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## The Direct Determination of Molecular Structure: The Crystal Structure of Himbacine Hydrobromide at $-150^{\circ}\text{C}$

BY J. FRIDRICHSONS AND A. McL. MATHIESON

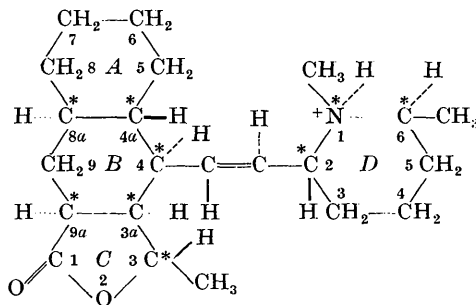
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Himbacine hydrobromide monohydrate,  $\text{C}_{22}\text{H}_{35}\text{O}_2\text{N}\cdot\text{HBr}\cdot\text{H}_2\text{O}$ , crystallizes in the orthorhombic system,

$$a = 6.678, b = 12.670, c = 26.317 \text{ \AA}$$

measured at *circa*  $-150^{\circ}\text{C}$ ., the space group being  $P2_12_12_1$  with  $Z=4$ . Starting with only the empirical formula, the structure was solved by means of zero-layer projections and first-layer generalized projections, image-seeking methods being discarded in favour of direct  $\varrho_0$  and  $\Delta\varrho$  syntheses. The absolute configuration was then established by reference to the anomalous dispersion of the Br atom.



The organic ion whose systematic name is *trans*-1-[2-(1,6-dimethyl piperidyl)]-2-[4-(1-oxo-3-methyl-dodecahydronaphtho [2,3-*c*] furanyl)]-ethylene has 9 asymmetric centres (starred atoms). The rings *A*, *B* and *D* are in the chair conformation. Between *A* and *B* there is a *trans*-junction, between *B* and *C* a *cis*-junction. The piperidine substituent at 6 is axial, those at 1 and 2 equatorial; the naphthofuran substituent at 3*a* is axial, those at 4 and 9*a* equatorial. Bond lengths and angles are presented, those in the  $\gamma$ -lactone system being discussed in more detail.

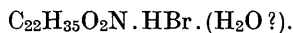
The experimental conditions of the analysis were selected to reduce the number of unobserved terms to a minimum and the influence of this factor on the process of analysis is discussed.

When the X-ray analysis was initiated in May 1959, himbacine was regarded from the chemical viewpoint as the most important of the alkaloids isolated from *Himantandra (Galbulimima)* species (Brown, Drummond, Fogerty, Hughes, Pinhey, Ritchie & Taylor, 1956) in that it appeared to provide a structural key to certain of the related alkaloids. Thus, a solution of the structure and the elucidation of its stereo-

chemistry in detail could be of considerable assistance in the correlation of the associated group of compounds and in relating himbacine to other natural products, especially if the absolute rather than the relative configuration could be defined.

Drs E. Ritchie, W. C. Taylor and J. T. Pinhey, of the Department of Chemistry in the University of Sydney, who were investigating the structures of

the *Himantandra* alkaloids by chemical and physico-chemical methods other than X-ray diffraction, very kindly prepared excellent crystals of the hydrobromide of himbacine and supplied them for the X-ray analysis. Since we were interested in deriving the complete structure *ab initio*, the only information requested by us was the empirical formula—given as



The molecular structure reported here was arrived at solely on the basis of the crystallographic data and chemical sensibility, the absolute configuration being subsequently established by the method of Bijvoet, Peerdeman & van Bommel (1951).

From the crystal-structure-analysis aspect, it was our aim to use the investigation of this compound as one of a group of analyses to study the dependence of the rate of solution and refinement on the quality and range of the diffraction data for molecules of this type of complexity (Mathieson, 1961) particularly where complications of interpretation could be reduced by experimental means.

Comments regarding this structure analysis formed part of a lecture given at the I.U.P.A.C. Symposium on Natural Products (Mathieson, 1961) where brief reports on the crystal structure (Fridrichsons & Mathieson, 1960*a*) and on the structure investigations on himbacine by chemical techniques (Ritchie, Taylor & Pinhey, 1960) were also given. A full report on the chemical investigations is now available (Ritchie, Taylor & Pinhey, 1961).

### Experimental

The crystals, lathe-like in shape, belong to the orthorhombic system, the cell dimensions, determined against a standard (Al,  $a=4.0494 \text{ \AA}$ ) (Fridrichsons, 1959), are

$$a=6.678, b=12.670, c=26.317 \text{ \AA}$$

at *circa*  $-150^{\circ}\text{C}$ . The existence of several odd axial terms introduced doubts regarding the assignment of the space group but when careful inspection of the shapes of these reflections revealed that they differed significantly from those of normal reflections in the same region, it was concluded that these could be ascribed to the Renninger effect and that the correct space group was  $P2_12_12_1$ . The density determined by flotation at room temperature indicated that there are four molecules in the unit cell.

The intensity data were recorded with filtered Cu  $K\alpha$  radiation at  $-150^{\circ}\text{C}$ . using a low-temperature adaptor (Fridrichsons & Mathieson, 1958) in combination with a high-intensity X-ray source, 200 mA. at 35 kV. (Davies, Mathieson & Stiff, 1959), the crystal, goniometer and X-ray source being accurately aligned (Fridrichsons, Mathieson & Stiff, 1959). Equi-inclination Weissenberg photographs with multiple-film packs were recorded for the 0–4 layers about the

$a$ -axis and for the 0-layer about the  $b$ -axis to provide cross-correlation of the  $a$ -axis data. For each layer, film-packs of four films each were exposed for 3 hr. and 6 min. respectively, the complete set of intensity data being recorded within 5 days. The intensities were estimated by eye against a set of timed exposures of a single reflection. The amount of data collected was moderately satisfactory for a molecule of this size, being 90% of the theoretical (Table 1).

