

- DEAN, C. (1955). *J. Chem. Phys.* **23**, 1734.
 DEHMELT, H. G. (1954). *Amer. J. Phys.* **22**, 110.
 DEHMELT, H. G. & KRUGER, H. (1951). *Z. Phys.* **129**, 401.
 GORDY, W., SMITH, W. V. & TRAMBARULO, R. F. (1953).
Microwave Spectroscopy. New York: Wiley.
 KOJIMA, S., TSUKADA, K., SHIMAUCHI, A. & HINAGA, Y.
 (1954). *J. Phys. Soc. Japan*, **9**, 795.
 MEAL, H. C. (1956). *J. Chem. Phys.* **24**, 1011.
 MONFILS, A. (1955). *C. R. Acad. Sci., Paris*, **241**, 561.
 ORVILLE-THOMAS, W. J. (1957). *Quart. Rev. Chem. Soc. Lond.* **11**, 162.
 TOWNES, C. H. & DAILEY, B. P. (1949). *J. Chem. Phys.* **17**, 782.
 TOWNES, C. H. & DAILEY, B. P. (1952). *J. Chem. Phys.* **20**, 35.
 TSUKADA, K. (1956). *J. Phys. Soc. Japan*, **11**, 956.

Acta Cryst. (1958). **11**, 718

The Structure of Annotinine Bromohydrin*

BY MARIA PRZYBYLSKA AND F. R. AHMED

Divisions of Pure Chemistry and Pure Physics, National Research Council, Ottawa, Canada

(Received 1 April 1958)

Crystals of annotinine bromohydrin are orthorhombic, space group $P2_12_12_1$ with $a = 11.89$, $b = 13.40$, $c = 9.68$ Å and $Z = 4$. Its crystal and molecular structure has been determined from a three-dimensional Patterson synthesis interpreted by vector convergence method. Ambiguities arising from the presence of the bromine atom close to a special position ($x = 0.779$, $y = 0.263$, $z = 0.012$) were discriminated by simultaneous study of the agreement between observed and calculated data and of q_0 and $q_0 - q_c$ maps for the three projections. Final atomic coordinates have been obtained from a three-dimensional observed differential synthesis which was not corrected for finite summation errors. Six-membered rings of the molecule are in 'chair' form and the bromine atom is *trans* with respect to the hydroxyl group. The carbon atom of the methyl group is directed towards the lactone ring.

Introduction

The alkaloid annotinine has been isolated by Manske & Marion (1943) from species of the *Lycopodium* family. A great deal of work has been done on the chemistry of this compound, and several different structures have been proposed on the basis of chemical degradation studies (Anet & Marion, 1954; Wiesner, Valenta & Bankiewicz, 1956; Martin-Smith, Greenhalgh & Marion, 1957).

In the present investigation no chemical assumptions have been made in deriving the skeleton structure of annotinine bromohydrin and chemical evidence has been used only in distinguishing the oxygen and nitrogen atoms from carbon atoms. The structure had already been determined from this X-ray analysis and was at the refinement stage (Przybylska & Marion, 1957) when Wiesner, Ayer, Fowler & Valenta (1957) proposed a complete structure for annotinine. Their structure has been fully confirmed by our results.

X-ray crystallographic data for several *Lycopodium* alkaloids have been published by Knop & MacLean (1952), but annotinine bromohydrin was not included in their work. It has been chosen for the present study since the bromine atom is directly bonded to a large-membered ring (MacLean & Prime, 1953).

