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CONFORMATIONAL EFFECTS IN THE OPENING OF *CIS/TRANS* 1,4-DIALKYL SUBSTITUTED 1,2-CYCLOHEXENE EPOXIDES WITH ACETIC ACID

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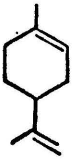
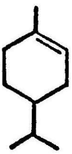
In our continuing studies on the reactions of terpene oxides[2] we wish to report the following cases of stereospecific epoxide openings in the *p*-menthane series.


I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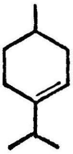
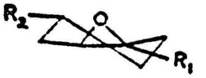
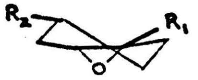

III

The peracid epoxidation of limonene (I), menthene-1 (II) and menthene-3 (III) leads, in each case, to approximately a 1:1 mixture of the corresponding *cis* and *trans* epoxides[3] as would be expected from the recent findings of Rickborn and Lwo[3d]. Although the *cis/trans* epoxide mixtures are separable by distillation only with difficulty, they may be separated conveniently on a 15 ft. 15% Carbowax 20M on chromosorb W GLPC column[4]. In each of the three cases cited, reaction of the *cis* epoxide (IVa,b,c) with a sodium



IV



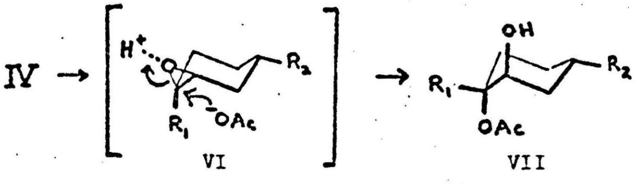
V

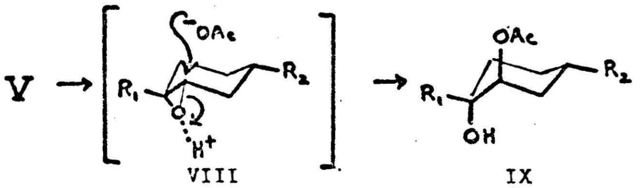
(a) $R_1 = CH_3$, $R_2 = C\genfrac{}{}{0pt}{}{\diagup CH_3}{\diagdown\!\!\diagdown CH_2}$

(b) $R_1 = CH_3$, $R_2 = CH(CH_3)_2$

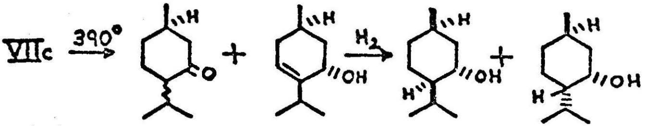
(c) $R_1 = CH(CH_3)_2$, $R_2 = CH_3$

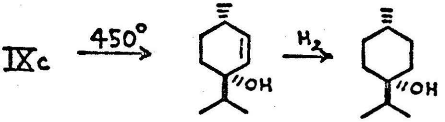
acetate buffered solution of acetic acid leads exclusively to a single product containing trans tertiary acetoxy and secondary hydroxyl groups and trans 1,4-alkyl groups (VII a,b,c), as would be expected by an extension of the Fürst-Plattner rule[5] to monocyclic systems[3a], assuming that R_2 "fixes" the conformation of the cyclohexane ring system. Similarly, reaction of the





trans epoxides (Va,b,c) leads predominantly[6] to epoxide opening resulting from cleavage of the "equatorial"-C-O linkage in the transition state (VIII) to afford the diaxial products (IXa,b,c) with secondary acetoxy and tertiary hydroxyl groups. The proof of structure in each case follows from pyrolysis of the acetate to yield known products[2,3a]. For example, (±)-*cis*-3-menthene epoxide (IVc) affords a hydroxyacetate (VIIc) which pyrolyzes at 390° to a mixture of (±)-*trans*-3-menthene-5-ol (X)[7a] and (±)-menthone-*iso*menthone (XI) in





a product ratio, 7:3. The (±)-*trans*-3-menthene epoxide affords a crystalline (±)-hydroxyacetate (IXc), m.p. 88.5-89.5°, which pyrolyzed at 450° to (±)-*trans*-2-

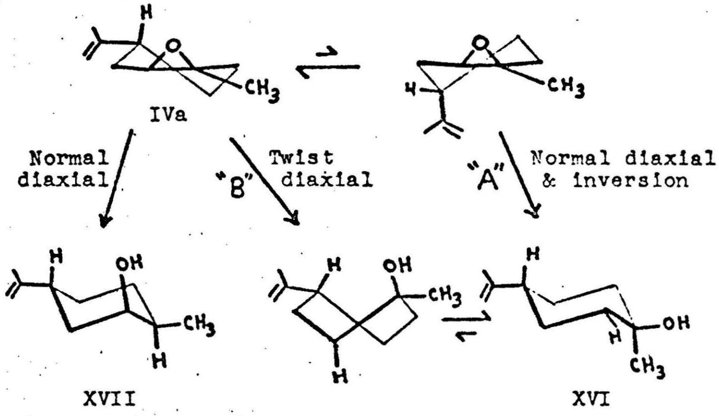
menthene-4-ol[7b] (XII). In each case, the infrared spectra of the pyrolysis products were superposible on those of authentic samples[7a,b]. Further structure proof of (X) came from hydrogenation (PtO_2 - ethyl acetate) to a mixture of 88% (±)-*iso*menthol (XIII) and 12% (±)-*neo*menthol (XIV). Hydrogenation of (XII) afforded *trans*-*p*-menthan-4-O1 (XV).

