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The Structure of Cleavamine: X-ray Analysis of Cleavamine Methiodide

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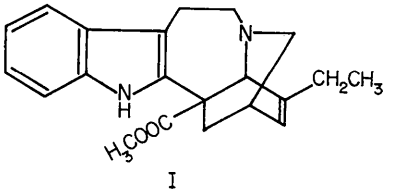
The structure of the alkaloid cleavamine, $C_{19}H_{24}N_2$, has been determined by X-ray analysis of the methiodide, crystals of which are orthorhombic with four molecules in a unit cell of dimensions $a=7{\cdot}86$, $b=14{\cdot}86$, $c=16{\cdot}32$ Å, space group $P2_12_12_1$. The intensities of about 600 reflexions were measured on a G. E. spectrogoniometer, a scintillation counter and Mo $K\alpha$ radiation being used. The iodine atom position was determined by Patterson methods; x_I was close to $\frac{1}{4}$, but although this gave rise to false symmetry all the carbon and nitrogen atoms were located on three successive three-dimensional electron-density distributions, and all the positional and individual isotropic thermal parameters were then refined by four cycles of differential synthesis and six cycles of least squares. The final R value was 0·084. The absolute configuration was determined by the anomalous dispersion method.

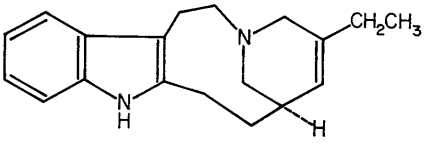
The presence of the iodine atom prevents accurate measurement of the bond distances and valency angles, despite the excellent agreement between measured and calculated structure factor data, but the measurements are sufficiently precise to distinguish between the different types of bonds and angles. The indole nucleus and the two attached carbon atoms are planar; the two ethylenic carbon atoms and the three carbon atoms bonded to them also lie in one plane. A significant feature of the molecular packing is a N–H · · · I hydrogen bond of length 3·4 Å, involving the indole nitrogen atom.

Introduction

The study of the action of acidic reagents on some of the simpler alkaloids isolated from *Vinca rosea* Linn provides important information about the effect of such reagents on the biologically important alkaloids vincaleukoblastine and leurosine. The reaction of catharanthine (I) with concentrated hydrochloric acid yields two products, one of which is simply desmethoxycarbonylcatharanthine. The second product, cleavamine, $C_{19}H_{24}N_2$, involves more drastic rearrangement; analytical, ultraviolet, infrared and nuclear magnetic resonance data suggest a tetracyclic ring skeleton for cleavamine, with retention of the indole chromophore and ethylenic double bond, and loss of the ester function of catharanthine (Kutney, Trotter, Tabata, Kerigan & Camerman, 1963).



I



II

The present paper describes an X-ray analysis of cleavamine methiodide, which establishes the structure of the alkaloid, including the absolute configuration, as (II). This formulation is in accord with all the chemical evidence.

Experimental

Crystals of cleavamine methiodide are plates elongated along c with (010) developed and smaller (100) faces. The density was measured by flotation in aqueous potassium iodide, and the unit-cell dimensions and space group were determined from various rotation, Weissenberg and precession photographs and on the G. E. spectrogoniometer.

Crystal data

(λ, Cu $K\alpha = 1{\cdot}5418$ Å, λ, Mo $K\alpha = 0{\cdot}7107$ Å).

Cleavamine methiodide, $C_{20}H_{27}N_2I$, mol.wt. 422·3, m.p. 244–245 °C (dec.).
Orthorhombic,

$$a = 7{\cdot}86 \pm 0{\cdot}02,\ b = 14{\cdot}86 \pm 0{\cdot}03,$$
$$c = 16{\cdot}32 \pm 0{\cdot}04 \text{ Å}.$$

$U = 1906$ Å^3.
$D_m = 1{\cdot}46$ g.cm^{-3}, $Z = 4$, $D_x = 1{\cdot}47$ g.cm^{-3}.
Absorption coefficient for X-rays,

$$\lambda = 0{\cdot}7107 \text{ Å},\ \mu = 16{\cdot}9 \text{ cm}^{-1}.$$

$F(000) = 856$.
Absent spectra: $h00$ when h is odd, $0k0$ when k is odd, $00l$ when l is odd.
Space group $P2_12_12_1$ (D_2^4).

A preliminary photographic survey revealed a rapid fall-off in intensity with increasing Bragg angle. The intensities of all reflexions with 2θ(Mo $K\alpha$) $\leq 35°$ (corresponding to an interplanar spacing $d = 1{\cdot}18$ Å) were measured on a General Electric XRD 5 Spectrogoniometer with Single-Crystal Orienter, a scintillation counter and Mo $K\alpha$ radiation being used, an approximately monochromatic beam being obtained by use of a zirconium filter and a pulse height analyser. The moving crystal–moving counter technique (Furnas, 1957) was used. 582 reflexions in the range $0 < 2\theta \leq 35°$ were observed, representing about 80% of the total number of reflexions in this range. For reflexions at higher Bragg angles to the limit of the Cu $K\alpha$ sphere, only those few visible on the preliminary films were examined in the spectrogoniometer, and the intensities (all very weak) recorded. All the intensities were corrected for background, which was found to be a function of θ only. Lorentz and polarization factors were applied and the structure amplitudes derived. The crystal used in recording the intensities was mounted with c parallel to the φ axis, and had dimensions 0·4 mm, 0·12 mm, 0·03 mm parallel to c, a and b respectively; absorption was fairly low and no corrections were applied.

Structure analysis

The position of the iodine atom was determined from the [100] and [010] Patterson projections as (0·250, 0·350, 0·140), and structure factors were calculated for all the data for the iodine only, the scattering factor listed by Sagel (1958) for uncharged I being used, with $B = 4{\cdot}0$ Å^2. The value of R, the usual discrepancy factor, was 33·0% for the observed reflexions. A three-dimensional Fourier series was summed with phases based on the iodine atom; since x_I was $\frac{1}{4}$, the resulting electron-density distribution had a false mirror plane at $x = \frac{1}{4}$. However it was possible to pick out fused five- and six-membered rings which obviously corresponded to the indole nucleus. Many other atoms were also clearly resolved, but the ambiguities introduced by the false symmetry prevented the deduction of the whole molecular structure at this stage. The nine atoms of the indole group and the two carbon atoms bonded to the five-membered ring were introduced into the structure factor calculations, all with the carbon scattering factor (Sagel, 1958) and $B = 4{\cdot}0$ Å^2; R was reduced to 23·2%. A second three-dimensional electron-density distribution revealed ten more atoms, introduction of these reduced R to 21·8%, and the final atom was located on a third three-dimensional electron-density distribution. At this stage all the gross features of the molecular structure had been established and R was 21·5%.