Table 1. Comparison of the number,  $N$ , of the reflections observed and theoretically observable in each layer  $hkl$

$hkl$	$N_{\text{obs.}}$	$N_{\text{theor.}}$	$R_1, R_2$ and $R_3$ are reliability indices at various stages of the analyses (see text)		
			$R_1$	$R_2$	$R_3$
0kl	370	438	0.32	0.120	0.104
1kl	424	458	0.28	0.190	0.148
2kl	421	438	—	0.235	0.160
3kl	389	412	—	—	0.209
4kl	296	367	—	—	0.234
	1900	2113			

Calculations were carried out mainly on the University of Sydney computer SILLIAC, the  $\sin^2 \theta$  values and correction factors for intensities from equi-inclination Weissenberg data by means of a programme devised by Mr J. E. W. L. Smith; the structure amplitudes and Fourier syntheses were calculated on programmes devised by Dr H. C. Freeman (1957, 1958). Bond lengths and angles were calculated on the Stantec Zebra computer in Sydney by Dr J. C. Schoone. Scattering factors employed in the calculation of structure factors were those of Berghuis *et al.* (1955) for C, N and O and of Thomas & Umeda (1957) for  $\text{Br}^-$ , a correction for the  $f'$  component of the anomalous dispersion (Dauben & Templeton, 1955) being applied in the later stages of the analysis. Correction factors for absorption were not applied. Correlation of the  $|F_o|$  and  $|F_c|$  values by Wilson (1942) plots were used to derive scale factors and average temperature factors.

### Structure analysis

Generalized Patterson (cosine) functions (Cochran & Dyer, 1952) for each layer  $Hkl$  for  $H=0$  to 4 were computed and from these the three-dimensional site of the Br atom determined. The subsequent steps leading to the location of the carbon–nitrogen–oxygen skeleton of the organic molecule involved only the 0kl and 1kl data.

The initial steps in the analysis were based on the geometrical structure factors for the Br atoms,  $S_{\text{Br}}$ , in two ways. The  $S_{\text{Br}}$  contributions were used to define the sign or phase of the terms  $|F_o(hkl)|$  and to permit the calculation of either the projection or the generalized components of the electron-density distribution. Secondly they were utilized to provide the terms  $F_o^2 \times A_{\text{Br}}$  and  $F_o^2 \times B_{\text{Br}}$  for the calculation of the

summation image-seeking functions (Thomas & MacLachlan, 1952) for the corresponding zero and first-layer components. The image-seeking function has the advantage of providing an automatic weighting of the significant contribution of the  $F_0^2$  term on the basis of the contribution of the search atom(s) whereas for the simple electron-density distribution an arbitrary

limit must be fixed. In general, for the latter functions the corresponding Fourier terms were discarded when  $|F_c| < \frac{1}{2}|F_0|$ .

For the zero layer the electron density,  $\rho_0$ , and the image-seeking function showed a certain similarity but not complete accord, and 21 peaks which appeared common to both distributions were accepted as

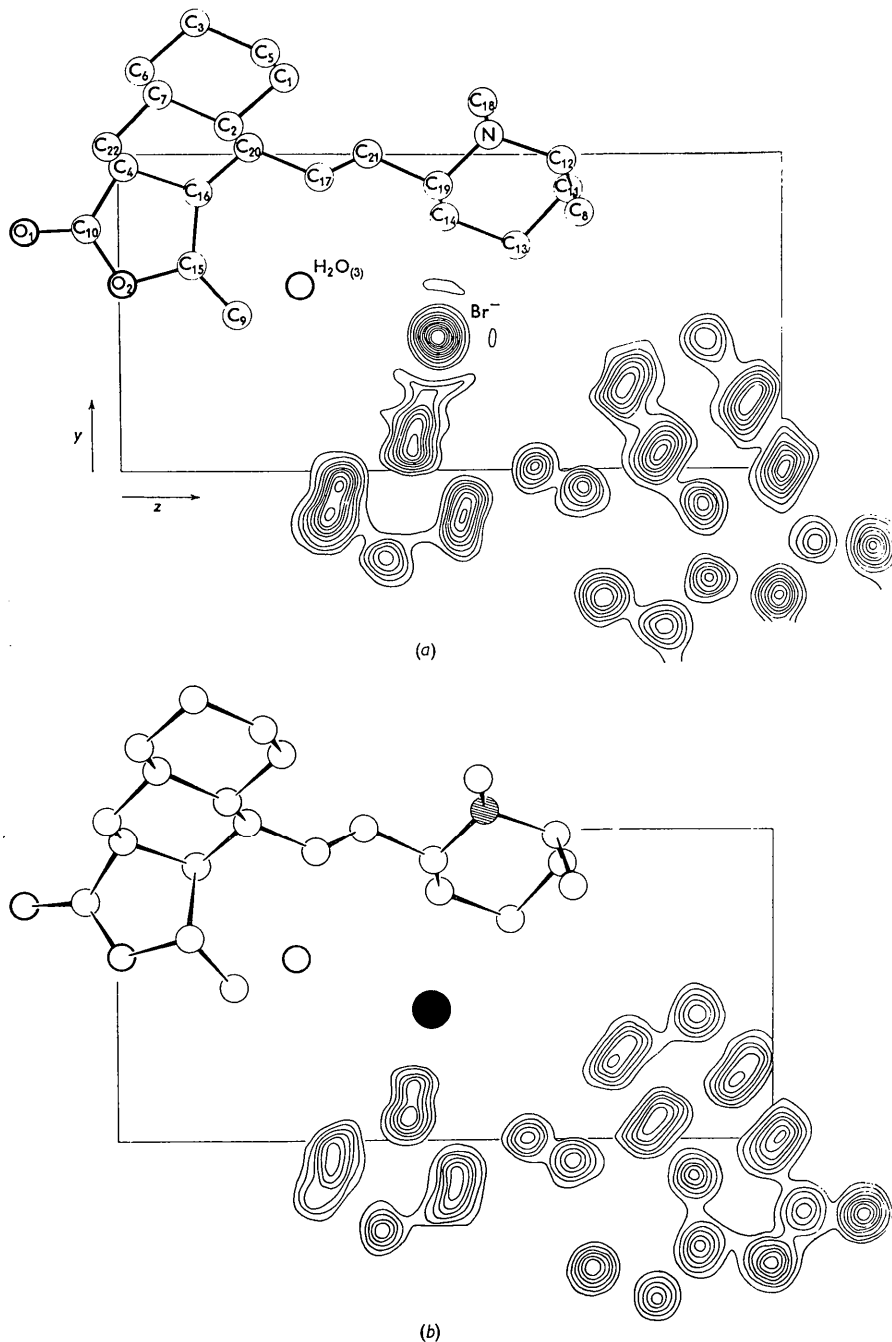


Fig. 1. Projected views of the structure of himbacine hydrobromide. (a) The zero-layer projection,  ${}_6\rho_0$ , down the  $a$ -axis, with a diagram of a molecule for comparison. The numbering of the atoms corresponds to that in the text. (b) The first-layer modulus projection,  ${}_3|\rho_1|$ , with a spatial diagram of the molecule (correct absolute configuration).



