The Preparation of the Amines (XII-XIV) by a Modified Craig Method [8]. N-(2-Hydrobenzyl)cytisine (XIV). A mixture of 1 g of cytisine and 1 ml of salicylaldehyde was boiled in 20 ml of toluene for 4 h. After cooling, the toluene was decanted off and to the reaction product melted in the form of an oil, was added 30 ml of methanol and sodium tetrahydroborate. After a working up process similar to that described above, N-(2-hydroxybenzyl)cytisine was isolated from the reaction mixture by trituration with acetone; it was an amorphous substance with M^+ 296.

N-(2-Hydroxybenzyl)nortropine (XIII). A mixture of 0.5 g of nortropine and 0.5 g of salicylaldehyde was boiled in 2 ml of methanol for 4 h, and then 0.5 g of sodium tetrahydroborate was added to the hot solution over 10 min. After the cessation of the evolution of hydrogen, the solvent was evaporated off. The residue after the appropriate working up gave an amine with mp 166-170°C, M^+ 233.

N-(2-Hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XII) was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and salicylicaldehyde by the method described above for the amine (XIII). For (XII) we found M^+ 299.

CONCLUSION

The thermal decomposition of 2-hydroxybenzylamines has been studied. It has been shown that the thermolysis reaction takes place smoothly and the corresponding amines can be obtained in good yield.

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THE NMR STUDY OF ALKALOIDS.

VI. A COMPARISON OF THE STEREOCHEMISTRIES OF PSEUDOCOPSININE AND 14,15-DIHYDROVINDOLININE BY ^{13}C NMR SPECTROSCOPY

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UDC 547.944.1.92

On the basis of a comparative study of the ^{13}C NMR spectra of the natural alkaloid pseudocopsinine and its synthetic analog 14,15-dihydrovindolinine it has been shown that their stereochemistries are not identical.

The alkaloid pseudocopsinine (I) [mp 136-138°C (benzene), $[\alpha]_D$–30.4° (c 1.51, methanol); dihydrochloride with mp 266-268°C (methanol, decomp.)] has been isolated from the epigeal part of *Vinca erecta* Regel et Schmalh., family Apocynaceae [1]. A structure was proposed for it on the basis of its chemical and spectral characteristics (UV, IR, PMR, and mass spectra [2, 3]). Then the structure was refined by the method of x-ray structural analysis and the spatial structure and absolute configuration of all the asymmetric centers of (I) were established unambiguously [4-6]. The skeleton of the alkaloid (19R)-pseudocopsinine (I) is identical with the skeleton of (19R)-vindolinine (II) isolated from various species of the family Catharanthus [7].

According to the results of ^{13}C NMR [8] and PMR at a frequency of 300 MHz [9] of (19R)-vindolinine and also its x-ray structural analysis [10], (I) and (II) have identical spatial structures with the cis linkage of rings F and G and with the S configuration of the C_{21} carbon atom except for ring G which contains a C_{14}=C_{15} double bond in (II) and not in (I). Con-

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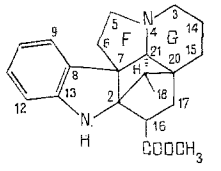
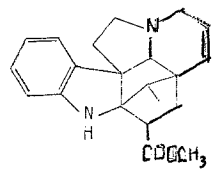
sequently, there are grounds for assuming that the stereochemistry of pseudocopsinine (I) and of 14,15-dihydrovindolinine (IIa) may be identical. Riche and Pascard-Billy [10] considered 14,15-dihydrovindolinine to be identical with pseudocopsinine. However, a comparison of the



I



II

IIa(14,15-dihydro-II)

melting points of the dihydrochlorides of pseudocopsinine (266-268°C) [1] and of 14,15-dihydrovindolinine (185-195°C) [7] showed a substantial difference. Unfortunately, in this paer [7] the melting point and $[\alpha]_D$ value of (IIa) are not given, and therefore it appeared of interest to compare the stereochemistries of pseudocopsinine and of 14,15-dihydrovindoline from their ^{13}C NMR spectra. The ^{13}C NMR spectrum of 14,15-dihydrovindolinine and the assignments of all the carbon atoms have been given elsewhere [8]. Our task amounted to obtaining the ^{13}C NMR spectrum of pseudocopsinine under the conditions of complete and incomplete decoupling of the C—H interactions and then to comparing and analyzing the CSs of the carbon atoms of (I) and (IIa). The results are given in Table 1 and Fig. 1.

