Tetrahedron, 1963, Vol. 19, pp. 1387 to 1396. Pergamon Press Ltd. Printed in Northern Ireland

SESQUITERPENES—IV

CONFORMATIONAL ANALYSIS IN THE PERHYDROAZULENIC SESQUITERPENES

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(*Received* 13 *November* 1962; *revised form* 19 *March* 1963)

Abstract—A simple qualitative procedure is outlined for the conformational analysis of cycloheptane derivatives with particular attention to the natural perhydroazulenes. The procedure allows discrimination amongst different configurational and conformational isomers on grounds of thermodynamic stability. Using this procedure it is possible, by analyzing the known reactions of each, to derive stereochemical structures for the sesquiterpenes lactucin, artabsin and arborescin, tenulin, balduilin, and helenalin.

THE principles and procedures of conformational analysis for cyclohexane derivatives, first presented by Barton,[2] have proved to be an exceedingly potent tool in modern organic chemistry, both in elucidating stereochemistry and in understanding the stereoelectronic course of reactions.[3] However, the procedures are only applicable generally to the common cyclohexane ring. A growing interest in similar reactions of cycloheptane compounds and a rising number of natural cycloheptane compounds now requires a comparable approach to the conformational analysis of the cycloheptane system. It seemed reasonable, therefore, to project such a system in a form capable of simple qualitative manipulation from the data recently derived in machine computation of the relative stabilities of conformations of cycloheptane and its substituted derivatives.[4] The conformational analysis procedures outlined below require no models or mathematics and are simply applied to afford a qualitative distinction in stability among various isomers. These procedures are then applied to the reactions and properties of several sesquiterpene lactones in order to ascertain their stereochemistry.

Method of cycloheptane analysis. Several important points of difference between cyclohexane and cycloheptane must be registered at the outset. Unlike cyclohexane, which has only a single chair form, cycloheptane with its lower order of symmetry has a family of chair forms, smoothly and readily interconvertible via pseudorotation. Of these, two forms are symmetrical, the twist-chair (I) with an axis of symmetry being the most stable and the chair (II) with a plane of symmetry being the least stable in the pseudorotation continuum. As in cyclohexane the chair forms of cycloheptane can

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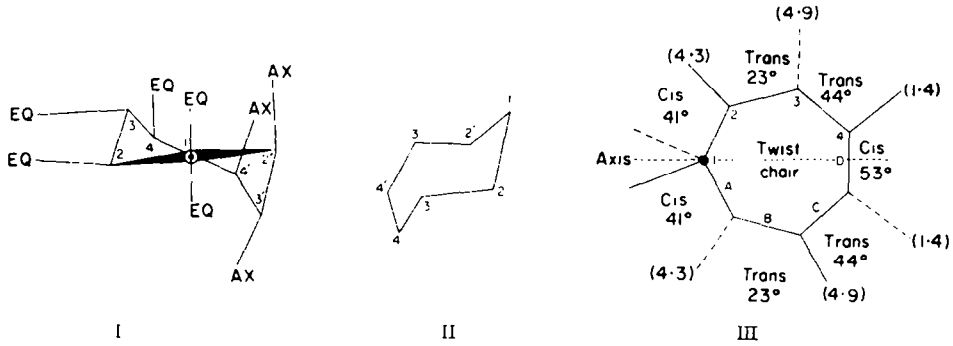
[2] D. H. R. Barton, *Experientia* **6**, 316 (1950); *J. Chem. Soc.* 1027 (1953).

[3] A variety of reviews are available: E. L. Eliel, *The Stereochemistry of Carbon Compounds*. McGraw-Hill, New York, (1962); W. G. Dauben and K. S. Pitzer, *Steric Effects in Organic Chemistry*, (Edited by M. Newman) Chap. 1. Wiley, New York (1956); D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 44 (1956).

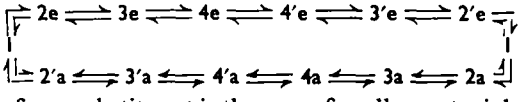
[4] J. B. Hendrickson, *J. Amer. Chem. Soc.* **83**, 4537 (1961); **84**, 3355 (1962).



