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The Crystal Structure of Heteratisine Hydrobromide Monohydrate*

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The space group of heteratisine hydrobromide monohydrate, $C_{22}H_{33}O_5N \cdot HBr \cdot H_2O$ is $P2_1$ and the unit-cell dimensions are: $a = 8.96$, $b = 14.54$, $c = 8.55$ Å, $\beta = 90^\circ 40'$, $Z = 2$. The structure was solved from a three-dimensional Fourier synthesis by the heavy-atom method. No chemical assumptions have been made, except that the nitrogen atom was identified by comparison of the skeleton with that of lycocotinine. Refinement was carried out by the least-squares method.

Introduction

In the course of isolation of atisine from the roots of *Aconitum heterophyllum*, Jacobs & Craig (1942) obtained small amounts of alkaloids, which they called heteratisine and hetisine. They assigned the empirical formula $C_{22}H_{33}O_5N$ to heteratisine and discovered that it contained a lactone group, one methoxyl group, two hydroxyl groups and an *N*-alkyl group, which they presumed to be methyl. No unsaturated linkage could be detected by hydrogenation.

The solution of the molecular structure of heteratisine presented an interesting problem, especially as it is the only known base from aconite and delphinium species to contain a lactone ring; and since only a very limited amount of the substance was available, Dr Edwards suggested a detailed X-ray analysis.

The preliminary account of this study which described the molecular structure has been published (Przybylska, 1963).

Edwards & Ferrari (1964) have described chemical and physical evidence which is fully consistent with our results.

Considerable chemical and spectroscopic studies leading to the same structural conclusion have recently been reported by Aneja & Pelletier (1964a).

Experimental

The hydrobromide derivative of heteratisine was prepared by Dr O. E. Edwards. Large colourless prisms of the monohydrate, $C_{22}H_{33}O_5N \cdot HBr \cdot H_2O$, were obtained on crystallization from water.

The chemical analysis carried out by Mr R. H. Séguin confirmed the presence of one molecule of water of crystallization. The density measured by the

flotation method in a mixture of carbon tetrachloride and toluene is 1.459 g.cm^{-3} and the calculated value for the monohydrate is 1.462 g.cm^{-3} .

The space group and unit-cell dimensions were determined with Cu $K\alpha$ radiation and a precession camera. They are:

$$a = 8.96 \pm 0.02, \quad b = 14.54 \pm 0.03, \quad c = 8.55 \pm 0.02 \text{ Å};$$

$$\beta = 90^\circ 40' \pm 10', \quad V = 1114 \text{ Å}^3.$$

$0k0$ reflexions for k odd are absent, and since the compound is optically active the space group is $P2_1$.

The number of electrons per unit cell, $F(000)$, is 516.

The data were collected for thirteen b -axis levels with Mo $K\alpha$ radiation with a Hilger and Watts automatic linear diffractometer designed by U. W. Arndt and D. C. Phillips (1961). The output was in the form of cards punched by the 26 IBM machine connected to the diffractometer.

The data was supplemented with measurements for the $0kl$, $1kl$ and $2kl$ levels. 1345 reflexions were obtained with a count higher than 20, after the two background readings were subtracted. They constituted about 52% of all intensities theoretically available with copper radiation.

All the crystals used were of either square or circular cross section, varying from 0.27 to 0.35 mm in thickness and the absorption corrections were not applied.

Structure analysis

A Patterson synthesis for the $h0l$ data indicated four different positions for the bromine atom. The interpretation of two additional syntheses for the $hk0$ and $0kl$ zones reduced the number of possible locations to two. To find the position of the heavy atom unambiguously, it was necessary to carry out a summa-

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tion for the section at $V = \frac{1}{2}$ using the three-dimensional data. The data for all these syntheses were sharpened by the zero level $1/Lp$ function. A program written by Dr E. J. Gabe and modified by Dr G. A. Mair, to deal with the diffractometer output, was used for processing the data.

The coordinates of the bromine atom used for the calculation of the phases were: $x=0.236$, $y=0.250$ and $z=0.080$, and a three-dimensional Fourier synthesis was carried out for sections perpendicular to the b axis by the heavy-atom technique. The electron density contours were drawn on sheets of Perspex and assembled to give a three-dimensional model. No chemical assumptions were made in the interpretation of this synthesis, which had mirror image peaks due to the plane of symmetry introduced at $y = \frac{1}{4}$ and $\frac{3}{4}$.

