that of benzoate esters.[33] The infrared spectrum showed absorption at 2.85, 2.91, 5.86, 7.80 and 8.50 μ.

1-Oxo-**4-indanacetic Acid (XVIII)**.—A mixture of 10 g. of *o*-(carboxymethyl)-hydrocinnamic acid (XVII), prepared by sodium and amyl alcohol reduction of 2-hydroxy-3-naphthoic acid,[13] and 260 g. of polyphosphoric acid was stirred vigorously and was maintained at 90–95° for 2.5 hr. While cooling the reaction externally with an ice-bath, 300 g. of cracked ice then was slowly added with stirring. The mixture containing the precipitated ketoacid was extracted continuously with ether and the ketoacid left on evaporation of the ether was recrystallized from water (6.91 g., 75%); m.p. of 151–153°. Further crystallization from water and sublimation (130° (5 μ)) gave material of m.p. 154–155°; λ_{max}^{EtOH} 247 mμ (ϵ 10,530), 291 (2,480).

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3; equiv. wt., 190. Found: C, 69.3; H, 5.3; equiv. wt., 187.

4-Indanacetic Acid (XIX).—A solution of 11.42 g. (0.06 mole) of 1-oxo-4-indanacetic acid (XVIII) in 200 ml. of abs. ethanol was hydrogenated at room temperature and atmospheric pressure using 2.3 g. of 5% palladized carbon as catalyst. After 8 hr., hydrogen absorption ceased at 94 mole % uptake. The mixture was filtered, the filtrate was evaporated and the residue was recrystallized from methanol–water to give 8.59 g. (81%) of acid, m.p. 101–102°; λ_{max}^{EtOH} 267 mμ (ϵ 869), 275 (894).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9; equiv. wt., 176. Found: C, 74.9; H, 6.8; equiv. wt., 175.

4-Indanpropionic Acid (XX).—Indanacetic acid (XIX) (8.57 g., 0.049 mole) dissolved in 35 ml. of purified[27] thionyl chloride was kept at room temperature for 3 hours after which the excess thionyl chloride was removed at reduced pressure. Distillation resulted in 6.88 g. (73%) of 4-indanacetyl chloride as the fraction boiling at 78–80° (0.3 mm.). A solution of this acid chloride in 25 ml. of abs. ether was allowed to react with 4.6 g. (0.11 mole) of diazomethane in 300 ml. of ether as described for the preparation of 2,2a-3,4 - tetrahydro - 1H - cyclopent[cd] - 1 - indenepropionic acid (V), above, and 5.19 g. of methyl 4-indanpropionate was obtained as the fraction boiling at 102–108° (0.6 mm.). Saponification gave 4-indanpropionic acid (4.1 g., 44% over-all yield) which was recrystallized from methanol–water, m.p. 113–114°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4; equiv. wt., 190. Found: C, 75.5; H, 7.3; equiv. wt., 188.

3-Oxo-1,2,3,6,7,8-hexahydro-*as*-indacene (XXI).—4-Indanpropionic acid (XX) (2.11 g., 0.011 mole) and 57 g. of polyphosphoric acid were stirred vigorously and maintained at 95–100° for 1 hour after which 50 grams of ice was added cautiously with stirring to the externally cooled reaction mixture. The aqueous mixture was extracted with ether the ether was washed with *N* carbonate, dried and evaporated, and the residual ketone crystallized from methanol–water in long fine needles; yield 1.65 g. (84%), m.p. 108–109°; λ_{max}^{EtOH} 209 mμ (ϵ 20,650), 218 (22,820), 261 (13,330).

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.7; H, 7.0. Found: C, 83.7; H, 7.1.

The *p*-toluenesulfonylhydrazone of XXI was prepared in the usual manner and crystallized from benzene–ethanol, m.p. 230–231° dec.

Anal. Calcd. for $C_{19}H_{20}O_2N_2S$: C, 67.0; H, 5.9; N, 8.2. Found: C, 66.8; H, 5.9; N, 8.5.

1,2,3,6,7,8-Hexahydro-*as*-indacene (XXII).—A solution of 4.1 g. (0.024 mole) of 3-oxo-1,2,3,6,7,8-hexahydro-*as*-indacene (XXI) in 100 ml. of abs. ethanol was hydrogenated at room temperature and atmospheric pressure with 0.8 g. of 5% palladized carbon as catalyst. After 15 hr. the hydrogen absorption ceased at 92% of the theoretical two-mole absorption. The mixture was filtered, the filtrate was evaporated, and the residue was dissolved in ether. The ethereal solution was washed with *N* carbonate, dried and evaporated, and the solid residue was sublimed, resulting in 3.4 g. (90%) of hydrocarbon of m.p. 40–42° (reported[14] m.p. 39–40°); λ_{max}^{hexane} 265 mμ (ϵ 513), 269 (775) 273 (635) 279 (896).

Anal. Calcd. for $C_{12}H_{14}$: C, 91.1; H, 8.9. Found: C, 90.8; H, 8.9.

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[33] H. E. Ungnade and R. W. Lamb, THIS JOURNAL, **74**, 3789 (1952).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

3-Acylindole Mannich Bases and their Transformation Products

BY J. SZMUSZKOVICZ

RECEIVED JULY 8, 1959

The Mannich-base reaction of several 3-acylindole derivatives was studied and in two cases the formation of bis-Mannich bases (X and XII) was observed. Several reactions of the bases were explored which included lithium aluminum hydride and sodium borohydride reduction of VI. The alcohol XIII was dehydrated to the vinylog of gramine XV. The Mannich base methiodide XVII underwent displacement with sodium cyanide to give the ketocyanide XVIII and elimination with sodium bicarbonate to give the vinylketone XX.

The reaction which is known in the literature as the "Mannich Base Condensation" has been reviewed by Blicke[1] and Hellman[2] and several mechanisms have been suggested.[3,4]

We have undertaken the present work with two objectives in mind. First, we have been interested in the indole field from the standpoint of biological activity and it was hoped that the Mannich base reaction would afford versatile intermediates in this respect. Secondly, we were interested in studying the results of the Mannich base condensation in a case where one could vary the alkyl substitution on the carbon adjacent to the reaction site and also on the indolic nitrogen.

The 3-acetylindole molecule (I) seemed to be a good candidate for this study. The carbonyl function gives rise to the hybrid formulated as I, in which ketonic and vinylogous amide structures contribute. The chemical and physical properties of this system correlate well with the properties expected from this formulation. Thus, 3-acetylindole forms a phenylhydrazone,[5] a hydrazone,[6] an oxime[7] and a thiosemicarbazone.[8] On the other

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[1] F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303.

[2] H. Hellmann, *Angew. Chem.*, **65**, 473 (1953).

[3] H. Hellmann and G. Opitz, *ibid.*, **68**, 265 (1956); H. Hellmann and G. Opitz, *Ber.*, **89**, 81 (1956); H. Hellmann and O. Schumacher, *ibid.*, **89**, 95 (1956); E. C. Wagner, *J. Org. Chem.*, **19**, 1862 (1954); E. R. Alexander and E. J. Underhill, THIS JOURNAL, **71**, 4014 (1949).

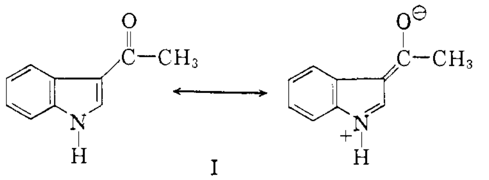
[4] S. V. Liebermann and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949).

