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An Acetoxy Lactam Acid from 4-Amino-4-deoxymethyleneanhydrolycoctonam*

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Abstract

$C_{24}H_{35}NO_8$ is orthorhombic, $P2_12_12_1$, with $a = 12.480$ (1), $b = 21.025$ (2), $c = 9.512$ (1) Å, $U = 2495.9$ Å³, $Z = 4$, $D_m = 1.233$ (by flotation in toluene and carbon tetrachloride at 297 K), $D_c = 1.239$ Mg m⁻³, $\mu(\text{Cu } K\alpha) = 0.73$ mm⁻¹. The structure was solved by direct methods. The parameters were refined by block-diagonal least squares to a final $R = 0.048$ for 2158 observed reflexions. Intermolecular OH...O hydrogen bonds link molecules into spirals along c .

Introduction

In early structural work the diterpenoid alkaloid lycoctonine† had been converted by oxidation and pinacolic rearrangement reactions into anhydrolycoctonamic acid (Edwards & Marion, 1952). The carboxyl group was then replaced by an amino group giving an amino-keto lactam. Nitrous acid deamination of this compound gave an aldehydo lactam acid with loss of

one skeletal carbon [almost certainly C(6)] and its attached methoxy group. Because the structure of the aldehydo acid could not be rigorously assigned by spectroscopic means, and because the reactions leading to it were unusual, it was decided to carry out X-ray analysis of the acetate of the primary alcohol produced by reduction of the aldehyde group.

Experimental

Colourless prisms, m.p. 471 K, were obtained from a mixture of ether and hexane. The space group was established from precession films. The data were collected at room temperature with the Nonius CAD-4 procedures using a crystal fragment of dimensions 0.27 × 0.29 × 0.32 mm and Ni-filtered Cu radiation.

The pertinent details are: ω - 2θ scan; $1^\circ < \theta < 70^\circ$; ω scan angle = $(0.8 + 0.2 \tan \theta)^\circ$; SIGPRE (the prescan acceptance parameter) = 1.0, ITMAX (the maximum scan time) = 120 s. Two final scans were made in opposite directions with double the variable scan speed. A measurement of two standard reflexions every 100 min revealed a decrease in intensity of <5% during data collection. Three reflexions were used as orientation controls and were measured every 60 reflexions. Of 2671 measured reflexions, 2158 (81%)

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† The C(1) configuration determined in the present analysis is opposite to that found for (+)-de(oxy)methylene)lycoctonine hydroiodide monohydrate (Przybylska & Marion, 1956).

Table 1. *Final fractional coordinates (for C, N, O × 10⁴; for H × 10³) and isotropic temperature factors with e.s.d.'s in parentheses*

The number of the parent C atom can be derived by omitting the last digit from the numbering of the H atoms. H(6) is attached to O(6).

