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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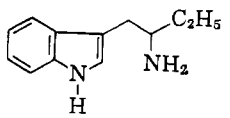
Crystallization of the creatinine sulfate salt of 3-(2-aminobutyl)-6-hydroxyindole (I) from acetone–water resulted in the formation of 1,1-dimethyl-3-ethyl-7-hydroxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (III). Other 3-(2-aminoethyl)indoles with oxygen substituents at C-6 (but not at C-5) were 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.

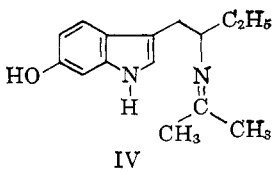
During the preparation of 3-(2-aminobutyl)-6-hydroxyindole (I),[1] a product of the human metabolism of 3-(2-aminobutyl)indole (etryptamine, II),[2] we had



II

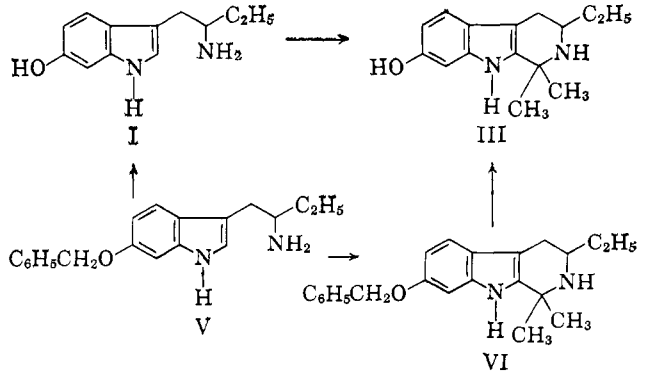
occasion to crystallize the creatinine sulfate salt of I from a mixture of acetone and water, a solvent system from which the corresponding salt of the natural product serotonin had previously been crystallized.[3] On several occasions the product isolated from this crystallization was not the creatinine 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

(1) J. B. Hester, Jr., M. E. Greig, W. C. Anthony, R. V. Heinzelman and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 274 (1964).

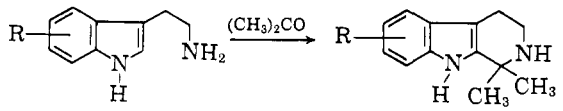
(2) F. S. Eberts, Jr., and E. G. Daniels, *Federation Proc.*, **21**, 180 (1962).

(3) M. E. Speeter, R. V. Heinzelman, and D. I. Weisblat, *J. Am. Chem. Soc.*, **73**, 5514 (1951).

(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.

derivatives to form 2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indoles has been known for many years,[6] the analogous reaction of 3-(2-aminoethyl)indoles with unactivated ketones has not been described in the literature. Since a possible explanation for the observed condensation was the mesomeric contribution of the C-6 oxygen substituent to the nucleophilicity of C-2 (*vide infra*), it was of interest to investigate this reaction with three 3-(2-aminoethyl)indoles which differed only in the substitution in the benzene ring.[7a] We thus investigated the condensation of acetone with compounds VII, VIII and IX. It was found that under the mild conditions

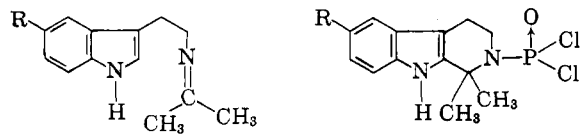


VII, R = 6-OCH_3
VIII, R = 5-OCH_3
IX, R = H

X, R = 7-OCH_3
XI, R = 6-OCH_3
XII, R = H

previously described (*vide supra*) 3-(2-aminoethyl)-6-methoxyindole (VII) yielded 92.5% of the expected condensation product (X). Amines VIII and IX yielded none of the analogous condensation products and could be recovered in moderate yield from the reaction mixture.

