THE MECHANISMS OF SOME REACTIONS OF

OPTICALLY ACTIVE 2,3-BUTANEDIOL AND ITS DERIVATIVES

Thesis by

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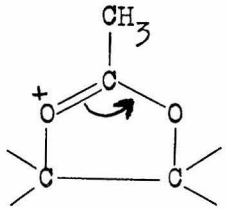
I wish to express my sincere appreciation for the aid and inspiration of Prof. Howard J. Lucas, under whose direction most of this research was carried out. The guidance of Prof. James Bonner during the course of the plant physiology research is also gratefully acknowledged.

ABSTRACT

Dextrorotatory 2,3-epoxybutane has been shown to belong to the D family by a consideration of the mechanisms of the reactions involved in its preparation from D(-)-2,3-butanediol. Similar considerations show dextrorotatory erythro-3-chloro-2-butanol to belong to the L family. The latter compound was oxidized by hypobromite to L(-)-α-chloropropionic acid, giving additional proof of its configuration.

The stereochemical results of, (a) the acetolysis of the p-toluenesulfonates of D(-)-2,3-butanediol, and (b) the reactions of the optically active erythro- and threo-3-iodo-2-butanols with the hydrohalic acids, can be satisfactorily explained only by assuming neighboring group participation in the replacement process. This participation is by way of the cyclic intermediate ions, I and II respectively.



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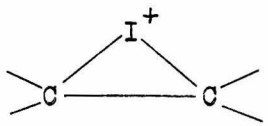

II

A number of cyclic acetals and esters of D(-)-2,3-butanediol were prepared, namely, the formal, acetal, carbonate, sulfite, sulfate, borate, and several phosphite derivatives. All of these behaved normally on hydrolysis except the sulfate, which gave the meso-glycol on acid hydrolysis, and the DL-glycol on basic hydrolysis.

The effect of 3-acetyl-6-methoxybenzaldehyde in inhibiting the growth of tomato plants was reduced somewhat by removing the roots from the test plants. The compound was also shown to inhibit germination and root growth of tomato seedlings.

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SECTION A

THE MECHANISMS OF SOME REACTIONS OF OPTICALLY ACTIVE 2,3-BUTANEDIOL AND ITS DERIVATIVES

PART I

THE CONFIGURATION OF OPTICALLY ACTIVE 2,3-EPOXYBUTANE AND *erythro*-3-CHLORO-2-BUTANOL

I

The Configuration of Optically Active 2,3-Epoxybutane and erythro-3-Chloro-2-butanol*

Although the lower boiling 2,3-epoxybutane was shown to be the trans isomer when Wilson and Lucas (2) succeeded in preparing a small sample which possessed optical activity, it was not possible then to determine the configuration of the active form. The compound from which the active oxide was prepared, (+)-α,β-dimethylcholine, was obtained by resolving the inactive material, and its optical configuration could not be established. Later, Winstein and Lucas (3) obtained active 2,3-epoxybutane from partially resolved erythro-3-bromo-2-butanol, but here also the starting material was of unknown optical configuration. Moreover, both of these samples of the active oxide were of low optical purity, for they possessed relatively low rotations.

The mechanisms of the reactions used in this investigation to establish the configuration of the active 2,3-epoxybutane had been correctly surmised at the time when the oxide was first prepared with optical activity, although they were not proved until later (3,4,5,6). However, the configuration of optically active 2,3-butanediol had not yet been established, and the active glycol was not available to Wilson and Lucas at that time. Now that levorotatory 2,3-butanediol has been obtained in a high state of optical purity (7,8,9), and the configurations of the

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* The material in this section was recently published in essentially its present form (1). The intr oductory remarks have been changed, and parts of the discussion have been expanded somewhat here.

active forms have been established (10,11), it has been possible to prepare an optically pure 2,3-epoxybutane by methods which establish its configuration. In the changes, which are shown by I to V in the figure, the stereo relationships of the compounds involved are based upon previous results, as discussed below. In addition, the configuration of the C-3 carbon atom in dextrorotatory erythro-3-chloro-2-butanol has been independently established as L by converting the chlorohydrin, through the bromoform reaction, to levorotatory α-chloropropionic acid, VI, which is known to have the L configuration (12,13,14,15).

In D(-)-2,3-butanediol, I, each carbon atom has the D configuration (10,11). When the glycol is converted to D(+)-2,3-diacetoxybutane, II, by acetic anhydride with either sulfuric acid or pyridine as a catalyst, the configuration of each carbon atom is still D. When II is converted to L(+)-erythro-3-chloro-2-butanol, III, by hydrochloric acid, the configuration of carbon atom C-3 is inverted, for a single Walden inversion has been shown to accompany the displacement of one of the acetoxy groups by chlorine in the change of DL-2,3-diacetoxybutane to DL-erythro-3-chloro-2-butanol (6).* In the last step, III to D(+)-2,3-epoxybutane, IV, the configuration of carbon atom C-3 is again inverted, for a single Walden inversion accompanies the closing of the oxide ring. This has been shown to be the case when DL-trans-2,3-epoxybutane is formed from DL-erythro-3-chloro-2-butanol (6).** There could not have been an odd number of inversions, otherwise the final product

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* In the analogous change of DL-2,3-diacetoxybutane to DL-erythro-3-bromo-2-butanol by hydrobromic acid, the single Walden inversion has been located at the step where DL-threo-3-acetoxy-2-butanol is changed to DL-erythro-2-acetoxy-3-bromobutane (5).

** A single Walden inversion is known to be associated with closing of the epoxy ring when cis-2,3-epoxybutane is formed from DL-threo-3-bromo-2-butanol (4).

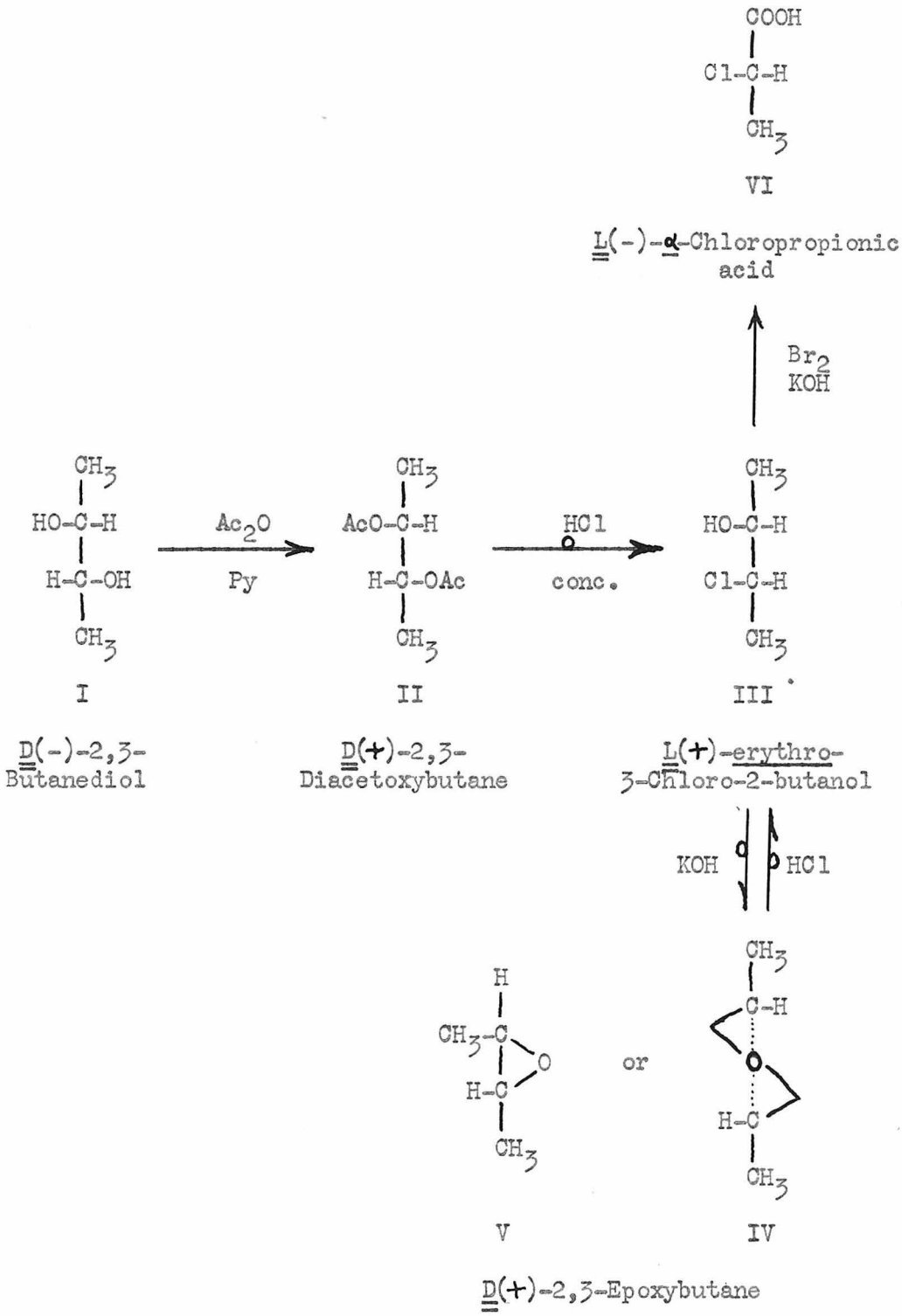


Figure 1.. Configurational relationships of D(+)-2,3-epoxybutane and L(+)-erythro-3-chloro-2-butanol to D(-)-2,3-butanediol.

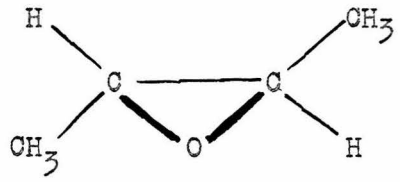
would have been the optically inactive cis-oxide rather than the active trans-oxide. Thus it seems reasonable to conclude, on the basis of the changes, I to IV, that the configuration of each carbon in IV is D, since there has been no inversion at C-2, and two inversions at C-3. It should be pointed out that if the attack by chloride ion in the change II to III is at C-2, rather than at C-3 as assumed for the purpose of discussion, the results are the same, i.e., C-2 is inverted twice while C-3 is not affected, and both therefore still have the D configuration in the oxide. The chlorohydrin is also the same in this case, for the carbon bearing the hydroxyl group has the same configuration as in the glycol, while the carbon bearing the chlorine has been inverted once.

The conversion of the chlorohydrin, III, to chloropropionic acid, VI, by establishing the configuration of carbon atom C-3 as L, presents additional proof that one inversion is associated with each of these changes, viz., II to III and III to IV. In addition it confirms the earlier evidence that the higher boiling chlorohydrin has the erythro configuration (6).

The configuration of α-chloropropionic acid cannot be unequivocally established by relating it directly to hydroxy compounds such as lactic acid by reactions not involving the asymmetric center. Neither can the Walden inversions in steps II to III, III to IV, and IV to III be proven unequivocally, although there is no reason to doubt that they occur. Nevertheless, the evidence presented here is consistent with the accepted configuration of α-chloropropionic acid, and with the assumption that one inversion accompanies each of the changes mentioned above. There can, therefore, no longer be any reasonable doubt either in regard to the configuration of the active α-chloropropionic acids or the mechanisms of the reactions of Fig. 1, because of the satisfactory way in which 3-chloro-

2-butanol forms a configurational link between the two independent lines of investigation.

When the carbon chain is written vertically, the configuration of the dextrorotatory oxide is correctly represented by IV. However, since this is an awkward looking formula, it seems preferable to write the oxide ring on one side, as shown by V. This, therefore, is the preferred way of writing the configuration of D(+)-trans-2,3-epoxybutane, or more simply, D(+)-2,3-epoxybutane, since there are only two active isomers of 2,3-epoxybutane. Structures IV and V are equivalent. A third way of representing the oxide, which emphasizes the trans position of the methyl groups to the epoxy ring, is given by VII.



VII

D(+)-2,3-Epoxybutane

The configuration of the dextrorotatory oxide and the dextrorotatory chlorohydrin are reasonably certain, since carbon atom C-2 is unaffected during the changes, and the configuration of carbon atom C-3 in the chlorohydrin is established by its conversion to levorotatory α-chloropropionic acid. The designation of these compounds as D or L is somewhat arbitrary, however, since there are no rules of nomenclature which specifically apply in this case. Either of the two asymmetric centers in the molecule might be taken as the point of reference. It seems preferable to take carbon atom C-3 as the point of reference, so as to correlate the nomenclature

with that of the carbohydrates.* This is in agreement with the designation of the 2,3-butanediols given by Morell and Auernheimer (11). On this basis, the configuration of the highest numbered asymmetric carbon atom determines the family to which the compound belongs. Thus I, II, and IV belong to the D family, since in these the functional group at carbon atom C-3 lies on the right, and III belongs to the L family, since the functional group lies on the left as a result of inversion during its formation from II.

The oxide is believed to be of high optical purity for the following reasons: (1) The active glycol used as starting material had one of the highest optical rotatory powers recorded for this compound in the literature; (2) The reactions involved have been shown to yield configurationally pure compounds; (3) Absence of cis-oxide was indicated by agreement in physical properties with previously prepared DL-oxide; (4) Rotations of three preparations agreed well, viz., 58.65°, 59.05°, and 58.05°.

The importance of (3) as an argument for optical purity is based on the assumption that if any reaction proceeded otherwise than with 100% retention or inversion of the configuration of carbon atom C-3, the resulting diastereomeric compound would lead to the presence of some cis-oxide in the final product. This would be the main contaminant, not the L(-)-oxide. In order for the latter to be formed there would have to be inversion at carbon atom C-2 as well as at C-3. Since the observed refractive index of the active oxide, 1.3705, is identical with that previously reported for the DL-oxide, while the refractive index for pure cis-oxide is 1.3802, the absence of the latter is indicated.

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* This has been done in conformity with the report of the Committee on Carbohydrate Nomenclature, Charles D. Hurd, Chairman (16).

Rotations and other physical constants of the compounds involved are shown in Table I. The rotation of the cyclic oxide is one more example of the well known effect of ring structure in enhancing rotations.

The specific rotation of the chlorohydrin prepared by the action of hydrochloric acid on the active oxide, + 8.87°, was only 0.05° less than that of the chlorohydrin prepared from the diacetate, + 8.92°. This indicates that in going from III to IV and back to III the reactions proceed with essentially 100% inversion of configuration.

Table I

Physical Constants of the D and L Compounds

Compound	B. P. °C. (cor.)	mm.	M. P. °C. (cor.)	d_4^{25}	n_D^{25}	M_D calc.	M_D obs.	α_D^{25} obs. pure liquid	$[\alpha]_D^{25}$ pure liquid
D(-)-2,3-Butanediol	77.5-77.6	10	19.4-19.7[a]	0.9869[b]	1.4308[b]	23.72	23.63	-13.00°	-13.17°[c]
D(+)-2,3-Diacetoxy-butane	82.2	10	25.7-25.9	1.0244	1.4134	42.45	42.34	+14.10°	+13.76°[d]
L(+)-erythro-3-Chloro-2-butanol	56.0	30		1.061	1.4397	27.06	26.95	+ 9.47°	+ 8.92°
D(+)-2,3-Epoxybutane	53.5-53.7[e]	745		0.7998[f]	1.3705[g]	20.11[h]	20.41	+47.23°	+59.05°

a) Previous values (7,9): 19°; 19°.

b) Ref. 9; also 7,8; n_D^{25}, 1.4307; 1.4318.

c) Previous values (7,8,9,11): -13.0°; -13.34°; -13.19°; -12.85°.

d) $[\alpha]_D^{25}$, +18.7° in $CHCl_3$; 0.9895 g. in 10 ml. $CHCl_3$; previous values (17): $[\alpha]_D^{28}$, +13.65°, pure liquid.

e) Previous values (4): cis-oxide, 59.7°, 742 mm.; DL-trans-oxide, 53.5°, 742 mm.

f) Previous values (4): cis-oxide, 0.8226; DL-trans-oxide, 0.8010.

g) Previous values (4): cis-oxide, 1.3802; DL-trans-oxide, 1.3705.

h) No correction for three-membered ring.

Experimental

D(-)-2,3-Butanediol. The sample of optically active 2,3-butanediol was furnished by the Northern Regional Research Laboratory, Peoria, Illinois. Dr. A. F. Langlykke of that laboratory stated that the material was produced by fermentation of starch by Bacillus polymyxa. The glycol contained a small amount of water and had an observed rotation of -12.4°. This became -13.00° ($[\alpha]_D^{25}$, -13.17°) after one distillation at reduced pressure.

D(+)-2,3-Diacetoxybutane; Acid Catalyzed Reaction. The diacetate could be prepared, as previously described for the inactive diacetate (2), from the glycol and acetic anhydride, using as catalyst one drop of sulfuric acid per 0.5 mole of glycol. Vacuum fractionation of the reaction mixture gave a 90% yield of material with an observed rotation of +13.8°. On standing at room temperature (approximately 22°) overnight, about two-thirds of the material crystallized in large, clear prisms. The liquid was decanted from these, and the solid recrystallized from 30-60° petroleum ether and redistilled. The diacetate thus obtained melted at 25.7-25.9° and had an observed rotation of +14.10°. These values could not be raised by further purification. Additional amounts of pure diacetate could be obtained by crystallization and distillation of the liquid fraction. The total yield of purified diacetate was 70%.

The amount of sulfuric acid used to catalyze the acetylation should not exceed two drops per mole and the reaction temperature should not rise above 80°, otherwise some optical inversion may occur.

Pyridine Catalyzed Reaction. In a 1-liter Erlenmeyer flask were

placed 1.00 mole (90.0 g.) of redistilled active 2,3-butanediol and 5 moles (400 g.) of redistilled anhydrous pyridine. The contents were thoroughly mixed, and then 2.20 moles (224 g.) of acetic anhydride were added slowly with stirring from a dropping funnel. As the mixture warmed, cooling was supplied to keep the temperature below 40°. After the reaction had subsided, the mixture was allowed to stand overnight, and was then fractionally distilled at reduced pressure, the final cut being taken at 82.1-82.2° (cor.) at 10 mm. The product weighed 170 g. (98%) and had an observed rotation of +13.94°. This material could be further purified so that finally α_D^{25} obs. = +14.06° and $[\alpha]_D^{25}$ = +13.72°, but this was found to be unnecessary since the chlorohydrin and oxide prepared from it had the same rotation as those from the more highly purified material.*

L(+)-erythro-3-Chloro-2-butanol. This was prepared by the method previously described for the inactive chlorohydrin (6). In a 1-liter ampoule were placed 0.93 mole (162 g.) of D(+)-2,3-diacetoxybutane and 375 g. of conc. aqueous hydrochloric acid (Bakers Analyzed, 36%). The contents were cooled to -20° in an ice and hydrochloric acid bath, and dry HCl gas was passed in until no more was taken up. The total amount of hydrogen chloride present was then 7.3 moles (267 g.). The ampoule was sealed and allowed to stand at room temperature for four days. It was then opened, and the contents poured into a suspension of 630 g. of sodium bicarbonate in one liter of water. The aqueous solution was extracted with five 100 ml. portions of isopropyl ether, and the ether extracts washed with water and dried. The ether was removed by distillation at atmospheric

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* K. A. Clendenning (17) gives these values for the active diacetate: n_D^{25}, 1.4132; d_4^{20}, 1.029; $[\alpha]_D^{25}$, +13.65°.

pressure, and the product distilled at reduced pressure; yield, about 70% of a mixture of 3-chloro-2-butanol and 3-chloro-2-acetoxybutane; b.p., 55-73°. Three fractionations of a portion of the product gave a pure sample of the chlorohydrin for the measurement of physical properties, but it was not necessary to separate the chlorohydrin from the chloroacetate in the preparation of 2,3-epoxybutane, since both are converted into the oxide.

When the reaction mixture is allowed to stand four weeks rather than four days, the yield of chlorohydrin is increased to about 90%, but the rotation of the oxide prepared from this material, $[\alpha]_D^{25} = +58.05°$, is slightly lower than when the reaction is carried out in the shorter time.

D(+)-2,3-Epoxybutane. This was prepared, as previously described for the inactive oxides (2), by adding the active chlorohydrin dropwise to hot (100°) 50% potassium hydroxide solution, and distilling out the product as formed. The material was dried over potassium hydroxide and purified by fractional distillation; no trace of the higher boiling cis-oxide was detected. The yield of purified oxide, from 71 g. of mixed chlorohydrin and chloroacetate, was 35.0 g. The over-all yield from the active glycol was 49%. The rotations of two preparations were: $[\alpha]_D^{25}$, +59.05° and +58.65°.

Better yields (70% from the glycol) can be obtained if the time allowed for the conversion of the diacetate to the chlorohydrin is lengthened to four weeks. In the one case where this was tried, however, the oxide was of slightly lower optical purity, $[\alpha]_D^{25} = +58.05°$.

DL-α-Chloropropionic Acid. Inactive 3-chloro-2-butanol was prepared, in the manner previously described (6), from a supply of inactive 2,3-epoxybutane (mixture of cis and trans) and cold concentrated hydrochloric acid.

The yield was 79%

A 3-necked 1-liter flask was fitted with a mechanical stirrer and two dropping funnels. In the flask was placed 0.25 mole (27 g.) of the inactive chlorohydrin, and in the two separatory funnels 1.00 mole (160 g.) of liquid bromine and 3 moles of potassium hydroxide (Baker's C. P., 86%, 195 g.) dissolved in 500 ml. of water, respectively. The stirrer was started, and the bromine added rapidly, about 15 minutes being required for the addition. When about one quarter of the bromine had been added, the addition of the base was begun and continued at such a rate that the bromine was always present in the reaction mixture in good excess. The mixture became hot, and cooling was supplied with an ice bath to keep the temperature around 50°. After all the bromine was in, addition of the base was continued until the reaction mixture became colorless, and then a slight excess was run in. A yellow color developed in the presence of the excess base.

Stirring was continued for about 15 minutes, after which the mixture was transferred to a separatory funnel, and the heavy layer of bromoform drawn off. The aqueous layer was washed once with 50 ml. of chloroform, and then acidified with 50% sulfuric acid, a 20 ml. excess of the acid being used. The bromine which formed was destroyed with formic acid, and the solution extracted five times with 100 ml. portions of ethyl ether. Following removal of the ether by ordinary distillation, the α-chloropropionic acid was distilled at 30 mm.; b.p., 100-105° (cor.); yield, 3.5 g. (13%). The product was redistilled at atmospheric pressure, the fraction boiling at 184-186° (cor.) being collected. The product gave a strong positive test for chlorine and had a neutralization equivalent of 115 (theoretical = 108.5). Its anilide melted at 89.5-90.5° (cor.), and its salt with phenylhydrazine at 95-96° (cor.). Shriner and Fuson (18) give the m.p. of the anilide as 92°, and Stempel and Schaffel

(19) give the m.p. of the phenylhydrazine salt as 95°.

