

## Rearrangement and Orientation in Citran Synthesis. X-Ray Crystal Structures of (-)-Bruceol and a ( $\pm$ )-Deoxybruceol Derivative

By Michael J. Begley, Leslie Crombie,\* David A. Slack, and Donald A. Whiting,\* Department of Chemistry, University of Nottingham, Nottingham NG7 2RD

Despite their co-occurrence in *Eriostemon brucei*, and the similarity between their chiroptical properties, an X-ray study confirms the structure of bruceol to be (1) and shows that of deoxybruceol (studied as a dibromo-derivative) to be (3), *i.e.* their *p*-menthane segments are of opposite orientation relative to the coumarin ring. Strain in these structures is similar to that in the citrans described in the preceding paper.

Two monochromens are formed when 5,7-dihydroxycoumarin is treated with citral and pyridine: one of these is a citran precursor and its orientation is shown by nuclear Overhauser effects. On heating this chromen, rearrangement occurs to give deoxybruceol as the major product; isodeoxybruceol, of the same orientation as the chromen, is the minor product. Reference is made to the curious biosynthetic situation in *E. brucei*.

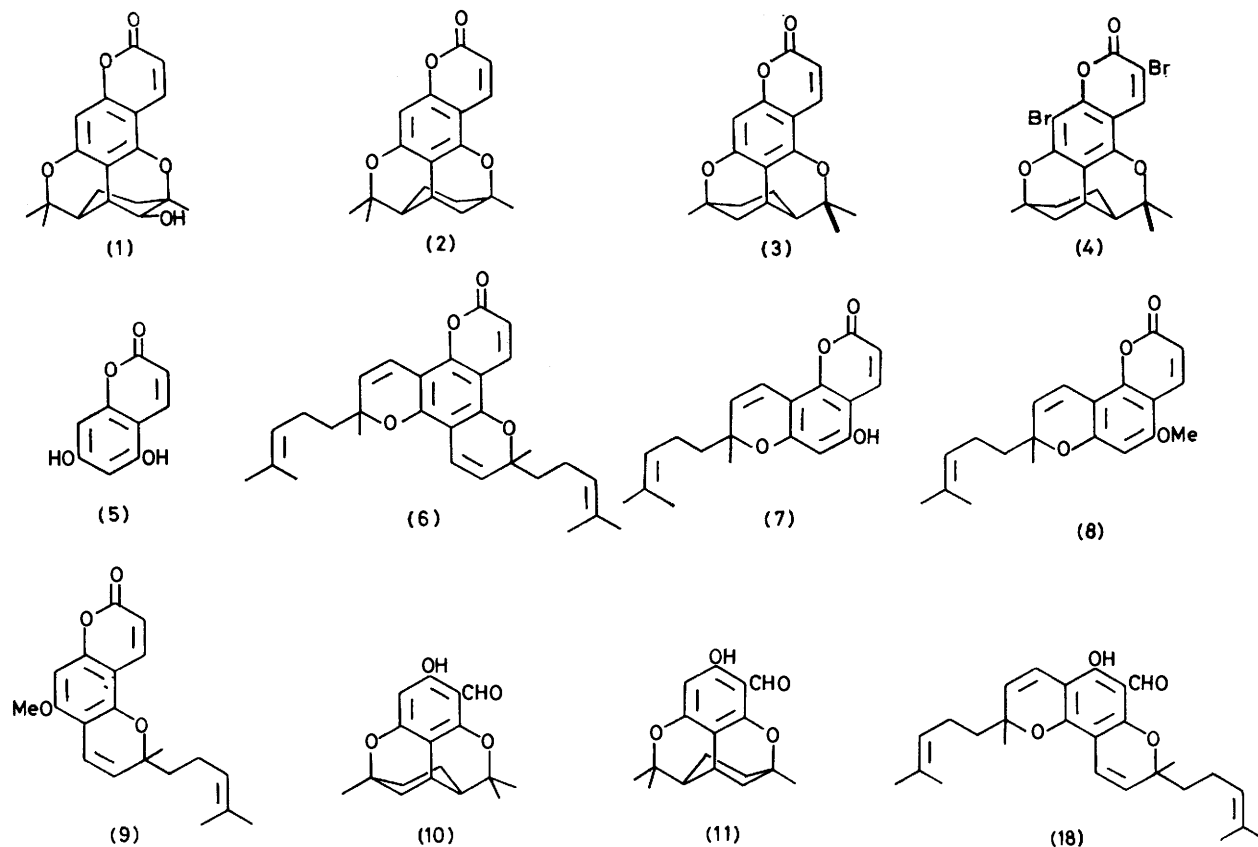
ISOPRENYLATED coumarins comprise a well-defined subgroup of the meroterpenoids, and many structurally interesting modifications are known. Among these is bruceol (1), from the Australian species *Eriostemon brucei*

F. Muell (Rutaceae), the first citran to be described.<sup>1</sup> Its assignment of structure rests on an X-ray study.<sup>1</sup>

<sup>1</sup> A. M. Duffield, P. R. Jeffries, F. N. Maslen, and A. I. M. Rae, *Tetrahedron*, 1963, **19**, 593.

Co-occurring with bruceol is a second compound, from spectral information shown to be closely related to (1), tacitly accorded structure (2) on the basis of its origins.<sup>2,3</sup> Indeed, the oxidation (2)  $\rightarrow$  (1) seemed an attractive

with (-)-deoxybruceol except for optical activity, has been synthesised<sup>3</sup> by the pyridine-catalysed condensation of citral with 5,7-dihydroxycoumarin, and this leaves little doubt as to the overall structure though the



biogenetic hypothesis. Other circumstantial evidence had tended to support this relationship: thus the o.r.d.

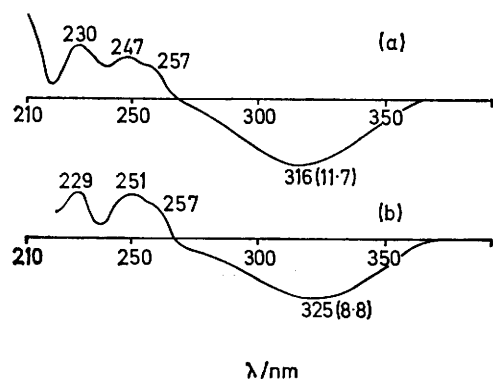


FIGURE 1 C.d. spectra in dioxan (a) natural bruceol and (b) natural deoxybruceol in dioxan

curves for bruceol and deoxybruceol are similar, as are the c.d. curves (Figure 1). ( $\pm$ )-Deoxybruceol, identical

<sup>2</sup> P. R. Jeffries and G. K. Worth, *Tetrahedron*, 1973, **29**, 903.

<sup>3</sup> L. Crombie and R. Ponsford, *J. Chem. Soc. (C)*, 1971, 788; *Chem. Comm.*, 1968, 368.

assignment of citran orientation [*i.e.* (2) or (3)] still rests on analogy. The rather subtle relationship between chromen and citran orientation is summarised in the preceding paper.<sup>4</sup> Because of uncertainties involved in the diagnosis of the citran orientation by chemical and spectral means, we have resorted to an X-ray crystallographic study to ascertain the orientation of deoxybruceol.

