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Hygrophylline, $C_{18}H_{27}NO_6$: a Pyrrolizidine Alkaloid

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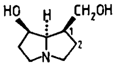
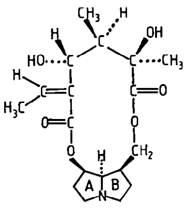
Abstract. $M_r = 353{\cdot}4$, orthorhombic, $P2_12_12_1$, $a = 8{\cdot}455\,(1)$, $b = 9{\cdot}367\,(1)$, $c = 22{\cdot}645\,(2)$ Å, $U = 1793{\cdot}4\,(2)$ Å^3, $Z = 4$, D_m(flotation) $= 1{\cdot}30\,(1)$, $D_x = 1{\cdot}309$ Mg m^{-3}, $\mu(\mathrm{Cu}\,K\alpha) = 0{\cdot}72$ mm^{-1}, $\lambda(\mathrm{Cu}\,K\alpha) = 1{\cdot}5418$ Å, $F(000) = 760$, $T = 289\,(1)$ K, $R = 0{\cdot}056$ for 1489 observed reflections. The pyrrolizidine nucleus adopts an *exo-endo* conformation and the conformation in the 12-membered macroring is essentially similar to its conformation in the hepatotoxic alkaloids. There are no unusual bond distances or angles.

Introduction. Hygrophylline was isolated from *Senecio hygrophyllus* Dyer and Sm. by Richardson & Warren (1943). The alkaloid on hydrolysis was found to yield the aminodiol platynecine (I) and a dicarboxylic acid identified from NMR and UV spectra and oxidation studies as [2*L*(or *R*),3*R*,4*R*]-2,4-dihydroxy-3-methylhept-*trans*-5-ene-2,5-dicarboxylic acid by Schlosser & Warren (1965) who consequently assigned the absolute structure (II) to (–)-hygrophylline. The alkaloids derived from platynecine are non-hepatotoxic. there being no double bond at the 1,2 position in the pyrrolizidine nucleus, and the X-ray analysis was undertaken to compare the conformational detail of a platynecine diester with that of the corresponding 12-membered-ring retronecine diesters.



(I)



(II)

Experimental. Colourless prismatic crystals from acetone; crystal *ca* 0·3 × 0·2 × 0·2 mm aligned on a Rigaku-AFC diffractometer; cell parameters determined by least squares from 2θ values for 25 strong reflections; 3 standard reflections, no significant intensity variation; Cu $K\alpha$ radiation (graphite-crystal monochromator); ω–2θ scan, 2θ scan rate 2° min^{-1}, scan range ($\Delta\omega$) $1{\cdot}2° + 0{\cdot}5°\tan\theta$, $2\theta_{\max} = 130°$; 1489 of the 1761 non-equivalent terms (h 0–9, k 0–10, l 0–26) with $I \geq 2{\cdot}5\sigma(I)$ used; intensities not corrected for absorption; four large terms apparently seriously affected by extinction omitted from final refinement; scattering factors for O, N and C from Cromer & Mann (1968), for H from Stewart, Davidson & Simpson (1965); anomalous-dispersion corrections with values of Cromer & Liberman (1970). Structure solved by direct methods with *SHELX*76 (Sheldrick, 1976). Apart from the H atoms of the methyl substituents at C(13) and C(20), which were included at idealized positions, and the H atom of the hydroxyl substituent at C(12), the H-atom sites were located on difference maps. Refinement, with anisotropic temperature factors given to the C, N and O atoms, and isotropic given to the H atoms, converged at $R = 0{\cdot}056$ and $R_w = 0{\cdot}058$; max. Δ/σ 0·03:1 for non-H atoms and 0·08:1 for H atoms; largest peaks on final difference map +0·28 and –0·32 e Å^{-3}; the function minimized was $\sum w(|F_o| - |F_c|)^2$, $w = (\sigma^2|F_o| + 0{\cdot}00005|F_o|^2)^{-1}$.

Discussion. Final atomic coordinates of the non-hydrogen atoms are given in Table 1,* and Fig. 1 which contains the atom numbering and Fig. 2 have been prepared from the output of *ORTEP* (Johnson, 1965). The molecular conformation is illustrated in Fig. 1, bond lengths and angles being given in Table 2 and selected torsional angles in Table 3.

