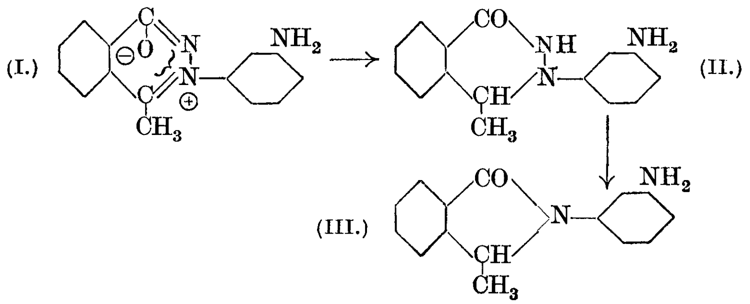
CCLX.—*A New Reaction of Certain Diazosulphonates derived from β-Naphthol-*1*-sulphonic Acid. Part VII. The* 3′*-Nitro- and* 3′*-Amino-derivatives of* 3*-Phenyl-*4*-methylphthalaz-*1*-one, and the Nitro-*3*-phenyl-*1*-methylphthalaz-*4*-ones.*

By Frederick Maurice Rowe and Arnold Thornton Peters.

In Parts V and VI of this series (this vol., pp. 1067, 1073), the 4′-nitro- and -amino-3-phenyl-4-methylphthalaz-1-ones and their 2′ : 6′-dihalogeno-derivatives were discussed. The investigation of 3′-nitro- and -amino-derivatives (J., 1928, 2556) has now been extended to include the corresponding derivatives of 3-phenyl-4-methylphthalaz-1-one.

The action of cold acid dichromate on 1-hydroxy-3-(3′-nitrophenyl)-1 : 3-dihydrophthalazine-4-acetic acid gives 3′-*nitro*-3-*phenyl*-4-*methylphthalaz*-1-*one* in about the same yield as was obtained with the 4′-nitro-isomeride. The reaction is best conducted so that a solution is obtained after the addition of the dichromate, but it is difficult to obtain concordant results and, if a solid separates after a solution has been obtained, it is almost impossible to crystallise the product, although it is reduced satisfactorily by sodium sulphide to 3′-*amino*-3-*phenyl*-4-*methylphthalaz*-1-*one*. Carefully dried solvents are essential for the crystallisation of 3′-nitro-3-phenyl-4-methylphthalaz-1-one, which is acid and dissolves in sodium hydroxide with a yellow colour; also it is basic and dissolves readily in mineral acids forming well-crystallised salts, stable to water; it forms a *picrate*. The oxygen atom can be methylated, but the methylation product behaves differently from the 4′-nitro-isomeride; it could not be crystallised and was not obtained pure. This led us to repeat the methylation of 3′-nitro-3-phenylphthalaz-1-one (*ibid*., p. 2562), and the earlier results were confirmed. We found, however, that it is not essential to crystallise the methylated base from an alcohol, prior to conversion into 4-keto-1-methoxy-3-(3′-nitrophenyl)-3 : 4-dihydrophthalazine by heating first at 100° and then at 140°, as this change occurs equally readily with the methylated base itself under similar conditions.

1-Hydroxy-3-(3′-aminophenyl)tetrahydrophthalazine-4-acetic acid is decarboxylated in similar ways to the 4′-amino-isomeride and 3′-*amino*-3-*phenyl*-4-*methylphthalaz*-1-*one* (I) is formed. The product obtained from it by reduction varies with the conditions used. Thus, reduction with alkaline hydrosulphite (hyposulphite), or preferably rapid reduction with zinc dust and dilute hydrochloric acid, gives the intermediate 1-*keto*-3-(3′-*aminophenyl*)-4-*methyltetrahydrophthalazine* (II), whereas zinc dust and more concentrated hydrochloric acid give 3′-*amino*-N-*phenyl*-3-*methylphthalimidine* (III); the former is best converted into the latter by zinc dust and aqueous sulphuric acid :



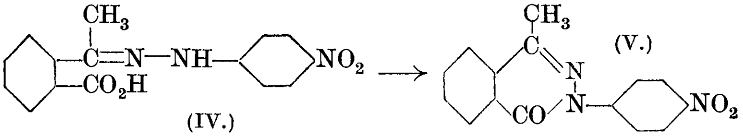
(I.)

