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SYNTHESIS, CONFORMATION, AND ABSOLUTE CONFIGURATION OF BIOLOGICALLY ACTIVE PHENETHYLAMINE DERIVATIVES

by

Richard Brian Walker
B.S., University of Southern California, 1970

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

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in

PHARMACEUTICAL CHEMISTRY

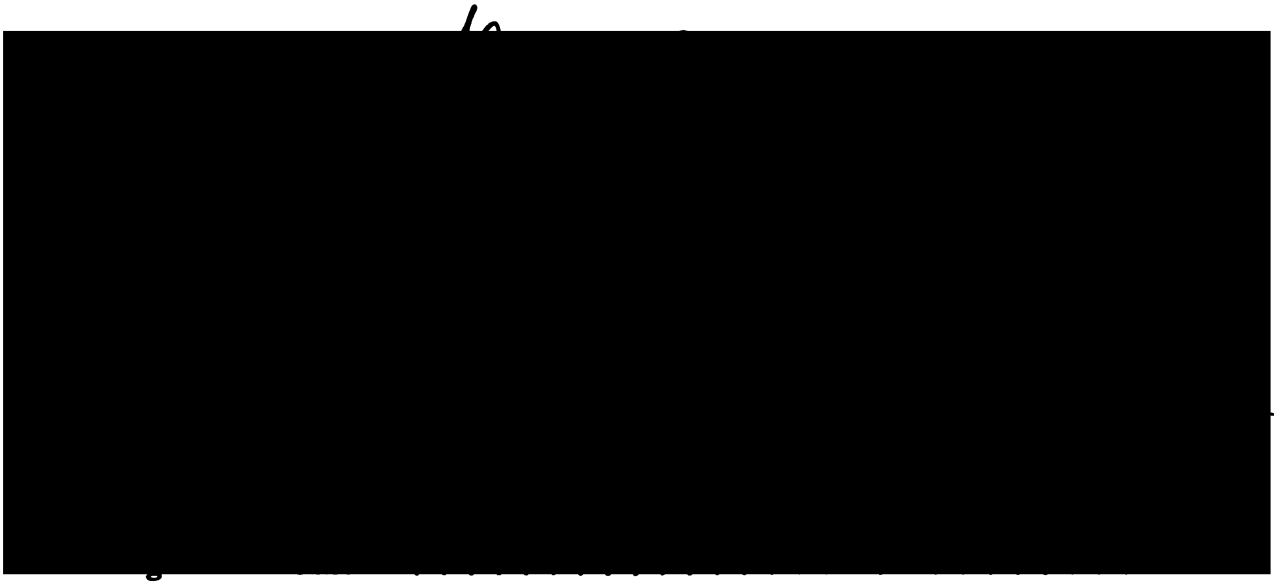
in the

GRADUATE DIVISION

(San Francisco)

of the

UNIVERSITY OF CALIFORNIA



ABSTRACT

Title: SYNTHESIS, CONFORMATION AND ABSOLUTE CONFIGURATION OF BIOLOGICALLY ACTIVE PHENETHYLAMINE DERIVATES

Richard Walker, Ph.D.

June 1975

Derivatives of CNS active phenethylamines were synthesized and their conformations and absolute configurations were determined by NMR, IR and circular dichroism spectra.

The tetrahydroisoquinoline alkaloids anhalonidine and pellotine were obtained from Lophophora williamsii and were found to be levorotatory and have the R configuration. This was established by comparing the CD spectra with resolved, synthetic O-methylanhalonidine and O-methylpellotine. Natural O-methylanhalonidine from the same plant is known to be dextrorotatory and have the S configuration. N-methylation of R (-) O-methylanhalonidine gave rise to (-) O-methylpellotine with a negative CD maximum, thus could be assigned the R configuration. Natural pellotine was levorotatory and also gave a negative CD maximum. Therefore it could also be assigned the R configuration.

The O-methyl derivatives were found to be stable with respect to racemization, while anhalonidine and pellotine are not. A mechanism of racemization is proposed.

Oxazolidines derived from reactions of ephedrine and pseudoephedrine isomers with various aldehydes and ketones were prepared. Reaction between ephedrine and an aromatic aldehyde was found to yield a single oxazolidine

where two diastereomers are possible. The chemical shift behavior observed and the presence of Bohlmann bands around 2700 cm^{-1} in the infrared showed that the N-methyl is fixed trans to the 4-methyl and 2-aryl groups and the new asymmetric center can be assigned the 2S configuration.

Reaction of ephedrine with (+) 3 methylcyclohexanone gave a single product while reaction with (+) methylcyclopentanone yielded a diastereomeric pair. However the absolute configuration could not be assigned.

Observations of coupling constants between vicinal protons and chemical shifts of oxazolidine ring substituents showed the five membered ring perfers a fixed conformation with the vicinal protons eclipsed in the ephedrine derivatives and antiparallel in the pseudoephedrine derivatives.

These oxazolidines were tested for their ability to separate and identify the ephedrines and pseudoephedrines by GLC. Oxazolidines derived from substituted cyclohexanones gave the best separation of ephedrine and pseudoephedrine derivatives, the t-butylcyclohexanone derivative giving the highest R factor. Also ephedrine and pseudoephedrine reacted with cyclohexanone and t-butylcyclohexanone upon injection onto the GLC column to give excellent separation of diastereomers. The d and l isomers could be readily separated by derivatization with N-pentafluorobenzoyl-S-(-)-prolyl l-imidazolide (PFPBI).

β-haloephedrines and β-O-alkylephedrines were prepared and their conformations were studied by NMR. The (-) haloephedrines were observed to prefer a gauche conformation, while the (+) halopseudoephedrines preferred a trans conformation, similar to (-) ephedrine and (+) pseudoephedrine respectively. However both the O-alkylephedrines and pseudoephedrines prefer the trans conformation.

Reaction of a (+) halopseudoephedrine with base yielded (-) cis 2-phenyl-1, 3-dimethylaziridine which readily underwent deuterolysis to β-deuterodeoxyephedrine. The reaction was not stereospecific, however, and partial racemization also occurred at the α carbon. l-P-(+) β-deuterodeoxyephedrine was synthesized by reaction of (-) bromoephedrine HBr with sodium borodeuteride in DMSO.

ACKNOWLEDGEMENTS

I am very grateful to Dr. John C. Craig, my research director, for his great patience and helpful instruction. I would like to thank Dr. Neal Castagnoli for giving me much encouragement and many helpful hints. I also thank Dr. S. B. Matin for his help on the isoquinoline work, and Dr. Ara Paul, at the University of Michigan, for kindly contributing the plant samples of anhalonidine and pellotine. I am very thankful to Cathy Lee for the CD spectra, to Trudy Beelen for much of the GLC work, and to Dr. Larry Gruenke for the mass spectra. I am also grateful to Drs. Patrick Callery, Joe Gal, Mark Cushman, and Kent Marshall for a concerned interest in my work. I thank Dr. Leslie Benet for the use of his GLC equipment. My best wishes extend to Ron Woodard who is currently completing the unfinished work on ephedrines and amphetamines.

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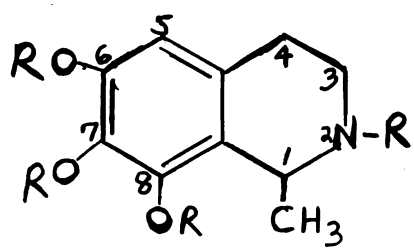
SYNTHESIS, CONFORMATION, AND ABSOLUTE CONFIGURATION OF BIOLOGICALLY ACTIVE PHENETHYLAMINE DERIVATIVES

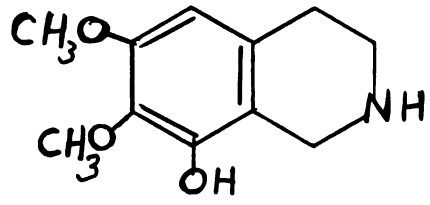
CHAPTER I. SYNTHESIS, RESOLUTION, AND ABSOLUTE CONFIGURATION OF ISOQUINOLINE ALKALOIDS FROM LOPHOPHORA WILLIAMSII

The simplest isoquinoline alkaloids, found mostly in members of the Cactacae, are tetrahydroisoquinolines bearing oxygen substituents at positions 6 and 7 and frequently at position 8, and a methyl substituent at position 1. The oxygen substituents may be hydroxyl, methoxyl or methylenedioxy groups, and the nitrogen may be secondary or tertiary.

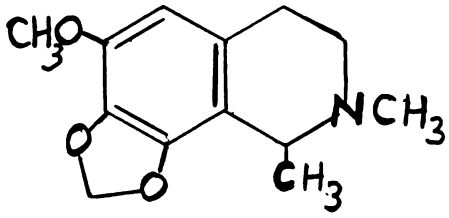


Introduction

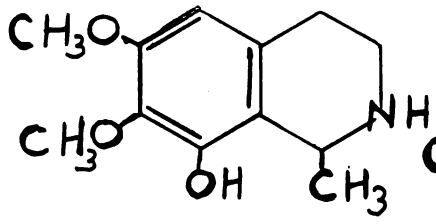
The peyote cactus (Lophophora williamsii) has been used for centuries for its hallucinogenic properties[1], which have been shown to be due to the presence of mescaline[2]. However, the cactus also contains a number of related tetrahydroisoquinoline alkaloids. The more common ones are anhalamine[3, 7], lophophorine[4, 7], anhalomidine[5, 7], and pellotine[6, 7].



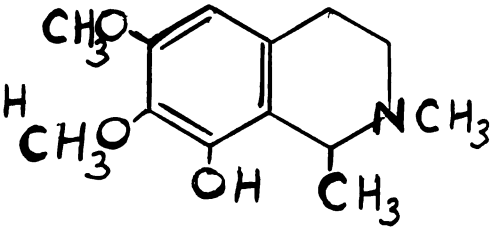
Anhalamine



Lophophorine



Anhalonidine



Pellotine

Limited pharmacological testing of these compounds suggests they possess some CNS activity, but do not have the pronounced psychotomimetic effects of mescaline[8].

Spath[9] first elucidated the structure and synthesized these compounds between 1919 and 1939. He reported the anhalonidine and pellotine obtained from peyote to be devoid of optical activity. Spath and Keszler[10] reported obtaining pellotine with slight optical activity after tartaric acid resolution, which rapidly racemized on standing. This suggests the alkaloids may be optically active in the plant but racemize during the extraction procedure. Later investigation of these compounds has been hindered by difficulty in their synthesis and their sensitivity to air oxidation and polymerization[11, 12].

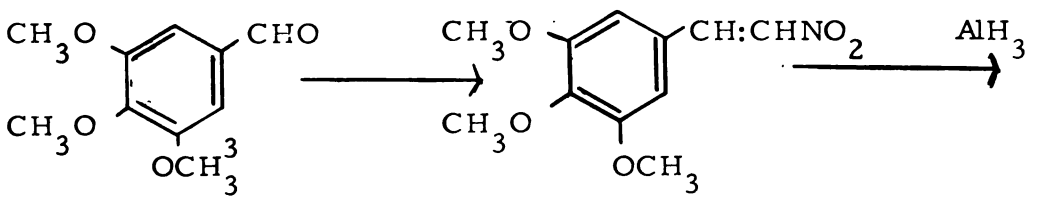
O-methyl-d-anhalonidine $[\alpha]_D$=(+) 20.5° was isolated from the cactus in samll amounts by Spath[13]. Brossi[14] established by X-ray crystallography that this compound has the S configuration. Matin[15] resolved O-methylanhalonidine and reported that an ethanolic solution of (-) O-methylanhalonidine racemizes rapidly on standing. To date, optically active anhalonidine has not been reported, therefore the absolute configuration of the cactus alkaloid is not known. The direct O-methylation of anhalonidine has also not been accomplished.

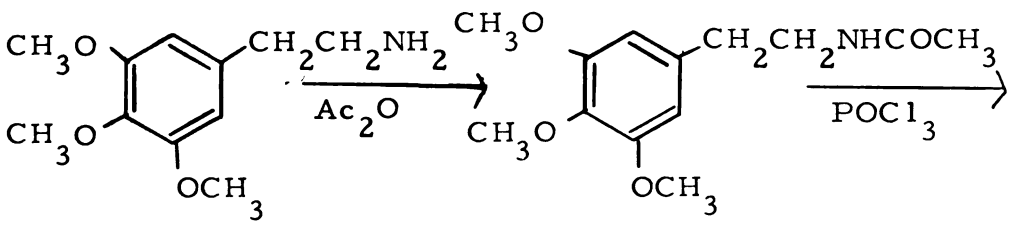
In this study, we tested several plant samples of anhalonidine and pellotine for optical activity, in an attempt to isolate optically active material and determine the absolute configuration by ORD/CD. Anhalonidine, O-methylanhalonidine, and O-methylpellotine were also resolved and their stability towards racemization was investigated. A mechanism for the racemization is proposed.

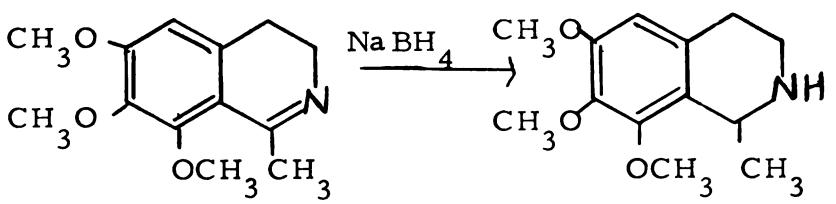
Results and Discussion

A. Synthesis and Resolution of O-methylanhalonidine

O-methylanhalonidine was prepared according to the procedure of Brossi[12].







However, several of the steps were modified to give improved yields over those reported in the literature. These are discussed in the experimental section.

The resolution of O-methylanhalonidine was done with orthonitrotantranilic acid (ONTA)[16] according to the method of Matin[15]. However, it was observed that when this resolving agent was used, the resolved base became easily contaminated with o-nitroaniline resulting from the facile hydrolysis of ONTA, resulting in lower rotations than reported. The aniline could be removed, however, by ethereal extraction of a pH 4.0 (phthalate buffer) solution of the amine--see experimental section.

The optical purity could easily be determined by using the asymmetric GLC derivatizing agent pentafluorobenzoylprolylimidazolide[17] (PFPBI).

B. Stability of O-methylanhalonidine Towards Racemization

In light of the reports[15] that ethanolic solutions of O-methylanhalonidine racemize upon standing, we synthesized and resolved O-methlanhalonidine and observed the change in optical rotation of an ethanolic solution of (+) O-methylanhalonidine base and hydrochloride over a four day period.

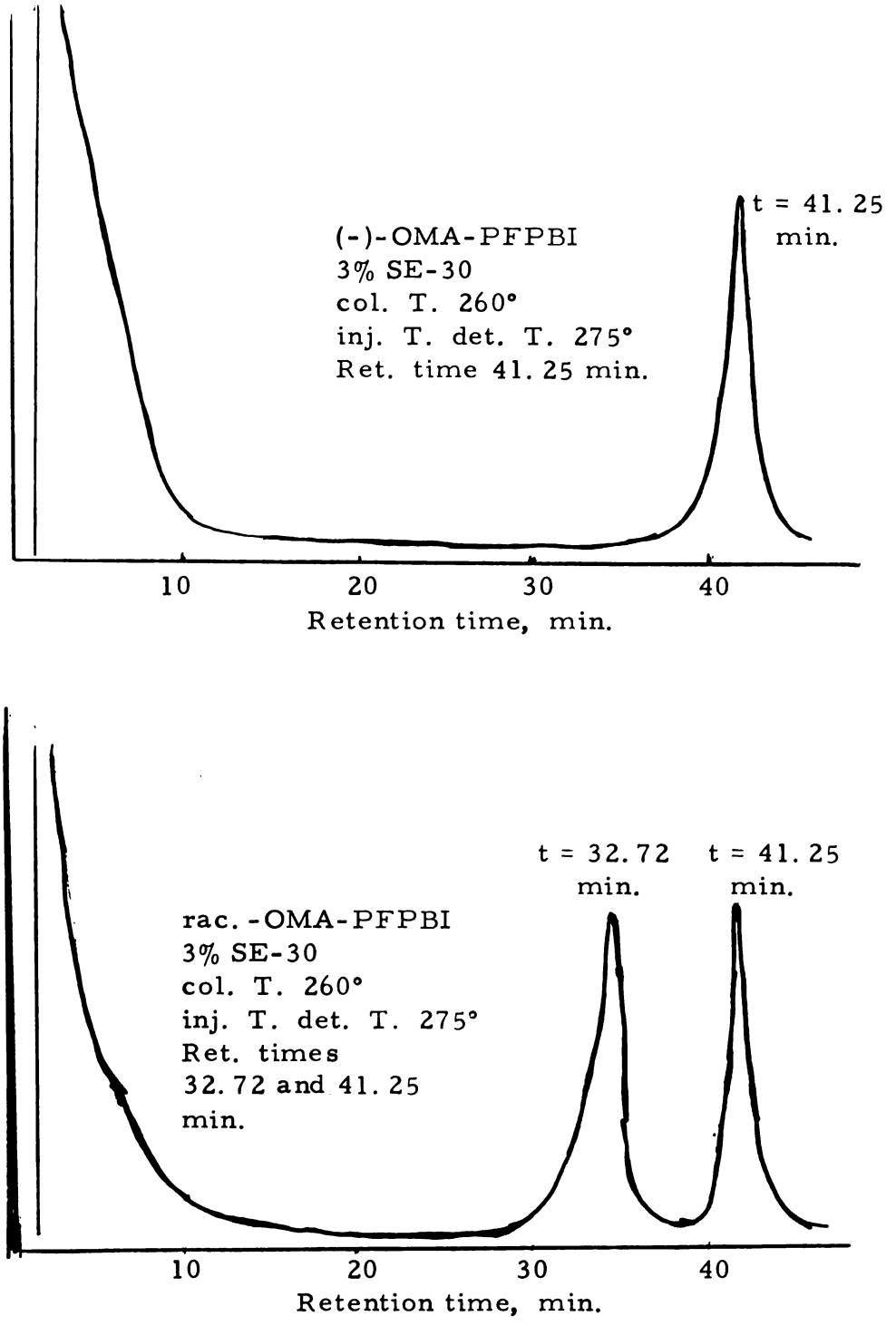


Figure I. 1. GLC Separation of (-) and (+) O-methylanhalonidine by use of PFPBI.

Table I. 1. Changes in Optical Rotation of Ethanolic Solutions of (+)-O-methylanhalonidine Base and Hydrochloride Upon Standing.

Time	$[\alpha]_D$ C = 0.8 in EtOH (+) OMA base	$[\alpha]_D$ C = 0.8 in EtOH (+) OMA. HCl
0 hr.	(+) 17.0°	(+) 33.5°
24 hr.	(+) 18.0°	(+) 28.0°
48 hr.	(+) 17.5°	(+) 30.0°
72 hr.	(+) 16.0°	(+) 30.5°
96 hr.	(+) 15.0°	(+) 31.0°

The results shown in Table I. 1 show that contrary to previous reports, no significant change in optical rotation occurred over this period for either the free base or the hydrochloride. A rotation taken on the solution of the free amine two weeks later had decreased about 30%, but the NMR spectrum suggests this was due to decomposition rather than racemization.

C. Synthesis and Resolution of O-methylpellotine

Secondary amines, such a O-methylanhalonidine can be easily monomethylated by a number of reductive amination methods. We investigated three such methods to determine which method would give the highest rotation upon methylation of optically active O-methylanhalonidine. The Eschweiler-Clarke reaction[18] is done with formaldehyde and formic acid under acidic conditions. The

second method was the use of sodium borohydride and formaldehyde under basic conditions[19], and the third method was using sodium cyanoborohydride under neutral conditions[20]. See Table I. 2.

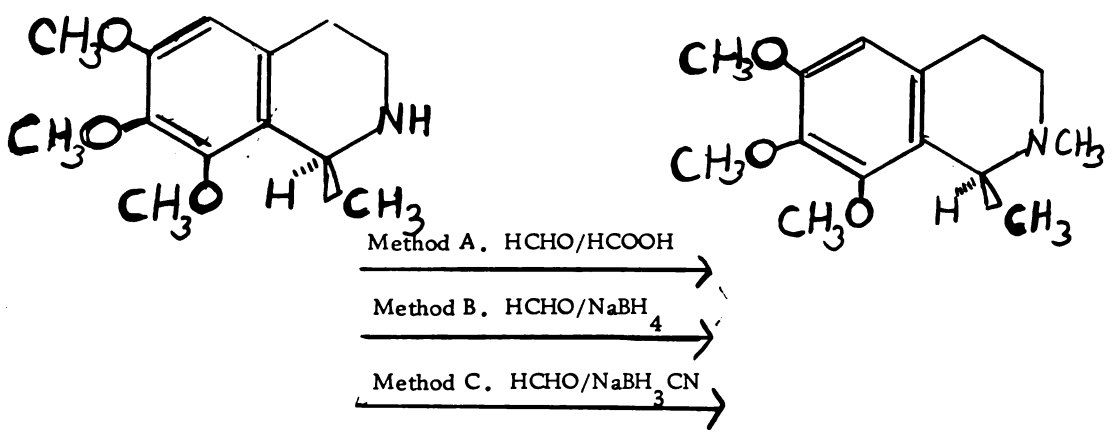


Table I. 2. Optical Rotation of O-methylpellotine Obtained by Various Methods.

Source of Compound	$[\alpha]_D$, c. 1. 5 in EtOH
(-) tartrate salt	(-) 14. 9°
(+) tartrate salt	(+) 16. 0°
(-) OMA-HCHO/HCOOH	(-) 15. 7°
(+) OMA-HCHO/$NaBH_4$	(+) 10. 3°
(-) OMA-HCHO/$NaBH_3CN$	(-) 13. 5°

Resolution of O-methylpellotine, obtained by Eschweiler-Clark methylation of rac-O-methylanhalonidine, was first attempted with mandelic acid without success. Attempted resolution with

O-benzoyltartaric acid was also unsuccessful. However, tartaric acid resolution gave (+) O-methylpellotine $[\alpha]_D$ = + 16.0°, c. 1.4 in EtOH, and (-) O-methylpellotine $[\alpha]_D$ = -14.9°, c. 1.4 in EtOH.

These data show that significant decrease in optical rotation occurred only when sodium borohydride was used as the reducing agent. This suggests the compound is more susceptible to racemization under basic conditions. Since the amine is tertiary, PFPBI derivatization was not possible, so the optical purity could not be determined.

D. (-) Anhalonidine and (-) Pellotine

The catcus alkaloids anhalonidine and pellotine had previously been isolated as racemic compounds[5, 6, 9]. We investigated several samples of anhalonidine all of shich had been isolated from the plant by Dr. Ara Paul (University of Michigan) by means of ion exchange chromatography. The compound proved to be optically active, $[\alpha]_D$ = -21.2°, c. 0.3 EtOH. This was methylated by $NaBH_3CN$/HCHO to give (-) pellotine, $[\alpha]_D$ = (-) 11.1°, c. 0.7 EtOH.

