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MOLECULAR ROTATION AND ABSOLUTE CONFIGURATION - III[1]

EPIMERIC KETONES

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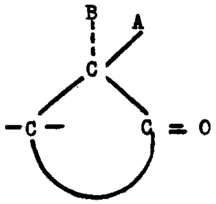
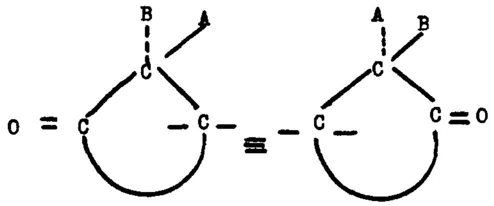
AN EMPIRICAL rule correlating molecular rotation with the absolute configuration of epimeric cyclic compounds was described earlier.[1,2] For the special case where the epimers have a keto group adjacent to the asymmetric center under consideration, the rule may be stated as follows:

In the epimeric ketones I and II, if B be the bulkier of the two exocyclic substituents A and B, I should be more dextrorotatory than II.[3]



I

more *dextro*



II

more *levo*

This rule was used to predict that the absolute configuration at C_{11}

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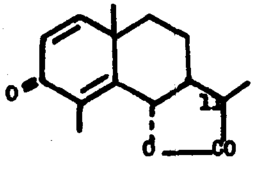
[1] Part II: A.K. Bose and B.G. Chatterjee, *J.Org.Chem.* 23, 1425 (1958).

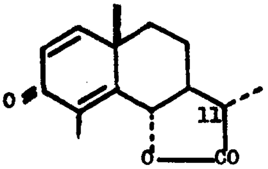
[2] A.K. Bose, Abstracts of XVIth International Congress of Pure and Applied Chemistry, Paris, 1957, p. 141.

[3] For the more generalized rule and a mnemonic, see ref. 1.

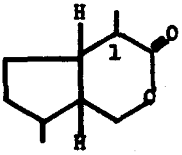
in (-)-santonin and (-)-β-santonin should be as shown in III and IV respectively.[2] The recent work of Barton and Pinhey[4] leaves little doubt that III does indeed represent the absolute configuration of (-)-santonin. From the $[\alpha]_D$ values of the lactones iridomyrmecin and isoiridomyrmecin which are epimeric at C_1 we predicted[5] that the absolute configuration of isoiridomyrmecin should be as shown in V. X-ray crystallography[6] of isoiridomyrmecin (iridolactone) has also led to the same stereoformula V.



III



IV



V

Dauben *et al.*[7] applied this rotation rule to γ-santonin derivatives which are epimeric at C_{11} and deduced absolute configurations which appear to be correct in the light of the subsequent work of Barton and Pinhey.[4]

To test our more general rule[1] we have scanned a very extensive compilation[8] on steroids and found only a few epimeric pairs that do not conform to the rule. The comments in the present communication, however, will be

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[4] D.H.R. Barton and J.T. Pinhey, *Proc.Chem.Soc.* 279 (1960).

[5] Presented before the "Meeting-in-Miniature", January 1960 of the North Jersey Section of the American Chemical Society.

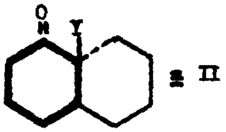
[6] J.F. McConnell and B.P. Schoenborn, Abstracts of the International Congress of Pure and Applied Chemistry Symposium on the Chemistry of Natural Products, Australia, August 1960, p. 44.

[7] W.G. Dauben, W.K. Hayes, J.S.P. Schwarz and J.W. McFarland, *J.Amer. Chem.Soc.* **82**, 2232 (1960).

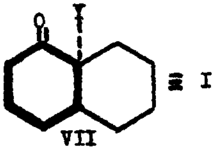
[8] J.P. Mathieu and A. Petit, *Constantes Selectionees Pouvoir Rotatoire Naturel I. Steroides*. Masson et Cie, Paris (1956).

restricted to only those epimeric steroids that have a keto group adjacent to the epimeric center.

