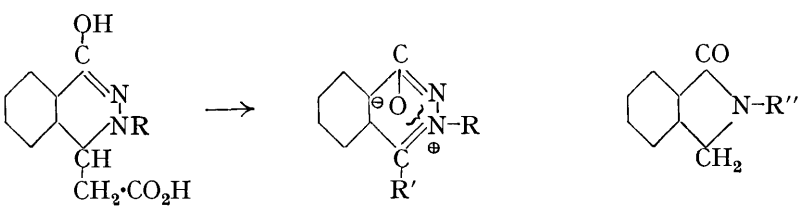
267. *A Reaction of Certain Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XII. Preparation of Phthalazine, Phthalazone, and Phthalimidine Derivatives from 2-Bromo-4-nitroaniline.*

By F. M. Rowe, G. B. Jambuserwala, and H. W. Partridge.

The preparation of phthalazine, phthalazone, and phthalimidine derivatives from 2-chloro-, 2 : 6-dichloro- and 2 : 6-dibromo-4-nitroanilines has already been described (J., 1932, 11; 1931, 1073). As in certain instances the results differed considerably from those obtained in the absence of the halogen atoms (J., 1926, 690; 1928, 2550; 1931, 1067; 1932, 473; 1933, 1067), the corresponding 2′-bromo-4′-nitro- and -amino-derivatives were investigated.

Conversion of 2′-bromo-4′-nitrobenzene-2-naphthol-1-diazosulphonate through sodium 1-(2′-bromo-4′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate into *sodium hydrogen* 3-(2′-*bromo*-4′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* and thence into 1-*hydroxy*-3-(2′-*bromo*-4′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* (I; R = 2′-bromo-4′-nitrophenyl) proceeds normally. Reduction to the corresponding *amino-acid* is best effected in an acid medium, as subsequent degradation occurs more readily with alkali, whereas the reverse is the case with the chloro-analogue (*loc. cit.*). The hydrochloride of the amino-acid is so sparingly soluble in concentrated hydrochloric acid that it is unaffected by prolonged boiling, but 2′-*bromo*-4′-*amino*-3-*phenylphthalaz*-1-*one* (II; R = 2′-bromo-4′-aminophenyl; R′ = H) is obtained in excellent yield by boiling the amino-acid with aqueous sulphuric acid.

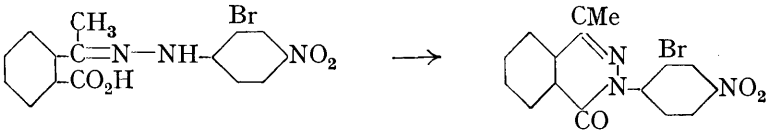


(I.) (II.) (III.)

In the reduction of chloro-4′-amino-3-phenylphthalaz-1-ones with zinc dust and hydrochloric acid no chlorine is removed, but with the 2′ : 6′-dibromo-compound under ordinary conditions bromine is eliminated, giving mainly 4′-amino-*N*-phenylphthalimidine, although under different conditions some of its 2′-bromo-derivative is formed (J., 1931, 1083). Similarly, 2′-bromo-4′-amino-3-phenylphthalaz-1-one is reduced to either 4′-amino-*N*-phenylphthalimidine (III; R″ = 4′-aminophenyl) or its 2′-bromo-derivative, but in each case the yield is very low, as fission is the predominating reaction.

The compounds obtained by methylating the oxygen atom in the keto-group of 4′-nitro-3-phenylphthalaz-1-one and its 2′ : 6′-dihalogeno-derivatives possess entirely different properties (J., 1931, 1075), and as 2′-chloro-4′-nitro-3-phenylphthalaz-1-one could not be

