Vol. XXIV No. 11 SCIENTIA SINICA November 1981

THE CRYSTAL STRUCTURE OF MONOCROTALINE-N-OXIDE

WANG SHOUDAO (王守道)
(*Institute of Chemistry, Academia Sinica*)
AND HU NINGHAI (胡宁海)
(*Institute of Applied Chemistry, Academia Sinica*)

Received May 22, 1980.

ABSTRACT

The crystal structure of monocrotaline-N-oxide ($C_{16}H_{23}NO_7 \cdot 2H_2O$), a pyrrolizidine alkaloid, has been determined by X-ray diffraction method. It crystallizes in the orthorhombic space group $P2_12_12_1$, with the unit cell dimensions: $a=22.330(4)$, $b=11.525(2)$, $c=7.013(1)$Å, and $Z=4$. 1938 independent reflections are collected on a four-circle diffractometer with CuK_α radiation. The structure is solved by the direct method and refined by the block-diagonal least-squares. The final R value is 0.073. All calculations are performed with the (GC-79) program system developed by the present authors[9]. Structural features of monocrotaline-N-oxide are discussed and compared with those of other pyrrolizidine alkaloids

The pyrrolizidine alkaloid monocrotaline-N-oxide was synthesized from monocrotaline ($C_{16}H_{23}NO_6$). Many pyrrolizidine alkaloids are known as antitumor agents, but they induce severe lesions. Several crystal structures of these compounds have been reported[1-4]. In order to make clear the relationship between structure and pharmacologic function of these compounds, the crystal structures of several pyrrolizidine alkaloids have been deternmined in our laboratory[5-7].

The chemical structure formula of monocrotaline -N-oxide is shown in Fig. 1. It differs from that of monocrotaline in the dative bond between N(4) and O(24) (Fig. 3) and eight water molecules per unit cell. The molecules of monocrotaline -N-oxide are linked by hydrogen bonds via the water molecules in the C direction[8].

I. EXPERIMENTAL

Monocrotaline -N-oxide was crystallized from ethyl alcohol. The Weissenberg photograph showed that the crystal was orthorhombic, space group $P2_12_12_1$. A $0.5 \times 0.3 \times 0.2$ mm crystal was chosen for data collection. With CuK_α radiation 1938 independent reflections were measured on a Philips PW 1100 four-circle diffractometer with $\theta = 3 \sim 68°$. 115 reflctions were considered to be unobserved according to the criterion $I < 3\sigma(I)$. The crystal data are summarized in Table 1.

The intensities were corrected for the Lorentz and polarization effects. An absolute scale and over all temperature factor were determined by Wilson's method. After intensity reduction the observed structure amplitudes $|Fo|$'s were obtained.

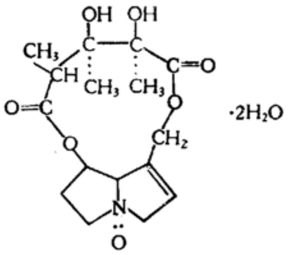

Fig. 1. The chemical structure formula of monocrotaline-N-oxide.

Table 1

Crystal Data

$C_{16}H_{23}NO_7 \cdot 2H_2O$	M. W. 377.39
Orthorhombic	space group $P2_12_12_1$
Unit cell parameters	$Z = 4$
$a = 22.330(4)$ Å	CuK_α radiation $\lambda = 1.5418$ Å
$b = 11.525$ (2)	$D_{obs.} = 1.391\ g \cdot cm^{-3}$
$c = 7.013(1)$	$D_{calc.} = 1.388\ g \cdot cm^{-3}$

II. STRUCTURE DETERMINATION

The structure was solved by the direct method. The normalized structure factors and their statistical averages were calculated and the latter is listed in Table 2.

Table 2

$|E_h|$'s Statistical Averages

Experimental Values		Theoretical Values	
		noncentro.	centro.
$\langle\|E_h\|^2\rangle$	1.01	1.00	1.00
$\langle\|E_h\|\rangle$	0.879	0.886	0.798
$\langle\|E_h^2 - 1\|\rangle$	0.768	0.736	0.968
$\|E_h\|>1$	34.6%	37%	32%
$\|E_h\|>2$	2.6	2	5
$\|E_h\|>3$	0.16	0.1	0.3

179 reflections with $|E_h| \geqslant 1.5$ were selected and the Σ_2 relationships of each reflection were searched. Nine reflctions were used as starting set (see Table 3) according to the rule of choosing starting phases in the (GC-79) program system[9]. Although the $P_+(E_{2h})$ values for the 22,0,4 and 10,2,0 are not very high, it has been found by our experience that the phases determined by the Σ_1 relation are often reliable for the space group $P2_12_12_1$ if the $|E_h|$ values are great enough.