Since supplies of natural (-)-deoxybruceol were scarce, synthetic ( $\pm$ )-deoxybruceol was investigated, but an acceptable crystal could not be obtained for a direct-methods approach. A suitable crystal was obtained, however, from the dibromo-compound. The crystal structure of ( $\pm$ )-dibromodeoxybruceol was determined from diffractometer data (1 494 reflections), solved by the heavy-atom method, and refined by least-squares and difference-Fourier methods to  $R = 7.4\%$ . A general view (Figure 2) of the resulting structure shows that the citran orientation is in fact the reverse of that in natural bruceol (1), and the same as in the acetyl- and formyl-citrans of the preceding paper.<sup>4</sup>

For crystallographic purposes the numbering scheme of Figure 3 was adopted; bond lengths and angles are <sup>4</sup> M. J. Begley, L. Crombie, R. W. King, D. A. Slack, and D. A. Whiting, preceding paper.

displayed in Figures 4 and 5, together with an indication of their standard deviations. In view of the larger

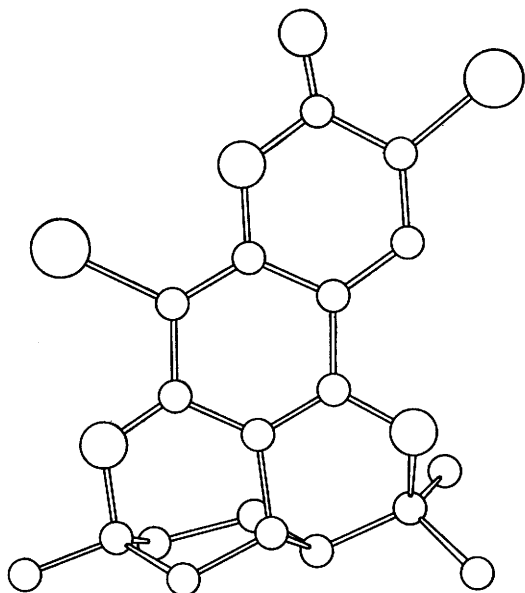


FIGURE 2 Dibromodeoxybruceol: general view

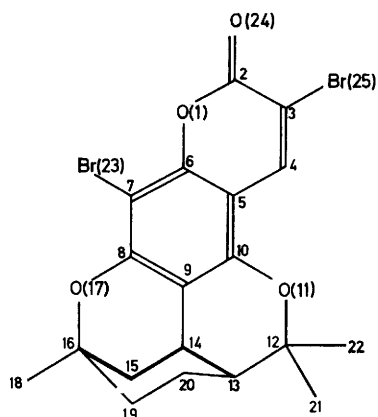


FIGURE 3 Dibromodeoxybruceol: crystallographic numbering scheme

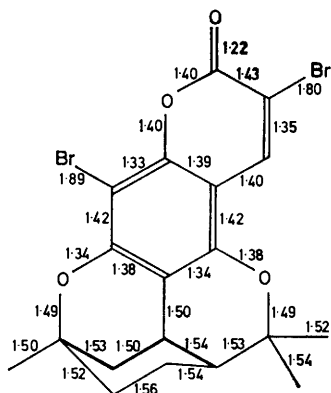


FIGURE 4 Dibromodeoxybruceol: bond lengths in Å (largest standard deviation 0.02 Å)

standard deviations (limitations of crystal size), the values of bond lengths and angles are as expected and, where applicable, are similar to those in the two citran structures of the preceding paper.<sup>4</sup> An exception was the C(3)–Br(25) bond, which appeared rather short

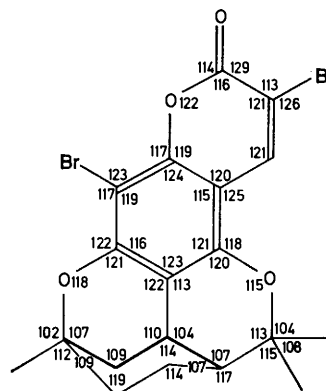


FIGURE 5 Dibromodeoxybruceol: bond angles (degrees; largest standard deviation 1.0°); additional angles O(11)–C(12)–C(21), 106°; C(13)–C(12)–C(22), 111°; C(15)–C(16)–C(18), 115°; O(17)–C(16)–C(19), 112°

(1.80 Å). The occupation fraction of Br(25) was therefore refined, and converged to 0.704 indicating that *ca.* 30% of monobromobruceol had co-crystallised with 70% of the dibromo-derivative. The site of Br(25) is therefore occupied by a hydrogen atom in 30% of the molecules. No intermolecular contacts less than the sum of the van der Waals radii were discovered with the exception of a Br(23) ··· Br(25') contact distance of 3.35 Å, which

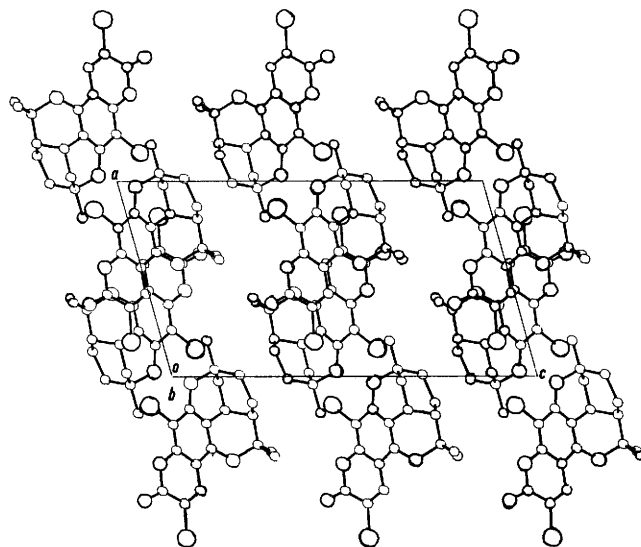


FIGURE 6 Dibromodeoxybruceol: arrangement of molecules in unit cell

is less than twice the van der Waals radius for bromine. This close contact is not present in the mono-bromo-derivative and is alleviated by the co-crystallisation.

The arrangement of molecules within the unit cell is shown in Figure 6.

Torsion angles are displayed in Table 1. They show considerable distortions from idealised values and are similar to those we have found in other cases. The mean plane through the aromatic ring again reveals a shallow 'boat' conformation with C(6) 0.05 Å and C(9) 0.07 Å above, and C(5) 0.04 Å, C(7) 0.00 Å, C(8) 0.06 Å, and C(10) 0.02 Å below the plane. The larger standard deviations in this structure make the differences less significant than the cases given in the preceding paper,

afforded three products: the bischromen (6) (2%) and two monochromens, (7), m.p. 136–138° (13%), and (12), m.p. 113–115° (15%). Unchanged coumarin was also isolated; the yields do not have synthetic significance as conditions were selected merely to minimise product complexity.

