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THE STRUCTURES OF FOUR NEW DITERPENE ALKALOIDS, SPIRAMINES A, B, C, AND D

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The structures of four new isoatisine-type alkaloids, spiramines A, B, C, and D, isolated from Spiraea japonica L. fil var acuminata Franch, were determined.

KEYWORDS—Spiraea japonica; spiramine A; spiramine B; spiramine C; spiramine D; X-ray analysis; diterpene alkaloid

Isomerization of the oxazolidine ring of atisine (1) into isoatisine (2) via immonium salt is well known and has been studied extensively.[1] Although the existence of epimeric mixtures at C-20 in the atisine series and at C-19 in the isoatisine series has been demonstrated by ^1H and ^{13}C NMR studies,[2,3] no epimeric pair has ever been isolated in pure form. Here we report the structures of the isoatisine-type alkaloids spiramine A (3), B (4), C (5) and D (6) isolated from Spiraea japonica L. fil var acuminata Franch, the former two and the latter two of which are epimeric at C-19, respectively.

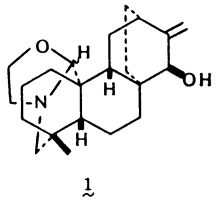
The basic skeleton of spiramine A (3),[4] $C_{24}H_{33}NO_4$, mp 137.5 - 139°C (from hexane), $[\alpha]_D^{25}$ -103.1° (c 0.9, benzene), was established by comparing its ^{13}C NMR shift values (Table I) with the literature data.[6] Hydrolysis of spiramine A (3) afforded an approximately 2:1 mixture of spiramine C (5), $C_{22}H_{31}NO_3$, mp 167 - 169°C (from Et_2O), $[\alpha]_D^{25}$ -149.9° (c 1.0, benzene) and spiramine D (6), $C_{22}H_{31}NO_3$, mp 160 - 162°C (from Et_2O), $[\alpha]_D^{25}$ -169.0° (c 0.7, benzene), which are epimeric at C-19. Spiramine A (3) has an isoatisine-type oxazolidine ring [^1H NMR (C_6D_6): δ 3.87 (1H, s, H-19), 3.01, 3.24, 3.37, 3.81 (each 1H, m, H-21 x 2, H-22 x 2); ^{13}C NMR ($CDCl_3$): δ 51.0 (t, C-21), 63.1 (t, C-22), 95.2 (d, C-19)], an ether linkage between C-7 and C-20 [^1H NMR 3.54 (1H, d, J 5Hz, H-7), 4.47 (1H, d, J 1.8 Hz, H-20); ^{13}C NMR 74.2 (d, C-7), 85.8 (d, C-20)], a secondary acetoxy-group [ν(KBr) 1708 cm^{-1}; ^1H NMR 1.65 (3H, s), 5.46 (1H, br.s); ^{13}C NMR 20.4 (q), 170.9 (s), 69.2 (d)], and an exo methylene group [^1H NMR 5.04, 5.30 (each 1H, br. s); ^{13}C NMR 114.2 (t, C-17), 150.1 (s, C-16)]. On irradiation at 5.46, both of the signals at 5.04 and 5.30 were changed to a doublet with J = 1.8 Hz, demonstrating the location of the secondary acetoxy-group on C-15.

Reduction of spiramine A (3) with sodium borohydride afforded a triol (7), which was not identical with dihydroajaconine (8).[7] Oxidation of spiramine C (5) with manganese dioxide followed by reduction with sodium borohydride in methanol gave a triol, which was identified as dihydroajaconine (8) by spectroscopic analysis including optical rotation $[\alpha]_D^{19}$ -36.6° (c 1.2, EtOH); lit.[7]: $[\alpha]_D^{24}$ -35.5° (c 1.0, EtOH). Except for the stereochemistry at C-19, this confirmed 3 as the absolute structure for spiramine A. Three-dimensional single-crystal X-ray analysis (Fig. 1) provided the total structure for spiramine A (3) including the stereochemistry of the oxazolidine ring.[8]

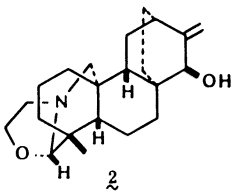
Table I. ^{13}C Chemical Shifts for Spiramines A(3), B(4), C(5), and D(6).