Other modifications of the above procedure were tried, but no improvement of the yield could be realized. It is important that there be no excess of base until all of the bromine has been added; otherwise considerable amounts of the chlorohydrin are lost by conversion to oxide.

L(-)-α-Chloropropionic Acid. The active chlorohydrin used in the oxidation was prepared from the active oxide and cold concentrated hydrochloric acid as previously described for the inactive compound (6) and had the following constants: b.p., 55.9-56.0° (cor.) at 30 mm.; $\underline{\alpha}_D^{25}$, +9.42°; $[\underline{\alpha}]_D^{25}$, +8.87°; n_D^{25}, 1.4394. The yield was 75%.

The oxidation of the active chlorohydrin was carried out similarly to that of the inactive material. From 12.0 g. of chlorohydrin was obtained 1.9 g. (16%) of α-chloropropionic acid; b.p., 100-102° (cor.) at 30 mm., 184-187° (cor.) at 745 mm.; neutralization equivalent, 108 (theoretical = 108.5). The rotations were as follows: pure liquid, $\underline{\alpha}_D^{25}$ = -14.2°, $[\underline{\alpha}]_D^{25}$ = -11.3°; aqueous solution (0.0433 g. in 2.00 ml. water soln.), $[\underline{\alpha}]_D^{25}$ = -9.1°; sodium salt (0.0736 g. of acid made up to 2.00 ml. with 3.94 f NaOH), $[\underline{\alpha}]_D^{25}$ = +3.8°. Freudenberg, Kuhn, and Bumann (13) report the rotation of pure L-α-chloropropionic acid as $\underline{\alpha}_{578}$ = -19.30°, $[\underline{\alpha}]_{578}$ = -15.4°, pure liquid. Levene and Haller (20) observed that the sign of the rotation changed in going from acid to basic solution.

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PART II

THE REACTIONS OF THE 3-IODO-2-BUTANOLS WITH HYDROCHLORIC AND HYDROBROMIC ACIDS

II

The Reaction of the 3-Iodo-2-butanols with Hydrochloric and Hydrobromic Acids

The transitory existence of a cyclic, positively charged bromonium ion has been demonstrated in the reaction of 3-bromo-2-butanol with hydrobromic acid (1,2), and a similar chloronium ion is formed in the reaction of 3-chloro-2-butanol with thionyl chloride (3). It has also been shown that the stereochemistry of the reaction of 3-bromo-2-butanol with phosphorus tribromide (4) is best explained by a cyclic bromonium ion, and an analogous intermediate satisfactorily accounts for the products of the reaction of 2-bromocyclohexanol with hydrobromic acid or phosphorus tribromide (5). Recently it has been shown that a neighboring iodine atom greatly increases the reactivity of the hydroxy group in 2-iodocyclohexanol (6), and of the tosyloxy group in 2-iodocyclohexyl tosylate (7,8), effects which are best explained on the basis of a cyclic iodonium ion.

In the present investigation, the transitory existence of a cyclic iodonium ion is necessary to account for the steric effects observed when the 3-iodo-2-butanols react with hydrochloric and hydrobromic acids. The results which were obtained are shown in Figure 1. The properties of the iodohydrins and the dihalides obtained from them are shown in Table I.

The configurations of the compounds in Figure 1 have not been proved unequivocally. However, there is a considerable body of evidence which indicates that the configurations shown are the correct ones.

There can be little doubt as to the configurations of the iodohydrins, for they were prepared from pure isomers of 2,3-epoxybutane by the addition

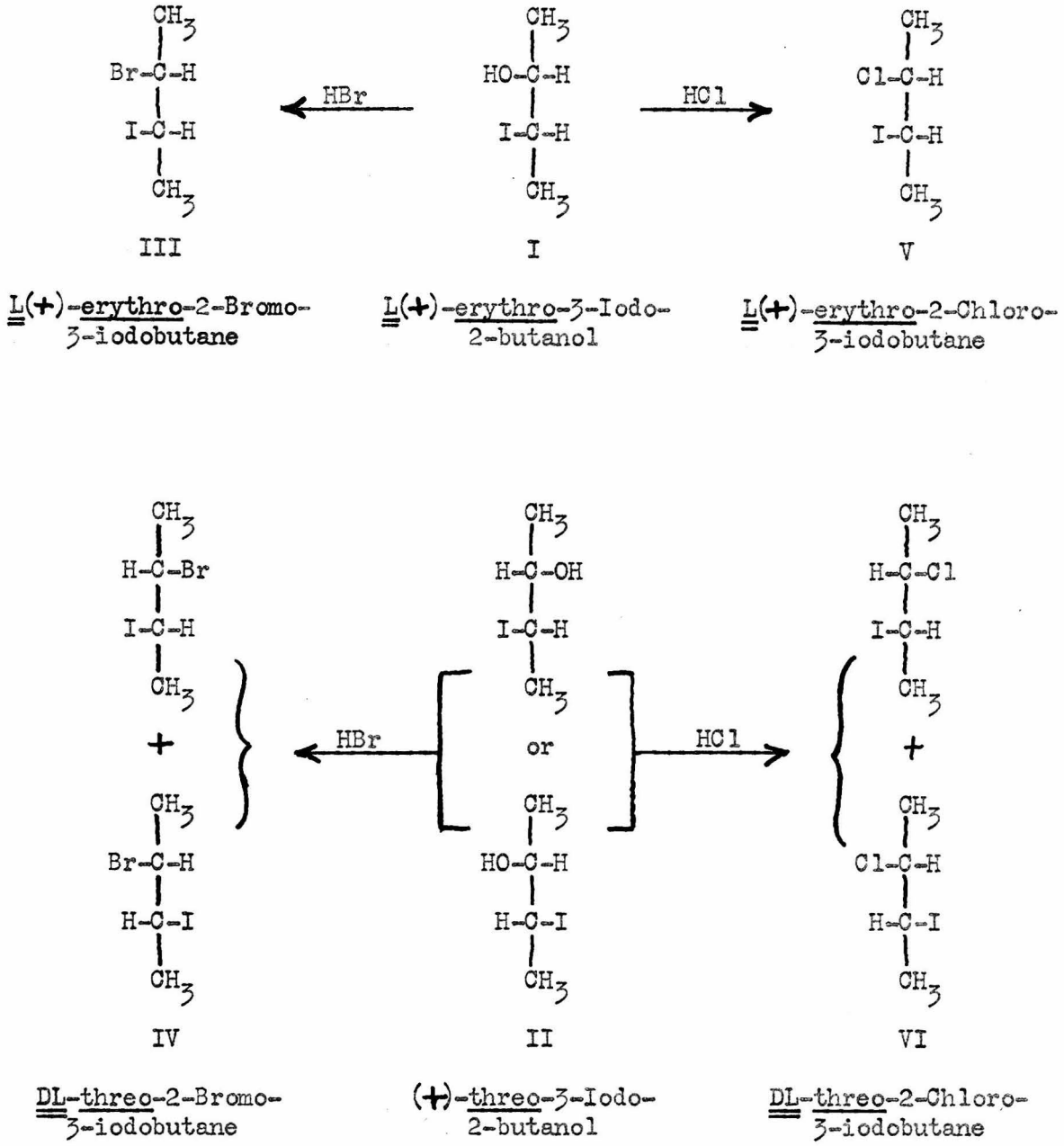

Figure 1. Stereochemical Results of the Reactions of L(+)-erythro-3-Iodo-2-butanol and (+)-threo-3-Iodo-2-butanol with Hydrochloric and Hydrobromic Acids.

Table I

Properties of the Iodohydrins and Dihalides

Compound	B. P. °C. (cor.)	B. P. p, mm	M. P. °C. (cor.)	n_D^{25}	d_4^{25}	α_D^{25} obs.	$[\alpha]_D^{25}$	M_D calc.	M_D obs.	diff.
L(+)-erythro-3-iodo-2-butanol (I)			18.4-18.9	1.5371	1.7753	+50.04	+28.19	35.00	35.19	0.19
(+)-threo-3-iodo-2-butanol (II)	28.8-30.8 43	0.7 2.5		1.5352	1.7692	+ 3.06	+ 1.73	35.00	35.21	0.21
L(+)-erythro-2-bromo-3-iodobutane (from I)	53.0 Decomp.	6	-9.5 to -9.0	1.5642	2.0362	+ 4.13	+ 2.03	41.24	42.01	0.77
L(+)-erythro-2-chloro-3-iodobutane (from I)	34.8-35.3	5		1.5312	1.7532	+13.98	+ 7.97	38.34	38.57	0.23
DL-threo-2-bromo-3-iodobutane (from II)	29-30	0.9		1.5736	2.0629	+ 0.01		41.24	42.04	0.80
DL-threo-2-chloro-3-iodobutane (from II)	33.2-33.5	4		1.5337	1.7587	+ 0.05		38.34	38.59	0.25

of hydrogen iodide. It has been proved that D(+)-2,3-epoxybutane reacts with aqueous hydrochloric acid with one inversion to give L(+)-3-chloro-2-butanol (9). It is also known that the inactive cis- and trans-oxides react with hydrochloric acid to give respectively the DL-threo- and DL-erythro-3-chloro-2-butanols (3). Furthermore, there is no known case where the 2,3-epoxybutane ring is opened otherwise than with a single inversion. Since D(+)-2,3-epoxybutane, the configuration of which is known (9, also Part I of this thesis), was used for the preparation of the active iodohydrin, I, the assumption that this iodohydrin has the L-erythro configuration is justified. Similarly, the preparation of an inactive iodohydrin from pure cis-oxide is justification for assigning it the threo configuration. The active threo isomer, II, however, was obtained by resolving the inactive material, so cannot be designated as D or L.

The best evidence for the configurations of the dihalides, III, IV, V, and VI, comes from physical data. These are summarized in Table II.

Table II

Name of Compound	Configuration	n_D^{25}	d_4^{25}
2,3-dichlorobutane (3)	meso	1.4392	
	DL	1.4410	
2,3-dibromobutane (12)	meso	1.5091	1.7747
	DL	1.5125	1.7836
2-chloro-3-iodobutane	L-erythro	1.5312	1.7532
	DL-threo	1.5337	1.7587
2-bromo-3-iodobutane	L-erythro	1.5642	2.0362
	DL-threo	1.5736	2.0629

The refractive indices and densities of the meso- and erythro-dihalides

are in each case lower than the refractive indices and densities of the corresponding DL- and threo-dihalides. The configurations of the 2,3-dichlorobutanes and 2,3-dibromobutanes have been established by partial resolution of the DL forms (3,12). The fact that the physical properties of the 2-chloro-3-iodobutanes and the 2-bromo-3-iodobutanes show the same relationship as those of the dichlorides and dibromides is therefore strong evidence that the configurations assigned these compounds are correct. The following evidence also can be presented as favoring the configurations as they appear in Figure 1: (a) The rotation of L(+)-erythro-2-chloro-3-iodobutane, V, is α_D^{25}, +13.98°, while that of L(+)-erythro-2-bromo-3-iodobutane, III, is α_D^{25}, + 4.13°. This is the trend that would be expected if both compounds have the erythro configuration, for as the two halogens become more nearly the same size, the rotation should become smaller, culminating in the di-iodo butane which would possess the meso configuration and thus be inactive. An attempt was made to prepare meso-2,3-di-iodobutane from the erythro-iodohydrin and hydriodic acid, in order to test this hypothesis and furnish further proof of the configurations of the other dihalides. However, the compound proved to be too unstable to isolate, decomposing rapidly into butene and iodine even at 0°. (b) The work of Lucas and Gould (3) indicates that pure active 2,3-dichlorobutane should have a rotation of about 44°.* An active threo-2-chloro-3-iodobutane would be expected to have an even higher rotation, rather than the relatively low one observed for V,

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* Lucas and Gould obtained 2,3-dichlorobutane with α_D^{25} = -3.80° by reacting L(+)-erythro-3-chloro-2-butanol, α_D^{25} = +0.82°, with thionyl chloride in the presence of pyridine. Since Lucas and Garner (9) have shown that pure L(+)-erythro-3-chloro-2-butanol has α_D^{25} = +9.47°, the pure active dichlorides have rotations, α_D^{25}, of at least 44°.

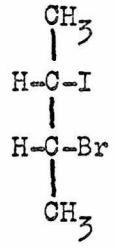
indicating that V probably has the erythro configuration. (c) Active erythro-3-bromo-2-butanol yields a meso-dibromide when it reacts with fuming hydrobromic acid. Therefore, if an analogy between the two cases is assumed, the active erythro-iodohydrin should yield an erythro-dihalide. (d) The mechanism which is proposed for the reactions of the iodohydrins with the hydrohalic acids could yield only dihalides of the configurations indicated. The evidence favoring this mechanism will be discussed in detail later.

It would have been of value in proving the configurations of the dihalides to prepare 2-bromo-3-iodobutane from L(+)-erythro-3-bromo-2-butanol, since the reactions of the bromohydrins have been studied more thoroughly than those of the iodohydrins. The bromo-iodobutane thus obtained should be the antipode of that from the L(+)-erythro-iodohydrin. To test this hypothesis, the active bromohydrin was prepared from the active oxide and hydrobromic acid. Treatment of this compound with either aqueous hydriodic acid or phosphorus and iodine, however, yielded only inactive secondary butyl iodide.

No analysis of the configurational purity of the dihalides could be made, since no samples of known purity were available for reference. However, it seems likely from theoretical considerations, from the optical changes involved, and from the analogy with the corresponding reactions of the bromohydrins, that they were relatively free of other isomers. These points will be amplified somewhat in the discussion of the mechanism which follows. In addition, the rotations of two preparations of L(+)-erythro-2-chloro-3-iodobutane, α_D^{25}, +13.98° and +14.02°, agreed well. It is unlikely that such a close check would have been obtained had other isomers been formed to an appreciable extent in the reaction. The melting point of

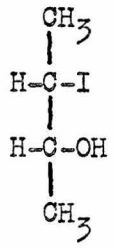
L(+)-erythro-2-bromo-3-iodobutane, -9.5 to -9.0°, is good evidence that this compound was reasonably pure. The presence of more than a trace of other isomers would undoubtedly have led to a melting point range greater than the 0.5° range observed.

The designation of the optically active compounds, III, I, and V, as L rather than D rests upon an arbitrary order of naming substituents. These compounds could, for example, be written and named as follows:



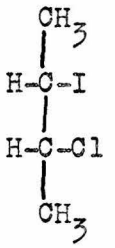
IIIa

D(+)-erythro-2-iodo-3-bromobutane



Ia

D(+)erythro-2-iodo 3-butanol



Va

D(+)-erythro-2-iodo 3-chlorobutane

Comparison of formulas IIIa, Ia, and Va with III, I, and V respectively shows that they are identical, although the naming of the compounds is different in the two cases. Formulas III, I, and V are preferred, since Chemical Abstracts normally names substituents in alphabetical order, which places the iodine atom on carbon atom C-3 rather than carbon atom C-2. The compounds are then assigned to the L series in conformity with carbohydrate nomenclature (10), whereby the highest numbered asymmetric carbon atom determines the family to which the compound belongs.

When L(+)-erythro-3-iodo-2-butanol, I, reacts with concentrated hydrobromic acid or concentrated hydrochloric acid, the dihalides, III and V, which are obtained possess optical activity. Furthermore, the configuration of the products is the same as that of the starting material, showing that

zero or an even number of inversions occurred at each asymmetric carbon atom during the reaction. However, when active threo-3-iodo-2-butanol, II, reacts under the same conditions, optical activity is lost, although the products IV and VI, still have the threo configuration. The number of inversions is therefore even, presumably two. In addition, the reaction must proceed through an internally compensated intermediate, in order for the D isomer of the DL mixture to be formed. These facts are best accounted for by the two mechanisms outlined in Figures 2 and 3.

In Figure 2, the first step is the addition of a hydrogen ion to the hydroxyl group of the iodohydrin, I, to form the protonated complex, VII. In the second step, the neighboring iodine atom swings in, displaces the water molecule, and closes the three membered ring to form the cyclic iodonium intermediate, VIII. This is undoubtedly a single process, that is, the closing of the ring occurs simultaneously with the departure of the water molecule. The closing of the ring is accompanied by a single Walden inversion at carbon atom C-2, and the cyclic intermediate therefore has the L-threo configuration and possesses optical activity. Therefore, when attack by bromide or chloride ion takes place at either C-2 or C-3, again with inversion (step three), the resulting dihalide is optically active, and, moreover, possesses the same configuration as the iodohydrin. It is evident that if the attacking ion were iodide rather than one of the other halogens, the di-iodide should have the meso configuration and thus be inactive. It is unfortunate that the di-iodide proved to be too unstable to isolate.

In Figure 3, the same steps are involved in the conversion of (+)-threo-3-iodo-2-butanol, II, into DL-threo-2-bromo-3-iodobutane, IV, or DL-threo-2-chloro-3-iodobutane, VI. However, in this case when the ring

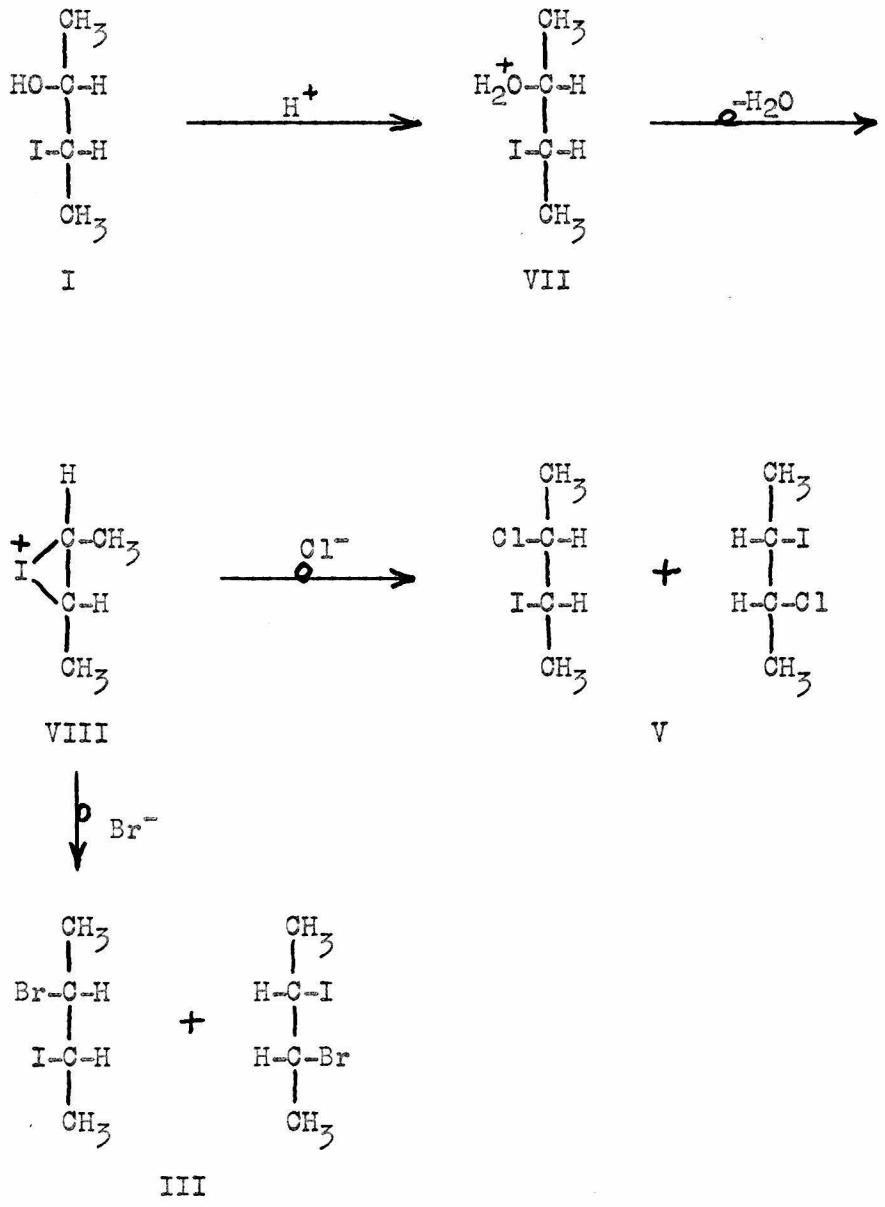


Figure 2. The Mechanism of the Reaction of L(+)-erythro-3-Iodo-2-butanol with Hydrohalic Acids.