The first set of atomic coordinates consisted of only thirteen light atoms, which were treated as carbon atoms. On examination of the second three-dimensional Fourier synthesis it was possible to add thirteen more atoms, and the third cycle yielded the last three atoms of the molecule. It was not until all the atoms were located that the similarity of the carbon-nitrogen skeleton to lycotonine (Przybylska, 1961a) was recognized. This allowed an easy identification of the nitrogen atom. There was no difficulty in distinguishing the oxygen peaks from those of carbon on the basis of electron density values.

A fourth three-dimensional summation did not show any spurious peaks, and it could be concluded that the structure was solved correctly. The coordinates were

obtained by means of Dr E. J. Gabe's program, which locates the centre of a Fourier peak by fitting the ellipsoid. The coefficients of this ellipsoid were calculated from twenty-seven values of electron density. The values of $\rho_{0 \max}$ at the centre, obtained by the same program, confirmed the identification of atoms.

The refinement of the structure was achieved by four least-squares cycles. The program written for this purpose by Dr G. A. Mair for use with the 1620 40K IBM computer is divided into two parts. One part calculates the structure factors and accumulates the least-squares totals, whereas the second gives the shifts, the new parameters, the thermal parameters, the scale and the R index. New bond distances, angles and their standard deviations can also be obtained. The third weighting scheme described by Mills & Rollett (1961) was used, with the values of $a=48$ and $b=36$. The value of b corresponds to approximately $5F_{\min}$. The fudge factors (Hodgson & Rollett, 1963) of 0.91, 0.71, 0.71 and 1.00 were used for each of the cycles.

The final atomic parameters with the corresponding B values are given in Table 1. All the light atoms have been refined isotropically, but for the bromine atom the anisotropic thermal vibration parameters were calculated. They are also given in Table 1, the temperature factor being of the form:

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

The atomic scattering factors were those of Thomas & Umeda (1957) for bromine and those of Freeman (1959) for the light atoms. The hydrogen atom con-

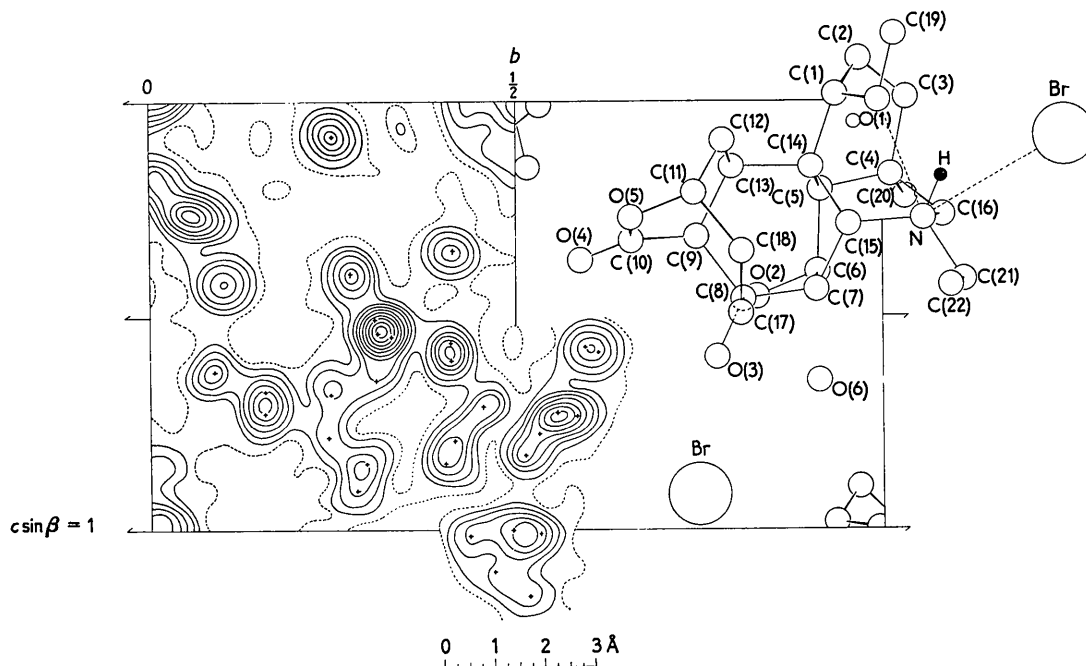


Fig. 1. The structure of heteratisine hydrobromide monohydrate along the a axis. Light-atom contours are drawn at intervals of $2 \text{ e.}\text{\AA}^{-2}$, starting with a broken line at $2 \text{ e.}\text{\AA}^{-2}$. The heavier lines of the bromine atom are at $10 \text{ e.}\text{\AA}^{-2}$.