[5] B. Oddo and L. Sessa, *Gazz. chim. ital.*, **41**, 234 (1911).

[6] C. Alberti, *ibid.*, **77**, 398 (1947).

[7] Ramart-Lucas and M. Roch, *Compt. rend.*, **232**, 843 (1951).

[8] G. Tsatsas, *ibid.*, **235**, 175 (1952).



I

hand, it undergoes hydrogenolysis with lithium aluminum hydride[9] and the ultraviolet spectrum in alkaline solution shows a new maximum at higher wave length (332 mμ; see experimental). Furthermore, the properties of certain derivatives of I indicate added stability due to the hybridization as is apparent, for example, from the alkaline hydrolysis of the ketonitrile XVIII to γ-(3-indolyl)-γ-ketobutyric acid which could be carried out in 99.5% yield.[10]

When compound I was subjected to reaction with dimethylamine hydrochloride and paraformaldehyde in ethanol, a 78% yield of 3-(β-dimethylaminopropionyl)-indole (VI) was obtained. The infrared spectrum showed NH and amide C=O absorption (1629 cm.$^{-1}$); ultraviolet maxima were at 242, 257 and 299 mμ and a new maximum at 330.5 mμ was obtained on addition of alkali which indicated an unsubstituted indolic nitrogen. Analogously, 1-methyl-3-acetylindole (II) gave the Mannich base VII and 1-ethyl-3-acetylindole (III), 1-methyl-3-propionylindole (V) and 3-acetyl-5-benzyloxyindole afforded VIII, IX and 3-(β-dimethylaminopropionyl)-5-benzyloxyindole, respectively.

Condensation of I with dibenzylamine hydrochloride and paraformaldehyde afforded 3-(β-dibenzylaminopropionyl)-indole.

When 3-propionylindole (IV) was subjected to the Mannich-base reaction under the conditions used for the above-mentioned condensation (namely, 1 mole of the acyl compound, 1 mole of dimethylamine hydrochloride and 1.5 moles of paraformaldehyde) only a 10% yield of a base was obtained which was isolated in the form of the dihydrochloride. It showed amide C=O absorption (1655 cm.$^{-1}$) in the infrared, but no NH. On treatment with an excess of ethanolic picric acid, dimethylamine picrate and also the picrate of XI were isolated. Therefore, in the case of 3-propionylindole, the Mannich-base condensation occurred both on the side chain and on the indolic nitrogen to afford the dihydrochloride of the base X. When an excess of reagents was used, the yield of the dihydrochloride was raised to 18%. The transformation of X to XI was also accomplished by means of alkaline treatment.

When the Mannich-base condensation with 3-acetylindole (I) was repeated using a large excess of reagents, the corresponding bis-Mannich base XII was obtained in good yield. On treatment with picric acid, a mixture of the picrates of VI and XII was obtained. Alkaline decomposition of the picrate of XII afforded the corresponding bis-Mannich base. This compound (XII) appears to be somewhat more stable than X and this effect must be attributed to absence of the methyl group in the 3-acetyl side-chain.[11]

The condensation products X and XII contain a N-dimethylaminomethyl group which is not uncommon.[12]

Unlike the case of simple methylenedialkylamines,[4] the system present in X and XII is somewhat stabilized due to the nature of the indolic nitrogen.

On reduction with lithium aluminum hydride (LAH) the vinylogous amide VI underwent hydrogenolysis to give 3-(γ-dimethylaminopropyl)-indole. A number of reactions of this type have appeared in the literature recently, *e.g.*, in the case of 3-formyl- and 3-acetylindole,[9] and 5-benzyloxy-3-indole-N,N-dibenzylglyoxylamide.[13]

Sodium borohydride reduction of VI afforded the secondary alcohol XIII and that of VII afforded XIV.[14] Dehydration of XIII was accomplished by treatment with ethyl chloroformate in pyridine.[15] This method afforded *directly* the desired *vinylogous gramine* XV. The structure of this compound is supported by the strong infrared absorption band at 1651 (C=C) and the ultraviolet absorption maximum at 261.5 mμ (18,800; see Experimental). On catalytic reduction of XV, one mole of hydrogen was taken up to give 3-(γ-dimethylaminopropyl)-indole, identical with the product obtained by LAH reduction of VI. The same method[15] was used to dehydrate XIV to XVI.

On heating with sodium cyanide in dimethylformamide solution, the methiodide XVII afforded β-cyanoethyl-3-indolyl ketone (XVIII) in 80.7% yield and a small amount of a by-product, the structure of which is indicated by the infrared spectrum as the Michael adduct XIX. Compared to XVIII (C=O band at 1629 cm.$^{-1}$) there is an additional C=O band present at 1648 cm.$^{-1}$. Zerewitinoff determination showed only one active hydrogen. This type of cationic alkylation of indolic nitrogen in the 3-acylindole system is not unusual.[16]

The ketonitrile XVIII was hydrolyzed to γ-(3-indolyl)-γ-ketobutyric acid which corresponded in properties to the known sample.[17,18]

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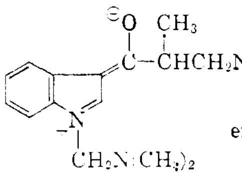
(9) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).

(10) See also footnote 9 in This Journal, **80**, 3784 (1958).

(11) It is likely that the enol form of X is less preferred than the keto form. This would bring about a weakening of the bond between the indolic nitrogen and the $-CH_2N(CH_3)_2$ substituent and greater susceptibility of X to hydrolysis as compared to XII.



enol of X

(12) S. Swaminathan, S. Ranganathan and S. Sulochana, *J. Org. Chem.*, **23**, 707 (1958), and references therein.

(13) M. E. Speeter and W. C. Anthony, This Journal, **76**, 6208 (1954).

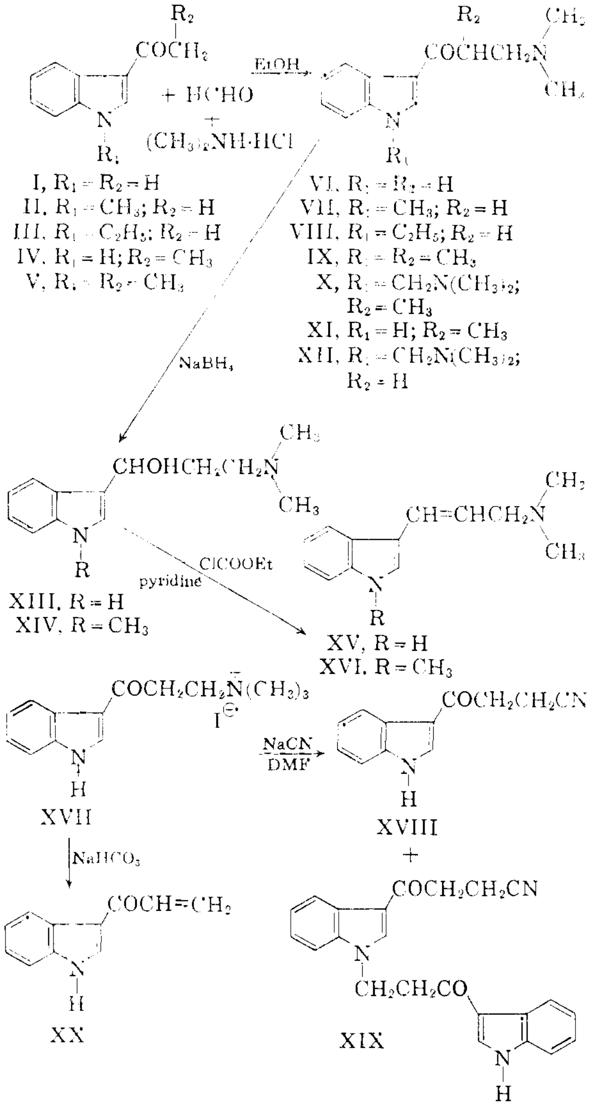
(14) Interestingly no hydrogenolysis occurred in these two cases of the sodium borohydride treatment; XIII and XIV can be regarded as vinylogous carbinolamines and are, therefore, somewhat reminiscent of systems reported by S. Bose [*J. Indian Chem. Soc.*, **32**, 350 (1955)], although in our case the aromatic system, substituted by electron-releasing groups, is lacking.