Table 2 (cont.)

$h$	$k$	$l$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$	$F_o$	$F_c$								
1	78	59	0	49	67	0	56	64	0	76	87	0	38	33	7	-	0	5	10	26	-	1	0	60	48	9	39	26	0	10	11	18	9	8		
2	12	21	1	34	53	1	28	66	1	28	18	1	20	18	8	13	20	7	19	14	1	51	56	10	9	21	1	10	11	19	13	13				
3	64	87	2	54	92	2	61	41	2	45	34	2	38	38	9	24	28	2	-	2	28	-	1	2	28	11	46	40	2	10	16	20	13	11		
4	35	48	3	58	41	3	43	39	3	18	15	3	8	9	10	10	8	3	16	18	29	15	19	3	46	43	12	24	30	3	9	19	7	15		
5	95	95	4	2	17	4	46	51	4	36	33	4	33	36	11	15	17	4	5	12	30	5	5	4	46	11	41	30	4	9	11	22	4	11		
6	10	13	5	55	52	5	55	60	5	30	37	5	41	42	12	16	19	5	15	13	-	-	5	41	38	14	14	10	5	8	16					
7	64	68	6	27	14	6	74	73	6	48	39	6	32	41	13	24	18	6	15	13	-	-	6	41	41	15	25	30	6	28	17					
8	9	15	7	68	59	7	22	23	7	16	16	7	32	27	14	-	12	7	18	20	4	8	7	41	27	16	17	21	7	20	25					
9	18	22	8	31	33	8	39	35	8	27	28	8	27	28	15	18	18	8	10	10	0	78	92	6	38	38	17	16	17	8	29	39	0	27	29	
10	28	37	9	46	43	9	22	29	9	18	29	9	22	13	16	6	12	9	14	12	1	25	25	9	25	30	18	-	2	9	11	1	7	6		
11	13	28	10	46	39	10	45	41	10	36	46	10	39	42	17	8	8	10	13	12	2	59	65	10	22	22	19	12	15	10	29	26	2	25	10	
12	11	9	11	36	38	11	37	39	11	41	18	11	11	8	18	5	10	11	14	15	3	25	7	11	27	34	20	9	5	11	16	15	3	9	14	
13	40	45	12	24	27	12	43	44	12	19	30	12	24	25	19	5	7	12	15	12	4	84	61	12	33	31	21	18	20	12	17	11	4	20	24	
14	17	23	13	35	52	13	26	21	13	24	27	13	23	18	20	12	12	13	6	9	5	9	12	13	21	15	22	17	15	13	16	16	5	8	16	
15	38	45	14	30	25	14	28	29	14	9	8	14	28	29	21	6	9	14	13	11	6	52	55	14	29	9	23	-	7	14	24	28	6	20	16	
16	14	25	15	18	16	15	26	31	15	-	5	15	14	16	22	10	8	15	7	10	7	25	35	15	13	26	24	6	1	15	-	6	7	11	16	
17	11	10	16	13	11	16	43	50	16	-	16	16	15	17	23	5	5	16	17	19	8	26	63	16	12	16	25	-	5	16	25	24	8	17	30	
18	12	11	17	19	21	17	29	32	17	30	36	17	30	36	17	18	19	24	3	5	17	3	5	9	21	26	17	9	3	26	12	16	4	9	8	
19	9	8	18	22	27	18	18	12	18	19	10	18	19	10	20	11	17	24	3	5	10	43	37	18	24	21	27	8	10	18	19	22	10	17	20	
20	21	18	19	15	12	19	10	20	19	9	9	19	15	13	-	-	-	-	-	-	3	11	12	16	19	-	7	28	-	7	19	7	8	11	-	
21	6	10	20	21	34	20	15	17	20	-	3	20	11	16	12	40	32	20	10	10	-	-	-	-	-	-	-	-	20	15	17	12	18	15		
22	9	12	21	23	26	21	11	15	21	17	22	21	16	18	0	7	9	0	-	4	13	17	17	21	-	14	-	-	21	8	7	13	-	10		
23	-	0	22	24	28	22	5	22	22	9	7	22	5	3	1	24	27	1	18	16	14	30	32	22	10	15	-	5	0	7	18	22	17	14	14	
24	22	19	23	21	19	23	11	11	23	10	12	23	14	16	2	13	15	2	12	12	15	21	23	-	-	-	0	7	18	22	10	17	14	14		
25	-	0	24	10	17	24	14	15	24	7	5	24	14	15	3	12	13	3	17	14	34	34	24	13	12	1	8	17	24	9	10	16	18	17		
26	7	12	25	3	3	25	12	17	25	18	20	25	13	19	4	-	3	17	9	7	25	-	6	2	10	5	25	-	7	17	5	6	6	8		
27	5	4	26	10	12	26	10	9	26	4	4	26	8	7	5	20	22	5	13	16	18	14	14	26	-	5	3	28	33	19	18	5	8	18		
28	18	22	27	5	10	27	10	9	27	3	4	27	13	14	6	8	9	6	7	2	21	16	28	-	6	5	-	21	-	49	-	19	5	10		
29	6	4	28	6	9	28	12	13	28	9	6	28	9	6	7	16	21	3	21	-	2	29	-	6	33	21	0	35	28	-	4	12	28	4	12	
30	11	13	29	-	7	29	6	10	29	8	14	-	-	-	8	20	22	8	-	3	21	-	2	29	-	6	-	-	-	-	-	-	-	-		
31	3	6	30	11	11	30	10	8	-	-	-	-	-	-	9	13	15	9	10	18	6	23	7	12	-	44	-	8	18	25	2	29	18	0	-	
32	3	11	31	11	11	-	-	-	0	15	23	10	25	24	10	18	6	23	7	12	-	-	-	-	-	-	44	-	0	35	28	-	4	12	28	
									1	14	16	11	11	9	11	12	15	24	-	7	25	-	7	0	16	3	10	17	12	0	17	12	0	1	3	19
									2	23	23	12	7	5	12	9	5	12	9	6	7	26	-	5	1	20	17	11	12	11	5	26	31	3	-	4
									3	16	24	13	5	2	13	6	7	27	-	8	2	13	15	23	-	5	23	-	6	15	12	12	5	15	12	12
									4	19	27	14	16	15	11	12	15	24	-	7	20	-	7	0	16	3	10	17	12	0	17	12	0	1	3	19
									5	6	6	15	9	9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
									6	29	39	16	19	21	-	6	4	29	48	6	4	15	12	14	16	30	30	8	20	23	6	8	13	6	8	13
									7	15	17	16	13	11	-	4	5	6	30	32	11	5	6	27	31	16	15	40	10	20	20	6	10	8	10	8
									8	28	29	18	29	18	16	13	11	-	9	3	4	15	12	14	16	30	30	8	20	23	6	8	13	6	8	13
									9	16	19	17	16	13	-	4	3	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
									10	21	29	19	21	19	16	13	11	-	7	20	11	12	7	8	27	34	15	16	14	10	-	11	17	20	7	2
									11	21	29	19	21	19	16	13	11	-	7	20	11	12	7	8	27	34	15	16	14	10	-	11	17	20	7	2
									12	11	14	11	11	9	-	6	2	3	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
									1																											