Table 1. *Fractional atomic coordinates and temperature factors*

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
C(1)	0.6479	0.4356	0.0167	2.0 Å ²
C(2)	0.5042	0.4685	0.0990	7.3
C(3)	0.4014	0.5316	0.0090	2.6
C(4)	0.3987	0.5110	-0.1726	2.2
C(5)	0.4415	0.4145	-0.2074	2.1
C(6)	0.4504	0.4107	-0.3967	2.1
C(7)	0.6200	0.4097	-0.4378	1.8
C(8)	0.6849	0.3105	-0.4607	1.7
C(9)	0.6375	0.2466	-0.3172	2.2
C(10)	0.7213	0.1574	-0.3257	2.0
C(11)	0.9338	0.2427	-0.2156	2.7
C(12)	0.8252	0.2820	-0.0911	3.6
C(13)	0.6595	0.2942	-0.1530	1.9
C(14)	0.6116	0.4026	-0.1525	1.4
C(15)	0.6956	0.4536	-0.2885	1.8
C(16)	0.4910	0.5820	-0.2660	2.7
C(17)	0.8598	0.3071	-0.4920	2.5
C(18)	0.9715	0.3078	-0.3510	3.5
C(19)	0.8433	0.5159	0.1559	5.1
C(20)	0.2308	0.5305	-0.2232	3.1
C(21)	0.7178	0.6113	-0.4160	3.0
C(22)	0.8920	0.5940	-0.4280	3.8
N	0.6573	0.5554	-0.2743	1.9
O(1)	0.7719	0.4943	0.0024	4.7
O(2)	0.3726	0.3287	-0.4555	2.6
O(3)	0.6247	0.2740	-0.5974	2.1
O(4)	0.6647	0.0880	-0.3717	3.1
O(5)	0.8662	0.1565	-0.2739	3.0
O(6)	0.1687	0.4132	-0.6494	4.3
Br	0.2373	0.2496	0.0812	

Thermal vibration parameters of bromine ($\times 10^4$)

B_{11}	B_{22}	B_{33}	B_{12}	B_{23}	B_{13}
187	43	134	-3	41	-110

tributions have not been included in the structure factor calculations.

The maximum shift applied to a light atom in the fourth cycle was 0.058 Å and the average shift was

0.009 Å. Since these values decreased to only 0.027 and 0.005 Å respectively, in the fifth cycle the structure was considered to be adequately refined. The last set of small shifts was therefore not applied and the structure factors were not recalculated. The final *R* value for all observed reflexions was 0.12.

A projection along the *a* axis is shown in Fig. 1, and the bond lengths in Fig. 2.

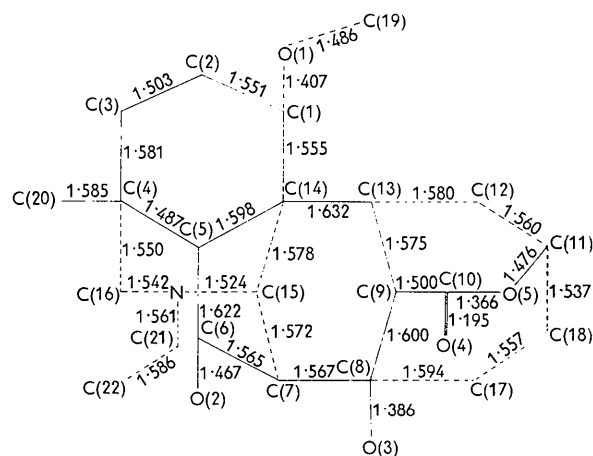


Fig. 2. Bond lengths.

Discussion

The absolute configuration of heteratisine has not been determined in this study but there is no doubt that it is represented by the drawings in Figs. 1, 2 and 3. It is consistent with the absolute configuration of other closely related diterpenoid alkaloids (Przybylska & Marion, 1959).

