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Studies in Stereochemistry. I. The Stereospecific Wagner–Meerwein Rearrangement of the Isomers of 3-Phenyl-2-butanol[1]

BY DONALD J. CRAM[2]

A considerable amount of our more intimate knowledge of the mechanisms of molecular rearrangements rests on the use of stereochemical relationships which exist between particular groups of carbon atoms in reactants and products of a given reaction. Thus Wallis and co-workers[3] and others have unequivocally demonstrated in their fundamental researches on the subject that in the Curtius, Hofmann, Lossen and Wolff rearrangements the migrating species when asymmetric is capable of maintaining optical configuration throughout the course of the reaction. There is good reason to expect that this stereospecificity with regard to the migrating group can be equally well applied to the pinacol and Wagner–Meerwein rearrangements.

Bartlett and Pöckel[4] called attention to evidence that in the Wagner–Meerwein rearrangement the carbon atom where replacement occurs undergoes a Walden inversion. Bernstein and Whitmore[5] in their elegant study of the semipinacolic deamination reaction of optically active 1,1-diphenyl-2-amino-1-propanol have demonstrated that a Walden inversion of the carbon atom originally bearing the amino group accompanies the reaction.

The Wagner–Meerwein reaction is unique, in that the stereochemistry of all three of the carbon atoms involved in the bond-making and breaking processes can be examined through the use of the proper systems. This rearrangement has been studied extensively in bicyclic systems with the use of such reactions as the conversion of camphene hydrochloride to isobornyl chloride,[4,6,7,8] and the reverse reaction of the conversion of isobornyl chloride to camphene hydrate.[9] In these and other examples investigated that involve asymmetric carbon atoms at both sites of reaction (the carbon atoms *from which* and *to which* migration of a methylene group occurs), the complete stereochemical structures of both starting material and product were not known.[10] In every case the starting materials as well as the products are bicyclic compounds, and the reactions are limited to the methylene group as the migrating species.

Wallis, *et al.*,[11] have studied the migration of a phenyl group in optically active 2-methyl-2-phenyl-1-butanol when this compound is treated with thionyl chloride. These authors have suggested on the basis of changes in sign of rotatory power during rearrangement that inversion occurred at the carbon atom originally bearing the phenyl group. They also considered the existence of any true carbonium ions during the course of the reaction to be very doubtful, and looked upon their reaction as taking place by a concerted mechanism in which all bond-making and bond-breaking processes occurred at the same time, once the thionyl chloride derivative of the starting carbinol

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[1] This paper was presented in part before the Organic Division of the American Chemical Society, San Francisco Meeting, March, 1949.

[2] American Chemical Society Postdoctoral Fellow, 1947–1948.

[3] A summary of the vast literature on this subject, as well as a generalized mechanism for a number of intramolecular rearrangements, was published by Lane and Wallis, THIS JOURNAL, **63**, 1674 (1942).

[4] Bartlett and Pöckel, *ibid.*, **59**, 820 (1937); **60**, 1585 (1938).

[5] Bernstein and Whitmore, *ibid.*, **61**, 1324 (1939).

[6] Meerwein and van Emster, *Ber.*, **53**, 1815 (1920); **55**, 2500 (1922).

[7] Asahina, Ishidate and Sans, *ibid.*, **69**, 343 (1936).

[8] Nevell, Salas and Wilson, *J. Chem. Soc.*, 1188 (1939).

[9] Meerwein, *Ann.*, **453**, 16 (1927).

[10] The configurations of the carbon atom bearing the chlorine atom in camphene hydrochloride and the carbon atom bearing the hydroxyl in camphene hydrate have not been determined.

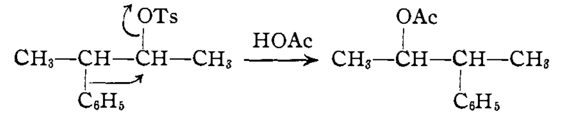
[11] Wallis and Bowman, *J. Org. Chem.*, **1**, 383–392 (1936).

was formed. This work, however, represents the only attempt to study the stereochemistry of the Wagner–Meerwein rearrangement in an acyclic system.

Among others, Wilson, *et al.*,[8] have postulated an ionic intermediate in the Wagner–Meerwein rearrangement, but more concrete evidence for an ionic intermediate is found in the work of Winstein, *et al.*,[12] on the *i*-cholesteryl system which involves a pair of electrons as the migrating species.

In contrast to the findings of the above authors, the present investigation (see papers I, II, III and IV in this series) will unequivocally demonstrate for the first time the existence of a *discrete molecular species*, a carbocyclic three-membered carbonium ion as an intermediate in a Wagner–Meerwein rearrangement in an acyclic system.[13] It should be stated, however, that the results of this work are in a sense not unlike the demonstration of the existence of a bromonium ion by Winstein and Lucas,[14] whose work has served as an inspiring model in the present investigation.