I II III

undergo a conformational flip into a family of higher energy boat forms, also interconvertible by pseudorotation with an axially-symmetric twist-boat the most stable and a plane-symmetric boat the least stable form in this separate pseudorotation sequence.[4] The energetic distinction between chair and boat families in the cycloheptanes is less by about half than that in the cyclohexanes.

In chair cyclohexane there are only two distinguishable substituent positions, axial and equatorial, the latter more stable by 1·6–2·0 kcal/mole for a methyl substituent; as one proceeds around the ring these positions alternate in being above and below the plane of the ring. In the most stable, twist-chair form of cycloheptane there are seven distinguishable substituent positions, the unique axis-carbon with two identical positions, both equatorial in energetic status, and three other carbons on each side of the axis, each with a distinguishable axial and equatorial position (cf., I); the latter alternate in being above and below the ring plane as they do in cyclohexane.[4] Diagram III show the equatorial positions of the twist-chair (TC) with dotted bands below the ring plane and solid bonds above. Whereas in cyclohexane interconversion of a substituent between axial and equatorial positions requires a conformational flip to a twist-boat form and back, interconversions in cycloheptane can all occur by facile pseudorotational passage of the substituent[5] through an itinerary of all possible positions without any flip to the boat forms (although that is still a possible though higher-energy route).[4] This itinerary in the twist-chair is as follows:



The strain energy for a substituent is the same for all equatorial positions, including both positions on the axis-carbon. The strain energies of the three axial positions, comparable to the 1·6–2·0 kcal/mole figure for cyclohexane, are noted in parentheses (in kcal/mole) on Figure 3. These are computed[4] for methyl groups and the actual values should not be accepted as having more than a qualitative meaning, with the 4a-position comparable to an axial position in cyclohexane and a 2a- or 3a-position significantly worse. Several features of interest arise from this different orientation of axial and equatorial positions in the two sizes of rings. Thus, a gem-disubstituted cycloheptane can be fully equatorial by taking up the 1,1-conformation. Such a situation is impossible in chair cyclohexane, as are 1,2-*cis*-diequatorial substituents or

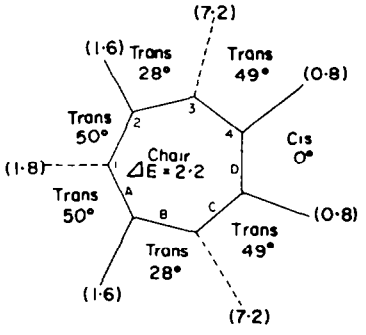
[5] It is more correct to consider the pseudorotation as passage of the axis-carbon designation from one carbon to another around the ring with the attendant changes in the environment of the substituent.

1,3-*trans*-diequatorial substituents; both of the latter orientations can occur in twist-chair cycloheptane, the former by utilizing the axis-carbon for one substituent, the latter by placing the axis-carbon between the two substituted carbons. Thus the greater conformational complexity of cycloheptane and the free pseudorotational interconversions of substituent positions afford more strain-free combinations for attached groups than is possible in cyclohexane.

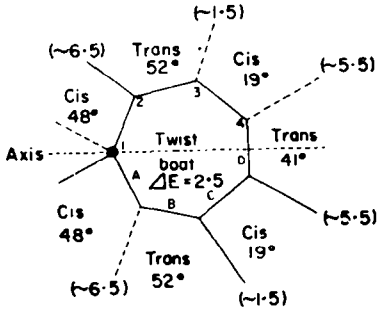
The fusion of a five-membered ring to cycloheptane is a very restrictive process since such a ring will not tolerate fusion at a dihedral angle of greater than 45–50° without the rapid introduction of considerable strain.[4] Diagram III distinguishes the four kinds of bonds in twist-chair cycloheptane (labeled A, B, C, D) and shows the dihedral angles they afford for fusion of a five-membered ring. Thus, such a ring may be fused *cis* only at bonds A and D and *trans* only at B and C, although with that restriction accepted both *cis*- and trans-fusions are equally stable, and better than fusion of a five- with a six-ring. The *cis*-fused cyclopentane at A may be diequatorial (impossible in the hydrindanes, cf. above) or equatorial-axial (1, 2a) while that at bond D must be equatorial-axial (4e, 4'a) and will be poorer in stability owing to some strain in the 53° fusion angle. Like its fusion to cyclohexane, fusion of the five-membered ring *trans* to cycloheptane (at bonds B or C) can only be diequatorial.