Structure (7) was assigned to the higher melting isomer on the basis of a nuclear Overhauser effect (n.O.e.) observed with its methyl ether (8). Irradiation at the OMe frequency resulted in enhancement of the aromatic proton (36%) and coumarin  $\beta$ -proton (15%) signals. The

TABLE 1  
Torsion angles (degrees) for dibromodeoxybruceol (4)

C(6)–O(1)–C(2)–C(3)	6.5	C(6)–O(1)–C(2)–O(24)	–171.8	C(2)–O(1)–C(6)–C(5)	–0.5
C(2)–O(1)–C(6)–C(7)	–176.3	O(1)–C(2)–C(3)–C(4)	–6.5	O(1)–C(2)–C(3)–Br(25)	178.4
O(24)–C(2)–C(3)–C(4)	171.4	O(24)–C(2)–C(3)–Br(25)	–3.7	C(2)–C(3)–C(4)–C(5)	0.6
Br(25)–C(3)–C(4)–C(5)	175.0	C(3)–C(4)–C(5)–C(6)	5.7	C(3)–C(4)–C(5)–C(10)	–177.4
C(4)–C(5)–C(6)–O(1)	–5.7	C(4)–C(5)–C(6)–C(7)	169.7	C(10)–C(5)–C(6)–O(1)	177.1
C(10)–C(5)–C(6)–C(7)	–7.5	C(4)–C(5)–C(10)–C(9)	–177.2	C(4)–C(5)–C(10)–O(11)	–2.2
C(6)–C(5)–C(10)–C(9)	–0.1	C(6)–C(5)–C(10)–O(11)	174.9	O(1)–C(6)–C(7)–C(8)	179.6
O(1)–C(6)–C(7)–Br(23)	5.9	C(5)–C(6)–C(7)–C(8)	4.1	C(5)–C(6)–C(7)–Br(23)	–169.6
C(6)–C(7)–C(8)–C(9)	6.7	C(6)–C(7)–C(8)–O(17)	–167.4	Br(23)–C(7)–C(8)–C(9)	–169.2
Br(23)–C(7)–C(8)–O(17)	6.7	C(7)–C(8)–C(9)–C(10)	–14.4	C(7)–C(8)–C(9)–C(14)	–178.8
O(17)–C(8)–C(9)–C(10)	159.8	O(17)–C(8)–C(9)–C(14)	–4.7	C(7)–C(8)–O(17)–C(16)	159.3
C(9)–C(8)–O(17)–C(16)	–14.5	C(8)–C(9)–C(10)–C(5)	11.2	C(8)–C(9)–C(10)–O(11)	–163.7
C(14)–C(9)–C(10)–C(5)	176.9	C(14)–C(9)–C(10)–O(11)	2.1	C(8)–C(9)–C(14)–C(13)	106.6
C(8)–C(9)–C(14)–C(15)	–13.5	C(10)–C(9)–C(14)–C(13)	–57.1	C(10)–C(9)–C(14)–C(15)	–179.3
C(5)–C(10)–O(11)–C(12)	–131.6	C(9)–C(10)–O(11)–C(12)	43.4	C(10)–O(11)–C(12)–C(13)	–27.6
C(10)–O(11)–C(12)–C(21)	98.4	C(10)–O(11)–C(12)–C(22)	–147.8	O(11)–C(12)–C(13)–C(14)	–26.4
O(11)–C(12)–C(13)–C(20)	93.4	C(21)–C(12)–C(13)–C(14)	–147.2	C(21)–C(12)–C(13)–C(20)	–27.4
C(22)–C(12)–C(13)–C(14)	89.2	C(22)–C(12)–C(13)–C(20)	–150.9	C(12)–C(13)–C(14)–C(9)	67.0
C(12)–C(13)–C(14)–C(15)	–173.3	C(20)–C(13)–C(14)–C(9)	–59.0	C(20)–C(13)–C(14)–C(15)	60.7
C(12)–C(13)–C(20)–C(19)	–164.5	C(14)–C(13)–C(20)–C(19)	–44.4	C(9)–C(14)–C(15)–C(16)	47.7
C(13)–C(14)–C(15)–C(16)	–68.2	C(14)–C(15)–C(16)–O(17)	–65.1	C(14)–C(15)–C(16)–C(18)	–177.5
C(14)–C(15)–C(16)–C(19)	55.7	C(15)–C(16)–O(17)–C(8)	48.9	C(18)–C(16)–O(17)–C(8)	169.8
C(19)–C(16)–O(17)–C(8)	–70.0	C(15)–C(16)–C(19)–C(20)	–45.2	O(17)–C(16)–C(19)–C(20)	72.4
C(18)–C(16)–C(19)–C(20)	–173.5	C(16)–C(19)–C(20)–C(13)	41.3		

but the 'boat' conformation is also confirmed by a study of the deviations from the mean plane of the aromatic ring of the directly substituted atoms. Those substituted at C(5), C(7), C(8), and C(10), *i.e.* C(4) 0.19 Å, Br(23) 0.16 Å, O(17) 0.36 Å, and O(11) 0.21 Å, are all significantly below the plane; the remaining substituents, O(1) 0.10 Å and C(14) 0.00 Å, are on or above the plane. The distortion at C(9) observed earlier<sup>4</sup> is confirmed by the summation of the bond angles at that atom to 358°. Although the larger standard deviations make this difference from 360° (for planarity) less statistically significant, it is nevertheless a much larger deviation than is found in the summation of bond angles about any other 'planar' atom in the structure. In contrast to the aromatic ring, the chromen ring, *i.e.* O(1) to C(6), is planar within the limits of the standard deviations.

With dibromodeoxybruceol correctly represented as (4), the structure of deoxybruceol is (3) and not its regioisomer (2). A more detailed examination of the reaction between 5,7-dihydroxycoumarin (5) and citral was therefore instituted to isolate intermediate chromens, and to see if the isomer (2) could be obtained.

At 90 °C for 18 h, in the presence of pyridine (2 mol equiv.), equimolecular proportions of the two reagents

lower m.p. isomer (12) afforded, with diazomethane, the methyl ether (9), in the n.m.r. spectrum of which the aromatic proton signal was augmented by 21% when the methoxy-frequency was irradiated. Neither of the coumarins (7) and (12) gives a positive Gibbs test. The absence of the chromen (15) accords with our earlier rationalisation of this and other chromenylations: those regioisomers are favoured which permit maximum delocalisation in the transition state leading to them.<sup>5</sup>

