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# SESQUITERPENOIDS–XVI[1]

## CONFORMATIONS OF CYCLOHEPTANE AND $\alpha$-METHYLENE-$\gamma$-LACTONE RINGS IN SESQUITERPENOIDS: X-RAY DETERMINATION OF THE CONSTITUTION, ABSOLUTE STEREOCHEMISTRY, AND CONFORMATION OF EUPAROTIN BROMOACETATE

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**Abstract**—The molecular structure of euparotin, a highly oxygenated sesquiterpene of the guaianolide type, has been determined by crystal-structure analysis of euparotin bromoacetate. The bromo-derivative crystallizes from benzene-petrol as a benzene solvate, $C_{22}H_{25}O_8Br\cdot\frac{1}{2}C_6H_6$, crystals of which are monoclinic, of space group $C2$, with $a = 34{\cdot}85$, $b = 7{\cdot}04$, $c = 10{\cdot}90$ Å, $\beta = 106°35'$, and $Z = 4$. The atomic co-ordinates were determined by Fourier and least-squares calculations which employed 1947 photographic $|F_o|$ values and converged at $R = 12{\cdot}8\%$ with isotropic thermal parameters for the C and O atoms and anisotropic parameters for the Br atom. The absolute configuration was established by the anomalous-dispersion effect. The cycloheptane ring of the sesquiterpenoid has a conformation which is closer to a twist chair ($C_2$) than a chair ($C_s$) form, and a survey shows that this is also true for other perhydroazulene sesquiterpenoids. In the $\alpha$-methylene-$\gamma$-lactone of euparotin and several other sesquiterpenoids the C=C—C=O torsion angle has the same sign as the C($\alpha$)—C($\beta$)—C($\gamma$)—O torsion angle, establishing the basis for Stöcklin *et al*'s correlation between the position and stereochemistry of lactone fusion and the sign of the Cotton effect of the $n \rightarrow \pi^*$ transition of the C=C—C=O chromophore.

Euparotin acetate, $C_{22}H_{26}O_8$, a compound which exhibits significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB), was isolated by Kupchan *et al.* from *Eupatorium rotundifolium L.* (Compositae).[2] Further chromatography of the plant extracts yielded euparotin, and acylation of this with bromoacetic anhydride gave euparotin bromoacetate which crystallized from benzene-petrol as a benzene solvate, $C_{22}H_{25}BrO_8\cdot\frac{1}{2}C_6H_6$. We undertook an X-ray analysis of this material to determine the molecular structure of euparotin, and the derived assembly of atoms is shown in Fig 1. The final co-ordinates and thermal parameters of the atoms are listed in Table 1, the interatomic distances and angles in Table 2.

The results of the analysis establish that the bromoacetate has the constitution and absolute stereochemistry (**1a**), from which it follows that euparotin and euparotin acetate are represented by **1b** and **1c**, respectively. The absolute configuration was deduced by Bijvoet's anomalous-dispersion method.[3]

Euparotin is a highly oxygenated guaianolide and the pattern of *cis*-1,5 and *trans*-6,7 ring junctions places it in a category of sesquiterpenoid lactones two other examples of which, solstitalian (**2**)[4] and bromodihydroisophotosantonic lactone acetate (**3**),[5] have been characterized by X-ray studies. Several further sesquiterpenoids with cycloheptane rings have been subjected to X-ray measurements: *e.g.* bromogeigerin (**4**),[6] bromohelenalin (**5**),[7] and bromomexicanin-E (**6**).[8] However, the reports of these analyses provide little information about the conformations of the cycloheptane rings.

Both chair and boat forms of cycloheptane are flexible and may undergo pseudorotation, and in each family the twist form with an axis of symmetry ($C_2$) is the most stable, and the pure chair or boat form with a plane of symmetry ($C_s$) is the least stable, in the pseudorotation continuum. The chair family is more stable than the boat family, by *ca* 1–2·5 kcal,[9] and, accordingly, Hendrickson has discussed the stereochemistries of several sesquiterpenes in terms of the twist chair conformation of the cycloheptane rings.[10] On the other hand, Sekita *et al* have attributed a boat conformation to the cycloheptane ring of bromomexicanin-E and a variety of deformed chair conformations to the cycloheptane rings of other perhydroazulene sesquiterpenes.[11]

The $C_2$ and $C_s$ conformations of cycloheptane are

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Table 1. Atomic co-ordinates (as fractions of the cell edges), positional standard deviations (Å), and isotropic temperature factors (Å$^2$)