The procedure for conformational analysis of a cycloheptane derivative with a given *configuration* is simply to apply diagram III to the molecule in the twist-chair form; it is examined in each of the seven possible conformations obtained by placing the axis-carbon at each possible location in turn and adding the strain energies of all axial substituents. The conformer with lowest energy will then presumably be the one adopted by the molecule, thus defining its conformation; if several conformations appear to exhibit equal strain energies the molecule may be expected to pseudorotate rapidly amongst them.

In some cases a multiplicity of substituents or fused rings (*vide infra*) will, as in cyclohexane systems, cause ring conformations which are less favorable in the parent to become preferred. Therefore, conformational keys are provided in IV and V for the chair and twist-boat forms with the allowed cyclopentane fusions and the energies of axial methyls[4] indicated as in III (the latter are only estimated for the twist boat as the detailed computation seemed unjustified in view of the presumed rarity of the form). In each of these forms an increment of energy (ΔE in the ring center) must be added to the overall computed strain to account for the less favorable comformation of the ring itself.



IV



V

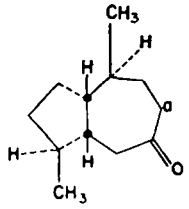
In making such calculations in the subsequent sections all carbon substituents were simplified by use of the methyl strain energy values (III) and oxygen substituents assigned half the methyl value (cf. Winstein's A-values[6]); *cis*-fusions of five-membered rings at dihedral angles of 45°–50° were assigned an extra 0·5 kcal/mole and those at 50–55° (cf., *cis* at bond D in III) an extra 1·0 kcal/mole of strain. *cis*-Di-axial substituents will have of course several kcal/mole extra strain owing to the mutual interaction of the substituents themselves. A single sp^2-carbon in the cycloheptane ring is not considered to change the conformational situation significantly as the bond angles in cycloheptane are already larger than tetrahedral[4] and the change occasioned by increase of one to 120° is slight.

The above procedure can be of value in determining the relative energies of two isomers in an equilibration situation such as the epimerization of a secondary alcohol of an asymmetric hydrogen α- to a carbonyl group, in choosing stereoelectronically correct conformations for certain reaction mechanisms or in defining the molecular geometry for optical rotatory dispersion[7] or nuclear magnetic resonance considerations.

Lactucin and artabsin. The chemistry of lactucin[10] includes a base-catalyzed epimerization of hexahydrolactucin (VI) to isohexahydrolactucin (VII) under conditions which do not open the lactone ring; the iso-compound (VII), but not VI, reacts with benzaldehyde in acid to form the cyclic acetal VIII, the formation of which dictates the relative stereochemistry as shown at the four centers C_1, C_4, C_5 and C_8; C_{10} stereochemistry was assigned on grounds of *cis*-hydrogenation. There are four possible configurations of the γ-lactone in the C_1-epimer pair, VI and VII; analysis of these in the foregoing semi-quantitative terms shows that only in the two possibilities with *trans*-fused lactones does the equilibrium favor VII. If we accept an absolute C_7-β configuration, which is true of all known sesquiterpenes to date, the two *trans*-lactones

[6] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.* **77**, 5562 (1955).

[7] Optical rotatory dispersion can be used via the octant rule[8] to assign absolute configurations in cycloheptane cases only if the actual conformation is known first. The pseudorotation capabilities of cycloheptanes can often invert the Cotton effect so that judgments made without consideration of the foregoing conformational analysis can often be incorrect. Thus the ketone (i) made from guaiaol and of known absolute configuration as shown may be subjected to the above conformational analysis: placement of the axis-carbon at either ring-fusion carbon (heavy dot) gives an all equatorial circumstance, while the situation with the axis-carbon at "a" is less good with one 4a substituent and a D-*cis*-fusion; hence the former are preferred. The preferred conformations, examined with Dreiding models in the light of the octant rule, require a positive Cotton effect, as in fact observed,[9] while the other conformation would yield a negative curve. (The prediction is also correct for the epimeric *cis*-fused ketone.[9])