Refinement of the structure

Further refinement proceeded by computation of difference electron-density projections on (010) and (001). It was felt that these projections, being centrosymmetrical, were more likely to reveal any small deviations of x_I from $\frac{1}{4}$, than a synthesis using the three-dimensional data.* The maps did suggest a reduction of x_I to about 0·248, small shifts in the y and z coordinates of the iodine, and an increase in the temperature factor to 5·5 Å^2. At this stage also more realistic scattering factors were introduced. That for I^- was obtained from the curve for uncharged I (*International Tables for X-ray Crystallography*, 1962) by comparison with the differences in the values of X^- and X (X = F, Cl, Br); it was corrected for anomalous dispersion, according to the expression

$$f(\text{corrected}) = \sqrt{\{(f_{I^-} + \Delta f_I')^2 + (\Delta f_I'')^2\}}$$

using the values $\Delta f'$, $\Delta f''$ given in *International Tables for X-ray Crystallography* (1962). The nitrogen scattering factor was introduced for N(2) and the carbon curve was used for all the carbon atoms and for N^+(3). These changes reduced R for the three-dimensional data to 15·4%.

All the positional and isotropic thermal parameters, together with an overall scale factor, were then refined by least squares, using a program for the IBM 1620 computer (Appendix). The function minimized was $\Sigma w(|F_o| - |F_c|)^2$, with $w = F_o/40$ when $F_o < 40$, and

* We are indebted to Dr A. W. Hanson for suggesting this procedure.

Table 1. *Measured and calculated structure amplitudes*

[Unobserved reflexions, for which F_o is listed as 0·0, have threshold values in the range 7–18]