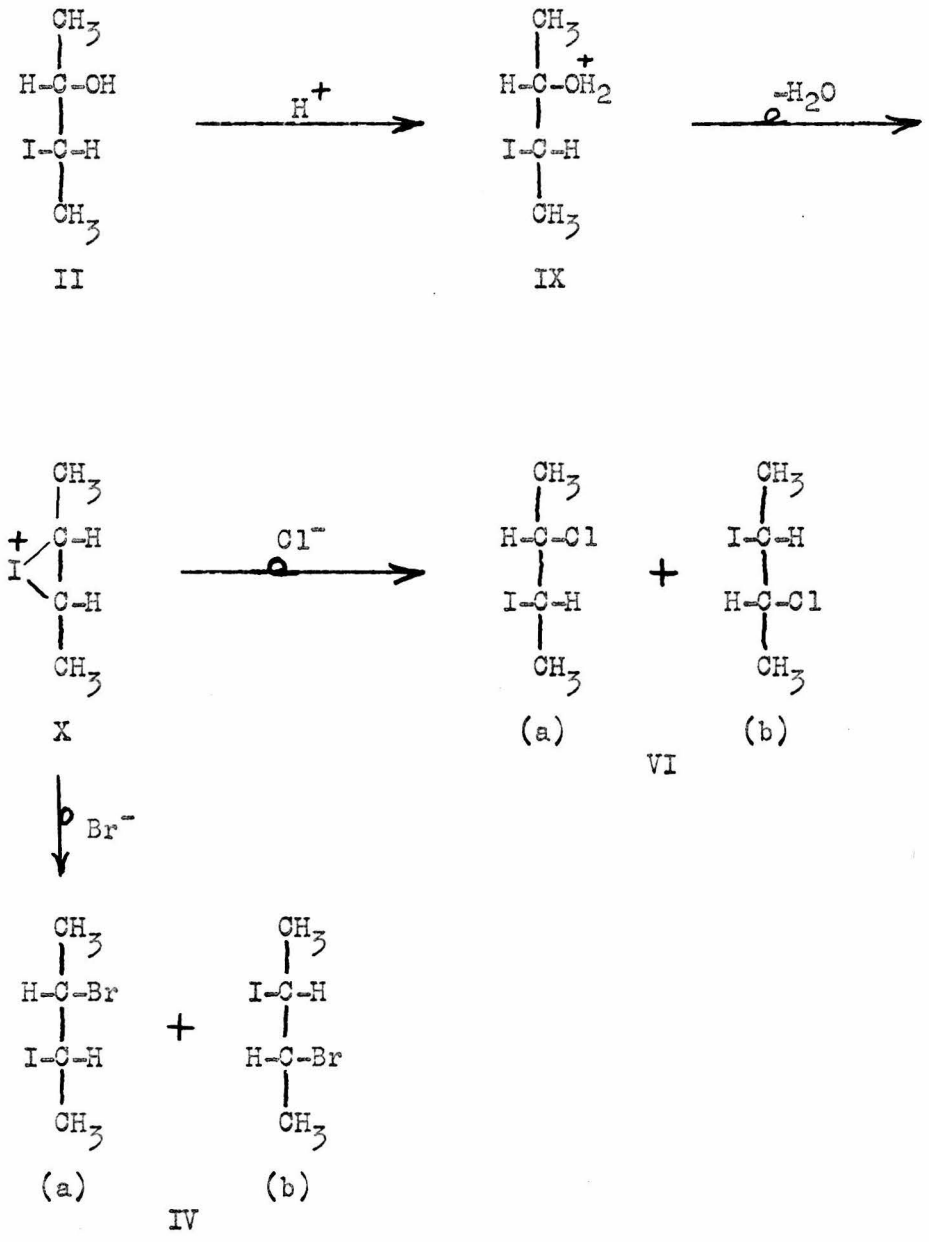


Figure 3. The Mechanism of the Reaction of Active threo-3-Iodo-2-butanol with Hydrohalic Acids.

is closed to form the cyclic iodonium intermediate, X, with one inversion, the resulting ion has the internally compensated cis configuration, and optical activity is lost. Attack by chloride ion can now give rise to two different products, the D- and L-threo-2-chloro-3-iodobutanes, VIa and VIb, which are formed in equal amounts. Attack by bromide ion similarly yields both the D- and L-2-bromo-3-iodobutanes, IVa and IVb. Thus loss of activity in the reaction of active threo-3-iodo-2-butanol with hydrohalic acids is strong evidence for an intermediate cyclic iodonium ion.

Other evidence that the reaction actually goes by the proposed path is provided by the rate. While no quantitative measurements were made, a qualitative comparison with other replacement reactions is possible. It was observed that when either isomer of 3-iodo-2-butanol was mixed with ordinary concentrated hydrochloric or hydrobromic acid, the resulting clear solution suddenly became cloudy after about 15-60 seconds, and the reaction appeared to be complete in a matter of minutes. Winstein and coworkers (6) have shown that the corresponding 3-bromo-2-butanols, on the other hand, require about three hours with fuming hydrobromic acid for 50% conversion into the dibromides, and the chlorohydrins do not yield any dihalide on standing for 25 days with fuming hydrobromic acid. Secondary butyl alcohol is 50% converted into 2-bromobutane in 75 minutes by the fuming aqueous acid. The rate sequence, therefore, is: I $\gg$ unsubstituted $\approx$ Br $\gg$ Cl.

The high reactivity of the iodine compounds is best explained on the basis of a direct participation of the iodine atom in the replacement process. Other possible mechanisms which involve direct replacement of the hydroxyl group are in fact effectively ruled out by this high reactivity of the iodohydrins.

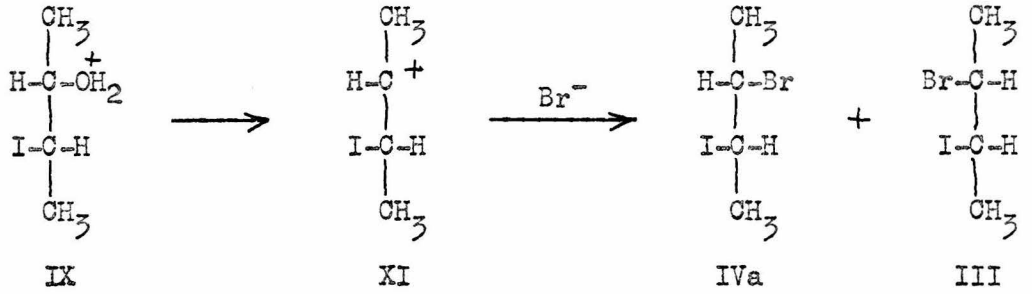
Three mechanisms are currently recognized by which direct replacement may take place at a saturated aliphatic carbon atom: (a) S_N1; primary, solvent-induced ionization of the departing group to give a carbonium ion, which then can react with nucleophilic ions or molecules in the vicinity to give the substitution product; (b) S_N2; the familiar bimolecular replacement with complete Walden inversion; (c) S_Ni; the rearrangement of an intermediate product with retention of configuration. None of these is compatible with the observed order of reactivity discussed above, however. As Winstein has pointed out (6), physical evidence such as the ionization constants of the aliphatic halogen acids and the dipole moments of the alkyl halides would lead one to expect the effect on the rate to be approximately equal for the various halogens if the rate determining step were the removal of the hydroxy group to form a carbonium ion (S_N1). This argument can be extended to include the other two cases, S_N2 and S_Ni, for if the influence of the halogen were exerted only through an inductive effect, no great difference would be expected in going from chlorine to iodine. Since from the observed rate sequence, the reactivities are not even of the same order of magnitude, the exclusion of any mechanism not involving the iodine in a direct way is justified.

On the other hand, the mechanisms shown in Figures 2 and 3 are entirely compatible with the rate data. Iodine, because of its greater polarizability, is generally a much better nucleophilic reagent than bromine or chlorine. Therefore, if the closing of the iodonium ring is presumed to be the rate determining step, the sequence of reactivities becomes understandable.

Stereochemical considerations can also be employed to eliminate the mechanisms not involving the iodonium ion, for none of the three discussed

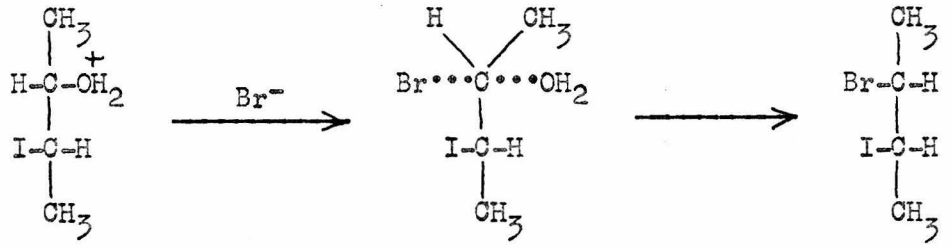
above, S_N1, S_N2 or S_Ni, would explain the loss of optical activity when the <u>threo</u>-iodohydrin, II, reacts with the hydrohalic acids.

S_N1:



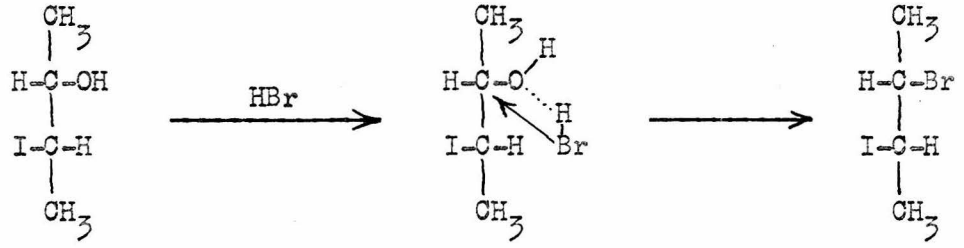
IX XI IVa III

S_N2:



IX XII III

S_Ni:



II XIII IVa

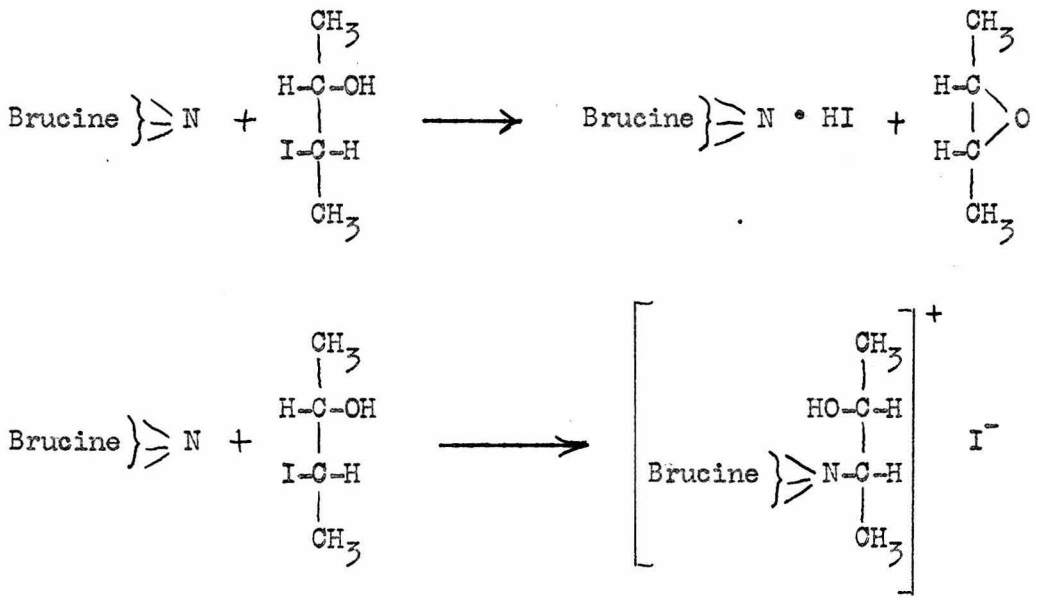
An S_N1 mechanism would lead to racemization of carbon atom C-2 because of the planar carbonium ion intermediate, XI, and two optically active diastereomeric products, IVa and III, would be formed. The <u>erythro</u> isomer, III, would be present in the larger amount, since an S_N1 mechanism usually gives predominant inversion of configuration with only partial racemization. This mechanism can therefore be excluded, for the product actually isolated

was the threo isomer, with no evidence for the presence of any erythro-dihalide. It would also be surprising if these two isomers were formed in exactly the proportion necessary to give zero rotation. An S_N2 mechanism can be excluded for two reasons; the product would have the erythro rather than the threo configuration, and it would be optically active. An S_Ni replacement would give the threo isomer as observed, but it would be active, so this mechanism too must be eliminated from consideration.

The exaltations of the molecular refractions of the iodohydrins and dihalides, given in the last column of Table I are of interest, since increases in the refractivity are not usually observed for any of the structural features present in the compounds. That the effect is real and not due to impurities is shown by the excellent agreement in the observed values for each pair of isomers. The exaltation appears to be due to the position of the substituents on adjacent carbon atoms, the greatest effect appearing in the bromo-iodo compounds where the largest interaction would be expected. The dibromobutanes also show slightly increased molar refractivity; calculated for meso and DL, 36.20; observed, meso, 36.34; DL, 36.36. The refractive indices and densities for the dibromides were determined by Lucas and Gould (12).

The reaction used for the partial resolution of the threo-iodohydrin was studied in order to determine the nature of the products. Lucas and Gould (12) succeeded in partially resolving a number of dibromoalkanes with brucine, and showed that the product of the reaction was a quarternary salt of the alkaloid. The solid obtained from the reaction of the iodohydrin with brucine, however, contained considerable quantities of brucine hydroiodide in addition to the quarternary iodide. Since brucine is a base, it is suggested that dehydrohalogenation to the oxide plays a

part in the resolution, as well as the alkylation of the brucine nitrogen.



The partial resolution is due to the difference in rate with which the antipodal iodohydrins undergo these two reactions.

Experimental*

meso-2,3-Butanediol. The meso-glycol was obtained free of other isomers by the method described by Mitchell (11). Crude butylene glycol, obtained from the Lucidol Company, was allowed to stand at room temperature for several months until a large part of the meso-isomer had crystallized out. The liquid was then drained off, care being taken to exclude moisture. The solid glycol was washed with isopropyl ether, and then recrystallized from that solvent; m.p., 33.9-34.3° (cor.).

D(+)-2,3-Epoxybutane. The active oxide used was that described in Part I of this thesis (9) prepared from D(-)-2,3-butanediol through the steps: D(-)-2,3-butanediol ⟶ D(+)-2,3-diacetoxybutane ⟶ L(+)-erythro-3-chloro-2-butanol ⟶ D(+)-2,3-epoxybutane. The physical constants were: b.p., 53.5-53.7° (cor.); n_D^{25}, 1.3705; d_4^{25}, 0.7998; $[\alpha]_D^{25}$, +59.05°.

cis-2,3-Epoxybutane. This was prepared in 71% yield from the meso-glycol in the same manner as the active oxide: meso-2,3-butanediol ⟶ meso-2,3-diacetoxybutane ⟶ DL-threo-3-chloro-2-butanol ⟶ cis-2,3-epoxybutane. The physical constants were: b.p., 59.7-60.0° (cor.); n_D^{25}, 1.3802.

L(+)-erythro-3-Iodo-2-butanol. In a 200 ml. three-necked flask fitted with a sealed stirrer, dropping funnel, reflux condenser, and ther-

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* Analyses, except for halogen in the iodohydrins and brucine salts, by Dr. G. Oppenheimer and Mr. G. Swinehart.

mometer, was placed 0.15 mole (10.8 g.) of D(+)-2,3-epoxybutane. The oxide was cooled to about -10° with an ice and hydrochloric acid bath, and then 0.15 mole (35 g., Merck Reagent, 55% aqueous) of hydriodic acid was added dropwise with vigorous stirring, the rate being adjusted so that the temperature of the reaction mixture remained below 0°. About 40 minutes were required. Stirring was continued for about 10 minutes after the addition was complete, and then the cold mixture was brought to neutrality with 3 f potassium carbonate solution. After transferring to a separatory funnel, the light yellow organic phase was drawn off; weight, 28.0 g. (93%). The material was washed to water-whiteness with 5 ml. of dilute sodium thiosulfate solution, and then was washed twice with 10 ml. portions of water and quickly dried with anhydrous potassium carbonate. Final drying was accomplished in a vacuum desiccator over calcium chloride at 8 mm. pressure. The purified product weighed 22.0 g. (73%), and had the following constants: m.p., 18.4-18.9° (cor.); n_D^{25}, 1.5371; d_4^{25}, 1.7753; α_D^{25}, +50.04°; $[\alpha]_D^{25}$, +28.19° (pure liquid).

The material was analyzed for iodine by the Volhard method. The sample (200-300 mg.) was weighed out from a weighing pipet into a 100 ml. Kjeldhall flask containing about 1 g. of potassium hydroxide dissolved in 5 ml. of water. The mixture was digested for 20 minutes at 100°, diluted to 50 ml. with water, neutralized with nitric acid, and transferred to a 200 ml. Erlenmeyer. Then 5 ml. of chloride free 6 n nitric acid, 2 ml. of 1 n ferric nitrate solution, and 25.00 ml. of standard 0.1 n silver nitrate solution were added in order, and the sample was back titrated with standard 0.1 n potassium thiocyanate.

Anal.-- Calc. for C_4H_9OI: I, 63.45%

Found: I, 63.45%

DL-erythro-3-Iodo-2-butanol. The inactive erythro-iodohydrin was prepared in 80% yield from a sample of pure DL-trans-oxide (prepared by Sargent; b.p., 53.5°; n_D^{25}, 1.3705; d_4^{25}, 0.8010) in exactly the same manner as the active iodohydrin. The physical constants and iodine content were not determined until after the product had been partially resolved (see below).

DL-threo-3-Iodo-2-butanol. This was prepared in 74% yield from the cis-oxide in the same manner as the erythro-iodohydrins. Final drying and purification was accomplished in this case, however, by distillation; b.p., 43.0°/2.5 mm. The other physical constants and the iodine content were not determined until after partial resolution (see below).

L(+)-erythro-3-Bromo-2-butanol. In a 200 ml. three-necked flask fitted with a mechanical stirrer and thermometer was placed 0.20 mole of hydrochloric acid bath, and 0.10 mole (7.2 g.) of D(+)-2,3-epoxybutane was added slowly with a dropper at such a rate as to keep the temperature below -10°. About 20 minutes were required. When the addition was complete, stirring was continued for about 5 minutes, and then the mixture was poured into a suspension of 10 g. of sodium bicarbonate in 40 ml. of water and ice. The mixture was then transferred to a separatory funnel, the organic phase drawn off, and the aqueous layer washed three times with 20 ml. portions of ethyl ether. The bromohydrin and extracts were combined and dried with anhydrous potassium carbonate, and the ether removed by distillation at atmospheric pressure. Two fractionations of the remaining material at reduced pressure gave 11.2 g. (73%) of pure bromohydrin; b.p., 49.0°/ 10 mm.; n_D^{25}, 1.4758; d_4^{25}, 1.4466; α_D^{25}, + 20.15°; $[\alpha]_D^{25}$, + 13.93°; M_D, Calc.,

29.96, Found, 29.83. Three cuts were taken in the second distillation; the refractive index and boiling point of all three were identical.

A second preparation gave 11.3 g. (74%) of bromohydrin with b.p., 49.0°/10 mm.; n_D^{25}, 1.4757; α_D^{25}, +20.14°, in good agreement with the values given above.

Winstein and Lucas (1) give the following values for DL-erythro-3-bromo-2-butanol: n_D^{25}, 1.4767; d_4^{25}, 1.4474. Both of these values are significantly higher than those found above for the active bromohydrin. However, their preparation was carried out at a higher temperature (5°, using DL-trans-oxide), and it is possible that their product was contaminated with a trace of the dibromide. There is considerable evidence, outlined above, that the material obtained in the present work was quite free of other compounds.

Partial Resolution of the DL-Iodohydrins: DL-threo-3-Iodo-2-butanol. To 0.100 mole (40.0 g.) of brucine dissolved in 200 ml. of chloroform was added 0.369 mole (73.8 g.) of DL-threo-3-iodo-2-butanol. After standing at room temperature for 20 hours, the chloroform was pumped off with an aspirator. The oil which remained was shaken with 400 ml. of 30-60° petroleum ether until the excess iodohydrin was extracted and the brucine salts solidified. The solid was filtered off and washed twice with petroleum ether (weight, 53 g.), filtrate and washings were combined, and the petroleum ether was pumped off with an aspirator at room temperature. The product which remained was distilled at reduced pressure to give 36.0 g. of iodohydrin; b.p., 28.8-30.8°/0.7 mm. (cor.); n_D^{25}, 1.5352; d_4^{25}, 1.7692; α_D^{25}, +3.06°. An analysis for iodine was carried out as discribed above:

Anal.-- Calc. for C_4H_9OI: I, 63.45%
Found: I, 63.69%

A portion of this iodohydrin (10 g., 0.05 mole) was converted into the oxide with concentrated base in the usual manner, b.p., 59.6-60.5° (cor.); n_D^{25}, 1.3796; α_D^{25}, -0.11°. These constants show that the oxide contained about 6% of the DL-trans isomer, and 0.2% of the L isomer. The threo-iodohydrin, therefore, contained about 6% of the erythro isomer, but only a negligible portion of the rotation was due to this impurity. Some stereomutation to the diastereomer apparently took place during the brucine treatment.

Two other methods were tried for the partial resolution of the threo-iodohydrin: (a) Selective adsorption on a suspension of brucine in 30-60° petroleum ether, in which the alkaloid is only slightly soluble. This method was used by Lucas and Gould for the resolution of threo-3-chloro-2-butanol (3). (b) Selective acetylation of the iodohydrin with acetic anhydride in the presence of brucine. Lucas and Gould also used this method for the resolution of the 3-chloro-2-butanols (3), and Winstein and Lucas resolved the 3-bromo-2-butanols in this way (2). The results obtained with the iodohydrins by either of these methods were in general less satisfactory than by the direct reaction with brucine described above. Method (a) gave a rotation of only -0.21°. Method (b) involves the separation of the iodohydrin from the iodoacetate, which proved to be difficult; rotations ranging from +0.92° to -0.43° were obtained depending on the degree of purification attained.

DL-erythro-3-Iodo-2-butanol. This was resolved by reaction with brucine in chloroform solution in exactly the same manner as the threo isomer, b.p., 34.3-34.9°/0.9 mm.; n_D^{25}, 1.5377; α_D^{25}, -3.42°; Iodine, calc.: 63.45%, found: 63.77%. Since the pure D(+)-erythro-3-iodo-2-butanol

had a rotation, α_D^{25}, +50.04°, the amount of resolution attained in this case was 6.8%.

A portion of the resolved erythro-iodohydrin, on treatment with base, gave an oxide with b.p., 53.5-54.0° (cor.); n_D^{25}, 1.3707; α_D^{25}, -3.16°. These constants indicate the presence of 2% of the threo-iodohydrin as an impurity in the resolved product. Stereomutation of one iodohydrin to the diastereomer in the presence of brucine appears to take place to a measureable extent under the conditions used for the resolution.

Composition of the Brucine Salts from the Resolutions. The brucine salt from the resolution of the erythro-iodohydrin was recrystallized three times from water, and dried over P_2O_5 at 0.4 mm. pressure at room temperature. Analysis for iodine: calc. for brucine·HI, 24.3%; found, 24.1%.

The salt from the resolution of the threo-iodohydrin was recrystallized three times from water and dried as above. Iodine analysis: found, 22.3%; calc. for brucine·HI, 24.3%; calc. for brucine·C_4H_9OI, 21.4%. This value indicated that the material was a mixture of brucine hydroiodide, and the quarternary salt of brucine and the iodohydrin. A fractional crystallization from water yielded two crops: (a) Iodine analysis: found, 21.9%; calc. for brucine·C_4H_9OI, 21.4%. (b) Iodine analysis: found, 24.1%; calc. for brucine·HI, 24.3%.

L(+)-erythro-2-Chloro-3-iodobutane. To 0.05 mole (10.0 g.) of L(+)-3-iodo-2-butanol in a 125 ml. Erlenmeyer flask was added, at room temperature, 0.3 mole of concentrated hydrochloric acid (25 ml., Bakers C.P., 37%). The resulting clear solution suddenly turned cloudy after about a minute, and a second phase separated out. The mixture was stirred

mechanically for another hour, transferred to a separatory funnel, and the organic phase, which had turned brown from liberated iodine, was drawn off; weight, 9.4 g. (86%). The material was washed with 10 ml. of dilute potassium carbonate solution to remove hydrochloric acid, and then with dilute sodium thiosulfate solution until water-white. Two washings with 10 ml. portions of water followed by drying with anhydrous calcium chloride and distillation at reduced pressure yielded 6.9 g. (63%) of colorless product, b.p., 34.8-35.3°/5 mm.; $\underline{n}_D^{25}$, 1.5313; $\underline{d}_4^{25}$, 1.7532; $\underline{\alpha}_D^{25}$, +13.98°; $[\underline{\alpha}]_D^{25}$, + 7.97°.

