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# Analogs of Amphenone. The Synthesis of Aminosubstituted Diphenylacetones and Related Compounds

BY JOHN B. WRIGHT AND ERWIN S. GUTSELL[1]

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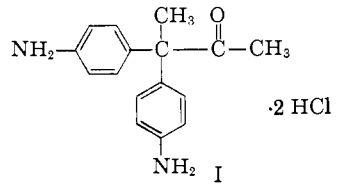
A number of compounds chemically related to Amphenone (I) were prepared. Most of these compounds differed from Amphenone in possessing a hydrogen atom in place of the methyl group attached to the tertiary carbon atom. The general method of synthesis for these compounds involved reaction of an aminophenyllithium derivative with α-ethoxy esters to give 4,4'-diamino-(1-α-ethoxyethyl)-benzhydrols (IV) which on treatment with dilute acid yielded the desired compounds II. The latter compounds were readily reduced to the carbinols and formed oximes which could be reduced readily to amines. Reaction of an aminophenyllithium derivative (or a Grignard reagent) with α-alkoxyketones followed by hydrolysis gave similar compounds (VII and IX). The preparation of related compounds based upon the reaction of aminophenyllithium derivatives with other esters and lactones is discussed also. Preliminary biological data indicate that several of these derivatives possess a high order of Amphenone-like activity.

3,3-Bis-(*p*-aminophenyl)-butanone-2 dihydrochloride (Amphenone) (I) is a substance possessing

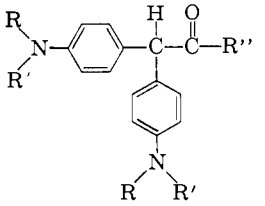



I

interesting biological activity. Its most noteworthy action is its effect upon the adrenal glands, producing inhibition of adrenocortical activity in animals and in man.[2,3] However, its undesirable side effects have prompted the search for other compounds[4,5] which would possess the adrenal inhibitory activity of Amphenone.

Amphenone was first prepared by Allen and Corwin.[6,7] The structure of the product that they obtained was later shown to be that indicated by I.[8,9]

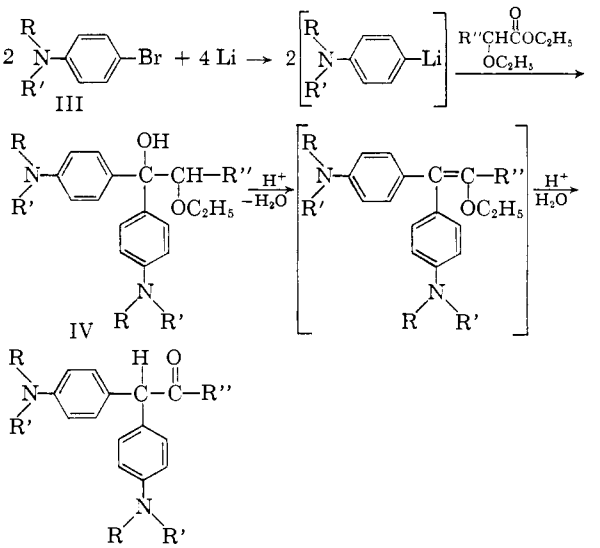
In our search for other compounds that would possess the biological properties shown by Amphenone we decided to investigate compounds of the type II. These compounds would differ from




II, R = H, lower alkyl
R' = H, lower alkyl
R'' = $CH_3$, lower alkyl, aryl

Amphenone mainly in the fact that they do not possess the methyl group on the tertiary carbon atom. Furthermore, it was hoped that it would be possible to synthesize these compounds by strictly chemical means thus avoiding an electrolytic reduction used in the synthesis of Amphenone.[6,7]

The general method of synthesis that was used is




IIa, R = R' = $CH_3$, R'' = $CH_3$
b, R = R' = $CH_3$, R'' = $C_2H_5$
c, R = R' = $CH_3$, R'' = $C_6H_5$
d, R = R' = H, R'' = $CH_3$
e, R = H, R' = $CH_3$, R'' = $CH_3$
f, R = R' = benzyl, R'' = $CH_3$

The *p*-bromoaniline III was converted to the corresponding lithio derivative in the usual way by reaction with lithium ribbon[10] in ether solution. Addition of an α-ethoxy ester to this ethereal solution gave the tertiary carbinol IV in yields averaging 65–70%. Conversion of IV to II was brought about by refluxing in dilute hydrochloric acid.

In the preparation of II where R and/or R' is H, the reaction sequence was carried through with the corresponding benzyl compounds and the benzyl groups were removed ultimately in the final compound by hydrogenolysis with hydrogen and palladium catalyst. Compounds of the type II that were prepared are listed in Table I.

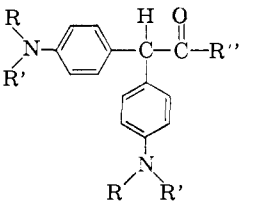
Compounds of this type in which the two aryl groupings were different were prepared by reaction of the requisite lithium derivative with α-alkoxyketones or α-phenoxyketones (V, R'' = $C_2H_5$,

(1) Ott Chemical Co., Muskegon, Mich.
(2) H. Kless, *Arzneimittel-Forsch.*, **8**, 83 (1958).
(3) *Lancet*, 237 (1956).
(4) W. L. Bencze, L. I. Barsley, M. J. Allen and E. Schlittler, *Helv. Chim. Acta*, **41**, 882 (1958).
(5) J. J. Chart, *et al.*, *Experientia*, **14**, 151 (1958).
(6) M. J. Allen and A. H. Corwin, THIS JOURNAL, **72**, 117 (1950).
(7) M. J. Allen, U. S. Patent 2,539,388.
(8) W. L. Bencze and M. J. Allen, *J. Org. Chem.*, **22**, 352 (1957).
(9) J. Korman and E. C. Olson, *ibid.*, **22**, 870 (1957).

(10) Several grades of lithium ribbon were tried in these reactions. In our hands, the most successful was a grade obtained from the Lithium Corporation of America containing approximately 0.6% sodium. Experiments with the newer low-sodium (0.02–0.005%) grades were less successful.