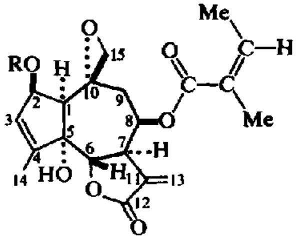
| | $x$ | $y$ | $z$ | $\sigma(X)$ | $\sigma(Y)$ | $\sigma(Z)$ | $B$ |
|---|---|---|---|---|---|---|---|
| C(1) | 0·1455 | −0·2819 | 0·5228 | 0·013 | 0·018 | 0·013 | 3·9 |
| C(2) | 0·1584 | −0·0705 | 0·5330 | 0·014 | 0·019 | 0·014 | 4·3 |
| C(3) | 0·1205 | 0·0419 | 0·4873 | 0·014 | 0·020 | 0·015 | 4·3 |
| C(4) | 0·0877 | −0·0754 | 0·4722 | 0·014 | 0·019 | 0·015 | 4·3 |
| C(5) | 0·0985 | −0·2719 | 0·5109 | 0·011 | 0·018 | 0·012 | 3·5 |
| C(6) | 0·0915 | −0·3352 | 0·6359 | 0·013 | 0·015 | 0·013 | 3·4 |
| C(7) | 0·1034 | −0·5407 | 0·6723 | 0·013 | 0·019 | 0·013 | 3·9 |
| C(8) | 0·1434 | −0·5603 | 0·7753 | 0·012 | 0·017 | 0·013 | 3·6 |
| C(9) | 0·1748 | −0·4220 | 0·7537 | 0·014 | 0·019 | 0·014 | 4·0 |
| C(10) | 0·1738 | −0·4109 | 0·6138 | 0·012 | 0·017 | 0·013 | 3·4 |
| C(11) | 0·0671 | −0·6215 | 0·7007 | 0·014 | 0·019 | 0·014 | 4·2 |
| C(12) | 0·0350 | −0·4911 | 0·6618 | 0·013 | 0·016 | 0·014 | 3·9 |
| C(13) | 0·0636 | −0·7905 | 0·7533 | 0·018 | 0·024 | 0·020 | 6·2 |
| C(14) | 0·0459 | −0·0057 | 0·4245 | 0·017 | 0·021 | 0·018 | 5·6 |
| C(15) | 0·2094 | −0·4602 | 0·5775 | 0·016 | 0·022 | 0·017 | 5·1 |
| C(16) | 0·1533 | −0·6090 | 0·9975 | 0·014 | 0·018 | 0·015 | 4·4 |
| C(17) | 0·1394 | −0·5544 | 1·1089 | 0·016 | 0·022 | 0·016 | 4·9 |
| C(18) | 0·1526 | −0·6500 | 1·2216 | 0·021 | 0·026 | 0·022 | 7·2 |
| C(19) | 0·1134 | −0·3836 | 1·0955 | 0·024 | 0·030 | 0·025 | 8·1 |
| C(20) | 0·1797 | −0·7887 | 1·2604 | 0·027 | 0·035 | 0·029 | 9·9 |
| C(21) | 0·2166 | 0·0216 | 0·6972 | 0·013 | 0·017 | 0·014 | 4·1 |
| C(22) | 0·2312 | 0·0563 | 0·8360 | 0·015 | 0·021 | 0·016 | 4·9 |
| O(23) | 0·1783 | −0·0174 | 0·6653 | 0·008 | 0·011 | 0·009 | 3·6 |
| O(24) | 0·2365 | 0·0243 | 0·6231 | 0·012 | 0·016 | 0·012 | 6·2 |
| O(25) | 0·0799 | −0·4038 | 0·4117 | 0·009 | 0·012 | 0·009 | 4·1 |
| O(26) | 0·0476 | −0·3231 | 0·6196 | 0·009 | 0·010 | 0·009 | 3·8 |
| O(27) | −0·0002 | −0·4991 | 0·6631 | 0·013 | 0·016 | 0·014 | 6·5 |
| O(28) | 0·1364 | −0·5069 | 0·8984 | 0·010 | 0·012 | 0·010 | 4·3 |
| O(29) | 0·1770 | −0·7320 | 0·9989 | 0·015 | 0·022 | 0·015 | 8·6 |
| O(30) | 0·1779 | −0·5974 | 0·5582 | 0·010 | 0·012 | 0·010 | 4·8 |
| Br | 0·2742 | 0·2500 | 0·8779 | 0·002 | — | 0·002 | † |
| C(31) | 0·000 | −0·112 | 1·000 | — | 0·13 | — | 6 |
| C(32) | 0·028 | 0·010 | 1·070 | 0·12 | 0·13 | 0·12 | 8 |
| C(33) | 0·028 | 0·213 | 1·070 | 0·07 | 0·10 | 0·08 | 6 |
| C(34) | 0·000 | 0·305 | 1·000 | — | 0·10 | — | 4 |
| C(35) | 0·020 | −0·075 | 1·058 | 0·09 | 0·11 | 0·09 | 7 |
| C(36) | 0·043 | 0·089 | 1·095 | 0·06 | 0·09 | 0·07 | 5 |
| C(37) | 0·020 | 0·248 | 1·058 | 0·07 | 0·11 | 0·07 | 6 |

†For the bromine atom we employed an anisotropic temperature factor of the form

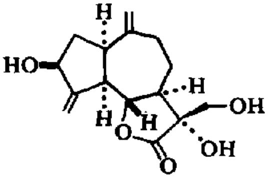
$$T = \exp[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{23}kl + b_{13}hl)]$$

with parameters

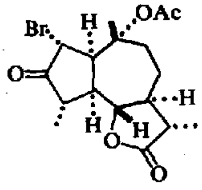
| $b_{11}$ | $b_{22}$ | $b_{33}$ | $b_{12}$ | $b_{13}$ | $b_{23}$ |
|---|---|---|---|---|---|
| 0·0011 | 0·0290 | 0·0174 | −0·0014 | 0·0004 | −0·0054 |



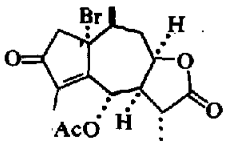
**1a**: R = COCH$_2$Br
**1b**: R = H
**1c**: R = Ac



**2**



**3**



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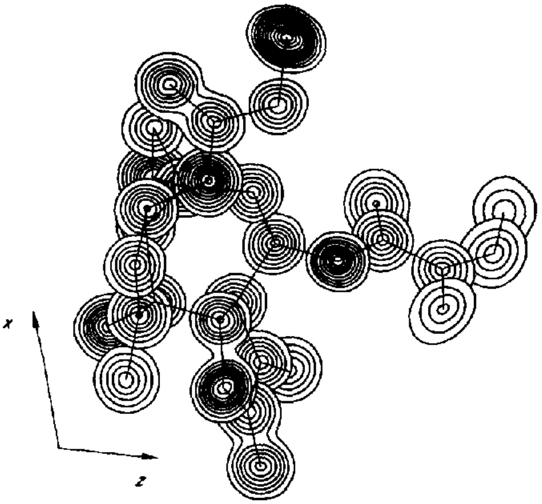


Fig 1a. The electron-density distribution over one molecule of euparotin bromoacetate.

