[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

The Synthesis of α-Methyltryptophans and α-Alkyltryptamines

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This paper reports the synthesis of a series of α-alkyltryptophans and tryptamines in which the indole nucleus may be substituted in the 5-position. The tryptophans were prepared by condensation of the appropriate gramine with ethyl α-nitropropionate followed by reduction and saponification. The tryptamines were prepared by four procedures: a) decarboxylation of the above nitroester followed by reduction of the nitro groups; b) alkylation of a nitroparaffin with a gramine or c) with an indole-3-carboxaldehyde, followed by reduction; d) treatment of tryptophan with an appropriate alkanoic anhydride followed by Wolff-Kishner reduction of the resulting acylaminoketone.

During the past few years many reports have been published concerning the formation[1] and metabolism[1,2] of serotonin as well as its possible role in such conditions as mental disease,[3] hypertension,[4] inflammatory processes[5] and gastrointestinal function.[6] Woolley[3b] has suggested that mental aberration might be due to lack of serotonin in the brain, and has reported[7a] that increasing brain serotonin by the administration of its precursor, 5-hydroxytryptophan, resulted in clinical improvement in cases of schizophrenia. Shore[7b] has demonstrated that iproniazide, a monaminoxidase inhibitor, *increases* serotonin brain levels by preventing its metabolism and Udenfriend[8] suggested that aminoxidase inhibitors, active *in vivo*, should be potentially useful in treating mental disease. Numerous reports on the use of iproniazide and other monaminoxidase inhibitors in depressive states have since appeared.[9]

On the other hand, three Rauwolfia alkaloids—reserpine, deserpidine and rescinnamine—also used in mental disease, *decrease* serotonin in the brain[10] and at least the first of these produces a decrease in both brain and peripheral norepinephrine and epinephrine.[11] Attempts to rationalize these facts have been made,[12] but from the conflicting data available it is impossible to predict the ultimate effect of an increased serotonin brain level. Indeed it is possible that both stimulation and depression could result depending on the dose of aminoxidase inhibitor administered or the brain serotonin level achieved.[12c]

In the course of a continuing study of the biological effects of various types of indole-containing compounds we undertook the preparation of a series of α-alkyltryptamines and tryptophans. Such tryptamines could conceivably act as serotonin-like compounds or as true serotonin antagonists in a manner similar to Woolley's BAS.[13] On the other hand they could act as competitive inhibitors of monamine oxidase and hence increase levels of serotonin and perhaps other physiologically active amines. The corresponding α-alkyltryptophans might represent potential sources of these tryptamines in the brain by acting as precursors capable of crossing the blood-brain barrier. This situation would resemble the case of 5-hydroxytryptophan,[1a] which enters the brain and is converted to serotonin which itself does not cross into the brain. On the other hand the tryptophans could act as 5-hydroxytryptophan decarboxylase inhibitors and thus decrease brain serotonin levels. In any event a study of the effects of these two classes of compounds would appear fruitful.

The tryptophans and tryptamines which we prepared are of the general types I and II.

(1) (a) S. Udenfriend, H. Weissbach, and D. F. Bogdanski, *Ann. N.Y. Acad. Sci.*, **66**, 602 (1957); (b) *J. Biol. Chem.* **224**, 803 (1957).

(2) (a) H. Blashko, *Biochem. J.*, **52** (Proceedings), page x (1952); (b) A. Sjoerdsma, T. E. Smith, T. D. Stevenson, and S. Udenfriend, *Proc. Soc. Exp. Biol. Med.*, **89**, 36 (1955); (c) W. M. McIsaac and I. Page, *J. Biol. Chem.*, **234**, 858 (1959).

(3) (a) J. H. Gaddum, Ciba Foundation Symposium on Hypertension, Humoral and Neurogenic Factors, Little, Brown and Company (Boston) 1954, page 75; (b) D. W. Woolley and E. Shaw, *Proc. Nat. Acad. Sci.*, **40**, 228 (1954); (c) B. B. Brodie and P. A. Shore, *Ann. N.Y. Acad. Sci.*, **66**, 631 (1957).

(4) (a) I. Page and J. W. McCubbin, *Circulation Res.*, 1 354 (1953); (b) D. W. Woolley and E. Shaw, *Science*, **124**, 34 (1956).

(5) (a) M. A. Fink, *Proc. Soc. Exp. Biol. Med.*, **92**, 673 (1956); (b) S. Udenfriend, P. A. Shore, D. F. Bogdanski, H. Weissbach, and B. B. Brodie, *Recent Progress in Hormone Research*, Vol. 13, page 4; (c) W. C. Spector and D. A. Willoughby, *Nature*, **179**, 318 (1957).

(6) (a) E. Bülbring and R. C. Y. Lin, *J. Physiol. (London)*, **140**, 381 (1958); (b) R. R. P. Warner, *J. Mt. Sinai Hosp.*, N.Y., **26**, 450 (1959).

(7) (a) D. W. Woolley, *Science*, **125**, 752 (1957); (b) P. A. Shore, J. A. R. Mead, R. G. Kuntzman, S. Spector, and B. B. Brodie, *Science*, **126**, 1063 (1957).

(8) S. Udenfriend, paper presented at the Medicinal Chemistry Symposium, East Lansing, Michigan, June 1956.

(9) For example, *Ann. N.Y. Acad. Sci.*, **80**, 551–1045 (1959).

(10) B. B. Brodie, P. A. Shore, and A. Pletscher, *Science*, **123**, 992 (1956).

(11) B. B. Brodie, J. S. Olin, R. G. Kuntzman, and P. A. Shore, *Science*, **125**, 1293 (1957).

(12) (a) B. B. Brodie, E. G. Tomich, R. G. Kuntzman, and P. A. Shore, *J. Pharmacol. Exp. Therap.*, **119**, 461 (1957); (b) M. Chessin, E. R. Kramer, C. C. Scott, *J. Pharmacol. Exp. Therap.*, **119**, 453 (1957); (c) P. A. Shore and B. B. Brodie, *Proc. Soc. Exp. Biol. Med.*, **94**, 433 (1957).

(13) D. W. Woolley and E. Shaw, *Ann. N.Y. Acad. Sci.*, **66**, 649 (1957).

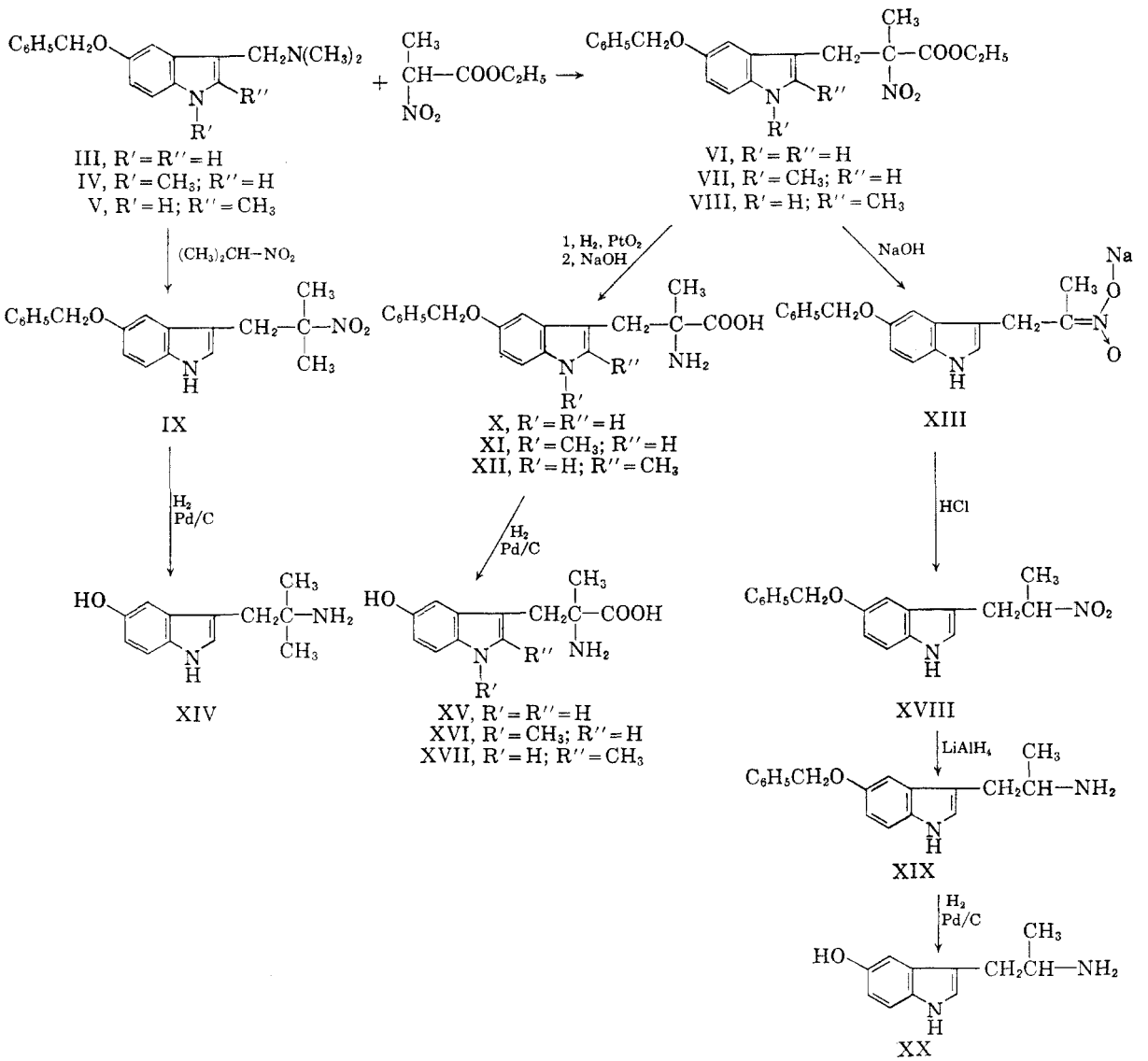
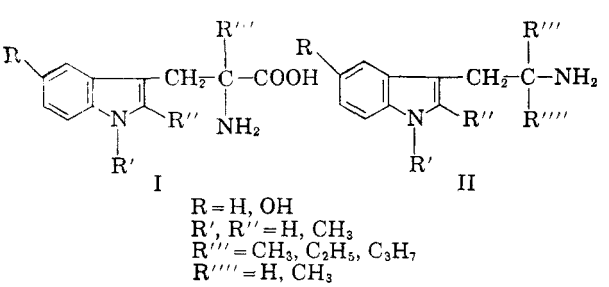


Fig. 1. Preparation of α-methyltryptophans



For the preparation of α-methyltryptophans (I R‴ = CH_3) we chose the general method, outlined in Fig. 1, involving interaction of the appropriately substituted gramine with ethyl α-nitropropionate following the published method used for tryptophan itself.[14] In the present case, however, the problem of dialkylation is eliminated by the presence of only one *alpha* hydrogen atom in the nitroester. Compound VII could also be prepared by methylation of VI using methyl iodide in the presence of sodium hydride.