The permutations of the phases $\pm\pi/4$ and $\pm 3/4\pi$ for the three general reflections made up 64 possible solutions.

Table 3

Starting Set

	H K L	$\lvert E_{2\boldsymbol{h}}\rvert$	$\phi_{2\boldsymbol{h}}$
Origin:	19 3 0	3.00	$\pi/2$
	18 1 0	2.55	0
	17 0 1	2.65	$-\pi/2$
Enantiomorph:	8 0 7	2.43	$\pi/2$
Σ_1:	22 0 4	2.45	π $P_+(E_{2\boldsymbol{h}})=0.18$
	10 2 0	2.86	O $P_+(E_{2\boldsymbol{h}})=0.59$
General:	20 1 1	2.83	$\pm\frac{1}{4}\pi$、$\pm\frac{3}{4}\pi$
	17 3 3	2.63	
	9 3 4	2.53	

The phases were extended and refined by tangent formula for each possible solution with the multi-solution program (GCMS), a part of the (GC-79) program system[9]. The program specified several restrictive criteria as follows:

1) "*IR*" criterion was effective all through the process of searching the Σ_2 relationships[10].

2) The phases with $t \geqslant 0.25$, $\alpha \geqslant 2.6$ were accepted.

3) The deviations of phases in two successive cycles were not allowed to exceed a specified limit of ± 80°.

4) The symmetry-restricted two-dimensional phases should not deviate from the expected value by ± 50°.

5) When the accepted phase is more than a hundred, three general reflections in the starting set should not keep fixed.

For the ninth set of solution ($\phi_{20\,1\,1} = -\dfrac{3}{4}\pi$, $\phi_{17\,3\,3} = \dfrac{1}{4}\pi$, $\phi_{9\,3\,4} = -\dfrac{3}{4}\pi$) 170 phases were obtained after eight cycles of tangent calculation, $R_{(\text{Karle})} = 0.251$. The E map calculated with these phases revealed the positions of all non-hydrogen atoms in the unit cell. Fourier synthesis was made with these atomic co-ordinates for all observable reflections. R index was 0.24 after four cycles of Fourier syntheses.

III. STRUCTURE REFINEMENT

Structure parameters were refined by the block-diagonal least-squares method using the (GCLS-BLOCK) program, a part of the (GC-79) system[11]. A flow-diagram of (GCLS-BLOCK) is shown in Fig. 2. The matrices used were 9×9, 12×12 and 27×27 for co-ordinates and thermal parameters of the three atoms corresponding to the overall, isotropic and anisotropic refinement respectively. The weights used were $W(\boldsymbol{h}) = 1/\sigma^2(F_h)$, where $\sigma(F_h) = [\sigma^2(I)/4I]^{1/2}$ and $\sigma(I)$, the standard deviation of intensity.

After the refinements of overall, isotropic and anisotropic thermal parameters, R value was 0.100 for all reflections. The 24 hydrogen atoms were found on the difference Fourier map. The hydrogen atoms took part in subsequent calculation of Fc's and their thermal parameters were assigned to those values of the nonhydrogen atoms to which they bonded, based on the last cycle of isotropic refinement. 14 reflections affected by the second extinction were excluded from the subsequent refinement and R was reduced to 0.079.

The three hydrogen atoms remained were found on the second differential map. The final R value was 0.073 for 1778 observable reflections.

The estimated standard deviations of atomic co-ordinates and thermal parameters were calculated from the inverse matrices of the final block-diagonal least-squares cycle[12]. The co-ordinates and thermal parameters of the atoms are given in Table 4.

