^{13}C Nuclear Magnetic Resonance Spectra of the *Senecio* Alkaloids, Retrorsine, Swazine, Isoline, and Hygrophylline

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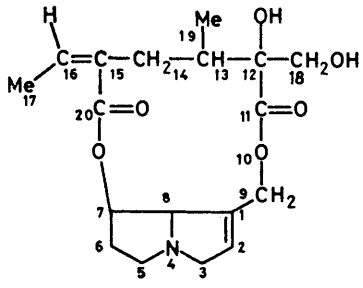
Examination of the ^{13}C n.m.r. spectra of retrorsine and its hydrolysis products has permitted a complete ^{13}C n.m.r. analysis of this alkaloid and the related pyrrolizidine alkaloids swazine, isoline, and hygrophylline.

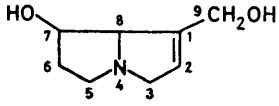
^{13}C N.M.R. ANALYSES of retrorsine (1), swazine (6), isoline (7), and hygrophylline (8) were undertaken as part of a continuing study of the synthesis and structure of *Senecio* alkaloids.[1] Retrorsine [(*Z*)-12,18-dihydroxysenecionan-11,20-dione] (1), chosen as the model for this study, is a hepatotoxic [2] macrocyclic diester alkaloid which contains the pyrrolizidine base, retronecine (2). This base occurs in a large number of pyrrolizidine alkaloids [3] and, since there are only a few reported ^{13}C n.m.r. studies of these compounds,[4-6] the present study should be useful in structure determination in this area. Furthermore, although Moyna *et al.*[4] have reported ^{13}C n.m.r. data for retrorsine, we have been led to conclusions which differ from theirs in several important respects.

RESULTS AND DISCUSSION

Assignment of the signals in the ^{13}C n.m.r. spectra of the various compounds examined (Table) was based on considerations of shielding effects, off-resonance decoupling multiplicities, selective heteronuclear decoupling data, and shift responses to structural modification. Analysis of retrorsine (1) was facilitated by examination of the ^{13}C n.m.r. spectra of retronecine (2) and isatinecic acid (3) [the constituents of retrorsine (1)], retronecic acid (4) [the geometric isomer of (3)], and the hydrogenated derivative, dihydroretronecine (5).



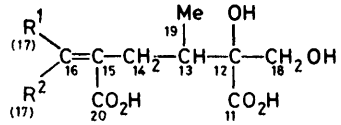
(1)



(2)

Retronecine (2).—The low-field singlet at δ 138.4 † has been assigned to C(1) and the doublet at δ 126.0 to the remaining olefinic carbon C(2). Comparison with the spectrum of dihydroretronecine (5) suggests assignment of the doublets at δ 71.5 and 77.3 to C(7) and C(8), respectively. The assumptions (*i*) that the signal for the allylic C(8) in retronecine (2) should be downfield from the corresponding signal in the hydrogenated derivative (5), and (*ii*) that C(7) should have similar chemical shifts in both bases, are supported by analogy with the ^{13}C n.m.r. data for cyclopentane and cyclopentene.[7] Similar considerations were used to distinguish between the triplet signals for C(3), C(5), and C(9), while the higher-field triplet at δ 36.3 was allocated to the more shielded carbon C(6).

Isatinecic Acid (3).—The conjugated carboxy carbon C(20) is expected to resonate at higher field than C(11),[8] and the signals at δ 172.4 and 178.0 were allocated accordingly. Assignment of the C(20) signal was confirmed by



(3) R^1=H, R^2=Me
(4) R^1=Me, R^2=H

means of a selective heteronuclear decoupling experiment, in which decoupling of the C(16) proton (665 Hz) caused the C(20) doublet to collapse into a singlet. Similar decoupling data require assignment of the quartets at δ 12.8 and 16.1 to the methyl carbons C(19) and C(17), respectively.