H	K	L	F OBS	F CALC
0	0	2	11.3	9.5
0	0	4	100.4	116.9
0	0	6	49.0	55.1
0	0	8	92.5	88.6
0	0	10	73.7	79.9
0	0	12	35.0	36.9
0	1	1	84.9	77.7
0	1	2	51.3	53.8
0	1	3	169.0	183.3
0	1	4	48.1	41.4
0	1	5	43.5	40.1
0	1	6	86.6	96.4
0	1	7	83.8	82.0
0	1	8	53.2	46.9
0	1	9	0.0	1.4
0	1	10	54.6	50.4
0	1	11	48.6	52.6
0	1	12	26.5	23.7
0	1	13	41.7	41.4
0	2	0	83.1	77.1
0	2	1	72.1	83.2
0	2	2	0.0	3.8
0	2	3	84.0	89.9
0	2	4	63.3	61.0
0	2	5	192.0	198.3
0	2	6	32.9	28.3
0	2	7	43.0	47.4
0	2	8	45.3	44.3
0	2	9	83.1	81.8
0	2	10	28.1	26.0
0	2	11	12.0	8.4
0	2	12	27.4	25.5
0	2	13	55.5	51.3
0	3	1	71.6	69.4
0	3	2	168.5	186.8
0	3	3	19.6	24.8
0	3	4	32.7	30.0
0	3	5	36.4	39.5
0	3	6	82.9	79.7
0	3	7	0.0	9.4
0	3	8	58.9	65.7
0	3	9	0.0	0.2
0	3	10	40.1	35.9
0	3	11	25.8	20.4
0	3	12	44.4	46.8
0	3	13	0.0	19.2
0	4	0	103.4	115.7
0	4	1	105.2	109.9
0	4	2	0.0	0.7
0	4	3	51.6	42.0
0	4	4	99.4	108.4
0	4	5	0.0	9.7
0	4	6	42.4	39.3
0	4	7	53.4	50.5
0	4	8	53.4	62.3
0	4	9	40.1	38.2
0	4	10	46.7	40.4
0	4	11	0.0	2.7
0	4	12	38.2	40.0
0	4	13	20.9	19.4
0	5	1	107.7	97.5
0	5	2	21.6	22.9
0	5	3	118.8	118.1
0	5	4	14.5	13.1
0	5	5	0.0	1.6
0	5	6	41.9	41.7
0	5	7	110.3	111.1
0	5	8	29.7	24.3
0	5	9	0.0	3.4
0	5	10	0.0	8.0
0	5	11	64.7	60.0
0	5	12	0.0	5.6
0	6	0	68.6	63.1
0	6	1	65.6	60.8
0	6	2	29.2	29.4
0	6	3	47.9	45.9
0	6	4	109.1	112.2
0	6	5	70.4	71.2
0	6	6	41.0	47.1
0	6	7	46.5	40.1
0	6	8	49.3	52.2
0	6	9	36.1	34.2
0	6	10	38.7	41.0
0	6	11	14.0	11.4
0	6	12	0.0	2.3
0	7	1	0.0	5.7
0	7	2	110.5	118.6
0	7	3	18.4	16.5
0	7	4	0.0	11.4
0	7	5	44.7	36.1
0	7	6	52.5	60.5
0	7	7	0.0	11.9
0	7	8	40.5	36.9
0	7	9	0.0	5.9
0	7	10	43.3	48.6
0	7	11	0.0	1.0
0	8	0	33.4	35.6
0	8	1	55.0	50.7
0	8	2	0.0	18.0
0	8	3	45.3	47.6
0	8	4	50.4	52.1
0	8	5	67.9	74.6
0	8	6	24.6	22.5
0	8	7	0.0	3.0
0	8	8	31.5	29.2
0	8	9	47.2	50.0
0	8	10	27.6	29.3
0	9	1	69.8	64.2
0	9	2	51.8	51.3
0	9	3	76.4	70.9
0	9	4	0.0	6.6
0	9	5	38.9	38.3
0	9	6	34.5	32.6
0	9	7	52.7	51.2
0	9	8	21.4	20.6
0	9	9	0.0	10.7
0	10	0	51.8	54.4
0	10	1	0.0	3.4
0	10	2	32.7	31.1
0	10	3	0.0	8.1
0	10	4	45.3	52.1
0	10	5	0.0	8.5
0	10	6	32.2	28.0
0	10	7	0.0	3.4
0	10	8	31.1	29.7
0	11	1	29.2	26.5
0	11	2	42.4	45.9
0	11	3	39.6	33.4
0	11	4	0.0	16.2
0	11	5	18.6	13.7
0	11	6	33.8	38.9
0	11	7	32.2	43.2
0	12	0	0.0	1.9
0	12	1	39.1	43.6
0	12	2	11.0	8.6
0	12	3	35.2	29.0
0	12	4	0.0	9.5
0	13	2	25.6	26.6
0	14	0	14.5	24.8
1	0	1	14.3	3.7
1	0	2	134.0	144.1
1	0	3	6.4	10.7
1	0	4	12.7	12.3
1	0	5	32.9	29.8
1	0	6	95.5	91.3
1	0	7	36.1	25.9
1	0	8	79.0	82.9
1	0	9	0.0	14.5
1	0	10	60.8	53.6
1	0	11	0.0	20.8
1	0	12	58.2	50.6
1	0	13	18.4	11.5
1	1	0	81.7	89.2
1	1	1	102.7	110.7
1	1	2	34.5	33.7
1	1	3	101.5	99.3
1	1	4	141.3	135.2
1	1	5	91.6	98.4
1	1	6	47.2	50.0
1	1	7	26.0	25.7
1	1	9	77.3	72.3
1	1	8	50.9	50.5
1	1	10	38.4	31.0
1	1	11	12.0	14.4
1	1	12	26.2	20.2
1	1	13	52.7	49.4
1	2	0	107.3	107.6
1	2	1	54.1	59.4
1	2	2	12.4	6.1
1	2	3	170.3	175.3
1	2	4	17.3	16.1
1	2	5	58.2	60.5
1	2	6	35.2	31.5
1	2	7	121.5	124.1
1	2	8	23.7	6.1
1	2	9	0.0	7.2
1	2	10	11.5	14.5
1	2	11	59.4	52.0
1	2	12	21.9	9.2
1	2	13	25.8	30.1
1	3	0	237.6	250.3
1	3	1	107.3	105.4
1	3	2	35.7	39.7
1	3	3	29.7	34.3
1	3	4	139.7	145.4
1	3	5	20.3	28.6
1	3	6	59.2	61.1
1	3	7	13.8	13.3
1	3	8	86.8	85.9
1	3	9	42.8	45.3
1	3	10	59.4	57.6
1	3	11	0.0	2.0
1	3	12	29.0	31.2
1	3	13	21.4	24.5
1	4	0	0.0	15.5
1	4	1	43.5	49.3
1	4	2	125.9	130.6
1	4	3	64.2	77.0
1	4	4	19.8	26.9
1	4	5	0.0	17.9
1	4	6	61.5	63.2
1	4	7	60.5	62.5
1	4	8	51.7	58.1
1	4	9	0.0	8.5
1	4	10	56.4	58.1
1	4	11	33.1	31.5
1	4	12	41.0	36.1
1	5	0	0.0	0.0
1	5	1	91.8	88.1
1	5	2	30.4	35.9
1	5	3	80.1	81.8
1	5	4	20.3	24.3
1	5	5	123.8	129.2
1	5	6	18.6	17.8
1	5	7	38.9	40.1
1	5	8	12.2	10.2
1	5	9	75.3	74.6
1	5	10	0.0	0.6
1	5	11	0.0	12.1
1	5	12	0.0	14.0
1	6	0	12.2	14.4
1	6	1	61.0	67.7
1	6	2	101.7	104.3
1	6	3	67.5	68.1
1	6	4	18.6	21.0
1	6	5	15.7	23.9
1	6	6	65.8	66.3
1	6	7	48.3	54.5
1	6	8	35.9	36.0
1	6	9	0.0	8.1
1	6	10	26.2	25.6
1	6	11	34.8	35.2
1	7	0	87.0	96.0
1	7	1	35.2	40.8
1	7	2	35.7	39.7
