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THE DIRECTION OF RING OPENING OF *TRANS*-α-METHYLSTILBENE OXIDE BY ORGANIC ACIDS

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Abstract—In the reaction of mesitoic acid with *trans*-α-methylstilbene oxide the anion adds exclusively to the tertiary carbon atom, to give the hydroxy ester of type III, which also can be prepared from α-methylbenzoin mesitoate with KBH_4 and is transformed into the isomeric ester of type V by the action of alkali; the latter ester also being formed by reaction of threo-1,2-diphenyl-1,2-propanediol with mesitoyl chloride. Other acids yield only esters of type V, probably formed from primary products of type III by a rapid acyl group shift. All esters thus prepared belong to the threo series; corresponding erythro esters were prepared for comparison. The reductions of α-methylbenzoin acetate and mesitoate with $LiAlH_4$ produce exclusively threo-1,2-diphenyl-1,2-propanediol, in contrast with the low stereoselectivity of the similar reduction of α-methylbenzoin itself.

IN THE literature on the stereochemistry and orientation of additions to epoxides[1] definite data on the direction of the oxirane ring opening by organic acids is limited. Only two recent papers[2,3] have shown in two different ways that carboxylic acids add to styrene oxide giving as primary products exclusively, or at least predominantly, 2-acyloxy-2-phenylethanols; it has also been found that the analysis of the reaction products can give misleading information on the primary course of the reaction, because of the ease of acyl shift from the secondary to the primary hydroxyl group.

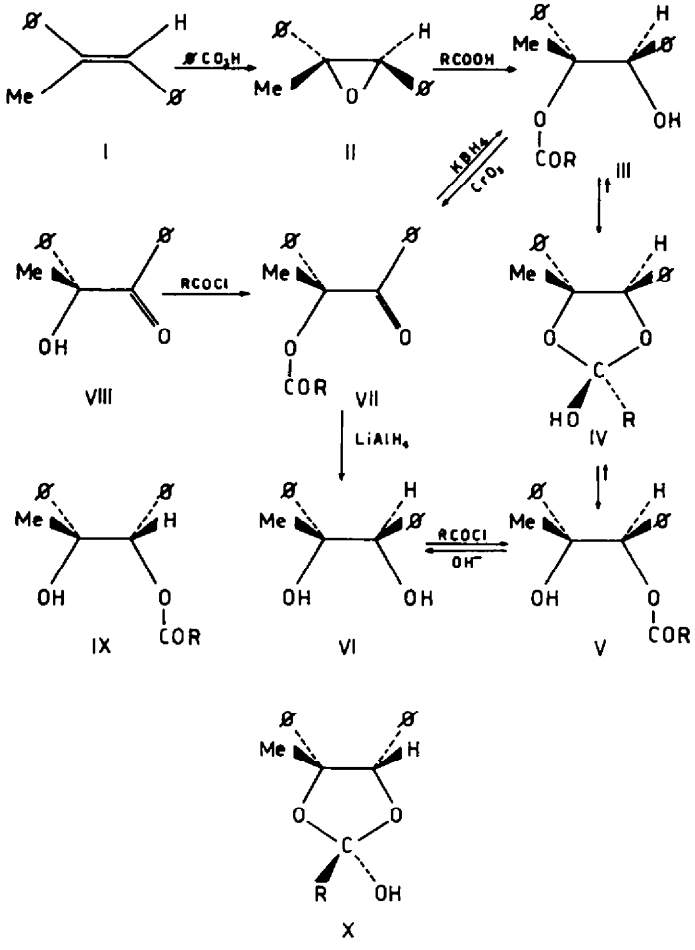
The present work deals with the reaction of *trans*-α-methylstilbene oxide (II) with acids; this epoxide was chosen to establish if even a quite hindered tertiary carbon atom can be the site of preferential attack by the anion. Reactions have been carried out with acetic, trichloroacetic and mesitoic acids, the latter acid giving the most valuable information, because of the very limited tendency of its acyl group to undergo intramolecular shifts.[2,4]

