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SYNTHESIS IN THE INDOLE SERIES—III*

PREPARATION OF 5-, 6-, AND 7-CYANO AND -CARBOXYINDOLINES AND -INDOLES

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Abstract—The synthesis of 5-, 6-, and 7- cyanoindolines from indoline and their transformation into the corresponding cyanoindoles and indole-carboxylic acids is described.

A NUMBER of methods have been reported for the preparation of cyanoindoles[1-3]; but some of the steps involved are cumbersome, and all of them give low yields. A synthetic route was, therefore, explored, which did not involve either cyclization or decarboxylation reactions, but started from the preformed indole system.

5- and 6-Cyanoindolines were prepared from 5- and 6-nitroindolines[4], which were acetylated or formylated and hydrogenated to the corresponding 1-acyl-5- and -6-aminoindolines. In these compounds, the protection of the N_1-position permits Sandmeyer reactions of the amino group. Thus, the neutralized[5] diazonium salts gave at 50° the 1-acyl-cyanoindolines in fair yields. The products were then deacetylated and dehydrogenated to the desired 5- and 6-cyanoindoles; the dehydrogenation by means of Pd–C generally gives better yields and purer products than chloranil.

In the preparation of 7-cyanoindole, the necessary 1-acetyl-7-aminoindoline was prepared according to Gall, *et al.*[6] These authors failed in their attempt to convert the 7-amino- into the 7-cyano-compound but we found conditions under which this reaction could be carried out in 35% yield.

In the hydrolysis of the 1-acyl-cyanoindolines, the two possible steps can be separated easily. At 140°, only deacylation at N_1 takes place, whilst at higher temperatures also the cyano group is transformed into carboxyl. Thus, the indoline- and, by dehydrogenation, the indole-5-, 6- and 7-carboxylic acids became available.

The weak point in these syntheses is the Sandmeyer reaction which gives only fair yields. The observation is, therefore, of practical interest that the much more easily available 1-acetyl-5-bromoindoline and 5-bromo-indole give, upon treatment with cuprous cyanide in boiling N-methylpyrrolidone,[7] over 70% of the corresponding cyano- compounds.

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* Part II. E. Hoffmann, R. Ikan and A. Galun, *J. Heterocyclic Chem.* **2**, 298 (1965).

[1] J. Thesing, G. Semler and G. Mohr, *Chem. Ber.* **95**, 2205 (1962).

[2] H. Singer and W. Shive, *J. Org. Chem.* **20**, 1458 (1955).

[3] W. O. Kermack, *J. Chem. Soc.* **125**, 2285 (1924).

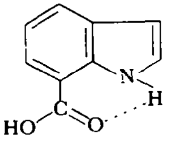
[4] Cf. e.g. R. Ikan, E. Hoffmann, E. D. Bergmann and A. Galun, *Israel J. Chem.* **2**, 37 (1964).

[5] H. H. Hodgson and F. Heyworth, *J. Chem. Soc.* 1131 (1949).

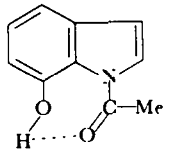
[6] W. G. Gall, B. A. Astill and V. Boekelheide, *J. Org. Chem.* **20**, 1538 (1955).

[7] M. S. Newman and H. Boden, *J. Org. Chem.* **26**, 2525 (1961).

A comparison of the IR spectra of the isomeric series studied has shown differences between the 7-substituted compounds and the 5- and 6-isomers. Similar differences have been reported[8] for the isomeric 1-acetyl-5-, 6- and 7-hydroxyindolines; and have been ascribed to hydrogen bonding of the 7-hydroxy compound with the carbonyl of the 1-acetyl group. The following observations can be explained analogously; (1) In the indole carboxylic acids, the NH band appears at 3395 cm^{-1} for the 7-compound, at 3345 cm^{-1} for the 5- and 6-isomers. Only the 7-carboxylic acid can give hydrogen bonding, as in I.



