860. *Reactivity of Xanthones bearing* 1- *and* 3-*Chloro-substituents towards Nucleophilic Reagents.*

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1-Chloroxanthones with toluene-*p*-sulphonamide give high yields of 1-toluene-*p*-sulphonamidoxanthones: 3-chloroxanthones do not react. The reaction has been employed to determine the ratio of products formed by cyclisation on to the 2′- and the 6′-position in 2-carboxy-3′-chloro- and 2-carboxy-3′ : 5-dichloro-diphenyl ether. In both cases this ratio is *ca.* 1·0 and is independent of the cyclising agent.

Both 1- and 3-chloroxanthone react quantitatively with sodium methoxide to yield the methoxyxanthone. The method constitutes a novel and easy route to 3-alkoxy-, 3-aryloxy-, and 3-arylthio-xanthones.

1-Chloroxanthone was required for chemotherapeutic studies and various synthetic routes to the compound have been explored. Dhar [1] cyclised 2-carboxy-3′-chlorodiphenyl ether with sulphuric acid and obtained a monochloroxanthone, m. p. 100°, which he believed to be the (then) unknown 1-chloroxanthone. Repetition of Dhar's work, using acetic anhydride as cyclising agent, gave a compound of the same m. p. but this was not 1-chloroxanthone because the latter, obtained by the Sandmeyer reaction from 1-aminoxanthone, had m. p. 137°. Exhaustive fractional crystallisation and chromotography failed to raise the m. p. of Dhar's compound which evidently contained much 3-chloroxanthone since synthetic mixtures of 1- and 3-chloroxanthone (m. p. 137° and 130° respectively) all had m. p. 100—102° provided not less than 25% of either isomer was present.

[1] Dhar, *J.*, 1920, 1061.

Comparison of the ultraviolet spectrum of Dhar's compound with those of pure 1- and 3-chloroxanthone indicated the presence of 40—60% of 3-chloroxanthone but the spectra of the pure isomers were too similar to allow of greater precision. Accordingly a method of analysis and possible separation was sought making use of an expected difference between the reactivity of xanthone at the 1- and the 3-position with nucleophilic reagents. Reactivity at the 1-position is known to be considerable with both amines [2] and alkoxide ions.[3]

It was found that 1-chloroxanthone reacted with toluene-*p*-sulphonamide in refluxing pentyl alcohol, in the presence of potassium carbonate and a copper catalyst, to give 1-toluene-*p*-sulphonamidoxanthone with release of 74% of the theoretical amount of halide ion in 6 hours; under the same conditions 3-chloroxanthone did not react. Determination of the halide ion released when Dhar's compound was submitted to this procedure showed that it consisted of 56% of 1-chloroxanthone and 44% of 3-chloroxanthone. Since the sulphonamide is far less soluble than either of the monochloroxanthones it can be separated almost quantitatively; hydrolysis affords a new route to 1-aminoxanthone.

With the more reactive nucleophile, methoxide ion in refluxing methyl alcohol, both 1- and 3-chloroxanthone reacted quantitatively to give the corresponding methoxyxanthone. With Dhar's compound, the mixture of the 1- and 3-methoxyxanthone thus obtained, upon fractional crystallisation, yielded 3-methoxyxanthone in *ca.* 25% overall yield; the more soluble 1-methoxyxanthone could not be isolated. It is of passing interest, since 3-chloroxanthone is readily accessible from 2 : 4-dichlorobenzoic acid, that this method constitutes a novel and easy route to 3-alkoxy-, 3-aryloxy-, and 3-aralkyloxy-xanthones.

Cyclisation of 2-carboxy-3′ : 5-dichlorodiphenyl ether with sulphuric acid gave a mixture of 1 : 6- and 3 : 6-dichloroxanthone. Fractional crystallisation gave the less soluble 3 : 6-dichloroxanthone in *ca.* 20% yield, identified by reference to unequivocal material obtained from 3 : 6-diaminoxanthone [4]; 1 : 6-dichloroxanthone could not be isolated from the mixture. Treatment of the crude cyclisation mixture of 1 : 6- and 3 : 6-dichloroxanthones with toluene-*p*-sulphonamide in refluxing pentyl alcohol (134°) did not result in reaction; in a refluxing mixture of hexyl and octyl alcohol (166°), however, reaction took place with production of 6-chloro-1-toluene-*p*-sulphonamidoxanthone. The structure of this compound was ascertained by hydrolysis to an amino-chloro-xanthone, identical with the compound obtained by cyclisation of 2-carboxy-5-chloro-3′-nitrodiphenyl ether and reduction of the chloronitroxanthone thus obtained; this identity proved both to be 1-amino-6-chloroxanthone. The yield of 6-chloro-1-toluene-*p*-sulphonamidoxanthone indicated that the crude cyclisation mixture consisted of 1 : 6- and 3 : 6-dichloroxanthone in the ratio of 52 : 48. It is noteworthy that neither the cyclising agent (acetic anhydride or sulphuric acid or polyphosphoric acid) nor the 5-chloro-substituent affects the ratio of products formed by ring closure on to the 2′- and the 6′-position; this ratio appears to be a function of the 3′-chloro-substituent alone.