The corresponding set of  $0kl$  structure factors improved to  $R=0.14$  and  ${}_5\rho_0$  and  ${}_5\Delta\rho$  were computed.

Combining the information contained in the electron-density distributions and in  ${}_2C_1$  and  ${}_2S_1$ , approximate  $x$  parameters for all atoms were deduced and a set of three-dimensional structure factors gave a measure of agreement  $R_2$  in Table 1. Although the pattern of agreement confirmed the basic correctness of the three-dimensional molecular skeleton and the differentiation of the nitrogen and oxygen atoms, the  $x$  parameters clearly required some further improvement for the more certain definition of bond lengths.

A new set of generalized syntheses,  ${}_3C_1$  and  ${}_3S_1$ , were computed and also projections  ${}_6\rho_0$ , Fig. 1(a) and  ${}_6\Delta\rho$ . The  ${}_3C_1$  and  ${}_3S_1$  functions permitted the derivation of improved values of  $x = \tan^{-1} {}_3S_1(y, z) / {}_3C_1(y, z)$  at the  $(y, z)$  sites of the respective atoms. By combining  ${}_3C_1$  and  ${}_3S_1$ , a modulus projection  ${}_3|\rho|_1 = ({}_3C_1^2 + {}_3S_1^2)^{1/2}$  (Fridrichsons & Mathieson, 1955) Fig. 1(b) was derived and by selecting the best fit of  ${}_6\rho_0$  and

$2.25 \text{ \AA}^2$  for all atoms except the oxygen of the water molecule for which a more appropriate value of  $3.50 \text{ \AA}^2$  was deduced from the difference syntheses. The use of data collected at  $-150^{\circ}\text{C}$ . eliminated the need to introduce asymmetric temperature factors.

### Absolute configuration of himbacine

The original conditions for the determination of absolute configuration proposed by Bijvoet, Peerdeman & van Bommel (1951) have been shown capable of extension to more general cases (Peterson, 1955) and Peerdeman (1956) has been able to define the absolute configuration of strychnine by invoking the anomalous dispersion of Cu  $K\alpha$  radiation by the Br atom using only photographic techniques of recording intensities. This method has been applied in the definition of the absolute configuration of himbacine hydrobromide using  $f' = -0.9$  and  $f'' = +1.5$  (Dauben & Templeton, 1955).

To locate comparable groups of  $hkl$  reflection on the same film and hence ensure standard development, the Weissenberg goniometer (Mathieson, 1951) was slightly modified since the film holder was hemicylindrical and recorded only over  $200^{\circ}$  crystal rotation. A new lead-screw was fitted to permit recording over a range of  $290^{\circ}$  on the same film-holder. The proper indexing of the film followed the definitive work of Bijvoet & Peerdeman (1956).

Table 3. Atomic parameters of the asymmetric unit

Atom	$x/a$	$y/b$	$z/c$
C <sub>1</sub>	0.9361	0.1188	0.3750
C <sub>2</sub>	0.8750	0.0438	0.4164
C <sub>3</sub>	0.1667	0.2047	0.4430
C <sub>4</sub>	0.4139	0.4797	0.0047
C <sub>5</sub>	0.1500	0.1578	0.3891
C <sub>6</sub>	0.0889	0.1281	0.4836
C <sub>7</sub>	0.8778	0.0922	0.4695
C <sub>8</sub>	0.2917	0.4094	0.3477
C <sub>9</sub>	0.4722	0.2438	0.0883
C <sub>10</sub>	0.9639	0.1172	0.0258
C <sub>11</sub>	0.6722	0.4453	0.3391
C <sub>12</sub>	0.4528	0.4906	0.3344
C <sub>13</sub>	0.7083	0.3563	0.2992
C <sub>14</sub>	0.7111	0.4016	0.2445
C <sub>15</sub>	0.3611	0.3234	0.0547
C <sub>16</sub>	0.4444	0.4391	0.0602
C <sub>17</sub>	0.3639	0.4641	0.1508
C <sub>18</sub>	0.7361	0.0813	0.2250
C <sub>19</sub>	0.5000	0.4500	0.2406
C <sub>20</sub>	0.6583	0.0109	0.4016
C <sub>21</sub>	0.5222	0.0016	0.3117
C <sub>22</sub>	0.3028	0.4844	0.4930
N	0.5417	0.0313	0.2203
O <sub>1</sub>	0.0139	0.1234	0.0703
O <sub>2</sub>	0.4194	0.2938	0.0023
O <sub>3</sub>	0.9611	0.2922	0.1359
Br	0.1996	0.2102	0.2396

${}_3|\rho|_1$ , slight improvement in the  $y, z$  parameters was achieved. The resultant set of structure factors, Table 2, is in reasonable agreement with the measured values, *vide*  $R_3$  in Table 1. (N.B. The 2-, 3- and 4-layer data have not been used in the analysis of the organic molecule but operate as a final check on the essential correctness of the atom locations.) To improve the agreement would be feasible but was not deemed necessary for the purpose of the analysis, namely the solution of the structure adequate to define the atom and bond types.

