521. *Aspects of Stereochemistry. Part V.* Some Properties of* 1,2-O-*Methyleneglycerol and Related Compounds.*

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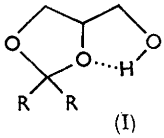
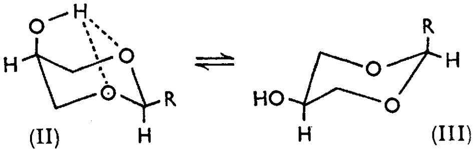
The extent of intramolecular hydrogen-bonding in 1,2-*O*-methyleneglycerol and in a series of related compounds has been determined and the results are considered in the light of the reaction patterns of aldehydes with glycerol and higher polyhydric alcohols. The cyclic acetals are readily characterised as *p*-phenylazobenzoates (azoates). The stability of 1,2- and 1,3-*O*-methyleneglycerol towards acidic hydrolysis has been measured.

It has been found[1] that, in carbon tetrachloride solution at a suitable concentration, the hydroxyl group in tetrahydrofurfuryl alcohol is completely hydrogen-bonded (bonded), intramolecularly, to the ring oxygen; an analogous acyclic compound, 2-ethoxyethanol, is also completely bonded.[2] However, the hydroxyl group in 1,2-*O*-isopropylideneglycerol (I; R = Me) is only partly bonded since infrared absorptions for both free and bonded hydroxyl groups have been found.[1] In order to ascertain whether bonding in 1,2-*O*-isopropylideneglycerol is sterically hindered by one of the *gem*-dimethyl groups the series of 1,2-*O*-cyclic ketals of glycerol shown in the Table were prepared and their infrared spectra in the hydroxyl stretching region examined.


(I)


(II) (III)

Infrared spectral data on certain alcohols and analytical data on their p-*phenylazobenzoates.*

No.	Glycerol derivatives	$\nu_{max.}$ (cm.$^{-1}$) and (ε) Free OH	Bonded OH	Δν[a]
1	1,2-*O*-Methylene	3646 (32)	3608 (59)	38
2	1,2-*O*-Isopropylidene	3647 (25)[b]	3608 (49)[b]	39
3	1,2-*O*-3′-Pentylidene	3645 (16)	3606 (45)	39
4	1,2-*O*-Diphenylmethylene	3642 (31)	3601 (57)	41
5	1,2-*O*-Cyclopentylidene	3645 (13)	3600 (37)	45
6	1,2-*O*-Cyclohexylidene	3645 (22)	3605 (53)	40
7	1,2-*O*-Cycloheptylidene	3644 (19)	3605 (41)	39
8	1,2-*O*-Cyclo-octylidene	3640 (16)	3603 (40)	37
9	1,3-*O*-Methylene	3635 (21)	3594 (100)	41

	p-*Phenylazobenzoate*								
				Found (%)			Required (%)		
No.	Yield (%)	M. p.	Formula	C	H	N	C	H	N
1	70	108—110°	$C_{17}H_{16}N_2O_4$	65·5	5·4	8·8	65·4	5·2	9·0
2	63	81—82	$C_{19}H_{20}N_2O_4$	67·0	5·9	8·1	67·0	5·9	8·2
3	54	55—57	$C_{21}H_{24}N_2O_4$	68·4	6·65	7·2	68·5	6·5	7·6
4	84	137—138	$C_{29}H_{26}N_2O_4$	74·1	5·3	5·6	75·0	5·2	6·0
5	54	75—77	$C_{21}H_{22}N_2O_4$	68·8	6·3	7·3	68·85	6·0	7·65
6	60	101—103	$C_{22}H_{24}N_2O_4$	69·55	6·3	7·1	69·5	6·3	7·4
7	57	96—98	$C_{23}H_{26}N_2O_4$	70·1	6·5	6·8	70·0	6·6	7·1
8	43	95—96	$C_{24}H_{28}N_2O_4$	70·8	6·9	6·7	70·55	6·9	6·9
9	64	175—176	$C_{17}H_{16}N_2O_4$	65·6	5·1	8·8	65·4	5·1	9·0

[a] Arithmetical difference between $\nu_{max.}$ for free and bonded hydroxyl groups (cf. Kuhn [2]). [b] Data from ref. 1.

