Open-Chain Analogs of LSD II

Synthesis of Some 2-(3-Indolylethyl)- and 2-(3-Methyl-2-indolylethyl)piperidines

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6-Methylpyridines substituted in the 3-position, which were quaternized with methyl or ethyl iodide, were condensed under Knoevenagel conditions with 3-indolealdehyde or with 3-methyl-2-indolealdehyde. The indolylethenylpyridinium iodides thus produced were hydrogenated to the corresponding indolylethylpiperidines. Conversion of the hydrogenation products into acid salts or into quaternary salts provided compounds for pharmacological testing. Some of these are open-chain analogs of LSD.

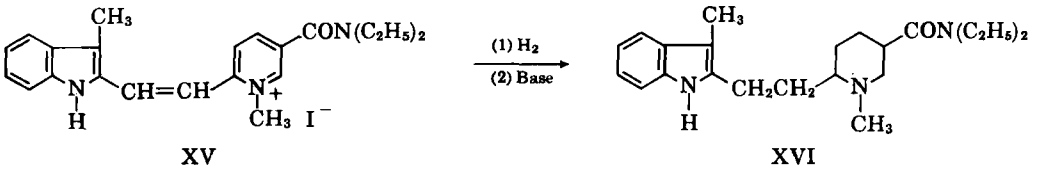
THE FIRST PAPER in this series (1) reported the synthesis of a number of 2-(3-indolylethenyl)-1-alkyl-5-substituted pyridinium iodides and some hydrogenation products. This series has now been extended and some of the compounds previously reported have been hydrogenated to the corresponding indolylethylpiperidines.

6-Methylnicotinoyl chloride was prepared by the action of oxalyl chloride on potassium 6-methylnicotinate according to the method of Wingfield (2). The acid chloride was not isolated but allowed to react directly with a secondary amine. In this manner 1-(6-methylnicotinoyl)-piperidine (I) and 4-(6-methylnicotinoyl)morpholine (II) were prepared. When I and II were allowed to react with methyl iodide, the quaternary salts were formed. When allowed to condense with 3-indolealdehyde, the quaternary salts of I and II gave 1-[6-(3-indolylethenyl)-nicotinoyl]piperidine methiodide (III) and 4-[6-(3-indolylethenyl)nicotinoyl]morpholine methiodide (IV).

Young (3) has shown that 3-indolealdehyde could be prepared in good yield by formylation of indole with a complex of N,N-dimethylformamide and phosphorus oxychloride. Using the same complex, Silverstein, Ryskiewiecz, and Willard (4) prepared 2-pyrrolealdehyde in 76% yield. Attempts to prepare 3-methyl-2-indolealdehyde (V) from skatole by the method of Young (3) gave 1-formyl-3-methylindole (VI) (55%) and V (20%). When the reaction temperature was changed from 5 to 60°, the yield of VI remained the same but the yield of V decreased. This is a contrast to the experience of Potokhin (5) who found that increased temperatures favored the formlyation of indole at position 3 over position 1.

Alessandri and Passerini (6) reported (without yields) that the 1-formyl-2-methylindole, when heated at 200° in the presence of zinc chloride, rearranged into 2-methyl-3-indolealdehyde. When VI was heated at 200° with zinc chloride no aldehyde was obtained. When it was heated at 250° a small amount of V was isolated. When V was allowed to react with 5-(N,N-diethylcarbamyl)-1,2-dimethylpyridinium iodide, 5 - (N,N - diethylcarbamyl) - 1 - methyl - 2-(3 - methyl - 2 - indolylethenyl)pyridinium iodide (XV) was obtained. When XV was hydrogenated, 5-(N,N-diethylcarbamyl)-1- methyl - 2 - (3 - methyl - 2 - indolylethyl)piperidine (XVI) was obtained as the hydriodide salt. This was readily converted into XVI by treatment with alkali.

Several indolylethenylpyridinium iodides were hydrogenated under high pressure to give the corresponding indolylethylpiperidines. These were converted into quaternary salts or into acid salts. The piperidine quaternary salts prepared were found to be less hygroscopic than the piperidine acid salts. Some of these transformations are shown.



