INDOLES. XII.* AN INVESTIGATION OF RING-CHAIN TAUTOMERISM IN COMPOUNDS OF THE ESERINE SERIES

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The ring-chain tautomerism of compounds with the eserine skeleton has been investigated by UV and PMR spectroscopy. It is shown that these compounds exist in neutral solution in the cyclic α-aminoindoline form. In acid solution, the pyrrolidine ring opens to form the indolenine salt. The relationships between the position of the tautomeric equilibrium and the pH of the medium and the regions in which equilibrium mixtures exist have been determined. The reversibility of the ring-opening process of the tricyclic system in acid media has been shown. It has also been shown that dinor-9-methylesermetol exists even in neutral solutions as a mixture of the ring and chain tautomers.

It has been shown previously that ring-chain tautomerism is possible in several alkaloids of the eserine type, in strongly acid solution [1]. Eserine, dinordesoxyseroline, esermetol, folicanthine, and calycanthine in weakly acid solution undergo only protonation at the N_b atom. Under these conditions, the UV spectra show a modified indoline pattern.

We were particularly interested in the problem of proving the reversibility of the process, the regions in which the equilibrium A ⇌ B ⇌ C exists, and the effect on it of structural factors, since these could be decisive factors in the physiological activity of compounds of this type.

Our results indicate that, in all the compounds examined (see Table 1), reduction in pH results in the establishment of the equilibrium A ⇌ B ⇌ C.

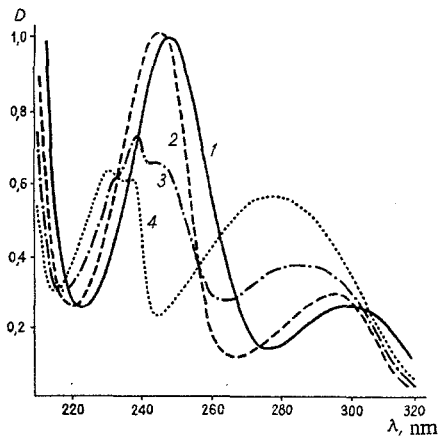

Fig. 1. UV Spectra of V in 50% ethanol at various pH values. 1) pH 8.1, 2) pH 4.7, 3) ph 2.9, 4) pH 1.8.

In neutral solution, compounds I-XII preserve the pyrrolo-[2,3-b]indole fragment, with the ring structure intact, as shown by the UV and PMR spectra [4, 5].

Compounds V-XI, which are substituted at the indole nitrogen atom, exist in weakly acid media (pH 4.7-4.15) as the protonated cyclic forms B. This is seen clearly on examining the UV spectra, for example of nordesoxy-9-methyleseroline (V) (Fig. 1). The spectrum of this compound in 50% aqueous-alcoholic solution (pH 8.1) shows two maxima (λ_{max} 249, 300 nm, log ε 4.02, 3.44), characteristic of the indoline absorption in tricyclic eserine bases. Acidification of the solution to pH 4.7 results in a hypsochromic shift of both maxima by 4 nm as a result of protonation of the N_b atom of the tricyclic form. On further acidification to pH 2.9, fission of the pyrrolidine ring takes place, and the UV spectrum takes a form typical of indolenine salts (form C at pH 1.8). Similar changes in the UV spectra are observed for

* For Part XI, see [5].

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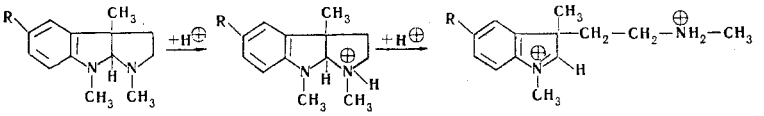
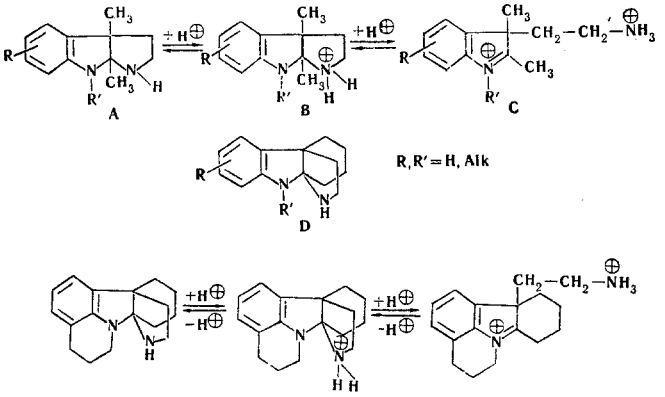
other N_a-substituted echibolines (see Table 1).



