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SYNTHESIS AND ANTISPASMODIC ACTIVITY OF 4-ALKYL(ARYL)AMINO-6,6-DIMETHYL-5,6-DIHYDRO-8H-PYRANO(THIOPYRANO) [3.4-b]THIENO[5.4-d]-PYRIMIDINES

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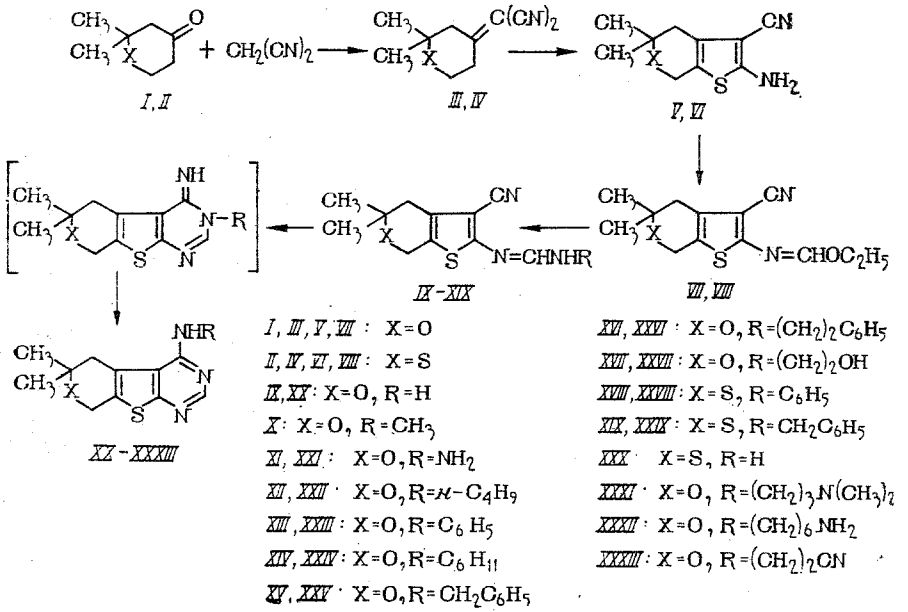
Certain derivatives of condensed thiophene systems are interesting as potential pharmacologically active compounds [1, 2]. The present work describes the synthesis of condensed pyrano(thiopyrano)[3.4-b]thieno[5.4-d]pyrimidines and the study of their antispasmodic activity.

Dinitriles of 2,2-dimethyl-4-tetrahydropyranylidene(thiopyranylidene)malonic acid (III, IV) are obtained by condensing 2,2-dimethyltetrahydropyran- or 2,2-dimethyltetrahydrothiopyran-4-one (I, II) with malonitrile.



The IR spectra of III and IV contain absorption bands in the 1590 (C—C), and 2250 (CN) cm^{-1} regions, The structure of these compounds was also confirmed by PMR spectra: δ (2-$(CH_3)_2$) = 1.2 ppm, δ (3-CH_2) = 2.78 ppm, and δ (6-CH_2) = 2.91 ppm. Their reaction with sulfur leads

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TABLE 1. 2-Alkyl(aryl)aminomethyleneamino-3-cyano-5,5-dimethyltetrahydropyrano(thiopyrano)[3.4-b]thiophenes

Compound	Yield, %	Melting Point, °C	Found, %		Empirical formula	Calculated, %	
			N	S		N	S
IX	77,7	172	17,66	13,74	$C_{11}H_{13}N_3OS$	17,85	13,62
X	87,8	118—9	16,51	12,80	$C_{12}H_{15}N_3OS$	16,85	12,85
XI	50,0	160—1	22,29	12,82	$C_{11}H_{14}N_4OS$	22,38	12,80
XII	72,9	89—90	14,58	11,17	$C_{15}H_{21}N_3OS$	14,42	11,00
XIII	52,9	132—4	13,50	10,31	$C_{17}H_{17}N_3OS$	13,49	10,29
XIV	43,9	142—3	12,54	10,21	$C_{17}H_{23}N_3OS$	12,92	10,09
XV	57,6	128—9	12,78	9,73	$C_{18}H_{19}N_3OS$	12,91	9,84
XVI	40,4	125—6	12,78	9,11	$C_{19}H_{21}N_3OS$	12,37	9,44
XVII	71,9	82—4	15,21	11,64	$C_{13}H_{17}N_3OS$	15,04	11,47
XVIII	45,8	181—2	12,66	19,50	$C_{17}H_{17}N_3S_2$	12,83	19,61
XIX	52,1	106—7	12,40	18,92	$C_{18}H_{19}N_3S_2$	12,30	18,77

