520. *Aspects of Stereochemistry. Part IV.* Configuration and Some Reactions of the* 1,3-O-*Benzylideneglycerols* (5-*Hydroxy*-2-*phenyl*-1,3-*dioxans*).†

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Configurations have been allocated to the isomers of 1,3-*O*-benzylideneglycerol (5-hydroxy-2-phenyl-1,3-dioxan) on the basis of the extent of intramolecular hydrogen-bonding in dilute CCl_4 solutions, which affects the conformational stability and reactivity of certain cyclic acetals. Whereas acylation and etherification of *cis*-1,3-*O*-benzylideneglycerol yields *cis*-derivatives, the *trans*-isomer yields mixtures of *cis*- and *trans*-derivatives. Equilibration with aluminium isopropoxide reveals the *cis*-isomer as the more stable, whereas the *trans*-2-*O*-benzyl ether is the more stable when it is equilibrated with its isomer by acid. *trans*-1,3-*O*-Benzylideneglycerol has a greater affinity than the *cis*-isomer for alumina in chromatography: of esters and ethers the *cis*-compounds are the more strongly adsorbed.

A variety of crystalline cyclic acetals has apparently been obtained by reaction of benzaldehyde with glycerol.[1-7] Of these compounds, that having m. p. *ca.* 80° first encountered by Gerhardt [8] crystallises readily when the benzaldehyde–glycerol condensate is stored in the presence of acid.[3,5,8] The cyclic acetal was shown to be a 1,3-*O*-benzylideneglycerol (5-hydroxy-2-phenyl-1,3-dioxan) when acidic hydrolysis of its crystalline methyl ether gave 2-*O*-methylglycerol,[3,9] and hydrogenolysis [10] of its benzoate catalysed by palladium black gave 2-*O*-benzoylglycerol [11] under conditions which precluded acyl migration; [12] it has been widely used in β-glyceride syntheses.[10,12]

In 1942 Verkade and van Roon [5] isolated the second isomeric form of 1,3-*O*-benzylideneglycerol (m. p. 63—64°) as its *O*-acetate (m. p. 115—116°) in low yield after treatment of Gerhardt's *O*-benzylideneglycerol mixture [8] with acetic anhydride and pyridine; the Gerhardt mixture, obtained [2,3,8] by passing a stream of carbon dioxide through a mixture of benzaldehyde and glycerol at 140°, is a liquid containing predominantly 1,2-*O*-benzylideneglycerol.[3] Hydrolysis of the *O*-acetate readily gave the parent 1,3-*O*-benzylideneglycerol.[5] The size of the ring in this cyclic acetal was inferred from the isolation [5] of 2-*O*-benzoylglycerol after catalytic hydrogenolysis [10] of its benzoate.

Evidence is now presented which permits the allocation of the *cis*- and the *trans*-configuration respectively to the 1,3-*O*-benzylideneglycerols of m. p.s 84° and 63—64°.

Whilst *cis*-1,3-*O*-benzylideneglycerol may be isolated directly [3,5] after treatment of the Gerhardt mixture with acid and is easily purified by recrystallisation, the *trans*-isomer cannot be freed from the *cis*-compound by this process, and Verkade and van Roon [5]

* Part III, *J.*, 1960, 201.

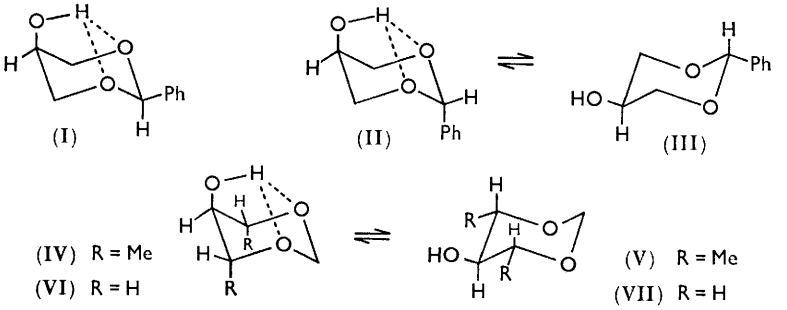
† Preliminary reports of part of this work have appeared in *Chem. and Ind.*, 1958, 1128, 1129.

[1] Fischer, *Ber.*, 1894, **27**, 1524.
[2] Irvine, Macdonald, and Soutar, *J.*, 1915, **107**, 337.
[3] Hill, Whelen, and Hibbert, *J. Amer. Chem. Soc.*, 1928, **50**, 2235.
[4] Davies, Heilbron, and Jones, *J.*, 1934, 1232.
[5] Verkade and van Roon, *Rec. Trav. chim.*, 1942, **61**, 831.
[6] Evans and Owen, *J.*, 1949, 244.
[7] Johary and Owen, *J.*, 1955, 1299.
[8] Gerhardt, Ger. P. 253,083, 1910; *Chem. Zentr.*, 1912, **83**, 1953.
[9] Hibbert and Carter, *J. Amer. Chem. Soc.*, 1929, **51**, 1601; Hibbert, Whelen, and Carter, *ibid.*, p. 302; Hibbert, Platt, and Carter, *ibid.*, p. 3644.
[10] Bergmann and Carter, *Z. physiol. Chem.*, 1930, **191**, 211.
[11] Helferich and Sieber, *Z. physiol. Chem.*, 1927, **170**, 31.
[12] Daubert and King, *J. Amer. Chem. Soc.*, 1938, **60**, 3003; Stimmel and King, *ibid.*, 1934, **56**, 1724; Daubert, *ibid.*, 1940, **62**, 1713; 1945, **67**, 1033; Daubert, Fricke. and Longenecker, *ibid.*, 1943, **65**, 1718; Martin, *ibid.*, 1953, **75**, 5482.