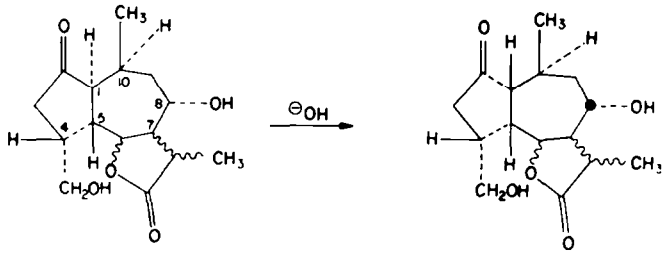


(i)

[8] C. Djerassi, *Optical Rotatory Dispersion* (especially Chap. 13.) McGraw-Hill, New York (1960); W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* **83**, 4013 (1961).

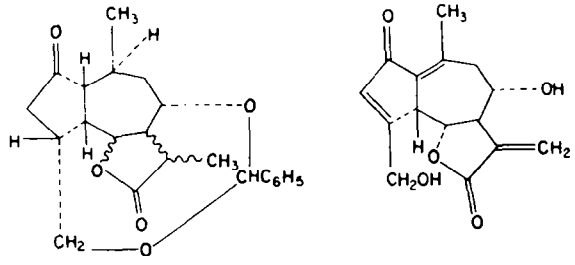
[9] E. J. Eisenbraun, T. George, B. Riniker and C. Djerassi, *J. Amer. Chem. Soc.* **82**, 3648 (1960).

[10] D. H. R. Barton and C. R. Narayanan, *J. Chem. Soc.* 963 (1958); L. Dolejs, M. Soucek, M. Horak, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **23**, 2195 (1958).



VI VII

show reverse predictions for the change in the Cotton effect of the optical rotatory dispersion curves on going from VI to VII. This therefore allows only one absolute stereochemical formulation for lactucin, viz., IX. In isohexahydrolactucin, then, the axis-carbon (heavy dot) is at C_8 with only one axial substituent, C_4; this circumstance in fact places the hydroxymethyl group well under the cycloheptane ring in a position it must have to cyclize to the hydroxyl on C_8 with benzaldehyde.



VIII IX

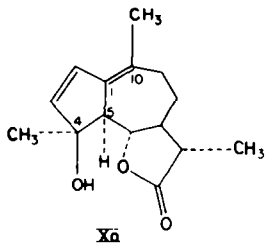
Since artabsin has been oxidized to a lactone di-acid identical to one obtained from santonin and dehydration of tetrahydroartabsin yielded a tetra-substituted (Δ^4) double bond, it was assigned one of the formulas Xa or Xb with absolute configurations as in santonin and C_5-H *trans* to C_4-OH[11,12]. Furthermore, artabsin reacts with permanganate to yield a triol ether XI the formation of which is most rationally envisioned as an attack of C_4-OH on C_{10} at the backside of the bond from C_{10} to an oxygen of the intermediate cyclic manganate ester. If this intermediate is analyzed in conformational terms the axis-carbon must be located at C_1 in each and in only one of these two forms, XII, is C_4 in the axial disposition required to provide the C_4-OH with a suitable geometry for this oxide formation. This is pictorialized in XIII, which incidentally illustrates the value of the axis view (i.e., I) of twist-chair cycloheptane for perspective representations. Xb is therefore the correct absolute configuration of artabsin so that arborescin,[13] which is related by hydrogenation to tetrahydroartabsin, must have the absolute stereochemistry XIV.

Tenulin, balduilin and helenalin. The chemistry of these (XV) and certain related

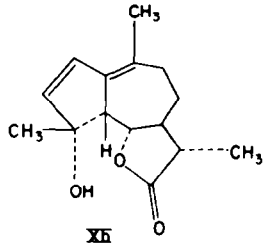
[11] L. Novothy, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **25**, 1500 (1960); V. Herout, L. Dolejs and F. Sorm, *ibid.* **22**, 1914 (1957).

[12] The proof of structure X is meager and not entirely consistent with the uv spectrum but the conformational analysis given here will probably apply in other double-bond isomers as well should X be proved incorrect in that particular.

