NMR INVESTIGATION OF ALKALOIDS I. ^{13}C NMR SPECTRA AND STEREOCHEMISTRY OF PENTACYCLIC OXINDOLE ALKALOIDS OF THE HETEROYOHIMBINE GROUP OF THE epiallo AND allo SERIES*

M. R. Yagudaev and S. Yu. Yunusov

UDC 547.944.1.92

The ^{13}C NMR spectra of pentacyclic oxindole alkaloids of the heteroyohimbine group of the allo and epiallo series have been studied and an assignment has been made of the CSs of the carbon atoms. Characteristic differences have been noted in the ^{13}C CSs of the C_2, C_3, C_7, C_{14}, C_{15}, and C_{19} carbon atoms that may be useful for solving stereochemical problems in new bases of this series from their ^{13}C NMR spectra.

Previously, on the basis of a detailed study of the proton magnetic resonance (PMR) and circular dichroism spectra the stereochemistries and absolute configurations have been established for pentacyclic oxindole alkaloids of the heteroyohimbine group of two series: epiallo [vinerine (I) and vineridine (II)] and allo [isovineridine (III), N-acetylvineridine (IV), majdine (V), and isomajdine (VI)] [2-4]; characteristic indications of differences were found between them in the chemical shifts (CSs) and spin–spin coupling constants (SSCCs) of the protons [5]. In addition to PMR spectroscopy, the method of NMR on ^{13}C nuclei has recently come into wide and successful use for the solution of stereochemical and conformational problems among alkaloids of indole series [6-10], the isoquinoline series [12], the quinolizidine series [13], and the diterpene series [14, 15], the *Amaryllidaceae* alkaloids [16-18], and other natural compounds [19]. There is information in the literature on the study of the ^{13}C NMR spectra of two model tetracyclic oxindoles with C_3-S differing in the configuration of the C_7 spiro center, and also of two tetracyclic natural alkaloids similar to them, rhynchophylline (7R, 3S), and isorhynchophylline (7S, 3S) [6] and other oxindole alkaloids gelsemine and gelsevirine [7], having a more complex structure. Borges et al. [31] have given the ^{13}C CSs for two pentacyclic oxindole alkaloids of the allo-7S series. However, the ^{13}C spectra of alkaloids of the epiallo- and allo-7R series have remained completely unstudied. In the present paper we discuss the results of an investigation of the ^{13}C NMR spectra of alkaloids (I-VI) in order to find a correlation of the ^{13}C CSs with the stereochemistries of these compounds (Table 1, Figs. 1-4). In the ^{13}C NMR spectra of the substances studied, the signals from the sp^2 and sp^3 hydrocarbons appear clearly, corresponding completely in number and multiplicity to structures (I-VI). We made the assignment of the ^{13}C signals on the basis of an experiment on incomplete decoupling of C–H interactions, i.e., from the multiplicity of the ^{13}C signal in the off-resonance spectra, and on the basis of a comparison with literature information on the ^{13}C NMR spectra of the molecules of similar structure — oxindole [7, 20], dihydropyran [8, 28, 29], some model and natural oxindole bases [6], and pentacyclic indole alkaloids [11] — also taking into account spatial effects on the ^{13}C CSs [21, 22]. In the assignment of the ^{13}C signals of the aromatic carbon atoms we started from the values of their π-charge contributions which we calculated by the HMO and PPP methods [4], since it is known that the π-charges in aromatic and heteroaromatic systems correlate qualitatively with the CSs of the ^{13}C nuclei [23-26]. In addition, the assignment of the signal of the C_{12} aromatic carbon atom in N-acetylvinerine (IV) was made with allowance for the influence on it of the electrical field of the C=O group of the N-acetyl radical [21]. We had previously [4] established by analyzing the PMR spectrum of (IV) that the C=O group of the $COCH_3$ radical had the endo conformation:

*Communicated at the All-Union Conference on Recent Advances in High-resolution NMR spectroscopy, Tashkent, September, 1979 [1].

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 217-224, March-April, 1980. Original article submitted December 17, 1979.

