Cytotoxic Compounds. Part VII.[1] α-Aryl-α-halogenoacetophenones, their Enol Acetates, and Some Related Compounds

By D. J. Cooper and L. N. Owen

To obtain detoxicated derivatives of α-halogenoketones, enol acetates have been prepared from ten α-aryl-α-halogenoacetophenones by reaction of the sodium enolates with acetyl chloride; the conventional method using isopropenyl acetate was completely ineffective. Simple α-halogenoacetophenones are resistant to both procedures, and the conjugative influence of an α-aryl substituent on the stability of the enolate anion is thus demonstrated. The ultraviolet and infrared absorption maxima of the enol acetates are recorded.

Evidence is presented for the structure of the α-arylphenacylpyridinium halides, and the features of their infrared and nuclear magnetic resonance spectra are discussed. The rates of reaction of several α-aryl-α-halogenoacetophenones with pyridine and with aniline have been measured, and the results are discussed from the point of view that the compounds are substituted benzyl halides. The expected reduction in reactivity brought about by conversion of an α-aryl-α-halogenoacetophenone into its enol acetate is confirmed kinetically.

Syntheses of 4-sulphamoyl-α-chloroacetophenone and of the enol phosphates of α-bromoacetophenone and of methyl bromopyruvate are described.

The possibility that alkylating agents of the lachrymator type might possess anti-tumour action led to the preparation of the series of substituted benzyl halides described in Part IV,[2] and this approach has now been extended to some α-halogeno-ketones. The precise mechanism by which the carbonyl group in such compounds (I) increases the reactivity of the halogen atom towards S_N2 displacement is debatable,[3] but, whether or not it is the initial target for the attacking nucleophile, masking of this function should diminish

$$\underset{\text{(I)}}{-CO\cdot CHX-} \qquad \underset{\text{(II)}}{-C(OR){:}CX-}$$

the reactivity. If this were done by conversion into an enolic derivative (II), the effect should be very large, for not only has the carbonyl function disappeared but the halide has become of the vinyl type. Such a derivative should, therefore, be much less toxic than the α-halogeno-ketone (I), and, whilst this property in itself would not be expected to confer any biological advantage with respect to anti-tumour action, any preferential reconversion into the parent compound (I) at the site of a tumour would result in selective action. This application of the principle of enzymic activation [4] requires that the O–R bond in the deactivated compound (II) should be readily cleaved by an enzyme which is either naturally more abundant in tumour cells than in normal tissue [5] or can be artificially induced in the tumour; [6] an enol ester, such as an acetate or a phosphate, would be a suitable derivative for examination.

There are only two reports of the formation of enol acetates from α-halogeno-ketones; [7,8] both of these concerned alicyclic systems and involved the interaction of the enolate anion with acetyl chloride. We first chose to study the ring-substituted α-halogenoacetophenones (III; X = Cl or Br) because many of them are easily available and their alkylating powers can be varied both by the choice of halogen and by the nature and position of the ring substituent.[9–11] However, neither the route *via* the sodium enolate nor direct enol acetylation with isopropenyl acetate was successful when applied to α-chloro-, α-bromo-, α,4-dibromo-, α-bromo-4-nitro-, and α-bromo-4-phenyl-acetophenone; alkyl substitution in the side-chain (α-bromopropiophenone) made no difference, and for all six α-halogeno-ketones the recovery of pure starting material exceeded 90% in each experiment. It seemed that these α-halogeno-ketones were not sufficiently enolised under either basic or acidic conditions, and we therefore turned to the α-aryl-α-halogenoacetophenones (IV) in which the enol form (V) would be additionally stabilised by conjugation with both aromatic rings.

$$\underset{\text{(III)}}{R\cdot C_6H_4\cdot CO\cdot CH_2X} \qquad \underset{\text{(IV)}}{Ph\cdot CO\cdot CHX\cdot C_6H_4\cdot R}$$

$$\underset{\text{(V)}}{Ph\cdot C(OH){:}CX\cdot C_6H_4\cdot R} \qquad \underset{\text{(VI)}}{Ph\cdot C(OAc){:}CBr\cdot Ph}$$

Under conditions similar to those used by Rutherford and Stevens,[8] α-bromo-α-phenylacetophenone (IV; X = Br, R = H) reacted with a suspension of an excess of sodium methoxide in ether at −50°, and subsequent addition of acetyl chloride afforded the enol acetate (VI) in 22% yield. Since the formation of the enolate anion involves the equilibrium

$$Ph\cdot CHBr\cdot COPh + OMe^- \rightleftharpoons Ph\cdot CBr{:}C(O^-)Ph + MeOH$$

some improvement should be effected by inhibition of the backward reaction. We therefore used only 1 mol. of

[1] Part VI, B. J. Johnson and L. N. Owen, *J. Chem. Soc.*, 1964, 3401.
[2] R. Grice and L. N. Owen, *J. Chem. Soc.*, 1963, 1947.
[3] J. W. Baker, *Trans. Faraday Soc.*, 1941, **37**, 632; R. G. Pearson, S. H. Langer, F. V. Williams, and W. J. McGuire, *J. Amer. Chem. Soc.*, 1952, **74**, 5130; A. Streitwieser, *Chem. Rev.*, 1956, **56**, 600; E. L. Eliel in "Steric Effects in Organic Chemistry," ed. M. S. Newman, Wiley, New York, 1956, p. 103.
[4] W. C. J. Ross, "Biological Alkylating Agents," Butterworths, London, 1962, p. 148.
[5] F. Bergel, "Chemistry of Enzymes in Cancer," Thomas, Illinois, 1961.
[6] J. F. Danielli, *Ann. Reports British Empire Cancer Campaign*, 1959, **37**, 575.
[7] R. E. Lyle and R. A. Covey, *J. Amer. Chem. Soc.*, 1953, **75**, 4973.
[8] K. G. Rutherford and C. L. Stevens, *J. Amer. Chem. Soc.*, 1955, **77**, 3278.
[9] J. W. Baker, *J. Chem. Soc.*, 1932, 1148.
[10] J. W. Baker, *J. Chem. Soc.*, 1938, 445.
[11] F. J. Ozog, V. Comte, and L. C. King, *J. Amer. Chem. Soc.*, 1952, **74**, 6225.

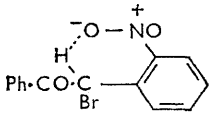
sodium methoxide, prepared *in situ* from equivalent amounts of methanol and sodium hydride in dry ether, but added one further equivalent of sodium hydride; the latter not only regenerated sodium methoxide from the methanol formed in the subsequent reaction but also, from the rate of evolution of hydrogen, provided a useful indication of the progress of the enolisation. With this modification the yield of enol acetate was raised to 56% and the method was successfully applied to ten α-aryl-α-halogenoacetophenones to give the corresponding enol acetates in yields ranging from 28 to 70%. The products, all crystalline, showed infrared absorption maxima in chloroform at about 1190 (C–O), 1630 (C=C), and 1765 cm.$^{-1}$ (C=O); the ultraviolet absorption maxima are recorded in Table 1.

