137. Homoisoflavanones. V. Crystal and Molecular Structure of (−)-7-*O*-(*p*-Bromophenacyl)-eucomol. The Absolute Configuration of (−)-Eucomol[1])

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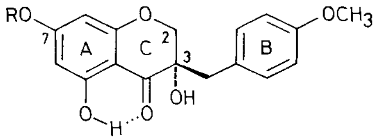
Zusammenfassung

Zur Abklärung der absoluten Konfiguration von (−)-Eucomol wurde eine Röntgenstrukturanalyse des 7-*O*-*p*-Bromphenacylderivates durchgeführt. Auf Grund der anomalen Streuung von CuK_α-Strahlung durch Brom liess sich 3*S*-Chiralität der Verbindung nachweisen. Die durch 372 Atomparameter beschriebene Struktur wurde mit 1745 Strukturfaktoren bis zu R = 0,071 verfeinert.

The homoisoflavanones are a class of natural products isolated from the bulbs of different *Eucomis* species [1–5] and *Scilla scilloides* DRUCE [6]. Eucomol (**1**), the major metabolite from *Eucomis bicolor* BAK, isolated first by *Böhler & Tamm* in 1967 [3] is known to be optically active ($[\alpha]_D^{24} = +26 \pm 2°$, $c = 0.505$, chloroform) due to its chiral carbon atom C(3). An attempt to determine its absolute configuration by means of CD./ORD. studies gave an equivocal result [7]. Having recently found a new and simple method for preparing derivatives of these compounds using the activated phenolic hydroxyl group at C(7) [1], we decided to prepare the title compound (**2**) in order to establish the absolute configuration by X-ray analysis using the anomalous dispersion effect of bromine.

Crystal Data. - (−)-7-*O*-(*p*-Bromophenacyl)-eucomol (**1**), $C_{25}H_{21}BrO_7$, M = 513.55, pale-yellow prismatic crystals, grown from a solution in chloroform/hexane, space group $P2_1$, $a = 22.540(6)$, $b = 5.680(2)$, $c = 8.523(3)$ Å, $\beta = 98.57(2)°$, V = 1079 Å^3, Z = 2, $d_{calc} = 1.58$ g/cm^3, $d_{exp} = 1.57(2)$ g/cm by floatation in 1,6-dibromohexane/chlorobenzene.



1 R = H Eucomol
2 R = $pBrC_6H_5COCH_2$

Intensity Data. – Intensity profiles of reflexions were measured on a CAD-4F-diffractometer in the normal-beam equatorial method, ($\omega/2\theta$)-scan mode, variable scan width of $\Delta\omega = 0.7° + 0.3 \text{ tg } \theta$, scan time adjusted to the peak intensity so as to maintain a constant (σ(I)/I) ratio of about 2% (max. scan time limited to 120 s). The profile analysis proposed by *Diamond* [8] was used to evaluate optimal values of net intensity, I, and variance, V(I), based on *Poisson* distribution. An intensity dependent term, c^2I^2, was added to the variance to obtain an experimental standard deviation $\sigma(I) = [V(I) + c^2I^2]^{1/2}$ ($c = 0.02$).

1793 unique reflexions within $\sin\theta/\lambda \geqslant 0.562$ Å^{-1} were measured using Cu*K*α-radiation ($\bar{\lambda} = 1.542$ Å, graphite monochromator), of which 1743 were judged to be significant ($I \geqslant 3\sigma(I)$). Data reduction by the *Wilson* method [9] yielded the averages $\overline{B} = 3.7$ Å^2, $\langle |E| \rangle = 0.867$, $\langle |E^2 - 1| \rangle = 0.790$, and $\langle |E|^2 \rangle = 0.998$. Intensities were not corrected for absorption; a maximal error of about 7% was estimated for the size of crystal used ($\mu(\text{Cu}K\alpha) = 33$ cm^{-1}).

Structure solution, refinement and determination of absolute configuration. – The bromine position could be determined by inspection of the *Patterson*-function. To avoid the spurious mirror plane in a bromine-phased electron density map, the phases, ϕ^{Br}, for which $|E| \geqslant 2.0$, and $|F_c^{\text{Br}}| \geqslant 0.5 F_o$, were accepted as basis to calculate the phases of about 400 *E*-values by the tangent procedure [10] using 4600 triple reactions. The resulting *E*-map showed the complete structure without the superimposed mirror image.