(15) G. L. O'Connor and H. R. Nace, This Journal, **74**, 5454 (1952).

(16) J. Thesing, S. Klüssendorf, P. Ballach and H. Meyer, *Ber.*, **88**, 1295 (1955).

(17) R. Majima, T. Shigematsu and T. Rokkaku, *ibid.*, **57**, 1453 (1924).

(18) Unlike the case of the alkaline hydrolysis of methyl 3-indolebutyrate, where 2-keto-2,3,4,5-tetrahydrocarbazole was obtained as a by-product [R. W. Jackson and R. H. Manske, This Journal, **52**, 5029 (1930)], no cyclized material was isolated from the hydrolysis of XVIII. This effect is likely due to the electronic inhibition of activation at the 2-position imparted by the 3-acyl substituent.



The methiodide XVII could be converted *via* a reverse Michael reaction to 3-indolylvinyl ketone XX and the best yield was obtained employing sodium bicarbonate under controlled conditions (see Experimental). The infrared spectrum of the vinyl ketone showed NH, amide C=O and strong C=C absorption. The ultraviolet spectrum indicated additional conjugation (λ_{max} 258, 269.5, 274.5, 324 mμ)[19] as compared to 3-propionylindole. The chemical properties of XX agree with the proposed structure. Thus, on addition of dimethylamine the Mannich base VI was isolated, and on reduction with LAH a mixture resulted from which 3-propionylindole (IV) was isolated in small yield.[20]

Addition of ethylene-imine to XX furnished 3-(β-aziridinylpropionyl)-indole.

Experimental[21,22]

Preparation of Starting Materials.—3-Acetylindole (I) was prepared by the Grignard reaction[23] and also by acetylation of indole[24]; ultraviolet spectrum: 241 (12,600), 259 (8,650), 297 (12,275); in 0.01 *N* alcoholic KOH: 241 (10,775), 263 (9,800), 275 (8,650), 298 (10,825), 332 (4,750); infrared spectrum: NH (3140), C=O (1620, 1610sh), C=C (1575, 1524, 1492).

1-Methyl- and 1-ethyl-3-acetylindole (II and III) were prepared according to the literature[25] but using a sufficient amount of alkali so as to produce a basic mixture at the end of the reaction.

3-Propionylindole (IV) was prepared by the Grignard reaction.[5] Recrystallization from methanol afforded colorless plates, m.p. 170–171.5° (reported[5] m.p. 157–158°); ultraviolet spectrum: 241 mμ (12,225), 258 (8,500), 297 (12,175); in 0.01 *N* alcoholic alkali: 241 (11,175), 260 (8,650), 297 (11,125), shoulder 332 (2,075).

1-Methyl-3-propionylindole (V).—A suspension of 3-propionylindole (51.0 g., 0.295 mole) in 530 ml. of water and 52 g. of sodium hydroxide was heated to 70° on the steam-bath. Heating was discontinued and 56 ml. of dimethyl sulfate was added during 5 minutes. The process of addition was repeated two more times and the mixture was then heated at 95° for 2.5 hours. The oily layer solidified overnight. The solid was filtered and washed with water to give 52.75 g. melting at 74–79°. It was dissolved in 800 ml. of ether, filtered from a brown impurity and evaporated down till crystallization started, m.p. 80–81.5° (40.15 g., 73% yield). A sample was recrystallized from ether to give rods melting at 80.5–81.5°; ultraviolet spectrum: 211.5 (25,975), 244 (13,800), flex 250 (12,625), 302 (1395); infrared spectrum: C=O (1643), C=C (1615, 1605, 1576).

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.00; H, 6.80; N, 7.73.

5-Benzyloxyindole was prepared according to the literature.[26]

3-Acetyl-5-benzyloxyindole.—5-Benzyloxyindole (11.15 g., 0.05 mole), dissolved in 100 ml. of ether and 150 ml. of benzene, was added during 5 minutes to a Grignard reagent prepared from magnesium (2.68 g., 0.11 mole) and methyl iodide (17 g., 0.12 mole). The mixture was refluxed for 75 minutes. It was then cooled in ice and 8.65 g. (0.11 mole) of acetyl chloride in 25 ml. of ether was added dropwise. The resulting mixture was stirred for 3 hours at room temperature. It was then cooled in ice and acidified with a solution of 15 ml. of acetic acid in 50 ml. of water. After stirring for 15 minutes, the precipitate (a) was filtered, washed with water, then ether, and finally water. The filtrate was evaporated down in a current of air. The resulting oily product was filtered and washed with a little ether to give solid (b). The crude product (a) was suspended in 50 ml. of ethanol, a solution of 3.0 g. of potassium hydroxide in 10 ml. of water was added and the resulting solution was evaporated down to about half its volume to give 5.95 g. of 3-acetyl-5-benzyloxyindole melting at 186–190°. For analysis it was recrystallized from ethanol, m.p. 188–190°, colorless short rods; ultraviolet spectrum: 250.5 mμ (18,175), flex 268 (11,300), 299 (10,775), no peak at 332 (a_M 1750); in 0.01 *N* KOH: 250 (16,350), 268.5 (12,300), 298 (10,525), no peak at 332 (a_M 3,625); infrared spectrum: NH (3140, 3050), C=O (1614, 1630w), C=C (1584, 1526), C—O (1199).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.36; H, 5.43; N, 5.39.

Solid b was hydrolyzed with ethanolic alkali as described for (a) and afforded, along with the second crop from a and a second crop from b, an additional 2.60 g., m.p. 185–188° (total yield 65.6%).

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[19] *Cf.* F. Bohlmann, *Ber.*, **89**, 2191 (1956).

[20] *Cf.* J. Bruesch and P. Karrer, *Helv. Chim. Acta*, **38**, 905 (1955); J. P. Freeman and M. F. Hawthorne, THIS JOURNAL, **78**, 3366 (1956).

[21] All melting points are uncorrected. Ultraviolet spectra were determined in 95% ethanol using Cary spectrophotometers, models 11 and 14. Infrared spectra were determined in Nujol (except when otherwise specified) using a Perkin-Elmer recording infrared spectrophotometer, model 21.

[22] Acknowledgments: The author is indebted to Prof. D. J. Cram for stimulating discussions, Dr. J. L. Johnson and his staff for spectral data, Mr. W. A. Struck and his associates for microanalysis and neut. equiv. determinations, and Mr. L. G. Laurian for laboratory assistance.

[23] R. Majima and M. Kotake, *Ber.*, **55**, 3865 (1922); J. W. Baker, *J. Chem. Soc.*, 461 (1946). Acknowledgment is due to Mr. P. E. Marlatt and his group who improved the original procedure by carrying out the reaction of acetyl chloride with the indole Grignard complex in benzene solution.

