Compound I was examined in doses of 550, 400, and 300 mg/kg, II in doses of 15 and 10 mg/kg, III and IV in doses of 75 and 50 mg/kg, V in doses of 20 and 15 mg/kg, VI in doses of 10 and 5 mg/kg, and VII in doses of 400 and 200 mg/kg. The experimental results were evaluated statistically. In order to compare quantitatively the anti-leishmaniasis activity of the compounds under investigation, the index of effectiveness, expressed as a percentage, was calculated [6].

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SYNTHESIS AND NEUROPHARMACOLOGICAL ACTIVITY OF 3(5)-SUBSTITUTED PYRAZOLES

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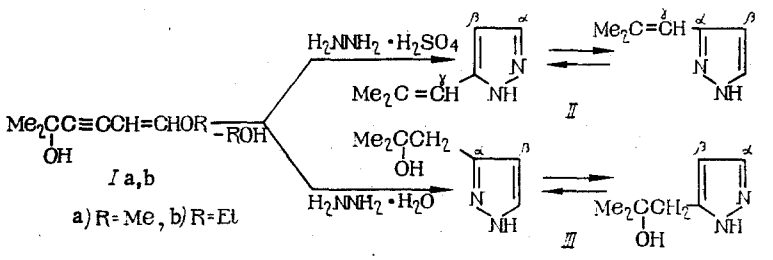
Pyrazoles alkylated in various positions have proved to have narcotic [1, 2], analgesic [3, 4], antiinflammatory [4], sedative [5], spasmolytic [3, 5, 6], and antispasmodic action [7]. 1-Phenyl-3,5-dimethylaminopyrazole methiodide [8, 9] displays curare-like activity of the concurrent blocking type and a ganglion blocking effect. Certain derivatives of pyrazole are able to potentiate the soporific action of chloral hydrate and barbamyl.

A tranquillizing, antispasmodic, myelorelaxant type of action is clearly marked in certain representatives of this class [10]. The appearance of a dependence between chemical structure and pharmacological activity in a series of pyrazoles may serve temporarily as a basis for subsequently directed synthesis of new substances with neuropharmacological properties.

With this aim we have obtained 3(5)-substituted pyrazoles containing an olefinic fragment or a tertiary hydroxyl group in the side chain [11]. Heterocyclization of 1-alkoxy-1-en-3-one carbinols (Ia-c) with hydrazine sulfate and hydrazine hydrate proceeded in acidic and in alkaline media respectively leading to the formation of 3(5)-substituted pyrazoles (II) and (III):



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The interaction of alcohols (Ia, b) with hydrazine sulfate was effected at 80-85°C (3 h). In this way a 70% yield was obtained of pyrazole (II) which contains an olefinic fragment in the side chain. IR spectrum: 1533 cm^{-1} (C=N); 1667, 1673, 3110 cm^{-1} (C=C in ring and side chain); 3190 cm^{-1} (N-H). The PMR spectrum contained signals (δ, ppm), assigned to H_α (7.46 dd), H_β (6.15 dd), H_γ (6.22 m) [J, Hz: $H_\alpha H_\beta$ 1.8; $H_\beta H_\gamma$ < 0.5; CH_γ=C-CH_3 or CH_γ=C-CH_2 < 0.5]; $(CH_3)_2C$ (1.91 d and 1.90 d); NH (8.50).

The condensation of enyne carbinols (Ia, b) with hydrazine hydrate proceeded at 160-220°C for 7-8 h and led to the formation in 40-75% yield of a 3,5-substituted pyrazole (III) containing a hydroxyl group in the side chain. The structure of (III) was demonstrated on the basis of data of elemental analysis, IR, and PMR spectra. The PMR spectra (δ, ppm) corresponded to the 3,5-substituted pyrazole structure (III)*: H_α (7.20 d), H_β (5.88 d) [J, Hz: $H_\alpha H_\beta$ 1.4]; CH_2 (2.74 s); $(CH_3)_2C$ (1.21 s); NH (8.30); OH (8.30).