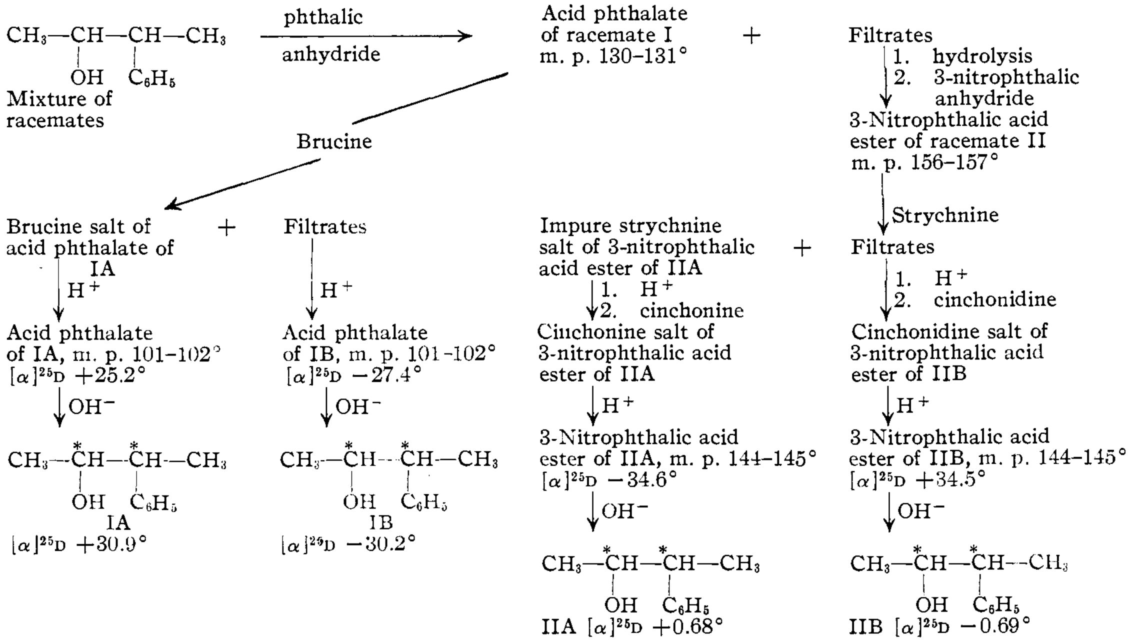
Paper I in the present series is devoted to an investigation of the mechanism of the Wagner–Meerwein reaction which takes place during the acetolysis of the *p*-toluenesulfonates of the stereoisomers of 3-phenyl-2-butanol. When rearrangement occurs in the molecule, the product is a derivative of an alcohol of the same structural formula as is the reactant, but not necessarily the same stereochemical formula. This fact simplifies the procedures of isolation and identification of products as well as giving some information in regard to the possible existence of symmetrical intermediates. This system also allows a study at the same time of the stereochemical transformations that occur at both the carbon atoms *from which* and *to which* migration takes place; these carbon atoms are free to rotate, and the substituents attached to them are not held in a definite position in space with respect to each other.



$$\mathrm{CH_3{-}\underset{\underset{C_6H_5}{|}}{C}H{-}\overset{\overset{OTs}{|}}{C}H{-}CH_3} \xrightarrow{\mathrm{HOAc}} \mathrm{CH_3{-}\overset{\overset{OAc}{|}}{C}H{-}\underset{\underset{C_6H_5}{|}}{C}H{-}CH_3}$$

Preparation and Resolution of 3-Phenyl-2-butanol

A mixture of the two racemates of 3-phenyl-2-butanol[15] was obtained by the treatment of 2-phenylpropionaldehyde (this compound was prepared by the procedure of Claisen[16]) with the methyl Grignard reagent. The resolution of this carbinol into the four optically pure stereoisomers was accomplished according to the scheme indicated. The four alcohols are designated as IA, IB, IIA and IIB, the numerals referring to the racemate series and the letters to the enantiomorphs within the series.



The acid phthalates of II, IIA and IIB were prepared as well as the 3-nitrophthalic acid esters of I, IA and IB, and in each case where an enanti-

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(12) Winstein and Adams, THIS JOURNAL, **70**, 838 (1948); Winstein and Schlesinger, *ibid.*, **70**, 3528 (1948).

(13) Such an intermediate represents not a transition state (maximum in a potential energy curve) but an actual intermediate ion containing a three-membered ring and situated at a minimum in the curve of potential energy *vs.* reaction coördinate. The experiments leading to the previously discussed three-membered cycle of Lane and Wallis were not such as to distinguish between these possibilities.

(14) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939).

(15) The preparation of this alcohol was first carried out by Geissman and Akawie (unpublished work) and will be reported by these authors at a future date.

(16) Claisen, *Ber.*, **38**, 705 (1905).

TABLE I

PHYSICAL DATA PERTAINING TO THE STEREOISOMERS OF 3-PHENYL-2-BUTANOL AND DERIVATIVES

Compound alcohols	Yield, %	B. p. °C.	Mm.	$[\alpha]^{25}D$ Pure liq.	Formula	Analyses, % Calcd. C	H	Found C	H
I[a]	90	108	10	.....	$C_{10}H_{14}O$	79.95	9.39	79.58	9.47
II[b]	84	105	10	.....	$C_{10}H_{14}O$	79.95	9.39	79.91	9.55
IA	93	118	25	+30.9	$C_{10}H_{14}O$	79.95	9.39	80.08	9.29
IB	89	118	25	−30.2	$C_{10}H_{14}O$	79.95	9.39	79.64	9.67
IIA	87	119	30	+ 0.68	$C_{10}H_{14}O$	79.95	9.39	79.73	9.40
IIB	85	119	30	− 0.69	$C_{10}H_{14}O$	79.95	9.39	80.02	9.57
Acid phthalates		M. p., °C.		In ethanol $c \cong 3\%$					
I[c]	27	130–131		.....	$C_{18}H_{18}O_4$	72.41	6.08	72.60	6.30
II[d]	86	83–84		.....	$C_{18}H_{18}O_4$	72.41	6.08	72.50	6.25
IA[d]	42	101–102		+25.2	$C_{18}H_{18}O_4$	72.41	6.08	72.69	6.26
IB[d]	29	101–102		−27.4	$C_{18}H_{18}O_4$	72.41	6.08	72.09	6.16
IIA[e]	82	101–102		−63.7	$C_{18}H_{18}O_4$	72.41	6.08	72.63	6.26
IIB[e]	86	102–103		+64.1	$C_{18}H_{18}O_4$	72.41	6.08	72.53	6.33
3-Nitrophthalic acid esters									
I[f]	90	143–144		.....	$C_{18}H_{17}NO_6$	62.97	5.00	63.28	5.05
II[f]	52	156–157		.....	$C_{18}H_{17}NO_6$	62.97	5.00	63.25	5.06
IA[f]	84	150–151		+34.2	$C_{18}H_{17}NO_6$	62.97	5.00	63.16	5.11
IB[f]	87	148–149		−33.4	$C_{18}H_{17}NO_6$	62.97	5.00	63.32	5.37
IIA[f]	34	144–145		−34.6	$C_{18}H_{17}NO_6$	62.97	5.00	62.97	5.03
IIB[f]	40.5	144–145		+34.5	$C_{18}H_{17}NO_6$	62.97	5.00	63.25	5.23
p-Toluenesulfonates									
IA[f]	84	62–63		.....	$C_{17}H_{20}SO_3$	67.08	6.62	66.97	7.79
IB[e]	78	35–36		.....	$C_{17}H_{20}SO_3$	67.08	6.62	66.96	6.74