obtained satisfactorily (J., 1932, 13), the behaviour of the 2′-*bromo*-compound (II; R = 2′-bromo-4′-nitrophenyl; R′ = H) was examined. This compound was prepared only in small quantity, but attempted methylation afforded resins. On the other hand, 1-hydroxy-3-(2′-bromo-4′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid is converted readily into 2′-*bromo*-4′-*nitro*-3-*phenyl*-4-*methylphthalaz*-1-*one* (II; R = 2′-bromo-4′-nitrophenyl; R′ = Me), but this compound differed considerably from any analogue prepared previously. It is much less basic and does not form salts with mineral acids or with picric acid; moreover, we were unable to methylate it, whereas all corresponding compounds containing a 4′-nitro-group yet examined, on treatment with methyl sulphate, followed by alkali, are converted into 4′-nitro-1-methoxy-3-aryl-4-methylene-3 : 4-dihydrophthalazines. This difference in properties suggested that the phthalaz-1-one might have been converted into the inactive phthalaz-4-one, as such a conversion can be carried out (unpublished work; cf. J., 1933, 1068). Consequently, 2′-*bromo*-4′-*nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one* (V) was synthesised (cf. J., 1931, 1923) from o-*carboxyacetophenone*-2-*bromo*-4-*nitrophenylhydrazone*



(IV.) (V.)

(IV) by boiling it with acetic anhydride and a little pyridine; the product is isomeric with the corresponding 4-methylphthalaz-1-one (above).

Reduction of 2′ : 6′-dibromo-4′-amino-3-phenyl-4-methylphthalaz-1-one with zinc dust and hydrochloric acid gives some 2′-bromo-4′-amino-*N*-phenyl-3-methylphthalimidine and 2 : 6-dibromo-*p*-phenylenediamine. Various reductions of 2′-*bromo*-4′-*amino*-3-*phenyl*-4-*methylphthalaz*-1-*one* (prepared as for the chloro-compound; J., 1932, 18), however, give only a substance which, by analogy, is probably 1-*keto*-3-(2′-*bromo*-4′-*aminophenyl*)-4-*methyltetrahydrophthalazine*, and this apparently undergoes complete fission on further reduction.

Experimental.

Where no details of preparation are given, the 2′-bromo-compounds were prepared as described for the corresponding 2′ : 6′-dibromo-compounds (J., 1931, 1078).

2-*Bromo*-4-*nitroaniline*.—Since large quantities of this were required, its preparation was improved by Dr. A. T. Peters. Bromine (25·5 g.; 1·05 mols.) in dry chloroform (50 c.c.) was added quickly to a solution of *p*-nitroaniline (21 g.; 1 mol.) in dry chloroform (600 c.c.) containing anhydrous aluminium bromide (0·1 g.) at 30—35°, and the mixture shaken vigorously. 2-Bromo-4-nitroaniline hydrobromide was precipitated immediately; it was collected and basified with dilute sodium carbonate. The base crystallised from alcohol in pale yellow, prismatic needles, m. p. 106—107° (yield, 29·8 g.; 90·2%, calc. on *p*-nitroaniline). This method of monohalogenation also gives improved yields in other cases, and it is the only method by which certain monochloroxylenols can be monobrominated.

Sodium Hydrogen 3-(2′-*Bromo*-4′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate*.—A filtered solution of commercial 50% sodium β-naphthol-1-sulphonate (96 g.) in water (250 c.c.) was stirred slowly at 0° into a solution of diazotised 2-bromo-4-nitroaniline, prepared by rapidly adding a cold solution of the base (37 g.) in concentrated sulphuric acid (150 c.c.) to a mixture of crushed ice (500 g.) and powdered sodium nitrite (15 g.) with good stirring. 2′-Bromo-4′-nitrobenzene-2-naphthol-1-diazosulphonate separated as a brownish-red precipitate. After several hours, it was washed free from acid, mixed with cold water (250 c.c.), and stirred into a cold solution of anhydrous sodium carbonate (48 g.) in water (250 c.c.). The suspension thickened, and after ¼ hour's stirring, it was added to a cold solution of sodium hydroxide (40 g.) in water (100 c.c.); the temperature rose by about 10°, and the reddish-violet mixture slowly became brownish-red. The acid *sodium* salt was isolated after 2 days as yellowish-brown crystals (yield, 73 g.). It crystallised from water (charcoal) in small yellow prisms, decomp. 234—236° (Found: S, 6·7; Br, 16·5. $C_{16}H_{11}O_7N_3BrSNa$ requires S, 6·5; Br, 16·3%). It is a yellow acid dye of much less tinctorial power than the corresponding unhalogenated compound, and fugitive to light.

