Phytochemistry, 1978, Vol. 17, pp 1343–1347 © Pergamon Press Ltd Printed in England. 0031-9422/78/0801-1343$02.00/0

APPLICATIONS OF THE METHOD OF MOLECULAR ROTATION DIFFERENCES IN STRUCTURAL AND STEREOCHEMICAL PROBLEMS IN TRITERPENES*

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(*Revised received* 13 *January* 1978)

Key Word Index—Triterpenes; molecular rotation differences and structure.

Abstract—The specific rotation data of some triterpenoid alcohols and their simple functional derivatives have been correlated by the Barton and Jones method of molecular rotation differences (MRD). Cases in the literature in which the recorded specific rotation data are erroneous have been indicated for possible correction.

INTRODUCTION

Barton and Jones recognised [1] a relationship between the changes in molar optical rotations of triterpenoid alcohols on acetylation (ΔM_1), benzoylation and oxidation (ΔM_2 in this paper) and their basic stereoskeleton, and went on to show that the ΔM values were characteristic of the basic stereoskeleton of the molecule. In an extension [2] of this work specific rotation data were collated for tetracyclic and pentacyclic triterpenoid alcohols together with their acetates and ketones. The triterpenoids included were unsaturated with 4,4-dimethyl groups and oxygenated, at least, at the C-3 position; they were assigned into groups 1 to 8 on structural grounds [2]. By so doing, it was possible to divide all the known triterpenoids with the above structural features into nineteen stereoskeletal types on the basis of their ΔM_1 and ΔM_2 values considered together. From these studies, a number of generalisations were made on the application of the MRD method in the structural elucidation of triterpenoids.

The ultimate objective of the present series of studies is to set up standard and diagnostic ΔM values for all known stereoskeletal types of triterpenoids for which the necessary data are available in the literature.

RESULTS AND DISCUSSION

In the present work, specific rotation data have been collated for triterpenoids with a cycloartenol skeleton, for saturated pentacyclic triterpenoids with different atomic skeletons like oleanane, dammarane and hopane skeletons but with a stereoskeleton similar to the lupane type up to ring C/D junction, and also for 4α-methylsterols (which are described by some authors [3, 4] as friedelane-type tetracyclic triterpenoids). Furthermore, some of the generalisations made in the earlier paper [2] are elaborated upon in order to specificy and amplify the scope of their applications. As in the previous work,

* This paper is part of a series. For the preceeding paper see ref. [2].

Table 1. Molecular rotation data for cycloartenol-type compounds

Compound	M_0	M_1	M_2	ΔM_1	ΔM_2	references
Lithocarpdiol (**1**)	+255	—	+132	—	−123	10
Cycloartenol (**2**)	+217	+281	+98	+64	−119	3
Cycloartanol (**3**l	+197	+263	+102	+66	−95*	3, 11
Cyclolaudenol (**4**)	+202	+265	+83	+63	−119	3
Methylambolate (**5**)	+174	—	+58	—	−116	12
Methylmangiferolate (**6**)	+239	—	+110	—	−129	13
Cyclosadol (**7**)	+180	+241	—	+61	—	14
Isocycloartenol (**8**)	+191	+253	+83	+62	−108	15
24-Methylenecycloartanol (**9**)	+189	+260	+88	+71*	−101*	3
Cycloartenediol (**10**)	+168	+208	—	+40*	—	3
Cyclobalanol (**11**)	+204	+263	+77	+59	−127	5, 6
Group average				+62.5	−120	

For the methods used to obtain $(M)_D$ values, and for the acceptable margin of error in the magnitude of ΔM values, see ref. [2].
* Indicates figures which are considered erroneous and hence not used to calculate the group averages.

Table 2. Molecular rotation data of 4α-methylsterols

Compound	M_0	M_1	M_2	ΔM_1	ΔM_2	references
Lophenol (**12**)	+20	+124	+48	+104	+28	16
24-Ethylidenelophenol (**13**)	+101	+198	—	+97	—	3
24-Methylenelophenol (**14**)	+25	+135	—	+110	—	3, 16
Group average				+104	—	

analysis of the ΔM values revealed definite trends which strongly corroborated earlier generalisations.

