SEARCH FOR NEW DRUGS

CONDENSED THIENOPYRIMIDINE DERIVATIVES. PART 20: SYNTHESIS AND NEUROTROPIC ACTIVITY OF A SERIES OF NEW PYRANO[4′,3′:4,5]THIENO[3,2-e]IMIDAZOLIDINO-[2,1-b]PYRIMIDINES

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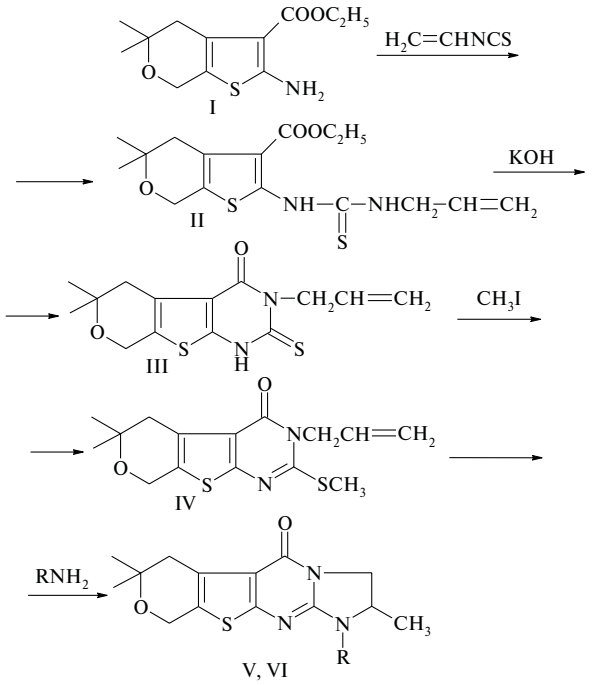
Previously we reported on the neurotropic properties of condensed thieno[2,3-d]pyrimidine derivatives [1 – 3]. To our knowledge, the synthesis and pharmacological activity of pyranothienoimidazolidino[2,1-b]pyrimidines have not been described so far. To fill the gap, we have developed a method for the synthesis of new pyranothienoimidazopyrimidines that are condensed and studied their neurotropic and antiamnesic properties.



V: R = CH_3; VI: R = CH_2CH_2OH.

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The interaction of 2-aminothiophene I [4] with allylisothiocyanate led to the corresponding thioureido derivative II. Under the action of potassium hydroxide solution in aqueous ethanol, this compound converted into 2-thio-4-oxothieno[2,3-d]pyrimidine III. By alkylating compound III with methyl iodide, we obtained the corresponding S-methyl derivative IV. Finally, the condensation of compound IV with primary amines led to the target imidazo[2,1-b]pyrimidines V and VI.

EXPERIMENTAL CHEMICAL PART

The IR absorption spectra were measured on an UR-20 spectrophotometer (Germany) using samples suspended in Vaseline oil. The IR spectra of the synthesized compounds exhibit characteristic absorption bands in the regions of 1665 – 1675 cm^{-1} (amide C=O bonds) and 3100 – 3300 (NH). The ^1H NMR spectra were recorded on a Varian T-60 spectrometer using TMS as the internal standard. TLC was performed on Silufol UV-254 plates; the spots were visualized by exposure to iodine vapors. The data of elemental analyses agree with the results of calculations using the proposed empirical formulas.

2-(N′-Allylthioureido)-5,5-dimethyl-3-ethoxycarbonyl-4,5-dihydro-7H-thieno[2,3-c]pyran (II). A mixture of 2.55 g (0.01 mole) of compound I [4] and 0.99 g (0.01 mole) of allylisothiocyanate in 40 ml of methanol was boiled for 12 h and allowed to stand overnight. The precipitate crystals were separated by filtration and washed with diethyl ether to obtain 1.6 g (45.2%) of compound II; m.p., 151 – 152°C; R_f, 0.62 (acetone – hexane, 1 : 1); $C_{16}H_{22}N_2O_3S_2$; ^1H NMR spectrum in $CDCl_3$ (δ, ppm): 11.90 (s, 1H, NH), 6.93 (t, 1H, NH–CH_2–), 6.23 – 4.96 (m, 3H, CH=CH_2), 4.0 (t, 2H,

