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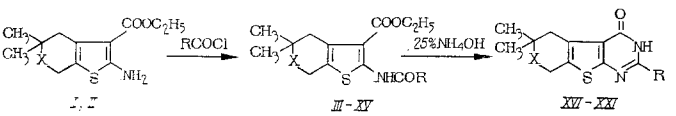
During recent years a systematic search has been carried out for new antispasmodic compounds in the condensed thieno[2,3-d]pyrimidine derivatives. The present work is a continuation of the previous studies in [1, 2] and is devoted to the synthesis of new 2-alkyl substituted pyrano(thiopyrano)[4', 3':4,5]thieno[2,3-d]pyrimidin-4-ones.

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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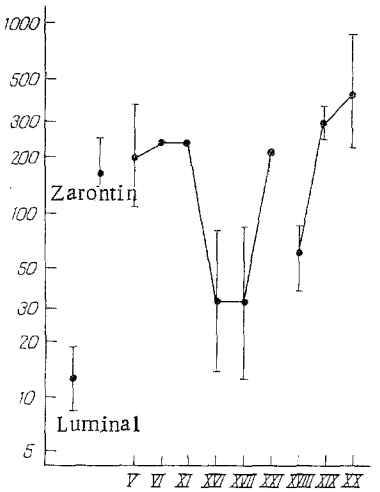

Fig. 1. Comparative anticorazole activity of 2-substituted thieno[2,3-d]pyrimidin-4-ones. The ED_{50} (mg/kg) is given on the ordinate in a logarithmic scale and compounds are shown on the abscissa.

[4] and the subcutaneous anticorazole test [5]. The central m-cholinolytic effect was studied in the prevention of arecoline tremor [6] and the n-cholinolytic action in protection from nicotine tremor [7]. In addition the appearance of "neurological deficit", an undesirable action of preparations, was determined. For this purpose procedures were used for "mice laying down on a grid" for recording the orientation reaction [8] and the "rotating rod" test of [9] for clarifying disturbed motor coordination. The daily toxicity in mice was also determined.

Substances were administered intraperitoneally in the form of a Tween-80 suspension. The emulsifying agent was administered to control animals. Statistical treatment of data was carried out by the probit analysis method of [10]. The known anticonvulsants luminal and zarontin were used as reference substances.

Study of the antispasmodic activity of nine of the indicated substances showed that at a dose of 200 mg/kg no substance gave a protective effect in relation to nicotine, arecoline, and electroshock. Their action in relation to corazole was displayed somewhat differently. It is evident from Fig. 1 that compounds (V, VI, XI) possessed insignificant antispasmodic activity. The presence of a pyrimidine ring in (XVI, XVII, XXI) led to a sharp growth in the effect for (XVI) and (XVII). The ED_{50} for these compounds was 32 (13.3-76.8) and 32 (12.3-83.2) mg/kg, respectively. However the addition of a coumaryl radical was accompanied once again by a weakening anticorazole action. In the series of thiopyranothieno[2,3-d]pyrimidines (XVIII-XX) the most marked antagonism of corazole was possessed by by compound (XVIII) the ED_{50} of which was 56 (30.7-84) mg/kg. An increase in the radical to C_4H_9 or C_5H_{11} led to a weakening of the antispasmodic action. The most effective among all the studied compounds (XVI-XVIII) differed statistically insignificantly from one another. In the anticorazole test they superseded zarontin [ED_{50} = 155 (117.5-204.5) mg/kg] but were superseded by luminal [ED_{50} = 12.5 (8.3-18.7) mg/kg] (see Fig. 1).

At doses of 700-2000 mg/kg the studied substances caused disturbances of motor coordination and depressed the orienting reaction in 100% animals. Death of all experimental mice was recorded at a dose of 1000 mg/kg for compounds (V, XVIII-XX) and at 2000-3000 mg/kg for compounds (XVI-XVII).

