

The Crystal and Molecular Structure of Licoricone Monobromoacetate

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The crystal structure of licoricone bromoacetate, $C_{24}H_{23}O_7Br$, has been determined in order to elucidate the molecular structure of licoricone, an isoflavone isolated from the root of licorice (*Glycyrrhiza spp.*). The crystals are triclinic with space group $P\bar{1}$ and the unit-cell dimensions are: $a = 11.70$, $b = 13.11$, $c = 8.16 \pm 0.01$ Å, $\alpha = 103.8$, $\beta = 91.6$, $\gamma = 103.4 \pm 0.1^\circ$; $Z = 2$. The crystal structure was solved by the heavy-atom method and refined by the block-matrix least-squares method. The final R value for 2664 observed reflexions measured on a diffractometer was 0.112. The molecular structure of licoricone was determined by the present study to be 2',7-dihydroxy-4',6'-dimethoxy-5'-(3,3-dimethylallyl)isoflavone, which is a unique example of a naturally occurring flavonoid having phloroglucinol-type O -functional groups in the B ring.

Introduction

Licoricone, $C_{22}H_{22}O_6$, is one of the isoflavones isolated from the root of licorice, *Glycyrrhiza spp.* (Leguminosae), as an active principle in the treatment of stomach ulcers along with some other phenolic constituents (Shibata & Saitoh, 1968; Saitoh & Shibata, 1969).

The structure of licoricone was only partially revealed by chemical and spectrographic methods as an isoflavone having two hydroxyl groups. Eleven possible structures were formulated but no conclusive evidence for the structure of licoricone had been obtained. An X-ray structure analysis of licoricone monobromoacetate, Fig. 1 (II), was therefore undertaken.

Experimental

Licoricone was treated with bromoacetyl bromide in chloroform containing a few drops of pyridine to give a dibromoacetate which underwent a partial deacylation when passing through a silica gel column giving licoricone monobromoacetate. The crystals grown from methanol solution were colourless plates with well developed $\{1\bar{1}0\}$ faces. The crystal density

was measured by the flotation method in a mixture of hexane and carbon tetrachloride. The space group was determined from precession photographs of the three equatorial layers, $hk0$, $h0l$ and $0kl$. The crystal data are given in Table 1.

Table 1. Crystal data

Licoricone monobromoacetate, $C_{24}H_{23}O_7Br$, M.W. 503, m.p. 205 ~ 208 °C.
Triclinic
 $a = 11.70 \pm 0.01$, $b = 13.11 \pm 0.01$, $c = 8.16 \pm 0.01$ Å,
 $\alpha = 103.8 \pm 0.1$, $\beta = 91.6 \pm 0.1$, $\gamma = 103.4 \pm 0.1^\circ$.
 $U = 1167$ Å³,
 $D_m = 1.426$ g cm⁻³, $D_x = 1.438$ g cm⁻³, $Z = 2$.
 $F(000) = 516$.
 μ for Mo $K\alpha = 19.9$ cm⁻¹.
Space group: $P\bar{1}$.

The precise lattice constants and three-dimensional intensity data were derived from the measurements on a Rigaku computer controlled four-circle diffractometer. A prismatic crystal of the dimensions $0.26 \times 0.13 \times 0.58$ mm was mounted with the c axis coincident with the ϕ axis of the diffractometer. Reflexions were measured within a 2θ angle of 50° using Mo $K\alpha$ radiation and the ω - 2θ scan technique. The scanning speed was chosen as $2^\circ 2\theta/\text{min}$ and the background was measured on both sides of the scan in 10 s. The intensities were corrected for Lorentz and polarization factors but no absorption correction was applied. A total of 2664 independent structure factors having net intensities greater than three times each standard deviation were finally derived.