[a] $n^{25}D$ 1.5159. [b] $n^{25}D$ 1.5167. [c] Rod-shaped crystals. [d] Clusters of thick square plates. [e] Flat irregular needles [f] Fine needles.

omorphic pair was obtained, the magnitude of the rotation of the one is in good agreement with that of the other. The melting points of the solid derivatives also coincide. These data indicate that complete resolution was accomplished. The *p*-toluenesulfonates of IA and IIA were prepared by treating the corresponding alcohols with *p*-toluenesulfonyl chloride in a pyridine solution. Table I records the physical constants, analytical data and yields pertaining to these compounds.

Acetolysis of the *p*-Toluenesulfonates of the Stereoisomers of 3-Phenyl-2-butanol

The *p*-toluenesulfonates of IA and IIA were prepared and heated at 70° for thirty hours[17] in a solution of glacial acetic acid which contained 1% of acetic anhydride and enough potassium acetate to neutralize the toluenesulfonic acid produced in the reaction.[18] The following formulations indicate the procedures used for isolation of the products, the yields and rotations. The alcohol IIA was isolated as the acid phthalate because this derivative possesses more desirable crystallization properties than the corresponding 3-nitrophthalic acid ester.

The observed rotation of the liquid acetate–olefin mixture obtained from the acetolysis of the *p*-toluenesulfonate of IA is very small (−0.22°) indicating that almost complete racemization took place. Had simple inversion of the carbon atom bearing the *p*-toluenesulfonate group occurred to any extent, one would have expected a corresponding increase in this rotation since the magnitude of the rotation of the acetate of IIA or IIB is quite high (>26°). The magnitude of the rotation obtained by the reduction of this mixture is also very low (+0.21°) indicating that there is little, if any, predominance of the amount of IA over IB, or *vice versa*.

The observed rotation of the liquid acetate–olefin mixture obtained from the acetolysis of the *p*-toluenesulfonate of IIA is quite large (−26.45°), which indicates that there is a considerable amount of optically active compound present. When reduced to the carbinol–olefin mixture, however, the rotation drops to +0.85°, a fact consistent with the large amount of IIA alcohol ($[\alpha]^{25}D$ +0.68°) present in this mixture There can be little if any of either IA or IB present, however, (products of simple inversion), because these alcohols have a high magnitude of rotation

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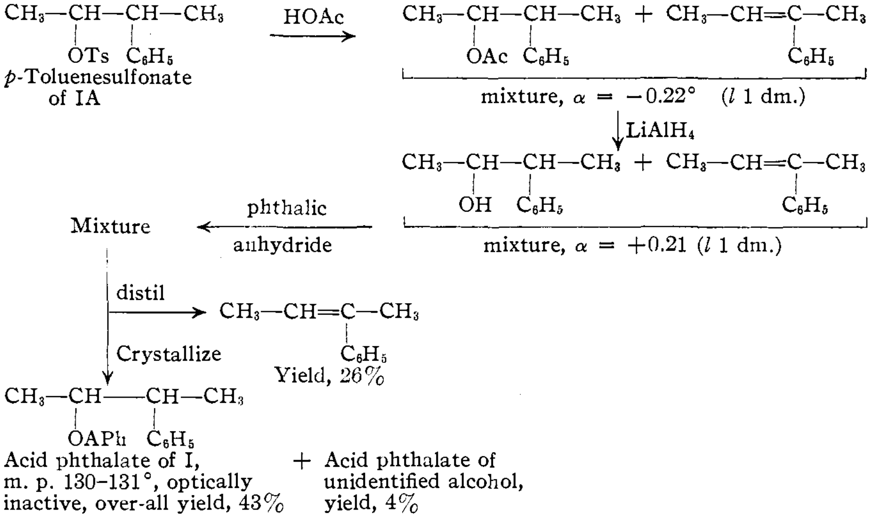
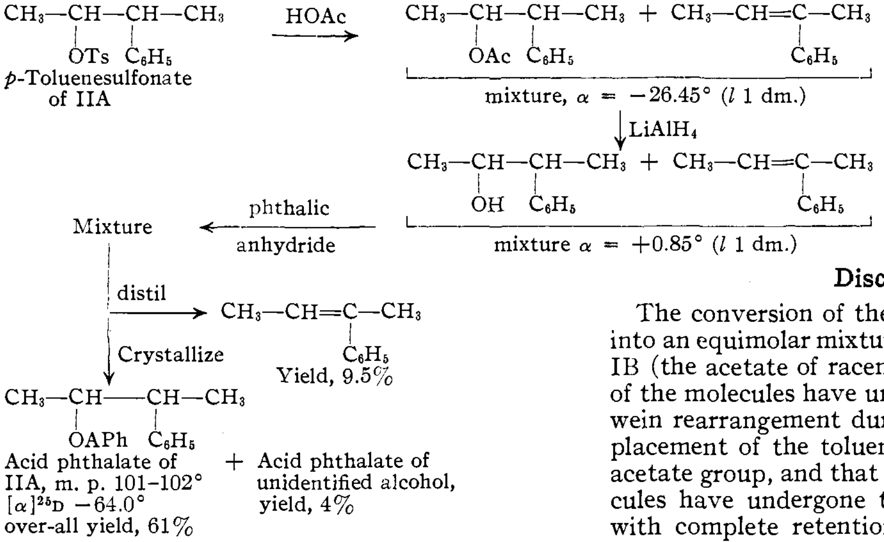
[17] This period of heating is equal to about six half-lives of the starting material under these conditions, as calculated from the kinetic data obtained for acetolysis of these compounds by S. Winstein and B. Friess[23] (unpublished work).