found that an equimolar mixture of the *cis*- and the *trans*-isomer crystallised as a molecular compound (m. p. 65—66°). We have found that mixtures of *cis*- and *trans*-1,3-*O*-benzylideneglycerol are readily separated by chromatography on alumina for which the isomer of m. p. 63—64° has the greater affinity. By analogy with the behaviour of the 4-phenylcyclohexanols on alumina, for which the *trans*-isomer has the greater affinity, the 1,3-*O*-benzylideneglycerol of m. p. 63—64° may thus be tentatively allocated the *trans*-configuration.

It is probable that the *O*-benzylideneglycerols reported in the literature [1,4,6,7] with m. p.s in the range 60—70° are mixtures of *cis*- and *trans*-isomers. Irvine, Macdonald, and Soutar [2] reported a crystalline 1,2-*O*-benzylideneglycerol but other workers have not been able to reproduce this result; crystalline derivatives of a 1,2-*O*-benzylideneglycerol are known [9] but their configuration has not been established.

The configurations of the 1,3-*O*-benzylideneglycerols were proved by infrared spectroscopic determination of the extent of intramolecular hydrogen-bonding. In $>0{\cdot}005$M-solutions of hydroxy-compounds in CCl_4 intermolecular hydrogen-bonding is negligible and, for secondary hydroxyl groups, absorption near 3630 and 3590 cm.$^{-1}$ may be associated [13] with free and intramolecularly bonded hydroxyl groups respectively. Further, the extent of bonding may be approximately assessed from the relative extinction coefficients for free and bonded hydroxyl groups.[14] Under these conditions 1,3-*O*-benzylideneglycerol, m. p. 84°, showed absorption, characteristic of bonded hydroxyl groups, at 3593 cm.$^{-1}$; absorption associated with free hydroxyl groups could not be detected. This indicates a *cis*-configuration for the cyclic acetal and a predominant existence in the conformation (I). The bulky phenyl group would be expected [15] to occupy an equatorial position with the hydroxyl group consequently in an axial position where hydrogen-bonding with the ring-oxygen atoms can occur. Accurate models reveal the close proximity of such an axial hydroxyl group to the ring oxygens. Replacement of the hydroxyl-hydrogen atom in *cis*-1,3-*O*-benzylideneglycerol with deuterium by multiple treatment with D_2O, markedly diminished the absorption at 3593 cm.$^{-1}$ and a new band at 2642 cm.$^{-1}$ (ε 79) appeared.



Surprisingly, perhaps, chromatographically homogeneous 1,3-*O*-benzylideneglycerol, m. p. 63—64°, showed absorption at 3633 and 3593 cm.$^{-1}$ indicative of free and bonded hydroxyl groups respectively, and the relative extinction coefficients (55 and 70) revealed extensive intramolecular hydrogen-bonding. If it is assumed that chair conformations are preferred,[15] this observation is consistent with a *trans*-cyclic acetal existing as an equilibrium of approximately equal proportions of the conformations (II) and (III). The absorption at 3633 cm.$^{-1}$ is near the value 3629 cm.$^{-1}$ given by Cole and Jefferies [14] as typical of secondary hydroxyl groups and thus confirms the ring-size of the cyclic acetal.

There was a marked diminution in the absorptions at 3633 and 3593 cm.$^{-1}$ on *O*-deuteration of *trans*-1,3-*O*-benzylideneglycerol and the appearance of strong absorptions at 2673

[13] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492; 1954, **76**, 4323.
[14] Cole and Jefferies, *J.*, 1956, 4391.
[15] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.

(ε 64) and 2642 cm.$^{-1}$ (ε 104) presumably due to free and bonded deuteroxyl groups. Stuart and Sutherland [16] have observed that, for methanol, ethanol, and hexan-1-ol in carbon tetrachloride, *O*-deuteration results in replacement of the OH absorption at 3640 cm.$^{-1}$ by OD absorption at 2670 cm.$^{-1}$.

The relative extinction coefficients of the OH and OD absorptions in *trans*-1,3-*O*-benzylideneglycerol indicate that the strengths of deuterium- and hydrogen-bonding are not grossly different. Other workers have reached a similar conclusion.[17]

Allsop *et al.*[18] have shown that, in the triterpene series, axial and equatorial free hydroxyl groups absorb respectively in the ranges 3629—3630 and 3637—3639 cm.$^{-1}$. Such a correlation seems unlikely to obtain for the 1,3-*O*-alkylideneglycerols since an axial 2-hydroxyl group will probably be completely bonded and further, since the monocyclic molecules are flexible, the precise steric location of a free hydroxyl group will be uncertain.

