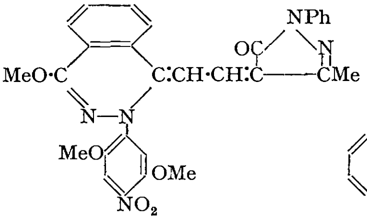
70. *A Reaction of Certain Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XXIII. Phthalazine Derivatives from 4′-Nitro-2′ : 5′-dimethoxybenzene-2-naphthol-1-diazosulphonate.*

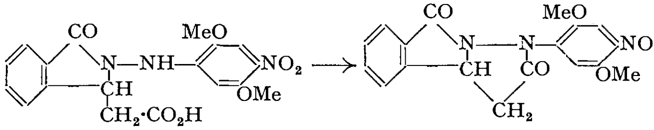
By (the late) F. M. Rowe, R. L. Desai, and A. T. Peters.

The use of 4-nitro-2 : 5-dimethoxyaniline as diazotisable base in the reactions leading to complex phthalazine derivatives is examined. Whereas 1-hydroxy-3-(4′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid is readily converted by aqueous sulphuric acid into 4′-nitro-3-phenylphthalaz-1-one, a corresponding reaction with the 4′-nitro-2′ : 5′-dimethoxy-derivative (I) follows an unusual course, to give *4′-nitro-2′ : 5′-dimethoxy-3-phenyl-4-methylphthalaz-1-one* (II), also formed from (I) by cold acid dichromate, nitric acid (*d* 1·5) at 50°, or fuming hydrochloric acid in a sealed tube at 140—160°. Compound (II) is isomerised by aqueous hydrochloric acid in a sealed tube at 180° to *4′-nitro-2′ : 5′-dimethoxy-3-phenyl-1-methylphthalaz-4-one*. Restricted action of sodium hydroxide on sodium 1-(4′-nitro-2′ : 5′-dimethoxybenzeneazo)-β-naphthaquinone-1-sulphonate, followed by acid hydrolysis, affords compound (I) and 11·6% of *2-(4′-nitro-2′ : 5′-dimethoxyphenylamino)*iso*indolinone-3-acetic acid.*

4′-Nitro-2′ : 5′-dimethoxybenzene-2-naphthol-1-diazosulphonate and aqueous sodium carbonate yielded sodium 1-(4′-nitro-2′ : 5′-dimethoxybenzeneazo)-β-naphthaquinone-1-sulphonate, converted by aqueous sodium hydroxide into *sodium hydrogen 3-(4′-nitro-2′ : 5′-dimethoxyphenyl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate*, and thence by boiling dilute hydrochloric acid into *1-hydroxy-3-(4′-nitro-2′ : 5′-dimethoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid* (I). With boiling aqueous sulphuric acid (b. p. 140°) or with fuming hydrochloric acid (*d* 1·19) in a sealed tube at 140—160°, (I) gave 4′-*nitro*-2′ : 5′-*dimethoxy*-3-*phenyl*-4-*methylphthalaz*-1-*one* (II). The more normal course of reaction is shown by the action of cold acid dichromate. Methylation of (I) afforded 1-*methoxy*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine*, which condensed with 2 : 4-dinitrochlorobenzene or 1-phenyl-3-methyl-4-anilinomethylene-5-pyrazolone to yield 1-*methoxy*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-4-(2″ : 4″-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine* or -4-(5″-*keto*-1″-*phenyl*-3″-*methylpyrazolinylidene*-*ethylidene*)-3 : 4-*dihydrophthalazine* (III), respectively.



(III.)



(IV.) (V.)

The nitro-compound (I) was reduced, best with alkaline hydrosulphite, to the corresponding *amine*, which could not be converted into 4′-*amino*-2′ : 5′-*dimethoxy*-3-*phenyl*-4-*methylphthalaz*-1-*one* by the usual methods. The latter, however, was readily obtained by reducing the corresponding nitro-compound (II) with sodium sulphide; by the action of zinc dust and hydrochloric acid, compound (II) afforded 4′-*amino*-2′ : 5′-*dimethoxy*-N-*phenyl*-3-*methylphthalimidine*. 4′-*Nitro*-2′ : 5′-*dimethoxy*-3-*phenyl*-1-*methylphthalaz*-4-*one* could not be synthesised, but it was formed by isomerisation of compound (II) by heating with aqueous hydrochloric acid (1 : 8) in a sealed tube at 180°.

