

### 130. The Crystal Structure of 1,2-Didehydrocrotalanine Picrate: A Macrocyclic Pyrrolizidine Alkaloid Analogue

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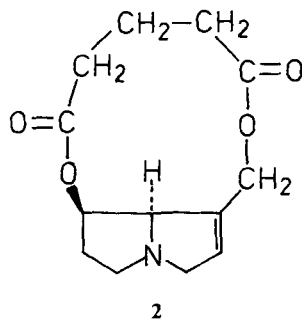
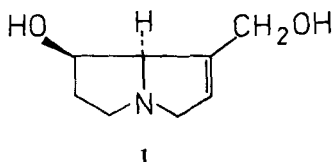
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#### Summary

1,2-Didehydrocrotalanine (**2**) is the first synthetic macrocyclic pyrrolizidine alkaloid analogue to be studied by X-ray crystallography. The crystal structure was solved by multiresolution direct methods and refined by full-matrix least-squares to  $R=0.036$  for 693 reflections. The alkaloid analogue has an 11-membered macrocycle containing two ester groups with their carbonyl groups nearly antiparallel.

**Introduction.** – The present analysis continues our structural studies of pyrrolizidine alkaloids whose structure and/or toxicity is of particular interest [1–5]. Pyrrolizidine alkaloids frequently occur naturally as macrocyclic diesters in which a pyrrolizidine diol (necine) is esterified with a diacid to produce 11-, 12-, 13- or 14-membered rings [6] [7]. Retronecine (**1**) is the most common necine and its macrocyclic diesters are hepatotoxic [8]. About 25 naturally occurring 11-membered pyrrolizidine alkaloids have been isolated, but synthesis of these macrocyclic diesters has proved difficult [9]. Recently, *Robins* and co-workers [10] have synthesised one natural and six unnatural 11-membered macrocyclic diesters from (+)-



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retronecine and substituted glutaric anhydride derivatives. Here we report on the crystal structure of one of the unnatural pyrrolizidine alkaloids 1,2-didehydrocrotalanine (**2**).

**Experimental.** – The pyrrolizidine alkaloid analogue **2** was prepared as an oil and characterized as a picrate [10]. Crystals were difficult to obtain. Eventually small but suitable crystals were grown by slow evaporation of an EtOH-solution.

**Crystal Data.**  $C_{13}H_{18}O_4N^+ \cdot C_6H_2O_7N_3^-$ , Mol. Weight 480.4, space group  $P2_12_12_1$ ,  $a = 15.28$  (1),  $b = 7.50$  (1),  $c = 18.651$  (6) Å,  $V = 2137.4$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.491$  Mg/m<sup>3</sup>,  $MoK\alpha$ ,  $\lambda = 0.7107$  Å,  $\mu = 0.81$  cm<sup>-1</sup>. Two crystals of similar dimensions (0.1 × 0.2 × 0.2 mm) were used for data collection. Preliminary Weissenberg and precession photographs indicated the crystals to be orthorhombic, space group  $P2_12_12_1$ . Intensity data for layers with  $k = 0-5$  and  $l = 0-10$  and with  $\theta < 25^\circ$  were measured on a Stoe STADI-2 two-circle diffractometer (graphite-monochromated  $MoK\alpha$ -radiation) using the variable  $\omega$ -scan technique [11]. Only 696 unique reflections could be considered observed [ $I > 1.5\sigma(I)$ ]. The structure was solved by multisolution direct methods using MULTAN-78 [12]. All other calculations were carried out using the SHELX-76 system [13]. In the final cycles of least-squares refinement H-atoms were included at calculated positions (C–H 1.08 Å), with an overall isotropic thermal parameter (final value  $U = 0.10$  Å<sup>2</sup>). Weighted anisotropic full-matrix least-squares refinement for 693 reflections (3 reflections suffering from extinction were removed) converged at  $R = 0.036$ ,  $R_w = 0.032$ ,  $w = 1.575/[\sigma^2(F_o) + 0.0005(F_o)^2]$ . In the final cycle the average parameter shift was less than 0.5 e.s.d. A final difference map showed no significant residual density.

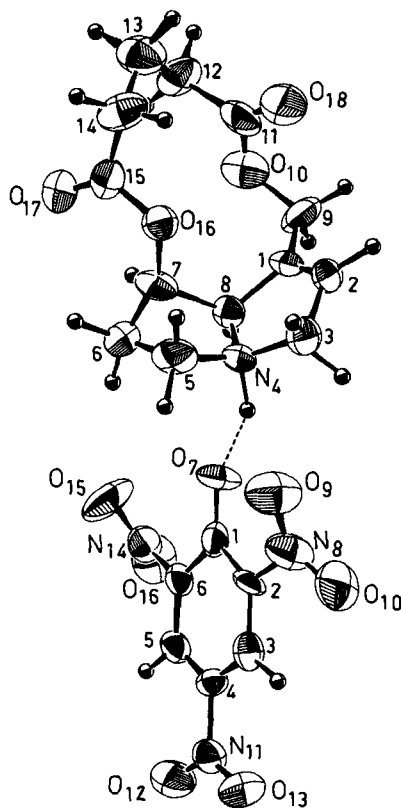


Figure. View of the molecule showing the atomic numbering and vibrational ellipsoids (50% probability level [14]). Symmetry operation to picrate-ion atomic coordinates in Table 1 is  $(1+x, y, z)$ .