Diagonal least squares procedures were used to refine the structure. After initial refinement of coordinates, isotropic temperature factors, and a scale factor (k), the set of parameters was successively extended to include anisotropic vibrational parameters for the heavier atoms, hydrogen atoms in theoretical positions [11]1), with fixed isotropic temperature factors, and an isotropic extinction factor, *G*, [12]. The weighting scheme proposed by *Dunitz & Seiler* [13] was used

$$\omega_{\mathbf{h}} = (1/\sigma_F^2) \text{ exp. } \{ 8\pi^2 q \sin^2\theta/\lambda^2 \, p(p+q) \}$$

with $p = 5$ Å^{-2}, $q = 7$ Å^{-2}, and $\sigma_F = \sigma_{F^2}/2 F_o$ for significant reflexions ($\omega_h = 0$ for insignificant reflexions).

In a medium stage of refinement, the intensities of a number of *Friedel* pairs (h, k, l) and (–h, –k, –l), for which the anomalous dispersion effect was calculated to be large were remeasured. The results are compiled in *Table 1*. The complete correspondence between the signs of $\Delta I_{\mathbf{h}}$, the measured difference of $I_{\mathbf{h}} - I_{-\mathbf{h}}$, and of $\Delta F^2_{\text{calc}} = F^2_{\mathbf{h},\text{calc}} - F^2_{-\mathbf{h},\text{calc}}$, proved unequivocally the assumed 3*S* chirality of **2**.

The final LS-cycles leading to convergence of all 374 structural parameters resulted in an $R = 0.071$, and $R_\omega = 0.107$1), including 1743 significant structure factors. A remarkably low value of $G =$

Table 1. *Anomalous dispersion effect of Cu*$^{\text{K}}{}_\alpha$*-radiation measured on some* Friedel *reflexions.* $I_{\mathbf{h}}$ and $I_{-\mathbf{h}}$ are the observed intensities, $\Delta I_{\mathbf{h}} = I_{\mathbf{h}} - I_{\mathbf{h}}$, ΔF^2_{calc} is the theoretical difference of $|F^2_{\mathbf{h},\text{calc}}| - |F^2_{-\mathbf{h},\text{calc}}|$, assuming 3*S* chirality of **2**.

h	k	l	$I_{\mathbf{h}}$	$I_{-\mathbf{h}}$	$\Delta I_{\mathbf{h}}$	$\Delta F_c^2/\lvert F_c \rvert^2$ (3*S*)
1	1	1	68 850	74 400	−5 500	−0.13
1	2	1	26 300	24 550	+2 250	+0.10
1	4	4	730	625	+ 105	+0.39
1	5	2	5 100	5 900	− 800	−0.19
2	2	2	24 300	21 200	+2 100	+0.18
2	3	4	6 370	5 470	+ 900	+0.18
2	4	3	10 600	12 100	−1 500	−0.17
3	1	3	11 350	9 300	+2 050	+0.22

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1) The position of the hydroxyl group and methoxy hydrogen atoms were taken from a difference electron density map.

2.3(6), assuming a mean path length of t = 0.15 mm, was reached, resulting in a maximum extinction effect of 5% for some of the strongest low angle reflexions. – Atomic scattering factors were taken from Vol. III, International Tables of X-Ray Crystallography (1962). A list of the structure factors can be obtained from the authors (*HPW*).

Results. – Atomic coordinates and LS-derived e.s.d.'s are listed in *Table 2.* Mean positional e.s.d.'s are about 0.006 Å for C-, 0.005 Å for O-, 0.001 Å for Br-, and 0.15 Å for H-atoms. Labeling of atoms and rings is given in *Figure 1,* which also contains bond lengths and some torsion angles. None of the bond lengths and bond angles in the structure show large deviations from accepted, 'normal' values [14].

Figure 2, a stereoscopic view of the molecule, shows the conformation of the compound. It can be seen that the heterocyclic ring C has an envelope conformation with C(2) the flap. The C(3)-hydroxyl group is in *axial* position. There is an angular *intra*molecular hydrogen bond between the C(4)-oxo group and the C(5) hydroxyl with O(4) ... O(5) = 2.58(1) Å, and ∢(O(4) ... H–O(5)) = 156(2)°. The phenacyl group

Table 2. *Coordinates and e. s. d.'s. Values for C, O and Br are multiplied by 10^5, for H by 10^4*

