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# HALODEACYLATION OF ARYL KETONES

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**Abstract**—Bromination and chlorination of phloroacetophenones in acetic anhydride resulted in deacylation with the formation of halophloroglucinol derivatives. This halodeacylation reaction also occurred in chloroform solution in the presence of silver acetate.

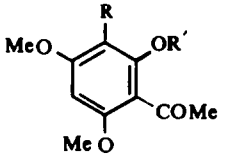
THE variety of reactions,[1] involving the mutual displacement of electrophiles (other than protons) from an aromatic nucleus, is steadily increasing. Recent additions[2] to the class are dehalogenoacylation and bromodeacylation. In the latter case it has been observed that bromination of 2′-hydroxy-4′,6′-dimethoxyacetophenone (Ia) in acetic anhydride results in deacylation with the formation of 2,6-dibromo-3,5-dimethoxyphenyl acetate (IIa). A further study of this bromodeacylation and the related chlorodeacylation has now been undertaken.

Grovenstein and Henderson,[3] in their study of the bromodecarboxylation of hydroxybenzoic acids, concluded that a dienone, such as III, was an intermediate in the reaction. It seemed likely that the formation of a similar intermediate (IV) was a requirement for bromodeacylation. Bromination of 2′,4′,6′-trimethoxyacetophenone (Ib) in acetic anhydride gave, however, an excellent yield of the bromodeacylated product, 1,3-dibromo-2,4,6-trimethoxybenzene (IIb). In this case a dienone intermediate such as IV is impossible and its formation is, therefore, not a requirement for bromodeacylation. Bromination of 2′-hydroxy-4′,6′-dimethoxyacetophenone (Ia) in acetic anhydride with half the quantity of bromine required for deacylation gave a mixture of 3′-bromo-2′-hydroxy-4′,6′-dimethoxyacetophenone (Ic) and its acetate (Id). Thus nuclear bromination precedes bromodeacylation and, more importantly, the hydrogen bromide so formed does not effect deacylation.

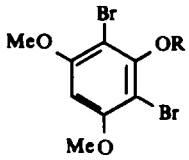
Addition of an excess (because of its relatively fast reaction with the solvent) of chlorine to an acetic anhydride solution of 2′,4′,6′-trimethoxyacetophenone (Ib) resulted in chlorodeacylation of the acetophenone with the formation of 1,3-dichloro-2,4,6-trimethoxybenzene (Va) and 1,3,5-trichloro-2,4,6-trimethoxybenzene (Vb).

The di-substituted acetophenones, 2′-hydroxy-4′-methoxyacetophenone (VIa) and 2′-hydroxy-6′-methoxyacetophenone (VIIa), did not undergo deacylation. The former, with bromine in acetic anhydride, gave 5′-bromo-2′-hydroxy-4′-methoxyacetophenone (VIb), while the latter, under the same conditions, gave 3′-bromo-2′-hydroxy-6′-methoxyacetophenone (VIIb). 2′,4′,6′-Trimethylacetophenone (VIIIa), which is readily deacylated[4] by such acids as sulphuric and phosphoric, was converted* into

* It was sometimes necessary, as in this case, to use a third molar equivalent of halogen in the various halogenation reactions to circumvent the formation of complex mixtures of mono-, di-, and tri-halides which otherwise occurred.



I a: R = R′ = H
b: R = H, R′ = Me
c: R = Br, R′ = H
d: R = Br, R′ = Ac
e: R = Br. R′ = Me



II
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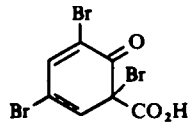
b: R = Me



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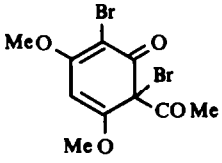

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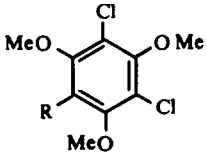

V
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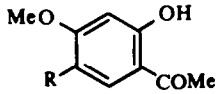
b: R = Cl



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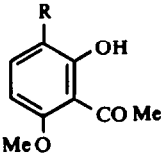
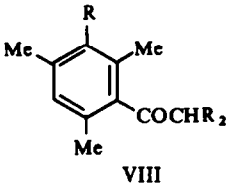
b: R = Br



VII
a: R = H
b: R = Br



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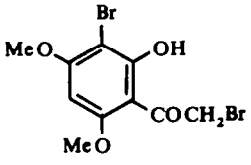
b: R = Br



