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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-AMINOALKYL(ARYL)-3-PHENYL-5-NITROINDOLES

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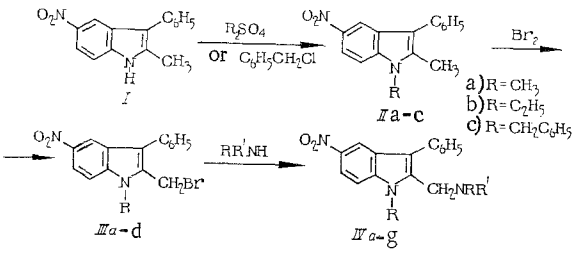
In conncetion with the search for biologically active compounds among the analogs of the alkaloid gramine, its structural analogs were obtained by reacting secondary amines with derivatives of 2-bromomethyl-3-phenyl-5-nitroindole [1]. The reaction of the latter compounds with other nucleophilic agents was also studied.



III: a) R = H; b) R = CH_3; c) R = C_2H_5; d) R = $CH_2C_6H_5$.

IV: a) R = H, $R^1 = R^2 = C_2H_5$; b) R = H, $R^1 = R^2 = CH_2C_6H_5$;
c) R = H, $R^1 + R^2 = -(CH_2)_4-$; d) R = H, $R^1 + R^2 = -(CH_2)_5-$;
e) R = H, $R^1 + R^2 = -(CH_2)_2O(CH_2)_2-$; f) R = CH_3, $R^1 = R^2 = C_2H_5$;
g) R = CH_3 $R^1 = R^2 = CH_2C_6H_5$; h) R + CH_3, $R^1 + R^2 = -(CH_2)_4-$;
i) R = CH_3, $R^1 + R^2 = -(CH_2)_5-$; j) R = CH_3, $R^1 + R^2 = -(CH_2)_2O(CH_2)_2-$;
k) R = CH_3, $R^1 + R^2 = -(CH_2)_2N(CH_3)(CH_2)_2-$; l) $R = R^1 = R^2 = CH_3$;
m) R = CH_3, R^1 = H, $R^2 = CH_2C_6H_5$;
n) R = CH_3, R^1 = H, R^2 = adamantyl; o) $R = CH_2C_6H_5$, $R^1 = R^2 = C_2H_5$;
p) $R = CH_2C_6H_5$, $R^1 + R^2 = -(CH_2)_5$; q) $R = CH_2C_6H_5$;
$R^1 + R^2 = -(CH_2)_2O(CH_2)_2-$.

2-Methyl-3-phenyl-5-nitroindole (I), previously obtained by the Fischer reaction in a low yield [2, 3], served as the starting material. However, by changing the conditions of the indolization reaction of p-nitrophenylhydrazone of benzyl methyl ketone, we were able to increase the yield of compound I to 70%.

1-Alkyl(aralkyl)-2-methyl-3-phenyl-5-nitroindoles (IIa-c) were synthesized in an 80-97% yield by alkylation of I by dimethyl and diethyl sulfate and benzylation with benzyl chloride.

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TABLE 1. Derivatives of 2-Aminoalkyl(aryl)-3-phenyl-5-nitroindole