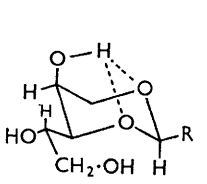
Maximum intramolecular hydrogen-bonding can occur only in the conformation (II) of *trans*-1,3-*O*-benzylideneglycerol which contains both the hydroxyl and the phenyl group in axial positions. The non-bonded interactions associated with the axial phenyl group in conformation (II) might result in some deformation of the chair structure but the extent would be difficult to assess and, moreover, it would adversely affect the intramolecular hydrogen bonding. The apparently high percentage of this conformation (II) in the equilibrium mixture suggests that the conformation must be considerably stabilised by intramolecular hydrogen-bonding. Other examples of this effect have been observed. Thus, 1,5-dideoxy-2,4-*O*-methyleneribitol shows [19] absorptions at 3645 (ε 109) and 3601 cm.$^{-1}$ (ε 35), indicating that the molecule exists as an equilibrium of the conformations (IV) and (V) with a significant percentage of the former. Conformation (IV) contains the sterically unfavourable arrangement of two methyl groups in 1,3-diaxial positions. A related effect has been observed [13] with cyclohexane-*cis*-1,3-diol which exhibits appreciable intramolecular bonding and must have the hydroxyl groups in 1,3-axial positions for this to occur. Also, 1,3-*O*-methyleneglycerol (VI—VII) exists predominantly in conformation (VI) in CCl_4 solution,[20] whereas in cyclohexanol the hydroxyl group is predominantly equatorial.[21]

The hydroxyl groups in conformations (I), (II), (IV), and (VI) are shown for convenience bonded to both ring oxygens, but whether a bifurcated hydrogen bond is present in the actual compounds is not known. Bifurcated hydrogen bonds have been postulated for certain crystal structures.[22] That both ring-oxygen atoms in conformations such as (II) are important in intramolecular-hydrogen bonding is suggested by the facts [20] that intramolecular hydrogen-bonding between the hydroxyl group and the ring-oxygen atom in tetrahydropyran-3-ol occurs to an extent of *ca.* 50% (ε 40 and 50 for free and bonded hydroxyl groups respectively), whereas the introduction of a second ring-oxygen atom to give 1,3-*O*-methyleneglycerol results in much more extensive intramolecular hydrogen-bonding (ε 20 and 100 for free and bonded hydroxyl groups respectively).

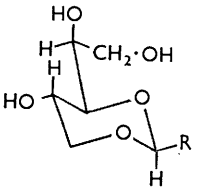
Recent work [23] has elegantly illustrated the influence of intramolecular hydrogen-bonding on certain reaction rates and patterns. It is possible that the course of reaction of aldehydes with certain polyhydric alcohols may be influenced similarly. Thus, the rationalisations [24] of the observed pattern of condensation of aldehydes and polyhydric

[16] Stuart and Sutherland, *J. Chem. Phys.*, 1956, **24**, 559; *J. Phys. Radium*, 1954, **15**, 321.
[17] Hoyer, *Z. phys. Chem.*, 1940, **45**, 389; *Naturwiss.*, 1938, **26**, 774; Davies, *Ann. Reports*, 1946, **43**, 5.
[18] Allsop, Cole, White, and Willix, *J.*, 1956, 4868.
[19] Barker, Foster, and Zweifel, unpublished results.
[20] Barker, Brimacombe, Foster, Whiffen, and Zweifel, *Tetrahedron*, 1959, **7**, 10.
[21] Pickering and Price, *J. Amer. Chem. Soc.*, 1958, **80**, 4931.
[22] Allbrecht and Corey, *J. Amer. Chem. Soc.*, 1939, **61**, 1087; cf. Hunter in "Progress in Stereochemistry," Butterworths, London, Vol. I, p. 228.
[23] Henbest and Wilson, *J.*, 1957, 1958; Henbest and Lovell, *J.*, 1957, 1965.
[24] Barker, Bourne, and Whiffen, *J.*, 1952, 3865; Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.

alcohols cannot account for the formation [25] of a 1,3-*O*-benzylidene and 1,3-*O*-methylene derivative (VIII) of D- or L-arabitol in preference to the corresponding 3,5-substituted derivatives (IX). From formulæ (VIII) and (IX) (L-arabitol series) it may be seen that



(VIII)



(IX)

the possibilities for intramolecular hydrogen-bonding are much greater in the 1,3- (VIII) than in the 3,5-derivative (IX) since the former contains an axial hydroxyl group in its 1,3-dioxan ring.

