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A non-stereospecific alkene hydroxylation. Stereochemistry of the ring opening of *dl-cis-* and *dl-trans-N,N*-dimethyl-3-phenylglycidamide by acids

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Attempts to prepare *dl-erythro-N,N*-dimethyl-2,3-dihydroxy-3-phenylpropionamide by the usual organic peracid hydroxylation of *dl-trans-N,N*-dimethylcinnamamide gave unexpectedly a 40:60 mixture of both diastereomers, the *threo* form being predominant. The anomaly prompted a closer investigation of each of the intermediate stages in the overall hydroxylation process. Epoxidation of *dl-trans-N,N*-dimethylcinnamamide by monoperphthalic acid gave only *dl-trans-N,N*-dimethyl-3-phenylglycidamide. Opening of the epoxide ring by acids gave a mixture of *dl-erythro* and *dl-threo* diols in a ratio of 40:60. *cis-N,N*-Dimethyl-3-phenylglycidamide, when subjected to the same ring-opening processes, also gave a mixture, but in a ratio of 75:25.

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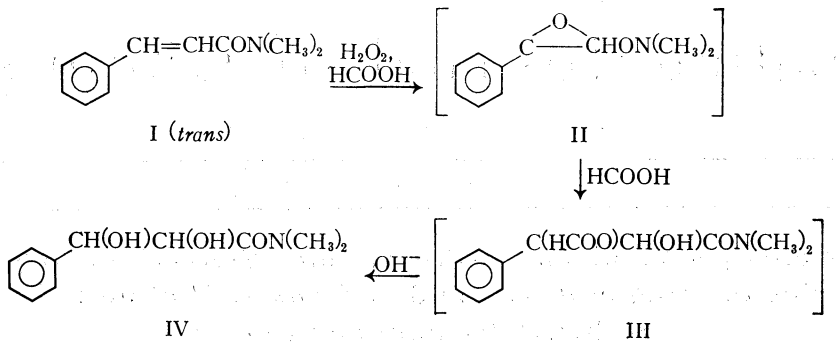
The hydroxylation of an alkene by acid-catalyzed hydrolytic cleavage of the epoxide ring initially given by the reaction with organic peracids is commonly regarded (1–3) as leading stereospecifically to *trans* addition. In this paper we draw attention to an olefinic system which yields predominantly the *cis* addition product when subjected to this treatment.

Hydroxylation

dl-trans-N,N-Dimethylcinnamamide (*trans* I), m.p. 94–95 °C, was hydroxylated by the standard method with hydrogen peroxide and formic acid (4). The epoxide II that was first formed was rapidly opened in the formic acid solvent to give the hydroxy formyloxy compound III. Hydrolysis of the monoformate III with base gave *N,N*-dimethyl-2,3-dihydroxy-3-phenylpropionamide (IV). IV, after recrystallization from benzene, melted sharply at 92–93 °C; the product could not be separated by thin-layer or column chromatography on alumina.

The 60 MHz proton magnetic resonance spectrum of IV in $CDCl_3$ or D_2O at 42 °C displays not one but two *N*-methylamide doublets around τ 7.2 of different intensity, the intensity ratio being independent of temperature over the range −50 (in $CDCl_3$) to +200 °C (in molten neat product). The splitting within each pair is the normal amide chemical shift caused by the magnetic anisotropy of the carbonyl bond, and by hindered rotation about the carbon–nitrogen bond (5–7). The coalescence temperature for both pairs was 60–65 °C in $CDCl_3$, and 75–80 °C in D_2O. The two lines remaining above 75 °C did not coalesce even up to 200 °C in the molten product. In addition, the proton magnetic resonance spectrum shows two AB quartets around τ 5.2 arising from the vicinal methine protons, the less intense quartet having J about 5 Hz, and the more intense having J about 6 Hz. The intensity ratio of these quartets is identical (within experimental error) with that of the *N*-methyl group. The doubling of both the *N*-methyl



and the vicinal methine proton spectrum cannot be ascribed to rotameric isomerization in IV caused by hindered rotation about the CH—CH bond as a result of intramolecular hydrogen bonding or by steric factors, etc., because (*i*) the intensity ratio is temperature independent (8), (*ii*) the observed value for $J_{H_\alpha H_\beta}$ (5–6 Hz) is indicative of an averaged vicinal coupling over the three rotamers (9, 10), and (*iii*) the hydroxyl proton resonance in $CDCl_3$ at $\tau \approx 6.2$ shows no evidence of a strong intramolecular hydrogen bond (11).