 0009-3130/80/1602-0170$07.50

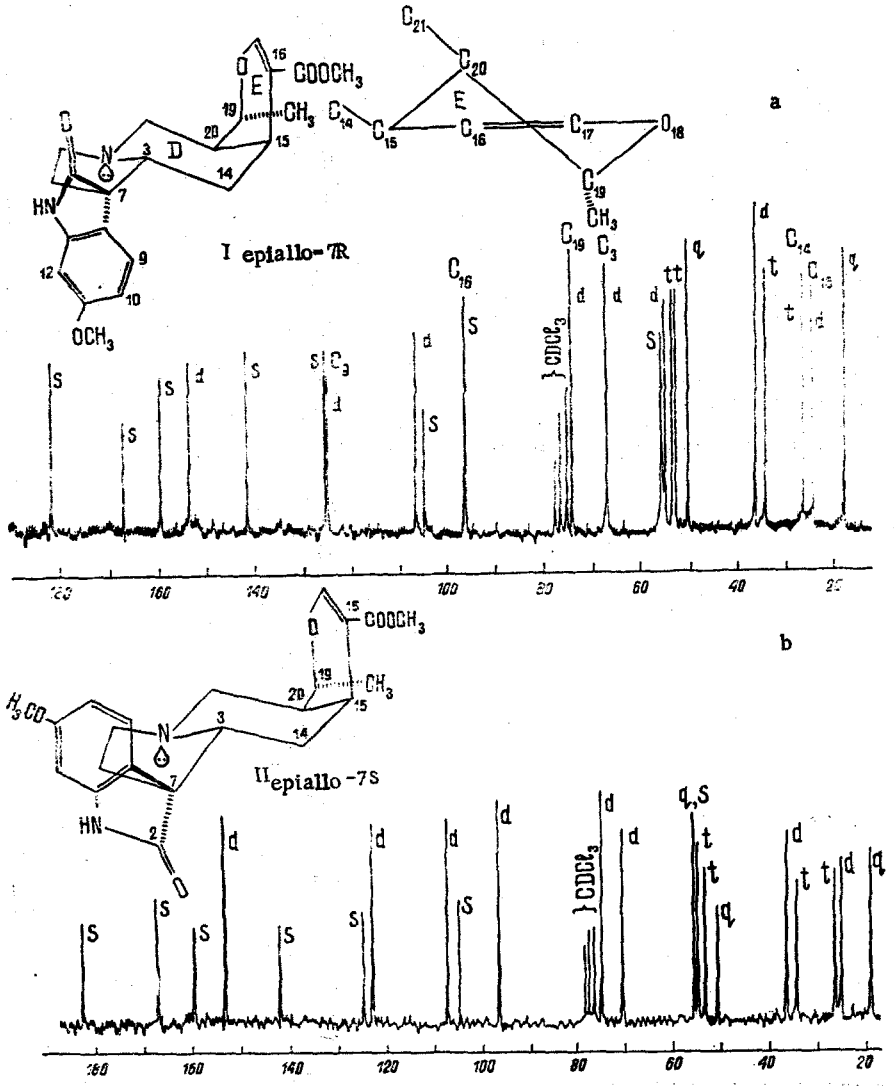
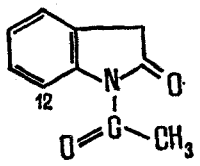


Fig. 1. ^{13}C NMR spectra of vinerine (a) and vineridine (b).



It follows from a comparison of the ^{13}C CSs of the aromatic carbons of dihydroindole [27] and its N-acetyl derivative [21] that in this conformation the C=O group shifts the signal of the C_{12} carbon downfield by approximately 6.5 ppm.

A consideration of Table 1 and Fig. 1a, b shows that in the ^{13}C NMR spectrum of vinerine (I) the signals of all 22 carbon atoms appear clearly, while in the spectrum of vineridine the CSs of two ^{13}C nuclei coincide, because of which only 21 signals are observed.

Since the CS of the C_{19} carbon is scarcely affected by a change in the C_7 configuration to allo in the oxindoles (III-VI) and by the remote ring B in the pentacyclic indoles [11], there are grounds for considering that in the epiallo alkaloids the C_{19} CS will change less than the C_3 CS. Consequently, in the epiallo alkaloids (I) and (II) we assigned the doublets at 67.2 and 70.1 ppm, respectively, to the C_3 carbon atoms in them.

