203. *A Reaction of Certain Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XXV. The Phthalazine Reaction with Bases not containing a Nitro-group. Derivatives of 2′-Chlorobenzene-2-naphthol-1-diazosulphonate.*

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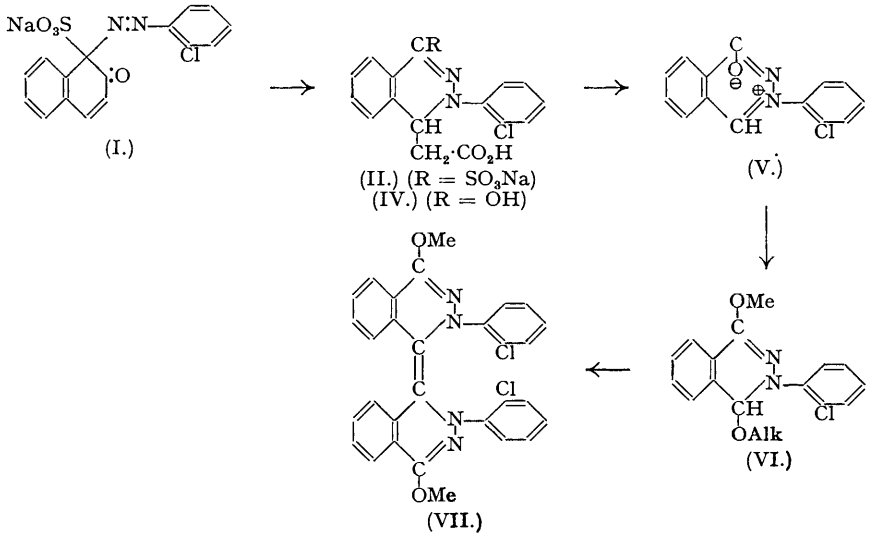
This paper confirms that the presence of a nitro-group is not essential for the conversion of aryl-2-naphthol-1-diazosulphonates into phthalazine and phthalazone derivatives (cf. Part XXIV, this vol., p. 597). Thus, the diazosulphonate derived from *o*-chloroaniline is convertible into *sodium hydrogen* 3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* (II), which possesses the expected properties. 2′-*Chloro*-3-*phenylphthalaz*-1-*one* and 2′-*chloro*-3-*phenyl*-4-*methylphthalaz*-1-*one* are isomerised to 2′-*chloro*-3-*phenylphthalaz*-4-*one* and its 1-*methyl* derivative, respectively, and the constitutions of the two last-named compounds are confirmed by synthesis.

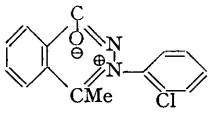
2′-Chlorobenzene-2-naphthol-1-diazosulphonate was converted by aqueous sodium carbonate into sodium 1-(2′-chlorobenzeneazo)-β-naphthaquinone-1-sulphonate (I), which with cold aqueous sodium hydroxide gave 66·2% of (II). This yield is similar to that (69·8%) observed in the case of the 2′-nitro-analogue, and there was no increase in yield on prolonged reaction of (I) with sodium hydroxide. Sodium benzaldehyde-2′-chlorophenylhydrazone-ω-sulphonate-2-β-acrylic acid (III) could not be detected by the restricted action (*e.g.*, 1 minute) of sodium hydroxide on (I), whereas the 2′-nitro-analogue of (III) was formed in 81·8% yield (cf. *J.*, 1935, 1796).

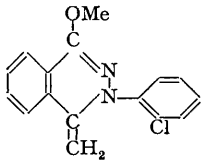
1-*Hydroxy*-3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* (IV), which was formed when the sodium salt (II) was boiled with dilute hydrochloric acid, was converted by boiling aqueous sulphuric acid, or by a mixture of sulphuric and acetic acid, or by fuming hydrochloric acid (*d* 1·19) at 180°, into 2′-*chloro*-3-*phenylphthalaz*-1-*one* (V) (which forms a *picrate*).

