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ABSOLUTE CONFIGURATION OF THE PYRROLIZIDINE ALKALOID ACETYLGYNURAMINE

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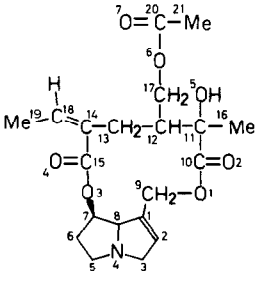
Key Word Index—*Gynura scandens*; Compositae; acetylgynuramine; pyrrolizidine alkaloid; absolute configuration; X-ray diffraction.

Abstract—The absolute configuration of the pyrrolizidine alkaloid acetylgynuramine was determined by X-ray diffraction to be (−)-(1a*R*,6b*R*,10*R*,11*S*)-9,14-dioxo-10-hydroxy-13-*cis*-ethylidene-11-methoxyacetyl-10-methyl-1a,2,3,6b-tetrahydro-5*H*-pyrrolizino-(1a,6b,6a,b,c)-1,8-dioxa-cyclododecane.

INTRODUCTION

From *Gynura scandens* two new pyrrolizidine alkaloids (PA), gynuramine and acetylgynuramine, have been isolated [1]. Structural analysis has been carried out by spectroscopic methods. On account of the elucidated structures these PAs can be classified as hepatotoxic, the double bonds between C-1 and C-2 in the necic ring and in the acid part of both molecules, and the esterification of O-1 and O-3 particularly indicating such effects [2].

Because *G. scandens* is used as a medicinal herb in Africa, and because of the many reported intoxications with PAs [2–10], we decided to determine the absolute configuration of acetylgynuramine, **1**, in order to relate structure and toxicity by comparing its structure with those of already known hepatotoxic PAs.



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RESULTS AND DISCUSSION

The specimen selected for X-ray diffraction was recrystallized from acetone. The colourless crystal showed an irregular shape with maximum diameter of 0.4 mm. Mp 154°; $[\alpha]_D^{20} - 33°$ ($CHCl_3$). From Weissenberg photographs and single crystal diffractometry the crystallographic data were determined to: orthorhomic, $a = 10.325$ (3) Å; $b = 11.407$ (5) Å; $c = 17.303$ (5) Å; $V = 2037.9$ Å^3; space group $P2_12_12_1$; $Z = 4$; $D_x = 1.28$ g/cm^3; $\mu MoK_\alpha = 0.1$ mm^{-1}.

The intensity measurements were carried out on an automatic four circle diffractometer (SYNTEX $P2_1$) in the w-mode using graphite monochromated MoK_α radiation ($\lambda = 0.7107$ Å). The scan angle was 2°, the scan speed variable between 3 and 20°/min, and the time for the peak count equalled the time spent for background determination. One standard reflexion was remeasured after every 33 records. Up to a maximum angle of $2\theta = 50°$ 2070 unique reflections were measured of which 1112 were regarded unobserved ($I < 3\sigma(I)$).

The structure was solved by use of the direct method program MULTAN [11] and refined by full matrix least squares calculations. In the final stage of refinement the positions of 18 hydrogen atoms being accessible from chemical considerations were calculated, and the hydrogens were included in the model. The inclusion of the methyl group hydrogens was regarded unnecessary. Refining all atomic positions, anisotropic temperature factors for the heavy atoms, and isotropic ones for the hydrogen atoms the final R-values obtained were: $R_{overall} = 0.133$, $R_{omitting\ unobserved} = 0.053$; $R_w = 0.070$, $R_{w,o.u.} = 0.050$. The atomic co-ordinates are given in Table 1, the resulting bond distances and angles in Table 2.