Determination and refinement of the structure

The structure was solved by the heavy-atom method. Refinement of the atomic parameters for all the atoms except for hydrogen was carried out by the block-matrix least-squares method [program by Okaya & Ashida (1967)]. Five cycles of calculations with iso-

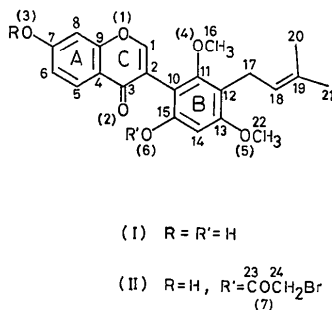


Fig. 1. Chemical formulae of (I) licoricone, (II) licoricone monobromoacetate.

tropic followed by four cycles with anisotropic temperature factors reduced the R value to 0.11 for 2664 non-zero observed structure factors. The weighting function used for the calculations was:

$$w = 1.0 \text{ when } F_o > 9, \\ w = 0 \text{ when } F_o \leq 9.$$

The final atomic parameters and their estimated standard deviations are given in Table 2. The observed and calculated structure factors are listed in Table 3.

Discussion of the structure

The molecular structure of licoricone monobromoacetate determined by the present analysis is shown in Fig. 2. The structure of licoricone is therefore established as shown in Fig. 1 (I). It is now found that licoricone is an isoflavone derivative having a unique 2', 4', 6' arrangement of O -functional groups in the B ring. In the present structure, the hydroxyl group at C(7) is free but the one at C(15) is still bromoacetylated. As was described previously, the dibromoacetate of licoricone was partially hydrolysed during the purification process giving the monobromoacetate. The hydroxyl group at C(7) should be more active than that at C(15), so that the bromoacetyl group linked to

C(7)-OH has been removed when passing through a silica gel column.

The bond lengths and angles of the molecule are shown in Fig. 3, and are in good agreement with those found in 4'-bromo-3-hydroxyflavone and 4'-bromo-5-hydroxyflavone (Hayashi, Kawai, Ohno, Iitaka &

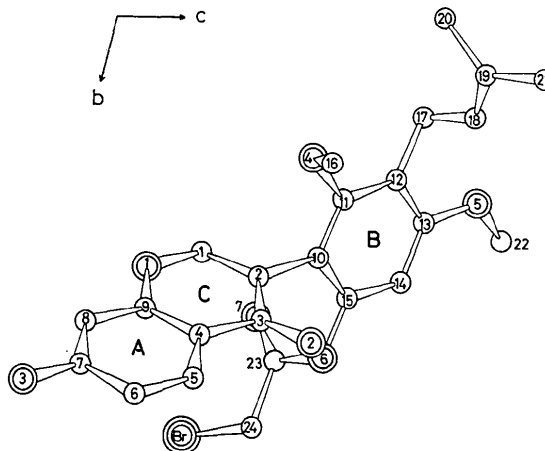


Fig. 2. Molecular structure of licoricone monobromoacetate. Single circles represent carbon, double circles oxygen and triple circles bromine atoms.

Table 2. Final atomic parameters and their standard deviations

Temperature factors are of the form $T = \exp [-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

The e.s.d.'s are given in parentheses in units of the least significant digits. All parameters are multiplied by 10^4 .

