INFLUENCE OF SOLVENTS ON THE PARAMETERS OF THE PMR SPECTRA OF *Amaryllidaceae* ALKALOIDS. IV

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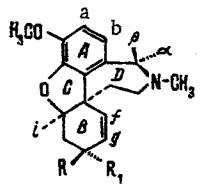
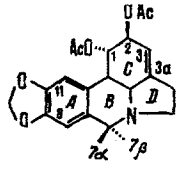
Continuing investigations of the laws of the influence of solvents on the parameters of the PMR spectra of alkaloids [1-3], we give the results for galanthamine [4], narwedine [5], dihydrolycorine diacetate and lycorine diacetate [6], ungerine [7], and hippeastrine [8].



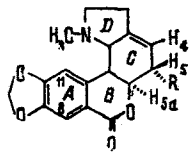
I. R=OH, R_1=H

II. R+R_1=O



IV. lycorine diacetate

III. 3-3a-dihydro



V. R=OCH$_3$

VI. R=OH

Influence of Aromatic Solvents

Galanthamine (I) and Narwedine (II). The cause of the shift of the resonance signals in aromatic solvents is the formation of molecular complexes between the molecules of the substances and the solvents. We have established (Tables 1 and 2) that the change in the chemical shift (CS) of the methoxy group in (I) and (II) due to the influence of C_6D_6 is 0.48 ppm. A similar value of Δ for the OCH_3 group in an aromatic nucleus has also been found in the case of γ-fagarine [2], which agrees with information in the literature [9, 10]. To explain the changes in the CSs of the olefinic protons and the H_i protons of ring B of narwedine in benzene it is apparently possible to bring in the "rule of the carbonyl plane of reference," which has been used, in particular, in the 2-cycloalkenone series [11]. The inapplicability of this rule for explaining Δ of the same protons in galanthamine is obvious, since the latter does not have a carbonyl group. At the same time, benzene has a fairly appreciable influence on the CSs of the protons of ring B in (I). Thanks to the mutual repulsion of the π-currents of the benzene ring and of the double bond of ring B in galanthamine, the preferential orientation of C_6D_6 is apparently close to H_i, as a result of which its relative CS is greater than that of H_f and H_g (see Table 1). The difference $\Delta N - CH_3$ for galanthamine (+0.16) and narwedine (+0.23), and also for the H_a, H_b, and $ArCH_2N$ protons can obviously be explained by changes in the conformations of the labile seven-membered ring D, the orientation of the unshared pair of electrons of the nitrogen atom, and the different orientations of the benzene molecule. The aromatic protons *a* and b of ring A and those of the $Ar-CH_2-N$ group in (I) and (II), falling within the screening cone of the benzene, undergo considerable diamagnetic shifts. The influence of pyridine on the CSs of the protons in the bases (I) and (II) is basically insignificant and has a variable nature. In view of this, there is no necessity for discussing the results obtained in detail.

Dihydrolycorine Diacetate (III) and Lycorine Diacetate (IV). A comparison of the results obtained (Tables 3 and 4) shows that $\Delta^{C_6D_6}_{CDCl_3}$ of the H_8 protons and the OCH_2O groups for (III) and (IV) is +0.15 and 0.57 ppm, respectively. The influence of pyridine on the CSs of these protons is insignificant. Considerable diamagnetic shifts (from +0.33 to +0.50 ppm)

