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Author

Geissman, T. A.

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THE PREPARATION OF C¹⁴-LABELED BENADRYL, PYRIBENZAMINE
AND 1,1-DIPHENYL-4-DIMETHYLAMINO BUTENE-1

T. A. Geissman

April 11, 1951

Berkeley, California

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THE PREPARATION OF C¹⁴-LABELED BENADRYL, PYRIBENZAMINE AND
1,1-DIPHENYL-4-DIMETHYLAMINO BUTENE-1

by

T. A. Geissman(*)

April 11, 1951

ABSTRACT

The preparations of labeled Benadryl, Pyribenzamine and 1,1-diphenyl-4-dimethylaminobutene-1, as hydrochlorides and as methiodides, have been described.

(*) John Simon Guggenheim Memorial Fellow, 1950-51; Professor of Chemistry, University of California, Los Angeles.

THE PREPARATION OF C¹⁴-LABELED BENADRYL, PYRIBENZAMINE AND
1,1-DIPHENYL-4-DIMETHYLAMINO BUTENE-1

by

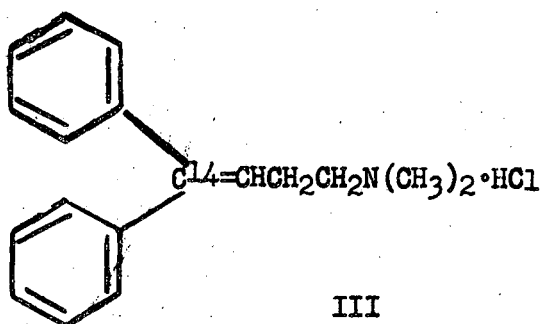
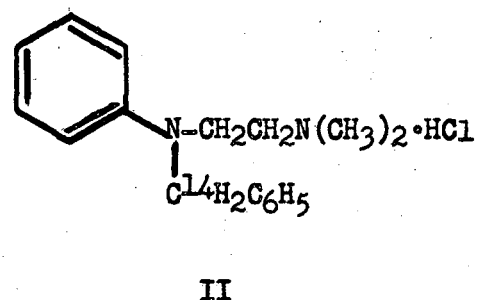
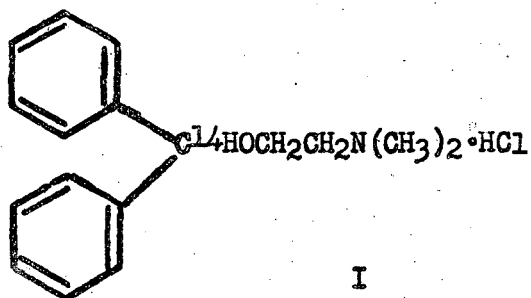
T. A. Geissman¹

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- 1) John Simon Guggenheim Memorial Fellow, 1950-51; Professor of Chemistry, University of California, Los Angeles.
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As part of a study of the mechanism and site of action of physiologically active substances, the preparation of three C¹⁴-labeled compounds was carried out. These were the two well-known antihistaminic drugs, Benadryl (I) and Pyribenzamine (II); and the structurally-related (to Benadryl) amine, 1,1-diphenyl-4-dimethylaminbutene-1 (III)*,

* All were isolated as the hydrochloride salts.

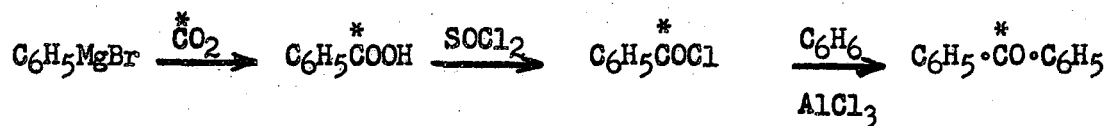
which is known to be devoid of antihistaminic activity. Compound III was included in the study to serve as a control substance which it is anticipated will allow a distinction to be made between the specific antihistaminic effects of these drugs and those non-specific physiological effects related to the chemical properties which the physiologically-active and -inactive possess in common. The compounds are labeled in the positions marked in the structural formulas:

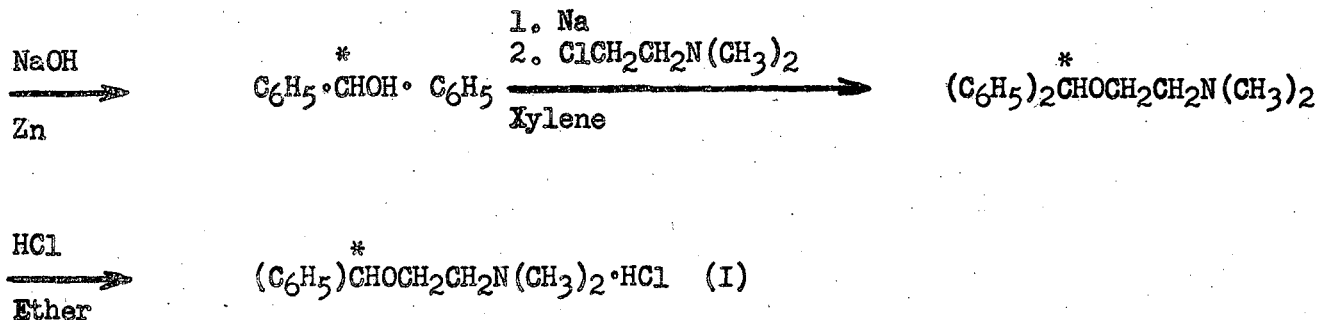


Benadryl labeled in the same position as I has been prepared by Fleming and Rieveschl², whose product had an activity of 0.224 μ c/mg. The experimental details

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- 2) Fleming and Rieveschl, Abstracts of Papers, American Chemical Society Fall Meeting, September, 1947.
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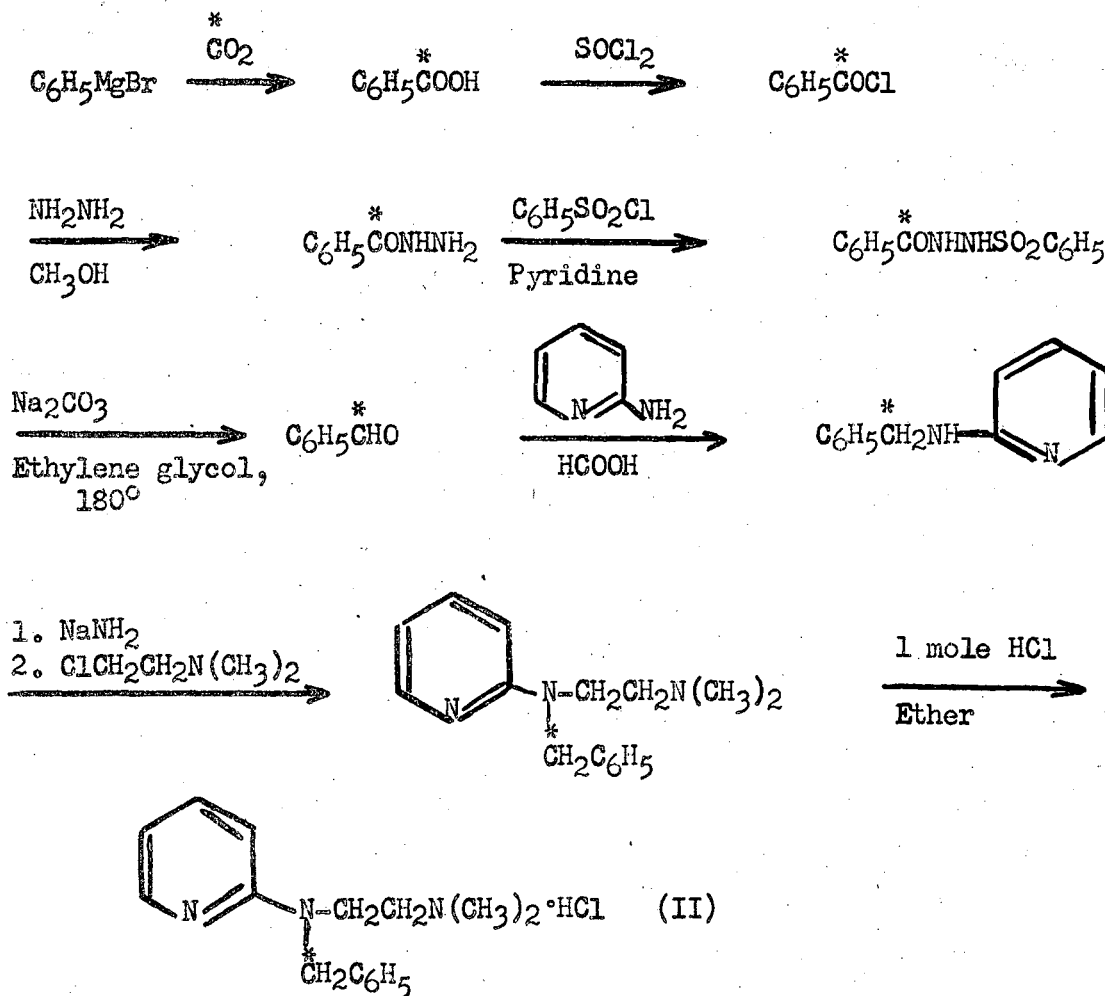
of this work have not yet been published, but the synthetic route, which was outlined², was different in certain details from that followed in the present work. The method adopted in this study is represented by the following:





The synthesis proceeded smoothly in all respects, the only serious losses in yield being sustained in the purification of the hydrochloride. The final product had an activity of 0.64 mc./mM, or 2.24 μ c/mg.

Pyribenzamine (II) was prepared by the following route:



Of the various available means of converting benzoic acid into benzaldehyde, the MacFadyen-Stevens method was finally adopted after control runs had demonstrated the ease and reproducibility of the method. The yield (60-65% overall from benzoic acid) of benzaldehyde was less than that reported for those of aromatic aldehydes prepared by the Rosenmund reduction³, but the results of control runs using the latter

3) See "Isotopic Carbon," by Calvin, Heidelberger, Reid, Tolbert and Yankwich, John Wiley & Sons, Inc., New York, New York (1949), pp. 197-199.

procedure led to the observations that (1) the Rosenmund method was subject to occasional unpredictable failures, and (2) the isolation of 10-millimole quantities of aldehyde from large volumes of the solvent (xylene) was attended with serious difficulties.

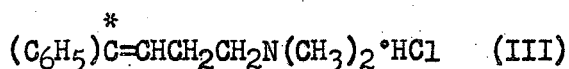
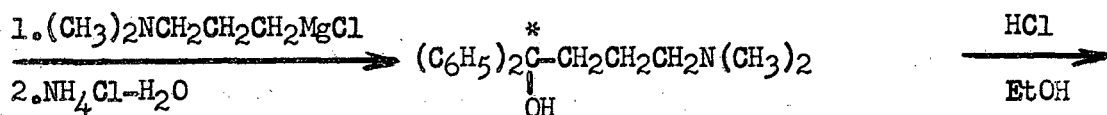
The reductive alkylation of α -aminopyridine with benzaldehyde, to form α -benzylaminopyridine, and the alkylation of the latter with β -chloroethyldimethylamine proceeded smoothly. Since the dihydrochloride of Pyribenzamine base is oily, the preparation on a small scale of the crystalline monohydrochloride is accompanied by some losses: the use of slightly less than the required amount of hydrochloric acid leaves some base unconverted, while the introduction of a slight excess of acid results in the formation of a gummy salt which can be purified by recrystallizations but with the usual manipulative losses encountered in such a procedure. It was found advantageous to purify the base by distillation (without special care in fractionation) and to calculate the amount of hydrochloric acid required on the basis of the weight of the distillate.

For the recovery of Pyribenzamine residues from crystallization mother liquors the crude residues were converted into the well-crystallized dipicrate. The picrate can be recrystallized from acetic acid and reconverted into the base by the use of ethanolamine.

In the cases of both Benadryl and Pyribenzamine the residual amines recovered from recrystallization mother liquors were used for the preparation of the corresponding methiodides.