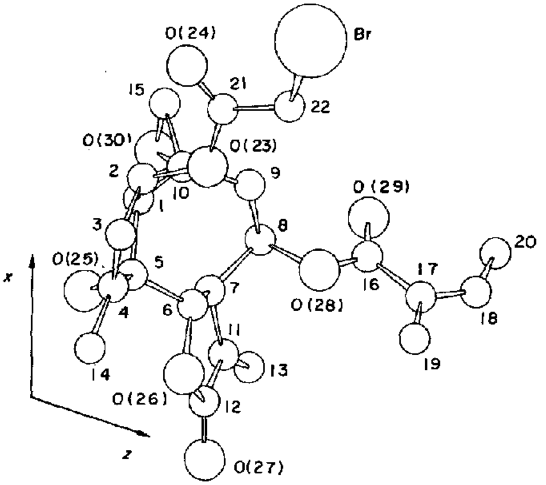


Fig 1b. The arrangement of atoms corresponding to Fig 1a.

characterized by the constraints on the torsion angles shown in **7**. An unsymmetrically substituted cycloheptane may well be most stable in a conformation intermediate between the symmetrical forms, and measures of the deviation of the ring from $C_2$ or $C_s$ symmetry are given by:

$$\Sigma_2 = (|\omega_1 - \omega_6| + |\omega_2 - \omega_5| + |\omega_3 - \omega_4|),$$
$$\Sigma_s = (|\omega_1 + \omega_7| + |\omega_2 + \omega_6| + |\omega_3 + \omega_5| + |\omega_4|).$$

The torsion angles in the cycloheptane rings of **1a**–**6** are listed in Table 3, along with the angles calculated by Hendrickson for the chair, twist chair, boat, and twist boat forms of cycloheptane.[9] The pattern of signs for the torsion angles shows that none of these sesquiterpenoid cycloheptanes

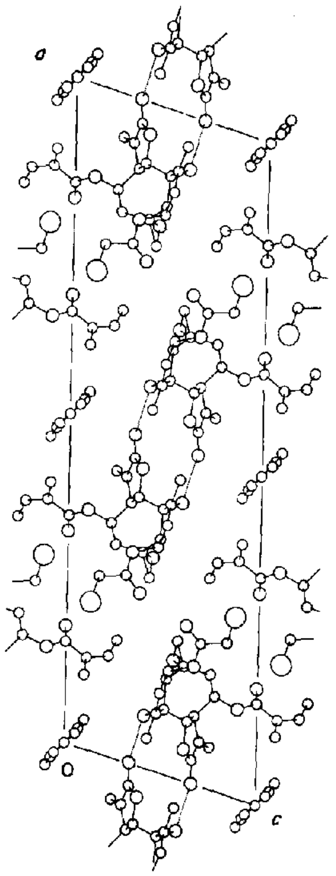
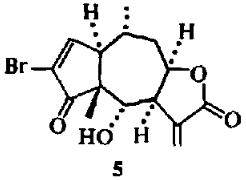
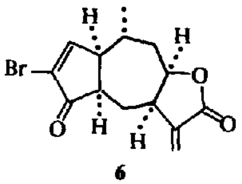


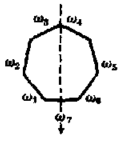
Fig 1c. The crystal structure of euparotin bromoacetate benzene solvate.



**5**

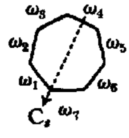


**6**



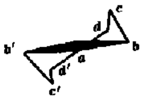
$\omega_1 = \omega_6$
$\omega_2 = \omega_5$
$\omega_3 = \omega_4$

**7a**



$\omega_1 = -\omega_7$
$\omega_2 = -\omega_6$
$\omega_3 = -\omega_5$
$\omega_4 = 0$

**7b**



**8**

Table 2. Interatomic distances (Å) and angles (deg.) with their standard deviations in parentheses

(*a*) Bond lengths

| | | | |
|---|---|---|---|
| C(1)—C(2) | 1·55(0·026) | C(11)—C(13) | 1·34(0·029) |
| C(1)—C(5) | 1·61(0·017) | C(12)—O(26) | 1·39(0·018) |
| C(1)—C(10) | 1·49(0·021) | C(12)—O(27) | 1·23(0·018) |
| C(2)—C(3) | 1·50(0·022) | C(15)—O(30) | 1·43(0·022) |
| C(2)—O(23) | 1·46(0·017) | C(16)—C(17) | 1·48(0·022) |
| C(3)—C(4) | 1·38(0·023) | C(16)—O(28) | 1·29(0·019) |
| C(4)—C(5) | 1·46(0·026) | C(16)—O(29) | 1·19(0·025) |
| C(4)—C(14) | 1·48(0·023) | C(17)—C(18) | 1·36(0·029) |
| C(5)—C(6) | 1·52(0·018) | C(17)—C(19) | 1·49(0·035) |
| C(5)—O(25) | 1·43(0·018) | C(18)—C(20) | 1·34(0·040) |
| C(6)—C(7) | 1·53(0·024) | C(21)—C(22) | 1·47(0·021) |
| C(6)—O(26) | 1·49(0·016) | C(21)—O(23) | 1·31(0·016) |
| C(7)—C(8) | 1·53(0·018) | C(21)—O(24) | 1·21(0·018) |
| C(7)—C(11) | 1·50(0·020) | C(22)—Br | 1·98(0·018) |
| C(8)—C(9) | 1·53(0·022) | C(31)—C(32) | 1·36(0·15) |
| C(8)—O(28) | 1·48(0·017) | C(32)—C(33) | 1·43(0·16) |
| C(9)—C(10) | 1·52(0·019) | C(33)—C(34) | 1·24(0·10) |
| C(10)—C(15) | 1·45(0·021) | C(35)—C(36) | 1·40(0·13) |
| C(10)—O(30) | 1·47(0·020) | C(36)—C(37) | 1·37(0·13) |
| C(11)—C(12) | 1·42(0·022) | C(35)—C(35)$_{\text{VI}}$ | 1·59(0·13) |