Compounds XI and XII have been prepared by the three-step synthesis described below for 1,1-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (XII). *p*-Toluenesulfonic acid catalyzed condensation of 3-(2-aminoethyl)indole (IX) with acetone in refluxing benzene yielded the Schiff base (XIII). This compound

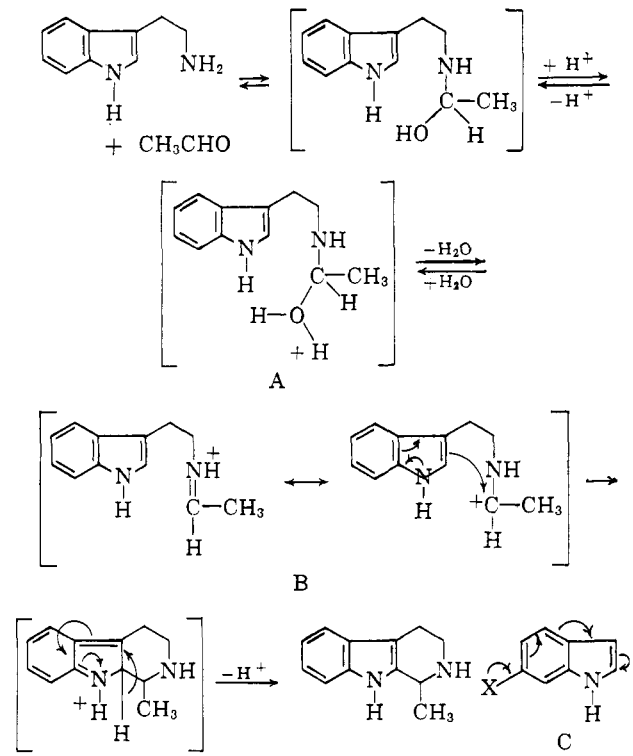


XIII, R = H
XIV, R = CH_3

XV, R = H
XVI, R = OCH_3

had the expected C=N absorption at 1665 cm.$^{-1}$ in the infrared; the n.m.r. spectrum[4a] had two signals at 103 and 121 c.p.s. which corresponded to the two methyl groups of the *gem*-dimethyl system. A difference in chemical shielding of the two methyl groups in this case was not unexpected since a similar splitting had been observed for the analogous *gem*-dimethyl system of the 2,4-dinitrophenyl hydrazone of acetone.[5a] Reaction of Schiff base XIII with phosphorus oxychloride in refluxing benzene yielded the phosphoramidic dichloride (XV) which could be either isolated or converted directly to the amine (XII) by warming the crude product with water. The n.m.r. spectrum[4a] of XV and XII had signals at 117 and 86 c.p.s., respectively, which corresponded to the *gem*-dimethyl groups. An interesting splitting pattern was observed for the C-3

SCHEME I



and C-4 hydrogens of XV. Instead of the pair of triplets centered at 161 and 191 c.p.s. (apparent J = 6 c.p.s.) which were found for the amine XII, compound XV had a quintet centered at 217 c.p.s. and a triplet centered at 172 c.p.s. (apparent J = 5 c.p.s.). It is probable that the quintet is the result of the spin–spin coupling of phosphorus with the C-3 hydrogens to give a pair of partially superimposed triplets (apparent J = 10 c.p.s.).[7b]

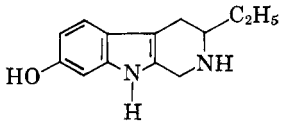
The generally accepted mechanism[6] for the Pictet–Spengler reaction is illustrated above (Scheme I) for the condensation of 3-(2-aminoethyl)indole with acetaldehyde. Since the final irreversible stage of this reaction must be accomplished by the condensation of the nucleophilic indole 2-position with the electrophilic carbon of the protonated species (A or B), substituents on the indole nucleus which are able to influence the nucleophilicity of C-2 would be expected to influence the relative ease of reaction. In particular, it may be seen (C) that substituents at C-6 should be able to exert a mesomeric influence on C-2 analogous to that of *para* substituents on the benzene ring. Electron-donating substituents at C-6 would be expected to increase the electron density at C-2 and thus facilitate the Pictet–Spengler condensation. That the observed reaction of 6-methoxy-3-(2-aminoethyl)indole was not the result of a purely inductive effect was demonstrated by the fact that a 5-methoxy substituent did not promote the cyclodehydration reaction with acetone. Reasoning similar to that advanced for C-6 substituents allows one to predict that C-4 substituents would produce electronic effects at C-2 analogous to those of *ortho* benzene substituents without the concomitant steric interactions.