Anal.-- Calc. for C_4H_8ClI: C, 21.99%; H, 3.67%; AgX, 173.1%

Found: C, 21.78%; H, 3.76%; AgX, 170.4%

A second preparation, on a much smaller scale, gave a product with $\underline{n}_D^{25}$, 1.5318; $\underline{\alpha}_D^{25}$, +14.02°. The material was not distilled in this case, but the agreement in physical properties of the two preparations was nevertheless satisfactory.

L(+)-erythro-2-Bromo-3-iodobutane. This material was prepared in 66% yield from the active erythro-iodohydrin (0.043 mole, 8.7 g.) and 48% aqueous hydrobromic acid (0.2 mole, 34 g.) in a similar manner to the chloro-iodo compound. The reaction was started at 0°, and about two minutes were required for the appearance of the first cloudiness. Attempted distillation of the product at 6 mm. pressure (b.p., 53.0°) led to decomposition, so this step in the purification was omitted. The physical properties of the dihalide were: m.p., -9.5 to -9.0°; $\underline{n}_D^{25}$, 1.5642; $\underline{d}_4^{25}$, 2.0362; $\underline{\alpha}_D^{25}$, +4.13°; $[\underline{\alpha}]_D^{25}$, +2.03°.

Anal.-- Calc. for C_4H_8BrI: C, 18.27; H, 3.05; AgX, 160.7%

Found: C, 19.32; H, 3.52; AgX, 161.3%

meso-2,3-Di-iodobutane. To 1 g. of the active iodohydrin cooled to 0°, was added 5 ml. of 55% aqueous hydriodic acid, also cooled to 0°. The mixture rapidly turned dark with iodine, and a heavy oil began to separate out. However, even near the ice temperature, rapid decomposition set in and the oil layer appeared to boil vigorously due to gas evolution. The products were apparently butene, identified by odor, and iodine. No product could be isolated for the measurement of physical properties.

DL-threo-2-Chloro-3-iodobutane. This was prepared in a crude yield of 92% from (+)-threo-3-iodo-2-butanol (0.05 mole, 10.0 g.; α_D^{25}, +3.06°) and concentrated hydrochloric acid (0.3 mole, 25 ml. of Bakers C.P., 37%) in the same manner as the corresponding erythro compound. The first cloudiness appeared after 30 seconds. Distillation of the product gave 7.9 g. (73%) of the pure dihalide, b.p., 33.2-33.5°/4 mm.; n_D^{25}, 1.5337; d_4^{25}, 1.7587; α_D^{25}, + 0.05°.

Anal.-- Calc. for C_4H_8ClI: C, 21.99; H, 3.67; AgX, 173.1%

Found: C, 22.45; H, 3.75; AgX, 167.1%

A second sample of iodohydrin, α_D^{25}, +0.92°, gave a chloro-iodobutane with b.p., 45.6-46.4°/8 mm.; n_D^{25}, 1.5338; α_D^{25}, 0.00°, in good agreement with the values given above.

DL-threo-2-Bromo-3-iodobutane. This material was prepared in 84% crude yield from the active threo-iodohydrin (0.05 mole, 10 g.; α_D^{25}, + 3.06°) and aqueous hydrobromic acid (0.3 mole, 35 ml. Bakers C.P., 48%) in the same way as the other dihalides. The first cloudiness appeared in about 15 seconds. Distillation of the product gave 7.2 g. (55%) of colorless material with b.p., 29-30°/0.9 mm.; n_D^{25}, 1.5736; d_4^{25}, 2.0629; α_D^{25}, +0.01°.

Anal.-- Calc. for C_4H_8BrI: C, 18.27; H, 3.05; AgX, 160.7%

Found: C, 18.72; H, 3.18; AgX, 163.6%

The Reaction of L(+)-erythro-3-Bromo-2-butanol with Hydriodic Acid. To 0.047 mole (7.25 g.) of the active bromohydrin in an ampoule was added 25 ml. of aqueous 57% hydriodic acid. The solution was cooled to 0°, and gaseous HI, prepared by dropping the aqueous acid onto P_2O_5, was passed in until 26 g. had been taken up. The ampoule was sealed and allowed to stand overnight at room temperature. The ampoule was then opened, and the contents (rather dark with iodine) were poured onto an equivalent amount of sodium bicarbonate and ice. The oil layer was separated, washed to water-whiteness with sodium thiosulfate solution, and dried with calcium chloride; weight, 6.4 g. The material had n_D^{25}, 1.4965; b.p., 110-111° (Emich); α_D^{25}, 0.00°. These constants indicate that the product was inactive 2-iodobutane.

The Reaction of L(+)-erythro-3-Bromo-2-butanol with Phosphorus Triiodide. To 0.03 mole (4.5 g.) of the active bromohydrin in a 25 ml. Erlenmeyer flask was added 0.03 mole (0.9 g.) of red phosphorus and 0.03 mole (3.8 g.) of iodine. The mixture warmed somewhat, and was cooled as necessary to keep the temperature at 25-30°. After standing overnight, the mixture was shaken with concentrated HCl to remove any remaining bromohydrin, then with dilute sodium bicarbonate solution to neutralize, and finally with sodium thiosulfate solution to remove iodine. After drying with calcium chloride, the colorless oil had n_D^{25}, 1.4823. Distillation at reduced pressure yielded no 2-bromo-3-iodobutane, and it therefore seems probable that the main product here also was 2-iodobutane.

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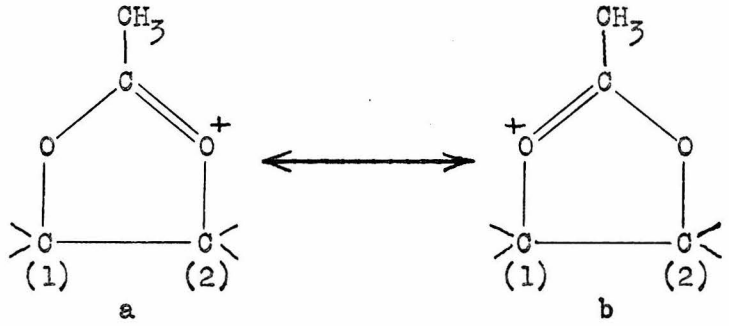
PART III

THE ACETOLYSIS OF D(+)-,2,3-DI-p-TOLUENESULFONOXYBUTANE

III

The Acetolysis of D(+)-2,3-Di-p-toluenesulfonoxybutane

Previous studies on the acetolysis of the p-toluenesulfonates of glycols have been limited to the cis- and trans-cyclohexanediols (1,2,3), and to meso-2,3-butanediol (4). In the cyclohexanediol derivatives, the six-membered ring prevents free rotation about the bond connecting the two hydroxyl-bearing carbon atoms. Winstein has shown that cyclic intermediate ions of the general type, I, play a part in these reactions. It is evident,



I

however, that when C-1 and C-2 are part of a cyclohexane ring, structures such as I are much more stable in the cis configuration than in the highly strained trans configuration. The meso-butylene glycol derivatives eliminate this difficulty, but since they are not optically active they do not yield all the information necessary to establish the mechanism of the replacements. An optically active acyclic glycol, therefore, represents the most general case in that the cis and trans forms of I are more nearly equivalent in the energy required for their formation, and loss or retention of optical activity provides additional data from which to deduce the mechanisms of the reactions. D(-)-2,3-butanediol was chosen for the present investigation because it was

most readily available,* and because it possessed the additional advantage of a symmetrical structure, eliminating differences in reactivity of the two hydroxyl groups.

When the p-toluenesulfonate of an optically active monohydric alcohol is heated in glacial acetic acid containing acetate ion, the tosyloxy group is replaced by an acetoxy group with nearly complete inversion of configuration (5,6). Moreover, the replacement is a typical S_N2 reaction, the driving force being the approach of the acetate ion to the back face of the carbon atom bearing the tosyloxy group. The analogous treatment of the p-toluenesulfonate of a glycol, however, leads to products which cannot be explained by a simple extension of this mechanism.

The acetolysis reactions, shown in Fig. 1, have been carried out under (a) anhydrous conditions, and (b) with a limited amount of water present, for it has been noted by Winstein that water influences the course of the reaction in the case of cyclohexane derivatives (1,2). The isomeric compositions of the reaction products, in terms of diacetate, are shown in Table 1. Products from reactions when water was present were mixtures of monoacetates and diacetates with the former predominating. For analysis, these were converted to the diacetates, and the isomeric compositions of t he product determined by means of melting points, refractive indices, and optical rotations. The compositions determined independently by the different constants were in good agreement.

The configurations shown for the optically active compounds are based on the known configuration of D(-)-2,3-butanediol (7).. D(+)-2,3-di-p-toluenesulfonoxybutane, II, and D(+)-threo-2-acetoxy-3-p-toluenesulfonoxy-

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* The active glycol was made available through the kindness of Dr. A. F. Langlykke of the Northern Regional Research Laboratory, Peoria, Illinois.

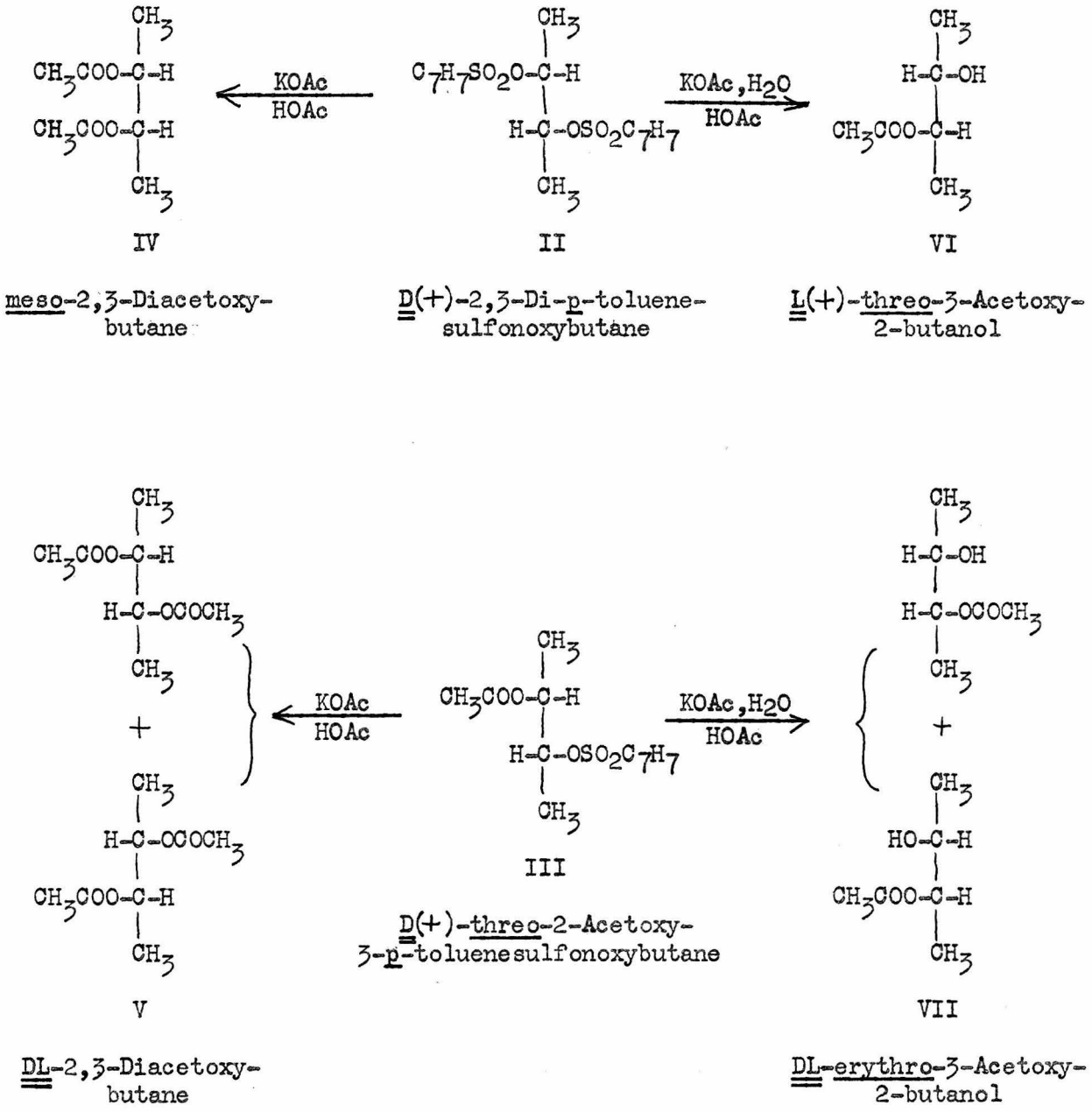


Figure 1. Acetolysis of the Ditosylate and Acetate-Tosylate of D(-)-2,3-Butanediol.

Table I

Starting Material	Water moles/mole of ester	Method of Isolation[a]	Properties of Diacetate			Composition of Diacetate		
			m.p. °C. (cor.)	n_D^{25}	α_D^{25}	meso %	DL %	L(-) %
D(+)-2,3-Di-p-toluene-sulfonoxybutane	0	I	0.7	1.4119	- 0.26°	91.1	7.0	1.9
	0	I	0.3	1.4119	- 0.26°	90.0	8.1	1.9
	0	II	0.8	1.4116	- 0.21°	91.5	7.0	1.5
	2.7	I	18.5	1.4135	-11.64°	15.9	0	84.1[b]
	4.2	II	21.3	1.4133	-12.61°	9.9	0	90.1[b]
D(+)-threo-2-Acetoxy-3-p-toluenesulfonoxybutane	0	II	41.2		+ 0.06°	3.7	96.3	0
	3.4	II	1.4	1.4112	0.00	93.2	6.8	0

45.

(a) Method I. The reaction mixture was poured onto a mixture of sodium bicarbonate and ice, and the solution extracted with ether.

Method II. Most of the solvent (acetic acid) was removed by distillation at reduced pressure until solid KOAc began to precipitate out. The mixture was then extracted directly with ether.

(b) These values were obtained from the m.p.'s. Values from the rotations are 82.7% and 89.5% respectively. The difference could arise either from the presence of a small amount of DL-diacetate which would raise the m.p., or from non-linearity of the rotation-composition curve.

butane, III, were obtained from the active glycol by reactions not involving the asymmetric center. The dextrorotatory monoacetate, VI, yields a levorotatory diacetate on acetylation with acetic anhydride. Since a dextrorotatory diacetate is obtained by direct acetylation of D(-)-2,3-butanediol, (+)-threo-3-acetoxy-2-butanol must belong to the L series. The monoacetate was not isolated in a pure state, but a mixture with 30% of the L(-)-diacetate, from the acetolysis of the active ditosylate in the presence of water, had a rotation of + 4.75°, showing the rotation of the pure compound to be positive.

The designation of any particular compound as D or L is based upon the configuration about carbon atom C-3 in conformity with carbohydrate nomenclature, where the configuration of the highest numbered asymmetric carbon atom determines the family (8). In some cases a compound could be assigned to either family. For example, it might seem logical to assign the monoacetate, VI, to the D family, since it is named as a derivative of D-2-butanol. However, introduction of the acetoxy group adds a new asymmetric center and changes the compound to a derivative of L-2,3-butanediol. Therefore, it seems preferable to adhere to the rules of carbohydrate nomenclature and assign the compound to the L family.

When D(+)-2,3-di-p-toluenesulfonoxybutane, II, is heated with potassium acetate in anhydrous acetic acid, the formation of meso-2,3-diacetoxybutane, IV, shows that an odd number of inversions have occurred. Mitchell (4) found that the meso-ditosylate gave DL-diacetate, showing that an odd number of inversions occur in that case also. Although an intermediate acetate-tosylate was not isolated, it is reasonable to assume that the reaction proceeds in steps and that the tosylate groups are replaced one at a time.

When the acetate-tosylate of D-2,3-butanediol, III, is treated similarly,

the product is the optically inactive DL-diacetate, V. This shows that the number of inversions involved in this transformation must be two, for one inversion of each asymmetric carbon atom is necessary for the formation of the L component of the DL mixture. Since the second stage of the replacement takes place with an even number of inversions while the overall conversion of ditosylate to diacetate takes place with an odd number, it follows that the first stage of the reaction, ditosylate to acetate-tosylate, involves an odd number of inversions. This is completely consistent with an S_N2 replacement of the first tosylate by acetate ion, just as in the case of the monohydric alcohols, that is, one inversion is involved in this step, and three in the overall change, ditosylate to diacetate (II to IV). It will be shown later how the formation from D-threo-2-acetoxy-3-p-toluenesulfonoxybutane, III, of DL-2,3-diacetoxybutane, V, rather than an active diacetate, is strong evidence for the formation of an intermediate cyclic ion.

When water is present in amounts at least equivalent to the ester, the reaction takes a different course, an effect first observed by Winstein and Buckles in the reaction of 2-acetoxy-3-bromobutane with silver acetate (9), and later by Winstein, Hess and Buckles in the acetolysis of 2-acetoxycyclohexyl-p-toluenesulfonate (1). The ditosylate of D-2,3-butanediol, II, yields L-threo-3-acetoxy-2-butanol, VI, showing not only that the total number of inversions is even, but that each of the asymmetric carbon atoms is inverted an odd number of times. Furthermore, the acetate-tosylate of the active glycol, III, gives rise to an inactive erythro-monoacetate, VII, indicating an internally compensated intermediate in addition to an odd number of Walden inversions in this step. The reaction is again presumed to proceed in two stages, the acetate-tosylate

being the intermediate product. Each stage of the reaction takes place with an odd number of Walden inversions. On the assumption that this number is one in each case, it follows that two inversions are involved in the overall change (II to VI). The formation of inactive erythro-monoacetate, VII, instead of an active monoacetate, from the active threo-acetate-tosylate, III, is later shown to be additional evidence for a cyclic intermediate ion.

All of the phenomena described above are satisfactorily accounted for by the two mechanisms outlined in Figures 2 and 3. Each of these involves the formation of a cyclic intermediate ion, IX and XII, respectively, of the type previously described by Winstein and coworkers as intermediates in similar changes.

In Figure 2 there are three steps in the change of D-ditosylate, II, to meso-diacetate, IV. Step one is the S_N2 displacement of the tosyloxy group by an acetoxy group, similar to the well known behavior of derivatives of monohydric secondary alcohols (5,6). Step two is the displacement of the second tosyloxy group by the carbonyl oxygen of the acetoxy group with one inversion to form the cyclic intermediate, IX. This is comparable to similar changes in the cyclohexanediol series (1,2,3). The third step is a second attack by acetate ion, with one inversion at either carbon atom, to yield the meso-diacetate, IV. Thus C-2 is inverted at step one, C-3 at step two, and either C-2 or C-3 at step three. Therefore, in the overall change either C-2 is inverted twice and C-3 once, or else C-2 is inverted once and C-3 twice.

The cyclic intermediate, IX, Figure 2, has the L-threo configuration and thus possesses optical activity. Activity is lost when this reacts with acetate ion since the resulting diacetate possesses the meso configura-

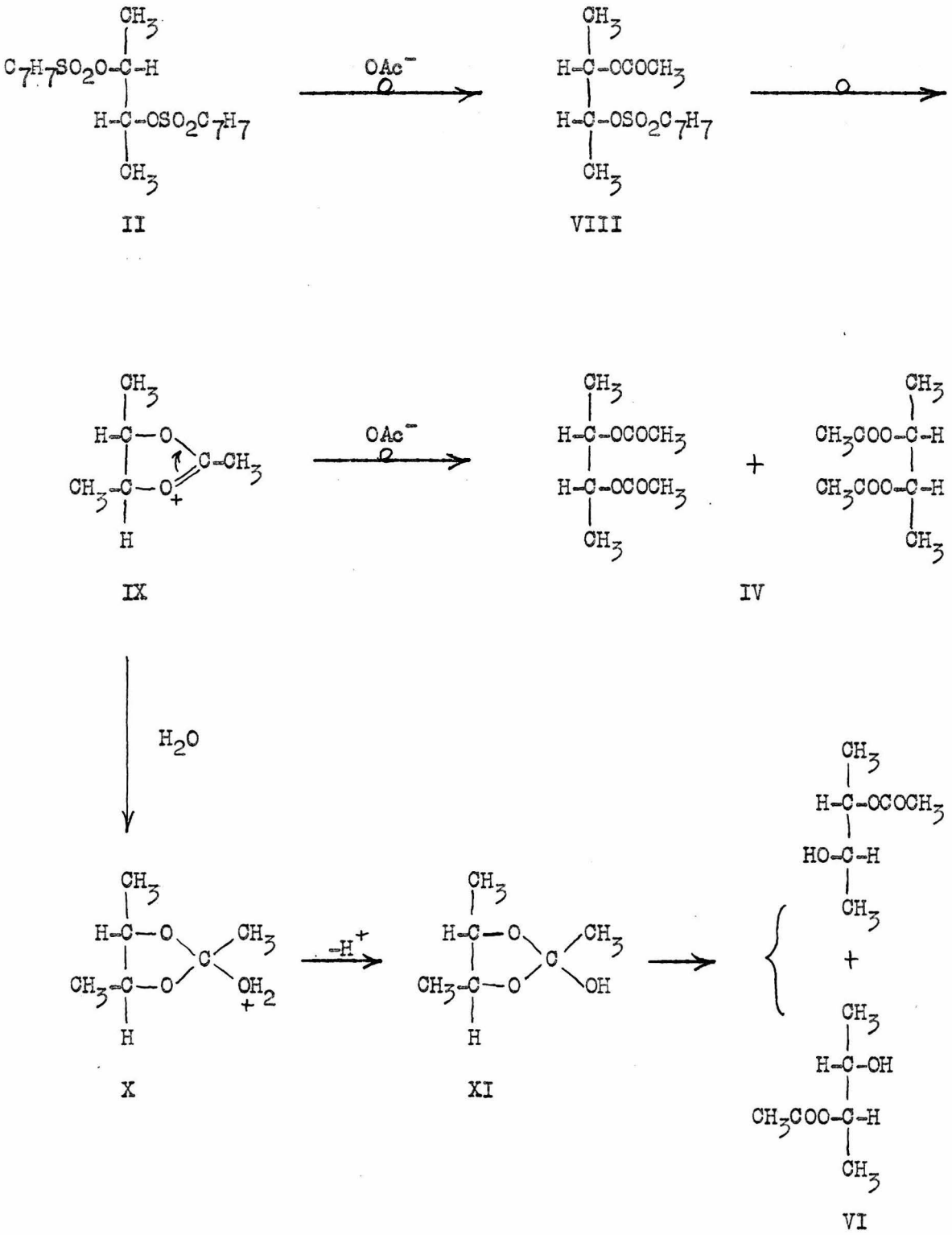


Figure 2. The Reaction Steps in the Acetolysis of D(+)-2,3-Di-p-toluenesulfonoxybutane.