[24] J. E. Saxton, *J. Chem. Soc.*, 3592 (1952).

[25] Y. A. Baskakov and N. N. Mel'nikov, *C. A.*, **49**, 1006 (1955).

[26] W. E. Boehme, THIS JOURNAL, **75**, 2502 (1953).

3-(β-Dimethylamino)-propionylindole (VI).—A mixture 3-acetylindole (15.9 g., 0.1 mole), dimethylamine hydrochloride (8.15 g., 0.1 mole), paraformaldehyde (4.5 g., 0.15 mole) and 150 ml. of absolute ethanol was refluxed for 24 hours. The clear brown solution was allowed to stand at room temperature for another day and was then evaporated *in vacuo* to a viscous oil. Water (200 ml.) was added and the precipitate obtained was filtered and washed with water, m.p. 170–180°, 3.25 g. (20.4% recovery). Recrystallization from methanol afforded pure 3-acetylindole, m.p. 191–193°, which did not depress the melting point of the authentic sample. The aqueous filtrate was extracted twice with ether (ether was discarded). The clear aqueous solution was then cooled in ice and made alkaline with a cold solution of potassium hydroxide (10 g.) in 25 ml. of water. The resulting oil was extracted twice with ether, and the ethereal extracts were washed twice with a saturated salt solution and dried over sodium sulfate at which point partial precipitation of the product occurred. The ethereal solution was evaporated and gave 13.06 g. of pale yellow crystalline product. The rest of the product was recovered by extraction of the drying agent with chloroform and evaporation, and afforded 3.78 g. of product bringing the yield to 78%. Recrystallization of either crop from benzene gave pale yellow plates, m.p. 116–118.5°. Once a polymorphic form, m.p. 128–130°, was obtained; ultraviolet spectrum: 242 (13,175), 257 (9,250), 299 (12,650); in 0.01 *N* alcoholic alkali: 242 (11,250), 264 (10,925), 300 (10,525), 330.5 (5.850). It compared well with the spectrum of 3-acetylindole (*vide supra*); infrared spectrum: NH (3440, 3250), C=O (1640), C=C (1581, 1524).

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.96. Found: C, 72.37; H, 7.28; N, 12.72.

The hydrochloride precipitated as an oil when hydrogen chloride was passed through a chloroform solution of VI. Ether was added to complete the precipitation. Trituration with acetone produced a solid which crystallized from methanol–ether as white needles, m.p. 179–180°.

Anal. Calcd. for $C_{13}H_{17}ClN_2O$: C, 61.77; H, 6.78; Cl, 14.03; N, 11.09. Found: C, 61.36; H, 6.93; Cl, 13.97; N, 10.69.

The picrate was formed in ethanolic solution and was recrystallized from ethanol as long yellow needles, m.p. 175.5–178°.

Anal. Calcd. for $C_{19}H_{19}N_5O_8$: C, 51.24; H, 4.30; N, 15.73. Found: C, 51.83; H, 4.42; N, 15.50.

1-Methyl-3-(β-dimethylaminopropionyl)-indole (VII).—A mixture of 13.6 g. (0.0785 mole) of 1-methyl-3-acetylindole (II), dimethylamine hydrochloride (6.4 g., 0.0785 mole), paraformaldehyde (3.54 g., 0.118 mole) and absolute ethanol (120 ml.) was refluxed for 27 hours. The solution was evaporated *in vacuo* and the crude solid was recrystallized twice from methanol–ether, m.p. 186–187°, 11.4 g. (54% yield of the hydrochloride); second crop, 0.55 g., m.p. 185–186°.

Anal. Calcd. for $C_{14}H_{19}ClN_2O$: C, 63.03; H, 7.35; Cl, 13.29; N, 10.50. Found: C, 62.81; H, 6.93; Cl, 13.33; N, 9.96.

Ultraviolet spectrum: 211 (26,300), 244 (13,575), 304 (14,100); infrared spectrum: 3580w, 3440w (possibly traces of water), $\succ N^{+}HCl^{-}$ (2570, 2520, 2470), C=O(1645), C=C (1577, 1534, 1486), *o*-disubstituted benzene (752).

The mother liquors, remaining after the removal of the hydrochloride, were evaporated to dryness, water was added and the mixture was extracted twice with ether. The ethereal extracts yielded, after drying and evaporation, 3.66 g. (26.9% recovery) of 1-methyl-3-acetylindole, m.p. 86–102°.

The aqueous layer was cooled in ice and basified with 5.0 g. of potassium hydroxide in 10 ml. of water. The oil was extracted thrice with ether, washed with water, salt solution and dried over sodium sulfate. Evaporation gave 3.37 g. (18.7%) of brown oil which could not be crystallized. A small amount of the oil was converted to the hydrochloride, m.p. 179–187°. Mixed m.p. with the above hydrochloride was 180–183°.

1-Ethyl-(β-dimethylaminopropionyl)-indole (VIII).—A mixture of 1-ethyl-3-acetylindole (III) (49.32 g., 0.264 mole), dimethylamine hydrochloride (25.8 g., 0.316 mole) and paraformaldehyde (15.85 g., 0.528 mole) in 400 ml. of absolute ethanol was refluxed for 19 hours. The resulting solution was evaporated to dryness on the steam-bath *in vacuo*. The residue was dissolved in 350 ml. of water and extracted twice with ether. The ethereal extracts were washed once with water, then with saturated salt solution, dried over sodium sulfate and evaporated to give 6.0 g. (12.2% recovery) of unchanged III, m.p. 81–82°.

The brown aqueous solution was cooled in ice and basified with a solution of potassium hydroxide (33.6 g.) in water (110 ml.). The resulting oil was extracted thrice with ether (total extracts *ca.* 700 ml.). The ethereal extracts were washed with saturated salt solution, dried through sodium sulfate and evaporated to give 56 g. (87% yield) of a brown oil (VIII) which could not be crystallized.

Methiodide of VIII.—Fifteen grams of the crude oil was dissolved in 65 ml. of methanol and cooled in ice. Methyl iodide (17.5 g.) was added during 10 minutes and the mixture was kept in ice for 0.5 hour and then at room temperature for 40 minutes. The crystals were filtered, washed with methanol and then with ether, m.p. 192–194°, 20.6 g. A second crop amounted to 1.15 g., m.p. 185–193° (total yield 91.9%). Recrystallization from methanol afforded pale yellow needles, m.p. 192–194° (s, 190°); ultraviolet spectrum: 244 (11,625), sh 252, 260 (8,625), 309 (12,725).

Anal. Calcd. for $C_{16}H_{23}IN_2O$: C, 49.75; H, 6.00; I, 32.86; N, 7.25. Found: C, 49.61; H, 6.09; I, 32.51; N, 7.03.

1-Methyl-3-(α-methyl-β-dimethylaminopropionyl)-indole (IX).—A mixture of 1-methyl-3-propionylindole (9.35 g., 0.05 mole), dimethylamine hydrochloride (20.4 g., 0.25 mole), paraformaldehyde (11.3 g., 0.375 mole) and absolute ethanol (175 ml.) was refluxed for 21 hours. It was then evaporated to dryness and the resulting oily solid was treated with 100 ml. of water, filtered and washed with water. The solid amounted to 5.85 g. and melted at 79–80.5°; mixed m.p. with the starting material showed no depression (62.5% recovery).

