The crystal and molecular structure of echitamine iodide, $C_{22}H_{29}O_4N_2I$

By H. Manohar and S. Ramaseshan *

Department of Physics, Indian Institute of Science, Bangalore, India

With 8 figures

(Received December 6, 1961)

Auszug

Echitaminjodid $C_{22}H_{29}O_4N_2J$ und Echitaminchlorid sind isomorph und gehören der Raumgruppe $P2_12_12_1$ an. Die Gitterkonstanten sind $a = 18,45$ Å, $b = 13,83$ Å, $c = 8,48$ Å; die Elementarzelle enthält 4 Moleküle. Die Kristallstruktur wurde aus Interferenzen $hk0$, $h0l$ und $0kl$ mittels zweidimensionaler Fourier-Synthese bestimmt. Zur Ermittlung der Interferenz-Vorzeichen wurden die Methoden des isomorphen Ersatzes und des schweren Atoms herangezogen. Für 379 Interferenzen meßbarer Intensität ergab sich zuletzt $R = 0,145$. Der Aufbau des Echitaminmoleküls wird festgestellt; es zeigt sich, daß dieses Dihydroindol-Alkaloid insofern einzigartig ist, als in ihm zwei Fünferringe zu einem bootförmigen Cyclohexanring längs einer gemeinsamen Bindung verschmolzen sind. Die Lagen der Seitengruppen lassen sich unter Annahme schwacher intramolekularer Wasserstoffbindungen gut erklären.

Abstract

The paper reports the detailed x-ray analysis of the structure of echitamine iodide. This substance and the chloride which are isomorphous belong to the orthorhombic space group $P2_12_12_1$ with four molecules in the unit cell. The axial dimensions of the iodide are $a = 18.45$ Å, $b = 13.83$ Å, $c = 8.48$ Å. The structure has been solved from the $hk0$, $h0l$ and $0kl$ data by Fourier-projection methods, use being made of the 'isomorphous replacement' technique and the 'heavy atom' method to obtain the phases of the reflections. The final R index for 379 reflections of measurable intensity is 0.145. The molecular configuration of the quarternary echitamine ion has been established, and it has been shown that this dihydro-indole alkaloid is unique in having two five-membered rings fused to a 'boat'-shaped substituted cyclohexane ring along a common bond. The positions of all the side-groups are well explained by postulating weak intramolecular hydrogen bonds.

* Present Address: S. Ramaseshan, Professor of Physics, Indian Institute of Technology, Madras-36, India.
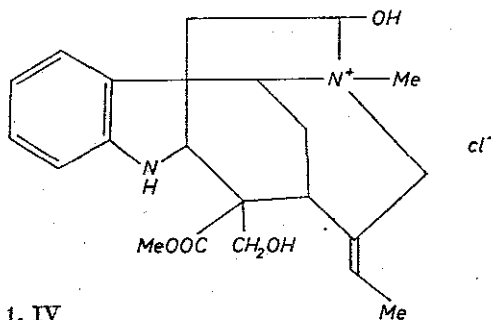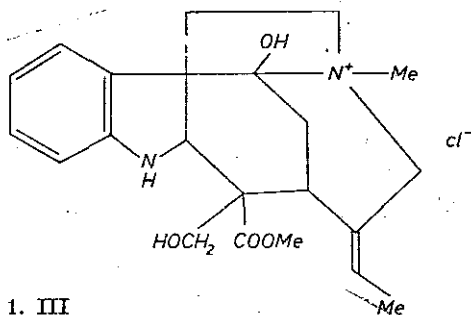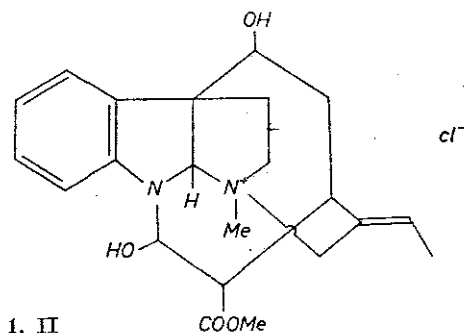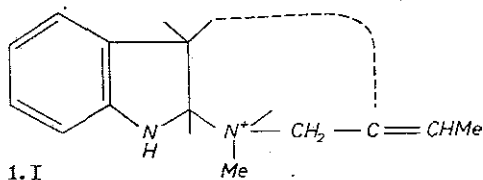
1. I

1. II

1. III

1. IV

Fig. 1. Various structures that have been proposed for echitamine chloride

Introduction

Echitamine ($C_{22}H_{28}O_4N_2$), the major alkaloid derived from the bark of the *Alstonia* species has lately been attracting the attention of organic chemists. The alkaloid was isolated[1] in 1875 and was reported[2] later to have an indole nucleus with a methoxyl and a methyl-amino group. Recently Govindachari and Rajappa[3] established that the chloride ($C_{22}H_{29}O_4N_2Cl$) is a quarternary salt and not a hydrochloride as suggested earlier. From spectroscopic studies they also deduced that the substance is a dihydro-indole derivative with the two nitrogen atoms separated by one carbon atom forming a φ-N-C-N structure. Interest in the substance seems to have been stimulated by the appearance of

---

[1] v. Group-Besanez, Notiz über ein unter dem Namen Ditain in den Handel gebrachtes Chininsurrogat. Ann. Chemie **176** (1875) 88—89.

[2] J. A. Goodson and T. A. Henry, Echitamine. J. Chem. Soc. [London] **127** (1925) 1640 to 1648.

[3] T. R. Govindachari and S. Rajappa, Echitamine. Proc. Chem. Soc. 1959, 134; Echitamine: Confirmation of the presence of the N_a—C—N_b system. Proc. Chem. Soc. 1959, 1549.

these papers, and one partial and three complete structures (Fig. 1) have been proposed for the quarternary chloride — I on the φ-N-C-N model[4], II based on E_a-dihydromavacurine[5], III on the strychnine-vomicine model[6] and IV based on methyl-ajmaline[7]. BIRCH, HODSON, MOORE, POTTS and SMITH[8] in a critical review object to the three structures II, III and IV in the light of available evidence and feel that the φ-N-C-N system affords the best rationalization of the data. Despite the controversy about the structure, purely from chemical evidence, the presence of a dihydro-indole nucleus, a quarternary nitrogen, CH_2OH, COOMe, $=CH$—Me, N^+—Me and OH groups seems to be established beyond doubt.

Investigation of the crystal structure of the quarternary iodide and chloride was commenced by the present writers soon after the appearance of the paper by CONROY[6]. The substances were kindly prepared by Prof. T. R. GOVINDACHARI and the iodide and chloride were chosen since GOODSON and HENRY[2] report that, "the iodide crystallizes in the anhydrous state while the bromide always contains one molecule of water of crystallization. The chloride, on the other hand, crystallizes as 'stumpy prisms' with one molecule of water when crystallized slowly from water, and as long anhydrous needles when crystallized rapidly". Chemical analysis of the iodide made in Prof. GOVINDACHARI's laboratory showed that it was anhydrous having the formula $C_{22}H_{29}O_4N_2I$. No analysis was done on the chloride but the needle shape of the crystals was taken to indicate the absence of water of crystallization.

Crystal data

The substances were in the form of pale yellow flaky needles. Parallel extinction under the polarizing microscope suggested ortho-rhombic symmetry. Table 1 gives the crystal and physical data for echitamine iodide and chloride. The measured value of density for the

[4] A. J. BIRCH, H. F. HODSON and G. F. SMITH, Echitamine. Proc. Chem. Soc. 1959, 224.

[5] A. CHATTERJEE, S. GHOSAL and S. GHOSH MAJUMDAR, Echitamine, the major alkaloid of *Alstonia scholaris* R. BR. Chem. and Ind. 1960, 265—267.

[6] H. CONROY, R. BERNASCONI, P. R. BROOK, R. IKAN, R. KURTZ and K. W. ROBINSON, The structure of echitamine. Tetrahedron Letters. No. 6, 1960, 1—9.

