

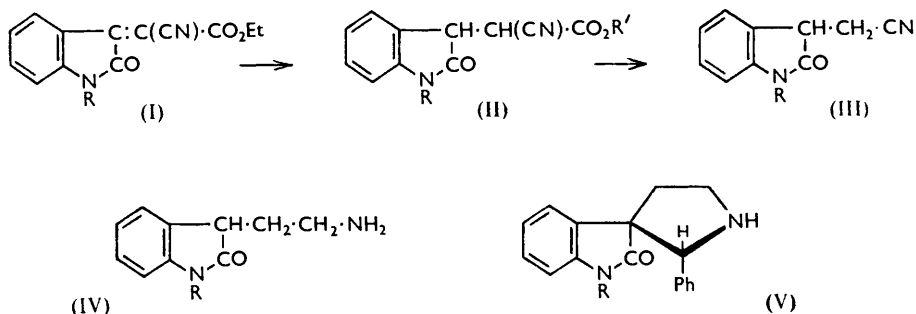
728. Hydroxytryptamines. Part IV.* Synthesis and Reactions of 2-3'-Oxindolyethylamines.

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2-3'-Oxindolyethylamine is readily obtained in four stages from isatin *via* its condensation product with ethyl cyanoacetate. The 1-methyl derivative is obtained similarly. Reaction with benzaldehyde gave 2'-phenyl-oxindole-3-*spiro*-3'-pyrrolidines.

3-Oxindolyglyoxylic acid has been obtained by a new route and some earlier reports concerning its rearrangement have been clarified.

A RECENT synthesis by Witkop and his collaborators¹ of 2-3'-oxindolyethylamine (2-hydroxytryptamine) (IV; R = H) in low yield from tryptamine prompts us to record our earlier work² on the synthesis of the amine and some derivatives from isatin. Isatin was condensed with ethyl cyanoacetate, piperidine being used as catalyst, to give ethyl α -cyano-3-isatyldeneacetate³ (I; R = H) which was reduced to the oxindolyl ester (II; R = H, R' = Et). Brief alkaline hydrolysis gave the acid (II; R = R' = H) which was readily decarboxylated to β -3-oxindolylacetonitrile (III; R = H); this had earlier been obtained by another route.⁴ Hydrogenation of the nitrile over Adams's catalyst in acid solution gave the amine (IV; R = H) provided that hydrogenation was



interrupted after 2 mols. of hydrogen had been absorbed. A similar sequence, starting with *N*-methylisatin (of which an improved preparation is described), led to the 1-methylamine (IV; R = Me). The 1-benzyl-nitrile (III; R = benzyl) was obtained similarly but its reduction to the amine was unsatisfactory.

The amines readily underwent an internal Mannich reaction with benzaldehyde giving 2'-phenyloxindole-3-*spiro*-3'-pyrrolidines (V; R = H and R = Me). That the products were not the isomeric Schiff's bases was shown by their stability to acid. Only one product was formed in each case despite the fact that the structure (V) contains two asymmetric centres. Examination of a model showed clearly that in one of the two possible configurations (not illustrated) interference between the two benzene rings is so great that it is most unlikely to be formed, and that our products must have the configuration illustrated, the reaction being stereospecific. A similar ring system occurs in the alkaloid rhynchophylline,⁵ and the biogenetic parallel is of interest.

Short boiling of the isatyldene ester (I; R = H) with alkali followed by acidification gave a bright yellow acidic product, corresponding in composition and melting point to

* Part III, *J.*, 1955, 374.

¹ Freter, Weissbach, Redfield, Udenfriend, and Witkop, *J. Amer. Chem. Soc.*, 1958, **80**, 983.

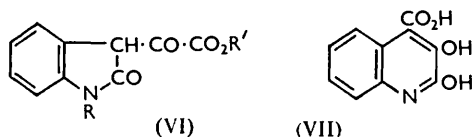
² Ingleby, Dissertation, Cambridge, 1956.

³ Cf. Yokayama, *J. Chem. Soc. Japan*, 1936, **57**, 251.

⁴ Cornforth, Cornforth, Dalgliesh, and Neuberger, *Biochem. J.*, 1951, **48**, 591.