It is possible that the enhanced nucleophilicity of the 2-position of indole nuclei which have oxygen substituents at C-6 may have important physiological implications especially since many indoles [*viz.*, 3-(N,N-di-

(6) This is the well-known Pictet–Spengler reaction which has been reviewed by W. M. Whaley and T. R. Govindachari [*Org. Reactions*, **6**, 151 (1951)].

(7) (a) Indole substituent effects have been studied by Y. Otsuji and H. H. Jaffé, Abstracts, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960, p. 76O; A. N. Hall, J. A. Leeson, H. N. Rydon, and J. C. Tweedle, *Biochem. J.*, **74**, 209 (1960); M. S. Melzer, *J. Org. Chem.*, **27**, 496 (1962). (b) It has been reported that phosphorus and hydrogen of a P–N–C–H system have a coupling constant of 10–15 c.p.s. by L. C. D. Groenweghe, L. Maier, and K. Moedritzer, *J. Phys. Chem.*, **66**, 901 (1962); N. Muller, P. C. Lauterbur, and J. Goldenson, *J. Am. Chem. Soc.*, **78**, 3557 (1956).

methyl-2-aminoethyl)indole,[8] 3-(N,N-diethyl-2-aminoethyl)indole,[9] 3-(2-aminopropyl)indole,[10] and 3-(N-acetyl-2-aminoethyl)-5-methoxyindole[11]] are metabolized by 6-hydroxylation. In particular it has been found that 7-hydroxy-3-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (XVII) is an important human metabolite of 3-(2-aminobutyl)indole[12] (II). It is probable that XVII is formed *in vivo* by the condensation



XVII

of 3-(2-aminobutyl)-6-hydroxyindole (I), the major etryptamine metabolite with a precursor of formaldehyde. The preparation of XVII from 3-(2-aminobutyl)-6-benzyloxyindole hydrochloride (V) by standard chemical means is described in the Experimental section.

Experimental

Melting points were taken in a capillary tube and are corrected. Ultraviolet spectra were determined with a Cary spectrophotometer, Model 14. Infrared spectra were determined with a Perkin-Elmer recording infrared spectrophotometer, Model 421. Skellysolve B is commercial hexane, b.p. 60–70°, made by Skelly Oil Co., Kansas City, Mo. Florisil is a synthetic magnesia–silica gel manufactured by the Floridin Co., Tallahassee, Fla. Celite is a filter aid manufactured by Johns-Manville, New York 16, N.Y.

2,3,4,9-Tetrahydro-1,1-dimethyl-3-ethyl-7-hydroxy-1H-pyrido-[3 4-*b*]indole (III).—A solution of 4.41 g. (6.26 mmoles) of the sulfate salt of 3-(2-aminobutyl)-7-benzyloxyindole[1] in a mixture of 95% ethanol (280 ml.) and water (20 ml.) was treated with 4.0 g. of 10% palladium on carbon and hydrogenated at room temperature in a Parr apparatus for 1.5 hr. at an initial hydrogen pressure of 43 p.s.i. The catalyst was removed from the resulting mixture by filtration through Celite, and the filtrate was concentrated under nitrogen and reduced pressure. Creatinine sulfate (2.09 g., 6.45 mmoles) was added to the residue and the resulting mixture was dissolved in warm water. The solution was cooled, treated with acetone, and allowed to crystallize. The crystalline solid which resulted was collected by filtration and recrystallized twice from acetone–water to yield 2.77 g. (48.7%) of 2,3,4,-9-tetrahydro-1,1-dimethyl-3-ethyl-7-hydroxy-1H-pyrido[3,4-*b*]indole creatinine sulfate, m.p. 207–210° dec. The analytical sample, m.p. 223° dec., was prepared by recrystallizing some of this material several times from acetone–water. The ultraviolet spectrum (0.01 *N* aqueous acid) had λ_{max} 222, 267, and 293 mμ (ε 38,500, 4820, and 5120, respectively) with an inflection at 262 mμ (ε 4570).

Anal. Calcd. for $C_{19}H_{29}N_5O_6S$: C, 50.09; H, 6.42; N, 15.38; S, 7.04. Found: C, 50.42; H, 6.50; N, 15.10; S, 6.74.