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TABLE 1

Solvent	Chemical shifts of the protons of galanthamine (δ, ppm) and their relative diff. (Δ)									
	NCH_3	OCH_3	H_t	Ar–CH_2–N		H_g	H_f	H_a	H_b	C(OH)H
				H_β	H_α					
$CDCl_3$	2,43	3,86	4,62	3,68	4,12	6,05	6,05	6,65	6,65	4,14
CCl_4	2,29 +0,14	3,79 +0 07	4,48 +0,14	3,54 +0,14	4,05 +0,07	5,93 +0,12	5,93 +0,12	6,52 +0,13	6,46 +0,19	3,98 +0,16
CS_2	2,29 +0,14	3,72 +0,14	4,41 +0,21	3,50 +0,18	3,96 +0,16	5,88 +0,17	5,88 +0,17	6,46 +0,19	6,46 +0,19	3,89 +0,25
CD_3CN	2,30 +0,13	3,80 +0,06	4,56 +0,06	3,61 +0,07	4,09 +0,03	5,88 +0,17	6,10 −0,05	6,75 −0,10	6,45 +0,20	4,09 +0,05
CD_3OD	2,39 +0,04	3,80 +0,06	4 56 +0,06	3,64 +0,04	4,10 +0,02	5,91 +0,14	6,13 −0,08	6,73 −0,08	6,65 0,00	4,16 −0,02
$(CD_3)_2CO$	2,30 +0,13	3,76 +0,10	4,54 +0,08	3,62 +0,06	4,11 +0,01	5,89 +0,16	6,12 −0,07	6,70 −0,05	6,60 −0,05	4,07 +0,07
DMSO	2,27 +0,16	3,73 +0,13	4,48 +0,14	3,58 +0,10	4,12 0,00	5,80 +0,25	6,06 −0,01	6,68 −0,03	6,56 +0,09	4,02 +0,12
DMF	2,56 −0,13	3,82 +0,04	4,60 +0,02	3,93 −0,25	4,46 −0,34	5,92 +0,13	6,17 −0,12	6,78 −0,13	6,70 −0,05	4,13 +0,01
CF_3COOH	2,95 −0,52	4,02 −0,16	4,77* −0,15	4,77* −1,09	4,49* −0,37	6,11* −0,06	6,11* −0,06	6,93 −0,28	6,93 −0,28	4,49* −0,35
C_5D_5N	2,40 +0,03	3,60 +0,26	4,57 +0,05	3,91 −0,23	4,25 −0,13	6,14 −0,09	6,14 −0,09	6,68 −0,03	6,68 −0,03	4,36 −0,22
C_6D_6	2,27 +0,16	3,36 +0,50	4,18 +0,44	3,57 +0,11	3,97 +0,15	5,79 +0,26	5,79 +0,26	6,45 +0,20	6,45 +0,20	4,00 +0,14

*The chemical shifts were determined in a mixture of $CDCl_3$ and TFA (8:1); the assignments of the signals of the H_α and H_β protons may be reversed.

TABLE 2

Solvent	Chem. shifts of the protons of narwedine (δ, ppm) and their relative diff. (Δ)								
	NCH_3	OCH_3	H_t	Ar–CH_2–N		H_g	H_f	H_a	H_b
				H_β	H_α				
$CDCl_3$	2,47	3,87	4,72	3,74	4,10	6,03	6,96	6,69	6,64
CD_3CN	2,35 +0,12	3,79 +0,08	4,75 −0,03	3,68 +0,06	4,13 −0,03	5,95 +0,08	7,07 −0,11	6,77 −0,08	6,68 −0,04
CD_3OD	2,42 +0,05	3,79 +0,08	4,73 −0,01	3,72 +0,02	4,17 −0,07	5,98 +0,05	7,13 −0,17	6,75 −0,06	6,69 −0,05
$(CD_3)_2CO$	2,36 +0,11	3,79 +0,08	4,76 −0,04	3,69 +0,05	4,18 −0,08	5,93 +0,10	7,15 −0,19	6,76 0,07	6,65 −0,01
DMSO	2,30 +0,17	3,73 +0,14	4,69 −0,03	3,70 +0,04	4,16 −0,06	5,91 +0,12	7,15 −0,19	6,76 −0,07	6,65 −0,01
DMF	2,55 −0,08	3,83 +0,04	4,86 −0,14	4,10 −0,36	4,48 −0,38	6,09 +0,03	7,28 −0,32	6,88 −0,19	6,78 −0,14
CF_3COOH	3,01 −0,54	4,02 −0,15	*			6,41 −0,38	7,22 −0,26	7,07 −0,38	6,96 −0,32
C_5D_5N	2,40 +0,07	3,73 +0,14	4,71 +0,01	3,74 0,00	4,19 −0,09	6,12 −0,09	7,07 −0,11	6,79 −0,10	6,71 −0,07
C_6D_6	2,24 +0,23	3,40 +0,47	4,12 +0,60	3,53 +0,21	3,84 +0,26	5,82 +0,21	6,35 +0,61	6,45 +0,24	6,45 +0,19

*The assignment of the chemical shifts of the signals is difficult because of the superimposition of the signals of other protons.