We therefore ascribe the doubling observed in the spectrum of IV to a mixture of diastereomers. Specific *trans* hydroxylation of *trans* I would yield *erythro* IV, whereas non-stereospecific hydroxylation gives both the *erythro* and *threo* isomers. Integration of the peak heights in the nuclear magnetic resonance spectra of three independently prepared samples yielded a relative intensity ratio of $1:(1.5 \pm 0.2)$ for the two isomer concentrations.

The above interpretation was confirmed by comparison of the spectrum of IV with that of the *threo* IV (m.p. 117–118 °C) obtained by hydroxylation of *trans* I with $KMnO_4$ (12), and by mixed spectra of the two products. The proton spectrum of the *threo* isomer is identical with that of the major component of the organic peracid hydroxylation product. As a further check, the synthesis of pure *erythro* diol amide (*erythro* IV) by $KMnO_4$ hydroxylation of *cis-N,N*-dimethylcinnamamide (*cis* I) was desirable, but attempts to prepare *cis* I were unsuccessful. However, we conclude that the performic acid hydroxylation of *dl-trans-N,N*-dimethylcinnamamide (*trans* I) gives predominantly *cis* hydroxylation in a 60:40 ratio.

Epoxidation

To discover where the non-stereospecificity occurs, each of the individual stages involved in the overall hydroxylation process was investigated. Oxidation of *dl-trans-N,N*-dimethylcinnamamide (*trans* I) by monoperphthalic acid gave only *trans* epoxide (*trans* II), as expected for specific *cis* addition to the double bond (2, 3, 13–16). The *trans* epoxide was identified by comparison of its nuclear magnetic resonance spectral parameters (Table I) with those obtained by Tung *et al.* (17) for *trans-N,N*-diethyl-3-phenylglycidamide. A mixture of *cis*- and *trans-N,N*-dimethyl-3-phenylglycidamide was also prepared from benzaldehyde and *N,N*-dimethyl-α-chloroacetamide by Darzens condensation (17, 18); the isomers were separated by chromatography on alumina to give a light-yellow liquid (b.p. 176 °C under 3 mm pressure) and a colorless solid (m.p. 96–97 °C). The nuclear magnetic resonance spectrum of the liquid was identical with that of *trans* II prepared by epoxidation of *trans* I with monoperphthalic acid; the spectral parameters of the solid in $CDCl_3$ agreed with those for *cis-N,N*-diethyl-3-phenylglycidamide (17), and confirmed the assignment of the *cis* form to this isomer.

Epoxide Ring Opening

Treatment of *dl-trans-N,N*-dimethyl-3-phenylglycidamide (*trans* II) with 80% aqueous formic acid, followed by base hydrolysis, and treatment with 25% sul-

TABLE I

Nuclear magnetic resonance data at 60 MHz and 42 °C

Compound	Solvent	Chemical shifts						$J_{H\alpha H\beta}$ (Hz)
		CH_3 (τ)		$\delta_{CH_3-CH_3}$ (Hz)	H_α (τ)	H_β (τ)	$\delta_{\alpha\beta}$ (Hz)	
trans I	$CDCl_3$	7.01		—	3.18	2.42	45.5	15.5
trans II	$CDCl_3$	7.03	6.92	6.5	6.38	5.96	25.0	2.0
cis II	$CDCl_3$	7.29	7.12	10.0	6.13	5.79	20.5	4.5
threo IV	$CDCl_3$	7.61	7.17	26.5	5.63	5.33	18.0	6.5
	D_2O	7.41	7.27	8.5	5.32	5.21	6.5	7.0
erythro IV	$CDCl_3$	7.26	7.11	9.0	5.37	5.09	17.0	5.5
	D_2O	7.09	6.98	6.5	5.19	5.13	3.5	6.0

furic acid in aqueous acetone both gave a mixture of diastereomeric glycols (approximately 40% *erythro* (inversion) and 60% *threo* (retention), as in the performic acid hydroxylation product). Formic acid was deliberately used in the opening of the epoxide to make the reaction conditions in this isolated step as similar as possible to those involved in the hydrogen peroxide – formic acid hydroxylation process. The ring opening was repeated with dilute sulfuric acid to avoid using a base in the process. The possibility of isomerization in the alkaline hydrolysis of the glycol monoester was excluded by the observations of Curtin *et al.* (19) and by the fact that the same mixture was obtained from ring openings with and without alkaline hydrolysis. Opening of the ring in *dl-cis-N,N*-dimethyl-3-phenylglycidamide (*cis* II) with the same two processes gave approximately 75% of *erythro* IV (retention) and 25% of *threo* IV (inversion).