Group 9 (*cycloartenol-type compounds, Table* 1)

There is excellent agreement between the ΔM values for practically all members of the group to give a reliable average of +62.5 and −120 for ΔM_1 and ΔM_2 respectively. Cyclobalanol (**11**) was first obtained by Tachi *et al.* [5] by the reduction of cyclobalanone which the workers isolated from the plant *Quercus glauca*. This triterpenoid alcohol was later isolated by Rangsawami *et al.* [6] from the fern *Polypodium juglandifolium*, and oxidised to the ketone cyclobalanone. The wide variation in the physical constants, especially the mps. of these compounds including the derived acetates, created [6] confusion as to their structural identities. From the present work, it is clear that the optical rotation value of +22 recorded for the alcohol by Tachi *et al.* [5] cannot be correct since this would give a ΔM_2 of −10 which is completely at variance with the group average; the alternative values of +42 and +48 give much better agreement; the physical data on the ketone is reasonably consistent. Furthermore, from this work (see also ref. 2) the configuration of the C-3 hydroxyl must be β and equatorial, thus settling this stereochemical problem [6]. In the previous paper [2], the generalisation was made that, of all the naturally-occurring compounds examined, only those with Δ^5, Δ^7, $\Delta^{9(11)}$ and $\Delta^{7,9(11)}$ unsaturation, irrespective of their basic stereoskeleton and configuration at C-3, have significantly negative ΔM_2 values. The cycloartenol-type structures make an addition to this generalisation. This is not too surprising judging from the geometries of these compounds at C-9 and C-10; and especially as isosimarenol and isoglutinol, two $\Delta^{5(10)}$ compounds obtained [7] by acid-induced migration of simiarenol and glutinol respectively also have negative ΔM_2 values. A similar situation was observed [2] with phyllanthol, a 13(14)-cyclopropyl triterpenoid, and Δ^{14} compounds.

Group 10 (*4α-methyl sterols* [3, 4], *Table* 2)

Necessary data were found for only three Δ^7 compounds with a 4α-methyl group. And even for these, data were available for computing only ΔM_1 values, for which a group average of +104 was obtained. As pointed out in the earlier work, a stereoskeleton cannot be safely assigned to a molecule on the basis of either ΔM_1 or ΔM_2 value alone. For example a ΔM_1 value of +104 could also apply equally well to a Δ^5, or Δ^7 compound. However these two skeletons have negative ΔM_2, whereas the only ΔM_2 value computed for a member of Group 10 is positive. This is of course still provisional.

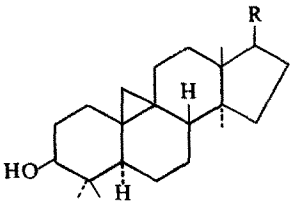
Group 11

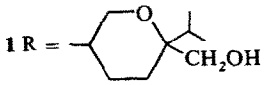
This group consists of saturated pentacyclic triterpenoids with different atomic skeletons but with the same stereoskeleton up to the ring C/D junction as in the lupane skeleton. Compounds with the lupane stereoskeleton up to the ring C/D junction and the C=C located in ring E or outside ring E have been considered [2]. It was found that, of all the structural types studied, Class A (with C-3β-hydroxyl) of this group (Group 8) provided the most consistent values of both ΔM_1 and ΔM_2 (average +60.5 and +146 respectively) over a wide range of compounds. It was later conceived that a fully saturated compound but with the same stereoskeleton up to the ring C/D junction, irrespective of the nature of the rest of the molecule, should also have the same ΔM values. This has now been established, at least in the ΔM_1 values (only for which specific rotation data were available in the literature, Table 3). It therefore

Table 3. Molecular rotation data for saturated compounds related to the lupane stereoskeleton up to the ring C/D junction

Compound	M_0	M_1	M_2	ΔM_1	ΔM_2	references
Cyclamigenin A^2 (**15**)	−75	−10	—	+65	—	17
Stellatogenine (**16**)	+182	+244	—	+62	—	3
Panaxadiol (**17**)	+5	+60	—	+55	—	18
Monogynol A (**18**)	+27	+78	—	+51	—	3
Cyclamigenin D (**19**)	−26	+22	—	+48	—	17
Hopanediol* (**20**)	+178	+194	+305	+16	+127	3
Desoxoxylamiretin D* (**21**)	+87	+80	—	−7	—	8
Cyclamigenin B* (**22**)	−5	−5	—	0	—	8

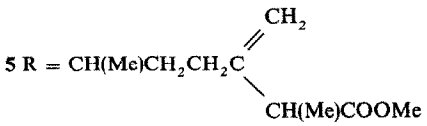
* Indicates compounds whose specific rotation data are considered seriously erroneous and hence unsuitable for characterisation purposes.