The plant alkaloids were identified by the TLC method of Paul[21], using DMF/Me-Et ketone/0.880 NH_3 1.9/14/0.9, and were compared with authentic synthetic samples.

Table I. 3. Thin Layer Chromatography of Tetrahydroisoquinoline Alkaloids.

Compound	R_f	Detection method
(+) O-methylanhalonidine	0. 18	I_2
(+) O-methylpellotine	0. 24	I_2
rac. anhalonidine	0. 36	U. V.
(-) anhalonidine	0. 36	U. V.
(+) anhalonidine	0. 36	U. V.
rac. -pellotine	0. 44	U. V.
(-) pellotine	0. 44	U. V.

Resolution of a synthetic sample of rac. -anhalonidine was attempted with (+) o-nitrotartranilic acid. A salt was obtained from absolute EtOH/acetone which analyzed as the o-nitrotartranilate of anhalonidine. However, the anhalonidine base isolated from this salt had an optical rotation $[\alpha]_D$ of only (+) 3. 7°, c. 0. 5 EtOH.

The NMR spectrum of the o-nitrotartranilate salt of anhalonidine was interesting as it showed four peaks for the methoxy groups. Apparently the two methoxyl groups of one diastereomeric salt differ in chemical shift from the other diastereomer. This behavior was not observed for the O-methylated compound.

Investigation of several samples of natural pellotine showed these to be racemic except for one sample, which was again obtained

by Dr. Ara Paul using an ion exchange chomatographic method. This material had a rotation of $[\alpha]_D$ -1.1° (c. 0.3, EtOH), and its hydrochloride had $[\alpha]_D$ -0.7° (c. 0.34, EtOH).

Since (-) pellotine obtained by room temperature methylation of natural (-) anhalonidine (see above) had $[\alpha]_D$ -11.1° and its HCl salt $[\alpha]_D$ -7.8° (c. 0.69, EtOH0, this indicated that the sample of natural (-) pellotine was only 9-10% optically active, i.e. had racemized to an appreciable extent during isolation.

Nevertheless, the conversion of natural (-) anhalonidine into (-) pellotine is sufficient to establish the configurational identity of these two alkaloids, neither of which has been previously reported in an optically active form.

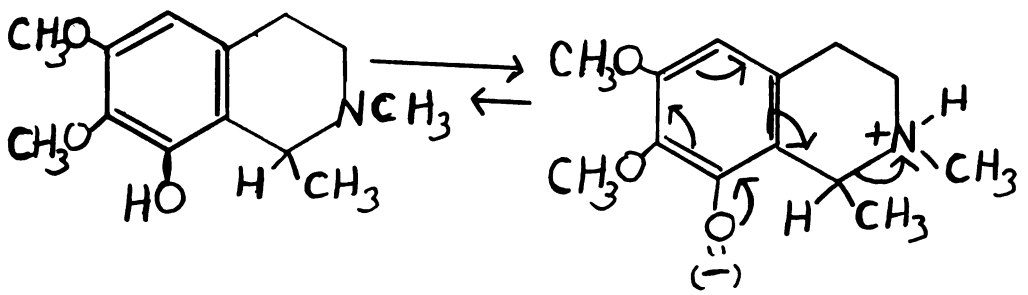
Natural (+) O-methylanhalonidine has been shown by X-ray crystallography[14] to have the S configuration. Since this compound was converted by N-methylation into (+)-O-methylpellotine, this also establishes the configuration of (+) O-methylpellotine as S. This is confirmed by the circular dichroism spectrum of these compounds, in the hydrochloride form, which show positive CD maxima in the 280 nm region corresponding to the ^1L_b transition of the molecule (Table I. 4). (The salts were used for these measurements in order to exclude any zwitterionic species which could be present in the free base form.) In the same way, CD measurements of the hydrochlorides of natural (-) anhalonidine and (-) pellotine

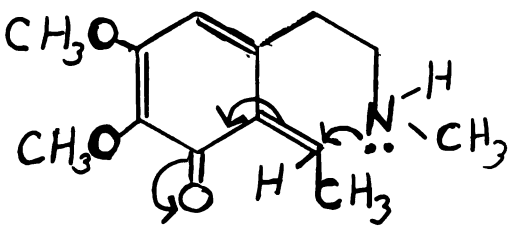
showed these to have negative CD maxima in the 280 nm region (Table I. 4), indicating that both these compounds belong to the R series.

Table I. 4. Circular Dichroism Spectra (Molecular Illipticity) in 95% EtOH Solution.

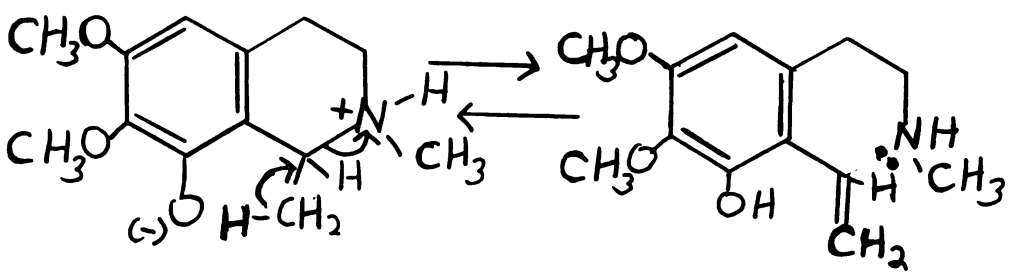
Compound	$[\alpha]_D$ (base)	$[\alpha]_D$ (HCl salt)	CD at 280 nm (HCl salt)	Configuration
O-methylanhalonidine	+20°		+170	S
O-methylpellotine	+16°		+237	S
Natural Andalonidine	-21. 2°		-1337	R
Pellotine (from natural anhalonidine	-11. 1°	-7. 8°	-1043	R
Pellotine (natural)	- 1. 1°	-0. 7°		

Since the 8-methoxy compounds of this series do not undergo the facile racemization characteristic of the 8-hydroxy substituted alkaloids, it is tempting to postulate a racemization mechanism involving the zwittenious form, as shown below. The ring-opening and reclosing steps would result in rapid racemization.

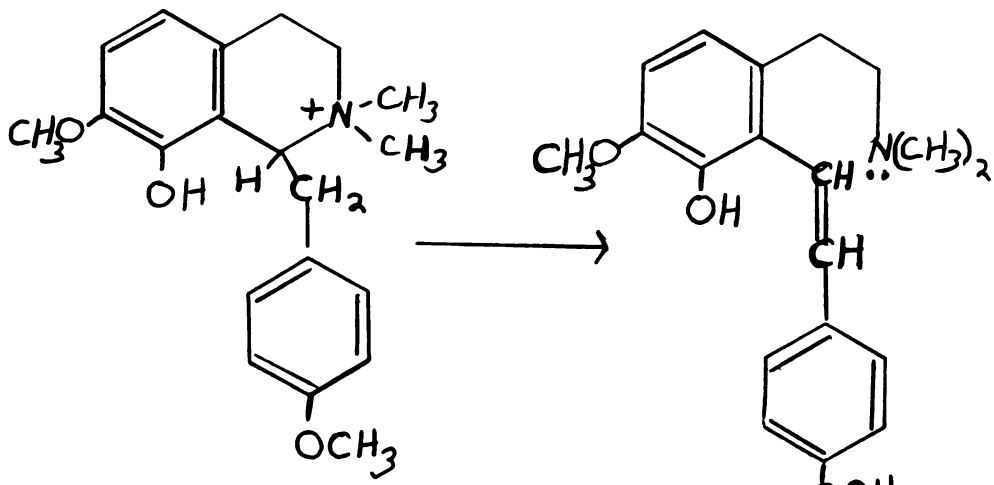




It is possible, however, to write an alternate mechanism



by analogy with the case of petaline methine, easily formed by ring-opening of the optically active quaternary alkaloid[23, 24] petaline. This could be tested by the study of the racemization of e. g. anhalonidine containing a CD_3 group at position 1.



petaline

Experimental

NMR spectra were taken on Varian A-60 model V 6040 60mHz NMR.

GLC was done on Varian model 2100 gas chromatograph with flame ionization detector.

Infared Spectra were taken on Perkin Elmer 337 Grating Infared Spectrometer.

ORD spectra and optical rotations were taken on Jasco ORD/UV-5.

CD spectra were taken on Jouan Dichrographe II.

Abbreviations used in experimental section; EtOH refers to 95% ethanol unless otherwise designated. ONTA--o-nitrotartranilic acid. PFPBI--pentafluorobenzoylprolylimidazolide. OMA--O-methylanhalonidine. OMP--O-methylpellotine.

3, 4, 5 Trimethoxynitrostyrene

20.0 g (0.11 m.) 3, 4, 5 trimethoxybenzaldehyde was dissolved in 20 ml. glacial acetic acid to which was added 2.0 ml. acetic anhydride and 6.4 g. ammonium acetate and 6.0 g (0.1 m) nitromethane. The mixture was refluxed 3 hr., and cooled on an ice bath until crystallization occurred. The crystals were filtered, washed with cold water, and recrystallized from acetic acid to give upon drying 22.65 g (90%) yellow needles, mp. 121° (lit. 121)[22].

Mescaline

11.7 g (.048 m) trimethoxynitrostyrene was dissolved in 150 ml freshly dried THF. 11.7 g $LiAlH_4$ was added slowly to 100 ml dry THF while stirring. The flash was cooled in an ice bath, and 3 ml 100% H_2SO_4 (prepared from .22 ml water in 3 ml fuming H_2SO_4) was added slowly under nitrogen. The nitrostyrene solution was added to the hydride suspension through a dropping funnel under nitrogen. Mixture was stirred overnight at room temperature. Hydride was decomposed by adding 20 ml water in 50 ml THF under nitrogen. Inorganic salts were filtered, and the filter cake was placed in 200 ml hot benzene, and stirred 10 min. The benzene and THF filtrates were combined and evaporated in vacuo to yield 11.4 g crude oil. This was distilled at 100/0.5 mm to give 9.2 g (92%)

mescaline base as a clear oil which solidified on cooling. NMR-singlet 6.3 ppm (2) Ar-H, singlet 3.8 ppm (9) $-OCH_3$, quartet 2.7 ppm (4) $-CH_2CH_2$, and singlet at 1.3 ppm (2) exch. c. D_2O-NH_2.

Mescaline Hydrochloride

5.0 g mescaline base was dissolved in 100 ml dry benzene, and 10 ml of benzene saturated with HCl gas was added to the solution of the amine. Mixture was cooled, and 6.2 g white crystals were filtered. Methanol recrystallization gave 4.6 g crystals mp. 179-180° (lit. 180°)[22].

N-Acetylmescaline

6.0 g (.03 m) mescaline base was acetylated according to the method of Brossi[16], and upon methanol recrystallization 5.3 g (75%) white crystals mp. 92° (lit. 92°)[16] were obtained. NMR-singlet 6.5 ppm (2) Ar-H, broad singlet 5.7 ppm, (1), exch. c. D_2O N-H, singlet 4.0 ppm (9), $-OCH_3$, quartet 3.6 ppm (4) $-CH_2CH_2-$, and singlet 1.9 ppm (3) $-COCH_3$.

rac-O-methylanhalonidine

5.3 g (.02 m) N-acetylmescaline was converted to rac-O-methylanhalonidine via Bischler-Napieralski cyclization and $NaBH_4$ reduction according to the method of Brossi[16]. However, it was

found that heating the borohydride complex in water 45 min. on a steam bath followed by ether extraction of the amine gave significantly higher yields than reported. After distillation (125°/1.0 mm) 4.7 g (95%) clear oil was obtained (lit. yield 75%). Compound solidified in the refrigerator to a white solid mp. 30-31°. Analysis of solid: Calc. for $C_{13}H_{19}NO_3$: 65.83% C, 8.02% H, 5.91% N. Found 5.54% C, 7.84% H, 5.83% N. NMR-($CDCl_3$) singlet 6.2 ppm (1) Ar-H, quartet 4.1 ppm (1) CHCMe, triplet 3.9 ppm (9) $-OCH_3$, multiplet 2.7 ppm (4) $-CH_2CH_2-$, singlet 1.7 ppm (1), exch. c. D_2O N-H, and doublet 1.3 ppm (2) $-CH_3$. 0.5 g of the base was converted to 0.5 g of the hydrochloride by addition of 2.0 ml of HCl saturated ether to a solution of the amine in 5 ml ether, followed by methanol recrystallization of the precipitate. Mp. of hydrochloride 176-178°.

Resolution of O-methylanhalonidine

4.45 g (.02 m) crystalline O-methylanhalonidine base was dissolved in 20 ml abs. ethanol. 5.11 g (.02 m) (-) orthonitrotartranilic acid was placed in 80 ml hot ethanol, and this solution was added to the solution of amine while warming on a steam bath. 1.7 g white solid remained, mp. 223°, and was filtered off and discarded. The filtrate was cooled to 4°, and after two days 3.2 g (70%) crude crystals mp. 101-105° were collected. These were twice recrystallized from methanol to give 2.4 g pale yellow crystals mp 117° (lit. 105°)[15].

Calc. for $C_{23}H_{29}N_3O_{10}$: 54.44% C, 5.76% H, 8.23% N, found 54.63% C, 5.72% H, 7.77% N. $[\alpha]_D$ (-) 60.0° c. = 1.0 (H_2O (lit.[15] + 62°).

(+) O-methylanhalonidine Hydrochloride

0.7 g of the (-) diastereomeric salt obtained from the resolution was dissolved in conc. NH_4OH and extracted twice with 10 ml dichloromethane, which was dried over Na_2SO_4 and evaporated in vacuo. The resultant crude base was dissolved in 10 ml phthalate buffer (pH 4.0) and extracted twice with 10 ml ether to remove any o-nitroaniline present. Aqueous phase was made basic with conc. NH_4OH, and twice extracted with 10 ml ether, which was dried over Na_2SO_4. 5 ml. HCl saturated ether was added dropwise, and the resultant white solid was recrystallized from methanol/ether to give 0.32 g white crystals, mp. 180°, $[\alpha]_D$ + 33.5° c. 0.4 in 50% methanol-water. Calc. for $C_{13}H_{20}NO_3Cl$: 57.14% C, 7.18% H, 5.13% N, 12.82% Cl; found 57.06% C, 7.18% H, 5.29% N, 12.92% Cl.

(+) O-methylanhalonidine

A solution of 0.15 g (+) O-methylanhalonidine HCl in conc. NH_4OH was extracted with two 25 ml portions of methylene chloride, which was dried over Na_2SO_4 and evaporated to give 0.08 g base as a clear oil, which solidified on standing, mp. 30-31°. $[\alpha]_D$ = (+) 20.0°, c. 0.4 in 95% EtOH (lit. (+) 20.5°[13]).

(-) O-methylanhalonidine (+) orthonitrotartranilate

After all of the (-) o-nitrotartranilate salt had been recovered from the resolution mixture, 1.9 g (+) o-nitrotartranilic acid was added, and solution was warmed on an ice bath. 0.3 g high melting white solid was filtered off and discarded. Volume of filtrate was reduced to 40 ml in vacuo, and mixture was refrigerated overnight. Crude crystals were filtered, 1.2 g, 63%, and two methanol recrystallizations gave 0.9 g pale yellow needles which melted sharply at 121°, $[\alpha]_D$ = (+) 60.5, c. 1.0 in water. Calc. for $C_{23}H_{29}N_3O_{10}$: 54.44% C, 5.72% H, 8.23% N; found 54.63% C, 5.64% H, 8.44% N.

(-) O-methylanhalonidine Hydrochloride

The above (+) o-nitrotartranilate salt was dissolved in NH_4OH and extracted in the same manner as described for its mirror image to yield 0.4 g crude amine. This was purified and converted to the hydrochloride in the same manner as described for the other isomer to give 0.15 g white crystals, m. p. 181° $[\alpha]_D$ = (-) 34.6, c. 0.4 95% EtOH). A mixed melt was taken of 1 mg of each d and l hydrochlorides: m. p. 176-177, same as that of the racemic hydrochloride.

(-) O-methylanhalonidine

40.0 mg of (-) O-methylanhalonidine HCl was dissolved in

50 ml conc. NH_4OH sat'd with NaCl, and extracted into 50 ml ether, which was dried over Na_2SO_4 and evaporated in vacuo, giving 20.0 mg O-methylanhalonidine base $[\alpha]_D$ = (-) 19.0 c. 0.4. in 95% EtOH.

Rac-O-methylpellotine--Method A

7.0 g .03 m of rac-O-methylanhalonidine base was dissolved in a solution of 20 ml 90% formic acid and 30 ml 37% formaldehyde. Mixture was refluxed for 22 hr. under nitrogen, and effluent gases were bubbled through a sat'd $Ba(OH)_2$ solution until solution turned clear. Mixture was then cooled, basified with Na_2CO_3 to pH 11 and extracted three times with 15 ml portions of ether. Ether was dried and evaporated, yielding 9.5 g of a crude viscous oil which smelled of formaldehyde. Distillation at 145°/1.0 mm gave 3.7 g (51%) clear liquid. NMR-singlet 6.5 ppm (1) Ar-H, singlet 4.0 ppm (6) $(OCH_3)_2$, singlet 3.7 ppm (1), OCH_3, multuplet 2.9 ppm (4) $-CH_2CH_2-$, singlet 2.5 ppm (3) NCH_3, and doublet 1.3 ppm (3) 1-CH_3. TLC-R_f 0.24 (see description).

Rac-O-methylpellotine--Method B

To a stirring solution of 0.2 g rac-O-methylanhalonidine base in 10 ml anhyd. methanol was added 0.4 ml 37% HCHO· $NaBH_4$, 0.11 g, was added slowly to the solution, and mixture was stirred 30 min. at RT. Then 10 ml water was added, and mixture was extracted with

10 ml portions of ether, which was dried over Na_2SO_4 and evaporated to give 196 mg (97%) pale yellow oil. TLC and NMR was identical with product from method A.

Rac-O-methylpellotine--Method C

Rac-O-methylanhalonidine HCl, 0.2 g, was dissolved in 15 ml methanol, solution was stirred, and 0.1 g 37% HCHO, 0.11 g $NaBH_3CN$, and 10 molecular sieves, size 3A, were added. Mixture was stirred at RT for 48 hr, then solution was filtered and 20 ml sat'd Na_2CO_3 was added. Mixture was extracted with 3 x 10 ml ether, which was dried over Na_2SO_4 and removed in vacuo to give 0.19 g (95%) clear oil. TLC and NMR identical with above.

Rac-O-methylpellotine Hydrochloride

20 mg rac-O-methylpellotine base obtained from Method A was converted to the hydrochloride by the same procedure described for O-methylanhalonidine. 15 mg white crystals, m.p. 175°, were obtained. Calc. for $C_{14}H_{22}NO_3U$: 58.5% C, 7.3% H, 4.9% N; found 58.23% C, 7.13% H, 4.90% N.

(-) O-methylpellotine--Method A

(-) O-methylanhalonidine, 0.35 g, was dissolved in a solution of 1.0 ml HCHO in 4.0 ml 37% HCHO, and refluxed 9 hr under nitrogen.

Solution was basified to pH 11 with Na_2CO_3, and extracted with 2 x 10 ml benzene, which in turn was extracted with 2 x 15 ml potassium acid phthalate buffer (pH 4.0). The aqueous phase was again basified with Na_2CO_3, and extracted 2 x 15 ml benzene, which was dried over Na_2SO_4 and removed in vacuo to give 0.32 g (95%) clear oil, NMR and TLC identical with racemic. $[\alpha]_D$ = (-) 15.7, c. 0.7 in 95% EtOH.

(+) O-methylpellotine--Method B

(+) O-methylanhalonidine, 40 mg was methylated by CH_2O/ $NaBH_4$ under the conditions described for the racemic compound. Yield 40 mg (96%) clear oil, TLC identical with racemic. $[\alpha]_D$= (+) 10.3, c. 0.8 in 95% EtOH.

(-) O-methylpellotine--Method C

(-) O-methylanhalonidine HCl, 45 mg, was reacted with 25 mg 37% HCHO and 25 mg $NaBH_3CN$ under the conditions described for the racemic compound. Yield 35 mg (90%) clear oil. TLC identical with racemic. $[\alpha]_D$ = (-) 13.5 c. 0.7 in 95% EtOH.

Resolution of O-methylpellotine

Freshly distilled O-methylpellotine base, 2.5 g, .01 m, was dissolved in 100 ml isopropanol to which was added 4.5 g (0.03 m)

d-tartaric acid, and solution was warmed on a steam bath until everything dissolved. Solution was filtered and cooled overnight at which time 0.6 g (34%) white crystals m. p. 177-180° were collected. These were twice recrystallized from isopropanol to give 0.45 g crystals m. p. 104-195°. $[\alpha]_D$ = (+) 20.0 c. 2.0 in 95% EtOH. NMR-(D_2O) singlet 396 cps (1) Ar-H, singlet 263 cps (2) tartrate H, singlet 232 cps (3), OCH_3, singlet 225 cps (6) $(OCH_3)_2$ multuplet 185 cps (4) $-CH_2CH_2-$, singlet 170 cps (3) NCH_3, and doublet 85 cps (3) $C-CH_3$. Calc. for $C_{18}H_{27}O_9N$ 53.9% C, 6.8%H, 3.5% N found 53.81% C, 6.94% H, 3.3%N.

(+) O-methylpellotine base

0.1 g of the above (+) tartrate salt was dissolved in 30 ml sat'd K_2CO_3 and extracted three times with 20 ml portions of ether, which was dried over Na_2SO_4, evaporated in vacuo, and dried in a vacuum desiccator to yield 60 mg clear oil. $[\alpha]_D$ = (+) 16.0 c. 1.2 in EtOH. TLC identical with racemic compound. Calc. for $C_{14}H_{21}N$: 5.6% N; found 5.87% N.

(-) O-methylpellotine (-) tartrate

The mother liquor was evaporated in vacuo and the residue was dissolved in 30 ml sat'd Na_2CO_3 and extracted with ether 3 x 30 ml which yielded, upon evaporation and drying 2.0 g of O-methylpellotine

base. This was dissolved in 100 ml isopropanol, and treated with (-) tartaric acid in the same manner as the opposite isomer to yield 920 mg (46%) crystals m. p. 166-170° which upon two isopropanol recrystallizations gave 740 mg crystals m. p. 194-195°, $[\alpha]_D$ = (-) 20. 0° c. 1. 5 in 95% EtOH. Calc. for $C_{18}H_{27}O_9N$: 53. 9% C, 6. 8% H, 3. 5% N; found 53. 67% C, 6. 68% H 3. 42% N.

