84. *The Alkaline Hydrolysis of the Azlactones derived from Certain o-Nitrobenzaldehydes. The Formation of Isatins.*

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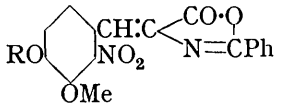
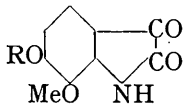
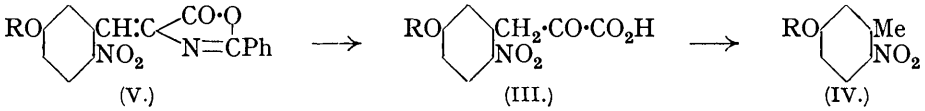
GULLAND, ROSS, and SMELLIE (J., 1931, 2890) were unable to isolate homogeneous material when 5-keto-2-phenyl-4-(2′-nitro-4′-acetoxy-3′-methoxybenzylidene)-4 : 5-dihydro-oxazole (I; R = Ac) was hydrolysed with baryta, but they deduced the probable formation of an isatin from colour reactions. Their failure to isolate the isatin was probably due to the use of too small a quantity of the oxazolone, since we have had no difficulty in showing that 6-*hydroxy*-7-*methoxyisatin* (II; R = H) is formed in 60% yield when it is hydrolysed with 10% aqueous sodium hydroxide.

(I.)  (II.) 

The new isatin is readily characterised through its sparingly soluble *semicarbazone*. The course of this oxidation–reduction reaction appears to differ slightly from that with 5-keto-2-phenyl-4-(2′-nitro-3′ : 4′-dimethoxybenzylidene)-4 : 5-dihydro-oxazole (I; R = Me)—which was shown by Gulland, Robinson, Scott, and Thornley (J., 1929, 2924) to be hydrolysed by aqueous-alcoholic sodium hydroxide to 6 : 7-dimethoxyisatin and 2-aminoveratric acid—since the formation of 2-amino-4-hydroxy-3-methoxybenzoic could not be proved. We have found that 6 : 7-dimethoxyisatin and 2-aminoveratric acid are also formed when the oxazolone (I; R = Me) is hydrolysed with 10% aqueous sodium hydroxide. The suggestion previously made (Burton, J., 1935, 1265) that the 2-aminoveratric acid results by intramolecular dismutation of the intermediate 2-nitrohomoveratrole has not been capable of experimental proof, since the amount of alkali-insoluble material formed during the hydrolysis with aqueous sodium hydroxide was too small to allow of identification. This negative result must not be considered to disprove the suggestion, since the amount of 2-aminoveratric acid isolated is relatively small, thus indicating that the concentration of the nitrohomoveratrole, if produced, must also be small.

We have shown, however, that 2-*nitro*-5-*benzyloxyphenylpyruvic acid* (III; R = CH_2Ph), which was synthesised from 2-nitro-5-benzyloxytoluene (IV; R = CH_2Ph) and ethyl oxalate in the presence of potassium ethoxide, is rapidly converted by boiling 10% aqueous sodium hydroxide into 2-nitro-5-benzyloxytoluene, thus affording strong evidence that the hydrolysis of the oxazolones of type (V) previously studied (Burton, *loc. cit.*) probably occurs in the following way :



(V.) (III.) (IV.)

It is not unlikely that the hydrolysis of the oxazolones (I; R = Ac or Me) also gives the corresponding *o*-nitrophenylpyruvic acids, which, owing to some structural feature, undergo an oxidation–reduction process to give 6-hydroxy-7-methoxy- and 6 : 7-dimethoxyisatin respectively (compare Reissert, *Ber.*, 1897, **30**, 1036). The structural feature in question is probably the presence of a substituent adjacent to the nitro-group rather than to the presence of two substituents in addition to nitro, since Oliverio (*Gazzetta*, 1935, **65**, 143) has shown that 5-keto-2-phenyl-4-(2′-nitro-4′ : 5′-dimethoxybenzylidene)-4 : 5-dihydro-oxazole reacts in the same manner as (V) to give 6-nitrohomoveratrole but no isatin.

EXPERIMENTAL.

6-*Hydroxy*-7-*methoxyisatin* (II; R = H).—9·55 G. of 5-keto-2-phenyl-4-(2′-nitro-4′-acetoxy-3′-methoxybenzylidene)-4 : 5-dihydro-oxazole, m. p. 171—172° (Found : C, 59·4; H, 3·7. Calc. for $C_{19}H_{14}O_7N_2$: C, 59·7; H, 3·7%), prepared from 2-nitroacetylvanillin (Slotta and

Lauerson, *J. pr. Chem.*, 1934, **139**, 220) and hippuric acid by Gulland, Ross, and Smellie's method (*loc. cit.*), was boiled with 10% sodium hydroxide solution (150 c.c.) under reflux for 4 hours; ammonia was evolved after the first few minutes. The dark brown solution was cooled and acidified by a stream of sulphur dioxide. The precipitated material was collected, dried in a vacuum desiccator, and extracted with boiling benzene. This treatment removed benzoic acid and left a dark-coloured amorphous material, which was warmed with moderately concentrated hydrochloric acid; the acidic extract did not give a dye when treated successively with nitrous acid and alkaline β-naphthol.

