[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Configuration of Atrolactic Acid. Retention of Configuration in the Acid-catalyzed Ring Opening of Stilbene Oxides[1]

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trans-α-Methylstilbene is oxidized by osmium tetroxide to "α"-1,2-diphenyl-1,2-propanediol, demonstrating that this isomer has the *threo* configuration. This result permits a correlation of configuration of (−)-mandelic and (−)-atrolactic acids in agreement with those made by various other methods. The *threo*-glycol is also formed on acid hydrolysis of the epoxide of *trans*-α-methylstilbene, the ring opening thus occurring with retention of configuration. The stereochemistry of hydrogenolyses of derivatives of atrolactic acid is briefly discussed.

(−)-Atrolactic acid[2] has been assigned configuration Ia[3] on the ground that trends in the optical rotation of a series of its derivatives are parallel to those observed in the corresponding series of derivatives of (−)mandelic acid (II[4]) and (−)-lactic acid (III[5,6]). Support for this conclusion is provided by Prelog's studies of asymmetric reactions of the methyl Grignard reagent with the phenyl glyoxylates of optically active alcohols of known configuration.[7,8] On the other hand, the one chemical determination of the configuration of I[9] (Fig. 1, broken arrows) *appears* to demonstrate that (−)-atrolactic acid has the enantiomorphic configuration Ib. This disagreement would disappear if the acid-catalyzed hydrolysis of the epoxide of *trans*-α-methylstilbene (VIII) occurs with *retention of configuration*,[10] rather than with inversion as assumed by McKenzie and Ritchie.[9] Retention during hydrolysis leads to configurations for the isomeric 1,2-diphenyl-1,2-propanediols (VI) which are in accord with current theories of "asymmetric induction." Support for these configurational assignments has now been obtained by osmium tetroxide oxidation of *trans*-α-methylstilbene.

McKenzie and Ritchie[9] found that (−)-mandelic acid (II) and (−)-atrolactic acid (Ia or Ib) can be converted to the same (+)-"α"-1,2-diphenyl-1,2-propanediol (VIa or VIb) by the sequence of reactions shown in Fig. 1.[11] It is clear from this flow sheet that if (−)-I and (−)-II are related as Ia and II then the glycol should have the *threo* configuration (VIa). If, however, they are related as Ib and II then the glycol should have the *erythro* configuration (VIb). The *erythro* configuration was assigned[9] to the "α"-glycol on the ground that it could be prepared from *trans*-α-methylstilbene[12] (VII) by epoxidation and hydrolytic ring cleavage with "acidulated water,"[13] the last step being presumed[9] to occur with inversion of configuration.

The studies of Curtin[14] and of Cram[12] on steric control of asymmetric reactions have led to generalizations which permit the prediction that reaction of the phenyl Grignard reagent with the ketol IV should produce the *threo*-glycol VIa as the main product. An application of the same principles to the mechanism proposed in part I[15] for neutral catalytic hydrogenation of ketones leads to the prediction that benzoin should be reduced to *meso*-hydrobenzoin (as it is[16]) but that V should be reduced to the *threo*-glycol VIa. If the catalyst coördinates with the carbonyl oxygen atom of Va, as postulated in part I[15], the most favored conformation of the complex will be one in which the coördinated oxygen atom is flanked by the hydroxyl and methyl substituents of the carbinol atom. Since it appears that the effective bulk of the relevant substituents is: $C_6H_5 > CH_3 > OH$,[12] attack by a solvated proton at the least hindered side of the carbonyl carbon atom of this rotational isomer will give VIa. This diol would be formed if the epoxide of *trans*-α-methylstilbene (VIII) were hydrolyzed with retention of configuration at the site of reaction.

It has now been found that the "α"-glycol is formed by osmium tetroxide oxidation of *trans*-α-methylstilbene (VII → VI). Since this reagent gives *cis*-dihydroxylation with *trans*-stilbene and all other olefins so far studied[17] it follows that the "α"-glycol has the *threo* configuration (VIa). From this, in turn, it follows that (−)-atrolactic acid has the configuration Ia, in agreement with the work of Freudenberg[3] and Prelog.[7,8]

The stereochemistry of the acidic hydrolysis of VIII requires some comment since it differs from

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[1] Reductions at Metal Surfaces, IV.