TABLE 1

Ultraviolet light absorption, in ethanol, of the compounds $Ph{\cdot}C(OAc){:}CX{\cdot}C_6H_4{\cdot}R$

R	X	$\lambda_{max.}$ (mμ) (log ε)
H	Br	205 (4·33), 226 (4·25), 283 (3·86)
H	Cl	205 (4·39), 223 (4·26), 276 (3·99)
o-Cl	Br	208 (4·40), 233 (4·18)
o-Cl	Cl	207 (4·40), 263 (4·01)
m-Cl	Br	209 (4·45), 228 (4·30), 285 (3·88)
p-Cl	Br	206 (4·32), 232 (4·30), 290 (3·91)
p-Cl	Cl	204 (4·29), 229 (4·26), 280 (3·99)
m-NO_2	Br	207 (4·40), 219 (4·42), 265 (4·10)
p-NO_2	Br	204 (4·36), 252 (4·20), 321 (3·88)
o-Me	Br	214 (4·13), 230 (4·12), 263 (3·92)

In contrast to the *m*- and the *p*-nitro-compounds, α-bromo-α-(*o*-nitrophenyl)acetophenone showed no sign of enolisation when treated with sodium methoxide–sodium hydride and consequently could not be converted into an enol acetate. This lack of reactivity of the α-hydrogen atom is unlikely to be due to steric hindrance since an *o*-chloro- or an *o*-methyl group does not inhibit the reaction, but it may be the result of hydrogen bonding with the *o*-nitro-group (VII).



(VII)

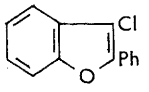
α-Chloro-α-phenylacetophenone, which readily gave an enol acetate under the conditions just described, was quite unaffected by prolonged heating with isopropenyl acetate in the presence of an acid catalyst. As mentioned above, this conventional method was also unsuccessful with the α-halogenoacetophenones, and it is interesting that it has been reported to fail with a steroid α-halogeno-ketone.[12]

The α-halogeno-ketones from which the enol acetates were synthesised were also required for biological examination *per se* and for kinetic measurements of halide reactivity. Apart from α-bromo-α-phenyl-,[13] α-chloro-α-phenyl-,[14] and α-bromo-α-(*p*-chlorophenyl)-acetophenone,[15] they have not been previously described. The general procedure involved in the preparation of the α-arylacetophenone (IX) by a Friedel–Crafts condensation of the appropriately substituted arylacetyl chloride (VIII) with benzene,[16] followed by bromination [15] to give the required α-bromo-compound (X). Hydrolysis of the bromide, preferably *via* the diethyl ketal,[15] gave the benzoin (XI) from which the α-chloro-compound (XII) was obtained by reaction with thionyl chloride and pyridine.[14]

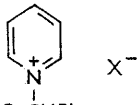
$$ArCH_2{\cdot}COCl \longrightarrow Ph{\cdot}CO{\cdot}CH_2Ar \longrightarrow Ph{\cdot}CO{\cdot}CHBr{\cdot}Ar$$
(VIII) (IX) (X)

$$\longrightarrow Ph{\cdot}CO{\cdot}CH(OH){\cdot}Ar \longrightarrow Ph{\cdot}CO{\cdot}CHCl{\cdot}Ar$$
(XI) (XII)

This route is not suitable for phenolic acetophenones, so 4′-hydroxybenzoin was synthesised from the cyanohydrin of *p*-hydroxybenzaldehyde by reaction with phenylmagnesium bromide, following the method used [17] for the 2′-hydroxy-compound. Neither of these hydroxybenzoins could be converted into the required chlorides; the 4′-compound gave a tar, whilst the 2′-isomer gave a crystalline product deficient by the elements of water from expected formula. By analogy with the ease with which 2-hydroxy-α-phenylacetophenone undergoes dehydration to 2-phenylbenzofuran [18] this product is 3-chloro-2-phenylbenzofuran (XIII); the ultraviolet absorption spectrum was very similar to that reported [19] for 2-phenylbenzofuran.

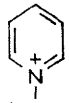


(XIII)



X^-

(XIV: X = Br)
(XV : X = Cl)
(XVI: X = picrate)



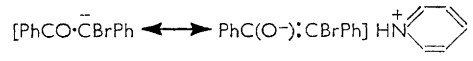
X^-

(XVII)

To confirm the nature of the reaction which was to be used in kinetic measurements α-bromo-α-phenylacetophenone (α-phenylphenacyl bromide) was treated with pyridine in aqueous ethanol at 50°. The product, a non-crystalline salt, which was expected to be α-phenylphenacylpyridinium bromide (XIV), showed a positive test for ionic bromide and with picric acid gave a bromine-free crystalline picrate (XVI). A similar reaction with α-phenylphenacyl chloride at 100° gave the non-crystalline pyridinium chloride (XV) which furnished the same picrate. The infrared spectrum of the picrate was in accord with structure (XVI) but the two pyridinium halides showed absorption not only

[12] G. P. Mueller and W. F. Johns, *J. Org. Chem.*, 1961, **26**, 2403.
[13] E. Knoevenagel, *Ber.*, 1888, **21**, 1355.
[14] A. M. Ward, *Org. Synth.*, Coll. Vol. II, 1943, p. 159.
[15] S. S. Jenkins, *J. Amer. Chem. Soc.*, 1934, **56**, 683.
[16] A. Fischer, B. A. Grigor, J. Packer, and J. Vaughan, *J. Amer. Chem. Soc.*, 1961, **83**, 4208.
[17] Y. Asahina and M. Teresaka, *J. Pharm. Soc. Japan*, 1923, **494**, 219.
[18] J. W. Schulenberg and S. Archer, *J. Amer. Chem. Soc.*, 1960, **82**, 2035.
[19] P. Yates, *J. Amer. Chem. Soc.*, 1952, **74**, 5376; M. M. Bokadia, B. R. Brown, and W. Cummings, *J. Chem. Soc.*, 1960, 3308.

at 1685 (C=O) but also at 1630 (C=C) and *ca.* 3400 cm.$^{-1}$ (OH), suggesting that the enolic form (XVII) was also present; furthermore, they both showed the absorption at 2450 cm.$^{-1}$ which is usually associated [20] with the $=\overset{+}{N}H-$ stretching mode. This was not due to the presence of pyridine hydrohalide (which might have been formed by concomitant solvolysis of some of the phenacyl halide) because treatment of α-phenylphenacyl bromide with pyridine in dry benzene gave a crystalline α-phenylphenacylpyridinium bromide, containing benzene of crystallisation, which had a similar absorption spectrum. The possibility that the anomalous band at 2450 cm.$^{-1}$ was due to contamination with the isomeric pyridinium



