CCCXXXVII.—*A New Reaction of Certain Diazo-sulphonates derived from β-Naphthol-*1*-sulphonic Acid. Part II. The Constitution of Nitro- and Amino-phenylphthalazones.*

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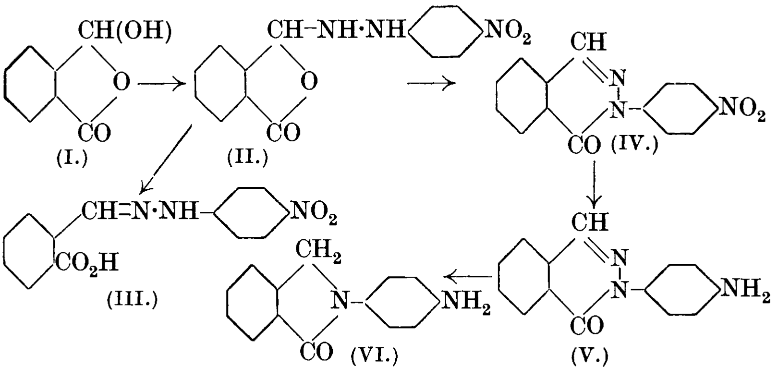
IN a former communication (J., 1926, 700) we stated that 1-hydroxy-3-(4′-nitrophenyl)-1 : 3-dihydrophthalazine-4-acetic acid (VII) is reprecipitated unaltered by diluting a solution in cold concentrated sulphuric acid, but boiling with aqueous sulphuric acid gives a substance which is not precipitated from the solution on further dilution. The latter substance has now been examined more closely. Acetic acid is eliminated during the reaction, and analysis of the product, yellow needles, m. p. 333°, gave the formula $C_{14}H_9O_3N_3$, which is that of a nitrophenylphthalazone. Consequently, this reaction is analogous to the conversion of 1-hydroxy-3-(4′-aminophenyl)-tetrahydrophthalazine-4-acetic acid (VIII) into an aminophenylphthalazone by boiling with aqueous mineral acid (*loc. cit.*, p. 703). The product obtained by the reduction of the nitrophenylphthalazone varies with the conditions used. Thus, reduction with aqueous sodium sulphide gives the aminophenylphthalazone, which we described previously as 4′-amino-3-phenylphthalaz-4-one, whereas zinc dust and hydrochloric acid give 4′-amino-*N*-phenylphthalimidine.

Seekles (*Rec. trav. chim.*, 1924, **43**, 329) has described as a nitrophenylphthalazone a substance, deep orange needles, becoming paler at 228° and melting at 259°, which he obtained by condensing *o*-phthalaldehydic acid with *p*-nitrophenylhydrazine in alcoholic solution. This compound obviously is not identical with ours, and its method of preparation should lead to 4′-nitro-3-phenylphthalaz-4-one. If that is the case, our compound is the isomeric 4′-*nitro*-3-*phenylphthalaz*-1-*one* (IX), and the compound which we described previously as 4′-amino-3-phenylphthalaz-4-one is actually 4′-*amino*-3-*phenylphthalaz*-1-*one* (X). Consequently, in converting 1-hydroxy-3-(4′-aminophenyl)tetrahydrophthalazine-4-acetic acid into the aminophenylphthalazone with elimination of acetic acid, it is not the $>CH\cdot CH_2\cdot CO_2H$ group, but the $>CH\cdot OH$ group, which is converted into a keto-group.

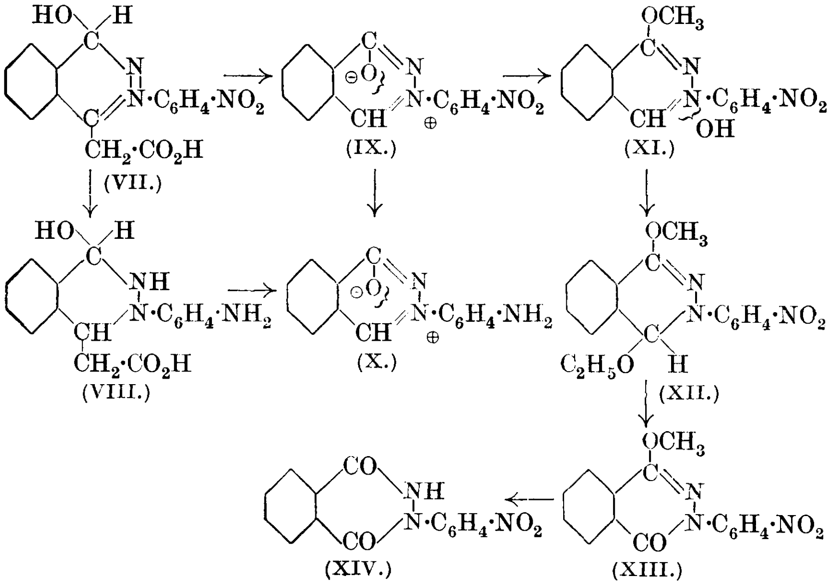
Unsuccessful attempts were made to confirm this hypothesis by eliminating the amino-group from our aminophenylphthalazone, so that the corresponding phenylphthalazone could be compared with 3-phenylphthalaz-4-one (Racine, *Annalen,* 1887, **239**, 86; Thiele and Falk, *ibid.*, 1906, **347**, 112), of which the constitution is definitely known. Diazotisation and boiling with alcohol under a variety of conditions, or diazotisation, and reduction of the diazonium compound to the hydrazine, followed by oxidation with copper acetate, gave no phenylphthalazone. In the latter case, disruption of the molecule undoubtedly occurred.

