had been stirred at 170° for 30 min. precipitated a bright yellow acid-insoluble solid (0.28 g., m.p. 175–200°). Recrystallization from glacial acetic acid gave yellow needles, m.p. 211–212°, identical (mixture melting point) with the sample prepared in A. 9-Phenylacridine (0.3 g.) when similarly treated with benzoic acid and PPA was recovered unchanged.

6-Phenylphenanthridine (VII). A.—A mixture of 2-benzamidobiphenyl (1 g., m.p. 89–90°, lit.[25] 84–86°) and PPA (10 g.) was stirred at 170° for 30 min. during which period effervescence occurred. The dark orange solution, which exhibited a violet fluorescence, was diluted with water and freed from negligible acid-insoluble impurities. The filtrate contained no ketonic material and on adding ammonia deposited a gum which gradually solidified (0.9 g., 96%, m.p. 102–107°). Recrystallization from ethanol (charcoal) furnished glistening, tiny, colorless crystals, m.p. 106–107° (lit.[26] 105–107°), giving, no precipitate with 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{19}H_{13}N$: N, 5.49. Found: N, 5.28.

The substance dissolved readily in dilute mineral acids and the pale green solutions on dilution exhibited a notable violet fluorescence.

B.—After reaction of 2-aminobiphenyl (1 g., 0.006 mole), benzoic acid (0.7 g., 0.006 mole), and PPA (15 g.) at 180° for 30 min., the dark red solution was treated with water and a small amount of acid-insoluble impurity was removed. The filtrate gave an orange precipitate with 2,4-dinitrophenylhydrazine, and on adding ammonia yielded a gum which gradually solidified. The crude 6-phenylphenanthridine (1.23 g., m.p. 85–96°) was contaminated with ketonic material (most likely 2-benzoyl-6-phenylphenanthridine) and, after several recrystallizations from ethanol, furnished colorless crystals (~0.5 g.), m.p. 106–107°, free of ketone impurity, and identical (mixture melting point) with the base prepared in A. Use of excess of benzoic acid (2.2 g., 0.018 mole) in the reaction gave substantially the same result.

(25) E. Wenkert and B. F. Barnett, *J. Am. Chem. Soc.*, **82**, 4671 (1960).
(26) H. W. Moore and H. R. Snyder, *J. Org. Chem.*, **28**, 535 (1963).

Beckmann Rearrangement of Benzophenone Oxime to 4-Aminobenzophenone.—A mixture of the oxime (1 g.) and PPA (20 g.) was heated with manual stirring at 120–130° for 30 min.[19] and then at 180° for a further 30 min. Isolation by method A furnished crude 4-aminobenzophenone (0.4 g., 40%, m.p. 112–120°). The recrystallized material was identical (mixture melting point and infrared spectrum) with authentic amino ketone.

4-Aminobenzophenone by a Modified Lossen Reaction.—Hydroxylamine hydrochloride (0.8 g., 0.012 mole) and PPA (20 g.) were stirred together at 100–130° for 30 min. or until the frothing had subsided. Excess benzoic acid (2.5 g., 0.02 mole) was added to the solution and the temperature was gradually raised from 130 to 150° over 20 min. and then kept at 180° for a further 30 min. to yield crude amino ketone (0.71 g., 35%, based on benzoic acid). Snyder, *et al.*,[20] employed approximately equimolar proportions of the two reactants in a similar reaction, and obtained aniline. Use of benzophenone (1.8 g., 0.01 mole) in place of the benzoic acid led to 4-aminobenzophenone in 35% yield, *via* a Beckmann rearrangement of the intermediate benzophenone oxime formed *in situ*. Reaction of the benzophenone with a 2 mole excess of hydroxylamine hydrochloride in PPA at 160–165° was reported by Snyder, *et al.*,[20] to furnish aniline in 66% yield.

Conversion of Benzanilide to N,N'-Diphenylbenzamidine.—The orange solution at benzanilide (2 g.) and PPA (2 g.) resulting from reaction at 180° for 30 min. was treated with dilute hydrochloric acid and the acid-insoluble material was removed. Addition of ammonia to the filtrate (charcoal) deposited crude N,N'-diphenylbenzamidine (0.3 g., 15%, m.p. 133–141°, no precipitate with 2,4-dinitrophenylhydrazine). Recrystallization from dilute ethanol (charcoal) furnished colorless, woolly needles, m.p. 145–146°, identical (mixture melting point and infrared spectrum) with an authentic specimen. The acid-insoluble material was found to consist of benzanilide and 4-benzaminobenzophenone (infrared spectrum). The use of 4 g. of PPA in the reaction led to an increased proportion of 4-benzaminobenzophenone in the acid-insoluble mixture; the acid filtrate contained some 4-aminobenzophenone and negligible amidine.

