859. *Xanthones: Cyclisation of 3′-Substituted 2-Carboxydiphenyl Ethers.*

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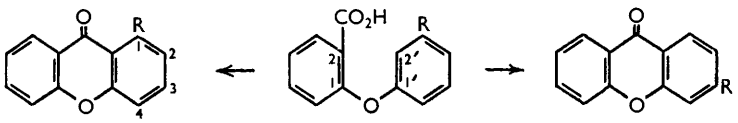
Cyclisation of 3′-substituted 2-carboxydiphenyl ethers has been studied in order to determine the effect of the 3′-substituent on the direction of ring closure. For substituents having a strong $-I$, $-M$ effect (NO_2, CO_2H, CN) the ratio of products respectively formed by cyclisation on to the 2′- and the 6′-position is of the order of 80 : 20. For substituents with a strong $-I$, $+M$ effect (NHAc, MeO) this ratio is approximately 25 : 75. When the substituent is Me or Cl (next paper) the ratio is *ca.* 50 : 50. The ratios are independent of the cyclising agent.

Cyclisation of a 3′-substituted 2-carboxydiphenyl ether may give a 1- or a 3-substituted xanthone according to whether ring closure takes place on the 2′- or the 6′-position.

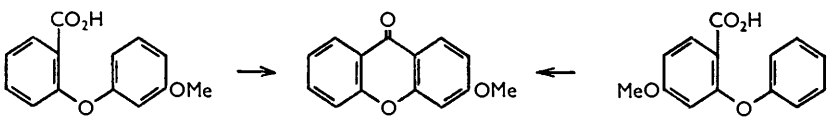
Former work [1] has shown that when R is NO_2 ($-I$, $-M$) the principal product is the 1-substituted xanthone (II), but that when R is NHAc ($-I$, $+M$) it is the isomer (III). The present communication relates to the cyclisation of acids of type (I) in which R is OMe, Me, CO_2H, CN, NO_2, or NHAc; the following paper refers to cases in which R is Cl.



(II) (I) (III)

It was of interest to examine the effect of variations of the electronic nature of R on the ratio of the two products formed by ring closure on to the 2′- and the 6′-position and also to determine whether the cyclising agent affects this ratio.

The cyclisation of acids of type (I) is an intramolecular acylation and appears to comprise two steps. The first is the rapid reversible acid-catalysed formation of a carbonium



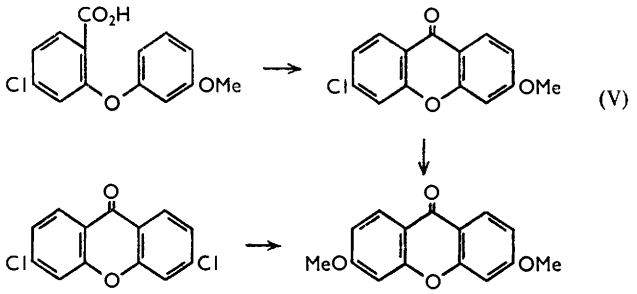
(IV)

ion $-C^+=O$ and the second, the rate-determining step, involves electrophilic attack of the carbonium ion on the non-carboxylated ring. The direction of cyclisation will therefore be controlled by the relative electron-densities at positions 2′ and 6′ in the excited structures. Cyclisation of 2-carboxydiphenyl ether by polyphosphoric acid has been shown to obey first-order kinetics with 10^4k equal to 3·2 and 18·7 at 63° and 83° respectively. From these values the Arrhenius and Eyring equations give the energy of activation E^* 20,900 cal. mole^{-1} and the entropy of activation ΔS^* −13 cal. deg.$^{-1}$. The comparatively large ΔS^* apparently reflects the loss in rotational freedom about the oxygen bridge when the rigid tricyclic transition structure is formed.

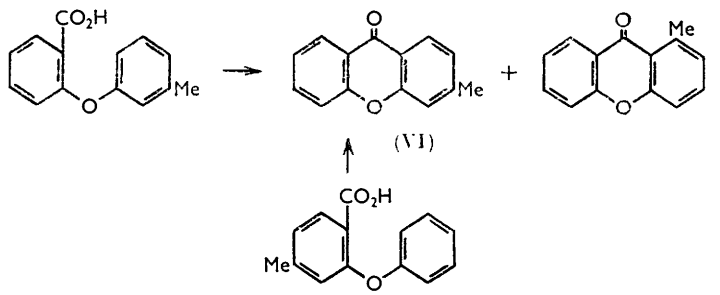
Cyclisation of 2-carboxy-3′-methoxydiphenyl ether with polyphosphoric acid gave 3-methoxyxanthone (IV) in high yield, identified by reference to unequivocal material obtained by ring closure of 2-carboxy-5-methoxydiphenyl ether. Similarly, cyclisation of 2-carboxy-5-chloro-3′-methoxydiphenyl ether gave a high yield of 3-chloro-6-methoxyxanthone (V), converted by sodium methoxide into 3 : 6-dimethoxyxanthone. The orientation of the latter was proved by its identity with 3 : 6-dimethoxyxanthone obtained from authentic 3 : 6-dichloroxanthone (see below).

