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THE EFFECTS OF THE AMINO GROUP AND THE HETEROATOM ON THE ANTICONVULSANT ACTIVITY OF 2-SUBSTITUTED 3-AMINO-6,6-DIMETHYL-5,6-DIHYDRO-8H-PYRANO [THIOPYRANO][4',3':4,5]THIENO[2,3-d]PYRIMIDINE-4-ONES

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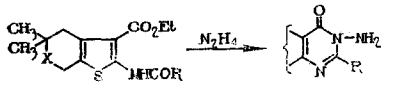
In earlier work we showed that 4,5-condensed 2-aminosubstituted 3-carbethoxythiophenes, 4-alkyl(aryl)aminosubstituted thieno[2,3-d]pyrimidines and 2-alkyl substituted thieno[2,3-d]pyrimidinones exhibited anticorazole properties [1-3]. It was noted that the anticonvulsant activity was influenced by the character and position of the substituent in the pyrimidine ring, and also by the nature of the heteratom [4].

In order to investigate further the effects of the amino group at position 3 of the pyrimidine ring and the heteroatom on the anticonvulsant activity, we have prepared 2-alkyl-3-amino-6,6-dimethyl-5,6-dihydro-8H-pyrano(thiopyrano)[4',3':4,5]thieno[2,3-d]pyrimidine-4-ones (XIV-XXVI) by the action of N_2H_4 on substituted 2-amino-3-carbethoxythiophenes I-XIII [1, 2].



I-XIII XIV-XXVI

I, XIV: X = O, R = Me; II, XV: X = O, R = Et; III, XVI: X = O, R = Pr; IV, XVII: X = O, R = *i* = Pr; V, XVIII: X = O, R = Bu; VI, XIX: X = O, R = *i* = Bu; VII, XX: X = O, R = C_5H_{11}; VIII, XXI: X = O, R = C_9H_{10}; IX, XXII: X = O, R = $C_6H_4OBu = i\text{-}n$; X, XXIII: X = S, R = Pr; XI, XXIV: X = S, R = *i* = Pr; XII, XXV: X = S, R = Bu; XIII, XXVI: X = S, R = C_5H_{11}.

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TABLE 1. Compounds XIV-XXVI

Compound	Yield, %	R_f^*	Mp, °C	Found, %		Empirical formula	Calculated, %		NMR spectrum ($CDCl_3$), δ, ppm
				N	S		N	S	
XIV	71,5	0,51	148—50	16,0	12,2	$C_{12}H_{15}N_3O_2S$	15,8	12,1	1,33 s ($2CH_3$), 2,53 s (CH_3), 4,90 s (NH_2)
XV	61,9	0,64	140—2	15,2	11,4	$C_{13}H_{17}N_3O_2S$	15,0	11,5	1,33 t (CH_3), 4,91 s (NH_2)
XVI	79,1	0,52	162	14,5	11,1	$C_{14}H_{19}N_3O_2S$	14,3	10,9	0,80—2,00 m ($3CH_3$, CH_2), 2,95 t (CH_2), 4,80 t (CH_2O), 4,90 s (NH_2)
XVII	78,4	0,59	175—6	14,8	10,2	$C_{14}H_{19}N_3O_2S$	14,3	10,9	1,35 t ($4CH_3$), 2,90 s (CH_2), 3,70 q (CH), 4,75 t (CH_2O), 4,90 s (NH_2)
XVIII	86,8	0,73	154	13,4	10,5	$C_{15}H_{21}N_3O_2S$	13,7	10,4	0,80—2,00 m ($3CH_3$, $2CH_2$), 4,93 s (NH_2)
XIX	55,1	0,70	156—8	13,3	10,1	$C_{15}H_{21}N_3O_2S$	13,7	10,4	0,90—1,50 s ($4CH_3$), 4,85 t (NH_2)
XX	79,1	0,63	180—2	12,9	10,0	$C_{16}H_{23}N_3O_2S$	13,1	9,9	0,80—2,00 m ($3CH_3$, $3CH_2$), 4,95 s (NH_2)
XXI	69,8	0,70	141—2	11,2	8,6	$C_{20}H_{21}N_3O_2S$	11,1	8,5	0,70—2,00 m ($3CH_3$, $7CH_2$), 4,85 s (NH_2)
XXII	54,8	0,70	235—7	10,6	8,1	$C_{21}H_{25}N_3O_2S$	10,5	8,0	. . .
XXIII	78,9	0,53	155—7	13,9	20,2	$C_{14}H_{19}N_3O_2S_2$	13,6	20,7	1,00—2,00 m ($3CH_3$), 3,10 t (CH_2), 3,40 t (CH_2), 3,92 t (CH_2S), 6,16 s ($NH)_2$
XXIV	43,8	0,53	201—3	13,2	20,9	$C_{14}H_{19}N_3OS_2$	13,6	20,7	1,20—1,50 m ($4CH_3$), 4,80 s (NH_2)
XXV	82,3	0,51	118—20	13,0	19,6	$C_{15}H_{21}N_3OS_2$	12,9	19,8	0,80—2,00 m ($3CH_3$, $2CH_2$), 4,93 s (NH_2)
XXVI	73,0	0,60	110—1	12,8	18,3	$C_{16}H_{23}N_3OS_2$	12,4	18,9	0,80—2,00 m ($3CH_3$, $3CH_2$), 4,70 s (NH_2)