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* Part IV, preceding paper.

[1] Barker, Brimacombe, Foster, Whiffen, and Zweifel, *Tetrahedron*, 1959, **7**, 10.

[2] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74** 2492; 1954, **76**, 4323.

The 1,2-*O*-cyclic ketals were prepared by acid-catalysed condensation of the appropriate ketone with glycerol;[3] 1,3-*O*-cyclic ketals are not formed under these conditions[4] and are obtained only by indirect methods.[5] 1,2-*O*-Cyclo-octylideneglycerol was hitherto unknown. Direct reaction of formaldehyde with glycerol yields[6] a mixture of 1,2- and 1,3-*O*-methyleneglycerol which may be separated as the benzoates or *p*-nitrobenzoates. Since these esters of 1,2-*O*-methyleneglycerol are difficult to crystallise an alternative synthesis of the cyclic acetal was devised. 1-*O*-Benzylglycerol[7] which could be characterised as the di-(*p*-phenylazobenzoate), condensed readily with formaldehyde in the presence of hydrogen chloride, to yield 1-*O*-benzyl-2,3-*O*-methyleneglycerol. The benzyl group was removed from this compound by palladium-catalysed hydrogenolysis,[8] to yield 1,2-*O*-methyleneglycerol.

Mixtures of 1,2- and 1,3-*O*-methyleneglycerol could not be separated by vapour-phase chromatography or as the *p*-phenylazobenzoates (azoates) or ferrocenecarboxylates by chromatography on alumina.

All the alcohols in the Table readily gave crystalline azoates, exemplifying the value of this derivative for characterisation.[9]

For primary alcohols in $\not> 0{\cdot}005$M-carbon tetrachloride solution, intermolecular hydrogen-bonding is negligible and the infrared absorption at *ca.* 3640 and 3600 cm.$^{-1}$ may be associated respectively with free and intramolecularly bonded hydroxyl groups.[1,2] Further, the proportion of free and bonded hydroxyl groups may be assessed approximately from the relative extinction coefficients (ε) for the respective absorptions.[10] 1,2-*O*-Methyleneglycerol showed absorption at 3608 (ε 59) and 3646 cm.$^{-1}$ (ε 32), indicating that, unlike those in tetrahydrofurfuryl alcohol and 2-ethoxyethanol, a significant percentage of the hydroxyl groups are not bonded. Moreover, closely similar absorptions were observed for the series of 1,2-*O*-cyclic ketals shown in the Table where the bulk of R in formula (I) varies considerably (H, Me, Et, Ph, etc.). Thus, there is no significant steric hindrance of intramolecular hydrogen-bonding by the groups attached to the acetal carbon in these compounds. The similarity of the absorptions for 1,2-*O*-diphenylmethyleneglycerol on the one hand and the aliphatic 1,2-*O*-cyclic ketals on the other suggests that the bonding in these compounds is largely independent of electronic effects at the acetal carbon. The similar $\Delta\nu$ values indicate[2,10] that the intramolecular hydrogen-bonds are of similar strength.

Neither 1,2- nor 1,3-*O*-methyleneglycerol has a completely bonded hydroxyl group, and values of the relevant extinction coefficients suggest that there are significant proportions of free and bonded hydroxyl groups in each cyclic acetal. If chair conformations are preferred,[11] then the presence of free and bonded hydroxyl groups in carbon tetrachloride solutions of 1,3-*O*-methyleneglycerol is a reflection of the conformational equilibrium (II) $\rightleftharpoons$ (III) (R = H). The hydroxyl group in conformation (II) is, for convenience, shown bonded to both ring oxygen atoms, but whether this is really the case is not known although bifurcated hydrogen bonds have been postulated in other connections.[12] Introduction of a suitably located substituent (*e.g.*, R = Me, Et, Pr^{i}, and Ph) into

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[3] Boekelheide, Liberman, Figueras, Krespan, Pennington, and Tarbell, *J. Amer. Chem. Soc.*, 1949, **71**, 3303.

