

The Crystal and Molecular Structure of Lappaconine Hydrobromide*

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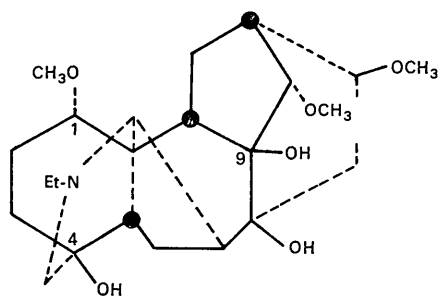
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Crystals of lappaconine hydrobromide, $C_{23}H_{37}O_6N \cdot HBr$, are orthorhombic, space group $P2_12_12_1$, with $a = 26.194$, $b = 10.160$, $c = 8.809$ Å. Data were collected with an automatic Picker diffractometer. The structure was solved by the heavy-atom method and the refinement was carried out by the least-squares procedure. All hydrogen atoms except one were located in a difference Fourier synthesis. The final R value is 0.050. The ring system of lappaconine is identical with that of lycotoconine. Two of the six-membered rings are in chair form, the other two are boat-shaped. One of the latter is stabilized by an intramolecular hydrogen bond which is part of a heterologous bifurcated hydrogen bond system.

Introduction

Lappaconine is a diterpenoid alkaloid of the aconite family which is obtained from the alkaline hydrolysis of lappaconitine. The latter was originally isolated from *Aconitum septentrionale* Koelle (Schulze, 1922). Khaimova, Mollov, Cerneva, Antonova & Ivanova (1964) established that the six oxygen atoms in lappaconine ($C_{23}H_{37}O_6N$) appeared in three hydroxyl and three methoxyl groups and that an *N*-ethyl group was present in the molecule. The structure has been investigated by Marion and his colleagues since 1963, but certain reactions remained uninterpretable, thus precluding a conclusive elucidation of the skeleton and of the positions of the oxygenated substituents. The difficulties were partly due to the presence in lappaconine, hitherto unknown in this class of alkaloids, of oxygen functions attached to C(4) and C(9). The complete structure (I) was first reported in a preliminary communication (Birnbaum, 1969).



(I)

Experimental

Crystal data

Lappaconine hydrobromide, $C_{23}H_{37}O_6N \cdot HBr$; F. W. 504.5. Orthorhombic:

$$\begin{aligned} a &= 26.194 \pm 0.003 \text{ \AA} \\ b &= 10.160 \pm 0.003 \text{ \AA} \\ c &= 8.809 \pm 0.003 \text{ \AA} \\ V &= 2344.3 \text{ \AA}^3 \\ D_x &= 1.429 \text{ g.cm}^{-3} \\ D_m &= 1.43 \text{ g.cm}^{-3} \\ Z &= 4 \\ \mu &= 36.8 \text{ cm}^{-1} (\text{Cu } K\alpha), F(000) = 1064 \end{aligned}$$

Absent reflexions: $h00$ when h is odd, $0k0$ when k is odd, $00l$ when l is odd.

Space group: $P2_12_12_1$.

The crystals were obtained from a mixture of ethanol and petroleum spirit. They were colourless prisms elongated in the direction of the b axis, with a diamond-shaped cross-section. At first, the data were recorded with an equi-inclination Weissenberg camera, using the multiple-film technique and nickel-filtered $\text{Cu } K\alpha$ radiation ($\lambda = 1.5418$ Å). The crystals were deteriorating as a result of X-ray exposure and thus it was necessary to use two of them in order to collect the zones $h0l$ to $h8l$ and another one to collect $hk0$ to $hk5$.

Subsequently a Picker automatic diffractometer became available, and the data were remeasured with this instrument. The cell dimensions were determined at 1° take-off angle with a 0.02° slit, assuming $\lambda = 1.54051$ Å for $\text{Cu } K\alpha_1$ and $\lambda = 1.54433$ Å for $\text{Cu } K\alpha_2$. All results reported here are based on diffractometer data. Two crystals were used, each having been cut to a size of $0.09 \times 0.09 \times 0.28$ mm. Monochromatization was achieved by a nickel filter and a pulse-height analyzer. The moving-crystal, moving-counter method ($\theta/2\theta$ scan) was used. Of the 2291 reflexions accessible to the diffractometer ($2\theta \leq 130^\circ$) 1854 (81%) were observed. They were indexed with respect to a right-handed set of axes. In view of the crystal size a correction for absorption was considered unnecessary.

Structure determination

The structure was solved with the photographic data by the use of the heavy-atom method. After applying Lo-

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rentz and polarization corrections all the values of F^2 were correlated by the method of Hamilton, Rollett & Sparks (1965), using a program obtained from Dr Sparks. The atomic scattering factors for Br^- were those given by Cromer (1965) and Cromer & Waber (1965), the values of Hanson, Herman, Lea & Skillman (1964) were used for C, N, and O, and those of Stewart, Davidson & Simpson (1965) for bonded H. The bromide ion was found at (0.187, 0.095, 0.061) in a three-dimensional Patterson map. The whole structure was revealed after several rounds of structure factor calculations and Fourier syntheses. After three cycles of isotropic refinement by least-squares calculated with the block-diagonal approximation the value of R dropped to 23%. At this point the data were abandoned and refinement was continued with the diffractometer data.