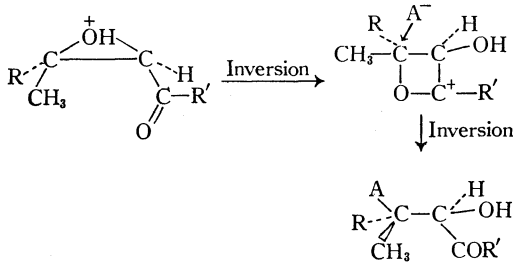
We point out that, in the present case, *trans* epoxide gave a mixture of diastereomeric diols when the ring was cleaved with dilute sulfuric acid, in agreement with the results of Curtin *et al.* (19) but in contrast to the results of Tung *et al.* (17), who obtained only *erythro* diol from *trans-N,N*-diethyl-3-phenylglycidamide. Our *cis* epoxide opened with more or less the same ease as the *trans*, giving also a mixture of diastereomers, again in contrast to the observation of Tung *et al.* (17), whose *cis* epoxyamide resisted ring opening under more or less the same conditions.

DISCUSSION

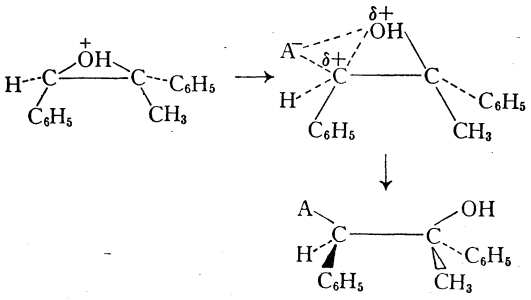
Epoxide ring opening has been the subject of several recent reviews (13–15). Normally the ring opening is accompanied by Walden inversion at the reaction site independently of whether the reaction is conducted in acid, neutral, or basic media. This has led Parker and Issacs (14) to formulate the mechanism in terms of either a true S_N2 process or what they call a "borderline S_N2" process, a subtle distinction being drawn between the relative proportions of bond forming and bond breaking in the transition states. However, both descriptions imply configuration inversion. Acid-catalyzed cleavage proceeds by initial protonation of the epoxide oxygen (13), but the subsequent steps in the mechanism are apparently the same as those in neutral or alkaline ring opening. In acid media the possibility of an S_N1 mechanism through a stable carbonium ion yielding mixed stereochemical products seems to be ruled out by the great stereospecificity of the process in most cases.

On the other hand, there are a number of examples of ring openings which give complete retention of configuration (19–23). These cases are characterized by having an aryl and (or) a carbonyl group directly bonded to one or both of the epoxide ring carbon atoms. For complete retention of configuration, neither the S_N2 nor the S_N1 mechanism can be the general explanation. A retention scheme resulting from two inversions at the reaction site has been proposed by Wasserman and Aubrey (22)

by invoking neighboring-group participation (24, 25).



An alternative mechanism (proposed by Brewster (20)) that accounts for retention is ion-pair formation between the charged nucleophilic reagent and the charge center of the protonated oxygen and developing carbonium ion pair.



This ion-pair mechanism changes into the internal displacement mechanism (S_Ni) of Ingold (26) when the attacking ion is attached exclusively to the epoxide oxygen, and into the modified S_N2 mechanism of Parker and Isaacs (14) when the attacking ion is attached to the incipient carbonium center.

Moreover, there are several cases, in addition to the one reported here, of epoxide ring openings yielding both stereoisomeric products (19, 27–29). Again, the parent epoxides contain an aryl or carbonyl function attached to the epoxide carbon atom, and the double-inversion mechanism may be operative. Our results can be explained by the Wasserman–Aubrey sequence if the intramolecular complex at the transition state is weak, so that a balance is struck between the normal S_N2 inverting path and the path through the weak complex yielding retention. The higher specificity of the reaction from the *cis* isomer compared with that from the *trans* isomer is understandable in terms of a stabilization of the four membered ring transition complex relative to the *cis* reactant as a result of the aryl–carbonyl repulsion present in the *cis* reactant. In the case discussed here, the neighboring-group effect could operate alternatively through the lone pair on the nitrogen atom. We have no evidence to choose between the two, apart from analogy with the other carbonyl systems which give retention.

