Perhalo Ketones. VIII. Hydrolysis of Mono- and Bis(2-hydroxyhexahalo-2-propyl)arenes to Carboxylic Acids

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Thirty-three aromatic compounds, mono- or disubstituted by the $C(CX_3)_2OH$ moiety (X = Cl,F), were converted to the corresponding carboxylic acids in generally good to excellent yields at 175° with excess potassium hydroxide in diethylene glycol. The reaction is shown to proceed by slow initial conversation to $ArCOCF_3$, followed by rapid cleavage to the acid.

The synthesis in high yields of a series of mono- and bis(2-hydroxyhexahalo-2-propyl)arenes by the interaction of perhalogenated acetones with various types of aromatic compounds in the presence of acid catalysts was reported by the present authors.[2] A simple and

$$CX_3COCX_3 + ArH \xrightarrow{\text{catalyst}} ArC(CX_3)_2OH \quad (X = Cl,F)$$

general hydrolytic procedure has now been developed for converting these tertiary alcohols to the corresponding acids. The method, which involves heating at reflux (*ca.* 175°) the halo alcohol with a large excess of potassium hydroxide in diethylene glycol, works best with the hexafluoro compounds. The reaction proceeds

$$ArC(CF_3)_2OH + KOH \xrightarrow[\text{diethylene glycol}]{175°} ArCOOK + 2CF_3H$$

to completion in about 1–3 hr. to yield, upon acidification, the desired mono- or dicarboxylic acid and 2 equiv. of fluoroform almost quantitatively. The method was developed in order to establish the positions of the entering 2-hydroxyhexahalo-2-propyl moieties with respect to substituents already present on the aromatic nuclei. However, the versatility of this procedure, as shown in Tables I–III, taken with the ease of preparation of the starting carbinols from hexafluoroacetone,[2] suggests this approach as a possibly practical one for preparing certain aromatic acids. Since the presence of substituents resistant to alkaline hydrolysis does not hinder the progress of the desired reaction, it is thus possible to prepare aryl mono- and dicarboxylic acids containing alkyl, halo, hydroxy, amino, or methoxy substituents on the aromatic nuclei.

The hydrolysis apparently proceeds in two stages through the intermediacy of an aryl trifluoromethyl ketone, which then undergoes the fluoroform reaction very rapidly[3] compared with the initial alcohol. In actual experiments, I was recovered unchanged after refluxing 24 hr. with 10% aqueous KOH solution, while II underwent the haloform reaction immediately and

TABLE I

HYDROLYSIS OF $ArC(CF_2Cl)_2OH$

Acid produced	% yield	Obsd. m.p., °C.	Lit.[a] m.p., °C.
Salicylic	58	158–160	159
2-Hydroxy-5-methylbenzoic	36	153–154	153
3,5-Dimethyl-4-hydroxybenzoic	3	220–221	222–224[b]

[a] Except when otherwise noted, literature values in Tables I and II are taken from I. M. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1936. [b] M. S. Neuman and H. L. Gildenhorn, *J. Am. Chem. Soc.*, **70**, 317 (1948).

TABLE II

HYDROLYSIS OF $ArC(CF_3)_2OH$

Acid produced	% yield	Obsd., m.p., °C.	Lit.[a] m.p., °C.
Benzoic	85	122	122
p-Toluic	85	178	181
3,4-Xylic	30	166–167	166
2,4-Xylic	87	125–126	126–127
2,5-Xylic	89	131–132	132
4-Chlorobenzoic	82	240–242	242
3-Chloro-4-methylbenzoic	41	206	199
2-Chloro-4-methylbenzoic	40	155	155–156
2-Methyl-5-chlorobenzoic	82	168	169
α-Naphthoic	82	160	161
p-Anisic	91	184	184
Salicylic	87	158–160	159
p-Hydroxybenzoic	6	212–214	213–214
p-Aminobenzoic	80	184–186	186–187
4-Amino-3-methylbenzoic	63	169–170	169
4-Amino-2-methylbenzoic	73	176–177	165
2-Amino-5-methylbenzoic	70	172–174	175
4-Amino-3,5-dimethylbenzoic	53	252–254	242
p-Dimethylaminobenzoic	61	235–237	233
4-Amino-3-hydroxybenzoic	59	213–215	216–217[b]
4-Amino-3-methoxybenzoic	60	186–187	185–186[c]
1-Amino-2-naphthoic	64	202–203	205

[a] See footnote *a*, Table I. [b] E. Boyland and P. Sims, *J. Chem., Soc.*, 980 (1954). [c] V. Froelicher and J. B. Cohen, *ibid.*, **119**, 1425 (1920).