TABLE 2. 4-Alkyl(aryl)-6,6-dimethyl-5,6-dihydro-8H-pyrano(thiopyrano)[3.4-b]thieno[5.4-d]pyrimidines

Compound	Yield, %	Melting* point, °C	Found, %		Empirical formula	Calculated, %	
			N	S		N	S
XX	82,0	212—2	17,66	13,74	$C_{11}H_{13}N_3OS$	17,85	13,62
XXI	83,3	266—8	22,33	12,86	$C_{11}H_{14}N_4OS$	22,38	12,80
XXII	86,3	100—2	14,58	11,14	$C_{15}H_{21}N_3OS$	14,42	11,00
XXIII	71,4	162—2,5	13,53	10,20	$C_{17}H_{17}N_3OS$	13,49	10,29
XXIV	43,9	142—3	12,94	10,50	$C_{17}H_{23}N_3OS$	12,92	10,09
XXV	73,3	94—5,5	12,93	10,01	$C_{18}H_{19}N_3OS$	12,91	9,84
XXVI	85,0	161,5—3	13,07	10,00	$C_{19}H_{21}N_3OS$	12,37	9,44
XXVII	80,0	109—11	15,14	11,60	$C_{13}H_{17}N_3O_2S$	15,04	11,47
XXVIII	51,0	130—2	12,71	19,63	$C_{17}H_{17}N_3S_2$	12,83	12,61
XXIX	50,0	96—7	12,39	18,84	$C_{18}H_{19}N_3S_2$	12,30	18,70
XXX	76,0	172—4	16,69	25,81	$C_{11}H_{13}N_3S_2$	16,71	25,50
XXXI	40,8	130	17,63	10,13	$C_{16}H_{24}N_4OS$	17,51	10,00
XXXII	50,6	202—2,5	17,19	9,76	$C_{17}H_{26}N_4OS$	16,75	9,58
XXXIII	65,6	217—8	19,38	11,20	$C_{14}H_{16}N_4OS$	19,43	11,11

*XXXI: bp 250-252°C (6 mm), hydrochloride: mp 175-177°C.
XXXII: hydrochloride: mp 243-244°C.

to the formation of 2-amino-3-cyano-5,5-dimethyltetrahydropyrano(thiopyrano)[3.4-b]thiophane (V, VI).

The IR spectra of V and VI contain absorption bands in the 2220 cm^{-1} region (CN). In the 3200-3500 cm^{-1} region there are three absorption bands corresponding to the NH_2 groups. PMR spectra: δ (5-$(CH_3)_2$) = 1.25 ppm, δ (4-CH_2) = 2.7 ppm, δ (7-CH_2) = 3.7 ppm, and δ (NH_2) = 4.85 ppm.

The reaction of V and VI with the orthoformic acid ester in the presence of acetic anhydride yielded the corresponding 2-ethoxy-methyleneamino-3-cyano-5,5-dimethyltetrahydropyrano(thiopyrano)[3.4-b]thiophenes (VII, VIII). The IR spectra of these compounds contain absorption bands in the 1630 (C=N) and 2230 (CN) cm^{-1} regions. PMR spectra: δ (CH_2CH_3) = 1.47, 4.42 ppm, δ (2=CH) = 8.0 ppm; the chemical shifts of the remaining protons are almost the same as in the spectra of V and VI.

The condensation of compound VII with ammonia and hydrazine, and also of VII and VIII with primary amines, yielded the corresponding 2-alkyl(aryl)aminomethyleneamino-3-cyano-5,5-dimethyltetrahydropyrano(thiopyrano)[3.4-b]thiophenes (IX-XIX) (Table 1). In the IR spectra of the latter, absorption bands in the 1630 (C=N), 2225 (CN), and 3100-3350 (NH) cm^{-1} region were found. The PMR spectra of these compounds contain a singlet of the =CH group proton at 8.4 ppm.

When they are heated in alcohol in the presence of sodium ethoxide, compounds IX-XIX undergo cyclization into the corresponding intermediate amines, which during the reaction isomerize into the more stable 4-alkyl(aryl)amino-6,6-dimethyl-5,5-dihydro-8H-pyrano(thiopyrano)[3.4-b]thieno[5.4-d]pyrimidines (XX-XXXIII) (Table 2). The actual formation of 4-alkyl(aryl)amino derivatives XX-XXXIII is confirmed by the fact that when they are boiled in an alkaline or acidic medium, the compounds do not change and are reversibly recovered [3]. It should be noted that under these conditions, compound X does not undergo cyclization, but resinification occurs.