The Oxidative Cyclization of 2,5-Dihydroxyphenylalkylamines to 5-Hydroxyindoles and 6-Hydroxyquinolines[1]

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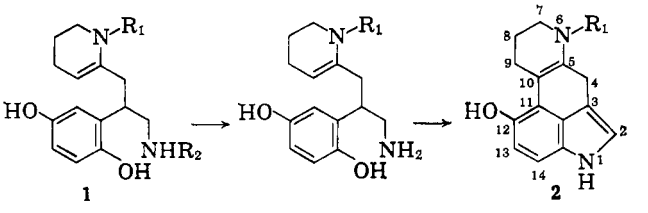
Received June 16, 1964

2-(2,5-Dihydroxyphenyl)-3-(1-methyl-2-piperidyl)propylamine (11) was prepared and cyclized to the 5-hydroxy-3-(2-piperidylmethyl)indole 12. The attempted mercuric acetate oxidation of derivatives of 11 to the enamine was unsuccessful. Ferricyanide oxidation of γ-(2,5-dihydroxyphenyl)propylamine (15) gave a mixture of 6-hydroxyquinoline and 6-hydroxy-1,2,3,4-tetrahydroquinoline. The reversible redox system of these quinolines is discussed.

In an earlier paper[2] we reported the synthesis of 6-hydroxy-1,3,4,5-tetrahydrobenz[*cd*]indole as a preliminary stage in developing a total synthetic approach to ergoline derivatives containing a 12-hydroxyl group. Since this report, interest in 12-hydroxyergolines has been heightened by the finding that lysergic acid diethylamide and propanolamide are hydroxylated *in vivo* at the 12-position.[3] The introduction of a hydroxyl group at this site in lysergic acid amides by chemical oxidation has very recently been described.[4] We now present the results of further work on the projected synthesis of 12-hydroxyergoline and some related experiments.

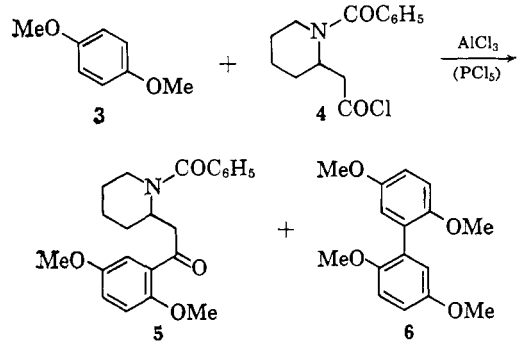
The over-all synthetic plan envisioned the preparation of a 2,5-dihydroxyphenethylpiperidene 1 and closure of both rings C and B by oxidation and accompanying nucleophilic attack on the quinoid ring A by the enamine and primary amino groups, respectively. The enamine cyclization step was projected on the findings of Henbest and co-workers[5]; the application of the Harley-Mason cyclization to a benz[*cd*]-



(1) Supported by a grant from the Geshickter Fund for Medical Research.
(2) J. A. Moore and M. Rahm, *J. Org. Chem.*, **26**, 1109 (1961).
(3) M. B. Slaytor and S. E. Wright, *J. Med. Chem.*, **5**, 483 (1962).
(4) P. A. Stadler, *Oesterr. Chemiker-Ztg.*, **64**, H.10, 298 (1963); we are grateful to Dr. A. Hofmann, Basel, for informing us of this work.
(5) D. Buckley, H. B. Henbest, and P. Slade, *J. Chem. Soc.*, 4891 (1957).

indole was demonstrated previously.[2] In this general approach, several alternative sequences of steps leading to the $\Delta^{5(10)}$-ergoline **2**[6] could be considered, including the simultaneous closure of both rings by oxidation of **1** ($R_1 = CH_3$; $R_2 = H$).

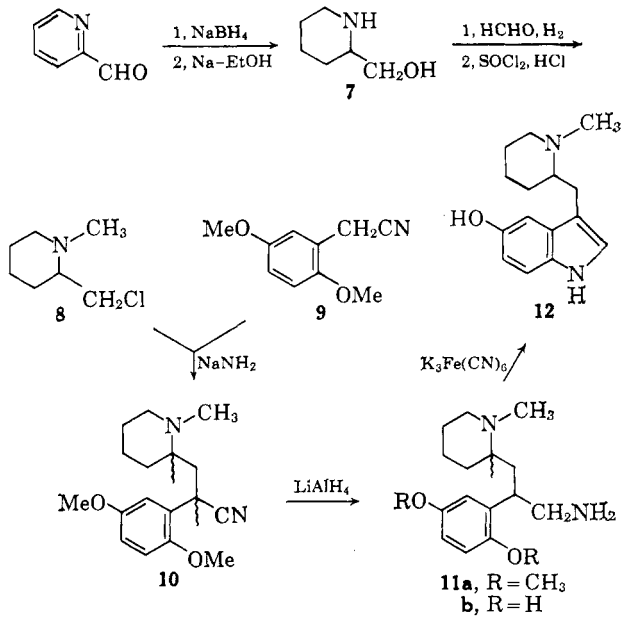
The initial approach to a bicyclic precursor was based on the steps used for the tricyclic model compound.[2] Acylation of *p*-dimethoxybenzene with N-benzoyl-2-piperidineacetyl chloride[7] in the presence of a large excess of aluminum chloride led to the ketone **5** which was isolated in 42% yield together with a small amount of 2,5,2′,5′-tetramethoxybiphenyl (**6**). The latter by-product evidently arose from chlorination of **3** by traces of phosphorus pentachloride in the crude acid chloride and subsequent condensation. The ketone **5** furnished an oxime, but a cyanohydrin could not be obtained. The conversion of **5** to a nitrile *via* the alcohol and chloride might have been possible, but this route was abandoned in favor of an approach patterned on the synthesis of 2,5-dimethoxy-α-dimethylaminoethylphenylacetonitrile.[8]