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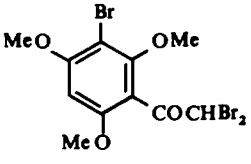
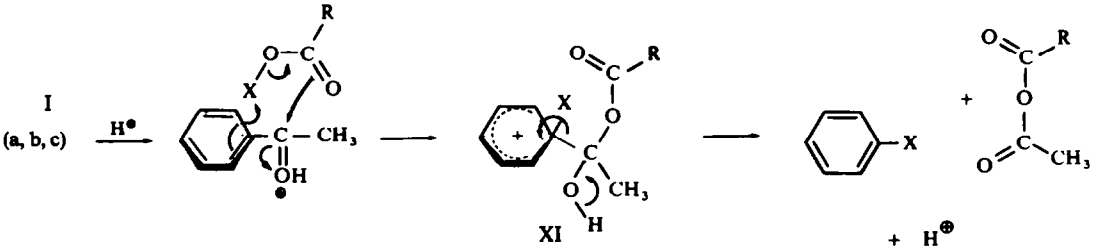


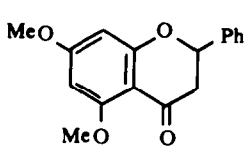
X



XI

X = halogen

SCHEME I

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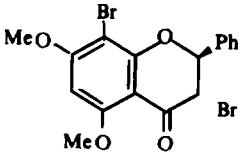
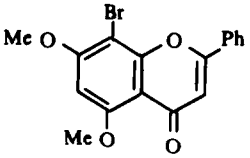
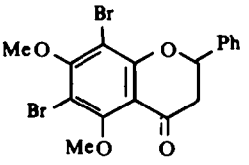


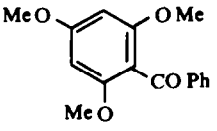

XIII



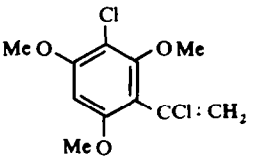

XIV




XV




XVI




XVII

2,2,3′-tribromo-2′,4′,6′-trimethylacetophenone (VIIIb) under bromodeacylation conditions. The failure of these acetophenones to undergo bromodeacylation is probably due to the lack of sufficient nuclear activation for electrophilic substitution of their acyl groups to compete successfully with acetic anhydride for bromine.

Bromination of phloracetophenones (Table 1), in solvents other than acetic anhydride, gave side-chain and/or nuclear brominated phloroacetophenones. The non-occurrence of deacylation in these solvents suggested the existence of a more electrophilic halogen species in acetic anhydride solutions of bromine and chlorine and that halodeacylation might be readily effected by acetyl hypohalite.[5] In accord with this, the addition of a solution of bromine or chlorine in chloroform to a similar solution of 2′,4′,6′-trimethoxyacetophenone (Ib) containing suspended silver acetate resulted in immediate uptake of halogen and good yields of the halodeacylated products (IIb and Vb) were obtained.

It is possible that halodeacylation occurs (Scheme I; nuclear substituents omitted) by a cyclic mechanism involving the conjugate acid[2] of the nuclear halogenated phloracetophenone and the acyl hypohalite and leading to the aronium ion XI. Such a mechanism would account for the halogenation of the 1′-position rather than the normal halogenation of the side-chain or the remaining unsubstituted nuclear position.[2]

An attempt to determine the fate of the acyl group by bromodeacylating a cyclic analogue of 2′,4′,6′-trimethoxyacetophenone (Ib), i.e. 5,7-dimethoxyflavanone (XII), failed. Bromination of this flavanone in acetic anhydride gave *trans*-3,8-dibromo-5,7-dimethoxyflavanone (XIII), $J_{2,3}$ 6 c/s, which was dehydrobrominated to 8-bromo-5,7-dimethoxyflavone (XIV) by aqueous ethanolic potassium hydroxide. On the other hand, bromination of 5,7-dimethoxyflavanone (XII) in chloroform in the presence of silver acetate gave 6,8-dibromo-5,7-dimethoxyflavanone (XV). The failure of this flavanone (XII) to undergo bromodeacylation may be attributed to the nuclear deactivation resulting from conjugation between the carbonyl group and the aromatic nucleus. Apparently, halodeacylation requires activation not only by suitable substituents but also by ortho group inhibition of resonance between the acyl group and the aromatic ring.

