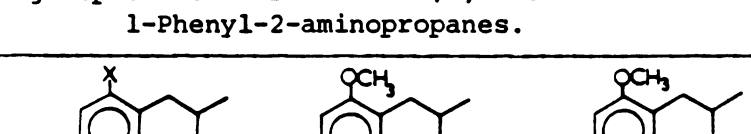
B. A. ($1^{o}$ amine)= 2.418(B. A. ($1^{o}/2^{o}$ amines)) - 4.784

n=6; r= 0.971

Comparison of the potency ratios indicates that the most potent primary amino analogues undergo the greatest reductions in activity upon N-methylation, whereas the potencies of the least active primary amines are least attenuated by comparison to their respective N-methyl counterparts. Accordingly, a significant correlation is found between the potency of the primary amine and the ratio of potencies of the primary and

secondary amines. The differences between these two sets of derivatives is further underscored by the observation that in the ring substituted primary amino derivatives, the most potent member of the enantiomeric pair has the "R" configuration, whereas with the N-methyl compounds, the "S" enantiomer is the most active. While it is difficult to formulate a definitive explination based on this limited data, it is possible that the addition of a methyl group to the amine drastically reduces the psychotomimetic potency thereby revealing other pharmacological actions present perhaps even in the primary amines but overwelmed by the much larger psychotomimetic actions.

Table 23. "Regiospecific" π Data for 2,4,5-Substituted 1-Phenyl-2-aminopropanes.



| Aromatic Sub. Pattern | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $\pi_{ortho}$ [a] | $\pi_{meta}$ [a] | $\pi_{para}$ [a] | Log SRU [b] |
| $OCH_3$ | H | $OCH_3$ | H | H | -0.02 | 0.0 | -0.02 | 0.39 |
| $OCH_3$ | H | H | $OCH_3$ | H | -0.02 | -0.02 | 0.0 | 0.43 |
| H | H | $OCH_3$ | $OCH_3$ | H | 0.0 | -0.02 | -0.02 | -0.52 |
| $OCH_3$ | H | $OCH_3$ | $OCH_3$ | H | -0.02 | -0.02 | -0.02 | 1.07 |
| $CH_3$ | H | $OCH_3$ | $OCH_3$ | H | 0.56 | -0.02 | -0.02 | -0.30 |
| $SCH_3$ | H | $OCH_3$ | $OCH_3$ | H | 0.61 | -0.02 | -0.02 | 0.23 |
| OEt | H | $OCH_3$ | $OCH_3$ | H | 0.51 | -0.02 | -0.02 | -0.15 |
| Br | H | $OCH_3$ | $OCH_3$ | H | 0.86 | -0.02 | -0.02 | 0.53 |
| $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | -0.02 | -0.02 | 0.56 | 2.00 |
| $OCH_3$ | H | $SCH_3$ | $OCH_3$ | H | -0.02 | -0.02 | 0.61 | 1.73 |
| $OCH_3$ | H | OEt | $OCH_3$ | H | -0.02 | -0.02 | 0.51 | 0.53 |
| $OCH_3$ | H | Br | $OCH_3$ | H | -0.02 | -0.02 | 0.86 | 2.61 |
| $OCH_3$ | H | $OCH_3$ | $CH_3$ | H | -0.02 | 0.56 | -0.02 | -0.05 |
| $OCH_3$ | H | $OCH_3$ | $SCH_3$ | H | -0.02 | 0.61 | -0.02 | 0.45 |
| $OCH_3$ | H | $OCH_3$ | OEt | H | -0.02 | 0.51 | -0.02 | 0.11 |
| $OCH_3$ | H | $OCH_3$ | Br | H | -0.02 | 0.86 | -0.02 | 0.36 |

[a] Values taken from Hansch ref. 1d. [b] Values complied in Table 22.

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# ELECTRONIC PROPERTIES

# INTRODUCTION

The first application of molecular orbital parameters to the SAR of a series of methoxy-substituted phenylalkylamines was reported in 1965 by Snyder and Merrill[1a] using Extended Huckel Theory (EHT) calculations. Although this early study encompassed a very limited compound set and employed M.O. methods which are, by today's standards, quite primitive, nonetheless, a qualitative relationship between the potencies and energies of the HOMO's resulted. Following this initial report, Kang and Green[1b] have reinvestigated the relationship between $E_{HOMO}$ and the biological activities of an expanded set of analogues and have reported the following SAR:

$$\text{Log B.A.(m.u.)}=35.1\ E_H+18.7 \qquad \text{(EQ14)}$$

$$N=13;\ r=0.756;\ F=14.62$$

While the statistical regression parameters obtained were not admirable ($r^2=0.57$) and the compound set consisted of methoxy substituted analogues, perhaps the most enlightening single fact to emerge from this study was the observation that the best regression relationships occurred when nonplanar conformations of sterically crowded methoxy groups were used in the calculations of the $E_{HOMO}$. Subsequently, Domelsmith and Houk[1c,d,e] have applied both M.O. theory ("Ab Initio" STO-3G) and photoelectron spectroscopy (pes) methods and obtained the following regression relationship:

$$\log MMU = -2.37IP + 19.53 \quad \text{(EQ15)}$$

$$n = 11,\ r = 0.86$$

All of the above investigations are consistent in that they predict that as electron donating substituents are added to the aromatic ring, the HOMO energies decrease as the biological potencies increase accordingly. This fact suggests that these phenylalkylamines are involved in an electron donor-acceptor complex with the receptor site as has been described by Szent-Gyorgy[1f]. Experimentally, complexation of this type has been reported for a variety of methoxy-substituted benzenes and tetrachanoethylene (TCNE)[1g,h] and chlorinil[1i]. Similarly, Sung and Parker[1j] have reported stability constants (K) for various methoxy-substituted phenylalkylamines and 1,4-dinitrobenzene (DNB). Excluding three compounds, all of which contained nonplanar methoxy groups, there authors obtain the following SAR:

$$MU = -3.798 + 7.918K \quad \text{(EQ16)}$$

$$n = 8,\ r = 0.97$$

Shifrin[1k], using uv difference spectroscopy, has reported that the intramolecular charge-transfer band in a series of N-(β-X-phenylethyl)-3-carbamoylpyridinium chlorides (X=$NH_2$, $OCH_3$, OH, $CH_3$, and Cl) was directly related to the Hammet constant of the particular X substitutent.

Since these previous studies considered only methoxy-substituted compounds, it is now possible to investigate the

SAR's in larger sets of analogues which include the "rearranged" 2,4,5-substituted compounds. In this regard, both theoretical CNDO/2 calculated $E_{HOMO}$ values and experimentally determined pes ionization potentials have been determined, and these parameters are related to the B.A.'s. Further the regional charge distributions and dipole moments of these compounds are defined and their relationship to potency are explored.

# ELECTRON DONOR-ACCEPTOR PROPERTIES

A variety of experimental techniques have been devised which provide measures related to the ionization potential (IP) of a compound. For example, photoelectron spectroscopy (pes), developed mainly by Turner et al.[2a-c] yields a direct measure of IP's in the gas phase. Conversely, in solution, IP's have been determined from polarographic half-wave oxidation potentials ($E^{OX}_{1/2}$), as well as the frequencies of the charge-transfer bands present in the UV-visible spectra of electron donor-acceptor complexes. Extensive applications of these methodologies has permitted a direct comparison of the IP derived from these techniques for a series of methoxybenzenes; the pertinent data are presented in Table 24 , and graphically illustrated in Figure 80. As can be seen, a reasonable correlation exists between the pes IP, and the IP's derived from the $E_{1/2}$ values (n = 6 , r = 0.83 ). Although this correlation is not as good as that obtained by Yang and Psych[2d] from a study of mostly aromatic hydrocarbons, it must be remembered that solvent stabilization of either the parent or the ionized species will probably result in some discrepancies between the gas phase and solution state values. Due to the reactive nature of the oxidized species, only one oxidation potential can be measured using this method[1e] .

The electronic spectra of electron donor-acceptor complexes has also been extensively applied as an experimental measure of IP, since the stabilizing forces in these

aggregates are related to the electron donor capabilities hence IP) of a series of analogues when a single acceptor is considered. For complexes stabilized by charge-transfer (EQ 17) or dispersion (EQ 18) interactions, these relationships have the following grossly simplified forms:

$$\Delta E_{Stab} \simeq - \sum_{d,a} \frac{H_{d,a}^2}{IP_d - EA_a - Q} \qquad EQ(17)$$

where $H_{d,a}$ is the resonance overlap integral between the orbitals on the donor and the acceptor. EA is the electron affinities of the acceptor orbitals. Q is the difference in energy required to transfer an electron from the donor to the acceptor in the complex relative to the same process when the donor and acceptor are separated by infinite distance.

$$\Delta E_{Stab} \simeq \frac{K}{IP_d + K'} \qquad EQ(18)$$

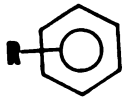
where K is related to the interaction energies of the singly-excited electronic configurations of the donor and acceptor. K' is related to the energy difference between the ground state and singly-excited state in the acceptor.

