

## A New Synthesis of Methoxyindoles

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The synthesis of 5-, 6-, and 7-methoxyindoline from indoline, and their dehydrogenation to the corresponding methoxyindoles, is described

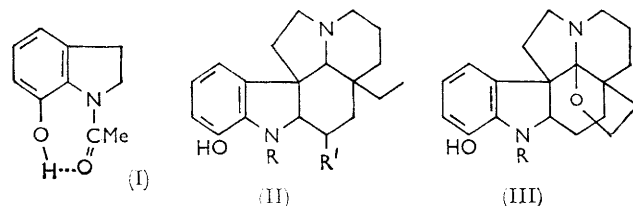
METHOXYINDOLES have been prepared by a variety of routes<sup>1-4</sup> but all involved the direct formation of the methoxyindole from suitably substituted non-indolic intermediates. We have prepared 5-, 6-, and 7-methoxyindole, in good overall yields (15–25%), starting from indoline.

Diazotisation of 1-acetyl-5-aminoindoline, prepared by reduction of 1-acetyl-5-nitroindoline,<sup>5,6</sup> and decomposition of the diazonium salt in boiling cupric sulphate solution gave 1-acetyl-5-hydroxyindoline. *O*-Methylation gave 1-acetyl-5-methoxyindoline which was deacetylated to 5-methoxyindoline. Dehydrogenation of this with 10% palladium-charcoal in boiling mesitylene gave 5-methoxyindole. 6- and 7-Methoxyindole were prepared similarly.

*O*-Methylation of 1-acetyl-5- or -6-hydroxyindoline gave a 70% yield of the methyl ether whereas only a 40% yield of 1-acetyl-7-methoxyindoline was obtained under more vigorous conditions (about 40% of starting material was recovered). This difference in reactivity of the hydroxyl group is probably due to strong intramolecular hydrogen-bonding, as illustrated in (I). The infrared spectral evidence accords with this suggestion. Thus, 1-acetyl-7-hydroxyindoline has three strong bands at 1634, 1597, and 1567 cm.<sup>-1</sup> (KBr) whereas 1-acetyl-5- and -6-hydroxyindoline (in which similar intramolecular hydrogen-bonding cannot occur) have only one strong band, at 1613 and 1634 cm.<sup>-1</sup> (KBr), respectively, in the same region of the spectrum. A similar suggestion was made<sup>7</sup> following the observation that the methylation of the phenolic hydroxyl of spagazzinine (II; R = COMe, R' = OH), which contains the 1-acetyl-7-hydroxyindoline residue, was only 45% complete after 6 days whereas a similar methylation of deacetylspagazzinine (II; R = H, R' = OH), in which no hydrogen-bonding can occur, was 95% complete.

The following dihydroindole alkaloids (all of which contain a 1-acyl-7-hydroxyindoline residue) exhibit a

similar infrared absorption pattern (KBr) to that of 1-acetyl-7-hydroxyindoline: (II; R = COMe, R' = OH),  $\nu_{\max}$ . 1629, 1597, and 1572 cm.<sup>-1</sup>;<sup>7</sup> (II; R = COMe, R' = H),  $\nu_{\max}$ . 1621, 1590, and 1567 cm.<sup>-1</sup>;<sup>8</sup>



(III; R = COMe),  $\nu_{\max}$ . 1623, 1597, and 1560 cm.<sup>-1</sup>;<sup>9</sup>  
(III; R = COEt),  $\nu_{\max}$ . 1631, 1603, and 1570 cm.<sup>-1</sup>.<sup>9</sup>

### EXPERIMENTAL

**1-Acetyl-5-aminoindoline.** — 1-Acetyl-5-nitroindoline<sup>5,6</sup> (7.85 g.) and 10% palladium-charcoal (3 g.) in ethanol (250 ml.) were shaken with hydrogen (3 atm.) until uptake ceased. The catalyst was filtered off, and filtrate evaporated to dryness, and the residue recrystallised from benzene, to give 1-acetyl-5-aminoindoline (5.6 g., 83%), m. p. 184–185° (Found: C, 68.0; H, 7.1; N, 15.85. C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O requires C, 68.2; H, 6.9; N, 15.9%).

**1-Acetyl-5-hydroxyindoline.** — 1-Acetyl-5-aminoindoline (35 g.) was dissolved in dilute sulphuric acid (25 ml. of conc. acid and 400 ml. of water) and the solution cooled to 0° (the amine sulphate separated as a finely divided crystalline mass). To the stirred suspension was slowly added sodium nitrite (14 g.) in water (100 ml.), the temperature of the reaction mixture being kept at 0–5°. On completion of the addition (about 1 hr.) the clear, pale brown solution of the diazonium salt was rapidly added to a boiling solution of cupric sulphate (200 g.) in water (350 ml.). When the evolution of nitrogen had subsided the mixture were cooled, and the precipitated solid collected, washed, and dried. Recrystallisation from ethyl acetate gave 1-acetyl-5-hydroxyindoline (27 g., 77%) as needles, m. p. 249–250° (Found: C, 67.7; H, 6.4; N, 8.4. C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub> requires C, 67.8; H, 6.3; N, 7.9%); the 3,5-dinitrobenzoate had m. p. 203–205°.