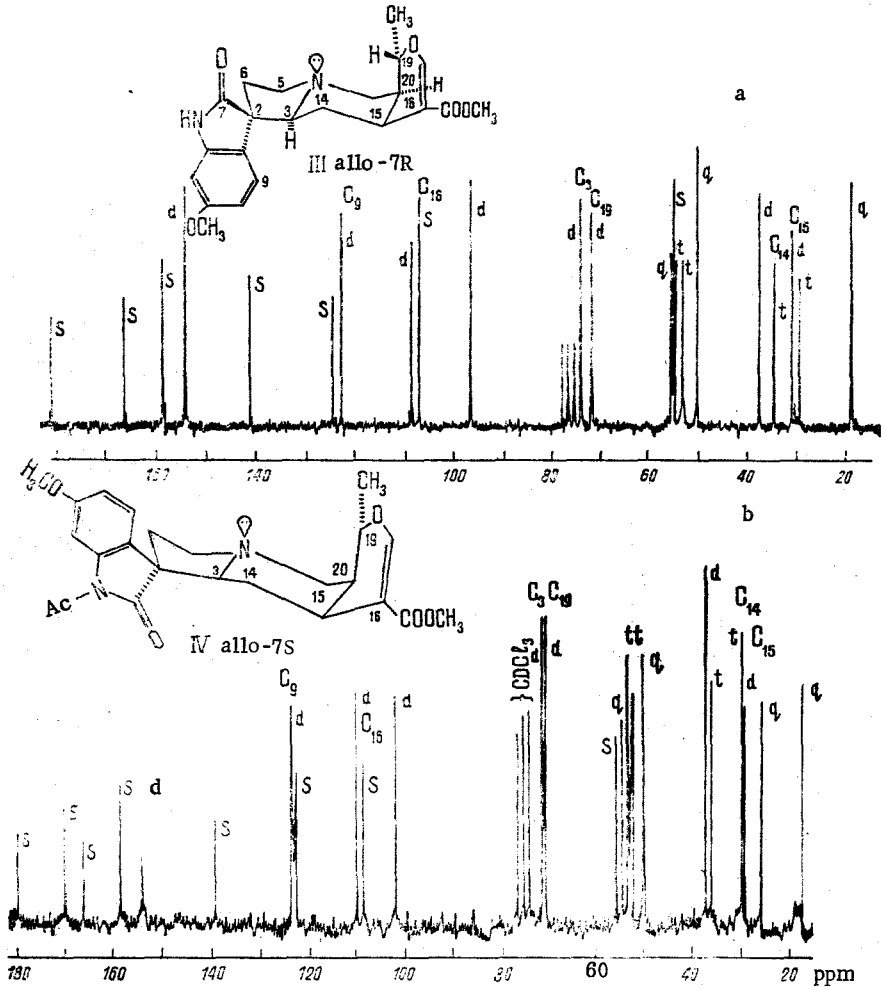


Fig. 2. ^{13}C NMR spectra of isovineridine (a) and N-acetylvinerine (b).

A comparison of the ^{13}C CSs in the spectra of (I) and (II) shows that a change in the configuration of the C_7 spiro center leads to a downfield shift of the C_3 signal by 2.9 ppm, while the signal of the C_7 spiro center itself shifts upfield by 0.7 ppm (Table 1). In addition, the change in the C_7 center from the R configuration in (I) to S in (II) causes an upfield shift of the signal of the C_9 carbon of the aromatic ring by 1.7 ppm. The latter is apparently due to the influence of the unshared pair of electrons (UPE) of the N_4 nitrogen atom on the screening of C_9, since the distance from the center of the N_4 UPE to C_9 in (II) is considerably less than in (I). An analysis of the figures in Table 1 shows that a change in the configuration of the C_7 center from R to S in the epiallo alkaloids (I) and (II) also leads to an appreciable change in the CSs of the C_2, C_{10}, C_{13}, C_{14}, and C_{21} carbon atoms.

On passing from the epiallo series of alkaloids (substances I and II) to the allo series (III and IV), the ^{13}C CSs of the carbon atoms of rings D and E change considerably. This is apparently due to a stereochemical difference of these rings in the two series, in which the simultaneous change in the configuration of the C_3 and N_4 centers leads to the conversion of the piperidine ring (D) and the dihydropyran ring (E) from one chair conformation for D and one half-chair conformation for E (a) into others (b) [5].