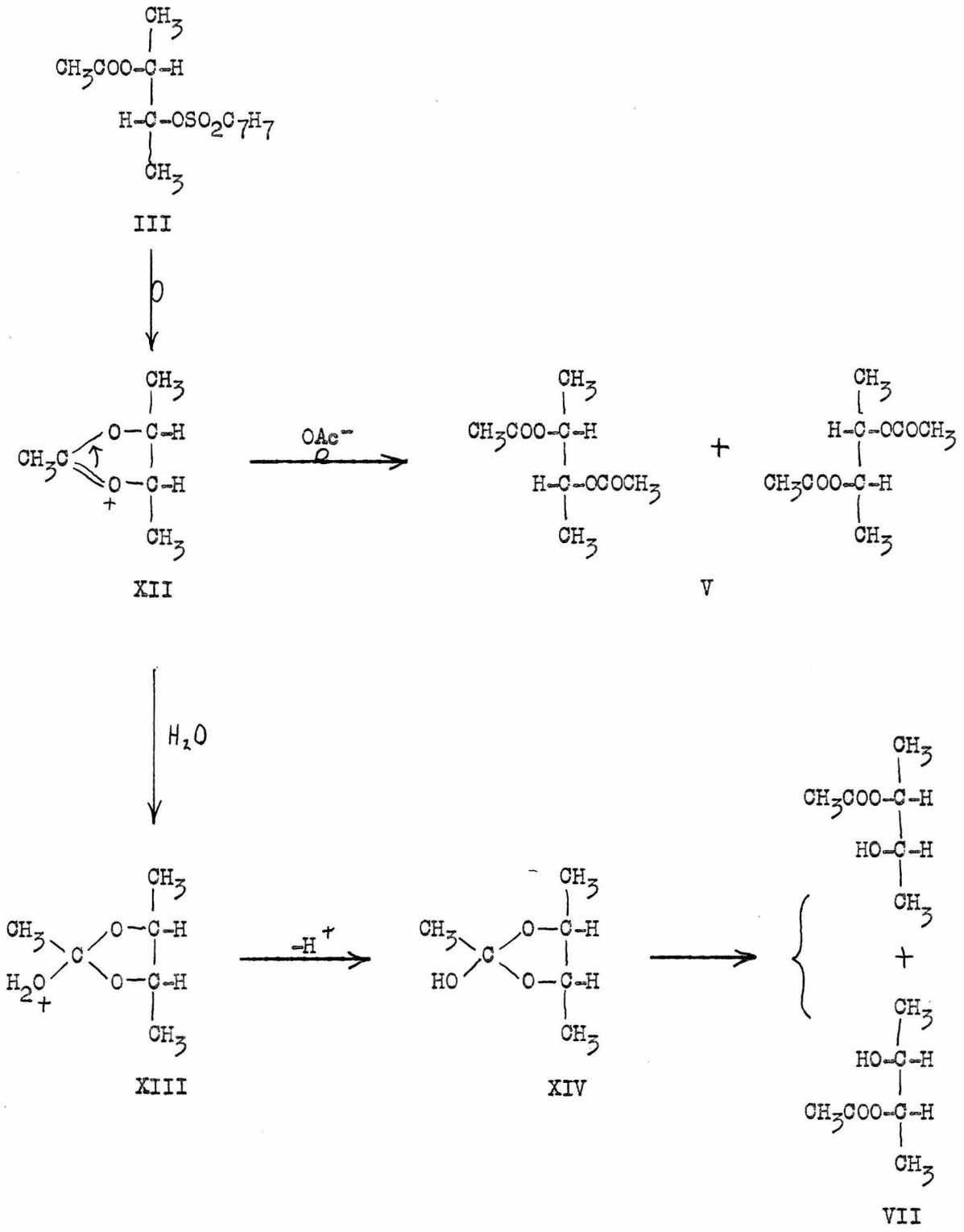


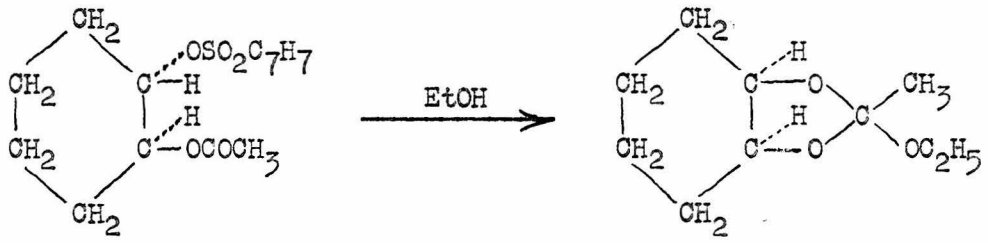
Figure 3. The Reaction Steps in the Acetolysis of D(+)-2-Acetoxy-3-p-toluenesulfonoxybutane.

tion. However, activity is retained when water is present, for then, instead of attack by acetate ion at either C-2 or C-3, water reacts to open the ring without inversion. Probably it attacks the acetoxy carbon atom to form another intermediate which may be represented by X. Then a proton is lost to form the orthoester, XI, which rearranges to the normal mono-ester, L(+)-threo-3-acetoxy-2-butanol, VI. Only one product is formed, since C-2 and C-3 have the same configuration. When water is present both C-2 and C-3 are inverted once. Thus the formation of an L-monoacetate from the original D-ditosylate is strong evidence for the formation of the cyclic intermediate, IX.

Similarly, the mechanism shown in Figure 3 satisfactorily accounts for the results obtained from D-acetate-tosylate, III. Here the first step is attack at C-3 by the carbonyl oxygen with one inversion to form the cyclic intermediate, XII. This has the meso-configuration and thus is inactive. The second step, attack by acetate ion, takes place at either C-2 or C-3 with one inversion. Thus either C-2 and C-3 are each inverted once, or else C-3 is inverted twice. The fact that the resulting diacetate has the threo configuration and yet is inactive is explained on the basis of these two configurational changes. The cyclic intermediate is necessary, therefore, in order for the D- and L-diacetates to be formed in equal amounts.

When water is present the ring of XII is opened without an inversion, as in Figure 2, probably going through XIII. Thus there is only one inversion, the one at C-3. The final product, VII, therefore has the erythro configuration. The fact that it is a mixture of the D and L forms, rather than the D form only, is a powerful argument for the formation of the inactive cyclic intermediate, XII.

The plausibility of the cyclic structures, IX and XII, as intermediates is enhanced by the strain-free nature of the five membered ring, and by the stabilization due to resonance between the two equivalent forms, shown in Ia and Ib. In addition, Winstein and Buckles have shown that when the solvolysis of trans-2-acetoxycyclohexyl-p-toluenesulfonate, XV, is carried out in extremely dry alcohol, cis-cyclohexene ethyl orthoacetate, XVI, can be isolated in good yield (10).



XV XVI

The fact that the reaction product, when water is present, is mainly a monoacetate rather than a diacetate, is additional evidence that the reaction proceeds through the cyclic intermediate. The products formed in reactions II to VI and III to VII could be accounted for by assuming that the replacement of the second tosyloxy group took place similarly to the first, viz., by a simple S_N2 mechanism, and that the monoacetate arose from partial hydrolysis of the diacetate formed. However, pure D(+)-diacetate was only 7% hydrolyzed under the conditions of the acetolysis experiments, contrasted with the 60-70% of monoacetate from the tosyl esters. Therefore, the monoacetate must be the primary reaction product, and the presence of diacetate must be ascribed to partial acetylation of the monoacetate by the solvent, acetic acid.

A consideration of the relative rates of the possible reactions is

also valuable evidence for the cyclic intermediate when water is present. Simple S_N2 replacement of the second tosyloxy group by acetate ion occurs under anhydrous conditions to the extent of only about 2% as shown by the small amount of L(-)-diacetate obtained from II in addition to the meso-diacetate, IV. The reaction by way of the ion IX is therefore about fifty times faster than the S_N2 attack by acetate ion. It does not seem reasonable that the addition of small amounts of water would completely reverse this order, as would be necessary for predominant S_N2 replacement of the second tosyloxy group to take place.

Analysis of Reaction Products: The products obtained from the anhydrous solvolyses, and from the solvolyses in the presence of water after further acetylation, were mixtures of two or more of the following: meso-, DL-, D-, and L-2,3-diacetoxybutane. Mixtures of two components could be analyzed satisfactorily by their melting points, taken by slowly melting the whole sample while the thermometer bulb was immersed directly in it, and noting the temperature at which the last of the solid disappeared. The refractive index, found to be a linear function of the composition, served as an auxiliary aid in determining the position on the melting point curve, in case this was necessary. The amount of optically active form was calculated from the rotation of the product. The rotation was assumed to be a linear function of the concentration, since the active form either was present in small amount, or else it was the major constituent, comprising 90% of the mixture. In one case, the anhydrous solvolysis of D(+)-ditosylate, II, the product was a mixture of three components, and both the melting point and rotation were necessary to establish its composition.

Melting point curves are shown for the three systems of 2,3-diacetoxybutane, viz., meso and DL, Figure 4, meso and D, Figure 5, and D and L, Figure 6. The first two of these are due to Mitchell (4, and unpublished work); the last was taken in the course of the present work to complete the series. The curves were constructed from the data listed in Table II, which are the temperatures at which the last part of the solid disappears. It is interesting that whereas the first two curves are normal in having a eutectic, the last is unusual in that a racemic compound is indicated, and this forms solid solutions with the active forms.

Table II

Melting Points of Diacetate Mixtures

meso %	DL %	D %	m.p. °C (cor.)
0.0	100.0		43.0
8.9	91.1		39.1
18.2	81.8		35.7
30.5	69.5		29.7
40.9	59.1		24.2
49.9	50.1		18.6
61.5	38.5		10.7
69.9	30.1		2.8
77.7	22.3		-3.5
87.2	12.8		-0.8
94.5	5.5		2.1
100.0	0.0		3.5
0.0		100.0	25.9
9.5		90.5	21.0
29.6		70.4	11.4
39.0		61.0	6.1
49.7		50.3	-1.0
60.2		39.8	-8.8
65.6		34.4	-9.7
68.1		31.9	-8.6
69.3		30.7	-8.1
74.9		25.1	-6.1
79.8		20.2	-4.0
89.9		10.1	-0.6
	3.9	96.1	27.8
	12.6	87.4	31.9
	19.8	80.2	34.3
	26.6	73.4	36.1
	33.8	66.2	37.7
	45.0	55.0	39.5
	52.0	48.0	40.3
	60.2	39.8	41.2
	71.4	28.6	42.1
	77.8	22.2	42.3
	86.8	15.2	42.7
	95.2	4.8	42.9

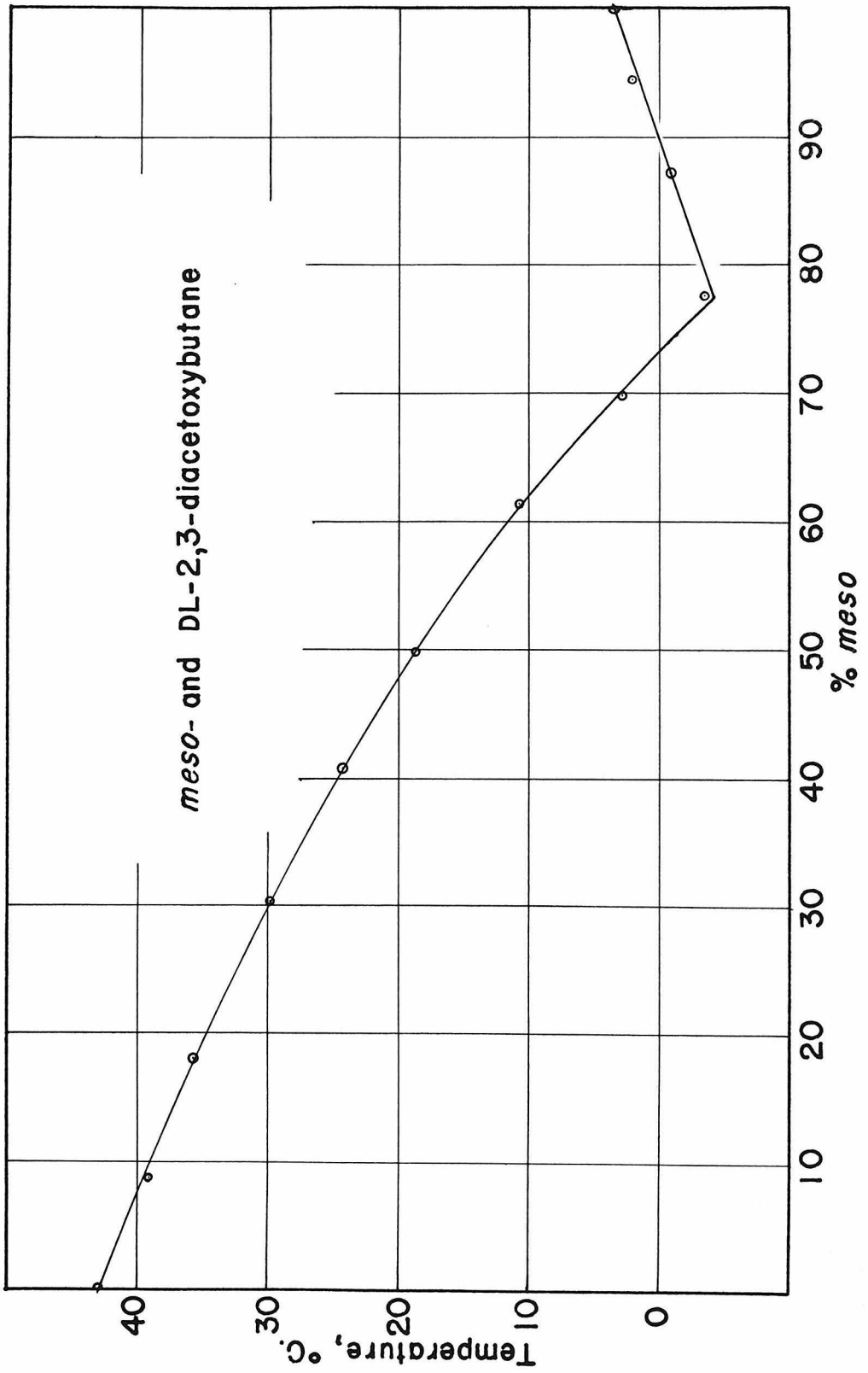


Figure 4. Melting Point Curve for meso- and DL-2,3-Diacetoxybutanes.

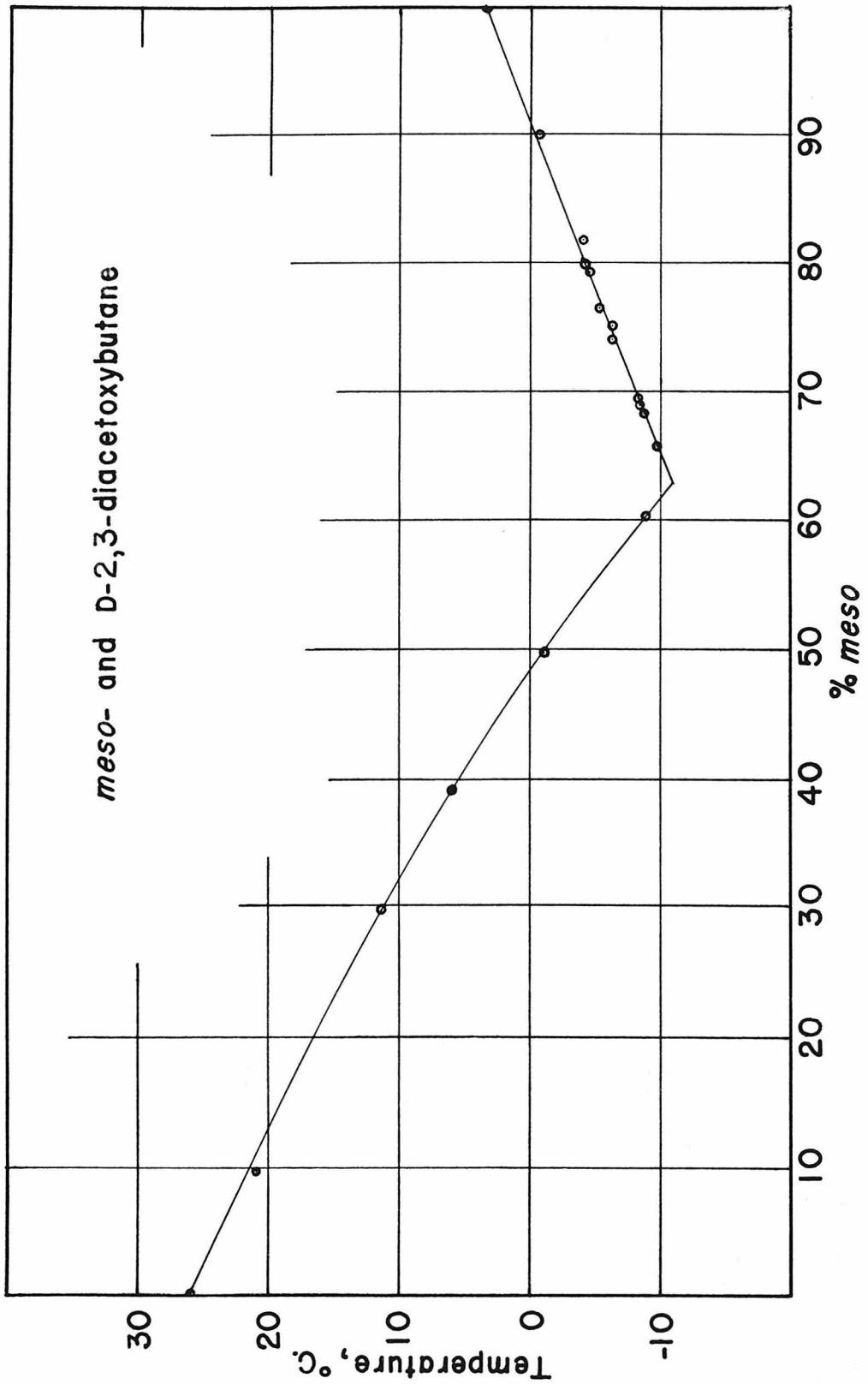


Figure 5. Melting Point Curve for meso- and D-2,3-Diacetoxybutanes.

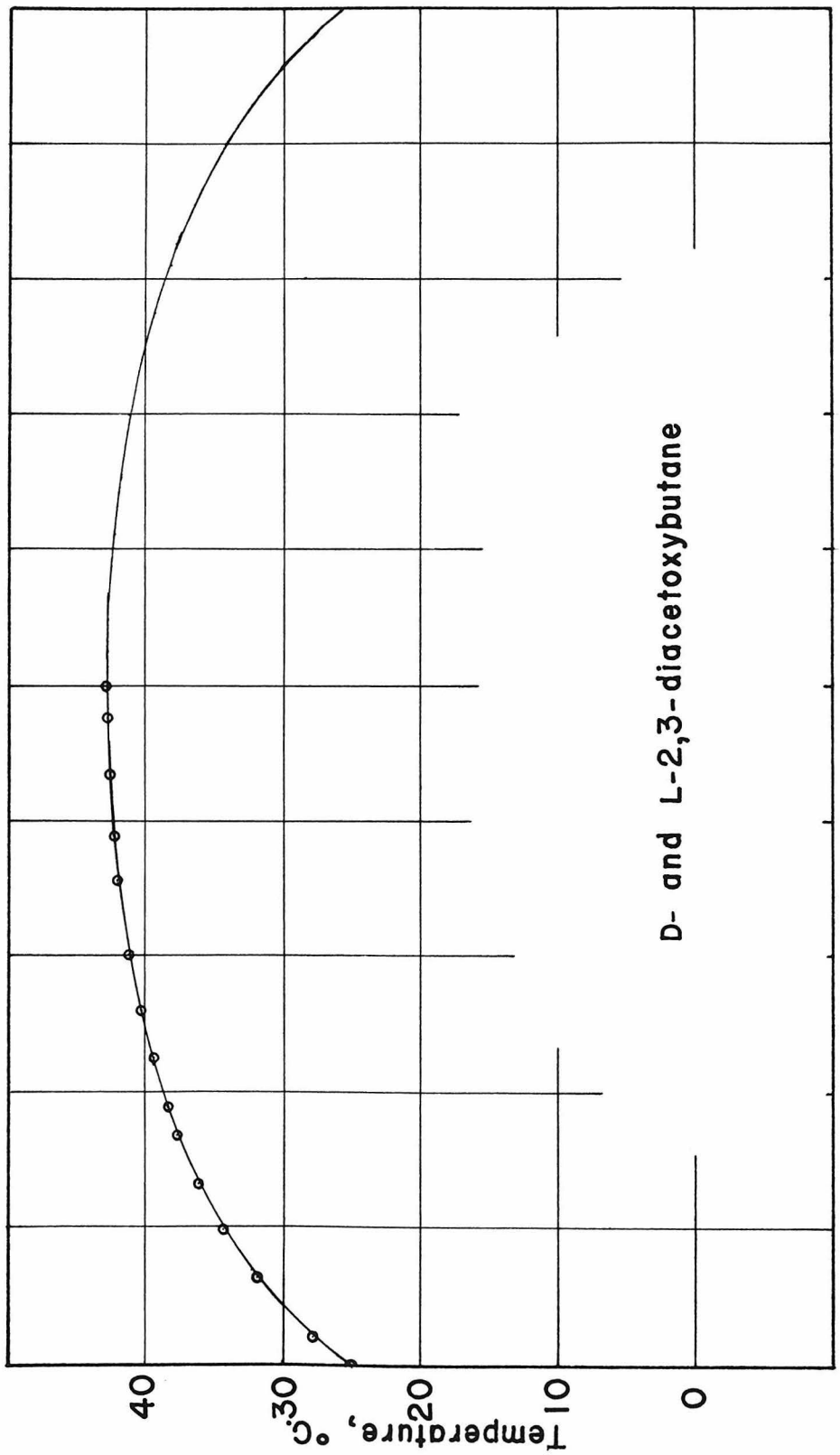


Figure 6. Melting Point Curve for D- and DL-2,3-Diacetoxybutanes.

