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Edited by

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PREFACE

The present volume consists of state-of-the-art accounts on four distinct areas of NMR spectroscopy. The relevant literature has been covered up to the first half of 1977.

Dr. Crabb has updated his review on alkaloids which appeared in Volume 6A of this series. This valuable report includes a timely account of the published work on indole alkaloids. A previous review on the ^{13}C NMR spectroscopy of steroids has been brought up to date by Professor W. B. Smith. The more theoretical aspects of dynamic NMR are covered by Dr. Witanowski and his co-workers. Finally, it is a pleasure to include a review on ^{119}Sn NMR spectroscopy for the first time in this series.

It is with gratitude that I acknowledge the encouraging remarks made by various reviewers and readers following the appearance of Volume 7 of this series. Such comments reflect on the considerable efforts made by the authors of the reviews presented. I am very grateful both to them and the authors of the present volume for the cooperation and enthusiasm they have shown in preparing their contributions and submitting them promptly.

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Nuclear Magnetic Resonance of Alkaloids

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I. INTRODUCTION

A. General remarks

This review updates the one written for Volume 6A of the series (1) and describes characteristic features of the ^{1}H and ^{13}C NMR spectra of alkaloids with selected examples taken from papers published during the period from June 1972 to the early part of 1977. Steroidal alkaloids and

peptide alkaloids are not included since these are best covered in reviews on steroids and on peptides, but the NMR spectra of some intermediates in the synthesis of a particular alkaloid and of selected alkaloid degradation products are described.

In some of the papers taken from the period under consideration the NMR spectra of previously described alkaloids are recorded when, for example, comparison between synthetic and natural material is being made. In such cases, and where these alkaloids were not included in the last review, only reference to the most recent paper is given. In addition, reference to work carried out prior to mid-1972 is normally made to Volume 6A of this series rather than to the original literature.

In Sections II–XIV chemical shifts and coupling constants of many of the alkaloids and related systems are given with the structural formulae in order to provide a reference collection of alkaloid NMR data. Many of the recorded proton–proton coupling constants are in fact splittings and are therefore only an approximation to the true coupling constants. ^{1}H and ^{13}C chemical shifts are in ppm to high frequency from internal TMS unless otherwise stated; coupling constants (or splittings) are in Hz. In the displays and tables of ^{13}C NMR data asterisks signify possible reversal of shift assignments.

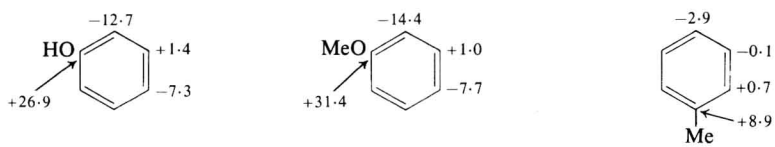
B. ^{13}C NMR spectra of alkaloids

Since the period covered by the last review there has been a great increase in the number of papers describing the ^{13}C NMR spectra of alkaloids, and an excellent introduction to this area of research is available. (2) The books by Stothers (3) and by Levy and Nelson (4) on ^{13}C NMR spectroscopy are invaluable and are quoted in the majority of papers concerned with the ^{13}C NMR spectra of alkaloids.

Certain ^{13}C NMR substituent effects (3, 4) are utilized so frequently in the assignment of alkaloid structure that these are summarized in Tables I–III in order to facilitate reference. The γ-effect [illustrated by a

TABLE I

^{13}C NMR substituent effects in substituted benzenes (4)



Negative sign denotes shift to lower frequency; positive sign denotes shift to higher frequency.

TABLE II

Effects of α-, β-, and γ-methyl substituents on ^{13}C shifts in alkanes (5)

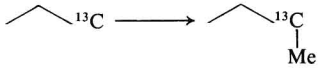
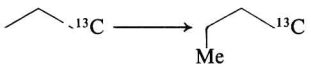
	α-effect	shift of *ca.* 9 ppm to higher frequency
	β-effect	shift of *ca.* 9 ppm to higher frequency
	γ-effect	shift of *ca.* 2 ppm to lower frequency

TABLE III

Effects of α-, β-, and γ-methyl substituents on ^{13}C shifts in cyclohexanes (6)

Equatorial methyl	α-effect	+5·6 ppm	Axial methyl	α-effect	+1·1 ppm
	β-effect	+9·8 ppm		β-effect	+5·2 ppm
	γ-effect	0·0 ppm		γ-effect	−5·4 ppm

substituent methyl in Tables II (5) and III (6)] is of particular importance. Detailed discussions of these effects are available. (3, 4)

In the work described in the following sections, ^{13}C assignments are made utilizing a variety of ^{1}H decoupling methods which are conveniently summarized here.