Compound	Yield, %	mp, °C*	Empirical formula	Found, %				Calculated, %				IR spectrum ν_{max}, cm^{-1}	UV spectrum λ_{max}, nm (log ε)
				C	H	Cl	N	C	H	Cl	N		
IVa	54,4	210—211	$C_{19}H_{21}N_3O_2 \cdot HCl$	63,4	6,1	9,8	11,7	63,4	6,2	9,8	11,6	3080 (NH), ser. of bands at 2800—2640 (NH)	270 (4,39), 330 (3,94)
IVb	77,2	203—205	$C_{29}H_{25}N_3O_2 \cdot HCl$	71,8	5,5	7,1	8,4	71,9	5,4	7,3	8,6	3110 (NH), ser. of bands at 2740—2550 (NH)	270 (4,31), 330 (3,86)
IVc	53,3	253—254	$C_{19}H_{19}N_3O_2 \cdot HCl$	63,8	5,8	9,8	11,8	63,8	5,6	9,9	11,7	3120 (NH), ser. of bands at 2600—2480 (NH)	270 (4,29), 330 (3,73)
IVd	67,5	239—241	$C_{20}H_{21}N_3O_2 \cdot HCl$	64,3	5,8	9,7	11,2	64,6	5,9	9,5	11,3	3100 (NH), 2750—2500 (NH)	270 (4,3), 330 (3,83)
IVe	45,2	230—232	$C_{19}H_{19}N_3O_2 \cdot HCl$	61,0	5,5	9,2	11,3	61,0	5,4	9,5	11,2	3100 (NH), ser. of bands at 2750—2440 (NH)	
IVf	64,5	105—106	$C_{20}H_{23}N_3O_2$ (base)	71,0	6,8	—	12,5	71,2	6,9	—	12,4		sh. 270 (4,33),
		219—220	$C_{20}H_{23}N_3O_2 \cdot HCl$	64,0	6,4	9,2	11,2	64,2	6,5	9,5	11,2		282 (4,36), 336 (3,94)
IVg	67,4	156—157	$C_{30}H_{27}N_3O_2$ (base)	78,0	5,9	—	9,0	78,0	5,9	—	9,1		sh. 270 (4,42),
		199—201	$C_{30}H_{27}N_3O_2 \cdot HCl$	72,4	5,8	6,3	8,3	72,3	5,7	6,4	8,4		282 (4,67), 336 (3,94)
IVh	67,3	148—149	$C_{20}H_{21}N_3O_2$ (base)	71,9	6,3	—	12,5	71,6	6,3	—	12,5		280 (4,39), 336 (3,94)
		235—237	$C_{20}H_{21}N_3O_2 \cdot HCl$	64,3	6,0	9,5	11,2	64,5	6,0	9,5	11,3		
IVi	66,6	173—174	$C_{21}H_{23}N_3O_2$ (base)	72,0	6,6	—	12,0	72,2	6,6	—	12,0		
		232—234	$C_{21}H_{23}N_3O_2 \cdot HCl$	65,0	6,1	9,6	10,7	65,3	6,2	10,0	10,9		
IVj	77,7	190—191	$C_{20}H_{21}N_3O_2$ (base)	68,4	6,2	—	12,3	68,4	6,0	—	12,0		
		247—248	$C_{20}H_{21}N_3O_2 \cdot HCl$	61,8	5,7	9,1	10,7	61,9	5,7	9,1	10,8		
IVk	85,7	246—249	$C_{21}H_{24}N_4O_2 \cdot HCl$	57,1	5,9	16,1	13,0	57,7	6,0	16,2	12,8		

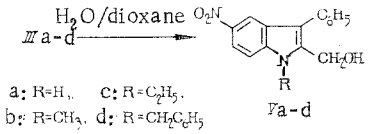
*Compounds IVb-d, f-g are crystallized from alcohol—dioxane mixture (1:1), compounds IVa, h-k, from a methanol—acetone mixture (1:1).

The structure of the compounds obtained was confirmed by the data of IR spectra, in which there is no absorption band due to imino group vibrations (ν_{NH} 3340 cm^{-1}).

As the result of investigation in the bromination reaction of compounds I, IIa-c, a preparative method of synthesis of 2-bromomethyl derivatives of 3-phenyl-5-nitroindole (IIIa-d) was found. The bromination of compounds I, IIa-c by N-bromosuccinimide was successfully carried out in the presence of benzoyl peroxide and with illumination, and by dioxane dibromide in dioxane. However, a higher yield of compound IIIa-d was achieved by using bromine as the brominating agent. The structure of the 2-bromomethyl derivatives of 3-phenyl-5-nitroindole IIIa-d was confirmed by PMR and mass spectra. In the PMR spectrum of 1-methyl-2-bromomethyl-3-phenyl-5-nitroindole IIIb, the position and multiplicity of the proton signals of aromatic nuclei are similar to those of the same protons in the initial 1,2-dimethyl-3-phenyl-5-nitroindole IIa. In the PMR spectrum of compound IIIb, the singlet signal of the methyl group at position 2 at δ = 2.46 ppm is absent, and there is a signal at δ = 4.69 ppm, corresponding to protons of methylene groups at position 2 of the indole ring. In the mass spectrum of IIIb there is a molecular ion peak with m/e 344/346. The maximum peak corresponds to the fragment with m/e 265 (M–Br), which can be explained by splitting of the bromine atom from the methylene group, since in this case a stable ion is formed.

By the action of primary or secondary amines on 2-bromomethyl derivatives IIIa-d, the bromine atom is readily replaced by the amine residue. As a result, a series of derivatives of 2-aminomethyl-3-phenyl-5-nitroindole (IVa-k) are formed in a high yield. Data on compounds IVa-k are listed in Table 1. An excess of amine is used to bind the hydrogen bromide evolved in the course of the reaction. The molecular masses of compounds IVk (M^+•364) and IVn (M^+•415) determined by the mass spectrometric method correspond to the proposed structures.

It was also found that the bromine atom in the 2-bromomethyl-3-phenyl-5-nitroindole derivatives IIIa-d is readily hydrolyzed. During the reaction of 2-bromomethylindole derivatives IIIa-d with aqueous dioxane, 2-hydroxymethyl-3-phenyl-5-nitroindoles (Va-d) were obtained in a yield of 71-74%.



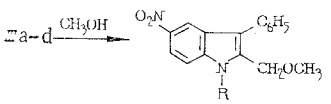
IIIa-d

a: R=H, c: R=C_2H_5,
b: R=CH_3, d: R=$CH_2C_6H_5$

Va-d

The presence in the IR spectra of Va-d of an absorption band of the stretching vibrations of the hydroxyl group in the 3320-3480 cm^{-1} region, which is not present in the initial compounds IIIa-d, confirms the structure of the 2-hydroxymethylindole derivatives obtained.