Reaction of II with mesitoic acid produces the hydroxy ester III (R = Mst),[5] reduction of which with lithium aluminium hydride yields threo-1,2-diphenyl-1,2-propanediol, the configuration of which has been firmly established.[6] A stereospecific *cis*-addition therefore takes place, as in the case of the hydrolysis of II with aqueous sulphuric acid[7] and in the ring opening of *cis*- and *trans*-stilbene oxide with carboxylic acids;[8] the recent literature indicates that this is the normal course of ring opening for oxiranes in acidic media.[1]

The tertiary ester structure (III) of the mesitoic acid addition product was proved

[1] R. E. Parker and N. S. Isaacs, *Chem. Revs.* **59**, 737 (1959).
[2] G. Berti, F. Bottari and B. Macchia, *Ann. Chim., Rome* **52**, 1101 (1962).
[3] T. Cohen, M. Dughi, V. A. Notaro and G. Pinkus, *J. Org. Chem.* **27**, 814 (1962).
[4] O. E. van Lohuizen and P. E. Verkade, *Rec. Trav. Chim.* **79**, 133 (1960).
[5] The abbreviation Mst is used for the 2,4,6-trimethylphenyl group throughout this paper.
[6] J. H. Brewster, *J. Amer. Chem. Soc.* **78**, 4061 (1956).
[7] M. Tiffeneau and J. Lévy, *Bull. Soc. Chim. Fr.* [4] **41**, 1351 (1927).
[8] G. Berti and F. Bottari, *J. Org. Chem.* **25**, 1286 (1960).

by the oxidation with chromic acid in acetone to the keto ester VII (R = Mst), which also is obtained by the reaction of VIII with mesitoyl chloride. The latter keto ester is again reduced to the hydroxy ester III (R = Mst) with potassium borohydride in the absence of alkali. If this reduction is carried out in the presence of potassium hydroxide, or if III (R = Mst) is treated with potassium hydroxide, the isomeric



hydroxy ester V (R = Mst) is obtained. The same compound may be prepared from the glycol VI and mesitoyl chloride. Infrared analysis of the crude reaction product of II with mesitoic acid proved the absence of the ester V (R = Mst).

These results confirm that even in the case of an acid of high steric requirements the epoxide ring is opened at the more substituted carbon atom—a so-called "abnormal opening" [1] taking place and in contrast with additions in basic media, steric factors are of little importance; stabilization of the positive charge on carbon in the transition state apparently being a deciding factor. No doubt the course of the reaction is the same in other less hindered carboxylic acids, even although it has not been possible to prove it directly as with mesitoic acid. The reaction of II with acetic acid yields only one hydroxy ester, together with some ketonic and aldehydic rearrangement products. This ester was also obtained, mixed with some VI, directly from the

reaction of I with peroxyacetic acid.[9] As monoacetylation of VI gives the same ester, it must be V (R = Me). Similarly, II and trichloroacetic acid, as well as the reaction of I with perbenzoic acid in the presence of trichloroacetic acid, and VI with trichloroacetyl chloride produce one and the same ester V ($R = CCl_3$).

Evidently, in the latter cases, the ease of acyl shift prevents isolation of one of the two isomeric esters, as was observed in the analogous cases with styrene oxide.[2,3] Equilibration should strongly favour the secondary esters, because of the steric decompression involved in passing from III to V. Only in the case of the mesitoic ester the acyl shift in acidic medium, which is likely to imply an attack by a proton on the very hindered ester carbonyl group, is prevented. It can take place, although slowly, in the presence of base, being probably initiated by deprotonation of the neighbouring hydroxyl group.[2]

Structure V for the esters, and the equilibrium between III and V through IV was confirmed by oxidation of the acetate and trichloroacetate with chromic acid which is much slower than that of the mesitoate III, or the trichloroacetate of hydrobenzoin.[10] This cannot be explained, if the structures are of type III. Under certain conditions it is, however, possible to isolate some of the keto esters VII (R = Me or CCl_3), evidently formed through equilibration to III. As the diacylation of VI with trichloroacetyl chloride takes place with less difficulty than would be expected for the esterification of a tertiary hydroxyl group, it is likely that this is due to the equilibrium existing between the isomers V and III, and that the second acylation takes place on the monoesters III. Attempts to saponify selectively the diesters to the monoesters failed, the rapidity of the acyl shift probably prevents taking advantage of the difference in reactivity between the two ester groupings.