(II.)

(III.)

Attempts to reoxidise (II) to (I) were unsuccessful. An intermediate substance is also formed by the reduction of 3′-amino-3-phenylphthalaz-1-one with alkaline hydrosulphite, or rapidly with zinc dust and dilute hydrochloric acid, but it was impossible to determine the formula analytically, owing to the presence in it of variable amounts of alcohol of crystallisation, although its conversion into 3′-amino-*N*-phenylphthalimidine indicates that it is probably the corresponding 1-*keto*-3-(3′-*aminophenyl*)*tetrahydrophthalazine*. The demonstration of the existence of a compound intermediate between a 3′-phenylphthalaz-1-one and an *N*-phenylphthalimidine is of interest, because 4′-amino-3-phenylphthalaz-1-one and its 4-methyl derivative under similar conditions are recovered unaltered, whilst the halogeno-derivatives did not definitely give such an intermediate (*loc. cit.*).

For purposes of comparison, we have also prepared the nitro-3-phenyl-1-methylphthalaz-4-ones by condensing acetophenone-*o*-carboxylic acid with *o*-, *m*-, or *p*-nitrophenylhydrazine. There is an interesting difference between the ease with which this condensation occurs in the various cases. Thus, with *p*-nitrophenylhydrazine the intermediate o-*carboxyacetophenone*-p-*nitrophenylhydrazone* (IV) (or its lactone form) is formed, but is converted readily into 4′-*nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one* (V) in a variety of ways :


(IV.)

(V.)

o-Nitrophenylhydrazine also gives the intermediate o-*carboxyacetophenone*-o-*nitrophenylhydrazone* (or its lactone form), which is much more stable than the *p*-nitro-isomeride and is best converted into 2′-*nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one* by the method of Aggarwal, Darbari, and Rây (J., 1929, 1942). *m*-Nitrophenylhydrazine, on the other hand, gives 3′-*nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one* directly, and the intermediate hydrazone appears to exist only momentarily. This is also the case with phenylhydrazine, and nitration of the resulting 3-*phenyl*-1-*methylphthalaz*-4-*one* gives mainly the 4′-nitro-derivative, identical with that obtained from *p*-nitrophenylhydrazine. 1-Methylphthalaz-4-one is very difficult to condense with *p*-chloronitrobenzene, but a little 4′-nitro-3-phenyl-1-methylphthalaz-4-one was prepared in this way. A double compound crystallises from an alcoholic solution of equimolecular proportions of 1-methylphthalaz-4-one and *p*-chloronitrobenzene.

Finally, the nitro-3-phenyl-1-methylphthalaz-4-ones possess the properties anticipated: they are insoluble in sodium hydroxide, and do not form salts either with mineral acids or with picric acid.

EXPERIMENTAL.

3′-*Nitro*-3-*phenyl*-4-*methylphthalaz*-1-*one*.—A solution of finely powdered 1-hydroxy-3-(3′-nitrophenyl)-1 : 3-dihydrophthalazine-4-acetic acid (12 g.) (J., 1928, 2559) in cold concentrated sulphuric acid (110 c.c.) was poured on ice (220 g.), the mixture stirred for 4 hours, and powdered potassium dichromate (3 g.) added in portions during the first hour. The green solution was almost neutralised by slowly adding concentrated sodium hydroxide with cooling so that the temperature remained below 30°, and the pale yellow precipitate produced was washed with water and dried. 3′-*Nitro*-3-*phenyl*-4-*methylphthalaz*-1-*one* crystallised from a mixture of dry ethyl acetate and dry ethyl alcohol (10 : 1) in small yellow prisms, m. p. 249° (yield, 6·1 g.; 59·1%) (Found: C, 63·9; H, 4·0; 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 very much lower yield by the gradual addition of saturated aqueous potassium permanganate to a suspension of 1-hydroxy-3-(3′-nitrophenyl)-1 : 3-dihydrophthalazine-4-acetic acid in dilute sulphuric acid at 50—60°. The mixture was filtered, sodium hydroxide added to the pale yellow filtrate until the colour was just orange, the liquid extracted with chloroform, and the latter removed.