When the 2-bromomethyl derivatives of indole IIIa-d are boiled in methanol, 2-methoxymethyl-3-phenyl-5-nitroindoles (VIa-d) were obtained in a yield of 70-74%.



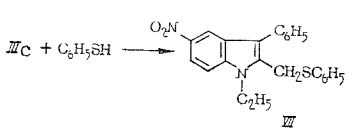
IIIa-d

VIa-d

a: R=H, c: R=C_2H_5,
b: R=CH_3, d: R=$CH_2C_6H_5$

The structure of compound VIb was confirmed by the PMR spectrum, in which a singlet of methyl group protons in the 3.86 ppm region (CH_2OCH_3) is observed.

By the reaction of compound IIIc with thiophenol in isopropanol in the presence of potassium hydroxide, 1-ethyl-2-phenylthiomethyl-3-phenyl-5-nitroindole (VII) was obtained.



VII

EXPERIMENTAL PHARMACOLOGY

In the study of various pharmacological indexes of hydrochlorides IVa-c, e, it was found that these compounds have neurotropic activity. The most pronounced elements of neuroleptic

activity were discovered in compound IVc. In experiments on white mice, compound IVc decreased the hypothermal action and "group" toxicity of phenamine. Thus, after the oral administration of this compound in doses of 100-250 mg/kg, the body temperature in mice was 3°C lower than during the administration of phenamine by itself. Compound IVb was less active, while compounds IVa, e did not change the hyperthermal action of phenamine. The ability to decrease the "group" toxicity of phenamine was observed only in the case of compound IVc. When phenamine was subcutaneously administered to grouped mice (10 mice in a group) in a dose of 10 mg/kg, death occurred in 90% of cases, while when IVc was preliminarily administered in a dose of 200 mg/kg (orally), in 50% of cases. The remaining compounds did not change the "group" toxicity of phenamine.

Compound IVc was also most active with reference to anti-anxiety effects of tetrabenazine. Thirty minutes after the introduction of tetrabenazine, the body temperature in mice was equal to 33 (31.4-35)°C, and blepharoptosis was 1.8 ± 0.5 points.

When tetrabenazine was introduced on the background of the action of IVc, the body temperature of mice was 30.9 (30.6-31.2)°C, blepharoptosis 3.5 ± 0.35 points. Compound IVb caused intensification of the hypothermal effect of tetrabenazine, but was less active than IVc.

In the study on the influence of the compounds on the central serotoninergic systems, it was found that all the compounds have a serotonin-negative effect.

In experiments in white mice, compounds IVa, c had the highest ability to decrease the number of head shakings induced by 5-hydroxytryptophan (280 mg/kg into abdominal cavity). When these compounds were administered subcutaneously in a dose of 200 mg/kg, the number of head shakings decreased by 50-65%, and after administration of IVb, e by 35-40%.

All the compounds were slightly active with reference to dopaminergic systems. They did not show any appreciable influence on the hypothermia in mice induced by L-DOPA and apomorphine, and also on sterotypia in rats induced by apomorphine.

The ability of compounds IVa-c to influence corazole-induced spasms (125 mg/kg, subcutaneously) and spasms induced by electric current (150 V, 50 mA) was studied in experiments on white mice. It was found that all the compounds had elements of antispasmodic activity. When IVa-c, e were introduced, beginning at a dose of 200 mg/kg, in 40-60% of the animals there was no tonic spasmodic phase such as that observed in all animals when corazole was introduced. The compounds had no effect on spasms induced by electrical current.

When the compounds studied were administered orally in a dose of 100 mg/kg 30 min before intravenous administration of hexenal (50 mg/kg) to rats and subcutaneous administration (2 mg/kg) of promedol to mice, they intensified the action of the last compounds. The most active was compound IVc. Thus, the duration of the soporific action of hexenal was 18 (12-24) min, and after the introduction of IVc, it was 36 (28-44) min. Compounds IVb, e were less active, and sleep was prolonged to 27 (23-31) and 24 (21-27) min, respectively.

After the administration of promedol, the mice were kept on a hot plate for 13 (6-20) sec, and after administration of compounds IVa, b, e, the ability to hold on the hot plate increased by 90-110%, and after the introduction of IVc by 140%.

During oral administration of the compounds, the LD_{50} for white mice was: 620 mg/kg for IVa, more than 1000 mg/kg for IVb, e, and 675 mg/kg for IVc.

Thus, with reference to the neurotropic activity spectrum, the 2-aminomethyl-3-phenyl-5-nitroindole derivatives IVa-c, e studied have properties characteristic of a compound with neuroleptic activity (decrease in the effect of phenamine, serotonin; intensification of anti-anxiety properties of tetrabenazine, soporific action of hexenal, and the analgesic action of promedol).