I



II

(2) The carbonyl bands of 5- and 6-amino-1-acetylindoline lie at 1620 and 1645 cm^{-1}, whilst the 7-isomer shows two bands, at 1640 and 1608 cm^{-1}. Formula II for the latter compound would account for the lowering of the carbonyl absorption. However, 7-membered hydrogen-bonded rings are generally not very stable; moreover, the carbonyl frequency is also decreased in the 5-amino derivative, where no structure analogous to II is possible. Thus, we cannot offer an acceptable explanation for this effect.

(3) In the 1-acetylcyanoindolines the strong interaction between the two polar groups causes the carbonyl absorption to shift from 1650 (5- and 6- compounds) to 1680 cm^{-1} (7-isomer) and the peak of the nitrile group from 2225 (5-compound) and 2215 (6-compound) to 2200 cm^{-1} (7-isomer).

EXPERIMENTAL

UV spectra were determined in EtOH and IR spectra in Nujol.

1-*Acetyl-5-cyanoindoline*

1-acetyl-5-aminoindoline[4, 9] (5 g) was dissolved in 18% HCl (17 ml) and diazotized at 0° with a soln of $NaNO_2$ (2·07 g) in water (20 ml). The soln of the diazonium salt was neutralized with solid Na_2CO_3 and added slowly, with stirring and at 0°, to a soln of CuCN (2·7 g), NaCN (3 g) and water (20 ml). The mixture was heated to 50° and stirred for 30 min, cooled to 0° and solid phase filtered off. The latter was recrystallized from aqueous MeCN, yielding 1·9 g (33%) of pure material of m.p. 148–150°. UV spectrum: 220 and 278 mμ (log ε 4·10 and 4·20). IR spectrum: 1650 cm^{-1} (C=O); 2225 cm^{-1} (C≡N). (Found: C, 70·7; H, 5·5; N, 14·7. Calc. for $C_{11}H_{10}N_2O$: C, 70·9; H, 5·3; N, 15·0%.)

5-*Cyanoindoline*

1-acetyl-5-cyanoindoline (2 g) was heated at 140° (bath temp) for 1 hr with conc HCl (20 g) and the mixture concentrated *in vacuo* to ½ its original volume. After cooling, an excess conc aqueous alkali was added and the ppt collected. It was dried and repeatedly extracted with hot EtOH and the extract treated with charcoal and filtered. Distillation of the EtOH and recrystallization of the residue from aqueous EtOH yielded 1·2 g (80% of material of m.p. 86°. UV: 222 and 293 mμ (log ε 4·12 and 4·18). IR: 3390 cm^{-1} (N—H); 2200 cm^{-1} (C≡N). (Found: C, 75·0; H, 5·5; N, 19·3. Calc. for $C_9H_8N_2$: C, 75·0; H, 5·6; N, 19·4%.)

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[8] R. R. Hunt and R. L. Richard, *J. Chem. Soc.* 344 (1966).

[9] A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobkov and G. M. Sorokina *J. Gen. Chem. U.S.S.R.* **29**, 2541 (1959).

5-Cyanoindole

(a) A mixture of 160 ml xylene, 9·2 g chloranil and 4 g 5-cyanoindoline was refluxed for 4 hr, cooled, filtered and washed twice with a 20% aqueous alkali soln and twice with water. The xylene was removed under reduced press, and the residue dissolved in EtOH and treated with charcoal. Removal of EtOH under reduced press and recrystallization of the resulting solid from water gave 1·8 g (45%), m.p. 107° (lit. m.p. 107°,[1] 107–108°[2]). UV: 237 and 281 mμ (log ε 4·51 and 3·44). IR: 3340 cm^{-1} (broad, N—H); 2215 cm^{-1} (C≡N). (Found: C, 76·1; H, 4·6; N, 19·6. Calc. for $C_9H_6N_2$: C, 76·0; H, 4·3; N, 19·7%.)

