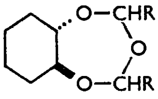
352. *Reactions of Simple Aldehydes with* cis- *and* trans-*Cyclohexane-1,2-diol.*

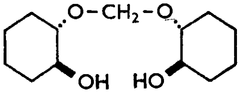
By Frank S. H. Head.

With formaldehyde and acetaldehyde *trans*-cyclohexane-1,2-diol gives *trans*-hexahydro-1,3,5-benzotrioxepan and its 2,4-dimethyl derivative, respectively, as the principal products, whereas the *cis*-diol gives *cis*-hexahydro-1,3-benzodioxolan and its 2-methyl derivative. With formaldehyde traces of di-(*trans*-2-hydroxycyclohexyloxy)methane (two isomers) and the corresponding *cis*-compound (one form) are also formed. Interaction of the *trans*-diol and glyoxal at room temperature gives a bishemiacetal shown to be *trans*-hexahydro-2,3-dihydroxy-1,4-benzodioxan.

In connexion with work on the cross-linking of cotton cellulose with aldehydes an investigation of the action of aldehydes on *cis*- and *trans*-cyclohexane-1,2-diol has been carried out. The *trans*-diol was chosen as a model of the α-glycol system in the anhydroglucose units of cellulose, since its hydroxyl groups are secondary, *trans*-, and equatorial. Derivatives of the *cis*-diol were included for comparison. It is well known that the *cis*-diol gives an isopropylidene derivative,[1] and more recently it has been found that the *trans*-diol does so too,[2] but the reaction of the two diols with simple aldehydes does not seem to have received attention.



(I)



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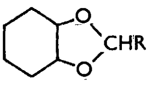

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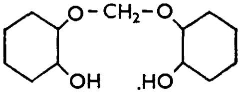

(IV)

When the *trans*-diol was heated with paraformaldehyde at about 135° in the presence of an acid catalyst (ferric chloride or calcium chloride) the principal product was *trans*-hexahydro-1,3,5-benzotrioxepan (I; $R = H$). The seven-membered ring system in (I) is uncommon, but it is known to occur in Appel and Haworth's methyl 4,6-*O*-ethylidene-2,3-*O*-oxydiethylidene-α- and -β-D-glucosides, prepared by treating methyl α- or β-D-glucoside with paraldehyde in the presence of sulphuric acid at room temperature, and in

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[1] Böeseken and Derx, *Rec. Trav. chim.*, 1921, **40**, 519.

[2] Christian, Gogek, and Purves, *Canad. J. Chem.*, 1951, **29**, 911.

similar substances.[3] Honeyman and Morgan [4] have shown that methyl α-D-mannoside (in which the 2,3-hydroxyl groups are *cis* to one another) gives 2,3:4,6-di-*O*-ethylidene-α-D-mannoside. Andrews, Hough, and Jones,[5] on the other hand, found that L-rhamnose with formaldehyde in aqueous sulphuric acid gave principally an oxydimethylene compound, in which the 3,4-(*trans*-)positions were bridged, together with much smaller amounts of other substances, including a second oxydimethylene compound with the 2,3-(*cis*-)-positions bridged.

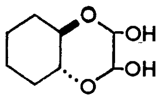
In addition to compound (I; R = H) the reaction mixture contained unchanged *trans*-diol and a syrup from which two crystalline isomeric forms of di-(*trans*-2-hydroxycyclohexyloxy)methane (II) were isolated in small amounts; these forms gave isomeric di-*p*-nitrobenzoates and bis-3,5-dinitrobenzoates, and they are assumed to be DL- and *meso*-forms. The yield of compound (I; R = H) was 74% when an excess of aldehyde was used: the yield of syrup was greatest when equimolecular proportions were taken and the yield of (I) was then only 19%. Ferric chloride was used as the catalyst because Adams and Adkins [6] claim that it gives the best results with paraformaldehyde, but it was later found that calcium chloride gave better yields of compound (I) (32% with equimolecular proportions of reactants). A modification of Appel and Haworth's method (using trioxan dissolved in chloroform) gave poor results with the *trans*-diol.

