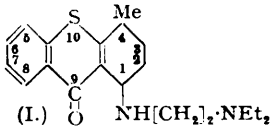
162. *Xanthones and Thioxanthones. Part I. The Synthesis of 2- and 3-Dialkylaminoalkylamino-derivatives.*

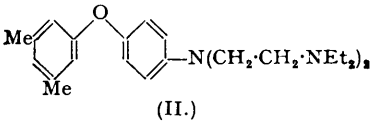
By FREDERICK G. MANN and J. HEDLEY TURNBULL.

A number of 2- and 3-dialkylaminoalkylamino-xanthones and -thioxanthones, with and without other nuclear substituents, have been synthesised and their value as possible drugs for the treatment of schistosomiasis and amœbiasis has been assayed. Although several showed amœbicidal activity *in vitro*, none showed significant activity towards schistosomiasis infections in mice.

A CONSIDERABLE number of xanthones and thioxanthones having the diethylaminoethylamino-group in the 1 or the 4 position have been prepared by Mauss (*Chem. Ber.*, 1948, **81**, 19) and tested as possible drugs for treatment of schistosomiasis. The most effective of these compounds is 1-2′-diethylaminoethylamino-4-methylthioxanthone (I), known as " Miracil-D."

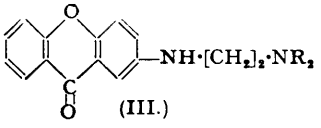


(I.)

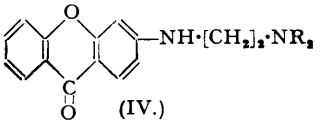


(II.)

In the diphenyl ether series, however, it is known that *p*-di-(2-diethylaminoethyl)aminophenyl *m*-5-xylyl ether (II), known as Gavano base, has considerable activity against amœbiasis.



(III.)

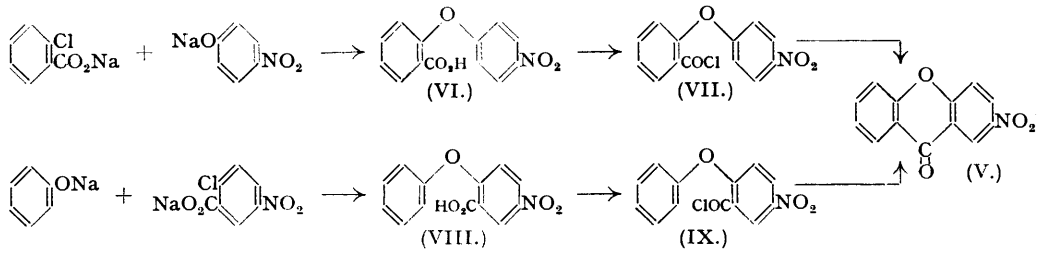


(IV.)

In general, type (I) and (II) are clearly not widely dissimilar, and we have therefore investigated in particular the synthesis of various xanthones and thioxanthones having basic

side chains in the 2 or the 3 position, in view of the fact that Mauss's work was limited to the more readily accessible derivatives having these groups in the 1 or the 4 position.

The synthesis of 2-(2-dialkylaminoethylamino)xanthones (III) and of the 3-substituted analogues (IV) involved in each case the preparation of the corresponding 2- and 3-nitroxanthones. 2-Nitroxanthone (V) was initially prepared by a modification of Dhar's method (*J.*, 1920, **117**, 1057), sodium *o*-chlorobenzoate and sodium *p*-nitrophenoxide condensing to



give *o*-carboxyphenyl *p*-nitrophenyl ether (VI), which was then converted into the chloride (VII); the latter on treatment with aluminium chloride underwent cyclisation to (V). In a second method, which afforded larger yields, sodium phenoxide and sodium 2-chloro-5-nitrobenzoate were condensed to give 2-carboxy-4-nitrophenyl phenyl ether (VIII), which was similarly converted into the chloride (IX) and then cyclised to (V). The use of the sodium derivatives of *p*-chlorophenol and of *m*-5-xylenol in this second method similarly gave 7-chloro-2-nitroxanthone and 6 : 8-dimethyl-2-nitroxanthone.

When this method was similarly applied to the condensation of sodium phenoxide and sodium 2-chloro-4-nitrobenzoate 3-nitroxanthone (Ullmann and Wagner, *Annalen*, 1907, **355**, 362) was obtained.

The nitroxanthones were then reduced to the aminoxanthones by stannous chloride, which left the carbonyl group unchanged. The aminoxanthones were crystalline, feebly basic compounds, and their hydrochlorides were readily hydrolysed by water. The 2-aminoxanthones were yellow and the 3-aminoxanthones colourless; both series dissolved in sulphuric acid to give a blue fluorescence (cf. Purgotti, *Gazzetta*, 1914, **44**, 644; Ullmann and Wagner, *loc. cit.*).

The aminoxanthones readily condensed with 2-diethylaminoethyl chloride to give the corresponding diethylaminoethylaminoxanthones (III and IV). In the case of 2-amino-7-chloroxanthone the corresponding 7-chloro-2-(2-di-*n*-butylaminoethylamino)xanthone was similarly prepared in order to determine the therapeutic effect of increasing the carbon chain of the terminal alkyl groups.

The substituted xanthones thus obtained are listed, with their melting points, in Table I. The 2-dialkylaminoalkylamino-derivatives were yellow crystalline solids, whereas the 3-substituted analogues were colourless. Certain physical and chemical properties were clearly parallel to those of the corresponding thioxanthones which are discussed in greater detail later.

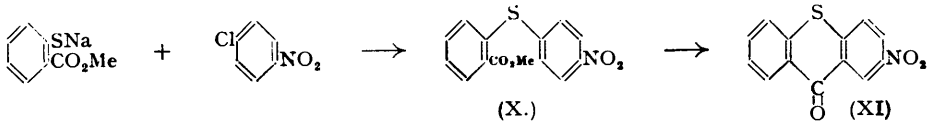
TABLE I.

Xanthone.	M. p.	Xanthone.	M. p.
2-Nitro-	203—204°	3-Amino-	228—230°
7-Chloro-2-nitro-	254—255	(i) 2-(2-Diethylaminoethylamino)-	79—81
6 : 8-Dimethyl-2-nitro-	222—223	(ii) 7-Chloro-2-(2-diethylaminoethylamino)-	124—126
3-Nitro-	173—175	(iii) 7-Chloro-2-(2-di-*n*-butylaminoethylamino)-	105—106
2-Amino-	210—212	(iv) 2-(2-Diethylaminoethylamino)-6 : 8-dimethyl-	85—87
2-Amino-7-chloro-	231—232	3-(2-Diethylaminoethylamino)-	87—89
2-Amino-6 : 8-dimethyl-	209—210		

In addition to the above compounds, it was clearly desirable to investigate another series carrying the di-(2-diethylaminoethyl)amino-side-chain present in (II). All attempts to condense 2-iodoxanthone with di-(2-diethylaminoethyl)amine, failed, however, and further work on these lines has been postponed.

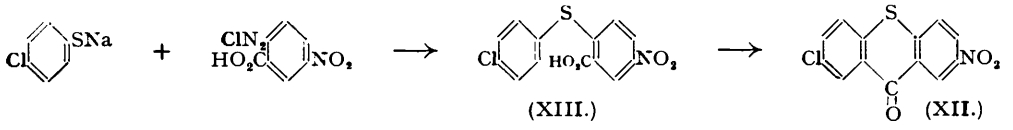
In the thioxanthone series, the most important intermediate compounds were again the 2-nitro- and the 3-nitro-derivatives. For the synthesis of the former, the sodium derivative of methyl *o*-mercaptobenzoate was condensed with *p*-chloronitrobenzene giving *o*-carbomethoxyphenyl *p*-nitrophenyl sulphide (X). This ester was then hydrolysed and converted into the carboxychloride, and the latter cyclised with aluminium chloride to the 2-nitrothioxanthone (XI) (cf. Mayer, *Ber.*, 1909, **42**, 3046). This method was also used for the prepar-

ation of 7-methyl-, 6 : 8-dimethyl-, and 7-chloro-2-nitrothioxanthone (XII), although the last of these compounds was obtained only in low yield.



(X.) (XI)

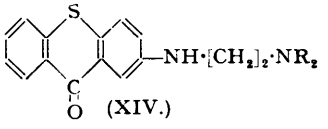
For the preparation of the 7-chloro-compound (XII) in reasonable yield however, a second (but similar) synthesis was employed. Sodium *p*-chlorothiophenoxide was brought into reaction with diazotised 5-nitroanthranilic acid whereby 2-carboxy-4-nitrophenyl *p*-chlorophenyl sulphide (XIII) was obtained, and then by the usual stages converted into (XII).



