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Note

Synthesis and properties of some *O*-(2,2-dialkoxyethyl)glycolaldehydes*

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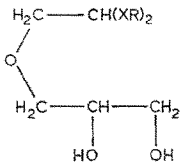
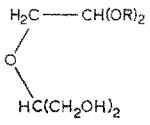
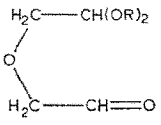
The reaction of bromoacetaldehyde dialkyl acetals and the monosodium salt of glycerol gave mixtures of the *O*-(2,3-dihydroxypropyl)glycolaldehyde dialkyl acetals (**1a–c**) and *O*-(1,3-dihydroxy-2-propyl)glycolaldehyde dialkyl acetals (**2a–c**). The components were identified, after acetylation, by comparison (t.l.c., i.r., and ^{1}H-n.m.r. data) with the authentic compounds described below. When the mixtures of diols were oxidised with aqueous periodate, the corresponding *O*-(2,2-dialkoxyethyl)-glycolaldehydes (**3a–c**) were obtained in good yield by distillation, and acetylation of the residue then gave the corresponding *O*-(1,3-diacetoxy-2-propyl)glycolaldehyde dialkyl acetal. The aldehydes **3a,b** were also prepared from 2,3-*O*-isopropylidene-glycerol by application, in sequence, of *O*-alkylation with bromoacetaldehyde diethyl acetal, reaction with ethanethiol in hydrochloric acid to give *O*-(2,3-dihydroxy-propyl)glycolaldehyde diethyl dithioacetal (**4**), acetylation, treatment with the corresponding alcohol in the presence of $HgCl_2$ and HgO, transesterification (MeONa–MeOH), and periodate oxidation.



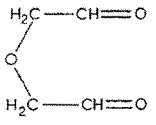
1a X = O, R = Et
1b X = O, R = Pr
1c X = O, R = Pr^i
4 X = S, R = Et



2a R = Et
2b R = Pr
2c R = Pr^i



3a R = Et
3b R = Pr
3c R = Pr^i



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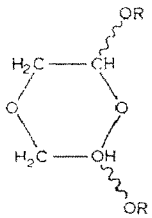
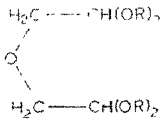
The aldehydes **3a–c** hydrated readily when exposed to moisture, and this process could be monitored by i.r. spectroscopy. Aldehyde **3c** was identified by transformation into the known diglycolaldehyde bis(2,4-dinitrophenylhydrazone)[1].

*Derivatives of Diglycolaldehyde, Part XVII. For Part XVI, see ref. 1.

Mixtures of *cis*- and *trans*-2,6-dialkoxy-1,4-dioxanes (**6a–c**) were obtained in good yields (~80%) when **3a–c** were treated with anhydrous 1,4-dioxane containing boron trifluoride. When these reactions were monitored by t.l.c., it was found that neither diglycolaldehyde bis(dialkyl acetal) (**7**) nor a polymer was formed. The *cis* isomers preponderated in the mixtures, as shown by comparison (t.l.c., i.r., and ^{1}H-n.m.r. data) with authentic specimens[2]. This procedure is more suitable than that reported[2] for the preparation of mixtures of *cis*- and *trans*-2,6-dialkoxy-1,4-dioxanes from diglycolaldehyde (**5**) and alcohols.



6a R = Et
6b R = Pr
6c R = Pr^i
6d R = H



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On the other hand, aldehydes **3a–c** have been hydrolysed in aqueous acid media, giving diglycolaldehyde (**5**) in almost quantitative yields. Thus, **5** as 2,6-dihydroxy-1,4-dioxane (**6d**) could be prepared in 50% overall yield from bromoacetaldehyde dipropyl acetal.

EXPERIMENTAL

General methods. — Organic solutions were dried over anhydrous Na_2SO_4. Solutions were concentrated under diminished pressure at <40°. Melting points (uncorrected) were obtained with an Electrothermal melting-point apparatus. I.r. spectra were recorded for films on NaCl discs with a Pye-Unicam SP 1000 spectrometer. ^{1}H-N.m.r. spectra (internal Me_4Si) were recorded with a Perkin-Elmer-Hitachi R-20 B spectrometer. Chemical shifts are given on the δ scale, and couplings in Hz.

