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Note

A new improved synthesis of anhydrous diglycolaldehyde*

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Diglycoaldehyde (2,2′-oxybisacetaldehyde) (**1**) has been prepared by oxidation of 1,5-anhydro-L-arabinose[1] with periodate and isolated in the polymeric state (**2**), but this is not a convenient procedure. The same product (**2**) may be obtained by periodate oxidation of α,α'-diglycerol[2] (**3**), but **2** can be prepared only in yields of 15–25% and is difficult to free from inorganic salts. However, when unpurified **2** was treated with methanol in acid media, pure diglycolaldehyde bis(dimethyl acetal)[3] (**4**) was formed from which pure **2** was obtained in good yield by hydrolysis with aqueous acetic acid. The conversion **2**→**1** was effected by distillation under diminished pressure[2].

We now report a new method for the preparation of **1** from bromoacetaldehyde di-isopropyl acetal (**5a**). Treatment[4] of **5a** with boiling, aqueous, ethanolic potassium hydroxide followed by fractional distillation gave 2-ethoxy-1,1-di-isopropoxyethane (**7c**, 22.5%), 2,2-di-isopropoxyethanol (**7a**, 14.4%), and diglycolaldehyde bis(di-isopropyl acetal) (**6a**, 0.2%). Pure **7c** was prepared from **5a** and sodium ethoxide, and **6a** was obtained by reaction of **1** and 2-propanol in acid media[3] and characterised by transformation into the known bis(2,4-dinitrophenylhydrazone). Compound **7a**, which was isolated as 2,2-di-isopropoxyethyl benzoate (**75**), was also synthesised from 1,2-*O*-isopropylideneglycerol by application in sequence of benzoylation, acid hydrolysis, periodate oxidation[6], treatment with acidified 2-propanol, and saponification. These results suggest that if a less nucleophilic alcohol is used as solvent and the concentration of hydroxyl ion is decreased, the yield of **6a** may be increased. Thus, with 2-methylpropan-2-ol as the solvent in the presence of powdered potassium hydroxide, **5a** gave 60.8% of **6a** after boiling the mixture for 7 days. Under similar conditions, bromoacetaldehyde diethyl acetal (**5b**) gave 18% of diglycolaldehyde bis(diethyl acetal)[3] (**6b**). Although the above method for preparing **6a** involves only one stage from **5a**, a long reaction time is needed. When a mixture of sodium 2,2-di-isopropoxyethoxide and **5a** in anhydrous 1,4-dioxane was boiled for 12 h, 67.4% of **6a** was obtained.

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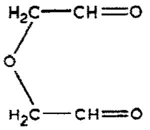
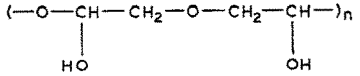
*Derivatives of Diglycolaldehyde, Part XVI. For Part XV, see ref. 3.

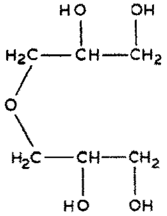


1



$(\!-\mathrm{O{-}CH(OH){-}CH_2{-}O{-}CH_2{-}CH(OH)-})_n$

2



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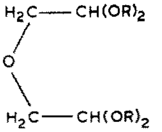


4 R = Me

6a R = Pr^i

6b R = Et

$\mathrm{BrCH_2{-}CH(OR)_2}$

5a R = Pr^i

5b R = Et

The polymer **2** was formed when **6a** was treated with boiling acetic acid for 6 h, and converted into anhydrous diglycolaldehyde (**1**) by distillation.

The di-isopropyl acetal **5a** was prepared[7] from vinyl acetate, bromine, and 2-propanol. Attempts to obtain **5a** by acid-catalysed reaction of bromoacetaldehyde diethyl acetal (**5b**) and 2-propanol gave a mixture of **5a** (major) and 1-bromo-1,2-di-isopropoxyethane (**8**) (minor). When this mixture was treated with sodium 2,2-di-isopropoxyethoxide, a mixture of **6a** and *O*-(1,2-di-isopropoxyethyl)glycolaldehyde di-isopropyl acetal **9** was obtained. When the latter mixture was treated with ethanethiol in acid media, diglycolaldehyde bis(diethyl dithioacetal)[8] (**10**) was the main product together with 1,1-bis(ethylthio)-2-isopropoxyethane, 1,1,2-tris(ethylthio)-ethane[9], and glycolaldehyde diethyl dithioacetal[8]; under similar conditions, **6a** reacted with ethanethiol to give **10** (73.4%) as the only product[8]. The components of the mixture were isolated by distillation followed by column chromatography, and identified by comparison with authentic samples[8,9]. 1,1-Bis(ethylthio)-2-isopropoxyethane was obtained by reaction of 1,1-dimethoxy-2-isopropoxyethane (**7e**) with ethanethiol in acid media. The formation of **5a** (major) and **8** (minor) by the reaction of bromoacetaldehyde diethyl acetal and 2-propanol in acid media could involve the intermediary bromonium ion **11**.

