SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF DERIVATIVES OF PYRANO- AND PYRIDO[3,2-*a*]CARBAZOLES

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The intramolecular cyclization of diaminodienyl diketones Ia, b has been previously used [1, 2] to synthesize coumarin derivatives IIa, b, the reaction of which with ammonium acetate gave substituted carbostyrils IIIa, b. The alkylation of the Na salts of the latter with benzyl chloride and N,N-dimethylaminoethyl chloride proceeds at the ring nitrogen atom to give N-alkylcarbostyrils IIIc-e. The compounds that were synthesized by this method contain a carbonyl function in their structure; this ensures the possibility of their use in the Fischer reaction to obtain four-ring indole-containing systems that are of interest for the investigation of their psychotropic activity.

The reaction of two-ring systems IIa, b and IIIa-e with phenylhydrazine hydrochloride without isolation of the intermediate phenylhydrazones leads smoothly and in high yields to pyrano- (IVa, b) and pyrido[3,2-*a*]carbazole derivatives (Va-e). The structures of the compounds obtained were proved by the results of elementary analysis and data from the mass spectra [see Experimental(Chemical)] and PMR spectroscopy. Signals of protons of the NH group of the carbazole fragment are observed in the PMR spectra (d_6-DMSO) of IVb and Va, b in the form of a singlet with an intensity of 1H with δ 11.41 ppm (IVa) and 11.32 ppm (Va, b). The protons of the CH_2 groups attached to the C_5 and C_6 atoms of the dihydrogenated benzene ring in carbazole IVb proved to be equivalent, and the signals of these protons show up in the form of a singlet with an intensity of 4H with δ 2.99 ppm. On passing to Vb the signals of these protons are converted to a multiplet at 2.89-2.98 ppm. Signals of the protons of a 5-CH_2 group at 2.77 ppm (s, 2H) and a 6-$C(CH_3)_2$ group at 1.37 ppm (s, 6H) appear in the PMR spectum of Va.

The signals of the protons of the 1,2-CH groups for all three compounds are found at weak field and show up in the form of two doublets with an intensity of 1H with a characteristic spin-spin coupling constant (SSCC) (cis) on the order of 9.3-9.5 Hz: IVb 7.97 (1-CH) and 6.38 ppm (2-CH) with SSCC $^3J_{HH}$ = 9.5 Hz; Vb 7.835 (1-CH) and 6.355 ppm (2-CH) with $^3J_{HH}$ = 9.3 Hz; Va 7.85 (1-CH) and 6.34 ppm (2-CH) with $^3J_{HH}$ = 9.3 Hz. The signals of the protons of the 7,10-CH groups of the indole fragment show up in the form of split doublets with SSCC $^3J_{HH}$ 6.5-6.7 Hz (cis), while the signals of the protons of the 8,9-CH groups show up in the form of split triplets with an intensity of 1H. This splitting of the signals constitutes evidence for spin-spin coupling of the protons of the 7,9- and 8,10-CH groups with SSCC $^4J_{HH}$ 1.5-3 Hz. The positions of the signals of these protons are as follows: IVb 7.37 ppm (7-CH) with SSCC $^3J_{7,8\text{-CH}}$ = 7 Hz and 7.43 ppm (10-CH) with $^3J_{9,10\text{-CH}}$ = 6.7 Hz and 7.00 and 7.06 ppm (8,9-CH); Vb 7.34 ppm (7-CH) with $^3J_{7,8\text{-CH}}$ = 6.5 Hz, 7.39 ppm (10-CH) with $^3J_{9,10\text{-CH}}$ = 6.7 Hz, and 6.975 and 7.03 ppm (8,9-CH); Va 7.34 ppm (7-CH) with $^3J_{7,8\text{-CH}}$ = 7 Hz, 7.62 ppm (10-CH) with $^3J_{9,10\text{-CH}}$ = 6.7 Hz, and 6.95 and 7.02 ppm (8,9-CH). The precise assignment of the signals of the 8,9-CH groups and the precise determination of the $^4J_{HH}$ SSCC were not accomplished, since these questions are not fundamental within the framework of confirming the structures of the compounds obtained. Signals of the NH proton of the pyridone fragment appear in the PMR spectra of Va, b in the form of a broad singlet at weak field: Vb 12.04 ppm and Va 11.97 ppm.