Experimentally, it has been possible to relate $IP_{pes}$ with the frequency of the charge-transfer band ($\gamma_{CT}$) according to the general equation [2f]:

$$IP_{pes} = a(h\gamma_{CT} + b)$$

Comparison of the $IP_{pes}$ values with those derived from the charge-transfer spectra of the TCNE complexes reveals a good correlation between the two ($n = 13$ , $r = 0.915$). However, ortho-dimethoxybenzene is not well described by this linear relationship since its charge-transfer IP is considerably higher than its $IP_{pes}$ value. According to previous discussion of the nonplanar preference of the methoxy groups in this compound (see Chapter IIIB),as well as the diminished

Table 24. Comparison of the Ionization Potentials Determined By Several Methods of Methoxy-Substituted Benzenes.



| Aromatic Substitution Pattern | Photoelectron Ionization Potential [a] | Polarographic Oxidation Potential [b] | TCNE Complex Stability [c] | TCNE Complex Stability [d] | Chloronil Complex Stability [e] |
|---|---|---|---|---|---|
| H | 9.20 [f] | | 25.8(9.25) | ——— | 29.5(9.87) |
| | d | | ——— | ——— | |
| OMe | 8.39 | 1.76(8.65) | 19.7(8.27) | 19.7(8.27) | 22.3(8.87) |
| | 9.22 | | 26.1(9.23) | 25.8(9.18) | 29.2(9.83) |
| 1,2-diOMe | 8.44 | 1.45(8.32) | 16.9(7.84) | 16.9(7.84) | ——— |
| | 8.94 | | 23.3(8.81) | 23.1(8.77) | ——— |
| 1,3-diOMe | 8.18 | ——— | 17.9(8.00) | 18.2(8.05) | 19.4(8.46) |
| | 8.72 | | 22.7(8.71) | 21.3(8.51) | 23.8(9.08) |
| 1,4-diOMe | 7.90 | 1.34(8.20) | 15.7(7.69) | 16.1(7.73) | 18.3(8.31) |
| | 9.19 | | 26.3(9.25) | 26.3(9.25) | 29.0(9.80) |
| 1,2,3-triOMe | 8.29 | 1.42(8.28) | 19.4(8.23) | 19.4(8.23) | ——— |
| | d | | ——— | | |

| | | | | | |
|---|---|---|---|---|---|
| 1,2,4-triOMe | 7.31 | 1.12(7.96) | 14.6(7.51)<br>23.4(8.82) | 14.6(7.51)<br>22.4(8.67) | ——— |
| 1,3,5-triOMe | 8.15<br>d | 1.49(8.36) | ——— | 18.2(8.05) | 20.5(8.62) |

[a]Values taken from L. N. Domelsmith and K. N. Houk, Int. J. Quant., 5, 257 (1978).

[b]$E_{\frac{1}{2}}$ values taken from A. Zweig, W. G. Hodgson and W. H. Jura, J. Am. Chem. Soc., 86, 4124 (1964); values in ( ) represent conversion of the solution phase $E_{\frac{1}{2}}$ values to gas phase IP values according to the equation of R. Miller, J. O. C., 37, 916 (1972): $E_{\frac{1}{2}}=0.92IP-6.2$.

[c]Frequency ($\gamma$) of the charge-transfer absorption bands taken from E. M. Voigt and C. Reid, J. Amer. Chem. Soc., 86, 3930 (1964); IP values in ( ) are derived from the relationship derived by R. Foster, "Organic Charge-Transfer Complexes," Academic Press, New York (1969) p.44: $I^D=(h\gamma_{CT}+4.42)/0.83$.

[d]Frequencies ($\gamma$) of the charge-transfer absorption bands taken from A. Zweig, J. Phys. Chem., 67, 506 (1963); IP values in ( ) are derived from the TCNE equation in Ref. c.

[e]Frequencies ($\gamma$) of the charge-transfer absorption bands taken from A. Kuboyama, Tokyo Kogyo Shikensho Hokoku, 57, 11 (1962); IP values derived from Foster's equation in Ref. c: $I^D=(h\gamma_{CT}+5.13)/0.89$.

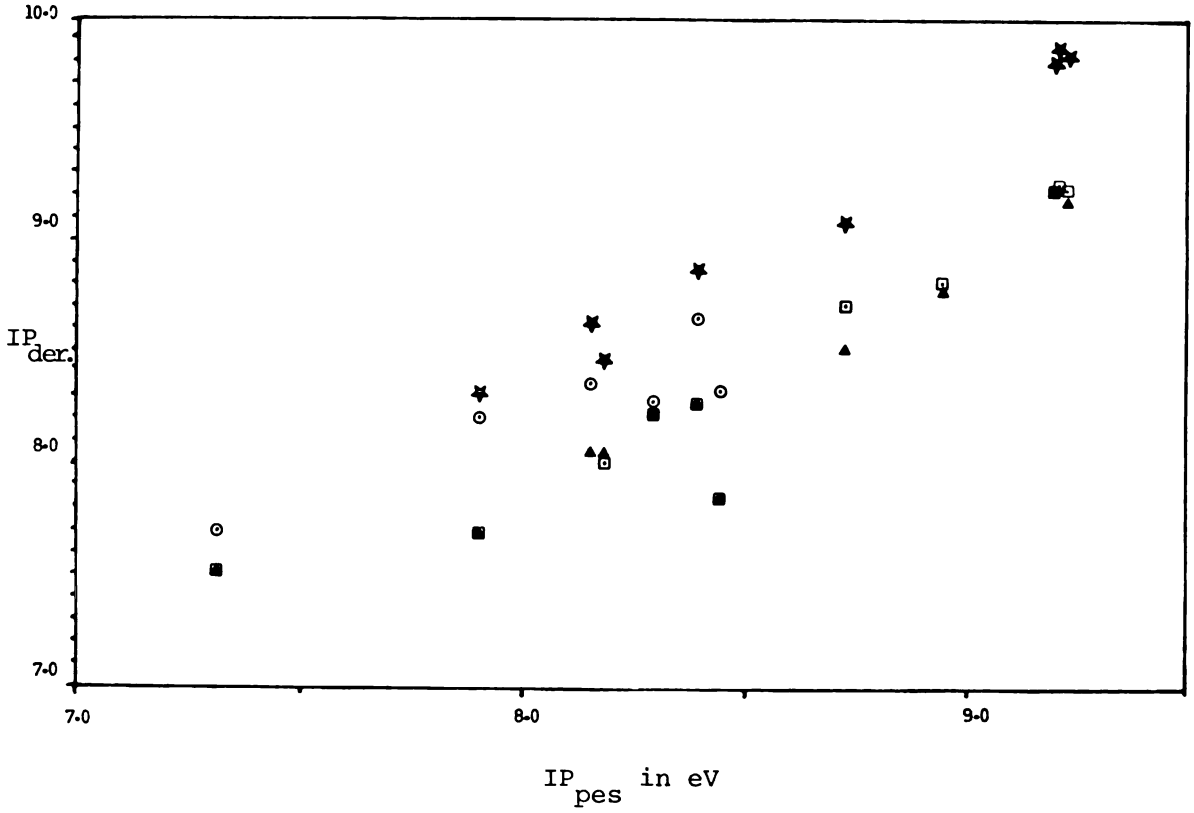


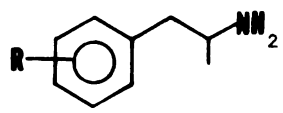

FIGURE 80. **Comparison of the Gas Phase pes IP's** Values **with Those Derived from Polaragraphic, $E_{\frac{1}{2}}$ (Δ), TCNE Electron Donor-Acceptor Complex Stabilities (○,□), and Chlorinil Complex Stabilities** ★ for a Series of Methoxy-substituted Benzenes.

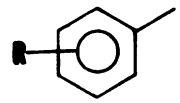
magnitude of this effect in solution, this deviation is well explained. Somewhat unusual is the good agreement between these measures for the 1,2,4-trimethoxybenzenes which might also be expected to fall outside the linear correlation line. While fewer compounds are available for the complexes with chlorinil, again an excellent correlation between these IP's and those obtained from pes is found (n = 8 , r =0.989). Of further interest is the fact that these correlations are equally good considering either the first or second IP. The origin and significance of the second charge-transfer absorption band has been the subject of numerous explanations in the literature. Essentially three theories seem appropriate: 1) the two charge-transfer bands arise from electron donation from two energy levels in the donor [2g,h], 2) from acceptance of electrons into two unfilled energy levels in the acceptor [2i], or, 3) from two different orientations of the donor-acceptor molecules in the complex [2j-l].

While undoubtedly good arguments can and have been made supporting each explanation for various complexes, concerning the TCNE- or chlorinil-methoxybenzene complexes reported here, the first alternative appears most applicable.

Molecular orbital calculations are also capable of yielding valuable information concerning IP's. Koopman[2m] has demonstrated that the IP were linearily related to the negative of the orbital electron energies. This relationship is useful since it allows one to predict the effects of conformational changes on an experimentally determined observable

Table 25. Comparison of Experimental Ionization Potentials and CNDO/2 Frontier Orbital Energies.