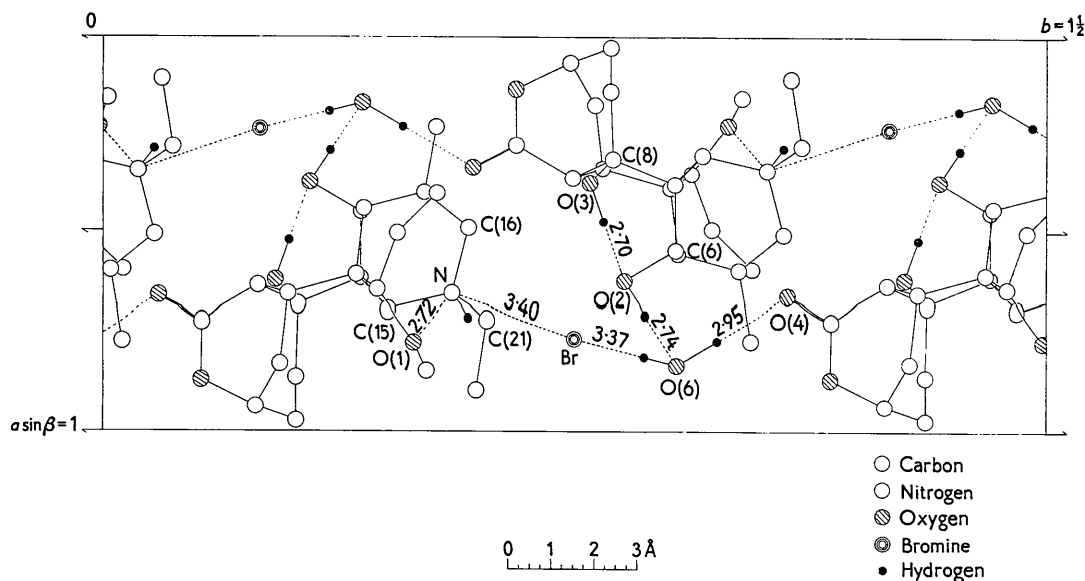
Fig. 3. The structure along the *c* axis, showing the hydrogen bonds.

Table 2. Bond angles and standard deviations

Angle	Value	σ
C(2)-C(1)-C(14)	110.6	2.1
C(2)-C(1)-O(1)	120.9	2.3
C(14)-C(1)-O(1)	105.2	1.7
C(1)-C(2)-C(3)	117.5	2.8
C(2)-C(3)-C(4)	112.9	2.3
C(3)-C(4)-C(5)	112.0	1.9
C(3)-C(4)-C(16)	112.3	1.9
C(3)-C(4)-C(20)	103.7	1.8
C(5)-C(4)-C(16)	112.6	1.8
C(5)-C(4)-C(20)	111.1	1.9
C(16)-C(4)-C(20)	104.6	1.9
C(4)-C(5)-C(6)	104.4	1.8
C(4)-C(5)-C(14)	106.9	1.8
C(6)-C(5)-C(14)	103.3	1.6
C(5)-C(6)-C(7)	106.6	1.7
C(5)-C(6)-O(2)	109.9	1.7
C(7)-C(6)-O(2)	111.9	1.8
C(6)-C(7)-C(8)	113.6	1.9
C(6)-C(7)-C(15)	102.9	1.7
C(8)-C(7)-C(15)	108.6	1.8
C(7)-C(8)-C(9)	109.6	1.8
C(7)-C(8)-C(17)	114.6	1.8
C(7)-C(8)-O(3)	108.5	1.7
C(9)-C(8)-C(17)	112.4	1.7
C(9)-C(8)-O(3)	108.7	1.7
C(17)-C(8)-O(3)	102.7	1.6
C(8)-C(9)-C(10)	109.1	1.6
C(8)-C(9)-C(13)	113.4	2.2
C(10)-C(9)-C(13)	111.5	1.7
C(9)-C(10)-O(4)	122.4	2.0
C(9)-C(10)-O(5)	117.8	1.9
O(4)-C(10)-O(5)	119.7	2.1
C(12)-C(11)-C(18)	115.7	2.4
C(12)-C(11)-O(5)	106.5	1.7
C(18)-C(11)-O(5)	111.2	1.8
C(11)-C(12)-C(13)	113.8	1.9
C(9)-C(13)-C(12)	110.8	1.7
C(9)-C(13)-C(14)	113.4	1.8
C(12)-C(13)-C(14)	110.7	1.7
C(1)-C(14)-C(5)	115.3	1.7
C(1)-C(14)-C(13)	104.4	1.6
C(1)-C(14)-C(15)	116.4	1.7
C(5)-C(14)-C(13)	110.7	1.7
C(5)-C(14)-C(15)	101.2	1.6
C(13)-C(14)-C(15)	108.9	1.6
C(7)-C(15)-C(14)	101.7	1.7
C(7)-C(15)-N	111.4	1.7
C(14)-C(15)-N	106.7	1.6
C(4)-C(16)-N	112.3	1.8
C(8)-C(17)-C(18)	119.6	1.9
C(11)-C(18)-C(17)	115.8	2.2
C(22)-C(21)-N	108.7	2.0
C(15)-N-C(16)	117.8	1.7
C(15)-N-C(21)	111.3	1.6
C(16)-N-C(21)	104.5	1.7
C(1)-O(1)-C(19)	112.5	2.0
C(10)-O(5)-C(11)	119.0	1.8