1,1-Diphenyl-4-dimethylaminobutene-1 (III) was prepared by the following procedure:

$\text{C}_6\text{H}_5 \cdot \overset{*}{\text{C}}\text{O} \cdot \text{C}_6\text{H}_5$ (prepared as above in the case of I)



This synthesis, which has been applied to the preparation of numerous non-labeled compounds⁴, was first employed by Marxer⁵. Its use with radiocarbon-labeled benzophenone

4) R. T. Fukuto, Ph.D. Thesis, University of California, Los Angeles, 1950.

5) Marxer, *Helv. chim. Acta*, 24, 209E (1941).

in the present work was uneventful, the desired amino alcohol being formed in good yield. The preparation of γ -dimethyl-aminopropylmagnesium chloride was found to occur smoothly when the particular technic described in the Experimental Part was used. The reaction of γ -dimethylaminopropyl chloride with magnesium is erratic⁴ and often results in low yields of the Grignard reagent. It is possible to aid the formation of the magnesium derivative by the concurrent reaction of ethyl bromide with the magnesium (the so-called "entrainment" method), but the introduction of a second Grignard reagent in a tracer run is undesirable since this would result in the consumption of some of

the labeled benzophenone to yield a useless by-product. The use of pre-activated magnesium, as described herein, obviated this difficulty and gave a satisfactory result.

The recovery of residual amounts of the three amines from recrystallization mother liquors was not attempted since the plans for the use of the drugs in physiological studies included experiments with quaternary salts (metho-salts) of the amines. The conversion of the residual amines into methiodides afforded sufficient amounts of the quaternary salts for the studies projected.

Activity measurements of the final compounds were carried out by direct plating of the hydrochlorides, from aqueous solution, onto glass or aluminum planchets. When time permits these activities will be redetermined by oxidation and conversion of the carbon dioxide into barium carbonate. This work has not yet been undertaken.

Experimental Part

Benzoic acid-carboxyl-C¹⁴

The carbonation of 25 ml. of 3 M phenylmagnesium bromide (Arapahoe Chemicals) in 100 ml. of ether was carried out on the vacuum line. The carbon dioxide was generated from 4.969 gms. of barium carbonate containing 24.4 millicuries of C¹⁴ (from 2.132 gms. of Oak Ridge sample #19985). The carbon dioxide contained 0.97 mc/mM.

The reaction mixture was worked up in the usual manner. The final product was purified by passing its ether solution through a column of Celite-Norite-anhydrous sodium sulfate; evaporation of the ether left 2.88 gms. (95%) of dry, nearly white crystalline product.

The combined residues, containing no alkali-soluble material, were found to contain a total activity of 0.38 mc. (direct plate from benzene-methanol).

A second preparation of labeled benzoic acid, from 3.201 gms. of barium carbonate containing 27.8 millicuries, yielded 1.81 gms. (92%). To this was added 0.1 gm. of

active material (recovered from earlier experiments with the first preparation), and to this combined material was added 1.14 gm. of inactive benzoic acid. The resulting 3.05 gms. (25 mM) was estimated to contain 25 mc., but activity determinations made on final products indicated that the original sample of barium carbonate (C^{14} -221) had a lower activity than that stated on the label. See remarks, in later section.

Benzophenone-carbonyl- C^{14} . -

A solution of 3.05 gms. of benzoic acid (25 mc. assumed) in 25 ml. of purified thionyl chloride was refluxed for 3 hrs. The excess thionyl chloride was removed under reduced pressure, and two portions of 10 ml. each of dry benzene were added and removed in the same way. To the residual benzoyl chloride as added, with stirring, 40 ml. of dry benzene and 3.8 gms. of aluminum chloride. The dark brown solution was allowed to stand for 12 hrs., refluxed for one hour, cooled and poured onto iced, dilute HCl. The resulting mixture was freed of benzene by distillation with steam and, after cooling, the oily residual product removed with ether. The ether solution was washed with dilute alkali (saved for benzoic acid recovery), dried and evaporated. The residue was distilled under reduced pressure, yielding a colorless distillate which crystallized completely. The yield of 4.35 gms. included the recovered material from 0.25 gms. of crude benzophenone collected from earlier runs and added just before the final distillation. If it be assumed that all of the added 250 mg. was recovered, the yield in the run was 4.11 gms. (91%).

