592. *Benzyloxymalondialdehyde. An Intermediate in the Oxidation of 2-O-Benzyl-*D*-arabinose with Sodium Periodate.*

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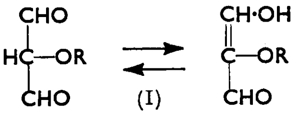
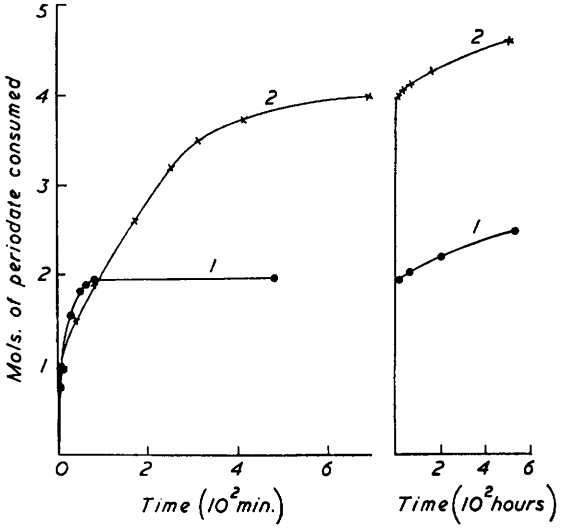
Benzyloxymalondialdehyde has been isolated as an intermediate in the oxidation of 2-*O*-benzyl-D-arabinose with periodate, and its reactions have been investigated.

Substituted hydroxymalondialdehydes of the general formula (I) have frequently been postulated as intermediates in the oxidation of carbohydrates with periodate [1, 2] and lead tetra-acetate.[3] However, no account of the isolation and identification of these intermediates could be found in the literature, although compounds of the type (I) have been obtained by other routes. The benzoyl ester (I; R = Bz) can be prepared from reductone (I; R = H),[4, 5] and methylation of anilino-derivatives of reductone yields derivatives of methoxymalondialdehyde (I; R = Me).[5] Grard has reported the synthesis of ethoxymalondialdehyde (I; R = Et) from bromomalondialdehyde and sodium ethoxide,[6] but other workers [5] have been unable to repeat this. The present paper describes the synthesis of benzyloxymalondialdehyde (I; R = CH_2Ph) by controlled periodate oxidation of 2-*O*-benzyl-D-arabinose, the benzyl compound being chosen to facilitate isolation from aqueous solution.


(I)

$$\mathrm{OHC{-}CH(OR){-}CHO} \rightleftharpoons \mathrm{HO{\cdot}CH{=}C(OR){-}CHO}$$



Periodate oxidations.

1, 0·0125M-*Benzyloxymalondialdehyde in* 0·050M-*periodate at* 15—18°.
2, 0·0125M-2-O-*Benzyl*-D-*arabinose in* 0·075M-*periodate at* 15—18°.

2-*O*-Benzyl-D-arabinose was prepared from 3-*O*-benzyl-D-glucose. Oxidation of the latter with sodium periodate yielded a crystalline formate ester,[7] presumably 2-*O*-benzyl-4(?)-*O*-formyl-D-arabinose, which was contaminated with some 2-*O*-benzyl-D-arabinose.

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[1] Huebner, Ames, and Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621; Ness, Fletcher, and Hudson, *ibid.*, 1951, **73**, 3742; Wolfrom, Thompson, O'Neill, and Galkowski, *ibid.*, 1952, **74**, 1062; Courtois and Ramet, *Bull. Soc. Chim. biol.*, 1945, **27**, 610; 1947, **29**, 240; Head and Hughes, *J.*, 1954. 603; Lemieux and Bauer, *Canad. J. Chem.*, 1953, **31**, 814; McKeown and Hayward, *ibid.*, 1955, **33**, 1392.

[2] Halsall, Hirst, and Jones, *J.*, 1947, 1427.

[3] Hockett, Nickerson, and Reeder, *J. Amer. Chem. Soc.*, 1944, **66**, 472; Perlin, *Analyt. Chem.*, 1955, **27**, 396.

[4] Von Euler and Hasselquist, *Arkiv Kemi*, 1951, **3**, 140.