1	7	3	0.0	7.3
1	7	4	67.7	74.2
1	7	5	25.8	32.4
1	7	6	38.4	40.6
1	7	7	0.0	21.4
1	7	8	62.2	57.7
1	7	9	16.6	5.4
1	7	10	38.2	36.4
1	7	11	0.0	13.7
1	8	0	0.0	12.7
1	8	1	64.2	75.6
1	8	2	47.7	57.5
1	8	3	57.3	64.5
1	8	4	0.0	11.6
1	8	5	0.0	12.3
1	8	6	32.2	33.8
1	8	7	59.9	60.1
1	8	8	0.0	6.9
1	8	9	0.0	9.8
1	8	10	0.0	9.9
1	9	0	29.2	38.0
1	9	1	47.4	52.4
1	9	2	0.0	7.1
1	9	3	31.5	35.3
1	9	4	27.2	31.2
1	9	5	47.4	42.8
1	9	6	12.2	19.1
1	9	7	11.3	17.4
1	9	8	0.0	10.5
1	9	9	38.7	36.2
1	10	0	0.0	4.7
1	10	1	0.0	11.3
1	10	2	62.6	64.4
1	10	3	0.0	17.4
1	10	4	19.1	16.8
1	10	5	0.0	13.1
1	10	6	58.7	65.1
1	10	7	16.6	19.8
1	10	8	19.1	18.7
1	11	0	38.4	41.3
1	11	1	36.8	28.3
1	11	2	0.0	8.1
1	11	3	0.0	7.8
1	11	4	38.0	37.5
1	11	5	31.1	32.8
1	11	6	23.9	31.4
1	12	0	0.0	5.7
1	12	1	35.9	44.3
1	12	2	0.0	7.9
1	12	3	41.4	42.1
1	13	0	26.2	35.6
2	0	0	113.9	115.3
2	0	1	44.7	41.3
2	0	2	37.5	37.7
2	0	3	17.0	20.4
2	0	4	140.2	145.4
2	0	5	0.0	4.4
2	0	6	50.6	54.2
2	0	7	12.7	4.4
2	0	8	96.2	91.3
2	0	9	0.0	3.8
2	0	10	57.8	57.2
2	0	11	18.9	13.3
2	0	12	47.9	46.4
2	0	13	0.0	22.6
2	1	0	102.4	97.2
2	1	1	86.1	91.1
2	1	2	156.5	158.5
2	1	3	109.6	114.3
2	1	4	53.2	49.6
2	1	5	37.8	37.1
2	1	6	38.4	42.0
2	1	7	94.8	95.5
2	1	8	23.0	16.8
2	1	9	0.0	6.3
2	1	10	26.7	26.6
2	1	11	54.3	49.6
2	1	12	48.1	39.0
2	1	13	0.0	11.5
2	2	0	192.7	184.6
2	2	1	125.2	129.0
2	2	2	50.2	46.8
2	2	3	57.3	65.2
2	2	4	50.4	44.3
2	2	5	97.6	103.9
2	2	6	26.5	24.0
2	2	7	40.5	43.2
2	2	8	19.1	24.0
2	2	9	80.6	82.7
2	2	10	24.6	23.5
2	2	11	0.0	9.0
2	2	12	0.0	8.3
2	3	0	66.3	67.9
2	3	1	80.6	79.2
2	3	2	70.2	76.9
2	3	3	23.0	16.3
2	3	4	42.1	43.5
2	3	5	0.0	9.6
2	3	6	95.8	100.5
2	3	7	60.1	55.2
2	3	8	42.6	46.8
2	3	9	0.0	13.7
2	3	10	56.6	51.6
2	3	11	19.3	20.2
2	3	12	35.5	34.6
2	4	0	105.9	117.6
2	4	1	70.9	74.2
2	4	2	29.7	24.8
2	4	3	28.1	34.3
2	4	4	116.0	119.1
2	4	5	51.6	53.1
2	4	6	44.9	53.2
2	4	7	0.0	7.9
2	4	8	44.9	41.7
2	4	9	46.3	43.5
2	4	10	41.9	36.1
2	4	11	0.0	10.2
2	4	12	18.6	10.0
2	5	0	11.5	12.9
2	5	1	72.1	77.6
2	5	2	0.0	12.6
2	5	3	92.8	102.3
2	5	4	13.1	16.1
2	5	5	50.6	54.8
2	5	6	17.0	22.9
2	5	7	64.7	65.9
2	5	8	0.0	13.5
2	5	9	0.0	7.2
2	5	10	0.0	17.4
2	5	11	61.2	50.7
2	6	0	65.4	74.1
2	6	1	58.7	63.0
2	6	2	10.8	10.4
2	6	3	12.0	15.9
2	6	4	66.3	64.8
2	6	5	64.2	64.2
2	6	6	20.9	25.8
2	6	7	0.0	9.0
2	6	8	41.4	41.2
2	6	9	52.3	50.9
2	6	10	22.8	22.8
2	6	11	0.0	1.6
2	7	0	0.0	3.2
2	7	1	15.4	11.5
2	7	2	104.7	109.8
2	7	3	0.0	8.7
2	7	4	25.3	26.1
2	7	5	12.2	14.2
2	7	6	80.6	79.9
2	7	7	23.7	26.2
2	7	8	47.2	48.2
2	7	9	0.0	1.3
2	7	10	33.8	31.7
2	8	0	26.0	28.6
2	8	1	58.0	59.7
2	8	2	0.0	8.5
2	8	3	54.6	55.5
2	8	4	31.1	29.0
2	8	5	70.0	68.2
2	8	6	12.0	17.7
2	8	7	0.0	17.8
2	8	8	14.0	16.9
2	8	9	39.4	36.2
2	9	0	18.0	23.7
2	9	1	35.9	36.0
2	9	2	40.5	40.2
2	9	3	51.3	54.4
2	9	4	0.0	13.0
2	9	5	20.5	20.8
2	9	6	17.7	16.1
2	9	7	65.6	61.3
2	9	8	25.8	21.3
2	10	0	61.5	60.1
2	10	1	19.8	21.1
2	10	2	21.4	19.1
2	10	3	0.0	9.4
2	10	4	59.2	53.9
2	10	5	18.2	14.2
2	10	6	22.8	25.7
2	10	7	0.0	10.2
2	11	0	0.0	7.7
2	11	1	26.9	32.0
2	11	2	37.1	38.9
2	11	3	29.7	33.2
2	11	4	0.0	11.7
2	11	5	0.0	21.0
2	14	0	19.8	28.3
3	0	1	0.0	2.0
3	0	2	89.3	105.1
3	0	3	27.9	19.1
3	0	4	38.0	37.1
3	0	5	0.0	0.6
3	0	6	127.3	114.3
3	0	7	29.5	30.8
3	0	8	50.4	48.4
3	0	9	14.7	14.5
3	0	10	26.7	21.6
3	0	11	30.8	19.9
3	0	12	34.3	23.5
3	1	0	80.8	86.0
3	1	1	59.4	66.7
3	1	2	16.3	16.5
3	1	3	70.9	72.2
3	1	4	65.6	69.2
3	1	5	71.4	76.5
3	1	6	23.0	30.2
3	1	7	0.0	9.8
3	1	8	47.2	48.1
3	1	9	66.3	67.0
3	1	10	32.9	32.6
3	1	11	0.0	4.6
3	1	12	0.0	5.6
3	2	0	12.0	13.0
3	2	1	101.7	103.4
3	2	2	42.8	43.2
3	2	3	92.5	104.8
3	2	4	30.4	36.9
3	2	5	19.6	23.4
3	2	6	15.4	18.5
3	2	7	73.0	73.4
3	2	8	0.0	4.1
3	2	9	12.0	13.8
3	2	10	0.0	10.3
3	2	11	62.8	59.9
3	2	12	24.6	22.8
3	3	0	92.1	78.5
3	3	1	30.6	29.0
3	3	2	19.1	18.2
3	3	3	23.0	16.2
3	3	4	87.7	94.9
3	3	5	40.3	40.5
3	3	6	50.0	46.3
3	3	7	27.6	14.3
3	3	8	57.8	53.6
3	3	9	32.2	30.2
3	3	10	35.0	33.9
3	3	11	0.0	17.5
3	4	0	44.4	43.3