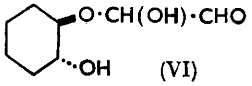
When *cis*-cyclohexane-1,2-diol was treated, as above, with an equimolecular proportion of paraformaldehyde in the presence of ferric chloride, it gave a 74% yield of *cis*-hexahydro-1,3-benzodioxolan (III; R = H) and a trace of di-(*cis*-2-hydroxycyclohexyloxy)methane (IV). The crystalline substance (IV) and its 3,5-dinitrobenzoate differed from both of the isomers of (II) and their 3,5-dinitrobenzoates. Treatment of *trans*-cyclohexane-1,2-diol with paraldehyde under these conditions gave disappointing results, most of the diol being recovered unchanged, but when Appel and Haworth's method was used a good yield of *trans*-hexahydro-2,4-dimethyl-1,3,5-benzotrioxepan (I; R = Me) was obtained. The *cis*-diol treated similarly gave rise to *cis*-hexahydro-2-methyl-1,3-benzodioxolan (III; R = Me). The formation of substances corresponding to (II) and (IV) was not observed. The cyclic formals of types (I) and (III) have characteristic odours and are all peroxidised fairly rapidly in contact with air.

From these results it appears that cyclic acetals with five-membered rings are readily formed from the *cis*-diol, but that with the *trans*-diol seven-membered rings form more easily. Comparison of the yields (19 and 74% respectively) of compounds (I) and (III) (R = H) obtained with equimolecular proportions of reactants suggests that the latter process proceeds less readily than the former.

The results as a whole make it probable that in reactions between simple aldehydes and cellulose the formation of cyclic acetals will occur much more readily than cross-linking [typified by the formation of (II)].

(V)





(VI)

No attempts have been made to prepare acetals of the *trans*-diol with glyoxal, but the formation under mild conditions of a crystalline bishemiacetal, *trans*-hexahydro-2,3-dihydroxy1,4-benzodioxan (V), has been observed. Its properties were similar to those of the bishemiacetal of glyoxal and ethylene glycol (2,3-dihydroxydioxan [7]) which dissociates readily into its components and behaves as a source of glyoxal.

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[3] Appel and Haworth, *J.*, 1938, 793; Mellies, Mehltretter, and Rist, *J. Amer. Chem. Soc.*, 1951, **73**, 294; Ansell and Honeyman, *J.*, 1952, 2778.

[4] Honeyman and Morgan, *J.*, 1954, 744.

[5] Andrews, Hough, and Jones, *J. Amer. Chem. Soc.*, 1955, **77**, 125.

[6] Adams and Adkins, *J. Amer. Chem. Soc.*, 1925, **47**, 1358.

[7] Head, *J.*, 1955, 1036; see also Raudnitz, *Chem. and Ind.*, 1956, 166.

The constitution (V) was confirmed by periodate oxidation; the substance reduced 1 mol. of periodate in 15 min. and yielded fairly pure *trans*-cyclohexane-1,2-diol diformate together with 0·07 mol. of formic acid. The latter probably arose by oxidation of the partly dissociated form of the substance (VI). When a solution of the substance was left for an hour before being oxidised the amount of acid rose to 0·12 mol. It appears probable from these results that compound (V) is much more stable in solution than 2,3-dihydroxydioxan, which also reduced 1 mol. of periodate rapidly, but gave 0·68 mol. of formic acid and 0·10 mol. of formaldehyde.

Three isomers (V) are possible; one if the hydroxyl groups are *cis* to each other, and two if they are *trans*. Only one has been observed. Attempts to separate other isomers failed and, moreover, the crude preparation (V) and the purified substance both gave good yields of crude di-*p*-nitrobenzoate of the same m. p.

Theoretically it should be possible to add further molecules of glyoxal to the hemiacetal (V) and obtain a series of polymers. When this was attempted with two or ten mols. of glyoxal, amorphous glasses resulted. Equimolecular proportions of the *cis*-diol and glyoxal also gave a syrup.

EXPERIMENTAL

The infrared absorption spectra of the cyclic acetals (types I and III) were measured on liquid films between rock-salt plates. All exhibited strong bands between 1150 and 1060 cm.$^{-1}$ indicative of ether groupings, but were free from hydroxyl and carbonyl absorption. The spectra of the hydroxylic substances (II), (IV), and (V) (in Nujol mulls) exhibited the same general features, but there was strong hydroxyl absorption at about 3400 cm.$^{-1}$ [about 3300 cm.$^{-1}$ for (IV)]. The spectra of the isomers (II) differed in the " finger print " region from each other and from that of compound (IV).

Reactions of trans-*Cyclohexane*-1,2-*diol with Paraformaldehyde*.—(*a*) A mixture of *trans*-cyclohexane-1,2-diol (29 g.), paraformaldehyde (30 g.), and anhydrous ferric chloride (1 g.) was heated at 130—140° for 7 hr., for half the time under reflux and for the remainder with the condenser set for distillation. The homogeneous product was poured into a solution of sodium carbonate (2 g.) in water (50 c.c.) and steam-distilled. Extraction of the distillate (250 c.c.) with chloroform and fractionation of the dried extract (K_2CO_3), gave trans-*hexahydro*-1,3,5-*benzotrioxepan* (I; R = H) (29·3 g., 74%), b. p. 55—58°/0·8 mm., 97°/20 mm., n^{21} 1·4686 [Found: C, 60·6; H, 9·0%; *M* (in camphor), 149. $C_8H_{14}O_3$ requires C, 60·7; H, 8·9%; *M*, 158]. The liquid was to some extent soluble in water and did not reduce Fehling's solution.

