Conformational Analysis of 6-Bromo-7-oxoditerpenoids by Application of the Nuclear Overhauser Effect

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THE stereochemistry of 6-bromo-7-oxoditerpenoids has recently been seriously questioned.[1] However, an *X*-ray structure determination of methyl 6-bromo-12-methoxy-7-oxopodocarpa-8,11,13-trien-16-oate (Ia) has shown unequivocally that the bromine atom possesses an α-configuration and that in the solid state the central ring (ring B) adopts a classical boat conformation.[2] We report on the conformation in solution of the related compound methyl 12-acetoxy-6-bromo-7-oxopodocarpa-8,11,13-trien-16-oate (Ib)[3] by the application of the nuclear Overhauser effect (NOE).[4] The observation of this effect in (Ib) serves not only to define precisely the configuration of the 6-bromine atom but also to give invaluable information on the preferred conformation of ring B in solution. The experimental method is remarkably simple, and in the case of (Ib) consists of recording the ^{1}H n.m.r. spectrum of (Ib) and then of measuring the area of the 6-H signal whilst a second, *saturating*[5] field is applied to the transitions of spatially proximate nuclei. The example we report here is a further demonstration of the power of this experimental method in stereochemical and conformation analysis.

The nuclear Overhauser effect data were obtained for an 0·21M-solution of the bromoketone (Ib) in carbon tetrachloride and for an 0·20M-solution in perdeuterio-acetone. A small quantity (5%) of benzene was added to both solvents to act as an internal frequency–field lock.† The results obtained for both solvents were essentially identical. The percent area increases observed for the 6-H signal when protons proximate to it were saturated are recorded in the Table. The fact that any NOE was observed on saturation of the 17-methyl absorption[6] indicates that the 6-proton must be on the same side of the molecule as the 17-methyl group, that is, the bromine possesses an α-configuration. To place the bromine atom in a β-configuration would mean that the 17-methyl and the 6-proton would be at least 3·5 Å apart, and this distance is too great to permit any observable NOE.[4a] The 21% NOE observed on saturation of the 15-methyl group is considerably greater than the 10% observed on saturation of the 17-methyl group. This implies that the 6-proton is closer to the 15-methyl than the 17-methyl and therefore that the preferred conformation of ring B in solution must be a boat or twist-boat conformation (see Figure) as has been found in the solid state by *X*-ray crystallography.[2] Perhaps even more interesting is the observation of a small (4—5%), but nonetheless reproducible, NOE between the protons on C(5) and C(6). In a half-chair conformation these protons are approximately 3·1—3·2 Å apart‡ and at too great a distance to exhibit any NOE. However, in the boat conformation the C(6) proton has moved around towards the C(5) proton and is 2·9—3·0 Å away and sufficiently close for a small but observable NOE to be present. Likewise, the methyl group of the ester function [18-Me] in one of its preferred conformations is 2·9—3·0 Å away from H(6) and again gives rise to a small NOE. It is our view that, for protons in organic structures, those protons which lie close to, or within, each others van der Waals radius will be able to relax each other efficiently and will therefore show a substantial (*ca.* 20% or greater) NOE. Protons which lie outside each others van der Waals radius will show a smaller and rapidly diminishing NOE.[7]

TABLE

Protons saturated	% Area increase of 6-H signal	Internuclear distance (Å)‡
5-H	4–5	2·95
15-CH$_3$	21	2·6
17-CH$_3$	10	2·3
18-CH$_3$	2—3	3·0

‡ As measured from a Dreiding molecular model.

The configuration and conformation of (Ib) are further supported by the reactivity of the corresponding acid (Ic). Chemical reactivity data has only been used peripherally in discussions on the stereochemistry of 6-bromo-7-oxoditerpenoids. The ester derivatives of compounds related to (Ia) have been examined in base-catalyzed elimination reactions[8] and comment has been made on the direct formation the lactone (II) during the attempted bromination of 12-acetoxy-7-oxopodocarpic acid.[3] We have been able to obtain the

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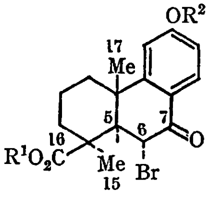
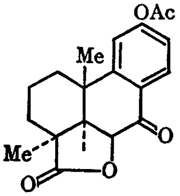
† A Varian HA-100 in frequency sweep mode was used.

‡ As measured from a Dreiding Molecular Model.

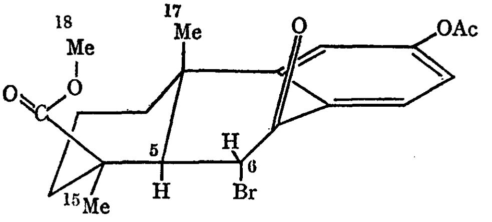
bromo-keto-acid (Ic) (m.p. 89—92°) by bromination of the corresponding keto-acid in glacial acetic acid under carefully controlled conditions. The bromo-ketone was found to be quite unstable in the presence of weak acids or bases. For example, treatment of a chloroform solution of the bromo-acid (Ic) with a trace of pyridine or alternatively mere dissolution in dilute aqueous acetic acid resulted in the rapid and quantitative transformation of (Ic) into the lactone (II).[3] Such behaviour is typical[9] of an intramolecular S_N2 displacement reaction in which the oxygen of the carboxyl group can readily adopt a collinear position with the breaking carbon–bromine bond. From the inspection of a molecular model it is apparent that this requirement can only be met if the bromine possesses an α-configuration and if ring B exists either as a boat conformation or can adopt such a conformation with the expenditure of very little energy.



(I) a; R^1=R^2=Me
b; R^1=Me, R^2=Ac
c; R^1=H, R^2=Ac



(II)



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[5] Care should be taken in distinguishing between the conditions for a saturating field and a decoupling field (see J. D. Baldeschwieler, E. W. Randall, *Chem. Rev.*, 1963, **63**, 81). In many examples a saturating field has proved to be a relatively weak field (R. A. Bell and J. K. Saunders, unpublished results).

[6] For assignment of the principal absorptions in common diterpenes see E. Wenkert, A. Afonso, P. Beak, R. W. J. Charney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, 1965, **30**, 713.

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