(XVIII)

enolate (XVIII) was ruled out by the finding that the mass spectrum of the crystalline bromide (kindly determined by Dr. E. S. Waight) showed the absence of covalently bound bromine; the presence of a small proportion of the pyridinium enolate of the pyridinium salt (XVII) might be the explanation, since this would not greatly affect the analytical figures. The nuclear magnetic resonance spectrum of the crystalline bromide showed a singlet at τ 0·31 (one proton), well separated from the next lowest resonance at τ 0·49 (two protons at the α-positions in the pyridine ring). The singlet must represent the aliphatic proton in the salt (XIV), and its appearance at such low field is not surprising for such a structure in view of Warnhoff's report [21] on the γ-picolinium salt derived from 2α-bromocholestan-3-one. The unexpected feature of the n.m.r. spectrum was in fact its simplicity, in that it corresponded to a single structure; no hydroxyl resonance was apparent, and the integrated singlet signal at τ 0·31 corresponded well to one proton. This can only mean that the proportion of enol form (XVII) is quite small in spite of the moderately strong bands at 1630 and 3400 cm.$^{-1}$ in the i.r. spectrum.

Under the conditions used by Baker [9] for determining the reactivities of a series of substituted phenacyl halides $ArCO{\cdot}CH_2X$ (pyridine in 90% aqueous ethanol at 30·5°) our α-phenylphenacyl halides reacted inconveniently slowly. Measurements were therefore made on the bromides at 50° and on the chlorides at 100°; the results are shown in Tables 2 and 3. Pseudo-first-order kinetics were shown by all the compounds, though the values for the *o*- and the *m*-chlorophenyl derivatives in the chloride series may be less accurate than the others because the "infinity" titrations of chloride ion, measured at ten times the half-lives, corresponded, respectively, to only 93·5 and 84% of the calculated figure, although both derivatives were analytically pure.

Baker,[9,10] found that electron-attracting ring substituents in the phenacyl halides increased the reactivity, and he explained this in terms of a rate-controlling attack by the nucleophile on the carbonyl carbon atom. Whether or not this view is correct it is clearly not applicable to the α-phenylphenacyl halides, which in any event cannot properly be compared with the phenacyl halides because the substituents are not on the

TABLE 2

Pseudo-unimolecular rate constants for the reaction of compounds $PhCO{\cdot}CHBr{\cdot}C_6H_4R$ with pyridine in 90% aqueous ethanol at 50°

R	H	*o*-Cl	*m*-Cl	*p*-Cl	*o*-NO_2	*m*-NO_2	*p*-NO_2
10^4k (min.$^{-1}$)	212	60	88	158	17	98	117

TABLE 3

Pseudo-unimolecular rate constants for the reaction of compounds $PhCO{\cdot}CHCl{\cdot}C_6H_4R$ with pyridine in 90% aqueous ethanol at 100°

R	H	*o*-Cl	*m*-Cl	*p*-Cl
10^4k (min.$^{-1}$)	67	42	61	114

ring attached to the carbonyl group but on that attached to the α-carbon atom. The α-phenylphenacyl halides can therefore best be considered as ring-substituted benzyl halides, all carrying a benzoyl substituent in the α-position, with the reservation that the conventional mechanism for bimolecular halide displacement can be applied only as an approximation since it does not take into account any significant participation of the carbonyl group in the transition state. The pseudo-unimolecular rates recorded are a true representation of the bimolecular process because it was shown that, at 50° in 90% aqueous ethanol alone, the rate of solvolysis of α-phenylphenacyl bromide is negligible.

Substituent effects in the S_N2 reactions of benzyl halides have usually been interpreted in terms of their influence on the bond-formation and bond-breaking processes. In an attack by a tertiary amine it has been argued [22] that electron-withdrawing ring substituents would retard bond formation because the α-carbon atom in this step is made more positive by the inductive effect of the adjacent quaternary nitrogen. Such substituents would certainly also retard the loss of halide anion in the bond-breaking process, and hence, irrespective of the relative importance of bond formation and bond breaking, the effect would be to reduce the reactivity. The α-phenylphenacyl bromides appear to conform to this pattern, but in the chloride series the *p*-chloro-compound shows enhanced reactivity over the unsubstituted parent. It has been recognised [22] that such an apparent anomaly can occur when very powerful electron-attracting groups are present, it being assumed that the over-riding effect is then simply the facilitation of the initial attack by the nucleophile, but it is surprising that a single chloro-substituent should

[20] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd edn., Methuen, London, 1958, p. 260.
[21] E. W. Warnhoff, *J. Org. Chem.*, 1962, **27**, 4587, footnote 17.
[22] J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 1935, 1840; E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Reinhart, and Winston, New York, 1959, p. 283; J. Hine, "Physical Organic Chemistry," 2nd edn., McGraw-Hill, New York, 1962, p. 171.

provide sufficient attraction, even allowing for the added presence of the benzoyl group.

Measurements were also made of the rates of reaction of the α-phenylphenacyl bromides with aniline. In each of these experiments there was a fall in the value of k as the reaction proceeded (as is also apparent in Baker's work [23] on benzyl bromide), and the figures recorded in Table 4 are those at 50% completion. The overall

TABLE 4

Pseudo-unimolecular rate constants at 50% reaction of compounds PhCO·CHBr·C_6H_4R with aniline in 90% aqueous ethanol at 50°

R	H	*o*-Cl	*m*-Cl	*p*-Cl	*p*-NO_2
10^4k (min.$^{-1}$)	390	136	430	860	410

accelerating effect of the *p*-chloro-substituent is now very marked, and even with the *p*-nitro-compound the retardation of bond fission is more than balanced by the promotion of bond formation. The generally low rates for *o*-compounds (Tables 2—4) can be ascribed to steric factors.

Confirmation of the expected considerable decrease in reactivity brought about by conversion into an enol acetate was afforded by measurements on the esters derived from α-phenylphenacyl chloride and bromide. At 100°, with pyridine in 90% aqueous ethanol, the pseudo-unimolecular rate constants were, for α-acetoxy-α′-chlorostilbene $1{\cdot}0 \times 10^{-4}$ and for α-acetoxy-α′-bromostilbene (VI) $1{\cdot}9 \times 10^{-4}$ min.$^{-1}$. The relatively small difference between the chloride and the bromide suggests that the rate-determining step is essentially a very slow removal of the acetyl group followed by the more rapid reaction of the liberated α-phenylphenacyl halide.

