THE NMR INVESTIGATION OF ALKALOIDS.

IX. ^{13}C NMR SPECTRA AND STEREOCHEMISTRY OF CONVOLVINE, CONVOLAMINE, CONVOLINE, CONVOLIDINE, SUBHIRSINE, AND 6-HYDROXYHYOSCYAMINE

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On the basis of the results of a study of the ^{13}C NMR spectra, a correlation has been made of the CSs of the ^{13}C carbon nuclei with the structure and stereochemistry of the tropane alkaloids convolvine, convolamine, convoline, convolidine, subhirsine, and 6-hydroxyhyoscyamine. It has been established that the $N-CH_3$ group in convolamine and the N—OH group in convoline are oriented equatorially, and the $N-CH_3$ in hydroxyhyoscyamine axially.

Previously, the tropane alkaloid convolvine (I) and convolamine (II) were isolated from Convolvulus pseudocantabrica Schrenk, and their structures were established on the basis of purely chemical transformations [1]. Then the same alkaloids were isolated from Convolvulus krauseanus Rgl. et Schmalh. and Convolvulus subhirsutus Rgl. et Schmalh. [2-4] and, together with them, the new tropane alkaloids convoline (III) [6], convolidine (IV) [2-5], and subhirsine (V) [7], while 6-hydroxyhyoscyamine (VI) was isolated from the plane Physochlaina alaica A. Korot. [8]. The structures of these compounds were proposed on the basis of chemical and UV, IR, mass, and PMR spectrometric studies.

However, some questions relating, in particular, to the orientation of the $N-CH_3$ and N—OH groups of convolamine (II), convoline (III), and 6-hydroxyhyoscyamine (VI) remained unelucidated. The results of ^{13}C NMR spectroscopy have been used fairly successfully to answer such questions in recent times [9-11]. We have therefore made a correlation of the chemical shifts of the carbon atims in the ^{13}C NMR spectra with the structures of the tropane alkaloids (I-VI)

TABLE 1. ^{13}C Chemical Shifts (ppm, 0 — TMS) and Assignments of the Signals of the Carbon Atoms of the Tropane Alkaloids

Carbon atom	Multiplicity	Convolvine	Convolamine	Convoline	Convolidine	Subhirsine	6-Hydroxyhyoscyamine
C-1	d	52,77	59,10	64,27	52.45	54,60	58,44
C-2	t	36,88	35,86	37.40	36.80	35,83	30.48
C-3	d	67,85	67,00	66,30	68,00	67,97	67,44
C-4	t	36,88	35,86	37,40	36.80	35.83	29,20
C-5	d	52,77	59,10	64,27	52,46	54.60	66,96
C-6	t	28,80	25,11	25,91	28,90	27,61	75,10
C-7	t	28,80	25,11	25,91	28,90	27,61	39,11
C=O	s	164,70	164,32	165,44	164,80	165,19	171,91
α-C	d	—	—	—	—	$N\underset{\overset{\parallel}{O}}{C}$—160,78	54,57
β-C	t	—	—	—	—	—	63,85
C-1′	s	122,76	122,70	123,07	121,00	122,94	135,59
C-2′	d	122,54	122,40	123,24	123,05	122,97	128,72
C-3′	d	111,43	111,35	112,03	115,29	111,82	128,20
C-4′	s	152,32	152,26	153,06	151,60	152,85	127,97d
C-5′	s	148,09	148,03	148,76	147,35	148,54	128,72d
C-6′	d	109,88	109,80	110,46	112,50	110,29	128,15
$Ar-OCH_3$	q	55,24	55,10	55,94	55,50	55,66	—
	q	55,17	55,05	55,90	—	55,74	—
$N-\overset{*}{C}H_3$	q		39,60	—	—	—	36,82

