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CONFORMATIONS OF THE PULEGONE OXIDES AND THE QUESTION OF OCTANT RULE REVERSAL

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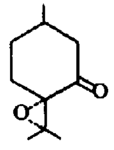
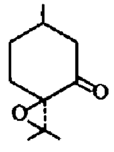
Abstract—Independent work of several research groups[1-3] has established the configurations of the stereoisomeric pulegone oxides (Ia and b). This reverses the tentative assignment made in 1963,[4] and in this paper a conformational analysis of the pulegone oxide isomers consistent with their physical properties has been developed.

m.p. 59°

$[\alpha]_D$ +48



Ia

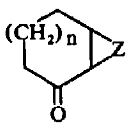


Ib

m.p. 55°

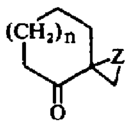
$[\alpha]_D$ −20

THE opposite Cotton effects exhibited by Ia and Ib played an important role in our initial configuration assignment, and indicate that the principle conformations of the stereoisomers have essentially enantiomeric configurations in the neighborhood of the CO group. However, application of the Octant Rule to this system has been questioned by Djerassi *et al.*[5] These authors proposed a Reverse Octant Rule for conjugated cyclopropyl and epoxy ketones, and in fact suggested that the pulegone oxide configurations should be changed to agree with this new rule. Despite the recently established validity of this prediction, we are not convinced that a Reverse Octant Rule should be applied to the pulegone oxides. The data presented by Djerassi *et al.* falls into two categories: fused ring systems (A) and spiro systems (B). Numerous examples of the former system are reported, and the arguments supporting a Reverse Octant Rule for these compounds are convincing. Thus, the strong positive Cotton effect displayed by 4β,5β-epoxycholestan-3-one (rotational strength ca. 12×10^{-40} cgs) contrasts strikingly with the weaker negative effect found for 5β-cholestan-3-one (rotational strength ca. 2×10^{-40})[6] and suggests that conjugated epxoy ketones of this type (A) behave as inherently disymmetric chromophores.

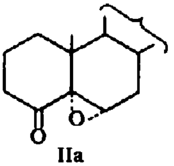


A

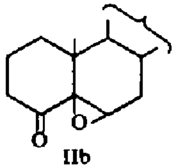
($Z = CH_2$, O)



B



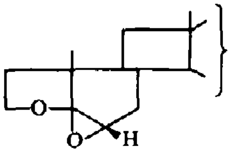
IIa



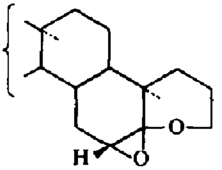
IIb

An extension of the Reverse Octant Rule principle to include spiro epoxyketones (Type B) has been supported by only a few examples.[5] In several cases orbital overlap in near octants has been arbitrarily assumed in order to accommodate inconsistent facts. Since the pulegone oxide stereoisomers fall into this category, we felt that more information would be needed before our conformational analysis could proceed, and the isomeric alpha (IIa) and beta (IIb) 5,6-epoxycholestan-4-ones were chosen as models for further study. Shortly after we completed our measurements with these compounds a similar study by Lavie *et al.* appeared.[7] To the extent that our work overlaps with that of the Israeli group the facts agree very well. However, since our interpretation of these facts is different, we will briefly report our findings here.

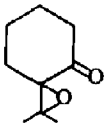
The ORD and CD measurements of IIa and IIb (Experimental) showed negative and positive Cotton effects respectively. Rotational strengths were calculated: IIa $-2{\cdot}38 \times 10^{-40}$ (EtOH), $-2{\cdot}53 \times 10^{-40}$ (cyclohexane); IIb $+2{\cdot}02 \times 10^{-40}$ (EtOH), $+2{\cdot}31 \times 10^{-40}$ (cyclohexane). When compared with the rotational strength of 5α-cholestan-4-one ($-4{\cdot}15 \times 10^{-40}$),[8] our measurements provide no evidence of rotational strength enhancement due to epoxide conjugation in IIa or IIb. A Dreiding model shows that in IIa the epoxy ketone must assume conformation C (Octant Rule projection). Since the major portion of the steroid skeleton lies in a negative octant, normal application of the Octant Rule to C reasonably accounts for the negative Cotton Effect observed for IIa. Inspection of a Dreiding model discloses three plausible conformations for IIb (D, E and F), and analysis of this isomer is consequently less simple.† On the basis of non-bonded interaction measurements (model) D has been chosen as the most stable conformation. In this case a positive Cotton effect is predicted by the normal Octant Rule. The other conformations would, by a similar argument, have negative Cotton effects. In conformations C and D the C-6 H atom is the only substituent which lies in or near a front octant, and no significant contribution to the rotational strength is expected from this source.