Attempts to prepare enol acetates from the known [24] difunctional halogeno-ketones (XIX; X = Cl or Br) and from the 1,2-dibenzoyl-1,2-dihalogenoethanes (XX; X = Cl or Br) were unsuccessful. Although the reactions undoubtedly occurred it was not possible to purify the products.

p-XCH_2·CO·C_6H_4·CO·CH_2X (XIX)

PhCO·CHX·CHX·COPh (XX)

Enol phosphates can be prepared by the Perkow reaction,[25–27] which involves treatment of an α-halogeno-aldehyde or -ketone with a trialkyl phosphite. If αα-dihalogeno-ketones are used the product is the enol phosphate of an α-halogeno-ketone; thus 2-chloro-1-phenylvinyl diethyl phosphate (XXI) [28] and the dimethyl analogue [29] have been made from αα-dichloro-acetophenone. We have now obtained 2-bromo-1-phenylvinyl diethyl phosphate (XXII) from αα-dibromo-acetophenone; the product did not give triethyl phosphate when subjected to acid-catalysed solvolysis in ethanol, a reaction said [26] to distinguish enol phosphates from the isomeric phosphonates (which may also be formed in the Perkow reaction), but its structure was confirmed by the i.r. absorption at 1630 cm.$^{-1}$ (C=C) and by the observation that it reacted with chlorine to give 2-bromo-1,2-dichloro-1-phenylethyl diethyl phosphate (XXIII).

PhC(O·PO(OEt)$_2$)=CHX (XXI; X = Cl) (XXII; X = Br)

PhCCl(O·PO(OEt)$_2$)·CHBrCl (XXIII)

CHBr=C(O·PO(OEt)$_2$)·CO_2Me (XXIV)

The n.m.r. spectrum of the latter showed resonances at τ 8·70 (triplet, 6H), 5·87 (quartet, 4H), 3·32 (singlet, 1H), *ca.* 2·5 (multiplet, 3H) and *ca.* 2·3 (multiplet, 2H), in accordance with that structure.

In an attempt to obtain the monobasic phosphoric acid derivative, 2-bromo-1-phenylvinyl diethyl phosphate was treated with sodium iodide in acetone under the conditions which normally [30] cause the loss of one of the ethyl ester groups, but no reaction occurred.

Treatment of methyl dibromopyruvate with triethyl phosphite gave a good yield of 2-bromo-1-methoxycarbonylvinyl diethyl phosphate (XXIV), though dibromopyruvic acid itself gave a product which could not be purified.

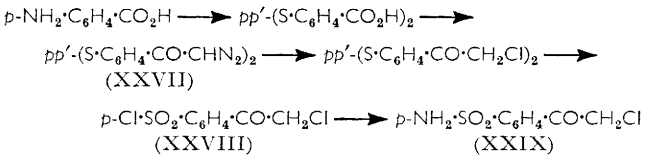
Although the sulphonamide (XXV) [31] is active against the Walker 256 rat carcinoma, it produces unusual side effects, possibly because of interaction with sites

p-$(BrCH_2·CH_2)_2N·C_6H_4·SO_2·NH_2$ (XXV)

p-Cl·$SO_2·C_6H_4$·CO·CH_2Br (XXVI)

normally available as folic acid receptors.[32] It would, therefore, be interesting to test analogues in which the alkylating group is of the lachrymator type rather than a nitrogen mustard. *p*-Bromomethylbenzenesulphonamide is known,[33] but the corresponding phenacyl halides are not. 4-Chlorosulphonylacetophenone was therefore brominated to give α-bromo-4-chlorosulphonylacetophenone (XXVI), but attempts to prepare the amide from this were fruitless because of the high reactivity of the bromo-ketone moiety. Accordingly the chloro-compound (XXVIII) was synthesised from *p*-aminobenzoic acid *via* 4,4′-bisdiazoacetyldiphenyl disulphide (XXVII). When this sulphonyl chloride (XXVIII) was briefly treated with ammonia, the required amide (XXIX) was obtained.

[23] J. W. Baker, *J. Chem. Soc.*, 1932, 2631.
[24] W. C. J. Ross, *J. Chem. Soc.*, 1950, 752.
[25] W. Perkow, K. Ullerich, and F. Meyer, *Naturwiss.*, 1952, **39**, 353.
[26] F. W. Lichtenthaler, *Chem. Rev.*, 1961, **61**, 607.
[27] P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, 1965, **21**, 1961.
[28] A. N. Pudovik and L. G. Biktimirova, *Zhur. obshchei Khim.*, 1957, **27**, 1708 (*Chem. Abs.*, 1958, **52**, 3714).
[29] Y. Nishizawa, *Bull. Agric. Chem. Soc. Japan*, 1960, **24**, 261 (*Chem. Abs.*, 1960, **54**, 18,858).
[30] L. Zervas and I. Dilaris, *J. Amer. Chem. Soc.*, 1955, **77**, 5354; R. J. Cremlin, G. W. Kenner, J. Mather, and A. R. Todd, *J. Chem. Soc.*, 1958, 528.
[31] M. H. Benn, A. M. Creighton, B. J. Johnson, L. N. Owen, and G. R. White, *J. Chem. Soc.*, 1964, 3395.
[32] R. Hawkins, L. N. Owen, and J. F. Danielli, *J. Theoret. Biol.*, 1963, **5**, 236.
[33] J. Klarer, G.P. 853,444/1952 (*Chem. Abs.*, 1955, **49**, 15,960).



Ethyl α-bromophenylorthoacetate (XXX) was synthesised by bromination of ethyl phenylorthoacetate to provide an example of a way in which a lachrymator of the α-halogeno-ester type, in this case (XXXI), could be deactivated.

Biological tests on many of the compounds described in this and the following Paper are being carried out under the direction of Professor J. F. Danielli, F.R.S., and will be reported elsewhere.

EXPERIMENTAL

Petroleum, without further qualification, refers to light petroleum (b. p. 40—60°). Infrared spectra were measured in chloroform. Nuclear magnetic resonance spectra were determined in deuteriochloroform with a Varian A-60 spectrometer on permanent loan to Professor D. H. R. Barton, F.R.S., from the Wellcome Trustees; tetramethylsilane was the internal standard.

α-Bromo-α-phenylacetophenone.—Prepared from deoxybenzoin, by the general method described by Jenkins,[15] this had m. p. 55° (lit.,[13] 54—55°).

α-Chloro-α-phenylacetophenone.—Prepared from benzoin, by Ward's method,[14] this had m. p. 68—69° (lit.,[14] 66—67°).

α-Arylacetophenones.—These were all prepared by a Friedel–Crafts reaction of the arylacetyl chloride with benzene under the general conditions described by Fischer *et al.*[16] Several had not previously been made this way.

