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## **Reactions of 1,3-Dichloroacetone with Phenols**

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*p*-Nitrophenol and toluene-*p*-thiol reacted with 1,3-dichloroacetone in acetone, in the presence of potassium carbonate and potassium iodide, to give the expected 1,3-bis-*p*-nitrophenoxy- and bis-*p*-tolylthio-acetone, respectively. In contrast, the less acidic phenols *p*-cresol, *p*-methoxyphenol, and *p*-chlorophenol, under similar conditions, gave the corresponding 1,1-disubstituted acetones as the major products.

PHENOLS, when treated with 1,3-dichloroacetone, in acetone in the presence of potassium carbonate and potassium iodide, gave either the expected 1,3-disubstituted acetone (III) or the 1,1-disubstituted acetone (III). The results with phenols (Ia—d) and the thiol (Ie) are given in Table 1.

Phenol (Id) and thiol (Ie), which are ionised under the reaction conditions, reacted exothermically with 1,3-dichloroacetone to give the expected products (IIId) and (IIIe) respectively. Phenols (Ia—c), which are not significantly ionised, reacted slowly to give a

(田)

 $(p - MeC_{6}H_{4} \cdot S)_{2}$ 

(p-MeC<sub>6</sub>H<sub>2</sub>·O·CH<sub>2</sub>)<sub>2</sub>CH·OH

(111)

XCH,Ac

OCH, CO.CH, Cl

(VI)

∩н

och, ch.ch, cl

(IX)

(IV)

 $(p - RC_6H_4 \cdot X \cdot CH_2)_2 CO$ 

a;R=Me,X=0 b;R=OMe,X=0 c;R=Cl,X=0 d;R=NO<sub>2</sub>,X=0 e;R=Me, X=S

complex mixture containing the 1,1-bisaryloxyacetone (II) as the major component. Repeated chromato-

\* In the presence of potassium iodide, replacement of chlorine by iodine occurs.

graphy of the mixture from p-cresol (Ia) revealed the presence of a small amount (<1%) of 1,3-bis-p-tolyloxy-acetone (IIIa).

The behaviour of  $\alpha$ -halogenoketones of type (A; X = Cl) with nucleophiles (in particular with acetate



anion), in which products (C) of rearrangement were formed, was reported by Rosnati and his co-workers.<sup>1</sup> The mechanism of this rearrangement, outlined in the Scheme ( $\mathbb{R}^1 = \operatorname{Ac}$ , Me, or Et,  $\mathbb{R}^2 = \operatorname{H}$  or alkyl, X = Cl), involves formation of an allylic (enol) carbonium ion (B), with anchimeric assistance to ionisation, and/or stabilisation of the resulting carbonium ion, by the ether oxygen.

If an intermediate of type (A; X = Cl or I) \* is formed in the reaction of dichloroacetone with a phenol, then further reaction with the phenol could give either



(I)

a;R=Me

c;R=Cl

b;R=OMe

MeC=N·NHR

(VII) R= 2,4-

ĊH=N•NHR

dinitrophenyl

 $(p-RC_6H_4\cdot O)_2CHAc$ 

**(□**)

<sup>&</sup>lt;sup>1</sup> V. Rosnati, D. Misiti, and F. De Marchi, *Gazzetta*, 1966, 96, 497; V. Rosnati, G. Pagani, and F. Sannicolò, *Tetrahedron Letters*, 1967, 1241.

the product of direct substitution (III) or, by prior ionisation to an allylic carbonium ion [type (B)], the product of rearrangement [(II) or (C;  $R^1 = Ar$ ,  $R^2 =$ H)]. When the type (A) chloro-ketone (VI) was treated with p-cresol, the bis-p-tolyloxyacetones (IIa) and (IIIa) were obtained in the ratio 6:1.

An alternative explanation for the reaction  $(I) \rightarrow (II)$  $[or (A) \rightarrow (C)]$  requires the formation of a cyclopropane intermediate, as in the Favorskii rearrangement.<sup>2</sup> This seems less likely, as no products of a Favorskii rearrangement, which might be expected from such an intermediate, were detected.