3′-Nitro-3-phenyl-4-methylphthalaz-1-one is insoluble in sodium carbonate solution, but dissolves in warm sodium hydroxide solution with a yellow colour; with mineral acids it forms salts (hydrochloride, colourless prisms), which are not decomposed by water. With an alcoholic solution of picric acid it forms a *picrate*, small yellow needles, m. p. 197° (Found: C, 49·2; H, 2·9. $C_{21}H_{14}O_{10}N_6$ requires C, 49·4; H, 2·7%).

Action of Methyl Sulphate on 3′-*Nitro*-3-*phenyl*-4-*methylphthalaz*-1-*one*.—Methylation was carried out as described for the 4′-nitro-isomeride (this vol., p. 1071), except that the mixture was preferably kept at 100°. The colourless aqueous residue gave, when rendered alkaline with sodium carbonate, a brown semi-crystalline precipitate, m. p. about 70°, which was very soluble in most organic solvents, but could not be purified (Found, in crude product: OMe, 8·2%). This substance was insoluble in sodium hydroxide, but dissolved in dilute mineral acids.

3′-*Amino*-3-*phenyl*-4-*methylphthalaz*-1-*one* (I).—(*a*) 1-Hydroxy-3-(3′-aminophenyl)tetrahydrophthalazine-4-acetic acid (20 g.) (J., 1928, 2559) was treated as described for the 4′-amino-isomeride (this vol., p. 1071), except that a solution of sodium dichromate

(7 g.) in water (30 c.c.) was used. No transient colour was produced by the dichromate. The yellowish-green solution was left overnight, neutralised cold with 20% aqueous sodium hydroxide, and the orange-brown precipitate produced was washed with hot water and dried. After crystallisation from dry alcohol (charcoal), *3′-amino-3-phenyl-4-methylphthalaz-1-one* formed brownish-yellow plates or prisms, m. p. 271° (yield, 11·6 g.; 69·1%) (Found: C, 71·9; H, 5·3; N, 16·5. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2; N, 16·7%).

(*b*) A solution of 1-hydroxy-3-(3′-aminophenyl)tetrahydrophthalazine-4-acetic acid (3 g.) in saturated alcoholic potassium hydroxide (50 c.c.) was refluxed for 8 hours and the product then separated in orange needles (yield, 0·45 g.; 17·9%). It was obtained also in similar yield by almost boiling a solution in aqueous sodium hydroxide for 2 days.

(*c*) 3′-Nitro-3-phenyl-4-methylphthalaz-1-one (10 g.) was reduced with sodium sulphide as described for the 4′-nitro-isomeride (*loc. cit.*). No colour change occurred, and, after filtration of the hot solution, orange-yellow needles separated from the cold filtrate (yield, 5·7 g.; 63·8%). The products in all cases melted at 271° and were identical in every respect. *Acetyl derivative.* A solution of 3′-amino-3-phenyl-4-methylphthalaz-1-one (1 g.) in acetic anhydride (6 c.c.) and a little pyridine was boiled. After a few minutes the *acetyl* derivative separated; it crystallised from alcohol in colourless plates, m. p. 274°, which soon became pink on the surface on exposure to light (Found: C, 69·9; H, 5·3; N, 14·1. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·1; N, 14·3%).

1-Keto-3-(3′-aminophenyl)-4-methyltetrahydrophthalazine (II).—A solution of 3′-amino-3-phenyl-4-methylphthalaz-1-one (3 g.) in dilute hydrochloric acid (50 c.c. of 1 : 4) was boiled, and zinc dust (2·5 g.) added in small portions during 10 minutes. The solution gradually became colourless and was then filtered, the filtrate rendered alkaline with sodium hydroxide, the dry precipitate extracted with alcohol, and the alcohol distilled. *1-Keto-3-(3′-aminophenyl)-4-methyltetrahydrophthalazine* crystallised from alcohol in colourless glistening rhombohedral plates, m. p. 188° (yield, 2 g.; 66%) (Found: C, 71·3; H, 6·2; N, 16·7. $C_{15}H_{15}ON_3$ requires C, 71·1; H, 5·9; N, 16·6%). Treatment with acetic anhydride did not give the acetyl derivative, but a substance, colourless plates, m. p. 147° (decomp.), was obtained.

