

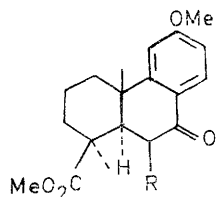
Conformations of Diterpenoids: An X-Ray Determination of the Molecular Structure of 6 α -Bromo-13-hydroxy-14-isopropylpodocarpa-8,11,13-trien-7-one and of the Structure and Absolute Configuration of Methyl 6 α -Bromo-13-isopropyl-7-oxopodocarpa-8,11,13-trien-15-oate

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The crystal and molecular structures of the title compounds have been determined by X-ray diffraction methods from photographic data by the heavy-atom method: the absolute configuration was established for the second named. Crystals of the former (II) are tetragonal, $a = 12.54$, $c = 23.97$ Å, space group $P4_12_12$; the structure was refined by least squares to R 0.088. The latter (III) is triclinic, $a = 6.20$, $b = 7.73$, $c = 10.79$ Å, $\alpha = 97.0$, $\beta = 79.3$, $\gamma = 104.6^\circ$, space group $P1$; refined to R 0.064. In (II) ring A has a chair conformation with a *trans* A/B ring fusion; ring B has an approximate boat conformation and the bromine atom has the α -configuration. The bromine is in the same configuration in compound (III) and ring A also adopts the chair conformation. There is *trans* A/B ring fusion with ring B somewhat distorted but describable as a 'half-boat'. The stereochemistries at asymmetric centres confirm earlier evidence. There is considerable variation in detailed conformation, however, and a comparison between these compounds and with the molecular structure of methyl 6 α -bromo-12-methoxy-7-oxopodocarpa-8,11,13-trien-16-oate leads to the view that steric rather than electronic factors are largely responsible for the path of bromine attack.

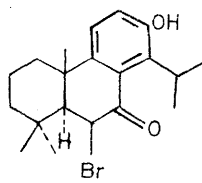
THE application of spectroscopic techniques to the elucidation of the stereochemistry of 6-bromo-7-oxo-derivatives of ring-C aromatic diterpenes has produced a conflict of interpretations requiring more definitive evidence. These range from earlier difficulties in assigning an α - or β -configuration to the bromine atom¹ to later observations of anomalous spectral results among members of the series.²

On the basis of i.r. and u.v. measurements an α -configuration was originally suggested for the bromine atom in the 6-bromo-7-oxo-derivative (I) of podocarpaic acid.

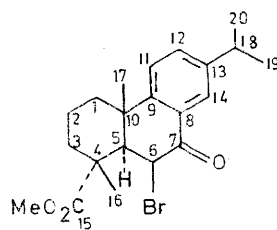


(I) R = Br

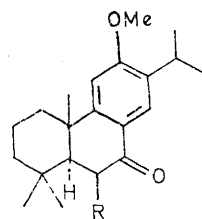
(Ia) R = H



(II)



(III)



(IV) R = Br

(IVa) R = H

A 17 cm^{-1} shift to higher frequency in the carbonyl i.r. band and a bathochromic shift of only 5 nm in the u.v.

¹ E. Wenkert, P. Beak, R. W. J. Carney, J. W. Chamberlain, D. B. R. Johnston, C. D. Roth, and A. Tahara, *Canad. J. Chem.*, 1963, **41**, 1924.

² A. K. Bose, M. S. Manhas, and R. C. Cambie, *J. Org. Chem.*, 1965, **30**, 501.

³ S. Winstein, D. Darwish, and N. Holness, *J. Amer. Chem. Soc.*, 1956, **78**, 2915.

absorption maximum, when compared with unbrominated ketones, was taken as evidence for this assignment.³ Purely *a priori* considerations were also thought to favour the α -configuration since strong steric interference by the axial substituents at C(4) and C(10) would inhibit the usual axial approach of the brominating agent. It has been suggested that only slight bond distortions would be needed to permit full π -orbital overlap in the transition state resulting from an equatorial approach.

Later it was shown that the n.m.r. spectra of a number of 6-bromo-7-oxo-diterpenoids all showed, with one exception, coupling constants of 6–7 Hz for the C(5), C(6) protons.² This was then interpreted by means of the Karplus equation as implying an α -configuration for the bromine atom in accord with a dihedral $\text{H}\alpha\text{C}(5)\text{--C}(6)\text{H}\beta$ angle of 140° . The Karplus equation also predicts an angle of 20° for a 7 Hz coupling constant and this interpretation, and a consequent β -configuration for the bromine atom, was subsequently pressed.⁴ The strong deshielding of the C(15) methyl group and the positive o.r.d. shift observed on bromination of the 7-oxo-derivative (Ia) were quoted in support of this.

The lack of correlation between o.r.d., c.d., and u.v. spectral observations among various 6-bromo-7-oxo-diterpenoids has also been noted^{5,6} and two members [(II) and (III)] have aroused interest as a result of their contrasting n.m.r. spectra. One of these, methyl 6-bromo-13-isopropyl-7-oxopodocarpa-8,11,13-trien-15-oate (III) has a C(5), C(6) proton coupling constant of 12 Hz, markedly different from the expected value of 6–7 Hz. This again suggested that the bromine atom possessed the β -configuration. Alternatively ring B must be sufficiently distorted to allow the two protons to lie almost diaxially. The other compound, 6-bromo-13-hydroxy-14-isopropylpodocarpa-8,11,13-trien-7-one (6-bromo-7-oxototarol) (II), showed the 7 Hz coupling

⁴ A. E. Lickei, A. C. Rieke, and D. M. S. Wheeler, *J. Org. Chem.*, 1967, **32**, 1647.

⁵ R. C. Cambie, G. R. Clark, D. R. Crump, and T. N. Waters, *Chem. Comm.*, 1968, 183.

⁶ R. C. Cambie, D. R. Crump, W. A. Denny, and T. J. Fullerton, *Austral. J. Chem.*, 1971, **24**, 1237.

constant but the C(17) methyl group of the parent was first shielded upon oxidation to the ketone and then de-shielded on bromination, a result which does not parallel behaviour in the corresponding podocarpate derivatives.

The X-ray structural study of methyl 6-bromo-12-methoxy-7-oxopodocarpa-8,11,13-trien-16-oate (I) revealed an α -bromo configuration with ring B in an almost classical boat conformation.⁷ The observed dihedral angle, H α C(5)-C(6)H β , of 154° agrees with the measured coupling constant of 7 Hz.

To provide further definitive information on the bromine configuration in view of the conflicting n.m.r. evidence from (III) and to investigate the relation between structure and spectroscopic results compounds (II) and (III) were chosen for an X-ray diffraction study.