Benzohydroxyl- C^{14} (Diphenyl- C^{14} -carbinol). -

A portion of the benzophenone- C^{14} , weighing 2.38 gms., was dissolved in a solution of 2.5 gms. of KOH in 25 ml. of ethanol. The solution was heated to boiling and 2.5 gms. of zinc dust added in one portion. A vigorous reaction, accompanied by a momentary bright blue color, occurred and quickly subsided. The mixture was refluxed for another hour and filtered onto ice. After the addition of 15 ml. of 6 N HCl the

solution was cooled overnight in ice. The shining white leaflets of benzohydrol were collected, washed and dried. The yield was 2.01 gms. (84%). In comparable "cold" runs substantially quantitative yields were obtained.

Benadryl-C¹⁴. -

The benzohydrol (2.01 gms.) was dissolved in 40 ml. of dry xylene, 0.5 gms. of sodium was added, and the mixture stirred and refluxed under nitrogen for 6 hrs. After the addition of 4.0 ml. of freshly-distilled β -chloroethyldimethylamine, refluxing was resumed and continued for 4 hrs. The mixture was filtered onto ice, the solid (NaCl) being washed with ether.

The combined ether-xylene solution was extracted with a total of 25 ml. of 2 N HCl in several portions. The acid extract was washed with ether, made basic and extracted with ether. The ether solution was dried (K_2CO_3) and evaporated, yielding 2.25 gms. of a deep yellow oil (81% of crude product). This material was distilled under reduced pressure yielding a pale yellow distillate. To a solution of the distilled product in 5 ml. of dry ether was added 3 ml. of 4 N ethanolic hydrochloric acid and then an excess of dry ether. The oily hydrochloride crystallized when seeded with Benadryl hydrochloride. After chilling overnight, the crystalline product was collected; it weighed 2.27 gms. It was recrystallized by dissolving it in 5 ml. of hot isopropyl alcohol, filtering through Norite (washing the flask and funnel with 5 ml. of fresh isopropyl alcohol) and diluting the filtrate with 20 ml. of dry ether acetate and 10 ml. of dry ether. The white crystalline product weighed 1.59 gms.

The mother-liquors were combined and extracted with dilute HCl. The recovered Benadryl was converted into the methiodide by reaction with methyl iodide in ether solution. The recrystallized (absolute ethanol) methiodide formed shining buff leaflets; 0.48 gms.

One-dimensional chromatography of Benadryl hydrochloride on Whatman #1 filter paper with methanol-acid (see details below) resulted in a single, sharply-defined spot.

The data are as follows:

<u>Solvent</u>	<u>R_f</u>
10 ml. methanol + 1 drop gl. acetic acid	0.88
10 ml. methanol + 1 drop 6 N HCl	0.88
10 ml. methanol + 3 drops 6 N HCl	0.90

2-(Benzyl- α -C¹⁴)aminopyridine. -

This was prepared from labeled benzoic acid by the reduction of the latter to benzaldehyde and reductive alkylation of 2-aminopyridine with the benzaldehyde. The synthesis was carried out with the isolation and purification of only one of the intermediates: benzenesulfonyl-(carbonyl-C¹⁴-benzhydrazide).

A solution of 1.6 gms. of carboxyl-labeled benzoic acid (13.1 mM, approximately 13.1 mc.) in 10 ml. of thionyl chloride was refluxed for 5 hrs. The thionyl chloride was removed in vacuo and to the oily residue was added 20 ml. of methanol. The resulting solution was allowed to stand overnight and to it was added 10 ml. of 85% hydrazine hydrate. After 3 hrs. refluxing, part of the methanol was removed by distillation, the residual solution was filtered through Norite and evaporated to dryness at 50°/15 mm. The dry, white crystalline material was dissolved in 10 ml. of dry pyridine and, while cooling in ice, 3 ml. of benzenesulfonyl chloride was slowly added. After 2 hrs. at 0°, iced, dilute HCl was added, and after 2 hrs. the crystalline material was collected, washed and dried. The reddish-yellow product was recrystallized from dilute acetic acid (60 ml. acetic acid-125 ml. water) to yield 3.50 gms. of white needles of benzenesulfonyl-benzhydrazide. This represents a 97% yield if the product contained no bis-benzenesulfonylhydrazine. This possible contaminant does not affect the use of the product in the next step and so no further purification was attempted.