The most active of the compounds was found to be 1-methyl-2-pyrrolidinomethyl-3-phenyl-5-nitroindole IVc, but in this case these properties were evident in large doses.

EXPERIMENTAL CHEMISTRY

The IR spectra of the synthesized compounds were run on the Perkin-Elmer (Sweden) and UR-10 (GDR) spectrometers in the form of a suspension in mineral oil, in a thin film. The UV spectra were run on the EPS-3T Hitachi spectrometer (Japan) in methanol. The PMR spectra

were measured on XL 100-A-12 apparatus (Varian, USA) with 60HL and JNM-4H-100 (JOL, Japan). The chemical shifts are given on the δ scale (in ppm), with reference to TMS as internal standard. In the description of spectra, the following abbreviations are used: s) singlet, br.s.) broad signal, d) doublet, t) triplet, q) quartet, m) multiplet. The mass spectra were recorded on LKB-9000 chromatomass spectrometer with direct introduction of the material into the ionic source, at an energy of the ionizing electrons of 70 eV and at a source temperature of 150°C. To evaluate the individuality of the synthesized compounds, and to control the reaction course, TLC on Silufol-254 plates was used in the systems benzene–methanol (9:1), and benzene–acetone (9:1). The development was carried out in UV light.

2-Methyl-3-phenyl-5-nitroindole (I). Concentrated hydrochloric acid, 20 ml, is added, with stirring, to a suspension of 13.4 g (0.05 mole) of p-nitrophenylhydrazone of benzyl methyl ketone in 20 ml of 98% acetic acid, heated to 80°C. The reaction mixture is stirred at 80°C for 2 h, and cooled. The precipitate is filtered, washed with acetic acid (3 × 30 ml), and water, and dried. The yield of I is 8.82 g (70%), mp 197-198°C (from dichloroethane). The melting point of the compound obtained agrees with the literature data [3]. Found, %: C 71.4; H 4.7; N 11.2. $C_{15}H_{12}N_2O_2$. Calculated, %: C 71.4; H 4.7; N 11.1. IR spectrum, ν_{max}, cm^{-1}: 3340 (NH). UV spectrum, λ_{max}, nm (log E): 274 (4.5); 332 (3.82).

1,2-Dimethyl-3-phenyl-5-nitroindole (IIa). A 50% aqueous solution of potassium hydroxide (2.3 g of KOH) and 1.9 g (0.017 mole) of dimethyl sulfate are added at 20°C, with stirring, to a solution of 2.52 g (0.01 mole) of I in 50 ml of acetone. The reaction mixture is stirred for 1 h at 20°C and poured into 100 ml of water. The precipitate is filtered, washed with water, and dried. The yield of IIa is 2.16 g (82%), mp 169-170°C (from methanol). Found, %: C 71.9; H 5.3; N 10.5. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.1; H 5.3; N 10.5. UV spectrum, λ_{max}, nm (log E): 276 (4.31); 332 (3.87). PMR spectrum ($CDCl_3$): 2.46 s, 3H (CH_3), 3.73 s 3H (N–CH_3), 7.13 d (1H); $J_{7,6}$ = 10 Hz (4-H), 7.37 m 5H (C_6H_6), 7.95 q (1H), $J_{6,7}$ = 10 Hz, $J_{4,6}$ = 2.5 Hz (6-H), 8.37 d 1H, $J_{4,6}$ = 2.5 Hz (4-H).

1-Ethyl-2-methyl-3-phenyl-5-nitroindole (IIb). This is obtained in the same way as IIa. The yield is 80%, mp 154.5-155.5°C (from acetone). Found, %: C 72.8; H 5.8; N 9.96. $C_{17}H_{16}N_2O_2$. Calculated, %: C 72.8; H 5.7; N 10.0. UV spectrum, λ_{max}, nm (log E): 280 (4.25); 332 (3.88).

1-Benzyl-2-methyl-3-phenyl-5-nitroindole (IIc). A 12.6 g portion (0.05 mole) of I is added to a solution of 11.2 g (0.2 mole) of potassium hydroxide in 200 ml of DMSO and the reaction mixture is stirred at 20°C for 1 h. Benzyl chloride, 12.6 g (0.1 mole), is then added, the mixture is stirred for 1.5 h, and poured into water. The precipitate is filtered, washed with water, and dried. The yield of IIc is 16.8 g (97%), mp 179-180°C (from acetone). Found, %: C 77.2; H 5.4; N 8.2. $C_{22}H_{18}N_2O_2$. Calculated, %: C 77.2; H 5.3; N 8.2. UV spectrum λ_{max} (dioxane), nm (log E): 280 (4.45); 332 (3.91).

