INDOLES

XXIV.* INVESTIGATION OF THE RING-CHAIN TAUTOMERISM OF STRUCTURAL ANALOGS OF PHYSOVENINE

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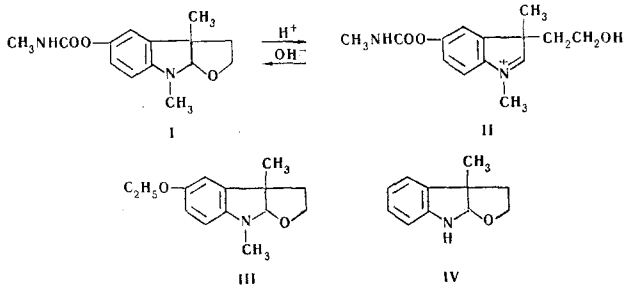
It was shown by UV and PMR spectroscopy that most of the structural analogs of physovenine exist in the closed three-ring form in neutral solutions, while in acid solutions most exist as protonated indolenine derivatives (open form). The region of the equilibrium existence of the closed and open forms as a function of the solution pH was found by UV spectroscopy.

It is known that physovenine (I) and its analogs (III and IV) undergo structural changes in strongly acidic media [2-5]. The UV spectrum of physovenine in 11 N hydrochloric acid has the absorption characteristic for structure II as a consequence of rupture of the C–O bond in the C_6H_5–N–C–O system, while the UV spectrum in dilute acid indicates the presence of a mixture of structures I and II. A similar change in the UV spectrum is also observed for III.



I II III IV

The UV spectrum of furoindoline IV differs somewhat from the spectra of I and III. Thus indoline absorption is characteristic for it in neutral alcohol solution, while benzoid absorption (i.e., that which is characteristic for an alkylaniline salt) is characteristic in dilute acid. A mixture of benzoid absorption and protonated indolenine absorption is observed in concentrated acid. The authors explain this difference in the behavior of these compounds by the absence of an electron-donor substituent in the 5-position of furoindoline IV.

We previously accomplished the synthesis of V-XXII by the reaction of arylhydrazine hydrochlorides with γ-hydroxy ketones containing an α-methylidene group [1, 6, 7].

In this communication we have investigated the ring-chain tautomerism of V-XXII, particularly the clarification of the effect of substituents in various positions of the major ring of 2,3,3a,8a-tetrahydrofuro-[2,3-b]indole on the ease of opening the tetrahydrofuran ring (see scheme on p. 1125).

As seen from the data presented in Tables 1 and 2, two absorption maxima at 240-250 and 290-310 nm, characteristic for indoline absorption, are observed in the UV spectra of neutral solutions of tetrahydrofuro[2,3-b]indole derivatives. In addition, an additional absorption maximum appears at 215-235 nm for several nitrogen-unsubstituted compounds, and the long-wave maximum sometimes vanishes.

*See [1] for communication XXIII.

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TABLE 1. UV Spectra of 2,3,3a,8a-Tetrahydrofuro[2,3-b]indoles Substituted in the Benzene Ring and at the Junction Carbon Atoms at Various pH Values

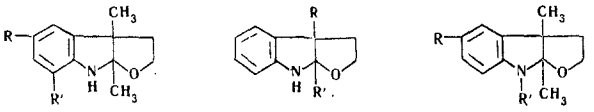
Comp.	Neutral solution in 80% ethanol			Region of equilibrium of the open and closed forms, pH units	Acid solution in 80% ethanol	
	pH	λ_{max}, nm	lg ε		λ_{max}, nm	lg ε
V	8,0	216	4,02	3,7—2,7	228	3,88
		223	3,87		235	3,83
		243	3,78		275	3,71
VI	8,3	220*	4,09	3,6—2,5	234	3,87
		251	3,75		240	3,83
					283	3,76
IX	8,1	251	4,08	2,4—1,2	228*	3,64
		308	3,30		234	4,01
					282	3,99
X	9,0	221	4,03	3,9—2,7	226*	3,75
		228	3,91		232	3,88
		244	3,73		239	3,81
					280	3,72
XI	9,0	224*	3,92	3,6—2,4	236	3,64
		231	3,86		242	3,62
		245	3,78		276	3,55
		293	3,40		315	3,58
XII	8,0	234	3,81	1,2—0,6	235	3,90
		243	3,84		242	3,89
		299	3,50		282	3,59
XIII	8,0	217	4,26	3,8—1,8	230	3,97
		223	4,10		233	3,93
		250	3,79		270	3,78
XIV	7,5	247	3,70	3,5—1,8	232	3,93
					237*	3,91
					270	3,72
XV	7,5	216	4,13	3,2—1,6	230	3,88
		223*	3,98		235	3,84
		247	3,76		277	3,76
XVI	8,1	225*	3,93	3,0—1,5	232	3,85
		243	3,86		236	3,84
					280	3,74

*Inflection.