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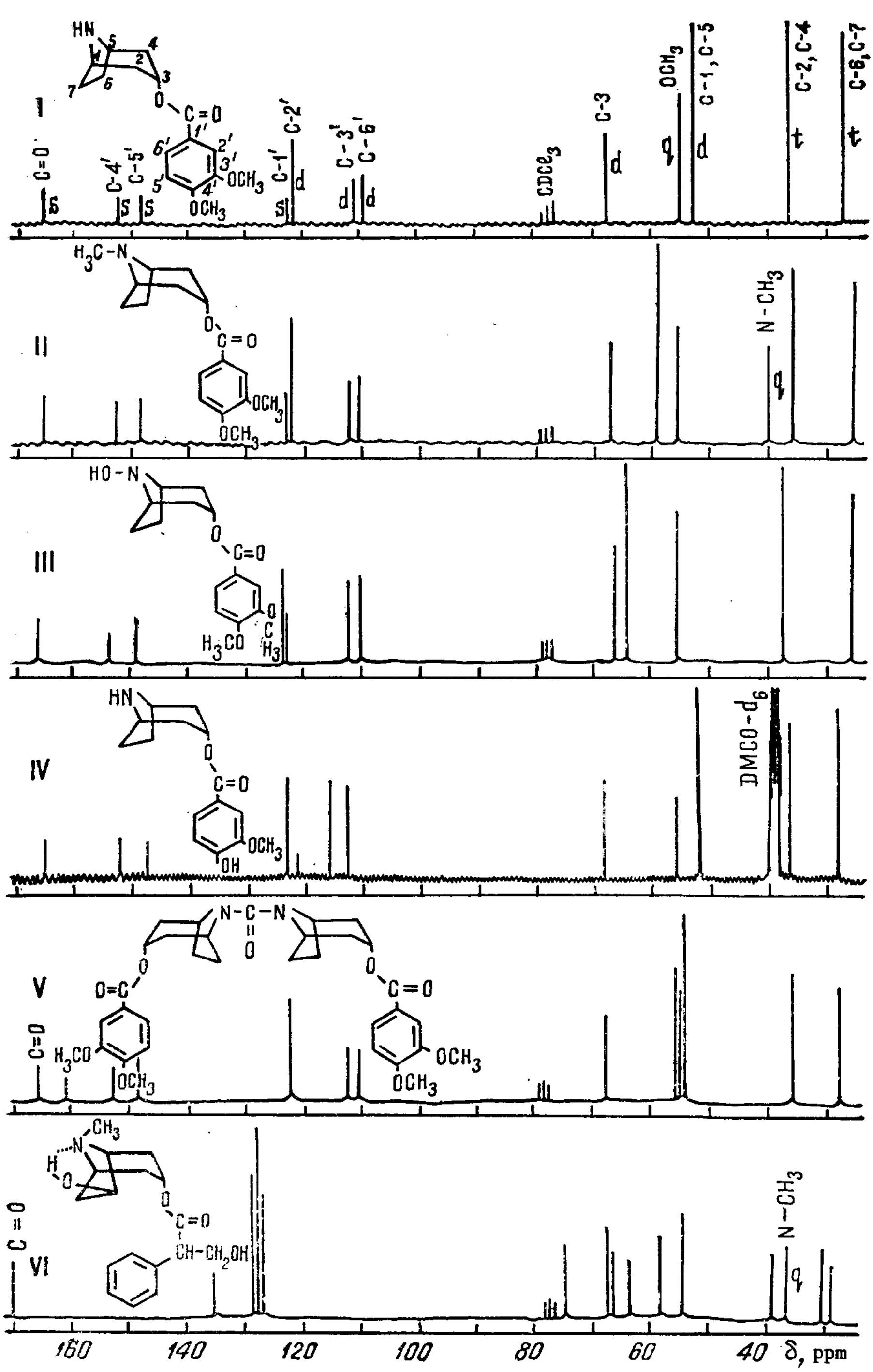

Fig. 1. ^{13}C NMR spectra of convolvine (I), convolamine (II). convoline (III), convolidine (IV), subhirsine (V), and 6-hydroxyhyoscyamine (VI).

in order to check the validity of the proposed structures and to determine some of their stereochemical features more accurately. The chemical shifts of the carbon atoms of bases (I-VI) and their assignments are given in Table 1 and Fig. 1.

We made the assignment of the signals of the carbon atoms on the basis of an experiment on incomplete decoupling of C—H interactions, i.e., from the multiplicity of the signals in the off-resonance spectrum (below, in the text, multiplicities from the off-resonance spectra are given), and then by comparison with the ^{13}C-NMR spectra given in the literature for the molecules of tropane bases similar in structure — tropane [9], tropine [9-11], ℓ-cocaine and ℓ-scopolamine [11], hyoscyamine [9, 11], 2-benzyltropine, and 2-benzyl-6-hydroxytropine [12], taking into account also the α-, β-, and γ-contributions of CH_3, OH, and OCH_3 groups and the spatial influence of $N—CH_3$ groups on the ^{13}C CSs of a number of carbon atoms [12-14].