α-Methyltryptophan, prepared previously[15] from 3-indoleacetone *via* the hydantoin, was produced in good yield through the nitropropionate. 5-Hydroxytryptophan itself[16] was obtained using the ethyl nitromalonate method of Weisblat and Lyttle.[17]

The tryptamines were prepared by four procedures, depending on the substituents present. The first method involved decarboxylation of the appropriate α-nitroester followed by reduction of the resulting nitroalkane by means of lithium

(14) D. A. Lyttle and D. I. Weisblat, *J. Am. Chem. Soc.*, **69**, 2118 (1947).

(15) K. Pfister and W. J. Leanza, U. S. Patent **2,766,255** (1956).

(16) Previously prepared by B. Witkop, *J. Am. Chem. Soc.*, **75**, 500 (1953); **76**, 5579 (1954), using the diethylformamidomalonate method.

(17) D. I. Weisblat and D. A. Lyttle, *J. Am. Chem. Soc.*, **71**, 3079 (1949).

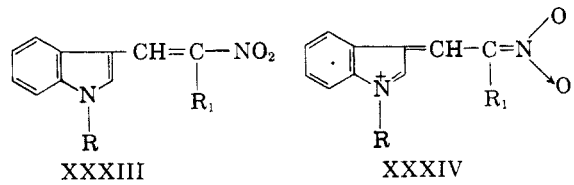
aluminum hydride (Fig. 1). According to the second method alkylation of 2-nitropropane with 5-benzyloxygramine to give IX occurred readily. In those cases in which the nitroparaffin contained two *alpha* hydrogen atoms dialkylation resulted, in agreement with the experience of Snyder and Katz[18] with gramine itself. The third procedure involved alkylation of the nitroparaffin with the appropriate indole 3-carboxaldehyde as outlined in Figure 2.[19] Compound XXIX was also prepared from tryptophan using the Dakin-West reaction[22] followed by Wolff-Kishner reduction of the resulting 1-(3′-indolyl)-2-acetamido-butanone-3. The same method was also used to prepare α-*n*-propyltryptamine.

The preparation of two of the substituted gramine intermediates required somewhat lengthy procedures. 5-Benzyloxy-1-methylgramine (IV) was prepared *via* 5-benzyloxyindole-3-carboxaldehyde, which, by virtue of the blocking group in the 3-position, could be methylated on the indole nitrogen using potassium carbonate as the base to yield XXIII. The blocking group was then eliminated by oxidation to the corresponding indole-3-carboxylic acid, followed by decarboxylation to 5-benzyloxy-1-methylindole, which was converted to the gramine in the usual way. In the synthesis of 5-benzyloxy-2-methylgramine, V, benzoquinone was condensed with ethyl β-aminocrotonate according to the method of Nenitzescu[23] to yield ethyl 5-hydroxy-2-methylindole-3-carboxylate. The latter was then converted to the corresponding 5-benzyloxy derivative, decarboxylated, and treated with formaldehyde and dimethylamine to yield V.

Two methods for the preparation of nitroalkenes XXIV to XXVII were available from the literature. The first method was reported by Majima and Kotake[24] in which 1-acetylindole-3-carboxaldehyde, nitromethane, and sodium hydroxide were used. The second method was reported by Seka[25] in which 2-methylindole-3-aldehyde, methylamine hydrochloride and sodium carbonate were employed. Neither of these methods was satisfactory, as the former did not afford a route to the 1-substituted indole-3-nitroalkenes and the latter was time-consuming and resulted in low yields.

Investigation of this problem disclosed that a satisfactory method for the preparation of these nitroalkenes was the reaction between the nitroalkane and indole-3-carboxaldehyde in the presence of acetic acid, ammonium acetate, and sodium acetate. This method was applicable to the preparation of both the 1-substituted and 1-unsubstituted indole nitroalkenes.

During the course of this work it became apparent that the structure of the reaction products was not represented by XXXIII. The absence of absorption bands corresponding to the nitro group in the infrared and the appearance of a new band at 1270 and 1223 cm.$^{-1}$, correlated with ultraviolet absorption in the 400 mμ region, strongly suggested that the compounds were actually inner nitronium salts as shown by formula XXIV. These compounds could be converted to the corresponding amines catalytically but were preferably reduced with lithium aluminum hydride in tetrahydrofuran.



XXXIII XXXIV

R = H, $-CH_3$
R_1 = H, $-CH_3$, $-C_2H_5$

Pharmacology. Some of the pharmacological testing carried out with certain of our compounds has already been published. Govier, Howes, and Gibbons[26] studied the action of monamine oxidase on α-ethyltryptamine (XXIX) *in vitro* and concluded that deamination did not occur. Barlow and Khan[27] have described the effects of 5-benzyloxy-α-methyltryptamine (XIX), 5-hydroxy-α-methyltryptamine (XX), and α-methyltryptamine (XXX) on the isolated rat uterus and isolated rat fundus strip preparation. Greig, Walk, and Gibbons[28a] have published the *in vitro* and *in vivo* effects of 5-hydroxy-α-methyltryptamine (XX), α-methyltryptamine (XXVIII), and α-ethyltryptamine (XXIX)[28b] in blocking the enzymes, monamine oxidase, and 5-hydroxytryptophan decarboxylase. The first two compounds are potent inhibitors of both enzymes *in vitro* while the third compound is much more selective in favor of monamine oxidase. *In vivo* studies indicate that XX is effective in inhibiting 5-hydroxytryptophan decarboxylase,

(18) H. R. Snyder and L. Katz, *J. Am. Chem. Soc.*, 69, 3140 (1947).

(19) After the completion of our work Young[20] and Ash and Wragg[21] reported the preparation of XX by reaction of the indolealdehyde and nitroethane, followed by reduction. Our overall yield *via* the nitroester was approximately twice that reported[21] by the latter authors. These authors also describe the synthesis of XXVIII and XXIX by the procedure used in this paper, but few experimental details are given.

(20) E. H. P. Young, *J. Chem. Soc.*, 3493 (1958).

(21) A. S. F. Ash and W. R. Wragg, *J. Chem. Soc.*, 3887 (1958).

(22) T. N. Ghosh and S. Dutta, *J. Ind. Chem. Soc.*, **33**, 296 (1956).

(23) C. Nenitzescu, *Bull. Soc. Chim., Romania*, **11**, 37 (1929). [Chem. Abst., **24**, 110 (1930)].

(24) R. Majima and M. Kotake, *Ber.*, **58**, 2037 (1925).

(25) R. Seka, *Ber.*, **57**, 1868 (1924).

(26) W. M. Govier, B. G. Howes, and A. J. Gibbons, *Science*, **118**, 596 (1953).

(27) R. B. Barlow and I. Khan, *Brit. J. Pharmacol.*, **14**, 265 (1959).

(28a) M. E. Greig, R. A. Walk, and A. J. Gibbons, *J. Pharmacol. Exp. Therap.*, **127**, 110 (1959).

(28b) Currently undergoing extensive clinical trial under the Upjohn tradename MONASE.

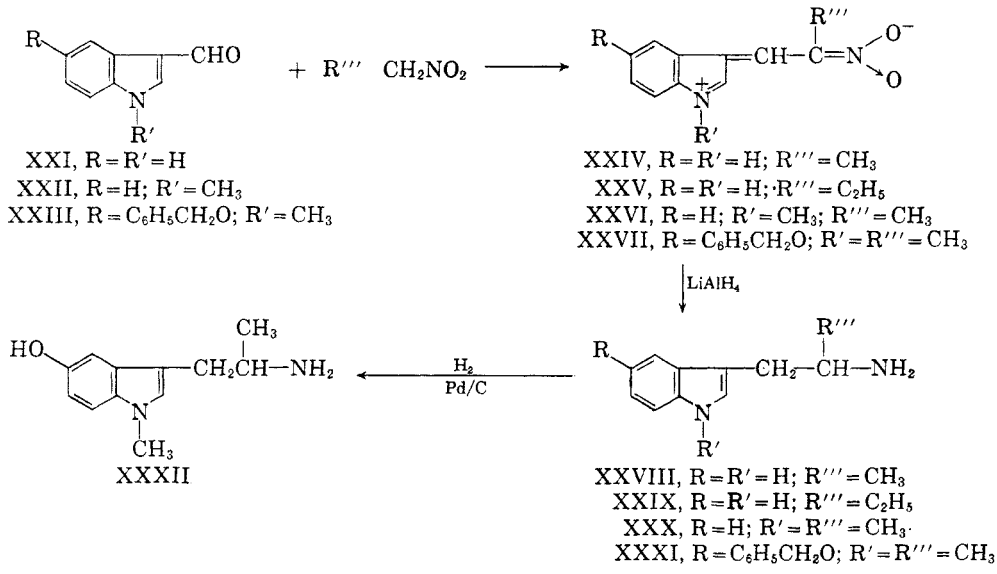


Fig. 2. Alkylation of the nitroparaffin with the appropriate indole

XXIX inhibits only monamine oxidase while XXVIII blocks both enzyme systems. Substitution of methyl groups in the 1- or 2-position of the indole ring decreases inhibitory activity somewhat. This effect of substitution in the indole ring is similarly apparent in the ability of 5-hydroxy-α-methyltryptophan (XV), 5-hydroxy-1-α-dimethyltryptophan (XVI), and 5-hydroxy-2,α-dimethyltryptophan (XVII) to block 5-hydroxytryptophan decarboxylase. Compound XV is a potent selective inhibitor of this enzyme, both *in vitro* and *in vivo* but, in rats at least, does not appear to be orally absorbed. This is somewhat surprising in view of its amino acid structure and the fact that that 5-hydroxytryptophan itself has been found by Dr. Greig to be orally active. Many factors, such as relative effects on various enzyme systems, relative effects on each enzyme system in brain *vs.* liver, relative toxicities, and other pharmacological effects, play a major role in the overall biological profile of even such a closely knit group of compounds as those reported in this paper.