The monoacetate of the erythro-glycol (IX, R = Me) can also be oxidized to the keto ester VII (R = Me), but the conditions are even more drastic than those required for the threo analogue; equilibration is certainly slower, because of the unfavourable conformation of the intermediate X with the two eclipsed phenyl groups.

The stereoselective reduction of VII (R = Mst) to III (R = Mst) with potassium borohydride is noteworthy; also the reduction of VII (R = Mst or R = Me) with lithium aluminum hydride produces exclusively the threo-glycol VI. This is in contrast with the low stereoselectivity in the reduction of VIII,[11,12] and other reductions with mixed hydrides.[13] Evidently, the ketonic carbonyl group is reduced much faster than the ester group. The stereoselectivity may be explained by means of Cram's open chain model,[14] if one assumes that the order of effective bulks of substituents on the tertiary carbon is acyloxy > C_6H_5 > CH_3 or C_6H_5 > CH_3 > acyloxy; the latter order is certainly valid in the case of the acetyloxy group, and probably also for the mesitoyloxy group, as the trimethylphenyl group should be too far from the tertiary carbon to influence the order of effective bulks. The dipolar model[15] predicts the same steric result, but is less likely to be applicable in this case.

[9] This appears to be a better method for the preparation of VI.

[10] G. Berti, F. Bottari and B. Macchia, *Farmaco (Pavia) Ed. sci.* **15**, 377 (1960).

[11] D. J. Cram, K. R. Kopecky, F. Hauck and A. Langemann, *J. Amer. Chem. Soc.* **81**, 5754 (1959).

[12] R. A. Barnes and B. R. Juliano, *J. Amer. Chem. Soc.* **81**, 6462 (1959).

[13] J. H. Stocker, P. Sidisunthorn, B. M. Benjamin and C. J. Collins, *J. Amer. Chem. Soc.* **82**, 3913 (1960).

[14] D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.* **74**, 5828 (1952).

[15] D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.* **85**, 1245 (1963).

EXPERIMENTAL

M.ps were determined on a Kofler apparatus and are uncorrected. IR spectra were taken on a Perkin–Elmer Infracord 137 on Nujol mulls. All comparisons between compounds described in this paper and with others prepared according to the literature were made on the basis of IR spectra. Pet. ether refers to petroleum ether boiling at 40–60°. Usual work-up means precipitation with water, extraction with ether, washing with 2N HCl and NaOH, and evaporation of the ether.

Esters of threo-1,2-diphenyl-1,2-propanediol

1-*Acetate* (V, R = Me). (a) A solution of 0·21 g II[16] in 5 ml acetic acid was stored overnight at room temp and then diluted with water. The product was extracted with ether, the ether layer washed (10% Na_2CO_3) dried and evaporated: the solid residue, treated with hexane gave 0·16 g V (R = Me), needles, m.p. 134–135°, λ_{OH} 2,82, λ_{CO} 5, 82 μ. (Found C, 75·90; H, 6·87. $C_{17}H_{18}O_3$ requires: C, 75·53; H, 6·71%.)

(b) A solution of 3·9 g I[17] in 20 ml acetic acid was treated drop-wise with 5 ml 40% peroxyacetic acid (in acetic acid), under external cooling with ice. After 24 hr water was added, the product treated as above and the residue, taken up in pet. ether, gave 3·1 g of a solid mixture of VI and of its 1-acetate. Repeated crystallization from hexane gave 1·2 g pure V (R = Me), m.p. 134–135°. If the initial mixture was refluxed 30 min with 3% ethanolic KOH and the product crystallized from hexane, 2·5 g pure VI, m.p. 95–97°,[7] was obtained.