| Compound | Aromatic Sub. Pattern $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Exp. Gas Phase Ion. Pot.[a] $IP_1$ | $IP_2$ | Cal. Frontier Orbital Energies[b] $E_{HOMO(1)}$ | $E_{HOMO(2)}$ |
|---|---|---|---|---|---|---|---|---|---|
| (1AB) | H | H | H | H | H | 8.99 | 9.35 | -0.472 | -0.505 |
| (2AB) | H | H | $OCH_3$ | H | H | 8.16 | 8.90 | -0.429 | -0.493 |
| (3AB) | H | $OCH_3$ | H | H | H | 8.28 | 8.93 | -0.445 | -0.488 |
| (4AB) | $OCH_3$ | H | H | H | H | 8.24 | 8.93 | -0.437 | -0.489 |
| (6AB) | $OCH_3$ | $OCH_3$ | H | H | H | 8.30 | 8.72 | -0.421 (-0.430) | -0.458 (-0.458) |
| (7AB) | $OCH_3$ | H | $OCH_3$ | H | H | 7.91 | 8.75 | -0.410 | -0.417 |
| (8AB) | $OCH_3$ | H | H | $OCH_3$ | H | 7.70 | 8.86 | -0.409 | -0.478 |
| (9AB) | $OCH_3$ | H | H | H | $OCH_3$ | 8.18 | 8.39 | -0.440 | -0.442 |
| (10AB) | H | $OCH_3$ | H | $OCH_3$ | H | ___ | ___ | -0.443 | -0.454 |
| (11AB) | H | H | $OCH_3$ | $OCH_3$ | H | 8.03 | 8.86 | -0.411 (-0.419) | -0.480 (-0.478) |
| (12AB) | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | H | 8.09 | 8.36 | -0.415 (-0.419) | -0.426 (-0.442) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (13AB) | $OCH_3$ | H | $OCH_3$ | $OCH_3$ | H | 7.66 | 8.69 | -0.392<br>(-0.397) | -0.472<br>(-0.473) |
| (14AB) | $OCH_3$ | H | $OCH_3$ | H | $OCH_3$ | 7.76 | 8.19 | -0.416 | -0.447 |
| (15AB) | H | $OCH_3$ | $OCH_3$ | $OCH_3$ | H | 8.16 | 8.16 | -0.404<br>(-0.417) | -0.447<br>(-0.446) |
| (16AB) | $OCH_3$ | H | $CH_3$ | $OCH_3$ | H | 7.62 | 8.68 | -0.400 | -0.470 |
| (17AB) | $OCH_3$ | H | Br | $OCH_3$ | H | 7.94 | 8.92 | -0.375 | -0.439 |
| (23AB) | $SCH_3$ | H | $OCH_3$ | $OCH_3$ | H | 7.75[c] | 9.1[c] | -0.406<br>(-0.412) | -0.476<br>(-0.474) |
| (24AB) | $OCH_3$ | H | $SCH_3$ | $OCH_3$ | H | 7.64[c] | 9.42[c] | -0.405<br>(-0.406) | -0.465<br>(-0.461) |
| (25AB) | $OCH_3$ | H | $OCH_3$ | $SCH_3$ | H | 7.64[c] | 9.2[c] | -0.409<br>(-0.413) | -0.475<br>(-0.476) |
| (26AB) | $CH_3$ | H | $OCH_3$ | $OCH_3$ | H | 7.83[c] | 8.65[c] | -0.401<br>(-0.407) | -0.471<br>(-0.472) |
| (27AB) | $OCH_3$ | H | $OCH_3$ | $CH_3$ | H | 7.68[c] | 8.61[c] | -0.403 | -0.472 |
| (28AB) | Br | H | $OCH_3$ | $OCH_3$ | H | 7.89[c] | 8.87[c] | -0.375<br>(-0.377) | -0.423<br>(-0.423) |
| (29AB) | $OCH_3$ | H | $OCH_3$ | Br | H | 7.89[c] | 8.87[c] | -0.371 | -0.434 |

[a] IP's for the appropriately substituted 1-phenyl-2-aminopropanes taken from L. N. Domelsmith and K. N. Houk in "QuaSAR: Research Monograph #22," G. Barnett, M. Trsic, and R. E. Willette (1978), pp. 423-440.

[b] $E_{Homo}$ values in a.u. obtained from CNDO/2 calculations on planar and minimum energy ( ) conformations.

[c] IP values from L. N. Domelsmith and K. N. Houk, personal communication.

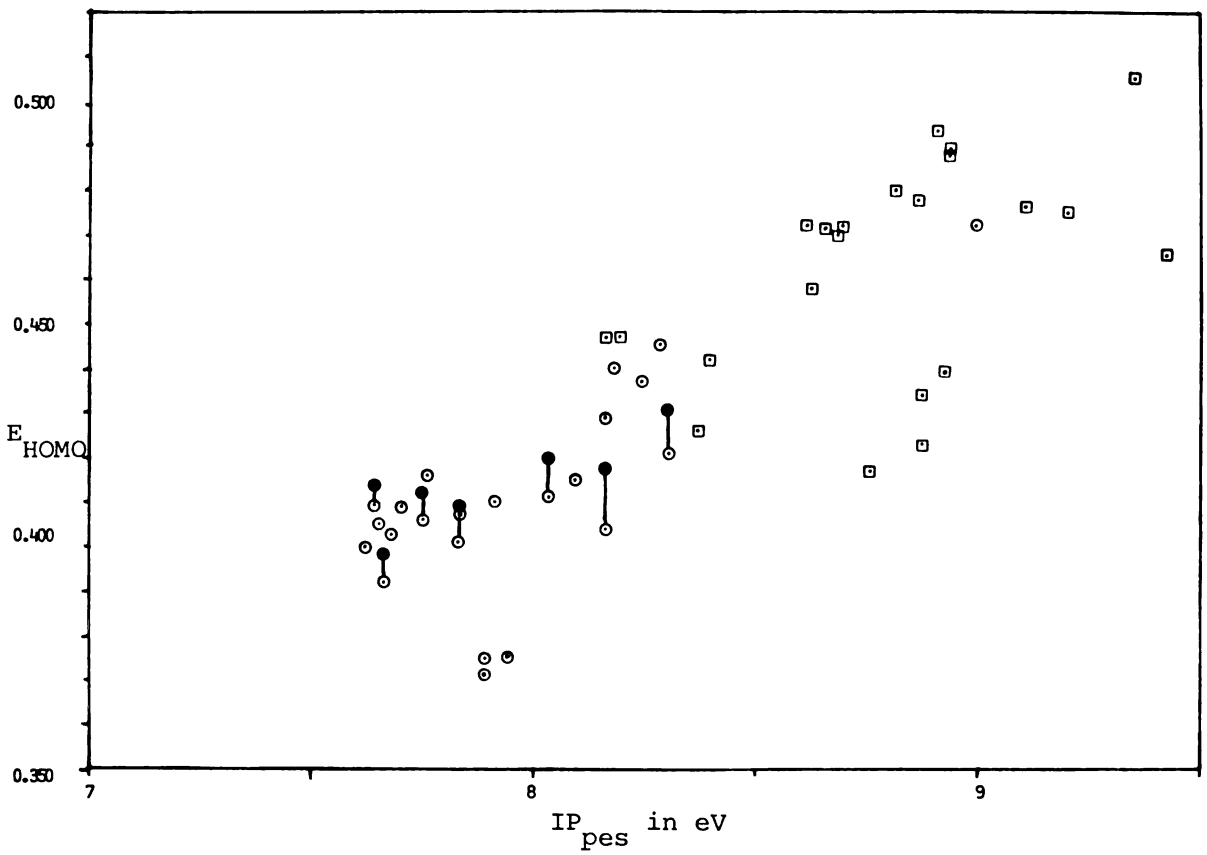



FIGURE 81. Comparison of the IP Obtained from pes Measurement with CNDO/2 Calculated HOMO Energies of a Series of Ring-substituted 1-Phenyl-2-aminopropanes. (Open Circles Indicate the $E_{HOMO}$ Values for the Planar Conformations; Solid Circles Indicate the $E_{HOMO}$ Values for the Nonplanar Global Minimum Conformations; the Squares Represent the $E_{SHOMO}$ Values for the Planar Conformations.

such as IP. In order to study this, CNDO/2 frontier orbital energies were calculated for the appropriately substitued toluene model compound and these energies have been compared in Table 25 to the pes $IP_1$'s. Graphical illustration of this data is presented in Figure 81. This graph and table demonstrate a reasonable correlation between these calculated $E_{HOMO}$ and measured IP for the planar conformation ($n = 20$, $r = 0.89$). This correlation is considerably improved when the $E_{HOMO}$s of the seven sets of nonplanar compounds are used ($n = 20$, $r = 0.92$). The three deviant $E_{HOMO}$ points are all bromo-substituted compounds in which case it appears that the parameterization of the bromine leaves much to be desired with regard to orbital energies . Even excluding the bromo-substituted compounds, a much poorer correlation exists between the calculated and measured $IP_2$ regardless of the substitutent group conformation and this appears to be an inherent infirmity of the CNDO/2 method.

Direct comparison of the gas phase IP's for a series of methoxy-substituted 1-phenyl-2-aminopropanes with the 1,4-dinitrobenzene (DNB) complex stabilities is graphically illustrated in Figure 82 ; the correlation between these two parameters showed considerable scatter ($n = 13$, $r = 0.61$). The two points which had the greatest deviation from linearity were the 3,4,5-trimethoxy analogues, whose complex stability was much higher than expected on the basis of the pes IP, and the 3,4-methylenedioxy compound in which the complex stability is much lower than the IP would indicate. This is

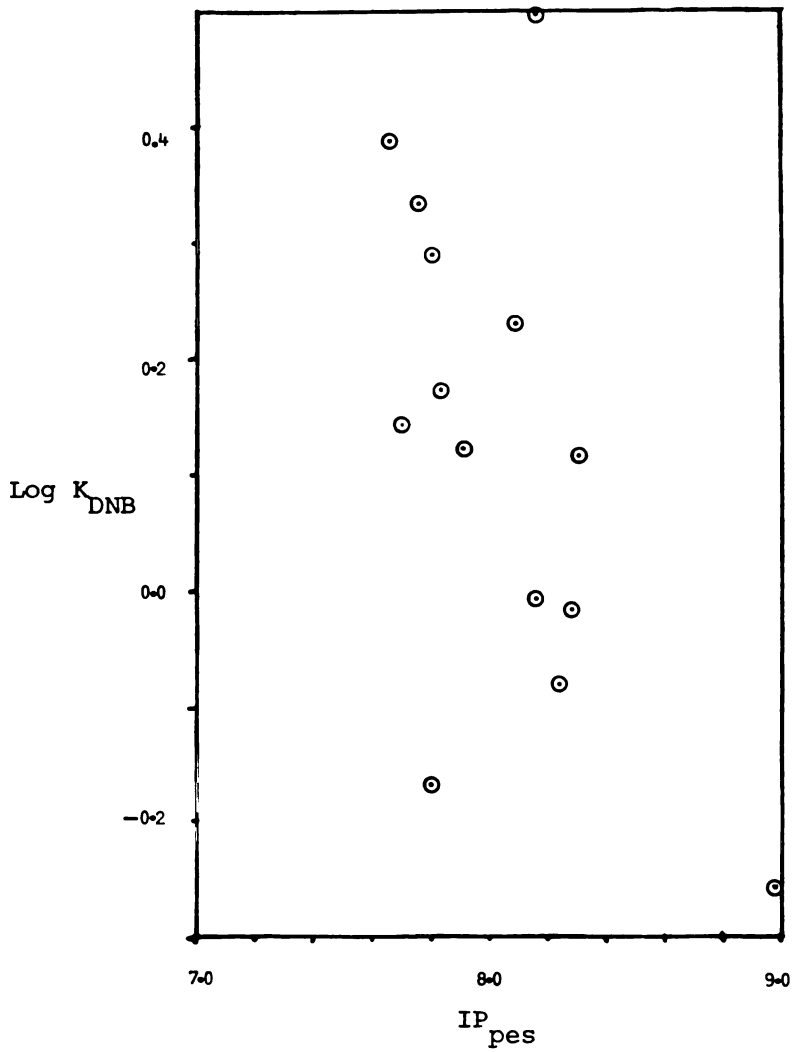



FIGURE 82. Comparison of the $IP_{pes}$ Values with the Log of the DNB Complex Stabilities for a Series of Methoxy-substituted 1-Phenyl-2-amino-propanes.