EXPERIMENTAL

(A) 6-Bromo-13-hydroxy-14-isopropylpodocarpa-8,11,13-trien-7-one (6-Bromo-7-oxototarol) (II)

Totaryl acetate was treated to form the 7-oxo-derivative and subsequently brominated. After heating under reflux with sodium hydrogen carbonate in aqueous methanol the product was isolated and colourless crystals (unequally truncated tetragonal bipyramid) obtained from methanol.

Crystal Data.—C₂₀H₂₇BrO₂, *M* = 379.4. Tetragonal, *a* = *b* = 12.45(2), *c* = 23.97(4) Å, * *U* = 3769 Å³, *D_m* (by flotation) = 1.32, *Z* = 8, *D_c* = 1.337, *F*(000) = 1576. Space group *P*4₁2₁2 or *P*4₃2₁2. Cu-*K α* radiation λ = 1.5418 Å μ (Cu-*K α*) = 33.4 cm⁻¹ (1 Å \equiv 10⁻¹ nm).

Intensity data were collected by Weissenberg photography for the reciprocal lattice sections 0-*hkl*, the data being self-correlating to give 1077 independent reflexions (50% of the copper sphere). One crystal (maximum dimensions 0.28 × 0.19 × 0.19 mm) was used throughout although a darkening in colour suggested some decomposition. Absorption corrections were made.⁸

The space group was assumed to be *P*4₁2₁2 and the phase problem solved through the heavy-atom approach. Refinement was by the block-diagonal least-squares approximation. An adjustment of -0.95 e was applied to the atomic scattering factor for bromine as an approximate correction for dispersion. Observations were weighted by the relation $w = [1 + (F_0 - b)^2/a^2]^{-1}$ with *a* and *b* adjusted to maintain reasonably constant values of $\langle w\Delta^2 \rangle$ over $|F_0|$ ranges. *R* converged at 0.231 for a model which excluded hydrogen atoms and assumed individual isotropic temperature parameters. With the bromine vibrations described anisotropically, *R* was reduced to 0.116. A difference-Fourier synthesis then showed the approximate positions of all hydrogen atoms and these were added to the model at calculated co-ordinates and temperature factors of 5.0 Å². Their parameters were not refined subsequently. The last cycles of adjustments, in which all non-hydrogen atoms were assigned anisotropic vibrational parameters, were undertaken with a full-matrix least-squares program to produce a final *R* of 0.088. The improvements in *R* at the various stages of refinement were all shown to be statistically significant at the 0.5% level.⁹

Atom positions and their standard deviations are listed

* For both compounds, the camera was calibrated with a sodium chloride crystal; standard deviations are from the spread of independent measurements.

† For details see Notice to Authors No. 7 in *J.C.S. Dalton*, 1972, Index issue.

in Table 1, temperature factor data in Table 2, and calculated bond lengths and angles in Tables 3 and 4. Structure factors are listed in Supplementary Publication No. SUP 20801 (7 pp.).† The numbering system for crystallography is that of Figure 1. Hydrogen atoms are numbered to the atoms to which they are attached.

TABLE I
Atom positions for molecule (II)

Atom	$\frac{x}{a}$	$\frac{y}{b}$	$\frac{z}{c}$
Br(1)	0.3138(2)	0.5699(2)	0.1563(1)
O(1)	0.4597(10)	0.7307(9)	0.0738(5)
O(2)	0.5928(8)	0.9267(8)	0.2577(5)
C(1)	0.7096(12)	0.4515(11)	0.1773(6)
C(2)	0.7101(15)	0.3385(11)	0.1525(7)
C(3)	0.5948(14)	0.2931(12)	0.1489(7)
C(4)	0.5190(12)	0.3656(11)	0.1157(6)
C(5)	0.5266(11)	0.4802(11)	0.1407(5)
C(6)	0.4460(12)	0.5547(12)	0.1141(6)
C(7)	0.4826(10)	0.6737(11)	0.1136(7)
C(8)	0.5469(10)	0.7065(10)	0.1617(6)
C(9)	0.6282(11)	0.6352(11)	0.1775(5)
C(10)	0.6395(10)	0.5291(10)	0.1452(5)
C(11)	0.6957(12)	0.6632(11)	0.2185(6)
C(12)	0.6852(11)	0.7637(11)	0.2441(6)
C(13)	0.6041(11)	0.8313(10)	0.2289(6)
C(14)	0.5318(11)	0.8086(11)	0.1878(6)
C(15)	0.4032(16)	0.3203(15)	0.1230(9)
C(16)	0.5466(16)	0.3577(14)	0.0516(7)
C(17)	0.6941(12)	0.5557(12)	0.0877(6)
C(18)	0.4403(11)	0.8780(11)	0.1740(6)
C(19)	0.4845(15)	0.9845(14)	0.1483(8)
C(20)	0.3670(14)	0.8974(17)	0.2218(8)
H(1,1) *	0.681	0.455	0.217
H(1,2)	0.790	0.475	0.171
H(2,1)	0.726	0.351	0.108
H(2,2)	0.750	0.282	0.183
H(3,1)	0.562	0.292	0.195
H(3,2)	0.606	0.229	0.124
H(5,1)	0.495	0.475	0.180
H(6,1)	0.440	0.540	0.070
H(11,1)	0.740	0.615	0.244
H(12,1)	0.749	0.810	0.258
H(hydroxy)	0.660	0.955	0.274
H(15,1)	0.349	0.371	0.114
H(15,2)	0.420	0.240	0.105
H(15,3)	0.403	0.323	0.172
H(16,1)	0.625	0.385	0.043
H(16,2)	0.500	0.380	0.015
H(16,3)	0.540	0.277	0.045
H(17,1)	0.758	0.595	0.098
H(17,2)	0.660	0.610	0.050
H(17,3)	0.700	0.483	0.065
H(18,1)	0.400	0.840	0.140
H(19,1)	0.480	0.980	0.105
H(19,2)	0.423	1.040	0.152
H(19,3)	0.560	1.000	0.162
H(20,1)	0.330	0.826	0.244
H(20,2)	0.305	0.950	0.233
H(20,3)	0.403	0.900	0.265

* The first number in parentheses indicates the carbon atom to which the hydrogen is bonded.

Results for (II).—The standard deviations listed for bond lengths and angles are those derived from the least-squares variances and include correlation effects.

Figure 1 illustrates the overall molecular geometry. The aromatic ring is planar (Table 5); ring A has the chair conformation with a *trans* A/B ring fusion; ring B has an approximate boat conformation and the bromine atom on

⁷ G. R. Clark and T. N. Waters, *J. Chem. Soc. (C)*, 1970, 887.

⁸ W. R. Busing and H. A. Levy, *Acta Cryst.*, 1957, **10**, 180.

⁹ W. C. Hamilton, *Acta Cryst.*, 1965, **18**, 502.

