

759. *Extrusion of Sulphur. Part II.* A New Route to Phenanthridine Derivatives.*

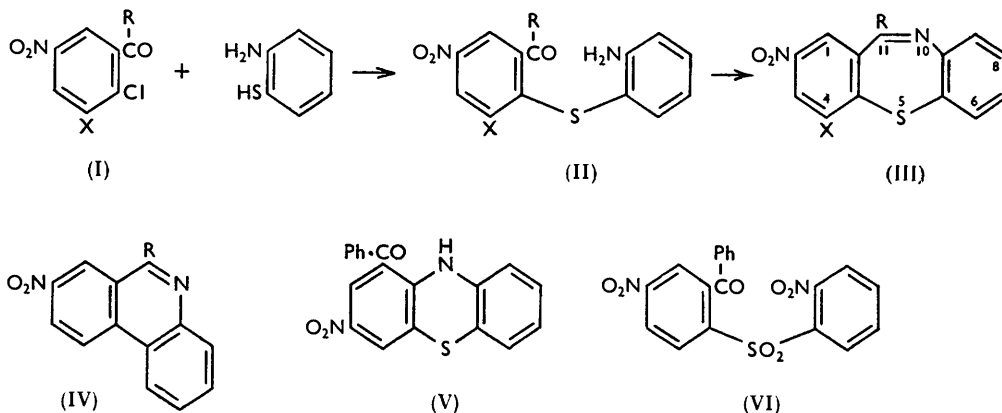
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Compounds such as 2-chloro-5-nitro-benzaldehyde or -benzophenone react with *o*-aminothiophenol forming derivatives of dibenzo[*b,f*]-1:4-thiazepine from which by extrusion of sulphur corresponding derivatives of phenanthridine are obtained.

THE conversion of dibenzo[*b,f*]thiepins into phenanthrenes * suggested the possibility of an analogous conversion of dibenzo[*b,f*]-1:4-thiazepines into phenanthridines. Dibenzo[*b,f*]-1:4-thiazepines have not been described hitherto, but representatives were readily obtained by condensing *o*-aminothiophenol with compounds such as 2-chloro-5-nitro-benzaldehyde or -benzophenone. Extrusion of sulphur from these thiazepines afforded in several but not all of the cases acceptable yields of the appropriate phenanthridines.

* Part I, preceding paper.

The immediate products of reaction between compounds of type (I) and *o*-aminothiophenol in presence of alkali are aminodiaryl sulphides (II). These were occasionally isolated and were cyclised with varying ease to the corresponding thiazepines (III). Thus from the ketonic reagents (I; R = Me, X = H) and (I; R = Ph, X = H) well-defined



intermediates (II; R = Me, X = H) and (II; R = Ph, X = H) were respectively obtained, but intermediates from aldehydes, *e.g.*, (I; R = X = H), were generally too readily cyclised for convenient isolation. Thiophenols react with 2:4- or 2:6-dinitrophenylpyridinium salts to form diaryl sulphides¹ and the process may be extended to pyridinium salts² derived from compounds of type (I) or from analogues in which the chloro-substituent is replaced by the toluene-*p*-sulphonyloxy-group. In this way 2:4-dinitrodibenzo[*b,f*]-1:4-thiazepine was prepared from 3:5-dinitrosalicylaldehyde by successive reaction with toluene-*p*-sulphonyl chloride and *o*-aminothiophenol in pyridine. Such reactions however do not invariably yield thiazepines. For instance, *o*-aminothiophenol and 2-chloro-3:5-dinitrobenzophenone (I; R = Ph, X = NO₂) in pyridine solution afforded, by elimination of hydrogen chloride and nitrous acid, a red crystalline product, C₁₉H₁₂O₃N₂S. This compound, by analogy with the condensate from picryl chloride and *o*-aminothiophenol,³ is formulated as 1-benzoyl-3-introphenothiazine (V). Its formation presumably involves Smiles rearrangement of an intermediate *o*-aminodiaryl sulphide (II; R = Ph, X = NO₂) to the isomeric *o*-mercaptodiphenylamine and subsequent elimination of nitrous acid. Reaction in aqueous ethanol in presence of sodium hydroxide (1 mol.) gave as main product dibenzothiazepine (III; R = Ph, X = NO₂), accompanied by some of the thiazine (V).