Atomic parameters in one quadrant of the unit cell are listed in Table 3, the temperature factor  $B$  being

Table 4. Comparison of forms to establish the absolute configuration

$hkl$	$F^2(hkl)$		$F^2(h\bar{k}l)$
118	166	>	95
125	661	>	511
127	82	>	29
142	951	>	794
146	717	<	889
151	661	>	598
1,5,11	59	<	125

For the determination of the absolute configuration, particularly by eye-estimation of intensities, it is of importance to seek out reflections for which the contribution of the anomalous scatterer to the structure amplitude is appreciable but the structure amplitude itself is small. Those selected as most suitable for the test are given in Table 4. Careful inspection of the first-layer film about the  $a$  axis permitted fixing with certainty the intensity order of the forms of 118, 127 and 1,5,11 and in the other forms with reasonable assurance—no contradictory indications to this decision were encountered. The absolute configuration determined in this manner is correctly indicated by the atomic parameters in Table 3 when considered in relation to a right-handed set of axes with symmetry elements grouped as in the space group  $P2_12_12_1$ . The molecular skeleton in Fig. 1(b) is also oriented in accord with this decision.

### Discussion

In the determination of molecular structure, there are two main stages—the location of the atom sites in the correct region of the unit cell (i.e. the molecular skeleton) and the refinement of the height, shape and location of the electron-density peaks of these atom types and the types of bonds between the atoms.

For compounds of moderate complexity where the main aim of the investigation is to establish the molecular structure (previously unknown), the first stage of the analysis is critical. It is important that the process of arriving at the correct molecular skeleton should involve the minimum number of steps. In the initial stages of the analysis where phase (sign) is mainly defined by the heavy atom(s), considerable errors occur in the distributions  $\rho$  or  $C$  or  $S$ , this being particularly so where a general phase angle is involved. At this low level of structural significance, the possibility exists of selecting a peak for an atom site which later turns out to be completely spurious. Any such false choice incurs wasteful cycles of calculation before the error is rectified and eradicated. Further, in this type of analysis, it appears important to us that reliance on structural evidence from chemical investigations should be restrained particularly in the early stages of the analysis, and that structural speculation should be discouraged.\* The aim of the analysis should be to locate the real peaks of electron density without chemical assumption and hence attain the skeleton of the molecule. Once the skeleton is defined, the process of refinement leads to the assignment of the atom types C, N or O and hence the complete structure.

Two general factors govern the quantity and quality of the diffraction data—series termination and amplitude termination. The former is particularly important for complex molecules in which the temperature factor,  $B$ , is frequently sufficiently large to reduce to insignificance terms beyond  $s (=2 \sin \theta/\lambda) = 0.8 \text{ \AA}^{-1}$ . The latter factor, although of lesser importance cannot be ignored. If the lower limit of observation is high, many terms are not measured and not assigned a specific value.†

From our earlier experience with compounds of this

\* This comment should not be construed as minimizing the value of structural deduction from chemical argument but rather that in the early part of a crystallographic investigation, such information, being partial, may mislead one's deductions so that the X-ray data is forced to conform with it. Also the relation of partial information regarding radicals or groups of atoms to their location in the molecule is dubious at this stage since the location of specific regions within the unit cell occupied by individual molecules is still unknown.

† Satisfying this condition of an adequate amplitude range also permits more trustworthy application of modification functions to achieve the solution of vector maps. When a considerable proportion of reflections in the region of high  $s$  are below the experimental limit of intensity measurement, doubts can exist regarding the validity of enhancing the influence of the remaining restricted group of terms by application of modification functions.

size, we came to the conclusion that the basic condition necessary to achieve the aims above (i.e. for analysis) was to be able to specify for as many reflexions as possible within the observable range, an intensity ( $F^2$ ) value of experimental significance. This condition has been largely satisfied by maintaining the crystal at a low temperature and increasing the intensity of the X-ray beam. This combination has been applied to the analysis of a group of natural products. We have been made particularly aware of the improved basis for analysis and refinement afforded by this experimental set-up in comparing the progress of an earlier analysis, that of lanostenol iodacetate (Fridrichsons & Mathieson, 1953) with that of the present compound.

Diffraction data obtained in this way go far towards fulfilling certain of the conditions which Cruickshank (1960) has recently laid down as necessary for refinement of atomic positions to an accuracy adequate to define bond lengths within 0.01 Å. It is perhaps not unexpected that the conditions necessary for accurate refinement are also those which we consider necessary for a successful and rapid analysis—basically both demand a large value of the ratio of the number of *measured* data to the number of parameters to be determined.

We may note that the fulfilment of these experimental conditions underlies all the theoretical treatments for either analysis or refinement. The present analysis supports the value of this experimental approach in that, although only  $0kl$  and  $1kl$  data were