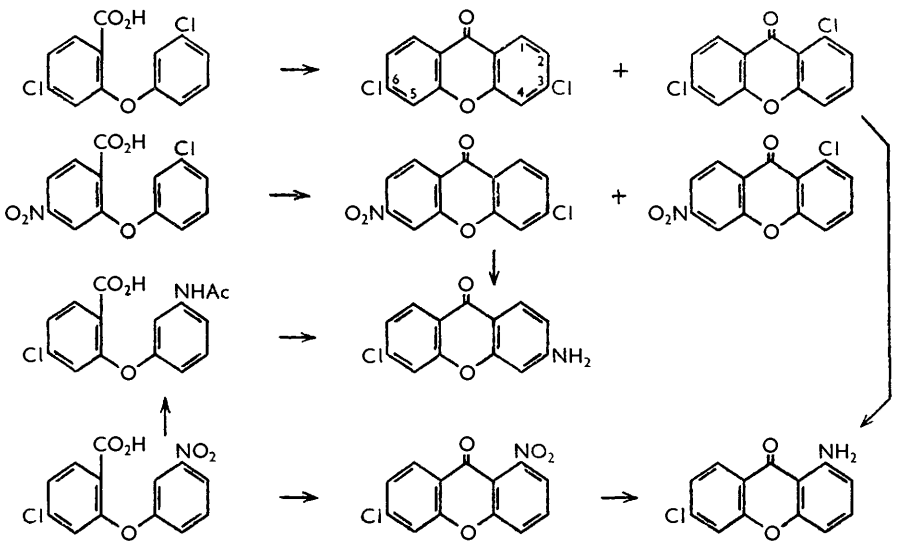
Reaction of 3 : 6-dichloroxanthone with methoxide gave 3 : 6-dimethoxyxanthone; with the crude product of cyclisation of 2-carboxy-3′ : 5-dichlorodiphenyl ether, sodium methoxide gave a mixture of dimethoxyxanthones from which only 3 : 6-dimethoxyxanthone could be isolated.

Cyclisation of 2-carboxy-3′-chloro-5-nitrodiphenyl ether yielded a mixture of the less soluble 3- and the more soluble 1-chloro-6-nitroxanthone. The structure of the former was proved by reduction to 6-amino-3-chloroxanthone identical with the product obtained by cyclisation of 3′-acetamido-2-carboxy-5-chlorodiphenyl ether followed by hydrolysis.

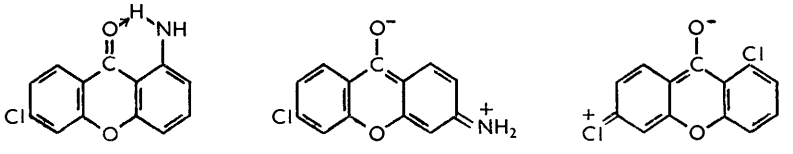
The extent of the reaction of a nucleophile at the position *para* to a carbonyl group is a function of the intensity of the polarisation or polarisability of the carbonyl group and also of the transmissibility of the $-E$ mechanism of the latter to the *para*-position. As the series α-methylbenzyl alcohol, di- and tri-phenylmethanol, 9-hydroxyxanthen is

[2] Mauss, *Chem. Ber.*, 1948, **81**, 19.
[3] Eckert and Engler, *J. prakt. Chem.*, 1922, **104**, 95.
[4] Goldberg and Walker, *J.*, 1953, 1348.

ascended there is increasing tendency for ionisation [5] (with fission of hydroxyl ion) because of increasing resonance stabilisation of the residual cation. Similarly, as the series acetophenone, benzophenone, xanthone is ascended there would be expected to be increasing polarisation of the carbonyl group ($C\overset{\curvearrowright}{=}O$) because of increasing resonance stabilisation of



the cyclic portion of the dipole. Accordingly the reactivity of 4-chloroacetophenone, 4-chlorobenzophenone, and 3-chloroxanthone towards nucleophiles should increase in this order. This has been shown to be the case; Table 1 indicates the extent of the reaction of the chloro-compound with sodium methoxide under standard conditions as measured by release of chloride ion or yield of methoxy-compound. With 3-chloroxanthones bearing a second substituent in the non-chlorinated ring, the second substituent may inhibit transmission of the $-E$ mechanism of the carbonyl group to the 3-position. Thus, while 2-amino-6-chloroxanthone reacts with methoxide ion at substantially the same speed as 3-chloroxanthone, 3-amino-6-chloroxanthone reacts extremely slowly and 1-amino-6-chloroxanthone not at all. This lack of reactivity is attributable, in the latter case, to hydrogen-bonding between the 1-amino-substituent and the carbonyl-oxygen atom (cf. I)



(I) (II) (III)

and, in the case of 3-amino-6-chloroxanthone, to the substantial weight which must be attributed to the *p*-quinonoid structure (II) in the resonance hybrid.