	x	y	z	B _{eq} */B (Å ²)
O(1)	3759 (2)	2281 (1)	14255 (3)	6.1 (0.1)
O(2)	6621 (2)	440 (2)	13299 (4)	7.6 (0.1)
O(3)	7362 (3)	-312 (3)	12059 (7)	12.6 (0.2)
O(4)	3330 (2)	-74 (1)	13332 (4)	7.3 (0.1)
O(5)	4276 (2)	469 (1)	9483 (4)	6.7 (0.1)
O(6)	2862 (2)	1057 (1)	8974 (3)	4.8 (0.1)
O(7)	5798 (2)	2094 (1)	8348 (3)	5.8 (0.1)
O(8)	4096 (2)	3237 (1)	9393 (3)	5.6 (0.1)
N	3102 (2)	897 (1)	12302 (3)	4.2 (0.1)
C(1)	4499 (3)	1781 (2)	14418 (3)	5.1 (0.1)
C(2)	4173 (3)	1273 (2)	15488 (4)	6.4 (0.1)
C(3)	4822 (3)	712 (2)	15046 (4)	6.2 (0.1)
C(4)	4753 (2)	713 (2)	13432 (4)	4.7 (0.1)
C(5)	5589 (3)	283 (2)	12733 (5)	5.6 (0.1)
C(7)	3796 (2)	961 (1)	9585 (3)	3.9 (0.1)
C(8)	4169 (2)	1524 (1)	10442 (3)	3.1 (0.1)
C(9)	5419 (2)	1518 (1)	10604 (3)	3.6 (0.1)
C(10)	5631 (2)	1693 (1)	12148 (3)	4.0 (0.1)
C(11)	4686 (2)	1432 (1)	12998 (3)	3.8 (0.1)
C(12)	5755 (3)	2433 (2)	12135 (4)	5.0 (0.1)
C(13)	5523 (2)	2638 (1)	10611 (4)	4.5 (0.1)
C(14)	5962 (2)	2066 (2)	9817 (3)	4.3 (0.1)
C(15)	3777 (2)	2147 (1)	9767 (3)	3.5 (0.1)
C(16)	4326 (2)	2737 (1)	10367 (3)	4.0 (0.1)
C(17)	3721 (2)	1470 (1)	11994 (3)	3.4 (0.1)
C(19)	3650 (3)	458 (1)	13013 (4)	5.1 (0.1)
C(20)	3723 (6)	2719 (3)	15392 (6)	10.0 (0.2)
C(21)	7446 (4)	114 (3)	12887 (6)	8.1 (0.1)
C(22)	8460 (4)	319 (5)	13542 (8)	11.5 (0.3)
C(23)	1941 (2)	853 (2)	12048 (5)	5.7 (0.1)
C(24)	1321 (3)	1134 (3)	13214 (7)	8.9 (0.2)
C(25)	6529 (4)	1777 (4)	7572 (5)	9.4 (0.2)
C(26)	4191 (5)	3848 (2)	10025 (6)	7.4 (0.1)
H(6)	273 (3)	74 (2)	865 (4)	3.6 (0.8)
H(11)	520 (3)	195 (2)	1476 (4)	3.5 (0.7)
H(21)	340 (3)	118 (2)	1532 (4)	6.4 (0.8)
H(22)	433 (3)	142 (2)	1645 (4)	6.4 (0.9)
H(31)	460 (4)	23 (2)	1535 (6)	6.7 (1.2)
H(32)	561 (3)	75 (2)	1535 (4)	6.2 (0.8)
H(51)	538 (3)	-15 (2)	1286 (4)	5.6 (0.8)
H(52)	555 (3)	29 (2)	1165 (4)	5.6 (0.8)
H(91)	572 (2)	109 (1)	1034 (3)	3.0 (0.4)
H(101)	637 (3)	148 (2)	1249 (4)	3.8 (0.8)
H(121)	523 (3)	265 (2)	1276 (4)	3.6 (0.8)
H(122)	636 (4)	259 (2)	1243 (4)	4.3 (0.9)
H(131)	585 (2)	299 (1)	1034 (3)	3.5 (0.6)
H(141)	671 (4)	207 (2)	1002 (5)	3.6 (0.9)
H(151)	301 (2)	216 (1)	996 (3)	3.0 (0.5)
H(152)	390 (3)	214 (1)	876 (3)	3.0 (0.6)
H(161)	400 (3)	283 (1)	1132 (3)	3.2 (0.6)
H(171)	327 (2)	183 (1)	1225 (3)	3.0 (0.5)
H(201)	334 (4)	307 (2)	1515 (5)	10.0 (1.2)
H(202)	338 (5)	251 (3)	1622 (6)	10.0 (1.2)
H(203)	447 (6)	285 (3)	1564 (7)	10.0 (1.2)
H(221)	837 (4)	48 (2)	1457 (5)	11.5 (1.0)
H(222)	899 (8)	-7 (4)	1355 (10)	11.5 (1.0)
H(223)	879 (9)	69 (4)	1293 (11)	11.5 (1.0)
H(231)	178 (4)	106 (2)	1124 (5)	4.4 (1.0)

Table 1 (cont.)

	x	y	z	B (Å ²)
H(232)	179 (4)	44 (2)	1194 (5)	4.7 (0.9)
H(241)	59 (6)	108 (3)	1305 (7)	8.9 (1.6)
H(242)	149 (5)	160 (3)	1329 (6)	8.9 (1.6)
H(243)	151 (5)	92 (3)	1411 (7)	8.9 (1.6)
H(261)	500 (8)	395 (4)	1020 (10)	7.4 (1.5)
H(262)	378 (5)	384 (3)	1099 (6)	7.4 (1.5)
H(263)	385 (6)	419 (3)	936 (7)	7.4 (1.5)

$$* B_{eq} = \frac{1}{3} \pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

were above threshold [$2\sigma(I_{net})$]. The net intensities, after scaling, were corrected for Lorentz and polarization factors, but not for absorption.

