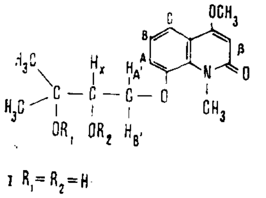
INFLUENCE OF SOLVENTS ON THE PARAMETERS OF THE NMR SPECTRA OF Haplophyllum ALKALOIDS. II

K. L. Seitanidi and M. R. Yagudaev

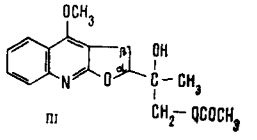
UDC 577,94:543,42:542,61

We have continued our study of the influence of solvents on the parameters of the NMR spectra of some alkaloids of the genus Haplophyllum [1], in particular foliosidine (I) [2, 3] and its diacetate (II), dubinine (III) [4, 5], and γ-fagarine (IV) [6, 7] (the experimental conditions have been described previously [1]).

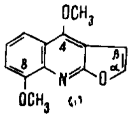


I $R_1=R_2=H$

II $R_1=R_2=Ac$



III



IV

Positive values of Δ mean diamagnetic shifts relative to CCl_4 for substances (II–IV) and relative to $CDCl_3$ for foliosidine in view of its poor solubility in CCl_4.

Influence of Aromatic Solvents. Pyridine causes paramagnetic shifts of the signals of all the protons in the spectra of the alkaloids mentioned with the exception of the protons in the 4-OCH_3 and 8-OCH_3 groups of γ-fagarine, which undergo diamagnetic shifts (Tables 1-4). On comparing the influence of C_5D_5N and C_6D_6 on the change in the chemical shifts (CSs) of the β proton and of the 4-OCH_3 group in compounds (I-IV) it can be seen that the signal of the methoxy group in the furanoquinoline alkaloids in pyridine solution shifts upfield and in the 2-quinolone alkaloids it shifts downfield. The H_β signal in foliosidine and its diacetate undergoes a greater paramagnetic shift in C_5D_5N than the corresponding signal in dubinine and γ-fagarine.

In benzene, the following facts were established for these groups of protons: in the alkaloids (III) and (IV) large diamagnetic shifts are observed, and in (II) paramagnetic shifts (foliosidine is insoluble in benzene); the changes in the CSs of the protons of the 4-OCH_3 groups and of H_β are apparently due to the formation of complexes between the substance and molecules of the solvents. In these complexes a decisive role is played by the presence or absence of exocyclic oxygen [8].

Since, because of its electron-donating properties, benzene tends to be located as far as possible from the negatively charged part of the molecule, its influence on the groups adjacent to the exocyclic oxygen upon which a high π-electronic negative charge is concentrated will be decreased, as is found in the NMR spectrum of foliosidine diacetate. Conversely, the overwhelming action of the nitrogen heteroatom over the π currents of the ring leads to considerable paramagnetic shifts of the signals of H_β and 4-OCH_3 in foliosidine and its diacetate. Williams [9], investigating the influence of benzene in quinolines and related compounds, came to the conclusion that a proton or methyl group in positions 4, 5, and 6 to the nitrogen undergoes greater (about 0.58 ppm) diamagnetic shifts because of complex formation between the solvent and the substance. We observed similar upfield shifts for the 4-OCH_3 group in (III) and (IV) in deuterobenzene solutions. Furthermore, our results (see Table 4) on the influence of C_6D_6 on the signals of the

---

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 755-760, November-December, 1974. Original article submitted September 25, 1973.

STRUCTURE OF CAULOSIDE B — A GLYCOSIDE OF A NEW TRITERPENOID CAULOPHYLLOGENIN FROM Caulophyllum robustum

L. I. Strigina, N. S. Chetyrina,
V. V. Isakov, A. K. Dzizenko,
and G. B. Elyakov

UDC 547.918+547.597

We have previously reported the isolation from Caulophyllum robustum Maxim. of four glycosides of hederagenin (caulosides A, C, D, and E) and of cauloside B — the glycoside of an unidentified triterpenoid which we have called caulophyllogenin [1].