On increasing the strength of acid (1-5 M HCl), opening of the pyrrolidine ring occurs, with the formation of indolenine salts whose structure was shown spectroscopically.

In investigating the tautomeric conversions of compounds containing the Ph–N–C–N system, Fritz et al. [2, 3] found that, in the case of echiboline, formation of the indolenine salt occurred even with an 0.1 N alcoholic solution of hydrogen chloride.

In order to examine further the ring-chain tautomerism of compounds of types A and D, we examined the UV spectra of several compounds which we had synthesized previously [4], in aqueous-alcoholic solution, at varying pH values.



For N_a-substituted echibolines, the hypsochromic shift on protonation in weakly acid media amounted to 2 nm. The hypsochromic shift in the UV spectra in weakly acid solutions (pH ~4) was observed only in those compounds which possessed an alkyl substituent on the N_a atom, i.e., those containing the Ph—N—C—NH group.

R

In the case of compounds I-IV, containing the Ph–NH–C–NH group, the nature of the absorption did not change in weakly acid solution: at pH 2 (compound I) and pH 1.5 (compound II), opening of the pyrrolidine ring began, and at pH 1 these compounds were completely transformed into the C form (cf Fig. 2).

Echiboline (II) opens the pyrrolidine ring in a more acid medium than compound (I), which can probably be explained either by steric hindrance to the attack by a proton of the N_b atom or by the smaller donor capacity of a 9-CH_2 group as compared with a 9-CH_3 group.

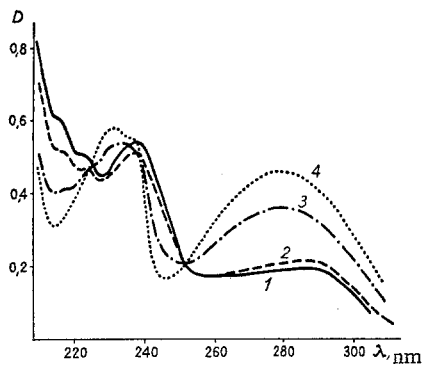
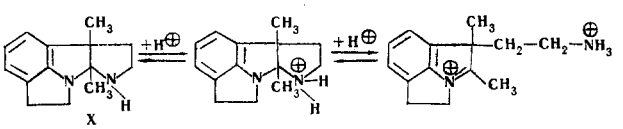


Fig. 2. UV Spectra of echiboline (II) at various pH values (in 50% ethanol). 1) pH 7.5, 2) pH 4.5-2.2, 3) pH 1.5, 4) pH 1.0.

In compounds I-IV, the protolytic fission took place in strongly acid solutions that in their N_a–alkyl analogs.

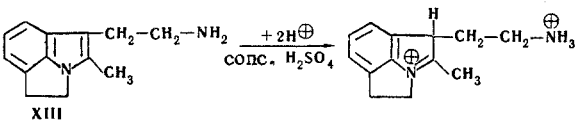
Dinordesoxy-9-methyl-7, 8-dimethyleneeseroline (X) and 7,8-dimethyleneechiboline (XI) to judge from the UV and PMR spectra, exist in neutral media in the cyclic form [4, 5]. In weakly acid solution (pH 5.15 for X, and pH 4.4-3.0 for XI) (see Table 1), protonation at the N_b atom takes place. On further acidification of the solutions, the indolenine salts are formed.