[4] Hibbert and Morazain, *Canad. J. Res.*, 1930, **2**, 35, 214.

[5] Bergmann and Carter, *Z. physiol. Chem.*, 1930, **191**, 211.

[6] Hibbert and Carter, *J. Amer. Chem. Soc.*, 1928, **50**, 3120.

[7] Schmidt and Blank, *Chem. Ber.*, 1956, **89**, 283.

[8] McCloskey, *Adv. Carbohydrate Chem.*, 1957, **12**, 137.

[9] Reich, *Compt. rend.*, 1939, **208**, 748; *Biochem. J.*, 1939, **33**, 1000; Coleman, Farnham, and Miller, *J. Amer. Chem. Soc.*, 1942, **64**, 1501; Coleman and McCloskey, *ibid.*, 1943, **65**, 1589; Coleman, Rees, Sundberg, and McCloskey, *ibid.*, 1945, **67**, 381; Mertzweiller, Carney, and Farley, *ibid.*, 1943, **65**, 2367; Boissonnas, *Helv. Chim. Acta*, 1947, **30**, 1689, 1703; Woolfolk, Beach, and McPherson, *J. Org. Chem.*, 1955, **20**, 391.

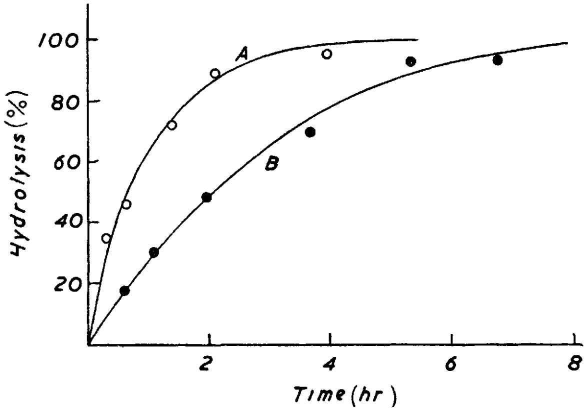
[10] Cole and Jefferies, *J.*, 1956, 4391.

[11] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.

[12] Albrecht and Corey, *J. Amer. Chem. Soc.*, 1939, **61**, 1087; cf. Hunter in " Progress in Stereochemistry," Butterworths, London, Vol. I, p. 228.

(II) $\rightleftharpoons$ (III) to yield *cis*-1,3-*O*-alkylideneglycerols, causes the molecules to exist predominantly, if not exclusively in conformation (II) since absorption for free hydroxyl groups cannot be detected in solutions of these cyclic acetals in carbon tetrachloride.[13] On the other hand, 1,2-*O*-methyleneglycerol contains the relatively rigid 1,3-dioxolan ring and although the ring has limited flexibility,[14] there cannot be gross differences between the various conformations. Thus, the presence of free hydroxyl groups indicates incomplete bonding and not a mixture of conformations separately containing free and completely bonded hydroxyl groups. It is not apparent why bonding is complete in 2-ethoxyethanol and tetrahydrofurfuryl alcohol, but not in 1,2-*O*-methyleneglycerol. It is possible that differences in molecular geometry may be involved together with a transannular effect of the second ring oxygen.

