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THE ABSOLUTE MOLECULAR STRUCTURE OF HODGKINSINE

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Abstract—Preliminary crystallographic analysis of crystals of the respective benzene and bromobenzene adducts of hodgkinsine, an alkaloid from *Hodgkinsonia frutescens* F. Muell. (family Rubiaceae), together with mass spectral evidence suggested a formulation for hodgkinsine based on three N-methyltryptamine units. X-ray analysis of crystals of the trimethiodide monohydrate, $C_{33}H_{38}N_6.3CH_3I.H_2O$, has defined the absolute molecular structure of hodgkinsine. These crystals are monoclinic belonging to the space group $P2_1$, with $a = 12{\cdot}779$, $b = 13{\cdot}923$, $c = 11{\cdot}190$ Å, $\beta = 107{\cdot}78°$, $Z = 2$. The crystal structure has been solved from data collected with CuKα radiation on a single-crystal diffractometer and refined by least-squares procedures from intensity data re-collected with MoKα radiation. The absolute chirality was defined by Bijvoet's technique. The molecular structure of hodgkinsine is given as I. Two of the N-methyltryptamine units T'' and T''' are in the same configuration while T' is in the opposite. The CD spectrum of hodgkinsine is discussed in relation to these units of different chiralities.

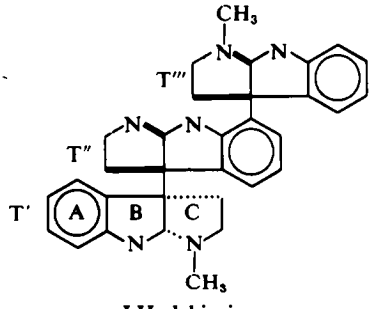
INTRODUCTION

Hodgkinsine was isolated by Anet *et al.*,[1] following observations by Webb[2] in 1949 that positive spot tests for alkaloids were obtained from the leaves of *Hodgkinsonia frutescens*, a shrub growing on the coastal and tableland region of tropical Queensland. Early chemical evidence[1,3] and subsequent mass-spectral data[4] were interpreted as indicating hodgkinsine to be a dimeric indole alkaloid, akin to calycanthine and chimonanthine, both $C_{22}H_{26}N_4$. The structure of calycanthine (II) was established independently by X-ray[5] and chemical study[6] and that of chimonanthine (IIIa; R=R'=H) confirmed by X-ray analysis,[7] following chemical deductions.[8,9]

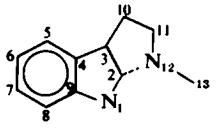
A biosynthetic procedure involving β,β - oxidative dimerisation of two N-methyl tryptamine molecules was suggested[3,6,10] for II, IIIa and other closely-related alkaloids, calycanthidine, $C_{23}H_{28}N_4$, (IIIb; R=H, R'=Me) and folicanthine, $C_{24}H_{30}N_4$, (IIIc; R=R'=Me). Synthesis of *dl*-calycanthine and *dl*-chimonanthine has illustrated the effectiveness of this theory and hence of its potential applicability to hodgkinsine.[1,4]

In our initial attempts to determine the molecular structure of hodgkinsine, the benzene and bromobenzene adducts were studied. Preliminary crystallographic data revealed that $C_{22}N_4$ formulation was unacceptable and necessitated alteration to $C_{33-34}H_{38-39}N_6$. This conclusion was supported by mass spectroscopy with three principal peaks at 172, 344 and 518 indicating a trimeric structure, $C_{33}H_{38}N_6$. Attitulah *et al.*[11] reported similar conclusions regarding the molecular constitution of hodgkinsine in accord with the overall features of our analysis.