α-(*o*-Chlorophenyl)acetophenone (yield 65%) had m. p. 69—70° (lit.,[34] 70·5°); α-(*m*-chlorophenyl)acetophenone (75%), b. p. 140°/10^{-2} mm., m. p. 42—43° (lit.,[16] 43°); α-(*p*-chlorophenyl)acetophenone (63%), m. p. 136—137° (lit.,[16] 136·5°); α-(*o*-nitrophenyl)acetophenone (31%), m. p. 75° (lit.,[35] 73—74°); α-(*m*-nitrophenyl)acetophenone (64%), m. p. 82° (lit.,[16] 82°); α-(*p*-nitrophenyl)acetophenone (4%), m. p. 45° (lit.,[16] 144°); and α-o-*tolylacetophenone* (27%), plates, m. p. 68° (from methanol) (Found: C, 85·6; H, 6·7. $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%).

α-Aryl-α-bromoacetophenones.—Following the general procedure used by Jenkins,[15] a solution of bromine (1·6 g.) in carbon tetrachloride (20 c.c.) was added dropwise during 20 min. to a stirred solution of α-(*o*-chlorophenyl)acetophenone (2·3 g.) in carbon tetrachloride (30 c.c.) illuminated and warmed by a 300-w tungsten lamp. After filtration through charcoal, and removal of the solvent, the oily residue was distilled to give *α-bromo-α-(o-chlorophenyl)-acetophenone* (2·5 g., 80%), b. p. 143°/10^{-2} mm., n_D^{18} 1·6267 (Found: C, 54·6; H, 3·2. $C_{14}H_{10}BrClO$ requires C, 54·3; H, 3·3%). After storage for some weeks at 0° it solidified, and recrystallisation from ethanol gave needles, m. p. 29—30°.

In a similar way were prepared: *α-bromo-α-(m-chlorophenyl)acetophenone* (80%), b. p. 154°/10^{-4} mm., n_D^{21} 1·6337 (Found: C, 53·8; H, 3·5%); α-bromo-α-(*p*-chlorophenyl)acetophenone (70%), m. p. 63° (lit.,[15] 62—62·5°); *α-bromo-α-(o-nitrophenyl)acetophenone* (88%), m. p. 115—116° (decomp.) (from methanol) (Found: C, 52·4; H, 3·1; Br, 25·7. $C_{14}H_{10}BrNO_3$ requires C, 52·5; H, 3·1; Br, 25·0%); *α-bromo-α-(m-nitrophenyl)acetophenone* (88%), m. p. 87—88° (from methanol) (Found: C, 52·6; H, 3·3; Br, 24·8%); and *α-bromo-α-(p-nitrophenyl)acetophenone* (51%), m. p. 100° (from chloroform–petroleum) (Found: C, 52·4; H, 2·8; N, 4·5. $C_{14}H_{10}BrNO_3$ requires C, 52·5; H, 3·1; N, 4·4%). α-Bromo-α-*o*-tolylacetophenone (79%), b. p. 150°/10^{-4} mm., distilled with extensive decomposition, but the crude material (which was satisfactorily converted into the enol acetate as described below) showed the expected n.m.r. spectrum, which included the methyl singlet (3H) at τ 7·5 and the methyne singlet (1H) at τ 3·4.

α-Aryl-α-chloroacetophenones.—α-(*o*-Chlorophenyl)acetophenone (2·3 g.) was brominated as described above, and to a solution of the crude bromide in ethanol (20 c.c.) a solution prepared by the addition of sodium (0·7 g.) to ethanol (20 c.c.) was added. After 1 hr., the mixture was poured into 5N-hydrochloric acid (100 c.c.) and the yellow precipitate was collected. Recrystallisation from chloroform–petroleum gave *2′-chlorobenzoin* (2·3 g., 93%) as plates, m. p. 83° (Found: C, 68·2; H, 4·4; Cl, 14·5. $C_{14}H_{11}ClO_2$ requires C, 68·2; H, 4·5; Cl, 14·4%). A solution of this product (1·27 g.) in pyridine (0·5 g.) was treated at 0° with thionyl chloride (0·75 g.). After 1 hr., water (10 c.c.) was added and the precipitate, on recrystallisation from ethanol, gave large prisms (0·85 g., 64%) of *α-chloro-α-(o-chlorophenyl)acetophenone*, m. p. 44—45° (Found: C, 63·7; H, 3·9. $C_{14}H_{10}Cl_2O$ requires C, 63·5; H, 3·8%).

In a similar way, crude α-bromo-α-(*m*-chlorophenyl)-acetophenone gave *3′-chlorobenzoin* (92%) as needles (from light petroleum, b. p. 60—80°), m. p. 95° (Found: C, 68·2; H, 4·6%) and thence *α-chloro-α-(m-chlorophenyl)-acetophenone* (70%) b. p. 142°/10^{-3} mm., n_D^{22} 1·6108 (Found: C, 63·1; H, 3·7; Cl, 26·5. $C_{14}H_{10}Cl_2O$ requires C, 63·5; H, 3·8; Cl, 26·8%).

4′-Chlorobenzoin [15] was likewise converted into *α-chloro-α-(p-chlorophenyl)acetophenone*, needles (from ethanol), m. p. 40—41° (Found: C, 63·3; H, 3·9; Cl, 27·0%).

Reaction of 2′-Hydroxybenzoin with Thionyl Chloride.—Thionyl chloride (1·5 g.) was added to a solution of 2′-hydroxybenzoin [17] (2·1 g.) in pyridine (1·0 g.). After 1 hr. the mixture was diluted with water (10 c.c.) to give a solid (1·3 g.) which on crystallisation from methanol gave colourless needles of *3-chloro-2-phenylbenzofuran*, m. p. 47°, $\lambda_{max.}$ (EtOH) 200, 302, and 317 mμ (log ε 4·38, 4·47, and 4·32) (Found: C, 73·3; H, 3·7; Cl, 15·7. $C_{14}H_9ClO$ requires C, 73·5; H, 4·0; Cl, 15·5%).

4′-Hydroxybenzoin.—*p*-Hydroxybenzaldehyde (40 g.) was converted into its cyanohydrin, which was treated with phenylmagnesium bromide according to the method described [17] for similar compounds. The product (6·0 g.), m. p. 165—170°, on recrystallisation from aqueous dioxan gave *4′-hydroxybenzoin* as rhombs, m. p. 187—189° (Found: C, 73·6; H, 5·2. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%).

When treated with thionyl chloride and pyridine it gave a tar which could not be purified.

Enol Acetates from α-Aryl-α-halogenoacetophenones.—Dry methanol (0·64 g.) was added to a stirred suspension of sodium hydride (0·96 g.) in dry ether (20 c.c.). When the evolution of hydrogen ceased the mixture was cooled to

[34] S. S. Jenkins and E. M. Richardson, *J. Amer. Chem. Soc.*, 1933, **55**, 1618.
[35] O. List, *Ber.*, 1893, **26**, 2453.