Initial attempts to solve the structure by direct methods using *MULTAN* 78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) met with failure. Consequently 8 *E*'s with assigned phases were used as a starting set in the *DP4* program (Ahmed, Hall, Pippy & Huber, 1973). Three cycles, of five iterations each, were calculated for different permutations for 152 $|E|$ values ≥ 1.80 . 43 phased *E*'s were chosen from the best trial as an input to *MULTAN*.

Tangent refinement with input phases kept constant, except for the last few cycles, led to figures of merit: *ABSFOM* = 0.97, *PSI ZERO* = 1.9, *RESID* = 31.4. The *E* map, carried out with 236 *E*'s, revealed a fragment of the molecule consisting of one five- and one six-membered ring. The remaining atoms were located from Fourier and difference maps. Some H atoms did not refine well, and their *B* values were adjusted for the final cycle, while those attached to C(25) were eliminated.

Refinement was by block-diagonal least squares, assuming anisotropic vibration for C, N and O and isotropic for H. The weighting scheme was: $\sqrt{w} = g(F_o) \cdot h(\sin^2\theta)$, where $g(F_o) = 1$ for $|F_o| < 4.5$ and $g(F_o) = 4.5/|F_o|$ for $|F_o| > 4.5$, and $h(\sin^2\theta) = 0.22/\sin^2\theta$ for $\sin^2\theta < 0.22$ and $h(\sin^2\theta) = 1$ for $\sin^2\theta > 0.22$. The refinement was carried out with the observed reflexions only, excluding reflexion 120, which suffered from extinction effects. In the final cycle, *R* = 0.048, *R_w* = 0.064 for 2158 observed reflexions. The final mean shift/e.s.d. was 0.53 for non-H atoms and the largest shifts/e.s.d.'s (2.0–2.9) were for the methyl C atoms [C(20), C(22) and C(25)]. The final difference map revealed the presence of a peak of $\sim 0.3 \text{ e \AA}^{-3}$ near O(7), which was probably due to a slight disorder of that methoxy group.

Scattering factors were those of Hanson, Herman, Lea & Skillman (1964) for non-H atoms and of Stewart, Davidson & Simpson (1965) for H.

Calculations were carried out with the NRC program system (Ahmed, Hall, Pippy & Huber, 1973).

The final atomic coordinates are in Table 1.*

Discussion

A stereoscopic view of the molecule produced by Johnson's *ORTEP* (1965) program is shown in Fig. 1. Its absolute configuration was not determined, but it corresponds to that of lycocotinine, from which it was derived. The C(1) configuration is opposite to that found for (+)-de(oxy)methylene)lycocotinine hydroiodide monohydrate (Przybylska & Marion, 1956). The origin of this discrepancy will be discussed in a future paper. The bond lengths and valency angles are in Fig. 2. The numbering agrees with that of the skeleton of lycocotinine (Edwards, 1971); consequently C(6) and C(18) are missing.

The C—H lengths are in the range 0.87 to 1.10 Å (mean = 0.99, e.s.d. \leq 0.10 Å). The C—C bonds vary in length from 1.475 to 1.582 Å, the longest being associated with the fully substituted C(8) and C(11) atoms.