When sodium 1-(4′-nitro-2′ : 5′-dimethoxybenzeneazo)-β-naphthaquinone-1-sulphonate was treated with cold aqueous sodium hydroxide for 30 seconds, and the resulting mixed sodium salts were hydrolysed, compound (I) was accompanied by the isomeric 2-(4′-*nitro*-2′ : 5-*dimethoxyphenylamino*)iso*indolinone*-3-*acetic acid*, (IV), the constitution of which was confirmed by boiling it with acetic anhydride, when cyclisation to 2 : 5-*diketo*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)iso*indolinopyrazolidocoline* (V) occurred; reduction with iron and aqueous acetic acid gave the corresponding 4′-*amino*-compound.

Experimental.

(Microanalyses are by Drs. Weiler and Strauss, Oxford.)

1-*Hydroxy*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid* (I).—A filtered solution of commercial 50% sodium β-naphthol-1-sulphonate (60 g.) in water (250 c.c.) was stirred slowly at 0° into a solution of diazotised 4-nitro-2 : 5-dimethoxyaniline, prepared in aqueous hydrochloric acid, using 20 g. of base. 4′-Nitro-2′ : 5′-dimethoxybenzene-2-naphthol-1-diazosulphonate separated immediately, and it was collected, washed free from acid with brine, made into a paste with water (200 c.c.), and stirred into 30% aqueous sodium carbonate (150 c.c.); after 15 minutes, a solution of sodium hydroxide (25 g.) in water (120 c.c.) was added and the mixture left at room temperature for 48 hours. *Sodium hydrogen* 3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* was isolated after separation of 4′-nitro-2′ : 5′-dimethoxybenzeneazo-β-naphthol (2·2 g.; 6·2%); it separated from aqueous alcohol as a yellow powder (Found : S, 5·8. $C_{18}H_{16}O_9N_3SNa,H_2O$ requires S, 6·6%), which dyes wool a level orange-brown from an acid bath. The sodium hydrogen salt (25 g.) was boiled with water (500 c.c.), and concentrated hydrochloric acid (60 c.c.) was added gradually until evolution of sulphur dioxide had ceased. The *acid* (I) crystallised from ethyl acetate in small, pale yellow prisms, m. p. 212—213° (14·7 g.; 71·4%) (Found : C, 56·0; H, 4·5; N, 10·85. $C_{18}H_{17}O_7N_3$ requires C, 55·8; H, 4·4; N, 10·85%).

The *methyl* ester crystallised from methyl alcohol in small, pale yellow needles, m. p. 164° (Found : N, 10·7. $C_{19}H_{19}O_7N_3$ requires N, 10·5%), and the *ethyl* ester formed similar needles from ethyl alcohol, m. p. 152° (Found : C, 58·3; H, 5·1; N, 10·1. $C_{20}H_{21}O_7N_3$ requires C, 57·8; H, 5·1; N, 10·1%); the *acetyl* derivative crystallised from acetic acid in yellow hexagonal plates, m. p. 201—202° (Found : C, 55·7; H, 4·55; N, 9·7. $C_{20}H_{19}O_8N_3$ requires C, 55·9; H, 4·4; N, 9·8%), and the *anilide* crystallised from ethyl acetate in pale yellow needles, m. p. 255° (softens at 249°) (Found : C, 62·4; H, 5·0; N, 12·0. $C_{24}H_{22}O_6N_4$ requires C, 62·3; H, 4·8; N, 12·1%).

1-*Keto*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-2-*methyltetrahydrophthalazine*-4-*acetic acid*, prepared as described for the analogous *N*-methyl ethers (*J.*, 1933, 1069), crystallised from aqueous acetic acid in pale yellow needles, m. p. 195° (Found : C, 56·9; H, 4·8; N, 10·3. $C_{19}H_{19}O_7N_3$ requires C, 56·85; H, 4·7; N, 10·5%), soluble in warm aqueous alkalis with a yellow colour.