Alkylation of the nitrile **9** with 1-methyl-2-piperidinemethyl chloride (**8**), prepared by the steps indicated in Chart I, provided a very satisfactory preparation of the bicyclic nitrile **10**, which was isolated as an oil. This compound was presumably a mixture of diastereoisomers, but since one or both asymmetric centers would be lost in subsequent transformations, extensive efforts were not made to separate stereoisomers. No fractionation was observed in preliminary examination by thin layer or vapor phase chromatography. Reduction of **10** with lithium aluminum hydride furnished the diamine **11a** as an oil; no crystalline derivatives were obtained.

Introduction of the double bond in the potential D ring was explored with the free dimethoxyamine **11a**, the acetyl derivative, and also the nitrile **10**. The dehydrogenation of 1,2-dialkylpiperidines to 2-piperidenes with mercuric acetate has been developed by Leonard and co-workers[9] as a standard and generally reliable procedure, and we had counted on this reaction to provide the necessary double bond in **1**. No unsaturated amines were detected, however, in the products of **10** or **11a** after treatment with mercuric acetate under a variety of conditions. As much as 80% of the theoretical quantity of mercurous acetate was obtained,

CHART I



but a substantial amount of the starting amine was recovered, indicating that oxidation proceeded beyond the enamine stage. Since the very selective mercuric acetate was the reagent of choice for this dehydrogenation, the use of other oxidants appears to hold little promise, and further efforts may require an entirely different approach to the enamine system.

With the amine **11a** in hand, demethylation and conversion to the indole **12** was carried out since this compound was of interest as an analog of bufotenine or a tricyclic fragment of the ergoline system. The only other 3-(1-methyl-2-piperidyl)methylindole that has been described is the deoxy counterpart of **12**.[10] Demethylation of **11a** was accomplished with refluxing hydrobromic acid and the amorphous dihydroxydiamine dihydrobromide **11b** was oxidized with ferricyanide. The 5-hydroxyindole was obtained in 35% yield and characterized by typical picrate and oxalate derivatives and the similarity in properties to those of bufotenine. Preliminary pharmacological evaluation of **12** revealed no central nervous system stimulation in mice comparable with that elicited by bufotenine, nor does the compound antagonize or potentiate the effects of intravenous tryptamine.[11]

The formation of **12** from **11b** is a direct extension of the very effective bufotenine synthesis of Harley-Mason,[8] who has shown in a series of studies[12-14] that the cyclization of β-(2,5-dihydroxyphenyl)ethylamines occurs exclusively by 1,2-addition to the quinone system, leading to the 5-hydroxyindole. A similar discrimination is observed in the formation of 5-hydroxyindoles in the Nenitzescu condensation of quinones and β-aminocrotonic esters.[15] It was also found[8] that the oxidation of the diamine **13** gave serotonin (**14**) and no detectable amounts of quinoline products arising by cyclization of the γ-aminopropyl chain.

(6) The numbering used, indicated in **2**, is that suggested by Jacobs and Gould [*J. Biol. Chem.*, **120**, 142 (1937)] for the ergoline nucleus. It seems appropriate to retain this nonsystematic numbering with ergoline or lysergic acid names; this practice has been consistently followed in the past. Systematic numbering would be used with names based on indolo[4,3-*f,g*]quinoline.

(7) B. R. Baker, *et. al.*, *J. Org. Chem.*, **17**, 53 (1952).

(8) J. Harley-Mason and A. H Jackson, *J. Chem. Soc.*, 1165 (1954).

(9) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(10) A. M. Akkermann and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954).

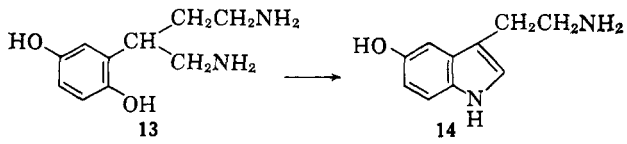
(11) We thank the Upjohn Co., Kalamazoo, Mich., for these tests.