Experimental*

D(-)-2,3-Butanediol. Dr. A. F. Langlykke of the Northern Regional Research Laboratory, Peoria, Illinois, stated that this isomer was obtained by the fermentation of starch by Bacillus polymyxa. The glycol contained a small amount of water and had an observed rotation of -12.4°. This became -13.00° ($[\alpha]_D^{25}$ = -13.17°) after one distillation at reduced pressure.

DL-2,3-Butanediol. The racemic glycol used in this work was from a supply prepared by Mitchell from pure meso-glycol through the steps: meso-glycol ⟶ meso-diacetate ⟶ DL-threo-3-chloro-2-butanol ⟶ cis-2,3-epoxybutane ⟶ DL-2,3-butanediol. The reactions used have all been described elsewhere (11).

D(+)-2,3-Diacetoxybutane. This material was prepared as described previously (12), from the active glycol and acetic anhydride, $[\alpha]_D^{25}$, + 13.72°; m.p., 25.7-25.9° (cor.).

DL-2,3-Diacetoxybutane. The racemic diacetate was prepared by the method of Wilson and Lucas from the DL-glycol and acetic anhydride using sulfuric acid as a catalyst, m.p., 42.6-43.0°(cor.).

Melting Point Curve of D- and DL-2,3-Diacetoxybutanes. The method of Collett and Johnston (13) was used. The samples (about 150 mg.) were weighed into thin walled soft glass test tubes about 8 mm. in diameter and

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* Microanalyses by Dr. G. Oppenheimer and Mr. G. A. Swinehart.

3 to 4 cm. long. The upper end was then sealed off, and a section of 2 mm. glass rod sealed on for a handle. The melting points were taken in an electrically heated bath fitted with a mechanical stirrer. The samples were vigorously agitated in the bath while raising the bath temperature at a rate of about 0.1°/min. until they were about half melted. The rate of heating was then slowed to about 0.02°/min., and the temperature held stationary at 0.1° intervals for about 5 minutes to insure equilibrium. The melting point was taken as the temperature at which the last solid disappeared. Temperatures were read on a thermometer (immersed in the bath) which was graduated in 0.1° intervals and which had been calibrated by the Bureau of Standards.

D(+)-2,3-Di-p-toluenesulfonoxybutane. To 0.50 mole (45.0 g.) of the active glycol dissolved in 3 moles (240 g.) of pyridine (Merck reagent, redistilled) was added 1.02 moles (194.5 g.) of p-toluenesulfonyl chloride (Eastman White Label, recrystallized from benzene). The acid chloride was added in portions over a period of about an hour, and the temperature of the reaction mixture was kept below 40°. When about half of the tosyl chloride had been added, crystals of pyridine hydrochloride began to separate out. The mixture was allowed to stand overnight at room temperature, and was then poured into two liters of cold 3 f C.P. hydrochloric acid. The product separated as an oil which soon solidified to a crystalline mass. This was ground in a mortar with dilute hydrochloric acid to remove traces of pyridine, filtered, and washed with water until the filtrate was neutral to litmus. The air-dried material weighed 192 g. (97% yield) and melted at 60.5-62.0°. This was recrystallized three times from isopropyl ether, and gave: m.p., 65.1-65.5° (cor.); $[\alpha]_D^{25}$, +37.2°

(0.9989 g. in 10.00 ml. of $CHCl_3$ solution). These values could not be raised by further recrystallization from ethanol, isopropyl ether, or ethyl ether. By working up mother liquors, a total of 148 g. (75%) of purified material was obtained.

Anal.-- Calc. for $C_{18}H_{22}O_6S_2$: C, 54.25; H, 5.56; S, 16.09

Found: C, 54.25; H, 5.65; S, 15.72

If the molar ratio of pyridine to glycol is less than about five to one, the reaction mixture sets to a solid mass of pyridine hydrochloride crystals. This apparently prevents the reaction from going to completion, and in the one case where a two to one ratio of pyridine to glycol was tried, no ditosylate could be isolated.

D(+)-threo-2-Acetoxy-3-p-toluenesulfonoxybutane. To 0.500 mole (45.0 g.) of the active glycol dissolved in 5 moles (395 g.) of freshly distilled anhydrous pyridine (Merck reagent) was added 0.500 mole (95.3 g.) of p-toluenesulfonyl chloride (recrystallized from benzene to constant melting point). The acid chloride was added portionwise over a period of about an hour. The temperature of the reaction mixture rose to about 40°, and after a short time, pyridine hydrochloride began to separate out. The mixture was allowed to stand at room temperature for three hours, and then 0.500 mole (51.0 g.) of freshly distilled acetic anhydride (Bakers C.P.) was run in slowly, about thirty minutes being required for the addition. The mixture was allowed to stand overnight, and was then poured into two liters of 2.5 f hydrochloric acid. The oil layer which separated was drawn off in a separatory funnel and the aqueous solution washed with ethyl ether. Oil and washings were combined, the total volume brought to 500 ml. with ether, and the solution washed twice with water and dried with anhy-

drous potassium carbonate. On cooling to dry ice temperature for several days, a quantity of white crystals separated out. The liquid was decanted off, and the last of the solvent removed from the solid at reduced pressure, yield, 106 g. (74%); m.p., 45-55°. This material was recrystallized six times from isopropyl ether and four times from ethanol to give 17 g. (12%) of product melting at 74.5-75.3° (cor.); $[\alpha]_D^{25}$, +4.9° (1.0005 g. in 10.00 ml. of $CHCl_3$ solution). The melting point of a small sample was not changed by ten more recrystallizations from ethanol.

Anal.-- Calc. for $C_{13}H_{18}O_5S$: C, 54.53; H, 6.33; S, 11.20;
Saponification equivalent, 143

Found: C, 54.41; H, 6.31; S, 11.42;
Saponification equivalent, 141

Acetylation followed by tosylation without isolation of the monoacetate gave the same product but the crude yield, 20%, was much lower. However, the crude product, m.p., 71-73°, was much purer than that obtained by tosylating first. Better yields could probably be obtained if the monoacetate intermediate were isolated before reacting with tosyl chloride.

Solvolysis Experiments, Anhydrous Conditions:

D(+)-2,3-Di-p-toluenesulfonoxybutane. To a mixture of 0.20 mole (19.5 g.) of freshly fused potassium acetate and 50 ml. of glacial acetic acid (m.p. = 15.5°, 0.5% water) was added 5 ml. of acetic anhydride. The flask was fitted with a reflux condenser and the solution brought to boiling for five minutes to remove the water. Then 0.050 mole (19.9 g.) of D(+)-2,3-di-p-toluenesulfonoxybutane was added and the mixture was refluxed for four hours. Two methods of isolation were used on duplicate runs.

Method I: The mixture was poured onto 1 mole (84 g.) of solid sodium bicarbonate and 400 g. of ice. The resulting solution was extracted

four times with 50 ml. portions of isopropyl ether. The ether extracts were washed twice with 50 ml. portions of water, and then dried with anhydrous potassium carbonate. The ether was removed by distillation at atmospheric pressure, and the residues were distilled at reduced pressure to give 5.6 g. (65%) of colorless liquid boiling at 76.5-76.8°/10 mm.; m.p., 0.7°; n_D^{25}, 1.4119; α_D^{25}, -0.26°. These constants indicate a composition of 91.1% meso-, 7.0% DL-, and 1.9% L-diacetate.

A duplicate run, using this same method of isolation, gave 5.9 g. (68%) of material, m.p., 0.3°; n_D^{25}, 1.4119; α_D^{25}, -0.26°; % meso, 90.0; % DL, 8.1; % L, 1.9. The values from the two runs are therefore in satisfactory agreement.

Method II: The product was isolated by removing acetic acid from the reaction mixture through a fractionating column at reduced pressure until the excess potassium acetate began to separate out. On cooling, the entire mass solidified. The cake was broken up and extracted twice with 100 ml. portions of isopropyl ether. Distillation of the ether solution gave 44% of product with m.p., 0.8°; n_D^{25}, 1.4116; α_D^{25}, -0.21°; % meso, 91.5; % DL, 7.0; % L, 1.5, in satisfactory agreement with the material obtained by Method I.

In this last run, the mixture of acetic acid, acetic anhydride, and potassium acetate was refluxed for two hours before adding the ditosylate, instead of five minutes as described for the first two runs. This shows that the small amount of levorotatory diacetate present in the product did not arise as a result of small amounts of water remaining in the mixture.

D(+)-threo-2-Acetoxy-3-p-toluenesulfonoxybutane. In a 200 ml. flask fitted with a reflux condenser were placed 0.060 mole (5.6 g.) of

freshly fused potassium acetate, 35 g. of glacial acetic acid (m.p. = 15.7°, 0.4% water), and 5 g. of acetic anhydride. The mixture was brought to boiling for ten minutes to remove traces of water, and then 0.030 mole (8.6 g.) of D(+)-threo-2-acetoxy-3-p-toluenesulfonoxybutane was added. The mixture was refluxed for 2½ hours, and then stood overnight at room temperature. Isolation of the product by method II gave 3.22 g. (62%) of product, b.p., 81.1-82.6°/10 mm.; m.p., 37.7-41.2° (cor.); α_D^{25}, + 0.06° (0.9530 g. in 2.00 ml. of $CHCl_3$ solution). The composition was therefore 96.3% DL-diacetate, 3.7% meso-diacetate, and possibly a trace of the D isomer.

Solvolysis Experiments in the Presence of Water:

D(+)-2,3-Di-p-toluenesulfonoxybutane. In a 200 ml. flask fitted with a reflux condenser were placed 0.050 mole (19.9 g.) of D(+)-2,3-di-p-toluenesulfonoxybutane, 0.20 mole (19.5 g.) of fused potassium acetate, 50 g. of glacial acetic acid (m.p., 15.5°, 0.5% water), and 1.55 g. of water, bringing the total water in the solution to 0.10 mole (1.80 g.). The mixture was refluxed for four hours, another 2.0 g. of water being added in 0.5 g. portions at 15 minute intervals during the first hour of this period. The product was isolated by method II above; yield, 4.6 g. (64%); b.p., 76.0-79.3°/10 mm.; n_D^{25}, 1.4188; α_D^{25}, +4.75°. The saponification equivalent was 118.5, indicating that its composition was 70% monoacetate and 30% diacetate.

Five ml. of acetic anhydride and one drop of sulfuric acid were added to the mixture, and the resulting solution was fractionally distilled at reduced pressure. There was obtained 3.6 g. of liquid boiling at 81.1-81.5°/10 mm.; m.p., 14.5-21.3°; n_D^{25}, 1.4133; α_D^{25}, -12.61°. These

constants indicate a composition of 90.1% L(-)-2,3-diacetoxybutane and 9.9% of the meso isomer. Two recrystallizations from 30-60° petroleum ether raised the observed rotation to -14.08°, the value for pure L(-)-2,3-diacetoxybutane.

When the isolation was carried out by method I, the yield was lower, and the saponification equivalent indicated that the original product was only 31% monoacetate with 69% diacetate. Since the monoacetate is miscible with water, it is probable that it was not all extracted from the aqueous solution. The properties of the diacetate prepared from the mixture, m.p., 18.5°; n_D^{25}, 1.4135; α_D^{25}, -11.64°; % L, 84.1; % meso, 15.9, were not far different from those obtained when method II was used, however.

A sample of D(+)-2,3-diacetoxybutane, $[\alpha]_D^{25}$, + 13.64°; m.p., 24.5-25.6°, was put through the same procedure. The material recovered melted at 18.0-21.5° and had a saponification equivalent of 90.1, indicating the presence of only 7% of the monoacetate. On complete acetylation, the material melted at 26.2-27.1°; α_D^{25}, +13.91°; $[\alpha]_D^{25}$, +13.57°, indicating a slight amount of racemization (2%) during the treatment.

D(+)-threo-2-Acetoxy-3-p-toluenesulfonoxybutane. In a 200 ml. flask fitted with a reflux condenser were placed 0.040 mole (11.2 g.) of D(+)-threo-2-acetoxy-3-p-toluenesulfonoxybutane, 0.080 mole (7.9 g.) of fused potassium acetate, 40 g. of glacial acetic acid (m.p., 15.7°, 0.4% water) and 1.28 g. of additional water, bringing the total water present to 0.080 mole (1.44 g.). The mixture was refluxed for 2½ hours, an additional 1.0 g. of water being added in 0.5 g. portions at 15 minute intervals during the first half hour. After standing overnight at room temperature, the product was isolated by method II, yield, 3.80 g. (65%);

b.p., 76.5-79.0°/10 mm. This material had a saponification equivalent of 114, indicating a composition of 60% monoacetate and 40% diacetate. Further acetylation with acetic anhydride, using sulfuric acid as a catalyst, gave on distillation 3.4 g. of diacetate, b.p., 76.8-77.1°/10 mm.; m.p., 1.4°; α_D^{25}, 0.00°. The composition was therefore 93.2% meso- and 6.8% DL-2,3-diacetoxybutane.

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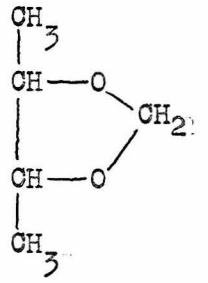
PART IV

THE PREPARATION AND HYDROLYSIS OF SOME CYCLIC ESTERS AND ACETALS OF D(-)-2,3-BUTANEDIOL

IV

The Preparation and Hydrolysis of Some Cyclic Esters and Acetals of D(-)-2,3-Butanediol

A convenient method for the recovery of 2,3-butanediol from dilute aqueous solutions involves its conversion to the cyclic formal, I, in which form it is readily distilled from the mixture as an azeotrope with water (1).



I

The glycol may be recovered from the formal by adding water, methanol, and hydrochloric acid and distilling; the formaldehyde is removed as methylal, and the free glycol is purified by distillation at reduced pressure.

Before applying this method to the recovery of optically active butylene glycol, it was necessary to know that the formation and hydrolysis proceeded without racemization. The mechanism proposed by Hammett (2) for the hydrolysis of acetals involves the formation of an intermediate carbonium ion, and therefore suggests that extensive racemization should occur. It was found, by preparing and hydrolyzing the formal of D(-)-2,3-butanediol, that this was not the case; there was complete retention of configuration throughout.

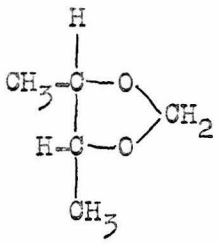
Because of the results with the formal, it became of interest to

prepare a number of cyclic esters and acetals of the active glycol, and to study their hydrolysis. The cyclic phosphites were of especial interest, since work was in progress in these laboratories on their use as intermediates in the resolution of glycols. The configurations of the compounds which were synthesized are shown in Figure 1, and their physical properties are listed in Table I.

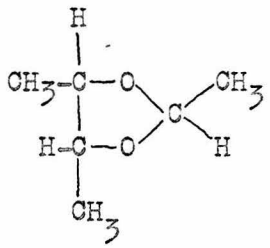
Nomenclature. The esters and acetals described here may be correctly named as indicated in Figure 1, or the more common names, as shown in Table I, may be used. Each system has certain advantages, and the use of one or the other depends on which property of the compound it is desired to emphasize.

The names given in Figure 1 are based on the designation of the parent ring systems found in the Ring Index (3). Thus II, III, and IV are derivatives of 1,3-dioxolane, and VI and VII are derivatives of 1,3,2-dioxathiolane. The ring system of the phosphorus derivatives is not given in the Ring Index, but Scully (4) and Mitchell (5) derived the names used here by analogy with the dioxathiolanes. The compounds, V, therefore become derivatives of 1,3,2-dioxaphospholane. The borate, VIII, is somewhat more complex; no name for the ring system could be found, and it seemed better to avoid confusion and use only the common name for the compound.

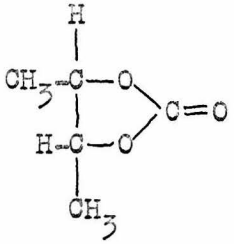
Whereas the names given in Figure 1 emphasize the heterocyclic nature of the compounds, the common names, Table I, are to be preferred in many cases since they indicate more clearly the chemical nature of the compounds. Thus II and III are aldehyde derivatives, the formal and acetal, respectively, while IV is clearly a carbonate. The four compounds given by V are phosphorous acid esters, and are therefore called phosphites; VI is a sulfite, and VII a sulfate. Since the present work was concerned largely



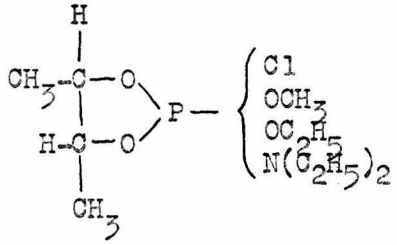
II
D(-)-4,5-Dimethyl-1,3-dioxolane



III
D(-)-2,4,5-Trimethyl-1,3-dioxolane

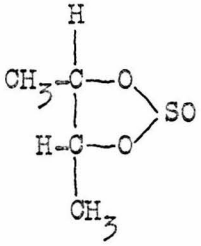


IV
D(+)-2-Oxo-4,5-dimethyl-1,3-dioxolane

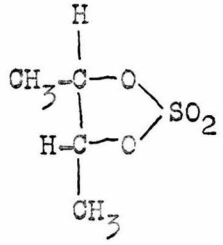


V

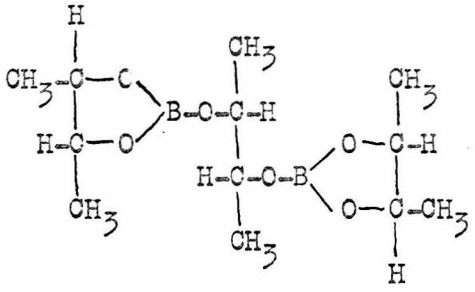
D-2-{Chloro / Methoxy / Ethoxy / Diethylamino}-4,5-dimethyl-1,3,2-dioxaphospholane*



VI
D(+)-2-Oxo-4,5-dimethyl-1,3,2-dioxathiolane



VII
D(+)-2,2-Dioxo-4,5-dimethyl-1,3,2-dioxathiolane



VIII
Neutral borate of D(-)-2,3-butanediol

* The rotation is positive for the Cl, OCH_3, and OC_2H_5 derivatives, negative for the diethylamino derivative.

Figure 1. The Configurations of Some Cyclic Acetals and Esters of D(-)-2,3-Butanediol.

Table I

Properties of the Cyclic Esters and Acetals of D(-)-2,3-Butanediol

Compound	B. P. °C.(cor.)	B. P. p,mm	M. P. °C.(cor.)	n_D^{25}	d_4^{25}	α_D^{25}	$[\alpha]_D^{25}$
II Formal	95.6-95.9	746		1.3959	0.9346	- 23.38°	-25.01°
III Acetal	102.6-103.1	746		1.3920	0.8915	- 9.63°	-10.80°
IV Carbonate	104.8-104.9	10	21.2-21.5	1.4160	1.1122	+ 36.39°	+32.72°
Va Chlorophosphite	49.1-49.2	10		1.4604	1.2038	+116.91°	+97.12°
Vb Methoxyphosphite	46.0-46.2	10		1.4318	1.0830	+ 58.08°	+53.63°
Vc Ethoxyphosphite	54.3	10		1.4297	1.0408	+ 51.99°	+49.95°
Vd Diethylaminophosphite	85.1-85.2	10		1.4549	0.9922	- 11.09°	-11.18°
VI Sulfite	60.5-60.7	10		1.4300	1.1942	+ 24.29°	+20.32°
VII Sulfate	123.8-124.0 92.9-93.1	10 2	6.1-6.4	1.4159	1.2898	+ 2.26°	+ 1.75°
VIII Borate (neutral)	138.0-138.5 105.3-105.7	6 0.6		1.4252	1.0383	- 2.58°	- 2.49°

with the hydrolytic behavior of the compounds, this nomenclature will be used mainly throughout the rest of the discussion.

Configurations. All of the compounds described were prepared from D(-)-2,3-butanediol (6) by reactions not involving the asymmetric centers, and therefore have the D configuration. Additional evidence of optical purity and absence of inversion was obtained in all cases (except the sulfate) by hydrolyzing to yield the glycol (or glycol formal) unchanged in sign and magnitude of rotation. It is interesting to note the extreme variations in the rotations observed for the various derivatives (Table I) emphasizing again that conclusions as to configuration should never be drawn from the sign or magnitude of the rotation in the absence of other evidence.

Experimental*

D(-)-2,3-Butanediol. This material was part of the same supply described in Part I of this thesis, $[\alpha]_D^{25}$, -13.17° after distillation at reduced pressure.

D(-)-4,5-Dimethyl-1,3-dioxolane. The method described by Senkus (1) was used. In a 100 ml. flask fitted with a fractionating column were placed 0.10 mole (9.0 g.) of D(-)-2,3-butanediol, 0.15 mole of formaldehyde (4.5 g. of trioxymethylene), and 50 ml. of 0.5 f sulfuric acid. The mixture was then distilled, and the azeotrope of formal and water removed at the top of the column. The two phase distillate was transferred to a separatory funnel, and the aqueous layer saturated with potassium carbonate to salt out dissolved formal. The water was then drained off and the formal dried with anhydrous potassium carbonate, yield, 10.0 g. (98%). Distillation of the product at atmospheric pressure gave 8.7 g. (85%) of material, b.p., 95.6-95.9°/746 mm.; n_D^{25}, 1.3959; d_4^{25}, 0.9346; α_D^{25}, -23.38°; $[\alpha]_D^{25}$, -25.01°.

Neish and MacDonald (7) prepared the active formal by simply allowing the reaction mixture to stand until equilibrium was reached, separating the phases, and distilling. Their yield (63%) was somewhat lower than in the present case. The physical properties found by them, n_D^{25}, 1.3960; d_4^{25}, 0.9346; $[\alpha]_D^{25}$, -24.9°, check well with those given above, however.

D(-)-2,4,5-Trimethyl-1,3-dioxolane. The cyclic acetal was prepared by two different methods.

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* Microanalyses by Dr. G. Oppenheimer and Mr. G. Swinehart.

Method A. The procedure worked out in these laboratories by M. Guthrie for the preparation of propylene glycol acetal was followed. To 0.25 mole (22.5 g.) of the active glycol in a 200 ml. flask was added 0.30 mole (60.6 g.) of diamyl acetal (prepared from n-amyl alcohol, paraldehyde, and sulfuric acid catalyst) and 1 g. of p-toluenesulfonic acid. The flask was fitted to a fractionating column and heated to refluxing, the glycol acetal being removed at the top of the column. A total of 27.2 g. (94%) of distillate was collected at 101-105°. This material was allowed to stand overnight over sodium to remove amyl alcohol and water, and subjected to two fractional distillations. The refractive index did not change between the first and second distillations. There was finally obtained 19.0 g. (66%) of pure acetal, b.p., 102.5-103.1° (cor.); n_D^{25}, 1.3920; α_D^{25}, -9.63°; $[\alpha]_D^{25}$, -10.80°.