The C—N bond lengths are 1.332 (4), 1.461 (3) and 1.471 (4) Å, in good agreement with those at N(7) [1.329 (4), 1.467 (4) and 1.477 (4) Å] in a cyclol tripeptide related to ergot alkaloids (Przybylska & Ahmed, 1981). The oxygen of the CO group attached to N(7) in the tripeptide is hydrogen bonded to NH of a neighbouring molecule. O(4) of the present structure is also involved in an intermolecular hydrogen bond. The O(6)···O(4) distance is 2.619 (4), O—H = 0.76 (4), H(6)···O(4) = 1.94 (4) Å and \angle O(6)—H(6)···O(4) is 148 (4)°. The lengthening of the C(19)—O(4) acceptor bond to 1.226 (4) Å as compared to the other CO bonds of 1.198 (8) and 1.200 (4) Å, and the shortening of the C(7)—O(6) donor bond to 1.318 (4) Å is in accordance with the expected bond-length changes caused by the hydrogen-bond formation (Jeffrey, Ruble, McMullan, DeFrees, Binkley & Pople, 1980).

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36256 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

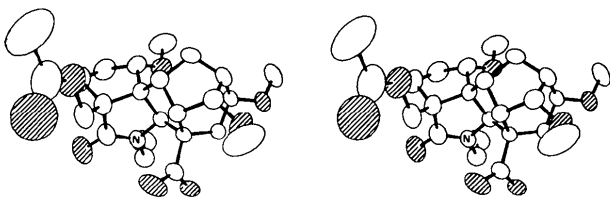


Fig. 1. A stereoscopic view showing thermal ellipsoids at the 50% probability level. O atoms are cross-hatched.

The angles of the five-membered rings vary from 100.3 to 110.6° with the exception of the angle at N which is 113.7°. The other two angles at N are \sim 123°. Similar angles at N in five-membered rings were reported in the above mentioned cyclol tripeptide.

The endocyclic torsion angles are shown in Fig. 2(c) and the results of calculations of mean planes in Table 2. The ring junctions A/B, B/C, C/D and C/E are *cis*. Ring A is a half-chair with C(2) at -0.37 and C(3) at $+0.27$ Å from the plane of C(1), C(4) and C(11). This conformation prevents eclipsing of C(5) and C(10). Ring B is also a half-chair, but considerably flattened, with the torsion angle along the amide bond 5.6° and C(11) at -0.20 and C(17) at 0.13 Å from the plane of N, C(4) and C(19). The asymmetry parameters (Duax

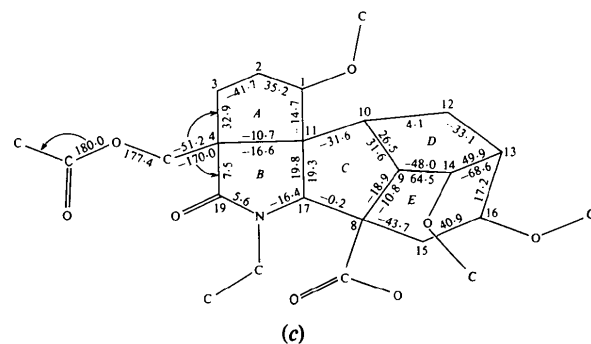
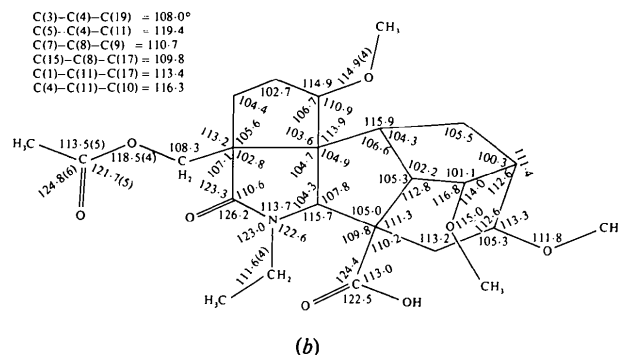
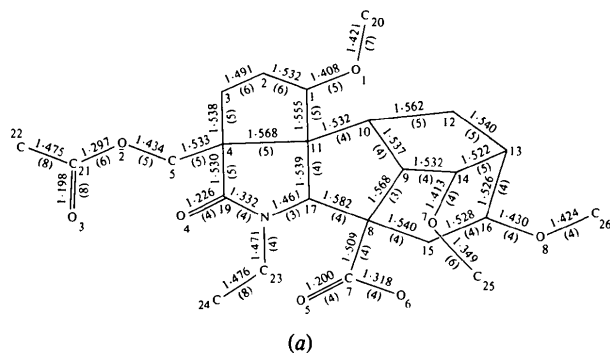


Fig. 2. (a) Bond lengths (Å) with e.s.d.'s in parentheses. (b) Bond angles (°); e.s.d.'s are 0.2 to 0.3° with the exception of those shown in the drawing. (c) Torsion angles (°); e.s.d.'s are \leq 0.6°.

