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THE EPOXIDATION OF 3-METHYLCYCLOPENTENE

AN UNEXPECTED CONFORMATIONAL EFFECT*

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Abstract—The reaction of 3-methylcyclopentene with *m*-chloroperbenzoic acid provides a mixture of epoxides in which the *cis*-isomer predominates. Alternatively, treatment of the olefin with N-bromosuccinimide (NBS) and alkali provides a mixture rich in the *trans*-epoxide. The isomeric epoxides were characterized by their NMR spectra, including measurements of europium induced shifts, and their stereochemistry proven by examination of their lithium aluminium hydride reduction products.

A simple conformational argument is presented to account for the isomer distribution in the epoxidations.

IN CONNECTION with studies on a new approach to iridoid synthesis,[1] we required, as starting materials, the isomeric 3-methylcyclopentene oxides, II and III. While these could be obtained conveniently by oxidation of 3-methylcyclopentene (I), their planned use in stereospecific reaction sequences required a rigorous determination of their stereochemistry.

The presumption that the Me group in I would exert a simple steric hindrance effect[2-4] on the approach of the co-reactant formed the basis for our initial structure assignments. Thus, the major isomer obtained by treatment of I with *m*-chloroperbenzoic acid was assigned the *trans* structure III and, corroboratively, the major isomer resulting from the two stage (NBS/OH^-) treatment of I was alloted the *cis* structure II. These arguments exactly parallel those used by Henbest and McCullough[2] to describe the results obtained on epoxidation of 4-methylcyclopentene (IV). However, the next step in our synthetic sequence[1] afforded results difficult to rationalize on the basis of these naive assignments. Therefore, armed with authentic samples of all the isomeric 2- and 3-methylcyclopentanols, the epoxides II and III were subjected to lithium aluminum hydride reduction.[2] The results of these experiments (Experimental) unambiguously required the reversal of our initial assignments. Accordingly, the correct formulation of the epoxidation results are illustrated in Fig. 1.†

The NMR data collected in the table below show that the methyl doublet in the *cis*-isomer II appears at slightly lower field than the corresponding doublet in the *trans*-isomer III. These relative shifts constitute a reversal of the situation observed for 3-methylcyclohexene oxides.[4] The signals arising from the protons on the oxide

* This article is considered Part V in the series "Studies on Terpenes." For Part IV, see R. A. Finnegan and P. L. Bachman, *J. Org. Chem.*, 36, 3196 (1971).

† Sometime after this work was completed, we noted a report[5] which included the epoxidation of I; however, no indication of the stereochemistry of the product was given.

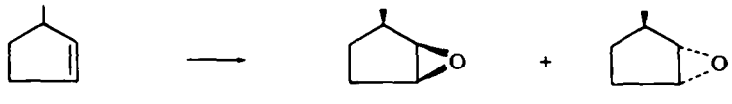
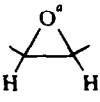
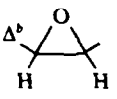


FIG 1. Epoxidation of 3-Methylcyclopentene

ring appear as a pair of slightly broadened doublets in both isomers. The 3 Hz splitting was demonstrated by appropriate decoupling experiments to represent vicinal coupling between H-1 and H-2. The relative shifts observed in the NMR spectra of II and III when measured in the presence of tris(dipivalomethanato)europium[6] are also included in the table. The downfield shift of the Me signal in the *cis*-isomer II is greater than that observed for the Me in III. The reverse is true of the protons H-1 and H-2 where the effect of the europium is greater in the *trans*-isomer III. Thus, it appears that the Me group in II interferes with the close approach of the europium to the oxygen which is possible in III.

TABLE. NMR DATA FOR *cis*-(II) AND *trans*-3-METHYLCYCLOPENTENE OXIDE (III)

Compound	CH_3[a]		Δ_{CH_3}[b]	
II	1·05[c]	3·08,[d] 3·25[d]	2·27	6·52, 6·55
III	0·88[c]	3·22,[d] 3·47[d]	1·86	7·18, 7·23

[a] Numbers in these columns are chemical shifts in ppm downfield from tetramethylsilane used as internal standard.

[b] Numbers in these columns show the absolute magnitude of the downfield shift (in ppm) occasioned by the presence of 0·25 molar equivalents of $Eu(DPM)_3$ in the solutions.

[c] Doublet, J = 7 Hz.

[d] Doublet, J = 3 Hz.