The function minimized was $\sum w(F_o - F_c)^2$. A partial shift factor of 0.8 was applied in each cycle. A correc-

tion for both the real and the imaginary parts of the anomalous scattering of the bromide ion was applied during the refinement. After four cycles of isotropic refinement R was reduced to 18.4%. At this stage anisotropic thermal parameters were assigned to all 31 atoms and a further four cycles of least-squares refinement lowered R to 7.9%. A difference Fourier synthesis (Fig. 1) calculated at this point revealed the positions of all hydrogen atoms except the one attached to O(3). The map also showed two peaks close to the bromide position which, along with two negative regions, formed a cross pattern indicative of incomplete refinement of anisotropic temperature parameters of that ion. The only other peak higher than 0.25 e. \AA^{-3} was near the position of O(6) and was attributable to a free pair of electrons. The contributions of the 37 hydrogen atoms were included in the next three cycles of refinement, but their parameters were not refined. Af-

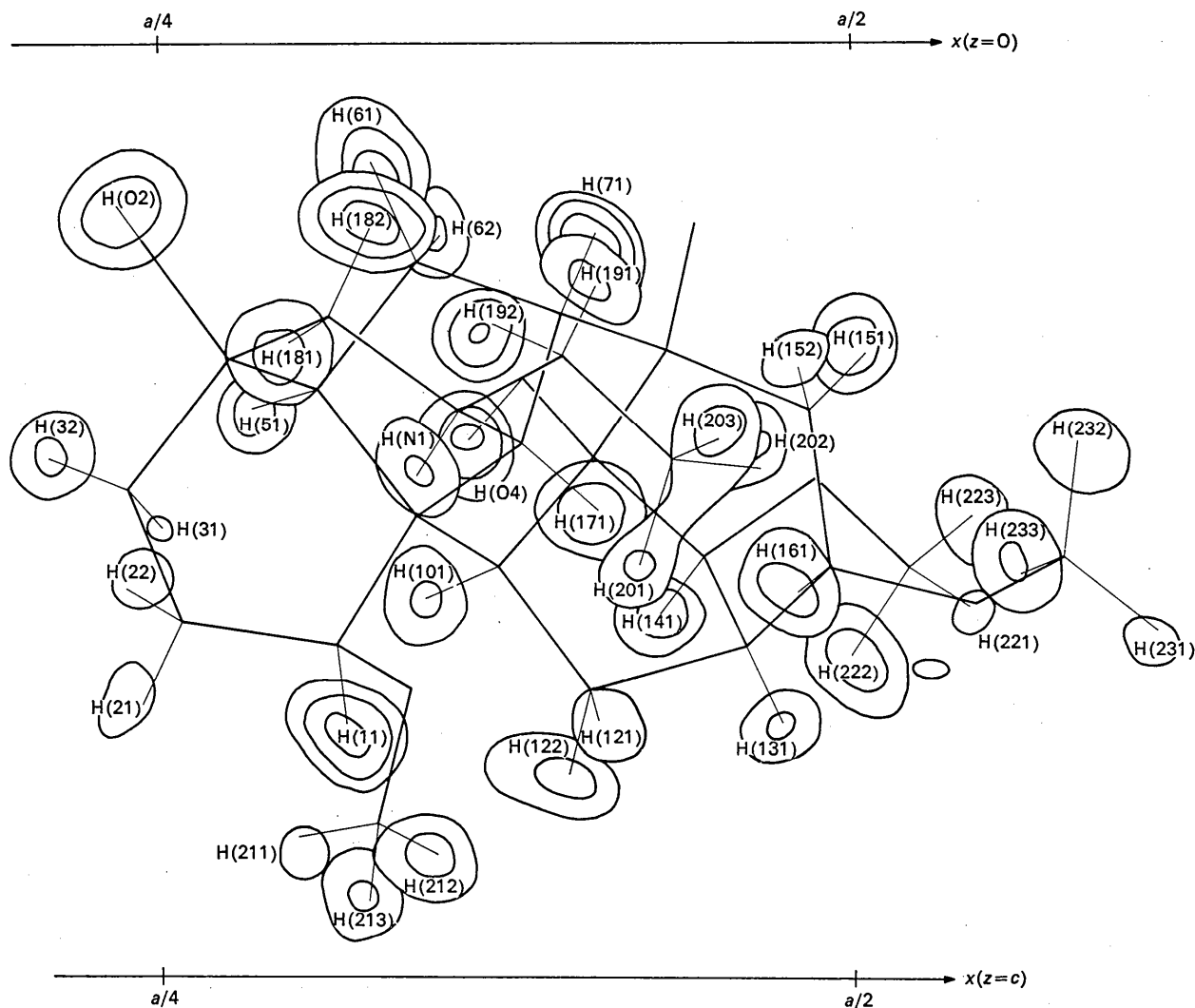


Fig. 1. Difference Fourier synthesis showing hydrogen atom positions. Contours begin at 0.25 e. \AA^{-3} and are drawn at intervals of 0.10 e. \AA^{-3} .

ter that another three cycles of least-squares were calculated during which only the hydrogen atom parameters were being refined. All the shifts decreased to less than 0.65σ , the average being 0.18σ . Until this stage unobserved reflexions were excluded from the refinement. In subsequent cycles those for which $F_o(=F_{th}) < F_c$ were included. The threshold values were obtained by assigning net intensity counts of 40 or 10% of the background, whichever was higher, to those reflexions whose intensities were below these thresholds. The following weighting scheme was introduced and kept until the end of the refinement:

where $\sqrt{w} = \sqrt{w'[1/(2 - 0.85 \sin^2\theta)]^{1/2}}$
 or $\sqrt{w'} = (|F_o|/25)^{1/6}$ when $|F_o| \leq 25$
 or $= (25/|F_o|)^{1/2}$ when $|F_o| > 25$.

Five more cycles in which the parameters of the non-hydrogen atoms were refined led to convergence. A total of 19 cycles of least-squares had been calculated with the diffractometer data.

At the end of the last cycle the average coordinate shift was 0.1σ and the maximum shift equalled 0.37σ . The final agreement index calculated for 1926 reflexions (1854 observed and 72 unobserved with $F_o < F_c$) was 5.0%. The final coordinates of non-hydrogen atoms

and their temperature parameters are listed in Table 1. The coordinates of the hydrogen atoms are given in Table 2. The estimated standard deviations were derived from the inverse of the least-squares matrix. Observed and calculated structure factors are shown in Table 3. A summary of the agreement between these values can be found in Table 4. Bond lengths and angles are listed in Tables 5 and 6 respectively.