Table 2. Mean planes and atomic displacements

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

Ring	l	m	n	p
A	0.9885	0.0880	0.1231	7.5672
B	0.3825	-0.3456	-0.8569	-9.1979
C	0.0008	0.9969	0.0788	3.9814
D	0.9808	-0.0661	-0.1833	4.5613
E	0.1191	-0.0233	-0.9926	-9.2996

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

Ring A	Ring B	Ring C	Ring D	Ring E			
C(1)	0	C(8)	1	C(9)	12	C(8)	-14
C(4)	0	C(19)	0	C(9)	-1	C(10)	21
C(11)	0	N	0	C(11)	1	C(12)	29
C(2)*	-371	C(17)*	130	C(17)	-1	C(13)	-16
C(3)*	273	C(11)*	-200	C(10)*	-483	C(14)*	738
						C(16)	20
						C(14)*	816
						C(15)*	534

* Atoms not included in the calculation of the plane.

& Norton, 1975) of the two rings are $\Delta C_2\{C(2)-C(3)\} = 3.3^\circ$ and $\Delta C_2\{C(11)-C(17)\} = 1.4^\circ$. Rings C and D are envelopes with C(10) and C(14) at -0.48 and 0.74 Å from their respective mean planes, but ring D is more distorted from an ideal conformation.

The D and E rings form a bicyclo[3.2.1]octane system, in which normally the five-membered ring is an envelope and the six-membered ring is a chair. The degree of puckering of the six-membered ring at the junction (torsion angles $62-72^\circ$) and the degree of its flattening at the opposite end (torsion angles $30-40^\circ$) depend on the nature and configuration of its substituents (Brisse, Battat, Pérez, Favre & Richer, 1977; Chacko, Bhattacharjee, Zand & Water, 1978). Ring E in the present structure is forced into a boat form by the fusion with ring C having C(14) and C(15) at 0.82 and 0.53 Å from the plane of the remaining four atoms.

The bicyclo[3.2.1]octane system is common to all alkaloids with the lycocotinine skeleton and it is of interest to compare its conformation with that in lappaconine HBr (Birnbau, 1970). The torsion angles of the five-membered rings agree very well; however, some of the endocyclic torsion angles of ring E differ considerably. In lappaconine HBr the values at the C(8)-C(15) and C(15)-C(16) bonds are smaller (~ 30 vs $\sim 42^\circ$) and at C(8)-C(9) it is larger (25 vs 11°). These effects are due to the differences in the adjoining ring, fused at C(8)-C(9)-C(10) which in lappaconine is a six-membered ring in a distorted-chair form. Its endocyclic torsion angle at C(8)-C(9) is considerably larger than in the present structure (36 vs 19°) and this gives rise to a more staggered conformation of C(8) and C(9). As a result the six-membered ring in lappaconine is of a more distorted and flattened boat form with C(15) at 0.36 Å from the plane of C(8), C(9), C(13) and C(16).

The C(22), C(21), O(3), O(2) and C(4), C(19), O(4), N groups are planar ($\chi^2 = 5.6$ and 0.1 respectively), but C(8), C(7), O(5), O(6) shows a slight deviation from planarity ($\chi^2 = 11.0$), which is probably due to the formation of an intermolecular hydrogen bond between O(6) and O(4). The hydrogen-bonded molecules form spirals along c. The H atoms attached to C(22) are relatively acidic due to the vicinity of the CO group and weak intermolecular interactions may be present between H(221) and O(3), and H(222) and O(5). The H...O contacts are 2.56 (5) and 2.49 (9) Å and the C(22)-H...O angles are 149 (3) and 144 (7)°, respectively.

The closest intermolecular distances are: H(223)...H(241) = 2.41 (13) Å and H(223)...H(263) = 2.20 (13) Å.

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