Experimental

Crystal data

Pure, chemically analysed, large colourless crystals of annotinine bromohydrin, $C_{16}H_{22}O_3NBr$, were prepared by Dr M. Martin-Smith, who obtained this compound by heating annotinine with 20% HBr. This reaction was first described by Manske & Marion (1947). The crystals were recrystallized from ethyl alcohol. They were found to belong to the orthorhombic disphenoidal class. They were elongated along the c axis and showed prism faces (110), sphenoids (111) and small brachypinacoids (010). The systematic extinctions determined uniquely the space group as $P2_12_12_1$, (D_2^4). The unit-cell dimensions, measured from precession photographs (Cu $K\alpha$, $\lambda = 1.5418$ Å) are:

$$a = 11.89 \pm 0.03, \quad b = 13.40 \pm 0.03, \quad c = 9.68 \pm 0.02 \text{ Å}.$$

There are four molecules per unit cell. The density measured at 23.2 °C. by flotation method using carbon tetrachloride and 1,1,1-trichloroethane mixture was found to be 1.528 g.cm.⁻³. The calculated value is 1.533 g.cm.⁻³. The number of electrons per unit cell, $F(000)$, is 736. The absorption coefficient for Cu $K\alpha$ radiation is 39.5 cm.⁻¹.

* Issued as N.R.C. No. 4896.

Intensity data

Three-dimensional data were collected from equi-inclination, multiple-film Weissenberg photographs of $hk0$, $hk7$, $0kl$, $8kl$, $h0l$ and $h1l$ levels. All reflections on films taken around the c (shortest) axis, and those of $\{h0l\}$, $\{0kl\}$ and $\{h1l\}$ zones were measured, whereas the remaining photographs were used only to supplement the data. Out of a possible 2035 reflections within the range of $\text{Cu } K\alpha$ radiation, 1761 (87%) were observed. The intensities were measured by visual comparison with a logarithmic scale intensity strip. All crystals used were cylindrical in shape with diameters varying from 0.29 to 0.35 mm.; hence absorption corrections were not applied. Since the crystals were becoming yellow in the X-ray beam, a fresh specimen was prepared for each Weissenberg exposure taken around the c axis and for $(h0l)$ and $(0kl)$ reflections. This was not done, however, for the remaining photographs as only limited data were collected from them.

No systematic corrections for variation in spot size were applied, but some intensities were roughly corrected. The intensities were corrected for Lorentz and polarization factors and correlated. Overall scale and temperature factors ($B = 4.5 \text{ \AA}^2$) were calculated by Wilson's method (1942), but when the structure was solved, the absolute scale of observed F 's was re-adjusted by direct comparison with calculated F values.

Determination of the structure

Two-dimensional methods were employed in the first attempts to solve the structure. The position of the bromine atom was determined from Patterson syntheses calculated for the three projections, and was found to be close to a special position ($x = 0.779$, $y = 0.263$, $z = 0.012$). As a result, it was not possible to determine the phases of many structure factors, and they had to be omitted from the first Fourier syntheses. The effect was particularly harmful on the $\rho(0, y, z)$ projection which offered the greatest resolution, but due to the presence of many mirror-image peaks, it was complicated by a pseudo centre of symmetry appearing at $(0, \frac{1}{2}, \frac{1}{4})$. Due to these difficulties the two-dimensional heavy-atom technique had to be abandoned. Another attempt to solve the structure was made using the generalized Patterson projection of hkl data, but due to overlapping this method also failed.

Three-dimensional data were therefore collected with the view of carrying out a Patterson synthesis and interpreting it by vector convergence method. This method was used by Robertson (1951) in interpretation of the Patterson synthesis for rubidium benzyl penicillin. The rubidium atoms were very close to $z = 0$ and $\frac{1}{2}$ and mirror planes were created at $z = 0$ and $z = \frac{1}{2}$. Robertson stated that the ambiguity resulting from the duplication of peaks would constitute a serious weakness of the method as applied

to rubidium benzyl penicillin were it not possible to overcome it, to some extent at least, by additional information from Fourier projections, based on signs derived from contributions made by rubidium and sulphur atoms. In the case of vector convergence distribution for annotinine bromohydrin, two sets of mirror planes at $y = \frac{1}{4}, \frac{3}{4}$ and $z = 0, \frac{1}{2}$ would be introduced. Fourier projections on (100) and (010) could not be used in the initial stages of interpretation because of the presence of spurious peaks and overlapping. It was possible, however, to derive a great deal of useful information from the projection along the c axis. It indicated that the molecule probably lies between $y = \frac{1}{4}$ and $y = \frac{3}{4}$ (see Fig. 3). In such a case, atoms of one molecule might not overlap with their images through the mirror planes at $y = \frac{1}{4}$ and $\frac{3}{4}$. Hence it seemed possible that the duplication of peaks only along the c axis would have to be dealt with in solving the structure.