The filtrate after removal of the above precipitate containing benzoic acid was mixed with an excess of concentrated hydrochloric acid and boiled to expel all the sulphur dioxide, and the cooled solution filtered from a small amount of tarry matter and extracted four times with ether. The dried extract (sodium sulphate) afforded 2·9 g. (60% yield) which, recrystallised twice from a small amount of glacial acetic acid, gave the *isatin* in dark red needles, m. p. 246—247° (decomp.) (Found : C, 56·0; H, 3·8; N, 7·15. $C_9H_7O_4N$ requires C, 55·95; H, 3·6; N, 7·25%), readily soluble in water and alcohol but much less soluble in chloroform, benzene, and ether. The *semicarbazone* separated in golden-yellow plates when a solution of the isatin in alcohol was mixed with aqueous semicarbazide acetate; it was insoluble in all the usual solvents except hot glacial acetic acid (from which it did not separate). When heated, it darkened gradually but had not melted at 270° (Found : N, 20·5, 20·6. $C_{10}H_{10}O_4N_4,H_2O$ requires N, 20·9%).

6 : 7-*Dimethoxyisatin and* 2-*Aminoveratric Acid.*—A mixture of 5-keto-2-phenyl-4-(2′-nitro-3′ : 4′-dimethoxybenzylidene)-4 : 5-dihydro-oxazole (8·85 g.) and 10% sodium hydroxide solution (100 c.c.) was boiled under reflux for 3½ hours. A little steam-volatile oil was formed, but extraction of the dark red solution with ether after 1 hour removed less than 0·2 g. of a yellow oil (? 2-nitrohomoveratrole). Benzoic acid, 2-aminoveratric acid (0·4 g.), m. p. 184° after crystallisation from water, and 6 : 7-dimethoxyisatin (2·2 g.), m. p. 212—213° after crystallisation from alcohol, were isolated from the hydrolysate by Gulland, Robinson, Scott, and Thornley's procedure (*loc. cit.*).

6-*Nitro*-m-*cresol.*—Blaikie and Perkin's method (J., 1924, **125**, 307) of preparation led, in our hands, to unworkable tarry products. The following procedure proved satisfactory. Acetyl nitrate, prepared from nitric acid (*d* 1·5; 47 g.) and acetic anhydride (110 g.) below 0°, was added slowly with stirring to a solution of *m*-cresol (65 g.) in acetic anhydride (171 g.) at − 5°; the mixture was then kept for 6 hours, poured on ice, and left overnight. Steam-distillation of the nitrated product removed 4-nitro-*m*-cresol (23 g.); on cooling, the non-volatile residue solidified to a dark crystalline mass. Recrystallisation of this from benzene gave 16 g. of 6-nitro-*m*-cresol, m. p. 125—126°, which was sufficiently pure for the preparation of its benzyl ether.

2-*Nitro*-5-*benzyloxyphenylpyruvic Acid* (III; R = CH_2Ph).—Potassium ethoxide from powdered potassium (6·6 g.) and sodium-dried alcohol (7·7 g.) in ether (250 c.c.) was treated with ethyl oxalate (26 g.) and then with 2-nitro-5-benzyloxytoluene (41 g. dissolved in the minimum amount of ether). The mixture was heated under reflux for 18 hours, water added to dissolve the solid which separated, and the aqueous extract acidified (Congo-red) with concentrated hydrochloric acid. The *pyruvic acid* separated as a red oil which gradually solidified (yield, 22 g.). Recrystallisation from water gave pale yellow needles, m. p. 103°, containing water of crystallisation (Found : C, 59·8; H, 4·7; N, 4·3. $C_{16}H_{13}O_6N,\frac{1}{2}H_2O$ requires C, 59·3; H, 4·3; N, 4·3%). A dilute alcoholic solution of the acid gave a deep green coloration with ferric chloride.

The acid was also prepared with sodium ethoxide as the condensing agent, but was obtained in a less pure condition. The reduction of the acid to 5-benzyloxyindole-2-carboxylic acid is reserved for a future communication dealing with the synthesis of various derivatives of indole.

Conversion of 2-*Nitro*-5-*benzyloxypyruvic Acid into* 2-*Nitro*-5-*benzyloxytoluene.*—A solution of the acid (3·25 g.) in 10% sodium hydroxide solution (30 c.c.) was boiled under reflux for 1 hour; oil separated after the first few minutes. Extraction with ether removed 1·7 g. (70% yield) of 2-nitro-5-benzyloxytoluene, m. p. 72—73° (after crystallisation from alcohol) either alone or mixed with an authentic specimen.

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