[18] Experiments run without the potassium acetate gave a slightly lower yield of product and more tar.





(≅30°). One can conclude, therefore, that these acetolysis reactions proceeded with little, if any, *simple inversion* of the carbon atom bearing the *p*-toluenesulfonate group.

Another interesting point that should be noted is that the sum of the yields of the final carbinol derivative and the olefin in the I series (≅70%) is just about equal to the sum of the yields of the carbinol derivative and the olefin obtained in the II series, even though the relative amounts of olefin and carbinol differ.

Walden Inversion of the *p*-Toluenesulfonate of IIA

It seemed desirable to relate the configurations of the two asymmetric carbon atoms of one of the enantiomorphs of racemate I to those of one of the enantiomorphs of racemate II. This relationship could be established if a simple inversion without rearrangement could be performed on the carbon atom bearing the oxygen of one of the stereoisomers of 3-phenyl-2-butanol or a derivative. Accordingly, one of the diastereoisomers would be converted into another without altering the stereochemistry of the carbon atom bearing the phenyl group. Simple inversion was accomplished through the use of the method that Phillips[19] employed for the inversion of the *p*-toluenesulfonate of 1-phenylpropanol-2. Treatment of the *p*-toluenesulfonate of IA with a solution of a large amount of potassium acetate dissolved in absolute ethanol produced a small amount of the acetate of IIA (most of the *p*-toluenesulfonate was converted to the ethyl ether). This acetate was converted to the acid phthalate for identification purposes.

Discussion

The conversion of the *p*-toluenesulfonate of IA into an equimolar mixture of the acetates of IA and IB (the acetate of racemate I) indicates that half of the molecules have undergone a Wagner–Meerwein rearrangement during the course of the displacement of the toluenesulfonate groups by the acetate group, and that the other half of the molecules have undergone the displacement reaction with complete retention of configuration. Furthermore, those molecules that have undergone rearrangement have done so in a highly stereospecific manner.[20] In the acetolysis of IIA there is no concrete proof that any rearrangement has taken place, but it would seem highly probable that since rearrangement took place in the I series, the same occurred in the II series. If the analogy between systems I and II is maintained, half of the molecules of *p*-toluenesulfonate of IIA must rearrange to IIA acetate, and half of the molecules produce IIA acetate without rearrangement.[21]

The isolation of the acetates of IA and IB in equimolar proportion from the acetolysis with

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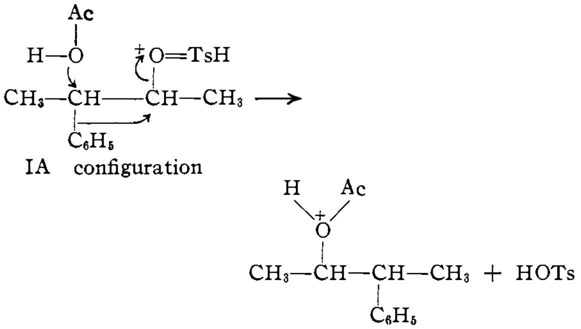
[19] Phillips, *J. Chem. Soc.*, **123**, 44 (1923).

[20] The reaction giving rise to the acetates was at least 90% stereospecific since the ratio of the yield of the acid phthalate of racemate I to the yield of the acid phthalates of other alcohols was ten to one. Stereospecificity of even a higher degree was found in the II series.

[21] Strong evidence for this suggestion is found in paper III of this series. The *p*-toluenesulfonates of the two racemates series of 3-phenyl-2-pentanol were submitted to acetolysis, and in both cases the product was a mixture of the acetate of starting material and the acetate of rearranged material (2-phenyl-3-pentanol acetate).

glacial acetic acid of the *p*-toluenesulfonate of IA is strong evidence that both products arose from a symmetrical intermediate ion, and that the reaction was *not* completely concerted. Had the latter been the case, only rearranged product (IB) would have been obtained. The acetate group would have entered the molecule at the same time that the phenyl group migrated and the *p*-toluenesulfonate group left.[22]

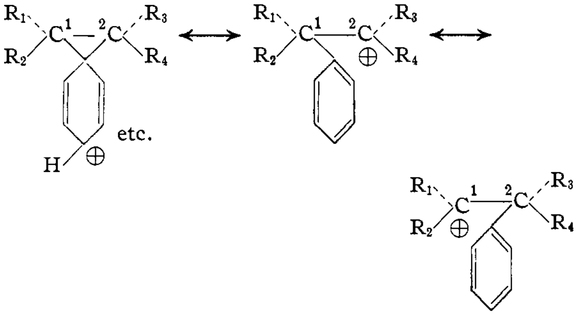


IA configuration

IB configuration

In the acetolysis experiments with glacial acetic acid the lack of products belonging to the II racemate series when the starting materials belong to the I racemate series and *vice versa* indicates that any intermediate ions formed during the reaction are capable of maintaining their optical integrity. Furthermore, very little, if any, simple bimolecular displacement of the *p*-toluenesulfonate group by acetic acid molecules could have taken place under these conditions. When the reaction was conducted in ethanol containing acetate ion, simple bimolecular displacement was the only reaction encountered exclusive of the reaction with ethanol, the nature which was not examined.