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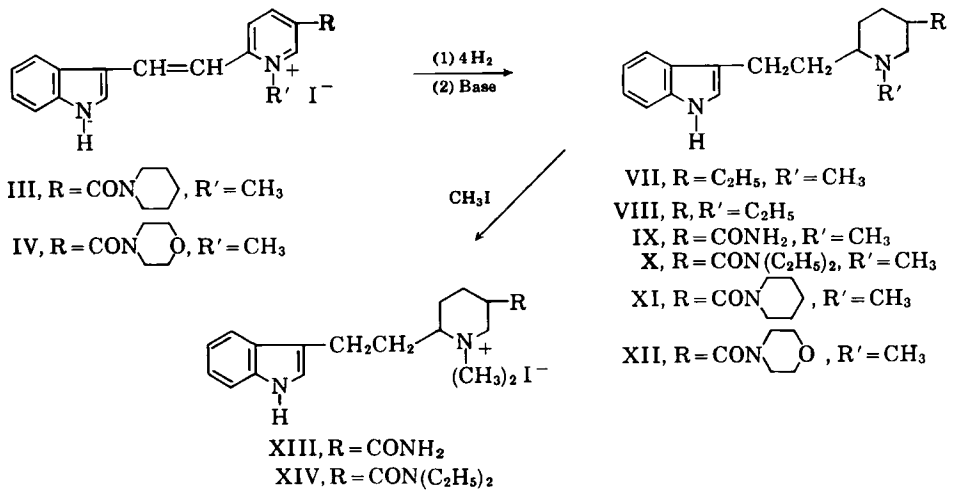

3-Methylindole-1-carboxylic acid, which occurs in the beet, has been prepared from skatole in 86% yield *via* the Grignard reaction.

The pharmacological screening of this group of compounds was discontinued because of the lack of interesting activity[1] when screened for mouse behavior, oxytocic, and antimicrobial activity.

EXPERIMENTAL

The melting points are uncorrected. The micro melting points (m.m.p.) were determined on a Kofler hot stage. Carbon, hydrogen, and nitrogen analyses were performed by Tanabe Seiyaku Co., Ltd., Tokyo, Japan.[2] Basic nitrogen was determined by nonaqueous titration with perchloric acid in acetic acid (7).

1-(6-Methylnicotinoyl)piperidine.—6-Methylnicotinoyl chloride was prepared by allowing 26.0 Gm. (0.148 mole) of potassium 6-methylnicotinate to react with 18.0 Gm. (0.148 mole) of oxalyl chloride in a manner previously described (2). Eighteen milliliters of dry piperidine was added to the crude acid chloride solution. The product was extracted as the hydrochloride into water, decolorized with charcoal, then made basic with sodium hydroxide solution. The water was removed by vacuum evaporation; the solid residue was extracted into ether by Soxhlet extraction. After evaporation of the dried (calcium chloride) ether solution, the compound was distilled at 143–146° at 0.25 mm. Thirteen and one-half grams (45%) of product was obtained, m.p. 63 to 64.5°.

Anal.—Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.22; H, 7.79; N, 13.52.

4-(6-Methylnicotinoyl)morpholine.—Twenty milliliters of dry morpholine was added dropwise to a solution of 6-methylnicotinoyl chloride (prepared as above); the reaction mixture was refluxed for 30 minutes. The cooled reaction product was extracted into water as the hydrochloride and decolorized twice with charcoal. After neutralization with sodium hydroxide solution, the water was removed by vacuum evaporation and the organic material was extracted into hot benzene. Removal of the benzene left a green oil which distilled at 135–136° at 0.08 mm. The liquid was dissolved in anhydrous ether, and a stream of dry hydrogen chloride was bubbled through the ethereal solution until precipitation was complete. The salt was collected, washed with dry ether, dried, and then recrystallized twice from ethanol-ethyl acetate to give the hydrochloride, m.p. 232–233°.

Anal.—Calcd. for $C_{11}H_{14}N_2O_2 \cdot HCl$: C, 54.44; H, 6.23; N, 11.54. Found: C, 54.70; H, 6.33; N, 11.71.

The salt was decomposed with ammonium hydroxide solution. After vacuum evaporation, the compound was extracted into ether. Removal of the dried ether gave 17.0 Gm. (58%) of the purified liquid compound.

Anal.—Calcd. for $C_{11}H_{14}N_2O_2$: C, 63.89; H, 6.84; N, 13.58. Found: C, 64.02; H, 6.62; N, 13.38.

1-(6-Methylnicotinoyl)piperidine Methiodide.—A precipitate separated from the reaction mixture when 10.0 Gm. (0.049 mole) of 1-(6-methylnicotinoyl)piperidine and excess methyl iodide dissolved in 300 ml. of benzene were allowed to reflux for 20 hours. The solid product was collected, washed with benzene, and dried. Upon crystallization from ethanol, 15.8 Gm. (93%) of a white solid was obtained m.p. 185–186°.

