Rearrangement of Aryl Halogenoacetates during Nucleophilic Substitution

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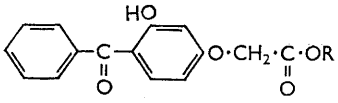
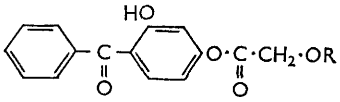
The reaction between aryl halogenoacetates and alcohols or phenols in acetone containing potassium carbonate leads to derivatives in which the more basic nucleophile is attached to the carbonyl group. Rearrangement occurs if necessary to produce this derivative.

DURING investigation of the preparation of 4-substituted derivatives of 2,4-dihydroxybenzophenone,[1] the reaction of certain halogenoacetates with alcohols and phenols has been examined. A halogen atom α to the carbonyl group of a ketone or (to a lesser extent) an ester, is highly reactive in bimolecular substitution reactions. We find that rearrangement can occur during the reaction of phenols and alcohols with aryl halogenoacetates.

Two types of ester derivative of 2,4-dihydroxybenzophenone have been prepared (I) and (II). Esters (I) of 4-carboxymethoxy-2-hydroxybenzophenone were prepared either directly or *via* the acid chloride, whilst esters of type (II) were prepared by direct esterification of the appropriate aryloxyacetic acid with 2,4-dihydroxybenzophenone. They were characterised by i.r. spectroscopy, elemental analysis and hydrolysis to the starting materials.



(I)



(II)

R = Pentachlorophenyl, 2,4,6-trichlorophenyl, 2,4,5-trichlorophenyl, 2,4,6-tribromophenyl, phenyl, ethyl, or methyl [(I) only].

When the bromoacetate of pentachlorophenol, 2,4,6-trichlorophenol, 2,4,5-trichlorophenol, or 2,4,6-tribromophenol was treated with 2,4-dihydroxybenzophenone in ethanolic sodium ethoxide, no reaction was observed,

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[1] F. S. H. Head, preceding paper.

but in acetone containing potassium carbonate esters of type (II) were obtained. Phenyl and ethyl bromoacetate, on the other hand, gave the expected esters (I) in acetone–potassium carbonate, although with ethyl bromoacetate the yield was small and better results were obtained with ethanolic sodium ethoxide. Aryl chloroacetate did not react with 2,4-dihydroxybenzophenone in either solvent system, but gave the same products as the bromoacetates with acetone–potassium carbonate in the presence of sodium iodide (1 equiv.).

Treatment of 4-bromoacetoxy-2-hydroxybenzophenone with pentachlorophenol, 2,4,6-trichlorophenol, 2,4,5-trichlorophenol, or 2,4,6-tribromophenol in acetone–potassium carbonate gave the expected esters (II), but treatment with phenol, ethanol, or methanol gave the alternative esters (I). Yields from reactions with ethanol and methanol were small, but the reaction also occurred to a small extent in ethanolic sodium ethoxide. 4-Chloroacetoxy-2-hydroxybenzophenone did not react with phenols or alcohols under either set of conditions.

The anomalous reactions might be attributed to acyl exchange, when the added phenol or alcohol was more basic than that in combination, followed by reaction of the displaced phenol with the new bromoacetate formed. Acyl migration occurs, for example, when *p*-nitrophenyl bromoacetate is used to bromoacetylate the amino-group of an amino-acid in polypeptide synthesis.[2] During the reaction of 4-bromoacetoxy-2-hydroxybenzophenone with ethanol a smell reminiscent of ethyl bromoacetate can indeed be detected, but it seems unlikely that rapid and complete migration of a bromoacetoxy-group would occur with a phenol of only slightly greater basicity. In agreement with this when 2,4-dihydroxybenzophenone was heated with pentachlorophenyl acetate and potassium carbonate in acetone, only 5% of 4-acetoxy-2-hydroxybenzophenone could be isolated. A mechanism involving acyl exchange would be expected to lead to mixtures of products, but attempts to isolate type (I) esters from reactions producing those of type (II) and *vice versa* were invariably unsuccessful.

Consideration of the mechanisms advanced for the enhanced reactivity of α-halogeno-carbonyl compounds in nucleophilic substitutions,[3] suggests that an intramolecular mechanism may operate.