TABLE I

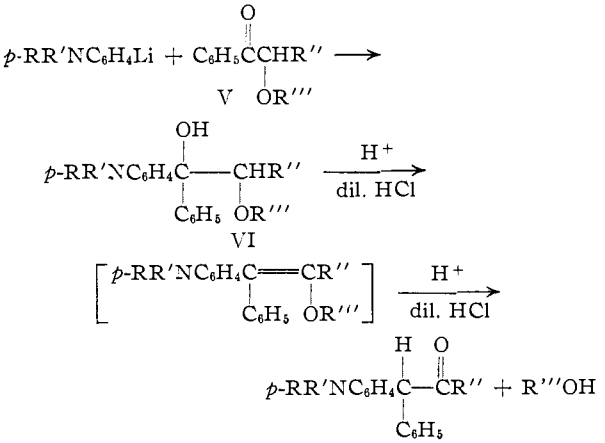
DI-(*p*-AMINOPHENYL)-METHYL KETONES



| R | R' | R'' | Procedure | Yield, % | M.p., °C. | Recrystn. solvent | Molecular formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | $CH_3$ | $CH_3$ | A | 98 | 65–66[a] | Ethanol | $C_{17}H_{24}N_2O$ | 76.99 | 8.16 | 9.45 | 77.20 | 8.23 | 9.34 |
| $CH_3$ | $CH_3$ | $C_2H_5$ | A | 98 | 71.5–72.5[b] | Ethanol | $C_{20}H_{26}N_2O$ | 77.38 | 8.44 | 9.03 | 77.58 | 8.09 | 9.29 |
| $CH_3$ | $CH_3$ | $C_6H_5$ | A | 86 | 166–167[c,d,e] | Benzene–cyclohexane (1:1) | $C_{24}H_{26}N_2O$ | 80.41 | 7.31 | 7.82 | 80.43 | 7.72 | 7.76 |
| $C_6H_5CH_2$ | $C_6H_5CH_2$ | $CH_3$ | B | 22[f] | 189–192.5 | Benzene | $C_{45}H_{46}N_2O$ | 85.91 | 6.71 | 4.66 | 85.94 | 6.75 | 4.72 |
| H | H | $CH_3$ | C | 40 | 143.5–144 | Isopropanol | $C_{15}H_{18}N_2O$ | 74.97 | 6.71 | 11.66 | 74.77 | 7.06 | 11.70 |
| $CH_3$ | $C_6H_5CH_2$ | $CH_3$ | B[g] | 60[f] | 105–107 | Acetone–methanol (1:3) | $C_{31}H_{32}N_2O$ | 83.00 | 7.19 | 6.25 | 83.15 | 7.40 | 6.46 |

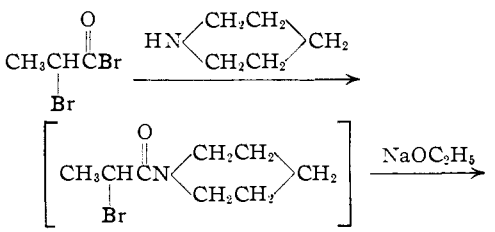
[a] The *dihydrochloride* after recrystallization from anhydrous ethanol melted at 212° dec. *Anal.* Calcd. for $C_{19}H_{24}N_2O\cdot 2HCl$: C, 61.78; H, 7.10; N, 7.59; Cl, 19.20. Found: C, 61.71; H, 7.12; N, 7.68; Cl, 19.11. [b] The *dihydrochloride* after recrystallization from anhydrous ethanol melted at 215° dec. *Anal.* Calcd. for $C_{20}H_{26}N_2O\cdot 2HCl$: C, 62.66; H, 7.36; N, 7.31. Found: C, 62.82; H, 7.25; N, 7.53. [c] This compound was prepared by a different method by F. Kröhnke [*Chem. Ber.*, **72**, 1731 (1939)], who reports a melting point of 168°. [d] The *monohydrochloride* was prepared by dissolving the free base in acetone and adding an excess of an ethereal hydrogen chloride solution, m.p. 224° dec., after recrystallization from ethanol and drying at 100°. *Anal.* Calcd. for $C_{24}H_{26}N_2O\cdot HCl$: C, 72.99; H, 6.89; N, 7.09. Found: C, 72.64; H, 7.01; N, 7.43. The reason for the isolation of the *monohydrochloride* rather than the *dihydrochloride* here is not clear. The second molecule of HCl may have been lost during the drying at 100°. [e] The reaction mixture was extracted with chloroform rather than with ether. [f] This is the over-all yield for two steps. [g] One-fifth of the amount of ether was employed. The product was extracted with benzene instead of chloroform.

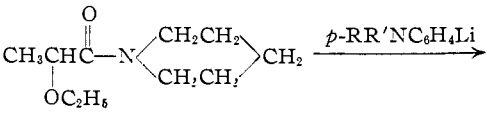
$C_6H_5$). The crude intermediate tertiary carbinol VI was found usually to melt over a wide range, probably due to the presence of a mixture of diastereoisomers. In these cases the crude product was treated directly with dilute hydrochloric acid to give the desired ketone VII.

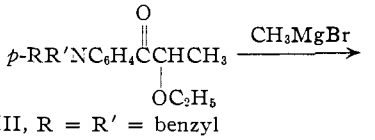


VIIa, R = R' = $CH_3$; R'' = $CH_3$
b, R = R' = H; R'' = $CH_3$
c, R = H, R' = $CH_3$; R'' = $CH_3$
d, R = R' = benzyl; R'' = $CH_3$
e, R = $CH_3$, R' = benzyl; R'' = $CH_3$

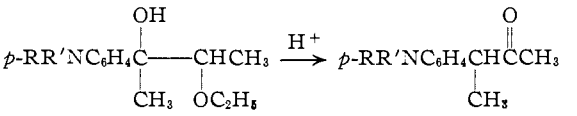
An alternate method of synthesis that was employed involved first the preparation of an $\alpha$-ethoxy-*p*-aminopropiophenone (VIII).







VIII, R = R' = benzyl



IXa, R = R' = benzyl
b, R = R' = H

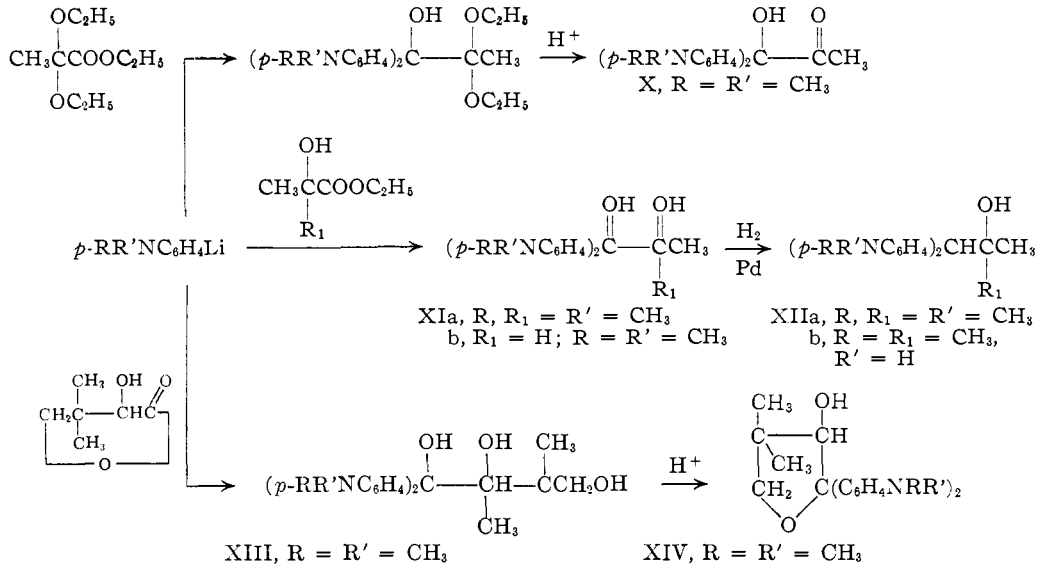
Reaction of VIII with an ethereal solution of methylmagnesium bromide gave, after treatment with acid, the 2-*p*-aminophenylbutanone-2 (IX).