Table 4

Atomic Co-ordinates and Their Estimated Standard Deviations

(Anisotropic temperature factors are expressed as exp $(-b_{11}h^2 - b_{22}k^2 - b_{33}l^2 - b_{12}hk - b_{13}kl - b_{23}kl)$. The b_{ij}'s are multiplied by 10^4. The estimated standard deviations are given in parentheses and correspond to the last significant decimal place.)

	x/a	y/b	z/c	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	0.4329(2)	0.5729(4)	0.2462(6)	9(1)	65(6)	67(12)	8(6)	22(8)	−4(16)
C(2)	0.4081(2)	0.6420(5)	0.3731(7)	11(1)	81(7)	149(16)	9(7)	−1(9)	−45(20)
C(3)	0.3476(2)	0.6822(4)	0.3173(6)	13(1)	44(5)	104(12)	12(5)	19(8)	0(16)
N(4)	0.3321(1)	0.6013(3)	0.1533(5)	9(1)	36(4)	92(10)	8(4)	17(7)	−2(12)
C(5)	0.3039(2)	0.6647(4)	−0.0084(7)	13(1)	67(6)	141(15)	−2(6)	5(9)	11(19)
C(6)	0.3556(2)	0.7223(5)	−0.1090(7)	14(2)	80(7)	155(16)	−3(7)	11(10)	−44(20)
C(7)	0.4047(2)	0.6283(4)	−0.1035(6)	11(1)	51(5)	104(13)	4(6)	7(8)	−1(16)
C(8)	0.3923(2)	0.5574(4)	0.0794(6)	9(1)	43(5)	97(11)	14(5)	9(8)	3(15)
C(9)	0.4912(2)	0.5079(4)	0.2674(7)	13(1)	70(6)	133(15)	6(6)	4(9)	13(19)
O(10)	0.5389(1)	0.5817(3)	0.1934(4)	12(1)	53(4)	152(11)	7(4)	−2(6)	20(13)
C(11)	0.5876(2)	0.5274(4)	0.1321(7)	13(1)	67(6)	191(17)	−2(6)	−7(9)	−41(19)
O(12)	0.5939(2)	0.4236(4)	0.1358(9)	18(1)	58(5)	435(25)	−1(5)	30(11)	33(22)
C(13)	0 6361(2)	0.6116(4)	0.0583(7)	10(1)	59(6)	145(15)	3(6)	20(9)	−32(18)
C(14)	0.6970(2)	0.5571(6)	0.0894(10)	14(2)	90(8)	274(21)	−3(7)	−3(11)	41(23)
O(15)	0.6307(2)	0.7184(3)	0.1529(5)	16(1)	80(5)	155(11)	−1(5)	5(7)	−9(14)
C(16)	0.6246(2)	0.6404(4)	−0.1613(7)	10(1)	40(5)	128(14)	5(5)	7(8)	21(16)
O(17)	0.6699(1)	0.7210(3)	−0.2137(5)	10(1)	48(4)	155(11)	15(4)	15(6)	−14(12)
C(18)	0.6333(2)	0.5373(5)	−0.2894(8)	19(2)	78(7)	228(19)	−7(7)	−7(11)	−52(22)
C(19)	0.5628(2)	0.7023(4)	−0.1865(6)	13(1)	41(5)	106(13)	−4(5)	7(8)	14(16)
C(20)	0.5569(2)	0.7619(4)	−0.3824(7)	16(2)	83(7)	131(16)	−17(7)	46(10)	−46(22)
C(21)	0.5083(2)	0.6256(4)	−0.1668(6)	11(1)	40(5)	72(12)	5(5)	12(8)	16(15)
O(22)	0.5037(2)	0.5256(3)	−0.2157(6)	14(1)	56(4)	166(14)	−5(4)	31(7)	5(15)
O(23)	0.4613(1)	0.6870(3)	−0.1034(4)	11(1)	53(4)	106(10)	7(4)	5(6)	−24(11)
O(24)	0.2962(1)	0.5127(3)	0.2218(5)	12(1)	49(4)	117(9)	−1(4)	16(6)	6(12)
O(25)	0.1776(1)	0.5480(3)	0.1153(5)	15(1)	83(5)	149(11)	−18(4)	16(7)	37(14)
O(26)	0.7156(2)	0.7843(3)	0.4143(5)	18(1)	86(5)	154(11)	−6(5)	12(7)	−4(14)

(to be continued)

