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SYNTHESIS AND PSYCHOTROPIC ACTIVITY OF PYRAZIDOLE ANALOGS

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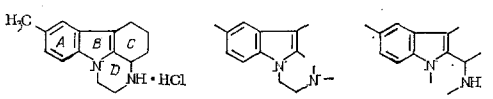
Among the antidepressants, imizin, amitriptyline, azafen, ftoratsizin, and other medicinals that are classified as tricyclic antidepressants have remained the most effective preparations [1]. The presence of a nonplanar tricyclic linear structure with a pharmacophore side chain in which the amino function is separated from the heterocyclic system by three carbon atoms is characteristic for these substances. This molecular structure ensures considerable freedom of rotation of the side chain, which opens up a greater possibility for adaptation of the antidepressant molecule with respect to the receptor. At the same time, an increase in the rigidity of the molecule by inclusion of N-aminoalkyl chains in a cyclic system could ensure greater selectivity of the biological activity. We have precisely this type of molecule in the case of pyrazidole [pirlindol (I)], a new original antidepressant, which, in contrast to classical antidepressants, has a tetracyclic structure [2, 3]. Continuing our study of the dependence of the antidepressive activity of pyrazino[1,2-a]indoles and pyrazino-[3,2,1-jk]carbazoles, to which class pyrazidole belongs, on their chemical structure we have found that opening of the C and D rings in the heterocyclic pyrazidole system., i.e., conversion to bicyclic structures of the II and III type, is accompanied by a loss of antidepressive activity [4]. In connection with the fact that



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classical antidepressants ahve tricyclic structures, it seemed of interest to synthesize tricyclic analogs of pyrazidole with an open C ring, viz., pyrazino[1,2-a]indole derivatives (IV), and to study their psychotropic activity. We obtained these compounds via a scheme similar to that used in the synthesis of pyrazidole [5].

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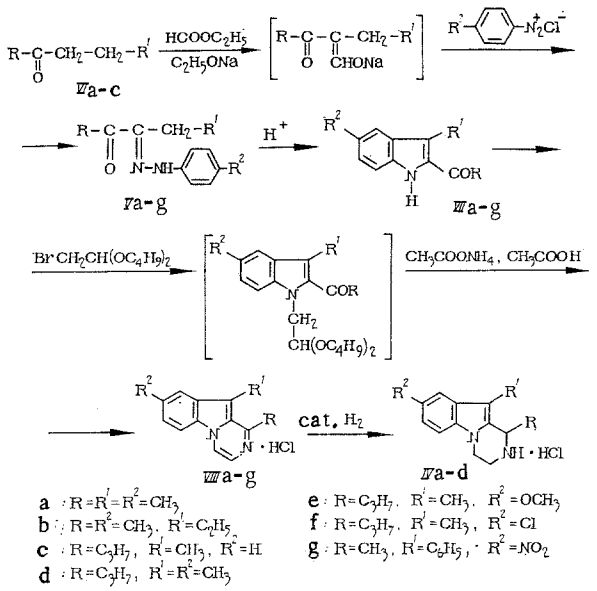

As the starting compounds in the synthesis of pyrazino[1,2-a]indoles we used the previous unknown monoarylhydrazones (Va-f) of dicarbonyl compounds, which were obtained from methyl propyl ketone (VIa), methyl butyl ketone (VIb), and dipropyl ketone (VIc) by the method described in [6], as well as the previously synthesized [7] 1-phenylbutane-2,3-dione 2-(p-nitrophenylhydrazone) (Vg).

The spectral characteristics of Va-f are in good agreement with the spectral data for monoarylhdrazones of α-dicarbonyl compounds [6]. Indolization of Va-g leads to 2-acylindoles VIIa-g. Pyrazino[1,2-a]indole derivatives VIIIa-g were obtained by alkylation of VIIa-g with α-bromoacetaldehyde dibutylacetal in the presence of sodium ethoxide with subsequent cyclization with ammonium acetate in acetic acid. Compounds VIIIa-d were converted to tetrahydropyrazino[1,2-a]indoles IVa-d by catalytic reduction.

The structure of the synthesized pyrazino[1,2-a]indole derivatives was confirmed by UV spectral data. Thus, in contrast to the spectrum of starting VIIb, the UV spectrum of VIIIb contains eight absorption bands with a maximum at 265 nm (log ε 4.64). At the same time, two absorption maxima at 230 nm (log ε 4.31) and 280 nm (log ε 3.8) are observed in the UV spectrum of IVb. The overall character of the UV spectra is similar to the character of the UV spectra of other pyrazino[1,2-a]indole derivatives [8].

EXPERIMENTAL CHEMISTRY

The UV spectra of solutions of the compounds in ethanol were recorded with a Hitachi EPS-3-T spectrophotometer. The PMR spectra of solutions in deuterochloroform were recorded with a JEOL JHM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions and thin layers of the compounds were recorded with a Perkin–Elmer spectrometer.