**Discussion.** – Final positional and thermal parameters are given in *Table 1*. The *Figure* shows how the picrate ion and the alkaloid analogue are linked through the phenolic O-atom, O(7), of the picrate and the N-atom, N(4), of the alkaloid analogue. [O(7)...N(4), 2.664(5) Å; O(7)...H(4), 1.684(5) Å, angle O(7)...H(4)–N(4), 148.3(4)°]. The dimensions of the picrate ion are normal. The ring angle at C(1) is typically low at 110.1(5)° and the bonds C(1)–C(2) and C(1)–C(6) are long, 1.453(9) and 1.442(10) Å, respectively. C(1)-atom is displaced by 0.03 Å from the mean-

Table 1. *Final positional parameters* ( $\times 10^4$ ) *and equivalent isotropic thermal parameters* ( $\times 10^4$ ), *with e.s.d.'s in parentheses*

$$U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* \bar{a}_i \cdot \bar{a}_j$$

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>U<sub>eq</sub></i>
a) Picrate ion				
C(1)	5798 (4)	4957 (8)	2349 (4)	500 (28)
C(2)	5048 (4)	4737 (8)	1878 (3)	427 (25)
C(3)	4207 (4)	4545 (8)	2107 (4)	471 (30)
C(4)	4031 (3)	4498 (8)	2829 (4)	393 (27)
C(5)	4689 (4)	4618 (8)	3350 (4)	488 (29)
C(6)	5524 (4)	4851 (8)	3088 (4)	455 (28)
O(7)	6563 (2)	5281 (7)	2163 (2)	601 (20)
N(8)	5174 (5)	4729 (12)	1101 (4)	729 (33)
O(9)	5879 (4)	4280 (9)	874 (3)	905 (27)
O(10)	4550 (4)	5120 (9)	715 (3)	961 (30)
N(11)	3126 (4)	4228 (9)	3084 (5)	564 (30)
O(12)	3020 (3)	4057 (9)	3725 (3)	804 (26)
O(13)	2550 (3)	4115 (9)	2629 (3)	799 (25)
N(14)	6215 (5)	5036 (10)	3618 (4)	590 (30)
O(15)	6869 (4)	4133 (10)	3581 (3)	1076 (30)
O(16)	6124 (4)	6129 (9)	4102 (3)	908 (30)
b) 1,2-didehydrocrotalanine (2)				
C(1)	– 1054 (4)	7031 (10)	931 (5)	427 (28)
C(2)	– 1511 (5)	6964 (10)	338 (4)	466 (30)
C(3)	– 2275 (5)	5747 (10)	410 (4)	571 (32)
N(4)	– 2209 (3)	5004 (8)	1155 (3)	448 (24)
C(5)	– 2100 (5)	3031 (10)	1208 (5)	668 (37)
C(6)	– 1549 (5)	2818 (11)	1880 (4)	665 (35)
C(7)	– 880 (4)	4249 (11)	1788 (4)	560 (31)
C(8)	– 1418 (4)	5878 (10)	1529 (4)	434 (28)
C(9)	– 317 (4)	8344 (10)	1079 (5)	743 (36)
O(10)	478 (4)	7383 (7)	3110 (3)	724 (25)
C(11)	958 (6)	6636 (11)	809 (6)	667 (44)
C(12)	1726 (4)	5566 (11)	1106 (4)	748 (36)
C(13)	1835 (5)	3766 (11)	757 (5)	855 (41)
C(14)	1034 (5)	2582 (11)	734 (5)	726 (37)
C(15)	449 (6)	2837 (11)	1404 (5)	560 (38)
O(16)	– 280 (3)	3767 (6)	1214 (2)	539 (19)
O(17)	587 (3)	2295 (8)	1988 (3)	828 (25)
O(18)	804 (4)	6813 (9)	169 (3)	951 (29)

plane through the other five atoms. O(7)-atom is displaced by 0.14 Å from this plane, but forms a good mean-plane with C(1) and its two adjoining C-atoms. The two adjacent NO<sub>2</sub>-groups are considerably tilted from the ring mean-plane; 24.3° for group N(8), with distance O(7)...O(9) of 2.727(7) Å, and 50.6° for group N(14) with distance O(7)...O(15) of 2.820(7) Å. Group N(11) is tilted by only 5.1°.