Treatment of *cis*-1,3-*O*-benzylideneglycerol with a boiling mixture of aluminium isopropoxide, propan-2-ol, and acetone for 4·5 days resulted in the formation of a mixture from which 59% of pure *cis*- and 18% of pure *trans*-isomer were recovered by chromatography on alumina. Under the same conditions, 57% of *cis*- and 35% of *trans*-isomer were recovered after treatment of *trans*-1,3-*O*-benzylideneglycerol. Decomposition may have contributed to the incomplete recovery of the cyclic acetals since they are hydrolysed under drastic alkaline conditions.[26] Although complete equilibration was not effected it is clear from the result with *trans*-1,3-*O*-benzylideneglycerol that the *cis*-isomer predominates in the equilibrium mixture. Eliel and Ro [27] found that aluminium isopropoxide-catalysed equilibration of the *cis*- and *trans*-forms of 4-t-butyl-, 4-methyl-, and 4-phenyl-cyclohexanol gave mixtures in which the *trans*-isomer predominated (69—81%). Thus, with 1,3-*O*-benzylideneglycerol, the predominance of the *cis*-isomer in the equilibrium mixture appears to be a consequence of intramolecular hydrogen-bonding.

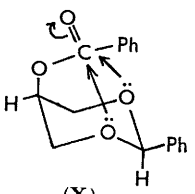
cis-1,3-*O*-Benzylideneglycerol with acetic anhydride and pyridine gave chromatographically homogeneous 2-*O*-acetyl-*cis*-1,3-*O*-benzylideneglycerol from which the parent alcohol was regenerated on saponification (Zemplén–Pacsu). Under similar conditions, *trans*-1,3-*O*-benzylideneglycerol, gave a mixture of 2-*O*-acetyl-*cis*- and -*trans*-1,3-*O*-benzylideneglycerol as the only detectable products; the acetates were readily separated by chromatography on alumina for which the *cis*-acetate had the greater affinity. The *trans*-*O*-acetate, which did not isomerise during chromatography on alumina, gave the chromatographically homogeneous parent alcohol on saponification. Variation of the conditions of acetylation of *trans*-1,3-*O*-benzylideneglycerol always gave a mixture in which the *cis*-*O*-acetate predominated. Treatment of the *trans*-*O*-acetate with acetic anhydride and pyridine and with the same mixture supplemented with benzene–hydrogen chloride did not yield any *cis*-*O*-acetate although only *ca.* 50% of the *trans*-*O*-acetate could be recovered. This suggests that *trans* ⟶ *cis*-isomerisation precedes acetylation. Although the tendency of *trans*-1,3-*O*-benzylideneglycerol to isomerise in the presence of acid has not been studied the *cis*-isomer is known [26] to be sensitive to acid and to be rapidly and predominantly converted into 1,2-*O*-benzylideneglycerol. However, treatment of *cis*- and *trans*-1,3-*O*-benzylideneglycerol with pyridine–benzene–hydrogen chloride at 30° for 24 hr. had little effect.

The failure of *cis*-1,3-*O*-benzylideneglycerol to yield any *trans*-*O*-acetate on treatment with acetic anhydride and pyridine could be explained if the rate of acetylation greatly exceeded that of isomerisation. Evidence has been obtained which suggests that intramolecular hydrogen-bonding in *cis*-1,3-*O*-benzylideneglycerol markedly enhances esterification rates. Thus the rate of esterification of *cis*-1,3-*O*-benzylideneglycerol by

[25] Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 1663; Zissis and Richtmyer, *ibid.*, 1954, **76**, 5515.
[26] Hibbert and Timm, *J. Amer. Chem. Soc.*, 1924, **46**, 1283.
[27] Eliel and Ro, *J. Amer. Chem. Soc.*, 1957, **79**, 5992.

p-phenylazobenzoyl chloride and pyridine is much greater [28] than that of *cis*- or *trans*-4-phenylcyclohexanol. This effect is being studied.

Attempts to equilibrate the *O*-acetates of *cis*- and *trans*-1,3-*O*-benzylideneglycerol by acid were unsuccessful. Bergmann and Carter [10] observed that condensation of benzaldehyde with 2-*O*-benzoylglycerol gave a high yield of 2-*O*-benzoyl-*cis*-1,3-*O*-benzylideneglycerol. Whilst hydrogen-bonding effects are precluded in this reaction, dipolar interaction between the carbonyl group and the ring-oxygen atoms (cf. X) could be responsible for the formation of the *cis*-*O*-benzoate since the effect would be most significant in this isomer.



(X)

Benzoylation and methylation of *cis*-1,3-*O*-benzylideneglycerol gave respectively only the *cis*-*O*-benzoate and *cis*-*O*-methyl ether, whereas both the *cis*- and the *trans*-compounds were formed from *trans*-1,3-*O*-benzylideneglycerol under the same conditions.[29]

As noted above, the affinity of *trans*-1,3-*O*-benzylideneglycerol for alumina is greater than that of the *cis*-isomer whereas the reverse is true for the respective *O*-acetates (and *O*-benzoates and *O*-methyl ethers [29]). Brooks, Klyne, and Miller [30] have shown that, in the steroid series, cases are known where axial acyloxy-compounds are adsorbed more strongly than their epimers by alumina. On mechanical grounds alone, the steric inaccessibility of axial groups [15] should tend to impede their interaction with alumina; although this is often the case, exceptions are known.[30]

Esters and ethers of *cis*- and *trans*-1,3-*O*-benzylideneglycerol may be readily distinguished and identified by nuclear magnetic resonance spectroscopy,[31] as will be described later.

