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Retention of Configuration in the Opening of *cis*- and *trans*-Dypnone Oxides[1]

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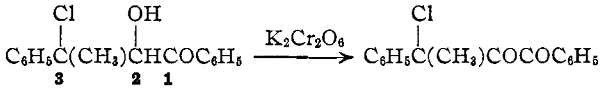
cis- and *trans*-dypnone oxides of established configurations were converted to the corresponding chlorohydrins by the action of hydrogen chloride in acetic acid. The diastereomeric chlorohydrins were shown to be β-chloro-α-hydroxy ketones by oxidation of each to the same α-diketone, 3-chloro-1,3-diphenyl-1,2-butanedione. By the action of sodium methoxide, the β-chlorohydrin, derived from *cis*-dypnone oxide, was converted to *trans*-dypnone oxide. The diastereomeric α-chlorohydrin, derived from *trans*-dypnone oxide, was transformed by sodium methoxide to *cis*-dypnone oxide. A side-product in the latter case was a yellow oil, considered to be 1,3-diphenyl-1,2-butanedione. These results are interpreted on the basis of a retention of configuration in the step involving opening of the epoxide ring.

In the formation of epoxides by the reactions of halohydrins with base, it is well established that the ring-closure is an intramolecular displacement involving Walden inversion.[2] Likewise, the opening of epoxide rings by hydrogen halides to form halohydrins is generally considered to proceed *via* inversion of configuration, since one can regenerate, with base, the same epoxide from which the halohydrin was derived.[3–5] Thus, *cis*-stilbene oxide is converted by hydrogen chloride to the *threo*-chlorohydrin, while *trans*-stilbene oxide yields the *erythro* isomer under the same conditions. When treated with base, the *threo*-chlorohydrin reverts to the *cis*-oxide, and the *erythro* isomer, to the *trans*-oxide.[6] On the other hand, there is some evidence to indicate that certain epoxides may undergo ring opening by a process which does not involve inversion of configuration. For example, *trans*-epoxysuccinic acid is hydrolyzed to a mixture of *threo*- and *erythro*-diols,[7] indene oxide yields predominantly *cis*-diol on acid hydrolysis,[8] and *trans*-β-phenylglycidic acid opens in acid to form the *threo*-diol.[8] The present paper describes the reactions of a pair of *cis*- and *trans*-epoxides with hydrogen chloride in which halohydrin formation takes place clearly *with retention of configuration.*

cis- and *trans*-dypnone oxides (I and II) were treated with hydrogen chloride, in acetic acid or in ethanol, to form the respective chlorohydrins. Assignment of configuration to the starting epoxides was based on their ultraviolet absorption spectra[9] and an independent stereospecific synthesis of the *trans*-oxide from *trans*-dypnone.[9]

The α-chlorohydrin which was formed in 70% yield from the *trans*-oxide, melted at 97–98° dec. and had a distinctly different infrared spectrum from that of the β-chlorohydrin (m.p. 100–101°), formed in 84% yield from *cis*-dypnone oxide. A mixture of the two chlorohydrins melted 92–96°.

The gross structure of the two chlorohydrins was established as that corresponding to 3-chloro-1,3-diphenyl-2-hydroxy-1-butanone (III) on the basis of

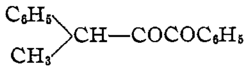


$$C_6H_5\underset{3}{\overset{Cl}{C}}(CH_3)\underset{2}{\overset{OH}{C}}H\underset{1}{C}OC_6H_5 \xrightarrow{K_2Cr_2O_6} C_6H_5\overset{Cl}{C}(CH_3)COCOC_6H_5$$

III IV

the following evidence: (i) neither product liberated iodine from potassium iodide in acetic acid, indicating absence of an α-haloketone grouping[10,11]; (ii) both chlorohydrins could be oxidized by potassium dichromate to the same product (superimposable infrared spectra), 3-chloro-1,3-diphenyl-1,2-butanedione (IV). The empirical composition and infrared spectrum[12] of this α-diketone (strong bands at 5.80 and 5.93 μ) are in accord with the assigned structure. Since all differences between the two chlorohydrins are removed by the oxidation reaction, the two substances must differ only in the configuration at C-2 (III). The fact that only one diastereomer is formed from each epoxide in the formation of the halohydrins indicates that the ring opening reaction of the dypnone oxides under these conditions is stereospecific.[13]