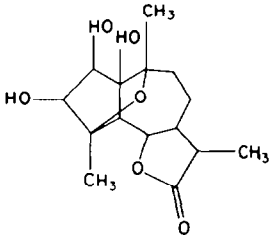
[13] Y. Mazur and A. Meisels, *Chem. and Ind.* 492 (1956).



XIa



XIb



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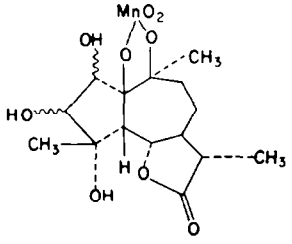
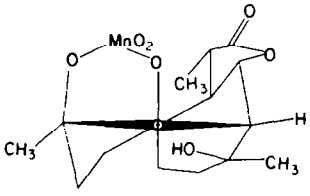
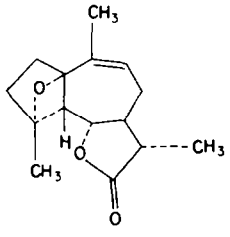


XII



XIII



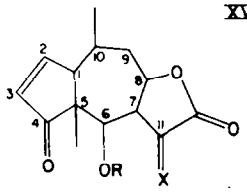
XIV

TABLE 1. CONFIGURATIONS AND ENERGIES OF THE POSSIBLE ISOMERS[a]

	$C_1\alpha$:				$C_1\beta$			
	$C_7\alpha$		$C_7\beta$		$C_7\alpha$		$C_7\beta$	
	$C_8\alpha$	$C_8\beta$	$C_8\alpha$	$C_8\beta$	$C_8\alpha$	$C_8\beta$	$C_8\alpha$	$C_8\beta$
$C_5\alpha$, $C_6\alpha$	*1* (+5·4)	*2* (+2·0)	**3** (0)	**4** (−1·0)	**17** (0)	*18* (+4·5)	**19** (+0·5)	**20** (0)
$C_5\alpha$, $C_6\beta$	**5** (0)	*6* (−1·1)	*7* (+8·1)	*8* (+9·6)	*21* (−1·4)	**22** (0)	**23** (0)	**24** (0)
$C_5\beta$, $C_6\alpha$	*9* (−1·1)	**10** (0)	*11* (+1·2)	*12* (+1·5)	*25* (+2·3)	*26* (−4·5)	**27** (0)	*28* (−2·3)
$C_5\beta$, $C_6\beta$	**13** (0)	**14** (0)	**15** (+1·0)	**16** (0)	**29** (0)	*30* (−6·8)	*31* (+12·4)	*32* (+10·2)

[a] Computed strain energy difference between normal and allo isomer given in parenthesis, positive sign indicating normal isomer preferred. Orientations given for C_1 and C_5 refer to the attached carbon of the cyclopentane ring, i.e., compounds designated as $C_5\alpha$ above will have the $C_5\beta$-methyl group.

sesquiterpene lactones has had an interesting and extensive history in recent years;[14–28] nearly one hundred derivatives of these natural lactones have appeared in the literature largely through the extensive and critical efforts of Professor Herz and his colleagues who have succeeded in relating the configurations at C-5, 6 7, 8 and 11 in these three major families of lactones.[29] Six of the seven asymmetric centers (all except C_{11}) in the tetrahydro derivatives are in the cycloheptane ring so the series should provide a reasonable test of the conformational analysis proposed above; the structures of these derivatives are shown in XV.



XV a, Isotenulin, R = Ac, X = H,CH_3
b, Balduilin, R = Ac, X = CH_2
c, Helenalin, R = H; X = CH_2

Unfortunately, despite the large number of reactions which have been carried out in this series there are few which serve to distinguish relative stabilities of isomers. In general the only reactions which do this are the saponification and reclosure of the lactones between C_8 (normal) and C_6 (allo) and the concomitant equilibration of the C_{11}-methyl group which is α- to the lactone carbonyl but not on the cycloheptane ring.