(b) The dehydrogenation can be more conveniently carried out by refluxing a mixture of 2 g indoline, 0·5 g 10% Pd–C and 130 ml xylene for 3 hr. Filtration of the hot soln and concentration under reduced press, followed by recrystallization from water yielded 1·56 g (81%), m.p. 107°, identical with the above product.

1-Formyl-5-nitroindoline

Ac_2O (83 ml) was added dropwise to 5-nitroindoline[4, 9] (17 g) in formic acid (250 ml) 88% at 50–60°.[10] The mixture was stirred for an additional hr, concentrated under reduced press and poured onto ice (100 g). The product was collected to give 10 g, m.p. 176°. IR: 1675 cm^{-1} (C=O); 1512, 1320 cm^{-1} (NO_2). (Found: C, 55·9; H, 4·2. Calc. for $C_9H_8N_2O_3$: C, 56·2; H, 4·2%.)

1-Formyl-5-aminoindoline

1-Formyl-5-nitroindoline (30 g), suspended in abs EtOH (120 ml), was hydrogenated with 10% Pd–C at an initial press of 80 psi and at about 50°. After the theoretical amount of H_2 had been adsorbed, the mixture was filtered while still hot, part of the EtOH removed under reduced press, and the residue precipitated by addition of water. Thus, 22·1 g (86%), m.p. 172°, sufficiently pure for the next step, was obtained. IR: 3390, 3350, 3295, 3195 cm^{-1} (NH_2); 1625 cm^{-1} (C=O). (Found: C, 66·4; H, 6·2. Calc. for $C_9H_{10}N_2O$: C, 66·6; H, 6·2%.)

1-Formyl-5-cyanoindoline

1-Formyl-5-aminoindoline (1·6 g) was dissolved in a mixture of conc HCl (2·3 ml) and water (5 ml) and diazotized at 0° with a soln of $NaNO_2$ (0·7 g) in water (3 ml). The soln of the diazonium salt was then neutralized with Na_2CO_3 and added slowly, with stirring and at room temp, to a soln of CuCN (0·9 g), NaCN (1 g) and water (6 ml). After an additional 30 min, the mixture was cooled and the solid product filtered off. It was recrystallized from MeCN–water affording 0·6 g (35%), m.p. 144°. UV: 220 and 278 mμ (log ε 4·02 and 4·05). IR: 1655 cm^{-1} (C=O); 2225 cm^{-1} (C≡N). (Found: C, 69·9; H, 4·3; N, 15·8. Calc. for $C_{10}H_8N_2O$: C, 69·7; H, 4·6; N, 16·2%.)

5-Cyanoindoline

Deformylation was carried out similarly to deacetylation, using HCl (1 : 1), yield, 83%; m.p. 86°.

1-Acetyl-5-cyanoindoline

A mixture of 1-acetyl-5-bromoindoline[6] (72 g), N-methylpyrrolidone (300 ml) and CuCN (40 g) was refluxed for 4 hr,[7] cooled and poured on ice. The product was collected, washed thoroughly with ammonia soln (20%) and repeatedly extracted with hot $CHCl_3$. Removal of the $CHCl_3$ gave 40 g (73%) which was recrystallized from MeCN–water, m.p. 148°.

Indoline-5-carboxylic acid

A mixture of 2 g 1-acetyl-5-cyanoindoline and 20 ml conc HCl was refluxed for 3 hr and 15 ml of the acid was distilled off. The soln was cooled, made alkaline with NaOH and filtered. The filtrate was neutralized with HCl and the ppt collected to give 1·8 g (75%), m.p. after recrystallization from water, 168–170°. UV: 228 and 306 mμ (log ε 3·86 and 4·04). IR: 3365 cm^{-1} (NH); 1655 cm^{-1} (C=O). (Found: C, 66·6; H, 5·7; N, 8·7. Calc. for $C_9H_9NO_2$: C, 66·3; H, 5·6; N, 8·6%.)

