

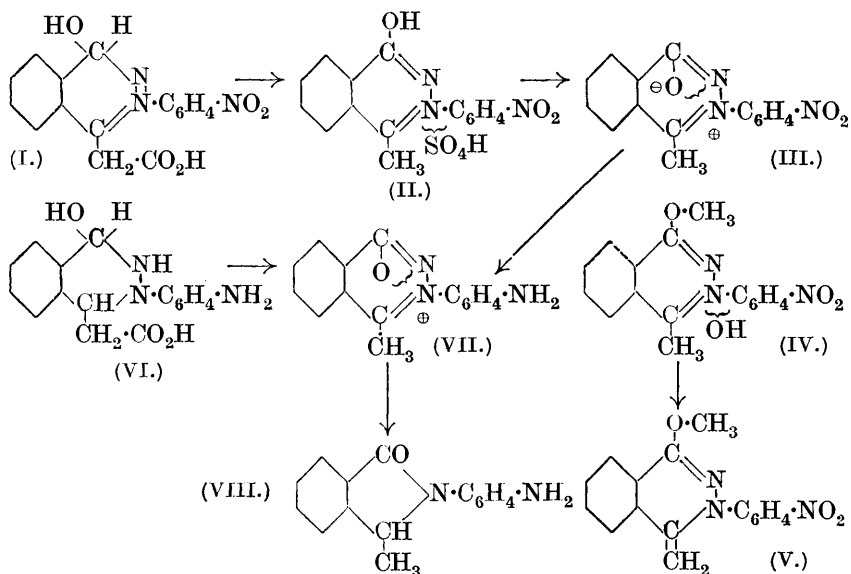
CXXXVII.—*A New Reaction of Certain Diazosulphonates derived from β -Naphthol-1-sulphonic Acid. Part V. The 4'-Nitro- and 4'-Amino-derivatives of 3-Phenyl-4-methylphthalaz-1-one.*

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IN a former communication (J., 1926, 702) reference was made to attempts to degrade 1-hydroxy-3-(4'-nitrophenyl)-1 : 3-dihydrophthalazine-4-acetic acid (I) and 1-hydroxy-3-(4'-aminophenyl)-tetrahydrophthalazine-4-acetic acid (VI) (*loc. cit.*, p. 703) by treatment with acid dichromate. Fission did not occur, however, and the constitution of the respective products was not determined. We have now examined them more closely, indications as to their constitution and mode of formation having been afforded not only by the study of the corresponding dihalogeno-derivatives by Dunbar and Williams, but also by the failure of these authors to prepare

1-hydroxy-3-(2':6'-dihalogeno-4'-aminophenyl)-tetrahydrophthalazine-4-acetic acids satisfactorily by the use of alkaline hydro-sulphite (hyposulphite), because of the further action of alkali on these tetrahydrophthalazine derivatives (see following paper).

The product of the action of cold acid dichromate on 1-hydroxy-3-(4'-nitrophenyl)-1:3-dihydrophthalazine-4-acetic acid separates apparently as a *sulphate* (II), which readily gives uncrystallisable resins if treated with sodium hydroxide, probably owing to hydration, but with sodium carbonate gives the base, golden-yellow needles, m. p. 251°. Analysis of the latter gave the formula $C_{15}H_{11}O_3N_3$, which is that of a nitrophenylmethylphthalazone. It is undoubtedly the 4-methyl derivative of 4'-nitro-3-phenylphthalaz-1-one (J., 1928, 2550), which it resembles closely in most of its general properties. For instance, 4'-nitro-3-phenyl-4-methylphthalaz-1-one (III) is acidic and dissolves readily in sodium hydroxide with a deep orange-red colour; also it is basic and dissolves readily in mineral acids, forming well-crystallised salts, which are moderately stable to water; it forms a *picrate*; and the oxygen atom can be methylated.



