X-RAY CRYSTAL ANALYSIS OF SOME NATURAL PRODUCTS.

THESIS

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BY

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PREFACE.

This thesis describes research work carried out in the years 1959 - 1962 in the Chemistry Department of the University of Glasgow.

I wish to express my gratitude to my supervisor, Professor J.M. Robertson, for suggesting the topics of research, and for his guidance and constant encouragement. I would also like to thank Dr. G.A. Sim and Dr. T.A. Hamor for helpful advice on many points during this work.

I am indebted to Dr. D.C. Gilles, and the staff of the Computing Laboratory of Glasgow University for facilities on the English Electric DEUCE computer, and to Dr.J.S. Rollett, Dr. J.G. Sime and others, who devised the programmes for the extensive numerical calculations described in this thesis.

In conclusion I acknowledge the award of a Maintenance Grant from the Department of Scientific and Industrial Research.

SUMMARY.

The main part of the work described in this thesis is concerned with the determination of the structure of the alkaloid echitamine by an X-ray analysis of the methanol solvate of echitamine bromide.

Two additional sections deal with the structure determination of acetylbromogeigerin (a reduced azulene system), and of cedrelone iodoacetate (a triterpenoid). The work on the former was shared with Mr. A.T. McPhail and on the latter with Mr. I.J. Grant. As far as possible alternate structure factor calculations and Fourier syntheses were carried out by each partner. A fourth section describes the analysis of a "supposed oxepin".

In all of these structure determinations the heavy atom technique was used to overcome the phase problem. This consists of deriving approximate phases for the structure from the heavy atom and using them to calculate the electron density distribution. The method essentially converts the unmeasurable phase relationships into certain intensity relationships which can be measured directly. This technique is excellent for structure analysis of the type described in this thesis but is less suitable for the study of structural features of small molecules where accurate atomic positions are required.

In the appendix various alternative methods of structure determination are described which were used in attempts

to solve the structure of two hydrocarbons, dianthracene and circumanthracene. A note is also included on echitamine hydrobromide dihydrate for which considerable three-dimensional data were collected and preliminary investigations carried out.

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PART I.

SOME METHODS OF CRYSTAL STRUCTURE ANALYSIS.

1.1. INTRODUCTION.

Von Laue's discovery in 1912 of the diffraction of X-rays by crystals provided crystallographers with a powerful new tool. It became possible for them to investigate the structure of matter on the atomic scale and to determine the arrangement of atoms within molecules and crystals.

At first X-ray analyses of compounds were undertaken only when some knowledge of the atomic arrangement was available, but it has now become possible to determine structures in cases where the traditional methods of the organic chemist have failed. The recent increase in the availability of electronic computers has resulted in a vital speeding-up of hitherto lengthy and tedious calculations and further extended the choice of structures suitable for study by X-ray crystallography. This technique is now in a position to challenge strongly the method of structure determination by the degradative processes of organic chemistry.

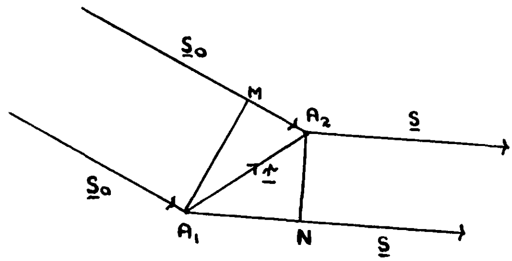
2. THE STRUCTURE FACTOR AND CALCULATION OF ELECTRON DENSITY.

2.1. DIFFRACTION FROM A CRYSTAL.

A crystal lattice is composed of groups of atoms repeated at regular intervals, with the same orientation, in three dimensions. If it is assumed that each lattice point is the site of an electron then the positions of these electrons can be defined by the ends of a vector $\underline{r}$ such that

$$\underline{r} = u\underline{a} + v\underline{b} + w\underline{c}$$

where $\underline{a},\underline{b},\underline{c}$ are primitive translations of the lattice, and u,v,w are integers. On irradiation by an X-ray beam these electrons vibrate and act as sources of secondary radiation.



Lipson and Cochran, 1952.

In the above diagram a parallel X-ray beam, of wave length λ and direction specified by $\underline{S}_o$ (modulus $\frac{1}{\lambda}$), falls on lattice points A_1 and A_2 separated by a vector distance $\underline{r}$. The direction of the diffracted rays is given by the vector $\underline{S}$ (modulus $\frac{1}{\lambda}$). Under these conditions the path difference between the scattered waves is

$$A_1N - A_2M = \lambda(\underline{r}.\underline{S} - \underline{r}.\underline{S}_o)$$

$$= \lambda\underline{r}.\underline{\mathcal{S}} \qquad \text{where } \underline{\mathcal{S}} = \underline{S} - \underline{S}_o$$

To ensure that the waves scattered by A_1 and A_2 are in phase, this path difference must be a whole number of wave lengths $\underline{i}.\underline{e}.$ $\underline{r}.\underline{\mathcal{S}}$ must be an integer. Hence $(u\underline{a} + v\underline{b} + w\underline{c}).\underline{\mathcal{S}}$ must be integral and since u,v,w change by integral values each of the above products separately must be integral.

$\underline{i}.\underline{e}.$

$$\underline{a}.\underline{\mathcal{S}} = h$$

$$\underline{b}.\underline{\mathcal{S}} = k \qquad \ldots\ldots. (1)$$

$$\underline{c}.\underline{\mathcal{S}} = \ell$$

where h, k, ℓ are integers. These equations (1) are known as the Laue equations.

These Laue equations, however, are unsuitable for direct application to diffraction problems. W.L. Bragg, (1913), showed their physical significance by relating the integers h, k, ℓ, to the Miller indices of the lattice planes. The relationship between Bragg's law and the Laue equations is shown as follows

$$\underline{a}/h . \underline{S} = 1$$

$$\underline{b}/k . \underline{S} = 1 \qquad \text{Laue equations}$$

$$\underline{c}/\ell . \underline{S} = 1$$

Subtraction of the first two equations gives

$$(\underline{a}/h - \underline{b}/k).\underline{S} = 0.$$

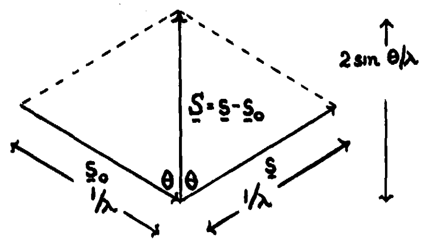
which means that the vector $\underline{S}$ is perpendicular to $(\underline{a}/h - \underline{b}/k)$. It can be shown that the latter is the plane of Miller indices h, k, ℓ. Similarly $\underline{S}$ is perpendicular to $(^a/_h - {}^c/_\ell)$. Thus $\underline{S}$ is perpendicular to the plane h, k, ℓ. But $\underline{S}$ is a vector in the direction of the bisector of the incident and diffracted rays, since the moduli of $\underline{S}$ and $\underline{S}_o$ are equal, and thus the bisector is identified with the normal to the plane h, k, ℓ. This argument justifies the concept of each diffraction as a reflection of the rays from the lattice planes.

If d is the spacing of the planes $hk\ell$ then d is the projection of $\underline{a}/h$, $\underline{b}/k$, $\underline{c}/\ell$ on the vector $\underset{\sim}{S}$

$$\text{i.e.} \quad d = \frac{\underline{a}/h \cdot \underset{\sim}{S}}{|S|}$$

$$\text{But } \underline{a}/h . \underset{\sim}{S} = 1 \text{ from the Laue equations}$$

$$\text{and } |S| = \frac{2 \sin\theta}{\lambda} \quad \text{from (I)}$$



Lipson and Cochran, 1953.

(I)

$$\therefore d = \frac{\lambda}{2 \sin\theta}$$

$$\therefore \lambda = 2d \sin\theta$$

This is Bragg's law which with the Laue equations is used to interpret X-ray spectra and determine the structure of crystals.

2.2. THE ATOMIC SCATTERING FACTOR.

In 2.1. it was implied that the scattering unit in the atom is the electron. Since these electrons are assumed to be loosely held in the atom any change of phase on scattering is the same for all of them and so the amplitude scattered in the forward direction is Z times that due to a single electron, where Z is the atomic number.

On the other hand, in a direction making a finite angle with the direction of incident radiation, there will be path differences between waves scattered from electrons in different parts of the atom. These waves will interfere and produce a resultant amplitude less than Z times that due to a single electron. The phase difference will depend on the angle of scattering, the wave length, and the volume throughout which the electrons are distributed. The scattering factor f will thus approach Z for small angles of scattering and will fall away with increasing angle at a rate that, for a given wave length, is determined by the distribution of electrons within the atom. Atomic scattering factors have been calculated by James and Brindley, (1932), Thomas, (1927), Fermi, (1928), McWeeny, (1951), Berghuis *et al.* (1955), Tomiie and Stam, (1958), and others.

2.3 TEMPERATURE FACTOR.

In these theoretical scattering factors the atoms are assumed to be at rest, but thermal movements have an important effect in all practical cases. At all temperatures, including absolute zero, atoms have a finite amplitude of oscillation. The frequency of this oscillation is so much smaller than the frequency of the X-rays that to a train of X-ray waves the atoms would appear stationary but displaced from their true positions in the lattice. The general result is to spread the electron distribution and so decrease the intensities of the spectra.

If X-rays are incident at an angle θ and the thermal displacement of an atom, normal to the reflection plane, is u then the path difference compared to that of an atom at rest is $2\,u \sin\theta$ and the phase change is

$$\frac{2\pi}{\lambda} \cdot 2\,u \sin\theta \quad = \quad 4\pi u\left(\frac{\sin\theta}{\lambda}\right).$$

If the scattering factor of the undisplaced atom is f_o then the effect of thermal motion may be calculated as

$$f \quad = \quad f_o \sum e^{4\pi i\, u_j \left(\frac{\sin\theta}{\lambda}\right)}$$

summed over the displacements u_j.

If these displacements are assumed to be isotropic and hence centrosymmetric the sine terms disappear and the above expression can be written

$$f \quad = \quad f_o \cos\left[4\pi\bar{u}\left(\frac{\sin\theta}{\lambda}\right)\right]$$

$$\text{But} \quad \cos x \quad = \quad 1 - \frac{x^2}{2!} + \frac{x^4}{4!} - \ldots\ldots\ldots\ldots$$

$$\exp.(-\tfrac{1}{2}x^2) \quad = \quad 1 - \frac{x^2}{2} + \frac{x^4}{4.2!} - \ldots\ldots\ldots\ldots$$

Thus to a good approximation

$$\cos x \quad = \quad \exp.(-\tfrac{1}{2}x^2)$$

and hence

$$f \quad = \quad f_o\, e^{-8\pi^2 \bar{u}^2 \left(\frac{\sin^2\theta}{\lambda^2}\right)}$$

or

or $$f = f_o e^{-B\left(\frac{\sin^2\theta}{\lambda^2}\right)}$$

where $B = 8\pi^2\overline{u}^2$ and $\overline{u}^2$ is the mean square displacement of the atom at right angles to the reflecting plane.

The factor B which is called the Debye temperature factor (Debye, 1914), can be treated as an empirical constant derivable from measurements of the intensities of X-ray reflections from a crystal.

In many organic crystals the molecules behave like rigid bodies. They are linked in the crystal by relatively weak Van der Waals attraction and perform oscillations which are large compared with the movements of atoms within the molecule against the much stronger covalent bonds. An anisotropic temperature factor is therefore required and this problem has been discussed by Cruickshank, (1956, a,b).

In general the thermal displacements are now different in different directions and require the assumption of an elliptical distribution instead of a sperical distribution. The mean displacement is now represented by a vector function or tensor instead of a simple vector normal to the reflecting plane. This can be a symmetrical tensor with six independent coefficients

$$U^r \text{ sym.} = \begin{vmatrix} U_{11} & U_{12} & U_{13} \\ U_{12} & U_{22} & U_{23} \\ U_{13} & U_{23} & U_{33} \end{vmatrix}$$

Each atom in the structure requires one such tensor U^r. The mean square displacement or amplitude of vibration $\overline{u}^2$ in a direction ℓ (components $\ell_1 \ell_2 \ell_3$ along x y z) is then

$$\overline{u}^2 = \sum_{i=1}^{3}\sum_{j=1}^{3} U_{ij}^{r} \ell_i \ell_j$$

$$= U_{11}\ell_1^2 + U_{22}\ell_2^2 + U_{33}\ell_3^2 + 2U_{12}\ell_1\ell_2 + 2U_{13}\ell_1\ell_3 + 2U_{23}\ell_2\ell_3$$

The temperature factor $e^{-8\pi^2\overline{u}^2\left(\frac{\sin^2\theta}{\lambda^2}\right)}$ now becomes

$$e^{-8\pi^2\left(\sum_{i=1}^{3}\sum_{j=1}^{3} U_{ij}\ell_i\ell_j\right)\frac{\sin^2\theta}{\lambda^2}}$$

for the anistropic case.

This may be written in the form

$$T(hk\ell) = \exp -\left[b_{11}h^2 + b_{22}k^2 + b_{33}\ell^2 + b_{12}hk + b_{13}h\ell + b_{23}k\ell\right]$$

where for example

$$b_{11} = 2\pi^2 a^{*2} U_{11}$$

$$b_{12} = 4\pi^2 a^* b^* U_{12}$$

a^* and b^* being reciprocal axes.

In modern refinement procedures, convenient numerical methods have been developed for evaluating the six thermal parameters for each atom in addition to the three positional ones. The lengthy calculations for complex molecules require the use of electronic computers.

In practice the atoms in a molecule do not vibrate independently. The thermal effects in some cases may be described in terms of rigid body motions of the molecule as a unit. These motions may be resolved into vibrational and rotational components T and ω given with respect to the centre of mass (Cruickshank, 1956 c).

2.4 DEFINITION OF THE STRUCTURE FACTOR.

In a crystal atoms are distributed between the successive crystal planes thus producing a modification of the amplitude of the scattered wave.

If there are N atoms in the unit cell of a crystal, situated at points $x_n y_n z_n$ (the coordinates being fractions of the unit cell parameters and measured with respect to the crystallographic axes) then the position of the n^{th} atom in the unit cell can be represented by a vector $\underline{r}_n$ where

$$\underline{r}_n = x_n \underline{a} + y_n \underline{b} + z_n \underline{c}$$

The path difference between the waves scattered by these atoms and those that would be scattered by a set of atoms at the points of the lattice which define the unit cell is $\lambda \underline{r}_n \cdot \underline{S}$

Thus the expression for the complete wave scattered by the n^{th} unit cell contains a term

$$f_n \exp.\left(\frac{2\pi i}{\lambda} . \lambda \underline{r}_n . \underline{S}\right)$$

$$\text{or} \quad f_n \exp.(2\pi i \ \underline{r}_n . \ \underline{S})$$

where f_n is the atomic scattering factor of the n^{th} atom. Hence a term

$$F = \sum_{n=1}^{N} f_n \ \exp \ (2\pi i \ \underline{r}_n \ . \ \underline{S})$$

will occur in the expression for the complete wave scattered by a crystal. This can be written as

$$F = \sum_{n=1}^{N} f_n \ \exp. \ 2\pi i \ (x_n \underline{a}. \underline{S} + y_n \underline{b}. \underline{S} + z_n \underline{c}. \underline{S})$$

$$= \sum_{n=1}^{N} f_n \ \exp. \ 2\pi i \ (hx_n + ky_n + \ell z_n)$$

This quantity F is called the structure factor. It depends on the arrangement of matter in each individual crystal. It is a complex resultant which can be characterised by an amplitude $|F|$ and a phase constant α.

$$|F(hk\ell)| = \sqrt{A^2 + B^2}$$

$$\alpha(hk\ell) = \tan^{-1} \frac{B}{A}$$

where
$$A = \sum_{n=1}^{N} f_n \cos 2\pi (hx_n + ky_n + \ell z_n)$$

$$B = \sum_{n=1}^{N} f_n \sin 2\pi (hx_n + ky_n + \ell z_n)$$

If the space group is known these summations can be carried out over the coordinates of the equivalent positions and this results in a simplified expression. In particular if a centre of symmetry is present and is chosen as the origin for the coordinates, the structure factor can be obtained by summing over the cosine terms alone and the possible phase angles are thus limited to 0 or π .

A more generalised form of the structure factor expression can be obtained as follows. If $\rho(xyz)$ is the electron density at the point (xyz), the amount of scattering matter in the volume element dxdydz is ρdxdydz and the structure factor equation is

$$F(hk\ell) = \int_{x=0}^{1}\int_{y=0}^{1}\int_{z=0}^{1} V\rho(xyz)\exp 2\pi i\,(hx + ky + \ell z)\,dxdydz \quad \ldots\ldots\ldots(2)$$

2.5 THE EXPRESSION OF ELECTRON DENSITY BY FOURIER SERIES.

Since a crystal is periodic in three dimensions its electron density $\rho(xyz)$ at the point (xyz) can be represented by a three-dimensional Fourier series.

$$\rho(xyz) = \sum\sum_{-\infty}^{\infty}\sum A(pqr)\, e^{2\pi i(px + qy + rz)}$$

where p,q,r are integers and A(pqr) is the unknown coefficient of the general term. This coefficient can be evaluated by substituting the value of the electron density in expression (2) above

$$F(hk\ell) = \int_0^1\int_0^1\int_0^1 \sum\sum_{-\infty}^{\infty}\sum VA(pqr)\exp 2\pi i(px + qy + rz)$$
$$\exp 2\pi i(hx + ky + \ell z)dxdydz$$

Since the exponential functionsare periodic the integral of their product is zero in general over a single complete period. It is only non-zero if $h = -p$, $k = -q$, $\ell = -r$.

This gives

$$F(hk\ell) = \int_0^1\int_0^1\int_0^1 VA(pqr)dxdydz$$

Thus

$$F(hk\ell) = A(pqr)V$$

The electron-density distribution at every point in a crystal can be represented by the Fourier series

$$\rho(xyz) = \frac{1}{V}\sum\sum_{-\infty}^{\infty}\sum F(hk\ell)\exp\left[-2\pi i\ (hx + ky + \ell z)\right]$$

It is convenient to write this series in the form

$$\rho(xyz) = \frac{1}{V}\sum\sum_{-\infty}^{\infty}\sum|F(hk\ell)|\cos\left[2\pi hx + 2\pi ky + 2\pi\ell z - \alpha(hk\ell)\right].$$

where $\alpha(hk\ell)$ represents the phase constant associated with the amplitude $|F(hk\ell)|$. The constant term in the series F(ooo) is defined by $F(ooo) = V\int_0^1\int_0^1\int_0^1 \rho(xyz)dxdydz = Z.$

From the observed intensities of the diffracted spectra $|F(hk\ell)|$ can be calculated but no information can be obtained concerning the relative values of the phase constants. This limitation prevents any immediate or direct application of the series to the solution of crystal structures except in special cases.

2.6. FOURIER TRANSFORMS.

The transform of a set of points related to the origin by a set of vectors $\underline{r}_n$ is a continuous function whose value is given by

$$G(s) = \sum_{n=1}^{N} f_n \exp 2\pi i \, \underline{r}_n \cdot \underline{s}$$

where $\underline{s}$ is a vector in reciprocal space, and f_n is the weighting factor of each point. If the set of points have a centre of symmetry the equation may be reduced to

$$G(s) = 2 \sum_{n=1}^{\frac{N}{2}} f_n \cos 2\pi (hx + ky + lz)$$

where x, y, z are related to arbitrary axes and h, k, ℓ, may have any value. If the set of points do not have a centre of symmetry the transform is complex and the real and imaginary parts must be computed separately.

The placing of several units in a three-dimensional array causes the Fourier transform to be observed only at the intersections of three sets of planes corresponding to the three Laue conditions. These intersections form the reciprocal lattice. Therefore the reciprocal lattice with weights attached to each point proportional to the structure factor, is a complete representation of the diffraction pattern of the crystal.

For the purposes of crystal structure determination the Fourier transform of several unit cells is derived optically by means of the optical diffractometer and compared with the weighted reciprocal lattice. Many trial structures can therefore be tested quickly and the more promising ones used to calculate structure factors in the normal manner.

3. THE PHASE PROBLEM AND METHODS OF SOLUTION.

3.1 TRIAL AND ERROR METHODS

It has been shown in the preceeding discussion that the course of a crystal structure determination cannot in general be direct, because, in the process of recording the diffraction pattern, knowledge of the phases of the various diffracted beams is lost. The first indirect methods used to overcome this problem are known as trial and error methods. These consist in general of postulating a possible structure, calculating structure factors and comparing these with the measured amplitudes. Trial and error methods vary from one crystal to another and use must be made of any evidence concerning the atomic positions which can be obtained from the physical and chemical properties of the compound or from the X-ray reflections themselves.

The method of Fourier transforms has already been mentioned. The contents of several unit cells are punched on a mask which is placed in an optical diffractometer. The Fraunhofer diffraction pattern is then effectively the Fourier transform. This method was applied to the structure determination of dianthracene (Appendix II). It is useful in distinguishing between a possible structure and an incorrect one but provides little information which could be applied to an incorrect structure to bring it nearer the true one.

3.2 THE F^2 SERIES OF PATTERSON

A.L. Patterson in 1934 developed a new approach to the phase problem of crystal analysis. Attempts are no longer made to determine the unknown phases but instead use is made of the information available viz:- the structure amplitudes which are directly related to the intensities and can thus be measured. He used the squares of the moduli as Fourier coefficients to give a vector representation of the crystal structure. The Patterson function is defined as

$$P(uvw) = V\int_0^1\int_0^1\int_0^1 \rho(xyz)\,\rho(x+u,\ y+v,\ z+w)\,dxdydz$$

For the purposes of computing this is expressed as

$$P(uvw) = \frac{1}{V}\sum_h\sum_k\sum_{\ell=-\infty}^{\infty}|F(hk\ell)|^2 \exp 2\pi i\ (hu+kv+\ell w)$$

P(uvw) can clearly only have large values when both $\rho(xyz)$ and $\rho(x+u,\ y+v,\ z+w)$ are large. This occurs if there are atoms at (xyz) and (x+u, y+v, z+w) separated by a vector distance u, v, w. This method therefore can give direct evidence about relationships between atomic positions with no preliminary assumptions.

In practice the difficulties of solving any but the simplest structure by this method are formidable. For a system of N atoms there will be $\frac{N(N-1)}{2}$ distinct peaks in the vector distribution. These will tend to overlap and the Patterson peaks will therefore tend to be broad and ill-defined.

3.3 HEAVY ATOM TECHNIQUES.

In the case of a structure containing one or more relatively heavy atoms, the peaks corresponding to interatomic vectors between these atoms are prominent in the Patterson synthesis and the latter can lead directly to the crystal structure. The coordinates of the heavy atom determined from the Patterson map are used to calculate approximate phase constants and application of the Fourier method will then give a direct representation of the structure. Certain ambiguities may persist depending on the crystallographic situation of the heavy atom.

Although this method of approach leads to a correct solution of the structure, since the atomic positions of the light atoms are determined from only a small part of the structure amplitude precision data are required to ensure that their accuracy is equal to that in a structure consisting of all light atoms. This is complicated by the fact that the presence of the heavy atom means a higher absorption coefficient and makes the initial measurements of intensities more difficult.

This difficulty is minimised in the method of isomorphous replacement. This approach is applicable if it is possible to substitute successively two different heavy atoms in a molecule so that the resulting crystal structures are isomorphous. Use is then made of the changes in structure amplitude which occur when one heavy atom is replaced by the other. The replaceable atom requires a smaller proportion of the electron content than is required for the heavy-atom method. Both of the methods described above were first applied to the structure analysis of heavy-atom derivatives of the phthalocyanines (Robertson and Woodward, 1937,).

The expression for the structure factor in the case of a crystal with one heavy atom in the unit cell is

$$F(hk\ell) = f_H \exp\left[2\pi i\,(hx_H + ky_H + \ell z_H)\right] + \sum_{j=1}^{n} f_j \exp\left[2\pi i\,(hx_j + ky_j + \ell z_j)\right]$$

where f_H is the scattering factor of the heavy atom whose parameters are $x_H y_H z_H$ and n is the number of light atoms.

4. METHODS OF STRUCTURE REFINEMENT.

4.1 DIFFERENCE FOURIER SERIES.

The discussion up to this point has concerned methods of determining the atomic coordinates. These initial coordinates however are seldom sufficiently accurate to give the correct phase angle associated with each structure amplitude. The process of refinement i.e. successive calculation of electron density and structure factors is carried out using the normal F_o synthesis.

A more efficient method is based on the calculation of a Fourier series where the residuals $(F_o - F_c)$ are used as Fourier coefficients. This has been discussed by Booth,(1948 b), and Cochran, (1951).

If the calculated coordinates $(x_c\ y_c\ z_c)$ are plotted on the difference map, the directions of steepest ascent at these points give the directions of the shifts. The magnitude of the shift can be calculated from the relation

$$\epsilon = r = \frac{\frac{d(\rho_o - \rho_c)}{dr}}{2\rho_o(o)\,p} \quad \text{where } \rho_o \text{ is approximately } Z\left(\tfrac{p}{\pi}\right)^{\frac{3}{2}}.$$

ϵ is the magnitude of the shift

$\rho_o\ \rho_c$ are the observed and calculated electron densities

$\rho_o(o)$ is theelectron density at the atomic centre

p has an average value of 5.0.

This results from the following argument. Near the centre of an atom the electron density at a distance r from the centre is given closely by

$$\rho(r) = \rho_o\, e^{-pr^2}$$

where $\rho(o)$ is the maximum density. For very small values of x

$e^x \sim 1 + x$ so that for small values of r

$e^{-pr^2} \sim 1 - pr^2$

A good approximation therefore if r is small is

$$\rho(r) \sim \rho(o)(1 - pr^2)$$

Now the gradient of $\rho_o - \rho_c$ is the gradient of ρ_o less the gradient of ρ_c. At the peak of ρ_c its gradient is zero so that

$$\frac{d(\rho_o - \rho_c)}{dr} = \frac{d(\rho_o)}{dr}$$

$$= \frac{d(\rho_o(o) - \rho_o(o)pr^2}{dr}$$

$$= 2\rho_o(o)p\,r$$

$$\therefore \epsilon = r = \frac{\dfrac{d\,\rho_o - \rho_c)}{dr}}{2\rho_o(o)p}$$

The value of ρ_o is given approximately by $\rho_o = Z(\frac{p}{\pi})^{\frac{3}{2}}$ where p is ~ 5.0.

Temperature motion has the effect of spreading the electrons of an atom over a large volume. If the temperature correction has been underestimated $\rho_o < \rho_c$ at the peak and the atom location appears in a difference synthesis in a depression surrounded by a raised ring (Fig. 1) Alternatively if the temperature correction has been over-estimated then $\rho_o > \rho_c$ at the peak and the opposite

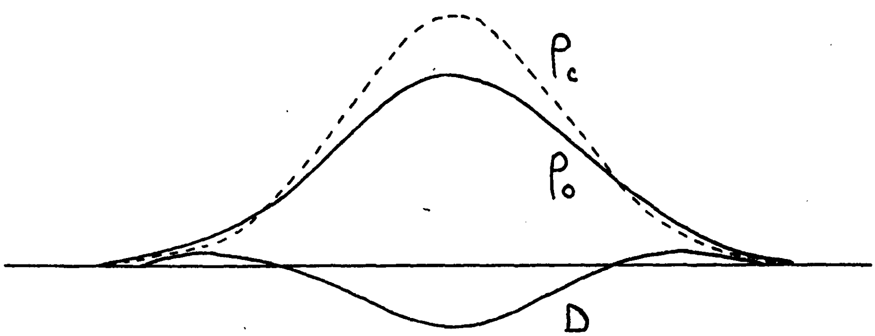


Fig. 1.

(Lipson and Cochran, 1953).

situation occurs.

If the thermal motion is anisotropic then the observed electron distribution is drawn out in the direction of maximum vibration and narrowed in a direction at right angles to it (Fig.2.).

4.2 LEAST-SQUARES REFINEMENT.

The method of least-squares introduced by Hughes, (1941), in the structure analysis of melamine is another method of refinement which like the difference synthesis overcomes the effects due to termination of series and also provides a method of decreasing the influence of inaccurate coefficients on the results. This method, however, suffers certain disadvantages in comparison with the Fourier method. The main ones are that an absolute scale must be established and scattering factors f_c are used to calculate both the structure factors and $\frac{\partial F}{\partial x_c}$ etc. Errors in either scale or scattering factors are bound to influence the results.

The object of the process is to find the most probable values for the atomic parameters i.e. those which result in a minimisation of the quantity

$$R = \sum w_1 (hk\ell) \left[|F_o (hk\ell)| - |F_c (hk\ell)| \right]^2$$

where the weight w_1 of a particular term should be taken as inversely proportional to the square of the probable error of the corresponding F_o. The value of R is influenced by the atomic coordinates and the temperature factor.

In order to start a series of successive approximations of this type the trial parameters must be reasonably good.

Each structure factor is computed by a relation which is in general

$$F_c = \sum_n f_n e^{2\pi i\,(hx_n + ky_n + \ell z_n)}$$

The variables in this expression are exponentials and do not supply the desired linear equations. These, however, can be devised by using the first two terms of Taylor's expansion. If the unrefined coordinates of the nth atom are $x_n y_n z_n$ the correct position can be defined by $x_n + \epsilon x_n$, $y_n + \epsilon y_n$, $z_n + \epsilon z_n$

$$f(x_n + \epsilon x_n,\ y_n + \epsilon y_n,\ z_n + \epsilon z_n) \longrightarrow F_o$$

$$f(x_n y_n z_n) \longrightarrow F_c$$

By Taylor's expansion

$$\Delta F = F_o - F_c = F_c + \sum_n \left(\epsilon x_n \frac{\partial F_c}{\partial x_n} + \epsilon y_n \frac{\partial F_c}{\partial y_n} + \epsilon z_n \frac{\partial F_c}{\partial z_n} \right) - F_c$$

$$\therefore\ \Delta F = \sum_n \left(\epsilon x_n \frac{\partial F_c}{\partial x_n} + \epsilon y_n \frac{\partial F_c}{\partial y_n} + \epsilon z_n \frac{\partial F_c}{\partial z_n} \right)$$

An equation of this type can be set up for all the measured structure amplitudes and these equations usually greatly outnumber the unknowns. These observational equations are reduced to 3N normal equations (N is the number of atoms) the n^{th} of these, for instance, being obtained by multiplying both sides of each of the observational equations by $w \dfrac{\partial F_c}{\partial x_n}$

and adding the q left hand sides and q right hand sides separately, w being the weighting function for the summation over all the terms within the limiting sphere.

$$\sum_q w\,(\Delta F)\frac{\partial F_c}{\partial x_n} = \sum_n w\left[\left(\frac{\partial F_c}{\partial x_n}\right)^2 \epsilon x_n + \left(\frac{\partial F_c}{\partial x_n}\right)\left(\frac{\partial F_c}{\partial y_n}\right)\epsilon y_n + \left(\frac{\partial F_c}{\partial x_n}\right)\left(\frac{\partial F_c}{\partial z_n}\right)\epsilon z_n\right]$$

$$+\sum_m \frac{\partial F_c}{\partial x_n}\left(\frac{\partial F_c}{\partial x_m}\epsilon x_m + \frac{\partial F_c}{\partial y_m}\epsilon y_m + \frac{\partial F_c}{\partial z_m}\epsilon z_m\right)$$

where $\sum_m$ denotes a sum over all the terms except the n^{th}.

If the atoms are well resolved such terms as $\sum_q w\frac{\partial F_c}{\partial x_n}\frac{\partial F_c}{\partial x_m}$ are likely to be small compared with $\sum_q w\left(\frac{\partial F_c}{\partial x_n}\right)^2$. Also if the axes are orthogonal or nearly so $\sum_q w\frac{\partial F_c}{\partial x_n}\frac{\partial F_c}{\partial y_n}$ can be neglected and the above normal equation reduces to

$$\epsilon x_n \sum_q w\left(\frac{\partial F_c}{\partial x_n}\right)^2 = \sum_q w\,(\Delta F)\frac{\partial F_c}{\partial x_n}$$

The normal equations can now be solved by ordinary methods. Similar equations can be obtained for changes in temperature factors, the variables x_n being replaced by each of the six thermal parameters b_{11} b_{22} b_{33} b_{23} b_{31} b_{12} to give 6 N normal equations. The scale factor can also be refined by the least-squares method.

The least-squares programme of Dr. J.S. Rollett, (1961), computes a 3 x 3 matrix for each atomic position, a 6 x 6 matrix for each atomic vibration and a 2 x 2 matrix for the overall scale factor. The choice of weighting system used in the programme can be varied depending on the structure being refined.

5. THE ACCURACY OF CRYSTAL STRUCTURE DETERMINATION.

Certain tests of accuracy were applied to the results of the structure determinations in this thesis. The accuracy of the positional parameters was estimated from the values of the least-squares totals in the final cycle of refinement, using the formula

$$\sigma(x) = a \sqrt{\left\{ \sum \frac{w\Delta^2}{(n-s)} \left[\sum w \left(\frac{\partial \Delta}{\partial \frac{x}{a}} \right)^2 \right] \right\}} \ \text{Å}$$

where n is the total number of reflections used in the refinement and s is the number of degrees of freedom. The standard deviations in bond angles were calculated using the formula of Cruickshank & Robertson, (1953).

The significance of the mean plane calculations was tested using the χ^2 distribution. This distribution has been worked out and tables are available showing the frequency with which different values of χ^2 are exceeded and also the value of χ^2 corresponding to these particular frequencies (Fisher and Yates, 1957.)

The quantity χ^2 can be regarded as the sum of the squares of n variable which vary normally and independently about zero

$$\chi^2 = \sum \frac{\Delta^2}{\sigma^2}$$

where Δ is the deviation in Å of an atom from the calculated plane and σ is the mean standard deviation in Å in the positional parameters.

The probability that no atoms deviate significantly from the calculated plane can be found from tables knowing the value of χ^2 and the number of degrees of freedom $(n - 3)$.

The discrepancy factor R is a rough measure of the accuracy of the structure determination. It is defined by

$$R = \frac{\sum \big|\, |F_o| - |F_c| \,\big|}{\sum |F_o|}$$

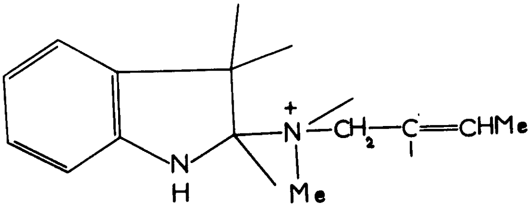
Although it does not contain any of the functions normally minimised during refinement it is nevertheless a fairly reliable estimate of the accuracy.

6. METHODS OF COMPUTATION.

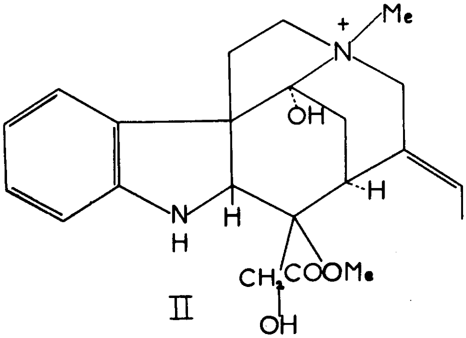
The calculations for the work included in this thesis were performed for the most part on the English Electric DEUCE computer. The majority of the programmes used were prepared by Dr. J.G. Sime and Dr. J.S. Rollett. The Computing Department of Glasgow University do not provide a computing service. Instruction is given in programming and efficient use of the machine to enable users to carry out their own computing.

PART II.

THE X-RAY STRUCTURE ANALYSIS OF ECHITAMINE BROMIDE METHANOL SOLVATE.



