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The Direct Determination of Molecular Structure. The Crystal Structure of Thelepogine Methiodide at −150 °C

By J. Fridrichsons and A. McL. Mathieson

Division of Chemical Physics, Chemical Research Laboratories, C.S.I.R.O., Melbourne, Australia

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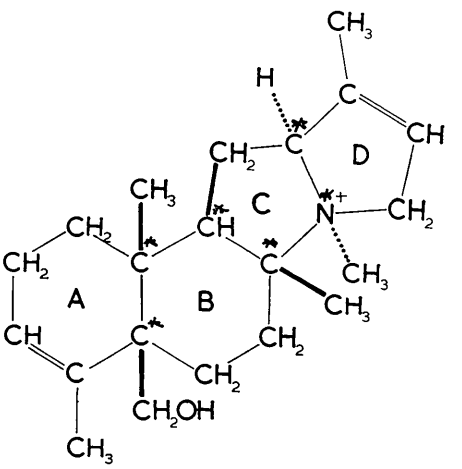
From the grass *Thelepogon elegans*, an alkaloid of unknown structure, thelepogine, has been isolated by Crow. The methiodide of this compound crystallizes in the monoclinic space group $P2_1$ with

$a = 7{\cdot}462$, $b = 13{\cdot}044$, $c = 11{\cdot}117$ Å; $\beta = 109{\cdot}05°$ at -150 °C., $Z = 2$.

Structure analysis, based only on $h0l$, $0kl$ and $1kl$ data, was initiated by means of the heavy atom. Correlation of normal and generalized projections, $\varrho(x, z)$, $\varrho(y, z)$, $C_1(y, z)$ and $S_1(y, z)$ permitted extraction of a three-dimensional array of mirror-image sites corresponding to the majority of atom locations for the molecule. Progressive selection of atom sites from each mirror-pair was made on the basis of rational bond lengths and angles and the possible stereochemical relationships of adjacent atoms. From the detailed stereochemistry, hydrogen atoms were allocated leading to the formula $C_{20}H_{31}ON.CH_3I$ and the structure I. The absolute configuration of this derivative, as shown in I, was defined by Bijvoet's method using the anomalous dispersion of Cu radiation by the iodine atom.



I

The conformational and configurational aspects of the structure are discussed. A close similarity in conformation and absolute configuration of the ring system CD to the pyrrolizidine ring system in jacobine is noted while a possible biosynthetic origin for the alkaloid is suggested by its structural and configurational relationship to the diterpene manno-ol.

Certain inconsistencies exist between the structure I derived from the X-ray data and other measurements of structural significance made independently on the alkaloid. A semi-independent check on the X-ray result was made by the use of $h1l$ and $h2l$ data but these allowed no modification to the earlier conclusion. These discrepancies, which may arise from non-identity of the samples used in the different experiments, have not been resolved.

Thelepogine is an alkaloid which was isolated by Dr W. D. Crow* (1961) from the grass *Thelepogon elegans*, a finding of interest since the occurrence of alkaloids in grasses is relatively rare. Thus, a systematic survey in New Zealand of approximately 200 *Lolium* and allied grasses led to the isolation of an alkaloid perloline in only four species (White &

* Then of the Organic Chemistry Section, Chemical Research Laboratories, C.S.I.R.O., Melbourne. Now at the Chemistry Department, National University, Canberra, A.C.T.

Reifer, 1945). From the grass *Lolium cuneatum* Nevski, a group of alkaloids, lolindine, loline and lolinine were isolated by Yunusov & Akramov (1955) and another, norloline, was later isolated from the same source by these authors (1960). Following a report on the occurrence of 'staggers' in sheep confined to pastures predominantly of the perennial grass *Phalaris tuberosa* (8th Annual Report, C.S.I.R.O. (1956)), Wilkinson (1958) investigated *Phalaris arundinacea* L and isolated an alkaloid shown to be 5-methoxy-N_b-methyltryptamine.

For these few grass alkaloids, characterisation by complete structure determination has been limited. The structure of perloline remains unsolved while the partial structures proposed earlier by Yunusov & Akramov (1960*a*) for the closely-related alkaloids from *Lolium cuneatum* have only recently been fully elucidated (Yunusov & Akramov, 1960*b*). Hence the molecular structure of thelepogine is of considerable interest not only from the viewpoint of increasing information on grass alkaloids but also because the analysis offered the prospect of a new structure type as had eventuated in the analysis of cryptopleurine (Fridrichsons & Mathieson, 1954, 1955).

The total amount of thelepogine available was insufficient for chemical studies and the empirical formula, based on microanalyses of the alkaloid and its methiodide, was later found to be only approximate. With a suitable derivative available in the methiodide and the chemical data very limited, the alkaloid provided an excellent test of the capacity of the X-ray method to yield, unassisted, complete structural information.

Comments regarding this structure analysis formed part of a Section lecture given at the 1960 IUPAC Symposium on Natural Products (Mathieson, 1961—see also Fridrichsons & Mathieson, 1960*a*). Essential points of the structure and absolute configuration of thelepogine methiodide have been published (Fridrichsons & Mathieson, 1960*b*).

Experimental

The crystals, laths elongated parallel to the *a* axis, belong to the monoclinic system, the cell dimensions, determined against a standard (Al, $a=4{\cdot}0494$ Å) being

$$a=7{\cdot}462,\ b=13{\cdot}044,\ c=11{\cdot}117\ \text{Å};$$
$$\beta=109{\cdot}05°\ \text{at}\ -150\ °\text{C}.$$

The space group is $P2_1$ with two molecules in the unit cell.