rather curious since each of these cases represents conformational extremes. Clearly the central methoxy group in 3,4,5-trimethoxy compound is nonplanar and, conversely, the conformation of the 3,4-methylenedioxy compound is planar. These results may be evidence that a substantial amount of the complexation between these analogues may result from the δ-donating properties of the oxygen lone pairs rather than the pure π donation.[2p,q] Alternately, complexation between the amine and DNB may play a considerable role in the stabilization of these complexes which are clearly weak (even the highest $K_{DNB}$ value predicts that the association energy is only 0.3 kcal/mol.).[2r] Questions such as these could be answered by examining the IP's of compounds bearing substitutents having no lone pair electrons.

Measurement of the IP's of many derivatives of 1-phenyl-2-aminopropane have been reported by Domelsmith and Houk[1c-e]. In collaboration with these experimentalists, the photoelectron spectra (Figures 83-87) of a series of 2,4,5-dimethoxy-X-substituted 1-phenyl-2-aminopropanes were measured and the IP's were tabulated in Table 25. While detailed discussion of these spectra as well as trends in the IP's of various of these compounds have been reported, a brief discussion of the most pertinent results will be made.

The photoelectron spectrum of 1-phenyl-2-aminopropane is similar to that of toluene with respect to the

$\pi$ ionization potentials, both of which are found in the region between 8.9-9.2 eV. The difference between the spectra of these two compounds is due to the lone pair ionization of the amine group which occurs at 9.2-9.5 eV, which is very similar to the lone pair IP's of isopropylamine[3a] which is found at 9.31 eV. Larger differences between the two high lying $\pi$ molecular orbitals result from substitution of powerful electron donating groups such as methoxy or thiomethyl substituent on the aromatic ring. While the second IP ($IP_2$) is relatively unaffected by these substituents, considerably lower first IP ($IP_1$) are observed (toluene $IP_1$=8.72eV, anisole $IP_1$=8.04 eV). Addition of multiple methoxy groups result in in even greater decreases in $IP_1$'s only in those cases where these substituents are allowed to exist in a planar conformation. For example, 2,5-, 2,4-dimethoxy- and 2,4,6-trimethoxy-substituted 1-phenyl-2-aminopropanes are planar and have $IP_1$'s of 7.70, 7.91, and 7.76 eV respectitavely. Whereas, 2,3-, 3,4-dimethoxy, 3,4,5-, 2,3,4-, and 2,4,5-trimethoxy substituted 1-phenyl-2-aminopropanes are nonplanar compounds which have higher $IP_1$'s (8.30, 8.03, 8.16,8.09 and 7.66 eV). In all these cases, except the 2,4,5-trimethoxy compound, substitution of additional methoxy groups to the parent dimethoxy compounds has resulted in trimethoxy derivatives with $IP_1$'s similar

to those occuring in the monomethoxy analogues. The one exception to this conclusion is the 2,4,5-trimethoxy compound which has the lowest $IP_1$ of any of the various mono, di and tri-methoxy isomers, however, even in this exceptional case, the observed $IP_1$ is abnormally greater than expected since the 2,5-dimethoxy-4-methyl compound, DOM, has an even smaller $IP_1$ even though methoxy groups are greater electron donators than methyl groups.

Inspection of the $IP_1$'s of the 2,4,5-dimethoxy-X-substituted compounds reveals entirely analogous trends in that the order of the various compounds follows that of the respective dimethoxy compounds: 3,4 > 2,4 > 2,5. With regard to the X substituents, the $IP_1$'s are generally ordered according to the electron donating ability of the particular group: H > Br > $CH_3$ > $SCH_3$ > $OCH_3$.

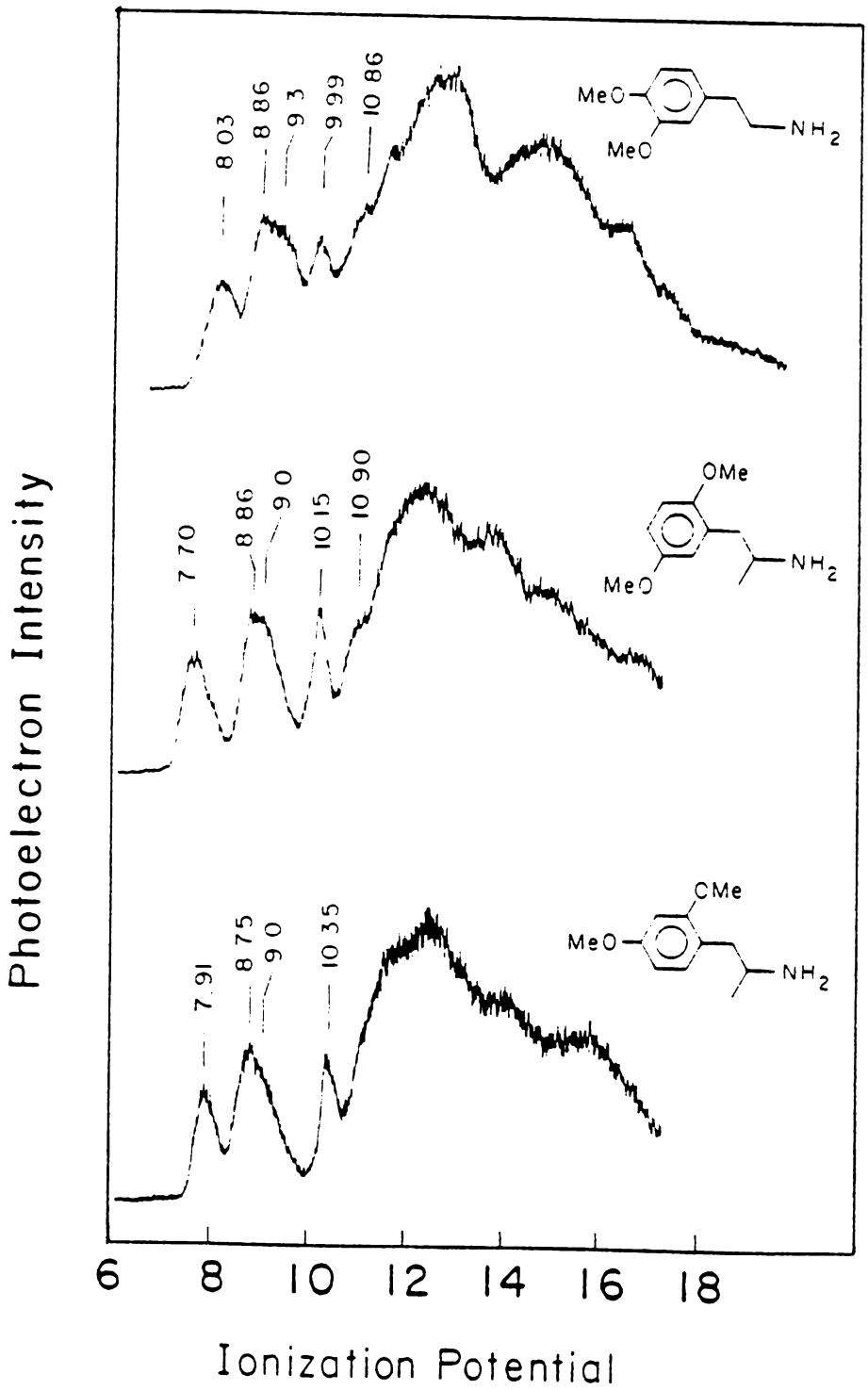



FIGURE 83. Photoelectron Spectra of the 3,4-, 2,5-, and 2,4-Dimethoxy Derivatives of 1-Phenyl-2-amino-propane.