TABLE 2. UV Spectra of N-Substituted 2,3,3a,8a-Tetrahydrofuro-[2,3-b]indole Derivatives at Various pH Values

Comp.	Neutral solution in 80% ethanol			Region of equilibrium of the open and closed forms, pH units	Acid solution in 80% ethanol	
	pH	λ_{max}, nm	lg ε		λ_{max}, nm	lg ε
XVII	8,8	250	3,95	4,3—2,5	230	3,75
		300	3,40		235	3,72
					274	3,66
XVIII	7,4	255	4,08	4,5—2,6	231	3,77
		307	3,65		237	3,77
					274	3,70
XIX	8,0	250	4,08	2,0—0,6	232	3,89
		302	3,47		238	3,86
					277	3,72
XXI	8,5	250	4,11	4,0—2,5	235	3,93
		308	3,49		242	3,87
					285	3,84
XXII	7,2	247	4,00	4,3—3,2	242	3,79
		316	3,48		288*	3,75
					296	3,81
					306	3,81

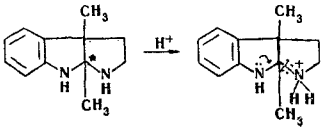
*Inflection.



V–XII XXXIII–XVI XVII–XXII

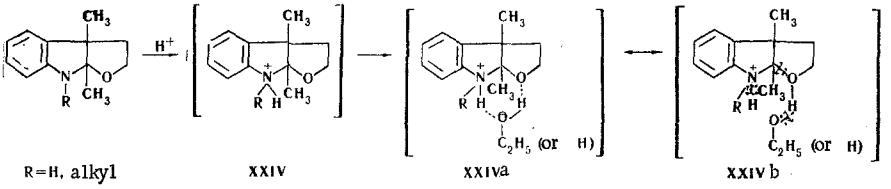
V R=R′=H; VI R=CH_3, R′=H; VII R=OCH_3, R′=H; VIII R=$OCH_2C_6H_5$, R′=H; IX R=Br, R′=H; X R=H, R′=CH_3; XI R=H, R′=OCH_3; XII R=H, R′=Br; XIII R=C_3H_7, R′=CH_3; XIV R=$CH_2C_6H_5$, R′=CH_3; XV R=CH_3, R′=C_3H_7; XVI R=CH_3, R′=$CH_2C_6H_5$; XVII R=H, R′=CH_3; XVIII R=H, R′=i-C_3H_7; XIX R=H, R′=$CH_2C_6H_5$; XX R=H, R′=C_6H_5; XXI R=CH_3, R′=CH_3; XXII R=OCH_3, R′=CH_3

In acid solutions (pH ~ 2), the UV spectrum takes on the form typical for the absorption spectrum of an indolenine salt: λ_{max}, nm, (log ε) 231 (3.83), 238 (3.81), 277 (3.77) (Fig. 1). The formation of an oxonium ion as a consequence of protonation of the oxygen atom of the tetrahydrofuran ring hardly occurs at such pH values, which correspond to acid concentrations of about 0.01 N. The previously proposed mechanism for the opening of the pyrrolidine ring of dinordeoxy-9-methyleseroline (XXIII) is therefore not suitable in this case, since the basis for it is protonation of the N_b atom with subsequent heterolytic cleavage of the C*–N_b bond and a synchronous shift of the p electrons of the N_a atom to the junction C* atom [8].

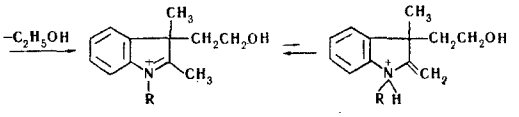


XXIII

We assume that the opening of the tetrahydrofuran ring of the compounds under investigation during acidification of their aqueous alcohol solutions proceeds with the participation of the solvent:



R=H, alkyl XXIV XXIVa XXIVb



XXVa XXVb

The indoline cation (XXIV) that forms as a result of protonation immediately undergoes attack by a solvent molecule (alcohol or water) with the formation of hydrogen bonds and XXIVa. Detachment of alcohol from form XXIVb, which is formed from XXIVa through a shift of electrons, leads to the protonated indolenine form (XXVa).