In the ^{13}C NMR spectra of the alkaloids (I), (III), and (IV), six carbon atoms of the traopane moiety of the molecule give three signals in each case (one doublet and two triplets), since because of the coincidence ofthe CSs of the C-1 and C-5, the C-2 and C-4, and the C-6 and C-7 carbon atoms they give three signals of doubled intensity, and the doublet signal of the C-3 carbon atom attached to the oxygen of the ester group is observed in the 66.3-68.0 ppm interval (see Table 1).

A comparison of the CS values and numbers of the signals of these carbon atoms in the tropane moieties of the molecules (I), (III), and (IV) (see Table 1) with those for the analogous model compounds tropine and its analogs and the tropane alkaloids shows their good agreement [9-12]. In the ^{13}C NMR spectrum of convolamine (II), in addition to the four signals already mentioned for compounds (I), (III), and (IV) there is a quartet signal at 39.60 ppm relating to the $N{-}CH_3$ carbon. The value of the CS of the carbon of the $N{-}CH_3$ group in convolamine clearly shows its predominant equatorial orientation [11].

A comparison of the figures in Table 1 shows that the CSs of the signals of carbons C-1 and C-5 in convolamine (II) and convoline (III) are shifted downfield by approximately 6.5 and 11.5 ppm as compared with the analogous signals of convolvine (I) and convolidine (IV), respectively. This fact is obviously due to the β-contribution to the CSs of the C-1 and C-5 carbon atoms from the CH_3 group in (I) and the OH group in (IV) on the introduction of a CH_3 group into (I) to give (II) and of an OH group into (IV) to give (III). This contribution of a methyl group to the CSs of the carbon in the α position with respect to the nitrogen atom in convolamine (II) is close to the increment (Δ ~ 6 ppm) for five- and six-membered nitrogen-containing systems [9], and the considerable β-contribution of the OH group to the CS of the carbons under consideration in (III) corresponds to the analogous contribution of equatorially oriented OH groups in cyclohexanols [13].

In addition to the β-contribution of the CH_3 and OH groups of convolamine (II) and convoline (III), there is also an appreciable steric γ-effect on the C-6 and C-7 carbon atoms in the syn relationship to the $N{-}CH_3$ and N—OH, as a result of which their CSs are shifted upfield by approximately 3.7 and 3.1 ppm, respectively, in comparison with convolvine (I) and convolidine (IV) (see Table 1). At the same time, the γ-effect of these groups on the carbon atoms C-2 and C-4 in the anti relationship to them in the bases (II) and (III) is only slight. Apparently, in the bicyclic tropane system the magnitude of the γ-effect of CH_3 and OH groups is of the same order as in the quinuclidine system and depends on their syn or anti relationship to the γ-carbon atoms under consideration [15, 16].

Subhirsine (V) is a symmetrical dimer (it has a twofold axis passing through the NC=O double bond) formed by two identical monomeric molecules. Because of this symmetry, in its ^{13}C NMR spectra the CSs of the carbon atoms of the two halves of the dimer coincide completely and it gives only 14 signals [four tropane signals, nine veratroyl signals, and one of the amide carbonyl NC=O (δ 160.78 ppm), which is common to both halves of the dimer]. Because of the influence of the C=O group attached to the tropane nitrogen atoms in (V), the CS of the C-1 and C-5 carbon atoms undergoes a slight paramagnetic shift (Δ ~ 2 ppm) and that of C-6 and C-7 a diamagnetic shift in comparison with those for (I) and (IV) (see Table 1).

The assignment of the signals of the six sp^2 carbon atoms of the trisubstituted benzene ring in each of compounds (I)-(V) was made with allowance for the eincrements of ArO—C=O and OCH_3 groups, and in base (IV) also for the effect of the methylation of the phenolic hydroxyl [17] (see Table 1).

It must be mentioned that the mutual positions of the OH and OCH_3 groups in convolidine (IV) was established previously from the formation of vanillic acid [5].

A comparative study of the PMR spectra of convolidine and its O-acetyl derivative confirmed its structure, since when the phenolic hydroxyl of (IV) was acetylated the greatest paramagnetic shift (Δ = 0.40 ppm) was experienced by the signal of the proton having an orthocoupling constant (J = 9 Hz). Another proof of the correctness of the location of the OCH_3 group in (IV) was the detection of an appreciable intramolecular nuclear Overhauser effect between the $Ar{-}OCH_3$ group (δ 3.80) and the proton with δ 7.58 having J_{meta} = 2 Hz in the acetate (IV) (about 20%). The CS of the C=O carbon of the ester group in each of the alkaloids (I)-(V) changed little and was practically identical with the CS of the C=O groups of similar tropane alkaloids [9-11], while the CSs of the carbons of the aromatic OCH_3 groups also agreed with those given in the literature [13].