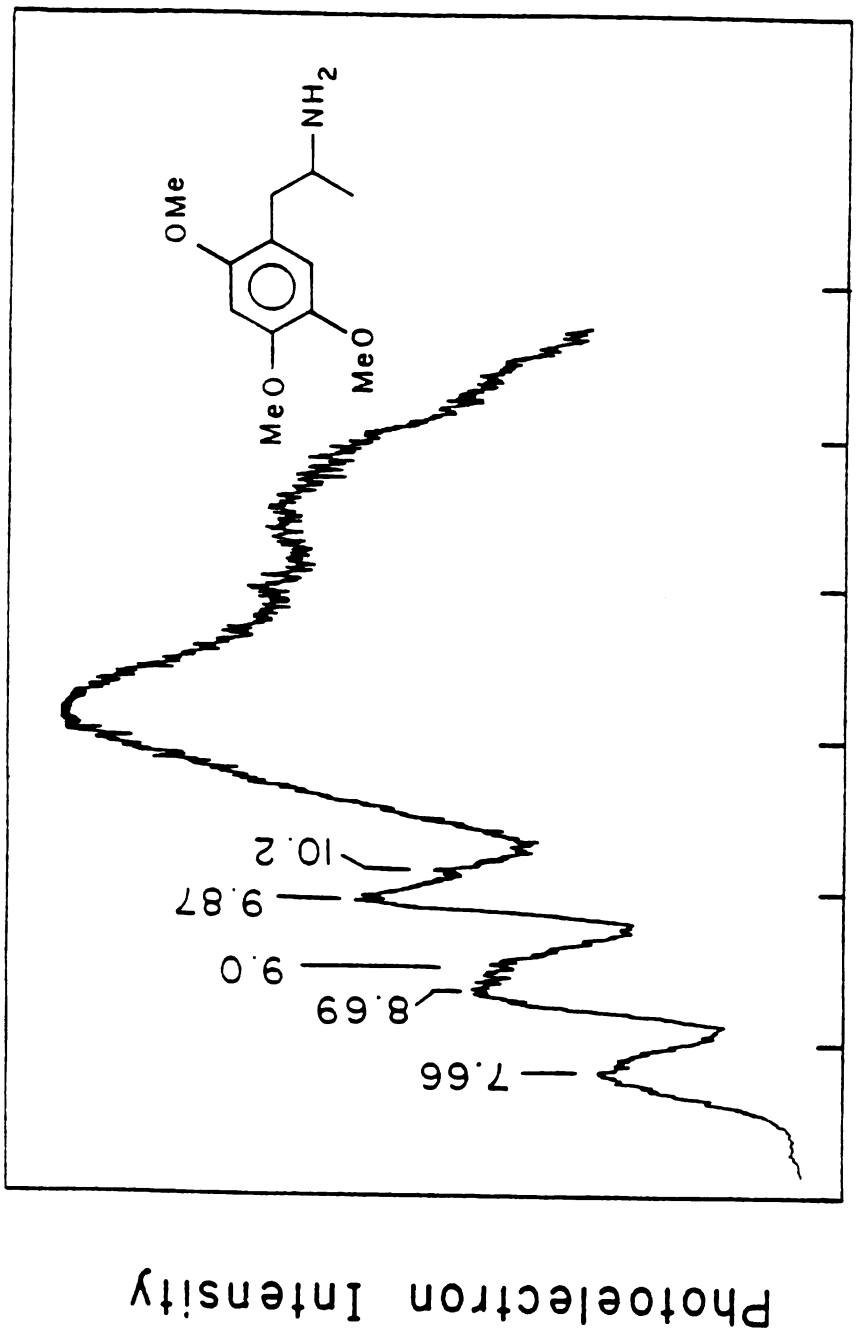



FIGURE 84. Photoelectron Spectra of 1-(2,4,5-Trimethoxy-phenyl)-2-aminopropanes.

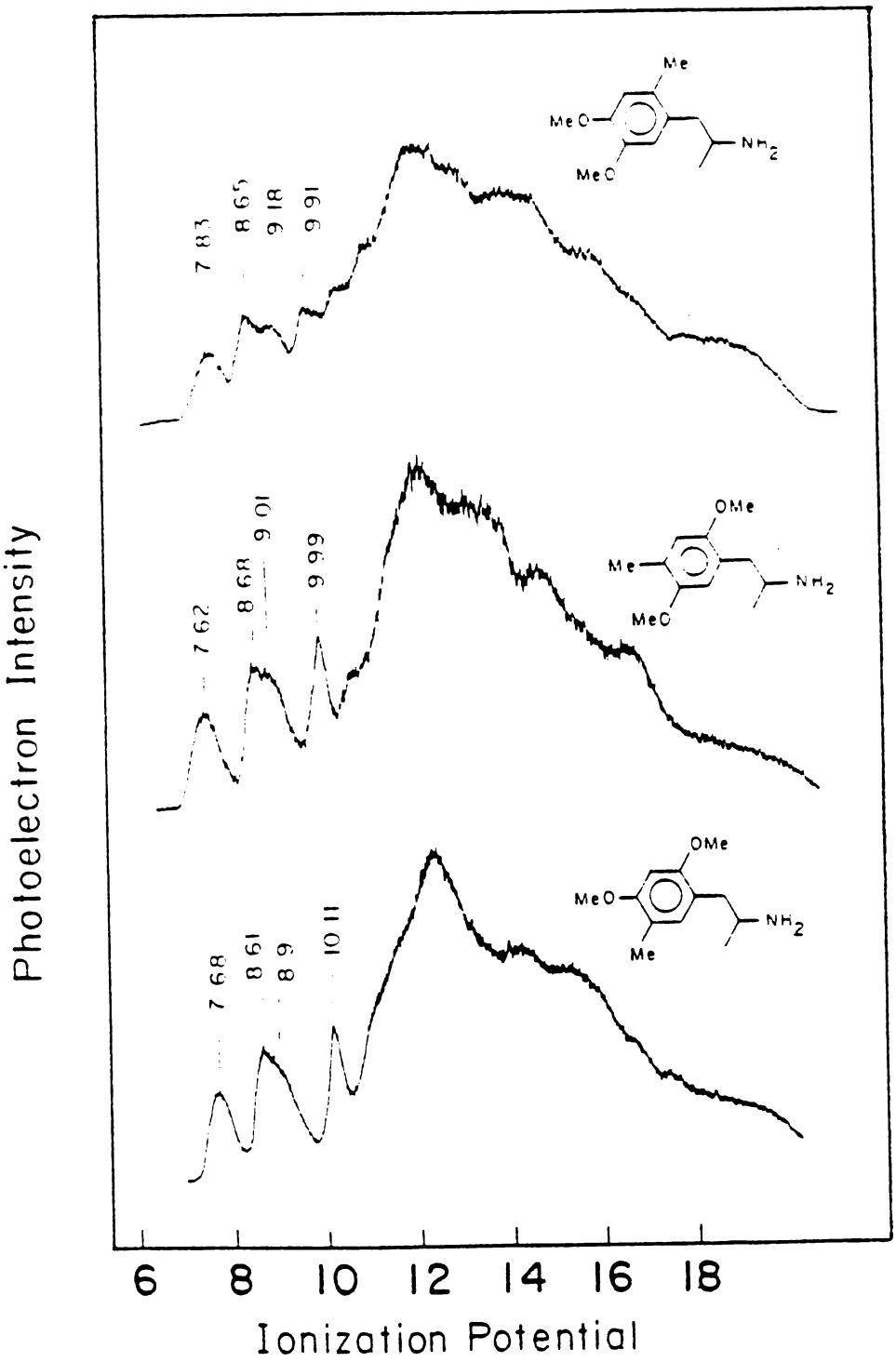



FIGURE 85. Photoelectron Spectra of the Isomeric 2,4,5-Methyldimethoxy Derivatives of 1-Phenyl-2-aminopropane.

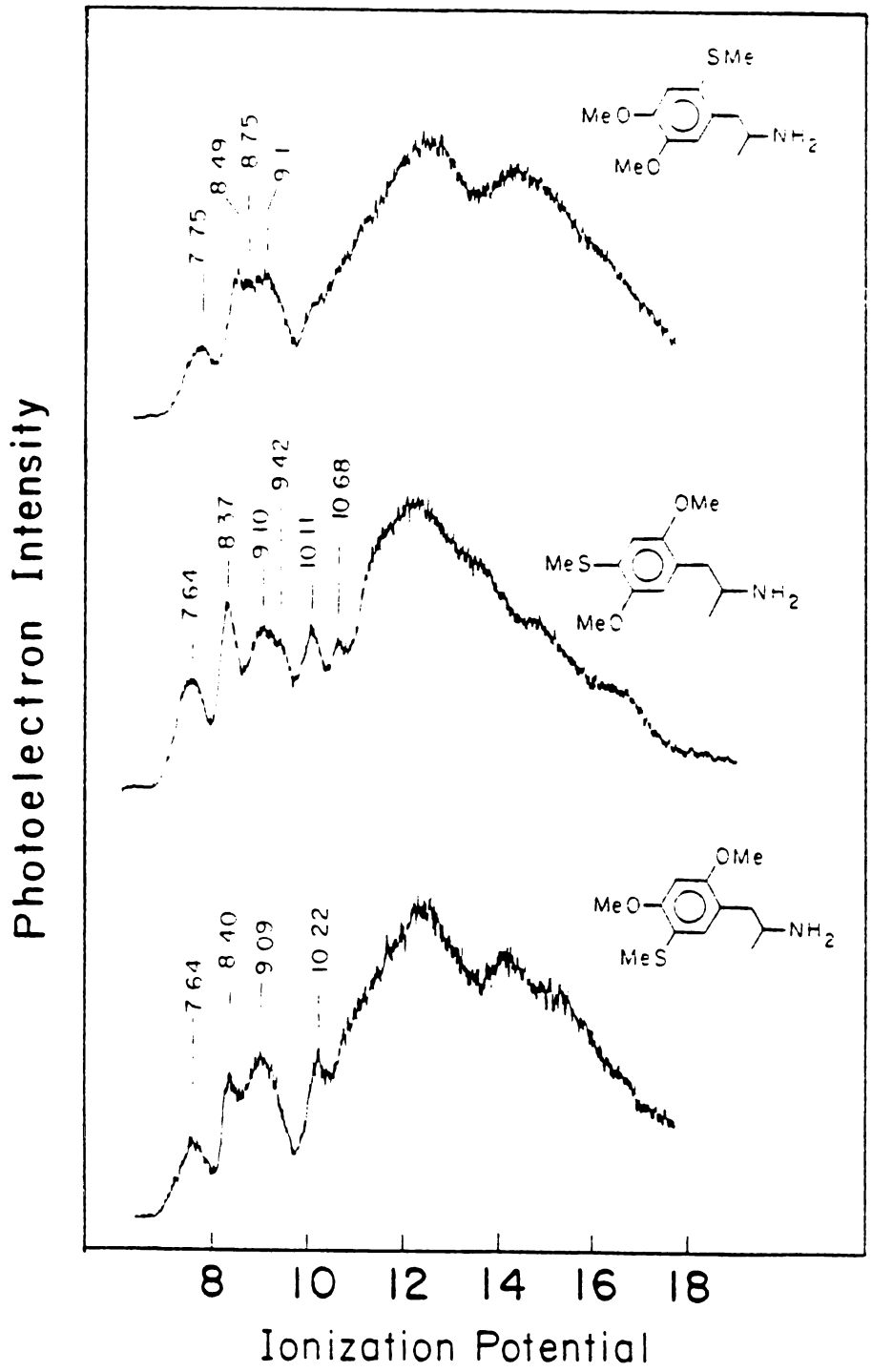



FIGURE 86. Photoelectron Spectra of the Isomeric 2,4,5-Thiomethyldimethoxy Derivatives of 1-Phenyl-2-aminopropane.

