INDOLE DERIVATIVES.

XLIII. SYNTHESIS AND PHARAMCOLOGICAL INVESTIGATIONS OF SOME TETRAHYDRO-γ-CARBOLINE AND 2-β-AMINOISOBUTYL-3R-INDOLE DERIVATIVES

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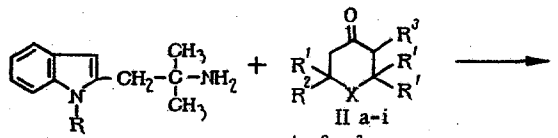
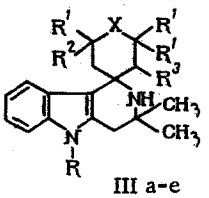
We previously reported [1] that spiro compounds of the 1,2,3,4-tetrahydro-γ-carboline series (III) or isomeric compounds, to which the structure of the corresponding imines (IV) was ascribed on the basis of their properties, are formed during the cyclization of 1-R2(β-aminoisobutyl)indoles (I) with various cyclic ketones (II) depending on the conditions under which the reactions are carried out and the structure of the ketone. We observed an inclination toward forming compounds of the second type when various alkyl-substituted 4-piperidones



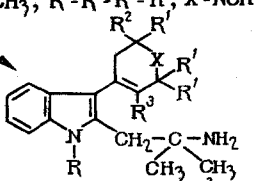
I a,b
a) R=H
b) R=CH$_3$

II a-i
a) $R^1=R^2=R^3=H$, X=NH
b) $R^1=R^2=R^3=H$, X=NCH$_3$
c) $R^1=CH_3$, $R^2=R^3=H$, X=NH
d) $R^1=R^2=CH_3$, $R^3=H$, X=NH
e) $R^1=R^2=CH_3$, $R^3=H$, X=NCH$_3$
f) $R^1=R^2=H$, $R^3=CH_3$, X=NH;
g) $R^1=H$, $R^2=R^3=CH_3$, X=NCH$_3$
h) $R^1=R^2=R^3=H$, X=CH$_2$
i) $R^1=R^2=R^3=H$, X=S



III a-e

a) $R=R^1=R^2=R^3=H$, X=CH$_2$; b) $R=R^1=R^2=R^3=H$, X=S
c) $R=R^1=R^2=R^3=H$, X=NCH$_3$; d) $R=R^1=R^2=R^3=H$, X=NH
e) R=CH$_3$, $R^1=R^2=R^3=H$, X=NCH$_3$



V a-i

a) $R=R^1=R^2=R^3=H$, X=NCH$_3$;
b) $R=R^2=R^3=H$, $R^1=CH_3$, X=NH,
c) $R=R^1=CH_3$, $R^2=R^3=H$, X=NH;
d) $R=R^3=H$, $R^1=R^2=CH_3$, X=NH;
e) $R=R^1=R^2=CH_3$, $R^3=H$, X=NH;
f) $R=R^3=H$, $R^1=R^2=CH_3$, X=NCH$_3$
g) $R=R^1=R^2=CH_3$, $R^3=H$, X=NCH$_3$
h) $R=R^1=R^2=H$, $R^3=CH_3$, X=NH
i) $R=R^1=H$, $R^2=R^3=CH_3$, X=NCH$_3$

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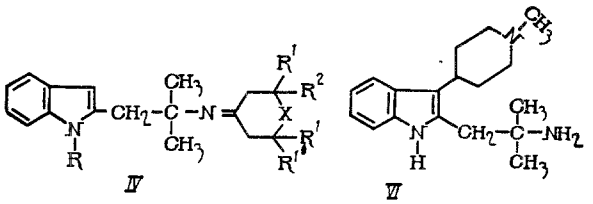
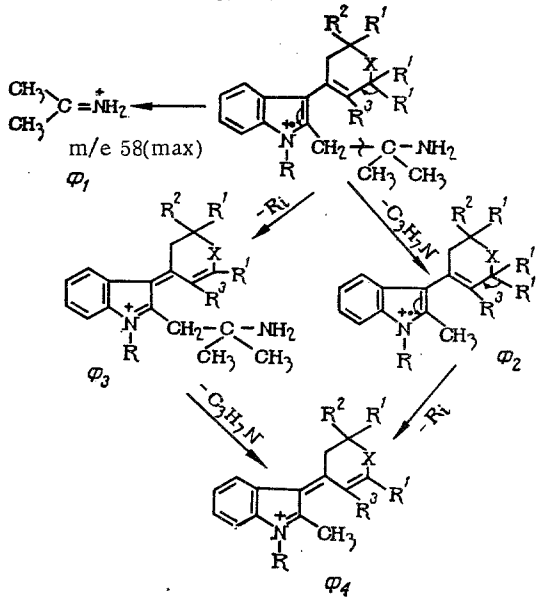


IV V

were used as the ketonic components. In connection with that fact that these compounds manifested cartain chemical characteristics — they did not give a color with Erlich's reagent, they did not cyclize to the corresponding spiro compounds, and had a proton signal in the 5.2 to 5.5 ppm region in the PMR spectra, i.e., toward stronger fields than that described for 3-H-indole — we undertook further investigations in this direction. The mass spectra which did not correspond to structure IV were primarily investigated, as a result of which structure V was considered.