Reaction of glycerol with bromoacetaldehyde acetals. — A mixture of anhydrous glycerol (170 g) and NaH (10 g) was stirred at 56° until the hydride disappeared (~15 h). After cooling, the appropriate bromoacetaldehyde dialkyl acetal was added, the mixture was heated at 140° and then cooled, aqueous 50% K_2CO_3 (100 mL) was added, the mixture was extracted with ether (6 × 50 mL), and the combined extracts were dried, filtered, and concentrated. The following mixtures were obtained in this manner.

(*a*) With bromoacetaldehyde diethyl acetal (22.5 g) and reaction for 2 days, a product (**1a,2a**; 16.4 g, 69%), b.p. 118–120°/0.2 mmHg, was obtained which, with acetic anhydride–pyridine, gave a 6:1 mixture (as shown by ^{1}H-n.m.r. spectroscopy;

97.4%) of *O*-(2,3-diacetoxypropyl)glycolaldehyde diethyl acetal and *O*-(1,3-diacetoxyprop-2-yl)glycolaldehyde diethyl acetal, b.p. 116–119°/0.1 mmHg (Found: C, 53.7; H, 8.2. $C_{13}H_{24}O_7$ calc.: C, 53.4; H, 8.3%).

(*b*) With bromoacetaldehyde dipropyl acetal (25 g) and reaction for 2 days, a product (**1b**,**2b**; 17.2 g, 65.5%), b.p. 124–126°/0.2 mmHg, was obtained which, on acetylation, gave a 6:1 mixture (84%) of *O*-(2,3-diacetoxypropyl)glycolaldehyde dipropyl acetal and *O*-(1,3-diacetoxyprop-2-yl)glycolaldehyde dipropyl acetal, b.p. 122–124°/0.1 mmHg (Found: C, 56.2; H, 8.7. $C_{15}H_{28}O_7$ calc.: C, 56.2; H, 8.8%).

(*c*) With bromoacetaldehyde di-isopropyl acetal (25 g) and reaction for 3 days, a product (**1c**,**2c**; 12.1 g) was obtained which was acetylated to give a 9:1 mixture (94%) of *O*-(2,3-diacetoxypropyl)glycolaldehyde di-isopropyl acetal and *O*-(1,3-diacetoxyprop-2-yl)glycolaldehyde di-isopropyl acetal, b.p. 118–122°/1 mmHg; ν_{max} 1748, 1240, 1124, and 1044 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 5.02 (m, 1 H), 4.52 (t, 1 H, *J* 5.1 Hz), 4.18–3.26 (m, 8 H), 1.97 (s, 6 H), 1.15 (d, 6 H, *J* 6 Hz), and 1.10 (d, 6 H, *J* 6 Hz) (Found: C, 56.1; H, 8.8. $C_{15}H_{28}O_7$ calc.: C, 56.2; H, 8.8%).

1-O-(2,2-Diethoxyethyl)-2,3-O-isopropylideneglycerol. — Sodium (4.6 g) was allowed to react with 2,3-*O*-isopropylideneglycerol (56 g), and bromoacetaldehyde diethyl acetal (10.2 g) was then added. The mixture was stirred at 120–130° for 12 h, cooled, diluted with aqueous 50% K_2CO_3 (100 mL), and extracted with ether (3 × 100 mL), and the combined extracts were dried, filtered, and concentrated. Distillation of the residue gave 2,3-*O*-isopropylideneglycerol (41.5 g), b.p. 80–84°/16 mmHg, and the title compound (10.9 g, 86%), b.p. 82–83°/0.05 mmHg; ν_{max} 1377, 1369, 1254, 1215, 1162–1052, and 815 cm^{-1}. ^{1}H-N.m.r. data (CCl_4): δ 4.38 (t, 1 H, *J* 5.5 Hz), 4.10–3.25 (m, 11 H), 1.28 (s, 3 H), 1.25 (s, 3 H), and 1.12 (t, 6 H, *J* 7 Hz) (Found: C, 58.3; H, 9.9. $C_{12}H_{24}O_5$ calc.: C, 58.0; H, 9.7%).