In the IR spectra of compounds XX-XXIX absorption bands at 1630 (C-N) and 3100-3400 (NH) cm^{-1} were found, and in the spectrum of XXXIII at 2225 (CN) cm^{-1}. In the 3100-3300 cm^{-1} region, compounds XX, XXI, XXX, and XXXII give three absorption bands corresponding to the NH_2 groups. In the PMR spectra: δ ($CH_2C_6H_5$) = 4.92 ppm and δ (=CH) = 8.42 ppm; XXIII: δ (C_6H_5) = 7.2 ppm and δ (=CH) = 8.42 ppm; XXII: δ (=CH) 9.42 ppm; XXVI: δ (CH_2CH_2) = 3.18, 4.19 ppm and δ (=CH) = 8.42 ppm; XXXIII: δ (CH_2CH_2) = 2.73, 4.43 ppm, and δ (=CH) = 7.87 ppm; the chemical shifts of the remaining protons are practically the same as in the spectra of V and VI. In all compounds XX-XXXIII, the hydrogen atoms of the NH= and NH_2 groups in the 4-position can be subjected to deuterium exchange. Compound XX was also obtained by the reaction of V with formamide. Compound XXX was similarly obtained from VI.

During the reaction of VII with γ-dimethylaminopropylamine, 1,6-hexamethylenediamine, and β-cyanoethylamine, cyclization occurs with the formation of XXXI-XXXIII.

EXPERIMENTAL

Pharmacological

The antispasmodic effects of pyranothiophene derivatives were studied on mice weighing 18-20 g from the antagonism to Corazole at its subcutaneous administration [4] and from the degree of prevention of a tonic extension during maximal electrical shock [5]. The central m- and n-cholinolytic properties were evaluated from the degree of prevention of arecoline tremor during the subcutaneous administration of arecoline, as well as from the degree of protection against tonic spasms caused by intraperitoneal administration of nicotine. All the compounds were introduced in a dose of 200 mg/kg intraperitoneally, in suspension with Tween-80. The effective 50% doses (ED_{50}) and their confidence intervals were calculated.

As the result of the study of the antispasmodic properties of compounds XX-XXXII, we found that compounds XX-XXII, and XXXII in a dose of 200 mg/kg partially prevent the Corazole and nicotine induced spasms. The most active compound was XX, whose ED_{50} in a Corazole test was equal to 220 (157.1-308.0 mg/kg), and in protection against nicotine induced spasms 240 (182.2-302.1) mg/kg. The compounds studied had weak antispasmodic properties with reference to maximal electrical shocks and arecoline tremor. It was only when compound XX was introduced in a dose of 200 mg/kg that protection against tonic extension was observed in 40% of the animals.

Thus, from our studies we concluded that compound XX has more marked antispasmodic properties and a broader spectrum of activity than XXI, XXII, and XXXII.

Chemical

The IR spectra of the compounds were run in Vaseline oil on a UR-20 spectrometer with NaCl and ZiCl prisms. The PMR spectra were measured on the Varian T-60 apparatus, in CCl_4 and $CdCl_3$ with TMS as the internal standard. The values of the signals are listed in the δ scale.

2,2-Dimethyl-4-tetrahydropyranylidene(thiopyranylidene)malonic Acid Dinitriles (III, IV). A mixture of 0.5 mole of I or II, 0.5 mole of malononitrile, 1 ml of glacial acetic acid and 2 ml of diethylamine is boiled for 5 h in 100 ml of dry benzene until the complete removal of water. When cool, the mixture is washed with water and dried over magnesium sulfate. When the solvent has been removed, the product is distilled *in vacuo*. Yield of III, 62.4%, mp 36-38°C (from nonane). Found, %: C 68.41; H 6.95; N 8.13. $C_{10}H_{12}N_2O$. Calculated, %: C 68.18; H 6.82; N 7.95. Yield of IV, 72.3%, mp 34-35°C (from nonane). Found, %: 14.67; S 16.93. $C_{10}H_{12}N_2S$. Calculated, %: C 14.56; S 16.67.