(12) F. I. T. Cromartie and J. Harley-Mason, *J. Chem. Soc.*, 2525 (1952).

(13) J. Harley-Mason, *ibid.*, 200 (1953).

(14) J. Harley-Mason, Special Publication No. 3, The Chemical Society, London, 1953.

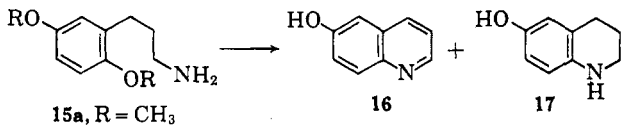
(15) R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951).



13 14

In planning the projected ring closure of **1**, it was of interest to examine the possibility of cyclization of a γ-(2,5-dihydroxyphenyl)propylamine, and to determine the direction of ring closure, *i.e.*, 1,2-addition to the quinone carbonyl, or 1,4-addition at the double bond. To this end the dimethoxyamine **15a** was prepared by a standard sequence from 2,5-dimethoxyhydrocinnamic acid and cleaved to the dihydroxyamine salt **15b**.

Successful oxidation of this amine required conversion to the chloride, very limited reaction time, and rapid extraction of the product. In this way a 43% yield of crystalline basic product was obtained. Paper chromatography showed the presence of two components, and separation was effected by chromatography on silica gel (alumina caused extensive decomposition). Two amphoteric compounds were obtained in nearly equal amounts: these were identified as 6-hydroxyquinoline (**16**) and 6-hydroxy-1,2,3,4-tetrahydroquinoline (**17**)[17] by direct comparison with authentic samples.



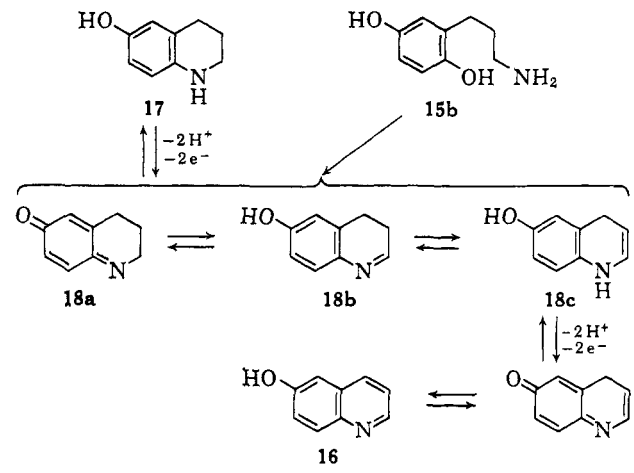
15a, R = CH_3
b, R = H

16 17

The isolation of **16** *and* **17** *established that the cyclization occurred by attack of the amino group at 2-carbonyl position of the quinone, paralleling the behavior of the phenethylamines. There was no evidence of the formation of 5,8-dihydroxytetrahydroquinoline, which would arise from conjugate addition, although it is possible that decomposition products of this compound were present in the noncrystalline fraction of the reaction mixture.* As expected, treatment of **15b** with 2 molar equiv. of ferricyanide gave only the 6-hydroxyquinoline **16**. Moreover, the tetrahydro compound **17** was smoothly converted to **16** with excess ferricyanide.

The initial product of the oxidation of **15b** must be the 3,4-dihydroquinoline **18**, which produces **16** and **17** by disproportionation. This behavior is characteristic of 1,2-dihydroquinolines[18,19] and presumably other double-bond isomers as well. The 6-hydroxydihydroquinoline is a special case, however, since, in its various tautomeric forms **18a–c**, the compound can be considered as simultaneously the reduced and oxidized forms of two aminophenol–quinoneimine couples. The facile dehydrogenation of **17** by ferricyanide and preliminary polarographic data are consistent with this view. The quinoline **16** gave an irreversible reduction wave (E *vs.* S.C.E.: −1.13 v. at pH 3.6, −1.33 v. at pH 6.9, −1.424 v. at pH 9.2); **17** gave a reversible two-electron oxidation wave (E *vs.* S.C.E.: −0.036 v. at pH 6.9 and −0.212 v. at pH 9.2).[20] (See Chart II.)

CHART II



17 15b 18a 18b 18c 16

Experimental

Melting points were determined on a Fisher-Johns apparatus with calibrated thermometer. Infrared spectra of solid compounds were obtained in KBr pellets on a a Perkin-Elmer Model 130 Infracord spectrophotometer.

