INDOLES

XIII.* SYNTHESIS AND INVESTIGATION OF THE RING–CHAIN TAUTOMERISM OF COMPOUNDS OF THE HOMOESEROLINE SERIES

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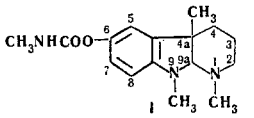
Dinordeoxy-10-methylhomoeseroline and a number of its derivatives, substituted in the benzene ring and at the indole nitrogen atom, were obtained by condensation in neutral, aqueous alcoholic solutions of arylhydrazines with δ-haloketones with an α-methine group. The compounds of the homoeseroline series exist in neutral solutions in the form of a mixture of ring and chain tautomers, and the position of the tautomeric equilibrium depends on the solvent. The dependence of the ring–chain tautomeric equilibrium on the pH of the medium was determined, and the region of the existence of an equilibrium mixture in acidic solutions was found.

The known methods for the synthesis of homoeserine (I) involve many steps and are based on intramolecular dehydration of 3-(γ-methylaminopropyl)indolinones [2,3].

We previously developed a method for the synthesis of compounds of the eseroline and echiboline type involving condensation of arylhydrazines with γ-haloketones with an α-methine group by refluxing the components in neutral, aqueous alcoholic solutions [4].



If a δ-haloketone with an alkyl substituent in the α position with respect to the carbonyl group is entered into this sort of condensation, the product is a tricyclic homoeserine system. The reaction of phenylhydrazine with 6-chloro- or 6-bromo-3-methyl-2-hexanone (II) leads to the formation of dinordeoxy-9a-methylhomoeseroline (III) (4a,9a-dimethylpiperidino[2,3-b]indoline). The use of various substituted arylhydrazines in this reaction makes it possible to obtain a number of dinordeoxy-9a-methylhomoeseroline derivatives (IV-VIII).

Pentacyclic compounds of the homoeseroline series (XI, XII) are obtained by condensation of chloroketone II with 1-aminoindoline (IX) and 1-amino-1,2,3,4-tetrahydroquinoline (X).

In almost all cases, heating the components of the condensation leads to partial resinification of the reaction mixture; this is also observed during vacuum distillation of the bases obtained. This naturally affects the yields of the pure condensation products. Compounds in which R" = H are obtained in 40-56% yield. The introduction of an alkyl substituent at the indoline nitrogen atom lowers the yield to 30-35%. An exception is dinordeoxy-9a-methyl-3,9-dimethylenehomoeseroline (XI), which is obtained in 69% yield. The reason for the decreased yields is the ability (examined below) of homoeseroline compounds to readily open the piperidine ring to form indolenine systems of low stability.

*See [1] for Communication XII.

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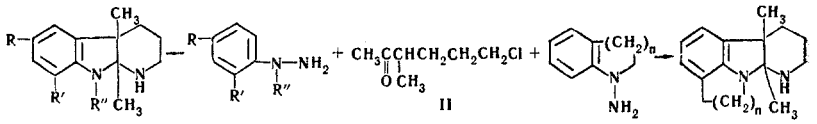


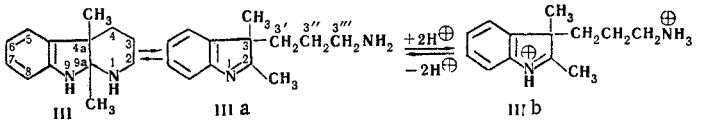
III-VIII II X,IX XI,XII

III R=R′=R″=H; IV R=CH_3, R′=R″=H; V R′=CH_3, R=R″=H; VI R″=CH_3, R=R′=H; VII R=OCH_3, R′=R″=H; VIII R′=OCH_3, R=R″=H; IX n=1; X n=2; XI n=1; XII n=2

All of the compounds obtained give dipicrates with bimolar amounts of picric acid. Diacetal derivatives could not be isolated because of pronounced resinification.

The UV and PMR spectra of the homoeseroline compounds were obtained to prove their structures. The features of the UV spectra (Table 1) will be discussed below.

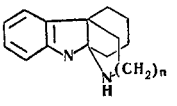
In acidic solutions (pH ~ 3), compounds of the eseroline series undergo opening of the pyrrolidine ring to form protonated indolenines [1,5]. In neutral alcohol solution, dinordeoxy-9a-methylhomoeseroline (III) partially opens its piperidine ring and exists in the form of an equilibrium mixture of the indoline and indolenine forms (III ⇌ IIIa).