2:4-Dinitrobenzaldehyde reacts with sodium tolyl sulphide to form, as part product, 4-nitro-2-*p*-tolylthiobenzaldehyde⁴ and it was therefore examined as a potential source of 3-nitrobenzothiazepine through similar condensation with *o*-aminothiophenol. This reaction, however, led by elimination of water to a red crystalline solid which afforded yellow solutions in benzene or ethanol. The red colour is perhaps best accommodated by the anil structure (VII) or the derived zwitterionic structure (VIII), although in solution equilibrium may well be established with the benzothiazoline (IX).⁵ Oxidation, according to the conditions used, afforded the disulphide corresponding to (VII) or the benzothiazole corresponding to (IX): each of these oxidation products was independently synthesised.

The dibenzothiazepines were stable, feebly basic compounds. Oxidation of 2-nitro-11-phenyldibenzothiazepine (III; R = Ph, X = H) by hydrogen peroxide in acetic acid led,

¹ Bielig and Reidies, *Chem. Ber.*, 1956, **89**, 550.

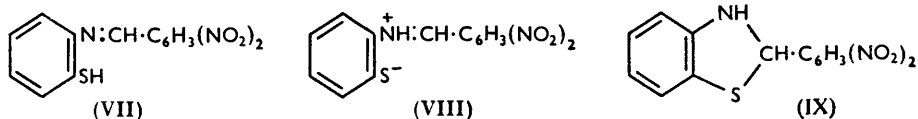
² Allan and Loudon, *J.*, 1949, 821.

³ Kehrmann and Steinberg, *Ber.*, 1911, **44**, 3011; Wight and Smiles, *J.*, 1935, 340.

⁴ Campbell, Dick, and Loudon, *J.*, 1941, 747.

⁵ Lankelma and Sharnhoff, *J. Amer. Chem. Soc.*, 1931, **53**, 2654; 1932, **54**, 379.

through stages which were not closely defined, to the diaryl sulphone (VI). The structure of this sulphone was established by an independent synthesis and also by scission of the compound by piperidine into 5-nitro-2-piperidinobenzophenone and *o*-nitrobenzenesulphinic acid, the latter being characterised by conversion into *o*-nitrobenzenesulphonamide. This oxidative rupture of the thiazepine ring is essentially similar to the oxidation of quinoline (or of quinoline *N*-oxide) to *o*-nitrobenzoic acid by successive treatment with hydrogen peroxide and potassium permanganate.⁶



When heated briefly with copper in diethyl phthalate the nitrobenzothiazepines (III; X = H and R = H, Me, Ph, or *m*-NO₂·C₆H₄) yielded corresponding phenanthridines (IV) in good yield: in absence of the solvent, much poorer yields were obtained. Dinitrobenzothiazepines (III; X = NO₂ and R = H or Ph) were unaffected by similar brief treatment in diethyl phthalate and were completely destroyed by prolonged or more vigorous treatment. The phenanthridine structure assigned to the sulphur-free products (IV) is fully authenticated. Oxidation of 7-nitrophenanthridine and of its 9-methyl homologue afforded in each case 7-nitrophenanthridone. This compound had m. p. 325° in good agreement with recently recorded values, *viz.*, m. p. 326—327°⁷ and m. p. 329°,⁸ and on vigorous oxidation it afforded 4-nitrophthalic acid with some oxalic acid but no phthalic acid. In contrast, a mixture of phthalic and 4-nitrophthalic acids was similarly obtained from the material of m. p. 282—284° prepared as described by Moore and Huntress⁹ from 2-nitrofluorenone oxime and regarded by these authors as 7-nitrophenanthridone. The oxidation results therefore support the conclusion of Nunn, Schofield, and Theobald⁷ that the material of m. p. 282—284° is a complex of 2- and 7-nitrophenanthridones. Finally, direct comparison of m. p.s and infrared spectra proved the identities of two of our phenanthridines, (IV; R = Me, X = H) and (IV; R = *m*-NO₂·C₆H₄, X = H), with authentic specimens which were kindly supplied by Dr. L. P. Wallis, whom we warmly thank.

EXPERIMENTAL

Ultraviolet absorption spectra were taken in 95% ethanol.