[7] D. CHAKRAVRATI, R. N. CHARKAVARTI, R. GHOSE and Sir ROBERT ROBINSON, Echitamine. Tetrahedron Letters. No. 11, 1960, 25—26.

[8] A. J. BIRCH, H. F. HODSON, B. MOORE, H. POTTS and G. F. SMITH, Echitamine. Tetrahedron Letters. No. 19, 1960, 36—42.

Table 1. *Crystal data for echitamine halides*

	Echitamine iodide	Echitamine chloride
Formula-weight	512.4	420.9
Melting point	267°C	295°C
Space group	Orthorhombic $P2_12_12_1 - D_2^4$	Orthorhombic $P2_12_12_1 - D_2^4$
Axial dimensions in Å units a	18.45	17.29
b	13.83	14.97
c	8.48	7.94
Volume of the unit cell (Å³)	2163.8	2055.1
Density (measured) g/cm³	1.583	
Density (calculated) g/cm³	1.573	1.361
Number of molecules per unit cell	4	4
Total number of electrons per unit cell $F(000)$	1040	896
Linear absorption coefficient for Cu$K\alpha$ radiation per cm	130	20

iodide confirmed the anhydrous nature of the crystal. The differences in cell dimensions which were obtained from rotation and Weissenberg photographs seemed to indicate that the isomorphism between the two halides may not be exact.

Intensity data

Intensity data were collected for the $hk0$, $0kl$ ($l = 1$ to 5) and $h0l$ zones with Cu$K\alpha$ radiation employing the multiple-film Weissenberg technique. Linear integration[9] of the spots was effected by moving the cassette in the direction of its motion through equal distances of approximately 0.15 mm at periodic intervals using a simple screw arrangement. Eight to twelve movements were normally made. The intensities were measured visually with calibrated intensity scales prepared from the same crystal with the spots integrated in a similar manner. In the $hk0$ zone there were 196 and 166 reflections of measur-

[9] E. Stanley, A one-dimensional integrating method for estimating the intensities on upper level equi-inclination Weissenberg photographs. Acta Crystallogr. 8 (1955) 58—59.

able intensity for the iodide and chloride respectively, while in the $h0l$ zone there were 114 spots in the case of the iodide.

The hkl reflections for the iodide were photographed with a needle-like crystal of nearly cylindrical cross-section ($r = 0.11$ mm). There was therefore no difficulty in obtaining the absorption factors. On the other hand, the specimen used for getting the $h0l$ data was not satisfactory as it was obtained by cutting the crystal perpendicular to the needle axis. Its dimensions varied between 0.16 and 0.48 mm. The absorption correction was however applied assuming that the crystal was cylindrical with a mean radius of 0.16 mm. No correction was considered necessary for the chloride data. Lorentz and polarization corrections were also applied for the different layers and the intensities were approximately scaled up by WILSON's method.

$hk0$ projection

It was intended to solve the structure in projections owing to lack of computational facilities for three-dimensional work. Though the space-group has no centre of symmetry, it is fortunate that all three projections are centrosymmetric (pgg*)for this considerably simplified the calculations. Since there are four molecules in the unit cell, with the space-group having four general equivalent positions, all the atoms should occupy general positions.

An $hk0$ Patterson synthesis gave the position of iodine in fractional coordinates. The phases of 70 reflections for the iodide and 52 for the chloride were deduced with some degree of certainty by the 'isomorphous replacement' method, true isomorphism being assumed. However it was decided to proceed with the solution of the structure of the iodide as it was felt that the 'heavy atom' method would be particularly suitable here in the determination of phases $\left(\frac{Z^2_{\text{iodine}}}{\Sigma Z^2_{\text{light atoms}}} = 2.4\right)$.

A Fourier synthesis with the 70 amplitudes confirmed the iodine position and in addition it showed a large number of peaks. On making a structure-factor calculation putting seventeen atoms at the peaks, all the atoms being assigned the scattering factor of carbon, the signs of 66 more reflections could be deduced. In the Fourier projection (Fig. 2) with these terms included, the phenyl ring and a five-membered ring could be easily distinguished. The iterative process of Fourier synthesis was continued incorporating more high-angle amplitudes and omitting doubtful ones, until all 28 light atoms in the molecule

* International tables for x-ray crystallography, 1952, Vol. I, p. 63, No. 8.

(excluding hydrogens) could be put at the peaks. A structure factor computation assuming all the atoms to be carbons gave the signs of 169 amplitudes and the R index for the observed reflections was 0.28. A fairly accurate idea of the scale and temperature factors ($B = 2.6$) could also be obtained.

A subtraction Fourier synthesis with the temperature-corrected iodine contribution removed from the observed amplitudes was next made and it showed very much better resolution. Calculation of the
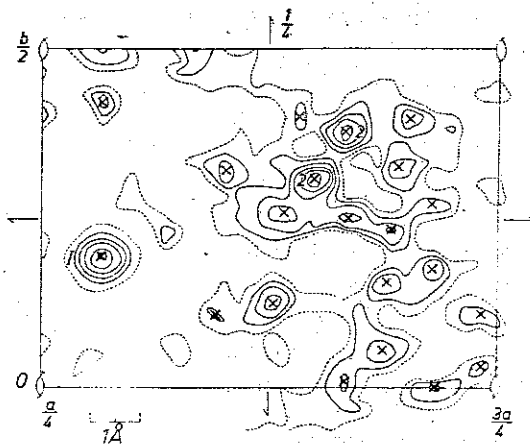
Fig. 2. Echitamine iodide. Second ($hk0$) Fourier synthesis. Contours are drawn at arbitrary intervals. Positions where atoms were placed for the structure factor computation are indicated by crosses

structure factors for the 'bad' reflections with the atoms moved to the peaks gave the phases of six more reflections, all of which made significant contributions to the iodine-removed synthesis. The Fourier map that followed indicated movements of eight atoms and these when made brought down the R factor to 0.22.

In spite of this improvement there were large discrepancies in the case of quite a few reflections. A difference-error synthesis was therefore indicated and this (Fig. 3) showed six atoms in deep negative areas. On moving them to high positive regions, not only did the R index come down to 0.19, but most of the large differences were considerably reduced, resulting in the signs of 33 more reflections, most of them medium to weak ones, being fixed. The most important sign obtained at this stage was that of 210 and it proved to be opposite

to that given by the heavy atom method. ($F_o = +21.5$; $F^{I}_{calc.} = -35$). This reflection made a large contribution of $+56.5$ to the subtraction Fourier which was subsequently made. A second difference synthesis was simultaneously computed.

The Fourier map showed significant changes compared to the previous one. The positive region had shrunk considerably owing to the suppression of many spurious peaks and the positions of some peaks had shifted. A structure factor calculation after making three
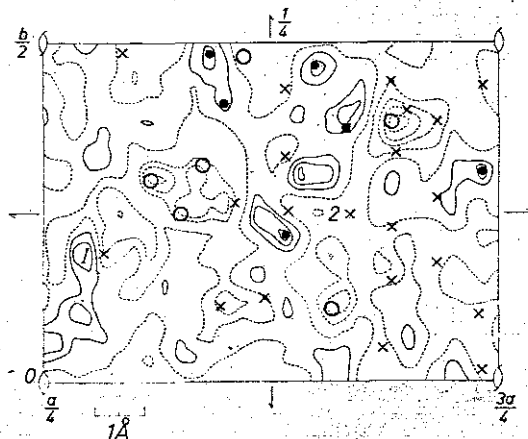
Fig. 3. Echitamine iodide. Difference-error synthesis ($hk0$). Contours are drawn at arbitrary intervals. Negative areas are indicated by broken lines. The atoms that were removed on the basis of this synthesis are shown by open circles, their new positions by full circles and the rest of the atoms by crosses

atomic movements gave the phases of 192 out of 196 reflections. A Fourier map including all these amplitudes formed the basis for the identification of the molecule, full use being made of the available chemical data.