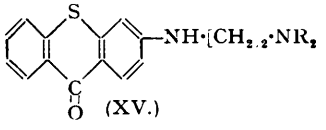
(XIII.) (XII.)

The latter synthesis, diazotised 4-nitroanthranilic acid being used however, was employed to prepare 3-nitrothioxanthone (Mayer, *loc. cit.*) and also, by the use of the appropriately substituted thiophenols, to prepare 7-chloro-3-nitro- and 7-methyl-3-nitro-thioxanthone.

The nitrothioxanthones were reduced as before by stannous chloride to the aminothioxanthones. It is noteworthy that the 2-amino-compounds were orange and the 3-amino-analogues pale yellow. Both series dissolved in sulphuric acid to give a green fluorescence. In both the xanthone and the thioxanthone series, therefore, the 2-amino-derivatives were darker than the 3-amino-analogues.



(XIV.)



(XV.)

Condensation of these amino-derivatives with 2-diethylaminoethyl chloride as before gave the 2- and 3-diethylaminoethylaminothioxanthones (XIV and XV; R = Et). As in the xanthone series, the 7-chloro-2-(2-di-*n*-butylaminoethylamino)-compound was also prepared. The compounds thus obtained, and the intermediate compounds required, are listed in Table II.

TABLE II.

Thioxanthone.	M. p.	Thioxanthone.	M. p.
2-Nitro-	224—225°	3-Amino-	252—254[c]
7-Chloro-2-nitro-	271—272	3-Amino-7-chloro-	278—279
7-Methyl-2-nitro-	257—260	3-Amino-7-methyl-	234—236
6 : 8-Dimethyl-2-nitro-	225—226	(v) 2-(2-Diethylaminoethylamino)-	52—53
3-Nitro-	252	(vi) 7-Chloro-2-(2-diethylaminoethylamino)-	128—129
7-Chloro-3-nitro-	322—323	(vii) 7-Chloro-2-(2-di-*n*-butylaminoethylamino)-	104—105
7-Methyl-3-nitro-	274—275	(viii) 2-(2-Diethylaminoethylamino)-7-methyl-	73—75
2-Amino-	227—228	(ix) 3-(2-Diethylaminoethylamino)-	91—92
2-Amino-7-chloro-	228—230	(x) 7-Chloro-3-(2-diethylaminoethylamino)-	112—113
2-Amino-7-methyl-	194—195	(xi) 3-(2-Diethylaminoethylamino)-7-methyl-	81—83

Certain properties of the final products merit brief discussion. The orange-red 2-dialkylaminoethylamino-compounds (XIV) readily formed stable dihydrochlorides, whereas the pale-yellow 3-substituted isomers (XV) formed poorly crystalline dihydrochlorides which readily dissociated to the monohydrochlorides in the presence of water; both series of compounds formed highly crystalline mono-3 : 5-dinitrobenzoates, which were excellent for characterisation. Furthermore, both series, when treated with a solution of zinc chloride in hydrochloric acid, readily gave crystalline chlorozincates, $C_6H_4\langle^{S}_{CO}\rangle C_6H_3\cdot NH[CH_2]_2\cdot NEt_2,H_2ZnCl_4$. These chlorozincates in the 2-substituted series formed white needles which crystallised unchanged from hydrochloric acid, but dissolved in water to give orange-yellow solutions. In the 3-substituted series, however, the chlorozincates formed brilliant orange plates, which were

easily hydrolysed even in dilute hydrochloric acid solution but dissolved in water to colourless solutions. The colours of the chlorozincates of the two series are thus the reverse of those of the monoamino-compounds and of the diamino-compounds (XIV and XV), in which the 2-substituted members are darker than the 3-substituted analogues.

The activity of compounds (i)—(iv) in Table I and of compounds (v)—(xi) in Table II, in the form of their water-soluble hydrochlorides or acetates, has been tested towards schistosomiasis by Dr. O. D. Standen at the Wellcome Research Institution and, with the exception of (ii), (iii), and (vii), towards amœbiasis by Dr. J. D. Fulton at the National Institute for Medical Research. The compounds proved inactive towards *Schistosoma mansoni* infections in mice, but all those tested showed amœbicidal activity *in vitro*. Compound (vi) was most promising as an amœbicidal agent, and was lethal to *E. histolytica* in dilutions of 1 : 100,000; this can be compared with Gavano base (II) which under comparable conditions was lethal at a dilution of 1 : 1,000,000. It is noteworthy that the compounds (i), (v), (vi), (ix), (x), and (xi) had antibacterial properties.

Experimental.

2-*Nitroxanthone* (V). *Method* 1.—o-*Carbomethoxyphenyl* p-*nitrophenyl ether*. *p*-Nitrophenol (42 g.) was dissolved in methanol (50 c.c.), mixed with a solution of sodium (7 g.) in methanol (100 c.c.), and *o*-chlorobenzoic acid (47 g.) added. The methanol was slowly distilled off on a steam-bath and the temperature raised to 160—165° for 1 hour. After a further hour at 160—165° the product was dissolved in methanol (250 c.c.), boiled under reflux for 3 hours in a stream of dry hydrogen chloride, and poured on ice, and the oil extracted with ether. The extracts were shaken with excess of ice-cold dilute sodium hydroxide solution, filtered, washed free from sodium *p*-nitrophenoxide, and then steam-distilled. The residual oily product crystallised on cooling, to give the *methyl* ester, which separated from methanol in large crystals (13 g.), m. p. 76—78° (Found : C, 61·9; H, 4·3; N, 5·1. $C_{14}H_{11}O_5N$ requires C, 61·5; H, 4·05; N, 5·15%).

o-*Carboxyphenyl* p-*nitrophenyl ether* (VI). The foregoing ester (0·6 g.) was hydrolysed by heating it under reflux with N-potassium hydroxide (10 c.c.) for 2 hours. The *carboxylic acid* separated from benzene in clusters of crystals (0·5 g.), m. p. 153—155° (Found : C, 60·3; H, 3·7; N, 5·2. $C_{13}H_9O_5N$ requires C, 60·2; H, 3·5; N, 5·4%).

The xanthone. A mixture of the acid (13 g.), benzene (130 c.c.), and thionyl chloride (13 c.c.) was heated on the water-bath for 2 hours. The benzene was removed, the residue dissolved in nitrobenzene (130 c.c.), and the solution cooled to 0° and dropped into a mixture of aluminium chloride (13 g.) and nitrobenzene (130 c.c.) with ice-cooling. The mixture was set aside overnight at 0°, ice was then added, and excess of nitrobenzene removed by steam-distillation. The residual solution was cooled, and the xanthone (9·7 g.), m. p. 200—202°, collected and recrystallised from glacial acetic acid, giving white crystals. m. p. 203—204° (Found : C, 64·8; H, 3·0; N, 5·8. Calc. for $C_{13}H_7O_4N$: C, 64·7; H, 2·95; N, 5·8%). Dhar (*loc. cit.*) records m. p. 200°.

2-*Nitroxanthone* (V). *Method* 2.—2-*Chloro*-5-*nitrobenzoic acid*. This was prepared by the nitration of *o*-chlorobenzoic acid (20 g.) (Rupe, *Ber.*, 1897, **30**, 1099), and after recrystallisation from water was obtained as glistening plates (14 g.), m. p. 161—163°.

2-*Carbomethoxy*-4-*nitrophenyl phenyl ether*. 2-Chloro-5-nitrobenzoic acid (17 g.) was added to a solution of sodium (3·9 g.) in methanol (80 c.c.), and the semi-solid product mixed with phenol (31·6 g.). The bulk of the methanol was distilled off and the temperature of the residue then raised to 175—189° during 30 minutes with occasional stirring; the mass melted and effervesced. As soon as the reaction had subsided, the product was steam-distilled to remove excess of phenol, and the residual solution acidified with hydrochloric acid. The precipitate was collected, dried (21·5 g.), dissolved in methanol (200 c.c.), heated under reflux in a stream of dry hydrogen chloride for 2 hours, and then poured on ice, whereupon the *ester* slowly crystallised; it (18·5 g.) had m. p. 80—82°, and recrystallised from methanol as white needles, m. p. 82° (Found : C, 61·8; H, 3·9; N, 5·0. $C_{14}H_{11}O_5N$ requires C, 61·5; H, 4·1; N, 5·1%).