Pearson *et al.*[4] have postulated that the strength of binding of a group to a carbonyl function is a function of the basicity of the parent hydroxy-compound. In accordance with this view, the products we obtained are in all cases those in which the more basic group is attached to the carbonyl carbon; the order of decreasing basicity is ethanol $\sim$ methanol $>$ phenol $>$ 2,4-dihydroxybenzophenone $>$ 2,4,5-trichlorophenol $\sim$ 2,4,6-trichlorophenol $\sim$ 2,4,6-tribromophenol $>$ pentachlorophenol.

EXPERIMENTAL

I.r. spectra were measured for Nujol mulls.

4-Carboxymethoxy-2-hydroxybenzophenone.—A cooled solution of chloroacetic acid (47 g.) in water (250 c.c.) was added gradually to a solution of 2,4-dihydroxybenzophenone (107 g.) in water (250 c.c.) containing sodium hydroxide (40 g.), with the temperature kept below 20°. The mixture was boiled under reflux for 3 hr., cooled, and treated with sodium hydroxide (22 g.) in water (500 c.c.) to re-dissolve the precipitate. Carbon dioxide was passed into the solution until the pH fell to about 9·5. The sparingly soluble sodium salt was collected, washed with water, suspended in acetone (500 c.c.), and stirred with concentrated hydrochloric acid (50 c.c.). Acetone was distilled from the filtered solution and the residue was mixed with water. The solid product gave the *acid* (58 g., 43%) as pale yellow crystals, m.p. 160—161° (from benzene) (Found: C, 66·0; H, 4·6; O, 29·2. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4; O, 29·4%), $\lambda_{max.}$ (EtOH) 244, 287, and 326 mμ (ε 8900, 13,500 and 8530), $\nu_{max.}$ 1740 and 1625 cm.$^{-1}$ (A preparation of this acid from bromoacetic acid has been described,[5] but neither m.p. nor analysis is given.)

The *methyl ester*, prepared by boiling the acid with methanol containing hydrogen chloride, formed pale yellow crystals, m.p. 134—135° (from methanol) (Found: C, 67·2; H, 4·9; O, 27·9; OMe, 10·9. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9; O, 28·0; OMe, 10·8%), $\lambda_{max.}$ (EtOH) 240, 285, and 325 mμ (ε 8150, 11,900 and 6650), $\nu_{max.}$ 1750 and 1610 cm.$^{-1}$. The *ethyl ester*, prepared similarly or by heating 2,4-dihydroxybenzophenone in ethanolic sodium ethoxide with ethyl bromoacetate, formed pale yellow crystals, m.p. 97—98° (from ethanol) (Found: C, 67·9; H, 5·5; O, 27·0; OEt, 14·7. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4; O, 26·7; OEt, 15·0%), $\lambda_{max.}$ (EtOH) 240, 285, 325 mμ (ε 11,100, 16,000, and 9300), $\nu_{max.}$ 1750 and 1610 cm.$^{-1}$.

The *acid chloride* was prepared by suspending the acid (27·2 g.) in benzene (1500 c.c.), adding thionyl chloride (43 c.c.), and heating under reflux for 2 hr. The residue after removal of the benzene and surplus thionyl chloride under reduced pressure gave pale yellow crystals (26·1 g., 90%), m.p. 133—134° [from light petroleum (b.p. 100—120°)] (Found: C, 62·1; H, 4·1; O, 22·0. $C_{15}H_{11}ClO_4$ requires C, 62·0; H, 3·8; O, 22·0%), $\nu_{max.}$ 1800 and 1620 cm.$^{-1}$.

General Procedure for Preparation of Aryl Esters (I) *of 4-Carboxymethoxy-2-hydroxybenzophenone.*—(*a*) Phosphoryl chloride (17·5 c.c.) was added to a vigorously stirred suspension of the acid or its sodium salt (0·1 mole) and a phenol (0·1 mole) in benzene (1 l.; dried over $CaCl_2$), and the mixture was warmed to 30°. After 5 min., pyridine (25 c.c.) was added dropwise during 10 min. and the mixture was stirred for a further 20 min. and poured into 2% hydrochloric acid (1 l.). The benzene layer was separated, washed with 2% sodium hydroxide solution (2 × 500 c.c.) and water (500 c.c.) and evaporated to dryness under reduced pressure. The residue solidified on

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[2] D. W. Russell, *Biochem. J.*, 1961, **72**, 696.