2-Bromomethyl-3-phenyl-5-nitroindole (IIIa). A solution of 10.4 ml (0.02 mole) of bromine in 70 ml of dichloroethane is added dropwise, in the course of 1 h, with stirring and illumination by a 150 W lamp, to a suspension of 50.4 g (0.2 mole) of I in 800 ml of dry dichloroethane. The reaction mixture is stirred at 20°C for 1 h, and the precipitate is filtered and dried. The yield of IIIa is 56.3 g (85.1%), mp 236-237°C (from dichloroethane). Found, %: C 54.0; H 3.3; Br 24.0; N 8.3. $C_{15}H_{11}BrN_2O_2$. Calculated, %: C 54.4; H 3.3; Br 24.1; N 8.3. IR spectrum, ν_{max}, cm^{-1}: 3332 (NH). UV spectrum, λ_{max} (dioxane), nm (log E): 250 (4.25); 274 (4.45); 330 (3.98).

1-Methyl-2-bromomethyl-3-phenyl-5-nitroindole (IIIb). This is obtained under the conditions of synthesis of IIIa, from 13.3 g (0.05 mole) of IIa and 2.6 ml (0.05 mole) of bromine. The yield of IIIb is 16.3 g (95.1%), mp 211-213°C (from benzene). Found, %: C 55.8; H 3.5; Br 23.0; N 8.1; M^+ 344/346. $C_{16}H_{13}BrN_2O_2$. Calculated, %: C 55.7; H 3.3; Br 23.1; N 8.1. M 345.2. UV spectrum, λ_{max} (dioxane), nm (log E): 285 (4.38); 330 (3.95). PMR spectrum ($CDCl_3$): 3.91 s 3H (N–CH_3), 4.69 s 2H (CH_2Br), 7.37 1H, J_o = 9 Hz (7-H), 7.53 m 5H (C_6H_5), 8.18 q 1H, J_o = 9 Hz, J_m = 2 Hz (6-H), 8.59 d 1H J = 2 Hz (4-H).

2-Diethylaminomethyl-3-phenyl-5-nitroindole (IVa). A solution of 3.3 g (0.01 mole) of IIIa and 1.5 g (0.02 mole) of diethylamine in 60 ml of benzene is left to stand overnight at 20°C. The diethylamine hydrobromide precipitate is filtered, and a solution of hydrogen chloride in ether is added to the filtrate. The yield of hydrochloride of IVa is 1.96 g (54.4%), mp 210-211°C (decomp., from a mixture of methanol and acetone). Found, %: C 63.4; H 6.1; Cl 9.8; N 11.6. $C_{19}H_{21}H_3O_2 \cdot HCl$. Calculated, %: C 63.4; H 6.2; Cl 9.8; N 11.6. IR

spectrum, ν_{max}, cm^{-1}: 3080 (NH); series of bands in 2800-2640 region ($\overset{\oplus}{NH}$). UV spectrum, λ_{max}, nm (log E): 270 (4.39); 330 (3.94).

The data on other similarly obtained 2-aminomethyl derivatives (IVb-k) are listed in Table 1.

1-Methyl-2-dimethylaminomethyl-3-phenyl-5-nitroindole (IVl). A solution of 0.9 g (0.02 mole) of dimethylamine and 3.45 g (0.01 mole) of IIIb in 60 ml of benzene is left to stand overnight at 20°C. The dimethylamine hydrobromide precipitate is filtered, and the filtrate is evaporated *in vacuo*. To the residue, 20 ml of aqueous ethanol (1:1) are added and the crystals formed are filtered, washed with water, and dried. The yield of IVl is 2.03 g (66%), mp 127-128°C (from alcohol). Found, %: C 69.8; H 6.2; N 13.5. $C_{18}H_{19}N_3O_2$. Calculated, %: C 69.9; H 6.2; N 13.6. UV spectrum, λ_{max}, nm (log E): shoulder at 270 (4.15); 282 (4.36); 336 (3.94).

1-Methyl-2-benzylaminomethyl-3-phenyl-5-nitroindole (IVm). This is obtained under the conditions of synthesis of IVl, from 3.45 g (0.01 mole) of IIIb and 2.14 g (0.02 mole) of benzylamine in 60 ml of benzene. The yield of IVm is 2.71 g (73.2%), mp 142-43°C (from a mixture of methanol and acetone). Found, %: C 74.4; H 5.6; N 11.3. $C_{23}H_{21}N_3O_2$. Calculated, %: C 74.4; H 5.6; N 11.3. UV spectrum, λ_{max}, nm (log E): shoulder at 270 (4.23); 282 (4.4); 336 (3.9).

1-Methyl-2-(1-adamantylaminomethyl)-3-phenyl-5-nitroindole (IVn). A suspension of 3.45 g (0.01 mole) of IIIb, 4.5 g (0.03 mole) of aminoadamantane, 2.1 ml (0.01 mole) of triethylamine and 45 ml of freshly distilled DMFA is boiled for 1 h in a flask with Bunsen valve. The solution is poured onto ice, the precipitate is filtered, and is heated with 250 ml of distilled water to 90°C to dissolve aminoadamantane hydrobromide. The hot reaction mixture is filtered, the precipitate is washed with water, and dried. The yield of IVn is 3.41 g (82.3%), mp 232-232.5°C (from an acetone–methanol–benzene mixture, 1:1:1). Found, %: C 75.0; H 7.0; N 10.3. M^+•415. $C_{26}H_{29}N_3O_2$. Calculated, %: C 75.1; H 7.0; N 10.1; M 415.5.