2-*Carboxy*-4-*nitrophenyl phenyl ether* (VIII). This *acid* was prepared by heating the ester (17 g.) with N-potassium hydroxide solution (300 c.c.) under reflux, and was ultimately crystallised from ethanol–water (1 : 1 by volume), forming minute white needles (14 g.), m. p. 166—168° (Found : C, 60·3; H, 3·4; N, 5·2. $C_{13}H_9O_5N$ requires C, 60·2; H, 3·5; N, 5·4%).

The xanthone. The acid (13 g.), suspended in benzene (130 c.c.), was warmed on the water-bath with thionyl chloride (13 c.c.) for 4 hours. The solution was evaporated to dryness in a vacuum, and the residue dissolved in nitrobenzene (130 c.c.) and treated with aluminium chloride (13 g.) in the usual way, to give the nitroxanthone, m. p. 200—202°, (9·7 g.), which crystallised from glacial acetic acid in white crystals, m. p. 203°, identical with the material prepared by the first method.

7-*Chloro*-2-*nitroxanthone*.—2-*Carbomethoxy*-4-*nitrophenyl* p-*chlorophenyl ether*. 2-Chloro-5-nitrobenzoic acid (4·0 g.) was mixed with a solution of sodium (0·92 g.) in methanol (20 c.c.), and *p*-chlorophenol (10·3 g.) added. The condensation, carried out in the usual way, gave the crude acid, m. p. 160—175° (5·6 g.), which was converted into the *methyl* ester (5·0 g.), m. p. 160—162°. This ester was recrystallised from methanol, giving long white needles, m. p. 162° (Found : C, 54·6; H, 3·0; N, 4·7. $C_{14}H_{10}O_5NCl$ requires C, 54·6; H, 3·25; N, 4·55%).

2-*Carboxy*-4-*nitrophenyl* p-*chlorophenyl ether*. This acid was prepared by heating the ester (4·5 g.) under reflux with N-potassium hydroxide (100 c.c.) for 30 minutes, and was obtained as a solid (4·1 g.),

m. p. 177—179°, which separated from benzene as white crystals of the *ether*, m. p. 180—181° (Found : C, 52·9; H, 3·0; N, 5·1. $C_{13}H_8O_5NCl$ requires C, 53·2; H, 2·75; N, 4·8%).

The xanthone. The acid (3·6 g.), benzene (36 c.c.), and thionyl chloride (3·6 c.c.) were heated on the water-bath for 4 hours. The benzene was removed, and the residue cyclised by treatment with aluminium chloride (3·6 g.) in nitrobenzene to give the *nitroxanthone* (3·0 g.) which crystallised from glacial acetic acid in glistening plates, m. p. 254—255° (Found : C, 56·6; H, 2·6; N, 5·3. $C_{13}H_6O_4NCl$ requires C, 56·6; H, 2·2; N, 5·1%).

6 : 8-*Dimethyl*-2-*nitroxanthone.*—2-*Carbomethoxy*-4-*nitrophenyl* m-5-*xylyl ether.* 2-Chloro-5-nitrobenzoic acid (4 g.) was added to a solution of sodium (0·92 g.) in methanol (20 c.c.), and the reddish semi-solid product mixed with *m*-5-xylenol (9·8 g.). The condensation was carried out as already described, and gave the crude acid (5·4 g.), which was converted into the *methyl* ester, recrystallising from methanol, as glistening plates (4·5 g.), m. p. 83—85° (Found : C, 63·4; H, 4·65; N, 5·0. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0; N, 4·7%).

2-*Carboxy*-4-*nitrophenyl* m-5-*xylyl ether.* The ester (4·5 g.) was heated under reflux with N-potassium hydroxide (100 c.c.) for 1 hour. The acid crystallised from ethanol–water (1 : 1 by volume) as white needles (3·7 g.), m. p. 184—185° (Found : C, 62·5; H, 4·95; N, 5·1. $C_{15}H_{13}O_5N$ requires C, 62·7; H, 4·6; N, 4·9%).

The xanthone. This acid (14·1 g.), benzene (140 c.c.), and thionyl chloride (14 c.c.) were heated on a water-bath for 2 hours. The benzene was removed, and the residue dissolved in nitrobenzene (140 c.c.) and treated with aluminium chloride (14 g.), to give the *nitroxanthone* (12·4 g.), m. p. 217—219°, which crystallised from glacial acetic acid in needles, m. p. 222—223° (Found : C, 66·9; H, 3·7; N, 5·3. $C_{15}H_{11}O_4N$ requires C, 66·9; H, 4·1; N, 5·2%).

3-*Nitroxanthone.*—2-Chloro-4-nitrobenzoic acid (2 g.) (Ullmann and Wagner, *loc. cit.*) and phenol (4 g.) were added in turn to sodium (0·46 g.), dissolved in methanol (10 c.c.). The condensation was carried out in the usual way and the product (2·1 g.) was treated with thionyl chloride and cyclised in the presence of aluminium chloride to give 3-nitroxanthone (1·0 g.), m. p. 173—175°. Ullmann and Wagner record m. p. 176°.

2-*Aminoxanthone.*—2-Nitroxanthone (9·2 g.) was suspended in acetic acid (140 c.c.), stannous chloride (41 g.) in concentrated hydrochloric acid (57·5 c.c.) was added, and the mixture was heated for 3 hours at 100°. The solid was collected and digested with excess of hot 2·5N-sodium hydroxide, and the precipitate recrystallised from ethanol giving small bright-yellow needles (4·7 g.), m. p. 210—212° (Found : C, 74·0; H, 4·4; N, 6·9. Calc. for $C_{13}H_9O_2N$: C, 73·9; H, 4·3; N, 6·6%). Purgotti (*loc. cit.*) records m. p. 205°.

2-*Amino*-7-*chloroxanthone.*—7-Chloro-2-nitroxanthone (2·5 g.) was suspended in acetic acid (45 c.c.), stannous chloride (7·3 g.) in concentrated hydrochloric acid (11·5 c.c.) added, and the mixture warmed on the water-bath for 2 hours. The solid was collected, reduced again under the same conditions, and then shaken with 2·5N-sodium hydroxide (175 c.c.) for 2 hours, giving the *amine* which crystallised from ethanol in yellow needles (1·6 g.), m. p. 231—232° (Found : C, 63·4; H, 3·4; N, 5·95. $C_{13}H_8O_2NCl$ requires C, 63·6; H, 3·3; N, 5·7%).

2-*Amino*-6 : 8-*dimethylxanthone.*—This *amine* was obtained by the reduction of the nitro-compound precisely as described for the chloro-base, and after crystallisation from ethanol, furnished yellow needles, m. p. 209—210° (Found : C, 75·2; H, 5·6; N, 5·5. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·5; N, 5·8%).

3-*Aminoxanthone.*—This was similarly prepared, and recrystallised from benzene in glistening plates, m. p. 228—230° (Found : C, 73·9; H, 4·5; N, 6·6. Calc. for $C_{13}H_9O_2N$: C, 73·9; H, 4·3; N, 6·6%). Ullmann and Wagner (*loc. cit.*) give m. p. 232°.

2-(2-*Diethylaminoethylamino*)*xanthone* (III; R = Et).—2-Aminoxanthone (1 g.) and 2-diethylaminoethyl chloride hydrochloride (0·9 g.) were intimately mixed and heated for 1 hour at 150—155°. The product was extracted with hot dilute acetic acid (60 c.c.), the extracts were filtered, and the filtrates basified with sodium hydroxide solution and steam-distilled. The residual suspension was extracted with ether, the ethereal extracts were shaken with 10% acetic acid, and the acid solution was basified with ammonia solution. The liberated *base*, isolated by extraction with ether, was obtained as a gum which crystallised from light petroleum (b. p. 40—60°) in glistening yellow plates (0·64 g.), m. p. 79—81° (Found : C, 73·3; H, 7·0; N, 9·1. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·2; N, 9·05%).

The 3 : 5-*dinitrobenzoate* crystallised from methanol in bright-red plates, m. p. 179—181° (Found : C, 59·9; H, 4·9; N, 10·4. $C_{19}H_{22}O_2N_2,C_7H_4O_6N_2$ requires C, 59·8; H, 5·0; N, 10·7%).

The *dihydrochloride*, prepared by adding cold saturated ethanolic hydrogen chloride (30 c.c.) to a solution of the base (3·0 g.) in warm ethanol (150 c.c.), crystallised as small faintly-yellow plates (3·6 g.), m. p. 210° (decomp.) (sinters 205°) (Found : N, 7·2. $C_{19}H_{22}O_2N_2,2HCl$ requires N, 7·3%).