The aqueous filtrate was extracted twice with 100-ml. portions of ether (discarded) and was then cooled in ice and basified with a solution of 17 g. of potassium hydroxide in 50 ml. of water. The resulting mixture was extracted thrice with ether (350 ml.). The extracts were washed once with water, once with saturated salt solution, dried through sodium sulfate and evaporated to give 4.0 g. (32.7% yield) of an oil which solidified on standing, m.p. 77–78°. Crystallization from Skellysolve B afforded rods, m.p. 79.5–80.5°; ultraviolet spectrum: 210.5 (27,175), 244 (16,255), 303 (14,925); infrared spectrum: C=O (1630, 1623), C=C (1608, 1568).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 74.00; H, 8.12; N, 11.48.

In a later experiment a more stable polymorph was isolated as leaflets (from Skellysolve B), m.p. 110–111.5°.

3-(β-Dimethylaminopropionyl)-5-benzyloxyindole.—A mixture of 2.65 g. (0.01 mole) of 3-acetyl-5-benzyloxyindole, 0.98 g. (0.012 mole) of dimethylamine hydrochloride, paraformaldehyde (0.6 g., 0.02 mole) and 25 ml. of absolute ethanol was refluxed for 26 hours. Crystals appeared after a few hours of refluxing. The mixture was allowed to stand overnight; it was then cooled in ice, filtered and washed with cold methanol, then ether, m.p. 199–201°; 2.48 g. (69.5% yield of the hydrochloride). The hydrochloride was recrystallized twice by dissolving in 75 ml. of absolute ethanol and evaporating down to 40 ml., colorless prisms, m.p. 199.5–200.5°; ultraviolet spectrum: 213 (34,200), 252 (18,150), 269 (11,125), 302 (10,900), at 332 no peak or flex (a_M 2775); in 0.01 *N* alcoholic alkali: 213 (32,250), 252 (16,025), 270 (12,825), 298 (10,450), at 332 no peak or flex (a_M 4975).

Anal. Calcd. for $C_{20}H_{23}ClN_2O_2$: C, 66.93; H, 6.46; Cl, 9.88; N, 7.81. Found: C, 67.30; H, 6.86; Cl, 9.82; N, 8.05.

3-(β-Dibenzylaminopropionyl)-indole.—A mixture of 3-acetylindole (4.35 g., 0.0274 mole), dibenzylamine hydrochloride (6.4 g., 0.0274 mole), paraformaldehyde (1.23 g., 0.041 mole) and 41 ml. of absolute ethanol was refluxed for 24 hours. The solution was cooled to room temperature, whereupon crystallization occurred. Water waas added and the solution (a) extracted three times with ether. The ethereal extracts (c) were washed once with water and the aqueous wash added to solution a. The ether (c) was then washed once with a saturated sodium chloride solution and this wash (b) allowed to stand at room temperature whereupon it deposited crystals. The solution (a) was cooled and basified with potassium hydroxide (3 g. in 10 ml. of water). The oil was extracted twice with ether. The ethereal extracts were washed with saturated salt solution, dried over sodium sulfate and evaporated to give 5.19 g. of an oil. Trituration with ether–petroleum ether (30–60°) gave 2.1 g. of the free base, m.p. 121–127° (20.8% yield).

Two recrystallizations from benzene–petroleum ether gave faint yellow rods, m.p. 130.5–132°; ultraviolet spectrum: 242.5 (13,975), sh 260 (10,100), 299 (12,425); infrared spectrum: NH (3160, 3110), C═O (1612), C═C (1579, 1521, 1494), mono- and *o*-disubstituted benzene (737, 689).

Anal. Calcd. for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.97; N, 7.61. Found: C, 81.38; H, 6.35; N, 7.78.

The crystals which formed in wash b were filtered, 0.6 g., m.p. 188–190°. Recrystallization from methanol–ether (5:1) gave colorless needles of the base as the hydrochloride, m.p. 189–189.5°.

Anal. Calcd. for $C_{25}H_{25}ClN_2O$: Cl, 8.76. Found: Cl, 8.85.

The original ethereal extract c was dried over sodium sulfate and evaporated to give 4.4 g. of brown oil which afforded crystals from methanol–ether, 0.9 g., m.p. 170–175°. Recrystallization gave material melting at 189–190°, which did not give melting point depression with the above hydrochloride. The yield of the hydrochloride was 1.5 g. (13.5%) and the total yield 32.3%.

Preparation of 1-Dimethylaminomethyl-3-(α-methyl-β-dimethylaminopropionyl)indole (X).—A mixture of 3-propionylindole (3.46 g., 0.02 mole), dimethylamine hydrochloride (8.16 g., 0.1 mole), paraformaldehyde (4.5 g., 0.15 mole) and absolute ethanol (70 ml.) was refluxed for 28 hours. The mixture was then evaporated down to *ca.* 15 ml. and water was added. The resulting solid was washed with water, 1.85 g., m.p. 169–172° (53.5% recovered starting material as shown by mixed m.p.). The filtrate was extracted twice with chloroform (chloroform was discarded). The aqueous layer was basified with 10% potassium hydroxide solution and extracted with chloroform. The chloroform extracts were washed with saturated salt solution, dried over sodium sulfate and evaporated to give 1.5 g. of yellow oil. The dihydrochloride was prepared in ether with ethereal hydrogen chloride. It was dissolved in 5 ml. of methanol, 20 ml. of acetone was added and then 80 ml. of anhydrous ether; m.p. 187–190°, 1.3 g. (18% yield as dihydrochloride); ultraviolet spectrum: 208.5 mμ (28,700), 242 (13,300), 258 (9,400), 300 (12,800); infrared spectrum: NH absent; N^+HCl^- (2600, 2500, 2450, 2410), C═O (1655), C═C (1614, 1546), *o*-disubstituted benzene (744, 732).

Anal. Calcd. for $C_{17}H_{27}Cl_2N_3O$: C, 56.66; H, 7.55; Cl, 19.68; N, 11.66. Found: C, 55.95; H, 7.22; Cl, 19.51; N, 11.51.

The dihydrochloride was treated with 10% potassium hydroxide in water. Extraction with ether gave rise to the free base X which was an oil.

Proof of Structure of the Bis-Mannich Base (X). (a) Synthesis of 3-(α-Methyl-β-dimethylaminopropionyl)-indole (XI) from X by Picric Acid Treatment.—The crude bis-Mannich base X (2.0 g.) was dissolved in 10 ml. of ethanol and treated with 40 ml. of saturated ethanolic picric acid solution whereupon a heavy oil separated. When the solution was heated to boiling the oil dissolved and then a crystalline yellow picrate precipitated out. The mixture was allowed to stand at room temperature for 4 hours; it was then filtered and washed with ethanol (original ethanolic filtrate); m.p. 201–203°, 2.7 g. The picrate of XI was recrystallized by dissolving in 1 l. of boiling ethanol and concentrating until crystallization started, 2.38 g., m.p. 217–219°. A second crop was obtained by concentrating the mother liquor; 0.23 g., m.p. 216–217°.

Anal. Calcd. for $C_{20}H_{21}N_5O_8$: C, 52.28; H, 4.61; N, 15.25. Found: C, 52.21; H, 4.62; N, 15.63.

The original ethanolic filtrate was evaporated down to *ca.* 20 ml. and allowed to crystallize overnight; well defined blocks, m.p. 154–155° (0.98 g.). Recrystallization from ethanol gave the picrate of dimethylamine, m.p. 156–157°; mixed m.p. with authentic sample (m.p. 159.5–160°) was 157–158.5°.