The $hk0$ Fourier map (Fig. 4) showed very clearly a phenyl ring with a five-membered ring fused to it. This five-membered ring appeared to be fused on to two other rings, one five-membered and the other a six-membered 'boat'-shaped ring (dotted lines) along a common bond. The carbomethoxy group
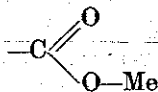
is attached to the six-membered ring at the equatorial position. The heavy peak at the centre of the first five-membered ring is due to two atoms and is therefore presumably the C and O of the CH_2OH. This group is attached to the same carbon atom of the 'boat' as the carbomethoxy
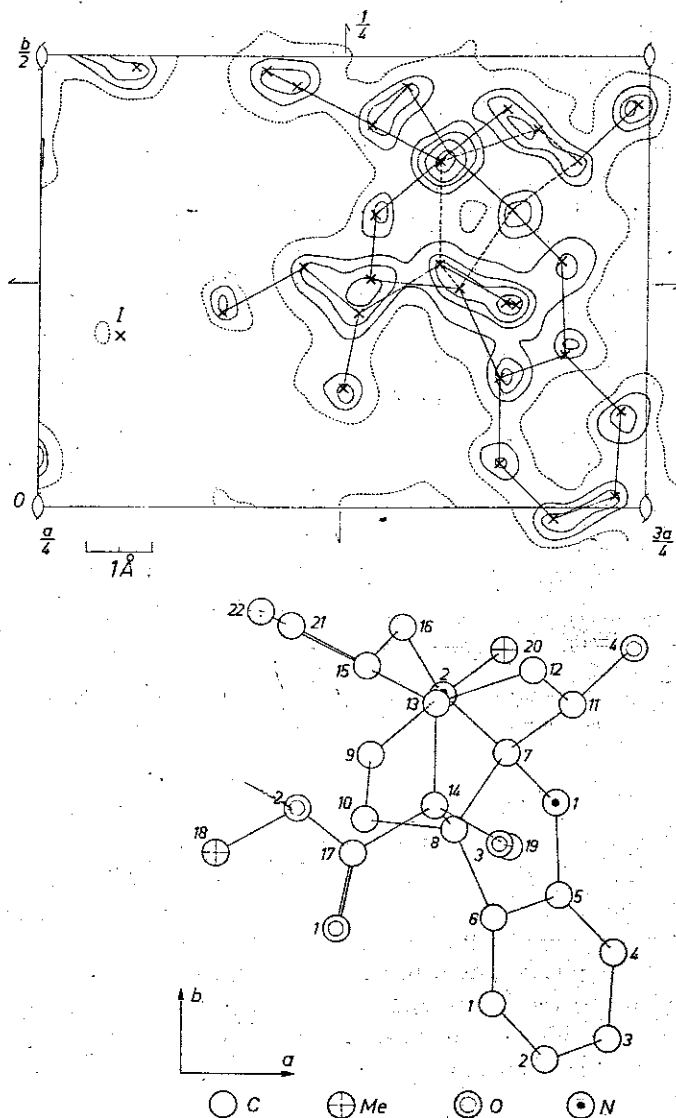
Fig. 4. Echitamine iodide. Final $(hk0)$ iodine removed Fourier projection and view of the molecule down the c axis. Contours are drawn at arbitrary intervals

group. An oxygen atom, probably the OH group, is attached to the opposite end of the 'boat'. The N^+—Me and =CH—Me groups could also be approximately identified although the manner in which the latter is joined to the main structure was not clear. However, it was obvious even at an early stage of the work that none of the structures II, III and IV (Fig. 1) are compatible with the $hk0$ Fourier map.

For deducing the structure, a model given by V (Fig. 5) which satisfied all the points mentioned above was tried. It appeared to have the further merit in having the φ-N-C-N structure advocated by both GOVINDACHARI[3] and BIRCH[8], and also the same number of five and six-membered rings as in the structures of CONROY[6] and ROBINSON[7]. A structure-factor calculation identifying the peaks according to the model gave an R factor of 0.16 for the observed reflections and the unobserved ones also calculated quite low. However, when the three-dimensional model was made, it was found to explain all the peaks in the map except two which correspond to the present positions of atoms C_{21} and C_{22}.
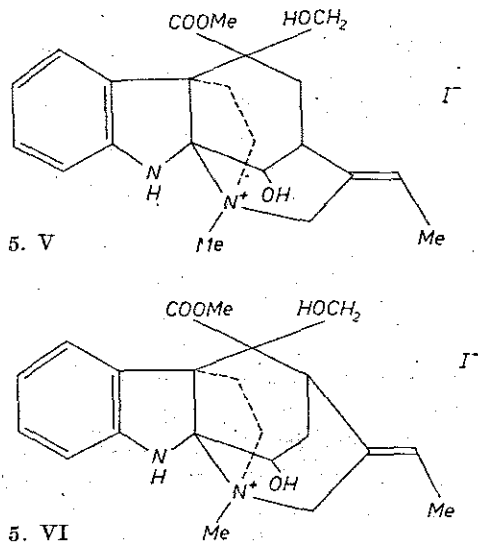
Fig. 5. V shows the tentative structure proposed for echitamine iodide and VI the correct structure

At this stage information was received that Prof. J. M. ROBERTSON had solved the structure of echitamine bromide. Prof. ROBERTSON subsequently informed the authors that the compound used by him was echitamine bromide with one molecule of methanol as solvate $(C_{22}H_{29}O_4N_2Br$, MeOH. Space-group: $P2_12_12_1$; $a = 14.72$ Å, $b = 14.17$ Å, $c = 11.09$ Å) and he was also gracious enough to send a prepublication report of his work[10] which showed that the structure corresponded to VI (Fig. 5). This differed from the tentative structure V in that C_{15} was bonded to C_{13} instead of to C_{12}, making the lower six-membered

[10] J. A. HAMILTON, T. A. HAMOR, J. M. ROBERTSON and G. A. SIM, The structure of echitamine. Proc. Chem. Soc. 1961, 63—64.

ring into a seven-membered one. With structure VI, all the atomic peaks could be most satisfactorily explained. A preliminary note[11] on the work done upto this stage was published. The existence of the seven-membered ring has been established beyond doubt in the other two projections.

$h0l$ projection

The coordinates of the iodine atom in this projection were obtained from a Patterson synthesis, and the phases of 101 amplitudes deduced by the 'heavy atom' method. The amplitudes were scaled up by comparing the axial spots $(h00)$ with the same reflections in the $hk0$ zone. An iodine-removed Fourier synthesis was now made but the molecule could not be unambiguously identified. A structure-factor calculation putting 28 atoms at the peaks gave an R index of 0.22 for the observed reflections. Some large discrepancies for many low-angle spots suggested an error-difference synthesis on the basis of which six atoms were shifted to positive regions. The movements resulted in a fall of the R factor to 0.19. Now using the three-dimensional model and the $hk0$ projection, atoms were placed along the common x coordinates, and the molecule tentatively identified.

It was noticed that the phenyl ring and the attached five-membered ring were practically vertical in this projection with the iodine atom also situated in this region. Thus owing to the considerable overlap of these atoms, the identification in this region was uncertain. Also, the atom C_{22} could either be *cis* or *trans* with respect to C_{13}, and a choice between the two corresponding z coordinates could not be unequivocally made in this projection. The presence of a large peak in the region ($z = 0.667$ in fractional coordinates) resulted in its being placed *trans* to C_{13}. On the other hand, the second five-membered ring (containing the quarternary nitrogen) and the six and seven-membered rings were well resolved , and it was evident that C_{15} could be linked only to C_{13} and not to C_{12}. The possible ambiguity was thus resolved and structure VI confirmed. A structure-factor calculation putting atoms according to this identification showed that the R factor had risen to 0.23 indicating that a few atomic positions were incorrect.