The methylation product of (V) combined with methyl or ethyl alcohol to give 1 : 4-*dimethoxy*- or 1-*methoxy*-4-*ethoxy*-3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine* [as (VI)], respectively (cf. *J.*, 1928, 2554).



Usually, such derivatives are converted by heating at 100—140° into the corresponding 4-keto-1-methoxy-derivatives (*J.*, 1928, 2554), or, as in the case of the 2′-nitro-analogues, are decomposed by heat (cf. *J.*, 1935, 1796). In the present case, however, compounds (VI) lost the respective alcohol at 140° and gave (VII), formed by the joining of two molecules at C_4. The constitution of the phthalazone (V) was confirmed by Clemmensen reduction to 1-*keto*-3-(2′-*chlorophenyl*)*tetrahydrophthalazine* and thence to 2′-*chloro*-N-*phenylphthalimidine*. On heating with aqueous hydrochloric acid (1 : 8) in a sealed tube at 180° for 28 hours, compound (V) was partly isomerised to give 30% of 2′-*chloro*-3-*phenylphthalaz*-4-*one*, which did not form a picrate and could not be methylated. The phthalaz-4-one was identical with a synthetic specimen prepared from *o*-phthalaldehydic acid and *o*-chlorophenylhydrazine, followed by cyclisation of the resulting o-*carboxybenzaldehyde* 2′-*chlorophenylhydrazone*. When the hydroxy-compound (IV) was oxidised with cold acid dichromate or cold nitric acid, 2′-*chloro*-3-*phenyl*-4-*methylphthalaz*-1-*one* (VIII) was formed; this yielded a picrate and was readily methylated to 1-*methoxy*-3-(2′-*chlorophenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine* (IX).

(VIII.) 

 (IX.)

This reactive methylene derivative (IX) formed a perchlorate, and with 2 : 4-dinitrochlorobenzene in boiling alcohol in presence of potassium acetate gave 1-*methoxy*-3-(2′-*chlorophenyl*)-4-(2″ : 4″-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine*. The constitution of the phthalazone (VIII) was further confirmed by reduction with sodium dithionite (hydrosulphite) or by the Clemmensen procedure to 1-*keto*-3-(2′-*chlorophenyl*)-4-*methyltetrahydrophthalazine*, and by its partial isomerisation by aqueous hydrochloric acid (1 : 8) at 180° to give 13·3% of 2′-*chloro*-3-*phenyl*-1-*methylphthalaz*-4-*one*. This compound was synthesised from acetophenone-*o*-carboxylic acid and *o*-chlorophenylhydrazine, followed by cyclisation of the resulting o-*carboxyacetophenone* 2′-*chlorophenylhydrazone* with cold concentrated sulphuric acid.

Permanganate oxidation of the hydroxy-compound (IV) gave 1 : 4-*diketo*-3-(2′-*chlorophenyl*)*tetrahydrophthalazine*, which was converted through its silver salt and methyl iodide into 4-*keto*-1-*methoxy*-3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine*, also formed by boiling the methylene compound (IX) with *p*-nitrosodimethylaniline in alcohol.

Experimental.

Sodium Hydrogen 3-(2′-*Chlorophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* (II).—*o*-Chlorobenzenediazonium chloride, prepared from 25·5 g. of *o*-chloroaniline, was well stirred during the addition of 50% sodium β-naphthol-1-sulphonate (100 g.) in water (240 c.c.) at 0°. The yellow precipitate of 2′-chlorobenzene-2-naphthol-1-diazosulphonate was collected, washed with brine, and pasted with sodium carbonate (50 g.) in water (200 c.c.); the orange sodium 1-(2′-chlorobenzeneazo)-β-naphthaquinone-1-sulphonate was formed after grinding for 15 minutes, and to it was added sodium hydroxide (50 g.) in water (120 c.c.). After 2 hours at <5°, the mixture was acidified with hydrochloric acid, made just alkaline with sodium carbonate, 2′-chlorobenzeneazo-β-naphthol (3 g.; 5·3%) filtered off, and the filtrate made faintly acid. Addition of sodium chloride precipitated a resinous black mass, which was purified by dissolution in alcohol and addition of ether. The resulting pale brown crystals of the *sodium hydrogen* salt were dried at 140° (53·4 g.; 66·2%) (Found: S, 7·1. $C_{16}H_{12}O_5N_2ClSNa$ requires S, 7·95. $C_{16}H_{12}O_5N_2ClSNa,C_2H_6O$ requires S, 7·1%). At 150°, some decomposition occurred and the product became progressively darker and decomposed at 235—240°.