Table 1 (*cont.*)

3	4	1	8.5	15.9
3	4	2	143.2	143.0
3	4	3	34.8	37.6
3	4	4	27.2	33.2
3	4	5	34.3	42.1
3	4	6	71.6	75.1
3	4	7	63.5	62.6
3	4	8	33.8	32.5
3	4	9	0.0	11.1
3	4	10	27.4	29.3
3	4	11	15.7	14.5
3	5	0	52.7	45.4
3	5	1	110.7	116.5
3	5	2	19.8	21.8
3	5	3	52.5	50.7
3	5	4	14.3	15.6
3	5	5	72.7	78.3
3	5	6	0.0	7.2
3	5	7	0.0	9.3
3	5	8	0.0	3.7
3	5	9	58.2	56.1
3	5	10	0.0	3.7
3	5	11	0.0	10.5
3	6	0	0.0	7.6
3	6	1	35.9	39.3
3	6	2	45.1	50.7
3	6	3	32.2	32.8
3	6	4	28.1	33.0
3	6	5	29.7	30.1
3	6	6	52.3	36.6
3	6	7	67.7	66.0
3	6	8	37.3	36.1
3	6	9	14.0	13.2
3	6	10	33.1	35.8
3	7	0	94.8	96.7
3	7	1	12.2	15.2
3	7	2	19.3	13.5
3	7	3	0.0	10.6
3	7	4	71.8	73.8
3	7	5	29.0	30.4
3	7	6	24.2	23.5
3	7	7	11.0	15.8
3	7	8	41.4	35.5
3	7	9	16.8	14.9
3	8	0	0.0	11.6
3	8	1	41.9	42.1
3	8	2	24.6	26.3
3	8	3	49.0	51.4
3	8	4	0.0	14.2
3	8	5	25.1	31.5
3	8	6	25.1	31.8
3	8	7	21.6	23.4
3	8	8	0.0	6.5
3	9	0	24.4	18.3
3	9	1	43.0	44.4
3	9	2	0.0	2.4
3	9	3	16.6	13.1
3	9	4	23.3	22.2
3	9	5	56.2	53.3
3	9	6	0.0	14.5
3	9	7	0.0	0.8
3	10	0	0.0	6.9
3	10	1	0.0	7.9
3	10	2	58.7	57.8
3	10	3	0.0	13.3
3	10	4	24.2	20.4
3	10	5	18.9	21.1
3	11	0	31.5	31.4
3	11	1	28.1	24.4
3	11	2	14.7	13.4
3	13	0	18.4	27.2
4	0	0	105.7	116.0
4	0	1	10.1	6.6
4	0	2	30.2	26.8
4	0	3	23.7	8.3
4	0	4	67.0	73.3
4	0	5	18.2	10.5
4	0	6	32.2	34.6
4	0	7	10.4	12.5
4	0	8	65.4	58.9
4	0	9	0.0	8.6
4	0	10	45.8	45.1
4	0	11	0.0	2.0
4	1	0	0.0	4.6
4	1	1	38.2	45.8
4	1	2	68.6	72.9
4	1	3	71.4	75.8
4	1	4	29.0	27.7
4	1	5	30.2	32.1
4	1	6	38.9	39.3
4	1	7	58.0	59.7
4	1	8	16.3	15.7
4	1	9	0.0	5.8
4	1	10	0.0	29.4
4	2	0	24.2	28.4
4	2	1	87.2	86.5
4	2	2	24.9	24.4
4	2	3	59.9	62.5
4	2	4	26.5	29.6
4	2	5	61.7	66.4
4	2	6	11.5	7.7
4	2	7	0.0	5.5
4	2	8	20.5	20.8
4	2	9	56.6	54.8
4	2	10	0.0	8.6
4	3	0	51.1	49.1
4	3	1	20.5	23.1
4	3	2	90.0	97.3
4	3	3	28.8	31.6
4	3	4	23.5	26.8
4	3	5	25.8	28.5
4	3	6	65.8	67.9
4	3	7	35.2	32.9
4	3	8	41.0	40.5
4	3	9	0.0	7.2
4	3	10	15.7	17.1
4	4	0	38.7	36.1
4	4	1	41.0	42.5
4	4	2	24.9	25.6
4	4	3	19.1	17.8
4	4	4	61.2	59.2
4	4	5	46.1	41.6
4	4	6	20.5	19.9
4	4	7	15.4	14.7
4	4	8	42.8	42.5
4	4	9	26.7	30.9
4	4	10	30.6	29.0
4	5	0	0.0	15.6
4	5	1	57.6	64.7
4	5	2	31.3	34.2
4	5	3	50.0	50.3
4	5	4	13.8	12.7
4	5	5	22.6	21.1
4	5	6	13.4	14.7
4	5	7	49.3	46.0
4	5	8	0.0	10.9
4	5	9	0.0	16.0
4	6	0	58.2	66.0
4	6	1	42.1	43.3
4	6	2	0.0	8.0
4	6	3	29.7	27.1
4	6	4	48.3	51.1
4	6	5	55.7	54.5
4	6	6	15.9	18.2
4	6	7	0.0	3.8
4	6	8	34.3	28.9
4	7	0	26.7	19.0
4	7	1	14.3	16.7
4	7	2	65.6	62.4
4	7	3	0.0	2.1
4	7	4	22.1	18.4
4	7	5	0.0	7.6
4	7	6	56.4	54.7
4	7	7	0.0	9.7
4	8	0	33.4	34.9
4	8	1	37.3	32.4
4	8	2	0.0	7.4
4	8	3	26.5	23.5
4	8	4	19.8	17.4
4	8	5	56.6	58.3
4	8	6	0.0	7.5
4	9	0	0.0	2.4
4	9	1	37.1	40.2
4	9	2	20.9	24.9
4	9	3	39.4	36.4
4	9	4	19.8	18.0
4	10	0	51.8	51.7
4	10	1	0.0	11.2
5	0	1	0.0	7.8
5	0	2	78.3	80.6
5	0	3	18.6	18.7
5	0	4	12.9	16.8
5	0	5	26.5	11.7
5	0	6	73.9	73.8
5	0	7	0.0	3.5
5	0	8	25.6	22.9
5	0	9	0.0	9.1
5	1	0	25.6	32.3
5	1	1	48.6	47.8
5	1	2	0.0	2.8
5	1	3	34.3	36.1
5	1	4	23.7	31.0
5	1	5	47.4	47.8
5	1	6	35.0	31.1
5	1	7	0.0	5.2
5	1	8	21.9	21.8
5	1	9	30.6	32.1
5	2	0	11.5	10.1
5	2	1	38.9	42.4
5	2	2	0.0	4.1
5	2	3	49.7	50.2
5	2	4	21.4	18.3
5	2	5	18.2	17.4
5	2	6	14.7	10.6
5	2	7	54.3	54.7
5	2	8	0.0	6.5
5	3	0	87.2	88.6
5	3	1	38.4	39.9
5	3	2	15.9	16.0
5	3	3	18.4	13.2
5	3	4	54.3	57.1
5	3	5	23.5	25.8
5	3	6	20.5	21.7
5	3	7	14.3	13.2
5	3	8	33.6	37.2
5	4	0	20.0	13.9
5	4	1	41.4	41.3
5	4	2	42.4	49.0
5	4	3	33.1	29.8
5	4	4	26.5	26.2
5	4	5	15.0	21.1
5	4	6	44.4	41.6
5	4	7	13.1	15.4
5	5	0	47.7	45.1
5	5	1	32.9	37.5
5	5	2	13.6	12.8
5	5	3	25.6	31.4
5	5	4	0.0	9.3
5	5	5	63.5	64.0
5	5	6	0.0	1.7
5	5	7	17.0	6.0
5	6	0	12.7	0.2
5	6	1	34.8	33.6
5	6	2	56.4	56.2
5	6	3	37.5	32.5
5	6	4	25.3	21.3
5	6	5	22.8	20.7
5	6	6	26.7	26.0
5	7	0	30.2	30.8
5	7	1	25.3	27.4
5	7	2	17.5	13.4
5	7	3	19.6	13.4
5	7	4	41.7	41.9
5	8	0	0.0	7.9
5	8	1	23.3	21.9
5	8	2	29.5	29.1
6	0	0	70.4	67.7
6	0	1	26.0	24.8
6	0	2	37.1	32.4
6	0	3	11.5	11.5
6	0	4	46.3	51.5
6	0	5	0.0	9.6
6	1	0	0.0	7.0
6	1	1	26.0	33.0
6	1	2	25.6	26.4
6	1	3	37.8	36.9
6	1	4	0.0	3.5
6	1	5	14.5	14.3
6	2	0	0.0	2.8
6	2	1	39.6	41.0
6	2	2	0.0	13.0
6	2	3	31.3	31.1
6	2	4	16.6	14.9
6	2	5	38.7	40.2
6	3	0	17.3	6.3
6	3	1	16.3	8.9
6	3	2	58.7	47.5
6	3	3	16.6	14.1
6	3	4	22.3	16.3
6	3	5	0.0	12.5
6	4	0	27.6	32.9
6	4	1	23.5	23.9
6	4	2	0.0	4.8
6	4	3	0.0	6.4
6	4	4	39.6	43.6
6	5	0	0.0	3.9
6	5	1	27.4	27.8
6	5	2	0.0	6.2
6	6	0	19.3	15.1
7	7	0	33.8	37.2
8	0	0	26.2	22.9