These facts can be rationalized in the following manner. The first step in the rearrangement is probably the transfer of a proton from a glacial acetic acid molecule to one of the two negative oxygens of the *p*-toluenesulfonate group placing a positive charge on the sulfur that can be distributed through resonance on the oxygen bearing the carbon. The carbon–oxygen bond is thus weakened and the second step is the departure of a molecule of *p*-toluenesulfonic acid, leaving a carbonium ion that must in some way be capable of maintaining optical and hence tetrahedral character. A cyclic ion existing as a resonance hybrid as shown below fulfills this requirement and offers an attractive hypothesis for explaining the racemization of the *p*-toluenesulfonate of IA on the one hand, and the maintenance of configuration of the same derivative of IIA on the other, during acetolysis with acetic acid. If R_1 and R_3 are methyl groups and R_2 and R_4 are hydrogens, this intermediate possesses a plane of symmetry, and the cycle could be opened by an acetic acid molecule at either carbon atoms 1 or 2 (with equal probability), giving rise to racemic acetate after the departure of a proton from the molecule. If R_1 and R_4 are methyl groups and R_2 and R_3 are hydrogens, the intermediate is asymmetric, and when the cycle is opened at either carbon atoms 1 or 2 (with equal probability), optically active product is obtained. Since there are no cases known of simple front-side displacement unattended by the possibility of reaction by a cyclic mechanism, it is logical to assume that the cycle was formed with inversion of the carbon atom bearing the *p*-toluenesulfonate group, and that when the cycle is opened, the carbon atom hit by the acetic acid molecule is inverted. The latter reaction is probably bimolecular. The question as to whether the cycle is formed by a concerted displacement of the *p*-toluenesulfonate by the phenyl group is difficult to settle. The stereospecificity of the reaction would seem to demand that this step is concerted. On the other hand, kinetic determinations[23] of the comparative rates of the liberation of *p*-toluenesulfonic acid from the *p*-toluenesulfonates of I, II and 2-butanol in glacial acetic acid showed that these reactions all take place with very little difference in rate. Since the butanol derivative does not and the derivatives of I and II do rearrange, the breaking of the carbon–oxygen bond in the latter molecules cannot be much aided energetically by the formation of a new carbon–carbon bond in a cycle, or there would be divergence in the activation energies and hence the rates of the reactions in the two types of molecules. These data suggest that either intermediate ions of other than a cyclic nature exist, or that the loss of the *p*-toluenesulfonate group and the formation of the intermediate cycle take place in concert with one another, but that the energy gained by the formation of a new carbon–carbon bond of the cycle approximately cancels the energy needed to compensate for the decrease of resonance energy and for the energy needed to distort the bond angles into a three-membered ring. The latter explanation is preferred because the stereochemistry of the reaction is not compatible with the existence of intermediates of a non-cyclic character.



The hypothesis favored for the mechanism is summarized in the formulations.

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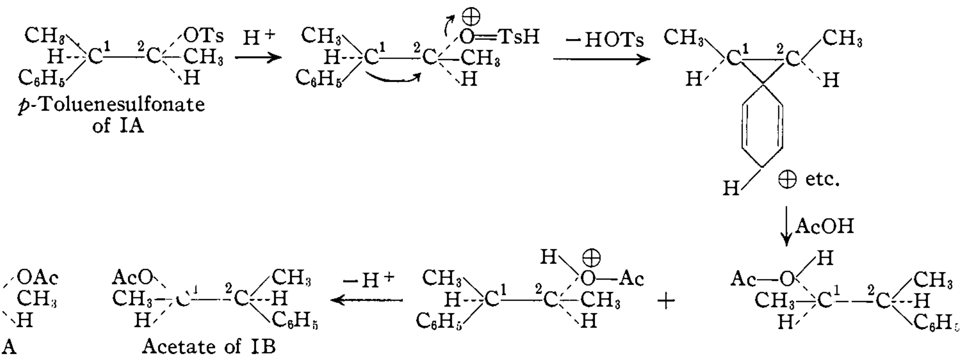
[22] This evidence is in accord with the suggestion of C. G. Swain [THIS JOURNAL, **70**, 1126 (1948); **70**, 2989 (1948)] that Wagner–Meerwein rearrangements are concerted processes as far as the carbonium ion intermediates.

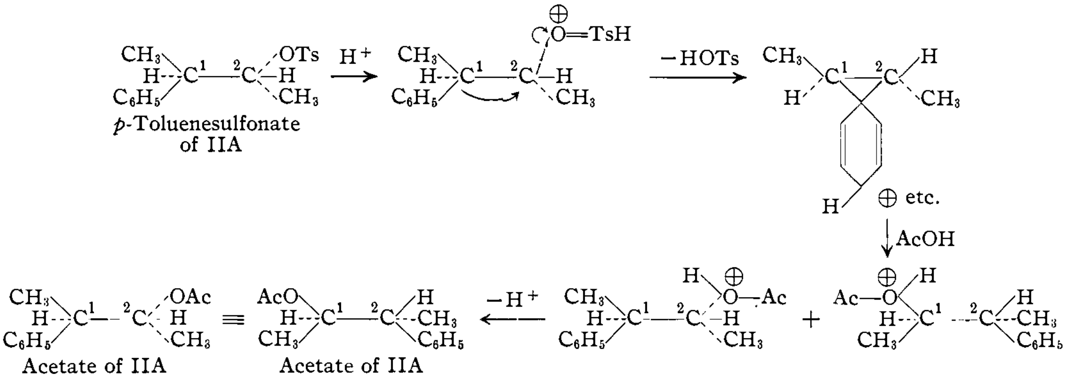
[23] Private communication from S. Winstein and B. Friess of work carried out in connection with a general investigation of the Wagner–Meerwein rearrangement.