Carbon	Spiramines A[a]	B[a]	C[a]	D[b]
1(t)	41.0	33.9	40.8	34.2
2(t)	22.9	22.9	23.0	23.0
3(t)	29.8	29.8	29.9	30.0
4(s)	35.4[c]	35.4[c]	35.4[c]	35.6[c]
5(d)	45.2	47.4	45.5	47.3
6(t)	25.2	25.3	25.2	25.5
7(d)	74.2	74.3	74.3	74.5
8(s)	40.8	41.0	41.5	41.9
9(d)	43.0	43.9	43.1	44.3
10(s)	34.2[c]	34.9[c]	34.1[c]	34.2[c]
11(t)	23.5	23.1	23.5	23.1
12(d)	36.7	36.4	37.0	37.6
13(t)	21.1[d]	21.2[d]	19.9[d]	21.3[d]
14(t)	20.9[d]	20.8[d]	20.4[d]	20.4[d]
15(d)	69.2	69.7	69.0	69.6
16(s)	150.1	150.1	155.3	156.2
17(t)	114.2	114.3	112.0	111.6
18(q)	26.0	25.9	26.4	26.9
19(d)	95.2	91.3	95.3	91.5
20(d)	85.8	83.5	85.9	83.6
21(t)	51.0	45.7	51.0	45.7
22(t)	63.1	64.9	63.1	64.9
O=C	170.9	171.1		
CH_3	20.4	20.8		

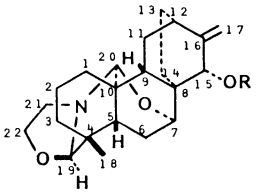
[a]In $CDCl_3$. [b]In C_6D_6. [c,d]These assignments may be interchanged in any vertical column.



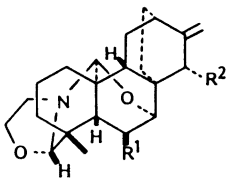
1



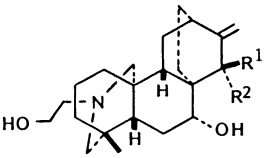
2



3, R=Ac
5, R=H



4, R^1=H, R^2=OAc
6, R^1=H, R^2=OH
9, R^1=OAc, R^2=H
10, R^1=OH, R^2=H



7, R^1=H, R^2=OH
8, R^1=OH, R^2=H

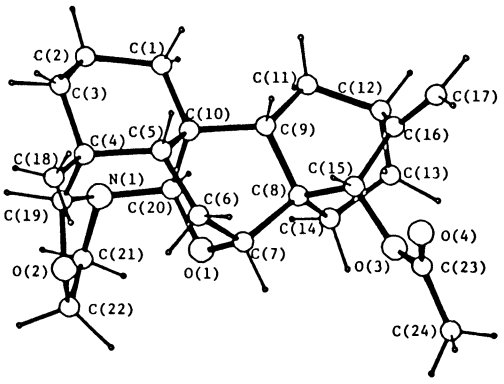


Fig. 1. The Molecular Structure of Spiramine A (3).

Spiramine B (4) $C_{24}H_{33}NO_4$, mp 129 - 131°C (from hexane), $[\alpha]_D^{25}$ -159.5° (c 0.9, benzene), epimerized at C-19 in polar solvents such as methanol to give a pair of C-19 epimers, spiramine A and B, in an approximate ratio of 1:1. Thus, structure 4 was assigned to spiramine B. A close inspection of ^{13}C chemical shifts (Table I) for the carbons of the oxazolidine ring in spiramines clearly revealed that the stereochemistries at C-19 of spiramines C and D correspond to spiramines A (3) and B (4), respectively. This suggests the structure 5 for spiramine C and 6 for spiramine D.

Two closely related alkaloids, spiradines F (9) and G (10) have been isolated from Spiraea japonica L. fil.[9] However, the corresponding epimers at C-19 have not been reported.

REFERENCES AND NOTES

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4) A slight modification of dry-column flash chromatography[5] was used to isolate pure alkaloids. Thus, Kieselgel 60H (Merck) (8 g) was packed under reduced pressure in a glass filter 3 cm in diameter and 4.3 cm in height. A mixture (460 mg) of spiramine A and B in methylene chloride (1 ml) was adsorbed and elution with n-hexane-ether (3:1) afforded spiramine A (211 mg) first and then spiramine B (56 mg). This process requires about 30 min.

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8) Crystal data: $C_{24}H_{33}NO_4$, orthorhombic, a = 10.341 (3), b = 12.718 (7), c = 16.043 (4) Å. U = 2110 Å^3, space group $P2_12_12_1$, Z = 4, M = 399.5, D_c = 1.26 g cm^{-3}. Some 1719 independently observed reflections [$|F_o| > 3\sigma(|F_o|)$, $\theta \leq 60°$] were measured on a Rigaku AFC-5RU diffractometer (Cu-K_α radiation, graphite monochromator) using ω-2θ scans. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically to R = 0.056, R_w = 0.083. All the hydrogen atoms were located from a ΔF map and refined isotropically. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Roak, Cambridge, CB2 1EW.

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