

Chasmanine Intermediate, $C_{24}H_{33}NO_6$ †

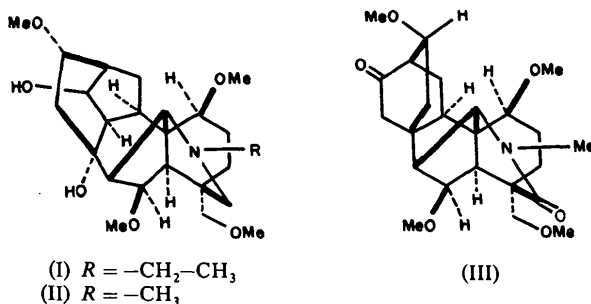
BY M. PRZYBYLSKA AND F. R. AHMED

Division of Biological Sciences, National Research Council of Canada, Ottawa, Canada K1A 0R6

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Abstract. Monoclinic, $P2_1/a$, $a = 17.566(2)$, $b = 14.298(2)$, $c = 9.737(2)$ Å, $\beta = 116.46(5)^\circ$, $Z = 4$, $D_x = 1.315$, $D_m = 1.301$ Mg m $^{-3}$ (flotation in toluene and CCl_4 mixture). Final $R = 0.045$ for 2894 observed reflexions. This study has confirmed that the synthetic procedure has successfully produced the required chasmanine intermediate.

Introduction. New stereospecific methods for the total synthesis of delphinine-type alkaloids, chasmanine and 13-desoxydelphonine, have been developed (Wiesner, Tsai & Nambiar, 1978). Chasmanine, (I), which has an ethyl group attached to N can be obtained from 13-desoxydelphonine, (II), by oxidative demethylation followed by ethylation. An important intermediate in the synthesis of these compounds, (III), has been subjected to X-ray analysis to characterize and confirm the predicted structure. The skeleton of (III) differs considerably from chasmanine, (I), the structure of which has been determined in the form of the 14 α -benzoate hydrochloride (De Camp & Pelletier, 1977).



A molecular drawing based on the present study, showing the stereochemistry of (III), was presented by Wiesner (1978) at a plenary lecture of IUPAC.

Colourless prismatic crystals, m.p. 442–443 K, were obtained from an ether–chloroform mixture. The data were measured on a Picker diffractometer with Ni-filtered Cu radiation [$\lambda(K\alpha_1) = 1.54050$, $\lambda(K\alpha_2) = 1.54434$ Å] and a crystal $0.29 \times 0.24 \times 0.17$ mm mounted along a^* . The integrated intensities of the hkl and $hk\bar{l}$ reflexions with $2\theta < 130^\circ$ were obtained with the θ - 2θ scan method, at a 4.0° take-off angle. The

background was measured for 20 s at the lower and upper limits of each scan. The 040 and 003 reflexions were used as standards for scaling. The intensities were corrected for background and the Lorentz and polarization effects. The absorption correction was considered negligible [$\mu(\text{Cu}) = 0.774$ mm $^{-1}$]. 3685 independent reflexions were scanned and, of these, 2894 (77%) were observed above threshold.

The structure was solved by symbolic addition (Karle & Karle, 1963). The E map computed with 337 signed reflexions, out of 459 with $|E| > 1.5$, showed all the non-hydrogen atoms except two methyl groups. The missing C atoms were obtained from a Fourier map.

Least-squares refinement brought R to 0.11, and the H atoms were then located from a difference map. However, H(16,1) did not refine satisfactorily giving an unacceptably long C–H bond. The difference map carried out close to the end of refinement showed again the presence of a peak of ~ 1.1 e Å $^{-3}$ in the vicinity of H(16,1) that was originally accepted. The residual electron density in that map in all other regions was within -0.15 to 0.24 e Å $^{-3}$. This unexpected anomaly indicated that a small amount of an identical compound but with an OH group attached to C(16) had co-crystallized with chasmanine intermediate without giving rise to any disorder. The refinement of the structure was completed by including O(7) at 0.12 occupancy (as derived from least squares) with coordinates of 0.2730, 0.1966 and -0.0484 and $B = 4.26$ Å 2 . The position of H(16,1) was also fixed with an occupancy of 0.88.

