FINE STRUCTURE OF 9-[2-(2-METHYLPYRIDIN-5-YL)-ETHYL]-1,2,3,4-TETRAHYDRO-γ-CARBOLINES

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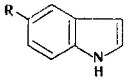
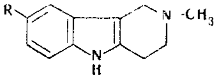
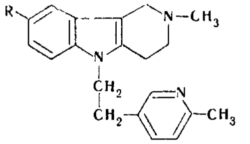
On the basis of the results of PMR and mass spectra it has been shown that the pyridinylethylation at the indole nitrogen atom of tetrahydro-γ-carbolines in the protonated form gives rise to charge-transfer complexes. The UV spectra of the tetrahydro-γ-carbolines and their pyridinylethylated analogs have been investigated.

In view of the promising nature of the use in medicine as antihistamine agents of the 9-[2-(2-methylpyridin-5-yl)ethyl]-1,2,3,4-tetrahydro-γ-carbolines and their broad spectrum of physiological action [1,2], it appeared of interest to study their fine structure by spectral means, as this could throw light on the mechanism of their biological action.

The presence in a single system of the electron-donating indole system and the electron-accepting pyridine system permitted a suggestion of the possibility of their interaction through space in the manner of a charge-transfer complex (CTC). It was found that a necessary condition for the appearance of such interaction is the protonation of the molecule, leading to an enhancement of the acceptor properties of the pyridine nucleus.


I a-d


II a-d


III a-d

I, II, III a R=H; b R=CH_3; c R=OCH_3; d R=Br

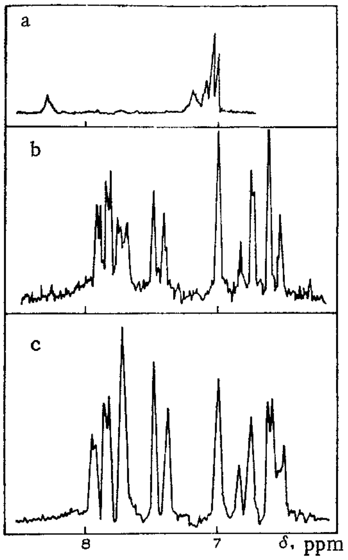


Fig. 1. PMR spectrum of (IIIb): a) in carbon disulfide; b) in trifluoroacetic acid; c) in deuterotrifluoroacetic acid.

In actual fact, while in the PMR spectrum of (IIIb) in carbon disulfide solution the aromatic protons of the benzene and pyridine rings give an unresolved multiplet in the δ 7.2-7.6-ppm region [the signals of the benzene protons of the model structure (IIb) lie in the same region] and the chemical shift of the α-proton of the pyridine ring is 8.6 ppm, in trifluoroacetic acid the spectrum of (IIIb) changes sharply (Fig. 1). In place of the unresolved aromatic multiplet, a clear pattern of all the aromatic protons of both the benzene and the pyridine rings appears. The signals of the aromatic protons of the benzene ring form a doublet with δ 6.2 ppm (8-H J_{87} = 8 Hz), a quartet at 6.8 ppm (7-H, J_{78} = 8 Hz, J_{75} = 2 Hz) and a broadened (through meta coupling) singlet in the 7.0-ppm region (5-H). While for the model structure (IIb) passage from carbon disulfide to trifluoroacetic acid causes no shift in the signals of the benzene protons, for structure (IIIb) it becomes extremely considerable for the 7-H and 8-H

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protons, amounting to $\Delta\delta$ 0.2 and 0.8 ppm, respectively. A doublet at 7.5 ppm corresponds to the β proton of the protonated pyridine ring ($J_{\gamma\beta}$ = 8 Hz), and a quartet with δ 7.9 ppm to the γ proton ($J_{\beta\gamma}$ = 8 Hz, $J_{\gamma\alpha}$ = 2 Hz). However, the signal of the α-pyridine proton is located in anomalously strong fields (7.8 ppm, quartet), while for the model structure of 5-ethyl-2-methylpyridine (in trifluoroacetic acid) it appears at 9.3 ppm. Furthermore, in addition to the coupling of the α proton with the γ proton of the pyridine nucleus (J = 2 Hz) the splitting of the α-H signal on the proton at $>\overset{+}{N}$—H of the pyridine ring is observed, which shows a retarded exchange of the N–H proton under these conditions. The PMR spectrum in deuterotrifluoroacetic acid completely confirms the assignment of the signal of the α-pyridine proton that we have made, this proton giving a broadened singlet in this case. Thus, on the basis of what has been said above, it may be assumed that interaction of the CTC type mainly affects the 8-H and α-H protons, since the chemical shifts of these protons in trifluoroacetic acid undergo the greatest change as compared with the spectrum in an aprotic solvent.