The smaller facility with which 1 : 6-dichloroxanthone reacts with toluene-*p*-sulphonamide than does 1-chloroxanthone reflects the statistical weighting attributable to the quinonoid structure (III).

The high reactivity of 1- and the non-reactivity of 3-chloroxanthone with toluene-*p*-sulphonamide is significant in view of the greater reactivity of methoxide ion with 3-chloroxanthone. It appears that the reaction of 1-chloroxanthone with the sulphonamide is

[5] Shriner in " Roger Adams Symposium," Chapman and Hall, London, 1954, p. 103; Goldberg and Wragg, *J.*, 1957, 4823.

TABLE 1. *Methoxydechlorination of chloro-ketones in refluxing methanol with* 10 *mols. of methoxide ion in* 72 *hours.*

Compound	Reaction (%)
4-Chloroacetophenone	27
4-Chlorobenzophenone	55
3-Chloroxanthone	100

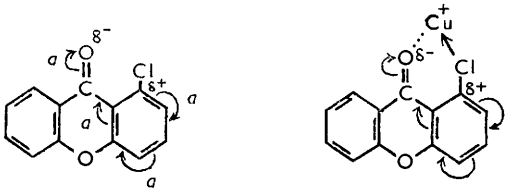
TABLE 2. *Methoxydechlorination of chloroxanthones in a refluxing mixture of* 66% *methanol and* 33% *dioxan with* 10 *mols. of methoxide ion in* 72 *hours.*

Compound	Reaction (%)	Compound	Reaction (%)
1-Chloroxanthone	~95 [a]	1-Amino-6-chloroxanthone	0
2-Chloroxanthone	0	2-Amino-6-chloroxanthone	100
3-Chloroxanthone	100 [b]	3-Amino-6-chloroxanthone	15
4-Chloroxanthone	0		

[a] 54% in 30 hours. [b] 61% in 30 hours.

mediated by two mechanisms, (*a*) the electromeric polarisation of the system C=C—C=O and (*b*) the formation of a 6-membered chelate copper complex in which the normal inductive effect of the C→Cl bond and the inductomeric polarisability of the bond in the presence of an attacking anionoid reagent will be strongly augmented by the co-ordination of the chlorine with the copper. Both these processes will operate in concert to create electron-defect at position 1, the combined total effect being sufficient to allow this position to be easily susceptible to attack by the sulphonamide with ejection of the halogen as chloride ion. The electromeric polarisation (*a*) will be fully transmitted to the 3-position but no copper chelate complex can be formed between the carbonyl-oxygen atom and a 3-halogen substituent; accordingly the net electron-defect at position 3 will be insufficient to initiate attack by the sulphonamide at this point. Formation of a chelate copper complex in the reaction of 1-chloroxanthone with toluene-*p*-sulphonamide is supported by the familiar sequence of unusual colours which accompany the reaction; these colours are frequently diagnostic of metallic inner complex salts.[6,7]

With the smaller and more vigorous nucleophile, methoxide ion, the electromeric polarisation (*a*) will create sufficient electron-defect at both positions 1 and 3 to initiate



attack at both these positions; but, because of the greater distance from the negative charge on the oxygen of the polarised carbonyl group, the approach of the methoxide ion will be less hindered at position 3 than at position 1.

It is pertinent to compare the high reactivity of the 2- and non-reactivity of the 4-halogen atom in 2 : 4-dichlorobenzoic acid towards arylamines and phenols in the presence of copper,[8] and the greater reactivity of the 4- than of the 2-halogen atom in 2 : 4-dichlorobenzoic acid towards methoxide.[9]

EXPERIMENTAL

2-Carboxy-3'-chlorodiphenyl Ether.—*o*-Chlorobenzoic acid (31·3 g., 0·2 mole), *m*-chlorophenol (28 g., 0·22 mole), potassium carbonate (35 g., 0·25 mole), and cuprous iodide (0·2 g.) were stirred with nitrobenzene (200 c.c.) at 160—165° for 6 hr. The mixture was acidified, the nitrobenzene distilled off in steam, and the residual solution strongly acidified. The black oil was collected and dissolved in diluted sodium carbonate, the solution acidified to pH 6, and the precipitated tar

[6] Morgan and Drew, *J.*, 1920, 1456.
[7] Diehl, *Chem. Rev.*, 1937, **21**, 39.
[8] Goldberg, *J.*, 1952, 4368.
[9] van der Lande, *Rec. Trav. chim.*, 1932, **51**, 98.

filtered off (charcoal); further acidification precipitated a buff oil which slowly solidified (18·5 g.; m. p. 90°). The acid was purified by dissolving it in boiling N-sodium carbonate (300 c.c.) and adding potassium permanganate (30 g.) portionwise; after 15 min. on the water-bath the mixture was cooled and acidified with dilute sulphuric acid, and the manganese oxides were removed by passing in sulphur dioxide. The residual colourless solid (13 g.; m. p. 100°) was collected and washed with water; a sample separated from aqueous alcohol in colourless leaves, m. p. 101° (Found: *M*, 252. Calc. for $C_{13}H_9O_3Cl$: *M*, 248·5).