O-(2,3-Dihydroxypropyl)glycolaldehyde diethyl dithioacetal (**4**). — A mixture of the above acetal (11 g), water (20 mL), and conc. H_2SO_4 (0.25 mL) was stirred at 60° for 1 h, and then concentrated (to 15 mL) under diminished pressure. Conc. hydrochloric acid (15 mL) and ethanethiol (15 mL) were added, the mixture was kept at room temperature for 30 min, basified with aqueous 40% KOH, and extracted with ether (3 × 50 mL), and the combined extracts were dried and concentrated. Distillation of the residue gave **4** (7.2 g, 67.7%), b.p. 140–143°/0.1 mmHg; ν_{max} 3600–3100, 1378, 1265, 1119, 1048, and 978 cm^{-1}. ^{1}H-N.m.r. data (Me_2SO-d_6): δ 4.53 (d, 1 H, *J* 4.5 Hz; proton exchangeable with D_2O), 4.38 (t, 1 H, *J* 5.5 Hz, proton exchangeable with D_2O), 4.18–3.28 (m, 8 H), 2.70 (q, 4 H, *J* 7 Hz), and 1.25 (t, 6 H, *J* 7 Hz) (Found: C, 44.9; H, 8.5. $C_9H_{20}OS_2$ calc.: C, 44.9; H, 8.4%).

Conventional treatment of **4** with pyridine and acetic anhydride gave the diacetate (22 g, 97%), b.p. 150–155°/0.4 mmHg; ν_{max} 1748, 1370, 1230, 1120, and 1048 cm^{-1}. ^{1}H-n.m.r. data ($CDCl_3$): δ 5.24 (m, 1 H), 4.60–3.62 (m, 7 H), 2.76 (q, 4 H, *J* 7.5 Hz), 2.11 (s, 3 H), 2.09 (s, 3 H), and 1.28 (t, 6 H, *J* 7.5 Hz) (Found: C, 47.9; H, 7.2; S, 19.5. $C_{13}H_{24}O_5S_2$ calc.: C, 48.1; H, 7.4; S, 19.8%).

O-(2,3-Dihydroxypropyl)glycolaldehyde dialkyl acetals. — (*a*) A mixture of **4** (21 g), ethanol (250 mL), HgO (50 g), and $HgCl_2$ (50 g) was stirred and heated under

reflux for 12 h, cooled, filtered, and concentrated. The residue was treated conventionally with pyridine–acetic anhydride, to give *O*-(2,3-diacetoxypropyl)glycolaldehyde diethyl acetal (13.2 g, 69.7%), b.p. 124–127°/0.5 mmHg; ν_{max} 1750, 1374, 1235, 1140–1045, 962, 880, and 850 cm^{-1}. ^{1}H-N.m.r. data (CCl_4): δ 4.98 (m, 1 H), 4.40 (t, 1 H, *J* 5.5 Hz), 4.07 (m, 2 H), 3.7–3.26 (m, 8 H), 1.94 (s, 6 H), and 1.12 (t, 6 H, *J* 6.7 Hz) (Found: C, 53.6; H, 8.3. $C_{13}H_{24}O_7$ calc.: C, 53.4; H, 8.3%).

The foregoing compound (5 g) was treated with methanolic 0.1M sodium methoxide at room temperature for 7 h, and the solution was then concentrated. Aqueous 50% K_2CO_3 (10 mL) was added to the residue which was then extracted with ether (3 × 30 mL). The combined extracts were dried and concentrated. Distillation of the residue gave *O*-(2,3-dihydroxypropyl)glycolaldehyde diethyl acetal (**1a**; 2.9 g, 81.5%), b.p. 110–112°/0.4 mmHg; ν_{max} 3600–3100, 1443, 1372, 1345, 1140–1040, 928, and 850 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 4.56 (t, 1 H), 3.52 (m, 11 H), 3.22 (bs, 1 H; proton exchangeable with D_2O), 2.75 (bs, 1 H; proton exchangeable with D_2O), and 1.29 (t, 6 H, *J* 6.7 Hz) (Found: C, 51.6; H, 9.7. $C_8H_{20}O_5$ calc.: C, 51.3; H, 9.7%).

(*b*) A mixture of **4** (14.5 g), 1-propanol (100 mL), HgO (22 g), and $HgCl_2$ (22 g) was stirred and heated under reflux for 7 h, and the product was acetylated to give *O*-(2,3-diacetoxypropyl)glycolaldehyde dipropyl acetal (11 g, 77%), b.p. 125–130°/0.2 mmHg; ν_{max} 1750, 1370, 1235, 1112, 1060, 990, and 957 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 5.05 (m, 1 H), 4.45 (t, 1 H, *J* 5.5 Hz), 4.1 (m, 2 H), 3.51 (d, 2 H, *J* 5.5 Hz), 3.4 (m, 6 H), 2.0 (s, 6 H), 1.49 (m, 4 H), and 0.9 (t, 6 H) (Found: C, 56.1; H, 8.9. $C_{15}H_{28}O_7$ calc.: C, 56.2; H, 8.8%).