Furthermore, the relative stabilities of normal and allo lactone positions in the several isomers do not emerge unequivocally from the evidence. Thus tetrahydrohelenalin in base yields the C_{11} epimer (normal lactone) while its C_4-desoxo derivative is converted instead to the allo lactone without C_{11}-epimerization. Similarly, tetrahydrobalduilin yields the C_{11} epimer (normal lactone) as the major product as well as a minor product, which may well be the allo-lactone without change at C_{11} since this is the product in the desoxo analog, just as in the helenalin case. In the dihydroisotenulin derivatives, the parent ketone is converted to an equilibrium mixture of C_{11}-epimerized allo-lactone and unepimerized normal-lactone (unchanged dihydroisotenulin configuration) while in the desoxo series only the C_{11}-epimerized allo-lactone is isolated.

[14] R. Adams and W. Herz, *J. Amer. Chem. Soc.* **71**, 2546–2559 (1949).
[15] G. Büchi and D. Rosenthal, *J. Amer. Chem. Soc.* **78**, 3860 (1956).
[16] D. H. R. Barton and P. de Mayo, *J. Chem. Soc.* 142 (1956).
[17] B. H. Braun, W. Herz, and K. Rabindran, *J. Amer. Chem. Soc.* **78**, 4423 (1956).
[18] C. Djerassi, J. Osiecki, ans W. Herz, *J. Org. Chem.* **22**, 1361 (1957).
[19] W. Herz and R. B. Mitra, *J. Amer. Chem. Soc.* **80**, 4876 (1958).
[20] W. Herz, R. B. Mitra, and P. Jayaraman, *J. Amer. Chem. Soc.* **81**, 6061 (1959).
[21] W. Herz, R. B. Mitra, K. Rabindran, and W. A. Rohde, *J. Amer. Chem. Soc.* **81**, 1481 (1959).
[22] W. Herz, P. Jayaraman and H. Watanabe, *J. Amer. Chem. Soc.* **82**, 2276 (1960).
[23] A. R. de Vivar and J. Romo, *J. Amer. Chem. Soc.* **83**, 2326 (1961).
[24] W. Herz, H. Watanabe, M. Miyazaki and Y. Kishida, *J. Amer. Chem. Soc.* **84**, 2601 (1962).
[25] B. A. Parker and T. A. Geissman, *J. Amer. Chem. Soc.* **84**, 4126 (1962).
[26] W. Herz, *J. Org. Chem.* **27**, 4043 (1962).
[27] W. Herz, A. R. de Vivar, J. Romo, N. Viswanathan, *J. Amer. Chem. Soc.* **85**, 19 (1963).
[28] W. Herz, W. A. Rohde, K. Radindran, P. Jayarman, and N. Viswanathan, *J. Amer. Chem. Soc.* **84**, 3857 (1962).
[29] W. Herz, A. R. de Vivar, J. Romo, N. Viswanathan, *Tetrahedron* **19**, 1359 (1963). Professor Herz's very helpful assistance in making this information available in advance of publication is gratefully acknowledged.

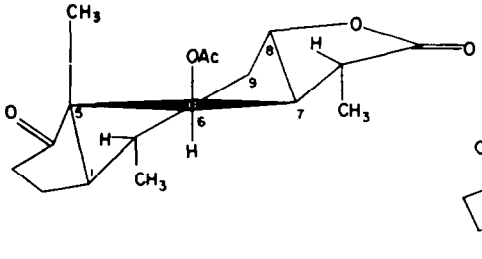
The salient feature of all these results seems to be that in none of the cases does the thermodynamic preference for one lactone orientation over the other outweigh the energy difference between the two possible C_{11}-methyl configurations, and so this preference must be quite small in each of the three families. If for the moment we ignore the C_{11}-methyl, we may construct a table of the 64 possible diastereomers obtained by varying the configurations at the six asymmetric centers on the cycloheptane ring and the two lactone orientations; each of these may be semi-quantitatively assessed in terms of key structures III–V and the foregoing conformational analysis, and a stability energy figure assigned to it. The results of such an assessment may be seen in Table 1 in which the 32 normal/allo pairs are grouped by configuration at C-1, 5, 6, 7, 8 with the C_{10}-methyl taken arbitrarily as having an α-configuration so as to provide only a single enantiomer of every possible diastereomeric structure (only relative stereochemistry being relevant here).

