The Reaction Steps in the Conversion of 2,3-Di-p-toluenesulfonoxybutane to 2,3-Diacetoxybutane

Thesis by

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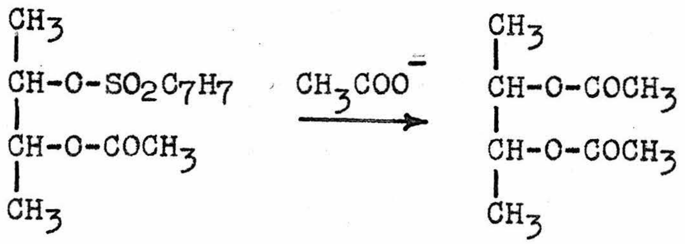
When replacement reactions take place in organic molecules which have a functional group on the carbon adjacent to the one affected, it has been shown that often this adjacent group influences the course of the reaction. This effect may be exerted inductively on the seat of the replacement as in the reaction below:

$$RX + HOR \longrightarrow ROR + HX.$$

In this reaction R is methyl, ethyl, isopropyl or tertiary butyl. With methyl, ethyl and isopropyl, reaction goes by an SN_2 mechanism with successively diminishing speeds and with isopropyl and tertiary butyl by an SN_1 mechanism with increasing speeds. Isopropyl undergoes reaction by both mechanisms simultaneously.[1,2]

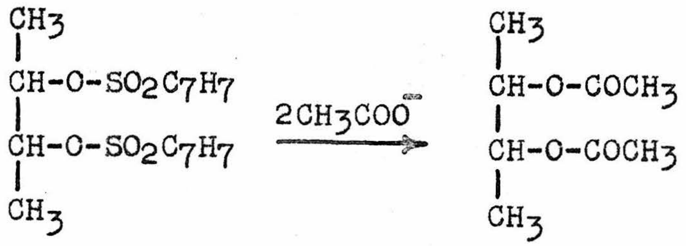
On the other hand the effect of an adjacent group may make itself felt by the actual formation of bonds between the carbon on which substitution is taking place and the adjacent group, to form a cyclic intermediate. The existence of cyclic bromonium and chloronium ion intermediates has already been shown.[3,4] The present investigation was undertaken to show the existence of a cyclic ortho-ester intermediate in the case of substitution reactions with an acetoxy group on an adjacent carbon atom. The reaction studied was the replacement of the p-toluenesulfonoxy group by the acetoxy group. The compounds studied were the p-toluenesulfonates and acetates of 2,3-butanediol.



$$\begin{array}{l} \mathrm{CH_3} \\ | \\ \mathrm{CH{-}O{-}SO_2C_7H_7} \\ | \\ \mathrm{CH{-}O{-}COCH_3} \\ | \\ \mathrm{CH_3} \end{array} \xrightarrow{\mathrm{CH_3COO^-}} \begin{array}{l} \mathrm{CH_3} \\ | \\ \mathrm{CH{-}O{-}COCH_3} \\ | \\ \mathrm{CH{-}O{-}COCH_3} \\ | \\ \mathrm{CH_3} \end{array}$$

2-acetoxy-3-p-toluenesulfonoxybutane

2,3-diacetoxybutane



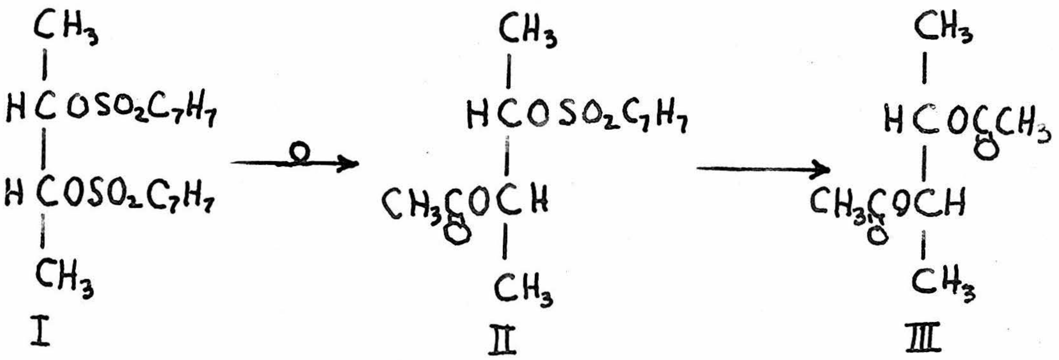
$$\begin{array}{l} \mathrm{CH_3} \\ | \\ \mathrm{CH{-}O{-}SO_2C_7H_7} \\ | \\ \mathrm{CH{-}O{-}SO_2C_7H_7} \\ | \\ \mathrm{CH_3} \end{array} \xrightarrow{\mathrm{2CH_3COO^-}} \begin{array}{l} \mathrm{CH_3} \\ | \\ \mathrm{CH{-}O{-}COCH_3} \\ | \\ \mathrm{CH{-}O{-}COCH_3} \\ | \\ \mathrm{CH_3} \end{array}$$