Table 2. The final parameters (and their e.s.d.'s) of the hydrogen atoms

	$10^3x/a$	$10^3y/b$	$10^3z/c$	B
H(11)	316 (2)	583 (7)	724 (8)	3.5 Å ²
H(21)	243 (4)	697 (10)	714 (12)	6.8
H(22)	238 (4)	566 (10)	583 (13)	8.9
H(31)	251 (4)	836 (11)	518 (13)	10.3
H(32)	210 (3)	729 (8)	444 (10)	4.9
H(51)	283 (2)	492 (6)	388 (7)	1.9
H(61)	327 (2)	592 (8)	127 (8)	3.5
H(62)	351 (3)	451 (7)	198 (8)	3.7
H(71)	407 (2)	652 (5)	203 (6)	0.7
H(101)	345 (2)	405 (7)	596 (8)	3.4
H(121)	407 (2)	581 (7)	726 (8)	3.6
H(122)	397 (3)	432 (7)	789 (9)	3.9
H(131)	474 (2)	426 (7)	735 (8)	3.0
H(141)	428 (2)	267 (6)	620 (7)	1.5
H(151)	503 (3)	498 (7)	325 (8)	3.0
H(152)	479 (3)	631 (7)	345 (8)	3.4
H(161)	480 (3)	656 (7)	588 (9)	3.8
H(171)	408 (2)	699 (6)	499 (7)	2.2
H(181)	297 (3)	890 (8)	318 (8)	3.7

Table 1. The final parameters (and their e.s.d.'s) of the non-hydrogen atoms

The anisotropic temperature parameters are defined by

$$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{23}klb^*c^* + 2U_{31}lhc^*a^* + 2U_{12}hka^*b^*)].$$

	$10^4 x/a$	$10^4 y/b$	$10^4 z/c$	$10^3 U_{11}$	$10^3 U_{22}$	$10^3 U_{33}$	$10^3 2U_{23}$	$10^3 2U_{13}$	$10^3 2U_{12}$
C(1)	3127 (3)	6509 (6)	6459 (8)	39 (3)	38 (3)	56 (4)	24 (6)	33 (7)	-14 (6)
C(2)	2576 (3)	6694 (12)	6187 (13)	52 (5)	118 (8)	86 (7)	-14 (13)	21 (10)	35 (10)
C(3)	2430 (3)	7319 (10)	4744 (13)	48 (5)	88 (6)	112 (8)	57 (13)	39 (10)	60 (9)
C(4)	2747 (3)	6936 (7)	3359 (10)	40 (4)	40 (4)	71 (5)	17 (8)	-34 (7)	7 (6)
C(5)	3063 (2)	5680 (6)	3670 (9)	38 (3)	32 (3)	64 (4)	20 (6)	-16 (6)	-3 (5)
C(6)	3431 (3)	5463 (7)	2340 (9)	60 (4)	35 (3)	51 (4)	2 (7)	-34 (7)	22 (6)
C(7)	3942 (2)	6038 (6)	2879 (7)	45 (3)	37 (3)	28 (3)	18 (6)	6 (5)	2 (6)
C(8)	4322 (2)	4913 (6)	3267 (7)	39 (3)	36 (3)	33 (3)	-9 (6)	0 (6)	2 (5)
C(9)	4061 (2)	3939 (6)	4422 (8)	40 (3)	29 (3)	40 (3)	-6 (6)	-5 (6)	-4 (5)
C(10)	3709 (2)	4668 (5)	5595 (8)	39 (3)	27 (3)	37 (3)	10 (6)	18 (6)	-11 (5)
C(11)	3414 (2)	5910 (6)	5053 (7)	28 (2)	28 (3)	42 (3)	16 (6)	-2 (5)	-2 (5)
C(12)	4066 (2)	4944 (7)	6955 (8)	40 (3)	44 (4)	39 (4)	8 (6)	13 (6)	7 (6)
C(13)	4603 (2)	4484 (6)	6484 (7)	45 (4)	34 (3)	30 (3)	8 (5)	-19 (6)	9 (5)
C(14)	4459 (2)	3315 (6)	5488 (7)	43 (3)	33 (3)	30 (3)	10 (6)	3 (6)	-13 (5)
C(15)	4840 (2)	5453 (6)	3914 (8)	42 (3)	33 (3)	50 (4)	2 (6)	5 (6)	2 (5)
C(16)	4904 (2)	5539 (6)	5623 (8)	33 (3)	45 (4)	45 (4)	-1 (7)	7 (6)	-2 (5)
C(17)	3804 (2)	6822 (6)	4281 (7)	38 (3)	31 (3)	31 (3)	1 (6)	7 (5)	1 (5)
C(18)	3109 (3)	8046 (7)	2907 (8)	56 (4)	34 (3)	50 (4)	-1 (6)	-22 (7)	20 (7)
C(19)	3945 (3)	9151 (7)	3329 (8)	68 (4)	34 (3)	47 (4)	8 (7)	41 (7)	-19 (7)
C(20)	4346 (3)	9473 (7)	4451 (11)	53 (4)	44 (4)	91 (6)	-26 (9)	63 (9)	-37 (7)
C(21)	3272 (5)	8096 (11)	8380 (12)	129 (9)	78 (7)	78 (7)	-66 (12)	80 (14)	-36 (13)
C(22)	5196 (3)	2019 (7)	5606 (10)	52 (4)	47 (4)	63 (5)	-1 (8)	19 (8)	35 (7)
C(23)	5756 (3)	6367 (9)	5497 (12)	46 (4)	69 (5)	90 (7)	-1 (11)	-17 (9)	-33 (7)
N(1)	3568 (2)	8148 (5)	3930 (6)	47 (3)	25 (2)	41 (3)	-5 (5)	15 (5)	-3 (4)
O(1)	3401 (2)	7642 (5)	6929 (6)	69 (3)	56 (3)	52 (3)	-16 (5)	46 (5)	-25 (5)
O(2)	2439 (2)	6631 (5)	2097 (8)	65 (4)	47 (3)	115 (5)	17 (7)	-82 (7)	11 (5)
O(3)	4429 (2)	4239 (5)	1907 (5)	59 (3)	47 (3)	34 (2)	-16 (4)	15 (4)	12 (5)
O(4)	3807 (2)	2963 (4)	3567 (6)	54 (2)	33 (2)	46 (3)	0 (4)	-5 (4)	-19 (4)
O(5)	4856 (2)	2706 (4)	4652 (5)	48 (2)	40 (2)	49 (3)	10 (5)	13 (4)	32 (4)
O(6)	5433 (2)	5342 (5)	6012 (7)	40 (2)	52 (3)	81 (4)	12 (6)	-26 (5)	-11 (4)
Br ⁻	1874.3 (4)	9060.4 (8)	614.2 (14)	83.7 (7)	36.8 (3)	114.0 (8)	25.6 (11)	-100.1 (12)	1.3 (8)

Table 2 (cont.)