A difference synthesis next made showed the iodine atom to be in a steep gradient. Small movements of 0.001 (in fractional coordinates) indicated by a 'least-squares' refinement did not, however, lead to

[11] H. MANOHAR and S. RAMASESHAN, Thestructure of echitamine iodide. Curr. Sci. **30** (1961) 5—7.

improvement in the structure-factor calculation, even though this served to confirm the accuracy of the iodine position. Difference syntheses made at this stage proved difficult to interpret and gave no clear indication of movements of the light atoms. An unexplained positive region (at $x = 0.767$, $z = 0.933$ in fractional coordinates) in
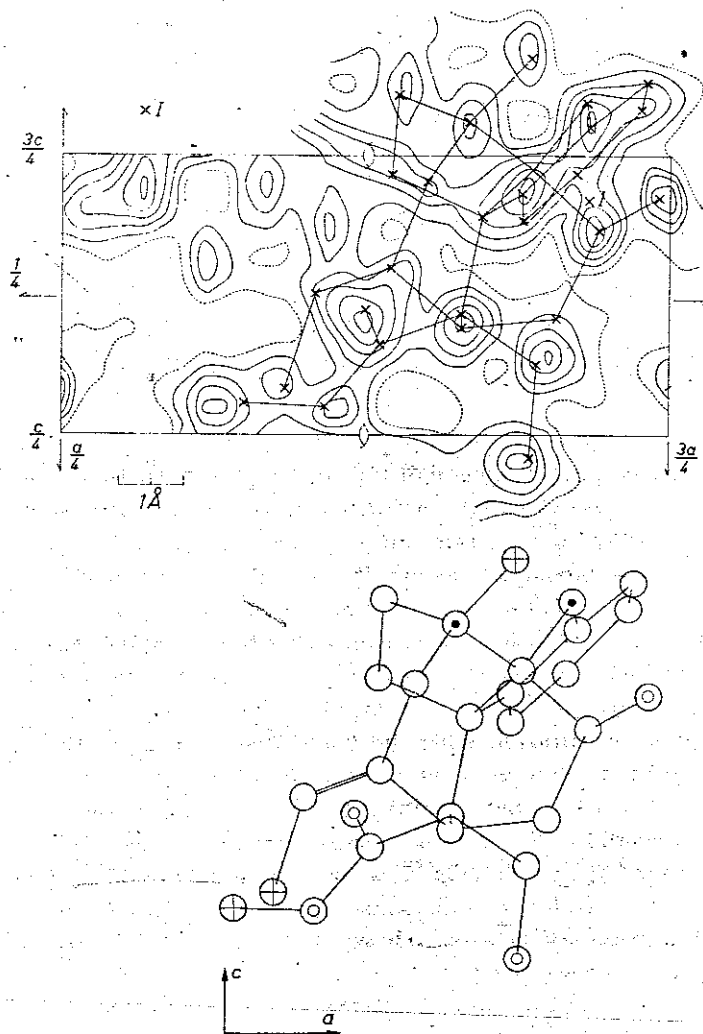
Fig. 6. Echitamine iodide. Final $(h0l)$ iodine removed Fourier projection and identification of the atoms in the molecule. Contours are drawn at arbitrary intervals

successive difference syntheses, however, suggested a slightly different
identification of the phenyl and attached five-membered rings, the
new orientation of the molecule having the additional merit of tallying
better with $hk0$ projection. These changes considerably improved
many 'bad' reflections. A few more small movements of atoms followed
by a slight increase in the scale factor on the observed amplitudes
brought the R factor down to 0.175.

The refinement of the atomic coordinates was stopped at this stage
for the following reasons. The diffraction effects due to the iodine atom
could never be completely eliminated and therefore the coordinates
of atoms lying in its vicinity could not be refined. It was hoped to
overcome this difficulty in the $0kl$ projection where this overlap did
not exist. Again the non-uniformity in the dimensions of the crystal
resulted in considerable variation in the size and shape of the spots
and this affected the accuracy of the intensity data. These factors
notwithstanding, the fairly good agreement between the F_o's and
F_c's testified to the correctness of the identification of the molecule.

$0kl$ projection

Since photographs had not been taken with the crystal mounted
along the a axis, data for this zone were obtained by selecting the
appropriate terms from the hkl reflections ($l = 0$ to 5). The intensity
data were incomplete as amplitudes with $l = 6$ to 10 were not available.
The intensities were corrected for Lorentz, polarization and absorption
factors[12] and scaled up by comparing the $h0l$ reflections in each layer
(l) picked out just as before from the hkl data with the corresponding
reflections obtained by rotating the crystal about its b axis. A structure
factor computation using the k and l coordinates of the previous two
projections gave an R index of 0.25 for reflections in the measurable
range. The calculation also gave the signs of 64 out of 68 observed
coefficients. A Fourier synthesis was made with the iodine contribution
removed. This map (Fig. 7) showed that the atoms of the phenyl ring
and attached five-membered ring were well separated with only C_5 being
close to the iodine atom. However, the resolution was poor with most
of the atoms lying in three large positive regions. Using the iterative
process of Fourier and difference syntheses, and comparing this pro-

---

[12] W. L. BOND, Equi-inclination Weissenberg intensity correction factors
for absorption in spheres and cylinders, and for crystal monochromatised radia-
tion. Acta Crystallogr. 12 (1959) 375—381.

jection with the other two, and the three-dimensional model, 12 atomic movements were made and the R factor brought down to 0.195.

In this projection large discrepancies were observed for six intense low angle reflections, the calculated values being greater than the observed ones in every case. This suggested a possible error in the
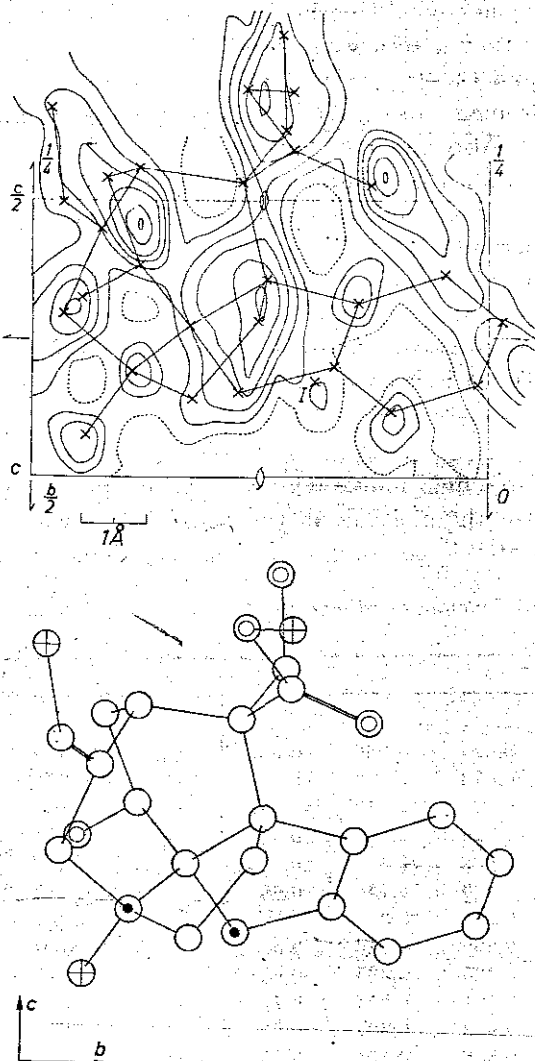
Fig. 7. Echitamine iodide. Final iodine removed Fourier projection (0kl), and view of the molecule down the a axis. Contours are drawn at arbitrary intervals

Lorentz and polarization factors which vary rapidly at very low and high angles of $\sin^2\theta$. A 'least-squares' refinement of the appropriate cell dimension c showed a small correction for ζ, the layer spacing, and when the corrected Lorentz and polarization factors were applied, most of the reflections showed considerable improvement and the R factor dropped to 0.165.