O(1)	6564(1)	6866(7)	10982(4)	C(6″)	9166(3)	3335(13)	4554(8)
C(2)	6583(2)	8030(9)	12481(7)	C(7″)	8260(2)	5474(14)	5246(7)
C(3)	6794(2)	10582(10)	12502(6)	O(7″)	7910(2)	7095(11)	4966(6)
O(3)	6347(1)	11818(8)	11430(5)	C(8″)	8200(2)	3704(14)	6508(8)
C(4)	7386(2)	10695(10)	11796(6)	O(8″)	7666(2)	3966(9)	7190(5)
O(4)	7742(2)	12309(9)	12198(6)	Br	10399(0)	4933(0)	1538(0)
C(4A)	7473(2)	8935(11)	10647(6)	H(2E)	615(4)	806(17)	1278(10)
C(5)	7982(2)	9020(11)	9834(6)	H(2A)	686(3)	717(17)	1332(10)
O(5)	8396(2)	10774(9)	10173(6)	H(3)	640(4)	1340(18)	1127(10)
C(6)	8065(2)	7421(14)	8684(7)	H(5)	827(5)	1174(23)	1101(13)
C(7)	7631(2)	5667(11)	8303(6)	H(6)	842(4)	754(18)	815(10)
C(8)	7122(2)	5509(10)	9064(6)	H(8)	681(4)	425(17)	875(10)
C(8A)	7063(2)	7125(10)	10227(6)	H(9X)	699(4)	1332(19)	1410(10)
C(9)	6889(2)	11567(12)	14154(7)	H(9Y)	724(3)	1072(17)	1478(10)
C(1′)	6372(2)	11429(11)	15109(6)	H(2′)	594(3)	1443(16)	1421(10)
C(2′)	5935(3)	13152(12)	14995(8)	H(3′)	516(3)	1427(16)	1587(10)
C(3′)	5477(3)	13046(12)	15953(8)	H(5′)	589(4)	818(17)	1793(10)
C(4′)	5471(2)	11224(12)	17017(7)	H(6′)	668(4)	841(18)	1625(10)
C(5′)	5901(3)	9486(13)	17154(8)	H(8X′)	532(4)	824(18)	1894(11)
C(6′)	6358(3)	9599(12)	16178(8)	H(8Y′)	456(4)	851(19)	1874(11)
O(7′)	5001(2)	11272(11)	17923(6)	H(8Z′)	501(4)	1004(23)	2015(10)
C(8′)	4976(3)	9409(18)	18999(9)	H(8X″)	854(4)	330(18)	738(10)
C(1″)	8786(2)	5271(12)	4360(6)	H(8Y″)	814(3)	234(18)	571(10)
C(2″)	8869(3)	7033(15)	3294(8)	H(2″)	860(4)	842(19)	313(10)
C(3″)	9344(3)	6877(17)	2420(9)	H(3″)	939(3)	813(17)	167(10)
C(4″)	9726(2)	4973(19)	2669(7)	H(5″)	994(4)	187(19)	383(11)
C(5″)	9660(3)	3233(15)	3698(9)	H(6″)	910(4)	204(17)	531(10)

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[1] $$R = \underset{\mathbf{h}}{\Sigma_o} \mid F - k\ G \mid F_c \mid \mid / \underset{\mathbf{h}}{\Sigma} F_o$$

$$R_\omega = \underset{\mathbf{h}}{\Sigma}\ \omega_{\mathbf{h}}(F_o - k\ G \mid F_c \mid)^2 / \underset{\mathbf{h}}{\Sigma} \omega_{\mathbf{h}}\ F_o{}^2$$

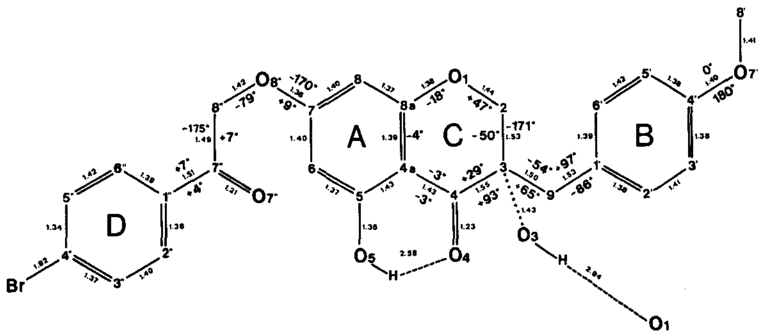

Fig. 1. *Numbering of atoms and rings.* Bond lengths in Å, mean e.s.d. around 0.01 Å, and torsion angles, mean e.s.d. about 1°.