The IR spectrum of caulophyllogenin obtained by the hydrolysis of cauloside B with 2 N H_2SO_4 in ethanol contained the bands of a hydroxy group (3595 cm^{-1}) and of a carboxy group (1705 cm^{-1}). The presence of the latter was confirmed by the preparation of the corresponding methyl ester (Ib). We obtained preliminary information on the structure of caulophyllogenin by a consideration of its mass spectrum. In the mass spectrum of (Ia) (Table 1), in addition to the peak of the molecular ion (M^+ 488) intense peaks of ions characteristic for the retro-Diels–Alder type of fragmentation of triterpenoids of the olean-12-ene type with a carboxy and one of the hydroxy groups in rings D/E [2] were observed. The treatment of (Ia) with acetone and p-toluenesulfonic acid gave a monoacetonide (Ii), the mass spectrum of which (see Table 1) showed the presence in it of an acetonide group and, consequently, the presence of the corresponding two hydroxy groups in rings A/B. The acetylation of (Ib) under the usual conditions gave (according to the results of thin-layer chromatography) a mixture of two acetates (c and d). On reacetylation of the mixture with heating, the amorphous acetate (Ic) was formed, with an IR spectrum in which the absorption of a hydroxy group was absent. The NMR spectrum of (Ic) (Table 2) showed that the substance contained six tertiary methyls, one methoxycarbonyl, and three acetyl groups. In the weak-field region the signals of one proton on a double bond and signals showing the presence of one acetoxymethyl and two acetoxymethylene groups appeared. The acetylation of (Ib) at 0°C gave an amorphous acetate (Id), in the IR spectrum of which the absorption band of a hydroxy group appeared (3630 cm^{-1}). The NMR spectrum of (Id) (see Table 2) showed that the substance contains two acetyl groups; one of them forms part of an acetoxymethyl and the other of an acetoxymethylene group. In the weak-field region was observed the signal of a proton attached to the same carbon atom as the hydroxy group.

Consequently, in caulophyllogenin there are one primary and two secondary hydroxy groups, one of the latter not being acetylated under the usual conditions.

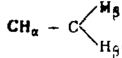
The hydrolysis of cauloside B with a mixture of concentrated HCl and MeOH (1 : 1) formed another aglycone which, according to its IR spectrum (1755 cm^{-1}) was the γ-lactone (II). The presence in the mass spectrum of (IIa) of the peak M^+ 488, and increase in the intensity of the peaks with m/e 236 and 223, and the absence of the absorption band of a double bond in the IR spectrum of the γ-lactone showed that the lactone group in it arose as the result of ring closure by the carboxy group with the Δ^{12} double bond during acid hydrolysis. In the acetylation of the lactone under ordinary conditions a mixture of acetates was obtained from which an amorphous triacetate (IIb) was isolated [NMR: δ 2.1, 2.15, 2.5 ($-3CO-CH_3$)]. On the basis of these facts it was assumed that caulophyllogen is structurally similar to hederagenin but bears an additional

TABLE 1. Mass Spectra of (Ia), (Ie), and (Ii)

Ia		Ie		Ii	
m/e	Relative intensity, %	m/e	Relative intensity, %	m/e	Relative intensity, %
488	8	584	25	528	7
264	56	276	100	264	73
246	100	—	—	246	100
218	32	216	44	—	—
201	50	199	88	201	40
200	16	—	—	200	86

Pacific Ocean Institute of Bioorganic Chemistry of the Far-Eastern Scientific Center, Academy of Sciences of the USSR. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 733-738, November-December, 1974. Original article submitted July 12, 1973.

TABLE 3. Chemical Shifts, Their Relative Differences $\Delta = \delta_{CCl_4} - \delta_{solvent}$, and Spin–Spin Coupling Constants of the Signals of the Protons of Dubinine in Various Solvents

Solvent	Chemical shifts of the protons (δ, ppm) and their relative differences (Δ)							Spin–spin coupling constants (J, Hz)		
								fragment  $CH_{\alpha}-C(H_{\beta})H_{\beta'}$		
	$C-CH_3$	$OCOCH_3$	$4-OCH_3$	CH_2	H_{β}	$H_{\beta'}$	H_{α}	$J_{H_{\alpha} \cdot H_{\beta}}$	$J_{H_{\alpha} \cdot H_{\beta'}}$	J_{gem}
CCl_4	1,25	2,10	4,13	4,42	3,48	3,90	4,91	9,4	6,5	15,3
$CDCl_3$	1,33 −0,08	2,15 −0,05	4,16 −0,03	4,50 −0,08	3,51 −0,03	3,93 −0,03	4,94 −0,03	9,5	6,6	15,5
CD_3CN	1,24 +0,01	2,08 +0,02	4,23 −0,10	4,25 +0,17	3,69 −0,21	3,69 +0,21	4,82 +0,09	8,2	8,2	0,0
CD_3OD	1,30 −0,05	2,09 +0,01	4,30 −0,17	4,23 +0,19	3,75 −0,27	3,75 +0,15	4,86 +0,05	8,1	8,1	0,0
$(CD_3)_2CO$	1,30 −0,05	*	4,30 −0,17	4,34 +0,08	3,81 −0,33	3,81 +0,09	4,88 +0,03	9,7	9,7	0,0
$(CD_3)_2SO$	1,20 +0,05	2,08 +0,02	4,27 −0,14	4,10 +0,32	3,70 −0,22	3,70 +0,20	4,76 +0,15	8,1	8,1	0,0
CF_3COOH	1,61 −0,36	2,35 −0,25	4,63 −0,50	4,58 −0,16	4,16 −0,68	4,16 −0 26	5,51 −0,60	8,7	8,7	0,0
C_5D_5N	1,49 −0,24	2,06 +0,04	4,09 +0,04	4,68 - 0,26	3,61 −0,13	4,00 −0,10	4,96 −0,05	9,2	7,2	15,9
C_6D_6	1,31 −0,06	2,08 +0,02	3,42 +0,71	4,93 −0,51	2,80 +0,68	3,71 +0,21	4,75 +0,16	8,2	6,5	15,4