The methylation product, however, behaves differently in the present case. The interaction of 4'-nitro-3-phenylphthalaz-1-one with methyl sulphate in nitrobenzene solution, followed by removal of the latter and making alkaline with sodium carbonate, gives a base, which combines with alcohols. Heating the compound after

crystallisation from alcohol first at 110° and then at 140° readily gives 4-keto-1-methoxy-3-(4'-nitrophenyl)-3 : 4-dihydrophthalazine, which is neither acidic nor basic (*loc. cit.*). Methylation of 4'-nitro-3-phenyl-4-methylphthalaz-1-one similarly, and removal of the nitrobenzene, also gives an aqueous solution of a methosulphate, from which a base (probably initially IV) is liberated as an orange-red semi-crystalline powder by means of sodium carbonate. This substance, however, crystallises from ethyl acetate or alcohols in red needles, m. p. 134°, in each case, and is then merely decomposed progressively by heating at 140°. Analysis indicated that the crystalline substance contains one molecule of water less than is required by formula (IV) and it appears to be 4'-nitro-1-methoxy-3-phenyl-4-methylene-3 : 4-dihydrophthalazine (V), as this formula agrees best with its properties, although no reaction occurred with acetone in presence of sodium hydroxide either before or after crystallisation. This compound is demethylated by heating with hydrobromic acid and glacial acetic acid at 110° with re-formation of 4'-nitro-3-phenyl-4-methylphthalaz-1-one.

The action of cold acid dichromate, or aqueous permanganate, on 1-hydroxy-3-(4'-aminophenyl)-tetrahydrophthalazine-4-acetic acid gives a substance, yellow needles, m. p. 277°, which appears from analysis to be an aminophenylmethylphthalazone, C₁₅H₁₃ON₃. The same substance, but in much lower yield, is obtained from 1-hydroxy-3-(4'-aminophenyl)-tetrahydrophthalazine-4-acetic acid by refluxing it with alcoholic potassium hydroxide, or by heating it with sodium carbonate solution at 170° in a sealed tube, whilst the fact that it is obtained also by reduction of 4'-nitro-3-phenyl-4-methylphthalaz-1-one with aqueous sodium sulphide shows that it is 4'-amino-3-phenyl-4-methylphthalaz-1-one (VII). In agreement with this constitution, when compound (VII) is reduced with zinc dust and hydrochloric acid, one nitrogen atom is eliminated as ammonia and 4'-amino-N-phenyl-3-methylphthalimidine (VIII) is produced, the formation of N-phenylphthalimidines in this way being a general reaction of phthalazones (J., 1926, 696).

The course of the degradation of 1-hydroxy-3-(4'-nitrophenyl)-1 : 3-dihydrophthalazine-4-acetic acid and of 1-hydroxy-3-(4'-aminophenyl)-tetrahydrophthalazine-4-acetic acid has now been shown to be dependent upon the conditions employed. By boiling with aqueous mineral acid, acetic acid is eliminated and the >CH·OH group in position 1 is converted into the >C=O group, giving 4'-nitro- and 4'-amino-3-phenylphthalaz-1-one respectively (J., 1928, 2550). On the other hand, although the >CH·OH group in position 1 is also converted into the >C=O group by cold acid dichromate, the acetic acid side-chain is merely decarboxylated with formation of

4'-nitro- and 4'-amino-derivatives of 3-phenyl-4-methylphthalaz-1-one respectively. Decarboxylation of 1-hydroxy-3-(4'-aminophenyl)-tetrahydrophthalazine-4-acetic acid is effected also by boiling alcoholic potassium hydroxide. Thus the behaviour is the converse of that of acetoacetic ester, which gives acetic acid by boiling with alkalis and is decarboxylated by boiling mineral acid.

EXPERIMENTAL.

4'-Nitro-3-phenyl-4-methylphthalaz-1-one (III).—A solution of 10 g. of finely powdered 1-hydroxy-3-(4'-nitrophenyl)-1:3-dihydrophthalazine-4-acetic acid (I) in 100 c.c. of cold concentrated sulphuric acid was poured on 400 g. of ice, and 4.5 g. of powdered sodium dichromate were added in small portions during $\frac{1}{2}$ hour. (The reaction is best carried out at 10° in a rough-walled vessel with vigorous stirring and scratching, as otherwise the product is intractable.) The mixture frothed considerably and the pale yellow precipitate was replaced gradually by an almost colourless crystalline precipitate, which was collected next day, pressed well (but not washed with water), and dried at the ordinary temperature (A; 11 g.).

The substance A frothed vigorously at 95° and melted at 231°. It dissolved readily in dry methyl or ethyl alcohol with effervescence and then almost colourless plates, m. p. 246°, crystallised. In spite of repeated crystallisation, the latter could not be obtained ash-free, but the product was probably the *sulphate* of 4'-nitro-3-phenyl-4-methylphthalaz-1-one (II) (Found: C, 48.8; H, 3.7; N, 11.2; S, 8.3. $C_{15}H_{13}O_7N_3S$ requires C, 47.5; H, 3.4; N, 11.1; S, 8.4%).