1-*Hydroxy*-3-(4′-*amino*-2′ : 5′-*dimethoxyphenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid*.—Sodium hydrosulphite was added to a solution of the corresponding nitro-compound (20 g.) in water (300 c.c.) and sodium hydroxide (20 g.) at about 70° until the deep red colour became yellow. Hydrochloric acid was carefully added until an almost colourless precipitate had separated completely (excess of acid redissolves it). Dissolution of the precipitate in hot aqueous sodium carbonate and careful acidification at 70° gave pale yellow prismatic needles, m. p. 193° (decomp.), of the *amine* (10·2 g.; 55·3%) (Found: C, 60·7; H, 5·3; N, 11·5. $C_{18}H_{19}O_5N_3$ requires C, 60·5; H, 5·3; N, 11·8%), which is diazotisable.

4′-*Nitro*-2′ : 5′-*dimethoxy*-3-*phenyl*-4-*methylphthalaz*-1-*one* (II).—(*a*) A solution of 1-hydroxy-3-(4′-nitro-2′ : 5′-dimethoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid (20 g.) in concentrated sulphuric acid (100 c.c.) and water (120 c.c.) was boiled for 1·5 hours under reflux. After filtration from some charred material, and dilution of the filtrate (charcoaled) with water, sodium carbonate was added until the mixture was alkaline. The precipitate of *phthalazone* (II) crystallised from alcohol in pale yellow needles, m. p. 254° (softening at 250°) (6·5 g.; 36·8%) (Found: C, 59·9; H, 4·6; N, 12·5. $C_{17}H_{15}O_5N_3$ requires C, 59·8; H, 4·4; N, 12·3%). It is insoluble in sodium carbonate solution, but dissolves in sodium hydroxide solution with an orange colour; salts are formed with mineral acids, *e.g.*, the hydrochloride separated in colourless needles. The *picrate*, prepared in dry alcohol, crystallised from the same solvent in yellow plates, m. p. 229° (Found: N, 14·9. $C_{23}H_{18}O_{12}N_6$ requires N, 14·7%).

(*b*) Compound (I) (7·5 g.) was boiled with concentrated sulphuric acid (50 c.c.) and acetic acid (60 c.c.) for 5 minutes and the mixture poured on ice. Basification with aqueous ammonia (*d* 0·88) gave the above phthalazone, m. p. and mixed m. p. 254° (3·6 g.; 54·5%).

(*c*) A solution of compound (I) (20 g.) in cold concentrated sulphuric acid (200 c.c.) was poured on ice (600 g.), and powdered potassium dichromate (9 g.) was added in small portions during 45 minutes, with continuous vigorous stirring. After being stirred for a total of 5 hours at room temperature, the mixture was basified with aqueous ammonia, when the phthalazone (II) separated (6·6 g.; 37·4%).

(*d*) In nitric acid (*d* 1·5; 50 c.c.) at 50°, compound (I) (10 g.) reacted vigorously; after 2 minutes, the mixture was added to ice and basified; yield, 3·7 g. (43·2%).

(*e*) Compound (I) (2 g.) and fuming hydrochloric acid (*d* 1·19; 15 c.c.) in a sealed tube at 160° for 2 hours gave the above phthalazone in 10% yield.

1-*Methoxy*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine*.—4′-Nitro-2′ : 5′-dimethoxy-3-phenyl-4-methylphthalaz-1-one (2 g.) and methyl sulphate (2 g.) were warmed to 60°; after 20 minutes at this temperature, boiling water (100 c.c.) was added and, after the mixture had been allowed to cool, sodium carbonate was added to precipitate the *methylene* base, which crystallised from ethyl acetate in red, prismatic needles, m. p. 131—132° (1·2 g.; 57·7%) (Found: C, 61·0; H, 4·7; N, 11·7. $C_{18}H_{17}O_5N_3$ requires C, 60·8; H, 4·8; N, 11·8%), soluble in dilute mineral acids. 20% Perchloric acid (10 c.c.) was added to 1 g. in aqueous hydrochloric acid; the precipitated 1-*methoxy*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-4-*methylphthalazinium perchlorate* crystallised from aqueous acetic acid containing perchloric acid in almost colourless, prismatic needles, m. p. 240° (softens at 233°) (1 g.; 78%) (Found: C, 47·5; H, 4·0; N, 9·3; Cl, 8·0. $C_{18}H_{18}O_9N_3Cl$ requires C, 47·4; H, 4·0; N, 9·2; Cl, 7·8%).