(-) O-methylpellotine base

120 mg of the (-) tartrate salt was extracted in the same manner as the (+) tartrate salt to yield 75 mg clear oil. $[\alpha]_D$ = (-) 14. 9, c. 1. 45 in 95% EtOH. TLC: R_f identical with racemic compound.

Resolution of anhalonidine

0. 27 g anhalonidine salicylate was dissolved in 50 ml 0. 5 N Na_2CO_3 solution sat'd with NaCl and ether extracted overnight in a Soxhlet apparatus to give 0. 2 g crystalline base m. p. 160-162° (lit. 106-161°). The base was dissolved in 20 ml 95% EtOH, to which was added 0. 16 g (+) o-nitrotartranilic acid in 5 ml 95% EtOH. Each flask was washed with 5 more ml 95% EtOH to bring total volume to 35 ml. Mixture was warmed, filtered and refrigerated overnight. The total volume was reduced in vacuo to 15 ml and again refrigerated. Addition of 0. 25 ml dry ether gave an oil which failed to crystallize. So solution was concentrated to 5 ml in vacuo

and again refrigerated. The next day 1 ml of acetone was added, and yellow crystals appeared. After 3 days 0.13 g (73%) crystals of anhalonidine (+) o-nitrotartranilate m.p. 160-161° were collected. Calc. for $C_{20}H_{28}N_3O_{10}$: 53.5% C, 5.5% H, 8.5% N; found 53.29% C, 5.37% H, 8.36% N. NMR singlet 5.8 ppm (1) Ar-H, quartet 3.95 ppm, OCH_3, multiplet 3.5 ppm (5) $-CH_2CH_2-$, and doublet 1.7 ppm (3) CCH_3. 80 mg of the tartrate salt was Sohxlet extracted as above to yield 38 mg anhalonidine base. TLC R_f 0.36, identical to plant sample. $[\alpha]_D$ = (+) 3.7°, c. 0.5 in EtOH; a drop of conc. HCl was added and rotation became $[\alpha]_D$ = (+) 1.6° c. 0.5 in EtOH.

(-) Pellotine HCl

40 mg (-) anhalonidine HCl of natural origin was dissolved in 5 ml abs. methanol to which was added 60 mg 37% HCO and 40 mg $NaBH_3CN$. Mixture was stirred at rt 72 hr. Then mixture was filtered, filterpaper was washed with 20 ml methanol, and filtrate was concentrated in vacuo to 5.0 ml, and $[\alpha]_D$ was taken. Then 15 ml sodium borate buffer, pH 9, 2 was added, and mixture was extracted 3 x 15 ml $CHCl_3$, 1 x 15 ml EtOAc, and 1 x 15 ml ether. Combined extracts were dried over Na_2SO_4 and solvents were removed in vacuo to yield 35 mg, 97%, pale yellow oil which crystallized on standing. $[\alpha]_D$ (-)11.1°, c. 0.7 in MeOH. TLC: R_f = 0.44, identical with racemic. The hydrochloride had $[\alpha]_D$ - 7.8°, c. 0.69 in EtOH.

O-nitrotartranilic acid

Diacetoxysuccinic anhydride, 10 g prepared by the method of Moutzka[16] was dissolved in 100 ml methylene chloride, and 7.0 g (.055 m) freshly recrystallized O-nitroaniline added to the mixture. The mixture was gently refluxed three days. The mixture was then extracted with a solution of 16 g KOH in 200 ml water, and again extracted with 100 ml water. The combined aqueous extracts were rapidly acidified with 35 ml conc. HCl. On cooling, crystals were collected, washed with water, and recrystallized from hot water. Yield 5.4 g pale yellow needles (40.3%) m.p. 198° (lit. 198°). $[\alpha]_D$ = (-) 90.3° (lit. 16 (-) 98°, c. 1.0 in EtOH).

Thin layer chromatography of tetrahydroisoquinolines

The method used was that of Paul[21]. Plates were prepared as follows: A 1 x 3 in microscope slide was immersed in a slurry of Silica Gel G in sodium borate buffer, pH 9.2, which was made by dissolving 48 g Na_3BO_3 and 15 g NaOH in 1 l. water. The plates were air dried approximately 1 hr. The solvent system was DMF/MeEt ketone/0.880 NH_3 1.9/14/0.9. Amine hydrochlorides were dissolved in water, and applied to the plate via a capillary tube. R_f's and detection methods are described in Table 3.

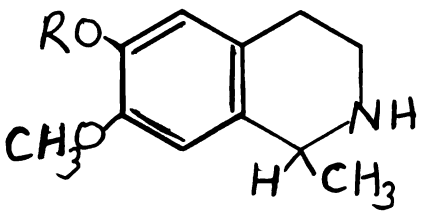
Derivatization of O-methylanhalonidine by pentafluorobenzoyl-prolylimidazolide (PFPBI)

O-methylanhalonidine, 5 mg was dissolved in 1 ml dry benzene, and 5 mg PFPBI, prepared as described by Matin and Castagnoli[17], was added. Mixture was stirred, warmed slightly and allowed to stand 1 hr. at rt. Then mixture was shaken with 1 ml water for several min., and centrifuged at 2000 rpm for 1 min. Benzene solution was decanted, dried over Na_2SO_4, and injected into GLC column by means of a Hamilton syringe.

Conclusion

Our study succeeded in determining that natural anhalonidine and natural pellotine are levorotatory, and bear the 1(R) configuration. This is in contrast to natural O-methylanhalonidine which is dextrorotatory and has the 1 (S) configuration. From this evidence we must conclude that O-methyl-d-anhalonidine cannot come from direct methylation of natural anhalonidine, as formerly was supposed, but must rather come from a different biosynthetic pathway.

These findings are closely paralleled by the configurational assignment in the closely related tetrahydroisoquinoline alkaloids Salsoline and Salsolidine.



R = H Salsoline

R = CH_3 Salsolidine

Natural (-) Salsolidine was shown to be related to L-alanine[25], while natural (+) salsoline had the oppsoite cofiguration. This co-occurence of closely related bases having opposite configurations can be compared with the presence of a similar pair[26], (+) laudanasoline and (-) laudanidine in opium.

REFERENCES

1. A. Brossi, F. Schenker Helv. Chim Acta 47, 2089 (1964)
2. L. Lewin Arch. Exp. Pathol. Pharmakol. 24, 40. 1888.
3. L. Dryon. J. Pharm. Belg. 12, 19. 1964.
4. D. Bella Acta Pharm. Hung. 23, 221, (1964)
5. L. Vignoli and J. Guillot Am. Pharm. Trans. 24 461 (1965)
6. M. Ikram, G. A. Miana, and M. Islam J. Chromatog. 11, 260, (1963)
7. J. Kapadia
8. A. Brossi, et. al. Helv. Cham. Acta 49, 404 (1966)
9. E. Spath and F. Beck, Ber Deutsch Chem. Ges. 67, 2100 (1934)
10. E. Spath and F. Kesztler Chem. Ber. 69, 755 (1936)
11. A. Brossi Tran. N. Y. Acad. Sci. 685 (1967)
12. A. Brossi, M. Baumann and R. Borer Mh. Chem. 96, 25, (1965)
13. E. Sapth and J. Bruck Chem. Ber. 70, 2446 (1937)
14. A. Brossi et. al. JACS 93 23 1971
15. S. B. Matin Doctoral Dissertation P. 52
16. Moutzka et. al. J. Org. Chem 33, 3993 1968.
17. S. B. Matin, M. Rowland, and N. Castagnoli, J. Pharm. Sci 62, 821 (1973)
18. Emerson Org. Reactions 4, 174-255 (1948)
19. Schellenberg J. Org. Chem. 28, 3259 (1963)

20. Borch, R., Bernstein, M. and H. Durst JACS (1971)

21. J. McLaughlin and A. Paul Lloydia 29, 315 (1966)

22. Shulgin, A. T. Nature, 221, 537 (1969)

23. N. J. McCorthindale, D. S. Magrill, M. Martin-Smith, S. J. Smith and J. B. Stenlake, Tetrah. Lett. 51, 3841 (1964)

24. G. Grethe, M. Uskokvic, and A. Brossi. Tetrah. Lett., 15, 1599 (1966)

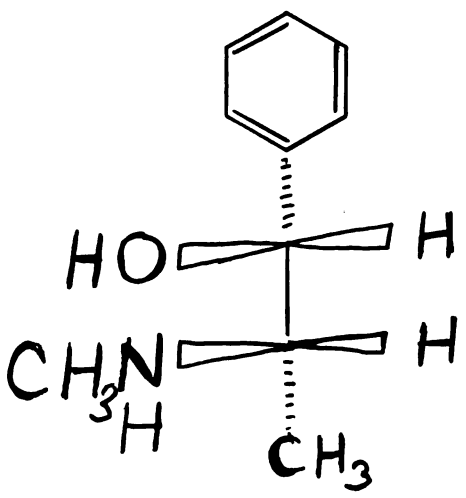
25. Battersby, A. R. and R. P. Edwards J. Chem. Soc. 1214 (1960)

26. Spath, E. and Berhauer, Ber. 58, 200 (1925)

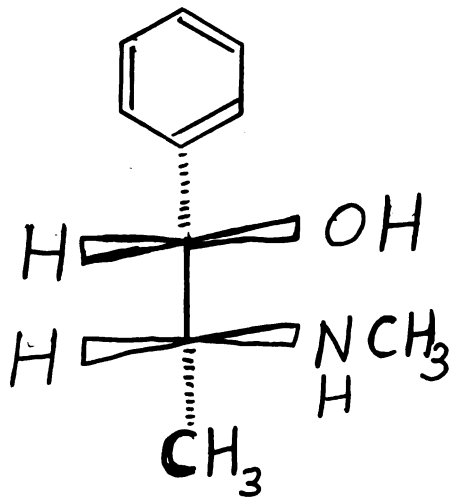
CHAPTER II. SYNTHESIS, CONFORMATION, AND ABSOLUTE CONFIGURATIONS OF OXAZOLIDINES DERIVED FROM DIASTEREOMERIC EPHEDRINES

Introduction

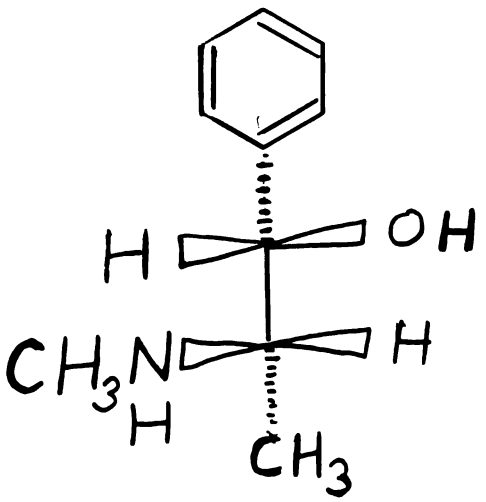
The stereochemistry of adrenergic compounds has been a much investigated topic. The ephedrines have presented an interesting problem, in light of their variety of effects on the sympathetic and central nervous systems, and their close structural resemblance to the endogeneous neurotransmitters norepinephrine and epinephrine. Four diastereomers are possible with the ephedrine molecule.



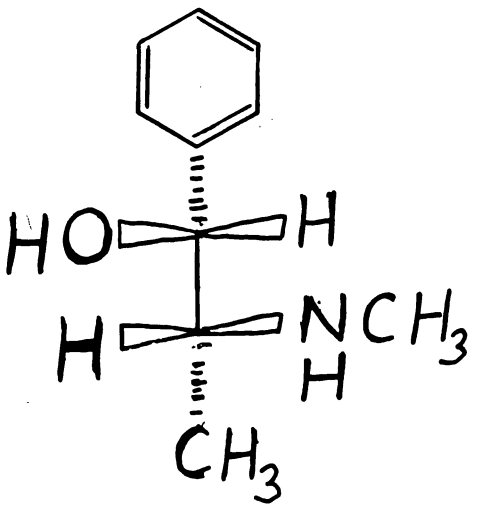
(-) ephedrine 1R:2S



(+) ephedrine 1S:2R



(+) pseudoephedrine 1S:2S



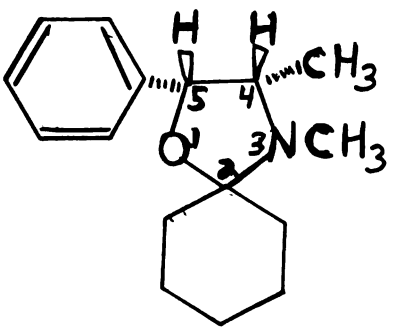
(-) pseudoephedrine 1R:2R

(-) Ephedrine and (+) pseudoephedrine occur naturally in Ephedra[1] species, low, shrubby plants which grow in arid places in many parts of the world. Although the Chinese knew of the bronchodilatory and nasal decongestant properties of Ephedra for centuries, the active principle was not isolated until 1888[2]. Since then the compounds have been widely used as nasal decongestants and anti-asthmatics.

The absolute stereochemistry of the four ephedrine diastereomers has been rigorously established[3, 4, 5]. However, the preferred conformation of these compounds is not as clear, and much investigation is still going on in this area. The NMR work of Portoghese[6] strongly suggests that ephedrine prefers a gauche conformation and

pseudoephedrine prefers a trans conformation in solution (between the two vicinal protons).

The ephedrines are known to condense readily with many carbonyl compounds to form oxazolidines[7, 8, 9]. These compounds are interesting in that the ephedrine backbone becomes locked into a rigid five membered ring which lends itself to conformational analysis by NMR. In a classic study Hyne[10] demonstrated that ephedrine reacts with cyclohexanone to form a <u>cis</u> oxazolidine and pseudoephedrine a <u>trans</u> oxazolidine respectively.



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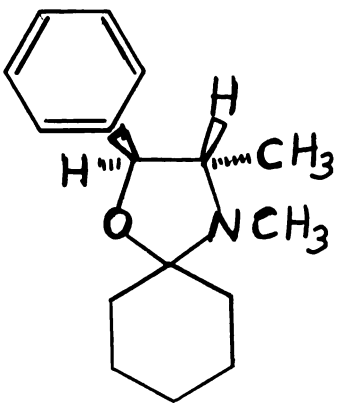


7

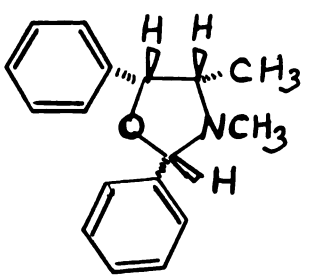
The stereochemistry at C_2 of the oxazolidine introduced during ring closure has not been established. In our study, we prepared a number of oxazolidines from the ephedrines and various aldehydes and ketones, and studied them by NMR, IR and other physical methods in order to determine the stereospecificity of the ring

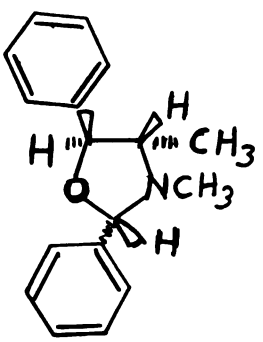
closure, and the absolute configuration of the new center at C_2. The vicinal coupling constants were also studied to gain more information concerning the preferred conformation of the oxazolidine ring. The use of these compounds as possible asymmetric derivatizing agents in GLC is discussed in the following chapter.

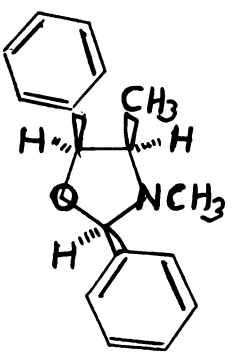
Results and Discussion

A. Aldehyde Derivatives

Oxazolidines prepared from the ephedrines and aromatic aldehydes have been reported[8, 11, 12]. We prepared the following compounds and studied their NMR and IR spectra.







1. R = H 3. R = CH_3 2. R = H 4. R = CH_3 5.

Synthesis

Table II. 1. Preparation of Oxazolidines from Ephedrines and Aromatic Aldehydes.

Compound	Aldehyde	Amine
1	p-hydroxybenzaldehyde	(-) ephedrine
2	p-hydroxybenzaldehyde	(+) pseudoephedrine
3	anisaldehyde	(-) ephedrine
4	anisaldehyde	(+) pseudoephedrine
5	anisaldehyde	(+) ephedrine

Compounds 1 and 3 were formerly prepared by Soliman et al.[11] by refluxing in benzene in the presence of anhydrous sodium sulfate. However, we found that preparation of these compounds by benzene reflux of the desired ephedrine with slight excess of aromatic aldehyde using a Dean-Stark trap gave better results, and excellent yields (85-95%) were obtained by this method. Compounds 3 and 5 are enantiomers, with identical IR and NMR spectra.

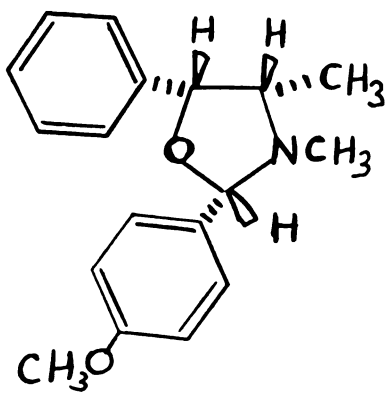
NMR Studies

The chemical shift behavior observed for these compounds is similar to that reported by Hyne[10] for the cylohexanone derivatives.

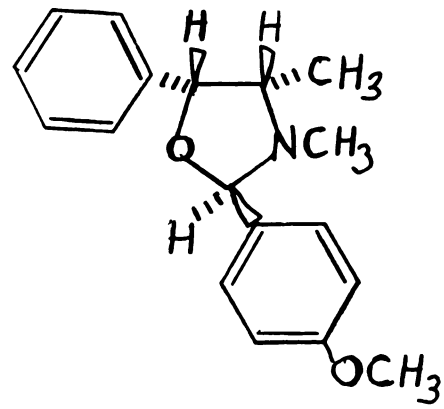
Table II. 2. Chemical Shifts of the Aldehyde Derivatives.

Compound	Chemical Shift, cps				
	H_2	H_4	H_5	N-CH_3	4-CH_3
1	281	179	309	130	48
2	305	153	296	131	71
3	280	178	309	130	46
4	295	152	284	126	71
5	280	178	309	130	46

During this condensation a new asymmetric center is formed at the 2 position. Therefore, from the reaction of (-) ephedrine with p-methoxybenzaldehyde, the following two diastereomers may be formed.



3a



3b

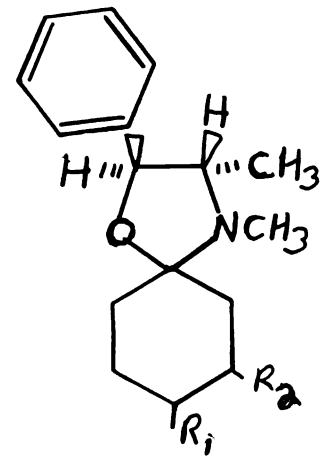
The product obtained from the reaction is sharp melting and gives a single set of signals in the NMR spectrum. Table II. 2 shows that the 4 proton occurs 17 cps upfield from that of the corresponding cyclohexanone derivative 6 (Table II. 4). Also, compared to 6, the 4-methyl protons are deshielded 11 cps and the N-methyl is shielded 7 cps. This behavior could either be explained by anisotropic effect of the aromatic substituent at position 2, or by change in conformation of the 5-phenyl ring due to steric interaction with the 2-substituent. Molecular models suggest both factors are involved. Since introduction of the aromatic substituent at C_2 has a noted effect on the chemical shifts of the oxazolidine ring substituents, it would be expected that if both 3a and 3b were formed, they should be distinguishable by their NMR spectra.

It has been shown that the presence of infared bands between 2700 and 2800 cm^{-1} [13, 14, 15] indicates the lone pair on nitrogen[15] fixed trans to two axial α-hydrogen. These Bohlmann[13] bands have been used to determine stereochemistry about nitrogen in compounds where steric factors eliminate the possibility of flipping of the lone pair. All these compounds (1-5) show pronounced shoulders on the C-H band in this region, which are not observed in the ketone derivatives. This strongly suggests that the N-methyl is fixed trans to the 4-methyl and the 2-aromatic groups. In this case the C_2 and the C_4 protons would bear a cis-diaxial relationship to one

another, therefore the product formed would be 3a. The new asymmetric center can therefore be assigned the 2S configuration. Models clearly show that this configuration eliminates steric interaction between the two aromatic substituents and the two methyl groups.

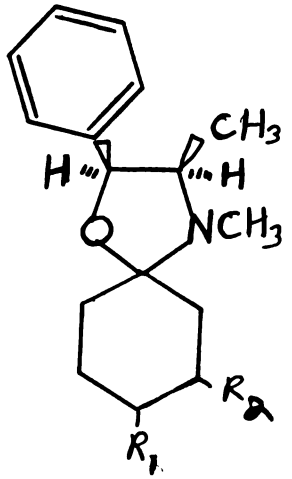
B. Ketone Derivatives

In addition to 6 and 7, the following compounds were prepared.



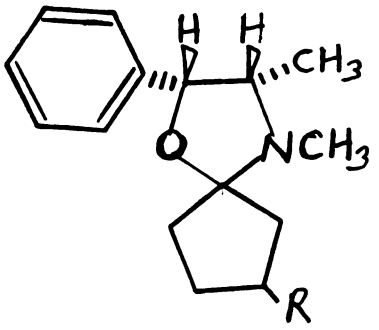
8. R_1 = t-Bu R_2 = H
11. R_1 = H, R_2 = CH_3
14. R_1 = H R_2 = (R) CH_3

9. R_1 = t-Bu R_2 = H
12. R_1 = H R_2 = CH_3
15. R_1 = H, R_2 = (R) CH_3

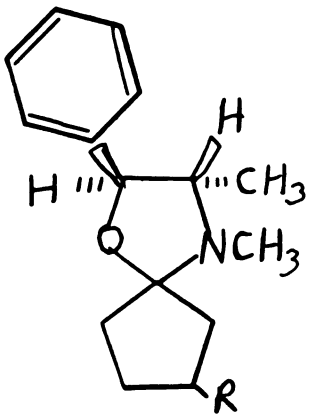


10. R_1 = H, R_2 = CH_3

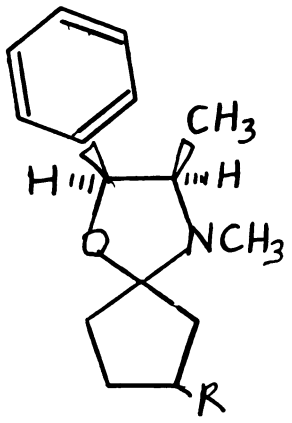
13. R_1 = H, R_2 = (R) CH_3



16. R = (R) CH_3



17. R = (R) CH_3



18. R = (R) CH_3

Synthesis

Table II. 3. Preparation of Oxazolidines From Ephedrines and Ketones.