1-*Hydroxy*-3-(2′-*chlorophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid* (IV).—The above sodium salt (II) (7 g.) was boiled with water (500 c.c.), and hydrochloric acid (40 c.c.) added slowly during 2 hours; the separated *acid* (IV) crystallised from aqueous acetic acid in colourless needles, m. p. 224—225° (shrinks from 210°) (4·6 g.; 83·6%) (Found: C, 60·6; H, 4·1; N, 9·3; Cl, 11·2. $C_{16}H_{13}O_3N_2Cl$ requires C, 60·7; H, 4·1; N, 8·85; Cl, 11·2%). For preparation in quantity, it was found convenient to proceed with the hydrolysis without prior separation of the sodium salt.

The *methyl* ester crystallised from methyl alcohol in colourless, hexagonal plates, m. p. 141—142° (Found: N, 8·8; Cl, 10·8. $C_{17}H_{15}O_3N_2Cl$ requires N, 8·5; Cl, 10·7%). The *ethyl* ester formed colourless prisms (alcohol), m. p. 132—133° (Found: N, 8·6. $C_{18}H_{17}O_3N_2Cl$ requires N, 8·1%).

With boiling acetic anhydride–pyridine (15 : 1) for 70 hours, or with phosphorus trichloride in boiling toluene for 8 hours, the hydroxy-compound (IV) gave the internal *anhydride*, which crystallised from nitrobenzene in colourless needles, darkening at 300° and decomposing at > 340° (Found: C, 64·2; H, 3·7; N, 9·8; Cl, 11·4. $C_{16}H_{11}O_2N_2Cl$ requires C, 64·3; H, 3·7; N, 9·4; Cl, 11·9%), reconverted into the acid (IV) on warming with concentrated sulphuric acid.

The *N*-methyl ether of (IV), *viz.*, 1-*keto*-3-(2′-*chlorophenyl*)-2-*methyltetrahydrophthalazine*-4-*acetic acid*, crystallised from aqueous acetic acid in colourless rhombs, m. p. 180—181° (Found: N, 8·7. $C_{17}H_{15}O_3N_2Cl$ requires N, 8·5%).

2'-Chloro-3-phenylphthalaz-1-one (V).—The hydroxy-compound (IV) (10 g.) was refluxed with concentrated sulphuric acid (40 c.c.) and water (50 c.c.) for 3 hours, and the mixture added to ice. The precipitated sulphate was basified with aqueous ammonia; the *phthalazone* crystallised from aqueous alcohol in almost colourless prisms, m. p. 202—203° (5·6 g.; 68·2%) (Found: C, 65·8; H, 3·6; N, 11·0; Cl, 13·6. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5; N, 10·9; Cl, 13·8%). It was also obtained in 69% yield by boiling (IV) with sulphuric acid and acetic acid (1 : 1 by vol.) for 15 minutes, or in 35·4% yield by heating (IV) with fuming hydrochloric acid (*d* 1·19) in a sealed tube at 180° for 4 hours; in the latter case, some unidentified substance, which crystallised from alcohol in fine colourless needles, m. p. 165°, was also isolated.

2'-Chloro-3-phenylphthalaz-1-one picrate crystallised from alcohol in bright yellow rectangular prisms, m. p. 233—234° (Found: N, 14·4. $C_{20}H_{12}O_8N_5Cl$ requires N, 14·4%).