*The assignment of the CSs is difficult because of superposition of signals from the solvent.

ment of the NCH_3 and OCH_3 signals we studied the temperature dependence of the change in the CSs of these groups in foliosidine diacetate in benzene. The chemical shifts of the signals considered in C_6D_6 change with a rise in the temperature because of a displacement of the equilibrium in the direction of the formation of free molecules of the substance [8]. If the signal in the 3.17 ppm region relates to the OCH_3 group and that at 4.02 ppm to the NCH_3, then with a rise in the temperature considerable changes in the CSs of both groups should be observed. It can be seen from Table 5 that with a change in the temperature the signal at 3.17 ppm undergoes a considerable downfield shift, while the signal at 4.02 ppm remains practically constant. Consequently, the singlet in the 3.17 ppm region relates to the signals of the protons of the methyl of the NCH_3 group.

The facts presented may be considered as a criterion of the difference and of the identification of these groups in the NMR spectra of the alkaloids of this series.

Influence of Polar Solvents. The strongly polar solvents CD_3OD, $(CD_3)_2CO$, CD_3CN, DMSO, and DMF (see Tables 1-4) shift the signals of almost all the protons in (I), (II), and (IV) downfield, which agrees with the theory of the "reaction field" [11, 12]. Exceptions are formed by the CH_2 and $H_{\beta'}$ protons in dubinine.

Tables 3 and 4 confirm the hypothesis that in deuteroacetone solution the β protons of the furan rings of the alkaloids (III-IV) are stronger acceptors than H_{α} [1]. Thus in the NMR spectrum of haplophyllidine [1], the greatest influence on the CSs of the protons of the substances investigated is exerted by trifluoroacetic acid, the shifts being in the downfield direction (see Tables 1-4). It has been found that the value of Δ for the methoxy groups, regardless of the substances concerned, is ~0.5 ppm, and the H_{β} signals of the furan ring in the alkaloids (III) and (IV) are shifted by 0.63 ± 0.04 ppm. The considerable shift of the signals of the β protons (about 1 ppm) for the 2-quinolone alkaloids in trifluoroacetic acid can be explained by the protonation of the carbonyl group [13].

Influence of Feebly Polar Solvents. On comparing the figures of Tables 1-4 for polar and feebly polar solvents it can be seen that the changes caused by $CDCl_3$ and CS_2 are less considerable than for polar sol-

TABLE 4. Chemical Shifts, Their Relative Differences $\Delta = \delta_{CCl_4} - \delta_{solvent}$, and the Spin–Spin Coupling Constants of the Protons of γ-Fagarine in Various Solvents

Solvent	Chemical shifts of the protons (δ, ppm) and their relative difference (Δ)				Spin–spin coupling constants (J, Hz)
	$8-OCH_3$	$4-OCH_3$	H_β	H_α	$J_{CH_\alpha - CH_3}$
CCl_4	4,05	4,42	6,95	7,56	2,7
$CDCl_3$	4,03 +0,02	4,41 +0,01	7,03 −0,08	7,61 −0,05	2,9
CS_2	3,96 +0,09	4,39 +0,03	6,97 −0,02	7,52 +0,04	2,8
CD_3CN	4,01 +0,04	4,42 0,00	7,22 −0,27	7,74 −0,18	3,0
CD_3OD	4,02 +0,03	4,39 +0,03	7,19 −0,24	7,72 −0,16	3,3
$(CD_3)_2CO$	4,04 +0,01	4,51 −0,09	7,37 −0,42	7,88 −0,32	3,1
$(CD_3)_2SO$	4,00 +0,05	4,45 −0,03	7,96 −1,01	8,06 −0,50	3,0
$(CD_3)_2NCOD$	4,07 −0,02	4,56 −0,14	7,49 −0,54	8,04 −0,48	2,7
CF_3COOH	4,26 −0,21	4,84 −0,42	7,57 −0,62	7,90 −0,34	2,6
C_5D_5N	4,00 +0,05	4,28 +0,14	7,16 −0,21	7,85 −0,29	3,0
C_6D_6	3,61 +0,44	3,66 +0,76	6,22 +0,73	6,98 +0,54	2,7