III III a III b

The position of the equilibrium between the open and cyclic forms should be determined by two factors: first, the degree of strain of the cyclic form and, second, the probability of the occurrence of an intramolecular nucleophilic addition of the amino group to the C=N bond. The probability of the occurrence of intramolecular nucleophilic addition decreases significantly with decreasing size of the ring formed, since the probability of the collision of the reaction centers decreases with increasing distance between them in the molecule. Since the strain of five- and six-membered rings differs only slightly, the probability factor should be the determining factor [6]. From this point of view, one can explain the presence in neutral solutions of homoeseroline compounds of a mixture of cyclic and open forms (III ⇌ IIIa), while the ring–chain tautomeric equilibrium for eseroline derivatives in neutral solutions is shifted almost completely to favor the cyclic form [1].

In the case of α-aminoindolines of the XIII type it was shown that ring opening is facilitated under neutral conditions for n > 1 [7].



XIII n=1,2,3

The position of the tautomeric equilibrium III ⇌ IIIa depends on the nature of the solvent and the pH of the solution. The UV spectra (Table 1) of III indicate that the equilibrium is shifted to favor the tricyclic form in neutral, anhydrous solutions. Absorption maxima at 247 and 291 nm, which are characteristic for indoline absorption of the ring tautomer, are observed in the spectra of III under these conditions. Changing the solvent polarity does not induce substantial changes in the UV spectra.

The PMR spectrum of III in deuterochloroform (Table 2) also corresponds to a mixture of the cyclic and open forms, and the ring–chain equilibrium in this case is shifted to favor the cyclic form by a factor of ~75%, as follows from a comparison of the signal intensities from the protons of the 4a-CH_3 and 3-CH_3 and 9a-CH_3 and 2-CH_3 groups.

Addition of water to an alcoholic solution of III shifts the ring–chain tautomeric equilibrium to favor indolenine form IIIa. In 50% ethanol UV absorption of the indolenine type is observed with λ_{max} 256 nm and log ε 3.78 (UV spectrum of 2,3,3-trimethylindolenine in 50% ethanol: λ_{max} 257 nm, log ε 3.76).

The PMR spectrum of III, obtained in a mixture of CD_3OD and D_2O (4:1), also corresponds to a pure indolenine structure: 3-CH_3 1.42 s, 2-CH_3 2.36 s, 3′-CH_2 1.85-2.15 m, 3″-CH_2 1.25-1.54 m, 3‴-CH_2 2.49 t (J = 7.5 Hz), aromatic protons 7.25-7.53 m, exchanged protons 4.82 s.

TABLE 1. UV Spectra of III in Various Solvents*

Solvent	λ_{max}, nm	lg ε
100% C_2H_5OH	*222*, 247 290	*3,96*, 3,75, 3,16
96% C_2H_5OH	*222*, 253	*4,02*, 3,73
50% C_2H_5OH	256	3,78
Acetonitrile	246, 293	3,81, 3,30
Dioxane	248, 291	4,06, 3,63
t-C_4H_9OH	*223*, 246, 292	*3,91*, 3,83, 3,33

*The UV spectra were obtained with an ERS-3T ("Hitachi") spectrophotometer. Here and elsewhere, values corresponding to inflections are given in italics.

TABLE 2. PMR Spectrum of III in $CDCl_3$*

Protons of form III	δ, ppm	Protons of form IIIa	δ, ppm
4a-CH_3	1,18 s	3-CH_3	1,05 s
9a-CH_3	1,23 s	2-CH_3	2,13 s
2-CH_2	2,52—2,95 m	3‴-CH_2	2,37 t (J=7Hz)
3-CH_2	1,11—1,35 m	3″-CH_2	1,11—1,35 m
4-CH_2	1,49—2,00 m	3′-CH_2	1,49—2,00 m
Aromatic protons	6,38—7,45 m	Aromatic protons	6,38—7,45 m

*The PMR spectra were obtained by Yu. A. Ustynyuk with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz with tetramethylsilane as the internal standard. The chemical shifts are given in the δ scale; s is singlet, d is doublet, t is triplet, and m is multiplet.