Thus substances have been discovered among the thienopyrans and thienothiopyrans condensed with pyrimidine which possess marked anticorazole activity. It should be recorded that the derivatives of thiopyranothieno[2,3-d]pyrimidin-4-one were somewhat more toxic than the pyranothieno[2,3-d]pyrimidin-4-ones.

EXPERIMENTAL CHEMISTRY

IR spectra were taken on a UR-20 instrument (East Germany) in Nujol mulls. PMR spectra were measured on a Varian T-60 (USA) instrument in chloroform, internal standard was TMS.

TABLE 1. Compounds (III-XV)

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	N	S		C	H	N	S
III	96,7	119—20	57,70	6,62	4,21	10,56	$C_{15}H_{21}NO_4S$	57,85	6,79	4,49	10,29
IV	65,0	138—9	59,00	7,20	4,16	10,10	$C_{16}H_{23}NO_4S$	59,05	7,12	4,30	9,85
V	67,8	107	60,08	7,23	3,87	9,65	$C_{17}H_{25}NO_4S$	60,15	7,42	4,12	9,44
VI	63,7	90	60,81	7,88	4,06	9,25	$C_{18}H_{27}NO_2S$	61,16	7,69	3,96	9,07
VII	69,7	82—3	55,21	6,42	4,50	19,74	$C_{15}H_{21}NO_3S_2$	55,02	6,46	4,27	19,58
VIII	88,8	68—70	56,13	6,67	3,99	18,40	$C_{16}H_{23}NO_3S_2$	56,27	6,78	4,09	18,77
IX	85,4	64—5	57,09	7,20	3,79	18,16	$C_{17}H_{25}NO_3S_2$	57,43	7,08	3,93	18,03
X	82,4	48—9	58,75	7,51	3,84	17,48	$C_{18}H_{27}NO_3S_2$	58,50	7,36	3,78	17,35
XI	53,4	175	63,23	5,55	3,80	8,26	$C_{21}H_{21}NO_5S$	63,14	5,29	3,50	8,02
XII	90,1	56	56,30	6,86	4,37	19,10	$C_{16}H_{23}NO_3S_2$	56,27	6,78	4,09	18,77
XIII	94,2	154	64,27	6,67	3,50	7,59	$C_{23}H_{29}NO_5S$	64,01	6,73	3,24	7,42
XIV	90,6	141—43	60,48	7,54	4,33	9,73	$C_{17}H_{25}NO_4S$	60,15	7,42	4,12	9,44
XV	75,0	64—5	64,80	8,86	3,16	8,00	$C_{22}H_{35}NO_4S$	64,51	8,61	3,41	7,82

TABLE 2. Compounds (XVI-XXI)

Compound	Yield, %	mp, °C	Empirical formula				Empirical formula	Calculated, %			
			C	H	N	S		C	H	N	S
XVI	51,5	239	61,50	6,76	9,68	10,80	$C_{15}H_{20}N_2O_2S$	61,61	6,89	9,57	10,96
XVII	51,3	212	62,83	7,10	8,97	10,55	$C_{16}H_{22}N_2O_2S$	62,70	7,23	9,14	10,46
XVIII	46,6	262—3	56,65	6,76	9,33	20,89	$C_{14}H_{18}N_2OS_2$	56,72	6,80	9,44	21,63
XIX	64,9	243—4	58,50	6,71	9,24	20,65	$C_{15}H_{20}N_2OS_2$	58,40	6,53	9,08	20,79
XX	71,5	230—1	59,74	6,73	8,56	19,90	$C_{16}H_{22}N_2OS_2$	59,59	6,87	8,68	19,88
XXI	59,0	232—3	64,60	4,36	7,88	9,27	$C_{19}H_{16}N_2O_3S$	64,75	4,57	7,79	9,09

The value of signals is given on the δ scale. TLC was carried out on Silufol-254 (Czechoslovakia) plates.