Decomposition of XI Picrate.—The picrate (2.38 g.) was suspended in ether and decomposed with a dilute solution of sodium and ammonium hydroxide. The colorless ethereal solution was washed with saturated salt solution, dried over sodium sulfate and evaporated. The resulting pale yellow oil solidified and crystallization from ethyl acetate–petroleum ether (30–60°) in *ca.* $^1/_{10}$ ratio gave colorless prisms of XI, m.p. 101–102°; ultraviolet spectrum: 241.5 (13,650), sh 260 (9,550), 297.5 (13,025); in 0.01 *N* alcoholic potassium hydroxide: 242 (12,025), 261 (10,350), 298 (11,725), 332 (3,675); infrared spectrum: NH (3280), tert. amine (2800), C═O (1634), C═C (1623, 1579, 1519, 1498), *o*-disubstituted benzene (747, 738).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.12; neut. equiv., 230.30. Found: C, 72.99; H, 7.61; N, 11.74; neut. equiv., 234.9.

(b) Synthesis of XI by Alkaline Treatment.—A solution of potassium hydroxide (1.95 g.) in 5 ml. of water was added to a solution of crude X in 12.5 ml. of methanol and the resulting solution was refluxed 0.5 hour. It was then evaporated on the steam-bath *in vacuo* to get rid of methanol, 20 ml. of water was added and the resulting product was extracted thrice with a total of 50 ml. of chloroform. The chloroform extracts were washed once with water (discarded water and saved chloroform) and then thrice with 10% hydrochloric acid (20-, 10- and 10-ml. portions). The combined acid extracts were washed once with 10 ml. of chloroform (saved chloroform) and then poured into an ice-cold solution of 25% potassium hydroxide (20 ml.). The resulting mixture was extracted thrice with ether (total 150 ml.). The ethereal extracts were washed once with water, once with a saturated sodium chloride solution, dried over sodium sulfate and evaporated to give 0.543 g. of a yellow glass. The product was crystallized (with seeding) by treatment with 3 ml. of ethyl acetate and 9 ml. of petroleum ether (30–60°) and warming until a clear solution resulted; 0.265 g. of product was obtained, m.p. 101–102°. The infrared spectrum, ultraviolet spectrum and neut. equiv. of this material established its identity with XI as obtained by the picrate procedure a. The second crop amounted to 0.089 g. bringing the total yield to 44%.

The combined chloroform solution (*vide supra*) was washed with water, dried over sodium sulfate and evaporated to give 0.244 g. of a gummy solid. It was crystallized from 2 ml. of methanol to give 50 mg. of 3-propionylindole (m.p. 167–170°) as established by mixed m.p. with an authentic sample.

Preparation of 1-Dimethylaminomethyl-3-(β-dimethylaminopropionyl)-indole (XII).—A mixture of 3-acetylindole (31.8 g., 0.2 mole), dimethylamine hydrochloride (81.55 g., 1.0 mole), paraformaldehyde (45.6 g., 1.52 moles) in 705 ml. of absolute ethanol was refluxed for 21 hours. The resulting solution was then evaporated on the steam-bath *in vacuo* to give a light brown oil. It was dissolved in 500 ml. of water and the solution was cooled in ice and basified with aqueous potassium carbonate solution to *p*H 8–9. The resulting mixture was extracted thrice with ether (total 700 ml.). The ethereal solution was washed once with water and once with saturated salt solution. It was then dried through sodium sulfate and evaporated to give a dark brown oil, 39.3 g. (90.3% yield); ultraviolet spectrum: 243 (14,035), sh 258 (10,825), 301 (13,775); infrared spectrum: tertiary amine (2820s, 2770s), C═O (1639), C═C (1513, 1575, 1525), *o*-disubstituted benzene (746).

Anal. Calcd. for $C_{16}H_{23}N_3O$: C, 70.29; H, 8.48; N, 15.37; neut. equiv., 136.69. Found: C, 69.79; H, 8.78; N, 15.01; neut. equiv., 141.40.

Dihydrochloride of XII.—Ten grams of XII was dissolved in 150 ml. of ether. The solution was cooled in ice and acidified with a solution containing 15 ml. of saturated ethereal hydrogen chloride and 45 ml. of ether. The resulting precipitate was filtered and washed with ether. The slightly wet product was triturated with 100 ml. of methanol, then 350 ml. of acetone was added. The colorless solid was filtered after 3 hours and washed with acetone; 5.8 g., m.p. 177.5–178° (s. 175°). Crystallization from methanol–acetone–ether afforded the dihydrochloride of XII, m.p. 184–187°.

Anal. Calcd. for $C_{16}H_{25}Cl_2N_3O$: C, 55.49; H, 7.28; Cl, 20.48; N, 12.13; neut. equiv., 173.15. Found: C, 54.72; H, 7.66; Cl, 20.51; N, 12.41; neut. equiv., 182.2.

Proof of Structure of the Bis-Mannich Base XII.—Five grams of XII was dissolved in 25 ml. of absolute ethanol and treated with 210 ml. of a saturated solution of picric acid in ethanol, whereupon a heavy oil was formed. On heating, the oil dissolved and shortly afterward crystallization took place. The mixture was allowed to cool to room temperature and was then filtered; yellow crystals, 7.56 g., m.p. 196–198°. Two recrystallizations from dimethylformamide–methanol afforded the dipicrate of XII, m.p. 204–205°.

Anal. Calcd. for $C_{28}H_{29}N_9O_{15}$: C, 45.97; H, 4.00; N, 17.23. Found: C, 46.33; H, 3.84; N, 16.87.

The original filtrate was evaporated down to about one-half its volume and allowed to crystallize overnight, m.p. 148–158°. It was dissolved in 175 ml. of ethanol, evaporated down to *ca.* 100 ml. and allowed to crystallize for 2 days; a mixture of deep yellow rods and small light yellow plates (likely the picrate of dimethylamine) was obtained. Treatment of this mixture with 200 ml. of boiling ethanol left some of the deep yellow rods undissolved, m.p. 183–185°, 280 mg.; mixed m.p. with authentic picrate of VI (m.p. 175.5–178°) was 179–184.5°.

Decomposition of the Dipicrate of XII.—The dipicrate was suspended in ether and decomposed in the usual manner with dilute alkali followed by extraction with ether. A colorless oil was obtained which was crystallized twice from benzene–petroleum ether (30–60°) and afforded XII as prisms, m.p. 128–128.5°; mixed m.p. with VI was 93–96°; ultraviolet spectrum: 243 (13,825), shoulder 258 (9,800), 301 (12,925); infrared spectrum: C=O (1650), C=C (1587, 1545, 1511), *o*-disubstituted benzene (756).

Anal. Calcd. for $C_{16}H_{23}N_3O$: C, 70.29; H, 8.49; N, 15.37; neut. equiv., 136.69. Found: C, 70.65; H, 8.38; N, 15.98; neut. equiv., 140.5.