Thus, the spectral data obtained confirm the proposed structures of IVa, b and Va-e.

In the case of dihydropyridocarbazole Vb we studied the possibility of dehydrogenation. It was found that this process takes place smoothly and can be accomplished by two methods – by heating Vb in nitrobenzene or by its reaction with chloranil – and pyridocarbazole VI was obtained in good yield in both cases. Just as in the case of Vb, the following

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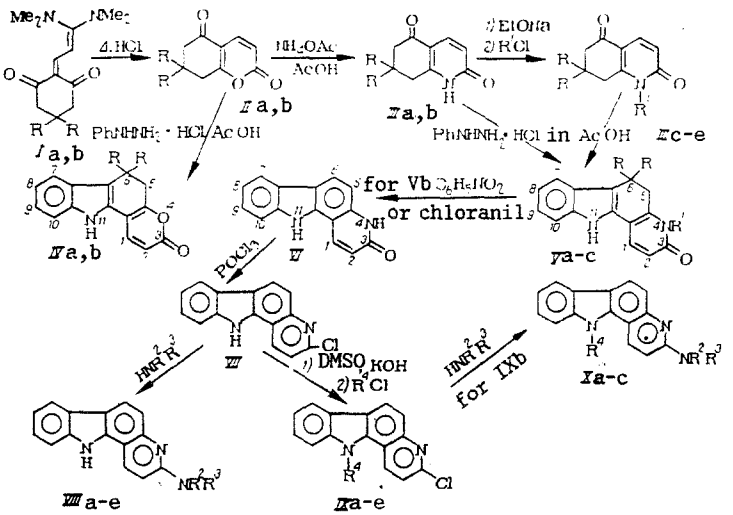
signals of the protons of the groups are observed in the PMR spectrum of VI: NH (carbazole) at 11.8 ppm (s, 1H), NH (pyridone) at 12 ppm (s, 1H), 1-CH at 8.49 ppm (d, 1H), 2-CH at 6.61 ppm (d, 1H) with SSCC $^3J_{HH}$ = 9.6 Hz, 10-CH at 8.09 ppm (d, 1H) with $^3J_{9,10\text{-CH}}$ = 7.6 Hz, 7-CH at 7.58 ppm (d, 1H) with $^3J_{7,8\text{-CH}}$ = 8.04 Hz, and 8,9-CH at 7.385 and 7.25 ppm (t, 1H each). In contrast to the spectrum of Vb, signals of protons of 5,6-CH_2 groups vanish in the spectrum of VI, and two new doublets with SSCC $^4J_{HH}$ = 8.6 Hz (cis), which can be ascribed to signals of protons of 5- and 6-CH groups [7.15 and 8.22 ppm (1H each)], appear at weak field. Thus, the spectral data attest to the formation of dehydrogenated product VI. The existence of a pyridone fragment in the structure of this compound made it possible to synthesize a group of 3-substituted and 3,11-substituted compounds of this series. With this end in mind we used the reaction of VI with $POCl_3$ to obtain 3-chloro derivative VII, which was the starting compound in subsequent transformations. Thus, a number of 3-amino derivatives (VIIIa-e) were obtained by its reaction with various amines. The alkylation of chloro compound VII with various alkyl halides proceeds smoothly at the indole NH group in DMSO in the presence of KOH; the chlorine atom is not involved under these conditions. A group of 3-substituted amino-11-alkylpyrido[3,2-*a*]carbazoles (Xa-e) was synthesized on the basis of the 3-chloro-11-alkyl derivative (IXb) obtained.