Cyclisation of 2-Carboxy-3'-chlorodiphenyl Ether.—The acid (26 g.) was refluxed with acetic anhydride (300 c.c.) and sulphuric acid (8 drops) for 1 hr. and the solution poured on ice. The oily precipitate was extracted with hot dilute aqueous sodium carbonate and the insoluble mixture of 1- and 3-chloroxanthones (21 g.; m. p. 90—96°) (*A*) collected. Crystallisation from aqueous alcohol gave colourless plates (18 g.) (*B*), m. p. 100—102° (Found: Cl,15·6. Calc. for $C_{13}H_7O_2Cl$: Cl, 15·4%), $\lambda_{max.}$ 2380 (ε 41,300), 2650 (ε 14,300), and 3350 Å (ε 7900), $\lambda_{min.}$ 2500 (ε 10,600), and 3050 Å (ε 1850). Comparison with the spectra of pure 1- and 3-chloroxanthone showed the mixture to contain 40—60% of 1- and 60—40% of 3-chloroxanthone.

Recrystallisation of this mixture (8 g.) twelve times gave material (3 g.) of m. p. 102—104°; the mother-liquors from the first six crystallisations were combined and evaporated, and the residue was crystallised six times to give material of the same m. p. A solution of the mixture (1·0 g.) in ethanol (15 c.c.) was chromotographed on a 30 cm. alumina column and eluted with ethanol into 7 fractions; all these had the same m. p.

Analysis of the 1- and 3-chloroxanthone mixture. The mixture of 1- and 3-chloroxanthone (2·305 g., 0·01 mole), toluene-*p*-sulphonamide (3·42 g., 0·02 mole), fused sodium acetate (1·64 g., 0·02 mole), and copper acetate (0·2 g.) was refluxed in pentyl alcohol (30 c.c.) for 6 hr. Potassium carbonate (2 g.) and distilled water were added, and the alcohol was distilled off in steam. The residual liquor was cooled and filtered, and the solid (*C*) washed, the washings being added to the filtrate which was then acidified with 5N-nitric acid; after several hours at room temperature the mixture was again filtered, and chloride ion was determined. The crude cyclisation product (*A*) gave 0·6848 g. and the once crystallised mixture (*B*) gave 0·7000 g. of silver halide; this corresponds to a composition of 56% of 1-chloroxanthone and 44% of 3-chloroxanthone.

In the same manner pure 1-chloroxanthone (2·305 g.) yielded 1·2594 g. of silver chloride (73·7%); pure 3-chloroxanthone gave no trace of silver chloride.

The solid (*C*), on crystallisation from aqueous pyridine, gave 1-*toluene*-p-*sulphonamidoxanthone* as yellow needles, m. p. 168—170° alone and mixed with material prepared from pure 1-chloroxanthone obtained from 1-aminoxanthone (Found: N, 4·1; S, 8·7. $C_{20}H_{15}O_4NS$ requires N, 3·9; S, 8·8%).

1-*Chloroxanthone.*—A mixture of finely divided 1-aminoxanthone (15·7 g.), 10N-hydrochloric acid (210 c.c.), and water (275 c.c.) was stirred at 2° until the hydrochloride was finely divided. Sodium nitrite (6·5 g.) in water (40 c.c.) was added dropwise; in 20 min. all the solid had dissolved. Cuprous chloride solution was prepared by adding a solution of sodium pyrosulphite (16 g.) and sodium hydroxide (10 g.) in water (115 c.c.) at 60° to a stirred solution at the same temperature of cupric sulphate pentahydrate (73 g.) and sodium chloride (25 g.) in water (230 c.c.); the cuprous chloride was washed by decantation and dissolved in 10N-hydrochloric acid (190 c.c.). The diazonium solution was slowly added to the stirred cuprous chloride solution at 40°; after 15 min. the mixture was stirred on the water-bath for 1 hr. and set aside overnight. The pale yellow solid (15·6 g.; m. p. 130°) was collected; crystallisation from aqueous alcohol gave 1-*chloroxanthone* as pale cream needles (12 g.), m. p. 136—137° (Found: C, 67·2; H, 2·9; Cl, 15·4. $C_{13}H_7O_2Cl$ requires C, 67·7; H, 3·0; Cl, 15·4%), $\lambda_{max.}$ 2380 (ε 41,500), 2670 (ε 10,800), 2960 (ε 9000), and 3430 (ε 8300); $\lambda_{min.}$ 2550 (ε 7800), 2900 (ε 1380), and 3020 Å (ε 920).

Treatment of the compound with toluene-*p*-sulphonamide as described above gave 1-toluene-*p*-sulphonamidoxanthone (65%), yellow leaves (from aqueous pyridine), m. p. 168—170° (Found: N, 4·0; S, 9·0%).