Compound	Ketone	Amine	Solvent
6	cyclohexanone	(-) ephedrine	benzene
7	cyclohexanone	(+) pseudoephedrine	benzene
8	4-t-butylcyclohexanone	(-) ephedrine	toluene
9	4-t-butylcyclohexanone	(+) pseudoephedrine	toluene
10	3-methylcyclohexanone	(+) ephedrine	xylene
11	3-methylcyclohexanone	(-) ephedrine	xylene
12	3-methylcyclohexanone	(+) pseudoephedrine	xylene
13	(+) 3-methylcyclohexanone	(+) ephedrine	xylene
14	(+) 3-methylcyclohexanone	(-) ephedrine	xylene
15	(+) 3-methylcyclohexanone	(+) psuedoephedrine	xylene
16	(+) 3-methylcyclopentanone	(-) ephedrine	xylene
17	(+) 3-methylcyclopentanone	(+) pseudoephedrine	xylene
18	(+) 3-methylcyclopentanone	(+) ephedrine	xylene

The cyclohexanone derivatives[10] 6 and 7 were prepared by azeotropic distillation of benzene with a Dean-Stark trap, under the same conditions as described for the aldehyde derivatives. However, we found it necessary to remove excess cyclohexanone by acidification of the reaction mixture with dilute HCl, followed by ether extraction. The aqueous layer on basification with Na_2CO_3 and ether extraction yielded the amine.

The 4-t-butyl derivatives 8 and 9 did not react under the conditions described above. However, two hour reflux in toluene with a Dean-Stark trap followed by acid-base extraction to remove excess ketone gave excellent yields (92-96%).

The 3-methylcyclohexanone derivatives 10 - 15 refused to react in benzene or toluene. However, 6 hr. azeotropic reflux in xylene gave good yields (> 70%). Ketone was removed in the same manner as above. The same conditions were used to obtain the 3-methylcyclopentanone derivatives, in good yield.

We also attempted to prepare oxazolidines from ephedrine by reaction with d-camphor and rac. 2-methylcyclohexanone. In both cases only partial reaction took place after 48 hr. reflux in xylene, and the products could not be isolated. Reaction was probably prevented by steric hindrance about the carbonyl group in these compounds.

NMR Studies

The chemical shifts observed in the cyclohexanone and t-butylcyclohexanone derivatives 6 - 9 agree with the observations of Hyne[10]. Table II. 4 shows that the 4-methyl protons of the ephedrine derivative appear 29 cps upfield from the corresponding signal in the pseudoephedrine derivative. On this basis, Hyne[10] concluded that the methyl group was eclipsed with the phenyl ring in the ephedrine derivative. This is discussed further in the section on coupling constants. However, he suggests that the N-methyl undergoes rapid inversion. The evidence that the N-methyl group is fixed trans to the 4-methyl and the C_2 substituent in the aldehyde derivatives suggests this may be true in these compounds also, as similar steric interactions exist.

Table II. 4. Chemical Shifts Observed in Cyclohehexanone Derivatives.

Compound	Chemical Shift, cps		
	H_4	H_5	4-CH_3
6	195	309	46
7	158	268	64
8	195	304	37
9	158	268	65

In compounds 10 - 18 diastereomer formation is possible around the spiro junction at C_2. We first considered the 3-methylcyclohexanone derivatives 10 - 15.

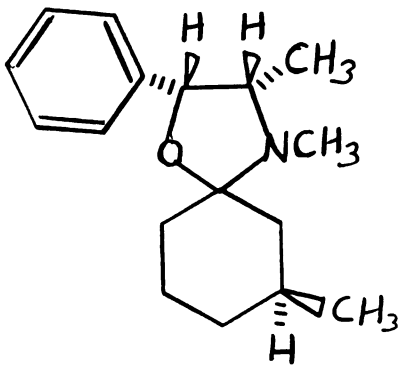
Table II.5. Observations of the 3-methylcyclohexanone Derivatives.

Compound	Base Used	Ketone Used	3-methyl (cps)	5-phenyl (cps)	m.p.
10	(+) ephedrine	rac-3-methylcyclohexanone	55	436	83°-89°
11	(-) ephedrine	rac-3-methylcyclohexanone	56	444, 440	73°-89°
12	(+) pseudoephedrine	rac-3-methylcyclohexanone	60, 50	441, 442	oil
13	(+) ephedrine	(+) 3-methylcyclohexanone	55	439	oil
14	(-) ephedrine	(+) 3-methylcyclohexanone	57	442	88°-89°
15	(+) pseudoephedrine	(+) 3-methylcyclohexanone	60	442	oil

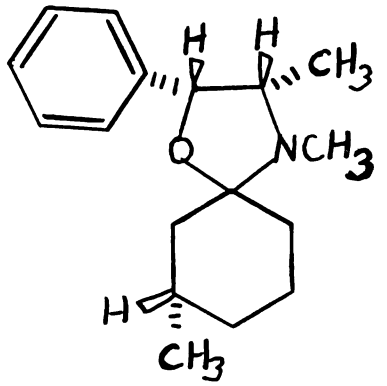
Table II. 5 shows that compounds 13 - 15, derived from (+) 3-methylcyclohexanone all give single sets of signals. 14 is a sharp melting solid. However, when the racemic ketone was used, 11 and 12 give two distinct phenyl peaks, while in 12 two distinct 3-methyl doublets are observed in the approximate ratio 70:30. 10 and 11 give wide melting products.

These observations suggest that reaction of an ephedrine with the optically active ketone gives rise to only one of two possible diastereomers, while 11 and 12 appear to be mixtures of two diastereomers. The fact that two distinct signals are observed for the phenyl group in each of these suggests possible interaction with

the 3' methyl group. Four diastereomers are possible with 10 - 12 while two are possible with 13 - 15.



14a



14b

There is insufficient evidence to determine which diastereomers are preferentially formed.

The (+) 3-methylcyclopentanone derivatives 16 - 18 were next considered.

Table II. 6. Observations of (+) 3-methylcyclopentanone Derivatives.

Compound	Amine	cps, 3-CH_3	m. p.
16	(-) ephedrine	63, 57 60:40	69-73
17	(+) ephedrine	63*	43-44*
18	(+) pseudoephedrine	63**	oil

*Before recrystallization an oily product was obtained that showed doublets at 63 and 57 cps, approximate ratio 40:60.

**Integration of 3-methyl was only 1. 8 opposed to 4. 4 for the adjacent 4-methyl. See discussion.

(-) ephedrine upon reaction with the ketone gave 16. The NMR spectrum showed two overlapping doublets in the approximate ratio 60:40 for the 3-methyl protons. Two recrystallizations gave a solid m. p. 67-73 with no observed reduction of peak ratio. This suggests the diastereomers have similar solubility.

(+) ephedrine gives a wide melting product whose NMR shows a pair of overlapping doublets. However, pentane recrystallization gives a sharp melting product 17, m. p. 43°-44°, in which the methyl group reduces to one single doublet. In this case, diastereomers are separable by fractional recrystallization.

The (+) pseudoephedrine derivative 18 is an oil. Only one 3-methyl doublet is observed. However, integration shows the adjacent 4-methyl signal to be about 40% larger. This suggests overlap between the 3-methyl of one diastereomer and the 4-methyl group.

This evidence suggests that (+) 3-methylcyclohexanone gives single products, while (+) 3-methylcyclopentanone gives mixtures of diastereomeric pairs. This could be explained by the fact that cyclohexanone[16] prefers the more stable chair form, while cyclopentanone[17] readily undergoes puckering. The cyclopentanone ring could undergo change of conformation much more readily to eliminate steric interactions.

Coupling Constants Between Vicinal Protons

Portoghese[6] showed by his analysis of coupling constants that ephedrine prefers a gauche conformation 19, while pseudoephedrine prefers a trans orientation 20a between the two vicinal protons.

Table II. 7. Comparison of Vicinal Coupling Constant J_{ab} Between Ephedrines and Oxazolidine Derivatives.

Compound	J_{ab} cps
19	4. 07
20	8. 23
3	8. 1
4	9. 0
5	8. 5
6	8. 7

All the oxazolidines studied had a $J_{trans} = 9 \pm .3$ for the pseudoephedrine derivatives and $J_{cis} = 8 \pm .5$ for the ephedrine derivatives. J_{trans} increases slightly from J = 8. 3 reported for pseudoephedrine. The rigidity of the five membered ring would rule out the other possible rotamers 20b and 20c, as the oxygen and the nitrogen must be cis to each other in the cyclic product.

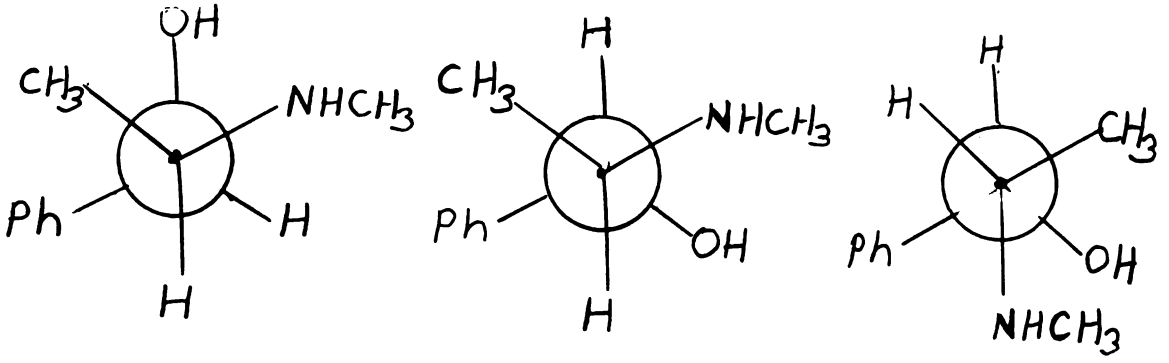
The vicinal coupling constant J_{cis} observed for the oxazolidines derived from ephedrine is considerably larger than J = 4. 0 observed

for ephedrine. According to the Karplus[18] relationship, this would imply a nearly eclipsed orientation of the two vicinal protons. It is known that cyclopentane rings prefer a puckered conformation[11] with two adjacent substitutents eclipsed, and the rest staggered. The fact that the C_4 and C_5 substituents are eclipsed in the ephedrine derivatives is further substantiated by the observation that the C_4 methyl protons of the cis oxazolidines occur approximately 15 cps upfield from those of ephedrine, as reported by Hyne[10]. Molecular models suggest this conformation (21) would place the methyl group nearly directly over the benzene ring, explaining the strong shielding effect.

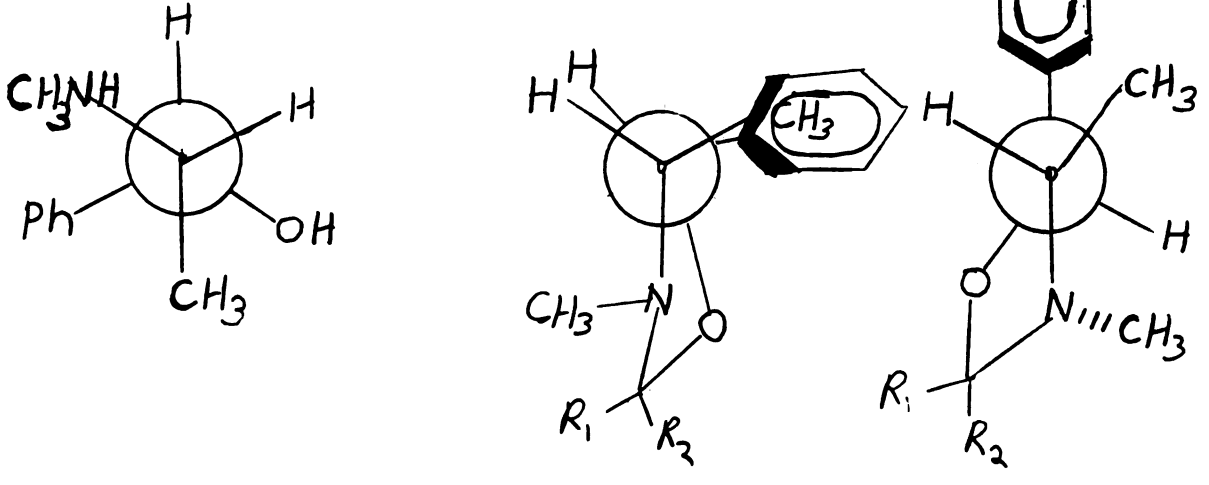
The observed J_{trans} for the pseudoephedrine derivatives suggests a nearly antiparallel orientation of the two vicinal protons. Models also favor this conformation (22), as it allows the greatest distance between the phenyl group and the C_2 and the C_4 substituents. Eclipsing would occur only between the 4-proton and the N-methyl group.

(-) cis p-hydroxyphenyl-N-methyl-4-methyl-5-phenyloxazolidine I

7.0 g (.043 m) (-) ephedrine was dissolved in 100 ml dry benzene, to which was added 6.2 g (.05 m) p-hydroxybenzaldehyde and 2.0 g anhyd. Na_2SO_4. Mixture was refluxed with Dean-Stark trap



(+) 19 (+) 20a 20b



20c cis-oxazolidine 21 trans-oxazolidine 22

Figure II. 1. Preferred Conformations of Ephedrines and Oxazolidine Derivatives.

6 hr. Solvents were removed in vacuo, leaving a white crystalline solid, which was recrystallized from 95% EtOH to give 12.1 g (.041 m, 95%) white crystals m.p. 142-143° (lit. m.p. 143°).

NMR--AB quartet, 420 and 454 cps, (4) 2-Ph, multiplet 445 cps (5), 5-Ph, doublet 309 cps (1), J 9, 5-H, singlet 281 cps (1), 2-H multiplex 179 cps (1), 4-H, singlet 130 cps (3), N-CH_3, and doublet at 48 cps (3) CH-CH_3 in pyridine-d_5.

$[\alpha]_D$ = (-) 50.0° c. = 1 in 95% EtOH

IR Bohlmann bands present at 2750 and 2840 cm^{-1}. ν_{max} (KBr) 2970, 2890, 1610, 1470, 1260, 1150, and 1005 cm^{-1}.

(+) trans-2p-hydroxyphenyl-N-methyl-4-methyl-5-phenyloxazolidine 2

1.6 g (0.1 m) (+) pseudoephedrine base was dissolved in 100 ml dry benzene, as was 1.8 g, 0.15 m p-hydroxybenzaldehyde, and misture was refluxed with Dean-Stark trap 12 hr. Solution was cooled, and 3.1 g crude crystals were filtered off. These were recrystallized from benzene to give 2.4 g (91.6%) white crystals m.p. 213° (lit. m.p. 213°).

NMR--AB quartet 464 and 437 cps (4) 2-Ph, multiplet 448 cps (5), 5-Ph, singlet 305 cps (1), 2-Ph, doublet 269 cps (1), 5-Ph, multiplet 153 cps (1), 4-H, singlet 131 cps (3), N-CH_3, and doublet 71 cps (3), CH-CH_3 in pyridine-D_5.

$[\alpha]_D$ = (+) 49.3°, c = 1 in 95% EtOH

Infared showed signs of Bohlmann bands at 2690 and 2750 cm^{-1}.

ν_{max} (KBr) 2920, 2780, 1490, 1460, 1265, 1160, and 1030 cm^{-1}.

(-) cis 2-p methoxyphenyl-N-methyl-4-methyl-5-phenyloxazolidine 3

2.0 g (.012 mole) (-) ephedrine base was refluxed with 2.2 g (.016 m) p-methoxybenzaldehyde in 50 ml dry benzene for 6 hr. Mixture was cooled, and 4.0 g white needles appeared, which were recrystallized from benzene-hexane to give 3.2 g (.01 m, 92%) prismatic needles m.p. 87° (lit. m.p. 87°).

NMR--AB quartet 458 and 420 cps (4) 2-Ph, multuplet 445 cps (5), 5-Ph, doublet 309 cps (1), 5-H, singlet 280 cps (1), 2-H, singlet 229 cps (3), $-OCH_3$, multuplet 178 cps (1), 4-H, singlet 130 cps (3) $N-CH_3$, and doublet 46 cps (3) $CH-CH_3$ in $CDCl_3$.

$[\alpha]_D$ = (-) 50.0°, c = 1 in 95% EtOH

The infared showed Bohlmann bands at 2780, 2700, and 2670 cm^{-1}.

ν_{max} (KBr) 2930, 2855, 1500, and 1005 cm^{-1}.

(+) trans-2p-methoxyphenyl-N-methyl-4-methyl-5-phenyloxazolidine 4

3.0 g (0.18 m) (+) pseudoephedrine and 2.9 g (0.22 m) p-methoxybenzaldehyde were dissolved in 50 ml dry benzene and refluxed 6 hr, with Dean-Stark trap. Solvents were removed in

vacuo to give an oil which crystallized to give 3.2 g crude product. Hexane recrystallization gave 2.7 g (.09 m, 53%) clear crystals m.p. 57° (lit. m.p. 57°).

NMR--AB quartet, 450 and 414 cps (4), singlet 441 cps (5), 5-Ph, singlet 295 cps (1), 2-H, doublet 284 cps (1), 5-H, singlet 225 cps (3), $-OCH_3$, multuplet 152 cps (1), 4-H, singlet 126 cps (3), $N-CH_3$, and doublet 71 cps (3), $CH-CH_3$ in $CDCl_3$.

$[a]_D$ = (+) 48.6° c. 1 in 95% EtOH

Infared showed Bohlmann bands at 2680 and 2730 cm^{-1}. ν_{max} (KBr) 2930, 2850, 1470, 1280, 1250, and 1040 cm^{-1}.

(+) cis, 2-p-methoxyphenyl-N-methyl-4-methyl-5-phenyloxazolidine 5

2.3 g (.014 m) (+) ephedrine base and 2.5 g (.016 m) p-methoxybenzaldehyde were refluxed 3 hr. in 50 ml dry benzene with Dean-Stark trap. Product crystallized on cooling, and was recrystallized from benezene-hexane to give 3.7 g (.013 m, 93%) clear needles m.p. 87° (lit. m.p. 87°).

$[\alpha]_D$ = (+) 50.0, c. 1 in 95% EtOH

NMR and IR spectra were identical to 3.

(-) cis-2-cyclohexylidene-N-methyl-4-methyl-5-pheyloxazolidine 6

(-) ephedrine (2.3 g, .014 m), and cyclohexanone (4.0 ml, .04 m)

were refluxed together in 50 ml benzene with Dean-Stark trap 5 hr. Mixture was cooled in an ice bath, and extracted with 2 x 25 ml 0.1 N HCl, which in turn was extracted once with ether. The aqueous phase was cooled in an ice bath, and pH was brought to 11 with Na_2CO_3. Product crystallized from this mixture as a hydrate. The crystals were filtered, dried and recrystallized from 95% EtOH to give 3.7 g (92.5%) white flakes m. p. 75°.

Calc. for $C_{16}H_{23}NO.\ 1/4\ H_2O$ 77.00% C, 9.48% H, 5.61% N

Found 77.03% C, 9.28% H, 5.62% N.

$[\alpha]_D$ = (-) 16.0°, c. 1 in 95% EtOH

NMR singlet 439 cps (5), Ar-H, doublet 305 cps J 8.7 (1), 5-H, multiplet 295 cps (1), 4-H, singlet 137 cps (3), N-CH_3, broad singlet 103 cps (10), $(-CH_2-)_5$, and doublet 35 cps (3), CH-CH_3.

Bohlmann bands were not observed in the infared spectrum. ν_{max} 2960, 1615, 1410, 1320, 1285, 1220, 1185, 1105, 1070, 945, 720, and 670 cm^{-1}.

(+) trans-2-cyclohexylidene-N-methyl-4-methyl-5-phenyloxazolidine 7

(+) pseudoephedrine, 1.6 g, .01 m, and cyclohexanone, 1.0 ml, .01 m were reacted and extracted in the manner as described for 6. Hexane recrystallization gave 1.7 g, 69% clear prismatic needles m. p. 71°.

Calc. for $C_{16}H_{23}NO$ 78.4% C, 9.4% H, 5.7% N. Found 78.17% C, 9.38% H, 5.92% N.

$[\alpha]_D$ = (+) 42.0°, c. 1 in 95% EtOH.

NMR, singlet 440 cps (5), Ph-H, doublet 367 cps J 8.5 (1), 5-H, multiplet 157 cps (1), 4-H, singlet 138 cps (3) $N-CH_3$, broad singlet 103 cps (10) $(-CH_2-)_5$ and doublet 64 cps (3) $CH-CH_3$.

No Bohlmann bands were observed in the infared spectrum. ν_{max} 2960, 1605, 1410, 1270, 965, 760, and 705 cm^{-1}.

(-) cis (2-4-t-butylcyclohexylidene-N-methyl-4-methyl-5-phenyloxazolidine 8

(-) ephedrine, 5.0 g, .03 m, and t-butylcyclohexanone 5.2 g, .03 m were dissolved in 150 ml toluene and refluxed for the hr. with Dean-Stark trap. Mixture was cooled in an ice bath and extracted with 2 x 50 ml ether, which was in turn extracted 1 x 25 ml ether. Aqueous phase was made basic with Na_2CO_3, and extracted with 2 x 25 ml ether, which was dried over Na_2SO_4 and removed in vacuo to yield a white solid which was recrystallized from hexane to give 8.3 g (92%) white needles, m.p. 151-152°.

Calc. for $C_{20}H_{30}NO$ 80.0% C, 10.0% H, 4.8% N. Found 79.90% C, 10.09% H, 4.6% N.

$[\alpha]_D$ = (-) 12.7°, c. 0.8 in THF.

NMR singlet 438 cps (5), Ph-H, doublet 304 cps J 9 (1), 5-H

multiplet 195 cps (1), 4-H, singlet 137 cps (3), N-CH_3 multiplet 100 cps (9) $(CH_2)_2CH(CH_2)_2$ singlet 53 cps (9), $(CH_3)_3$, and doublet 37 cps (3) CH-CH_3.

(+) trans 2-(4't-butylcyclohexylidene) N-methyl, 4-methyl, 5-phenyloxazolidine 9

5.0 g (.03 m) (+) pseudoephedrine was reacted with 5.2 g (0.3 m) 4-t-butylcyclohexanone under the conditions described for 8. Workup and hexane recrystallization gave 8.6 g (96%) white crystals m.p. 81-82°.

$[\alpha]_D$ = (+) 32.5°, 0.8% in THF.

Calc. for $C_{20}H_{30}NO$ 80.0% C, 10.0% H, 4.8% N. Found 79.96% C, 10.06% H, 4.94% N.

NMR singlet 441 cps (5) Ph-H, doublet 268 cps (1) 5-H multiplet 158 cps (1) 4-H, singlet 138 cps (3) N-CH_3, broad singlet 100 cps (9) $(CH_2)_2CH(CH_2)_2$ doublet 65 cps (3) CH-CH_3, and singlet 35 cps (9) $(CH_3)_3$.