$\mathrm{R{-}O{-}CH_2{-}CH(OR')_2}$

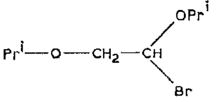
7a R = H, R′ = Pr^i

7b R = H, R′ = Et

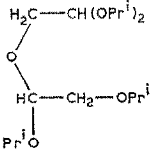
7c R = Et, R′ = Pr^i

7d R = Bz, R′ = Pr^i

7e R = Pr^i, R′ = Me



8



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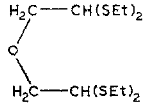

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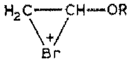

11 R = Et or Pr^i

EXPERIMENTAL

General methods. — Organic solutions were dried over anhydrous Na_2SO_4. Solvents were evaporated under diminished pressure at <40°. Column chromatography was performed on Silica Gel 60 (Merck, 70–230 mesh, ASTM). Melting points (uncorrected) were determined with an Electrothermal melting-point apparatus, I.r. spectra were recorded for films on NaCl or KBr discs with a Pye–Unicam SP 1000 spectrometer. ^{1}H-N.m.r. spectra were recorded for solutions in various solvents (internal Me_4Si) with a Perkin–Elmer–Hitachi R-20 B spectrometer. Chemical shifts are given on the δ scale, and couplings in Hz.

Bromoacetaldehyde di-isopropyl acetal (**5a**). — (*a*) *From vinyl acetate.* A mixture[7] of vinyl acetate (37 mL), bromine (20.4 mL), and 2-propanol (400 mL) was left at room temperature for 9 days. Distillation then gave **5a** (63.5 g, 71%), b.p. 75–78°/15 mmHg; ν_{max} 1327, 1125, 1035, and 675 cm^{-1}. ^{1}H-N.m.r. (CCl_4) data: δ 4.63 (t, 1 H, J 5.7 Hz), 3.82 (septet, 1 H, J 6 Hz), 3.21 (d, 2 H, J 5.7 Hz), 1.15 (d, 3 H, J 6 Hz), and 1.14 (d, 3 H, J 6 Hz).

(*b*) *From bromoacetaldehyde diethyl acetal* (**5b**). A mixture of **5b** (24.5 g), 2-propanol (190 mL), and conc. H_2SO_4 (2.5 g) was boiled under reflux for 24 h, basified (KOH–methanol), and concentrated. Aqueous 50% K_2CO_3 (100 mL) was added, the mixture was extracted with ether (4 × 50 mL), and the combined extracts were dried, filtered, and concentrated to dryness. A mixture (16.7 g) of **5a** (major product) and 1-bromo-1,2-di-isopropoxyethane (**8**, minor) was obtained when the residue was distilled.

Reaction of bromoacetaldehyde di-isopropyl acetal (**5a**). — (*a*) *In aqueous, ethanolic potassium hydroxide.* Bromoacetaldehyde di-isopropyl acetal (13.5 g) in aqueous 95% ethanol was boiled under reflux with KOH (9 g) for 7 days, filtered, and concentrated. Water (25 mL) was added, the mixture was extracted with ether (2 × 100 mL), the combined extracts were dried and concentrated to dryness, and the residue was distilled, to give a mixture (6.6 g) of glycolaldehyde di-isopropyl acetal (**7a**) and 2-ethoxy-1,1-di-isopropoxyethane (**7c**), b.p. 66–67°/14 mmHg, and diglycolaldehyde bis(di-isopropyl acetal)[3] (**6a**, 0.17 g), b.p. 75–80°/0.1 mmHg, ν_{max} 1128 and 1040 cm^{-1}. ^{1}H-N.m.r. ($CDCl_3$) data: δ 4.60 (t, 1 H, J 5.1 Hz), 3.82 (septet, 2 H, J 6 Hz), 3.40 (d, 2 H, J 5.1 Hz), 1.12 (d, 6 H, J 6 Hz), and 1.10 (d, 6 H, J 6 Hz).

The mixture **7a,c** (6.6 g) was treated with pyridine (10 mL) and benzoyl chloride (3.5 mL) in the usual manner. Distillation of the product gave **7c** (2.54 g), b.p. 69–70°/16 mmHg, identical with the authentic compound described below; and 1-*O*-benzoylglycolaldehyde di-isopropyl acetal (**7d**, 2.3 g), b.p. 110°/0.1 mmHg; ν_{max} 1724 1602, 1586, 1380, 1368, 1270, 1112, 1046, and 712 cm^{-1}. ^{1}H-N.m.r. (CCl_4) data: δ 8.1 (m, 2 H), 7.5 (m, 3 H), 4.86 (t, 1 H, J 5.5 Hz), 4.15 (d, 2 H, J 5.5 Hz), 3.90 (septet, 2 H, J 6.0 Hz), 1.20 (d, 6 H, J 6.0 Hz), and 1.15 (d, 6 H, J 6.0 Hz) (Found: C, 67.3; H, 8.3. $C_{15}H_{22}O_4$ calc.: C, 67.6; H, 8.3%).