In wide-band proton decoupled spectra complete proton decoupling is achieved and all carbon resonances appear as singlets. Enhancement of the ^{13}C signals is observed as a result of the NOE and collapse of the C–H spin multiplets.

In the noise off-resonance decoupling experiment inefficient decoupling conditions are maintained and, since residual coupling is related to coupling constants, the band widths of the signals arising from the methine, methylene, and methyl carbon nuclei, characterized by large ^{1}J(C–H) values, are affected most strongly. Quaternary carbon nuclei, characterized by very small long-range couplings, are decoupled under the off-resonance conditions and absorb as singlets. (7)

In single-frequency off-resonance decoupled (SFORD) spectra the magnitude of the coupling interaction between ^{13}C and ^{1}H is reduced so that normally only one bond C–H coupling patterns are observed and an A_nX situation is assumed. In such a decoupling the residual coupling J_R is less than ^{1}J(C–H) and depends upon the decoupling power (γB_2) and the decoupler offset ($\Delta\nu$). For most applications to structural work

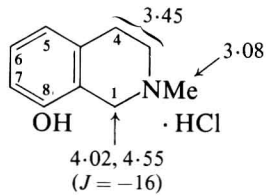
the equation $J_R = J(C-H)\Delta\nu(\gamma B_2)^{-1}$ is permissible. Differences in residual coupling, to their directly bound protons, provide a method of distinction between carbon nuclei (see discussion, for example, on vindoline in Section XII.I). Some problems associated with geminal non-equivalence and second-order coupling in SFORD spectra with reference to some examples taken from the alkaloid field have been discussed by Hagaman. (8) In particular it has been emphasized that the A_nX treatment in SFORD spectra is only legitimate when, for example, in a $^{13}C^1H_A{}^1H_B$ system $J(C-H_A) = J(C-H_B)$ and $\delta(H_A) = \delta(H_B)$. When $\delta(H_A) - \delta(H_B) > 3 \times J_{gem}$ a doublet of doublets is observed in the SFORD spectrum. Since differences between the chemical shifts of methylene group protons exceeding 0·5 ppm are quite frequently observed in the ^1H NMR spectra of natural products, care must be exercized in the interpretation of the SFORD spectra of such systems.

II. ISOQUINOLINE ALKALOIDS

The spectral features of all classes of the isoquinoline alkaloids have been described, (9) and NMR data on thirty-six thalictrum alkaloids described before 1970 have been tabulated. (10)

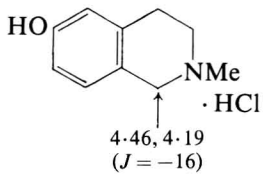
A. Simple isoquinoline alkaloids

The presence of the 8-hydroxyl in longimammidine hydrochloride [1]



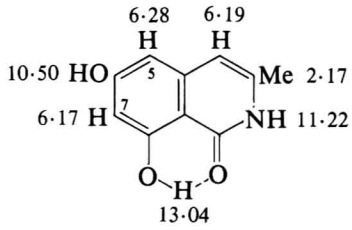
[1] Longimammidine hydrochloride (in D_2O)

produces a chemical shift difference of 0·53 ppm between the C(1) methylene group protons. In longimammosine hydrochloride [2] the corresponding chemical shift difference is 0·27 ppm. (11)



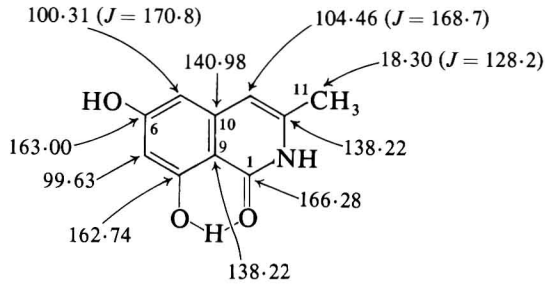
[2] Longimammosine hydrochloride (in D_2O)