Ia:R = Me, IIb:R = H, IIb:R = Me, IIb:R = H, IIIb:R = Me, IIIb:R = H,
IIIc:R = H, $R^1 = CH_2Ph$, IIId:h = H, $R^1 = (CH_2)_2NMe_2$, IIIe:R = Me,
$R^1 = (CH_2)_2NMe_2$ IVa:R = Me, IVb.R = H, Va.R = Me, R^1 = H, Vb.R = R^1 = H,
Vc:R = H, $R^1 = CH_2Ph$, Vd:R = H, $R^1 = (CH_2)_2NMe_2$, Ve.R = Me, $R^1 = (CH_2)_2NMe_2$,
VIIIe:R^2 = H, $R^3 = CH_2Ph$, VIIIb.R^2 = H, $R^3 = (CH_2)_2NEt_2$,
VIIIe:$R^2 + R^3 = (CH_2)_2O(CH_2)_2$, VIIId:$R^2 + R^3 = (CH_2)_5$,
VIIIc.$R^2 + R^3 = (CH_2)_2NMe(CH_2)_2$, IXd:$R^4$ = Et, IXe:$R^4 = CH_2Ph$,
IXc:$R^4 = (CH_2)_2NEt_2$, IXd:$R^4 = (CH_2)_2NMe_2$, IXe $R^7 = (CH_2)_3NMe_2$,
Xa:$R^2 + R^3 = (CH_2)_5$, Xb:$R^2 + R^3 = (CH_2)_2O(CH_2)_2$, Xc:$R^2 + R^3 = (CH_2)_2NMe(CH_2)_2$,
Xa-c:$R^7 = CH_2Ph$.

EXPERIMENTAL (CHEMICAL)

The PMR spectra were recorded with a Varian XL-200 spectrometer with tetramethylsilane (TMS) as the internal standard. The mass spectra were obtained with a Varian MAT-112 spectrometer (Phinnigan) with direct introduction of the samples into the ion source; the temperature of the ionization chamber was 180°C, and the ionizing-electron energy was 70 eV. The melting points were determined with a heating stage of the Boetius type. The characteristics of the synthesized compounds are presented in Table 1. The results of the elementary analyses were in agreement with the calculated values.

11H-3(3H)-Oxo-6,6-dimethyl-5,6-dihydropyrano[3,2-*a*]carbazole (IVa). A solution of 1.92 g (0.01 mole) of coumarin IIa and 1.45 g (0.0101 mole) of phenylhydrazine hydrochloride in 14 ml of glacial AcOH was refluxed for 2 h, after which it was evaporated. The resulting oil was triturated in 20 ml of water, and the mixture was filtered to give 1.96 g of carbazole IVa (M^+ 265).

11H-3(3H)-Oxo-5,6-dihydropyrano[3,2-*a*]carbazole (IVb). This compound was obtained from coumarin IIb in the same way as IVa. The yield of IVb (M^+ 237) was 1.68 g.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp,* °C	Empirical formula	Yield, %
Va	288—290	$C_{17}H_{16}N_2O$	95
Vb	348—350	$C_{15}H_{12}N_2O$	93
Vc	338—340	$C_{22}H_{18}N_2O$	90
Vd	193—196	$C_{19}H_{21}N_3O$	43
Ve	256—259	$C_{21}H_{25}N_3O$	81
IVa	248—250	$C_{17}H_{15}NO_2$	74
IVb	245—248	$C_{15}H_{11}NO_2$	71
VI	355—360	$C_{15}H_{10}N_2O$	94
VII	252—253	$C_{15}H_9N_2Cl$	96
VIIIa	276—277	$C_{22}H_{18}N_3Cl$	83
VIIIb	247—250	$C_{21}H_{26}N_4Cl$	73
VIIIc	296—300	$C_{19}H_{19}N_3OCl$	92
VIIId	282—283	$C_{20}H_{19}N_3$	99
VIIIe	269—271	$C_{20}H_{20}N_4$	64
IXa	191—197†	$C_{17}H_{13}N_2Cl$	99
IXb	276—277	$C_{22}H_{15}N_2Cl$	64
IXc	99—101	$C_{21}H_{22}N_3Cl$	55
IXd	158—161	$C_{19}H_{18}N_3Cl$	71
IXe	170—172	$C_{20}H_{20}N_3Cl$	66
Xa	207—210	$C_{27}H_{25}N_3$	98
Xb	239—240	$C_{26}H_{23}N_3O$	95
Xc	214—216	$C_{27}H_{26}N_4$	96