The $|F|_{hkl}^2$ values were modified by the function

$$\left(\frac{1}{f}\right)^2 \exp\left[-\frac{4\pi^2 \sin^2 \theta}{10.4\lambda^2}\right]$$

(Lipson & Cochran, 1953). It did not seem advisable to use for this first attempt a function which vanished at the origin since Waser & Schomaker (1953) pointed out that such a function could well be most confusing in failing to reveal unresolved concentrations of peaks. The asymmetric unit of a three-dimensional Patterson synthesis was computed at intervals of $\frac{1}{60}, \frac{1}{60}$ and $\frac{1}{30}$ along the u, v , and w axes, respectively. The $F(000)^2$ term was omitted. Vector-convergence density maps were constructed by adding only positive regions of the Patterson synthesis. The resolution was rather poor; nevertheless, through correlation with two-dimensional Fourier projections ten atoms of the molecule were located. These joined in a chain through the molecule, but so far no satisfactory closed rings were obtained.

A second three-dimensional Patterson function with the intensities sharpened and modified as described by Donohue & Trueblood (1952) was then evaluated. For derivation of the vector-convergence distribution the bromine atom was assumed to lie at $(\frac{47}{60}, \frac{15}{60}, 0)$ and the summation process was thus considerably simplified. The $F(000)^2$ term was again omitted, but this time, positive as well as negative values were taken into account. Due to the presence of mirror planes at $y = \frac{1}{4}, \frac{3}{4}$ and $z = 0, \frac{1}{2}$ four peaks were obtained for each atom of the molecule. The interpretation was further complicated by a number of additional spurious peaks. The resolution was, however, considerably greater than in the first vector convergence distribution, and a six-membered ring attached to the bromine together with a four-membered ring and the hydroxyl group were readily recognized. At some distance a five-membered ring was also distinguished, but it was not possible to decide which one of its two possible

forms related by the mirror plane at $z = 0$ should be connected to the rest of the molecule.

Selection of individual atoms, or of rings of atoms, belonging to one molecule from those reflected by the mirror plane at $z = 0$ was carried out by trial-and-error. The decisions were based on simultaneous study of the overall discrepancy factor, the agreement for individual reflections and the electron-density distribution in ρ_o and $\rho_o - \rho_c$ maps for the three projections. To aid this investigation, the necessary computations were carried out on FERUT using the programmes described by Ahmed (1957). An additional short programme was prepared to calculate and store in separate storage positions the following contributions: (a) F_{c_1} from those atoms whose positions were already fixed, (b) F_{c_2} from some of those atoms whose positions were not yet fixed, assumed in certain possible locations, (c) F'_{c_2} from the same atoms as (b) but assumed in locations different from (b), and (d) $F_{c_3} = F_{c_1} + F_{c_2}$ or $F_{c_1} + F'_{c_2}$. The reliability factors for each set of F_{c_3} before and after adjustment of the scale factor were then calculated. By this procedure it was possible to investigate, without repetition of the F_{c_1} calculations, the variation in R as a result of placing the unlocated atoms in different positions.

Starting with the $\{0kl\}$ zone, eight atoms comprising a six-membered ring and two more atoms attached to it were taken as fixed. The next step was to establish the z coordinate of the bromine atom. Assuming a positive z coordinate for the bromine atom and adding it to the fixed eight atoms gave an R value lower by 0.04 than that obtained when a negative z coordinate was assumed. This result was confirmed later when more atoms of the molecule were added. Study of the R factor was continued in order to establish z coor-

dinates for the atoms of the five-membered ring, taken as a whole, and then for two additional atoms. Similar calculations were carried out for the $h0l$ data, but in this case the R values, after adding the five-membered ring, did not confirm our previous results. Hence two different $F_o - F_c$ syntheses were computed based on F 's calculated with the contribution made by fifteen carbon atoms and the bromine atom, but with different z coordinates for the five-membered ring. The synthesis with the same set of z coordinates that gave a lower R value for the $0kl$ F 's was considerably cleaner.