TABLE 3

Solvent	Chemical shifts of the protons of dihydrolycorine diacetate (δ, ppm) and their relative differences (Δ)								
	OAc	OAc	H_{11}	H_8	OCH_2O	H_1	H_2	$H_{7\beta}$	$H_{7\alpha}$
$CDCl_3$	2,11	1,98	6,64	6,55	5,89	5,67	4,93	3,76	4,04
CCl_4	2,06 +0,05	1,95 +0,03	6,53 +0,11	6,45 +0,10	5,88 +0,01	5,56 +0,11	4,77 +0,16	3,63 +0,13	3,94 +0,10
CD_3OD	2,09 +0,02	1,91 +0,07	6,62 +0,02	6,62 −0,07	5,90 −0,01	5,68 −0,01	*	3,77 −0,01	4,02 +0,02
$(CD_3)_2CO$	*	1,89 +0,09	6,60 +0,04	6,60 −0,05	5,91 −0,02	5,63 +0,04	4,88 +0,05	3,66 +0,10	4,01 +0,03
CD_3CN	2,06 +0,05	1,94 +0,04	6,63 +0,01	6,63 −0,08	5,91 −0,02	5,62 +0,05	4,91 +0,02	3,78 −0,02	3,89 +0,15
DMF	2,12 −0,01	2,05 −0,07	6,82 −0,18	6,63 −0,08	6,02 −0,13	5,69 −0,02	5,00 −0,07	4,13 −0,37	4,13 −0,09
CF_3COOH	2,33 −0,22	2,17 −0,19	6,87 −0,23	6,71 −0,17	6,02 −0,13	6,02 −0,35	5,15 −0,22	†	
C_5D_5N	2,08 +0,03	1,89 +0,09	7,04 −0,40	6,68 −0,13	5,94 −0,05	6,03 −0,36	5,23 −0,30	3,84 −0,08	4,01 +0,03
C_6D_6	1,78 +0,33	1,56 +0,42	6,92 −0,28	6,41 +0,14	5,35 +0,54	5,92 −0,25	5,12 −0,19	3,45 +0,31	3,76 +0,28

*Masked by the signals of the solvent.

†The assignment of the chemical shifts is difficult because of the superimposition of the signals of other protons.

are found for the protons of the acetyl groups in benzene solution, and the protons geminal to the acetyl groups and H_{11} undergo paramagnetic shifts. The latter is due to the fact that benzene can interact by its partially positive peripheral region with the strong electronegative section of the molecule (in this case, with the oxygen of the acetyl group) and exert a descreening influence on the neighboring protons [12]. The considerable difference in Δ for H_1 and H_2 in the bases (III) and (IV) becomes understandable from a consideration of stereomodels of the Dreiding type. Ring C in lycorine diacetate, which has the half-boat conformation, can readily pass into the twist conformation on hydrogenation. Such a conformational state of this ring creates definite steric hindrance to the formation of a molecule complex by C_6D_6 with this section of the molecule in dihydrolycorine diacetate.

The assignment of the CSs of H_{11} and H_8 in (IV) in C_5D_5N solution was checked by the successive addition of pyridine to a solution of the base in CCl_4. In benzene, the CSs of these protons were determined with the aid of double resonance. On irradiation with ν 388 Hz, i.e., at the saturation of the $H_{7\alpha}$ signal with δ 3.88 ppm, the signal at 6.37 ppm contracted. This shows that the signal in the 6.37-ppm region relates to the H_8 proton. For dihydrolycorine diacetate, the assignment of the signals of the H_8 and H_{11} protons in aromatic solvents was also made on the basis of double-resonance experiments. On irradiation with a frequency ν 401 Hz in pyridine and ν 376 Hz in benzene, i.e., at the saturation of the $H_{7\alpha}$ signal, the signal of the proton in position 8 contracted, which is an unambiguous proof of its CS. As Tables 3 and 4 show, the signs of Δ for H_{11} and H_8 are opposite in benzene. This fact may probably serve as a criterion for the assignment of the signals of aromatic protons in alkaloids of the lycorenine group. Pyridine causes paramagnetic shifts of the H_1, H_2, and H_{11} signals because of the formation of complexes with the unshared electrons of the oxygens of the acetyl groups.

