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.); $n^{20}D$ 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., $n^{20}D$ 1.4586, and the secondary amine (VII) as a colorless oil in a yield of 80%, b. p. 84–86° at 6 mm., $n^{20}D$ 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.

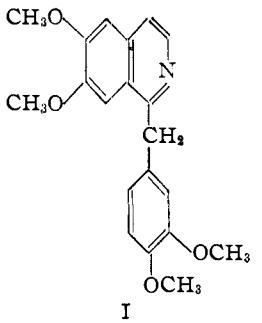
DETROIT, MICHIGAN RECEIVED OCTOBER 1, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Some Dihydroisoquinolines and their Absorption Spectra

BY JOHN L. BILLS[1] AND C. R. NOLLER

The pharmacological properties of the pyridyl analogs of papaverine (I) would be of interest. Clemo, McIlwain and Morgan[2] have synthesized what was believed to be 1-(α-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (II). They attempted to dehydrogenate both the dihydroisoquinoline 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 synthesis[3] 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.



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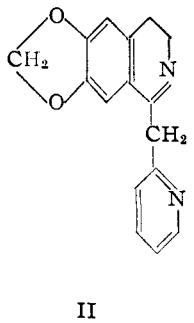


II

(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).

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-stilbazole[4] (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

(4) Blout and Eager, THIS JOURNAL, **67**, 1315 (1945).

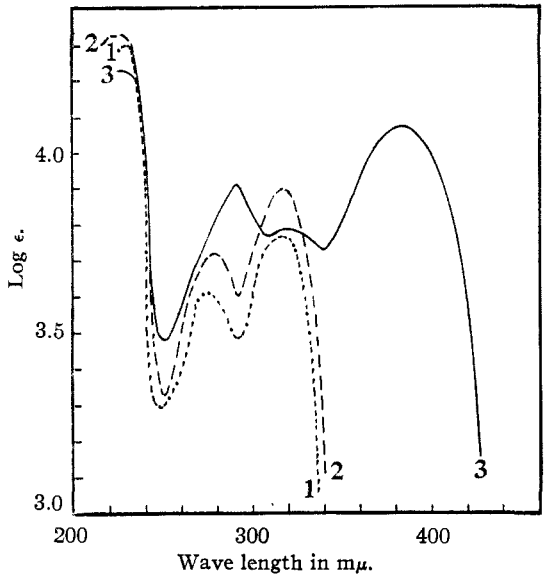


Fig. 1.—Ultraviolet absorption spectra: curve 1, - - - -, structure III; 2, — — —, structure IV; ——, structure V; all in ethyl alcohol.

the visible because of the conjugation between the two aromatic rings. For example the maximum for styrene[5] (Curve 1, Fig. 2) is shifted 45 mμ toward the visible, and the intensity of the absorption is greatly increased by conjugation with the second benzene ring in stilbene (Curve 2, Fig. 2). On this basis, the three compounds as free bases can be considered to be 1-methyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (III), 1-benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline (IV), and 1 - (α - picolal) - 1,2,3,4 - tetrahydro - 6,7 - methylenedioxyisoquinoline (V).

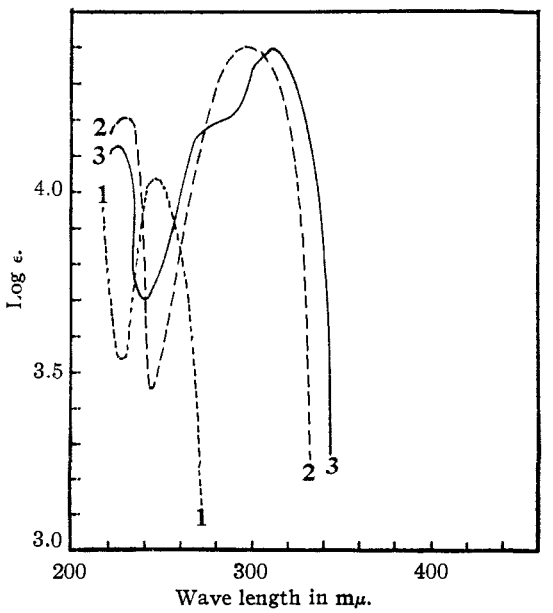
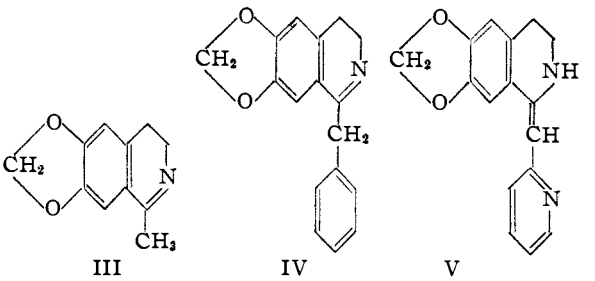


Fig. 2.—Ultraviolet absorption spectra: curve 1, - - -, styrene; 2, — — —, stilbene; 3, ——, α-stilbazole; all in ethyl alcohol.