The reaction pattern of aldehydes with glycerol differs significantly from that observed for the higher polyhydric alcohols. Tetritols must be excepted from this generalisation since the structure of the cyclic acetal derivatives is unknown.[15] Aldehydes react with pentitols and higher polyhydric alcohols,[15] to yield six-membered in preference to five-membered cyclic acetals and this behaviour has been rationalised.[16] On the other hand, and with one exception, at equilibrium of the acid-catalysed glycerol–aldehyde reaction the proportion of five-membered cyclic acetals always markedly exceeds that of the six-membered analogues providing that the reaction mixtures remain liquid. This result has been observed for a range of aldehydes [17,18] and for different reaction temperatures.[19] With the *O*-methyleneglycerols, acid-equilibration yielded [6] a mixture in which the six-membered cyclic acetal predominated, but it was not stated to what extent. If molar proportions of aldehyde, ethane-1,2-diol and propane-1,3-diol are acid-equilibrated, the ratio of five- to six-membered cyclic acetals is approximately 1 : 2. The predominance of the six-membered cyclic acetal would be expected from the relative stabilities of five- and six-membered rings.



Rate of hydrolysis of 1,2- (*A*) *and* 1,3-O-*methyleneglycerol* (*B*) *for approximately* 1% *solutions in* N-*sulphuric acid at* 89°. $t_{\frac{1}{2}}$ *are*: *A*, 42 *min.*; *B*, 129 *min.*

Although intramolecular hydrogen-bonding may determine the reaction pattern of certain higher polyhydric alcohols with aldehydes (see preceding Part) it is unlikely to be the main determinant in the case of glycerol. Were this so, then, on the basis of the extent of bonding in carbon tetrachloride solutions, the *cis*-1,3-*O*-alkylideneglycerols would be the expected major products, since these are probably the only completely

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[13] Baggett and Foster, unpublished results quoted in ref. 1.
[14] Barker, Bourne, Pinkard, and Whiffen, *J.*, 1959, 802.
[15] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 137.
[16] Barker, Bourne, and Whiffen, *J.*, 1952, 905; Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.
[17] Hill, Whelen, and Hibbert, *J. Amer. Chem. Soc.*, 1928, **50**, 2235.
[18] Trister and Hibbert, *Canad. J. Res.*, 1936, **14**, *B*, 415.
[19] van Roon, *Rec. Trav. chim.*, 1929, **48**, 175.

bonded cyclic acetal derivatives of glycerol. For example, among the *O*-benzylideneglycerols the *cis*-1,3-cyclic acetal is completely bonded whereas the *trans*-isomer is not.[20] Although the data for the 1,2-*O*-benzylideneglycerols are not available it is unlikely that the extent of bonding would differ significantly from that in either 1,2-*O*-methylene- or 1,2-*O*-diphenylmethylene-glycerol. A mixture of *cis*- and *trans*-1,2-*O*-ethylideneglycerol showed absorptions at 3610 (ε 62) and 3644 cm.$^{-1}$ (ε 36). However, the concentrations of components in the reaction mixture of an aldehyde and glycerol are much greater than in the carbon tetrachloride solutions employed for spectral determinations, so that intermolecular hydrogen bonding could be involved in determining the reaction pattern (cf. Kuhn [2]).

The *cis–trans*-1,2-*O*-ethylideneglycerol mixture was prepared by the reaction of acetaldehyde with 1-*O*-benzylglycerol followed by catalytic hydrogenolysis. A mixture of isomers was expected on analogy with the reaction [21] of acetaldehyde with propane-1,2-diol which yields a mixture of *cis*- and *trans*-2,4-dimethyl-1,3-dioxolan, each of which on acid-equilibration is converted into a mixture containing *ca.* 65% of the *cis*-isomer.[22] There is no *a priori* reason to expect the exclusive formation of one isomer. The 1,2-*O*-ethylideneglycerol mixture could not be separated as the azoates by chromatography on alumina, but the m. p. variation and crystal habits of the ester were strongly indicative of a mixture.