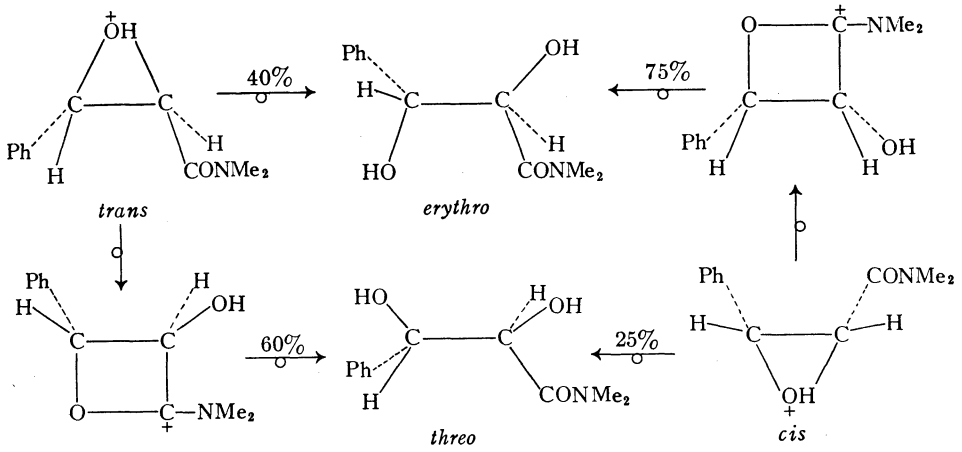
It is conceivable that the few non-stereospecific ring openings occur by an S_N1 mechanism through a stable carbonium ion. However, it is difficult to see why a carbonium ion should then not occur in those similar cases which lead specifically to retention of configuration. A related criticism may be levelled at the double-inversion process. Specific retention in the neighboring group participation scheme implies a specific stable intramolecular interaction; again, it is difficult to understand how such an interaction can compete with 100% effectiveness against the normal S_N2 process in most of the cases in which it is detectable.

Until answers to problems such as these are given, we agree with Curtin *et al.* (19) that epoxide ring openings, at present, are of dubious reliability for demonstrating configurational relationships.

EXPERIMENTAL

dl-trans-N,N-Dimethylcinnamamide (trans I)

The procedure was similar to that of Cromwell and Coughlan (30). A solution of dimethylamine (9.5 g, 0.21 mole) in 50 ml of benzene was added slowly, with constant stirring, to a solution of *trans*-cinnamoyl chloride (16.7 g, 0.1 mole) in 100 ml of benzene cooled in a water bath. After all of the amine solution had been added, the reaction mixture was stirred at room temperature for 4 h. The hydrochloride that precipitated was removed by filtration at the pump, and the filtrate was washed with two 100 ml portions of 3 *N* HCl–NaCl solution and then twice with 3 *N* NaCl solution. The benzene solution was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The solid was recrystallized from a 50:50 mixture of benzene and petroleum ether (b.p. 65–110 °C), yield 90%, m.p. 94–95 °C.



Hydroxylation of dl-trans-N,N-Dimethylcinnamamide (trans I) with Hydrogen Peroxide – Formic Acid

A solution of 17.5 g (0.1 mole) of *trans* I in 100 ml of 98–100% formic acid was cooled in a cold water bath; 25 g (~0.2 mole) of 30% hydrogen peroxide was added, with constant stirring, during about 10 min. Then the reaction mixture was kept at 40–45 °C, with constant stirring, for 24 h. The solvent was removed under reduced pressure and the residue heated under reflux with sufficient 3 *N* aqueous NaOH at 100 °C for 1 h. The product was extracted with chloroform, the extract dried, the solvent removed under reduced pressure, and the residue recrystallized from benzene, yield 40%, m.p. 92–93 °C.

dl-threo-N,N-Dimethyl-2,3-dihydroxy-3-phenylpropionamide (threo IV)