The *chlorozincate* separated when a warm concentrated alcoholic solution of the base was mixed with 2% zinc chloride–dilute hydrochloric acid reagent. It formed minute lustrous white plates, m. p. 255° (decomp.) (Found : C, 41·0; H, 5·0; N, 5·4. $C_{19}H_{22}O_2N_2,H_2ZnCl_4.2H_2O$ requires C, 41·1; H, 5·1; N, 5·0%). An aqueous solution of the salt was orange-yellow.

7-*Chloro*-2-(2-*diethylaminoethylamino*)*xanthone.*—2-Diethylaminoethyl chloride hydrochloride (1·8 g.) was shaken with cold aqueous potassium carbonate and xylene (35 c.c.). The xylene layer was separated, dried, mixed with 2-amino-7-chloroxanthone (0·7 g.) and anhydrous potassium carbonate (0·7 g.), and heated under reflux for 48 hours. The product was washed with dilute sodium hydroxide solution, then steam-distilled, and the residual suspension extracted with ether. The extracts were shaken with successive portions of 10% acetic acid, and the acid extracts made alkaline with ammonia

solution. The *base* (0·6 g.), isolated by extraction with ether, was obtained as a solid, m. p. 123—125°, which, when crystallised from light petroleum (b. p. 40—60°) and then from dilute ethanol, afforded yellow needles, m. p. 124—126° (Found: C, 66·4; H, 6·1; N, 8·3. $C_{19}H_{21}O_2N_2Cl$ requires C, 66·2; H, 6·1; N, 8·15%).

The 3 : 5-*dinitrobenzoate*, prepared and recrystallised in methanolic solution, formed orange-red crystals, m. p. 173—174° (Found: C, 56·3; H, 4·95; N, 10·7. $C_{19}H_{21}O_2N_2Cl,C_7H_4O_6N_2$ requires C, 56·1; H, 4·5; N, 10·1%). Persistently high nitrogen values were obtained on analysis.

7-Chloro-2-(2-*di*-n-*butylaminoethylamino*)*xanthone*.—2-Di-*n*-butylaminoethyl chloride hydrochloride (4·7 g.) was shaken with cold aqueous potassium carbonate and xylene (93 c.c.). The xylene layer was separated, dried, and heated under reflux with 2-amino-7-chloroxanthone (2 g.) during 40 hours. The *base* (0·6 g.), isolated as in the case of the ethyl analogue, was recrystallised from dilute ethanol, giving glistening golden-yellow plates, m. p. 105—106° (Found: C, 69·3; H, 7·4; N, 7·3. $C_{23}H_{29}O_2N_2Cl$ requires C, 68·9; H, 7·3; N, 7·0%).

2-(2-*Diethylaminoethylamino*)-6 : 8-*dimethylxanthone*.—A mixture of 2-amino-6 : 8-dimethylxanthone (5·8 g.) and 2-diethylaminoethyl chloride hydrochloride (5 g.) was heated for 1 hour at 150—155°. The *base*, isolated as in the foregoing experiments, crystallised from petroleum (b. p. 40—60°) and recrystallised from dilute ethanol (3 : 2 v/v; 60 c.c.) in glistening yellow needles (3·2 g.), m. p. 85—87° (Found: C, 74·6; H, 7·5; N, 8·5. $C_{21}H_{26}O_2N_2$ requires C, 74·5; H, 7·8; N, 8·3%).

The 3 : 5-*dinitrobenzoate*, prepared in methanolic solution, separated in red needles which were recrystallised from methanol giving yellow plates, m. p. 202—203° (Found: C, 61·05; H, 5·8; N, 10·3. $C_{21}H_{26}O_2N_2,C_7H_4O_6N_2$ requires C, 61·1; H, 5·5; N, 10·2%).

The *dihydrochloride*, prepared by adding cold saturated ethanolic hydrogen chloride (30 c.c.) to a solution of the base (3·0 g.) in warm ethanol (100 c.c.), crystallised in small faintly yellow needles (3·0 g.), m. p. 225° (decomp.), sintering at 215° (Found: N, 6·5. $C_{21}H_{26}O_2N_2,2HCl$ requires N, 6·8%).

The *chlorozincate* separated from the hot dilute zinc chloride reagent as a white microcrystalline powder, m. p. 240—242° (decomp.) (Found: C, 45·15; H, 5·25; N, 5·4. $C_{21}H_{26}O_2N_2,H_2ZnCl_4,\frac{1}{2}H_2O$ requires C, 45·3; H, 5·25; N, 5·1%). The salt gave a yellow solution in water.

3-(2-*Diethylaminoethylamino*)*xanthone* (IV; R = Et).—3-Aminoxanthone (1 g.) and 2-diethylaminoethyl chloride hydrochloride (0·9 g.) were heated together at 155—160° for 1 hour. The *base*, crystallised from light petroleum (b. p. 40—60°), had m. p. 87—89° (0·25 g.) (Found: C, 73·9; H, 7·2; N, 9·4. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·2; N, 9·1%).

The 3 : 5-*dinitrobenzoate* crystallised from methanol in bright-yellow prisms, m. p. 172—174° (Found: C, 59·4; H, 5·3; N, 10·3. $C_{19}H_{22}O_2N_2,C_7H_4O_6N_2$ requires C, 59·8; H, 5·0; N, 10·7%).

The *chlorozincate* (0·12 g.), m. p. 213°, slowly separated on mixing of a hot concentrated ethanolic solution of the base (0·145 g.) with 2% zinc chloride in concentrated hydrochloric acid. The salt crystallised in orange needles, m. p. 215° (decomp.) (Found: C, 43·6; H, 4·7; N, 5·4. $C_{19}H_{22}O_2N_2,H_2ZnCl_4$ requires C, 43·9; H, 4·7; N, 5·4%). An aqueous solution of the salt was colourless.

2-*Iodoxanthone*.—This compound has been prepared by Brewster and Strain (*J. Amer. Chem. Soc.*, 1934, **56**, 118) by the cyclisation of *o-p'*-iodophenoxybenzoic acid. Alternatively, a solution of 2-aminoxanthone (1 g.) in hot acetic acid (12 c.c.) was cooled with vigorous shaking, and slowly added to a solution of sodium nitrite (0·4 g.) in concentrated sulphuric acid (3 c.c.) at 15—20°. This mixture after 2 hours was in turn added with stirring to a solution of potassium iodide (5 g.) and hydrated sodium acetate (17 g.) in cold water (20 c.c.). The brown suspension was diluted with water, boiled, and filtered hot. The insoluble 2-iodoxanthone was sublimed at 200°/0·1 mm. and then recrystallised from ethanol, giving needles (0·8 g.), m. p. 160—161° (Found: C, 48·8; H, 2·6. Calc. for $C_{13}H_7O_2I$: C, 48·5; H, 2·2%).

Di-(2-*diethylaminoethyl*)*amine*.—2-Diethylaminoethyl chloride hydrochloride (50 g.) was shaken with xylene (120 c.c.) and aqueous potassium carbonate. A mixture of this xylene solution and 2-diethylaminoethylamine (58 g.) was heated at 100° for 32 hours, and after basification furnished the *triamine* as a hygroscopic liquid (33 g.), b. p. 155—157°/50 mm. (Found: N, 19·5. $C_{12}H_{29}N_3$ requires N, 19·5%). The *tripicrate* separated from methanol in yellow plates, m. p. 163—165° (Found: C, 40·2; H, 4·0; N, 18·6. $C_{12}H_{29}N_3,3C_6H_3O_7N_3$ requires C, 39·9; H, 4·25; N, 18·6%).