Interatomic bond lengths and valency angles were now calculated. Generally they agreed with standard values. However, two distances C_8-C_{14} and $C_{14}-C_{13}$ (≈ 1.75 Å) were in error and this necessitated large movements of C_{13} and C_{14} from high positive regions in the $0kl$ projection. Also the angle $C_{15}-C_{21}-C_{22}$ was found to calculate as low as $86°$, again raising doubts about the correctness of the z coordinate of C_{22}. In fact a calculation of intermolecular closest contact distance showed that the assigned position was not chemically feasible. When C_{22} was moved to the alternate position *cis* to C_{13} ($z = 0.333$ in fractional coordinates), not only did the above mentioned angle approach the theoretical value, but some of the existing discrepancies also improved. The R index with these changes was 0.145.

Results

The three final iodine removed Fourier projections and the identification of the molecule in the maps are shown in Figs. 4, 6 and 7. The final atomic coordinates are listed in Table 2. These are referred

Table 2. *Final atomic coordinates in the space group $P2_12_12_1$ for echitamine iodide expressed in fractions of the cell edges*

Atom	x	y	z	Atom	x	y	z
I	0.317	0.192	0.828	C_{15}	0.521	0.425	0.550
C_1	0.629	0.050	0.633	C_{16}	0.550	0.467	0.703
C_2	0.673	−0.012	0.717	C_{17}	0.513	0.217	0.412
C_3	0.725	0.013	0.833	C_{18}	0.400	0.217	0.308
C_4	0.729	0.108	0.883	C_{19}	0.642	0.225	0.375
C_5	0.683	0.171	0.800	C_{20}	0.633	0.442	0.925
C_6	0.629	0.146	0.683	C_{21}	0.458	0.467	0.504
C_7	0.638	0.329	0.725	C_{22}	0.433	0.483	0.333
C_8	0.596	0.246	0.642	N_1	0.679	0.275	0.846
C_9	0.525	0.325	0.858	N_2	0.583	0.392	0.808
C_{10}	0.521	0.254	0.717	O_1	0.500	0.133	0.475
C_{11}	0.692	0.383	0.617	O_2	0.467	0.267	0.300
C_{12}	0.658	0.421	0.458	O_3	0.633	0.229	0.208
C_{13}	0.579	0.383	0.442	O_4	0.742	0.446	0.675
C_{14}	0.579	0.271	0.467				

Table 3. *Observed and calculated structure factors for echitamine iodine.* The calculations have been made with the atomic coordinates given in Table 2 for the asymmetric unit containing one molecule

h	k	l	F_o	F_c	h	k	l	F_o	F_c	h	k	l	F_o	F_c	h	k	l	F_o	F_c
0	2	0	43.6	-49.7	7	7	0	15.4	-12.7	15	3	0	12.0	12.6	3	8	0		-4.9
0	4	0	29.6	28.3	7	9	0		-2.2	15	5	0	17.5	-18.0	3	10	0	12.4	-8.9
0	6	0	8.2	6.0	7	11	0	11.6	13.5	15	7	0	9.7	8.9	3	12	0	13.1	13.8
0	8	0	18.1	-16.3	7	13	0	11.0	-11.6	15	9	0		-0.7	3	14	0	9.8	-7.2
0	10	0	14.5	13.6	7	15	0	6.7	6.8	15	11	0	5.0	-4.6	3	16	0		1.3
0	12	0	6.1	-6.2	7	17	0		-0.7	15	13	0	7.2	7.6	4	1	0	30.0	-33.8
0	14	0	8.9	-5.7	8	0	0	23.8	-23.4	16	0	0	15.2	16.7	4	3	0	17.4	18.6
0	16	0	10.8	7.7	8	2	0	21.6	17.9	16	2	0	11.4	-7.8	4	5	0	8.2	12.3
1	1	0	*	18.7	8	4	0		-5.4	16	4	0		-1.1	4	7	0	20.3	-22.5
1	3	0	42.3	-44.8	8	6	0	20.7	-19.7	16	6	0	9.3	10.8	4	9	0	21.4	22.5
1	5	0	25.5	21.4	8	8	0	17.5	15.4	16	8	0	10.8	-11.2	4	11	0	12.3	-10.9
1	7	0	23.8	-25.5	8	10	0	20.0	-21.4	16	10	0	5.6	5.6	4	13	0		-1.0
1	9	0	5.3	-6.7	8	12	0		3.4	16	12	0	6.1	-4.6	4	15	0	8.8	8.8
1	11	0	11.4	-11.5	8	14	0	6.9	6.8	17	1	0		5.4	4	17	0	8.8	-8.1
1	13	0	15.5	-14.9	8	16	0	7.5	-7.1	17	3	0	8.4	-8.3	5	2	0	27.9	-29.3
1	15	0	8.0	8.0	9	1	0	10.5	-9.1	17	5	0	6.8	6.0	5	4	0	31.4	30.6
1	17	0		0.3	9	3	0	30.1	30.4	17	7	0		-2.6	5	6	0	12.8	-11.0
2	0	0	*	-12.8	9	5	0	21.2	-21.9	17	9	0		-0.5	5	8	0		3.9
2	2	0	8.4	4.6	9	7	0	10.5	13.1	17	11	0		5.0	5	10	0	9.2	8.1
2	4	0	6.6	4.3	9	9	0	16.3	-13.6	18	0	0	11.7	-9.5	5	12	0	17.6	-16.8
2	6	0	20.0	-18.9	9	11	0		-0.7	18	2	0	8.7	7.5	5	14	0	11.1	10.6
2	8	0	23.9	24.1	9	13	0	9.8	9.0	18	4	0		-0.1	5	16	0		-3.1
2	10	0	17.5	-16.1	9	15	0	5.3	-1.0	18	6	0		2.0	6	1	0	24.9	27.2
2	12	0		2.7	10	0	0	15.9	10.7	18	8	0		3.2	6	3	0	13.9	-16.6
2	14	0		2.1	10	2	0	21.3	-20.4	18	10	0		0.2	6	5	0		2.5
2	16	0	5.4	-6.2	10	4	0		-5.7	19	1	0		-3.2	6	7	0	14.2	14.7
3	1	0	4.6	2.5	10	6	0		5.6	19	3	0		-2.1	6	9	0	9.4	-8.0
3	3	0		1.4	10	8	0		-3.0	19	5	0		1.1	6	11	0		4.0
3	5	0	18.0	-18.6	10	10	0	9.6	9.2	19	7	0		-2.9	6	13	0		-1.5
3	7	0	11.1	8.3	10	12	0		-2.5	19	9	0		-0.8	6	15	0	3.2	-3.1
3	9	0	4.4	4.5	10	14	0		-1.1	20	0	0	6.4	-10.3	6	17	0	5.4	3.7
3	11	0		2.3	10	16	0	5.4	4.1	20	2	0		4.5	7	2	0	8.2	-5.3
3	13	0		2.5	11	1	0		-1.9	20	4	0		-1.6	7	4	0	3.3	-4.1
3	15	0		-3.1	11	3	0		0.2	20	6	0		-2.9	7	6	0	5.0	4.6
3	17	0		1.6	11	5	0		3.0	20	8	0		3.1	7	8	0		1.1
4	0	0	9.9	-10.1	11	7	0		3.4	21	1	0		-0.6	7	10	0	12.4	-13.7
4	2	0	12.4	15.5	11	9	0		-0.8	21	3	0	6.0	7.9	7	12	0	7.4	5.4
4	4	0	2.2	-4.5	11	11	0		4.6	21	5	0	5.1	-6.1	7	14	0		-0.9
4	6	0		0.2	11	13	0		-1.0	21	7	0	3.6	3.6	7	16	0		1.6
4	8	0		4.6	11	15	0		1.3	22	0	0	8.4	12.3	8	1	0	5.0	3.8
4	10	0		-1.4	12	0	0	9.1	10.4	22	2	0	6.9	-6.6	8	3	0		1.2
4	12	0		-0.2	12	2	0		-5.4	22	4	0		-0.7	8	5	0		-1.8
4	14	0		-0.6	12	4	0		-3.5	22	6	0	3.4	4.7	8	7	0		-1.0
4	16	0		0.3	12	6	0		-1.0	23	1	0		1.8	8	9	0		1.0
5	1	0		-4.8	12	8	0		-1.6	23	3	0	3.1	-5.1	8	11	0	5.7	7.2
5	3	0	10.6	14.6	12	10	0	6.5	8.7	1	2	0	3.0	1.1	8	13	0		2.2
5	5	0	14.8	-16.9	12	12	0		-0.9	1	4	0	35.5	40.6	8	15	0	3.2	-3.7
5	7	0	7.0	6.6	12	14	0		0.2	1	6	0	6.6	-5.7	9	2	0		0.0
5	9	0		-0.8	13	1	0	8.9	10.4	1	8	0	4.8	4.6	9	4	0	16.2	-17.7
5	11	0	10.7	-11.0	13	3	0	12.8	-14.2	1	10	0		3.4	9	6	0	8.9	7.7
5	13	0	6.2	7.2	13	5	0	9.7	12.3	1	12	0		-1.7	9	8	0		-2.1
5	15	0		-4.2	13	7	0	8.6	-10.1	1	14	0	6.3	7.5	9	10	0	10.8	-14.7
5	17	0		1.1	13	9	0		1.2	1	16	0	3.4	-3.5	9	12	0	4.5	6.8
6	0	0	35.1	43.7	13	11	0		3.1	2	1	0	19.8	-18.3	9	14	0	7.1	-7.9
6	2	0	35.4	-36.8	13	13	0	3.2	-4.3	2	3	0	20.2	-23.4	9	16	0		0.3
6	4	0		2.5	13	15	0		3.0	2	5	0	15.6	-14.7	10	1	0	24.5	-20.8
6	6	0	18.5	17.1	14	0	0	15.8	-17.9	2	7	0	25.5	25.9	10	3	0	3.7	6.9
6	8	0	19.1	-22.6	14	2	0	11.6	15.1	2	9	0	20.4	-19.1	10	5	0		5.0
6	10	0	15.6	11.6	14	4	0	4.7	-7.2	2	11	0	12.2	13.2	10	7	0	23.7	-21.9
6	12	0		-0.7	14	6	0		-8.5	2	13	0		0.4	10	9	0	18.2	12.6
6	14	0		-0.2	14	8	0	14.0	14.9	2	15	0		-2.7	10	11	0	6.6	-5.7
6	16	0	6.8	5.9	14	10	0	6.5	-8.2	2	17	0	7.4	7.4	10	13	0		-0.2
7	1	0	12.3	12.5	14	12	0		1.6	3	2	0	25.5	31.8	10	15	0	5.1	3.7
7	3	0	34.8	-34.1	14	14	0	3.2	3.4	3	4	0	38.0	-42.5	11	2	0	17.5	-17.6
7	5	0	24.2	22.6	15	1	0	4.8	-4.3	3	6	0	34.2	36.5	11	4	0	26.2	24.6

