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THE ABSOLUTE MOLECULAR STRUCTURE OF (+) KREYSIGININE

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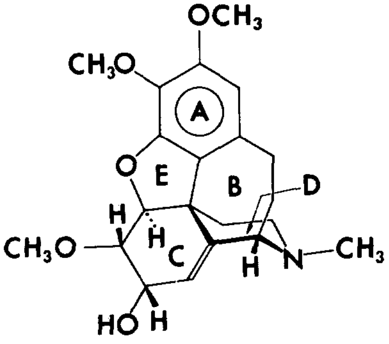
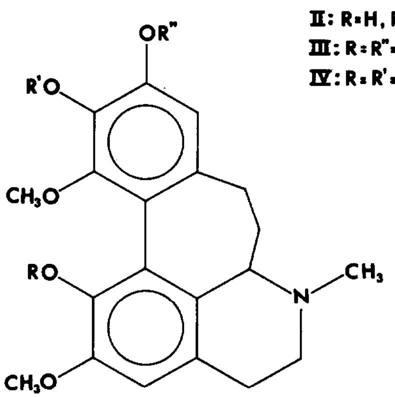
Abstract—X-ray analysis of crystals of the acetone adduct of kreysiginine methiodide, $C_{21}H_{27}O_5N.CH_3I.CH_3COCH_3$, has established the absolute structure of kreysiginine, an alkaloid from *Kreysigia multiflora* Reichb. (order Liliaceae). The crystals are orthorhombic, with unit cell dimensions, $a=8{\cdot}366$, $b=16{\cdot}349$, $c=18{\cdot}606$Å, Z=4,, the space group being $P2_12_12_1$. Intensity data for 2058 reflexions were measured with CuKα radiation on a single-crystal diffractometer. The crystal structure was solved by the heavy atom method and refined by difference and least-squares procedures. The absolute chirality was defined by Bijvoet's technique. Kreysiginine (I) was found to be a member of the class of homo-morphine alkaloids based on the 1-phenylethylisoquinoline system. Because it is opposite in absolute configuration to that of the main group of morphine alkaloids based on the benzylisoquinoline system, the absolute configuration of morphine was reconfirmed by application of Bijvoet's technique to the crystal data for morphine hydriodide dihydrate.



I

(+)-Kreysiginine, $C_{21}H_{27}O_5N$, was isolated from the Australian plant *Kreysigia multiflora* Reichb. (order Liliaceae) by Badger and Bradbury,[1] together with three other alkaloids of similar structure (±)-kreysigine, $C_{22}H_{27}O_5N$, (-)-floramultine, $C_{21}H_{27}O_5N$, (+)-floramultinine, $C_{21}H_{27}O_5N$, and certain stuctural details in these four compounds were deduced. More recently, chemical studies have established the structures of kreysigine, floramultine and another base, (-)-multifloramine, $C_{21}H_{25}O_5N$, also isolated from *K. multiflora.*[2] These three alkaloids were found to belong to the homo-aporphine class and are represented below as II, III, and IV respectively, and as their structures are based on the 1-phenylethylisoquinoline system they have been grouped together with androcymbine[3] and melanthiodine,[4] forming a new class of alkaloids, to which colchicine is related.[5,6]



II: $R = H$, $R' = R'' = CH_3$
III: $R = R'' = H$, $R' = CH_3$
IV: $R = R' = H$, $R'' = CH_3$

In an attempt to derive the complete absolute structure of kreysiginine, which the earlier spectroscopic data[1] had shown to be of a different type from II, III or IV, an X-ray analysis was carried out on this acetone adduct of kreysiginine methiodide.[1]

A report of this work which included the essential features of the structure has been presented earlier.[7] The results of two parallel independent chemical investigations[8,9] are in accord with our findings.