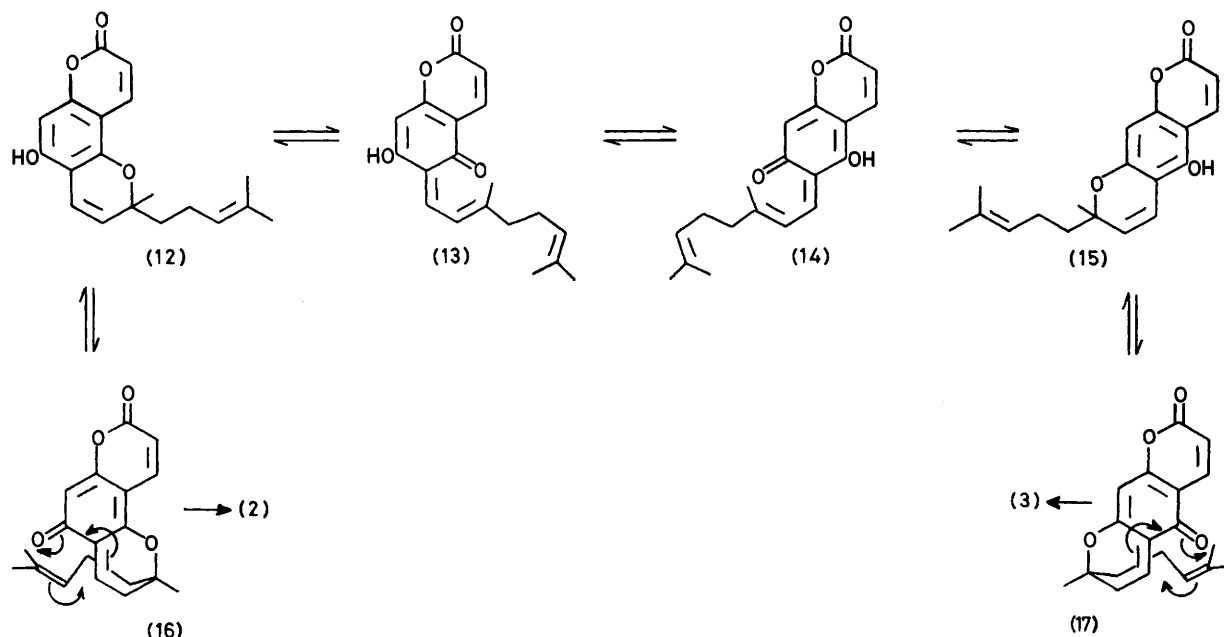
When the chromen (12) was heated in pyridine at 110 °C for 96 h, a mixture (22%) of the two very similar *cis-trans* was obtained, along with unchanged chromen (40%). The major isomer was isolated pure by crystallisation and was identical with the ( $\pm$ )-deoxybruceol isolated earlier,<sup>3</sup> and in all spectral characteristics with natural (–)-deoxybruceol. In order to effect a link with the work of the preceding paper,<sup>4</sup> the formylcitrin (10), the assignment of structure and orientation of which is founded on X-ray evidence, was converted into ( $\pm$ )-deoxybruceol (3) (69%), identical with that mentioned above, by treatment with 1-dimethylamino-1,1-dimethoxyethane.<sup>6</sup> By using this reagent, the isomeric formylcitrin (11) was converted into the regioisomer (2) now

<sup>5</sup> D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Perkin I*, 1974, 1007.

<sup>6</sup> D. H. R. Barton, G. Hewitt, and P. G. Sammes, *J. Chem. Soc. (C)*, 1969, 16; E. Effenberger and R. Maier, *Annalen*, 1969, 729, 246.

referred to as isodeoxybruceol (70%); the bischromenyl-coumarin (6) from (18) was also made (40%). Although very similar  $^1\text{H}$  n.m.r. data are given by (2) and (3), the

of that of deoxybruceol. Figure 8 shows crystallographic numbering, and Figures 9 and 10 show bond lengths and angles together with standard deviations. Bonding to



SCHEME

small shift differences allow detection of their presence in admixture and show that (2) is not structurally the same as natural deoxybruceol.

It is now clear that thermal citran formation from the chromen (12) affords the citrans (3) and (2) in the ratio *ca.* 7 : 3, *i.e.* the major isomer is formed *via* a rearrangement involving electrocyclic ring opening, isomerisation [*cf.* (13) and (14)], and reclosure in the opposite sense to give the chromen (15). Although the latter was not found in observable quantity at 90 °C, it apparently serves as the intermediate on the way to the major citran (3). As discussed in the preceding paper,<sup>4</sup> delocalisation in (17) leading to the major citran (3) is more favourable than in (16), leading to the minor citran (2). Although it was not appreciated in earlier work on the direct thermal citran formation from (5) and citral,<sup>3</sup> we have now established that a citran mixture similar to that obtained by heating the chromen (12) is formed, and only the major isomer was isolated by crystallisation: the course of the reaction is thus more complex than we envisaged.<sup>5</sup>

The original *X*-ray investigation of bromobruceol<sup>1</sup> was carried out with limited photographic data, and difficulties in refinement, together with degradation of the sample, were encountered. Because of the result obtained for deoxybruceol we have therefore re-determined the structure of natural (–)-bruceol by direct methods, using 2 109 observed reflections, and refining by least-squares and difference-Fourier methods to *R* = 3.8%. A general view (Figure 7) of the resulting structure confirms that the orientation of bruceol is indeed the reverse

hydrogen is not shown, but all C–H bond lengths were in the range 0.91–1.05 Å ( $\sigma$  0.03 Å) and all bond angles

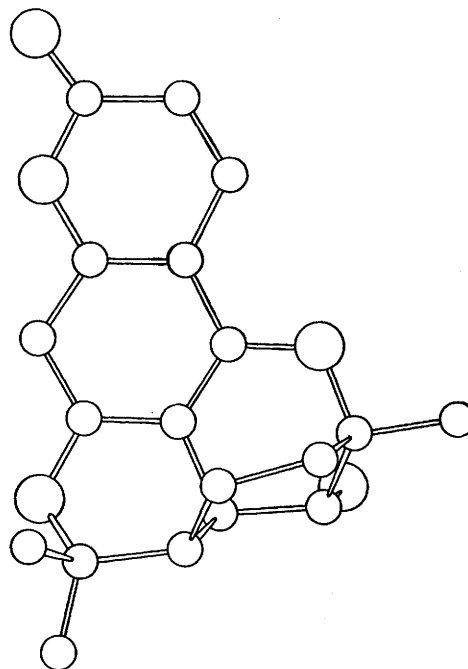


FIGURE 7 Bruceol: general view of molecule

involving hydrogen were between 115 and 126° at  $sp^2$ -hybridised carbon, and between 100 and 114° at  $sp^3$ -hybridised carbon ( $\sigma$  3.0°). Bond lengths and angles

all adopt values similar to those we have found for other citran structures. Comparison with values obtained in the original study of bromobruceol does not give good

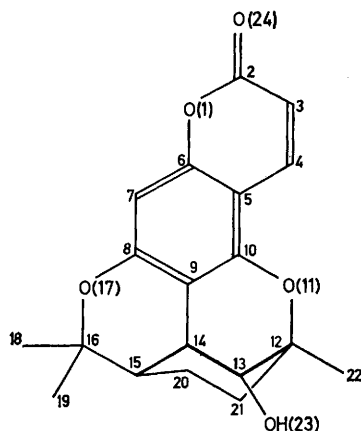


FIGURE 8 Bruceol: crystallographic numbering scheme

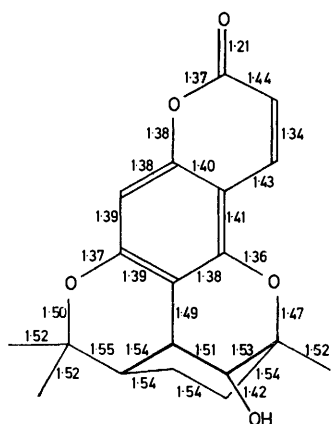


FIGURE 9 Bruceol: bond lengths in Å (largest standard deviation 0.004 Å)