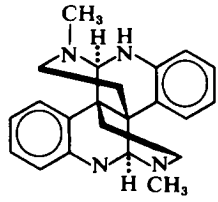
While the X-ray studies of the adducts proved useful in resolving the trimeric nature of hodgkinsine they were less valuable in establishing the detailed structure. For this, an alternative derivative, the tri-methiodide of hodgkinsine proved more successful, defining the structure of hodgkinsine as I. A preliminary report of our conclusions has been presented.[12]



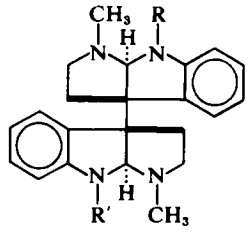
I Hodgkinsine



I(a) N-Methyltryptamine



II Calycanthine



III(a) Chimonanthine (R = R′ = H)
(b) Calycanthidine (R = H,R′ = CH_3)
(c) Folicanthine (R = R′ = CH_3)

STRUCTURE AND DISCUSSION

With three I atoms in the presence of 43 light (non-H) atoms, the parameter precision for the light atoms is relatively low. Estimates from the least-squares refinement and internal evidence *e.g.* the benzene rings, indicate that the probably value for σI (light atom-light atom bonds) is 0·04 Å. Hence comments on the dimensional and conformational aspects of this structure are at a descriptive rather than numerical level.

The average bond lengths for the various types of bonds are as follows, the sample number being given in brackets; $C(sp^2)$—$C(sp^2)$ (18) = 1·40 Å, $C(sp^2)$—$C(sp^3)$ (3) = 1·51 Å, $C(sp^3)$—$C(sp^3)$ (10) = 1·56 Å, N—$C(sp^3)$ (15) = 1·49 Å, N—$C(sp^2)$ (3) = 1·41 Å.

The organic cation consists of three N-methyltryptamine units T′, T″ and T‴—see I and Fig 1*. The T units are essentially alike except in their chirality. T″ and T‴ are identical in absolute configuration while T′ is of opposite configuration. Each L-shaped unit T, **Ia**, involves an essentially planar moeity, the benzene ring and substituent atoms $C_T(3)$ and $N_T(1)$. Ring B is therefore envelope in form with the fifth atom $C_T(2)$ lying 0·20 Å out-of-plane. Ring C is *cis*-fused to ring B. Its shape varies from T′ to T‴ being mainly envelope in form with the out-of-plane atom $C_T(10)$ for T′ and T‴ and $C_T(11)$ for T″.

To form the molecule, units T′ and T″ are linked through C(6), C(15), the grouping around C(6)–C(15) hving a staggered conformation with C(5) C(6) C(15) C(23) virtually coplanar. In chimonanthine, atoms C_T (2), C_T (3), C_T (3), C_T (2) are nearly coplanar. Despite the different chirality relationships of T′ and T″, in both chimonanthine and hodgkinsine the T′T″ entitity tends to *syn*-conformation of rings A_T and A_T. The mode of linkage of T″ and T‴ is different. Unit T‴ is bonded through C(29) [≡C_T(3)] but its junction to T″ is at C(20) [≡C_T(8)], a component atom of the T″ benzene ring. Around C(20)(sp^2)–C(29)(sp^3) the conformation is such that bond C(29)–C(30) lies almost at right angles to the T″ benzene ring. The benzene ring components of T‴ and that of T″ together with C(29) constitute a diphenylmethane unit in which the dihedral angle between the benzene rings is

*In the X-ray analysis, atoms were numbered in an arbitrary sequence *vide* Fig 3. For convenience in discussion, atoms in the text are identified in relation to the N-methyltryptamine unit, **Ia**, by use of a subscript T. Specific units are identified as T′, T″, and T‴. Where specific bonds are referred to, they are identified by the arbitrary numbering in Fig 3 and Table 1. Rings A, B and C are identified in I.