EXPERIMENTAL[29]

A. *5-Hydroxy-α-methyltryptamine* (XX). *a. Preparation of ethyl α-methyl, α-nitro-β-[3-(5-benzyloxyindolyl)]propionate* (VI). (1) A mixture of 9.76 g. (0.0348 mole) of 5-benzyloxygramine[30] (III), ethyl α-nitropropionate[31] (5.13 g., 0.0348 mole), and 58 ml. of anhydrous toluene was stirred and refluxed for 3.5 hr. while a rapid stream of nitrogen was passed through the solution.

The reaction mixture was cooled to room temperature and 100 ml. of chloroform was added. The ice cold mixture was then washed with two portions of 10% hydrochloric acid (30 ml. each), once with 30 ml. of water, and then with two portions of 5% potassium hydroxide (30 ml. each). The organic layer was washed once with water (30 ml.), once with saturated salt solution, then dried over sodium sulfate and evaporated to dryness. A brown oil (II) was obtained, 12.8 g. (97% yield). The infrared spectrum was very similar to that of the sample which was purified by chromatography as described below.

(2) Sixty-six grams (0.236 mole) of 5-benzyloxygramine, 34.7 g. (0.236 mole) of ethyl-α-nitropropionate, and 235 ml. of dry xylene were placed in a 500 ml., three necked flask fitted with a stirrer, an efficient condenser, and a nitrogen inlet tube. The mixture was heated with stirring under reflux with a vigorous stream of nitrogen passing through to remove dimethylamine as it was formed. After 10 hr. dimethylamine evolution had practically stopped. The solution was cooled and washed with 2*N* hydrochloric acid, 2*N* sodium hydroxide, then water. It was dried over magnesium sulfate, decolorized with 10 g. of Magnesol, filtered, and the filtrate was concentrated *in vacuo*. The reddish-orange oil weighed 78.3 g. (90.0%). Fifteen grams was chromatographed over 1 kg. of Florisil. The oil was put on the column in benzene solution and the column was developed with 2l. of 5% acetone in petroleum ether (b.p. 60–71°), 2 l. of 7.5% acetone in petroleum ether (b.p. 60–71°), and finally with five 3-l. portions of 10% acetone in petroleum ether (b.p 60–71°). The first 12 l. of 10% eluate gave, on concentration, 12.5 g. of clear, light yellow oil. Infrared: NH: 3425; C=O· 1740; C=C: 1623, 1587; NO_2: 1552; C—O: 1255, 1218, 1200; phenyl: 795, 733, 693.

Anal. Calcd. for $C_{21}H_{22}N_2O_5$: C, 65.95; H, 5.80; N, 7.33. Found: C, 66.02; H, 5.61; N, 7.54.

The remainder of the crude material was purified and decolorized by dissolving it in methylene chloride and treating it with 40 g. of Florisil, filtering and treating again with 30 g. After the solvent was evaporated, 36.4 g. of clear, light yellow oil (VI) remained. Florisil is a very specific adsorbent for impurities in this material.

b. *Preparation of α-methyl-β[3-(5-benzyloxyindolyl)]nitroethane* (XVIII). A solution of sodium hydroxide (3.6 g.) in 10 ml. of water was added to a solution of 12.8 g. of crude VI [prepared as described in (1) above] in 53 ml. of absolute

(29) Melting points were taken in a capillary tube and are uncorrected. Ultraviolet spectra (recorded in mμ) were determined in 95% ethanol using a Cary spectrophotometer Model 14. Infrared spectra (recorded in $cm.^{-1}$) were determined in Nujol using a Perkin-Elmer recording infrared spectrophotometer Model 21.

(30) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **76**, 5579 (1954).

(31) N. Kornblum, M. E. Chalmers, and R. Daniels, *J. Am. Chem. Soc.*, **77**, 6654 (1955); a better procedure appears in R. K. Blackwood Ph.D. thesis, June 1955, Purdue University, pages 125–138; N. Kornblum and R. K. Blackwood, *Org. Syntheses*, **37**, 44 (1957).

ethanol. The mixture was allowed to stand at room temperature for 24 hr. The resulting suspension was then diluted with 10 ml. of absolute ethanol, filtered, and the precipitate washed with two portions of ethanol (10 ml. each), then with a total of 40 ml. of ether. The resulting solid sodium salt (III) (12.28 g.) contained sodium carbonate (as evidenced by titration).

The infrared clearly indicates that it is the *sodium salt of the corresponding nitronic acid* (XIII): No NO_2; NH: 3380, 3240, 3130, 3020; C=C: 1616, 1600, 1580; Na—O: 1450 $cm.^{-1}$.

The sodium salt (XIII) could be purified for analysis in the following way: *Ca.* 1.5 g. of the crude sodium salt was slurried in about 10 ml. of cold water. The resulting suspension was filtered and washed very slowly with 3.0 ml. of water. The slightly wet solid was transferred to a flask and mixed with acetone. The mixture was warmed on the steam bath and warm water added until the solution became clear. Warm acetone was then added dropwise until precipitation occurred (volume ratio *ca.* 10:1 acetone-water). The mixture was cooled in an ice bath and filtered. The white lustrous plates weighed 1.1 g. and melted to a glassy liquid at 112–115°. Neut. equiv. Calcd.: 332.33. Found: 345.4.

Anal. Calcd. for $C_{18}H_{17}N_2O_3Na \cdot 1.5H_2O$: C, 60.16; H, 5.61; N, 7.80. Found: C, 60.05; H, 6.13; N, 7.86.

The crude sodium salt was dissolved in 1 l. of water by warming to 40°. The solution was cooled to about 7° and acidified with 25 ml. of 10% hydrochloric acid while cooling. The resulting precipitate was filtered and washed with 100 ml. of water, sucked dry, and transferred to a beaker. This filtration and drying *should not* take more than 20 min., as the solid starts turning oily after standing for a short time. The solid was allowed to stand at room temperature for 56 hr. The resulting product was dissolved in 150 ml. of ether, dried over magnesium sulfate, and evaporated. The oily product (XVIII) weighed 7.5 g. and showed a small amount of carbonyl impurity at 1696 $cm.^{-1}$ (probably resulting from a side Nef-reaction).

A sample was recrystallized from ether–petroleum ether (b.p. 30–60°); m.p. 83–85°. Ultraviolet: f 224 (30,275); 276 (6,925); f 296 (5,350); f 308 (3,700). Infrared: NH: 3360; C=C: 1624, 1581, 1605; NO_2: 1550; C—O: 1211, 1182; aromatic: 796, 726, 689 cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 70.15; H, 6.11; N, 9.27.

c. *Lithium aluminum hydride reduction of* XVIII *to α-methyl-β-[3-(5-benzyloxyindolyl)ethylamine]*(XIX): The crude XVIII (7.5 g.) in 50 ml. of anhydrous ether was added to a solution of lithium aluminum hydride (10 g.) in 600 ml. of ether with stirring and ice bath cooling. The resulting suspension was refluxed 2.5 hr. and then allowed to stand overnight at room temperature. It was then cooled in ice and decomposed first with 50 ml. of water, then with a large excess of 15% potassium hydroxide solution. The ethereal extracts were washed with water, dried over sodium sulfate, and concentrated to about 100 ml. Eight milliliters of saturated ethereal hydrogen chloride was then added while swirling in the cold. The resulting precipitate was filtered and washed with ether; 5.34 g., m.p. 244.5–246.5°. The hydrochloride was recrystallized by dissolving in 110 ml. of warm methanol and adding 420 ml. of ether. The mixture was allowed to stand overnight in the cold, filtered and washed with ether, 4.58 g., m.p. 253–254°. Ultraviolet: 220 (30,575); 277 (6,675); 296 (5,150); 308 (3,425). Infrared: NH: 3270; HCl: 2680, 2570, 2480, 2360; C=C: 1617, 1601, 1590, 1501, 1482; C_6H_5: 796, 755, 744, 710, 690.

Anal. Calcd. for $C_{18}H_{21}ClN_2O$: C, 68.23; H, 6.68; Cl, 11.19; N, 8.84. Found: C, 68.39; H, 6.65; Cl, 10.95; N, 8.66.

d. *Hydrogenolysis of* V *to 5-Hydroxy-α-methyltryptamine* (XX)[32]: Sixty grams (0.19 mole) of XVIII hydrochloride was suspended in 3 l. of water and 600 ml. of 10% aqueous potassium hydroxide was added. The resulting oil was extracted with three 3-l. portions of ether. The combined ether extract was washed with water, then with saturated salt solution, and dried over sodium sulfate. The solution was evaporated *in vacuo* at <50° to give 53 g. of product.

In order to ensure a minimum of coloration in the final product all subsequent operations should be run on the same day and all equipment should be rinsed with acetic acid and then with ethanol immediately before use.

The product was dissolved in 900 ml. of absolute ethanol, a slurry of 10% palladium on charcoal (30 g.) in ethanol was added, and the mixture was hydrogenated at 50 p.s.i. with good agitation until the theoretical amount of hydrogen had been taken up (5–6 hr.). The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo* at <50°. The crude product (36.4 g., 0.19 mole) was very hygroscopic and no satisfactory analytical data could be obtained. It was dissolved in 191 ml. of 1.0*N* sulfuric acid (0.095 mole) and water (492 ml.) was added. Creatinine sulfate (31.4 g. containing 2% of water; 0.095 mole) was then added and the mixture was stirred to achieve solution (filtered if necessary) and then it was freeze-dried. The resulting amorphous solid was ground and dried at 0.1 mm. to constant weight to give 70.6 g. of α-methyl serotonin (XX) creatinine sulfate complex. Ultraviolet (in 0.01*N* alcoholic sulfuric acid): 217.5 (24,725); 276 (5,175); 296 (4,250).

Anal. Calcd. for $C_{15}H_{25}N_5O_6S$: N, 17.45. Found: N, 17.18.