The downfield shift of the ^1H n.m.r. signal for the C(16) proton in retronecic acid (4) relative to the corresponding signal in the (*Z*)-isomer, isatinecic acid (3), has been attributed to magnetic anisotropic effects.[3] The ^{13}C n.m.r. shift for the allylic carbon C(14) also appears to be diagnostic of the double-bond geometry in these systems. Thus, in isatinecic acid (3) and retrorsine (1) [both having (*Z*)-configurations] the C(14) signal resonates at δ 37.3 and 38.2, respectively, whereas in retronecic acid (4) [(*E*)-configuration] it appears at δ 28.4.

Retrorsine (1).—The ^{13}C n.m.r. chemical shifts allocated to carbons C(5), C(6), C(8), C(9), C(12), C(13), C(17), C(18), and C(20) in retrorsine (1) lie within *ca.* 1 p.p.m. of the signals for the corresponding carbons in retronecine (2) and isatinecic acid (3). Assignment of the signals at δ 131.5 [131.1 in $CDCl_3$] and 132.5 [132.3 in $CDCl_3$], to C(1) and C(15), respectively, is

† In D_2O unless specified otherwise.

based on a comparison with the corresponding signals in isoline (7) (which lacks the Δ^{15} double bond) and hygrophylline (8) (which lacks the $\Delta^{1,2}$ double bond). Similar comparisons serve to distinguish between C(2) and C(16). The carboxy carbons C(11) and C(20) in the diester alkaloid (1) resonate, predictably,[8] at slightly lower frequencies than the corresponding carbons in the free acid (3). The significant difference (5.3 p.p.m.) between the C(7) signals in retrorsine (1) and the free base (2) is presumably due to strain in the (former) macrocyclic compound. Moyna's value [4] for C(14) [δ 61.0 ($CDCl_3$)] is outside the typical range for alkyl carbons and we believe that this signal is best correlated with the more deshielded C(3), an interpretation which is consistent with other work [6] on pyrrolizidine alkaloids. The consistency of the chemical shifts [δ 35 $\pm$ 1 ($CDCl_3$)] for C(6) in the four alkaloids, (1), (6), (7), and (8), support our assignment for this carbon in retrorsine (1).

The foregoing arguments require signal allocations which differ from those of Moyna *et al.*[4] (Table) at nine different positions, *i.e.* C(1), C(2), C(3), C(6) C(9), C(14), C(15), C(16), and C(18).

Swazine (6) and isoline (7) both yield retronecine (2) on hydrolysis,[9] and the assigned resonances for C(1) to C(9) in these compounds are almost identical with those for retrorsine (1). In swazine (6), C(17) is adjacent to a quarternary carbon, and may thus be assigned [10] to the clearer high field quartet [δ 21.9 ($CDCl_3$)].

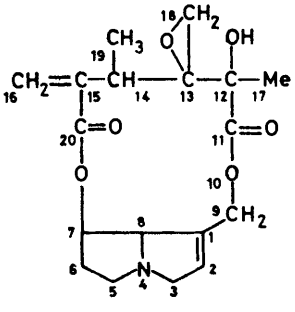
The quartet at δ 21.4 ($CDCl_3$) in the isoline (7) spectrum is typical of an acetate methyl carbon, while the high-field resonance at δ 7.4 ($CDCl_3$) has been allocated to C(17) (being shielded by the γ-hydroxy-group); the remaining methyl signals correspond to C(18) and C(19), the clearer quartet [δ 14.9 ($CDCl_3$)] being assigned to C(18). The singlets at δ 83.6 and 78.8 ($CDCl_3$) were allocated to the quaternary carbons C(12) and C(15), respectively, the former being deshielded by the adjacent acetyl group.[11]

Hygrophylline (8) contains the base, dihydroretronecine (5), and the assigned resonances for C(1)—C(8) are within *ca.* 2 p.p.m. of those in the free base. The signals for C(1) and C(13), however, differ by only 1.2 p.p.m. and these allocations are therefore uncertain. The high-field quartet [δ 5.9 ($CDCl_3$)] has been assigned to C(19) (having two γ-hydroxy-groups) and the lower-field

^{13}C N.m.r. chemical shifts (δ from $SiMe_4$) for retrorsine (1), retronecine (2), dihydroretronecine (5), isatinecic acid (3), retronecic acid (4), swazine (6), isoline (7), and hygrophylline (8)