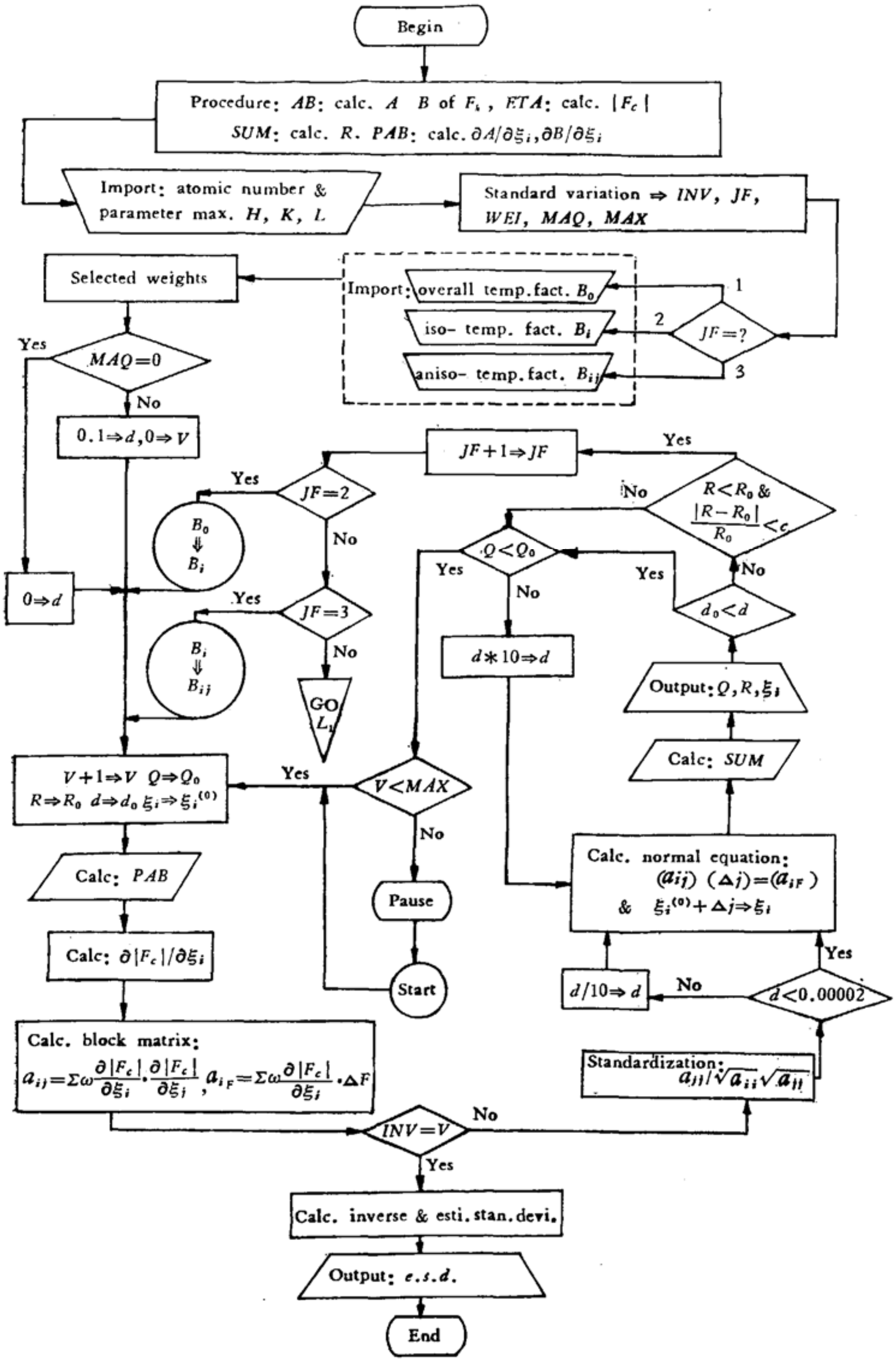

Fig. 2. A simplified flow-diagram of (GCLS-BLOCK) (ALGOL-60).