$w=40/F_o$ when $F_o \geq 40$. Five cycles reduced R to 8·4%. The shifts in the fifth cycle were generally less than about one-third of a standard deviation, except for one or two as large as one standard deviation.

An attempt was then made to refine the structure independently by the differential synthesis method, using calculated syntheses to apply 'backshift' corrections to the atomic coordinates (Booth, 1946; Ahmed & Cruickshank, 1953), and corrections to the thermal parameters. Starting with the final least-squares positions the first differential syntheses cycle increased R to 9·7%, two more cycles reduced this to 8·9%, and a fourth cycle caused a slight increase to 9·1%. The changes in positional parameters from those of the least-squares refinement were generally small, but there were several fairly large differences in bond lengths and valency angles (to be described later). The temperature factors were generally about the same as or a little larger than those of the least-squares analysis. A final least-squares cycle, using as input the parameters from the fourth differential syntheses, shifted the atoms towards the positions given by the fifth least-squares cycle.

The final measured and calculated structure factors, calculated from the parameters output from the fifth least-squares cycle ($R=8·4\%$ for the 591 observed reflexions), are listed in Table 1. A final three-dimensional Fourier series was summed using as coefficients the measured structure amplitudes with calculated phase angles. Superimposed sections of the resulting electron-density distribution taken through the atomic centres are shown in Fig. 1. All the peak heights are quite low (Fig. 1 and Table 2), a consequence of the rapid fall off in intensity of the reflexions. This is particularly so for atom C(23) (Fig. 1), and this was also the atom which was last to appear in the electron-density distributions, and for which the coordinate differences between least-squares and dif-

Table 2. *Positional parameters (fractional) with standard deviations* (Å), *thermal parameters and standard deviations* (Å^2), *and peak electron-densities* (e.Å^{-3})

	5th Least-squares cycle								3rd Differential cycle				
Atom	x	y	z	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$	B (Å^2)	$\sigma(B)$	x	y	z	B (Å^2)	ϱ (e.Å^{-3})
I (1)	0·2474	0·3530	0·1378	0·0049	0·0025	0·0024	5·78	0·05	0·2486	0·3528	0·1378	5·8	51·8
N (2)	0·064	0·443	0·309	0·031	0·029	0·029	4·26	0·72	0·064	0·442	0·313	4·3	5·2
N$^+$(3)	−0·456	0·532	0·416	0·034	0·031	0·032	3·91	0·77	−0·452	0·533	0·416	3·9	4·8
C (4)	−0·030	0·509	0·336	0·041	0·040	0·036	3·48	0·92	−0·041	0·508	0·340	3·5	4·5
C (5)	−0·048	0·523	0·429	0·034	0·031	0·030	3·29	0·75	−0·053	0·523	0·432	3·3	4·7
C (6)	0·031	0·435	0·457	0·033	0·034	0·032	2·72	0·77	0·035	0·432	0·455	3·5	4·9
C (7)	0·054	0·400	0·532	0·040	0·039	0·038	4·02	0·93	0·063	0·398	0·528	4·0	4·3
C (8)	0·158	0·317	0·536	0·037	0·036	0·036	3·20	0·91	0·150	0·319	0·538	4·0	4·2
C (9)	0·209	0·278	0·467	0·036	0·033	0·033	4·70	0·90	0·210	0·280	0·468	4·7	4·4
C(10)	0·195	0·308	0·385	0·034	0·037	0·034	3·81	0·98	0·193	0·312	0·392	3·8	4·4
C(11)	0·092	0·395	0·385	0·039	0·037	0·036	3·80	0·95	0·090	0·394	0·386	4·5	4·3
C(12)	−0·141	0·587	0·477	0·040	0·039	0·038	3·65	0·92	−0·145	0·588	0·479	4·5	4·2
C(13)	−0·104	0·581	0·286	0·040	0·038	0·036	2·69	0·95	−0·103	0·584	0·287	3·5	4·6
C(14)	−0·244	0·543	0·223	0·065	0·034	0·032	4·47	0·86	−0·237	0·548	0·228	5·5	3·9
C(15)	−0·428	0·532	0·264	0·036	0·034	0·033	3·38	0·84	−0·431	0·533	0·270	3·4	5·0
C(16)	−0·519	0·620	0·265	0·047	0·041	0·041	5·13	1·11	−0·515	0·624	0·267	5·8	3·5
C(17)	−0·624	0·643	0·337	0·041	0·042	0·037	3·79	0·95	−0·623	0·644	0·332	4·5	4·9
C(18)	−0·618	0·581	0·416	0·037	0·034	0·036	2·30	0·81	−0·622	0·579	0·415	3·3	4·8
C(19)	−0·323	0·608	0·445	0·039	0·043	0·040	5·27	1·17	−0·326	0·605	0·441	5·3	3·8
C(20)	−0·750	0·727	0·351	0·072	0·035	0·037	7·31	0·90	−0·747	0·730	0·354	7·3	3·7
C(21)	−0·740	0·778	0·265	0·076	0·043	0·043	8·65	1·19	−0·739	0·776	0·265	8·7	3·4
C(22)	−0·472	0·468	0·499	0·046	0·042	0·040	5·38	1·14	−0·470	0·468	0·498	5·4	4·4
C(23)	−0·418	0·485	0·352	0·051	0·046	0·045	7·62	1·22	−0·413	0·481	0·343	7·6	3·0

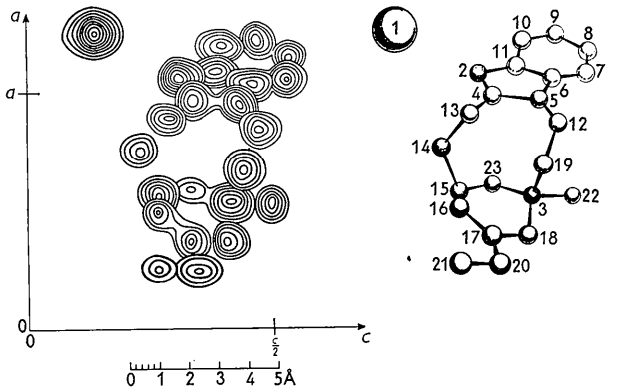


Fig. 1. Superimposed sections of the final three-dimensional electron-density distribution, through the atomic centres parallel to (010); contours for the carbon and nitrogen atoms are at intervals of $\frac{1}{2}$ e.Å^{-3} starting at 2 e.Å^{-3}, and for the iodine at intervals of 5 e.Å^{-3} starting at 5 e.Å^{-3}. Also shown is a perspective drawing of the molecule. Both drawings show the correct absolute configuration, the positive direction of the b axis being towards the viewer.

ferential syntheses were largest; however in no other region was there any electron density which might indicate another position for or any disordering of atom C(23).