(*b*) Intermolecular distances (≤ 3·8 Å)

| | | | |
|---|---|---|---|
| O(25)···O(27)$_{\text{II}}$ | 2·75 | C(20)···O(24)$_{\text{III}}$ | 3·59 |
| C(21)···O(30)$_{\text{I}}$ | 3·18 | O(26)···O(26)$_{\text{II}}$ | 3·59 |
| O(23)···O(30)$_{\text{I}}$ | 3·18 | C(14)···C(36)$_{\text{IV}}$ | 3·63 |
| C(3)···O(30)$_{\text{I}}$ | 3·19 | C(17)···Br$_{\text{III}}$ | 3·66 |
| C(15)···O(24)$_{\text{V}}$ | 3·27 | C(12)···C(12)$_{\text{II}}$ | 3·67 |
| C(22)···O(29)$_{\text{I}}$ | 3·29 | C(3)···C(7)$_{\text{I}}$ | 3·71 |
| O(26)···O(27)$_{\text{II}}$ | 3·29 | C(14)···C(32)$_{\text{IV}}$ | 3·74 |
| O(24)···O(30)$_{\text{I}}$ | 3·31 | C(12)···O(26)$_{\text{II}}$ | 3·75 |
| C(2)···O(30)$_{\text{I}}$ | 3·39 | O(24)···C(15)$_{\text{I}}$ | 3·75 |
| C(12)···O(27)$_{\text{II}}$ | 3·40 | O(23)···C(8)$_{\text{I}}$ | 3·76 |
| O(30)···C(20)$_{\text{IV}}$ | 3·53 | C(5)···O(27)$_{\text{II}}$ | 3·77 |
| O(30)···C(18)$_{\text{IV}}$ | 3·54 | C(14)···C(13)$_{\text{I}}$ | 3·78 |
| C(16)···Br$_{\text{III}}$ | 3·56 | O(29)···C(22)$_{\text{III}}$ | 3·78 |
| O(27)···O(27)$_{\text{II}}$ | 3·56 | | |

The subscripts refer to the following transformations of the atomic co-ordinates:

I $x, 1+y, z$
II $-x, y, 1-z$
III $\frac{1}{2}-x, -\frac{1}{2}+y, 2-z$
IV $x, y, -1+z$
V $\frac{1}{2}-x, -\frac{1}{2}+y, 1-z$
VI $-x, y, 2-z$

(*c*) Valency angles

| | | | |
|---|---|---|---|
| C(2)—C(1)—C(5) | 103(1·3) | C(15)—C(10)—O(30) | 59(1·1) |
| C(2)—C(1)—C(10) | 114(1·2) | C(7)—C(11)—C(12) | 109(1·5) |
| C(5)—C(1)—C(10) | 123(1·2) | C(7)—C(11)—C(13) | 128(1·5) |
| C(1)—C(2)—C(3) | 106(1·2) | C(12)—C(11)—C(13) | 123(1·4) |
| C(1)—C(2)—O(23) | 111(1·2) | C(11)—C(12)—O(26) | 111(1·2) |
| C(3)—C(2)—O(23) | 109(1·3) | C(11)—C(12)—O(27) | 132(1·6) |
| C(2)—C(3)—C(4) | 110(1·6) | O(26)—C(12)—O(27) | 117(1·4) |
| C(3)—C(4)—C(5) | 113(1·3) | C(10)—C(15)—O(30) | 61(1·0) |
| C(3)—C(4)—C(14) | 123(1·7) | C(17)—C(16)—O(28) | 111(1·4) |
| C(5)—C(4)—C(14) | 124(1·4) | C(17)—C(16)—O(29) | 124(1·6) |
| C(1)—C(5)—C(4) | 104(1·2) | O(28)—C(16)—O(29) | 124(1·5) |
| C(1)—C(5)—C(6) | 110(1·0) | C(16)—C(17)—C(18) | 120(1·8) |
| C(1)—C(5)—O(25) | 105(1·1) | C(16)—C(17)—C(19) | 118(1·7) |