B. *Preparation of α,α-dimethylserotonin* (XIV). a. *5-Benzyloxy-3-(α,α-dimethyl-α-nitroethyl)indole* (IX). A suspension of 20.0 g. (0.07 mole) of 5-benzyloxygramine, 100 ml. of 2-nitropropane, and 5.2 g. (0.13 mole) of solid sodium hydroxide was agitated by a slow stream of nitrogen and refluxed for approximately 8 hr. until the evolution of dimethylamine ceased. The mixture was cooled and 50 ml. of 10% acetic acid was added. Ether (200 ml.) was added to the resulting solution and the layers were separated. The ether layer was washed four times with water and dried over magnesium sulfate. A mixture of Darco G-60 and Celite was added, the suspension was filtered, and the solution was concentrated. The residue was crystallized by trituration with ether, then recrystallized from benzene to yield 16.4 g. (70%) of product which melted at 114–115°. An analytical sample was prepared by recrystallization from alcohol, m.p. 114.5–116.5°.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.46; H, 5.98; N, 8.80.

b. *5-Hydroxy-3-(β,β-dimethyl-α-aminoethyl)indole* (XIV). A solution of 5.0 g. (0.015 mole) of IX in 200 ml. of absolute methanol and 1.0 g. of 10% palladium on charcoal were shaken for 20 hr. under 50 p.s.i. initial hydrogen pressure. After 4 mole equivalents of hydrogen were absorbed the mixture was filtered through Celite. The filtrate was concentrated to dryness under reduced pressure to yield 2.2 g. (71.8%) of a white solid. The solid melted at 74–84°, resolidified, and resinified. Ultraviolet: 216 (19,950); 276 (4,900); 300 (3,700).

Anal. Calcd. for $C_{12}H_{16}N_2O \cdot {}^1/_2\ CH_3OH$: C, 68.15, H, 8.23; N, 12.71. Found: C, 68.47; H, 7.95; N, 12.79.

Creatinine sulfate (250 mg.) was added to a solution of 304.8 mg. of the above amine in 4.8 ml. of water and 1.5 ml. of 1*N* sulfuric acid. The solution was warmed to about 60° and 35 ml. of boiling acetone was added. After cooling at −5–0°, 600 mg. of the creatinine sulfate complex was collected by filtration. The complex softened at 91°, melted at 161°, and decomposed at 212°. The complex was 98–100% pure by ultraviolet analysis as compared with serotonin creatinine sulfate. Ultraviolet [*p*H 4.4 (sulfuric acid)]: 220 (17,425); 276 (4,800); 292 (4,025).

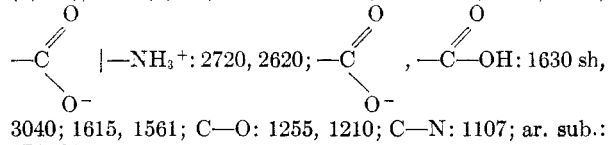
C. *5-Hydroxy-α-methyltryptophan* (XV). a. *5-Benzyloxy-α-methyltryptophan* (X). Ethyl α-nitro-α-methyl-β[3-(5-benzyloxyindole)]propionate (VI) (purified as described in the second experiment of the Experimental by successive treatments with Florisil; 60.3 g., 0.1628 mole) and 12.0 g. of fresh, brown platinum oxide (Adams catalyst, Baker) in 500

(32) We would like to acknowledge the assistance of Mr. P. E. Marlatt in carrying out this reaction.

ml. of 3-A alcohol were treated with hydrogen at 40 p.s.i. in a stirring autoclave. The calculated amount of hydrogen was taken up in 2.5 hr., at which time uptake had ceased. The autoclave was purged thoroughly with nitrogen, opened, and 81 g. of 20% sodium hydroxide was added. The autoclave was closed, a hydrogen atmosphere was re-established, and hydrolysis of the ester was allowed to proceed overnight at 35°. When the autoclave was opened, a few crystals of sodium hydrosulfite were added to retard air oxidation which is otherwise very rapid. Glacial acetic acid (25 ml.) was added, the catalyst was removed by filtration, and washed with 3-A alcohol. The filtrate was concentrated under vacuum, and when about 400 ml. had been removed, crystallization occurred. Four hundred milliliters of water was added and the mixture was cooled at 4° for 12 hr. The tan crystalline solid was collected and washed with water; 35.1 g. A second crop was obtained by concentrating the filtrate, 5.14 g.; total wt., 40.2 g. (75.7%). A sample from another run was recrystallized from alcohol-water (1:1); m.p. 273–275° dec. Ultraviolet: 275 (6,350); f 294 (4,950); f 306 (3,350). Infrared: NH: 3250; NH_3^+: s 2740, 2600, 2500; COO^-/C=C: s 1645, s 1630, 1610, 1586, 1487; aromatic substitution: 806, 796, 735, 692.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22: N, 8.64. Found: C, 70.74; H, 6.50; N, 8.76.

b. *5-Hydroxy-α-methyltryptophan* (XV). 5-Benzyloxy-α-methyltryptophan (X) (43.8 g., 0.135 mole) suspended in 200 ml. of 3-A alcohol and 400 ml. of water was reductively debenzylated in a Parr hydrogenator in the presence of 25 g. of 10% palladium-on-charcoal catalyst. The calculated amount of hydrogen was taken up in 1.5 hr. Most of the catalyst was removed by filtration, but some appeared to be colloidal, giving the solution a dark appearance which did not lighten on addition of a little sodium hydrosulfite. The alcohol was removed by concentration under vacuum. An equal volume of hot water was added and the dark solution was forced through a Seitz sterilizing filter under nitrogen pressure. Some black material was removed, but the solution was still dark. It was concentrated under slight vacuum until crystallization began. The mixture was chilled at 4° overnight, then the greyish-tan crystals were collected and washed with a little cold water; 17.8 g. The filtrate, to which a little sodium hydrosulfite had been added, was concentrated and a second crop was obtained; 6.39 g.; total wt., 23.9 g. (75.5%). A sample from another batch was recrystallized several times from water; the colorless product gradually darkens from 250°, does not melt below 296°.

The infrared spectrum of this compound contains all the expected absorptions and is quite similar to that of 5-hydroxytry ptophan. Ultraviolet: 208 (27,500); 274 (6,400); 299 (4,700); 308 (4,000). Infrared: NH/OH: 3270, 3238, 3110, 
3040; 1615, 1561; C—O: 1255, 1210; C—N: 1107; ar. sub.: 874, 811.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.29; H, 5.68; N, 11.75.

D. *1,α-Dimethyl-5-hydroxytryptophan dihydrate* (XVI). a. *1-Methyl-5-benzyloxyindole-3-carboxaldehyde* (XXIII). A mixture of 37.5 g. (0.15 mole) of 5-benzyloxyindole-3-carboxaldehyde,[20,21] 300 ml. of Carbitol, 25 g. of methyl iodide and 22 g. of potassium carbonate was heated overnight on the steam bath, cooled, and diluted with water. The solid was collected, washed well with water, and recrystallized from alcohol to yield 30.4 g. of product (76%) which melted at 128–129°. Infrared: NH: absent; C=O: 1645; C=C: 1621, 1582, 1537.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.69; N, 5.27. Found: C, 76.97; H, 5.51; N, 5.24.

b. *1-Methyl-5-benzyloxy-3-indole carboxylic acid.* A solution of 20.0 g. (0.075 mole) of 1-methyl-5-benzyloxyindole-3-carboxaldehyde (XXIII) and 380 ml. of acetone was stirred and a solution of 24.0 g. (0.15 mole) of potassium permanganate and 300 ml. of water was added at such a rate as to keep the temperature below 40°. The mixture was stirred for 1 hr. and filtered. The solid was washed with 50% acetone and the combined filtrates were acidified with dilute hydrochloric acid. The solid was filtered, washed well with water, and air dried to yield 14.8 g. (70.0%) of product. After recrystallization from a large volume of alcohol, 12.0 g. (57% yield) of product was obtained which melted at 219–220.5°.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.54; H, 5.37; N, 4.98. Found: C, 72.75; H, 5.32; N, 5.16.

c. *Decarboxylation to 1-methyl-5-benzyloxyindole.* 1-Methyl-5-benzyloxyindole-3-carboxylic acid (10 g., 0.035 mole) was placed in a flat-bottomed flask and immersed in an oil bath preheated to 245°. After 15 min. the flask was removed and allowed to cool. The dark solid was dissolved in hot acetone and diluted with 3-A alcohol to yield 7.0 g. (78.6%) of light tan product which melted at 130–131°. Infrared: C=C: 1616, 1600, 1573, 1555, 1494; C—O: 1235; ar. sub.: 846, 835, 797, 749, 745, 720, 693.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.03; H, 6.14; N, 5.61.

d. *5-Benzyloxy-1-methylgramine* (IV): A solution of 15 ml. of dioxane and 15 ml. of acetic acid was cooled to 10° and 1.2 ml. of 37% aqueous formaldehyde was added. A total of 3.3 ml. of 25% aqueous dimethylamine was then added over 5 min. The solution was stirred at 10° and a solution of 3.35 g. (0.014 mole) of 5-benzyloxy-1-methylindole in 15 ml. of dioxane was added over 30 min. The solution was allowed to stand overnight, 187 ml. of water was added and the mixture was filtered through Celite. An ice-cold solution of 14.0 g. of potassium hydroxide and 150 ml. of water was added to the filtrate. The resulting mixture was cooled in an ice bath and filtered. The product was washed well with water and dried in air to yield 3.3 g. (80%) of crude solid. After treatment with Nuchar 190-N and recrystallization from dilute alcohol the solid melted at 48–50°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.51. Found: C, 78.08; H, 7.86; N, 9.69.

e. *Ethly α-methyl-α-nitro-β-[3-(1-methyl-5-benzyloxyindole)]propionate* (VII). (1) A mixture of 32.0 g. (0.108 mole) of 5-benzyloxy-1-methylgramine (IV), 15.8 g. (0.108 mole) of ethyl-α-nitropropionate, 1.0 g. (0.025 mole) of sodium hydroxide, and 120 ml. of xylene was refluxed for 24 hr. under a slow stream of nitrogen. The mixture was cooled and filtered. The filtrate was washed with water, dilute hydrochloric acid, and then with water until acid free. The solution was dried over potassium carbonate, then passed through Florisil in order to remove the dark color. Concentration of the solution yielded 5.5 g. (14%) of an impure amber-colored oil. Infrared: NH/OH absent; Ester C=O: 1745 $cm.^{-1}$; C=C: 1623, 1580, 1495; NO_2: 1555, 1355; C—N/C—O: 1305, 1262, 1225, 1210, 1125, 1020; ar. sub.: 854, 792, 730, 690 cm^{-1}.

Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.06. Found: C, 68.53; H, 7.20; N, 7.20.

(2) A solution of 45 g. (0.118 mole) of ethyl 1,α-dimethyl-α-nitro-β-[3-(5-benzyloxyindole)]propionate (VI) and 100 ml. of anhydrous dimethylformamide was added to a mixture of 5.0 g. (0.21 mole) of sodium hydride and 100 ml. of dimethylformamide which had been previously cooled to approximately −50°. When the liberation of hydrogen ceased, 29.8 g. (0.21 mole) of methyl iodide was added over 1 hr. The mixture was stirred at room temperature overnight and carefully diluted with 9.0 ml. of alcohol. The mixture was poured into water, refrigerated for several hours, and filtered. After four recrystallizations from methanol, the solid weighed 14.0 g. (30%) and melted at 75–76.5°. Infrared: NH: absent; Ester C=O: 1740; C=C: 1625, 1583, 1498; NO_2: 1557, 1365 sh, 1350 sh; CN/CO: 1311, 1268, 1260, 1240, 1222, 1205, 1135, 1123 sh, 1075, 1025; ar. sub.: 742, 722, 695, 653.

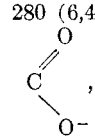
Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.06. Found: C, 66.41; H, 6.10; N, 7.04.

f. *1,α-Dimethyl-5-benzyloxytryptophan* (XI). A mixture of 5.4 g. (0.013 mole) of the above nitroester (VII), 1.0 g. of platinum oxide, 60 ml. of alcohol, and 30 ml. of ethyl acetate was hydrogenated at 50 p.s.i. for 1.5 hr. The vessel was opened and 6.6 ml. of 20% sodium hydroxide was added. The mixture was then shaken for 24 hr. under nitrogen. A few crystals of sodium hydrosulfite and 2.1 ml. of acetic acid were added and the mixture was filtered. The solid was washed with alcohol. The filtrates were combined and concentrated to dryness to yield 8.0 g. of crude solid. The solid was recrystallized from an alcohol-ether mixture to yield sodium acetate. The filtrate was concentrated and the solid was washed with water and recrystallized from an alcohol-ether mixture to yield 0.9 g. of product which melted at 234–238°.

Infrared data indicate the presence of an unexplained NH/OH component which may account for the low carbon value. Ultraviolet: 224 sh (28,125); 282 (7,650); f 288 (7,525); f 254 (7,272); f 305 (4,550). Infrared: NH/OH: 3400, 3080 sh, 2660, 2550, 2380, 2100; COOH: 1650 sh, 1622, 1592, 1515, 1488, 1400; C—O: 1285, 1220, 1205; ar. sub.: 802, 733, 695.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 69.75; H, 6.57; N, 8.47.

g. *1,α-Dimethyl-5-hydroxytryptophan dihydrate* (XVI). A mixture of 1.4 g. (0.0041 mole) of 1,α-dimethyl-5-benzyloxytryptophan, 4.1 ml. of 0.1*N* hydrochloric acid, 25 ml. of water, 25 ml. of 3-A alcohol, and 1.0 g. of 10% palladium-on-carbon was shaken at 40° for 4 hr. at 50 p.s.i. hydrogen pressure. The mixture was neutralized with 4.1 ml. of 0.1*N* sodium hydroxide and filtered through a Seitz filter. The filtrate was concentrated to 10 ml. at a temperature below 25°. The solution was diluted with 100 ml. of acetone and filtered. The filtrate was again diluted with an additional 100 ml. of acetone and refrigerated at 0°. The filtrate was decanted from a colored oil and further diluted with 100 ml. of acetone. After 1 week at 0° a solid precipitated. After recrystallization from 6 ml. of water the product weighed 300 mg. (26%) and melted at 270–271°. Ultraviolet: 214 (25,875); 280 (6,425); 307 (5,175); f 317.5 (4,150). Infrared:



, NH_3^+, (H_2O), 1650 sh, 1630, 1610, 1430 sh, 1418; C=C: 1585, 1515, 1505; C—O/C—N: 1293, 1260, 1155, 1128; OH deformation (acid): 920; ar. sub.: 855, 815, 800, 776, 725.

Anal. Calcd. for $C_{13}H_{15}N_2O_3 \cdot 2H_2O$: C, 55.11; H, 6.75; N, 9.88. Found: C, 55.00; H, 7.21; N, 9.83.

The anhydrous material was obtained after drying at 55° (0.1 mm.) for 24 hr.

Anal. Calcd. for $C_{13}H_{15}N_2O_3$: C, 63.14; H, 6.11; N, 11.33. Found: C, 63.31; H, 6.62; H, 11.06.

E. *2-α-Dimethyl-5-hydroxytryptophan* (XVII). a. *5-Benzyloxy-3-carbethoxy-2-methylindole.* A solution of sodium ethoxide was prepared from 2.9 g. (0.126 mole) of sodium and 175 ml. of absolute ethanol. 2-Methyl-3-carbethoxy-5-hydroxyindole (27 g., 0.123 mole) and 16.5 g. (0.13 mole) of benzyl chloride were added and the mixture was refluxed under nitrogen for 2 hr. The resulting mixture was poured into water and the sticky solid filtered. The solid was boiled with 500 ml. of dry ether, the suspension was cooled, and the solid filtered and washed with ether; 9.5 g., m.p. 148.5–151°. The material was washed with alkali and this process raised the melting point to 152–152.5°.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.73; H, 6.19. Found: C, 73.78; H, 6.12.

b. *5-Benzyloxy-2-methylindole and 5-benzyloxy-2-methylindole-3-carboxylic acid.* Five grams (0.016 mole) of 5-benzyloxy-3-carbethoxy-2-methylindole was added to a solution of 10 g. (0.18 mole) of potassium hydroxide in 10 ml. of water and 50 ml. of 95% ethanol. The mixture was refluxed for 18 hr. and the resulting solution was poured into 400 ml. of water. A gummy mass separated which was extracted into ether. The aqueous alkaline solution was light brown in color. On acidification a light brown solid separated which was filtered and dried. The material melted at 184–187° efferv. After recrystallization from ethyl acetate-methylcyclohexane crystals of 5-benzyloxy-2-methyl-indole-3-carboxylic acid were obtained which melted at 186–187°. Ultraviolet: 216 (37,875); 241.5 (20,500); 285 (9,675); 292 (9,625); f 304 (5,125). Infrared: NH: 3310; carboxyl OH: 3020, 2540, 2320; Conj. C=C: 1624, 1585, 1577, 1535; C—O: 1207, 1166; C_6H_5: 799, 731, 690.

Anal. Calcd. for $C_{17}H_{18}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.88, 72.83; H, 5.38, 5.48; N, 4.76, 4.85.

The ether solution of the alkali insoluble gum was dried and concentrated. A crystalline solid remained which was purified by crystallization from benzene-methylcyclohexane and finally from methylcyclohexane to give 2-methyl-5-benzyloxyindole; 4 g., m.p. 81–82°. Infrared: NH: 3365; Conj. C=C: 1650, 1618, 1599, 1585, 1545, 1481; C—O: 1180, 1174; ar. sub.: 976, 746, 695.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.97; H, 6.37; N, 5.90. Found: C, 81.11, 81.11; H, 6.42, 6.47; N, 5.63, 5.85.

c. *5-Benzyloxy-2-methylgramine* (V). A solution of 92 ml. of dioxane, 92 ml. of acetic acid, and 7.4 ml. of 37% aqueous formaldehyde was cooled to 10° and 20 ml. of 25% aqueous dimethylamine was slowly added. The solution was stirred for about 15 min. and a solution of 20 g. (0.08 mole) of 5-benzyloxy-2-methylindole and 92 ml. of dioxane was added over 30 min. The solution was allowed to stand overnight and then 1150 ml. of water and Nuchar 190-N were added. The mixture was filtered through Celite and the filtrate was made basic with 100 g. of potassium hydroxide and 900 ml. of water. The mixture was filtered and the solid was washed well with water and dried in air to yield 19.1 g. of crude product. After treatment with Nuchar 190-N and recrystallization from benzene the product weighed 16.1 g. (71%) and melted at 150–153°. Ultraviolet: 278 (8,525); 292 (7,750); 304 (4,600). Infrared: NH: 3110, 3000; tert. amine: 2780; C=C: 1625, 1588, 1495; C—O: 1237, 1220, 1195; ar. sub.: 840, 785, 727, 690.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 78.17; H, 7.27; N, 9.67.

d. *Ethyl α-methyl-α-nitro-β-[3-(2-methyl-5-benzyloxyindole)]propionate* (VIII). A mixture of 32.0 g. (0.108 mole) of the above gramine V, 15.8 g. (0.108 mole) of ethyl nitropropionate, 1.0 g. (0.025 mole) of sodium hydroxide, and 120 ml. of xylene was refluxed under a stream of nitrogen for 5 hr. when the evolution of dimethylamine ceased. The mixture was cooled and filtered. The filtrate was washed three times with water, dilute hydrochloric acid, then with water and dried over potassium carbonate. The filtrate was heated twice with Nuchar 190-N and filtered. The solution was concentrated to yield 32.5 g. (82%) of crude product.

A 5.0-g. aliquot was dissolved in 50 ml. of benzene and chromatographed on 300 g. of Florisil. The column was then eluted with 660 ml. of 7.5% acetone–petroleum ether (b.p. 60–71°) (discarded) followed by 4000 ml. of 10% acetone–petroleum ether (b.p. 60–71°). The separation was discontinued when a green band appeared at the bottom of the column. The filtrate from the second elution was concentrated to yield 4.8 g. of an amber-colored oil. Ultraviolet: 278 (8,250); f 293 (7,350); f 305 (4,200). Infrared: NH: 3400; Ester C=O: 1738; C=C: 1625, 1588, 1488; NO_2: 1550, 1350; Ester C—O: 1257, (1217, 1205); C—N/C—O: 1125, 1080, 1015; ar., 850, 798, 735, 695.

Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.06. Found: C, 66.68; H, 6.00; N, 7.03.

e. *2,α-Dimethyl-5-benzyloxytryptophan* (XII). A mixture of 4.5 g. (0.0134 mole) of the above nitro compound VIII, 0.9 g. (0.004 mole) of platinum oxide and 37.5 ml. of 95% alcohol was subjected to hydrogenation for 2 hr. (reduction took place in 20 min. and stopped). After reduction was complete, 6.0 ml. of 20% sodium hydroxide was added and

the mixture was shaken under hydrogen for 18 hr. A small quantity of sodium hydrosulfite and 1.9 ml. of acetic acid were then added and the mixture was filtered. The solid was washed with alcohol. The filtrates were combined and concentrated under reduced pressure to yield a white solid. The solid was recrystallized twice from an alcohol-water mixture and then from alcohol to yield 3.3 g. of product. The solid became dark at 218° and decomposed at 222–224°. Infrared: OH/NH: 3340, 3220, 2660; COO^-, NH_3^+: 1645, 1638, 1625, 1587, 1560, 1485; C—O/C—N: 1290, 1200, 1135, 1023; ar. sub.: 795, 732, 695.

Anal. Calcd. for $C_{20}H_{22}N_2O_3.H_2O$: C, 67.39; H, 6.79. Found: C, 67.33; H, 6.85.

The sample was dried at 100° for twelve hours to give a hygroscopic solid.

Wt. loss. Calcd.: 4.83%. Found: 4.85%.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28; Eq. wt., 354. Found: C, 71.81; H, 6.60; N, 8.02; Eq. wt., 358.

f. *2,α-Dimethyl-5-hydroxytryptophan* (XVII). A mixture of 3.0 g. (0.0084 mole) of 2,α-dimethyl-5-benzyloxytryptophan (XII), 20 ml. of 95% alcohol, 40 ml. of water, and 3.0 g. of 10% palladium-on-charcoal was hydrogenated at 50 p.s.i. initial pressure for approximately 30 min. The mixture was filtered and the solid was refluxed with water and filtered under nitrogen. The filtrates were combined and concentrated to dryness. The resulting semisolid was dissolved in hot water and diluted with acetone. A small amount of dark solid was removed and the filtrate was further diluted with acetone. A small amount of amorphous material was removed and the solution was concentrated to dryness. The residue was again recrystallized from a water-acetone mixture to yield 100 mg. of product. The melting point was indefinite. Ultraviolet: 220 (20,634); 279 (6,542); f 296 (6,621); 308 (3,811). Infrared: NH/OH: 3380, 3180; NH_3^+: 2730 sh, 2630 sh, 2550 sh, 2440 sh; COO^-: 1620 sh, 1584, 1398, 1392; C=C: 1510; C—N/C—O: 1265, 1233, 1207, 1093; ar. sub.: 880, 840, 790.

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.49; N, 11.28. Found: C, 62.35; H, 6.82; N, 10.72.

F. *α-Methyltryptamine* (XXVIII). *Method A.* a. *α-Methyl-β-indolenideniumethyl Nitronate* (XXIV). (1) *With ammonium acetate.* A mixture of 22.0 g. (0.28 mole) of crystalline ammonium acetate, 6 ml. of acetic anhydride, and 20 ml. of glacial acetic acid was stirred and warmed for approximately 20 min. A mixture of 28.8 g. (0.2 mole) of indole-3-aldehyde (XXI), 100 ml. of nitroethane, and 120 ml. of acetic acid was added to the solution. When the mixture was brought to near reflux, 14.0 g. of anhydrous sodium acetate was added. At reflux, 20 ml. of acetic anhydride was added to the dark solution during 2 hr. After 2 hr., the solution was allowed to cool while 45 ml. of water was slowly added. The solid was collected, and washed with a solution of 100 ml. of acetic acid and 45 ml. of water. After crystallization from dilute alcohol, the product weighed 20.2 g. (50%) and melted at 190–192°. The analytical sample melted at 192–193°. Ultraviolet: 218 (28,400); 277 (7,450); 282.5 sh (7,100); 400 (14,950). Infrared: OH/NH: 3400; C=C: 1634, 1624, 1585, 1530; N—O: 1270, 1223; ar.: 747.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.85. Found: C, 65.23; H, 5.01; N, 14.03.

(2) *With ammonium phosphate.* A mixture of 7.2 g. (0.05 mole) of indole-3-aldehyde, 7.2 g. (0.054 mole) of dibasic ammonium phosphate, 25 ml. of nitroethane, and 28 ml. of acetic acid was refluxed for 3 hr., allowed to cool and filtered. After two crystallizations from alcohol, 6.0 g. (60%) of a product was obtained. It was identical with that obtained from the experiment with ammonium acetate.

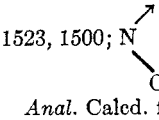
b. *α-Methyltryptamine* (XXVIII). Five grams (0.024 mole) of α-methyl-β-indolenideniumethyl nitronate was placed in a drip extractor. A mixture of 5.7 g. (0.15 mole) of lithium aluminum hydride and 2000 ml. of ether was stirred and refluxed for 4 hr. until all the compound was extracted into the reaction mixture. The mixture was decomposed with wet ether, followed by the addition of water and then potassium hydroxide. The suspension was filtered and the filtrate dried over potassium carbonate and concentrated. The residue was crystallized from ethyl acetate–petroleum ether (b.p. 60–71°) to give 2.0 g. (71%); m.p. 97–100°. Infrared: NH/OH: 3370, 3110, 3100; C=C: 1621, 1581, 1549, 1505; ar. sub.: 736.

Anal. Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.09; N, 16.08. Found: C, 75.78; H, 8.07; N, 16.31.

An 0.85-g. sample of α-methyltryptamine was dissolved in 10 ml. of methanol and 0.5 ml. of acetic acid was added. The mixture was concentrated to dryness. The residue was dissolved by warming in 10 ml. of ethyl acetate and 2 ml. of alcohol. After refrigeration for 4 hr. 1.0 g. of α-methyltryptamine acetate was obtained; m.p. 143–146°. Ultraviolet: 219 (36,700); f 274 (5,700); 281 (6,150); 289 (5,300). Infrared: NH: 3300; Salt: 2700, 2660, 2590, 2500, 2140; NH_3, COO^-, C=C: 1630, 1565, 1555, 1510, 1490, 1412; ar. sub.: 745.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.63; H, 7.74; N, 11.95. Found: C, 66.43, 66.62; H, 7.56, 7.38; N, 11.62.

Method B. A solution of 10.0 g. (0.049 mole) of 3-indolyl-β-nitro-β-methylethylene[18] in 100 ml. of tetrahydrofuran was added dropwise (over 2.5 hr.) to a mixture of 10.7 g. (0.28 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was gradually heated to reflux during the addition. After the addition was complete the mixture was refluxed for 2 hr. and allowed to stand overnight. A solution of 20 ml. of water and 60 ml. of tetrahydrofuran was slowly added until the excess lithium aluminum hydride was destroyed, followed by 10 ml. of concd. sodium hydroxide. Ether (150 ml.) was then added and the mixture was rapidly stirred until no solid remained on the sides of the flask. The mixture was filtered and the solid was washed with 150 ml. of ether. The ether solutions were combined, dried over potassium carbonate, and concentrated to yield 9.2 g. of crude amine. The amine was dissolved in 110 ml. of methanol and 5.5 ml. of acetic acid was added. The solution was concentrated to dryness under reduced pressure and the residue was dissolved in 110 ml. of hot ethyl acetate. Upon cooling 8.2 g. (73.2%) of α-methyltryptamine acetate precipitated. After drying the salt melted at 143–144°.

G. *α-Ethyltryptamine* (XXIX) *acetic acid salt. Method A.* a. *α-Ethyl-β-indolenideniumethyl nitronate* (XXV). A solution of 66.0 g. of crystalline ammonium acetate, 18 ml. of acetic anhydride, and 60 ml. of acetic acid was stirred for 20 min. at 50°. A mixture of 87.0 g. (0.6 mole) of indole-3-carboxaldehyde, 300 ml. of 1-nitropropane, and 360 ml. of acetic acid was added. The mixture was refluxed for 3 hr., cooled, diluted with 360 ml. of water, cooled for 6 hr. at 10°, and filtered. The solid was recrystallized from 600 ml. of 40% alcohol to yield 44.5 g. (34%) of product which melted at 128–131°. This solid contained traces of a nitrile but was satisfactory for the next step. Ultraviolet: 218 (31,250); 278 (7,950); f 283 (7,550); 402 (14,700). Infrared: NH: 3280; C≡N (weak): 2230; C=C/C=N: 1630, 1590, 1523, 1500;  : 1265, 1220; ar. sub.: 742.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.64; H, 5.59; N, 12.95. Found: C, 67.54; H, 5.57; N, 12.77.

b. *α-Ethyltryptamine* (XXIX). Lithium aluminum hydride (1.7 g.) was added to 300 ml. of tetrahydrofuran. When the reaction ceased, 30.0 g. of lithium aluminum hydride was added and the mixture was stirred for 1.5 hrs. A solution of 36.0 g. (0.17 mole) of XXIV in 285 ml. of tetrahydrofuran was added dropwise over 3 hr. while the mixture was being gradually brought to reflux temperature. The suspension was refluxed an additional 2 hr. and allowed to stand overnight at room temperature. Wet ether (500 ml.) was cautiously added followed by a solution of 70 ml. of water and 100 ml. of tetrahydrofuran. When the reaction

ceased, 20 ml. of concd. sodium hydroxide was added. The mixture was stirred for 1 hr. and filtered. The solid was washed with 1500 ml. of ether and the filtrates were combined, dried over 50 g. of potassium carbonate, and concentrated. The residual oil (78.0 g.) was dissolved in 100 ml. of methanol and 12 ml. of acetic acid was added. The mixture was concentrated to dryness and the residue was dissolved in 250 ml. of ethyl acetate and 30 ml. of methanol. The product did not precipitate upon cooling. The solution was then concentrated to one third volume and 2 ml. of acetic acid was added. Upon cooling 17.0 g. (40%) of product precipitated; m.p. 164–165.5°. Ultraviolet: 220.5 (37,050); f 274 (5,750); 281 (6,150); 289.5 (5,350). Infrared: NH: 3280; acid salt: 2710, 2650, 2540, 2120 (1625), 1565, 1518; C=C: 1625, 1493.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.11; N, 11.28. Found: C, 67.63; H, 7.60; N, 10.90.