—20° and treated with a solution of α-bromo-α-phenylacetophenone (5·5 g.) in dry ether (10 c.c.). A deep yellow colour, and the evolution of more hydrogen, showed that the sodium enolate was being formed. When the reaction ceased (*ca.* 30 min.), acetyl chloride (3 c.c.) was added, whereupon the colour was discharged. Filtration, then concentration of the filtrate, gave a solid which was recrystallised from methanol to give *α-acetoxy-α′-bromostilbene* (3·5 g., 56%) as plates, m. p. 108—109° (Found: C, 60·8; H, 4·3; Br, 25·6. $C_{16}H_{13}BrO_2$ requires C, 60·6; H, 4·1; Br, 25·2%), $\nu_{max.}$ 1190 (C–O), 1630 (C=C), and 1760 cm.$^{-1}$ (C=O).

The same procedure was used to prepare the following enol acetates: *α-acetoxy-α′-chlorostilbene* (70%), m. p. 94° (from ethanol), $\nu_{max.}$ 1190, 1620, and 1760 cm.$^{-1}$ (Found: C, 70·6; H, 4·9; Cl, 13·1. $C_{16}H_{13}ClO_2$ requires C, 70·6; H, 4·8; Cl, 13·0%); *α′-acetoxy-α-bromo-2-chlorostilbene* (54%), m. p. 90° (from methanol), $\nu_{max.}$ 1190, 1645, and 1765 cm.$^{-1}$ (Found: C, 54·7; H, 3·5. $C_{16}H_{12}BrClO_2$ requires C, 54·7; H, 3·4%); *α′-acetoxy-α-bromo-3-chlorostilbene* (31%), m. p. 84° (from light petroleum, b. p. 60—80°), $\nu_{max.}$ 1190, 1635, and 1765 cm.$^{-1}$ (Found: C, 54·8; H, 3·4%); *α′-acetoxy-α-bromo-4-chlorostilbene* (40%), m. p. 75° (from light petroleum, b. p. 80—100°), $\nu_{max.}$ 1190, 1630, and 1760 cm.$^{-1}$ (Found: C, 54·7; H, 3·3%); *α′-acetoxy-α,2-dichlorostilbene* (54%), m. p. 71° (from ethanol), $\nu_{max.}$ 1190, 1640, and 1765 cm.$^{-1}$ (Found: C, 62·6; H, 4·0. $C_{16}H_{12}Cl_2O_2$ requires C, 62·6; H, 4·0%); *α′-acetoxy-α,4-dichlorostilbene* (41%), m. p. 80—81° (from light petroleum, b. p. 60—80°), $\nu_{max.}$ 1200, 1600, 1640, and 1770 cm.$^{-1}$ (Found: C, 62·6; H, 4·0; Cl, 23·0. $C_{16}H_{12}Cl_2O_2$ requires C, 62·6; H, 4·0; Cl, 23·1%); *α′-acetoxy-α-bromo-3-nitrostilbene* (48%), m. p. 109—110° (from methanol), $\nu_{max.}$ 1190, 1635, and 1765 cm.$^{-1}$ (Found: C, 53·2; H, 3·3; O, 17·8. $C_{16}H_{12}BrNO_4$ requires C, 53·1; H, 3·4; O, 17·7%), *α′-acetoxy-α-bromo-4-nitrostilbene* (28%), m. p. 114° (from methanol), $\nu_{max.}$ 1180, 1600, 1630, and 1765 cm.$^{-1}$ (Found: C, 53·2; H, 3·3; N, 4·0. $C_{16}H_{12}BrNO_4$ requires C, 53·1; H, 3·4; N, 3·9%); and *α′-acetoxy-α-bromo-2-methylstilbene* (50%), m. p. 88° (from methanol), $\nu_{max.}$ 1200, 1600, 1640, and 1760 cm.$^{-1}$ (Found: C, 61·8; H, 4·9. $C_{17}H_{15}BrO_2$ requires C, 61·7; H, 4·6%).

When α-bromo-α-(*o*-nitrophenyl)acetophenone was treated in the same way there was no hydrogen evolved, no yellow colour developed, and after the addition of acetyl chloride the product consisted only of starting material (98% recovery).

Unreactivity of α-Chloro-α-phenylacetophenone towards Isopropenyl Acetate.—The chloride (5 g.), isopropenyl acetate (20 g.), and toluene-*p*-sulphonic acid (0·2 g.) were boiled together under reflux for 24 hr. The solution was then concentrated, diluted with ether, washed with aqueous sodium hydrogen carbonate, and evaporated to a solid. Recrystallisation from light petroleum (b. p. 60—80°) gave α-phenylphenacyl chloride (4·5 g., 90% recovery), m. p. and mixed m. p. 66—67°.

Reaction of α-Halogeno-α-phenylacetophenones with Pyridine.—(i) α-Bromo-α-phenylacetophenone (0·34 g.), dissolved in a 0·25M-solution of pyridine in 90% aqueous ethanol (100 c.c.), was heated at 50° under nitrogen for 24 hr. The solvent was removed under reduced pressure and the residual oil was dissolved in water (10 c.c.) and extracted once with ether (10 c.c.). The etheral extract was resolved in the usual way into acidic, neutral, and basic components to yield benzoic acid (0·01 g.), m. p. and mixed m. p. 122°, and traces of pyridine and ethyl benzoate. Evaporation of the aqueous portion gave a colourless oil (0·31 g.), $\nu_{max.}$ 1580, 1600, 1630, 1685, 2450, and 3400 cm.$^{-1}$; with aqueous silver nitrate it gave an immediate precipitate of silver bromide, and on treatment with methanolic picric acid it was converted into *α-phenylphenacylpyridinium picrate*, m. p. 183° (from methanol), $\nu_{max.}$ 1615, 1630, and 1685 cm.$^{-1}$ (Found: C, 59·9; H, 3·7; N, 11·5. $C_{25}H_{18}N_4O_8$ requires C, 59·7; H, 3·6; N, 11·2%).

(ii) α-Chloro-α-phenylacetophenone (0·58 g.) was treated with a 0·5M-solution of pyridine in 90% aqueous ethanol (50 c.c.) in a sealed tube at 100° for 16 hr. The solution was worked up in the same way as for the bromide, and again gave traces of benzoic acid and ethyl benzoate, and, as the main product, a colourless oil (0·54 g.), $\nu_{max.}$ 1580, 1595, 1630, 1685, 2450, and 3370 cm.$^{-1}$. The latter furnished the same picrate, m. p. 183°, as described above.

(iii) α-Bromo-α-phenylacetophenone (5·5 g.), pyridine (1·6 g.), and dry benzene (25 c.c.) were heated together at 50° in a sealed tube for 24 hr. The white crystalline precipitate (6·8 g.) of the *α-phenylphenacylpyridinium bromide–benzene complex* had m. p. 120—123°, $\nu_{max.}$ 1580, 1600, 1630, 1685, 2450, and 3400 cm.$^{-1}$ (Found: C, 70·1; H, 4·4; Br, 18·5. $C_{25}H_{22}BrNO$ requires C, 69·7; H, 4·7; Br, 18·6%). It was soluble in water, reacted immediately with silver nitrate, gave an intense yellow colour with aqueous sodium hydroxide, and formed the same picrate, m. p. 183°.