	$10^3x/a$	$10^3y/b$	$10^3z/c$	<i>B</i>
H(182)	326 (2)	782 (5)	195 (6)	0.7 Å ²
H(191)	407 (2)	877 (6)	244 (7)	1.6
H(192)	369 (2)	1002 (6)	297 (7)	2.3
H(201)	423 (2)	949 (7)	557 (9)	3.5
H(202)	464 (3)	873 (8)	454 (10)	4.7
H(203)	451 (3)	1013 (8)	421 (10)	5.4
H(211)	300 (4)	862 (10)	849 (12)	9.7
H(212)	349 (3)	875 (7)	871 (9)	4.0
H(213)	324 (4)	733 (11)	923 (12)	8.5
H(221)	541 (3)	260 (8)	605 (9)	4.0
H(222)	498 (2)	157 (7)	658 (8)	2.8
H(223)	542 (3)	144 (7)	507 (9)	4.5
H(231)	605 (4)	628 (11)	619 (13)	9.1
H(232)	580 (3)	631 (9)	426 (11)	6.1
H(233)	560 (4)	726 (10)	571 (12)	8.5
H(N1)	342 (3)	842 (8)	465 (9)	5.2
H(O2)	235 (3)	736 (8)	171 (10)	5.3
H(O4)	360 (2)	254 (6)	429 (7)	2.2

The mean e.s.d. of *B* is 1.9 Å².

Discussion of the structure

The ring system of lappaconine (I) is very similar to that of heteratisine (Przybylska, 1965) and it is identical with that of lycocotinine (Przybylska, 1961*a*), demethanolaconinone (Przybylska, 1961*b*) and delcosine (Marion, 1963). A perspective view of the molecule can be seen in Fig. 2. Six rings can be easily discerned and are designated *A* to *F*. They are fused to one another as follows: *A/C*, *cis*; *B/D*, *cis*; *D/E*, *cis*; *D/F*, *cis*. The six-membered rings *A* and *F* are in boat conformations, the other two six-membered rings (*B* and *D*) are in chair forms. One five-membered ring (*C*) is a half-chair while the other (*E*) is envelope-shaped.

The azabicyclo[3,3,1]nonane system of rings *A* and *B* is similar to other systems which have recently been described (Tamura & Sim, 1968). It has been found

(Webb & Becker, 1967) that the simple saturated bicyclo[3,3,1]nonane compounds adopt a twin-chair conformation, with both chairs flattened. Such a conformation was found in lycocotinine hydriodide, but in the present structure, as well as in delcosine hydrobromide and heteratisine hydrobromide, ring *A* is a strained and flattened boat. There are two reasons for this: the formation of an intramolecular hydrogen bond between N(1) and O(1) and the avoidance of the very close contact between O(1) and C(12) which would be present if ring *A* was a chair. In lycocotinine, in which the methoxy group is epimeric at C(1), these reasons do not apply. The ring is considerably flattened at C(2) and C(3), as shown by greatly increased bond

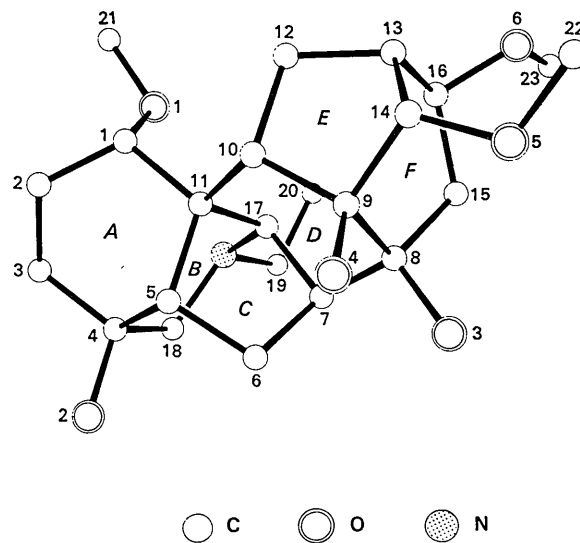
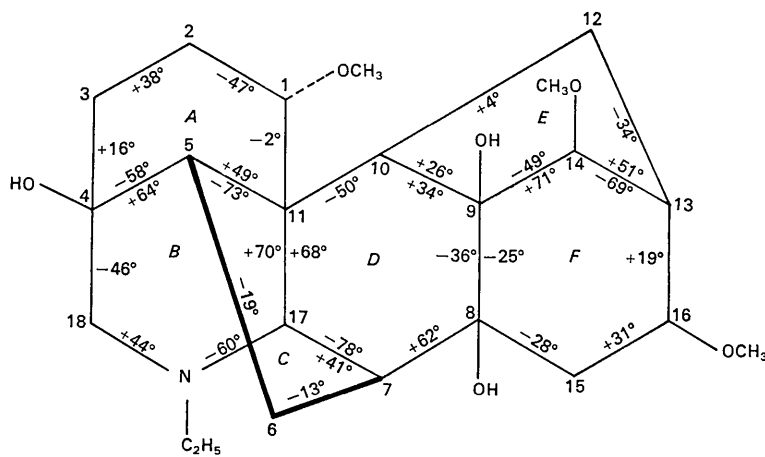


Fig. 2. A perspective view of lappaconine.



$$C(7)-C(17)-C(11)-C(5) = -51^\circ$$

$$C(17)-C(11)-C(5)-C(6) = +43^\circ$$

Fig. 3. Torsional angles. The convention used is that of Klyne & Prelog (1960).