I



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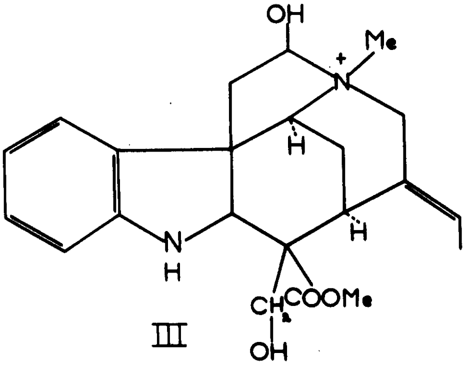

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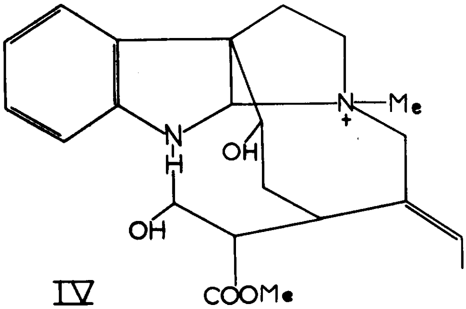

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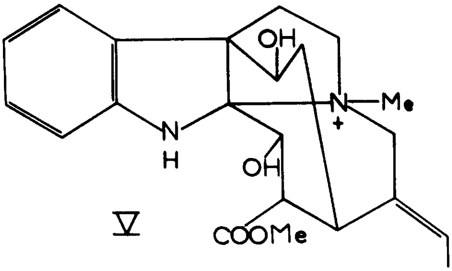
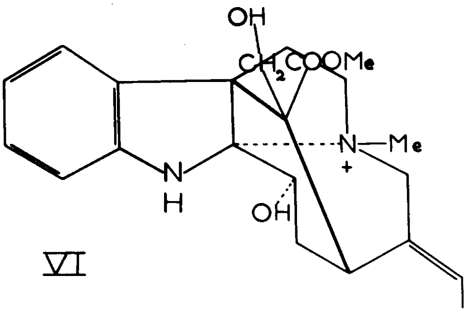


V



VI

ECHITAMINE BROMIDE METHANOL SOLVATE.

1. INTRODUCTION.

Since the Seventeenth Century, the bark of the tree Alstonia scholaris, R. Br. (Echites scholaris, L.) found in India, China and the Phillipines has been used as an anti-malarial drug. Gorup - Besanez, (1875), Hesse, (1875-1880) and Harnack, (1878, 1880), independently isolated echitamine, the chief alkaloidal constituent of this bark, as the chloride. Hesse assigned to it the formula $C_{22}H_{29}N_2O_4C\ell$. Goodson and Henry in 1925 confirmed this formula, extended the earlier investigations and isolated echitamine from various other Alstonia species.

In 1957 Birch, Hodson and Smith suggested the partial structure (I) for echitamine. Conroy et al., (1960), proposed structure (II). Structure (III) was due to Chakravarti et al. (1960 a,b,c). A series of publications by Chatterjee et al. (1960 a,b) and Ghosal and Majumdar, (1960), led to structure (IV).

Birch et al. (1960) reviewed these proposed structures and the chemical and spectroscopic evidence in support of them. Their conclusions indicated that none of the formulae were entirely satisfactory. The evidence did establish however that echitamine is an indole alkaloid containing a methyl ester, an ethylidene and two hydroxyl groups, and one N-methyl group in which the nitrogen atom is quaternary. Professor Birch in a private communication suggested structure (V) for echitamine. This is rather similar to (VI) which is the structure of echitamine deduced from the X-ray crystal analysis of echitamine bromide methanol solvate. This summarises the existing knowledge available from chemical and spectroscopic sources at the time at which the X-ray structure determination was undertaken.

A sample of echitamine bromide was supplied by Professor A.J. Birch. Slow recrystallisation from water to obtain a specimen suitable for X-ray diffraction purposes yielded orthorhombic crystals of the dihydrate. Inspection of the Patterson projections however showed that the position of the bromide ion in the crystal lattice was such as to give rise to false symmetry in the course of phase determination based on the bromide ion.

Orthorhombic crystals of a methanol solvate were obtained by recrystallisation from methanol and since for these crystals the bromide ions were found to occupy quite general positions in the lattice they were used for the structure determination.

2.1 CRYSTAL DATA.

ECHITAMINE BROMIDE METHANOL SOLVATE $C_{22}H_{29}Br\ N_2O_4.CH_3OH$

Molecular weight 497.43

Density calculated = 1.430 gm/cm^3

Density measured = 1.416 gm/cm^3
(By flotation using carbon tetrachloride/petroleum ether).

The crystal is orthorhombic with

$\underline{a}$ = 14.72 ± 0.04 Å

$\underline{b}$ = 14.17 ± 0.02 Å

$\underline{c}$ = 11.09 ± 0.02 Å

Volume of the unit cell = 2312 Å^3

Number of molecules per unit cell = 4

Absent spectra

oko when k is odd

ooℓ when ℓ is odd

hoo when h is odd

Space group $P2_12_12_1(D_2^4)$

Absorption coefficient for X-rays (Cuk_α radiation) μ = 29cm^{-1}

Total number of electrons per unit cell = F(ooo) = 1040

$\sum f^2$(light atoms) = 1279

$\sum f^2$(heavy atoms) = 1296

Well formed prisms elongated along $\underline{a}$ were obtained by slow crystallisation from methanol.

2.2 INTENSITY DATA.

The unit cell parameters were determined from oscillation and rotation films taken about the three crystallographic axes. The space group $P2_12_12_1 (D_2^4)$ was uniquely determined from the systematic absences observed on moving film photographs. The intensity data, which consisted of the layer lines $0k\ell$ - $12k\ell$ $h0\ell$ and $hk0$, were collected by means of equi-inclination Weissenberg exposures and estimated visually using the multiple-film technique (J.M. Robertson, 1943,). Lorentz and polarisation corrections and appropriate rotation factors (Tunell, 1939.), were applied to these intensities and in all 2,115 independent structure amplitudes were evaluated.

Relative scaling factors were found by comparison of common reflections and the structure amplitudes were later placed on the absolute scale by comparison with the calculated values. No absorption corrections were applied, the crystals being cut so that the cross-section perpendicular to the rotation axis was approximately 0.2 mm x 0.2 mm. CuK_α radiation was used for all photography.

2.3 STRUCTURE DETERMINATION.

Preliminary coordinates for the bromide ion were determined from the two-dimensional Patterson maps shown in Figs.1 and 2. The bromide-bromide vector peaks are marked A,B,C and D,E,F. A three-dimensional Patterson synthesis was computed and more

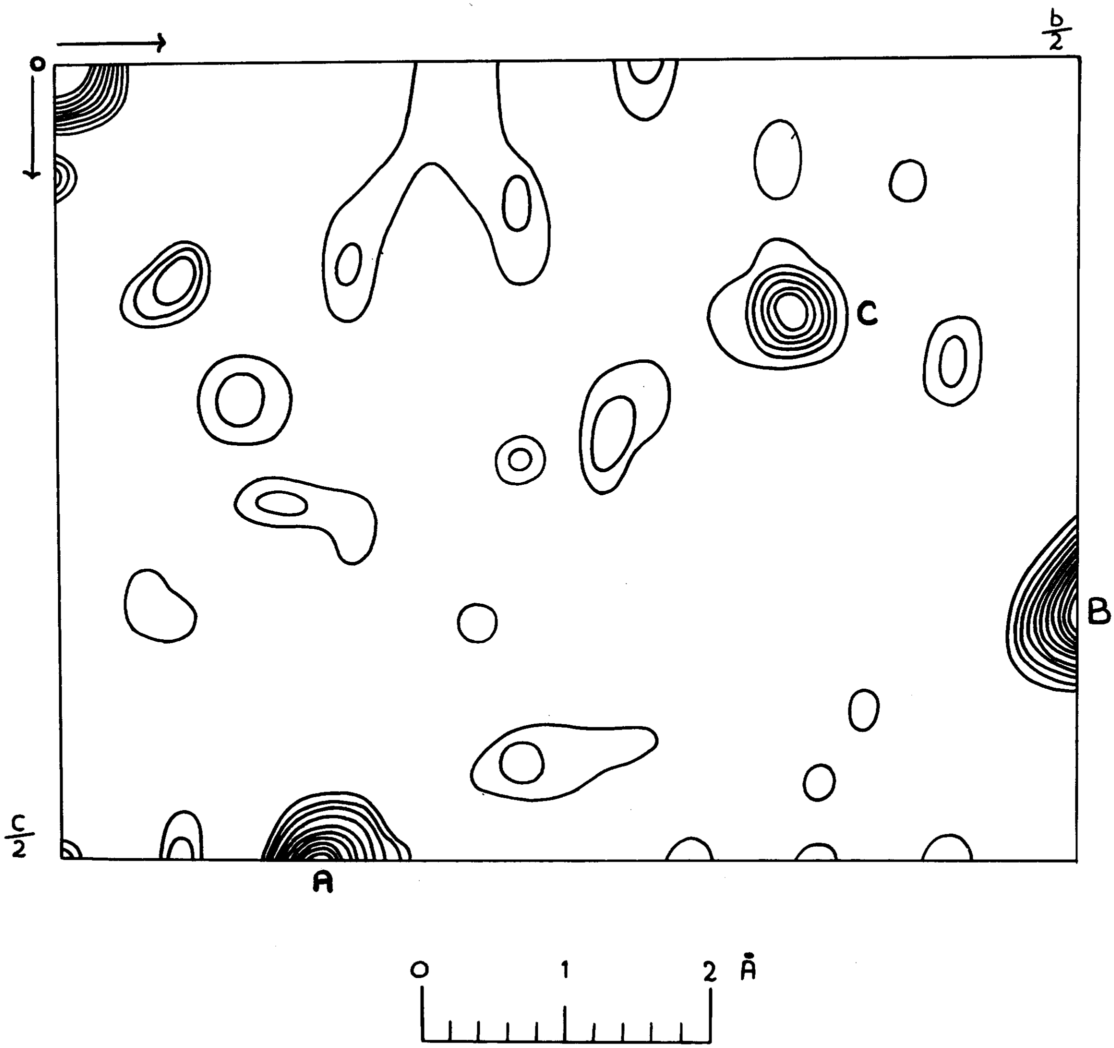


Fig. 1. Patterson projection along the a axis. The bromide-bromide vector peaks are marked A,B and C. The contour scale is arbitrary.

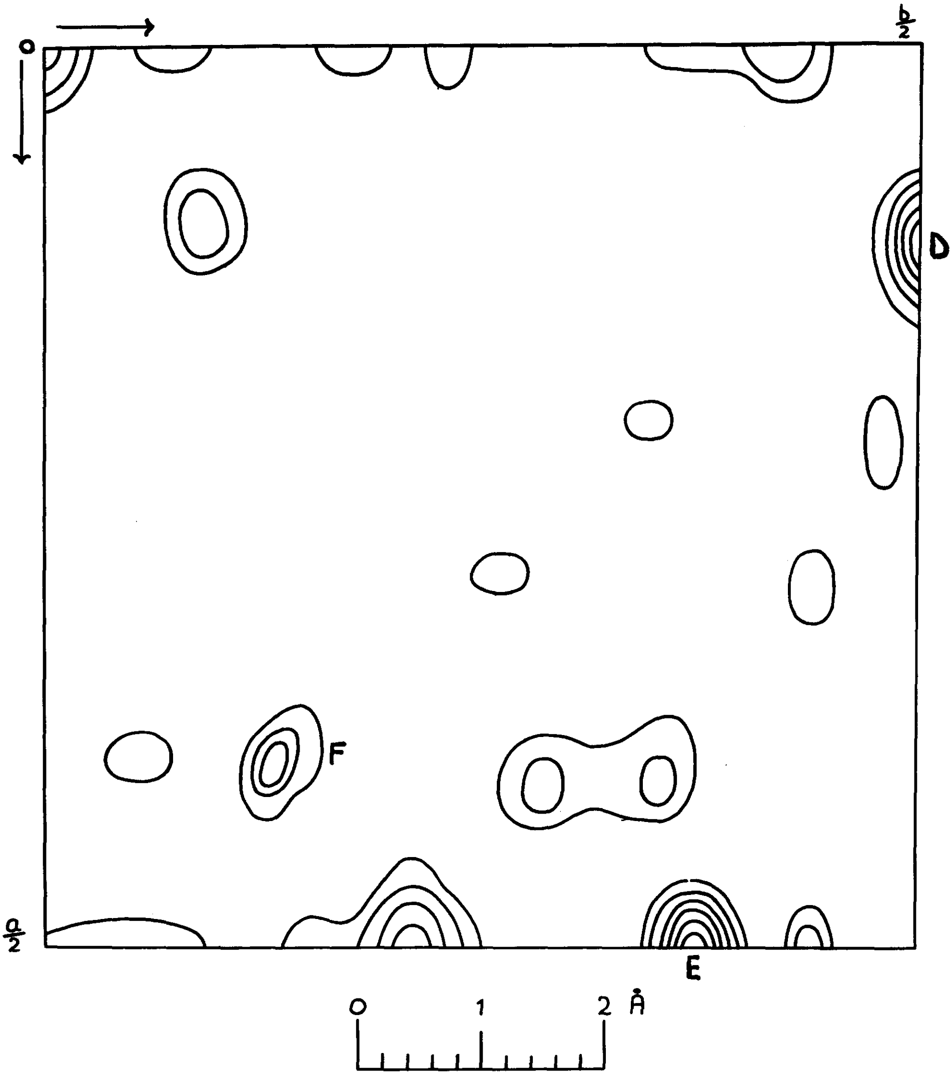


Fig. 2. Patterson projection along the c axis D,E and F denote the bromide-bromide vector peaks. The contour scale is arbitrary.

accurate coordinates for the bromide ions were calculated from the Harker sections. Approximate phase constants for the structure were computed using these coordinates. Since $\sum f^2$ bromide ion is 1,269 and $\sum f^2$ 'light' atoms is 1,279, it is reasonable to assume that the majority of the phases determined by the bromide ion will be good approximations, so that a three-dimensional Fourier map computed on the basis of these phases will contain information about the positions of the 'light' atoms in the structure. In fact significant peaks, which could be attributed to twelve of the thirty carbon, nitrogen and oxygen atoms of echitamine bromide, were located from the first such three-dimensional Fourier map. Coordinates assigned to these peaks were included in the calculation of a more accurate set of structure amplitudes and phase angles. An over-all isotropic temperature factor of $B = 4.0 \text{ Å}^2$ was assumed. The value of R, the average discrepancy between the observed and calculated structure amplitudes, was 33.6%.

A second Fourier synthesis based on the improved phase angles enabled a further nine atoms to be placed with certainty. These atoms were included in the next cycle of calculations to further refine the phases and in the resulting Fourier map peaks could be assigned to all the atoms except the hydrogens. In the subsequent cycle of phasing calculations with the atoms weighted as carbon the value of R fell to 26.2%.

The nitrogen and oxygen atoms were distinguished from carbon firstly by consideration of the peak heights in the previous electron-density distributions, secondly by consideration of the extra-molecular contacts and thirdly by taking into account the available information concerning the functional groups known to be present. Assignment of the correct weight to the atoms in the phasing calculations decreased the value of R to 19.0%

2.4 STRUCTURE REFINEMENT.

Up to this stage in the analysis the methanol molecule of solvation had been omitted. Its position and confirmation of the choice of hetero atoms were obtained by evaluating a three-dimensional Fourier difference synthesis using as coefficients $(F_o - F_c)$ where F_c had been calculated on the basis of an all-carbon structure for the echitamine molecule and the methanol molecule had been omitted. It was observed that the atoms which had been designated as oxygen and nitrogen fell on peaks of positive electron density while the remaining atoms did not. The methanol molecule showed up clearly. Calculation of a further set of structure factors, with each atom of the echitamine and methanol molecules assigned its correct chemical type, gave a value of 17% for R.

A second difference synthesis showed that the temperature factors of many of the atoms of the echitamine molecule required small adjustments and that, for the methanol molecule, a considerably larger value of B was required. It was evident that in the case of the bromide ion there was marked anisotropic thermal motion. These adjustments lowered the value of R to 15.8%.

The analysis was completed by means of two cycles of least-squares refinement of the positional and temperature parameters. The least-squares programme which was devised by Dr. J.S. Rollett (1961), refines six vibrational parameters for each atom, the anisotropic temperature factor being of the form

$$t = 2^{-(b_{11}h^2 + b_{22}k^2 + b_{33}\ell^2 + b_{23}k\ell + b_{31}\ell h + b_{12}hk)}$$

It was felt that for the light atoms the anisotropic parameters had little significance and an average isotropic temperature factor B was evaluated for each atom (Rossmann,1959). These B values are in general agreement with the earlier deductions based on the second Fourier difference synthesis, as is the anisotropic temperature factor derived from the bromide ion. The atomic coordinates and temperature factors are listed in Table I. The course of the analysis is outlined in Table II.

The weighting scheme used for the least-squares refinement was

$$\sqrt{w} = \frac{|F_o|}{|F^*|} \quad \text{if} \quad |F_o| < |F^*|$$

$$\sqrt{w} = \frac{|F^*|}{|F_o|} \quad \text{if} \quad |F_o| > |F^*|$$

TABLE I.

Atomic coordinates and temperature factors.
(Origin of coordinates as in "International Tables.")

Atom	x/a	y/b	z/c	B
N_1	0.5876	0.1239	0.5122	4.4
C_2	0.5415	0.2121	0.4991	3.7
C_3	0.4380	0.1945	0.4552	3.7
N_4	0.5436	0.2654	0.6198	4.1
C_5	0.6429	0.3038	0.6294	4.0
C_6	0.6591	0.3385	0.4973	3.7
C_7	0.6010	0.2752	0.4138	3.3
C_8	0.6631	0.2000	0.3520	4.2
C_9	0.7243	0.2050	0.2567	4.6
C_{10}	0.7719	0.1212	0.2259	4.9
C_{11}	0.7576	0.0388	0.2869	4.6
C_{12}	0.6952	0.0275	0.3829	4.4
C_{13}	0.6462	0.1137	0.4161	4.1
C_{14}	0.3919	0.2857	0.4113	4.2
C_{15}	0.4533	0.3694	0.3972	3.8
C_{16}	0.5437	0.3388	0.3286	3.8
C_{17}	0.5159	0.2833	0.2102	4.2
C_{18}	0.4400	0.5835	0.4707	5.9
C_{19}	0.4624	0.5027	0.5545	4.4
C_{20}	0.4725	0.4103	0.5218	3.8

TABLE I (contd)

Atom	x/a	y/b	z/c	B
C_{21}	0.4756	0.3480	0.6288	4.1
C_{22}	0.5943	0.4293	0.2892	4.5
C_{23}	0.7364	0.4877	0.2118	5.5
C_{24}	0.5279	0.2038	0.7322	4.9
O_{25}	0.3880	0.1507	0.5446	4.7
O_{26}	0.4519	0.3344	0.1411	4.8
O_{27}	0.5579	0.5053	0.2729	5.6
O_{28}	0.6778	0.4071	0.2568	4.7
*C_{29}	0.2691	0.2068	0.0492	10.8
*O_{30}	0.2667	0.2787	0.1324	11.6
Br	0.5520	0.4354	-0.0769	†

* Denotes the atoms of the methanol molecule

† For the bromide ion an anisotropic temperature factor was employed. This was of the form

$$t = 2^{-(\underline{b}_{11}\underline{h}^2 + \underline{b}_{22}\underline{k}^2 + \underline{b}_{33}\ell^2 + \underline{b}_{23}\underline{k}\ell + \underline{b}_{13}\underline{h}\ell + \underline{b}_{12}\underline{hk})}$$

with parameters.

$\underline{b}_{11} = 0.00930$ $\underline{b}_{22} = 0.00850$ $\underline{b}_{33} = 0.01373$

$\underline{b}_{23} = -0.00130$ $\underline{b}_{13} = 0.00137$ $\underline{b}_{12} = -0.00160$

TABLE II

Course of analysis.

	Operation		Data used	Atoms included	R(%)	$\sum w\Delta^2$
2D	Patterson syntheses		$ok\ell$ and hko reflections	--	-	-
3D	Patterson synthesis		2115 F_o	--	-	-
1st	3D F_o	"	1997 F_o	1 Br	40.6	-
2nd	"	"	2032 F_o	1 Br + 12 C	33.6	-
3rd	"	"	2115 F_o	1 Br + 21 C	26.2	-
4th	"	"	2115 F_o	1 Br + 28 C	20.8	-
1st	3D F_o-F_c	"	2115 F_o	1 Br + 28 C	19.0	-
2nd	"	"	2115 F_o	1 Br + 23 C + 2 N + 5O	17.0	-
1st	Least-squares cycle		2115 F_o	1 Br + 23 C + 2 N + 5O	15.8	3440
2nd	"	"	2115 F_o	1 Br + 23 C + 2 N + 5O	13.8	2720
5th	3D F_o synthesis		2115 F_o	1 Br + 23 C + 2 N + 5O	13.4	-

where $|F^*|$ is a constant. It was taken as eight times the minimum value of F_o.

In all the above calculations the atomic scattering factors of Berghuis et al. (1955), were used for carbon, oxygen and nitrogen and those of Thomas and Fermi, (1935), for bromine.

2.5 MOLECULAR DIMENSIONS.

The structure factors calculated from the final atomic parameters (Table I) are listed in Table III. The discrepancy R over the 2,115 observed reflections is 13.4%. Of 234 unobserved reflections only 54 calculate $> 1\frac{1}{2}\,|F_{min}|$, $|F_{min}|$ being the minimum observable value of the structure amplitude. The final three-dimensional electron-density distribution evaluated on the basis of the phase constants in Table III is shown in Fig.3 by means of superimposed contour sections drawn parallel to the (001). The corresponding atomic arrangement is explained in Fig. 4. Fig. 5 shows the atomic arrangement in the molecule as seen in projection along the b axis.

The standard deviations of the final atomic coordinates were derived from the least-squares residuals by application of the equation

$$\sigma(x) \quad = \quad a\sqrt{\left\{\sum\frac{w\Delta^2}{(n-s)} \left[\sum w\left(\frac{\partial\Delta}{\partial\frac{x}{a}}\right)^2\right]\right\}}\ \text{Å}$$

where n = total number of reflections used in the refinement and s = number of degrees of freedom. The results are listed in Table IV.

Table III. Measured and calculated values of the structure factors.

h	k	l	$\|F_o\|$	$\|F_c\|$	α
0	0	2	68	71	0
		4	20	12	0
		6	66	[illegible]	180
		8	6	6	0
		10	6	6	0
		12	14	10	0
		14	12	12	0
0	1	1	97	[illegible]	270
		2	66	47	90
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table III (contd.)

ECHITAMINE BROMIDE METHANOL SOLVATE

h	k	l	$\lvert F_o \rvert$	$\lvert F_c \rvert$	α
5	12	3	10	10	13
		4	4	6	181
		5	14	16	156
		6	6	6	243
		7	13	14	171
		8	< 3	4	[illegible]
		9	5	6	157
5	13	0	9	10	90
		1	6	6	98
		2	12	13	[illegible]
		3	17	20	88
		4	16	8	341
		5	6	4	90
		6	10	10	267
		7	3	5	167
		8	7	6	335
		9	5	4	278
5	14	0	4	7	90
		1	10	9	19
		2	13	13	195
		3	6	8	151
		4	16	16	170
		5	10	11	185
		6	< 3	2	176
		7	5	4	[illegible]
		8	5	5	16
5	15	0	11	13	90
		1	< 3	3	118
		2	5	7	70
		3	8	4	116
		4	3	2	157
		5	4	5	10
[illegible]					

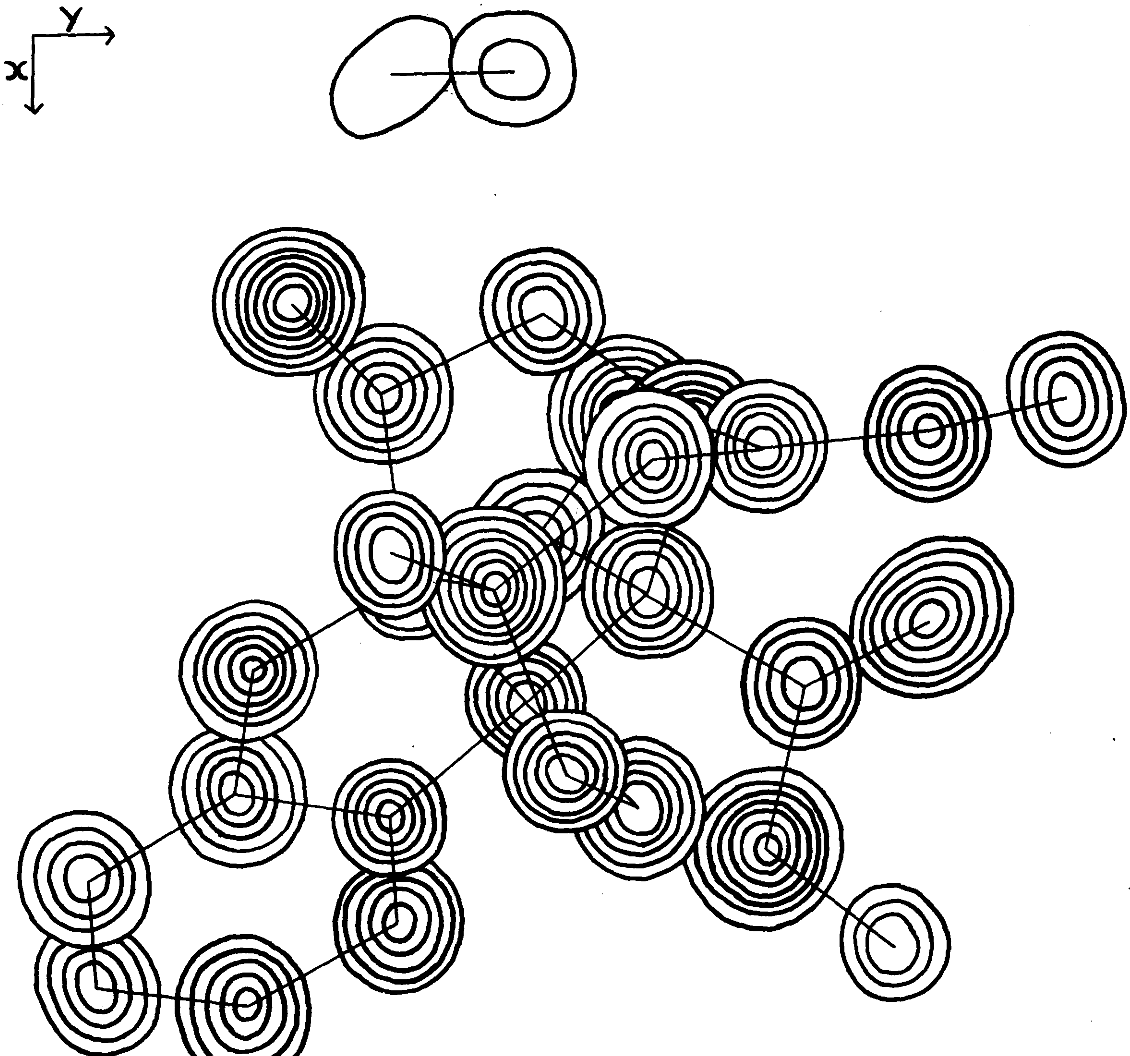


Fig. 3. Final three-dimensional electron-density distribution for echitamine bromide methanol solvate shown by means of superimposed contour sections parallel to (001). The contours are at unit intervals beginning at the 2 e $Å^{-3}$ level. The bromide ion, which lies beyond the field of this diagram, has been omitted.

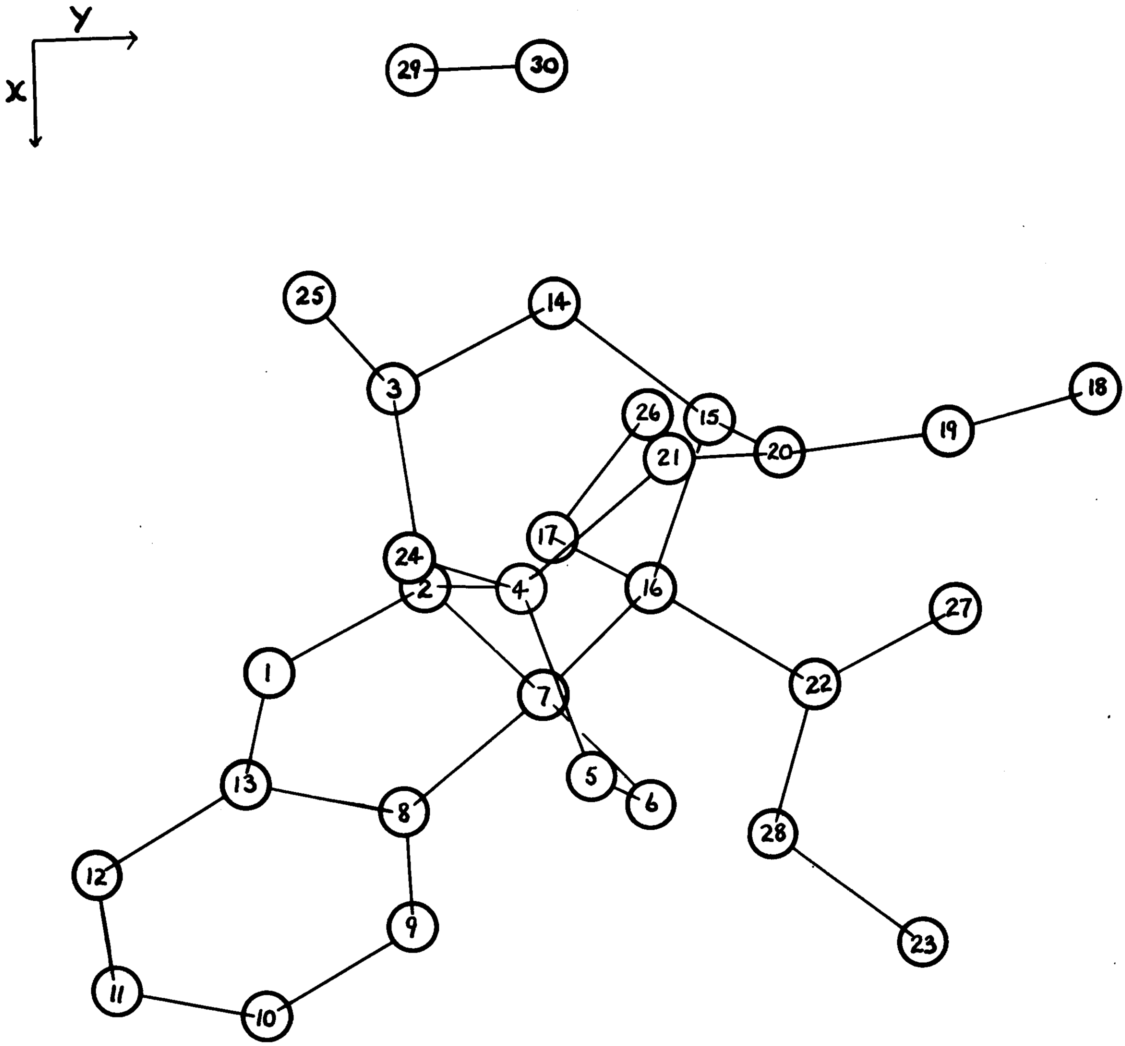


Fig. 4. The arrangement of atoms corresponding to Fig. 3.

Fig. 5. The molecule of echitamine bromide methanol solvate as seen in projection along the $\underline{b}$ axis.

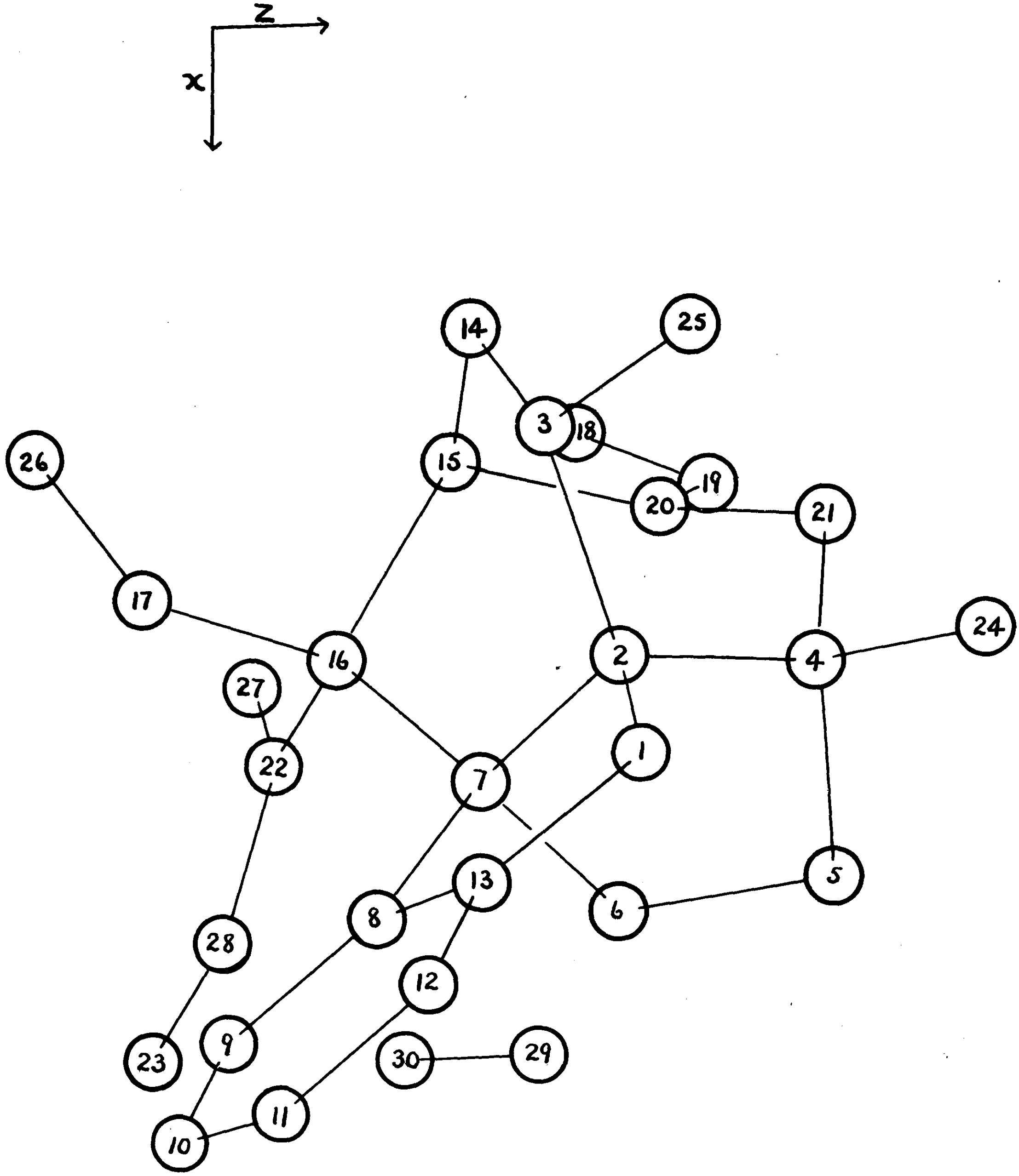


TABLE IV

Standard deviations of the final atomic coordinates (Å).

Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
N_1	0.016	0.015	0.016
C_2	0.020	0.016	0.017
C_3	0.019	0.016	0.016
N_4	0.016	0.014	0.014
C_5	0.019	0.018	0.018
C_6	0.019	0.018	0.019
C_7	0.017	0.016	0.018
C_8	0.019	0.019	0.020
C_9	0.020	0.019	0.020
C_{10}	0.020	0.019	0.020
C_{11}	0.020	0.018	0.019
C_{12}	0.019	0.018	0.019
C_{13}	0.018	0.017	0.020
C_{14}	0.018	0.017	0.019
C_{15}	0.019	0.015	0.016
C_{16}	0.020	0.016	0.017
C_{17}	0.018	0.018	0.018
C_{18}	0.023	0.020	0.020
C_{19}	0.020	0.018	0.018
C_{20}	0.017	0.017	0.018

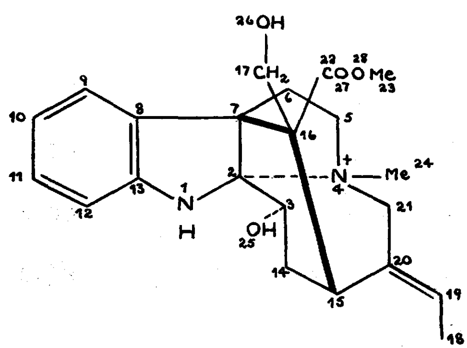
TABLE IV. (contd.)