3-(γ-Dimethylaminopropyl)-indole.—A solution of VI (1.0 g.) in 10 ml. of tetrahydrofuran was added to a suspension of lithium aluminum hydride (0.5 g.) in 25 ml. of tetrahydrofuran. The mixture was stirred for 15 minutes at room temperature and refluxed for 1.5 hours. It was then allowed to stand overnight and decomposed first with water, then with 50 ml. of 10% potassium hydroxide solution. The mixture was extracted thrice with methylene chloride. The combined extracts were washed once with 10% salt solution, dried over sodium sulfate and evaporated. The resulting oil was crystallized from benzene–petroleum ether (30–60°) with seeding, m.p. 90–96° (0.905 g., 97% yield). Recrystallization from Skellysolve B afforded prisms, m.p. 92–95°; ultraviolet spectrum: 223.5 (33.400), 275 (4,900), 283 (5,425), 292 (4,675); infrared spectrum: NH (3140, 3110, 3000), C=C (1623, 1575, 1550, 1505), *o*-disubstituted benzene (730).

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 76.96; H, 8.65; N, 14.18.

3-(α-Hydroxy-γ-dimethylaminopropyl)-indole (XIII).—One-half gram of VI in 5 ml. of methanol was added to a solution of sodium borohydride (0.5 g.) in 10 ml. of methanol. The solution was stirred at room temperature for 6 hours. Water was then added and the mixture extracted thrice with ether. The ethereal extracts were washed twice with saturated salt solution, dried over sodium sulfate and evaporated. A crystalline residue was obtained, m.p. 144–146° (0.48 g., 95% yield). Recrystallization from benzene–methanol afforded colorless plates, m.p. 149–151°; ultraviolet spectrum: 275 (5,550), 281 (5,825), 290 (4,925); infrared spectrum: NH, OH (3190), C=C (1660, 1618, 1585, 1554), *o*-disubstituted benzene (739).

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.84. Found: C, 71.74; H, 8.36; N, 12.83.

1-Methyl-3-(α-hydroxy-γ-dimethylaminopropyl)-indole (XIV).—Three and three-tenths grams of VII in 15 ml. of methanol was added to an ice-cold solution of 3.5 g. of sodium borohydride in 20 ml. of methanol. The mixture was stirred in the cold for 15 minutes, then 19 hours at room temperature. It was cooled in ice, diluted with water and extracted three times with ether. The ethereal extracts were washed with water, salt solution, dried over sodium sulfate and evaporated. The resulting product was an oil and the infrared showed some residual borate ester absorption (2370, 2320, 2280 cm.$^{-1}$). The oil was, therefore, dissolved in 75 ml. of methanol, 10 g. of potassium hydroxide and 25 ml. of water was added and the solution was refluxed for 2 hours. Methanol was then removed on the steam-bath *in vacuo*, the product was extracted thrice with ether and worked up as before. Crystallization from ether–petroleum ether (30–60°) gave 1.1 g., m.p. 85–87°. Recrystallization from the same pair gave colorless prisms, m.p. 87.5–88.5°.

Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.37; H, 8.68; N, 12.06. Found: C, 72.76; H, 8.64; N, 12.18.

The crude yield of this product was quantitative, but crystallization was rendered difficult because of the presence of traces of borate esters even after the alkaline hydrolysis[27]; ultraviolet spectrum: 287 (5,750), flex 297 (4,875); infrared spectrum: OH (3140), C=C (1614, 1602, 1550, 1487). *o*-disubstituted benzene (748).

Synthesis of the Gramine Vinylog (XV).—Twenty-nine grams of XIII was dissolved in dry pyridine and cooled in ice. Freshly distilled ethyl chloroformate (120 ml.) was then added dropwise as fast as possible while swirling by hand. The solid mixture was allowed to stand in the cold for 2 hours, then at room temperature for 21 hours, at which time two liquid layers were present. Ice and water were added and the mixture was extracted twice with ether (discard ether). The aqueous solution was cooled in ice, basified with a solution of 160 ml. of concentrated ammonia and 300 ml. of water (resulting *p*H 8–9), and extracted four times with ether. The ethereal extracts were washed once with water, twice with saturated salt solution, dried over sodium sulfate and evaporated. A yellow oil was obtained (21 g.) which was dissolved in 30 ml. of benzene and 40 ml. of petroleum–ether (30–60°). The solution was allowed to stand overnight in the cold. The crystals were filtered, washed with 5% benzene in petroleum ether, then with 50 ml. of ether–petroleum ether (1:1); 17 g. (69% yield), m.p. 105–109°. Recrystallization from benzene–petroleum ether afforded prisms, m.p. 108–112°; ultraviolet spectrum: 227 (26,725), flex 254, 261.5 (18,800), 284.5 (10,925), flex 291, flex 301; infrared spectrum: NH (3420, 3140, 3100, 3040), C=C (1651 v.s., 1622, 1594, 1534, 1508), *o*-disubstituted benzene (742).

Proof of Structure of the Gramine Vinylog (XV) by Reduction to 3-(γ-Dimethylaminopropyl)-indole.—A solution of 0.1 g. of XV in 15 ml. of ethanol was hydrogenated in the presence of 0.1 g. of 10% palladium-on-carbon. One mole of hydrogen was absorbed during a few minutes. The product (a colorless oil) was dissolved in 1 ml. of benzene, 5 ml. of petroleum ether (30–60°) was added and the mixture was filtered to separate a small amount of a colloidal precipitate. The resulting solution was evaporated down to about 1 ml., and 1 ml. of petroleum ether was added. Crystallization was induced by seeding and afforded well defined prisms, m.p. 91.5–96° (85 mg.). Mixed m.p. with authentic sample of 3-(γ-dimethylaminopropyl)-indole showed no depression.

1-[3′-(1′-Methyl)-indolyl]-3-dimethylaminopropene-1 (XVI).—Compound XIV (1.0 g.) was dissolved in pyridine (18 ml.) and treated in the cold during 5 minutes with 5 ml. of ethyl chloroformate. The mixture was kept in ice for 2.5 hours then at room temperature for 19 hours. Ice and water were added and the solution extracted twice with ether (ether was discarded). The yellow aqueous solution was cooled in ice, basified with a solution of 10 ml. of concentrated ammonia and 16 ml. of water, extracted four times with ether, washed once with water, twice with saturated salt solution, dried over sodium sulfate and evaporated to give a yellow oil which could not be induced to crystallize; ultraviolet spectrum: 229 (23,840), 263 (17,100), 288 (9,525), 305 (7,850); infrared spectrum: No OH; C=C (1656 v.s., 1613, 1570, 1538); *o*-disubstituted benzene (736). For analysis the sample was dried at 50° (0.1 mm.) overnight. On further drying the carbon value continued to decrease.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 77.48; H, 8.05; N, 12.73.

Trinitrofluorenone Complex.—A mixture of trinitrofluorenone (90 mg.) and the oily product XVI (71.5 mg.) in 10 ml. of ethanol was refluxed for 5 minutes. It was filtered from a small amount of undissolved material and evaporated to *ca.* 5 ml. After 0.5 hour it was decanted and allowed to crystallize for 2 hours; black needles, m.p. 97–99°.

Anal. Calcd. for $C_{27}H_{23}N_5O_7$: C, 61.24; H, 4.38; N, 13.23. Found: C, 61.27; H, 4.72; N, 13.11.

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(27) Recently a new method of decomposition of borate esters was recommended in the literature employing potassium fluoride [M. S. Newman and W. B. Lutz, THIS JOURNAL, **78**, 2469 (1956)].

3-(β-Dimethylaminopropionyl)-indole Methiodide (XVII)—A mixture of methyl iodide (20 ml.) and VI (1.0 g.) was refluxed for 21 hours. It was then cooled, the precipitate was filtered and washed with benzene; 1.45 g. (87.5% yield), m.p. 208–213°. Two crystallizations from methanol afforded pale yellow rods, m.p. 207.5–208.5°; ultraviolet spectrum: flex 240 (11,325), 258 (9,150), 275 (7,800), 308 (10,525); infrared spectrum: NH (3260), C=O (1645), C=C (1621, 1583, 1525, 1485), *o*-disubstituted benzene (757, 750).