(+) cis-2(3'methylcyclohexylidene)-3, 4 dimethyl 5-phenyloxazolidine 10

1.6 g (.01 m) (+) ephedrine and 3.2 g (.02 m) 3-methylcyclohexanone were dissolved in 50 ml xylene and refluxed 6 hr. with Dean-Stark trap. Mixture was cooled in an ice bath, then extracted 2 x 25 ml 0.1 N HCl, which was in turn extracted

with 1 x 25 ml ether. Aqueous phase was brought o pH 11 with Na_2CO_3, and extracted with benzene 1 x 40 ml and ether 2 x 25 ml. Organic phase was dried over anhyd. Na_2SO_4 and evaporated in vacuo to give crude product, which was recrystalized three times from hexane to give 1.2 g (45%) white sheets m. p. 83-89°.

Calc for $C_{17}H_{25}NO$ 78.7% c, 9.7% H, 5.4% N. Found 78.80% C, 9.54% H, 5.58% N.

NMR singlet 436 cps (5), Ph-H, doublet 302 cps (1), %-H, octet 195 cps (1) 4-H, singlet 136 cps (3), N-CH_3, broad singlet 100 cps (9) (*$CH_2CH(CH_2)_3$) doublet 55 cps (3), J 6.0 $CHCH_3$, and doublet 35 cps (3), J 65. 4-CH_3.

(-) cis-2(3'methylcyclohexylidene)-3, 4 dimethyl-5-phenyloxazolidine 11

2.0 g (.013 m) (-) ephedrine was reacted with 4.0 g (.03 m) rac-3-methylcyclohexanone under the conditions described for 10. Workup and two hexane recrystallizations gave 2.1 g (69%) white crystals m. p. 73-89°.

Calc for $C_{17}H_{25}NO$: 78.71% C, 9.72% H, 5.40% N. Found 78.88% C, 9.69% H, 5.41% N.

NMR--toothed singled 444 and 440 cps (5), 5-Ph, doublet 302 cps (1) 5-H, octet 195 cps (1) 4-H, singlet 136 cps (3) N-CH_2 broad singlet 100 cps (9), ($CH_2CH(CH_2)_2$), doublet 55 cps $CHCH_3$, and doublet 35 cps (3) 4-CH_3.

(+) trans 2-(3' methylchclohexylidene) 3, 4 dimethyl 5-phenyloxazolidine 12

(+) pseydoephedrine, 1.6 g, .01 mole and rac-3-methylcyclohexanone 2.0 g, 1.16 mole were reacted under the conditions described for 10. Workup gave 2.8 g crude product which distilled at 67-70°, 0.3 mm to give 2.3 g, (77%) clear oil.

Calc. for $C_{17}H_{25}NO$. 78.4% C, 9.4% H, 5.7% N. Found 78.17% C, 9.38% H, 5.92% H.

NMR--toothed singlet 441 and 442 cps (5), 5-Ph, doublet 265 cps (1) 5-H, octet 157 cps (1), 4-H, singlet 138 cps (3), N-CH_3 broad singlet 96 cps (9) ($CH_2CH(CH_2)_2$), doublet 60 cps (1.8) $CHCH_3$, doublet 54 cps (3), 4-CH_3 and doublet 50 cps (1.2) $CHCH_3$.

(+) cis 2-(3'R-methylcyclohexylidene)-3, 4-dimethyl-5-phenyloxazolidine 13

(+) ephedrine, 1.6 g (.01 m) was reacted with 3.2 g (.025 m) (+) 3-methylcyclohexanone under the conditions described for 10. Workup gave 1.8 g (70%) clear oil Bp. 65-70°, 0.03 mm.

Calc. for $C_{17}H_{25}NO$: 78.7% C, 9.7% H, 5.4% N. Found 78.70% C, 9.46% H, 5.68% N.

$[\alpha]_D$ = (+) 4.93°, c. 1 in 95% EtOH.

NMR singlet 442 cps (5) PH-H, doublet 304 cps (1) 5-H, octet 196 cps (1), 4-H, singlet 139.5 cps (3) N-CH_3, broad multiplet 100 cps

(9) $-CH_2CH(CH_2)_2$ doublet 57 cps (3), $CHCH_3$, and doublet 37 cps (3) 4-CH_3.

(-) cis 2-(3'R methylcyclohexylidene-3, 4 dimethyl-5-phenyloxazolidine 14

3.0 g of (-) ephedrine (.018 m) was reacted with 6.0 g (.05 m) ( ) 3-methylcyclohexanone under the conditions described for 10. Workup followed by three hexane recrystallizations gave 3.1 g (69%) clear needles m.p. 88-89°.

Calc. for $C_{17}H_{25}NO$. 78.7% C, 9.7% H, 5.4% N. Found 78.74% C, 9.56% H, 5.36% N.

$[\alpha]_D$ = (-) 36.1, c. 1 in 95% EtOH

NMR singlet 439 cps (5), 5-Ph, doublet 304 cps (1), 5-H, multiplet 196 cps (1) 4-H, singlet 136 cps (3) N-CH_3 broad singlet 101 cps (9), $-CH_2CH(CH_2)_2$ doublet 55 cps (3) $CHCH_3$, and doublet 37 cps (3) 4-CH_3.

(+) trans-2(3'R-methylcyclohexylidene)-3, 4-dimethyl-5-phenyloxazolidine 15

3.0g (+) pseudoephedrine and 6.0 g (.05 m) (+) 3-methylcyclohexanone were reacted in the manner described for 10. Workup and distillation gave 3.2 g (69%) clear oil b.p. 65-70°/.03 mm.

Calc. for $C_{17}H_{25}NO$. 78.7% C, 9.7% H, 5.4% N. Found 78.80% C,

9.76% H, 5.59% N.

$[a]_D$ = (+) 12.3°, c. 1 in 95% EtOH

NMR singlet 442 cps (5), 5-Ph, doublet 265 cps (1) 5-H, octet 158.5 cps (1), 4-H, singlet 138.5 cps (3) N-CH_3 broad singlet 96 cps (9) -$CH_2CH(CH_2)_2$ doublet 66 cps (3), 4-CH_3, and doublet 60 cps (3) $CHCH_3$.

(-) cis 2-(3'R methylcyclopentylidene)-3, 4-dimethyl-5-phenyloxazolidine 16

(-) ephedrine, 1.6 g (.01 m) and ( ) 3-methylcyclopentanone, 3.2 g (.03 m) were reacted in the manner described for 10. Workup as described for 10, followed by isopropanol recrystallization gave 1.8 g (75%) white crystals m. p. 71-73°.

Calc. for $C_{16}H_{23}NO$. 78.3% C, 9.4% H, 5.7% N. Found 78.31% C, 9.14% H, 5.95% N.

$[\alpha]_D$ = (-) 18.5°, c. 1 in 95% EtOH

NMR singlet 433 cps (5) 5-Ph, doublet 295 cps (1) 5-H, octet 177 cps (1), 4-H, singlet 132 cps (3) N-CH_3, multiplet 110 cps (7), -CH_2CHCH_2 broad doublet 60 cps (3) $CHCH_3$, and doublet 43 cps (3), 4-CH_3.

(+) trans 2-(3R-methylcyclopentylidene)-3, 4-dimethyl-5-phenyloxazolidine 17

(+) pseudoephedrine, 1.6 g, .01 m, and (+) 3-

methylcyclopentanone, 3.2 g, .03 m, were reacted under the conditions described for 10. Workup followed by distillation gave 1.5 g (62.6%) clear liquid b.p. 155-160°/3.2 mm.

Calc. for $C_{15}H_{23}NO$. 78.3% C, 9.45% H, 5.7% N. Found 78.22% C, 9.29% H, 5.78% H.

$[\alpha]_D$ = (+) 28.2°, c. 1 in 95% EtOH

NMR singlet 435 cps (5), 5-Ph, doublet 266 cps (1), 5-H, multiplet 140 cps (1), 4-H, singlet 134 cps (3) N-CH_3, broad multiplet 100 cps (7), -CH_2CHCH_2 doublet 65 cps (4), J 5.5, 3'CH_3 + 4-CH_3, and doublet 63 cps (2), J = 5.5 3'CH_3.

(+) cis 2-(3R cyclopentylidene)-3, 4-dimentyl-5-phenyloxazolidine 18

(+) ephedrine, 1.6 g (.01 m) and (+) 3-methylcyclopentanone, 3.2 g (.03 m) were reacted as described for 10. Workup yielded 1.8 g (75%) white crystals m.p. 35-44° which were recrystallized from pentane to give 0.9 g white flakes m.p. 43-44°.

Calc. for $C_{16}H_{23}NO$. 78.3% C, 9.45% H, 5.7% N. Found 78.10% C, 9.40% H, 5.70% N.

$[\alpha]_D$ = (+) 14.5°, c. 1 in 95% EtOH

NMR singlet 432 cps (5), 5-Ph, doublet 297 cps (1), 5-H, octet 179 cps (1), 4-H singlet 135 cps (3), N-CH_3 diffuse multiplet 103 cps (7), -CH_2CH-$(CH_2)_2$ doublet 63 cps (3), $CHCH_3$, and doublet 37

cps (3), 4-CH_3, in $CDCl_3$.

Note: Crude product had doublets at 63 and 57 cps in the approximate ratio 40:60.

REFERENCES

1. C. nielsen and H. J. McCausland, Amer. Pharm. Soc. 1927, xvi 288.

2. E. Merck, Ber. 1893, 13.

3. K. Freudebberg, E. Schoffel, and E. Braun, J. Am. Chem. Soc. 54, 231, (1932).

4. K. Freudenberg and F. Nikolai, Ann 510, 223, (1934).

5. D. C. Phillips, Acta Cryst. 7, 159, (1954).

6. P. Portoghese, J. Med. Chem. 10(6), 1057 (1967).

7. L. Knorr and H. Mathes, Ber. 34, 3484 (1901).

8. E. Schmidt, Arch. Pharm. 252, 89, (1974).

9. E. Bergmann, Chem. Rev. 3, 309, (1953).

10. J. B. Hyne, Am. Chem. Soc. 81, 6058, (1959).

11. S. Soliman, El-Neaey and I. M. Roushdi, UAR J. Chem. 1-5 (1970).

12. H. Pfanz and G. Kirchner. Ann. 614, 149 (1958).

13. F. Bohlmann, Angew. Chem. 69, 641 (1957): Ber. 91, 2157 (1958).

14. W. E. Rosen, Tetrahedron Letters 481 (1961).

15. M. Uskovic', H. Bruderer, C. Von Planta, T. Williams and A. Brossi, J. Am. Chem. Soc. 86, 3364 (1964).

16. E. Hendrickson, J. Am. Chem. Soc. 83, 4537 (1961).

17. J. Astor, H. Fink, and P. Doty, J. Am. Chem. Soc. 63, 2029 (1941).

18. M. Karplus, J. Chem. Phys. 20, 11, (1959).

CHAPTER III. OXAZOLIDINE DERIVATIVES OF THE EPHEDRINES AS STEREOSPECIFIC ASSAYING AGENTS IN GAS CHROMATOGRAPHY

Introduction

Several methods[1-7] have been described for the identification and determination of ephedrine and pseudoephedrine in biological materials by GLC. Brochmann-Hanssen[1] found that an acetone solution of ephedrine and pseudoephedrine separated well after mild heating. He postulated that this was due to imine formation, and found that pseudoephedrine reacted faster than ephedrine with the ketone. Later the compound was identified as the oxazolidine 23a. This method proved to be sufficiently sensitive for detection of ephedrine and pseudoephedrine in biological fluids. Heptafluorobutyryl[4] anhydride was reported to be well suited for use with electron capture detectors, having sensitivity in the nannogram level, sufficient for quantitation of ephedrine and pseudoephedrine in blood after oral administration.

Beckett and Testa[5] reported that N-trifluoracetyl l-prolylchloride[5, 6, 7] gave fair separation of (+) and (-) ephedrine. However, separation of the pseudoephedrine enantiomers was poor, and between ephedrine and pseudoephedrine no separation was seen. To date, no reagent has been reported which usuably separates all four diastereomers.

In our study, we investigated the oxazolidines described in Chapter II. Direct reaction between amine and ketone under GLC column conditions was also investigated. Separation of all four diastereomers by using optically active 3-methyl cyclohexanone was attempted.

Results and Discussion

A. Aldehyde Derivatives

We first tested the aldehyde derivatives 1-4 described in Chapter II to determine if they were suitable for separation and identification of (-) ephedrine and (+) pseudoephedrine.

Table III. 1. Oxazolidines Derived From Aldehydes Tested for GLC Separability.

Compound	Aldehyde	Amine
1	p-hydroxybenzaldehyde	(-) ephedrine
2	p-hydroxybenzaldehyde	(+) pseudoephedrine
3	anisaldehyde	(-) ephedrine
4	anisaldehyde	(+) pseudoephedrine

The p-hydroxbenzaldehyde derivatives 1 - 2 had retention times too long to be observed under the described column conditions. Silylation with BSA gave reasonable retention times (ca. 18 min.). However no separation of ephedrine and pseudoephedrine was seen. The anisaldehyde derivatives 3 and 4 gave fair separation on 1. 5%

OV-17. As discussed in Chapter II, each of these compounds could possibly exist as diastereomeric pairs at C_2. However spectroscopic evidence strongly suggests only the 2-(S) isomer is formed. The fact that each of these compounds shows a single, sharp peak in GLC further confirms this evidence.

Table III. 2. Separation of Aldehyde Derivatives of Ephedrine and Pseudoephedrine.

Compound	Retention Time min.	R factor	Comment
1[a]	18.90	0.28	No separation seen
2	18.48		
3[b]	15.42	0.71	Useable resolution
4	14.70		

Column: 6 ft. U tube packed with 1.5% OV-17 on Gas Chrom. Q.

N_2 flow rate 20 ml/min; H_2 15 psi; enj T° = det T° = 200°; Air 30 psi.

[a]Col T° = 200°, silylated with BSA in THF (see experimental).

[b]Col T° = 405°.

B. Ketone Derivatives

The aldehyde derivatives studied gave poorer separation of ephedrine and pseudoephedrine than was reported for acetone. Therefore we decided to investigate the GLC behavior of the ketone derivatives 6 - 18 described in Chapter II.

Table III. 3. Oxazolidines Derived From Ketones Tested for GLC Separability.

Compound	Ketone	Amine
6	cyclohexanone	(-) ephedrine
7	cyclohexanone	(+) pseudoephedrine
8	6-butylcyclohexanone	(-) ephedrine
9	t-butylcyclohexanone	(+) pseudoephedrine
13	(+) 3-methylcyclohexanone	(+) ephedrine
14	(+) 3-methylcyclohexanone	(-) ephedrine
15	(+) 3-methylcyclchexanone	(+) pseudoephedrine
16	(+) 3-methylcyclopentanone	(-) ephedrine
18	(+) 3-methylcyclopentanone	(+) ephedrine

We first investigated the cyclohexanone derivatives 6 and 7. Table III. 4. results show that the cyclohexanone derivatives have short retention times on 3%-OV17, and give slightly better separation than was reported for acetone.

Brochmann-Hanssen[1] reported that ephedrine and pseudoephedrine could be derivatized from acetone by mild heating. Therefore we decided to investigate the conditions under which the amines might react with cychohexanone upon injection onto a GLC column.

Table III. 4. Retention Times of Cyclohexanone Derivatives in Benzene.

Compound	Retention Time min.	R factor
6	5.67	1.28
7	5.07	

Conditions: 6 ft. U-tube, 3% OV-17 on Gaschrom Q N_2 = 20 ml/min; H_2 = 15 psi, air = 30, Col = 150°, inj. = det = 200°.

Table III. 5. Retention Times in Cyclohexanone on 3% OV-17.

Compound	Retention Time min.	R factor
6	12.8	1.0
7	11.40	
(-) ephedrine	12.48	0.91
(+) ψ-ephedrine	11.28	

6-ft. spiral column, 3% OV-17 on Gaschron Q. N_2 = 15 ml/min, H_2 = 15 psi; air = 30 psi; Col = 140°, inj. = det = 200°.

These data show that pseudoephedrine reacts completely with a tenfold excess of cyclohexanone in benzene under the described column conditions, while ephedrine reacts completely only in neat cyclohexanone. This agrees with Brochmann-Hanssen's[1] observation that ψ ephedrine reacts much faster than ephedrine with acetone. Ephedrine and pseudoephedrine gave excellent separation when dissolved in neat cyclohexanone, giving peak height and retention time corresponding to complete conversion to 6 and 7. This is in contrast to other derivatizing agents where preliminary heating or overnight standing is required for reaction.

Table III. 6. Comparative Reaction With Cyclohexanone in Benzene.

Compound	Mole ratio $(\frac{\text{Cyclohexanone}}{\text{amine}})$	Peak Height in.
(-) ephedrine	1.0	0.0
(+) ψ-ephedrine	1.0	1.3
(-) ephedrine	5.0	1.2
(+) ψ-ephedrine	5.0	3.3
(-) ephedrine	10.0	2.6
(+) ψ-ephedrine	10.0	5.6
(-) ephedrine	Neutral	5.6
(+) ψ-ephedrine	Neutral	5.6

6 ft. v tube, 3% OV-17 on Gaschrom Q, Col = 150°, inj = det = 200°, N_2 = 15 ml/min, H_2 = 30 psi, air = 30 psi.

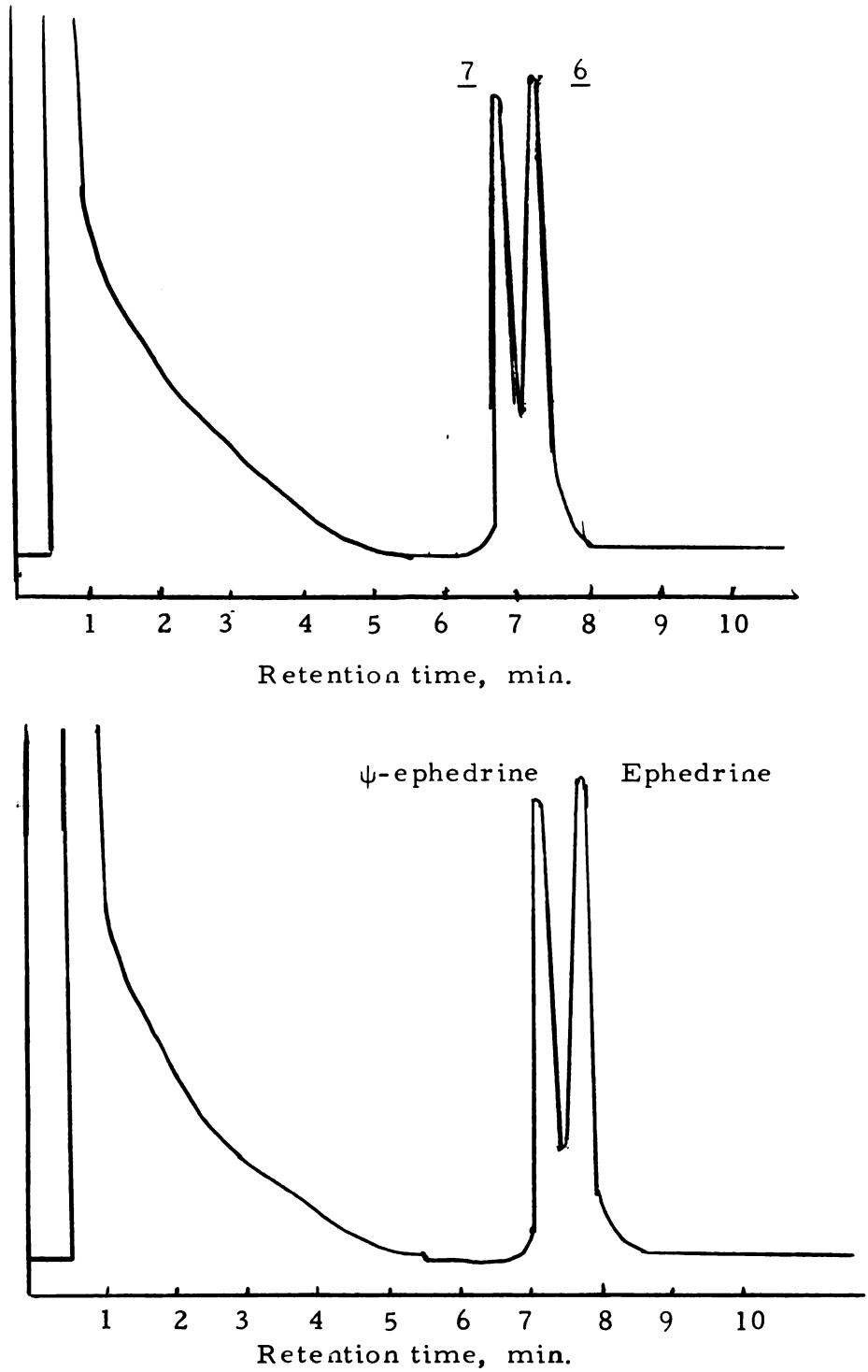


Figure III. 1. Comparison of Oxazolidines and Ephedrines in Neat Cyclohexanone.

The 4-t-butyl cyclohexanone derivatives 8 and 9 were found to give the best speration on 1% SE-30.

Table III. 7. Retention Times of +-Butyl Cyclohexanone Derivatives.

Compound	Retention Time min.	R factor	Ephedrine Area ψ-ephedrine
8	10. 32	3. 6	1. 17
9	8. 82		
Ephedrine + t Bu 	9. 84	4. 4	1. 15
ψ-ephedrine + t Bu 	8. 52		

6 ft. u-tube, 3% SE-30 on Gaschrom Q Col = 190°, inj. = det = 240°, N_2 = 20 ml/min; H_2 = 150 psi, air = 30 psi.

The separation factors of around 4 reported here are the best for any of the compounds studied. Also, we found that a benzene solution containing a twofold excess of 4-t-butyl cyclohexanone gave peaks corresponding to complete reaction with both ephedrine and pseudoephedrine under the described conditions. However, reaction would not take place on 3% OV-17 under the same conditions.

Cyclohexanone and 4-t-butylcyclohexanone were found to react during injection to give excellent separation of (-) ephedrine and (+) pseudoephedrine. The next possibility we considered was that introduction of a fixed asymmetric center on the cyclohexanone ring might also separate d and l isomers.