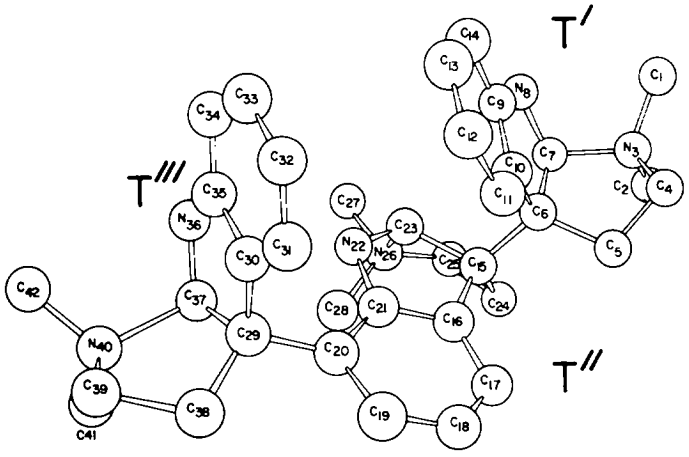


Fig 1. A perspective view of the trimethylated hodgkinsine molecule. The orientation of the view is indicated by the broad arrow in Fig. 2. The diagram was prepared from the output of the ORTEP programme.

82·6°. T‴ being of the same chirality as that of T″, the C_T ring is turned away from the region of T″. So far as ring A_T and ring A_T are concerned, their dihedral angle is 36·1°, while between ring A_T and A_T it is 47·8°.

The resultant shape of the trimethylated hodgkinsine cation is therefore as shown Fig 1 and 2a. The three planar aromatic components form a "pocket" while the methylated nitrogens $N_T(12)$ are arranged along one outer edge of the molecule. These are the nitrogen atoms which are ionised to N^+ and they lie at virtually the same *y* level: N(3) at −0·0696, N(26) at −0·0662, N(40) at −0·0598. Around each N^+ is usually disposed a trio of I^- ions, Fig 2b. Each iodine lies opposite the triad of atoms associated with $N_T(12)$. Where it can approach more readily the $N_T(1)$ atoms which have a H attached and hence a smaller effective atomic radius, as in the case of T′ and T‴, it does so. Hence I(2)...N(8), 3·59 Å and I(3)...N(36) 3·54 Å. N(22) in T″ is apparently screened sufficiently so that no iodine ion can make a sufficiently close approach and a water molecule forming a H—bond, N(22)...H_2O, 2·95 Å is interposed to act as a substitute. The water molecule, presumably *via* an induced charge, forms two short approach distances, to I(1), 3·56 Å and to I(3), 3·62 Å. The use of a water molecule as an intermediate polariser has been noted earlier in the structure of isolunine.[13]

The structure of the hodgkinsine cation suggests the possibility that the stable adducts formed by hodgkinsine with benzene and with bromo-benzene could involve locking of the adduct molecules in the "pocket" formed of the three aromatic rings of T′, T″ and T‴. Unfortunately failure to analyse the adduct crystal structure prevented clarification of this hypothesis.

Hodgkinsine constitutes the first member of the trimeric indole alkaloids. In it, the units T′ and T‴ are linked via atoms $C_T(3)$ and $C_T(3)$ in the same manner as the two corresponding component units in chimonanthine. However, whereas in chimonanthine both units T′ and T″ are of the same chirality, in hodgkinsine they are opposite and hence the situation is more suitably compared with that in *meso*-chimonanthine.[4] In each of these cases, the units are linked through $C_T(3)$, the atom which is β to both $N_T(1)$ jand $N_T(12)$. In hodgkinsine, an additional type of linkage is introduced. Unit T‴ is linked via $C_T(3)$ to $C_T(8)$ which is β only to $N_T(1)$. Given this additional mode of linking T units (of either chirality?), the possibilities appear to exist for molecules of greater polymeric elaboration involving 4,5.... N-methyltryptamine units.