2-Nitro-11-phenyldibenzo[b,f]-1:4-thiazepine.—A warm solution of 2-chloro-5-nitrobenzophenone (1.5 g.) in ethanol-water (4 : 1; 20 c.c.) was stirred into a warm solution prepared from *o*-aminothiophenol hydrochloride (1 g.) and sodium hydroxide (0.5 g.) in the same solvent (10 c.c.). There gradually separated 2'-amino-2-benzoyl-4-nitrodiphenyl sulphide as brown-yellow prisms, m. p. 136—138° (from ethanol) (Found: C, 65.5; H, 3.8; N, 8.2. C₁₉H₁₄O₃N₂S requires C, 65.15; H, 4.0; N, 8.0%); λ_{max}. 241 and 332 mμ (log ε 4.37 and 4.12). When the reaction mixture was boiled the main product (yield 83%) was 2-nitro-11-phenyldibenzo[b,d]-1:4-thiazepine, pale-yellow needles, m. p. 160° (from benzene), into which the amino-sulphide was also converted quantitatively by crystallisation from acetic acid (Found: C, 68.7; H, 4.95; N, 8.7. C₁₉H₁₂O₂N₂S requires C, 68.7; H, 3.65; N, 8.5%); λ_{max}. 238, 266, and 323 mμ (log ε 4.44, 4.38, and 3.93).

7-Nitro-9-phenylphenanthridine.—(a) 2-Nitro-11-phenyldibenzothiazepine and copper bronze (0.3 g. each) were heated in nitrogen at 280—290° (metal-bath temp.), a vigorous reaction ensuing. The resultant sublimate formed pale-yellow needles (0.01 g.), m. p. 236° (from ethanol). (b) The thiazepine and copper bronze were heated under nitrogen with diethyl phthalate (3 c.c.) at the b. p. for 5—7 min. The cooled mixture was diluted with dry benzene (30 c.c.), heated with charcoal, filtered, and concentrated. Addition of light petroleum (b. p.

⁶ Kosuge and Miyashita, *Pharm. Bull. (Japan)*, 1954, **2**, 397; *Chem. Abs.*, 1956, **50**, 12057.

⁷ Nunn, Schofield, and Theobald, *J.*, 1952, 2792.

⁸ Arcus and Coombs, *J.*, 1954, 4319.

⁹ Moore and Huntress, *J. Amer. Chem. Soc.*, 1927, **49**, 2618.

60—80°) afforded 7-nitro-9-phenylphenanthridine, m. p. and mixed m. p. with the sample from (a) 235—236° (yield 85%) (Found: C, 76.4; H, 3.9; N, 9.5. $C_{19}H_{12}O_2N_2$ requires C, 76.0; H, 4.0; N, 9.3%).

Oxidation of 2-nitro-11-phenyldibenzo[b,f]-1:4-thiazepine.—The dibenzothiazepine (2 g.) and hydrogen peroxide (30%; 2 c.c.) in acetic acid were heated at 100° for 30 min. The cooled solution deposited pale yellow needles, apparently of a mono-oxide of the thiazepine, although the analytical figures were high and rather variable (Found: C, 66.9, 66.3; H, 4.0, 3.6; N, 8.2, 8.3. Calc. for $C_{19}H_{12}O_3N_2S$: C, 65.5; H, 3.5; N, 8.0%). This substance was converted quantitatively into 7-nitro-9-phenylphenanthridine when boiled (2 min.) with copper bronze in diethyl phthalate.

2-Benzoyl-2':4-dinitrodiphenyl Sulphone.—(a) To a boiling solution of 2-nitro-11-phenyldibenzothiazepine (2 g.) in acetic acid (20 c.c.) hydrogen peroxide (30%; 1 c.c.) was added every $\frac{1}{2}$ hr. for 6 hr. The yellow solid, obtained after cooling and diluting with water, afforded 2-benzoyl-2':4-dinitrodiphenyl sulphone as needles, m. p. 217° (from ethanol) (Found: C, 55.6; H, 3.3; N, 7.0. $C_{19}H_{12}O_7N_2S$ requires C, 55.35; H, 2.95; N, 6.8%). This sulphone was heated for a few min. with piperidine, and the resultant solution was cooled, acidified with 5*N*-hydrochloric acid, and extracted with ether. The ethereal extract was washed with a small volume of water, then with aqueous sodium carbonate and again with water. 5-Nitro-2-piperidinobenzophenone, m. p. and mixed m. p. 100—102°,⁴ was recovered from the ethereal residue. Chlorine was passed into the carbonate washings and the precipitated gum was collected, washed with water and treated with ammonia solution (*d* 0.88) affording *o*-nitrobenzenesulphonamide, m. p. and mixed m. p. 191°. (b) 2-Benzoyl-2':4-dinitrodiphenyl sulphide, m. p. 139° (from benzene-ethanol), was prepared (15 min. at 70°) from sodium *o*-nitrophenyl sulphide and 2-chloro-5-nitrobenzophenone in aqueous ethanol (Found: C, 60.25; H, 3.3; N, 7.5. $C_{19}H_{12}O_5N_2S$ requires C, 60.0; H, 3.2; N, 7.4%). It was oxidised to the sulphone, m. p. and mixed m. p. 215—217°, by hydrogen peroxide (30%) in acetic acid (1 hr. at 100°).

