

directly, an attempt was made to N-methylate the cyclohexyl base (IV) by the Becker and Decker method. Although the intermediate Schiff base (VIII) formed readily, its treatment with methyl iodide in a sealed tube at 100–120° for twenty-eight hours, followed by hydrolysis, failed to produce the desired amine (VII).

A preliminary pharmacological evaluation of the pressor activity in anesthetized dogs of both the phenyl- (III and VI) and the cyclohexylalkylamines (IV and VII) was carried out.⁸ The secondary phenylalkylamine (VI) showed practically no activity. The other three amines displayed pressor activity of only low order, the cyclohexyl compounds being somewhat more active than the phenyl and the primary amines more active than the secondary. In general, the activity of the cyclohexyl compounds (IV and VII) is comparable to that of the β,β -dimethyl- β -cyclohexylethylamines, the weaker members of the previously reported series.^{2a}

Experimental⁹

1-Phenyl-2-methyl-2-nitropropanol (I).—To a solution prepared from 9.2 g. (0.4 mole) of sodium and 700 ml. of anhydrous methanol was added 187 g. (2.1 moles) of 2-nitropropane and 212 g. (2.0 moles) of freshly distilled benzaldehyde. After twenty-four hours at room temperature, the yellow solution was acidified with acetic acid and the methanol was distilled. The residue was dissolved in a mixture of water and ether. The ether layer was washed with water, extracted with four 200-ml. portions of 15% aqueous sodium bisulfite solution to remove the unreacted benzaldehyde, again washed with water and was dried over anhydrous sodium sulfate.

The ether was distilled. The residual oil was heated on a steam-bath *in vacuo* to remove any remaining benzaldehyde and 2-nitropropane. It was then stirred in an ice-bath with petroleum ether until it solidified. After filtration, the solid was recrystallized from 700 ml. of heptane to give the nitro alcohol as yellow crystals, m. p. 64–66°; reported^{2b} m. p. 53–62°; yield of 37%.

1-Phenyl-2-methyl-2-aminopropanol (II). A.—Sodium amalgam, prepared from 27.6 g. (1.2 moles) of sodium and 900 g. of mercury, was added, in portions, over a one-hour period to a stirred solution of 19.5 g. (0.1 mole) of the nitro alcohol (I) in a mixture of 100 ml. of alcohol, 100 ml. of glacial acetic acid and 50 ml. of water. Then, after one-half hour, the mercury was separated. The solution was filtered, diluted with water to 500 ml. and concentrated under reduced pressure to about 250 ml. to remove the alcohol. Acetic acid (6 ml.) and sufficient water to redissolve the sodium acetate which began to precipitate were added.

The solution was washed with ether and made basic with 40% aqueous sodium hydroxide. The amino alcohol which separated was extracted with ether, the ether solution was washed with a little water and dried over anhydrous sodium carbonate. Distillation of the ether and recrystallization of the residue from 200 ml. of heptane gave the amino alcohol as colorless crystals, m. p. 100–101°, in a yield of 41%; reported^{2b} m. p. 100–101°.

Anal. Calcd. for $C_{10}H_{15}NO$: N, 8.48. Found: N, 8.68.

B.—A solution of 39 g. (0.2 mole) of the nitro alcohol in a mixture of 150 ml. of alcohol, 165 ml. of glacial acetic acid and 200 ml. of water was stirred with 78.5 g. (1.2

moles) of zinc dust for six hours at 60–70°. Small portions of water were added from time to time to redissolve the precipitate which formed. The mixture was diluted with 350 ml. of water and the unreacted zinc was filtered. The filtrate was washed with ether and made basic with 600 ml. of 40% aqueous sodium hydroxide. The amine which separated was extracted with ether and the ether solution was washed with 40% sodium hydroxide followed by water. After drying over anhydrous sodium carbonate, the ether was distilled and the solid residue was recrystallized from heptane to give the amino alcohol as colorless crystals in a yield of 80–88%, m. p. 101–102°.

The hydrochloride, prepared by adding one equivalent of 2-propanolic hydrogen chloride to a cold solution of the base in 2-propanol and diluting the solution with diisopropyl ether, melted at 201–202° after recrystallization from ethanol-anhydrous ether.

Anal. Calcd. for $C_{10}H_{15}NOCl$: N, 6.95; Cl, 17.58. Found: N, 6.99; Cl, 17.45.