Atom	σ(x)	σ(y)	σ(z)
C_{21}	0.018	0.018	0.018
C_{22}	0.020	0.021	0.020
C_{23}	0.023	0.021	0.020
C_{24}	0.019	0.019	0.021
O_{25}	0.013	0.012	0.012
O_{26}	0.014	0.012	0.013
O_{27}	0.015	0.013	0.013
O_{28}	0.013	0.012	0.014
C_{29}	0.033	0.031	0.033
O_{30}	0.022	0.021	0.022
Br	0.002	0.002	0.002

The final bond lengths calculated from the atomic coordinates in Table I are listed in Table V. The intramolecular non-bonded distances are given in Table VI and the more interesting intermolecular contacts in Table VII. Table VIII contains the interbond angles. For bonds between the light atoms (carbon, nitrogen and oxygen) the standard deviation in length is 0.03 Å and for bond angles 1.5°. For distances between the light atoms and the bromide ion the standard deviation is about 0.02 Å.

2.6 DISCUSSION OF RESULTS.

The echitamine molecule has a compact three-dimensional structure (VI.)



(VI).

MOLECULAR DIMENSIONS.

INTERATOMIC DISTANCES (Å) AND ANGLES

TABLE V.

Intramolecular bonded distances.

N_1	-	C_2	1.43	C_{10}	-	C_{11}	1.37
N_1	-	C_{13}	1.38	C_{11}	-	C_{12}	1.42
C_2	-	C_3	1.62	C_{12}	-	C_{13}	1.47
C_2	-	N_4	1.54	C_{14}	-	C_{15}	1.50
C_2	-	C_7	1.57	C_{15}	-	C_{16}	1.59
C_3	-	C_{14}	1.54	C_{15}	-	C_{20}	1.52
C_3	-	O_{25}	1.38	C_{16}	-	C_{17}	1.59
N_4	-	C_5	1.56	C_{16}	-	C_{22}	1.55
N_4	-	C_{21}	1.54	C_{17}	-	O_{26}	1.41
N_4	-	C_{24}	1.54	C_{18}	-	C_{19}	1.51
C_5	-	C_6	1.56	C_{19}	-	C_{20}	1.37
C_6	-	C_7	1.55	C_{20}	-	C_{21}	1.48
C_7	-	C_8	1.56	C_{22}	-	O_{27}	1.22
C_7	-	C_{16}	1.55	C_{22}	-	O_{28}	1.32
C_8	-	C_9	1.39	C_{23}	-	O_{28}	1.52
C_8	-	C_{13}	1.44	C_{29}	-	O_{30}	1.38 (methanol)
C_9	-	C_{10}	1.42				

TABLE VI.

Intramolecular non-bonded distances.

N_1	... C_6	3.22	C_3	... C_{20}	3.19
N_1	... C_9	3.66	C_3	... C_{21}	2.96
N_1	... C_{11}	3.74	C_3	... C_{24}	3.35
N_1	... C_{14}	3.85	N_4	... C_8	3.57
N_1	... C_{16}	3.72	N_4	... C_{13}	3.46
N_1	... C_{21}	3.81	N_4	... C_{14}	3.23
N_1	... C_{24}	2.83	N_4	... C_{15}	3.17
N_1	... O_{25}	2.99	N_4	... C_{16}	3.39
C_2	... C_9	3.80	N_4	... C_{19}	3.64
C_2	... C_{12}	3.69	N_4	... O_{25}	2.93
C_2	... C_{15}	2.82	C_5	... C_8	3.42
C_2	... C_{17}	3.38	C_5	... C_{13}	3.59
C_2	... C_{20}	3.00	C_5	... C_{15}	3.91
C_2	... C_{22}	3.94	C_5	... C_{16}	3.68
C_3	... C_5	3.9[illegible]	C_5	... C_{19}	3.96
C_3	... C_6	3.87	C_5	... C_{20}	3.16
C_3	... C_8	3.51	C_6	... C_9	3.41
C_3	... C_{13}	3.30	C_6	... C_{13}	3.32
C_3	... C_{16}	2.93	C_6	... C_{15}	3.26
C_3	... C_{17}	3.21	C_6	... C_{17}	3.90

TABLE VI. (contd.)

C_6	... C_{19}	3.77	C_8	... C_{17}	2.93
C_6	... C_{20}	2.94	C_8	... C_{22}	3.48
C_6	... C_{21}	3.07	C_8	... O_{28}	3.13
C_6	... C_{22}	2.81	C_9	... C_{16}	3.36
C_6	... C_{23}	3.97	C_9	... C_{17}	3.30
C_6	... C_{24}	3.76	C_9	... C_{22}	3.73
C_6	... O_{27}	3.74	C_9	... O_{28}	2.94
C_6	... O_{28}	2.85	C_{13}	... C_{16}	3.66
C_7	... C_{10}	3.93	C_{13}	... C_{17}	3.83
C_7	... C_{12}	3.79	C_{14}	... C_{17}	2.88
C_7	... C_{14}	3.08	C_{14}	... C_{19}	3.61
C_7	... C_{17}	2.59	C_{14}	... C_{21}	2.85
C_7	... C_{20}	2.95	C_{14}	... C_{22}	3.85
C_7	... C_{21}	3.19	C_{14}	... O_{26}	3.20
C_7	... C_{24}	3.83	C_{15}	... C_{17}	2.58
C_7	... O_{25}	3.88	C_{15}	... C_{18}	3.15
C_7	... O_{26}	3.83	C_{15}	... O_{25}	3.63
C_7	... O_{27}	3.67	C_{15}	... O_{26}	2.88
C_7	... O_{28}	2.79	C_{15}	... O_{27}	2.82
C_8	... C_{15}	3.94	C_{15}	... O_{28}	3.69

TABLE VI (contd.)

$C_{16} \cdots C_{19}$	3.62	$C_{20} \cdots C_{22}$	3.15
$C_{16} \cdots C_{21}$	3.48	$C_{20} \cdots C_{24}$	3.83
$C_{16} \cdots C_{23}$	3.77	$C_{20} \cdots O_{25}$	3.89
$C_{17} \cdots C_{20}$	3.95	$C_{20} \cdots O_{27}$	3.32
$C_{17} \cdots O_{27}$	3.28	$C_{21} \cdots O_{25}$	3.22
$C_{17} \cdots O_{28}$	3.01	$C_{22} \cdots O_{26}$	2.98
$C_{18} \cdots C_{21}$	3.81	$C_{23} \cdots O_{27}$	2.73
$C_{18} \cdots C_{22}$	3.74	$C_{24} \cdots O_{25}$	3.02
$C_{18} \cdots O_{27}$	3.01	$O_{26} \cdots O_{27}$	3.22
$C_{19} \cdots C_{22}$	3.68	$O_{26} \cdots O_{28}$	3.71
$C_{19} \cdots O_{27}$	3.42		

TABLE VII

The shorter intermolecular contacts (< 4 Å) and some associated angles.

$O_{26} \cdots O_{30}$	2.84	$O_{30} \cdots C_{12}^{I}$	3.58
$O_{26} \cdots Br$	3.17	$C_{14} \cdots O_{30}$	3.60
$Br \cdots O_{25}^{I}$	3.20	$Br \cdots C_{21}^{V}$	3.67
$O_{26} \cdots C_{29}$	3.40	$C_{9} \cdots C_{29}^{VI}$	3.68
$C_{6} \cdots O_{25}^{II}$	3.40	$C_{3} \cdots O_{27}^{III}$	3.69
$C_{5} \cdots O_{30}^{II}$	3.42	$C_{19} \cdots C_{24}^{VII}$	3.71
$C_{10} \cdots C_{21}^{II}$	3.43	$C_{11} \cdots C_{21}^{II}$	3.71
$Br \cdots N_{1}^{I}$	3.45	$C_{18} \cdots C_{24}^{VII}$	3.74
$C_{12} \cdots O_{26}^{III}$	3.50	$C_{6} \cdots C_{23}^{IV}$	3.75
$C_{18} \cdots C_{17}^{I}$	3.53	$C_{17} \cdots O_{30}$	3.77
$C_{11} \cdots C_{19}^{II}$	3.54	$C_{29} \cdots Br^{VIII}$	3.79
$C_{5} \cdots C_{23}^{IV}$	3.57	$O_{30} \cdots C_{11}^{I}$	3.81

TABLE VII. (contd.)

$C_{24} \cdots O_{30}^{II}$	3.83	$C_{10} \cdots C_{29}^{VI}$	3.91
$C_{18} \cdots C_{10}^{I}$	3.84	$Br \cdots C_{24}^{V}$	3.92
$C_{9} \cdots O_{25}^{II}$	3.85	$Br \cdots C_{3}^{I}$	3.92
$C_{11} \cdots C_{20}^{II}$	3.88	$O_{27} \cdots C_{13}^{I}$	3.97
$C_{17} \cdots Br$	3.88	$C_{6} \cdots C_{14}^{II}$	3.98
$O_{28} \cdots O_{25}^{II}$	3.89	$C_{9} \cdots C_{21}^{II}$	3.98
$C_{18} \cdots C_{9}^{I}$	3.90	$O_{28} \cdots C_{29}^{VI}$	3.99
$C_{5} \cdots C_{14}^{II}$	3.90	$Br \cdots C_{5}^{V}$	3.99

N_1	Br_{III}	O_{25}	53°
O_{25}	Br_{III}	$O_{26\,III}$	118
C_2	N_1	Br_{III}	115
C_{13}	N_1	Br_{III}	117
C_3	O_{25}	Br_{III}	111
C_{17}	O_{26}	Br	110
C_{30}	O_{26}	Br	123
C_{29}	O_{30}	O_{26}	102
O_{30}	O_{26}	C_{17}	121
N_1	Br_{III}	$O_{26\,III}$	85

<u>TABLE VII</u> (contd.)

The subscripts used in the preceeding table refer to the following positions:

I	$1 - x,$	$\frac{1}{2} + y,$	$\frac{1}{2} - z.$
II	$\frac{1}{2} + x,$	$\frac{1}{2} - y,$	$1 - z.$
III	$1 - x,$	$-\frac{1}{2} + y,$	$\frac{1}{2} - z.$
IV	$1\frac{1}{2} - x,$	$1 - y,$	$\frac{1}{2} + z.$
V	$x\ ,$	$y\ ,$	$z - 1.$
VI	$\frac{1}{2} + x,$	$\frac{1}{2} - y,$	$-z\ .$
VII	$1 - x,$	$\frac{1}{2} + y,$	$1\frac{1}{2} - z.$
VIII	$-\frac{1}{2} + x,$	$\frac{1}{2} - y,$	$-z\ .$

TABLE VIII.

Interbond angles.

C_2	N_1	C_{13}	108°	C_8	C_7	C_{16}	117°
N_1	C_2	C_3	110	C_7	C_8	C_9	133
N_1	C_2	N_4	109	C_7	C_8	C_{13}	105
N_1	C_2	C_7	107	C_9	C_8	C_{13}	122
C_3	C_2	N_4	111	C_8	C_9	C_{10}	117
C_3	C_2	C_7	116	C_9	C_{10}	C_{11}	121
N_4	C_2	C_7	104	C_{10}	C_{11}	C_{12}	125
C_2	C_3	C_{14}	112	C_{11}	C_{12}	C_{13}	115
C_2	C_3	O_{25}	111	N_1	C_{13}	C_8	114
C_{14}	C_3	O_{25}	112	N_1	C_{13}	C_{12}	126
C_2	N_4	C_5	104	C_8	C_{13}	C_{12}	120
C_2	N_4	C_{24}	115	C_3	C_{14}	C_{15}	116
C_5	N_4	C_{21}	110	C_{14}	C_{15}	C_{16}	110
C_{21}	N_4	C_{24}	106	C_{14}	C_{15}	C_{20}	109
N_4	C_5	C_6	101	C_{16}	C_{15}	C_{20}	112
C_5	C_6	C_7	107	C_7	C_{16}	C_{15}	109
C_2	C_7	C_6	106	C_7	C_{16}	C_{17}	111
C_2	C_7	C_8	102	C_7	C_{16}	C_{22}	113
C_2	C_7	C_{16}	113	C_{15}	C_{16}	C_{17}	108
C_6	C_7	C_{16}	109	C_{15}	C_{16}	C_{22}	108

TABLE VIII.

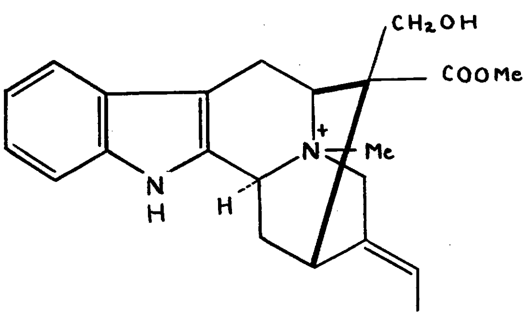
Interbond angles.

C_{17}	C_{16}	C_{22}	108°	N_4	C_{21}	C_{20}	115°
C_{16}	C_{17}	O_{26}	112	C_{16}	C_{22}	O_{27}	124
C_{18}	C_{19}	C_{20}	126	C_{16}	C_{22}	O_{28}	109
C_{15}	C_{20}	C_{19}	126	O_{27}	C_{22}	O_{28}	126
C_{15}	C_{20}	C_{21}	120	C_{22}	O_{28}	C_{23}	116
C_{19}	C_{20}	C_{21}	111				

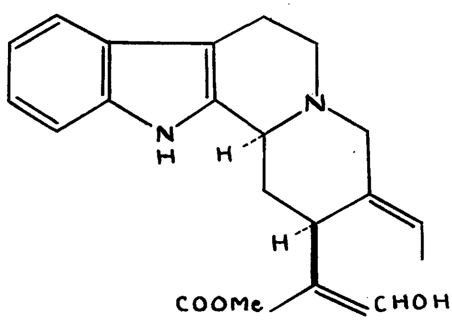
The two five-membered rings are fused <u>cis</u> and the six-membered ring C_2 C_3 C_7 C_{14} C_{15} C_{16} is in the boat form. Apart from the benzene ring there also result three other interlocking rings, two seven-membered (one of which C_2 C_3 C_{14} C_{15} C_{20} C_{21} N_4 is in the boat form) and an eight-membered ring.

These results, however, do not imply any particular absolute configuration. This is shown for echitamine in structure (VI) and was deduced by application of Bijvoet's method (1951), to echitamine iodide by Manohar and Ramaseshan, (1961). It is in accordance with the rule of uniform absolute stereochemistry at C_{15} in the various indole alkaloids.

The structure of echitamine is supported by the available chemical and spectroscopic evidence. From structural and stereochemical considerations it is closely related to such indole alkaloids as macusine-A (VII) and geissoschizine (VIII), one of the products of hydrolytic fission of geissospermine.



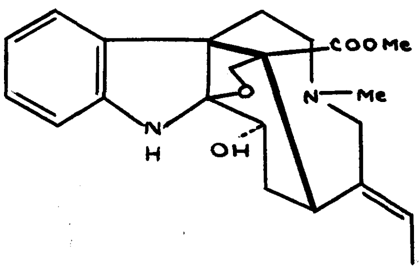
(VII).



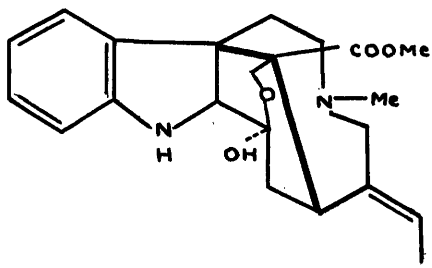
(VIII).

A biogenetic route to echitamine from a precursor of the geissoschizine type has been proposed by Smith, (1961).

Although this analysis determines without doubt the structure of the quaternary salt there still remains some difference of opinion as to the nature of the echitamine base $C_{22}H_{28}N_2O_4$ and two structures (IX) and (X) have been suggested.



(IX).



(X).

The equation of the mean molecular plane calculated through the atoms of the benzene ring by the method of Schomaker et al, (1959), is

$$0.724\,X + 0.237\,Y + 0.648\,Z - 10.261\,\text{Å} = 0.$$

where X, Y, Z, are coordinates expressed in Angstrom units and referred to orthogonal axes a, b, and c. The ring is planar to within 0.008 Å, the adjacent atoms C_7 and N_1 being displaced by 0.01 Å and 0.04 Å respectively from it.

The average length of the carbon-carbon aromatic bond is 1.42 Å, not significantly different from the length of 1.395 Å in benzene and none of the individual bonds differ significantly from this value. The average of the carbon-carbon single-bond lengths between sp^3-hybridised atoms is 1.56 Å and between sp^2- and sp^3-hybridised atoms 1.52 Å. There are in agreement with the accepted values of 1.545 Å and 1.525 Å respectively. (Tables of Interatomic Distances, 1958). Again none of the individual lengths differ significantly from the accepted values. The length of the double bond in the ethylidene group ($C_{19} - C_{20}$) at 1.37 Å is in reasonable agreement with that of 1.334 Å found in ethylene (Bartell and Bonham, 1957).

The dimensions of the methyl ester group compare favourably with those found in the structure of dimethyl oxalate (Dougill and Jeffrey, 1953), and for the ester and lactone groups in acetylbromogeigerin (This thesis page 51). and epilimonol iodoacetate (Arnott et al. 1961). As in dimethyl oxalate the methyl group C_{23} is trans to the bond $C_{16} - C_{22}$. The five atoms C_{16}, C_{22}, C_{23}, C_{27}, C_{28}, lie on a plane with equation

$$0.270X + 0.219Y + 0.938Z - 6.642 = 0$$

None of the atoms deviate significantly from the plane.

The carbon-oxygen single bonds $C_3 - O_{25}$ 1.38 Å, $C_{17} - O_{26}$ 1.41 Å and $C_{29} - O_{30}$ 1.38 Å, appear to be rather short, but within the limits of experimental error agree with the accepted value of 1.43 Å. (Tables of Interatomic Distances, 1958).

The carbon-nitrogen bond lengths vary in magnitude from 1.38Å to 1.56Å. Three different types of carbon-nitrogen single bonds are involved, carbon(*sp*^{2}-hybridised)-nitrogen, carbon(*sp*^{3}-hybridised)-nitrogen and carbon(*sp*^{3}-hybridised)-N^+. The length of the carbon(*sp*^{2}-hybridised)-nitrogen bond $C_{13} - N_1$ is 1.38Å which agrees reasonably with values reported for acetanilide 1.33Å (Brown and Corbridge, 1954), 2-chloro-4-nitroaniline 1.37Å (McPhail and Sim, unpublished results) and ibogaine hydrobromide 1.39Å and 1.40Å (Arai *et al*. 1960). The carbon(*sp*^{3})-nitrogen bond $C_2 - N_1$ at 1.43Å does not differ significantly from the accepted value of 1.47Å (Tables of Interatomic Distances, 1958). Three of the bonds to the positively charged nitrogen atom N_4 are 1.54Å and the fourth is 1.56Å giving an average length of 1.54Å for carbon(*sp*^{3})-N^+. The occurrence of long carbon(*sp*^{3})-N^+ bonds in amino acids has been discussed by Hahn, (1957). He lists the results of a large number of investigations and finds a mean value of 1.503Å. However, some recent more accurate measurements suggest that this value is rather high. Wright and Marsh, (1962), report values of 1.480Å and 1.484 ± 0.006Å for the carbon(*sp*^{3})-N^+ bonds in ℓ-lysine monohydrochloride dihydrate, and Marsh (1958), finds a value of 1.474 ± 0.003Å for a similar bond in glycine. In Table IX are collected the results of a number of X-ray measurements of carbon(*sp*^{3})-N^+ bonds in alkaloidal structures. The weighted mean of the more accurate results (estimated standard deviation $\leqslant$ 0.05Å) is 1.52Å, possibly even

TABLE IX.

Comparison of Carbon(sp^3) - N^+ bond lengths in alkaloids.

Compound	Bond Length (Å)	e.s.d. (Å)	Reference.
Ibogaine hydrobromide	1.49, 1.51, 1.58	0.03	Arai *et al.* 1960.
Calycanthine dihydrobromide dihydrate	1.43, 1.49, 1.56 1.50, 1.49, 1.53	0.03	Hamor *et al.* 1960. Further work, 1962.
dl Alphaprodine hydrochloride	1.50, 1.50, 1.53	0.01	Kartha *et al.* 1960.
d - Methadone hydrobromide	1.55, 1.49, 1.48	0.03	Hanson & Ahmed 1958.
(+) - Demethanolaconinone hydriodide trihydrate	1.54, 1.57, 1.52	0.04	Przybylska 1961
Hunterburnine methiodide	1.51, 1.54, 1.57, 1.64	0.05	Asher *et al.* 1962 and further unpublished results
Macusine - A iodide	1.46, 1.66, 1.36, 1.50	0.06	McPhail & Sim 1961 and further unpublished results.
Codeine hydrobromide dihydrate	1.51, 1.52, 1.56	0.06	Lindsey & Barnes 1955

TABLE IX. (contd.)

Compound	Bond Length (Å)	e.s.d. (Å)	Reference.
(+) - Des - (oxymethylene) - lycoctonine hydriodide monohydrate	1.51, 1.51, 1.49	---	Przybylska 1961
Strychnine hydrobromide dihydrate	1.55, 1.44, 1.59	---	Robertson & Beevers 1951.

larger than the value found for amino acids. The mean carbon(sp^3)-N^+ bond length in echitamine 1.542 Å is rather greater than this but not significantly so.

A model of the echitamine molecule constructed on the basis of standard bond lengths and angles indicates that the distance between the carbonyl carbon atom of the ester group C_{22} and the terminal carbon C_{18} of the ethylidene group is about 2.5 Å. However the results of the analysis show that these atoms are actually 3.74 Å apart and this increased separation appears to be brought about by the ethylidene group bending out of its ideal position away from the ester group. Thus the angle $N_4\ C_{21}\ C_{20}$ at 115° is distorted from the tetrahedral value and the angles $C_{15}\ C_{20}\ C_{19}$ and $C_{21}\ C_{20}\ C_{19}$ which might have been expected to be equal have values of 126° and 111° respectively. Also $C_{20}C_{19}C_{18}$ is 126° instead of the expected 120°.

The mean of the bond angles of the five-membered ring $C_2\ C_7\ C_6\ C_5\ N_4$ is 106°, possibly significantly smaller than tetrahedral but in agreement with the mean value of 105° found for the angles of the five-membered ring in isoclovene hydrochloride (Clunie and Robertson, 1961), and 106° for those in clerodin bromolactone (Sim et al. 1961, and further unpublished work). The average bond angle of the benzene ring is 120°, individual angles varying from 115° to 125°.

In the crystal the positively charged molecules and the bromide ions form a three-dimensional network held together both by the normal ionic forces and by a system of hydrogen bonds involving the two hydroxyl groups O_{25} O_{26}, the indole nitrogen atom N_1 and the bromide ion. The hydrogen atoms on O_{25} O_{26} and N_1 are presumably directed towards the bromide ion. This pattern is illustrated in Figs 7 and 8 which show the contents of the unit cell in projection on the (001) and (010) respectively. The hydrogen bonded distances O - H .... Br^- of 3.17 and 3.20 Å and N - H ....Br^- of 3.45 Å are similar to those found in the structures of L-cystine dihydrobromide (Peterson et al.1960), and calycanthine dihydrobromide dihydrate (Hamor et al.1960, 1962).

The molecule of methanol of solvation is hydrogen bonded to the hydroxyl group O(26), the distance O(26).... H - O(30) being 2.84Å. The angles C - OH .... Br^-, C - NH .... Br^- and C - OH .... O are all within 8^o of the expected tetrahedral value. The positively charged nitrogen atom forms no particularly close contacts to the bromide ions in the unit cell, the four values of $d(N_4 - Br)$ being 4.14 Å, 4.91 Å, 7.63 Å and 8.10 Å.

The closest contact between a carbon atom and a bromide ion is 3.67 Å, rather similar to the minimum carbon - Br^- distances found in the structures of d-methadone hydrobromide 3.62 Å (Hanson and Ahmed, 1958), calycanthine dihydrobromide dihydrate 3.60 Å (Hamor et al. 1960, 1962), and ibogaine hydrobromide 3.59 Å (Arai et al. 1960.).

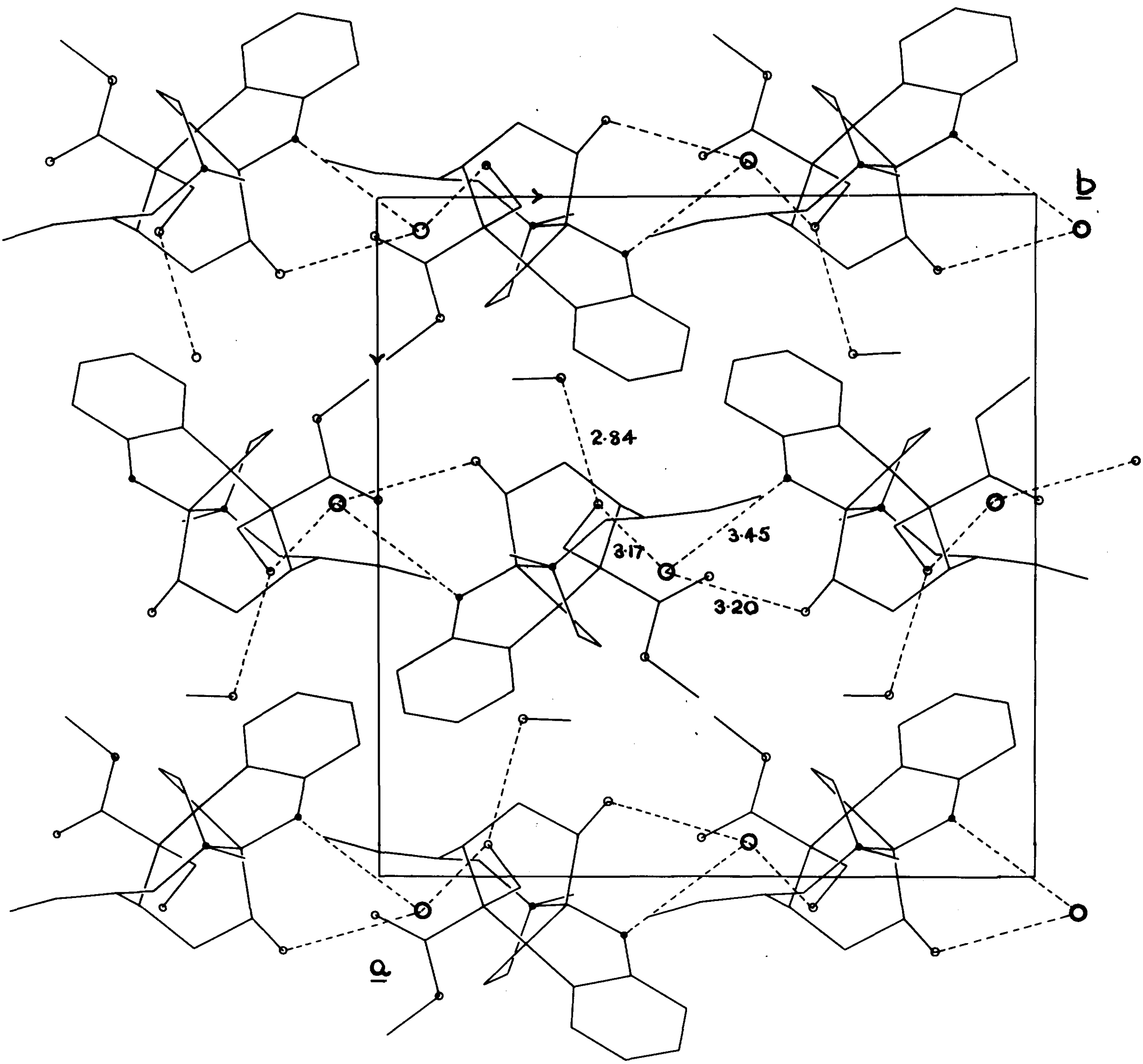


Fig. 7. The arrangement of molecules in the crystal as viewed in projection along the c axis. A few of the more interesting non-bonded distances and hydrogen bond lengths are shown.

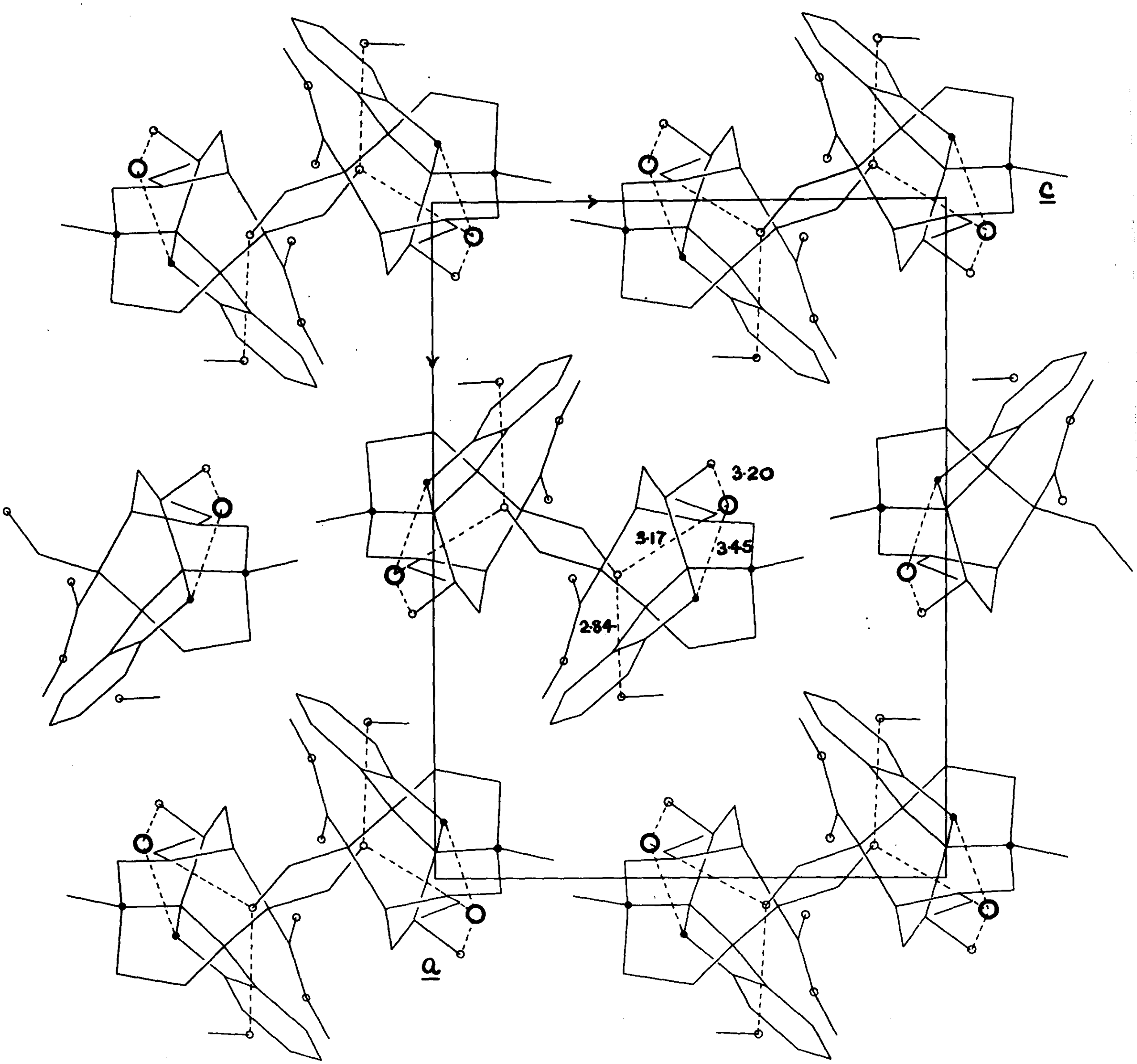


Fig. 8. The packing of the molecules in the unit cell as seen in projection along the b axis. The lengths of a few of the more interesting non-bonded distances and hydrogen bonds are given.

The distance of closest approach between two echitamine molecules is 3.40 Å and occurs between C_6 of the reference molecule and O_{25} of the one relatedto it by a two-fold screw axis parallel to <u>a</u>. Between these molecules there occurs another short contact C_{11} - C_{15} 3.43 Å. There are two close contacts between methanol and echitamine molecules: C_{29} .... O(26) 3.40 Å and O_{30}^{II} .... C(5) 3.42 Å where II refers to the equivalent position $\frac{1}{2} + x$, $\frac{1}{2} - y$, $1 - z$. All other extra - molecular contacts are greater than 3.5 Å (Table VII).

The final isotropic temperature factors for the atoms of the echitamine molecule are shown in Fig 6. It is observed that the atoms of the ring system have on the whole a lower temperature factor than those of the peripheral groups. Also those atoms of the peripheral groups which take part in hydrogen bonding viz:- O_{25} and C_{20} O_{26}, have smaller temperature factors than the methyl ester, ethylidene and methyl groups which are much less tightly bound.

The temperature factor derived from the carbon (B = 10.8 Å^2) and oxygen (B = 11.2 Å^2) atoms of the methanol molecule are exceptionally high. This suggests that there is only partial occupancy of the methanol sites in the crystal Inspection of the various Fourier syntheses showed that the peak heights of the atoms of the methanol molecule were much lower than for the echitamine molecule. This is shown in Fig. 3.

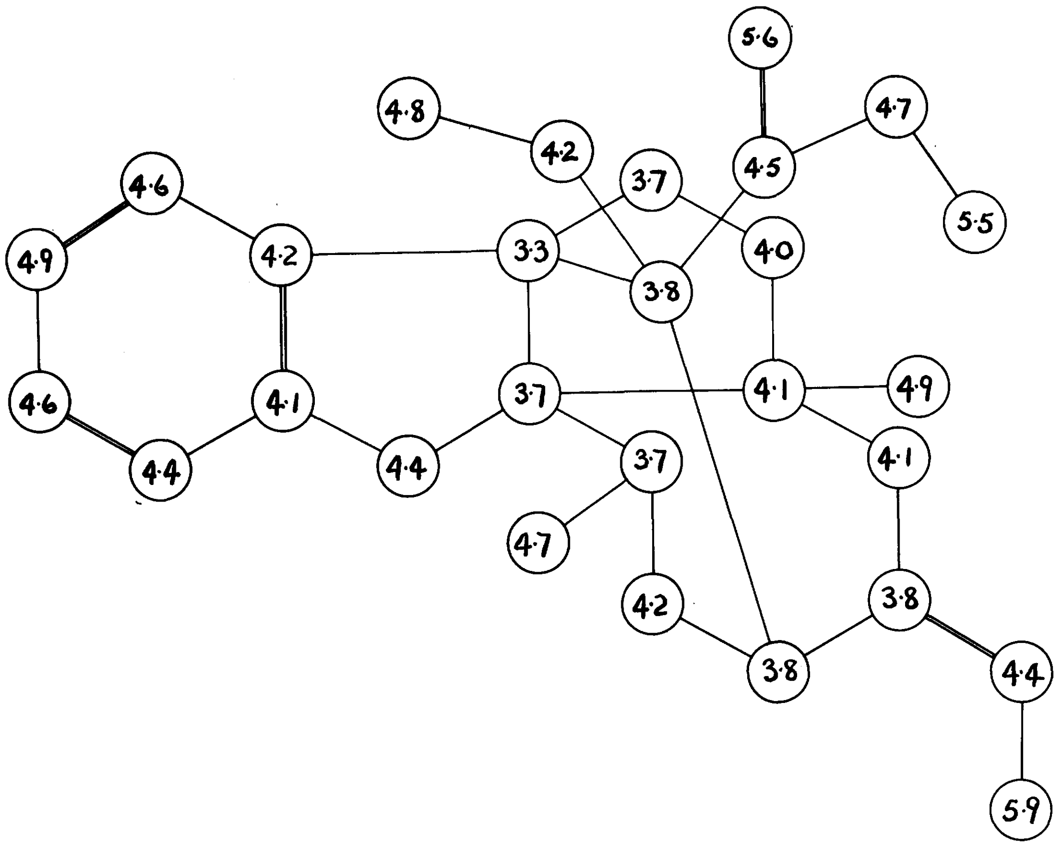


Fig. 6. Diagram showing the final isotropic temperature factors (Å^2) for the echitamine molecule.

If it is assumed that the difference between d calculated ($1.430 \ gm/cm^3$) and d measured ($1.416 \ gm/cm^3$) is due to partial occupancy of the methanol sites, then on the average only 85% of the methanol sites are occupied. Electron counts on the final Fourier synthesis support this, indicating 79% occupancy of the sites.