2,3-di-p-toluene-sulfonoxybutane

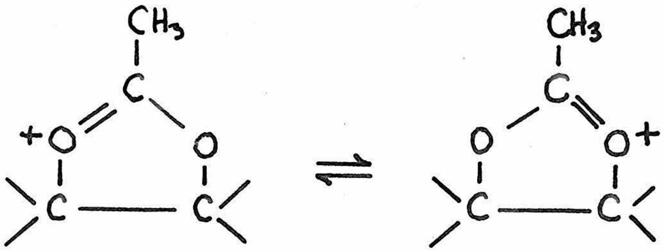
2,3-diacetoxybutane

At the same time that this investigation was being carried out, roughly paralleled investigations of the acetates and p-toluenesulfonates of cyclohexanediol were being carried out elsewhere.[5,6] The cyclic structure of the cyclohexane derivatives introduces certain extraneous structural effects which are not present in the butane series; for example, it is possible for a neighboring group on a cyclohexane molecule to form a bicyclic intermediate in the replacement reaction only when starting with a trans cyclic compound which will give a cis bicyclic intermediate.[7,8] However, the results of the two investigations are mutually confirmative.

When meso 2,3-di-p-toluenesulfonoxybutane is heated with potassium acetate in glacial acetic acid under anhydrous conditions, the two p-toluenesulfonoxy groups are replaced by acetoxy groups with predominant inversion of configuration (100% meso → 86% dl). Furthermore when erythro 2-acetoxy-3-p-toluenesulfonoxybutane is treated under the same conditions it yields the diacetoxy compound with almost complete retention of configuration. Since the 2-acetoxy-3-p-toluenesulfonoxybutane is an intermediate in the first reaction these results localize the inversion at the carbon from which the first sulfonoxy group is displaced.

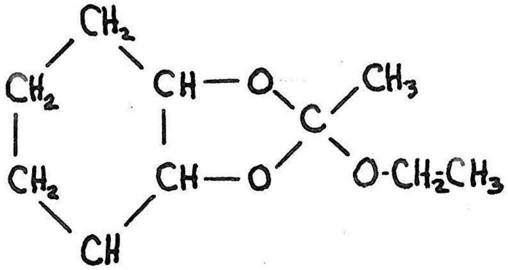


The reaction of acetate ion with I to give II presumably goes by a typical SN_2 replacement mechanism and gives one inversion. If the carbon bearing the remaining sulfonoxy group were unaffected by the adjacent acetoxy group, replacement on it would be expected to take place in an identical manner giving another inversion. However, the neighboring acetoxy group does affect the replacement and the second stage of the reaction, from II to III, goes with either zero or an even number of inversions. The most likely mechanism is that proposed by Winstein[8], involving formation of a cyclic intermediate (IV), an ester of ortho-acetic acid.



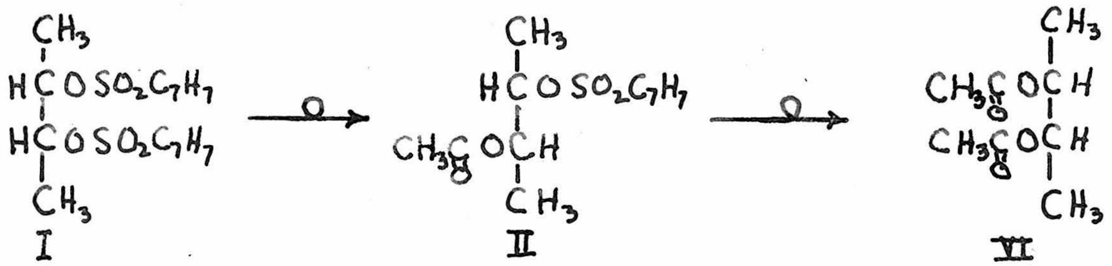
IV

Its formation would involve one inversion and its reaction with acetate ion to give the diacetate would involve another inversion, giving an overall effect of retention of configuration. The likelihood of the formation of this intermediate is emphasized by the strain-free ring and the possibility of resonance between the two equivalent forms. Further evidence of the existence of this cyclic intermediate would be provided if the action of acetate ion on optically active threo 2-acetoxy-3-p-toluenesulfonoxybutane under the same conditions as above would bring about complete racemization. Time did not permit this experiment to be carried out; but this racemization has been observed in a closely related reaction, the action of silver acetate on optically active 1-acetoxy-2-bromocyclohexane[8]. Furthermore an ortho-ester (V) has been isolated from the reaction mixture of the solvolysis of 1-acetoxy-2-p-toluenesulfonoxycyclohexane with ethanol[6].