p-Toluenesulfonate of IA

Acetate of IA

Acetate of IB

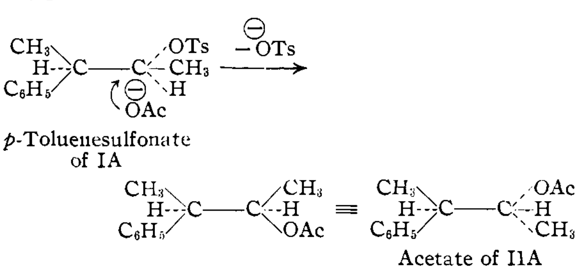


p-Toluenesulfonate of IIA

Acetate of IIA

Acetate of IIA

In presenting this mechanism, IA has been assumed to have a certain stereochemical configuration. This assumption was made because it leads to a symmetrical intermediate cyclic ion which in turn gives equal molecular amounts of IA and IB acetates. The assignment of IA to the configuration shown and not to that assumed for IB was purely arbitrary. Having assigned the configuration of IA, the configuration of IIA is determined through the conversion of the *p*-toluenesulfonate of IA to the acetate of IIA by acetate ion through simple inversion of the carbon atom bearing the oxygen bond. The configurations of IB and IIB become fixed through their enantiomorphic relationship to IA and IIA, respectively. The configurations of IIA and IIB are such that each would give rise to an asymmetric cyclic intermediate, these two intermediates being enantiomorphic in relationship. This type of intermediate for the II series is just what the results of the acetolysis experiments demand. Thus this series of experiments not only provides a certain insight into the mechanism of the Wagner–Meerwein rearrangement, but also presents a unique method of determining the stereochemical structure of this type of compound. The results of an independent determination of the stereochemical structure of each of these four isomers is presented in the fourth paper in this series, and the results are in full agreement with the above assignments. A discussion of the mechanism of the formation and the configuration of the olefin formed in the acetolysis experiments will also be found in the fourth paper of this series.



p-Toluenesulfonate of IA

Acetate of IIA

It is interesting to note in regard to the studies of the inversion by acetate ion in ethanol of the *p*-toluenesulfonates of 1-phenyl-2-propanol[19] and 3-phenyl-2-butanol that the yields of acetate product decreased respectively and that the yields of ether increased. Since the rate-determining step in the reaction with acetate ion is in each case bimolecular, the rate is more sensitive to steric hindrance than is the rate of the reaction with the ethanol, which probably proceeds by a different mechanism.

Experimental

Separation of the Mixture of Isomers of 3-Phenyl-2-butanol into Racemates I and II.—The mixture of the isomers of 3-phenyl-2-butanol[15] (112 g.) obtained from the action of methylmagnesium bromide on 2-phenylpropionaldehyde was heated to 100° for one hour with 112 g. of phthalic anhydride and 125 g. of pyridine. The resulting mixture was cooled, dissolved in benzene, extracted twice with excess dilute sulfuric acid, washed with water, dried, evaporated, dissolved in two volumes of ethyl acetate, and low-boiling petroleum ether added until the solution became slightly turbid. The product that crystallized was recrystallized from ethyl acetate and petroleum ether to give 35.5 g. of pure phthalic acid ester of racemate I, m. p. 130–131° (white flat needles).

The filtrates from the crystallization and purification of the above substance were combined, evaporated to an oil, and brought to reflux for fifteen hours in a solution of 80 g. of sodium hydroxide dissolved in 400 ml. of water. The mixture was then cooled, extracted with petroleum ether, and the organic layer was separated, washed with water, dried, evaporated to an oil and distilled. This alcohol (90.0 g.) was mixed with 116 g. of 3-nitrophthalic anhydride and 120 g. of pyridine and heated to 100° for one hour. The mixture was then cooled, dissolved in benzene, and this solution was extracted with excess dilute sulfuric acid, washed with water, dried and evaporated to an oil. This oil was dissolved in two volumes of ethyl acetate and low-boiling petroleum ether added until the solution became turbid. On standing, a solid separated which, when recrystallized from ethyl acetate and petroleum ether, produced 91 g. of the 3-nitrophthalic acid ester of racemate II, m. p. 156–157° (fine white needles).

The filtrates from the above crystallizations were combined, evaporated, and hydrolyzed to the alcohol in the same manner as described above, weight 46 g. This mixture of racemates was submitted to the same cycle as described above to produce 25 g. of additional acid phthalate of racemate I (m. p. 130–131°) and 28 g. of additional 3-nitrophthalic acid ester of racemate II (m. p. 156–157°).

Resolution of the Phthalic Acid Ester of Racemate I.—A mixture of 52 g. of the acid phthalate of racemate I, 40 g. of brucine and 900 ml. of acetone was brought to boiling, filtered and allowed to cool. The needles that separated were recrystallized from acetone to give 70.5 g. of salt which was shaken with ether and excess 2 *N* sulfuric acid. The ether layer was washed with water, dried and evaporated to an oil, and this oil crystallized from ethyl acetate and petroleum ether to give 18.2 g. of white square plates of the acid phthalate of IA, m. p. 101–102°, which was depressed by admixture with a small amount of the acid phthalate of racemate I.