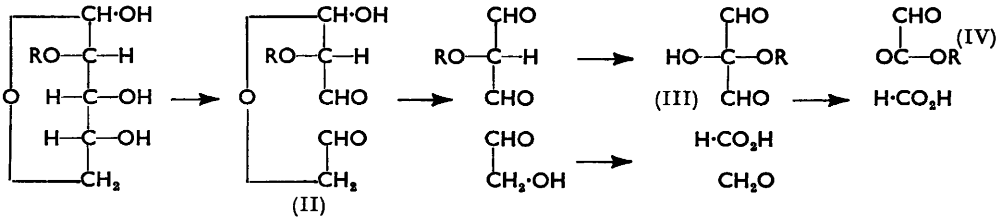
[5] Eistert, Arnemann, and Haupter, *Chem. Ber.*, 1955, **88**, 939.

[6] Grard, *Ann. Chim.* (*France*), 1930, **13**, 336.

[7] Meyer and Rathgeb, *Helv. Chim. Acta*, 1949, **32**, 1102; Barker and Smith, *Chem. and Ind.*, 1952, 1035; Huffman, Lewis, Smith, and Spriesterbach, *J. Amer. Chem. Soc.*, 1955, **77**, 4346; Gorin and Jones, *Nature*, 1953, **172**, 1051.

Hydrolysis of this formate under acidic conditions gave 2-*O*-benzyl-D-arabinose containing a trace of arabinose, which was removed on a cellulose column. Paper chromatography indicated that 2-*O*-benzyl-D-arabinose suffers partial debenzylation when heated at 100° with 0·01N-sulphuric acid for 4 hours; this seems surprising, although benzyl ethers are known to be more sensitive to acid than the corresponding methyl compounds.[8] 2-*O*-Benzyl-D-arabinose, free from arabinose, was obtained when the formate was hydrolysed under mild alkaline conditions.

The oxidation of 2-*O*-benzyl-D-arabinose with sodium periodate was found to proceed in three stages (Figure). 1 Mol. of periodate was consumed rapidly (*ca.* 5 min.). After 12 hours the total periodate uptake had reached 4 mols.; further oxidation then proceeded only very slowly and was not followed to completion. Benzyloxymalondialdehyde could be isolated in good yield when the reaction was stopped at the end of the first stage. It is presumably formed from the dialdehyde (II; R = CH_2Ph), which may be expected to decompose readily to benzyloxymalondialdehyde and glycollaldehyde. Oxidation of the latter to formic acid and formaldehyde requires only 1 mol. of periodate, and the above results therefore suggest that benzyloxymalondialdehyde consumed 2 mols. of periodate in the second stage of the reaction, although this compound does not contain α-glycol or α-hydroxyaldehyde groups.



Consumption of periodate beyond the amount expected from the fission of only α-glycols and α-hydroxyaldehydes has also been observed in other periodate oxidations.[1, 2] To explain this " over-oxidation," it has been suggested [1, 2] that an intermediate of the type (I) may undergo hydroxylation to (III), which is then oxidised to a glyoxylic acid derivative (IV) and formic acid. The glyoxylic acid derivative may then undergo further changes. Investigation of the oxidation of benzyloxymalondialdehyde with sodium periodate has now provided additional evidence for these assumptions.

Benzyloxymalondialdehyde consumed 2 mols. of periodate in about 90 minutes (Figure). Titration with iodine (see below) then indicated that at least 99% of the benzyloxymalondialdehyde had been oxidised. At this stage, the solution contained 1 equivalent of acid, presumably formic acid, and benzyl glyoxylate (IV; R = CH_2Ph) which was isolated as the 2 : 4-dinitrophenylhydrazone. The presence of benzyl glyoxylate was confirmed by its hydrolysis to glyoxylic acid, which was isolated as the known 2 : 4-dinitrophenylhydrazone.

When oxidation of benzyloxymalondialdehyde was prolonged, periodate uptake and acidity exceeded 2 mols. and 1 equivalent respectively. It is not clear whether this is due to direct oxidation of benzyl glyoxylate or to hydrolysis of this ester followed by oxidation of the glyoxylic acid formed.

Benzyloxymalondialdehyde decolorises two equivalents of iodine in the presence of sodium hydrogen carbonate. Estimation of periodate by titration with arsenite after addition of sodium hydrogen carbonate and potassium iodide therefore gives unreliable results in the presence of benzyloxymalondialdehyde or related compounds.[9] Periodate uptake during the initial stages of the above oxidations was therefore followed by titration with sodium thiosulphate after addition of acidified potassium iodide.[9] Benzyloxymalondialdehyde does not decolorise iodine in the presence of hydrogen iodide.

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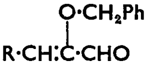
[8] Burwell, *Chem. Rev.*, 1954, **54**, 615.