Table 5. Bond lengths and approach distances

Atoms	Bond lengths	Remarks	Atoms	Approach dist.
C <sub>1</sub> -C <sub>2</sub>	1.51 Å	Single bonds, mean 1.54 Å, mean deviation 0.02 Å, 1.54 ± 0.04 Å	Br-N <sub>C</sub> <sup>+</sup>	3.25 Å
C <sub>1</sub> -C <sub>5</sub>	1.56		Br-C <sub>18C</sub>	3.52
C <sub>5</sub> -C <sub>3</sub>	1.54		Br-C <sub>21C</sub>	3.90
C <sub>3</sub> -C <sub>6</sub>	1.53		Br-C <sub>5C</sub>	4.00
C <sub>6</sub> -C <sub>7</sub>	1.53		Br-C <sub>13A</sub>	4.17
C <sub>7</sub> -C <sub>2</sub>	1.53		Br-C <sub>13A'</sub>	4.08
C <sub>7</sub> -C <sub>22</sub>	1.50		Br-C <sub>14A</sub>	4.19
C <sub>22</sub> -C <sub>4</sub>	1.55		Br-C <sub>14A'</sub>	4.07
C <sub>4</sub> -C <sub>16</sub>	1.56		Br-H <sub>2</sub> O	3.33
C <sub>16</sub> -C <sub>20</sub>	1.53			
C <sub>20</sub> -C <sub>2</sub>	1.56		H <sub>2</sub> O-C <sub>17A</sub>	3.48
C <sub>16</sub> -C <sub>15</sub>	1.58		H <sub>2</sub> O-C <sub>15A</sub>	3.44
C <sub>15</sub> -C <sub>9</sub>	1.53		H <sub>2</sub> O-C <sub>9A</sub>	3.55
C <sub>15</sub> -C <sub>14</sub>	1.54		H <sub>2</sub> O-C <sub>9A'</sub>	3.68
C <sub>14</sub> -C <sub>13</sub>	1.55	H <sub>2</sub> O-O <sub>1B</sub>	2.77	
C <sub>13</sub> -C <sub>11</sub>	1.56			
C <sub>11</sub> -C <sub>12</sub>	1.58			
C <sub>12</sub> -C <sub>8</sub>	1.53			
N-C <sub>19</sub>	1.48	Pyramidal nitrogen mean 1.49 Å	C <sub>9A</sub> -O <sub>1B</sub>	3.68
N-C <sub>12</sub>	1.53		C <sub>9A'</sub> -O <sub>1B</sub>	3.96
N-C <sub>18</sub>	1.45		O <sub>2A</sub> -O <sub>2B</sub>	3.52
			O <sub>1D</sub> -C <sub>11A</sub>	3.90
			O <sub>1D</sub> -C <sub>8A</sub>	4.02
			C <sub>8A</sub> -C <sub>22D</sub>	3.93
C <sub>20</sub> -C <sub>17</sub>	1.51	Double bond	C <sub>8A</sub> -C <sub>5C</sub>	3.50
C <sub>17</sub> -C <sub>21</sub>	1.33		C <sub>8A</sub> -C <sub>3C</sub>	3.70
C <sub>21</sub> -C <sub>19</sub>	1.53			
O <sub>1</sub> -C <sub>10</sub>	1.22	$\gamma$ -lactone ring system		
C <sub>10</sub> -C <sub>4</sub>	1.50			
C <sub>10</sub> -O <sub>2</sub>	1.38			
O <sub>2</sub> -C <sub>15</sub>	1.48			

Table 5a. Bond angles

Atoms	Angle	Atoms	Angle
C <sub>2</sub> -C <sub>1</sub> -C <sub>5</sub>	106.1°	C <sub>6</sub> -C <sub>7</sub> -C <sub>22</sub>	110.1°
C <sub>1</sub> -C <sub>5</sub> -C <sub>3</sub>	114.1	C <sub>22</sub> -C <sub>4</sub> -C <sub>16</sub>	114.4
C <sub>5</sub> -C <sub>3</sub> -C <sub>6</sub>	111.9	C <sub>4</sub> -C <sub>22</sub> -C <sub>7</sub>	110.8
C <sub>3</sub> -C <sub>6</sub> -C <sub>7</sub>	109.4	C <sub>22</sub> -C <sub>7</sub> -C <sub>2</sub>	110.2
C <sub>6</sub> -C <sub>7</sub> -C <sub>2</sub>	110.7	C <sub>2</sub> -C <sub>20</sub> -C <sub>17</sub>	115.2
C <sub>7</sub> -C <sub>2</sub> -C <sub>1</sub>	113.9	C <sub>16</sub> -C <sub>20</sub> -C <sub>17</sub>	108.9
C <sub>7</sub> -C <sub>2</sub> -C <sub>20</sub>	110.4	C <sub>20</sub> -C <sub>17</sub> -C <sub>21</sub>	126.3
C <sub>1</sub> -C <sub>2</sub> -C <sub>20</sub>	103.9	C <sub>17</sub> -C <sub>21</sub> -C <sub>19</sub>	124.6
C <sub>2</sub> -C <sub>20</sub> -C <sub>16</sub>	114.6	C <sub>21</sub> -C <sub>19</sub> -N	111.7
C <sub>20</sub> -C <sub>16</sub> -C <sub>4</sub>	111.2	C <sub>14</sub> -C <sub>19</sub> -N	106.7
C <sub>20</sub> -C <sub>16</sub> -C <sub>15</sub>	117.3	C <sub>21</sub> -C <sub>19</sub> -C <sub>14</sub>	108.6
C <sub>4</sub> -C <sub>16</sub> -C <sub>15</sub>	100.1	C <sub>19</sub> -C <sub>14</sub> -C <sub>13</sub>	101.4
C <sub>16</sub> -C <sub>15</sub> -C <sub>9</sub>	112.8	C <sub>14</sub> -C <sub>13</sub> -C <sub>11</sub>	111.1
C <sub>16</sub> -C <sub>15</sub> -O <sub>2</sub>	103.2	C <sub>13</sub> -C <sub>11</sub> -C <sub>12</sub>	110.7
C <sub>9</sub> -C <sub>15</sub> -O <sub>2</sub>	104.1	C <sub>11</sub> -C <sub>12</sub> -C <sub>8</sub>	113.0
C <sub>15</sub> -O <sub>2</sub> -C <sub>10</sub>	110.4	N-C <sub>12</sub> -C <sub>8</sub>	117.3
O <sub>2</sub> -C <sub>10</sub> -O <sub>1</sub>	121.4	N-C <sub>12</sub> -C <sub>11</sub>	100.0
O <sub>2</sub> -C <sub>10</sub> -C <sub>4</sub>	109.5	C <sub>12</sub> -N-C <sub>11</sub>	101.9
O <sub>1</sub> -C <sub>10</sub> -C <sub>4</sub>	128.7	C <sub>12</sub> -N-C <sub>19</sub>	113.5
C <sub>10</sub> -C <sub>4</sub> -C <sub>16</sub>	101.6	C <sub>19</sub> -N-C <sub>18</sub>	108.1
C <sub>10</sub> -C <sub>4</sub> -C <sub>22</sub>	108.9		

used, the analysis was relatively rapid (taking into account the location of the computer (Sydney)), the molecular skeleton and the differentiation of oxygen and nitrogen atoms being achieved by Sept. 1959.

The bond lengths and angles calculated from the atomic parameters (Table 3) are given in Table 5 and Fig. 2(a), the numbering of the atoms in the molecule being shown in Fig. 1(a). The bonds are arranged in Table 5 in related groups. As a guide to the internal accuracy of the analysis, those carbon-carbon bonds which, on chemical grounds may be regarded as single bonds have been grouped together and their mean value estimated. The mean deviation from this value is 0.02 Å, from which we may suggest that the bond lengths in general have a maximum inaccuracy of  $\pm 0.04$  Å from the measured value. Thus in the case of the N<sup>+</sup>-C bonds, the bond lengths all lie within the range permitted although rather extreme in spread. This estimate also gives a basis on which to assess the bond types in cases where only one example occurs in the structure.