The procedure was similar to that of Boeseken (12). A solution of 17.5 g (0.1 mole) of *trans* I in 500 ml of 95% ethanol was cooled in an ice–salt bath. A solution of 18 g (0.12 mole) of $KMnO_4$ and 12 g (0.1 mole) of anhydrous $MgSO_4$ in 300 ml of water was then added during 2½ h, the temperature being kept at about −10 °C. The ice bath was removed and the reaction mixture stirred at room temperature for another 2½ h. The mixture was then filtered and the filtrate evaporated nearly to dryness under reduced pressure. The residue was treated with 250 ml of warm water and the solution filtered. The water was then removed under reduced pressure, the residue dried, and the solid recrystallized from benzene, yield 25%, m.p. 117–118 °C.

dl-trans-N,N-Dimethyl-3-phenylglycidamide (trans II)

A solution of 17.5 g (0.1 mole) of *trans* I in 100 ml of benzene was mixed with 36.5 g (0.2 mole) of monoperphthalic acid in 600 ml of ether, and refluxed for 6 h. The solvent was then removed under reduced pressure and the residue dried under vacuum. The solid was digested with 500 ml of chloroform that had been dried over anhydrous potassium carbonate, the mixture was filtered, and the solvent was removed from the filtrate, leaving a viscous oil. The oil was chromatographed on alumina, with benzene as eluent. Some unreacted *trans* I was washed down in the first portion, and the required epoxide in the following four. The epoxide was a light-yellow liquid boiling at 180 °C under 3.5 mm pressure, yield 30%.

cis- and trans-N,N-Dimethyl-3-phenylglycidamide by Darzens Condensation (17)

A solution of potassium *t*-butoxide (11.5 g, 0.103 mole) in 100 ml of dried *t*-butanol was added to a mixture of 10.6 g (0.1 mole) of benzaldehyde and 12.2 g (0.1 mole) of *N,N*-dimethyl-α-chloroacetamide under an atmosphere of nitrogen at about 10 °C during 1½ h. The reaction was allowed to proceed for another hour, and the alcohol was removed under reduced pressure. The residue was treated with 100 ml of ether and sufficient water to dissolve the potassium chloride. The ether solution was washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, and evaporated to dryness. The viscous oil was distilled under vacuum, and the fraction distilling at 170–175 °C under 3 mm pressure was collected, yield 65%.

Separation of cis and trans-N,N-Dimethyl-3-phenylglycidamide by Chromatography on Alumina

Five grams of the distilled epoxyamide was chromatographed on alumina. The series of eluents used was 50:50 hexane–benzene, benzene, 50:50 benzene–chloroform, and chloroform; 2.2 g of a light-yellow liquid was obtained from the first few portions of eluate, followed by about 0.8 g of mixed compounds and finally 1.5 g of a white solid. The yellow oil distilled at 176 °C under 3 mm pressure, and the solid, after being recrystallized from benzene, melted at 96–97 °C.

Treatment of trans-N,N-Dimethyl-3-phenylglycidamide (trans II) with Formic Acid and Sodium Hydroxide

To a mixture of 5 ml of 98–100% formic acid and 2 ml of water was added 1 g of *trans* II. The reaction mixture was kept at 40–45 °C in a water bath for

3 h and the solvent removed under reduced pressure. The residue was heated under reflux with sufficient dilute aqueous NaOH at 100 °C for 1 h. The product was extracted with chloroform, dried, and evaporated to dryness under reduced pressure. The residue was then used directly for nuclear magnetic resonance measurements without further recrystallization. The spectra showed that the sample was pure.

Treatment of trans-N,N-Dimethyl-3-phenylglycidamide (trans II) with Dilute Aqueous Sulfuric Acid

To a mixture of 10 ml of 30% sulfuric acid and 5 ml of acetone was added 1 g of *trans* II. The reaction mixture was kept at 40–45 °C in a water bath for 3 h, the solvent removed under reduced pressure, 10 ml of fresh water added, and the mixture extracted with chloroform. The chloroform extract was dried and evaporated to dryness under reduced pressure. The residue was then used for nuclear magnetic resonance measurements without further recrystallization.

Treatment of cis-N,N-Dimethyl-3-phenylglycidamide (cis II) with Formic Acid and Sodium Hydroxide

The procedure was the same as for *trans* II.

Treatment of cis-N,N-Dimethyl-3-phenylglycidamide (cis II) with Dilute Aqueous Sulfuric Acid

The procedure was the same as for *trans* II.

Nuclear Magnetic Resonance Spectra

The spectra were run on a Varian A56/60 instrument, with tetramethylsilane as an internal standard in those samples run in $CDCl_3$ at room temperature and below, and as an external standard in those samples run in D_2O.

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