Structure **2** shows the ORTEP drawing [12] of the molecule. The results of this analysis establishes the absolute configuration of acetylgynuramine as a (−)-(1a*R*, 6b*R*, 10*R*, 11*S*)-9,14-dioxo-10-hydroxy-13-*cis*-ethylidene-11-methoxyacetyl-10-methyl-1a, 2, 3, 6b-tetrahydro-5*H*-pyrrolizino-(1a, 6b, 6a, b, c)-1,8-dioxa-cyclododecane. The saturated five-membered ring of the PA-nucleus (named retronecine) displays half-chair configuration corresponding to the exopuckered form [13]. The puckering angle between the planes formed by the atoms C-6–C-7–C-8 and C-5–C-8-N is 149.2°. Other PAs with the retronecine nucleus show similar corresponding angles: axillarine, 148° [14]; monocrotaline, 155.2° [15]; seneciphylline, 149.6° [16]; doronenine, 147.2° [17]. The angle between the planes formed by the atoms C-1–C-3–C-8–N and C-5–C-7–C-8–N of 126.1° is also similar to those in the above mentioned PAs.

Compared to the results of the earlier investigated doronenine [17], the bond lengths in the fragment

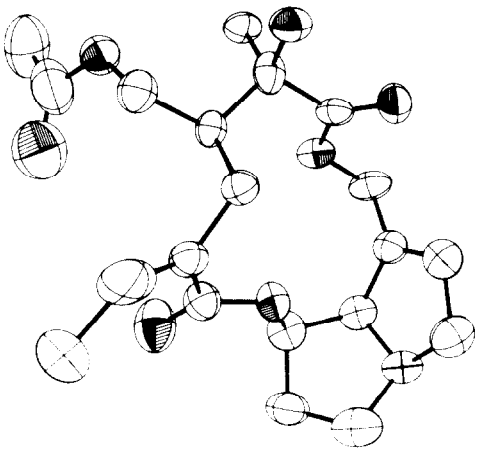

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Table 1. Fractional atomic co-ordinates (× 10^4) with s. d. (× 10^4) of acetylgynuramine

	x	*y*	*z*
C-1	4960 (9)	7550(7)	2603(4)
C-2	5908 (8)	8258(8)	2389(5)
C-3	6069 (10)	8268(9)	1535(6)
C-5	4375 (12)	7630(9)	577(6)
C-6	3065 (10)	7100(9)	778(5)
C-7	2997 (8)	7275(6)	1645(5)
C-8	4377 (8)	6968(6)	1900(5)
C-9	4551 (10)	7253(8)	3396(5)
C-10	3796 (8)	9072(5)	3928(7)
C-11	2599 (8)	9767(6)	4190(4)
C-12	1632 (7)	9876(6)	3505(4)
C-13	2260 (8)	10425(7)	2782(5)
C-14	1461 (7)	10126(7)	2076(4)
C-15	1568 (8)	8887(7)	1793(4)
C-16	2008 (8)	3136(7)	4908(4)
C-17	462 (9)	10646(7)	3709(6)
C-18	657 (9)	10888(8)	1747(5)
C-19	−274 (9)	10667(9)	1086(5)
C-20	−1305 (9)	9403(9)	3983(7)
C-21	−2079 (10)	8828(10)	4641(7)
N	5228 (6)	7330(5)	1249(4)
O-1	3462 (5)	8015(4)	3652(3)
O-2	4902 (6)	9401(5)	3980(3)
C-3	2785 (5)	8505(4)	1847(3)
O-4	678 (6)	8304(5)	1574(4)
O-5	2999 (5)	10885(4)	4448(3)
O-6	−376 (5)	10066(5)	4255(3)
O-7	−1471 (7)	9284(8)	3297(5)

Table 2. Interatomic distances (Å) and angles (°) with s. d. (× 10^3) of acetylgynuramine

C-1–C-2: 1.322 (12)
C-2–C-3: 1.488 (14)
C-3–N: 1.464 (12)
N–C-5: 1.499 (12)
C-5–C-6: 1.522 (16)
C-6–C-7: 1.516 (12)
C-7–C-8: 1.531 (12)
C-7–O-3: 1.462 (9)
C-8–C-1: 1.510 (11)
N–C-8: 1.487 (10)
C-1–C-9: 1.475 (12)
C-9–O-1: 1.489 (11)
O-1–C-10: 1.342 (9)
C-10–O-2: 1.205 (10)
C-10–C-11: 1.537 (11)
C-11–C-12: 1.555 (11)
C-11–C-16: 1.561 (11)
C-11–O-5: 1.413 (9)
C-12–C-13: 1.543 (11)
C-12–C-17: 1.535 (11)
C-13–C-14: 1.513 (11)
C-14–C-15: 1.499 (11)
C-14–C-18: 1.331 (12)
C-15–O-3: 1.334 (9)
C-15–O-4: 1.195 (10)
C-17–O-6: 1.441 (11)
C-18–C-19: 1.513 (13)
C-20–C-21: 1.538 (16)
C-20–O-6: 1.309 (12)
C-20–O-7: 1.206 (16)