The IVn base was dissolved in chloroform and tested with a solution of hydrogen chloride in ether to yield the hydrochloride of IVn, mp 266-267°C (dec.; from a mixture of acetone and methanol). Found, %: C 68.7; H 6.6; Cl 8.0; N 9.0; $C_{26}H_{30}ClN_3O_2$. Calculated, %: C 69.3; H 6.6; Cl 7.85; N 9.4. IR spectrum, ν_{max}, cm^{-1}: 3320 ($\overset{\oplus}{NH}$). UV spectrum, λ_{max}, (dioxane), nm (log E): 280 (4.42); 334 (3.93).

1-Benzyl-2-diethylaminomethyl-3-phenyl-5-nitroindole (IVo). 1-Benzyl-2-bromomethyl-3-phenyl-5-nitroindole (IIId) is obtained under the conditions of synthesis of IIIa from 6.8 g (0.02 mole) of IIc in 1.4 ml (0.025 mole) of bromine. The reaction mixture is evaporated to a volume of 50 ml, 3 g (0.04 mole) of diethylamine are added, and the mixture is left to stand overnight at 20°C. The solvent is evaporated *in vacuo*, 100 ml of water are added to the residue, and the mixture is extracted with three 50 ml portions of ether. The extract is dried and acidified by a solution of hydrogen chloride in ether. The yield of the hydrochloride IVo is 6 g (67.5%), mp 210-211°C (from a mixture of alcohol and acetone). Found, %: C 69.4; H 6.2; Cl 7.8; N 9.4. $C_{26}H_{28}ClN_3O_2$. Calculated, %: C 69.4; H 6.3; Cl 7.9; N 9.3. IR spectrum, ν_{max}, cm^{-1}: broad band at 2350 ($\overset{\oplus}{NH}$). UV spectrum, λ_{max}, nm (log ε): 278 (4.41); 330 (3.92).

1-Benzyl-2-piperidinomethyl-3-phenyl-5-nitroindole (IVp). Compound IIId is obtained under the conditions of synthesis of IIIa from 6.8 g (0.02 mole) of IIc and 1.4 ml (0.025 mole) of bromine. The reaction mixture is evaporated to a volume of 50 ml, 3.4 g (0.04 mole) of piperidine are added, and the mixture is left to stand overnight at 20°C. The solvent is evaporated *in vacuo*, 100 ml of water are added to the residue, and the precipitate is filtered, washed with water, and dried. The yield of IVp is 6.36 g (74.8%), mp 165-166°C (from a mixture of dioxane and acetone). Found, %: C 76.2; H 6.4; N 9.8. $C_{27}H_{27}N_3O_2$. Calculated, %: C 76.2; H 6.4; N 9.8. UV spectrum, λ_{max}, nm (log ε): 280 (4.43); 332 (3.96).

1-Benzyl-2-morpholinomethyl-3-phenyl-5-nitroindole (IVq). This is obtained in the same way as IVp. The yield of IVq is 6.17 g (72.3%), mp 177-178°C (from a mixture of acetone and methanol). Found, %: C 73.0; H 6.0; N 9.9. $C_{26}H_{25}N_3O_3$. Calculated, %: C 73.0; H 5.9; N 9.8. UV spectrum, λ_{max} (dioxane), nm (log ε): 280 (4.41); 330 (3.91).

The hydrochloride of IVq is prepared by the usual method, mp 195-196°C (from an acetone–methanol–ether, 1:1:1 mixture). Found, %: C 67.3; H 5.8; Cl 7.6; N 9.0. $C_{26}H_{26}ClN_3O_3$. Calculated, %: C 67.3; H 5.6; Cl 7.6; N 9.0. IR spectrum, ν_{max}, cm^{-1}: series of bands in 2750-2600 region (NH).

2-Hydroxymethyl-3-phenyl-5-nitroindole (Va). A mixture of 3.31 g (0.01 mole) of IIIa, 30 ml of dioxane, and 15 ml of water is boiled for 4 h. The reaction mixture is poured into 100 ml of water, and the precipitate is filtered and dried. The yield of Va is 2 g (74.5%), mp 193-194°C (from alcohol). Found, %: C 67.2; H 4.6; N 10.4. $C_{15}H_{12}N_2O_3$. Calculated, %: C 67.1; H 4.5; N 10.4. IR spectrum, ν_{max}, cm^{-1}: 3480 (OH); 3180 (NH). UV spectrum, λ_{max} (dioxane), nm (log ε): 272 (4.29); 334 (3.83).