**1-Acetyl-5-methoxyindoline.** — Dimethyl sulphate (2.85 ml., 3.68 g.) was added dropwise to a stirred solution of 1-acetyl-5-hydroxyindoline (5.3 g.) in *N*-sodium hydroxide (40 ml.), the temperature of the mixture being kept at 40°. On

<sup>5</sup> W. G. Gall, B. D. Astill, and V. Boekelheide, *J. Org. Chem.*, 1955, **20**, 1538.

<sup>6</sup> A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobkov, and G. M. Sorokina, *Zhur. obshechei Khim.*, 1959, **29**, 2541.

<sup>7</sup> O. O. Orazi, R. A. Corral, J. S. E. Holker, and C. Djerassi, *J. Org. Chem.*, 1956, **21**, 979.

<sup>8</sup> J. M. Ferreira, B. Gilbert, R. J. Owellen, and C. Djerassi, *Experientia*, 1963, **19**, 585.

<sup>9</sup> M. P. Cava, S. K. Talapatra, K. Nomura, J. A. Weisbach, B. Douglas, and E. C. Shoop, *Chem. and Ind.*, 1963, 1242.

<sup>1</sup> J. B. Bell and H. G. Lindwall, *J. Org. Chem.*, 1948, **13**, 547.

<sup>2</sup> N. N. Suvorov, M. V. Fedotova, O. B. Ogareva, and E. G. Balasheva, *Zhur. obshechei Khim.*, 1960, **30**, 3118.

<sup>3</sup> K. G. Blaikie and W. H. Perkin, *J. Chem. Soc.*, 1924, **125**, 296.

<sup>4</sup> W. O. Kermack, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 1921, **119**, 1602; W. H. Perkin and L. Rubenstein, *ibid.*, 1926, 357; D. G. Harvey and W. Robson, *ibid.*, 1938, 97; R. H. Marchant and D. G. Harvey, *ibid.*, 1951, 1808; F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, 1958, **23**, 1977; F. C. Pennington, L. J. Martin, R. E. Reid, and T. W. Lapp, *ibid.*, 1959, **24**, 2030; M. Amorosa, *Gazzetta*, 1955, **85**, 1445; G. Pappalardo and T. Vitali, *ibid.*, 1958, **88**, 564; W. C. Anthony, U.S.P. 2,813,128/1957; R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 1958, **2**, 1; T. Kralt, W. J. Asma, H. H. Haack, and H. D. Moed, *Rec. Trav. chim.*, 1961, **80**, 313.

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completion of the addition the temperature was raised to 45° for 10 min. and then to 50°. 2N-Sodium hydroxide (8 ml.) and dimethyl sulphate (1.45 ml., 1.9 g.) were added to the mixture which was kept at 50° for 1 hr. and then cooled. The precipitated solid was recrystallised from cyclohexane, to give 1-acetyl-5-methoxyindoline (4 g., 70%) as needles, m. p. 135—136° (Found: C, 69.6; H, 7.1; N, 7.2.  $C_{11}H_{13}NO_2$  requires C, 69.1; H, 6.9; N, 7.3%).

*5-Methoxyindoline Hydrochloride.*—A mixture of 1-acetyl-5-methoxyindoline (7.6 g.) and 6N-hydrochloric acid (160 ml.) was boiled for 30 min., cooled, made alkaline with sodium hydroxide solution, and extracted with ether (4 × 150 ml.). Dry hydrogen chloride was bubbled through the dried ethereal solution, and the precipitated solid recrystallised from benzene-methanol, to give 5-methoxyindoline hydrochloride (6.2 g., 85%) as needles, m. p. 179—180° (Found: C, 57.9; H, 6.8; N, 7.5.  $C_9H_{12}ClNO$  requires C, 58.2; H, 6.5; N, 7.5%).

*5-Methoxyindole.*—A mixture of 5-methoxyindoline (5 g.) (from 6.3 g. of the hydrochloride), 10% palladium-charcoal (0.5 g.), and mesitylene (50 ml.) was heated under reflux for 2½ hr. The catalyst was filtered off, the mesitylene evaporated under reduced pressure, and the residue recrystallised from cyclohexane, to give 5-methoxyindole (4.4 g., 90%) as pale yellow plates, m. p. and mixed m. p. 52—53° (lit.,<sup>1</sup> 54—55°).