[1] Goldberg and Walker, *J.*, 1953, 1348.

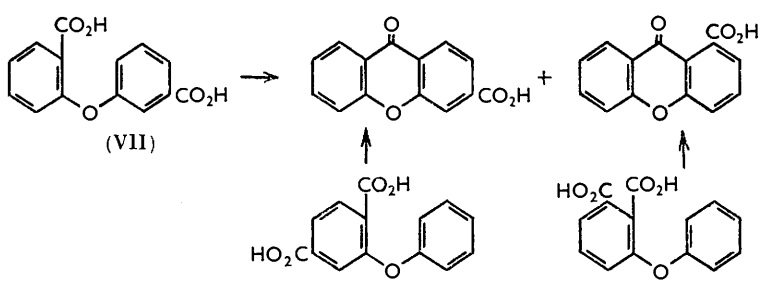
2-Carboxy-3′-methyldiphenyl ether cyclised in refluxing acetic anhydride to a mixture of two methylxanthones. These were separated by fractional crystallisation into the



less soluble 3-methylxanthone (VI), identified by reference to an unequivocal specimen obtained by cyclodehydration of 2-carboxy-5-methyldiphenyl ether, and the more soluble isomer which must be 1-methylxanthone. From the amounts of the pure isomers isolated



it was apparent that both isomers are formed in substantial quantity with a slight predominance of the 3-isomer.



Cyclisation of 2 : 3′-dicarboxydiphenyl ether (VII) with polyphosphoric acid gave a mixture of xanthonecarboxylic acids separable, by virtue of the large difference in solubilities of their pyridine salts, into xanthone-1- and -3-carboxylic acid in the ratio of 85 : 15. The orientation of the former was proved by its identity with xanthone-1-carboxylic acid obtained by condensation of 3-chlorophthalic acid with phenol and cyclisation of the resulting 2 : 3-dicarboxydiphenyl ether; the constitution of the other isomer was proved by reference to unequivocal material obtained by condensation of 2-chloro-4-methylbenzoic acid with phenol, and oxidation of the product to 2 : 5-dicarboxydiphenyl ether, followed by cyclisation. Separation of xanthone-1- and -3-carboxylic acid, *via* their pyridine salts, has been shown to be quantitatively reliable, within 1%, by application to synthetic mixtures of the pure isomers. Anschütz, Stoltenhoff, and Voeller [2] cyclised 2 : 3′-dicarboxydiphenyl ether by treatment of its diacid dichloride in tetrachloroethane

[2] Anschütz, Stoltenhoff, and Voeller, *Ber.*, 1925, **58**, 1736.

with anhydrous oxalic acid, obtaining a small yield of an acid stated to be either xanthone-1- or -3-carboxylic acid. Repetition of their work gave an 87% yield of crude product, separable by the pyridine method into xanthone-1- (77%) and -3-carboxylic acid (9%). Anschütz *et al.* apparently failed to find the principal product, the 1-carboxylic acid, because of its high solubility in the cyclising solvent. The formation of the 1- and the 3-carboxylic acid in substantially the same ratio whether polyphosphoric acid or oxalic acid (respectively a powerful and a feeble protonising agent) is used strongly supports the theoretical deduction that the cyclising agent does not affect the direction of ring closure.

m-Cyanophenol condensed with *o*-chlorobenzoic acid to yield 2-carboxy-3′-cyanodiphenyl ether; this cyclised on treatment with phosphoryl chloride to 1-cyanoxanthone, oriented by hydrolysis to xanthone-1-carboxylic acid.

Goldberg and Walker [1] cyclised 2-carboxy-3′-nitrodiphenyl ether, and also the 4-, 5-, and 6-nitro-derivative, with phosphoryl chloride or sulphuric acid, and obtained in each case *ca.* 80% yields of the product obtained by ring closure on the 2′-position, with, in some instances, a small amount (*ca.* 5—15%) of the isomer formed by cyclisation on to the 6′-position. In the present investigation the ratio of the isomers formed by cyclisation of 2-carboxy-3′-nitrodiphenyl ether has been determined with greater precision by using two novel methods of analysis. In one method the mixture was reduced and the mixed aminoxanthones were diazotised and converted into a mixture of 1- and 3-hydroxyxanthones, easily separable by virtue of the complete insolubility of the sodium salt of the former, and the comparatively large solubility of the sodium salt of the latter, in dilute sodium hydroxide. The results showed that the crude cyclisation product contained not less than 11% of 3-nitroxanthone. In the second method, the mixture of 1- and 3-aminoxanthone was photometrically analysed; 1-aminoxanthone is intensely yellow while 3-aminoxanthone is colourless. This method proved that the cyclisation product obtained with sulphuric acid at 100° contained 82% of 1- and 18% of 3-nitroxanthone.