1-Methyl-2-hydroxymethyl-3-phenyl-5-nitroindole (Vb). This is obtained in the same way as Va. The yield of Vb is 2.12 g (73%), mp 178-179°C (from dioxane). Found, %: C 68.0; H 5.0; N 10.0. $C_{16}H_{14}N_2O_3$. Calculated, %: C 68.0; H 5.0; N 9.9. IR spectrum, ν_{max}, cm^{-1}: 3330 (OH). UV spectrum, λ_{max} (dioxane), nm (log ε): shoulder at 266 (4.3), 282 (4.32), 336 (3.9).

1-Ethyl-2-hydroxymethyl-3-phenyl-5-nitroindole (Vc). 1-Ethyl-2-bromomethyl-3-phenyl-5-nitroindole IIIc is obtained under the conditions of the synthesis of IIIa from 7 g (0.025 mole) of IIb and 1.4 ml (0.025 mole) of bromine. The reaction mixture is evaporated *in vacuo* to dryness, and 50 ml of dioxane and 30 ml of water are added to the residue, and the mixture is boiled for 4 h. The reaction mixture is poured into 100 ml of water, and the precipitate is filtered and dried. The yield of Vc is 5.4 g (73%), mp 171-173°C (from acetone). Found, %: C 68.9; H 5.4; N 9.4. $C_{17}H_{16}N_2O_3$. Calculated, %: C 68.9; H 5.4; N 9.4. IR spectrum, ν_{max}, cm^{-1}: 3320 (OH). UV spectrum, λ_{max} (dioxane), nm (log ε): shoulder at 266 (4.32); 282 (4.35); 334 (3.88). PMR spectrum ($CDCl_3$): 1.49 t 3H (CH_3 in $-C_2H_5$), 4.41 q 2H (CH_2 in $-C_2H_5$), 4.85 br.s s 2H (CH_2 in 2-CH_2OH), 1.77 br.s s 1H (OH in 2-CH_2OH), 7.38 1H (7-H), 7.4-7.6 br.s. m (C_6H_5), 8.14 q 1H (6-H), 8.56 1H (6-H), $I(J)_{4,6}$ = 2.5 Hz, $I(J)_{6,7}$ = 9 Hz.

1-Benzyl-2-hydroxymethyl-3-phenyl-5-nitroindole (Vd). This is obtained in the same way as Vc. The yield of Vd is 71%, mp 191-192°C (from acetone). Found, %: C 73.5; H 5.1; N 7.7. $C_{22}H_{18}N_2O_3$. Calculated, %: 73.7; H 5.0; N 7.8. IR spectrum, ν_{max}, cm^{-1}: 3320 (OH). UV spectrum, λ_{max} (dioxane), nm (log ε); shoulder at 266 (4.35). 282 (4.38); 334 (3.9).

2-Methoxy-3-phenyl-5-nitroindole (VIa). A solution of 3.31 g (0.01 M) of IIIa in 30 ml of methanol is boiled for 2 h. It is then cooled, the precipitate is filtered, and dried. The yield of VIa is 1.96 g (70%), mp 181-182°C (from acetone). Found, %: C 68.0; H 4.9; N 9.8. $C_{16}H_{14}N_2O_3$. Calculated, %: C 68.0; H 5.0; N 9.9; IR spectrum, ν_{max}, cm^{-1}: 3400 (NH). UV spectrum, λ_{max}, nm (log ε): 270 (4.31); 332 (3.94).

1-Methyl-2-methoxymethyl-3-phenyl-5-nitroindole (VIb). This is obtained in the same way as VIa. The yield of VIb is 72%, mp 153-154°C (from acetone). Found, %: C 69.0; H 5.5; N 9.4, $C_{17}H_{16}N_2O_3$. Calculated, %: C 68.9; H 5.4; N 9.4. UV spectrum, λ_{max}, nm (log ε): 266 (4.3); 282 (4.37); 332 (3.85). PMR spectrum ($CDCl_3$): 3.38 s 3H ($-CH_3$), 3.86 s 3H (OCH_3 in 2-CH_2OCH_3), 4.59 s 2H ($-CH_2-$ in 2-CH_2OCH_3), 7.4-7.6 5H (C_6H_5), 7.3 d 1H (7-H), 8.09 q 1H (6-H), 8.53 s 1H (4-H) $I(J)_{6,7}$ = 9 Hz, $I(J)_{4,6}$ = 2-3 Hz.

1-Ethyl-2-methoxymethyl-3-phenyl-5-nitroindole (VIc). This is obtained from IIIc under the conditions of synthesis of VIa. The yield of VIc is 71%, mp 218-219°C (from a mixture of dioxane and acetone). Found, %: C 69.8; H 5.8; N 9.0. $C_{18}H_{18}N_2O_3$. Calculated, %: C 69.6; H 5.8; N 9.0. UV spectrum, λ_{max}, nm (log ε): 266 (4.29); 282 (3.47); 332 (3.87).