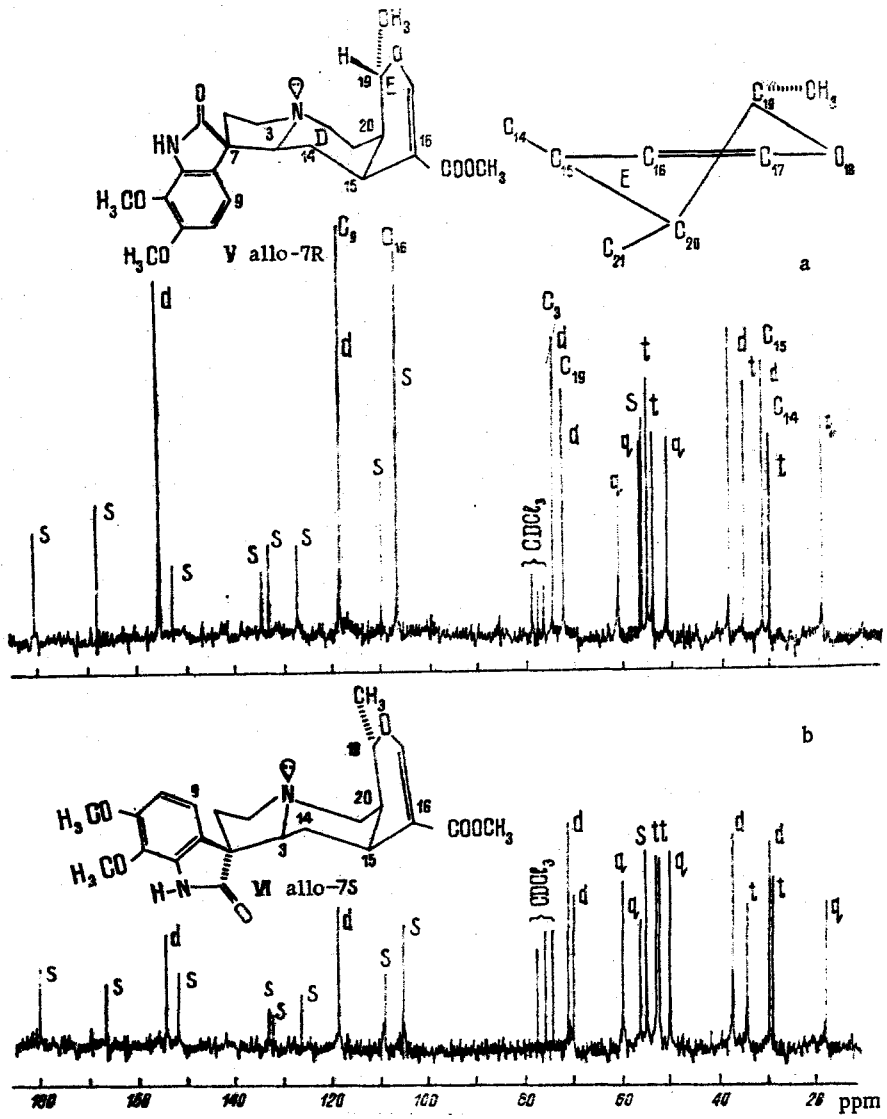
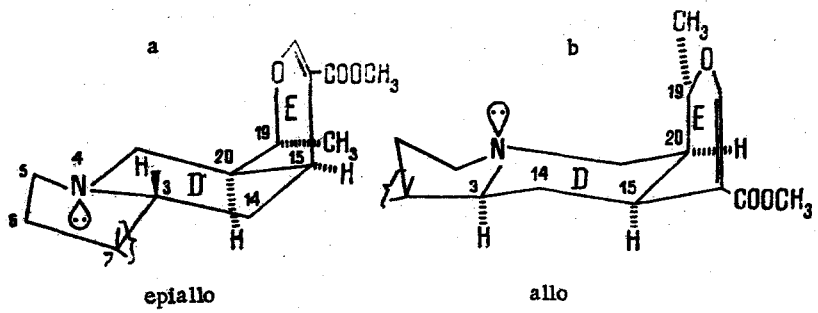


Fig. 3. ^{13}C NMR spectra of majdine (a) and isomajdine (b).