Referring again to the data shown in Fig. 1, it follows from the product composition data that the formation of the olefin-peracid complex (leading to the *cis*-epoxide) as well as the bromonium ion (leading to the *trans*-epoxide) is more favorable when it occurs *cis* to the methyl group. This apparent anomaly is most easily disposed of by considering the conformations of the olefin I. These are drawn as exaggerated envelope forms[7] in Fig. 2, and, on the reasonable assumption that Ia (*pseudo*-equatorial Me group) predominates in the mixture with Ib (*pseudo*-axial Me group), it can be seen that approach of a reagent to the double bond is impeded, not by the methyl group, but by either the *pseudo*-axial hydrogens at C-3 and C-5, or the flagstaff hydrogen at C-4. Our suggestion that the former effect is the greater, accords with the results in Fig. 1. Furthermore, the results of Henbest and McCullough[2] on the epoxidation of 4-methylcyclopentene (IV) may be dealt with in a similar manner. In this case, however, the difference in energy between the extreme conformations IVa and IVb (Fig. 2) is not so easily decided since in neither conformer does the Me group experience a

1,3 diaxial type of interaction which is apparent in Ib. On the other hand, the methyl group in IVb is involved in two skew-butane interactions which are absent in IVa. The direction of attack on IVa by peracid (to give *trans*-epoxide) or bromonium ion formation (to give *cis*-epoxide) is likewise postulated to be the result of hindrance offered by the *pseudo*-axial hydrogens at C-3 and C-5 rather than a direct involvement of the Me group.* The degree to which the actual conformations of I and IV resemble the extremes pictured in Fig. 2 is, of course, problematical. We believe, however, that application of this conformational hypothesis is appropriate to numerous reactions of variously substituted cyclopentenes and we are presently planning a number of further tests.

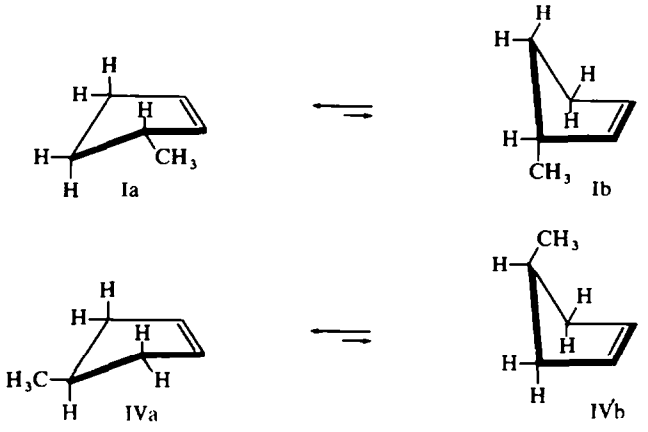


FIG 1. Conformational equilibria for cyclopentenes I and IV.

EXPERIMENTAL

The reaction of 3-*methylcyclopentene* (I) *with* m-*chloroperbenzoic acid*

The preparation of cis-3-*methylcyclopentene oxide* (II). To a stirred ice-cooled solon of 85% *m*-chloroperbenzoic acid (123 mmol) in 150 ml methylene chloride was added dropwise over 0·5 hr 10 g 3-methylcyclopentene (Columbia Chemical Company) (122 mmol). The benzoic acid precipitated as the reaction proceeded and the mixture was stirred an additional 1·5 hr after the addition was complete. After filtration, the soln was flash distilled at reduced pressure followed by distillation at atmospheric pressure through a 60 × 0·7 cm tantalum spiral column to give a fraction having bp 115–116° (atmos. pres.) (6·21 g, 52% yield) (Lit.[5] bp 116–117°). VPC analysis (6′ × 0·25″ 10% Carbowax 20M on Chromsorb W, 60 cc/min, 70°) showed this product to be a mixture of oxides II and III in the ratio 67:33; retention times: II, 3·7 min; III, 4·2 min. A pure sample of II could be obtained readily by preparative VPC: IR (film), 1470, 1390, 1370, 1310, 1290, 1230, 1200, 1010, 980, 960, 920, 905, 845, 797, 730, and 655 cm^{-1}; NMR, 1200, 1010, 980, 960, 920, 905, 845, 797, 730, and 655 cm^{-1}; NMR, δ 1·05 (doublet, 3H, J = 7 Hz, CH_3), 1·2–2·2 (envelope, 5H), 3·08 (incompletely resolved multiplet that can be collapsed to a doublet, J = 3 Hz, by irradiation at higher field, 1H, $\diagdown$CHO—$\diagup$), and 3·25 (incompletely resolved doublet, 1H, J = 3 Hz, $\diagdown$CHO—$\diagup$). (Found: C, 73·29; H, 10·42; $C_6H_{10}O$ requires: C, 73·43; H, 10·27%).

* Henbest and his students[3] have studied the epoxidation of a large number of 4-substituted and 4,4-disubstituted cyclopentenes and have interpreted the results primarily in terms of polar and steric effects. These considerations are clearly compatible with and complementary to the conformational hypothesis advanced here.

Other preparations gave 41 and 61% yields of oxide with ratios of II to III of 63:37 and 74:26. A single pass through a 24" Nester-Faust Spinning Band Teflon Annular Still provided a sample of II, bp 113, which contained only 10% of III.