Several additional compounds were prepared by reaction of the lithio derivatives with other esters and lactones. These reactions are shown in subsequent formula Chart and in most cases they proceed readily and in good yield.

The product XIII, formed by the reaction with *d,l*-pantolactone, on treatment with dilute acid, gave a compound which showed no carbonyl absorption in the infrared. On the basis of this fact and the known ease of cyclization of 1,4-glycols to tetrahydrofurans on treatment with acid, this product is assigned the structure XIV.

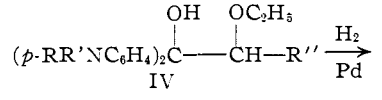
Hydrogenolysis of compounds of the type IV with hydrogen and palladium catalyst gave the ether XV.

1,1-Bis-(*p*-dimethylaminophenyl)-propanone-2 (IIa) readily gave an oxime (in 92% yield) which could be reduced to the corresponding amine with hydrogen and Raney nickel catalyst in 66% yield. Treatment of the same compound (IIa) with

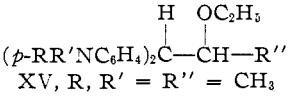


XIII, R = R′ = CH₃ XIV, R = R′ = CH₃

lithium aluminum hydride in ether solution gave the corresponding carbinol in almost quantitative yield. The carbinol undergoes acylation readily with the usual reagents to form esters and reacts with phenyl isocyanate to form a urethan.



IV



XV, R, R′ = R″ = CH₃

All of the compounds containing the amine group that were prepared were tested for adrenal inhibitory activity in the rat by measuring change in adrenal weight. Those showing significant activity were tested in dogs for inhibition of adrenal vein 17-hydroxycorticosteroid output. Preliminary biological results indicate that at least three of these compounds, namely, 1,1-bis-(*p*-dimethylaminophenyl)-2-propanone (IIa), 1,1-bis-(*p*-dimethylaminophenyl)-2-butanone (IIb) and 1,1-bis-(*p*-dimethylaminophenyl)-2-propanol (all three tested as the dihydrochlorides), possess a high order of activity, equaling or exceeding somewhat that shown by Amphenone.[11]

## Experimental[12]

**4,4′-Bis-(dimethylamino)-α-(1-ethoxyethyl)-benzhydrol (IVa).**—In a one-liter flask fitted with a stirrer, addition funnel, nitrogen inlet tube and a condenser fitted with a calcium chloride tube were placed 250 ml. of anhydrous ether[13] and 5.55 g. (0.8 mole) of lithium ribbon[10] previously cut into small pieces. Nitrogen was passed slowly over the reaction mixture. Over the course of about one hour was then added to the rather vigorously stirred mixture a solution of 80 g. (0.4 mole) of freshly distilled colorless *p*-bromodimethylaniline (Eastman Kodak Co.) in 200 ml. of anhydrous ether. Heat was applied occasionally to maintain reflux. When addition was completed the mixture was stirred and heated under reflux until practically all of the lithium had dissolved (total reflux time about four hours).

To the stirred solution was added a solution of 29.2 g. (0.2 mole) of ethyl α-ethoxypropionate in 100 ml. of anhydrous ether at a rate determined by the reflux. Upon addition of the ester an immediate precipitation of a white solid took place. The mixture was heated under reflux for two hours and allowed to stand overnight. To the stirred solution was then added cautiously 200 ml. of a 20% ammonium chloride solution.

The ether layer was separated and the aqueous layer extracted with ether.[14] The ethereal extracts were concentrated and the solid residue recrystallized from petroleum ether (Skellysolve C) after treatment with decolorizing carbon. There was obtained 44.9 g. (68%) of colorless needles melting at 120–121°.

*Anal.* Calcd. for $C_{21}H_{30}N_2O_2$: C, 73.64; H, 8.83; N, 8.18. Found: C, 74.09; H, 8.76; N, 8.09.

**1,1-Bis-(*p*-dimethylaminophenyl)-propanone-2 (IIa)(Procedure A).**—A solution of 13.68 g. (0.04 mole) of 4,4′ Bis-(dimethylamino)-α-(1-ethoxyethyl)-benzhydrol (IVa) in a mixture of 30.6 g. of concentrated hydrochloric acid and 70 ml. of water (a 10% HCl solution after neutralization of the amine groups present) was heated under reflux for four hours. The solution was basified by the addition of a saturated sodium carbonate solution and the resulting mixture extracted with ether. The ethereal extracts were dried over anhydrous sodium sulfate, the ether removed and the residue purified by recrystallization. An infrared spectrum showed carbonyl absorption at 1713 cm.$^{-1}$.

**4,4′-Bis-(dimethylamino)-α-(1-ethoxypropyl)-benzhydrol (IVb).**—The substitution of an equivalent amount of ethyl α-ethoxybutyrate for ethyl α-ethoxypropionate in the procedure outlined above for 4,4′-bis-(dimethylamino)-α-[1-ethoxyethyl)-benzhydrol (IVa) gave a 70% yield of product melting at 110–112° after recrystallization from petroleum ether (Skellysolve C).

*Anal.* Calcd. for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.00; H, 8.96; N, 7.82.

**1,1-Bis-(*p*-dimethylaminophenyl)-2-ethoxyphenethyl Alcohol (IVc).**—Substitution of an equivalent amount of ethyl α-ethoxyphenylacetate (41.64 g.) for ethyl α-ethoxypropionate in the procedure for the preparation for 4,4′-bis-(dimethylamino)-α-(1-ethoxy ethyl)-benzhydrol (IVa) gave a product which after recrystallization from cyclohexane with charcoal

(11) For these biological results we are indebted to Dr. Roy Hertz of the National Cancer Institute, National Institutes of Health, and to Drs. R. O. Stafford and W. E. Dulin and Mr. L. E. Barnes of the Department of Endocrinology of these laboratories.

(12) All melting points and boiling points are uncorrected. For the microanalytical determinations we are indebted to Mr. William Struck and his associates and for the infrared spectra determinations we are indebted to Mr. Marvin Grostic and Dr. James Johnson of these laboratories. We are especially indebted to Mr. Albert Lallinger for a great amount of technical assistance.

(13) Sodium-dried ether was used. It is important to pay close attention to all of the factors involved, such as purity of the reagents, rates of addition, etc., in order to have the reaction proceed as indicated.

(14) In at least one experiment the product began to precipitate out of the ether at this point. This was removed by filtration and the filtrate worked up as directed.

decolorization consisted of colorless needles melting at 154.5–156°, wt. 52.6 g. (65%).

*Anal.* Calcd. for $C_{26}H_{32}N_2O_2$: C, 77.19; H, 7.97; N, 6.93. Found: C, 77.20; H, 8.04; N, 7.08.