Table 4 (Continued)

(The isotropic temperature factors are of the form $\exp(-B \sin^2\theta/\lambda^2)$ with B values expressed in Å^2).

	x/a	y/b	z/c	B
H(2)	0.4242	0.6831	0.4863	3.4
H(3A)	0.3478	0.7473	0.2570	2.8
H(3B)	0.3235	0.7063	0.4175	2.8
H(5A)	0.2750	0.7199	0.0417	3.2
H(5B)	0.2827	0.6273	−0.0467	3.2
H(6A)	0.3631	0.7875	−0.0488	3.3
H(6B)	0.3437	0.7750	−0.2268	3.3
H(7)	0.3989	0.5538	−0.2357	2.5
H(8)	0.3766	0.4652	0.0625	2.5
H(9A)	0.5021	0.4656	0.4051	3.4
H(9B)	0.5016	0.4278	0.1583	3.4
H(14A)	0.7005	0.4750	0.0395	4.7
H(14B)	0.7387	0.5737	0.0667	4.7
H(14C)	0.7113	0.5250	0.2292	4.7
H(15)	0.6682	0.7272	0.2000	3.6
H(17)	0.6916	0.7770	−0.1650	3.0
H(18A)	0.6727	0.5250	−0.2983	3.6
H(18B)	0.6208	0.5625	−0.3917	3.6
H(18C)	0.6071	0.4750	−0.2458	3.6
H(19)	0.5678	0.7722	−0.0735	2.5
H(20A)	0.5594	0.7200	−0.4492	3.5
H(20B)	0.5194	0.7807	−0.4150	3.5
H(20C)	0.5833	0.8057	−0.3550	3.5
H(25A)	0.2227	0.5410	0.1250	3.4
H(25B)	0.1858	0.5000	−0.0517	3.4
H(26A)	0.6833	0.7962	−0.4583	3.8
H(26B)	0.7057	0.8482	−0.5941	3.8

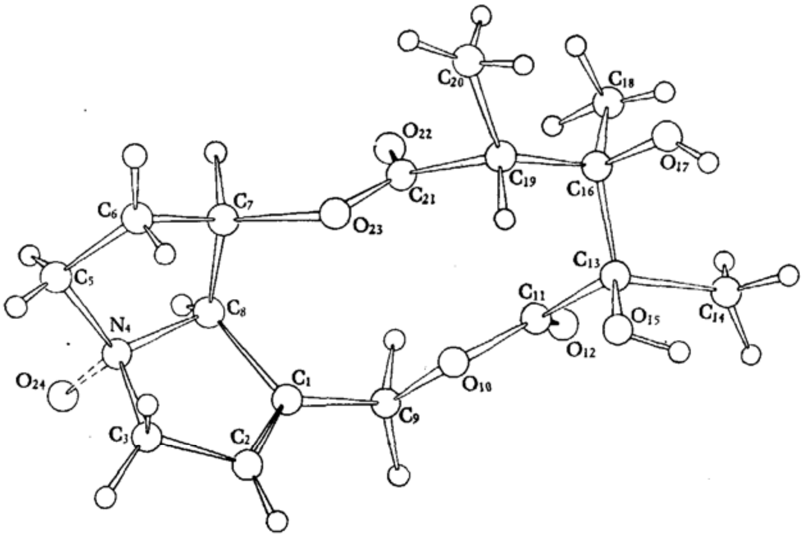

Fig. 3. Perspective view of the structure of monocrotaline-N-oxide, showing the numbering scheme of atoms.

Table 5

Bond Lengths (Å) in the Crystal Structure of Monocrotaline-N-Oxide (The estimated standard deviations are given in parentheses and correspond to the least significant figure).

C(1)—C(2)	1.317(7)	C(11)—O(12)	1.204(7)
C(1)—C(8)	1.491(6)	C(11)—C(13)	1.542(7)
C(1)—C(9)	1.508(6)	C(13)—C(14)	1.514(7)
C(2)—C(3)	1.481(6)	C(13)—O(15)	1.404(6)
C(3)—N(4)	1.521(6)	C(13)—C(16)	1.596(7)
N(4)—C(5)	1.488(6)	C(16)—O(17)	1.422(5)
N(4)—C(8)	1.528(5)	C(16)—C(18)	1.502(7)
C(5)—C(6)	1.507(7)	C(16)—C(19)	1.563(6)
C(6)—C(7)	1.542(7)	C(19)—C(20)	1.541(7)
C(7)—C(8)	1.546(6)	C(19)—C(21)	1.512(6)
C(7)—O(23)	1.433(5)	C(21)—O(22)	1.206(6)
C(9)—O(10)	1.459(5)	C(21)—O(23)	1.341(5)
O(10)—C(11)	1.328(5)	O(24)—N(4)	1.384(4)

Tabel 6

Bond Angles (°) in the Crystal Structure of Monocrotaline-N-Oxide (The estimated standard deviations are given in parentheses and correspond to the least significant figure).