*3′-Amino-*N*-phenyl-3-methylphthalimidine* (III).—A solution of 1-keto-3-(3′-aminophenyl)-4-methyltetrahydrophthalazine (2 g.) in aqueous sulphuric acid (30 c.c. of 1 : 3) was boiled, and zinc dust (2 g.) added in small portions during ½ hour. The base was isolated as described for the preceding compound. *3′-Amino-*N*-phenyl-3-*

methylphthalimidine crystallised from alcohol in almost colourless prisms, m. p. 165° (yield, 0·6 g.; 31·9%) (Found: C, 75·4; H, 5·8; N, 11·5. $C_{15}H_{14}ON_2$ requires C, 75·6; H, 5·9; N, 11·8%). The *acetyl* derivative crystallised from alcohol in colourless prisms, m. p. 181° (Found: N, 10·2. $C_{17}H_{16}O_2N_2$ requires N, 10·0%).

Reduction of 3′-*Amino*-3-*phenylphthalaz*-1-*one.*—A fine suspension of 3′-amino-3-phenylphthalaz-1-one (5 g.), obtained by dissolution in dilute hydrochloric acid and reprecipitation with sodium hydroxide, was boiled, and sodium hydrosulphite (50 g.) added in portions during ¾-hour, the mixture being kept alkaline throughout by addition of sodium hydroxide. The mixture was cooled, filtered, and the base crystallised from ethyl alcohol; it formed pale straw-coloured hexagonal prisms, m. p. 225°, which slowly became opaque on keeping or more rapidly when heated (yield, 3·3 g.) (Found: C, 67·2, 68·6; H, 5·7, 5·3; N, 16·0%). No definite conclusions as to the composition of the compound after crystallisation from ethyl alcohol could be based on these analyses, however, as specimens contained variable amounts of alcohol of crystallisation, and attempts to remove this completely by heating at 120° or 140° resulted in some decomposition. The same substance was obtained by the action of zinc dust and hot dilute hydrochloric acid on 3′-amino-3-phenylphthalaz-1-one for a short time, and as the base, m. p. 225°, was converted into 3′-amino-*N*-phenylphthalimidine by vigorous reduction with zinc dust and more concentrated hydrochloric acid, it was probably 1-*keto*-3-(3′-*aminophenyl*)*tetrahydrophthalazine.*

4′-*Nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one* (V).—(*a*) Phthalylacetic acid (19 g.) was dissolved in warm *N*-sodium hydroxide (300 c.c.), *N*-hydrochloric acid (200 c.c.) was added, and the mixture heated on the water-bath with gradual addition of boiling water until the evolution of carbon dioxide had ceased (Gabriel and Neumann, *Ber.*, 1893, **26**, 705). The resulting solution of acetophenone-*o*-carboxylic acid was filtered, and a concentrated alcoholic solution of *p*-nitrophenylhydrazine (15·3 g.) added to the hot filtrate. After about one minute's warming on the water-bath, o-*carboxyacetophenone*-p-*nitrophenylhydrazone* (IV) (or its lactone form) separated as an orange-yellow precipitate, which does not melt but becomes colourless above 155°, owing to formation of 4′-nitro-3-phenyl-1-methylphthalaz-4-one, and then melts at 214° (yield, 26·9 g.; 90%) (Found: C, 60·0; H, 4·55. $C_{15}H_{13}O_4N_3$ requires C, 60·2; H, 4·3%). It dissolved in cold sodium carbonate with an orange colour and in cold sodium hydroxide with a deep brownish-red colour, and was reprecipitated on acidifying the alkaline solution. It crystallised from warm alcohol in orange needles, but boiling with alcohol or toluene, heating with glacial acetic acid, nitrobenzene, dilute mineral acids, or even sodium hydroxide (partial conversion), or heating alone at 160—170°, resulted in conversion into 4′-*nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one*. The latter compound was prepared most conveniently by heating a glacial acetic acid solution for a short time; after cooling, it crystallised in colourless silky needles, m. p. 214° (Found: C, 64·2; H, 4·1; N, 14·95. $C_{15}H_{11}O_3N_3$ requires C, 64·1; H, 3·9; N, 14·9%). It is insoluble in sodium carbonate or hydroxide, and in hydrochloric acid, and does not form a picrate.