| | x | y | z | β_{11} | β_{22} | β_{33} | β_{12} | β_{13} | β_{23} |
|-------|-----------|-----------|------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Br | 439 (1) | 10115 (1) | 2180 (2) | 181 (1) | 130 (1) | 278 (2) | 65 (1) | 4 (2) | 100 (1) |
| C(1) | 2445 (7) | 6920 (7) | 1498 (11) | 73 (8) | 91 (8) | 196 (18) | -0 (7) | 22 (10) | 58 (10) |
| C(2) | 2982 (7) | 7342 (6) | 3113 (9) | 66 (7) | 71 (7) | 112 (14) | 14 (6) | -6 (8) | 32 (8) |
| C(3) | 4157 (7) | 8102 (6) | 3475 (9) | 73 (8) | 71 (7) | 109 (14) | 5 (6) | -13 (8) | 25 (8) |
| C(4) | 4681 (7) | 8376 (6) | 1980 (10) | 57 (7) | 65 (7) | 148 (15) | -0 (6) | -15 (8) | 31 (8) |
| C(5) | 5813 (7) | 9121 (7) | 2085 (10) | 69 (8) | 69 (7) | 180 (17) | -3 (6) | -30 (9) | 29 (9) |
| C(6) | 6315 (7) | 9400 (7) | 685 (11) | 78 (8) | 94 (8) | 170 (17) | -1 (7) | -20 (9) | 49 (10) |
| C(7) | 5625 (8) | 8903 (8) | -902 (11) | 88 (9) | 103 (9) | 176 (18) | 8 (7) | -3 (10) | 66 (10) |
| C(8) | 4512 (7) | 8158 (7) | -1073 (10) | 74 (8) | 77 (7) | 141 (15) | 4 (6) | -1 (9) | 33 (9) |
| C(9) | 4078 (6) | 7913 (6) | 392 (10) | 52 (7) | 67 (7) | 171 (16) | 8 (6) | -6 (8) | 36 (8) |
| C(10) | 2309 (7) | 6994 (6) | 4527 (9) | 64 (7) | 69 (7) | 125 (14) | 5 (6) | -16 (8) | 28 (8) |
| C(11) | 2158 (7) | 5957 (6) | 4802 (9) | 62 (7) | 58 (6) | 144 (15) | 12 (6) | -7 (8) | 24 (8) |
| C(12) | 1495 (7) | 5608 (6) | 6044 (10) | 59 (7) | 68 (7) | 150 (15) | 5 (6) | -25 (8) | 32 (8) |
| C(13) | 993 (7) | 6353 (7) | 7047 (9) | 61 (7) | 83 (7) | 130 (15) | 1 (6) | -5 (8) | 36 (8) |
| C(14) | 1100 (7) | 7403 (7) | 6823 (10) | 62 (7) | 70 (7) | 146 (15) | 2 (6) | -18 (8) | 26 (8) |