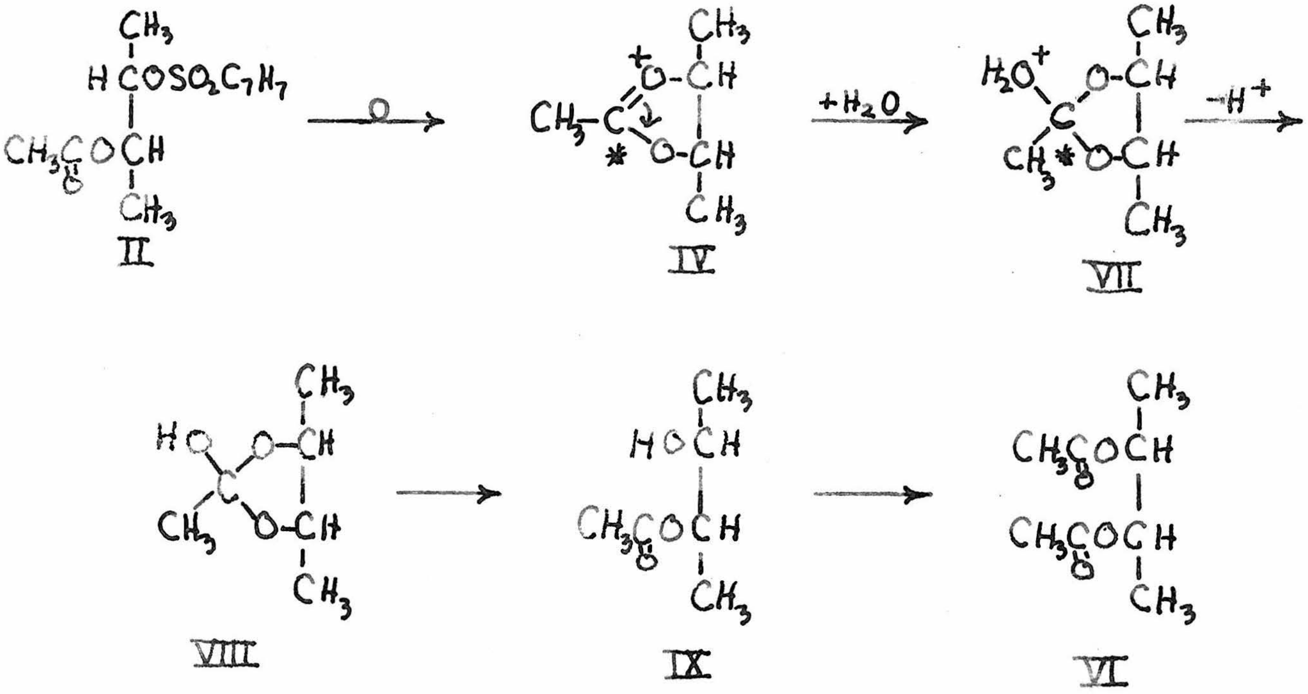


V

When the reaction of the meso di-p-toluenesulfonoxybutane with acetate ion to give 2,3-diacetoxybutane takes place in a mixture of acetic acid, potassium acetate and one mol of water per mol of ester, the product is meso 2,3-diacetoxybutane. Under the same conditions the conversion of 2-acetoxy-3-p-toluenesulfonoxybutane (II) to 2,3-diacetoxybutane (IV) goes with almost complete inversion (100% meso → 96% dl).



From this it is seen that the first stage of the reaction, from I to II, is unaffected by the presence of water but the second stage, from II to VI, is markedly affected by water. The second stage of the reaction, that from II to VI, has been explained[9] as going through the following steps:



Even in the presence of water the cyclic intermediate IV is assumed to be formed. If water is present, water adds at the starred carbon, and a proton drops off to give the ortho-monoacetate (VIII) which then rearranges to give the normal monoacetate (IX). Then, under the conditions of the experiment, about half of the monoacetate is acetylated to give the diacetoxybutane (VI). In the absence of water there is direct attack by acetate ion on either the C_2 or C_3 carbon of the butane chain of intermediate IV which gives rise to an inversion and yields the diacetoxybutane directly.

It would have been of interest to carry out the solvolysis of an optically active 2-acetoxy-3-*p*-toluenesulfonoxybutane with both anhydrous acetate and acetate in the presence of water. If the reaction does go through the cyclic intermediate IV, there would be complete racemization in both cases.

In order to prepare active butanediol the di-d-camphorsulfonoxybutanes were prepared. Three crystalline species of the di-(d)-camphorsulfonates of *dl*-butanediol were isolated. Their physical properties are shown in Table I.

Table I

Configuration of original glycol	m.p. °C	α^{25}_{D} °	$[\alpha]^{25}_{D}$ °
dl	42	2.50	41.0
dl	105	2.58	60.8
dl	149	1.57	37.9
meso	120	1.98	46.4

Enough of these materials to permit saponification and isolation of the active glycols had not been prepared when this investigation was suddenly terminated.