The hypothesis of the existence of a CTC is confirmed by an investigation of the temperature dependence of the PMR spectrum of (IIIb) in trifluoroacetic acid. As was to be expected, raising the temperature (from 20 to 50°C), leading to a weakening of the complex, causes a downfield shift of the α-H signal ($\Delta\delta$ 0.2 ppm). Lowering the temperature leads to the complete restoration of the spectrum.

Since the molecular ion formed on electron impact (in a mass spectrometer) is the prototype of the protonated molecule, we studied the mass-spectral behavior of compounds (IIIa-d).

If the predominant conformation in these compounds was that in which the pyridine nucleus lies above the indole nucleus and a CTC exists, it is to be expected that this conformation will be preserved in the molecular ion, and the stability of this ion (W_M) should rise with an increase in the electron-donating properties of the aromatic ring of indole.

We have shown previously [3] that in the series of compounds (IIa-d) the stability of the molecular ion falls, i.e., the introduction of any substituent into the benzene ring leads to the appearance of additional fragmentation pathways and to a decrease in the value of W_M.

It can be seen from Table 1, which gives the mass spectra of compounds (IIIa-d) that in this sequence of compounds the stability of the molecular ion does not fall but rises sharply on passing from (IIIa) (W_M 12.3) to (IIIb-d), and while for (IIIc) and (IIId) the stability increases [as compared with (IIIa)] by 35% (rel.), the introduction of a methyl group into the benzene nucleus leads to a rise in the stability of the molecular ion by 55%. The reduced value of W_M for (IIIc) as compared with (IIIb) is explained by the larger number of decomposition pathways in the case of the methoxy group.

Thus, the features of the PMR spectra have found good confirmation by an investigation of mass spectra.

