

The Identification and Crystal Structure of Imenine, a New Ketoaporphine Alkaloid*

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The structure of imenine, an alkaloid isolated from *Abuta imene*, has been solved by iterative application of the Sayre relationship to three-dimensional X-ray diffraction data. Imenine crystallizes in space group *P*1 with unit-cell dimensions $a=9.087$ (9), $b=8.359$ (9), $c=11.660$ (12) Å, $\alpha=111.68$ (1), $\beta=88.59$ (1), $\gamma=101.17$ (2)°, $\rho_{\text{calc}}=1.453$ for $Z=2$, $\rho_{\text{exp}}=1.458$ g.cm⁻³. The alkaloid is shown to be C₂₀H₁₇NO₅, 1,2,3,4-tetramethoxydibenzo[*de,g*]quinazolin-7-one, the first ketoaporphine to have substitution in the heterocyclic ring.

Introduction

The aporphines comprise a group of over 90 alkaloids whose basic ring system is the 4*H*-dibenzo[*de,g*]quinoline structure. In 1960 a subgroup of the aporphines was discovered which contained an oxygen bonded to the 7 position and was called 'keto' or 'oxo' aporphine. Since that time 12 naturally occurring members of this subgroup have been found whose members are distinguished by their oxygenation patterns. This area is discussed thoroughly by Cava & Venkateswarlu (1968).

The thirteenth member of this subgroup has been isolated by Cava & co-workers (Glick, Cook, Cava, Srivanasan, Kunitomo & da Rocha, 1969) from the Brazilian vine *Abuta imene* (Menispermaceae). The vine was chosen for study because several related species were known to be rich in alkaloids, and it was hoped that *Abuta imene* would contain new, unknown alkaloids.

Extractions made from the vine did produce several highly colored alkaloids, the most abundant of which was imenine. Unsuccessful characterization of the structure of imenine was attempted by nuclear magnetic resonance, infrared and ultraviolet spectroscopy, mass spectroscopy and chemical methods several months before crystallographic methods were employed. The above studies indicated the compound was aromatic, probably contained nitrogen-methyl groups and methoxy groups, and had a molecular weight of about 533.

Experimental

A large orange-yellow crystal of imenine was selected from those provided by Drs Cava and Srinivasan and cut to a final size of 0.34 × 0.19 × 0.19 mm. Silastic medical adhesive was used to hold the crystal to a

pulled glass fiber. Following preliminary film work the crystal was mounted on a Picker four-angle automatic diffractometer. After the crystal was centered with X-rays, 17 reflections were maximized for Mo *K*α₁ radiation using narrow rear slits and used to calculate the triclinic lattice constants* $a=9.087$ (9), $b=8.359$ (9), $c=11.660$ (12) Å, $\alpha=111.68$ (1), $\beta=88.59$ (1), $\gamma=101.17$ (2)°. The experimental density of 1.454 (8) g.cm⁻³ as measured by flotation was in excellent agreement with the final calculated density of 1.453 g.cm⁻³ based on two molecules of formula C₂₀H₁₇NO₅ per unit cell.

The diffraction data were collected automatically using Mo *K*α₁ radiation filtered through 2.8 mils of Zr foil with the pulse height analyser set to accept 90% of the incoming radiation. The moving-counter moving-crystal scan technique was used with a drive speed of 1° per minute and a take off angle of 2.0°. The intensities were obtained by a continuous scan of 1.6° (0.75° before and 0.85° after the maximum) through the peak (DATA) with stationary backgrounds of 15 seconds at both ends of the scan (BK1 and BK2). The reflection data were collected in the hemisphere +*h*, ±*k*, ±*l* out to a 2θ of 45°.

A total of 2160 reflections were measured of which 1554 had net intensities above 2 standard deviations. Five standard reflections, which were checked after every one hundred data, indicated no systematic change in intensity.

* The programs used in the solving of this structure include local versions of the following programs:

PICK2 - J. A. Ibers' least-squares program for lattice constants and orientation angles based on W. C. Hamilton's *MODE1*.

DACOR - a program for Lp corrections and calculation of intensity standard deviations and normalized structure factors.

FORDAP - A. Zalkin's Fourier program.

ORFLS and *ORFFE* - W. Busing, K. Martin & H. Levy's full-matrix least-squares program and function and error program.

ORTEP - C. K. Johnson's program for drawing thermal ellipsoids of crystal structures.