If the methanol molecules were missing in a regular pattern there should be some evidence for larger repeat distances than those observed. An effect of this kind has been observed by Cant, (1956), in the structure of cyclohexaglycyl hydrate. However no spots additional to those already indexed were visible on the diffraction photographs of echitamine bromide methanol solvate and it was therefore concluded that the methanol molecules present were distributed in some statistical fashion over the available sites. No precautions were taken to avoid methanol loss during the X-ray exposures. A variable solvent content has been reported in the crystal study of biuret hydrate (Hughes et al. 1961), caffeine hydrate (Sutor, 1958.) and thymine monohydrate (Gerdil, 1961).

PART III.

THE X-RAY STRUCTURE ANALYSIS OF

ACETYLBROMOGEIGERIN.

ACETYLBROMOGEIGERIN.

1. INTRODUCTION.

The bitter principle geigerin occurs in the vermeerbos (vomiting bush) represented by various Geigeria spp. which grow abundantly in many areas of South Africa. It has been reported by Rimington and Roets, (1936), to be associated in the plant with the suspected poisonous principle vermeeric acid with which it is apparently closely related chemically.

The sesquiterpenoid lactone geigerin was first isolated by the above authors from Geigeria aspera Harv. They showed that geigerin, $C_{15}H_{20}O_4$, was a ketonic lactone and made a preliminary study of its chemistry. Perold (1955, 1957), extended these investigations, showed that geigerin possessed a reduced azulene system and proposed structure (I) for it.

Barton and De Mayo (1957), recorded that evidence was found which contradicted Perold's results viz:- that geigerin was readily acetylated to the mono-acetate and hence the hydroxyl group must be primary instead of secondary. They proposed structure (II) for geigerin. However, later investigations did not confirm structure (II) but led them to structure (III) (Barton and Levisalles, 1958), which is confirmed by the X-ray analysis of acetylbromogeigerin.

Barton and Levisalles also elucidated the structure of allogeiric acid (IV). Since this acid does not lactonise readily they concluded that the hydroxyl group and the group at position 7 must be trans to one another. Also since allogeiric acid reverts to geigerin and not to the isomeric trans-lactone engaging the 6 hydroxyl group it is reasonable to expect that the lactone ring of geigerin is cis. They assumed the 7 side chain to be in the customary β position. Rotatory dispersion measurements showed that the hydrogen at C_1 is β-oriented. Thus on the basis of this evidence Barton and Levisalles defined a partial stereochemistry for geigerin (V).

Crystals of the derivative acetylbromogeigerin in which the bromine atom was considered to be in the 2-position were supplied by Professor Barton and an X-ray crystal structure analysis was undertaken to extend and verify the stereochemistry.

2.1 CRYSTAL DATA.

ACETYLBROMOGEIGERIN		$C_{17}H_{21}O_5Br$
Molecular weight		385.25
Melting point		147 - 153°C(decomposition)
Density calculated	=	1.505 gm/cm^3
Density measured	=	1.512 gm/cm^3

(By flotation using zinc chloride/water).

The crystal is orthorhombic with

$$\underline{a} = 8.11 \pm 0.02\ \text{Å}$$

$$\underline{b} = 13.77 \pm 0.03\ \text{Å}$$

$$\underline{c} = 15.24 \pm 0.03\ \text{Å}$$

Volume of the unit cell = 1702 $\mathring{A}^3$

Number of molecules
per unit cell = 4

Absent spectra

oko when k is odd

ooℓ when ℓ is odd

hoo when h is odd

Space group $P2_12_12_1(D_2^4)$

Linear absorption coefficient for X-rays (Cuk$_\alpha$ radiation) $\mu = 37 cm^{-1}$

Total number of electrons per unit cell = F(ooo) = 792

$\sum f^2$ (light atoms) = 953

$\sum f^2$ (heavy atoms) = 1225

2.2 INTENSITY DATA

Rotation, oscillation and moving film photographs showed that the crystals are orthorhombic with cell parameters

$\underline{a}$ = 8.11 ± 0.02 $\mathring{A}$

$\underline{b}$ = 13.77 ± 0.03 $\mathring{A}$

$\underline{c}$ = 15.24 ± 0.03 $\mathring{A}$

The systematic absences determined from Weissenberg photographs proved to be oko when k is odd, ooℓ when ℓ is odd, hoo when h is odd, thus determining the space group $P2_12_12_1 - D_2^4$ unambiguously.

The intensity data used in the analysis were obtained from photographs of the okℓ - 6kℓ reciprocal lattice nets.

In all 1,625 independent structure amplitudes were obtained from visual estimates of the intensities using the multiple-film technique (J.M. Robertson, 1943). The crystals were well-formed prismatic needles with uniform cross-section perpendicular to the axis of rotation. The linear absorption coefficient for CuK$_\alpha$ radiation is $37 cm^{-1}$ and no absorption corrections were applied. The intensities were corrected for Lorentz, polarisation and Tunell factors (1939) and put on the same absolute scale at a later stage by comparing $\sum F_o$ and $\sum F_c$ for each layer.

2.3 STRUCTURE DETERMINATION.

The Patterson projections, calculated from the okℓ and hko data, are shown in Figs. 1 and 2 respectively. The peaks marked A,B,C, and D,E,F, correspond to the bromine-bromine vectors and on this basis the coordinates of the bromine atom were evaluated.

A three-dimensional Fourier synthesis was computed using the phases determined by the heavy atom. This enabled peaks to be assigned to sixteen of the light atoms. Coordinates calculated for these sixteen atoms were included in the next structure factor computation allowing more accurate phase constants to be determined. A second three-dimensional Fourier map calculated using these improved phases enabled the positions of another five atoms to be determined. Two peaks in the Fourier map were possible sites for the remaining atom attached

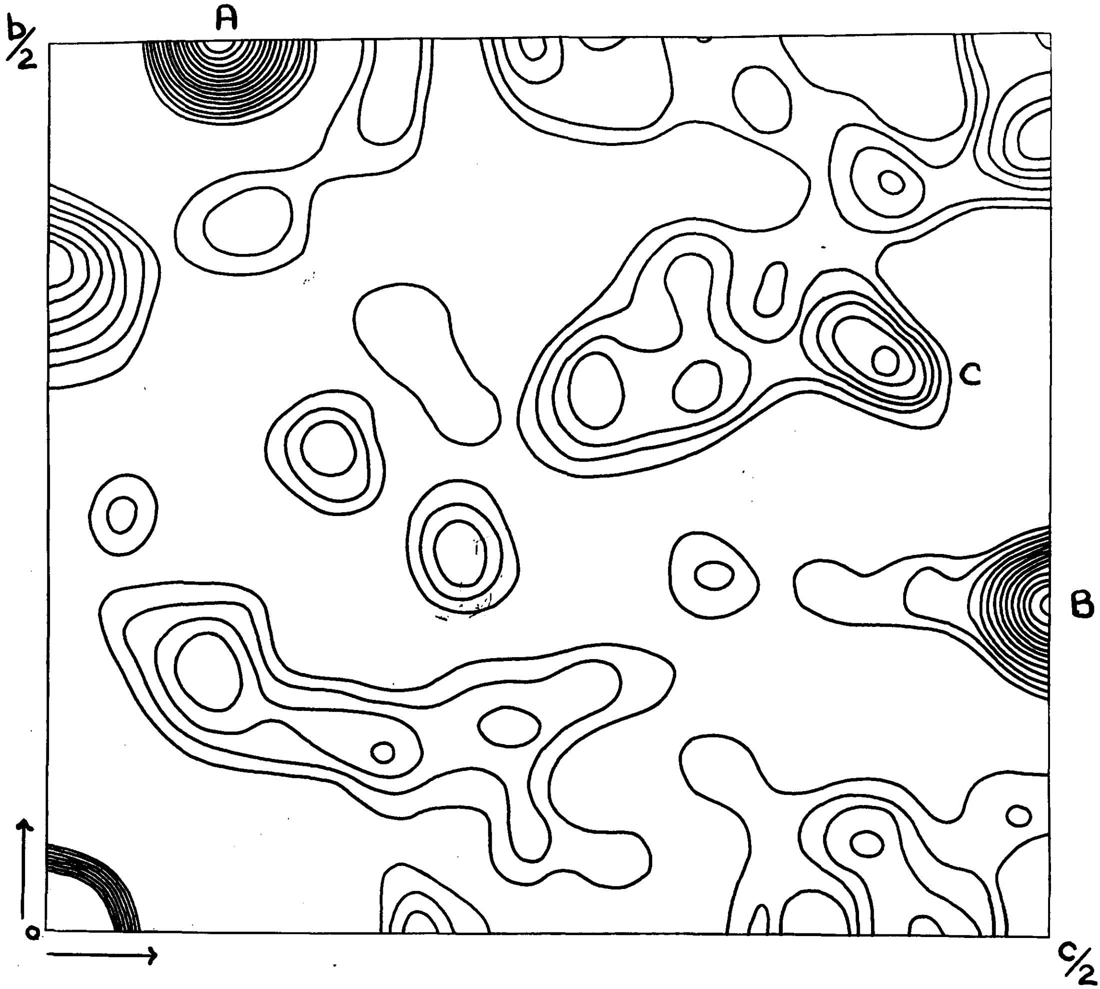


Fig. 1 Patterson projection on (100). Contour scale arbitrary. The bromine-bromine vector peaks are marked A, B and C.

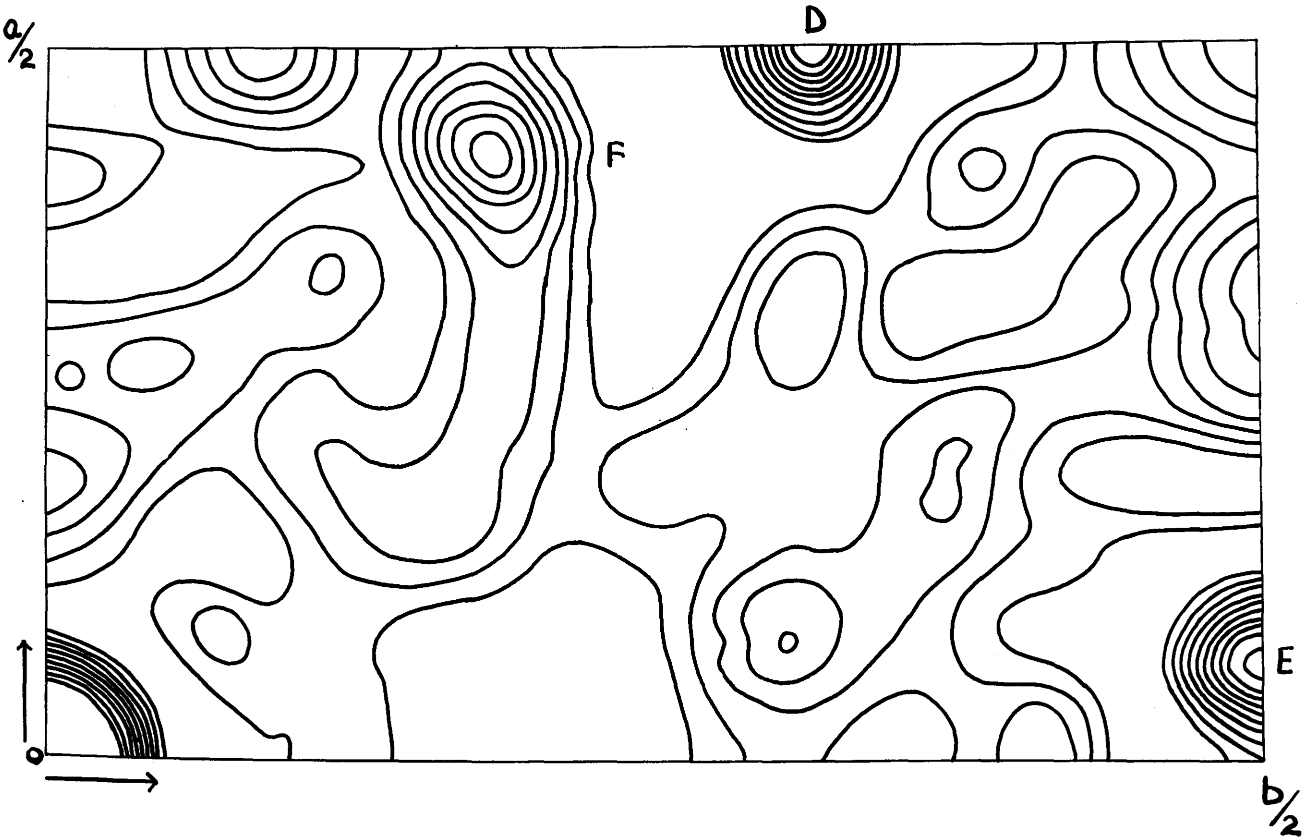


Fig. 2. Patterson projection on (001). Contour scale arbitrary.
The bromine-bromine vector peaks are denoted by D, E and F.

to the cyclopentanone ring, i.e. C_{14}. The peak heights were 5e $\mathring{A}^{-3}$(A) and 2e $\mathring{A}^{-3}$(B). A third cycle of phasing calculations were performed using the bromine and twenty-one other atoms. These twenty-one atoms were given their correct chemical type except for the oxygen atom of the acetyl group O_4. The phase constants obtained were used to compute the section of the three-dimensional Fourier map containing C_{14}. An increase in the height of peak B was observed and a large decrease in the peak height of A. Peak B was therefore assumed to correspond to the site of C_{14} and atomic coordinates were assigned accordingly. All twenty-three atoms were now entered in the structure factor calculations and the subsequent Fourier map revealed all the atoms clearly resolved.

The course of the analysis is shown in Table I. The value of R at this stage was 20.6%. An overall isotropic temperature factor B = 3.0 $\mathring{A}^2$ was assumed. The atomic form factors employed in the calculations were those of Berghuis _et al._ (1955), for carbon and oxygen and Thomas and Fermi for bromine (1935).

2.4 STRUCTURE REFINEMENT.

The initial refinement of the atomic coordinates was carried out by comparison of the peak positions on F_o and F_c maps. These maps also enabled the choice of hetero atoms to be confirmed and, on the basis of peak heights, variable isotropic temperature factors to be assigned to the various

TABLE I.

Course of analysis.

Operation	Data used	Atoms included	R(%)	$\sum w\Delta^2$
2D Patterson syntheses	okℓ and hko reflections	--	-	-
1st 3D F_o synthesis	1576 F_o	1 Br	-	-
2nd 3D F_o "	1587 F_o	1 Br + 16 C	28	-
3rd " "	1597 F_o	1 Br + 4O + 17 C	23	-
4th " "	1599 F_o	1 Br + 5O + 17 C	20.6	-
5th " " and 1st 3D F_c "	1625	1 Br + 5O + 17 C	19.5	-
1st Least-squares cycle	1625 F_o	1 Br + 5O + 17 C	19.1	-
2nd " "	1625 F_o	1 Br + 5O + 17 C	16.8	-
3rd " "	1625 F_o	1 Br + 5O + 17 C	15.5	2624
Final 3D F_o map	1625 F_o	1 Br + 5O + 17 C	13.5	-

atoms. The atomic coordinates obtained from the F_o, F_c maps with their appropriate temperature factors were used in further refinement by the method of least squares. When three cycles of such refinement had been completed the value of R was 13.5%.

The magnitude of $\sum w\Delta^2$ is listed for the final cycle. The totals for the two previous cycles are not valid for comparison because of scaling errors in certain reflections which were corrected in the penultimate cycle of refinement. The observed structure amplitudes are listed with the final values of the calculated phase constants in Table II. The weighting system used in the least squares refinement was

$$\sqrt{w} = \frac{|F_o|}{|F^*|} \quad \text{if } |F_o| < |F^*|$$

$$\sqrt{w} = \frac{|F^*|}{|F_o|} \quad \text{if } |F_o| > |F^*|$$

$$\text{where } |F^*| = 8\,|F\,\text{min.}|$$

2.5 RESULTS OF THE ANALYSIS.

The final electron-density distribution over the molecule, as superimposed contour sections parallel to the (001), is shown on Fig. 3. The stereochemistry is explained in Fig. 4. The coordinates obtained from the final least-squares refinement cycle are given in Table III. The anisotropic temperature parameters are listed in Table IV. Tables V and VI contain the bond lengths and angles of the molecule defined by the final coordinates. Some of the shorter intramolecular

Table II. Measured and calculated values of the structure factors.

h	k	l	$\lvert F_o \rvert$	$\lvert F_c \rvert$	α
0	0	2	51	60	180
		4	41	41	0
		6	18	21	180
		8	22	20	180
		10	60	61	0
		12	54	58	180
		14	19	21	0
		16	6	8	180
0	1	1	72	69	270
		2	77	83	90
		3	14	14	90
		4	98	89	90
		5	85	92	270
		6	41	44	270
		7	32	29	90
		8	8	13	90
		9	42	44	270
		10	7	6	270
		11	23	19	90
		12	< 4	4	90
		13	< 4	4	90
		14	19	18	90
		15	10	13	270
		16	10	14	270
		17	8	10	90
		18	14	16	90
		19	9	10	270
0	2	0	116	110	0
		1	47	57	180
		2	103	120	180
		3	38	27	180
		4	44	49	0
		5	31	26	180
		6	4	8	180
		7	8	7	180
		8	13	13	180
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0	13	1	11	12	90
		2	7	4	90
		3	35	42	90
		4	20	25	90
		5	29	32	270
		6	21	26	270
		7	17	21	90
		8	4	7	90
		9	16	14	270
		10	15	9	90
		11	14	11	90
		12	8	7	270
0	14	0	6	8	0
		1	19	26	180
		2	15	13	0
		3	< 4	7	0
		4	14	12	180
		5	7	7	180
		6	9	2	0
		7	6	9	180
		8	3	11	0
		9	20	22	0
		10	22	6	180
0	15	1	< 4	0	90
		2	< 4	3	270
		3	11	13	90
		4	9	8	270
		5	15	16	270
		6	3	2	90
		7	13	13	90
		8	17	16	270
		9	6	12	270
		10	12	12	90
0	16	0	25	30	180
		1	< 3	5	180
		2	19	21	0
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

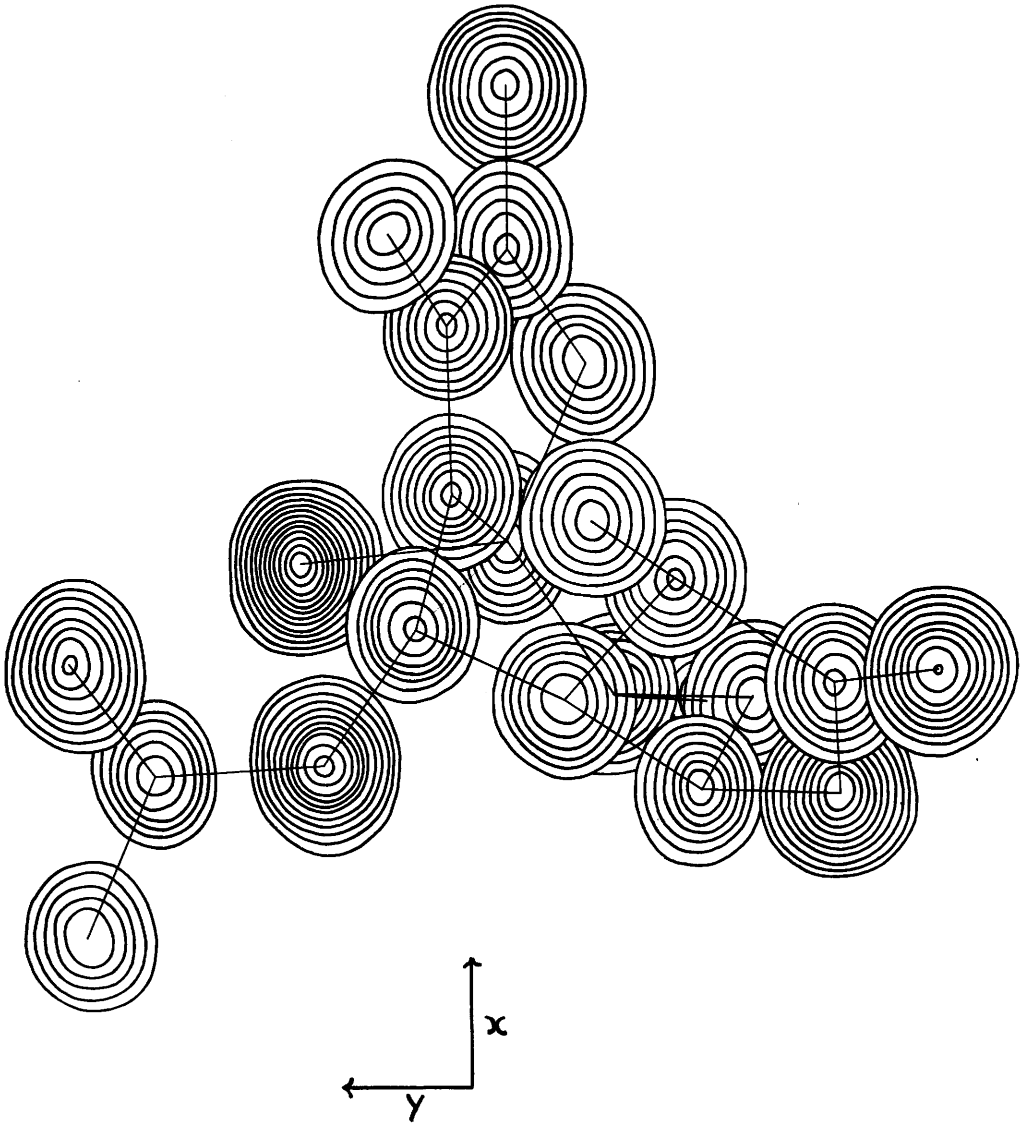


Fig. 3. Final three-dimensional electron-density distribution for acetylbromogeigerin. The superimposed contour sections are drawn parallel to (001). The contour interval is 1 e Å^{-3} except around the bromine atom where it is 5 e Å^{-3}.

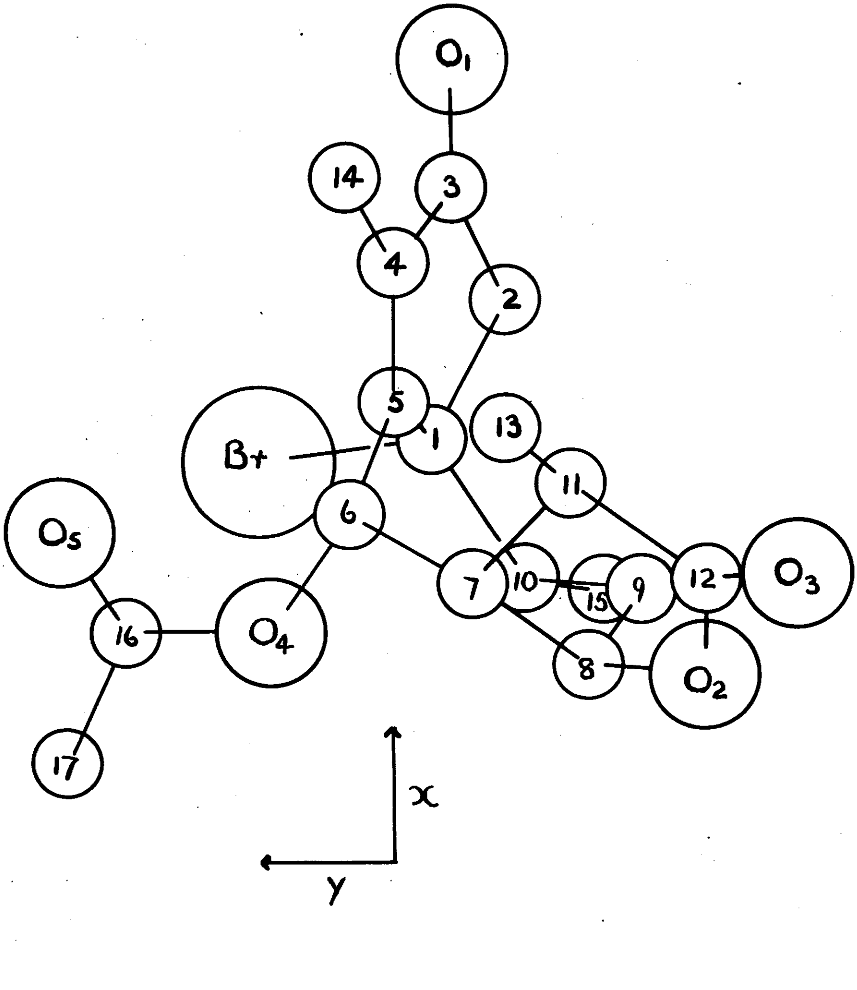


Fig. 4 Atomic arrangement corresponding to Fig. 3.

TABLE III.

Atomic Coordinates.

(Origin of coordinates as in "International Tables.")

Atom	x/a	y/b	z/c
C_1	0.4872	0.0270	0.7184
C_2	0.6497	0.0768	0.7521
C_3	0.7761	0.0384	0.6919
C_4	0.6912	-0.0003	0.6112
C_5	0.5324	-0.0008	0.6259
C_6	0.4028	-0.0286	0.5596
C_7	0.3199	0.0541	0.5122
C_8	0.2282	0.1304	0.5715
C_9	0.3139	0.1670	0.6549
C_{10}	0.3270	0.0855	0.7275
C_{11}	0.4371	0.1211	0.4602
C_{12}	0.3236	0.2107	0.4526
C_{13}	0.4978	0.0759	0.3690
C_{14}	0.7864	-0.0327	0.5336
C_{15}	0.3148	0.1397	0.8209
C_{16}	0.2631	-0.1804	0.5999
C_{17}	0.1111	-0.2225	0.6449
O_1	0.9248	0.0396	0.7015
O_2	0.2166	0.2117	0.5114
O_3	0.3318	0.2710	0.3928
O_4	0.2658	-0.0830	0.5994

TABLE III. (contd.)

Atom	x/a	y/b	z/c
O_5	0.3794	-0.2248	0.5587
Br	0.4646	-0.0914	0.7919

TABLE IV

Anisotropic temperature-factor parameters (b_{ij} x 10^5)

	b_{11}	b_{22}	b_{33}	b_{12}	b_{23}	b_{13}
C_1	1854	509	505	219	165	638
C_2	1986	635	401	-461	162	1
C_3	2206	352	459	274	424	-176
C_4	864	599	609	637	- 55	-215
C_5	1282	323	496	178	30	-358
C_6	1067	496	658	242	-191	9
C_7	2029	557	391	178	212	-132
C_8	1318	437	600	346	-186	3
C_9	2177	582	476	310	183	-341
C_{10}	1566	461	449	274	223	227
C_{11}	1257	499	441	- 20	52	-207
C_{12}	2280	461	437	-460	-79	-213
C_{13}	1417	702	582	42	311	17
C_{14}	1617	754	590	512	207	-131
C_{15}	1828	766	526	26	26	128
C_{16}	1643	430	590	-183	6	32
C_{17}	1733	494	766	-243	14	-242
O_1	1351	821	692	-65	270	-477
O_2	1215	603	532	278	307	-74
O_3	2128	705	750	-36	341	-417
O_4	1954	443	596	-130	354	449
O_5	2785	552	920	180	-272	490
Br	1594	599	542	4	308	187

MOLECULAR DIMENSIONS.

INTERATOMIC DISTANCES (Å) AND ANGLES

TABLE V.

Intramolecular bonded distances.

C_1	-	C_2	1.57	C_7	-	C_{11}	1.54
C_1	-	C_5	1.51	C_8	-	C_9	1.53
C_1	-	C_{10}	1.54	C_8	-	O_2	1.45
C_1	-	Br	1.99	C_9	-	C_{10}	1.58
C_2	-	C_3	1.47	C_{10}	-	C_{15}	1.61
C_3	-	C_4	1.51	C_{11}	-	C_{12}	1.54
C_3	-	O_1	1.22	C_{11}	-	C_{13}	1.60
C_4	-	C_5	1.31	C_{12}	-	O_2	1.25
C_4	-	C_{14}	1.48	C_{12}	-	O_3	1.24
C_5	-	C_6	1.51	C_{16}	-	C_{17}	1.53
C_6	-	C_7	1.51	C_{16}	-	O_4	1.34
C_6	-	O_4	1.47	C_{16}	-	O_5	1.29
C_7	-	C_8	1.57				

TABLE VI.

Intramolecular non-bonded distances.

$C_1 \cdots C_7$	3.44	$C_5 \cdots C_{15}$	3.96
$C_1 \cdots C_8$	3.38	$C_5 \cdots C_{16}$	3.32
$C_1 \cdots C_{14}$	3.81	$C_5 \cdots O_1$	3.43
$C_1 \cdots C_{16}$	3.84	$C_5 \cdots O_5$	3.48
$C_1 \cdots O_1$	3.56	$C_6 \cdots C_9$	3.14
$C_1 \cdots O_4$	2.97	$C_6 \cdots C_{10}$	3.06
$C_2 \cdots C_6$	3.84	$C_6 \cdots C_{12}$	3.73
$C_2 \cdots C_9$	3.34	$C_6 \cdots C_{13}$	3.33
$C_2 \cdots C_{14}$	3.82	$C_6 \cdots C_{14}$	3.14
$C_2 \cdots C_{15}$	3.04	$C_6 \cdots C_{17}$	3.80
$C_3 \cdots C_6$	3.75	$C_6 \cdots O_2$	3.71
$C_3 \cdots C_{10}$	3.74	$C_6 \cdots O_5$	2.71
$C_4 \cdots C_7$	3.45	$C_7 \cdots C_{10}$	3.31
$C_4 \cdots C_9$	3.89	$C_7 \cdots C_{14}$	3.98
$C_4 \cdots C_{10}$	3.64	$C_7 \cdots C_{16}$	3.53
$C_4 \cdots C_{11}$	3.51	$C_7 \cdots O_3$	3.50
$C_4 \cdots O_4$	3.64	$C_7 \cdots O_5$	3.93
$C_5 \cdots C_8$	3.17	$C_8 \cdots C_{13}$	3.86
$C_5 \cdots C_9$	2.95	$C_8 \cdots C_{15}$	3.87
$C_5 \cdots C_{11}$	3.13	$C_8 \cdots O_3$	3.45

TABLE VI.

C_8	...	O_4	2.99		
C_9	...	C_{11}	3.19		
C_9	...	C_{12}	3.14		
C_9	...	O_4	3.57		
C_{10}	...	O_2	3.83		
C_{10}	...	O_4	3.07		
C_{11}	...	C_{14}	3.71		
C_{11}	...	O_4	3.79		
C_{13}	...	C_{14}	3.74		
C_{13}	...	O_2	3.66		
C_{13}	...	O_3	3.03		
C_{14}	...	O_1	2.97		
Br	...	C_3	3.45		
Br	...	C_4	3.54		
Br	...	C_6	3.68		
Br	...	C_{15}	3.44		
Br	...	C_{16}	3.57		
Br	...	O_4	3.35		

distances are listed in Table VII and a few of the more interesting intermolecular approach distances ($\leqslant$ 4 Å) in Table VIII. The standard deviations in positional parameters, calculated from the least-squares normal-equation totals are listed in Table IX. The estimated standard deviations in bond lengths obtained from these values are carbon-carbon 0.040 Å, carbon-oxygen 0.035 Å and carbon-bromine 0.022 Å. The standard deviation in bond angle calculated by the method of Cruickshank and Robertson (1953), is 2°.

The best plane through atoms C_1, C_3, C_4, C_5, C_6 and C_{14} was calculated by the method of Schomaker et al. (1959), and the deviations of the atoms from this plane are listed in Table X. The displacement of C_2 = 0.32 Å is highly significant. The equation of the plane is

$$0.060X + 0.942Y - 0.338Z - 4.628 = 0$$

2.6 DISCUSSION OF RESULTS.

The structure of acetylbromogeigerin and the relative stereochemistry determined from the results of the X-ray analysis are shown in (VI). The stereochemistry can be better represented by (VII).

TABLE VII.

Interbond angles.

Br	C_1	C_2	105°	C_6	C_7	C_{11}	115°
Br	C_1	C_5	110	C_8	C_7	C_{11}	101
Br	C_1	C_{10}	108	C_7	C_8	C_9	119
C_2	C_1	C_5	102	C_7	C_8	O_2	101
C_2	C_1	C_{10}	117	C_9	C_8	O_2	107
C_5	C_1	C_{10}	115	C_8	C_9	C_{10}	112
C_1	C_2	C_3	103	C_1	C_{10}	C_9	112
C_2	C_3	C_4	109	C_1	C_{10}	C_{15}	112
C_2	C_3	O_1	128	C_9	C_{10}	C_{15}	107
C_4	C_3	O_1	124	C_7	C_{11}	C_{12}	99
C_3	C_4	C_5	108	C_7	C_{11}	C_{13}	114
C_3	C_4	C_{14}	121	C_{12}	C_{11}	C_{13}	115
C_5	C_4	C_{14}	131	C_{11}	C_{12}	O_2	112
C_1	C_5	C_4	114	C_{11}	C_{12}	O_3	124
C_1	C_5	C_6	122	O_2	C_{12}	O_3	124
C_4	C_5	C_6	125	C_{17}	C_{16}	O_4	113
C_5	C_6	C_7	116	C_{17}	C_{16}	O_5	129
C_5	C_6	O_4	112	O_4	C_{16}	O_5	117
C_7	C_6	O_4	104	C_8	O_2	C_{12}	114
C_6	C_7	C_8	116	C_6	O_4	C_{16}	122

TABLE VIII.

Intermolecular distances ($\leqslant 4$ Å).

$C_3 \cdots O_3^{I}$	2.96	$Br \cdots C_{12}^{III}$	3.76
$O_1 \cdots O_3^{I}$	3.07	$Br \cdots O_3^{III}$	3.78
$C_{11} \cdots O_2^{I}$	3.26	$C_{14} \cdots O_3^{I}$	3.79
$C_4 \cdots O_3^{I}$	3.36	$C_{17} \cdots O_3^{III}$	3.86
$C_2 \cdots O_3^{I}$	3.38	$C_{13} \cdots O_2^{I}$	3.88
$C_{12} \cdots O_2^{I}$	3.41	$Br \cdots C_{13}^{III}$	3.94
$O_3 \cdots O_2^{I}$	3.45	$C_{12} \cdots C_8^{I}$	3.96
$O_3 \cdots C_8^{I}$	3.53	$C_{15} \cdots C_{13}^{III}$	3.97
$O_5 \cdots C_{17}^{II}$	3.70	$C_{17} \cdots C_{15}^{IV}$	3.98
$C_{14} \cdots O_5^{II}$	3.70	$C_5 \cdots O_3^{I}$	4.00

The superscripts refer to the following positions:

I	$\frac{1}{2} + x$,	$\frac{1}{2} - y$,	$1 - z$.
II	$\frac{1}{2} + x$,	$-\frac{1}{2} - y$,	$1 - z$.
III	$\frac{1}{2} - x$,	$-y$,	$\frac{1}{2} + z$.
IV	$-x$,	$-\frac{1}{2} + y$,	$1\frac{1}{2} - z$.

TABLE IX.

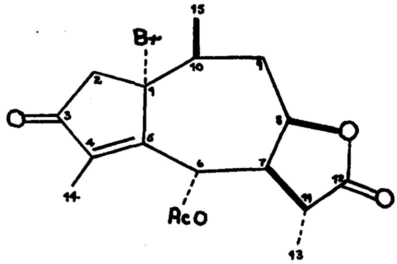
Standard deviations of the final atomic coordinates (Å)

Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
Br	0.003	0.002	0.002
C_1	0.024	0.018	0.019
C_2	0.025	0.021	0.020
C_3	0.024	0.017	0.019
C_4	0.024	0.020	0.020
C_5	0.025	0.017	0.018
C_6	0.023	0.020	0.022
C_7	0.025	0.020	0.020
C_8	0.024	0.020	0.021
C_9	0.026	0.020	0.020
C_{10}	0.023	0.019	0.017
C_{11}	0.024	0.018	0.019
C_{12}	0.026	0.020	0.020
C_{13}	0.022	0.020	0.020
C_{14}	0.027	0.023	0.021
C_{16}	0.024	0.019	0.021
C_{17}	0.026	0.020	0.022
O_1	0.017	0.014	0.015
O_2	0.016	0.013	0.014
O_3	0.018	0.015	0.016
O_4	0.016	0.013	0.014
O_5	0.020	0.015	0.017

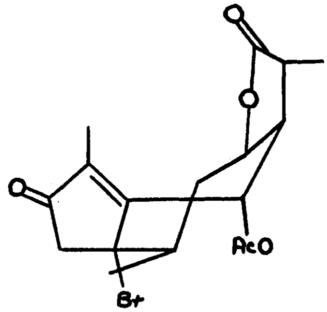
TABLE X.