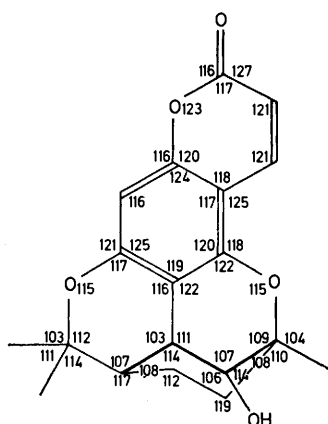


FIGURE 10 Bruceol: bond angles (degrees; largest standard deviation 0.3°); additional angles O(11)-C(12)-C(21), 113°; C(13)-C(12)-C(22), 114°; C(15)-C(16)-C(18), 110°; O(17)-C(16)-C(19), 106°

agreement, but is rendered less meaningful by the large standard deviations of the original work.<sup>1</sup>

Torsion angles (Table 2) are in poor agreement with those reported for bromobruceol,<sup>7</sup> but compare well with those of other citran types we have examined. The deviations from idealised values, and the resulting strain, are, as would be expected, very similar in the bruceol and deoxybruceol orientations and are unaffected by the additional hydroxy-group. The aromatic ring again adopts the shallow 'boat' conformation with C(6) 0.05 Å and C(9) 0.09 Å above the mean plane, and C(5) 0.02 Å, C(7) 0.01 Å, C(8) 0.06 Å, and C(10) 0.05 Å below the plane. The positions of the directly substituted atoms,

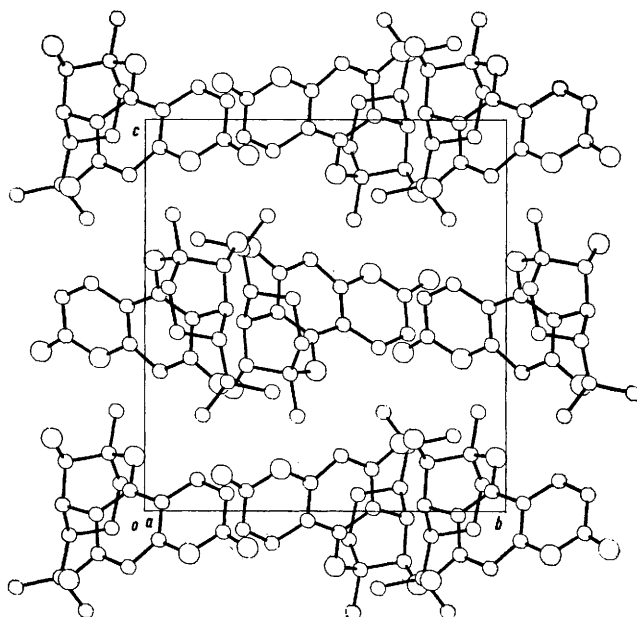


FIGURE 11 Bruceol: arrangement of molecules within the unit cell

with C(4) 0.13 Å, O(11) 0.30 Å, and O(17) 0.27 Å, below the mean aromatic plane, confirm the situation; O(1) is 0.07 Å above this plane while C(14) is 0.02 Å below the plane owing to the lack of planarity at C(9). Bond angles at C(9) sum to 357.4°, deviating significantly from 360° (for planarity). The very large deviations from mean planes (0.34 Å) claimed in bromobruceol, and attributed to general buckling,<sup>1</sup> were not confirmed. The chromen ring [O(1)-C(6)] was planar, with no atom more than 0.01 Å from the mean plane. Substituents C(10) and O(24) are also in the plane, but C(7) is 0.16 Å below this plane because of the 'boat' conformation of the aromatic ring.

The arrangement of molecules within the unit cell is shown in Figure 10 and an intermolecular hydrogen bond OH(23) ··· O(24'), 2.92 Å, was found, corresponding to that reported for bromobruceol.<sup>1</sup> The hydrogen atom H(23) was located in a difference map and refined to a position along the line between these oxygen atoms. An

<sup>7</sup> Bond angles and torsion angles were not originally presented in ref. 1 and are taken from 'Molecular Structures and Dimensions,' vol. A1, Crystallographic Data Centre, Cambridge, 1972.

intermolecular contact, C(4) ··· O(24'), 3.10 Å, was also discovered which is slightly less than the sum of the van der Waals radii, presumably owing to a weak dipolar interaction of the carbonyl group. No other intermolecular contacts less than the sum of van der Waals radii were discovered.

The result of the work in this and the preceding paper is that, although structural and chemical discrepancies have apparently been resolved, a curious situation has developed on the biosynthetic side. Although occurring side by side in *E. brucei*, deoxybruceol (3) and bruceol (1)

## EXPERIMENTAL

Analytical and spectroscopic data are listed in Supplementary Publication No. SUP 22107 (25 pp.).\* M.p.s were determined with a hot-stage microscope. Silica gel G was used in analytical t.l.c.; for preparative work, silica gel HF<sub>254</sub> (ca. 1 mm layers) was employed. Organic solutions were dried over magnesium sulphate and evaporated at reduced pressure.

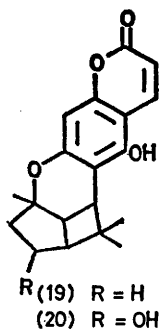
*5,7-Dihydroxycoumarin* (5).—A stirred mixture of phloroglucinol (40.5 g), ethyl propiolate (36.75 g), and zinc chloride (34 g) was heated on a steam-bath. After a few minutes the mixture reacted vigorously and was cooled until the

TABLE 2

Torsion angles for bruceol (1)