Ungerine (V) and Hippeastrine (VI). These compounds differ from one another only by the substituents at C_5. It was to be expected that the influence of the solvents on the CSs should be identical for alkaloids (V) and (VI), differing only for the protons of ring C. This hypothesis is confirmed by Tables 5 and 6. The influence of C_6D_6 on the change in the CS of the N–CH_3 group is of the order of +0.20 ppm, just as in (I) and (II). The greatest change in CS was observed in benzene solution for the protons of the methylenedioxy group (Δ = +0.91 ppm), upon which the positive charge is partially concentrated because of the redistribution of electron densities. This is almost 1.5 times greater than for the alkaloids (III) and (IV). A similar comparison can be made for the protons of the aromatic ring. The calculation of π-electron densities on the carbon atoms of the fragments of the molecules of (III) and (V) that we have made by the MO LCAO method in Hückel's approximation

TABLE 4

Solvent	Chemical shifts of the protons of lycorine diacetate (δ, ppm) and their relative differences (Δ)									
	OAc	OAc	H_{11}	H_8	OCH_2O	H_1	H_2	H_3	H_α	H_β
$CDCl_3$	2,12	2,00	6,75	6,54	5,90	5,75	5,30	5,53	4,20	3,52
CCl_4	2,05	1,92	6,60	6,40	5,81	5,58	5,05	5,41	4,01	3,38
	+0,07	+0,08	+0,15	+0,14	+0,09	+0,17	+0,25	+0,12	+0,19	+0,14
CS_2	2,02	1,88	6,50	6,36	5,80	5,53	5,02	5,22	4,02	3,42
	+0,10	+0,12	+0,25	+0,18	+0,10	+0,22	+0,28	+0,31	+0,18	+0,10
CD_3CN	2,10	1,91	6,71	6,61	5,89	5,60	5,26	5,45	4,11	3,46
	+0,02	+0,09	+0,04	−0,07	+0,01	+0,15	+0,04	+0,08	+0,09	+0,06
CD_3OD	2,13	1,97	6,71	6,62	5,89	5,71	5,27	5,52	4,17	3,71
	−0,01	+0,03	+0,04	−0,08	+0,01	+0,04	+0,03	+0,01	+0,03	−0,19
$(CD_3)_2CO$	*	1,94	6,72	6,62	5,92	5,73	5,25	5,46	4,15	3,70
		+0,06	+0,03	−0,08	−0,02	+0,02	+0,05	+0,07	+0,05	−0,18
DMF	2,15	1,99	6,76	6,73	6,00	5,77	5,27	5,50	*	3,52
	−0,03	+0,01	−0,01	−0,19	−0,10	−0,02	+0,03	+0,03		0,00
CF_3COOH	2,35	2,20	6,90	6,68	6,02	6,10	5,62	5,93	†	†
	−0,23	−0,20	−0,15	−0,14	−0,12	−0,35	−0,32	−0,40		
C_5D_5N	2,05	1,90	7,07	6,62	5,90	6,18	5,66	5,66	4,13	3,61
	+0,07	+0,10	−0,32	−0,08	0,00	−0,43	−0,36	−0,13	+0,07	−0,09
C_6D_6	1,70	1,50	6,93	6,37	5,30	6,10	5,63	5,63	3,88	3,27
	+0,42	+0,50	−0,18	+0,17	+0,60	−0,35	−0,33	−0,10	+0,32	+0,25

*Masked by a signal of the solvent.
†The assignment of the chemical shifts is difficult because of the superimposition of the signals of other protons.