Table 1 indicates the ΔE for each normal/allo lactone pair, a positive value taken as a preference for the normal, negative for the allo, orientation. The relative stereochemistry at the various centers in the different sesquiterpenes[29] puts certain restrictions on the places in the table at which potential sets of structures for them may be located. Since all three families have identical configurations at C_1 C_{10} C_5 and C_7 all three must be located in one box in the table, the tenulin configuration horizontally adjacent to balduilin and the helenalin representation vertically adjacent to balduilin since the tenulin family bears a C_8-epimeric relation to the balduilins and the helenalins are C_6-epimeric with them. If we now accept an energy of less than one kcal/mole in either direction for the difference between allo and normal lactone isomers in each family we shall find only the configurations in bold face acceptable structures, and to meet the relative stereochemistry restrictions above, only structures 13, 19, 20, 23 and 24 will be tenable for isotenulin since at least three energetically equivalent lactone pairs must co-occur in a single block.

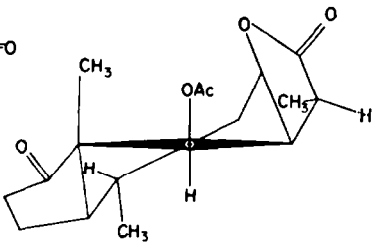
Dreiding models of the structures in Table 1 show that, in the set of five structures selected above (and in fact in almost all the structures in the table), the configuration with the C_{11}-methyl in the opposite orientation from the group at C_7 is strain-free, e.g., $C_7\beta$–$C_{11}\alpha$ and $C_7\alpha$–$C_{11}\beta$. The other configuration at C_{11} may or may not cause the methyl group to conflict with the adjacent hydroxyl at C_6 or C_8 in a manner analogous to the 1,3-diequatorial interactions observed in decalins and other fused ring systems; the conflict in the present cases will be less severe than that in the decalins owing to the greater flexibility of the five-membered lactone ring. This steric interaction presumably provides the thermodynamic impetus for the C_{11}-epimerizations observed and the particular epimerization observed in the tenulin cases requires that the same (α or β) methyl orientation at C_{11} must be hindered in both the normal and the allo lactone while only in the normal lactones of the balduilin and helenalin series is this strained interaction requisite.

Of the five acceptable structures above only two, 13 and 23, meet this criterion for the tenulins while of the corresponding candidates for the balduilin and helenalin families (10, 14, 19, 20, 23, 24) only 10, 20, 23 and 24 possess a hindered configuration for the C_{11}-methyl in the normal lactone. These selections taken together allow only No. 23 for the tenulin family with No. 24 representing balduilin and No 20 as helenalin. A selection of enantiomers may be made on the basis of the optical rotatory dispersion results[18,19,27] which show the C_5-methyl to be placed in the β-configuration;

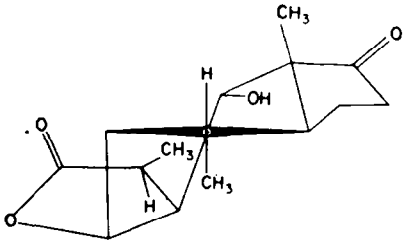
this also requires the group at C_7 in the three compounds (*cis* to the C_5-methyl from Table 1) to have an absolute β-configuration, which is consistent with all known sesquiterpenes to date.[30] These three structures may now be represented in the conformations calculated as preferred: dihydroisotenulin as XVI, tetrahydrobalduilin as XVII and tetrahydrohelenalin as XVIII; tenulin itself should then be XIX.



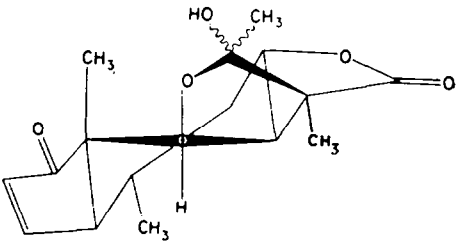
XVI



XVII



XVIII



XIX

Herz[29] has shown that the reverse aldol reaction involving the C_6-hydroxyl and the C_4-ketone and opening the cycloheptane ring does not take place in the tetrahydro derivatives of these three families although it is known in the parent ($\Delta^{2,3}$) compounds[27,28]. The ready base-catalyzed destruction of tetrahydrobigelovin, known to be another stereoisomer of dihydroisotenulin,[25] is then very likely to begin as just such a retroaldol cleavage, followed by base-initiated transformations of the freed aldehyde. That this should occur only in the bigelovin series suggests that its structure possesses more axial group compressions (higher strain energy) than the three considered heretofore.