Experimental

meso-2,3-Butanediol. -- The crude 2,3-butanediol was that of the Lucidol Company prepared by the action of areobacter areogenes on sugar. It is a mixture of about 90% meso and the rest dl with a preponderence of one of the forms to give a positive rotation. A five pound bottle of the viscous liquid glycol mixture was seeded with crystalline meso-2,3-butanediol and allowed to stand for several months at room temperature to increase the size of the crystals. Then the liquid was drained from the crystals, care being taken to exclude moisture from the glycol which is highly hygroscopic. This was accomplished by replacing the glass stopper of the bottle containing the glycol with a rubber stopper fitted with a drain tube and a vent tube (fig. 1) and inverting the bottle on a 2-liter suction flask with a drying tube attached to the side arm. The rubber stopper resting on the lip of the flask made an effective seal and the draining proceeded very satisfactorily. After 48 hours the draining was complete and the crystalline material remaining had a melting point of 30.4-32.0°. The mixed melting point curve of the 2,3-butanediols [10] indicates that this material was 96% meso glycol. The crystalline glycol was washed with a small amount of anhydrous isopropyl ether and then recrystallized from that solvent, using enough ether to prevent the formation of a second liquid phase. The recrystallized glycol was distilled under reduced pressure, b.p. 80°/10 mm. One recrystallization gave a product melting at 33.8°, which is 99.4% meso and two recrystallizations gave a product melting at 34.0°, which is 99.6% meso.

erythro-3-Acetoxy-2-butanol. -- To 90 g. (1.0 mol) of 99.6% meso glycol (m.p. 34.0°) were added 102 g. (1.0 mol) of freshly distilled acetic anhydride and the mixture was cooled to 0°. One drop of sulfuric acid was added and the flask containing the reaction mixture was immersed in ice water for 5 hours, allowed to stand at room temperature for 48 hours and then distilled under reduced pressure through a 24 inch fractionating column packed with helices. 98.9 g. of liquid distilled at 73.5-75.5°/10mm, N_D^{25} 1.4235. The yield of acetoxybutanol was 75%. The material was completely soluble in a small amount of water, showing that no diacetate was present since the diacetate is quite insoluble in water.

An experiment was performed in which the acetylation was allowed to take place at temperatures between 50 and 70 degrees. An 89% yield (calculated as the acetoxybutanol) was obtained of a liquid boiling at 78.5-80.0°/10 mm, N_D^{25} 1.4189 $d_{4^\circ}^{25^\circ}$ 1.0144. This material was not completely soluble in water. The physical properties and the solubility indicate that this material contains some diacetoxybutane. Apparently the acetylation must be carries out at low temperatures in order to prevent formation of some diacetate.

meso-2,3-Diacetoxybutane. -- To 32 g. (0.36 mol) of 99.2% *meso* glycol (m.p. 33.6°) were added 80 g. (o.78 mol) of freshly distilled acetic anhydride and one drop of sulfuric acid. The reaction mixture was cooled under the tap, allowed to stand at room temperature for 12 hours and distilled under reduced pressure through a 24 inch fractionating column. The yield was 47 g. (75%) of liquid b.p. 76-76.5°/10 mm.

Mixed melting point curve of 2,3-diacetoxybutanes. -- In order to provide a simple, accurate method of determining the composition of mixtures of *meso* and *dl*-2,3-diacetoxybutane, a mixed melting point curve was prepared. For the melting point determinations on the mixtures, thin walled pyrex bulbs 10 mm in diameter with necks 2 mm in diameter were used. About 0.8 g. of mixtures of *dl* and *meso*-diacetoxybutane were weighed into the bulbs and the necks sealed. The bulbs were then suspended in a water bath which was mechanically stirred and equipped with a thermometer graduated in tenths of degrees. By gently tapping the neck of the melting point bulb the contents could be violently agitated. The temperature was noted as the last crystals disappeared while the bath temperature was being raised about 0.2°/min. After the melting points had been determined the refractive indices were taken on all of the mixtures which were liquid at 25°. A new Abbe refractometer was used for these determinations. The results are presented in Table II and figures II and III.

Table II

Melting points and refractive indices of mixtures of *meso* and *dl*-2,3-diacetoxybutane.

meso %	m.p. °C	N_D^{25}
0	42.9	
8.94	39.1	
18.20	35.7	
30.48	29.7	
40.9	24.2	1.4128
49.9	18.6	1.4126
61.5	10.7	1.4124
69.9	2.8	1.4123
87.2	0.8	1.4119
94.5	2.1	1.4118
100.0	3.0	1.4117
100.0	2.5	1.4121[11]
41.5	---	1.4128[11]

meso-2,3-Di-*p*-Toluenesulfonoxybutane. -- To 90 g. (1.0 mol) of *meso*-2,3-butanediol (m.p. 33.8 99.4% *meso*) were added 400 g. (2.1 mol) of recrystallized *p*-toluenesulfonyl chloride and 174 g. (2.2 mol) of redistilled pyridine. The *p*-toluenesulfonyl chloride dissolved as the reaction mixture heated and after about 15 minutes a quantity of crystals of pyridine hydrochloride formed. The semi solid mass was allowed to stand overnight and was then poured into cold dilute hydrochloric acid. An oil separated which soon solidified. It was washed several times with cold dilute hydrochloric acid to remove the pyridine, then washed with water, filtered, dried and recrystallized from isopropyl ether. Yield: 212 g. 53%, m.p. 93-94°. Repeated recrystallizations from anhydrous isopropyl ether gave a product melting at 95.0-95.5°.