Indole-5-carboxylic acid

A mixture of 40 ml xylene, 0·2 g 10% Pd–C and 0·8 g indoline-5-carboxylic acid was refluxed for 3 hr and filtered, while still hot. The xylene was removed under reduced press and the residue recrystallized from EtOH yiesded 1·2 g (80% of material of m.p. 86°. UV: 222 and 293 mμ (log ε 4·12 and 4·18). IR: 3390 cm^{-1}

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[10] J. C. Sheehan and D. N. Yang. *J. Am. Chem. Soc.* **80**, 1154 (1958).

water, yield, 0·65 g (81 %), m.p. 208° (lit.[2] m.p. 208–209°). UV: 236 and 277 mμ (log ε 4·50 and 3·60). IR: 3345 cm^{-1} (NH); 1670 cm^{-1} (C=O). (Found: C, 67·2; H, 4·4; N, 8·8. Calc. for $C_9H_7NO_2$: C, 67·0; H, 4·4; N, 8·7 %.)

5-Bromoindoline hydrochloride

A mixture of 80 g 1-acetyl-5-bromoindoline[6] and 700 ml conc HCl was refluxed at 140° for 1 hr, and 500 ml of the acid distilled off. Upon cooling, the hydrochloride crystallized. It was filtered off and dissolved in MeOH; ether was added with stirring and the precipitated hydrochloride filtered off and dried; yield 65·5 g (86 %); m.p. 173–174°. UV: 255 and 309 mμ (log ε 3·66 and 2·56). IR: 3400–3500 cm^{-1}, broad (NH_2). (Found: C, 41·1; H, 4·1; Br, 33·5. Calc. for C_8H_9BrClN: C, 40·9; H, 3·8; Br, 34·1 %.)

5-Bromoindole

5-Bromoindoline hydrochloride (40 g) was treated with cold aqueous alkali to obtain the free base. After cooling, the mixture was extracted with xylene and after addition of chloranil (50 g) in xylene (500 ml), refluxed for 3 hr. The dark mixture was cooled and filtered and the filtrate washed several times with a 20 % aqueous alkali soln and twice with water. The xylene was removed under reduced press and the residue recrystallized from 70 % aqueous EtOH, yield 13·7 g (42 %); m.p. 91°. (lit. m.p. 90–91° [1], 91–93° [5]). UV: 224, 280, 287 and 297 mμ (log ε 4·44, 3·56, 3·56 and 3·37). IR: 3497 cm^{-1} (NH).

5-Cyanoindole

A mixture of 5-bromoindole (11 g), N-methyl-pyrrolidone (50 ml) and CuCN (8 g) was refluxed for 4 hr, cooled and poured on ice. The product was collected, washed thoroughly with 20 % ammonia soln and repeatedly extracted with hot $CHCl_3$. Removal of the $CHCl_3$ gave 6·2 g (78 %) m.p. 107°. It gave no depression of the m.p. on admixture of an authentic specimen.

1-Acetyl-6-cyanoindoline

This was obtained from 1-acetyl-6-aminoindoline similar to the 5- isomer, yield 30 % and recrystallization from aqueous MeCN m.p. 141°. UV: 233, 263 and 302 mμ (log ε 4·30, 4·15 and 3·30). IR: 2215 cm^{-1} ($C{\equiv}N$); 1650 cm^{-1} (C=O). (Found: C, 70·9; H, 5·2; N, 14·8. Calc. for $C_{11}H_{10}N_2O$: C, 70·9; H, 5·3; N, 15·0 %.)

6-Cyanoindoline

1-Acetyl-6-cyanoindoline was deacetylated in the manner described for 1-acetyl-5-cyanoindoline and the product recrystallized from water, m.p. 109°, yield, 79 %. UV: 226 and 267 mμ (log ε 4·34 and 3·58). IR: 3395 cm^{-1} (NH); 2215 cm^{-1} ($C{\equiv}N$). (Found: C, 74·8; H, 5·7; N, 19·5. Calc. for $C_9H_8N_2$: C, 75·0; H, 5·6; N, 19·4 %.)