*Eluant: benzene—ether—acetone, 3:3:1 (XIV, XV, XX, XXI); $CHCl_3$—ether—acetone, 3:3:1 (XVI); $CHCl_3$—ether, 1:1 (XVII); octane—ether—alcohol, 0.5:1:0.5 (XVIII); benzene—ether—hexane, 1:1:1.5 (XIX); $CHCl_3$—alcohol, 1:1 (XXII); hexane—ether, 1.5:1 (XXIII, XXV, XXVI); $CHCl_3$—ether—heptane, 3:3:1 (XXIV).

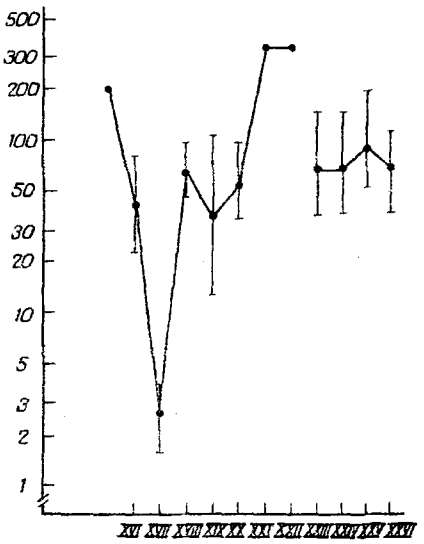

Fig. 1. Relative anticorazole activities of compounds XIV, and XVI-XXVI. Compound number is plotted along the x-axis and ED_{50} (in mg/kg) on a logarithmic scale along the y-axis.

EXPERIMENTAL CHEMISTRY

Infrared spectra of the compounds in mineral oil were taken on a UR-20 (GDR), NMR spectra in $CDCl_3$ on a "Varian-T-60" (USA) with a working frequency of 60 MHz, internal standard TMS, signals are given in δ ppm. TLC was carried out on Silufol-254 plates (ChSSR), silica gel L5/40μ (ChSSR), and developed with iodine vapor.

2-Substituted 3-Amino-6,6-dimethyl-5,6-dihydro-8H-pyrano(thiopyrano)[4',3':4,5]thieno-[2,3-d]pyrimidine-4-ones (XIV-XXVI). A mixture of 0.001 mole of I-XII and 10 ml of hydrazine hydrate in 4 ml of ethyl alcohol was refluxed for 6-8 h. On cooling, crystals separated out and were filtered off and washed with water, ether, and alcohol, and recrystallized from MeOH. Physical constants are given in Table 1. IR spectra (XIV-XXVI), ν_{max}, cm^{-1}: 1600-1610 (C=N), 1665-1680 (C=O), 3170-3260, 3300-3315 (NH_2).