Pentane-2,3-dione 3-(p-tolylhydrazone) (Va). A 0.8-mole sample of absolute ethanol was added dropwise with stirring to a suspension of 0.25 g of sodium metal in 25 ml of toluene, and the mixture was heated until the sodium had dissolved completely. The unchanged alcohol was then removed by distillation, and the suspension of sodium ethoxide in toluene was cooled to 20°C. A mixture of 0.5 mole of ethyl formate and 0.25 mole of VIa was then added at this temperature, and the mixture was stirred for 1 h and allowed to stand in a refrigerator overnight. The sodium derivative was extracted with water (two 100-ml portions), and the resulting aqueous solution was added at 0-5°C to an aqueous solution of p-toluenediazonium chloride prepared by the usual method from 0.25 mole of p-toluidine, 75 ml of concentrated hydrochloric acid, and 0.25 mole of sodium nitrite and neutralized to pH 6.0-7.0 by the addition of sodium acetate. The reaction mixture was stirred at 0°C for 2 h, and the precipitate was removed by filtration, washed with petroleum ether (bp 40-60°C), and dried to give Va. Data on this compound and the similarly obtained Vb-f are presented in Table 1.

1-Phenylbutane-2,3-dione 2-(p-nitrophenylhydrazone) (Vg). This compound, with mp 170-171°C (from alcohol), was obtained in 60% yield by the method in [7] by diazo coupling of the K salt of α-benzylacetoacetic acid with p-nitrobenzenediazonium chloride.

TABLE 1. Monophenylhydrazones (Va-f) of Dicarbonyl Compounds

Compound	Yield, %	mp, °C (from alcohol)	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
Va	58,3	146—8	70,8	7,9	—	13,8	$C_{12}H_{16}N_2O$	70,6	7,9	—	13,7
Vb	52,9	95—6	71,6	8,5	—	12,9	$C_{13}H_{18}N_2O$	71,5	8,3	—	12,8
Vc	48	92—3	71,8	8,4	—	13,0	$C_{13}H_{18}N_2O$	71,5	8,3	—	12,8
Vd	38,9	93—4	72,2	6,6	—	12,2	$C_{14}H_{20}N_2O$	72,4	8,7	—	12,0
Ve	60,8	89—90	67,9	8,0	—	11,3	$C_{14}H_{20}N_2O_2$	67,7	8,1	—	11,3
Vf	40,3	88—9	61,7	6,8	13,9	11,3	$C_{13}H_{17}ClN_2O$	61,8	6,8	14,0	11,1

TABLE 2. 2-Acylindole Derivatives VIIa-f

Compound	Yield, %	mp, °C (from methanol)	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
VIIa	54,6	199—200	77,2	6,9	—	7,4	$C_{12}H_{13}NO$	77,0	7,0	—	7,5
VIIb	60	124—6*	78	7,6	—	6,8	$C_{13}H_{15}NO$	77,6	7,5	—	7,0
VIIc	50	150—2	77,5	7,6	—	6,9	$C_{13}H_{15}NO$	77,6	7,5	—	7,0
VIId	60	172—3	78,0	7,9	—	6,6	$C_{14}H_{17}NO$	78,1	8,0	—	6,5
VIIe	44,5	196—7	73,0	7,4	—	6,2	$C_{14}H_{12}NO_2$	72,7	7,4	—	6,1
VIIf	65,4	190—1†	65,8	5,9	14,7	6,2	$C_{13}H_{14}ClNO$	66,2	6,0	15,0	6,0

*From aqueous acetone.
†From acetone.

2-Acetyl-3,5-dimethylindole (VIIa). A mixture of 0.1 mole of Va in 40 ml of acetic acid and 25 ml of orthophosphoric acid was refluxed for 3 h, after which it was cooled and allowed to stand for 12 h (at 20°C). The precipitate was removed by filtration, washed with 10 ml of acetic acid and 200 ml of water, and dried. Data on VIIa and the similarly obtained VIIb are presented in Table 2.

2-Butyryl-3-methylindole (VIIc). A solution of 0.1 mole of Vc in 200 ml of 10% aqueous dioxane saturated with hydrogen chloride (concentration ~15%) was allowed to stand for 24 h (at 20°C), after which the precipitate was removed by filtration, washed with 20 ml of water, and dried. Data on VIIc and the similarly obtained VIId-f are presented in Table 2.