[2] The D,L-nomenclature becomes cumbersome when applied to some of the stereoisomers referred to in this paper and therefore, will not be used. Configurations are denoted by Fischer projection formulas in which broken lines represent bonds directed behind the plane of the paper.

[3] K. Freudenberg, J. Todd and R. Seidler, *Ann.*, **501**, 199 (1933).

[4] K. Mislow, THIS JOURNAL, **73**, 3954 (1951).

[5] M. L. Wolfrom, R. U. Lemieux, S. M. Olin and D. I. Weisblat, *ibid.*, **71**, 4057 (1949).

[6] K. Freudenberg, *Ber.*, **47**, 2027 (1914).

[7] V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).

[8] V. Prelog and H. L. Meier, *ibid.*, **36**, 320 (1953).

[9] A. McKenzie and A. Ritchie, *Ber.*, **70**, 23 (1937).

[10] Precedent for this is found in the report that the stilbene oxides undergo acetolysis with predominating retention of configuration (J. Boeseken and G. Elsen, *Rec. trav. chim.*, **47**, 694 (1928); J. Boeseken and G. C. C. Schneider, *J. prakt. Chem.*, **131**, 285 (1931)). Indene oxide and 1-phenylcyclohexene oxide also give large amounts of *cis*-diols on acidic hydrolysis. The epoxide of 1,4-dihydronaphthalene, on the other hand, gives only the *trans*-diol.

[11] Actually (+)I was converted to (−)VI.

[12] Ultraviolet spectra indicate that the more stable and higher melting isomer of the two α-methylstilbenes has a higher degree of conjugation. By analogy with the unsubstituted stilbenes this isomer is assigned the *trans* configuration; D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 5828 (1952).

[13] M. Tiffeneau and J. Levy, *Bull. soc. chim.*, [4] **41**, 1351 (1927); **49**, 1810 (1931). These authors recognized that the stereochemistry of the glycol VI could not be established by means of this reaction alone.

[14] D. Y. Curtin, E. E. Harris and E. K. Meislich, THIS JOURNAL, **74**, 2901 (1952).

[15] J. H. Brewster, *ibid.*, **76**, 6361 (1954).

[16] J. S. Buck and S. S. Jenkins, *ibid.*, **51**, 2163 (1929).

[17] R. Criegee, B. Marchand and H. Wannowius, *Ann.*, **550**, 99 (1942).