It appeared desirable, therefore, to prepare Seekles's compound for purposes of comparison, and, as a result, it was found not to be a nitrophenylphthalazone. The condensation of an equimolecular proportion of phthalaldehydic acid and *p*-nitrophenylhydrazine in boiling alcoholic solution gives the compound described by Seekles, but it has the formula $C_{14}H_{11}O_4N_3$ and is actually only an intermediate stage in the formation of the nitrophenylphthalazone. In alcoholic solution, phthalaldehydic acid reacts mainly in the tautomeric form of hydroxyphthalide (I), and under these conditions condensation is limited to formation of the lactone form of o-*carboxybenzaldehyde*-p-*nitrophenylhydrazone* (II), which Seekles described as a nitrophenylphthalazone. This condensation product dissolves in sodium carbonate owing to conversion into the free *acid* (III), but on boiling a nitrobenzene solution a molecule of water is eliminated and gives the actual 4′-*nitro*-3-*phenylphthalaz*-4-*one* (IV), colourless needles, m. p. 258°, which is isomeric and not identical with the nitrophenylphthalazone we have obtained from 1-hydroxy-3-(4′-nitrophenyl)-1 : 3-dihydrophthalazine-4-acetic acid.



4′-Nitro-3-phenylphthalaz-4-one, although sparingly soluble in mineral acids, does not form salts with them and is insoluble in sodium hydroxide. Reduction with sodium sulphide gives the actual 4′-*amino*-3-*phenylphthalaz*-4-*one* (V), and reduction with zinc dust and hydrochloric acid gives 4-′amino-*N*-phenylphthalimidine (VI), but the conversion into the latter does not proceed so readily as in the case of 4′-nitro-3-phenylphthalaz-1-one.

The formula (IX) for 4′-*nitro*-3-*phenylphthalaz*-1-*one* appears to agree best with its properties. Thus, it is acidic and dissolves readily in sodium hydroxide with a bluish-red colour; also it is basic and dissolves readily in mineral acids, forming well-crystallised salts, decomposed by water; and it forms a *picrate*. Further, it would be anticipated that the oxygen atom of the keto-group in a compound of this constitution could be methylated, and this proved to be the case, although the course of the reaction was somewhat complicated. The product of the interaction of 4′-nitro-3-phenylphthalaz-1-one with methyl sulphate in nitrobenzene solution, after removal of the latter, is obtained as an aqueous solution of the *methosulphate,* and is isolated as an orange-yellow, amorphous powder by making alkaline with sodium carbonate. This *substance,* probably (XI), crystallises well from alcohol, but it combines with the alcohol, probably forming (XII), and is then so reactive that it was impossible to determine its formula analytically. This proved to be immaterial, however, for by heating the compound after crystallisation from alcohol first at 110° and then at 140° it is readily converted into 4-*keto*-1-*methoxy*-3-(4′-*nitrophenyl*)-3 : 4-*dihydrophthalazine* (XIII), which is neither acidic nor basic. This compound is demethylated by heating with hydrobromic acid and glacial acetic acid in a sealed tube at 100° with formation of 1 : 4-*diketo*-3-(4′-*nitrophenyl*)*tetrahydrophthalazine* (XIV).



On the other hand, 4′-nitro-3-phenylphthalaz-4-one is neither acidic nor basic, it does not form a picrate, and is unaltered by treatment with methyl sulphate under conditions identical with those used in the case of 4′-nitro-3-phenylphthalaz-1-one.

EXPERIMENTAL.