Preferential formation of the 1,3-disubstituted acetone (III) by phenol (Id) and thiol (Ie) may be due to displacement of the halogen \* in (A) by the strongly nucleophilic phenolate (thiolate) anions predominating over the ionisation  $(A) \rightarrow (B)$ . Furthermore, in the case of p-nitrophenol (Id), the nitro-group in the corresponding intermediate (A; Ar = p-nitrophenyl) would hinder anchimeric assistance to ionisation by the ether oxygen. The reaction of dichloroacetone with phenols (Ia—c), in which the phenols are largely un-ionised and less nucleophilic, is much slower, and the predominant reaction could involve formation of the allylic ion (B) and hence lead to a 1,1-bisaryloxyacetone [(II) or (C;  $R^1 = Ar, R^2 = H$ )] as the major product.

Aryloxyacetones (IV) were also formed from phenols (Ic and d) and thiol (Ie). These products may arise by reductive dehalogenation of a type (A) intermediate, or by a reaction involving the solvent, acetone. Both processes have been noted when phenols reacted with chloro-ketones in the presence of potassium iodide.<sup>3</sup> A disproportionation,  $(XCH_2)_2CO + MeAc \longrightarrow 2AcCH_2X$ , would also account for such products, but there is no evidence that such a reaction occurs under non-acidic conditions.

Chloro-ketone (VI) was prepared by oxidation of the corresponding alcohol<sup>4</sup> (IX), and 1,3-bis-p-tolyloxyacetone (IIIa) was obtained by oxidation with dimethyl sulphoxide <sup>5</sup> of the p-tolylsulphonyl derivative of the alcohol 6 (VIII).

The 1,1-bisaryloxyacetones (IIa) and (IIb), being diaryl acetals of pyruvaldehyde, reacted in acid with 2,4-dinitrophenylhydrazine to give a bis-2,4-dinitrophenylhydrazone (VII),<sup>7</sup> identical with that prepared from pyruvaldehyde. The structures of products (II), (III), and (IV) were also consistent with their n.m.r. spectra [Table 2; the spectrum of derivative (IVd) was reported recently<sup>8</sup>]. Aryloxyketones (IV) and disulphide (V) were identical with unambiguously synthesised materials.

- \* See Footnote, p. 462.
- <sup>2</sup> A. S. Kende, Org. Reactions, 1960, 11, 261.

<sup>3</sup> M. K. M. Dirania and J. Hill, J. Chem. Soc. (C), 1969, 2144.
<sup>4</sup> O. Stephenson, J. Chem. Soc., 1954, 1571.
<sup>5</sup> M. M. Baizer, J. Org. Chem., 1960, 25, 670.
<sup>6</sup> A. Fairbourne, G. P. Gibson, and D. W. Stephens, Chem. and Ind., 1930, 49, 1021.
<sup>7</sup> C. Neuberg and M. Kohel, Piechem. Z. 1022, 202, 462.

- <sup>7</sup> C. Neuberg and M. Kobel, *Biochem. Z.*, 1928, 203, 463.
   <sup>8</sup> M. K. M. Dirania and J. Hill, *J. Chem. Soc.* (C), 1968, 1311.
- <sup>9</sup> H. Suter and H. Zutter, Annalen, 1952, 576, 215.

TABLE 1

		Molar ratio	
	Chloro-	phenol : chloro-	
henol	ketone	ketone	Yield a (%) (product)
(Ia)	(ClCH <sub>2</sub> ) <sub>2</sub> CO	$2 \cdot 4$	7 (IIa), 0.6 (IIIa)
Ia)	$(ClCH_2)_2CO$	3.0	21 (IIa)
(Ia)	(VI)	$1 \cdot 2$	29 (IIa), 5 (IIIa)
(Ib)	(ClCH <sub>2</sub> ) <sub>2</sub> CO	$3 \cdot 0$	20 (IIb)
(Ic)	(CICH,),CO	2.4	12 (IIc), 6 (IVc) <sup>b</sup>
(Id)	(CICH,),CO	$2 \cdot 4$	29 (IIId), 11 (IVd) •
(Ie)	(ClCH <sub>2</sub> ) <sub>2</sub> CO	$2 \cdot 1$	14 (IIIe), <sup>d</sup> 38 (IVe),
• •			$27(V)^{f}$

<sup>a</sup> Based on amount of chloro-ketone used, except for product (V), in which case the yield was based on the amount of toluene-p-thiol used. <sup>b</sup> Ref. 9. <sup>c</sup> Ref. 10. <sup>d</sup> Ref. 13. <sup>e</sup> Ref. 11. J Ref. 12.