MacFadyen-Stevens reaction. -

The 3.50 gms. of benzenesulfonylbenzhydrazide was dissolved in 30 ml. of ethylene glycol. The solution was heated to 165°, 4 gms. of dry sodium carbonate was added, and the mixture was held at 165° for 75 seconds and then cooled, diluted, and carefully acidified. The solution was extracted with ether and the washed and dried solution was evaporated. The oily residue weighed 2.6 gms. (nearly twice the theoretical amount) but was not treated further before use in the next step.

Reductive benzylation of 2-aminopyridine.-

A mixture of the crude residue from the preceding step, 2.0 gms. of 2-aminopyridine and 2 ml. of 98% formic acid was heated under reflux (135°) for 6 hrs. Water and 10 ml. of 6 N sodium hydroxide were added and the resulting mixture was extracted with ether (the residual alkaline layer contained about 1.16 mc., as shown by a direct-plate count). The ether solution was washed with 1 N HCl in several portions. The acid layer was made alkaline and cooled, yielding Crop 1. The ether layer smelled strongly of benzaldehyde; it was dried and evaporated and the oily residue (less than 1 gm.) treated, as described above, with 1 gm. of 2-aminopyridine and 1 ml. of 98% formic acid. This mixture was worked up as before, yielding Crop 2 of the product. The total yield of dry, yellowish, crystalline product was 0.972 gm. (41%). (NOTE: The residual solutions were processed for recovery of activity. The benzoic acid which was isolated was added to other samples for use in subsequent experiments.)

To the 0.972 gm. of labeled 2-benzylaminopyridine was added 1.00 gm. of unlabeled material, and the resulting mixture (now containing approximately 0.5 mc./mM) recrystallized from dilute alcohol. The pure product weighed 1.93 gms.

Pyribenzamine-C¹⁴ hydrochloride. -

The 1.93 gms. of 2-benzylaminopyridine was dissolved in 20 ml. of dry benzene and the solution added to 1.00 gm. of sodamide. The mixture was refluxed with stirring

for 3-1/2 hrs. during which time it changed from yellow to red-brown. (NOTE: In a "cold" run the solid sodium derivative separated as a yellow powdery precipitate). To the solution was then added 2.5 ml. of freshly distilled β -chloroethyldimethylamine in 5 ml. of benzene. The mixture was refluxed for 7 hrs., cooled, and filtered into a mixture of ice and water. The organic layer was separated, washed with water, and passed through a column packed with dry potassium carbonate. The brown oil which remained after removal of the solvents was distilled at 15 mm., affording 2.07 gms. (77%) of a yellow oil boiling at 210-220°C.

To a solution of the oily base in 10 ml. of dry ethyl acetate was added 1.9 ml. of 4.1 N ethanolic hydrogen chloride, and dry ether was added to cloudiness. Upon seeding with authentic Pyribenzamine hydrochloride crystallization took place at once and was allowed to proceed overnight at 0°. The first crystallizate was recrystallized by dissolving it in 8 ml. of hot isopropyl alcohol, filtering the solution through Nuchar (which was washed with two 1 ml. portions of hot IPA and 5 ml. of hot ethyl acetate) and adding 15 ml. of dry ether to the filtrate. The product (1.57 gms.) was recrystallized again from ethanol-ether, yielding as a final product 1.282 gms. of pure, white Pyribenzamine hydrochloride, m.p. 185-6° (uncorr.).