TABLE III

HYDROLYSIS OF $Ar[C(CF_3)_2OH]_2$

Acid produced	% yield	Obsd., m.p., °C.	Lit. m.p., °C.
Isophthalic	91	345–346	345–347[a]
Terephthalic	88	...	Subl.[b]
4-Methylisophthalic	80	325	330–332[c]
4,6-Dimethylisophthalic	80	352	355[d]
2,5-Dimethylterephthalic	73	335 (subl.)	340–350[e] (subl.)
4,5-Dimethylisophthalic	87	330	320[f] (subl.)
4,4′-Dicarboxydiphenyl ether	89	312	>285[g]
4,4′-Dicarboxydiphenyl sulfide	86	325	*ca.* 315[h]

[a] Ref. 2. [b] The product was further identified by comparison of its infrared spectrum with that of an authentic sample. [c] T. Wagner-Jauregg and E. Helmert, *Ber.*, **71B**, 2535 (1938). [d] R. Coffey, *Rec. trav. chim.*, **42**, 421 (1922). [e] M. Freund and K. Fleischer, *Ann.*, **414**, 42 (1916). [f] E. Schnapauff, *Ber.*, **19**, 2508 (1886). [g] O. V. Schick, *ibid.*, **69**, 242 (1936). [h] K. W. Rosenmund and H. Harms, *ibid.*, **53**, 2238 (1920).

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(2) Perhalo Ketones. V: B. S. Farah, E. E. Gilbert, and J. P. Sibilia, *J. Org. Chem.*, **30**, 998 (1965); VI: E. E. Gilbert, E. S. Jones, and J. P. Sibilia, *ibid.*, **30**, 1001 (1965); VII: B. S. Farah, E. E. Gilbert, M. Litt, J. A. Otto, and J. P. Sibilia, *ibid.*, **30**, 1003 (1965).

(3) M. Hudlicky, "Chemistry of Organic Fluorine Compounds," The Macmillan Co., New York, N. Y., 1962, p. 208.

$$C_6H_5C(CF_3)_2OH \xrightarrow[\text{slow}]{KOH} C_6H_5COCF_3 \xrightarrow[\text{very fast}]{KOH} C_6H_5COOK + CF_3H$$

I II

completely on contact with base in the cold. In the absence of excess alkali, *i.e.*, upon pyrolysis of the potassium salt of I, compound II was actually isolated in poor yield.

$$C_6H_5C(CF_3)_2OK \xrightarrow{\Delta} II + CF_3^- + K^+ \qquad CF_3^- \xrightarrow{-F^-} :CF_2$$

The alkaline hydrolysis of the analogous (2-hydroxy-1,1,3,3-tetrafluoro-1,3-dichloro-2-propyl)arenes was studied only briefly and appears to proceed through a more complex path than that of the hexafluoro analogs owing to the hydrolytic instability of a *gem*-difluoromethyl group on a carbon bearing another substituent.[4] The yields of carboxylic acids were relatively poorer with the tertiary alcohols containing CF_2Cl groups (Table I) than with those containing CF_3 groups (Table II).

(4) See (a) G. C. Stoner, U. S. Patent 2,761,875 (1956); (b) ref. 3, p. 203.

Experimental

Typical Hydrolysis Procedure.—The following procedure, describing the hydrolysis of I, was used for the preparation of all of the acids listed in Tables I–III.