TABLE 1. HALOGENATION OF AROMATIC KETONES

| Substrate | Wt. (g) | Solvent (ml) | Halogen (g) | Product | M.p. (solvent[a]) | Yield (g) | Formula or reference | Found (%) / Required (%) C | H | Hal. | N.m.r. spectrum |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ia | 1·0 | $Ac_2O$ | $Br_2$ | Ic | 184–186 (ethanol) | 0·7 | 11 | | | | 7·36 Ac; 6·04 4′-OMe; 6·02 6′-OMe; 3·99 5′-H; −4·59 OH |
| | | (20) | (0·8) | Id[b] | 149–150 (aq. ethanol) | 0·3 | 16 | | | | 7·67 OAc; 7·50 Ac; 6·08 4′-OMe; 6·04 6′-OMe; 3·57 5′-H |
| Ia | 5·1 | AcOH | $Br_2$ | IC[c] | 186–188 (ethanol) | 7·0 | 11 | | | | |
| | | (90) | (8·3) | | | | | | | | |
| Ia | 1·5 | $CHCl_3$ | $Br_2$ | Ic[c] | 186–187 (ethanol) | 0·7 | 11 | | | | |
| | | (110) | (2·3) | IX | 194–195 (benzene) | 0·6 | $C_{10}H_{10}Br_2O_4$ | 34·1<br>33·9 | 2·8<br>2·8 | | 5·98 4′- and 6′-OMe; 5·37 $COCH_2Br$; 3·91 5′-H; −3·79 OH |
| Ia | 3·1 | $CCl_4$ | $Br_2$ | Ic[c] | 186–187 (benzene) | 3·7 | 11 | | | | |
| | | (100) | (5·1) | | | | | | | | |
| Ib | 1·0 | $Ac_2O$ | $Br_2$ | IIb[b] | 131–132 (ligroin) | 1·4 | 8 | | | | 6·11 2–OMe; 6·08 4- and 6·0 Me; 3·66 5-H |
| | | (20) | (1·6) | | | | | | | | |
| Ib | 2·0 | $Ac_2O$ | $Cl_2$ | Va[c] | 126–127 (light petroleum) | 1·0 | 9 | | | | 6·08 2-OMe; 6·04 4- and 6-OMe; 3·59 5-H |
| | | (40) | (1·4) | V[b] | 134–135 (aq. ethanol) | 0·6 | 10 | | | | 6·10 2-, 4-, and 6-OMe |
| Ib | 2·4 | THF[e] | $Br_2$ | X | 136–137 (ligroin) | 2·6 | $C_{11}H_{11}Br_3O_4$ | 30·0<br>29·6 | 2·6<br>2·5 | 52·9<br>53·6 | 6·07, 6·07, 6·03 2′-, 4′-, and 6′-OMe; 3·65 5′-H; 3·36 $COCHBr_2$ |
| | | (25) | (5·5) | | | | | | | | |
| Ib and AgOAc | 1·4<br>2·3 | $CHCl_3$ (60) | $Br_2$ (2·1) | IIb | 132–133 (ligroin) | 1·2 | 8 | | | | |
| Ib and AgOAc | 2·5<br>6·7 | $CHCl_3$ (80) | $Cl_2$ (2·6) | Vb | 133–134 (ligroin) | 1·1 | 10 | | | | |
| Ib | 1·6 | $CCl_4$[f] | $PCl_5$ | XVII | 129–131 (light petroleum[d]) | 0·6 | $C_{11}H_{12}Cl_2O_3$ | 50·3<br>50·2 | 4·8<br>4·6 | | 6·12, 6·10, 6·07 2-, 4-, and 6-OMe; 4·61 (d) and 4·25 (d, $J$ 1·3 c/s): $CH_2$; 3·66 5-H |
| | | (30) | (3·2) | | | | | | | | |
| Ib | 3·2 | $CHCl_3$ (55) $H_2O$ (30) | $Br_2$ (2·4) | Ie | 91–92 (ethanol) | 3·2 | $C_{11}H_{13}BrO_4$ | 45·8<br>45·7 | 4·7<br>4·5 | 27·7<br>27·6 | 7·52 Ac; 6·16, 6·16, 6·08 2′-, 4′-, and 6′-OMe; 3·69 5′-H |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| VIa | 1·0 | $Ac_2O$ (20) | $Br_2$ (1·9) | VIb | 170–172 (aq. ethanol) | 0·7 | 12 | | | | 7·45 Ac; 6·08 OMe; 3·53 3′-H; 2·13 6′-H; −2·73 OH |
| VIIa | 2·9 | $Ac_2O$ (60) | $Br_2$ (5·6) | VIIb | 101–102 (aq. ethanol) | 1·9 | 13 | | | | 7·35 Ac; 6·13 OMe; 3·65 (d) 5′-H; 2·40 (d, $J$ 9·1 c/s) 4′-H; −4·04 OH |
| VIIIa | 4·3 | $Ac_2O$ (60) | $Br_2$ (12·7) | VIIIb | 84–85 (ethanol) | 5·5 | $C_{11}H_{11}Br_3O$ | 33·3<br>33·1 | 2·7<br>2·8 | 58·5<br>60·1 | 7·72 4′-Me; 7·63, 7·60 2′- and 6′-Me; 3·77 $COCHBr_2$; 3·01 5′-H |
| XII | 1·0 | $Ac_2O$ (20) | $Br_2$ (1·1) | XIII | 183–184 (ethanol) | 0·8 | $C_{17}H_{14}Br_2O_4$ | 46·1<br>46·2 | 3·3<br>3·2 | 35·8<br>36·2 | [g] 6·12 7-OMe; 5·98 5-OMe; 4·56(d) 3-H; 4·04 (d, $J$ 6·0 c/s) 2-H; 3·50 6-H 2·58 2-Ph |
| XII and AgOAc | 1·2<br>1·4 | $CHCl_3$ (30) | $Br_2$ (1·3) | XV | 135–136 (ethanol) | 0·9 | $C_{17}H_{14}Br_2O_4$ | 46·5<br>46·2 | 3·0<br>3·2 | 36·2<br>36·2 | [h] 7·14 (s) 3-$H_{eq}$; 6·84 (q) 3-$H_{ax}$; 6·10 7-OMe; 6·07 5-OMe; 4·45 (q) 2-H; 2·58 2-Ph; $J_{2\cdot3(ax)}$ 8·8 c/s; $J_{2\cdot3(eq)}$ 6·8 c/s; $J_{3\cdot3}$ 16·8 c/s |