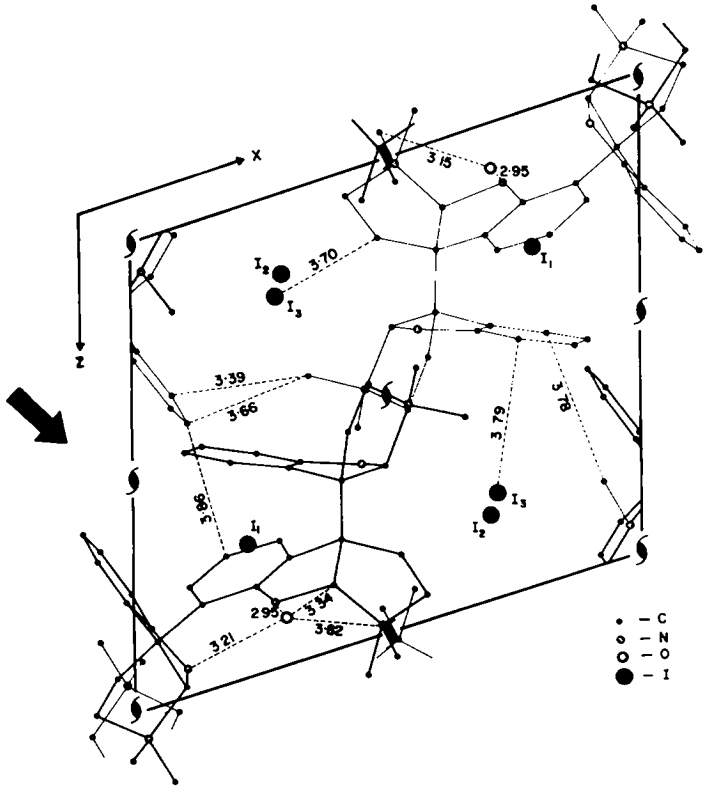


Fig 2(a).

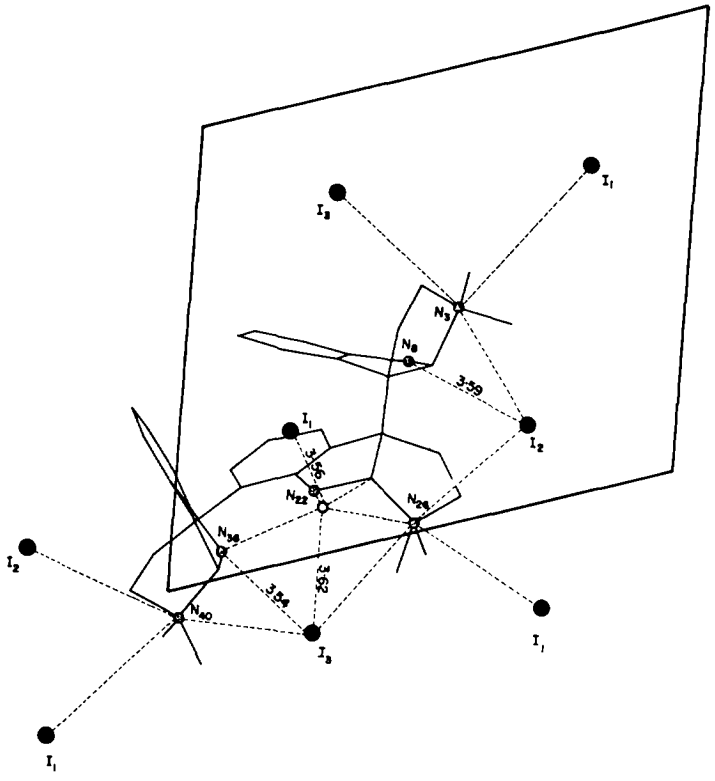


Fig 2(b).

Fig 2a. The projection of the structure down the *b* axis. b. The same projection with only one molecule shown. The relationships of iodine ions, the nitrogen atoms and the water molecule are indicated.