**1,1-Bis-(*p*-dibenzylaminophenyl)-2-propanone (IIf) (Procedure B).**—*p*-Bromodibenzylaniline[15] was used in place of *p*-bromodimethylaniline in the procedure for 4,4-bis-(dimethylamino)-α-(1-ethoxyethyl)-benzhydrol (IVa). The volume of ether was increased about five times. The oily residue from the ethereal extracts of the hydrolyzed reaction mixture was dissolved in acetone (3 ml./g.) and concentrated hydrochloric acid (added (1.5 ml./g.)). The resulting solution was heated under reflux for 16 hours. The acetone was removed by distillation at reduced pressure, and the mixture was diluted with water, neutralized with sodium bicarbonate, and extracted twice with one-liter portions of chloroform. The organic layers were combined, washed with water, dried over anhydrous sodium sulfate and concentrated at reduced pressure. The residue was triturated with ether and the solid purified by recrystallization.

**1,1-Bis-(*p*-aminophenyl)-2-propanone (IId) (Procedure C).**—1,1-Bis-(*p*-dibenzylaminophenyl-)2-propanone (IIf) (5.0 g., 0.00833 mole) which had been ground to pass through a 100-mesh screen was suspended in 300 ml. of ethanol and hydrogenated at room temperature over 2.0 g. of 10% palladium-on-charcoal catalyst with an initial pressure of 50 p.s.i. The theoretical amount of hydrogen was absorbed in about six hours.

The catalyst was removed by filtration, the solution concentrated at reduced pressure and the residue recrystallized.

**1,1-Bis-(*p*-[*p*-(N-methylacetamido)]-phenyl)-propanone-2.**—Ten grams (0.022 mole) of 1,1-bis-(*p*-methylbenzylaminophenyl)-propanone-2 was hydrogenated over 4.0 g. of 10% palladium-on-charcoal catalyst in 300 ml. of ethanol at an initial pressure of three atmospheres of hydrogen. When the uptake of the hydrogen ceased the catalyst was removed by filtration and the filtrate concentrated to dryness *in vacuo*. The residual oil was heated on the steam-bath for 15 minutes with 50 ml. of acetic anhydride. The yellow solution when cool was poured into ice-water and basified with a sodium carbonate solution. The mixture was extracted with chloroform and the chloroform removed by distillation. The resulting solid after recrystallization from ethyl acetate gave colorless needles melting at 169–176°, wt. 5.0 g. (64% of theory).

*Anal.* Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.66; H, 6.78; N, 7.97.

**α-Ethoxypropiophenone.**—To a solution of phenylmagnesium bromide, prepared from 47.1 g. (0.3 mole) of bromobenzene, 7.3 g. (0.3 mole) of magnesium turnings and 100 ml. of dry ether, was added dropwise over the course of about 30 minutes a solution of 23.8 g. (0.24 mole) of α-ethoxypropionitrile[16] in 30 ml. of ether. The mixture was stirred and heated under reflux for 1.5 hours and then allowed to stand overnight.

To the mixture was added dropwise 50 ml. of water, followed by 100 ml. of 3.6 *N* sulfuric acid. The mixture was stirred until all of the solid had dissolved, the ether layer was separated and the aqueous layer extracted twice with 100-ml. portions of ether. The ethereal extracts were dried over anhydrous magnesium sulfate, the ether removed and the residue distilled *in vacuo*. There was obtained 20.53 g. (48%) of a yellow liquid boiling at 121–126° (15 mm.), $n^{26}D$ 1.5163.[17]

**4-(Dimethylamino)-α-(ethoxyethyl)-benzhydrol.**—*p*-Dimethylaminophenyllithium was prepared in the usual way [*cf.* preparation of 4,4'-bis-(dimethylamino)-α-(1-ethoxyethyl)-benzhydrol (IVa)] from 20.0 g. (0.1 mole) of *p*-bromodimethylaniline and 100 ml. of anhydrous ether.

To the stirred reaction mixture was added dropwise a solution of 17.8 g. (0.1 mole) of α-ethoxypropiophenone in 25 ml. of dry ether. The mixture was stirred and heated under reflux for 2 hours, decomposed with a 20% ammonium chloride solution, the ether layer separated and the aqueous layer extracted with ether. Removal of the ethergave a semisolid; wt., 29.4 g. One recrystallization from 50 ml. of petroleum ether (Skellysolve C) gave yellow needles melting at 88–112°, undoubtedly a mixture of diastereoisomers; wt., 7.75 g. (26%). This material was used directly in the preparation of 1-*p*-dimethylaminophenyl-1-phenylpropanone-2 (VIIa).

**4-(Dimethylamino)-α-(1-phenoxyethyl)-benzhydrol.**—The procedure described above for 4-(dimethylamino)-α-(1-ethoxyethyl)-benzhydrol was used with an equivalent amount (22.6 g.) of α-phenoxypropiophenone. There was obtained 33.06 g. (95%) of material melting over a wide range (m.p. 115–150°) which could be used directly for the preparation of 1-*p*-dimethylaminophenyl-1-phenylpropanone-2 (VIIa). Repeated recrystallizations of a small sample from cyclohexane after treatment with decolorizing carbon raised the melting point to 160–162°.[18]

*Anal.* Calcd. for $C_{23}H_{25}NO_2$: C, 79.50; H, 7.25; N, 4.03. Found: C, 79.24; H, 7.51; N, 4.03.

**1-*p*-Dimethylaminophenyl-1-phenylpropanone-2 (VIIa).**—To 7.64 g. (0.0255 mole) of 4-(dimethylamino)-α-(1-ethoxyethyl)-benzhydrol (m.p. 88–112°) was added 45 ml. of water and 19.7 ml. of concentrated hydrochloric acid. The resulting solution was heated under reflux for four hours and basified with a sodium carbonate solution. The resulting mixture was extracted with ether and the ether removed. The resulting solid residue weighed 6.4 g. (99%) and melted at 64–67°. Recrystallization from petroleum ether raised the melting point to 67–68°.

*Anal.* Calcd. for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.89; H, 7.23; N, 5.71.

**The hydrochloride**, after recrystallization from ethyl acetate, consisted of rosettes melting at 152–153°.

*Anal.* Calcd. for $C_{17}H_{19}NO.HCl$: C, 70.46; H, 6.96; Cl, 12.23. Found: C, 70.54; H, 7.17; Cl, 12.11.

The same material could be prepared from 4-(dimethylamino)-α-(1-phenoxyethyl)-benzhydrol (m.p. 115–150°) by carrying out the hydrolysis in a similar manner. The reaction mixture was extracted with ether to remove phenol and the aqueous layer basified and worked up as described above. There was obtained an 81% yield of product melting at 67–68°.

