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A Keto Lactam Acid from Lycoctonine*

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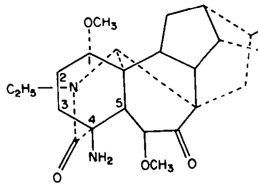
Abstract

$C_{24}H_{33}NO_8$ is orthorhombic, space group $P2_12_12_1$, with $a = 13{\cdot}810\ (1)$, $b = 15{\cdot}527\ (2)$, $c = 10{\cdot}644\ (1)$ Å, $Z = 4$, $D_c = 1{\cdot}349$, $D_m = 1{\cdot}341$ Mg m^{-3} (at 296 K, by flotation in toluene and carbon tetrachloride); μ(Cu $K\alpha$) = 0·80 mm^{-1}. The structure was solved by direct methods and refined to $R = 0{\cdot}037$ for 2475 observed reflexions. There is a strong intramolecular hydrogen bond between the adjacent COOH and CO groups. This work shows that the configuration at C(1) in lycoctonine and related alkaloids is the inverse of that previously accepted.

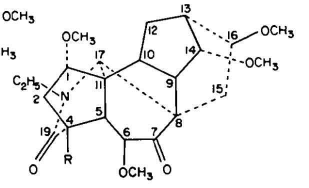
Introduction

During early attempts to solve the structure of lycoctonine by chemical means, nitrous acid deamination of an amino keto lactam (I), derived unambiguously from the alkaloid, was studied.

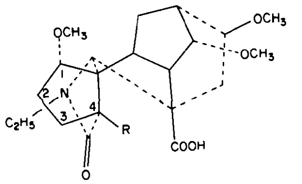
Unexpected molecular rearrangements had taken place giving two main products: a hydroxy keto lactam (II) and an aldehydo lactam acid (III), in 50 and 20% yield, respectively. Since difficulty was encountered in assigning structures to these products (Edwards, 1981), despite knowledge of the lycoctonine structure from X-ray analysis (Przybylska & Marion, 1956), X-ray investigations were undertaken of their corresponding derivatives: the keto lactam acid (IV) and the acetoxy lactam acid (V). These compounds were chosen because of the high quality of their crystals. The structure of (V) was described in an earlier paper (Cygler, Przybylska & Edwards, 1982). This work proved that the structure of the keto lactam acid is as shown in (IV), and thus that of the hydroxy keto lactam is (II).



(I)



(II) R = CH_2OH (IV) R = COOH



(III) R = CHO (V) R = CH_2OCOCH_3

Compound (IV) crystallized from ether as colourless prisms with m.p. 425 K. The space group was established from precession films. Final cell dimensions and intensities were measured at room temperature on a Nonius CAD-4 diffractometer with an irregular crystal fragment of dimensions 0·32–0·45 mm. Ni-

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Table 1. *Final fractional coordinates* (*for* C, N, O $\times 10^4$; *for* H $\times 10^3$) *and isotropic temperature factors, with e.s.d.'s in parentheses*

