192. 4,5,6,7-*Tetrahydroisatin and Related Compounds. Part I.* 4,5,6,7-*Tetrahydroisatin and* 3-*Amino*-2,4,5,6-*tetrahydro*-2-*oxoindole.*

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The two compounds named in the title have been synthesised by the action of ammonia on ethyl 2-oxocyclohexylglyoxylate. Their interconversion and other reactions are described. With nitrous acid, both compounds give 4,5,6,7-tetrahydro-7-hydroxyiminoisatin, which resembles isatin rather than tetrahydroisatin in its behaviour.

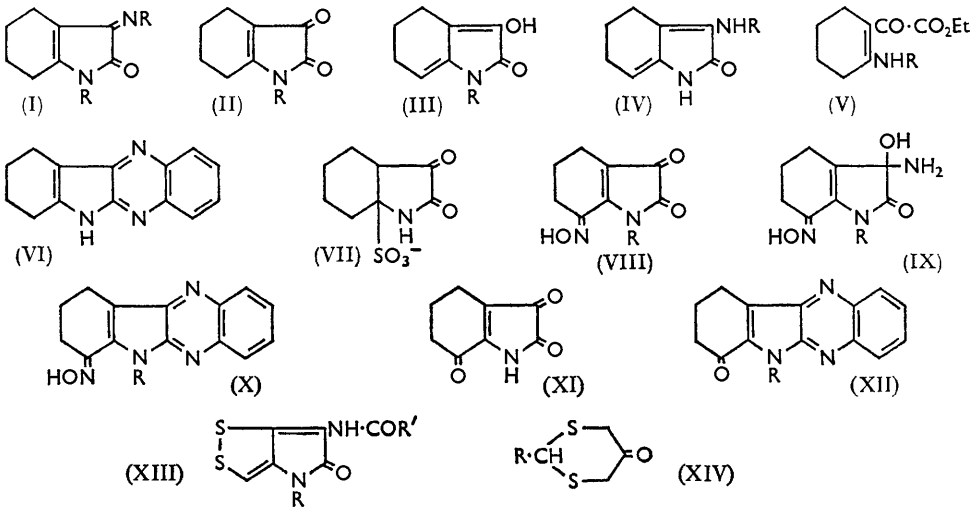
Primary aromatic amines react with 2-oxocyclohexylglyoxylic acid and its esters forming 4,5,6,7-tetrahydroisatin 3-anils [1,2] (I; R = Ar), which are converted by acid hydrolysis into *N*-aryl-4,5,6,7-tetrahydroisatins (II; R = Ar). The tetrahydroisatins, judging from their properties and infrared absorption spectra,[3] exist largely in the enolic form (III; R = Ar). The reaction of ammonia and ethyl 2-oxocyclohexylglyoxylate is reported [2] to give only unstable products which slowly evolve ammonia and yield oxamide.

In a re-investigation of the reaction with ammonia, we have found that both 4,5,6,7-tetrahydroisatin (III; R = H) *and* the corresponding amino-compound, 3-amino-2,4,5,6-tetrahydro-2-oxoindole (IV; R = H), are formed directly from the $\alpha\gamma$-diketo-ester, the relative proportions of the two products depending on the reaction temperature. Thus, at 78° the product was 4,5,6,7-tetrahydroisatin, whilst from a reaction at −10° only the amino-compound was isolated; at intermediate temperatures both compounds were produced, the proportion of the amino-compound decreasing with increasing reaction temperature.

The isolation of only 4,5,6,7-tetrahydroisatin from the reaction at 78° suggests that the first point of attack of ammonia on the diketo-ester is the γ-carbonyl group, giving the intermediate (V; R = H), or a tautomer, which rapidly cyclises with extrusion of ethanol. At lower temperatures, cyclisation may be slower, allowing the intermediate to react further with ammonia, at the α-carbonyl group, before cyclising to the 3-amino-compound. With aniline, on the other hand, reaction in refluxing methanol is reported to produce only the anil (I; R = Ph), a result which led Horwitz [2] to suggest that the diketo-ester is first attacked at the α-carbonyl group (under these conditions, 4,5,6,7-tetrahydro-*N*-phenylisatin is unaffected by aniline). Even in this case, however, the reaction may be assumed to give first the intermediate (V; R = Ph) or a closely related form, if it is supposed that cyclisation to the isatin is sufficiently retarded by the presence of the *N*-aryl group to permit the attack of a second molecule of aniline at the α-position.