Methylation of (V).—3 G. of (V) were heated with methyl sulphate (15 g.) at 70° for 2 hours, poured into water, and the mixture made alkaline with sodium carbonate; the *methoxy*-derivative [as (VI)] crystallised from methyl alcohol in colourless hexagonal prisms, m. p. 78° (Found: N, 9·0. $C_{16}H_{15}O_2N_2Cl$ requires N, 9·3%), or from ethyl alcohol in similar prisms, m. p. 86° (Found: N, 8·7. $C_{17}H_{17}O_2N_2Cl$ requires N, 8·9%), which are probably 1 : 4-*dimethoxy*- and 1-*methoxy*-4-*ethoxy*-3-(2'-*chlorophenyl*)-3 : 4-*dihydrophthalazine* respectively. On being heated at 110° for 4 hours and then at 140° for 1 hour, each compound lost the respective alcohol and yielded the same *substance* (VII), which crystallised from nitrobenzene in bright yellow cubes, m. p. 239° (decomp.) [Found: C, 66·7; H, 4·1; N, 9·9; Cl, 12·75. $(C_{15}H_{11}ON_2Cl)_2$ requires C, 66·55; H, 4·1; N, 10·35; Cl, 13·1%].

1-*Keto*-3-(2'-*chlorophenyl*)*tetrahydrophthalazine*.—2'-Chloro-3-phenylphthalaz-1-one (2 g.) was heated with hydrochloric acid (80 c.c.), water (80 c.c.), and zinc amalgam (120 g.) at 70—80° for 1 hour; the *keto*-compound crystallised from alcohol in colourless needles, m. p. 216—218° (1 g.; 49·6%) (Found: C, 65·6; H, 4·2; N, 10·8. $C_{14}H_{11}ON_2Cl$ requires C, 65·0; H, 4·3; N, 10·8%).

2'-Chloro-N-phenylphthalimidine.—2'-Chloro-3-phenylphthalaz-1-one (1 g.) was boiled with hydrochloric acid (40 c.c.), water (40 c.c.), alcohol (30 c.c.), and zinc amalgam (70 g.) for 4 hours; no solid separated, but, on pouring on ice, the *phthalimidine* was precipitated; it crystallised from alcohol in colourless prismatic needles, m. p. 124° (0·8 g.; 84·2%) (Found: C, 68·1; H, 4·1; N, 5·9; Cl, 14·2. $C_{14}H_{10}ONCl$ requires C, 69·0; H, 4·1; N, 5·75; Cl, 14·6%). It was also obtained in 85% yield by a similar reduction of 1-keto-3-(2'-chlorophenyl)tetrahydrophthalazine.

Conversion of 2'-Chloro-3-phenylphthalaz-1-one into 2'-Chloro-3-phenylphthalaz-4-one.—The phthalaz-1-one (3 g.) and aqueous hydrochloric acid (1 : 8; 36 c.c.) in a sealed tube at 180° for 28 hours gave *2'-chloro-3-phenylphthalaz-4-one* (0·9 g.; 30%), which crystallised from acetic acid in colourless prisms, m. p. 126—127° (Found: C, 65·6; H, 3·6; N, 11·2. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5; N, 10·9%), identical with a synthetic specimen.