TABLE 2	2
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N.m.r. spectra (CDCl<sub>3</sub>) ( $\tau$  at 60 MHz)

	ArMe or				Aromatic
Ketone	ArOMe	MeCO	$CH_2$	CH	multiplet a
IIa)	7.72(6H)	7.63		4.33	3.01
IIb)	6.25(6H)	7.63		4.46	3.13
IIc)		7.62		4.32	$2 \cdot 89$
IIIa)	7.7(6H)		5.17(4H)		$3 \cdot 02$
(IIId) »			4.71(4H)		$2 \cdot 23$
IIIe)	7.71(6H)		6.25(4H)		2.85
IVc)		7.74	5.47		2.94
(IVe)	7·7 or 7·77	7.7 or	6.41		2.82
		7.77			
(VI)	7.72		$5 \cdot 3$ and $5 \cdot 63$		3.03
	$^{a}$ A <sub>2</sub> B <sub>2</sub>	system.	<sup>b</sup> In (CD <sub>3</sub> ) <sub>2</sub> SO.		

EXPERIMENTAL

Silica gel used for column chromatography was Merck Kieselgel, grade 0.05-0.2 mm., unless otherwise stated. Light petroleum had b.p. 60-80° and acetone was dried over anhydrous potassium carbonate. Where the same compound was obtained by different routes, identity was established by comparison of the i.r. spectra.

Reaction of 1,3-Dichloroacetone with Phenols (Ia-d) and Thiol (Ie).-After completion of the reaction, the mixture was filtered and the filtrate was evaporated. The residue was extracted into ether; the extract was washed with aqueous alkali, dried, and evaporated to give a neutral product (an alternative procedure was used in the reaction with p-nitrophenol).

p-Cresol (Ia). (i) A solution of 1,3-dichloroacetone (21 g.) in acetone (75 ml.) was added during 1 hr. to a stirred refluxing mixture of p-cresol (54 g.), anhydrous potassium carbonate (71 g.), potassium iodide (5 g.), and acetone (200 ml.). The mixture was heated under reflux for a further 8 hr., then set aside for 18 hr. at room temperature. The neutral product (23.7 g.) was chromatographed over silica gel (240 g.); elution with benzene-light petroleum (1:1)gave 1,1-bis-p-tolyloxyacetone (IIa) (9.5 g.), b.p. 150-151°, 1.2 mm. (Found: C, 75.7; H, 6.5. C<sub>17</sub>H<sub>18</sub>O<sub>3</sub> requires C, 75.5; H, 6.7%), ν<sub>max</sub> (film) 1737 cm.<sup>-1</sup>.
(ii) Isolation of 1,3-bis-p-tolyloxyacetone (IIIa). A solu-

tion of 1,3-dichloroacetone (6.35 g.) in acetone (50 ml.) was added during 10 min. to a stirred mixture of p-cresol (12.96 g.), anhydrous potassium carbonate (16.8 g.),

- <sup>10</sup> R. Stoermer and H. Brockerhof, Ber., 1897, **30**, 1631.
- <sup>11</sup> O. Newell and P. K. Calaway, J. Amer. Chem. Soc., 1947, **69**, 116.
- J. Reilly, P. J. Drumm, and B. Daly, Proc. Roy. Irish Acad., 1930, **39***B*, 515. <sup>13</sup> V. Prey, Austrian P., 195,422/1958.

potassium iodide (3 g.), and acetone (150 ml.), and the mixture was stirred for 2 hr. at room temperature, and for a further 7 hr. under reflux. The neutral product (8.85 g.) was chromatographed over silica gel (350 g.); elution with benzene gave 1,1-bis-p-tolyloxyacetone (0.9 g.). Further elution, with benzene-ethyl acetate (4:1), gave a mixture (4.2 g.) which, after repeated chromatography over silica gel, afforded 1,3-bis-p-tolyloxyacetone (IIIa) (85 mg.), identical with a sample prepared by oxidation of the corresponding alcohol (see later).

p-Methoxyphenol (Ib). The reaction of 1,3-dichloroacetone (21 g.) with p-methoxyphenol (62 g.) [under the conditions described for p-cresol (Ia)] yielded a neutral product (36.5 g.) which was chromatographed over silica gel (400 g.). Elution with benzene gave 1,1-bis-p-methoxyphenoxyacetone (IIb) (10 g.), b.p. 187—189°/1.2 mm. (Found: C, 68.0; H, 6.1.  $C_{17}H_{18}O_5$  requires C, 67.5; H, 6.0%),  $v_{max}$  (film) 1735 cm.<sup>-1</sup>.