Table 1. *Comparison of the number,* $N_{obs.}$*, of terms observed and,* $N_{theor.}$*, theoretically observable in the layers specified. R is the final value of the reliability index for each layer*

	$N_{obs.}$	$N_{theor.}$	R
*h*0*l*	179	193	0·108
0*kl*	175	183	0·108
1*kl*	333	365	0·116

Intensity data were collected at −150 °C. for the *h*0*l*, 0*kl* and 1*kl* layers on a Weissenberg goniometer, packs of four films being exposed for 6 hr. and 10 min. respectively (Cu $K\alpha$, 200 mA., 35 kV.). For experimental conditions, see Fridrichsons & Mathieson (1962). The amount of data collected was regarded as satisfactory for a molecule of this size, being 93% of theoretical, Table 1. Intensity data for *h*1*l* and *h*2*l* layers were collected subsequently and used at a later

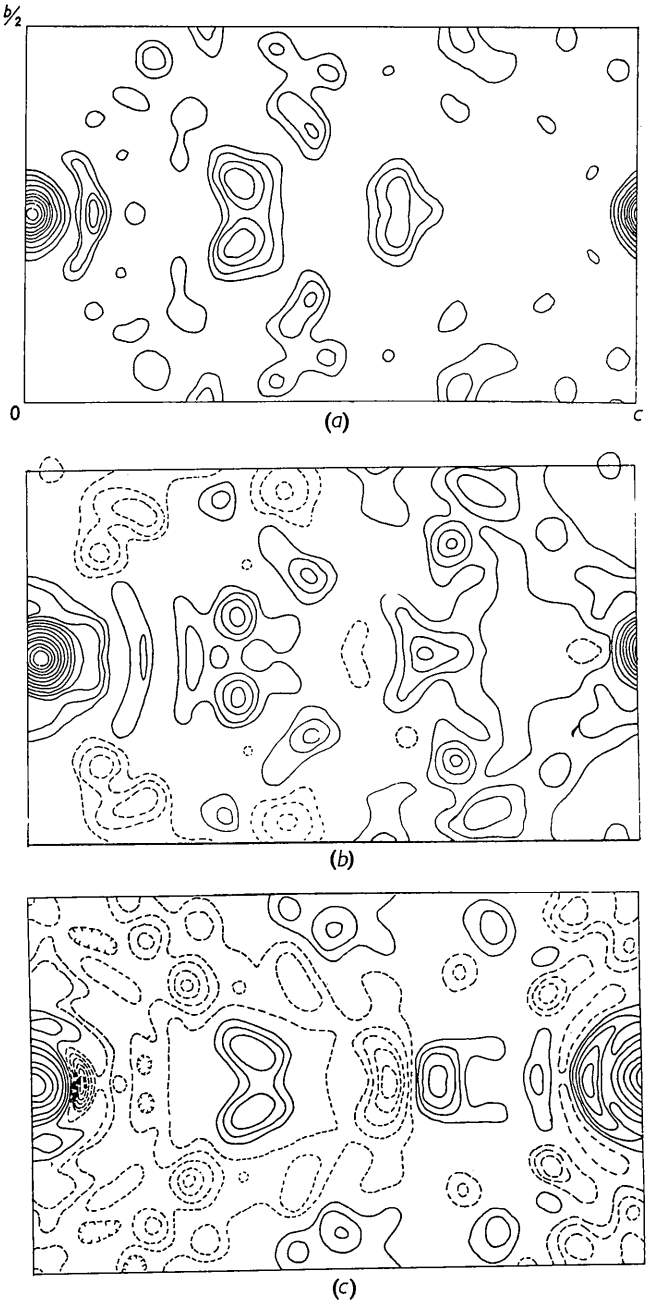


Fig. 1. The first electron density distribution symmetrized by use of the heavy atom. (*a*) The normal projection $_1\varrho_0(y, z)$ and the first-layer generalized projection components, (*b*) $_1C_1(y, z)$ and (*c*) $_1S_1(y, z)$.

stage to make a semi-independent check on the results of the analysis with *a*-axis data.

$\mathrm{Sin}^2\,\theta$ values, intensity-correction factors, *h*0*l* structure amplitudes and all Fourier syntheses were computed on SILLIAC (Freeman, 1957) while 0*kl* and 1*kl* structure amplitudes were computed on UTECOM (≡DEUCE). Final interatomic distances and bond angles were calculated on a STANTEC ZEBRA through the kind cooperation of Dr J. C. Schoone.

Analysis

The analysis was initiated assuming that the empirical formula of the methiodide was $C_{19}H_{32}ONI$, *i.e.* $C_{18}H_{29}ON$ for thelepogine, as indicated by the microanalytical results.

The *x*, *z* parameters of the iodine atom were derived from the Patterson function, $P(u, w)$, and, since the choice of the third parameter in space group $P2_1$ is arbitrary, $y=0{\cdot}25$ was selected in order to relate the iodine atoms by a centre. To restrict the amount of data to be handled, generalized functions (Cochran & Dyer, 1952) were used..

With signs given by the contributions of the iodine atoms (omitting those terms with $S_1<0{\cdot}1$), the projection ${}_1\varrho_0(x, z)$ was calculated. Similarly, with the 0*kl* and 1*kl* data, the symmetrized projection, ${}_1\varrho_0(y, z)$, and the symmetrized generalized components ${}_1C_1(y, z)$ and ${}_1S_1(y, z)$, (Fig. 1) (nomenclature as in Fridrichsons & Mathieson, 1955), were computed. It is feasible, at least theoretically, to extract from the four distributions the locations of the majority of the atoms in a three-dimensional array symmetrical about the reflection plane induced by the heavy-atom signs. Thus a peak at x_1, z_1 in $\varrho(x, z)$ will be related to a pair of peaks in $\varrho(y, z)$ having the same x_1 and to corresponding similarly-positioned pair of peaks in the component distributions $C(y, z)$ and $S(y, z)$. From these, a parameter $x_1=\tan^{-1} S(y, z)/C(y, z)$ can be deduced which should refer back to $\varrho(x, z)$. This procedure presumed that the distributions are wholly meaningful at this stage. Although this does not hold strictly, they may approximate sufficiently for the analysis to be initiated. The main complications arise where atoms overlap or where, for various reasons, one or more of the functions is misleading at certain sites by being of value zero or, in the case of generalized functions, opposite in sign to its true value.

The distribution of the light atoms in $\varrho_0(x, z)$ was sought first since this distribution involves only signs and is therefore defined with greater certainty by the iodine contributions. After several ϱ_0 and $\Delta\varrho$ distributions, the best fit, in terms of 21 atoms, was achieved although several features remained unexplained on this basis.

It is to be noted that, beyond this stage, it is not possible to arrive at a unique structural solution based solely on the X-ray data without recourse to the inherent asymmetry of anomalous dispersion effects. For this space group, it is necessary to invoke arguments based on chemical sense to resolve the symmetry introduced by the heavy atom. In this respect, $P2_1$ differs markedly from $P2_12_12_1$, the other 'popular' space group (Mathieson, 1961).