C.—The nitro alcohol (9.8 g., 0.05 mole) was hydrogenated in a mixture of 125 ml. of ethanol and 24 ml. of glacial acetic acid with 2 g. of palladium-charcoal catalyst¹⁰ at 80° and 60 pounds pressure. The theoretical amount of hydrogen was absorbed in about five hours.

The solvent was distilled, the residue was dissolved in 30 ml. of 28% ammonium hydroxide and the solution was saturated with sodium sulfate and cooled. The amino alcohol which separated was extracted with ether, the ether solution was washed with a little cold water and dried over anhydrous sodium carbonate. The crystalline residue remaining after distillation of the ether was recrystallized from a mixture of 10 ml. of benzene and 75 ml. of hexane to give 6.3 g. (76%) of colorless crystals, m. p. 99–101°.

α,α -Dimethyl- β -phenylethylamine (III).—A mixture of 66 g. (0.4 mole) of the amino alcohol (II), 20 g. of red phosphorus and 170 ml. of 57% hydriodic acid was refluxed for twenty-five hours. After standing twelve hours, a large amount of crystalline material had separated from the solution.

The reaction mixture was diluted with 700 ml. of water and was filtered through an asbestos mat to remove the phosphorus. The yellow filtrate was treated with a few crystals of sodium thiosulfate to remove any free iodine and was then made basic with 40% sodium hydroxide. The amine which separated was extracted with ether and the ether solution was washed with water and dried over anhydrous sodium carbonate. After removal of the ether, the residual oil was distilled to give the amine as a colorless oil in a yield of 80–88%, b. p. 89–90° at 10 mm., n_D^{20} 1.5130; reported b. p. 88–89° at *ca.* 16 mm.,^{2b} 203–205° at 760 mm.,^{2c} 100° at 21 mm.²

Anal. Calcd. for $C_{10}H_{15}N$: N, 9.39. Found: N, 9.44.

The hydrochloride, prepared by passing hydrogen chloride into a solution of the amine in 2-propanol-diisopropyl ether, melted at 199–200° after recrystallization from a mixture of 2-propanol and diisopropyl ether. Reported m. p. 200–201°,^{2b} 195–196°,² 147–148°.^{2b}

Anal. Calcd. for $C_{10}H_{15}NCl$: N, 7.54; Cl, 19.09. Found: N, 7.49; Cl, 19.01.

N,α,α -Trimethyl- β -phenylethylamine (VI).—The primary amine (III) was methylated by the Decker and Becker method as described by Woodruff, Lambooy and Burt.¹¹

A mixture of 29.8 g. (0.20 mole) of III and 23.3 g. (0.22 mole) of freshly distilled benzaldehyde was heated on a steam-bath for one-half hour and was then distilled. The intermediate Schiff base (V) was obtained as a viscous colorless oil in a yield of 95%, b. p. 146–147° at 2.6 mm., n_D^{20} 1.5730.

Anal. Calcd. for $C_{17}H_{19}N$: N, 5.90. Found: N, 5.87.

(8) We are indebted to the pharmacology staff of Frederick Stearns & Co., Division of Sterling Drug, Inc., for this pharmacological summary.

(9) All melting and boiling points are uncorrected.

(10) "Organic Syntheses," John Wiley & Sons, New York, N. Y., Vol. 26, 1946, p. 78, catalyst D.

(11) Woodruff, Lambooy and Burt, *THIS JOURNAL*, **62**, 922 (1940).

The Schiff base (45 g., 0.19 mole) and 28.4 g. (0.20 mole) of methyl iodide were heated in a sealed tube at 100–110° for twenty-eight hours. The contents of the tube were then refluxed for one-half hour with 160 ml. of ethanol and 20 ml. of water. The solution was acidified with acetic acid, diluted with 500 ml. of water and concentrated under reduced pressure to about one-half of the original volume to remove the alcohol and benzaldehyde.

The solution was washed several times with ether, made basic with 40% aqueous sodium hydroxide, and the amine which separated as an oil was extracted with ether. The extract was washed with water, dried over anhydrous sodium carbonate, and the solvent removed. The amine boiled at 94–97° (9 mm.); n_D^{20} 1.5112; yield 76%.

Anal. Calcd. for $C_{11}H_{17}N$: N, 8.58. Found: N, 8.59.

The hydrochloride, prepared by passing hydrogen chloride into a solution of the base in isopropyl ether, melted at 174–175° after several recrystallizations from 2-propanol-diisopropyl ether; reported^{2b} m. p. 174–175°.

Anal. Calcd. for $C_{11}H_{18}NCl$: N, 7.01; Cl, 17.75. Found: N, 7.14, Cl, 17.65.

