sometimes to zero. Low protection is also seen in trimetoxinol (XXVI), which has β-adrenomimetic activity.

Comparison of the RPE data with the mass spectra leads to the conclusion that there are no fundamental differences in behavior on electron impact between the noncyclic compounds (XXI) and (XXVII), which have high RPE, and noncyclic and cyclic analogs of low activity.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF N-SUBSTITUTED DERIVATIVES OF 9-(3-AMINO-2-HYDROXYPROPYL)CARBAZOLES

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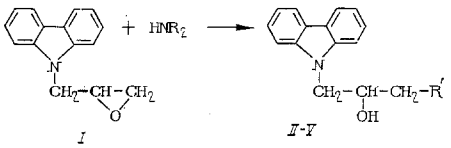
A new psychotropic agent, a derivative of 9-propylcarbazole with a 3,5-dimethylpiperazinyl radical in the propyl substituent, has been described in [1]. To study the pharmacological activity of carbazole derivatives, we synthesized N-substituted derivatives of 9-(3-amino-2-hydroxypropyl)carbazoles (II-V) according to the following scheme:



II: $R' = N(C_2H_5)_2$; III: $R' = N(CH_2)_5$; IV: $R' = N(CH_2)_6$; V: $R' = N(CH_2)_4O$.

Diethylamine, piperidine, hexamethylenediimine, and morpholine are added to 9-(2,3-epoxypropyl)carbazole (I), when the components are heated in boiling ethanol. The oxirane ring is opened with cleavage of the C–O bond at the primary atom, which corresponds to the direction of opening of the oxirane ring in the nucleophilic addition of the carbazolyl anion to I [2] and was confirmed by the study of compounds II-V by NMR spectroscopy.

To confirm the assignment of compounds II-V to the class of secondary alcohols, we obtained their PMR spectra in tetrachloromethane and dimethyl sulfoxide (Table 1). As the result of rapid chemical exchange in tetrachloromethane, the hydroxyl proton signal of compounds II-V is represented by a somewhat broadened singlet. With increase in temperature, it is shifted to the stronger field region, so that its position could be found in the PMR spectrum. The chemical exchange is appreciably slowed down in dimethyl sulfoxide: The hydroxyl proton signal of compounds II-V is represented by a broadened doublet, which is shifted by more than 1 ppm to a weak field region, compared with the spectrum in tetrachloromethane, and is characteristic of secondary alcohols [3].

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TABLE 1. Carbazole Derivatives I-V

Compound	Yield, %	mp. °C	Found % C	Found % H	Found % N	Found equivalent	Empirical formula	Calculated % C	Calculated % H	Calculated % N	Calculated equivalent	PMR spectrum, δ (OH), ppm CCl_4	PMR spectrum, δ (OH), ppm DMSO
II	79	96–8	77,19	8,16	9,79	314,4	$C_{19}H_{24}N_2O$	76,99	8,16	9,45	296	3,45	4,73
III	97	102–4	78,02	7,61	9,23	312	$C_{20}H_{24}N_2O$	77,88	7,84	9,08	308,4	3,44	4,86
IV	90	97–9	78,72	8,21	8,43	328,4	$C_{21}H_{26}N_2O$	78,25	8,08	8,69	323,3	3,67	4,72
V	71	97–8	74,04	7,31	9,57	324,8	$C_{19}H_{22}N_2O_2$	73,52	7,14	9,02	310,8	3,05	4,90

TABLE 2. Toxicity and Spectrum of Depressant Action of Carbazole Derivatives II-V

Compound	$LD_{50} \pm S_{\bar{x}} \cdot t$, mg/kg	$ED_{50} \pm S_{\bar{x}} \cdot t$, mg/kg: suppression of spontaneous motive activity	suppression of orientating reaction	myorelaxation	potentiation of hexenal effect	anticorazole action
II	250±98	17±3	19±6	40±8	30±12	50
III	250±9	15±6	21±5	36±4	28±6	40
IV	280±16	11±3	30±5	56±4	36±9	60
V	547±40	13±5	22±4	38±6	32±8	50
Melipramine	133±23	25±10	37±3	37±3	56±8	50
Diazepam	140±16	0,8±0,1	1,5±0,3	3,6±0,4	0,3±0,06	1,4±0,16

Compounds II-V (see Table 1) are crystalline substances, which are soluble in aromatic hydrocarbons, polychlorinated hydrocarbons, and ketones, and crystallize from ethanol. They react with aqueous hydrochloric acid to form water insoluble viscous pastelike hydrochlorides.

EXPERIMENTAL CHEMISTRY

The PMR spectra were run on the BS-487C spectrometer (CSSR) with a working frequency of 80 MHz. The chemical shifts were measured with reference to hexamethyldixiloxane as the internal standard, and were converted to the TMS scale. The measurement error of the chemical shifts did not exceed 0.01 ppm.