TABLE 2
Anisotropic thermal parameters * for molecule (II)
($\times 10^4$)

Atom	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
Br(1)	45(1)	89(2)	63(1)	-10(2)	22(2)	-41(2)
O(1)	102(11)	45(7)	19(2)	65(15)	-49(9)	2(8)
O(2)	53(8)	53(8)	24(3)	4(13)	-2(8)	-34(8)
C(1)	57(12)	27(9)	19(3)	60(17)	-13(10)	-15(9)
C(2)	95(15)	24(10)	26(4)	44(20)	-43(13)	-20(10)
C(3)	91(16)	34(11)	20(4)	-29(21)	-15(14)	-11(10)
C(4)	48(11)	30(10)	14(3)	-47(17)	-6(10)	-13(9)
C(5)	44(10)	28(9)	12(3)	-36(15)	0(9)	-4(9)
C(6)	38(10)	52(11)	18(3)	-1(16)	-12(9)	-26(11)
C(7)	23(9)	28(10)	20(4)	22(16)	-10(9)	-14(10)
C(8)	34(9)	26(9)	13(3)	-22(15)	-12(9)	-7(9)
C(9)	40(10)	28(9)	11(3)	29(15)	-1(9)	-16(9)
C(10)	36(9)	16(8)	10(3)	11(14)	5(9)	0(8)
C(11)	46(10)	47(11)	14(3)	-2(18)	-11(10)	-22(10)
C(12)	43(9)	38(9)	16(3)	-2(18)	5(11)	-5(10)
C(13)	44(10)	16(9)	15(3)	-24(16)	13(9)	-22(8)
C(14)	45(10)	31(9)	11(3)	18(18)	-9(9)	-8(9)
C(15)	83(17)	58(13)	38(6)	-36(26)	-3(15)	-38(15)
C(16)	108(17)	58(12)	14(3)	-46(24)	-4(13)	-30(11)
C(17)	58(11)	44(10)	18(3)	-20(19)	34(11)	-9(10)
C(18)	30(9)	36(10)	20(4)	52(17)	-1(10)	-10(10)
C(19)	77(15)	43(12)	33(5)	-8(21)	-49(15)	38(13)
C(20)	47(12)	111(19)	25(5)	82(25)	18(12)	-10(15)

* The scattering factor is expressed as $f = f_0 \exp -(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)$.

TABLE 3
Bond lengths (Å) within molecule (II)

Br(1)-C(6)	1.95(2)	C(7)-C(8)	1.47(2)
O(1)-C(7)	1.23(2)	C(8)-C(9)	1.41(2)
O(2)-C(13)	1.39(2)	C(8)-C(14)	1.44(2)
C(1)-C(2)	1.54(2)	C(9)-C(10)	1.55(2)
C(1)-C(10)	1.52(2)	C(9)-C(11)	1.35(2)
C(2)-C(3)	1.56(3)	C(10)-C(17)	1.57(2)
C(3)-C(4)	1.54(2)	C(11)-C(12)	1.41(2)
C(4)-C(5)	1.56(2)	C(12)-C(13)	1.37(2)
C(4)-C(15)	1.57(2)	C(13)-C(14)	1.37(2)
C(4)-C(16)	1.58(2)	C(14)-C(18)	1.48(2)
C(5)-C(6)	1.52(2)	C(18)-C(19)	1.59(2)
C(5)-C(10)	1.55(2)	C(18)-C(20)	1.49(2)
C(6)-C(7)	1.56(2)		

TABLE 4
Bond angles (deg.) within molecule (II) *

C(2)-C(1)-C(10)	113	C(8)-C(9)-C(10)	119
C(1)-C(2)-C(3)	111	C(8)-C(9)-C(11)	119
C(2)-C(3)-C(4)	113	C(10)-C(9)-C(11)	122
C(3)-C(4)-C(5)	108	C(1)-C(10)-C(5)	108
C(3)-C(4)-C(15)	108	C(1)-C(10)-C(9)	111
C(3)-C(4)-C(16)	109	C(1)-C(10)-C(17)	109
C(5)-C(4)-C(15)	110	C(5)-C(10)-C(9)	107
C(5)-C(4)-C(16)	115	C(5)-C(10)-C(17)	115
C(15)-C(4)-C(16)	107	C(9)-C(10)-C(17)	107
C(4)-C(5)-C(6)	111	C(9)-C(11)-C(12)	120
C(4)-C(5)-C(10)	117	C(11)-C(12)-C(13)	120
C(6)-C(5)-C(10)	113	O(2)-C(13)-C(12)	118
Br(1)-C(6)-C(5)	114	O(2)-C(13)-C(14)	118
Br(1)-C(6)-C(7)	99	C(12)-C(13)-C(14)	124
C(5)-C(6)-C(7)	113	C(8)-C(14)-C(13)	114
O(1)-C(7)-C(6)	120	C(8)-C(14)-C(18)	122
O(1)-C(7)-C(8)	125	C(13)-C(14)-C(18)	124
C(6)-C(7)-C(8)	115	C(14)-C(18)-C(19)	114
C(7)-C(8)-C(9)	116	C(14)-C(18)-C(20)	109
C(7)-C(8)-C(14)	121	C(19)-C(18)-C(20)	112
C(9)-C(8)-C(14)	123		

* The standard deviation is 1° in each instance.

C(6) is shown to be in the α -configuration. The configuration of the molecule as drawn in the diagram agrees with that deduced from other evidence^{10,11} and the space group is therefore confirmed as being $P4_22_2$.

Planes of best fit calculated for various groups of atoms

are tabulated in Table 5 together with distances therefrom and may be used to assess steric features of the molecule. The carbonyl oxygen is thus seen to be twisted from the plane defined by the aromatic nucleus in a direction which places it on the opposite side of the molecule from the

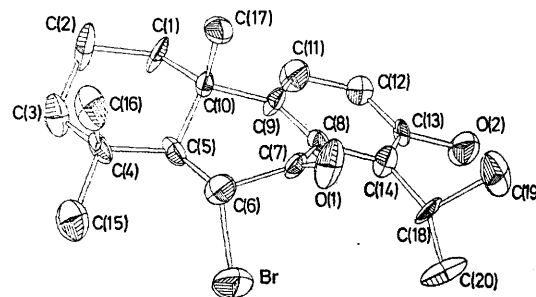


FIGURE 1 An ORTEP diagram of molecule (II)

TABLE 5
Planes of best fit and deviations (Å) therefrom: molecule (II). Equations are expressed in the cosine form $lX + mY + nZ + p = 0$, with reference to cell axes, and with p in Å units.