(*b*) *With potassium hydroxide in anhydrous 2-methylpropan-2-ol.* A mixture of freshly powdered KOH (60 g) and 2-methylpropan-2-ol (60 mL) was stirred and boiled under reflux for 3 h, cooled, treated with **5a** (90 g), and then stirred and heated at 120–130° (bath) for 7 days. Water was added to the cooled mixture until the salts dissolved. The mixture was then extracted with ether (3 × 50 mL), and the combined extracts were dried, filtered, and concentrated to dryness. Distillation of the residue gave **5a** (14 g), b.p. 74–78°/14 mmHg, and diglycolaldehyde bis(di-isopropyl acetal) (**6a**; 37.2 g, 60.8%), b.p. 140–142°/14 mmHg.

When bromoacetaldehyde diethyl acetal **5b** was used in a similar reaction, diglycolaldehyde bis(diethyl acetal)[3] (**6b**, 18%) was obtained.

(*c*) *With sodium 2,2-di-isopropoxyethoxide.* A mixture of glycolaldehyde di-isopropyl acetal (**7a**, 7.0 g), 1,4-dioxane (40 mL), and sodium (0.7 g) was stirred and boiled under reflux until the metal disappeared; the mixture was then cooled and **5a** (5.78 g) was added. The mixture was stirred and boiled under reflux for 12 h, cooled, filtered, and concentrated to dryness. Water (10 mL) was added and the mixture was extracted with ether (100 mL). The extract was dried, filtered, and concentrated, and then the residue was distilled to give **7a** (3.1 g), b.p. 80–82°/14 mmHg, and **6a** (5.3 g, 67.4%), b.p. 140–142°/14 mmHg.

Reaction of the mixture of bromoacetaldehyde di-isopropyl acetal (**5a**) *and 1-bromo-1,2-di-isopropoxyethane* (**8**) *with sodium 2,2-di-isopropoxyethoxide.* — In the same way as described above, a mixture of **6a** and *O*-(1,2-di-isopropoxyethyl)glycolaldehyde di-isopropyl acetal (**9**) was obtained, which showed an i.r. spectrum very similar to that of **6a**. ^{1}H-N.m.r. ($CDCl_3$) data: δ 3.38 (d, major), 3.40 (d, minor), 4.60 (t, major), and 4.57 (t, minor); J 5.1 Hz (Found: C, 62.5; H, 11.3. $C_{16}H_{34}O_5$ calc.: C, 62.7; H, 11.2%).

The foregoing mixture (1.5 g), ethanethiol (4 mL), and conc. H_2SO_4 (4 drops) were allowed to react as described for diglycolaldehyde acetals[8]. The residue was distilled to give a mixture (0.15 g), b.p. 115–135°/16 mmHg, of 1,1-bis(ethylthio)-2-isopropoxyethane, 1,1,2-tris(ethylthio)ethane[9], and glycolaldehyde diethyl dithioacetal[8]; and diglycolaldehyde bis(diethyl dithioacetal)[8] (**10**, 1.0 g), b.p. 150–155°/16 mmHg, ν_{max} 1117 cm^{-1}. ^{1}H-N.m.r. ($CDCl_3$) data: δ 3.85 (m, 3 H), 2.67 (q, 4 H, J 7.5 Hz), and 1.25 (t, 6 H, J 7.5 Hz).

The first three compounds were isolated by column chromatography (hexane) and identified by comparison with authentic samples (t.l.c., i.r., and ^{1}H-n.m.r.).

1,1-Bis(ethylthio)-2-isopropoxyethane. — Sodium (4.8 g) was treated with 2-propanol (100 mL), and then bromoacetaldehyde dimethyl acetal (8.8 g) was added. The mixture was boiled under reflux for 24 h, filtered, and concentrated. Distillation of the residue gave 1,1-dimethoxy-2-isopropoxyethane (3.35 g), b.p. 120–130°/500 mmHg. A mixture of this material (2.8 g), ethanethiol (10 mL), and conc. H_2SO_4 (10 drops) was stirred at room temperature for 6 h, basified with aqueous 10% NaOH, and extracted with ether (2 × 20 mL). The combined extracts were dried, filtered, and concentrated. Distillation of the residue yielded an impure product (1.8 g), b.p. 133–136°/14 mmHg, which was purified by column chromatography (50:1 hexane–ether), and had ν_{max} 1373, 1135, and 1087 cm^{-1}. ^{1}H-N.m.r. (CCl_4) data:

δ 3.60 (m, 4 H), 2.66 (q, 4 H, *J* 7.5 Hz), 1.22 (t, 6 H, *J* 7.5 Hz), and 1.12 (d, 6 H, *J* 6 Hz).