*The compounds were crystallized: VII and IXc-e from iso-PrOH, VIIIa, e from ethyl acetate, and the rest from DMF.
†Compound IXa sublimes at this temperature.

11H-2-Oxo-6,6-dimethyl-3,4,5,6-tetrahydropyrido[3,2-*a*]carbazole (Va). A solution of 1.91 g (0.01 mole) of carbostyril IIIa and 1.45 g (0.0101 mole) of phenylhydrazine hydrochloride in 14 ml of glacial AcOH was refluxed for 5 h, after which the resulting precipitate was removed by filtration and washed with 30 ml of water to give 2.5 g of carbazole Va ($M^{+\cdot}$ 264).

11H-3-Oxo-3,4,5,6-tetrahydropyrido[3,2-*a*]carbazole (Vb). This compound was obtained from carbostyril IIIb in the same way as Va. The yield of Vb ($M^{+\cdot}$ 236) was 2.2 g.

11H-3-Oxo-4-benzyl-3,4,5,6-tetrahydropyrido[3,2-*a*]carbazole (Vc). A solution of 2.81 g (0.01 mole) of carbostyril IIIc and 2.84 g (0.02 mole) of phenylhydrazine hydrochloride in 14 ml of glacial AcOH was refluxed for 5 h, after which the resulting precipitate was removed by filtration and washed with 10 ml of water to give 2.95 g of carbazole Vc ($M^{+\cdot}$ 326).

11H-3-Oxo-4-(β-dimethylaminoethyl)-3,4,5,6-tetrahydropyrido[3,2-*a*]carbazole (Vd). This compound was obtained from carbostyril IIId in the same way as Vc. The reaction time was 3 h. The reaction mixture was evaporated, and the oil was dissolved in 10 ml of water. The aqueous solution was made alkaline with KOH to pH 8, and the resulting precipitate was removed by filtration and washed successively with 10 ml of water and 2 ml of iso-PrOH to give 1.3 g of Vd ($M^{+\cdot}$ 307).

11H-3-Oxo-4-(β-dimethylaminoethyl)-6,6-dimethyl-3,4,5,6-tetrahydropyrido[3,2-*a*]carbazole (Ve). This compound was obtained from carbostyril IIIe in the same way as Vd. The yield of Ve ($M^{+\cdot}$ 336) was 2.73 g.

11H-3-Oxo-3,4-dihydropyrido[3,2-*a*]carbazole (VI). A) A 2.36-g (0.01 mole) sample of carbazole Vb was refluxed in 20 ml of nitrobenzene for 2 h, after which the mixture was cooled, and the precipitate was removed by filtration and washed with 20 ml of benzene to give 2.2 g of carbazole VI ($M^{+\cdot}$ 234).

B) A mixture of 2.36 g (0.01 mole) of carbazole Vb and 3 g (0.012 mole) of chloranil was refluxed in 20 ml of absolute benzene for 2 h, after which the precipitate was removed by filtration. It was then treated with 50 ml of 2 N NaOH solution, removed by filtration, and washed with 50 ml of water to give 2.2 g of carbazole VI.