2-(1-Benzoyl-2-piperidyl)-2′,5′-dimethoxyacetophenone (5).—1-Benzoyl-2-piperidineacetyl chloride was prepared by treatment of 10 g. of 1-benzoyl-2-piperidineacetic acid[7] (m.p. 147–148°) with 9 g. of PCl_5 and 50 ml. of acetyl chloride. After a clear solution was obtained the acetyl chloride was evaporated *in vacuo* and toluene was then added twice and removed by distillation at 50°. The resulting yellow oil was dissolved in 25 ml. of nitrobenzene and added during 20 min. to a solution of 21.1 g. of $AlCl_3$ and 10.9 g. of *p*-dimethoxybenzene in 75 ml. of nitrobenzene kept at 5–10°. After 4 hr. the color changed from orange to green and the reaction mixture was then poured into iced HCl. The mixture was extracted with $CHCl_3$ and the $CHCl_3$ solution was washed with HCl and Na_2CO_3 solutions and steam distilled. (Acidification of the carbonate solution gave 2.0 g. of 2-piperidineacetic acid.) The gummy residue from the distillation was chromatographed in benzene solution on 420 g. of alumina. Early fractions eluted with benzene contained a total of 420 mg. of 2,2′,5,5′-tetramethoxybiphenyl (**6**): melting point after recrystallization from EtOH, 102° (lit.[21] m.p. 105°); n.m.r. (CCl_4, Me_4Si = 0), two sharp peaks, 3.68 and 3.73 (twelve OMe protons combined) and one sharp peak at 6.87 p.p.m. (six aryl protons).

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 69.43; H, 6.59. Found: C, 69.40; H, 6.44.

Fractions eluted from the column with C_6H_6–$CHCl_3$ (4:1) contained crystalline solid; after recrystallization from ether, 6.2 g. (49% based on acid not recovered) of the amino ketone **5**, m.p. 87–88°, λ^{KBr} 6.02 μ, was obtained.

Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.92; H, 6.77; N, 3.88.

The **oxime** of **5** was prepared in the usual way and recrystallized from ethanol–water; the melting point was 169–171°.

Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.66; H, 6.72; N, 7.22.

Reduction of the ketone **5** with $NaBH_4$ in ethanol to the carbinol (λ^{neat} 2.88 μ) and conversion of this derivative to the chloride with $SOCl_2$ were carried out, but both of these products were colorless oils after chromatography on alumina, and they were not further characterized.

2,5-Dimethoxybenzyl Chloride.—This compound has been prepared previously[8] from the benzyl alcohol and by chloromethylation.[22] Since details of the latter preparation are not available, and the usual procedures[23] lead to extensive disubstitution, the method is described.[24]

(16) Z. Skraup, *Monatsh.*, **3**, 549 (1882).
(17) C. J. Cavallito and T. H. Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).
(18) W. P. Neumann, *Ann.*, **618**, 90 (1958).
(19) G. M. Badger, *et al.*, *Australian J. Chem.*, **16**, 814 (1963).
(20) We are greatly indebted to Mr. Harry F. Bell and Professor W. H. McCurdy, Jr., for these data.
(21) T. Posternak, W. Alcalay, R. Luzzati, and A. Tardent, *Helv. Chim. Acta*, **31**, 525 (1948).
(22) K. Hejno and Z. Arnold, *Chem. Listy*, **47**, 601 (1953).
(23) R. C. Fuson and C. H. McKever, *Org. Reactions*, **1**, 63 (1942).
(24) We wish to thank Mr. Donald Monaco for developing this method.

A stirred solution of 55 g. of *p*-dimethoxybenzene in 100 ml. of benzene and 200 ml. of concentrated HCl was saturated with hydrogen chloride. With a slow stream of HCl, 30 g. of formalin solution (37%) was added *dropwise* during *1 hr.* with intermittent cooling in an ice bath. The HCl stream was then increased and the mixture was stirred for 1 hr.; the temperature rose to 55°. The mixture was then extracted with benzene and the benzene layer was washed with water and $NaHCO_3$, dried, and evaporated. Recrystallization of the solid residue from heptane gave 45 g. (61%) of colorless crystals, m.p. 69–70° (lit.[8] m.p. 70–72°). Note: One of us experienced a very severe allergic-type reaction to this compound, with extensive dermatitis and edema.

2,5-Dimethoxyphenylacetonitrile, m.p. 52–53° (lit.[8] m.p. 52–53°), was obtained in 98% yield from the reaction of the dimethoxybenzyl chloride with NaCN in dimethyl sulfoxide according to the procedure of Friedman and Schechter.[25] Yields of 30% were obtained by the earlier procedure[8] using aqueous ethanol.

2-Piperidinemethanol (7).—A solution of 43 g. of 2-pyridinecarboxaldehyde in 1.12 l. of ethanol was cooled in ice and treated with 15.2 g. of $NaBH_4$. After 30 min. the solution was heated to boiling and 120 g. of sodium was added in walnut-sized pieces, as rapidly as possible. (*Safety precaution:* This reduction was carried out in a 5-l. flask equipped with two large-capacity, water-cooled bulb condensers. It is important for optimum yield to maintain as vigorous and rapid reaction as the capacity of the condensers permit, with vigorous shaking, cooling in an ice bath when foaming becomes excessive. Asbestos mittens and protective head covering are recommended.) After the addition of sodium the very thick solution was refluxed for 30 min., cooled, and diluted with 400 ml. of water. The solution was distilled, with addition of water as needed, until all alcohol had been removed, and then continuously extracted with ether. From the ether solution, 16 g. (35%) of **7** was obtained as a white solid, m.p. 67–68° (lit.[26] m.p. 67–69°).