2-Ethoxy-1,1-di-isopropoxyethane (**7c**). — A mixture of ethanolic sodium ethoxide [from sodium (1.5 g) and anhydrous ethanol (10 mL)] and **5a** (4.5 g) was boiled under reflux for 7 h, and then filtered and concentrated. Water (50 mL) was added, the mixture was extracted with ether (3 × 50 mL), and the combined extracts were dried and concentrated to dryness, to give **7c** (2.73 g, 82%), b.p. 68–71°/16 mmHg; ν_{max} 1380, 1367, 1125, 1055, and 980 cm^{-1}. ^1H-N.m.r. (CCl_4) data: δ 4.36 (t, 1 H, *J* 5.0 Hz), 3.8–3.0 (m, 6 H), and 1.1–0.85 (m, 15 H) (Found: C, 63.0; H, 11.6. $C_{10}H_{22}O_3$ calc.: C, 63.1; H, 11.6%).

Diglycolaldehyde[2] (**1**). — A solution of **6a** (10 g) in aqueous 50% acetic acid (60 mL) was boiled under reflux for 6 h, and then concentrated to a syrupy residue from which water was evaporated several times in order to remove traces of acetic acid. The syrupy product (3.9 g, ~100% as 2,6-dihydroxy-1,4-dioxane) was distilled in small portions to give anhydrous **1**, b.p. 67–68°/0.5 mmHg, in quantitative yield; ν_{max} 2850, 2750, 1733, and 1150 cm^{-1}. ^1H-N.m.r. (acetone-d_6) data: δ 9.6 (t, 1 H, *J* 0.6 Hz) and 4.2 (d, 2 H, *J* 0.6 Hz) (Found: C, 46.9; H, 5.9. $C_4H_6O_3$ calc.: C, 47.0; H, 5.9%).

The bis(2,4-dinitrophenylhydrazone), prepared in the usual manner[3,10], had m.p. 192–194° (from 1,4-dioxane–water).

O-Benzoylglycolaldehyde[6]. — 1-*O*-Benzoylglycerol[5] at <5° was treated with aqueous $NaIO_4$ (31 g in 460 mL) at room temperature for 30 min and then extracted with ether (3 × 100 mL), and the combined extracts were dried, filtered, and concentrated. Distillation of the residue gave the title compound (16.6 g, 69%), b.p. 104–105°/2 mmHg. A redistilled specimen had b.p. 85–86°/0.2 mmHg; ν_{max} 2793, 2688, 1733, 1274, 1130, and 712 cm^{-1}. ^1H-N.m.r. ($CDCl_3$) data: δ 9.59 (s, 1 H), 8.0 (m, 2 H), 7.40 (m, 3 H), and 4.80 (s, 2 H) (Found: C, 65.8; H, 5.0. $C_9H_8O_3$ calc.: C, 65.8; H, 4.9%). This compound was readily hydrated by atmospheric moisture. The semicarbazone had m.p. 194–195° (from ethanol–water); lit.[6] m.p. 194–195°.

Glycolaldehyde di-isopropyl acetal (**7a**). — A mixture of the foregoing compound (11.5 g), 2-propanol (90 mL), conc. H_2SO_4 (1 g), and benzene (40 mL) was boiled under reflux for 3.5 h with azeotropic removal of water. The cooled mixture was basified (KOH–MeOH), concentrated, and then boiled under reflux for 1 h with KOH (5 g) in 74% aqueous ethanol (190 mL). Aqueous 50% K_2CO_3 (40 mL) was then added, the mixture was extracted with ether (3 × 75 mL), and the combined extracts were dried, filtered, and concentrated, to give **7a** (8.2 g, 72.3%), b.p. 81–82°/15 mmHg; ν_{max} 3400, 1368, 1180, 1041, and 990 cm^{-1}. ^1H-N.m.r. ($CDCl_3$) data: δ 4.62 (t, 1 H, *J* 5.3 Hz), 3.90 (septet, 2 H, *J* 6 Hz), 3.50 (d, 2 H, *J* 5.3 Hz), 2.25 (bs, 1 H), 1.22 (d, 6 H, *J* 6 Hz), and 1.16 (d, 6 H, *J* 6 Hz) (Found: C, 59.5; H, 11.0. $C_8H_{18}O_3$ calc.: C, 59.2; H, 11.2%).

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