Treatment of *cis*-1,3-*O*-benzylideneglycerol with sodium, sodium hydride, or sodamide followed by benzyl bromide gave 2-*O*-benzyl-*cis*-1,3-*O*-benzylideneglycerol whereas, under the same conditions, *trans*-1,3-*O*-benzylideneglycerol gave a mixture in which the *trans*-*O*-benzyl ether predominated. The *trans*-*O*-benzyl ether was hitherto unknown. The two ethers were readily separated by chromatography on alumina, and, as in the case of the acetates, the *cis*-isomer had the greater affinity for the adsorbent; the *trans*-isomer did not isomerise on alumina. The isomerisation which occurred on benzylation of *trans*-1,3-*O*-benzylideneglycerol was probably acid-catalysed and occurred after addition of the benzyl bromide since prolonged treatment of benzene solutions of *cis*- or *trans*-1,3-*O*-benzylideneglycerol with sodium did not effect isomerisation.

Acid-hydrolysis of the *O*-benzyl ethers yielded 2-*O*-benzylglycerol in each case, confirming that the cyclic acetals were six-membered. Attempts to prove the configuration of the *O*-benzyl ethers by selective removal of the benzyl group failed; for example, palladium-catalysed hydrogenolysis cleaved both the benzyl and the benzylidene residue. Hydrogenolysis of the benzylidene residue also occurred in the presence of platinum when efforts were made to saturate the aromatic ring in *cis*-1,3-*O*-benzylideneglycerol.

Solutions of the *cis*- and the *trans*-*O*-benzyl ether in benzene at 50° were equilibrated by hydrogen chloride, to yield in each case a mixture in which the ratio of *cis* : *trans* isomers was approximately 1 : 2, thus confirming the allocated structures. The *O*-benzyl group in the *trans*-isomer is equatorial and will experience non-bonded interactions with the hydrogen atoms on the neighbouring methylene groups, whereas in the *cis*-compound an axial *O*-benzyl group will interact with each ring oxygen (cf. Barker and Shaw [32]) and its axial lone pair of electrons since the lone pairs are tetrahedrally disposed.[33] From the

[28] Baggett and Foster, unpublished results.
[29] Dobinson and Foster, unpublished work.
[30] Brooks, Klyne, and Miller, *Biochem. J.*, 1953, **54**, 212; Shoppee, *J.*, 1946, 1138; Elks and Shoppee, *J.*, 1953, 241; Ruzicka, Meister, and Prelog, *Helv. Chim. Acta*, 1947, **30**, 867.
[31] Baggett, Dobinson, Foster, Lemieux, and Thomas, unpublished work.
[32] Barker and Shaw, *J.*, 1959, 584.
[33] Brown, Brewster, and Schechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467; French and Rasmussen, *J. Chem. Phys.*, 1946, **14**, 389.

reactions of carbanions [34] and the relative rotational energy barriers in propane and dimethyl ether [35] it appears that the steric requirement of a lone pair of electrons is similar to that of the hydrogen in a C–H group.[36] This being so and provided that intramolecular hydrogen bonding is precluded, the non-bonded interactions associated with an axial substituent in a cyclohexane ring and an axial 2-substituent in 1,3-*O*-methyleneglycerol (and its analogues) will be similar and will tend to direct the substituent to an equatorial position.

The ease of purification and characterisation of *cis*-1,3-*O*-benzylideneglycerol and its behaviour on acylation and etherification in yielding solely derivatives of *cis*-configuration enables the *cis*-configuration to be allocated with reasonable certainty to numerous derivatives prepared from this cyclic acetal. The configuration of derivatives prepared from 1,3-*O*-benzylideneglycerol of m. p. *ca.* 65° remains uncertain.

cis- and *trans*-1,3-*O*-Benzylideneglycerol were readily hydrolysed ($t_{\frac{1}{2}}$ 17 min.) by 0·02N-sulphuric acid at 35° at essentially the same rate.

Experimental

1,3-O-*Benzylideneglycerols*.—(*a*) *cis*-1,3-*O*-Benzylideneglycerol, m. p. 79·5—80·5°, was obtained in *ca.* 20% yield by Verkade and van Roon's method,[5] and recrystallised from benzene–light petroleum (b. p. 60—80°). The homogeneity was demonstrated by chromatography on alumina.