2-Acetyl-3-phenyl-5-nitroindole (VIIg). A mixture of 0.034 mole of Vg, 50 ml of hydrochloric acid, and 50 ml of dioxane was heated at 100°C for 3 h, after which it was cooled and diluted with 0.5 liter of water, and the precipitate was removed by filtration and washed with 50 ml of hexane—isopropyl alcohol (1:1) to give VIIg, with mp 239-240°C (from alcohol), in 78% yield. Found, %: C 68.3, H 4.4, N 9.9; M+ 280. $C_{16}H_{12}N_2O_3$. Calculated, %: C 68.5, H 4.3, N 10.0; M 280.4. IR spectrum, ν_{max}, cm^{-1}: 3310 (NH) and 1640 (CO). UV spectrum, λ_{max}, nm (log ε): 295 (4.52) and 330 (3.08). PMR spectrum (d-pyridine): 2.13 s (3H, $COCH_3$), 7.48 broad s (5H, C_6H_5), 7.55 g [sic] (1H, 7-H), 8.25 q (1H, 6-H), and 8.45 g [sic] (1H, 4-H) ($J_{4,6}$ = 3 Hz, $J_{6,7}$ = 10 Hz).

4,5,7-Trimethylpyrazino[1,2-a]indole Hydrochloride (VIIIa). This compound was obtained from 3,5-dimethyl-2-acetylindole (VIIa) under the conditions described in [8]. Data on VIIIa and the similarly obtained VIIIb-g are presented in Table 3.

4,5,7-Trimethyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole Hydrochloride (IVa). A mixture of 0.02 mole of hydrochloride VIIIa, 1 g of a Pd/C catalyst (containing 4.5% Pd), and 150 ml of methanol was hydrogenated in an autoclave at 70°C and 50 atm for 2.5-3 h, after which the reaction mixture was cooled and filtered, and the catalyst was washed on the filter with 50 ml of methanol. The combined methanol solution was evaporated to give IVa, with mp 250-253°C (dec., from 65% aqueous acetone), in 91.2% yield. Found, %: C 67.5, H 7.6, Cl 14.2, N 11.0. $C_{14}H_{18}N_2 \cdot HCl$. Calculated, %: C 67.0, H 7.6, Cl 14.1, N 11.2.

4.7-Dimethyl-5-ethyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole Hydrochloride (IVb). This compound, with mp 255-257°C (dec., from 65% aqueous acetone), was obtained in 87.7% yield from VIIIb under the conditions of the synthesis of IVa. Found, %: C 68.1, H 8.0, Cl 13.2, N 10.3. $C_{15}H_{20}H_2 \cdot HCl$. Calculated, %: C 68.0, H 8.0. Cl 13.4, N 10.6.

4-Propyl-5-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole Hydrochloride (IVc). A mixture of 0.02 mole of the free base of VIIIc and 10 g of an Ni catalyst paste (W-5) in 200 ml

TABLE 3. Pyrazino[1,2-a]indole Derivatives VIIIa-g

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
VIIIa	62,5	287—9*	68,6	6,3	14,4	11,5	$C_{14}H_{14}N_2 \cdot HCl$	68,2	6,1	14,4	11,3
VIIIb	55,5	279—83* (decomp.)	69,4	6,4	13,5	10,5	$C_{15}H_{16}N_2 \cdot HCl$	69,1	6,6	13,6	10,7
VIIIc	54,3	173—5† (decomp.)	68,9	6,7	13,5	10,5	$C_{15}H_{16}N_2 \cdot HCl$	69,1	6,6	13,6	10,7
VIIId	64,0	193—4 ‡	67,8	7,2	12,5	9,7	$C_{16}H_{18}N_2 \cdot HCl \cdot {}^1/_2 H_2O$	67,7	7,1	12,5	9,9
VIIIe	62,3	211—2**	64,1	6,8	11,9	9,1	$C_{16}H_{18}N_2O \cdot HCl \cdot {}^1/_2 H_2O$	64,1	6,7	11,8	9,3
VIIIf	66,6	173—5† (decomp.)	59,5	5,9	23,1	9,1	$C_{15}H_{15}ClN_2 \cdot HCl \cdot {}^1/_2 H_2O$	59,2	5,6	23,3	9,2
VIIIg	65,7	251—2††	64,2	4,2	10,8	12,7	$C_{18}H_{13}N_3O_2 \cdot HCl$	63,6	4,1	10,4	12,4

*From water. †From acetone—alcohol. ‡From alcohol.
**From acetone—methanol. ††From DMF.

TABLE 4. Structure and Activity of the Investigated Compounds

Preparation	LD_{50}, mg/kg (mice)	Dose, mg/kg	Decrease in reserpine-induced (2,6 mg/kg intraperitoneally) blepharoptosis in mice, %	Increase in head shaking from 5-HTP (50 mg/kg intraperitoneally) in mice, %	Intensification of the temperature reaction to L-dopa (200 mg/kg intraperitoneally) in mice, °C
Pyrazidole	450 (internally)	5 (internally)			2,4
		10 (internally)			3,0
		25 (internally, subcutaneously)	50	60	
IVa	335 (internally)	20 (internally)			1,7
		25 (internally)	50	60	
IVb	355 (internally)	10 (internally)			2,5
		25 (internally)	52	40	
IVc	425 (subcutaneously)	25 (subcutaneously)	0	0	0,9
IVd	445 (subcutaneously)	25 (subcutaneously)	0	0	—0,3

of ethanol was hydrogenated at 50°C at 70 atm for 3-4 h, after which the reaction mixture was cooled, and the catalyst was removed by filtration and washed on the filter with 50 ml of ethanol. The alcohol solutions were combined and evaporated to one third of their original volume, and the residual mixture was acidified (to pH 3.0) with a solution of hydrogen chloride in ethanol to give hydrochloride IVc, with mp 215-217°C (dec., from acetone), in 84.5% yield. Found, %: C 67.8, H 7.9, Cl 13.1, N 10.4. $C_{15}H_{20}N_2 \cdot HCl$. Calculated, %: C 68.0, H 8.0, Cl 13.4, N 10.6.

4-Propyl-5,7-dimethyl-1,2,3-tetrahydropyrazino[1,2-a]indole Hydrochloride (IVd). This compound, with mp 167-169°C (dec., from acetone), was obtained in 85.6% yield from the free base of VIIId by a method similar to that used to prepare IVc. Found, %: C 68.9, H 8.4 Cl 12.8, N 9.08. $C_{16}H_{22}N_2 \cdot HCl$. Calculated, %: C 68.9, H 8.3, Cl 12.7, N 10.0.

EXPERIMENTAL PHARMACOLOGY

The pharmacological investigation was conducted in comparison with pyrazidole with respect to those tests in which pyrazidole is most active: antagonism with reserpine and potentiation of the effects of 5-hydroxytryptophan (5-HTP) and L-dopa. We also investigated the LD_{50} values. The experiments were conducted on mice of both sexes with masses of 16-22 g by administration internally or subcutaneously. Each dose of the preparation was administered to six mice. The experiments were repeated two to three times.

The results are presented in Table 4.

It is apparent from Table 4 that IVa, b approach pyrazidole in activity, although they are somewhat more toxic than pyrazidole. These compounds, like pyrazidole, decrease the effect of reserpine (blepharoptosis) in mice and intensify the effects of catechol- and indoleamines (L-dopa and 5-HTP).

Compounds IVc, d are considerably less active than pyrazidole. Thus opening of the C ring in the pyrazidole molecule when there is a methyl or ethyl substitutent in the 5 position of the heteroring and a methyl group in the 4 position was not accompanied by an appreciable loss of activity of the compounds.

The activity of the compounds with respect to the investigated indices was lost when there was a propyl group in the 4 position.

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SYNTHESIS OF CHLODITANE METABOLITES AND THEIR ADRENOCORTICOLYTIC ACTIVITY

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1,1-Dichloro-2-o-chlorophenyl-2-p'-chlorophenylethane (chloditane) is used for treating various forms of hypercorticism and for modeling adrenocortical pathology under experimental conditions [1, 2].

At the Kiev Scientific-Research Institute of Endocrinology and Metabolism a search is being carried out for new effective inhibitors of steroidogenesis. In this aspect, the problem of chloditane metabolites and their corticolytic activity is very interesting, since the experimental data brought several authors to suggest that the adrenocorticolytic effect of chloditane is due to the action of its metabolites in the organism [3-6]. However, we believe that these conclusions are contradictory, since in the experiments *in vitro* the adrenocorticolytic properties of chloditane are manifested in the direct action of the preparation on the adrenal glands tissue [7-9]. We also found that chloditane accumulates in the adrenal glands both in dogs and humans sensitive to it, and in guinea pigs and ribbits resistant to it. The fact that the preparation accumulates in the adrenal glands is thus not important for the manifestation of its specific properties. It has also been suggested that the active metabolite is formed in the glands themselves, and its effect is observed there directly, while in the resistant animals it is not formed [10]. Some authors believe that the mechanism of formation of metabolites and their corticolytic action are similar to the hepatotoxic effect of carbon tetrachloride [11].

At present it has been found that in the organism chloditane can metabolize in three ways: by dehydrochlorination of the aliphatic part of the molecule [12], hydroxylation of the aromatic part [13], and dehydrogenation of the ethane group [14, 15].

In the present work, we report the synthesis of certain possible chloditane metabolites and studied their influence on the functional state of the adrenal glands.

The chloditane metabolites were synthesized by the scheme on the next page.

The structure of the compounds obtained was confirmed by their IR spectral data.

EXPERIMENTAL CHEMISTRY

The IR spectra of the compounds synthesized were taken in KBr tablets in a mineral oil suspension of the Specord IR-75 spectrophotometer (GDR).

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