1-Methyl-2-piperidinemethanol, b.p. 74° at 2.5 mm. (lit.[27] b.p. 90–92° at 15 mm.), was obtained in 73% yield by hydrogenation of 11 g. of the above base and 24 ml. of 38% formalin solution in 100 ml. of ethanol containing 1 g. of sodium acetate, using 1.1 g. of 10% palladium–charcoal catalyst.

1-Methyl-2-piperidinemethyl Chloride Hydrochloride.—Following the procedure described by Feldkamp, *et al.*,[27] for the 3-methyl chloride, 9.4 g. of 1-methyl-2-piperidinemethanol in $CHCl_3$ solution was treated with hydrogen chloride and then 34 g. of thionyl chloride. After the removal of excess $SOCl_2$ and $CHCl_3$, evaporation with ethanol followed by addition of ether gave 11.7 g. (87%) of the hydrochloride as hygroscopic white crystals, m.p. 162–164°.

2-(2,5-Dimethoxyphenyl)-3-(1-methyl-2-piperidyl)propionitrile (10).—A benzene solution of 1-methyl-2-piperidinemethyl chloride was prepared by addition of excess NaOH to an aqueous solution of 20 g. of the hydrochloride and extraction with three 30-ml. portions of benzene. After drying over K_2CO_3 the solution was mixed with a solution of 19.2 g. of 2,5-dimethoxyphenylacetonitrile in 50 ml. of benzene. Sodium amide, 4.7 g., was added in small portions to the stirred solution during 15 min. at 30°. After refluxing for 2 hr. the solution was washed with water, dried, and evaporated; the residue was distilled to give 19.6 g. (63%) of **10** as a viscous yellow oil, b.p. 150–156° at 0.3 mm., λ^{neat} 4.40 μ.

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.45; H, 8.29; N, 9.56.

2-(2,5-Dimethoxyphenyl)-3-(1-methyl-2-piperidyl)propylamine (11a).—The nitrile **10**, 2.0 g., was reduced with 0.5 g. of lithium aluminum hydride in ether solution. After refluxing for 4 hr., water was added and the precipitated hydroxides were filtered and washed with ether. The combined ether layer was washed, dried, and concentrated to give 1.9 g. (93%) of the amine **11a** as a viscous oil. A sample was subjected to molecular distillation for analysis.

Anal. Calcd. for $C_{17}H_{28}N_2O_2$: C, 69.82; H, 9.65; N, 9.58. Found: C, 69.36; H, 9.66; N, 8.88.

5-Hydroxy-3-[(1-methyl-2-piperidyl)methyl]indole (12).—The dihydroxyamine **11b** was prepared by refluxing a solution of 1.5 g. of the dimethyl ether **11a** in 8 ml. of 48% hydrobromic acid for 45 min. and then evaporating under reduced pressure. The residue was dried to constant weight over P_2O_5 to give 2.5 g. (95%) of the dihydrobromide as an amber glass.

To a solution of 850 mg. of this amorphous salt in 25 ml. of water was added during 5 min. a solution of 1.36 g. of potassium ferricyanide and 0.68 g. $NaHCO_3$ in 25 ml. of water. After stirring for 20 min. a small amount of sodium dithionite was added and the inorganic material was removed by filtration. The filtrate was continuously extracted with ether for 2 days; the tan residue from the ether solution was sublimed to give 170 mg. (35%) of the indole **12** as a colorless solid, m.p. 233–235°. Recrystallization from methanol gave prisms: m.p. 236–237°; λ_{max}^{EtOH} 223 mμ (ϵ 26,700), 280 (7200), and 302 (5700); λ^{KBr} 3.05, 8.10, 9.55, 9.76, and 10.68 μ.

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.64; H, 8.28; N, 11.41.

The compound gave a red color with $FeCl_3$ and a magenta Ehrlich reaction. The R_f values on Whatman No. 1 paper for bufotenine and **12** were 0.53 and 0.69, respectively, in MEK–$(CH_3)_2CO$–HCO_2H–H_2O (40:2:1:6),[28] and 0.59 and 0.66 in *n*-BuOH–H_2O–AcOH (4:5:1).

The **picrate** was obtained as red-orange crystals, m.p. 156–158°, from ethanol solution.

Anal. Calcd. for $C_{21}H_{24}N_5O_8$: C, 53.28; H, 4.90; N, 14.79. Found: C, 53.58; H, 5.22; N, 14.73.