(5) Ramart-Lucas and Amagat, *Bull. soc. chim.*, [4] **51**, 965 (1932).



If one compares the absorption of the three compounds in 1.5 *N* alcoholic hydrogen chloride, an entirely different result is obtained (Fig. 3). The

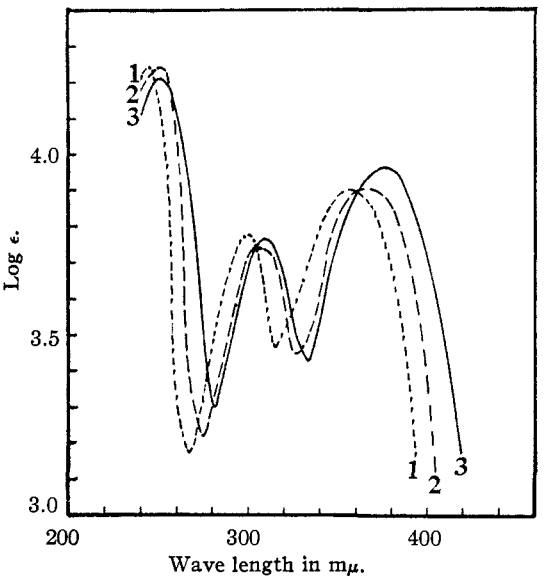
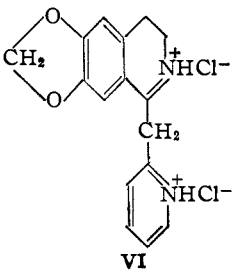


Fig. 3.—Ultraviolet absorption spectra: curve 1, - - - -, hydrochloride of III; 2, — — —, hydrochloride of IV; 3, ——, dihydrochloride of VI; all in ethyl alcohol.

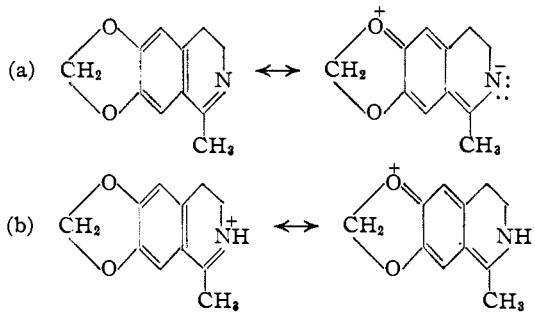
spectra for the 1-methyl- and 1-benzylisoquinolines have been spread out considerably toward the visible. In the case of the 1-(α-picolyl)-isoquinoline the position of the maximum nearest the visible has not changed appreciably, but the other maxima have shifted to shorter wave lengths, and all intensities have been changed considerably so that the spectrum now closely resembles that of the other two compounds. Hence there is little



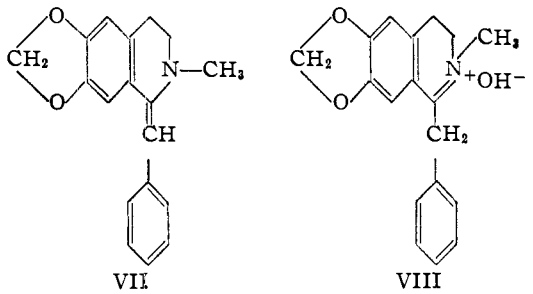
VI

doubt that the hydrochloride of the 1-(α-picolyl)-isoquinoline has structure VI. It is of interest that the spectra of the hydrochlorides of the 1-methyl and 1-benzyl derivatives in approximately 2×10^{-5} molar solutions in 95% alcohol (not shown in the figures) indicate that they are dissociated to the free base to the extent of 35 and 40%, respectively, whereas the dihydrochloride of the 1-(α-picolyl) derivative shows little dissociation.

The shift in the absorption toward the visible in going from the free base to the hydrochloride may be explained by assuming that bond resonance for the free base would require a separation of charge within the molecule (a), whereas for the hydrochloride bond resonance can occur without a separation of charge (b). Hence the latter process would take place more readily and could be brought about by light of longer wave length.