The mother liquors and washings were extracted with dilute HCl and the recovered traces of Pyribenzamine converted into the nicely crystalline dipicrate (m.p. 182-3°, bright yellow leaflets from acetic acid). The picrate was decomposed with aqueous ethanolamine and the resulting base treated with methyl iodide in ether solution. The methiodide was recrystallized from methanol-ether, yielding 0.44 gm., m.p. 169-70° dec. The activity of this product was 0.53 mc./mM (direct plate), while the picrate showed an activity of 0.49 mc/mM (direct plate), values which are in good agreement with the expected \approx 0.5 mc/mM based upon the dilution of the labeled 2-benzylaminopyridine with

inactive material. The Pyribenzamine hydrochloride (main sample of 1.282 gms.) showed 0.48 mc/mM by direct plates.

1,1-Diphenyl-4-dimethylaminobutene-1. -

To 1.0 gm. of magnesium under 10 ml. of dry ether was added (under N₂) 0.2 ml. of bromobenzene. When the reaction was proceeding with vigor the solution was removed with a pipet and to the still-wet magnesium was added, dropwise and with stirring, a solution of ^{5 ml. of} freshly-distilled γ -chloropropyl-dimethylamine in 30 ml. of dry ether. The reaction proceeded smoothly, a white pasty suspension being formed during a 5-hr. period of refluxing. To the Grignard reagent thus prepared was added 2.14 gms. of benzophenone-carbonyl-C¹⁴ (1 mc/mM) in 20 ml. of ether. The mixture was refluxed for 4 hrs., cooled and poured into iced ammonium chloride solution. Ether was added to dissolve the crystalline solid which was present and the mixture made alkaline with ammonium hydroxide and thoroughly extracted with ether. The combined ether extract was shaken with 20 ml. of 2 N HCl. A thick suspension of the hydrochloride of the amino alcohol formed. This was dissolved by the addition of water, and the ether layer further washed with dilute HCl until all of the amine was extracted. The aqueous extract was poured into cold, dilute ammonium hydroxide and the crystalline precipitate collected, washed and dried. There was obtained 2.43 gms. of amino alcohol, m.p. 118-20° (77%).

A solution of the 2.43 gms. of amino alcohol in 20 ml. of 1 N ethanolic hydrogen chloride was refluxed for 1-1/2 hrs., diluted with 100 ml. of dry ether and cooled at -20° for one hour. The crystalline hydrochloride was collected and recrystallized from ethanol and ether, yielding 2.24 gms. of pure white needles of 1,1-diphenyl-4-dimethylaminobutene-1 hydrochloride. An activity measurement (by direct plates) gave values of about 0.8 mc/mM (see Note).

(NOTE: Recent experience suggests that direct plates of amine hydrochlorides such as I and III give low values, probably because of volatility. This may be due to the liberation of the free base by the action of the aluminum plate upon the acidic deposit. A redetermination of the activity of the Benadryl hydrochloride by conversion to barium carbonate gave a value of 0.94 mc/mM. This is in accord with the value of 1.0 mc/mM at which the synthesis was aimed.)

Summary of Products.-

<u>Compound</u>	<u>Wt. (gms.)</u>	<u>mM</u>	<u>mc/mM*</u>	<u>mc.</u>
Pyribenzamine•HCl	1.282	4.40	0.48	2.11
Benadryl•HCl	1.590	5.45	0.64	3.49
UA**•HCl	2.240	7.80	0.80	6.24
Pyribenzamine•MeI	0.440	1.11	0.48	0.53
Benadryl•MeI	0.480	1.21	0.64	0.77
UA•MeI	0.15 (approx.)	0.38	0.80	0.30
Benadryl•HCl	0.551	1.89	1.22	<u>2.30</u>
				15.74***

* By direct plates; probably low. See preceding paragraph.

** 1,1-Diphenyl-4-dimethylaminobutene-1

*** Plus approx. 4 mc. of recovered (unused) benzoic acid-carboxyl-C¹⁴ and 1 mc. in tarry residues in acetone solution

The author acknowledges with gratitude the courtesy of Drs. Melvin Calvin and Bert M. Tolbert, and the kindness and cooperation of the personnel of the organic chemistry group at Donner Laboratory, in making possible and assisting in the completion of the work described in this report.

Summary

The preparations of labeled Benadryl, Pyribenzamine and 1,1-diphenyl-4-dimethylaminobutene-1, as hydrochlorides and as methiodides, have been described.