TABLE 5. Change in the CSs of the NCH_3 and OCH_3 Groups as a Function of the Temperature in (II)

T, °C	Chemical shifts, ppm	
	NCH_3	OCH_3
21	3,17	4,02
35	3,20	4,01
49	3,22	4,00
54	3,23	3,99
60	3,26	3,99
69	3,27	3,99
80	3,29	3,98

vents. Deuterochloroform shifts the signals of the protons of the compounds studied downfield, and carbon disulfide shifts them upfield.

It is known [14] that CS_2 should cause paramagnetic shifts because of the magnetic anisotropy of the C = S bond. The diamagnetic shifts of the signals in foliosidine diacetate are apparently connected with the steric factor, which explains these anomalies.

Influence of Solvents on the Spin–Spin Coupling Constants. As in the NMR spectrum of haplophyllidine [1], different solvents lead to some changes in the spin–spin coupling constants of the protons in the alkaloids (I-IV). It can be seen from Table 3 that in alkaloid (III), J_{gem} of the CH_2 protons of the dihydrofuran ring is 0 in strongly polar solvents, i.e., these protons become almost equivalent. Thus, the three protons of the dihydrofuran ring give a system of the ABX type in the NMR spectrum in the case of feebly polar and aromatic solvents and one of the A_2X type in strongly polar solvents.

SUMMARY

In a study of the influence of solvents on the parameters of the NMR spectra of the alkaloids (I-IV) it has been established that:

a) benzene shifts the signals of the $4-OCH_3$ and H_β protons of the furanoquinoline alkaloids by $+0.75 \pm 0.02$ and $+0.68 \pm 0.04$ ppm, respectively;

b) in γ-fagarine, the signal of the $4-OCH_3$ protons is shifted upfield under the influence of benzene to a greater degree (almost twofold) than the signal of the $8-OCH_3$ protons;

c) in foliosidine diacetate, benzene affects the signal of the protons in the NCH_3 group considerably more strongly than in the OCH_3 group;

d) trifluoroacetic acid shifts the signal of the β protons by -0.63 ± 0.04 ppm in the furanoquinoline alkaloids and by approximately 1 ppm in the 2-quinolone alkaloids; and

e) in all the alkaloids investigated, the shift in the signal of the 4-OCH_3 group under the influence of CF_3COOH is ≈ 0.5 ppm.

LITERATURE CITED

1. K. L. Seitanidi, M. R. Yagudaev, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 507 (1973).
2. V. I. Pastukhova, G. P. Sidyakin, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 27 (1965).
3. M. R. Yagudaev and S. Yu. Yunusov, Khim. Prirodn. Soedin., 201 (1968).
4. S. Yu. Yunusov and G. P. Sidyakin, Dokl. Akad. Nauk UzSSR, No. 10, 19 (1954).
5. I. A. Bessonova and S. Yu. Yunusov, Khim. Prirodn. Soedin., 6 (1968).
6. S. Yu. Yunusov and G. P. Sidyakin, Zh. Obshch. Khim., 25, 2009 (1955).
7. A. V. Robertson, Austr. J. Chem., 16, No. 3, 451 (1963).
8. J. H. Bowie, J. Ronaune, and D. H. Williams, J. Chem. Soc., B, 540 (1967).
9. D. H. Williams, J. Chem. Soc. (B), 805 (1967).
10. T. Schaefer, Can. J. Chem., 39, 1864 (1961).
11. L. Onzager, J. Amer. Chem. Soc., 58, 1486 (1936).
12. A. D. Buckingham, Can. J. Chem., 38, 300 (1960).
13. M. E. Perel'son and A. I. Ban'kovskii, Khim. Prirodn. Soedin., 579 (1966).
14. A. D. Buckingham and T. Schaefer, J. Chem. Phys., 32, 1227 (1960).