⁵ Seaton and Marion, *Canad. J. Chem.*, 1957, **35**, 1102.

Granacher and Mahal's⁶ 3-oxindolylglyoxylic acid (VI; R = R' = H); hydrogen cyanide was also obtained, so that the reaction clearly involved displacement of the cyano-group by hydroxyl in addition to hydrolysis of the ester. However, later⁷ Granacher and Kouniniotis assigned a revised structure, 2 : 3-dihydroxyquinoline-4-carboxylic acid (VII), to their product, and this revision has been supported.⁸



The ethyl ester (VI; R = H, R' = Et) was prepared later by Horner⁹ from oxindole and ethyl oxalate and was hydrolysed to the acid (assigned the unrearranged structure). We have now found that the absorption spectra of the ester and the free acid are very similar and further, that the acid is readily re-esterified to the original ester, so that rearrangement does not take place during the hydrolysis. Furthermore, we have found that 3-oxindolylglyoxylic acid is *not* rearranged even on prolonged boiling with acid or alkali; instead, slow hydrolysis to oxindole and oxalic acid takes place. Very similar results were obtained with the 1-methyl and 1-benzyl derivatives. The structure revision suggested by Granacher and Kouniniotis⁷ is thus clearly incorrect. In contrast, 3-oxindolylacetic acid is fairly readily rearranged¹⁰ to a quinoline, and consequently hydrolysis of the esters (II; R = H, Me or benzyl, R' = Et) must be conducted rapidly to avoid rearrangement.

EXPERIMENTAL

N-Methylisatin.—To a suspension of isatin (20 g.) in ethanol (300 ml.) ethanolic potassium hydroxide (100 ml.; 10%) was added portionwise during 20 min. with shaking. To the deep purple suspension, dimethyl sulphate (freshly distilled; 15 ml.) was added and the mixture was shaken for 30 min. The mixture was filtered and ethanol (340 ml.) removed from the filtrate by distillation. The residue from the filtration was added to hot water (60 ml.), the concentrated alcoholic solution was added, and the mixture heated to give a clear solution. On cooling, *N*-methylisatin (17.7 g.; 80%) separated as orange needles, m. p. 134—136° (lit.,¹¹ m. p. 136°).

Reaction of Isatins with Ethyl Cyanoacetate.—A solution of isatin (25 g.) and ethyl cyanoacetate (20 g.) in ethanol (150 ml.) containing piperidine (0.2 ml.) was refluxed for 4 hr. After being chilled overnight, ethyl α -cyano-3-isatylideneacetate (30 g.; 73%) was filtered off and washed with a little ether. The material formed dark red needles, m. p. 196—198° (Yokayama³ gives m. p. 202°).

Similarly, *N*-methylisatin (35.5 g.) and ethyl cyanoacetate (25 g.) yielded *ethyl α -cyano-1-methyl-3-isatylideneacetate* (47.3 g.; 84%) as dark red prisms, m. p. 188—192° (from ethanol) (Found: C, 65.6; H, 4.3; N, 11.0. C₁₄H₁₂O₃N₂ requires C, 65.6; H, 4.7; N, 10.9%).

Similarly, *N*-benzylisatin (5 g.) and ethyl cyanoacetate (2.5 g.) yielded the *benzyl compound* (5 g.; 75%) as dark purple needles, m. p. 166° (from ethanol) (Found: C, 72.3; H, 4.8; N, 8.7. C₂₀H₁₆O₃N₂ requires C, 72.3; H, 4.85; N, 8.4%).

3-Oxindolylacetoneitriles.—Ethyl α -cyano-3-isatylideneacetate (30 g.) was stirred vigorously with ethyl acetate (250 ml.) and 3*N*-hydrochloric acid (120 ml.) while zinc dust (15 g.) was slowly added. After filtration, the organic layer was separated and dried (Na₂SO₄), and the solvent removed leaving an oil which slowly crystallised. *Ethyl α -cyano-3-oxindolylacetate* (27 g.; 90%) formed plates, m. p. 108—111° (Found: N, 11.5. C₁₃H₁₂O₃N₂ requires N, 11.5%).