Kinetic Measurements.—(*a*) *With pyridine.* (i) The bromoketone (0·00125 mole) was dissolved in 90% aqueous ethanol (25 c.c., the stock solution being made from a mixture of 9 parts of pure ethanol and 1 part of water by volume) in a flask (fitted with stirrer and condenser) immersed in a thermostat at 50° ± 0·2°. A 0·5M-solution of AnalaR pyridine in the same solvent (25 c.c.), preheated to 50°, was added. At intervals, a 5·0-c.c. portion was withdrawn and run into a mixture of 0·025N-aqueous silver nitrate (5·0 or 10·0 c.c.), benzene (2 c.c.), saturated aqueous ferric alum (0·5 c.c.) and 2N-nitric acid (3 c.c.). The excess of silver nitrate was then titrated with 0·025N-ammonium thiocyanate. "Infinity" values were obtained by titration on a final aliquot portion taken at ten times the half-life; they agreed with the calculated value to within ±2%. The pseudo-unimolecular rate constant was obtained from the expression $k = (2{\cdot}3/t) \log (a/a - x)$, where t is in minutes, a is the volume of silver nitrate used at "infinity" and x that used at time t. The results, which are probably accurate to within ±3%, are shown in Table 2.

(ii) For the chloro-ketones the procedure was the same, except that 5-c.c. aliquot portions of the reaction mixture were sealed in Pyrex ampoules and heated in a thermostat at 100° ± 0·25°. At intervals, an ampoule was removed, quickly cooled, and the contents were treated as above. The results are shown in Table 3.

(iii) For α-acetoxy-α′-bromostilbene and α-acetoxy-α′-chlorostilbene the conditions were as described under (*a*) (ii). The "infinity" values were not measured experimentally, but were calculated, because of the very slow rates of reaction. The results for the two compounds were, respectively, $1{\cdot}9 \times 10^{-4}$ and $1{\cdot}0 \times 10^{-4}$ min.$^{-1}$.

(*b*) *With aniline.*—The method was the same as that described under (*a*) (i), a 0·5M-solution of aniline in 90% aqueous ethanol being used in place of the stock pyridine solution. The aniline was purified by repeated distillation from zinc dust. The results are shown in Table 4.

(*c*) *With* 90% *aqueous ethanol*.—When α-phenylphenacyl bromide was treated as in (*a*) (i), but in the absence of pyridine, no measurable amount of bromide ion was liberated after 1140 min. at 50°.

1,2-*Dibenzoyl*-1,2-*dichloroethane*.—A solution of chlorine (2·9 g.) in carbon tetrachloride (55 c.c.) was slowly added to *trans*-dibenzoylethylene (9·5 g.) in the same solvent. Evaporation of the mixture gave a solid which crystallised from chloroform–petroleum to give the *dichloride* (11·8 g.), m. p. 85° (Found: C, 62·2; H, 3·6. $C_{16}H_{12}Cl_2O_2$ requires C, 62·5; H, 3·9%).

When the compound was treated with sodium methoxide–sodium hydride under the conditions successfully used for enol acetylation of the α-aryl-α-halogenoacetophenones (except that it was now necessary to use tetrahydrofuran instead of ether as solvent) there was a vigorous evolution of hydrogen and development of the yellow solution typical of the formation of the sodium enolate. After the addition of acetyl chloride the product was isolated as an oil which could not be purified, but which showed $\nu_{max.}$ 1190, 1680, and 1755 cm.$^{-1}$. 1,2-Dibenzoyl-1,2-dibromoethane [36] also gave an oil, $\nu_{max.}$ 1185, 1680, and 1760 cm.$^{-1}$.

2-*Bromo*-1-*phenylvinyl Diethyl Phosphate*.—2,2-Dibromoacetophenone [37] (13·7 g.) in dry tetrahydrofuran (20 c.c.) was slowly added to stirred triethyl phosphite (12·5 g.), the temperature being kept below 30° by cooling in ice. The mixture was then distilled under reduced pressure through a 5-cm. Fenske column. Redistillation gave the required *enol phosphate* (10·3 g.), b. p. 153—154°/10^{-4} mm., n_D^{23} 1·5334, $\nu_{max.}$ 980 and 1040 (P–O), 1160 (P–OEt), 1280 (P=O), and 1630 cm.$^{-1}$ (C=C) (Found: C, 42·7; H, 4·9; Br, 24·1; P, 8·9. $C_{12}H_{16}BrO_4P$ requires C, 43·0; H, 4·8; Br, 23·9; P, 9·2%).

When the product (3 g.) was boiled under reflux for 18 hr. in ethanol containing toluene-*p*-sulphonic acid (1·25 g.) the recovered material (2·9 g.) showed the same i.r. absorption; no triethyl phosphate could be detected.

Treatment of the compound (1·2 g.) with anhydrous sodium iodide (0·5 g.) in boiling acetone (8 c.c.) for 30 min. (or for 18 hr.) also resulted in recovery of starting material (1·0 g.).

2-*Bromo*-1,2-*dichloro*-1-*phenylethyl Diethyl Phosphate*.—The preceding enol phosphate (3 g.) in carbon tetrachloride (10 c.c.) was treated with a slight excess of chlorine in the same solvent. Distillation then afforded an oil (3·5 g.), b. p. 153—158°/10^{-3} mm., n_D^{18} 1·5300, which when twice redistilled gave the *dichloride*, b. p. 163°/10^{-3} mm., n_D^{18} 1·5308, $\nu_{max.}$ 975, 1030, 1160, and 1285 cm.$^{-1}$ (Found: P, 7·4; total halogen, 37·5. $C_{12}H_{16}BrCl_2O_4P$ requires P, 7·6; total halogen, 37·1%).

Dibromopyruvic Acid.—A solution of pyruvic acid (7·1 g.) and bromine (28 g.) in chloroform (100 c.c.) was boiled under reflux for 30 hr. and then evaporated to give the crude dibromo-acid (21 g.). Repeated recrystallisation from dry benzene gave pure material (10 g.), m. p. 82—86° (Found: Br, 65·3. Calc. for $C_3H_2Br_2O_3$: Br, 65·0%). This procedure is less tedious than that which involves bromination in aqueous solution followed by dehydration of the hydrate.[38]

Methyl Dibromopyruvate.—Treatment of an ethereal solution of the dibromo-acid (2·4 g.) with a slight excess of diazomethane gave the *methyl ester* (1·6 g.), b. p. 75°/10^{-2} mm., n_D^{20} 1·5221, $\nu_{max.}$ 1740 and 1765 cm.$^{-1}$ (Found: C, 18·8; H, 1·9; Br, 62·4. $C_4H_4Br_2O_3$ requires C, 18·6; H, 1·6; Br, 61·5%).