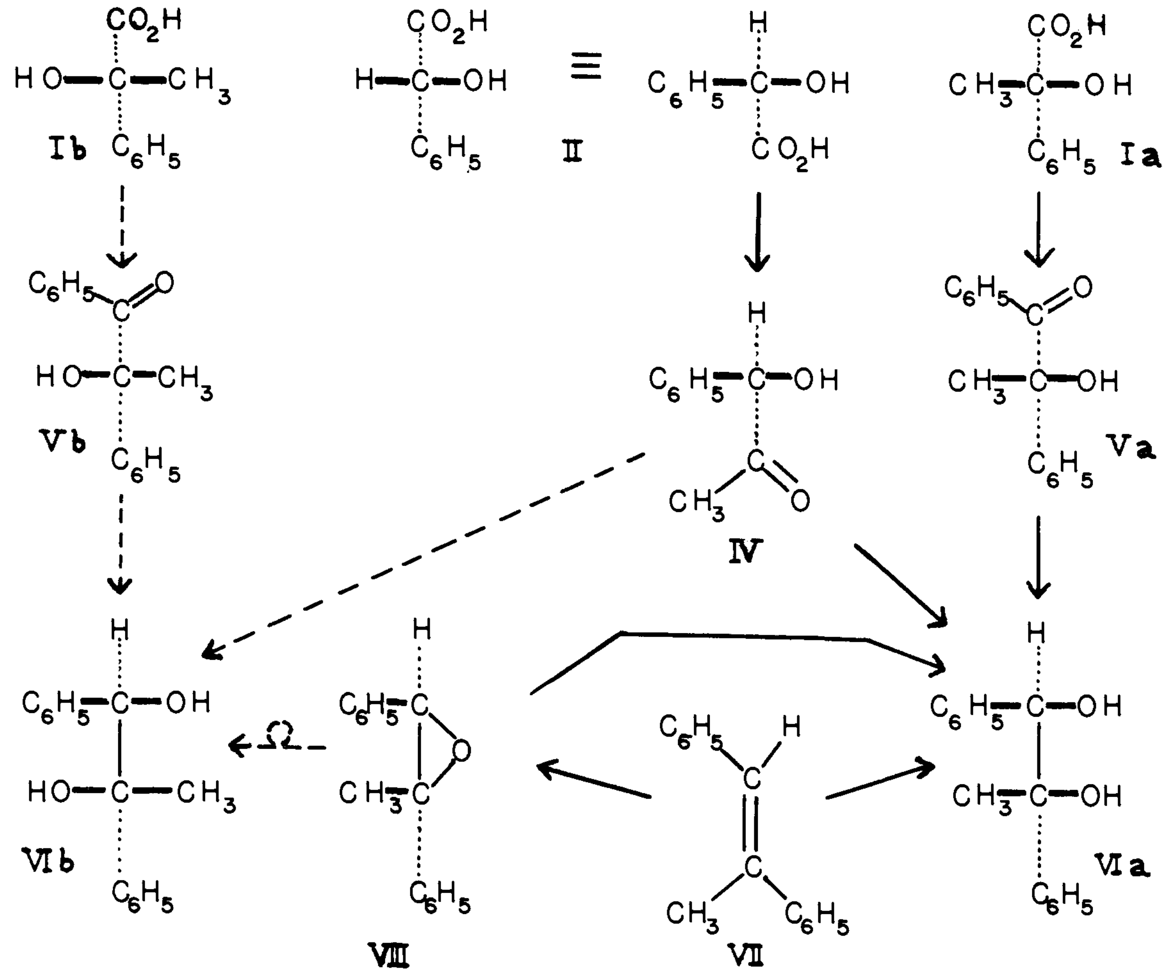
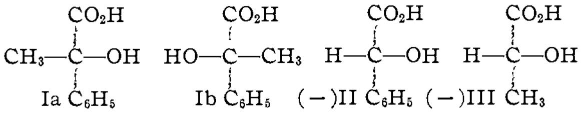


Fig. 1.—Flow sheet for the conversion of (−)I and (−)II to (+)VI *via* (−)IV and (+)V and for the conversion of VII to (±)VI. Solid arrows indicate reactions involving isomers the configuration of which was established previously or in this work. Broken arrows indicate the (hypothetical) stereochemical course required for these reactions if (−)I has configuration Ib or if hydrolysis of VIII occurs with inversion as assumed by McKenzie and Ritchie.[9]



$$\begin{array}{c} CO_2H \\ | \\ CH_3—C—OH \\ | \\ C_6H_5 \\ \text{Ia} \end{array} \quad \begin{array}{c} CO_2H \\ | \\ HO—C—CH_3 \\ | \\ C_6H_5 \\ \text{Ib} \end{array} \quad \begin{array}{c} CO_2H \\ | \\ H—C—OH \\ | \\ C_6H_5 \\ (-)\text{II} \end{array} \quad \begin{array}{c} CO_2H \\ | \\ H—C—OH \\ | \\ CH_3 \\ (-)\text{III} \end{array}$$

that observed in base-catalyzed ring openings[18a] and in acid-catalyzed ring openings of a number of *non-phenylated secondary* epoxides,[18b] where clean inversion is the rule. Kinetic data[18c] and isomer distribution studies[18a] show that in the acid-catalyzed process the reacting carbon atom has a high degree of carbonium ion character.[18d] The driving forces for this reaction appear, thus, to be the strain present in the three-membered ring, the "pull" effected by protonation of the ring oxygen atom, the "push" of a nucleophilic displacing agent, and generation of partial carbonium character at the site of reaction. It would be expected that tertiary or α-phenyl epoxides could develop a particularly high degree of carbonium character, *even to the point where a rearward nucleophilic "push" was not required for reaction.* The stereochemical outcome of the reaction would depend, then, largely on the location in space of the most accessible Lewis base capable of reacting with the developing carbonium center; if this base were