An aqueous solution of 2,3,4,9-tetrahydro-1,1-dimethyl-3-ethyl-7-hydroxy-1H-pyrido[3,4-*b*]indole creatinine sulfate (200 mg., 0.440 mmole) was made ammoniacal. The solid which precipitated was collected by filtration, washed with water, and dried *in vacuo* to yield 59.0 mg. (54.9%) of 2,3,4,9-tetrahydro-1,1-dimethyl-3-ethyl-7-hydroxy-1H-pyrido[3,4-*b*]indole, m.p. 272–274° dec. A sample of this material was recrystallized from methanol–ethyl acetate for analysis, m.p. 266–269° dec. The ultraviolet spectrum (ethanol) had λ_{max} 225, 269, and 298 mμ (ε 35,150, 4450, and 5600, respectively).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.59; H, 8.15; N, 11.77.

2,3,4,9-Tetrahydro-7-benzyloxy-1,1-dimethyl-3-ethyl-1H-pyrido[3,4-*b*]indole (VI).—To a solution of 3-(2-aminobutyl)-6-benzyloxyindole hydrochloride[1] (591 mg., 1.79 mmoles) in a pH 4.7 acetate buffer (25 ml.) was added 45 ml. of acetone. The resulting solution was allowed to stand in the dark, at 25°, under nitrogen for 7 days. It was then concentrated under reduced pressure. An aqueous solution of the residue was made ammoniacal and extracted with ether. The crude product, obtained by concentrating this ether solution, was chromatographed on silica with ether. Crystallization of the product thus obtained from ether–Skellysolve B yielded 305 mg. (50.8%) of 2,3,4,9-tetrahydro-7-benzyloxy-1,1-dimethyl-3-ethyl-1H-pyrido[3,4-*b*]indole, m.p. 108–111°. The analytical sample, m.p. 103.5–111° was prepared by recrystallizing this material several times from ether–Skellysolve B. The ultraviolet spectrum (ethanol) had λ_{max} 228, 267, and 294 mμ (ε 39,400, 5150 and 5500, respectively).

Anal. Calcd. for $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38. Found: C, 78.75; H, 8.02; N, 8.05.

2,3,4,9-Tetrahydro-7-hydroxy-1,1-dimethyl-3-ethyl-1H-pyrido-[3,4-*b*]indole (III).—A mixture of 146 mg. (0.437 mmole) of 2,3,4,9-tetrahydro-7-benzyloxy-1,1-dimethyl-3-ethyl-1H-pyrido-[3,4-*b*]indole, 75 mg. of 10% palladium on carbon, and 25 ml. of 95% ethanol was allowed to hydrogenate for 18 min. at 741.7 mm. and 26°. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure and nitrogen. Crystallization of the residue from methanol–ethyl acetate yielded 27 mg. (25%) of 2,3,4,9-tetrahydro-7-hydroxy-1,1-dimethyl-3-ethyl-1H-pyrido[3,4-*b*]indole, m.p. 265–267° dec. The infrared spectrum (Nujol) of this material was identical with that of the base obtained by crystallizing 3-(2-aminobutyl)-6-hydroxyindole creatinine sulfate from acetone–water. When the melting point of the two pure bases were taken in sealed, evacuated capillaries, they were 276–277° dec. and 277–278° dec., respectively. The mixture melting point was undepressed.

3-(2-Isopropylideneaminoethyl)indole (XIII).—A mixture of 5.41 g. (33.8 mmoles) of tryptamine, 150 ml. of benzene, 15 ml. of acetone, and a small amount of *p*-toluenesulfonic acid was allowed to reflux gently under nitrogen with azeotropic distillation of water formed in the reaction. After 2 hr. the clear reaction mixture was cooled and allowed to stand at room temperature for 18 hr. It was then concentrated under reduced pressure and the residue was dissolved in ethyl acetate and filtered through a little anhydrous potassium carbonate. Concentration of the filtrate under reduced pressure at 25° yielded two crops: 3.94 g., m.p. 141.5–144°, and 0.748 g., m.p. 139–143.5° (69.4% total yield) of the Schiff base. Some of this material was decolorized with Florisil and recrystallized three times from acetone for analysis, m.p. 142.5–145°. The ultraviolet spectrum (ethanol) had λ_{max} 221, 275, 281, and 289 mμ (ε 34,050, 5650, 6000, and 5150, respectively). The infrared spectrum (Nujol) showed NH, 3125, and C=N, 1665 $cm.^{-1}$.