As further evidence concerning the structure of the picolyl derivative, it was considered desirable to determine the absorption spectrum of 1-benzal-1,2,3,4 - tetrahydro - 2 - methyl - 6,7 - methylenedioxyisoquinoline (VII), in the belief that it



VII VIII

should resemble the 1-(α-picolal) derivative. Instead, the curve for the free base in 95% ethyl alcohol (1, Fig. 4) was almost identical with that for the chloride in 1.5 *N* alcoholic hydrogen chloride (2, Fig. 4) and for the hydrochloride of the 1-(α-picolyl) derivative (3, Fig. 3). Undoubtedly the free base (VII) is converted in 95% ethyl alcohol into the quaternary ammonium hydroxide (VIII) by the addition of water. To check this point the absorption of the free base in 0.7 *N* alcoholic sodium hydroxide solution was determined. The absorption changed markedly (3, Fig. 4) and now resembled that of the free base of the 1-(α-picolal)-isoquinoline (3, Fig. 1). The presence of sodium hydroxide had no appreciable effect on any of the other bases.

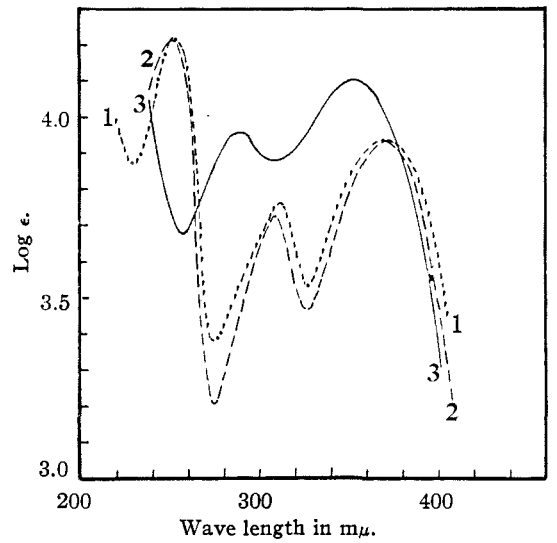
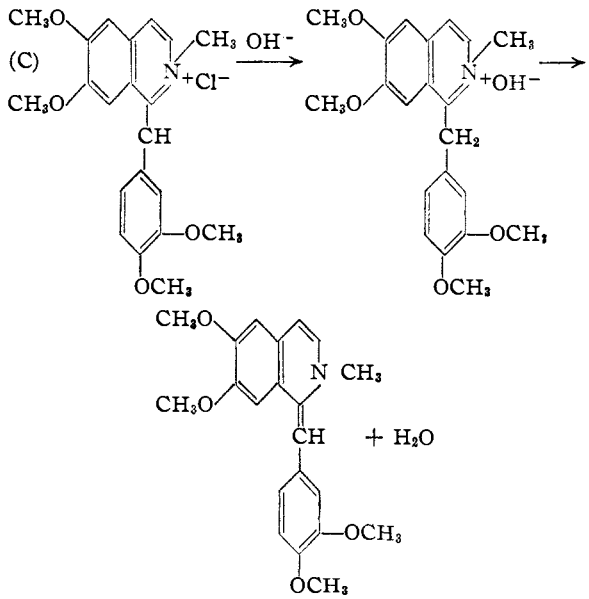


Fig. 4.—Ultraviolet absorption spectra: curve 1, - - - -, structure VIII in ethyl alcohol; 2, — — —, structure VIII in 1.5 *N* alcoholic hydrogen chloride; 3, ——, structure VII in 0.77 *N* alcoholic sodium ethoxide.

It is known that the quaternary salts of papaverine yield N-alkyl isopapaverines on reaction with concentrated alkali (c). It is evident from



the above absorption spectra that the proof of structure of the N-alkylisopapaverines based on the production of veratric acid and N-alkyldimethoxyisoquinolones by oxidation with potassium permanganate[6] depends on the oxidation being carried out in alkaline solution, since in neu-

(6) For references see Small and Lutz, "Chemistry of the Opium Alkaloids," U. S. Government Printing Office, Washington, 1932, p. 10 ff.

tral solution the N-alkylisopapaverines undoubtedly have a structure analogous to VIII rather than to VII.

The authors are indebted to Professor Melvin Calvin of the University of California for his helpful assistance in interpreting the absorption spectra.

