443. *Halogenation in Acid Solution. The Formation of Iodoform from Malonic Acid.*

By M. G. Brown.

Malonic acid gives iodoform when treated with iodine in the presence of a variety of oxidising agents in acid solution.

Malonic acid appears to be specific for this reaction since other compounds containing the groups $CH_3\cdot CO-$ and $-CO\cdot CH_2\cdot CO-$ do not give iodoform in these conditions.

During an investigation of the oxidation of kojic acid (5-hydroxy-2-hydroxymethyl-4-pyrone) by periodic acid, it was observed that iodoform separated simultaneously with iodine from the mixture. The present work was undertaken to discover the type of molecule which gives iodoform when treated with iodine and an oxidising agent in acid conditions.

The formation of iodoform in non-alkaline conditions has rarely been recorded. Bougault and Robin [1] treated acetic anhydride with an *N*-iodo-amidine and obtained a yellow, iodine-containing precipitate, which gave iodoform when boiled with ethanol.

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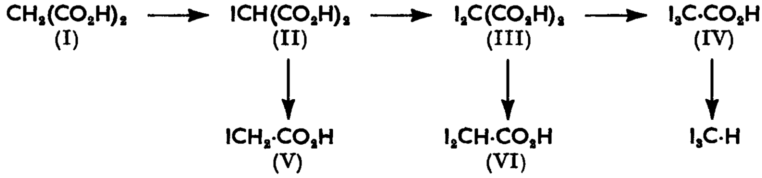
[1] Bougault and Robin, *Compt. rend.*, 1920, **171**, 38; 1921, **172**, 452.

(There appear to be two sources for the iodoform: the ethanol could be oxidised by the *N*-halogen compound and then iodinated; or the acetic anhydride could be iodinated and hydrolysed. The latter possibility is unlikely.) Angeli [2] prepared tri-iodoacetic acid by heating malonic acid with iodic acid. The tri-iodoacetic acid was separated, and it was decomposed to iodoform by boiling acetic acid.

Malonic acid appears as a possible intermediate in the oxidation of kojic acid with periodic acid (further work is in progress on this point) and might react with iodine (resulting from total reduction of the periodic acid) in the presence of residual periodic acid or of iodic acid. It was in fact found that on addition of iodine to a warm mixture of periodic acid and malonic acid iodine is absorbed and, finally, iodoform precipitated. The periodic acid may be replaced by a variety of oxidising agents, still with the formation of iodoform in the majority of cases.

The oxidising agent is responsible for the formation of the active iodinating agent and also prevents reversal of iodination by iodide ion.[3] In agreement with current theory, the active intermediate is thought to be H_2OI^+ which may be produced directly from iodine and iodide. Calculated free-energy changes support this. It is of interest, however, that in our hands perchloric and chloric acid failed to cause iodination in spite of favourable free-energy changes. This is in contrast to the effectiveness of bromine–chlorate mixtures for bromination [4] and is probably related to the slow oxidation of iodine by these acids.[5]

The reactions of primary interest are those in the annexed formulæ, together with the



$$\begin{tikzcd}
\underset{\text{(I)}}{CH_2(CO_2H)_2} \arrow[r] & \underset{\text{(II)}}{ICH(CO_2H)_2} \arrow[r] \arrow[d] & \underset{\text{(III)}}{I_2C(CO_2H)_2} \arrow[r] \arrow[d] & \underset{\text{(IV)}}{I_3C{\cdot}CO_2H} \arrow[d] \\
 & \underset{\text{(V)}}{ICH_2{\cdot}CO_2H} & \underset{\text{(VI)}}{I_2CH{\cdot}CO_2H} & I_3C{\cdot}H
\end{tikzcd}$$

decarboxylations which represent important side-reactions. Decarboxylation of iodomalonic acids occurs readily;[6] and it appears that di-iodoacetic acid (VI) is not further iodinated.[2] Another side-reaction which is important with some oxidising agents is the oxidation of malonic acid itself.

The acid oxidising conditions are specific for malonic acid. Datta and Prasad [7] obtained iodoform from malonic ester with iodine and aqueous alkali, although the ester gives only a red tar with iodine and liquid ammonia.[8] However, we find that malonic acid does not yield iodoform under a variety of alkaline conditions and it must be presumed that the iodoform produced from the ester results from hydrolysis and subsequent oxidation and odination of ethyl alcohol.

To discover if malonic acid is specific in this reaction, the iodine–periodic acid mixture was used with the following substances, each containing the grouping $\cdot CH_2 \cdot COR$: acetic acid, acetaldehyde, pyruvic acid, acetone, acetophenone, acetoacetic acid and its ethyl ester, acetonedicarboxylic acid and its ethyl ester, oxaloacetic acid, acetylacetone, and iodoacetic acid. None of them gave iodoform in the present conditions, although those with " active " methylene groups were iodinated. For example, acetonedicarboxylic acid readily gave tetraiodoacetone (cf. Angeli and Levi [9]).

It thus appears essential that iodination should lead to tri-iodoacetic acid and not merely the tri-iodoacetyl group. Qualitative observations in the literature suggest that

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[2] Angeli, *Ber.*, 1893, **26**, 596.

[3] Nylen, *Kgl. norske Videnskab. Selskabs, Skrifter*, 1938, No. 2; *Chem. Abs.*, 1939, **33**, 5731; Doak, *J. Amer. Chem. Soc.*, 1949, **71**, 159.

[4] Catch, Elliott, Hey, and Jones, *J.*, 1948, 272.

[5] Kahne and Tomesco, *Compt. rend.*, 1935, **201**, 1195; Klinger, *Chem.-Ztg.*, 1910, **34**, 1023; *Chem. Abs.*, 1911, **5**, 3547.

[6] Willstätter, *Ber.*, 1902, **35**, 1374.

[7] Datta and Prasad, *J. Amer. Chem. Soc.*, 1917, **39**, 441.

[8] Vaughn and Nieuwland, *ibid.*, 1932, **54**, 787.

[9] Angeli and Levi, *Gazzetta*, 1893, **23**, II, 97.

base-catalysis is necessary in the hydrolysis of the trihalogenoacetyl group.[10] Similar observations have been made in the present study: the oils obtained from pyruvic and acetoacetic acid on iodination (thought to be tri-iodoacetaldehyde and tri-iodoacetone respectively) remained unhydrolysed in water and aqueous sodium hydroxide. They were immediately hydrolysed to iodoform in aqueous-methanolic alkali.

The rates of decarboxylation increase rapidly on passing from the trifluoro- to the tribromo-acetic acids.[11] It is reasonable to assume that tri-iodoacetic acid will be still more readily decarboxylated (although this reaction is complicated by rapid decomposition to form iodine [12]).

EXPERIMENTAL

Solutions of acetoacetic acid and oxaloacetic acid were prepared by hydrolysis of their esters with 0·1N-sodium hydroxide followed by acidification with dilute hydrochloric acid.

Hypochlorous acid was obtained according to the instructions of Taylor;[13a] hypobromous acid was obtained by shaking a mixture of bromine, water, and excess of mercuric oxide for several hours, followed by decantation; hypoiodous acid was prepared *in situ* by adding silver nitrate and dilute nitric acid to the mixture of malonic acid and iodine.[13b]

Iodoform was identified in each case by its m. p., mixed m. p., and crystal shape, after recrystallisation from methanol.

Iodoform from Kojic Acid.—Periodic acid (4·3 g., 0·0189 mole) in water (100 ml.) was added to a solution of kojic acid (0·9 g., 0·0063 mole) in water (20 ml.) and the mixture was kept at room temperature for 72 hr. The resulting solution contained iodine but no periodic acid; and iodoform had separated.

Iodination Procedure.—(i) Malonic acid and potassium tri-iodide solution were added alternately to a concentrated solution (about 10 ml.) of the oxidant at 30—40°. In this way concurrent oxidation of the organic compound was kept at a minimum. When sufficient malonic acid had been added (0·5—1·0 g.), potassium tri-iodide solution was added dropwise, with increased heating, until the iodine colour persisted on boiling. Iodoform separated and was removed in steam.

This procedure was used with the following oxidising agents: periodic, iodic, hypoiodous, bromic, hypobromous, perchloric, chloric, and hypochlorous acid; sodium dichromate, potassium permanganate, and potassium persulphate each in dilute sulphuric acid; hydrogen peroxide; and ferric sulphate in dilute sulphuric acid. In every case except those of perchloric and chloric acid, potassium permanganate, and ferric sulphate, iodoform was produced. When procedure (i) was used with acetic acid and iodoacetic acid no iodination occurred.

(ii) This procedure was identical with (i) except that a solution of iodine in methanol was substituted for the potassium tri-iodide solution. This conserves the oxidising power and keeps water-insoluble intermediates in solution. Periodic acid was used as oxidant throughout. Procedure (ii) was used with the remaining compounds listed except acetonedicarboxylic acid. No iodoform was detected in the reaction mixtures.

Iodoform from Pyruvic and Acetoacetic Acid.—When procedure (ii) was used with pyruvic and acetoacetic acid, the iodine was immediately absorbed. On completion of the reactions, addition of water precipitated an oil in each case. These oils, thought to be tri-iodoacetaldehyde and tri-iodoacetone respectively, were separated by decantation and washed successively with water, aqueous sodium thiosulphate, and water. They darkened rapidly, liberating iodine.

The oils were neutral and insoluble in water, and remained unhydrolysed in aqueous caustic alkali, but were immediately hydrolysed to iodoform in aqueous-methanolic sodium hydroxide.

Tetraiodoacetone.—Acetonedicarboxylic acid was treated by iodination procedure (i). The iodine was rapidly absorbed, with formation of a yellow precipitate. When absorption ceased, the neutral solid was filtered off and extracted with benzene. The needles that separated on cooling of the benzene extracts were recrystallised from ligroin (b. p. 40—60°), to give yellow

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[10] Houben and Fischer, *Ber.*, 1931, **64**, 2636; Aston, Newkirk, Dorsky, and Jenkins, *J. Amer. Chem. Soc.*, 1942, **64**, 1413.

[11] Sutherland and Aston, *ibid.*, 1939, **61**, 241; Verhoek, *ibid.*, 1934, **56**, 571; Hall and Verhoek, *ibid.*, 1947, **69**, 613; Cochran and Verhoek, *ibid.*, p. 2987; Auerbach, Verhoek, and Henne, *ibid.*, 1950, **72**, 299.

[12] Fairclough, *J.*, 1938, 1186.

[13] Taylor, (*a*) *J.*, 1912, **101**, 451; (*b*) *J.*, 1913, **103**, 31.

needles of tetraiodoacetone, m. p. 140—142° (decomp.) (Found: C, 6·52; H, 0·4. Calc. for $C_3H_2OI_4$: C, 6·7; H, 0·3%).

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