REL - A program for Phase Determination by Reiterative Application for Sayre's Equation, R. E. Long, Ph. D. Thesis (part III), University of California, Los Angeles, 1965.

* A preliminary account of the structure analysis was presented at the Eighth International Congress of Crystallography, Buffalo, New York, August 1969.

† Based in part on a thesis submitted to the Graduate School of Wayne State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy,

The raw data were corrected for Lorentz and polarization factors and background. Standard deviations for the intensities were calculated using the formula $[(DATA + 3 \cdot 2 BK1 + 3 \cdot 2 BK2 - 0 \cdot 03^2(DATA - 3 \cdot 2 BK1 - 3 \cdot 2 BK2)^2)]^{1/2}$ (Corfield, Doedens & Ibers, 1967). Absorption of the crystal was not taken into account.

Solution to structure

Mass spectroscopic results, unit-cell data, and the distribution of normalized structure factors (22.1% of E values $> 1 \cdot 0$, 5.2% $> 2 \cdot 0$, 1.7% $> 3 \cdot 0$) pointed toward one molecule of molecular weight 702 in a

Table 1. Comparison of observed and calculated structure factors ($\times 10$) for imenine

h	k	l	F _o	F _c	h	k	l	F _o	F _c
0	0	0	100	100	0	0	0	100	100
1	0	0	100	100	1	0	0	100	100
2	0	0	100	100	2	0	0	100	100
3	0	0	100	100	3	0	0	100	100
4	0	0	100	100	4	0	0	100	100
5	0	0	100	100	5	0	0	100	100
6	0	0	100	100	6	0	0	100	100
7	0	0	100	100	7	0	0	100	100
8	0	0	100	100	8	0	0	100	100
9	0	0	100	100	9	0	0	100	100
10	0	0	100	100	10	0	0	100	100
11	0	0	100	100	11	0	0	100	100
12	0	0	100	100	12	0	0	100	100
13	0	0	100	100	13	0	0	100	100
14	0	0	100	100	14	0	0	100	100
15	0	0	100	100	15	0	0	100	100
16	0	0	100	100	16	0	0	100	100
17	0	0	100	100	17	0	0	100	100
18	0	0	100	100	18	0	0	100	100
19	0	0	100	100	19	0	0	100	100
20	0	0	100	100	20	0	0	100	100
21	0	0	100	100	21	0	0	100	100
22	0	0	100	100	22	0	0	100	100
23	0	0	100	100	23	0	0	100	100
24	0	0	100	100	24	0	0	100	100
25	0	0	100	100	25	0	0	100	100
26	0	0	100	100	26	0	0	100	100
27	0	0	100	100	27	0	0	100	100
28	0	0	100	100	28	0	0	100	100
29	0	0	100	100	29	0	0	100	100
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31	0	0	100	100	31	0	0	100	100
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33	0	0	100	100	33	0	0	100	100
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35	0	0	100	100	35	0	0	100	100
36	0	0	100	100	36	0	0	100	100
37	0	0	100	100	37	0	0	100	100
38	0	0	100	100	38	0	0	100	100
39	0	0	100	100	39	0	0	100	100
40	0	0	100	100	40	0	0	100	100
41	0	0	100	100	41	0	0	100	100
42	0	0	100	100	42	0	0	100	100
43	0	0	100	100	43	0	0	100	100
44	0	0	100	100	44	0	0	100	100
45	0	0	100	100	45	0	0	100	100
46	0	0	100	100	46	0	0	100	100
47	0	0	100	100	47	0	0	100	100
48	0	0	100	100	48	0	0	100	100
49	0	0	100	100	49	0	0	100	100
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78	0	0	100	100	78	0	0	100	100
79	0	0	100	100	79	0	0	100	100
80	0	0	100	100	80	0	0	100	100
81	0	0	100	100	81	0	0	100	100
82	0	0	100	100	82	0	0	100	100
83	0	0	100	100	83	0	0	100	100
84	0	0	100	100	84	0	0	100	100
85	0	0	100	100	85	0	0	100	100
86	0	0	100	100	86	0	0	100	100
87	0	0	100	100	87	0	0	100	100
88	0	0	100	100	88	0	0	100	100
89	0	0	100	100	89	0	0	100	100
90	0	0	100	100	90	0	0	100	100
91	0	0	100	100	91	0	0	100	100
92	0	0	100	100	92	0	0	100	100
93	0	0	100	100	93	0	0	100	100
94	0	0	100	100	94	0	0	100	100
95	0	0	100	100	95	0	0	100	100
96	0	0	100	100	96	0	0	100	100
97	0	0	100	100	97	0	0	100	100
98	0	0	100	100	98	0	0	100	100
99	0	0	100	100	99	0	0	100	100
100	0	0	100	100	100	0	0	100	100

Table 2(b). Final coordinates ($\times 10^3$), thermal parameters, and bond distances for hydrogen atoms of imenine

Standard deviations given in parentheses are for least significant figures. Estimated standard deviations for thermal parameters are 1.2 \AA^2 .