(*b*) Attempts to condense 1-methylphthalaz-4-one (stout, colourless, prismatic needles, m. p. 224°. Gabriel and Neumann, *loc. cit.*, give m. p. 222°) with *p*-chloronitrobenzene were mainly unsuccessful. By heating an alcoholic solution of equimolecular proportions in presence of fused sodium acetate and a little aqueous copper sulphate in a sealed tube at 180° for 2 hours, however, although most of the starting materials were recovered unaltered, a little 4′-nitro-3-phenyl-1-methylphthalaz-4-one, m. p. 214°, was isolated by repeated fractional crystallisation from alcohol. A mixture of equimolecular proportions of 1-methylphthalaz-4-one and *p*-chloronitrobenzene crystallised completely from alcohol in long, colourless silky needles, softening at 130° and melting at 140° when freshly prepared. On addition of a crystal of 1-methylphthalaz-4-one to such a solution, however, the whole of this crystallised and the *p*-chloronitrobenzene remained dissolved.

2′-*Nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one*.—A similar condensation of acetophenone-*o*-carboxylic acid with *o*-nitrophenylhydrazine (15·3 g.) gave o-*carboxyacetophenone*-o-*nitrophenylhydrazone* (or its lactone form) as a brownish-yellow precipitate, which crystallised from benzene in orange needles, becoming amorphous when dry, m. p. 184° (yield, 23·9 g.; 80%) (Found: C, 60·4; H, 4·5. $C_{15}H_{13}O_3N_3$ requires C, 60·2; H, 4·3%). It dissolves in sodium carbonate with an orange colour, and in sodium hydroxide with a deep brown colour. It is much more stable than the *p*-nitro-isomeride, but when a solution in concentrated sulphuric acid was warmed and poured on ice, it was converted into 2′-*nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one*. The latter compound was prepared most conveniently by refluxing the hydrazone (5 g.) with dry amyl alcohol (60 c.c.), which had been saturated with hydrogen chloride at 0°, for 2 hours (Aggarwal, Darbari, and Rây, *loc. cit.*); after removal of amyl alcohol, it crystallised from ethyl alcohol in almost colourless leaflets, m. p. 202° (Found: C, 63·9; H, 3·9; N, 14·9. $C_{15}H_{11}O_3N_3$ requires C, 64·1; H, 3·9; N, 14·9%). It possesses similar properties to the 4′-nitro-isomeride.

3′-*Nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one*.—A similar condensation of acetophenone-*o*-carboxylic acid with *m*-nitrophenylhydrazine (15·3 g.) did not result in the isolation of the intermediate hydrazone, but 3′-*nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one* separated immediately in almost colourless needles, and crystallised from alcohol in colourless leaflets or needles, m. p. 167° (yield, 22·5 g.; 80%) (Found: N, 14·8. $C_{15}H_{11}O_3N_3$ requires N, 14·9%). It possesses similar properties to the 4′-nitro-isomeride.

3-*Phenyl*-1-*methylphthalaz*-4-*one*.—A similar condensation of acetophenone-*o*-carboxylic acid with phenylhydrazine (10·8 g.) also resulted in the separation of 3-*phenyl*-1-*methylphthalaz*-4-*one*, which crystallised from alcohol in almost colourless rectangular prisms, m. p. 102° (yield, 18·9 g.; 80%) (Found: N, 12·1. $C_{15}H_{12}ON_2$ requires N, 11·9%). It was nitrated by dissolving 1 g. in fuming nitric acid (5 c.c.) at 0°. After standing at air temperature for 2 hours, it was poured on ice. The white precipitate (1 g.) was fractionally crystallised from alcohol and consisted mainly of 4′-nitro-3-phenyl-1-methylphthalaz-4-one, which separated first in colourless silky needles, m. p. 214°, identical with that described above.

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