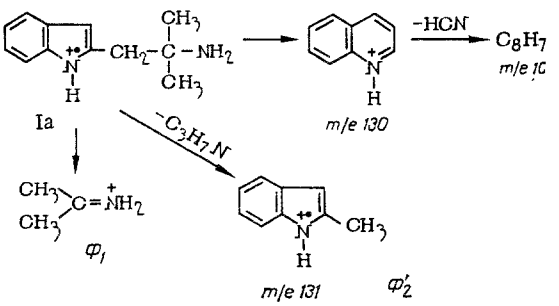
The very same maximum peak at m/e 58 (ion Φ_1) (C_3H_8N) occurred in the mass spectra of compounds Va-c, e, and g, and the dissociative ionization process of these compounds in the high mass number region took place similarly with a loss of 57 a.m.u. (C_3H_7N according to the high resolution mass spectrum) or a CH_3 group (ions Φ_2 and Φ_3 from which ion Φ_4 was subsequently formed according to Scheme 1).

Scheme 1



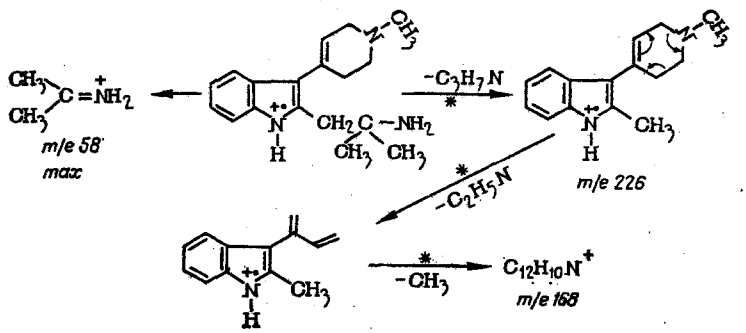
Similar decomposition of the molecular ion was observed in case Ia.

Scheme 2



Further decomposition of the Φ_2 ion took place in the case of compound Va, which contains only one methyl group in the piperidine ring; this was accomplished by the retrodiene splitting of the piperidine ring and elimination of C_2H_5N (43 a.m.u.), which was confirmed by the metastable ions and high resolution mass spectra (Scheme 3).

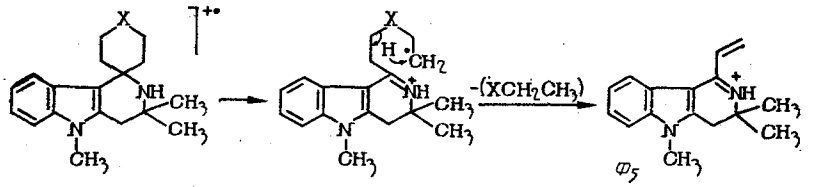
Scheme 3



Thus one can conclude that an aminoisobutyl substituent is present in compounds Va-e in position 2 and a piperidine substituent in position 3 on the basis of the nature of their dissociative ionization.

The mass spectra of compounds IIIa and c correspond to their structure and are characterized by the elimination of group X, the C_2H_5 group (Scheme 4), and by the formation of the maximum ion Φ_5 whose composition was also confirmed by their high resolution mass spectra. The ion with m/e 58 had a very low intensity or was completely absent in the spectra of these compounds.

Scheme 4



We also studied the condensation of Ia and Ib with piperidones IIa, b, e-g. One substance was obtained by the reaction of Ia with IIa and Ib with IIb in a benzene solution in the presence of catalytic amounts of p-toluenesulfonic acid. No vinyl proton is present in the 5-6 ppm region in the PMR spectra of these compounds; on the basis of this the structure of 2,2-dimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spiro-4^1-piperidine (IIId) and 2,2,9-trimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spiro-4'-(1^1-methyl)piperidine (IIIe) should be ascribed to these compounds.