| C(15) | 1768 (6) | 7681 (6) | 5547 (9) | 61 (7) | 65 (6) | 119 (14) | 20 (6) | -8 (8) | 16 (8) |
| C(16) | 3846 (8) | 5313 (9) | 4265 (13) | 89 (10) | 138 (11) | 295 (25) | 54 (9) | 28 (12) | 77 (14) |
| C(17) | 1315 (7) | 4475 (7) | 6329 (11) | 90 (9) | 64 (7) | 222 (19) | 6 (6) | -28 (10) | 57 (9) |
| C(18) | 2220 (7) | 4477 (6) | 7686 (10) | 89 (9) | 61 (7) | 164 (16) | 16 (6) | 14 (9) | 41 (9) |
| C(19) | 2767 (8) | 3719 (7) | 7661 (11) | 79 (9) | 71 (7) | 235 (20) | 9 (7) | 17 (10) | 39 (10) |
| C(20) | 2650 (11) | 2726 (9) | 6234 (16) | 160 (15) | 76 (10) | 436 (35) | 28 (10) | -32 (18) | -16 (14) |
| C(21) | 3604 (10) | 3785 (9) | 9216 (13) | 148 (13) | 114 (10) | 256 (24) | 33 (9) | -61 (14) | 42 (13) |
| C(22) | -361 (9) | 6652 (9) | 9165 (12) | 113 (11) | 133 (11) | 160 (18) | 24 (9) | 49 (11) | 28 (11) |
| C(23) | 1132 (7) | 8792 (7) | 4100 (10) | 74 (8) | 66 (7) | 179 (17) | 7 (6) | 1 (9) | 28 (9) |
| C(24) | 1480 (8) | 9960 (7) | 3918 (12) | 108 (10) | 75 (8) | 234 (20) | 21 (7) | -7 (11) | 60 (10) |
| O(1) | 2975 (4) | 7196 (5) | 161 (6) | 62 (5) | 96 (5) | 135 (10) | -15 (4) | -9 (6) | 29 (6) |
| O(2) | 4671 (5) | 8471 (5) | 4921 (7) | 96 (6) | 116 (6) | 123 (10) | -6 (5) | -10 (6) | 34 (6) |
| O(3) | 6120 (5) | 9192 (5) | -2287 (7) | 76 (6) | 125 (6) | 195 (12) | -10 (5) | 7 (7) | 70 (7) |
| O(4) | 2632 (5) | 5231 (4) | 3740 (7) | 92 (6) | 74 (5) | 194 (12) | 30 (4) | 10 (7) | 26 (6) |
| O(5) | 339 (5) | 5991 (5) | 8295 (7) | 98 (6) | 98 (5) | 152 (11) | -5 (5) | 11 (6) | 52 (6) |
| O(6) | 1904 (4) | 8726 (4) | 5302 (6) | 73 (5) | 57 (4) | 166 (11) | 7 (4) | -18 (6) | 25 (5) |
| O(7) | 333 (5) | 8041 (5) | 3309 (8) | 112 (7) | 82 (5) | 258 (14) | -5 (5) | -66 (8) | 50 (7) |