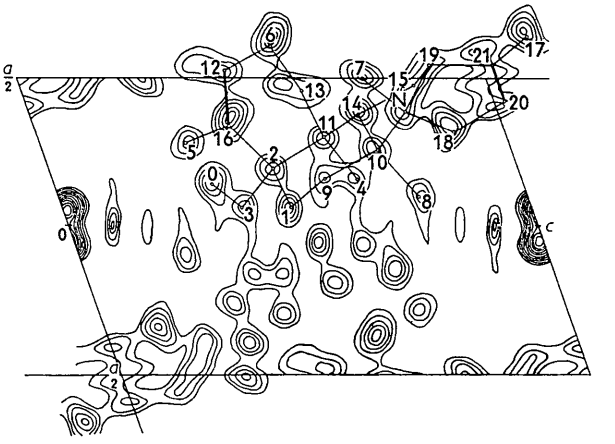


Fig. 2. The electron-density distribution projected down the $_cb$' axis ${}_7\varrho_0(x, z)$.

To determine the *y*-parameter of the atoms selected in $\varrho(x, z)$, attention was turned to the *a*-axis data. As many atom sites as appeared to fit the four distributions with reasonable certainty were selected and set up on an *x*, *z* grid as pairs of balls on spokes representing the two *y*-values of the mirror image. This construction proved particularly useful in determining whether sites gave acceptable interatomic distances and obeyed the general restrictions of stereochemistry *e.g.* Mathieson & Taylor (1961). The symmetrical distribution was resolved into the asymmetric one by the correct choice of the components of the mirror image, a process which may occasionally prove troublesome near the mirror planes of $y=0{\cdot}25$ and 0·75. In the present structure, it was noted that atom C_8, Fig. 2, is isolated in a position such that it can bond either C_4 or C_{10} but not to both. Since its $|y|$ parameter is reasonably well defined by the other functions, ${}_1\varrho_0(0kl)$, ${}_1C_1(y, z)$ and ${}_1S_1(y, z)$, we may select one image of C_8 provisionally as the correct spatial site for this atom. From this starting point, atoms were linked to form a meaningful chemical entity. One major step in this process for thelepogine was the recognition that suitable choice of one of the images of the pairs of atom sites C_{10}, C_{14}, C_9, C_{11}, C_1 and C_2 led to a grouping of atoms representing a cyclohexane ring in the chair conformation. From this ring, it was possible to build outwards in a structurally logical manner linking the various substituent sites.

Certain groups of atoms proved rather more resistent to identification *i.e.* whether real or artefact. Difference syntheses, $\Delta\varrho(x, z)$, failed to yield a decisive answer, there being persistent positive regions which indicated the presence of additional atoms. Re-

Table 2. *Micro-analytical data for the alkaloid and its methiodide*

	Found	Required for $C_{18}H_{29}ON$	Required for $C_{19}H_{31}ON$	Required for $C_{20}H_{33}ON$	Required for $C_{20}H_{31}ON$
C	78·8	78·6	79·0	79·2	79·7
H	10·7	10·6	10·8	11·0	10·4
O	6·2	5·8	5·5	5·3	5·3
N	4·8	5·1	4·8	4·6	4·6
$C-CH_3$	6·4	5·5	5·2	4·9	5·0

	Found	Required for $C_{21}H_{36}ONI$	Required for $C_{21}H_{34}ONI$
C	57·0	56·6	57·0
H	8·1	8·2	7·8
O	4·5	3·6	3·6
N	3·0	3·1	3·2
I	28·2	28·5	28·6
$N-CH_3$	3·9	3·4	3·4

assessment of the analytical data available at that time, Table 2 (Crow, unpublished results), showed that formulae $C_{19}H_{31}ON$ and $C_{20}H_{33}ON$ for the base could also be considered as possible. To decide between these three possibilities, an accurate estimate of the cell contents was required. The cell dimensions were re-measured at room temperature against a standard, giving

$$a=7{\cdot}517,\ b=13{\cdot}149,\ c=11{\cdot}227\ \text{Å};\ \beta=109{\cdot}48^\circ .$$

With the density, $d_{\text{meas}}=1{\cdot}416$, $M=446$, in definite support of the C_{20} formulation and confirming the trend of the $\Delta\varrho$ distributions.

Structure factors were accordingly recalculated including the full complement of $I+23$ atoms and the resulting b-axis projection was now in reasonable accord. Since the approximate x, z parameters were not in doubt, the resolution of the problem rested with the definition of the y parameters. From the a-axis data, it appeared probable that atoms N, C_{18}, C_{19}, C_{20} and C_{21} formed a five-membered ring system. The main questions remaining to be determined were, whether this ring system was saturated or contained a double bond, and whether atom C_{17} was attached to C_{15} or C_{18} or to be symmetrically related C_{21}, the two questions probably being inter-related.

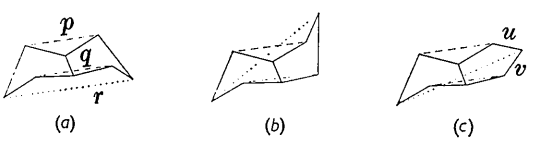


Fig. 3. Spatial relationships for linked five-membered rings CD in which ring C is saturated. In (*a*) and (*b*), ring D is saturated but in (*c*) has a double bond at *u* or *v*.

With regard to the first question, the stereochemistry of linked five-membered rings may be considered (Fig. 3). Ring C being saturated, the following pos-

