TABLE 2. Substituted 4-Amino-2-styrylquinazolines

Compound	Starting substances	Yield, %	Melting point, °C*	Empirical formula of salt	Melting point of salt, °C
IIIc	Ie + IIa	48	—†	$C_{25}H_{30}Cl_2N_4 \cdot 2H_3PO_4$	249—50
IIId	Ie + IIc	52	149—50	$C_{22}H_{30}Cl_2N_4 \cdot 2H_3PO_4$	237—8
IIIe	Ib + IIa	66	118—9	$C_{20}H_{19}Cl_2N_3 \cdot HCl \cdot H_2O$	245—6
IIIf	Ib + IIb	55	160—1	$C_{20}H_{19}ClN_4O_2 \cdot HCl$	267—8
IIIg	Ic + IIb	42	242—3	$C_{22}H_{15}ClN_4O_2$ ‡	—
IIIh	Id + IIa	52	148—9	$C_{21}H_{19}Cl_2N_3 \cdot HCl$	271—2
IIIi	Id + IIb	59	174—5	$C_{21}H_{19}ClN_4O_2 \cdot HCl$	274—5
IIIj	Ie + IIe	28	—†	$C_{26}H_{33}ClN_4O_2 \cdot 2H_3PO_4 \cdot 3H_2O$	238—40
IIIk	Ia + IIc	42	—†	$C_{25}H_{31}ClN_4 \cdot 2HCl$	240—1
IIIl	Ia + IIb	45	—†	$C_{23}H_{31}N_5O_2 \cdot HCl \cdot 1.5H_2O$	269—70

*Compound (IIId) was crystallized from cyclohexane, (IIIe) from methyl alcohol, (IIIf, h) from absolute ethyl alcohol, (IIIg) from ethyl acetate, (IIIi) from a mixture of equal volumes of absolute alcohol and ethyl acetate.
†Compounds were isolated only as salts.
‡Obtained as the base.

layer chromatography on aluminum oxide or silufol [one spot for substance (III) in the absence of spots of side products and starting compounds (I)].

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SYNTHESIS AND ANTICONVULSIVE ACTIVITY OF DERIVATIVES OF CONDENSED 1,4-DIAZEPINE SYSTEMS

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Thieno-1,4-diazepines possess anticonvulsive, muscle relaxing, and hyposedative properties [1]. The aim of the present work was the synthesis of condensed six-membered sulfur and oxygen-containing heterocycles with thienadiazepines.

By condensing 2,2-dimethyltetrahydropyran- and 2,2-dimethyltetrahydrothiopyran-4-ones (I, II) with substituted ω-cyanoacetophenones and sulfur in ethyl alcohol in the presence of diethylamine the corresponding substituted 5,5-dimethyl-7H,4,5-dihydropyrano(thiopyrano)[3,4-b]-2-amino-3-benzoylthiophenes (IIIa-f) were obtained.

By the interaction of (IIIa-f) with chloroacetyl chloride N-substituted derivatives (IVa-f) were obtained which were converted in chloroform by the action of gaseous ammonia into the corresponding substituted 5,5-dimethyl-7H,4,5-dihydropyrano(thiopyrano)[2,4-b]-2-aminoacetylamino-1-benzoylthiophenes (Va-f).

On heating in benzene compounds (V) cyclized with the formation of the corresponding 2-keto-5-aryl-7,7-dimethyl-1H,9H,2,3,6,7-tetrahydropyrano(thiopyrano)[4',3'-:4,5]thieno[2,3-e]-1,4-diazepines (VIa-f).

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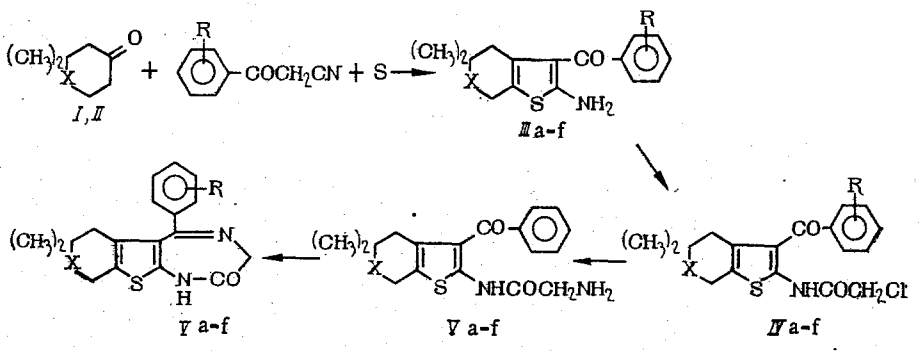

I X=O;
II X=S;
a X=O, R=H;
b X=S, R=o-Cl
c X=O, R=o-Cl
d X=O, R= p-Br;
e X=O, R=o-Br;
f X=O, R=m-NO_2.