C(6)–O(1)–C(2)–C(3)	0.6	C(6)–O(1)–C(2)–O(24)	–179.1	C(2)–O(1)–C(6)–C(5)	–1.8
C(2)–O(1)–C(6)–C(7)	175.1	O(1)–C(2)–C(3)–C(4)	–0.9	O(24)–C(2)–C(3)–C(4)	178.8
C(2)–C(3)–C(4)–C(5)	2.3	C(3)–C(4)–C(5)–C(6)	–3.4	C(3)–C(4)–C(5)–C(10)	–179.2
C(4)–C(5)–C(6)–O(1)	3.1	C(4)–C(5)–C(6)–C(7)	–171.3	C(10)–C(5)–C(6)–O(1)	179.2
C(10)–C(5)–C(6)–C(7)	4.8	C(4)–C(5)–C(10)–C(9)	–178.7	C(4)–C(5)–C(10)–O(11)	4.4
C(6)–C(5)–C(10)–C(9)	5.4	C(6)–C(5)–C(10)–O(11)	–171.4	O(1)–C(6)–C(7)–C(8)	–179.1
C(5)–C(6)–C(7)–C(8)	–4.5	C(6)–C(7)–C(8)–C(9)	–6.2	C(6)–C(7)–C(8)–O(17)	172.8
C(7)–C(8)–C(9)–C(10)	16.2	C(7)–C(8)–C(9)–C(14)	178.2	O(17)–C(8)–C(9)–C(10)	–162.8
O(17)–C(8)–C(9)–C(14)	–0.8	C(7)–C(8)–O(17)–C(16)	–132.5	C(9)–C(8)–O(17)–C(16)	46.5
C(8)–C(9)–C(10)–C(5)	–15.5	C(8)–C(9)–C(10)–O(11)	161.2	C(14)–C(9)–C(10)–C(5)	–176.4
C(14)–C(9)–C(10)–O(11)	0.4	C(8)–C(9)–C(14)–C(13)	–177.8	C(8)–C(9)–C(14)–C(15)	–55.8
C(10)–C(9)–C(14)–C(13)	–16.4	C(10)–C(9)–C(14)–C(15)	105.5	C(5)–C(10)–O(11)–C(12)	158.3
C(9)–C(10)–O(11)–C(12)	–18.5	C(10)–O(11)–C(12)–C(13)	51.3	C(10)–O(11)–C(12)–C(21)	–68.4
C(10)–O(11)–C(12)–C(22)	172.9	O(11)–C(12)–C(13)–C(14)	–65.6	O(11)–C(12)–C(13)–O(23)	51.6
C(21)–C(12)–C(13)–C(14)	57.3	C(21)–C(12)–C(13)–O(23)	174.5	C(22)–C(12)–C(13)–C(14)	179.3
C(22)–C(12)–C(13)–O(23)	–63.4	O(11)–C(12)–C(21)–C(20)	70.8	C(13)–C(12)–C(21)–C(20)	–49.6
C(22)–C(12)–C(21)–C(20)	–174.2	C(12)–C(13)–C(14)–C(9)	47.1	C(12)–C(13)–C(14)–C(15)	–67.8
O(23)–C(13)–C(14)–C(9)	–74.9	O(23)–C(13)–C(14)–C(15)	170.2	C(9)–C(14)–C(15)–C(16)	67.0
C(9)–C(14)–C(15)–C(20)	–59.4	C(13)–C(14)–C(15)–C(16)	–173.5	C(13)–C(14)–C(15)–C(20)	60.1
C(14)–C(15)–C(16)–O(17)	–27.8	C(14)–C(15)–C(16)–C(18)	86.3	C(14)–C(15)–C(16)–C(19)	–148.3
C(20)–C(15)–C(16)–O(17)	93.4	C(20)–C(15)–C(16)–C(18)	–152.6	C(15)–C(16)–C(19)–C(19)	–27.1
C(14)–C(15)–C(20)–C(21)	–44.9	C(16)–C(15)–C(20)–C(21)	–165.6	C(15)–C(16)–O(17)–C(8)	–29.4
C(13)–C(16)–O(17)–C(8)	–148.0	C(19)–C(16)–O(17)–C(8)	95.8	C(15)–C(20)–C(21)–C(12)	44.1

cannot now be connected by a simple direct hydroxylation relationship. On the other hand, the orientation found for deoxybruceol corresponds with that of erio-brucinol (19) and hydroxyerio-brucinol (20), which



have also been isolated from this plant.<sup>2</sup> The similarity in chiroptical properties of natural bruceol and deoxybruceol is also remarkable in view of their differing orientations; it is hoped to examine these strained chromophores and the question of absolute configurations more closely.

reaction subsided. Careful heating was then continued for 2 h. Cooling and addition of 5% hydrochloric acid gave a yellow solid, which was filtered off and recrystallised from acetic acid–water to yield needles of 5,7-dihydroxycoumarin (5), m.p. 268–269° (lit.,<sup>8</sup> 270°) (39 g, 66%).

*Reaction of 5,7-Dihydroxycoumarin with Citral and Pyridine.*—5,7-Dihydroxycoumarin (2.23 g, 0.0125 mol), citral (1.98 g, 0.0125 mol), and pyridine (1.90 g, 0.025 mol) were heated with stirring, at 90 °C for 18 h. T.l.c. indicated three products. The resulting brown mixture was diluted with chloroform and chromatographed on silica gel HF<sub>254</sub> [preparative plates, 45 × 45 cm; elution with benzene–ethyl acetate (9 : 1)]. Three products were removed. The most polar was a solid, which crystallised from cyclohexane to yield the *monochromen* (12), as a light tan powdery solid, m.p. 113–115° (618 mg, 15%). The second product was the isomeric *monochromen* (7), isolated as a pale yellow solid which crystallised from cyclohexane as yellow needles, m.p. 136–138° (511 mg, 13%). The third most polar compound was isolated as a light yellow gum (120 mg, 2%), identical with an authentic sample<sup>3</sup> of the bischromen (6) (u.v., i.r., and n.m.r. spectra and t.l.c.).

*Action of Heat on the Monochromen* (12).—The monochromen (12) (624 mg, 0.002 mol) was heated in pyridine (160 mg, 0.002 mol) at 110 °C for 4 days. The resulting brown solution was chromatographed on silica gel HF<sub>254</sub>

\* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

<sup>8</sup> K. D. Kaufman and R. C. Kelly, *J. Heterocyclic Chem.*, 1965, 2, 91.

[preparative plates, 45 × 45 cm; elution with benzene-ethyl acetate (9:1)]. Two main bands were observed under u.v. irradiation. The least polar of these was obtained as a pale yellow oil (140 mg, 22%). N.m.r. investigation indicated the presence of a mixture of the two isomeric citrans (3) and (2). The major isomer (3) was obtained by crystallisation, and was spectroscopically identical with natural deoxybruceol and synthetic (±)-deoxybruceol.<sup>2,3</sup> The minor isomer (2) was not purified from this reaction, but was recognised by comparison of n.m.r. data with those of a pure specimen.

The most polar product was obtained as a yellow solid (250 mg, 40%), and was identical with a sample of the monochromen (12) (n.m.r. and i.r. data, and m.p. and mixed m.p.).

*Methylation of the Monochromen (7).*—The monochromen (7) (380 mg) was dissolved in dry ether (20 ml). Excess of ethereal diazomethane was added and the solution was kept at room temperature for 24 h. T.l.c. indicated the presence of unchanged monochromen and one product of lower polarity. The solvent was evaporated off and the crude product chromatographed on silica gel HF<sub>254</sub> [preparative plates, 45 × 45 cm; elution with benzene-ethyl acetate (9:1)] yielding the ether (8) as a pale yellow gum (260 mg, 66%).

*Methylation of the Monochromen (12).*—The monochromen (12) (170 mg) was dissolved in dry ether (20 ml); an excess of ethereal diazomethane was added and the solution set aside at room temperature for 24 h. Work-up as above yielded the ether (9) a pale yellow gum (108 mg, 61%).

*Bromination of (±)-Deoxybruceol.*—(±)-Deoxybruceol (70 mg) in dioxan (10 ml) containing sodium carbonate (100 mg) was treated with bromine (50 mg) in dioxan (10 ml) until a yellow colour persisted for 15 min. Work-up gave a product which crystallised from benzene-n-hexane (54 mg) and was shown by n.m.r. to be a mixture of mono- and di-bromo-derivatives. Further crystallisation gave material with m.p. 164–166°. A crystal was selected for X-ray analysis.