[1] Kotz and Hesse, *Annalen*, 1905, **342**, 306.
[2] Horwitz, *J. Amer. Chem. Soc.*, 1953, **75**, 4060.
[3] O'Sullivan and Sadler, *J.*, 1959, 876.

4,5,6,7-Tetrahydroisatin, like its previously described *N*-aryl derivatives, is a typically enolic compound and is best represented as (III; R = H). In agreement with this structure, the infrared absorption spectrum shows only one maximum in the carbonyl region, at 1680 cm.$^{-1}$ (lactam C=O). The compound dissolves readily in cold dilute sodium



hydroxide solution and can be recovered by acidification, but is decomposed in warm alkali with evolution of ammonia. Further indications of enolic character are the intense coloration with ferric chloride, and the formation of a benzoate and an *O*-methyl derivative, 2,4,5,6-tetrahydro-3-methoxy-2-oxoindole, which very closely resembles the parent compound in its ultraviolet absorption spectrum.

Despite its predominantly enolic character, tetrahydroisatin reacts with phenylhydrazine and readily forms the quinoxaline (VI) when heated with *o*-phenylenediamine, but attempts to convert the isatin into the 3-amino-compound (IV; R = H) by the action of ammonia alone were unsuccessful. This conversion was effected, however, with ammonium hydrogen sulphite under the conditions of the Bucherer reaction; the immediate product was a highly insoluble sulphur-containing compound which decomposed, when heated *in vacuo*, to give 3-amino-2,4,5,6-tetrahydro-2-oxoindole in good yield. As with α-naphthol,[4] the reaction probably involves an initial addition of bisulphite ion giving, in this case, the keto-amide (VII) which is then attacked by ammonia at the 3-position.

3-Amino-2,4,5,6-tetrahydro-2-oxoindole (IV; R = H) is insoluble in cold aqueous alkalis but dissolves in cold dilute acids. It forms a normal *N*-acetyl derivative (IV; R = Ac) and reacts in the cold with an equivalent amount of nitrous acid to give 4,5,6,7-tetrahydroisatin, which is also produced by the action of hot dilute hydrochloric acid on the amine. With an excess of nitrous acid, 3-amino-2,4,5,6-tetrahydro-2-oxoindole is converted into a red crystalline product formulated as 4,5,6,7-tetrahydro-7-hydroxyiminoisatin (VIII; R = H); 4,5,6,7-tetrahydroisatin gives the same product with nitrous acid.

The hydroxyimino-compound differs from tetrahydroisatin (and resembles isatin) in a number of respects which reflect the presence of the unenolised dioxopyrroline system. Thus, it is intensely coloured, and it dissolves in cold aqueous sodium hydroxide to give a blue solution which very rapidly becomes yellow. Reaction with ammonia at room temperature affords a yellow addition product, probably (IX; R = H); the compound also forms a normal oxime with hydroxylamine, and combines with *o*-phenylenediamine

[4] Rieche and Seeboth, *Annalen*, 1960, **638**, 43, 57, 66.

to give the hydroxyiminoindoloquinoxaline (X; R = H). The infrared absorption spectrum of 4,5,6,7-tetrahydro-7-hydroxyiminoisatin clearly indicates the presence of the 3-carbonyl group, a well-defined maximum appearing at 1760 cm.$^{-1}$ as well as the normal lactam carbonyl-stretching band at 1690 cm.$^{-1}$.

An analogous hydroxyimino-compound (VIII; R = Ph) was obtained from 4,5,6,7-tetrahydro-*N*-phenylisatin but 4,5,6,7-tetrahydro-7-methylisatin, prepared by the action of ammonia on ethyl 3-methyl-2-oxocyclohexylglyoxylate, was unaffected by treatment with nitrous acid, in agreement with the formulation of the product from tetrahydroisatin as a 7-hydroxyimino-derivative.

Attempts to hydrolyse 4,5,6,7-tetrahydro-7-hydroxyiminoisatin to the diketone (XI) were unsuccessful but the hydroxyiminoindoloquinoxalines (X; R = H) and (X; R = Ph) were converted, by treatment with hot ethanolic hydrochloric acid, into the ketones (XII; R = H) and (XII; R = Ph), and from the former ketone the hydroxyiminoindoloquinoxaline (X; R = H) was regenerated by condensation with hydroxylamine.