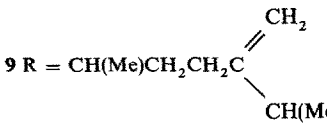


1 R =

2 R = $CH(Me)CH_2CH_2CH{=}C(Me)_2$
3 R = $CH(Me)CH_2CH_2CH_2CH(Me)_2$
4 R = $CH(Me)CH_2CH_2CH(Me)C(Me){=}CH_2$

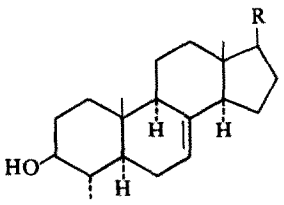
5 R = 

6 R = $CH(Me)CH_2CH_2CH{=}C(Me)COOMe$
7 R = $CH(Me)CH_2CH{=}C(Me)CH(Me)_2$
8 R = $CH(Me)CH_2CH_2CH_2C(Me){=}CH_2$

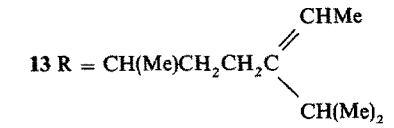
9 R = 

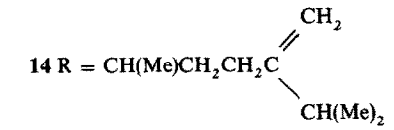
10 R = $CH(Me)CH_2CH{=}CHC(Me)_2OH$
11 R = $CH(Me)CH_2CH_2C(Me)_2C(Me){=}CH_2$

Group 9



12 R = $CH(Me)CH_2CH_2CH_2CH(Me)_2$

13 R = 

14 R = 

Group 10

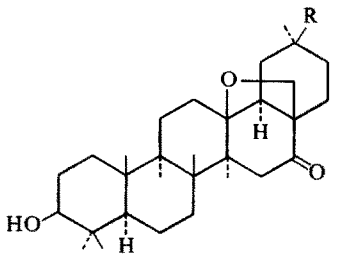
follows that the specific rotation data recorded for desoxoxylamiretin [8], cylamigenin B [8] and hopanediol [3] and/or their C-3-acetates are quite erroneous.

Configuration of C-3 oxygen function

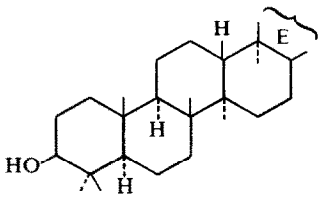
It was shown [2] that the MRD method could be used to establish the configuration of the C-3 oxygen function. In this respect, two problems normally arise. Is the function equatorial or axial? If equatorial (or axial) is it α or β? The MRD method can answer the second question with certainty. Thus for C-3α-hydroxy compounds (whether equatorial or axial) ΔM_1 is always significantly negative. For example, episimiarenol, a Δ^5 triterpenoid alcohol, has a C-3α-equatorial hydroxy group (similar to the 4α-methylsterols) yet the ΔM_1 for that particular stereoskeleton is negative; whereas simiarenol has a C-3β-axial hyroxy group and the ΔM_1 for that stereoskeleton is positive as it is with other C-3β oxygenated compounds in which the C-3 function is usually equatorial. Thus the MRD method unequivocally settles the problem of whether the C-3 oxygen function is α or β, but not whether it is axial or equatorial, though the latter information can, in most cases, be inferred from the former.