The bond-lengths within the  $\gamma$ -lactone ring system are of interest particularly with respect to the O<sub>2</sub>-C<sub>10</sub> and O<sub>2</sub>-C<sub>15</sub> bonds. These nominally equivalent single bonds differ by 0.1 Å and O<sub>2</sub>-C<sub>15</sub> is rather larger than what is regarded as a satisfactory O-C single-bond

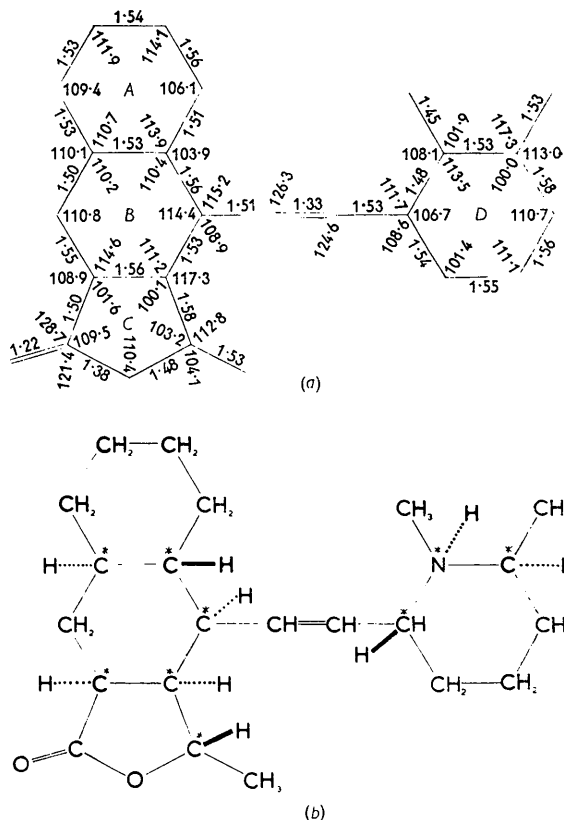


Fig. 2. The structure of the himbacine ion. (a) Showing the bond-lengths. (b) A diagram of the whole molecule according to chemical convention showing the absolute configuration. The asymmetric centres are starred.

length 1.43 Å (*Tables of Interatomic Distances and Configuration in Molecules and Ions*, 1958). There are no compounds with  $\gamma$ -lactone ring functions whose structure has been analyzed in sufficient detail to permit a direct comparison. However in Fig. 3 are grouped structures containing somewhat similar atom groups which permit a less direct comparison—(a) methyl formate and acetate (Gorman, Shand & Schomaker, 1950), (b) ethylene carbonate (Brown, 1954) and (c) ethylene thiourea (Wheatley, 1953). In (a) the initial structure determination was by electron diffraction of the vapour and the bond lengths,

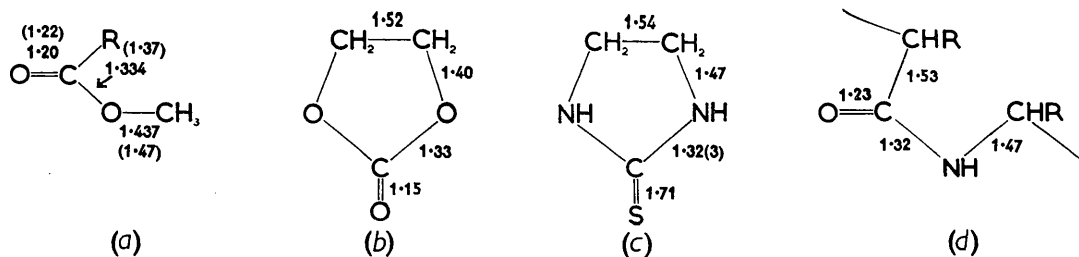


Fig. 3. The structure and dimensions of molecules containing groups with atomic environments similar to that of the lactone system. (a) Esters—methyl formate and acetate ( $R = \text{H}$  or  $\text{CH}_3$ ). (b) Ethylene carbonate. (c) Ethylene thiourea. (d) Peptide group (Corey & Donohue, 1950). The peptide group has been re-arranged to accentuate the similarity to the lactone group.



in brackets, are not of high accuracy; but for methyl formate a more exact set of values has been derived by microwave techniques (Curl, 1959). The values in (b) were not claimed to be of high accuracy due to high thermal vibration but for (c) the N-C bonds are claimed as accurate within 0.01 Å. It is of interest to note the similarity of the lactone to the peptide system, Fig. 3(d), in which also is evident a corresponding difference in formally similar bonds (N-C).

It would therefore appear that the observed difference in himbacine is consistent with the available comparable values.\* The two bonds under discussion particularly O<sub>2</sub>-C<sub>15</sub> have only a small *x* component and being relatively clear in projection (Fig. 1) their accuracy should be rather better than the average quoted so that both bond-lengths being longer than the best values available (Curl, 1959) would appear to have some real significance.

Assuming that these elongations are significant, we may consider what constraint is placed on this group by its being linked to the AB ring system. If C<sub>10</sub> and C<sub>15</sub> were not involved in ring-closure, then their calculated separation would be 2.95 Å assuming a normal dihedral angle of 60° between the planes defined by C<sub>10</sub>C<sub>4</sub>C<sub>16</sub> and C<sub>4</sub>C<sub>16</sub>C<sub>15</sub>. Being linked through O<sub>2</sub>, with the angle C<sub>10</sub>-O<sub>2</sub>-C<sub>15</sub>=110°, the measured distance C<sub>10</sub>-C<sub>15</sub> is 2.35 Å. Hence, as evidenced by the angles C<sub>4</sub>C<sub>16</sub>C<sub>15</sub> (100.1°) and C<sub>16</sub>C<sub>4</sub>C<sub>10</sub> (101.6°), a considerable distortion of the unstrained bond directions of C<sub>4</sub>-C<sub>10</sub> and C<sub>16</sub>-C<sub>15</sub> must have taken place to bring C<sub>10</sub> and C<sub>15</sub> closer together with a concomitant reduction of the dihedral angle to 45°. This strain may

\* The interpretation of bond length in terms of the number of nearest neighbours (Herzberg & Stoicheff, 1955; Stoicheff & Costain, 1959) or its allied treatment in terms of the state of hybridization (Dewar & Schmeising, 1959) appears to provide a more straightforward explanation of this difference than the interpretation on the basis of partial double-bond character.

therefore be partly relieved by a slight extension of the two C-O bond lengths.