2-Amino-3-cyano-5,5-dimethyltetrahydropyrano(thiopyrano)[3.4-b]thiophenes (V, VI). Method A. A mixture of 0.1 mole of III or IV, and 0.1 mole of powdered sulfur in 100 ml of 96% ethanol is heated, with stirring, to 50°C, and 10 ml of diethylamine are added during 30 min. The temperature is then raised to 60°C, and the mixture is stirred until the sulfur is completely dissolved. The mixture is cooled, and then poured into 200 ml of cold water and acidified with 18% hydrochloric acid (to Congo Red). The precipitate is separated and washed first with water and then with heptane. The material thus completely crystallizes. The crystals are filtered, washed twice with heptane, and dried in a vacuum-exsiccator. Yield of V, 83.0%, mp 109-111°C (from ethanol). Found, %: N 13.42; S 15.29. $C_{10}H_{12}N_2OS$. Calculated, %: N 13.46; S 15.38. Yield of VI, 91.7%, mp 97-98°C (from a 1:2 ethyl acetate–heptane mixture). Found, %: N 12.39; S 28.55. $C_{10}H_{12}N_2S_2$. Calculated, %: N 12.50; S 28.57.

Method B. A suspension of 0.1 mole of I or II, 0.1 mole of malononitrile, 0.1 mole of powdered sulfur in 80 ml of 90% ethanol is heated to 50°C, and a solution of 5 ml of diethylamine in 10 ml of ethanol is added dropwise, with stirring, during 30 min. The temperature is raised to 60°C. The preparation is then completed as in method A. Yield of V, 62.4%, mp 109-111°C (from ethanol). Yield of VI 89.3%, mp 97-98°C (from a 1:2 ethyl acetate–heptane mixture).

2-Ethoxymethyleneamino-3-cyano-5,5-dimethyltetrahydropyrano-(thiopyrano)[3.4-b]thiophenes (VII, VIII). A 0.5 ml portion of acetic anhydride is added to a solution of 10 g (0.048 mole) of V or VI in 30 ml of orthoformic acid ester, and the mixture is boiled for 2 h. The excess of orthoformic acid ester is removed under reduced pressure, and a thick precipitate crystallizes after the addition of petroleum ether. The crystals are filtered, washed with petroleum ether, and dried. Yield of VII, 89.0%, mp 66.67°C (from an alcohol–petroleum ether mixture). Found, %: N 10.69; S 12.29. $C_{13}H_{16}N_2O_2S$. Calculated, %: N 10.60; S 12.12. Yield of VIII, 85.7%, mp 65-66°C (from an alcohol–petroleum ether mixture). Found, %: N 11.26; S 13.06. $C_{13}H_{16}N_2OS_2$. Calculated, %: N 11.29; S 12.90.

2-Alkyl(aryl)aminomethyleneamino-3-cyano-5,5-dimethyltetrahydropyrano(thiopyrano[3.4-b]-thiophenes (IX-XIX). A 0.1 mole portion of a primary amine (ammonia or methylamine is passed as a gas), or hydrazine hydrate is added to 0.1 mole of VII or VIII, in 30 ml ethanol, and the mixture is boiled for 1.2 h. When cool, the alcohol is distilled, and the crystals are washed with cold ethanol and dried in a vacuum exsiccator. The constants are given in Table 1.

4-Alkyl(aryl)amino-6,6-dimethyl-5,6-dihydro-8H-pyrano(thiopyrano)[3.4-b]thieno[5.4-d] pyrimidines (XX-XXIX). A 0.01 mole portion of IX-XIX is added to sodium ethoxide obtained from 40 ml of ethanol and 0.12 g-atom of metallic sodium, and the mixture is boiled for 1 h. When cool, the precipitate is filtered, washed with water and cold ethanol, and dried. The constants are given in Table 2.

4-Amino-6,6-dimethyl-5,6-dihydro-8H-pyrano(thiopyrano)[3.4-b]-thieno[5.4-d]pyrimidines (XX, XXX). A mixture of 0.01 mole of V or VI and 15 ml of freshly distilled formamide is boiled for 4 h, and then left to stand overnight. The crystals which form are filtered, washed with water and ether, and dried. Yield of XX, 82.1%, mp 211-212°C (from ethanol). Yield of XXX 76.0%, mp 172-174°C (from ethyl acetate). Found, %: N 16.69; S 12.81. $C_{11}H_{13}N_3S_2$. Calculated, %: N 16.71; S 12.75.

4- Alkylamino-6,6-dimethyl-5,6-dihydro-8H-pyrano(thiopyrano)[3.4-b]thieno[5.4-d] pyrimidines (XXXI-XXXIII). A 0.1 mole portion of β-cyanoethylamine (or γ-dimethylaminopropylamine or 1,6-hexamethylenediamine) is added to a mixture of 0.1 mole of VII and 30 ml of ethanol, and the mixture is boiled for 90 min. When cool, the alcohol is distilled off, and the crystals are washed with cold alcohol and dried. Compound XXXIII crystallizes after distillation *in vacuo*. The constants are given in Table 2.

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