The refinement was carried out by the block-diagonal approximation, with only the observed reflexions, minimizing $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\{1 + [(|F_o| - 30)/25]^4\}$ and $2.3 \leq |F_o| \leq 181.6$. The final R for the observed reflexions was 0.045 and $R_w = 0.043$ and $[\sum w\Delta^2/(m-n)]^{1/2} = 0.77$. The final mean shift/e.s.d. for the parameters of all atoms was 0.08 and the maximum shift/e.s.d. was 0.53 for all atoms except C(16). The refinement of C(16) was affected by the presence of the contaminating compound and its maximum shift/e.s.d. was 0.98.

The atomic parameters are presented in Table 1. Two reflexions suffering from extinction (021, 40 $\bar{1}$) and © 1980 International Union of Crystallography

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Table 1. Fractional coordinates and isotropic temperature factors ($\times 10^4$ for C, N, O; $\times 10^3$ for H)

	x	y	z	U_{eq}/U_{iso}
C(1)	938 (1)	1040 (2)	3618 (2)	359 Å ²
C(2)	1104 (2)	339 (2)	4897 (3)	500
C(3)	2016 (2)	398 (2)	6133 (3)	459
C(4)	2676 (1)	272 (2)	5498 (2)	370
C(5)	2550 (1)	1058 (1)	4336 (2)	293
C(6)	3044 (1)	954 (1)	3343 (2)	316
C(7)	2364 (1)	609 (1)	1757 (2)	299
C(8)	1867 (1)	1454 (1)	826 (2)	297
C(9)	1546 (1)	1865 (1)	1953 (2)	297
C(10)	1618 (1)	1036 (1)	3060 (2)	290
C(11)	737 (1)	2429 (2)	1017 (3)	426
C(12)	824 (1)	2828 (2)	-395 (3)	448
C(13)	607 (2)	2030 (2)	-1558 (3)	475
C(14)	1123 (1)	1172 (2)	-717 (2)	394
C(15)	1738 (2)	3094 (2)	55 (3)	450
C(16)	2329 (1)	2255 (2)	454 (3)	404
C(17)	1715 (1)	162 (1)	2213 (2)	306
C(18)	2529 (2)	-673 (2)	4707 (3)	454
C(19)	-568 (2)	1237 (2)	2431 (3)	578
C(20)	3565 (2)	267 (2)	6875 (3)	472
C(21)	3893 (2)	1010 (2)	9251 (3)	555
C(22)	4265 (1)	421 (2)	3190 (3)	585
C(23)	1935 (2)	-1556 (2)	2346 (3)	555
C(24)	257 (3)	2863 (3)	-3865 (4)	1187
N(1)	2036 (1)	-677 (1)	3172 (2)	389
O(1)	141 (1)	845 (1)	2319 (2)	432
O(2)	3729 (1)	1118 (1)	7714 (2)	498
O(3)	3762 (1)	354 (1)	3999 (2)	452
O(4)	825 (1)	2251 (1)	-2763 (2)	726
O(5)	1985 (1)	3889 (1)	88 (2)	685
O(6)	2815 (1)	-1399 (1)	5431 (2)	671
H(1)	92 (1)	171 (1)	398 (2)	27 (5)
H(2,1)	72 (1)	47 (2)	537 (2)	44 (6)
H(2,2)	97 (1)	-31 (2)	444 (3)	48 (6)
H(3,1)	214 (1)	103 (2)	667 (3)	45 (6)
H(3,2)	215 (1)	-7 (2)	697 (2)	45 (6)
H(5)	270 (1)	166 (1)	489 (2)	26 (5)
H(6)	326 (1)	159 (1)	321 (2)	28 (5)
H(7)	262 (1)	22 (2)	124 (2)	37 (6)
H(9)	197 (1)	231 (1)	263 (2)	22 (5)
H(11,1)	70 (1)	291 (2)	168 (2)	40 (6)
H(11,2)	20 (1)	204 (1)	62 (2)	34 (5)
H(12)	48 (1)	337 (2)	-78 (3)	47 (6)
H(13)	-5 (2)	189 (2)	-208 (3)	59 (7)
H(14,1)	74 (1)	70 (1)	-55 (2)	36 (5)
H(14,2)	136 (1)	89 (2)	-138 (3)	50 (6)
H(16,1)*	237	215	-54	59
H(16,2)	288 (1)	245 (2)	131 (2)	41 (6)
H(17)	119 (1)	-2 (1)	135 (2)	24 (5)
H(19,1)	-58 (2)	108 (2)	336 (3)	75 (8)
H(19,2)	-110 (2)	107 (2)	150 (3)	83 (9)
H(19,3)	-51 (2)	195 (2)	246 (3)	87 (9)
H(20,1)	398 (2)	17 (2)	651 (3)	67 (8)
H(20,2)	357 (1)	-26 (2)	755 (3)	47 (6)
H(21,1)	339 (2)	68 (2)	930 (3)	85 (9)
H(21,2)	443 (2)	59 (2)	972 (3)	73 (8)
H(21,3)	398 (2)	167 (2)	973 (4)	100 (10)
H(22,1)	396 (2)	14 (2)	213 (3)	72 (8)
H(22,2)	477 (2)	14 (2)	378 (3)	85 (9)
H(22,3)	440 (2)	114 (3)	307 (4)	133 (13)
H(23,1)	148 (2)	-150 (2)	127 (4)	107 (12)
H(23,2)	178 (2)	-202 (3)	278 (4)	130 (13)
H(23,3)	245 (2)	-178 (3)	254 (4)	151 (15)
H(24,1)	9 (3)	335 (4)	-341 (6)	211 (20)
H(24,2)	-30 (3)	244 (3)	-442 (5)	181 (18)
H(24,3)	40 (2)	296 (3)	-460 (4)	125 (13)