Compounds Vf, h, and i were obtained by condensing Ia with IIe-g in alcoholic solutions of hydrogen chloride. There was a signal from the olefinic proton of the tetrahydropyridine ring in the 5.5 ppm region [2] in the PMR spectrum of Vf. There were no signals in this region in the PMR spectra of Vh, which provides a basis for concluding that the site of CH_3 group is at the olefinic carbon atom (according to the data in [3, 4], the double bond in the tetrahydropyridine ring is formed at the axial group during the dehydration of the corresponding alcohols).

The structure of the freshly prepared compounds V was also confirmed on Vd, f, and i by their mass spectra. The fragmentation of these compounds is analogous to the fragmentation of compounds Va-c, e, and g. The IR spectra of solutions of IIIa-e in carbon tetrachloride have the characteristic ν_{NH} band of the indole ring at 3460 cm^{-1}. The NH vibrations in the spectra of compounds Va-i, as for Ia, are shifted to 3340 cm^{-1} which can be explained by the presence of an intramolecular hydrogen bond. The UV spectra of Ia, b and IIIa-e are characteristic for the simplest indole derivatives, whereas the spectra of Va-i have less expressed maximums.

Compound Va was catalytically reduced to VI. There is no signal of an olefinic proton in the PMR spectrum of compound VI. The reaction of Ia with alkyl-substituted piperidones could serve as a method of synthesizing difficult-to-obtain indole derivatives.

The analytical data for compounds III and V are given in Table 1.

The effect of the series of compounds we obtained on the central nervous system was studied. Their ability to potentiate the narcotic effect of sodium thiopental (from the increase in the effect of a subnarcotic dose and thiopental narcosis), to cause ataxia (spinning rod

TABLE 1. Compounds III and V

Compound	Yield (in %)	mp (in deg)*	Found (in %)				Empirical formula	Calculated (in %)			
			C	H	Cl	N		C	H	Cl	N
IIIa	—	216—7	—	—	10,04	8,17	$C_{18}H_{24}N_2 \cdot HCl \cdot 2H_2O$	—	—	10,40	8,21
IIIb	—	85—7	—	—	10,64	8,56	$C_{17}H_{22}N_2S \cdot HCl$	—	—	10,98	8,67
IIIc	—	227—8	—	—	17,40	10,47	$C_{18}H_{25}N_3 \cdot 2HCl$	—	—	17,28	10,24
IIId	89	232,5—3,5	75,57	8,37	—	15,64	$C_{17}H_{23}N_3$	75,76	8,66	—	15,6
IIIe	27	123—4	76,67	9,29	—	13,99	$C_{19}H_{27}N_3$	76,72	9,14	—	14,13
Va	—	234—6	—	—	19,13	11,55	$C_{18}H_{25}N_3 \cdot 2HCl \cdot 1/2H_2O$	—	—	19,41	11,50
Vb	—	229—30	—	—	16,88	9,99	$C_{20}H_{29}N_3 \cdot 2HCl \cdot 2H_2O$	—	—	17,39	9,73
Vd	—	212—3	—	—	16,19	9,93	$C_{21}H_{31}N_3 \cdot 2HCl \cdot 2H_2O$	—	—	16,31	9,67
Vf†	—	207—8	—	—	17,59	9,74	$C_{22}H_{33}N_3 \cdot 2HCl$	—	—	17,19	10,18
Vf‡	100	127,5—29	77,90	9,87	—	12,28	$C_{22}H_{33}N_3$	77,82	9,80	—	12,37
Vg	—	215—6	—	—	16,5	9,7	$C_{23}H_{35}N_3 \cdot 2HCl$	—	—	16,62	9,85
Vh	95	181—3	76,12	9,13	—	14,72	$C_{18}H_{25}N_3$	76,28	8,89	—	14,83
Vi	90	127—9	76,94	9,25	—	13,60	$C_{20}H_{29}N_3$	77,12	9,38	—	13,49

*Compounds IIId and Vh were recrystallized from benzene, IIIe and Vi from petroleum ether, and Vf from n-heptane.
†Dichlorohydrate.
‡ Base.

method), catalepsy, to lower the spontaneous motor activity and amphetamine hyperactivity (actometer method) was considered; and their acute toxicity (LD_{50}) was also determined. Catalepsy was checked against rats, all the other tests mentioned were run on mice.

It was established that not one of the compounds studied causes catalepsy. The data on the remaining characteristics are given in Table 2. It is evident that all the compounds except IIIb possess to some extent or other a depressing effect on the central nervous system. Compound Vd proved to be the most active in this regard. A decrease or an increase in the number of methyl groups in compounds of this type led to a decrease in their activity compared to Vd.