	<i>x</i>	<i>y</i>	γ	<i>z</i>	<i>B</i>	<i>D</i>
H(C5)	973 (5)	86 (5)		911 (4)	2.89 \AA^2	1.06 (4) \AA
H(C8)	511 (4)	267 (5)		754 (4)	2.02	1.05 (4)
H(C9)	729 (6)	469 (7)		772 (5)	6.98	0.95 (6)
H(C10)	895 (5)	599 (6)		970 (4)	4.07	1.01 (5)
H(C11)	818 (4)	506 (5)		125 (4)	1.89	0.95 (4)
H(C12)	-5 (7)	356 (8)		234 (6)	6.45	0.86 (6)
H(C12')	882 (9)	201 (12)		253 (8)	11.37	0.96 (9)
H(C12'')	954 (9)	359 (11)		355 (9)	7.38	0.96 (9)
H(C13)	652 (6)	158 (8)		544 (5)	5.29	0.92 (6)
H(C13')	817 (7)	232 (8)		541 (6)	5.61	0.98 (7)
H(C13'')	714 (6)	75 (8)		422 (6)	6.11	1.00 (6)
H(C14)	306 (6)	246 (6)		597 (5)	4.17	0.93 (5)
H(C14')	226 (6)	316 (7)		491 (5)	4.63	1.01 (6)
H(C14'')	418 (7)	395 (9)		564 (6)	7.76	1.04 (7)
H(C15)	-9 (6)	853 (7)		359 (6)	5.85	0.95 (6)
H(C15')	-68 (6)	910 (6)		256 (5)	4.11	0.97 (6)
H(C15'')	25 (6)	764 (8)		219 (5)	4.42	0.99 (6)

of nitrogen and oxygen atoms proceeded smoothly.

The final full-matrix least-squares refinement* on all positional and isotropic thermal parameters of the ring atoms and the hydrogen atoms and all the positional and anisotropic thermal parameters on the nonring atoms yielded an unweighted discrepancy factor ($\sum ||F_o| - F_c| / \sum |F_o|$) of 0.062 and a weighted discrepancy factor $\{[\sum w(|F_o| - |F_c|)^2 / \sum wF_o^2]^{1/2}\}$ of 0.075.

A comparison between the calculated and observed structure amplitudes is given in Table 1 and the final positional and thermal parameters are in Table 2.

An analysis of the original phases produced with the Sayre equation showed the best set generated

contained only 62% correct phases and the set used to begin the structure solution contained only 44% correct phases. The apparent reason for the difficulty is that the structure contains a pseudo-center of inversion for 10 of the 26 atoms. The original phasing corresponded to the pseudocenter at the origin; thus the map contained real and image molecules superimposed on one another as in Fig. 1.

Description of the structure

Imenine, pictured in Fig. 2 with bond distances and angles, is shown to be 1,2,3,4-tetramethoxydibenzo-[*de*, *g*]quinazolin-7-one. An unusual feature of this compound is the bonding of a methoxy group to the heterocyclic *B* ring. Substitution in this ring has not

* Scattering factors were obtained from *International Tables for X-ray Crystallography*, 1968, p. 210.

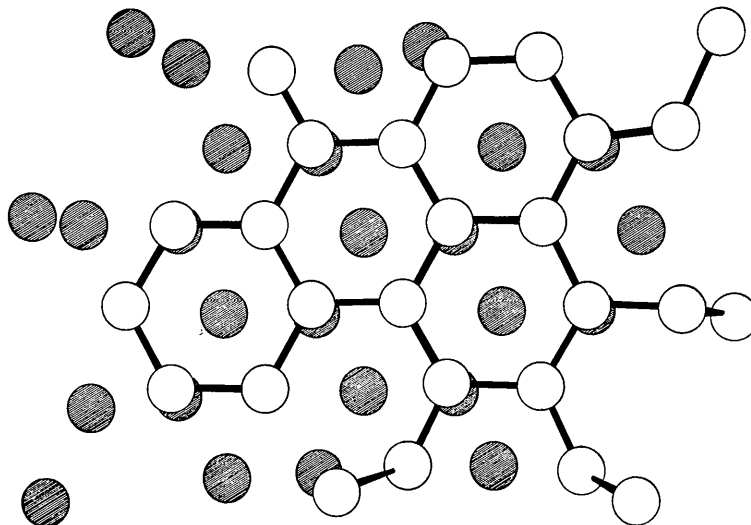


Fig. 1. The imenine molecule and its superimposed image created by the pseudo-center of inversion.