EXPERIMENTAL (PHARMACOLOGICAL) SECTION

The neuropharmacological properties of the synthesized substances were studied in experiments on male mice of weight 18-23 g. The following were investigated: acute toxicity on single intraperitoneal injection [13], the effect of the obtained compounds on the behavior of animals [14], motion orienting activity (by the number of movements in 10 min in a DAER-20 recorder), motor coordination [15], body temperature, the threshold of aggressive reaction to mice [16], influence on the effects of hexenal (60 mg/kg), apomorphine (10 mg/kg), amphetamine (6 mg/kg), arecoline (25 mg/kg), and morphine (40 mg/kg), influence on convulsions caused by maximal electroshock (50 mA, 0.2 sec, 50 Hz), corazole [17], and strychnine (1.4 mg/kg subcutaneously). When studying the analgesic properties of the synthesized substances and their influence on the effect of morphine the threshold of sickness sensitivity (in volts) in rats was determined by the squeaking reaction on annoying the rats with an electric current from an IES-01 electrostimulator.

As the results of the investigations showed, both substances (II) and (III) possessed sedative-tranquilizing properties but these were more marked for (II). The LD_{50} for (II) was 411 (377.8-477.2) and for (III) was 1220 (1042-2074) mg/kg. In doses equal to 20-50% of the LD_{50} (II) significantly reduced the motion orienting activity of animals and the effect was intensified with an increase in dose. In doses greater than 200 mg/kg the preparation proved to have a narcotic effect. The sedative effect was accompanied by myorelaxation, moderate hypothermia, and by an increase in the threshold of the aggressive reaction (Table 1).

Compound (II) strongly potentiated the soporific effect of hexenal, did not influence stereotypy caused by apomorphine and amphetamine, weakened the stimulating effect of morphine, and potentiated its analgesic action. The preparation weakly protected animals from the convulsive action of corazole and maximal electroshock, and did not influence convulsions caused by strychine (Table 2). Compound (III) only weakly prolonged the soporific effect of hexenal and proved to have an analgesic effect on rats.

At a dose of 40 mg/kg morphine causes agitation in animals and the appearance of the Schtraub symptom, preparation (II) at a dose of 123 and 205 mg/kg extended the latent period of these effects (from 3 to 7 and 14 min, respectively) and weakened their expression but did not block it completely. Thus the synthesized compounds are close in spectrum of activity to the known tranquilizers meprobamate and 1,4-benzodiazepine. However the anticorazole effect of 3,5-substituted pyrazoles was weak but the analgesic effect was stronger. The difference in action of preparations (II) and (III) alkylated in different positions was of interest.

EXPERIMENTAL (CHEMICAL) SECTION

IR spectra were taken on a UR-10 spectrophotometer in a microlayer (NaCl and LiF prisms, 600-3500 cm^{-1}). PMR spectra were obtained on a Tesla BS-487C spectrometer (80 MHz) for 20% solutions of compounds in carbon tetrachloride. Hexamethyldisiloxane was used in internal

*Assignment of lines to the resonances of each of the isomers was made in accordance with [12]. The resonance of OH and NH group protons was not detected evidently due to the moderate (on a PMR scale) rate of proton exchange between them.

TABLE 1. The Effect of the Synthesized 3,5-Substituted Pyrazoles on the Motion Orienting Activity, Threshold of Aggression Reaction, Body Temperature, and Motor Coordination

Substance	Dose mg/kg	Number of movements in 10 min	Hypothermia Δt °C	Disturbance of motor coordination ED_{50}	Threshold of aggression reaction, V
Control		419 (375—465)	0	—	20±0,3
II	20	331 (278—889)	0	147 (126,7–170,5)	25±0,4
	82	296 (240—346)	0	—	26±0,3
	123	236 (172—298)	0	—	30±0,4
	205	36 (0—44)	2,4±0,02	—	42±0,4
III	61	454 (412±511)	0	689 (570—833,7)	20±0,5
	244	400 (348—452)	0	—	20±0,3
	610	304 (262—360)	1,2±0,04	—	28±0,4

Note. ED_{50} is the dose causing a drop of 50% of the animals from a rotating rod in the first 2 min.