2-*Nitrothioxanthone* (XI).—*The sodium derivative of methyl o-mercaptobenzoate*. A solution of methyl *o*-mercaptobenzoate (17·6 g.), prepared by Gattermann's method (*Ber.*, 1899, **32**, 1150), in methanol (16 c.c.) was mixed with a solution of sodium (2·4 g.) in methanol (40 c.c.) at 0°. The mixture was evaporated to dryness at 30° in a vacuum, and the residue washed with ether and dried *in vacuo*, yielding a pale-yellow solid (20 g.).

o-*Carbomethoxyphenyl* p-*nitrophenyl sulphide* (X). The foregoing sodium derivative (7·5 g.) and *p*-chloronitrobenzene (15 g.) were heated to 160° for 30 minutes; the mass melted and effervesced. When the reaction had subsided, the product was cooled and acidified with hydrochloric acid, and unchanged *p*-chloronitrobenzene removed by steam-distillation. The residual suspension crystallised on cooling, giving the crude methyl ester which was recrystallised from methanol, giving pale-yellow crystals (7·3 g.), m. p. 131—132° (Found: C, 58·3; H, 3·8; N, 5·1. Calc. for $C_{14}H_{11}O_4NS$: C, 58·1; H, 3·8; N, 4·85%). Mayer (*loc. cit.*) records m. p. 131·5°.

o-*Carboxyphenyl* p-*nitrophenyl sulphide*. The ester (8·3 g.) was hydrolysed by boiling it under reflux with N-potassium hydroxide (160 c.c.) for 6 hours. The carboxylic acid crystallised from ethanol as pale-yellow crystals (6·6 g.), m. p. 227—228° (Found: C, 56·8; H, 3·4; N, 5·45. Calc. for $C_{13}H_9O_4NS$: C, 56·7; H, 3·30; N, 5·1%). Mayer records m. p. 229—231°, sintering at 210°.

The thioxanthone. This acid (2 g.) was converted into the acid chloride and cyclised by treatment with aluminium chloride in the usual way. This gave 2-nitrothioxanthone (1·55 g.), m. p. 221—223°

which was recrystallised from glacial acetic acid, forming pale-yellow silky needles, m. p. 224—225° (Found : C, 60·4; H, 2·7; N, 5·8. Calc. for $C_{13}H_7O_3NS$: C, 60·7; H, 2·7; N, 5·5%). Mayer (*loc. cit.*) records m. p. 219—221°.

7-*Methyl*-2-*nitrothioxanthone*.—5-*Methylanthranilic acid*. This acid, prepared from 5-methylisatin (20 g.) by Mayer, Schäfer, and Rosenbach's method (*Arch. Pharm.*, 1929, **267**, 579), was obtained as a pale-brown solid (17 g.), m. p. 168—173°. Mayer *et al.* record m. p. 175°.

4-*Mercapto*-m-*toluic acid*. The anthranilic acid (26 g.) was diazotised and then treated with sodium polysulphide, as described for anthranilic acid itself (*Org. Synth.*, Coll. Vol. II, p. 580), giving 4-mercapto-*m*-toluic acid (20·5 g.), m. p. 155—157°. Krollpfeiffer (*Ber.*, 1925, **58**, 1668) records m. p. 155—157°.

Methyl 4-*mercapto*-m-*toluate*. A solution of the acid (20 g.) in methanol (100 c.c.) was heated under reflux for 3 hours in a stream of dry hydrogen chloride. The product was cooled and poured on ice, whereupon the *ester* (18 g.), m. p. 58—60°, crystallised. It was collected, dried, and distilled, giving a liquid, b. p. 85—87°/0·5 mm., which solidified and was then recrystallised from methanol forming white crystals, m. p. 61—62° (Found : C, 59·3; H, 5·6. $C_9H_{10}O_2S$ requires C, 59·3; H, 5·5%).

3-*Carbomethoxy*-p-*tolyl* p-*nitrophenyl sulphide*. The sodio-derivative (6·7 g.) of the methyl toluate, prepared in the usual way, was mixed with *p*-chloronitrobenzene (14 g.) and heated at 165—170° for 2 hours. The product was cooled, acidified with hydrochloric acid, and steam-distilled to remove the excess of *p*-chloronitrobenzene. The residual suspension crystallised on cooling, giving the required *ester* (8·3 g.) which was recrystallised from methanol, forming yellow crystals (6·1 g.), m. p. 113—114° (Found : C, 59·5; H, 4·4; N, 4·7. $C_{15}H_{13}O_4NS$ requires C, 59·4; H, 4·3; N, 4·6%).

3-*Carboxy*-p-*tolyl* p-*nitrophenyl sulphide*. The ester (4·6 g.) was hydrolysed by heating it under reflux with N-potassium hydroxide (100 c.c.) for 3 hours. The *acid* was sublimed at 165—170°/0·1 mm., giving a yellow solid (2·5 g.), m. p. 178—180° which crystallised from benzene in pale-yellow crystals, m. p. 178—180° (Found : C, 58·5; H, 4·1; N, 4·9. $C_{14}H_{11}O_4NS$ requires C, 58·1; H, 3·8; N, 4·8%).

The thioxanthone. This acid (4 g.) was converted into the chloride and cyclised with aluminium chloride in nitrobenzene. The product was sublimed at 230°/0·1 mm., giving the thioxanthone as a yellow solid (1·85 g.), m. p. 257—260° (Found : C, 61·9; H, 3·4; N, 5·0. Calc. for $C_{14}H_8O_3NS$: C, 62·0; H, 3·3; N, 5·2%). Campbell, Dick, Ferguson, and Loudon (*J.*, 1941, 750) give m. p. 262°.

6 : 8-*Dimethyl*-2-*nitrothioxanthone*.—5-*Nitro*-m-*xylene*. Concentrated sulphuric acid (125 c.c.) was added gradually to a hot solution of 5-nitro-*m*-4-xylidine (195 g.) in ethanol (1560 c.c.). The mixture was heated on the water-bath until it began to reflux; it was then removed and powdered sodium nitrite (244 g.) added in small portions during 1 hour, with occasional shaking. The product was heated under reflux on the water-bath for 45 minutes, diluted with water, and steam-distilled until no more yellow solid passed over. The crude nitroxylene (90 g.) crystallised from petroleum (b. p. 40—60°) as a yellow solid (64 g.), m. p. 66—68°, which formed pale-yellow crystals, m. p. 71—72°, from methanol (Found : C, 63·8; H, 5·95; N, 9·6. Calc. for $C_8H_9O_2N$: C, 63·6; H, 6·0; N, 9·3%). Jacobson (*Annalen*, 1922, **427**, 207) gives m. p. 71°.

m-5-*Xylidine*. The nitroxylene (59 g.) was dissolved in ethanol (480 c.c.), stannous chloride (320 g.) in concentrated hydrochloric acid (355 c.c.) was added, and the solution set aside for 1 hour and finally warmed on the water-bath for 3 hours. The product was diluted with water and basified with an excess of 5N-sodium hydroxide. The amine, isolated by extraction with ether, distilled as a colourless liquid (38 g.), b. p. 114—117°/20 mm. The acetyl derivative crystallised from dilute ethanol in plates, m. p. 139—141° (Found : C, 73·7; H, 8·1; N, 8·7. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 8·0; N, 8·6%).

Oximinoacet-m-5-*xylidide*. This compound was prepared from the amine (60·5 g.) by using the method described for oximinoacetanilide (*Org. Synth.*, Coll. Vol. I, p. 327); the crude air-dried product weighed 70 g.

4 : 6-*Dimethylisatin*. The oximino-compound (50 g.) was gradually added to a well-stirred mixture of concentrated sulphuric acid (200 c.c.) and water (20 c.c.) at 50°. The temperature was allowed to rise to 60—70° during the addition, and when this was complete the mixture was warmed to 80° for 10 minutes, cooled, and poured on ice. The *isatin* was precipitated as an orange solid which was collected, thoroughly washed with water, and dried in the air; it (29 g.) had m. p. 200—215°. A portion was extracted with benzene (Soxhlet), and the extracts deposited a solid which crystallised from glacial acetic in glistening orange crystals, m. p. 241—243° (Found : C, 68·6; H, 5·0; N, 8·35. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·2; N, 8·0%).

4 : 6-*Dimethylanthranilic acid*. The crude isatin (29 g.) was suspended in hot water (100 c.c.) and N-sodium hydroxide (100 c.c.) added with stirring. The solution was filtered from tarry matter, hot N-sodium hydroxide (150 c.c.) added to the filtrate, and hydrogen peroxide (10%; 120 c.c.) dropped in at 100° during 30 minutes with stirring. The solution was cooled, filtered, and made slightly acid (Congo-red) by the addition of dilute hydrochloric acid, whereupon the anthranilic acid was slowly deposited. The crude product (17·5 g.) was used directly without further purification.

2-*Mercapto*-4 : 6-*dimethylbenzoic acid*. The anthranilic acid was converted into the corresponding mercapto-acid by essentially the same procedure as that employed in the preparation of 4-mercapto-*m*-toluic acid. The *acid*, isolated as a white solid (9·1 g.), m. p. 130—135°, recrystallised from petroleum (b. p. 60—80°) as pale-yellow rosettes, m. p. 138—140° (Found : C, 58·8; H, 5·85. $C_9H_{10}O_2S$ requires C, 59·4; H, 5·5%).