3-Amino-2,4,5,6-tetrahydro-2-oxoindole (IV; R = H) and its acetyl derivative (IV; R = Ac) show an interesting structural similarity to antibiotics of the thiolutin–holomycin group (type XIII), syntheses of which have only recently been described.[5] We are investigating the possibility of extending the $\alpha\gamma$-diketo-ester–ammonia reaction, by the use of sulphur-containing ketones, *e.g.*, 5-oxo-1,3-dithians (XIV), as starting materials, so as to provide a new route to holomycin, thiolutin, and analogous compounds.

Experimental

Infrared spectra are reported for Nujol mulls. Ultraviolet spectra were determined in ethanol.

Reaction of Ethyl 2-Oxocyclohexylglyoxylate with Ammonia.—Ammonia was passed through a refluxing solution of ethyl 2-oxocyclohexylglyoxylate [6] (25·0 g.) in ethanol (100 ml.) for 6 hr. After being kept at room temperature overnight, the reaction mixture was filtered (to remove oxamide) and then concentrated to give 4,5,6,7-*tetrahydroisatin* (III; R = H), which crystallised from acetone in needles (9·2 g.), m. p. 204—206° (sealed tube) (Found: C, 63·8; H, 5·95; N, 8·9; O, 21·5. $C_8H_9NO_2$ requires C, 63·6; H, 6·0; N, 9·3; O, 21·2%), $\lambda_{max.}$ 278 mμ (ε 19,000), $\nu_{max.}$ 1680 cm.$^{-1}$ (lactam C=O). The tetrahydroisatin gave an intense green coloration with alcoholic ferric chloride.

When ethyl 2-oxocyclohexylglyoxylate (115 g.) in ethanol (100 ml.) was treated with ammonia for 3 hr. at room temperature, 4,5,6,7-tetrahydroisatin (22·0 g.) crystallised from the reaction mixture. The crude product obtained by concentration of the mother-liquor was treated with dilute hydrochloric acid, giving a further quantity (4·0 g.) of the non-basic isatin. Addition of aqueous sodium hydroxide to the acid solution precipitated 3-*amino*-2,4,5,6-*tetrahydro*-2-*oxoindole* (IV; R = H), which crystallised from acetone in needles (17·1 g.), m. p. 154—156° (Found: C, 64·0; H, 6·75; N, 18·5. $C_8H_{10}N_2O$ requires C, 64·0; H, 6·7; N, 18·65%), $\lambda_{max.}$ 284 mμ (ε 16,275), $\nu_{max.}$ 1670 cm.$^{-1}$ (lactam C=O).

From a similar reaction at −10°, no tetrahydroisatin was obtained, the only product being 3-amino-2,4,5,6-tetrahydro-2-oxoindole, in 50% yield.

Derivatives of 4,5,6,7-*Tetrahydroisatin.*—When heated under reflux for 6 hr. with potassium carbonate (3·0 g.), dimethyl sulphate (5 ml.), and acetone (200 ml.), tetrahydroisatin (2·8 g.) gave 2,4,5,6-*tetrahydro*-3-*methoxy*-2-*oxoindole*, purified by sublimation at 120—130°/0·5 mm. and forming needles (2·6 g.), m. p. 164—166° (sealed tube) (Found: C, 65·2; H, 6·9; N, 8·4; O, 19·6; OMe, 18·8. $C_9H_{11}NO_2$ requires C, 65·4; H, 6·7; N, 8·5; O, 19·4; OMe, 18·8%), $\lambda_{max.}$ 279 mμ (ε 20,400).

Tetrahydroisatin (1·0 g.), dissolved in 2N-aqueous sodium hydroxide (15 ml.) and treated with benzoyl chloride (2 ml.), gave the 3-*benzoate* which crystallised from ethanol in pale yellow prisms (0·9 g.), m. p. 190—192° (Found: C, 70·5; H, 5·0; N, 5·4. $C_{15}H_{13}NO_3$ requires C, 70·6; H, 5·1; N, 5·5%), $\nu_{max.}$ 1740 (ester C=O), 1700 cm.$^{-1}$ (lactam C=O).

[5] Schmidt and Geiger, *Angew. Chem.*, 1962, **74**, 328; *Annalen*, 1963, **664**, 168; Büchi and Lukas, *J. Amer. Chem. Soc.*, 1963, **85**, 647.

[6] Snyder, Brooks, and Shapiro, *Org. Synth.*, Coll. Vol. II, 1943, p. 531.