Stuctural details

The conventional representation of the molecular structure is shown as (I) — see also Fig. 2. Kreysiginine has a molecular skeleton of five rings fused together forming a rigid framework, with the only mobile atoms being C(18), C(19), C(20) of the three OMe groups which are free to rotate around bonds O(1)—C(2), O(2)—C(3) and O(4)—C(6) respectively. The molecule is roughly T-shaped (*cf.* morphine[10]), with atoms of rings A and E lying close to one plane and those of C and D lying close to a second plane approximately normal to the first. Atoms in ring A and the associated atoms C(11), O(1), O(2), O(3) are generally coplanar within 0·05Å with C(14) being 0·19Å from the plane while C(5) of ring E is 0·26Å from the plane. Ring D is of nearly regular chair form with C(9), C(15), C(16), C(17) coplanar to within 0·01Å and atoms C(14) and N being 0·65 and 0·80Å respectively above and below this plane. The cyclohexene ring C, instead of the expected half-chair conformation is constrained by its fusion with rings B, D and E to adopt a conformation in which five of the ring atoms are nearly coplanar (maximum deviation 0·05Å) while the remaining atom C(6) is 0·72Å from this plane. Other examples of this conformation have been noted in codeine, bromomiroestrol, 3β-acetoxy-7α, 11α-dibromolanostane-8α,9α-epoxide and 7-chloro-4-hydroxytetracycloxide.* One result of this conformation is that the equatorial-axial disposition of the C(6), C(7) oxygens involves a dihedral angle of 45·9°. The C(5), C(6) oxygens disposition is di-equatorial with a dihedral angle of 60·6°. The

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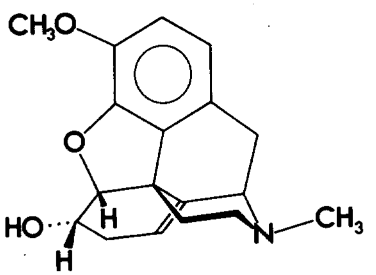
* See Ref. 11.

cycloheptene ring B is in a distorted chair conformation with atoms C(11), C(12), C(13), C(14) by virtue of ring A, being coplanar within 0·03Å. The dihedral angles associated with the groups of atoms, C(13) C(14) C(15) C(9), C(14) C(15) C(9) C(10), C(15) C(9) C(10) C(11), C(9) C(10) C(11) C(12) and C(10) C(11) C(12) C(13) are 66·0, 74·6, 68·8, 50·8, 65·4° repectively. Of the methoxyl groups, two are associated with the aromatic ring A. One C(18)—O(1) lies near the plane of ring A as expected but the other C(19)—O(2) is out of this plane so that the dihedral angle C(19) O(2) C(3) relative to the plane of ring A is 79·0°. The third group C(20)—O(4) presents an eclipsed conformation in relation to the bonds around C(6), the dihedral angle C(20) O(4) C(6) C(7) being 73·5°.

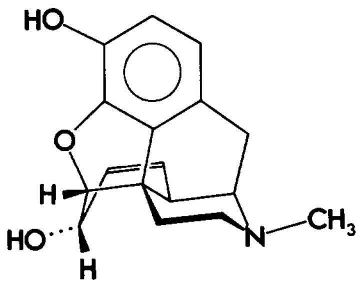
The aromatic C—C bond lengths and angles have average values of 1·39Å and 120° respectively. For the C—O bonds, those involving C(sp^3) have a mean of 1·42Å, those with C(sp^2), 1·36Å. The saturated C—C bonds have average value 1·53Å, and C—N(sp^3), 1·50Å. The closest contact between the iodine ion and the kreysiginine cation is I.....O(5)=3·61Å and other close approaches between I$^-$ and C(9), C(16), C(17), C(18), C(19), C(21) and C(22) are 4·18, 4·20, 4·09, 4·08, 4·16, 4·05 and 4·14Å respectively. There are relatively few close contacts between atoms in adjacent kreysiginine cations (see Table 2). Close approaches presumably exist between the latter and the acetone molecules, but these dimensions could not be determined as precise location of the acetone molecules in the unit cell was not made (see Fig. 1 for approximate location of acetone molecules).

DISCUSSION

Kreysiginine* is an alkaloid whose structure is based on the 1-phenylethylisoquinoline system. More specifically, it is a member of the class of homo-morphine alkaloids. In relation to the morphine group, the location of the double bond at C(8)—C(15) makes kreysiginine more closely comparable with neopine and its C(6) epimer, isoneopine, (V), than with morphine (VI) itself.