(*b*) In a modification of Bergmann and Carter's method,[10] a mixture of redistilled glycerol (121 g.), benzaldehyde (106 g.) and concentrated sulphuric acid (5 drops) was heated at 100° for 1 hr. periods successively at 10, 4, and 25 mm.; 0·60 mol. of water distilled. The cooled mixture was seeded with *cis*-1,3-*O*-benzylideneglycerol and stored at 0° for 2 days. The crystalline product was collected, dissolved in benzene, washed with aqueous ammonia, and recovered. Fractional crystallisation from benzene–light petroleum (b. p. 60—80°) and recrystallisation of each fraction from the same solvent system gave *cis*-1,3-*O*-benzylideneglycerol (17 g., 9·5%), m. p. 82—83·5°, and other fractions *A* (11·5 g., 6·4%), m. p. 60—63°, and *B* (9 g., 5%), m. p. 63—65°. The m. p.s of fractions similar to *A* and *B*, but from other experiments, were not significantly changed by repeated recrystallisation and the materials were shown to be heterogeneous by chromatography on alumina. The alumina used throughout was Peter Spence's Type H, treated at 70—80° with concentrated hydrochloric acid to pH 6·5 and stirred for 1 hr., then with 2% aqueous ammonia for 30 min. at 70—80°, and then washed free from chloride. The alumina was made into a slurry with 2N-acetic acid, filtered, dried at 120° overnight, and then heated at 600° for 3 hr. After addition of water (10% w/w) and shaking overnight, alumina of activity Brockmann III was obtained. Thus fraction *A* was found to contain 75% of *trans*-1,3-*O*-benzylideneglycerol, m. p. 59—64·5° (raised to 64·5—65·5° by recrystallisation), and 25% of the *cis*-isomer, m. p. 78—83° (83—84·5° after recrystallisation). On chromatography on alumina of artificial mixtures of the *cis*- and *trans*-1,3-*O*-benzylideneglycerols the *cis*-isomer emerged first on elution with benzene–ether (3 : 2 v/v), and the *trans*-isomer only when a more polar solvent mixture was used. Excellent separations and recoveries of the isomers from a mixture could be effected. The pure isomers did not isomerise on alumina and the *trans*-isomer isolated after chromatography was identical with that obtained by saponification [5] of 2-*O*-acetyl-*trans*-1,3-*O*-benzylideneglycerol.

(*c*) A continuous stream of air was drawn through a mixture of benzaldehyde (200 g.), glycerol (220 g.) and concentrated sulphuric acid (10 drops) at *ca.* 95°. Benzene (275 ml.) was added and the water (25 ml., *ca.* 70%) was removed azeotropically. The cooled mixture was seeded with *cis*-1,3-*O*-benzylideneglycerol and stored at 0° for 2 days. The crystalline product was collected, freed from acid as in (*b*), and fractionally crystallised from benzene–light petroleum (60—80°), to yield slightly impure *cis*-isomer (111 g., 32·5%), m. p. 70—78°, and a mixture of *cis*- and *trans*-compounds (92·9 g., 27%), m. p. 54—60°. The fractions were purified as required by chromatography on alumina. Method (*c*) proved the most convenient for the preparation of *trans*-1,3-*O*-benzylideneglycerol.

Treatment of the 1,3-O-*Benzylideneglycerols with Aluminium Isopropoxide*.—A solution of the 1,3-*O*-benzylideneglycerol (0·5 g.), acetone (0·1 ml.) and redistilled aluminium isopropoxide

[34] Roberts and Shoppee, *J.*, 1954, 3418.
[35] McCoubrey and Ubbelohde, *Quart. Rev.*, 1951, **5**, 364.
[36] Barton in "Perspectives in Organic Chemistry," Interscience, New York, 1956, p. 83.

(0·5 g.) in dry propan-2-ol (10 ml.) was boiled under reflux for 4·5 days (cf. Eliel and Ro [27]), the initially clear solution becoming turbid. The mixture was poured into N-sodium hydroxide (100 ml.) and extracted with ether (5 × 50 ml.). The combined and dried ($MgSO_4$) extracts were concentrated and the residue (0·4—0·45 g.) was chromatographed on alumina (15 g.).

In this way *trans*-1,3-*O*-benzylideneglycerol gave a product (0·429 g.) from which the *cis*- (0·244 g., 57%) and the *trans*-isomer (0·15 g., 35%) were recovered. Similarly *cis*-1,3-*O*-benzylideneglycerol gave a product (0·445 g.) from which the *trans*- (0·07 g., 18%) and the *cis*-isomer (0·250 g., 59%) were separated. The yields quoted are those before recrystallisation.

Benzylation of the 1,3-O-*Benzylideneglycerols*.—(*a*) *cis*-1,3-*O*-Benzylideneglycerol (1 g., m. p. 82°) in benzene (24 ml.) was boiled under reflux for 36 hr. in the presence of sodium wire (0·3 g.). To the cooled and decanted solution, benzyl bromide (1·4 g.) was added and the mixture was boiled under reflux for a further 16 hr. The cooled solution was washed twice with water to remove sodium bromide, dried ($MgSO_4$), and evaporated, and the residue recrystallised from light petroleum (b. p. 60—80°), to yield 2-*O*-benzyl-*cis*-1,3-*O*-benzylideneglycerol (0·74 g., 49%), m. p. 75·5—76·5° (Found: C, 75·8; H, 6·7. Calc. for $C_{17}H_{18}O_3$: C, 75·6; H, 6·7%). White [37] gives m. p. 77—78° and Porck and Craig [38] give m. p. 79—82°.