(*b*) A mixture of the *trans*-diol (116 g.), paraformaldehyde (30 g.), and ferric chloride (4 g.) was heated and worked up as above. After removal of the trioxepan (yield 19%) by steam-distillation, the residue was mixed with chloroform and filtered from inorganic salts. The aqueous layer contained unchanged *trans*-diol (31 g.) which was recovered by evaporation to dryness under reduced pressure, extraction with benzene, filtration, and precipitation with an equal volume of light petroleum (b. p. 60—80°). Evaporation of the dried (K_2CO_3) chloroform layer gave a syrup (54·4 g.) which was dissolved in ether (150 c.c.) and left in the refrigerator. *Di*-(trans-2-*hydroxycyclohexyloxy*)*methane* (II), *isomer A*, separated as colourless water-soluble needles (8·0 g., 3%), which after recrystallisation from light petroleum (b. p. 60—80°) melted at 104—105° (depressed on admixture with *trans*-diol) [Found: C, 64·0; H, 10·1%; *M* (in camphor), 222. $C_{13}H_{24}O_4$ requires C, 63·9; H, 9·9%; *M*, 244].

The substance (0·3 g.) in dry pyridine (5 c.c.) was treated with *p*-nitrobenzoyl chloride (0·7 g.), left for 2 days at room temperature, and then poured into water. The precipitate was collected, suspended in saturated sodium hydrogen carbonate solution, and collected again, giving the *di*-p-*nitrobenzoate* (83%) which separated from aqueous acetone (80%) as pale yellow needles, m. p. 144—146° (Found: C, 60·1; H, 5·9; N, 5·3. $C_{27}H_{30}O_{10}N_2$ requires C, 59·8; H, 5·6; N, 5·2%). The pale yellow *bis*-3,5-*dinitrobenzoate*, prepared similarly in 95% yield and recrystallised from aqueous pyridine and from acetone, had m. p. 205—206° (Found: C, 51·1; H, 4·9; N, 9·2. $C_{27}H_{28}O_{14}N_4$ requires C, 51·3; H, 4·4; N, 8·9%).

Concentration of the ethereal mother-liquors (from which Isomer A had separated) to half volume, and dilution with an equal volume of light petroleum (b. p. 60—80°), gave *di*-(trans-2-*hydroxycyclohexyloxy*)*methane* (II), *isomer B* (4·6 g., 2%), as colourless water-soluble prisms. After recrystallisation from 1 : 1 ether–light petroleum, and filtration after short storage to avoid contamination with isomer A, it melted at 81—82°, depressed on admixture with isomer A [Found: C, 64·2; H, 9·6%; *M* (in camphor), 215]. The *di*-p-*nitrobenzoate* (yield 90%) separated from 80% aqueous acetone as pale yellow needles, m. p. 108—109°, depressed on admixture with the derivative of isomer A (Found: C, 59·5; H, 5·5; N, 4·9%). The *bis*-3,5-*dinitrobenzoate* (yield 95%), purified as was its isomer, formed pale yellow needles, m. p. 181—182°, depressed on admixture with the A-derivative (Found: C, 51·4; H, 4·6; N, 8·9%).

Hydrolysis of the Formals (I *and* II; R = H).—A weighed amount of the formal [*e.g.*, 2·8 g. of (I)] was added to 2N-sulphuric acid (200 c.c.) in a reflux apparatus protected with a water trap to avoid loss of formaldehyde. The whole was refluxed for 1½ hr. and then distilled to 50 c.c. Water (150 c.c.) was added to the residue, which was then distilled again; this was done twice. The three distillates so obtained were each made up to 250 c.c. and the formaldehyde content was determined by the hypoiodite method.[8]

The residue from the distillations was neutralised by adding insufficient barium hydroxide (50 g.) in hot water (100 c.c.), followed by an excess of barium carbonate (20 g.). Evaporation of the filtered solution and washings under reduced pressure gave a residue consisting of nearly pure *trans*-diol (identified by m. p. and mixed m. p.). The percentage yields of products obtained were as follows:

	I; R = H	II, A	II, B
Formaldehyde	98·4	99·1	99·7
trans-Diol	88	93	87

Reactions of cis-*Cyclohexane*-1,2-*diol with Paraformaldehyde*.—The *cis*-diol (15 g.), paraformaldehyde (4 g.), and ferric chloride (0·5 g.) were heated for 7 hr. at 130—140°, working up being as for the *trans*-diol. The principal product was cis-*hexahydro*-1,3-*benzodioxolan* (III; R = H) (12·2 g., 74%), b. p. 167—168° (69—70°/27 mm.); n^{18} 1·4604 [Found: C, 65·0; H, 9·4%; *M* (in camphor), 173. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%; *M*, 128]. It dissolved to some extent in water and did not reduce Fehling's solution. Hydrolysis with hot dilute sulphuric acid gave 86·9 and 56% respectively of the theoretical yields of formaldehyde and *cis*-diol (the methods used for recovering the *trans*-diol did not give very good results with the *cis*-isomer).

The residue, from which (III; R = H) had been removed by steam-distillation, yielded unchanged *cis*-diol (1·0 g.) and a syrup (2·6 g.). The syrup was mixed with boiling water (250 c.c.), cooled, filtered, and extracted with chloroform, and the extract was dried (K_2CO_3) and evaporated. The residue, when dissolved in ether (2·5 c.c.), deposited *di*-(cis-2-*hydroxycyclohexyloxy*)*methane* (IV) (0·1 g.); recrystallised from ether it had m. p. 88—90°, depressed on admixture with the *cis*-diol or with (II, B) [Found: C, 63·8; H, 9·5%; *M* (in camphor), 227. $C_{13}H_{24}O_4$ requires C, 63·9; H, 9·9%; *M*, 244]. The 3,5-*dinitrobenzoate*, obtained in nearly theoretical yield, separated as almost colourless crystals from pyridine, m. p. 219—220°, depressed by admixture with either of the corresponding derivatives of (II, A or B) (Found: C, 51·3; H, 4·6; N, 9·1. $C_{27}H_{28}O_{14}N_4$ requires C, 51·3; H, 4·4; N, 8·9%).

Reaction of trans-*Cyclohexane*-1,2-*diol with Paraldehyde*.—The *trans*-diol (25 g.) was added to a mixture of paraldehyde (125 c.c.) and concentrated sulphuric acid (12 drops) and left for 3 days at room temperature, during which the solid all dissolved. The mixture was diluted with chloroform, neutralised, dried (K_2CO_3), and fractionated *in vacuo* to remove solvent and unchanged paraldehyde. The residue was freed from unchanged diol by mixing it with water and extracting the acetal with light petroleum (b. p. 60—80°). The washed extract was dried (K_2CO_3) and the solvent was removed. Fractionation of the residue gave trans-*hexahydro*-2,4-*dimethyl*-1,3,5-*benzotrioxepan* (I; R = Me) (17·6 g., 44%), b. p. 105—106°/22 mm., n^{23} 1·4561 [Found: C, 64·0; H, 9·5%; *M* (in camphor), 161. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·7%; *M*, 186]. Hydrolysis with hot dilute sulphuric acid yielded 97·3% and 82% of acetaldehyde and *trans*-diol respectively. The method of hydrolysis was generally similar to that used with the parent compound, but 3% sulphuric acid was used, the distillation was only repeated once, and the acetaldehyde distillates were collected in ice-cooled sodium metabisulphite

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[8] Head, *J. Text. Inst.*, 1947, **38**, *T* 389.

solutions and left for 1 hr. before titration. The acetaldehyde content of the distillates was then determined by back-titration with iodine.[9]

Reaction of cis-*Cyclohexane*-1,2-*diol with Paraldehyde*.—The method was similar to that used with the *trans*-diol and it gave cis-*hexahydro*-2-*methyl*-1,3-*benzodioxolan* (III; R = Me) (52%), b. p. 77—79°/33 mm., n^{20} 1·4497, with a clinging and rather unpleasant odour [Found: C, 67·4; H, 9·9%; *M* (in camphor), 134. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%; *M*, 142]. Hydrolysis with dilute sulphuric acid, as for (I; R = Me), yielded 91·2% of acetaldehyde.

trans-*Hexahydro*-2,3-*dihydroxy*-1,4-*benzodioxan* (V).—A mixture of *trans*-cyclohexane-1,2-diol (63·8 g.) and commercial 30% glyoxal solution (106·7 g.) was evaporated to dryness *in vacuo* over phosphoric oxide. The crystalline residue (97 g.) was extracted with cold acetone (100 c.c.). The undissolved portion (82·4 g.) melted at 118—122° (available glyoxal content by Friedemann peroxide method,[10] 33·4%). A second crop (6 g.), obtained by evaporation of the acetone extract and trituration of the residue with ether, melted at 113—115° and contained 33·7% of glyoxal. Repeated recrystallisation from acetone gave trans-*hexahydro*-2,3-*dihydroxy*-1,4-*benzodioxan* as needles, m. p. 140—143° (decomp.) (Found: C, 55·3; H, 8·3. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%). The available glyoxal contents determined by the Friedemann's alkali and peroxide methods [10] and by the hypoiodite method [8] were 32·9, 33·3, and 33·9% respectively (calc. for V: 33·3%). Attempts to isolate isomers or other substances from the acetone mother-liquors failed.