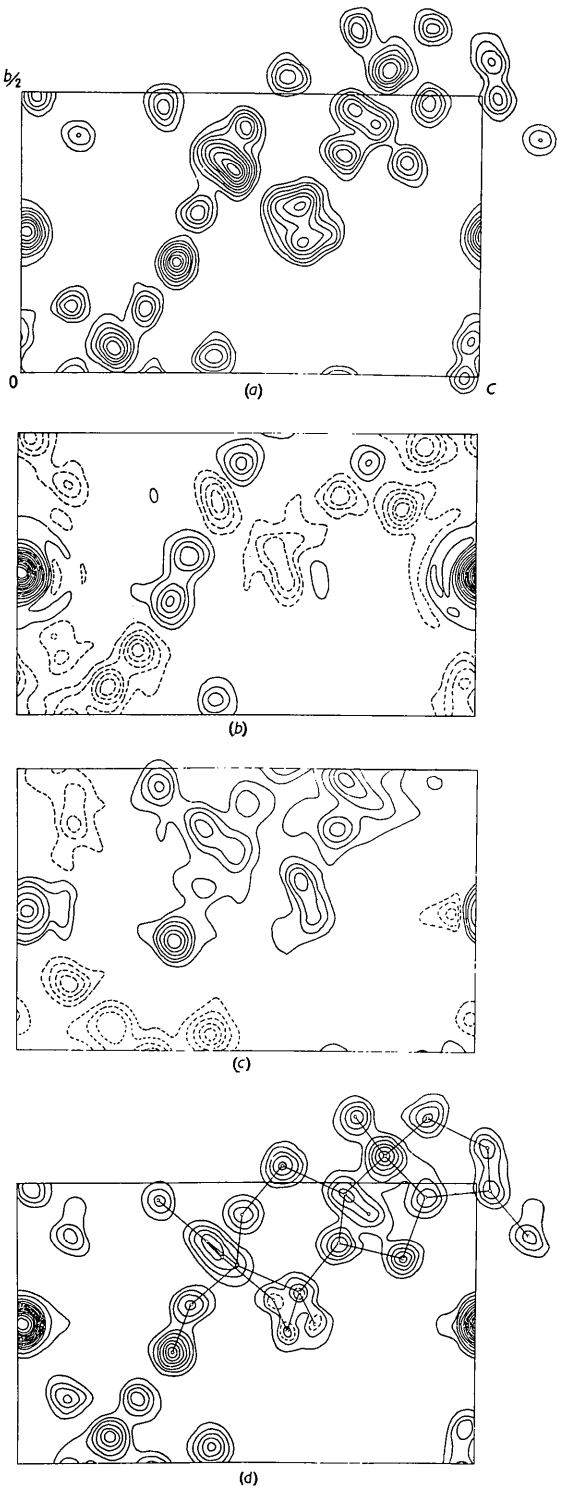


Fig. 4. Refined electron-density distributions projected down the *a*-axis. (*a*) The normal projection ${}_3\varrho_0(y, z)$, (*b*) and (*c*) the first-layer generalized projection components ${}_3C_1(y, z)$ and ${}_3S_1(y, z)$ respectively. (*d*) The first-layer modulus projection, ${}_3|\varrho|_1$.

sibilities are permitted by the present evidence; (*a*) and (*b*) with the ring D saturated and (*c*) with ring D containing one double bond *u* or *v*. In each case, lines *p* and *q* are parallel in space in all orientations. This is confirmed in the present instance by the lines C_{10}–C_{18} and C_{15}–C_{21} in Fig. 2. If the ring system is saturated and butterfly-shaped, *i.e.*, (*a*), then the line *r* is also parallel to *p* and *q* in all orientations. This condition is not satisfied by C_{14}–C_{20} in Fig. 2 and therefore ring D must be of type (*b*) or (*c*) (Fig. 3). Case (*b*) is excluded by the evidence in Fig. 2 and so ring D must be planar with a double bond at C_{20}–C_{21} or C_{18}–C_{20}. The dimensions in ring D suggested C_{20}–C_{21}, but a final decision in this matter rested with the correct siting of C_{17} to provide a further restriction on the location of C_{21}.

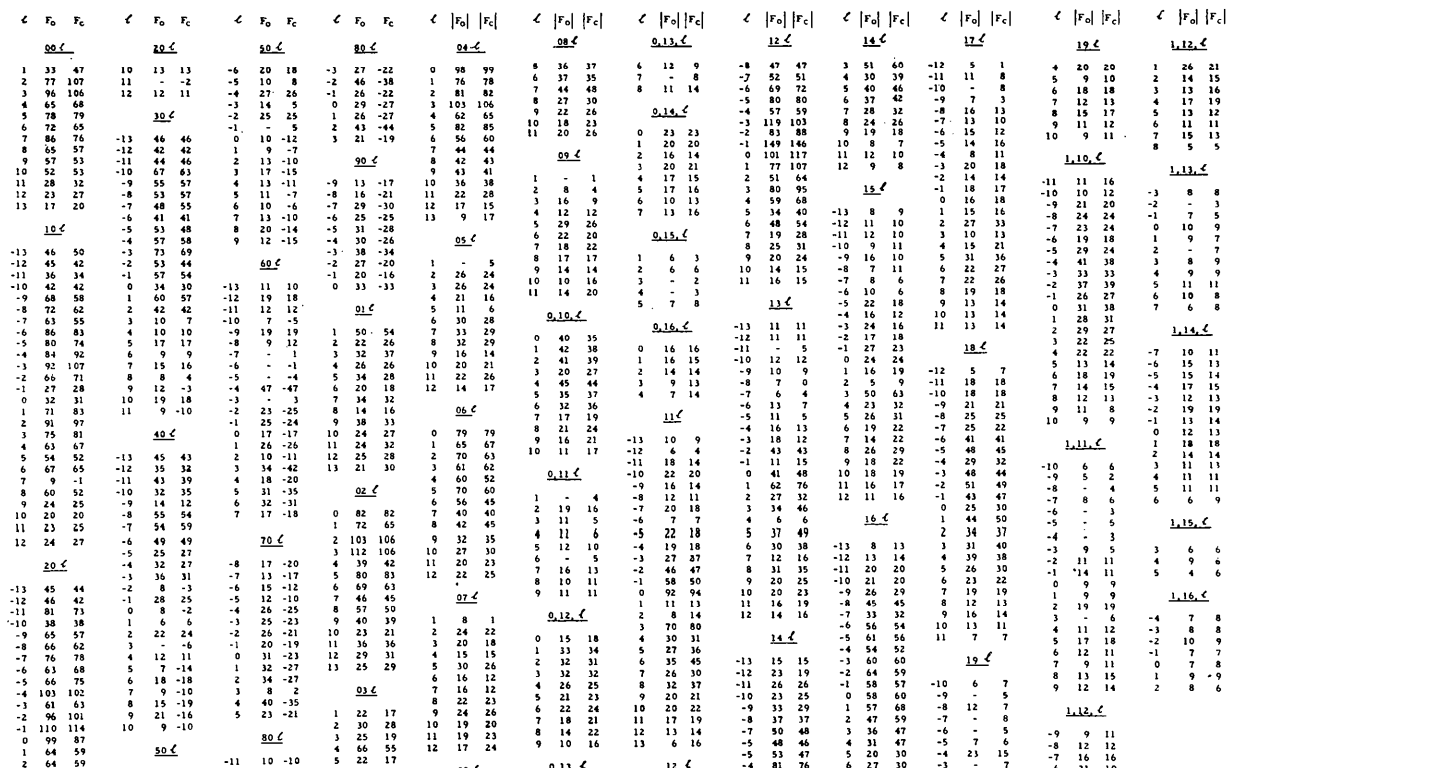
For C_{17}, the *a*-axis data permitted three possible sites—$y=0{\cdot}22$ (attachment of C_{18}) or $0{\cdot}41$ (C_{21}) or $0{\cdot}78$ (C_{15}). Careful consideration of all the evidence in $\varrho_0(y,z)$, $C_1(y,z)$ and $S_1(y,z)$ tended to assign the greatest probability to linkage to C_{21} but this was only feasible if C_{17}, C_{21}, C_{20} and C_{19} were coplanar, which would accord with a double bond in ring C at C_{20}–C_{21}. This was the solution to the structure analysis as far as could be deduced from the *h*0*l*, 0*kl* and 1*kl* data.