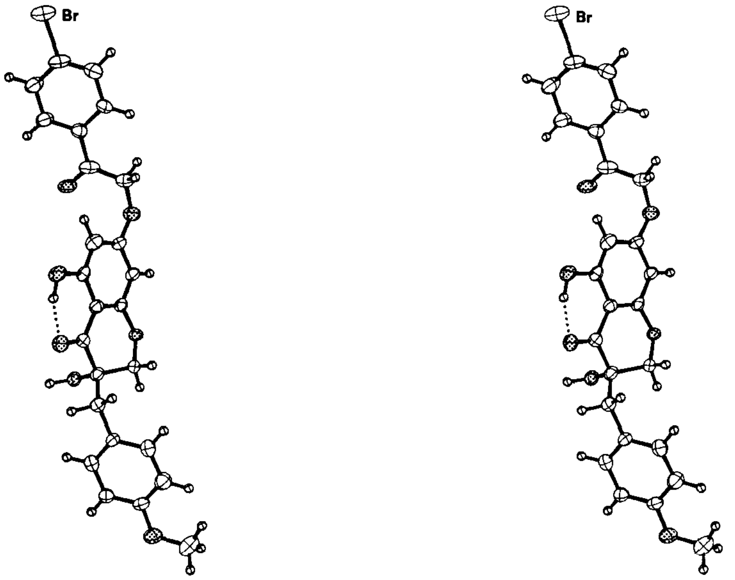

Fig. 2. *Stereoscopic projection of molecule. 50%* probability ellipsoid for anisotropic vibration are drawn for C, O, and Br, H-atoms have been given a uniform, isotropic B = 1 Å².

including C(8″) and O(8″) is approximately planar (see torsion angles around C(1″)–C(7″), and C(7″)–O(8″), in *Figure 1*). C(8″) and O(8″) are also approximately coplanar to the aromatic ring A (see torsion angles around C(7)–O(8″) in *Figure 1*). The methoxy group is in the plane of ring B with one hydrogen atom roughly *cis* to C(4′)–O(7′). *Figure 3* shows the molecular packing in the crystal. There is a linear, *inter*molecular hydrogen bond linking O(1), the heteroatom in ring C, with the C(3)-hydroxyl oxygen atom O(3), in the relative position (x, y + 1, z); O(1) ... O(3) = 2.94(1) Å (this hydrogen bond is not visible in the packing diagram).

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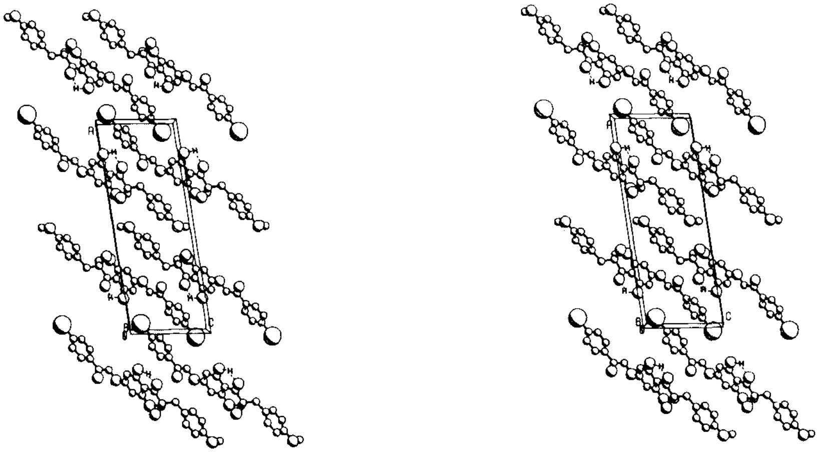

Fig. 3. *Stereoscopic packing diagram viewed along* **b**. The *inter*molecular H-bond is indicated by a dotted line, the *inter*molecular H-bond linking O(1)...O(3) (x,1+y,z,) cannot be drawn in this projection.

REFERENCES

[1] *W. Heller, P. Andermatt, W. A. Schaad & Ch. Tamm*, Helv. *59*, 2048 (1976).
[2] *Ch. Tamm*, Arzneimittel-Forschung, *22*, 1776 (1972).
[3] *P. Böhler & Ch. Tamm*, Tetrahedron Letters, *1967*, 3749.
[4] *W. T. L. Sidwell & Ch. Tamm*, Tetrahedron Letters, 1970, 475.
[5] *R. E. Finckh & Ch. Tamm*, Experientia, *26*, 472 (1970).
[6] *I. Kuomo, T. Komori & T. Kawasaki*, Tetrahedron Letters, *1973*, 4569.
[7] *P. Böhler*, Diss. Basel 1967.
[8] *R. Diamond*, Acta Crystallogr. *A25*, 43 (1969).
[9] *A. J. C. Wilson*, Nature, 151, 150 (1942).
[10] *J. Karle & I. L. Karle*, Acta Crystallogr. *21*, 849 (1966).
[11] *A. I. Kitaigorodskii*, 'Organic Chemical Crystallography', p. 12 ff., Consultants Bureau Entreprises, Inc., New York, 1961.
[12] *J. D. Dunitz & P. Seiler*, Acta Crystallogr. *B29*, 589 (1973).
[13] *P. Coppens & W. C. Hamilton*, Acta Crystallogr. *A26*, *71* (1971).
[14] *O. Kennard*, Ed., Molecular Structures and Dimensions, Vol. A1 (1972), p. S2.