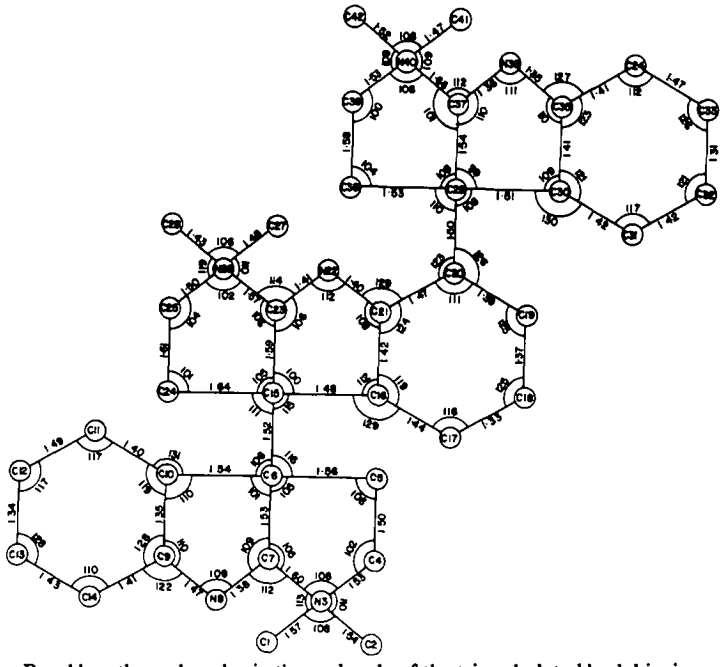


Fig 3. Bond lengths and angles in the molecule of the trimethylated hodgkinsine cation.

Table 1a. Atomic parameters of the asymmetric unit together with their estimated standard deviation, multiplied by 10^4, and individual isotropic temperature factors applied to the light atoms

	X	Y	Z	B
I(1)	7849(2)	0000	2867(1)	
I(2)	6945(2)	−2940(2)	8199(2)	
I(3)	2903(2)	−2647(2)	2132(1)	
C(1)	5622(26)	−1546(23)	4536(26)	5·07 Å^2
C(2)	6537(23)	−0188(22)	5966(25)	5·63
C(4)	4605(20)	0021(20)	4562(21)	4·61
C(5)	5788(21)	−4480(19)	4464(21)	3·73
C(6)	4049(19)	−0285(19)	6429(120)	4·00
C(7)	4926(21)	−1039(19)	6437(21)	4·46
C(9)	3240(20)	−1802(18)	5774(20)	3·82
C10)	2997(20)	−0861(17)	5820(20)	3·67
C(11)	1903(22)	−0558(19)	5299(22)	4·01
C(12)	1058(30)	−1317(26)	4837(21)	6·52
C(13)	1402(27)	−2230(23)	4968(29)	5·69
C(14)	2506(30)	−2574(30)	5355(31)	7·16
C(15)	5962(18)	−4959(17)	2275(18)	3·08
C(16)	6921(22)	−4365(21)	2255(24)	4·71
C(17)	7201(22)	−3406(20)	2719(22)	4·44
C(18)	8189(24)	−3095(23)	2726(25)	5·11
C(19)	8912(21)	−3597(19)	2280(22)	4·03
C(20)	8742(23)	−4525(21)	1793(23)	4·63
C(21)	7660(20)	−4887(18)	1780(20)	3·55
C(23)	3914(18)	−0823(16)	8602(18)	2·84
C(24)	4805(22)	−4440(20)	1505(23)	4·31
C(25)	5764(30)	−0265(31)	9487(33)	7·25
C(27)	5200(36)	−1592(33)	0518(35)	8·61
C(28)	4439(32)	−0122(32)	0749(35)	8·09
C(29)	0476(17)	−0098(17)	8689(18)	3·25
C(30)	−0041(21)	−0855(18)	7719(21)	3·56
C(31)	9219(22)	−0757(19)	6487(22)	4·38
C(32)	8890(24)	−1615(21)	5781(24)	4·95
C(33)	9244(25)	−2454(23)	6268(25)	5·47
C(34)	0015(31)	−2630(31)	7523(34)	7·49
C(35)	0318(23)	−1769(21)	8212(23)	4·42
C(37)	1026(21)	−0760(18)	9809(21)	3·91
C(38)	0310(23)	−4424(20)	0924(23)	4·16
C(39)	9173(23)	−0077(21)	9903(24)	5·39
C(41)	0806(28)	−0047(27)	1819(30)	6·97
C(42)	9885(28)	−1557(26)	1124(29)	5·99
N(3)	5429(17)	−0696(15)	5361(17)	4·06
N(8)	4437(19)	−1933(18)	6191(20)	5·20
N(22)	2838(15)	−0764(13)	8681(15)	2·57
N(26)	4832(15)	−0662(13)	9891(15)	2·64
N(36)	0999(18)	−1685(16)	9401(17)	4·14
N(40)	0208(20)	−0598(16)	0697(20)	4·98
O(H_2O)	2997(20)	−2872(19)	8941(22)	7·64