The filtrates from the crystallizations of the above brucine salt were combined and shaken with excess 2 *N* sulfuric acid and ether, the ether layer washed several times with water, dried and evaporated to an oil. This oil was taken up in two volumes of ethyl acetate and a slight turbidity produced by the addition of petroleum ether. The mixture was carefully seeded with the acid phthalate of racemate I and allowed to crystallize until an estimated one-third of the total amount of solid in the solution had crystallized. The mixture was filtered, 10.4 g., m. p. 128–131°. This material when submitted to the procedure recorded above produced an additional 3.8 g. (m. p. 130–131°) of the acid phthalate of IA, m. p. 101–102°.

The combined filtrates from the crystallization of racemate I were diluted with low-boiling petroleum ether, and when allowed to stand, 17.5 g. of square plates were deposited. This material was recrystallized from ethyl acetate and petroleum ether and the product collected in two crops, the first amounting to 4.2 g. (m. p. 103–106°) and the second to 11.7 g., m. p. 101–102° (square plates) of the acid phthalate of IB. An additional 3.3 g. (m. p. 101–102°) of pure acid phthalate of IB was obtained by fractional recrystallization of the other fractions of impure material.

Resolution of the 3-Nitrophthalic Acid Ester of Racemate II.—A solution of 90 g. of the 3-nitrophthalic acid ester of racemate II, 53 g. of strychnine, 300 ml. of chloroform and 100 ml. of acetone was allowed to stand overnight and the solid deposited was collected. The filtrate was shaken with a mixture of excess 2 *N* hydrochloric acid solution and ether. The ether layer was washed with water, dried, evaporated to an oil and mixed with 43 g. of cinchonidine and 300 ml. of acetone. The clear solution deposited fine white needles on standing, which were collected and recrystallized twice from acetone to give 58 g. of salt. This material was shaken with a mixture of ether and excess 2 *N* sulfuric acid, the ether layer was washed with water, dried, and evaporated to an oil, and the 3-nitrophthalic acid ester of IIB was crystallized and recrystallized from an ethyl acetate–petroleum ether mixture to give 28 g. of white needles, m. p. 144–145°, of pure 3-nitrophthalic acid ester of IIB.

The filtrates from the crystallization of the cinchonidine salt were combined with the strychnine salt and shaken with excess 2 *N* hydrochloric acid and ether, the ether layer was separated, washed with water, dried and evaporated to an oil. This oil was dissolved in 350 ml. of acetone and mixed with 43 g. of cinchonine and the resulting solution cooled. After standing for two days at 0°, the white needles that separated were collected and recrystallized twice from acetone to give 55 g. of cinchonine salt. This material was shaken with an excess of 2 *N* hydrochloric acid and ether, the ether layer was separated, washed with water, dried and evaporated to an oil which crystallized from ethyl acetate and petroleum ether. This compound (white needles) when recrystallized from ethyl acetate and petroleum ether amounted to 24.2 g., m. p. 144–145°, of pure 3-nitrophthalic acid ester of IIA.

The filtrates from the crystallization of the cinchonine salt were converted to a mixture of 3-nitrophthalic acid esters, which, when submitted to the same resolution procedure, produced 8.5 g. (m. p. 144–145°) of additional ester of IIB and 6.3 g. (m. p. 144–145°) of additional ester of IIA.

Conversion of the Phthalic Acid Esters of I, IA and IB and the 3-Nitrophthalic Acid Esters of II, IIA and IIB into the Corresponding Alcohols.—The procedure for the hydrolysis of the above esters to the corresponding alcohols is illustrated by the conversion of the acid phthalate of IA to IA. A mixture of 22 g. of this ester, 8 g. of sodium hydroxide, 8 g. of potassium hydroxide and 80 ml. of water was refluxed for sixteen hours, cooled and extracted twice with low boiling petroleum ether. The extracts were combined, washed once with water, dried, evaporated to an oil, and the oil distilled to produce 10.3 g. of IA, b. p. 118° (25 mm.).

Conversion of I, IA and IB to the Corresponding 3-Nitrophthalic Acid Esters and the Conversion of II, IIA and IIB to the Corresponding Phthalic Acid Esters.—The procedures for the above introconversions is illustrated by the preparation of the 3-nitrophthalic acid ester of IA. A mixture of 2.2 g. of IA, 2.83 g. of 3-nitrophthalic anhydride and 5 ml. of pyridine was heated to 100° for one hour, cooled and shaken with a mixture of ether and excess 2 *N* sulfuric acid. The ether layer was washed with water, dried and evaporated to an oil. This material was crystallized from one volume of ethyl acetate and two volumes of low-boiling petroleum and the product recrystallized from the same solvents to give 4.3 g. of fine white needles, m. p. 150–151°.

Preparation of the *p*-Toluenesulfonates of IA and IIA.—The procedure for the above preparations is illustrated by the conversion of IA to the *p*-toluenesulfonate of IA. A mixture of 10.3 g. of IA, 12.8 g. of pure *p*-toluenesulfonyl chloride and 20 ml. of pure pyridine was allowed to stand at room temperature for twenty-four hours. The mixture was then shaken with a cold mixture of excess 2 *N* sulfuric acid, ether and petroleum ether. The organic layer was separated, washed with water, with a dilute alkaline solution, and again with water. The solution was then dried, evaporated to an oil under reduced pressure and crystallized and recrystallized from a mixture of one volume of benzene and five volumes of low boiling petroleum ether to give 17.5 g. of white needles, m. p. 62–63°.

