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The Preparation and Configuration of D(−)-4,5-Dimethyl-1,3-dioxolane[1]

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The configuration of the formal of D(−)-2,3-butanediol has been established unequivocably by reactions of the diol under basic conditions with methylene iodide, methylene chloride, and chloromethyl acetate. The products are optically active, are alike and are the same as the one obtained in the acid-catalyzed reaction of the glycol with formaldehyde. Neither of the two Alk–O bonds is cleaved during formation of the formal in the reaction between formaldehyde and the glycol. Thus there is no possibility that either a carbonium ion or an S_N2 mechanism operates at either asymmetric carbon atom. A similar conclusion is drawn in regard to the acid catalyzed hydrolysis of the formal.

When optically active 4,5-dimethyl-1,3-dioxolane (the formal of D(−)-2,3-butanediol) is prepared by the action of formaldehyde on active 2,3-butanediol,[3] its configuration is not unequivocably established by this reaction because of the possibility, however remote, that there may be two inversions, one at each asymmetric carbon atom.[4] One inversion only is ruled out as a possibility because in such a case the product would be optically inactive formal, a derivative of the *meso*-form of the glycol.

The formal has been prepared from a salt of the glycol with three different reagents, *viz.*, methylene iodide,[5] methylene chloride and chloromethyl acetate. Methylene iodide was tried first but without production of formal. Under very strongly basic conditions this appears to be due in part to a reduction reaction producing D(−)-*threo*-3-methoxy-2-butanol with concurrent formation of iodine. Methylene chloride surprisingly enough gave much better results (49% of formal) and later so did chloromethyl acetate (44%). Methylene iodide, however, gave a low yield of formal (15%) when potassium hydroxide replaced metallic sodium.

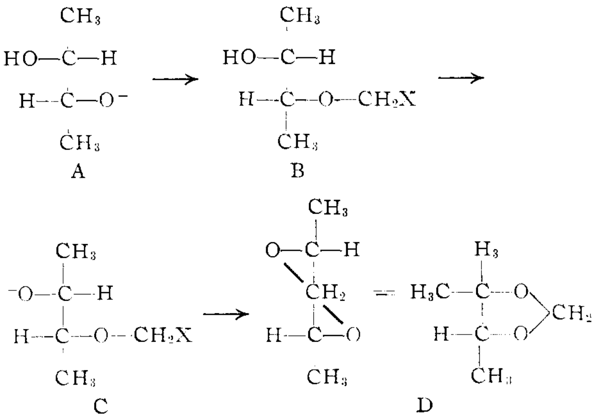
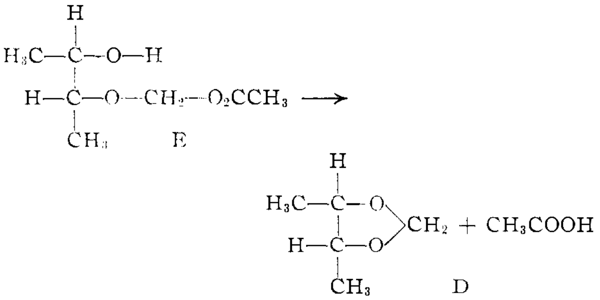


Fig. 1.—Formal from the anion of 2,3-butanediol.

The glycol in all cases is first converted to the anion, A, Fig. 1, and this reacts with any one of the three reagents to give an intermediate product, B (X = I, Cl, $OCOCH_3$, respectively). This with a second mole of base would yield the corresponding anion, C. When X is I or Cl the intermediate, C, undergoes an intramolecular ring closure to yield the cyclic formal, D, without change of configuration at either asymmetric carbon atom.

Methylene chloride gave best results with an excess (about 9 moles) of glycol[6] containing two moles of the monosodium salt per mole of dihalide. The salt was prepared by reaction of the glycol with metallic sodium. The intermediate, B (X = Cl), is converted into C by equilibration with A.

Chloromethyl acetate gave best results with an excess of glycol containing one mole of the monosodium salt to 1.5 mole (or higher) of ester. The formation of an intermediate, B (X = $OCOCH_3$), is indicated by a rapid formation of sodium chloride. However, the production of formal, D, does not proceed *via* the anion, C (X = $OCOCH_3$), because little or no D is obtained when the molal ratio of the salt to ester is unity or higher. This shows that acid conditions are necessary, as in acetal interchange.[7] The last step therefore is an intramolecular interchange taking place in E.