**1-(*p*-Dibenzylaminophenyl)-1-phenylpropanone-2 (VIId).**—To a solution of *p*-dibenzylaminophenyllithium (*cf.* procedure B) prepared from 173.3 g. (0.492 mole) of *p*-bromodibenzylaniline was added an ethereal solution of 111.1 g. (0.492 mole) of α-phenoxypropiophenone. After decomposition of the reaction mixture with 20% ammonium chloride solution the ether layer was separated and the ether removed. The residue was heated under reflux for 6 hours with 250 ml. of concentrated hydrochloric acid and 570 ml. of acetone. After removal of the acetone, the mixture was diluted with water, basified with a sodium hydroxide solution and extracted with chloroform. The chloroform was removed and the residue recrystallized from cyclohexane; wt. 81.2 g. (41% of theory), m.p. 121–123°.

*Anal.* Calcd. for $C_{29}H_{27}NO$: C, 85.89; H, 6.71; N, 3.45. Found: C, 86.01; H, 7.02; N, 3.50.

**1-(*p*-Aminophenyl)-1-phenyl-2-propanone Hydrochloride (VIIb).**—1-(*p*-Dibenzylaminophenyl)-1-phenyl-2-propanone (VIId) (50.0 g., 0.123 mole) was hydrogenated as a suspension in 1500 ml. of ethanol at room temperature using 10% palladium-on-charcoal as catalyst. The initial pressure was 50 p.s.i. The theoretical pressure drop took place in 1.5 hours.

The catalyst was removed and the filtrate evaporated to dryness at reduced pressure. The residue was dissolved in ether and converted to the hydrochloride by the addition of an ether solution of hydrogen chloride. The gummy brown precipitate was separated by decantation, triturated with boiling methyl ethyl ketone, and separated by filtration. Recrystallization from 1:5 ethanol–ethyl acetate yielded 19.45 g. (61% of theory) of material melting at 190.5–195°.

*Anal.* Calcd. for $C_{15}H_{15}NO.HCl$: C, 68.83; H, 6.16; Cl, 13.55; N, 5.35. Found: C, 68.59; H, 6.19; Cl, 13.56; N, 5.25.

**1-(*p*-Benzylmethylaminophenyl)-1-phenylpropanone-2 (VIIe).**—The procedure described above for 1-(*p*-dibenzylaminophenyl)-1-phenylpropanone-2 (VIId) was followed using an equivalent amount of *p*-methylbenzylphenyllith-

(15) R. W. Everatt, *J. Chem. Soc.*, **93**, 1236 (1908).

(16) H. R. Henze and T. T. Thompson, THIS JOURNAL, **65**, 1422 (1943).

(17) P. Yates [*ibid.*, **74**, 5376 (1953)] reports a boiling point of 97–98° (5 mm.), $n^{20}D$ 1.5143.

(18) This material evidently represents one of the two possible diastereoisomers.

ium solution. There was obtained a 48% yield of product melting at 76–78° after recrystallization from ethanol.

*Anal.* Calcd. for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.93; H, 7.06; N, 4.42.

**1-(*p*-Methylaminophenyl)-1-phenyl-2-propanone Hydrochloride (VIIc).**—The procedure for 1-(*p*-aminophenyl)-1-phenyl-2-propanone hydrochloride (VIIb) was followed. The product after recrystallization from an ethanol–ethyl acetate mixture (1:5) melted at 145–147°, yield 73% of theory.

*Anal.* Calcd. for $C_{16}H_{17}NO.HCl$: C, 69.68; H, 6.58; N, 5.08; Cl, 12.86. Found: C, 69.47; H, 6.65; N, 5.38; Cl, 12.84.

**1-(α-Ethoxypropionyl)-piperidine.**—A solution of 162.0 g. (1.902 moles) of piperidine in 500 ml. of anhydrous ether was added with stirring and ice-bath cooling to 205.4 g. (0.95 mole) of α-bromopropionyl bromide and 1200 ml. of anhydrous ether. The addition was complete in 1 hour, during which time the temperature of the reaction was maintained at 10–15°. The mixture was stirred with ice-bath cooling for an additional 10 minutes, and then filtered with vacuum[19] through a sintered glass funnel into a 5-l., 3-necked, round-bottomed flask containing a solution of 22.0 g. (0.957 mole) of sodium in 1200 ml. of ethyl alcohol. The solid cake on the filter funnel was washed with additional anhydrous ether. The solution was heated at reflux for one hour and was allowed to stand overnight. The sodium bromide which had precipitated was removed by filtration and the alcohol and ether were removed from the filtrate at reduced pressure. The product was diluted with ether, washed twice with water and dried over anhydrous magnesium sulfate. The ether was removed at reduced pressure and the residue was distilled through a 20-cm. helices-packed column *in vacuo*. There was obtained 107.7 g. (61%) of a colorless liquid boiling at 74–77° (0.01 mm.), $n^{25.5}D$ 1.4693.

*Anal.* Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 65.42; H, 10.33; N, 7.56.

***p*-Dibenzylamino-α-ethoxypropiophenone (VIII).**—To an ethereal solution of *p*-dibenzylaminophenyllithium prepared from 209.4 g. (0.594 mole) of N-(*p*-bromophenyl)-dibenzylamine was added 1-(α-ethoxypropionyl)-piperidine (106.6 g., 0.575 mole) dissolved in 400 ml. of anhydrous ether. The reaction mixture was heated under reflux for two hours and decomposed with aqueous ammonium chloride solution. The ether layer was separated and the ether removed.

The residual oil was dissolved in 3 l. of petroleum ether (Skellysolve B) with just enough benzene added to prevent cloudiness, and chromatographed over 3 kg. of Florisil.[20] The column was eluted with 1% acetone–Skellysolve B in 3-l. fractions. The first two fractions gave 60 g. of white crystalline material, which, when recrystallized from benzene–alcohol, gave 28.8 g. of recovered N-(*p*-bromophenyl)-dibenzylamine. When the eluate became yellow the receiver was changed and elution continued with 2% and 5% acetone–Skellysolve B. The combined yellow fractions were concentrated and recrystallized from cyclohexane to yield 111.1 g. (58% of theory, taking into account recovered starting material) of material melting at 91–94°. Further recrystallization from ethanol raised the melting point to 92.5–94.5°.

*Anal.* Calcd. for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.67; H, 7.27; N, 3.63.

**3-(*p*-Dibenzylaminophenyl)-butanone-2 (IXa).**—To a stirred solution of 37.3 g. (0.1 mole) of *p*-dibenzylamino-α-ethoxypropiophenone in 100 ml. of dry benzene was added 100 ml. (0.3 mole) of 3 *M* ethereal methylmagnesium bromide (Arapahoe Chem. Co.) in the course of 20 minutes.

The dark solution was left standing overnight before being heated at reflux for one hour. One hundred ml. of 20% $NH_4Cl$ solution was added cautiously over a 20-minute period. A gummy solid precipitated which subsequently redissolved. The ether–benzene layer was separated and the aqueous layer extracted with benzene. The combined ether–benzene layers were concentrated to dryness giving 39.7 g. of a yellow oil.