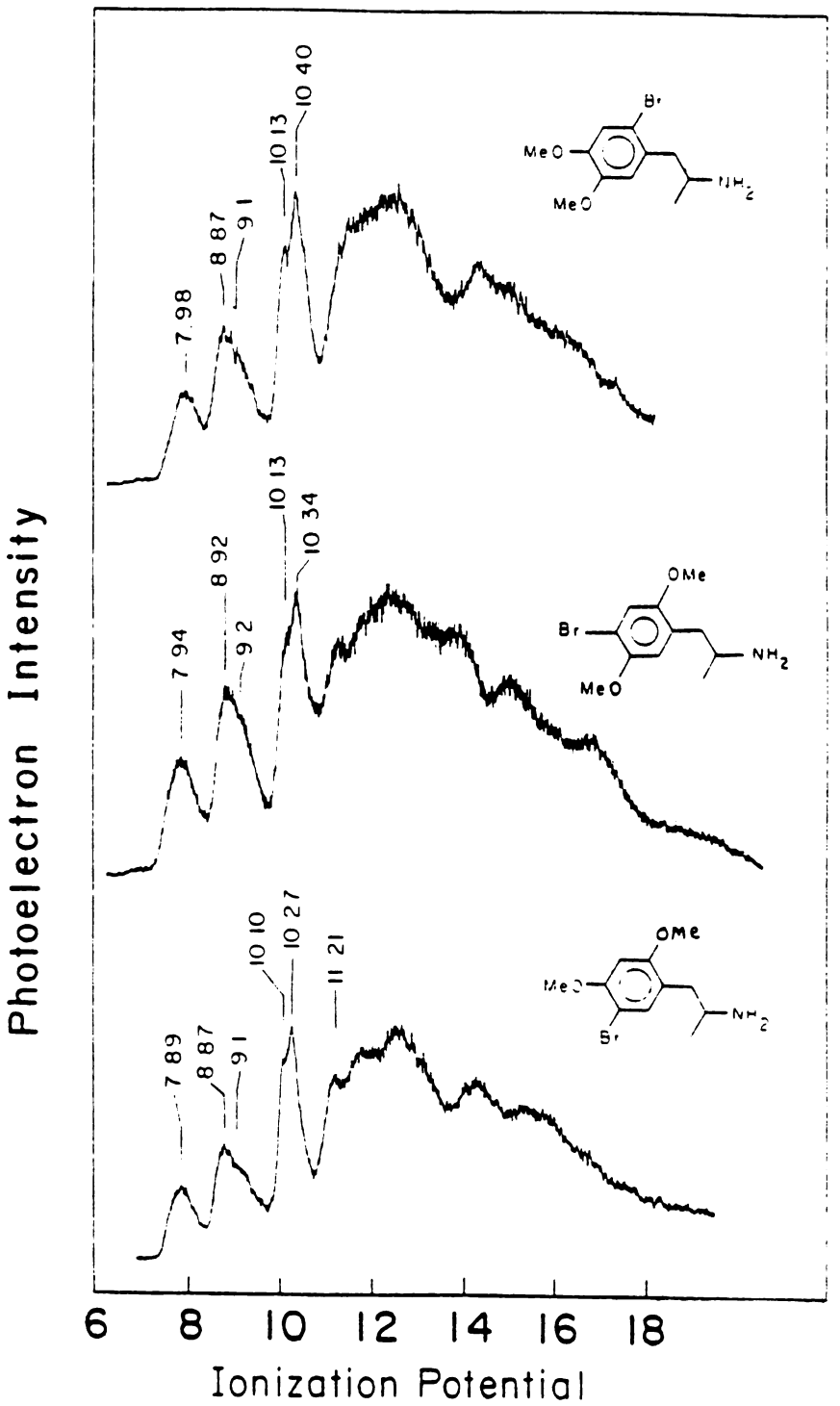



FIGURE 87. Photoelectron Spectra of the Isomeric 2,4,5-Bromodimethoxy Derivatives of 1-Phenyl-2-aminopropane.

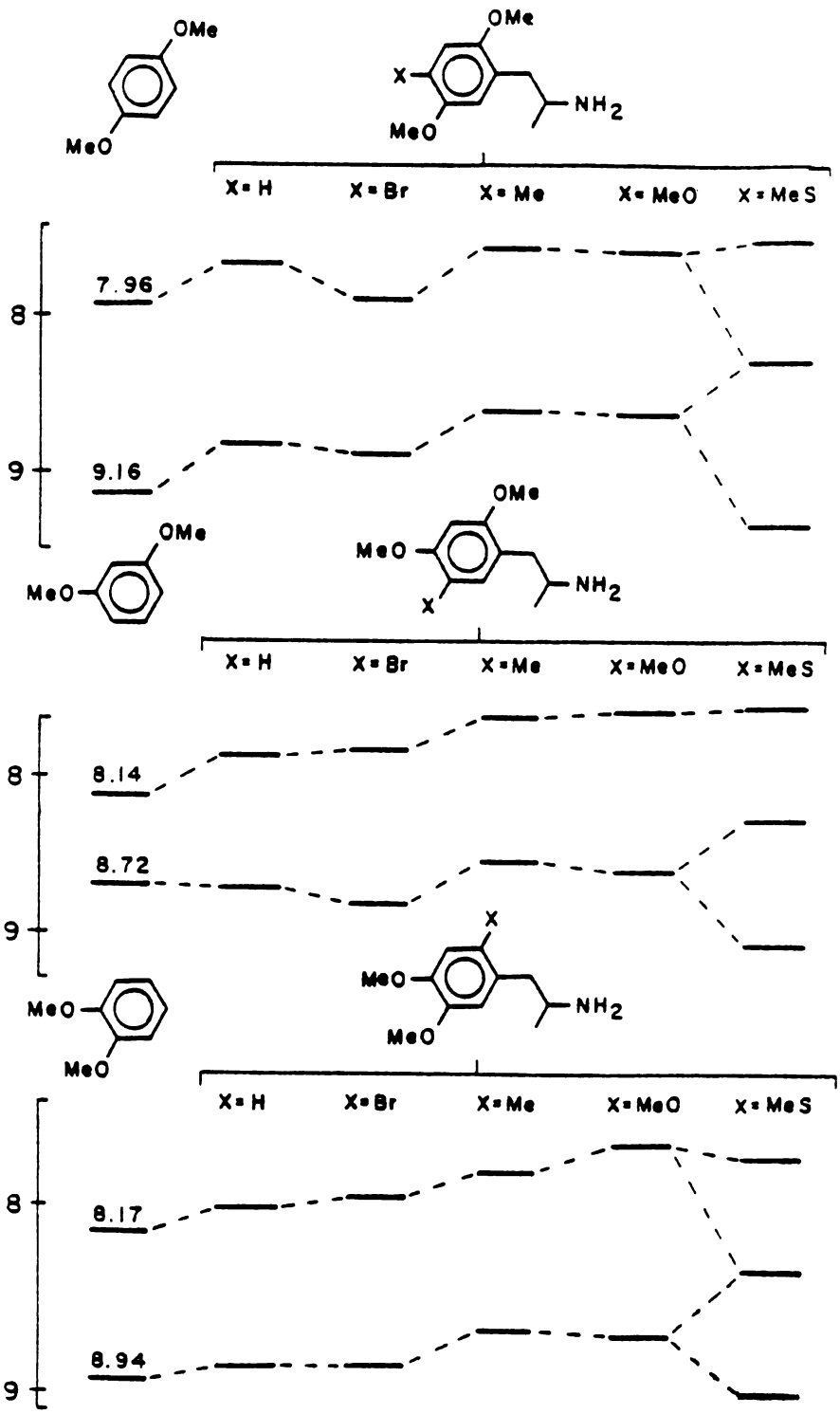
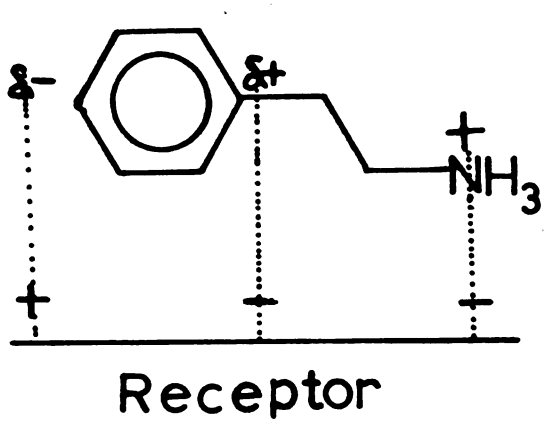



FIGURE 88. Correlation Between the π IP's of Dimethoxybenzenes and Dimethoxy-X-substituted Derivatives of 1-Phenyl-2-aminopropane where X=H, $OCH_3$, $CH_3$ $SCH_3$, and Br.