From the numbering of H atoms the number of the parent C atom can be derived by omitting the last digit. H(1) is attached to O(2). For non-hydrogen atoms $B = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B (Å^2)
O(1)	495 (1)	849 (1)	1619 (2)	4·9 (0·1)
O(2)	−1926 (1)	−1151 (1)	4695 (2)	6·1 (0·1)
O(3)	−2407 (1)	186 (2)	4961 (2)	6·4 (0·1)
O(4)	−215 (1)	−1449 (1)	4052 (2)	5·1 (0·1)
O(5)	−436 (1)	1174 (1)	7077 (2)	4·3 (0·1)
O(6)	1337 (1)	266 (1)	7350 (1)	4·1 (0·1)
O(7)	2711 (1)	2558 (1)	6424 (2)	3·8 (0·1)
O(8)	4119 (1)	1581 (1)	4615 (2)	5·1 (0·1)
C(1)	−191 (2)	1030 (2)	2574 (2)	3·9 (0·1)
C(2)	−951 (2)	319 (2)	2746 (2)	4·7 (0·1)
C(3)	−1792 (2)	−316 (2)	4650 (3)	4·9 (0·1)
C(4)	−818 (2)	8 (2)	4115 (2)	3·8 (0·1)
C(5)	−444 (1)	813 (1)	4808 (2)	3·3 (0·1)
C(6)	−100 (2)	579 (1)	6162 (2)	3·4 (0·1)
C(7)	1019 (1)	529 (1)	6371 (2)	3·1 (0·1)
C(8)	1600 (1)	902 (1)	5323 (2)	2·8 (0·1)
C(9)	1258 (1)	1886 (1)	5378 (2)	2·9 (0·1)
C(10)	789 (1)	2000 (1)	4095 (2)	3·2 (0·1)
C(11)	327 (1)	1121 (1)	3842 (2)	3·1 (0·1)
C(12)	1694 (2)	2236 (1)	3259 (2)	3·8 (0·1)
C(13)	2586 (2)	2257 (1)	4149 (2)	3·7 (0·1)
C(14)	2092 (2)	2527 (1)	5361 (2)	3·4 (0·1)
C(15)	2697 (1)	838 (1)	5375 (2)	3·2 (0·1)
C(16)	3125 (2)	1398 (2)	4318 (2)	3·6 (0·1)
C(17)	1172 (1)	523 (1)	4069 (2)	2·9 (0·1)
N	897 (1)	−396 (1)	4158 (2)	3·3 (0·1)
C(19)	−20 (2)	−671 (1)	4107 (2)	3·8 (0·1)
C(20)	155 (3)	1087 (4)	409 (3)	9·1 (0·1)
C(21)	1675 (2)	−1052 (1)	4052 (2)	3·9 (0·1)
C(22)	1877 (2)	−1506 (2)	5292 (3)	5·3 (0·1)
C(23)	−1314 (2)	930 (2)	7660 (3)	5·3 (0·1)
C(24)	2238 (2)	2889 (2)	7503 (2)	4·9 (0·1)
C(25)	4710 (4)	1471 (5)	3568 (7)	6·9 (0·2)
C(125)	4769 (4)	983 (4)	4601 (8)	6·6 (0·2)
H(1)	−129 (3)	−146 (2)	456 (4)	9·3 (1·1)
H(11)	−54 (2)	159 (2)	234 (2)	4·5 (0·6)
H(21)	−86 (2)	−14 (2)	218 (3)	6·6 (0·8)
H(22)	−160 (2)	50 (2)	269 (3)	5·9 (0·7)
H(51)	−97 (2)	122 (1)	488 (2)	3·2 (0·5)
H(61)	−36 (2)	0 (1)	636 (2)	3·0 (0·4)
H(91)	80 (2)	199 (1)	611 (2)	3·3 (0·5)
H(101)	31 (1)	244 (1)	410 (2)	2·9 (0·4)
H(121)	158 (2)	284 (2)	289 (2)	3·7 (0·5)
H(122)	178 (2)	181 (2)	250 (2)	4·2 (0·5)
H(131)	308 (2)	269 (2)	380 (2)	4·8 (0·6)
H(141)	177 (2)	313 (1)	528 (2)	3·6 (0·5)
H(151)	294 (2)	106 (1)	620 (2)	3·4 (0·5)
H(152)	288 (2)	24 (2)	527 (2)	3·9 (0·5)
H(161)	312 (2)	106 (1)	348 (2)	3·4 (0·5)
H(171)	163 (1)	58 (1)	335 (2)	2·9 (0·4)
H(201)	−2 (3)	48 (3)	36 (4)	11·2 (1·2)
H(202)	62 (3)	119 (3)	−21 (5)	12·2 (1·4)
H(203)	−40 (3)	125 (3)	27 (5)	12·6 (1·4)
H(211)	227 (2)	−73 (2)	369 (2)	5·0 (0·6)
H(212)	148 (2)	−148 (2)	336 (2)	4·6 (0·6)
H(221)	211 (2)	−102 (2)	601 (3)	6·8 (0·8)
H(222)	236 (2)	−197 (2)	515 (3)	5·4 (0·6)
H(223)	124 (2)	−183 (2)	559 (3)	8·4 (1·0)
H(231)	−121 (2)	36 (2)	808 (3)	7·1 (0·8)
H(232)	−183 (2)	85 (2)	704 (2)	4·3 (0·5)
H(233)	−147 (2)	139 (2)	825 (3)	7·5 (0·9)
H(241)	169 (2)	244 (2)	778 (3)	7·6 (0·8)
H(242)	274 (2)	301 (2)	818 (3)	5·7 (0·7)
H(243)	192 (3)	351 (2)	734 (3)	8·6 (0·9)
H(251)	459 (5)	98 (4)	284 (7)	8·6 (1·8)
H(252)	539 (3)	147 (3)	392 (5)	4·0 (1·1)
H(253)	474 (6)	209 (6)	313 (10)	13·1 (2·7)
H(1251)	542 (4)	106 (4)	490 (5)	4·7 (1·3)
H(1252)	460 (4)	55 (4)	374 (6)	6·0 (1·5)
H(1253)	456 (6)	64 (6)	555 (9)	10·0 (2·4)