Conversely the closing of ring *C* with the resultant distortion of the C<sub>4</sub>-C<sub>10</sub> and C<sub>16</sub>-C<sub>15</sub> bond directions and the change in dihedral angle modifies considerably the conformation of ring *B* from the unstrained chair form as may be seen in Fig. 1(a) and there is a suggestion in the data that this influence may be transmitted through ring *B* to ring *A*. For substantiation, this requires further refinement of the atomic parameters.

### Conformation and configuration

Rings *A* and *B*, Fig. 2, are saturated alicyclic rings in the chair conformation linked by a *trans*-junction (*trans*-decalin), whereas the junction between the six-membered ring *B* and the five-membered ring *C* is *cis*. Inspection of the molecular ball model for himbacine reveals that a *trans*-junction would result in a rather close approach of O<sub>2</sub> and the hydrogen attached to C<sub>4</sub> so the *cis*-junction is sterically favoured. This observation is in accord with the comments of Angyal & Mills (1952) regarding the preferred *cis*-fusion of a six- to a five-membered ring in simple systems although there is ample evidence from the steroid field that *trans*-fusion is possible without undue strain e.g. cholesterol (Carlisle & Crowfoot, 1945); lanostenol (Fridrichsons & Mathieson, 1953). The substituent to the decalin ring system at C<sub>16</sub> is axial, those at C<sub>4</sub> and C<sub>20</sub> normal equatorial. In the  $\gamma$ -lactone ring system O<sub>1</sub>O<sub>2</sub>C<sub>10</sub> and C<sub>4</sub> are coplanar and nearly coplanar with C<sub>15</sub> while C<sub>16</sub> lies markedly out of this plane in general accord with the results for 5-membered saturated ring systems (Beever & Cochran, 1947; Furberg, 1950; Zussman, 1951; Donohue & Trueblood, 1952; Beecham, Fridrichsons & Mathieson, 1958; Fridrichsons & Mathieson, 1953). Ring *D* is also in a normal chair conformation with the substituent at C<sub>12</sub> axial and

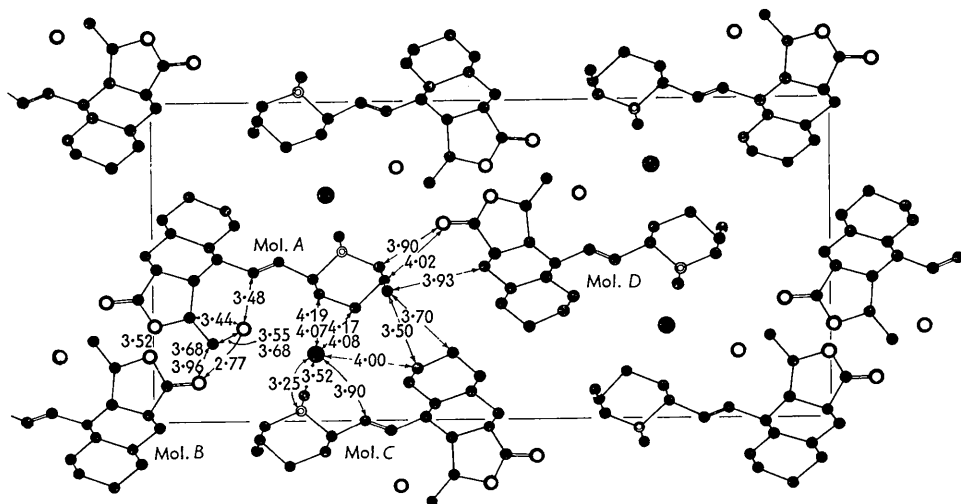


Fig. 4. Diagram of the contents of the unit cell, projected down the *a*-axis, showing some of the more important close-approach distances.

those at  $\text{C}_{19}$  and N equatorial. Since steric restriction does not force the axial conformation at  $\text{C}_{12}$ , its specific orientation may have some significance with respect to the bio-synthesis of this molecule as the stereochemical detail in jacobine bromhydrin (Fridrichsons, Mathieson & Sutor, 1960) offered possible guides to its biosynthesis and as in thelepogine (Fridrichsons & Mathieson, 1960b) a guide to a possible precursor.

The two ring systems  $AB(C)$  and  $D$  are linked *trans* through a double bond  $\text{C}_{17}\text{--}\text{C}_{21}$  in such a manner that the approximate planes of  $AB$  and of  $D$  are parallel to each other and perpendicular to the plane defined by  $\text{C}_{20}$ ,  $\text{C}_{17}$ ,  $\text{C}_{21}$  and  $\text{C}_{19}$ . These relationships are more clearly illustrated in Figs. 1 and 2.

In himbacine hydrobromide, there are nine asymmetric centres, these being starred in Fig. 2(b), which shows a more conventional chemical representation of the molecular structure. The details of the configuration have mostly been provided in the discussion above.

### Molecular packing

The packing of the molecular ions, Br ions and water molecules is illustrated in Fig. 4 with the main short approach distances indicated, see also Table 5. The Br ion sits at the apex of the triad of atoms  $\text{C}_{18}$ ,  $\text{C}_{19}$  and  $\text{C}_{12}$  above the N atom at a distance of  $3.25\text{ \AA}$ . The  $\text{H}_2\text{O}$  molecule clearly plays an important role in holding together the structure, with close approaches to the  $\text{Br}^-$  ion,  $3.33\text{ \AA}$ , to  $\text{C}_{17}$  of molecule  $A$ ,  $3.48\text{ \AA}$ , and a hydrogen-bonded distance to the keto-oxygen of molecule  $B$ ,  $2.77\text{ \AA}$ —with a short distance to the keto-oxygen  $\text{O}_1$ ,  $2.77\text{ \AA}$ . Other important factors are the packing of the  $\gamma$ -lactone ring systems and the packing of the neutral ends of the molecule.

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