Experimental

β-(3,4-Methylenedioxyphenyl)-ethylamine (Homopiperonylamine).—Piperonal was reduced to piperonyl alcohol in 93% yield in methyl alcohol solution using hydrogen at 800 lb. and 120° and Raney nickel catalyst,[7] or in 90% yields by a crossed Cannizzaro reaction.[8] The piperonyl alcohol was converted to the chloride in 96% yield using concentrated hydrochloric acid and calcium chloride.[7] The chloride was converted to the cyanide in 81% yield by treating 1 mole with 3.5 moles of sodium cyanide and 0.05 mole of mercuric cyanide in 250 cc. of water at 75–80° for six hours.[7] The cyanide was reduced to the amine in 85% yield.[9]

The amine could be prepared in 79% yield by the catalytic reduction of 3,4-methylenedioxy-ω-nitrostyrene.[10] The optimum conditions were the dropwise addition of a solution of 0.01 mole of the nitrostyrene in 50 cc. of dioxane and 0.6 cc. of concentrated sulfuric acid, to a stirred suspension of 0.7 g. of reduced platinum oxide in 50 cc. of dioxane in the presence of hydrogen at atmospheric pressure. Because of the easy preparation of the nitrostyrene this procedure is advantageous for the preparation of small quantities.

Methyl α-Pyridylacetate.—A solution of α-picolyllithium was prepared from 46.5 g. (0.5 mole) of α-picoline according to the procedure given in "Organic Syntheses."[11] While the stream of purified nitrogen continued to flow through the open stopcock of the separatory funnel, the condenser was replaced by a stopper, the stirrer removed, and the central neck fitted with a piece of 8-mm. glass tubing bent in the form of a U and of such dimensions that one leg reached to the bottom of the flask and the other over a 2-liter beaker containing 1 kg. of crushed solid carbon dioxide. When the stopcock of the separatory funnel was closed, the solution was forced onto the solid carbon dioxide which was stirred continuously. After the excess carbon dioxide had evaporated, 500 cc. of water was added, and most of the cream-colored solid dissolved. The mixture was filtered to remove about 10 g. of insoluble material, the filtrate separated with a separatory funnel, and the aqueous layer extracted three times with 100-cc. portions of ether.

The aqueous solution was transferred to a 3-liter beaker, diluted with 1500 cc. of water, and acetic acid added until Hydrion test paper indicated a *p*H of 4. A solution of 37.5 g. (0.15 mole) of copper sulfate pentahydrate in 300 cc. of water then was added gradually with good stirring. After the addition of the first 50 cc. of copper sulfate solution, the mixture was stirred for five minutes to ensure precipitation of the copper salt in a crystalline form before further addition. The precipitate was filtered and washed on the filter with water until the filtrate had only a faint bluish tinge. The air-dried precipitate weighed 40–42 g. (48–50%).

Dry hydrogen chloride was passed into a suspension of 40 g. (0.12 mole) of the dry copper pyridylacetate in 125 cc. of methyl alcohol until solution was complete. Then hydrogen sulfide was passed into the solution, the copper sulfide removed by filtration, and the filtrate saturated with hydrogen chloride. After allowing to stand for three days at room temperature, the solution was concentrated at reduced pressure to 300 cc., and solid sodium bicarbonate was added to neutralize the remaining hydrogen chloride. Dilution with 1500 cc. of water, extraction with two 200-cc. portions of benzene, concentration of the extract at reduced pressure, and distillation of the residue gave 20–22 g. (55–61%), b. p. 126–127° (15 mm.). The boiling point reported for the ester prepared through the anilide, which had been obtained by Beckmann rearrangement of the oxime of 2-phenacylpyridine, is 123° (12 mm.)[12] Ziegler and Zeiser[13] have reported that the carbonation of α-picolyllithium with gaseous carbon dioxide yields only α-picoline.

N-Acetylhomopiperonylamine.—Ten grams (0.06 mole) of homopiperonylamine was added to 10 g. (0.1 mole) of acetic anhydride. After the reaction was complete the acetic acid and excess acetic anhydride were removed by distillation at reduced pressure. The residue solidified on cooling and was recrystallized from ether giving 11.5 g. (93%) of white N-acetylhomopiperonylamine melting at 108–109°. Kaufmann and Radosevic[14] reported 101° for the product obtained by the Beckmann rearrangement of piperonylacetoxime.