TABLE 3. UV Spectra of 5-Methoxy- (VII) and 5-Benzyloxy-3a,8a-dimethyl-2,3,3a,8a-tetrahydrofuro[2,3-b]indoles (VIII) in Various Solvents

Comp.	Hexane		Dioxane		Aceto-nitrile		Absolute ethanol		80% ethanol		10% $HClO_4$	
	λ_{max}, nm	lg ε	λ_{max}, nm	lg ε	λ_{max}, nm	lg ε	λ_{max}, nm	lg ε	λ_{max}, nm	lg ε	λ_{max}, nm	lg ε
VII	241	3,98	244	3,97	243	3,90	274	3,90	217*	4,10	240	3,82
	315	3,60	281*	3,08	277*	3,31			272	3,88	295	3,78
			318	3,68	314	3,46					308	3,78
VIII	243	3,95			245	3,99	272	4,08	271	3,95	241	3,83
	317	3,48			314	3,52					287*	3,82
											295	3,86
											307	3,86

*Inflection.

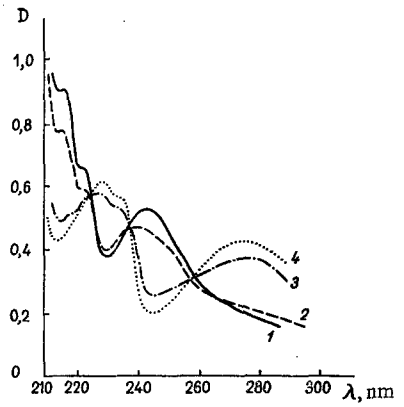


Fig. 1. UV spectrum of 3a,8a-dimethyl-2,3,3a,8a-tetrahydrofuro[2,3-b]indole in 80% ethanol at various pH values: 1) pH = 8; 2) 3.7; 3) 2.7; 4) 2.3.

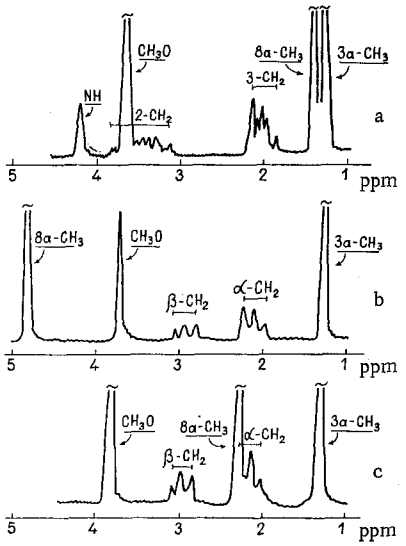


Fig. 2. PMR spectrum of the aliphatic protons of 5-methoxy-3a,8a-dimethyl-2,3,3a,8a-tetrahydrofuro[2,3-b]indole in various solvents: a) CCl_4; b) CD_3OD; c) CD_3OH.

A similar role of the solvent is not excluded in the case of ring-chain tautomerism of compounds of the XXIII type.†

It should be noted that the opening of the tetrahydrofuran ring of the compounds generally proceeds somewhat more readily (at higher pH values) than in the case of opening of the pyrrolidine ring of dinordeoxy-9-methyleseroline derivatives (XXIII). This is possibly caused by the high polarization of the C*–X bond in the C_6H_5–N–C*–X system when X is an oxygen rather than a nitrogen atom, which leads to a small decrease in the electrophilic character of the C* atom.

In explaining the effect of various substituents (V, VI, IX-XIX, XXI, and XXII), it was established that the character of the substituent and its location have a definite effect on the ease of opening of the tetrahydrofuran ring. Thus electron-donor substituents, especially those attached to the nitrogen atom, facilitate this process, and the equilibrium state of the indoline form and the alkylindolenine salt is already established at pH 2.5-4. The introduction of electron-acceptor substituents (IX and XII) shifts this equilibrium state to pH 2 and below (see Table 1). This can be explained by an increase (or a corresponding decrease) in the basicity of the nitrogen atom, which affects its ease of protonation and the electrophilic character of the 8a-carbon atom.

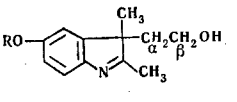
The strongest effect of an electron-acceptor substituent is displayed in XX. The UV spectra of this compound in neutral alcohol [λ_{max}, nm ($\log \varepsilon$): 245 (3.99), 281 (3.18)] and in 10% $HClO_4$ [λ_{max}, nm ($\log \varepsilon$): 235 (3.75), 240 (3.75), 278 (3.65)] indicate the presence of indoline and an indolenine salt, respectively. However, attempts to establish the pH range corresponding to the equilibrium state of the indoline form and the alkylindolenine salt were unsuccessful. Thus the UV spectrum remained typical for an indoline spectrum on acidification of a neutral solution to pH 0.6, while the UV spectrum remained typical for the spectrum of an indolenine salt when a solution in 10% $HClO_4$ (known to be the open form) was made alkaline to pH 2.6. This sort of phenomenon can be explained only by the fact that pronounced lowering of the basicity of the nitrogen atom leads to a sharp increase in the electrophilic character of the 8a-carbon atom and to the development of relaxation effects.