TABLE 2. The Influence of 3,5-Substituted Pyrazoles on the Effects of Hexenal, Apomorphine, Corazole, Morphine, and Strychnine

Substance	Dose mg/kg	Duration of hexenal action, min	Duration of apomorphine action, min	DTE of corazole 1%, ml	Strychine % protection of animals	Threshold of sickness reaction, V	
						morphine	substance + morphine
Control		29±5,5	61±1,3	0,144±0,08	0	3,9±0,5	
II	82	84±16,1	61,5±2,7	0,152±0,06	0	20±0,5	27±0,4
	123	114±17,4	62,1±0,8	0,178±0,08	0	20±0,5	30±0,2
	205	26 h	58±0,4	0,286±0,06	0	20±0,5	> 30
III	244	49±6,5	60±0,3	0,141±0,08	0	20±0,5	22±0,6
	610	58±4,5	60±0,3	0,151±0,06	0	20±0,5	27±0,5

Note. DTE is the dose of corazole in 1 ml 1% solution which which on slow intravenous injection to mice causes a tonic extensor phase of a convulsive fit.

standard. The precision of determining the chemical shift was ±0.01 ppm. The homogeneity of substances was checked by thin layer chromatography on aluminum oxide of activity grade II in the system benzene–methanol (9:1).

3,5-(2-Methylprop-1-enyl)pyrazole (II). A suspension of hydrazine sulfate (5.23 g; 0.04 mole) in water (10 ml) and methanol (5 ml) was heated to 70°C and at this temperature was added alcohol (Ia) (3.95 g; 0.028 mole) in methanol (5 ml). The mixture was stirred for 3-$3^1/_2$ h at 80–85°C then decanted and the solvent distilled off. The residue was washed repeatedly with ether, the obtained ether extracts were combined with the residue after removal of methanol, water was added, and the reaction product salted out with magnesium sulfate and (II) (2.53 g; 70.0%) was isolated by distillation. Bp 98–100°C (3 mm), n_D^{20} 1.5304. Found, %: C 68.81; H 8.26; N 22.75. $C_7H_{10}N_2$. Calculated, %: C 68.84; H 8.25; N 22.93.

IR spectrum, cm^{-1}: 3170, 3110, 1673, 1667, 1553, and 1463.

3,5-(2-Methyl-2-hydroxypropyl)pyrazole (III). A mixture of alcohol (Ia) (2.42 g, 0.017 mole) and hydrazine hydrate (2.58, 0.052 mole) was heated in an ampul at 160°C for 7-8 h. After cooling the reaction mass was treated with water, dried with potassium carbonate, extracted with ether, and the extract dried over magnesium sulfate. The solvent was removed and crystalline pyrazole (III) (1.79 g, 74.8%) was isolated. After vacuum sublimation it had

mp 86-87°C. Found, %: C 60.29; H 8.62; N 20.02. $C_7H_{12}N_1O$. Calculated, %: C 59.97; H 8.63; N 19.99.

IR spectrum, cm^{-1}: 3210, 3180, 3070, 1662, 1552, 1472, and 1452.

Pyrazole (III) (1.78 g, 55.6%) was also obtained in a similar manner (220°C, 8 h) from alcohol (Ib) (3.42 g, 0.022 mole) and hydrazine hydrate (4.47 g, 0.09 mole).

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ARYLSULFONIC ACID DERIVATIVES.

IX. SYNTHESIS OF 4-SULFAMIDO-5-(p-ALKOXYBENZYL)PYRIMIDINES

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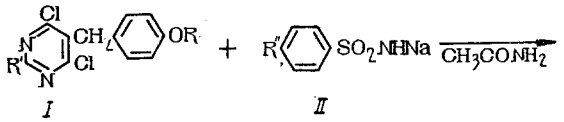
The synthesis of 4-sulfanilamidopyrimidines was carried out by us previously [1, 2] with the aim of studying hypoglycemic and antibacterial activity. According to literature data substitution of the amino group in the sulfanilyl residue by alkyl or alkoxyl reduced the toxicity of preparations [3]. Proceeding from this the synthesis of pyrimidines (III) and (IV) was carried out. The latter are of interest in a project for assessing the dependence of biological properties on structure. Pyrimidines (III) and (IV) were obtained according to the scheme:



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