1-*Hydroxy*-3-(2′-*bromo*-4′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid*.—A solution of

the preceding sodium hydrogen salt (100 g.) in water (500 c.c.) was boiled, and concentrated hydrochloric acid (100 c.c.) added gradually (to avoid precipitation of the free sulphonic acid) until evolution of sulphur dioxide had ceased. The *acid* separated in yellowish-brown crystals, and recrystallised from ethyl acetate in small, pale yellow prisms, m. p. 235° (yield 60 g.; 72·7%) (Found: C, 47·3; H, 2·9; N, 10·4. $C_{16}H_{12}O_5N_3Br$ requires C, 47·3; H, 2·9; N, 10·35%). It dissolved readily in sodium carbonate or hydroxide with a brownish-red colour.

The *methyl* ester crystallised from methyl alcohol in yellow, rhombic prisms, m. p. 179° (Found: C, 48·7; H, 3·3. $C_{17}H_{14}O_5N_3Br$ requires C, 48·6; H, 3·3%), and the *ethyl* ester from ethyl alcohol in yellow, prismatic needles, m. p. 178° (Found: C, 49·9; H, 3·6. $C_{18}H_{16}O_5N_3Br$ requires C, 49·8; H, 3·7%); both esters dissolve in sodium hydroxide solution with a reddish-brown colour. The *acetyl* derivative crystallised from ethyl alcohol in pale yellow, prismatic needles, m. p. 121° (Found: C, 48·3; H, 3·3. $C_{18}H_{14}O_6N_3Br$ requires C, 48·2; H, 3·1%), soluble in sodium carbonate with a yellowish-brown colour and in sodium hydroxide with a brownish-red colour. The *anilide* crystallised from alcohol in pale yellow prisms, m. p. 207° (Found: C, 54·7; H, 3·4. $C_{22}H_{17}O_4N_4Br$ requires C, 54·9; H, 3·5%), which became violet on the surface on exposure to light; it was sparingly soluble in sodium hydroxide solution with a brownish-red colour.

1-*Keto*-3-(2′-*bromo*-4′-*nitrophenyl*)-2-*methyltetrahydrophthalazine*-4-*acetic acid*, prepared as described for the corresponding *N*-methyl ethers (J., 1933, 1069), crystallised from methyl alcohol in yellow prisms, m. p. 229° (Found: C, 48·1; H, 3·2; Br, 18·6. $C_{17}H_{14}O_5N_3Br$ requires C, 48·5; H, 3·3; Br, 19·0%), soluble in alkalis with a yellow colour, and unchanged by heating with hydrobromic acid (*d* 1·7) in a sealed tube at 120°. Its *methyl* ester crystallised from methyl alcohol in pale yellow, hexagonal prisms, m. p. 212—213° (Found: C, 49·7; H, 3·7. $C_{18}H_{16}O_5N_3Br$ requires C, 49·8; H, 3·7%), insoluble in alkalis.

1-*Hydroxy*-3-(2′-*bromo*-4′-*aminophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid*.—The nitro-compound (50 g.) was added gradually to a boiling solution of stannous chloride (200 g.) in concentrated hydrochloric acid (500 c.c.) during ½ hour. The solution was then boiled for ¼ hour, left over-night, and diluted with water (150 c.c.). After 3 hours, the colourless crystalline hydrochloride was collected, dissolved in hot water (1 l.) containing concentrated hydrochloric acid (5 c.c.), and tin removed by hydrogen sulphide. Sodium carbonate solution was then added with ice-cooling until a white precipitate of the amino-acid had separated completely. A further quantity was isolated from the filtrate from the hydrochloride. The *acid* was obtained pure in small, colourless, vitreous prisms, m. p. 233—234°, by addition of hydrochloric acid to a hot solution in dilute sodium carbonate (yield, 35·5 g.; 76·7%) (Found: C, 50·95; H, 4·1; Br, 21·5. $C_{16}H_{14}O_3N_3Br$ requires C, 51·05; H, 3·7; Br, 21·3%). The *acetyl* derivative crystallised from glacial acetic acid in small, colourless prisms, m. p. 205° (Found: C, 51·6; H, 4·2. $C_{18}H_{16}O_4N_3Br$ requires C, 51·7; H, 3·8%), which became yellowish-brown on the surface on keeping.