The good agreement in the physical constants of the products from the three reagents with those of the formal prepared with formaldehyde, Table I, shows the identity of the compounds. The optical rotations are especially valuable data.

Significance of Results.—The formal has the configuration of the glycol. This is a confirmation of the configuration of the formal assumed earlier, and of the configuration of the acetal.[3] Any acetal

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[1] Presented before the Organic Division at the 126th Meeting of the American Chemical Society in New York, N. Y., Sept., 1954.

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[3] H. S. Garner and H. J. Lucas, THIS JOURNAL, **72**, 5497 (1950).

[4] Cleavage of the two Alk–O bonds by an S_N2 mechanism would be required for two inversions. This would not be expected since the view is generally held that in hemiacetal formation the Alk–O bond remains intact. E. R. Alexander, "Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 215.

[5] No formal could be isolated with methylene iodide under the following conditions: (1) at refluxing temperature for 20 hours with an ether solution of the bis-ethylmagnesium bromide salt of the glycol prepared with ethylmagnesium bromide; (2) at 100–110° by adding it slowly, over a period of three hours along with an equivalent amount of silver oxide in small portions to the glycol, and removing any volatile product so formed, (3) at 120–130° with the sodium salt of the glycol, prepared by the action of metallic sodium.

[6] G. K. Helmkamp and H. J. Lucas, THIS JOURNAL, **74**, 941 (1952), found an excess desirable in the preparation of ethers.

[7] H. J. Lucas and M. Guthrie, *ibid.*, **72**, 5490 (1950).

TABLE I

CONSTANTS OF D(−)-4,5-DIMETHYL-1,3-DIOXOLANE (FORMAL OF D(−)-2,3-BUTANEDIOL)

Reagent	B.p., °C.	Pressure, mm.	$\alpha^{25}D$	$n^{25}D$	d^{25}_4
Methylene iodide	93.5–95.3	745	−23.24°	1.3963	0.9282
Methylene chloride	95.5–96	748	−23.40	1.3978[a]	.936
Chloromethyl acetate	95.2–96.2	748	−22.40	1.3970[a]	
Paraformaldehyde	95.6–95.9	746	−23.38	1.3959	.9346

[a] After four months as well as at time of preparation.

of D-2,3-butanediol would be expected to have the D-configuration.

When the formal of the glycol is prepared by an acid-catalyzed reaction with formaldehyde, neither of the two Alk–O bonds is cleaved, Fig. 2. This rules out the possibility of a carbonium ion or an S_N2 mechanism at either asymmetric carbon atom. The same statement applies to the acid-catalyzed hydrolysis of the formal, the reverse of the steps shown in Fig. 2, because the product is optically pure D(−)-2,3-butanediol.[3] The rate-determining step is hemiacetal to acetal or *vice versa*. Thus the results described here substantiate the conclusions drawn from the acid hydrolysis of the acetal of D(+)-2-octanol,[8] namely, any carbonium ion characteristics of the acid-catalyzed hydrolysis of formals mentioned by Hammett[9] must be associated with the aldehyde carbon atom and not with the alkyl carbon atom.

Experimental

Materials.—D(−)-2,3-Butanediol.[10] after distillation at 4 mm. to remove water, had $\alpha^{25}D$ −12.25 or better. Methylene iodide, Mathieson, had f.p. 5–6° and methylene chloride had b.p. 50° on careful distillation. Chloromethyl acetate was prepared from paraformaldehyde and acetyl chloride[11] and by the liquid phase chlorination of methyl acetate,[12] respective b.p. 111–113° and 112.5–115° (747 mm.). Irradiation by sunlight during chlorination was more satisfactory than by ultraviolet light.

Reaction with Methylene Iodide.—To a solution of the sodium salt of the glycol (0.2 atom of sodium in 1.0 mole of D(−)-2,3-butanediol) was added 26.7 g. (0.1 mole) of methylene iodide. The system was kept at 60–80° for 1.5 hour. No odor of formal was detected. There was a slow precipitation of sodium iodide and an immediate darkening. This was due in part to the formation of iodine. Three drops of water was added and heating was continued at refluxing temperature for 2 hours. Volatile material was removed at 25 mm. and caught in a Dry Ice trap. The crude distillate was a mixture containing some butanone.

Fractionation through a semi-micro still gave 1.2 g. of a liquid at 124–127.5° (748 mm.), $\alpha^{25}D$ −23.35°, $n^{25}D$ 1.418.

