STUDIES IN THE CHEMISTRY OF PHENOTHIAZINE

IV. THE PREPARATION OF 2,2′-DINITRODIPHENYLSULPHIDES AND THEIR CONVERSION TO PHENOTHIAZINES

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Summary

The preparation of phenothiazine, and of some substituted phenothiazines from the 2,2′-dinitrodiphenylsulphides, is described.

I. INTRODUCTION

Certain substituted phenothiazines can only be made conveniently and unambiguously, by means of the Smiles rearrangement of the appropriate diphenylsulphides. The sulphides are prepared from the *o*-aminobenzenethiols and the *o*-halonitrobenzenes. Substituted *o*-aminobenzenethiols are difficult to prepare, and their syntheses involve lengthy processes affording only small yields. In this Laboratory it has been shown that, in certain cases, phenothiazines can be prepared from 2,2′-dinitrodiphenylsulphides by a selective reduction of a nitro group in the presence of alkali. Phenothiazines can also be obtained, in low yields, by the direct action of sodium sulphide on *o*-halonitrobenzenes, in a high boiling solvent. A Smiles rearrangement and ring closure takes place in these methods without the necessity of isolating and acetylating the amine intermediate.

II. DIPHENYLSULPHIDES

The dinitrodiphenylsulphides were prepared either by the action of sodium sulphide on the *o*-halonitrobenzenes, or by the condensation of the sodium salt of the *o*-nitrobenzenethiol with the *o*-halonitrobenzenes. No sulphide was obtained when 2,4-dichloronitrobenzene or 4-chloro-3-nitrotoluene (Hodgson and Ward 1948) reacted with sodium sulphide. 2,3-Dichloronitrobenzene gave negligible quantities of a sulphide which contained some amino compound. However, when 2,3-dichloronitrobenzene reacted with sodium sulphide in diethylene glycol instead of ethanol as the solvent, the product obtained appeared to be a sulphide which contained only one chlorine atom.

III. PHENOTHIAZINES

Phenothiazine was formed when 2,2′-dinitrodiphenylsulphide was treated with hydrazine hydrate in the presence of sodium hydroxide. Similarly, 4,4′-dichloro-2,2′-dinitrodiphenylsulphide gave 2,7-dichlorophenothiazine (Farrington and Warburton 1955), which indicated that a Smiles rearrangement

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had taken place. Sodium acetate can replace the sodium hydroxide and ethanol or diethylene glycol is a suitable solvent. It was also found that 2,7-dichlorophenothiazine could be prepared by the action of sodium sulphide on the dinitrodiphenylsulphide, if diethylene glycol was used as the reaction solvent. The best yields of phenothiazines were obtained from symmetrically substituted sulphides.

The direct action of sodium sulphide on some *o*-halonitrobenzenes in diethylene glycol gave low yields of phenothiazines. This method was useful for preparing 2,7-dimethylphenothiazine which could not be prepared by other means. Phenothiazine itself could not be obtained by this method although 2,7-dichlorophenothiazine and 2,7-dibromophenothiazine were prepared.

IV. Experimental

Analyses are by Dr. K. W. Zimmermann, C.S.I.R.O. Microanalytical Laboratory.

(*a*) *2,2′-Dinitrodiphenylsulphide.*—A solution of hydrated sodium sulphide (15 g) in water (10 ml) was added to a refluxing solution of *o*-chloronitrobenzene (20 g) in 95% ethanol (50 ml). After refluxing for 6 hr the unreacted *o*-chloronitrobenzene (13·8 g) was recovered by steam distillation. The residue was recrystallized from ethyl acetate–ethanol to give yellow needles (2·7 g, 50%), m.p. 122 °C; Hodgson and Ward (1948) report m.p. 122 °C (Found: C, 52·5; H, 3·1; O, 23·1; N, 9·8%. Calc. for $C_{12}H_8O_4N_2S$: C, 52·2; H, 2·9; O, 23·2; N, 10·1%).