Anal. Calc'd for $C_{18}H_{22}O_6S_2$ C, 54.25; H, 5.56; S, 16.09.
Found: C, 54.60; H, 5.64; S, 16.09.

A sample of this compound was recrystallized twice from methanol giving a product melting 95-96°. This product apparently contained two molecules of alcohol of crystallization since saponification gave an equivalent weight of 231; calc'd for $C_{18}H_{22}O_6S_2 \cdot 2CH_3OH$: 231.

erythro-2-Acetoxy-3-*p*-toluenesulfonoxybutane. -- To 45 g. (0.50 mol) of *meso*-2,3-butanediol (m.p. 34.0° 99.6% *meso*) were added 40 g. (0.51 mol) of redistilled pyridine and 95.2 g. (0.50 mol) of *p*-toluenesulfonyl chloride. After a few minutes the mixture heated strongly, was cooled under the tap, and after the reaction had subsided was allowed to stand at room temperature for 12 hours. Then 52 g. (0.5 mol) of freshly distilled acetic anhydride and three drops of sulfuric acid were added. Again the mixture was cooled under the tap. After standing for three hours it was poured over a mixture of 42 g. (0.5 mol) of sodium bicarbonate and ice.

The product separated as a white curd which was dissolved in ethyl ether, the ether solution washed several times with water, dried with calcium sulfate and cooled to 0°C. After standing for 12 hours at 0°C. a quantity of crystals had formed. The mother liquor was decanted and cooled to the temperature of solid carbon dioxide which caused another crop of crystals to appear. The two crops of crystals were combined giving 87 g. (60% yield) of material, m.p. 39-45°. Several recrystallizations from anhydrous isopropyl ether gave a white crystalline product melting 51.5-52.0°.

Anal. Calc'd for $C_{13}H_{18}O_5S$: C, 54.53; H, 6.33.
Found: C, 54.95; H, 6.33.

Acetylation of the <u>meso</u> glycol to the 2-acetoxy-3-butanol followed by tosylation gave an identical product but the yields were much lower, around 25%.

<u>meso</u>-di-2,3-<u>p</u>-Bromobenzenesulfonoxybutane. -- To 1.7 g. (0.019 mol) of <u>meso</u>-2,3-butanediol (m.p. 34° 99.6% <u>meso</u>) were added 10 g. (0.039 mol) of p-bromobenzenesulfonyl chloride and 5 ml. of pyridine. The product was isolated in the same manner as the tosylates and was recrystallized from absolute ethanol, m.p. 123-124°.

Solvolysis Experiments

1. The anhydrous solvolysis of <u>erythro</u>-2-acetoxy-3-<u>p</u>-toluenesulfonoxybutane. -- 35 g. of glacial acetic acid, 2 g.

of acetic anhydride and 6.9 g. (0.07 mol) of potassium acetate (dried over P_2O_5) were placed in a flask fitted with a reflux condenser having a drying tube at its outlet. It was brought to a boil and by this means all of the water was eliminated from the mixture. Then 10 g. (0.035 mol) of erythro-2-acetoxy-3-p-toluenesulfonoxybutane were added and the mixture refluxed for two hours, allowed to stand for 48 hours at room temperature and poured over sodium bicarbonate and ice. The neutralized solution was extracted several times with ether, the ether extracts combined and evaporated and the residue distilled under reduced pressure. The yield was 2.5 g. (41%) of colorless liquid boiling at 75-76°/10 mm, m.p. 3°, N_D^{25} 1.4117. These constants indicate that the product is pure meso-2,3-diacetoxybutane.

Some pure meso-2,3-diacetoxybutane was put through exactly the same treatment and was recovered with no change in physical constants.

2. The anhydrous solvolysis of meso-2,3-di-p-toluenesulfonoxybutane. -- 275 ml. of glacial acetic acid, 30 ml. of acetic anhydride and 80 g. (0.8 mol) of potassium acetate (dried over P_2O_5) were put in a flask and brought to a boil. Then 79.6 g. (0.20 mol) of meso-2,3-di-p-toluenesulfonoxybutane were added. A reflux condenser was fitted to the flask and the mixture refluxed for 6 hours. Then the liquid was put in a Claisen flask and as much liquid as possible distilled rapidly at 40 mm pressure. When about half of the liquid was

removed the contents of the flask solidified. The pressure was reduced to 2 mm and about 30 ml. more liquid distilled. This distillate was redistilled through a fractionating column and gave 3.3 g. of colorless liquid b.p. 60°/2 mm, which crystallized when seeded with a small crystal of dl-diacetoxybutane and melted at 32°.