By the same analytical procedure it has been shown that ring closure of 3′-acetamido-2-carboxydiphenyl ether with polyphosphoric acid at 100° gives a product containing 72% of 3- and 28% of 1-aminoxanthone.

The cyclodehydration of 2-carboxy-3′-nitrodiphenyl ether by polyphosphoric acid has been examined in more detail; with this reagent there is no loss by formation of water-soluble compounds (as with sulphuric acid) and the method lends itself to kinetic studies. Reduction of the mixture of 1- and 3-nitroxanthone and analysis of the product by the photometric method enabled the rate constants k_1 and k_3 (ring closure to give 1- and 3-nitroxanthone respectively) to be separated and the energies and entropies of activation calculated for the two simultaneous reactions. The energies of activation for cyclisation on to the 2′- and the 6′-position are equal within the experimental error, being *ca.* 16,000 cal. mole^{-1} above that for the cyclodehydration of 2-carboxydiphenyl ether. The ratio of the products formed by cyclisation on to the 2′- and the 6′-position is therefore independent of the activation energies but is governed entirely by the ratio of the frequency factors $A_1/A_2 = ca.\ 4{\cdot}0$.

It is apparent that for 3′-substituents having a strong $-I$, $-M$ effect (NO_2, CO_2H, CN) the ratio of products respectively formed by cyclisation on to the 2′- and the 6′-position (the 2′ : 6′-closure ratio) is of the order of 80 : 20. For substituents with a strong $-I$, $+M$ effect (NHAc, MeO) this ratio is approximately 25 : 75. When the substituent is Me or Cl (next paper), the ratio is *ca.* 50 : 50. The ratio of the two isomers formed is independent of the cyclising agent.

Experimental

General Procedure for the Condensation of o-*Chlorobenzoic Acids with Phenols.*—The method previously described [1] using nitrobenzene, hexyl alcohol, or anisole as diluent was used whenever possible since this procedure can be scaled up without loss of yield. A number of such reactions, however, give meagre yields but excellent yields are obtainable by the " dry "

method originally employed by Ullmann and his collaborators. The *o*-chlorobenzoic acid, phenol, and catalyst were added in this order to hot methanol containing 3 mols. of sodium methoxide; the methanol was distilled off, the glutinous residue heated for a short time at 180—200°, and the product isolated by the usual procedure. Unfortunately this method does not give good yields when scaled up. Molecular weights of acids were determined by titration.

2-*Carboxy*-3′-*methoxydiphenyl Ether*.—*o*-Chlorobenzoic acid (15·7 g.), potassium carbonate (34 g.), *m*-methoxyphenol (16·5 g.), copper bronze (0·2 g.), cuprous iodide (0·2 g.), and nitrobenzene (100 c.c.) were stirred at 160° for 6 hr. The purified *product* separated from dilute methanol in colourless needles (10 g.), m. p. 128—130° (Found: *M*, 240. $C_{14}H_{12}O_4$ requires *M*, 244).

3-*Methoxyxanthone*.—The foregoing acid (7·0 g.) was heated on the water-bath with acetic anhydride (70 c.c.) and sulphuric acid (0·7 c.c.) for 1½ hr., then poured into ice-water. The precipitate was collected, extracted with N-sodium carbonate, and washed; crystallisation from 95% alcohol gave 3-methoxyanthone (4·5 g., 70%), m. p. 130—132° alone and in admixture with authentic material obtained by cyclisation of 2-carboxy-5-methoxydiphenyl ether [3] (Found: C, 73·4; H, 4·4. Calc. for $C_{14}H_{10}O_3$: C, 74·3; H, 4·4%).

3-*Chloro*-6-*methoxyxanthone*.—2 : 4-Dichlorobenzoic acid (19·1 g., 0·1 mole), *m*-methoxyphenol (18·6 g., 0·15 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 (80 c.c.). The methanol was distilled off on the water-bath, nitrobenzene (10 c.c.) added, and the mixture placed in an oil-bath at 120° the temperature of which was raised during 10 min. to 190—200° and held thereat for 10 min. The product was a dark solid acid (16·1 g.) which could not be effectively purified. The crude acid was cyclised on the water-bath for 2 hr. with acetic anhydride (150 c.c.) containing sulphuric acid (0·5 c.c.), and then poured on ice. Recrystallisation from aqueous pyridine gave 3-*chloro*-6-*methoxyxanthone* as colourless needles (8·7 g., 33% overall), m. p. 166° (Found: Cl, 13·3. $C_{14}H_9O_3Cl$ requires Cl, 13·6%).