Edwards & Ferrari (1964) presented evidence in support of this absolute configuration. They studied the molar rotation change in heteratisine, obtained on oxidation of the hydroxyl attached to C(6). They found ΔM_D to be -370° . The absolute stereochemistry of related delpheline has been established by Cookson & Trevett (1956). Delpheline has a C(6) hydroxyl group of the same configuration as in heteratisine. The oxidation of this group in a deriva-

tive of delpheline also gave a large negative molar rotation change (-470°).

Recently additional evidence based on the study of optical rotatory dispersion, ΔM_D and nuclear magnetic resonance was given by Aneja & Pelletier (1964a).

The bond lengths had standard deviations varying from 0.026 to 0.046 Å. When these values are multiplied by 1.8 to correct for the lack of a centre of symmetry, and 1.96 in order to use the 5% significance criterion indicated by Cruickshank & Robertson (1953), we find that none of the differences from theoretical values are significant. The lengthening of C-N bonds, however, may be real, as these bonds in des(oxyethylene)lycoctonine, demethanolaconinone (Przybylska, 1961a, b) and delcosine, were also found to be appreciably longer and gave an average of 1.52 Å.

The valency angles with standard deviations, not multiplied by any factors, are listed in Table 2.

The equation of the plane passing through the C(10), C(11), O(4) and O(5) atoms of the lactone group was calculated and the distance from it of C(9) was found to be only 0.03 Å. Thus the whole C(9)-C(10)-O(5)-C(11) group can be considered as



planar and the six-membered lactone ring has the boat conformation. This is consistent with X-ray analyses of other compounds with six-membered lactone rings, *e.g.* in the case of iridomyrmecin and iso-iridomyrmecin (McConnell, Mathieson & Schoenborn, 1962). In heteratisine the C(10)-O(5) bond is 1.37 and O(5)-C(11) is 1.48 Å. They are in very good agreement with the corresponding bonds in the above mentioned compounds, for which the mean values are 1.36 and 1.46 Å respectively.

The five-membered ring as in the lycoctonine skeleton is puckered at C(15) (*cf.* Fig. 1). In the seven-membered ring the atoms C(8), C(9), C(11) and C(18) were found to be planar and the distance of C(17) from that plane came to 0.44 Å. The skeleton is distorted in such a way as to increase the distance O(3) \cdots O(4) to 3.34 Å.

The six-membered ring carrying the methoxyl group is of an appreciably distorted boat form. The distances of C(2) and C(5) from the plane given by the remaining four atoms of this ring were found to be 0.47 and 0.70 Å respectively. The ring is therefore flattened at C(2), leading to an increase in the angle C(1)-C(2)-C(3) (117.5°) and in the distance between C(1) and C(3) (2.61 Å). It is interesting that owing to the considerable strain in this ring the C(2) atom displays an abnormally high vibration. Its temperature factor was found to be 7.3 \AA^2 . In delcosine (Mair & Przybylska) the hydroxyl group attached to C(1) was found to have the same configuration as in heteratisine and the six-membered ring is also of the boat form. There is no doubt that the N⁺-H \cdots O(1) hydrogen bond

stabilizes the boat conformation of the ring. Edwards & Ferrari (1964) reported an additional contributing factor, namely that a chair form of this ring is destabilized relative to the boat by the repulsion of the C(1)-methoxyl by the C(12) β hydrogen.