A mixture of 4.88 g. (0.02 mole) of I, 11.2 g. (0.20 mole) of potassium hydroxide, and 20 ml. of diethylene glycol was heated at reflux (about 175°) for 3 hr. The cooled reaction mixture was acidified with concentrated hydrochloric acid. It was then made alkaline with 10% sodium bicarbonate solution and filtered to remove silica. The filtrate yielded, upon acidification, 2.20 g. of benzoic acid, m.p. 121–122°, corresponding to 90% yield.

For the identification of fluoroform as one of the reaction products, the reaction flask was equipped with a gas inlet tube and an outlet tube connected to a cold trap immersed in liquid air. The reaction was carried out as described above except that a positive pressure of helium gas was maintained over the system to avoid condensation of atmospheric gases into the cold trap. The liquid in the cold trap was identified as CHF_3 by its boiling point, −82°,[5] and by comparison of its infrared spectrum with that of an authentic sample.

Pyrolysis of the Potassium Salt of I.—The dried salt (5.64 g., 0.02 mole) and 5.64 g. of potassium chloride was heated in a 50-ml. round-bottom flask connected horizontally to a water-cooled condenser connected to a receiver cooled in Dry Ice–acetone. As the sample was heated, vapors were evolved and condensed in the traps and in the receiver. The condensed liquid was identified by its boiling point (150–152°[6]), by comparison of its infrared spectrum with that of an authentic sample, and by gas chromatographic analysis of synthetic mixtures of the collected sample with authentic samples of trifluoroacetophenone.

(5) A. L. Henne, *J. Am. Chem. Soc.*, **59**, 1200 (1937).
(6) T. F. McGrath and R. Levine, *ibid.*, **77**, 3656 (1955).

Aroylations at the Methyl Group of Benzoylacetone and Related β-Diketones with Esters to Form 1,3,5-Triketones by Sodium Hydride. Other Terminal Condensations[1]

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Terminal aroylations of benzoylacetone and certain related β-diketones were effected with sodium hydride in appreciably higher per cent conversions of the β-diketones and esters to the 1,3,5-triketones than has previously been observed with potassium amide. The mechanism of the reaction appears not to involve the intermediate formation of the β-diketone dicarbanion, which was the reactive intermediate with the alkali amide. Twofold terminal aroylations of acetone were effected with sodium hydride to form some new symmetrical 1,3,5-triketones, certain of which were cyclized to 4-pyrones and one to a 4-pyridone. Although sodium hydride is superior for aroylations, it was found not to be so satisfactory as potassium amide for certain other types of condensations.

Aroylation at the methyl group of a β-diketone such as benzoylacetone or acetylacetone to form a 1,3,5-triketone has previously been effected by means of potassium amide in liquid ammonia. This was accomplished by converting the β-diketone to its dicarbanion I with 2 molecular equiv. of the base and then adding 0.5 molecular equiv. of an aromatic ester (Scheme I).[2,3]

SCHEME I

$$RCOCH_2COCH_3 \xrightarrow[\text{liq. } NH_3]{2KNH_2} RCO\bar{C}HCO\bar{C}H_2 \quad (I)$$

$$I \xrightarrow{ArCOOCH_3} RCO\bar{C}HCOCH_2COAr \quad (II) \xrightarrow{I} RCO\bar{C}HCO\bar{C}HCOAr \quad (III)$$

Typical 1,3,5-triketones that have been obtained on acidification of the reaction mixtures were IVa–e.[2,3] The related hydroxy β-diketone V has been prepared similarly by benzoylation of *o*-hydroxyacetophenone.[3]

Although the per cent conversion of ester to triketone was generally good, for example 62% in the synthesis of triketone IVa,[4] the per cent conversion of the β-diketone to IVa was only half this value, as half of dicarbanion I was neutralized in the last step (II to III, Scheme I); in this acid–base reaction, the corresponding amount of β-diketone was regenerated as its monoanion. The use of an extra equivalent of

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(2) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958).
(3) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).
(4) The use of 2.2–3.0 molecular equiv. of I to 1 of the ester has recently been observed to increase the per cent conversion of the ester to IVa to 80%, but the per cent conversion of β-diketone was still only 40%: F. B. Kirby, T. M. Harris, and C. R. Hauser, *ibid.*, **28**, 2266 (1963).