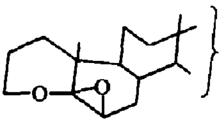
C



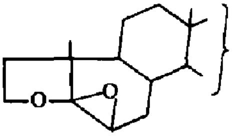
D



III



E



F

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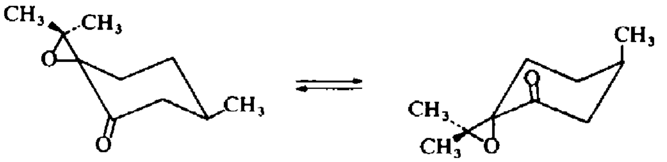
† Conformationally restrained examples of spiro epoxy ketones are difficult to find. Professor Lavie has kindly informed us that he and Dr. Glotter have examined the isomeric 4,5-epoxycholestan-6-ones and find that the Reverse Octant Rule cannot account for the observed Cotton effects.

The question of near octant involvement has yet to be resolved for the spiro epoxy ketones. It is difficult to reach a clear decision in many cases, since the surface separating near and far octants is not well defined. Furthermore, Wagniere[9] has pointed out that sign inversion may not take place and urges caution in applying the Octant Rule to near-octant perturbation.

As part of our pulegone oxide study, we have determined the chemical shifts of the geminal dimethyl groups in Ia, Ib and III in benzene and carbon tetrachloride solutions. In every case the methyl group *cis* to the CO function experiences very weak shielding by benzene ($\Delta = 0{\cdot}02$ to $0{\cdot}08$ ppm, where $\Delta = \tau_{\phi H} - \tau_{CCl_4}$), while the *trans* Me group is more strongly shielded ($\Delta = 0{\cdot}15$ to $0{\cdot}23$ ppm).[10] According to the simple model proposed by Williams and Bhacca[11a] this suggests that the *cis*-Me group lies very near a plane perpendicular to the CO bond axis and passing through the CO carbon atom. Although the reliability of this empirical rule is weakened here by the unknown effect of the oxirane ring, it appears safe to assume that significant perturbation of near octants does not occur in the pulegone oxides. Dreiding models support this conclusion for conformations G and M of Ia and IIb respectively.



G H

M N

Moderately substituted and unrestricted cyclohexane derivatives usually adopt a chair conformation.[12, 13] We therefore have considered the chair conformers G and H of the pulegone oxide isomer Ia and conformers M and N of isomer Ib. A positive Cotton effect is evident in the ORD and CD measurements of Ia ($R_0 = +2{\cdot}64 \times 10^{-40}$ in EtOH and $+1{\cdot}97 \times 10^{-40}$ in cyclohexane). Again, epoxide conjugation shows no evidence of rotational strength enhancement and the normal Octant Rule will be used with these compounds. The CD curve also exhibits a temperature dependence in EPA (Fig. 1). Two explanations are consistent with these results. Either conformer G is in equilibrium with a solvated species which has a smaller positive rotational strength, or G is in equilibrium with another conformation (e.g. a twist boat) which has a larger positive rotational strength but which is less stable than G. A lowering of the temperature would, in both cases, increase the population of the lower rotational strength species. Since Ia has a larger rotational strength in ethanol