Ring A planes defined by	l	m	n	p
(a) C(1), C(2), C(4), C(5)	-0.374	-0.348	0.860	1.654
(b) C(2), C(3), C(5), C(10)	-0.086	0.046	0.995	-3.072
(c) C(1), C(3), C(4), C(10)	-0.563	0.131	0.816	0.801

Deviations from:

(a)	(b)	(c)			
C(1)	0.011	C(2)	-0.007	C(1)	0.003
C(2)	-0.010	C(3)	0.007	C(3)	-0.003
C(4)	0.010	C(5)	-0.007	C(4)	0.003
C(5)	-0.011	C(10)	0.007	C(10)	-0.003
C(3)	0.655	C(1)	0.652	C(2)	-0.672
C(10)	-0.661	C(4)	-0.661	C(5)	0.626

Ring B plane defined by:

(d) C(5), C(6), C(8), C(9)	-0.521	-0.103	0.874	1.258
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Deviations from (d):

C(5)	0.056	C(9)	-0.060	O(1)	-1.189
C(6)	-0.055	C(7)	-0.456	Br(1)	1.647
C(8)	0.059	C(10)	-0.653		

Benzene ring plane defined by:

(e) C(8), C(9), C(11)-14)	-0.607	-0.413	0.680	5.172
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Deviations from (e):

C(8)	-0.007	C(5)	0.975	C(20)	1.353
C(9)	0	C(6)	0.769	O(1)	-0.902
C(11)	0.010	C(7)	-0.132	O(2)	0.069
C(12)	-0.013	C(10)	-0.063	Br(1)	2.384
C(13)	0.006	C(18)	0.116		
C(14)	0.004	C(19)	-1.200		

bromine atom. The dihedral angle O(4)C(7)-C(6)Br is 94° which may be compared with the 30° expected for an 'ideal' geometry in which the keto-aryl system is planar. Ring A can be seen to have a classical chair conformation and ring B to closely approximate to a boat geometry.

Some non-bonded intramolecular approaches are quoted in Table 6. These show that the bromine atom is situated almost equidistant from the keto-oxygen, O(1), and from C(15), although the closest approaches are from H(5,1) and H(15,1). Intermolecular distances less than the sum of

¹⁰ W. F. Short and H. Stromberg, *J. Chem. Soc.*, 1937, 516.

¹¹ Y.-L. Chow and H. Erdtman, *Acta Chem. Scand.*, 1962, **16**, 1291, 1305.

van der Waals radii are also listed in Table 6 and indicate that the only significant interaction is the one involving the

TABLE 6

Intra- and inter-molecular distances (Å): molecule (II)

Br(1) ··· O(1)	3·37	O(1) ··· H(18,1)	2·23
Br(1) ··· C(15)	3·42	C(15) ··· C(16)	2·53
Br(1) ··· C(5)	2·92	C(15) ··· H(16,3)	2·60
Br(1) ··· C(7)	2·69	C(15) ··· H(5,1)	2·64
Br(1) ··· H(5,1)	2·63	C(16) ··· H(15,2)	2·52
Br(1) ··· H(6,1)	2·63	C(17) ··· H(16,1)	2·55
Br(1) ··· H(15,1)	2·73	O(1) ··· O(2')	2·75
O(1) ··· H(6,1)	2·41		

oxygen atoms in what is clearly a hydrogen bond. Geometrical details are given in Table 7. This hydrogen atom

TABLE 7

Geometry of the hydrogen bond in structure (II)

(a) Distances (Å)			
O(1) ··· O(2')	2·75	H'-O(2')	1·00
O(1) ··· H'	1·82		
(b) Angles (°)			
O(1) ··· H'-O(2')	155	H'-O(2')-C(13')	114
C(7)-O(1) ··· H'	163		

was placed with reference to the electron-density map since it alone was not defined by the molecular skeleton. The angle at this atom, O(1) ··· H-O(2') 155°, is unremarkable

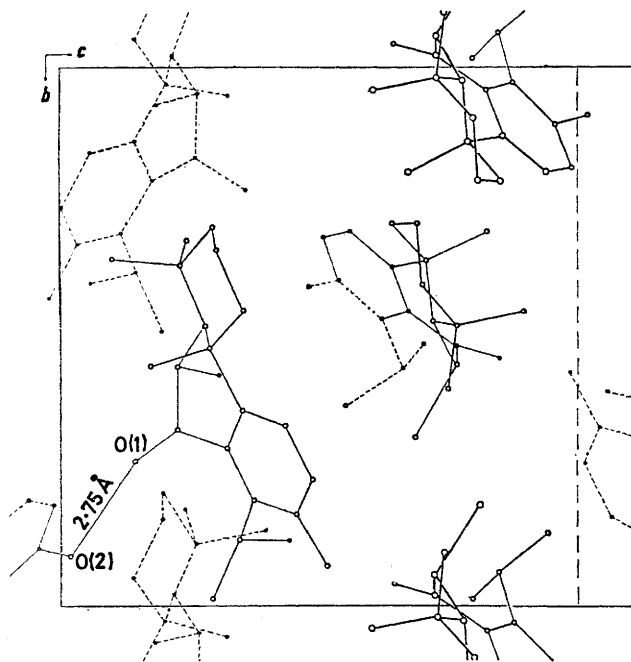


FIGURE 2 Crystal structure of (II) projected down a

since non-linearity of this magnitude is often observed even if the likely errors in placing the hydrogen are ignored.

The anisotropy allowed in the model, demonstrated as being significant, is confirmed by Figure 1 which also presents the vibrational ellipsoids. Atoms such as C(1), C(2), and C(3) which are not closely constrained vibrate perpendicularly to their bonding directions whereas the keto-oxygen, O(1), which is twisted out-of-plane by steric forces is seen to oscillate strongly along the direction of displacement. The bromine atom vibrates similarly although the

diagram does not represent the principal axis of vibration very clearly. No pronounced rigid-body motion seems evident.

A packing diagram of the crystal structure is shown in Figure 2.

(B) *Methyl 6-Bromo-13-isopropyl-7-oxopodocarpa-8,11,13-trien-15-oate* (6-Bromo-7-oxodehydroabietate) (III)

Methyl dehydroabietate was prepared by esterification with ethereal diazomethane. Oxidation with chromium trioxide in glacial acetic acid gave the keto-ester which was subsequently brominated with bromine-glacial acetic acid-hydrogen bromide. Recrystallisation from chloroform-light petroleum gave colourless needles, m.p. 155–156 °C, approximately diamond-shaped in cross-section.

Crystal Data.— $C_{21}H_{27}BrO_3$, $M = 407·4$. Triclinic, $a = 6·20(1)$, $b = 7·73(1)$, $c = 10·79(2)$ Å, $\alpha = 97·0(3)$, $\beta = 79·3(3)$, $\gamma = 104·6(3)$ °. (The cell corresponds to the Dirichlet reduced cell¹² with the origin at a non-standard corner), $U = 490$ Å³, $D_m = 1·36$ (by flotation), $Z = 1$, $D_c = 1·38$, $F(000) = 212$. Space group $P1$. $\mu(\text{Cu-K}\alpha) = 32·9$ cm⁻¹.