2,5-Dimethoxycinnamic acid,[29] β-(2,5-dimethoxyphenyl)propionic acid,[29] and **β-(2,5-dimethoxyphenyl)propionamide**, m.p. 110° (lit.[30] m.p. 111°), were prepared by published methods.

γ-(2,5-Dimethoxyphenyl)propylamine (15a).—The amide (18.5 g.) was extracted from a Soxhlet thimble into a solution of 6.7 g. of lithium aluminum hydride in 600 ml. of ether over a period of 34 hr. The reaction mixture was then treated with water and the ether solution was washed, dried, and concentrated; 2.4 g. of unreacted amide crystallized. The residue was distilled to give 10.1 g. (56%) of the dimethoxy amine **15a**, b.p. 119–120° (0.50 mm.), λ^{neat} 2.82 and 2.95 mμ.

The picrate was prepared for analysis and crystallized from methanol; the melting point was 195–197°.

Anal. Calcd. for $C_{17}H_{20}N_4O_9$: C, 48.11; H, 4.75. Found: C, 48.13; H, 4.83.

Oxidation of γ-(2,5-Dihydroxyphenyl)propylamine.—The dimethoxyamine was demethylated by refluxing for 45 min. with concentrated HBr; the crude hydrobromide was obtained as a hygroscopic brown glass.

A solution of 500 mg. (2.0 mmoles) of the hydrobromide was shaken for 30 min. with freshly precipitated AgCl and the filtered solution of the hydrochloride was treated with a solution of 0.55 g. of $NaHCO_3$ and 1.3 g. (3.95 mequiv.) of $K_3Fe(CN)_6$ in 15 ml. of water. The ferricyanide solution was added in one portion and as soon as CO_2 evolution diminished (4 min.) the solution was extracted with methylene chloride. The dried methylene chloride solution was evaporated to an amorphous residue which was sublimed to give 140 mg. of nearly colorless solid with a wide melting point range. Thin layer chromatography on silica gel (*n*-BuOH–AcOH–H_2O, 4:1:5) showed two ultraviolet absorbing spots of approximately equal intensity.

The mixture was separated on a silica gel column. Crystallization of fractions eluted with 0.6% MeOH in CH_2Cl_2 gave 75 mg. of white solid, m.p. 158–160°, $\lambda_{max}^{0.1\ N\ HCl}$ 237 mμ (5600) and 296 (9200), pK_A 5.6.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.34; H, 7.61. N, 9.35.

The **picrate** was recrystallized from methanol, m.p. 195–196°.

Anal. Calcd. for $C_{15}H_{14}N_4O_8$: C, 47.62; H, 3.73; N, 14.81. Found: C, 47.92; H, 3.88; N, 15.28.

The compound was soluble in dilute aqueous acid or base and gave a red $FeCl_3$ color. Benzoylation by the Scotten–Baumann procedure gave colorless crystals, m.p. 247–248°. The base was identified as 6-hydroxy-1,2,3,4-tetrahydroquinoline (**17**) (lit.[17] m.p. 160°; benzoyl derivative, m.p. 248°) by direct comparison (mixture melting point gave no depression) with a sample prepared by hydrogenation (palladium–charcoal) of 6-hydroxyquinoline.

Further elution of the column with 2% MeOH in CH_2Cl_2 removed a solid which was recrystallized from methanol–benzene to

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give 65 mg. of 6-hydroxyquinoline (**16**): m.p. 191–192° (lit.[16] m.p. 193°); $\lambda_{max}^{0.1\ N\ HCl}$ 246 mμ (ε28,000), 313 (4400), and 341 (3700); $\lambda_{max}^{pH\ 7}$ 226 mμ (ε 31,000), 273 (2800), and 326 (3650); $\lambda_{max}^{0.1\ N\ NaOH}$ 244 mμ (ε 37,000) and 358 (4600); pK_A 4.05 and 8.9; infrared identical with an authentic sample.

The **picrate** was crystallized from methanol, m.p. 234–235° (lit.[16] m.p. 235–236°).

Oxidation of 6-Hydroxy-1,2,3,4-tetrahydroquinoline.—A solution of 75 mg. of **17** in 4 ml. of water was added in one portion to a solution of 138 mg. of $NaHCO_3$ and 1.95 g. of $K_3Fe(CN)_6$ in 4 ml. of water. The orange solution turned green after 2 min.; after 4 min. the mixture was extracted with methylene chloride. The methylene chloride solution was treated with $MgSO_4$ and charcoal, and evaporated to a solid residue. Crystallization from ethanol gave 60 mg. (84%) of **16**, m.p. and m.m.p. 190–192°.

Acknowledgment.—We wish to thank Dr. J. M. Vandenbelt and Mrs. Carola H. Spurlock, Parke, Davis, and Company, for the ultraviolet and titration data.