From the properties of the *O*-methylene derivatives of the higher polyhydric alcohols [15] it is clear that six-membered are more stable than five-membered rings. In conformity with this reaction pattern is the greater rate of acid-hydrolysis of 1,2- than of 1,3-*O*-methyleneglycerol (see Figure). It is interesting to compare the acid conditions necessary to hydrolyse 1,3-*O*-methyleneglycerol (N-sulphuric at 89°, $t_{\frac{1}{2}}$ 129 min.) and the 1,3-*O*-benzylideneglycerols (0·02N-sulphuric acid at 35°, $t_{\frac{1}{2}}$ 17 min.) since these compounds effectively reflect the extremes of acid-lability and -stability encountered among carbohydrate cyclic acetals.[15]

EXPERIMENTAL

1,2-O-*Methyleneglycerol.*—1-*O*-Benzylglycerol, b. p. 130—134°/0·1 mm., prepared by Schmidt and Blank's [7] method gave a *di-*(p-*phenylazobenzoate*), m. p. 132—134° (Found: C, 72·6; H, 4·9; N, 9·05. $C_{36}H_{30}O_5N_4$ requires C, 72·1; H, 5·0; N, 9·4%).

Dry hydrogen chloride was passed for 15 min. into a mixture of 1-*O*-benzylglycerol (36 g.) and paraformaldehyde (10 g.), and the mixture stored at 120° overnight. Excess of formaldehyde and hydrogen chloride were removed at 100°/12—15 mm., and the residue was fractionally distilled, to yield 1-O-*benzyl*-2,3-O-*methyleneglycerol* (25·8 g., 66%), b. p. 91—94°/0·03 mm., n_D^{25} 1·5104 (after redistillation) (Found: C, 68·0; H, 7·4. $C_{11}H_{14}O_3$ requires C, 68·4; H, 7·2%). Storage of the compound in a stoppered bottle in the dark resulted in the development of the odour of benzaldehyde.

A solution of 1-*O*-benzyl-2,3-*O*-methyleneglycerol (5 g.) in ethanol (100 ml.) was shaken in hydrogen at a slight overpressure in the presence of palladium–barium sulphate.[23] After hydrogen uptake (595 ml. Calc. 650 ml.) was complete, the catalyst was removed, the filtrate was concentrated, and the residue distilled to yield 1,2-*O*-methyleneglycerol (1 g., 40%), b. p. 86—88°/12—15 mm., n_D^{25} 1·4482 (Found: C, 46·6; H, 7·85. Calc. for $C_4H_8O_3$: C, 46·15; H, 7·8%). Hibbert and Carter [6] record b. p. 84—85°/11 mm., n_D^{20} 1·4477, for the same compound prepared by hydrolysis of its benzoate.

Preparation of Azoates and Ferrocenecarboxylates.—The azoates recorded in the Table and elsewhere were prepared by essentially the method of Woolfolk *et al.*[9]

The ferrocenecarboxylates were prepared by the following general method.[24] A solution

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[20] Brimacombe, Foster, and Stacey, *Chem. and Ind.*, 1958, 1228; Baggett, Brimacombe, Foster, Stacey, and Whiffen, preceding paper.

[21] Lucas and Guthrie, *J. Amer. Chem. Soc.*, 1950, **72**, 5490.

[22] Barker, Bourne, Pinkard, Stacey, and Whiffen, *J.*, 1958, 3232.

[23] Mozingo, *Org. Synth.*, 1946, **26**, 77.

[24] Baggett and Foster, unpublished method.

of ferrocenecarboxylic acid [25] [0·1 g.; m. p. 160—170° (decomp.)] in dry benzene (1·1 ml.) was stirred at room temperature for 2 hr. with phosphorus pentachloride (100 mg.). The mixture was then filtered, and benzene was removed from the filtrate by freeze-drying. A solution of the alcohol (*ca.* 80 mg.) in dry pyridine (1·1 ml.) was added to the residue, and the mixture was stored overnight at room temperature. The mixture was then poured into water and extracted with chloroform, and the extract was washed successively with ice-cold N-hydrochloric acid, 10% aqueous cadmium chloride, and water. Ferrocenecarboxylic acid was removed by passage of the chloroform solution through a short column of alumina and elution with the same solvent. Evaporation of the eluate gave the ester.