Methyl 2-*mercapto*-4 : 6-*dimethylbenzoate*. The acid (8 g.) was dissolved in methanol (100 c.c.) and heated under reflux in a stream of dry hydrogen chloride for 10 hours. The ester (4 g.) was obtained as a liquid of unpleasant odour, b. p. 160—165°/25 mm. Further amounts of ester could be obtained by re-esterification of the residue after distillation.

4-*Carbomethoxy*-m-5-*xylyl* p-*nitrophenyl sulphide*. The sodium derivative (1·4 g.) of the above ester was mixed with *p*-chloronitrobenzene (3·8 g.) and heated to 155° during 10 minutes, and the temperature maintained at 155° for a further 30 minutes. The product was cooled and acidified, and the excess of *p*-chloronitrobenzene removed by steam-distillation. The residual oily suspension slowly crystallised to give the crude *ester* which formed pale-yellow plates (1·5 g.), m. p. 79—80°, from methanol (Found: C, 60·8; H, 4·9; N, 4·4. $C_{16}H_{15}O_4NS$ requires C, 60·6; H, 4·8; N, 4·4%).

The thioxanthone. The ester (200 mg.) was dissolved in concentrated sulphuric acid (2 c.c.) and heated at 100° for 3 hours. The product was cooled and poured on ice, and the pale-yellow *thioxanthone* collected, thoroughly washed with water and sodium hydroxide, dried at 100° (150 mg.), and recrystallised first from glacial acetic acid and then from ethanol, giving minute, pale-yellow needles, m. p. 225—226° (Found: C, 63·5; H, 4·3; N, 5·1. $C_{15}H_{11}O_3NS$ requires C, 63·1; H, 3·9; N, 4·9%).

7-*Chloro*-2-*nitrothioxanthone* (XII). *Method I.*—5-*Chloro*-2-*mercaptobenzoic acid*. Methyl 5-chloroanthranilate (21 g.) (Freundler, *Bull. Soc. chim.*, 1911, [iv], **9**, 606) was hydrolysed by boiling it with N-potassium hydroxide (420 c.c.) for 1 hour. The resulting 5-chloroanthranilic acid (20 g.), m. p. 208—210°, was diazotised and converted into the mercapto-acid as for the *m*-toluic acid. 5-Chloro-2-mercaptobenzoic acid was obtained as a solid (16 g.), m. p. 188—190°, which crystallised from benzene in pale-yellow needles, m. p. 190—192° (Found: C, 44·8; H, 2·8. Calc. for $C_7H_5O_2ClS$: C, 44·6; H, 2·7%). Hart and McClelland (*J.*, 1938, 2114) give m. p. 193°.

Methyl 5-*chloro*-2-*mercaptobenzoate*. A solution of this acid (15 g.) in methanol (200 c.c.) was heated under reflux for 3 hours in a stream of dry hydrogen chloride. The mixture was cooled, and poured on ice, and the *ester* collected, dried (15 g.) and distilled, giving a liquid (b. p. 110—112°/0·5 mm.) which rapidly solidified. The solid (12 g.) crystallised from petroleum (b. p. 40—60°) in clusters of white needles, m. p. 45—47° (Found: C, 47·6; H, 3·65. $C_8H_7O_2ClS$ requires C, 47·4; H, 3·5%). The ester was readily soluble in cold sodium hydrogen carbonate solution.

2-*Carbomethoxy*-4-*chlorophenyl* p-*nitrophenyl sulphide*. The sodium derivative (7 g.) of the above ester was mixed with *p*-chloronitrobenzene (14 g.) and heated to 155° during 10 minutes, and the temperature maintained at 155° for a further 30 minutes. The product was cooled and acidified with hydrochloric acid, and excess of *p*-chloronitrobenzene removed by steam-distillation. The residual oily suspension crystallised on cooling, and the crude *ester* was recrystallised from methanol, giving pale yellow prisms (6·2 g.), m. p. 114—115° (Found: C, 52·2; H, 3·0; N, 4·5. $C_{14}H_{10}O_4NClS$ requires C, 51·9; H, 3·1; N, 4·3%).

2-*Carboxy*-4-*chlorophenyl* p-*nitrophenyl sulphide*. The ester (6·2 g.) and N-potassium hydroxide (120 c.c.) were heated under reflux for 3 hours. The *acid* crystallised from toluene in yellow crystals (5·3 g.), m. p. 207—208° (Found: C, 50·7; H, 2·75; N, 4·4. $C_{13}H_8O_4NClS$ requires C, 50·4; H, 2·6; N, 4·5%).

The thioxanthone (XII). The acid (5 g.) was mixed with benzene (50 c.c.) and warmed on the water-bath with thionyl chloride (5 c.c.) for 3 hours. The benzene was removed, and the residue dissolved in warm nitrobenzene (50 c.c.) and cooled rapidly with vigorous shaking, whereupon the acid chloride separated as a fine precipitate. A cold solution of aluminium chloride (5 g.) in nitrobenzene (50 c.c.) was dropped into the suspension at 0°, the mixture set aside at 0° overnight, and decomposed by the addition of ice, and the nitrobenzene removed by steam-distillation. The residual solution was cooled and the tarry amorphous deposit collected, dried, and boiled with glacial acetic acid (60 c.c.) for 1 hour. The solution was cooled and the *thioxanthone* collected, washed with glacial acetic acid, water, and dilute sodium hydroxide solution, and then dried, yielding a brown solid (1·39 g.), m. p. 267—270°, which was sublimed (230°/0·5 mm.) and recrystallised from glacial acetic acid (500 c.c.), forming small pale-yellow plates (1 g.), m. p. 271—272° (Found: C, 53·5; H, 1·7; H, 4·9. $C_{13}H_6O_3NClS$ requires C, 53·5; H, 2·1; N, 4·8).

7-*Chloro*-2-*nitrothioxanthone* (XII). *Method* 2.—5-*Nitroanthranilic acid*. Acetylanthranilic acid (100 g.) was gradually stirred into concentrated sulphuric acid (270 c.c.) at 0—5°. A mixture of nitric acid (*d* 1·5; 30 c.c.) and concentrated sulphuric acid (50 c.c.) was then slowly dropped in at <5°, the product maintained at 0—5° for a further 4 hours and then poured on ice, and the crude nitro-acid (120 g.; m. p. 155—160°) collected. The acetyl group was removed by stirring the product into concentrated hydrochloric acid (600 c.c.) at 100° during ½ hour. The mixture was poured into water and the nitroanthranilic acid (63 g.), m. p. 263° (decomp.), recrystallised from methanol and finally from water, giving small orange-yellow needles, m. p. 270—273° (decomp.) (Found: N, 15·6. Calc. for $C_7H_6O_4N_2$: N, 15·4%). Rupe (*loc. cit.*) records m. p. 263°.

2-*Carbomethoxy*-4-*nitrophenyl* p-*chlorophenyl sulphide*. 5-Nitroanthranilic acid (42 g.) was ground with concentrated hydrochloric acid (284 c.c.) at 0° and diazotised by the gradual addition of an aqueous solution of sodium nitrite (10%; 168 c.c.) during 2 hours. The diazo-solution was filtered and slowly added to a well-stirred solution of *p*-chlorothiophenol (33·6 g.) in aqueous potassium hydroxide (potassium hydroxide, 212 g., and water, 656 c.c.) at 55—60°. The temperature of the mixture was raised to 100° during 30 minutes, then cooled, and acidified, and the solid collected, dried, and extracted with benzene (Soxhlet). The extracts deposited the crude acid, m. p. 228—230° (25 g.), which was converted into the *methyl* ester (24 g.), which crystallised from methanol in pale yellow prisms, m. p. 145—146° (Found: C, 52·0; H, 2·9; N, 4·5. $C_{14}H_{10}O_4NClS$ requires C, 51·9; H, 3·1; N, 4·3%).

2-*Carboxy*-4-*nitrophenyl* p-*chlorophenyl sulphide* (XIII). The ester (4·3 g.) and N-potassium hydroxide were boiled under reflux for 1 hour. The *acid* (3·8 g.) was recrystallised from benzene and finally from methanol, giving pale yellow crystals, m. p. 234—235° (Found: C, 50·4; H, 2·7; N, 4·5. $C_{13}H_8O_4NClS$ requires C, 50·4; H, 2·6; N, 4·5%).