[3] (*a*) S. Winstein, E. Grunwald, and H. W. Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 2700; (*b*) M. J. S. Dewar, 'The Electronic Theory of Organic Chemistry,' Oxford University Press, London, 1949, p. 73; (*c*) P. D. Bartlett and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, 1958, **80**, 5808.

[4] R. G. Pearson, S. H. Langer, F. V. Williams, and W. J. McGuire, *J. Amer. Chem. Soc.*, 1952, **74**, 5130.

[5] R. A. Coleman, U.S.P. 3,200,086.

addition of a little light petroleum (b.p. 80—100°) and was recrystallised from a suitable solvent.

(*b*) Pyridine (10 c.c.) was added dropwise during 30 min. to a stirred mixture of the acid chloride (0·1 mole) and the phenol (0·1 mole) in benzene (250 c.c.; dried over $CaCl_2$) heated to 50°. The mixture was boiled under reflux for 30 min., poured into 2% hydrochloric acid (1 l.) and worked up as described in (*a*).

The following esters were made: *pentachlorophenyl* [90% (*a*), 75% (*b*)], m.p. 139—140° (benzene) (Found: C, 48·3; H, 2·3; Cl, 34·0; O, 15·2. $C_{21}H_{11}Cl_5O_5$ requires C, 48·5; H, 2·2; Cl, 34·1; O, 15·4%), $\lambda_{max.}$ ($CHCl_3$) 283 and 325 mμ (ε 16,300 and 8050), $\nu_{max.}$ 1780 and 1600 cm.$^{-1}$; 2,4,6-*trichlorophenyl* [95% (*a*) 75% (*b*)], m.p. 135·5—136·5° (benzene) (Found: C, 55·9; H, 3·0; Cl, 23·6; O, 18·0. $C_{21}H_{13}Cl_3O_5$ requires C, 55·9; H, 2·9; Cl, 23·4; O, 17·7%), $\lambda_{max.}$ ($CHCl_3$) 285 and 322 mμ (ε 16,900 and 9050), $\nu_{max.}$ 1780 and 1600 cm.$^{-1}$; 2,4,5-*trichlorophenyl* [90% (*a*), 80% (*b*)], m.p. 158—159° (acetone) (Found: C, 56·0; H, 2·9; Cl, 23·3; O, 17·6. $C_{21}H_{13}Cl_3O_5$ requires C, 55·9; H, 2·9; Cl, 23·4; O, 17·7%), $\lambda_{max.}$ ($CHCl_3$) 285 and 325 mμ (ε 18,300 and 9500), $\nu_{max.}$ 1750 and 1615 cm.$^{-1}$; 2,4,6-*tribromophenyl* [92% (*a*) 80% (*b*)], m.p. 153—154° (benzene) (Found: C, 43·2; H, 2·4; O, 13·4; $C_{21}H_{13}Br_3O_5$ requires C, 43·1; H, 2·2; O, 13·7%), $\lambda_{max.}$ ($CHCl_3$) 285 and 325 mμ (ε 17,700 and 9250), $\nu_{max.}$ 1780 and 1600 cm.$^{-1}$; and *phenyl* [95% (*a*)], m.p. 138—139° (ethanol) (Found: C, 72·5; H, 4·5; O, 23·0. $C_{21}H_{16}O_5$ requires C, 72·5; H, 4·5; O, 22·9%), $\lambda_{max.}$ ($CHCl_3$) 285 and 325 mμ (ε 16,900 and 9200), $\nu_{max.}$ 1745 and 1615 cm.$^{-1}$.