4′-Nitro-3-phenylphthalaz-1-one (IX).—A mixture of 10 g. of finely-powdered 1-hydroxy-3-(4′-nitrophenyl)-1 : 3-dihydrophthalazine-4-acetic acid (VII), 50 c.c. of concentrated sulphuric acid, and 60 c.c. of water was boiled (b. p. 140°) under reflux. Solution was complete after ½ hour, and boiling was continued for a further 1½ hours, acetic acid being eliminated during the reaction. The mixture was cooled, diluted with 240 c.c. of water, boiled, and filtered. After cooling, the sulphate, colourless needles, was filtered off and neutralised with sodium carbonate. A further quantity, but less pure, was isolated by neutralising the filtrate. The united product was purified through the sparingly soluble hydrochloride, long, colourless needles, and, after neutralisation with sodium carbonate, the *base* crystallised from pyridine in fine yellow needles, m. p. 333° (not 331° as previously given) (yield 5·6 g.; 68·5%) (Found: C, 62·9; H, 3·5; N, 15·7. $C_{14}H_9O_3N_3$ requires C, 62·9; H, 3·4; N, 15·7%). The substance is readily soluble in glacial acetic acid, soluble in nitrobenzene, sparingly soluble in alcohol and ethyl acetate, and very sparingly soluble in benzene. It is insoluble in sodium carbonate, but dissolves in sodium hydroxide with a bluish-red colour, changing to orange-brown on keeping; with mineral acids it forms salts which are readily decomposed by water. With an alcoholic solution of picric acid it forms a *picrate*, fine bright yellow needles, m. p. 218°, which appear to be decomposed progressively by recrystallisation from alcohol (Found: C, 48·6; H, 2·5. $C_{20}H_{12}O_{10}N_6$ requires C, 48·4; H, 2·4%).

Reduction of 4′-Nitro-3-phenylphthalaz-1-one.—(*a*) A fine suspension of 2 g. of 4′-nitro-3-phenylphthalaz-1-one in 50 c.c. of water was heated to 50° with a solution of 16 g. of sodium sulphide crystals in 15 c.c. of water. The bluish-red colour of the solution changed to reddish-orange, and orange-coloured needles separated. The mixture was then boiled for 10 minutes, cooled, and filtered. The *4′-amino-3-phenylphthalaz-1-one* (X) crystallised from alcohol in deep straw-coloured, prismatic needles, m. p. 259° (yield 1 g.; 56%), and is identical with the compound which we described formerly as 4′-amino-3-phenylphthalaz-4-one. (*b*) A solution of 2 g. of 4′-nitro-3-phenylphthalaz-1-one in 50 c.c. of water and 75 c.c. of concentrated hydrochloric acid was boiled, and 4 g. of zinc dust were added gradually with vigorous boiling. The 4′-amino-*N*-phenylphthalimidine (VI), almost colourless, prismatic needles,

m. p. 198° (yield 1·3 g.; 77%), was isolated as previously described (*loc. cit.*, p. 704).

Action of Methyl Sulphate on 4′-*Nitro*-3-*phenylphthalaz*-1-*one*.—A solution of 5 g. of 4′-nitro-3-phenylphthalaz-1-one in 120 c.c. of boiling, dry nitrobenzene was cooled to about 140°, and 2·5 g. of methyl sulphate were added to the crystalline mixture. The crystals disappeared rapidly and the reaction was completed by heating under reflux at 150° for $\frac{1}{2}$ hour. Nitrobenzene was removed by distillation with steam, and the aqueous residue, after filtering from a little resin, gave an orange-yellow, flocculent precipitate when rendered alkaline with sodium carbonate. This *substance* (XI) forms a hydrochloride, stout colourless needles, and is unaltered by prolonged boiling with hydrochloric acid; it is insoluble in cold alkalis, but is decomposed by boiling with sodium hydroxide. On addition of alcohol to the dry compound, it became resinous and then crystalline, and after crystallising four times from ethyl alcohol formed large, orange, elongated, hexagonal prisms (XII), m. p. 138—141° (Found : C, 63·3; H, 5·7; N, 13·6; total OR, calculated as OMe, 18·3%). On the other hand, crystallisation from methyl alcohol gave orange leaflets and diamond-shaped crystals, m. p. 173—175° (Found : C, 62·3; H, 5·1; OMe, 18·5%). No definite conclusions as to the composition of these compounds after crystallisation from methyl or ethyl alcohol could be based on these analyses, however, because the substance has combined with the alcohols and the products are decomposed partially even by drying in a vacuum at the ordinary temperature, as was done for the preparation of the analytical specimens, whilst at 100° the crystals become opaque and are converted gradually into 4-keto-1-methoxy-3-(4′-nitrophenyl)-3 : 4-dihydrophthalazine (XIII). The latter change was best effected by heating first at 100° and then at 140°.