(18) (a) For reviews see S. Winstein in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 29–39; C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y.; (b) *cf.*, *inter alia*, J. Boeseken, *Rec. trav. chim.*, **47**, 683 (1928); G. K. Helmkamp and H. J. Lucas, THIS JOURNAL, **74**, 951 (1952), and earlier papers by H. J. Lucas and co-workers cited therein; D. Swern, *ibid.*, **70**, 1235 (1948); (c) F. A. Long and J. G. Pritchard, Abstracts, 128th Meeting, American Chemical Society, Minneapolis, Minn., 1955, p. 32-O; (d) reactions of this mixed nature have been considered in detail recently by N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, THIS JOURNAL, **77**, 6269 (1955); (e) P. A. Levene and A. Rothen, *J. Biol. Chem.*, **127**, 237 (1939); C. L. Arcus, *J. Chem. Soc.*, 236 (1944); J. Kenyon, A. G. Lipscomb and H. Phillips, *ibid.*, 415 (1930); W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *ibid.*, 1252 (1937); D. Reulos and C. Collin, *Compt. rend.*, **218**, 795 (1944); (g) E. Ott, *Ann.*, **488**, 188 (1931); E. H. White, THIS JOURNAL, **77**, 6014 (1955); (h) *cf.* D. J. Cram, *ibid.*, **71**, 3863 (1949), and later papers. (i) NOTE ADDED IN PROOF.—H. H. Wasserman and N. E. Aubrey, *ibid.*, **78**, 1726 (1956), have recently reported retention of configuration in the opening of both *cis*- and *trans*-dypnone oxides by hydrogen chloride in polar solvents. These authors suggest two mechanisms, one of which involves an oxonium ion pair (see also H. Hart and H. S. Eleuterio, *ibid.*, **76**, 1379 (1954)) similar to that shown in Fig. 2. Their work demonstrates that an α-phenyl-α-methyl oxirane can open with retention regardless of the thermodynamic stability of the stereoisomeric products and even in the presence of chloride ion. The author is indebted to Drs. E. L. Eliel and D. Y. Curtin for communications emphasizing that the present work leaves these points open as regards reactions of the α-methylstilbene oxides.

weakly nucleophilic no great advantage would accrue from an inversion process as opposed to one leading to retention of configuration. An "ion-pair" formed in a "solvent cage" by reaction of a proton donor with an epoxide would be oriented so that preferred retention of configuration would occur, provided enough carbonium character developed at the reaction site (see Fig. 2). Similar pictures can be devised to account for retention of configuration in a number of reactions of α-phenylethyl alcohol[18e] and α-phenylethylamine.[18g] Retention of configuration in acid-catalyzed cleavages of several 2-phenyloxiranes[10] indicates that a single phenyl group is sufficient (and probably necessary) for this result. The geometry of indene oxide (which reacts with predominating retention[10]) indicates that this effect cannot be ascribed to the formation of a "phenonium ion"[18h] and suggests strongly that the phenyl group must be attached to the reacting carbon atom, in accord with the picture developed above. Finally, it is noteworthy that the stilbene oxides react with hydrogen halides with inversion of configuration,[18f] a demonstration that the presence of highly nucleophilic ions, *at large in the solution* and thus available in all directions, can permit the inverting displacement process to come to the fore.