The distances $N^+ \cdots O(1)$ and $N^+ \cdots Br^-$ are 2.72 and 3.40 Å respectively, indicating a bifurcated hydrogen bond. On assuming that the hydrogen atom is at 1.08 Å from nitrogen and makes tetrahedral angles with N-C(15) and N-C(16) bonds, it is found that atoms O(1), N, H and Br are coplanar. Moreover the N-H bond almost bisects the $O(1) \cdots N^+ \cdots Br^-$ angle (angle $O(1) \cdots N^+-H = 44^\circ$ and angle $Br^- \cdots N^+-H = 39^\circ$). Bifurcated hydrogen bonds have been reported in a number of cases, but only in glycine (Marsh, 1958) and perdeuterated violuric acid monohydrate (Craven & Mascarenhas, 1964) has their presence been confirmed by neutron diffraction methods (Burns & Levy, 1958; Craven & Takei, 1964).

The hydrogen bonds are depicted in Fig. 3 and the interatomic distances and angles involving these bonds are listed in Table 3. The oxygen of water, O(6), appears to be hydrogen bonded to two oxygen atoms of neighbouring molecules, O(2) and O(4), and also to the bromine ion. The distances $O(2) \cdots O(3)$ and $O(2) \cdots O(6)$ are 2.70 and 2.74 Å respectively, showing the possible presence of hydrogen bonds. The distance between O(6) and Br^- was found to be 3.37 Å, which is in good agreement with the weighted average of 3.34 Å obtained by Clark (1963) in an extensive review of hydrated compounds.

Table 3. *Interatomic distances and angles involving hydrogen bonds*

Bond	Distance (Å)	Angle	Angle (°)
O(6)-H \cdots O(4)	2.95	O(4) \cdots O(6) \cdots Br ⁻	123.6
O(6)-H \cdots Br	3.37	O(4) \cdots O(6) \cdots O(2)	90.9
O(2)-H \cdots O(6)	2.74	O(2) \cdots O(6) \cdots Br ⁻	88.4
O(3)-H \cdots O(2)	2.70	C(6)-O(2) \cdots O(6)	98.8
N ⁺ -H \cdots O(1)	2.72	C(8)-O(3) \cdots O(2)	80.1
N ⁺ -H \cdots Br ⁻	3.40	C(6)-O(2) \cdots O(3)	89.8
		H-N ⁺ \cdots O(1)	43.8
		H-N ⁺ \cdots Br ⁻	39.2
		C(16)-N ⁺ \cdots Br ⁻	91.9
		C(15)-N ⁺ \cdots O(1)	70.7

The weakest hydrogen bond exists between oxygen of water and the carbonyl group, the $O(6) \cdots O(4)$ distance being 2.95 Å. The angle $O(4) \cdots O(6) \cdots Br^-$ is 123.6°. The infrared spectrum of heteratisine in a Nujol mull shows the C=O stretching vibration at 1742 cm⁻¹. Since the spectrum of heteratisine hydrobromide monohydrate has this peak at 1707 cm⁻¹, a shift due to hydrogen bonding is evident.

Since the molecule of water is donating its protons to O(4) and to the bromine ion, the O(2) atom must be donating to O(6) and accepting a proton from O(3).

Hydrogen bonding joins the molecules together forming spiral chains about the twofold axis. The presence of molecules of water appears to be essential

for imparting stability as the hydrobromide salt crystallized from methanol was found to be efflorescent (Aneja & Pelletier, 1964b).

The C \cdots C intermolecular contacts are normal, the shortest being 3.46 Å between C(3) and C(10), and all others being greater than 3.60 Å. The closest O \cdots O approach came to 3.61 Å.

The C \cdots O distances can also be considered as normal, as the shortest are $C(16) \cdots O(3) = 3.19$, $C(3) \cdots O(4) = 3.27$, and $C(2) \cdots O(4) = 3.29$ Å and all others are above 3.38 Å.

The shortest $Br^- \cdots C$ distance is to C(21) (3.52 Å), all others being larger than 3.70 Å.

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