Intensity data were collected by Weissenberg photography for the reciprocal lattice sections $0-4kl$ (maximum crystal dimensions $0·25 \times 0·10 \times 0·10$ mm) and $hk0-3$ (maximum dimensions $0·26 \times 0·08 \times 0·12$ mm), the needle direction corresponding to a . Some decomposition occurred as evidenced by discolouration and loss of diffracting power and absorption corrections were not therefore applied.

The heavy atom was used to define the cell origin, and thus the approximate phases, for a first electron-density map. Most of the carbon skeleton of the molecule was recognised, remaining atoms being found in a subsequent map. Block-diagonal least-squares refinement of a model allowing increasing degrees of freedom lead to a final R of 0·064 for 1557 data (70% of copper sphere). Hydrogen atoms were included at calculated positions, the remaining atoms being ascribed individual anisotropic temperature factors. Improvements in R at each relaxation in the model were shown to be significant at the 0·5% level⁹ and the values of a and b in the weighting formula were adjusted at intervals to keep $\langle w\Delta^2 \rangle$ as constant as possible over $|F_o|$ ranges.

The absolute configuration of the molecule was found by standard methods.^{13,14} Of 46 reflexions, for which both calculated and observed differences between the intensities of Friedel pairs was equal to or greater than 10% of $I(hkl)_{\text{calc}}$ or $I(hkl)_{\text{obs}}$, respectively, 37 (80%) showed agreement between observation and theory. The (+)-configuration as used in the original molecular model is thus confirmed as being the correct one, a result in accord with chemical evidence.^{10,11}

Atom positions with standard deviations are listed in Table 8, and temperature factor data in Table 9. Calculated bond lengths and angles are quoted in Tables 10 and 11. The crystallographic numbering scheme is shown in Figure 3, hydrogen atoms again being numbered according to their parent atoms.

Results for (III).—Standard deviations were derived from the block-diagonal least-squares refinement process and are likely to be under-estimated. Values calculated from the

¹² V. Balashov and H. D. Ursell, *Acta Cryst.*, 1957, **10**, 582.

¹³ J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, *Nature*, 1951, **168**, 271.

¹⁴ J. M. Bijvoet, *Nature*, 1954, **173**, 888.

spread of chemically identical bond lengths and angles confirm this, σ for carbon-carbon single-bonds being determined as 0.026 Å (*vs.* a mean of 0.015 Å from the

TABLE 8
Atom positions for molecule (III)

Atom	$\frac{x}{a}$	$\frac{y}{b}$	$\frac{z}{c}$
Br	0	0	0
O(1)	-0.0493(17)	0.1390(10)	0.2684(9)
O(2)	-0.1068(16)	-0.3778(14)	-0.2053(8)
O(3)	-0.4250(14)	-0.3101(13)	-0.1064(8)
C(1)	-0.5539(18)	-0.5653(13)	0.2478(9)
C(2)	-0.4666(20)	-0.6949(14)	0.1453(11)
C(3)	-0.4118(18)	-0.6166(13)	0.0148(10)
C(4)	-0.2279(17)	-0.4380(12)	0.0135(9)
C(5)	-0.2936(16)	-0.3092(12)	0.1318(9)
C(6)	-0.1269(26)	-0.1348(14)	0.1426(12)
C(7)	-0.1780(20)	-0.0109(13)	0.2558(10)
C(8)	-0.3771(18)	-0.0722(13)	0.3512(9)
C(9)	-0.4831(16)	-0.2561(13)	0.3505(9)
C(10)	-0.3751(15)	-0.3870(12)	0.2621(9)
C(11)	-0.6670(17)	-0.3032(17)	0.4480(10)
C(12)	-0.7470(21)	-0.1832(21)	0.5331(11)
C(13)	-0.6458(19)	0.0001(19)	0.5327(11)
C(14)	-0.4612(18)	0.0559(16)	0.4397(10)
C(15)	-0.2398(18)	-0.3712(15)	-0.1097(10)
C(16)	0.0045(21)	-0.4732(18)	0.0101(15)
C(17)	-0.1827(19)	-0.4180(16)	0.3232(11)
C(18)	-0.7445(25)	0.1299(27)	0.6271(16)
C(19)	-0.9506(26)	0.1709(24)	0.5957(18)
C(20)	-0.6087(32)	0.2517(31)	0.7032(21)
C(21)	-0.4515(30)	-0.2423(24)	-0.2240(14)
H(1,1)	-0.675	-0.518	0.219
H(1,2)	-0.561	-0.620	0.333
H(2,1)	-0.319	-0.712	0.170
H(2,2)	-0.575	-0.822	0.140
H(3,1)	-0.542	-0.568	-0.011
H(3,2)	-0.340	-0.700	-0.061
H(5,1)	-0.432	-0.264	0.120
H(6,1)	0.035	-0.155	0.148
H(11,1)	-0.710	-0.440	0.469
H(12,1)	-0.882	-0.222	0.600
H(14,1)	-0.375	0.205	0.440
H(16,1)	0.061	-0.570	-0.067
H(16,2)	0.102	-0.345	0.022
H(16,3)	0.010	-0.535	0.100
H(17,1)	-0.080	-0.285	0.319
H(17,2)	-0.135	-0.530	0.260
H(17,3)	-0.245	-0.480	0.400
H(18,1)	-0.799	0.052	0.725
H(19,1)	-1.030	0.260	0.670
H(19,2)	-0.930	0.220	0.500
H(19,3)	-1.060	0.040	0.595
H(20,1)	-0.512	0.190	0.766
H(20,2)	-0.700	0.320	0.775
H(20,3)	-0.530	0.350	0.648
H(21,1)	-0.610	-0.260	-0.235
H(21,2)	-0.345	-0.310	-0.290
H(21,3)	-0.390	-0.100	-0.220

variances), σ for benzene bonds as 0.026 Å (*vs.* 0.016 Å), and for benzene angles at 2.8° (1.0°).

Figure 3 indicates the molecular geometry. The bromine atom is in the α -configuration and the stereochemistries at the asymmetric centres C(4), C(5), and C(10) are as expected from chemical evidence. Ring A adopts the chair conformation with a *trans* A/B ring fusion. Ring B is somewhat distorted but can be described as 'half-boat' in which C(10) is the 'bow' atom. The aromatic ring is planar. Table 12 listing planes of best fit and deviations therefrom gives a more quantitative description of the skeletal geometry.