EXPERIMENTAL PHARMACOLOGY

The anticonvulsant activity of compounds XIV and XVI-XXVI was tested on mice weighing 18-25 g, and was compared with the known anticonvulsants zarontin and luminal. Suspensions of the compounds in Tween-80 were injected intraperitoneally 45 min before the injection of a substance which caused convulsions. Groups of 15-20 animals were used.

The anticonvulsant effect of the compounds was studied on convulsions caused either by the injection of corazole, nicotine, and arecoline, or by the application of electroshock. The myorelaxant and sedative effects (secondary properties of anticonvulsants) were studied by testing the animals' ability to cling to a rotating rod or climb a rotating screen. The acute daily toxicity for mice was also determined. The anticonvulsant and secondary properties, toxicities, and also the statistical treatment of the results to determine the 50% effective dose (ED_{50}) and neurotoxic (TD_{50}) dose were carried out by methods established by us in earlier work [2].

None of the test compounds, even at maximum dosage (200-300 mg/kg), prevented nicotine hyperkinesia, arecoline tremor, or electroshock-induced tonic extension. The exeption was compound XVII, which gave some protection from electroshock for 50% of animals in doses of 56 (24.3-128.8) mg/kg. All the test compounds in doses of 1000 mg/kg had a myorelaxant and sedative action on the animals, and in doses of 2000-3000 mg/kg caused destruction of 100% of the mice.

The majority of the test compounds exhibited anticorazole properties in varying degrees; moreover, among the pyranothienopyrimidines XIV-XXII, certain similarities were noted. For example, the corazole antagonism of compound XIV was negligible even in doses of 200 mg/kg. When the propyl group at position 2 was replaced by a C_5H_{11} group (XVI-XIX), the anticonvul-

TABLE 2. Relative Activities of Compound XVII, Zarontin, and Luminal

Compound	Elimination of action of corazole (ED_{50}, mg/kg)	Destruction of motor coordination (TD_{50}, mg/kg)	Acute daily toxicity (LD_{50}, mg/kg)	Therapeutic index	Protective index
XVII	2,6 (1,7—3,8)	26 (22,2—30,4)	1300 (757,8—2145)	500	10
Zarontin	155 (117,5—204,5)	520 (412—655,2)	1325 (1200—1462)	8,5	3,3
Luminal	8,0 (5,0—12,8)	46 (29,6—71,3)	92 (51,2—147.2)	11.5	5,7

sant action decreased for a wide range of doses — from 2.6 to 64 mg/kg (see Fig. 1). Replacement by a C_9H_{19} group led to further weakening of the action. The thiopyranothienopyrimidines XXIII-XXVI exhibited anticorazole activity over a narrower range of doses — from 62 to 92 mg/kg (see Fig. 1).

Of the test compounds, compound XVII showed the most marked anticorazole action; clonic convulsions were prevented in 50% of the mice for doses of 2.6 mg/kg, and here, XVII was more effective than compound XXIII (ED_{50} — 70 mg/kg) by a factor of 27; it was also more effective than zarontin and luminal by factors of 59.6 and 3 respectively (Table 2). Furthermore, compound XVII had negligible side effects and low toxicity. The therapeutic and protective indexes of XVII greatly exceeded the corresponding indexes for zarontin and luminal.

Thus, compounds XIV, and XVI-XXVI, like the 2,4-disubstituted thienopyrimidines [1-3], possess anticorazole activity; the degree of anticonvulsant exhibited by these compounds is largely influenced by the character of the heterocyclic atom, and by the substituent at position 2. It should be noted that the presence of extra electron-donor groups at positions 2 and 3 in the pyrano- and thiopyranthieno pyrimidines leads to an increase in anticorazole activity.

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