V



VI

The absolute chirality of (+)-kreysiginine (I) is opposite to that normally ascribed to morphine and allied structure, *e.g.* (V) and (VI), a point further established here by study of morphine hydriodide dihydrate crystals (see Experimental). Androcymbine

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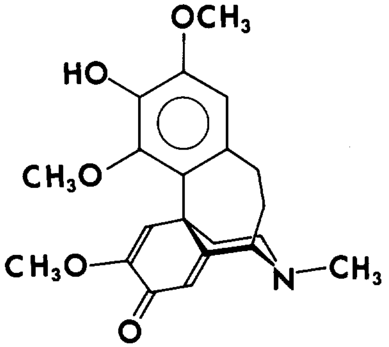
* It has been recently established that alkaloid CC–21 from *Colchicum cornigerum* (Sweinf.) Tackh. et Drar. (Liliaceae)[12, 13] is (–)-kreysiginine, the enantiomorphic form of the structure treated here.

(VII), is another phenylethylisoquinoline alkaloid, differing from kreysiginine in that rings A and C are not linked by a bridging oxygen. The absolute chirality of (+)-kreysiginine and androcymbine is the same, that for androcymbine having been deduced from the mirror relation of its ORD curve to that of the morphine alkaloid, salutaridine.[3] As with the morphine series, examples are known of the homo-morphine alkaloids appearing as (+) and (−), or partially racemic products, indicating a similar mode of synthesis[14] dependant on an enzymatic pathway specific to the plant source. On this basis, it is possible to visualise the synthesis of a further group of alkaloids involving the incorporation of two units of γ-phenylbutyrine.[7, 15]



VII

EXPERIMENTAL

(+)-Kreysiginine methiodide forms small, colourless, orthorhombic prisms from acetone. The unit cell parameters, determined from diffractometer settings, were $a = 8{\cdot}366$, $b = 16{\cdot}349$, $c = 18{\cdot}606$Å, $U = 2545$Å^3, the space group being $P2_12_12_1$. The density, $D_m = 1{\cdot}489$, measured by flotation in a mixture of bromobenzene and xylene is in accord with the value, $D_x = 1{\cdot}495$, calculated on the basis of four units of $C_{21}H_{27}NO_5.CH_3I.(CH_3)_2CO$ in the unit cell. Three-dimensional intensity data were recorded with CuKα radiation on a Picker automatic single crystal four-circle diffractometer. The scan in the $\omega/2\theta$ mode ranged from 0·80–1·35°, measurements being made out to a sin θ maximum of 0·90. Recorded intensity values for 2058 of a possible 2374 independent terms were made ranging in relative intensity from 1800 to 1. The intensities were corrected for background and for Lorentz and polarization factors, but not for absorption.

The iodine atom sites derived from the three-dimensional Patterson synthesis were $x = 0{\cdot}0033$, $y = 0{\cdot}0933$, $z = 0{\cdot}0033$. On appropriate adjustment of scale and temperature factor, structure factors calculated for the iodine atom alone yielded $R(\Sigma|F_o - F_c|/\Sigma|F_o|) = 0{\cdot}52$ for an isotropic B and 0·33 for anisotropic b_{ij}. Due to the position of the iodine atom with $x \sim 0{\cdot}0$, $z \sim 0{\cdot}0$, the three-dimensional electron-density distribution, phased on the iodine atom contribution to the structure factor and excluding terms for which $|F_o| > 3|F_c|$, displayed additional symmetry—a two-fold axis at $x = \frac{1}{4}, y = \frac{1}{4}$, and mirror planes at $x = \frac{1}{2}$ and $z = \frac{1}{4}$. This made correct site location of the lighter atoms less straightforward. However, the molecular skeleton was gradually built up and refined by successive electron-density and difference syntheses, the pseudo-symmetry being slowly eliminated as additional atoms were incorporated in the calculations. At this stage of the analysis, the atomic sites selected, when assembled with the aid of a spoke-model, corresponded to atoms of rings, designated subsequently as A, and apart from C(15), rings B, D (see (I) and Fig. 2). This fragment of the molecular skeleton provided a basis onto which the other atoms could be built. After several successive difference syntheses in conjunction with known chemical detail in the molecule such as the presence of three methoxy and one alcoholic hydroxyl groups and an

TABLE 1. ATOMIC PARAMETERS OF THE ABSOLUTE STRUCTURE, WITH THEIR ESTIMATED STANDARD DEVIATION ALL × 10^5, REFERRED TO A LEFT-HANDED SET OF AXES.