The carbonyl oxygen, O(1), attached to C(7) is twisted out of the plane of the aromatic nucleus; the dihedral angle

TABLE 9
Anisotropic thermal parameters * for molecule (III)
($\times 10^4$)

Atom	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
Br(1)	517(4)	199(2)	99(1)	-103(4)	51(3)	70(2)
O(1)	546(35)	151(13)	161(10)	-88(38)	-59(32)	-48(20)
O(2)	476(33)	416(22)	87(7)	218(46)	109(27)	44(22)
O(3)	333(26)	407(21)	104(7)	179(38)	-78(24)	131(20)
C(1)	244(32)	168(16)	92(9)	-54(40)	-105(29)	51(20)
C(2)	324(36)	165(18)	129(11)	-132(45)	-186(33)	26(24)
C(3)	236(31)	140(16)	109(10)	20(39)	-73(30)	-6(22)
C(4)	227(29)	156(15)	88(9)	120(36)	-2(29)	-19(20)
C(5)	185(27)	140(15)	81(8)	42(35)	-35(26)	9(19)
C(6)	588(55)	136(16)	117(11)	-147(52)	82(43)	-39(24)
C(7)	396(39)	161(17)	97(9)	98(43)	-14(34)	13(22)
C(8)	233(29)	181(17)	85(9)	96(38)	-64(28)	9(21)
C(9)	216(29)	205(17)	66(8)	139(37)	-22(27)	20(20)
C(10)	151(26)	136(15)	98(9)	29(34)	-36(27)	15(20)
C(11)	208(31)	337(26)	93(9)	106(47)	-31(31)	85(26)
C(12)	266(36)	487(35)	85(10)	316(58)	-50(33)	-108(32)
C(13)	289(31)	491(30)	98(10)	525(45)	-155(31)	-177(29)
C(14)	290(32)	306(24)	105(10)	339(44)	-162(31)	-113(27)
C(15)	230(32)	240(21)	93(10)	70(44)	-43(31)	-10(25)
C(16)	160(24)	286(25)	153(12)	220(39)	3(30)	-39(30)
C(17)	275(33)	255(22)	108(10)	145(45)	-162(31)	21(25)
C(18)	509(45)	845(52)	192(17)	886(70)	-351(47)	-499(49)
C(19)	460(52)	472(44)	220(22)	460(75)	-189(57)	-180(53)
C(20)	638(56)	863(50)	371(26)	949(80)	-551(68)	-806(51)
C(21)	596(59)	531(37)	144(13)	247(77)	-105(46)	292(31)

* The scattering factor is defined in Table 2.

TABLE 10
Bond lengths (Å) within molecule (III)

Br(1)-C(6)	1.90(1)	C(8)-C(14)	1.42(2)
C(1)-C(2)	1.52(2)	C(9)-C(10)	1.50(1)
C(1)-C(10)	1.55(1)	C(9)-C(11)	1.41(2)
C(2)-C(3)	1.55(2)	C(10)-C(17)	1.55(2)
C(3)-C(4)	1.55(1)	C(11)-C(12)	1.34(2)
C(4)-C(5)	1.58(1)	C(12)-C(13)	1.40(2)
C(4)-C(15)	1.50(2)	C(13)-C(14)	1.39(2)
C(4)-C(16)	1.53(2)	C(13)-C(18)	1.50(2)
C(5)-C(6)	1.49(2)	C(15)-O(2)	1.20(1)
C(5)-C(10)	1.54(1)	C(15)-O(3)	1.34(2)
C(6)-C(7)	1.50(2)	C(18)-C(19)	1.50(2)
C(7)-C(8)	1.47(2)	C(18)-C(20)	1.38(3)
C(7)-O(1)	1.24(1)	C(21)-O(3)	1.48(2)
C(8)-C(9)	1.41(1)		

TABLE 11
Bond angles (deg.) within molecule (III) *

Br(1)-C(6)-C(5)	121	C(6)-C(7)-C(8)	119
Br(1)-C(6)-C(7)	110	C(6)-C(7)-O(1)	119
C(2)-C(1)-C(10)	112	C(8)-C(7)-O(1)	122
C(1)-C(2)-C(3)	111	C(7)-C(8)-C(9)	119
C(1)-C(10)-C(5)	109	C(7)-C(8)-C(14)	119
C(1)-C(10)-C(9)	109	C(9)-C(8)-C(14)	122
C(1)-C(10)-C(17)	110	C(8)-C(9)-C(10)	119
C(2)-C(3)-C(4)	112	C(8)-C(9)-C(11)	115
C(3)-C(4)-C(5)	109	C(8)-C(14)-C(13)	120
C(3)-C(4)-C(15)	102	C(10)-C(9)-C(11)	125
C(3)-C(4)-C(16)	111	C(9)-C(10)-C(17)	107
C(5)-C(4)-C(15)	113	C(9)-C(11)-C(12)	124
C(5)-C(4)-C(16)	112	C(11)-C(12)-C(13)	121
C(4)-C(5)-C(6)	114	C(12)-C(13)-C(14)	118
C(4)-C(5)-C(10)	119	C(12)-C(13)-C(18)	120
C(15)-C(4)-C(16)	110	C(14)-C(13)-C(18)	122
C(4)-C(15)-O(2)	125	C(13)-C(18)-C(19)	114
C(4)-C(15)-O(3)	113	C(13)-C(18)-C(20)	120
C(6)-C(5)-C(10)	111	O(2)-C(15)-O(3)	121
C(5)-C(6)-C(7)	116	C(15)-O(3)-C(21)	117
C(5)-C(10)-C(9)	108	C(19)-C(18)-C(20)	120
C(5)-C(10)-C(17)	114		

* The standard deviation is 1° in every instance.

between the planes defined by C(8), C(7), O(1), and C(7), C(8), C(14) is 17° . The dihedral angle between the bonds C(7)-O(1) and C(6)-Br is 35° , and that between C(5)-H α and C(6)-H β is 175° . The C(18)-C(20) bond length of 1.38 \AA and the C(19)-C(18)-C(20) bond angle of 120° are apparently significantly different from the expected values of 154 \AA and 109° . However, we consider that the large anisotropic vibrations of the isopropyl group as indicated by Figure 3 make necessary corrections to these values. Thus C(18)-C(20) should be increased by something between the 0.04 and 0.25 \AA which can be computed for the

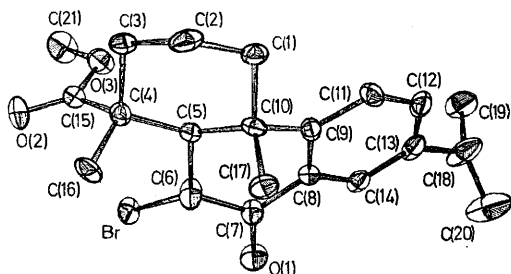


FIGURE 3 An ORTEP diagram of molecule (III)

two extreme models of Busing and Levy.¹⁵ Alternatively, of course, it can be argued that absorption effects are responsible for the discrepancy. A similarly large bond-angle of 121° is found for Br-C(6)-C(5) but in view of the satisfactory bond lengths this is taken to be significantly different from 109° as a result of intramolecular steric interactions in this region.