EXPERIMENTAL

Pharmacological

The anticonvulsive properties of the derivatives of the condensed 1,4-diazepine system (VIa-f) were studied in 250 mice of weight 18-22 g. The anticonvulsive activity of substances was judged according to their ability to protect animals from clonic spasm on subcutaneous injection of Corazole [2] and the tonic extensor component at maximal electroshock [3]. The central m and n cholinolytic action of preparations was assessed according to their ability to prevent arecoline tremor and nicotine convulsions. Substances were injected intraperitoneally at a dose of 200 mg/kg as a suspension in Tween 80.

Compounds (VI) did not prevent the actions of maximal electroshock and of arecoline. In addition protection from Corazole and nicotine spasm was recorded after injecting them in 40% of cases. Compound (VIa) was the the most active and gave an anticonvulsive effect against these types of spasm in 50% of cases. On injecting (VIb) at a dose of 200 mg/kg, toxic properties of the substance were detected and as a result the pharmacological effect of (VIb) was studied at a dose of 100 μg/kg.

Thus the introduction of chloro and nitro groups into the benzene ring leads to a weakening of the anticonvulsive action and introduction of bromine into the same ring is accompanied by an increase in toxicity.

Chemical

IR spectra of compounds as suspensions in Vaseline oil were taken on a UR-20 spectrophotometer with sodium chloride and lithium chloride prisms. PMR spectra were measured on a Varian T-60 instrument in deuterochloroform and carbon tetrachloride with tetramethylsilane as internal standard. Values of signals are given on a δ scale.

Substituted 5,5-Dimethyl-7H,4,5-dihydropyrano(thiopyrano)[3,4-b]-amino-3-benzoylthiophenes (IIIa-f). A mixture of (I) or (II) (0.1 mole), substituted ω-cyanoacetophenone (0.1 mole), and powdered sulfur (0.1 mole) in 96% ethanol (120 ml) was heated to 50°C and a mixture of morpholine (5 ml), diethylamine (3 ml), and ethanol (10 ml) was added dropwise with stirring during 30 min. The temperature was raised to 60°C and the mixture was stirred until complete solution of sulfur. After cooling in ice-water the mix was poured into cold water (200 ml) and acidified (to Congo paper) with 18% hydrochloric acid. The precipitate was removed, washed with methanol, and dried in a vacuum desiccator. Constants are given in Table 1.

The IR spectra of (IIIa-f) and (Va-f) contained three absorption bands for amino groups in the 3150-2450 cm^{-1} region. Stretching vibrations of a carbonyl group conjugated with an aromatic ring appeared in the 1680-1700 cm^{-1} region in the case of compounds (IIIa-f). The structures of (IIIa-f) were also confirmed with the aid of PMR spectra δ, ppm: $(CH_3)_2$ 1.03, 3-CH_2 1.77, 6-CH_2 4.47, NH_2 6.87, C_6H_4 7.18.

TABLE 1. Compounds (III)-(VI)