Atom	x/a ($\sigma x/a$)	y/b ($\sigma y/b$)	z/c ($\sigma z/c$)
I	00167 (12)	09315 (6)	00172 (4)
C(1)	04708 (159)	35896 (80)	38818 (68)
C(2)	08321 (128)	29018 (69)	42976 (61)
C(3)	07233 (147)	21075 (76)	39760 (67)
C(4)	02038 (125)	20608 (72)	33137 (58)
C(5)	92092 (145)	15026 (71)	23062 (70)
C(6)	73928 (146)	14032 (80)	24264 (68)
C(7)	64916 (168)	15906 (81)	17498 (73)
C(8)	69619 (211)	24457 (98)	15222 (90)
C(9)	86164 (144)	37138 (77)	15124 (65)
C(10)	84772 (180)	42914 (96)	21410 (84)
C(11)	96324 (149)	43050 (82)	27747 (71)
C(12)	99980 (136)	35197 (69)	31506 (62)
C(13)	99027 (123)	27245 (66)	28834 (61)
C(14)	95858 (139)	23901 (71)	21181 (67)
C(15)	82709 (146)	28059 (75)	17077 (66)
C(16)	15319 (140)	33535 (72)	14817 (62)
C(17)	11531 (147)	24394 (75)	16977 (77)
C(18)	19823 (225)	36763 (121)	52583 (105)
C(19)	25735 (292)	12212 (172)	45224 (144)
C(20)	55422 (224)	04264 (108)	29417 (103)
C(21)	99583 (160)	33742 (85)	03698 (76)
C(22)	06786 (196)	46116 (98)	09386 (89)
O(1)	13198 (122)	29439 (67)	49718 (51)
C (2)	09489 (96)	14179 (53)	44144 (47)
O(3)	99973 (89)	13319 (51)	29623 (44)
O(4)	71542 (106)	05613 (58)	26423 (53)
O(5)	66086 (137)	10336 (67)	12060 (63)
N	01902 (125)	37700 (71)	10824 (59)
C(23)	49300	30800	35200
C(24)	50700	38300	36700
C(25)	49700	45800	36700

TABLE 2. INTERMOLECULAR APPROACH DISTANCES <3·90Å

	d(Å)		d(Å)
I . . . O(5)	3·61	C(22) . . . O(4)	3·56
C(21) . . . O(5)	3·38	C(10) . . . C(20)	3·84
C(18) . . . O(2)	3·38	C(10) . . . O(3)	3·58
C(18) . . . C(19)	3·71	C(19) . . . C(1)	3·85
C(18) . . . C(22)	3·64	C(20) . . . C(18)	3·85
C(11) . . . O(4)	3·47	C(20) . . . C(10)	3·84
C(11) . . . C(5)	3·72	C(11) . . . O(3)	3·60
C(22) . . . C(19)	3·88	C(19) . . . O(1)	3·55
C(22) . . . O(2)	3·32	C(2) . . . C(19)	3·78
C(22) . . . O(3)	3·52	C(3) . . . C(18)	3·67

TABLE 3. COMPARISON OF INTENSITIES $I(hkl)$ AND $I(\bar{h}\bar{k}\bar{l})$ BASED ON THE APPROPRIATE SET OF AXES WITH THE ASSOCIATED VALUES $-(AB_I - A_IB)$. A,B REFER TO NON-DISPERSIVE STRUCTURE FACTOR COMPONENTS FOR THE WHOLE STRUCTURE AND A_I, B_I TO THE CORRESPONDING COMPONENTS FOR THE IODINE ATOMS ONLY

(a) Kreysiginine methiodide (acetone adduct), based on a left-handed set of axes.

Index	$I(hkl) >< I(\bar{h}\bar{k}\bar{l})$	$-(AB_I - A_IB)$
1, 3, 7	<	−370
1, 4, 10	<	−450
1, 5, 13	<	−1150
1, 6, 2	>	880
1, 10, 2	<	−330
1, 11, 3	<	−1290
2, 2, 4	<	−1920
2, 2, 6	<	−1645
2, 2, 10	<	−350
3, 1, 9	<	−470
3, 1, 11	<	−610
3, 6, 2	<	−600

(b) Morphine hydriodide dihydrate, based on a right-handed set of axes.