⁶ Granacher and Mahal, *Helv. Chim. Acta*, 1923, **6**, 467.

⁷ Granacher and Kouniniotis, *ibid.*, 1928, **11**, 1241.

⁸ Julian, Meyer, and Printy in "Heterocyclic Compounds," ed. Elderfield, New York, Interscience, 1952, vol. 3, p. 169.

⁹ Horner, *Annalen*, 1941, **548**, 117.

¹⁰ Julian, Printy, Ketcham, and Doone, *J. Amer. Chem. Soc.*, 1953, **75**, 5305.

¹¹ Borsche and Jacobs, *Ber.*, 1914, **47**, 361.

Similar reduction of ethyl α -cyano-1-methyl-3-isatylideneacetate gave ethyl α -cyano-1-methyl-3-oxindolylacetate, prisms, m. p. 118—120° (Found: C, 65.1; H, 5.2; N, 11.1. $C_{14}H_{14}O_3N_2$ requires C, 65.1; H, 5.5; N, 10.8%).

Similar reduction of ethyl α -cyano-1-benzyl-3-isatylideneacetate gave the oxindolylacetic (II; R = benzyl, R' = Et) as an oil.

Ethyl α -cyano-3-oxindolylacetate (10 g.) was added to boiling sodium hydroxide solution (40 ml.; 10%) under nitrogen. Boiling was continued for 4 min. and the solution was then at once chilled and acidified with hydrochloric acid. α -Cyano-3-oxindolylacetic acid (7.4 g.; 84%) was precipitated and formed tabular prisms, m. p. 165° with effervescence, from water (Found: C, 59.1; H, 4.3; N, 12.5. $C_{11}H_8O_3N_2 \cdot 0.5H_2O$ requires C, 58.7; H, 4.0; N, 12.4%).

Similarly obtained, α -cyano-1-methyl-3-oxindolylacetic acid formed prisms, m. p. 115° (Found: C, 57.8; H, 4.9; N, 11.5. $C_{12}H_{10}O_3N_2 \cdot H_2O$ requires C, 58.1; H, 4.8; N, 11.3%).

Similar hydrolysis of the 1-benzyl-3-oxindolylacetate gave the corresponding acid as an oil which was decarboxylated without further purification.

α -Cyano-3-oxindolylacetic acid (5 g.) was boiled under reflux with ethylene glycol monoethyl ether (15 ml.; redistilled to remove peroxides) for 2 hr. Water (10 ml.) was added and on storage at 0° the product (3 g.) slowly crystallised. 3-Oxindolylacetonitrile formed prisms, (from ethanol) m. p. and mixed m. p. with an authentic specimen 162°.4

Similarly obtained, 1-methyl-3-oxindolylacetonitrile formed prisms, m. p. 89.5—90° (from ether) (Found: C, 71.35; H, 5.2; N, 15.5. $C_{11}H_{10}ON_2$ requires C, 70.95; H, 5.4; N, 15.05%).

Similarly obtained, 1-benzyl-3-oxindolylacetonitrile formed fine needles, m. p. 150—151° (from ethyl acetate-ethanol) (Found: C, 78.0; H, 5.2; N, 10.9. $C_{17}H_{14}ON_2$ requires C, 77.8; H, 5.4; N, 10.7%).

Oxindolylethylamines.—A solution of 3-oxindolylacetonitrile (2.2 g.) in ethanol (100 ml.) and water (20 ml.) containing concentrated hydrochloric acid (3 ml.) was hydrogenated at room temperature and atmospheric pressure over Adams's platonic oxide. Uptake of hydrogen was rapid, and was interrupted after 10% more than the calculated quantity had been absorbed (there was no break in the hydrogenation curve). After filtration, the solvent was removed leaving the crude product which was twice recrystallised from ethanol containing a little water. 2-3'-Oxindolylethylammonium chloride (1.62 g.; 60%) formed prisms, 244—246° (decomp.) with preliminary darkening (lit.,¹ m. p. 236°) (Found: C, 56.5; H, 6.1; N, 13.2. Calc. for $C_{10}H_{13}ON_2Cl$: C, 56.8; H, 6.0; N, 13.2%). The picrate had m. p. 175° (lit.,¹ m. p. 175°). The mother liquors gave a weakly positive Ehrlich reaction.