(c) A solution of 0·23 g VI in 1 ml pyridine and 0·5 ml acetic anhydride was heated at 100° for 1 hr. After the usual work-up, 0·25 g V (R = Me), m.p. 132–134°, was obtained.

1-*Trichloroacetate* (V, R = CCl_3). (a) A solution of 3·2 g II in 15 ml benzene was treated with 18 ml 1M solution of trichloroacetic acid in benzene, left 16 hr at room temp, then washed with 10% Na_2CO_3 and evaporated. Crystallization from hexane gave 3·0 g V (R = CCl_3), needles, m.p. 127–128°, λ_{OH} 2·80, λ_{CO} 5·71 μ. (Found: C, 54·54; H, 3·90. $C_{17}H_{15}O_3Cl_3$ requires: C, 54·64; H, 4·04%.)

(b) A solution of 1·94 g I in 10 ml $CHCl_3$ was treated at 0° with 10·4 ml 1·15 M trichloroacetic acid in $CHCl_3$ and 20 ml 0·59 M peroxybenzoic acid in $CHCl_3$. After 6 hr at 5° the mixture was worked up as under (a), to give 2·5 g V (R = CCl_3), m.p. 127–128°.

(c) A mixture of 0·23 g VI, 0·12 g pyridine and 0·18 g trichloroacetyl chloride, left 15 min at room temp and worked up as usual, gave 0·27 g V (R = CCl_3), m.p. 127–128°.

1,2-*Bis(trichloroacetate)*. A mixture of 1·1 g trichloroacetyl chloride, 1·5 g pyridine and 0·46 g VI was heated 3 min on a steam bath, then worked up as usual; crystallization of the crude product from ethanol gave 0·70 g 1,2-diphenyl-1,2-propanediol bis(trichloroacetate), prisms, m.p. 110–111°. λ_{CO} 5·66 μ. (Found: C, 44·30; H, 2·95. $C_{19}H_{14}O_4Cl_6$ requires: C, 43·96; H, 2·72%.) Several attempts at partial saponification with calculated amounts of base failed to give the monoester, VI and starting material being the only isolated products.

2-*Mesitoate* (III, R = Mst). (a) A mixture of 1·05 g II and 1·15 g mesitoic acid [18] was heated 1 hr at 100°, cooled, taken up in ether, washed with Na_2CO_3 (0·8 g mesitoic acid was recovered on acidification), the solvent evaporated and the residue crystallized from pet. ether, to give 0·38 g III (R = Mst), needles, m.p. 123–125°, λ_{OH} 2·90, λ_{CO} 5·86 μ. (Found: C, 79·84; H, 6·82. $C_{25}H_{26}O_3$ requires: C, 80·18; H, 7·00%). The IR spectrum of the oil obtained on evaporation of the mother liquor showed that the isomeric ester V (R = Mst) was absent; it gave a strongly positive 2,4-dinitrophenylhydrazine test, and was not examined further.

A solution of 0·19 g III (R = Mst) in 15 ml ether was reduced by addition to 40 mg $LiAlH_4$ in 20 ml ether. After 30 min reflux, treatment with satd. sodium potassium tartarate, evaporation of the ether layer and crystallization from hexane, 80 mg VI, m.p. 95–97°, was obtained. The mother liquor contained more VI and 2,4,6-trimethylbenzyl alcohol, m.p. 87–89°.

(b) A solution of 2·71 g VIII[19], 2·74 g mesitoyl chloride[18] and 1·42 g pyridine in 30 ml benzene was refluxed 30 hr; usual work-up and crystallization from pet. ether yielded 3·5 g *α-methylbenzoin mesitoate* (VII, R = Mst), prisms, m.p. 176–178°, λ_{CO} 5·82, 5·94 μ. (Found: C, 80·47; H, 6·51. $C_{25}H_{24}O_3$ requires: C, 80·62; H, 6.50%.)