3 : 6-*Dimethoxyxanthone*.—The foregoing compound (2·0 g.) was refluxed for 100 hr. with a solution from sodium (2·0 g.) in methanol (100 c.c.) and dioxan (50 c.c.). The methanol was evaporated and the residue washed with dilute hydrochloric acid and then water; recrystallisation from alcohol gave 3 : 6-*dimethoxyxanthone* (1·9 g., 97%), m. p. 184—186° alone and in admixture with material obtained from 3 : 6-dichloroxanthone [4] (Found: C, 70·1; H, 4·5. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

Cyclisation of 2-*Carboxy*-3′-*methyldiphenyl Ether*. 1- *and* 3-*Methylxanthone*.—*o*-Chlorobenzoic acid (62·6 g.), *m*-cresol (87 g.), potassium carbonate (56 g.), nitrobenzene (300 c.c.), copper bronze (0·2 g.), and cuprous iodide (0·2 g.) were stirred at 160—165° for 5 hr. 2-Carboxy-3′-methyldiphenyl ether crystallised from aqueous alcohol as colourless needles (42 g.), m. p. 95° (Found: *M*, 229. Calc. for $C_{14}H_{12}O_3$: *M*, 228).

A solution of this acid (10 g.) in acetic anhydride (100 c.c.) and sulphuric acid (2 c.c.) was refluxed for 1½ hr., then poured on ice. The precipitate was collected, extracted with aqueous sodium carbonate, washed, and dried. The mixture of 1- and 3-methylxanthone (8·6 g.; m. p. 70—80°) was crystallised six times from 85% methanol, to give 1-*methylxanthone* (1·6 g.) as long colourless needles, m. p. 114°, which strongly depressed the m. p. of authentic 3-methylxanthone (m. p. 92°) obtained by cyclisation of 2-carboxy-5-methyldiphenyl ether (Found: C, 80·2; H, 4·6. $C_{14}H_{10}O_2$ requires C, 80·1; H, 4·8%).

The mother-liquors from the first, second, and third crystallisations above, when kept for 7 days, deposited needles, m. p. 65—75°. These were combined and crystallised six times from dilute methanol to give 3-*methylxanthone* (1·2 g.), m. p. 94°, depressed in admixture with 1-methylxanthone but not with authentic 3-methylxanthone (Found: C, 80·0; H, 4·7. $C_{14}H_{10}O_2$ requires C, 80·1; H, 4·8%).

2-Carboxy-3′-methyldiphenyl ether was not cyclised by acetic anhydride at 100° in 1 hr.

Cyclisation of 2 : 3′-*Dicarboxydiphenyl Ether*.—(i) *With polyphosphoric acid*. A mixture of 2 : 3′-dicarboxydiphenyl ether [2] (10 g.) and polyphosphoric acid (170 g.) was stirred at 100° for 80 min., kept at room temperature for a further 3 hr., then stirred with water (300 c.c.). The precipitate was collected and dissolved in excess of warm dilute sodium hydroxide solution, the solution filtered (charcoal), and the acid (8·7 g.; m. p. 218—224°) reprecipitated. The acid (8·0 g.) was dissolved in hot pyridine (20 c.c.), water (200 c.c.) was added, and the clear

[3] Ullmann and Wagner, *Annalen*, 1907, **355**, 369.
[4] Goldberg and Wragg, following paper.

solution left in the refrigerator for 10 days. The crystalline precipitate was collected, drained, and washed into the filtrate (*A*) with a little water, then boiled with water (200 c.c.) and 5N-sodium hydroxide (5 c.c.). The salt dissolved and the pyridine passed off in the steam. Acidification yielded *xanthone-3-carboxylic acid* (0·8 g., 10%), m. p. 304—306°. Crystallisation from alcohol–dioxan gave the pure compound as needles, m. p. 320° alone and in admixture with authentic material obtained by cyclisation of 2 : 5-dicarboxydiphenyl ether (Found; *M*, 241. $C_{14}H_8O_4$ requires *M*, 240).

The pyridine filtrate (*A*) was heated to 70°, excess of hydrochloric acid added, and the precipitate of xanthone-1-carboxylic acid (7·0 g., 88%; m. p. 230°) collected; crystallisation from alcohol–dioxan gave the pure acid, m. p. 232° alone and in admixture with authentic material obtained by cyclisation of 2 : 3-dicarboxydiphenyl ether but depressed in admixture with xanthone-3-carboxylic acid (Found: *M*, 242).

When an artificial mixture of pure xanthone-1- (3·5 g.; m. p. 320°) and -3-carboxylic acid (0·4 g.; m. p. 232°) was separated by the above procedure there were obtained 0·39 g. of the 3-carboxylic acid, m. p. 316—318°, and 3·49 g. of the 1-carboxylic acid, m. p. 226—228°.