Synthesis of 2'-Chloro-3-phenylphthalaz-4-one.—*o*-Phthalaldehydic acid (1·8 g.) and *o*-chlorophenylhydrazine (1·7 g.) in boiling alcohol (25 c.c.) for 20 minutes gave *o-carboxybenzaldehyde 2'-chlorophenylhydrazone*, which crystallised from alcohol in yellow prismatic needles, m. p. 175° (3 g.; 91%) (Found: N, 10·5. $C_{14}H_{11}O_2N_2Cl$ requires N, 10·2%), converted by cold concentrated sulphuric acid in 12 hours or by boiling with acetic acid for 30 minutes into 92% of 2'-chloro-3-phenylphthalaz-4-one, m. p. 127°, identical with that prepared above. With boiling acetic anhydride, the above hydrazone, m. p. 175°, was converted into *o-carboxybenzaldehyde α-acetylhydrazone* (lactone form), which crystallised from alcohol or acetic acid in colourless hexagonal plates, m. p. 169° (Found: C, 61·1; H, 4·5; N, 8·9; Cl, 11·2. $C_{16}H_{13}O_3N_2Cl$ requires C, 60·7; H, 4·1; N, 8·85; Cl, 11·2%).

2'-Chloro-3-phenyl-4-methylphthalaz-1-one (VIII).—(*a*) The hydroxy-compound (IV) (20 g.) in concentrated sulphuric acid (180 c.c.) was poured on ice (400 g.), and the fine suspension stirred during addition of potassium dichromate (9 g.) (30 minutes) at 5°. After being left overnight at room temperature, the separated sulphate was collected and basified with aqueous sodium hydroxide; it crystallised from aqueous alcohol in fine colourless needles, m. p. 253—255° (darken at 240°) (13·5 g.; 79%) (Found: C, 66·8; H, 4·2; N, 10·0; Cl, 13·1. $C_{15}H_{11}ON_2Cl$ requires C, 66·55; H, 4·1; N, 10·35; Cl, 13·1%). The *picrate* crystallised from alcohol in golden-yellow prisms, m. p. 199—200° (decomp.) (Found: N, 14·0. $C_{21}H_{14}O_8N_5Cl$ requires N, 14·1%).

(*b*) The hydroxy-compound (IV) (10 g.) was added slowly to nitric acid (*d* 1·5; 60 c.c.) at below 5°, and after 1 hour, the mixture was added to ice to give the nitrate of 2'-chloro-3-phenyl-4-methylphthalaz-1-one as colourless prisms (methyl alcohol), m. p. 253—255° (decomp.); conversion into the base was effected by cold aqueous sodium carbonate (yield, 7·2 g.; 84·3%).

1-*Methoxy*-3-(2'-*chlorophenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine* (IX).—2'-Chloro-3-phenyl-4-methylphthalaz-1-one (3 g.) and methyl sulphate (12 g.) at 70—80° for 2 hours gave, on addition to water, the *methylene* base, which crystallised from methyl alcohol in orange-brown diamond-shaped prisms, or in small yellow prisms, m. p. 119° (2·4 g.; 76·2%) (Found: C, 67·4; H, 4·6; N, 10·0; Cl, 12·4. $C_{16}H_{13}ON_2Cl$ requires C, 67·5; H, 4·6; N, 9·8; Cl, 12·5%). The *perchlorate* crystallised from alcohol containing a little perchloric acid in colourless prismatic needles, m. p. 202° (Found: N, 7·5; Cl, 18·4. $C_{16}H_{14}O_5N_2Cl_2$ requires N, 7·3; Cl, 18·4%).

1-*Methoxy*-3-(2'-*chlorophenyl*)-4-(2'' : 4''-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine*.—This was obtained by boiling the above methylene compound (IX) (1 g.) with chloro-2 : 4-dinitrobenzene (1 g.) in alcohol (60 c.c.) and potassium acetate (1·5 g.) for 5 hours. It crystallised from acetic anhydride in black prismatic needles with a bronze lustre, m. p. 186° (0·46 g.; 58·1%) (Found: C, 59·2; H, 3·4; Cl, 8·0. $C_{22}H_{15}O_5N_4Cl$ requires C, 58·6; H, 3·3; Cl, 7·9%).