TABLE 12

Planes of best fit and deviations (\AA) therefrom: molecule (III). Equations are expressed in the cosine form $lX + mY + nZ + p = 0$, with reference to orthogonal axes and with p in \AA units. The transformation from the cell axes is:

$$\begin{vmatrix} 1 & \cos \gamma & \cos \beta \\ 0 & \sin \gamma & r \\ 0 & 0 & S \end{vmatrix} \text{ where, } r = (\cos \alpha - \cos \beta \cos \gamma) / \sin \gamma$$

$$S = (1 + 2 \cos \alpha \cos \beta \cos \gamma - \cos^2 \alpha - \cos^2 \beta - \cos^2 \gamma)^{1/2} / \sin \gamma$$

Ring A planes defined by:	<i>l</i>	<i>m</i>	<i>n</i>	<i>p</i>
(a) C(2), C(3), C(5), C(10)	-0.994	0.099	0.047	0.824
(b) C(1), C(2), C(4), C(5)	0.894	-0.065	0.443	-0.144
(c) C(1), C(3), C(4), C(10)	0.835	-0.509	0.207	1.270

Deviations from:

(a)	(b)	(c)
C(2) -0.039	C(1) 0.060	C(1) 0.014
C(3) -0.039	C(2) -0.059	C(3) -0.014
C(5) -0.039	C(4) 0.056	C(4) 0.013
C(10) 0.039	C(5) -0.057	C(10) -0.013
C(1) 0.700	C(3) 0.673	C(2) -0.717
C(4) -0.612	C(10) -0.641	C(5) 0.554

Ring B planes defined by:

(d) C(6), C(7), C(9), C(10)	0.839	-0.133	0.527	0.866
(e) C(5), C(6), C(8), C(9)	0.836	-0.344	0.427	0.726

Deviations from:

(d)	(e)
C(6) 0.126	C(5) 0.105
C(7) -0.124	C(6) -0.100
C(9) 0.131	C(8) 0.108
C(10) -0.132	C(9) -0.112
C(5) 0.619	C(7) -0.059
C(8) 0.055	C(10) -0.654
O(1) -0.481	O(1) -0.165
Br(1) 0.866	Br(1) 0.726

TABLE 12 (Continued)

Benzene ring plane defined by:					
(f) C(8), C(9), C(11)-(14)	0.782	-0.150	0.604	1.179	
Deviations from (f):					
C(8)	-0.019	C(3)	1.43	C(7)	-1.653
C(9)	0.017	C(4)	1.017	C(18)	0.061
C(11)	-0.008	C(5)	0.727	C(19)	1.451
C(12)	0	C(6)	0.289	C(20)	-0.879
C(13)	-0.002	C(7)	-0.058	O(1)	-0.375
C(14)	0.012	C(10)	-0.147	Br(1)	1.179
C(1)	0.376	C(15)	2.252		
C(2)	0.425	C(16)	-0.160		

TABLE 13

Intramolecular distances (\AA): molecule (III)

Br(1) ... O(1)	2.95	O(1) ... C(6)	3.02
Br(1) ... C(5)	2.96	O(1) ... C(8)	2.37
Br(1) ... C(7)	2.78	O(2) ... Br(1)	3.45
Br(1) ... C(15)	3.09	O(3) ... Br(1)	3.36
Br(1) ... C(16)	3.68	C(1) ... C(3)	2.52
Br(1) ... H(16,2)	2.94	C(4) ... C(10)	2.68
Br(1) ... H(5,1)	3.10	C(16) ... H(17,2)	2.73
Br(1) ... H(6,1)	2.19	C(17) ... H(16,3)	2.65
O(1) ... H(6,1)	2.60	C(17) ... H(6,1)	2.85

Some non-bonded distances are given in Table 13. The bromine atom is seen to be equidistant from O(1), C(15), and H(16,2). The intermolecular approaches are not indicative of compact packing, only two carbon-carbon contacts being $< 3.6 \text{ \AA}$. The O(2)-H(12,1) distance of 2.54 \AA is the shortest non-bonded distance but is not likely to have influenced the relative orientation of the ester group since any free rotation about C(4)-C(5) is inhibited by the bromine atom. A consequence of the loose molecular packing seems to be the considerable thermal motion of the atoms. This is largely anisotropic perpendicular to bond directions and is most pronounced in side groups (see Figure 3). That these vibrations occur in a manner expected of a loosely held molecule is taken as further evidence of the reality, at least qualitative, of the anisotropic motion revealed by the analysis.

DISCUSSION

The crystal structures of compounds (I)-(III) have now been determined by X-ray methods so that three of the four compounds which have aroused recent interest may be compared in structural detail. *O*-Methyl-6-bromosugiol (6-bromo-13-isopropyl-12-methoxypodocarpa-8,11,13-trien-7-one) (IV) is the exception. Relevant comparisons can be made from Table 14.

All three compounds are known only in the α -bromo-configuration but 6-bromo-*O*-methylsugiol can be prepared as a mixture of α - and β -isomers.⁶ This observation has been attributed to the presence of a tetrahedral carbon atom at C(16) together with the presence of an electron-donating group on C(12) and is supported by the behaviour of a number of similar compounds, evidence involving 12-substituted derivatives of 7-oxopodocarpa-8,11,13-trien-16-yl acetate being particularly persuasive.⁶ On the other hand a trigonal atom at C(16), as in 7-oxopodocarpa derivatives, allows only α -bromination even though it is assumed that a trigonal centre is less demanding sterically than a tetrahedral one. It has therefore been suggested that an electronic effect

¹⁵ W. R. Busing and H. A. Levy, *Acta Cryst.*, 1964, **17**, 142.

is also present here, arising from a preferred orientation of the ester group in solution in which the carbonyl oxygen attached to C(16) points towards C(6). Protonation by any HBr present at bromination then inhibits β -face attack by positive bromine.