6-Cyanoindole

6-Cyanoindoline was dehydrogenated with Pd–C as described for 5-cyanoindoline and the product recrystallized from water m.p. 132°. (lit.[3] m.p. 129–130°). UV: 236 and 287 mμ (log ε 4·23 and 3·61). IR: 3390 cm^{-1} (NH); 2205 cm^{-1} ($C{\equiv}N$). (Found: C, 75·8; H, 4·3; N, 19·5. Calc. for $C_9H_6N_2$: C, 76·0; H, 4·3; N, 19·7 %.)

Indoline-6-carboxylic acid

A mixture of 2 g 1-acetyl-6-cyanoindoline and 20 ml conc HCl was refluxed for 3 hr, and 15 ml acid distilled off. Upon cooling the hydrochloride crystallized, yield 1·2 g (70 %); from water, m.p. 225–230°. UV: 288 and 325 mμ (log ε 4·06 and 2·78). IR: 3110 cm^{-1} ($\overset{+}{N}H_2$); 1695 cm^{-1} (C=O). (Found: C, 53·9; H, 4·8; N, 7·0 Calc. for $C_9H_{10}ClNO_2$: C, 54·3; H, 5·0; N, 7·0 %.) The salt was dissolved in aqueous alkali, filtered off and the filtrate neutralized. The precipitated acid melted at 203–205°.

Indole-6-carboxylic acid

Indoline-6-carboxylic acid was dehydrogenated with 10 % Pd–C in the same manner as the 5-isomer and the product recrystallized from AcOH, m.p. 245° (lit.[3] m.p. 243–244°), yield 83 %. UV: 235 and 286 mμ (log ε 4·13 and 3·80). IR: 3345 cm^{-1} (NH); 1670 cm^{-1} (C=O). (Found: C, 66·9; H, 4·4; N, 8·5. Calc. for $C_9H_9NO_2$: C, 67·0; H, 4·4; N, 8·6 %.)

1-*Acetyl-7-cyanoindoline*

This was obtained from 1-acetyl-7-aminoindoline[6] similar to the 5- isomer, yield 35% and was recrystallized from MeCN, m.p. 124°. UV: 224, 256 and 313 mμ (log 4·34, 3·76 and 3·52). IR: 2200 cm^{-1} (C≡N): 1680 cm^{-1} (C═O). (Found: C, 70·9; H, 5·5; N, 14·8. Calc. for $C_{11}H_{10}N_2O$: C, 70·9; H, 5·3; N, 15·0%.)

Indoline-7-carboxylic acid

This was obtained from 1-acetyl-7-cyanoindoline similar to the 5-isomer, yield 80% and crystallized from water, m.p. 162–164°. UV: 220, 248 and 349 mμ (log ε 2·06, 1·34 and 1·28). IR: 3410 cm^{-1} (NH); 1645 cm^{-1} (C═O). (Found: C, 66·6; H, 5·9; N, 8·5. Calc. for $C_9H_9NO_2$: C, 66·3; H, 5·6; N, 8·6%.)

Indole-7-carboxylic acid

Indoline-7-carboxylic acid was dehydrogenated with 10% Pd–C and recrystallized from aqueous EtOH, yield 81%, m.p. 202°. (lit.[11] m.p. 198–199°). UV: 225 and 310 mμ (log ε 4·25 and 3·76). IR: 3395 cm^{-1} (NH); 1665 cm^{-1} (C═O). (Found: C, 67·0; H. 4·5; N, 8·6. Calc. for $C_9H_7NO_2$: C, 67·0; H, 4·4; N, 8·7%.)

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[11] H. Singer and W. Shive, *J. Am. Chem. Soc.* 77, 5700 (1955).