1-*Keto*-3-(2'-*chlorophenyl*)-4-*methyltetrahydrophthalazine*.—2'-Chloro-3-phenyl-4-methylphthalaz-1-one (1 g.) was reduced with alkaline sodium dithionite (9 g.) to give the *keto*-compound, which crystallised from alcohol in colourless prisms, m. p. 199—200° (0·85 g.; 84·4%) (Found: C, 66·0; H, 4·8; N, 10·3; Cl, 12·4. $C_{15}H_{13}ON_2Cl$ requires C, 66·05; H, 4·8; N, 10·3; Cl, 13·0%). The same compound was obtained by heating the above phthalaz-1-one (2 g.) with boiling hydrochloric acid (70 c.c.), water (40 c.c.), and zinc amalgam (90 g.) at 70—80° for 4 hours (1·9 g.; 94%), and prolonged reduction failed to yield 2'-chloro-*N*-phenyl-3-methylphthalimidine.

Conversion of 2'-Chloro-3-phenyl-4-methylphthalaz-1-one into the Isomeric 1-Methylphthalaz-4-one.—This was effected by heating 1 g. with aqueous hydrochloric acid (1 : 8; 12 c.c.) at 180° for 28 hours. *2'-Chloro-3-phenyl-1-methylphthalaz-4-one* crystallised from acetic acid in colourless prismatic needles, m. p. 147° (0·2 g.; 13·3%) (Found: C, 66·8; H, 4·0; Cl, 12·6. $C_{15}H_{11}ON_2Cl$ requires C, 66·55; H, 4·1; Cl, 13·1%).

Synthesis of 2'-Chloro-3-phenyl-1-methylphthalaz-4-one.—Acetophenone-*o*-carboxylic acid (1·4 g.) and *o*-chlorophenylhydrazine (1·2 g.) in alcohol at room temperature gave an immediate precipitate of *o-carboxyacetophenone 2'-chlorophenylhydrazone*, which crystallised from alcohol in fine, pale yellow needles, m. p. 132° (1·05 g.; 85·3%) (Found: N, 9·5. $C_{15}H_{13}O_2N_2Cl$ requires N, 9·7%). Cold concentrated sulphuric acid in 12 hours caused 97% cyclisation to 2'-chloro-3-phenyl-1-methylphthalaz-4-one, m. p. 147°, identical with that obtained above.

1 : 4-*Diketo-3-(2'-chlorophenyl)tetrahydrophthalazine.*—Powdered potassium permanganate (10 g.) was added during 10 minutes to 1-hydroxy-3-(2'-chlorophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (10 g.) suspended in water (200 c.c.) at 80°, and after 30 minutes the mixture was filtered and the filtrate acidified to give the *tetrahydrophthalazine*, which crystallised from aqueous acetic acid in colourless rectangular prisms, m. p. 247—248° (4·2 g.; 48·8%) (Found: C, 61·6; H, 3·1; N, 10·2; Cl, 13·3. $C_{14}H_9O_2N_2Cl$ requires C, 61·6; H, 3·3; N, 10·3; Cl, 13·0%). The silver salt separated when aqueous silver nitrate was added to a solution of the compound in aqueous ammonia.

4-*Keto-1-methoxy-3-(2'-chlorophenyl)-3 : 4-dihydrophthalazine.*—(*a*) The above dry silver salt (1 g.) was refluxed with methyl iodide (0·7 c.c.) in dry toluene (40 c.c.) for 30 minutes, the mixture filtered, and the filtrate evaporated to dryness. On extraction of the residue with methyl alcohol, and cooling, the *methoxy-keto*-compound separated in colourless prisms, m. p. 136—137° (0·1 g.; 26·5%) (Found: C, 62·8; H, 3·9; N, 9·8. $C_{15}H_{11}O_2N_2Cl$ requires C, 62·8; H, 3·8; N, 9·8%).

(*b*) The methylene compound (IX) (0·9 g.) was boiled with *p*-nitrosodimethylaniline (1 g.) in alcohol (40 c.c.) for 3 hours; concentration caused separation of the 1-methoxy-4-keto-compound, which crystallised from methyl alcohol in colourless prisms, m. p. 137° (0·37 g.; 40·8%).

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