TABLE 3. UV Spectra of Dinordeoxyhomoeseroline Derivatives in Solutions of Various pH

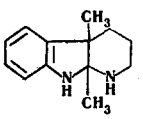
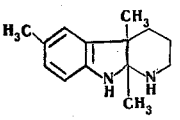
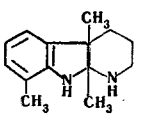
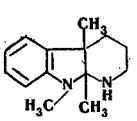
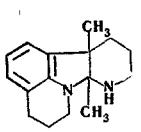
Compound	Formula	Solution in 50% C_2H_5OH			Strongly acid solution in 50% C_2H_5OH		Range of the III ⇌ IIIa equilibrium (in pH units)
		pH	λ_{max}, nm	lg ε	λ_{max}, nm	lg ε	
III		8,1	223 257	4,07 2,57	230 236 278	3,87 3,84 3,74	3,6—2,0
IV		7,2	221 229 242 266	3,94 3,88 3,75 3,62	237 242 292	3,88 3,80 3,61	3,1—1,8
V		7,4	221 227 259 287	4,18 4,05 3,70 3,44	233 240 285	3,76 3,72 2,85	3,6—1,4
VI		8,8	232 251 296	3,70 3,92 3,45	231 238 280	3,76 3,70 3,56	4,3—2,3
XI		8,0	233 250 293	3,87 3,83 3,47	233 242 281	3,83 3,77 3,61	5,5—3,0

TABLE 4. Yields, Constants, and UV Spectra of Homoeseroline Compounds

Compound	Bp, °C (mm)	Empirical formula	Found %		Calc. %		UV spectrum, 50% C_2H_5OH		R_{f_1} †	R_{f_2}	R_{f_3}	Yield %	Dipicrate					
							λ_{max}, nm	lg ε					mp, °C	empirical formula	found %		calc. %	
			C	H	C	H									C	H	C	H
III	125—130(1)	$C_{13}H_{18}N_2$	76,9	9,1	77,2	9,0	257	3,74	0,74	0,70‡ 0,88	—	56	164—165	$C_{13}H_{18}N_2 \cdot 2C_6H_3N_3O_7$	45,5	3,8	45,5	3,7
IV	130—132(2)	$C_{14}H_{20}N_2$	77,6	9,2	77,6	9,3	242 266 244* 265 *293*	3,75 3,62 3,73 3,68 *3,35*	0,75	0,72 0,89	—	46	173—174	$C_{14}H_{20}N_2 \cdot 2C_6H_3N_3O_7$	46,4	4,0	46,3	3,9
V	127—128(1)	$C_{14}H_{20}N_2$	77,6	9,2	77,7	9,3	259	3,70	0,75	0,71 0,89	—	41	160—162	$C_{14}H_{20}N_2 \cdot 2C_6H_3N_3O_7$	46,5	3,8	46,3	3,9
VI	120—122(1)	$C_{14}H_{20}N_2$	77,6	9,2	77,7	9,3	232 251 296 250* 295	3,70 3,92 2,96 3,95 3,40	0,46 0,82	0,70	0,76	35	161—162	$C_{14}H_{20}N_2 \cdot 2C_6H_3N_3O_7$	46,1	3,9	46,3	3,9
VII	124—127	$C_{14}H_{20}N_2O$	72,1	8,6	72,3	8,7	223 275 293	4,15 3,79 3,65	0,75	0,72	—	41	132—133	$C_{14}H_{20}N_2O \cdot 2C_6H_3N_3O_7$	45,4	3,7	45,2	3,8
VIII	155—157(1)	$C_{14}H_{20}N_2O$	71,9	8,6	72,3	8,7	243 269 293	3,75 3,64 3,57	0,78	0,68 0,79	—	40	145—146	$C_{14}H_{20}N_2O \cdot 2C_6H_3N_3O_7$	45,4	3,9	45,2	3,8
XI	131—132(1)	$C_{15}H_{20}N_2$	79,0	8,8	78,9	8,8	245 290	3,87 3,83	0,86	0,90	0,66	69	153—155	$C_{15}H_{20}N_2 \cdot 2C_6H_3N_3O_7$	46,8	3,9	47,2	3,8
XII	155—160(1)	$C_{16}H_{22}N_2$	79,1	9,1	79,3	9,1	233 250 293	3,87 3,83 3,47	0,43 0,81	0,86	0,71	20	150—151	$C_{16}H_{22}N_2 \cdot 2C_6H_3N_3O_7$	48,2	4,1	48,0	4,0

*In 80% C_2H_5OH.