X

The UV spectra of X and XI in acidic aqueous alcohol, in 10% $HClO_4$, and in concentrated sulfuric acid are similar to that of 2-methyl-1, 7-dimethylenetryptamine (XIII) in concentrated sulfuric

acid, this being protonated under these conditions in the 3-position of the indole ring to form the protonated indolenine [1]. UV Spectrum of XIII in concentrated sulfuric acid: λ_{max} 230, 264, 270, 289 nm, lg ε 3.11, 2.92, 2.90, 2.19.



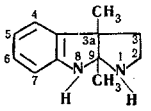
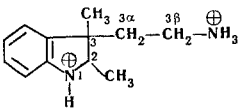
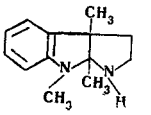
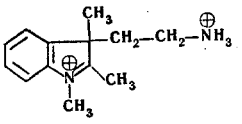
XIII

The spectra of X and XI in strongly acid solution (see Table 1) differ somewhat from those of dinordesoxy-9-methyleseroline (I) and echiboline (II), recorded under the same conditions. This could be due to structural differences, namely, to the 7, 8-dimethylene group, resulting in complete planarity of the N_a atom.

UV spectra recorded at various pH values possess isosbestic points (see Figs. 1 and 2), indicating the occurrence of an equilibrium between the ring and the open-chain forms. In order to prove more conclusively the reversibility of the process A ⇌ B ⇌ C, we recorded the UV spectra of all the compounds after acidification with changing pH in the alkaline region. The spectra of solutions with a given pH, obtained by basifying strongly acid solutions, were identical in all respects with those for the same pH values, obtained by basification of the initial solutions.

The PMR spectral data,* recorded in trifluoroacetic acid, confirmed the presence under these conditions of the protonated indolenine structure in compounds with the eseroline structure.

The substantial shift towards lower field (~1.5 ppm) of the methyl groups in the 8 and 9 positions of the eseroline compounds may simply be due to the formation of the indolenine salt.

CCl_4		CF_3COOH	
			
3a-CH_3	1,33 s	3-CH_3	1,69 s
9-CH_3	1,41 s	2-CH_3	2,90 s
2-CH_2	2,5—2,8 m	3α,β-CH_2	2,78 s
3-CH_2	1,6—2,1 m	aromatic protons	7,68 s
aromatic protons	6,38—6,94 m	NH_3^+	7,02 (broad hump)
NH	3,61 (broad hump)		
			
3a-CH_3	1,15 s	3-CH_3	1,66 s
9-CH_3	1,19 s	2-CH_2	2,88 s
2-CH_2	2,2—2,8 m	3α,β-CH_2	2,74 s
3-CH_2	1,4—1,9 m	1-CH_3	4,11 s
8-CH_3	2,67 s		
aromatic protons	6,04—6,81 m	aromatic protons	7,76 s
NH	2,16 s	NH_3^+	7,14 (broad hump)

* The PMR spectra were recorded on a JNM-4H-100 instrument, with a working frequency of 100 MHz, by Yu. A. Ustynyuk. The values for the chemical shifts are given on the scale relative to tetramethylsilane (s = singlet, d = doublet, t = triplet, m = multiplet).