The absolute configuration of retronecine (**1**) being known [10], the *Figure* and the atomic coordinates (*Table 1*) correspond to the absolute configuration of the compound. Within experimental error the bond distances and angles differ little from those observed previously. The crystal structures of seven 11-membered macrocyclic retronecine-derived pyrrolizidine alkaloids have been determined so far [1] [2] [5] [15–18] and all but one, trichodesmine [17], have the ester carbonyl bonds directed to the same side of the plane of the macrocycle [5]. In the title compound **2**, and trichodesmine, the direction of the C(11)–O(18) bond is reversed (see the *Figure*).

The pyrrolizidine nuclei of all eight pyrrolizidine alkaloids exist in the *exo*-puckered form with C(6)-atom and the unsaturated five-membered ring on opposite sides of the plane defined by atoms N(4), C(5) and C(7). The puckering angle between planes defined by atoms C(5), C(6), C(7) and C(5), N(4), C(8) varies from 35° to 46° [here 44.3(2)°]. The angle between the least-squares planes defined by atoms C(1), C(2), C(3), N(4), C(8) and C(5), N(4), C(8), C(7) is 124.5(0)°, close to the average value for retronecine-derived pyrrolizidine alkaloids. The distance N(4)–C(8) is 1.542(8) Å, rather longer than the average value of 1.50(1) Å observed previously.

Some short intra- and intermolecular nonbonded distances are given in *Table 2*. In the title compound transannular distance C(11)...O(16) is the shorter, 2.96(1) Å, while in trichodesmine it is C(15)...O(10), 2.83(1) Å. This difference is reflected in four specific torsion angles in the macrocycle which are compared in *Table 3*. A similar difference is noted for the macrocycle torsion angles in fulvine [15] and monocrotaline [2] compared to those in axillarine [1], junceine [5] and incanine [16], see *Table 3*. In the first pair of alkaloids C(15)...O(10) distance is the shorter [average distance 2.79(5) Å], while in the latter three C(11)...O(16) distance is the shorter (average distance 2.93(7) Å).

Table 2. *Short Intra- and Intermolecular Distances* (Symmetry operations i)  $1-x, \frac{1}{2}+y, \frac{1}{2}-z$ ,  
ii)  $1 \times x, y, z$ )

Picrate		1,2-didehydrocrotalanine	
O(7)...N(8)	2.933 (8)	C(11)...O(16)	2.964 (10)
O(7)...O(9)	2.727 (7)	O(10)...O(16)	2.954 (7)
O(7)...N(14)	2.771 (8)	N(4)...O(16)	3.092 (7)
O(7)...O(15)	2.820 (7)		
O(7)...N(11) <sup>i</sup>	3.034 (7)		
O(7)...O(13) <sup>i</sup>	3.203 (7)		
Picrate...1,2-didehydrocrotalanine			
O(7)...N(4) <sup>ii</sup>	2.664 (5)	O(9)...N(4) <sup>ii</sup>	3.017 (5)
O(7)...H(4) <sup>ii</sup>	1.684 (5)	O(9)...H(4) <sup>ii</sup>	2.355 (5)

Table 3. *Macrocycle Torsion Angles* (°) (e.s.d.'s. for title compound *ca.* 0.6°, A = average values for junceine, axillarine and incanine, B = average values for fulvine and monocrotaline)

Torsion angles	Observed	Tricho-desmine	A	B
C(8)–C(1)–C(9)–O(10)	63.1	56.1	98.1	112.9
C(1)–C(9)–C(10)–C(11) <sup>a)</sup>	79.6	129.6	–104.9	–155.9
C(9)–O(10)–C(11)–C(12)	–175.8	–180.0	176.1	172.8
O(10)–C(11)–C(12)–C(13) <sup>a)</sup>	134.7	90.7	–125.2	–84.8
C(11)–C(12)–C(13)–C(14)	–52.1	–38.2	58.2	51.6
C(12)–C(13)–C(14)–C(15)	–33.9	–57.2	–81.2	–73.5
C(13)–C(14)–C(15)–O(16) <sup>a)</sup>	106.4	142.7	108.9	153.3
C(14)–C(15)–O(16)–C(7)	–175.6	–159.3	–174.0	–176.5
C(15)–O(16)–C(7)–C(8) <sup>a)</sup>	157.0	137.5	160.9	115.1
O(16)–C(7)–C(8)–C(1)	–21.6	–24.8	–22.4	–27.4
C(7)–C(8)–C(1)–C(9)	–75.9	–70.5	–64.7	–60.8

<sup>a)</sup> The four specific torsion angles which differ depending on whether transannular distance C(11)...O(16) or C(15)...O(10) is the shorter.

Tables of the final structure factors *etc.* may be obtained from the correspondence author. D.J.R. wishes to thank the *Science and Engineering Research Council* (U.K.) for financial support.

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