The *derivative* obtained by heating tetrahydroisatin (2·0 g.) with phenylhydrazine (3 ml.) in ethanol (80 ml.) for 2 hr. crystallised in needles (2·2 g.), m. p. 267—268 (sealed tube) (Found: C, 69·65; H, 6·4; N, 17·7. $C_{14}H_{15}N_3O$ requires C, 69·7; H, 6·3; N, 17·4%). With *o*-phenylenediamine (1·1 g.) in boiling aqueous acetic acid for 2 hr., tetrahydroisatin (1·5 g.) formed 7,8,9,10-*tetrahydro*-6H-*indolo*[2,3-b]*quinoxaline* (VI) which crystallised from ethanol in yellow needles (1·7 g.), subliming above 200° (Found: C, 75·1; H, 6·0; N, 19·0. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·9; N, 18·8%).

Reactions of 3-*Amino*-2,4,5,6-*tetrahydro*-2-*oxoindole*.—Prepared by the action of acetic anhydride and pyridine on the amine (1·0 g.), and purified by sublimation at 160—170°/0·2 mm., 3-*acetamido*-2,4,5,6-*tetrahydro*-2-*oxoindole* formed plates (1·1 g.), m. p. 224—226° (sealed tube) (Found: C, 62·85; H, 6·0; N, 14·35; O, 16·9. $C_{10}H_{12}N_2O_2$ requires C, 62·5; H, 6·3; N, 14·6; O, 16·65%).

A solution of 3-amino-2,4,5,6-tetrahydro-2-oxoindole (1·0 g.) in 2N-aqueous hydrochloric acid (10 ml.), after being heated on the steam-bath for 1 hr., gave 4,5,6,7-tetrahydroisatin (0·6 g.).

Conversion of 4,5,6,7-*Tetrahydroisatin into* 3-*Amino*-2,4,5,6-*tetrahydro*-2-*oxoindole*.—Sulphur dioxide was passed into concentrated aqueous ammonia (*d* 0·88; 20 ml.) until the increase in weight was 5·0 g. and the resulting solution was heated with tetrahydroisatin (1·0 g.) in a sealed tube at 120° for 24 hr. The highly insoluble product, when heated to 170—180°/0·2 mm., gave 3-amino-2,4,5,6-tetrahydro-2-oxoindole (0·7 g.), m. p. and mixed m. p. 154—156°; this product gave the same infrared spectrum and the same acetyl derivative, m. p. 224—226°, as an authentic sample.

4,5,6,7-*Tetrahydro*-7-*hydroxyiminoisatin* (VIII; R = H).—An ice-cold solution of sodium nitrite (6·0 g.) in 2N-hydrochloric acid (50 ml.) was added slowly to a cooled, vigorously stirred suspension of 4,5,6,7-tetrahydroisatin (10 g.) in water (20 ml.) and concentrated hydrochloric acid (10 ml.). The crude product, recrystallised from acetic acid, gave 4,5,6,7-*tetrahydro*-7-*hydroxyiminoisatin* as red needles (6·5 g.), m. p. 192—194° (sealed tube) (Found: C, 53·5; H, 4·6; N, 15·2; O, 26·8. $C_8H_8N_2O_3$ requires C, 53·3; H, 4·5; N, 15·55; O, 26·6%), $\lambda_{max.}$ 249, 294, and 426 mμ (ε 9450, 6575, and 3225), $\nu_{max.}$ 1760 (ketone C=O) and 1690 cm.$^{-1}$ (lactam C=O). The same hydroxyimino-compound was obtained when 3-amino-2,4,5,6-tetrahydro-2-oxoindole was treated with an excess of nitrous acid.

The hydroxyimino-compound formed a normal oxime, 2,3,4,5,6,7-*hexahydro*-3,7-*dihydroxyimino*-2-*oxoindole*, crystallising from ethanol in yellow needles, m. p. above 300° (Found: C, 49·3; H, 4·7; N, 21·1. $C_8H_9N_3O_3$ requires C, 49·2; H, 4·65; N, 21·5%).

Passage of ammonia through a methanolic solution of 4,5,6,7-tetrahydro-7-hydroxyiminoisatin (1·0 g.) at room temperature and removal of the solvent *in vacuo* gave an adduct, which formed yellow plates (1·0 g.), m. p. 185—186° (decomp.), from ethanol (Found: C, 48·9; H, 6·0; N, 20·7. $C_8H_{11}N_3O_3$ requires C, 48·7; H, 5·6; N, 21·3%).