The thioxanthone (XII). This was prepared by conversion of the acid (2·9 g.) into the acid chloride which was subsequently treated with aluminium chloride in the usual way. The solid product (2·6 g.)

crystallised from glacial acetic acid (1000 c.c.) in small pale yellow plates, m. p. 269—271°, identical with 7-chloro-2-nitrothioxanthone prepared by method I (Found: C, 53·85; H, 2·2; N, 4·9%).

3-*Nitrothioxanthone*—2-*Carbomethoxy*-5-*nitrophenyl phenyl sulphide*. 4-Nitroanthranilic acid (5·3 g.) (Wheeler and Johns, *Amer. Chem. J.*, 1910, **44**, 443) was ground in a mortar with cold concentrated hydrochloric acid (24 c.c.), cooled in ice for 10 minutes, and diazotised by the gradual addition of sodium nitrite solution (10%; 21—24 c.c.) at 0—5°. The diazotised product was diluted with ice–water (40 c.c.), filtered, and dropped into a well-stirred solution of thiophenol (3·3 g.) and potassium hydroxide (26·4 g.) in water (80 c.c.) during 1 hour at 55—60°. The temperature of the mixture was then raised to 85°, and stirring was continued for a further hour. The product was acidified with hydrochloric acid, and the precipitate dried (7·5 g.) and extracted with benzene (100 c.c.) (Soxhlet). The benzene extracts deposited the crude carboxylic acid (4 g.), m. p. 200—208°, which was dissolved in methanol (100 c.c.) and esterified by boiling it for 3 hours in a stream of dry hydrogen chloride. The *methyl* ester (3·9 g.) recrystallised from methanol as bright-yellow plates, m. p. 102—103° (Found: C, 58·4; H, 3·8; N, 5·05. $C_{14}H_{11}O_4NS$ requires C, 58·1; H, 3·8; N, 4·85%).

2-*Carboxy*-5-*nitrophenyl phenyl sulphide*. The ester (2·2 g.) was hydrolysed by boiling it with N-potassium hydroxide (40 c.c.) for 3 hours. The acid (2 g.) was recrystallised from benzene, forming bright-yellow needles, m. p. 213—215° (Found: C, 56·7; H, 3·1; N, 5·2. Calc. for $C_{13}H_9O_4NS$: C, 56·7; H, 3·3; N, 5·1%). Mayer (*loc. cit.*) records m. p. 210—211°.

The thioxanthone. The above acid (1·4 g.) was converted into the acid chloride by treatment with thionyl chloride (1·4 c.c.) in benzene (14 c.c.). The product was treated with aluminium chloride in the standard way, to give 3-nitrothioxanthone (1·2 g.), m. p. 252°, which crystallised from glacial acetic acid in golden-yellow plates, m. p. 252° (Found: C, 60·7; H, 2·9; N, 5·8. Calc. for $C_{13}H_7O_3NS$: C, 60·7; H, 2·7; N, 5·5%).

7-*Chloro*-3-*nitrothioxanthone*.—2-*Carbomethoxy*-5-*nitrophenyl* p-*chlorophenyl sulphide*. 4-Nitroanthranilic acid (5·3 g.) was diazotised and the diazo-solution dropped into *p*-chlorothiophenol (4·2 g.) in potassium hydroxide solution (potassium hydroxide, 26·4 g., in water, 80 c.c.) as in the foregoing experiments. The crude acid (3·6 g.), purified by benzene extraction, had m. p. 213—216° and was converted into the *methyl* ester (3 g.) which crystallised from methanol in slender pale-yellow needles, m. p. 139—140° (Found: C, 52·2; H, 3·0; N, 4·6. $C_{14}H_{10}O_4NClS$ requires C, 51·9; H, 3·1; N, 4·3%).

2-*Carboxy*-5-*nitrophenyl* p-*chlorophenyl sulphide*. The ester (2·5 g.) was hydrolysed by boiling it under reflux with N-potassium hydroxide (45 c.c.) for 3 hours. The *acid* crystallised from benzene in small pale-yellow needles (1·3 g.), m. p. 217—219° (Found: C, 50·3; H, 2·4; N, 4·8. $C_{13}H_8O_4NClS$ requires C, 50·4; H, 2·6; N, 4·5%).

The thioxanthone. The acid (1·2 g.) was converted into the acid chloride and cyclised in the standard way, to give the required *thioxanthone*, which sublimed at 280°/0·1 mm. (0·9 g.; m. p. 322—323°) and was recrystallised from a large volume of glacial acetic acid forming small yellow needles (Found: C, 53·8; H, 1·7; N, 4·9. $C_{13}H_6O_3NClS$ requires C, 53·5; H, 2·1; N, 4·8%).

7-*Methyl*-3-*nitrothioxanthone*.—2-*Carbomethoxy*-5-*nitrophenyl* p-*tolyl sulphide*. 4-Nitroanthranilic acid (5·3 g.) was diazotised in hydrochloric acid, and the diazo-solution dropped into thio-*p*-cresol (3·7 g.) in potassium hydroxide solution, essentially the same method as that described for the preparation of 2-carboxy-5-nitrophenyl phenyl sulphide being used. The crude *acid* (3·3 g.; m. p. *ca.* 230°), isolated by benzene extraction, was recrystallised from toluene, and the product (2·5 g.) dissolved in methanol (100 c.c.) and converted into the *methyl* ester which crystallised from methanol in yellow prisms (2·0 g.), m. p. 112—114° (Found: C, 59·3; H, 4·5; N, 4·7. $C_{15}H_{13}O_4NS$ requires C, 59·4; H, 4·3; N, 4·6%).

2-*Carboxy*-5-*nitrophenyl* p-*tolyl sulphide*. The ester (2·2 g.) was hydrolysed by boiling it with N-potassium hydroxide (40 c.c.) for 2 hours. The *acid* (2·1 g.), m. p. 233—235°, recrystallised from toluene as bright-yellow needles (1·5 g.), m. p. 235—237° (Found: C, 58·0; H, 3·5; N, 4·6. $C_{14}H_{11}O_4NS$ requires C, 58·1; H, 3·8; N, 4·8%).

The thioxanthone. The foregoing acid (2·0 g.) was converted into the acid chloride and cyclised to give the thioxanthone (1·8 g.) which crystallised from glacial acetic acid in glistening orange-yellow needles, m. p. 274—275° (Found: C, 62·4; H, 3·6; N, 5·15. Calc. for $C_{14}H_9O_3NS$: C, 62·0; H, 3·3; N, 5·2%). Campbell *et al.* (*loc. cit.*) give m. p. 276°.

2-*Aminothioxanthone*.—2-Nitrothioxanthone (0·4 g.) was suspended in acetic acid (6 c.c.), a solution of stannous chloride (1·64 g.) in concentrated hydrochloric acid (2·5 c.c.) added, and the mixture warmed for 2 hours on the water-bath. The solid was collected, reduced again under the same conditions, and digested with 2·5N-sodium hydroxide; the amine recrystallised from ethanol, giving orange needles (0·25 g.), m. p. 227—228° (Found: C, 68·9; H, 3·95; N, 6·5. Calc. for $C_{13}H_9ONS$: C, 68·7; H, 4·0; N, 6·2%). Mayer (*loc. cit.*) records m. p. 221—222°.

2-*Amino*-7-*chlorothioxanthone*.—2-Chloro-7-nitrothioxanthone was similarly reduced and the *amine* recrystallised from ethanol, giving glistening orange needles, m. p. 228—230° (Found: C, 59·2; H, 2·8; N, 5·6. $C_{13}H_8ONClS$ requires C, 59·7; H, 3·1; N, 5·4%).

2-*Amino*-7-*methylthioxanthone*.—7-Methyl-2-nitrothioxanthone was reduced as above and the *amine* recrystallised from ethanol, giving glistening orange crystals, m. p. 194—195° (Found: C, 69·9; H, 4·9; N, 5·8. $C_{14}H_{11}ONS$ requires C, 69·7; H, 4·6; N, 5·8%).

3-*Aminothioxanthone*. This was similarly prepared by the reduction of 3-nitrothioxanthone; it crystallised from ethanol in pale-yellow needles, m. p. 252—254° (Found: C, 68·8; H, 4·1; N, 6·0. Calc. for $C_{13}H_9ONS$: C, 68·7; H, 4·0; N, 6·2%). Mayer (*loc. cit.*) gives m. p. 246°.

3-*Amino*-7-*chlorothioxanthone*. This *compound*, similarly prepared, also crystallised from ethanol in pale-yellow needles, m. p. 278—279° (Found: C, 59·7; H, 3·4; N, 5·6. $C_{13}H_8ONClS$ requires C, 59·7; H, 3·1; N, 5·4%).