C(9)—C(1)—C(2)	126.6(4)	O(10)—C(11)—C(13)	112.8(4)
C(9)—C(1)—C(8)	122.9(4)	O(12)—C(11)—C(13)	123.3(4)
C(8)—C(1)—C(2)	110.3(4)	C(11)—C(13)—O(15)	109.4(4)
C(1)—C(2)—C(3)	113.2(4)	C(11)—C(13)—C(14)	108.7(4)
C(2)—C(3)—N(4)	102.5(4)	C(14)—C(13)—O(15)	111.9(4)
C(3)—N(4)—C(5)	111.8(3)	C(14)—C(13)—C(16)	111.7(4)
C(3)—N(4)—O(24)	108.8(3)	C(11)—C(13)—C(16)	110.0(4)
O(24)—N(4)—C(5)	112.5(3)	O(15)—C(13)—C(16)	105.1(4)
C(3)—N(4)—C(8)	105.0(3)	C(13)—C(16)—O(17)	105.7(4)
C(5)—N(4)—C(8)	106.0(3)	C(13)—C(16)—C(19)	110.3(4)
O(24)—N(4)—C(8)	112.6(4)	C(13)—C(16)—C(18)	113.1(4)
N(4)—C(5)—C(6)	104.5(4)	O(17)—C(16)—C(19)	107.4(4)
C(5)—C(6)—C(7)	102.9(4)	O(17)—C(16)—C(18)	105.7(4)
C(6)—C(7)—C(8)	105.3(4)	C(18)—C(16)—C(19)	114.1(4)
C(6)—C(7)—O(23)	107.2(4)	C(16)—C(19)—C(20)	112.4(4)
C(8)—C(7)—O(23)	114.0(4)	C(16)—C(19)—C(21)	115.7(4)
C(7)—C(8)—C(1)	118.6(4)	C(20)—C(19)—C(21)	105.8(4)
C(7)—C(8)—N(4)	105.3(3)	C(19)—C(21)—O(22)	126.9(4)
C(1)—C(8)—N(4)	103.3(3)	C(19)—C(21)—O(23)	110.6(4)
C(1)—C(9)—O(10)	107.8(4)	O(22)—C(21)—O(23)	122.1(4)
C(9)—O(10)—C(11)	116.0(4)	C(21)—O(23)—C(7)	116.2(3)
O(10)—C(11)—O(12)	123.9(5)		

IV. DISCUSSION

The bond lengths of monocrotaline -N-oxide are listed in Table 5, and bond angles in Table 6. The geometry in monocrotaline -N-oxide (see Fig. 3) is very similar to that in monocrotaline[9] and in fulvine[2].

(1) *Description of the structure*

1) The unsaturated five membered ring and atom C(6) are at the same side of the plane defined by atoms N(4), C(5) and C(7). Hence, the pyrrolizidine nucleus of monocrotaline-N-oxide exists in the endo-puckered form, with a puckering angle of 44.5° between the planes defined by atoms C(5), C(6), C(7) and N(4), C(5), C(8). This configuration is different from monocrotaline, in which the pyrrolizidine nucleus is exo-puckered.

2) The angle between the least-squares planes defined by atoms C(1), C(2), C(3), N(4), C(8) and N(4), C(5), C(7), C(8) of pyrrolizidine nucleus is 116°.

3) The bond length of N(4)—C(8) is 1.528 Å, which is longer than that in monocrotaline (1.491Å) and other pyrrolizidine alkaloids. It results from the influence of the dative bond between N(4)—O(24).

4) The carbonyl bonds of the ester functions are directed above the plane of the macroring, or syn-parallel. This conformation is the same as that in fulvine but different from that in jacobine. The distance between the carbonyl groups is 3.394 Å.

The angle between the two lactone planes C(9)—O(10)—C(11)=O(12) and C(7)—O(23)—C(21)=O(22) is 24° in monocrotaline-N-oxide, comparing with 9° in fulvine. It results in a longer distance between these two carbonyl groups. However, the trans-annular O(10) ... C(21) in monocrotaline-N-oxide is shorter, 2.665 Å.