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.53; H, 7.88; N, 14.26.

1,3,4,9-Tetrahydro-1,1-dimethyl-2H-pyrido[3,4-*b*]indol-2-yl-phosphoramidic Dichloride (XV), 2,3,4,9-Tetrahydro-1,1-dimethyl-1H-pyrido[3,4-*b*]indole (XII), and 2,3,4,9-Tetrahydro-1,1-dimethyl-1H-pyrido[3,4-*b*]indole Cyclohexane Sulfamate.—A mixture of 700 ml. of benzene, 70 ml. of acetone, 20.0 g. (0.125 mole) of tryptamine, and a small amount of *p*-toluenesulfonic acid was allowed to reflux, under nitrogen for 3 hr. with azeotropic distillation of water. It was then cooled and filtered through anhydrous potassium carbonate. Concentration of the filtrate under reduced pressure yielded a white, crystalline solid which was suspended in 400 ml. of dry benzene and treated with 40 ml. of freshly distilled phosphorus oxychloride. The mixture was allowed to remain at room temperature for 70 min. and was then warmed slowly to the reflux temperature and refluxed for 1 hr. Concentration of the mixture under reduced pressure and nitrogen yielded a dark oil. Last traces of phosphorus oxychloride were removed by azeotropic distillation with benzene. The residue was treated with 500 ml. of water and warmed briefly on the steam bath. Much of the gummy material went into solution. The solid residue was collected by filtration and dissolved in methylene chloride. The methylene chloride solution was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. A solution of the residue in ethyl acetate was filtered through Florisil and crystallized to yield 9.60 g. (24.2%) of 1,3,-4,9-tetrahydro-1,1-dimethyl-2H-pyrido[3,4-*b*]indol-2-ylphosphoramidic dichloride, m.p. 192–202°.

The analytical sample, m.p. 195–198°, was prepared by recrystallizing this material from ethyl acetate. The ultraviolet spectrum (ethanol) had λ_{max} 223, 273, 280, and 289 mμ (ε 39,800,

(8) S. Szara and J. Axelrod, *Experientia*, **15**, 216 (1959).
(9) S. Szara, E. Hearst, and F. Putney, *Federation Proc.*, **19**, 23 (1960).
(10) S. Szara, *Experientia*, **17**, 76 (1961).
(11) S. Kveder and W. M. McIsaac, *J. Biol. Chem.*, **236**, 3214 (1961).
(12) F. S. Eberts, Jr., and E. G. Daniels, results to be published.

7640, 7660, and 6340, respectively). The infrared spectrum (Nujol) showed NH, 3315, and P=O, 1256 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{15}Cl_2N_2OP$: C, 49.23; H, 4.77; Cl, 22.36; N, 8.84. Found: C, 49.43; H, 5.01; Cl, 22.66; N, 8.47

The aqueous filtrate, from which the crude phosphoramidic dichloride was isolated, was decolorized with activated charcoal, made ammoniacal, and extracted with ether. The ether extracts were dried over anhydrous potassium carbonate and concentrated under reduced pressure. An ethyl acetate solution of the residue was acidified with methanolic hydrogen chloride. Tryptamine hydrochloride rapidly crystallized from the dark solution, yielding 4.49 g. (18.3%), m.p. 252–254°. The dark mother liquors from this crystallization were concentrated; the residue was dissolved in water, decolorized with activated charcoal, and treated with ammonium hydroxide. In this manner a crystalline base was obtained. It was collected by filtration, washed with water, and dried *in vacuo* to yield 6.72 g. (26.9%) of 2,3,4,9-tetrahydro-1,1-dimethyl-1H-pyrido[3,4-*b*]indole, m.p. 75–112°. Purification of this material was effected by chromatography on 350 g. of silica with 50% ether–chloroform. A sample of the base obtained in this manner was dissolved in acetone, decolorized with activated carbon, and crystallized three times from acetone–water for analysis, m.p. 111.5–115.5°. The ultraviolet spectrum (ethanol) had λ_{max} 224, 281, and 289 mμ (ε 30,950, 6200, and 5200, respectively) with an inflection at 274 mμ (ε 5950).