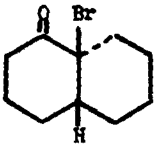
Of special interest are derivatives of 1-ketodecalones which are epimeric around the ring junction C_9 (such as VI and VII). For the purposes of our rule, VI and VII are considered to be derivatives of the ring bearing the keto group; the other ring and the angular substituent are counted as the two exocyclic substituents on this ring. It then follows from our rule that in general VI should be more levorotatory than VII. This relationship will be reversed, however, if Y has to be considered the "bulkier" of the two exocyclic substituents. One such example is the case when Y is bromine as in the epimeric pair VIII and IX (see Table 1). The stereochemistry of the few epimers that do not conform to the rule is being investigated.



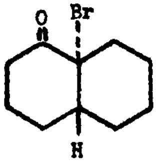
VI
more <u>levo</u>



VII
more <u>dextro</u>



VIII
more <u>dextro</u>



IX
more <u>levo</u>

Recently epimeric α-haloketones have attracted considerable attention. The empirical axial α-haloketone rule[9] and the more comprehensive Octant rule[10] have been used to deduce the absolute configuration of α-haloketones

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[9] C. Djerassi, <u>Optical Rotatory Dispersion</u> p. 120. McGraw-Hill, New York (1960).

[10] Ref. 9, p. 178.

Table 1

Prediction from rule:	more levo isomer			more dextro isomer				Ref.
Compound	$[\alpha]_D$	Cotton effect extremum		Epimer	$[\alpha]_D$	Cotton effect extremum		
		mμ	[α]			mμ	[α]	
2α-Bromo-2β-methylcholestan-3-one, ring A: boat	-30°	340	-1180°	2β-Bromo-2α-methyl-, ring A: chair	+140°	335	+2920°	11
2α-Bromo-2β-methylandrostan-17β-ol-3-one acetate, ring A: boat	-6°	338	-494°	2β-Bromo-2α-methyl-, ring A: chair	+100°	330	+2480°	12
(-)-2α-Bromo-cis-1-decalone	-175°	335	-2650°	(-)-2β-bromo-	-55°	319	-234°	13
(-)-9β-Bromo-trans-1-decalone (IX)	-150°	328	-2900°	9-epimer (VIII)	+50°	332	+3100°	13
16α-Bromoisoandrosterone acetate	+56°	342	+1290°	16β-Bromo-	+112°	342	+2097°	14
3-exo-Chlorocamphor	+35°	330	1810°	3-endo-Chloro-	+95°	331	+1798°	14
16α-Bromo-3β-acetoxy-5α, 14-β-androstan-17-one	+58	312	+942°	16β-Bromo-	+104°	342	+1195°	15

Table 2

	I.R. $(CHCl_3)$ cm^{-1}	Δν	U.V. (MeOH) λmax (mμ)	Δλ	R.D. trough mμ	[α]	R.D. peak mμ	[α]
3β-Methoxyandrostan-16-one	1736		296		319	-2860°	269	+2900° (MeOH)
					322	-2550°	277	+2560° (CCl_4)
17β-bromo-	1754	+18	297	+1	319	-3440°	272	+2810° (MeOH)
					327	-2240°	280	+2480° (CCl_4)
17α-bromo-	1748	+12	316	+20	345	-388°	308	+327° (MeOH)
					345	-276°	322	+260° (CCl_4)

[11] C. Djerassi, N. Finch, R.C. Cookson and C.W. Bird, J.Amer.Chem.Soc. 82, 5488 (1960).

[12] R. Mauli, H.J. Ringold and C. Djerassi, J.Amer.Chem.Soc. 82, 5494 (1960).

[13] C. Djerassi and J. Staunton, J.Amer.Chem.Soc. 83, 736 (1961).

[14] C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, J.Amer.Chem.Soc. 80, 1216 (1958).