*5-Nitro-2-*p*-tolylthiobenzaldehyde.*—Thio-*p*-cresol (0.13 g.) was added to a suspension of (2-formyl-4-nitrophenyl)pyridinium toluene-*p*-sulphonate² (0.4 g.) in anhydrous pyridine (3 c.c.) and after some hours the solution was poured into a mixture of ice and dilute hydrochloric acid affording 5-nitro-2-*p*-tolylthiobenzaldehyde, m. p. and mixed m. p. 196°⁴ (from acetic acid).

2-Nitrodibenzo[b,f]-1:4-thiazepine.—2-Chloro-5-nitrobenzaldehyde (1.15 g.) in ethanol-water (10 c.c.; 4:1) was slowly added to a solution prepared from *o*-aminothiophenol hydrochloride (1 g.) and sodium hydroxide (0.5 g.) in the same solvent (10 c.c.). After 30 min. the orange-coloured precipitate was rubbed with a little glacial acetic acid, affording 2-nitrodibenzo[b,f]-1:4-thiazepine as pale-yellow needles, m. p. 178° (from ethanol), λ_{\max} 224 and 317 μ ($\log \epsilon$ 4.36 and 3.86) (Found: C, 61.05; H, 3.15; N, 11.3. $C_{13}H_8O_2N_2S$ requires C, 60.9; H, 3.15; N, 10.95%). The yields (92% maximum) fell considerably (to *ca.* 45%) when the order of mixing the reacting solutions was reversed. (b) *o*-Aminothiophenol hydrochloride (0.16 g.) was added to a suspension of *N*-(2-formyl-4-nitrophenyl)pyridinium toluene-*p*-sulphonate² (0.4 g.) in anhydrous pyridine and after 1 hr. the red solution was poured into dilute hydrochloric acid at 0°. The resultant solid after chromatography (in benzene on alumina) afforded the above dibenzothiazepine, m. p. and mixed m. p. 178°.

7-Nitrophenanthridine, m. p. 174°, was obtained in poor yield when 2-nitrodibenzothiazepine was heated alone with copper bronze at 290°, and in 63% yield when diethyl phthalate was used as medium, the product being isolated as described for the 9-phenyl derivative (Found: C, 69.7; H, 3.65; N, 12.4. Calc. for $C_{13}H_{10}O_2N_2$: C, 69.6; H, 3.6; N, 12.5%). For this compound Arcus and Coombs⁸ record m. p. 180°. The present specimen on oxidation afforded 7-nitrophenanthridone, m. p. and mixed m. p. 326°.

11-Methyl-2-nitrodibenzo[b,f]-1:4-thiazepine.—Sodium hydroxide (0.5 g.) in ethanol-water (4:1; 4 c.c.) was slowly stirred into a warm solution of 2-bromo-5-nitroacetophenone (1.5 g.) and *o*-aminothiophenol hydrochloride (1 g.) in the same solvent. The resultant yellow solid afforded 2-acetyl-2'-amino-4-nitrodiphenyl sulphide (yield, 78%), m. p. 162° [from benzene-light petroleum (b. p. 60—80°)] (Found: C, 58.5; H, 4.0; N, 9.8. $C_{14}H_{12}O_3N_2S$ requires C, 58.3; H, 4.2; N, 9.7%), and this, when heated with acetic anhydride, yielded the corresponding 2-acetamido-compound, m. p. 148° (from benzene) (Found: C, 58.4; H, 4.2; N, 8.75. $C_{16}H_{14}O_4N_2S$ requires C, 58.2; H, 4.3; N, 8.5%). The amino-sulphide (0.8 g.) was heated for 30 min. at 140° with polyphosphoric acid [from phosphoric acid (4 c.c.) and phosphoric

oxide (10 g.], and the cooled mixture was diluted with water (75 c.c.) affording 11-methyl-2-nitrodibenzothiazepine as pale-yellow prisms, m. p. 139°, λ_{\max} . 226, 298, and 309 μ ($\log \epsilon$ 4.36, 3.85, and 3.85) (Found: C, 62.35; H, 3.8; N, 10.4. $C_{14}H_{10}O_2N_2S$ requires C, 62.2; H, 3.7; N, 10.4%).