3-*Chloroxanthone.*—2 : 4-Dichlorobenzoic acid (38·2 g.), potassium carbonate (55 g.), phenol (47 g.), copper bronze (1·0 g.), cuprous iodide (0·2 g.), and nitrobenzene (150 c.c.) were stirred at 160—165° for 6 hr. The crude dark product on crystallisation from 50% methanol gave 2-carboxy-5-chlorodiphenyl ether as needles (27 g., 55%), m. p. 166° (Found *M*, 250. Calc. for $C_{13}H_9O_3Cl$: *M*, 249). The acid (25 g.) was heated with sulphuric acid (120 c.c.) on the water-bath for ¾ hr., and the solution poured on ice. The precipitate, after extraction with boiling aqueous sodium carbonate, crystallised from a mixture of methanol (500 c.c.), pyridine (60

c.c.), and water (150 c.c.) to give 3-chloroxanthone (20 g., 87%) as nearly colourless needles, m. p. 130° (Found: Cl, 15·5. Calc. for $C_{13}H_7O_2Cl$: Cl, 15·4%), $\lambda_{max.}$ 2380 (ε 40,500), 2640 (ε 16,200), 2880 (ε 9000), and 3350 Å (ε 7600), $\lambda_{min.}$ 2540 (ε 10,850), 2800 (ε 6450) and 3050 Å (ε 2070).

3-*Methoxyxanthone*.—3-Chloroxanthone (10 g.) was refluxed with a solution from sodium (10 g.) in methanol (500 c.c.) for 72 hr. The solvent was distilled off, water added, the mixture neutralised with dilute sulphuric acid, and the solid (9·0 g.) collected. Crystallisation from dilute ethanol gave 3-methoxyxanthone (7·0 g.), m. p. 128—130° alone and in admixture with material obtained by cyclisation of 2-carboxy-5-methoxydiphenyl ether (Found: C, 74·1; H, 4·5. Calc. for $C_{14}H_{10}O_3$: C, 74·4; H, 4·4%).

Treatment of the crude mixture (4 g.) of 1- and 3-chloroxanthone (obtained by cyclisation of 2-carboxy-3′-chlorodiphenyl ether) in the same manner gave a mixture (3·8 g.) of methoxyxanthones; repeated crystallisation yielded 3-methoxyxanthone (0·9 g.), m. p. and mixed m. p. 128—130° depressed on admixture of 1-methoxyxanthone.

3-*Ethoxyxanthone* was obtained in the same manner in 96% yield as needles (from ethanol), m. p. 146° (Found: C, 75·5; H, 5·1. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%).

3-n-*Butoxyxanthone* was obtained (95%) as pale yellow prisms, m. p. 118° (Found: C, 76·8; H, 5·8. $C_{17}H_{16}O_3$ requires C, 76·2; H, 5·9%).

3-*Phenoxyxanthone*.—3-Chloroxanthone (10 g.) was refluxed with a solution from sodium (10 g.) in phenol (400 g.) for 8 hr. Water (1 l.) was added and 5N-hydrochloric acid to pH 2, and the excess of phenol removed in steam. The *compound* was obtained as needles (9·5 g.; from dilute ethanol), m. p. 116—118° (Found: C, 78·8; H, 4·4. $C_{19}H_{12}O_3$ requires C, 79·1; H, 4·2%).

3-(p-*Methylphenylthio*)*xanthone*.—Thio-*p*-cresol (7·4 g.) was added to a solution from sodium (1·4 g.) in ethanol (160 c.c.); 3-chloroxanthone (9·2 g.) was added and the mixture refluxed for 60 hr. The *product* separated from alcohol–dioxan as colourless needles (12 g.), m. p. 164° (Found: C, 75·5; H, 4·6; S, 9·8. $C_{20}H_{14}O_2S$ requires C, 75·5; H, 4·4; S, 10·1%).

1-*Methoxyxanthone*.—1-Chloroxanthone (2 g.) was refluxed with a solution from sodium (2·0 g.) in methanol (100 c.c.) for 96 hr. 1-Methoxyxanthone (1·4 g.) was isolated in the same manner as needles, m. p. 136° (Found: C, 74·1; H, 4·5%).

Methylation of 1-*Hydroxyxanthone*.—A mixture of 1-hydroxyxanthone (1·15 g.), methyl iodide (4·7 g.), potassium carbonate (1·15 g.), and acetone (25 c.c.) was refluxed for 6 days. The solvent was distilled off, 2N-sulphuric acid (10 c.c.) added, and the mixture extracted with ether (2 × 40 c.c.). The ether layer was shaken with 5N-sodium hydroxide (2 × 10 c.c.), the insoluble sodium derivative of 1-hydroxyxanthone (50 mg.) filtered off, and the ether layer separated, washed with water, and evaporated. Crystallisation of this residue (1·25 g.) twice from alcohol gave unidentified crystals, m. p. 200—202° (Found: C, 64·5; H, 3·2%); the mother-liquors were diluted with water and the precipitate collected. Recrystallisation of this from alcohol gave 1-methoxyxanthone (0·3 g.), needles, m. p. 136° alone and on admixture with a sample prepared from 2-chloro-6-methoxybenzoic acid by the method of Ullmann and Panchaud [10] (Found: C, 74·2; H, 4·4. Calc. for $C_{14}H_{10}O_3$: C, 74·4; H, 4·4%).