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 77.62; H, 7.98; N, 13.39 and 13.38.

Most of the product (XII) was isolated as the cyclohexane sulfamic acid salt which was crystallized from ethanol yielding 6.86 g., m.p. 234–236° dec. A sample of this material was recrystallized from ethanol and dried at 100° for analysis, m.p. 237–239° dec. The ultraviolet spectrum (ethanol) had λ_{max} 221, 270, 277.5, and 288 mμ (ε 36,000, 6900, 6700, and 5300, respectively) with an inflection at 280 mμ (ε 6600).

Anal. Calcd. for $C_{19}H_{29}N_3O_3S$: C, 60.13; H, 7.70; N, 11.07; S, 8.45. Found: C, 59.89; H, 7.48; N, 10.52; S, 8.07.

1,3,4,9-Tetrahydro-6-methoxy-1,1-dimethyl-2H-pyrido[3,4-*b*]indol-2-ylphosphoramidic Dichloride (XVI) and 2,3,4,9-Tetrahydro-6-methoxy-1,1-dimethyl-1H-pyrido[3,4-*b*]indole (XI).—A stirred mixture of 5.00 g. (26.3 mmoles) of 5-methoxytryptamine, 200 ml. of benzene, 20 ml. of acetone, and a small amount of *p*-toluenesulfonic acid was allowed to reflux under nitrogen with azeotropic distillation of water for 3.5 hr. The cooled mixture was treated with potassium carbonate and filtered. Concentration of the filtrate under reduced pressure yielded a tan oil (6.3 g.) which was dissolved in 150 ml. of dry benzene, treated with 15 ml. of freshly distilled phosphorus oxychloride, and refluxed under nitrogen for 2 hr. It was then concentrated under reduced pressure. The residue was dissolved in benzene and the solution was concentrated to remove last traces of phosphorus oxychloride. A solution of the residue in methylene chloride was washed with ice water and brine, dried over anhydrous sodium sulfate, and concentrated to yield a dark oil. This was heated briefly on the steam bath with 100 ml. of water. The solid which remained was collected by filtration, washed with water, and dried *in vacuo*. It was then extracted with ethyl acetate; the ethyl acetate solution was filtered through Florisil and crystallized to yield 757 mg. (8.3%) of 1,3,4,9-tetrahydro-6-methoxy-1,1-dimethyl-2H-pyrido-[3,4-*b*]indol-2-ylphosphoramidic dichloride, m.p. 187.5–189.5°. This material was recrystallized from ethyl acetate for analysis, m.p. 189–190.5°.

The ultraviolet spectrum (ethanol) had λ_{max} 226 and 274 mμ (ε 29,400 and 8900, respectively) with inflections at 293 and 306 mμ (ε 6350 and 3800, respectively). The infrared spectrum (Nujol) showed NH, 3320, and P=O, 1253 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{17}Cl_2N_2O_2P$: C, 48.43; H, 4.95; Cl, 20.42; N, 8.07. Found: C, 48.15; H, 4.65; Cl, 20.46; N, 7.93.

The aqueous washes from the initial methylene chloride solution were made ammoniacal and extracted with ether. The ether solution was washed with brine, dried over anhydrous sodium sulfate, and concentrated to yield a semicrystalline residue. Crystallization of this material from ethyl acetate yielded 1.16 g. (19.1%) of 2,3,4,9-tetrahydro-6-methoxy-1,1-dimethyl-1H-pyrido[3,4-*b*]indole, m.p. 170.5–171.5°. This material was recrystallized from ethyl acetate for analysis, m.p. 171–173°. The ultraviolet spectrum (ethanol) had λ_{max} 226 and 278 mμ (ε 27,500 and 8200, respectively) with inflections at 295 and 308 mμ (ε 7000 and 3850, respectively).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.12; H, 7.66; N, 11.88.