[15] J. Fishman and T. Nambara, Chem. & Ind. 79 (1961).

from their optical rotatory dispersion. Before these rules can be applied, it is necessary to determine whether the halogen is in the axial or equatorial position and whether the ring is in the chair or boat conformation. In contrast, our rule appears to be applicable to the $[\alpha]_D$ values of epimeric α-haloketones without regard to the conformation of substituents or the shape of the ring. In Table 1 we report the application of our rule to a few representative epimeric ketones for which the optical rotatory data also are available. It may be noted that the rule allows the correct prediction of the absolute configuration even when one of the epimeric pair is in the chair form and the other in the boat form. Furthermore, the predictions from this rule are valid for the comparison of the $[\alpha]_D$ values of the epimers as well as for the comparison of their Cotton effect curves. The rule therefore assumes added usefulness when both epimers give Cotton effect curves of the same sign.

For some epimeric cyclopentanone derivatives the application of the haloketone rule or the Octant rule might be precluded because of the difficulty in ascertaining the conformation of a substituent from spectroscopic data. As examples one can cite the epimeric 16-bromoisoandrosterone acetates and 3-chlorocamphors (see Table 1). The application of our rule leads to the correct stereochemistry in both of these cases as well as in the case of the epimeric 16-bromo-3β-acetoxy-5α, 14β-androstane-17-ones,[15] (see Table 1).

We have determined the spectra for epimeric 17-bromo-3β-methoxyandrostane-16-ones (see Table 2). Predictions from our rule, as well as from the axial α-haloketone rule, are in agreement with the stereochemistry assigned to these isomers by Fajkoš.[16]

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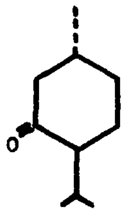
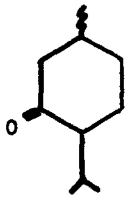
[16] Private communication.

Our empirical rule is similar to Brewster's Conformational Dissymmetry Rule[17,18] in some respects but not exactly equivalent to it. While the Octant Rule and Brewster's Rule permit predictions about the rotation of an individual epimer, our rule is more limited since it is explicitly stated in terms of the *difference* in rotation of an epimeric pair. There is an important advantage in comparing the $[\alpha]_D$ of two *epimers* (in the same solvent) because in general the effects of the distant environment on the keto group assume secondary importance at long wave lengths. Such a comparison therefore reveals the effect of the *immediate* environment of the keto group. This may account for the fact that our rule can lead to correct predictions of the configuration of epimers without taking into account their conformation.

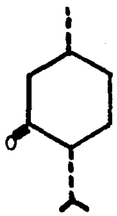
The difference in approach of these three rules can be illustrated by considering the ORD of (-)-menthone (X) and its epimer (+)-isomemthone (XI). The former gives a weak positive Cotton effect curve that starts on the negative side in the visible spectral range, while (+)-isomenthone is characterized by a strongly positive Cotton effect curve.[19] The Conformational Dissymmetry Rule leads to the prediction that XI in all chair forms should have a positive Cotton effect (not necessarily near 300 mμ) whereas



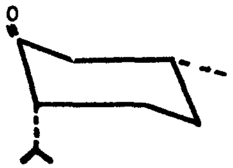
X



Xa



XI



XIa

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[17] J.H. Brewster, *J.Amer.Chem.Soc.* **81**, 5475, 5483, 5493 (1959).

[18] J.H. Brewster, *Tetrahedron* **13**, 106 (1961).

[19] Reference 9, p. 105.

the Octant Rule will permit a positive Cotton effect if isomenthone has the conformation XIa in which the bulky isopropyl group is in the axial position. In applying our rule we disregard the conformation and correctly predict that the more levo-rotatory of the two epimers (i.e. (-)-menthone, notwithstanding its positive Cotton effect curve) should have the absolute configuration Xa.

We are grateful to Dr. J. Fajkoš for samples of epimeric 17-bromo-16-ketones. Thanks are due to Dr. M.S. Manhas for assistance in determining the spectra and to Dr. L. Jampolsky and Dr. L.Z. Pollara for valuable suggestions. We also thank Dr. J.H. Brewster for sending us his manuscripts before publication, and for his helpful comments on our manuscript. This work was supported in part by a research grant from the National Science Foundation (NSF - G13290).