TABLE 1. Anticonvulsant Properties, Tranquilizer Activity, and Acute Toxicity of Compounds V and VI

Compound	Anxiolytic activity (number of water takes)	Anticorazole activity (ED_{50}), mg/kg	Myorelaxant (TD_{50}), mg/kg	TD_{50}/ED_{50}	LD_{50}, mg/kg
Compound V (100 mg/kg)	12.1 (9.1 ÷ 15.1)	50 (34.5 ÷ 72.5)	> 1000	20	1300 (1083 ÷ 1560)
Compound VI (100 mg/kg)	9.5 (8.4 ÷ 10.6)	86 (49.1 ÷ 110.5)	> 1000	12	1500 (1181 ÷ 1905)
Phenobarbital		12.5 (8.3 ÷ 18.5)	46 (29.5 ÷ 71.8)	3	92 (51.2 ÷ 147.2)
Diazepam (2 mg/kg)	16 (7.7 ÷ 24.3)	0.5 (0.4 ÷ 0.7)	2.7 (1.4 ÷ 5.5)	5	
Control	1.6 (1.1 ÷ 2.1)	–	–	–	–

7-CH_2), 4.23 (q, 2H, O$\underline{CH_2}CH_3$), 4.03 (t, 2H, NH–$\underline{CH_2}$–), 2.67 (t, 2H, 4-CH_2), 1.28 (t, 3H, OCH_2–$\underline{CH_3}$), 1.23 (s, 6H, $(CH_3)_2$).

3-Allyl-6,6-dimethyl-4-oxo-2-thio-5,6-dihydro-8H-pyrano[4′,3′:4,5]thieno[2,3-d]pyrimidine (III). A mixture of 3.54 g (0.01 mole) of compound II and 1.12 g (0.02 mole) of potassium hydroxide in 40 ml of 50% aqueous ethanol was boiled for 2 h. Upon cooling, the reaction mixture was acidified with a 10% aqueous hydrochloric acid solution to obtain a weak acid reaction. The precipitated crystals were separated by filtration, washed with water, and dried to obtain 3.0 g (97.8%) of compound III; m.p., 213 – 215°C (ethanol); R_f, 0.55 (chloroform – benzene – acetonitrile, 6 : 2 : 1); $C_{14}H_{16}N_2O_2S_2$; ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 9.50 (s, 1H, NH), 6.35 – 5.15 (m, 3H, CH=CH_2), 5.05 (d, 2H, N–CH_2), 4.63 (t, 2H, 8-CH_2), 2.83 (t, 2H, 5-CH_2), 1.23 (s, 6H, $(CH_3)_2$).

3-Allyl-6,6-dimethyl-2-methylhtio-4-oxo-5,6-dihydro-8H-pyrano[4′,3′:4,5]thieno[2,3-d]pyrimidine (IV). To a solution of 3.1 g (0.01 mole) of compound III and 0.56 g (0.01 mole) of potassium hydroxide in 20 ml of 90% aqueous ethanol at room temperature was added, with stirring, 1.4 g (0.01 mole) of methyl iodide. The precipitated crystals were separated by filtration, washed with water, and dried to obtain 2.5 g (78.4%) of compound IV; m.p., 145 – 146°C (ethanol); R_f, 0.64 (chloroform – benzene – acetonitrile, 6 : 2 : 1); $C_{15}H_{18}N_2O_2S_2$; ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 6.10 – 5.0 (m, 3H, CH=CH_2), 4.77 (d, 2H, N–CH_2), 4.62 (t, 2H, 8-CH_2), 2.90 (t, 2H, 5-CH_2), 2.57 (s, 3H, SCH_3), 1.27 (s, 6H, $(CH_3)_2$).

1,2,7,7-Tetramethyl-5-oxo-6,7-dihydro-9H-pyrano[4′,3′:4,5]thieno[2,3-e]imidazolidino[2,1-b]pyridine (V). A mixture of 3.22 g (0.01 mole) of compound IV and 40 ml of a 30% aqueous methylamine solution was heated in a metal bomb at 150°C for 18 h. Upon cooling, the precipitated crystals were separated by filtration, washed with water and ether, and dried to obtain 1.2 g (41.2%) of compound V; m.p., 209 – 211°C (ethanol); R_f, 0.50 (chloroform – benzene – acetone, 2 : 2 : 1); $C_{15}H_{19}N_3O_2S$; ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 4.63 (t, 2H, 9-CH_2), 4.30 – 3.30 (m, 3H, 2-CH, 3-CH_2), 2.90 (s, 3H, N–CH_3), 2.76 (t, 2H, 5-CH_2), 1.48 (d, 3H, –CH–$\underline{CH_3}$), 1.20 (s, 6H, $(CH_3)_2$).