(ii) *Cyclisation of the diacid dichloride with oxalic acid* (cf. Anschütz [2] *et al.*). 2 : 3'-Dicarboxydiphenyl ether (2·58 g., 0·01 mole) was suspended in cold tetrachloroethane (60 c.c.); phosphorus pentachloride (5·0 g., 0·024 mole) was added, and the mixture heated at 100° for ½ hr. and set aside overnight. The volatile materials were pumped off at 100° and the residual oil was redissolved in tetrachloroethane (60 c.c.). Anhydrous oxalic acid (1·8 g., 0·02 mole) was added, and the temperature raised during 10 min. to the b. p. and kept thereat for a further 10 min. The solvent was evaporated and the residue dissolved in water (60 c.c.) containing excess of sodium carbonate; the solution was extracted with chloroform (2 × 25 c.c.), the filtered (charcoal) aqueous layer adjusted to pH 1, and the precipitate (2·0 g., 84%; m. p. 214—220°) collected (Found: *M*, 236). Separation through the pyridine salts yielded 0·17 g. (9%) of xanthone-3-carboxylic acid, m. p. 316°, and 1·54 g. (78%) of xanthone-1-carboxylic acid, m. p. 228°.

1·0 g. of xanthone-1-carboxylic acid just dissolves in 4·5 c.c. of boiling tetrachloroethane and in 95 c.c. at room temperature; 1·0 g. of xanthone-3-carboxylic acid in 500 c.c. of boiling tetrachloroethane; 1·0 g. of 2 : 3'-dicarboxydiphenyl ether in 50 c.c. of tetrachloroethane at the b. p.

2 : 3-*Dicarboxydiphenyl Ether.*—3-Chlorophthalic acid (30·1 g.), phenol (70·5 g.), potassium carbonate (52 g.), nitrobenzene (250 c.c.), copper bronze (0·5 g.), and cuprous iodide (0·5 g.) were stirred at 165—170° for 6 hr. The product (17 g.) was dissolved in N-sodium carbonate (200 c.c.), potassium permanganate (10 g.) slowly added, and the solution boiled for ½ hr.: sodium metabisulphite (30 g.) was added and the *dicarboxylicacid* (14·6 g.; m. p. 202°) precipitated. It crystallised from dilute ethanol as colourless needles, m. p. 204° (Found: *M*, 132; C, 65·1; H, 3·9%. $C_{14}H_{10}O_5$ requires *M*, 129; C, 65·1; H, 3·9%).

Xanthone-1-carboxylic Acid (cf. below).—A mixture of the foregoing acid (5 g.) and polyphosphoric acid (95 g.) was stirred at 100° for 4 hr., then kept at room temperature for 2 days. Water (150 c.c.) was added, the precipitate collected and dissolved in diluted aqueous sodium hydroxide, and the filtered solution acidified. Crystallisation from alcohol–dioxan gave *xanthone-1-carboxylic acid* (3·1 g.), m. p. 231—232° (Found: C, 69·9; H, 3·3. $C_{14}H_8O_4$ requires C, 70·0; H, 3·3%).

2-*Carboxy-5-methyldiphenyl Ether.*—4-Amino-3-chlorotoluene (35·4 g.) in 10N-hydrochloric acid (50 c.c.) and water (200 c.c.) was diazotised at 2° by sodium nitrite (17·25 g.) in water (50 c.c.). After a further 15 min. the solution was added during 10 min. to a vigorously refluxing solution of nickel chloride hexahydrate (63 g.) and sodium cyanide (63 g.) in water (400 c.c.). The mixture was boiled for a further 30 min., then distilled in steam; 3-chloro-4-cyanotoluene (27 g., 70%) distilled and formed a white solid, m. p. 60—62°. This compound (15·2 g.) was refluxed with sodium hydroxide (30 g.) and water (70 c.c.) for 9 hr. In the morning the solution was reheated, then filtered (charcoal), and the 2-chloro-4-methylbenzoic acid (15·7 g.; m. p. 156°) precipitated by acidification.

This acid (25·6 g.), phenol (85 g.), potassium carbonate (52 g.), nitrobenzene (250 c.c.), copper bronze (0·5 g.), and cuprous iodide (0·5 g.) were stirred at 160—165° for 6 hr. 2-*Carboxy-5-methyldiphenyl ether* was isolated as colourless prisms (12·7 g.; from dilute methanol), m. p. 132—133° (Found: *M*, 229. $C_{14}H_{12}O_3$ requires *M*, 228).

2 : 5-*Dicarboxydiphenyl Ether.*—Potassium permanganate (55 g.) was added portionwise

during ½ hr. to a boiling solution of the foregoing acid (10 g.) in N-sodium carbonate (550 c.c.). The mixture was refluxed for a further ½ hr., then sodium pyrobisulphite (60 g.) was added and the stirred mixture strongly acidified with hydrochloric acid. The precipitate was collected and purified by dissolution in aqueous sodium carbonate, filtration (charcoal), and reprecipitation. The *acid* crystallised from aqueous ethanol as colourless needles (7·0 g.), m. p. 300° (Found: C, 65·0; H, 4·0. $C_{14}H_{10}O_5$ requires C, 65·1; H, 3·9%).