The position of fifteen light atoms and the bromine atom was therefore established and on the basis of their contributions ρ_o and $\rho_o - \rho_c$ projections on (100), (010) and (001) were evaluated, those reflections being omitted for which the phases were still doubtful. On close examination and simultaneous correlation of these electron-density maps it was possible to locate the remaining four atoms of the skeleton of the molecule. The position of the carbon atom of the methyl group was still doubtful, as two possible locations were indicated. Although one of these could be accepted on chemical grounds (Martin-Smith, Greenhalgh & Marion, 1957), no assumptions were made and only nineteen atoms, still treated as carbon atoms, and the bromine atom were used for subsequent structure-factor calculations and electron-density projections. There was a marked improvement in the agreement between the F_o and F_c values and on the basis of new projections the methyl group could be unambiguously located. Chemical evidence was then used to distinguish the oxygen and nitrogen atoms from carbon atoms (Meier, Meister & Marion, 1954; Wiesner, Valenta, Ayer & Bankiewicz, 1956). Their

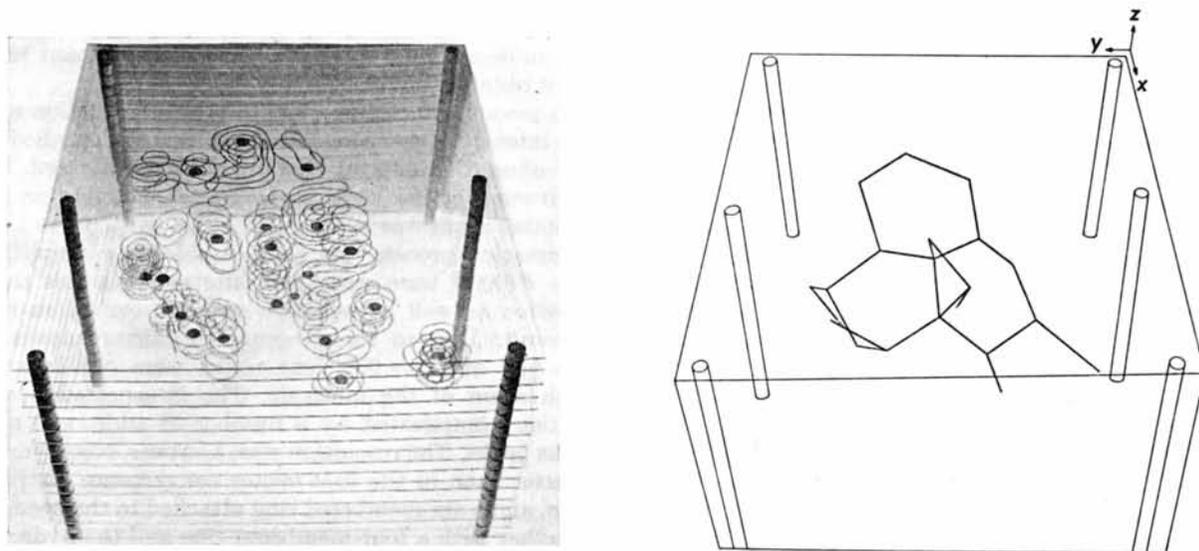


Fig. 1. A perspex model of vector convergence distribution of annotinine bromohydrin. Peaks of only two molecules, related by a mirror plane at $z = 0$ are shown and the atoms of one of them are marked by large dots. The contours of the bromine atom are drawn with thicker lines at greater arbitrary intervals.