Anal.—Calcd. for $C_{13}H_{19}IN_2O$: C, 45.10; H, 5.53; N, 8.09. Found: C, 44.89; H, 5.47; N, 8.09.

4-(6-Methylnicotinoyl)morpholine Methiodide.—When 15.0 Gm. (0.074 mole) of 4-(6-methylnicotinoyl)morpholine and excess methyl iodide were allowed to react as above, a precipitate separated from the reaction mixture. After two recrystallizations from ethanol, 19.0 Gm. (76%) of white platelets was obtained, m.p. 238–239°.

Anal.—Calcd. for $C_{12}H_{17}IN_2O_2$: C, 41.39; H, 4.92; N, 8.05. Found: C, 41.04; H, 5.04; N, 8.08.

3-Methylindole-1-carboxylic Acid.—To an ethereal solution of methyl magnesium iodide, prepared from 2.68 Gm. (0.11 mole) of magnesium

[1] The authors are indebted to the Lilly Research Laboratories for screening these compounds.
[2] The authors thank Dr. S. Yamada for this service.

turnings and 15.6 Gm. (0.11 mole) of methyl iodide, was added dropwise 13.1 Gm. (0.10 mole) of skatole in 25 ml. of dry ether. A heavy ether-insoluble oil resulted from the reaction to which an excess of dry ice was added in portions while the two phases were stirred vigorously with gentle heating. The complex was decomposed with dilute hydrochloric acid; the organic portion dissolved in ether and separated. The solid remaining after the removal of the ether was recrystallized twice from benzene. There was obtained 15.0 Gm. (86%) of 3-methylindole-1-carboxylic acid as fine white needles. The decomposition point of the acid was dependent on the rate of heating. At 2° per minute decomposition occurred at 128°, and at 8° per minute decomposition occurred at 140–141°. In each instance, skatole (m.p. 92°) and carbon dioxide were the decomposition products.

Anal.—Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.17; N, 7.97. Found: C, 68.82; H, 5.08; N, 7.72.

1-Formyl-3-methylindole and 3-Methyl-2-indolealdehyde.—While cooling and stirring, 42.2 Gm. (0.253 mole) of phosphorus oxychloride was added to 20.0 Gm. (0.253 mole) of N,N-dimethylformamide over a period of 30 minutes. The resulting complex was dissolved in 65 ml. of ethylene chloride and cooled to 5° before 12.8 Gm. (0.25 mole) of skatole in 100 ml. of ethylene chloride was added dropwise over a period of 1 hour. A light yellow solid separated after heating at the reflux temperature for 15 minutes. After cooling the reaction mixture, 188 Gm. (1.375 moles) of sodium acetate in 250 ml. of water was added rapidly while the reaction mixture was stirred vigorously. The organic layer was separated, decolorized with charcoal, and the solvent was evaporated. The residue was distilled at 100–120° at 0.05 mm. A saturated solution of sodium bisulfite was added to the distillate and the oily layer was removed by extraction with ethylene chloride. The aqueous layer was acidified with dilute hydrochloric acid, then extracted with ethylene chloride. Both ethylene chloride solutions were evaporated until all the solvent was removed. The second solution gave 8 Gm. (20%) of 3-methyl-2-indolealdehyde, m.p. 139–140° (8). The oily residue from the first ethylene chloride solution was distilled *in vacuo* and gave 22 Gm. (55%) of 1-formyl-3-methylindole, b.p. 98–100° at 0.03 mm., $n_D^{18.5} = 1.6138$.

The structure of 1-formyl-3-methylindole was demonstrated by the facile hydrolysis into sodium formate and skatole, by the infrared spectrum, and by elemental analysis.

Anal.—Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.88. Found: C, 75.66; H, 5.83; N, 9.00.

Rearrangement of 1-Formyl-3-methylindole.—A small amount of 3-methyl-2-indolealdehyde was obtained by heating 5 Gm. of 1-formyl-3-methylindole with a trace of zinc chloride in a nitrogen-filled Carius tube at 240–270° for 2 hours. The resulting black tar-like material was distilled under high vacuum leaving 2 Gm. of tar. The distillate was treated with sodium bisulfite solution to separate the aldehyde from the amide. A 2.8-Gm. quantity of starting material was recovered and about 0.1 Gm. of impure 3-methyl-2-indolealdehyde, m.p. 130–134° was obtained.