General procedure for Preparation of Aryloxyacetates (II) *of* 2,4-*Dihydroxybenzophenone*.—Phosphoryl chloride (17·5 c.c.) was added to a stirred suspension of an aryloxyacetic acid (0·1 mole) and 2,4-dihydroxybenzophenone (0·1 mole) in benzene (1 l.; dried over $CaCl_2$). After 5 min., pyridine (10 c.c.) was added dropwise during 10 min., stirring was continued for a further 10 min., and the mixture was poured into 2% hydrochloric acid (1 l.) and worked up as already described. The following esters were prepared: *pentachlorophenoxyacetate* (68%), m.p. 204—205° (benzene) (Found: C, 48·5; H, 2·2; Cl, 34·1; O, 15·4. $C_{21}H_{11}Cl_5O_5$ requires C, 48·5; H, 2·2; Cl, 34·1; O, 15·4%), $\nu_{max.}$ 1775 and 1630 cm.$^{-1}$; 2,4,6-*trichlorophenoxyacetate* (60%), m.p. 162—163° (benzene) (Found: C, 55·9; H, 2·8; Cl, 23·4; O, 17·6. $C_{21}H_{13}Cl_3O_5$ requires C, 55·9; H, 2·9; Cl, 23·4; O, 17·7%), $\nu_{max.}$ 1780 and 1630 cm.$^{-1}$; 2,4,5-*trichlorophenoxyacetate* (70%), m.p. 179—180° (benzene) (Found: C, 55·8; H, 2·9; Cl, 23·4; O, 17·6. $C_{21}H_{13}Cl_3O_5$ requires C, 55·9; H, 2·9; Cl, 23·4; O, 17·7%), $\nu_{max.}$ 1750 and 1620 cm.$^{-1}$; 2,4,6-*tribromophenoxyacetate* (75%), m.p. 177—178° (benzene) (Found: C, 43·0; H, 2·2; Br, 40·8; O, 13·5. $C_{21}H_{13}Br_3O_5$ requires C, 43·1; H, 2·2; Br, 41·0; O, 13·7%), $\nu_{max.}$ 1775 and 1615 cm.$^{-1}$; and *phenoxyacetate* (63%), m.p. 108—111° (ethanol) (Found: C, 72·4; H, 4·6; O, 23·0. $C_{21}H_{16}O_5$ requires C, 72·5; H, 4·5; O, 22·9%), $\nu_{max.}$ 1775 and 1615 cm.$^{-1}$.

Preparation of Aryl Halogenoacetates.—Application of method (*b*) to equimolar amounts of a phenol and chloroacetyl chloride or bromoacetyl bromide gave excellent yields. 4-*Chloroacetoxy*-2-*hydroxybenzophenone* formed pale yellow crystals, m.p. 113° (from ethanol) (Found: C, 61·9; H, 3·7; Cl, 12·3; O, 22·0. $C_{15}H_{11}ClO_4$ requires C, 62·0; H, 3·8; Cl, 12·2; O, 22·0%), $\nu_{max.}$ 1765 and 1610 cm.$^{-1}$. 4-*Bromoacetoxy*-2-*hydroxybenzophenone* formed pale yellow crystals, m.p. 104·5—105·5° (from ethanol) (Found: C, 53·7; H, 3·2; Br, 23·9; O, 19·1. $C_{15}H_{11}BrO_4$ requires C, 53·6; H, 3·3; Br, 23·9; O, 19·2%), $\nu_{max.}$ 1765 and 1610 cm.$^{-1}$.

Reactions of Halogenoacetates with Phenols and Alcohols.—A mixture of the halogenoacetate (0·01 mole) and the appropriate alcohol or phenol (0·01 mole) in acetone (70 c.c.) containing potassium carbonate (0·01 mole) was heated under reflux for 55 min., poured into water (250 c.c.), and extracted with benzene (2 × 50 c.c.). The benzene layer was washed with 2% sodium carbonate solution (2 × 100 c.c.) and water, and evaporated to dryness. The recrystallised product was characterised by i.r. spectroscopy and mixed m.p. The results are summarised in the Table.

Reaction of halogenoacetates with phenols and alcohols

Reactants	Type of product	Yield (%)
(*a*) 2,4-Dihydroxybenzopheone and the following bromoacetates:		
Pentachlorophenyl	(II)	60
2,4,6-Trichlorophenyl	(II)	35
2,4,5-Trichlorophenyl	(II)	20
2,4,6-Tribromophenyl	(II)	60
Phenyl	(I)	50
Ethyl	(I)	22
(*b*) 4-Bromoacetoxy-2-hydroxybenzophenone and the following compounds:		
Pentachlorophenol	(II)	80
2,4,6-Trichlorophenol	(II)	80
2,4,5-Trichlorophenol	(II)	50
2,4,6-Tribromophenol	(II)	60
Phenol	(I)	40
Methanol	(I)	15
Ethanol	(I)	20

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