Displacements (Å) of the atoms of the cyclopentenone system from the mean plane through C_1, C_3, C_4, C_5, C_6 and C_{14}.

C_1	0.076
C_2	-0.321
C_3	-0.066
C_4	-0.014
C_5	-0.010
C_6	-0.048
C_{14}	0.061
O_1	0.040



(VI).



(VII).

This agrees at positions 6, 7 and 8 with that proposed for geigerin by Barton and Levisalles. The cycloheptane ring has a chair conformation.

Barton and Pinhey, (1960), determined the absolute configuration at C_7 for geigerin from chemical and spectroscopic evidence and also by stereochemical correlation with artemisin (Cocker and McMurry, 1960).

Hence using the relative stereochemistry shown in (VI) the absolute configuration can be determined at all centres except C_1 where evidence of a β - H configuration depends on rotatory dispersion studies (Djerassi et al. 1957). Bromination of scetylgeigerin occurred at position 1 and not at the expected position 2. Hence the configuration of geigerin at position 1 could not be inferred from the results of the crystal analysis.

The average length of a carbon-carbon single bond between

sp^3-hybridised carbon atoms is 1.56 Å which agrees within experimental error with the value of 1.545 Å for the carbon-carbon distances in diamond. The average length of a carbon(sp^2)-carbon(sp^3) bond is 1.51 Å, not significantly different from the value of 1.525 Å given in Tables of Interatomic Distances,(1958). The length of the carbon-carbon double bond is 1.31 Å which is in agreement within the standard deviation with that of 1.334 Å found in ethylene (Bartell and Bonham, 1957).

The average value of the carbon(sp^3) - carbon(sp^3) distance in the seven-membered ring is 1.54 Å and this can be compared with that of 1.57 ± 0.04 Å found for the average bond length in the seven-membered ring of isoclovene hydrochloride (Clunie and Robertson, 1961). The average value for the seven-membered ring in bromodihydroisophotosantonic lactone, a similar compound to acetylbromogeigerin is 1.52 ± 0.045 Å (Asher and Sim, 1962). In acetylbromogeigerin the average bond angle for the seven-membered ring is 116 ± 2° which agrees with the value of 117 ± 2° in isoclovene hydrochloride and 116° in bromodihydroisophotosantonic lactone. The seven-membered rings in isoclovene hydrochloride, acetylbromogeigerin and bromodihydroisophotosantonic lactone are in the chair form. It is obvious however that all three are distorted since all the angles are consistently greater than tetrahedral. The increase in bond angles may be compared to those observed in cyclononylamine hydrobromide (Bryan and Dunitz,1960), and 1,6 trans-diaminocyclodecane dihydrochloride (Hüber-Buser and Dunitz,1960), where similar large values for the ring angles have been found.

The average carbon($\underline{sp}^3$) - oxygen distance is 1.47 Å which is not significantly different from the value of 1.50 Å in bromodihydroisophotosantonic lactone and that of 1.48 Å in clerodin bromolactone (Sim et al. 1961, and further unpublished work). The length of a similar bond in epilimonol iodoacetate is 1.49 Å (Arnott et al. 1961). The carbon-oxygen single-bond distance in the system $-O-\underset{\underset{O}{\|}}{C}-$ is 1.30 Å. This distance compares favourably with that of 1.32 Å in epilimonol iodoacetate, 1.34 Å in bromodihydroisophotosantonic lactone and 1.34 Å in clerodin bromolactone.

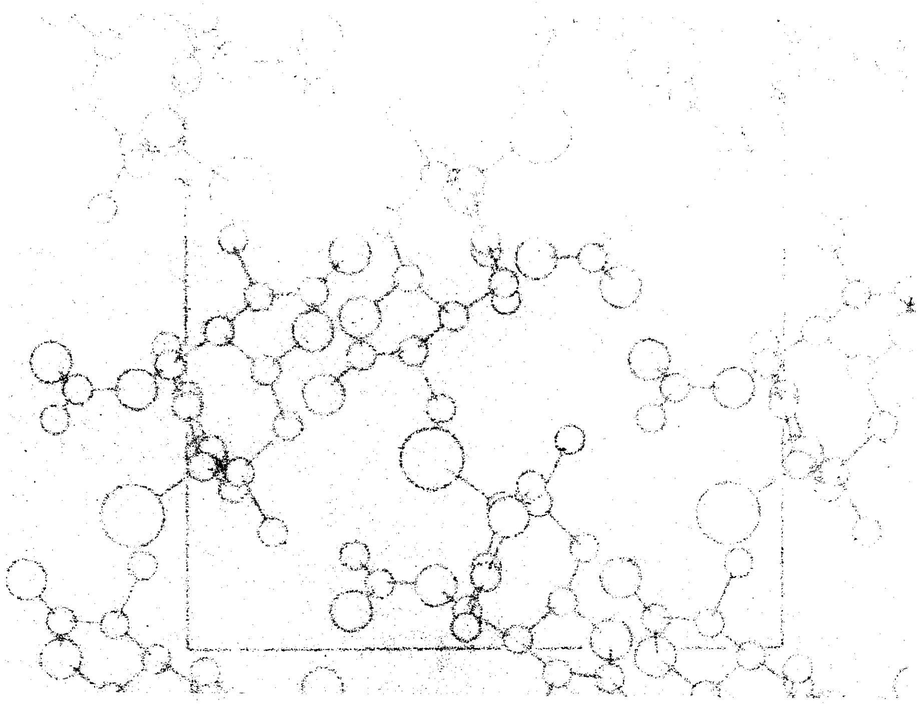
In the carbonyl groups the average carbon-oxygen distance is 1.25 Å. The length of a similar bond in the last three compounds mentioned is 1.28 Å, 1.23 Å and 1.20 Å respectively. These values are similar to those found in the carboxylic acids.

The carbon-bromine distance of 1.975 Å is in agreement with the average value of 1.937 ± 0.003 Å found in bromo derivatives of the paraffins such as bromoform (Williams et al. 1952). None of the individual bond lengths in acetylbromogeigerin differs significantly from the accepted value.

A short intermolecular contact between O_1 of the standard molecule and O_3 of the molecule defined by

$\frac{1}{2} + x$, $\frac{1}{2} - y$, $1 - z$ has a value of 3.07 Å. This is similar to a non-bonded oxygen-oxygen distance of 2.95 Å in the substituted cyclopentadiene structure described in Part V of this thesis.

In the crystal the molecules are held together by Van der Waals contacts. The arrangement of the molecules as seen in projection on the a axis is shown in Fig 5. Fig. 6 shows the molecule of acetylbromogeigern in projection on the (100).



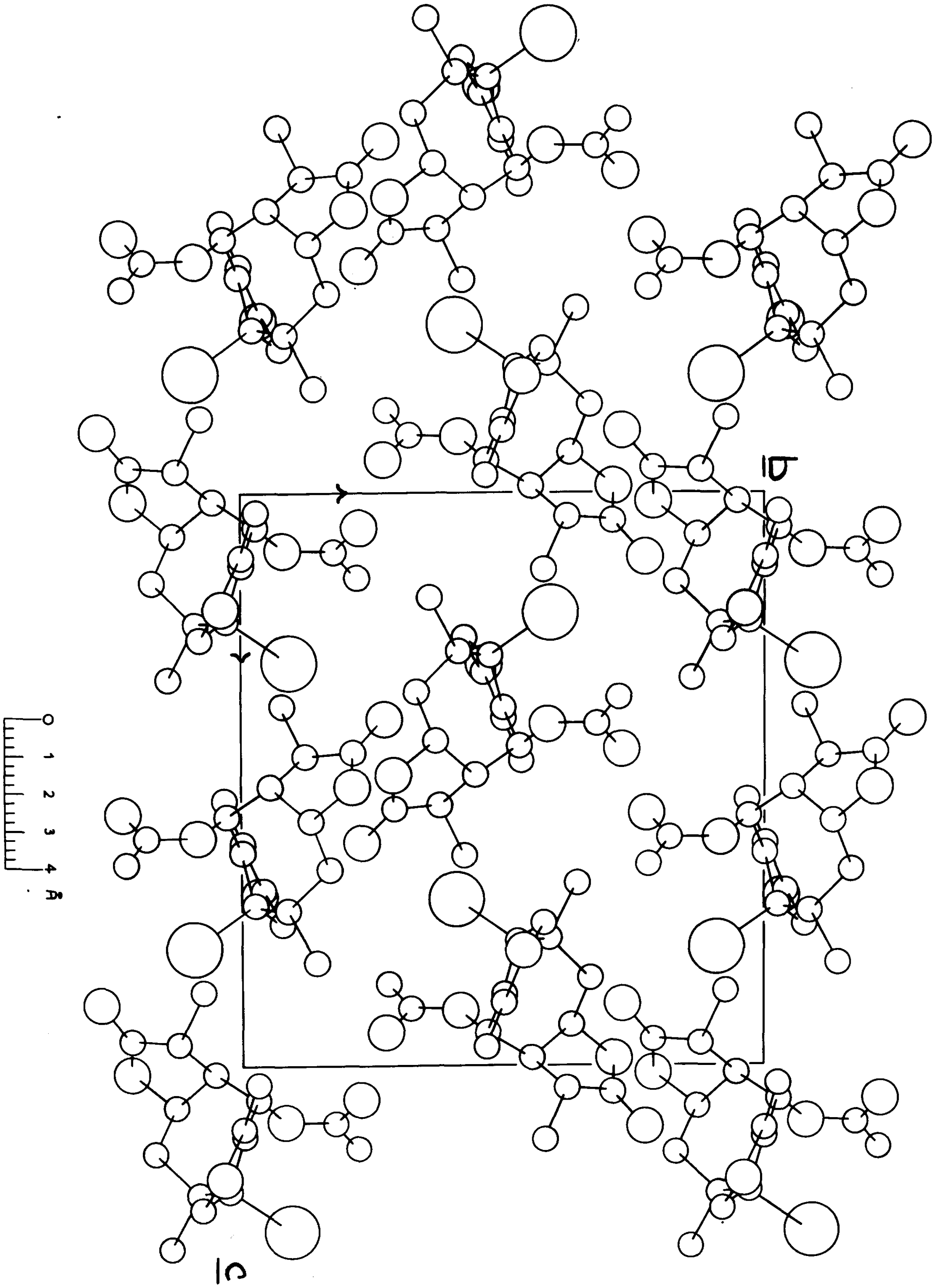


Fig. 5. The arrangement of molecules in the crystal as viewed in projection along the a axis.

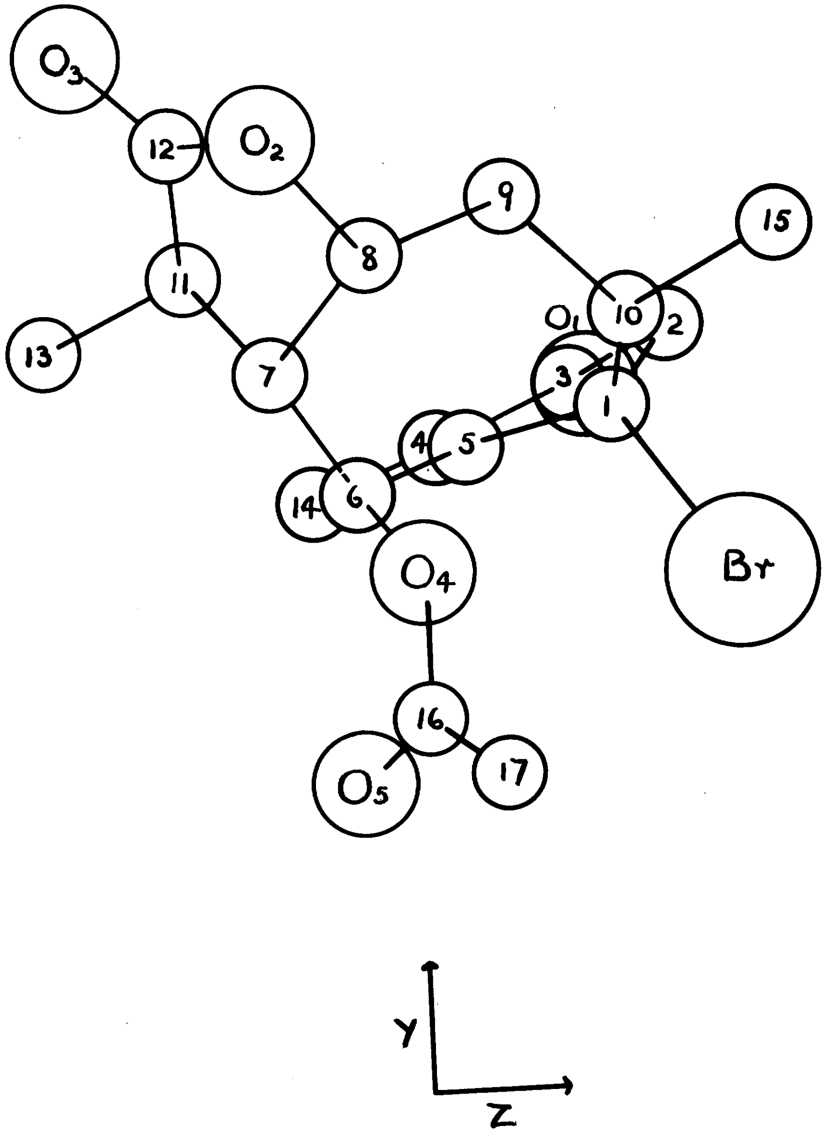


Fig. 6. The molecule of acetylbromogeigerin as seen in projection on the (100).

PART IV.

THE X-RAY STRUCTURE ANALYSIS OF CEDRELONE IODOACETATE

CEDRELONE IODOACETATE.

1. INTRODUCTION.

Cedrela Toona, a tree belonging to the natural order of Meliaceae, is found in abundance in the sub-Himalayan tract from the Indus eastwards. It grows to a height of 50 - 60 feet. The wood, which is brownish red with a faint aromatic odour, mainly due to the presence of a golden coloured essential oil, is used for medicinal purposes. It is also a source of dyestuff.

In view of the medicinal importance of the plant an investigation was undertaken by Parihar and Dutt, (1950), to study the active principles present. From the wood they isolated a 'supposed' lactone in 40% yield and an essential oil. Apart from an investigation of this essential oil no systematic work on the wood of the plant had been previously described. Parihar and Dutt stated that the lactone, which they named cedrelone, had a molecular formula $C_{25}H_{30}O_5$ and contained an ethylenic double-bond, one phenolic hydroxyl group, a ketonic group and a lactone ring. These data have since been proved to be inaccurate (Grant et al. 1961, Copinath et al. 1961).

The study of cedrelone was continued in the Chemistry Department of Glasgow University (Hodges et al.) and in Zurich (Copinath et al.). These workers showed that cedrelone has the formula $C_{26}H_{30}O_5$ and contains (from spectral evidence) a hydroxyl group, an $\alpha\beta$- unsaturated ketone and a furan ring

Spectral considerations also suggested the presence of a second enone function. No information was available however concerning the ring system of the compound when the X-ray structure analysis of the iodoacetate derivative was undertaken.

2.1 CRYSTAL DATA.

CEDRELONE IODOACETATE $C_{28}H_{31}O_6I$

Molecular weight 590.448

Melting point 149 - 150°C

Density calculated = 1.490 gm/cm^3

Density measured = 1.498 gm/cm^3

(By flotation using carbon tetrachloride and petroleum ether.)

The crystal is orthorhombic with

$\underline{a}$ = 6.97 ± 0.02 Å

$\underline{b}$ = 27.44 ± 0.03 Å

$\underline{c}$ = 13.74 ± 0.04 Å

Volume of the unit cell = 2628 Å^3

Number of molecules per unit cell = 4

Absent spectra

hoo when h is odd

oko when k is odd

ooℓ when ℓ is odd

Space group $P2_12_12_1(D_2^4)$

Linear absorption coefficient for X-rays (Cuk$_\alpha$ radiation) $\mu = 108\text{cm}^{-1}$

Total number of electrons per unit cell = F(ooo) = 1200

$\sum f^2$(light atoms) = 1423

$\sum f^2$(heavy atoms) = 2809

2.2 INTENSITY DATA.

Crystals of cedrelone iodoacetate in the form of small hexagonal plates were obtained from Mr. S.G. McGeachin, of the organic section of the Chemistry Department of Glasgow University. The crystal system was found from oscillation photographs to be orthorhombic and the unit cell parameters were determined from rotation and moving film photographs. The reciprocal lattice was explored by recording the intensities of the $0k\ell - 5k\ell$ and hko - hk6 layers with a Weissenberg camera. Intensities were estimated visually using the step-wedge technique and after the normal Lorentz, polarisation and Tunell factors had been applied 1163 structure amplitudes were evaluated. CuK$_\alpha$ radiation was used for all photography.

The space group $P2_12_12_1(D_2^4)$ was determined unambiguously from the systematic absences. It was noted that the data faded out rapidly on the photographs about both the <u>a</u> and <u>c</u> axes indicating a high temperature factor for the structure. Also the crystals were rather unstable and decomposed gradually during the period of photography.

This must result in certain inaccuracies in the observed structure amplitudes. No absorption corrections were applied.

2.3 DETERMINATION OF THE IODINE POSITION.

The two-dimensional Patterson maps, computed using the data from the $0k\ell$ and $hk0$ equatorial layers, are shown in Figs. 1 and 2. The iodine - iodine vector peaks are labelled A,B,C and D,E,F. Calculation of the iodine coordinates using these peak positions indicated that the fractional x coordinate of the iodine atom was 0.25. However since peaks A and B are elliptical the coordinate is obviously not exactly 0.25 but displaced slightly from it. It was decided to calculate this displacement since a fractional coordinate of 0.25 for the iodine atom would introduce spurious symmetry complications in the initial stages of a structure analysis using the heavy-atom phase-determining method.

The eccentricity of peak A was calculated since it is possible to relate this (Burns, 1955), to the separation of two peaks (2Δ), one on either side of the axis, which merge due to lack of resolution.

If the constituent peaks are situated at the points P_1 and P_2 giving rise to a resultant at P_o, the mid-point of the line joining P_1 and P_2, and if the coordinates of P_o, P_1, P_2 are $(x_o y_o)$, $(x_1 y_1)$ and $(x_2 y_2)$ respectively, referred to rectangular axes, then, since each of the constituent peaks can be adequately represented by a Gaussian function

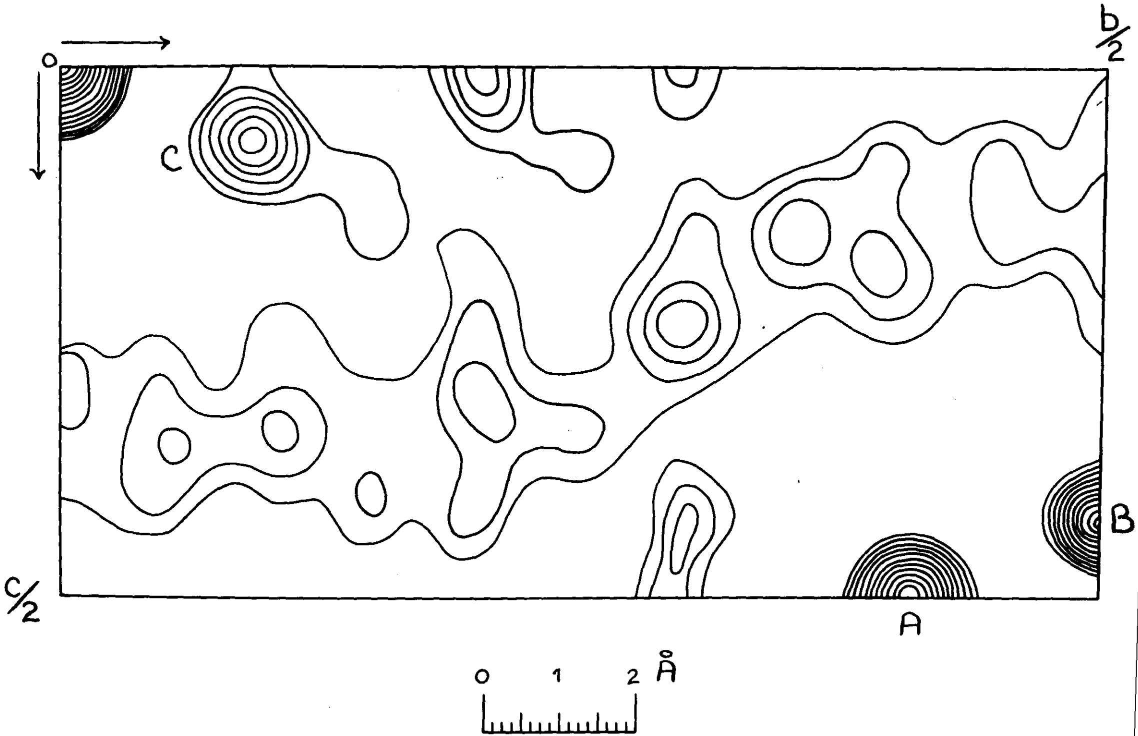


Fig. 1. Projection of Patterson function along the a axis. Contour scale arbitrary. The iodine-iodine vector peaks are marked A,B and C.

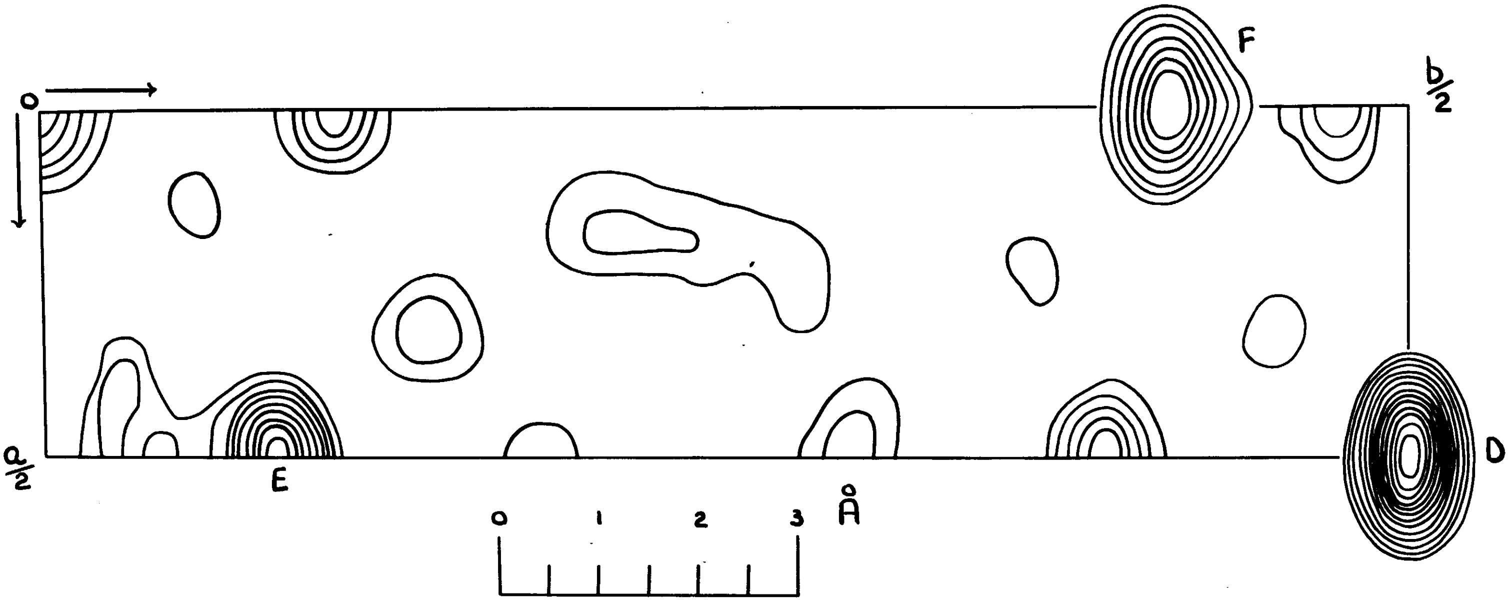


Fig. 2. Projection of Patterson function along the c axis. Contour scale arbitrary. The iodine-iodine vector peaks are marked D, E and F.

$$\rho(r) = \rho_o \exp(-pr^2)$$

the resultant electron density at the point (x,y) is given by

$$\rho(xy) = \rho_o \exp\left[-p\left\{(x-x_1)^2 + (y-y_1)^2\right\}\right] + \rho_o \exp\left[-p\left\{(x-x_2)^2 + (y-y_2)^2\right\}\right]$$

If the separation of the constituent peaks is 2Δ then

$$x_1 = x_o + \Delta_x \qquad y_1 = y_o + \Delta_y$$

$$x_2 = x_o - \Delta_x \qquad y_2 = y_o - \Delta_y$$

where Δ_x, Δ_y are the components of Δ. Hence the expression for the electron density becomes

$$(x,y) = 2\rho_o \exp\left[-p\left\{(x-x_o)^2 + (y-y_o)^2 + \Delta^2\right\}\right]$$
$$\left[\cosh 2p\left\{(x-x_o)\Delta_x + (y-y_o)\Delta_y\right\}\right]$$

If the logarithms of both sides are taken and only the first term of the expression

$$\ln \cosh u = \frac{u^2}{2} - \frac{u^4}{12} + \ldots \qquad \text{retained then}$$

$$\ln \rho(x,y) = \text{const} - p(1 - 2p\Delta_x^2)(x - x_o)^2$$
$$- p(1 - 2p\Delta_y^2)(y - y_o)^2$$
$$+ 4p^2\Delta_x \Delta_y (x - x_o)(y - y_o)$$

It can be seen from the above expressions that the electron density approximates to a series of ellipses with centre $P_o(x_o y_o)$. The eccentricity of the ellipses is given by the expression

$$\epsilon = \sqrt{2p}\,\Delta$$

The value of p is derived from the Gaussian function

$$\rho(r) = \rho_o \exp(-pr^2)$$

It can be determined from a plot of log. $\rho(r)$ against r^2. This is a straight line with negative gradient $\frac{p}{2.303}$ and intercept ρ_o.

Two methods are available for finding the eccentricity ϵ. The first involves drawing the elliptical vector peak of the iodine accurately and measuring the major and minor axes, whereupon the eccentricity is given by

$$\epsilon = \sqrt{1 - \frac{b^2}{a^2}}$$ where a,b are the major and minor axes respectively.

The second method is analytical and due to Ladell and Katz,(1954). In this method it is assumed that the peak resembles an elliptic paraboloid near the maximum. The value of the Patterson function at each point (x^1y^1) of the net is designated by $Z(x^1y^1)$. If the highest value of $Z(x^1y^1)$ is $Z(0,0)$ then the true maximum will be close to $Z(0,0)$. A good approximation to its true location can be determined from the value of $Z(0,0)$ and the values of the eight surrounding points. These nine values of the Patterson function are used to obtain the coefficients of the equation of the elliptic paraboloid.

$$Z(x,y) = Ax^2 + By^2 + Cxy + Dx + Ey + F$$

If K is the ratio of the repeat distances of the net then the values of the coefficients for the orthorhombic case are

$$F = Z(0,0)$$

$$A = \tfrac{1}{2}\left[Z(1,0) - Z(\bar{1},0) \right] - F$$

$$B = \tfrac{1}{2}\left[Z(1,0) - Z(\bar{1},0) \right]$$

$$E = \tfrac{1}{2}\left[Z(0,1) - Z(0,\bar{1})/K \right]$$

$$C = \tfrac{1}{4}\left[(g/K)\right]$$

$$D = \tfrac{1}{2}\left[Z(0,1) + Z(0,\bar{1}) - 2F/K^2 \right]$$

where $g = Z(1,1) + Z(\bar{1},\bar{1}) - Z(\bar{1},1) - Z(1,\bar{1})$

The eccentricity of the ellipse is then given by

$$\epsilon = \sqrt{1 - \frac{b^2}{a^2}} \quad \text{where}$$

$$\frac{b}{a} = \frac{A^1}{B^1}$$

A^1 being $\tfrac{1}{2}A\left[1 + \frac{(A-B)}{\psi}\right] + \tfrac{1}{2}B\left[1 - \frac{(A-B)}{\psi}\right] + \tfrac{1}{2}\frac{C^2}{\psi}$ and

B^1 being $\tfrac{1}{2}A\left[1 - \frac{(A-B)}{\psi}\right] + \tfrac{1}{2}B\left[1 + \frac{(A-B)}{\psi}\right] - \tfrac{1}{2}\frac{C^2}{\psi}$

where $\psi = \sqrt{\left[(A-B)^2 + C^2\right]}$

Both the graphical and analytical methods were used to determine the eccentricity of peak A in the case of cedrelone iodoacetate and from the values of Δ obtained a preliminary fractional coordinate of $x = 0.23$ was assigned to the iodine atom. Trial sets of structure factors computed with the two-dimensional data gave discrepancies of 61% and 55% when the fractional coordinates of the iodine atom in the $\underline{x}$ direction was 0.24 and 0.23 respectively.

2.4 STRUCTURE DETERMINATION.

Approximate phase constants were determined from a structure factor calculation based on the iodine coordinates. Using these phases a Fourier map was computed as sections parallel to (100). No information about the structure could be deduced from this map. The iodine coordinates obtained from the map were used to calculate better phase constants and a second Fourier map was calculated as sections parallel to (001) [to show more clearly the effects of the spurious symmetry.] However, no details of the structure could be determined from this map either. The difficulties encountered in attemps to solve the early electron density maps were due to the spurious symmetry and the high temperature factor which tended to make the atom peaks indistinct.

Nine of the most prominent peaks were chosen from the second Fourier synthesis and on the assumption that they were likely to be genuine, coordinates were assigned to them, and they were included in the third cycle of phasing calculations. The value of R dropped from 43% to 35.7%.

A third Fourier map was computed and coordinates were assigned to a further ten of the largest peaks. The coordinates of these nineteen peaks were entered with those of the iodine atom in the fourth structure factor calculation. However, the value of R merely dropped from 35.7% to 34.9%. The coordinates were then plotted on a two-dimensional Fourier map and those which did not fall on peaks were dropped from the fifth cycle of phasing calculations. In all five atoms were omitted. Inclusion of the remaining fifteen atoms lowered the discrepancy to 33.9% for the fifth cycle. The structure was solved from the subsequent Fourier map. Once the similarity of cedrelone iodoacetate to epilimonol iodoacetate (Arnott et al. 1961), had been realised a complete structure could be postulated.

Those atoms whose positions were certain were used to calculate the sixth set of structure factors and the fifth Fourier map revealed all the atoms clearly resolved. The correct chemical type was assigned to all the atoms except the oxygen in the furan ring and the seventh cycle of structure factors calculated over all the atoms gave a discrepancy of 27.4%.

The course of the analysis is shown in Table I. Atomic scattering values of Berghuis et al. (1955), were used for the light atoms and those of Thomas and Fermi (1935), for iodine, modified for anomalous dispersion as suggested by Dauben and Templeton, (1955). An average isotropic temperature factor of $B = 4.9\ \text{Å}^2$ was assumed.

2.5 STRUCTURE REFINEMENT

The atomic coordinates were refined initially by means of an F_o and F_c map. This also allowed the value of the over-all isotropic temperature factor to be adjusted from consideration of the peak heights. A second set of F_o, F_c

TABLE I

Course of analysis.

Operation		Data used	Atoms included	R(%)	$\sum w\Delta^2$
2D Patterson syntheses		okℓ and hko reflections	-----	-	-
1st 3D F_o	synthesis	1158 F_o	1 I	49	-
2nd "	"	1164 F_o	1 I	43	-
3rd "	"	1205 F_o	1 I + 9 C	35. 7	-
4th "	"	1227 F_o	1 I + 15 C	33.9	-
5th "	"	1285 F_o	1 I + 23 C + 50	29.6	-
6th "	"				
and 1st 3D F_c	"	1285	1 I + 29 C + 50	27.4	-
7th 3D F_o	"				
and 2nd 3D F_c	"	1285	1 I + 29 C + 50	24.2	-
1st Least-squares cycle		1285 F_o	1 I + 29 C + 50	20.5	10800
2nd "	"	1285 F_o	1 I + 29 C + 50	19.1	9800

TABLE I. (contd.)

Operation	Data used	Atoms included	R(%)	$\sum w\Delta^2$
3rd Least-squares cycle	1285 F_o	1 I + 29 C + 5O	18.4	8300
4th " "	1285 F_o	1 I + 29 C + 5O	18.0	7700
8th 3D F_o synthesis	1285 F_o	1 I + 29 C + 5O	17.5	-

1285 structure amplitudes were used in the phasing calculations.

In fact 122 of these were unobserved.

maps enabled different isotropic temperature factors to be assigned to the atoms. It was impossible from either of these cycles to distinguish the oxygen atom in the furan ring on the basis of peak heights.

Refinement was completed by four cycles of least-squares computation using anisotropic temperature factors for all atoms. After the fourth cycle the shifts in the atomic parameters were negligible. The discrepancy over the final set of structure factors was 17.5%. The course of analysis is shown in Table I.

2.6 MOLECULAR DIMENSIONS.

The final atomic coordinates are listed in Table II and the corresponding anisotropic thermal parameters in Table III. The final set of observed and calculated structure amplitudes is given in Table IV. The final electron density distribution over the molecule is shown in Fig 3 with the corresponding atomic arrangement in Fig. 4. A diagram of the molecule in projection along the <u>a</u> axis is given in Fig 5.

The bond lengths and interbond angles calculated from the coordinates listed in Table II are given in Tables V and VI respectively. The shorter intramolecular contacts are listed in Table VII and the intermolecular approach distances ($< 4 Å$) in Table VIII. The standard deviations in positional parameters calculated from the least-squares totals are shown in Table IX. The average standard deviation of a carbon-carbon bond

TABLE II.

Atomic Coordinates.

(Origin of coordinates as in "International Tables.")

Atom	x/a	y/b	z/c
C_1	-0.3157	-0.0520	0.1550
C_2	-0.3783	-0.0957	0.1406
C_3	-0.2634	-0.1337	0.1687
C_4	-0.1512	-0.1311	0.2654
C_5	-0.0985	-0.0781	0.2787
C_6	-0.0131	-0.0596	0.3679
C_7	0.0318	-0.0086	0.3925
C_8	0.0840	0.0185	0.2986
C_9	-0.0851	0.0093	0.2311
C_{10}	-0.1186	-0.0424	0.1949
C_{11}	-0.0764	0.0460	0.1412
C_{12}	-0.1651	0.0958	0.1854
C_{13}	-0.0779	0.1067	0.2925
C_{14}	0.0798	0.0744	0.3175
C_{15}	0.0235	0.1024	0.3824
C_{16}	0.1063	0.1495	0.3960

TABLE II. (contd.)

Atom	x/a	y/b	z/c
C_{17}	-0.0109	0.1585	0.3085
C_{18}	-0.2785	0.0931	0.3694
C_{19}	0.0544	-0.0578	0.1154
C_{20}	-0.1626	0.2006	0.3251
C_{21}	-0.2756	0.2147	0.4005
C_{22}	-0.3139	0.2093	0.2532
C_{23}	-0.4079	0.2487	0.2789
C_{28}	-0.2911	-0.1504	0.3437
C_{29}	0.0410	-0.1661	0.2702
C_{30}	0.2710	0.0030	0.2637
C_{31}	0.1412	-0.1035	0.4855
C_{32}	0.1435	-0.1425	0.5768
O_A	-0.2808	-0.1767	0.1316
O_B	-0.0223	-0.0932	0.4444
O_C	0.0597	0.0047	0.4678
O_D	0.2559	0.0974	0.2779
O_E	-0.3849	0.2467	0.3740
O_F	0.2847	-0.0888	0.4452
I	0.2808	-0.2054	0.5353

TABLE III.