5) Both hydroxyl groups on the asymmetry carbon atoms are on the same side of plane of the macroring.

As shown in Fig. 4, the configuration at C(13) and C(16) is the same as that at both monocrotaline-N-oxide and monocrotaline. Monocrotaline-N-oxide and jacobine have the same configurations at C(13) but different configurations at C(16).

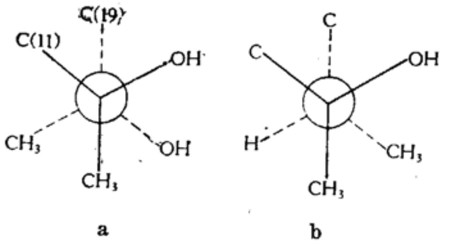

Fig. 4. Projections down the C(13)—C(16) bond (the numbering scheme refers to that of monocrotaline-N-oxide).
(a) monocrotaline-N-oxide and monocrotaline, (b) jacobine.

(2) *Crystal packing*

Fig. 5 is the *b*-axis projection of the molecular packing. As it is shown, the molecules are linked by hydrogen bond via the water molecules. A pair of hydrogen bonds are formed between O(25) and O(24) of the two neighbouring molecules and arranged in helices around the twofold screw axes parallel to C-axis at $x=1/4$, $y=0$ and $x=3/4$, $y=1/2$ in the unit cell. The distances between O(25) and two neighbouring O(24) are 2.774 Å and 2.905 Å respectively.

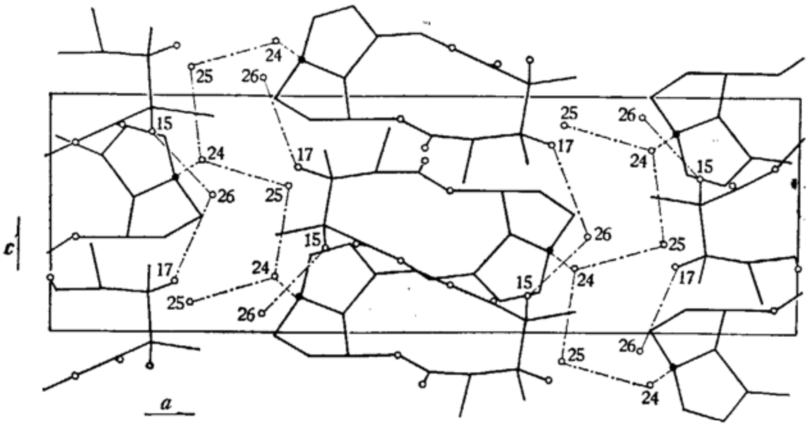

Fig. 5. The b-axis projection of monocrotaline-N-oxide molecular packing.

Another pair of hydrogen bonds are formed between O(26) and O(15) in one molecule and between O(26) and O(17) in the molecule translated one unit cell away in the C direction. The distance between O(26) and O(15) is 2.745 Å and between O(26) and O(17) 2.895 Å.

The authors would like to thank Chen Peixun and Wu Bomu for providing the beautiful crystals, and collecting data on a Philips diffractometer respectively.

REFERENCES

[1] Fridrichsons, J., Mathieson, A. McL. & Sutor, D. J., *Acta Cryst.*, **16**(1963), 1075.
[2] Sussman, J. L. & Wodak, S. J., *ibid.*, **B29**(1973), 2918.
[3] Wodak, S. J., *ibid.*, **B31**(1975), 569.
[4] Stoeckli-Evans, H. & Crout, D. H. G., *Helvetica Chimica Acta*, **59**(1976), 2168.
[5] 王守道,科学通报, **23** (1978), 670—672.
[6] 王守道,同上, **24** (1979), 1023—1026.
[7] 王守道,同上, **24** (1979), 1115—1118.
[8] 王守道,胡宁海,同上, **25** (1980), 1071—1074.
[9] 王守道,中国科学, (1980), 1183—1192.
[10] Ahemd, A. R., *Crystallographic Computing Techniques*, Munksgaard, Copenhagan, (1976), 52.
[11] 王守道,江建生,化学通报, (1981) No. 4, 12—14.
[12] 王守道,徐森根,同上, (1980) No. 8 17—19.