Establishment of the configuration of atrolactic acid permits consideration of the stereochemistry of reductive replacement reactions at metal surfaces.[19] Thus, retention of configuration is observed in the Raney nickel reduction of the methyl and ethyl esters of (+)-atrolactic acid to esters of (−)-2-phenylpropionic acid.[20,21] Similarly, (−)-2-chloro-2-phenylpropionic acid, prepared from (−)-atrolactic acid by reaction with thionyl chloride (and, thus, probably with retention of configuration[22]) has been reduced to (+)-2-phenylpropionic acid by means of palladium and hydrogen,[23] again with retention of configuration.[21] These results suggest that a short-lived organic ion or radical, formed by attack of the catalyst surface (either the metal itself or the hydrogen film) on the replaceable oxygen or chlorine atom, acquires hydrogen from the catalyst surface before it can become free enough to rotate. The reduction of (−)-2-chloro-2-phenylpropionic acid to (−)-2-phenylpropionic acid by zinc and acetic acid[23] occurs with inversion of configuration. This result suggests nucleophilic attack of the electron-rich metal surface on the chlorine atom to produce a carbanion which is at once protonated from the rear (by the solvent) before it can escape from the shielding action of the metal surface.[24] Insofar as they relate to the source of hydrogen atoms in reductions at metal surfaces these conclusions are consistent with the hypotheses of Part I.[15]

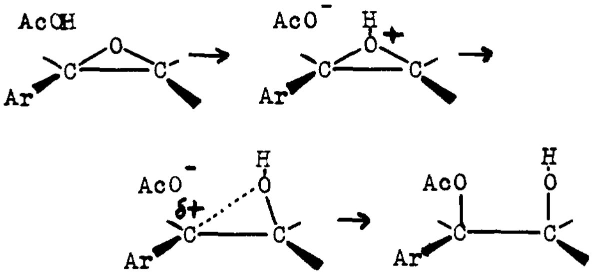


Fig. 2.

Experimental

All melting points are corrected.

"α"-1,2-Diphenyl-1,2-propanediol was prepared from methyl mandelate *via* the amide[25] and phenylacetylcarbinol[26,27] (IV). The preparation of the diol from IV and phenylmagnesium bromide[27,28] was modified only in that saturated ammonium chloride solution was used to decompose the Grignard solution. The product was obtained as an oil which proved very difficult to crystallize. A sample which finally crystallized on long standing was recrystallized from ligroin (b.p. *ca.* 90°) to give long white needles, m.p. 96.5–97.5° (lit. 94–96°[13]).

"β"-1,2-Diphenyl-1,2-propanediol was prepared by reaction of benzoin with methylmagnesium iodide,[29] the procedure being modified only in the use of ammonium chloride solution instead of dilute sulfuric acid in decomposition of the Grignard solution. The product crystallized readily and was recrystallized from aqueous methanol; m.p. 99–100°. This value was raised to 102.5–103.5° by systematic recrystallization from ether (lit. 103.5–104.5°,[29] 102.5–103°[30]).

***trans*-α-Methylstilbene** was prepared by dehydration of 1,2-diphenyl-2-propanol (from acetophenone and benzylmagnesium chloride[31]) with acetyl chloride and acetic anhydride.[32] The melting point of a sample which had been distilled, b.p. 178° at 16 mm., was 80.2–80.5° (lit. 82°[32]).

Osmium Tetroxide Oxidation of *trans*-α-Methylstilbene.—A solution of 0.76 g. of freshly distilled *trans*-α-methylstilbene in 30 ml. of thiophene-free benzene (dried over calcium hydride) was added to a solution of 1.0 g. of osmium tetroxide in 30 ml. of dry thiophene-free benzene. The solution became somewhat dark in color; 0.8 ml. of pyridine (rectified and dried over calcium hydride) was added, whereupon the solution became dark red in color. The solution was let stand for 68 hr. at room temperature (30–35°) during which time a mass of dark red-brown crystals deposited. The benzene solution was decanted and the crystals were washed twice with benzene and then dissolved in 100 ml. of methylene chloride. This solution was stirred for 6 hr. with 100 ml. of water containing 4.0 g. of potassium hydroxide and 4.0 g. of mannitol. At the end of this time the organic layer was a light yellow in color while the aqueous layer was dark red. The organic layer was separated and the water layer was washed with 100 ml. of methylene chloride. The combined methylene chloride solution was washed successively with 150 ml. of water, 100 ml. of saturated sodium bisulfite solution and 100 ml. of water. The solution was dried over calcium sulfate and evaporated to give 0.75 g. (85%) of light gray crystals. The product was dissolved in about 20 ml. of hot ligroin (b.p. *ca.* 90°) and filtered to