2-Substituted 3-Carbethoxy-5,5-dimethyl-4,5-dihydro-7H-thieno[2,3-c]pyranes(thiopyranes) (III-XV). Compound (I) or (II) (0.01 mole) was dissolved in dry dioxane (30 ml). After adding acid chloride (0.01 mole) the mixture was boiled for 3 h, cooled, and poured into cold water (150 ml). The crystals were filtered off, washed with water, cold ether, and dried. Constants are shown in Table 1.

IR spectrum, ν_{max}, cm^{-1}: IV 1660 (NCO), 1680 (COO), 3280-3200 (NH), PMR spectrum ($CDCl_3$), δ, ppm: IV 1.00 t (3 H, CH_3), 1.30 s (6H-$2CH_2$), 1.43 s (3H-OCH_2CH_3), 1.85 s (2H-CH_2), 2.46 s (2H-$CH_3C{=}O$), 2.75 s [2H$(CH_3)_2C{-}CH_2$], 4.33 s (2H-OCH_2CH_3), 4.66 s (2H-CH_2O), 11.26 s (1H-NH).

IR spectrum, ν_{max}, cm^{-1}: III, V-XV 1688-1665 (NCO), 1715-1690 (COO), 3250-3220 (NH).

PMR spectrum ($CDCl_3$), δ, ppm: V 0.80-2.00 m [16H-$(CH_3)_4$, $(CH_2)_2$]; VI 0.80-2.00 m [18H-$(CH_3)_4$, $(CH_2)_3$]; VII 0.80-2.00 m [12H-$(CH_3)_4$], 2.40 t (2H-CH_2); VIII 0.80-2.00 m [12H-$(CH_3)_4$]; IX 0.80-2.00 m [16H-$(CH_3)_4$, $(CH_2)_2$]; X 0.80-2.00 m [18H-$(CH_3)_4$, $(CH_2)_3$].

The chemical shifts of the remaining protons were practically indistinguishable from those of compound (IV).

Mass spectrum m/z (I rel.) XI 399(25), 398(100), 384(5), 370(5), 354(6), 353(6), 352(9), 343(11), 341(17), 342(60), 325(7), 324(33), 295(18), 270(8), 269(35), 254(16), 241(22), 146(9), 145(75).

2-Alkyl-4-oxo-6,6-dimethyl-5,6-dihydro-8H-pyrano(thiopyrano)[4',3':4,5]thieno[2,3-d]-pyrimidines (XVI-XXI). A mixture of (V) (or VI, VIII-XI) (0.01 mole) in 25% methanolic ammonia solution (50 ml) was heated at 100-120°C in a metal bomb for 18 h. The bomb was cooled to −10°C, opened, and the contents poured into an equal volume of ether. The precipitated crystals were filtered off, washed with ether, and with ethanol. The white crystals were dried in a vacuum desiccator. Compounds (XVI-XXI) were obtained. Constants are shown in Table 2.

IR spectrum, ν_{max}, cm^{-1}: XVI–XXI 1620-1610 (C=N), 1680-1660 (NC=O) 3110-3180 (NH); XXI 1590 (C=C).

PMR spectrum ($CDCl_3$), δ, ppm: XVI 0.80-2.00 m [13H-$(CH_3)_3$, $(CH_2)_2$], 2.80 t (2H-CH_2), 3.00 t (2H-CH_2), 4.80 t (2H-CH_2O); XVII 0.70-2.00 m [15H-$(CH_3)_3$, $(CH_2)_3$]; XVIII 1.00-2.00 m [11H-$(CH_3)_3$, CH_2]; XIX 1.00-2.00 m [13H-$(CH_3)_3$, $(CH_2)_2$]; XX 1.00-2.02 m [15H-$CH_3)_3$, $(CH_2)_3$].

PMR spectrum (CF_3COOD), δ, ppm: XXI 1.60 s (6H, $2CH_3$), 2.95 t (2H, CH_2), 5.03 t (2H-CH_2O), 7.35-7.90 m (5H-5CH).

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