The absolute molecular structure of (–)-hygrophylline (12*R*,13*R*,14*R*) illustrated in Fig. 1 (see also Table 3) has been assigned by comparison with that of platynecine. As in bulgarsinine (Stoeckli-Evans,

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* Lists of structure amplitudes, anisotropic temperature factors, H-atom parameters and short intermolecular contact distances have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39716 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Final atomic coordinates of the non-hydrogen atoms* ($\times 10^4$) *and equivalent isotropic temperature factors, with e.s.d.'s in parentheses*

$$B_{\rm eq} = 8\pi^2 U_{\rm eq} = \tfrac{8}{3}\pi^2 \textstyle\sum_i \sum_j U_{ij} a^*_i a^*_j \mathbf{a}_i . \mathbf{a}_j .$$

	x	y	z	$B_{\rm eq}$(Å^2)
C(1)	5080 (6)	−1883 (6)	4014 (3)	2·8 (2)
C(2)	4213 (8)	−1197 (6)	4537 (3)	3·2 (2)
C(3)	2508 (9)	−1735 (9)	4444 (3)	4·5 (2)
N(4)	2356 (5)	−2130 (5)	3827 (2)	3·0 (1)
C(5)	1116 (8)	−1401 (8)	3485 (4)	4·3 (2)
C(6)	1878 (6)	−864 (8)	2929 (3)	3·7 (2)
C(7)	3617 (6)	−610 (6)	3111 (2)	2·7 (2)
C(8)	3914 (6)	−1877 (6)	3518 (3)	2·6 (2)
C(9)	6774 (6)	−1411 (6)	3876 (3)	3·2 (2)
O(10)	6988 (4)	120 (4)	3831 (2)	2·7 (1)
C(11)	7439 (6)	792 (6)	4326 (2)	2·8 (2)
C(12)	7898 (6)	2359 (6)	4232 (2)	2·6 (2)
C(13)	6786 (6)	3093 (6)	3786 (2)	2·2 (2)
C(14)	5039 (6)	3077 (6)	4023 (2)	2·3 (2)
C(15)	3899 (6)	3208 (6)	3509 (2)	2·5 (2)
C(16)	3768 (6)	1928 (6)	3122 (2)	2·5 (2)
O(17)	3702 (4)	719 (4)	3445 (1)	2·5 (1)
C(18)	9646 (6)	2374 (9)	4014 (4)	3·8 (2)
C(19)	7303 (6)	4610 (6)	3635 (2)	3·4 (2)
C(20)	3098 (6)	4411 (6)	3402 (3)	3·0 (2)
C(21)	1974 (6)	4671 (6)	2893 (3)	4·3 (2)
O(22)	7534 (6)	199 (4)	4797 (2)	4·5 (1)
O(23)	7889 (5)	3065 (4)	4784 (2)	3·6 (1)
O(24)	4948 (5)	4203 (5)	4436 (2)	3·2 (1)
O(25)	3708 (6)	1951 (4)	2592 (2)	4·1 (1)

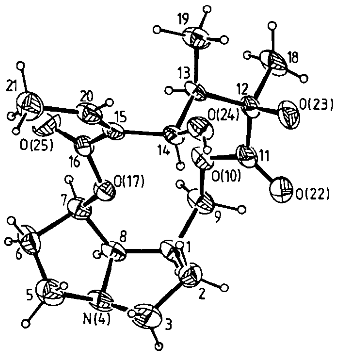

Fig. 1. Perspective view of the molecule with thermal ellipsoids scaled to 50% probability.

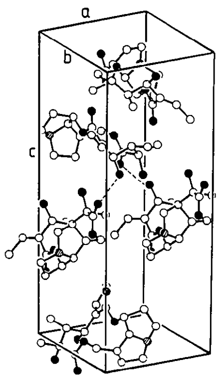

Fig. 2. The molecular packing.

1980), an alkaloid also derived from the aminodiol platynecine, the pyrrolizidine nucleus has ring *A* in an *exo* and ring *B* in an *endo* conformation. The *exo* ring has a pucker angle of 34·8 (4)° between planes defined by atoms C(5), C(6), C(7) and C(5), N(4), C(8) whilst the *endo* ring has a pucker angle of 158·5 (5)° between planes defined by atoms C(1), C(2), C(3) and C(3), N(4), C(8). In bulgarsinine the respective values are 34·3 (4) and 156·2 (5)°. The angle between the least-squares planes defined by atoms C(1), C(8), N(4), C(3) and C(5), N(4), C(8), C(7) of 127·7 (6)° is similar to the value of 126·8 (5)° in bulgarsinine.