N-Phenylacetylhomopiperonylamine.—Ten grams (0.06 mole) of homopiperonylamine and 12 g. (0.08 mole) of phenylacetyl chloride were shaken together in 200 cc. of a 10% potassium hydroxide solution. A thick, viscous, pale yellow oil was formed which soon solidified and was filtered from the aqueous solution. After crystallizing from ethyl alcohol–water, 16 g. (92%) of N-phenylacetylhomopiperonylamine was obtained as fine white needles melting at 96–97°. The compound prepared by Decker[15] from phenylacetic acid and homopiperonylamine melted at 96°.

N-(α-Pyridylacetyl)-β-phenylethylamine.—A mixture of 9.2 g. (0.076 mole) of β-phenylethylamine and 11.4 g. (0.076 mole) of methyl α-pyridylacetate in a 50-cc. round-bottomed flask equipped with an air-cooled reflux condenser was heated in an oil-bath at 200°. At the end of four hours the condenser was removed and the mixture heated an additional two hours. The reaction mixture was poured into a beaker and solidified on cooling. After crystallizing from benzene, 10 g. (55%) of N-(α-pyridylacetyl)-β-phenylethylamine was obtained melting at 74–75°. Three additional recrystallizations from ether raised the melting point to 75–76°.

Anal.[16] Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71. Found: C, 74.81; H, 6.67.

N-(α-Pyridylacetyl)-homopiperonylamine.—A mixture of 3 g. (0.018 mole) of homopiperonylamine and 3 g. (0.020 mole) of methyl α-pyridylacetate was heated at 200° for forty-five minutes in 10 cc. of tetralin[17] contained in a 50-cc. round-bottomed flask. A short air condenser was used to return to the reaction mixture the small amount of tetralin and methyl α-pyridylacetate which distilled. During the heating considerable frothing occurred. At the end of forty-five minutes the contents of the flask was poured into a 50-cc. beaker and allowed to cool. Crystallization was induced either by scratching the side of the beaker or by seeding the supersaturated solution with a trace of the amide. The precipitate was filtered and washed with several portions of petroleum ether to give 4.7 g. (92%) of a white product melting at 90–91°. The compound prepared through the ethyl ester in the absence of a solvent melted at 89°.[2]

1-Methyl-3,4-dihydro-6,7-methylenedioxyisoquinoline Hydrochloride.—A solution of 5 g. (0.024 mole) of N-

(7) G. A. Alles, private communication.

(8) "Org. Syn.," Coll. Vol. II, 590 (1943).

(9) "Org. Syn.," **23**, 72 (Note 5) (1943).

(10) Schales, *Ber.*, **68**, 1579 (1935).

(11) "Org. Syn.," **23**, 83 (1943). The lithium was cut into thin shavings by means of a spoke-shave mounted in an inverted position on two blocks to a board in such a way that an evaporating dish containing mineral oil could be placed under the blade of the spoke shave. During the cutting the blade was kept lubricated with mineral oil. The shavings dropped directly into the mineral oil and were washed with dry ether just before use.

(12) Oparina, *Khim. Farm. Prom.*, No. 4, p. 12 (1934); *Chem. Zentr.*, **106**, 2536 (1935).

(13) Ziegler and Zeiser, *Ann.*, **485**, 182 (1931).

(14) Kaufmann and Radosevic, *Ber.*, **49**, 680 (1916).

(15) Decker, *Ann.*, **395**, 294 (1913).

(16) Microanalyses for carbon and hydrogen by Huffman Microanalytical Laboratories, Denver, Colo.

(17) Kindler and Peschke, *Arch. Pharm.*, **272**, 236 (1934).

acetylhomopiperonylamine and 10 cc. of phosphorus oxychloride in 25 cc. of anhydrous toluene was heated under reflux for one and one-half hours. The mixture was cooled and added to a large volume of petroleum ether (b. p. 55–85°). The phosphate of the base separated as a dark yellow oil and solidified on standing. This material was crystallized from alcohol–ether to give pale yellow crystals melting with decomposition at 239–240°. The phosphate was dissolved in a little 10% hydrochloric acid and neutralized with potassium hydroxide. The pale yellow oil which separated was extracted with ether and an ethereal solution of dry hydrogen chloride added. The hydrochloride separated as a powdery yellow precipitate, which was filtered and crystallized from absolute ethyl alcohol to give 4.3 g. (79%) of 1-methyl-3,4-dihydro-6,7-methylenedioxyisoquinoline hydrochloride melting at 245–247° (dec.). The melting point has been reported as 242°.[14]

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: Cl, 15.71. Found: Cl, 15.80, 15.82, 15.87.