[9] Schwarz, *Chem. and Ind.*, 1954, 1000.

It is interesting that the product obtained from 2-*O*-benzyl-D-arabinose after consumption of 1 mol. of periodate, reduces periodate more slowly than an equivalent solution of benzyloxymalondialdehyde. Furthermore, attempts to estimate benzyloxymalondialdehyde, produced during the periodate oxidation of 2-*O*-benzyl-D-arabinose, by titration with iodine after addition of ethylene glycol followed by sodium hydrogen carbonate, gave rapidly fading end-points unless the solution had been allowed to stand for 10 minutes before titration. These facts suggest that fission of the dialdehyde (II; R = CH_2Ph) or enolisation of the resulting benzyloxymalondialdehyde may be comparatively slow.



$R{\cdot}CH{:}\overset{O\cdot CH_2Ph}{C}{\cdot}CHO$

(V)

Benzyloxymalondialdehyde, like other substituted malondialdehydes,[10] appears to exist largely in the enolic form. It gives a strong violet colour with ferric chloride and can be titrated as a monobasic acid to phenolphthalein. Reaction with benzoyl chloride in sodium hydrogen carbonate yields the enol-benzoate (V; R = BzO). This compound, which may be regarded as the vinylogue of an acid anhydride, is rapidly hydrolysed by dilute sodium hydroxide, and phenyl benzoate can be isolated if the hydrolysis is carried out in the presence of phenol. Condensation of benzyloxymalondialdehyde with aniline gives a monoanilino-derivative which, by analogy with the corresponding derivative of reductone,[11] probably has the structure (V; R = NHPh).

O'Dea [12] has found that, in certain periodate oxidations, the estimation of formaldehyde gives anomalous results, and he has suggested that intermediates of the type (I) may react with formaldehyde. Titration with iodine of a solution of benzyloxymalondialdehyde containing formaldehyde, iodate, and sodium hydrogen carbonate showed that the benzyloxymalondialdehyde reacted slowly with formaldehyde; in the absence of formaldehyde only a very slow decrease in the iodine titre was observed.

Liberation of iodine was observed when benzyloxymalondialdehyde was allowed to stand with iodate under weakly acidic conditions It has been suggested [2] that reduction of iodate by similar malondialdehyde intermediates may account for the iodine produced in certain periodate oxidations (see also ref. 13).

EXPERIMENTAL

Concentrations were carried out under reduced pressure. Two solvents were used in chromatography on Whatman No. 1 paper: (*a*) butanol–ethanol–water (4 : 1 : 5); (*b*) benzene–ethanol–water (169 : 47 : 15). The sugars were detected with aniline oxalate.

3-*O*-Benzyl-D-glucose, prepared from 1 : 2-5 : 6-di-*O*-*iso*propylidene-D-glucofuranose,[14] showed m. p. 126—128° and was found by paper chromatography (solvent *a*) to contain a trace of glucose which could not be removed by crystallisation. A portion, which was freed from glucose on a cellulose column with butanol half-saturated with water, had m. p. 130—140° after crystallisation from acetone. Paper chromatography indicated that 3-*O*-benzyl-D-glucose was partly hydrolysed to glucose on 5 hours' heating at 100° with N-sulphuric acid.

2-O-*Benzyl*-4(?)-O-*formyl*-D-*arabinose*.—3-*O*-Benzyl-D-glucose (7·7 g.) was dissolved in a solution of sodium periodate (9·12 g.) in water (120 c.c.). After 20 min. at room temperature, the solution was extracted with chloroform (15 × 150 c.c.). Concentration of the dried extract gave the required *formate ester* (7·0 g.; m. p. 120—130°). The m. p. remained unchanged on crystallisation of the compound from ethyl acetate or chloroform, which yielded prisms, $[\alpha]_D^{17}$ $-99°$ (10 min.; *c* 2·03 in acetone) (Found: C, 58·3; H, 5·9. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). Chromatography in solvent *b* indicated that the formate ester (R_G 0·75) was contaminated with 2-*O*-benzyl-D-arabinose (R_G 0·37). In solvent *a* the formate ester had R_G 0·97; no slower-moving spots were detected.

2-O-*Benzyl*-D-*arabinose from* 2-O-*Benzyl*-4(?)-O-*formyl*-D-*arabinose*.—(a) *By acid hydrolysis.*

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[10] Dieckmann and Platz, *Ber.*, 1904, **37**, 4638; Pino, *Gazzetta*, 1950, **80**, 768; Panizzi, *ibid.*, 1947, **77**, 283.