[16] M. Tiffeneau and J. Lévy, *Bull. Soc. Chim. Fr.* [4] **49**, 1806 (1931).
[17] C. F. Koelsch and R. V. White, *J. Org. Chem.* **6**, 602 (1941).
[18] R. P. Barnes, *Org. Syntheses* **21**, 77, (1941).
[19] L. Mehr, E. I. Becker and P. E. Spoerri, *J. Amer. Chem. Soc.* **77**, 984 (1955).

A suspension of 0·37 g of the latter compound in 15 ml methanol was treated with 0·11 g KBH_4 and shaken at room temp until the solid had dissolved (about 1 hr), dil. H_2SO_4 was added, the precipitate extracted with ether, the solvent evaporated and the residue crystallized from pet. ether to give 0·22 g III (R = Mst), m.p. 123–125°.

1-*Mesitoate* (V, R = Mst). (a) A mixture of 0·46 g VI, 0·24 g pyridine and 0·40 g mesitoyl chloride in 10 ml benzene was refluxed 15 min, then treated as usual to give, after crystallization of the crude product from pet. ether, 0·51 g V (R = Mst), as needles or clusters of prisms; the two types of crystals had λ_{OH} 2·89, λ_{CO} 5·89 μ, but showed some differences in the IR spectra. They both melted at 124–126° and gave no m.p. depression when mixed; both gave a large depression when mixed with III (R = Mst). (Found: C, 80·57; H, 6·95. $C_{25}H_{26}O_3$ requires: C, 80·18; H, 7·00%.)

(b) Reduction of 0·74 g VII (R = Mst) in 30 ml methanol with a solution of 0·2 g KBH_4 in 4 ml 0·05 N KOH gave 0·39 g V (R = Mst), m.p. 124–126°.

(c) A suspension of 0·19 g III (R = Mst) in 30 ml 2% methanolic KOH was shaken 2 hr at room temp. Dilution with water and crystallization from pet. ether gave 0·15 g V (R = Mst), m.p. 124–126°.

Esters of erythro-1,2-diphenyl-1,2-propanediol

1-*Acetate* (IX, R = Me). Treatment of 0·69 g erythro-1,2-diphenyl-1,2-propanediol[20] in 6 ml benzene with 0·36 g pyridine and 0·23 g acetyl chloride for 15 min at room temp, followed by the usual work-up, gave 0·68 g IX (R = Me), prisms, m.p. 115–116° (from hexane), λ_{OH} 2·82, λ_{CO} 5·82 μ. (Found: C, 75·69; H, 6·69. $C_{17}H_{18}O_3$ requires: C, 75·53; H, 6·71%).

1,2-*Diacetate*. A solution of 3 g of the erythro-glycol in 10 ml acetic anhydride was refluxed 5 hr, treated with water and the precipitate crystallized from hexane to give 3·1 g of the diester, m.p. 141–143°,[21] λ_{CO} 5·78 μ. (Found: C, 73·27; H, 6·52. $C_{19}H_{20}O_4$ requires: C, 73·06; H, 6·45%.)

1-*Trichloroacetate* (IX, R = CCl_3). Trichloroacetyl chloride (1·82 g) was slowly added to 2·23 g of the erythro-glycol and 1·2 g pyridine in 15 ml benzene and the product was isolated as usual, after 15 min at room temp. Crystallization from hexane yielded 3·15 g IX (R = CCl_3), needles, m.p. 118–120°, λ_{OH} 2·80, λ_{CO} 5·72 μ. (Found: C, 54·49; H, 4·03. $C_{17}H_{15}O_3Cl_3$ requires: C, 54·64; H, 4·04%.)