Cyclodehydration Reactions of Tryptamine Derivatives with Acetone

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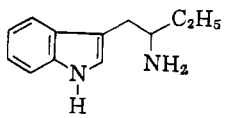
Received April 27, 1964

Crystallization of the creatinine sulfate salt of 3-(2-aminobutyl)-6-hydroxyindole (I) from acetone–water resulted in the formation of 1,1-dimethyl-3-ethyl-7-hydroxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (III). Other 3-(2-aminoethyl)indoles with oxygen substituents at C-6 (but not at C-5) were also found to condense with acetone under similar mild conditions. A study of the cyclodehydration reactions of several 3-(2-aminoethyl)-indoles with acetone has demonstrated that oxygen substituents at C-6 of the indole nucleus enhance the nucleophilicity of C-2. A general method for preparing 1,1-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indoles is described. Implications of this activation process to carboline formation in biological systems are discussed.

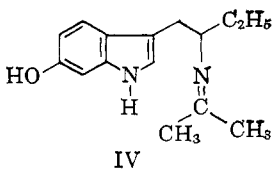
During the preparation of 3-(2-aminobutyl)-6-hydroxyindole (I),[1] a product of the human metabolism of 3-(2-aminobutyl)indole (etryptamine, II),[2] we had



II

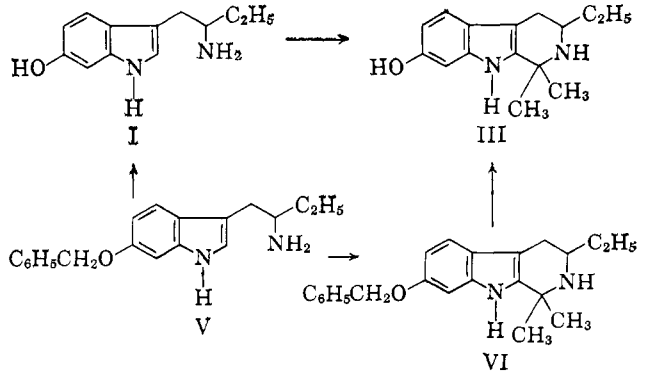
occasion to crystallize the creatinine sulfate salt of I from a mixture of acetone and water, a solvent system from which the corresponding salt of the natural product serotonin had previously been crystallized.[3] On several occasions the product isolated from this crystallization was not the creatinine sulfate salt of I, but of a new compound for which we propose structure III. Preliminary evidence for this structure was provided by analyses of the creatinine sulfate salt and by a negative Ehrlich's test which indicated that both the 2- and 3-positions of the indole nucleus were substituted. Further investigation of this material was carried out on the free base which was liberated from the salt with dilute ammonium hydroxide.

Both the nuclear magnetic resonance[4b] and the infrared spectra supported structure III. In particular the infrared spectrum demonstrated the absence of an imine (*viz.*, structure IV) which would be expected to



IV

absorb at 1665 cm.$^{-1}$ (*vide infra*). The *gem*-dimethyl system of III was represented in the n.m.r. spectrum by a doublet with peaks at 82.6 and 80.2 c.p.s. The aromatic region of this spectrum was easily recognized as the ABX system of a 1,2,4-trisubstituted benzene.[5a] It was possible to assign all of the peaks in this region to the three aromatic hydrogens of III in the following manner: H-5, a doublet centered at 426 c.p.s. (apparent J = 8 c.p.s.); H-6, a pair of doublets centered at 388 c.p.s. (apparent J = 2 and 8 c.p.s.); H-8, a doublet centered at 401 c.p.s. (apparent J = 2 c.p.s.). This spectrum thus demonstrated the absence of an aromatic hydrogen at C-2. Ultimately compound III was obtained by an alternate synthesis: 3-(2-aminobutyl)-6-benzyloxyindole hydrochloride (V) readily condensed with acetone at room temperature in a pH 4.7 acetate buffer to yield VI which was converted to III by a palladium-catalyzed hydrogenolysis. The *gem*-dimethyl system of VI gave a singlet at 84 c.p.s. in the n.m.r. spectrum.[4a,5b]



I III V VI

Although the cyclodehydration reaction of 3-(2-aminoethyl)indoles with aldehydes and pyruvic acid

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(4) The n.m.r. spectra were determined at 60 Mc. in one of the following solvents: (a) deuteriochloroform, (b) deuteriodimethyl sulfoxide, or (c), deuteriodimethylformamide. The peaks are reported in cycles per second downfield from tetramethylsilane.

(5) (a) The splitting pattern for the aromatic hydrogens in this spectrum was similar to that recorded for the 2,4-dinitrophenylhydrazone of acetone in the "Varian N.M.R. Spectra Catalog," N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, Ed., Varian Associates, Palo Alto, Calif., 1962, Spectrum 233. (b) When the n.m.r. spectrum of VI was run in deuteriodimethyl sulfoxide, the *gem*-dimethyl system gave two peaks at 83.7 and 81.3 c.p.s.