When heated with *o*-phenylenediamine (1·0 g.) in ethanol (100 ml.) for 1 hr., the hydroxyimino-compound (1·0 g.) formed 7,8,9,10-*tetrahydro*-7-*hydroxyimino*-6H-*indolo*[2,3-b]*quinoxaline* (X; R = H), as yellow needles (0·8 g.), m. p. above 300°, which could not be satisfactorily purified (Found: C, 65·7; H, 4·8; N, 21·6. $C_{14}H_{12}N_4O$ requires C, 66·65; H, 4·8; N, 22·2%). This quinoxaline (7·2 g.), ethanol (250 ml.), and concentrated hydrochloric acid (30 ml.) were heated on the steam-bath for 6 hr. After dilution with water, the mixture was made alkaline and the product extracted with ethyl acetate. 7,8,9,10-*Tetrahydro*-7-*oxo*-6H-*indolo*[2,3-b]*quinoxaline* (XII; R = H) crystallised from ethyl acetate in yellow plates (3·2 g.), m. p. 264—266° (Found: C, 71·15; H, 4·5; N, 17·4. $C_{14}H_{11}N_3O$ requires C, 70·9; H, 4·7; N, 17·7%), $\nu_{max.}$ 1670 cm.$^{-1}$ (conj. C=O). This ketone reacted normally with hydroxylamine to give 7,8,9,10-tetrahydro-7-hydroxyimino-6H-indolo[2,3-*b*]quinoxaline, identical in infrared absorption spectrum with the authentic sample.

4,5,6,7-*Tetrahydro*-7-*hydroxyimino*-1-*phenylisatin* (VIII; R = Ph).—4,5,6,7-Tetrahydro-1-phenylisatin (1·0 g.), suspended in a mixture of ethanol (10 ml.) and 2N-hydrochloric acid (20 ml.), was treated with an ice-cold solution of sodium nitrite in water. The dark red product was recrystallised from benzene, giving 4,5,6,7-*tetrahydro*-7-*hydroxyimino*-1-*phenylisatin* as red needles (0·9 g.), m. p. 202—204° (Found: C, 66·0; H, 4·85; N, 11·0. $C_{14}H_{12}N_2O_3$ requires C, 65·6; H, 4·7; N, 10·9%), $\nu_{max.}$ 1760 (ketone C=O) and 1692 cm.$^{-1}$ (lactam C=O). Reaction with *o*-phenylenediamine gave 7,8,9,10-*tetrahydro*-7-*hydroxyimino*-6-*phenyl*-6H-*indolo*[2,3-b]*quinoxaline* (X; R = Ph); yellow needles from aqueous ethanol, m. p. 265—267° (decomp.) (Found:

C, 72·7; H, 4·9; N, 17·1. $C_{20}H_{16}N_4O$ requires C, 73·15; H, 4·9; N, 17·1%). Hydrolysis of this product with ethanolic hydrochloric acid afforded 7,8,9,10-*tetrahydro*-7-*oxo*-6-*phenyl*-6H-*indolo*[2,3-b]*quinoxaline* (XII; R = Ph); yellow needles (from ethanol), m. p. 238—240° (Found: C, 76·9; H, 4·9; N, 13·35. $C_{20}H_{15}N_3O$ requires C, 76·6; H, 4·8; N, 13·4%), $\nu_{max.}$ 1672 cm.$^{-1}$ (conj. C=O).

4,5,6,7-*Tetrahydro*-7-*methylisatin*.—Ethyl 3-methyl-2-oxocyclohexylglyoxylate (20 g.) in ethanol, treated with ammonia at room temperature, gave 4,5,6,7-*tetrahydro*-7-*methylisatin*, forming plates (8·0 g.) (from ethanol), m. p. 226—228° (Found: C, 65·5; H, 6·8; N, 8·5. $C_9H_{11}NO_2$ requires C, 65·4; H, 6·7; N, 8·5%), and 3-amino-2,4,5,6-tetrahydro-7-methyl-2-oxoindole (3·5 g.). The latter was not obtained pure but was characterised as the 3-*acetamido*-*compound*, plates, m. p. 228° (sealed tube) (Found: C, 64·0; H, 6·45; N, 13·5. $C_{11}H_{14}N_2O_2$ requires C, 64·1; H, 6·8; N, 13·6%).

One of us (J. H.) thanks the D.S.I.R. for the award of a maintenance grant.

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The University of Liverpool. [*Received, August 2nd,* 1963.]