11H-3-Chloropyrido[3,2-*a*]carbazole (VII). A mixture of 2.34 g (0.01 mole) of carbazole VI and 1 g of $Et_3N \cdot HCl$ in 20 ml of $POCl_3$ was refluxed for 1 h, after which the $POCl_3$ was removed by distillation, and the reaction mixture was decomposed over ice. The aqueous mixture was made alkaline to pH 8 with concentrated NaOH solution and extracted with $CHCl_3$ (three 50-ml portions). The extract was dried over Na_2SO_4 and evaporated to give 2.43 g of carbazole VII [$M^{+\cdot}$ 252 (^{35}Cl)].

11H-3-Benzylaminopyrido[3,2-*a*]carbazole (VIIIa) Hydrochloride. A mixture of 2.52 g (0.01 mole) of carbazole VII and 2.68 g (0.0025 mole) of benzylamine in 40 ml of absolute ethanol was maintained at 200°C in an autoclave for 12 h, after which it was evaporated, and the residue was treated with 10 ml of water. The aqueous mixture was acidified with concentrated HCl to pH 1, and the resulting precipitate was removed by filtration to give 3 g of the hydrochloride of VIIIa ($M^{+\cdot}$ 323).

11H-3-(β-Diethylaminoethylamino)pyrido[3,2-*a*]carbazole (VIIIb) Dihydrochloride. This compound was obtained from carbazole VII and β-diethylaminoethylamine in the same way as VIIIa. The yield was 2.96 g.

11H-3-(1-Morpholino)pyrido[3,2-*a*]carbazole (VIIIc) Hydrochloride. This compound was obtained from carbazole VII and morpholine in the same way as VIIIa hydrochloride. The yield of VIIIc was 3.12 g (M^+ 303).

11H-3-(1-Piperidino)pyrido[3,2-*a*]carbazole (VIIId). The reaction was carried out as in the preparation of carbazole VIIIa, after which the reaction mixture was evaporated, and the resulting oil was triturated in 5 ml of iso-PrOH. This procedure gave 3 g of carbazole VIIId.

11H-3-[1-(4-Methyl)piperazino]pyrido[3,2-*a*]carbazole (VIIIe). This compound was obtained from carbazole VII and N-methylpiperazine in the same way as VIIId. The yield was 2.02 g.

3-Chloro-11-ethylpyrido[3,2-*a*]carbazole (IXa). A 2.52 g (0.01 mole) sample of carbazole VII was added to a suspension of 2.24 g (0.04 mole) of KOH in 20 ml of DMSO, after which the mixture was stirred for 45 min. A 3.12-g (0.02 mole) sample of EtI was then added, which resulted in an exothermic reaction. The mixture was allowed to stand for 6 h, after which 2.8 g of carbazole IXa was removed by filtration.

3-Chloro-11-benzylpyrido[3,2-*a*]carbazole (IXb). This compound was obtained from VII and $PhCH_2Cl$ in the same way as IXa. The yield was 2.19 g [$M^{+\cdot}$ 342 (^{35}Cl)].

3-Chloro-11-(β-diethylaminoethyl)pyrido[3,2-*a*]carbazole (IXc). This compound was obtained from VII and β-diethylaminoethyl chloride in the way way as IXa; however, the reaction mixture was heated at 60°C for 1 h, after which it was cooled and treated with 70 ml of water, and the resulting precipitate was removed by filtration to give 1.93 g of IXc.

3-Chloro-11-(β-dimethylaminoethyl)pyrido[3,2-*a*]carbazole (IXd). This compound was obtained from VII and β-dimethylaminoethyl chloride in the same way as IXa. The yield was 2.31 g.

3-Chloro-11-(γ-dimethylaminopropyl)pyrido[3,2-]carbazole (IXe). This compound was obtained from VII and γ-dimethylaminopropyl chloride in the same way as IXa. The yield was 2.23 g.

3-(1-Piperidino)-11-benzylpyrido[3,2-*a*]carbazole (Xa). This compound was obtained from carbazole IXb and piperidine in the same way as VIIId. The reaction time was 9 h, and the yield was 3.73 g.

3-(1-Morpholino)-11-benzylpyrido[3,2-*a*]carbazole (Xb). This compound was obtained from IXb and morpholine in the same way as Xa. The yield was 3.73 g.