with the hetero parameters of B. and A. Pullman [3], shows that the conjugation of the lactone carbonyl with the aromatic nucleus changes the electron density on the carbon atoms of ring A. Consequently, the difference in the value of Δ for the H_{11} and H_8 protons in alkaloids (III) and (IV) and in (V) and (VI) is due, on the one hand, to the presence in lycorine diacetate and its dihydro derivative of acetyl groups affecting the stereospecificity of the formation of the molecular complex with C_6D_6 and, on the other hand, to the conjugation of ring A with the carbonyl group in ungerine and hippeastrine. There is no doubt that the increase in Δ for the protons of the OCH_2O group in ungerine is due to the presence of the CO group in ring B, which leads to an appreciable redistribution of the electron densities in the methylenedioxy group. The influence of benzene on the CSs of H_{11} and H_8 of ungerine is opposite to the results obtained for (III) and (IV), i.e., the proton in position 8 undergoes a diamagnetic shift and that in position 11 a paramagnetic shift. In this case, to explain the observed facts it is possible to use the "rule of the carbonyl plane of reference" [14]. The H_4 olefinic proton is feebly affected by aromatic solvents. As shown above, pyridine exerts a considerable descreening influence on the CSs of protons located adjacent to oxygen.

Influence of Polar Solvents

When polar molecules are dissolved in polar solvents, the change in the CSs of the protons depends on the effect of the "reaction field of the medium," arising in consequence of the polarization of the solvent molecules by the solute molecules, a definite contribution being made by van der Waals and specific interactions of the hydrogen-bond type or by complex-formation of the solvent with the solute. The influence of polar solvents on the CSs of galanthamine and narwedine does not have such a specific nature as for aromatic solvents and is smaller. An exception is DMF, the complex-forming capacity of which is high, and which causes considerable shifts of the signals. However, for further investigations of the alkaloids of this series it is important that CD_3CN, CD_3OD, $(CD_3)_2CO$, DMF, and DMSO shift the signal of the H_g proton, in the α position to the functional group, upfield (Δ from +0.05 to +0.25), and the signal of H_f, in the β position, downfield (Δ from −0.05 to −0.32 ppm). In trifluoroacetic acid system the signal of the $N{-}CH_3$ group in bases (I) and (II) shifts downfield by 0.52 ppm, and that of the OCH_3 group by ~0.15 ppm.

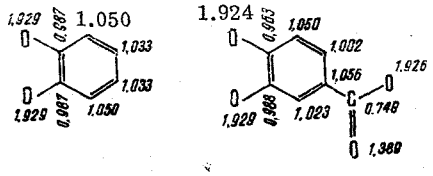
TABLE 5

Solvent	Chemical shifts of the protons of ungerine (δ, ppm) and their relative differences (Δ)							
	NCH_3	OCH_3	H_5	H_{5a}	H_4	OCH_2O	H_{11}	H_8
$CDCl_3$	2,02	3,46	3,94	4,67	5,65	6,08	6,97	7,50
CCl_4	1,96	3,41	3,81	4,49	5,56	6,05	6,88	7,41
	+0,06	+0,05	+0,13	+0,18	+0,09	+0,03	+0,09	+0,09
CS_2	1,92	3,36	3,74	4,45	5,52	6,00	6,78	7,28
	+0,10	+0,10	+0,20	+0,22	+0,13	+0,08	+0,19	+0,22
CD_3CN	1,98	3,41	3,89	4,72	5,66	6,10	7,09	7,41
	+0,04	+0,05	+0,05	−0,05	−0,01	−0,02	−0,12	+0,09
CD_3OD	2,04	3,44	3,90	4,74	5,72	6,11	7,07	7,40
	−0,02	+0,02	+0,04	−0,07	−0,07	−0,03	−0,10	+0,10
$(CD_3)_2CO$	1,99	3,45	3,83	4,71	5,64	6,17	7,09	7,37
	+0,03	+0,01	+0,11	−0,04	+0,01	−0,09	−0,12	+0,13
DMSO	1,94	3,36	3,83	4,73	5,64	6,17	7,19	7,37
	+0,08	+0,10	+0,11	−0,06	+0,01	−0,09	−0,22	+0,13
DMF	2,12	3,47	3,90	4,84	5,73	6,26	7,25	7,42
	−0,10	+0,01	+0,04	−0,17	−0,08	−0,18	−0,28	+0,08
CF_3COOH	2,96	3,76	4,34	5,11	6,15	6,20	7,25	7,66
	−0,94	−0,30	−0,40	−0,44	−0,50	−0,12	−0,28	−0,16
C_5D_5N	1,93	3,41	4,06	4,92	5,71	6,11	7,06	7,76
	+0,09	+0,05	−0,12	−0,25	−0,06	−0,03	−0,09	−0,26
C_6D_6	1,80	3,07	3,85	4,56	5,52	5,17	6,62	7,74
	+0,22	+0,39	+0,09	+0,11	+0,13	+0,91	+0,35	−0,24