2, 1, 1	>	1460
1, 7, 1	>	520
9, 1, 1	>	405
1, 8, 1	>	235
2, 9, 1	>	265
3, 6, 1	<	−1505
2, 4, 1	>	1065
2, 3, 1	>	1180
3, 5, 1	>	665
3, 8, 1	<	−1220

oxygen in the form of an ether linkage,[1] all the remaining atomic sites in the N-methylated kreysiginine cation were located and the light atoms differentiated as C, N or O. Isotropic least-squares refinement of the light atoms and anisotropic refinement of the iodine atom, yielded an R value 0·18. Calculation of bond lengths and angles and the spatial disposition of associated atoms established the position of the double bond, its presence previously indicated,[1] to be between C(8)—C(15).

As yet, the molecule of acetone of crystallization in the structure had not been considered. A diffuse, unresolved peak in the difference syntheses in the region $x = 0{\cdot}5$, $y = 0{\cdot}30$–$0{\cdot}45$, $z = 0{\cdot}35$, had persisted from the outset, and because of its location in the unit cell was assumed to arise from scattering matter in the form of solvent of crystallization. As the peak was diffuse, disorder involving the acetone molecule was indicated, and to allow for this, three atoms were included as carbon, C(23), C(24), C(25) (see Table 1 and Fig. 1) with a temperature factor $B = 20{\cdot}0\text{Å}^2$. Inclusion of these atoms in structure amplitude calculations markedly improved the agreement of fifty low-order terms where the previous calculated values had consistently given a rather poor fit. These three atoms however were not included as variables in any subsequent least-squares refinements.

Final least-squares refinement cycles were carried out in which the light atoms were refined isotropically and the iodine atom anisotropically, unit weight being given to all terms. Anomalous dispersion correction for CuKα radiation were applied to the iodine atom, and a final reliability index, $R = 0{\cdot}11$ was obtained for $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$. Attempt to refine the complete structure anisotropically, in blocks of 136 variables was unsatisfactory and part of the reason for this state of affairs was assumed to be the lack of absorption corrections, the linear absorption for this compound being relatively high ($\mu = 104$ cm^{-1}). Earlier least squares refinements involved full-matrix calculations but when anomalous dispersion was included block diagonal calculations had to be used. Scattering factors used in the analysis were from International Tables for X-ray Crystallography.[17]

Atomic parameters are listed in Table 1, and a line diagram of the structure projected down the *a* axis is shown in Fig. 1. Bond lengths and angles are given in Fig. 2, while some short intermolecular approach distances are given in Table 2 and Fig. 1.

The absolute configuration of the structure had been determined by Bijvoet's method,[18] utilizing the anomalous dispersion of CuKα radiation by the iodine atoms, for which $\Delta f' = -7{\cdot}1$, and $\Delta f'' = 13{\cdot}6$ (International Tables for X-ray Crystallography[17]). Comparison of intensity of selected Friedel pairs in conjunction with the relationship developed by Patterson[19]

$$D = |F(hkl)^+|^2 - |F(hkl)^-|^2 = -4(\Delta f_I''/f_I).(AB_I - A_IB)$$

has shown that the absolut structure is defined by the parameters listed in Table 1 when these are based on a left-handed set of axes. Table 3(a) lists a comparison of 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 for the whole structure and A_I, B_I to the corresponding components for the iodine atoms only. An additional check was provided by calculation of the index, R, corresponding to each chirality. The values for a right- and left-handed co-ordinate system were 0·18 and 0·16 respectively at this particular stage of the analysis. This result is in accord with that from Bijvoet's method.