TABLE 14

A comparison of molecular geometries

Feature	(I)	(II)	(III)
Br-C(6)/Å	1.98	1.95	1.90
Br-C(6)-C(5)/(°)	111	114	121
Br-C(6)-C(7)/(°)	102	99	110
Br...C(5)/Å	2.91	2.92	2.96
Br...C(7)/Å	2.70	2.69	2.78
Br...O(1)/Å	3.25	3.37	2.95
Br...C(15)/Å	3.43	3.42	3.09
Br...C(16)/Å	4.0	4.0	3.68
C(16)...C(17)/Å	3.09	3.22	3.38
H α C(5)-C(6)H β /(°)	154	151	175
BrC=C=O/(°)	90	94	35
O(1) above benzene ring/Å	0.62	0.90	0.38
Br below benzene ring/Å	2.41	2.38	1.18
C(7) above plane/Å ^a	0.33	0.46	0.06
C(10) above plane/Å ^a	0.59	0.65	0.65
Ring-B conf.	Boat	Boat	Half-boat
$\bar{U}_{\text{major}}(\text{Br})/\text{Å}$		0.44	0.36
Closest intermol. Br dist./Å	O'(1) 3.35	<i>b</i>	H'(18,1) 3.03

^a Plane through C(5), C(6), C(8), C(9). ^b None < 3.5 Å.

Although acknowledging the necessity to extrapolate from solid-state results we believe that a more important role in these reactions must be ascribed to steric forces. That we find, where comparison can be made, complete correlation between our measurements and those obtained from solution supports the relevance of deductions drawn from the crystal analyses. Thus in (I) the dihedral angle $\angle \text{H}\alpha\text{C}(5)-\text{C}(6)\text{H}\beta$ is 154° consistent with the value expected from the observed coupling constant of 7 Hz observed in the n.m.r. spectrum.² This agreement holds also for (II) where the dihedral angle is 151° .

In both compounds the keto-oxygens are tilted 'upwards' from the plane of the aromatic ring away from the α -oriented bromine atoms. The tilt is slightly greater in (II) where the ring B boat conformation is correspondingly nearer ideal, the displacements of the 'bow' and 'stern' atoms, C(7) and C(10), being here 0.46 and 0.65 Å as compared with 0.33 and 0.59 Å for (I).

In (I), as in (III), the trigonal carbon atom is orientated so that its carbonyl oxygen points away from C(6), in direct opposition to the requirement for the electronic interaction mentioned earlier.⁶ Although this positioning could be reversed in solution, we suggest that the lack of β -attack by bromine is a consequence of the crowding by the axial group on C(16) and by the C(17) methyl group which, between them, shield the β -face. The attack is thus 'underneath' at the α -face with a simultaneous enol-keto conversion to restore the tetrahedral nature of C(6). The exact direction of the C(6)-Br bond is then determined by the presence of the rigidly defined C(15) group and this direction in turn, through the tetrahedral geometry of C(6), controls the positioning of the keto-oxygen on C(7) and

the conformation of the B-ring. Thus in compound (I) C(6) lies 0.68 Å below the plane of the aromatic nucleus and ring B adopts a near-boat geometry.

In 7-oxototarol the situation is somewhat different, since here a *gem* dimethyl is present at C(4) and it is unlikely that these two groups present sufficient steric hindrance to discourage β -attack. Thus *O*-methylsugiol (IVa) which also possesses the C(4) *gem* dimethyl will undergo β -bromination. We support the suggestion that the isopropyl group on C(14) plays a significant role in the 7-oxototarol derivative by forcing the keto-oxygen up from the aromatic plane.⁶ The flanking hydroxy-group on C(13) is also important in dictating the observed orientation of the isopropyl group and ensuring its steric interaction with O(1). It is the out-of-plane twist of this keto-oxygen which then predisposes the molecule to the α -stereochemistry at C(6).

This buttressing effect is reflected in the n.m.r. results (Table 15). Chemical shifts for the C(17) methyl

TABLE 15

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

Compound	C(15)	C(16)	C(17)
(1)	1.27		1.03
(3)	0.94	0.94	1.19
(2)	0.95	0.95	1.21
(4)		1.25	1.20
(1a) = (Ia)	1.25		1.10
(3a) = (IVa)	0.93	1.00	1.25
(2a)	0.91	1.01	1.10
(4a)		1.33	1.26
(1b) = (I)	1.53		0.85
(3b) = (IV)	1.15	1.03	1.27
(2b) [cf. (II)]	1.15	1.08	1.23
(4b) = (III)		1.50	1.26
(3c) [cf. (IV)]	1.10	1.43	1.77

(1) Is methyl *O*-methylpodocarpate, (2) is *O*-methyltotarol, (3a) is *O*-methylsugiol, (4) is methyl dehydroabietate, and 'a' represents the 7-oxo-, 'b' the 6 α -bromo-7-oxo-, and 'c' the 6 β -bromo-7-oxo-derivative.

protons, after oxidation followed by bromination, show a striking difference between the 7-oxototarol and 7-oxopodocarpate derivatives. In the former, the methyl group is first shielded by 0.11 p.p.m. and then deshielded (0.13 p.p.m.) whereas a deshielding (0.07 p.p.m.) followed by a shielding (0.25 p.p.m.) is found for the 7-oxopodocarpate. The values for the 7-oxototarol derivative would be explained if the keto-oxygen atom were tilted upwards before bromination, *i.e.* by the steric effect of the isopropyl group. Ring B would then assume a partial boat conformation and the C(17) methyl would prematurely enter the core of shielding of the carbonyl group. It is pertinent that the 7-oxototarol compound is the only one of the four diterpenoids to display this effect.

The coupling constant of 12 Hz observed for the C(5) and C(6) protons of the 6-bromo-7-oxodehydroabietate derivative (III) is seen to result from the almost diaxial orientation of these two atoms, the dihedral angle $\angle \text{H}\alpha\text{C}(5)-\text{C}(6)\text{H}\beta$ being 175° . This in turn is a consequence of the 'half-boat' conformation of ring-B in which the keto-oxygen is now only 0.38 Å above the

aromatic plane. This compares with the respective values of 0.62 and 0.90 Å for compounds (I) and (II). This particular α -bromo-geometry can also be ascribed to steric factors, first on the assumption that the β -face is shielded by the two axial methyl groups and secondly by the tight steric control imposed on the bromine by the equatorial ester group [the Br \cdots O(2) and Br \cdots O(3) distances are 3.45 and 3.36 Å].

The claim that the β -face is shielded raises the question as to why *O*-methylsugiol (IVa), which has the same two methyl groups, should suffer β -bromination. It is here that the electronic effect of the methoxy-substituent on C(12) must be crucial, although only marginally so, since it is also known that the 12-*O*-methyl derivative of 7-oxopodocarpace gives the α -isomer only. That both steric and electronic arguments fail under extrapolation

is understandable, we suggest, in the light of the three *X*-ray analyses. Although these involve only the end-products of bromination they reveal the considerable variation in detailed geometry imposed by the steric, and presumably electronic, effects of substituents. The positioning of the keto-oxygen atom with respect to the aromatic ring and the positioning of substituents on C(4), clearly critical features governing the direction of bromine attack, show that substantial differences can exist between molecules and these are likely to negate conclusions and extrapolations drawn from the assumption of a rigid skeletal geometry.

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