Xanthone-3-carboxylic Acid.—The foregoing acid (2·58 g.) was heated with polyphosphoric acid (37 g.) at 100° for 1½ hr. The crude product (2·3 g.; m. p. 264°) on crystallisation from alcohol–dioxan yielded *xanthone-3-carboxylic acid* (1·5 g.) as colourless needles, m. p. 308° (Found: C, 69·8; H, 3·4. $C_{14}H_8O_4$ requires C, 70·0; H, 3·3%).

3-*Methylxanthone.*—A solution of 2-carboxy-5-methyldiphenyl ether (4·5 g.) in acetic anhydride (40 c.c.) and sulphuric acid (0·5 c.c.) was heated on the water-bath for 1½ hr., then kept at room temperature overnight. The solution was stirred with ice-water (300 g.) and set aside. The precipitate, after extraction with hot aqueous sodium carbonate, crystallised from aqueous methanol to give 3-methylxanthone (3·2 g.) as needles, m. p. 97° (Found: C, 79·9; H, 4·9. Calc. for $C_{14}H_{10}O_2$: C, 80·1; H, 4·8%).

m-*Cyanophenol.*—The following is the route used by Culbertson, Carpenter, and Nielsen [5] who did not give experimental details. *m*-Hydroxybenzaldehyde (48·8 g.) was added during 15 min. to a solution of hydroxylamine hydrochloride (28 g.) in water (60 c.c.) and 5N-sodium hydroxide (80 c.c.) stirred at room temperature, and the solution was then heated on the water-bath for 15 min. and set aside. In the morning the precipitated oil was separated and the aqueous layer saturated with ammonium sulphate and extracted with ether (4 × 100 c.c.). The oil and ether extracts were combined and dried (Na_2SO_4), and the ether distilled off. The residual oily oxime was dried at 100°/10 mm., refluxed with acetic anhydride (120 c.c.) for 3 hr., and poured on crushed ice (500 g.), and the mixture was rapidly stirred at 0°—10° for 2 hr. in order to free the precipitated oil from occluded acetic anhydride. The oil was collected and refluxed with 2·5N-sodium hydroxide (400 c.c.) for 45 min., and the solution filtered (charcoal), acidified with 10N-hydrochloric acid (90 c.c.), and extracted with ether (4 × 300 c.c.). The ether extracts were dried (Na_2SO_4), the ether was distilled off, and the oil dissolved in chloroform (250 c.c.) and carbon tetrachloride (100 c.c.). Distillation of *ca.* 200 c.c. of the solvent and then addition of ligroin to the residue precipitated pale ochre *m*-cyanophenol (25 g.), m. p. 80—85°.

2-*Carboxy-3'-cyanodiphenyl Ether.*—*o*-Chlorobenzoic acid (7·83 g., 0·05 mole), *m*-cyanophenol (6·6 g., 0·055 mole), and a trace of copper–copper iodide catalyst were added to a solution from sodium (2·3 g., 0·1 g.-atom) in methanol (50 c.c.). The methanol was distilled off at 10 mm. and the residual solid placed in an oil-bath at 120° and the temperature raised to 180° during 10 min. Boiling nitrobenzene (10 c.c.) was added with mixing and the heating continued for a further 20 min. Water (150 c.c.) and potassium carbonate (5 g.) were added, the nitrobenzene removed by extraction with ether, and the aqueous layer acidified. The precipitate was collected and dissolved in aqueous potassium carbonate, the solution filtered (charcoal), and the *acid* (10 g.) reprecipitated. Crystallisation from dilute methanol gave the pure acid (5 g.), as colourless prisms m. p. 148—150° (Found: *M*, 238; C, 70·6; H, 3·8; N, 6·0%. $C_{14}H_9O_3N$ requires *M*, 239; C, 70·3; H, 3·8; N, 5·9%).

1-*Cyanoxanthone.*—The foregoing acid (3 g.) was refluxed with phosphoryl chloride (25 c.c.) for 3 hr. and the solution poured on ice (200 g.). The precipitate was collected and extracted with hot aqueous potassium carbonate; crystallisation twice from aqueous dioxan gave 1-*cyanoxanthone* (1·4 g.) as fawn needles, m. p. 196—198° (Found: C, 76·7; H, 3·1; N, 6·2. $C_{14}H_7O_2N$ requires C, 76·1; H, 3·2; N, 6·3%).

Xanthone-1-carboxylic Acid (cf. above).—A solution of the cyano-compound (1 g.) in dioxan (20 c.c.) and 6N-sodium hydroxide (40 c.c.) was heated on the water-bath for 80 hr. The solvent was evaporated, water added, the insoluble material removed, the filtered solution acidified, and the precipitate crystallised from alcohol–dioxan–water. Xanthone-1-carboxylic acid (0·4 g.) was obtained in prisms, m. p. 230—232° alone and in admixture with a sample obtained from 3-chlorophthalic acid (Found: *M*, 238. Calc. for $C_{14}H_8O_4$: *M*, 240).