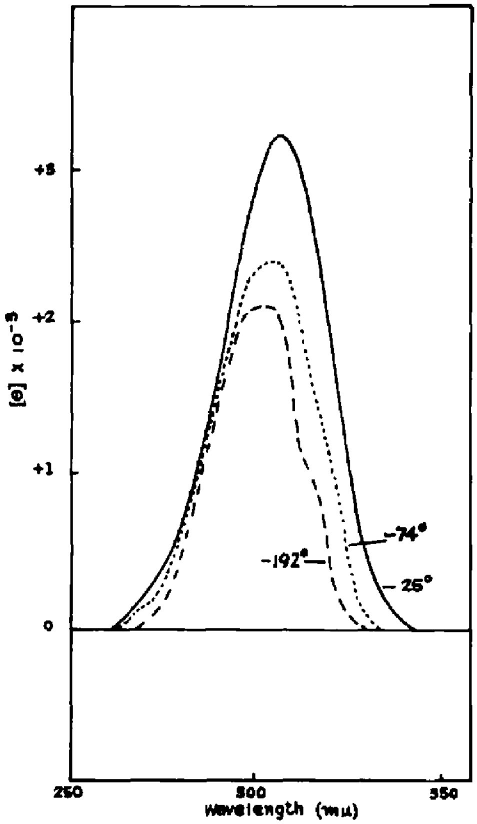


FIG. 1 Circular dichroism (25°, −74° and −192°) of Ia.

than in cyclohexane, we favor the latter explanation. In any event, G is the predominant conformer of Ia at room temperature.†

The CD curve of Ib in ethanol exhibits a negative Cotton effect at 305 mμ (R_0 = 0·60 × 10^{-40}) and a weak positive effect at 270 mμ (R_0 = 0·14 × 10^{-40}). In cyclohexane the rotational strengths are −0·42 × 10^{-40} and +0·04 × 10^{-40} respectively. The temperature dependence of the CD measurements in EPA is shown in Fig. 2. Djerassi *et al.*[14] have demonstrated that a CD curve having two opposite extrema separated by ca. 30 mμ will result whenever two Cotton effects of opposite sign and separated by 1–20 mμ are superimposed. A reduction in apparent rotational strength also occurs. The main problem in interpreting such a curve lies in distinguishing a solvation equilibrium from a conformational equilibrium. Since the $n \rightarrow \pi^*$ absorption of a solvated ketone is generally found at a shorter wavelength than the corresponding unsolvated chromophore and since the concentration of the solvated species increases at lower temperatures, a double-humped CD curve resulting from

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† A referee has pointed out that the sign of the Cotton curves may be determined by a minor conformer having a powerful rotational strength. This would of course make it impossible to use the optical measurements to answer the questions posed in this paper. While we agree that this is possible, we regard it as improbable; and in the absence of other evidence supporting such a species, we prefer the straightforward explanation presented here.

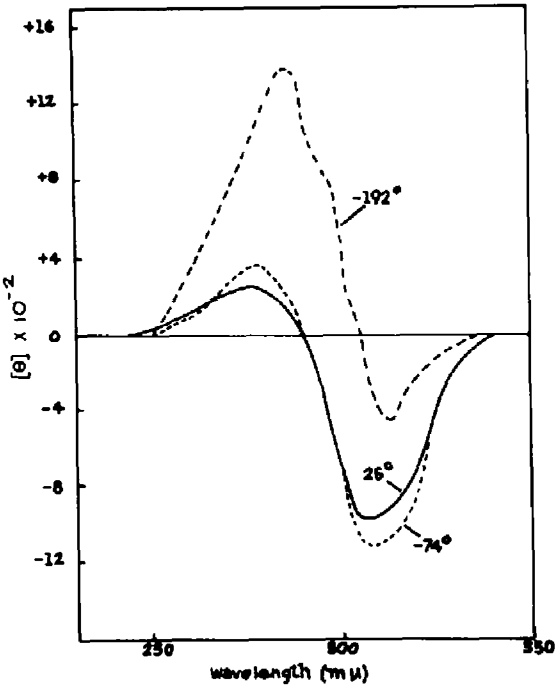
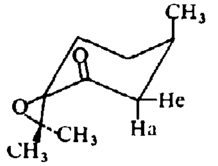


FIG. 2 Circular dichroism (25°, −74° and −192°) of Ib.