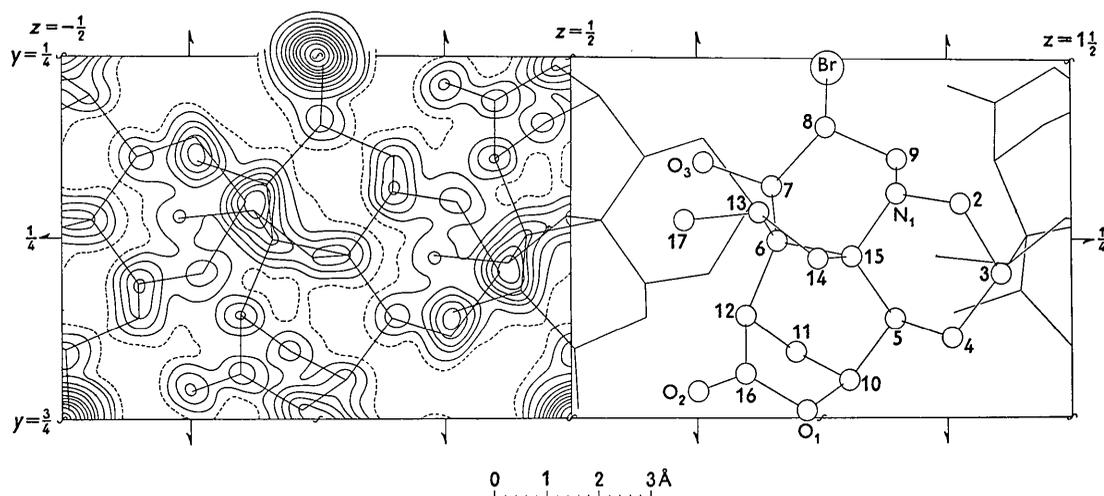


Fig. 2. The structure of annotinine bromohydrin viewed up the a axis. Light atom contours are drawn at intervals of $2 \text{ e.}\text{\AA}^{-2}$, starting with a broken line at $3 \text{ e.}\text{\AA}^{-2}$. The bromine atom contours above $7 \text{ e.}\text{\AA}^{-2}$ are at $7 \text{ e.}\text{\AA}^{-2}$.