In this way 2-O-*ferrocenecarbonyl*-1,3-O-*methyleneglycerol* (35%), m. p. 110—112° (Found: C, 57·0; H, 5·1. $C_{15}H_{16}FeO_4$ requires C, 57·0; H, 5·1%), and 3-O-*ferrocenecarbonyl*-1,2-O-*methyleneglycerol* (17%), m. p. 42—44° (Found: C, 57·2; H, 4·9%), were prepared.

cis,trans-1,2-O-*Ethylideneglycerol.*—Acetaldehyde (9 g.) was passed into a mixture of 1-*O*-benzylglycerol (38 g.) and a few drops of concentrated sulphuric acid. The mixture was neutralised with solid potassium carbonate and then distilled, to yield 1-O-*benzyl*-cis,trans-2,3-O-*ethylideneglycerol* (34·3 g., 81%, b. p. 94—100°/0·3 mm., n_D^{22} 1·5023 (Found: C, 68·9; H, 7·6. $C_{12}H_{16}O_3$ requires C, 69·1; H, 7·7%).

A solution of the foregoing *O*-benzyl ether mixture (33·5 g.) in dry ethanol (150 ml.) was hydrogenolysed as described above, to yield *cis,trans*-1,2-*O*-ethylideneglycerol, b. p. 90—92°/12 cm., $n_D^{27.5}$ 1·4360 (Found: C, 50·95; H, 8·6. Calc. for $C_5H_{10}O_3$: C, 50·9; H, 8·5%). Hill, Hill, and Hibbert [26] record b. p. 68—70°/1 mm., n_D^{17} 1·4413 for the product obtained by saponification of the oily benzoate.

cis,trans-1,2-*O*-Ethylideneglycerol readily gave a crystalline p-*phenylazobenzoate*, m. p. 67—76° (Found: C, 66·4; H, 5·8. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·5%). Attempted fractionation of the azoate on alumina (approx. Brockmann III in activity) gave a series of fractions all with m. p. *ca.* 65—75°. Recrystallisation of the azoate resulted in the simultaneous formation of two apparently distinct crystal types which, however, could not be satisfactorily separated.

Preparation of Cyclic Ketals.—The cyclic ketals recorded in the Table were prepared essentially by the method of Boekelheide *et al.*; [3] 1,2-O-*cyclo-octylideneglycerol* had b. p. 97—99°/0·1 mm., n_D^{19} 1·4896 (Found: C, 66·25; H, 10·3. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%).

Infrared Spectra.—These were measured in 2 cm. layers in CCl_4 solution with a grating having a 2500 lines per inch used in the third or fourth order on the spectrometer previously described.[27] The concentration of the cyclic acetal was approximately 0·005M; 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. It would be unwise to assume that the extinction coefficients of bonded and free hydroxyl groups are identical either in one molecule or between molecules, so that accurate values are not available for the proportion of each although they are certainly of comparable magnitude.

Acid-hydrolysis of the O-*Methyleneglycerols.*—A solution (50 ml.) of the *O*-methyleneglycerol (0·52 g., 5 mmoles) in N-sulphuric acid was stored at 89°. Aliquot parts (5 ml.) withdrawn at suitable time intervals were neutralised with sodium hydrogen carbonate, and the volume then adjusted to 50 ml. after addition of 0·25M-sodium metaperiodate (5 ml.). After 5 min. the consumption of periodate was determined on an aliquot part (5 ml.) by Jackson's [28] method of addition of excess of standard arsenite and back-titration with iodine. The results are shown in the Figure.

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[25] Rineheart, Motz, and Sung Moon, *J. Amer. Chem. Soc.*, 1957, **79**, 2753.
[26] Hill, Hill, and Hibbert, *J. Amer. Chem. Soc.*, 1928, **50**, 2242.
[27] Spedding and Whiffen, *Proc. Roy. Soc.*, 1956, *A*, **238**, 245.
[28] Jackson, " Organic Reactions," 1944, Vol. II, p. 361.