The solid material left in the Claisen flask was extracted with boiling isopropyl ether and the extracts distilled through a fractionating column. 19.5 g. of colorless liquid came over at 73.5-74.5°/10 mm. This material crystallized when seeded with dl-diacetoxybutane and melted at 38-39°.

The melting point of the first fraction, 32°, indicates a composition of 74% dl and the melting point of the second fraction, 39°, indicates 88% dl or a total of 86% inversion of the reaction products. This percentage of inversion was confirmed by a second experiment duplicating the one described.

3. Solvolysis of erythro-2-acetoxy-3-p-toluenesulonoxybutane in the presence of water. -- To 15 g. (0.0525 mol) of erythro-2-acetoxy-3-p-toluenesulfonoxybutane were added 15 g. of potassium acetate (dried over P_2O_5), 40 g. of acetic acid which contained 0.2% water (m.p. 16.3°) and 0.865 g. of water, a total of 0.0525 mols of water. The mixture was heated at 130-140° for 4 hours and left for 12 hours at room temperature. The product was isolated in the manner described for experiment 2 above. The yield was 5.4 g. of colorless liquid, b.p. 76-78.5°/10 mm, N_D^{25} 1.4173. This refractive index indicated that

the liquid was about 50% 2-acetoxy-3-butanol. So acetic anhydride and a trace of sulfuric acid were added, the mixture allowed to stand for 12 hours and then distilled through a 50 cm. spinning band column. The following three fractions were collected:

	b.p./10 mm. °C	m.p. °C	weight g.	composition % <u>dl</u>	wt <u>dl</u> g.
A	70-78.6	14	.27	43	0.12
B	79-80	41.5	2.55	97	2.47
C	80 --	43	2.65	100	2.65
		TOTAL	5.47		5.24

This shows that 96% inversion took place. Yield of diacetoxybutanes was 60%.

4. Solvolysis of <u>meso</u>-2,3-di-<u>p</u>-toluenesulfonoxybutane in the presence of water. -- To 25 g. (0.063 mol) of <u>meso</u>-2,3-di-<u>p</u>-toluenesulfonoxybutane were added 25 g. of potassium acetate (dried over P_2O_5), 50 g. of acetic acid containing 0.2% water (m.p. 16.3°) and 1.13 g. of water, a total of 0.063 mols of water. The mixture was heated to 130-140° for 6 hours, kept at room temperature for 12 hours and the product isolated by the procedure described for experiment 3 except that acetic anhydride was added before the mixture was distilled. The following three fractions were collected:

	b.p./10 mm °C	wt g.	N_D^{25}
A	69-75	0.45	
B	75-76	2.85	1.4120
C	76-76.2	3.03	1.4117

The refractive indices show this material to be more than 90% meso-2,3-diacetoxybutane. Yield 58%.

The 2,3-Di-d-camphorsulfonoxybutanes. -- To 4.5 g. (0.05 mol) of pure dl-2,3-butanediol, obtained from pure dl 2,3-diacetoxybutane (m.p. 42.5°) by saponification, were added 20 ml. of pyridine and 27.5 g. (0.11 mol) of freshly prepared d-camphorsulfonyl chloride. The reaction took place with evolution of heat. The mixture was kept at 50° for 3 hours, dissolved in 50 ml. of isopropyl ether, and water added. A white amorphous solid separated and gathered on the container walls and at the water-ether interface. The etherial phase was separated and after a few hours deposited about 2 grams of beautiful white crystals. The mother liquor was decanted, heated and used to extract the white amorphous solid. After being kept at 0° overnight some more of the crystals described above had been deposited and also a number of hemispherical clumps of finely divided crystals. The two types of crystals were separated manually. On recrystallization the first type had a melting point of 105.5° and the second a melting point of 148-149°.

In another experiment the reaction mixture was allowed to stand overnight and was poured into dilute HCl. An organic phase started to separate and was taken up in 200 ml. of ethyl ether and the ether extract dried and cooled to the temperature of solid carbon dioxide. A light feathery crystalline solid came out. On subsequent recrystallization it had a m.p. of 42-43°.

The *meso*-2,3-di-*d*-camphorsulfonoxybutane was prepared in the same way as the *dl* derivatives. It had a melting point of 119.5-120.5°.

Anal. Calc'c for $C_{24}H_{38}S_2O_8$: C, 55.57; H, 7.38; S, 12.36.
Found: m.p. 42° : C, 54.65; H, 7.46; S, 12.55.
m.p. 105°: C, 56.12; H, 7.54; S, 12.65.
m.p. 149°: C, 55.91; H, 7.46; S, 12.45.
m.p. 120°: C, 55.94; H, 7.65; S, 12.73.