TABLE 6

Solvent	Chemical shifts of the protons of hippeastrine (δ, ppm) and their relative differences (Δ)							
	NCH_3	H_5	H_{5a}	H_4	OCH_2O	H_{11}	H_8	H_{11b}
$CDCl_3$	2,05	4,40	4,60	5,65	6,08	6,97	7,49	2,93
CD_3CN	2,01	4,23	4,56	5,63	6,09	7,08	7,42	*
	+0,04	+0,17	+0,04	+0,02	−0,01	−0,11	+0,07	
CD_3OD	2,05	4,25	4,58	5,66	6,12	7,06	7,41	2,87
	0,00	+0,15	+0,02	−0,01	−0,04	−0,09	+0,08	+0,06
$(CD_3)_2CO$	2,01	4,24	4,60	5,63	6,18	7,13	7,38	2,92
	+0,04	+0,16	0,00	+0,02	−0,10	−0,16	+0,11	+0,01
DMSO	1,95	4,13	4,48	5,56	6,17	7,16	7,36	2,84
	+0,10	+0,27	+0,12	+0,09	−0,09	−0,19	+0,13	+0,09
DMF	2,22	*	4,65	5,71	6,24	7,29	7,42	*
	−0,17		−0,05	−0,06	−0,16	−0,32	−0,07	
CF_3COOH	2,96	4,82	5,06	5,76	6,20	7,25	7,64	†
	−0,91	−0,42	−0,46	−0,11	−0,12	−0,28	−0,15	
C_5D_5N	1,99	4,77	5,04	5,86	6,08	7,05	7,74	3,14
	+0,06	−0,37	−0,44	−0,21	0,00	−0,08	−0,25	−0,21

*Superimposition of the signal of the solvent.
†Superimposition of the signals of other protons.



In alkaloids (III) and (IV), just as in galanthamine and narwedine, polar solvents cause insignificant shifts. Our results show that for such complex substances as alkaloids there is no correlation between the functions of the dielectric constant of the solvent ε and Δ, although such a connection has been established for model compounds [15-17]. Trifluoroacetic acid (TFA) has the greatest influence on the CSs of the protons in the alkaloids (III) and (IV). The values of $\Delta^{TFA}_{CDCl_3}$ for all the protons considered in (III) and (IV) are specific and approximately equal. A value of Δ of from −0.15 ppm in (IV) to −0.25 ppm in (III) for the H_{11} proton can be explained by the closeness of the ester oxygen in position 1, which is protonated by TFA and exerts an inductive influence on the screening of H_{11}. The rise in Δ for H_2 in lycorine diacetate is connected with the formation of π complexes between the double bond and the TFA, the olefinic proton undergoing a paramagnetic shift of

about −0.40 ppm. The influence of polar solvents in the CSs of the protons of rings A, B, and D in bases (V) and (VI) is characteristic and approximately the same in magnitude and direction. The different functional groups in ring C of ungerine and hippeastrine cause different "reaction fields of the medium," which, in their turn, are responsible for the dissimilar change in the CSs of adjacent protons. The paramagnetic shifts of the H_5 and H_{5a} protons and also of the OCH_3 protons in ungerine in TFA solution are due to the protonation of the CO group [18] and of the oxygen of the methoxy group [19].

On the basis of a study of literature information [20] and our own results, we have established that the influence of TFA on the change in the CS of the N—CH_3 group in saturated five-membered rings is specific, and Δ is −0.90 ppm.