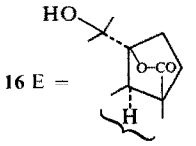
Assignment of a probable complete stereoskeleton

In the earlier paper, it was shown that the MRD method provides a relatively easy method for the solu-

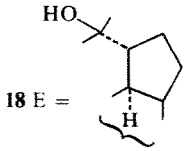


15 R = H
19 R = $CH(OMe)_2$
21 R = Me, C-16α-OH
22 R = CHO

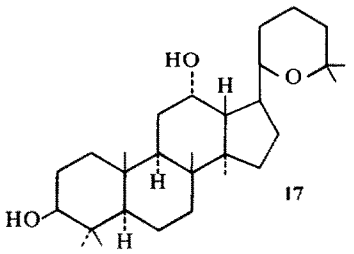




16 E =



18 E =



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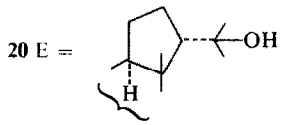

20 E =

Group 11

tion of stereochemical problems up to ring C/D junction in triterpenoid molecules. A further survey of all known [4] naturally occuring tetracyclic and pentacylic triterpenoid structural types has now revealed that, armed with a knowledge of the stereoskeleton up to the ring C/D junction, of the molecule, it is possible to postulate, with a high degree of probability, the complete stereoskeletal framework for the *entire* molecule. This is because there is usually a definite biogenetic stereochemical relationship between the H, Me or any other substituent at C-13 and C-18 and the geometry of the ring D/E junction. For example in the pentacyclic lupane, hopane, migrated hopane, arborane and serratane skeletons, the C-13 and C-18 H or Me are always *trans*, and the rings D and E are always *trans*-fused. In the tetracyclic series, there is always a *cis* (α, α or β, β) relationship between the C-13 H or Me and the C-17 substituent in compounds with either the euphane or lanostane/fusidane skeleton. The only known [9] exceptions to this generalisation are the pentacyclic alcohols, alangidiol and isoalangidiol, two new rearranged hopanes, isolated from the leaves of *Alangium lamarakii*, with *cis*-fused rings D and E. It is however probable that hydroxylation at C-18 in these compounds modifies their biogenesis somewhat.

Assessment of accuracy of optical rotation data

Standard and diagnostic ΔM values for all known stereoskeletal types will, apart from facilitating rapid identification of known compounds and structural elucidation of new ones, provide a means of checking the accuracy of optical rotation data recorded on new compounds and their functional derivatives. The importance of such an exercise lies in the fact that workers sometimes attempt to elucidate the structures of known compounds as a result of wrong and sometimes inconsistent physical data, especially specific rotations, quoted in the literature and in the absence of authentic samples for direct comparison. For example, if a triterpenoid is assigned a Δ^7 euphane skeleton with C-3β hydroxyl, then its ΔM_1 and ΔM_2 values must be +107 and −125 respectively [2]. A significant deviation from these values outside the allowed limits of experimental errors [2] must mean that the specific rotation data recorded on the compounds considered are erroneous and should be ignored. Otherwise the proposed structure is open to question.

The ORD and CD methods have been used extensively for similar purposes as the MRD method and, at present, with a greater degree of certainty. However the ORD and CD methods do not perform the same func-

tions of which the MRD method is capable. Furthermore, when fully developed for all known structural types, the MRD method should provide a much simpler structural tool than the ORD and CD methods. This is because the MRD method does not demand any additional work from the investigator. It simply involves making more use, than hitherto, of physical data which should normally be recorded to characterise triterpenoids obtained from plant extracts.

A major factor which has so far limited the general applicability of the MRD method is purely experimental and has been discussed earlier [2]. Furthermore, the method has, to date, been found to work only for C-3 oxygenated triterpenoids. If such compounds have hydroxyl groups at any other positions (which must be outside ring A) then it must be possible to selectively acetylate and oxidise the C-3 hydroxyl group for the MRD method to be applied. It has, so far, not been possible to correlate the changes in molar optical rotations with structures when bifunctional and polyfunctional transformations (like a dihydroxy to a diacetate or to a diketone) are simultaneously carried out. This constitutes the greatest limitation to the MRD method at present and merits further investigation. Another useful subject for further investigation will be the collation of ΔM values for x-oxygenated compounds (where x represents any position on the ring skeleton and must, on theoretical grounds, be limited to rings A and D preferrably E in a pentacyclic system), provided that there are sufficient numbers of known stereoskeletons for a particular value of x with necessary optical data for x-OH, x-OAc and x-CO.

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