Compound	Yield, %	Melting point, °C	Found, %		Empirical formula	Calculated, %	
			N	S		N	S
IIIa	40,6	121—3	4,65	10,90	$C_{16}H_{17}NO_2S$	4,87	11,15
IIIb	45,8	141—2	4,26	18,60	$C_{16}H_{16}ClNOS_2$	4,15	18,98
IIIc	66,1	133—5	4,30	9,91	$C_{16}H_{16}ClNO_2S$	4,35	9,96
IIId	50,9	175—7	3,86	8,84	$C_{16}H_{16}BrNO_2S$	3,82	8,75
IIIe	49,8	189—91	8,76	10,00	$C_{16}H_{16}N_2O_4S$	8,42	9,64
IIIf	46,0	146—8	3,88	8,66	$C_{16}H_{16}BrNO_2S$	3,82	8,75
IVa	71,4	184—6	3,77	8,89	$C_{18}H_{18}ClNO_3S$	3,84	8,81
IVb	82,3	161—3	3,27	15,66	$C_{18}H_{17}Cl_2NO_2S_2$	3,37	15,47
IVc	67,9	148—50	3,43	8,33	$C_{18}H_{17}Cl_2NO_3S$	3,51	8,04
IVd	78,1	222—4	3,09	7,56	$C_{18}H_{17}BrClNO_3S$	3,16	7,24
IVe	52,9	202—4	7,45	7,79	$C_{18}H_{17}N_2O_5S$	6,86	7,84
IVf	68,3	164—5	3,21	7,19	$C_{18}H_{17}BrClNO_3S$	3,16	7,24
Va	94,4	179—80	8,69	9,35	$C_{18}H_{20}N_2O_3S$	8,13	9,30
Vb	84,8	131—2	7,23	16,43	$C_{18}H_{19}ClN_2O_2S_2$	7,08	16,23
Vc	75,5	109—10	7,29	8,38	$C_{18}H_{19}ClN_2O_3S$	7,39	8,46
Vd	88,9	95—7	6,66	7,59	$C_{18}H_{19}BrN_2O_3S$	6,61	7,57
Ve	76,8	168—70	10,58	8,15	$C_{18}H_{19}N_3O_5S$	10,79	8,23
Vf	81,2	143—4	6,53	7,46	$C_{18}H_{19}BrN_2O_3S$	6,61	7,57
VIa	60,0	177—9	8,40	10,02	$C_{18}H_{18}N_2O_2S$	8,58	9,82
VIb	51,4	308—10 (charred)	6,97	16,96	$C_{18}H_{17}ClN_2OS_2$	7,44	17,01
VIc	44,4	156—8	7,56	8,49	$C_{18}H_{17}ClN_2O_2S$	7,77	8,88
VId	43,6	229—31	7,15	7,84	$C_{18}H_{17}BrN_2O_2S$	6,91	7,91
VIe	73,8	220—2	10,92	8,30	$C_{18}H_{17}N_3O_4S$	10,81	8,25
VIf	55,6	286—8	6,96	7,42	$C_{18}H_{17}BrN_2O_2S$	6,91	7,91

Substituted 5,5-Dimethyl-7H,4,5-dihydropyrano(thiopyrano)[3,4-b]-2-chloroacetylamino-3-benzoylthiophenes (IVa-f). To a solution of (IIIa-f) (0.01 mole) in dry chloroform (30 ml) was added chloroacetyl chloride (0.01 mole) and the mixture was boiled for 2 h. After evaporating the solvent the product was crystallized from ethyl alcohol (see Table 1). IR spectrum: ν_{NH} 3200 cm^{-1}. The PMR spectrum contained sharp singlets, δ ppm: $CONH_2$ 4.33, NHCO 9.2.

Substituted 5,5-Dimethyl-7H,4,5-dihydropyrano(thiopyrano)[3,4-b]-2-aminoacetylamino-3-benzoylthiophenes (Va-f). Gaseous ammonia was passed for 2 h into a stirred mixture of (IVa-f) (0.01 mole) and chloroform cooled in ice and then for 2 h more at room temperature. After washing the mixture with aqueous sodium bicarbonate solution the organic layer was separated and dried over magnesium sulfate. After removal of chloroform the substance was crystallized (see Table 1). The PMR spectrum contained sharp singlets, δ ppm: $CONH_2$ 4.33, NHCO 9.2, and a a signal for the NH_2 group was observed at 4.41-6.5 ppm. Chemical shifts of the remaining signals were practically unchanged from the chemical shifts of the corresponding absorptions in spectra (IIIa-f).

2-Keto-5-aryl-7,7-dimethyl-1H,9H,2,3,6,7-tetrahydro-9H-pyrano(thiopyrano)[4',3'-4,5]-thieno[2,3-e]-1,4-diazepines (VIa-f). A mixture of (IVa-f) (0.01 mole), pyridine (40 ml), and glacial acetic acid (0.01 mole), in benzene (20 ml) was heated to remove water completely. After removal of benzene, pyridine, and acetic acid, water (50 ml) was added to the residue which was washed with sodium bicarbonate. The residue was extracted with chloroform and dried over magnesium sulfate. After removal of solvent the substance was crystallized by dissolving it in petroleum ether and recrystallization from alcohol. Constants are given in Table 1.

Absorption bands were found in the IR spectra of (VIa-f) of ν, cm^{-1}: C_6H_4 1600, CO 1630, C=N 1660, NH 3100. The structures of these compounds were also confirmed by PMR spectra, δ ppm: CONH 9.89, $COCH_2$ 3.66. The chemical shifts of the remaining signals were practically unchanged from the chemical shifts of the corresponding absorption in the spectra of (IIIa-f).

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