The reaction of 3-methylcoclopentene with NBS followed by base treatment of the product

The preparation of trans-3-*methylcyclopentene oxide* (III). 3-Methylcyclopentene (5 g, 61 mmol) was added dropwise with stirring to an ice-cooled mixture of 10·9 g N-bromosuccinimide (61 mmol) in 30 ml water. The mixture was warmed slightly to initiate the reaction and then it was stirred for an additional 2 hr. The bromohydrins were extracted with ether and the ether layer was separated and concentrated under vacuum. The residue was treated with 16 ml of 30% aq NaOH and stirred for 1 hr at room temp. The ether layer was then separated, dried, and distilled through a 60 × 0·7 cm tantalum spiral column to give 3·14 g (56% yield) 3-methylcyclopentene oxide, bp 114–115° (atmos. pres.) (Lit.[5] bp 116–117°). VPC analysis (6' × 0·25" 20% DEGS on Chromsorb W, 60 cc/min, 70°) showed this material to consist of 13% II (retention times, 4·2 min) and 87% III (retention time, 4·7 min). The pure *trans*-oxide (III) was obtained by preparative VPC: IR (film) 1390, 1370, 1300, 1220, 1025, 1010, 965, 930, 895, 835, 805, 687, and 658 cm^{-1}: NMR, δ 0·88 (doublet, 3H, J = 7 Hz, CH_3), 1·1–2·5 (envelope, 5H), 3·22 (doublet, 1H, J = 3 Hz, >CHO—), and 3·47 (incompletely resolved doublet, 1H, J = 3 Hz, >CHO—). Irradiation at δ 3·22 causes collapse of the δ 3·47 doublet and *vice versa*. (Found: C, 73·40; H, 10·54; $C_6H_{10}O$ requires: C, 73·43; H, 10·27%).

In a similar preparation, a 59% yield was obtained which had a *cis*:*trans* ratio of 25:75. On the spinning band column referred to in the above experiment, a fraction of III, 95% pure (contaminated only by II), bp 116°, could be obtained in 27% yield.

The reduction of cis-3-*methylcyclopentene oxide* (II) *with lithium aluminum hydride*

To 38 mg LAH in 15 ml ether was added 100 mg of *cis*-oxide II and the resulting mixture stirred for 1 hr. Water was added, and after filtration and concentration, the organic layer provided 62 mg of product alcohol. VPC analysis (6' × 0·25" 20% DEGS on Chromsorb W, 60 cc/min, 85°) showed peaks at 5·7 min (67%) and 6·4 min (33%). By comparison with authentic samples of all the isomeric methylcyclopentanols, the peak at 5·7 min was unambiguously identified as *cis*-2-methylcyclopentanol. This result was verified on a second column (6' × 0·25" 10% Carbowax 20M on Chromsorb W, 60 cc/min, 45°) which again showed the major component, 8·3 min, to be identical with *cis*-2-methylcyclopentanol. The minor component (9·6 min under the latter conditions) could not be positively identified as no column conditions were found which would resolve the remaining three isomers, *i.e.*, *trans*-2- and *cis*- and *trans*-3-methylcyclopentanols.

Assuming the normal mechanistic course of LAH reduction,[2] the identification of the major portion of the reduction product as *cis*-2-methylcyclopentanol requires that the starting oxide have the *cis* stereochemistry.

The reduction of trans-3-*methylcyclopentene oxide* (III) *with lithium aluminum hydride*

To 0·35 g LAH in 25 ml ether was added 0·90 g 3-methylcyclopentene oxide (III:II = 86:14). The mixture was stirred overnight in a N-atmosphere, then water was added dropwise until the mixture just turned white. After filtration and concentration there was obtained 0·84 g oil which showed by VPC analysis (DEGS column and conditions as described in the previous experiment) peaks at 5·8 min (7·5%) and 6·4 min (92·5%). The 5·8 min peak was again shown to be *cis*-2-methylcyclopentanol and undoubtedly arises by reduction of the *cis*-oxide component (14%) of the starting material. The composition of the major (6·4 min) peak was demonstrated as follows. Jones[8] oxidation of a 100 mg sample of the alcohol mixture provided a ketone mixture which consisted (VPC comparison with authentic samples, DEGS column, 63°) of 2-methylcyclopentanone (83%) and 3-methylcyclopentanone (17%). This indicates that the major product (>80%) from the reduction of III was *trans*-2-methylcyclopentanol.

These data, then, along with those in the preceding experiment, coupled with the microanalytical and spectral data, are more than sufficient to prove the stereostructures assigned to II and III. Additionally, however, when 115 mg of the LAH reduction product of III (above) was heated for 5 min with 316 mg *p*-nitrobenzoyl chloride and 0·5 ml pyridine, then poured into water, filtered, washed with sodium bicarbonate solution, and filtered again, there was obtained, after three recrystallizations from ethanol and one from isohexane, 31 mg (>13%) of *trans*-2-methylcyclopentyl *p*-nitrobenzoate, mp 67–68° (Lit.[9] mp 68–68·4°). The mixture melting point with an authentic sample of this material was undepressed (mp 68–68·5°) while the mp of a mixture with an authentic sample of *cis*-3-methylcyclopentyl *p*-nitrobenzoate, mp 70·5–71° (Lit.[10] mp 71°) was depressed (mp 50–62°).

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