Table 2. (*Continued*)

| | | | |
|---|---|---|---|
| C(4)—C(5)—C(6) | 116(1·2) | C(18)—C(17)—C(19) | 122(1·8) |
| C(4)—C(5)—O(25) | 112(1·1) | C(17)—C(18)—C(20) | 132(2·2) |
| C(6)—C(5)—O(25) | 109(1·2) | C(22)—C(21)—O(23) | 110(1·2) |
| C(5)—C(6)—C(7) | 114(1·2) | C(22)—C(21)—O(24) | 126(1·3) |
| C(5)—C(6)—O(26) | 107(1·0) | O(23)—C(21)—O(24) | 124(1·3) |
| C(7)—C(6)—O(26) | 106(1·1) | C(21)—C(22)—Br | 112(1·1) |
| C(6)—C(7)—C(8) | 114(1·3) | C(2)—O(23)—C(21) | 119(1·0) |
| C(6)—C(7)—C(11) | 103(1·2) | C(6)—O(26)—C(12) | 109(1·0) |
| C(8)—C(7)—C(11) | 117(1·2) | C(8)—O(28)—C(16) | 118(1·2) |
| C(7)—C(8)—C(9) | 112(1·2) | C(10)—O(30)—C(15) | 60(1·0) |
| C(7)—C(8)—O(28) | 107(1·0) | | |
| C(9)—C(8)—O(28) | 107(1·2) | C(32)—C(31)—C(32)$_{\mathrm{VI}}$ | 102 |
| C(8)—C(9)—C(10) | 112(1·2) | C(31)—C(32)—C(33) | 129 |
| C(1)—C(10)—C(9) | 121(1·2) | C(32)—C(33)—C(34) | 122 |
| C(1)—C(10)—C(15) | 115(1·3) | C(33)—C(34)—C(33)$_{\mathrm{VI}}$ | 117 |
| C(1)—C(10)—O(30) | 113(1·1) | C(36)—C(35)—C(35)$_{\mathrm{VI}}$ | 122 |
| C(9)—C(10)—C(15) | 119(1·2) | C(35)—C(36)—C(37) | 111 |
| C(9)—C(10)—O(30) | 113(1·3) | C(36)—C(37)—C(37)$_{\mathrm{VI}}$ | 123 |

(*d*) Torsion angles. The angle A—B—C—D is defined as positive if, when viewed along the B—C bond, atom A has to be rotated clockwise to eclipse atom D. The standard deviation of a torsion angle is *ca* 2°

| | | | |
|---|---|---|---|
| C(5)—C(1)—C(2)—C(3) | −17 | C(7)—C(6)—O(26)—C(12) | 9 |
| C(5)—C(1)—C(2)—O(23) | 101 | C(6)—C(7)—C(8)—C(9) | −41 |
| C(10)—C(1)—C(2)—C(3) | −153 | C(6)—C(7)—C(8)—O(28) | 75 |
| C(10)—C(1)—C(2)—O(23) | −36 | C(11)—C(7)—C(8)—C(9) | −162 |
| C(2)—C(1)—C(5)—C(4) | 18 | C(11)—C(7)—C(8)—O(28) | −46 |
| C(2)—C(1)—C(5)—C(6) | −106 | C(6)—C(7)—C(11)—C(12) | 10 |
| C(2)—C(1)—C(5)—O(25) | 136 | C(6)—C(7)—C(11)—C(13) | −170 |
| C(10)—C(1)—C(5)—C(4) | 150 | C(8)—C(7)—C(11)—C(12) | 136 |
| C(10)—C(1)—C(5)—C(6) | 25 | C(8)—C(7)—C(11)—C(13) | −45 |
| C(10)—C(1)—C(5)—O(25) | −92 | C(7)—C(8)—C(9)—C(10) | −42 |
| C(2)—C(1)—C(10)—C(9) | 78 | O(28)—C(8)—C(9)—C(10) | −159 |
| C(2)—C(1)—C(10)—C(15) | −78 | C(7)—C(8)—O(28)—C(16) | 138 |
| C(2)—C(1)—C(10)—O(30) | −143 | C(9)—C(8)—O(28)—C(16) | −102 |
| C(5)—C(1)—C(10)—C(9) | −49 | C(8)—C(9)—C(10)—C(1) | 85 |
| C(5)—C(1)—C(10)—C(15) | 156 | C(8)—C(9)—C(10)—C(15) | −121 |
| C(5)—C(1)—C(10)—O(30) | 91 | C(8)—C(9)—C(10)—O(30) | −55 |
| C(1)—C(2)—C(3)—C(4) | 10 | C(1)—C(10)—C(15)—O(30) | −103 |
| O(23)—C(2)—C(3)—C(4) | −110 | C(9)—C(10)—C(15)—O(30) | 101 |
| C(1)—C(2)—O(23)—C(21) | 112 | C(1)—C(10)—O(30)—C(15) | 106 |
| C(3)—C(2)—O(23)—C(21) | −132 | C(9)—C(10)—O(30)—C(15) | −111 |
| C(2)—C(3)—C(4)—C(5) | 3 | C(7)—C(11)—C(12)—O(26) | −5 |
| C(2)—C(3)—C(4)—C(14) | −178 | C(7)—C(11)—C(12)—O(27) | 178 |
| C(3)—C(4)—C(5)—C(1) | −14 | C(13)—C(11)—C(12)—O(26) | 176 |
| C(3)—C(4)—C(5)—C(6) | 106 | C(13)—C(11)—C(12)—O(27) | −2 |
| C(3)—C(4)—C(5)—O(25) | −127 | C(11)—C(12)—O(26)—C(6) | −3 |
| C(14)—C(4)—C(5)—C(1) | 168 | O(27)—C(12)—O(26)—C(6) | 175 |
| C(14)—C(4)—C(5)—C(6) | −72 | O(28)—C(16)—C(17)—C(18) | 178 |
| C(14)—C(4)—C(5)—O(25) | 55 | O(28)—C(16)—C(17)—C(19) | −7 |
| C(1)—C(5)—C(6)—C(7) | −63 | O(29)—C(16)—C(17)—C(18) | −2 |
| C(1)—C(5)—C(6)—O(26) | 180 | O(29)—C(16)—C(17)—C(19) | 173 |
| C(4)—C(5)—C(6)—C(7) | −180 | C(17)—C(16)—O(28)—C(8) | −173 |
| C(4)—C(5)—C(6)—O(26) | 63 | O(29)—C(16)—O(28)—C(8) | 7 |
| O(25)—C(5)—C(6)—C(7) | 52 | C(16)—C(17)—C(18)—C(20) | 5 |
| O(25)—C(5)—C(6)—O(26) | −65 | C(19)—C(17)—C(18)—C(20) | −170 |
| C(5)—C(6)—C(7)—C(8) | 102 | O(23)—C(21)—C(22)—Br | −146 |
| C(5)—C(6)—C(7)—C(11) | −129 | O(24)—C(21)—C(22)—Br | 35 |
| O(26)—C(6)—C(7)—C(8) | −140 | C(22)—C(21)—O(23)—C(2) | −175 |
| O(26)—C(6)—C(7)—C(11) | −11 | O(24)—C(21)—O(23)—C(2) | 3 |
| C(5)—C(6)—O(26)—C(12) | 132 | | |