Table 1b. Anisotropic temperature factor components applied to the iodine atoms together with their estimated standard deviation, multiplied by 10^4

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

	β_{11}	β_{22}	β_{33}	β_{23}	β_{13}	β_{12}
I(1)	108(2)	62(1)	89(1)	12(2)	29(2)	23(2)
I(2)	110(2)	104(2)	199(3)	81(4)	110(4)	73(3)
I(3)	83(1)	65(1)	91(1)	18(2)	31(2)	32(2)

Table 2. Intermolecular approach distances < 3·90 Å

		d(Å)			d(Å)
I(1)	H_2O	3·56	C(18)	C(33)	3·88
I(1)	C(32)	3·85	C(18)	C(42)	3·86
I(2)	C(7)	3·80	C(19)	C(42)	3·50
I(2)	N(8)	3·59	C(34)	C(41)	3·67
I(2)	C(28)	3·87	H_2O	C(14)	3·89
I(3)	H_2O	3·62	H_2O	N(22)	2·95
I(3)	C(14)	3·79	H_2O	C(23)	3·34
I(3)	C(24)	3·70	H_2O	C(24)	3·78
I(3)	N(36)	3·54	H_2O	C(25)	3·87
C(2)	C(31)	3·39	H_2O	N(26)	3·82
C(2)	C(32)	3·66	H_2O	C(27)	3·15
C(11)	C(41)	3·78	H_2O	C(34)	3·67
C(12)	C(41)	3·74	H_2O	C(35)	3·61
C(17)	C(27)	3·89	H_2O	N(36)	3·21
C(18)	C(32)	3·86			

Table 3. Comparison of intensities I(hkl) and $I(\bar{h}\bar{k}\bar{l})$ based on a right-handed set of axes, with the associated values $-(AB_i - A_iB)$. A, B refer to the non-dispersive structure-factor components for the whole structure and A_i, B_i to the corresponding components for the iodine atoms only

Index	$I(hkl) > < I(\bar{h}\bar{k}\bar{l})$	$-(AB_i - A_iB)$
1,1,2	<	− 2360
1,1,3	<	− 2455
1,1,7	<	− 1240
1,2,3	>	+ 2930
1,2,4	>	+ 1330
1,2,5	>	+ 500
1,3,4	>	+ 865
1,3,6	>	+ 2190
1,4,6	<	− 4090

Mason and Vane[14] have referred briefly to the circular dichroism of hodgkinsine (even though at that stage the structure was not fully established). In terms of dissymmetric molecules comprising aniline chromophores, the CD spectrum of a rigid molecule of this type, calycanthine, was predicted by quantum mechanical procedures on the basis of the X-ray dimensional data.[14] For more flexible molecules, such as chimonanthine, even the X-ray data is not sufficient to establish the spectral pattern of optical activity in solution. For hodgkinsine where units of opposite chirality exist, the situation is even more complex. Although the structure is known absolutely, the range of departure from this conformation, due to flexing in solution, is not known. Hence prediction of its optical activity is a complex problem. While units T′ and T‴ alone would interact to produce zero optical activity, the presence of T‴ introduces further interactions between T‴ and T″ and T‴ and T′ which can be significant because the distances between the excitation dipole centres in the crystal structure are of the order of 4·5 Å.