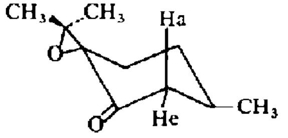
a solvation equilibrium will be characterized by an increase in the strength of the short wavelength band at low temperatures. This is the observed behavior of Ib (Fig. 2); and although a conformational equilibrium cannot entirely be ruled out, the decrease in strength of the positive band on going from an ethanol solution to cyclohexane indicates that the solvation equilibrium is the most reasonable explanation. The negative portion of the CD curve shows an interesting temperature dependence, the rotational strength increasing from 25° to −74° and decreasing from −74° to −192°. To explain this phenomenon we propose an equilibrium between M and some more positive and less stable conformation (e.g. N). Lowering the temperature to −74° increases the population of unsolvated M faster than its solvated form, but a further decrease in temperature (to −192°) favors the solvated species with the positive Cotton effect. Our arguments thus favor M as the predominant conformation of Ib. Measurements of non-bonded interactions in G, H, M and N have been made from Dreiding models, and these agree with the assignment of G and M as the favored conformations of Ia and Ib respectively.

Other properties of Ia and Ib are less informative and helpful in making conformational assignments. The CO stretching frequency in the IR and the $n \rightarrow \pi^*$ absorption in the UV are essentially the same for the two isomers. Roughly enantiomeric configurations in the neighborhood of the CO group are therefore expected. On the other hand, the steroid isomers IIa and IIb show differences that are difficult to explain (Experimental).

Previous arguments based on differences in the NMR spectra of Ia and Ib[4] must now be reconsidered. If G and M are tentatively accepted as the major conformers in Ia and Ib respectively, a difference in the chemical shift of the secondary Me group in each isomer would be expected as a consequence of the anisotropic effect of the CO group.[15] A close examination of models shows that the axial Me group in M would also lie closer ($<$ 4·0 Å) to the C—O edge of the oxirane ring than the equatorial Me in G. Since an oxirane ring seems to exert a deshielding influence on nuclei located near its edge,[16] the anisotropic effect of the CO group will be reduced and perhaps cancelled in these compounds. In fact we find that the high field Me doublets in Ia and Ib have chemical shifts within 2 c/s of each other in both benzene and carbon tetrachloride solution.



M



G

In our earlier paper[4] certain differences were noted in the low field portions of the NMR spectra of the pulegone oxides. Isomer Ia displays a single proton multiplet centred at τ 7·51 that appears to be part of an ABC system, while Ib gave a broad two proton doublet at τ 7·68. The assignment of these resonance signals to the protons alpha to the CO group has been confirmed by isotopic exchange with alkaline deuterium oxide. We now believe that the anisotropy of the secondary Me group is largely responsible for this variation. The calculation of such effects has been discussed by several groups of investigators[17] and we have applied their methods to conformations G and M. Measurements with Dreiding models showed no significant differences in the molecular parameters reported for the methylcyclohexanols by ApSimon *et al.*[18] and those obtained for G and M; consequently we have used the chemical shift increments reported by these workers. In Ib (M) both alpha protons (He and Ha) appear at 140 c/s (measured from TMS at 60 Mc). Changing the Me group in M from an axial to an equatorial orientation would form the enantiomer of G and would produce calculated shifts of 3 c/s downfield for He and 39·5 c/s upfield for Ha. In the spectrum of Ia (G) He is observed as a pair of doublets at 145 and 154 c/s; while Ha, which is obscured by the methylene envelope, must resonate at less than 130 c/s. This qualitative agreement is all one can expect from such a crude treatment in view of the unknown effect of the oxirane ring.

Finally, the thermal isomerization of Ia and Ib has been reported to favor Ia by a factor of ca. 3:1; this is consistent with the conformational assignments made in this paper.

EXPERIMENTAL

IR spectra were determined with a Perkin–Elmer 237-B spectrophotometer; UV spectra were obtained using a Carey Model 11 spectrophotometer; NMR spectra were determined with a Varian Associates A-60, high resolution, spectrometer; ORD and CD curves were recorded with a Durrum-JASCO Model UV/ORD/CD-5 automatic spectropolarimeter.