Benzyl Dibromopyruvate.—Reaction of the dibromo-acid (2·46 g.) in ether (80 c.c.) with phenyldiazomethane (1·18 g.) gave the benzyl ester, which crystallised from benzene as the *monohydrate* (2·42 g.), m. p. 103° with previous softening, $\nu_{max.}$ 1745, *ca.* 3250 (broad), and 3550 cm.$^{-1}$ (Found: C, 34·1; H, 3·0; Br, 45·2; O, 18·1. $C_{10}H_{10}Br_2O_4$ requires C, 33·9; H, 2·9; Br, 45·2; O, 18·1%).

2-*Bromo*-1-*methoxycarbonylvinyl Diethyl Phosphate*.—Methyl dibromopyruvate (2·6 g.) in ether (10 c.c.) was added slowly to stirred triethyl phosphite at 0—10°. Stirring was continued for a further 30 min. and then the mixture was washed with aqueous sodium hydrogen carbonate and with water, dried, and distilled to give the *enol phosphate* (21 g.), b. p. 107—110°/10^{-3} mm., n_D^{20} 1·4740, $\nu_{max.}$ 990, 1035, 1160, 1280, 1322, 1625, and 1740 cm.$^{-1}$ (Found: C, 29·9; H, 4·7; Br, 26·2; P, 8·7. $C_8H_{14}BrO_6P$ requires C, 30·3; H, 4·5; Br, 25·2; P, 9·8%). In addition to the characteristic infrared bands quoted, there was weak absorption in the hydroxyl region (3450 cm.$^{-1}$) which persisted after repeated distillation of the compound, and a better analysis could not be obtained.

α-*Bromo*-4-(*chlorosulphonyl*)*acetophenone*.—Bromine (1·46 g.) in carbon tetrachloride (10 c.c.) was added dropwise to a stirred solution of 4-(chlorosulphonyl)acetophenone [39] (2·0 g.) and benzoyl peroxide (5 mg.) in the same solvent (20 c.c.), illuminated and warmed by a 500-w tungsten lamp. When the reaction was complete (10 min.), the solvent was removed to give a solid which on recrystallisation from chloroform–light petroleum (b. p. 60—80°) gave needles (2·3 g.) of the *bromo-compound*, m. p. 98°, $\nu_{max.}$ 1180, 1390, and 1690 cm.$^{-1}$ (Found: C, 32·5; H, 2·3; S, 11·1; total halogen, 39·0. $C_8H_6BrClO_3S$ requires C, 32·3; H, 2·0; S, 10·8; total halogen, 38·8%).

4,4′-*Bisdiazoacetyldiphenyl Disulphide* (XXVII).—4,4′-Dicarboxydiphenyl disulphide [40] (3·1 g.) was boiled for 1 hr. with thionyl chloride under reflux. The excess of reagent was then distilled off, and the crude acid chloride, dissolved in dry ether (100 c.c.) was slowly added to diazomethane (1·8 g.) in dry ether (120 c.c.). Next day the yellow precipitate was collected, dissolved in chloroform and precipitated with petroleum to give the amorphous *bisdiazoacetyl compound*, m. p. 147—153° (Found: C, 55·4; H, 3·0; N, 15·4; S, 18·3. $C_{16}H_{10}N_4O_2S_2$ requires C, 54·2; H, 2·9; N, 15·7; S, 18·1%).

4,4′-*Bischloroacetyldiphenyl Disulphide*.—The foregoing diazo-compound (1·0 g.) was stirred for 1 hr. with ether (25 c.c.) and concentrated hydrochloric acid (2 c.c.). The solid product was filtered off and extracted with cold chloroform, in which most of it was soluble. Evaporation of this extract gave a crystalline residue (0·8 g.), which when precipitated from chloroform with petroleum yielded yellow crystalline granules of the *bischloroacetyl compound*, m. p. 131—132° (Found: C, 51·5; H, 3·3; Cl, 19·2. $C_{16}H_{12}Cl_2O_2S_2$ requires C, 51·8; H, 3·3; Cl, 19·1%).

α-*Chloro*-4-(*chlorosulphonyl*)*acetophenone* (XXVIII).—Chlorine (0·2 g.) in carbon tetrachloride (10 c.c.) was added to the bischloroacetyl compound (0·2 g.) in chloroform (10 c.c.); water (5 c.c.) was added, and the mixture was

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shaken for 15 min. Evaporation of the dried organic layer, and crystallisation of the residue from light petroleum (b. p. 60—80°) (in which the disulphide is insoluble) and then from chloroform–light petroleum (b. p. 60—80°) (1 : 2) gave colourless needles of the *sulphonyl chloride* (0·2 g.), m. p. 88°, $\nu_{max.}$ 1180, 1390, and 1695 cm.$^{-1}$ (Found: Cl, 28·5; S, 13·2. $C_8H_6Cl_2O_3S$ requires Cl, 28·0; S, 12·7%).

α-Chloro-4-sulphamoylacetophenone (XXIX).—A solution of the above sulphonyl chloride (0·3 g.) in acetone (1·5 c.c.) was vigorously stirred at 0° during the addition of 2·5N-aqueous ammonia (1 c.c.). After 5 min. the mixture became neutral and it was diluted with water (2 c.c.) and shaken with chloroform (50 c.c.). The organic layer was dried and evaporated to a solid (0·1 g.), m. p. 120—140°, which, when crystallised from cold chloroform by the addition of light petroleum (b. p. 60—80°), gave the *sulphonamide*, m. p. 141—145°, $\nu_{max.}$ 1170, 1360, 3380, and 3480 cm.$^{-1}$ (Found: C, 41·0; H, 3·1; N, 6·0. $C_8H_8ClNO_3S$ requires C, 41·1; H, 3·5; N, 6·0%).

Ethyl α-Bromophenylorthoacetate (XXX).—Bromine (47 g.) was added dropwise to a solution of ethyl phenylorthoacetate [41] (70 g.) in a mixture of pyridine (23 g.) and carbon tetrachloride (115 c.c.) at 0°. When the addition was complete the mixture was left at room temperature for 4 hr., then filtered from pyridine hydrobromide and distilled to give the *bromo-orthoester* (60 g.), b. p. 94—95°/10^{-4} mm., n_D^{25} 1·5080 (Found: C, 52·6; H, 6·3. $C_{14}H_{21}BrO_3$ requires C, 53·0; H, 6·7%).

We thank the University of London for the award (to D. J. C.) of a Postgraduate Studentship and an Arthur Jubber Studentship.

Chemistry Department,
Imperial College of Science and Technology,
London S.W.7. [5/1042 *Received, September 29th,* 1965]

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