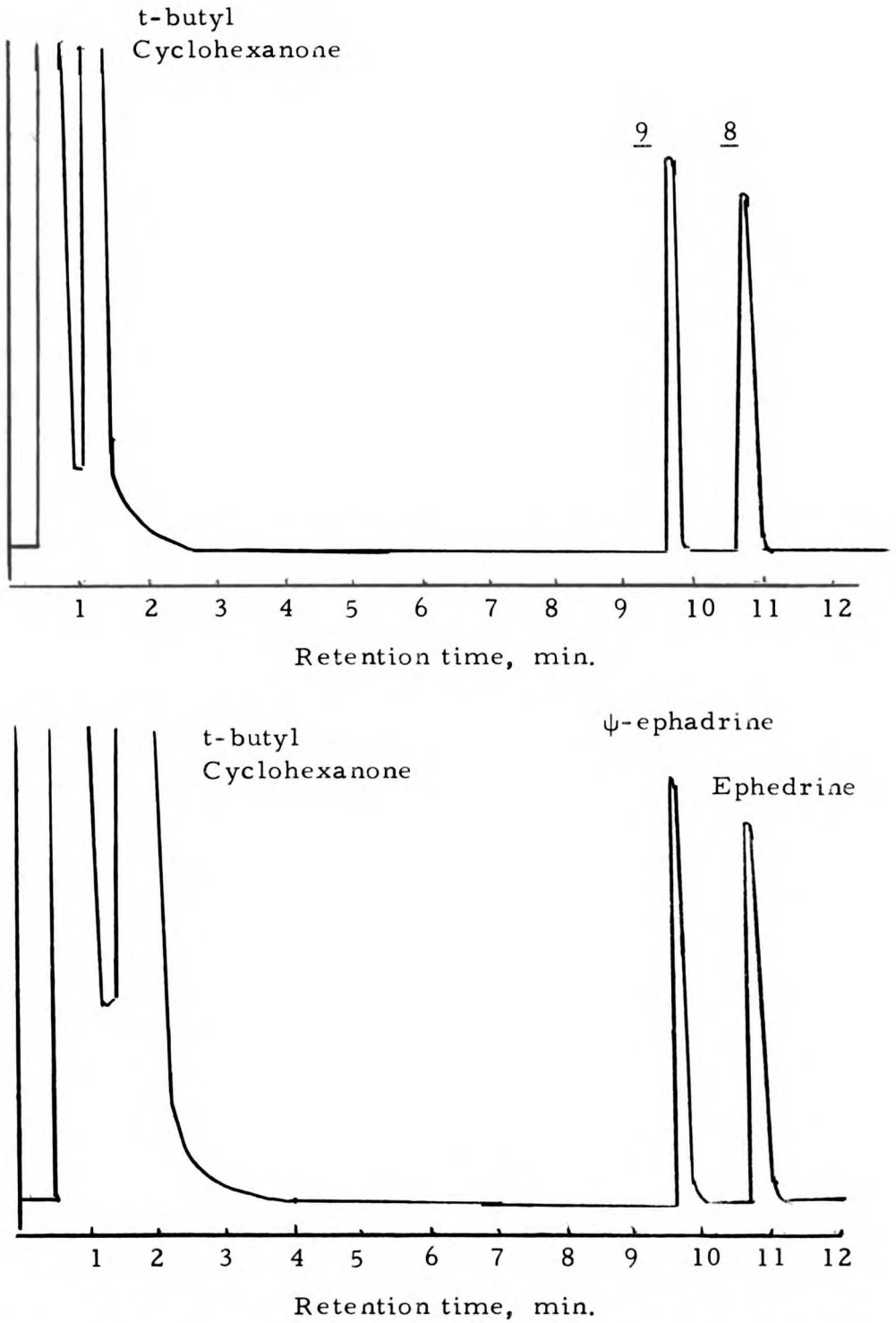


Figure III. 2. Reaction of t-butyl Cyclohexanone with Ephedrine and Pseudoephedrine in Benzene.

Table III.8. Gas Chromatography of (+) 3 Methylcyclohexanone Derivatives.

Compound	Retention Time Min.	R factor	
(-) cis (+) 3 methylcyclohexyl 13	6.12	0.17	
(+) cis (+) 3 methylcyclohexyl 14	6.00	1.28	
(+) trans (+) 3 methylcyclohexyl 15	4.98		
(±) cis (+) 3 methylcyclohexyl	6.06		No separation--broad peak
inj, det = 200°, N_2 20 ml/min; 3% OV-17, 150°			
(+) cis (+) 3 methylcyclohexyl 14	3.42	0.46	Shoulder seen
(-) cis (+) 3 methylcyclohexyl 13	3.60		
17	2.63	0.09	No separation
18	2.64		
3% SE-30, 175°			
inj. det = 200°, N_2 20 ml/min			

These results show that (+) 3 methylcyclohexanone gave excellent separation of ephedrine and pseudoephedrine, slightly better than cyclohexanone, but not as good as 4-t-butylcyclohexanone. However, compounds 13 and 15, prepared from d and l ephedrine, respectively, gave at best poor separation, only a shoulder being observed. It was found that these compounds when injected separately onto a carbowax column, gave differences of retention time of over one minute. However, when injected together, a single sharp peak of intermediate retention time was observed. This behavior could possibly be explained by some kind of molecular association between the two compounds. With the (+) 3-methylcyclopentanone derivatives

of d and l ephedrine 16 and 18 no separation was observed. The data expressed in Chapter II suggest that 16 and 18 are actually each diastereomeric pairs, while 13 and 15 are single compounds.

In conclusion, the oxazolidines prepared from substituted cyclohexanones gave much better separation of ephedrine and pseudo-ephedrine than the derivatives prepared from aromatic aldehydes. The order 4-t-butylcyclohexanone > (+) 3-methylcyclohexanone > cyclohexanone > acetone suggests the separability increases with increasing substituent size on the cyclohexanone ring.

Experimental

Synthesis

The preparation of the compounds used in this chapter is described in Chapter II.

Chromatograms were obtained on Varian 2100 and Varian 2400 gas chromatographs, both equipped with flame ionization detectors. Columns and column conditions used for the respective experiments are described in Tables III. 1-III. 8.

Procedure for GLC Analysis

Aldehyde derivatives; Benzene solutions containing 1 mg/ml of each compounds 1 - 4 were prepared. Samples were introduced to columns by means of 10 μl Hamilton Syringe. Injection size was

1 μl. Silylation of 1 - 2 was done by adding 0. 1 ml BSA to a solution of 10 mg oxazolidine in 1 ml dry THF.

Ketone derivatives; Benzene solutions containing 5 mg/ml of each 6 - 9, 13 - 15, and 17 - 18 were prepared and tested for separability on the columns and conditions described in Tables III. 4, III. 6, and III. 8.

Comparative reaction of ephedrine and pseudoephedrine with cyclohexanone; . 01 mmole ephedrine and . 01 mmole pseudoephrine were placed together in each of three tubes containing 1 ml benzene. Cyclohexanone was added, . 01 mmole, . 05 mmole, and . 10 mmole, respectively, to each of the three tubes by means of a 20 μl Hamilton Syringe. One μl injections were made under the conditions described in Table III5.

Cyclohexanone solutions; 5 mg each of (-) ephedrine, (+) pseudoephedrine, 6 and 7, were placed in four tubes containing 1 ml of cyclohexanone apiece. Injections of 0. 25 μl were made with a 1. 0 μl Hamilton Syringe. Results and conditions are shown in Table III. 6.

Comparative reaction of (-) ephedrine and (+) pseudoephedrine with 4-t-butylcyclohexanone; four tubes were prepared each containing 1 ml benzene and . 03 mmole 4-t-butylcyclohexanone. (-) ephedrine, . 01 mmole, (+) pseudoephedrine, . 01 mmole, S, . 01 mmole were added to each of the four tubes. Injections of 1 μl were

made with a 10 μl Hamilton Syringe. Results and conditions are described in Table III. 7.

Separation Factor

The separation factor R was calculated from the formula (Pattison[8], 1967) R = 2 NQ(AB + CD). See Figure III. 3.

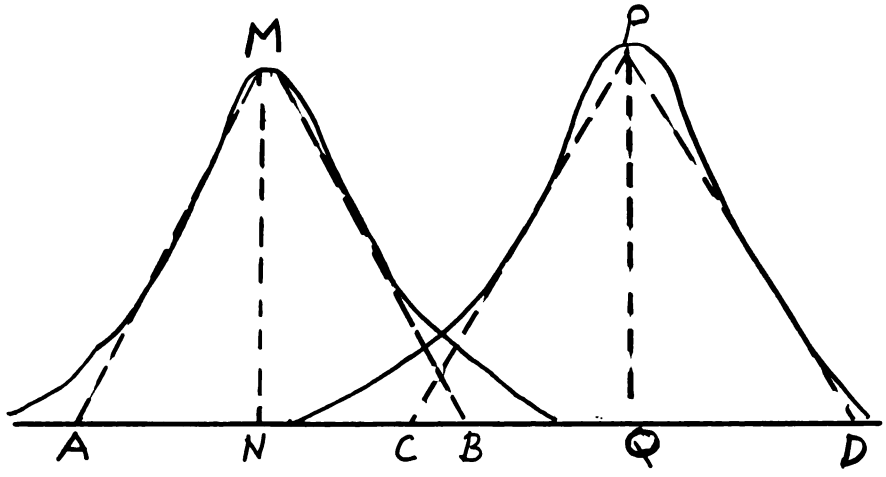


Figure III. 3. Calculation of R factor.

REFERENCES

1. E. Brochmann-Hanssen and A. Svendsen, J. Pharm. Sci. 51, 10, 1962.

2. K. Parker, C. Fontan and P. Kirk, Analyt. Chem. 34, 1345, 1962. Ibid, 35, 356, 1963.

3. A. Beckett and G. Wilkinson, Pharm. Pharmacol., 17, 1045, 1965.

4. L. Cummins and M. Fourier, Anal. Lett. 1969 2(7), 403-9.

5. A. Beckett and B. Testa, Pharm. Pharmacol. 25, 382, 1973.

6. B. Karger et al., Analyt. Chem. 39, 228, 1969.

7. J. Westley and B. Halpern, Analyt. Chem. 40, 2046, 1970.

8. J. B. Pattison, A Programmed Introduction to Gas Liquid Chromatography, p. 55, Heyden, London (1969).

9. H. Pfanz and G. Kircher, Ann. 614, 149 (1958).

CHAPTER IV. THE USE OF N-PENTAFLUOROBENZOYL-S-(-) PROLYL 1-IMIDAZOLIDE (PFPBI) IN GLC SEPARATION AND IDENTIFICATION OF ENANTIOMERIC EPHEDRINES

Introduction

The ketones and aldehydes described in Chapter III gave adequate separation of (-) ephedrine and (+) pseudoephedrine. However, usable separation of d and l isomers was not attained with this method. Therefore, we sought a new method of separating and identifying the d and l isomers of ephedrine and pseudeophedrine. Since these isomers are mirror images, the derivative formed must contain a new asymmetric center in order to form diastereomers which could be distinguished by GLC. Beckett and Testa[1] reported that usable separation of d and l ephedrine could be attained by derivatization with N-trifluoroacetyl l-prolylchloride (TPC). However, their separation of the pseudoephedrine isomers was poor. Matin, Rowland, and Castagnoli[2] found that a similar reagent, N-pentafluorobenzoylprolylimidazolide 22 gave good separation of the d and l isomers of several amphetamine derivatives. The reagent also gave excellent separation of O-methylanhalonidine, which is described in Chapter I. Therefore, we investigated this reagent's ability to separate and identify the d and l isomers of ephedrine and pseudoephedrine.

Results and Discussion

Pentafluorobenzolylprolyl derivatives of the ephedrine and pseudoephedrine isomers had reasonably short retention times (10 - 20 min.) at relatively low temperatures (90-110°). Best separation was attained on 1.5% OV-17. The results are shown in Table IV. 1.

These results show that this reagent gives excellent separation of d and l ephedrine, with a resolution factor of 3.3 compared to 0.78 reported for N-Trifluoroacetylprolyl chloride. Moreover, the retention times of 10-20 minutes for the PFPBI derivatives are much shorter than those reported for TPC (ca. 100 min.) resulting in much sharper peaks. The resolution factor of 0.43 for the pseudoephedrine derivatives is comparable to that reported by Beckett and Testa for the TPC derivatives. However, due to the relatively short retention times a usable separation was nevertheless observed. See figure IV. 1.

The pentafluorobenzoyl moiety is extremely sensitive to electron capture detectors. Matin and Rowland[3] report that the N-pentafluorobenzoyl derivative of amphetamine can be detected at 1/6000th the level of the corresponding trifluoroacetamide. Therefore pentafluorobenzoylprolyl derivatives of the ephedrines and pseudoephedrines should be easily detectable at submicrogram levels suitable for biological assay.

Table IV. 1. Retention Times of PFPBI Derivatives of the Ephedrines and Pseudoephedrines.

Compound	Column T	Retention Time 1/SO in	Inches	Minutes	Ratio	Date
(+)	110°	112	2.24	8.96	1.250	
(-)	110°	140	2.80	11.20		
						Dec. 14
(+)	110°	111.5	2.23	8.92	1.224	
(-)	110°	136.5	2.73	10.92		
(+)	110°	109	2.09	8.36	1.299	R = 3.63
(-)	110°	139	2.78	11.12		
(+)	110°	111.2	2.22	8.88	1.242	Dec. 17
(-)	110°	138	2.76	11.04		
(+)	110°	112	2.24	8.96	1.228	
(-)	110°	137.5	2.75	11.50		
(+)	93°	220.5	4.41	17.64	1.216	Dec. 18
(-)	93°	268.5	5.37	21.48		
(+)	90°	172.2	3.44	13.76		
(+)	110°	106.5	2.13	8.52		
(+) in (-)	110°	107.5[b]	2.15	8.60		
(+) in (-)	110°	106[b]	2.12	8.48		
						Dec. 18
(+)	110°	113[b]	2.26	9.04		
(-)	110°	113[b]	2.26	9.04		
(+)*	110°	108	2.16	8.64	1.273	R = 3.277
(-)* a	110°	137.5	2.75	11.00		
(+)*	110°	111	2.22	8.88	1.239	
(-)* a	110°	137.5	2.75	11.00		

*[a] From racemic ephedrine.

[b] (-) ephedrine sample of 12/18 was impure--not enough time allowed for (-) peak to appear.

Table IV. 1. (Continued).

Compound	Column T	Rentention Time I/SO in	Inches	Minutes	Ratio	Date
(+)ψ	80°	368	7.36	29.44	1.047	Dec. 14
(-)ψ	80°	351.5	7.03	28.12		
(-)ψ	90°	317.5	6.37	25.48		
(-)ψ	90°	310.5	6.21	24.84		
					1.055	1.013
(+)ψ	90°	327.5	6.57	26.28		R = 0.43
(+)ψ	90°	321.5	6.43	25.72		
(+)ψ	110°	119	2.38	9.52	1.018	
(-)ψ	110°	117	2.34	9.36		
						Dec. 17
(-)ψ	110°	117	2.34	9.36	1.021	
(+)ψ	110°	119.5	2.39	9.56		
(-)ψ	90°	314	6.28	25.52	1.02	
(+)ψ	90°	326	6.52	26.08		
(-)ψ	90°	322.4	6.45	25.80	1.029	
(+)ψ	90°	331.8	6.64	26.56		
(-)ψ	90°	317.5	6.37	25.48		
(-)ψ	90°	310.5	6.21	24.84		
					1.055	
(+)ψ	90°	327.5	6.57	26.28		
(+)ψ	90°	321.5	6.43	25.72		
(-)ψ	80°	351.5	7.03	28.12	1.047	
(+)ψ	80°	368	7.36	29.44		
(+)ψ	110°	119	2.38	9.52		
(-)ψ	110°	117	2.34	9.36		
						Dec. 17
(-)ψ	110°	117	2.34	9.36	1.027	
(+)ψ	110°	119.5	2.39	9.56		
(+)ψ	90°	314	6.28	25.52		
(-)ψ	90°	326	6.52	26.08		
(+)ψ	90°	322.4	6.45	25.80	1.029	
(-)ψ	90°	331.8	6.64	26.56		

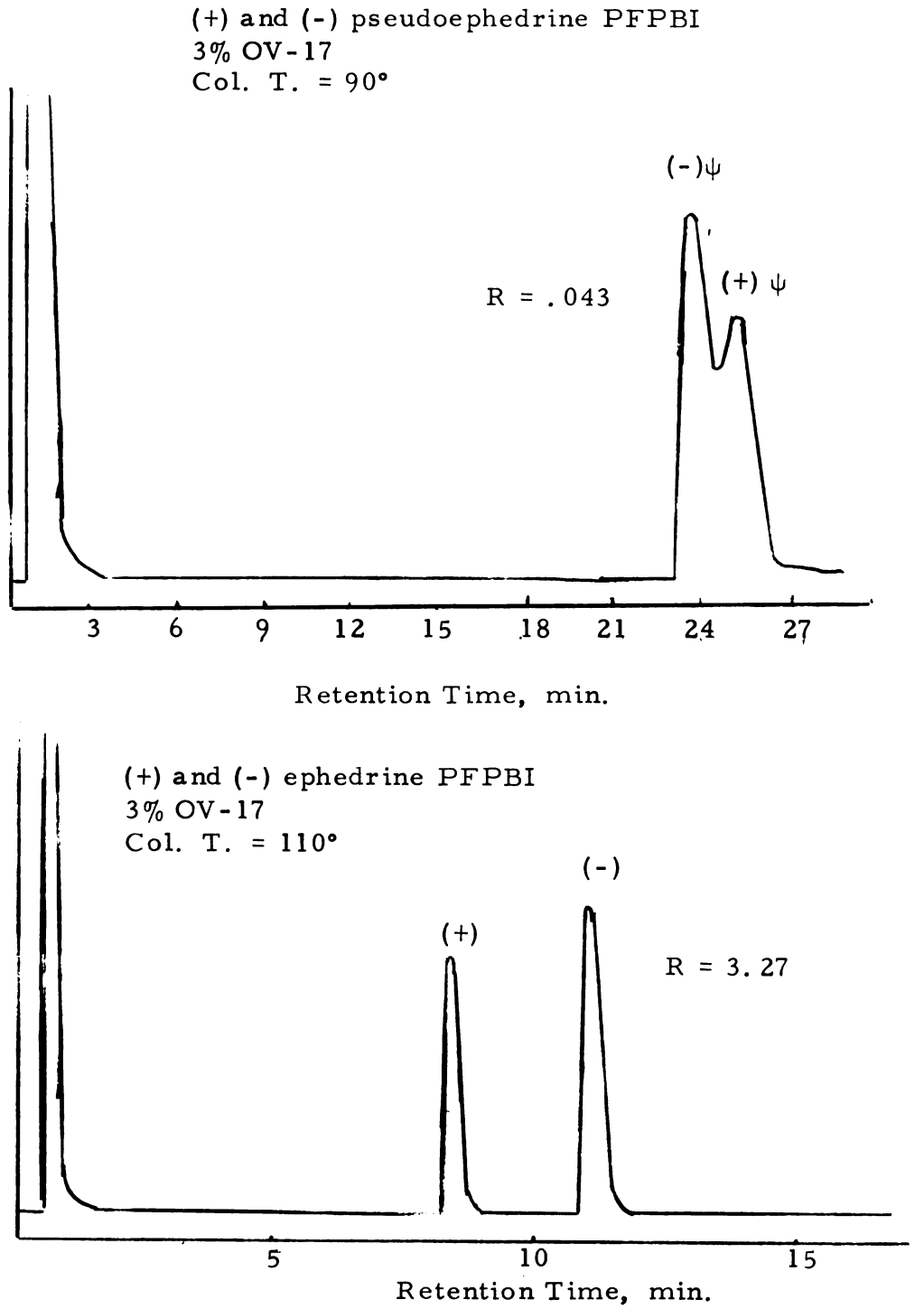


Figure IV. 1. GLC Separation of Ephedrine and Pseudoephedrine PFPBI Derivatives.

Experimental

Preparation of N-Pentafluorobenzoyl-S-(-) prolyl 1-Imidazolide (PFPBI)

The method used was that of Castagnoli et al[2]. To a stirred suspension of S-(-) proline (1.0 g, 8.7 mmoles) in 10 ml water, maintained at 0 by an ice bath, was added dropwise a 10 ml solution of ice cold 0.2 N NaOH. When the proline dissolved, pentafluorobenzoyl chloride 2.0 g, 8.7 mmoles was added slowly followed by periodic addition of 0.2 N NaOH over a 2-3 hr. period. pH was maintained as close to 8.0 as possible, monitored by a pH meter. When addition was complete, mixture was stirred 30 min. more at 0 then acidified with 0.2 N HCl and extracted twice with ether, which was dried over anhyd. Na_2SO_4 and removed in vacuo to yield a white solid, m.p. 80-81°. This compound, N-pentafluorobenzoyl-S-(-) proline was dissolved in 50 ml dry THF and stirred in an ice bath. A solution of N, N carbonyl diimidazole (1.4 g, 9.07 mmoles) in 20 ml dry THF was added dropwise over a 15 min. period to the stirred mixture. Stirring was continued 30 more min., over which time a white solid precipitated which was filtered and dried to yield 1.8 g, 5.8 mmoles, 52.7% imidazolide m.p. 175-178°.

Derivatization of the Ephedrines for GLC Analysis

The amine, 5.0 mg was dissolved in 1.0 ml dry benzene with an equimolar amount of PFPBI. Mixture was shaken and stored overnight at room temperature, then was shaken with 1 ml phthalate buffer pH 4.0 to remove excess reagent and unreacted amine. Benzene layer was pipetted into another tube, centrifuged at 2000 rpm for 1 min., then dried over anhyd. Na_2SO_4. This solution, 1 μl, was injected onto column by means of a 10 μl Hamilton Syringe.

Apparatus

A Varian model 2100 gas chromatograph was used, equipped with flame ionization detector.

Resolution factor was calculated as described by Pattison[4] (see Chapter III).

References

1. A. Beckett and B. Testa, J. Pharm. Pharmacol. 25, 382, 1973.

2. S. Matin, M. Rowland and N. Castagnoli. J. Pharm. Sci. 62, 5, 1973.

3. S. Matin and M. Rowland, J. Pharm. Sci. 61, 1235, 1972.

4. J. B. Pattison, A Programmed Introduction to Gas Liquid Chromatography, Heyden, London, p. 55 (1969).

CHAPTER V. SYNTHESIS OF (R) (+) β-DEUTERODEOXYEPHEDRINE

Introduction

The microsomal hydroxylation of drugs and other compounds has been extensively studied[1-5]. The microsomal oxygenase system of the liver is interesting in that, while it lacks substrate specificity, it hydroxylates a wide variety of compounds[2-4] with considerable stereoselectivity. For example, McMahon and Sullivan[5] found that hydroxylation of ethylbenzene proceeds in intact rats to give 90.3% D (+) α-methylphenylcarbinol, and 9.7% of the L-(-) isomer. In a later study McMahon, Sullivan, Craig and Pereira[6] showed that this hydroxylation proceeds with retention of configuration by a direct oxygen isertion mechanism. It has been shown that the oxygen in this reaction is derived from molecular oxygen rather than water.[7] However, the exact nature of the hydroxylating species has not been determined.