Table 3. Observed and calculated structure factors ($\times 10$)

An asterisk following $10F_o$ indicates an unobserved reflexion to which the estimated threshold value was assigned.

Table with multiple columns for different reflections, each containing observed (F_o) and calculated (F_c) structure factor values. The table is organized into several groups of columns, each representing a different reflection. Asterisks indicate unobserved reflections.

STRUCTURE OF LAPPACONINE HYDROBROMIDE

Table 3 (cont.)

Table with multiple columns containing numerical data, likely representing coordinates or structural parameters. The table is organized into several vertical sections, each with its own set of column headers (e.g., x, y, z, alpha, beta, gamma, delta, epsilon, zeta, eta, theta, iota, kappa, lambda, mu, nu, xi, omicron, pi, rho, sigma, tau, upsilon, phi, chi, psi, omega). The data points are arranged in rows, often grouped by a common label on the left (e.g., #1, #2, #3, #4, #5, #6, #7, #8, #9, #10, #11, #12, #13, #14, #15, #16, #17, #18, #19, #20, #21, #22, #23, #24, #25, #26, #27, #28, #29, #30, #31, #32, #33, #34, #35, #36, #37, #38, #39, #40, #41, #42, #43, #44, #45, #46, #47, #48, #49, #50, #51, #52, #53, #54, #55, #56, #57, #58, #59, #60, #61, #62, #63, #64, #65, #66, #67, #68, #69, #70, #71, #72, #73, #74, #75, #76, #77, #78, #79, #80, #81, #82, #83, #84, #85, #86, #87, #88, #89, #90, #91, #92, #93, #94, #95, #96, #97, #98, #99, #100). The values are typically integers or small decimals, representing the positions of atoms in a crystal lattice or similar structural data.

Table 3 (cont.)

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100
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Table 4. Agreement summary

1854 observed reflexions ($3 \cdot 3 \leq |F_o| \leq 250 \cdot 2$)

Category	Limits	Number
1	$ \Delta F \leq 1 \cdot 0 F_{th} $ or $ \Delta F / F_o \leq 0 \cdot 1$	1852
2	$1 \cdot 0 F_{th} < \Delta F \leq 2 \cdot 0 F_{th} $ or $0 \cdot 1 < \Delta F / F_o \leq 0 \cdot 15$	2
437 unobserved reflexions		
Category	Limits	Number
1	$ F_c \leq 1 \cdot 0 F_{th} $	365
2	$1 \cdot 0 F_{th} < F_c \leq 1 \cdot 5 F_{th} $	63
3	$1 \cdot 5 F_{th} < F_c \leq 2 \cdot 0 F_{th} $	9

Note. $|F_{th}|$ = threshold amplitude = 1.7 to 6.8.

angles and by the fact that C(2) is at a distance of only 0.48 Å from the mean plane through C(1), C(3), C(4) and C(11), while C(5) is displaced by 0.66 Å from that plane. This distortion is also manifested by the torsional angles (Fig. 3) adjacent to C(2) and C(3) which greatly deviate from the calculated values of ± 52 and 0° respectively (Hendrickson, 1967). The presence of a bond between C(6) and C(7) causes an appreciable closing of the valence angle C(5)-C(11)-C(17) ($97 \cdot 9^\circ$) and a concomitant increase in the adjacent angle C(1)-C(11)-C(5) ($113 \cdot 3^\circ$) in ring *A*.

The five-membered ring *C* can best be described as a distorted half-chair. The atoms C(11) and C(17) are displaced by 0.49 and 0.34 Å respectively to the opposite sides of the plane defined by C(5)-C(6)-C(7).

In an ideal half-chair these distances would amount to ± 0.39 Å (Brutcher & Bauer, 1962).

Ring *D* is badly distorted from an ideal chair conformation. Being in the centre of the structure this ring is strained by all other ring systems and this is made evident by abnormal bond angles and torsional angles. There is a significant flattening of the ring at C(9) and C(10), and the opposite effect at C(11) and C(17).

Ring *E* is fairly close to an envelope. C(14) is at a normal distance of 0.76 Å from the mean plane through the other four atoms. However, these four atoms do not lie in a plane ($\chi^2 = 54 \cdot 7$) and the torsional angle for the bond C(10)-C(12) equals $+4^\circ$ instead of 0° . The distortion can be ascribed to the strain transmitted from rings *D* and *F*.

STRUCTURE OF LAPPACONINE HYDROBROMIDE

Table 5. *Intramolecular bond lengths*

C(1)—C(2)	1.477 (11) Å	C(2)—H(21)	0.97 (10) Å
C(1)—C(11)	1.571 (9)	C(2)—H(22)	1.22 (11)
C(2)—C(3)	1.472 (16)	C(3)—H(31)	1.15 (11)
C(3)—C(4)	1.526 (13)	C(3)—H(32)	0.90 (8)
C(4)—C(5)	1.546 (9)	C(5)—H(51)	1.00 (6)
C(4)—C(18)	1.527 (10)	C(6)—H(61)	1.13 (7)
C(5)—C(6)	1.533 (10)	C(6)—H(62)	1.04 (7)
C(5)—C(11)	1.544 (9)	C(7)—H(71)	0.92 (5)
C(6)—C(7)	1.535 (10)	C(10)—H(101)	0.99 (7)
C(7)—C(8)	1.553 (9)	C(12)—H(121)	0.92 (8)
C(7)—C(17)	1.514 (9)	C(12)—H(122)	1.07 (8)
C(8)—C(9)	1.575 (9)	C(13)—H(131)	0.87 (7)
C(8)—C(15)	1.572 (9)	C(14)—H(141)	1.02 (6)
C(9)—C(10)	1.570 (9)	C(15)—H(151)	0.91 (7)
C(9)—C(14)	1.538 (9)	C(15)—H(152)	0.97 (7)
C(10)—C(11)	1.555 (8)	C(16)—H(161)	1.09 (7)
C(10)—C(12)	1.546 (9)	C(17)—H(171)	0.96 (6)
C(11)—C(17)	1.537 (8)	C(18)—H(181)	0.97 (8)
C(12)—C(13)	1.550 (9)	C(18)—H(182)	0.96 (5)
C(13)—C(14)	1.523 (9)	C(19)—H(191)	0.94 (6)
C(13)—C(16)	1.525 (9)	C(19)—H(192)	1.15 (6)
C(15)—C(16)	1.518 (10)	C(20)—H(201)	1.03 (8)
C(19)—C(20)	1.480 (11)	C(20)—H(202)	1.08 (7)
C(17)—N(1)	1.514 (7)	C(20)—H(203)	0.82 (8)
C(18)—N(1)	1.505 (9)	C(21)—H(211)	0.89 (10)
C(19)—N(1)	1.515 (9)	C(21)—H(212)	0.93 (8)
C(1)—O(1)	1.418 (9)	C(21)—H(213)	1.08 (11)
C(4)—O(2)	1.409 (10)	C(22)—H(221)	0.91 (8)
C(8)—O(3)	1.408 (8)	C(22)—H(222)	1.12 (7)
C(9)—O(4)	1.412 (8)	C(22)—H(223)	0.96 (7)
C(14)—O(5)	1.416 (8)	C(23)—H(231)	1.00 (11)
C(16)—O(6)	1.440 (7)	C(23)—H(232)	1.09 (10)
C(21)—O(1)	1.400 (12)	C(23)—H(233)	1.01 (10)
C(22)—O(5)	1.409 (9)	N(1)—H(N1)	0.79 (8)
C(23)—O(6)	1.417 (10)	O(2)—H(O2)	0.85 (9)
C(1)—H(11)	0.98 (7)	O(4)—H(O4)	0.94 (6)

