STUDIES IN THE CHEMISTRY OF PHENOTHIAZINE*

III. ATTEMPTS TO PREPARE SOME PENTACYCLIC COMPOUNDS

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In a search for compounds related to phenothiazine which might have greater anthelmintic activity than the parent compound, or which might give information about its mode of action *in vivo*, we have attempted the synthesis of 5,7-dithia-12,14-diazapentacene (I) and 5,12-dithia-7,14-diazapentacene (II). Preliminary results were discouraging because of the small yields of several of the intermediates, and because the two related compounds which were tested, the 6,13-quinol and the quinone derived from II (Fries, Pense, and Peters 1928) were found to be inactive against oxyurids in mice. This work has been discontinued, and we now report some experiments directed towards building up a second thiazine ring.

In Part II of this series (Farrington and Warburton 1956) it was shown that 1,3-dichloro-4,6-dinitrobenzene condensed readily with the sodium salt of 2-amino-4-chlorobenzenethiol to give 4,6-di-(2-amino-4-chlorobenzenethio)-1,3-dinitrobenzene (III). This compound suggested a route to compounds of class I, for a double Smiles rearrangement of the diacetyl derivative of III would give the 2,10-dichloro-derivative of I. Acetylation, rearrangement, and ring closure of III to give 2-(2-acetamido-4-chlorobenzenethio)-3-nitro-8-chlorophenothiazine (IV) was readily carried out, but a second rearrangement could not be induced by the action of alkali or sodium alkoxides in various ethanolic solvents, even in sealed vessels at temperatures of up to 150 °C.

The diacetyl derivative of III was difficult to purify and benzoylation was more satisfactory, but, similarly, the dibenzoyl derivative could not be made to undergo a second rearrangement, although the first rearrangement and ring closure proceeded well. The failure of IV to undergo Smiles rearrangement recalls that of 2-acetamido-4,3′-dichloro-2′-nitrodiphenyl sulphide (Farrington and Warburton 1956), and may be due to the same cause. On the other hand, it may be due to the presence of a nitro-group *para* to the imino-group, and, therefore, oxidizable readily to a quinone imine type of compound.

Attempts to prepare I itself from both the diacetyl and dibenzoyl derivative of 4,6-di-(2-aminobenzenethio)-1,3-dinitrobenzene gave similar results, and the second acetyl or benzoyl group resisted alcoholysis. For that reason, and because of the position of the ultraviolet absorption maxima, we have assigned the acetyl or benzoyl group to the exocyclic nitrogen atom.

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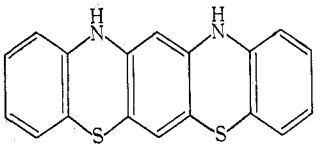
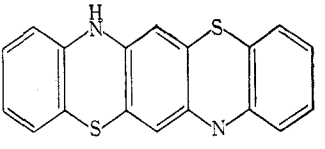
The preparation of II was attempted by fusing *NN'*-diphenyl-*p*-phenylenediamine with four equivalents of sulphur. The second ring closure could of course occur so as to give an angular isomer of II. However, after a long fractional sublimation *in vacuo*, only a small amount of a compound analysing correctly for II was obtained and no attempt to confirm that it had the linear structure was made. Chromatography of the more soluble fraction of the reaction mixture did not show any of the expected intermediate 3-anilidophenothiazine (V), even when only two equivalents of sulphur were used.



(I)



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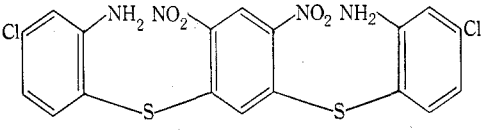
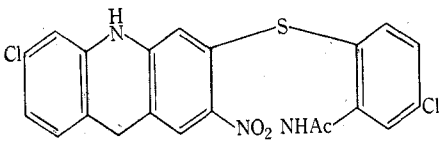
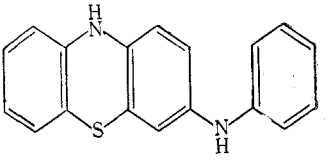


(III)



(IV)



(V)

It was thought that an alternate route to II or its isomer might lie in a sulphur fusion of V. However, 3-anilidophenothiazine could not be obtained by heating 3-aminophenothiazine (Bernthsen 1887) with bromobenzene in nitrobenzene or decalin in the presence of potassium bicarbonate and copper powder. A reaction carried out under similar conditions with 3-iodophenothiazine (Cymerman-Craig, Rogers, and Warwick 1955) and aniline gave only a very small quantity of an unrecognizable product.

Experimental

Melting points are corrected. Analyses are by Dr. K. W. Zimmermann, C.S.I.R.O. Microanalytical Laboratory at the University of Melbourne.