2′-*Bromo*-4′-*amino*-3-*phenylphthalaz*-1-*one*.—This was prepared from the foregoing acid (50 g.), and crystallised from alcohol (charcoal) in small, pale yellow needles, m. p. 242° (yield 37 g.; 88%) (Found: C, 53·3; H, 3·0; Br, 25·5. $C_{14}H_{10}ON_3Br$ requires C, 53·2; H, 3·2; Br, 25·3%).

Reduction. (a) A solution of the above phthalazone (20 g.) in water (1 l.) and concentrated hydrochloric acid (100 c.c.) was boiled, and zinc dust (20 g.) and dilute hydrochloric acid (1 l.; 1 : 3) were added gradually during 1½ hours. After cooling and filtering, the filtrate was rendered alkaline with sodium hydroxide, and the dry precipitate extracted with alcohol (charcoal). Fractional crystallisation gave 2′-*bromo*-4′-*amino*-N-*phenylphthalimidine* in almost colourless rhombic crystals, containing alcohol of crystallisation, rapidly lost at air temperature, m. p. 178° after removal of the solvent (yield, 3 g.; 15·6%) (Found: C, 55·2; H, 3·8; Br, 26·2. $C_{14}H_{11}ON_2Br$ requires C, 55·4; H, 3·6; Br, 26·4%), not depressed by admixture with the compound prepared from 2′ : 6′-dibromo-4′-amino-3-phenylphthalaz-1-one (J., 1931, 1083). The acetyl derivative was identical with that previously described (*loc. cit.*).

(b) A solution of the phthalazone (5 g.) was similarly reduced with proportionate quantities of reagents, but 10 g. of zinc dust. On concentration to about 150 c.c. and cooling, the hydrochloride of 4′-amino-*N*-phenylphthalimidine crystallised in colourless plates, and a further quantity was isolated from the filtrate, but no 2′-bromo-4′-amino-*N*-phenylphthalimidine was detected. The base crystallised from alcohol in colourless, prismatic needles, m. p. 198° (yield, 0·7 g.; 19·75%) as previously described (J., 1926, 704).

2′-*Bromo*-4′-*nitro*-3-*phenylphthalaz*-1-*one*.—This was prepared from 1-hydroxy-3-(2′-bromo-4′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (10 g.) as described for the corresponding chloro-compound (J., 1932, 17), except that 50 c.c. of concentrated sulphuric acid were used.

The yellow precipitate (2·8 g.) was very difficult to crystallise, but extraction with ethyl acetate and concentration of the extract gave a little *2'-bromo-4'-nitro-3-phenylphthalaz-1-one*, pale yellow prisms, m. p. 197° (decomp.) (Found : C, 48·3; H, 2·4; Br, 23·3. $C_{14}H_8O_3N_3Br$ requires C, 48·55; H, 2·3; Br, 23·1%). It was insoluble in sodium carbonate solution, but dissolved in sodium hydroxide with an orange-red colour; it was sparingly soluble in dilute mineral acids, but no salts could be isolated. Attempted methylation gave only resins.

2'-Bromo-4'-nitro-3-phenyl-4-methylphthalaz-1-one.—A solution of finely powdered 1-hydroxy-3-(2'-bromo-4'-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (25 g.) in cold concentrated sulphuric acid (300 c.c.) was poured on ice (1 kg.), and powdered potassium dichromate (14 g.) was added in small portions during 2 hours, with constant agitation. Next day, the yellowish-brown product was isolated as usual. *2'-Bromo-4'-nitro-3-phenyl-4-methylphthalaz-1-one* crystallised from ethyl acetate in small, pale yellow needles, m. p. 225° (yield, 14 g.; 63·2%) (Found : C, 50·8; H, 3·1; Br, 21·8. $C_{15}H_{10}O_3N_3Br$ requires C, 50·0; H, 2·8; Br, 22·2%). Its properties resemble those of the preceding compound; moreover, it did not react with alcoholic picric acid.