1-*Methoxy*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-4-(2″ : 4″-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine*.—2 : 4-Dinitrochlorobenzene (2 g.) was added to a boiling solution of 1-methoxy-3-(4′-nitro-2′ : 5′-dimethoxyphenyl)-4-methylene-3 : 4-dihydrophthalazine (2 g.) in alcohol (100 c.c.), followed by addition of potassium acetate (3 g.), and the mixture was refluxed for 30 minutes. A deep red colour developed; the *compound*, which separated progressively, crystallised from acetic anhydride in bluish-red prisms, m. p. 230° (2·8 g.; 95·4%) (Found: C, 55·5; H, 3·7; N, 13·6. $C_{24}H_{19}O_9N_3$ requires C, 55·3; H, 3·65; N, 13·4%).

1-*Methoxy*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-4-(5″-*keto*-1″-*phenyl*-3″-*methylpyrazolinylidene-ethylidene*)-3 : 4-*dihydrophthalazine* (III).—A solution of 1-methoxy-3-(4′-nitro-2′ : 5′-dimethoxyphenyl)-4-methylene-3 : 4-dihydrophthalazine (1 g.) and 1-phenyl-3-methyl-4-anilinomethylene-5-pyrazolone (1 g.) in acetic anhydride (4 c.c.) and acetic acid (6 c.c.) was heated at 100° for 7 hours, and the crystalline product collected next day. The *compound* crystallised from acetic anhydride in brownish-red prisms, m. p. 258° (softens at 240°) (1·3 g.; 85·6%) (Found: N, 12·9. $C_{29}H_{25}O_6N_5$ requires N, 13·0%).

4′-*Amino*-2′ : 5′-*dimethoxy*-3-*phenyl*-4-*methylphthalaz*-1-*one*.—A solution of sodium sulphide crystals (8 g.) in water (30 c.c.) was added gradually to a boiling aqueous suspension of 4′-nitro-2′ : 5′-dimethoxy-3-phenyl-4-methylphthalaz-1-one (1 g. in 60 c.c.), during 30 minutes, and the mixture was refluxed for a further hour. After cooling, the *amine* was collected; it crystallised from a mixture of alcohol and ethyl acetate (1 : 2) in small yellow needles, m. p. 260° (0·6 g.; 66%) (Found: C, 65·4; H, 5·5; N, 13·45. $C_{17}H_{17}O_3N_3$ requires C, 65·6; H, 5·5; N, 13·5%).

4′-*Amino*-2′ : 5′-*dimethoxy*-N-*phenyl*-3-*methylphthalimidine*.—A solution of 4′-nitro-2′ : 5′-dimethoxy-3-phenyl-4-methylphthalaz-1-one (5 g.) in concentrated hydrochloric acid (100 c.c.) was boiled, during the addition of zinc dust (10 g.) in small portions, for 1 hour. After being cooled and filtered, the filtrate was made alkaline with sodium hydroxide, and the dry precipitate extracted with alcohol. The *phthalimidine* crystallised from alcohol in small, colourless prisms, m. p. 155—156° (2·1 g.; 45·9%) (Found: C, 68·3; H, 5·8; N, 9·4. $C_{17}H_{18}O_3N_2$ requires C, 68·5; H, 6·0; N, 9·4%), insoluble in aqueous alkalis, but soluble in cold concentrated hydrochloric acid to give a colourless solution; it was diazotisable.

Conversion of 4′-*Nitro*-2′ : 5′-*dimethoxy*-3-*phenyl*-4-*methylphthalaz*-1-*one into* 4′-*Nitro*-2′ : 5′-*dimethoxy*-3-*phenyl*-1-*methylphthalaz*-4-*one*.—The 4-methylphthalaz-1-one (2 g.) was heated with aqueous hydrochloric acid (1 : 8; 36 c.c.) at 180° in a sealed tube for 6 hours. The resulting crystals were collected and boiled with dilute hydrochloric acid to remove unchanged material; the residue crystallised from acetic acid in small, pale yellow prisms, m. p. 222° (1·3 g.; 64%) (Found: C, 59·7; H, 4·5; N, 12·5. $C_{17}H_{15}O_5N_3$ requires C, 59·6; H, 4·4; N, 12·3%). The *phthalaz*-4-*one* is insoluble in boiling dilute mineral acids and aqueous alkalis.