A solution of the oil in 77 ml. of concentrated HCl and 175 ml. of acetone was heated at reflux for 6 hours. The acetone was removed and the residue diluted with water and basified with $NaHCO_3$. The mixture was extracted with benzene and the benzene removed. The yellow solid residue was recrystallized from petroleum ether (Skellysolve C) and treated with Magnesol[21] giving 25.6 g. of needles melting at 83–84°.

*Anal.* Calcd. for $C_{24}H_{25}NO$: C, 83.91; H, 7.34; N, 4.08. Found: C, 83.79; H, 7.21; N, 4.21.

**3-(*p*-Aminophenyl)-butanone-2 (IXb).**—Five grams (0.0145 mole) of 3-(*p*-dibenzylaminophenyl)-butanone-2 (IXa) was hydrogenated over 10% palladium-on-charcoal catalyst in ethanol at room temperature at an initial pressure of three atmospheres. The theoretical amount of hydrogen was absorbed in 20 minutes. The catalyst was removed and the filtrate concentrated to dryness. The residue was recrystallized from petroleum–ether (Skellysolve B) to give 1.91 g. (81%) of colorless plates melting at 83–84°.

*Anal.* Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.72; H, 8.17; N, 8.88.

**4,4′-Bis-(*p*-dimethylamino)-α-(1,1-diethoxyethyl)-benzhydrol.**—To a stirred ether solution of *p*-dimethylaminophenyllithium prepared in the usual way from 40.0 g. (0.2 mole) of *p*-bromo-N,N-dimethylaniline [*cf.* procedure for 4,4′-bis-(*p*-dimethylamino)-α-(1-ethoxyethyl)-benzhydrol] was added a solution of 19.02 g. (0.1 mole) of ethyl α,α-diethoxypropionate[22] in 50 ml. of ether, at a rate determined by the reflux rate. The mixture was heated under reflux for 1.5 hours and was then decomposed with a 20% aqueous ammonium chloride solution. The ether layer was separated, washed with water, dried over anhydrous potassium carbonate and the ether removed. The residue was recrystallized from cyclohexane, after treatment with decolorizing carbon, yielding 24.22 g. (63%) of material melting at 124–126°. Additional recrystallization raised the melting point to 125–127°.

*Anal.* Calcd. for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.62; H, 8.58; N, 7.30.

**1,1-Bis-(*p*-dimethylaminophenyl)-1-hydroxy-2-propanone (X).**—A solution of 7.19 g. (0.0186 mole) of 4,4′-bis-(*p*-dimethylamino)-α-(1,1-diethoxyethyl)-benzhydrol in 6.4 ml. of concentrated hydrochloric acid and 37 ml. of water was allowed to stand overnight. The mixture was neutralized with solid sodium bicarbonate and the solid that separated was removed by filtration and recrystallized from ethanol–water with charcoal treatment. There was obtained 5.24 g. (90%) of material melting at 74.5–76.5°.

*Anal.* Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.97. Found: C, 72.98; H, 7.45; N, 8.97.

**1,1-Bis-(*p*-dimethylaminophenyl)-1,2-propanediol (XIb).**—To an ethereal solution of *p*-dimethylaminophenyllithium, prepared in the usual way from 4.86 g. (0.7 mole) of lithium ribbon, 70 g. (0.35 mole) of *p*-bromo-N,N-dimethylaniline and 400 ml. of anhydrous ether, was added dropwise a solution of 11.81 g. (0.1 mole) of ethyl lactate in 25 ml. of anhydrous ether. The mixture was stirred and heated under reflux for 3 hours and was then decomposed by the addition of 200 ml. of a 20% ammonium chloride solution. The ether layer was separated and the aqueous layer extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the ether removed. The dark oily residue partially solidified upon standing for several days in the refrigerator. The oily material was decanted from the solid and the latter triturated with 25 ml. of cyclohexane and the mixture filtered. The resulting solid was recrystallized from ether–petroleum ether (2:1); wt. 6.69 g. (21%), m.p. 99–100°.

*Anal.* Calcd. for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.34; N, 8.91. Found: C, 72.62; H, 8.50; N, 8.54.

**1,1-Bis-(*p*-dimethylaminophenyl)-2-methyl-1,2-propanediol (XIa).**—To a solution of *p*-dimethylaminophenyllithium, prepared from 400 g. (2 moles) of *p*-bromodimethylaniline and 27.75 g. (4 moles) of lithium ribbon, in 2250 ml. of anhydrous ether, was added dropwise a solution of 66 g. (0.5 mole) of ethyl α-hydroxyisobutyrate in 250 ml. of ether. The mixture was heated under reflux for five hours and was

(19) A small amount of the ether solution of the intermediate, 1-(α-bromopropionyl)-piperidine came in contact with the operator's hands and caused severe pains in the fingers which lasted about 3 hours. It is recommended that rubber gloves be worn and extreme caution be used during this phase of the operation.

(20) Obtained from the Fluridin Co., Tallahassee, Fla.

(21) Absorbent hydrated magnesium silicate in a powdered form obtained from Westvaco Chemical Co.

(22) C. L. Stevens and A. E. Sherr, *J. Org. Chem.*, **17**, 1228 (1952).

then decomposed with 1 l. of a 20% ammonium chloride solution. The ether layer was separated and the aqueous layer extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate, the ether removed and the residue recrystallized from petroleum ether (Skellysolve C). There was obtained 141.3 g. (86% of theory based on ethyl α-hydroxyisobutyrate) of needles melting at 125.5–127.0°.

*Anal.* Calcd. for $C_{20}H_{28}N_2O_2$: C, 73.13; H, 8.59; N, 8.53. Found: C, 73.36; H, 8.36; N, 8.53.

**1,1-Bis-*p*-Dimethylaminophenyl-2-methyl-2-propanol (XIIa).**—A solution of 10 g. (0.03 mole) of 1,1-bis-*p*-dimethylaminophenyl-2-methyl-1,2-propanediol in 115 ml. of 95% ethanol and 15 ml. of acetic acid was hydrogenated over 4 g. of 10% palladium-on-charcoal catalyst at an initial pressure of 50 lb. The catalyst was removed by filtration and the filtrate concentrated to dryness *in vacuo* at 40°. The residue was diluted with 150 ml. of water, basified with a sodium carbonate solution and extracted with ether. The ether solutions were dried over anhydrous magnesium sulfate and evaporated to dryness giving 6.24 g. of a yellow oil which crystallized with scratching. Recrystallization from 95% ethanol gave 3.61 g. (39%) of colorless prisms melting at 98–99°.

*Anal.* Calcd. for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 77.16; H, 8.89; N, 8.87.

**1,1-Bis-(*p*-methylaminophenyl)-2-methylpropanol-2 (XIIb).**—To a stirred mixture of 11.1 g. (1.6 moles) of lithium ribbon in 500 ml. of anhydrous ether was added 221 g. (0.8 mole) of *p*-bromo-N-methyl-N-benzylaniline dissolved in 400 ml. of anhydrous ether. The mixture was refluxed for 4 hours and a solution of 26.4 g. (0.2 mole) of ethyl α-hydroxyisobutyrate in 100 ml. of ether was added. The mixture was then heated at reflux for 4 hours before decomposing with a 20% $NH_4Cl$ solution. The ether layer was separated and the ether removed. The dark yellow oily residue was washed with 200 ml. of ethanol and the latter decanted. The last traces of ethanol were removed *in vacuo* giving 171.6 g. of an oil.