5-(N,N-Diethylcarbamyl)-1-methyl-2-(3-methyl-2-indolylethenyl)pyridinium Iodide.—A solution of 9.1 Gm. (0.057 mole) of 3-methyl-2-indolealdehyde and 18.0 Gm. (0.057 mole) of 5-(N,N-diethylcarbamyl)-1,2-dimethylpyridinium iodide in 300 ml. methanol which contained ten drops of piperidine was refluxed for 22 hours. After chilling overnight, fine orange crystals separated. After crystallization from ethanol, 21.5 Gm. (79%) of the product, m.p. 275° dec. was obtained.

Anal.—Calcd. for $C_{22}H_{26}IN_3O$: C, 55.59; H, 5.51; N, 8.84. Found: C, 55.68; H, 5.42; N, 8.38.

1-[6-(3-Indolylethenyl)nicotinoyl]piperidine Methiodide.—In a procedure similar to that given above, 10 Gm. (0.0303 mole) of 1-(6-methylnicotinoyl)piperidine methiodide and 5.5 Gm. of 3-indolealdehyde were allowed to react. After collection and purification of the product, 10.3 Gm. (72%) of a red compound was obtained m.p. 234–236° dec.

Anal.—Calcd. for $C_{22}H_{24}IN_3O$: C, 55.86; H, 5.11; N, 8.93. Found: C, 55.90; H, 5.34; N, 8.80.

5-Ethyl-2-(3-indolylethyl)-1-methylpiperidine.—A solution of 9.35 Gm. (0.0238 mole) of 5-ethyl-2-(3-indolylethenyl)-1-methylpyridinium iodide in 250 ml. of ethanol was hydrogenated at an initial pressure of 50 p.s.i. using 2 Gm. of 5% rhodium on alumina as the catalyst. The theoretical amount of hydrogen was absorbed during 9 hours at room temperature. Removal of the catalyst and evaporation of the solvent left the hydriodide salt as a syrup. This was not purified but converted directly to the free base by the addition of sodium hydroxide. The viscous, sticky compound was partially dried by azeotropic distillation with benzene. The balance of the moisture was removed by allowing the compound to stand over phosphorus pentoxide *in vacuo* for 3 weeks. Attempts to crystallize the compound from a variety of solvents were not successful. It was necessary to dry the compound *in vacuo* after each attempt. Attempts to purify the compound as the hydrochloride salt were also unsuccessful. The salt, although readily formed, was extremely hygroscopic. The micro melting point of the compound was 135–139°.

Anal.—Calcd. for $C_{18}H_{26}N_2$: Basic N, 5.18. Found: Basic N, 4.88.

1,5-Diethyl-2-(3-indolylethyl)piperidine.—1,5-Diethyl-2-(3-indolylethenyl)pyridinium iodide, 11.25 Gm. (0.0275 mole), was hydrogenated in the same manner as described above over a period of 30 hours. The product was isolated as above but remained as a semisolid after storage over phosphorus pentoxide *in vacuo* for 1 year.

Anal.—Calcd. for $C_{19}H_{28}N_2$: Basic N, 4.94; Found: Basic N, 4.55.

5-Carbamyl-1,1-dimethyl-2-(3-indolylethyl)-piperidinium Iodide.—The hydrogenation of 10.0 Gm. (0.0247 mole) of 5-carbamyl-2-(3-indolylethenyl)-1-methylpyridinium iodide in 200 ml. of ethanol was accomplished in 3 days at 100° and at 2,500 p.s.i. pressure over 0.5 Gm. of platinum oxide as the catalyst. The semisolid product obtained after removal of the catalyst and the solvent solidified upon drying *in vacuo* over phosphorus pentoxide. This salt was dissolved in methanol containing 0.0247 mole of sodium methoxide. After heating to the reflux temperature, the solvent was removed and the residue dried. Benzene was added to dissolve the or-

ganic compound and the solution was decanted from the insoluble portion. To the benzene solution was added 3.5 Gm. (0.0248 mole) of methyl iodide and this solution refluxed for 14 hours. The product separated when the solution was allowed to cool. After crystallization from ethyl acetate, 5.5 Gm. (52%) of quaternary salt was obtained. This compound does not possess a true melting point but decomposes over a wide range.

Anal.—Calcd. for $C_{18}H_{26}IN_3O$: C, 50.92; H, 6.13; N, 9.83. Found: C, 51.06; H, 6.06; N, 9.43.

5-(N,N-Diethylcarbamyl)-1-methyl-2-(3-indolylethyl)piperidine.—The low pressure hydrogenation of 5-(N,N-diethylcarbamyl)-2-(3-indolylethenyl)-1-methylpyridinium iodide has been described (1). At low pressure this reaction was very slow, but the uptake of hydrogen was steady. The reaction at 2,500 p.s.i. pressure over platinum oxide requires only 24 hours. The resulting hydriodide was converted to the free base as described in the preceding example. This compound was identical with that previously obtained by low pressure hydrogenation (mixed m.p., 213–214°).