The substance A was dissolved in 120 c.c. of 10% aqueous sodium carbonate, and the orange-red solution acidified carefully with hydrochloric acid. The hydrochloride of 4'-nitro-3-phenyl-4-methylphthalaz-1-one separated at first as a pale yellowish precipitate, followed by almost colourless, prismatic needles. The combined solid (6.2 g.), after extraction with ethyl acetate, melted at 218°, and was shaken with cold 10% sodium carbonate solution. The base crystallised from dry ethyl acetate, alcohol or pyridine in golden-yellow needles, m. p. 251° (not 247° as previously given) (yield, 5.2 g.; 60.5%) (Found: C, 64.2; H, 4.1; N, 14.7. $C_{15}H_{11}O_3N_3$ requires C, 64.1; H, 3.9; N, 14.9%). It was obtained also in much lower yield by the action of a warm solution of potassium permanganate in commercial pyridine on 1-hydroxy-3-(4'-nitrophenyl)-1:3-dihydrophthalazine-4-acetic acid.

4'-Nitro-3-phenyl-4-methylphthalaz-1-one is insoluble in cold sodium carbonate solution, but dissolves in sodium hydroxide solution with a deep orange-red colour; with mineral acids it forms salts which

are not decomposed by water, and with hydrobromic acid it forms a hydrobromide, which crystallises from glacial acetic acid in colourless needles, m. p. 270°. With an alcoholic solution of picric acid it forms a *picrate*, yellow plates, m. p. 208°, which is decomposed progressively by recrystallisation from alcohol (Found: C, 49.3; H, 3.0. $C_{21}H_{14}O_{10}N_6$ requires C, 49.4; H, 2.7%).

When the substance A was dissolved in aqueous sodium hydroxide in place of sodium carbonate, and the solution acidified with hydrochloric acid, a yellow precipitate (B), free from chlorine, was obtained. The dry substance B was very soluble in ethyl acetate or alcohol and could not be crystallised, yet it gave the picrate of 4'-nitro-3-phenyl-4-methylphthalaz-1-one satisfactorily and was also readily reduced by sodium sulphide to 4'-amino-3-phenyl-4-methylphthalaz-1-one, m. p. 277°.

Action of Methyl Sulphate on 4'-Nitro-3-phenyl-4-methylphthalaz-1-one.—A solution of 3.3 g. of the phthalazone in 30 c.c. of hot dry nitrobenzene, to which 1.5 g. of methyl sulphate were added, was kept at 130° for 1½ hours, the nitrobenzene then being removed by distillation with steam. The colourless aqueous residue gave, when rendered alkaline with sodium carbonate, an orange-red semi-crystalline precipitate (yield, 2.2 g.; 63%) (probably initially IV) which, crystallised from ethyl acetate, or methyl or ethyl alcohol, appeared to lose water, giving 4'-nitro-1-methoxy-3-phenyl-4-methylene-3:4-dihydrophthalazine (V) in red needles, m. p. 134° (Found: C, 64.7; H, 4.4; N, 13.7; OMe, 10.7; *M* in phenol, 289; *M* in benzene, 285. $C_{16}H_{13}O_3N_3$ requires C, 65.1; H, 4.4; N, 14.2; OMe, 10.5%; *M*, 295). This substance was insoluble in sodium hydroxide but dissolved readily in mineral acids. When it (1 g.) was heated with glacial acetic acid and hydrobromic acid (2 vols.) at about 110° for 3 minutes, a brown resin separated: crystallisation from glacial acetic acid gave the hydrobromide of 4'-nitro-3-phenyl-4-methylphthalaz-1-one, which, by treatment with sodium carbonate solution, followed by crystallisation from ethyl acetate, gave the base in golden-yellow needles, m. p. 251°.