Anisotropic temperature-factor parameters ($b_{ij} \times 10^5$).

	b_{11}	b_{22}	b_{33}	b_{12}	b_{23}	b_{13}
C_1	3743	243	642	597	124	-2186
C_2	5176	238	558	-282	461	0
C_3	8289	213	768	-1498	177	3246
C_4	3464	188	729	-166	82	-1779
C_5	3791	138	730	1007	178	-1821
C_6	4980	163	523	249	359	0
C_7	5221	386	426	-1494	678	-2774
C_8	3979	134	389	502	567	0
C_9	1678	103	955	-211	58	-2396
C_{10}	5893	315	658	-243	381	1248
C_{11}	7183	240	1047	201	241	0
C_{12}	5452	140	1301	432	158	1120
C_{13}	3849	277	514	652	-196	3074
C_{14}	2400	277	439	761	- 51	0
C_{15}	6076	164	562	312	- 82	-1924
C_{16}	6744	142	829	595	265	-1385
C_{17}	3669	170	1017	-702	- 98	1171
C_{18}	411	181	1113	204	132	- 280
C_{19}	2492	324	528	0	-153	3237

TABLE III (contd.)

	b_{11}	b_{22}	b_{33}	b_{12}	b_{23}	b_{13}
C_{20}	7048	298	274	1308	749	2656
C_{21}	6734	550	850	658	87	1876
C_{22}	4880	257	1400	-328	-404	-4043
C_{23}	11336	186	1440	0	381	0
C_{28}	5574	250	1065	-440	-102	0
C_{29}	8943	266	928	379	-443	0
C_{30}	1576	284	1012	649	304	3046
C_{31}	3786	239	1319	-254	-431	979
C_{32}	2258	424	925	-350	- 25	0
O_A	9457	283	901	14	-498	660
O_B	4094	247	855	-575	65	-2712
O_C	6168	216	402	-297	236	2189
O_D	2497	179	941	-419	- 64	2861
O_E	11733	143	1192	1981	367	1894
O_F	6717	210	790	513	186	0
I	6717	183	983	356	- 34	-438

Table IV. Measured and calculated values of the structure factors.

h	k	l	$\|F_o\|$	$\|F_c\|$	α
0	0	2	43	20	180
		4	48	57	0
		6	[illegible]	83	0
		8	< 11	1	0
		10	48	45	180
0	1	1	94	157	90
		2	[illegible]	61	270
		3	[illegible]	[illegible]	90
		4	10	4	90
		5	78	73	90
		6	53	49	270
		7	10	[illegible]	270
		8	51	51	90
		9	51	54	270
		10	[illegible]	15	270
		11	58	51	270
0	2	1	43	[illegible]	180
		2	162	143	180
		3	[illegible]	89	180
		4	74	72	180
		5	55	57	180
		6	< 9	13	180
		7	46	47	180
		8	20	11	0
		9	< 12	9	0
		10	[illegible]	[illegible]	0
		11	[illegible]	41	180
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

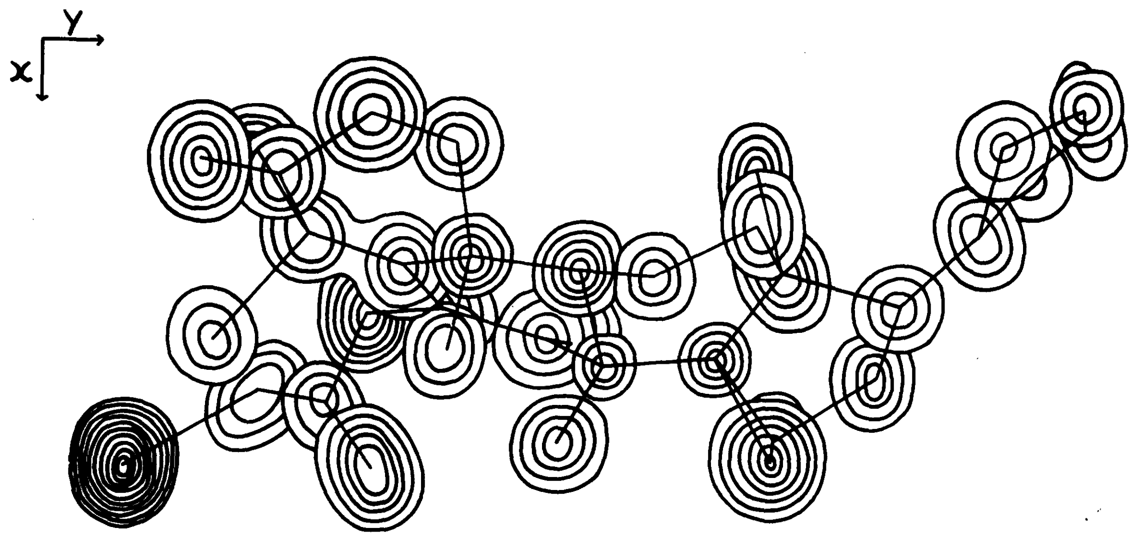


Fig. 3 The final three-dimensional electron-density distribution for cedrelone iodoacetate. The superimposed contour sections are drawn parallel to (00I). Contour level 1 e Å^{-3} except around the bromine atom where it is 5 e Å^{-3}. The first contour level is omitted in both cases.

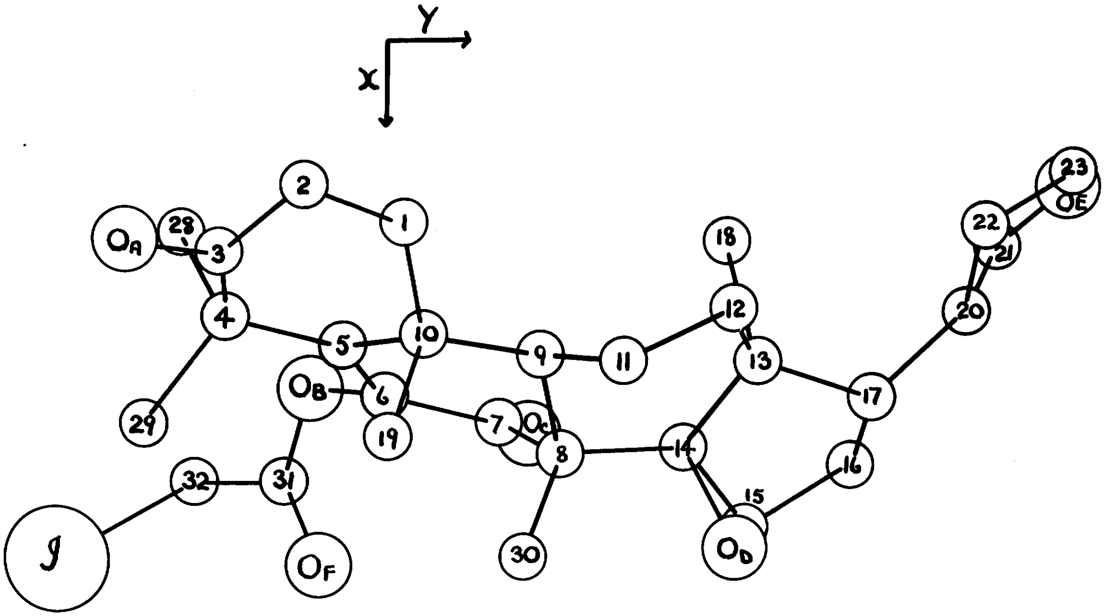


Fig. 4. Atomic arrangement corresponding to Fig. 3.

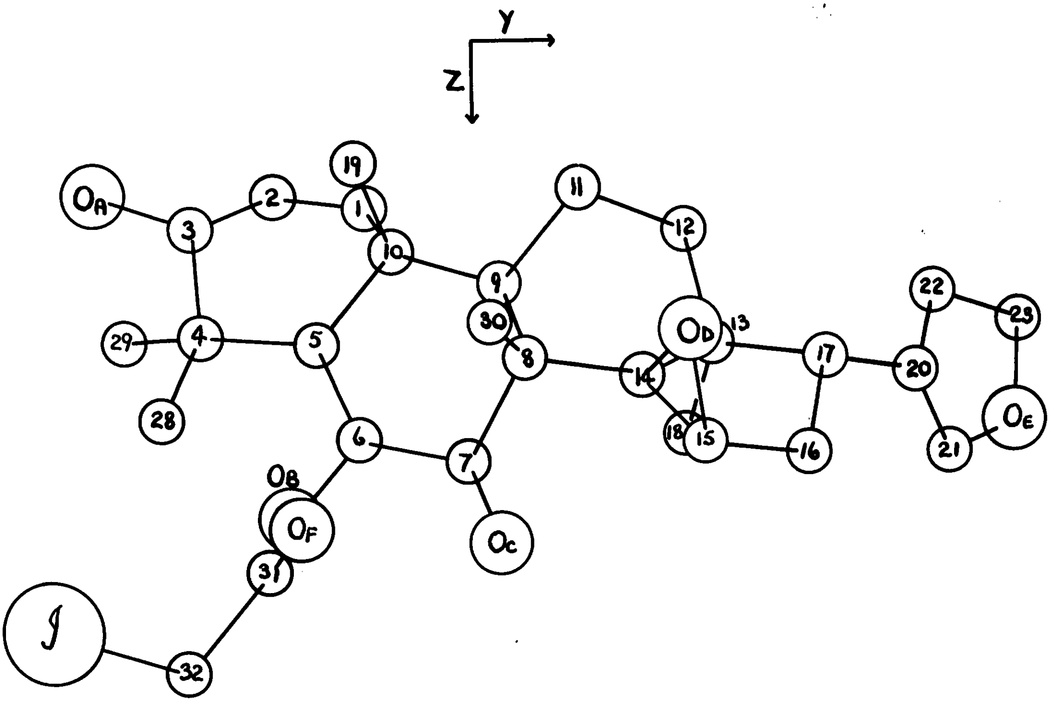


Fig. 5. The arrangement of atoms in the molecule as viewed in projection along the <u>a</u> axis.

MOLECULAR DIMENSIONS.

INTERATOMIC DISTANCES (Å) AND ANGLES

TABLE V.

Intramolecular bonded distances.

C_1 - C_2	1.29		C_8 - C_{30}	1.45
C_1 - C_{10}	1.50		C_9 - C_{10}	1.52
C_2 - C_3	1.37		C_9 - C_{11}	1.59
C_3 - C_4	1.54		C_{10} - C_{19}	1.68
C_3 - O_A	1.29		C_{11} - C_{12}	1.62
C_4 - C_5	1.51		C_{12} - C_{13}	1.62
C_4 - C_{28}	1.55		C_{13} - C_{14}	1.45
C_4 - C_{29}	1.65		C_{13} - C_{17}	1.51
C_5 - C_6	1.45		C_{13} - C_{18}	1.79
C_5 - C_{10}	1.52		C_{14} - C_{15}	1.55
C_6 - C_7	1.48		C_{14} - O_D	1.48
C_6 - O_B	1.40		C_{15} - C_{16}	1.54
C_7 - C_8	1.53		C_{15} - O_D	1.46
C_7 - O_C	1.11		C_{16} - C_{17}	1.47
C_8 - C_9	1.52		C_{17} - C_{20}	1.58
C_8 - C_{14}	1.56		C_{20} - C_{21}	1.36

TABLE V. (contd.)

C_{20} - C_{22}	1.47	C_{31} - C_{32}	1.65
C_{21} - O_E	1.22	C_{31} - O_B	1.30
C_{22} - C_{23}	1.31	C_{31} - O_F	1.21
C_{23} - O_E	1.32	I - C_{32}	2.05

TABLE VI.

Interbond angles.

C_2	C_1	C_{10}	122	C_7	C_8	C_9	104
C_1	C_2	C_3	118	C_7	C_8	C_{14}	110
C_2	C_3	C_4	120	C_7	C_8	C_{30}	110
C_2	C_3	O_A	122	C_9	C_8	C_{14}	105
C_4	C_3	O_A	115	C_9	C_8	C_{30}	117
C_3	C_4	C_5	106	C_{14}	C_8	C_{30}	111
C_3	C_4	C_{28}	105	C_8	C_9	C_{10}	118
C_3	C_4	C_{29}	115	C_8	C_9	C_{11}	110
C_5	C_4	C_{28}	114	C_{10}	C_9	C_{11}	110
C_5	C_4	C_{29}	111	C_1	C_{10}	C_5	104
C_{28}	C_4	C_{29}	107	C_1	C_{10}	C_9	115
C_4	C_5	C_6	123	C_1	C_{10}	C_{19}	112
C_4	C_5	C_{10}	120	C_5	C_{10}	C_9	110
C_6	C_5	C_{10}	117	C_5	C_{10}	C_{19}	105
C_5	C_6	C_7	128	C_9	C_{10}	C_{19}	110
C_5	C_6	O_B	113	C_9	C_{11}	C_{12}	103
C_7	C_6	O_B	118	C_{11}	C_{12}	C_{13}	111
C_6	C_7	C_8	109	C_{12}	C_{13}	C_{14}	113
C_6	C_7	O_C	124	C_{12}	C_{13}	C_{17}	115
C_8	C_7	O_C	126	C_{12}	C_{13}	C_{18}	102

TABLE VI. (contd.)

C_{14}	C_{13}	C_{17}	108	C_{13}	C_{14}	C_{15}	109
C_{14}	C_{13}	C_{18}	109	C_{13}	C_{14}	O_D	106
C_{17}	C_{13}	C_{18}	111	C_{15}	C_{14}	O_D	58
C_8	C_{14}	C_{13}	125	C_{14}	C_{15}	C_{16}	98
C_8	C_{14}	C_{15}	125	C_{14}	C_{15}	O_D	59
C_8	C_{14}	O_D	110				

<u>TABLE VII.</u>

<u>Intramolecular non-bonded distances.</u>

C_1	... C_4	2.89	C_5	... O_A	3.61
C_1	... C_{11}	3.17	C_5	... O_C	3.62
C_1	... C_{28}	3.75	C_5	... O_F	3.53
C_1	... O_A	3.44	C_6	... C_9	2.71
C_2	... C_5	2.76	C_6	... C_{19}	3.50
C_2	... C_9	3.74	C_6	... C_{28}	3.17
C_2	... C_{19}	3.21	C_6	... C_{29}	3.24
C_2	... C_{28}	3.23	C_6	... C_{30}	2.99
C_2	... C_{29}	3.93	C_6	... C_{32}	3.82
C_3	... C_6	3.83	C_6	... O_F	2.47
C_3	... C_{10}	2.72	C_7	... C_{10}	3.06
C_3	... C_{19}	3.13	C_7	... C_{11}	3.84
C_4	... C_9	3.91	C_7	... C_{13}	3.53
C_4	... C_{19}	3.22	C_7	... C_{15}	3.33
C_4	... C_{31}	3.72	C_7	... C_{18}	3.54
C_4	... O_B	2.82	C_7	... C_{31}	3.00
C_5	... C_8	2.95	C_7	... O_D	3.66
C_5	... C_{11}	3.90	C_7	... O_F	2.91
C_5	... C_{30}	3.41	C_8	... C_{12}	3.15
C_5	... C_{31}	3.37	C_8	... C_{16}	3.84

TABLE VII. (contd.)

C_8	... C_{17}	3.90	C_{29}	... C_{31}	3.49
C_8	... C_{18}	3.39	C_{29}	... O_A	2.96
C_{18}	... C_{20}	3.12	C_{29}	... O_B	3.15
C_{18}	... C_{21}	3.37	C_{29}	... O_F	3.63
C_{18}	... C_{22}	3.58	C_{30}	... O_C	3.17
C_{18}	... O_C	3.64	C_{30}	... O_D	2.60
C_{18}	... O_D	3.93	C_{30}	... O_F	3.55
C_{19}	... C_{29}	3.65	C_{31}	... O_C	3.03
C_{19}	... C_{30}	3.04	O_B	... O_C	2.76
C_{28}	... C_{31}	3.81	O_C	... O_D	3.89
C_{28}	... O_A	3.00	O_C	... O_F	3.02
C_{28}	... O_B	2.81			

TABLE VIII.

Intermolecular distances ($< 4\ \mathring{A}$).

$C_{32} \cdots O_D^{I}$	3.11	$C_{15} \cdots C_{19}^{I}$	3.76
$O_E \cdots O_A^{IV}$	3.14	$C_{32} \cdots C_{22}^{II}$	3.81
$C_{23} \cdots O_A^{IV}$	3.23	$C_{23} \cdots C_{28}^{IV}$	3.86
$O_C \cdots C_1^{II}$	3.35	$C_{32} \cdots C_{12}^{II}$	3.87
$C_{21} \cdots O_A^{II}$	3.36	$C_{18} \cdots C_2^{II}$	3.88
$C_{23} \cdots C_{29}^{III}$	3.53	$O_E \cdots C_{29}^{III}$	3.92
$O_F \cdots C_{11}^{I}$	3.57	$C_{22} \cdots C_{29}^{III}$	3.93
$O_C \cdots C_{19}^{I}$	3.67	$O_B \cdots C_{12}^{II}$	3.96
$O_C \cdots C_2^{II}$	3.67	$C_{20} \cdots C_{29}^{III}$	3.98

The superscripts refer to the following positions:

I	$\frac{1}{2} - x,$	$-y$,	$\frac{1}{2} + z$
II	$-\frac{1}{2} - x,$	$-y$,	$\frac{1}{2} - z$
III	$-x$,	$\frac{1}{2} + y,$	$\frac{1}{2} - z.$
IV	$-1 - x,$	$\frac{1}{2} + y,$	$\frac{1}{2} - z$

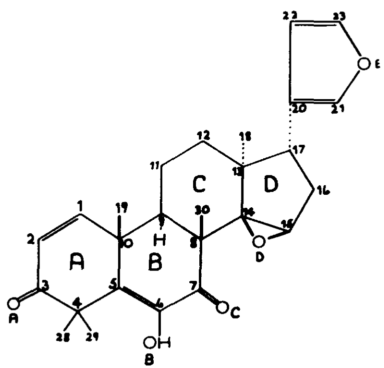
TABLE IX.

Standard deviations of the final atomic coordinates (Å)

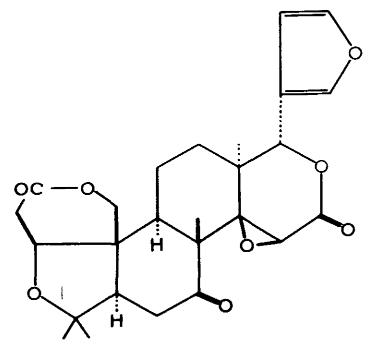
Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
C_1	0.059	0.042	0.046
C_2	0.058	0.045	0.044
C_3	0.069	0.042	0.043
C_4	0.051	0.043	0.047
C_5	0.049	0.038	0.044
C_6	0.061	0.040	0.044
C_7	0.064	0.051	0.049
C_8	0.056	0.041	0.046
C_9	0.047	0.035	0.048
C_{10}	0.072	0.050	0.048
C_{11}	0.068	0.049	0.055
C_{12}	0.063	0.042	0.051
C_{13}	0.054	0.047	0.044
C_{14}	0.053	0.047	0.041
C_{15}	0.069	0.038	0.043
C_{16}	0.059	0.040	0.050
C_{17}	0.055	0.041	0.049
C_{18}	0.051	0.036	0.047

TABLE IX. (contd.)

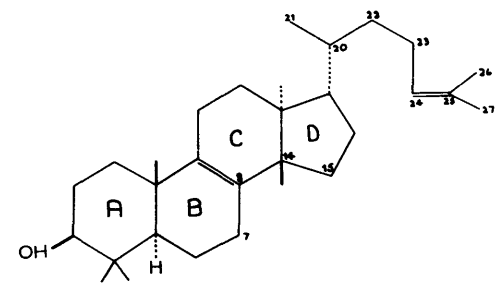
Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
C_{19}	0.053	0.048	0.050
C_{20}	0.059	0.048	0.043
C_{21}	0.069	0.058	0.055
C_{22}	0.050	0.046	0.053
C_{23}	0.084	0.046	0.063
C_{28}	0.067	0.046	0.051
C_{29}	0.075	0.050	0.055
C_{30}	0.063	0.045	0.044
C_{31}	0.052	0.045	0.056
C_{32}	0.057	0.058	0.051
O_A	0.051	0.031	0.032
O_B	0.037	0.028	0.030
O_C	0.037	0.028	0.033
O_D	0.033	0.024	0.027
O_E	0.078	0.042	0.058
O_F	0.042	0.026	0.028
I	0.004	0.003	0.004



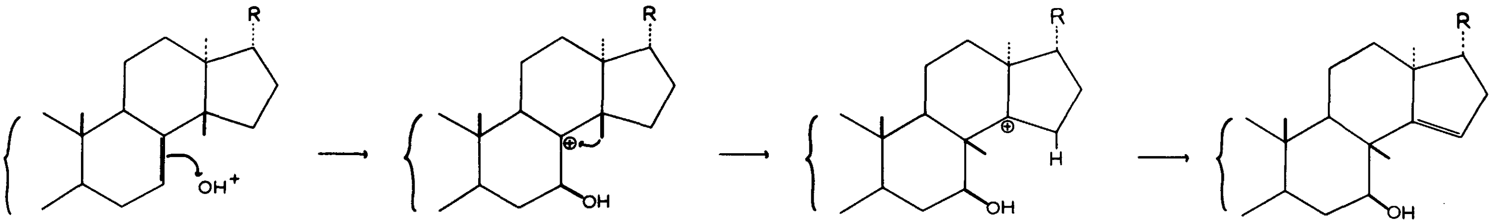
I



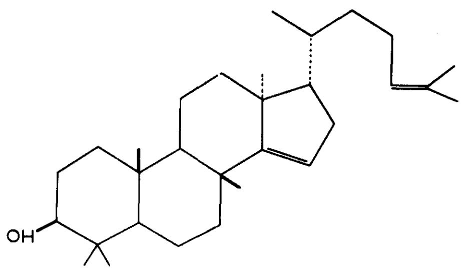
II



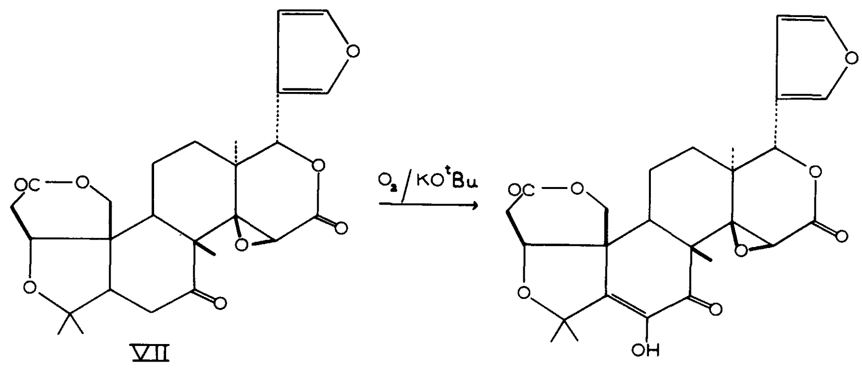
III



IV → → → V



VI



VII → VIII

is 0.09 Å, that of a carbon-oxygen bond 0.07 Å and of the carbon-iodine bond 0.06 Å. The standard deviation in bond angle is 4°

2.7 DISCUSSION.

The establishing of the structure of cedrelone iodoacetate was the primary objective of this analysis. From structural and stereochemical considerations cedrelone (I) like limonin (II) is clearly a triterpenoid of the euphol type (III). This class of triterpenoids is characterised by the presence of a carbonyl function at C_7, a methyl at C_8 and an epoxide ring between C_{14} and C_{15}. Barton et al (1961), have proposed a biogenetic route to limonin, and cedrelone can be assumed to occur in a similar fashion.

By means of a prototropic shift of a hydrogen atom from C_7 in a precursor of the euphol type, a $\Delta^{7,8}$ unsaturated intermediate is formed which undergoes oxygenation at C_7 by means of attack of the double bond by (OH^+) or its equivalent. A Wagner-Meerwein migration of the methyl group from C_{14} to C_8 followed by a loss of a proton from C_{15} leads as shown (IV - V) to a structure of the apoeuphol type (VI). Reactions carried out by various workers in the field support this hypothesis (Lawrie et al. 1956). Loss of four carbon atoms from the side chain with cyclisation of the remainder C_{20} - C_{23} affords the furan ring. Further oxidation in rings A and D give rise to the remaining oxygen functions of limonin.

In cedrelone ring D is not oxydised to a δ - lactone

It is the only member of this class of compounds so far isolated in which this is so. It is also unusual in being a diosphenol of which relatively few examples occur naturally. However it has been observed (Lawrie et al. 1956), that oxidation of limonin and its derivatives to diosphenols of this type is easily carried out by means of oxygen in the presence of potassium t - butoxide (VII - VIII).

In cedrelone ring C adopts a boat conformation and ring A a half-boat confirmation. The latter stereochemical feature is presumably due to steric interaction between the 28 and 29 methyl groups and the oxygen substituent at position 6. From measurements on a standard model the $O_A - C_{28}$ distance is 2.7 Å whereas that of the $O_A - C_{29}$ distance is 3.4 Å. From Table VII it can be seen that $O_A - C_{28}$ is 2.96 Å and $O_A - C_{29}$ is 3.00 Å. The stereochemistry shown in (I) is only the relative stereochemistry. No absolute configuration has yet been determined.

It was impossible at any stage of the refinement to distinguish the oxygen atom of the furan ring from consideration either of temperature factors or peak heights. It is possible that the furan ring which is normally free to rotate adopts a different configuration in different positions in the crystal structure. This would account for the difficulties encountered. The bond lengths in the ring, Table V, show some evidence for the configuration shown in (I).
As was inferred from the initial photographs, the temperature

factors are all high and markedly anisotropic (Table III). The elliptical nature of the atoms can be seen in the diagram of the final electron density distribution over the molecule Fig. 3.

The average single-bond length between carbon($\underline{sp}^3$) atoms is 1.55 Å which is not significantly different from the value of 1.545 Å in diamond. The length of a similar bond in two other compounds of this type epilimonol iodoacetate (Arnott _et al_ 1961), and guarigenyl iodoacetate (Sutherland, unpublished papers), is 1.52 Å and 1.55 Å respectively. None of the individual carbon-carbon single-bond lengths can be regarded as significantly different from the standard value. The distance carbon($\underline{sp}^3$) - carbon($\underline{sp}^2$) is also 1.55 Å. However, this is not significantly different from the accepted value of 1.525 Å. The average carbon-carbon double-bond length is 1.35 Å which compares reasonably with that of 1.337 ± 0.006 given in Tables of Interatomic Distances, 1958.

In the two carbonyl groups the average carbon-oxygen distance is 1.20 Å which agrees with the value of 1.22 ± 0.02 Å for the carbonyl distance in acraldehyde ($CH_2 = CH.CHO$). (Tables of Interatomic Distances, 1958). The carbon-oxygen single-bond distance 1.30 Å in the grouping $-\,O-\underset{\underset{O}{\|}}{C}-C-I$ compares well with the value of 1.32 Å in epilimonol iodoacetate and in general with the values in carboxylic acids.

In the epoxide ring the average carbon-oxygen distance is 1.47 Å which is similar to values of 1.436 Å and 1.472 Å quoted for ethylene oxide (Erlandsson, 1955), and cyclopentene oxide (Cunningham <u>et al</u>. 1951), measured from micro-wave spectra. The value for the carbon-oxygen distance in the epoxide ring of epilimonol iodoacetate is 1.53 ± 0.08 Å, for guarigenyl iodoacetate 1.40 ± 0.08 Å and 1.49 Å for clerodin bromolactone

Comparison of the bond lengths within the furan ring with those given for furan itself viz:- carbon-oxygen 1.372 Å, carbon-carbon double-bond length 1.355 Å and carbon-carbon 1.433 Å (Bak <u>et al</u>. 1955) shows that there is no significant deviation from the expected values although the carbon-oxygen distance of 1.22 Å is rather short. Table X shows a comparison of the distances in the furan ring for epilimonol iodoacetate and guarigenyl iodoacetate.

In the iodoacetate group the distances are normal and the carbon-iodine bond length of 2.15 Å compares favourably with the value of 2.12 Å for epilimonol iodoacetate, 2.10 Å for guarigenyl iodoacetate and the value of 2.14 Å quoted for alkyl iodides (Miller, 1952., Lister, 1941). In general the molecular dimensions agree within the estimated standard deviation with those in epilimonol iodoacetate, guarigenyl iodoacetate and with accepted values.

One interesting intramolecular non-bonded distance is that between C_{19} and C_{30}. From measurements on a standard model this distance is 2.6 Å. The length calculated from the

TABLE X.

Comparison of the bond lengths in some furan rings.

Compound	Bond lengths C – C Å	C – O Å	C = C Å	$\sigma(\ell)$ Å	Reference.
Furan	1.433	1.372	1.355	---	Bak *et al.* 1955.
Cedrelone Iodoacetate	1.46	1.32 1.22	1.34	0.09	This thesis
Epilimonol "	1.44	1.42	1.25	0.08	Arnott *et al.* 1961.
Guarigenyl "	1.45	1.36 1.25	1.25	0.08	Sutherland (unpublished results.)

final coordinates is 3.04 Å. This steric repulsion between the 1,3 axial methyl groups is reflected in the angle $C_8\ C_9\ C_{10}$ in ring C which at 119° is greater than the expected tetrahedral value. All other non-bonded intramolecular distances and intermolecular distances are normal.

The equation of the mean plane through the furan ring is

$$0.651X + 0.750Y - 0.115Z - 7.238 = 0.$$

The deviations of the atoms from the plane are shown in Table XI. Application of the χ^2 - test to these deviations suggested that they are possibly significant. It is difficult, however, to see any chemical reason for non-planarity.

The contents of the unit cell are shown in projection along the c axis in Fig. 6 and along the a axis in Fig. 7. In the crystal the molecules are held together by Van der Waals contacts.

TABLE XI.

Displacements (Å) of atoms from the mean plane through C_{20} C_{21} C_{22} C_{23} O_E.

C_{17}	0.020
C_{20}	0.180
C_{21}	-0.160
C_{22}	-0.213
C_{23}	0.130
O_E	0.044

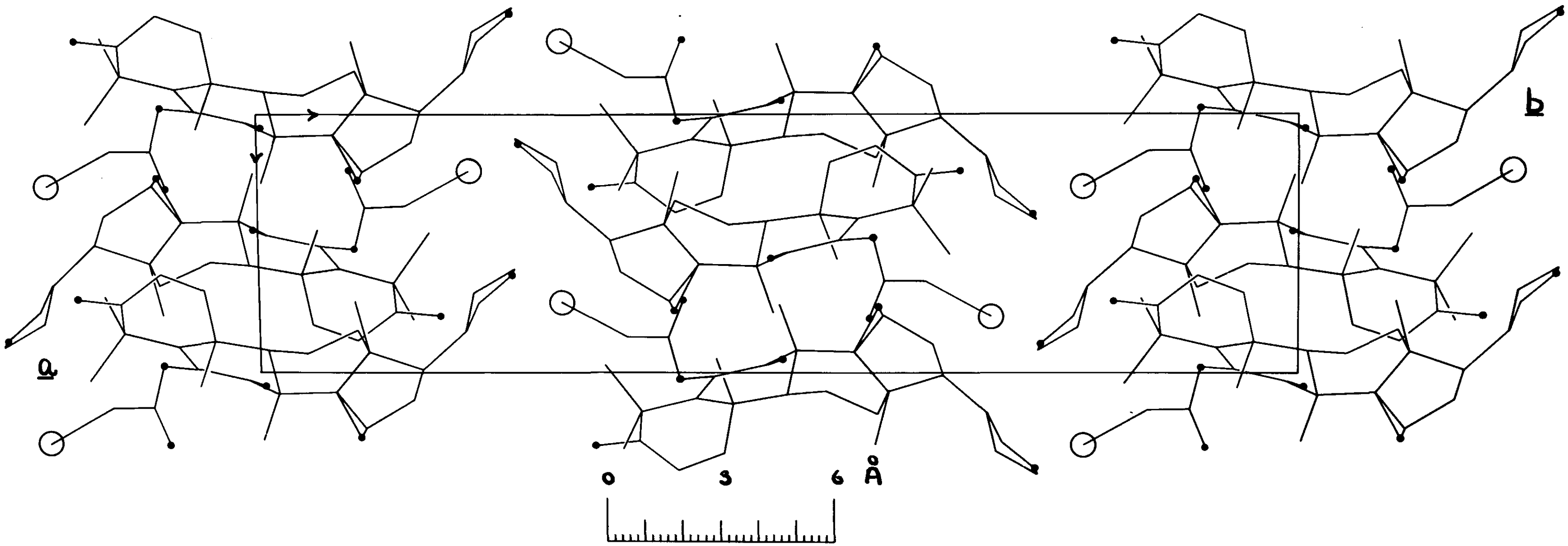


Fig. 6. The crystal structure of cedrelone iodoacetate as viewed in projection along the c axis.

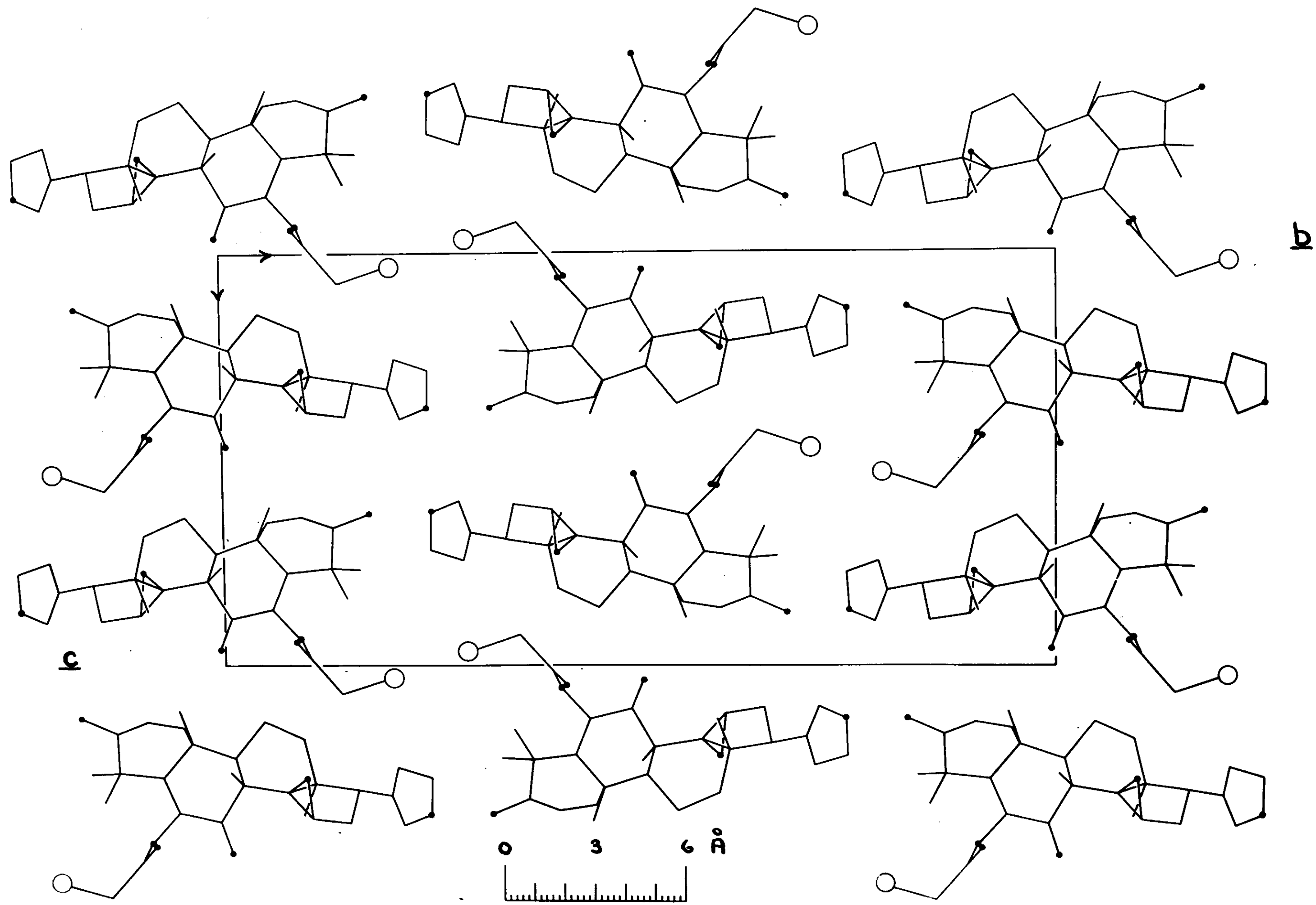
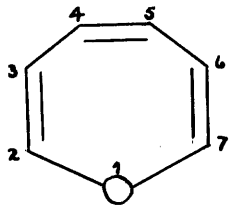


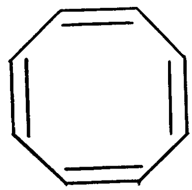
Fig. 7. The crystal structure of cedrelone iodoacetate as viewed in projection along the a axis.

PART V.