REGIOSPECIFIC ELECTRONIC PROPERTIES

In the previous section, relationships were explored between the biological activities and IP's of a series of ring substituted derivatives of 1-phenyl-2-aminopropane. These studies indicated a general relationship between the capacity of these compounds to donate electron (as reflected by low IP's) and the magnitude of the association constant. However, the stability of the electron donor-acceptor complex is dependent not only on the strength of the electron donor but also the orbital arrangement and densities of the outer filled molecular orbitals. Accordingly, factor governing the stability of the drug receptor complex are likely to be related to regiospecific electronic properties of these derivatives. A complete study of the electronic structure of these compounds will not be attempted here, however a general discussion of effect of various substituents on the dipole moment and charge densities of the aromatic carbons based on CNDO/2 calculations will be made.

The electronic factors involved in the binding of derivatives of 1-phenyl-2-aminopropanes to the biological receptor site has been postualted to dependent upon a strong association of the ammonium group with complimentary anionic site as well as an attraction between partial electronic charges located on the aromatic ring carbons.




Total charge densities of the aromatic ring carbons of various substituted toluenes are presented in Figures 89-93. Inspection of Figure 89 shows that addition of a methoxy group to toluene results in considerable polarization of the charge densities of the aromatic carbons as well as a large increase in the dipole moment. Comparison of the densities of the isomeric monomethoxytoluenes indicates that the carbon to which the methoxy group is attached bears a large positive charge, whereas carbons ortho to this positive center acquire a negative charge. The charge seperation is greatest in the meta methoxytoluene since both electron donating substituents are located at positions which do not allow resonance conjugation to diminish the contribution of each.

The dipole moment of the planar dimethoxytoluenes (Figure 90) are ordered as follows: 3,4 > 2,4 $\gg$ 2,5. An even larger dipole moment results in the 3,4-dimethoxytoluene when the methoxy group in the 4 position is in

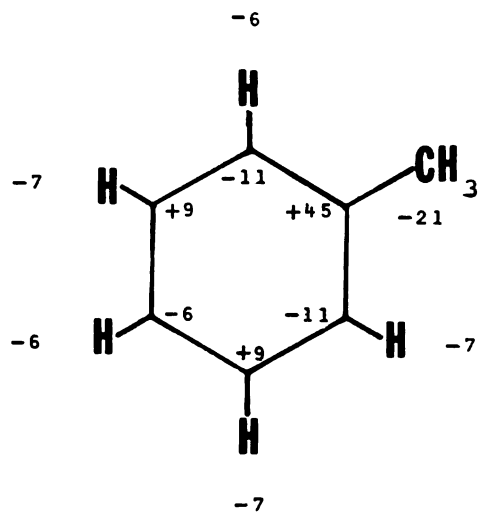
a nonplanar confirmation. The low dipole moment of the 2,5-dimethoxytoluene results from the cancellation of the opposing dipole moments of the C-O-$CH_3$ atoms and yet, even in this compound, a great degree of electronic polarization of the aromatic carbons occurs.

The trends in the planar dimethoxythiomethyltoluenes are similar to that found in the simpler dimethoxy compounds with the dipole moments ordered as follows: 2,4-dimethoxy-5-thiomethyl> 3,4-dimethoxy-2-thiomethyl> 2,5-dimethoxy-4-thiomethyl-toulene. Unlike a methoxy group, a thiomethyl substituent is clearly less powerful electron donor and therefore induces much weaker charge pertubation on the aromatic carbon to which it is attached. Scrutiny of Figure 91 also reveals an unexplained reduction of the dipole moment in the nonplanar compared with the planar 3,4-dimethoxy-2-thiomethyltoluene molecule.

Of the isomeric dimethoxymethyltoluenes illustrated in Figure 92, the dipole moments follow the trends established in the dimethoxytoluenes and due to the diminished strength of the electron donor relative to both a methoxy and thiomethyl group, the polarization of the aromatic carbons is correspondingly less.

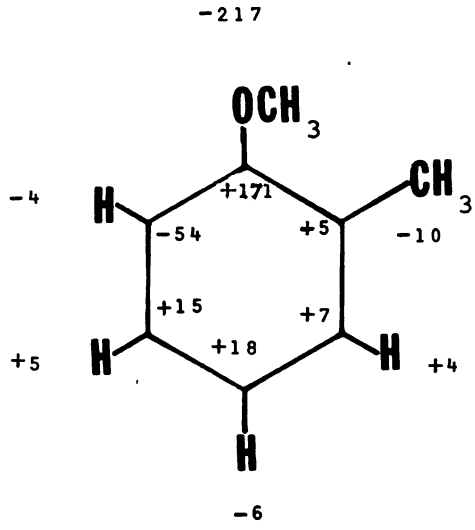
While definitive conclusion regarding which electronic features of these agents is related to potent psychotomimetic activity can not be made without serious reser-

vations, an association between activity and either low dipole moment or large positive charge on the aromatic ring carbons located at the 2 and 5 positions can be made.



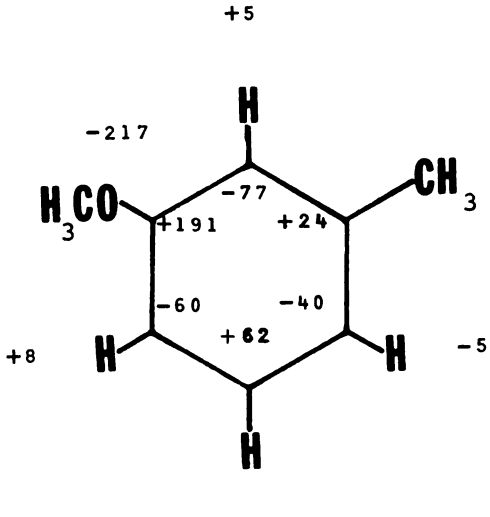

(a)

Dipole Moment = 0.23 D

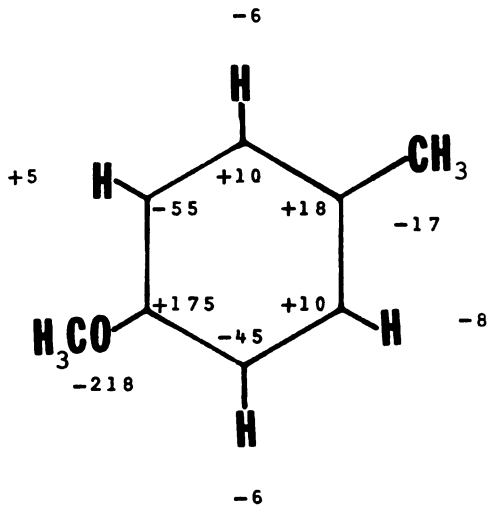



(b)
$T_2=180^{o}$

Dipole Moment = 1.42 D

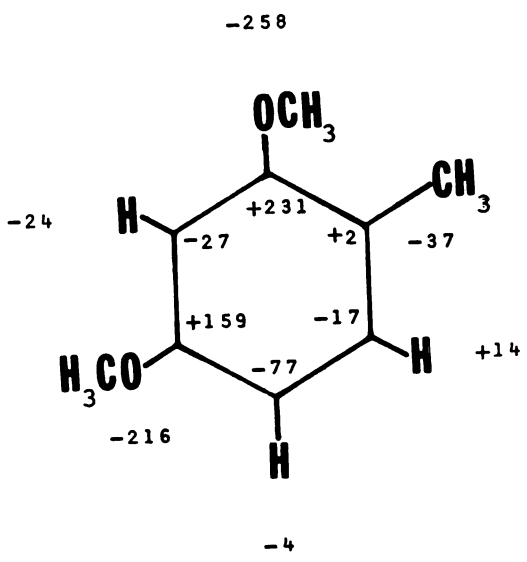



(c)
$T_3=180^{o}$
Dipole Moment = 1.80 D

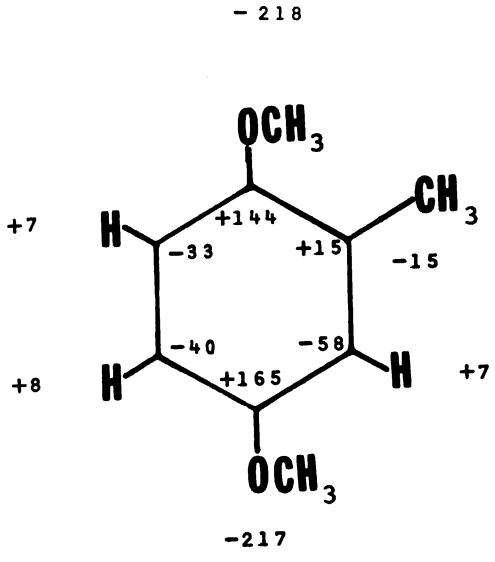



(d)
$T_4=180^{o}$
Dipole Moment = 1.60 D

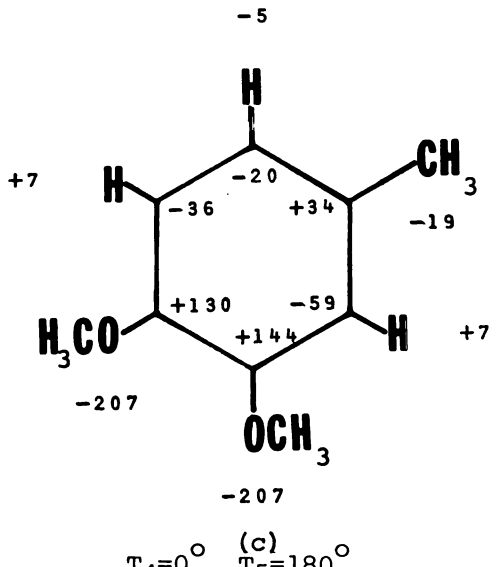
FIGURE 89. CNDO/2 Calculated Atomic Charge Densities (Units of $10^{-3}$ Electrons) and Dipole Moments (D) of a) Toluene, b) 2-, c) 3-, and d) 4-Methoxy toulenes.