Treatment of 1,1-bis-*p*-tolyloxyacetone (or 1,1-bis-*p*-methoxyphenoxyacetone) with 2,4-dinitrophenylhydrazine in ethanol containing conc. hydrochloric acid, gave the bis-2,4-dinitrophenylhydrazone of pyruvaldehyde <sup>7</sup> (VII).

p-Chlorophenol (Ic). The reaction of 1,3-dichloroacetone (12.7 g.) with p-chlorophenol (30.8 g.) [under the conditions described for p-cresol (Ia)] yielded a neutral product (15 g.) which was distilled at 0.5 mm.; fractions b.p. 100—140° and 150—210° were collected. The lower-boiling fraction (1.5 g.) was chromatographed over silica gel (Hopkin and Williams MFC; 150 g.); elution with benzene gave p-chlorophenoxyacetone (IVc) (1.1 g.), b.p. 95—96°/0.3 mm. (lit.,<sup>9</sup> b.p. 147—148°/17 mm.).

The higher-boiling fraction (7·4 g.) was redistilled at 0·5 mm. and the material b.p. 175—215° was chromatographed over silica gel (Hopkin and Williams MFC; 440 g.). Elution with benzene gave 1,1-bis-p-chlorophenoxyacetone (IIIc) (3·72 g.), m.p. 61° (from ether-light petroleum) (Found: C, 58·0; H, 4·1.  $C_{15}H_{12}Cl_2O_3$  requires C, 57·9; H, 3·9%),  $v_{max}$ . (CHCl<sub>3</sub>) 1737 cm.<sup>-1</sup>.

p-Nitrophenol (Id). A solution of 1,3-dichloroacetone (6:35 g.) in acetone (50 ml.) was added during 1 min. to a stirred mixture of p-nitrophenol (16:8 g.), anhydrous potassium carbonate (16:8 g.), potassium iodide (3 g.), and acetone (150 ml.), and the mixture was stirred for 2 hr. at room temperature. The mixture was filtered, ether (50 ml.) and water (5 ml.) were added to the filtrate, and on cooling, 1,3-bis-p-nitrophenoxyacetone \* (IIId) (3:13 g.) separated, m.p. 169–170° (from ethyl methyl ketone) (Found: C, 53:9; H, 3:7; N, 8:3.  $C_{15}H_{12}N_2O_7$  requires C, 54:2; H, 3:6; N, 8:4%),  $\nu_{max.}$  (Nujol) 1755 cm.<sup>-1</sup>.

The remaining solution was evaporated and extracted into ether-acetone (ca. 5:1); the extract was washed with aqueous sodium carbonate, dried, and evaporated. More ketone (IIId) (1.45 g.) separated when the residue was stirred with ether containing a little methanol. Evaporation of the solution, after removal of the solid, gave an oil (6 g.) which was chromatographed over silica gel (60 g.). Elution with chloroform yielded an oil (1.86 g.) and further elution, with ether, gave the ketone (IIId) (0.22 g.). The oil was rechromatographed over silica gel (63 g.); elution with benzene-light petroleum (1:1) yielded p-nitro-

\* First prepared by K. Denham (personal communication).

phenoxyacetone (IVd) (1·1 g.), which was extracted into hot light petroleum (b.p.  $100-120^{\circ}$ ) and crystallised from ether-light petroleum; m.p.  $80\cdot5^{\circ}$  (lit., <sup>10</sup> m.p.  $81^{\circ}$ ).