Table 3. Comparison of the torsion angles (deg.) in sesquiterpenoid cycloheptane rings with Hendrickson's values for the boat, twist boat, chair, and twist chair conformations of cycloheptane

| | B | TB | C | TC | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|---|---|---|
| $\omega_1$ | 57 | 19 | −70 | −76 | −49 | −69 | −72 | −69 | 61 | 51 |
| $\omega_2$ | 34 | 68 | 92 | 97 | 85 | 92 | 81 | 90 | −98 | −86 |
| $\omega_3$ | −74 | −48 | −71 | −41 | −42 | −45 | −42 | −43 | 53 | 60 |
| $\omega_4$ | 0 | −48 | 0 | −41 | −41 | −35 | −31 | −37 | 32 | 19 |
| $\omega_5$ | 74 | 68 | 71 | 97 | 102 | 88 | 79 | 84 | −81 | −82 |
| $\omega_6$ | −34 | 19 | −92 | −76 | −63 | −74 | −78 | −59 | 59 | 68 |
| $\omega_7$ | −57 | −79 | 70 | 53 | 25 | 51 | 63 | 44 | −36 | −36 |
| $\Sigma_2$ | 205 | 0 | 114 | 0 | 32 | 19 | 19 | 22 | 40 | 62 |
| $\Sigma_s$ | 0 | 215 | 0 | 141 | 147 | 114 | 80 | 134 | 154 | 74 |
| $\Sigma_2/(\Sigma_2+\Sigma_s)$ | 1 | 0 | 1 | 0 | 0·18 | 0·14 | 0·19 | 0·14 | 0·21 | 0·46 |
| $C_2$-axis (approx.) | | | | | C(8) | C(5) | C(5) | C(1) | C(10) | C(1) |

1 Euparotin bromoacetate
2 Solstitalian[4]
3 Bromodihydroisophotosantonic lactone acetate[5]
4 Bromogeigerin[6]
5 Bromohelenalin[7]
6 Bromomexicanin-E[8]

adopts a conformation in the boat pseudorotation cycle. The values calculated for the measures $\Sigma_2$ and $\Sigma_s$ show that the rings in **1a**–**5** are much closer to the $C_2$ twist chair than to the $C_s$ chair form, while bromomexicanin-E (**6**) has a conformation which is *ca* midway between the $C_2$ and $C_s$ extremes. In **1a** the approximate $C_2$ axis of the ring passes through C(8), whereas in **2** and **3** it passes through C(5).

Hendrickson suggested that *cis*-fusion of a 5-membered ring is most favoured at bond *a*–*b* in the twist chair cycloheptane (**8**), but can also take place at *d*–*d'*; *trans*-fusion can take place at *b*–*c* or *c*–*d*.[10] In euparotin bromoacetate the *cis*-fused cyclopentene and *trans*-fused γ-lactone are found at bonds of the *d*–*d'* and *b*–*c* types, respectively. In the closely related compounds **2** and **3** the *cis*-fused 5-membered rings are found at bonds of the *a*–*b* type.

Following the earlier discussion of the pseudorotational puckering of cyclopentane,[12] Altona *et al*[13] and Dunitz[14] have shown that the torsion angles in cyclopentane and the flexible boat form of cyclohexane can be expressed in the form

$$\omega = \omega_{\max} \cos\left\{\frac{4\pi}{n} j + \alpha\right\}, \quad j = 1, \dots n \qquad \text{(1a)}$$

where $\omega_{\max}$ is the maximum torsion angle attained in the pseudorotational circuit, $\alpha$ is a phase angle, and $n$ is the number of sides in the non-planar polygon. The torsion angles for the boat family of cycloheptane conformations satisfy the equation

$$\omega = \omega_{\max} \cos\left\{\frac{4\pi}{7} j + \alpha\right\}, \quad j = 1, \dots 7 \qquad \text{(1b)}$$

where $\alpha = 0, 2\pi/14, 4\pi/14$, etc. yield $C_2$ forms and $\alpha = \pi/14, 3\pi/14$, etc yield $C_s$ forms, and this equation with $\omega_{\max} = 76{\cdot}6°$ reproduces Hendrickson's values[8] for the torsion angles of the boat and twist boat forms of cycloheptane with a mean deviation of only 1·4° (Table 4). The equation can be expressed in the alternative form:

$$\begin{aligned} \omega &= \omega_{\max} \cos\left\{\frac{4\pi}{7} j\right\} \cos\alpha + \omega_{\max} \sin\left\{\frac{4\pi}{7} j\right\} \sin\alpha \\ &= \omega(C_2)\cos\alpha + \omega(C_s)\sin\alpha \qquad \text{(1c)} \end{aligned}$$

and intermediate conformations in the boat pseudorotation cycle can be obtained by appropriate choice of the phase angle $\alpha$.