Coordinates and molecular dimensions

The final positional and thermal parameters are listed in Table 2. Two sets of parameters are listed, those from the fifth least-squares cycle and those from the third differential syntheses; the least-squares coordinates give a slightly lower discrepancy factor (8·4 as against 8·9%), but we feel that it is not really possible to decide between them. Despite the reliable counter intensities, it appears that the difficulty of obtaining accurate carbon positions in the presence of the heavier iodine is the limiting factor in the analysis. Also given in Table 2 are the standard deviations of the atomic parameters, calculated from the least-squares residuals (Appendix), and the peak electron densities from the third observed differential synthesis.

The bond distances in the molecule, calculated from both sets of coordinates of Table 2, are shown in Fig. 2(a), and the valency angles (least-squares parameters) in Fig. 2(b). The standard deviations of these are about 0·05 Å for bond distances and 3° for angles. The most significant intermolecular contacts are given in Table 3 (least-squares parameters), and the molecular packing is illustrated in Fig. 3.

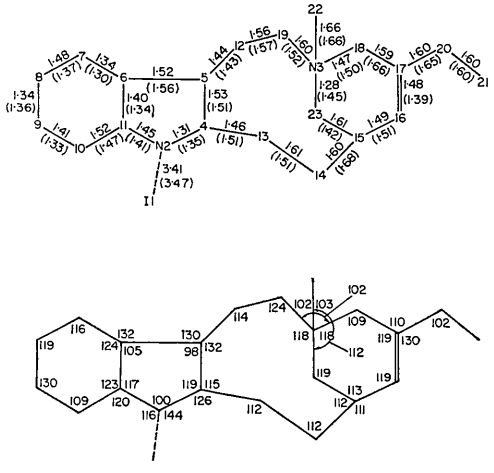


Fig. 2. (a) Bond distances from least-squares, and (in parentheses) differential syntheses refinements. (b) Valency angles (least-squares parameters).

Table 3. *Shorter intermolecular distances*

(For C–C, C–N, all distances ≤ 3·8 Å are listed; for C–I, N–I, all distances ≤ 5·0 Å)

Atom (molecule 1)	Atom	in Molecule	Distance
1	2	1	3·41 Å
1	15	2	4·22
1	16	2	4·84
1	23	2	4·80
5	1	5	4·54
6	1	5	4·66
7	1	5	4·35
12	1	3	4·45
12	1	5	4·16
13	1	3	4·38
16	1	3	4·37
17	1	3	4·32
19	1	3	3·93
20	1	3	4·38
21	1	3	4·33
2	18	2	3·68
4	17	2	3·77
4	18	2	3·66
5	18	2	3·50
6	18	2	3·58
8	22	2	3·73
9	7	4	3·78
9	8	4	3·79
11	18	2	3·62
13	20	2	3·69

Molecule	General coordinates
1	x, y, z
2	$1+x, y, z$
3	$-x, \frac{1}{2}+y, \frac{1}{2}-z$
4	$\frac{1}{2}+x, \frac{1}{2}-y, 1-z$
5	$\frac{1}{2}-x, 1-y, \frac{1}{2}+z$

There are only two parts of the molecule where it is useful to examine planarity of the atoms; one of these is the indole group and the other the neighbourhood of the ethylenic double bond. The best plane through the nine atoms of the indole rings has equation (least-squares parameters):

$$0{\cdot}8546X+0{\cdot}5114Y+0{\cdot}0902Z=4{\cdot}2135 \qquad (A)$$

where X, Y and Z are coordinates in Å. The plane through these nine atoms plus the two carbon atoms bonded to the five-membered ring is:

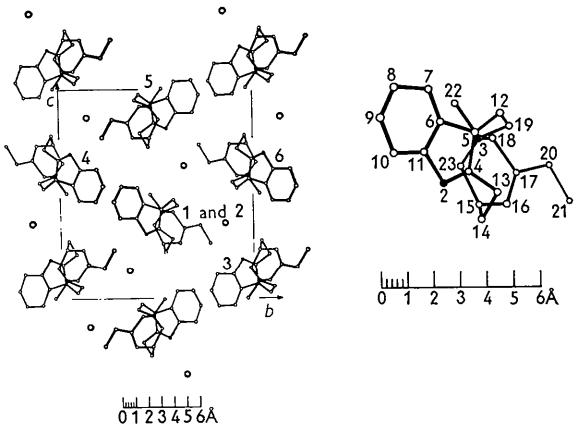


Fig. 3. Projection of the structure onto (100), illustrating the packing of the molecules.

$$0{\cdot}8532X+0{\cdot}5150Y+0{\cdot}0831Z=4{\cdot}1804\,. \qquad (B)$$

The best plane through the two atoms of the ethylenic double bond plus the three atoms bonded to them is:

$$0{\cdot}7802X+0{\cdot}5198Y+0{\cdot}3480Z=3{\cdot}0449\,. \qquad (C)$$

The deviations of the atoms from these various planes (Table 4) indicate that, within experimental error, the indole nucleus and the two attached carbon atoms are planar, and that the two ethylenic carbons and the three carbon atoms bonded to them also lie in one plane.