Cyclisation of 2-Carboxy-3'-nitrodiphenyl Ether.—The acid was cyclised with sulphuric acid by the method of Goldberg and Walker.[1] The *crude* product (25 g.; m. p. 182—192°) was crystallised five times from 90% pyridine to yield 13·2 g. of pure 1-nitroxanthone, m. p. 202°;

[5] Culbertson, Carpenter, and Nielsen, *Proc. Iowa Acad. Sci.*, 1930, **37**, 248.

evaporation of the mother-liquors gave 9·5 g. of a mixture of 1- and 3-nitroxanthone. The latter (9·5 g.) was reduced with stannous chloride (60 g.) and 10N-hydrochloric acid (60 c.c.) by the method previously described, and the mixture of 1- and 3-aminoxanthone (8·2 g.) isolated. This was dissolved in sulphuric acid (25 c.c.), and the solution poured into water (130 c.c.) with vigorous stirring. The fine suspension was diazotised at 2° with sodium nitrite (2·9 g.) in water (12 c.c.) and, after 15 minutes' stirring at room temperature, added dropwise to a boiling solution of copper sulphate pentahydrate (18 g.) in 5N-sulphuric acid (650 c.c.). After boiling for a further 10 min. the mixture was cooled, the insoluble material collected and ground with excess of 5N-sodium hydroxide and the mixture filtered. The insoluble portion was extracted again in the same manner. Acidification of the combined extracts gave 3-hydroxyxanthone (2·5 g.), m. p. and mixed m. p. 240—242°. The insoluble sodium salt of the 1-hydroxyxanthone was ground in a ball-mill with 5N-sulphuric acid, and the mixture extracted in the ball-mill with ether (5 × 25 c.c.). Evaporation of the ether gave crude 1-hydroxyxanthone (1·86 g.); distillation of this in steam gave the pure compound (1·1 g.), m. p. 148°. The isolation of 2·5 g. of 3-hydroxyxanthone indicated that the original crude product of cyclisation of 2-carboxy-3'-nitrodiphenyl ether contained not less than 11% of 3-nitroxanthone.

Photometric Analysis of Mixtures of 1- *and* 3-*Aminoxanthone.*—The optical density of a 0·02% solution of 1-aminoxanthone in methanol in a 2 cm. cell in a Spekker Photometer with the No. 7 Purple Chance glass filter [6] (transmitting principally in the 4000—4700 Å range) was 0·58 (ε 306); that of a similar solution of 3-aminoxanthone was 0·015 (ε 7·95). For synthetic mixtures of the pure isomerides containing a *total* of 0·02% of aminoxanthones (with % 1-aminoxanthone in parentheses) the optical densities were 0·015 (0); 0·18 (10); 0·275 (20); 0·340 (30); 0·390 (40); 0·44 (50); 0·48 (60); 0·51 (70); 0·53 (80); 0·56 (90); 0·58 (100). From the plot it was possible to analyse unknown mixtures with an estimated precision of ±1%.

Experiments on Reaction Kinetics.—Polyphosphoric acid was prepared by the portionwise addition of phosphoric oxide (186 g.) to 90% orthophosphoric acid (d = 1·75; 120 c.c.) with hand-swirling. The temperature rose steeply. After ½ hr. the mixture was heated on the water-bath for 2 hr. with occasional shaking. The product was a colourless viscous liquid which slowly solidified; it was used within 6 weeks of preparation.

(i) *Cyclisation of* 2-*carboxydiphenyl ether.* Polyphosphoric acid (50 g.) was stirred in a thermostat until temperature equilibrium was attained, and the 2-carboxydiphenyl ether (5·0 g.) then added. After a given time interval the flask was removed, ice-water (400 c.c.) quickly added, and the whole set aside for 2 hr. The precipitate was collected, washed with water, extracted with boiling 10% aqueous sodium carbonate (200 c.c.) to remove uncyclised carboxylic acid, again washed, dried, and weighed. Acidification of the alkali extract gave unchanged starting acid; the amount of unrecovered material was usually 0·1—0·2 g. The first-order reaction equation $kt = \ln [a/(a - x)]$, where a was the initial concentration of 2-carboxydiphenyl ether and x the concentration of xanthone at time t, gave 10^4k, for reaction times 15, 30, 50, and 80 min., at 63°, respectively, 3·4, 3·4, 3·1, and 2·9 (average 3·2). At 83° the values of 10^4k, for reaction times 10, 10, 15, and 20 min., were 20·7, 19·1, 16·4, and 18·7 (average 18·7). By using the Arrhenius and Eyring equations $k = A \exp - E^*/\boldsymbol{R}T$ and $k = (\boldsymbol{R}T/\boldsymbol{N}h) \exp(-E^*/\boldsymbol{R}T) . \exp(\Delta S^*/\boldsymbol{R})$ where $\boldsymbol{R}$ = 1·987 cal. deg.$^{-1}$, $\boldsymbol{R}/\boldsymbol{N}$ (Boltzmann constant) = 1·3805 × 10^{-16} erg deg.$^{-1}$, h (Planck constant) = 6·624 × 10^{-27} erg sec., these values for the k's give E^* = 20,900 cals. mole^{-1}; log A = 10·1; and ΔS^* = −13 cals. deg.$^{-1}$.