H. MANOHAR and S. RAMASESHAN

Table 3. (Continued)

h k l	F_o	F_c	h k l	F_o	F_c	h k l	F_o	F_c	h k l	F_o	F_c
11 6 0	24.3	− 21.4	22 3 0		− 0.3	4 0 6		− 0.2	12 0 3	15.0	15.4
11 8 0		− 2.3	22 5 0		− 1.8	6 0 6	9.2	9.4	14 0 3	11.6	− 10.6
11 10 0	11.6	11.9	22 7 0		0.7	8 0 6	13.4	− 15.6	16 0 3	4.6	− 6.3
11 12 0	11.8	− 10.1	23 2 0		− 2.7	10 0 6		5.7	18 0 3	8.9	7.3
11 14 0	9.1	9.4	23 4 0		1.4	12 0 6		4.1	20 0 3	7.4	− 6.5
12 1 0	21.4	22.2	1 0 1	31.3	34.7	14 0 6	8.3	− 10.0	22 0 3	3.8	2.2
12 3 0	4.9	− 7.6	3 0 1	51.0	− 61.8	16 0 6	7.2	6.6	1 0 4	33.3	− 39.6
12 5 0		− 1.6	5 0 1	42.2	47.7	18 0 6	2.8	− 0.9	3 0 4	9.2	− 6.3
12 7 0	17.8	15.3	7 0 1	16.2	− 11.3	20 0 6		− 2.2	5 0 4	14.5	12.0
12 9 0	12.9	− 13.5	9 0 1	16.6	− 13.7	1 0 7		4.0	7 0 4	14.7	− 19.5
12 11 0	8.3	8.9	11 0 1	25.3	22.0	3 0 7	11.7	− 13.5	9 0 4	5.4	6.5
12 13 0		− 1.8	13 0 1	18.4	− 13.4	5 0 7	9.4	12.6	11 0 4		0.8
12 15 0	3.2	− 3.6	15 0 1	3.8	− 3.1	7 0 7		− 2.0	13 0 4	4.6	− 7.2
13 2 0	10.8	10.5	17 0 1	10.0	10.9	9 0 7		− 5.9	15 0 4	10.1	10.8
13 4 0	14.8	− 12.9	19 0 1	12.7	− 11.1	11 0 7	6.0	7.8	17 0 4	7.7	− 6.9
13 6 0	11.3	10.3	21 0 1	6.4	3.8	13 0 7	4.5	− 6.9	19 0 4		0.0
13 8 0		− 2.8	23 0 1		1.9	15 0 7		− 0.9	21 0 4	3.1	4.0
13 10 0	8.7	− 8.5	0 0 2	45.6	− 47.7	17 0 7	3.4	4.1	2 0 5		− 5.0
13 12 0	6.4	6.5	2 0 2	27.5	29.2	0 0 8	9.8	− 11.0	4 0 5	13.0	17.7
13 14 0	5.3	− 5.3	4 0 2	14.1	13.3	2 0 8		4.5	6 0 5		− 5.6
14 1 0	9.1	− 9.6	6 0 2	13.7	− 11.8	4 0 8		1.7	8 0 5		− 3.8
14 3 0		1.8	8 0 2	16.0	15.7	6 0 8		− 4.1	10 0 5	5.4	7.9
14 5 0		− 1.0	10 0 2	5.6	− 1.8	8 0 8		6.1	12 0 5		− 4.7
14 7 0		− 0.9	12 0 2		1.0	10 0 8		− 2.5	14 0 5		2.0
14 9 0	7.5	6.3	14 0 2	12.0	12.7	12 0 8		− 2.7	16 0 5		3.6
14 11 0		− 2.4	16 0 2	9.7	− 7.0	14 0 8		3.9	18 0 5	3.3	− 5.2
14 13 0		− 2.3	18 0 2		2.9	16 0 8	3.2	− 3.0	20 0 5	2.1	1.8
15 2 0	4.3	− 4.8	20 0 2		3.7	1 0 9		− 0.9	1 0 6		5.7
15 4 0		− 0.6	22 0 2	5.1	− 3.9	3 0 9		3.4	3 0 6		− 0.9
15 6 0		− 2.0	1 0 3	12.3	− 8.7	5 0 9		− 1.9	5 0 6		0.3
15 8 0		− 0.3	3 0 3		1.3	7 0 9		0.7	7 0 6	5.1	5.1
15 10 0		− 1.3	5 0 3	9.1	− 5.1	9 0 9		2.2	9 0 6	9.6	5.9
15 12 0		4.1	7 0 3	6.1	− 0.3	11 0 9		− 1.9	11 0 6		2.7
16 1 0	11.0	− 13.5	9 0 3	5.8	6.5	13 0 9		− 0.5	13 0 6		2.0
16 3 0		5.5	11 0 3	5.5	− 7.9	0 0 10		0.0	15 0 6		− 0.7
16 5 0		− 0.1	13 0 3	8.7	− 4.4	2 0 10		1.2	17 0 6		0.9
16 7 0		− 3.0	15 0 3		− 1.4	4 0 10		0.4	19 0 6		0.4
16 9 0		4.0	17 0 3		− 1.5	6 0 10		− 0.6	2 0 7		− 4.7
16 11 0		− 2.2	19 0 3		0.0	8 0 10		0.9	4 0 7	5.0	5.6
16 13 0		0.3	21 0 3		− 0.3	2 0 1	27.6	− 28.5	6 0 7		2.5
17 2 0	10.6	− 13.1	23 0 3		− 0.5	4 0 1	22.6	20.5	8 0 7		1.2
17 4 0	9.7	11.8	0 0 4	19.5	− 13.8	6 0 1	4.4	− 4.1	10 0 7		2.5
17 6 0		− 4.0	2 0 4	20.6	19.3	8 0 1	4.3	− 4.9	12 0 7	3.5	− 1.6
17 8 0		2.4	4 0 4		2.5	10 0 1	20.2	14.2	14 0 7		3.5
17 10 0		4.4	6 0 4	3.6	− 3.7	12 0 1	10.6	− 10.8	16 0 7		0.1
17 12 0	6.0	− 5.5	8 0 4	10.2	6.7	14 0 1	4.7	0.4	18 0 7		− 0.6
18 1 0	7.7	5.2	10 0 4	3.8	− 5.0	16 0 1		− 1.4	1 0 8		5.7
18 3 0		− 5.6	12 0 4		− 0.7	18 0 1	6.1	− 5.6	3 0 8		− 1.8
18 5 0		− 4.7	14 0 4	5.7	4.6	20 0 1	4.3	2.4	5 0 8		1.0
18 7 0	6.7	5.8	16 0 4	5.9	− 3.9	22 0 1		− 1.3	7 0 8		3.8
18 9 0	8.4	− 8.6	18 0 4		1.4	1 0 2	34.1	34.2	9 0 8		− 6.5
18 11 0	3.3	4.7	20 0 4		1.9	3 0 2		− 1.8	11 0 8		− 1.6
19 2 0		5.2	22 0 4	2.5	− 1.7	5 0 2	17.7	− 13.2	13 0 8		1.4
19 4 0	9.7	− 9.9	1 0 5	13.6	− 14.7	7 0 2	24.1	22.3	15 0 8	2.9	− 3.7
19 6 0	7.4	8.3	3 0 5	18.9	20.7	9 0 2	14.4	− 14.9	2 0 9		5.0
19 8 0		− 0.1	5 0 5	17.2	− 16.7	11 0 2	6.2	4.4	4 0 9		− 6.1
19 10 0	4.1	− 4.4	7 0 5	8.3	5.8	13 0 2	10.8	9.6	6 0 9		4.1
20 1 0		− 5.0	9 0 5		4.3	15 0 2	18.8	− 17.3	8 0 9		1.1
20 3 0		5.5	11 0 5	14.0	− 14.4	17 0 2	9.3	6.6	10 0 9		− 4.2
20 5 0		1.4	13 0 5		4.4	19 0 2		− 0.8	12 0 9		4.2
20 7 0	5.4	− 5.7	15 0 5		3.0	21 0 2	3.2	− 2.1	1 0 10		− 5.9
20 9 0	6.1	6.7	17 0 5	4.3	− 5.6	23 0 2	4.0	3.3	3 0 10		− 0.2
21 2 0	3.4	− 4.7	19 0 5	5.1	5.4	2 0 3	25.2	19.7	5 0 10		− 0.3
21 4 0	5.5	6.5	21 0 5	4.5	− 2.1	4 0 3	35.6	− 38.3	7 0 10		− 4.5
21 6 0	3.5	− 3.3	0 0 6	25.0	28.1	6 0 3	9.1	9.1	9 0 10		4.7
21 8 0	2.8	2.9	2 0 6	14.9	− 12.7	8 0 3	9.1	10.2			
22 1 0		1.3				10 0 3	16.0	− 14.2			