9-Methyl-7-nitrophenanthridine, m. p. and mixed m. p. 242—243°,¹⁰ was obtained (yields, 48—55%) from 11-methyl-2-nitrodibenzothiazepine as described under the preparation (b) of its 9-phenyl analogue (Found: C, 70.7; H, 4.1; N, 11.75. Calc. for $C_{14}H_{10}O_2N_2$: C, 70.6; H, 4.2; N, 11.8%). The compound was oxidised⁷ by sodium dichromate in acetic acid to 7-nitrophenanthridone, m. p. and mixed m. p. 325°.

Oxidation of Nitrophenanthridones.—(a) A finely divided suspension of 7-nitrophenanthridone (1 g.; m. p. 326°), prepared by dissolution in concentrated sulphuric acid (5 c.c.) and made alkaline after dilution with water (100 c.c.), was heated (15 min.) with potassium permanganate (6 g.). The filtrate and washings from precipitated manganese dioxide were concentrated, acidified, and extracted with ether first briefly (extract A) and then exhaustively (extract B). Phthalic acid was not detected in extract A. Extract B afforded a solid which when treated with aniline in ethanol gave 4-nitrophthalic acid as the aniline salt, m. p. and mixed m. p. 181—182° (decomp.), also identified by its infrared absorption spectrum. (b) Similar treatment of material (m. p. 282—284°) prepared as described by Moore and Huntress⁹ afforded, from extract A, phthalic acid which was identified as the aniline salt, m. p. and mixed m. p. 159° (decomp.), and by infrared spectrum; while from extract B 4-nitrophthalic acid was again obtained. When the oxidation times in (a) and (b) were extended to 4 hr., extract B afforded only oxalic acid which was identified as the aniline salt, by its m. p. and mixed m. p. 163° (decomp.), and by its infrared spectrum.

2-Nitro-11-*m*-nitrophenyldibenzo[b,f]-1:4-thiazepine.—To a hot suspension of 2-chloro-3':5-dinitrobenzophenone¹¹ (1.9 g.) in ethanol-water (25 c.c.; 4:1) was slowly added a solution prepared from *o*-aminothiophenol hydrochloride (1 g.) and sodium hydroxide (0.5 g.) in the same solvent (15 c.c.). After several hours the thiazepine was obtained as yellow prisms, m. p. 246° (from acetic acid; yield, 76%) (Found: C, 60.7; H, 3.3; N, 11.3. $C_{19}H_{11}O_4N_3S$ requires C, 60.5; H, 2.95; N, 11.1%).

7-Nitro-9-*m*-nitrophenylphenanthridine, m. p. 264° (from benzene—ethanol), was obtained from 2-nitro-11-*m*-nitrophenyldibenzothiazepine as described for the 9-phenyl analogue, in traces by method (a) and in 70% yield by method (b) (Found: C, 66.1; H, 3.05; N, 12.2. Calc. for $C_{19}H_{11}O_4N_3$: C, 66.1; H, 3.2; N, 12.2%). The m. p. was undepressed on admixture with an authentic specimen,¹² and the infrared spectra of the specimens were identical.

2:4-Dinitro-11-phenyldibenzo[b,f]-1:4-thiazepine.—A suspension of 2-chloro-3:5-dinitrobenzophenone (1.9 g.) in ethanol-water (4:1; 25 c.c.) was treated at 0° with a solution prepared from *o*-aminothiophenol hydrochloride (1 g.) and sodium hydroxide (0.5 g.) in the same solvent; a reddish solid was deposited which was adsorbed on alumina from dry benzene and eluted with benzene—light petroleum (b. p. 60—80°) (1:1). This eluate (for a later eluate, see next para.) afforded the thiazepine as yellow prisms (yield 50%), m. p. 200° (from ethanol); λ_{\max} . 233 and 320 μ ($\log \epsilon$ 4.46 and 3.86), shoulder at 265 μ ($\log \epsilon$ 4.29) (Found: C, 60.9; H, 3.15; N, 11.0. $C_{19}H_{11}O_4N_3S$ requires C, 60.5; H, 2.9; N, 11.1%). This thiazepine was either unchanged or, on prolonged treatment, was extensively charred when heated with copper alone or in ethyl phthalate.