Pulegone oxide isomers Ia *and* Ib. The oxides Ia and Ib were prepared and separated according to the procedure described.[4] Isomer Ia, m.p. 58°, displayed the following properties: $\nu_{\max}^{CCl_4}$ 1725 cm^{-1}; $\lambda_{\max}^{\text{cyclohexane}}$ 302 mμ (ε 33·8); ORD in 95% EtOH (*c*, 0·047), $[\phi]_{317}$ +2260°, $[\phi]_{300}$ ±0°, $[\phi]_{278}$ −2780°; ORD in cyclohexane (*c*, 0·050), $[\phi]_{326}$ +1936°, $[\phi]_{317}$ +925°, $[\phi]_{310}$ ±0°, $[\phi]_{290}$ −2080°, $[\phi]_{285}$ −2103°; CD in 95% EtOH (*c*, 0·047), $[\theta]_{333}$ ±0, $[\theta]_{298}$ +3370, $[\theta]_{254}$ ±0 ($R_0 = 2{\cdot}64 \times 10^{-40}$ cgs); CD in cyclohexane (*c*, 0·050), $[\theta]_{345}$ ±0, $[\theta]_{320}$ +1990, $[\theta]_{313}$ +2480, $[\theta]_{309}$ +2560, $[\theta]_{271}$ ±0 ($R_0 = 1{\cdot}97 \times 10^{-40}$ cgs); CD in EPA (*c*, 0·177), $[\theta]^{25^\circ}_{305}$ +3257, $[\theta]^{-74^\circ}_{302{\cdot}5-305}$ +2442, $[\theta]^{-192^\circ}_{302{\cdot}5}$ +2153 (Fig. 1). The following spectral properties of Ib m.p. 54°, were obtained: $\nu_{\max}^{CCl_4}$ 1726 cm^{-1}; $\lambda_{\max}^{\text{cyclohexane}}$ 303·5 mμ (ε 31·4); ORD in 95% EtOH (*c*, 0·049); $[\phi]_{321}$ −492°, $[\phi]_{308}$ ±0°, $[\phi]_{289}$ +1044°; ORD in cyclohexane (*c*, 0·048), $[\phi]_{326}$ −297°, $[\phi]_{320}$ ±0°, $[\phi]_{303}$ +732°, $[\phi]_{295}$ +854°, $[\phi]_{287}$ +753°; CD in 95% EtOH (*c*, 0·049), $[\theta]_{330}$ ±0, $[\theta]_{305}$ −984, $[\theta]_{284}$ ±0, $[\theta]_{270}$ +247, $[\theta]_{236}$ ±0 ($R_0 = -0{\cdot}597 \times 10^{-40}$ and $+0{\cdot}141 \times 10^{-40}$ cgs); CD in cyclohexane (*c*, 0·048), $[\theta]_{348}$ ±0, $[\theta]_{312-317}$ −608, $[\theta]_{307}$ −643, $[\theta]_{298}$ −345, $[\theta]_{287}$ ±0, $[\theta]_{275-280}$ +78, $[\theta]_{272}$ +96, $[\theta]_{266-269}$ +70, $[\theta]_{256}$ ±0 ($R_0 = -0{\cdot}422 \times 10^{-40}$ and $+0{\cdot}036 \times 10^{-40}$ cgs); CD in EPA (*c*, 0·180), $[\theta]^{25^\circ}_{308}$ −963, $[\theta]^{25^\circ}_{275-277}$ +252, $[\theta]^{-74^\circ}_{308-310}$ −1104, $[\theta]^{-74^\circ}_{278}$ +359, $[\theta]^{-192^\circ}_{312}$ −453, $[\theta]^{-192^\circ}_{285}$ +1411 (Fig. 2).

Deuterium exchange of Ia *and* Ib. A soln of Ia (1·0 g) in reagent grade cyclohexane (5 ml) was added to a soln of anhyd K_2CO_3 (0·3 g) in D_2O (5 ml). This mixture was refluxed with stirring for 72 hr, cooled and extracted with ether. The ether extracts yielded a solid which, when crystallized from pentane, gave 589 mg of colorless needles, m.p. 57–58°. The labeled Ia showed absorption at 2100 and 2215 cm^{-1} in the IR, and displayed a molecular ion at *m/e* 168 in the mass spectrum. Calculations based on the abundance of neighboring ions indicated the sample to be 3·4% d_0, 17·9% d_1, 75·7% d_2 and 3·1% d_3. The intensity of the τ 7·43 and 7·58 resonance peaks in the NMR spectrum was reduced to ca. 10% of that in undeuterated Ia.