filtered Cu $K\alpha$ radiation was used with the following instrumental settings: scan mode $\omega/2\theta$; $1° \le \theta \le 75°$; $\Delta\omega = 0{\cdot}8 + 0{\cdot}2 \tan\theta$ (°); aperture $= 3{\cdot}0 + 0{\cdot}5 \tan\theta$ (mm). Two scans were made in opposite directions. 2475 independent reflexions (93%), with $I > \sigma(I_{\text{net}})$, were observed out of a total of 2662. Absorption corrections were not applied. Four reflexions, which suffered from extinction, were excluded from the refinement.

The structure was solved by *MULTAN* 78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) having permuted five phases in 50 sets (using magic integers). The E map and weighted Fourier syntheses revealed all atoms of the molecule. Refinement was by block-diagonal least squares with anisotropic temperature factors for all non-H atoms (Hanson, Herman, Lea & Skillman, 1964) and isotropic for H (Stewart, Davidson & Simpson, 1965). The weighting scheme $\sqrt{w} = 16/|F_o|$ was applied only if $|F_o| > 16$. The final $R = 0{\cdot}037$ and $R_w = 0{\cdot}043$ were obtained for all observed reflexions. The methyl group attached to O(8) was disordered as two peaks were observed, C(25) and C(125). Both were refined independently, giving final occupancies of 0·52 and 0·48, respectively. It was possible to locate H atoms attached to both of them. The final mean and maximum shift/e.s.d for all atoms were 0·20 and 0·92, respectively.

The difference map, obtained towards the end of the refinement in order to locate the H atoms of the disordered methyl group, did not show any other significant peaks.

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

The final atomic coordinates are presented in Table 1.*

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36541 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion

A view of the molecule produced by Johnson's (1965) *ORTEP* program is shown in Fig. 1. The two ellipsoids for C(25) and C(125), of the disordered methyl group, are shown at the top of the molecule. The absolute configuration was not determined, but it must be the same as that of lycoctonine (Przybylska & Marion, 1959). The C(1) configuration is the same as in the acetoxy lactam acid (V) (Cygler, Przybylska & Edwards, 1982) but opposite to that given for (+)-de(oxymethylene)lycoctonine hydroiodide monohydrate (Przybylska & Marion, 1956). The lycoctonine samples from various sources used throughout the years in this laboratory have been shown to be identical (Barnes & Przybylska, 1953; Edwards & Przybylska, 1982); hence the configuration now found for the 1-methoxy group must be the correct one. Fuller comment on this corrected assignment will be published elsewhere.

The C—H lengths vary from 0·82 to 1·17 Å with e.s.d.'s ≤ 0·09 Å.

The bond lengths and angles are presented in Fig. 2, where the second atom of the disordered methyl group C(125), is not shown for the sake of clarity. O(8)—C(125) is 1·292 (7) Å and ∠C(16)—O(8)—C(125) is 121·2 (4)°.