4'-Amino-3-phenyl-4-methylphthalaz-1-one (VII).—(a) A solution of 20 g. of 1-hydroxy-3-(4'-aminophenyl)-tetrahydrophthalazine-4-acetic acid (VI) in a cold mixture of 100 c.c. of concentrated sulphuric acid and 400 c.c. of water was stirred mechanically at air temperature for 3 hours, during which 9 g. of powdered sodium dichromate were added in small portions. A transient wine-red colour was produced after each addition, but any further addition merely gave a brown colour. The mixture was left overnight, rendered alkaline with sodium hydroxide, boiled, and filtered and the filtrate was rendered just alkaline with sodium carbonate and

concentrated. After recrystallisation from water in orange needles, 4'-amino-3-phenyl-4-methylphthalaz-1-one crystallised from ethyl acetate, dry alcohol or pyridine in yellow needles, m. p. 277° (not 276° as previously given) (yield, 13 g.; 77.5%) (Found: C, 71.7; H, 5.3; N, 16.7. $C_{15}H_{13}ON_3$ requires C, 71.7; H, 5.2; N, 16.7%). It was obtained also when powdered 1-hydroxy-3-(4'-aminophenyl)-tetrahydrophthalazine-4-acetic acid was added to a boiling solution of potassium permanganate in commercial pyridine, or better (yield, about 50%) when shaken with cold 3% aqueous potassium permanganate, the solution then being rendered just alkaline with sodium carbonate and concentrated. In the latter case the temperature rose and evolution of carbon dioxide was detected. (b) A solution of 4 g. of 1-hydroxy-3-(4'-aminophenyl)-tetrahydrophthalazine-4-acetic acid and 3 g. of potassium hydroxide in 60 c.c. of dry alcohol was refluxed for 6 hours, and the dark product crystallised from water (charcoal) (yield, 1.2 g.; 36%). It was obtained also by heating 2 g. with 1 g. of anhydrous sodium carbonate, 6 c.c. of saturated aqueous sodium carbonate, and a few drops of alcohol in a sealed tube at 170° for 2 hours. (c) A mixture of 10 g. of finely powdered 4'-nitro-3-phenyl-4-methylphthalaz-1-one and a solution of 75 g. of sodium sulphide crystals in 75 c.c. of water was boiled: after about 10 minutes, the reddish-orange colour of the solution changed to yellow and orange needles separated (yield, 7.6 g.; 85%). The products in all cases melted at 277° and were identical in every respect. 4'-Amino-3-phenyl-4-methylphthalaz-1-one was recovered unaltered after an aqueous alkaline solution had been boiled with sodium hydrosulphite for $\frac{1}{2}$ hour. It was acetylated readily, and the *acetyl* derivative crystallised from alcohol in colourless, stout, prismatic needles, m. p. 316—317°, which rapidly became blue on the surface on exposure to light, particularly when powdered (Found: C, 69.5; H, 5.3; N, 14.2. $C_{17}H_{15}O_2N_3$ requires C, 69.6; H, 5.1; N, 14.3%).

4'-Amino-N-phenyl-3-methylphthalimidine (VIII).—A solution of 20 g. of 4'-amino-3-phenyl-4-methylphthalaz-1-one in 1 litre of water and 200 c.c. of concentrated hydrochloric acid was vigorously boiled while 30 g. of zinc dust were added in small portions during 4 hours. After cooling, the solution, in which ammonia was detected, was rendered strongly alkaline with sodium hydroxide and filtered, the dry precipitate extracted with alcohol, and the alcohol distilled. The residue was converted into the hydrochloride (charcoal) and reprecipitated with sodium carbonate. The *base* crystallised from much water in almost colourless, fern-shaped leaflets, m. p. 166° (yield, 12 g.; 63%) (Found: C, 75.6; H, 5.8; N, 11.7. $C_{15}H_{14}ON_2$ requires C, 75.6; H, 5.9; N, 11.8%). The *acetyl* deriv-

ative crystallised from alcohol or much water in colourless lustrous prisms, m. p. 250° (Found : C, 72.8; H, 5.8; N, 10.2. $C_{17}H_{16}O_2N_2$ requires C, 72.9; H, 5.7; N, 10.0%).

4'-Hydroxy-N-phenyl-3-methylphthalimidine was prepared from *4'-amino-N-phenyl-3-methylphthalimidine* (10 g.) exactly as described for *4'-hydroxy-N-phenylphthalimidine* from the corresponding amino-derivative (*loc. cit.*, p. 704). It crystallised from water (charcoal) in colourless prismatic needles containing $\frac{1}{2}H_2O$, or from toluene in small colourless prisms, m. p. 192° (yield, 8.2 g.; 82%) (Found : C, 75.5; H, 5.6; N, 6.0. $C_{15}H_{13}O_2N$ requires C, 75.3; H, 5.4; N, 5.9%). Its *ethyl* ether crystallised from dilute ethyl alcohol in large, colourless, prismatic needles, m. p. 136° (Found : N, 5.3. $C_{17}H_{17}O_2N$ requires N, 5.2%).

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