3-*Amino*-7-*methylthioxanthone*. This *compound* was similarly prepared; it separated from ethanol in pale-yellow plates, m. p. 234—236° (Found: C, 69·9; H, 4·55; N, 5·6. $C_{14}H_{11}ONS$ requires C, 69·7; H, 4·6; N, 5·8%).

2-(2-*Diethylaminoethylamino*)*thioxanthone* (XIV; R = Et).—2-Aminothioxanthone (1·0 g.) and 2-diethylaminoethyl chloride hydrochloride (0·85 g.) were heated at 170° for 1 hour. The *base* (0·52 g.), isolated as in the xanthone series, crystallised from petroleum (b. p. 40—60°) in glistening orange plates, m. p. 52—53° (Found: C, 69·8; H, 7·1; N, 8·4. $C_{19}H_{22}ON_2S$ requires C, 69·9; H, 6·8; N, 8·6%). The *dinitrobenzoate* crystallised from methanol in ruby-red crystals, m. p. 183—184° (Found: C, 58·0; H, 4·8; N, 10·5. $C_{19}H_{22}ON_2S,C_7H_4O_6N_2$ requires C, 58·0; H, 4·9; N, 10·4%). The *picrate* crystallised from methanol in clusters of golden-yellow needles, m. p. 178—180° (Found: C, 54·0; H, 4·5; N, 12·6. $C_{19}H_{22}ON_2S,C_6H_3O_7N_3$ requires C, 54·0; H, 4·5; N, 12·6%). The *dihydrochloride*, prepared by adding saturated ethanolic hydrogen chloride (30 c.c.) to a warm solution of the base (3·0 g.) in ethanol (150 c.c.), crystallised in small pale yellow plates (3·75 g.), m. p. 220° (decomp.) (Found: N, 7·0. $C_{19}H_{22}ON_2S,2HCl$ requires N, 6·85%).

The *chlorozincate*, prepared in a similar way to the analogous salt in the xanthone series, crystallised from the hot dilute zinc chloride reagent in greenish-white needles, m. p. 255° (decomp.) (Found: C, 42·6; H, 4·5; N, 5·0. $C_{19}H_{22}ON_2S,H_2ZnCl_4$ requires C, 42·6; H, 4·5; N, 5·2%). The salt gave an intense yellow solution in water.

7-*Chloro*-2-(2-*diethylaminoethylamino*)*thioxanthone*.—7-Chloro-2-aminothioxanthone (2·25 g.) and 2-diethylaminoethyl chloride hydrochloride (1·7 g.) were heated at 160—165° for 1 hour. The *base* (1·0 g.) crystallised from petroleum (b. p. 40—60°) in lustrous orange-red plates, m. p. 128—129° (Found: C, 63·6; H, 5·8; N, 7·7. $C_{19}H_{21}ON_2ClS$ requires C, 63·2; H, 5·85; N, 7·8%). The *dihydrochloride* prepared by adding saturated ethanolic hydrogen chloride (9 c.c.) to a solution of the base (0·9 g.) in ethanol (70 c.c.), crystallised as minute pale yellow needles (1·05 g.), m. p. 255° (decomp.) (Found: N, 6·7. $C_{19}H_{21}ON_2ClS,2HCl$ requires N, 6·5%). The *dinitrobenzoate* crystallised from methanol in red needles, m. p. 183—184° (Found: C, 54·45; H, 4·5; N, 9·6. $C_{19}H_{21}ON_2ClS,C_7H_4O_6N_2$ requires C, 54·5; H, 4·4; N, 9·8%).

The *chlorozincate* crystallised from the dilute zinc chloride reagent in minute white needles, m. p. 270° (decomp.) (Found: C, 40·1; H, 4·2; N, 4·8. $C_{19}H_{21}ON_2ClS,H_2ZnCl_4$ requires C, 40·0; H, 4·1; N, 4·9%). The salt gave a bright yellow solution in water.

7-*Chloro*-2-(2-*di*-n-*butylaminoethylamino*)*thioxanthone*.—2-Amino-7-chlorothioxanthone (1·5 g.) was alkylated with 2-di-*n*-butylaminoethyl chloride in a similar way to the corresponding condensation in the xanthone series. The *base* (0·9 g.) recrystallised from dilute ethanol in small orange-red needles, m. p. 104—105° (Found: C, 66·5; H, 6·9; N, 7·05. $C_{23}H_{29}ON_2ClS$ requires C, 66·2; H, 7·0; N, 6·7%).

2-(2-*Diethylaminoethylamino*)-7-*methylthioxanthone*.—2-Amino-7-methylthioxanthone (0·63 g.) and 2-diethylaminoethyl chloride hydrochloride (0·54 g.) were heated at 155° during 1 hour. The *base* (6·25 g.) crystallised from petroleum (b. p. 40—60°) in glistening orange plates, m. p. 73—75° (Found: C, 70·1; H, 6·8; N, 8·3. $C_{20}H_{24}ON_2S$ requires C, 70·5; H, 7·1; N, 8·2%). The *dinitrobenzoate* crystallised from methanol in small orange-red needles, m. p. 186—187° (Found: C, 58·85; H, 5·25; N, 10·0. $C_{20}H_{24}ON_2S,C_7H_4O_6N_2$ requires C, 58·7; H, 5·1; N, 10·1%). The *dihydrochloride* crystallised in small pale-yellow plates, m. p. 255° (decomp.) (Found: N, 6·7. $C_{20}H_{24}ON_2S,2HCl$ requires N, 6·8%).

The *chlorozincate* crystallised from the dilute zinc chloride reagent in pale yellow needles, m. p. 272° (decomp.) (Found: C, 44·0; H, 4·8; N, 5·1. $C_{20}H_{24}ON_2S,H_2ZnCl_4$ requires C, 43·7; H, 4·8; N, 5·1%). The salt gave an intense yellow solution in water.

3-(2-*Diethylaminoethylamino*)*thioxanthone* (XV; R = Et).—This *thioxanthone* was prepared precisely as the 2-substituent analogue; it crystallised from petroleum (b. p. 40—60°) in pale yellow plates, m. p. 91—92° (Found: C, 70·0; H, 7·1; N, 8·5. $C_{19}H_{22}ON_2S$ requires C, 69·9; H, 6·8; N, 8·6%). The *dinitrobenzoate* crystallised from methanol in yellow plates, m. p. 189—190° (Found: C, 58·0; H, 5·1; N, 10·4%). The *chlorozincate* separated when a hot concentrated ethanolic solution of the base was mixed with 2% zinc chloride in concentrated hydrochloric acid. The salt was recrystallised from the concentrated reagent, giving glistening vermilion plates, m. p. 240—245° (decomp.), sintering at 235° (Found: C, 42·7; H, 4·7; N, 5·1%).

7-*Chloro*-3-(2-*diethylaminoethylamino*)*thioxanthone*.—This *compound*, similarly prepared, crystallised from petroleum (b. p. 100—120°) as an orange solid which was recrystallised from ethanol, forming pale golden plates, m. p. 112—113° (Found: C, 63·4; H, 5·8; N, 7·6%). The *dinitrobenzoate* formed yellow crystals (from methanol), m. p. 197—198° (Found: C, 54·4; H, 4·5; N, 9·7%).

3-(2-*Diethylaminoethylamino*)-7-*methylthioxanthone*.—This *base* was similarly prepared; it crystallised from petroleum (b. p. 40—60°) in pale yellow crystals, m. p. 81—83° (Found: C, 70·6; H, 7·5; N, 8·2%). The *dinitrobenzoate* separated from methanol as yellow crystals, m. p. 186—188° (Found: C, 58·9; H, 5·5; N, 10·3%). The *chlorozincate* crystallised from the concentrated reagent in glistening orange plates, m. p. 232° (decomp.), sintering at 225° (Found: C, 43·7; H, 4·5; N, 5·21%). The salt gave a colourless solution in water. The *chlorocadmiate*, prepared by mixing a concentrated ethanolic solution of the base with 2% cadmium chloride in concentrated hydrochloric acid, was recrystallised from the reagent, giving orange crystals, m. p. 210° (decomp.) (Found: C, 40·0; H, 4·6; N, 4·8. $C_{20}H_{24}ON_2S,H_2CdCl_4$ requires C, 40·3; H, 4·4; N, 4·7%).

We are indebted to Trinity College for a Research Studentship (J. H. T.) and to the Medical Research Council for financial assistance, in connection with the work described in this and the following two papers.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 21st*, 1950.]