†R_{f_1} and R_{f_2} are given for the following conditions: "slow" paper from the Volodarskii Plant, development with ninhydrin; R_{f_1} was obtained with a butanol–acetic acid–water system (4 : 1 : 5); R_{f_2} was obtained with a butanol–pyridine–water system (1 : 1 : 1); R_{f_3} is given for the following conditions: activity II Al_2O_3, benzene–isopropyl alcohol system (9 : 1), development with iodine vapors.

‡Here and elsewhere, the presence of two spots is explained by the presence of two tautomeric forms in a given solvent system.

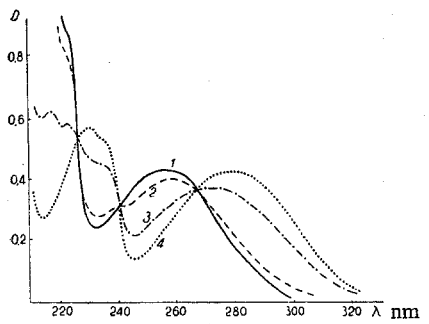


Fig. 1. UV spectra of III at various pH values (in 50% C_2H_5OH): 1) 8.1; 2) 3.6; 3) 2.6; 4) 1.5.

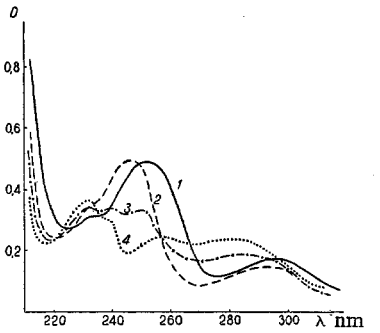
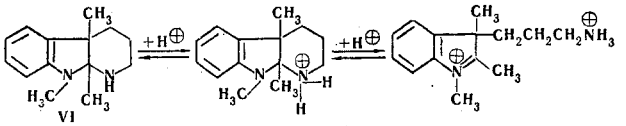


Fig. 2. UV spectra of VI at various pH values (in 50% C_2H_5OH): 1) 8.8; 2) 6.8; 3) 4.0; 4) 2.3.

Compounds IV-VI and XI, which are dinordeoxyhomoeseroline derivatives, also exist in the form of an equilibrium mixture of ring and chain tautomers in neutral 50% aqueous alcohol solutions (Tables 3 and 4), judging from their UV spectra. In 50% ethanol dinordeoxy-9a-methyl-8,9-dimethyleneeseroline (X) has a tetracyclic structure.

For compound III in acidic medium, starting at pH 3.6, the IIIa ⇌ IIIb equilibrium exists and is completely shifted to favor protonated indolenine at pH 2.0 (Fig. 1). Compounds IV, V, and XI (see Table 3) undergo similar transformations in acidic solutions.

For nordeoxy-9a-methylhomoeseroline (VI) in 50% ethanol the cyclic form apparently prevails and, like N_a-substituted eseroline derivatives [1], is protonated at the N_b atom (λ_{max} 232, 246, and 292 nm, log ε 3.75, 3.92, and 3.40) in weakly acidic solutions (pH 5.1-6.8). The protonated cyclic form and the indoleninium salt are in equilibrium at pH 2.3-4.3 (Fig. 2).



It should be noted that protonation of the N_b atom and opening of the tricyclic system for this compound are accomplished in a medium of lower acidity than for its eseroline analog, which is associated with the lower probability of closing the piperidine ring.

EXPERIMENTAL

6-Bromo-4-methyl-2-hexanone. This was obtained in 12% yield via the method in [8] and had bp 110-112° (20 mm), n_D^{20} 1.4671, and d_4^{20} 1.2885. PMR spectrum (CCl_4, TMS): 1-CH_3 2.06 s, 3-CH_3 1.10 d (J = 7.1 Hz), 3-CH 2.45 poorly resolved sextet, 4-CH_2 and 5-CH_2 1.76 m, 6-CH_2 3.49 t (J = 7.1 Hz).

6-Chloro-4-methyl-2-hexanone. This was similarly obtained in 26% yield and had bp 85-87° (18 mm), n_D^{20} 1.4401, and R_f 0.56 [on activity II Al_2O_3 in benzene–chloroform (17:3)]. IR spectrum:* 1720 cm^{-1} (C=O), no hydroxyl group absorption.

Compounds of the Homoeseroline Series. These were synthesized by the general method of condensation of haloketones with arylhydrazines previously described for the synthesis of compounds of the eseroline series [4]. The yields and constants of the compounds obtained are presented in Table 4.

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*The IR spectra were obtained in a thin layer with a JASCO-IR-S spectrometer with an NaCl prism.

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