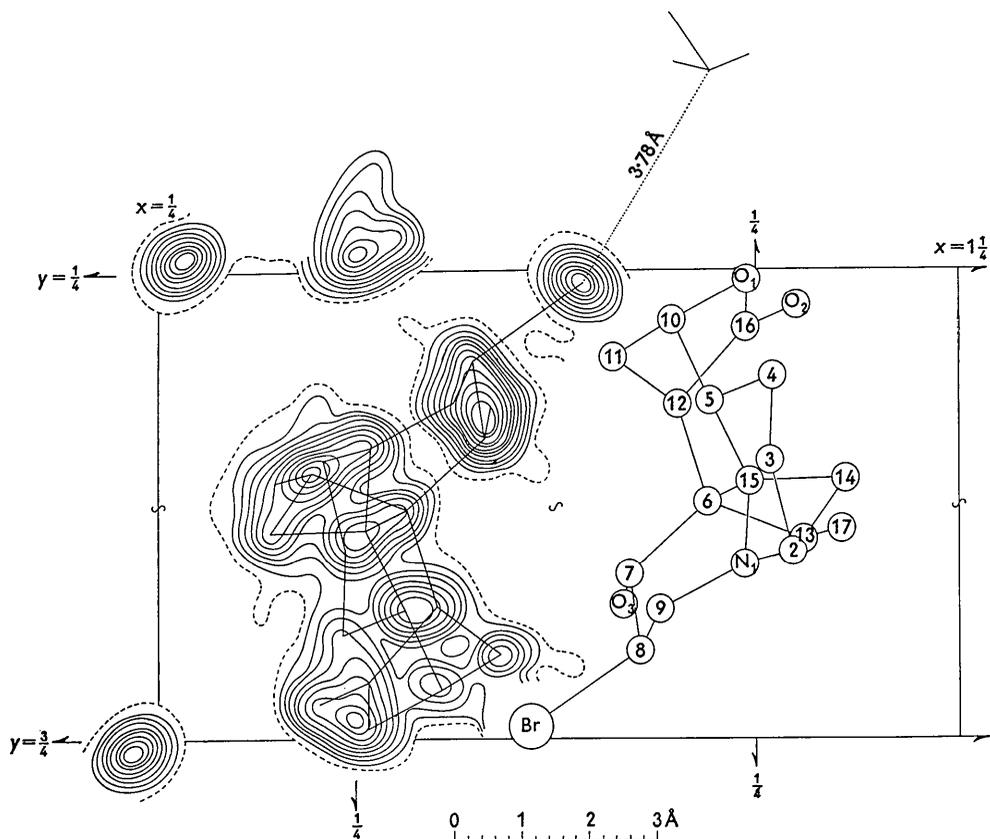


Fig. 3. A projection of the structure along the c axis. Contour interval is $1 \text{ e.}\text{\AA}^{-2}$, except for the bromine atom, which is drawn at intervals of $5 \text{ e.}\text{\AA}^{-2}$, starting at $10 \text{ e.}\text{\AA}^{-2}$. The first broken line is at $3 \text{ e.}\text{\AA}^{-2}$. The dotted line shows van der Waals contact between Br and C_{13} .

positions were confirmed by the difference maps, and by a decrease in the discrepancy factors of the three projections.

The three-dimensional vector-convergence distribution was re-examined and found in good agreement

with the results obtained. Its photograph, given in Fig. 1, shows only two molecules related by the mirror plane at $z = 0$. The atoms of one of these are marked by large circles. The O_1 atom lies very close to two mirror planes at $z = 0$ and $y = \frac{3}{4}$, hence a heavy peak

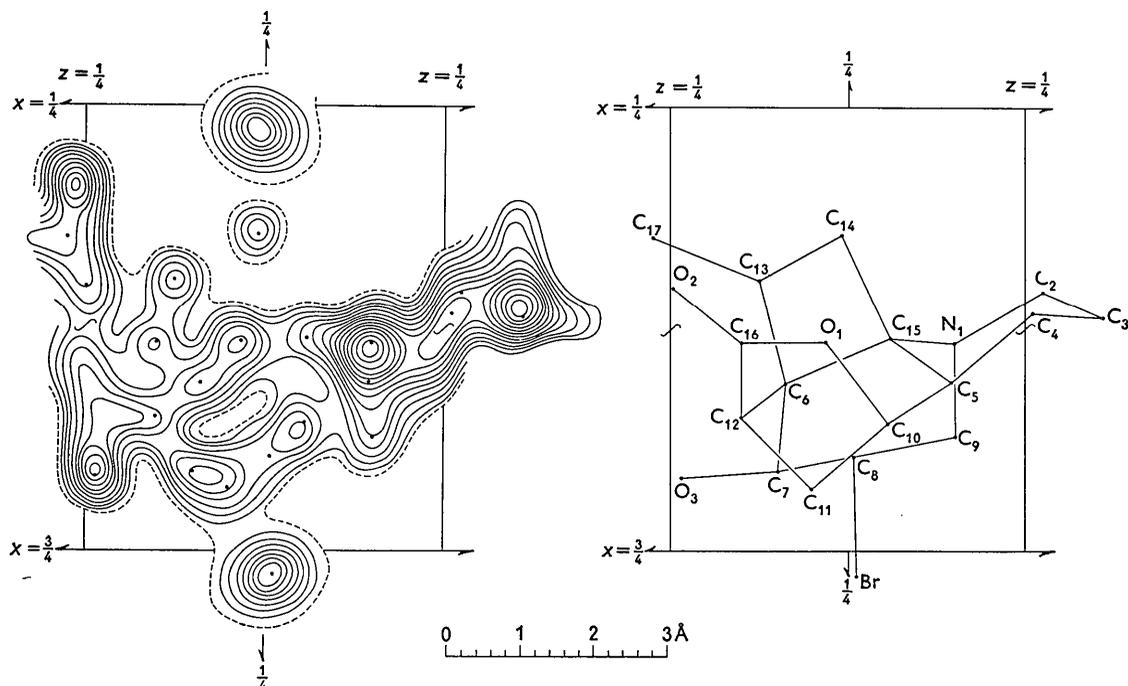


Fig. 4. An asymmetric unit projected on (010), with atoms of only one molecule marked. The outline of that molecule is also shown. Each contour for light atoms represents a density increment of $1 \text{ e} \cdot \text{Å}^{-2}$ and for the bromine atom of $5 \text{ e} \cdot \text{Å}^{-2}$. The first broken contour is at $5 \text{ e} \cdot \text{Å}^{-2}$.