Anal.—Calcd. for $C_{21}H_{31}N_3O$: Basic N, 4.11. Found: Basic N, 4.08.

5-(N,N-Diethylcarbamyl)-1,1-dimethyl-2-(3-indolylethyl)piperidinium Iodide.—A benzene solution of 5-(N,N-diethylcarbamyl)-2-(3-indolylethyl)-1-methylpiperidine was allowed to react with methyl iodide in the usual fashion. The product was recrystallized from ethyl acetate under anhydrous conditions. This quaternary salt decomposed over a wide range at about 200° with the evolution of gas.

Anal.—Calcd. for $C_{22}H_{34}IN_3O$: C, 54.66; H, 7.09. Found C, 54.41; H, 7.14.

5-(N,N-Diethylcarbamyl)-1-methyl-2-(3-methyl-2-indolylethyl)piperidine Hydriodide.—A solution containing 10.0 Gm. (0.0221 mole) of 5-(N,N-diethylcarbamyl)-1-methyl-2-(3-methyl-2-indolylethenyl)pyridinium iodide in 200 ml. of ethanol was hydrogenated at 2,500 p.s.i. over 0.5 Gm. of platinum oxide at 90° for 2 days. The solid remaining after removal of the catalyst and solvent was dried *in vacuo*. Platelets were obtained after crystallization from ethyl acetate, m.p. 113–115°.

Anal.—Calcd. for $C_{22}H_{34}N_3O \cdot HI$: C, 54.66; H, 7.09. Found: C, 54.59; H, 6.97.

5-(N,N-Diethylcarbamyl)-1-methyl-2-(3-methyl-2-indolylethyl)piperidine.—The hydriodide salt described above was dissolved in methanol. An excess of sodium methoxide was added to this solution and the mixture heated at the reflux temperature. The solvent was removed by flash evaporation; the resulting semisolid was dried. The residue was extracted with benzene, the solution decolorized, and the benzene evaporated. An analytical sample was prepared by crystallization from ligroin under anhydrous conditions, mmp 158–161°.

Anal.—Calcd. for $C_{22}H_{33}N_3O$: Basic N, 3.94. Found: Basic N, 3.58.

5-(N,N-Diethylcarbamyl)-1-methyl-2-(3-methyl-2-indolylethyl)piperidine Acid Tartrate.—The free base described above (about 0.02 mole) was dissolved in 20 ml. of methanol. A methanolic solution containing 3.0 Gm. (0.02 mole) of *d*-tartaric acid was added to this solution. The volume of the solution was reduced to about one-half before 50 ml. of anhydrous ether was added to precipitate the salt. After decantation, the residue was crystallized from methanol-ethyl acetate. There was obtained 6.8 Gm. (61%) (based on the amount of pyridinium iodide originally hydrogenated) of the salt, m.p. 67–69° (sealed tube).

Anal.—Calcd. for $C_{22}H_{33}N_3O \cdot C_4H_6O_6$: C, 61.76; H, 7.77. Found: C, 61.33; H, 7.95.

4-[6-(3-Indolylethyl)-1-methylnipecotoyl]-morpholine Hydriodide.—A solution containing 10.0 Gm. (0.0212 mole) of 4-[6-(3-indolylethenyl)-nicotinoyl]morpholine methiodide in 200 ml. of ethanol was hydrogenated at 3,000 p.s.i. pressure and at 90° over 0.5 Gm. of platinum oxide for 1.5 days. After removal of the catalyst and solvent, the residue was crystallized from absolute ethanol to give a white salt, m.p. 109–110°.

Anal.—Calcd. for $C_{21}H_{29}N_3O_2 \cdot HI$: C, 52.18; H, 6.26; N, 8.89. Found: C, 52.31; H, 6.20; N, 8.76.

4-[6-(3-Indolylethyl)-1-methylnipecotoyl]-morpholine.—The hydriodide salt described above was dissolved in hot water and the solution was made faintly alkaline with sodium hydroxide. Water was removed by flash evaporation and then by azeotropic distillation with benzene. The benzene mixture was decolorized with charcoal after which the insoluble salts and the charcoal were removed by filtration. After evaporation of the benzene, the solid was crystallized from ethyl acetate to give 7.1 Gm. (95%) of white plates, m.p. 65–67°.

Anal.—Calcd. for $C_{21}H_{29}N_3O_2$: Basic N, 3.94. Found: Basic N, 4.01.

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