1-Benzyl-2-methoxymethyl-3-phenyl-5-nitroindole (VId). This is obtained from IIId under the conditions of synthesis of VIa. The yield of VId is 74%, mp 160-161°C (from alcohol). Found, %: C 74.1; H 5.4; N 7.4. $C_{23}H_{20}N_2O_3$. Calculated, %: C 74.1; H 5.4; N 7.5. UV spectrum, λ_{max}, nm (log ε): 266 (4.33); 282 (4.36); 332 (3.86).

1-Ethyl-2-phenylthiomethyl-3-phenyl-5-nitroindole (VII). A solution of 0.75 ml of thiophenol in 4 ml of absolute isopropanol is added to a solution of 5.6 g (0.01 mole) of potassium hydroxide in 10 ml of absolute isopropanol and the mixture is stirred for 15 min at 20°C. A suspension of 3.6 g (0.01 mole) of IIIc in 60 ml of absolute alcohol is added to the reaction mixture. This is stirred for 1.5 h at 20°C, and then boiled on a water bath for 2 h, and left to stand overnight. The precipitate is filtered, washed with alcohol, and dried. The yield of VII is 2.9 g (70%), mp 176-177°C (from dioxane). Found, %: C 71.1; H 5.1; N 7.4; S 8.1. $C_{23}H_{20}N_2SO_2$. Calculated, %: C 71.1; H 5.2; N 7.2; S 8.2.

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SYNTHESIS AND INVESTIGATION OF THE ANTIANAPHYLACTIC ACTIVITY OF 2-(1-ALKOXYETHYL)-4-METHYLFURO[3, 2-c]QUINOLINES

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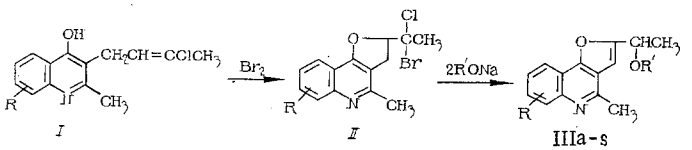
In the search for new biologically active chemical compounds we have synthesized a series of 2-(1-alkoxyethyl)-4-methylfuro[3, 2-c]quinolines and have studied the influence of these substances on the development of anaphylactic reactions in animals.

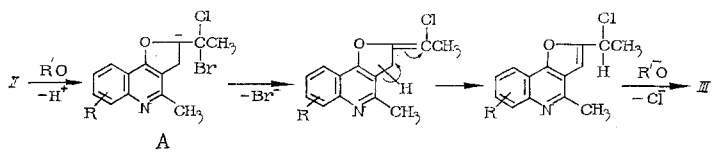
The 2-(1-alkoxyethyl)-4-methylfuro[3, 2-c]quinolines (III) were synthesized from 2-(1-chloro-1-bromoethyl)-4-methyl-2,3-dihydrofuro[3, 2-c]quinolines (II). The latter were obtained from the corresponding 2-methyl-3-(3-chloro-2-butenyl)-4-hydroxyquinolines (I) [1, 2].

The appropriate compounds (II) were heated with Na alcoholates of the corresponding alcohols to obtain the alkoxyfuroquinolines (III).



III (substance), R, R'); IIIa, H, H; IIIb, H iso-C_3H_7; IIIc, H, iso-C_4H_9; IIId, H, C_4H_9; IIIe, H, iso-C_5H_{11}; IIIf, 6-OCH_3, iso-C_3H_7; IIIg, 6-OCH_3, iso-C_4H_9; IIIh, 6-Cl, iso-C_3H_7; IIIi, 6-Cl, C_2H_5; IIIj 8-Br, C_2H_5; IIIk, 8-Br, iso-C_4H_9; IIIl, 8-Br, C_4H_9; IIIm, 8-Br, iso-C_5H_{11}; IIIn, 8-Br, C_5H_{11}; IIIo, 8-OCH_3, H; IIIp, 8-OCH_3, CH_3; IIIq, 8-OCH_3, iso-C_3H_7; IIIr, 8-OCH_3, iso-C_4H_9; IIIs, 8-OCH_3, C_5H_{11}.

The transition from (II) to (III) is evidently represented by the following multistage process.



It is possible to suggest that the nucleophilic substitution reaction proceeds as follows. Initially carbanion A is formed under the action of the alkoxy anion, then 2-(1-chloroethyl)-4-methylfuro[3,2-c]quinolines are obtained by aromatization. These actively enter into the S_N reaction in which nucleophilic substitution of chlorine by the alkoxy group occurs rapidly under the action of a second molecule of alkoxy anion.

EXPERIMENTAL CHEMISTRY

PMR spectra were taken on a Hitachi–Perkin-Elmer R20B instrument (60 MHz at 34 ± 1°C, internal standard tetramethylsilane). The purity of the obtained compounds was verified by TLC on Al_2O_3 plates of activity grade II, visualized with iodine vapor, solvent was chloroform–petroleum ether, 1:1.

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