α,α -Dimethyl- β -cyclohexylethylamine (IV) and N,α,α -Trimethyl- β -cyclohexylethylamine (VII).—By the catalytic hydrogenation procedure previously described,^{2a} the primary amine (IV) was obtained as a colorless oil in a yield of 89%, b. p. 75–76° at 7 mm., n_D^{20} 1.4586, and the secondary amine (VII) as a colorless oil in a yield of 80%, b. p. 84–86° at 6 mm., n_D^{20} 1.4640.

Anal. of IV. Calcd. for $C_{10}H_{21}N$: N, 9.02. Found: N, 8.80.

Anal. of VII. Calcd. for $C_{11}H_{23}N$: N, 8.27. Found: N, 8.44.

The hydrochlorides were prepared by passing hydrogen chloride into isopropyl ether solutions of the bases. The hydrochloride of IV melted at 158–159° after several recrystallizations from isopropyl ether containing 5% of 2-propanol.

Anal. Calcd. for $C_{10}H_{22}NCl$: N, 7.31; Cl, 18.49. Found: N, 7.31; Cl, 18.35.

The hydrochloride of VII melted at 153–154° after recrystallization from 2-propanol-diisopropyl ether.

Anal. Calcd. for $C_{11}H_{24}NCl$: N, 6.80; Cl, 17.24. Found: N, 6.70; Cl, 17.11.

Summary

Two β -cyclohexylalkylamines, α,α -dimethyl- β -cyclohexylethylamine and its *N*-methylated derivative, have been prepared by catalytic hydrogenation of the corresponding phenyl analogs.

The synthesis of the phenyl intermediates is described and a pharmacological summary of the pressor activity of the phenyl and cyclohexylalkylamines is presented.

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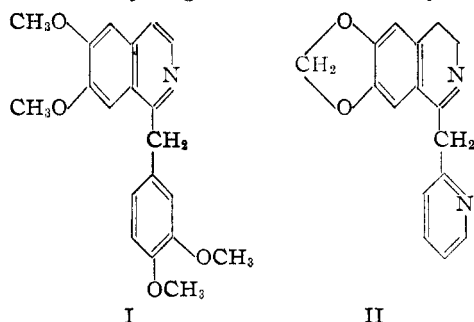
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Some Dihydroisoquinolines and their Absorption Spectra

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The pharmacological properties of the pyridyl analogs of papaverine (I) would be of interest. Clemo, McIlwain and Morgan² have synthesized what was believed to be 1-(α -picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (II). They attempted to dehydrogenate both the dihydroiso-



quinoline and the tetrahydroisoquinoline derived from it to the isoquinoline, but were unsuccessful. The present work attempted to obtain the isoquinoline by the Pictet and Gams synthesis³ in which the amide of a β -hydroxy- β -phenylethylamine is dehydrated, and to extend the efforts of Clemo, McIlwain and Morgan to dehydrogenate the hydroisoquinolines, but none of these attempts was successful.

During the course of the work the greater depth of color of the picolyldihydroisoquinoline and its hydrochloride compared with the 1-methyl or 1-benzyl derivatives prompted an investigation of their absorption spectra in order to obtain further information concerning their structure. Figure 1 gives the absorption in 95% ethyl alcohol of what were considered to be the 1-methyl-, 1-benzyl- and 1-(α -picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinolines. It is seen at once that whereas the curves for the 1-methyl and 1-benzyl derivatives are very similar, they differ markedly from that for the 1-(α -picolyl) derivative. This difference might be due to the presence of the nitrogen in the pyridine ring, or to the position of the double bond which might be either endocyclic or exocyclic to the isoquinoline ring. If one compares the curves for stilbene and α -stilbazole⁴ (2 and 3, Fig. 2), it is evident that the introduction of a nitrogen into one of the rings has little effect on the absorption, and it appears, therefore, that the difference in absorption depends on the position of the double bond. Which compound or compounds contain the double bond in the exocyclic position can be determined by recalling that the 1-methyl and 1-benzyl derivatives have practically identical absorption spectra. If the double bond were exocyclic, one would expect the spectrum of the 1-benzyl derivative to be shifted markedly to

(1) Du Pont Fellow in Chemistry, 1946–1947.

(2) Clemo, McIlwain and Morgan, *J. Chem. Soc.*, 610 (1936).

(3) Pictet and Gams, *Ber.*, **42**, 2943 (1909).

(4) Blout and Eager, *This Journal*, **67**, 1315 (1945).