Table 6. *Bond angles*

C(2)—C(1)—C(11)	112.9 (6)°	C(9)—C(10)—C(11)	118.2 (5)°
C(2)—C(1)—O(1)	116.0 (7)	C(9)—C(10)—C(12)	103.9 (5)
C(11)—C(1)—O(1)	107.6 (5)	C(11)—C(10)—C(12)	113.0 (5)
C(1)—C(2)—C(3)	116.7 (9)	C(1)—C(11)—C(5)	113.3 (5)
C(2)—C(3)—C(4)	116.0 (8)	C(1)—C(11)—C(10)	108.1 (5)
C(3)—C(4)—C(5)	111.2 (6)	C(1)—C(11)—C(17)	115.7 (5)
C(3)—C(4)—C(18)	111.0 (7)	C(5)—C(11)—C(10)	114.5 (5)
C(3)—C(4)—O(2)	112.0 (7)	C(5)—C(11)—C(17)	97.9 (5)
C(5)—C(4)—C(18)	108.9 (6)	C(10)—C(11)—C(17)	107.1 (5)
C(5)—C(4)—O(2)	105.4 (6)	C(10)—C(12)—C(13)	106.9 (5)
C(18)—C(4)—O(2)	108.2 (6)	C(12)—C(13)—C(14)	98.9 (5)
C(4)—C(5)—C(6)	108.7 (6)	C(12)—C(13)—C(16)	112.7 (5)
C(4)—C(5)—C(11)	109.5 (5)	C(14)—C(13)—C(16)	113.0 (5)
C(6)—C(5)—C(11)	104.5 (5)	C(9)—C(14)—C(13)	101.7 (5)
C(5)—C(6)—C(7)	104.9 (6)	C(9)—C(14)—O(5)	111.1 (5)
C(6)—C(7)—C(8)	110.3 (5)	C(13)—C(14)—O(5)	116.7 (5)
C(6)—C(7)—C(17)	104.1 (5)	C(8)—C(15)—C(16)	118.3 (5)
C(8)—C(7)—C(17)	111.2 (5)	C(13)—C(16)—C(15)	113.4 (5)
C(7)—C(8)—C(9)	109.1 (5)	C(13)—C(16)—O(6)	105.9 (5)
C(7)—C(8)—C(15)	112.1 (5)	C(15)—C(16)—O(6)	109.5 (5)
C(7)—C(8)—O(3)	107.4 (5)	C(7)—C(17)—C(11)	101.7 (5)
C(9)—C(8)—C(15)	111.1 (5)	C(7)—C(17)—N(1)	113.5 (5)
C(9)—C(8)—O(3)	109.3 (5)	C(11)—C(17)—C(1)	110.8 (5)
C(15)—C(8)—O(3)	107.8 (5)	C(4)—C(18)—N(1)	113.0 (6)
C(8)—C(9)—C(10)	112.6 (5)	C(20)—C(19)—N(1)	112.2 (6)
C(8)—C(9)—C(14)	111.1 (5)	C(17)—N(1)—C(18)	112.8 (5)
C(8)—C(9)—O(4)	107.5 (5)	C(17)—N(1)—C(19)	113.8 (5)
C(10)—C(9)—C(14)	101.0 (5)	C(18)—N(1)—C(19)	110.9 (5)
C(10)—C(9)—O(4)	114.0 (5)	C(1)—O(1)—C(22)	114.3 (7)
C(14)—C(9)—O(4)	110.8 (5)	C(14)—O(5)—C(22)	111.8 (5)
		C(16)—C(6)—C(23)	113.4 (6)

Ring *F* is forced into the boat form in order to make the substituents at C(8) and C(16) equatorial and thus reduce 1,3-interactions. Since C(14) is at the flap of the envelope of ring *E* it cannot assume its normal position in ring *F*. It is being forced further away from the mean plane of ring *F* [defined by C(8), C(9), C(13), and C(16)] and its distance from that plane is 0.85 Å instead of the normal distance of 0.73 Å. Consequently, the axial methoxy group attached to C(14) pushes away the C(15) methylene group, causing a considerable flattening. This is shown by the large angle C(8)–C(15)–C(16) (118.3°) and the short distance (0.36 Å) of C(15) from the mean plane of the ring. The torsional angles are correspondingly abnormal.