Norephedrines and p-hydroxynorephedrines have been identified as metabolites after administration of amphetamines to several species[8, 9]. While p-hydroxylation appears to occur equally well for both (+) S and (-) R amphetamine, β-hydroxylation only seems to occur with the (+) S isomer[10, 12]. Since (+) S amphetamine possesses most of the central stimulant and adrenergic activity associated with

dl amphetamine, there has been interest in the role of metabolism in the CNS activity of these compounds. Goldstein and Contrera[11] showed that (+) S amphetamine is a substrate for dopamine β-hydroxylase, the enzyme which converts dopamine to norepinephrine in adrenergic nerve fibers. In a later study[9], he showed that after administration of (+) S amphetamine high concentrations of the metabolite p-hydroxynorephedrine were found in heart, brain and adrenal medulla. Since these tissues are rich in dopamine β-hydroxylase, he proposed the β-hydroxylation occurs in sympathetic nerve fibers via dopamine β-hydroxylase, while p-hydroxylation occurs in the liver by microsomal oxygenases. In a recent study Taylor[13] showed that (+) S amphetamine, which had been labeled in the pro-1-(S) configuration with tritium is converted by the enzyme to norephedrine with retention of tritium. This implies that the product formed has the 1(R)2(S) configuration and the hydroxylation proceeds with retention of configuration.

Whether β-hydroxylation of amphetamines occurs solely under the control of dopamine β-hydroxylase, or is also performed by microsomal enzymes, is not clear. Therefore we decided to introduce deuterium stereospecifically at the benzylic position of amphetamine and methamphetamine. These compounds would then be subjected to the microsomal oxidase system and the loss or retention of deuterium from any norephedrine or p-hydroxy

norephedrine formed would determine the stereochemistry of the hydroxylation. Therefore we attempted several different routes of preparing deuterated methamphetamines in order to determine which method gave the highest stereoselectivity of deuteration.

Methods and Discussion

A. Deuterated Ethylbenzenes

The α-deuterated ethylbenzene system described by Craig and Pereira[5] was chosen as a model system for our preparation of β-deuterodeoxyephedrine. We prepared α deuteroethylbenzene and α, α-dideuteroethylbenzene by several different methods to determine which method gave the best yield and the highest deuterium incorporation.

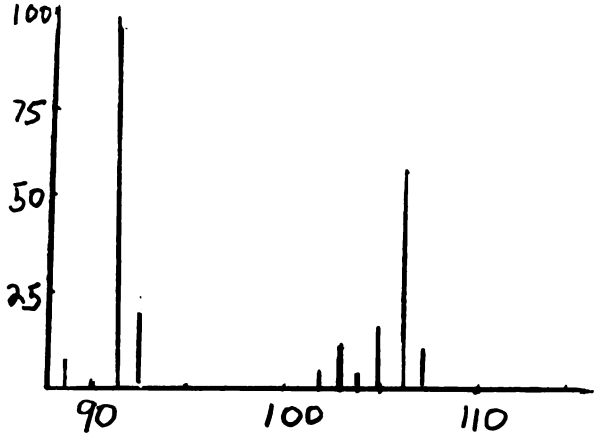
Reduction of acetophenone with sodium borodeuteride in isopropanol/water gave almost a quantitative yield of α-deuterophenylmethylcarbinol. This compound was then converted to α-deuterophenylmethylchloride and α deuterophenylmethyl bromide by thionyl chloride and phosphorus tribromide respectively.

We first attempted reduction of α-deuterophenylmethyl chloride by lithium aluminum hydride in THF. However, the yields were poor, as after 12 hours of reflux ca. 40% starting material still remained as well as a considerable amount of styrene which was

inseparable from the desired product and rapidly polymerized on distillation. Attempts to remove THF in vacuo also led to removal of most of the α-deuteroethylbenzene due to azeotrope formation with water present in the solvent.

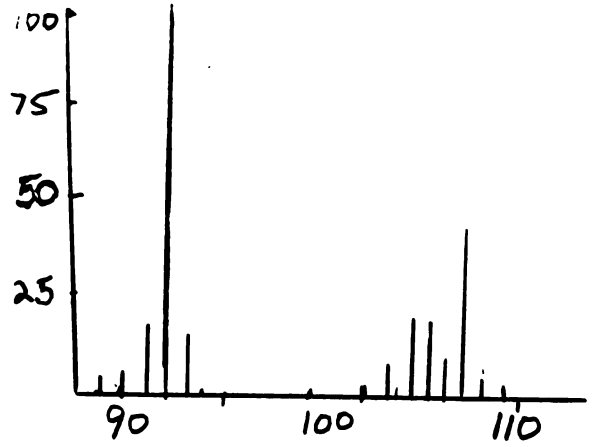
Next we attempted reduction of α-deuteromethylphenylbromide with sodium borohydride in dimethyl sulfoxide as described by Hutchkins[14]. This method gave a fair yield (45%), but the product still contained some styrene which was difficult to remove. α, α-Dideuteroethylbenzene was prepared in this manner, using sodium borodeuteride instead of sodium borohydride, in similar yield.

Finally α-methylbenzylchloride was reduced with lithium aluminum deuterideand lithium deuteride[15, 16] (1:10) in THF. This method gave complete reduction in good yield (ca. 70%). THF was removed by several aqueous extractions of a pentane solution of the reaction mixture. (See experimental section.) α-Deuteromethybenzylchloride was reduced in like manner to give α, α-dideuteroethylbenzene in similar yield. A comparison of the size of the molecular ion and the parent peak in the mass spectrum of the dideuterated, monodeuterated and undeuterated ethylbenzenes showed that deuterium incorporation at the benzylic position was > 90% for both monodeuterated and dideuterated ethylbenzenes. The NMR spectrum shows a complex quartet with an integration of 0.95 compared to the methyl group for the benzylic proton of the



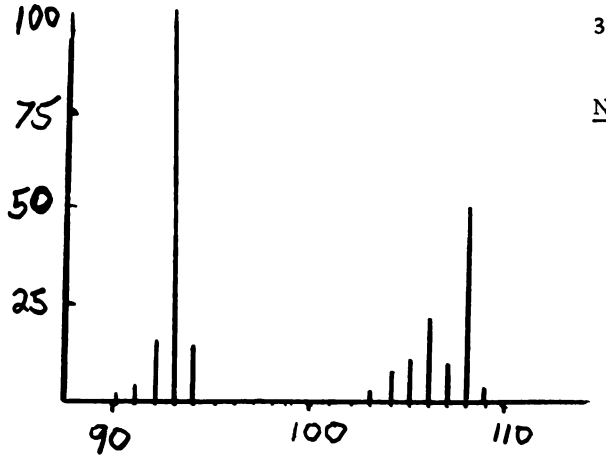
1. Ethylbenzene C_8H_{10}

Nominal mass	% int. Base
107	3.9
106	46.8
105	7.9
104	1.8
103	4.6
102	1.2
92	7.3
91	100.0
90	0.8



2. D_1-Ethylbenzene C_8H_9D

Nominal mass	% int. Base
108	2.6
107	28.4
106	6.2
105	10.5
104	10.9
103	6.2
102	1.7
93	8.6
92	100.0
91	9.6
90	3.3



3. D_2-Ethylbenzene $C_8H_8D_2$

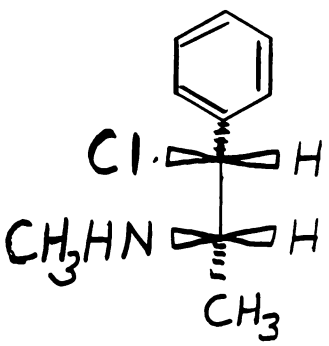
Nominal mass	% int. Base
109	2.8
108	32.4
107	6.0
106	16.7
105	6.5
104	3.3
103	1.2
94	8.8
93	100.0
92	9.1
91	2.9
90	1.6

Figure V.1. Mass Spectra of Deuterated Ethylbenzenes.

monodeuterated compound. The dideuterated compound showed a complex quintet for the methyl group with J = 1 resulting from splitting by the deuterium. No trace of a benzylic proton was seen.

B. Synthesis, Conformation and Reactions of β Haloephedrines

Since it is known that β-haloephedrines readily undergo a number of displacement reactions at the benzylic carbon[17, 18], we prepared compounds 1-4 in search of methods of stereospecific displacement of halogen by deuterium.



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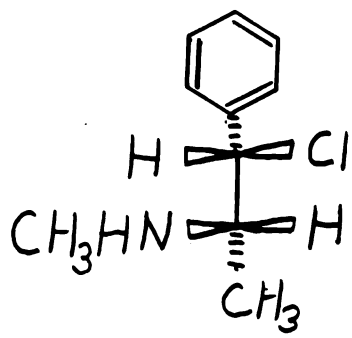

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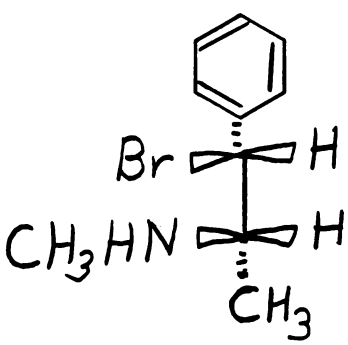

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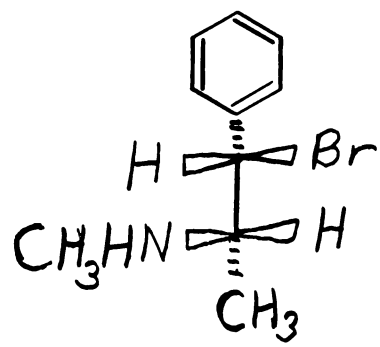


4

Reaction of (-) ephedrine sulfate with thionyl chloride in chloroform yielded 2 in excellent yield (91%), whereas pseudoephedrine hydrochloride under the same conditions gave approximately a 1: 1 mixture of 1 and 2. However, when (+) pseudoephedrine was reacted with phosphorus trichloride in chloroform, only 1 was obtained. (-) Ephedrine HCl reacted with phosphorus tribromide in chloroform to give 4 in good yield, but (+) ephedrine hydrochloride reacted under the same conditions gave only an oil which failed to crystallize. When acetone was used as the solvent, 3 was obtained in fair yield. Attempted extraction of the free base of 4 from the reaction mixture gave rise to the aziridine 5.

The NMR spectra of these compounds had not been previously reported in the literature. Therefore we compared the chemical shifts of the benzylic proton and the methyl protons of 1 - 4 with the corresponding protons of ephedrine and pseudoephedrine hydrochlorides, respectively, in order to gain conformational information concerning the compounds. The vicinal coupling constant between H_a and H_b are also compared.

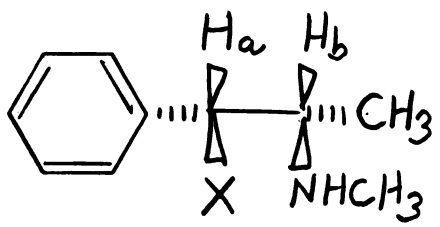


Table V. 1. Chemical Shifts and Coupling Constants of Isomeric Ephedrine and Haloephedrine Salts, in Cycles per second (cps).

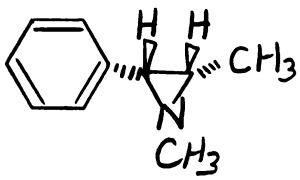
Compound	H_a	CCH_3	ΔH_a	ΔCCH_3	Jab
(-) ephedrine HCl	312	71	27	2	3.63
(+) pseudoephedrine HCl	285	69			9.21
1. HCl	328	70			3.80
2. HCl	305	57	23	13	9.50
3. HBr	326	75			5.0
4. HBr	310	63			9.80

First considered was the magnitude of the coupling constant J_{ab}. In the psuedoephedrine series it increases 0.29 cps from the hydroxy to the chloro derivative, and 0.30 cps from the chloro to the bromo derivatives. These changes are relatively small and can be attributed largely to the decrease in electronegativity[19] in going from hydroxy to bromo. This would imply little conformational difference between the three compounds. However in the ephedrine derivatives, there is a change of only 0.17 cps between the hydroxy and chloro compounds, but a change of 1.2 cps between the bromo and chloro derivatives. Since the electronegativity difference between chlorine and bromine is small, this probably implies a small conformational change with bromine substitution. Probably the bromo derivative contains a higher proportion of the trans

conformer, although the gauche form still predominates.

The chemical shift data show a downfield shift with halogen substitution for the benzylic proton, which parallels the pattern usually observed in benzylic alcohols and halides. The shifts observed for the alpha methyl group for the haloephedrines differ only slightly from those of ephedrine and pseudoephedrine. Therefore no definite conclusion can be made concerning conformation from these data.

In search of new conformational information concerning ephedrine derivatives, we dediced to prepare the methyl and ethyl ethers of (-) ephedrine and (+) pseudoephedrine 6 - 9.



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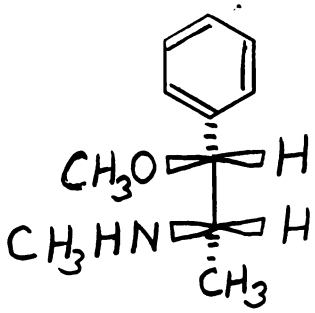

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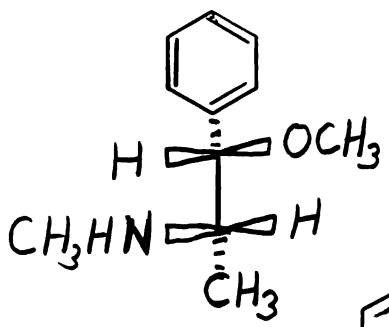

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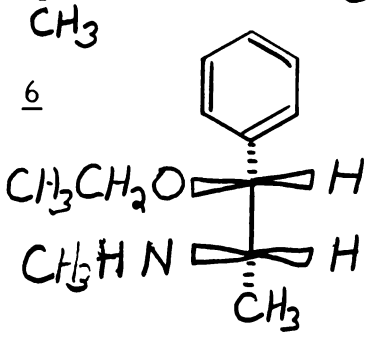

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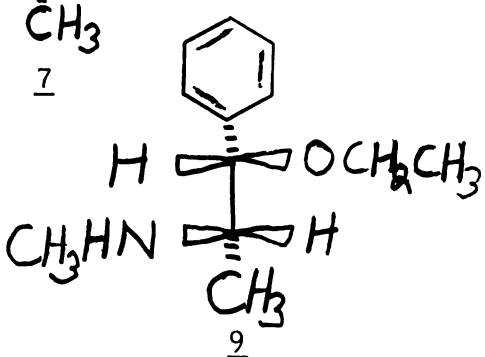


9

Attempts to form the ethyl ether of (-) ephedrine with ethanol and acid catalyst led to recovery of starting material in all cases. Next we attempted synthesis of 6 from reaction of 2 with sodium methoxide in methanol. However, the aziridine 5 was obtained in good yield. Acid catalyzed ethanolysis of 5 gave a mixture of approximately 60% 8 and 40% 9, determined by NMR. However this mixture, on standing three days in ethereal HCl, converted entirely to 9. Pure 7 could be obtained by 18 hr. reflux of 1 (free base) in methanol. An NMR spectrum taken after 5 hr. showed both 6 and 7 to be present, along with unreacted starting material. Pure 9 was also obtained in this manner.

This evidence implies that the threo isomers 7 and 9 are thermodynamically more stable than the erythro isomers 6 and 8, which convert to the threo isomers on extensive heating or on treatment with acid.

It would be expected that the acid catalyzed alcoholysis of the aziridine 5 would proceed via a benzylic carbonium ion resulting in formation of both diastereomers, which was observed. However it might be expected that the reaction of 1 (free base) with methanol would proceed via SN_2 displacement of chlorine by solvent, catalyzed by the nitrogen of the amine accepting the proton released. However the observation that both diastereomers are present after 5 hr. of reflux implies that the reaction probably proceeds via the initial

formation of the aziridine, followed by solvolysis of the protonated aziridine. The erythro isomers therefore were never isolated.

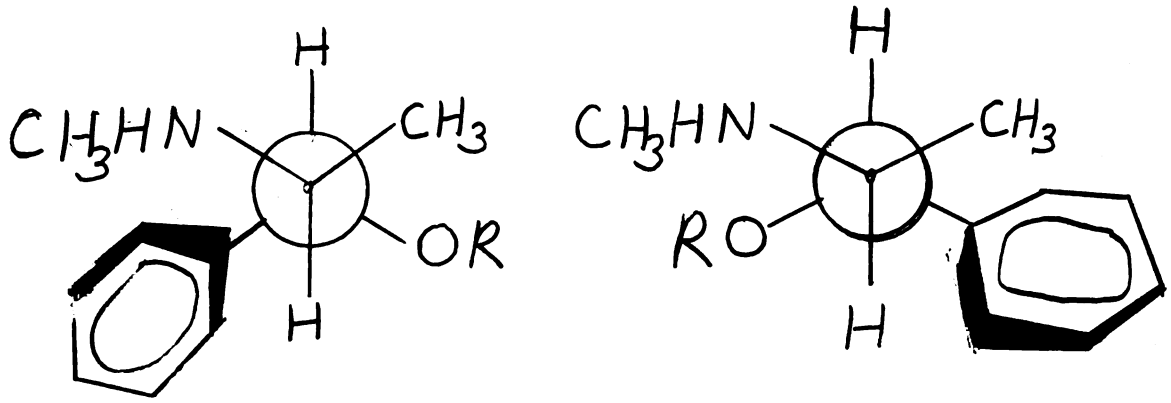
The chemical shifts of the benzylic proton and the alpha methyl group were compared to those of ephedrine and pseudoephedrine in search of conformational information concerning these compounds. The vicinal coupling constant J_{ab} was also compared.

Table V. 2. Chemical Shifts and Coupling Constants of Isomeric Ephedrines and O-alkylephedrines, in cps.

Compound	H_a	CCH_3	ethyl-CH_3	J_{ab}
(-) Ephedrine	282	49. 2	--	4. 07
(+) pseudoephedrine	249	56. 4	--	8. 23
6	242	73	78	8. 30
7	236	44	65	8. 50
8	245	71	--	8. 30
9	234	47	--	8. 50

The vicinal coupling constant J_{ab}= 8. 5 for the threo derivatives 7 and 9 increases only slightly from J_{ab}=8. 23 reported for (+) pseudoephedrine. This can be accounted for by the slight decrease in electronegativity of the methoxyl group compared to the hydroxyl, rather than from a conformational change. However in the erythro isomers 6 and 8 the coupling constant increases to 8. 3 cps compared to J=4. 07 observed for ephedrine. By the Karplus

relationship[20], this would correspond to a dihedral angle of approximately 150°, suggesting that the trans conformer predominates in this series in contrast to ephedrine where the gauche conformation is favored. Also the benzylic proton occurs 40 cps upfield from the corresponding signal in ephedrine, while the C-methyl occurs 23 cps down field from the ephedrine methyl group. From the molecular models, it can be seen that the trans conformer would favor the orientation of the phenyl group in the same plane with the alpha methyl group, in contrast to the gauche conformer where the methyl group is perpendicular to the plane, and therefore in the shielding cone of the ring. This orientation would also place the benzylic proton perpendicular to the plane of the ring, in contrast to the gauche conformer where it would be parallel to that plane. It is also observed that the methyl protons of the O-ethyl group occur 13 cps downfield from the corresponding threo derivative 7, where models show the ethyl group would be perpendicular to the plane of the ring, thus shifted upfield from the threo derivative.



(-) O-alkylephedrine (+) O-alkylpseudoephedrine

Figure V.2. Preferred Conformations of O-alkylephedrines.

C. β-Deuterodeoxyephedrine

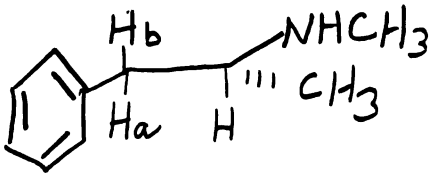
Next we sought a method of introducing deuterium stereospecifically into the benzylic position of deoxyephedrine. Since reflux with lithium aluminum deuteride and lithium deuteride in THF gave the best results in preparing deuteroethylbenzene, we reacted 4 under the same conditions. However, the aziridine 5 was obtained in good yield.

Sugi and Mitsui[21] report that a number of substituted aziridines can be atereospecifically hydrogenated with either retention of inversion of configuration depending on catalyst used or solvent conditions. Taylor prepared both 2(R) and 2(S)

tritioamphetamines by reacting (+) trans-1, 2 dimethyl-3-phenylaziridine with tritium gas in presence of palladium hydroxide under different solvent conditions. Therefore we reacted 5 with deuterium gas and palladium hydroxide in ethanolic NaOH (method 1), which reportedly gives retention of configuration, and secondly using benzene as solvent (method II) which supposedly gives inversion. However, in both cases the NMR spectrum showed that the deuterolysis proceeded without stereospecificity at the benzylic position. Also, both products had $[\alpha]_D$ (-) 3.6°, c. 1 in 95% EtOH compared to (-) 11.8° for (+) deoxyephedrine HCl, indicating partial racemization at the α carbon also.

Next we tried reduction of 3 with sodium borodeuteride in DMSO. This time a product was obtained whose NMR spectrum showed that the deuterium was introduced with inversion of configuration, giving 2(R) (+)- deuterodeoxyephedrine in good yield. Its rotation $[a]_D$ = (-) 12.2, c. 1 95% EtOH shows that no racemization occurred at the α-carbon.

The stereospecificity of deuteration was determined by the chemical shift of the remaining benzylic proton after deuterium has been introduced. The NMR spectrum of deoxyephedrine[22] hydrochloride shows two doublets for the benzylic protons, one at 185 cps, J = 5.6, corresponding to proton b, and another at 177 cps, J = 8.0, corresponding to H_a.



While the products obtained from deuterolysis of the aziridine both showed two benzylic doublets split by deuterium, the product obtained from reduction of 3 with $NaBD_4$/DMSO showed only one doublet at 185 cps, J = 5.5, corresponding to H_b. This shows the bromine was removed with inversion, and the deuterated product could be assigned the I(R) configuration.

Reaction of 4 with sodium borodeuteride in DMSO under the same conditions gave only partial reaction. Possibly the reaction was hindered in this case, and a longer reflux time was needed. To complete this study, this reaction must be repeated allowing a longer reflux time to see if the 1 (S) isomer can be obtained. Lithium triethyl borodeuteride[25] (super-deuteride) has been reported to easily remove benzylic halogen with inversion of configuration. Therefore 3 and 4 could be reacted with this reagent to see if the same products are obtained.

Experimental

α-deuterophenylmethylcarbinol

To a solution of 6.0 g, .05 m acetophenone in 12 ml isopropanol was added 1.0 g fresh $NaBD_4$. Then 12 ml water was added at which time heat and gas bubbles were evolved, indicating that reaction was occurring. Mixture was stirred 30 min, then acetic acid was added dropwise until solution was acid to litmus. Isopropanol was removed in vacuo, and sodium bicarbonate was added until solution was basic to litmus. Mixture was then extracted with ether, 3 x 20 ml which was dried over anhyd. Na_2SO_4 and evaporated in bacuo to give 5.8 g, .048 m, 96.6% clear liquid.