EXPERIMENTAL

Adduct derivatives. For the benzene and bromobenzene adducts of hodgkinsine, crystal data for the monoclinic crystals are:

	Benzene	Bromobenzene
a	13·56	13·50 Å
b	13·27	13·38 Å
c	9·445	20·16 (2 × 10·08) Å
β	104·4	102·2°
Space Group	$P2_1$	$P2_1$
D_m	1·20	1·30 g.cm^{-3}
D_x	1·20	1·29 g.cm^{-3}
Mass of asymmetric unit calc. from crystal data	595	1396 (2 × 696)
Molecular formula	$C_{33}H_{38}N_6.C_6H_6$	$2(C_{33}H_{38}N_6.C_6H_5Br)$

Microanalysis* of the benzene adduct gave C = 78·50, H = 7·34, N = 13·8% whereas, after prolonged heating, the values were C = 75·8, H = 7·45, N = 15·4%. For an N_6 formulation, these values accord reasonably with $C_{33}H_{38}N_6.C_6H_6$ and $C_{33}H_{38}N_6$ respectively. The mass spectrum of the benzene adduct (using a heated inlet to ensure vaporization of the alkaloid and removal of the benzene) yielded three principal peaks at 172, 344 and 518 mass units. This evidence, with the other chemical data, rather suggests the formulation of hodgkinsine as a trimeric entity based on three N-methyltryptamine units.

Comparison of the bromobenzene adduct data with that for the benzene adduct shows not only a doubling of the *c* axis but also an effective expansion from ~9·4 to ~10·1 Å. One may presume that this expansion and the change in the *β* angle are associociated with the replace-

*Microanalyses were carried out by the CSIRO Microanalytical Laboratory.

ment of benzene by bromobenzene. If so, the evidence should provide a useful guide, as in an earlier example,[15] to the orientation of the bromobenzene molecule and hence be of assistance in the analysis of the vector map.

3-Dimensional intensity data for the bromobenzene adduct were collected using CuKα radiation. Equi-inclination Weissenberg multiple-film packs were recorded for the first six layers about *b* and for three about *a*. The intensities for 2210 independent terms were estimated visually; this coresponded to only 30% of the total sphere for CuKα radiation, the effective data limit being 1·2 Å. Vector distributions were calculated to establish the Br parameters. The data used in these syntheses were sharpened to varying degrees by the functions developed by Wunderlich[16], but no consistent pattern of possible Br sites emerged. It was concluded that the bromine atoms did not occupy uniquely-defined sites. The possibilites suggested by visualising the bromobenzene as occupying a number of locations in a cavity were investigated but without success.

In respect of the adduct structure, the vector map contained an interesting feature. The distribution adjacent to $z = 0{\cdot}0$ closely resembled that at $y = 0{\cdot}723$ adjacent to $z = 0{\cdot}500$. This suggested that, in the bromobenzene adduct, the basic 'benzene adduct' structure unit cell was displaced along one benzene unit cell and down *b* by $\Delta y = 0{\cdot}223$ to create a two-unit cell, the doubling being produced by the change from symmetrical benzene to the less symmetric bromobenzene.* While suggestive of the important role played by the adduct molecule, it unfortunately did not assist in solving the structure of the alkaloid. However, since hodgkinsine will not readily crystallise except in the presence of adduct molecules *cf* Ref 1, knowledge of the adduct structure would be of interest in its own right in respect of intermolecular forces.

Regretfully this aspect of the investigation had to be discontinued and an alternative derivative of hodgkinsine used.