For reasons treated in the Discussion, it was considered advisable to make a direct experimental check on the absolute chirality of morphine. This was readily carried out on crystals of morphine hydriodide dihydrate whose structure had been solved previously by Mackay and Hodgkin.[10] Comparison of the intensities of selected Friedel pairs confirmed the absolute structure as (VI)–see Table 3(b)–a result in complete accord with that for codeine determined also by X-rays,[20] the correlation between morphine and codeine being in agreement with recent circular dichroism measurements.[16]

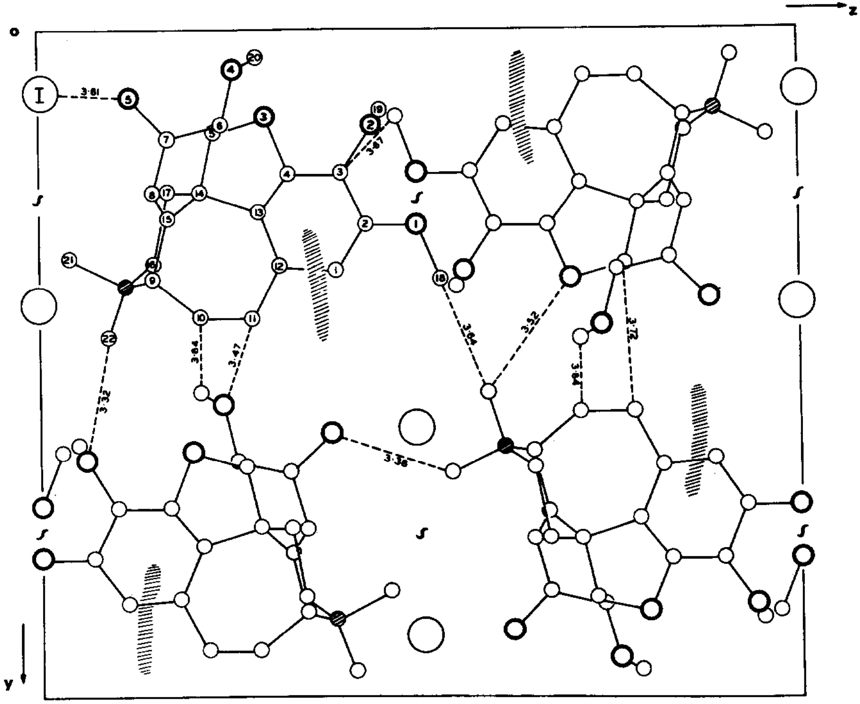


FIG. 1

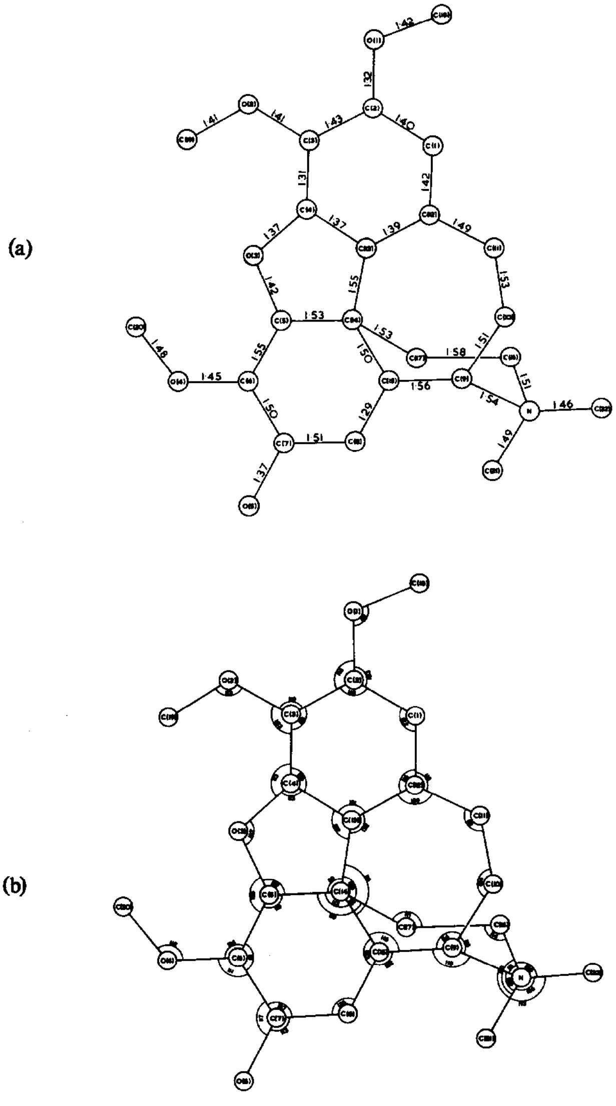


FIG. 2

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