The torsion angles for the more interesting chair family of cycloheptane conformations cannot be fitted to a simple equation of this type, but the symmetrical $C_2$ and $C_s$ conformations can be dealt with by the expressions:

$$\left.\begin{aligned} \omega(C_2) &= \Sigma A_k \cos\left\{k\frac{4\pi}{7} j\right\}, \quad j = 1, \dots 7 \\ \omega(C_s) &= \Sigma A_k \sin\left\{k\frac{4\pi}{7} j\right\}, \quad j = 1, \dots 7 \end{aligned}\right\} \qquad (2)$$

These are only useful if relatively few terms are required, and we have tested a limited series with four coefficients, $A_1$–$A_4$. A least-squares calculation showed that Hendrickson's torsion angles for the twist chair and chair forms are best reproduced by $A_1 = -35{\cdot}80°$, $A_2 = 95{\cdot}28°$, $A_3 = -3{\cdot}02°$, and $A_4 = -0{\cdot}74°$, the mean deviation between the two sets of angles being 3·4°. Since $A_3$ and $A_4$ are small, a two-term series with only $A_1$ and $A_2$ is almost as good, and in this case with $A_1 = -36{\cdot}22°$ and $A_2 = 94{\cdot}87°$ the mean deviation is 4·0° (Table 5).

The valency angles in the cycloheptane ring in euparotin bromoacetate are generally larger than

Table 4. Comparison of Hendrickson's torsion angles for the boat and twist boat conformations of cycloheptane with the angles calculated by equation 1b, using $\omega_{max} = 76{\cdot}6°$

| | Hend. | | Calc. 1b | |
|---|---|---|---|---|
| | B | TB | B | TB |
| $\omega_1$ | 56·7 | 19·0 | 59·9 | 17·0 |
| $\omega_2$ | 34·4 | 67·7 | 33·2 | 69·0 |
| $\omega_3$ | −73·7 | −47·8 | −74·7 | −47·8 |
| $\omega_4$ | 0 | −47·8 | 0 | −47·8 |
| $\omega_5$ | 73·7 | 67·7 | 74·7 | 69·0 |
| $\omega_6$ | −34·4 | 19·0 | −33·2 | 17·0 |
| $\omega_7$ | −56·7 | −78·9 | −59·9 | −76·6 |

Table 5. Comparison of Hendrickson's torsion angles for the chair and twist chair conformations of cycloheptane with the angles calculated by equation 2, using $A_1 = -36{\cdot}22°$ and $A_2 = 94{\cdot}87°$

| | Hend. | | Calc. 2 | |
|---|---|---|---|---|
| | C | TC | C | TC |
| $\omega_1$ | −69·9 | −75·8 | −64·2 | −77·5 |
| $\omega_2$ | 91·8 | 97·0 | 89·9 | 91·8 |
| $\omega_3$ | −70·6 | −41·2 | −76·5 | −43·6 |
| $\omega_4$ | 0 | −41·2 | 0 | −43·6 |
| $\omega_5$ | 70·6 | 97·0 | 76·5 | 91·8 |
| $\omega_6$ | −91·8 | −75·8 | −89·9 | −77·5 |
| $\omega_7$ | 69·9 | 52·9 | 64·2 | 58·6 |

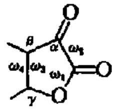
tetrahedral, the mean value being 115·1°. Similar mean values apply to the other cycloheptane rings in Table 3: 114·5° in **2**, 115·4° in **3**, 115·9° in **4**, 115·6° in **5** and 115·9° in **6**. The valency angle in the 6-membered ring of cyclohexane, 111·9°, is slightly greater than tetrahedral,[15] and still larger values are found in other medium-ring compounds, *e.g.* 115–118° in the cyclodecane ring.[16]

The $\alpha\beta'$-unsaturated $\gamma$-lactone ring approximates to an envelope form and is somewhat flatter than related $\gamma$-lactones lacking a C=C double bond; thus, the sum $\Sigma|\omega|$ derived from the endocyclic torsion angles of the lactone ring is 38° in euparotin, 87° in solstitalian (**2**), and 130° in bromodihydroisophotosantonic lactone acetate (**3**). A number of $\alpha$-methylene $\gamma$-lactones have been subjected to X-ray examination and the results listed in Table 6 for the torsion angle C($\gamma$)—O—C(carbonyl)—C($\alpha$) show that most of these lactone rings deviate significantly from the ideal envelope conformation. The CO and ethylenic groups of the unsaturated lactone in euparotin deviate only slightly from coplanarity, the C(13)—C(11)—C(12)—O(1) torsion angle being −2°. Somewhat larger torsion angles of this type are found in other $\alpha\beta'$-unsaturated $\gamma$-lactones, *viz* 9–23° in the compounds listed in Table 6.