is obtained due to overlapping with neighbouring images. It should be added that, as expected, the mirror plane at $y = \frac{3}{4}$ did not pass through the molecule and thus did not cause its overlapping with image peaks through that plane. This was a very important factor contributing to the successful interpretation of the vector-convergence distribution.

Two more refinement stages brought the R factor to about 0.21 for F_{0kl} , F_{h0l} , and F_{hk0} data.

Only one cycle of refinement of the atomic coordinates was carried out using the observed three-dimensional data. The structure factors and their phases were calculated showing a reliability factor of 0.21. An observed differential synthesis was then computed, and the shifts applied directly to the assumed atomic coordinates. The average shifts were 0.024, 0.019, and 0.017 Å, in the x , y , and z directions, respectively, and the corresponding maximum shifts were 0.048, 0.070, and 0.051 Å. No corrections for finite summation errors were carried out. This cycle gave much better agreement between the observed and theoretical values for the bond lengths, but did not show any marked improvement in the overall R factors for $0kl$, $h0l$ and $hk0$ structure factors.

McWeeny's f -curves (1951) were employed for the C, N, O atoms, and that of Thomas & Umeda (1957) was used for the bromine atom. Throughout the work the temperature factor for all atoms was taken as 4.5 Å^2 . The $F_o - F_c$ syntheses indicated, however, a higher B value for the bromine atom and a slightly lower one for the light atoms. The structure factors

for the three projections were therefore recalculated using different B factors. The lowest reliability factors were obtained with $B = 4.0 \text{ Å}^2$ for the C, N, O atoms and $B = 6.0 \text{ Å}^2$ for the bromine atom. All difference maps showed high positive and negative peaks due to the anisotropic vibration of the bromine atom, but no allowance was made for this motion in the structure-factor calculations. The final values of R , taking into account unobserved reflections, are 0.17, 0.18 and 0.20 for $h0l$, $0kl$ and $hk0$ spectra, respectively. The three Fourier projections of the structure of annotinine

Table 1. Fractional atomic coordinates

Atom	x	y	z
N ₁	0.517	0.437	0.149
C ₂	0.457	0.451	0.275
C ₃	0.486	0.548	0.360
C ₄	0.482	0.639	0.262
C ₅	0.560	0.611	0.146
C ₆	0.562	0.504	-0.089
C ₇	0.660	0.428	-0.100
C ₈	0.645	0.345	0.007
C ₉	0.621	0.389	0.151
C ₁₀	0.607	0.697	0.056
C ₁₁	0.680	0.658	-0.052
C ₁₂	0.601	0.607	-0.152
C ₁₃	0.444	0.464	-0.126
C ₁₄	0.393	0.528	-0.009
C ₁₅	0.510	0.525	0.059
C ₁₆	0.515	0.688	-0.152
C ₁₇	0.397	0.475	-0.274
O ₁	0.515	0.739	-0.032
O ₂	0.453	0.713	-0.249
O ₃	0.667	0.395	-0.237
Br	0.7791	0.2628	0.0121

proceeds *trans*, with inversion at the carbon carrying the chlorine atom.

The closest intermolecular contacts are made by the molecules shown in Fig. 3. The distances between O₃ of one molecule and C₅, C₁₀ and C₁₁ of the other are 3.44, 3.58 and 3.62 Å respectively. They can be regarded as normal, if we assume that the hydrogen atom of the hydroxyl group is not directed towards these atoms. Of C···C distances, only five are somewhat lower than 4.0 Å and they range from 3.68 to 3.87 Å. The shortest Br···C approach, shown in Fig. 3, is 3.78 Å. All other intermolecular distances are equal to or longer than the sum of the corresponding van der Waals radii.