A mixture of the oil obtained above, 620 ml. of ethanol, 55 ml. of glacial acetic acid and 5.5 g. of 10% palladium-on-charcoal catalyst was hydrogenated at an initial pressure of about three atmospheres. The theoretical uptake of hydrogen took place in 11 hours. The catalyst was removed and the filtrate concentrated to dryness. To the residue was added 800 ml. of water and the mixture basified with sodium carbonate. The resulting mixture was extracted with ether and the ether removed. The residue after recrystallization from petroleum ether–benzene (4:1) weighed 19.5 g. (34% over-all yield) and melted at 107.5–108.5°.

*Anal.* Calcd. for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.90; H, 8.41; N, 9.74.

**1,1-Bis-(*p*-dimethylaminophenyl)-3,3-dimethyl-1,2,4-butanetriol (XIII).**—To a solution of *p*-dimethylaminophenyllithium, prepared in the usual way from 7.64 g. of lithium ribbon, 100 g. (0.5 mole) of *p*-bromodimethylaniline and 500 ml. of anhydrous ether, was added slowly a solution of 13.0 g. (0.1 mole) of *d,l*-pantolactone in 100 ml. of ether. The mixture was heated under reflux for 2 hours, allowed to stand overnight and was then decomposed by the addition of 300 ml. of a 20% ammonium chloride solution. The yellow solid was removed by filtration and recrystallized from ethanol; wt. 25.1 g. (67% of theory), m.p. 147.5–149.5°.

*Anal.* Calcd. for $C_{22}H_{32}N_2O_3$: C, 70.93; H, 8.66; N, 7.52. Found: C, 70.61; H, 8.52; N, 7.28.

**2,2-Bis-(*p*-dimethylaminophenyl)-tetrahydro-4,4-dimethyl-3-furanol (XIV).**—A solution of 14.9 g. (0.04 mole) of 1,1-bis-(*p*-dimethylaminophenyl)-3,3-dimethyl-1,2,4-butanetriol and 30.5 ml. of concentrated hydrochloric acid in 100 ml. of water was heated under reflux for 4 hours. The solution was basified with sodium carbonate and extracted with benzene The benzene was removed by distillation and the solid residue recrystallized from ethanol; wt. 8.87 g. (62% of theory), m.p. 140–141°. An additional recrystallization raised the melting point to 141–142°. An infrared spectra indicated no carbonyl absorption.

*Anal.* Calcd. for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 74.40; H, 8.34; N, 7.72.

**The dihydrochloride,** prepared by dissolving the free base in acetone and adding a saturated ethereal hydrogen chloride solution, after recrystallization from ethanol–methyl ethyl ketone (1:1) melted at 206° dec.

*Anal.* Calcd. for $C_{22}H_{32}N_2O_2 \cdot 2HCl$: C, 61.53; H, 7.98; Cl, 16.51; N, 6.53. Found: C, 61.76; H, 7.63; Cl, 16.61; N, 6.64.

**1,1-Bis-(*p*-dimethylaminophenyl)-2-ethoxypropane (XV).**—A suspension of 17.1 g. (0.05 mole) of 4,4-bis-(dimethylamino)-α-(1-ethoxyethyl)-benzhydrol (IVa) in 200 ml. of ethanol and 25 ml. of acetic acid was hydrogenated at 3 atmospheres using 10% palladium-on-charcoal as catalyst. The theoretical pressure drop took place in one hour.

The catalyst was removed, the filtrate treated with decolorizing carbon, the alcohol and acetic acid were removed by distillation *in vacuo* and to the residue was added 250 ml. of water. The mixture was basified by the addition of sodium bicarbonate, extracted with ether and the ether removed. The residue was recrystallized from ethanol; wt. 13.1 g. (80%), m.p. 82.5–83.5°.

*Anal.* Calcd. for $C_{21}H_{30}N_2O$: C, 77.25; H, 9.26; N, 8.58. Found: C, 76.91; H, 9.46; N, 8.81.

**1,1-Bis-(*p*-dimethylaminophenyl)-propanone-2 Oxime.**—A mixture of 8.88 g. (0.03 mole) of 1,1-bis-(*p*-dimethylaminophenyl)-propanone-2 and 35 ml. of ethanol was warmed on a steam-bath until a homogeneous solution was obtained. To this solution was then added a solution containing 4.17 g. (0.06 mole) of hydroxyamine hydrochloride and 5.91 g. (0.06 mole) of potassium acetate in 35 ml. of water. An oil precipitated immediately. The mixture was heated on the steam-bath and ethanol was added at the boil-point until a homogeneous solution was obtained. The solution was allowed to cool and the colorless needles removed by filtration, wt. 8.54 g. (91.5%), m.p. 155–157°. Recrystallization from ethanol–water (9:2) gave colorless prisms melting at 157–158°.

*Anal.* Calcd. for $C_{19}H_{25}N_3O$: C, 73.28; H, 8.09; N, 13.49. Found: C, 73.38; H, 8.24; N, 13.30.

**2,2-Bis-(*p*-dimethylaminophenyl)-1-methylethylamine.**—To 100 ml. of anhydrous ethanol was added approximately 9 g. of gaseous ammonia and to this was then added 3.18 g. of 1,1-bis-(*p*-dimethylaminophenyl)-propanone-2 oxime and Raney nickel catalyst. The mixture was hydrogenated at an initial pressure of about three atmospheres. When the theoretical amount of hydrogen had been absorbed (about 2 days) the catalyst was removed by filtration and the solvent removed *in vacuo*. The residue was recrystallized from petroleum ether (Skellysolve C). There was obtained 2.0 g. (66% of theory) of prisms melting at 115.5–117°.

*Anal.* Calcd. for $C_{19}H_{27}N_3$: C, 76.72; H, 9.15; N, 14.13. Found: C, 76.68; H, 9.24; N, 13.97.

**1,1-Bis-(*p*-dimethylaminophenyl)-propanol-2.**—A mixture of 1.14 g. (0.03 mole) of lithium aluminum hydride and 100 cc. of anhydrous ether was heated under reflux until most of the hydride had dissolved and then a solution of 8.89 g. (0.03 mole) of 1,1-bis-(*p*-dimethylaminophenyl)-propanone-2 in 60 ml. of anhydrous ether was added at a rate determined by the reflux rate. When addition was complete, the mixture was stirred and heated under reflux for 45 minutes and then decomposed by the successive addition of 1.33 ml. of water, 1.0 ml. of 20% NaOH solution and 4.7 ml. of water. The mixture was filtered and the white insoluble residue washed with ether. The combined ethereal solution was dried over anhydrous sodium sulfate and the ether removed by distillation, the last traces *in vacuo*. The light amber oil solidified upon standing; wt. 8.8 g. (98%), m.p. 80–81°. The material upon recrystallization from petroleum ether (Skellysolve C) gave colorless prisms possessing the same melting point. An infrared spectrum showed strong OH absorption.