The two chlorohydrins showed completely different behavior when treated with sodium methoxide in ethanol. The β-chlorohydrin IIIb was converted in 90% yield to *trans*-dypnone oxide, whereas the α-chlorohydrin IIIa, under identical conditions, formed *cis*-dypnone oxide in 50% yield. In the latter case there was also formed a yellow oil, the infrared spectrum of which is in accord with the α-diketone structure VI.[14] In both of the above ring-closure reactions, only one epoxide was isolated from each chlorohydrin.



$$\left.\begin{matrix}C_6H_5\\CH_3\end{matrix}\right\rangle CH—COCOC_6H_5$$

VI

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[1] Taken from a thesis submitted to the Graduate School of Yale University by N. E. Aubrey, in partial fulfillment of the requirements for the Ph.D. degree, 1954.

[2] S. Winstein and H. J. Lucas, THIS JOURNAL, **61**, 1576 (1939); H. J. Lucas and C. W. Gould, Jr., *ibid.*, **63**, 2541 (1941).

[3] For a discussion of the mechanism and stereochemistry of this reaction see S. Winstein and R. B. Henderson, Chapter 1, in "Heterocyclic Compounds," edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. I, pp. 27ff.

[4] P. D. Bartlett, THIS JOURNAL, **57**, 224 (1935).

[5] D. Swern, *ibid.*, **70**, 1235 (1948).

[6] D. Reulos, *Compt. rend.*, **216**, 774 (1943); D. Reulos and C. Collin, *ibid.*, **218**, 795 (1944).

[7] R. Kuhn and F. Ebel, *Ber.*, **58**, 919 (1925).

[8] J. Böeseken, *Rev. trav. chim.*, **41**, 199 (1922).

[9] H. H. Wasserman and N. E. Aubrey, THIS JOURNAL, **77**, 590 1955).

[10] R. Altschul and P. D. Bartlett, *J. Org. Chem.*, **5**, 623 (1940).

[11] N. H. Cromwell and R. A. Wankel, THIS JOURNAL, **70**, 1320 (1948).

[12] H. O. House, *ibid.*, **76**, 1235 (1954), reports that the related α-diketone, phenyl benzhydryl diketone, absorbs at 5.85 μ (1710 cm.$^{-1}$) and 5.95 μ (1680 cm.$^{-1}$).

[13] Jorlander, *Ber.*, **49**, 2782 (1916), found that 1-(*p*-anisyl)-3-phenyl-2,3-epoxy-1-propanone formed two different chlorohydrins with hydrogen chloride depending on whether the solvent was ethanol or acetic acid. In the present work, change of solvent (acetic acid *vs.* ethanol) produced no marked change in the course of the reaction.

[14] Jorlander[13] found that the chlorohydrin m.p. 110°, formed on treating the epoxide with hydrogen chloride in acetic acid, yielded only α-diketone when treated with base.

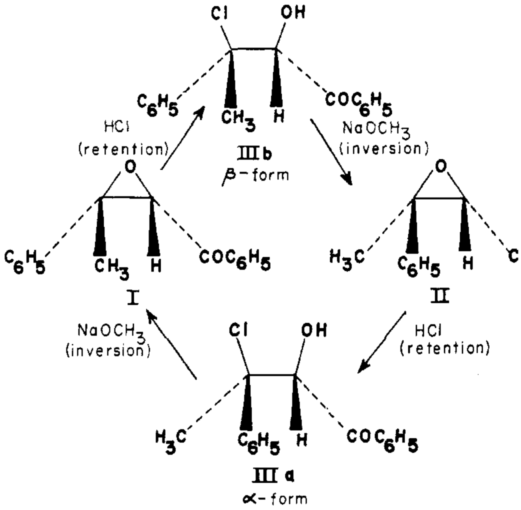
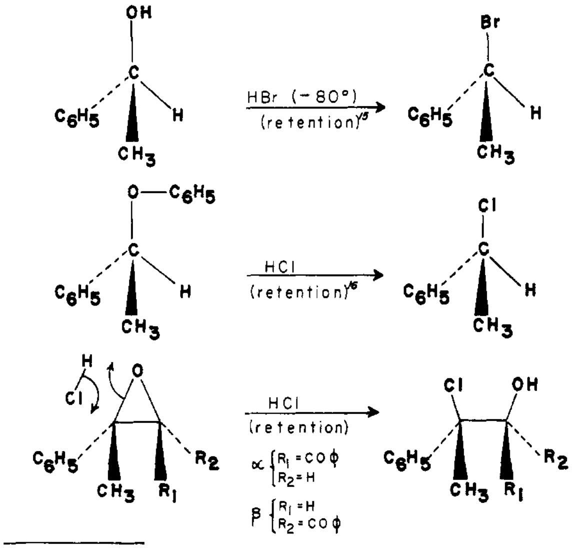