3-[1-(4-Methyl)piperazino]-11-benzylpyrido[3,2-*a*]carbazole (Xc). This compound was obtained from IXb and N-methylpiperazine in the same way as Xa. The yield was 3.9 g.

EXPERIMENTAL (BIOLOGICAL)

The pharmacological study of the compounds obtained was carried out with respect to the indices of the psychotropic and, primarily, antidepressive activity.

The activity of the compounds in the "saving from water" behavioral swimming test [5], as well as in neuropharmacological tests of the interaction with reserpine [6], 5-hydroxy-

tryptophan (5-HTP) [3], L-DOPA [4], apomorphine, and tremorine, was investigated. The tests used made it possible not only to evaluate the effect of the compounds on various aminergic systems of the organism (noradrenergic, serotoninergic, and cholinergic) but also to form a preliminary judgment regarding the possible mechanism of the activity (in particular, the possible effect on the monoamine oxidase activity).

The acute toxicities of the compounds in the case of administration into white mice (LD_{50}) were also studied. All of the investigated compounds proved to be only slightly toxic. In a dose of 750 mg/kg they did not have a substantial effect on the general state and behavior of the animals; no animals perished. Thus the LD_{50} of these compounds exceeds 750 mg/kg.

The investigated compounds did not have a substantial effect on the "saving" behavior.

Some of the investigated compounds decreased the activity of reserpine (2.5 mg/kg intraperitoneally; blepharoptosis and hypothermia in mice). The greatest effect was noted for Ve – a pyridocarbazole derivative. In a dose of 50 mg/kg (internally) it decreased blepharoptosis in the animals from 3.6 ± 0.13 points to 1.5 ± 0.16 points ($n = 18$, $p < 0.001$). Compounds IIId, VII, and VIIIa, b, d decreased ptosis to 2.5 ± 0.12 points ($n = 18$, $p < 0.02$). With an increase in the dose of the compounds to 100 mg/kg (internally) their antireserpine activity decreased. The remaining compounds did not have a substantial effect on the activity of reserpine.

Compounds VIIIb, d in a dose of 25 mg/kg (internally) and IIId and Ve in a dose of 50 mg/kg (internally) also intensified the hypothermic effect of L-DOPA (200 mg/kg intraperitoneally) from 36.3 ± 0.18°C to 38.0 ± 0.32°C, 38.9 ± 0.39°C, 38.7 ± 0.33°C, and 39.1 ± 0.46°C ($n = 12$, $p < 0.001$), respectively. The other investigated compounds also gave rise to a smaller degree of intensification of the activity of L-DOPA.

The compounds were less active with respect to the convulsive activity of 5-HTP. In a dose of 50 mg/kg (internally) they increased the phenomenon of head shaking in mice induced by 5-HTP by 20-50%. All of the investigated compounds had virtually no effect on the hypothermic activity of apomorphine and tremorine.

Thus the investigated compounds display elements of an activating effect which is manifested in antireserpine and L-DOPA-potentiating effects.

LITERATURE CITED

1. V. G. Granik, A. K. Shanazarov, N. P. Solov'eva, et al., Khim. Geterotsikl. Soedin., No. 11, 1470-1476 (1987).
2. A. K. Shanazarov, N. P. Solov'eva, V. V. Chistyakov, et al., Khim. Geterotsikl. Soedin., No. 11, 1477-1482 (1987).
3. S. Corne, R. W. Pickering, and B. T. Warner, Br. J. Pharmacol., 20, No. 1, 106-120 (1963).
4. G. M. Everet and J. W. Borcherding, Science, 168, No. 3933, 849-850 (1970).
5. S. Nomure, S. Shimizi, and M. Kinjo, Eur. J. Pharmacol., 83, Nos. 3-4, 171-175 (1982).
6. B. Rubin, J. Pharmacol. Exp. Ther., 120, 125-136 (1957).