NMR singlet 441 cps (5), Ph-H, singlet 280 cps, (1), exch. c. D_2O, -OH, and singlet 77 cps (3), $-CH_3$ in $CDCl_3$.

α-deutero α-methylbenzyl chloride

To 15 ml of thionyl chloride stirred at room temperature was added 6.0 g, .05 m deuterophenylmethylcarbinol through a dropping funnel, which was then washed with 2 ml chloroform. Flask was fitted with reflux condenser and stirred 45 min. in a water bath originally at rt. Reaction mixture was cooled in an ice bath and excess thionyl chloride was destroyed by addition of 50 ml ice cold sat'd $NaHCO_3$. Solution was extracted with ether 3 x 30 ml which was dried over anhyd. Na_2SO_4 and removed in vacuo to give 6.2 g,

. 044 m., 88% crude product, which was distilled at 87-92°/28 mm to give 4. 5 ml clear liquid.

NMR--complex multiplet 435 cps (5), Ph-H and triplet at 108 cps (3), J = 1 $-CH_3$ in $CDCl_3$.

α-deutero α-methylbenzylbromide[13, 14]

To an ice cold solution containing 3. 0 g, . 025 m α-deuterophenylmethylcarbinol in 25 ml anhyd. ether was added a solution of 1. 5 ml phosphorus tribromide in 20 ml ether through a dropping funnel. Ice bath was removed and mixture was stirred for 90 min. at rt. Reaction mixture was then poured over 75 ml ice water and extracted with 2 x 25 ml ether, which was dried over anhyd. Na_2SO_4 and removed in vacuo to give 3. 4 g, . 018 m, 72% crude product which was dried over size 3A molecular sieve and distilled at 73-75°/5 mm to give 3. 0 g clear liquid.

NMR--complex multiplet 440 cps (5) Ph-H and sharp singlet 121 cps (1), $-CH_3$ in $CDCl_3$.

α-deuteroethylbenzene[13, 14]

To a stirred suspension of 0. 4 g lithium aluminum deuteride (. 009 m) and lithium deuteride, 1. 0 g, 0. 11 m, in 50 ml THF was added dropwise a solution containing 4. 0 g, . 028 m of α-methylbenzylchloride in 20 ml dry THF. Misture was gently

refluxed under nitrogen for 24 hr, then stirred at rt. for 9 more hr. Then mixture was cooled in ice and excess deuteride was decomposed by adding 2 ml water in 10 ml THF. It was then poured onto ice containing 10 ml of sulfuric acid, and mixture was extracted with 4 x 30 ml pentance. The combined pentane extracts were washed successively with water, 2 x 50 ml, 85% phosphoric acid, 4 x 30 ml, water, 2 x 50 ml, sat'd sodium carbonate solution, 1 x 50 ml, and water, 1 x 50 ml. The pentane layer was dried over anhyd. calcium chloride and removed in vacuo to leave 3.42 g, 71% crude product, which was distilled at 63-65°/18 mm to give 2.1 g clear liquid. NMR--complex multiplet at 431 cps (5) Ph-H, complex quarter 156 cps (1) CD-H, and complex doublet 70 cps (3), $-CH_3$.

Mass Spectrum molecular ion at 107, 28.4% 106, 6.2% parent peak 92, 100% 91, 9.6% compared to ethylbenzene; Molecular ion at 106 46.8%, 105, 7.9% parent peak 91, 100%, 0.8%.

<u>α, α-dideuteroethylbenzene</u>[13, 14]

4.0 g, .028 m of α deutero α methylbenzyl chloride was reacted with .009 mole lithium aluminum deuteride and 0.11 mole lithium deuteride under the conditions described for preparation of deuteroethylbenzene. Workup as before gave 2.51 g, 75% crude product which was distilled at 63-65°/18 mm to give 2.26 g clear liquid.

NMR complex multiplet 429 cps (5) Ph-H and complex singlet 72 cps (3), $-CH_3$.

Mass Spectrum--Molecular ion at 108, 32.4% 107, 6.0% Parent peak 93, 100% 92, 9.1% compared to ethylbenzene molecular ion at 106, 46.8%, 105 7.9% parent peak at 91, 100%, 90, 0.8%.

(+) β-chloropseudoephedrine hydrochloride[15]

To a stirred solution of 10.0 g .05 m (-) ephedrine HCl in 40 ml chloroform was added through a dropping funnel 40 ml thionyl chloride. Flash was fitted with a reflux condenser, and an infared light was shined on the reaction vessel until reflux initiated. Misture refluxed on heat generated by reaction for slightly over an hour, and when mixture began to cool light was again shined on flask. When mixture cooled, flask was refrigerated and white crystals appeared. These were filtered and washed with ether to give 9.8 g, .046 m, 91.1% white crystals, which were recrystallized from absolute ethanol to give 8.7 g white crystals m.p. 203-204°. NMR--singlet 443 cps (5), Ph-H, doublet 305 cps (1) = J - 10, CCl-H, multiplet 228 cps (1) CMe-H, singlet 161 cps (3) $N-CH_3$ and doublet 57 cps (3), $C-CH_3$

$[\alpha]_D$ = (+) 125°, c. 0.5 in 95% EtOH (lit. m.p. 203° - 204°).

(-) β-chloroephedrine Hydrochloride[15]

To an ice cold stirred solution of 5.0 g of (1) pseudoephedrine base (.032 m) in 20 ml chloroform was added 5.0 g, .036 m phosphorus trichloride through a dropping funnel, which was then washed with 5 ml chloroform. Ice bath was warmed to 75, and mixture was stirred 1 hr. with reflux condenser. Mixture was then cooled in ice bath, and excess phosphorus trichloride was destroyed with methanol. Solution was concentrated in vacuo, and 10 ml absolute ethanol was added. Mixture was then cooled in refrigerator and 4.7 g crude crystals, .021 m, 67% were filtered. These were recrystalized from absolute ethanol to give 3.7 g white crystals m. p. 198°.

$[\alpha]_D$ = (-) 70.6°, c. 1% in 95% EtOH (lit. m. p. 198°)

NMR - singlet 442 cps (5) Ph-H, doublet 328 cps (1) J=3, CCl-H, multiplet 222 cps (1), CMe-H, singlet 163 cps (3) NCH_3, and doublet 70 cps (3), $C\text{-}CH_3$.

(+) β-bromopseudoephedrine Hydrobromide[15]

To an ice cold stirred suspension of 2.62 g (.01 m) (-) ephedrine sulfate in 50 ml dry chloroform was added a solution of 8.1 g (.03 m) phosphorus tribromide in 10 ml chloroform through a dropping funnel, at a rate at which the reaction temperature did not exceed 15°. Ice bath was gradually warmed to 35°, and mixture

was stirred 2 hr. Phosphorus tribromide was then destroyed by adding 15 ml absolute ethanol, and solvents were concentrated in vacuo. Mixture was refrigerated overnight, and 1.6 g white needles were filtered, m.p. 181-183° (Lit. m.p. 183°). 10 ml ether was added to the mother liquor, and upon cooling 0.7 g more crystals were collected. Total yield 2.3 g (.0076 m) 76.6%.

$[a]_D$ = (+) 72.0°, c. 1% in H_2O

NMR - singlet 440 cps (1), Ph-H, doublet 310 cps (1) J = 10, CBr-H, multiplet 240 cps (1) CMe-H, singlet 163 cps (3) NCH_3 and doublet 63 cps (3) $C-CH_3$ in D_2O.

(-) β-Bromoephedrine Hydrobromide[15]

To a stirred ice cold suspension of 3.5 g (+) pseudoephedrine HCl (.017 m) in 20 ml $CHCl_3$ was added a solution of 5.6 g phosphorus tribromide (.018 m) in 15 ml acetone through a dropping funnel. Ice bath was removed, and mixture was stirred at room temperature 1 hr. Mixture was refrigerated, and 2.3 g crude crystals were filtered and washed with ether. Yield .006 m, 34.8%. These were recrystallized from absolute ethanol to give 1.7 g white needles m.p. 179° - 181° (Lit. m.p. 181°).

$[\alpha]_D$ = (-) 170, c. 1% in H_2O

NMR - singlet 443 cps (5) Ph-H, doublet 326 cps (1) J = 6, multiplet 210 cps (1), singlet 160 cps (3) NCH_3 and doublet 75 cps (3) $C-CH_3$ in D_2O.

(-) N-methylephedrine[16]

To a stirred solution containing 2.0 g, .0125 m (-) ephedrine in 50 ml absolute ethanol was added 4.0 ml of 37% aqueous formaldehyde. Potassium borohydride, 2.0 g, .037 m was added gradually over a 10 min. period, and mixture was stirred at rt. for 1 hr. Then 50 ml water was added, and mixture was extracted with 3 x 30 ml ether, which was dried over anhyd. sodium sulfate and removed in vacuo to give 2.1 g, .0118 m, 94.5% white crystals, which were recrystallized from ether to give 1.7 g white needles m.p. 87-88°. NMR - singlet 438 cps (5) Ph-H, doublet 294 cps (1), C(OH)-H, singlet 241 cps (1), exch c. D_2O -OH, multiplet 150 cps (1) CMe-H, singlet 136 cps (3) N-CH_3 and doublet 50 cps (3) C-CH_3 (Lit. m.p. 88°).

(-) cis 2 phenyl, 1, 3 dimethylaziridine[25, 26]

A solution containing 2.2 g (+) β-chloropseudoephedrine HCl (.01 m) and 2.5 g of sodium methoxide in 25 ml anhydrous methanol was refluxed for 2 hr. The sodium chloride precipitate was filtered, dried and weighed. 1.16 g, .02 m was collected indicating reaction was complete. Filtrate was concentrated to 10 ml in vacuo, and 25 ml of a saturated aqueous solution of sodium carbonate was added. Mixture was extracted 3 x 30 ml ether, which was dried over anhyd. sodium sulfate and removed in vacuo to give 1.42 g clear liquid

(.095 m) 94.5% which distilled at 49°-51°/5 mm to give 1.1 g product.

$[\alpha]_D$ = (-) 80.8, c.048 in 95% EtOH

NMR - doublet 444 cps (5), Ph-H, singlet 151 cps (3) N-CH_3, doublet 149 cps (1) C(Ph)-H, multiplet 103 cps (1), CMe-H, and doublet 55 cps (3) C-CH_3.

Calc. for $C_{12}H_{19}ON$ 74.6% C, 9.91% H, 7.25% N Found 74.36% C, 9.87% H, 7.38% N.

Ethanolysis of (-) cis 2 phenyl, 1, 3 dimethylaziridine

A solution containing 0.7 g, .005 m (-) cis 2 phenyl, 1, 3 dimentylaziridine and .08 ml conc. sulfuric acid in 30 ml absolute ethanol was refluxed 3 hr under nitrogen. Then ethanol was removed in vacuo, and residue was dissolved in 40 ml conc. sodium carbonate solution and extracted 3 x 20 ml ether, which was dried over anhyd. sodium sulfate and removed in vacuo to leave 0.8 g clear oil (.041 m, 82.1% yield). This mixture of O-ethylephedrine and O-ethylpseudoephedrine was distilled at 50-51°/.02 mm to give 0.65 g pure product.

Calc. for $C_{12}H_{19}$ ON 74.5% C, 9,91% H, 7.25% N, Found 74.36% C, 9.87% H, 7.38% N.

NMR - doublet 445 cps (5) Ph-H doublet 249 cps (0.6) J = 9, benylic H of erythro isomer, doublet 227 cps (0.4) J = 7 benzylic H of

threo isomer, quartet 206 cps (2) $-CH_2-$, singlet 180 cps (1), exch c. D_2O N-H, multiplet 161 cps (1) CMe-H, singlet 151 (3) $N-CH_3$, doublet 86 cps (1.8) CCH_3 of threo isomer, triplet 83 cps (3) methyl of ethyl group, and doublet 50 cps (1.2) CCH_3 of erythro isomer.

(+) O-methylpseudoephedrine Hydrochloride

A solution of 1.6 g, 0.84 m (+) chloropseudoephedrine base in 50 ml anhydrous methanol was refluxed 18 hr. Methanol was removed in vacuo, leaving 1.8 g, .081 m, 96.2% white solid, which was recrystallized from isopropanol-ether to give 1.2 g white crystals m.p. 163-164°.

Calc. for $C_{11}H_{18}NOCl$ 61.25% C, 8.35% H, 6.49% N, 16.49% Cl.
Found 61.23% C, 8.35% H, 6.32% N, 16.62% Cl.

$[\alpha]_D$ = (+) 156°, c. 0.5 in 95% EtOH

NMR - singlet 436 cps (5) Ph-H, doublet 252 cps (1) J = 10, benzylic-H, multiplet 209 cps (1) CMe-H, singlet 188 cps (3) OCH_3 singlet 141 cps (3) NCH_3, and doublet 44 cps (3) CCH_3 in D_2O. Extraction of this compound with sat'd Na_2CO_3/ether gave rise to a clear oil which distilled at 50-52°/.02 mm.

$[\alpha]_D$ = (+) 74.5°, c. 02 in 95% EtOH

NMR of O-methylpseudoephedrine base singlet 443 cps (5), doublet 228 cps (1) benzylic-H, singlet 188 cps (3) OCH_3, singlet 173 cps (1) exch c. D_2O NH singlet 143 cps (3) NCH_3 and doublet 44 cps (3) CCH_3.

(+) O-ethylpseudoephedrine

To 100 mg of the mixture of O-ethylephedrine and O-ethylpseudoephedrine obtained from the ethanolysis of the aziridine was added 2 drops of conc. HCl in 10 ml ether. Mixture was allowed to stand three days, and was then extracted with sat'd sodium carbonate and 10 more ml ether. Ether layer was dried over anhyd. sodium sulfate and removed in vacuo, leaving a clear oil, which was purified by microdistillation: b. p. (bath temperature) °/mm.

$[\alpha]_D$ = (+) 74.5, c. 0.2 in 95% EtOH

NMR - singlet 423 cps (5) Ar-H, doublet 234 cps (1) J = 10, quartet 193 cps (2) $-CH_2-$, octet 157 cps (1) CMe-H singlet 141 cps (3) NCH_3 triplet 66 cps (3) ethyl-CH_3 and doublet 45 cps (3) CCH_3.

(+) Desoxyephedrine Hydrochloride[19, 11]

To a stirred suspension of 3.3 g sodium borohydride (.082 m) in 25 ml freshly dried DMSO was added a solution containing 5.0 g (-) α bromoephedrine (.016 m) HBr in 25 ml dry DMSO through a dropping funnel. Mixture was refluxed three hr, then stirred at rt. overnight. Then borohydride was destroyed by addition of 1N NCl until bubbling ceased, and then 5.0 g NaOH pellets were added

and mixture was stirred 30 min. for purpose of hydrolyzing any bromide present. Then mixture was extracted with ether, 3 x 50 ml, and benzene, 2 x 50 ml. Organic phase was extracted with water, 3 x 50 ml, and was dried over Na_2SO_4 and removed in vacuo to leave a clear oil, which was dissolved in 50 ml anhyd. ether. Ethereal HCl was added dropwise until precipitation ceased, and crystals were filtered and dried, giving 2.35 g white crystals (.012 m, 78.3% yield). Recrystallization from isopropanol gave 2.09 g white crystals m.p. 170-173°, lit. 172-173°. A mixed m.p. showed no depression.

$[\alpha]_D$ = (+) 18.0°, c. 0.5 in H_2O, (-) 11.8°, c. 1.3 in 95% EtOH. NMR - singlet 460 cps (5) Ph-H, multiplet 214 cps (1) CMe-H, doublet 185 cps (1) benzylic H <u>trans</u> to proton, J = 5.6, doublet 177 cps (10) J = 8.0 benzylic H <u>cis</u> to proton, singlet 166 cps (3) NCH_3 and doublet 74 cps (3) CCH_3.

<u>Deuterolysis of (-) cis 2 phenyl, 1, 3 dimethylaziridine Method I</u>[11, 20]

To a solution of 1.4 g (-) cis 2 phenyl, 1, 3 dimethylaziridine (.01 m) in 20 ml absolute ethanol was added 50 mg palladium hydroxide and 40 mg sodium hydroxide, and mixture was shaken in Paar apparatus under 20 lb D_2 48 hr. Mixture was filtered, filter paper washed with 5 ml abs. ethanol, and filtrate was removed

in vacuo to yield a brown solid, which was recrystallized from methanol to give 1.1 g white crystals m. p. 162-165°. It was water soluble and gave an NMR similar to desoxyephedrine HCl, so it was assumed to be the carbonate. This solid was placed in 10 ml dry ether, and 1.0 ml etheral HCl was added, at which time bubbling occurred. The remaining white solid was filtered, dried, 1.2 g .069 m, 69% and recrystallized from absolute ethanol to give 0.97 g white flakes m. p. 167-169°.

$[\alpha]_D$ = (-) 3.6°, c. 1% in 95% EtOH

NMR - singlet 435 cps (5) Ph-H, multiplet 151 cps (1) CMe-H, complex doublet 175 cps (0.5) CD-H of threo isomer, complex doublet 167 cps (0.5) CD-H of erythro isomer, singlet 156 cps (3) NCH_3 and doublet 71 cps (3) CCH_3.

Deuterolysis of (-) cis 2-phenyl, 1, 3 dimethylaziridine Method II[11, 20]

To a solution of 1.6 g (-) cis 2 phenyl, 1, 3 dimethylaziridine in 20 ml dry benzene was added 50 mg palladium hydroxide. Mixture was shaken in Paar apparatus for 25 hr under 20 lb D_2. Mixture was filtered, and catalyst was washed with 20 ml ether. Solvents were removed in vacuo, leaving a clear liquid, which was dissolved in 10 ml dry ether. Ethereal HCl was added until precipitation ceased. Solid was filtered, giving 1.7 g white crystals

(.0097) m, 81.6% yield) which were recrystallized from methanol-ether to give 1.53 g white flakes m.p. 166-167°.

$[\alpha]_D$ = (-) 3.8 c. 1% in 95% EtOH

NMR was identical to product from deuterolysis I.

Infrared showed C-D band at 2450 cm^{-1}.

2 (R) - (+) β-deuterodesoxyephedrine HCl

To a stirred solution of 1.5 g (-) bromoephedrine HBr (.005 m) in 50 ml freshly dried DMSO was added 1.0 g, .024 m sodium brordeuteride, and mixture was stirred 2 hr. at 120, 12 hr. at 65, and 1 more hr. at 120. Mixture was cooled, and 5.0 g NaOH and 100 ml water were added, and mixture was stirred 30 min. at rt. Mixture was then extracted with 3 x 30 ml ether, which was extracted with 2 x 30 ml water. Ether extracts were dried over anhyd. sodium sulfate and evaporated to give a clear liquid, which was dissolved in 15 ml dry ether, and ethereal HCl was added until precipitation stopped. Solid was filtered to give 0.64 g crude product (.035 m, 70% yield) which was twice recrystallized from absolute ethanol to give 0.38 g white flakes m.p. 166-167°.

$[\alpha]_D$ = (-) 12.2, c. 1% in 95% EtOH

Infrared spectrum shows C-D band at 2450 cm^{-1}. ν_{max} 2950, 2710, 1480, 690 and 745 cm^{-1}.

NMR - singlet 432 cps (1) Ph-H, complex octet 200 cps (1) CHe-H,

complex doublet 185 cps (1) CD-H, singlet 155 cps (3) NCH_3 and doublet 68 cps (3) CCH_3.

Reaction of (+) β-Bromopseudoephedrine HBr with Lithium Aluminum Deuteride

To a stirred suspension containing 0.5 g lithium aluminum deuteride (.02 m) 0.5 g lithium deuteride (.04 m) in 50 ml dry THF was added a solution of 1.5 g (+) bromopseudoephedrine HBr in 25 ml THF. Mixture was refluxed 3 hr, stirred at rt. 14 hr, then refluxed 5 more hr. Mixture was then cooled in an ice bath, and excess deuteride was destroyed by adding dropwise a mixture of 2 ml H_2O in 10 ml THF. Residue was filtered, washed with 10 ml THF, and filtrate was evaporated in vacuo to give a clear liquid whose NMR and $[\alpha]_D$ were identical to (-) cis 2 phenyl, 1, 3 dimethylaziridine.

REFERENCES

1. B. Brodie and J. Gillette, Concepts in Biochemical Pharmacology Part 2 Springer-Verlag, New York 1971, pp. 286-290.

2. J. Smith, R. Smithies and R. Williams, Biochem. J. 56, 317 (1954).

3. J. Tagg, D. Yasuda, M. Tanabe and C. Mitoma. Biochem Pharmacol. 16, 143 (1967).

4. R. McMahon and W. Miller, Biochem Pharmacol. 12, 1207 (1963).

5. R. McMahon and H. Sullivan, Life Sci, 5, 921 (1966).

6. R. McMahon, H. Sullivan, W. Pereira and J. C. Craig, Arch. Biochem. Biophys. 132, 575 (1969).

7. F. Omura, R. Sato, D. Cooper, O. Rosenthal and R. Estabrook, Fed. Proc. 24, 1181 (1965).

8. J. Caldwell, L. Dring and R. Williams. Biochem J. 129, 23, (1972).

9. A. Gropetti, and E. Costa, Life Sci, Vol. 8, 1, 653, (1969).

10. M. Goldstein and B. Anagnoste, Biochim. Biophys. Acta 107, 166 (1969).

11. M. Goldstein and J. Contrera, J. Biol. Chem. 237, 6 (1962).

12. M. Goldstein, M. Kereghan and E. Lauber, Biochem. Biophys Acta 89, 191 (1964).

13. K. J. Taylor, Biol. Chem. 219, 454 (1974).

14. R. Hutchkins, D. Hoke, J. Keough and D. Koharski. Tet. Lett. 40, 3495, 1969.

15. Wilfred Pereira, Doctoral Dissertation, p. 149.

16. E. J. Eliel, Am. Chem. Soc. 3970, 1949.

17. H. Emde, Helv. Chem. Act. 12, 365 (1929).

18. K. Tanaka and T. Sugawa, Yakugaku Zasshi 72, 1548 (1952).

19. J. Schaefer, Can. J. Chem. 40 (1) 1962.

20. M. J. Karplus, Chem. Phys. 20, 11, 1959.

21. Y. Sugi and S. Mitsui, J. Chem. Soc. Jap. 43, 1489 (1970).

22. G. Neville, R. Deslauiers, B. Blackburn and I. Smith, J. Med. Chem. 14, 8, (1971).

23. H. C. Brown and S. Krishnamurthy, J. Am. Chem. Soc. 95, 5 (1973).

24. A. Skita and F. Keil, Moanatsh. 53, 54 753 (1929).

25. S. Brois, J. Org. Chem. 27, 3532 (1962).

26. T. Taguchi and M. Kojima.

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