The Stereochemistry of 6-Bromo-7-oxoditerpenoids

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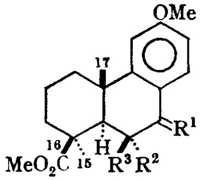
ON the basis of n.m.r. measurements Wheeler and his co-workers[1] have suggested that the bromide of methyl 6-bromo-12-methoxy-7-oxopodocarpa-8,11,13-trien-16-oate (Ib) has a β-configuration rather than the α-configuration assigned by Wenkert,[2] Cambie,[3] and their co-workers. Since Wheeler's arguments appeared to apply equally well for an α-configuration we have determined the structure of (Ib) by X-ray methods in order to obtain an unequivocal solution.

The crystals were orthorhombic with $a = 10{\cdot}85$, $b = 11{\cdot}16$, $c = 15{\cdot}05$ Å and space group $P2_12_12_1$. Three-dimensional intensity data were collected with Cu-K_α radiation and the structure was solved by Patterson and heavy-atom syntheses, the *R*-factor being reduced to 8·8% by least-squares refinements. The analysis confirms that the bromine is α and shows that the conformation of ring-B is nearly a classical boat (see Figure).† The distances of bromine to the carbonyl O, C(15), C(5), and C(7) atoms are 3·25, 3·43, 2·91, and 2·70 Å respectively, while the carbonyl O is 0·61 Å above, and the Br 1·68 Å below the plane of the aromatic ring. The dihedral angle $H_\alpha(C5)–C(6)H_\beta$ is 154 ± 8° in agreement with the observed coupling constant of J = 7 c./sec. from the n.m.r. spectrum. Comparison of (Ib) with (Ia) (see Table) shows that the C(15)-methyl of (Ib) is deshielded by 0·28 p.p.m., an amount comparable to that induced by a 1,3-diaxial interaction in a steroid.[4] Oxidation of (I) to (Ia) causes a deshielding of the C(17)-methyl group but introduction of a C(6)-bromine (Ib) then causes a shielding with respect to (Ia). This can be interpreted as a change in conformation of ring-B from a half-boat (Ia) to a boat, the C(17)-methyl of (Ib) thus entering the cone of shielding of the carbonyl group. However, such first-order approximations do not correlate with the chemical shifts observed for related diterpenoids [*e.g.* (II), (III), and (IV)], and thus the shift of the C(17)-methyl group cannot be satisfactorily interpreted in terms of the expected shielding by the C(7)-carbonyl group alone. For example, conversion of totaryl methyl ether (III) to (IIIa) causes the C(17)-methyl to be shielded by 0·11 p.p.m. while subsequent introduction of a C(6)-bromine atom causes a further deshielding of 0·13 p.p.m. rather than shielding. If the bromine here possessed a β-configuration [*i.e.* (IIIc)] a marked deshielding of both the C(17)- and C(16)-methyl groups would be expected as is shown below.

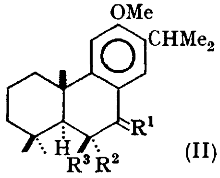
TABLE

N.m.r. data (δ) *for methyl groups of diterpenoids*

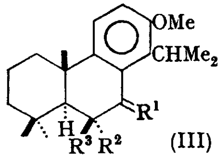
	$R^1=H_2,R^2=R^3=H$				$R^1=O,R^2=R^3=H$				$R^1=O,R^2=Br,R^3=H$				$R^1=O,R^2=H,R^3=Br$		
	C(15)	C(16)	C(17)		(C15)	C(16)	(C17)		C(15)	C(16)	C(17)		C(15)	C(16)	C(17)
(I)	1·27	—	1·03	(Ia)	1·25	—	1·10	(Ib)	1·53	—	0·85	(Ic)	—	—	—
(II)	0·94	0·94	1·19	(IIa)	0·93	1·00	1·25	(IIb)	1·15	1·03	1·27	(IIc)	1·10	1·43	1·77
(III)	0·95	0·95	1·21	(IIIa)	0·91	1·01	1·10	(IIIb)	1·15	1·08	1·23	(IIIc)	—	—	—
(IV)	—	1·25	1·20	(IVa)	—	1·33	1·26	(IVb)	—	1·50	1·26	(IVc)	—	—	—



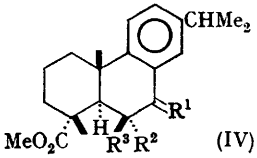
(I)



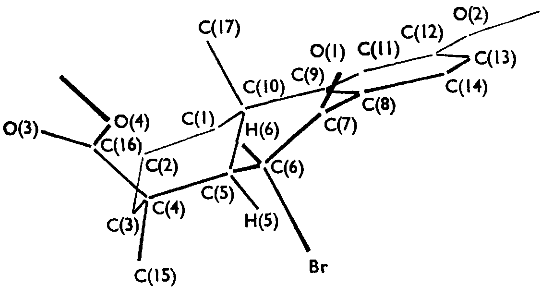
(II)



(III)



(IV)



FIGURE

Re-investigation of the bromination of sugiyl methyl ether (II) which earlier gave a 6β-bromo-derivative,[3] has now afforded two epimers, m.p.'s 199° and 156°, which have been assigned the 6β-bromo- and 6α-bromo-structures, (IIb) and (IIc), respectively. Whereas the C(16)- and C(17)-methyl groups of the β-epimer are deshielded by 0·43 and 0·03 p.p.m. those of the 6α-isomer are only deshielded by 0·10 and 0·03 p.p.m. Moreover the C(15)-methyl group of (IIc) shows a marked deshielding (0·22 p.p.m.) as would be expected for a 6α-bromo-configuration. Dreiding models of the 6β-isomer (IIb) give an $H_\alpha C(5)–C(6)H_\alpha$ dihedral angle of *ca.* 60° for a ring-B half-boat conformation in agreement with a coupling constant of 3 c./sec. A model of the 6α-isomer (IIc) with a ring-B boat conformation gives a didedral angle of *ca.* 130° in agreement with the observed coupling constant of 8·5 c./sec.

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† Full details of this analysis will be published elsewhere.

Thus configuration of C(6)-bromo-derivatives of 7-oxoditerpenoids is best assigned by a consideration of the deshielding effects of the bromine atom. Bromination of methyl 7-oxoabieta-8,11,13-trien-15-oate (IV) produces no shift in the C(17)-methyl resonance but the C(16)-methyl is deshielded by 0·17 p.p.m., and hence a 6α-bromo-configuration can be assigned here. A coupling constant of 12·5 c./sec. indicates a dihedral angle $H_\alpha C(5)$-$C(6)H_\beta$ of about 150°, a result consistent with a ring-B boat conformation. This conformation would be similar to that of (IIc) but with the C(6)-bromine twisted slightly upwards to increase the dihedral angle as a result of interaction with the C(15)-carboxymethyl group.

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[4] N. S. Bhacca and D. H. Williams, "Applications of N.M.R. Spectroscopy in Organic Chemistry," Holden Day, San Francisco, 1964, pp. 19–21.