1,2-*Bis(trichloroacetate)*. Prepared as described for the corresponding threo-diester, from 0·69 g of the erythro-glycol: 1·08 g, m.p. 100–103° (from pet. ether), λ_{CO} 5·65 μ. (Found: C, 43·41; H, 2·64. $C_{18}H_{14}O_4Cl_6$ requires: C, 43·96; H, 2·72%.)

1-*Mesitoate* (IX, R = Mst). A mixture of 0·46 g of the erythro-glycol, 0·37 g mesitoyl chloride and 1 ml pyridine was heated 1 min at 100°; usual work-up yielded 0·32 g of the ester, m.p. 134–136° (from pet. ether), λ_{OH} 2·82, λ_{CO} 5·88 μ. (Found: C, 80·36; H, 7·04. $C_{25}H_{26}O_3$ requires: C, 80·18; H, 7·00%.)

Oxidations

(a) *With* CrO_3 *in acetone*. A solution of 0·19 g III (R = Mst) in 3 ml acetone was treated with 0·15 ml of an 8N solution of CrO_3 in H_2SO_4aq.;[22] water was added after 5 min at room temp to precipitate 0·17 g of the keto ester VII (R = Mst), m.p. 176–178°.

Under the same conditions V (R = Mst or R = Me or R = CCl_3), IX (R = Me or R = CCl_3) were recovered completely unchanged. When the reaction mixtures were left at room temp overnight V (R = Me or R = CCl_3) gave mixtures of the starting material and of some keto ester VII; IX (R = Me or R = CCl_3) were recovered unchanged.

(b) *With* CrO_3 *in acetic acid*. A solution of 0·27 g V (R = Me) in 5 ml acetic acid was treated with 0·12 g CrO_3 in 3 ml acetic acid, heated 15 min on a steam bath, diluted with water, extracted with ether and the extract evaporated. The oily residue gave, on fractional crystallization from pet. ether, 0·04 g of the starting material and 0·08 g VII (R = Me), prisms, m.p. 72–74°, λ_{CO} 5·78, 5·96 μ.[23] (Found: C, 75·91; H, 5·96. $C_{17}H_{16}O_3$ requires: C, 76·10; H, 6·01%).

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

[21] M. Tiffeneau and H. Dorlencourt, *Ann. Chim. et Phys.* [8] **16**, 237 (1909), give for the same product a m.p. 105°; the difference may be due to the fact that shorter reaction times produce mixtures of the mono- and diacetate, having approximatively this m.p.

[22] R. G. Curtis, I. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.* 457 (1953).

[23] T. I. Temnikova [*Vestnik Leningrad Univ.* 138 (1947); *Chem. Abstr.* **42**, 4155 (1948)] describes the formation of this compound as side-product of the reaction between 1,1-diphenyl-1-hydroxyacetone and acetyl chloride, without giving experimental details.

Under the same conditions IX (R = Me) gave only 0·03 g VII (R = Me), while 0·37 g V (R = CCl_3) yielded 0·27 g VII (R = CCl_3), prisms, m.p. 83–84° (from hexane), λ_{CO} 5·68, 5·96 μ. (Found: C, 55·00; H, 3·62. $C_{17}H_{13}O_2Cl_3$ requires: C, 54·93; H, 3·52%.)

Reductions with $LiAlH_4$

(a) A solution of 0·2 g α-methylbenzoin mesitoate (VII, R = Mst) in 20 ml ether was refluxed 30 min with 0·1 g $LiAlH_4$; excess hydride was decomposed with a satd. solution of Seignette salt, the product extracted with ether, the ether evaporated and the residue crystallized from hexane to give 0·07 g VI, m.p. 95–96°. The mother liquor contained more VI and 2,4,6-trimethylbenzyl alcohol, m.p. 87–89°, but no erythro-1,2-diphenyl-1,2-propanediol could be detected in it by IR analysis.

(b) A solution of 0·08 g α- methylbenzoin acetate (VII, R = Me) was reduced with 0·05 g $LiAlH_4$ as described under (a). The crude residue of the ether solution was practically pure VI, m.p. 95–96°.