In a comparison of the compounds that we investigated and physovenine analogs (I, III, and IV), it became clear that the presence or absence of a substituent at the 8a-carbon atom has a considerable effect on the ease of opening of the tetrahydrofuran ring. The presence of electron-donor substituents in V-XXII leads to a pronounced decrease in the electrophilic character of the 8a-carbon atom. A consequence of this is the establishment of the equilibrium state of the indoline form and the indolenine salt under much milder conditions and the practical absence of the benzoid form.

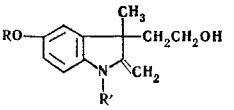
Proton magnetic resonance spectroscopy also confirms the existence of the open form of the XXVa type of the compounds considered above in acidic solutions. The disappearance of the signal corresponding to the 8a-methyl group was observed during recording of the PMR spectrum of V in CF_3COOH–D_2O (1:4), which can be observed only for the open form (XXVa) due to deuterium exchange when the equilibrium of the

† In a number of individual cases, the situation involves an equilibrium between the base and the salt, and the concept of ring-chain tautomerism is not valid in the strict sense of this concept.

XXVa and XXVb forms is shifted to favor the XXVa form. In addition, the signal of the 3a-methyl group in the PMR spectrum of an acid solution is shifted to weak field by 0.26 ppm as compared with its position in the spectrum of a neutral solution [9], while the signals of the α- and β-methylene groups give multiplets at 2.23-3.08 ppm. A similar phenomenon is observed in the PMR spectra of acid solutions of other compounds.



XXVI



XXVII a R′=H, b R′=CH_3

The UV spectra of VII and VIII have a number of interesting peculiarities (Table 3). In aprotic solvents, the UV spectrum indicates the presence of a typical indoline form, while in acid solutions the spectrum indicates the presence of an indolenine salt. However, the UV spectrum of these compounds in absolute ethanol corresponds to the unprotonated form of indolenine (XXVI). This can be explained by the fact that a strong electron-donor substituent, such as an alkoxy group, in the 5-position of the benzene ring reduces the electrophilic character of the 8a-carbon atom and polarizes the C−O bond in the C_6H_5−N−C−O system to such an extent that these compounds react with hydroxyl-containing compounds without prior protonation.

The existence of VII and VIII in alcohol solution as the indolenine form is confirmed by PMR spectroscopy. Thus when the PMR spectrum of VII in CD_3OD is recorded, the singlet of the 8a-methyl group vanishes due to deuterium exchange with the solvent in accordance with the equilibrium between forms XXVI and XXVIIa (Fig. 2b). In CD_3OH solution (Fig. 2c) the singlet of the 8a-methyl group is shifted by 0.87 ppm due to the appearance of a double bond in the weak-field region (in CCl_4, it was situated at 1.36 ppm [9]). In both CD_3OD and CD_3OH, the signals of the protons of the α- and β-methylene groups are clearly expressed triplets with J 6.8 Hz at 2.13 and 2.95 ppm, respectively. The singlet of the 3a-methyl group (1.26 ppm) does not undergo any changes when different solvents are used. The PMR spectrum of VIII in CD_3OH looks like the spectrum of VII in the same solvent.

Such anomalous phenomena are not observed for nitrogen-substituted XXII, since the XXVIIb form is probably energetically less favorable.

EXPERIMENTAL

Method Used to Record the UV Spectra at Various pH Values of the Media. A solution of the substance under investigation (~10^{-5} mole in 100 ml of 80% aqueous ethanol) was titrated with 5 N hydrochloric acid with stirring by a magnetic stirrer and with determination of the pH of the solution with an OR/401/1 TITRI-pH-METER at 20°. The change in volume of the solution was so insignificant in the process that it had practically no effect on the intensity of the UV absorption. Samples were removed at definite pH values, and their UV spectra were recorded.† To prove the reversibility of the process, an acid solution was back titrated with 5 N potassium hydroxide.

The UV spectra of the compounds were recorded with an ERS-3T spectrometer. The PMR spectra were recorded by Yu. A. Ustynyuk with a JNM-60 spectrometer (60 MHz) with tetramethylsilane (for neutral solutions) or methanol (for acid solutions) as the internal standard.

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† The pH values below unity are not quite accurate because of the increasing error in the readings of the pH meter in this region.