Because the end-result for the siting of C_{17} could not be considered completely persuasive, the conclusions were cross-checked by an independent approach. With the *h*1*l* and *h*2*l* data, the iodine atoms

Table 3. *Atomic parameters of a molecule*

Atom	*x*	*y*	*z*
I	0·0538	0·7500	0·0102
C_1	0·938	0·056	0·513
C_2	0·806	0·147	0·525
C_3	0·938	0·216	0·620
C_4	0·847	0·250	0·352
C_5	0·722	0·028	0·692
C_6	0·388	0·207	0·441
C_7	0·500	−0·116	0·265
C_8	0·900	0·053	0·234
C_9	0·841	−0·030	0·421
C_{10}	0·744	0·019	0·286
C_{11}	0·697	0·193	0·392
C_{12}	0·472	0·130	0·553
C_{13}	0·547	0·264	0·411
C_{14}	0·619	0·107	0·299
C_{15}	0·522	0·130	0·159
C_{16}	0·662	0·103	0·588
C_{17}	0·362	0·094	−0·111
C_{18}	0·667	−0·116	0·110
C_{19}	0·450	0·020	0·112
C_{20}	0·578	−0·062	−0·022
C_{21}	0·453	0·008	−0·022
N	0·600	−0·048	0·197
O	0·859	0·300	0·664

Table 4. *Comparison of the measured and calculated structure amplitudes*



define signs for the terms of the symmetrical functions $S_1(x, z)$ and $C_2(x, z)$, but do not contribute to the anti-symmetric functions $C_1(x, z)$ and $S_2(x, z)$. The synthesis of $S_1(x, z)$ and $C_2(x, z)$ with signs determined in this way involves therefore no assumptions regarding the organic skeleton. From these two distributions, the y parameters of all atoms other than the controversial C_{17}, C_{20} and C_{21} were deduced and found to be in good agreement with the earlier values. The adequacy of these functions being thus confirmed, the y parameters of C_{17}, C_{20} and C_{21} were estimated and found to accord with the results of earlier data.

The skeleton of the molecule being thus defined with adequate precision, there remained the differentiation of the N and O atoms. The difference maps, $\Delta\varrho(x, z)$, had, in their later stages, clearly shown the oxygen atom and calculation of the approach distance of this atom to the iodide ion served to confirm this deduction. The nitrogen atom was defined partly from the evidence of $\Delta\varrho$ maps, but also from structural and stereochemical argument.

The normal projection, ${}_3\varrho_0(y, z)$ (Fig. 4(*a*)), and the modulus projection ${}_3|\varrho|_1(y, z)$ (Fig. 4(*d*)), yield reasonably accurate y, z parameters, while comparison of ${}_3C_1(y, z)$ and ${}_3S_1(y, z)$ (Figs. 4(*b*) and (*c*)) with ${}_7\varrho_0(x, z)$ (Fig. 2), gave satisfactory precision for x parameters. Atomic parameters have been refined far enough to define bond lengths and angles adequately. The final parameters are listed in Table 3, while the structure amplitudes, calculated from these parameters, are compared with the measured values in Table 4.

Absolute configuration

The absolute configuration of thelepogine methiodide was defined by the method of Bijvoet, Peerdeman & van Bommel (1951), using the anomalous dispersion of the iodine atom. For Cu $K\alpha$, the magnitude of the correction term $f'' = +7{\cdot}2$ ($f' = -1{\cdot}1$) (Dauben & Templeton, 1955) is such that eye-estimation of the distinction between forms is relatively easy and much less critical than for Br, *e.g.* Peerdeman (1956); Fridrichsons & Mathieson (1962). Przybylska & Marion (1959) have used the anomalous dispersion of iodine to define the absolute configurations of (+)-des-(oxymethylene)-lycoctonine.HI.H_2O and (+)-demethanol aconinone.HI.3 H_2O.

Table 5. *Forms used for the establishment of absolute configuration*

$0kl$	$F^2(0kl)$	$F^2(0\bar{k}l)$	$I(0kl) \gtrless I(0\bar{k}l)$
035	659	368	>
055	96	163	<
077	134	468	<
029	1540	1940	<
0,2,11	1350	1515	<

The crystal was set on the a-axis as the rotation axis and a +1-layer Weissenberg film used to define the +c-axis. The zero-layer film for intensity comparison was recorded over a rotation angle of 270° (for the experimental conditions, see Fridrichsons & Mathieson, 1962). The required conditions of small magnitude of $|F_o|$ and reasonable magnitude of S_I are satisfied by the forms in Table 5.

The absolute configuration, determined in this manner, is correctly indicated by the atomic parameters in Table 3, when considered in relation to a right-hand set of axes with symmetry elements grouped as in the space group $P2_1$, No. 4 in *International Tables for Crystallography* (1952). The molecular skeleton in Fig. 7(*a*) is also oriented in accord with this decision.