Method B. In a 50 ml. graduated cylinder were placed 0.25 mole (22.5 g.) of D(-)-2,3-butanediol, 0.17 mole (22 g.) of paraldehyde, and 2 g. of p-toluenesulfonic acid. The cylinder was stoppered and allowed to stand at room temperature. After 24 hours, a second phase (about 1/3 of the total volume) had separated out. Then 5 g. of sodium bisulfate were added to decrease the activity of the water, and the mixture allowed to stand for three more days. At the end of this time, three liquid phases were present; bottom, 5.5 ml.; middle, 4 ml.; top, 43 ml. The top phase was separated from the two bottom phases (both of which were miscible with water) and washed with concentrated potassium carbonate solution to remove acid. It was then dried with anhydrous potassium carbonate, and distilled, 23.0 g. (79%) being collected at 102-105°, and an additional 4.0 g. (14%) at 105-110°. Two refractionations of this material gave 14.5 g. (50%) of

pure acetal, b.p., 102.6-103.1° (cor.); $\underline{n}_D^{25}$, 1.3920; $\underline{d}_4^{25}$, 0.8915; $\underline{\alpha}_D^{25}$, -9.63°; $[\underline{\alpha}]_D^{25}$, -10.80°.

Anal. Calc. for $C_6H_{12}O_2$: C, 62.03; H, 10.42

Found : C, 62.44; H, 10.98

The direct reaction of the glycol with paraldehyde can be made to give nearly as good yields as the exchange reaction with diamyl acetal, but the final purification of the product is more difficult. Amyl alcohol can be conveniently removed from the acetal with sodium, but careful fractionation is necessary to remove paraldehyde (b.p., 124°).

Neish and MacDonald (7) prepared the cyclic acetal of D(-)-2,3-butanediol by a procedure similar to Method B, but omitting the sodium bisulfate. Their yield, 34%, was somewhat lower than in the present case. They give the following properties for their product: $\underline{n}_D^{25}$, 1.3924; $\underline{d}_4^{25}$, 0.8914; $[\underline{\alpha}]_D^{25}$, -21.8°. This rotation is almost exactly twice that observed above. A private communication from Dr. Neish states that they have rechecked their material, and now find the value, $\underline{\alpha}_D^{25}$, -9.62°, to be correct.

D(+)-2-Oxo-4,5-dimethyl-1,3-dioxolane. In a one-liter three-necked flask fitted with a sealed stirrer, reflux condenser, and dropping funnel was placed 0.25 mole (22.5 g.) of active butylene glycol dissolved in 100 ml. of toluene. The stirrer was started, and a solution of 0.30 mole (30 g.) of phosgene in 200 ml. of toluene was run in slowly from the dropping funnel, about 30 minutes being required for the addition. The temperature rose to 40-45° during the addition, and at one point the solution became cloudy and a second phase started to separate out, but only a single clear phase was present at the end of the reaction. Stirring was continued for 15 minutes after the phosgene had all been added, and the mixture then

stood for another hour. Finally hydrogen chloride, excess phosgene, and most of the toluene were removed by distillation at atmospheric pressure through a short fractionating column, and the product was fractionally distilled at reduced pressure. There was obtained 22.0 g. (76%) of material with b.p., 104.7-104.9° (cor.)/10 mm.; $\underline{n}_D^{25}$, 1.4160; $\underline{\alpha}_D^{25}$, +35.96. There were no high boiling residues.

A sample was redistilled, recrystallized three times from ethyl ether, and again distilled; b.p., 104.8-104.9° (cor.)/10 mm.; $\underline{n}_D^{25}$, 1.4160; $\underline{d}_4^{25}$, 1.1122; m.p., 21.2-21.5° (cor.); $\underline{\alpha}_D^{25}$, +36.39°; $[\underline{\alpha}]_D^{25}$, +32.72°.

Anal. Calc. for $C_5H_8O_3$: C, 51.72; H, 6.94; m.wt., 116

Found : C, 52.34; H, 7.08; m.wt. (Rast), 125

Kolfenbach, Fulmer, and Underkofler (8) prepared a cyclic carbonate of 2,3-butanediol, but apparently used a mixture of meso- and DL-glycol. No solvent was used, and the reaction was carried out at a higher temperature (150°). The constants for their compound, $\underline{n}_D^{26}$, 1.4226, and $\underline{d}_4^{26}$, 1.129, are considerably higher than for the active isomer.

Neutral Borate of D(-)-2,3-Butanediol. To 0.25 mole (22.5 g.) of D(-)-2,3-butanediol in a 100 ml. flask were added 0.167 mole (10.3 g.) of boric acid and 25 ml. of benzene. The flask was fitted to a fractionating column provided with a liquid separator and distillation started. The azeotrope of benzene and water was removed at the top of the column; benzene was returned to the boiler by the separator, and the water was collected in a graduated cylinder. After two hours, 8.8 ml. of water had been removed (theory, 9.0 ml.). The benzene was then removed by distillation at atmospheric pressure, and the product distilled at reduced pressure, yield, 21.3 g. (90%); b.p., 138.0-138.5°/6 mm.; $\underline{n}_D^{25}$, 1.4252. This material was

redistilled twice to finally give a product with b.p., 138.6-138.9°/6 mm., 105.3-105.7°/0.6 mm.; $\underline{n}_D^{25}$, 1.4252; $\underline{d}_4^{25}$, 1.0383; $\underline{\alpha}_D^{25}$, -2.33°; $[\underline{\alpha}]_D^{25}$, -2.24°.

Anal.	Calc. for $C_{12}H_{24}O_6B_2$:	C, 50.40; H, 8.46; neut.eq., 143; m.wt., 286
	Found	: C, 50.72; H, 8.63; neut.eq., 139; m.wt. (Rast), 167

The molecular weight found was far too low for the formula given for the compound in Figure 1. However, the borate is very hygroscopic and is hydrolyzed almost instantly by water, and it is probable that the sample picked up sufficient water during the weighing to lower the apparent molecular weight to the value found.

Morell and Lathrop (9) have prepared the corresponding borate of meso-2,3-butanediol, but distilled off the water directly without using benzene. They discuss the chemical properties of the compound, but give no physical constants.

D(+)-2-Chloro-4,5-dimethyl-1,3-dioxaphospholane. The method developed by Mitchell (5) for the preparation of the corresponding propylene glycol derivative was used. The apparatus consisted of a one-liter three-necked flask fitted with a reflux condenser, sealed stirrer, and a side tube about 40 cm. long and inclined upward at an angle of about 10° with the horizontal. The side tube was fitted with two dropping funnels. About 50 ml. of chloroform was placed in the flask, and in the two dropping funnels were placed 0.50 mole (45 g.) of active glycol in 150 ml. of chloroform solution, and 0.50 mole (69 g.) of phosphorus trichloride in 150 ml. of chloroform solution, respectively. The stirrer was started, and the solutions in the dropping funnels were run into the side tube simultaneously

and at as near the same rate as possible. The reaction took place at the point of mixing of the two solutions, and the product then drained down into the flask. The side tube became warm where the two reactants came together, but the solution in the flask cooled below room temperature. When the addition was complete (40 min.), the chloroform was removed by distillation at atmospheric pressure, and the product was fractionated at reduced pressure, yield, 51 g. (66%). The chlorophosphite was further purified by a second distillation to give 46.7 g. of material, b.p., 49.1-49.2° (cor.)/10 mm.; $\underline{n}_D^{25}$, 1.4604; $\underline{d}_4^{25}$, 1.2038; $\underline{\alpha}_D^{25}$, +116.91°; $[\underline{\alpha}]_D^{25}$, + 97.12°.

Anal. Calc. for $C_4H_8O_2PCl$: C, 31.09; H, 5.22; Cl, 22.95; P, 20.05

Found : C, 31.36; H, 5.56; Cl, 22.94; P, 20.08

D(+)-2-Methoxy-4,5-dimethyl-1,3-dioxaphospholane. To 0.05 mole (7.7 g.) of the active chlorophosphite dissolved in 15 ml. of 30-60° petroleum ether was added 0.075 mole (8.6 g.) of N-ethylmorpholine, and then, dropwise, 0.05 mole (1.6 g.) of methanol in 10 ml. of 30-60° petroleum ether. The reaction took place rapidly with a hissing sound, and a precipitate of ethylmorpholine hydrochloride formed immediately. When the addition was complete, the solution was filtered away from the solid hydrochloride, and the crystals were washed with three 25 ml. portions of 30-60° petroleum ether. Special care was taken during all of these operations to exclude atmospheric moisture as much as possible. Filtrate and washings were combined, and the ligroin removed at atmospheric pressure. Two fractionations at reduced pressure separated the phosphite from the excess ethylmorpholine; yield, 3.6 g. (48%); b.p., 46.0-46.2° (cor.)/10 mm.; $\underline{n}_D^{25}$, 1.4318; $\underline{d}_4^{25}$, 1.0830; $\underline{\alpha}_D^{25}$, +58.08°; $[\underline{\alpha}]_D^{25}$, +53.63°.

Anal. Calc. for $C_5H_{11}O_3P$: C, 40.00; H, 7.39; P, 20.64

Found : C, 40.70; H, 7.25; P, 20.66

D(+)-2-Ethoxy-4,5-dimethyl-1,3-dioxaphospholane. This was prepared in exactly the same manner as the methoxy derivative, using ethanol instead of methanol. Two fractionations of the product gave 3.6 g. (52%) of material with b.p., 54.3° (cor.)/10 mm.; n_D^{25}, 1.4297; d_4^{25}, 1.0408; α_D^{25}, +51.99°; $[\alpha]_D^{25}$, +49.95°.

Anal. Calc. for $C_6H_{13}O_3P$: C, 43.90; H, 7.98; P, 18.87

Found : C, 44.18; H, 8.54; P, 18.97

D(-)-2-Diethylamino-4,5-dimethyl-1,3-dioxaphospholane. The same procedure was used as for the alkoxy derivatives, using diethylamine. The product was distilled twice, yield, 5.8 g. (61%); b.p., 85.1-85.2° (cor.)/10 mm.; n_D^{25}, 1.4549; d_4^{25}, 0.9922; α_D^{25}, -11.09°; $[\alpha]_D^{25}$, -11.18°.

Anal. Calc. for $C_8H_{18}O_2NP$: C, 50.25; H, 9.49; N, 7.33; P, 16.20

Found : C, 51.07; H, 9.75; N, 7.34; P, 15.96

When a portion of the diethylamino derivative was allowed to stand in moist air for a few hours, the entire sample crystallized to a hygroscopic solid. This material was recrystallized four times from dioxane, m.p., 82-83°; $[\alpha]_D^{25}$, -10.5° (0.0934 g. in 2.00 ml. of $CHCl_3$ solution). The compound behaved as a salt, giving an immediate strong odor of diethylamine with aqueous base. It was probably the diethylamino salt of the mono-acid phosphite of D-2,3-butanediol.

Anal. Calc. for $C_8H_{22}O_4NP$: C, 42.28; H, 9.76; N, 6.17; P, 13.63

Found : C, 42.25; H, 9.75; N, 6.12; P, 13.65

D(+)-2-Oxo-4,5-dimethyl-1,3-dioxathiolane. In a 200 ml. three-

necked flask fitted with a sealed stirrer, reflux condenser, and dropping funnel was placed 0.25 mole (22.5 g.) of D(-)-2,3-butanediol dissolved in 100 ml. of methylene chloride. The stirrer was started, and 0.30 mole (35.7 g.) of thionyl chloride was run in slowly from the dropping funnel, about 30 min. being required for the addition. The mixture warmed to about 40° at first, but as the reaction proceeded, hydrogen chloride was evolved copiously and the temperature dropped to near 0°. When the addition of thionyl chloride was complete, the mixture was heated to boiling (about 45°) and allowed to reflux for about 10 min. Then 50 ml. of water was added to decompose excess thionyl chloride. The layers were separated, and the organic phase was washed successively with 50 ml. of water, 50 ml. of dilute potassium carbonate solution, and 50 ml. of water. After drying over anhydrous potassium carbonate, the methylene chloride was removed by distillation at atmospheric pressure, and the sulfite was distilled at reduced pressure; yield, 31.0 g. (91%); b.p., 60.5-60.7° (cor.)/10 mm.; n_D^{25}, 1.4300; d_4^{25}, 1.1942; α_D^{25}, +24.29°; $[\alpha]_D^{25}$, +20.32°.

Anal. Calc. for $C_4H_8O_3S$: C, 35.29; H, 5.89; S, 23.55; m.wt., 136

Found : C, 35.35; H, 6.27; S, 22.98; m.wt. (Rast), 134

Robertson and Neish (10) prepared the active sulfite, but did not use a solvent, and their yield, 70%, was somewhat lower than in the present case. The physical constants of their product, n_D^{25}, 1.4296; d_4^{25}, 1.192; $[\alpha]_D^{25}$, +19.92°, check reasonably well with those given above.

D(+)-2,2-Dioxo-4,5-dimethyl-1,3-dioxathiolane. The active sulfate was prepared from the sulfite by a modification of the procedure developed by Evans (11), using calcium permanganate rather than the less soluble potassium salt. A solution of calcium permanganate was prepared by dis-

solving 0.150 mole (50 g.) of the tetrahydrate in water. The material was somewhat impure, and a considerable quantity of solid material remained; this was filtered off before use. The active sulfite, 0.20 mole (27.2 g.) was dissolved in 100 ml. of glacial acetic acid, and the mixture cooled to about 10° with an ice bath. The permanganate solution was then added slowly with mechanical stirring, at such a rate that the temperature could be held below 15° with the ice bath. About 45 minutes were required. The reaction was rapid and strongly exothermic; an immediate colloidal precipitate of manganese dioxide appeared as the permanganate solution was added. When further addition of permanganate caused no rise in temperature, and the pink color of the permanganate ion could be detected in the solution, the addition was stopped, and the mixture was poured into 150 g. of sodium bicarbonate and ice water. Excess MnO_4^- was destroyed with bisulfite, and the solution was extracted six times with 100 ml. portions of ethyl ether. The extracts were dried over calcium chloride, and the ether was stripped off at room temperature with an aspirator. The product remaining was fractionally distilled at reduced pressure, yield, 13.6 g. (45%); b.p., 92.9-93.1° (cor.)/2 mm., 123.8-124.0° (cor.)/10 mm.; m.p., 6.1-6.4° (cor.); $\underline{n}_D^{25}$, 1.4159; $\underline{d}_4^{25}$, 1.2898; $\underline{\alpha}_D^{25}$, +2.26°; $[\underline{\alpha}]_D^{25}$, +1.75°

Anal. Calc. for $C_4H_8O_4S$: C, 31.57; H, 5.30; S, 21.07; m.wt., 152

Found : C, 32.02; H, 5.33; S, 20.51; m.wt. (Rast), 152

Hydrolysis of D(-)-4,5-Dimethyl-1,3-dioxolane. The active formal, 0.05 mole (5 g.), was placed in a flask with 2 ml. of water, 0.1 ml. of concentrated hydrochloric acid, and 10 ml. of methanol. The flask was fitted to a fractionating column, and the mixture was refluxed until the temperature at the top of the column dropped to 41.5°, the boiling point

of methylal. The methylal was taken off intermittently as it accumulated at the column head, about 10 hours being required. Finally, the excess methanol was distilled over, the residues were neutralized by adding solid potassium carbonate (0.2 g.), and the glycol was distilled at reduced pressure, b.p., 77.3-77.4° (cor.)/10 mm.; m.p., 18.3-19.0° (cor.); α_D^{25}, -12.96°. The value of the rotation was only 0.04° less than that of the original glycol, and therefore essentially complete retention of configuration prevailed through the preparation and hydrolysis of the formal.

Hydrolysis of D(-)-2,4,5-Trimethyl-1,3-dioxolane. The active acetal, 0.10 mole (11.6 g.), was placed in a flask with 50 ml. of 1 f sulfuric acid, and the flask fitted to a fractionating column. The mixture was refluxed until acetaldehyde was no longer evolved, and finally part of the water was distilled over to remove the last traces of acetal and acetaldehyde. Then 4.5 g. of trioxymethylene was added to the boiler, and the formal was distilled out as the azeotrope with water. After drying, the product weighed 9.5 g. (93%). On distillation, the formal boiled at 95.4-96.8° (cor.) and had n_D^{25}, 1.3959; α_D^{25}, -23.39°. These constants are essentially identical with those of the formal prepared directly from the glycol.

Hydrolysis of the Cyclic Esters, General Procedure: Acid Hydrolysis. The ester, usually 0.05 mole, was placed in a flask with 50 ml. of 1 f sulfuric acid. The flask was then fitted to a reflux condenser, and the mixture heated, to refluxing if necessary, until the ester all dissolved. The solution was then cooled to room temperature, 3.0 g. of trioxymethylene were added, and the formal was distilled out through a fractionating column. The formal was dried and distilled, and its refractive index and rotation taken.

Basic Hydrolysis. The ester, 0.05 mole, was heated with 2 *f* potassium hydroxide in a manner similar to the treatment with acid. When solution was complete, the mixture was made acid with sulfuric acid, and the glycol was converted to the formal as above.

The results of the hydrolyses are shown in Table II.

Table II

The Hydrolysis of the Cyclic Esters of D(-)-2,3-Butanediol

Compound	Acid Hydrolysis					Basic Hydrolysis				
	Hydrolysis	Properties of Formal				Hydrolysis	Properties of Formal			
	Temp, °C.	b.p.(cor.)	n_D^{25}	α_D^{25}	Yield*	Temp, °C.	b.p.(cor.)	n_D^{25}	α_D^{25}	Yield*
IV Carbonate	80-90	95.3-96.3	1.3959	-23.54°	85%	30	95.8-96.3	1.3959	-23.63°	86%
Va Chlorophosphite	25	95.3-96.3	1.3956	-23.42°	93%	25	94.8-96.3	1.3956	-23.34°	94%
VI Sulfite	100	95.5-95.7	1.3962	-23.37°	90%	100	95.3-96.3	1.3960	-23.61°	94%
VII Sulfate	100	100.4-102.4	1.4041	0.00	95%	100	94-98	1.3972	- 0.46°	83%
VIII Borate	25	95.4-95.9	1.3959	-23.39°	97%					

* This is the yield of dried product before distillation. In each case, the whole sample was distilled over, however.

Discussion

Preparation. Since all the cyclic compounds described here, except the sulfate, VII, and the phosphite derivatives, Vb, c, and d, were formed by the reaction of two polyfunctional molecules,* it would not have been surprising if extensive polymer formation had cut the yields down to rather low values. This was not the case, however; indeed, under the conditions used, the cyclization reaction seemed to go almost to the exclusion of the linear condensation. In the preparation of the formal, II, and in Method A for the preparation of the acetal, III, the desired product was the lowest boiling component of the reaction mixture. Since it could therefore be removed continuously as formed, and since conditions in the reaction vessel were such that the polymer could be easily converted to the cyclic compound, it is not surprising that high yields were obtained. However, in Method B for the preparation of the acetal, III, a high crude yield was also obtained, showing that even in the equilibrium mixture the concentration of polymer is low.

The preparation of the carbonate, IV, and the sulfite, VI, gave high yields of the cyclic product; indeed, the yields of sulfite were nearly quantitative. These reactions are not of the equilibrium type, so the absence of polymer must here be ascribed to the faster rate of the cyclization process. Both preparations were carried out in solution, but the concentration of reactants was relatively high and the absence of polymer in the product cannot have been entirely a dilution effect.

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* The aldehydes may also be considered polyfunctional here, since each aldehyde group reacts with two hydroxyl groups.

More care was necessary in the preparation of the chlorophosphite, Va, since here the desired product still had an acid chloride group capable of reacting with a hydroxyl group. There were high boiling polymeric residues in this case, the nature of which was not investigated.

The most surprising case, perhaps, is the borate, VIII, where one would expect to obtain a mixture of compounds of varying molecular weight. From the boiling range of the product obtained, it is evident that this was not the case. A possible explanation is found in the fact that the ester linkages are very weak in this compound, as shown by the great ease of hydrolysis. During distillation, the material may well have been converted entirely to the most volatile component as this was removed from the mixture. This component is the one represented by VIII, the simplest neutral ester that can be formed from the tribasic boric acid and the bifunctional glycol.

The preparation of the phosphite derivatives, Vb, c, and d, involved the reaction of simple, monofunctional compounds, and offered no complications.

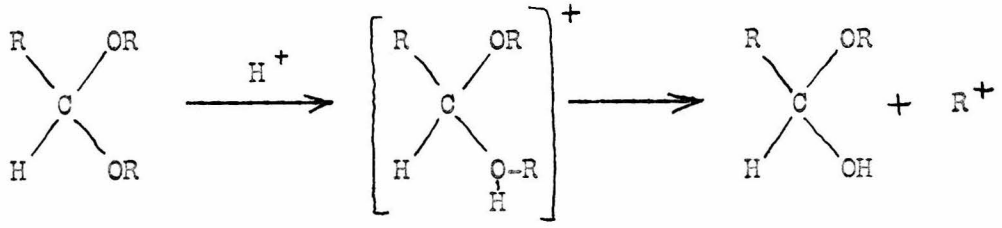
The method of preparing the sulfate is of interest in that it opens the way for the synthesis of a whole new series of compounds. The preparation of cyclic sulfites from glycols and thionyl chloride in high yield is a general method, and most of these should oxidize to the corresponding sulfates without complication. Ethylene and trimethylene sulfates have been previously prepared (12) by the reaction of the proper bromides with silver sulfate in xylene solution, but the yields were very low. No other cyclic sulfates are known.

The use of the more soluble calcium permanganate instead of the potassium salt as originally proposed by Evans (11) for the oxidation of sulfites

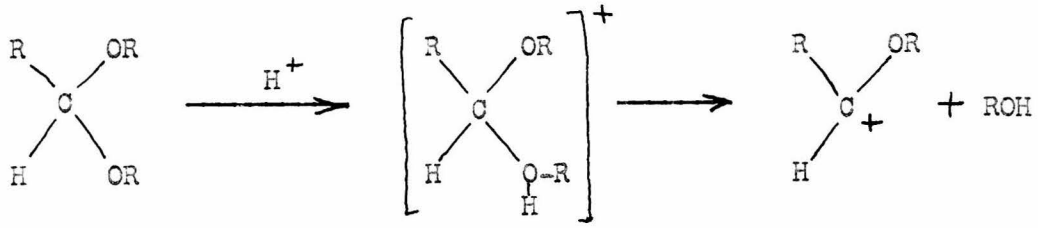
offers some advantage, since the reaction can be carried out at a lower temperature. The sulfates and sulfites will react slowly with both the acetic acid and the water in the reaction mixture, but since the oxidation takes place rapidly even below room temperature, these side reactions can be minimized by keeping the solution cold.