As a result of this, the CSs of the signals of the carbon atoms of rings D and E — C_3, C_{14}, C_{15}, C_{16}, and C_{19} — undergo considerable changes, the greatest downfield shift of $\Delta\delta$ = 7.0 ppm being undergone by the C_3 signal on passing from an epiallo-7R alkaloid (I) to allo-7R alkaloids (III and V) (Table 1). This paramagnetic shift of the C_3 carbon atom in (I) as compared with (III) and (IV) can obviously be used as a test characteristic for the differentiation and stereochemical identification of oxindole bases of the epiallo-7R and allo-7R series from their ^{13}C NMR spectra. In addition to the change in the CSs of the

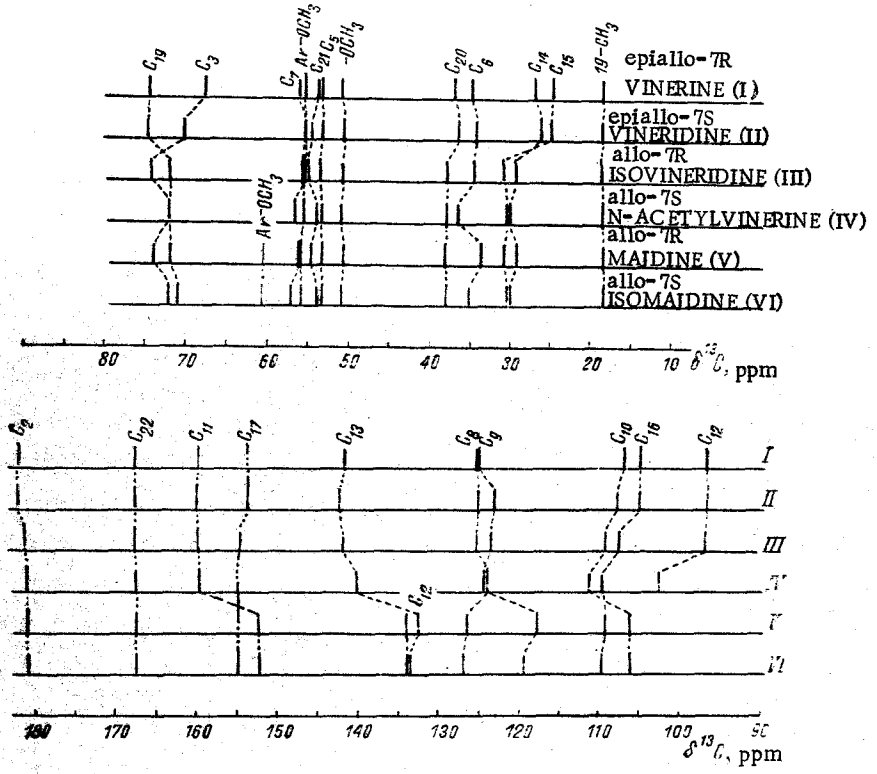
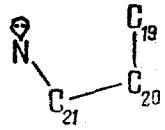


Fig. 4. ^{13}C chemical shifts, their assignment and correlation with the stereochemical differences of the oxindole alkaloids of the epiallo and allo series.

C_3, C_{14}, C_{15}, and C_{16} carbon atoms, because of the conversion of rings D and E and the inversion of the N_4 UPE the observed characteristic upfield shift of 2.5 ppm of the signal of the C_{19} carbon in the alkaloids of the allo series (III-VI) as compared with those of the epiallo series (I, II) is mainly caused by the "γ-gauche" effect of the UPE of the N_4 atom on the C_{19} carbon atom in the alkaloids of the allo series (see Scheme), in which the N_4 UPE is almost twice as close to C_{19} as in the alkaloids of the epiallo series [4]. This is confirmed by the results reported by Tourwe and Van Binst [22], who report that the γ-effect of the UPE of a nitrogen atom is of the same order of magnitude as that of a C—H bond, the nitrogen atom and its UPE being considered as a single whole. In addition to this, a contribution to the change in the CS of the



C_{19} carbon may also be made by the C_{19}—CH_3 reorientation taking place as the result of the conversion of ring E from one half-chair conformation [Fig. 1a, epiallo (I)] to another [Fig. 3a, allo (V)]. Although a strict quantitative account of this fact is difficult because of the absence of literature information on the ^{13}C NMR spectroscopy of methyl-substituted dihydropyrans [28, 29], it is known that in 4-methyl-substituted cyclohexanes the weak-field α-contribution from an axial CH_3 group is only half that from an equatorial one [30]. Consequently, it could be expected that in the epiallo alkaloids (I) and (II) with an axial CH_3 group the signal from the C_{19} carbon would be present in a stronger field than the corresponding one for alkaloids of the allo series (III-VI). Since experiment shows the opposite values of the C_{19} CSs in the two series considered, it is obvious that the upfield shift of the C_{19} signal in the allo alkaloids is due mainly to the γ-effect of the UPE of the N_4 nitrogen atom on the C_{19} carbon atom.