Discussion

From the atomic parameters (Table 3), bond lengths and angles and approach distances were calculated (Table 6—see also Fig. 5 and 6). When the three-dimensional stereochemical atomic arrangement is considered, there is then little doubt as to the bond-types specified in Fig. 7. In Table 6, the bond lengths are arranged in groups of similar type and, from the

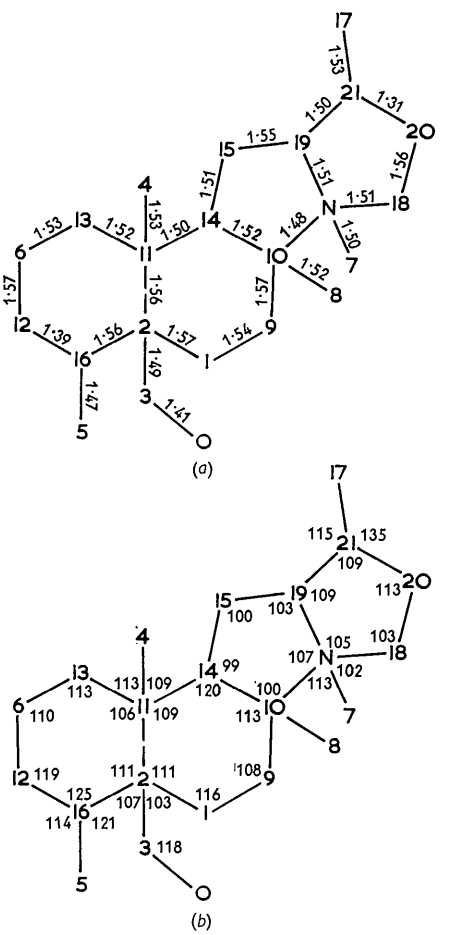
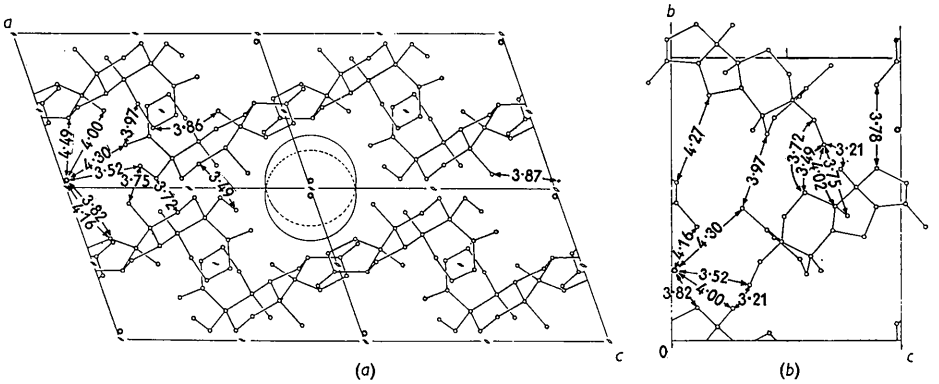


Fig. 5. Diagram of molecular skeleton with the atoms numbered. Bond lengths and angles are indicated.



(a) (b)

Fig. 6. Packing of the molecules and iodide ions (*a*) as viewed down the '*b*' axis. The effective packing radius of the iodine atom is shown. (*b*) As viewed down the '*a*' axis.

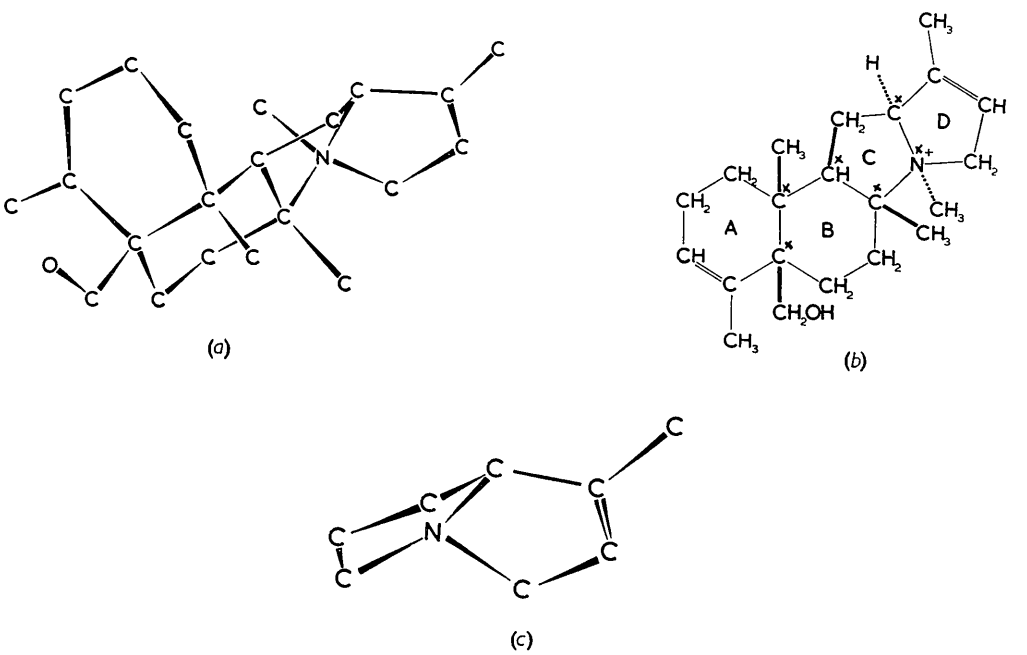


Fig. 7. (*a*) The molecular skeleton as derived from the analysis and (*b*) a more conventional molecular formula. Both are shown in correct absolute configuration. In (*b*) asymmetric atoms are starred. (*c*) For comparison with rings *CD* the corresponding skeleton of the pyrrolizidine ring system in jacobine bromhydrin is shown.

internal consistency of those C–C bonds which may be considered single, it appears probable that the individual values are not likely to be in error by more than 0·06 Å. With this measure of certainty regarding the bond types, it is possible to allot hydrogen-atom sites, arriving at structure Fig. 7(*b*)—$(C_{21}H_{34}ON)^+I^-$.

The mode of packing of the molecular ions and iodide ions in the crystal may be seen in Fig. 6(*a*) and (*b*). The iodide ions, by virtue of their small x, z parameters, form a two-dimensional array extending along the *b*-axis (separation approximately 6·5 Å) and along the *a*-axis (7·46 Å). From the packing radius for iodine, Fig. 6(*a*), it is evident that there is a considerable region forbidden to any part of the organic molecule, while a similar but less extensive region occurs along the *a*-axis, Fig. 6(*b*). From this viewpoint, the structure may be considered a tunnel type which may be of wider interest since it would appear feasible to exchange other halide ions along such molecular tubes. Similar types of tunnel structure where cations may move along the tube have been observed in inorganic structures (*e.g.* Wadsley, 1955).