All bond lengths in this structure appear to be normal. It should be noted that the standard deviations obtained from the least-squares refinement are underestimated owing to the block-diagonal approximation and the lack of an absorption correction. An increase of the calculated values by 50% appears justified. There are three C(*sp*³)–C(*sp*³) single bonds [C(1)–C(2), C(2)–C(3), C(19)–C(20)] which are significantly shorter than normal, ranging from 1.472 to 1.480 Å. They all involve carbon atoms with large thermal motion, and this must be the cause of the apparent shortening of these bonds. An attempt to correct bond lengths by assuming rigid-body vibration of the molecule failed since the assumption was not justified.

All bonds involving hydrogen atoms are of reasonable length, being within 2σ of values normally found

in X-ray analyses. The angles, which are not listed, range from 92 to 127°. Their mean e.s.d. being 4.3° (for angles involving one hydrogen atom) and 6.8° (for angles involving two hydrogen atoms), they are all either normal within experimental error, or their deviations can be explained by the distortions discussed above.

The hydrogen bond system is illustrated in Fig. 4. The bromide ion accepts two hydrogen atoms from hydroxyl groups in two symmetry-related molecules. It also appears probable that there is a bifurcated hydrogen bond present in which the proton attached to the quaternized nitrogen atom is donated to O(1) in the same molecule as well as to Br⁻. Bifurcated hydrogen bonds have been reported in the past, but they are rare. In a recent review (Donohue, 1968) only five acceptable cases were listed. In all reported cases both acceptors were the same type of atom. This appears to be the first case of what may be called heterologous bifurcated hydrogen bonds, in which two very different atoms act as acceptors. It is remarkable that one of them is an ether oxygen atom, a type of atom rarely found to play the rôle of an acceptor. Although the presence of a heavy atom resulted in rather high e.s.d.'s in hydrogen positions the following arguments can be put forward in favour of such a hydrogen bond occurring in this structure. (a) The position of H(N1) was clearly indicated in the difference Fourier synthesis and it was refined by least-squares to give reasonable values for the covalent bond length and bond angles.

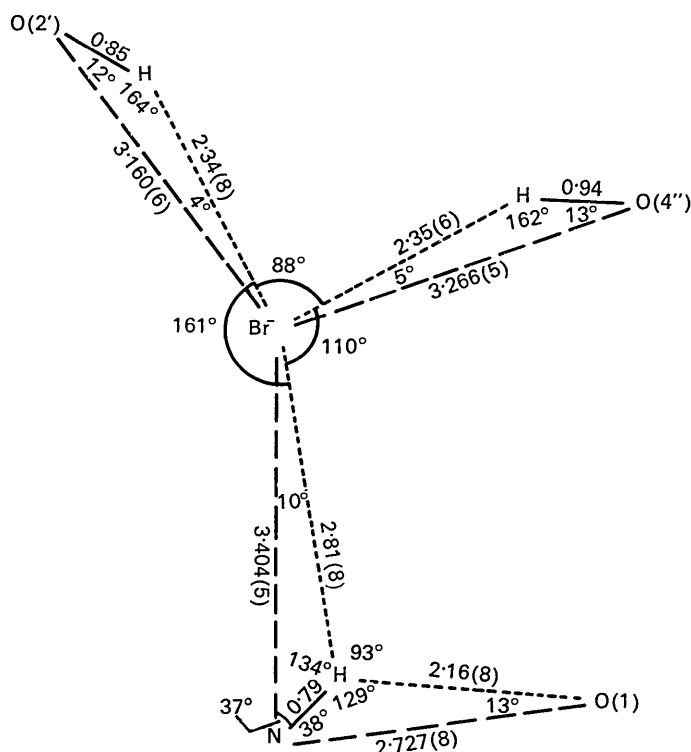


Fig. 4. Hydrogen bond system; O(2') is in the molecule at $\frac{1}{2} - x, \bar{y}, \frac{1}{2} + z$, O(4'') is in the molecule at $x, 1 + y, z$.

(b) The H(N1)...O(1) distance of 2.16 Å is significantly shorter (by 0.4 Å) than the sum of the van der Waals radii. The H...O distance in 'linear' N-H...O hydrogen bonds has been found to lie in the range of 1.83–2.17 Å. Hamilton & Ibers (1968) list 2.0 Å as the 'observed value'. An increase of this distance by 0.1–0.2 Å has generally been observed in cases of symmetrical bifurcation. (c) Hamilton & Ibers (1968) give 2.4 Å as the observed H...Cl⁻ distance in 'linear' N-H...Cl⁻ hydrogen bonds. In a bifurcated hydrogen bond in glycine hemihydrochloride (Hahn & Buerger, 1957) in which a hydrogen atom is being donated to two chloride ions the two H...Cl⁻ distances were found to be 2.52 and 2.62 Å. Since the ionic radius of Br⁻ is 0.15 Å longer than that of Cl⁻ (Pauling, 1960) the H...Br⁻ distance in a bifurcated N-H...Br⁻ hydrogen bond could be as long as 2.7–2.8 Å. (d) The N-H bond bisects exactly the angle Br⁻...N(1)...O(1). The angles Br⁻...N-H (37°) and O(1)...N-H (38°) are too large for 'linear' hydrogen bonds, but are quite normal for bifurcated hydrogen bonds (Donohue, 1968). (e) H(N1) lies in the same plane as Br⁻, H(O2') and H(O4'). The equation for this plane is 0.6772X + 0.0024Y + 0.7358Z = 9.1812 and $\chi^2 = 4.6$.

Considering all these points, the inference of a heterologous bifurcated hydrogen bond appears reasonable although not much can be said about its strength. It should be noted that a similar bifurcated hydrogen bond system was postulated in the closely related structure of heteratisine hydrobromide (Przybylska, 1965) although the hydrogen atom was not located.

This postulate is now indirectly confirmed since the N⁺...O and the N⁺...Br⁻ distances are practically identical in both structures. A heterologous bifurcated hydrogen bond system was recently claimed to have been found in the alkaloid haloxine (Nilsson, 1968). In view of the H...O and N...O distances (2.52, 3.12 Å) the presence of such a system in that structure appears very unlikely. Considering the very short distance between O(3) and O(4) (2.545 Å) there exists the possibility of another intramolecular hydrogen bond with O(3) donating a proton to O(4). Although the appropriate region of the difference Fourier synthesis was carefully searched no peak ascribable to the missing hydrogen atom could be found. One can therefore assume that the hydrogen atom is disordered and that there is no hydrogen bond between these two hydroxyl groups.