Table 3. Observed and calculated structure factors. Reflexions marked with an asterisk were omitted from the refinement.

Table with multiple columns of numerical data representing structure factors. Headers include 'K' and 'FD' for observed and calculated values, and 'FC' for structure factor components. The table is organized into several groups corresponding to different Miller indices (hkl).

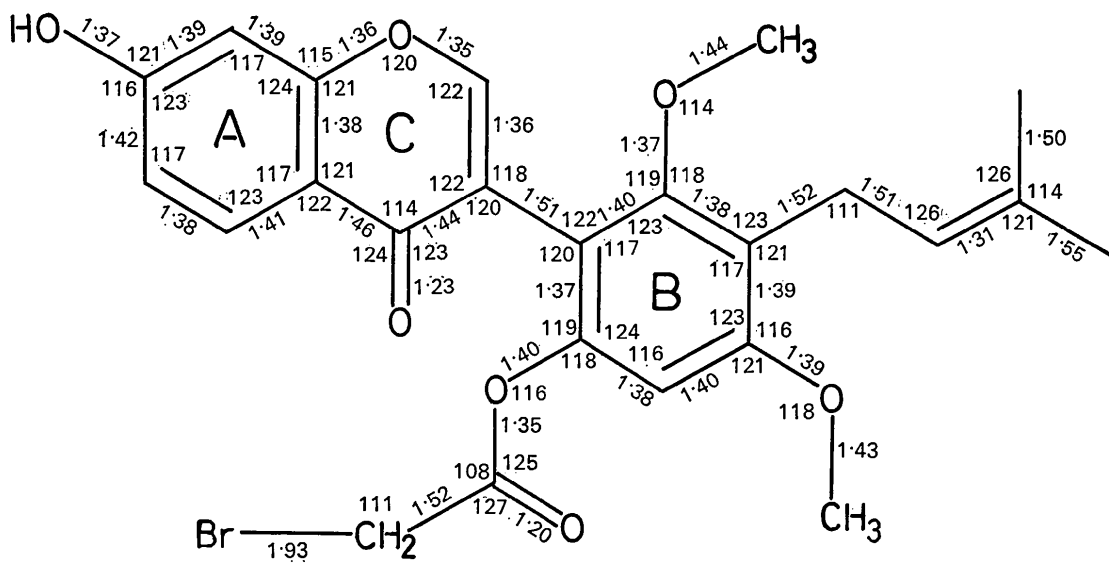
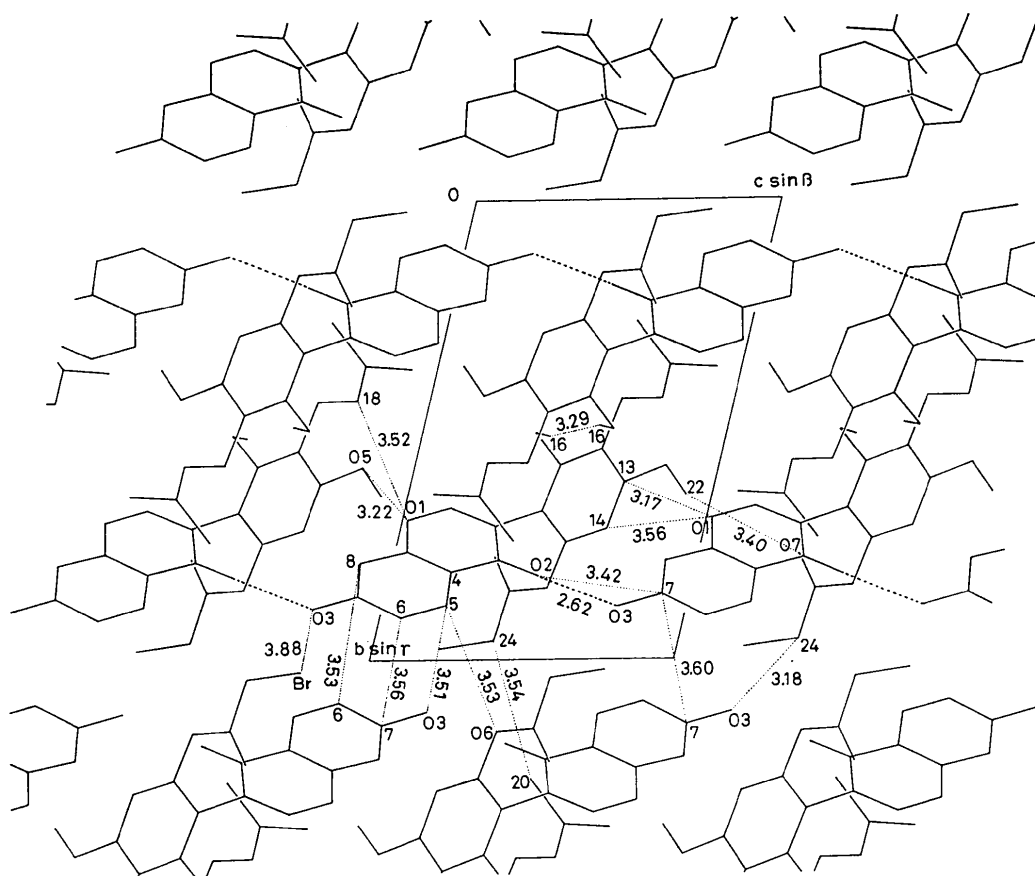