The organic ions extend approximately perpendicular to (001), their lateral packing being mainly through van der Waals forces, while their active end-groups, –OH and N^+R_4, provide stronger bonding to the iodide ions. The hydroxyl oxygen has a short

Table 6. *Bond lengths and approach distances*

Atoms	Bond lengths (Å)		Atoms	Approach dist. (Å)
C_1-C_2	1·57		$C_1-C_4^1$	4·31
C_1-C_9	1·54		$C_3-C_9^1$	3·72
C_9-C_{10}	1·57		$C_5-C_{13}^1$	3·97
$C_{10}-C_{14}$	1·52		$C_6-C_7^1$	3·86
$C_{14}-C_{11}$	1·50		$C_6-C_5^1$	4·42
$C_{11}-C_2$	1·56		$C_7-C_{12}^1$	3·89
C_2-C_3	1·49		$C_{15}-C_{20}^1$	4·27
C_2-C_{16}	1·56		$C_{17}-C_{18}^1$	3·78
$C_{16}-C_5$	1·47		$O-C_7^1$	3·21
$C_{11}-C_{13}$	1·52	Mean	$O-C_8^1$	3·75
$C_{13}-C_6$	1·53	1·53	$O-C_9^1$	3·49
C_6-C_{12}	1·57		$O-C_{10}^1$	4·02
$C_{11}-C_4$	1·53		$I-O$	3·52
$C_{10}-C_8$	1·52		$I-C_5$	4·30
$C_{14}-C_{15}$	1·51		I^1-C_8	3·87
$C_{15}-C_{19}$	1·55		$I-C_7$	4·00
$C_{19}-C_{21}$	1·50		$I-C_{17}$	4·16
$C_{21}-C_{17}$	1·53		$I-C_{18}$	3·82
$C_{18}-C_{20}$	1·56		$I-C_{19}$	4·49
$C_{12}-C_{16}$	1·39			
$C_{20}-C_{21}$	1·31			
C_3-O	1·41			
$N-C_{10}$	1·48			
$N-C_7$	1·50	Mean		
$N-C_{18}$	1·51	1·50		
$N-C_{19}$	1·51			

approach distance of 3·57 Å to the iodide ion, while the positively charged nitrogen is closely associated with two iodide ions. For tetracovalent $N^+(R)_4$ ions, the closest approach of the negative ion is through the centre of a triad of the atoms directly linking three of the R groups to the N^+ (see Fig. 8(*a*)). A similar situation existed in cryptopleurine methiodide. This arrangement is in marked contrast to that in which one R is hydrogen. Then, the halide ion occupies a site on the line N^+–H $\cdots$ X, Fig. 8(*b*), *e.g.*, as in himbacine hydrobromide (Fridrichsons & Mathieson, 1962). This difference may provide a measure of the transfer of positive charge to the hydrogen atom in the latter case whereas, with N^+R_4, the charge may be spread more evenly over the four C atoms adjacent to N^+. Other approach distances are listed in Table 6.

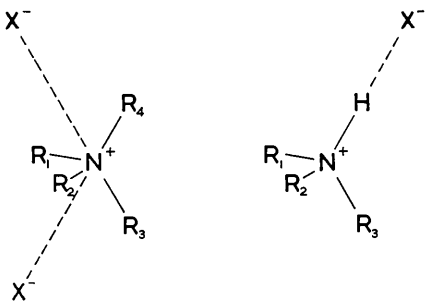


Fig. 8. Comparison of the spatial relationships of the halide anion X^- to the groups (*a*) N^+R_4 and (*b*) N^+R_3H.

It is of interest in this analysis to compare the preliminary information with the end-result. The limited chemical data on which the analysis was initiated suggested the formula $C_{18}H_{29}ON.CH_3I$ with one *N*-methyl and one (possibly two) *C*-methyl groups. In the course of the analysis, it became necessary to alter the formula to $C_{20}H_{33}ON.CH_3I$ and when the stereochemistry of the molecular skeleton was defined adequately to permit location of the hydrogen atoms, the final formula arrived at was $C_{20}H_{31}ON.CH_3I$ containing one *N*-methyl and four *C*-methyl groups. In particular, the gross discrepancy between the chemical and X-ray determination of the number of *C*-methyl groups may be noted. From these results, it should be clear that reliance on specific items of chemical information should not be allowed to restrict the process of X-ray analysis.

The conformation and configuration of the structure may now be described in more detail. Ring A with one double bond constrains C_2, C_{16}, C_{12}, C_6 (and C_5) to be coplanar, with C_{11} above and C_{13} below this plane. Rings A and B are linked by a *cis*-junction. Ring B is in the chair conformation. The junction between rings B and C is *trans*. Rings C and D are, by their nature, *cis*-fused. The six asymmetric centres are starred in Fig. 7(*b*), their absolute configuration having been defined earlier.

In the light of our parallel analysis of jacobine bromhydrin (Fridrichsons, Mathieson & Sutor, 1960), it was intriguing to discover that the pyrrolizidine

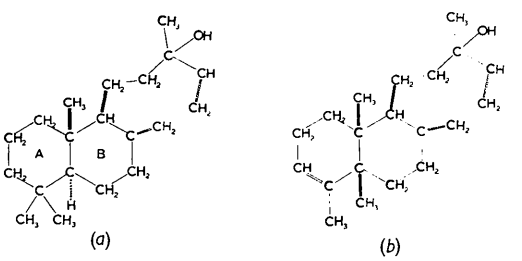


Fig. 9. (*a*) Structure of the diterpene manno-ol (correct absolute configuration) which may be readily converted to (*b*) by means of a 1;2 shift. (*b*) May be compared with respect to configurational features with Fig. 7(*b*).

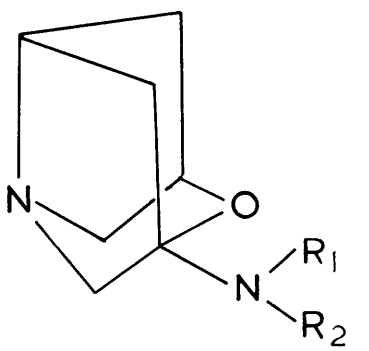


Fig. 10. Structures of the alkaloids from the grass *Lolium cuneatum* Nevski. For norloline, $R_1=R_2=H$, for loline, $R_1=CH_3$, $R_2=H$ and for lolinine, $R_1=CH_3$, $R_2=COCH_3$.

ring in thelepogine (Fig. 7(*a*)) had a remarkable resemblance to the corresponding ring in jacobine (Fig. 7(*c*)) even to the extent of the location of the double bond and the absolute configuration. In this connection, it may be of interest to point out that the four closely related grass alkaloids (Fig. 10) from *Lolium cuneatum* Nevski (Yunusov & Akramov, 1955, 1960) also contain pyrrolizidine as a principal component. Because thelepogine is a C_{20} compound, it may be considered to have originated from a terpenoid precursor and this possibility is further strengthened by the close accord of its absolute configuration with that of manno-ol, Fig. 9(*a*), by invoking 1,2 shifts and the corresponding introduction of a double bond, Fig. 9(*b*). The ring-closure to form the pyrrolizidine ring system may occur through a reaction akin to that of Adams & Leonard (1944). If the compound originated from a manno-ol-type precursor then the CD ring closure may be constrained by steric factors (mainly the shape of the AB ring system) to accept the configuration shown, the alternative being sterically impossible. Whether these structural similarities are coincidental or have some bearing on the origin or biological relationships of thelepogine will only be shown by further chemical studies.