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

C(1)–C(2)	1·533 (9)	C(11)–O(22)	1·205 (6)
C(1)–C(8)	1·497 (9)	C(12)–C(13)	1·541 (7)
C(1)–C(9)	1·531 (8)	C(12)–C(18)	1·558 (8)
C(2)–C(3)	1·542 (10)	C(12)–O(23)	1·414 (6)
C(3)–N(4)	1·451 (8)	C(13)–C(14)	1·573 (7)
N(4)–C(5)	1·471 (9)	C(13)–C(19)	1·525 (8)
N(4)–C(8)	1·510 (7)	C(14)–C(15)	1·517 (7)
C(5)–C(6)	1·501 (11)	C(14)–O(24)	1·410 (7)
C(6)–C(7)	1·546 (8)	C(15)–C(16)	1·489 (7)
C(7)–C(8)	1·523 (8)	C(15)–C(20)	1·337 (8)
C(7)–O(17)	1·459 (6)	C(16)–O(17)	1·349 (6)
C(9)–O(10)	1·449 (7)	C(16)–O(25)	1·201 (6)
O(10)–C(11)	1·341 (6)	C(20)–C(21)	1·514 (9)
C(11)–C(12)	1·533 (8)		

C(2)–C(1)–C(8)	105·2 (5)	C(11)–C(12)–C(13)	111·3 (4)
C(2)–C(1)–C(9)	119·0 (5)	C(11)–C(12)–C(18)	107·0 (4)
C(8)–C(1)–C(9)	117·4 (5)	C(11)–C(12)–O(23)	108·9 (4)
C(1)–C(2)–C(3)	101·9 (5)	C(13)–C(12)–C(18)	111·5 (5)
C(2)–C(3)–N(4)	107·3 (6)	C(13)–C(12)–O(23)	111·6 (4)
C(3)–N(4)–C(5)	116·8 (5)	C(18)–C(12)–O(23)	106·3 (5)
C(3)–N(4)–C(8)	109·2 (5)	C(12)–C(13)–C(14)	110·1 (4)
C(5)–N(4)–C(8)	107·7 (5)	C(12)–C(13)–C(19)	112·8 (4)
N(4)–C(5)–C(6)	106·9 (6)	C(14)–C(13)–C(19)	110·8 (4)
C(5)–C(6)–C(7)	103·7 (5)	C(13)–C(14)–C(15)	109·4 (4)
C(6)–C(7)–C(8)	101·4 (5)	C(13)–C(14)–O(24)	105·7 (4)
C(6)–C(7)–O(17)	108·4 (4)	C(15)–C(14)–O(24)	114·4 (5)
C(8)–C(7)–O(17)	110·1 (4)	C(14)–C(15)–C(16)	115·8 (4)
C(1)–C(8)–N(4)	103·1 (5)	C(14)–C(15)–C(20)	121·9 (5)
C(1)–C(8)–C(7)	124·5 (5)	C(16)–C(15)–C(20)	122·3 (5)
N(4)–C(8)–C(7)	105·0 (4)	C(15)–C(16)–O(17)	111·1 (4)
C(1)–C(9)–O(10)	114·7 (5)	C(15)–C(16)–O(25)	125·2 (5)
C(9)–O(10)–C(11)	116·2 (4)	O(17)–C(16)–O(25)	123·7 (5)
O(10)–C(11)–C(12)	113·9 (4)	C(7)–O(17)–C(16)	115·9 (4)
O(10)–C(11)–O(22)	122·9 (5)	C(15)–C(20)–C(21)	126·3 (5)
C(12)–C(11)–O(22)	123·2 (5)		

Table 3. *Torsional angles in the macrocyclic ring* (°); *e.s.d.'s are about* 0·5°

Atoms are represented by their identification number. Values for senecionine and anacrotine are included for comparison.