It must be mentioned that the assignment of the signals of the aminoethylene carbon atoms, C-3 and C-5, in vindolinine and its 14,15-dihydro derivative is ambiguous [8] and may be reversed, since the hydrogenation of the isolated double bond in N-methyl-3,4-dehydropiperidine, taken as a model [11], led to a downfield shift of the signal of the 2-aminomethylene carbon by 2 ppm, while in the ^{13}C NMR spectrum of compound (IIa) the signal of the C-5 aminomethylene carbon atom is shifted upfield by 3 ppm in comparison with that in (II). In alkaloids close in structure to (I) and (IIa) a strong-field signal (46.5 ppm) has been assigned to the C-3 carbon atom [12].

It can be seen from Table 1 and Fig. 1 that in the ^{13}C NMR spectrum of pseudocopsinine with complete decoupling of C—H interactions the signals of 21 carbon atoms appear clearly in the 175-6 ppm region. In the 175-110 ppm region are observed the signals of seven sp^2-carbons (one C=O and six aromatic carbons), while three of the signals in the off-resonance spectrum are represented by singlets (C=O, C-13, and C-8) and the remaining four by doublets (C-11, C-9, C-10, and C-12). The number and multiplicities of the signals of the sp^3-carbon atoms correspond accurately to the nonaromatic part of the structure of (I). A comparison of the CSs of the signals of the carbon atoms in (I) and (IIa) (see Table 1) shows an appreciable difference for many of them, thereby indicating different stereochemistries of pseudocopsinine and 14,15-dihydrovinine. The CSs of carbon atom C-21, linked to the nitrogen atom N_4, have a particularly large difference in (I) and (IIa), amounting to 6.7 ppm. In addition to this, the differences in the CSs of the C-8, C-17, and C-6 carbon atoms are considerable. The positions of the other signals in (I) and (IIa) are either close (with differences of 0.5-2 ppm) or coincide.

Ahond et al. [8] have reported that the anomaly of the CSs of the C-21 carbon atoms in the ^{13}C NMR spectra of vindolinine derivatives, including the 14,15-dihydro derivative, re-

TABLE 1. Characteristics of the ^{13}C NMR Spectra of Pseudocopsinine and of 14,15-Dihydrovindolinine in $CDCl_3$

Carbon atom	Multiplicity	CS, ppm		Carbon atom	Multiplicity	CS, ppm	
		I	IIa [8]			I	IIa [8]
C-2	s	79.9	80,6	C-14	t	19,1	20,7
C-3	t	55.5*	55,0*	C-15	t	33,2	31,2
C-5	t	47.3*	48.1*	C-16	d	40,0	40,2
C-6	t	34.6	37.3	C-17	t	24,8	29,0
C-7	s	60,0	60,3	H_3C-18	q	6,8	7,5
C-8	s	135,0	140,1	C-19	d	51,6	51,0
C-9	d	125,3	123.6	C-20	s	42.6	44.5
C-10	d	121,8	121,1	C-21	d	72,1	78,8
C-11	d	128,1	127,2	C=O	s	173,4	175,0
C-12	d	112 0	112,7	OCH_3	q	52,1	52,0
C-13	s	148,3	149,5				

*The assignment of the C-3 and C-5 signals is ambiguous and they may be interchanged.

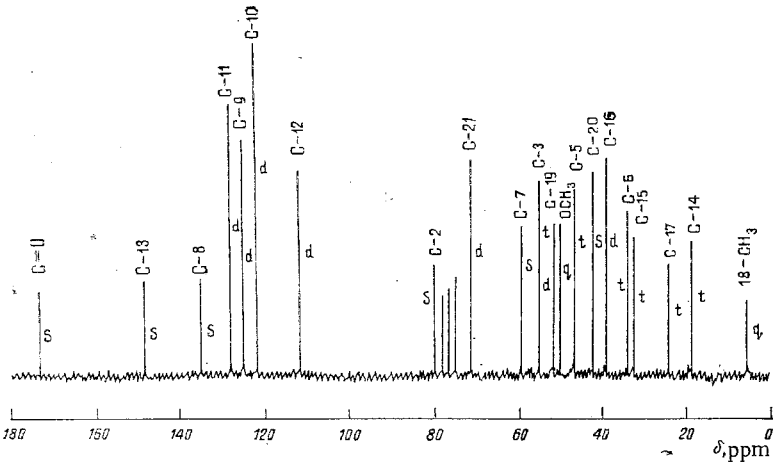


Fig. 1. ^{13}C NMR spectrum of pseudocopsinine in $CDCl_3$.