Similar treatment of a 1·0 g sample of Ib yielded 423 mg of needles, m.p. 54–55°. This material showed IR absorption at 2090 and 2215 cm^{-1} and a molecular ion having *m/e* 168 in the mass spectrum. Analysis of the mass spectrum gave the following composition: 6·6% d_0, 20·8% d_1, 72% d_2 and 0·6% d_3. The intensity of the τ 7·68 peak in the NMR was reduced to ca. 30% that in undeuterated Ib.

5α,6α-*Epoxycholestan-4-one* (IIa). A soln of 6·8 g of cholest-5-en-4α-ol (prepared by LAH reduction of cholest-5-en-3β,4β-diol 3β-tosylate[18]) and 4·9 g *m*-chloroperbenzoic acid (85%) in 275 ml benzene was stirred at room temp for 19 hr. The excess oxidizing agent was destroyed with Na_2SO_3, and the benzene layer was washed with NaOHaq followed by water. The dried benzene soln yielded a gum, which was immediately treated in pyridine soln with the CrO_3 complex prepared from 7 gr oxide and 120 ml pyridine. After stirring for 5 days at room temp, the oxidation mixture was treated with ethyl acetate and filtered. Evaporation of the filtrate, followed by chromatography of the residue on 70 g silica gel, gave 1·4 g solid ketone. This material was further purified by preparative TLC and yielded (after two recrystallizations from MeOH) 500 mg IIa, m.p. 84–86° (lit. (7): 86–87°). The spectral properties were: $\nu_{\max}^{CCl_4}$ 1725 cm^{-1}; $\lambda_{\max}^{\text{cyclohexane}}$ 297 mμ (ε 37·7); ORD in 95% EtOH (*c*, 0·058), $[\phi]_{328}$ −1748°, $[\phi]_{321}$ −1870°, $[\phi]_{303}$ ±0°, $[\phi]_{279}$ +1665°; ORD in cyclohexane (*c*, 0·073), $[\phi]_{329}$ −1900°, $[\phi]_{324}$ −1620°, $[\phi]_{319}$ −1860°, $[\phi]_{311}$ −725°, $[\phi]_{305}$ ±0°, $[\phi]_{281}$ +1618°; CD in 95% EtOH (*c*, 0·058), $[\theta]_{300}$ −2360 ($R_0 = -2{\cdot}38 \times 10^{-40}$ cgs); CD in cyclohexane (*c*, 0·073), $[\theta]_{324}$ −1160, $[\theta]_{313}$ −2310, $[\theta]_{310}$ −2240, $[\theta]_{304}$ −2640, $[\theta]_{296-298}$ −2340 ($R_0 = -2{\cdot}53 \times 10^{-40}$ cgs).

5β,6β-*Epoxycholestan-4-one* (IIb). Cholest-5-en-4-one was oxidized with alkaline H_2O_2 in MeOH according to the procedure of LeMahieu.[19] The ketone IIb was obtained in 65% yield, m.p. 105–106° (lit.[7] m.p. 102–104°). The spectral properties were: $\nu_{\max}^{CCl_4}$ 1711 cm^{-1}; $\lambda_{\max}^{\text{cyclohexane}}$ 304 mμ (ε 44·5); ORD in 95% EtOH (*c*, 0·077), $[\phi]_{325}$ +1925°, $[\phi]_{306}$ ±0°, $[\phi]_{280}$ −1935°; ORD in cyclohexane (*c*, 0·079), $[\phi]_{337}$ +2220°, $[\phi]_{316}$ ±0°, $[\phi]_{295}$ −2020°; CD in 95% EtOH (*c*, 0·077), $[\theta]_{307}$ +2650 ($R_0 = 2{\cdot}02 \times 10^{-40}$ cgs); CD in cyclohexane (*c*, 0·079), $[\theta]_{318}$ +2780 ($R_0 = 2{\cdot}31 \times 10^{-40}$).

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