TABLE 1. UV Spectra of Dinordesoxyeseroline Derivatives at Various pH Values

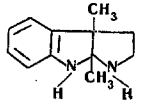
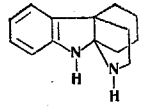
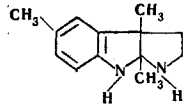
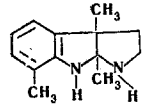
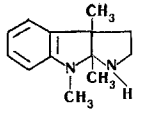
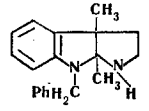
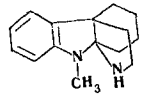
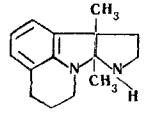
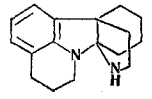
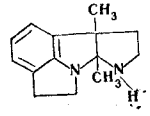
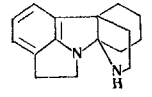
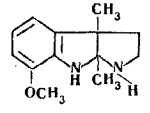
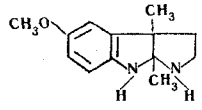
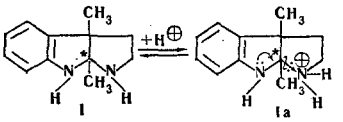
Compound	Formula	Solution in 59% ethanol			Weakly acid solution in 50% ethanol (protonated form B)		Region in which form B exists, pH units	Strongly acid solutions in 50% ethanol (ring-opened form C)		Region of equilibrium B—C, pH units	10% $HClO_4$	
		pH	λ_{max}, nm	lg ε	λ_{max}, nm	lg ε		λ_{max}, nm	lg ε		λ_{max}, nm	lg ε
1	2	3	4	5	6	7	8	9	10	11	12	13
I		7,1	217 223* 238 283	4,03 3,94 3,87 3,40	—†	—	—	230 235 276	4,04 4,02 3,84	2,0—1,0	231 237 282	3,88 3,84 3,82
II		7,5	216 224 238 286	3,96 3,86 3,89 3,43	—	—	—	232 237 280	3,92 3,89 3,81	1,5—1,0	233 238 281	3,72 3,69 3,65
III		8,0	220 227 243 263	4,03 3,93 3,75 3,65	—	—	—	236 241 292	3,86 3,83 3,76	2,2—1,1	237 243 296	3,86 3,82 3,80
IV		7,9	220 227 241 285	4,02 3,90 3,75 3,33	—	—	—	233 240 286	3,78 3,76 3,74	2,2—1,2	234 240 288	3,76 3,75 3,76
V		8,1	249 300	4,02 3,44	245 295	4,06 3,47	4,7—3,8	231 238 277	3,83 3,81 3,77	2,9—1,8	231 238 280	3,66 3,63 3,62
VI		8,3	251 302	4,00 3,39	247 297	3,98 3,39	4,15—3,0	234 239 280	3,76 3,74 3,56	2,6—1,3	232 238 276	3,81 3,78 3,69

TABLE 1 (continued)

VII		7,8	247 293	3,92 3,38	245 291	3,87 3,33	4,6—3,6	233 239 276	3,66 3,63 3,70	2,7—1,5	233 238 278	3,66 3,63 3,60
VIII		8,4	254 304	3,84 3,33	250 300	3,82 3,38	4,4	234 242 285	3,72 3,72 3,67	3,4—2,15	234 241 285	3,89 3,88 3,84
IX		8,04	251 300	3,84 3,38	249 298	3,86 3,38	4,7—4,3	235 243 286	3,81 3,79 3,73	3,3—2,1	235 243 285	3,73 3,75 3,73
X		7,3	243 292	3,89 3,46	241 290	3,93 3,47	5,15	230 257 265 273	3,66 3,19 3,11 3,08	2,6—1,0	230 263 270 287	3,01 2,82 2,76 2,35
XI		7,0	244 290	3,76 3,41	242 288	3,77 3,41	4,4—3,0	242 263 271 286	3,25 3,09 3,05 2,83	2,5—1,5	242 264 271 285	2,98 2,97 2,95 2,66
XII		8,2	225 232 242 292	3,95 3,90 3,81 3,41	—	—	—	237 243 285 324	3,65 3,64 3,58 3,57	2,0—1,1	243 283 325	3,43 3,45 3,46
XIII		7,7	218 273	4,02 3,87	—	—	—	242 287 297 310	3,79 3,71 3,75 3,78	3,1—1,1	244 287 297 315	3,81 3,62 3,68 3,78

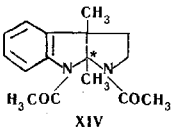
*Values of $\lambda_{inflection}$ are underlined.
†Underlining signifies that the spectra are identical with those of the initial solution.