CHART I

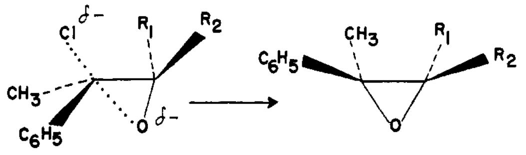
These reactions, illustrated in Chart I, represent cases where, in the successive opening and reformation of the epoxide ring, an odd number of inversions takes place. It is suggested that the opening of the epoxide ring takes place with retention of configuration, whereas the ring closure involves Walden inversion.

There are analogies for the retention of configuration in the opening of systems related to dypnone oxide. Reaction of α-phenylethanols with hydrogen halides at low temperatures has been reported to bring about C–O cleavage with retention of configuration,[15] and recent studies[16] on the cleavage of optically active α-phenethyl aryl ethers by hydrogen chloride provide further examples of retention in cleavage of the carbon–oxygen bond. The structural feature which makes these systems (alcohols, ethers and epoxides) susceptible to this type of cleavage appears to involve the attachment of a phenyl group to the carbon undergoing C–O fission.

To account for the retention of configuration in the case of the alcohols, an internal displacement mechanism (SNi) has been proposed,[17] while Hart[16] has suggested that the mechanism of retention in the α-phenethyl aryl ether cleavages involves an oxonium ion-pair. Decomposition of the ion-pair is thought to take place in such a way that the phenol molecule leaves from the side to which the entering halide becomes attached. It is possible that the dypnone oxide–halohydrin conversions proceed by a process similar to those described above.[18] Studies in progress on halohydrin formation from substituted α-methylstyrene oxide systems should shed further light on the mechanism of the reaction.



It is noteworthy that under the conditions which bring about nearly complete conversion of the β-chlorohydrin to the *trans*-epoxide, the α-chlorohydrin yields a considerable amount of α-diketone as well as *cis*-epoxide. These differences in reactivity of the two diastereomers can be explained by considering the steric factors operating in the pertinent transition states.



VII

In the formation of epoxide from the β-chlorohydrin, the bulky phenyl and benzoyl groups would be oriented *trans* in the transition state (VII, R_1 = COC_6H_5, R_2 = H) whereas the corresponding transition state for ring closure of the α-chlorohydrin has a *cis* arrangement of bulky groups (VII, R_1 = H, R_2 = COC_6H_5).[19] On the other hand, the elimi-

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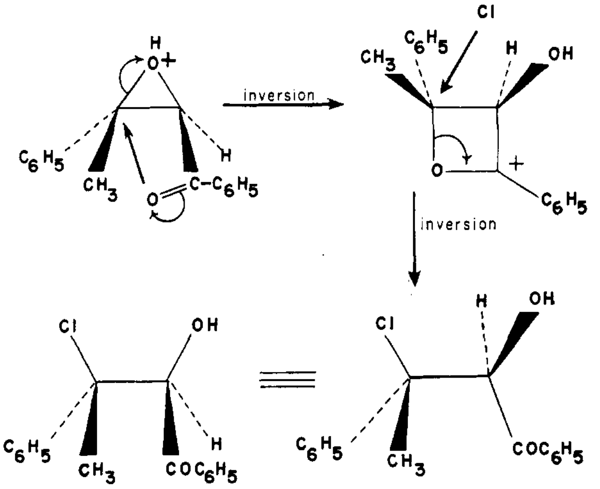
[15] P. A. Levene and A. Rothen, *J. Biol. Chem.*, **127**, 237 (1939).

[16] H. Hart and H. S. Eleuterio, THIS JOURNAL, **76**, 1379 (1954).