Table 4. *Deviations from mean planes*

Atom	*A*	*B*	Atom	*C*
2	−0·038 Å	−0·058 Å	15	0·059 Å
4	0·055	0·033	16	−0·067
5	−0·069	−0·081	17	−0·009
6	0·030	0·028	18	−0·018
7	0·030	0·038	20	0·038
8	−0·040	−0·026		
9	0·013	0·022		
10	−0·004	−0·006		
11	0·027	0·018		
12	−0·005	−0·015		
13	0·082	0·050		

Absolute configuration

The final step in the analysis was the determination of the absolute configuration of the molecule by the anomalous dispersion method (Bijvoet, Peerdeman & van Bommel, 1951). Structure factors were calculated for all the *hkl* and $\bar{h}\bar{k}\bar{l}$ reflexions, using a scattering factor for I^- of the form

$$f=(f_{I^-}+\Delta f'_I)+i\,.\,\Delta f''_I\,.$$

With Mo $K\alpha$ radiation the differences between $F_c(hkl)$ and $F_c(\bar{h}\bar{k}\bar{l})$ were small, and for about only a dozen reflexions did the differences seem large enough to be detectable even with the counter equipment. These differences could have been increased by using Cu $K\alpha$ radiation, but probably only at the expense of introducing absorption corrections (and of realigning the instrument). In an effort to make the determination as objective as possible one of the authors calculated the structure factors and suggested which pairs of reflexions were to be measured, carefully omitting any mention of the indicated directions of the differences. The other author then measured the intensities. The results are given in Table 5. Of the fourteen pairs of reflexions for which the differences were expected to be measurable, four showed no significant difference; the other ten pairs unambiguously indicated that the parameters used to calculate the structure factors (those of Table 2 referred to a conventional right-handed set of axes) represent the true absolute configuration. (II) and Fig. 1 therefore also depict the correct absolute configuration.

Discussion

The present analysis has established the structure of cleavamine methiodide, including the absolute configuration, as that shown in Figs. 1, 2 and 3, and the structure of the parent alkaloid as (II). The general shape of the molecule is clear from Figs. 1 and 3. The atoms of the indole rings and the two attached

Table 5. *Determination of the absolute configuration*

(Mo $K\alpha$ radiation)

h	k	l	$\lvert F_o\rvert$	$\lvert F_c(hkl)\rvert$	$\lvert F_c(\bar{h}\bar{k}\bar{l})\rvert$	$\frac{\lvert F_c(hkl)\rvert^2}{\lvert F_c(\bar{h}\bar{k}\bar{l})\rvert^2}$	$I_o(hkl)$	$I_o(\bar{h}\bar{k}\bar{l})$	$\frac{I_o(hkl)}{I_o(\bar{h}\bar{k}\bar{l})}$
1	2	2	12·4	3·8	8·2	0·21	34	59	0·58
2	3	3	23·0	18·6	13·9	1·79	39	30	1·30
1	4	6	61·5	61·1	65·5	0·87	189	224	0·84
3	4	1	8·5	17·5	14·4	1·48	6	3	2·00
2	9	6	17·7	17·5	14·5	1·46	8	8	1·00
1	12	3	41·4	41·5	47·4	0·77	64	64	1·00
1	3	3	29·7	32·9	36·0	0·84	87	104	0·84
4	6	6	15·9	17·4	19·1	0·83	5	6	0·83
1	11	1	36·8	27·3	29·4	0·86	31	31	1·00
2	2	3	57·3	63·7	66·6	0·91	250	291	0·86
1	3	2	35·7	40·8	38·7	1·11	141	134	1·05
2	1	5	37·8	38·1	36·1	1·11	82	82	1·00
1	2	6	35·2	30·4	32·6	0·87	65	81	0·80
3	3	10	35·0	32·5	35·1	0·86	34	45	0·76

carbon atoms all lie in one plane. In the other six-membered ring four of the atoms (those of the C=C bond and the two attached atoms) are coplanar, C(23) is only slightly displaced (−0·14 Å), but N(3) lies significantly off the plane (−0·63 Å); C(20) and C(21) do not deviate significantly from the plane (displacements +0·04 Å and +0·07 Å respectively). The general boat conformation of the nine-membered ring is also evident from Figs. 1 and 3. The structure is very markedly changed from that of catharanthine (I), the atoms C(13) and C(18), which are directly bonded in catharanthine, being separated in cleavamine by 4·6 Å.

The differences between the bond distances determined by the least-squares and differential syntheses refinements (Fig. 2(*a*)) suggest that the measurements are of limited accuracy; only for the bonds involving C(23) do the differences exceed 2σ however. The C=C bond, C(16)–C(17) (whose position in the molecule is well established chemically, and in the present analysis by the planar arrangement of the atoms around it) has a length of 1·39 Å (differential syntheses parameters) or of 1·48 Å (least-squares parameters); even the latter value is less than the mean* C–C single bond distance in the molecule, which is 1·55 Å, not significantly different from the normal single bond distance. The mean $C–N^+$ length is 1·52 Å, the mean C–C bond length in the aromatic six-membered ring is 1·39 Å, and the mean C–N(2) distance 1·38 Å. The two C–C bonds in the five-membered ring appear rather long (average value 1·53 Å); the presence of an indole nucleus, rather than dihydroindole, is again well established chemically and by the planar arrangement of atoms, and the length of these bonds might indicate a slight inaccuracy in the position of atom 5, the valency angles at this atom being somewhat anomalous (Fig. 2(*b*)).

The valency angles (Fig. 2(*b*)) are all quite reasonable; the mean tetrahedral angle is 111°, mean angle in the aromatic six-membered ring 120°, mean in the five-membered ring 108°, and mean at C=C double bond 119°.

The most significant packing distance is an I^--indole nitrogen separation of 3·41 Å (least-squares; 3·47 Å differential syntheses) as shown in Figs. 1 and 3. This probably represents an I···H–N hydrogen bond, although the hydrogen, if it is situated on the bisector of the C(4)–N(2)–C(11) angle, is displaced from the I···N line (N–H bond displaced 14°, Fig. 2(*b*)). All the other distances involving the iodide ion correspond to normal separations, the next shortest being 3·93 Å (Table 3). All the C–C and C–N intermolecular contacts involve normal van der Waals interactions, the shortest being 3·50 Å.

* The mean values are averages of the least-squares and differential syntheses results.

APPENDIX

The least-square program was written in FORTRAN-2 for the IBM 1620 computer with 40K memory and card input unit.

The general method followed was that given by Cruickshank (1961). The block-diagonal approximation was used, 3×3 and 1×1 matrices for the coordinates and isotropic temperature parameters, and a 2×2 matrix for correlation of the scale factor and the average temperature factor (the memory size prevented the use of anisotropic temperature factors). The standard deviations of the positional and temperature parameters were computed according to Cruickshank's equation (2·5).

The input cards (one per plane) contained the indices, $\sin^2\theta$, and the scattering-factors for that plane (this was chosen as input because these cards were available for the structure factor program on hand).

Since the program was in FORTRAN, and the calculations were in floating-point mode, the time taken was necessarily quite long, being for cleavamine methiodide (23 atoms and 4 equivalent positions, with 23 different isotropic temperature factors) approximately one minute per reflexion. The advantages of FORTRAN with floating-point are ease of programming and of modification of the program, and automatic handling of the decimal point.

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