The ease of fission of these compounds appears to depend to a considerable extent on the electron density at the N_a atom. The salt Ia, formed by protonation of the N_b atom in I, undergoes heterolytic fission of the C $-N_b$ bond, with synchronous shift of the p electrons on the N_a atom to the nodal atom C*.



The more readily this shift is able to occur, the milder are the conditions under which fission of the pyrrolidine ring takes place.

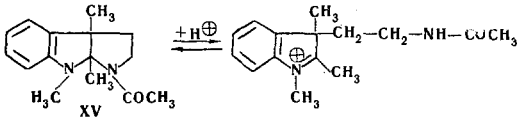
It has been shown previously [3, 6, 7] that introduction of electron-donating groups into the 5 position of the aromatic ring results in a reduction in the electrophilic character of the nodal C* atom. The same effect should be produced in the presence of N_a- alkyl substituents. By increasing the electron density at N_a, the alkyl group facilitates the shift of p electrons from the N_a atom to the nodal atom C*, and the fission of the C*$-N_b$ bond. The same effect should also be observed on introducing electron-donating substituents into the benzene ring (see below). Hence, in compounds with nitrogen substituents, fission of the pyrrolidine ring and formation of the indolenine salt proceed at lower acidities than in the case of I and II (see Table 1).



The diacetyl derivative of dinordesoxy-9-methyleseroline (XIV) [4] possesses a tricyclic structure which is unchanged on treatment with acids. In this case, the p electrons of the N_a atom are bound to the acetyl group, and cannot be transferred to the nodal C*. Consequently, heterocyclic fission of the C* $-N_b$ bond is not possible. The UV spectrum of XIV is unchanged at all pH values, having two absorption maxima: λ_{max} 246, 281 nm, log ε 3.95, 2.91 (in 50% ethanol). The PMR spectrum of XIV exhibits the following signals (in $CDCl_3$), in agreement with the tricyclic structure: 3a-CH_3 (1.25, s), 1, 8-$COCH_3$ (1.85, s), 9-CH_3 (2.68, s, shifted strongly towards lower field as a result of descreening by the acetyl groups), 2-CH_2 (2.96-3.51, m), 3-CH_2 (2.33, t), aromatic protons (7.1-7.3, m, H_7 8.09, d; J_{7-6} = 8 Hz).

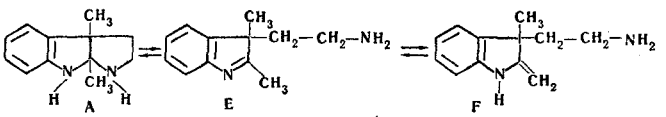
The monoacetyl derivative of nordesoxy-9-methleseroline (XV) in neutral solution also possesses the tricyclic form. The PMR spectrum (in $CDCl_3$) contains four singlets corresponding to the four methylene groups: 3a-CH_3 (1.12), 9-CH_3 (1.72), CH_3CO (1.89), 8-CH_3 (3.01).

In 50% alcohol at pH 7.2, the UV spectrum of XV shows two maxima (λ_{max} 255, 301 nm, log ε 3.96, 3.01), characteristic of the absorption of the tricyclic form (Fig. 3, curve 1). Acidification of the solution to pH 6.6 causes the fission of the tricyclic ring to begin, and at pH 4.9 the monoacetyl derivative is completely converted into the open-chain form (curve 3, Fig. 3, λ_{max} 234, 237, 279 nm, log ε 3.74, 3.72, 3.67).



This anomalous ease of fission of the monoacetyl derivative XV is to be explained by the fact that, in this case, there is no necessity for protonation of the N_b atom, since the required shift of σ electrons from the C$-N_b$ bond to the N_b atom has already been accomplished by the acetyl group. In practice, there is sufficient solvation to bring about the fission process.

In saying that, in neutral solutions, compounds of the eseroline type exist in the cyclic form, it must not be forgotten that one is speaking only of a shift in the tautomeric equilibrium A ⇌ E ⇌ F.