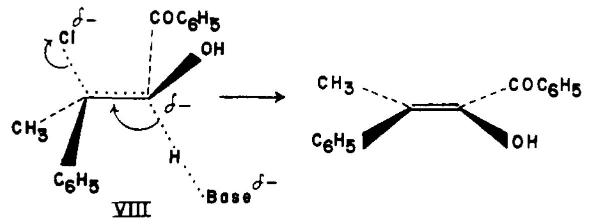
[17] W. A. Cowdry, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *J. Chem. Soc.*, 1252 (1937).

[18] An alternative mechanism for the retention in the epoxy aroyl system involves a double inversion, with participation of the adjacent carbonyl group (*trans*-case shown)



[19] D. Y. Curtin, Abstracts of the Thirteenth National Organic Chemistry Symposium of the American Chemical Society, June 15–18, 1953, Ann Arbor, Mich., pp. 40–49, has reviewed a number of cases where elimination and ring-closure reactions of diastereomers show dependence on the steric factors involved in the transition states. Among the examples chosen to illustrate this phenomenon, termed the "*cis* effect," is the difference in the rates of formation of *cis*- and *trans*-stilbene oxides from the *threo*- and *erythro*-bromohydrins, respectively.

nation of hydrogen halide from the α-chlorohydrin takes place through a sterically favorable transition state VIII and the latter reaction, leading to the enol of the α-diketone, thus competes with epoxide formation.



VIII

Experimental[20]

***cis*- and *trans*-Dypnone Oxides.**—The *cis*- and *trans*-dypnone oxides used as starting material in this work were prepared by a method previously reported.[21] The *cis* form (β) melted 163–164°, λ_{max} 247, ε 13,300; the *trans* form (α) melted 94–95°, λ_{max} 249, ε 16,600.

α-3-Chloro-1,3-diphenyl-2-hydroxy-1-butanone. (Chlorohydrin from *trans*-Dypnone Oxide.)—To 5.1 g. (0.021 mole) of *trans*-dypnone oxide (α-isomer, m.p. 93°) was added a cold, saturated solution of hydrogen chloride in glacial acetic acid. The reaction flask was placed in a water-bath, maintained at 20°, and allowed to stand for 40 minutes. The mixture was then chilled in an ice-bath, and the precipitate which formed, filtered. Additional material was obtained by diluting the filtrate. The solid was washed once with water, dried, and taken up in ether. The ether solution was washed with cold, dilute sodium bicarbonate solution, then with water, and dried over sodium sulfate. Removal of the ether left 4.5 g. (76%) of slightly yellow crystals. After one recrystallization from ligroin, the product (3.9 g., 67%) melted 97–98° dec. Repeated recrystallization raised the melting point to 98–99° (the heating rate was 1°/minute). This material did not liberate iodine from potassium iodide in glacial acetic acid. The mixture m.p. with the chlorohydrin derived from *cis*-dypnone oxide was 92–96°.

Anal. Calcd. for $C_{16}H_{15}O_2Cl$: C, 69.94; H, 5.50; Cl, 12.91. Found: C, 69.69; H, 5.81; Cl, 12.99.

Treatment of α-3-Chloro-1,3-diphenyl-2-hydroxy-1-butanone with Base.—One gram (0.0037 mole) of the chlorohydrin of *trans*-dypnone oxide was dissolved in 30 ml. of 95% ethanol and the mixture was cooled in an ice-bath. A solution of sodium methylate (0.0037 mole of sodium in 12 ml. of methanol) was added dropwise during stirring over a period of eight minutes. Stirring was continued for 20 minutes, the reaction mixture diluted with water, and the precipitate which formed filtered immediately. The slightly yellow solid thus obtained was washed with water and dried. The infrared spectrum of this crude material was identical with that of *cis*-dypnone oxide; yield, 0.43 g. (50%), m.p. 146–154°. One recrystallization from ethanol gave 0.40 g. of white needles, m.p. 161–163.5°. Admixture with pure *cis*-dypnone oxide gave no depression of the melting point.

From the above ethanolic mother liquors there was obtained, by dilution with water and extraction with ether, 0.30 g. of a yellow oil. The infrared spectrum of this crude material shows strong bands at 5.80 and 5.95 μ and corresponds very closely to the spectrum of 1,3-diphenyl-1,2-butanedione,[22] a yellow oil obtained by the isomerization of dypnone oxide in warm potassium hydroxide. The latter formed a mono-2,4-dinitrophenylhydrazone, m.p. 196–197°.