The ^{1}H and ^{13}C NMR spectra of siamin are summarized in [3] and [4], (12) and of amphibin in [5]. (13) The ^{13}C shifts of 163·00 and

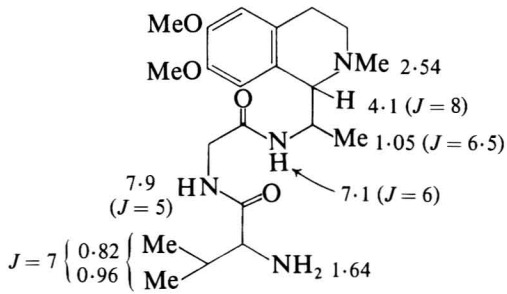


$J_{5,7} = 2{\cdot}5$

[3] Siamin



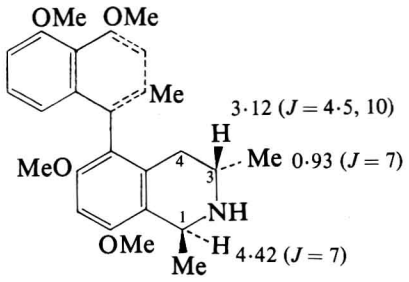
[4]



OMe	3·82
	3·85
Ar-H	6·56
	6·61

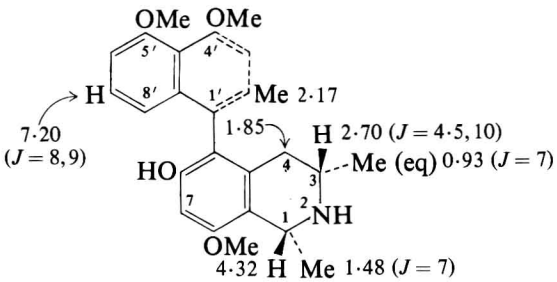
[5] Amphibin (in $CDCl_3$)

162·74 are typical of the resorcinol moiety. In both *O*-methylancistrocladine [6] and isoancistrocladine [7] the 3-methyl group is shown to be equatorial by vicinal couplings between the 3ax-proton and the 4-methylene protons of 4·5 and 10 Hz. The stereochemical assignments of the 1-methyl groups in [6] and [7] are based on the observation of homoallylic coupling of 1 Hz between the 1ax-proton and the 4ax-proton in the spectrum of [7] which is not observed in that of [6]. (14)



$J_{1,4} = 0$

[6] *O*-Methylancistrocladine (in $CDCl_3$)



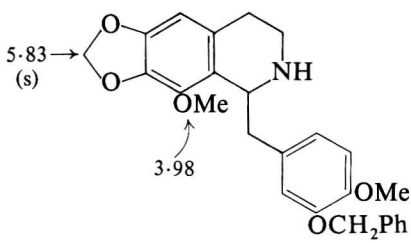
3′- or 7-H	6·50
6′- or 8′-H	6·76
	(J = 2·5, 9)
3′- or 7-H	6·80

$J_{1,4ax} = 1$
$J_{1\text{-H},1\text{-Me}} = 7$

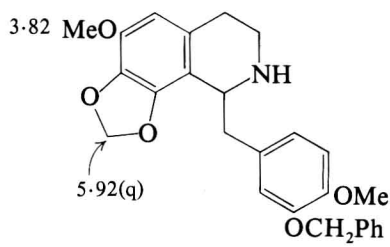
[7] Isoancistrocladine (in $CDCl_3$)

B. Benzylisoquinoline alkaloids

In line with previous correlations (15) the 8-methoxyl protons in the spectrum of [8] absorb at higher frequency than, for example, the 6-methoxyl protons in that of [9]. In the spectrum of [9] the



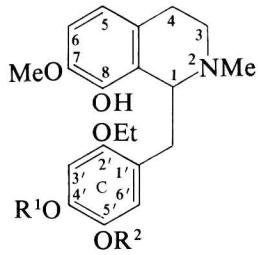
[8] (in $CDCl_3$)



[9] (in $CDCl_3$)

methylenedioxy protons absorb as an AB quartet as a result of the neighbouring bulky group. (16)