1-Benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline Hydrochloride.—A mixture of 5 g. (0.018 mole) of N-phenylacetylhomopiperonylamine and 10 cc. of phosphorus oxychloride in 25 cc. of dry toluene was heated under reflux for two hours. The light red solution was cooled and poured into a large excess of petroleum ether (b. p. 55–85°), and a red oil separated which solidified on standing. It was crystallized from alcohol, dissolved in dilute hydrochloric acid, and the aqueous solution neutralized with sodium hydroxide. The pale yellow oil which separated was extracted with ether and an ethereal solution of dry hydrogen chloride added. The 1-benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline hydrochloride precipitated as minute pale yellow crystals. After crystallizing from anhydrous alcohol–ether, 3.3 g. (70%) of the hydrochloride was obtained melting at 215–216° (dec.).

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: Cl, 11.75. Found: Cl, 11.90, 11.73.

The picrate after crystallization from alcohol melted at 202–206°.[18]

1-(α-Picolal)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline.—This compound was prepared in 62% yield by the method of Clemo, McIlwain and Morgan,[3] and melted at 102–103°. The dihydrochloride decomposed at 208–209°.

1-Benzyl-2-methyl-3,4-dihydro-6,7-methylenedioxyisoquinolinium Chloride.—A modification of the procedure described by Hamilton and Robinson[19] for the preparation of 1-benzal-2-methyl-1,2,3,4-tetrahydroisoquinoline was used. A mixture of 7 g. (0.026 mole) of 1-benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline and 4 g. (0.032 mole) of dimethyl sulfate in 75 cc. of benzene was heated, allowing the benzene to distil slowly. The addition compound gradually separated on the bottom of the flask. The sirupy residue which remained after all of the benzene was distilled was dissolved in water, and the aqueous solution was made strongly basic with solid potassium hydroxide. This basic solution was extracted with four 50-cc. portions of ether, the ether extracts dried over sodium sulfate, and an anhydrous ethereal solution of hydrogen chloride added. A pale yellow precipitate formed which was recrystallized from anhydrous alcohol–ether. Six grams (77%) of 1-benzyl-2-methyl-3,4-dihydro-6,7-methylenedioxyisoquinolinium chloride was obtained.

Anal. Calcd. for $C_{18}H_{18}ClNO_2$: Cl, 11.23. Found: Cl, 11.13, 11.41.

Attempt to Dehydrogenate 1-(α-Picolal)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline.—Dehydrogenation was attempted with nitrobenzene in the presence of Raney nickel, with nitric acid in acetic acid,[20] and with permanganate in acetic acid.[21] In no case could an isoquinoline be isolated.

The picolal derivative was hydrogenated to the picolyl derivative, and a benzene suspension of the latter dropped onto a bed of molybdena-alumina catalyst at 250°. Although the catalyst was capable of dehydrogenating tetralin to naphthalene, and tetrahydroquinoline to quinoline quantitatively, the only product that could be isolated from the picolyl derivative was α-picoline.

Aminomethylphenylcarbinol Hydrochloride.—A saturated solution of 23 g. (0.13 mole) of ω-aminoacetophenone hydrochloride, prepared by the procedure of Rupe,[22] in 95% ethyl alcohol was hydrogenated in the presence 0.52 g. of platinum black at 40 lb. gage pressure. A total of 0.15 mole of hydrogen was absorbed. After no more hydrogen was taken up the catalyst was filtered and the filtrate evaporated to dryness at reduced pressure. Twenty-two grams (97%) of aminomethylphenylcarbinol hydrochloride was obtained melting at 176–177° (dec.). The material could be crystallized from alcohol–ether to give small white crystals of the hydrochloride, but the melting point was not changed. The picrate melted at 153–154° after crystallization from alcohol, and the benzoyl derivative melted at 148.5–149.5° after crystallization from dilute alcohol. Kolshorn[23] prepared the free base by reducing isonitrosoacetophenone with sodium amalgam but could not obtain the hydrochloride in crystalline form. His picrate melted at 146–147° and his benzoyl derivative at 144–145.5°.

Aminomethyl-3,4-dimethoxyphenylcarbinol Hydrochloride.—This compound was prepared by catalytic hydrogenation of ω-aminoacetoveratrone hydrochloride by the same procedure used for the preparation of aminomethylphenylcarbinol hydrochloride. The reduction was nearly quantitative. The material melted at 168–170° after crystallization from ethyl alcohol. Rosenmund[24] reported 163° for the melting point of the hydrochloride prepared by the reduction of α-(3,4-dimethoxyphenyl)-β-nitroethyl alcohol.