In two parallel experiments benzyl bromide which had been stored over anhydrous potassium carbonate was used and the crude product was chromatographed on alumina. A single benzyl ether, m. p. 75—76°, was obtained (yield 49—60%).

Replacement of the sodium in the above experiments with sodium hydride gave a low yield (13—32%) of the *cis*-*O*-benzyl ether whereas the use of sodamide gave a yield of *ca.* 50%.

(*b*) *trans*-1,3-*O*-Benzylideneglycerol (0·5 g.; m. p. 64·5—65°) was treated with sodamide (0·12 g.) and benzyl bromide (0·7 g.) as in (*a*). Chromatography of the crude product (0·45 g.) on alumina (20 g.) gave 2-*O*-benzyl-*trans*-1,3-*O*-benzylideneglycerol (0·27 g., 35%), m. p. 91—92° [from light petroleum (b. p. 60—80°)] [Found: C, 75·55; H, 6·9%; *M*, 305, 318 (Rast in camphor). $C_{17}H_{18}O_3$ requires C, 75·6; H, 6·7%; *M*, 270]. The *trans*-isomer emerged first on elution with light petroleum (b. p. 60—80°)–benzene (7 : 3 v/v); the *cis*-isomer (0·16 g., 21%) m. p. 75—77°, was eluted with a more strongly polar solvent mixture. The *trans*-benzyl ether did not isomerise during chromatography on alumina.

Benzylation of *trans*-1,3-*O*-benzylideneglycerol (0·5 g., m. p. 64·5—65°) with sodium and benzyl bromide, as in (*a*), improved the yields of both products, *e.g.*, *trans*-*O*-benzyl ether (0·378 g., 50%), m. p. 91—91·5°, and *cis*-*O*-benzyl ether (0·273 g., 36%), m. p. 77—78°.

trans-1,3-*O*-Benzylideneglycerol was recovered unchanged after treatment with sodium and benzene.

Acid-hydrolysis of the 2-O-*Benzyl*-1,3-O-*benzylideneglycerols*.—A solution of the *trans*-*O*-benzyl ether (2 g.; m. p. 85—86°) in methanol (24 ml.) and 4N-hydrochloric acid (8 ml.) was boiled under reflux for 1 hr. The cooled and filtered mixture was diluted with water (150 ml.) and freed from benzaldehyde by extraction with light petroleum (b. p. 60—80°). The mixture was then extracted with chloroform, and the combined extracts were dried ($MgSO_4$) and concentrated. Distillation of the residue gave 2-*O*-benzylglycerol (0·663 g., 49%), b. p. 140° (bath)/0·05 mm., m. p. 38—40° (Found: C, 66·9; H, 7·6. Calc. for $C_{10}H_{14}O_3$: C, 66·0; H, 7·7%). Porck and Craig [38] give m. p. 37—39°.

Similar hydrolysis of 2-*O*-benzyl-*cis*-1,3-*O*-benzylideneglycerol (88·5 g.; m. p. 73—75°) gave 2-*O*-benzylglycerol (42 g., 70%), b. p. 130—136° (bath)/0·05 mm., which solidified when seeded with the product described above.

Hydrolysis of the *cis*-*O*-benzyl ether by *p*-nitrophenylhydrazine according to Karrer's method [39] gave a low yield (3·9%) of 2-*O*-benzylglycerol.

Hydrogenolysis of 2-O-*Benzyl*-cis-1,3-O-*benzylideneglycerol*.—Attempts to hydrogenolyse selectively the benzyl group in 2-*O*-benzyl-*cis*-1,3-*O*-benzylideneglycerol were unsuccessful. *E.g.*, the *cis*-*O*-benzyl ether (1 g.), hydrogenated in presence of 2% palladised charcoal (2 g.) in methanol (35 ml.), gave only glycerol, isolated as tri(naphthylcarbamate), m. p. 191—192° (from ethanol).

Acid-equilibration of the 2-O-*Benzyl*-1,3-O-*benzylideneglycerols*.—A solution of chromatographically homogeneous 2-*O*-benzyl-1,3-*O*-benzylideneglycerol (0·1 g.) in dry benzene (10 ml.) which was 0·2N with respect to hydrogen chloride at room temperature was stored under anhydrous conditions at 50° for 66 hr. The solution was then quickly washed with aqueous

[37] White, *J. Amer. Chem. Soc.*, 1952, **74**, 3451.
[38] Porck and Craig, *Canad. J. Chem.*, 1955, **33**, 1286.
[39] Karrer, *Helv. Chim. Acta*, 1954, **37**, 381.

ammonia, dried ($MgSO_4$), and evaporated. The residue was chromatographed on alumina (15 g.). Thus, 2-*O*-benzyl-*cis*-1,3-*O*-benzylideneglycerol (m. p. 78°) gave the *trans*-isomer (73 mg., 73%), m. p. 92°, and the *cis*-isomer (33 mg., 33%), m. p. 75°. 2-*O*-Benzyl-*trans*-1,3-*O*-benzylideneglycerol (m. p. 91—91·5°) gave the *trans*-isomer (68 mg., 66%) and the *cis*-isomer (35 mg., 35%).