Hydrochloride (V · HCl): m.p., 218 – 220°C (anhydr. ethanol); $C_{15}H_{19}N_3O_2S \cdot HCl$.

2,7,7-Trimethyl-5-oxo-1-(β-hydroxy)-ethyl-6,7-dihydro-9H-pyrano[4′,3′:4,5]thieno[2,3-e]imidazolidino[2,1-b]pyridine (VI). A mixture of 3.22 g (0.01 mole) of compound IV and 20 ml of monoethanolamine was heated in a metal bomb at 150°C for 20 h. Upon cooling, the mixture was diluted with water. The precipitated crystals were separated by filtration, washed with water and ether, and dried to obtain 1.3 g (38.7%) of compound VI; m.p., 219 – 220°C (ethanol); R_f, 0.50 (chloroform – benzene – acetone, 2 : 1 : 3); $C_{16}H_{21}N_3O_3S$; ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 4.69 (t, 2H, 9-CH_2), 4.31 – 3.27 (m, 7H, CH_2–CH_2, 2-CH, 3-CH_2), 2.92 (t, 2H, 6-CH_2), 1.40 (d, 3H, –CH–CH_3), 1.09 (s, 6H, $(CH_3)_2$).

Hydrochloride (VI · HCl): m.p., 228 – 230°C (anhydr. ethanol); $C_{16}H_{21}N_3O_3S \cdot HCl$.

EXPERIMENTAL PHARMACOLOGICAL PART

The substances to be tested were introduced by intraperitoneal injections in the form of suspensions with Tween-80 in a dose of 25, 50, 100, 500, 1000, or 2000 mg/kg. The injections were made 45 min before the administration of convulsant (corazole) or the test for tranquilizer, myorelaxant, or neurotoxicity.

The effect of compounds V – VI on the clonic convulsion component was studied using 340 white mongrel mice weighing 18 – 24 g and 60 rats weighing 180 – 220 g (each test was performed in a group of eight animals). The model convulsions were induced by corazole (90 mg/kg, s.c.), arecoline (15 mg/kg, s.c.), or nicotine (8 mg/kg, i.p.), or by the maximum electroshock technique. The tranquilizer effect was studied using the "conflict situation" test. In addition, we monitored the side effects (disturbed coordination of movements) and determined the acute toxicity. The methods used in the investigation of anticonvulsant, tranquilizer, and myorelaxant properties, as well as the method of statistical data processing and determining the effective dose (ED_{50}), acute toxicity (LD_{50}), and neurotoxicity (TD_{50}) values, were described elsewhere [5, 6]. In addition, we calculated the

protection index, defined as the ratio of TD_{50} and ED_{50}. The reference drugs were phenobarbital and diazepam [6].

It was found that compounds V and VI in the dose range studied do not prevent convulsions induced by nicotine, arecoline, or maximum electroshock. However, beginning with a dose of 25 mg/kg, both compounds decreased or prevented corazole-induced convulsions (Table 1). In a dose corresponding to ED_{50}, these substances produced a weak myorelaxant effect; only a very significant increase in the dose dose level (almost 20-fold for compound V) led to myorelaxation and loss of animals.

Beginning with a dose of 25 and 50 mg/kg, compounds V and VI led to an increase in the number of water takes in the conflict situation test, but the tranquilizer activity of both drugs was significantly lower as compared to that of diazepam. The protection indices (determined as the ratio of anticonvulsant and myorelaxant doses) of compounds V and VI amount to 20 and 12 (against 5 and 3 for diazepam and phenobarbital), respectively. Although diazepam and phenobarbital show more pronounced anticorazole activity and the former drug produces a tranquilizer effect as well, the significantly greater protection ratios of compounds V and VI may be evidence of higher selectivity and lower toxicity of the newly synthesized imidazolidinopyrimidine derivatives.

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