The high degree of stereospecificity in these epoxide openings leads us to propose the following:

(1) The appreciable amount of abnormal, "diequatorial", opening observed with nucleophilic reagents on monocyclic *cis*-1,4-dialkyl cyclohexene epoxides (*vide infra*) does not necessarily arise from reaction of the less stable conformational isomer[8] (as is observed in conformationally mobile cyclohexene epoxide systems[9]) but rather, perhaps, from the inate difficulty of nucleophilic displacements at tertiary centers[10].

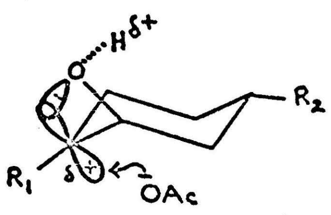
(2) The 4-alkyl substituent determines the conformation in which the *cis*- and *trans*-[6] 1,4-alkyl substituted cyclohexene-1,2-epoxides react with acidic reagents (i.e., HOAc) via a normal, "diaxial", opening (Fürst-Plattner Rule[5]).

Thus the lithium aluminum hydride (LAH) reduction of (+)-cis-1,2-limonene epoxide (IVa)^{3a,11a} affords a product ratio of 15% cis-β-terpineol (XVI) via "effective diequatorial opening" and 85% (+)-neodihydrocarveol (XVII) via "normal diaxial opening". With other nucleophilic reagents, i.e., dimethylamine, the percentage of "diequatorial" opening is even greater (30-40%)^{11b}.

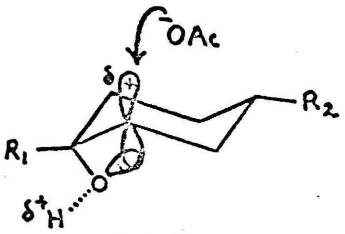


There are two ways in which such diequatorial openings may occur; (a) through diaxial opening of the less stable epoxide conformer with subsequent inversion (process "A") or (b) via diaxial opening of a "twist" transition state (process "B"). Inasmuch as there should be a considerable steric (shielding) effect exhibited by the "axial" 4-alkyl group on the incoming nucleophile in process "A", in addition to the already energetically unfavorable epoxide conformation, we tend to favor process "B".

In the opening of the cis-dialkyl epoxide (VIc) with acetic acid, although R_1 is isopropyl and R_2 is methyl, only a single product is obtained (governed by diaxial opening with R_2 equatorial). Therefore, even though the 1,4-dialkyl substituted cyclohexene epoxide has been postulated[12] to assume a "nearly chair" conformation in the reaction transition state, the 1-alkyl substituent plays little or no part in determining the conformational preference of the transition state[13]. It is probable, therefore, that the transition states for the reactions of the cis/trans-1,4-dialkyl cyclohexene epoxides as illustrated above (VI and VIII) are a bit exaggerated, since to develop a true "chair" conformation the C-O bond must effectively be broken (or at the least very stretched). Transition states such as (VId) and (VIIId) might be better representations. In such transition states, as the protonated oxirane starts to assume the status of an axial hydroxyl there is still effective overlap between the p-orbital of oxygen and the vacant p-orbital of the "incipient carbonium ion". Since R_1 in such a transition state for the cis epoxide (VI) can be neither axial nor equatorial it should not have any effect on conformational preference (as indeed is the case). Such overlap would be less favorable for a



VId



VIIId

diequatorial opening (which is not observed for the *cis* epoxides of type IV). The small percentage (ca. 10%) of an "effective diequatorial opening" observed for the *trans* epoxides (Va and Vb) may occur by either a process of type "A" or "B" (*vide supra*). Although the results presented do not distinguish between these two mechanisms it is again feasible that process "B" may function inasmuch as the normal diaxial opening of a "twist" conformer of (V) would be enhanced by formation of an incipient tertiary positive carbon center.

In any event, the stereospecific opening of 4-alkyl substituted cyclohexene epoxides, coupled with the convenient pyrolysis of the resultant hydroxyacetates affords an excellent method for the preparation of specific allylic alcohols.

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(5). A. Furst and P. A. Plattner, Abstracts of Papers, 12th International Congress of Pure and Applied Chemistry, New York, 1951, p. 409; see also, D. H. R. Barton, *J. Chem. Soc.*, **1953**, 1027.

(6). In the case of (Va,b) ca. 10% of the abnormal product arising from an effective "diequatorial" opening was observed; see Ref. 3a.

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(13). The term 1-alkyl and 4-alkyl substituent refers to the systematic naming of cyclohexane systems in general. Therefore, in each of the cases cited here, the alkyl substituent substituted on the epoxide bearing carbon is the 1-alkyl substituent. The fact that the isopropyl group in the 3-menthene epoxides is on the 4-carbon atom according to nomenclature in the p-menthane systems thus should not confuse the reader in the interpretation of the general effect.