C-8–C-1–C-2: 109.82 (720)
C-8–C-1–C-9: 122.24 (730)
C-2–C-1–C-9: 127.75 (800)
C-1–C-2–C-3: 111.42 (790)
C-2–C-3–N: 105.24 (770)
C-3–N–C-8: 107.39 (650)
C-3–N–C-5: 116.32 (700)
C-5–N–C-8: 107.70 (690)
N–C-5–C-6: 104.73 (730)
C-5–C-6–C-7: 102.39 (740)
C-6–C-7–C-8: 102.26 (690)
C-6–C-7–O-3: 111.69 (640)
O-3–C-7–C-8: 106.88 (600)
C-7–C-8–C-1: 120.10 (680)
C-7–C-8–N: 105.54 (620)
C-1–C-8–N: 104.56 (640)
C-1–C-9–O-1: 111.06 (680)
C-9–O-1–C-10: 115.91 (610)
O-1–C-10–O-2: 123.38 (720)
O-1–C-10–C-11: 111.22 (640)
O-2–C-10–C-11: 125.36 (690)
C-10–C-11–C-16: 108.15 (600)
C-10–C-11–C-12: 109.45 (600)
C-10–C-11–O-5: 108.92 (620)
C-12–C-11–O-5: 110.86 (580)
C-12–C-11–C-16: 113.13 (620)
C-16–C-11–O-5: 106.20 (590)
C-11–C-12–C-13: 112.41 (620)
C-11–C-12–C-17: 112.11 (640)
C-13–C-12–C-17: 106.54 (630)
C-12–C-13–C-14: 109.52 (640)
C-13–C-14–C-15: 115.85 (640)
C-13–C-14–C-18: 122.55 (720)
C-15–C-14–C-18: 121.50 (710)
C-14–C-15–O-3: 110.79 (620)
C-14–C-15–O-4: 124.76 (710)
O-3–C-15–O-4: 124.41 (700)
C-15–O-3–C-7: 116.01 (580)
C-11–O-5–H: 103.16 (6330)
C-12–C-17–O-6: 111.12 (660)
C-17–O-6–C-20: 117.99 (750)
O-6–C-20–C-21: 111.17 (980)
O-6–C-20–O-7: 121.51 (990)
O-7–C-20–C-21: 127.31 (950)
C-14–C-18–C-19: 128.00 (840)

O-3–C-15–O-4–C-14 are also shortened. Instead of the normal value of 1.45 Å for O-3–C-15 and 1.54 Å for C-14–C-15 these bonds show lengths of 1.33 and 1.50 Å in acetylgynuramine and of 1.34 and 1.46 Å in doronenine, respectively. In the same way, the carbonyl bonds C-15–O-4 are somewhat shortened showing 1.20 and 1.23 Å in doronenine. The second ester function O-1–C-10–O-2–C-11 shows similar values in both molecules; for O-1–C-10 (normal 1.45 Å) 1.34 and 1.37 Å and for C-10–O-2 (1.23 Å) 1.21 and 1.20 Å. Contrary to the first mentioned ester bondings the C-10–C-11 bond lengths are not shortened indicating that the double bond C-14–C-18 takes part at the conjugated system, too.

In the necine nucleus all C–C bondings are somewhat shortened whereas the C–N bondings (C-3–N/C-5–N/C-8–N) show in the same way longer than normal values. As in doronenine it is concluded, that these bondings cause the great stability of the investigated molecule. The X-ray analysis shows that acetylgynuramine is not only an isomeric form of the toxic PA retrorsine but its steric structure is the same as of hepatotoxic PAs like seneciphylline.

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