*1-Acetyl-6-hydroxyindoline.*—This was prepared by diazotisation of 1-acetyl-6-aminindoline<sup>6</sup> and decomposition of the diazonium salt. The crude product was recrystallised from ethyl acetate, to give 1-acetyl-6-hydroxyindoline (82%), m. p. 282—284° (Found: C, 68.3; H, 6.35; N, 8.3.  $C_{10}H_{11}NO_2$  requires C, 67.8; H, 6.3; N, 7.9%).

*1-Acetyl-6-methoxyindoline.*—Methylation of 1-acetyl-6-hydroxyindoline with dimethyl sulphate gave the methyl ether (70%) as pale yellow needles (from cyclohexane), m. p. 105—106° (lit.,<sup>10</sup> 105°) (Found: C, 69.2; H, 7.0; N, 7.7. Calc. for  $C_{11}H_{13}NO_2$ : C, 69.1; H, 6.9; N, 7.3%).

*6-Methoxyindoline Hydrochloride.*—Deacetylation of 1-acetyl-6-methoxyindoline gave the indoline hydrochloride (77%) as plates (from methanol-ether), m. p. 232—233° (lit.,<sup>10</sup> 202°) (Found: C, 58.0; H, 6.7; N, 7.8. Calc. for  $C_9H_{12}ClNO$ : C, 58.2; H, 6.5; N, 7.5%).

*6-Methoxyindole.*—Dehydrogenation of 6-methoxyindoline gave the indole (83%) as yellow plates (from cyclohexane), m. p. 91—92° (lit.,<sup>2</sup> 91.5—92°) (Found: C, 73.6; H, 6.6; N, 9.9. Calc. for  $C_9H_9NO$ : C, 73.45; H, 6.2; N, 9.5%).

*1-Acetyl-7-hydroxyindoline.*—This compound was obtained (75%) from 1-acetyl-7-aminindoline<sup>5</sup> as needles, m. p. 112—114° (Found: C, 68.0; H, 6.55; N, 8.2.  $C_{10}H_{11}NO_2$  requires C, 67.8; H, 6.3; N, 7.9%).

*7-Methoxyindoline Hydrochloride.*—A solution of 1-acetyl-7-hydroxyindoline (10.62 g.) in ethanol (100 ml.) was added to a solution of sodium (1.38 g.) in ethanol (30 ml.), and the resultant mixture heated on a water-bath for 10 min. Methyl iodide (10 ml.) was added and the reaction mixture boiled for 3 hr. The ethanol was removed by distillation and the residue treated with water (100 ml.). The insoluble material was collected and dried, giving 4.5 g. (42% recovery) of 1-acetyl-7-hydroxyindoline, m. p. 103—105° undepressed on admixture with an authentic sample. The filtrate was extracted with ether (3 × 100 ml.), the ethereal solution was dried, and the ether evaporated. The residue of crude 1-acetyl-7-methoxyindoline was boiled with 6N-hydrochloric acid (100 ml.) for 20 min., and the acidic mixture cooled, made alkaline with dilute sodium hydroxide solution, and extracted with ether (3 × 100 ml.). Dry hydrogen chloride was bubbled through the dried ethereal solution, to give 3.75 g. (30% from 1-acetyl-7-hydroxyindoline) of 7-methoxyindoline hydrochloride. Recrystallisation from methanol-ether gave white crystals, m. p. 230—231° (Found: C, 58.5; H, 6.9; N, 7.5.  $C_9H_{12}ClNO$  requires C, 58.2; H, 6.5; N, 7.5%).

*7-Methoxyindole.*—Dehydrogenation of 7-methoxyindoline gave 7-methoxyindole (95%) as a colourless oil, b. p. 110°/0.9 mm. (lit.,<sup>3</sup> 157°/17 mm.),  $n_D^{25}$  1.6122; picrate, red needles (from benzene), m. p. 152—153° (lit.,<sup>3</sup> 156°).

*6-Hydroxyindoline.*—Deacetylation of 1-acetyl-6-hydroxyindoline with 6N-hydrochloric acid gave 6-hydroxyindoline (80%), m. p. 112—113° (Found: C, 71.6; H, 6.8; N, 10.9.  $C_8H_9NO$  requires C, 71.1; H, 6.7; N, 10.4%).

*7-Hydroxyindoline.*—This obtained (85%) from 1-acetyl-7-hydroxyindoline as white plates (from ethyl acetate), m. p. 182—183° (Found: C, 71.2; H, 7.1; N, 10.4%); hydrochloride (from methanol-ether), m. p. 232—234°.

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<sup>10</sup> T. Wieland and O. Unger, *Chem. Ber.*, 1963, **96**, 253.