In the ^{13}C NMR spectrum of 6-hydroxyhyoscyamine (VI), with the introduction of an OH group into the N-methylpyrrolidine ring of the tropane system, considerable changes in the CSs of many of the carbon atoms of the latter were observed and, because of the differences in the α-, β-, and γ-contributions introduced by the OH group, the CSs of the C-1 and C-5 and the C-2 and C-4 carbon atoms naturally became different. The greatest paramagnetic shift was undergone by the signal of the C-6 carbon because of the α-contribution of the OH group. The CSs of the C-6 carbon atoms in 6-hydroxyhyoscyamine and in 2-benzyl-6-hydroxytropine [12] then practically coincided.

The results of a comparison of the values of the β-contribution of the C_6—OH group to the CSs of the C-7 and C-5 carbon atoms show that this magnitude depends substantially on the degree of substitution of the corresponding atoms. A similar pattern is observed in an analysis of the γ-contribution of the group under consideration to the CSs of the C-1 and C-4 carbon atoms, i.e., the magnitude of the contribution of the C_6—OH group to the tertiary C-1 carbon atom is approximately 0.9 ppm, and that to the secondary C-4 carbon atom 7 ppm. At the same time, the CS of the C-4 atom may also be appreciably affected by the reorientation of the N—CH_3 group and, as a result of the interaction of these two factors, undergo an equally pronounced shift. The signal of the N—CH_3 carbon atom of 6-hydroxyhyoscyamine has shifted upfield as compared with hyoscyamine by 3.8 ppm and coincides with that of 2-benzyl-6-hydroxytropine [12]. As in the case of 2-benzyl-6-hydroxytropine [12], this upfield shift in the N—CH_3 signal of (VI) obviously takes place as the result of the formation of a O—H···N intramolecular hydrogen bond leading to the inversion of the unshared electron pair of the nitrogen atom and, correspondingly, to a reorientation of the N—CH_3 group from the equatorial position in hyoscyamine to the axial position in 6-hydroxyhyoscyamine. It is just the γ-influence of the CH_3 of the axially oriented N—CH_3 group in (VI) that can apparently explain the upfield shift ($\Delta \approx 6$ ppm) of the signal of the C-2 carbon atom as compared with hyoscyamine, since under these conditions the N—CH_3 group and the C-2 carbon atom are syn-oriented and the γ-contribution of the methyl radical of this group is a maximum. The CSs of the other carbon atoms of 6-hydroxyhyoscyamine practically coincide with those of hyoscyamine (see Table 1).

EXPERIMENTAL

The ^{13}C NMR spectra of alkaloids (I), (II), (III), (V), and (VI) were obtained on a Bruker WM-250 spectrometer at a frequency of 62.90 MHz in $CDCl_3$ solution, and that of (IV) in DMSO-d_6, 0 — TMS, in the pulsed regime with subsequent Fourier transformation under conditions of complete and incomplete decoupling of C—H interactions. The PMR spectra of (IV) and its acetyl derivative were taken on JNM-C-60HL spectrometer with a working frequency of 60 MHz in DMSO-d_6 (0 — HMDS). The NOE measurements of the acetate (IV) were performed on a Variant XL-100 instrument.

SUMMARY

1. On the basis of the results of a study of ^{13}C NMR spectra, a correlation has been made between the CSs of the ^{13}C carbon nuclei with the structure and stereochemistry of the tropane alkaloids convolvine, convolamine, convoline, convolidine, subhirsine, and 6-hydroxyhyoscyamine.

2. It has been established that the N—CH_3 group in convolamine and the N—OH group in convoline are oriented equatorially, and the N—CH_3 group in 6-hydroxyhyoscyamine has the axial arrangement.

LITERATURE CITED

1. A. P. Orekhov and R. A. Konovalova, Zh. Obshch. Khim., 7, 646 (1937).
2. E. G. Sharova, S. F. Aripova, and S. Yu. Yunusov, Khim. Prir. Soedin., 672 (1980).
3. S. F. Aripova and S. Yu. Yunusov, Khim. Prir. Soedin., 527 (1979).
4. S. F. Aripova, E. G. Sharova, S. Yu. Yunusov, and A. Dzhabbarov, Khim. Prir. Soedin., 245 (1983).
5. S. F. Aripova, V. M. Malikov, and S. Yu. Yunusov, Khim. Prir. Soedin., 290 (1977).
6. S. F. Aripova, E. G. Sharova, U. A. Abdullaev, and S. Yu. Yunusov, Khim. Prir. Soedin., 749 (1983).
7. E. G. Sharova, S. F. Aripova, and S. Yu. Yunusov, Khim. Prir. Soedin., 640 (1982).
8. R. T. Mirzamatov, V. M. Malikov, and S. Yu. Yunusov, Khim. Prir. Soedin., 493 (1972).