(ii) *Cyclisation of* 2-*carboxy*-3'-*nitrodiphenyl ether.* The values found by the same method for $10^4(k_1 + k_3)$, where k_1 is the reaction rate for cyclisation to 1-nitroxanthone and k_3 that for cyclisation to 3-nitroxanthone at 63° (with reaction time in min. in parentheses) were 0·15 (70), 0·16 (90), 0·19 (150), 0·17 (210), and 0·14 (300) with an average of 0·16. At 83° the values for $10^4(k_1 + k_3)$ were 3·46 (8), 3·74 (15), 3·68 (22), and 3·36 (30) with an average value of 3·56.

In order to obtain separate values for k_1 and k_3 it was necessary to determine the ratio of 1- and 3-nitroxanthone formed at each reaction temperature. The mixture of nitroxanthones (5·0 g.), stannous chloride dihydrate (40 g.), and 10N-hydrochloric acid (40 c.c.) was stirred on the water-bath for 2½ hr. In the morning the mass was stirred with 5N-sodium hydroxide (250 c.c.) and ice (250 g.) for 2 hr., and the solid collected and ground with cold N-sodium hydroxide (150 c.c.) in a glass ball-mill to remove traces of tin. The yellow solid was collected washed, and dried at 40°/10 mm.; the recovery was ~ 95%. The mixture obtained from each

[6] Delory, " Photoelectric Methods in Clinical Biochemistry," Hilger and Watts, 1949, p. 19.

series was analysed photometrically. For the cyclisations at 63° the optical density of the standard 0·02% solution was 0·524 (76% of 1- and 24% of 3-aminoxanthone); for the cyclisation at 83° the optical density was 0·518 (74% of 1- and 26% of 3-aminoxanthone). Accordingly, at 63°, $10^4k_1 = 0{\cdot}12$, and $10^4k_3 = 0{\cdot}04$; and at 83°, $10^4k_1 = 2{\cdot}68$, and $10^4k_3 = 0{\cdot}88$. These values give for ring closure on to the 2′-position to yield 1-nitroxanthone: $E^*_1 = 36{,}920$ cal. mole^{-1}, log $A_1 = 19{\cdot}1$, $\Delta S^*_1 = 29$ cal. deg.$^{-1}$; and for simultaneous ring closure on to the 6′-position to give 3-nitroxanthone, $E^*_3 = 36{,}740$ cal. mole^{-1}, log $A_3 = 18{\cdot}5$, $\Delta S^*_3 = 26$ cal. deg.$^{-1}$.

Cyclisation of 3-Acetamido-2′-carboxydiphenyl Ether.—Acetic anhydride (20 g.) was added during 45 min. to a solution of the 3′-amino-2-carboxylic acid [1] (11 g.) in sodium carbonate (23 g.) and water (200 c.c.) stirred at 15°. After a further 15 minutes' stirring the mixture was adjusted to pH 8·5, filtered (charcoal), and acidified. The precipitated *acetamido-acid* (11·5 g., m. p. 196°) crystallised from aqueous-alcoholic dioxan in prisms, m. p. 198—200° (Found: N, 5·2. $C_{15}H_{13}O_4N$ requires N, 5·2%).

(i) The acetamido-acid (5 g.) was heated for 2 hr. at 100° with polyphosphoric acid (50 g.); water (20 c.c.) was added, heating continued for 1 hr., and the solution poured on ice. In the morning the precipitate (3·2 g.; m. p. 190—210°) was collected, washed, and dried. A 0·02% solution in methanol in a 2 cm.cell had an optical density of 0·328 (No. 7 light filter); this indicated a composition of 72% of 3- and 28% of 1-aminoxanthone.

(ii) The acetamido-acid (5 g.) was heated at 100° with acetic anhydride (15 c.c.) and sulphuric acid (10 c.c.) for ½ hr., the solution poured into ice water, and the precipitate collected and extracted with dilute sodium carbonate. Crystallisation from aqueous pyridine gave 3-acetamidoxanthone (2·0 g.) as buff plates, m. p. 312° (Found: N, 5·6. Calc. for $C_{15}H_{11}O_3N$: N, 5·5%): hydrolysis with 75% sulphuric acid at 100° for 1 hour yielded 3-aminoxanthone, m. p. 234—235°.

The authors thank Mr. R. J. Crabbe for technical assistance.

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[*Received, June 5th*, 1958.]