Hydrolysis. Only one case, that of the sulfate, VII, was found where the hydrolysis took place otherwise than with complete retention of configuration. This case will be discussed in some detail later.

Hammett (2) has proposed that the hydrolysis of acetals takes place by a mechanism involving a free carbonium ion, and cites certain rate data in support of this contention. This mechanism is as follows:



It is evident, however, that this cannot be correct, for if a free carbonium ion were formed from the alcohol, extensive racemization should occur, and retention of configuration was observed for both the cyclic formal, II, and the cyclic acetal, III. A mechanism involving the formation of a carbonium ion from the aldehyde would, on the other hand, be consistent with both the stereochemical data and the rate data:



The hydrolyses of the carbonate, IV, chlorophosphite, Va, sulfite, VI, and borate, VIII, take place in both acid and basic solution with complete retention of configuration. Thus these compounds are probably hydrolyzed by the same mechanism as the ordinary esters of carboxylic acids. Of interest, however, is the extreme rapidity with which the borate undergoes cleavage, even in pure water. The reaction is nearly instantaneous; crystals of boric acid appear immediately on adding a few drops of the ester to a little water.

In all cases, the glycol was isolated from the hydrolysis mixture as the formal, since the retention of configuration in the formation and hydrolysis of the formal had been demonstrated. The properties of the pure active formal were known, so measurements could be made directly on this compound without converting to the glycol.

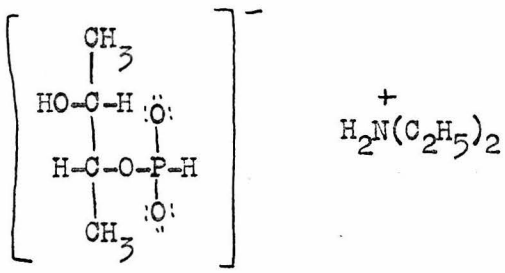
The sulfate, VII, represents an abnormal case in that both acid and basic hydrolysis resulted in complete or nearly complete loss of activity (Table II). The formal isolated from the acid hydrolysis was probably the pure meso isomer, although none of this has as yet been prepared for comparison. Senkus (1), however, gives the refractive indices of the DL- and meso-formals as n_D^{25}, 1.3984 and 1.4055 respectively. Thus, by comparison with n_D^{25}, 1.3959, for the D isomer, the refractive index of the meso-formal at 25° would be 1.4030. Senkus separated the isomers by fractionation, and it is quite probable, since there is only 6° difference in the boiling points, that the separation was not complete. Therefore, the value, n_D^{25}, 1.4041, for the formal from acid hydrolysis of the sulfate is a reasonable one to assume for the pure meso-formal.

Basic hydrolysis, on the other hand, gave mainly the DL-formal, with a small excess of the D(-) compound, and about 15% of the meso, as shown

by the rotation, α_D^{25}, -0.46°, and the refractive index, n_D^{25}, 1.3972.

It is not possible at present to suggest complete mechanisms for these reactions. It should be pointed out, however, that Burwell and Holmquist (13) observed an inversion in the alkaline hydrolysis of optically active secondary butyl hydrogen sulfate, and extensive racemization in the acid hydrolysis of this compound. In the present case, the formation of meso-glycol from the active sulfate, VII, on acid hydrolysis shows that one, or at least an odd number of inversions occurred. The DL-glycol obtained on alkaline hydrolysis suggests not only an even number of inversions, but an internally compensated intermediate. The possibility of the participation of neighboring groups therefore should not be overlooked.

The solid compound obtained on exposing to moist air the diethylaminophosphite, Vd, undoubtedly represented a product of partial hydrolysis. Its salt-like character, and the excellent elementary analysis, suggests the following structure:



IX

Molar Refractions. The molar refractions of the cyclic esters and acetals, with the exception of the sulfite and sulfate, are given in Table III.

The values found for the atomic refraction of phosphorus in the cyclic phosphites are in good agreement with those found by Mitchell (5) for the

corresponding propylene glycol derivatives. There also, the chlorophosphite showed a small exaltation while the phosphorus values for the other derivatives fell in the range 6.8-7.0.

No values of the atomic refraction of sulfur in sulfites and sulfates were available, so the calculations for these esters were not made.

Table III

Molar Refractions of the Cyclic Esters and

Acetals of D(-)-2,3-Butanediol

	M_D Calc.	M_D obs.
II Formal	26.38	26.26
III Acetal	30.98	31.03
IV Carbonate	26.39	26.20
VIII Borate	70.70*	70.69

	Calc. (less P)	M_D obs.	P
Va Chlorophosphite	27.725	35.185	7.460
Vb Methoxyphosphite	29.119	35.937	6.818
Vc Ethoxyphosphite	33.737	40.715	6.978
Vd Diethylaminophosphite	45.270	52.274	7.004

* Using the value 7.64 for the BO_3 group. This was calculated from the values of the refractive index and density for tri-isobutyl borate and tri-isoamyl borate (14).

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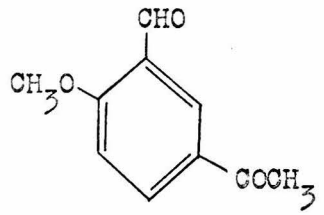
SECTION B

STUDIES ON THE INHIBITION OF GROWTH OF TOMATO PLANTS BY 3-ACETYL-6-METHOXYBENZALDEHYDE

Studies on the Inhibition of Growth

of Tomato Plants by 3-Acetyl-6-methoxybenzaldehyde

Recently it was shown by Gray and Bonner (1) that the leaves of Encelia farinosa, when applied to young tomato plants, caused marked inhibition of growth and even death of the plant. A crystalline compound was isolated from Encelia leaves, which was shown (2) to be 3-acetyl-6-methoxybenzaldehyde, I, (AMB), and which was toxic when applied to tomato seedlings in solution culture.



II

3-Acetyl-6-methoxybenzaldehyde

It would be of interest to know how this compound inhibits growth. The experiments described here do not give the final answer to this question, but they do decrease the number of possibilities, and indicate what further work is necessary.

The toxic material used was some of that synthesized by Gray and Bonner (2).

Experimental

Comparison of Inhibitory Effect on Plants with and without Roots.

The tests were carried out in essentially the manner described by Gray and Bonner (1). The test solutions were made up by dissolving the required amount of 3-acetyl-6-methoxybenzaldehyde in a known volume of four times diluted Hoagland's nutrient solution. The tomato seedlings were transplanted into 16 ml. shell vials filled with this solution. The vials were closed with corks in which a notch had been cut for the stem of the plants. A small wad of cotton around the stem where it passed through the notch served to hold the plant firmly in place. A small hole in the center of the cork made it possible to add water to replace transpiration losses without disturbing the seedling. The vials were set in wooden boxes, twenty to a box. They fitted closely through holes bored in the top of the box, so that the roots were kept in darkness, and the stems and leaves remained in the light. Measurements of the height of the plants were made at intervals. Water uptake was determined by marking the original level in the vial, and measuring the amount of water necessary to restore the level after a given time interval.

The results of experiments carried out in this way on intact tomato seedlings are shown in Table I. In Table II are the results of similar experiments on plants from which the roots had been removed.

In all cases, the first symptom of poisoning was death of the leaf tips and cotyledon tips. The dead areas, brown in color, gradually spread inward. In cases where the entire plant died, the growing point was one of the last parts remaining alive. The roots on intact plants seemed not to be affected by the toxic material, but when adventitious roots appeared

Table I

The Growth of Intact Tomato Plants in the Presence of AMB

Conc. of AMB mg/l		Growth in mm./plant					
		1 day	Water used (ml.)	3 days	5 days	7 days	9 days
0	(Control, 10 plants)	3.3	2.11	9.4	15.4	19.9	23.1
500	(5 plants)	0	1.46	3 plants dead	4 plants dead	4 plants dead	4 plants dead
250	(10 plants)	0.5	1.37	1.5	4.0	6.0	9.0
125	(10 plants)	3.2	1.42	9.1	14.1	17.7	22.0

Table II

The Growth of Tomato Plants with Roots Removed in the Presence of AMB

Conc. of AMB mg/l		Growth in mm./plant					
		1 day	Water used (ml.)	3 days	5 days	7 days	9 days
0	(Control, 10 plants)	0	1.46	1.7*	8.6	15.1	19.5
500	(5 plants)	0	1.46	0.8	0.8*	1.2	2.0
250	(10 plants)	0	0.95	0.1*	0.9	3.4	6.1
125	(10 plants)	0.2	1.66	0.9*	4.1	8.4	13.2

* Adventitious roots appeared at base of stems.

on the stems of the plants in the higher concentrations of AMB, they soon blackened and died.

The solutions from these experiments were retested with fresh plants after the tests above had been completed. Only a trace of the original activity remained.

The Effect of 3-Acetyl-6-methoxybenzaldehyde when Applied to the Tops of Tomato Plants. Distilled water solutions of the toxic compound were prepared containing 500 and 250 mg./l. of the material. Tomato seedlings were then placed with their tops immersed in these solutions, the beakers containing them were placed in a vacuum desiccator, and the system was evacuated. On releasing the vacuum, the intercellular spaces of the leaves were filled with the solution. The amount of solution taken up per plant was about 0.1 ml. The plants were then set out as before in vials containing nutrient solution, and the growth measured. The results are shown in Table III.

Table III

The Effect of AMB when Applied to the Tops of Tomato Plants

Conc. of AMB	Growth in mm./plant		
mg/l	2 days	4 days	7 days
0 (Control)	4.3	10.7	17.7
500	3.8	9.3	16.3
250	4.2	10.3	17.3

The Effect of 3-Acetyl-6-methoxybenzaldehyde on Root Growth. Tomato seeds were germinated for three days in the dark at 25°C in Petri dishes containing a filter paper wet with water. When the roots were about 2-4 mm. in length, 5 sets of 50 seedlings each were selected, and set out in separate Petri dishes, each containing a piece of filter paper wet with 4 ml. of distilled water containing a) none, b) 500 mg./l., c) 250 mg./l., d) 125 mg./l., e) 62.5 mg./l., of AMB. The plants were then replaced in the dark, and daily measurements of root growth were made. The results are given in Table IV.

Table IV

The Effect of AMB on Root Growth

Conc. of AMB	Growth in mm./plant	
mg/l	1 day	2 days
0	10.0	21.8
500	10.6	29.5
250	14.1	37.3
125	15.7	43.5
62.5	16.1	47.6

The Effect of 3-Acetyl-6-methoxybenzaldehyde on the Germination of Tomato Seeds. Five Petri dishes were prepared, each containing a filter paper wet with 4 ml. of AMB solution of the following concentrations: a) none, b) 500 mg./l., c) 250 mg./l., d) 125 mg./l., e) 62.5 mg./l. In each

dish, 100 tomato seeds were set out, and these were then kept in the dark at 25°. At intervals, the percent of germination and the total root growth in each dish were determined. The results are shown in Table V.

Table V

The Effect of AMB on Germination

Conc. of AMB	3 days		4 days		5 days	
mg/l	Germination %	Total Root Growth (mm.)	Germination %	Total Root Growth (mm.)	Germination %	Total Root Growth (mm.)
0	61	142	85	889	89	2650
500	3	3	43	51	82	238*
250	23	32	84	254	88	1024*
125	55	88	85	609	89	2341
62.5	65	140	87	899	89	3088

* The root tips were mostly blackened and dying in these two sets.

The Effect on Germination of Pretreating Tomato Seeds with 3-Acetyl-6-methoxybenzaldehyde. Tomato seeds were placed for 24 hours in Petri dishes containing AMB solutions of various concentrations, and were then transplanted to fresh solutions as indicated in Table VI. The germination and total root growth were observed at intervals.

The Distribution of Toxic Material in Tomato Plants Killed by 3-Acetyl-6-methoxybenzaldehyde. Three sets of 50 plants each were grown in the

Table VI

Effect of Pretreatment with AMB on the Germination of Tomato Seeds

No. of Seeds	Conc. of AMB (Pretreatment) mg/l	Conc. of AMB (Germination) mg/l	3 days		4 days		5 days	
			No. Seeds Germ.	Total root Growth (mm.)	No. Seeds Germ.	Total root Growth (mm.)	No. Seeds Germ.	Total root Growth (mm.)
25	0	0	16	36	24	273	24	884
25	0	500	0	0	10	15	18	104
25	0	250	8	9	21	100	22	464
25	500	0	11	16	24	177	24	749
25	500	500	4	4	19	39	21	193
25	500	250	4	5	17	74	20	353
25	250	0	16	35	21	289	21	835
25	250	500	0	0	6	9	11	43
25	250	250	7	8	16	83	20	330

following solutions: Set I, nutrient solution; Set II, nutrient solution containing 500 mg./l. of AMB; Set III (plants with roots removed), same as II. After two days, the plants were removed from the solutions and each set was divided into leaf tips, leaf bases, stems, and (except III) roots. These fractions were then dried for 20 hours at 70°, ground to a powder, and extracted with benzene. The benzene extracts were evaporated almost to dryness, and then extracted with nutrient solution, 30 ml. per 100 mg. dry weight of original material. These solutions were tested with tomato seed-

lings; the results are given in Table VII.

The original solutions, in which the tomato seedlings were partly killed, were retested with fresh seedlings. The solutions from Set II showed less than 125 mg./l., and from Set III, about 250 mg./l. of AMB remaining.

Table VII

Extracts of:	No. plants tested	Growth in mm./plant		
		2 days	4 days	7 days
I - Leaf tips	3	6.0	13.0	24.0
I - Leaf bases	3	5.7	14.0	24.7
I - Stems	2	6.0	13.5	23.5
I - Roots	1	5.0	11.0	23.0
II - Leaf tips	4	5.5	15.5*	23.8*
II - Leaf bases	1	7.0	10.0*	26.0*
II - Stems	1	5.0	16.0	23.0*
II - Roots	1	4.0	12.0	22.0
III - Leaf tips	4	3.0	9.0	19.8*
III - Leaf bases	2	1.0	5.0	16.0*
III - Stems	2	4.5	12.0	21.5
Control	10	7.2	18.2	27.3

* Leaf tips and cotyledon tips dead.

The Effect of 3-Acetyl-6-methoxybenzaldehyde in the Presence of Pyridoxal. The results of growing tomato plants in solutions of AMB

containing varying amounts of pyridoxal hydrochloride are shown in Table VIII.

Table VIII

The Effect of AMB in the Presence of Pyridoxal

No. of Plants	Conc. of AMB mg/l	Conc. of Pyridoxal Hydrochloride mg/l	Growth in mm./plant		
			2 days	4 days	7 days
5	500	100	1.0	2 dead (1.3)	3 dead (2.0)
5	500	10	0.4	1 dead (0.8)	1 dead (1.5)
5	500	1	0.4	1 dead (1.0)	2 dead (1.7)
5	500	0	0.4	5 dead	5 dead
5	250	100	0.2	0.6	5.0
5	250	10	0.8	3.0	9.6
5	250	1	1.2	3.8	10.0
5	250	0	0.8	3.8	11.4
5	0	100	2.8	8.0	21.0
5	0	10	4.8	12.4	22.6
5	0	1	5.8	14.2	22.6
5	0	0	5.4	14.8	24.4

Discussion

It can be seen from Tables I and II that AMB is considerably more toxic to intact plants than to plants which have had their roots removed. There are two possible explanations for this; either the toxic material is not taken up as rapidly by the rootless plants, or else the roots of the intact plants change it into something more toxic than AMB itself. The water uptake for the first day, shown in the tables, indicates that there is little difference between the two sets of plants in this respect, and if AMB is taken up passively with the water, the amounts entering the plant in the two cases should be roughly equal. It should be mentioned, however, that these measurements were not accurate enough to allow definite conclusions to be drawn.

The application of AMB to the tops of the test plants produced little effect; the small inhibition indicated in Table III is within the experimental error of measurement. The actual amount of toxic material entering the plant was, however, very small.

The application of AMB has a definite inhibitory effect on root growth (Table IV). The data show that the control actually grew less than any of the other sets; however, several of the plants in the control group died from an unknown cause, and this discrepancy therefore is probably without significance. The inhibition was much more pronounced when the seeds were germinated in solutions of AMB (Table V). Germination was delayed here a day or two by high concentrations of the toxic material, although the final percentage of germination was about the same in all cases. However, the growth of the roots was almost completely stopped by the higher concentrations, and indeed many of the plants died.

The pretreatment of seeds in solutions of AMB seems to have little effect on their germination and subsequent growth (Table VI). Apparently the toxic substance is not absorbed through the seed coat; it must actually be present at the time of or after germination to influence the growth of the seedling.

The results given in Table VII appear to show that the toxic material is not taken up as such to any great extent. If all the AMB removed from the original solutions had been present in plant parts tested, the average concentration of AMB in the extracts would have been about 200 mg./l. Obviously, it was very much less. It is possible that the material is bound in the plants, and is therefore not removed by extraction. However, other factors must be considered. The toxic material is an aldehyde, and could have been destroyed to a considerable extent (oxidation, polymerization, etc.) during the experiment, for example.

From growth inhibition alone, it appears that the leaves of the plants without roots accumulated the largest amounts of toxic material. However, it should be noted that the symptoms of AMB poisoning, death of the leaf tips, appeared first in the extracts of the leaves of the plants with roots.

The structure of 3-acetyl-6-methoxybenzaldehyde, I, resembles pyridoxal more closely than any of the other known growth factors. An experiment, the results of which are given in Table VIII, was carried out to see if the effect of AMB could be offset in part by supplying the test plant with pyridoxal. The results were inconclusive; pyridoxal was apparently destroyed in the test solutions, giving rise to compounds which were themselves toxic to the test plants.

References

1. R. Gray and J. Bonner, Am. J. Bot., 35, 52 (1948)

2. R. Gray and J. Bonner, J. Am. Chem. Soc., 70, 1249 (1948)

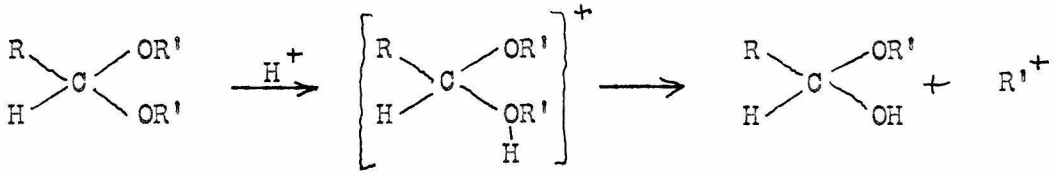
Propositions Submitted by Harold K. Garner

1. The interesting question of whether the closing of the ring in the formation of intermediate cyclic ions is a one-stage (S_N2) or a two-stage (S_N1) process, has recently been partially answered by Winstein and co-workers through a comparison of the rates of reaction of 2-chlorocyclohexanol, 2-bromocyclohexanol, and 2-iodocyclohexanol with hydrobromic acid. I propose to make use of the more general structural criterion of the English school to confirm and extend Winstein's results.

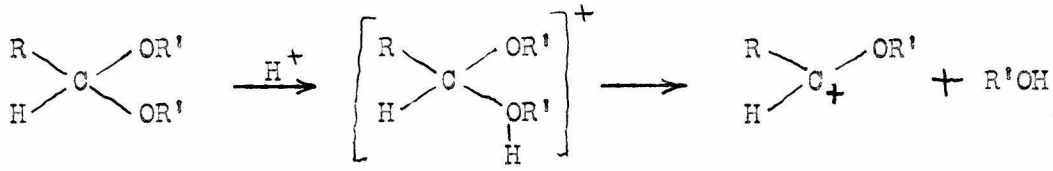
Winstein, Grunwald, Buckles, and Hanson, J. Am. Chem. Soc., 70, 816 (1948)

Bateman, Hughes, and Ingold, J. Chem. Soc., 881 (1938)

2. The mechanism proposed by Hammett for the hydrolysis of acetals:



cannot account for the stereochemical results when the acetal of an optically active alcohol is hydrolyzed. I propose instead the mechanism:



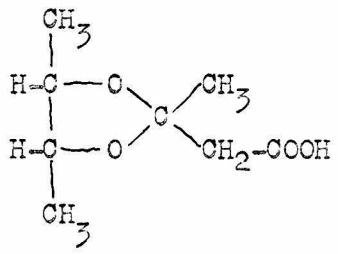
Hammett, Physical Organic Chemistry, McGraw-Hill Book Co., New York, 1940, p. 303

3. a. I propose the adoption of a general system of nomenclature for the designation of the configuration of optically active compounds.

b. I propose the adoption of a rule standardizing the order of naming

of substituents in aliphatic compounds.

4. a. Neish has shown that butylene glycol can be reacted with aceto-acetic ester to give a cyclic ketal-ester. On basic hydrolysis, the ester group is removed to give the free acid:



I propose that compounds of this type would be useful intermediates in the resolution of glycols.

Neish, Can. J. Research, B, 25, 423 (1947)

b. I predict that optically active 1,2-glycols could be prepared by reduction of the corresponding active α-hydroxy acids with lithium aluminum hydride.

Nystrom and Brown, J. Am. Chem. Soc., 69, 2548 (1947)

5. I propose that the arguments of McKay and Bader for the configurations of the 9, 10, 12, 13-tetrahydroxystearic acids are incorrect almost without exception, and their conclusions need thorough revision.

In addition, their proposed system of nomenclature is not acceptable, and cannot be applied to this type of compound.

McKay and Bader, J. Org. Chem., 13, 75 (1948)

6. I propose that 3-acetyl-6-methoxybenzaldehyde exists in the leaves of Encelia farinosa mainly in the form of a derivative, and that this derivative has a much higher toxicity towards tomato plants than the aldehyde

itself.

7. I propose that the toxic effect of 3-acetyl-6-methoxybenzaldehyde is due to its accumulation in the plant parts affected. I further propose that AMB containing a radioactive carbon atom could be easily synthesized and would be useful in determining the final distribution of the material in the plant.

8. I propose the incorporation of a device into the cartesian manostat, manufactured by the Emil Greiner Co., which will greatly facilitate the adjustment of the pressure to an exact value.

9. a. I predict that optically active propylene bromide could be prepared from optically active propylene glycol through the steps: active glycol $\xrightarrow{Ac_2O}$ active diacetate $\xrightarrow{HBr}$ active propylene bromide. Furthermore, pure D-glycol would yield L-dibromide, and the optical purity of the product would be about 80%.

b. A method is proposed for proving the number of inversions involved in preparations such as that described in (a).

10. Many of the higher α-methyl carboxylic acids are resolved only with difficulty, and the method of Stallberg-Stenhagen for their preparation in an optically active form is rather long. I propose a general method for the synthesis of these compounds from D(+)-2,3-epoxybutane which will yield the active acids of known configuration: