D_1: a_{01} = —7.64358; a_{i1}: —2.25414; 6.15983; —5.91401; 1.67315; 5.46602; —5.41757.

D_2: a_{02} = —1.48883; a_{i2}: —0.32892; —1.10970; 0.51149; 0.35075; —0.09985; 3.08028.

D_3: a_{03} = —3.41514, a_{i3}: 0.34554; 6.58802; —9.93933; —1.11610; 1.45083; 4.78505.

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SYNTHESIS AND NEUROTROPIC ACTIVITY OF HETEROCYCLIC DERIVATIVES OF 1-PIPERAZINYLALKYLINDOLES

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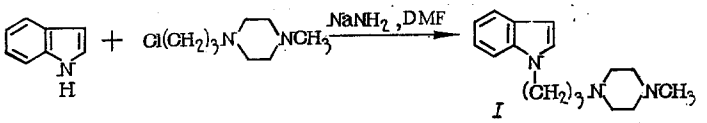
UDC 615.21:547.861.3'751

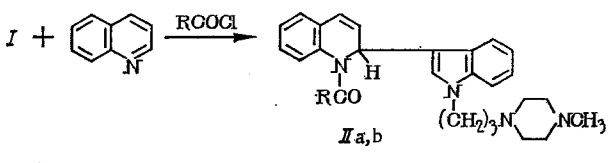
Several piperazinylalkylindoles and indolines are known to have sedative, hypotensive, antipyretic, anti-inflammatory, and tranquilizing activity [1-3]. We have prepared some heterocyclic piperazinylalkylindole derivatives with the aim of examining the effect of the position of the substituents in the indole ring on the physiological activity.

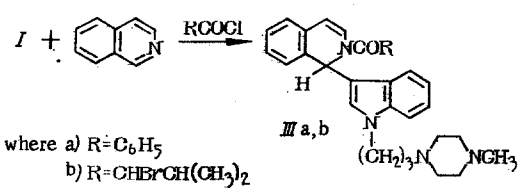
We synthesized the starting 1-piperazinylpropylindole (I) by the Eisleb reaction [4]:



The IR spectrum of compound (I) lacked the absorption band in the 3300-3600 cm^{-1} region, implying substitution at position 1 of the indole ring.

We attached the partially hydrogenated heterocyclic residues to indole (I) by the heterarylation reaction [5]:





where a) R = C_6H_5
b) R = $CHBrCH(CH_3)_2$

The IR spectra of the synthetic compounds (IIa), (IIb), (IIIa), and (IIIb) had $\nu_{C=O}$ bands in the 1720-1740 cm^{-1} region; the set of bands in the $\nu_{C=C}$ region at 1620-1630 cm^{-1} (styrene structure) and 1500-1565 cm^{-1} (indole ring) and the absence of the ν_{NH} band in the 3300-3600 cm^{-1} region further supported the structures.

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TABLE 1. Comparative Pharmacological Activity of the Test Compounds and Levomepromazine

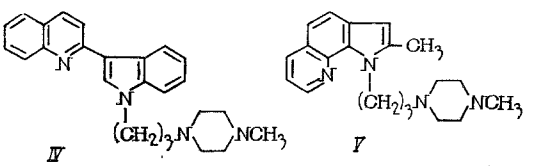
Compound	LD_{50} (mg/kg) intraperitoneally in mice	ED_{50} (mg/kg), suppressing			ED_{50} (mg/kg), potentiating hexenal sleep	Antagonism (mg/kg) of effects of		
		spontaneous motor activity	orienting reactions	muscular tonicity		arecoline	nicotine	apomorphine
I	96±24	5,3±1,2	11±4	60±20	4,8±1,8	>80	>80	68±18
IIa	>500	74±33	45±15	>400	>80	>300	>300	>80
IIb	>500	68±7,5	80±18	>400	>80	>300	>300	>80
IIIa	200±22	88±7,4	51±14	113±11,4	25±5	80	>80	>80
IIIb	>500	>120	>120	>400	>80	>300	>300	>80
II	290±73	24±9	26±6	136±89	31±9	>80	>80	>80
III	138±15	20±4	14±3	124±17	16±8	>80	>80	>80
Levomepromazine	15±5,2	2,7±1,7	3,1±1,7	2,7±1,7	7,9±2,1	6±3	9±2	6±0,4

TABLE 2. Piperazinylalkylindoles (I)-(VIII)

Compound	Yield, %	Melting point, °C	R_f	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
I	55,5		0,72	74,96	9,11	16,67	$C_{16}H_{28}N_3$	74,71	8,95	16,34
IIa	42,5	110—1	—	60,15	6,03	6,75	$C_{44}H_{50}N_4O_{15}$	60,41	5,72	6,40
IIb	45,5	80—1	—	54,42	5,25	8,33	$C_{43}H_{53}BrN_4O_{15}$	54,01	5,68	8,57
IIIa	67,3	158—60	0,50	78,53	6,87	11,61	$C_{32}H_{34}N_4O$	78,37	6,94	11,43
IIIb	63,5	132—3	0,47	65,38	6,85	10,12	$C_{30}H_{37}BrN_4O$	65,57	6,74	10,20
IV	60,1	175—6	0,31	78,33	7,08	14,68	$C_{25}H_{28}N_4$	78,13	7,29	14,58
V	37,2	265—6	0,36	74,72	8,23	17,21	$C_{21}H_{28}N_4$	74,53	8,07	17,39
VI	93,5	278—80	—	68,43	7,35	14,39	$C_{22}H_{29}ClN_4$	68,66	7,54	14,56
VII	45,3	153—5	0,46	72,57	9,43	13,25	$C_{19}H_{29}N_3O$	72,38	9,21	13,33
VIII	33,2	132—4	0,52	80,61	9,65	11,38	$C_{21}H_{31}N_3O_3$	80,43	9,84	11,26

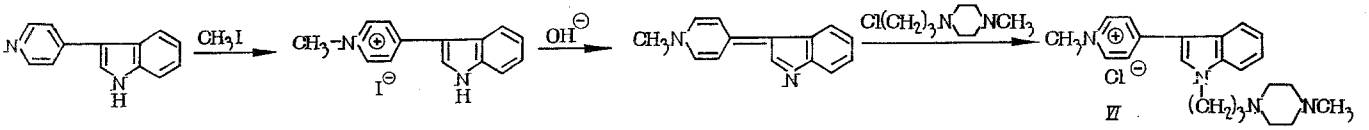
Note. Compound (I) had a bp of 208-210°C (3 mm); (IIa) and (IIb) were characterized as the citrates.

We synthesized compounds (IV) and (V) by alkylation of 3-(2-quinolinyl)indole and 2,3-dimethylpyrrolo-[3,2-h]quinoline with 1-methyl-4-(3-chloropropyl)piperazine under the conditions of the Eisleb reaction. Their structures were supported by the IR spectra (absence of NH absorption):



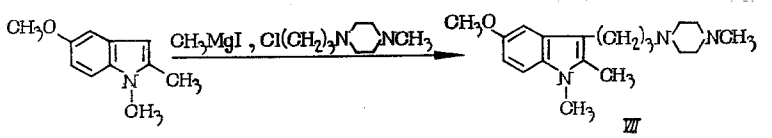
IV V

The alkylation of the indole nitrogen in the heterocyclic indole derivatives became much simpler if these compounds were first converted to the anhydro bases, in which the indole nitrogen is more basic than the pyridine nitrogen:

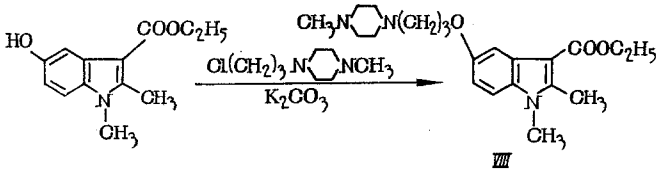


VI

We decided to examine the dependence of the activity of indole derivatives on the position of the piperazinylalkyl group. For this we prepared 3- and 5-piperazinylalkylindoles:



VII



VIII

EXPERIMENTAL PHARMACOLOGY

We examined the central neurotropic activity of the compounds by conventional neuropharmacological screening methods [6] in randomly bred white mice and rats. We compared the potency of the test compounds with that of the well-known neuroleptic levomepromazine (tizercine).

The most potent central nervous system depressant was compound (I), which efficiently suppressed spontaneous motor activity and orienting reactions and potentiated hexenal sleep (Table 1). The activity of compound (I) in these tests was comparable with that of levomepromazine. The muscle-relaxant action of compound (I) was less intense than in levomepromazine; the ED_{50} was more than 50% LD_{50}. Central cholinolytic activity and any effect on the central monoaminergic systems were almost absent. It did not eliminate arecoline tremor or nicotine spasm, nor modify reserpine hypothermia in rats, and antagonized apomorphine stereotypy in mice only if administered in subtoxic doses (ED_{50} 68 ± 18 mg/kg).

The benzoylisoquinoline analog of (I) – compound (IIIa) – had an activity spectrum similar to that of (I), but was much less active (Table 1). Replacement of benzoyl by 3-bromoisovaleryl (IIIb) removed all central activity.

The corresponding quinoline derivatives (IIa) and (IIb) showed moderate activity only in suppressing locomotor activity and orienting reactions. Compounds (VII) and (VIII) were less toxic than (I) but also less active in tests as central nervous system depressants.

Thus the central neurotropic activity of the test compounds is typified by a tranquilizing type of action, which is reduced in (IIa), (IIb), and (IIIa) or lost in (IIIb) by introduction into position 3 of indole of partially hydrogenated heterocyclic substituents. The activity is also reduced by the shift of the 4-methylpiperazinylpropyl residue to position 3 (VI) or 5 (VII) of indole.

Compounds (IV) and (V) did not display central neurotropic activity. They modified neither the spontaneous motor activity, orienting reactions, nor muscular tonicity in a dose of 120-420 mg/kg. Compound (IV) potentiated the soporific effect of hexenal only at 62 ± 23 mg/kg. These compounds did not kill the animals by intraperitoneal injection in doses of up to 640 mg/kg.

EXPERIMENTAL CHEMISTRY

The IR spectra were recorded on an IR-20 instrument in Vaseline oil or in chloroform solution (sodium or lithium chloride prisms, 1600-3600 cm^{-1}). Chromatography was carried out on a layer of aluminum oxide (no binder) with elution in chloroform–benzene–hexane (30:6:1). Visualization was by iodine vapor or UV light.

1-Methyl-4-[3-(3-indolyl)propyl]piperazine (I). A mixture of indole (8.8 g, 0.075 mole), 1-methyl-4-(3-chloropropyl)piperazine (13.7 g, 0.078 mole), and sodium amide (3.7 g, 0.08 mole) in dry dimethylformamide (40 ml) was stirred at 70-90°C for 5-7 h. Afterwards cooling water (150 ml) was added and the precipitated oil was extracted with ether. The ethereal extract was treated with 10% hydrochloric acid (40 ml). The hydrochloric acid solution was made alkaline and extracted with ether. The ethereal extract was dried over sodium sulfate; the solvent was then stripped off and the residue was distilled under vacuum in a stream of inert gas. The yield was 10 g (55.5%), bp 208-210°C (3 mm Hg), R_f 0.72, n_D^{20} 1.5619, d_{20}^4 1.0348, MR_D 80.65, calculated 79.44; mol. wt. 256.5, 257.8, calculated 257.3. Found, %: N 12.67, $C_{16}H_{23}N_3$. Calculated, %: N 12.72.

The same method was used to prepare 1-methyl-4-{3-[3-(2'-quinolyl)1-indolyl]propyl}piperazine (IV) and 1-methyl-4-[3-(2'-methylpyrrolo[3,2-h]quinolin-1'-yl)propyl]piperazine (V), whose main parameters are summarized in Table 2.

1-Methyl-4-{3-[3-(2'-benzoyl-1',2'-dihydroisoquinolin-1'-yl)-1-indolyl]propyl}piperazine (IIIa). To a mixture of 1-methyl-4-[3-(1indolyl)propyl]piperazine (2.6 g, 0.02 mole) and isoquinoline (2.6 g, 0.02 mole) in benzene (15 ml) was slowly added benzoyl chloride (1.5 g, 0.01 mole). The reaction mixture was refluxed for 15 h, whereupon it was treated with 25% ammonia and steam-distilled. The residue was filtered off and recrys-

tallized from methanol. The yield was 3.3 g (67.3%), mp 158-160°C. Found, %: C 78.53; H 11.61; N 11.61. $C_{32}H_{34}N_4O$. Calculated %: C 78.37; H 6.94; N 11.43.

