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AN EMPIRICAL CORRELATION BETWEEN STRUCTURE AND OPTICAL ACTIVITY IN A SERIES OF LABDANE DITERPENOIDS

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UDC 547.913.7

On the basis of the results of an analysis of the optical rotatory dispersion curves and a consideration of possible conformations of labdane diterpenoids, the conclusion has been drawn that labd-8(17)-ene derivatives with a 13E double bond or a voluminous substituent in the side chain do not obey Garman's additive scheme, and when there are no asymmetric centers in the side chain they have more negative values of the molecular optical rotation than is preducted by this scheme.

On the basis of an analysis of the molecular optical rotations of a large number of labdane diterpenoids, Carman [1] put forward an additive scheme for calculating these magnitudes for new derivatives of the labdane series. According to the scheme, the optical rotation at 589 nm (sodium D line) of a labdane derivative is considered as the sum of the contributions of two moieties of the molecule of a compound with a labdane carbon skeleton (I) — the aliphatic (C_{11}—C_{16}) and the cyclic (C_1—C_{10}). This scheme is based on the assumption of the free rotation of the aliphatic fragment of the molecule around the C_9—C_{11} and C_{11}—C_{12} bonds. When there are no asymmetric centers in the aliphatic part of the molecule, it is considered that the observed optical rotation is due only to the cyclic fragment, which contains at least three asymmetric centers (at C_5, C_9, and C_{10}).

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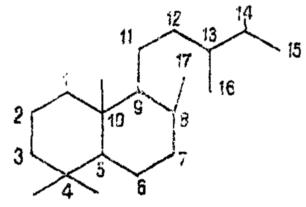
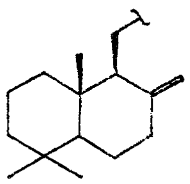


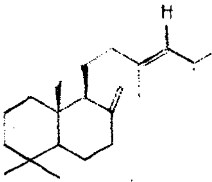
I



A

For the cyclic fragment A, on the basis of information on twenty-two compounds given in the literature, Carman proposes a value of +97° as the contribution to the most active optical rotation at 589 nm. This magnitude, according to the additive scheme, is predicted for all compounds having fragment A and containing no asymmetric centers in the side chain. When only crystalline compounds are taken into account, Carman proposes a value of +110°C as the contribution of fragment A to the molecular rotation of labdane derivatives.

While Carman gave only a small a number of exceptions from his scheme [1], in recent years new experimental facts have appeared which do not agree with the proposed additive scheme. Thus, of the pair of stereoisomeric alcohols (II) and (III) described by McCreadie [2] and the corresponding aldehydes (IV) and (V), which we have isolated from the oleoresin of the Japanese stone pine [3], only compounds (II) and (IV) have values of $[M]_D$ close to those predicted by Carman's scheme (+78.3° and +116.6°, respectively). For alcohol (III), $[M]_D$ is +14.5°, and for the aldehyde (V) it even has a negative sign (–41.5°).



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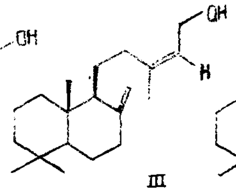

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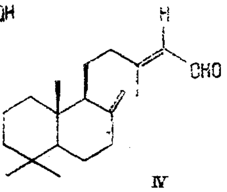
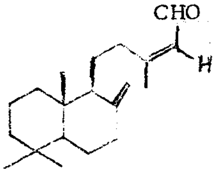


IV



V

To elucidate the causes of this marked change in optical activity with only a slight change, not affecting the asymmetric centers, in the stereochemistry of the molecule one must consider the possible optically active transitions in molecules of this type and the influence of structural and stereochemical factors on them.

Adopting Carman's assumption [1] of the free rotation of the side chain in labdane compounds of the type of the alcohol (II), which is confirmed by a consideration of Deriding molecular models, it is possible to assume that the optical rotation of alcohol (II) and its analogs will be due to σ–σ^* transitions in the cyclic part of the molecule and to a π–π^* transition in the exomethylene double bond. The latter transition should appear in an experiment if this double bond is located in an asymmetric environment, which is the case in compounds (II)-(V). It could also be assumed that the size of the contribution of this transition to the "background" rotation [5] due to the σ–σ^* transitions will determine the value of [M] at 589 nm in the diterpenoids under investigation.

In actual fact, on the optical rotatory dispersion (ORD) curve of alcohol (II) (Fig. 1), in the 265-500 nm region a smooth positive curve is observed, which passes sharply below 260 nm into the region of negative rotation. Since the center of the Cotton effect for the π–π^* transition in the exomethylene double bond is located at 200 nm [4], this curve can be interpreted as a superposition of the negative Cotton effect due to the π–π^* transition in the exomethylene double bond on a smooth positive curve due to the short-wave σ–σ^* transitions. A similar ORD curve was obtained by Scott and Wrixon [6] for the diterpene hydrocarbon (+)-phyllocladene.