Acetylation of the 1,3-O-*Benzylideneglycerols.*—(*a*) *trans*-1,3-*O*-Benzylideneglycerol (0·2 g.) in pyridine (0·245 g.) was treated with acetic anhydride (0·2 g., 1·76 mol.) at 18° for 13 hr., then poured into ice-water; the precipitate was collected, dissolved in chloroform, washed successively with ice-cold N-hydrochloric acid, 10% aqueous cadmium chloride, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated. The residue (0·225 g., 92%) was chromatographed on alumina (10—15 g.). 2-*O*-Acetyl-*trans*-1,3-*O*-benzylideneglycerol (0·028 g., 17%), m. p. 115—116°, emerged first on elution with light petroleum (b. p. 60—80°)–benzene (3 : 1 v/v); the *cis*-*O*-acetate (0·134 g., 73%), m. p. 99—100°, was eluted by a more polar solvent mixture. The *trans*-*O*-acetate was not isomerised by chromatography on alumina. The ratio of *cis* : *trans*-acetates in the above experiment was 4·8 : 1 and in two parallel experiments carried out at 40° the ratios were 1·4 : 1 and 2·5 : 1.

In separate experiments at 40°, 2-*O*-acetyl-*trans*-1,3-*O*-benzylideneglycerol was treated with (*a*) an acetylating mixture similar to that described above and (*b*) the same mixture supplemented by a small amount of a 0·2N-solution of hydrogen chloride in benzene. Although no *cis*-*O*-acetate was detected by chromatography on alumina after these treatments the *trans*-*O*-acetate could be recovered in only *ca.* 50% yield.

(*b*) A mixture of *cis*-1,3-*O*-benzylideneglycerol (0·2 g.), pyridine (0·242 g.), and acetic anhydride (0·2 g.) was stored at 18° and worked up as in (*a*). Chromatography of the crude product (0·181 g., 73%) on alumina revealed that it contained only the *cis*-*O*-acetate, m. p. 100—101° [from benzene–light petroleum (b. p. 60—80°)].

Attempts to equilibrate the acetates in benzene solution containing dry hydrogen chloride were unsuccessful.

Deacetylation of the 2-*O*-*Acetyl*-1,3-*O*-*benzylideneglycerols.*—A solution of chromatographically homogeneous 2-*O*-acetyl-*cis*-1,3-*O*-benzylideneglycerol (0·187 g.; m. p. 99·5—100°) in dry methanol (5 ml.) was treated with a trace of clean sodium (Zemplén–Pacsu). After 1 day the solution was treated with water (*ca.* 0·5 ml.), neutralised with carbon dioxide, and filtered. After evaporation of the filtrate the dry residue (0·13 g., 86%, yield reduced by spillage) was chromatographed on alumina; it contained only *cis*-1,3-*O*-benzylideneglycerol, m. p. 79—81° before recrystallisation.

Under the same conditions 2-*O*-acetyl-*trans*-1,3-*O*-benzylideneglycerol (0·125 g.; m. p. 115—116°) gave a crude product (0·098 g., 97%) which gave only *trans*-1,3-*O*-benzylideneglycerol, m. p. 57—62° (before recrystallisation), on chromatography on alumina.

Infrared Spectra.—These were measured in 2 cm. layers in CCl_4 solution (~0·005M) with a grating of 2500 lines/in.[2] used in the fourth order on the spectrometer previously described.[40] The extinction coefficients, ε, are maximum values, and are equal to $(1/cl) \log_{10} (I_0/I)$ with l in cm. and c in moles/l., and are accurate to ±10. See also the comments in ref. 20.

The cyclic acetals were deuterated by addition of D_2O (0·5 ml.) to a weighed amount (*ca.* 8 mg.) of the hydroxy-derivative in a special vitreosil cell (Thermal Syndicate). The cell, which had a 2 cm. path-length, and a volume of 10 ml., was fitted with a stopcock. After 0·5 hr. at room temperature excess of D_2O and H_2O was removed by freeze-drying. The process was repeated twice and the cell then filled with dry CCl_4. Operations (except freeze-drying) were performed in a dry-box.

Acid-hydrolysis of the 1,3-O-*Benzylideneglycerols.*—Separate solutions of each cyclic acetal (100 mg.) in 0·02N-sulphuric acid (50 ml.) were kept at 35°. The glycerol content in aliquot parts (5 ml.) was determined, after neutralisation with sodium hydrogen carbonate, by periodate according to Jackson's method.[41] Both the *cis*- and the *trans*-isomer yielded glycerol at approximately the same rate; the following is a typical result.

Time (min.)	3	5	10	15	20	30	45	61	76
Hydrolysis (%)	13	16·5	35·5	45	55	71	83·5	91	99

$t_{\frac{1}{2}}$ 17 min.

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[40] Spedding and Whiffen, *Proc. Roy. Soc.*, 1956, *A*, **238**, 245.
[41] Jackson, "Organic Reactions," 1944, Vol. II, p. 361.