The same method was used to prepare 1-methyl-4-{3-[3-(1-bromoisovaleryl-1,2-dihydroquinolin-2-yl)-1-indolyl]propyl}piperazine (IIb), 1-methyl-4-{3-[3-(1-benzoyl-1,2-dihydroquinolin-1-yl)-1-indolyl]propyl}-piperazine (IIa), and 1-methyl-4-{3-[3-(2'-bromoisovaleryl-1',2'-dihydroisoquinolin-1'-yl)-1-indolyl]propyl}-piperazine (IIIb), whose main parameters are summarized in Table 2. Compounds (IIa), (IIb), (IIIa), and (IIIb) were racemates.

1-Methyl-4-{3-[3-(4'-pyridyl)-1-indolyl]propyl}piperazine Methochloride (VI). A solution of 4-(3-indolyl)pyridine methiodide (1.7 g, 0.005 mole) in aqueous alcoholic alkali (15 g sodium hydroxide in 15 ml water and 75 ml ethanol) was refluxed for 5 min. The reaction mixture was then poured into water. The resulting precipitate was filtered off, washed with water, dried, and dissolved in ethanol (20 ml) and 1-methyl-4-(3-chloropropyl)piperazine (0.88 g, 0.005 mole) was added. This mixture was refluxed for 1 h; then cooling ether (20 ml) was added and the resulting precipitate was filtered off and recrystallized from ethanol–ether (1:1). The yield was 1.8 g (93%), mp 278-280°C. Found, %: C 68.43; H 7.35; N 14.39; Cl 9.43. $C_{22}H_{29}ClN_4$. Calculated %: C 68.66; H 7.54; N 14.56; Cl 9.23.

1-Methyl-4-[3-(1,2-dimethyl-5-methoxy-3-indolyl)propyl]piperazine Dihydrochloride (VII). To the Grignard reagent prepared from magnesium (1.2 g), ethyl iodide (7.8 g), and 1,2-dimethyl-5-methoxyindole (8.75 g, 0.005 mole) in dry ether (50 ml) was added 1-methyl-4-(3-chloropropyl)piperazine (8.8 g, 0.05 mole). The ether was stripped off and the reaction mixture was kept at 130-140°C for 3 h. After cooling the reaction mixture was diluted with water and extracted with chloroform. The chloroform extract was washed with 10% hydrochloric acid (30 ml). The hydrochloric acid extracts were made alkaline, extracted with chloroform, and dried over sodium sulfate. The chloroform solution was then saturated with dry hydrogen chloride and the resulting precipitate was filtered off. The yield was 8.8 g (45.3%), mp 195-196°C (from ethanol). Found, %: Cl 18.43; $C_{19}H_{29}N_3 \cdot 2HCl$. Calculated, %: Cl 18.30. The free base was prepared by treatment of the dihydrochloride with alkali.

1-Methyl-4-[3-(1,2-dimethyl-3-ethoxycarbonyl-5-indolyl)oxypropyl]piperazine Dihydrochloride (VIII). A mixture of 1,2-dimethyl-3-ethoxycarbonylindole (2.3 g, 0.01 mole), 1-methyl-4-(3-chloropropyl)piperazine (1.7 g, 0.01 mole), and potassium carbonate (5 g) in dry ethanol (50 ml) was refluxed for 5 h. The precipitate was filtered off. The filtrate was poured into water (100 ml) and extracted with chloroform. After drying over sodium sulfate the chloroform solution was saturated with dry hydrogen chloride and the resulting precipitate was filtered off. The yield was 1.5 g (33.2%), mp 165-168°C (from propanol). Found, %: Cl 15.84. $C_{21}H_{31}N_3O_3 \cdot 2HCl$. Calculated, %: Cl 15.92. The free base was prepared by treatment of the dihydrochloride with alkali.

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