It is frequently true of the structures in Table 1 that opening the lactone ring, with the consequent release of conformation restriction attendant on the fusion of the two rings, will allow the molecule to take up a conformation with fewer substituents in axial positions. For this reason examination of the isomers for axial compression strain which might trigger a retroaldol reaction in alkali should be made on the carboxylate form resulting from lactone saponification.

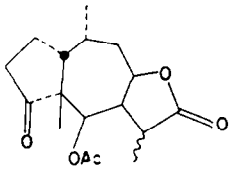
Of the three families considered thus far, the tetrahydrobalduilins show the greatest strain energy (6·8$^+$ kcal/mole calculated for both lactone forms) and this is

[30] This correlation appears to be sufficiently widespread to deserve special notice, like the case of common absolute configuration at C_{18} in the indole alkaloids[31], and to become a serious factor in biogenetic considerations[32] of the sesquiterpenes.

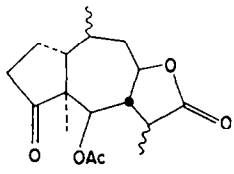
[31] F. Wenkert and N. V. Bringi, *J. Amer. Chem. Soc.* **81**, 1474 (1959).

[32] J. B. Hendrickson, *Tetrahedron* **7**, 82 (1959).

not reduced on separate consideration of the various conformations available to the acid after lactone opening. Thus tetrahydrobigelevin should be one of the structures of Table 1 with a higher strain energy than tetrahydrobalduilin. Only structures 2, 8, 9, 16, 17 and 32 have such a higher energy in both lactone forms and further consideration of the strain release possible with cleavage of the lactone ring shows that structures 2, 9 and 32 would be expected to be of lower energy than the balduilins after lactone-opening. This leaves structure 8 (XX, calculated as 7·5+ kcal/mole in the conformation shown: axial carbon at C_1) and structures 16 and 17, generalized as their $C_7\beta$ enantiomers in XXI (calc. energies, 7·0 and 8·4+ kcal/mole), as candidates



XX



XXI

for tetrahydrobigelovin in these terms. It is worth noting that the excessive compression strains of these structures result from the difficulty of accommodating four adjacent *cis*-substituents ($C_{5,6,7,8}$) in any cycloheptane conformation.[4]

Since this analysis was undertaken an X-ray crystallographic study of bromoisotenulin has been completed[33] which confirms structure 23 for isotenulin. While it is gratifying that the present analysis accords with this result, the accord may well be fortuitous for several reasons which it is important to bear in mind in the use of this conformational method. Basically, the energies calculated in this way are in fact much less reliable than is suggested by the foregoing, based as they are on extensions of calculated preferences for methyl groups only in simple monosubstituted hydrocarbons. If a greater allowance than $\pm 1{\cdot}0$ kcal/mole is made for the thermodynamically equivalent lactones there results a larger number of choices from which no unique selection for tenulin is possible.[34] On the other hand it should be noted that very few reactions in this series were done with a specific view to determining relative isomer stabilities for use in conformational analysis. It may be hoped that the method may lead to more fruitful results when equilibration experiments on cycloheptanes are done with its use in mind. Finally, it should be emphasized again that in the more complex cycloheptane conformations smaller energetic distinctions separate the forms than is true of cyclohexane derivatives so that results will often be less clearcut in interpretation.

Acknowledgement—The author wishes to gratefully acknowledge the support of a research grant from the National Instutites of Health for this work and related sesquiterpene studies.

[33] D. Rogers and Mazhar-il Hague, *Proc. Chem. Soc.*, 92 (1963).

[34] For example, if $\pm 2{\cdot}0$ kcal/mole for the allo-normal energy difference is acceptable, then there are fourteen instead of five condidates for tenulin, of which eight (5, 9, 10, 13, 15, 16, 22, 23) meet the C_{11}-methyl hindrance criterion. Of these, only 10 and 23 have corresponding balduilin and helenalin structures exhibiting C_{11}-methyl interaction with the C_6-hydroxyl in the normal lactone.