(*a*) *4,6-Di-(2-acetamido-4-chlorobenzenethio)-1,3-dinitrobenzene* (*III*).—Acetylation of the corresponding diamine with acetic anhydride in acetic acid gave yellow *plates*, m.p. 121 °C (decomp.) from aqueous alcohol in 30% yield (Found: C, 46·9; H, 2·9; N, 9·6%. Calc. for $C_{22}H_{16}O_6N_4S_2Cl_2$: C, 46·5; H, 2·8; N, 9·9%). The corresponding dibenzoyl derivative was prepared in 60% yield by the action of benzoyl chloride on the amine in pyridine. It crystallized from acetone in clusters of yellow needles, m.p. 213 °C (Found: C, 55·5; H, 3·2; N, 8·3%. Calc. for $C_{32}H_{20}O_6N_4S_2Cl_2$: C, 55·6; H, 2·9; N, 8·1%).

(*b*) *2-(2-Acetamido-4-chlorobenzenethio)-3-nitro-8-chlorophenothiazine* (*IV*). — The preceding acetyl derivative (160 mg) in anhydrous acetone (2 ml) was treated on the water-bath with five successive equivalents of sodium hydroxide in ethanol at intervals of ½ hr. The solution was refluxed for another ½ hr and after removal of most of the acetone poured into water. Several recrystallizations from ethanol gave dark red *needles* (30 mg), m.p. 271 °C (decomp.) (Found: C, 49·9; H, 2·9; N, 8·8; Cl, 15·1%. Calc. for $C_{20}H_{13}O_3N_3S_2Cl_2$: C, 50·0; H, 2·7; N, 8·8; Cl, 14·9%), $\lambda_{max.}$ 260 mμ.

(*c*) *2-(2-Benzamido-4-chlorobenzenethio)-3-nitro-8-chlorophenothiazine.*—The benzoyl derivative described in (*a*) (320 mg), when treated as described in (*b*), gave dark red needles (50 mg) (from benzene and light petroleum), m.p. 238 °C (decomp.) (Found: N, 7·9%. Calc. for $C_{25}H_{15}O_3N_3S_2Cl_2$: N, 7·8%), $\lambda_{max.}$ 231 and 259 mμ.

(*d*) *4,6-Di-(2-aminobenzenethio)-1,3-dinitrobenzene.*—A solution of *o*-aminobenzenethiol (10·6 g) and sodium hydroxide (3·4 g) in dry ethanol (40 ml) was carefully added to a warm solution of 1,3-dichloro-4,6-dinitrobenzene (10·8 g) in ethanol (40 ml) and the mixture finally refluxed for 1 hr. After cooling, the dark yellow *plates*, m.p. 252 °C (decomp.), were collected (15·4 g) and washed with ethanol and water, unchanged by recrystallization from benzene (Found: C, 52·1; H, 3·4; N, 13·5%. Calc. for $C_{18}H_{14}O_4N_4S_2$: C, 52·2; H, 3·4; N, 13·5%). *Diacetyl* derivative, yellow needles (from acetone and ethanol), m.p. 213 °C (Found: C, 53·5; H, 3·9%. Calc. for $C_{22}H_{18}O_6N_4S_2$: C, 53·0; H, 3·6%). *Dibenzoyl derivative* yellow plates (from toluene), m.p. 225 °C (Found: C, 62·1; H, 3·8%. Calc. for $C_{32}H_{22}O_6N_4S_2$: C, 61·7; H, 3·5%). No absorption between 230 and 265 mμ.

(*e*) *2-(2-Benzamidobenzenethio)-3-nitrophenothiazine.*—Smiles rearrangement of the preceding benzoyl compound as in (*b*), followed by adsorption on magnesium oxide from benzene and elution with acetone gave orange *plates* (from benzene in 10% yield), m.p. 264 °C (decomp.) (Found: C, 64·3; H, 3·7; O, 10·5; S, 13·6%. Calc. for $C_{25}H_{17}O_3N_3S_2$: C, 63·6; H, 3·6; O, 10·2; S, 13·6%), $\lambda_{max.}$ 260 mμ.

(*f*) *2-(2-Acetamidobenzenethio)-3-nitrophenothiazine.*—Smiles rearrangement of the acetyl derivative described in (*d*) as in the preceding paragraph gave a small yield of dark red *plates* (from ethanol), m.p. 174 °C (decomp.) (Found: C, 59·3; H, 3·8%. Calc. for $C_{18}H_{13}O_2N_3S_2$: C, 59·0; H, 3·6%), $\lambda_{max.}$ 260 mμ.

(*g*) *5,12-Dithia-7,14-diazapentacene* (*II ?*).—*NN'*-Diphenyl-*p*-phenylenediamine (Calm 1883) (2·0 g) was heated at 170–190 °C with sulphur (0·99 g) and iodine (0·1 g) for 1 hr. The product was extracted with hot benzene, which dissolved only a small amount of material. The dry residue (2·4 g) was dark and of high m.p. Fractional sublimination of 0·4 g of the residue at 0·01 mm gave a light coloured fraction (27 mg) which sublimed between 230 and 280 °C, followed by a yellow-brown fraction between 310 and 330 °C. Resublimation of this fraction gave yellow plates (46 mg), m.p. 360 °C (Found: C, 66·8; H, 3·9%. Calc. for $C_{18}H_{12}N_2S_2$: C, 67·5; H, 3·8%).

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