Anal. Calcd. for $C_{14}H_{19}IN_2O$: C, 46.94; H, 5.35; I, 35.43; N, 7.82. Found: C, 47.03; H, 5.50; I, 35.39; N, 7.58.

Reaction of XVII with Sodium Cyanide to give XVIII and XIX.—A mixture of the methiodide XVII (15.1 g.), sodium cyanide (6.38 g.) and dimethylformamide (117 ml.) was heated on the steam-bath for 2 hours. It was then evaporated at reduced pressure on the steam-bath to a thick slurry; water was added to give a precipitate which was filtered and washed well with water. The precipitate was refluxed with 750 ml. of methanol and the suspension was filtered to get rid of the methanol-insoluble material. The filtrate was evaporated to *ca.* 80 ml. and allowed to crystallize. The first crop amounted to 6.35 g.; second crop, 0.35 g.; yield of XVIII, 80.7%; m.p. 212–214°. Recrystallization from methanol afforded pale yellow needles, m.p. 211–213.5°; ultraviolet spectrum: 242 (12,300), 259 (8,425), 300 (12,050); infrared spectrum: NH (3320, 3120), CN (2255), C=O (1629), C=C (1584, 1535, 1490), *o*-disubstituted benzene (747).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.75; H, 5.09; N, 14.14. Found: C, 72.52; H, 4.90; N, 14.38.

The methanol-insoluble precipitate (0.9 g., m.p. 260–266°) was recrystallized from 300 ml. of acetic acid. An additional recrystallization gave short needles of a compound for which structure XIX is proposed, m.p. 274–276.5° (s. 250°). This compound could also be recrystallized from dimethylformamide–water; ultraviolet spectrum: (in HOAc–EtOH) 245 (23,300), sh 264 (14,900), 303.5 (23,900); infrared spectrum: NH (3210, 3120), CN (2260), C=O (1648, 1630, 1616_{w}), C=C (1579, 1535, 1524, 1493), *o*-disubstituted benzene (748).

Anal. Calcd. for $C_{23}H_{18}N_3O_2$: C, 74.98; H, 4.92; N, 11.41; active H, 1. Found: C, 74.58; H, 5.13; N, 11.02; active H, 0.98.

Hydrolysis of XVIII to γ-(3-Indolyl)-γ-ketobutyric Acid.—A mixture of the ketonitrile XVIII (3.0 g.), potassium hydroxide (10 g.), methanol (60 ml.) and water (12 ml.) was refluxed for 23 hours. The clear yellow solution was evaporated down to *ca.* 10 ml. It was then cooled and acidified with a cold solution containing 20 ml. of concentrated hydrochloric acid and 50 ml. of water. The resulting pale yellow precipitate was filtered, m.p. 234–237° (s. 220°), 3.25 g. (99.5% yield). It was crystallized from acetone, m.p. 235–237° (reported[17] m.p. 235–236°, from acetic acid).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.35; H, 5.24; N, 6.26.

Ultraviolet spectrum: 241 (12,675), 262 (8,650), 297.5 (12,275); infrared spectrum: NH (3285), carboxyl OH (2680, 2600), C=O carboxyl (1692), C=O carbonyl (1637), C=C (1619, 1528).

Preparation of 3-Indolyl Vinyl Ketone (XX).—Compound XVII (9.3 g.) was added to a solution of 10.2 g. of sodium bicarbonate in 300 ml. of distilled water. While stirring and heating on the steam-bath the inside temperature was raised from 60 to 89° during 9 minutes (in one experiment refluxing the aqueous solution for 7 minutes did not yield the desired vinyl ketone but, apparently, a further transformation product). The mixture was then cooled for 3 hours in ice, filtered and the precipitate washed with a minimum of cold water, m.p. 142–190°. The solid was boiled with 50 ml. of acetone and the suspension was filtered from the unchanged methiodide (m.p. 208–212°, 3.0 g.). The yellow filtrate was evaporated down to a small volume, 150 ml. of benzene was added, 20 ml. was boiled off to get rid of the residual acetone and filtered to separate a small amount (0.1 g., m.p. 208–212°) of unchanged methiodide. The clear solution was then evaporated till crystallization commenced; m.p. 153–156°, 2.50 g. A second crop (0.2 g.) of the same melting point was obtained by evaporation of the filtrate and precipitation with petroleum ether (30–60°); yield of recovered starting material (3.1 g.) 33.4%. The yield of product (2.7 g.) was 91.2% based on recovered methiodide. An analytical sample was obtained by sublimation at 140–142° (0.1 mm.); colorless prisms, m.p. 157–159°; ultraviolet spectrum: 258 (9,700), 269.5 (10,025), 274.5 (9,900), 324 (13,450); infrared spectrum: NH (3140), C=O (1632), C=C (1592s, 1519s, 1492s), *o*-disubstituted benzene (757, 747).

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.33; H, 5.28; N, 8.54.

Proof of Structure of XX. (a) LAH Reduction to 3-Propionylindole.—The vinyl ketone XX (0.2 g.) was added to a solution of LAH (1.0 g.) in 50 ml. of tetrahydrofuran. The mixture was refluxed for 1.75 hours and allowed to stand at room temperature overnight. It was then decomposed with 15 ml. of 50% aqueous acetic acid and extracted four times with ether. The extracts were washed with 10% potassium hydroxide solution, then with saturated salt solution and dried over sodium sulfate. Crystallization from benzene–petroleum ether gave an impure first crop. The mother liquor deposited after one month 20 mg. of well defined prismatic plates, m.p. 170–171°; mixed m.p. with authentic 3-propionylindole (m.p. 170–171.5°) showed no depression. The infrared spectra of the two samples were identical.

(b) Addition of Dimethylamine to XX.—A solution of the vinyl ketone XX (70 mg.) in 1 ml. of dioxane was treated with 5 ml. of dimethylamine (25% aqueous solution) and allowed to stand at room temperature for 10 days. The solution was then evaporated to dryness *in vacuo* on the steam-bath. The product was separated from polymeric material by two recrystallizations from benzene–petroleum ether (30–60°); colorless rods, m.p. 114–115° (10 mg.) were obtained; mixed m.p. with authentic VI (m.p. 116–118°) was 115–116°.

3-(β-Aziridinylpropionyl)-indole.—Five grams of the vinyl ketone XX was added in portions during 5 minutes to an ice-cooled solution of ethylenimine (29 ml.). The mixture was swirled until all was in solution, allowed to stand in ice for 1.5 hours, then in the refrigerator for 22 hours. The resulting pale yellow solution was evaporated to dryness at reduced pressure at 35° and the residual solid was washed with petroleum ether (30–60°), m.p. 139–141° (6.2 g. or 99.5% yield). The analytical sample was prepared by recrystallization from methanol–benzene–petroleum ether; pale yellow elongated needles, m.p. 142–144°; ultraviolet spectrum: 241 (14,450), sh 260, 296.5 (14,100); infrared spectrum: NH (3100, 3060, 3020), C=O (1642), C=C (1619, 1581, 1522, 1504), *o*-disubstituted benzene (756).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.88; H, 6.59; N, 13.08. Found: C, 72.54; H, 6.75; N, 12.97.

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