Summary

The mechanism of the reaction in the substitution of acetoxy groups for p-toluenesulfonoxy groups in the 2,3-butanediol series has been studied by means of the steric changes in the products. The reactions were carried out in acetic acid solutions of potassium acetate, both anhydrous and with water present. Both with and without water, the reactions going from the 2,3-di-p-toluenesulfonoxybutane to the 2-acetoxy-3-p-toluenesulfonoxybutane were identical, but the course of the second substitution step was different in the two mediums. Under anhydrous conditions there was 100% retention of configuration going from the acetoxy-p-toluenesulfonoxybutane to the diacetoxy butane; but with one mol water present for each mol of ester, there was 96% inversion.

These reactions are explained by the existence of a cyclic ortho-ester intermediate.

The di-d-camphorsulfonates of 2,3-butanediol were prepared as a step in the possible resolution of the glycol. However, the conclusion of this phase of the work was prevented by the sudden calling of the author into the military service.

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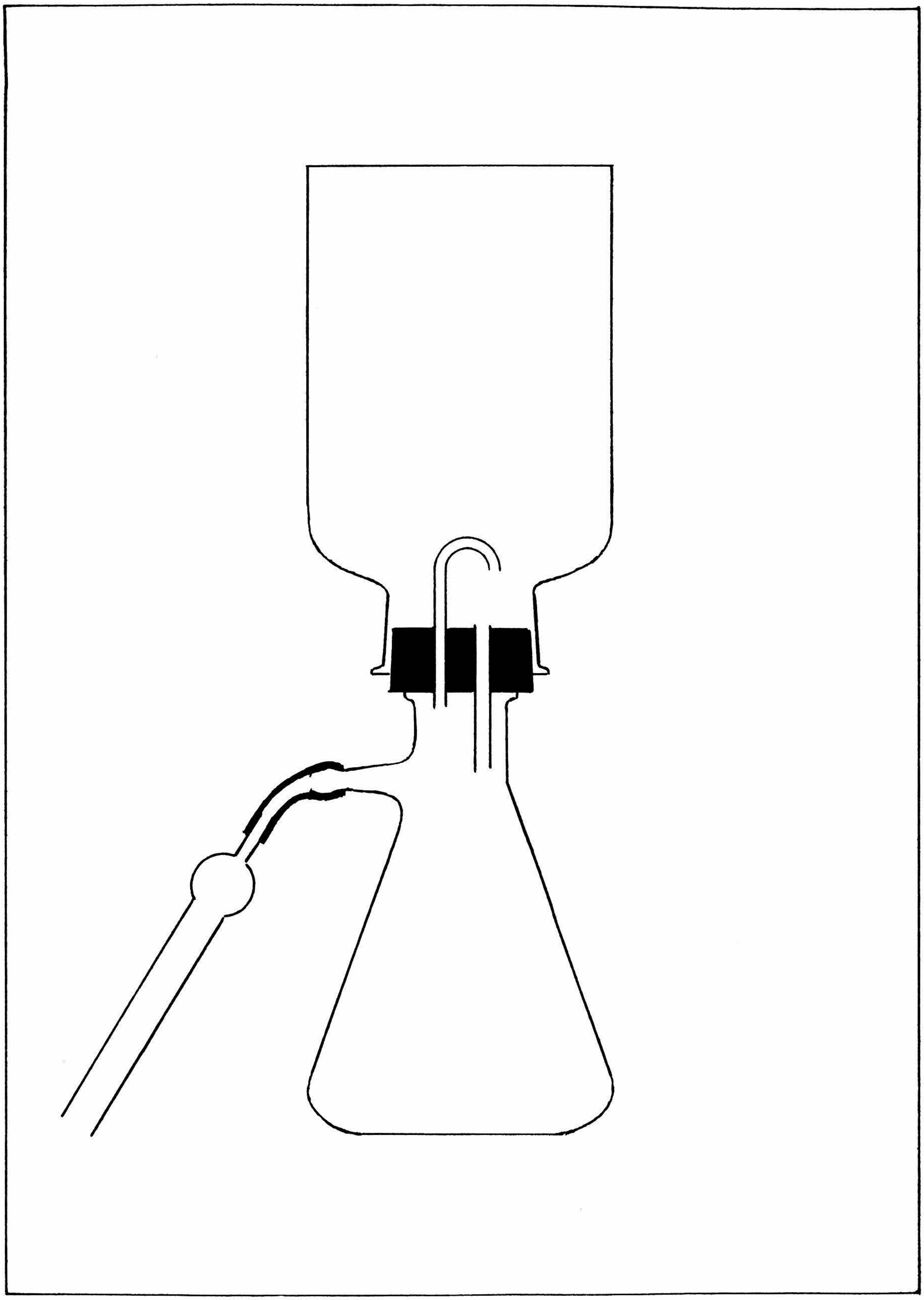