Table 3. *(Continued)*

h k l	F_o	F_c	h k l	F_o	F_c	h k l	F_o	F_c	h k l	F_o	F_c
0 1 1	*	− 6.6	0 9 3	23.0	22.7	0 2 1	13.5	13.6	0 10 3		2.4
0 3 1	18.1	− 17.8	0 11 3	14.4	− 12.7	0 4 1	26.7	− 33.1	0 12 3		1.5
0 5 1	13.9	− 16.1	0 13 3	3.3	− 2.3	0 6 1	13.0	12.3	0 14 3		2.2
0 7 1	16.2	16.6	0 15 3	4.9	4.3	0 8 1		0.3	0 16 3		− 1.3
0 9 1	18.4	− 17.2	0 17 3	6.9	− 5.6	0 10 1	12.5	− 12.0	0 1 4	10.9	12.4
0 11 1	6.8	4.7	0 2 4	15.7	9.0	0 12 1	12.6	14.2	0 3 4	13.9	− 18.0
0 13 1		2.4	0 4 4		− 1.7	0 14 1	8.2	− 8.6	0 5 4	26.3	21.8
0 15 1		− 4.0	0 6 4	6.1	− 2.9	0 16 1	4.4	4.5	0 7 4	12.7	− 13.5
0 17 1		2.1	0 8 4	11.6	7.8	0 1 2	13.7	− 13.4	0 9 4	10.8	− 9.2
0 2 2	33.7	30.9	0 10 4	6.5	− 6.3	0 3 2	34.2	31.3	0 11 4	11.7	11.2
0 4 2	23.0	− 21.9	0 12 4		1.4	0 5 2	30.2	− 26.2	0 13 4	10.5	− 11.5
0 6 2	16.2	− 14.9	0 14 4		0.8	0 7 2	12.4	11.8	0 15 4	3.5	− 5.4
0 8 2	13.6	9.6	0 16 4		− 2.4	0 9 2		1.9	0 2 5	14.3	− 14.1
0 10 2	10.3	− 7.5	0 1 5	12.2	12.2	0 11 2	14.3	− 11.7	0 4 5	15.9	14.1
0 12 2		− 1.0	0 3 5	10.1	− 10.2	0 13 2	14.9	12.0	0 6 5	11.8	− 12.4
0 14 2	4.0	4.0	0 5 5	4.7	− 6.8	0 15 2	7.9	− 6.1	0 8 5		− 2.3
0 16 2		− 2.8	0 7 5		7.1	0 17 2		1.0	0 10 5	7.0	5.0
0 1 3	31.4	− 39.1	0 9 5	9.3	− 12.5	0 2 3		− 2.3	0 12 5	8.2	− 7.9
0 3 3	15.5	10.3	0 11 5	7.0	7.8	0 4 3	8.7	8.9	0 14 5	6.0	5.1
0 5 3	14.9	17.1	0 13 5		− 0.6	0 6 3		− 2.8			
0 7 3	16.1	− 20.4	0 15 5		− 2.5	0 8 3		0.7			

The reflections marked * could not be recorded as they were cut off by the beam-catcher.

to the same origin as that given in the International Tables. Table 3 gives the observed and calculated structure amplitudes for the three zones. It should be mentioned that the contributions of the 29 hydrogen atoms have not been taken into account in the calculated amplitudes; nor have the observed intensities been corrected for extinction. The B values used in the $hk0$, $h0l$ and $0kl$ projections are 3.1, 4.0 and 3.6 respectively, the differences being obviously due to the slight inaccuracies in the absorption corrections. The final R factors for reflections of measurable intensity in the three projections are 0.127, 0.175 and 0.145 respectively, the over-all R index for the 379 reflections being 0.145.