Carbon no.	Retrorsine (1)			Retronecine (2)		Dihydro-retronecine (5)	Isatinecic acid (3)	Retronecic acid (4)	Swazine (6)	Isoline (7)	Hygrophylline (8)
	$CDCl_3$ *	D_2O	$CDCl_3$	D_2O	$CDCl_3$	(D_2O)	(D_2O)	(D_2O)	($CDCl_3$)	($CDCl_3$)	($CDCl_3$)
1	132.4	131.5	131.1	138.4	138.0	43.9			131.8	131.6	41.9
2	134.7	137.1	136.5	126.0	127.1	28.6			136.6	135.7	29.8
3	34.7	61.2	60.8	59.4	58.7	55.3			61.2	60.6	54.4
5	52.9	52.9	52.8	53.6	54.1	53.8			53.1	53.2	52.2
6	37.5	34.9	34.5	36.3	35.1	36.5			34.1	34.6	35.3
7	75.0	76.8	75.3	71.5	71.1	71.3			75.9	76.9	73.5
8	77.4	77.5	77.3	77.3	79.5	73.0			77.6	77.5	75.4
9	66.9	62.6	62.7	62.3	61.9	61.5			62.6	63.3	65.2
11	175.7	176.4	175.4				178.0	178.2	176.6	176.1	178.2
12	81.3	83.1	81.3				82.1	82.3	77.4	83.6	78.1
13	35.7	36.5	35.5				37.5	37.6	79.4	37.3	40.7
14	61.0	38.2	37.8				37.3	28.4	35.6	39.6	70.0
15	131.2	132.5	132.3				131.2	131.0	143.1	78.8	133.5
16	136.6	136.7	134.4				140.3	143.3	122.0	33.3	135.1
17	14.9	15.2	14.8				16.1	15.1	21.9	7.4	15.6
18	62.7	67.4	66.8				67.0	67.0	41.7	14.9	25.7
19	11.6	11.4	11.4				12.8	12.7	16.9	15.9	5.9
20	167.3	171.1	167.2				172.4	172.6	168.1	172.1	167.6

* Values of Moyna *et al.*[4]



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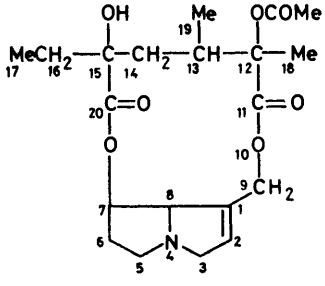

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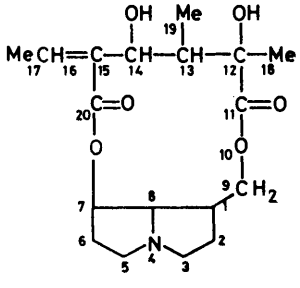

(8)

quartet [δ 25.7 ($CDCl_3$)] to C(18) (having a β-hydroxy-group). The signal at δ 15.6 ($CDCl_3$) has been assigned to C(17) by analogy with retrorsine (1).

EXPERIMENTAL

The isolation from *Senecio* species of retrorsine (1), swazine (6), isoline (7), and hygrophylline (8) has been reported previously.[12] Specific methods of hydrolysis of retrorsine to yield isatinecic acid (3) and retronecic acid (4) have been improved, but follow essentially the procedure described by Warren and his co-workers.[9] Hydrogenation of retronecine (2) to dihydroretronecine (5) was accomplished under standard conditions using a PtO_2 catalyst (Parr hydrogenator, 1 atm pressure).

Varian CFT20 and FT80A instruments were used to record the spectra at 20 MHz. Solutions of the compounds (0.3—0.5M) in $CDCl_3$ or D_2O were recorded at 40 °C using 10-mm tubes. Spectra in $CDCl_3$ were referenced to this solvent (δ 76.9), spectra in D_2O to 1,4-dioxan (δ 67.4 p.p.m.). A pulse delay of 10—20 s was necessary to obtain good signals for the carboxy groups.

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