Method B. a. *1-(3′-Indolyl)-2-acetamido-butanone-3.*[22] A solution of acetic anhydride (1800 ml.) and pyridine (1280 ml.) was added to *dl*-tryptophan (480 g.; 2.35 moles) and the mixture was heated on the steam bath with stirring for 5.5 hr. Water (4 l.) was added to the resulting solution and it was then steam-distilled until about 8 l. were collected. The mixture was allowed to stand overnight and the resulting oily product was filtered and washed with water. It was crystallized from methanol to give 227.1 g. of a solid, m.p. 134–135.5°. The second crop amounted to 64.2 g., m.p. 133–135°.

The original filtrate was extracted five times with ethyl acetate (total 3250 ml.). The extracts were washed with water, 5% sodium bicarbonate solution, then with water, dried through sodium sulfate, and evaporated. The resulting brown oil was crystallized from methanol to give 58.9 g., of crystals, m.p. 134–136°. The total product amounted to 350.1 g. (61% yield).

A sample was recrystallized from methanol-water, needles, m.p. 136.5–137.5°. (Ghosh and Dutta[22] obtained this compound as an oil, which gave a well defined 2,4-dinitrophenylhydrazone derivative.) Ultraviolet: 221 (35,675); 275 (5,800); 281.5 (6,175); 290 (5,375). Infrared: NH: 3320, 3240; C=O: 1708; amide: 1660, 1548.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.50; H, 6.67; N, 11.40.

b. *α-Ethyltryptamine* (XXIX). A mixture of 56.1 g. (0.23 mole) of 1-(3′-indolyl)-2-acetamido-butanone-3, 43.8 g. (0.78 mole) of 85% potassium hydroxide, 31.2 ml. (0.825 mole) of 85% hydrazine hydrate, and 325 ml. of diethylene glycol was heated to 110° for 1–2 hr. The solvent was distilled until the temperature reached 195–205°. The solution was held at this temperature for 2.5 hr. The solution was cooled and water was added until precipitation occurred. The mixture was extracted with ether. The ether was washed with water, dried, and concentrated. The residue was dissolved in ethyl acetate and diluted with Petroleum ether (b.p. 60–71°) until precipitation occurred. The crystallization was repeated three times using Nuchar 190-N to yield 8.1 g. (19%) of α-ethyltryptamine; m.p. 97–99°. Ultraviolet: 220.5 (20,500), f 275 (1,100); 281 (6,000); 289.5 (5,200). Infrared: NH: 3320, 3270, 3100, 3060, 2740 sh, 2700 sh, 2590, 2550 sh; C=C: 1620, (1577), 1545, 1505; NH_2: 1577; C—N: 1380, 1336, 1345, 1230, 1110, 1093; ar. sub.: 800, 758, 733.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.54; H, 8.56; N, 14.82. Found: C, 76.51; H, 8.54; N, 15.13.

The hydrochloride salt melted at 215.5–218° and showed no depression when mixed with an authentic sample prepared by the condensation of gramine with 1-nitropropane followed by lithium aluminum hydride reduction.

A mixture of 5.0 g. of the base, 3.0 ml. of acetic acid and 25 ml. of methanol was concentrated to dryness. The residue was crystallized from ethyl acetate–methanol to yield 6.5 g. of the acetic acid salt which melted at 165–166°.

The filtrates from the base recrystallizations were combined and concentrated. The residue was distilled to yield 3.0 g. of a yellow oil, b.p. 80°/0.6 mm., which was not investigated further.

Anal. Found: C, 81.70, 82.20; H, 7.48, 7.89; N, 8.78.

The picrate melted at 165–166°.

Anal. Found: C, 49.58; H, 3.58; N, 14.85.

H. *α-n-Propyltryptamine.* a. *1-(3′-Indolyl)-2-propionamidopentanone-3.* A mixture of *dl*-tryptophan (107 g., 0.525 mole), propionic anhydride (400 ml.), and pyridine (285 ml.) was stirred and heated on the steam bath for 5.5 hr. It was then allowed to stand at room temperature for 2 days. Water (890 ml.) was added with cooling, maintaining the inside temperature at 30–40°.

The mixture was then steam distilled until 2 l. of distillate was collected. The resulting mixture containing a brown oil was extracted with ethyl acetate (500 ml., 2 × 250 ml.). The ethyl acetate extracts were washed with water (3 × 250 ml.), then with sodium bicarbonate solution, saturated salt solution, and dried over sodium sulfate. Evaporation *in vacuo* afforded 150 g. of a brown oil. The oil (146 g.) was dissolved in 100 ml. of benzene and 20 ml. of acetone and was chromatographed on 4380 g. of Florisil.

Elution with 5% acetone-benzene (38 l.), 10% acetone-benzene (6 l.), and 20% acetone-benzene (4 l.) gave 52.138 g. of material which was crystallized from 50 ml. of ether to give 22.9 g. (16% yield) of clusters of needles melting at 102–104°.

Two crystallizations from ether (with Nuchar 190-N) gave colorless needles, m.p. 104.5–106°. Ultraviolet: 220 (33,500); 274 (5,950); 281 (6,300); 288.5 (5,500). Infrared: NH: 3410, 3290, 3200 sh; C—O: 1715, 1645; amide II: 1500; C=C: 1620 sh, 1580 sh, 1512 sh; ring: 763, 752.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.53; H, 7.36; N, 10.00.

b. *α-n-Propyltryptamine.* A mixture of 27.0 g. (0.1 mole) of the crude (not chromatographed) 1-(3′-indolyl)-2-propionamidopentanone-3, 15 ml. of 85% hydrazine hydrate, 21.9 g. of 85% potassium hydroxide, and 160 ml. of diethylene glycol was heated to 110° over approximately 2 hr. The solvent was distilled until the temperature reached 195–205° (1 hr.). The temperature of the mixture was held at 195° for 2.5 hr. The mixture was cooled and water was added until precipitation occurred. The mixture was extracted with ether. The ether solution was washed with water (discarded); the ether solution was then extracted with 8% hydrochloric acid. The acid solution was made basic and extracted with ether. The resulting ether extract was dried over potassium carbonate and concentrated to yield a red viscous oil. The oil was dissolved in methanol and 4 ml. of acetic acid was added. The resulting deep green solution was concentrated to dryness on a Rinco. The residue was triturated with ethyl acetate and filtered. The solid was washed with ethyl acetate until all color was removed, then recrystallized from ethyl acetate containing a small amount of methanol; 1.3 g. (5%), m.p. 158–158.5°. Ultraviolet: 220 (35,700); 274 sh (5,750); 281 (6,150); 289.5 (5,350).

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.45; H, 8.61; N, 10.77.

I. *1,α-Dimethyltryptamine* (XXX). a. *1,α-Dimethyl-β-indolenidenium ethyl nitronate* (XXVI). A mixture of 2.2 g. (0.028 mole) of crystalline ammonium acetate, 0.6 ml. of acetic anhydride, and 2.0 ml. of acetic acid was warmed and stirred until the ammonium acetate became anhydrous. Then a mixture of 4.2 g. (0.026 mole) of 1-methyl-3-indolealdehyde (XXII),[33] 10 ml. of nitroethane, and 12 ml. of acetic acid was added. The mixture was heated to gentle reflux and 1.4 g. of anhydrous sodium acetate was added. The solution was heated to reflux and 20 ml. of acetic anhydride was added over 2 hr. The stirred solution was allowed to cool and 4.5 ml. of water was slowly added. The precipitated oil was neutralized with sodium bicarbonate and taken into ether. The ether solution was concentrated and the residue

(33) H. Wieland, W. Konz, and H. Mittash, *Ann.*, **513**, 23 (1934).

was recrystallized from alcohol to yield 1.9 g. (34%) of the desired product which melted at 132–134°. Ultraviolet (0.01*N* H_2SO_4): 224 (28,600); 281 (4,329); 405 (10,030).

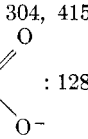
Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.64; H, 5.59; N, 12.95. Found: C, 66.91; H, 5.05; N, 12.94.

b. *1,α-Dimethyltryptamine* (XXX). The nitronate XXVI (10.8 g., 0.05 mole) was extracted (with drip type extractor) into a stirred mixture of 10.2 g. (0.27 mole) of lithium aluminum hydride and 2500 ml. of ether over 6 hr. The mixture was cooled and treated with wet ether. When the excess lithium aluminum hydride was destroyed, water followed by potassium hydroxide solution was carefully added until a gelatinous mass precipitated. The mixture was filtered and the ether was dried over potassium carbonate and concentrated to yield a clear oil. The oil was dissolved in anhydrous ether and treated with anhydrous hydrogen chloride to yield 10.5 g. (93.7%) of 1,α-dimethyl-3-aminoethyl indole hydrochloride which melted at 223–227°.

Anal. Calcd. for $C_{12}H_{17}N_2Cl$: C, 64.13; H, 7.63; N, 12.47; Cl, 15.78. Found: C, 64.36; H, 7.65; N, 12.07; Cl, 15.66.

The picrate melted at 198–200°.

Anal. Calcd. for $C_{18}H_{19}N_5O_7$: C, 51.79; H, 4.59; N, 16.78. Found: C, 52.08; H, 5.47; N, 16.07.

J. *1,α-Dimethylserotonin* (XXXII). a. *5-Benzyloxy-1-α-dimethyl-β-indolenidenium ethyl nitronate* (XXVII). This compound was prepared in the same manner as XXVa from 1-methyl-5-benzyloxy-indole-3-aldehyde (XXIII) and nitroethane to yield 40% of product which melted at 163–164°. Ultraviolet (qualitative): 224, 283, sh 304, 415; in 0.01*N* KOH: 206, 278, 304, 405. Infrared  : 1280, 1230.

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.78; H, 5.62; N, 8.68. Found: C, 70.96; H, 5.48; N, 8.96.

b. *5-Benzyloxy-1-α-dimethyltryptamine* (XXXI). This compound was prepared in the same manner as XXVIII to yield 84% of crude product. After crystallization from methylcyclohexane the yield dropped to 55%; m.p. 62–64°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.87; H, 7.29; N, 9.67.

The *hydrochloride* was crystallized from methanol-ether and melted at 193–195°.

c. *5-Hydroxy-1,α-dimethyltryptamine* (XXXII) *creatinine sulfate.* A mixture of 1.0 g. (0.0034 mole) of 5-benzyloxy-1,α-dimethyltryptamine, 150 ml. of absolute methanol and approximately 300 mg. of 10% Pd/C was hydrogenated at 50 p.s.i. (initial pressure) for 8 hr.