Acetolysis of the *p*-Toluenesulfonate of IA.—The *p*-toluenesulfonate of IA (5.0 g.) was dissolved in 100 ml. of a mixture of 1 ml. of acetic anhydride, 100 ml. of dry glacial acetic acid and 1.96 g. of freshly fused potassium acetate. The resulting solution was held at 70° for thirty hours, cooled, and shaken with a mixture of 300 ml. of low boiling petroleum ether and one liter of water. The layers were separated, the organic layer washed with water, with a dilute alkaline solution, again with water, and dried, evaporated to an oil and the oil distilled; weight 2.70 g., observed rotation on the liquid ($l = 1$, $\lambda = \mathrm{D}$), −0.22°. This distillate was added dropwise to a solution of 3 g. of lithium aluminum hydride in ether, the excess reagent was decomposed with ethanol and the mixture shaken with a mixture of petroleum ether and dilute sulfuric acid. The organic layer was washed with water, dried, evaporated to an oil and the oil distilled, weight 2.05 g., observed rotation on the liquid ($l = 1, \lambda = \text{D}$), +0.21°. This liquid was mixed with 2.05 g. of phthalic anhydride and 3 g. of pyridine and heated to 100° for one hour, cooled, and shaken with a mixture of benzene and excess 2 N sulfuric acid. The benzene layer was washed with water, dried, evaporated to an oil, and this oil distilled at 130° at 20 mm. of pressure. The olefin that distilled amounted to 0.55 g. The residue was crystallized from ethyl acetate and low boiling petroleum ether and the product recrystallized from the same solvents to give 2.10 g. of the acid phthalate of racemate I, m. p. 130–131°, not depressed by admixture with an authentic sample of racemate I acid phthalate, $[\alpha]^{25}\text{D}$ 0° ($c = 3.12$) in absolute ethanol. The filtrates were combined and evaporated to give 0.11 g. of residue.

Acetolysis of the *p*-Toluenesulfonate of IIA.—This reaction was carried out in exactly the same manner as described above for the acetolysis of the *p*-toluenesulfonate of IA. From 2.9 g. of the *p*-toluenesulfonate of IIA was obtained 1.67 g. of a mixture of acetate and olefin, observed rotation ($l = 1, \lambda = \text{D}$), −26.5°. Reduction with lithium aluminum hydride produced 1.26 g. of a mixture of alcohol and olefin, observed rotation ($l = 1, \lambda = \text{D}$), +0.85°. Treatment of this liquid with phthalic anhydride gave a mixture from which was isolated 0.12 g. of olefin and 1.33 g. of the acid phthalate of IIA, m. p. 101–102°, m. m. p. with an authentic sample, 101–102°, $[\alpha]^{25}\text{D}$ −64.0°. The filtrates from the crystallizations were combined, evaporated and fractionated on a small column of acid-washed alumina. The material was absorbed from a benzene solution, and the column was developed with a 30% acetone–70% benzene mixture. From the 1st fraction coming through the column was isolated 0.4 g. more of the acid phthalate of IIA, m. p. 101–102°, m. m. p. with an authentic sample, 101–102°. No crystalline compounds were obtained from the other fractions. The column was flushed with methanol and all residues combined to give 0.11 g. of unidentified material.

Inversion of the *p*-Toluenesulfonate of IA with Acetate Ion to Produce the Acetate of IIA.—A mixture of 1.0 g. of the *p*-toluenesulfonate of IA, 5 ml. of absolute ethanol and 0.70 g. of freshly fused potassium acetate was heated to reflux for twenty-four hours. The material was then cooled and shaken with a mixture of water and petroleum ether, the layers separated and the organic layer was washed twice with water, dried, evaporated to an oil and distilled; 0.42 g. This oil was added dropwise to a solution of 0.5 g. of lithium aluminum hydride dissolved in dry ether, and at the end of the addition the excess hydride was decomposed with ethanol. The resulting mixture was shaken with petroleum ether and dilute sulfuric acid, the organic layer was washed with water, dried, evaporated to an oil and distilled; 0.35 g. This mixture of alcohol and ether was heated at 100° with 0.35 g. of phthalic anhydride and 1 ml. of pyridine. This resulting mixture was cooled, shaken with benzene and excess 2 N sulfuric acid, and the organic layer was washed with water, dried and evaporated. The resulting oil was distilled at 1 mm. and 130°, the ether distilling first and the excess phthalic anhydride coming over last. The residue was crystallized from ethyl acetate and low-boiling petroleum ether, and two recrystallizations of the product from the same solvents produced 120 mg. of the acid phthalate of IIA, m. p. 100–101°, m. p. with an authentic sample, 101–102°. This melting point was depressed 25° by the acid phthalates of either IA or IB. Crystallization of the above product with an equal amount of the acid phthalate of IIB produced the acid phthalate of racemic II, m. p. 83–84°, not depressed by admixture with an authentic sample.

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Summary

1. The compound 3-phenyl-2-butanol has been completely resolved into its four optically pure stereoisomers, IA, IB, IIA and IIB, and a series of derivatives of the isomers prepared.

2. When the *p*-toluenesulfonate of IA was submitted to acetolysis, the acetate of racemic I was obtained whereas when the *p*-toluenesulfonate of IIA was submitted to acetolysis, the acetate of IIA was obtained. These results are interpreted as evidence for an intermediate cyclic carbonium ion in a Wagner–Meerwein rearrangement, this ion being symmetrical in the I series and asymmetrical in the II series. The carbon atom bearing the bond to oxygen is inverted when the cycle is formed and another inversion takes place on the carbon atom whose bond is broken when the cycle is opened.

3. These reactions provide a unique proof of stereochemical structure with respect to the configuration of racemate I and racemate II.

4. The configuration of IA has been related to IIA by the simple inversion by acetate ion of the carbon atom bearing the oxygen in the *p*-toluenesulfonate of IA.

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