The IR spectrum indicated a very strong intramolecular OH···O=C—N bond ($\nu_{\max}$ 1604 cm^{-1}). It exists between the adjacent COOH and CO groups [O(2)···O(4) 2·503 (3), O—H 1·01 (4), H(1)···O(4) 1·58 (4) Å and ∠O(2)—H(1)···O(4) 149 (3)°]. It is shown by a broken line in Fig. 1. The appreciable shortening of the C(3)—O(2) donor bond to 1·311 (4) Å and the degree of lengthening of the C(19)—O(4) bond to 1·240 (3) Å are in agreement with the strength of the hydrogen bond (Jeffrey, Ruble, McMullan, DeFrees, Binkley & Pople, 1980).

The angles of the five-membered rings vary from 99·3 to 106·8°.

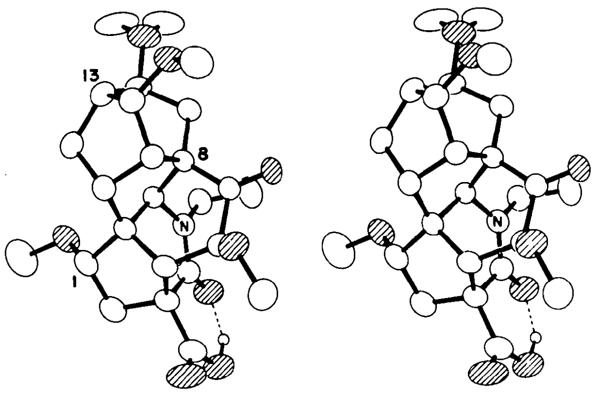

Fig. 1. A stereoscopic view showing thermal ellipsoids at the 50% probability level. O atoms are cross-hatched.

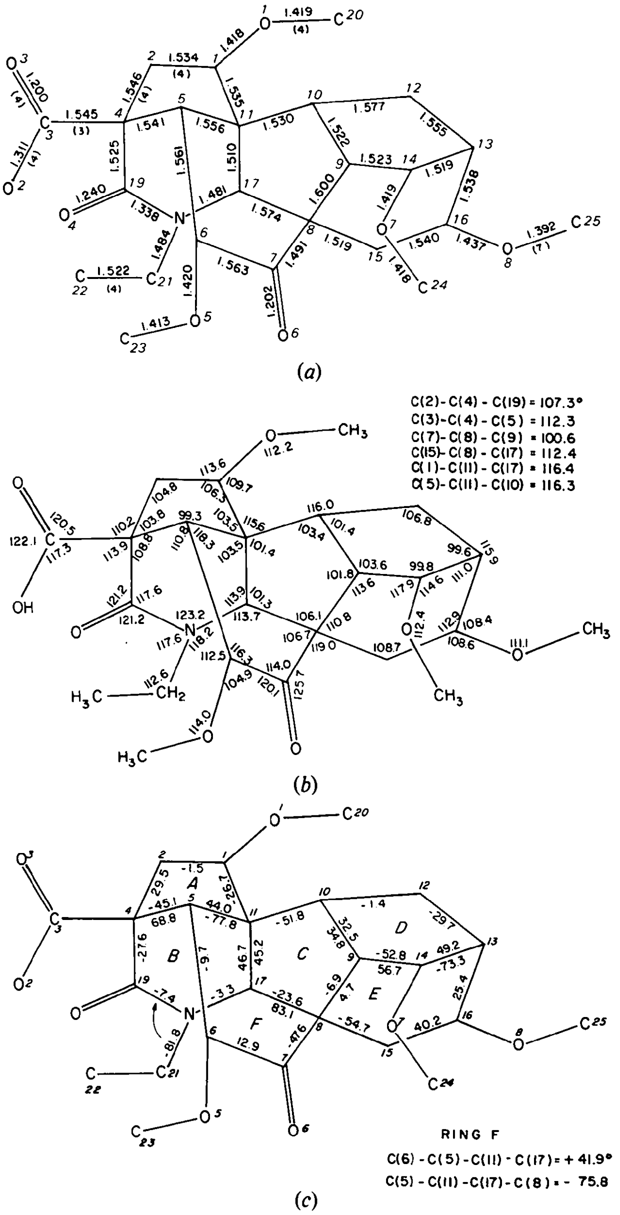

Fig. 2. (*a*) Bond lengths (Å), e.s.d.'s not given are 0·003 Å. (*b*) Bond angles (°); e.s.d.'s are 0·2 to 0·3°. (*c*) Torsion angles (°); e.s.d.'s are ≤0·6°.