Fig. 3. Bond lengths and angles.

Fig. 4. Projection of the crystal structure along the *a* axis. Hydrogen bonds are shown by broken lines.

Akimoto, 1973). In Table 4 are listed the bond lengths arranged in groups of similar type. The mean bond lengths averaged over each type of bond agree well with the normally accepted values.

Table 4. Mean bond lengths arranged in groups of similar bonds

| | |
|---|--------|
| C-Br | 1.93 Å |
| C(aromatic)-OH or OCH ₃ | 1.38 |
| C=O | 1.23 |
| C(sp ²)-O | 1.35 |
| O-CH ₃ | 1.44 |
| C(sp ²)-C(sp ²) | 1.47 |
| C(sp ²)-C(sp ³) | 1.52 |
| C=C | 1.34 |
| Aromatic C-C | |
| A ring | 1.39 |
| B ring | 1.39 |

The planarity of each ring and the perpendicular distances of the atoms from the least-squares planes can be seen in Table 5. Both the aromatic rings *A* and *B* are almost planar. The heterocyclic *C* ring is also planar and is almost coplanar with the *A* ring. The

Table 5. Deviations of the atoms from the least-squares planes

| Plane forming atoms and distances from the plane | Distances from the plane | | Coefficients of the equation of the plane | |
|--|--------------------------|---------|---|--------|
| <i>A</i> ring | | | | |
| C(4) 0.007 Å | C(3) | 0.032 Å | <i>A</i> | -0.660 |
| C(5) 0.000 | O(1) | 0.015 | <i>B</i> | 0.750 |
| C(6) -0.006 | O(2) | 0.011 | <i>C</i> | -0.048 |
| C(7) 0.006 | O(3) | 0.017 | <i>D</i> | -5.586 |
| C(8) 0.001 | | | | |
| C(9) -0.007 | | | | |
| <i>B</i> ring | | | | |
| C(10) 0.004 | C(2) | -0.055 | <i>A</i> | 0.752 |
| C(11) 0.002 | O(4) | -0.066 | <i>B</i> | 0.358 |
| C(12) -0.008 | C(16) | 1.217 | <i>C</i> | 0.553 |
| C(13) 0.009 | C(17) | -0.031 | <i>D</i> | 4.041 |
| C(14) -0.003 | O(5) | 0.010 | | |
| C(15) -0.004 | O(6) | -0.001 | | |
| | C(22) | -0.204 | | |
| <i>C</i> ring | | | | |
| C(1) 0.000 | C(5) | 0.023 | <i>A</i> | -0.647 |
| C(2) 0.004 | C(8) | 0.041 | <i>B</i> | 0.759 |
| C(3) -0.006 | C(10) | 0.025 | <i>C</i> | -0.067 |
| C(4) 0.004 | O(2) | -0.037 | <i>D</i> | -5.563 |
| C(9) 0.000 | | | | |
| O(1) -0.002 | | | | |
| Acyl group | | | | |
| O(6) -0.002 | C(15) | -0.096 | <i>A</i> | -0.700 |
| C(23) 0.007 | Br | -0.032 | <i>B</i> | 0.236 |
| O(7) -0.003 | | | <i>C</i> | 0.674 |
| C(24) -0.002 | | | <i>D</i> | 0.900 |

Table 5 (cont.)

| Dimethylallyl group | | | | |
|---------------------|--------|-------|-------|-----------------|
| C(17) | -0.029 | C(12) | 0.908 | <i>A</i> 0.636 |
| C(18) | 0.035 | C(11) | 2.193 | <i>B</i> 0.524 |
| C(19) | 0.016 | C(13) | 0.501 | <i>C</i> -0.566 |
| C(20) | 0.002 | | | <i>D</i> -5.151 |
| C(21) | -0.025 | | | |

The equations of the planes are of the form $AX + BY + CZ = D$, where X , Y , Z and D are in Å units relative to the orthogonal axes, $X \parallel b^* \times c$, $Y \parallel b^*$, $Z \parallel c$.

dihedral angle between the two rings *B* and *C* is $75^\circ 13'$ which differs greatly from $18^\circ 48'$ found in 4'-bromo-3-hydroxyflavone and $6^\circ 36'$ in 4'-bromo-5-hydroxyflavone. It is clearly seen that the more bulky the substituents attached at the *ortho* positions with respect to the bond connecting *B* and *C* rings, the larger the twist angle about the bond. One of the methoxyl groups on the *B* ring is nearly coplanar with the ring while the other turns about 90° from the ring and gives rise to a strong intermolecular interaction with the one related to it by a centre of symmetry, the dihedral angles between the planes formed by the methoxyl groups and the ring being $9^\circ 15'$ and $86^\circ 50'$ respectively. The five atoms comprising the 3,3-dimethylallyl group lie on a plane which makes an angle of $69^\circ 20'$ with the *B* ring. The atoms in the bromoacetyl group, O(6), C(23), O(7), C(24) and Br, lie also on a plane and the angle between the in mean plane and the *B* ring is $86^\circ 2'$.

The projection of the crystal structure along the *a* axis is shown in Fig. 4. In this Figure are shown, by dotted lines, the intermolecular short distances less than 3.6 Å (where the bromine atom is involved the limit is extended to 3.9 Å). Although hydrogen atoms were not located in the present analysis, the hydrogen bond may be considered for $C=O(2) \cdots H-O(3)$ (2.62 Å). The molecules are linked by the hydrogen bonds in the *c* direction to form a chain and the chains are held together mainly by the interactions between the phenolic groups and by van der Waals forces.

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