A mixture of the foregoing compound (10 g), water (20 mL), ethanol (50 mL), and KOH (7 g) was heated under reflux for 2 h and then concentrated. Aqueous 50% K_2CO_3 (20 mL) was added to the residue and extracted with ether (3 × 75 mL). The combined extracts were dried, filtered, and concentrated, to yield *O*-(2,3-dihydroxypropyl)glycolaldehyde dipropyl acetal (**1b**; 7.3 g, 99%), b.p. 124–126°/0.01 mmHg, ^{1}H-N.m.r. data ($CDCl_3$): δ 4.57 (t, 1 H), 3.50 (m, 11 H), 3.18 (bs, 1 H; proton exchangeable with D_2O), 2.80 (bs, 1 H; proton exchangeable with D_2O), 1.48 (m, 4 H), and 0.9 (t, 6 H).

O-(*2,2-Dialkoxyethyl)glycolaldehydes.* – A solution of starting material (**1.2a–c**) in aqueous $NaIO_4$ was cooled in an ice-bath for 10 min and then left at room temperature for 1 h. Ethanol (80 mL) was added, the mixture was filtered and concentrated, chloroform (50 mL) and water (4 mL) were added, and the organic layer was separated. The aqueous solution was extracted with chloroform (25 mL), and the combined organic solutions were dried, filtered, and concentrated to dryness.

(*a*) O-(*2,2-Diethoxyethyl)glycolaldehyde* (**3a**). A mixture of **1a**.**2a** (6.6 g) and aqueous $NaIO_4$ (6.8 g in 80 mL) gave **3a** (3.7 g, 66.2%), b.p. 59–62°/0.5 mmHg (see below). The undistilled residue was acetylated, to give *O*-(1,3-diacetoxypropyl)-glycolaldehyde diethyl acetal (1.1 g), b.p. 125–128°/0.5 mmHg; ν_{max} 1750, 1444, 1370, 1235, 1122, 1065, 930, and 850 cm^{-1}. ^{1}H-N.m.r. data (CCl_4): δ 4.37 (t, 1 H,

J 5.2 Hz), 3.98 (m, 4 H), 3.75 –3.25 (m, 7 H), 1.94 (s, 6 H). and 1.10 (t, 6 H, *J* 6.7 Hz) (Found: C, 53.3; H, 8.4. $C_{13}H_{24}O_7$ calc.: C, 53.4; H, 8.3%).

A mixture of **1a** (2.55 g) and aqueous $NaIO_4$ (2.7 g in 30 mL) gave **3a** (1.85 g, 88.7%), b.p. 58–60°/0.5 mmHg; ν_{max} 3450, 2800, 2700, 1736, 1370, 1342, 1250, 1130, 1060, 880, and 845 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 9.51 (t, 1 H, *J* 0.8 Hz), 4.52 (t, 1 H, *J* 5.2 Hz), 4.08 (d, 2 H, *J* 0.8 Hz), 3.58 (m, 4 H), 3.50 (d, 2 H, *J* 5.2 Hz), and 1.18 (t, 6 H, *J* 6.7 Hz) (Found: C, 52.8; H, 9.4. $C_8H_{16}O_4 \cdot H_2O$ calc.: C, 49.5; H, 9.3. $C_8H_{16}O_4$ calc.: C, 54.5; H, 9.1%).

(*b*) O-(*2,2-Dipropoxyethyl)glycolaldehyde* (**3b**). A mixture of **1b**,**2b** (6.82 g) and aqueous $NaIO_4$ (6.8 g in 80 mL) gave **3b** (5 g, 76.7%), b.p. 70°/0.5 mmHg (see below). The undistilled residue was acetylated, to give *O*-(1,3-diacetoxypropyl)-glycolaldehyde dipropyl acetal (1.6 g), b.p. 124–126°/0.1 mmHg; ν_{max} 1747, 1230, 1120, and 1060 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 4.46 (t, 1 H, *J* 5 Hz), 4.06 (m, 4 H), 3.86–3.2 (m, 7 H), 2.02 (s, 6 H), 1.58 (m, 4 H), and 0.90 (t, 6 H) (Found: C, 56.3; H, 9.0. $C_{15}H_{28}O_7$ calc.: C, 56.2; H, 8.8%).