With regard to matters of crystallographic interest, the analysis provides further support for the use of the combination of low-temperature and high-power generator to provide data of adequate range in the structure analysis of moderately complex compounds (Mathieson, 1961; Fridrichsons & Mathieson, 1962). Structure factors for each layer were calculated with an individual symmetrical temperature factor and an approximate correction was applied to the 0*kl* and 1*kl* data for asymmetric vibrations (with maximum displacement parallel to the *b*-axis, in accord with the tunnel structure of the compound), by modifying the F_c results with $\exp(-Ak^2)$, A being derived by a Wilson-type plot. A similar correction was applied to the *h*0*l* data, the direction of maximum displacement (nearly perpendicular to (100)) being derived from difference maps. The iodine scattering factor would appear to require considerable modification. Such modifications have been already found necessary for Cl^- (Dawson, 1960) and, for iodine, the changes to be introduced would probably be larger. Since no Hartree-Fock scattering curve was available for I, the Thomas–Umeda curve (Thomas & Umeda, 1957) was modified by applying to it a correction corresponding to the difference observed between the Hartree–Fock and Thomas–Umeda values for Ag^+. For an analysis of this type with the number of light atoms around 20, iodine as heavy atom is probably too weighty for efficient balance of structure analysis and adequate parameter accuracy for the light atoms (Matheison, 1961).

APPENDIX

A slight difference between the measured density, $d_m = 1{\cdot}416$ and that calculated for $C_{21}H_{34}ONI$, $d_x = 1{\cdot}408$ raised some doubt, during the preparation of the manuscript, with regard to the number of hydrogen atoms in the molecule. The densities would agree more closely for 36 H but this would involve the loss of one double bond. $C_{12}=C_{16}$ was beyond dispute but $C_{20}=C_{21}$, adjacent to the screw axis, is not so soundly based and some independent check seemed desirable.

Discussion with Dr C. C. J. Culvenor of the Division of Organic Chemistry led to the suggestion that a proton resonance spectrum and a microhydrogenation estimation should assist in the decision regarding the number of double bonds. For this purpose, a new sample of the alkaloid was prepared by recrystallisation of thelepogine residues available. Both measurements indicated the presence of only one double bond.

In view of this, the internal consistency of the X-ray results was subjected to further test by a semi-independent approach. The *h*1*l* and *h*2*l* data had already been used as a rough check through the symmetrical functions $S_1(x, z)$ and $C_2(x, z)$ derived from the iodine contribution. This calculation was extended by introducing into the structure-factor calculations those light atoms located with certainty. Only C_{17}, C_{18}, C_{20} and C_{21} were omitted. With the resultant phase angles, the generalized distributions S_1, C_1, S_2 and C_2 were computed and, based on their evidence, the existence of the four carbon atoms was confirmed and their y parameters determined. There remained little doubt that, *with respect to the derivative which provided the X-ray data for the analysis*, the group C_{17}, C_{18}, C_{20} and C_{21} is planar. Modification of atom sites to accord with a tetrahedral disposition around C_{20} would alter the grouping of atoms so radically, even in a simple projection, that it could not be fitted to the available data. We have therefore been forced to the conclusion that, so far as the derivative used in the analyses is concerned, the end-result represents the correct structure of the compound.

We are grateful to Dr W. D. Crow for the preparation of the crystals of thelepogine methiodide and desire to thank Drs C. C. J. Culvenor and C. S. Barnes for valuable discussions on the chemical relationships with other natural products of the structure derived here for thelepogine and for arranging for the microhydrogenation and NMR results respectively.

We desire to express appreciation for the assistance in calculations from Mr J. Boas and from the respective staffs of the computers UTECOM (University of New South Wales) and SILLIAC (University of Sydney).

Note added in proof.—Reasons for the conformation of Ring A as a half-chair rather than the alternative

boat conformation have been given by Mathieson (1962).

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The Crystal Structure of 2,8-Dihydroxy-5,6,11,12,4b,10b-hexahydrochrysene*

BY MARIANNE EHRENBERG

Department of Crystallography, University College, Gower Street, London W.C. 1, England

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Crystals of $C_{18}H_{16}(OH)_2$ are monoclinic with two centrosymmetric molecules in special positions in a unit cell of dimensions

$$a = 17{\cdot}27,\ b = 5{\cdot}13,\ c = 7{\cdot}93\ \text{Å};\ \beta = 105{\cdot}3°,$$

space group $P2_1/a$. The structure has been determined using two-dimensional Patterson and electron-density syntheses and methods involving Fourier and optical transforms, and refined by diagonal least-squares calculations using anisotropic temperature factors. An analysis of the thermal vibrations is attempted.

Introduction

The interest of the structure of $C_{18}H_{16}(OH)_2$ lies in the configuration of atoms about the bond shared between the benzene and reduced rings. The substance is of biological interest owing to its outstanding oestrogenic activity as reported by Ramage & Robinson (1933). The preparation is described by Dodds, Golberg, Lawson & Robinson (1939).

* This paper is based on a thesis accepted by the University of London in fulfilment of the requirements of the degree of Doctor of Philosophy.

Experimental

The crystals of $C_{18}H_{16}(OH)_2$ were kindly supplied by Sir Charles Dodds of the Courtauld Institute of Biochemistry, Middlesex Hospital. They are small transparent monoclinic parallelepipeds with [010] parallel to the needle axis of the crystal. The faces (001) and (100) are inclined to each other at an angle of approximately 105°. (11l) and ($\bar{1}$1l) faces are also present.

The optic axial plane is parallel to (010), *i.e.* the β-vibration direction lies along the symmetry axis b and the γ-vibration direction makes an angle of