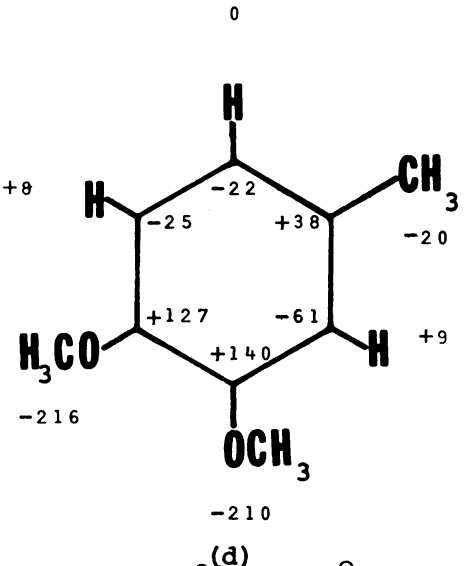

$T_2=180^{o}$,(a) $T_4=180^{o}$
Dipole Moment = 1.78 D




$T_2=180^{o}$,(b) $T_5=180^{o}$
Dipole Moment = 0.20 D

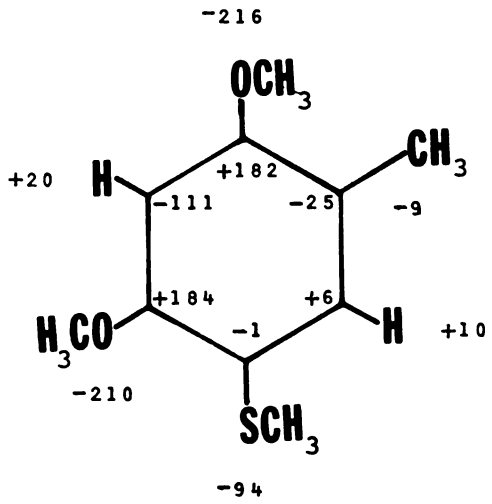



$T_4=0^{o}$, (c) $T_5=180^{o}$
Dipole Moment = 2.55 D

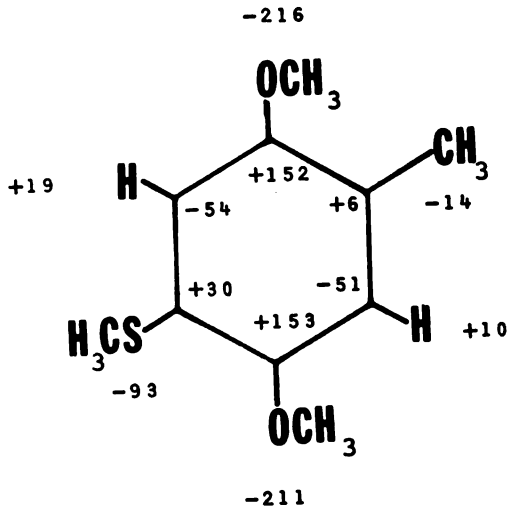



$T_4=120^{o}$,(d) $T_5=180^{o}$
Dipole Moment = 2.93 D

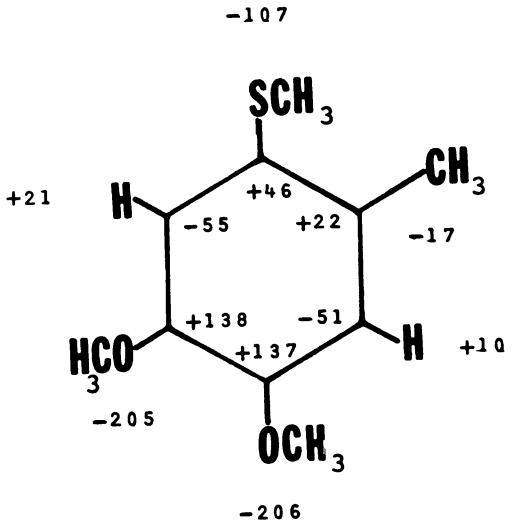
FIGURE 90. CNDO/2 Calculated Atomic Charge Densities (Units of $10^{-3}$ Electrons) and Dipole Moments (D) of a) 2,4-, b) 2,5- and c) & d) 3,4-Dimethoxytoluenes.



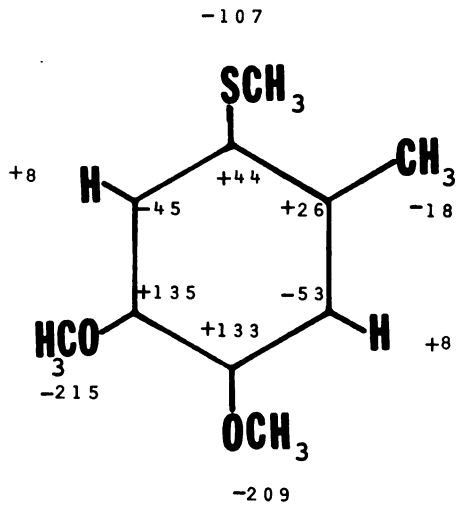

(a)
$T_2=180^\circ$, $T_4=0^\circ$, $T_5=180^\circ$
Dipole Moment = 2.75 D




(b)
$T_2=180^\circ$, $T_4=0^\circ$, $T_5=180^\circ$
Dipole Moment = 0.55 D

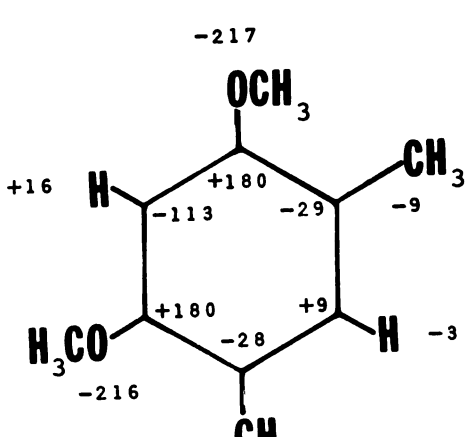



(c)
$T_2=180^\circ$, $T_4=0^\circ$, $T_5=180^\circ$
Dipole Moment = 2.36 D



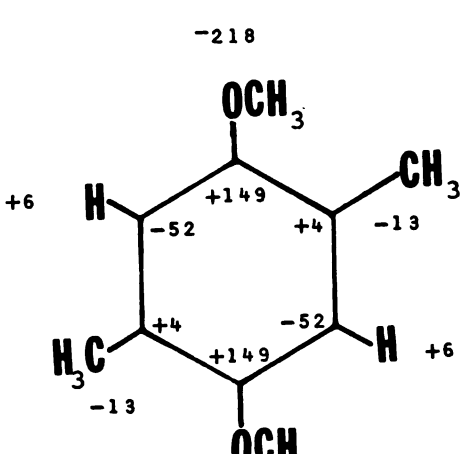

(d)
$T_2=180^\circ$, $T_4=120^\circ$, $T_5=180^\circ$
Dipole Moment = 2.17 D

FIGURE 91. CNDO/2 Calculated Atomic Charge Densities (units of $10^{-3}$ Electrons) and Dipole Moments (D) of a) 2,4-Dimethoxy-5-thiomethyl-, b) 2,5-Dimethoxy-4-thiomethyl-, and c) & d) 4,5-Dimethoxy-2-thiomethyl-toluene.



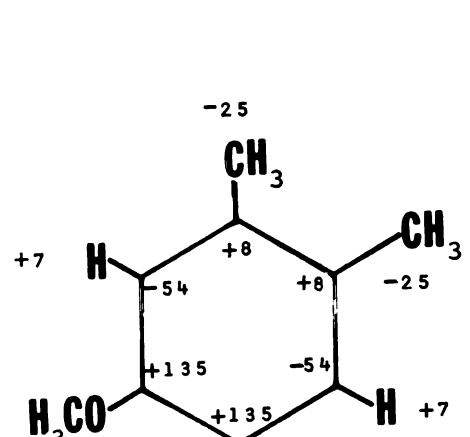

(a)

$T_2=180^{\circ}$, $T_4=0^{\circ}$
Dipole Moment = 1.98 D



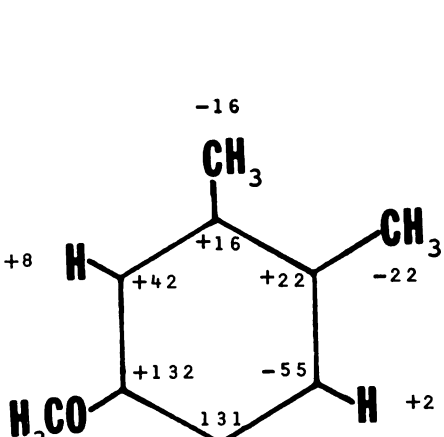

(b)

$T_2=180^{\circ}$, $T_5=180^{\circ}$
Dipole Moment = 0.0 D




(c)

$T_4=0^{\circ}$, $T_5=180^{\circ}$
Dipole Moment = 2.67 D




(d)

$T_4=120^{\circ}$, $T_5=180^{\circ}$
Dipole Moment = 2.99 D

FIGURE 92. CNDO/2 Calculated Atomic Charge Densities (Units of $10^{-3}$ Electrons) and Dipole Moments (D) of a) 2,4-Dimethoxy-5-methyl-, b) 2,5-Dimethoxy-4-methyl- and c) & d) 4,5-Dimethoxy-2-methyl-toluene.

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