Fig. 1

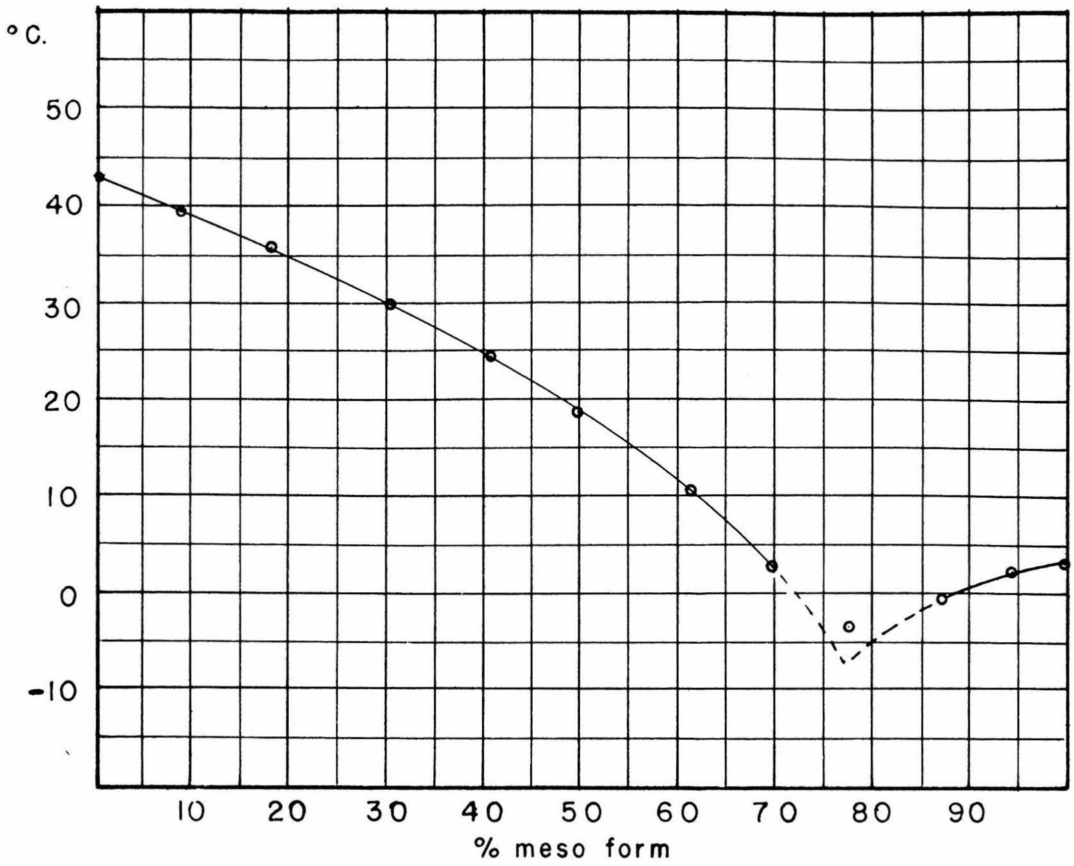

Fig. II

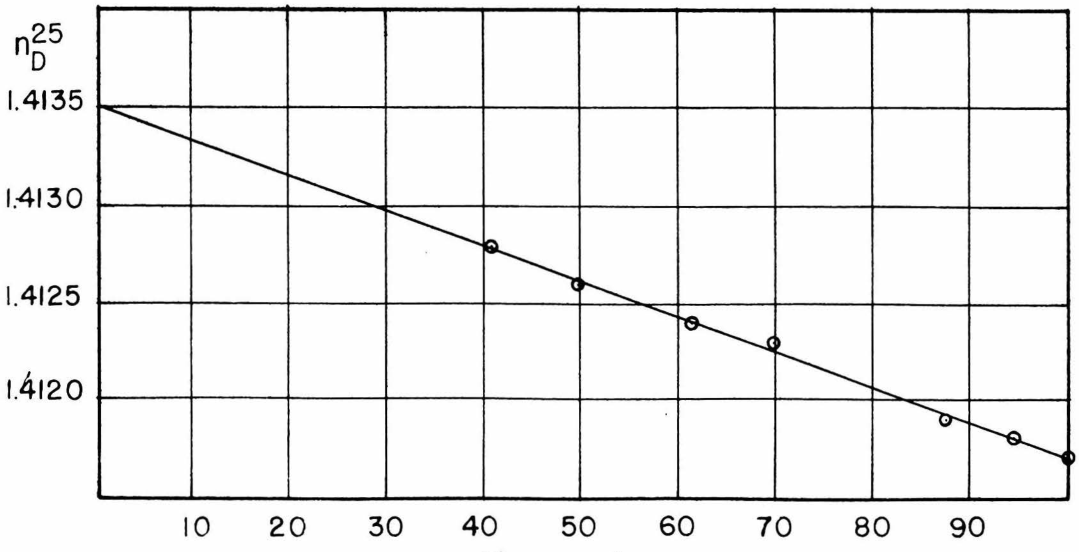

Fig. III