[11] Cocker, O'Meara, Schwarz, and Stuart, *J.*, 1950, 2052.

[12] O'Dea, *Chem. and Ind.*, 1953, 1338.

[13] Ahlborg, *Svensk kem. Tidskr.*, 1942, **54**, 205; *Chem. Abs.*, 1944, **38**, 4254.

[14] Adams, Reeves, and Goebel, *J. Biol. Chem.*, 1941, **140**, 653.

The crude formate ester (prepared from 9·5 g. of benzylglucose) in water (200 c.c.) was heated at 100° with Amberlite IR-120 (H^+ form; 3 g.) until the alkali titre (methyl-red) of filtered samples became constant (4 hr.). After cooling, the solution was filtered, brought to pH 4 by addition of sodium hydroxide, and evaporated. Extraction of the dry residue with hot chloroform gave *2-O-benzyl-D-arabinose* (6·3 g.), m. p. 105—107°. Chromatography in solvent *a* indicated that the sugar (R_G 0·91) contained a trace of arabinose which was only partly removed by crystallisation from chloroform or ethanol–light petroleum. Purification on a cellulose column, with butanol half-saturated with water, yielded needles (free from arabinose), m. p. 110—112°, $[\alpha]_D^{17}$ −80° (5 min.) $\longrightarrow$ −75° (30 min., equil.) (*c* 1·1 in H_2O) (Found: C, 59·5; H, 6·1. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7%). Paper chromatography showed that this material underwent partial hydrolysis, giving a small quantity of arabinose, when heated for 4 hr. in 0·01N-sulphuric acid.

(b) *By alkaline hydrolysis.* The crude formate ester (from 0·7 g. of benzylglucose) was dissolved in 0·1N-sodium hydroxide (30 c.c.) and kept at room temperature for 20 min. After neutralisation the solution was evaporated and the dry residue extracted with hot chloroform. The 2-*O*-benzyl-D-arabinose (0·45 g.; m. p. 105—109°) obtained on concentration was free from arabinose, but required repeated crystallisation from chloroform before it showed m. p. and mixed m. p. 109—111°.

Benzyloxymalondialdehyde.—2-*O*-Benzyl-D-arabinose (16·5 g.) was dissolved in a solution of sodium periodate (29·4 g.) in water (600 c.c.). After 5 min., ethylene glycol was added to reduce excess of periodate to iodate, which was then precipitated with 2M-strontium chloride (150 c.c.). A small quantity of iodate remaining after filtration was reduced to iodide with sulphur dioxide. The filtered solution slowly deposited *benzyloxymalondialdehyde* (8·9 g.), m. p. 134—136°. Crystallisation from water gave needles, m. p. 135—137° (Found: C, 67·9; H, 5·5%; equiv., 182. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%; equiv., 178).

Benzyloxymalondialdehyde was also isolated when the reaction of 0·0125M-2-*O*-benzyl-D-arabinose with 0·075M-periodate (see below) was stopped after 5 min. by addition of ethylene glycol. After removal of iodate as above, the benzyloxymalondialdehyde was extracted with chloroform.

The aldehyde (0·9 g.) in water (50 c.c.) containing sodium hydrogen carbonate (2·0 g.) was shaken with benzoyl chloride (0·75 g.) for 45 min. Alcohol-free chloroform (10 c.c.) was then added and shaking continued for 1 hr. After addition of more chloroform, the organic phase was separated, dried ($MgSO_4$), and evaporated. Crystallisation of the *enol benzoate* from light petroleum containing a little benzene gave needles, m. p. 62·5—63·5° (Found: C, 72·1; H, 5·1. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%).

Phenol (0·1 g.) and the enol benzoate (0·1 g.) were dissolved in acetone (5 c.c.), and 0·2N-sodium hydroxide (5 c.c.) was added dropwise. Phenyl benzoate (0·06 g.) separated on evaporation of the acetone. Crystallised from aqueous ethanol, this had m. p. and mixed m. p. 68·5—69·5°.

3-Anilino-2-benzyloxyprop-2-enal (V; R = NHPh).—Benzyloxymalondialdehyde (0·3 g.) in water (150 c.c.) was treated with aniline (0·2 g.) in water (5 c.c.) containing a little hydrochloric acid. After 6 hr. at room temperature, the precipitate was filtered off and washed with water. Crystallisation of the *anilino-derivative* from benzene gave plates, m. p. 150—151° (Found: C, 76·0; H, 5·9; N, 5·4. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0; N, 5·5%).