*Anal.* Calcd. for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.60; H, 8.49; N, 9.53.

**The dihydrochloride** prepared in the usual way after recrystallization from 97.5% ethanol melted at 225° dec.

*Anal.* Calcd. for $C_{19}H_{26}N_2O \cdot 2HCl$: C, 61.45; H, 7.60; Cl, 19.10; N, 7.55. Found: C, 61.27; H, 7.62; Cl, 19.49; N, 7.48.

**The acetate,** prepared by treatment of the free base with acetic anhydride, melted at 102–105° after recrystallization from petroleum ether.

*Anal.* Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. C, 74.15; H, 8.38; N, 8.34.

**The benzoate** melted at 148–149° after recrystallization from petroleum ether.

*Anal.* Calcd. for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.77; H, 7.59; N, 6.76.

**The carbanilate** melted at 171.5–173° after recrystallization from methyl ethyl ketone.

*Anal.* Calcd. for $C_{26}H_{31}N_3O_2$: C, 74.79; H, 7.48; N, 10.06. Found: C, 74.67; H, 7.37; N, 9.83.

**1,1-Bis-(*p*-dimethylaminophenyl)-butanol-2 Dihydrochloride.**—The procedure described above when carried out with an equivalent amount of 1,1-bis-(*p*-dimethylaminophenyl)-butanone-2 gave a quantitative yield of the dihydrochloride. After recrystallization from absolute ethanol–ethyl acetate (3:1) the material melted at 215° dec.

*Anal.* Calcd. for $C_{20}H_{28}N_2O \cdot 2HCl$: C, 62.33; H, 7.85; N, 7.27. Found: C, 62.21; H, 8.10; N, 7.29.

KALAMAZOO, MICH.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# The Metabolism of 2-(Butylaminomethyl)-1,4-benzodioxane-C$^{14}$

BY ROBERT E. MCMAHON

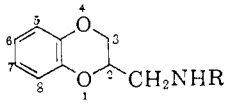
RECEIVED MAY 8, 1959

The metabolism of 2-(butylaminomethyl)-1,4-benzodioxane-C$^{14}$ has been studied in dogs and in rats. Both metabolize the drug by the same pathways. The major route is *via* hydroxylation to 6(or 7)-hydroxy-2-(butylaminomethyl)-1,4-benzodioxane. Oxidative degradation of the butylamino side chain represents a minor route.

## Introduction

The adrenolytic activity of the 2-(dialkylaminomethyl)-1,4-benzodioxanes was first observed in 1933 by Fourneau and Bovet.[1] Interest was recently renewed when Mills and co-workers[2] found that the 2-(monoalkylaminomethyl)-1,4-benzodioxanes produced pronounced behavioral changes in experimental animals.

No studies on the metabolic fate of drugs which contain the benzodioxane nucleus have as yet been published.[3] The present study concerns the *in vivo* metabolism of I, 2-(butylaminomethyl)-1,4-benzodioxane, which contains the basic structural features of the active compounds reported by Mills and co-workers.[2]




I, R = *n*-butyl
II, R = *n*-butyl-1-C$^{14}$

## Results and Discussion

Radiocarbon labeling was employed in order to simplify the experimental work. 2-(Butyl-1-C$^{14}$-aminomethyl)-1,4-benzodioxane (II) was prepared in good yield through the reaction of butyryl-1-C$^{14}$ chloride with 2-aminomethyl-1,4-benzodioxane followed by reduction of the resulting amide with lithium aluminum hydride.

The initial animal studies were performed in the dog (chihuahua). After administration of the radioactive drug by the intraperitoneal route the rate and extent of elimination of radioactivity in respiratory carbon dioxide and in urine was followed (Table I).

About 10% of the radioactivity was recovered as radiocarbon dioxide during the 10 hour collection period. This was an interesting finding since radiocarbon dioxide represents the final product of oxidative degradation of the butylaminomethyl side chain and this route of metabolism has rarely been observed to occur.[4]

TABLE I

ELIMINATION OF RADIOACTIVE METABOLITES OF II

Dose: rat, 10 mg./kg.; dog, 2.5 mg./kg.

| Time (accumulated), hr. | % of R.A. dose recovered in Respired $CO_2$ | | Urine | |
|---|---|---|---|---|
| | Rat | Dog | Rat | Dog |
| 0–1 | 2.0 | 3.3 | .. | .. |
| 0–2 | 2.8 | 7.0 | 38.8 | .. |
| 0–4 | 3.2 | 8.7 | 48.0 | .. |
| 0–10 | 3.8 | 10.5 | 65.9 | 42.2 |
| 0–24 | 4.0 | .. | 77.8 | 58.1 |
| 0–48 | .. | .. | .. | 66.6 |

The major portion of the radioactivity (66%) was, however, found in the urine collections. After the urine had been hydrolyzed with acid, most of the radioactivity could be extracted into ether at *p*H 8. Paper chromatography of extracted material showed it to contain only one radioactive component, and the fact that it could be readily visualized by spraying with a phenol reagent (diazotized sulfanilamide)[5] suggested strongly that the metabolite was a phenol, *i.e.*, the product of ring hydroxylation, a commonly observed pathway of metabolism of aromatic compounds. Four isomeric hydroxy derivatives of I are possible. Of these, two, the 5- and the 8- have been prepared by Mills and co-workers[2b] who have kindly supplied us with samples of each. The 6- and 7-isomers are unknown. The 8-OH compound had an $R_f$ value of 0.35, while the value for the 5-OH was 0.22. Both gave a rich orange color with the phenol reagent. The metabolite, however, had an $R_f$ value of 0.28 and gave a rose colored spot when sprayed. Thus the major metabolite of I in the dog appeared to be one of the two unknown phenols (III).

(1) E. Fourneau and D. Bovet, *Arch. internat. pharmacodyn. therap.*, **46**, 178 (1933).

(2) (a) J. Mills, R. C. Rathbun and I. H. Slater, Abstracts, A.C.S., 132nd Meeting, September 1957, p. 6-O. (b) J. Mills, M. M. Boren, W. E. Buting, W. N. Cannon, Q. F. Soper and M. J. Martell, ref. 2a, p. 7-O.

(3) For a preliminary report on the metabolism of (−)-2-(butylaminomethyl)-8-ethoxy-1,4-benzodioxane see R. E. McMahon, J. Welles and H. Lee, ref. 2a, p. 8-O.

(4) The *in vitro* dealkylation of butylaminoantipyrine has been reported by B. N. La Du, L. Gaudette, N. Trousof and B. B. Brodie, *J. Biol. Chem.*, **214**, 748 (1955).

(5) R. J. Block, R. LeStrange and G. Zweig, "Paper Chromatography," Academic Press, Inc., New York, N. Y., 1952, p. 64.