Anal. Calcd. for $C_{22}H_{18}N_4O_5$ (mono-DNP): C, 63.15; H, 4.33; N, 13.39. Found: C, 62.89; H, 4.15; N, 13.07.

β-3-Chloro-1,3-diphenyl-2-hydroxy-1-butanone. (Chlorohydrin from *cis*-Dypnone Oxide.)—Finely ground *cis*-dypnone oxide[21] (1.43 g., 0.0060 mole) (β-isomer, m.p. 160–162°) was added to a cold saturated solution of hydrogen chloride in glacial acetic acid. The reaction flask was allowed to stand at room temperature for 35 minutes. The mixture was chilled and the product, which gradually separated, was removed by filtration. The solid was washed thoroughly with water, taken up in ether, washed with dilute aqueous sodium bicarbonate, and dried. The yield of crude material was 1.39 g. (84%), m.p. 96–101°. One recrystallization from benzene–ligroin gave 1.25 g. of product, m.p. 100–101°. Repeated recrystallization failed to alter the melting point. No isomeric crystalline material was found. This product did not liberate iodine from potassium iodide in glacial acetic acid. On admixture of this product with the chlorohydrin derived from *trans*-dypnone oxide the melting point was 92–96°.

Anal. Calcd. for $C_{16}H_{15}O_2Cl$: C, 69.94; H, 5.50; Cl, 12.91. Found: C, 69.81; H, 5.54; Cl, 12.52.

Treatment of β-3-Chloro-1,3-diphenyl-2-hydroxy-1-butanone with Base.—One gram (0.0037 mole) of the β-chlorohydrin derived from *cis*-dypnone oxide was dissolved in 30 ml. of 95% ethanol, and the solution was cooled in an ice-bath. A solution of sodium methylate (0.0037 mole of sodium in 12 ml. of methanol) was added over a period of eight minutes. Stirring was continued for 22 minutes. A small amount of water was then added and the solid which formed was filtered immediately. The white solid was washed with water and dried. The infrared spectrum of this product was identical in every respect with that of *trans*-dypnone oxide; yield 0.81 g. (93%), m.p. 89–92.2°. A mixture melting point with pure *trans*-dypnone oxide showed no depression.

Oxidation of the Chlorohydrins Derived from Dypnone Oxide. Formation of 3-Chloro-1,3-diphenyl-1,2-butanedione.—One gram (0.0037 mole) of the β-chlorohydrin derived from *cis*-dypnone oxide was dissolved in 27 ml. of glacial acetic acid. An oxidizing solution consisting of 1.20 g. (0.0041 mole) of potassium dichromate in 20 ml. of water, 5 ml. of concentrated sulfuric acid and 10 ml. of acetic acid was added dropwise during stirring. The addition of oxidant took one hour; stirring was continued for an additional two hours. The mixture was then diluted with water, saturated with sodium chloride and extracted with ether. The ether extracts were washed with sodium bicarbonate solution and dried. Removal of the ether gave 0.65 g. of yellow oil. This material was purified by molecular distillation at 1 mm., n^{28}_{D} 1.5788.

Identical treatment of the chlorohydrin from *trans*-dypnone oxide gave 0.50 g. of yellow oil which was purified in the same manner; n^{28}_{D} 1.5760.

The infrared spectra of these two products are superimposable. Strong bands in the carbonyl region at 5.80 and 5.92 μ are characteristic of α-diketones in this series.[12]

Anal. Calcd. for $C_{16}H_{13}O_2Cl$: C, 70.46; H, 4.81; Cl, 13.00. Found: C, 70.08; H, 5.24; Cl, 13.22.

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[20] All melting points are corrected. Microanalyses are by the Schwarzkopf Microanalytical Laboratory, Woodside 17, N. Y. The infrared spectra were determined with a Perkin–Elmer double beam infrared spectrophotometer, model 21.

[21] H. H. Wasserman, N. E. Aubrey and H. E. Zimmerman, THIS JOURNAL, **75**, 96 (1953).

[22] We are indebted to Joan S. Mazo for the preparation of this compound and its dinitrophenylhydrazone.