2-(4′-*Nitro*-2′ : 5′-*dimethoxyphenylamino*)isoindolinone-3-*acetic Acid* (IV).—A solution of sodium-1-(4′-nitro-2′ : 5′-dimethoxybenzeneazo)-β-naphthaquinone-1-sulphonate was prepared from 4-nitro-2 : 5-dimethoxyaniline (20 g.), and a cold solution of sodium hydroxide (25 g.) in water (70 c.c.) was run in, with vigorous stirring. After 30 seconds, the mixture was rendered strongly acid with hydrochloric acid (with the use of a defrothing agent), and was then made alkaline with aqueous sodium carbonate, the insoluble 4′-nitro-2′ : 5′-dimethoxybenzeneazo-β-naphthol (7 g.; 19·9%) collected, and the filtrate rendered faintly acid. The whole acid mixture was boiled for 10 hours, the volume being kept constant by adding dilute hydrochloric acid; on cooling, a precipitate (22·4 g.) separated. It was fractionally crystallised from ethyl acetate; the first crop was 1-hydroxy-3-(4′-nitro-2′ : 5′-dimethoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid, m. p. and mixed m. p. 212—213° (7·5 g.; 19·3%); after the separation of further crops of mixtures, a product, m. p. 221°, was obtained, which on admixture with the above compound, m. p. 212—213°, was depressed in m. p. to 195°. Further purification from ethyl acetate afforded 2-(*4′-nitro-2′ : 5′-dimethoxyphenylamino*)iso*indolinone-3-acetic acid* in fine, pale yellow needles, m. p. 221—223° (4·5 g.; 11·6%) (Found: C, 56·3; H, 4·4; N, 10·8. $C_{18}H_{17}O_7N_3$ requires C, 55·8; H, 4·4; N, 10·85%), soluble in cold aqueous alkalis with an orange-yellow colour. The *methyl* ester crystallised from methyl alcohol in pale yellow prisms, m. p. 146° (Found: N, 10·4. $C_{19}H_{19}O_7N_3$ requires N, 10·5%).

2 : 5-*Diketo*-3-(*4′-nitro-2′ : 5′-dimethoxyphenyl*)iso*indolinopyrazolidocoline* (V).—2-(4′-Nitro-2′ : 5′-dimethoxyphenylamino)*iso*indolinone-3-acetic acid (3 g.) was refluxed with acetic anhydride (14 c.c.) for 15 minutes. The crystals, which separated on cooling, recrystallised from ethyl acetate in pale yellow prisms, m. p. 208° (2·4 g.; 84%) (Found: C, 58·6; H, 4·4; N, 11·6. $C_{18}H_{15}O_6N_3$ requires C, 58·5; H, 4·1; N, 11·4%), of the *anhydro*-derivative (V), insoluble in aqueous alkalis.

2 : 5-*Diketo*-3-(*4′-amino-2′ : 5′-dimethoxyphenyl*)iso*indolinopyrazolidocoline*.—The above nitro-compound (2 g.) was dissolved in acetic acid (30 c.c.) and water (30 c.c.), and iron powder (4 g.) was added gradually during 10 minutes. The mixture was filtered (charcoal), diluted with water, and partly neutralised; the *amine* then separated (1·1 g.; 70·7%); it crystallised from ethyl acetate in brownish-grey prisms, m. p. 174° (Found: C, 63·6; H, 5·4; N, 12·4. $C_{18}H_{17}O_4N_3$ requires C, 63·7; H, 5·0; N, 12·4%), soluble in dilute mineral acids and diazotisable. The *acetyl* derivative separated from acetic anhydride in colourless prisms, m. p. 259° (Found: N, 10·7. $C_{20}H_{19}O_5N_3$ requires N, 11·0%).

The authors thank Imperial Chemical Industries (Dyestuffs Division) for gifts of chemicals.

CLOTHWORKERS' RESEARCH LABORATORY,
THE UNIVERSITY, LEEDS.

[*Received, April* 16*th*, 1947.]