(*b*) *Phenothiazine.*—Sodium hydroxide (0·8 g) and 2,2′-dinitrodiphenylsulphide (2 g) were dissolved with heating in diethylene glycol (15 ml). To the refluxing solution was added hydrazine hydrate (0·4 g), and 30 min later more hydrazine hydrate (0·8 g) was added to the mixture. After a further hour, the reaction mixture was poured into a saturated salt solution and left in the refrigerator for some hours. The fawn coloured precipitate, after purification by passage of its benzene solution through an alumina column and recrystallization from ethanol (charcoal) gave yellow plates (0·5 g, 35%), m.p. and mixed m.p. with phenothiazine 185 °C (Found: C, 72·3; H, 4·9; N, 7·1%. Calc. for $C_{12}H_9NS$: C, 72·3; H, 4·6; N, 7·0%).

(*c*) *4-Chloro-2,2′-dinitrodiphenylsulphide.*—The reaction of *o*-nitrobenzenethiol (2·3 g) with sodium hydroxide and 2,5-dichloronitrobenzene (3·1 g) gave yellow needles (2·2 g, 48%), m.p. 139 °C, from acetic acid (Found: C, 46·6; H, 2·5; N, 8·6; Cl, 11·1%. Calc. for $C_{12}H_7O_4N_2SCl$: C, 46·4; H, 2·3; N, 9·0; Cl, 11·4%). The action of a large excess of hydrazine hydrate in the presence of alkali on the above compound gave a low yield of straw coloured needles, m.p. 196 °C, from benzene–light petroleum. Qualitative tests indicated the presence of a phenothiazine (Found: N, 5·7%. Calc. for $C_{12}H_8NSCl$: N, 6·0%).

(*d*) *6-Chloro-2,2′-dinitrodiphenylsulphide.*—The reaction of *o*-nitrobenzenethiol (3·0 g) with sodium hydroxide and 2,3-dichloronitrobenzene (4·0 g) gave lemon needles (4·3 g, 72%), m.p. 172 °C, from ethanol–acetone (Found: C, 46·4; H, 2·3; N, 8·6%. Calc. for $C_{12}H_7O_4N_2SCl$: C, 46·4; H, 2·3; N, 9·0%). When the compound was treated as in (*b*) the presence of a phenothiazine was confirmed by qualitative tests, but the yield was too low for isolation and identification.

(*e*) *4,4′-Dichloro-2,2′-dinitrodiphenylsulphide.*—When 2,5-dichloronitrobenzene (24 g) was treated as in (*a*), unreacted starting material (7·7 g) was recovered by steam distillation. The residue gave yellow needles (8·9 g, 61%), m.p. 149–150 °C, from acetic acid; Beilstein and Kurbatow (1879) report m.p. 149–150 °C (Found: C, 42·1; H, 2·1; Cl, 20·7%. Calc. for $C_{12}H_6O_4N_2SCl_2$: C, 41·8; H, 1·7; Cl, 20·6%).

(*f*) *2,7-Dichlorophenothiazine.*—(i) The reaction described in (*b*) was carried out on 4,4′-dichloro-2,2′-dinitrodiphenylsulphide (2 g) to give colourless plates (0·8 g, 52%) from benzene–light petroleum, m.p. 216 °C, undepressed by authentic 2,7-dichlorophenothiazine for which Farrington and Warburton (1955) report m.p. 216–217 °C (Found: C, 54·0; H, 2·8; N, 5·1%. Calc. for $C_{12}H_7NSCl_2$: C, 53·7; H, 2·6; N, 5·2%).

(ii) When 4,4′-dichloro-2,2′-dinitrodiphenylsulphide (3 g) and crystalline sodium sulphide (12 g) were reacted in diethylene glycol for 2 hr, a fawn coloured precipitate was collected after pouring the reaction mixture into water. After chromatography and recrystallization from benzene–light petroleum the product (0·6 g, 24%) was obtained as colourless plates, m.p. and mixed m.p. 216 °C.

(iii) A solution of anhydrous sodium sulphide (12·5 g) and 2,5-dichloronitrobenzene (10 g) in diethylene glycol (20 ml) was refluxed for 4 hr and then poured into water. The product (0·25 g), purified as above, had m.p. and mixed m.p. 216 °C.