* H(16,1) was not refined.

two affected by multiple diffraction (404, 615) were excluded from the final stages.*

All calculations were carried out with the NRC programs (Ahmed, Hall, Pippy & Huber, 1973). The scattering factors were those of Hanson, Herman, Lea & Skillman (1964) for C and O, and of Stewart, Davidson & Simpson (1965) for H.

Discussion. An *ORTEP* drawing (Johnson, 1965) of chasmanine intermediate is shown in Fig. 1. Its stereochemistry corresponds to that proposed by Wiesner.

The bond lengths and angles, not corrected for thermal vibration, are presented in Fig. 2. The longest C—C bonds of 1.569 Å are in the two strained five-membered rings and the shortest (1.512 to 1.520 Å) display partial double-bond character because they adjoin carbonyl groups. The C—O bonds range from 1.400 to 1.435 and the C=O bonds are 1.212 and 1.228 Å. Two C—N bonds can be considered normal,

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34878 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

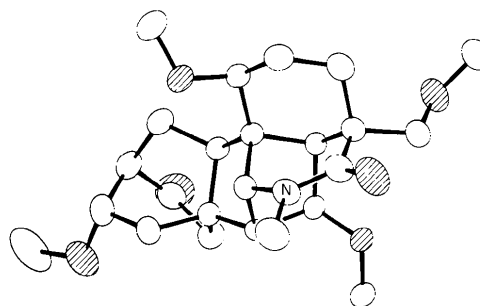


Fig. 1. A parallel projection of chasmanine intermediate showing thermal ellipsoids at the 50% probability level.

Table 2. Mean planes and atomic displacements

(a) Parameters for the planes $lX + mY + nZ = p$, where X, Y, Z are orthogonal coordinates in Å

Ring	l	m	n	p
A	0.2981	-0.9228	-0.2440	-1.5552
D	-0.1735	-0.6111	-0.7723	-3.1100
E	0.6301	0.0185	-0.7763	2.0799
F	0.9907	0.0860	-0.1052	1.8360

(b) Deviations from the mean planes ($\text{Å} \times 10^3$), e.s.d. = 0.003 Å

Ring A	Ring D	Ring E	Ring F				
C(5)	11	C(9)	-158	C(13)	126	N(1)	-29
C(10)	-11	C(11)	155	C(14)	-125	C(17)	14
C(2)	11	C(15)	-155	C(15)	-127	C(18)	27
C(3)	-11	C(16)	158	C(16)	126	C(4)	-12
C(1)*	-562	C(8)*	776	C(12)*	-717	C(5)*	469
C(4)*	717	C(12)*	624	C(8)*	-759	C(10)*	-488

* Atoms excluded from the calculation of the plane.