1-Methyl-3-oxindolylacetonitrile on similar reduction gave 2-(1-methyl-3-oxindolyl)ethylammonium chloride (as IV; R = Me), m. p. 193—194° (Found: C, 57.8; H, 6.9; N, 12.4. $C_{11}H_{15}ON_2Cl$ requires C, 58.3; H, 6.6; N, 12.3%).

Similar reduction of 1-benzyl-3-oxindolylacetonitrile was unsatisfactory. Partial debenzylation appeared to occur and the resulting mixture of products was not further investigated.

Condensation of Oxindolylethylamines with Benzaldehyde.—To 2-3'-oxindolylethylammonium chloride (0.76 g.) and hydrated sodium acetate (0.5 g.) in water (3 ml.) and ethanol (20 ml.) benzaldehyde (0.38 g.) was added and the mixture refluxed for 2 hr. The solvent was removed under vacuum and the residue dissolved in dilute hydrochloric acid and extracted with ether. Sodium hydrogen carbonate was added to the aqueous layer until pH 7.3 was reached, and the precipitate was filtered off after being kept overnight at 0°. As the material was difficult to recrystallise it was characterised as 2'-phenyloxindole-3-spiro-3'-pyrrolidine picrate, m. p. 206° from methanol (Found: C, 55.7; H, 4.1; N, 14.5. $C_{17}H_{16}ON_2 \cdot C_6N_3O_7N_3$ requires C, 56.0; H, 3.9; N, 14.2%). To 2-(1-methyl-3-oxindolyl)ethylammonium chloride (0.5 g.) in water (2 ml.) ethanolic benzaldehyde (0.22 g. in ethanol, 7 ml.) and aqueous sodium hydroxide (1.5 ml.; 10%) were added. The product slowly separated at room temperature, and was collected after 2 days. 1-Methyl-2'-phenyloxindole-3-spiro-3'-pyrrolidine (V; R = Me) (0.6 g.) formed compact prisms, m. p. 172° (Found: C, 77.4; H, 5.85; N, 10.4. $C_{18}H_{18}ON_2$ requires C, 77.7; H, 5.6; N, 10.1%).

The material was recovered unchanged when a solution in dilute hydrochloric acid which had been boiled for 1 hr. was basified.

Reaction of α -Cyano-isatylideneacetates with Alkali.—Ethyl α -cyano-3-isatylideneacetate (1 g.) was boiled for 5 min. with sodium hydroxide solution (30 ml.; 5%). The initial dark colour changed to bright yellow. After cooling, the solution was acidified, hydrogen cyanide was then liberated and identified by smell and reaction with copper acetate-benzidine test

paper. The yellow precipitate was twice recrystallised from acetic acid giving 3-oxindolylglyoxylic acid, m. p. 259—262° (decomp.) (lit.,^{6,9} m. p. 265°), as golden-yellow plates (Found: C, 58.7; H, 3.7; N, 7.3. Calc. for $C_{10}H_7O_4N$: C, 58.5; H, 3.4; N, 6.8%). The ethyl ester (ethanol-sulphuric acid), m. p. 185—187°, was identical (mixed m. p.) with a specimen prepared by Horner's⁹ method. Brief alkaline hydrolysis of the ester regenerated the original acid: the ultraviolet spectra of the ester and acid were almost superposable.

Similarly, ethyl α -cyano-1-methyl-3-isatylideneacetate gave 1-methyl-3-oxindolylglyoxylic acid, yellow plates, m. p. 238° (Found: C, 60.05; H, 3.85; N, 6.5. $C_{11}H_9O_4N$ requires C, 60.3; H, 4.1; N, 6.4%), and the benzyl compound gave 1-benzyl-3-oxindolylglyoxylic acid, yellow prisms, m. p. 236° (Found: C, 68.8; H, 4.5; N, 4.7. $C_{17}H_{13}O_4N$ requires C, 69.1; H, 4.4; N, 4.7%).

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