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[19] This has been done in a preliminary way by E. L. Eliel and J. P. Freeman, THIS JOURNAL, **74**, 923 (1952).

[20] W. A. Bonner, J. A. Zderic and G. A. Casaletto, *ibid.*, **74**, 5086 (1952).

[21] The stereochemical correlation of 2-phenylpropionic acid with 1-phenylethanol (and thus with mandelic acid and glyceraldehyde) is outlined by J. A. Mills and W. Klyne in W. Klyne, "Progress in Stereochemistry," Vol. I, Academic Press, Inc., New York, N. Y., 1954, p. 187.

[22] W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *J. Chem. Soc.*, 1266 (1937).

[23] E. Ott and K. Krämer, *Ber.*, **68**, 1655 (1935).

[24] Similar carbanion intermediates are readily envisioned in similar reactions, in particular the formation of olefins by the reaction of a metal with a 1,2-dihalide or a β-haloether. D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954), have explicitly suggested that non-planar carbanions are formed in reductions of halides by lithium and ammonia. See, especially, M. C. Hoff, K. W. Greenlee and C. E. Boord, THIS JOURNAL, **73**, 3329 (1951).

[25] H. Wren, *J. Chem. Soc.*, **95**, 1593 (1990).

[26] D. H. Hey, *ibid.*, 1232 (1930).

[27] R. Roger, *Z. Biochem.*, **230**, 320 (1931).

[28] K. v. Auwers, H. Ludewig and A. Müller, *Ann.*, **526**, 143 (1936).

[29] A. McKenzie and H. Wren, *J. Chem. Soc.*, **97**, 473 (1910).

[30] H. O. L. Fischer and C. Taube, *Ber.*, **59**, 857 (1926).

[31] C. Hell, *ibid.*, **37**, 453 (1904).

[32] H. Ley, *ibid.*, **50**, 243 (1917).

give a water-white solution from which long white needles separated on cooling; m.p. 96.5–97.5°. The melting point of this material was not depressed by admixture with authentic "α"-1,2-diphenyl-1,2-propanediol, but was depressed by similar admixture with authentic "β"-diol. An oily sample of the authentic "α"-diol crystallized readily when seeded with a small sample of this product.

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LAFAYETTE, IND.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The *cis*-Oxidation of Olefins to Glycol Monobenzoates with Perbenzoic Acid.[1] Evidence of Epoxide Ring Opening with Retention of Configuration

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cis- and *trans-p*-methoxystilbene have been found to react with perbenzoic acid to give predominately in each case that glycol monobenzoate formed by over-all *cis*-addition of the elements of perbenzoic acid to the double bond. If, as has been commonly assumed, the epoxides are intermediates in these reactions the conclusion is suggested that the epoxides react with benzoic acid in chloroform to give predominately glycol monobenzoates formed with retention of configuration—contrary to the generally held belief about such reactions. *dl-trans-p*-Methoxystilbene oxide does, in fact, react with benzoic acid under the conditions employed above to give the *threo*-hydroxy benzoate with predominant retention. All efforts to prepare *cis-p*-methoxystilbene oxide in order to test its behavior have failed. Results similar to those above have also been obtained with the *p*-methoxy-*p'*-methylstilbenes. It is concluded that such epoxide ring openings are at present of dubious reliability for demonstrating configurational relationships.