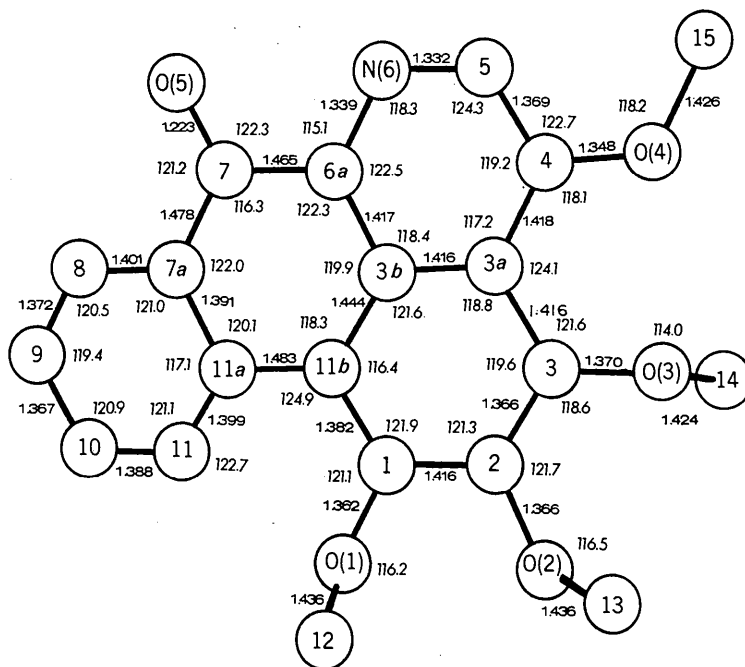


Fig. 2. The structure of imenine with bond distances and angles. Estimated standard deviations are 0.005–0.006 Å and 0.3–0.5° respectively.

been observed in the 12 previously isolated keto-aporphines, while virtually every other available position has had oxygenated functions attached.

Examination of the carbon-carbon bond distances reveals a relatively large range from 1.366 to 1.483 Å. This variation can partially be explained by drawing the common resonance structures for imenine (Fig. 3). None of these structures contain a double bond between C(11a)–C(11b) or around C(7) thus suggesting that these bonds should be somewhat longer. The average carbon-carbon distance in rings *A*, *B* and *C* is 1.399 Å while the C(11a)–C(11b), C(7)–C(6a) and C(7)–C(7a) bonds are 1.483, 1.465 and 1.478 Å respectively. The resonance structures also indicate that the π electrons are not completely delocalized over the entire structure but can be viewed as an aromatic two-ring system (*A* and *B*) and a benzene ring (*D*)

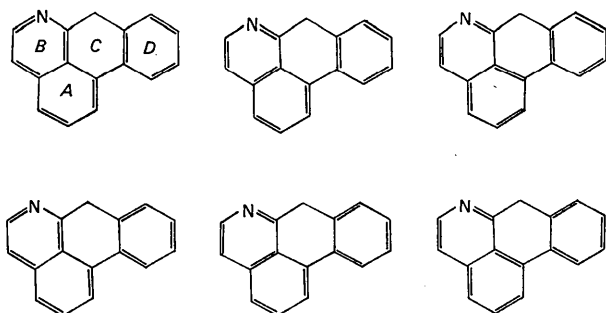


Fig. 3. Simple resonance structures of imenine.