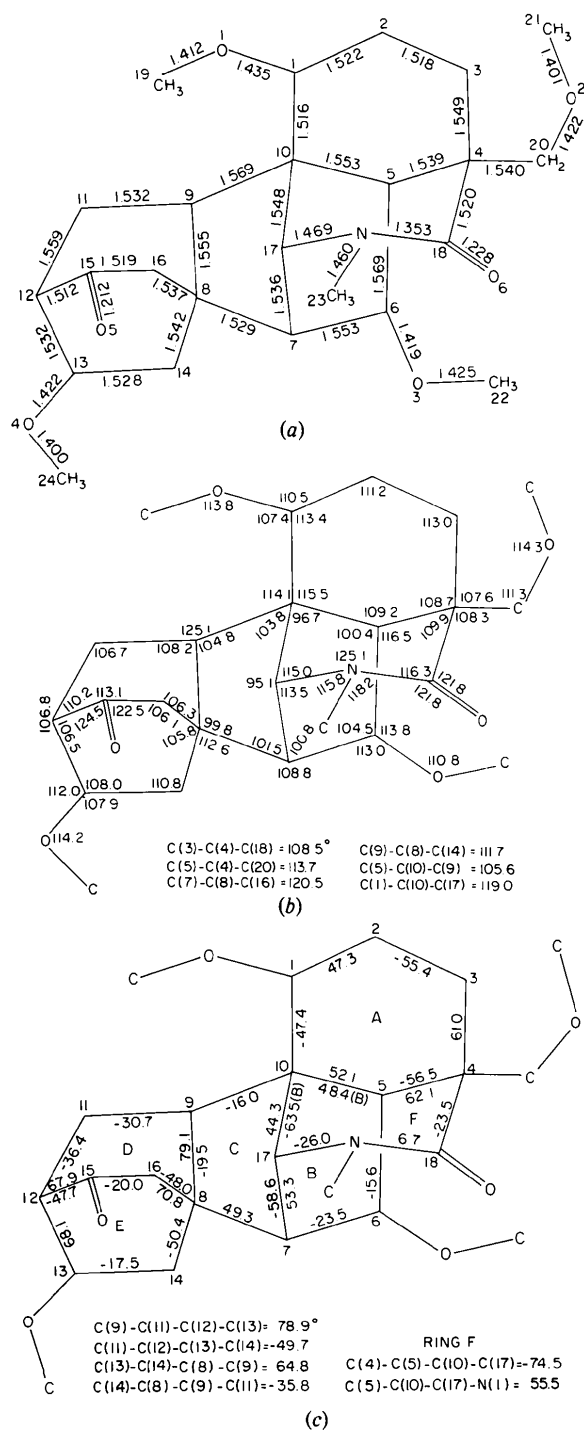


Fig. 2. (a) Bond lengths (Å). The e.s.d.'s are within 0.004 Å except that for C(24)–O(4) which is 0.005 Å. (b) Valency angles (°); the e.s.d. is <0.3°. (c) Endocyclic torsion angles (°); the e.s.d. is <0.6°.

but the third, due to its proximity to the carbonyl group, is considerably shortened (1.353 Å). O–H and C–H vary from 0.87 to 1.08 Å.

The angles within the six-membered rings have an average value of 110.3°. The largest angles are associated with the carbonyl groups (121.8 to 124.5°) and at the tri-covalent N atom (125.1°). The angles of the five-membered rings give a mean value of 100.8°. The smallest angle of 95.1° at the bridging C(17) of the norbornane skeleton agrees well with the value of ~94° in a tetracyclic diketone (Przybylska, 1972) and a tetracyclic bromobenzoate (Przybylska & Ahmed, 1974).

The torsion angles are presented in Fig. 2(c) and details of the mean planes through the atoms of the six-membered rings in Table 2. Their signs are according to the convention of the IUPAC–IUB Commission on Biochemical Nomenclature (1970). Ring A has a chair form, slightly flattened at C(1). Ring F is of half-chair form; C(5) and C(10) are 0.47 and –0.49 Å from a plane calculated for the other four atoms.

The bicyclo[2.2.2]octane moiety is considerably distorted. The average absolute deviation of the torsion angles in D, E and D/E rings from the ideal values of 0, 60 or –60° is 16.6° and the maximum is 30.7°. Average deviation values of 2.9, 4.7 and 11.1° were reported by Pelletier, De Camp & Mody (1978) for bicyclo[2.2.2]octane systems in three derivatives of atisine. In the atisine skeleton, however, there is no bridging between C(17) and C(7) and much less strain in the molecule, resulting in better agreement with the ideal values.