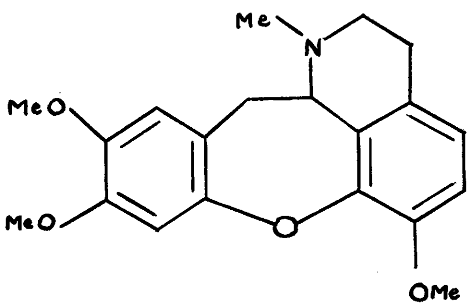
THE X-RAY STRUCTURE ANALYSIS OF A 'SUPPOSED OXEPIN'.



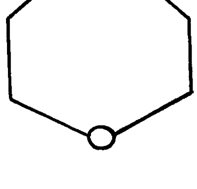
(I).



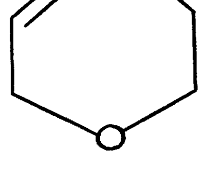
(II).



(III).



(IV).



(V).

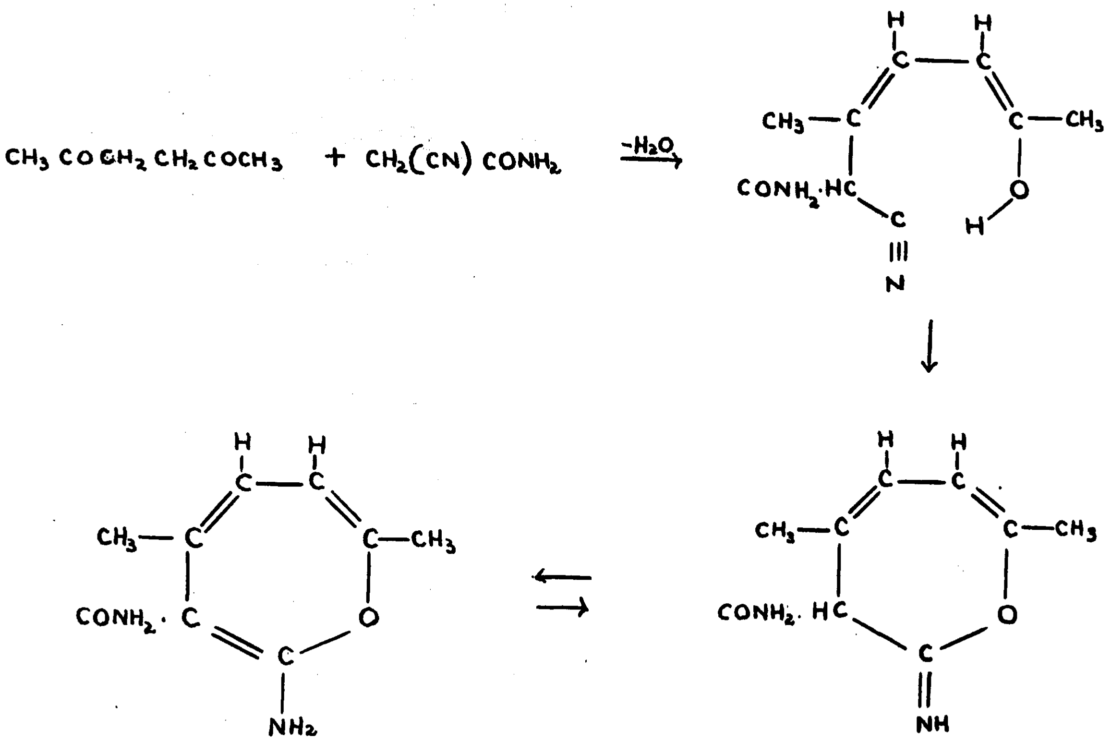
A 'SUPPOSED' OXEPIN.

1 INTRODUCTION.

Simple heterocyclic compounds such as oxepin (I) are of considerable theoretical interest to organic chemists since they bear the same electronic relationship to cyclooctatetraene (II) as furan and pyrrole do to benzene. This comparison is especially intriguing since models reveal that the seven-membered heterocycles in contrast to cyclooctatetraene can attain planarity with a relatively small amount of steric strain.

Several workers (Braunholtz and Mann, 1957, Dimroth and Freyschlag, 1957), investigated the chemistry of benzo-derivatives of oxepin, when it became known that the alkaloid cularine (III) involved a dibenzdihydro-oxepin skeleton (Manske, 1950). Syntheses of two tetrahydro derivatives of oxepin have also been reported (IV) and (V). [Olsen and Bredoch, 1958, Meinwald and Nozaki, 1958.]

Until 1959 however, in spite of efforts of many investigators, no one had published a synthesis of the parent oxepin or a derivative containing a single oxepin ring. It was all the more surprising, therefore, when Gunnel Westöö (1959), described a one-step reaction between an alkaline solution of acetonyl acetone and cyanoacetamide leading to the formation of 2-amino-4, 7- dimethyl -3-carbonamide oxepin (VI) according to the equation:-



(VI).

Measurements of infra-red spectra are quoted in support of this structure and a few reactions are described. No concrete structural evidence is offered.

Dr. G. Buchanan of the Chemistry Department of Glasgow University expressed doubt as to the validity of this structure. He performed the above reaction from the given method and obtained a sample of the compound which agreed with the infra-red spectra and other evidence given. However, all attempts to confirm the structure by degradation either failed to have any effect or completely destroyed the compound. He prepared a salt derivative by reaction of the compound with cold acqueous hydrobromic acid. It is unlikely that the latter affects the rest of the structure since crystals of the hydrobromide were obtained immediately on mixing.

2.1 CRYSTAL DATA

MOLECULAR FORMULA.	$C_9H_{13}N_2O_2Br.H_2O$
Molecular weight	279.026
Melting point	230 - 260°C (decomposition)
Density calculated	= 1.589 gm/cm^3
Density measured	= 1.588 gm/cm^3

(By flotation using carbon tetrachloride and petroleum ether 80 - 100)

The crystal is monoclinic with

$\underline{a}$ = 8.44 ± 0.01 Å

$\underline{b}$ = 7.45 ± 0.02 Å

$\underline{c}$ = 19.05 ± 0.01 Å

β = 102.9° ± 15'

Volume of the unit cell = 1167 Å^3

Number of molecules per unit cell = 4

Absent spectra

$h0\ell$ when ℓ is odd

$0k0$ when k is odd

Space group $P2_1/C$ (C^5_{2h})

Linear absorption coefficient for X-rays (CuK_α radiation) $\mu = 49cm^{-1}$

Total number of electrons per unit cell = F(000) = 564

$\sum f^2$(light atoms) = 629

$\sum f^2$(heavy atoms) = 1296

2.2 INTENSITY DATA.

Crystals of the hydrobromide of the 'supposed' oxepin were obtained in the form of prismatic needles. Single-crystal oscillation and rotation photographs were taken about the three crystallographic axes using CuK_α radiation. Weissenberg photographs were taken of the $h0\ell$ - $h5\ell$ and $0k\ell$ reciprocal lattice nets. The monoclinic cell parameters obtained from rotation and moving film photographs are

$$\underline{a} = 8.44 \pm 0.01 \text{ Å}$$
$$\underline{b} = 7.45 \pm 0.02 \text{ Å}$$
$$\underline{c} = 19.05 \pm 0.01 \text{ Å}$$
$$\beta = 102.9^\circ \pm 15'$$

Inspection of the Weissenberg photographs showed that the systematic absences are

$h0\ell$ when ℓ is odd

$0k0$ when k is odd

These conditions determine the space group to be $P2_1/C$.

Intensities were estimated visually from the Weissenberg series using a standard step-wedge technique. The total number of structure amplitudes evaluated after normal Lorentz, polarisation and Tunell factors had been applied was 1,640. Small crystals of uniform cross-section perpendicular to the rotation axis were employed and no corrections for absorption were made. The linear absorption coefficient for X-rays of wave length 1.542 Å is $47 cm^{-1}$. The absolute scale was determined during refinement by comparison of $\sum F_o$ and $\sum F_c$ for each layer.

2.3 STRUCTURE DETERMINATION.

The Patterson maps computed from the $h0\ell$ and $0k\ell$ data are shown in Figs. 1 and 2. The bromine-bromine vector peaks are labelled A,B,C and D. Calculation of the bromine atomic coordinates from these peaks indicated that the fractional x coordinate was zero. The actual value was determined by Booth's method (Booth,1948), and confirmed by calculation of a three-dimensional Patterson map.

Using these bromine coordinates a structure factor calculation was carried out. The discrepancy was 47.4% at

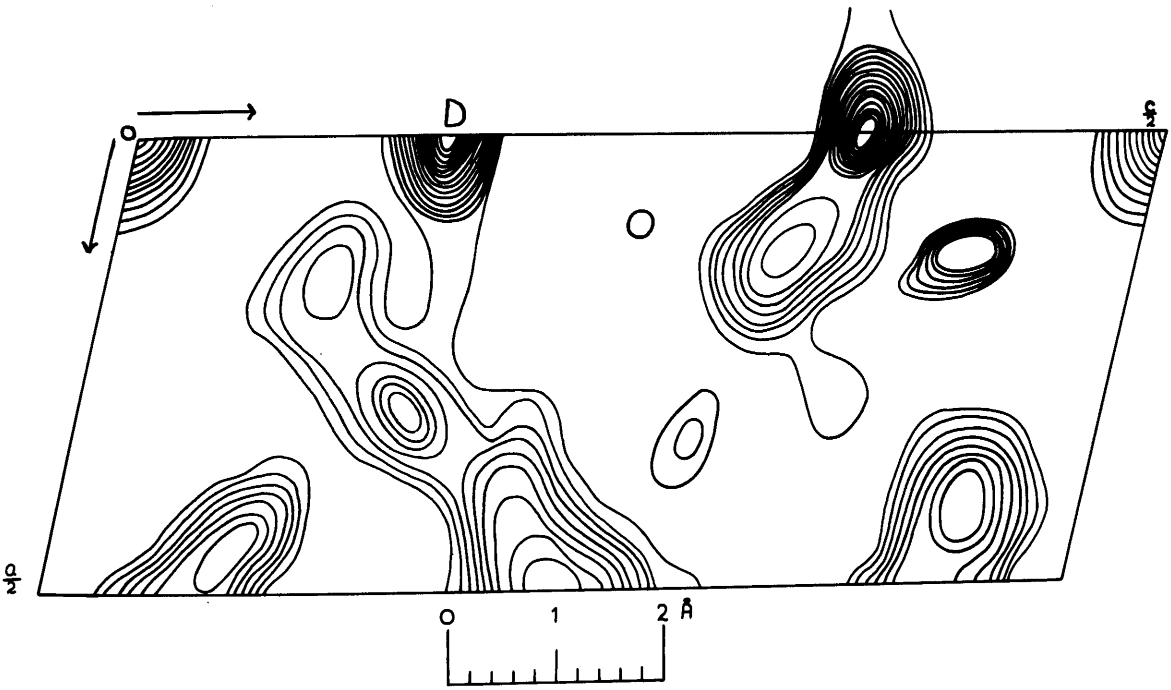


Fig. 1. The Patterson projection along the b axis. The contour scale is arbitrary. The bromide-bromide vector peak is marked D.

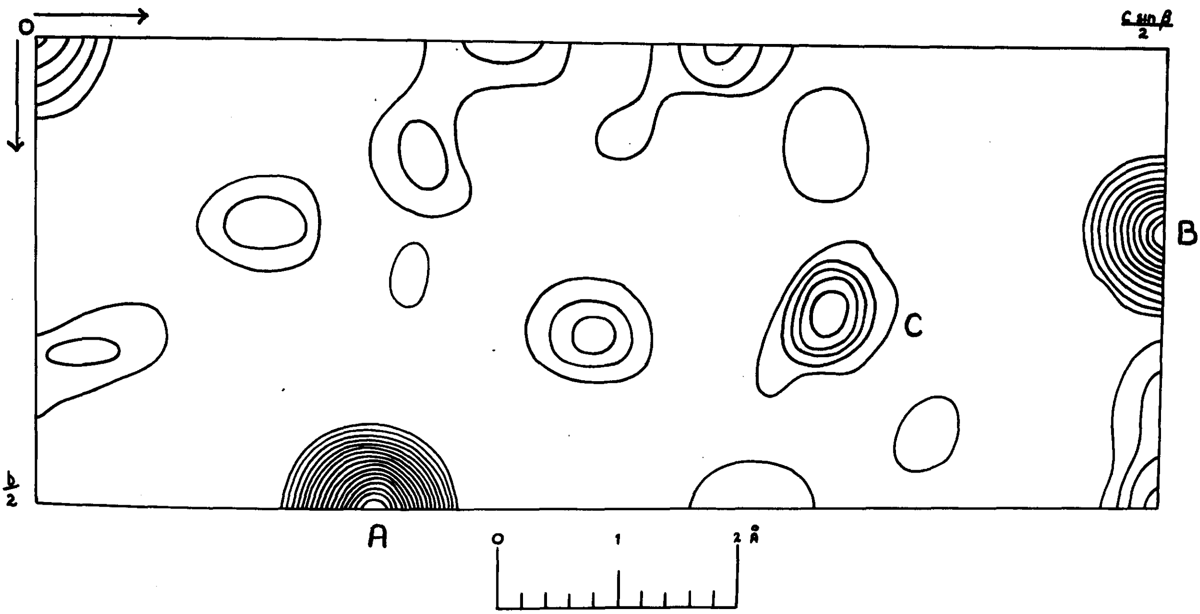


Fig. 2. The Patterson projection along the <u>a</u> axis. The contour scale is arbitrary. The bromide-bromide vector peaks are marked A, B and C.

this stage. A first Fourier map calculated from the structure factors revealed the complete molecule. The bromine atom and fourteen other atoms weighted as carbon were used to compute more accurate structure factors. The value of R dropped to 20.0%. A subsequent Fourier map enabled the hetero atoms to be distinguished on the basis of peak height and intermolecular contacts. A third cycle of structure factor calculations with the atoms given the correct chemical type reduced the R factor to 17.3%.

2.4 STRUCTURE REFINEMENT.

Individual isotropic temperature factors were assigned to the atoms from a comparison of the peak heights on F_o and F_c maps. The atomic coordinates and temperature factors obtained from these maps were used in further refinement by the least-squares method. After three cycles of such refinement the R factor dropped to 15.8% and shifts in the atomic parameters were negligible. The final value of R was 15.5%. A mean individual isotropic temperature factor was calculated for each cycle of the least-squares refinement.

The course of the analysis is described in Table I. Superimposed contour sections illustrating the final three-dimensional electron density distribution over one molecule are shown in Fig. 3. Figs 4 and 5 illustrate the molecule projected along the <u>a</u> and <u>b</u> axes.

TABLE I.

Course of analysis

Operation	Data used	Atoms included	R(%)	$\sum w\Delta^2$
2D Patterson syntheses	$h0\ell$ and $0k\ell$ reflections	---	---	---
3D " synthesis	1643 F_o	---	---	---
1st 3D F_o "	1435 F_o	1 Br	47.4	---
2nd " "	1578 F_o	1 Br + 14 C	20.0	---
3rd " " and 1st 3D F_c "	1643	1 Br + 3O + 2 N + 9 C	17.3	---
1st Least-squares cycle	1643 F_o	1 Br + 3O + 2 N + 9 C	16.9	904
2nd " "	1643 F_o	1 Br + 3O + 2 N + 9 C	16.5	860
3rd " "	1643 F_o	1 Br + 3O + 2 N + 9 C	15.8	836
4th " "	1643 F_o	1 Br + 3O + 2 N + 9 C	15.5	---

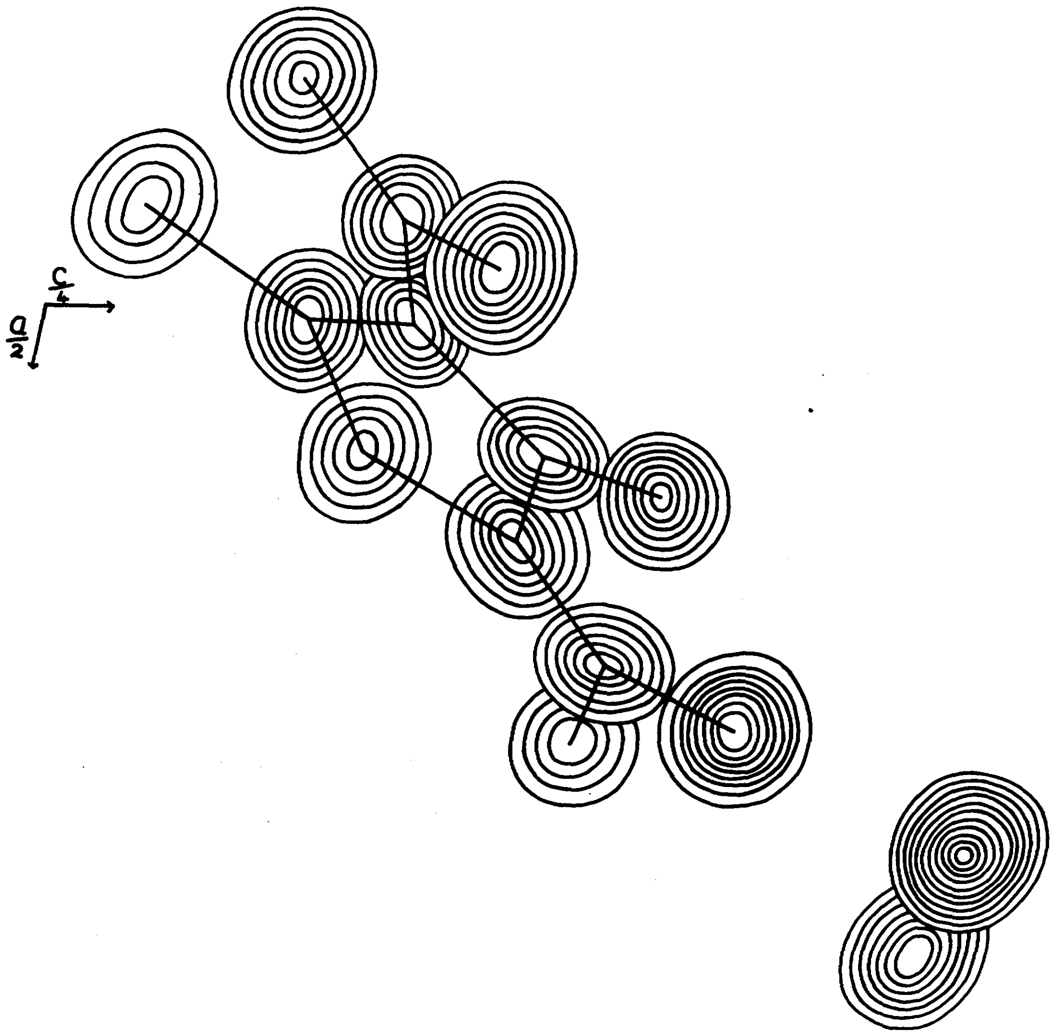


Fig. 3. The final three-dimensional electron-density distribution for the substituted cyclopentadiene shown by means of superimposed contour sections parallel to (010). The bromide ion and oxygen atom of the water molecule are included. Contour interval 1 e Å^{-3} except round the bromide ion where it is 5 e Å^{-3}. The first contour level is omitted in both cases.

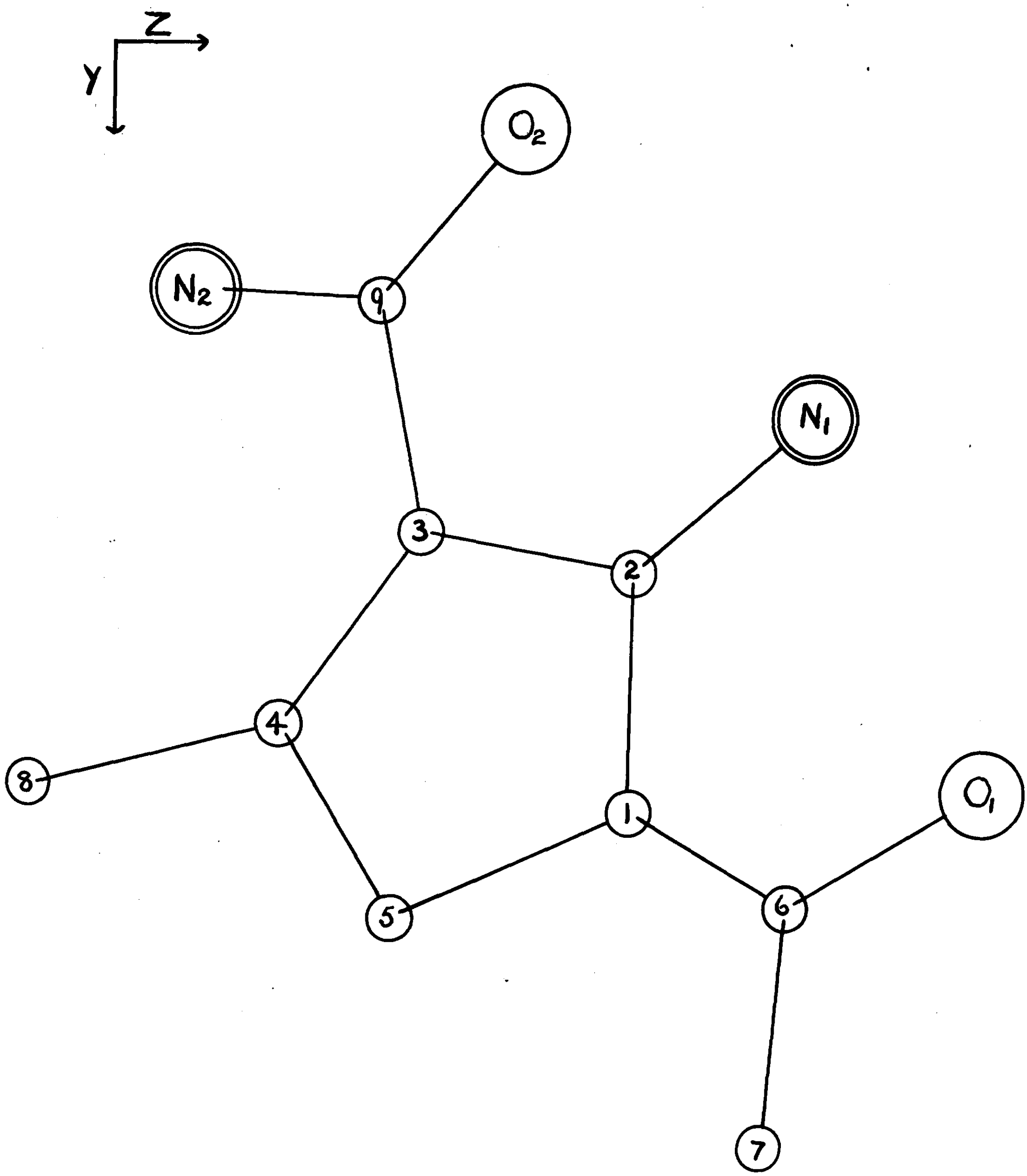


Fig. 4. Diagram showing the atomic arrangement as seen in projection along the a axis.

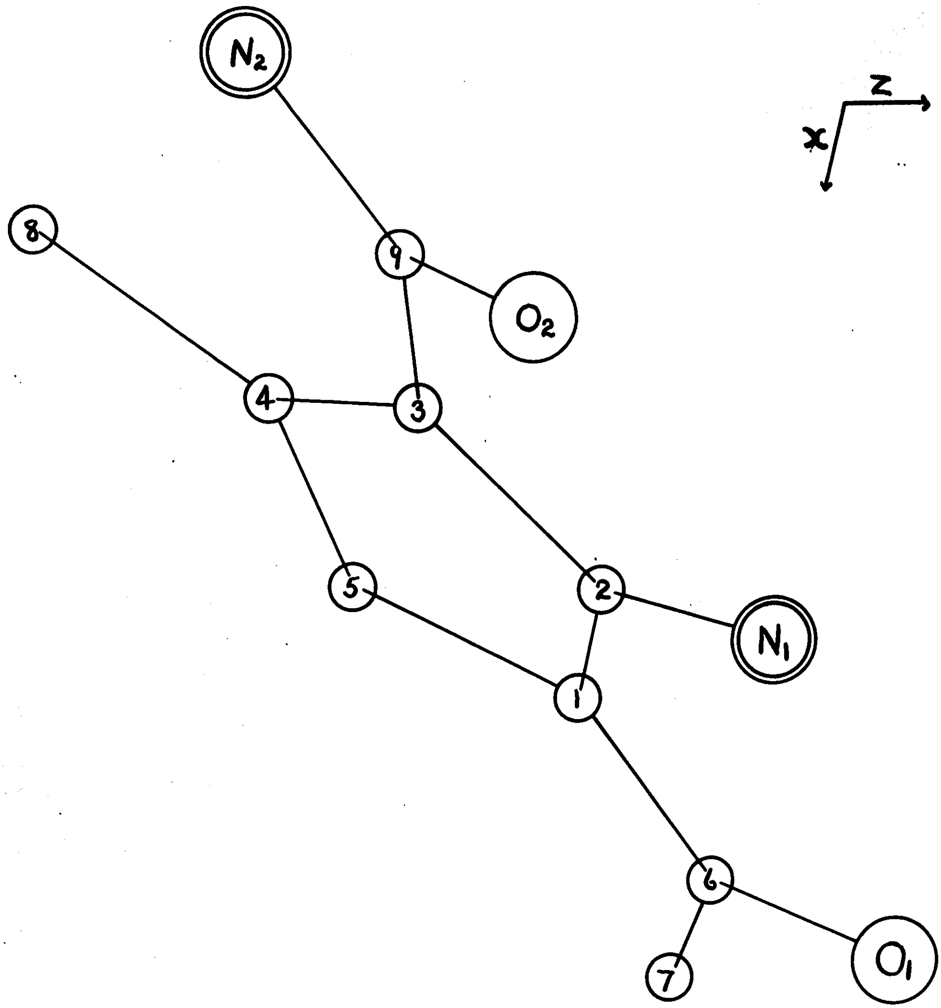


Fig. 5. Diagram showing the arrangement of atoms in the molecule corresponding to Fig. 3.

2. 5 MOLECULAR DIMENSIONS.

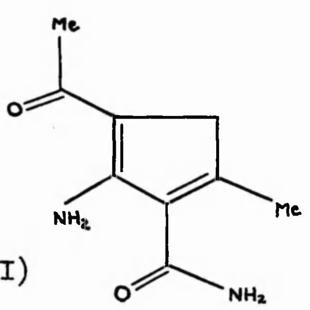
The final atomic coordinates and isotropic temperature factors are listed in Table II. Bond lengths and interbond angles calculated from the coordinates are given in Tables III and IV respectively. The shorter intramolecular contacts are shown in Table V and intermolecular approach distances ($\leqslant$ 4 Å) in Table VI. Some of the more interesting angles between interatomic vectors are listed in Table VII.

The estimated standard deviations in atomic parameters are given in Table VIII. The average standard deviation of a carbon-carbon bond is 0.03 Å, of a carbon-oxygen bond 0.02 Å and of a carbon-nitrogen bond 0.02 Å. The standard deviation in bond angle is 1.6°. The final structure factors are listed in Table IX.

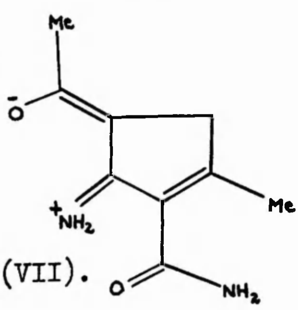
2.6 DISCUSSION.

The results of the X-ray analysis show that the compound is in fact the hydrobromide of a tetra-substituted cyclopentadiene. The fact that it does not exist as a dimer as does cyclopentadiene is probably due to resonance stabilisation of the structure.

The original substance before salt formation (VI) has contributions from the resonance structure (VII).



(VI)



(VII).

TABLE II.

Atomic coordinates and temperature factors.

The fractional coordinates are referred to the monoclinic axes. Coordinates X' Y Z' are expressed in Å units and are referred to orthogonal axes a, b and c', c' being taken perpendicular to the a and b crystal axes.

Atom	x/a	y/b	z/c	X'	Y	Z'	B
Br	0.0029	0.6464	0.8224	-3.474	4.819	15.271	3.5
C_1	0.7102	0.5603	0.4621	4.028	4.176	8.580	2.7
C_2	0.6402	0.3806	0.4617	3.438	2.837	8.573	3.0
C_3	0.5184	0.3531	0.3968	2.687	2.632	7.367	2.9
C_4	0.5114	0.4993	0.3551	2.805	3.722	6.595	3.0
C_5	0.6321	0.6424	0.3896	3.677	4.788	7.234	3.5
C_6	0.8311	0.6310	0.5156	4.837	4.703	9.500	2.6
C_7	0.8951	0.8091	0.5058	5.402	6.031	9.392	3.8
C_8	0.4009	0.5491	0.2797	2.193	4.093	5.195	4.9
C_9	0.4189	0.1827	0.3821	1.910	1.362	7.096	3.0
O_1	0.8882	0.5408	0.5713	5.064	4.031	10.609	3.6
O_2	0.4612	0.0575	0.4241	2.089	0.429	7.874	3.9
O_3	0.1023	0.7088	0.6691	-1.983	5.283	12.424	4.4
N_1	0.6748	0.2641	0.5155	3.501	1.969	9.573	3.0
N_2	0.2920	0.1784	0.3277	1.071	1.330	6.084	4.1

MOLECULAR DIMENSIONS.

INTERATOMIC DISTANCES (Å) AND ANGLES

TABLE III.

Intramolecular bonded distances.

C_1	-	C_2	1.46
C_1	-	C_5	1.52
C_1	-	C_6	1.33
C_2	-	C_3	1.44
C_2	-	N_1	1.33
C_3	-	C_4	1.34
C_3	-	C_9	1.51
C_4	-	C_5	1.52
C_4	-	C_8	1.57
C_6	-	C_7	1.45
C_6	-	O_1	1.32
C_9	-	O_2	1.23
C_9	-	N_2	1.32

TABLE IV.

Interbond angles.

C_2	C_1	C_5	106°
C_2	C_1	C_6	128
C_5	C_1	C_6	126
C_1	C_2	C_3	110
C_1	C_2	N_1	125
C_3	C_2	N_1	124
C_2	C_3	C_4	109
C_2	C_3	C_9	123
C_4	C_3	C_9	129
C_3	C_4	C_5	112
C_3	C_4	C_8	132
C_5	C_4	C_8	116
C_4	C_5	C_1	103
C_1	C_6	C_7	123
C_1	C_6	O_1	119
C_7	C_6	O_1	118
C_3	C_9	O_2	117
C_3	C_9	N_2	119
O_2	C_9	N_2	124

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C_3	-	C_9	1.51
C_4	-	C_5	1.52
C_4	-	C_8	1.57
C_6	-	C_7	1.45
C_6	-	O_1	1.32
C_9	-	O_2	1.23
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C_1	C_2	N_1	125
C_3	C_2	N_1	124
C_2	C_3	C_4	109
C_2	C_3	C_9	123
C_4	C_3	C_9	129
C_3	C_4	C_5	112
C_3	C_4	C_8	132
C_5	C_4	C_8	116
C_4	C_5	C_1	103
C_1	C_6	C_7	123
C_1	C_6	O_1	119
C_7	C_6	O_1	118
C_3	C_9	O_2	117
C_3	C_9	N_2	119
O_2	C_9	N_2	124

TABLE V.

Intramolecular non-bonded distances.

C_1	...	C_8	3.85
C_1	...	C_9	3.82
C_2	...	C_7	3.84
C_2	...	C_8	3.81
C_2	...	O_1	2.87
C_2	...	O_2	2.85
C_2	...	N_2	3.75
C_3	...	C_6	3.67
C_4	...	C_6	3.68
C_4	...	O_2	3.61
C_4	...	N_1	3.53
C_4	...	N_2	3.00
C_5	...	C_7	3.03
C_5	...	C_9	3.86
C_5	...	O_1	3.73
C_5	...	N_1	3.67
C_6	...	N_1	3.04
C_8	...	C_9	3.34
C_8	...	N_2	3.11
C_9	...	N_1	3.01
O_1	...	N_1	2.79
O_2	...	N_1	2.69

TABLE VI.

Intermolecular distances (< 4 Å).

$O_1 \cdots O_3^{I}$	2.61	$C_3 \cdots O_1^{VI}$	3.70
$O_2 \cdots O_2^{II}$	2.95	$C_3 \cdots O_3^{VI}$	3.72
$O_2 \cdots N_1^{II}$	3.00	$C_6 \cdots N_2^{VI}$	3.73
$Br \cdots O_3$	3.25	$C_4 \cdots O_3^{VI}$	3.73
$C_7 \cdots O_3^{I}$	3.30	$N_1 \cdots Br^{VI}$	3.74
$O_3 \cdots Br^{III}$	3.39	$C_3 \cdots C_6^{VI}$	3.75
$C_6 \cdots O_3^{I}$	3.39	$C_7 \cdots C_9^{VI}$	3.76
$O_1 \cdots N_2^{VI}$	3.42	$C_8 \cdots N_2^{VII}$	3.77
$O_3 \cdots N_2^{V}$	3.45	$C_5 \cdots O_3^{VI}$	3.77
$C_6 \cdots C_9^{VI}$	3.52	$C_6 \cdots O_2^{VI}$	3.79
$C_2 \cdots C_2^{VI}$	3.53	$C_1 \cdots O_3^{VI}$	3.81
$C_5 \cdots N_1^{VI}$	3.54	$C_2 \cdots C_3^{VI}$	3.82
$C_9 \cdots O_1^{VI}$	3.57	$Br \cdots C_8^{V}$	3.82
$O_1 \cdots Br^{IV}$	3.57	$C_2 \cdots N_1^{VI}$	3.84
$N_2 \cdots Br^{V}$	3.59	$C_3 \cdots N_1^{VI}$	3.85
$C_2 \cdots C_1^{VI}$	3.60	$C_7 \cdots N_2^{VI}$	3.85
$C_1 \cdots N_1^{VI}$	3.62	$C_8 \cdots C_9^{VII}$	3.86
$C_4 \cdots N_1^{VI}$	3.66	$C_1 \cdots C_9^{VI}$	3.89
$C_7 \cdots O_2^{VI}$	3.69	$C_4 \cdots O_1^{VI}$	3.94
$C_3 \cdots C_1^{VI}$	3.70		

The superscripts used in the preceeding table refer to the following positions:-

I	$1 + x$,	y ,	z .
II	$1 - x$,	$-y$,	$1 - z$,
III	$-x$,	$\frac{1}{2} + y$,	$1\frac{1}{2} - z$
IV	$1 - x$,	$-\frac{1}{2} + y$,	$1\frac{1}{2} - z$.
V	$-x$,	$1 - y$,	$1 - z$.
VI	$1 - x$,	$1 - y$,	$1- z$.
VII	$1 - x$,	$\frac{1}{2} + y$,	$\frac{1}{2} - z$.

TABLE VII.

Some of the more interesting angles associated with the bromide ions and water molecules.

C_6	O_1	O_3^{I}	116°
O_1	O_3^{I}	Br^{I}	107
O_1	O_3^{I}	Br^{II}	110
Br^{I}	O_3^{I}	Br^{II}	88
O_3^{I}	Br^{I}	O_3^{II}	90
O_3^{II}	Br^{II}	O_3^{I}	108
C_2	N_1	Br^{III}	142
Br^{I}	O_3^{II}	Br^{II}	74
C_6	O_1	N_1	88
C_2	N_1	O_1	80
C_2	N_1	O_2	83
C_9	O_2	N_1	92

The superscripts refer to the following positions:-

I	$1 + x$,	y,	z,
II	$1 - x$,	$\frac{1}{2} + y$,	$1\frac{1}{2} - z$.
III	$1 - x$,	$-\frac{1}{2} + y$,	$1\frac{1}{2} - z$.

TABLE VIII.