2,3,4,9-Tetrahydro-7-methoxy-1,1-dimethyl-1H-pyrido[3,4-*b*]indole (X).—To a solution of 2.00 g. (8.83 mmoles) of 6-methoxytryptamine hydrochloride in 50 ml. of a pH 4.7 acetate buffer was added 50 ml. of acetone. The resulting solution was allowed to stand in the dark, under nitrogen, at 25° for 7 days. It was then concentrated *in vacuo;* the residue was diluted with water, cooled in an ice bath, and made ammoniacal. The white solid which precipitated was collected by filtration, washed with water, and dried *in vacuo* to yield 2.04 g., m.p. 205–206°. Recrystallization of this material from methanol–ethyl acetate yielded two crops: 1.51 g., m.p. 205–206.5°, and, 0.430 g., m.p. 204–206° (95.2%), of 2,3,4,9-tetrahydro-7-methoxy-1,1-dimethyl-1H-pyrido[3,4-*b*]indole. A portion of the first crop was recrystallized three times from ethyl acetate for analysis, m.p. 206–208°. The ultraviolet spectrum (ethanol) had λ_{max} 226, 269, and 296 mμ (ε 37,600, 4600, and 5700, respectively).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.91; H, 8.00; N, 12.21.

2,3,4,9-Tetrahydro-7-benzyloxy-3-ethyl-1H-pyrido[3,4-*b*]indole.—To a solution of 2.22 g. (6.73 mmoles) of 3-(2-aminobutyl)-6-benzyloxyindole hydrochloride in 150 ml. of warm pH 4.7, acetate buffer was added 0.62 ml. (7.4 mmoles) of 36% aqueous formaldehyde. In a few minutes a white crystalline precipitate began to form. The mixture was allowed to stand at room temperature, under nitrogen, in the dark for 4 days; the solid product was then collected by filtration, washed with water, and dried *in vacuo* at 30° to yield 2.22 g., m.p. 224° dec., of the β-carboline hydrochloride. A suspension of this material in dilute ammonium hydroxide was stirred with ether. The ether solution was washed with brine and dried over anhydrous potassium carbonate. The aqueous filtrate was made ammoniacal and extracted with ether. The ether solution was washed with brine and dried over anhydrous potassium carbonate. Concentration of the combined ether solutions yielded a base which was crystallized from ethyl acetate–Skellysolve B to yield 1.81 g. (87.7%), m.p. 152.5–153.5°, of 2,3,4,9-tetrahydro-7-benzyloxy-3-ethyl-1H-pyrido-[3,4-*b*]indole. A sample of this compound was recrystallized four times from ethyl acetate for analysis, m.p. 152–153°. The ultraviolet spectrum (ethanol) had λ_{max} 228, 268, and 296 mμ (ε 38,600, 5500, and 5400, respectively) with a slight inflection at 258 mμ (ε 4950).

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.44; H, 7.54; N, 9.50.

2,3,4,9-Tetrahydro-7-hydroxy-3-ethyl-1H-pyrido[3,4-*b*]indole Hydrochloride (XVII).—A mixture of 1.80 g. (5.89 mmoles) of 2,3,4,9-tetrahydro-7-benzyloxy-3-ethyl-1H-pyrido[3,4-*b*]indole, 350 mg. of 10% palladium on carbon, and 200 ml. of 95% ethanol was allowed to hydrogenate at atmospheric pressure for 2 hr. and 7 min. The catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure. A methanolic solution of the tan, crystalline residue was acidified with hydrogen chloride and crystallized from methanol–ethyl acetate to yield 1.19 g. (79.9%) of 2,3,4,9-tetrahydro-7-hydroxy-3-ethyl-1H-pyrido[3,4-*b*]indole hydrochloride, m.p. 254–255°. A sample of this material was recrystallized three times from methanol–ethyl acetate for analysis, m.p. 254–256° dec. The ultraviolet spectrum (ethanol) had λ_{max} 221.5, 269, and 295 mμ (ε 32,600, 5050, and 5700, respectively) with inflections at 263 and 306 mμ (ε 5000 and 3550, respectively).

Anal. Calcd. for $C_{13}H_{17}ClN_2O$: C, 61.77; H, 6.78; Cl, 14.03; N, 11.09. Found: C, 61.70; H, 6.80; Cl, 13.86; N, 10.73.

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