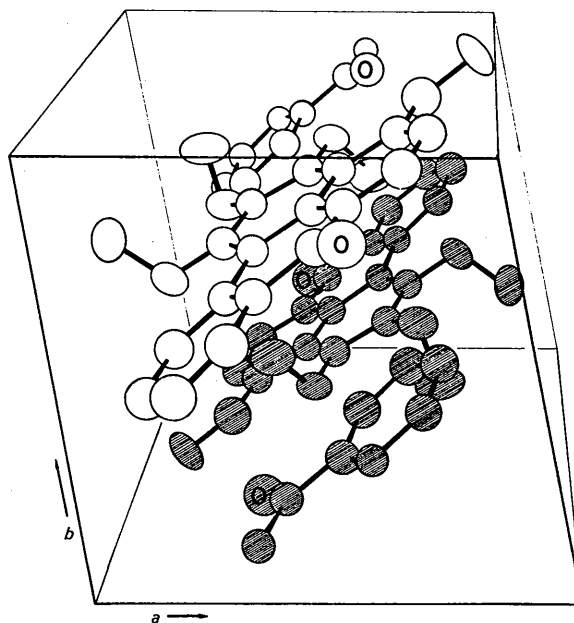


Fig. 4. Packing diagram of imenine showing thermal ellipsoids for non-ring atoms.

separated by the center non aromatic ring (*C*). The lack of complete delocalization is also manifested in the non-planarity of the rings. The structure is V-shaped with ring *B* making a 9° dihedral angle with ring *D*.

The bond angles of $120(\pm 4)^\circ$ indicate that the ring carbon atoms are sp^2 hybridized. The angles about the methoxy groups average 116° .

A packing diagram (Fig. 4) shows the two molecules positioned in parallel planes spaced about 4.4 \AA apart. Least-squares planes calculated through the structure indicate that the substituted oxygen atoms along with C(15) are positioned near the plane of the ring ($+0.04 \text{ \AA}$) while the remaining non-ring carbon atoms are above and below the planes at distances from 1.2 to 1.4 \AA .

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The Crystal Structure of a Proposed Fusidic Acid Intermediate

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The structure of a proposed intermediate in the synthesis of the abnormal steroid fusidic acid was determined by means of X-ray analysis. The compound, $C_{23}H_{27}O_3Br$, forms triclinic crystals, space group $P\bar{1}$, with cell dimensions $a=8.681$, $b=7.361$, $c=16.077 \text{ \AA}$, $\alpha=90.85$, $\beta=99.44$, $\gamma=84.97^\circ$; there are two molecules in the cell. The structure was refined to an R index of 6.3% for 1979 non-zero reflections measured on a diffractometer. The results of the analysis revealed that the proposed intermediate has a structure incompatible for conversion to the desired steroid.

Introduction

A proposed intermediate (Ia) in the synthesis of the abnormal steroid fusidic acid (II) was prepared in the laboratories of Professor W. G. Dauben at the University of California at Berkeley (Fig. 1). Subsequent conversion of the intermediate was not a trivial undertaking, and conventional methods of organic structure analysis were inconclusive. Therefore, an X-ray analysis was undertaken to establish the structure of the intermediate with certainty.

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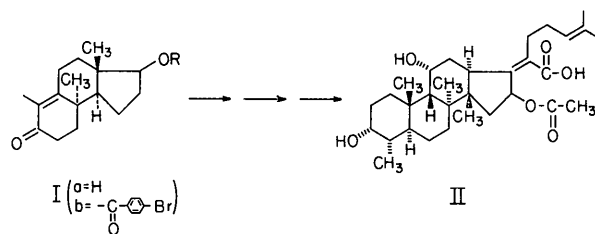


Fig. 1. Proposed synthesis.

Experimental

A suitable heavy-atom derivative (Ib) was prepared by reacting the intermediate with 4-bromobenzoyl chloride in pyridine. The resulting reaction product was washed with sodium bicarbonate and was purified by two crystallizations from ethanol. Thin-layer chromatography (silica gel), nuclear magnetic resonance, and infrared and mass spectra revealed that the desired 4-bromobenzoate derivative had been formed in high purity.

Crystals suitable for an X-ray analysis were grown from acetone by slow evaporation. The plate-like crystals were cut to a size of $0.2 \times 0.2 \times 0.1 \text{ mm}$. A precession camera survey of the crystal indicated that it belonged to a triclinic space group, $P1$ or $P\bar{1}$. Sodium-chloride calibrated, zero level, precession photographs established approximate cell dimensions. More accurate cell dimensions were obtained with a General Electric-Datex diffractometer. Unit-cell dimensions measured on the diffractometer with nickel-filtered copper radiation were as follows:

$$\begin{aligned} a &= 8.681 \pm 0.002 \text{ \AA} & \alpha &= 90.85 \pm 0.04^\circ \\ b &= 7.361 \pm 0.002 & \beta &= 99.44 \pm 0.05 \\ c &= 16.077 \pm 0.003 & \gamma &= 84.97 \pm 0.02 \end{aligned}$$