The absolute configuration of several closely related alkaloids has been established in the past (*e.g.* lycotonine, Przybylska & Marion, 1959). The assignment was confirmed in lappaconine by refining both enantiomers. The respective weighted *R* factors, $R' = (\sum w\Delta^2 / \sum wF^2)^{1/2}$, were 0.065 and 0.058 and the ratio 1:1 is highly significant (Hamilton, 1965). All diagrams are drawn with a right-handed set of axes and show the correct enantiomer.

Apart from the hydrogen bonds there are no intermolecular distances which are significantly shorter than the sum of van der Waals radii. The crystal structure can be described as consisting of pleated sheets formed by anti-parallel chains of lappaconine cations,

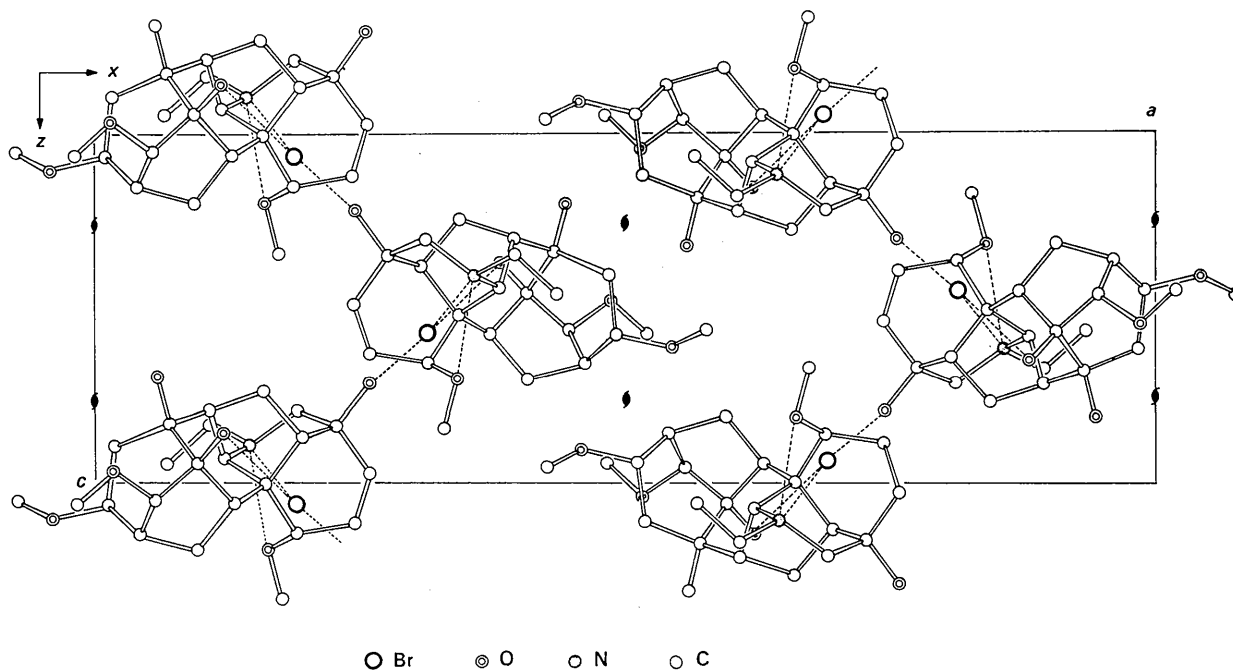


Fig. 5. Projection of the structure along the *b* axis. The hydrogen bonds O(4)–H...Br⁻ involve molecules related to those shown by a translation along the *b* axis (*cf.* Fig. 4).

arranged head-to-tail and connected to each other *via* N-H---Br⁻---H-O(4) hydrogen bonds. The chains are parallel to the *y* axis and within each sheet they are cross-linked by N-H---Br⁻---O(2) hydrogen bonds. A view of the structure is shown in Fig. 5.

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The Structure of a New Natural Amino Acid, 2,3-*cis*-3,4-*trans*-3,4-Dihydroxy-L-proline

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The formula of a new amino acid isolated from the cell walls of the diatom *Navicula pelliculosa* was confirmed by X-ray analysis to be 2,3-*cis*-3,4-*trans*-3,4-dihydroxyproline. The material crystallizes in space group $P2_12_12_1$ with cell dimensions $a = 8.38 \pm 0.01$, $b = 8.43 \pm 0.01$ and $c = 8.56 \pm 0.01$ Å, $Z = 4$ and a calculated density of 1.613 g.cm^{-3} . Atoms C(4), C(5), N and C(2) of the five-membered ring lie in a plane to within ± 0.009 Å while C(3) is 0.60 Å above the plane. The carboxyl group is equatorial while each of the two hydroxyl groups is axial to the ring. Four different hydrogen bonds, two $\text{NH} \cdots \text{O}$ bonds and two $\text{OH} \cdots \text{O}$ bonds, bind the molecules into a tight network. The structure was determined with the use of the symbolic addition procedure for phase determination.

Introduction

Proline, an imino acid rather than an amino acid, occurs in many proteins but is present in especially large quantities in collagen. 4-Hydroxyproline is found in scleroproteins and keratins. It was isolated from gelatin by Fischer in 1902. Recently, a dihydroxyproline was isolated from the protein material of the cell walls of the diatom *Navicula pelliculosa* (Nakajima & Volcani, 1969). The X-ray analysis was undertaken in order to confirm the structural formula of this new naturally occurring amino acid and to compare its

structure with that determined for proline (Kayushina & Vainshtein, 1966) and hydroxyproline (Donohue & Trueblood, 1952). A preliminary report on the structure and mass spectrum of dihydroxyproline has been published (Karle, Daly & Witkop, 1969).

Experimental

Crystals in the form of colorless acicular prisms were provided by Dr B. E. Volcani of the Scripps Institute of Oceanography. The largest of these was selected for the X-ray analysis. Even though the cross-section of