*Coumarin Syntheses with 1-Dimethylamino-1,1-dimethoxyethane.*—(a) The formylbischromen (18) (250 mg) was dissolved in dry ether (4 ml) under dry nitrogen, and 1-dimethylamino-1,1-dimethoxyethane (0.2 ml) was then added through a septum. The solution was heated under reflux for 2 h. The ether was removed and the residue chromatographed on silica gel HF<sub>254</sub> [preparative plates, 20 × 20 cm; n-hexane-ether (3:1) as eluant]. Only one product was isolated, obtained as a yellow oil (120 mg, 45%), identical (n.m.r., i.r., and u.v. spectra and t.l.c.) with an authentic sample of the bischromen (6).

(b) The formylcitrans (10) (104 mg) was dissolved in dry ether (4 ml) under dry nitrogen, and 1-dimethylamino-1,1-dimethoxyethane (0.2 ml) was then added. The solution was heated under reflux for 2 h, the ether was removed, and the residue was chromatographed on silica gel HF<sub>254</sub> [preparative plates, 20 × 20 cm; benzene-ethyl acetate (5:1) as eluant]. Only one product was isolated, obtained as a white solid (48 mg, 69%), identical (m.p., mixed m.p., n.m.r., i.r., and u.v. spectra and t.l.c.) with authentic (±)-deoxybruceol (3).

(c) The formylcitrans (11) (104 mg) was treated as in experiment (b). (±)-Isodeoxybruceol (2) was isolated from HF<sub>254</sub> plates as a white solid, m.p. 146–148°.

<sup>9</sup> J. M. Stewart, F. A. Kindell, and J. C. Baldwin, University of Maryland Technical Report, TR67-58, 1967, revised 1970.

*Crystallographic Analyses of Dibromodeoxybruceol (4) and Bruceol (1).*—Oscillation and Weissenberg photographs were taken to establish unit-cell dimensions and space group. For intensity measurement a crystal of dimensions ca. 0.5 × 0.15 × 0.01 mm<sup>3</sup> (4) or 0.5 × 0.5 × 0.5 mm<sup>3</sup> (1) was mounted on an automatic, computer-controlled, four-circle diffractometer. Only small, thin specimens of (4) were available. Unit-cell dimensions were refined by a least-squares fit on the positions of 12 peaks found on the diffractometer. Intensity data were collected with Mo-K<sub>α</sub> radiation using an ω-2θ scan for 2θ < 50° (4), of which most reflections with 2θ > 40° were unobserved, or for 2θ < 60° (1). Reflections with a net count greater than 3.0σ were considered observed and used in the subsequent structure refinement. Totals of 3 097 (4) and 2 685 (1) independent reflections were measured, of which 1 494 (4) or 2 109 (1) were considered observed. No absorption corrections were made. Data reduction and subsequent crystallographic calculations were performed using the 'X-Ray '70' system of programs.<sup>9</sup> Atomic scattering factors were taken from ref. 10.

*Crystal data.* Dibromodeoxybruceol (4). C<sub>19</sub>H<sub>18</sub>O<sub>4</sub>Br<sub>2</sub>, *M* = 470.185. Monoclinic, *a* = 10.338(3), *b* = 9.624(3), *c* = 18.304(4), β = 105.49(2)°, *U* = 1 755.10 Å<sup>3</sup>, *Z* = 4, *D*<sub>c</sub> = 1.78 g cm<sup>-3</sup>, *F*(000) = 936. Space group *P*2<sub>1</sub>/*c* uniquely from systematic absences; Mo-K<sub>α</sub> radiation, λ = 0.710 69 Å; μ(Mo-K<sub>α</sub>) = 49.2 cm<sup>-1</sup>.

Bruceol (1). C<sub>19</sub>H<sub>20</sub>O<sub>5</sub>, *M* = 328.369. Orthorhombic, *a* = 10.343(3), *b* = 12.014(4), *c* = 13.093(4), *U* = 1 626.88 Å<sup>3</sup>, *Z* = 4, *D*<sub>c</sub> = 1.34 g cm<sup>-3</sup>, *F*(000) = 696. Space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> uniquely from systematic absences; Mo-K<sub>α</sub> radiation, λ = 0.710 69 Å; μ(Mo-K<sub>α</sub>) = 1.04 cm<sup>-1</sup>.

Initial attempts at interpretation of the Patterson synthesis of (4) were unsuccessful because they were based on an assumption that only one bromine atom was present in the major reaction product. Several attempts at solution by direct methods also failed. Finally a set of phases from direct methods suggested an interpretation of the Patterson map based on two bromine atoms with nearly identical *y* and *z* co-ordinates, and that the crystalline product was the dibromo-derivative. A subsequent Fourier synthesis based on these two bromine positions revealed the remaining non-hydrogen atom positions in the structure. The structure of (1) was solved by direct methods using the Multan<sup>11</sup> program. 250 reflections with *E* > 1.58 were used, and the best set of phases produced had a figure of merit 1.0807. A subsequent *E* map, based on these phases, revealed all non-hydrogen atoms as the largest peaks on the map.

Block-diagonal least-squares refinements of atomic positions were commenced, initially with isotropic temperature factors and later including anisotropic vibrations. After apparent convergence with agreement factor *R* 13.6% (4) or 7.4% (1), difference-Fourier syntheses were calculated. For (4) this revealed a large hole in the neighbourhood of the coumarin bromine atom Br(25). This atom also had large temperature factors and a short C-Br bond length, and it was therefore assumed that some monobromo-derivative had co-crystallized. Accordingly its population fraction was allowed to vary in subsequent refinement. The map also revealed positive areas in the neighbourhood

<sup>10</sup> International Tables for X-Ray Crystallography, vol. III, Kynoch Press, Birmingham, 1965.

<sup>11</sup> G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 360.



of expected hydrogen atom positions. The positions of the hydrogen atoms were then calculated from bond length and angle considerations and included in subsequent structure factor calculations with fixed isotropic temperature factors ( $B = 5.0$ ) without refinement. The difference map for (1) revealed the approximate positions of all the hydrogen atoms as the largest peaks in the map. The hydrogen atoms were then included in the refinement with isotropic temperature factors. Analyses of the agreement of  $F_o$  and  $F_c$  suggested the adoption of weighting schemes in the form  $w = 1/\{1 + [(|F_o| - 50.0)/30.0]^2\}$  (4) or  $w = 1$  for  $|F_o| \leq 10.0$  with  $w = (10.0/|F_o|)^2$  for  $|F_o| > 10.0$  (1).