A mixture of **1b** (7.2 g) and aqueous $NaIO_4$ (6.6 g in 100 mL) gave **3b** (5.45 g, 87.6%), b.p. 75–76°/1 mmHg; ν_{max} 3470, 2800, 2700, 1738, 1353, 1250, 1130, 1070, 990, and 890 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 9.54 (t, 1 H, *J* 0.8 Hz), 4.54 (t, 1 H, *J* 5.1 Hz), 4.02 (d, 2 H, *J* 0.8 Hz), 3.48 (d, 2 H, *J* 5.1 Hz), 3.42 (m, 4 H), 1.56 (m, 4 H), and 0.90 (t, 6 H) (Found: C, 54.1; H, 9.9. $C_{10}H_{20}O_4 \cdot H_2O$ calc.: C, 54.0; H, 10.0%).

(*c*) O-(*2,2-Di-isopropoxyethyl)glycolaldehyde* (**3c**). A mixture of **1c**,**2c** (7.9 g) and aqueous $NaIO_4$ (6.4 g in 90 mL) gave **3c** (3.95 g, 65.7%), b.p. 68–70°/1 mmHg; ν_{max} 1738, 1376, 1363, 1125, 1040, and 978 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 9.56 (t, 1 H, *J* 0.8 Hz), 4.66 (t, 1 H, *J* 5.1 Hz), 4.06 (d, 2 H, *J* 0.8 Hz), 3.78 (m, 2 H, *J* 6 Hz), 3.46 (d, 2 H, *J* 5.1 Hz), 1.18 (d, 6 H, *J* 6 Hz), and 1.13 (d, 6 H, *J* 6 Hz) (Found: C, 53.9; H, 10.1. $C_{10}H_{20}O_4 \cdot H_2O$ calc.: C, 54.0; H, 10.0%). This compound was transformed into the known[1] diglycolaldehyde bis(2,4-dinitrophenylhydrazone), m.p. 192–194° (from 1,4-dioxane–water).

Acetylation of the undistilled residue and column chromatography (3:1 hexane–ether) of the crude product gave *O*-(1,3-diacetoxyprop-2-yl)glycolaldehyde di-isopropyl acetal (1.07 g); ν_{max} 1748, 1370, 1230, 1125, and 1044 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 4.53 (t, 1 H, *J* 5.2 Hz), 4.03 (m, 4 H), 3.73 (m, 3 H), 3.43 (d, 2 H, *J* 5.2 Hz), 1.97 (s, 6 H), 1.14 (d, 6 H, *J* 6 Hz), and 1.08 (d, 6 H, *J* 6 Hz) (Found: C, 56.2; H, 8.7. $C_{15}H_{28}O_7$ calc.: C, 56.2; H, 8.8%).

2,6-Dialkoxy-1,4-dioxanes. — A solution of the appropriate compound (**3a–c**) in anhydrous 1,4-dioxane was treated with $BF_3 \cdot (Et_2O)_2$ at room temperature. When the starting material had disappeared (t.l.c.), the mixture was basified with aqueous K_2CO_3 (15 mL), concentrated to half of its volume, and extracted with ether (3 × 25 mL). The combined extracts were dried, filtered, and concentrated to dryness, to give the corresponding mixture (**6**) of stereoisomers, which were identified by comparison (t.l.c., i.r., and ^{1}H-n.m.r. spectra) with authentic samples[2].

The following amounts and conditions were used:

Starting material (g)	*Solvent (ml)*	$BF_3 \cdot (Et_2O)_2$ *(mL)*	*Time (days)*	*Products (g)*	cis,trans *Ratio*
3a (1.1)	10	0.3	2	**6a** (0.85, 77%)	2.8:1
3b (4.37)	30	0.6	2	**6b** (3.6, 82.4%)	2.8:1
3c (3.5)	30	0.6	4	**6c** (2.9, 82.8%)	3:1

Diglycolaldehyde[1] (**5**). — A solution of **3b** (5 g) in aqueous 50% acetic acid (40 mL) was heated under reflux for 6 h, and then concentrated. Traces of acetic were eliminated from the residue by azeotropic distillation with water. A light-yellow, syrupy product [2.94 g, ~100% as 2,6-dihydroxy-1,4-dioxane (**6d**)] was obtained. Diglycolaldehyde bis(2,4-dinitrophenylhydrazone) (92%), prepared in the usual manner[1], had m.p. 192–194° (from 1,4-dioxane–water). Compound **3a** reacted in the same way, to give **5**.

REFERENCES

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2 F. J. Lopez Aparicio, F. Zorrilla Benitez, and F. Santoyo Gonzalez, *Carbohydr. Res.*, 107 (1982) 279–284.