Although the reaction of perbenzoic acid with olefins in general leads to epoxides, an alternative reaction resulting in the addition of a hydroxyl and a benzoate residue to the carbon atoms of the double bond frequently has been observed.[4] Such glycol monobenzoate formation commonly has been assumed to consist of two stages: first, the oxidation of the olefin to the epoxide and then ring-opening of the epoxide by benzoic acid known to be present.[4] The stereochemistry of the epoxidation step has, furthermore, been shown not to involve any change of configuration about the olefinic double bond[4] and the opening of epoxide rings with acids has, in general, occurred with predominant inversion of configuration.[5] The conclusion which follows from these assumptions is that the glycol monobenzoate formed by the reaction of a peracid with an olefin should be the racemate with the hydroxyl and benzoate groups added in a *trans* fashion.

In an attempt to prepare *trans-p*-methoxystilbene oxide, *trans-p*-methoxystilbene (*trans*-I) was treated with perbenzoic acid in chloroform. The product, was, however, a glycol monobenzoate ester II, m.p. 120–121°, as shown by its analysis, saponification equivalent and infrared spectrum.[6] On hydrolysis, the hydroxy benzoate II was converted to a racemic glycol which was not, however, the anticipated *erythro*-racemate but was instead the *threo*-isomer (*threo*-III) formed by a net *cis* addition of the elements of perbenzoic acid to the double bond. The estimated yield of *threo*-glycol (*threo*-III) from *trans*-olefin (*trans*-I), was 43% and no evidence for the formation of the *erythro*- isomer was obtained.

Oxidation of *cis-p*-methoxystilbene (*cis*-I) in an analogous fashion yielded, after saponification of the intermediate glycol monobenzoate(s), an over-all 42% yield of a mixture of glycols from which the only product which could be separated was the *erythro*-glycol (*erythro*-III) in 12% yield. The crude glycol mixture consisted, according to an infrared analysis, of approximately 76% of the *erythro*-racemate (*erythro*-III) and 20% of the *threo*-glycol. It seems clear, therefore, that although the oxidation of the *cis* isomer was somewhat less stereospecific than that of the *trans*, the predominant steric course was again that of over-all *cis* addition of the elements of perbenzoic acid (see Chart I).

The possibility that an inversion of configuration occurred in the alkaline hydrolysis of the glycol monobenzoates was excluded by the observation that each ester could be converted to the same glycol with lithium aluminum hydride as with alkaline hydrolysis.

Configurations of the olefins (*cis*- and *trans*-I) had been assigned by Stoermer and Prigge[7] and were confirmed by a comparison of the ultraviolet absorption spectra with those of *cis*- and *trans*-stilbene. The *p*-methoxy glycols (*erythro*- and *threo*- III) had been prepared previously by the reduction of *p*-methoxybenzoin.[8] While no ex-

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[1] From the Ph.D. Dissertation submitted to Columbia University in 1952 by Arthur Bradley and the Ph.D. Thesis submitted to the University of Illinois in 1955 by Yngve Gust Hendrickson.

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[3] American Cyanamid Co. Fellow, 1953–1954. We are indebted also to E. I. du Pont de Nemours Co., Inc., for a Grant-in-Aid which supported a part of this work.

[4] (a) D. Swern, *Chem. Revs.*, **45**, 30 (1949); (b) "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, Chapter 7.

[5] See S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Editor, John Wiley and Sons, Inc., New York, N. Y., p. 27.

[6] It had been reported by M. Tiffeneau and J. Levy [*Bull. soc. chim. France*, **39**, 763 (1926)] that *trans-p*-methoxystilbene gave one of the racemic epoxides (m.p. 118–119°). The only evidence for this structural assignment was the elementary analysis which was, however, 1% low in carbon, and the observation that the substance rearranged to *α-p*-anisylacetophenone on distillation. The question of which of the two glycolic hydroxyl groups of the ester II is esterified cannot be answered at present and the structures have been written, therefore, with this detail unspecified.

[7] R. Stoermer and L. Prigge, *Ann.*, **409**, 30 (1915).

[8] S. S. Jenkins, THIS JOURNAL, **54**, 1157 (1932).