All rings in the molecule are *cis* fused. The endocyclic torsion angles are shown in Fig. 2(*c*) and the data concerning mean planes in Table 2. Five-membered rings *A* and *D* adopt envelope conformations with C(5) and C(14) at 0·71 and 0·77 Å, respectively, from the plane of the other ring atoms. Ring *C* is also of the envelope form, but considerably distorted, with C(11) at 0·59 and C(10) at −0·18 Å from the plane of C(8), C(9) and C(17). The six-membered ring *B* is close to an envelope form but distorted into a half-chair conformation, as C(5) is at 0·79 and C(11) at

Table 2. *Mean planes and atomic displacements from them*

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

Ring	l	m	n	p
A	0·6754	−0·6745	−0·2982	−1·0911
B	0·0025	−0·0332	−0·9994	−6·2718
C	0·8284	0·2751	−0·4880	−4·6452
D	0·1612	−0·9682	−0·1914	1·6191
E	−0·4445	−0·2225	−0·8677	−2·9382
F	0·1131	−0·9270	−0·3577	−0·7571

(*b*) Deviations from the mean planes (Å × 10^3) (e.s.d. = 0·002 Å)

Ring *A*		Ring *B*		Ring *C*	
C(1)	−9	C(4)	14	C(8)	0
C(2)	8	C(19)	−31	C(9)	0
C(4)	−5	N	32	C(17)	0
C(11)	5	C(17)	−15	C(10)*	−179
C(5)*	709	C(5)*	791	C(11)*	592
		C(11)*	−222		

Ring *D*		Ring *E*		Ring *F*	
C(9)	−5	C(9)	94	C(5)	21
C(10)	8	C(8)	−87	C(11)	−23
C(12)	−8	C(16)	91	C(7)	−22
C(13)	5	C(13)	−98	C(8)	24
C(14)*	769	C(14)*	811	C(6)*	144
		C(15)*	612	C(17)*	−930

* Atoms not included in the calculation of the plane.

−0·22 Å from the plane calculated for the remaining atoms. Ring *E* exists in a conformation intermediate between boat and twist with C(14) and C(15) displaced above the plane by 0·81 and 0·61 Å, respectively. Ring *F* is an envelope slightly distorted towards a chair with C(17) at −0·93 Å and C(6) at only 0·14 Å from the plane for the other four atoms.

The groups C(4), C(19), N, O(4), and O(2), C(3), C(4), O(3) are planar ($\chi^2 = 0{\cdot}7$ and 38·1, respectively) but C(6), C(7), C(8), O(6) is not ($\chi^2 = 246$), undoubtedly due to the strain present in ring *F*.

A comparison of the endocyclic torsion angles for the fused *CDE* ring system in the keto lactam acid with those for the acetoxy lactam acid revealed considerable differences due to the strain imposed by the ring *F* in the title compound, which is not present in (V). The largest differences are for the values of ring *C* [with the exception, as expected, for bond C(9)—C(10), which is not joined to ring *F*] and for C(8)—C(15) of ring *E*. These differences vary from 11 to 26°, whereas all the remaining differences in torsion angles of this moiety vary from 0·7 to 8·2°. Ring *C* in the acetoxy lactam acid has an undistorted envelope form with C(10) at −0·48 Å as opposed to C(11) being at the flap in the present structure. Rings *D* in both structures have similar conformations. Ring *E* in the acetoxy lactam acid exists in a slightly distorted boat form, the asymmetry parameter ΔC_s being 4·7° (Duax & Norton, 1975). In the present compound its conformation has been shifted towards a twist form with appreciable deviation from mirror symmetry along the C(14)—C(15) line, ΔC_s being 21·5°.

There are no intermolecular contacts closer than the sum of the appropriate van der Waals radii. The shortest H···H distances are ≥2·42 Å.

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