Influence of Solvents on SSCCs

A change in SSCC is observed as a consequence of a conformational transformation of the molecules or of an electronic rearrangement of the environment of the proton which is connected with an interaction of the substance and the solvent [21]. The change in J_{AB} in the Ar—CH_2—N fragment by 2 Hz in bases (I) and (II) undoubtedly shows that the conformation of ring D changes in dependence on ε and other characteristics of the solvents. This is connected mainly with the influence of the solvents on the unshared pair of electrons of the nitrogen in the N—CH_3 group, and with the different contributions of the neighboring π systems of ring A with a change in the angles. Furthermore, when the two ortho aromatic or olefinic protons give an AB pattern with close CSs, i.e., when it is difficult to determine δ and J_{AB}, in polar solvents the protons become nonequivalent and the parameters can be determined from first-order considerations. The use of polar solvents in the case of galanthamine also permits J_{H_1Hg} to be determined unambiguously, while in nonpolar and aromatic solvents, because of the closeness of the CSs of these protons, it was impossible to determine the value of this constant. In bases (III) and (IV), the change in $J_{H_1\ H_2}$ may be a consequence both of a change in the conformation of ring C and of a rearrangement of the electronic environment of these protons. We have also established that in TFA solution a $J_{H_8\ H_{7a}}$ of 2 Hz in the case of base (III) and of 3 Hz in (IV) appears. According to a well-known relationship [22, 23] between the value of an allyl constant J_{all} and the angle between the plane of the double bond of the C_7—H_α bond, such constants are observed at Θ = 90-100°. Our results show that in polar and aromatic solvents the conformation of ring B remains in the half-chair form, and in TFA it changes to a distorted boat form [24, 25].

SUMMARY

On the basis of a study of the influence of solvents on the parameters of the NMR spectra of the alkaloids of *Amaryllidaceae* the following facts have been established:

A) A methoxy group in the aromatic ring of (I) and (II) undergoes a diamagnetic shift of 0.5 ppm in C_6D_6:

B) The influence of benzene on the change in the CS of an N—CH_3 group is ~+0.20 ppm

C) There is a characteristic influence of TFA on the CS of an N—CH_3 group in a saturated five-membered ring;

D) The conformation of ring B in bases (III) and (IV) in different solvents changes from the half-chair to the distorted boat.

A method is proposed for assigning the aromatic protons in the lycorenine group. The desirability has been shown of using polar solvents for determining the values of J and the CSs of the aromatic and olefinic protons in the galanthamine group.

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SYNTHESIS AND BIOLOGICAL PROPERTIES OF A TRYPTOPHAN-CONTAINING FRAGMENT OF A MYELIN PROTEIN AND ITS ANALOGS

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It has been shown previously [1] that the main protein of brain myelin when administered to animals with an adjuvant causes a disease which has been given the name of experimental allergic encephalomyelitis (EAE) and which may be a good model of some autoimmune diseases of man (disseminated sclerosis, etc.) [1, 2].

The complete amino-acid sequences of the main proteins of human and bovine myelins have been determined, and it has been shown that the hydrolysis of these proteins by proteases can give a series of fragments possessing EAE activity [1]. One such fragments is a peptide corresponding to sequence 111-121 of the main protein of myelin, and also the peptide 113-121:

$$Ser^{111}\text{-}Arg^{112}\text{-}Phe^{113}\text{-}Ser^{114}\text{-}Try^{115}\text{-}Gly^{116}\text{-}Ala^{117}\text{-}Glu^{118}\text{-}Gly^{119}\text{-}Gln^{120}\text{-}Arg^{121}\text{-}Pro^{122}\text{-}Gly^{123}.$$

Westall et al. [3] have synthesized a number of peptide analogs of fragment 111-121 by the solid-phase method and have shown that the amino-acid residues tryptophan-115, glutamin 120, and arginine-121 (or lysine-121) are essential for the appearance of EAE activity. Later, Japanese workers synthesized peptides 112-121 and 113-121, and also a number of analog of them and showed that the minimum peptide inducing EAE is the nonapeptide 113-121 [4, 5].

Carrying out a program of structural-functional investigations including the synthesis and physicochemical and biological study of encephalitogenic peptides, we have synthesized the nonapeptide 113-121 and one of its glycine analogs [6, 7].

In the present paper we give experimental details of the synthesis of these compounds and a number of other analogs of the nonapeptide 113-121. Scheme 1 shows the synthesis of

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