N-(α-Pyridylacetyl)-aminomethylphenylcarbinol.—Thirteen grams (0.075 mole) of aminomethylphenylcarbinol hydrochloride was added to 30 cc. of dilute sodium hydroxide. The two layers were separated, and the aqueous layer was extracted with two 15-cc. portions of benzene. The benzene extracts were added to the free amine, the benzene solution was washed once with water, and the benzene removed by distillation at reduced pressure. Ten grams (0.073 mole) of free amine was obtained, which was added to 15 g. (0.10 mole) of methyl α-pyridylacetate, and the mixture was heated for two hours in an oil-bath at 200°. It then was cooled and the green mass poured into 100 cc. of benzene. After several days the material separated as fine white crystals which were filtered and recrystallized from benzene. Nine grams (48%) of N-(α-pyridylacetyl)-aminomethylphenylcarbinol melting at 114–115° was obtained. A sample was prepared for analysis by recrystallizing four times from benzene and drying at 100° at reduced pressure. The melting point of the purified product was unchanged at 114–115°.

Anal.[16] Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.67; H, 6.29. Found: C, 70.91; H, 6.24.

A picrate was prepared by adding an alcoholic picric acid solution to the base dissolved in alcohol. An orange sirup precipitated and solidified on long standing. After recrystallizing once from benzene–alcohol and twice from ethyl acetate the picrate melted at 131–132°.

Attempts to cyclize the free base to 1-(α-picolyl)-isoquinoline using phosphorus pentoxide in toluene[25] or in tetralin[26] were unsuccessful. Red oils were obtained from which only α-picoline could be isolated as the picrate.

N-(α-Pyridylacetyl)-aminomethyl-(3,4-dimethoxyphenyl)-carbinol.—An alcoholic solution of aminomethyl-(3,4-dimethoxyphenyl)-carbinol was prepared by neutralizing 3.5 g. (0.011 mole) of the hydrochloride in 15 cc. of alcohol

(18) Decker, Kropp, Hoyer and Becker, *Ann.*, **395**, 305 (1913).

(19) Hamilton and Robinson, *J. Chem. Soc.*, **109**, 1029 (1916).

(20) Rodionov and Yavorskaya, *J. Gen. Chem.* (*U. S. S. R.*), **11**, 446 (1941); *C. A.*, **35**, 6592 (1941).

(21) Pictet and Kay, *Ber.*, **42**, 1973 (1909).

(22) Rupe, *ibid.*, **28**, 254 (1895).

(23) Kolshorn, *ibid.*, **37**, 2474 (1904).

(24) Rosenmund, *ibid.*, **46**, 1049 (1913).

(25) Späth and Lang, *Monatsh.*, **42**, 273 (1921).

(26) Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930).

with sodium ethylate using phenolphthalein as an indicator. The precipitated sodium chloride was removed by filtration and 2.5 g. (0.016 mole) of methyl α-pyridylacetate added. The mixture was heated gradually in a 50-cc. round-bottomed flask to 200° by allowing the alcohol to escape through a short air-cooled reflux condenser. The mixture was heated at 200° for twenty minutes. On cooling, a thick red-brown resin was obtained which was soluble in benzene, alcohol, or chloroform, but insoluble in ether or petroleum ether. A number of attempts to crystallize the amide were unsuccessful. Some of this sirupy material was dissolved in ethyl alcohol, and an alcoholic solution of picric acid was added. A resinous precipitate formed which could not be made to solidify. An anhydrous alcoholic solution of hydrogen chloride was added to an anhydrous alcoholic solution of the amide. Upon the addition of dry ether a sirupy hydrochloride precipitated which did not crystallize even at −80°. The solvent was decanted and the hydrochloride placed in a vacuum desiccator. The material gradually crystallized but on exposure to the atmosphere immediately became a sticky mass. The dried hydrochloride melted with decomposition at 105–110°. No analysis was made.

Attempts to cyclize the crude free base by the procedures of Clemo, McIlwain and Morgan,[3] of Pictet and Gams,[3] or of Bruckner and Fodor,[27] gave tars from which only α-picoline could be isolated as the picrate.