The torsion angles of the five-membered rings, B and C, are within 6° of the half-chair model for fused-ring systems (Brutcher & Bauer, 1962). The torsion angles of the norbornane system indicate the presence of *synchro-twist* (Altona & Sundaralingam, 1970). The atoms of the C(12)–CO–C(16) group are coplanar ($\chi^2 = 3.6$), but some strain is indicated in the N–CO–C(4) group which deviates significantly from planarity ($\chi^2 = 30.7$).

Three short intermolecular approaches indicate slight inaccuracy in the position of H(22,2). They are: C(22)···H(22,2) 2.79, H(20,1)···H(22,2) 2.37, and H(22,2)···H(22,2) 2.18 Å. The distances O(5)···H(7,1), 2.57 Å, and O(6)···H(9,1), 2.54 Å, can be considered as normal. There are no other contacts shorter than the sums of the appropriate van der Waals radii.

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Refinement of the Structure of Nalidixic Acid*

BY CAROL P. HUBER

Division of Biological Sciences, National Research Council of Canada, Ottawa, Canada K1A 0R6

AND D. S. SAKE GOWDA AND K. RAVINDRA ACHARYA

Department of Physics, Central College, Bangalore University, Bangalore 560 001, India

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Abstract. $C_{12}H_{12}N_2O_3$, 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid, monoclinic, $P2_1/c$, $a = 8.921$ (1), $b = 13.156$ (2), $c = 9.369$ (1) Å, $\beta = 100.04$ (2)°, $V = 1082.7$ Å³, $D_m = 1.41$, $Z = 4$, $D_x = 1.42$, $Mg\ m^{-3}$. The structure was refined with 1284 observed independent reflections measured on a four-circle diffractometer to a final R value of 0.039. The present work generally confirms the earlier results of Achari & Neidle [*Acta Cryst.* (1976), **B32**, 600–602], but offers significantly improved precision.

Introduction. Nalidixic acid, which is used clinically to treat urinary-tract infections, exerts its antibacterial action on Gram-negative bacteria (*Escherichia coli*, *Staphylococcus*, most species of *Proteus*, etc.) by inhibiting DNA replication (Gale, Cundliffe, Reynolds, Richmond & Waring, 1972). Recent work (Gellert, Mizuuchi, O'Dea, Itoh & Tomizawa, 1977; Sugino, Peebles, Kreuzer & Cozzarelli, 1977) has established that it does this by inhibiting the P_{nal} component of DNA gyrase; gyrase introduces negative supercoils into DNA, using ATP as energy source, thereby preventing snarls during the unwinding of the DNA double helix and reducing the energy cost of strand separation. The P_{nal} component is involved in the

nicking-closing activity required in the supercoiling reaction.

With the improved understanding of the drug action of nalidixic acid, it seemed worthwhile to establish its crystal structure with greater precision than the earlier analysis (Achari & Neidle, 1976), based on 797 photographic data, provided.

Colourless prismatic crystals, elongated along a , were grown by slow evaporation of a methanol/water solution. A specimen $0.11 \times 0.20 \times 0.45$ mm was used for the diffractometer measurements, made with Ni-filtered Cu radiation. Cell parameters were obtained by a least-squares refinement based on the 2θ values of 22 reflections (with $63^\circ < 2\theta < 105^\circ$). Integrated intensities were measured for the 1829 independent reflections with $2\theta \leq 130^\circ$, using $\theta/2\theta$ scans of 2.0° (in 2θ) for $0^\circ < 2\theta \leq 90^\circ$ and 3.0° for $90^\circ < 2\theta \leq 130^\circ$. Background counts of 20 s each were recorded at the beginning and end of each scan. The threshold level, below which reflections were considered 'unobserved', was determined experimentally as a net count of 15 (decacounts) or a net count at least 10% of the total background count; 1284 reflections were considered 'observed'. Lorentz and polarization corrections were made, and an extinction correction ($g/\mu = 0.254 \times 10^{-3}$) was applied at a later stage.

The structure was refined by block-diagonal least squares, starting from a set of non-hydrogen-atom

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