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THE ABSOLUTE STEREOCHEMISTRY OF THE SESQUITERPENE KETONE, VALERANONE.[1]

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The stereochemistry of the sesquiterpene ketone, valeranone, has been the subject of much discussion, and a succession of papers has appeared suggesting different versions of both the relative and the absolute stereochemistry[2,3,4,5,6]. The relative stereochemistry of the centres in the molecule is fixed without doubt as IA or IB, by the X-ray work[4] and also by other evidence.

Hitherto, no convincing evidence has been presented regarding the absolute stereochemistry of the molecule except for 'monochromatic' rotations (ref.[5]). The difficulty arises from the fact that valeranone is a cisdecalone, which can always take up one of two possible two-chair conformations; this makes the application of physical methods such as optical rotatory dispersion ambiguous. Secondly, the compound is most unusual in having angular methyl groups at both the ring junctions between the two rings A and B. For this reason, no easily accessible reference compounds are available to which the compound can be degraded; this may be the explanation of the failure of the extended lactone rule in this case[4,7]. (Contrast the situation for compounds with two hydrogens at the ring-junctions, or one methyl and one hydrogen; many of these can be degraded to relatively simple cyclohexane derivatives including dicarboxylic acids, which have been summarized by Jeger *et al*[8].)

The problem of the absolute stereochemistry of valeranone has now been resolved by degradation to a compound (cf 5) in which *one* of the angular methyl groups has been removed (the αβ- unsaturated ketoester, IIA or IIB); the compound from valeranone is identical in all respects, except for its optical rotatory properties, with the compound similarly obtained from eudesmol (III). We know that the compound from eudesmol must be IIB. However, the optical rotatory dispersion curve of the derivative from valeranone is the *mirror-image* (including fine structure) of the curve given by IIB. Therefore, the two compounds are enantiomers; from this it follows that the absolute stereochemistry of valeranone must be as shown in (IA) and *not* (IB).

A number of other valeranone derivatives have been studied (the compounds were prepared in Poona and in Prague, and the rotatory dispersion curves have been measured in London). The results all fit the formulae given, with two important exceptions, viz:- valeranone itself, and the five-membered ring ketone nor-valeranone (IV), which is derived from it. In both these compounds it is difficult to rationalize the amplitudes (a) of the O.R.D. curves obtained (IA; a, -166; IV; a, -80) in terms of the Octant Rule[9]. The only tentative suggestion that we can make at present is that there is perhaps some conformational anomaly associated with fully substituted ring-junctions. This clearly demands further study.

The course of the investigations on valeranone over the last five years underlines the need for caution in drawing stereochemical conclusions from rotatory dispersion measurements, in all but the most thoroughly-explored fields, and particularly the importance of choosing true analogies. In the trans-decalone series, it is generally possible, thanks to the almost ubiquitous regularity of the conformations presented, and to the very extensive series of data available[10], to draw firm conclusions with a minimum of experimental O.R.D. work; the reverse is the case with cis-decalones, because of their conformational flexibility - and there seems to be the further complication in valeranone of the fully substituted ring-junction. The present work has reached a satisfactory conclusion only thanks to a combination of X-ray work[4], classical degradation, and straightforward chemical indentification; the O.R.D. curves of IIA and IIB serve merely to prove their enantiomeric character.

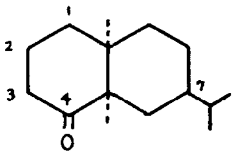
Provided we accept that the O.R.D. curve of valeranone (IA) itself is abnormal, then the curves of the monobromovaleranone and dibromovaleranone[2] (VA; a, -119; VB; a, +63) can be rationalized by comparison with that for valeranone itself; in other words, the differences in amplitude are of the kind that might be expected in terms of the Octant Rule.

The curves of the dicarboxylic acids (VI, VII) obtained by opening ring A of valeranone have now been measured with the new Bellingham and Stanley Bendix-Ericsson automatic spectropolarimeter ("Polarmatic 62") which has a range extending to about 200 mμ. It has therefore been possible to measure the first extremum of the Cotton effect due to the carboxylic acid group[11]. When further reference compounds are available, no doubt further confirmatory evidence can be obtained from these. Compounds (VI) and (VII) both show small negative Cotton effects at about 230 mμ on a positive background. The anhydride of (VI) shows a large negative Cotton effect.

Two other A -ring ketones derived from valeranone have been prepared in Poona (as IA, with keto group at C-3 or C-2, instead of C-4), viz:

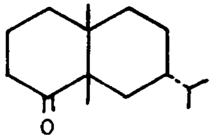
3-Oxo; a, -28; this should be negative on Octant Rule, although a larger amplitude might have been expected.

2-Oxo; a, -37; fits Octant Rule well .

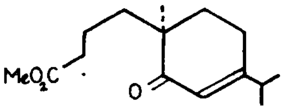


(IA)

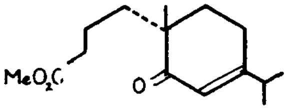
Valeranone



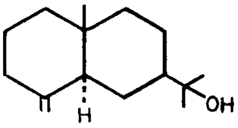
(IB)



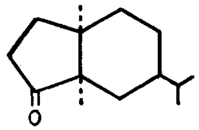
(IIA)



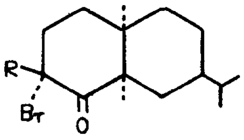
(IIB)



(III)

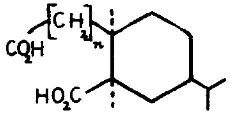


(IV)



(VA), R=H

(VB), R=Br



(VI), n=1

(VII), n=2

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   (a) Paper 162 in the series "On Terpenes" from the Czechoslovak Academy of Science. For preceding article see: M. Romanuk, V. Herout, F. Šorm, Y. R. Naves, P. Tullen, R. B. Bates, and C. V. Siegel, Coll. Czech. Chem. Comm., **29**, 1048 (1964).

   (b) Part LI in the series "Terpenoids" from Poona. Contribution No. 667 from the National Chemical Laboratory, Poona, India.

   (c) Part XI in the Westfield College series on Optical Rotatory Dispersion. Preceding paper, Part X, J.P. Jennings, W. Klyne, and P. M. Scopes, J. Chem. Soc., (1964), in Press.

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