2'-Bromo-4'-nitro-3-phenyl-1-methylphthalaz-4-one (V).—Acetophenone-*o*-carboxylic acid and 2-bromo-4-nitrophenylhydrazine (cf. J., 1931, 1923) afforded the *hydrazone* (IV), which formed small yellow prisms, m. p. 152—154° (Found : C, 47·3; H, 3·3. $C_{15}H_{12}O_4N_3Br$ requires C, 47·6; H, 3·2%), soluble in alkalis with a deep orange-red colour, and reprecipitated on acidification. Crystallisation from alcohol, glacial acetic acid, or nitrobenzene did not result in ring closure, which was effected by refluxing with acetic anhydride and pyridine for 1 hour. Next day, the mixture was poured on ice, the solid (V) collected, washed with dilute sodium carbonate and water, and crystallised from alcohol; colourless needles, m. p. 200—202°, with previous softening (Found : Br, 22·3. $C_{15}H_{10}O_3N_3Br$ requires Br, 22·2%), insoluble in dilute mineral acids and in alkalis.

2'-Bromo-4'-amino-3-phenyl-4-methylphthalaz-1-one.—(*a*) A solution of 1-hydroxy-3-(2'-bromo-4'-aminophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (10 g.) in cold concentrated sulphuric acid (60 c.c.) and water (250 c.c.) was treated gradually (2 hrs.) with powdered potassium dichromate (4·8 g.), with constant agitation. Next day, the orange-brown product was isolated as usual (yield 7 g.; 79·8%), and then crystallised from ethyl alcohol in yellow needles, m. p. 279—280°, containing 1 mol. of alcohol of crystallisation which could not be removed completely by heat (Found : C, 54·0; H, 4·5; N, 11·0; Br, 21·0. $C_{15}H_{12}ON_3Br,C_2H_6O$ requires C, 54·25; H, 4·8; N, 11·2; Br, 21·3%). It crystallised from ethyl acetate in yellow needles, m. p. 275—277°, which tenaciously retained solvent. It dissolves in concentrated hydrochloric acid with a pink colour and can be diazotised.

(*b*) A solution of the same initial material (5 g.) in sodium hydroxide (5 g.) and water (50 c.c.) was heated under reflux at about 95° for 24 hours; the product separated continuously in yellow needles, m. p. 276° (yield 0·6 g.; 13·7%).

(*c*) 2'-Bromo-4'-nitro-3-phenyl-4-methylphthalaz-1-one (1 g.) was heated with alcohol (3 c.c.) and a solution of sodium sulphide crystals (7 g.) in water (15 c.c.) for ½ hour, and the alcohol removed; the product separated in yellow needles, m. p. 276° (yield 0·73 g.; 80%).

Reduction of 2'-Bromo-4'-amino-3-phenyl-4-methylphthalaz-1-one.—A solution of the base (6 g.) in concentrated hydrochloric acid (135 c.c.) and water (135 c.c.) was boiled, and zinc dust (3 g.) added gradually (1 hr.), the volume being kept constant by addition of dilute hydrochloric acid (1 : 6). The pale yellow solution was filtered, cooled, neutralised with sodium hydroxide, the dried precipitate extracted with toluene, and the extract concentrated, yielding a small amount of pale yellow prisms, m. p. 211—212°. This substance is a diazotisable amine, not identical with 2'-bromo-4'-amino-*N*-phenyl-3-methylphthalimidine obtained from 2' : 6'-dibromo-4'-amino-3-phenyl-4-methylphthalaz-1-one (J., 1931, 1088), but, by analogy with the reduction of the corresponding monochloro-compound (J., 1932, 19), it is probably impure *1-keto-3-(2'-bromo-4'-aminophenyl)-4-methyltetrahydrophthalazine* (Found : C, 55·2; H, 4·7; Br, 23·7. $C_{15}H_{14}ON_3Br$ requires C, 54·2; H, 4·2; Br, 24·1%). Many other reductions were carried out under various conditions, but only small quantities of the above compound were isolated, together with oils which gave strong reactions for *p*-diamines.

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CLOTHWORKERS' RESEARCH LABORATORY,
LEEDS UNIVERSITY.

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