An ORD curve of similar nature is also obtained for alcohol (III), except that the Cotton effect of the π–π^* transition in this case is expressed considerably more strongly, which leads to a decrease in the value of the observed optical rotation at 589 nm (Fig. 1).

The interpretation of the electronic transitions of an isolated double bond, the number of which in strained olefins may amount to three has been the object of a large number of investigations in recent years, which have been generalized by Kirk [4]. α-Onoceradiene, actually consisting of two fragments A, can be considered as a model for all labdane

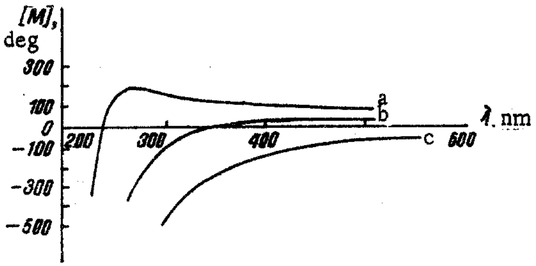


Fig. 1

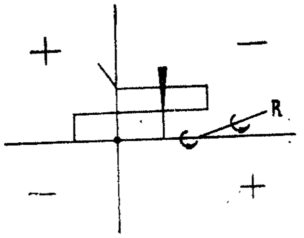


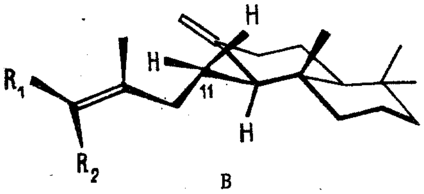
Fig. 2

Fig. 1. ORD curves: a) alcohol (II) (c 0.362; methanol); b) alcohol (III) (c 0.620; chloroform); c) pumiloxide (c 0.707; chloroform).

Fig. 2. Octant projectionof the molecule of a labdane diterpenoid containing fragment A (rear octants).

diterpenoids containing this fragment. In the 180-210 nm region α-onoceradiene has only one optically active transition (π_x—π_x^*), which is shown in intensive dichroic absorption at 202 nm (Δε −14.5) [4].

For methylcyclohexane derivatives, to which the labdane diterpenoids with fragment A also belong, the sign of the Cotton effect for the π_x—π_x^* transition can be determined from an octant rule similar to that for ketones [4]. For the compounds considered, this rule predicts a negative Cotton effect (Fig. 2). As can be seen from the octant diagram, the magnitude of the Cotton effect may be influenced by the side chain (R), which, according to Dreiding molecular models, can be present either in the front or in the rear positive and negative octants. The difference in the optical properties of alcohols (II) and (III) may thus be ascribed to a difference in the contents of the conformers of these alcohols in their equilibrium mixtures. According to the Dreiding models, the side chain of alcohol (III) has a smaller free rotation around the single C—C bonds because of the overlapping of the hydroxymethylene group with the C_{10} methyl and the exomethylene groups in certain conformations and therefore it is forced to exist predominantly in the most suitable extended conformation B.



B

Using the ABP model of optical activity [7, 8], which, as Kirk [4] notes, is well applicable to methylenecyclohexane derivatives, it may be assumed that the decisive factor in the increase of the intensity of the negative Cotton effect for the π—π* transition in alcohol (III) is the levorotatory system formed by the exomethylene double bond with the homoallyl hydrogen atom H_{11a} in conformation B. On the other hand, the side chain of alcohol (III) in the same conformation falls into the front negative octant and, according to the octant rule [4] it must also give a negative contribution to the Cotton effect, as is actually observed in experiment.

Thus, the applicability of Carman's additive scheme for certain labdane derivatives with fragment A is due to the fact that for these compounds, apparently, the same distribution of conformers differing by the orientation of the side chain with respect to the cyclic part of the molecule exists. A disturbance of this distribution, leading to an increase in the proportion of the conformers with the extended side chain, must lead to an increase in the intensity of the negative Cotton effect for the π—π* transition, and, thereby, to a reduction in the observed value of the molecular rotation at 589 nm.

The ORD curve of aldehyde (IV) (Fig. 3a) is qualitatively similar to that for alcohol (II) and it is possible only to observe a weak perturbation in the region of the n—π* transition of the enone system (300-400 nm) and a rise in the optical rotation in the 240-300 nm

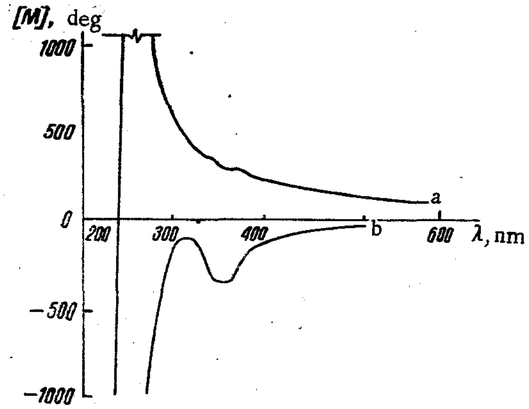
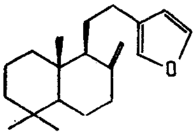


Fig. 3. ORD curves: a) the aldehyde (IV) (c 0.142; methanol); b) the aldehyde (V) (c 0.160; methanol).