	Hygrophylline	Anacrotine	Senecionine
1–9–10–11	93·2	92·6	92·4
9–10–11–12	170·9	179·0	179·3
10–11–12–13	39·3	54·0	53·7
11–12–13–14	61·3	60·5	62·6
12–13–14–15	−156·5	−163·9	−161·6
13–14–15–16	71·6	62·5	56·8
14–15–16–17	43·0	46·4	58·5
15–16–17–7	−178·3	−172·6	−176·0
16–17–7–8	167·6	169·8	157·9
17–7–8–1	−37·6	−29·5	−27·9
7–8–1–9	−51·4	−75·3	−77·3
8–1–9–10	78·1	80·1	80·7

The conformation of the 12-membered macroring in hygrophylline is essentially similar to its conformation in the hepatotoxic alkaloids, for example senecionine (Mackay & Culvenor, 1982) and anacrotine (Mackay, Sadek & Culvenor, 1984) – see Table 3. Atoms in the primary ester groups, C(9), O(10), C(11), O(22), C(12) are coplanar within ±0·07 (1) Å. One H atom at C(9) lies closer to the ester plane than the other [torsional angle H(9*b*)–C(9)–O(10)–C(11) −22 (6)°] as noted in senecionine and anacrotine. However, unlike the situation in the latter, in which the α-OH substituent at C(12) lies almost in the ester plane, a twisting about the C(11)–C(12) bond results in a torsional angle O(22)–C(11)–C(12)–O(23) of −20 (5)° compared with the values −3·8 (3) and −3·4 (5)° in senecionine and anacrotine respectively. Atoms C(7), O(17), C(16), O(25), C(15) in the secondary ester are coplanar within ±0·02 (1) Å [torsional angles C(7)–O(17)–C(16)–C(15) −178·3 (5) and C(7)–O(17)–C(16)–O(25) 2·5 (5)°]. The angle between the planes defined by atoms H(7), C(7), O(17) and O(17), C(16), O(25), C(15) is 1·7 (5)° so that H(7) lies within the ester plane [the H(7)···O(25) distance is 2·45 (6) Å], whereas in anacrotine and senecionine H(7) does not lie within the ester plane; the comparable interplanar angles have the respective values 34 (3) and 68 (1)°. As observed in anacrotine, the unsaturated side chain C(15)=C(20)–C(21) is in a nearly *cis* arrangement with the carbonyl group [atoms C(14), C(15), C(20), C(21), C(16) coplanar within ±0·01 (1) Å], the torsional angle C(20)–C(15)–C(16)–O(25) of 40·5 (5)° being similar to the value 46·2 (3)° in senecionine but significantly different from the value 60·6 (5)° in anacrotine in which there is a greater twist about the C(15)–C(16) bond.

The carbonyl bonds of the ester functions in hygrophylline are antiparallel as observed in other alkaloids containing the 12-membered macroring. The angle between the bonds is 26·5 (6)° compared with the values of 14·0 (5)° in anacrotine and 16·8 (3)° in senecionine. The transannular distance O(10)···O(17) of 2·966 (5) Å is shorter than the distance in anacrotine [3·349 (6) Å] and in senecionine [3·293 (3) Å]; other close contacts within the macroring are O(10)···C(13) 2·792 (7), O(10)···C(14) 3·252 (7) and C(11)···C(14) 3·028 (8) Å. The O(23)···O(24) and O(22)···O(24) distances of 2·818 (6) and 2·701 (5) Å respectively are indicative of hydrogen bonding, but this could not be verified as the H atom of the hydroxyl substituent at C(12) was not located in the analysis.

The crystal packing is illustrated in Fig. 2. An intermolecular H bond involving the hydroxyl substituent at C(14) and the carbonyl O of the primary ester system of an adjacent molecule related by the twofold screw axis ($y = \frac{1}{4}$, $z = \frac{1}{2}$) links the molecules into helices along **a**. The O(24)···O(22), O(24)–H(24) and H(24)···O(22) distances are 2·738 (6), 0·66 (8) and 2·17 (6) Å and the angle O(24)–H(24)···O(22) is 145 (5)°. It is interesting to note that the N atom in the pyrrolizidine nucleus does not enter into hydrogen bonding in this crystal.

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Structure of the β Form of 2,4,6-Triphenyl-1,3,5-trithiane, $C_{21}H_{18}S_3$

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Abstract. $M_r = 366{\cdot}5$, monoclinic, $C2/c$, $a = 19{\cdot}711\ (4)$, $b = 9{\cdot}578\ (2)$, $c = 19{\cdot}459\ (4)$ Å, $\beta = 92{\cdot}09\ (2)°$, $V = 3671{\cdot}0$ Å^3, $Z = 8$, $D_x = 1{\cdot}326$, $D_m = 1{\cdot}323$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}7107$ Å, $\mu = 4{\cdot}12$ mm^{-1}, $F(000) = 1536$, $T = 296$ K, final $R = 0{\cdot}069$ for 4395 independent reflections. The trithiane ring, which

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