flect the pronounced strain imposed by the norbornane unit on the piperidine ring. At the same time, the value of the CS of the C-21 carbon atom of pseudocopsinine shows the absence of strain, or an extremely weak strain, imposed by the norbornane chain on the piperidine ring G. Apparently, such a substantial difference in the CSs of the signals of the C-21 carbon atoms in the ^{13}C NMR spectra can be explained through a change in the configuration of the C-21 center or of the UEP of the N_4 nitrogen atom of ring G in (IIa) possible taking place as the result of the hydrogenation of the 14,15-double bond of vindolinine. A change in one of the centers in (IIa) must naturally lead to a change in the linkage of rings F and G from cis in (I) and (II) to trans in (IIa). For a definitive confirmation of this hypothesis the stereochemistry of 14,15-dihydrovindolinine must be determined by x-ray structuralanalysis. Thus, a comparative analysis of the ^{13}C NMR spectra of synthetic 14,15-dihydrovindolinine and the natural alkaloid pseudocopsinine has shown that their stereochemistries are not identical.

EXPERIMENTAL

The ^{13}C NMR spectra of pseudocopsinine were obtained on a Varian XL-100-15 spectrometer with a frequency of 25.16 MHz in $CDCl_3$ (0 — TMS; $\delta_{TMS} = \delta_{CDCl_3} + 76.91$ ppm) in the pulsed regime followed by Fourier transformation under the conditions of complete and incomplete decoupling of C—H interactions.

CONCLUSION

1. On the basis of a comparative study of the ^{13}C NMR spectra of the natural alkaloid pseudocopsinine and its synthetic analog 14,15-dihydrovindolinine it has been shown that their stereochemistries are not identical.

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IONIZATION CONSTANTS OF A NUMBER OF ALKALOIDS USED IN MEDICINE

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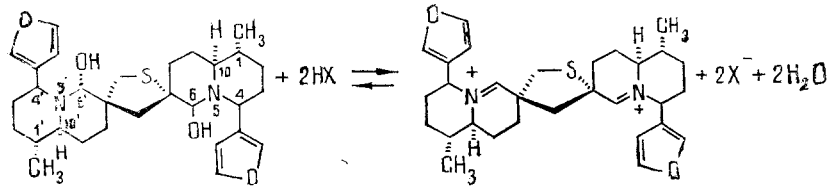
UDC 541.127+537.57+547.94+615.322

The pK_a values of a number of alkaloids in water or in aqueous ethanol have been measured by the potentiometric titration method: nuphleine — 4.59, 6.98; brevicolline — 5.17, 8.02; chelidonine — 6.40; sanguinarine — 7.32; chelerythrine — 7.53; stepharine — 8.48; d-pseudoephedrine — 9.49. For nuphleine and brevicolline, each of which has two nitrogen atoms capable of protonation, assignments have been made of pK_a values to the corresponding atoms on the basis of the results of UV spectroscopy.

Information on the extent to which substances are ionized at a particular pH value is necessary both for choosing the optimum technology of isolating alkaloids from plant sources and also for the correct determination of the quality indices of the substances of the preparations and their medicinal forms.



We have determined the pK_a values of a number of alkaloids used in medical practice as drugs or present in plants used as drugs: d-pseudoephedrine, stepharine, brevicolline, nuphleine, sanguinarine, chelerythrine, and chelidonine (Table 1). All the alkaloids investigated are bases of medium strength in water or aqueous ethanol and their ionization constants differ by several orders of magnitude.

The nuphleine and brevicolline molecules each have more than one nitrogen atom, and therefore we shall consider the features of their ionization. Salt formation by nuphleine, as an α-carbinolamine, is accompanied by the splitting out of two molecules of water and the appearance of two $C=\overset{+}{N}$ double bonds [1]. This is confirmed, in particular, by the presence in the PMR spectrum of nuphleine in trifluoroacetic acid of two one-proton singlets at 7.96 and 8.27 ppm (0 — TMS) due to two $HC=\overset{+}{N}$ groups, and an absorption band at 293 nm in the UV spectrum (96% ethanol) of a salt of hydrochloric acid.

The fact that two nitrogen atoms separated by five saturated carbon atoms have ionization constants differing by more than two orders of magnitude indicates their different basicities. The question of which of the nitrogen atoms is the more basic (pK_a 6.98) was answered with the aid of UV spectroscopy.

It has been shown [2] that absorption in the 290-295-nm region in acid solutions of thiospiran alkaloids is connected with an intermolecular interaction of the sulfur atom and

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