2-*Carboxy*-3′ : 5-*dichlorodiphenyl Ether*.—2 : 4-Dichlorobenzoic acid (19·1 g., 0·1 mole), *m*-chlorophenol (26 g., 0·2 mole), copper bronze (0·1 g.), and cuprous iodide (0·1 g.) were added to a solution from sodium (4·6 g., 0·2 g.-atom) in methanol (120 c.c.). The methanol was distilled off and the semi-solid residue placed in an oil-bath at 100° the temperature of which was raised to 180° during 10 min. and held there for a further 15 min. The mixture was cooled and acidified and the excess of *m*-chlorophenol distilled in steam. The residual solid was collected and dissolved in dilute aqueous potassium hydroxide, the solution filtered (charcoal) and acidified, and the acid (25·6 g.; m. p. 120—124°) collected. This was dissolved in warm 2N-sodium hydroxide and the solution chilled; the precipitated sodium salt was filtered off, washed with a little acetone, and redissolved in boiling water, the solution strongly acidified, and the *acid* (20 g.; m. p. 146—148°) collected. It separated from aqueous alcohol in needles, m. p. 147—148° (Found: *M*, 285; Cl, 25·0%. $C_{13}H_8O_3Cl_2$ requires *M*, 283; Cl, 25·1%).

Cyclisation of 2-*Carboxy* 3′ : 5-*dichlorodiphenyl Ether*. 1 : 6- *and* 3 : 6-*Dichloroxanthone*.—The foregoing crude acid (15 g.) was heated with sulphuric acid (150 c.c.) for 1 hr. on the water-bath, and the solution poured on ice. The precipitate was collected and extracted with hot aqueous sodium carbonate, washed with water, and dried; the yield of the mixture of 1 : 6- and 3 : 6-dichloroxanthone was 12·5 g. (m. p. 125—130°).

Crystallisation of this from ethanol seven times yielded 3 : 6-*dichloroxanthone* (3·0 g.) in long

[10] Ullmann and Panchaud, *Annalen*, 1906, **350**, 108.

colourless prisms, m. p. 184—186° alone and on admixture with unequivocal material obtained from 3 : 6-diaminoxanthone [4] by Julia's method [11] (Found: Cl, 26·6. $C_{13}H_6O_2Cl_2$ requires Cl, 26·8%). Evaporation of the combined mother-liquors gave 9·0 g. of recovered mixture rich in 1 : 6-dichloroxanthone: this was used for the following reaction.

6-*Chloro*-1-*toluene*-p-*sulphonamidoxanthone*.—The foregoing recovered mixture (9·0 g.), toluene-*p*-sulphonamide (9·0 g.), fused sodium acetate (4·5 g.), and copper acetate (0·5 g.) were refluxed (168°) with *n*-hexyl alcohol (112 c.c.) and *sec.*-octyl alcohol (112 c.c.) for 6 hr. The solvents were distilled off in steam and the residual solid (12 g.) extracted with boiling 75% alcohol (250 c.c.) to remove unchanged 3 : 6-dichloroxanthone; the insoluble 6-*chloro*-1-*toluene*-p-*sulphonamidoxanthone* (9·5 g.) crystallised from 90% pyridine in golden plates (8·5 g.), m. p. 210—212° (Found: N, 3·6; Cl, 9·0; S, 8·2. $C_{20}H_{14}O_4NSCl$ requires N, 3·5; Cl, 8·9; S, 8·0%). This yield indicates that the original crude mixture obtained by cyclisation of 2-carboxy-3′ : 5-dichlorodiphenyl-ether acid contained 52% of 1 : 6- and 48% of 3 : 6-dichloroxanthone.

1-*Amino*-6-*chloroxanthone*.—The foregoing sulphonamide (1·5 g.) was heated with 80% sulphuric acid (40 g.) at 150° for 10 min., then at 100° for 10 min., and kept at room temperature overnight. The mixture was poured on ice and excess of aqueous sodium hydroxide, and the precipitate was collected and washed. Crystallisation from alcohol gave 1-*amino*-6-*chloroxanthone* (0·5 g.) in yellow needles, m. p. 164° alone and on admixture with material obtained by cyclisation of 2-carboxy-5-chloro-3′-nitrodiphenyl ether followed by reduction (Found: N, 5·7; Cl, 14·3. $C_{13}H_8O_2NCl$ requires N, 5·7; Cl, 14·5%).

1 : 6-*Dichloroxanthone*.—This was obtained in 35% yield from 1 : 6-diaminoxanthone [4] by the method described [11] for the 3 : 6-isomeride. The *compound* crystallised from ethanol as colourless needles, m. p. 140—142° (Found: C, 58·9; H, 2·05%).