Toluene-p-thiol (Ie). A solution of 1,3-dichloroacetone (10 g.) in acetone (30 ml.) was added over 30 min. to a mixture of toluene-p-thiol (20.5 g.), anhydrous potassium carbonate (23 g.), potassium iodide (3 g.), and acetone (100 ml.), and the mixture was stirred for 1 hr. at room temperature, and for a further 2.5 hr. under reflux. The neutral product was distilled at 2 mm. and fractions b.p.  $40-155^{\circ}$  and  $180-225^{\circ}$  were collected. The lower-boiling fraction (5.8 g.) was redistilled to give p-tolylthio-acetone (IVe) (5.4 g.), b.p.  $118-120^{\circ}/2-2.5$  mm. (lit.,<sup>11</sup> b.p.  $133-135^{\circ}/7-9$  mm.).

The higher-boiling material (13.5 g.) was chromatographed over silica gel (540 g.); elution with benzenelight petroleum (1:1) yielded di-*p*-tolyl disulphide (V) (5.5 g.), m.p. 44—45° (from methanol) (lit.,<sup>12</sup> m.p. 45.6°).

Further elution, with benzene-ethyl acetate (5:1), gave an oil (5.6 g.) which was distilled to give 1,3-bis-*p*-tolylthioacetone (IIIe) (3.4 g.), b.p. 220—222°/1.7 mm., m.p. 66— 67° (from methanol) (lit.,<sup>13</sup> m.p. 67°).

1-Chloro-3-p-tolyloxypropan-2-one (VI).--A mixture of conc. sulphuric acid (16 ml.) and water (7.5 ml.) was added dropwise during 4.5 hr. to a stirred mixture of 1-chloro-3-p-tolyloxypropan-2-ol<sup>4</sup> (IX) (30 g.), sodium dichromate dihydrate (25.4 g.), and water (17 ml.), and the mixture was stirred for a further 4.5 hr. It was then stirred with water, and the neutral oil (26 g.) obtained by ether extraction was chromatographed over silica gel (675 g.). Elution with benzene gave ketone (VI) (1.32 g.), m.p. 59° [from light petroleum (b.p. 40-60°)] (Found: C, 61.1; H, 5.2.  $C_{10}H_{11}ClO_2$  requires C, 60.5; H, 5.6%),  $v_{max}$  (CHCl<sub>3</sub>) 1748 cm.<sup>-1</sup>. An alternative procedure <sup>1</sup> for the preparation of similar chloro-ketones usually gives mixtures of the isomeric 3-chloro- and 1-chloro-1-aryloxypropan-2-ones, from which the former often cannot readily be separated pure.

Reaction of p-Cresol with 1-Chloro-3-p-tolyloxypropan-2-one.—The chloro-ketone (VI) (0.5 g.) was stirred under reflux for 5 hr. with *p*-cresol (0.33 g.), anhydrous potassium carbonate (0.42 g.), potassium iodide (0.1 g.), and acetone (5 ml.). The neutral product (0.5 g.) was chromatographed over silica gel (25 g.). Elution with benzene gave 1,1-bis-*p*-tolyloxyacetone (IIa) (0.2 g.), and further elution, with benzene–ethyl acetate (9:1), gave 1,3-bis-*p*-tolyloxyacetone (IIIa) (0.033 g.).

1,3-Bis-p-tolyloxyacetone (IIIa).—Treatment of 1,3-bisp-tolyloxypropan-2-ol<sup>6</sup> (VIII) with toluene-p-sulphonyl chloride and pyridine gave the p-tosyl ester, m.p. 91° (from ethanol) (Found: C, 67.3; H, 6.1.  $C_{24}H_{26}SO_5$  requires C, 67.6; H, 6.1%).

The tosyl ester (4 g.) was heated for 3 hr. at 140—160° (bath) with dimethyl sulphoxide (16 ml.) and sodium hydrogen carbonate (0.84 g.). The cooled mixture was stirred into water; ether extraction gave a neutral product (1.82 g.) which was chromatographed over silica gel (55 g.). Elution with benzene gave 1,3-bis-p-tolyloxyacetone (0.36 g.), m.p. 63° [from light petroleum (b.p. 40—60°)] (Found: C, 75.55; H, 6.6.  $C_{17}H_{18}O_3$  requires C, 75.5; H, 6.7%),  $\nu_{max}$ . (CHCl<sub>3</sub>) 1748 cm.<sup>-1</sup>.

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