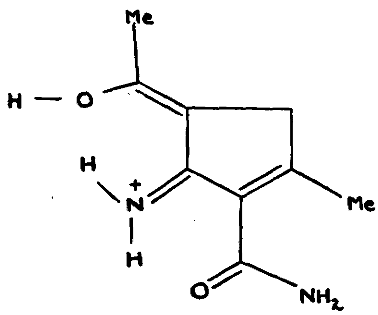
Standard deviations of the final atomic coordinates (Å)

Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
C_1	0.017	0.017	0.020
C_2	0.017	0.016	0.021
C_3	0.016	0.015	0.024
C_4	0.017	0.017	0.020
C_5	0.017	0.017	0.024
C_6	0.015	0.015	0.022
C_7	0.020	0.019	0.022
C_8	0.022	0.021	0.025
C_9	0.017	0.017	0.020
O_1	0.012	0.012	0.015
O_2	0.013	0.013	0.015
O_3	0.014	0.013	0.015
N_1	0.014	0.014	0.017
N_2	0.016	0.015	0.019
Br	0.002	0.002	0.003

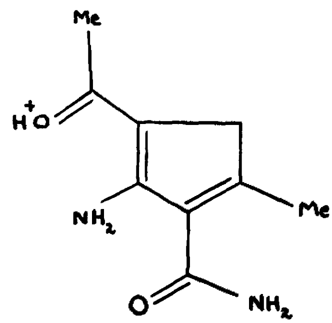
Table IX. Calculated and measured values of structure factors.

h	k	l	$\lvert F_o \rvert$	F_c	h	k	l	$\lvert F_o \rvert$	F_c	h	k	l	$\lvert F_o \rvert$	F_c
0	0	2	19	21	1	2	2	40	38	2	1	20	< 3	2
		4	32	- 40			3	30	- 29			21	< 2	4
		6	97	123			4	5	0			22	7	5
		8	64	- 73			5	38	- 43	2	2	-23	9	- 9
		10	24	24			6	43	- 45			-22	< 4	- 2
		12	58	59			7	71	7			-21	< 4	22
		14	51	- 49			8	6	- 2			-20	< 5	1
		16	18	18			9	50	- 55			-19	11	- 9
		18	18	19			10	11	- 11			-18	13	- 12
		20	32	- 27			11	22	- 22			-17	[illegible]	7
		22	14	11			12	31	- 30			-16	< 5	- 3
0	1	-23	13	- 9			13	39	39			-15	33	38
		-22	9	- 4			14	< 5	0			-14	26	24
		-21	< 3	4			15	32	- 31			-13	46	- 56
		-20	12	- 9			16	< 5	1			-12	< 4	- 1
		-19	19	15			17	10	10			-11	17	10
		-18	21	17			18	< 5	- 1			-10	< 4	5
		-17	24	- 26			19	29	24			- 9	39	43
		-16	18	- 16			20	< 4	3			- 8	32	- 12
		-15	8	5			21	22	- 17			- 7	56	- 69
		-14	6	- 2			22	10	- 8			- 6	23	- 21
		-13	10	7	1	3	-23	7	12			- 5	64	64
		-12	27	29			-22	< 2	- 1			- 4	11	- 5
		-11	62	- 53			-21	< 3	1			- 3	9	2
		-10	34	- 29			-20	< 3	- 2			- 2	19	- 19
		- 9	47	42			-19	23	- 18			- 1	85	-127
		- 8	19	19			-18	9	10			0	8	3
		- 7	8	- 2			-17	36	33			1	63	66
		- 6	36	35			-16	14	- 10			2	41	46
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

During salt formation addition of a proton to (VII) gives rise to (VIII) which can be stabilised by contribution from the resonance form (IX).

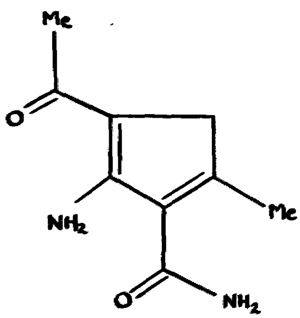


(VIII).

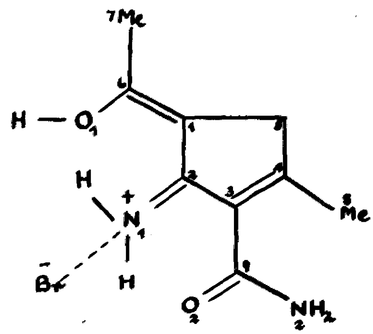


(IX).

Similar addition of a proton to (VI) results in (X) which has no resonance forms. Therefore the more likely product of salt formation is (XI).



(X)



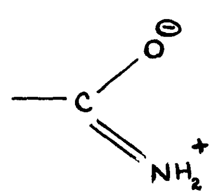
(XI).

That (XI) is in fact the correct structure is confirmed by inspection of the inter- and intramolecular distances. The oxygen atom of the water molecule (O_3) forms two close contacts of 3.25 Å and 3.38 Å to the bromide ions and a third of 2.61 Å to O_1. If it is assumed that the hydrogen atoms of the water molecule are directed towards the bromide ions then O_1 must provide the hydrogen atom in its bond to the water molecule.

The *sp*^{2}- hybridised nitrogen atom N_1 forms two short intramolecular contacts $N^+ - O_1$ 2.79 Å and $N^+ - O_2$ 2.69 Å and a long contact to the bromide ion 3.74 Å.

The bond lengths within the molecule are also consistent with structure (XI). The $C_6 - O_1$ distance of 1.32 Å is longer than a normal carbon-oxygen double bond in conjugated systems *c.f.* that of acraldehyde ($CH_2 = CH.CHO$) which is 1.22 ± 0.02 Å (Mackle and Sutton, 1951). Also the bond $C_1 - C_6$ at 1.33 Å is shorter than the corresponding length of 1.46 ± 0.03 Å in acraldehyde and the distance $C_1 - C_2$ of 1.46 Å is longer than the corresponding carbon-carbon double-bond distance in acraldehyde (1.36 ± 0.02 Å). Finally the $C_2 - N^+$ distance is 1.33 Å which is shorter than the carbon(*sp*^{2}) - nitrogen distance in *p* - nitroaniline 1.371 ± 0.007 Å (Trueblood, Goldish and Donohue, 1961). The distances $C_1 - C_5$ and $C_4 - C_5$ at 1.52 Å compare favourably with the carbon(*sp*^{3}) - carbon (*sp*^{3}) single-bond length of 1.545 Å in diamond.

In the amide group the carbon-nitrogen length is 1.32 Å and the carbon-oxygen length is 1.23 Å. Amide groups like carboxylic acid groups can have contributions from resonance forms *e.g*:-



This phenomenon has been reported in the study of many compounds containing this grouping. The carbon-nitrogen bonds are found to have considerable double-bond character and the carbon-oxygen bonds are considerably longer than pure double bonds. The average carbon-nitrogen and carbon-oxygen bond lengths from compounds of this type are shown in Table X. A survey of the bond lengths and angles in these and related molecules has been published by Davies and Pasternak, (1956).

The average values of the carbon-nitrogen and carbon-oxygen bonds compare well with those found in this analysis (1.32 ± 0.02 Å, 1.23 ± 0.02 Å respectively). The value of the nitrogen-carbon-oxygen angle of 122.8° agrees reasonably with that of 124° for the amide group in the substituted cyclopentadiene. However, the carbon-carbon-nitrogen and carbon-carbon-oxygen angles of 119.1° and 116.7° are slightly different from the above average of 116.0° and 121.2° respectively. The contraction in the angle $C_3 - C_9 - O_2$ and corresponding increase in $C_3 - C_9 - N_2$ is probably due to the formation of the intramolecular hydrogen bond $O_2 \ldots . H - N^+$. All other bond lengths and interbond angles in the compound are normal.

On the basis of structure (XI) the atoms adjacent to the partial double bonds $C_1 - C_6$ and $C_2 - N^+$ should be planar. This is in fact true. The equation of the plane through $C_1\ C_2\ C_5\ C_6\ C_7\ O_1$ is

$$0.814X' - 0.395Y - 0.427Z' + 8.868 = 0$$

TABLE X.

	Compound		Bond Length C - O	Bond Length C - N	$\sigma(\ell)$	Bond Angle C - C - N	Bond Angle C - C - O	Bond Angle N - C - O
(1)	Oxamide		1.243	1.315	0.004	114.8	119.5	125.7
(2)	Succinamide		1.238	1.333	0.002	115.6	122.4	122.0
(3)	Urea		1.262	1.335	0.002	118.0	121.0	121.0
(4)	Biuret	(a)	1.255	1.33_2	0.024	113.8	125.0	120.9
		(b)	1.246	1.36_1	0.024	117.8	117.2	124.9
(5)	Benzamide		1.24	1.31	0.017	116.0	122.0	122.0
	Average		1.25	1.33		116.0	121.2	122.8

References

(1) Ayerst and Duke 1954.
(2) Davies and Pasternak 1956.
(3) Vaughan and Donohue 1952.
(4) Hughes, Yakel and Freeman 1961.
(5) Penfold and White 1959.

TABLE XI.

Displacements (Å) of atoms from the mean plane through $C_1\ C_2\ C_5\ C_6\ C_7\ O_1$.

C_1	-0.039
C_2	0.013
C_5	0.009
C_6	0.019
C_7	0.001
O_1	-0.004

TABLE XII.

Displacements (Å) of atoms from the mean plane through $C_1\ C_2\ C_3\ N_1$.

C_1	-0.008
C_2	0.025
C_3	-0.008
N_1	-0.010

TABLE XIII.

Displacements (Å) of atoms from the mean plane through $C_1\ C_2\ C_3\ C_4\ C_5$

C_1	-0.023
C_2	0.019

TABLE XIII. (contd.)

C_3	-0.006
C_4	-0.009
C_5	0.019

and the deviations of the atoms from the plane are given in Table XI. X', Y, Z' are coordinates expressed in Ångstrom units and referred to orthogonal axes $\underline{a}$, $\underline{b}$ and $\underline{c}'$. The plane through $C_1\ C_2\ C_3\ N_1$ has equation

$$0.823\ X' - 0.384\ Y - 0.420\ Z' + 8.834 = 0$$

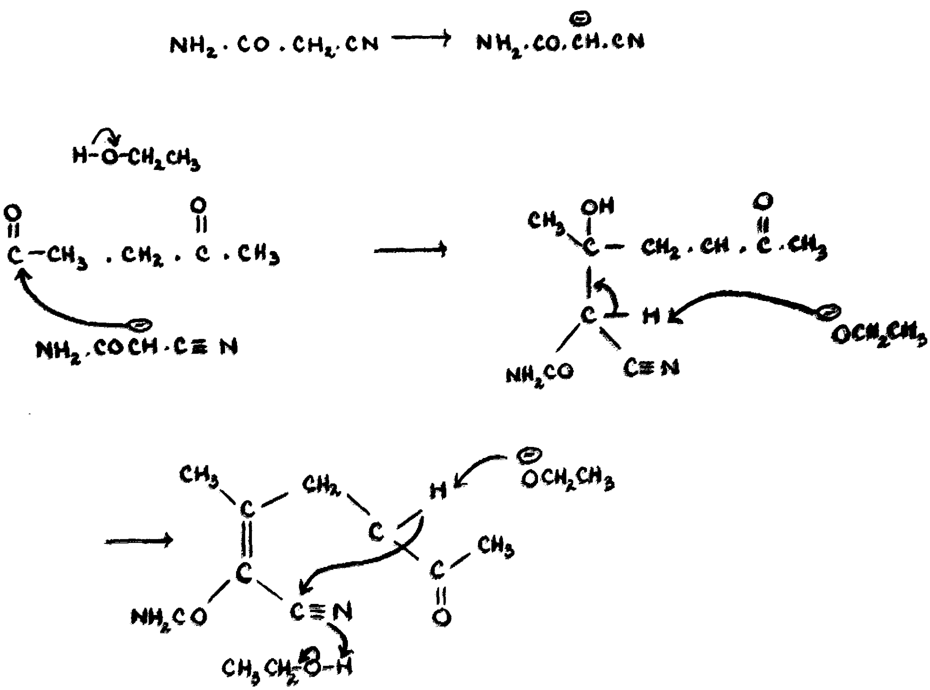
and the deviations of the atoms from the plane are shown in Table XII.

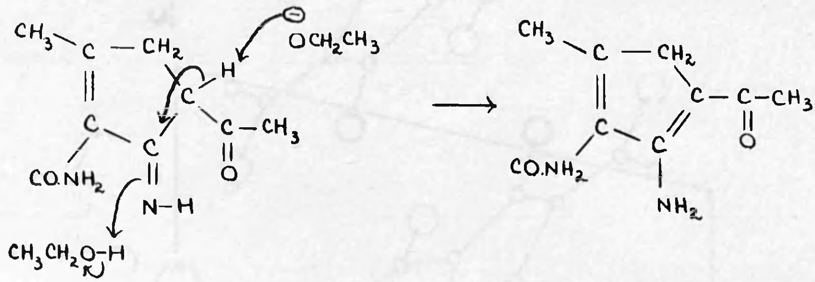
The equation of the plane through the cyclopentadiene ring is

$$0.819\ X' - 0.390\ Y - 0.422\ Z' + 8.843 = 0$$

Table XIII shows the deviations of the atoms from this plane.

The formation of the parent compound of the salt from acetonyl acetone and cyanoacetamide can be explained by the following reaction mechanism.





This reaction product can explain equally well the evidence given by Westöö. It also agrees with evidence from infra-red spectra which contrary to the claims of Westöö indicate two carbonyl bands at $1660cm^{-1}$ and $1643cm^{-1}$ and not one at $1670cm^{-1}$. These bands would be consistent with an amide group attached to an unsaturated system ($1643cm^{-1}$) and a CH_3CO unsaturated ring group ($1660cm^{-1}$).

The packing of the molecules in the unit cell is shown in Figs. 6 and 7. The molecules are held together in the crystal by means of hydrogen bonds involving the water molecules and the bromide ions. Large tunnels run through the structure in the a and b directions. In these tunnels, connected to the molecules on either side by weak hydrogen bonds, are situated the water molecules and the bromide ions. The values of the more interesting intermolecular contacts are marked on Figs. 6 and 7. A short Van der Waals contact of

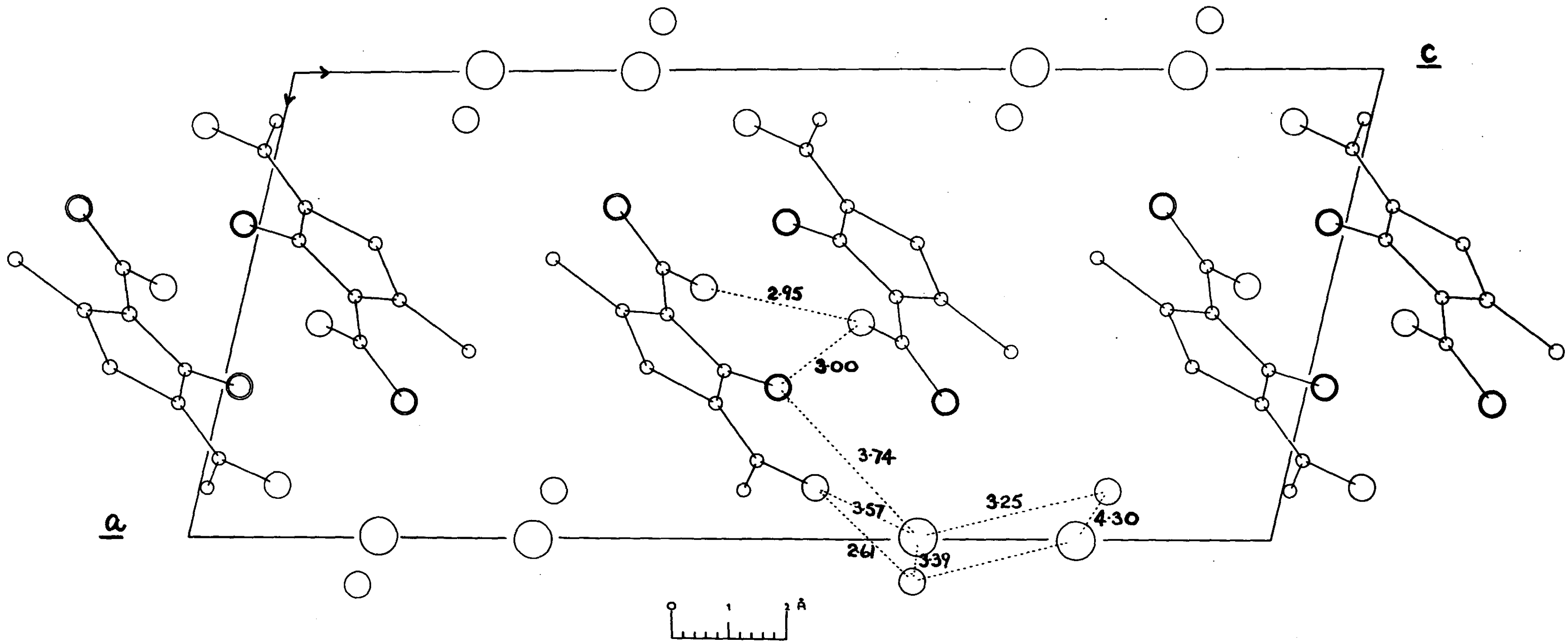


Fig. 6. The arrangement of molecules in the unit cell as viewed in projection along the b axis. The lengths of a few of the more interesting non-bonded distances and hydrogen bonds are shown.

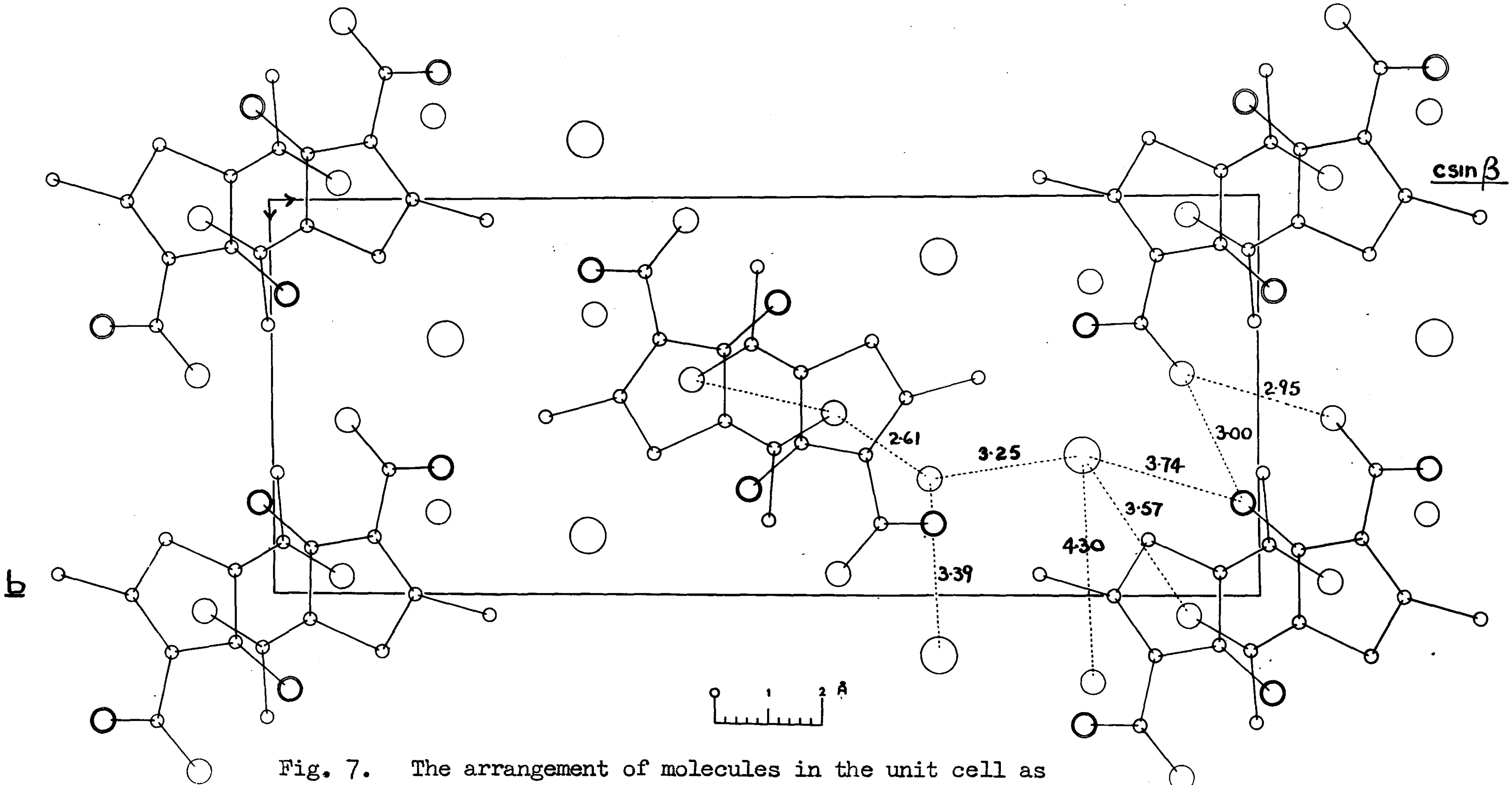


Fig. 7. The arrangement of molecules in the unit cell as viewed in projection along the a axis. The lengths of a few of the more interesting non-bonded distances and hydrogen bonds are shown.

2.95 Å occurs between O_2 of the standard molecule and O_2 of the molecule related to it by a centre of symmetry.

APPENDICES.

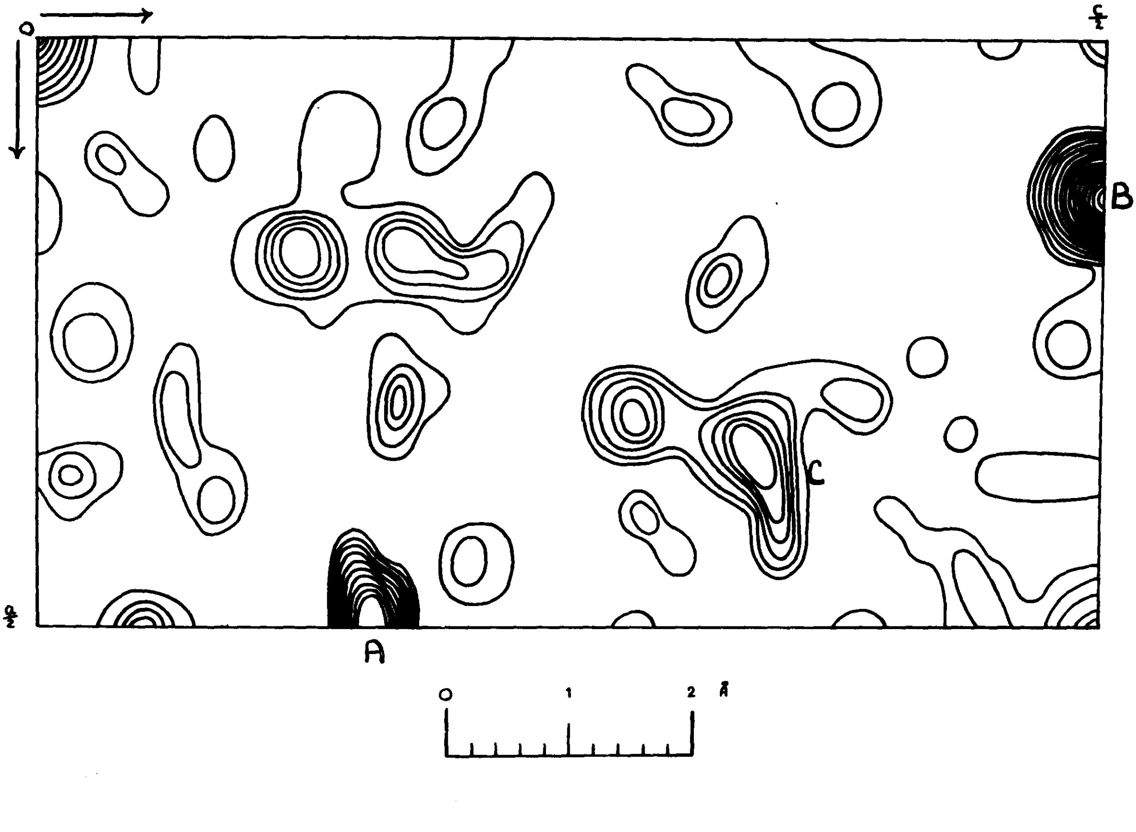


Fig. 1. Patterson projection along the b axis. The bromide-bromide vector peaks are marked A,B and C. The contour scale is arbitrary.

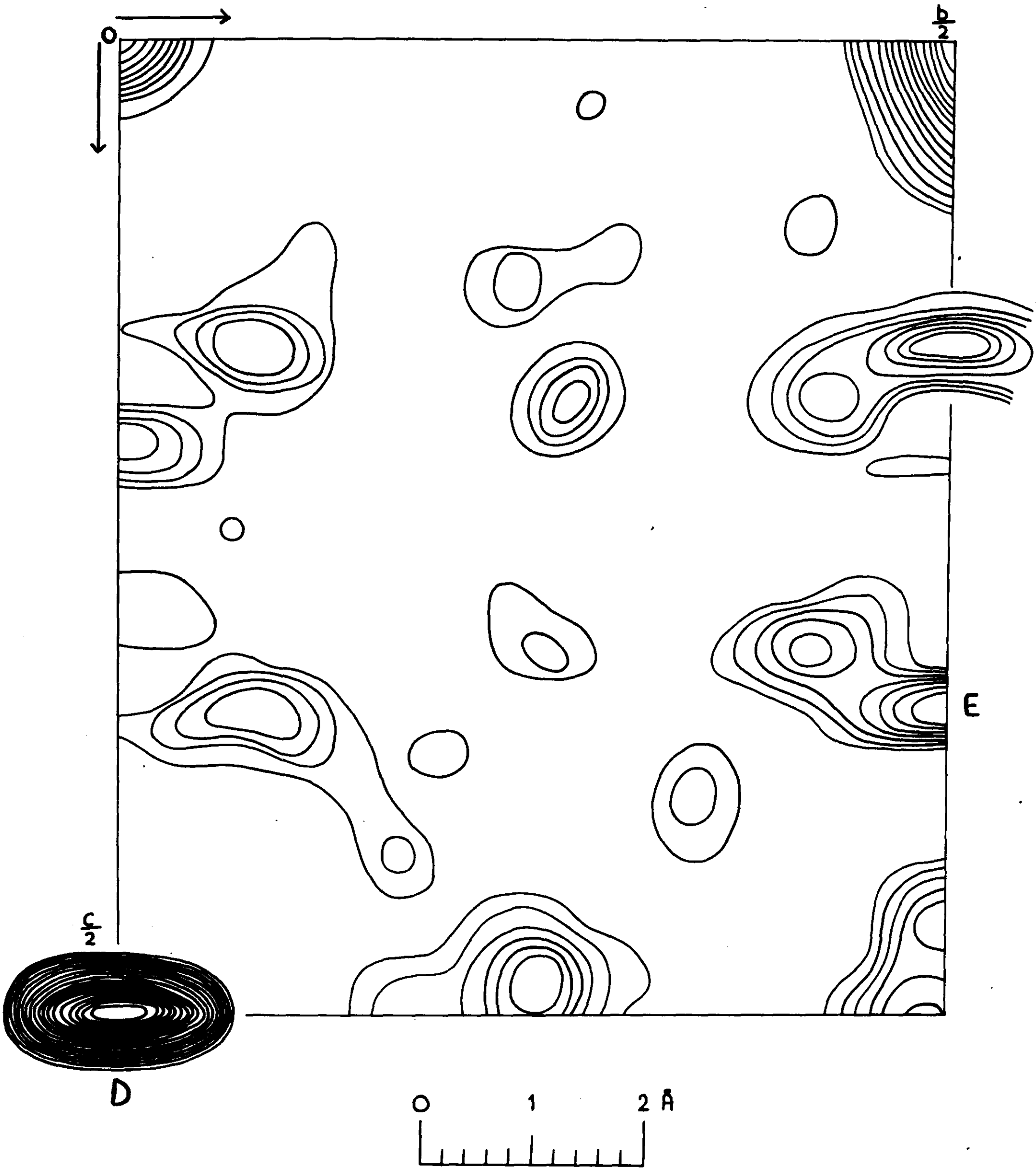


Fig. 2. Patterson projection along the a axis. The bromide-bromide vector peaks are marked D,E and F. The contour scale is arbitrary.

Intensity data were collected from the series $0k\ell$ - $4k\ell$ by visual estimation and the complete data were sent to Dr. J.S. Rollett at Oxford to be used in testing a new automatic heavy-atom programme for the DEUCE computer.

APPENDIX II.

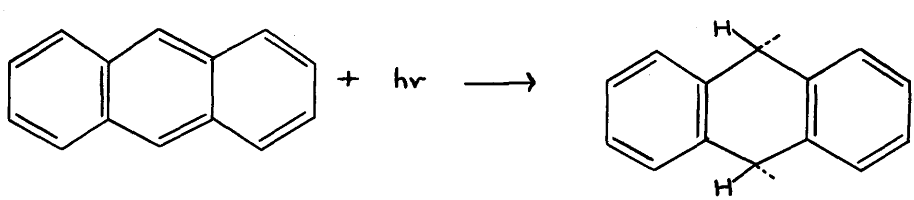
DIANTHRACENE

The stable form of anthracene is the monomer. When solutions of the monomer are exposed to ultra-violet radiation the unstable dimer is produced. In solution the reaction reverses in the dark until at equilibrium the solute consists almost exclusively of monomer.

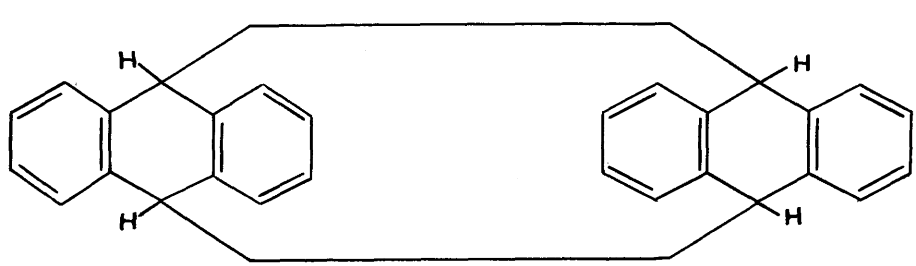
$$2C_{14}H_{10} \underset{\text{dark}}{\overset{\text{u.v. radiation}}{\rightleftharpoons}} C_{28}H_{20}$$

The concentration of the dimer in the photostationary state and the influence of such factors as temperature, concentration and solvent have been studied (Luther and Weigert, 1905).

The mechanism of photodimerisation has been discussed by Schönberg (1936), who assumed the intermediate formation of a biradical i.e. the primary reaction is assumed to be



Two radicals formed thus may then combine to give



A quantity of dianthracene was prepared by ultra-violet irradiation of a very pure solution of anthracene intoluene. Crystals were obtained in the form of white hexagonal plates. Dianthracene is insoluble in most ordinary solvents e.g:- hexane, cyclohexane, alcohol, glacial acetic acid, benzene, chloroform and acetone. It is, however, soluble in nitrobenzene and attempts were made to recrystallise it from this solvent. However, the crystals obtained were not good enough for X-ray studies. The very thin laminae showed a tendency to form aggregates and those which did crystallise as single plates were frequently distorted. Finally the crystals prepared directly from the ultra-violet irradiation were used, care being taken to ensure maximum purity of the materials used in the preparation.

The object of the X-Ray study was to confirm and amplify the work done on dianthracene by Hengstenberg and Palacios (1932). The main interest in the study of the molecule is in the type of bonding involved in dimerisation.

The dimensions of the orthorhombic cell which had already been determined in the previous work were confirmed from oscillation and rotation photographs taken about the three crystallographic axes using CuK_{α} radiation. A comparison of the results is shown in Table I. The space group was confirmed to be $Pbca(D_{2h}^{15})$. The number of equivalent positions allowed for this space group is four. The density d calculated = 1.28 gm/cm^3

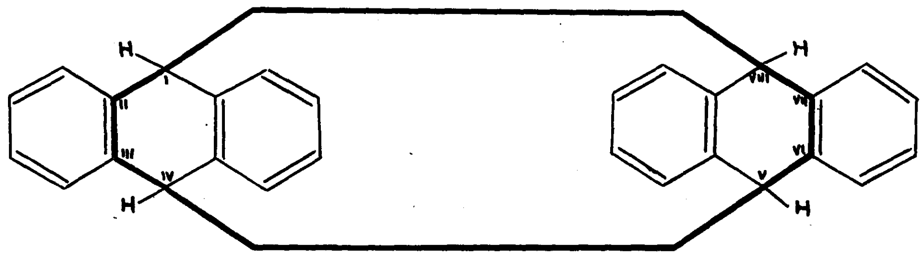
d measured = 1.24 gm/cm^3

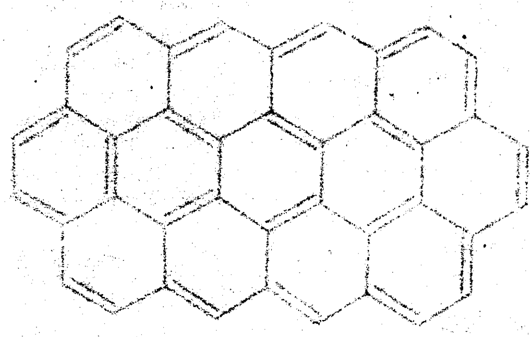
determines that there are eight anthracene molecules in the unit cell. It follows that dianthracene is in fact a dimer of anthracene and that the molecule of dianthracene has a centre of symmetry.

On the assumption that the structure of dianthracene consists of two anthracene flaps joined by cross links in the $9,9'$ and $10,10'$ positions, attempts were made to solve the crystal structure using the Fourier transform method. The contents of several unit cells for a trial structure were punched on a mask. The Fourier transform was observed in the optical diffractometer and compared with the $0k\ell$ weighted reciprocal lattice. Better comparisons were obtained when the dianthracene molecule was placed along the b axis. However no postulated structure could be found which gave reasonable agreement between the observed and calculated structure amplitudes.

The normal methods of structure analysis such as Patterson synthesis could not be used due to the complexity introduced by the overlapping flaps of the dianthracene molecule.

Diamagnetic susceptibility measurements carried out by Farquarson and Sastri(1940) and Bhatnagar, Kapur and Gurbaksh Kaur (1939) confirm that the anthracene molecules are joined in the 9 and 10 positions with the formation of an eight-membered puckered ring as shown by the thick lines.





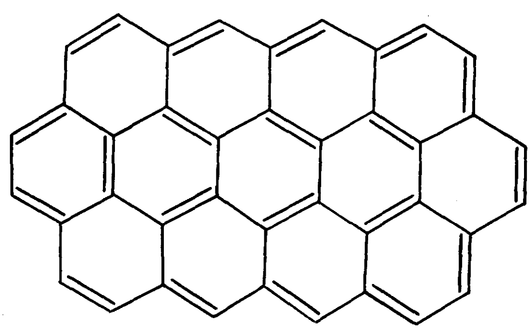
(I)

[illegible]-ray study of the crystals was carried out by [illegible] and [illegible]semann, the main interest in the structure being the bond lengths. Refinement proved difficult due to a

APPENDIX III.

CIRCUMANTHRACENE $C_{40}H_{16}$

Circumanthracene (I) is obtained along with di(3':1'-2:9)(3":1"-6:10) pyrene anthracene by treating 1:9-5:10 diperinaphthylene anthracene with maleic anhydride and decarboxylating the adduct (Clar, Kelly, Robertson and Rossmann, 1956). It was crystallised by sublimation at 400°C and was obtained in the form of fine black needles.



(I).

An X-ray study of the crystals was carried out by Robertson and Rossmann, the main interest in the structure being in the bond lengths. Refinement proved difficult due to a rapid decrease in the intensities of high order reflections, which appeared to be due to an unusually high temperature factor ($B = 10\ \text{Å}^2$).

Better crystals have since been obtained from Dr. Clar and an effort has been made to collect further data. These new crystals, however, proved to have a different crystalline form from those used in the earlier analysis and showed differences in the axial lengths. This phenomenon is common in the case of hydrocarbons (McIntosh *et al*. 1954, Harnik *et al*. 1954).

COMPARISON OF CRYSTAL DATA.

Robertson and Rossmann	New crystals
$a = 23.776 \pm 0.005$ Å	$a = 9.4$ Å
$b = 4.59 \pm 0.02$ Å	$b = 28.1$ Å
$c = 9.981 \pm 0.005$ Å	$c = 3.86$ Å
$\beta = 99^{\circ}\ 54' \pm 30'$	
Crystal system monoclinic	The crystal system appears to be orthorhombic.
Space group $P2_1/a$	The hko projection has plane group pgg.

In contrast to the findings of Robertson and Rossmann, in the case of the new crystals the projection down the short axis shows symmetry. The plane group for this projection is pgg. However data for these new crystals are difficult to obtain and indicate a very high temperature factor as for the previous analysis.

Several possible structures have been postulated on the basis of packing considerations, molecular dimensions and the calculated tilt of the molecule. None of these has yet proved satisfactory. It is hoped to collect further data from precession photographs.

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