The interatomic bond lengths and valency angles are shown in Fig. 8 and their mean values are tabulated in Table 4. Since very great accuracy is not claimed for the structure, (the accuracy of the

Table 4. *Mean interatomic bond lengths and valency angles*

Bond	Mean value	Angle	Mean value
C—C (aromatic)	1.41 Å	C—C—C (aromatic)	119° 10′
C—C (aliphatic)	1.55	C—C—C (tetrahedral)	110° 12′
C=C	1.35	C—C—O ⎫ (double bond)	− 119° 10′
C—O	1.41	C—C—C ⎭	
C—N	1.50		
C=O	1.30		

parameters of the light atoms is ~ 0.05 Å, while those of iodine ~ 0.01Å) small deviations from theoretical values are not of much significance. However, an explanation has been hazarded in the next section in case of two angles $C_7-C_{11}-O_4$ and $C_9-N_2-C_{20}$ which show comparatively large discrepancies.
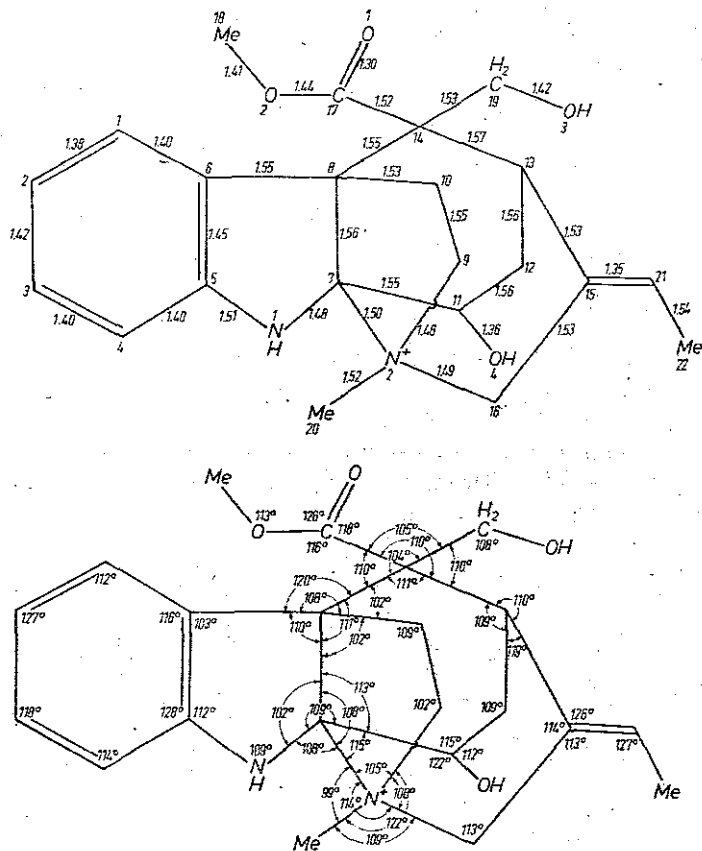

Fig. 8. Interatomic bond lengths and valency angles in echitamine iodide

Table 5 gives the intermolecular closest contact distances. There are 16 contacts of atoms of one molecule with those of other molecules with distances varying between 3.40 to 4.0 Å and these can be regarded as normal van der Waals' contacts. No evidence of hydrogen bonds linking neighbouring molecules is available. The iodine ion is surrounded by 11 atoms at distances less than 4.20 Å satisfying usual packing considerations.

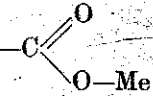Table 5. *Intermolecular closest approach distances*

Bond	Length (Å)	Bond	Length (Å)	Bond	Length (Å)
$C_{18}{}^I$—$O_4{}^{II}$	3.69	$C_{20}{}^I$—$O_1{}^{III}$	3.70	I^I—$C_{10}{}^I$	3.97
$C_1{}^I$—$C_{21}{}^{III}$	3.66	$C_{22}{}^I$—$O_1{}^{III}$	3.55	I^I—$C_4{}^{II}$	4.04
$C_2{}^I$—$C_{21}{}^{III}$	3.40	$C_{22}{}^I$—$O_3{}^{III}$	3.63	I^I—$C_{12}{}^{II}$	4.11
$C_3{}^I$—$C_{21}{}^{III}$	3.71	$C_1{}^I$—$C_3{}^{IV}$	3.80	I^I—$C_{19}{}^{II}$	3.84
$C_6{}^I$—$C_{21}{}^{III}$	3.97	$C_2{}^I$—$C_3{}^{IV}$	3.76	I^I—$N_1{}^{II}$	3.79
$C_{16}{}^I$—$O_1{}^{III}$	3.69	$C_2{}^I$—$C_4{}^{IV}$	3.61	I^I—$O_3{}^{II}$	3.58
$C_{16}{}^I$—$C_1{}^{III}$	3.76	$O_4{}^I$—$C_{12}{}^{IV}$	3.55	I^I—$C_2{}^{III}$	4.11
$C_{17}{}^I$—$C_{22}{}^{III}$	3.98	$O_4{}^I$—$C_{20}{}^{IV}$	3.50	I^I—$C_{12}{}^{III}$	4.19
				I^I—$C_{16}{}^{III}$	3.98
				I^I—$C_{20}{}^{III}$	4.18
				I^I—$O_4{}^{III}$	3.57

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

Discussion

The structure of echitamine iodide, in spite of its complexity, is characterised by an elegant compactness. The fusion of two five-membered rings and a cyclohexane ring along a common bond is of interest from the chemical point of view, as this feature has not been met with in alkaloids so far. The positions of all the attached groups have been definitely established from the x-ray analysis. The COOMe and OH groups are found to be equatorial with respect to the six-membered ring while the CH_2OH is axial. The methyl group of $=CH—CH_3$ is *cis* to C_{13} and *trans* with respect to C_{16}.

There are indications that the various side-chains in the molecule are held together or bound to the main structure by weak hydrogen bonds. For example the short distances $N_1—O_4$ and $O_4—C_{20}$ suggest weak NH—O and CH—O bonds. The formation of these linkages is probably responsible for the distortion of the bonds $N_2—C_{20}$ and $C_{11}—O_4$ resulting in large values for the two angles already mentioned. Again, the $-C\begin{smallmatrix}O\\O-Me\end{smallmatrix}$ group can orient itself in any position about the $C_{14}—C_{17}$ bond and the actual disposition of this group is probably governed by the formation of CH—O bonds linking O_1 to C_1 and O_2 to C_{22} making these distances a minimum. It is also interesting to observe that the CH_2OH group is vertical in the $hk0$ projection with O_3 being approximately symmetrically disposed with respect to C_{13} and C_{17}. This can be explained as due to the effect of hydrogen bonds

$C_{13}H$—O_3 and O_3H—C_{17}. The six short distances which suggest intramolecular hydrogen bonding are shown in Table 6. Finally the attachment of C_{22} *cis* with respect to C_{13} is, as mentioned already, governed by steric considerations, and further stabilised by the formation of the hydrogen bond $C_{22}H$—O_2. The positions of all the attached groups are thus very well explained on the basis of the structure.

Table 6. *Short distances suggesting intramolecular hydrogen bond formation*

Bond	Length (Å)	Bond	Length (Å)
N_1—O_4	3.00	C_{22}—O_2	3.07
O_4—C_{20}	2.92	O_3—C_{17}	2.81
O_1—C_1	2.96	O_3—C_{13}	3.08

It may be mentioned in conclusion that the Fourier summations were made with Beevers-Lipson strips and the rest of the computations using a Marchant electrical calculating machine. The analytical expression of VAND, EILAND and PEPINSKY[13] was used for computing atomic scattering factors.

Acknowledgements

Note added in proof: The ball model shown in Figs. 4, 6 and 7 corresponds to the enantiomorph of the molecular configuration given by the atomic coordinates in Table 2.

That the molecular configuration in the crystal corresponds to this ball model has been subsequently found from the analysis of the absolute configuration of the crystal by anomalous scattering of x-rays (see H. MANOHAR and S. RAMASESHAN, The absolute configuration of echitamine iodide, Tetrahedron Letters No 22, 1961, 814—816).

[13] V. VAND, P. F. EILAND and R. PEPINSKY, Analytical representation of atomic scattering factors. Acta Crystallogr. 10 (1957) 303—306.