9-(3-Diethylamino-2-hydroxypropyl)carbazole (II). A reaction mixture consisting of 4 g (0.018 mole) of 9-(2,3-epoxypropyl)carbazole (I), 8 ml of diethylamine, and 25 ml of ethanol is boiled for 30 min. Then, 5 ml of water are added to the hot solution, which is left to stand to crystallize. The crystalline precipitate is filtered and recrystallized from ethanol. The material is dried at 50-60°C, and held in an exsiccator over solid potassium hydroxide.

Compounds III-V are obtained in a similar way, using 4 ml of the amine per 0.018 mole of I. Compound V precipitates from the reaction mixture in the form of a difficultly crystallizable oil. The formation of oil can be prevented by adding crystal seeds.

The equivalent of solutions of bases in acetone was determined by potentiometric titration with a glass electrode by an aqueous solution of hydrochloric acid.

EXPERIMENTAL PHARMACOLOGY

The central neurotropic activity activity of the compounds synthesized was pharmacologically studied by generally accepted methods [4]. Compounds II-V were administered to the animals in aqueous suspensions with Tween-80.

All the compounds studied have a depressant action. In doses consisting of 10% of LD_{50} they markedly depress the spontaneous motive activity, suppress the orientating reactions, and cause disturbance in movement coordination (Table 2). In doses of 28-36 mg/kg, the compounds studied potentiate the narcotic effect of hexenal, and in the same doses they intensify the analgesic effect of promedol.

When estimating the influence of compounds II-V on the duration of nicotine-induced spasms and are coline-induced tremor in mice, we should note that all the compounds studied do not change the duration of the observed effects. Corazole-induced spasmolytic activity

is eliminated by the preparations studied in doses of more than 50 mg per kg body weight of the animal.

In a dose consisting of 10% of LD_{50}, the preparations increase the hypothermia induced by a reserpine-like compound PO-4-1284, but do not change, or inappreciably potentiate, phenamine stereotypia in mice. In experiments on narcotized cats, the preparations (5 mg/kg, intravenously) slightly increase (by 10-20%) the effect of noradrenaline on the arterial pressure.

The compounds II-V studied have an inherent central neurotropic action. In contrast to other known tricyclic systems (for example, β-carbonyls) exhibiting antidepressant properties, the carbazole derivatives studied have inappreciable adrenopotentiating properties and a more pronounced depressant action on the central nervous system.

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SYNTHESIS AND ANTISPASMODIC ACTIVITY OF 2-ALKYL SUBSTITUTED THIENO[2,3-d]PYRIMIDIN-4-ONES

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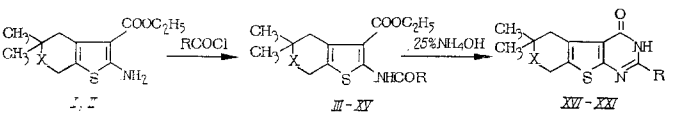
During recent years a systematic search has been carried out for new antispasmodic compounds in the condensed thieno[2,3-d]pyrimidine derivatives. The present work is a continuation of the previous studies in [1, 2] and is devoted to the synthesis of new 2-alkyl substituted pyrano(thiopyrano)[4', 3':4,5]thieno[2,3-d]pyrimidin-4-ones.

2-Amino-3-carbethoxythiophenes served as starting materials for synthesis and were condensed with six-membered heterocycles containing sulfur or oxygen (I, II) [3]. By reacting the latter with acid chlorides a series of acylated derivatives (III-XV) was obtained. On heating in methanolic ammonia solution (V, VI, VIII-X) were converted into the corresponding 2-alkyl substituted thieno[2,3-d]pyrimidin-4-ones (XVI-XXI).



I: X = O; II: X = S; III: X = O, R = C_2H_5; IV: X = O, R = C_3H_7; V, XVI: X = O, R = C_4H_9; VI, XVII: X = O, R = C_5H_{11}; VII: X = S, R = C_2H_5; VIII, XVIII: X = S, R = C_3H_7; IX, XIX: X = S; R = C_4H_9; X, XX: X = S, R = C_5H_{11}; XI, XXI: X = O, R = coumaryl; XII: X = S, R = iso-C_3H_7; XIII: X = O, R = p-iso-C_4H_9O) C_6H_4; XIV: X = O, R = iso-C_4H_9; XV: X = O, R = C_9H_{19}.

EXPERIMENTAL PHARMACOLOGY

Experiments were carried out on mice of weight 18-22 g using procedures for the assessment of substances possessing antispasmodic properties, viz., the maximum electroshock test

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