Trimethiodide derivative. Hodgkinsine trimethiodide crystallises from water as the monohydrate, $C_{33}H_{38}N_6.3CH_3I.H_2O$, forming fine pale-yellow monoclinic needles. The unit-cell parameters, measured on a diffractometer, were $a = 12{\cdot}799$, $b = 13{\cdot}923$, $c = 11{\cdot}190$ Å, $\beta = 107{\cdot}78°$, $U = 1896{\cdot}8$ Å, the space group being $P2_1$, with $Z = 2$, $D_x = 1{\cdot}685$ g.cm^{-3}. 3-Dimensional intensity data for the structure analysis were measured with CuKα radiation on a Picker four-circle diffractometer, from two crystals both having approximate dimensions $0{\cdot}2 \times 0{\cdot}14 \times 0{\cdot}12$ mm^3. The intensity measurements involved an $\omega/2\theta$ scan out to a sin θ maximum of 0·90, with 2θ ranging from 2·0° to 2·6°. Absorption corrections, using a linear absorption coefficient of 202 cm^{-1} were applied. Significant intensity values for 3343 independent terms were recorded. Scattering factors used were taken from standard sources.[17]

For refinement purposes, the Cu data set did not prove wholly satisfactory, even with correction for absorption. Accordingly, subsequent to the structure analysis a further set of intensity data was collected with MoKα radiation out to a sin θ maximum of 0·39. This yielded 1410 terms significantly greater than background. These intensities were not corrected for absorption, the linear absorption coefficient for MoKα radiation being 25·4 cm^{-1}. During data collection with both CuKα and MoKα radiation, there were indications of radiation damage from the steady decrease in intensity of the reference reflections.

From the 3-dimensional vector map, a number of interpretations appeared possible. Structure factors employing an isotropic B were calculated for 5 possible sets of iodine sites and an agreement index, $R = \Sigma|Fo\text{-}Fc|/\Sigma|Fo|$ evaluated. The set with the lowest R(= 0·29) was assumed correct, the derived iodine parameters being

	x	*y*	*z*
I(1)	0·790	0·000	0·290
I(2)	0·290	0·280	0·210
I(3)	0·695	0·300	0·820

Phased on the iodine contributions, an electron-density and a difference distribution were calculated. With the assistance of a ball-on-spike model, the complete molecular skeleton of the trimethylated hodgkinsine cation was revealed. In conjunction with known chemical detail and the proximity relationships to the iodine ions, the nitrogen atoms could be differentiated. Least-squares refinement in which iodines were dealt with anisotropically and carbon and nitrogen isotropically reduced R to 0·15. A difference synthesis at this stage revealed a peak, which by its nature and position, was assumed to correspond to a water molecule.

The absolute configuration of the structure has been determined by comparison of Bijvoet pairs,[18] utilizing the anomalous dispersion of CuKα radiation by the iodine atoms, for which $\Delta f'' = 7{\cdot}2$ (and $\Delta f' = -1{\cdot}1$). Comparison of selected Friedel pairs in conjunction with the relationship derived by Patterson[19]

$$D = |F(hkl)^+|^2 - |F(hkl)^-|^2 = -4(\Delta f_i''/f_i)(AB_i - A_iB)$$

has shown that the absolute structure is defined by the parameters listed in Table 1 when these are referred to a right-handed set of axes. Table 3 compares intensities I(*hkl*) and I($\overline{hkl}$) with the associated values $-(AB_i - A_iB)$ in which A, B refer to non-dispersive structure factor components and A_i, B_i to the corresponding components for the I atoms only.

Final atomic parameters were derived from the Mo set of intensities and full anisotropic refinement by block-diagonal least squares reduced R to 0·052 for the 1410 observed terms. In all refinement cycles, unit weights were used. The final atomic parameters are listed in Table 1. The derived bond lengths and angles are detailed in Fig 3 and short approach distances are given in Table 2.

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*On this basis, a *p*-dibromobenzene adduct would probably revert to the simpler cell.

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