3 : 6-*Dimethoxyxanthone*.—3 : 6-Dichloroxanthone (2·5 g.) was refluxed with a solution from sodium (5·0 g.) in methanol (150 c.c.) for 48 hr. The solution was kept on ice overnight, and the crystalline precipitate (2·4 g.; m. p. 184°) collected and washed with cold water. Recrystallisation from methanol gave the pure *compound* in colourless needles, m. p. 184—186° (Found: C, 70·0; H, 4·8. $C_{15}H_{12}O_4$ requires C, 70·4; H, 4·7%).

When the crude cyclisation mixture of 1 : 6- and 3 : 6-dichloroxanthone (4·0 g.) was treated in the same manner, the product (3·8 g.) had m. p. 144—148°; four crystallisations gave 3 : 6-dimethoxyxanthone (1·1 g.), m. p. and mixed m. p. 184°.

6-*Chloro*-2-*nitroxanthone*.—A mixture of nitric acid (4·83 c.c.; *d* 1·50; 0·115 mole) and sulphuric acid (25 c.c.) was added during 20 min. to a solution of 3-chloroxanthone (23 g.; 0·1 mole) in sulphuric acid (150 c.c.) stirred at 10—15°. Stirring at room temperature was continued for 2 hr., then at 80° for ½ hr., and the solution was poured on ice. The precipitate was extracted with boiling dilute aqueous sodium carbonate, then with boiling alcohol (300 c.c.), and washed with water; the crude *product* (25 g.; m. p. 240—250°) was pure enough for further use. A sample crystallised from pyridine in buff needles, m. p. 254—256° (Found: N, 5·3; Cl, 12·9. $C_{13}H_6O_4NCl$ requires N, 5·1; Cl, 12·9%). The orientation is based upon the rules previously established [4] for the nitration of xanthones.

2-*Amino*-6-*chloroxanthone*.—The foregoing crude compound (20 g.) was added portionwise during 15 min. to a solution of stannous chloride dihydrate (120 g.) in 10N-hydrochloric acid (120 c.c.) stirred at 95°. Stirring was continued at this temperature for a further 105 min. and the mixture set aside. In the morning the mass was drained on sintered glass and the solid stirred with cold 2N-sodium hydroxide (1·5 l.) for 2 hr.; 2-*amino*-6-*chloroxanthone* (17 g.; m. p. 250—260°) was filtered off and washed with water. A sample separated from dilute pyridine in yellow needles, m. p. 268—270° (Found: N, 6·0; Cl, 14·2%).

2-*Carboxy*-3′-*chloro*-5-*nitrodiphenyl Ether*.—*m*-Chlorophenol (12·9 g., 0·1 mole), 2-chloro-4-nitrobenzoic acid (10·1 g., 0·05 mole), copper bronze (0·1 g.), and cuprous iodide (0·1 g.) were added to a solution from sodium (2·3 g.) in methanol (60 c.c.). After removal of the methanol the residue was heated at 110—180° during 15 min. and then at 180° for 15 min. The product (10·0 g.; m. p. 116—118°) crystallised from dilute alcohol in yellow prisms; recrystallisation from toluene–ligroin (b. p. 80—100°) gave the *compound* in yellow needles (8·8 g.), m. p. 120—121° (Found: *M*, 294. $C_{13}H_8O_5NCl$ requires *M*, 293·5).

3- *and* 1-*Chloro*-6-*nitroxanthone*.—The foregoing acid (7·0 g.) was heated on the water-bath with sulphuric acid for 1½ hr. and the solution poured on ice. Recrystallisation of the precipitated mixture (4·8 g.; m. p. 180°) of 3- and 1-chloro-6-nitroxanthone six times from aqueous

[11] Julia, *Bull. Soc. chim. France*, 1952, 546.

pyridine gave 3-*chloro*-6-*nitroxanthone* (1·7 g.) in yellow needles, m. p. 224—226° (Found: N, 5·1; Cl, 12·7. $C_{13}H_6O_4NCl$ requires N, 5·1; Cl, 12·9%). The mother-liquors from the 3rd and 4th crystallisations were diluted with water and the combined precipitates crystallised twice from aqueous pyridine; 1-*chloro*-6-*nitroxanthone* (0·8 g.) was obtained in pale yellow needles, m. p. 214—216° strongly depressed in admixture with the foregoing isomer (Found: N, 5·0; Cl, 12·6. $C_{13}H_6O_4NCl$ requires N, 5·1; Cl, 12·9%).

3-*Amino*-6-*chloroxanthone*.—3-Chloro-6-nitroxanthone (1·7 g.) was stirred at 100° with stannous chloride dihydrate (13·6 g.) and 10N-hydrochloric acid (13·6 c.c.) for 4 hr., and the mixture cooled and stirred with cold 2·5N-sodium hydroxide (300 c.c.) for ½ hour. The precipitate of 3-*amino*-6-*chloroxanthone* (1·0 g.) separated from aqueous-alcoholic pyridine as pale yellow prisms, m. p. 280—282° alone and on admixture with material obtained by cyclisation of 3′-acetamido-2-carboxy-5-chlorodiphenyl ether followed by deacetylation (Found: N, 5·6; Cl, 14·8. $C_{13}H_8O_2NCl$ requires N, 5·7; Cl, 14·5%).