1-Benzoyl-3-nitrophenothiazine, bright red needles, m. p. 179° (from ethanol or benzene), was obtained (a) (yield, 20%) by eluting, with benzene containing a little ethanol, the alumina column from which the foregoing thiazepine had been removed; (b) (yield, 58%) as the only product from the interaction of 2-chloro-3:5-dinitrobenzophenone and *o*-aminothiophenol in pyridine as solvent and base (Found: C, 64.8; H, 3.3; N, 8.0. $C_{19}H_{12}O_3N_2S$ requires C, 65.5; H, 3.5; N, 8.0%); λ_{\max} . 242, 301, and 462 μ ($\log \epsilon$ 4.7, 4.45, and 3.21). Oxidation by hydrogen peroxide in acetic acid (1½ hr. at 100°) converted the phenothiazine into the SS-dioxide, m. p. 258° (from acetic acid) (Found: C, 59.85; H, 3.4; N, 7.7. $C_{19}H_{12}O_5N_2S$ requires C, 60.0; H, 3.2; N, 3.4%).

2:4-Dinitrodibenzo[b,f]-1:4-thiazepine.—Powdered toluene-*p*-sulphonyl chloride (0.45 g.) was added to a cooled suspension of 3:5-dinitrosalicylaldehyde (0.5 g.) in pyridine (4 c.c.);

¹⁰ Morgan and Walls, *J.*, 1932, 2225.

¹¹ Loudon, Robertson, and Watson, *J.*, 1950, 55.

¹² Walls, *J.*, 1945, 294.

after 1 hr. the solution was treated with *o*-aminothiophenol hydrochloride (0.38 g.), and after another hour poured into ice-dilute hydrochloric acid. The brown-red solid was chromatographed on alumina (from benzene) yielding, in the first eluate, yellow prisms of the *thiazepine*, m. p. 234° (from chloroform); λ_{\max} . 234 and 317 $m\mu$ ($\log \epsilon$ 4.45 and 3.82) (Found: C, 52.0; H, 2.6; N, 14.2. $C_{13}H_7O_4N_3S$ requires C, 51.8; H, 2.3; N, 13.95%). Attempts to convert this compound into a phenanthridine failed.

2-(2 : 4-Dinitrobenzylideneamino)thiophenol (VII) was obtained as red crystals, m. p. 131° (from ethanol), from 2 : 4-dinitrobenzaldehyde and *o*-aminothiophenol hydrochloride (1 mol. each) at 0° (for 2 hr.) in aqueous ethanol and under nitrogen, both in presence and, better, in absence of sodium hydroxide (Found: C, 51.3; H, 3.4; N, 13.85. $C_{13}H_9O_4N_3S$ requires C, 51.5; H, 3.0; N, 13.9%). λ_{\max} . 318 $m\mu$ ($\log \epsilon$ 3.94). When heated (30 min.) with acetic anhydride it afforded an *acetyl* derivative, as yellow needles, m. p. 141° (from methanol) (Found: C, 52.5; H, 3.2; N, 12.2. $C_{15}H_{11}O_5N_3S$ requires C, 52.5; H, 3.2; N, 12.2%); λ_{\max} . 230 $m\mu$ ($\log \epsilon$ 4.36), shoulders at 255 and 297 $m\mu$ ($\log \epsilon$ 4.35 and 3.84). When the thiol in ethanol was treated dropwise with a solution of iodine in aqueous ethanolic potassium iodide *bis*-[2-(2 : 4-dinitrobenzylideneamino)phenyl] disulphide was precipitated. It had m. p. 201° (from acetic acid) and was identical with a specimen prepared by condensing 2 : 4-dinitrobenzaldehyde with di-*o*-aminophenyl disulphide in aqueous ethanol containing a little concentrated hydrochloric acid (Found: C, 52.1; H, 3.1. $C_{26}H_{16}O_8N_6S_2$ requires C, 51.6; H, 2.7%).

2-(2 : 4-Dinitrophenyl)benzothiazole, m. p. 162° (from ethanol), was prepared (a) by careful admixture of 2 : 4-dinitrobenzoyl chloride with zinc *o*-aminophenyl sulphide (1 mol. each) followed by heating (5 min. at 100°), washing the cooled mixture with *n*-sodium hydroxide, and purifying the residue in ethanol (charcoal); (b) by oxidation of the thiophenol (VII) by ferric chloride in ethanol or by dissolution in pyridine or in ethanolic sodium hydroxide (Found: C, 52.0; H, 2.7; N, 13.7. $C_{13}H_7O_4N_3S$ requires C, 51.3; H, 2.35; N, 13.95%); λ_{\max} . 330 $m\mu$ ($\log \epsilon$ 4.12).

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