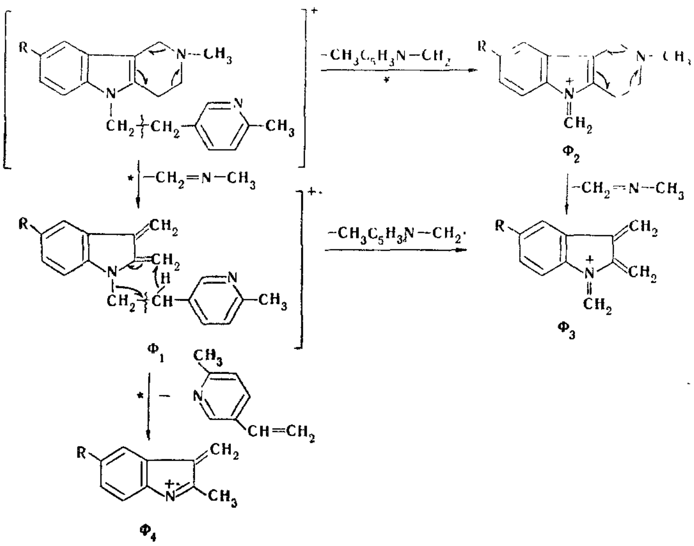


TABLE 1. Mass Spectra of the Tetrahydro-γ-carbolines

Intensity, % of maximum ion *					Intensity, % of maximum ion *				
m/e	IIIa	IIIb	IIIc	IIId	*m/e*	IIIa	IIIb	IIIc	IIId
81	5,8	—	9,0	—	229	—	—	9,0	—
83	11,6	—	12,0	—	234	—	—	—	100,0
84	—	—	5,0	—	235	—	—	—	7,68
85	9,3	—	—	—	236	—	—	—	95,6
95	5,3	—	7,0	—	237	—	—	—	6,7
97	10,6	—	10,0	—	238	—	—	6,0	—
111	5,8	—	6,0	—	246	7,3	—	—	—
119	6,0	—	5,1	14,7	261	—	5,1	—	5,7
120	16,6	—	7,0	59,0	262	25,0	—	—	—
121	—	—	—	7,7	263	6,3	—	—	5,1
128	9,3	—	—	—	276	—	36,3	—	—
129	14,6				277	—	8,1	—	9,0
143	85,9	—	11,0	—	279	—	—	—	8,0
144	9,6	—	—	—	290	5,0	—	—	—
154	—	—	—	14,0	292	—	—	34,0	—
155	5,3	—	—	27,0	304	47,0	—	—	—
156	100,0	—	—	5,1	305	84,0	—	—	—
157	11,1	72,6	—	—	306	14,0	—	—	—
158	—	8,7	—	—	318	—	35,0	—	—
161	—	—	9,0	—	319	—	57,8	—	—
170	—	100,0	—	—	320	—	12,0	—	—
171	—	13,4	—	—	334	—	—	40,0	—
172	—	—	34,0	—	335	—	—	96,0	—
183	5,8	—	—	—	336	—	—	14,0	—
186	—	—	100,0	—	340	—	—	—	26,6
187	—	—	7,0	—	341	—	—	—	5,7
197	6,8	—	—	—	342	—	—	—	25,9
199	10,3	—	—	—	343	—	—	—	5,4
213	—	13,4	—	—	382	—	—	—	39,0
221	—	—	—	88,3	383	—	—	—	72,2
222	—	—	—	5,8	384	—	—	—	48,6
223	—	—	—	86,1	385	—	—	—	66,3
224	—	—	—	5,4	387	—	—	—	7,7
					W_M	12,3	19,1	16,7	16,7

*The table includes the ions having intensities greater than 5.0%.

The further decomposition of the molecular ions of compounds (IIIa-d) is shown in the scheme and includes the two main characteristic types of primary dissociative ionization: in the first place, fragmentation of the "γ-carboline type" [3], i.e., the retrodiene decomposition of the tetrahydro-γ-carboline nucleus with the splitting out of the neutral fragment $CH_2=N-CH_3$ (43 amu) (the ion Φ_1); and, in the second place, the "β decomposition" of the pyridinylethyl residue that is observed in all systems containing a β-alkylpyridinyl grouping [4, 5], leading to the formation of the ion Φ_2 (M − 106). In this process, the intensity of the ion Φ_1 exceeds the intensity of the ion Φ_2. The ion Φ_1 then decomposes by two routes. The main route is that of the "β decomposition" of the pyridinylethyl chain, leading to the maximum ion Φ_3, or, undergoing a rearrangement of the McLafferty type, the ion Φ_1 loses a molecule of 2-methyl-5-vinylpyridine, giving the second most intense ion Φ_4. The ion Φ_3 can also be formed from the ion Φ_2.

The one-stage nature of the processes of the formation of the ions Φ_1, Φ_2, and Φ_4 is confirmed by the corresponding metastable peaks.

It is easy to see that in the mass spectra of compounds (IIIa-d) both the presence of the pyridinylethyl chain and of the tetrahydro-γ-carboline ring is clearly shown.

Confirmation of the existence of a CTC by means of electron spectroscopy is associated with technical difficulties. The protonated compound is insoluble in nonpolar solvents, and polar solvents decompose the complex completely. However, some qualitative confirmation can be obtained by comparing the UV spectra of the hydrochloride of (IIb) and of the dihydrochloride (IIIb) in the solid state. In actual fact, in the spectrum of the latter a considerable increase in the intensity of the absorption curve can be seen, particularly in the long-wave region.