2-*Carboxy*-5-*chloro*-3′-*nitrodiphenyl Ether*.—2 : 4-Dichlorobenzoic acid (19·0 g., 0·1 mole), *m*-nitrophenol (15·3 g., 0·11 mole), potassium carbonate (13·8 g., 0·1 mole), copper bronze (0·1 g.), and cuprous iodide (0·1 g.) were stirred with nitrobenzene (100 c.c.) for 6 hr. at 160—170°. Crystallisation of the crude product (22 g.; m. p. 140—160°) from alcohol gave the *acid* (12 g.), m. p. 180—182° (Found: *M*, 294. $C_{13}H_8O_5NCl$ requires *M*, 293·5).

6-*Chloro*-1-*nitroxanthone*.—The foregoing acid (11 g.) was cyclised by sulphuric acid (88 c.c.) at 100° for 1½ hr. The *product* crystallised from 80% pyridine in pale cream needles (8 g.), m. p. 216° (Found: C, 56·6; H, 2·1; N, 4·9; Cl, 12·8. $C_{13}H_6O_4NCl$ requires C, 56·6; H, 2·1; N, 5·1; Cl, 12·9%).

1-*Amino*-6-*chloroxanthone*.—Reduction of the foregoing compound (5·0 g.), with stannous chloride as described for the 2 : 6-isomer gave 1-*amino*-6-*chloroxanthone* (4·1 g.) which separated from aqueous-alcoholic dioxan in yellow needles, m. p. 164° alone and on admixture with material obtained from 6-chloro-1-toluene-*p*-sulphonamidoxanthone (Found: C, 63·2; H, 3·4; N, 5·9; Cl, 14·7. $C_{13}H_8O_2NCl$ requires C, 63·6; H, 3·3; N, 5·7; Cl, 14·5%).

3′-*Amino- and* 3′-*Acetamido*-2-*carboxy*-5-*chlorodiphenyl Ether*.—80% Hydrazine hydrate (16·5 c.c.) and Raney nickel (*ca.* 0·2 g.) were added to a solution of 2-carboxy-5-chloro-3′-nitrodiphenyl ether (12·9 g.) in ethanol (160 c.c.) stirred at room temperature. The temperature rose to 40° and remained there for 1 hr.; the mixture was stirred at room temperature for 4 hr., then at the b. p. for 2½ hr. The filtered solution was evaporated to dryness, the residual oil dissolved in N-hydrochloric acid (210 c.c.) at *ca.* 70°, and the filtered (charcoal) solution adjusted to pH 3·5 with dilute aqueous sodium hydroxide. The *amino-acid* (10·6 g.; m. p. 158—160°) was collected, washed, and dried at 40°; a sample crystallised from dilute alcohol in needles, m. p. 160° (Found: N, 5·1. $C_{13}H_{10}O_3NCl$ requires N, 5·3%). Acetic anhydride (25·5 g., 23 c.c.) was added dropwise during ½ hour to a solution of the amino-acid (13·4 g.) in 2N-sodiun carbonate vigorously stirred at 25°. The mixture was adjusted to pH 9 with sodium hydroxide, heated to 70°, and filtered (charcoal), and the 3′-acetamido-2-carboxy-5-chlorodiphenyl ether (14·5 g., m. p. 216°) precipitated with hydrochloric acid. A sample crystallised from dioxan in plates m. p. 216—218° (Found: N, 4·7. Calc. for $C_{15}H_{12}O_4NCl$: N, 4·6%).

3- *and* 1-*Amino*-6-*chloroxanthone*.—A solution of the foregoing acetamido-acid (6 g.) in sulphuric acid (60 c.c.) was heated on the water-bath for 2 hr , then cooled, water (16 c.c.) added, and the solution again heated on the water-bath for 1 hr. and poured on ice. After extraction with aqueous sodium carbonate the crude product (4·7 g.) had m. p. 258—260° with much pre-softening. Three crystallisations from pyridine yielded the less soluble 3-amino-6-chloroxanthone (2·3 g.) as pale buff needles, m. p. 280—282° alone and on admixture with a sample obtained from cyclisation of 2-carboxy-3′-chloro-5-nitrodiphenyl ether with subsequent reduction (Found: N, 5·6; Cl, 15·0. Calc. for $C_{13}H_8O_2NCl$: N, 5·7; Cl, 14·5%).

The mother-liquors were evaporated and the residue was crystallised twice from ethanol; 1-amino-6-chloroxanthone (0·25 g.) was obtained as yellow needles, m. p. 164° alone and on admixture with material obtained by hydrolysis of 6-chloro-1-toluene-*p*-sulphonamidoxanthone, but depressed by admixture with the foregoing 3-amino-6-chloro-isomer (Found: N, 5·8; Cl, 14·4. Calc. for $C_{13}H_8O_2NCl$: N, 5·7; Cl, 14·5%).

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