Oxidation of 2-O-Benzyl-D-arabinose and Benzyloxymalondialdehyde with Periodate (Figure).—The reaction mixtures were prepared by treating 0·025M-solutions of benzylarabinose and benzyloxymalondialdehyde with equal volumes of 0·15M- and 0·1M-sodium periodate respectively (0·025M-benzyloxymalondialdehyde is supersaturated at room temperature). Oxidation was allowed to proceed in the dark at 15—18°.

Periodate uptake was determined by (*a*) titration with arsenite after addition of sodium hydrogen carbonate and potassium iodide,[15] and (*b*) titration with sodium thiosulphate after addition of a mixture of dilute sulphuric acid and potassium iodide. The initial stages of both oxidations were followed by method *b*; method *a* was used only in the final slow stage of the oxidations. Results are recorded in the Figure.

After 90 min. a sample (5 c.c.) of the aldehyde reaction mixture was treated with ethylene glycol, followed after 10 min. by sodium hydrogen carbonate. The resulting solution decolorised only 0·01 c.c. of 0·01N-iodine, indicating that *ca.* 99% of the benzyloxymalondialdehyde had been oxidised.

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[15] Müller and Friedberger, *Ber.*, 1902, **35**, 2652.

In the oxidation of benzyloxymalondialdehyde, the acidity was followed by the method of Halsall, Hirst, and Jones.[2] Equivs. of acid/mole of benzyloxymalondialdehyde: 0·94 (10 min.), 0·99 (30 min.), 1·02 (80 min.), 1·55 (651 hr.).

Benzyl Glyoxylate 2 : 4-*Dinitrophenylhydrazone.*—0·025M-Benzyloxymalondialdehyde (50 c.c.) and 0·1M-sodium periodate (50 c.c.) were mixed and kept at room temperature for 90 min. 2M-Strontium chloride (5 c.c.) was then added. After filtration, excess of periodate was reduced by passing sulphur dioxide into the ice-cooled solution until the liberated iodine had been decolorised. Addition of a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid (175 c.c.) yielded a yellow 2 : 4-*dinitrophenylhydrazone* (0·30 g.) which crystallised from ethanol–ethyl acetate as orange plates, m. p. 190—192° (Found : C, 52·2; H, 3·1; N, 15·4. $C_{15}H_{12}O_6N_4$ requires C, 52·3; H, 3·5; N, 16·3%).

Glyoxylic Acid 2 : 4-*Dinitrophenylhydrazone.*—0·05M-Benzyloxymalondialdehyde (50 c.c.; supersaturated solution) and 0·2M-sodium periodate (50 c.c.) were mixed and kept at room temperature for 90 min. Extraction with chloroform (8 × 50 c.c.) followed by evaporation of the solvent yielded an oil, which was hydrolysed at room temperature with 0·06N-sodium hydroxide (50 c.c.). After 15 min. the solution was acidified and treated with a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid (150 c.c.). Purification of the precipitate gave glyoxylic acid 2 : 4-dinitrophenylhydrazone (0·3 g.), m. p. and mixed m. p. 195—200° (decomp.). Chromatography in butanol–ethanol–0·5N-aqueous ammonia (70 : 10 : 20) gave two spots;[16] glyoxylic acid 2 : 4-dinitrophenylhydrazone obtained from periodate-oxidised tartaric acid showed identical behaviour.

Reaction of Benzyloxymalondialdehyde with Formaldehyde and with Iodate.—The dialdehyde (0·23 g.) in 4% sodium hydrogen carbonate (50 c.c.) was mixed with approx. 0·2M-formaldehyde (50 c.c.), prepared by treating 0·1M-periodate (100 c.c.) with ethylene glycol (2 c.c.). The solution was kept at *ca.* 15° and samples were titrated at intervals with 0·1N-iodine to determine the quantity of benzyloxymalondialdehyde remaining: 99% (10 min.), 88% (9 hr.), 71% (24 hr.), 26% (75 hr.).

The following results were obtained when 0·1M-potassium iodate was substituted for the formaldehyde–iodate solution used above: 100% (1 hr.), 99% (6 hr.), 97% (22·5 hr.), 93% (50·5 hr.), 81% (147 hr.).

Liberation of iodine was observed about 20 min. after mixing of 0·025M-benzyloxymalondialdehyde with an equal volume of 0·1M-potassium iodate which had been acidified with acetic acid.

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[16] Stewart, *Biochem. J.*, 1953, **55**, xxvi.