Absorption Spectra.—Absorption spectra not previously reported were obtained with a Beckman Quartz Spectrophotometer, Model DU, using 1-cm. quartz cells, a hydrogen discharge lamp for the ultraviolet light source, and a tungsten filament lamp for wave lengths above 325 mμ. The concentrations were from 1 to 2 × 10^{-5} molar in 95% ethyl alcohol or alcohol containing dry hydrogen chloride or sodium hydroxide. In each case freshly recrystallized material was used, and the absorption determined immediately without allowing the solutions to stand. If these precautions were not taken, inconsistent results sometimes were obtained. The spectra for styrene,[5] stilbene[4] and α-stilbazole[4] were taken from the literature.

(27) Bruckner and Fodor, *Ber.*, **71**, 547 (1938).

Summary

It is concluded from their absorption spectra that the cyclization products of N-acetyl- and N-phenylacetylhomopiperonylamine are 1-methyl- and 1-benzyl-3,4-dihydro-6,7-methylenedioxyisoquinoline, respectively, whereas the cyclization product of N-(α-pyridylacetyl)-homopiperonylamine is 1-(α-picolal)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline. Reaction of the last compound with hydrochloric acid converts it into 1-(α-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline hydrochloride. It is further concluded that 1-benzal-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline has the structure corresponding to this name when in solution, only in the presence of strong bases, and that when dissolved in alcohol alone it is largely in the form of the quaternary hydroxide. Further attempts to synthesize 1-(α-picolyl)-isoquinolines have been unsuccessful.

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The Reaction of 2,5-Dimethylfuran with *p*-Nitrobenzenediazonium Chloride

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The ease with which the furan nucleus undergoes typical aromatic substitution reactions is well known[2] and suggested to us that alkylated furans, as analogs of mesitylene,[3] should undergo a coupling reaction with reactive dizonium halides. Both Gilman and Ochaiai[4] have reported that furan reacts with diazonium halides. Johnson[5] has reported formation of 2-(and some 3-)arylfurans by interaction of furan with a diazotate. Recently, a report[6] of the coupling of sodium *anti-p*-nitrobenzenediazotate with ethyl 2-furylcarbamate has appeared.

We chose for our study of this reaction an available furan with unsubstituted β-positions, 2,5-dimethylfuran and the reactive *p*-nitrobenzenediazonium chloride. These components were combined in an ice-cold aqueous alcoholic solution that contained an excess of potassium acetate as a buffer.[7] The initial coupling product separated as a semi-solid red mass which could not be crystallized to a state of assured purity. When the initial coupling product was heated *in vacuo* or hydrolyzed with dilute acid it was converted in good yield to a substance $C_{12}H_{11}O_3N_3$ which is formulated as 1-*p*-nitrophenyl-3-acetyl-5-methylpyrazole (II) on the basis of its giving a positive iodoform reaction and its smooth oxidation to an acid, $C_{11}H_9O_4N_3$ shown to be identical with 1-*p*-nitrophenyl-5-methyl-3-pyrazolecarboxylic acid (III), m. p.[8] 216–217°, prepared by an unequivocal synthesis.

Consideration of the properties and easy transformation to II of the initial, red coupling product (*cf.* Experimental Part) suggests the tentative structual assignment I for this material.

(1) Part of the work described in this article is taken from a thesis presented to Stanford University by Francis L. Detert in partial fulfillment of the requirements for the degree of Master of Science.

(2) Gilman and Towne, *Rec. trav. chim.*, **51**, 1054 (1932); Gilman, Calloway and Burtner, THIS JOURNAL, **57**, 906 (1935).

(3) Meyer and Tochtermann, *Ber.*, **54**, 2283 (1921).

(4) Gilman, Wooley and Vanderwal, *Proc. Iowa Acad. Sci.*, **29**, 176 (1932); Ochaiai, *J. Pharm. Soc., Japan*, **58**, 1025 (1938).

(5) A. W. Johnson, *J. Chem. Soc.*, 895 (1946).

(6) Hurd and Priestley, THIS JOURNAL, **69**, 859 (1947).

(7) Similar reaction conditions were employed by Fischer and Hepp (*Ber.*, **19**, 2251 (1886)) in the successful coupling of pyrrole with diazonium halides, and by Johnson (Ref. 5).

(8) An isomer of this compound, but reported in Beilstein, 4th ed., **25**, 120, as this compound, was prepared by Knorr and Macdonald, *Ann.*, **279**, 224 (1894). It melted at 122° and was prepared by reaction of 1-phenyl-5-methyl-3-pyrazolecarboxylic acid with fuming nitric acid. On repeating this work we obtained an acid of m. p. 153–154° without establishing its identity.