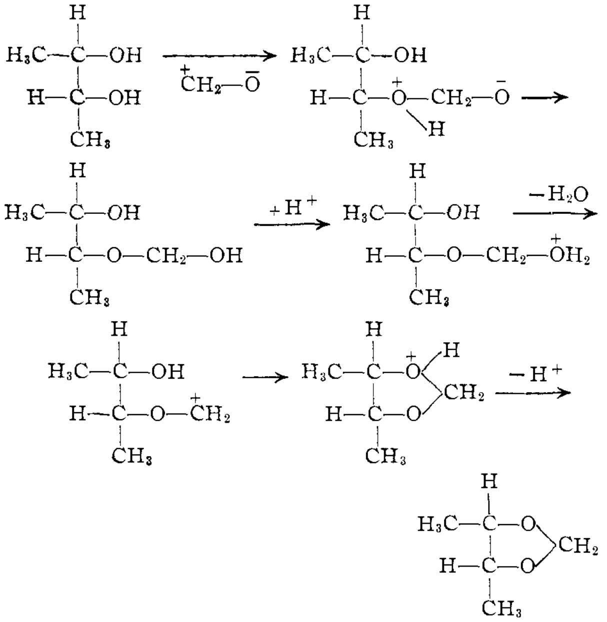

Fig. 2.—Probable steps in and mechanism of the acid-catalyzed reaction of D(-)-2,3-butanediol with formaldehyde to produce the formal.

It is believed to be impure D(−)-*threo*-3-methoxy-2-butanol,[6] b.p. 126.4–126.5° (748 mm.), $\alpha^{25}D$ −24.25°, $n^{25}D$ 1.4067. It is the result of reduction, iodine being formed simultaneously.

Anal. Calcd. for $C_5H_{12}O_2$: C, 57.66; H, 11.62. Found: C, 56.4; H, 11.15.

In a number of other experiments in which the reactants were heated as high as 150° no formal could be recovered.

With 0.2 mole of potassium hydroxide in place of 0.2 atom of sodium, 53 g. (0.2 mole) of methylene iodide yielded 1.5 g. (15%) of almost pure formal. About 0.1 mole of methylene iodide was recovered.

Reaction with Methylene Chloride.—In 90.5 g. (1.0 mole) of D(−)-2,3-butanediol there was dissolved 4.5 g. (0.2 atom) of sodium and then 8.7 g. (0.1 mole) of methylene chloride was added. The mixture was heated to refluxing temperature with a small flame for 1 hour. There was a slow precipitation of sodium chloride and a distinct odor of formal after 1 hour. At this time volatile material was removed at reduced pressure, caught in a cold trap, and dried over potassium carbonate for a day. Redistillation gave 4.9 g. (49%) of formal, b.p. 95.5–96° (748 mm.), $\alpha^{25}D$ −23.40°. In later experiments yields of liquid in this boiling range (no other constants taken) were 70%.

Reaction with Chloromethyl Acetate.—To a solution of 2.3 g. (0.1 atom) of sodium in 100 g. (1.1 moles) of D(−)-2,3-butanediol was slowly added 16.3 g. (0.15 mole) of chloromethyl acetate. The temperature rose spontaneously to 80° and sodium chloride formed rapidly. After the mixture had been heated at refluxing temperature for 2 hours it was cooled and allowed to stand overnight, open to air. Moisture was absorbed. Next day the azeotrope with water was driven over by heating. Redistillation of the dried distillate gave 5.0 g. (44%) of formal, 95–96° (748 mm.), $\alpha^{25}D$ −22.40 .

When only 10 g. (0.1 mole) of chloromethyl acetate was added no volatile product was recovered, and when only 5 g. (0.05 mole) was added, about 1 g. of halogen-free, optically inactive liquid, b.p. 40°, possibly a water–methyl acetate azeotrope, was recovered.

PASADENA, CALIF.

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[8] J. M. O'Gorman and H. J. Lucas, THIS JOURNAL, **72**, 5489 (1950).

[9] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 304.

[10] Kindly supplied some years ago by the Northern Regional Research Laboratories, Peoria, Ill.

[11] M. Descudé, *Bull. soc. chim.*, [3] **27**, 867 (1902); E. H. Huntress in "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 664, lists b.p. 115° (757 mm.).

[12] L. Henry, *Ber.*, **6**, 740 (1873); J. B. Conant, W. R. Kirner and R. E. Hussey, THIS JOURNAL, **47**, 499 (1925). This method was found to be much superior to the one from paraformaldehyde and acetyl chloride.