Since there is practically no information in the literature on the UV spectra of the tetrahydro-γ-carbolines, we undertook a comparative investigation of them for the structures (IIa-d) and (IIIa-d). Just as for the indoles (Ia-d) [6], the UV spectra of compounds (IIa-d) are characterized by the presence of two groups of absorption bands. The first, short-wave and strongest, band is in the 225-228-nm region and undergoes practically no influence from electron-donating substituents in position 6. The second, less intense, band with a resolved fine structure undergoes a regular bathochromic shift with a change in R in the sequence CH_3, Br, OCH_3 from 285 to 306 nm (Fig. 2). Similar laws of spectral behavior can be observed for (Ia-d) [6-8]. On the basis of the assumption that the behavior of halogen substituents in the benzene

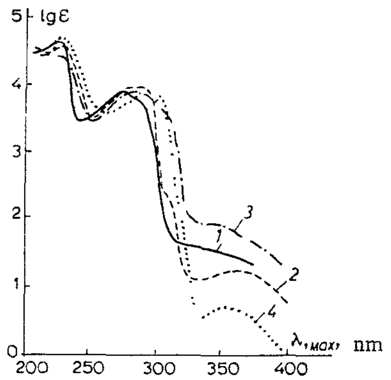


Fig. 2. UV spectra of 6-substituted 1,2,3,4-tetrahydro-γ-carbolines (IIa-d) in methanol: 1) (IIa), R = H; 2) (IIb), R = CH_3; 3) (IIc), R = OCH_3; 4) (IId), R = Br.

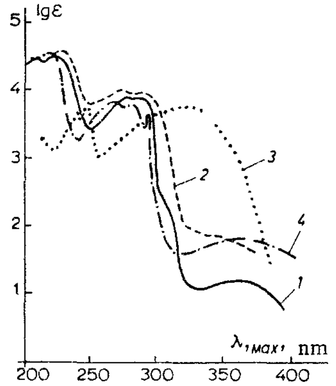
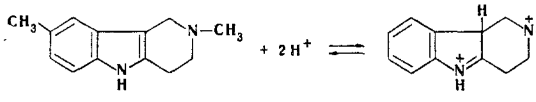


Fig. 3. UV spectra: 1) (IIb) in methanol; 2) (IIIb) in methanol; 3) (IIb) in concentrated sulfuric acid; 4) hydrochloride of (IIb) in methanol.

ring of (I) and (II) in the UV and mass spectra fit into the sequence of donor substituents, it may be concluded that their predominant influence in these systems is that of a positive mesomeric effect. The only difference of the UV spectra of (IIa-d) from the spectra of (Ia-d) is the presence of a low-intensity maximum in the 350-360-nm region with log ε 0.74, 1.20, and 1.80 for compounds (IId), (IIb), and (IIc), respectively.

Pyridinylethylation at the indole nitrogen atom (compounds IIIa-d) does not lead to substantial changes in the UV spectrum and causes only an increase in the intensity of absorption in the 275-300-nm region, apparently due to the superposition of the absorption band of the pyridine chromophore (Fig. 3). The UV spectra of (II) and (III) scarcely change on passing from a nonpolar solvent (isooctane) to a polar one (methanol).

Since compounds (II) form hydrochlorides at the piperidine nitrogen atom (which is confirmed by the doublet splitting of the protons of the 3-CH_3 group in the PMR spectra in trifluoroacetic acid), the nature of the UV spectrum, which is determined by the aromatic part of the molecule, is retained on passing from the spectra of the bases (II) to their hydrochlorides (Fig. 3).



A B

However, when a stronger protonating agent such as concentrated sulfuric acid is used, the UV spectrum becomes characteristic not for the indole but for the indolenine system [9] (Fig. 3), i.e., in this case protonation takes place not only at $N_{(3)}$ but also at $C_{(4a)}$. But, in contrast to the spectra of the indolenines, in the spectra of the compounds B there is a bathochromic shift of the long-wave absorption band (with full retention of the ratios of the intensities of the maxima) which is connected with features of the structure of the cyclic system of B as compared with the open indolenine system.

EXPERIMENTAL

The synthesis of the 9-[2-(2-methylpyridin-5-yl)ethyl]-1,2,3,4-tetrahydro-γ-carbolines was effected by the direct pyridinylethylation of the corresponding tetrahydro-γ-carbolines with 2-methyl-5-vinylpyridine [10].

The PMR spectra were taken on T-60 and XL-100 instruments in sulfur dioxide, trifluoroacetic acid, and deuterotrifluoroacetic acid, and the UV spectra were taken on a Cary instrument. The mass spectra were recorded on an MKh-1303 instrument with a modified system for the introduction of the substance directly into the ion source. The energy of the ionizing electrons was 35 eV, the emission current 150 mA, the accelerating voltage 2 kV, and the temperature 100-120°C.

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