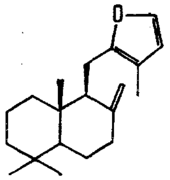
region which is due to the contribution of the positive Cotton effect of the π—π* transition of the enone system. The appearance of the n—π* transition in the form of a weak perturbation, not characteristic for asymmetric α-enones [9], indicates a small degree of predominance of the conformer giving this effect above the other conformers of the aldehyde (IV).

A completely different picture is observed for the aldehyde (V). Here the Cotton effect for the n—π* transition is expressed very well (Fig. 3b), which indicates a preferential nature of the conformations giving the observed Cotton effect, and this makes the magnitude of the molecular rotation of the aldehyde (V) at 589 nm still more anomalous (from the point of view of Carman's scheme). This result well illustrates the appearance of steric hindrance to the free rotation of the side chain in a labdane derivative with the cis (Z) configuration of the C_{13} double bond.

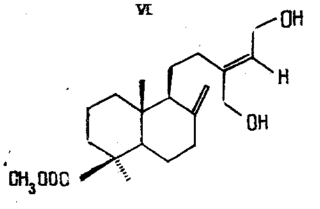
Another pair of closely related compounds with fragment A may be represented by lambertianene (VI), having $[M]_D^{21}$ +84.4° [3], and pumiloxide (VII) ($[M]_D^{20}$ −57.2°) [3]. While in lambertianene the side chain has no hindrance to rotation, in pumiloxide its free rotation is substantially restricted, and it must exist predominantly in the front negative octant, thereby leading to an increase in the intensity of the Cotton effect for the π—π* transition (Fig. 3).



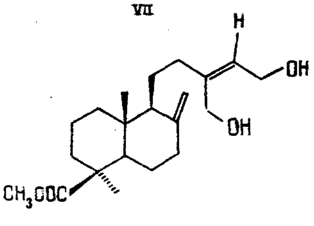
VI



VII



VIII



IX

The "anomalous" value $[M]_D$ −3° for methyl sciadopate (VIII) given by Carman [1] can be explained similarly. In the cis isomer of this compound (IX) the $[M]_D$ value of +126° [10] is already considerably closer to that predicted by Carman additive scheme (+183°), and its deviation from this value can be explained by the presence of additional steric hindrance to the rotation of the side chain introduced by the hydroxy group at C_{17}. In actual fact, methyl isocupressate (17-deoxy-IX) [11] gives $[M]_D$ +167°, which is already far closer to the figure predicted by Carman's additive scheme for such compounds.

Thus, Carman's additive scheme is inapplicable, at least, to labd-8(17),13E-diene derivatives and to other labd-8(17)-ene derivatives in which, with the possibility of free rotation, the side chain is nevertheless forced to exist in certain preferred conformations. As can be seen for the case of the aldehyde (V), when a chromophore is also present in the side chain, the situation becomes still more complicated and can be clarified only by considering the ORD curves of similar compounds.

EXPERIMENTAL

The ORD curves were recorded at room temperature on a Spectropol I instrument in quartz cells with a layer thickness of the solution of the substance of 1 cm.

SUMMARY

Labd-8(17)-ene diterpenoids with a 13Z double bond or voluminous substituents in the side chain do not obey Carman's additive scheme, and when there are no asymmetric centers in the side chain they have more negative values of the molecular optical rotation than is predicted by this scheme.

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STEREOSELECTIVITY OF THE EXHAUSTIVE EPOXIDATION OF CEMBRENE BY PERACETIC ACID.

CRYSTALLINE AND MOLECULAR STRUCTURE OF TRIEPOXYCEMBRENE

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and Yu. V. Gatilov

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The epoxidation of the diterpene hydrocarbon cembrene with peracetic acid in methylene chloride in the presence of sodium bicarbonate forms a single triepoxide — 4,5:7,8:11,12-triepoxycembrene with the 4S,5R,7S,8S,11S,12S configuration of the asymmetric centers. The structure and stereochemistry of triepoxycembrene have been determined with the aid of x-ray structural analysis.

It has been established previously [1], that the epoxidation of cembrene (I) with peracetic and perbenzoic acid takes place stereospecifically at each of the trisubstituted double bonds, and on further epoxidation the 7S,8S- and 11S,12S-epoxycembrenes give one and the same 7S,8S:11S,12S-diepoxycembrene. The stereochemistry of the epoxidation of 4S,5R-epoxycembrene has not been studied because of the instability of this epoxide with respect to adsorbents.

We have found that when cembrene is treated with an excess of peracetic acid in methylene chloride in the presence of sodium bicarbonate, according to TLC all the mono- and

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