The mixture was treated with 3.5 ml. of 1*N* sulfuric acid and filtered. The filtrate was concentrated to dryness at 40–50° under reduced pressure. The dark residue was dissolved in 16.4 ml. of water, treated with a trace of Darco-60 and filtered. The flask and solid were washed with 5 ml. of water. A 500-mg. sample of creatinine sulfate was added to the combined filtrates. The filtrate was heated to about 50° and 105 ml. of boiling acetone was added. After refrigeration, 100 mg. of creatinine sulfate precipitated. The mixture was filtered and the filtrate was further diluted with acetone. After 2 days at 5°, 500 mg. (35%) of product was collected which was 91% pure by ultraviolet assay (compared with a standard sample of serotonin creatinine sulfate). Ultraviolet (*p*H 4.5 sulfuric acid): 304 (4,800); 281 (5,675); 222 (6,800).

K. *Synthesis of α-methyltryptophan.* a. *Ethyl α-nitro-α-methyl-β-(3-indole)propionate.* Gramine (34.85 g., 0.2 mole), ethyl-α-nitropropionate (29.42 g., 0.2 mole), and 200 ml. of dry toluene were placed in a 500 ml., three necked flask fitted with stirrer, nitrogen inlet tube, and an efficient condenser. The mixture was heated for 10 hr. under reflux with stirring and vigorous nitrogen flow to sweep out dimethylamine. The amber solution was cooled and washed with two 50-ml. portions of 2*N* hydrochloric acid, 100 ml. of water, two 50-ml. portions of 1*N* sodium hydroxide, then with two 50-ml. portions of water. The toluene solution was dried over anhydrous magnesium sulfate and the solvent was removed under vacuum. An oil (51.0 g., 91.8%) remained. It was used directly for the reduction-hydrolysis steps.

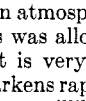
b. *α-Methyltryptophan.* Ethyl α-nitro-α-methyl-β-(3-indole)propionate (48.0 g., 0.1735 mole) was placed in a stirring autoclave with 400 ml. of 3-A alcohol and 12.0 g. of fresh, brown platinum oxide. Reduction was carried out at 30° under 40–50 p.s.i. hydrogen pressure. Reduction went smoothly and the calculated amount of hydrogen was absorbed. The autoclave was purged with nitrogen, opened, and 80 g. of 20% sodium hydroxide was added. Hydrolysis was accomplished by heating at 40° under hydrogen for 16 hr. The catalyst was removed by filtration and was washed with water. Glacial acetic acid (25 ml.) was added to the combined filtrate and washes. The solution was concentrated *in vacuo* leaving a mixture of gum and some crystals. This was heated with about 300 ml. of absolute alcohol and then allowed to stand at room temperature overnight. Crystals were collected and washed with alcohol (8.47 g.). These were identified by infrared as sodium acetate. A second crop of sodium acetate was obtained after concentrating the mother liquor (8.1 g.). The solvent was removed from the filtrate *in vacuo* leaving a gum which resisted all attempts to induce crystallization. After it had stood for about 9 months, it had largely crystallized. A small amount was removed for seed, then the remainder was dissolved in 450 ml. of hot water. The hot solution was treated with charcoal, and an equal volume of acetone was added to the filtrate. After seeding, crystals slowly formed and after 4 days at 4° the crystals were collected and washed with water-acetone (1:1) to give 28.3 g. of the monohydrate; m.p. 178–194°. This material was recrystallized from a minimum of hot water to give 17.57 g. of needles, m.p. 198–203° (lit.,[15] m.p. 203–205°). This was recrystallized from water to give 12.73 g. of the monohydrate; m.p. 204–9°. Ultraviolet (in 0.01*N* alcoholic sulfuric acid): 218 (33,975); 273 (5,575); 280 (5,800); 289 (6,000). Infrared: NH: 3580, 3465, 3440, 3380, 3280, 2660, 2560; NH_3^+: 3100, 1635, 1530; COO^-: 1590, 1395; aromatic substitution: 740, 730.

L. *Synthesis of 5-hydroxytryptophan.* a. *Ethyl α-nitro-α-carbethoxy-β[3-(5-benzyloxyindole)]propionate.* 5-Benzyloxygramine[29] (28.0 g., 0.1 mole), ethyl nitromalonate (20.52 g., 0.1 mole), and 225 ml. of dry toluene were placed in a 300 ml., three necked flask fitted with stirrer, nitrogen inlet tube and an efficient spiral tube condenser. The mixture was heated under reflux with stirring and with a vigorous stream of nitrogen passing through. When the materials were first mixed, a solution was obtained, but after heating was started a solid formed which made stirring difficult. As stirring and heating were continued, the solid disappeared. The solid is undoubtedly the salt of 5-benzyloxygramine and ethyl nitromalonate which decomposes to dimethylamine and the alkylated nitroester. The solution was heated until no more dimethylamine was evolved (about 4 hr.). The cool solution was washed twice with 100 ml. of 2*N* hydrochloric acid, twice with 100 ml. of 1*N* sodium hydroxide and twice with water. It was then dried with magnesium sulfate and partially decolorized with Magnesol. The clear solution obtained by filtration contained the ethyl α-nitro-α-carbethoxy-β[3-(5-benzyloxyindole)]propionate and was used directly for decarbethoxylation to the compound described below.

b. *Ethyl α-nitro-β[3-(5-benzyloxyindole)]propionate.* A solution of 2.3 g. (0.1 g.-atom) of sodium in 100 ml. of absolute alcohol was slowly added to the toluene solution above, while cooling in ice and stirring. When about 25 ml. of the alcohol solution had been added, a very thick precipitate formed which made stirring difficult. It was necessary to add 100 ml. of anhydrous ether in order to obtain a fluid slurry. The remainder of the alcohol solution was then added over 1.5 hr. and the slurry was stirred at room temperature overnight. The solid was collected and washed with ether, then placed in a separatory funnel with 200 ml. of ether and 75 ml. of 2*N* hydrochloric acid. The mixture was shaken until all of the solid disappeared. The ether layer

was washed twice with 50-ml. portions of 2*N* hydrochloric acid and then with water. It was dried over magnesium sulfate, treated with some Magnesol to remove color and, concentrated *in vacuo* to give the 5-benzyloxy nitroester as a red oil. The infrared spectrum of this material contained the expected absorptions.

c. *5-Benzyloxytryptophan.* Ethyl α-nitro-β[3-(5-benzyloxyindole)]propionate (3.7 g., 0.01 mole) in 50 ml. of absolute alcohol was hydrogenated at 40 p.s.i. of hydrogen using 1.0 g. of platinum oxide catalyst. Uptake of hydrogen ceased after 1.75 hr. After carefully purging with nitrogen, the bottle was opened and 4.0 g. of a 20% (by weight) solution of sodium hydroxide was added. A hydrogen atmosphere was re-established in the bottle and hydrolysis was allowed to proceed at room temperature overnight. It is very important to exclude air; otherwise, the solution darkens rapidly and purification of the product is difficult. Twenty milliliters of water was added and the catalyst was removed by filtration. The *p*H of the filtrate was adjusted to 6 with glacial acetic acid whereupon a gelatinous solid formed. On heating it gradually changed to solid material. The mixture was cooled and the solid was collected and washed with water to give 2.64 g. of 5-benzyloxytryptophan. The compound is amphoteric and can be partially purified by dissolving in either acid or base, treating with charcoal and then adjusting the *p*H to 6. A small amount was purified in this manner and then crystallized from water containing a little alcohol; m.p. (introduced at 270°) 280° dec. (lit.,[16] m.p. 280° dec.).

d. *5-Hydroxytryptophan.* 5-Benzyloxytryptophan (3.42 g.) was suspended in 50 ml. of alcohol and 50 ml. of water with 1.0 g. of 10% palladium-on-charcoal and hydrogenated at 10 p.s.i. Reduction was rapid and complete. The catalyst was removed by filtration, but the filtrate was dark because of the presence of colloidal catalyst. The filtrate was concentrated to a small volume under vacuum and the resulting dark crystals were dissolved in water. The hot solution was filtered and allowed to crystallize. The crystalline material was still dark; therefore it was recrystallized from water, using a Seitz filter to remove the colloidal catalyst; white crystals were obtained (1.23 g.). A second crop was obtained by concentrating the mother liquor (0.29 g.). Total weight, 1.52 g. (62.5%). A small sample was recrystallized for analysis; m.p. 285° dec.[16] Ultraviolet: 220 sh (23,850); 275 (6,050); 300 (5,750); 312 (3,725). Infrared: OH/NH: 3380, 3240; NH_3^+: 3120, 3060, 2720, 2630, 2510, 2420;  deformation: 1632, 1596, 1403; C=C: 1612, 1495; C—O: 1233, 1221; ar. sub.: 855, 843, 813, 791, 765.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.50; N, 12.73. Found: C, 59.94; H, 5.50; N, 12.47.

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[CONTRIBUTION FROM THE MEDICAL CENTER, UNIVERSITY OF CALIFORNIA, LOS ANGELES, AND THE DEPARTMENT OF CHEMISTRY, FRESNO STATE COLLEGE]

Syntheses and Resolutions Involving Papain-Catalyzed Reactions between (Hydroxyalkyl)anilines and *N*-Acylamino Acids[1]

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Papain catalysis provides a means for acylating the amino group of substituted anilines containing an alcoholic hydroxyl without concurrent acylation of the alcoholic hydroxyl. These substituted anilines can be employed for resolution of certain *N*-acylamino acids like carbobenzoxy-DL-alanine, with papain as the catalyst and resolving agent. When the asymmetric center is shifted to the substituted aniline, as with *m*-(1-hydroxyethyl)aniline in its reaction with non-asymmetric hippuric acid, papain does not cause a resolution to take place, but a racemic product is formed in good yield instead. Reduction of *m*-aminoacetophenone to racemic *m*-(1-hydroxyethyl)aniline has been found to occur in good yield by means of lithium aluminum hydride. The optimum *p*H for the papain-catalyzed reaction between *m*-(1-hydroxyethyl)aniline and hippuric acid is about 4.7 for the experimental conditions employed.

Numerous papain-catalyzed syntheses of anilides[4-6] and phenylhydrazides[4,7,8] of *N*-acylamino acids have been studied, especially with reference to resolutions of *dl*-*N*-acylamino acids. Also, rates of precipitation of substituted hippuric anilides[9] have been investigated in relation to the effect of position of a given substituent on the aniline nucleus. However, nothing has been reported on the

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