The 7-methoxyl proton resonances in [10] and [11] are shifted to lower frequency on changing solvent from $CDCl_3$ to $CDCl_3$–C_6H_6 [$\delta(CDCl_3) - \delta(C_6H_6)$ 0·50 ppm]. The ring-c methoxyl proton



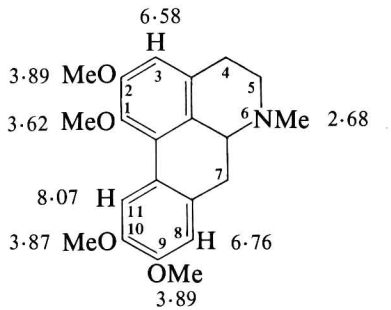
[10]	$R^1 = Me$	$R^2 = Et$	7-OMe	3·86 ($CDCl_3$)
				3·36 ($CDCl_3 + C_6H_6$)
			4′-OMe	3·86 ($CDCl_3$)
				3·72 (C_6H_6)
[11]	$R^1 = Et$	$R^2 = Me$	7-OMe	3·86 ($CDCl_3$)
				3·36 ($CDCl_3 + C_6H_6$)
			5′-OMe	3·77 ($CDCl_3$)
				3·62 ($CDCl_3 + C_6H_6$)

resonances are shifted to a smaller extent [$\delta(CDCl_3) - \delta(C_6H_6)$ *ca.* 0·14 ppm]. (17)

C. Aporphine, oxa-aporphine, and proaporphine alkaloids (including dioxoaporphine, aristolactams, and phenanthrene alkaloids)

1. Aporphines

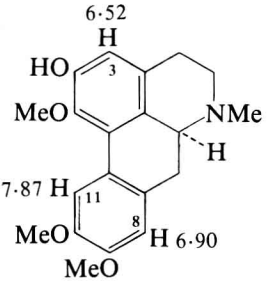
The ^1H NMR spectrum of glaucine [12] (18) shows features typical of aporphine alkaloid spectra, with low frequency absorption of the



[12] (±)-Glaucine (in $CDCl_3$)

C(1)-methoxyl protons and the 3-proton, and high frequency absorption of the 11-proton. (9)

Addition of the chiral lanthanide reagent tris-(3-trifluoromethylhydroxymethylene-*d*-camphorato)europium(III) to a solution of (±)-

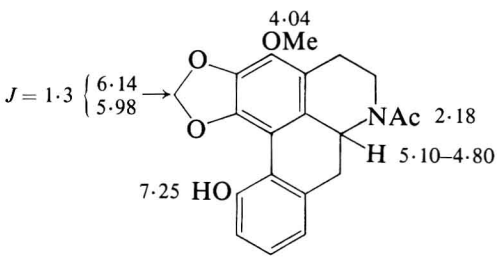


[13] 2-*O*-Demethylglaucine (in DMSO-d_6)

glaucine in $CDCl_3$ shifts the signals from the C(1)-methoxyl protons and from the 11-proton in the *S*-enantiomer to lower frequencies. Shifts of these types permit an estimation of the enantiomeric purity of a variety of isoquinoline alkaloids. (19)

The position of demethylation in 2-*O*-demethylglaucine, a metabolite of glaucine, is located by the observation of ^1H chemical shift changes on the addition of NaOD to a DMSO-d_6 solution of the metabolite. The 8-proton signal is not shifted and the 11-proton signal moves to higher frequency (0·08 ppm). In contrast the signal arising from the 3-proton, *ortho* to the phenolic function, moves to lower frequency (0·14 ppm). (20)

The methoxyl and hydroxyl substituents in *N*-acetylelmerrillicine [14]



[14] *N*-Acetylelmerrillicine (in $CDCl_3$)

were located (21) at C(3) and C(11) after a consideration of the normally encountered chemical shifts of the 11- and 3-protons and C(1)- and C(11)-methoxyl protons. (9)

1,2-Methylenedioxyaporphines are characterized by a low frequency shift of the 11-proton signals (δ 7·47 to 7·86) [cf. δ 7·80 to 8·21 for the 11-protons in C(1) hydroxylated or methoxylated aporphines]. (22)

In the spectrum of apomorphine [15] the 1-proton absorbs at high frequency as a consequence of deshielding by the 11-hydroxyl and the D ring. Assignment of the 8- and 9-proton signals is possible since the low