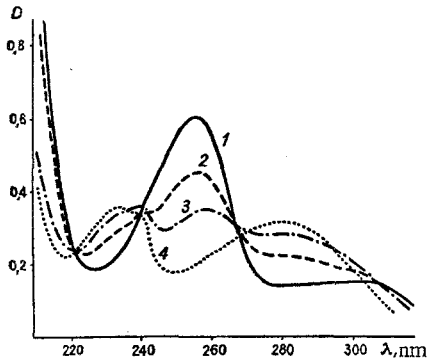


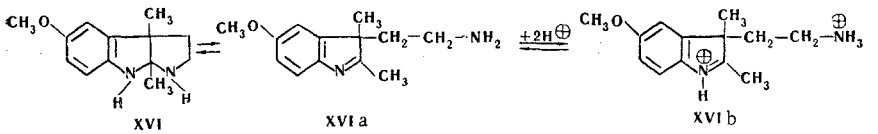
Fig. 3. UV Spectra of XV at various pH values (in 50% ethanol). 1) pH 7.2, 2) pH 6.6, 3) pH 6.1, 4) pH 4.9.

The deuterium exchange PMR spectra [5] show that the tautomeric interconversion A ⇌ E ⇌ F takes place even at pH 8-9 in protic solvents, since deuterium exchange at the 9-CH_3 group is possible only in the presence of form F in the equilibrium mixture (by analogy with deuterium exchange in carbonyl compounds).

It was shown in the case of echiboline derivatives [3] that opening of the pyrrolidine ring in neutral solution was facilitated by the presence of the electron-donating methoxy group in the p position to the N_a atom. In methanolic solution, 6-methoxyechiboline exists as an equilibrium mixture of the ring-opened and cyclic forms, whereas in cyclohexane this compound has the tetracyclic structure.

The PMR spectrum of dinor-9-methylesermetol (XVI) in CCl_4 at 20° is in agreement with the tricyclic structure: 3a-CH_3 – 1.27 (s), 9-CH_3 – 1.35 (s), 5-OCH_3 – 3.85 (s), 3-CH_2 – 1.77-2.15 (m), 2-CH_2 – 2.55-2.92 (m), NH – 1.90 ppm.

It follows from the UV spectra of XVI (see Table 2) that, in neutral aqueous-alcoholic solutions, the tautomeric equilibrium XVI ⇌ XVIa is almost completely shifted towards the ring-opened indolenine form characterized by the absorption of 275 nm [3].



In absolute t-butanol, the UV spectrum consists of the superimposed absorptions due to the indoline and indolenine chromophores. In dioxane, acetonitrile, and cyclohexane, the equilibrium is shifted towards the tricyclic indoline form XVI. In acid solutions (pH 3.1-1.1), the indolenine salt XVIb is formed, the UV spectrum of which is identical with that of protonated 6-methoxyechiboline [3].

EXPERIMENTAL

Method of Recording UV Spectra at Differing pH Values. The spectra were recorded on an ERS-3T ("Hitachi") instrument. A solution of the given compound of the required concentration (~1.10^{-5} M) in 50% ethanol (100 ml) in a titration flask was titrated with a 5 N solution of hydrochloric acid, the pH of the solution being determined with an OP[401]1 (Hungary) titrimeter at 20°, with stirring with a magnetic stirrer. The change in volume was so small as to have no effect on the UV absorption. To measure the pH, samples were withdrawn and placed in cuvets for spectrophotometry. In order to check the reversibility of the spectra, the acid solutions were back-titrated with 5 N potassium hydroxide.

TABLE 2. UV Spectra of Dinor-9-methylesermetol (XVI) in Various Solvents

Solvent	λ_{max}, nm	lg ε
Absolute t-C_4H_9OH	248, 274, 309	3,55, 3,55, 3,15
90% t-C_4H_9OH	274	3,69
80% C_2H_5OH	275	3,66
Dioxane	248, 280, 314	3,95, 3,59, 3,57
Acetonitrile	246, 280, 310	3,82, 3,57, 3,47
Cyclohexane	254, 284, 310	3,69, 3,36, 3,40

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