(*g*) *4,5′-Dichloro-2,2′-dinitrodiphenylsulphide.*—The reaction of 4-chloro-2-nitrobenzenethiol (1·9 g) and sodium hydroxide with 2,4-dichloronitrobenzene (2·2 g) gave yellow clustered needles (1·2 g, 35%) from acetic acid, m.p. 184 °C (Found: C, 42·1; H, 1·9; N, 8·0%. Calc. for $C_{12}H_6O_4N_2SCl_2$: C, 41·8; H, 1·7; N, 8·1%). When this compound was treated as in (*b*), the presence of a phenothiazine was detected by qualitative tests, but the yield was so low that the compound was not isolated.

(*h*) *4,6′-Dichloro-2,2′-dinitrodiphenylsulphide.*—The reaction of 4-chloro-2-nitrobenzenethiol (8 g) and sodium hydroxide with 2,3-dichloronitrobenzene (9·3 g) gave yellow needles (7·1 g, 49%) from acetic acid, m.p. 132 °C (Found: C, 41·9; H, 1·9; N, 8·0%. Calc. for $C_{12}H_6O_4N_2SCl_2$: C, 41·8; H, 1·7; N, 8·1%). When the compound was treated as in (*b*), qualitative tests indicated the presence of a phenothiazine in very poor yield.

(*i*) *4,4′-Dibromo-2,2′-dinitrodiphenylsulphide.*—When 2,5-dibromonitrobenzene was treated as in (*a*), yellow needles formed in the reaction mixture almost immediately. After refluxing for 3 hr the compound was collected and recrystallized from acetone-ethanol to give yellow needles (59%), m.p. 165 °C; Blanksma (1901) gives m.p. 165 °C (Found: C, 33·2; H, 1·7; N, 6·3%. Calc. for $C_{12}H_6O_4N_2SBr_2$: C, 33·2; H, 1·4; N, 6·5%).

(*j*) *2,7-Dibromophenothiazine.*—(i) The action of hydrazine hydrate and alkali on 4,4′-dibromo-2,2′-dinitrodiphenylsulphide as in (*b*) did not give a phenothiazine. However, treatment of the compound (2 g) with a large excess of hydrazine hydrate (6 ml), gave a product (10%) which crystallized from benzene–light petroleum as fawn needles, m.p. 213·5 °C (decomp.) (Found: C, 40·6; H, 2·1; N, 3·9%. Calc. for $C_{12}H_7NSBr_2$: C, 40·3; H, 2·0; N, 3·9%).

(ii) 2,5-Dibromonitrobenzene (10 g) when treated as in (*f*) (iii) gave a poor yield of fawn needles, m.p. and mixed m.p. 213 °C (decomp.).

(*k*) *2,2′, 4,4′-Tetranitrodiphenylsulphide.*—When 1-chloro-2,4-dinitrobenzene was treated as in (*a*), a vigorous reaction took place. The product was obtained in high yield (84%) as fawn coloured plates, m.p. 196 °C, from acetic acid (Found: C, 39·3; H, 1·9; N, 15·0%. Calc. for $C_{12}H_6O_8N_4S$: C, 39·3; H, 1·6; N, 15·3%). No phenothiazine was obtained when the compound was treated with hydrazine as in (*b*).

(*l*) *2,7-Dimethylphenothiazine.*—The reaction of 4-chloro-3-nitrotoluene (10 g) with sodium sulphide as in (*f*) (iii) gave cream plates (0·17 g), m.p. 213 °C, from benzene–light petroleum (Found: C, 74·3; H, 5·7; N, 5·8; S, 13·9%. Calc. for $C_{14}H_{13}NS$: C, 74·0; H, 5·7; N, 6·2; S, 14·1%).

(*m*) *Reaction of 2,3-Dichloronitrobenzene with Sodium Sulphide in Diethylene Glycol.*—When 2,3-dichloronitrobenzene (10 g) was treated with a large excess of hydrated sodium sulphide (12 g) as in (*f*) (iii), the product (0·7 g) was obtained as dark purple needles, m.p. 202 °C, after recrystallization from aqueous acetic acid (Found: C, 52·0; H, 2·5; N, 9·5; O, 11·7; S, 11·3; Cl, 13·3%. Calc. for $C_{12}H_7O_2N_2SCl$: C, 51·7; H, 2·5; N, 10·1; O, 11·5; S, 11·5; Cl, 12·8%). The molecular weight could not be determined by the Rast method because of the dark colour of the camphor solution.

V. References

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