We wish to express our sincere gratitude to Dr Léo Marion for suggesting this problem for a detailed X-ray study, for his unflinching support and helpful discussions. An acknowledgment is made with thanks to Dr W. H. Barnes for his continued interest in this investigation, to Mr C. N. Hellyer for calculating some of the structure factors with I.B.M. equipment, and to the staff of the Computation Centre, University of Toronto, for making the computer available to us. We also wish to thank Miss W. Paisley and Miss C. Saunderson for their help in computing and plotting some of the electron-density maps.

References

- AHMED, F. R. (1957). *Acta Cryst.* **10**, 747.
 ANET, F. A. L. & MARION, L. (1954). *Chem. Ind.* p. 1232.
 CRUICKSHANK, D. W. J. (1949). *Acta Cryst.* **2**, 65.
 CRUICKSHANK, D. W. J. & ROBERTSON, A. P. (1953). *Acta Cryst.* **6**, 698.
 DONOHUE, J. & TRUEBLOOD, K. N. (1952). *Acta Cryst.* **5**, 414.
 KNOP, O. & MACLEAN, D. B. (1952). *Canad. J. Chem.* **30**, 598.
 LIPSON, H. & COCHRAN, W. (1953). *The Determination of Crystal Structures*. London: Bell.
 MACLEAN, D. B. & PRIME, H. C. (1953). *Canad. J. Chem.* **31**, 543.
 MANSKE, R. H. F. & MARION, L. (1943). *Canad. J. Research*, **B**, **21**, 92.
 MANSKE, R. H. F. & MARION, L. (1947). *J. Amer. Chem. Soc.* **69**, 2126.
 MARTIN-SMITH, M., GREENHALGH, R. & MARION, L. (1957). *Canad. J. Chem.* **35**, 409.
 MCWEENY, R. (1951). *Acta Cryst.* **4**, 513.
 MEIER, H. L., MEISTER, P. D. & MARION, L. (1954). *Canad. J. Chem.* **32**, 268.
 PRZYBYLSKA, M. & MARION, L. (1957). *Canad. J. Chem.* **35**, 1075.
 ROBERTSON, J. H. (1951). *Acta Cryst.* **4**, 63.
 THOMAS, L. H. & UMEDA, K. (1957). *J. Chem. Phys.* **26**, 293.
 WASER, J. & SCHOMAKER, V. (1953). *Rev. Mod. Phys.* **25**, 671.
 WIESNER, K., AYER, W. A., FOWLER, L. R. & VALENTA, Z. (1957). *Chem. Ind.*, 564.
 WIESNER, K., VALENTA, Z., AYER, W. A. & BANKIEWICZ, C. (1956). *Chem. Ind.*, 1019.
 WIESNER, K., VALENTA, Z. & BANKIEWICZ, C. (1956). *Chem. Ind.* **R**, 41.
 WILSON, A. J. C. (1942). *Nature, Lond.* **150**, 152.

Acta Cryst. (1958). **11**, 724

The Crystal Structure and Absolute Configuration of the Monoclinic Form of *d*-Methadone Hydrobromide

BY A. W. HANSON AND F. R. AHMED

Division of Pure Physics, National Research Council, Ottawa, Canada

(Received 24 March 1958)

The crystal is monoclinic, probably $P2_1$, $a = 10.69$, $b = 8.74$, $c = 10.74$ Å, $\beta = 94.6^\circ$, $Z = 2$. The structure determination, which was essentially three-dimensional, was begun by the heavy-atom method, and completed by means of differential syntheses. The absolute configuration of the molecule was determined by measuring the effect on two selected sets of reflexions of the imaginary part of the dispersion of copper radiation by the bromine atom.

Introduction

Methadone (Amidone, Dolophine, etc.) is a synthetic narcotic (Small, 1948; Attenburrow, Elks, Hems & Speyer, 1949; Baizer, 1953). It occurs in dextro- and laevo-rotatory isomers, the latter having by far the stronger analgesic properties. The structure determination was undertaken in order to assist investigations into the physiological properties of this compound by