9. E. Wenkert, J. S. Bindra, C. J. Chang, D. W. Cochran, and F. M. Schell, Accounts Chem. Res., 7, 46 (1974).
10. L. Simeral and G. E. Maciel, Org. Magn. Res., 6, 223 (1974).
11. H. W. Avdovich and G. A. Neville, Can. J. Spectroscopy, 28, No. 1, 1 (1983).
12. F. W. Wehrli and T. Nishida, Fortschr. Chem. Org. Naturst., 36, 158 (1979).
13. F. W. Wehrli and T. Wirtlin, Interpretation of Carbon-13 NMR Spectra, Heyden, London (1976).
14. E. Breitmaier and W. Voelter, ^{13}C-NMR Spectroscopy, Verlag Chemie, Weinheim (1974).
15. F. I. Carrol, D. Smith, M. E. Waii, and C. G. Moreland, J. Med. Chem., 17, 985 (1974).
16. F. I. Caroll, A. Philip, and N. C. Coleman, Tetrahedron Lett., 1757 (1976).
17. M. Fuyita, M. Nagai, and T. Inoue, Chem. Pharm. Bull. (Tokyo), 30, No. 4, 1151 (1982).

ALKALOIDS OF *Haplophyllum leptomerum*.

I. THE STRUCTURE OF LEPTOMERINE

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From the epigeal part of the plant *Haplophyllum leptomerum* Lincz. et Vved. growing in the mountains of Babatag, Tadzhik SSR, which has not been studied previously, have been isolated β-sitosterol, the known alkaloids γ-fagarine, skimmianine, and N-methyl-2-phenyl-4-quinolone, and the new alkaloid leptomerine. On the basis of spectral characteristics, the structure of N-methyl-2-propyl-4-quinolone has been established for leptomerine.

Of 23 species of plants of the genus *Haplophyllum* growing on the territory of Central Asia, eight have not so far been studied by anyone. These include, in particular, *Haplophyllum leptomerum* Lincz. et Vved. We have begun the study of the alkaloid composition of the epigeal part of this plant collected by S. A. Khamidkhodzhaev in Babatag, Tadzhik SSR, in the budding period on May 20, 1984.

An ethanolic extract of the raw material was treated with ether, and from this the alkaloids were extracted in the usual way. The combined ether-extracted alkaloids were separated by chromatography on a column of silica gel. Ethereal eluates yielded the known alkaloids γ-fagarine, skimmianine, and N-methyl-2-phenyl-4-quinolone, and chloroform eluates, a new base which has been called leptomerine (I). β-Sitosterol was isolated from the neutral ether-soluble fraction of the extract with the aid of column chromatography. All the known substances were identified by TLC and mixtures with authentic specimens.

Leptomerine has mp 147-148°C (acetone) and is readily soluble in acids, chloroform, and ethanol and less readily in acetone and ether, and it is insoluble in water and alkalis.

The UV spectrum of (I) had the following absorption bands: λ_{max} 213, 230.5, 285.5, 294 nm (log ε 3.63, 3.61, 3.31, 3.40); λ_{min} 219, 246, 289 nm (log ε 3.42, 2.06, 3.24). On alkalinization the spectrum did not change, but in an acid medium the double maximum of the longwave band underwent a hypsochromic shift and was observed in the form of a single maximum at 273.5 nm. Such behavior is typical for the 2-alkyl-4-quinoline alkaloids containing an alkyl group at the nitrogen atom [1]. The IR spectrum of (I) contained absorption bands at 1635, 1600, and 1580 cm^{-1} of approximately equal intensity, which is characteristic for compounds of the 4-quinoline series [2].

In the PMR spectrum of leptomerine, the signals of the protons of an unsubstituted benzene ring of a 4-quinolone were observed at δ 8.34 ppm (q, 1H, J_{ortho} = 9 Hz, J_{meta} = 3 Hz; H_5) and 7.42 ppm (m, 3H, $H_{6,7,8}$); of a proton at C_3 with δ 6.11 ppm (s, 1H); of the protons of a

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