When heated, compound (V) gave off a greenish-yellow vapour (presumably monomeric glyoxal) and in hot xylene it gave a yellow solution which became colourless again on cooling. With phenylhydrazine in aqueous acetic acid solution it gave glyoxal bisphenylhydrazone immediately, in nearly theoretical yield. When the solid purified substance (0·4 g.) was added to *p*-nitrobenzoyl chloride (1·3 g.) in dry pyridine (25 c.c.) and left for 3 days at room temperature, and the product was worked up as for the *p*-nitrobenzoates of (II; R = H), it gave the *di*-p-*nitrobenzoate* (0·8 g., 73%), m. p. 232—235°. Recrystallisation from toluene and from acetone gave pale yellow rhombic plates, m. p. 243—244° [Found: C, 55·5; H, 4·3; N, 6·3%; *M* (in camphor), 385. $C_{22}H_{20}O_{10}N_2$ requires C, 55·9; H, 4·3; N, 5·9%; *M*, 472]. Infrared examination (Nujol mull) provided no evidence of free hydroxyl groups. Neither the di-*p*-nitrobenzoate of the *trans*-diol (m. p. 128—129°) nor any other substance was observed. Similarly, when the crude preparation of (V) was used, either in the solid form (as above) or dissolved in pyridine, it gave a crude di-*p*-nitrobenzoate of the same m. p. as that from the purified substance, and no other product.

Periodate Oxidation of the Dioxan (V).—(*a*) The substance (0·435 g.) was dissolved in 0·075M-sodium metaperiodate and made up to 100 c.c. with more of the same solution. At intervals aliquot parts were added to water containing a large excess of ethylene glycol, then aerated for 15 min. with carbon dioxide-free air, and the free acid was titrated with alkali. Subsequently an excess of alkali was added, and the whole back-titrated with acid after 2 hr. in order to determine the total formic acid (free and esterified). Periodate consumption was determined on other aliquot parts by Müller and Friedberger's method.[11] The following results were obtained:

Time (min.)	Periodate reduced (mol.)	Free acid formed (mol.)	Total acid found after hydrol. (mol.)
15	0·98	0·07	1·89
30	1·01	0·07	2·01
60	1·02	0·07	2·05

(*b*) The substance (*ca.* 0·1 g.) was dissolved in water (25 c.c.), left for 1 hr., and treated with 0·075M-sodium metaperiodate (25 c.c.). After 15 min. the amount of free acid (determined as above) was 0·12 mol. When the substance was dissolved first in the periodate solution (25 c.c.), diluted immediately with water (25 c.c.), and titrated after 15 min., the yield of acid was 0·06 mol.

(*c*) The substance (26·1 g.) was dissolved in a solution of sodium metaperiodate (30·5 g., 95% of the calculated amount) in water (500 c.c.) and cooled with water. After 30 min. no periodate was detected. The oil which separated was extracted with chloroform, and the extract washed, dried ($CaCl_2$), and evaporated. Fractionation of the residue (23·3 g.) under

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[9] Ripper, *Monatsh.*, 1900, **21**, 1079.

[10] Friedemann, *J. Biol. Chem.*, 1927, **73**, 331.

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

reduced pressure gave trans-*cyclohexane*-1,2-*diol diformate* (18·7 g., 72%), b. p. 118°/15 mm., n^{19} 1·4576 (Found: C, 56·2; H, 7·4; CHO, 33·3. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0; CHO, 33·7%). Hydrolysis with alkali gave an almost theoretical yield of the *trans*-diol (recovered as described earlier). Infrared examination of the ester (liquid film) showed that it contained little (if any) hydroxyl group, but bands corresponding to carbonyl groups (*ca.* 1725 cm.$^{-1}$) and ether linkages (between 1150 and 1060 cm.$^{-1}$) were observed.

The author is indebted to Dr. H. Spedding for measuring the infrared absorption spectra and to Mr. J. F. Fernie and Miss M. M. Williamson for assistance with some of the experimental work.

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