4-*Keto*-1-*methoxy*-3-(4′-*nitrophenyl*)-3 : 4-*dihydrophthalazine* crystallised from alcohol in fine pale yellow needles, or from glacial acetic acid in colourless needles, m. p. 199° (Found : C, 60·9; H, 3·9; N, 14·3; OMe, 10·3. $C_{15}H_{11}O_4N_3$ requires C, 60·6; H, 3·7; N, 14·1; OMe, 10·4%). The substance is readily soluble in chloroform, ethyl acetate and toluene, but insoluble in dilute mineral acids or alkalis. When 1 g. was heated with glacial acetic acid and twice the volume of hydrobromic acid in a sealed tube at 100° for about 10 minutes, 1 : 4-*diketo*-3-(4′-*nitrophenyl*)*tetrahydrophthalazine* (XIV) separated, and after recrystallisation from glacial acetic acid, formed colourless needles, m. p. 307° (Found : C, 59·5; H, 3·4; N, 15·0. $C_{14}H_9O_4N_3$ requires C, 59·4; H, 3·2; N, 14·8%), insoluble in dilute mineral acids, but soluble in dilute sodium carbonate, giving a pale yellow colour.

4′-*Nitro*-3-*phenylphthalaz*-4-*one* (IV).—A mixture of a solution of 4·5 g. of *o*-phthalaldehydic acid in 100 c.c. of alcohol and a solution of 4·6 g. of *p*-nitrophenylhydrazine in 80 c.c. of alcohol was boiled under reflux for about 5 minutes after the lactone form of o-*carboxybenzaldehyde*-p-*nitrophenylhydrazone* (II) had separated in orange needles, m. p. 254° after shrinking and becoming paler at 228° (Found: C, 58·6; H, 4·0; N, 14·9. $C_{14}H_{11}O_4N_3$ requires C, 58·9; H, 3·9; N, 14·7%). It is sparingly soluble in dilute hydrochloric acid and soluble in dilute sodium carbonate owing to opening of the ring with formation of o-*carboxybenzaldehyde*-p-*nitrophenylhydrazone* (III), which is precipitated on acidifying the alkaline solution as a red powder, decomposing at 218° and then melting at 249°. Attempts to recrystallise the lactone form from alcohol or pyridine resulted in its conversion into 4′-*nitro*-3-*phenylphthalaz*-4-*one*. The latter compound was prepared most conveniently by boiling a nitrobenzene solution for a short time; after cooling, it crystallised in long, colourless, glistening needles, m. p. 258° (Found: C, 63·0; H, 3·4; N, 15·7. $C_{14}H_9O_3N_3$ requires C, 62·9; H, 3·4; N, 15·7%). It is almost insoluble in alcohol, insoluble in sodium carbonate or hydroxide, but very sparingly soluble in hydrochloric acid. It neither forms a picrate nor reacts with methyl sulphate.

4′-*Amino*-3-*phenylphthalaz*-4-*one* (V).—A fine suspension of 2 g. of the lactone in 50 c.c. of water was heated to 50° with a solution of 16 g. of sodium sulphide crystals in 15 c.c. of water. The bluish-red colour of the solution changed to orange-yellow, and on further heating, almost colourless crystals separated in small yield. The 4′-*amino*-3-*phenylphthalaz*-4-*one* crystallised from alcohol or water in long, pale yellow needles, m. p. 184° (Found: C, 70·7; H, 4·7; N, 17·9. $C_{14}H_{11}ON_3$ requires C, 70·9; H, 4·6; N, 17·7%). It is soluble in hot water, insoluble in alkalis, but soluble in dilute acids (*hydrochloride*, colourless needles), and can be diazotised. A solution of 1 g. in 10 c.c. of glacial acetic acid was boiled with 0·2 c.c. of acetic anhydride for 2 hours and poured into water; the *acetyl* derivative crystallised from dilute alcohol in colourless, feathery needles, m. p. 233° (Found: N, 15·0. $C_{16}H_{13}O_2N_3$ requires N, 15·0%). Reduction of the lactone form with zinc dust and hydrochloric acid, as described on p. 2553, resulted also in the formation of 4′-amino-*N*-phenylphthalimidine (VI), almost colourless needles, m. p. 198°, although with greater difficulty and in much lower yield.

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