TABLE 3

Dibromodeoxybruceol (4): atomic co-ordinates with their standard deviations in parentheses; hydrogen atoms are numbered according to the atom to which they are bonded

Atom	<i>x</i>	<i>y</i>	<i>z</i>
O(1)	0.441 2(7)	0.388 1(8)	0.600 9(4)
C(2)	0.579 6(12)	0.410 3(13)	0.614 8(6)
C(3)	0.643 9(11)	0.345 9(12)	0.563 4(6)
C(4)	0.576 6(11)	0.257 5(11)	0.509 4(5)
C(5)	0.441 7(10)	0.226 5(11)	0.501 2(6)
C(6)	0.371 1(10)	0.296 5(11)	0.544 8(6)
C(7)	0.238 7(10)	0.289 7(11)	0.533 7(5)
C(8)	0.162 3(11)	0.199 4(11)	0.477 2(6)
C(9)	0.233 8(10)	0.112 6(10)	0.442 5(5)
C(10)	0.364 2(10)	0.131 0(9)	0.448 3(6)
O(11)	0.423 8(7)	0.065 4(7)	0.398 6(4)
C(12)	0.343 9(10)	0.068 1(10)	0.317 7(5)
C(13)	0.193 2(11)	0.077 3(10)	0.309 2(5)
C(14)	0.166 8(11)	0.013 1(11)	0.380 7(6)
C(15)	0.020 6(12)	-0.000 8(13)	0.377 1(6)
C(16)	-0.038 7(10)	0.144 7(12)	0.378 3(6)
O(17)	0.028 5(7)	0.206 3(8)	0.453 8(4)
C(18)	-0.183 8(12)	0.147 6(14)	0.378 4(7)
C(19)	-0.012 2(12)	0.229 1(12)	0.313 9(6)
C(20)	0.131 1(10)	0.223 7(11)	0.300 7(5)
C(21)	0.402 5(12)	0.188 5(11)	0.281 0(6)
C(22)	0.380 4(12)	-0.067 7(12)	0.286 2(6)
Br(23)	0.143 5(1)	0.408 5(2)	0.583 3(1)
O(24)	0.628 0(9)	0.479 8(9)	0.671 0(5)
Br(25)	0.820 8(2)	0.385 3(2)	0.585 0(1)
H(4)	0.626	0.213	0.474
H(13)	0.156	0.016	0.264
H(14)	0.194	-0.089	0.384
H(15A)	0.009	-0.058	0.421
H(15B)	-0.030	-0.052	0.328
H(18A)	-0.197	0.094	0.423
H(18B)	-0.213	0.248	0.384
H(18C)	-0.241	0.109	0.330
H(19A)	-0.040	0.329	0.319
H(19B)	-0.080	0.193	0.264
H(20A)	0.192	0.201	0.338
H(20B)	0.128	0.263	0.247
H(21A)	0.380	0.280	0.302
H(21B)	0.503	0.180	0.294
H(21C)	0.365	0.187	0.226
H(22A)	0.345	-0.147	0.310
H(22B)	0.483	-0.077	0.298
H(22C)	0.344	-0.070	0.230

Further refinement finally converged when the largest parameter shifts were  $< 0.7\sigma$ , lowering  $R$  to 7.4% (4) or 3.8% (1) after totals of 18 cycles (4) or 16 cycles (1). In (4) the population fraction of Br(25) refined to 0.704 (4) and its temperature factors reverted to values similar to

those of the other bromine atom. Thus the crystal examined consisted of 70% of the dibromo-derivative co-crystallised with 30% of the monobromo-derivative.

TABLE 4

Bruceol (1): atomic co-ordinates with their standard deviations in parentheses; hydrogens are numbered according to the atom to which they are bonded

Atom	<i>x</i>	<i>y</i>	<i>z</i>
O(1)	0.165 9(1)	-0.124 0(1)	0.391 7(1)
C(2)	0.141 3(2)	-0.218 4(2)	0.447 3(2)
C(3)	0.202 0(2)	-0.227 7(2)	0.546 1(2)
C(4)	0.280 8(2)	-0.147 3(2)	0.581 1(1)
C(5)	0.302 7(2)	-0.048 7(1)	0.523 0(1)
C(6)	0.245 8(2)	-0.040 6(1)	0.426 5(1)
C(7)	0.272 4(2)	0.043 3(1)	0.357 3(1)
C(8)	0.354 5(2)	0.127 2(1)	0.390 9(1)
C(9)	0.397 2(2)	0.132 5(1)	0.491 6(1)
C(10)	0.384 7(2)	0.039 4(1)	0.552 9(1)
O(11)	0.454 5(1)	0.027 1(1)	0.639 7(1)
C(12)	0.569 7(2)	0.098 0(2)	0.647 8(1)
C(13)	0.531 0(2)	0.218 7(2)	0.626 6(2)
C(14)	0.488 2(2)	0.225 3(1)	0.516 2(2)
C(15)	0.597 9(2)	0.207 1(2)	0.438 6(2)
C(16)	0.541 1(2)	0.230 2(2)	0.330 7(2)
O(17)	0.398 7(1)	0.207 6(1)	0.325 8(1)
C(18)	0.549 3(3)	0.353 9(2)	0.305 7(2)
C(19)	0.601 5(3)	0.161 0(3)	0.246 0(2)
C(20)	0.654 8(2)	0.090 4(2)	0.456 7(2)
C(21)	0.676 5(2)	0.066 0(2)	0.571 1(2)
C(22)	0.616 9(2)	0.077 6(2)	0.756 2(2)
O(23)	0.424 3(2)	0.256 0(1)	0.686 1(1)
O(24)	0.070 4(2)	-0.286 1(1)	0.407 4(1)
H(3)	0.184(2)	-0.294(2)	0.583(2)
H(4)	0.321(2)	-0.153(2)	0.648(2)
H(7)	0.236(2)	0.037(2)	0.289(2)
H(13)	0.610(2)	0.264(2)	0.639(2)
H(14)	0.446(2)	0.295(2)	0.503(2)
H(15)	0.665(2)	0.262(2)	0.450(2)
H(18A)	0.517(3)	0.399(3)	0.355(2)
H(18B)	0.505(4)	0.371(3)	0.247(3)
H(18C)	0.617(4)	0.373(3)	0.291(3)
H(19A)	0.563(3)	0.184(3)	0.182(2)
H(19B)	0.699(3)	0.176(3)	0.240(2)
H(19C)	0.579(3)	0.076(3)	0.255(2)
H(20A)	0.593(2)	0.031(2)	0.425(2)
H(20B)	0.742(3)	0.084(2)	0.425(2)
H(21A)	0.752(3)	0.101(3)	0.597(2)
H(21B)	0.696(2)	-0.007(2)	0.584(2)
H(22A)	0.638(3)	-0.003(3)	0.765(2)
H(22B)	0.696(3)	0.120(2)	0.762(2)
H(22C)	0.560(3)	0.101(3)	0.804(2)
H(23)	0.435(3)	0.257(3)	0.744(3)

Final difference maps were calculated which showed no peaks or depressions  $> 0.6 \text{ e}\text{\AA}^{-3}$  (4) or  $0.2 \text{ e}\text{\AA}^{-3}$  (1). In (4) the largest features were associated with the bromine atom positions. Final atomic co-ordinates are listed in Tables 3 and 4; temperature factors and observed and calculated structure factors are listed in Supplementary Publication No. SUP 22107.

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