TABLE 1. Chemical Shifts and Assignments of the ^{13}C Signals of Pentacyclic Oxindole Alkaloids of the epiallo and allo Series

Carbon and multiplicities	epiallo		allo			
	vinerine (I) 7R3R4S	vinderidine (II) 7S3R4S	isovineridine (III) 7R3S4R	N-acetylvinerine (IV) 7S3S4R	majdine V 7R3S-4R	isomajdine (VI) 7S3S4R
C_2s	182,0	182,5	181,5	180,7	180,8	180,8
C_3d	67,2	70,1	74,3	72,3	74,0	72,1
C_5t	53,2*	53,2*	53,6*	53,5*	53,3*	53,4*
C_6t	34,8	34,2	34,6	36,6	33,7	35,1
C_7s	56,0	55,3	55,4	56,6	55,9	57,1
C_8s	125,4	125,0	125,1	123,9	126,5	126,9
C_9d	125,3	123,0	123,3	124,3	117,8	119,4
$C_{10}d$	106,8	107,6	109,1	111,1	106,1	106,6
$C_{11}s$	159,6	159,8	159,7	159,6	152,2	152,1
$C_{12}d$	96,6	96,7	96,8	102,7	133,9S	132,9S
$C_{13}s$	141,5	142,2	141,8	140,2	132,5	133,7
$C_{14}t$	27,0	26,2	29,5	30,1	29,3	30,2
$C_{15}d$	24,8	25,1	31,0	30,4	30,8	30,4
$C_{16}s$	104,9	105,1	107,5	109,6	109,1	109,8
$C_{17}d$	153,5	153,5	154,5	154,9	154,9	154,8
$C_{19}d$	74,5	74,6	72,1	72,0	72,0	71,1
$C_{20}d$	36,8	36,5	37,9	37,8	38,1	38,0
$C_{21}t$	53,7*	54,6*	55,0*	54,0*	54,6*	53,9*
$C_{22}s$	167,3	167,3	167,4	167,3	167,4	167,4
$19-CH_3q$	18,4	18,5	18,9	18,5	18,6	18,4
$Ar-OCH_3q$	55,3	55,3	55,7	55,5	56,2	55,9
					60,5	60,7
$-OCH_3q$	50,7	50,3	50,7	50,8	50,6	50,8
$N\langle^{C=Os}_{CH_3q}$				170,7 26,6		

*The assignments of the signals of the C_3 and C_{21} carbons may be the reverse.

It can be seen from the figures given in Table 1 that within the allo series of substances (III-VI) characteristic differences can be traced in the CSs of the C_3, C_7, and C_9 carbon atoms which depend on the configuration of the C_7 spiro center: in the C_7-R case (III-V), the signal of the C_3 carbon atom shifts downfield by about 2 ppm and the signals of the C_7 and C_9 carbon atoms upfield by 1.2 and 1-1.6 ppm, respectively, as compared with their corresponding positions in the C_7-S case (IV, VI). These differences in the ^{13}C CSs of the C_3, C_7, and C_9 carbon atoms for substance (III-VI) are in complete harmony with the analogous results reported for model and natural tetracyclic oxindoles [6]. The correlations of the CSs of the ^{13}C carbon atoms with the conformations and absolute configurations of the alkaloids studied that have been found may be useful for solving stereochemical problems of new bases of this series.

EXPERIMENTAL

The ^{13}C NMR spectrum of all the substances were obtained on a Varian XL-100-15 spectrometer at a frequency of 25.16 MHz in the pulsed regime followed by Fourier transformation under the conditions of complete and partial off-resonance decoupling from protons. Deuterochloroform was used as the solvent. The concentration of the solutions was 0.2-0.3 M. To calculate the ^{13}C CSs of substances (I-VI) we started from the CS of the central peak of the ^{13}C signal (triplet) of the solvent, which is 76.91 ppm relative to TMS. The accuracy of the determination of the ^{13}C CSs was ± 0.04 ppm.

SUMMARY

1. The ^{13}C NMR spectra of pentacyclic oxindole alkaloids of the heteroyohimbine group of the epiallo and allo series have been studied and assignments of the CSs of the carbon atoms have been made.

2. Characteristic differences have been found in the ^{13}C CSs of the C_2, C_3, C_7, C_9, C_{14} C_{15}, and C_{19} carbon atoms which will permit the stereochemical identification of such bases from their ^{13}C NMR spectra.