[a] Solvent of crystallisation; [b] identical with the acetate prepared from Id with acetic anhydride and sodium acetate; [c] identical with the product from the addition of chlorine (1·7 g) in acetic acid (30 ml) to a solution of 1,3,5-trimethoxybenzene (2·0 g) in acetic acid; [d] b.p. 60–80°; [e] the tetrahydrofuran was eventually removed by distillation on a steam-bath under reduced pressure; [f] refluxed for 1 hr; [g] in deuterated dimethyl sulphoxide; [h] the ABC portion was analysed by the computer program[15] ABCLSQ.

At least one reaction similar to the chlorodeacylation described here has previously been reported. In 1892, Ciamician and Silber[6] converted 2,4,6-trimethoxybenzophenone (XVI) into 1,3,5-trichloro-2,4,6-trimethoxybenzene (Vb) by fusing the ketone with phosphorous pentachloride. In view of the recent publication of the results of a study by Newman *et al.*[7] of the reactions of ketones with phosphorous pentachloride, it seemed opportune to test this reagent as a chlorodeacylating agent under the milder conditions of refluxing carbon tetrachloride. It failed to deacylate 2',4',6'-trimethoxyacetophenone (Ib) but converted it into 1-chloro-1-(3-chloro-2,4,6-trimethoxyphenyl)ethylene (XVII).

## EXPERIMENTAL

NMR spectra were obtained on a Varian HR60A spectrometer in $CDCl_3$ (unless otherwise stated) with TMS as internal reference. Chemical shifts are given in tau values. M.ps were taken on a Kofler hot-stage apparatus. The IR spectra (Beckman IR 5) of previously known products were compared with those of the same products prepared as in the quoted reference.

Halogenations (see Table for details) in $Ac_2O$ were carried out by adding the halogen to the well-stirred soln of the ketone in the anhydride and allowing the mixture to stand overnight before pouring it on crushed ice and collecting the ppt. Those in other solvents were generally carried out by adding a 10% w/v soln of the halogen to a soln of the ketone. After an hr the solvent was allowed to evaporate in a fumehood. Similarly for the bromination in AcOH except that the product was obtained by pouring the soln into ice-water. In the halogenations involving AgOAc, the reaction mixtures were filtered before allowing the solvent to evaporate.

*8-Bromo-5,7-dimethoxyflavone* (XIV). 20% KOH aq (3 ml) was added to a boiling soln of XIII (0·19 g) in aqueous EtOH (95%; 20 ml). Water was then added to produce a slight turbidity and, on cooling, the flavone[14] crystallized in white needles (0·14 g), m.p. 257°. (Found: C, 56·5; H, 3·6; Br, 21·9. Calc. for $C_{17}H_{13}BrO_4$: C, 56·5; H, 3·6; Br, 22·1%).

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