Stöcklin *et al*[17] have measured the CD spectra of a large number of sesquiterpenoid lactones and shown that with a few exceptions the sign of the Cotton effect of the $n \rightarrow \pi^*$ transition of the $\alpha$-methylene $\gamma$-lactone chromophore is related to the position and stereochemistry of the ring fusion in the following way:

| Ring fusion | *cis* | *trans* |
|---|---|---|
| 6–7 | + | − |
| 7–8 | − | + |

Table 6. Conformational parameters for sesquiterpenoid $\alpha$-methylene $\gamma$-lactones



| Compound | I | II | III | IV | V | VI | VII |
|---|---|---|---|---|---|---|---|
| $\omega_1$ (deg.) | −3 | −14 | −14 | 7 | 13 | −12 | 9 |
| $\omega_2$ (deg.) | −2 | −10 | −19 | 23 | 10 | −9 | 17 |
| $\omega_3$ (deg.) | −11 | −41 | −41 | 40 | 25 | −28 | 38 |
| $\omega_4$ (deg.) | 102 | 71 | 64 | −66 | −93 | −36 | 59 |
| Ring junction | 6–7 | 6–7 | 6–7 | 7–8 | 7–8 | 7–8 | 7–8 |
| Stereochemistry | *trans* | *trans* | *trans* | *trans* | *trans* | *cis* | *cis* |

| | | | |
|---|---|---|---|
| I | Euparotin bromoacetate | V | Bromogaillardin[c] |
| II | Vernolepin[a] | VI | Bromomexicanin-E[d] |
| III | Berlandin[b] | VII | Bromohelenalin[e] |
| IV | Miscandenin[b] | | |

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[a] A. T. McPhail and G. A. Sim, *J. Chem. Soc.* **B**, 198 (1971).

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[c] T. A. Dullforce, G. A. Sim, and D. N. J. White, *J. Chem. Soc.* **B**, 1399 (1971).

[d] Ref. 8.

[e] Ref. 7.

Beecham has related this Cotton effect to the chirality of the C=C—C=O chromophore.[18] Since *trans*-fused lactones on six-membered or seven-membered rings are relatively rigid (as judged by molecular models), it is not unexpected that the chirality of the C=C—C=O group in these lactones should be determined by the position of the ring junction, and the X-ray results summarized in Table 6 indicate that a C(6),C(7)-*trans* ring junction gives rise to a left-handed chirality ($\omega$ negative) and a C(7),C(8)-*trans* ring junction to a right-handed chirality ($\omega$ positive). The greater flexibility of the *cis*-lactone and the variety of twist chair conformations accessible to the cycloheptane ring give rise to the possibility that the chirality of the C=C—C=O group in sesquiterpenoids such as bromohelenalin (**5**)[7] may not be determined solely by the position of the ring junction, and indeed bromohelenalin (**5**) and bromomexicanin-E (**6**)[8] have opposite chiralities for this group. The results in Table 6 show that in all these sesquiterpenoids the C($\alpha$)—C($\beta$)—C($\gamma$)—O and C=C—C=O torsion angles have paired signs, with the former angle being *ca* 2–3 times as large as the latter: it follows that knowledge of the sign of the Cotton effect of the $n \rightarrow \pi^*$ transition of the C=C—C=O chromophore should permit conformational deductions to be made about the ring junction at C($\beta$)—C($\gamma$) even when the rules proposed by Stöcklin *et al* are not valid.

The benzene solvent molecule in the crystal structure of euparotin bromoacetate is situated on the two-fold axis of the space group and is disordered over two alternative orientations. There are only normal van der Waals interactions between the solvent and the sesquiterpenoid molecules, the shortest separations between them being 3·63 and 3·74 Å.

The sesquiterpenoid molecules are held together in pairs by OH···O H-bonds of 2·75 Å.

## EXPERIMENTAL

*Crystal data.* $C_{22}H_{25}O_8Br\cdot\frac{1}{2}C_6H_6$, m.p. 156–157°, $M = 536{\cdot}4$. Monoclinic, $a = 34{\cdot}85$, $b = 7{\cdot}04$, $c = 10{\cdot}90$ Å, $\beta = 106°35'$, $U = 2563$ Å$^3$, $D_m = 1{\cdot}39$, $Z = 4$, $D_c = 1{\cdot}39$, space group $C2$ ($C_2^3$), $F(000) = 1028$. Absorption coefficient for Cu$K_\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å), $\mu = 28{\cdot}0$ cm$^{-1}$.

*Structure analysis.* Three dimensional X-ray intensity data were recorded on equi-inclination Weissenberg photographs and estimated visually; 1947 independent $|F_o|$ values were derived.

Approximate co-ordinates of the Br atom were obtained from a Patterson synthesis, and the C and O atoms of the sesquiterpenoid lactone were then located in 3-dimensional electron-density distributions calculated with weighted Fourier coefficients.[19] Several rounds of full-matrix least-squares adjustment of the co-ordinates and isotropic thermal parameters gave $R = 20{\cdot}9\%$. At this stage a difference electron-density distribution revealed the solvent benzene molecule disordered over two orientations, with the two-fold axis passing through opposite carbon atoms of the ring in one orientation, and through opposite bonds in the other. These carbon atoms were then included, with appropriate occupation numbers, in the least-squares calculations. The bromine atom was assigned an anisotropic temp factor, but isotropic parameters were retained for the other atoms in order to conserve computer time, and several rounds of calculations reduced $R$ to 13·2%.

The absolute configuration was established at this point. Values of $\Delta f'$ and $\Delta f''$ for bromine (Cu$K_\alpha$ radiation) were taken from 'International Tables'[20] and structure factors were calculated with co-ordinates corresponding to the absolute stereochemistry shown in **1a** and to the mirror image: the former alternative gave $R = 13{\cdot}1\%$ and the latter $R = 13{\cdot}4\%$, and Hamilton's test[21] indicated that this difference is highly significant.

The refinement procedure was concluded with two additional rounds of least-squares calculations incorporating proper allowance for anomalous dispersion, and this gave $R = 12{\cdot}8\%$. The weighting scheme used in all the least-squares calculations was $\sqrt{w} = 1$ when $|F_o| \leq 26$, $\sqrt{w} = 26/|F_o|$ when $|F_o| > 26$.

The calculations were performed on the IBM 7094 computer at the University of Illinois. We are indebted to the U.S. National Science Foundation for generous financial support.

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