Additional experiments were set up to study the central effects of Vd which is the one of greatest interest. The investigations carried out showed that Vd exerts hypothermal and antispasmodic effects in doses of 75 mg/kg (lowering of the body temperature by 5°C, prevention of Corazol convulsions and death for 75% of the mice). Compound Vd has no analgesic effect (Haffner's method, mice).

Compound Vd eliminates intragroup conflicts in rats (a tranquilizing effect): using a 0.36 mg/kg dose, motivated agression [5] and using a 3.2 mg/kg dose, avoidance reaction when irritated by a partner [6, 7]. The sedative properties of Vd are less expressed: The substance eliminates nonmotivated agression for rats in doses of 7.8 mg/kg and depresses the defensive conditional reflex in doses of 11.5 mg/kg.

On the basis of the data presented compound V can be classified as a tranquilizer with short term effect. It surpasses Librium in the strength of its tranquilizing activity, but is inferior to diazepam.

EXPERIMENTAL

The mass spectra were run on a JEOL JMS-01-SG 2 instrument at an energy of 75 eV for the ionizing electrons; the high resolution spectra were recorded on a photoplate and processed with a JEC-6 computer in the assembly using a microphotometer.

2,2-Dimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spiro-4'-piperidine (IIId). To 2 g of IIa in 10 ml of absolute alcohol was added 50 ml of absolute benzene and 50 mg of p-toluenesulfonic acid. The reaction mixture was boiled for 8 h, cooled, the precipitate was dissolved in hot water and made alkaline with an aqueous potassium carbonate solution. A total of 2.5 g of IIId was obtained.

TABLE 2. Pharmacological Activity of Compounds III and V (ED_{50}, in mg/kg)

Compound	Increase in the narcotic effect of sodium thiopental		Ataxia	Decrease in spontaneous motor activity		Decrease in phenamine hyperactivity		Acute toxicity, LD_{50} in mg/kg
	subnarcotic activity	narcosis		within 15 min	within 1 h	within 15 min	within 1 h	
IIIa	62	45	70	46	72,5	27	66	240
IIIb	In doses up to 500 mg/kg, it causes no changes in behavior							
IIIc	58	40	55	150	260	84	140	175
Va	None	None	None	58	110	39	78	>1500
Vb	55	30	108	—	—	—	—	150
Vd	17	12	90	8	25	2,5	10	120
Vf	25	20	72	18	13	14,5	19,5	—
Vg	37	27	54	27	44	39,5	62,5	—

2,2,9-Trimethyl-1,2,3,4-tetrahydro-γ-carboline-4-spiro-4'-(1'-methyl)piperidine (IIIe). Compound IIIe, 0.4 g, was obtained similarly to IIId from 1 g of Ib, 0.7 g of IIb in 4 ml of absolute alcohol, 30 ml of absolute benzene, and 25 mg of p-toluenesulfonic acid.

2-(β-Aminoisobutyl)-3-(3-methyl-1,2,5,6-tetrahydro-4-pyridyl)indole (Vh). A mixture of 1.5 g of Ia and 1.2 g of the hydrochloride of IIf in 13 ml of a 29% alcoholic solution of hydrogen chloride was boiled for 7 h. The solvent was evaporated *in vacuo*, the precipitate was dissolved in hot water and made alkaline with an aqueous potassium carbonate solution. The precipitate was filtered off; 2.1 g of Vh was obtained.

2-(β-Aminoisobutyl)-3-(1,3,6-trimethyl-1,2,5,6-tetrahydro-4-pyridyl)indole (Vi). Compound Vi, 2 g, was obtained similarly to Vh from 2 g of Ia and 1.5 g of IIg in 15 ml of a 29% alcoholic hydrogen chloride solution.

2-(β-Aminoisobutyl)-3-(1,2,2,6,6-pentamethyl-2,5,6-tetrahydro-4-pyridyl)indole (Vf). Compound Vf, 3.5 g, was obtained similarly to Vh from 2 g of Ia and 2.2 g of the hydrochloride of IIe in 15 ml of a 29% alcoholic hydrogen chloride solution after boiling for 2 h.

2-(β-Aminoisobutyl)-3-(1-methylpiperidyl)indole (VI). A solution of 2 g of Va in 40 ml of acetic acid and 10 ml of a 21% alcoholic hydrogen chloride solution was hydrogenated under the usual conditions over 0.2 g of platinum until the absorption of hydrogen ceased. The catalyst was removed and the alcohol evaporated *in vacuo*. The residue was dissolved in water, made alkaline with an aqueous potassium carbonate solution, and extracted with ether. The extract was dried over magnesium sulfate and the ether was evaporated. The residue was crystallized several times from n-heptane. A total of 0.7 g of VI was obtained, mp 137-138.5°C; the substance yields a melting point depression in a mixture with Va.

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