LITERATURE CITED

1. M. R. Yagudaev and S. Yu. Yunusov, in Abstracts of Lectures at an All-Union Conference on Modern Advances in High-Resolution NMR Spectroscopy, Tashkent, September 25-27, 1979 [in Russian], Tashkent (1979), p. 81.
2. M. R. Yagudaev, N. Abdurakhimova, and S. Yu. Yunusov, Khim. Prir. Soedin., 197 (1968).
3. I. Ognyanov, B. Pyuskyulev, I. Kompis, T. Sticzay, G. Spiteller, and M. Shamma, Tetrahedron, 24, 4641 (1968).
4. M. R. Yagudaev and S. Yu. Yunusov, Abstracts of the Third Soviet–Indian Symposium on the Chemistry of Natural Products, Tashkent, October 22-25 (1973), p. 173; M. R. Yagudaev, V. M. Malikov, and S. Yu. Yunusov, Khim. Prir. Soedin., 70 (1973); 493 (1974)
5. M. R. Yagudaev and S. Yu. Yunusov, Khim. Prir. Soedin., 345 (1976).
6. E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, Acc. Chem. Res., 7, 46 (1974).
7. E. Wenkert, C.-J. Chang, D. W. Cochran, and R. Pellicciari, Experientia, 28, 378 (1972).
8. E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neues, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, J. Am. Chem. Soc., 90, 4990 (1973).
9. Y. Rolland, N. Kunesch, J. Poisson, E. W. Hagaman, F. M. Schell, and E. Wenkert, J. Org. Chem., 41, 3270 (1976).
10. S. R. Johns, J. A. Lamberton, B. P. Moore, and A. Sioumis, Austr. J. Chem., 28, 1627 (1975).
11. R. H. Levin, J.-Y. Lallemand, and J. D. Roberts, J. Org. Chem., 38, 1983 (1973).
12. D. W. Hughes, H. L. Holland, and D. B. Maclean, Can. J. Chem., 54, 2252 (1976).
13. F. Bohlmann and R. Zeisberg, Chem. Ber., 108, 1043 (1975).
14. A. J. Jones and M. N. Benn, Can. J. Chem., 51, 586 (1973).
15. S. W. Pelletier and Z. Djarmati, J. Am. Chem. Soc., 98, 2626 (1976).
16. W. O. Crain, Jr., W. C. Wildman, and J. D. Roberts, J. Am. Chem. Soc., 93, 990 (1971).
17. L. Zetta, G. Gatti, and C. Fuganti, J. Chem. Soc., Perkin Trans. 2, 1180 (1973).
18. E. Breitmayer and W. Voelter, ^{13}C NMR Spectroscopy, Verlag Chemie., Weinheim (1974).
19. E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gasic, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, P. M. Wovkulich, and A. Zheleva, Topics in Carbon-13 NMR Spectroscopy, 2, 81 (1976).
20. P. G. Gassman, D. P. Gilbert, and T. Y. Luh, J. Org. Chem., 42, 1340 (1977).
21. H. Fritz and T. Winkler, Helv. Chim. Acta, 59, 903 (1976).
22. D. Tourwe and G. Van Binst, Heterocycles, 9, 507 (1978).
23. J. B. Stothers, Quart. Revs., 144 (1967).
24. U. Ewers, H. Gunter, and L. Jaenicke, Chem. Ber., 107, 876 (1974).
25. G. T. Martin, M. L. Martin, and S. Odiot, Org. Magn. Reson., 7, 2 (1975).
26. D. G. Farnum, Adv. Phys. Org. Chem., 11, 123 (1975).
27. S. Mamatas-Kalamara, T. Sevenet, C. Thal, and P. Potier, Phytochemistry, 14, 1637 (1975).
28. T. Pehk and E. Lippmaa, Eesti NSV Tead. Acad. Toim Geol, 17, 291 (1968).
29. S. D. Stothers, Carbon-13 NMR Spectroscopy, Academic Press, New York (1972).
30. T. I. Pekhk, Kh. É. Kooskova, É. T. Lippmaa, V. I. Lysenkov, and I. I. Bardyshev, Vestsi Akad. Navuk BSSR, Ser. Khim., No. 2, 28 (1976).
31. J. Borges, M. T. Manresa, J. L. Martin Ramon, C. Pascual, and Y. A. Rumbero, Tetrahedron Lett., 3197 (1979).