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SYNTHESIS AND NEUROTROPIC ACTIVITY OF NEW PYRIMIDO[4′,5′:4,5]THIENO[2,3-*b*]QUINOLINE DERIVATIVES

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New methods for preparing pyrimido[4′,5′:4,5]thieno[2,3-*b*]quinoline derivatives based on 3-cyanohexahydro-2-quinoline were developed. The neurotropic activity of these compounds was studied.

Keywords: synthesis, pyrimido[4′,5′:4,5]thieno[2,3-*b*]quinoline; neurotropic activity.

As derivatives of condensed thieno- and furopyridines have valuable biological properties [1 – 3], there is interest in studying the properties of analogous derivatives containing the tetrahydroquinoline ring. With this aim we developed an accessible synthesis method based on 3-cyanohexahydro-2-quinoline (I) [4]. Boiling of this compound in phosphorus oxychloride led to synthesis of 2-chloro derivative II, interaction of which with thioglycolic acid ethyl ester yielded the amino ester of condensed thieno[2,3-*b*]pyridine III. Use of the Niementowski reaction by heating with formamide led to formation of a pyrimidine ring (compound IV). The effects of the nature of the substituents in positions 3 and 4 on the biological activity of the resulting compounds were assessed by chlorodehydroxylation with phosphorus oxychloride followed by substitution of the chlorine with various amines. On the other hand, condensed pyrimidinones were alkylated, with substitution in position 3, the resulting compounds lacking the absorption band characteristic of the NH group but retaining the band characteristic of the C=O group at 1670 cm^{-1}.

Hydrolysis of amino ester III with aqueous sodium hydroxide solution was used to synthesize the corresponding amino acid VIII, boiling of which in acetic anhydride produced condensed oxazine IX.

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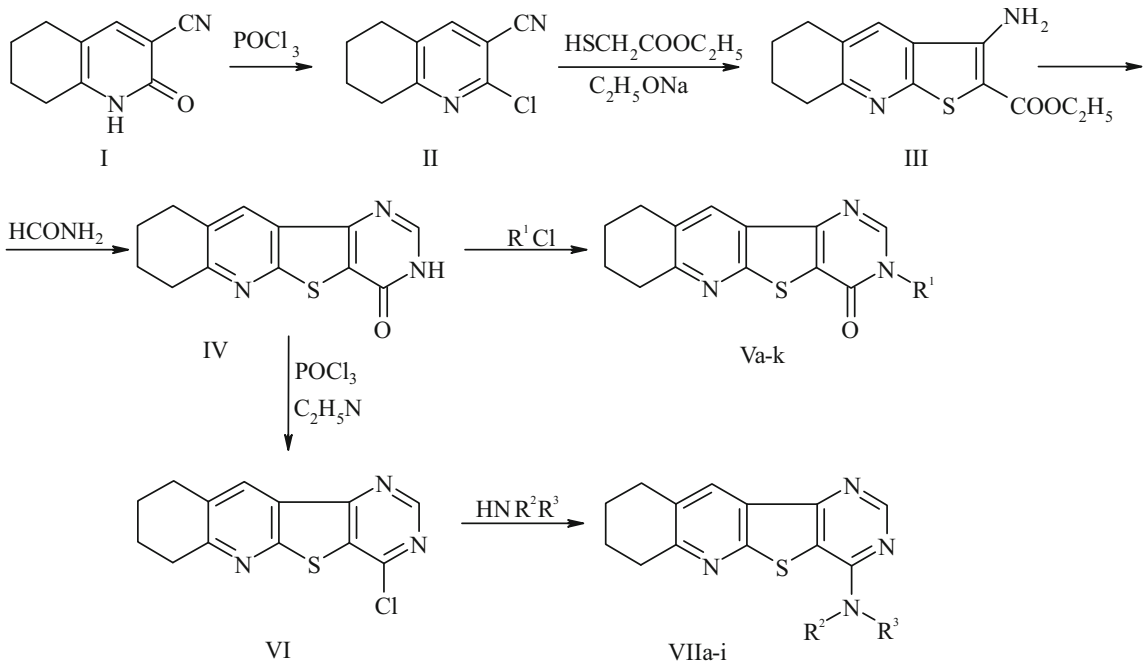
EXPERIMENTAL CHEMICAL SECTION

IR spectra were taken on a UR-20 spectrometer in Vaseline grease. PMR spectra were taken on a Mercury-300 spectrometer in DMSO-d_6. TLC was run on Silufol UV-254 plates run in systems consisting of ethyl acetate and petroleum ether (1:2) (II, III), pyridine and butanol (1:3) (IV, V, VIII, IX); and chloroform and ether (1:3) (VI, VII); plates were developed in iodine vapor. Found values for elemental analyses corresponded to atomic formulas.

2-Chloro-3-cyano-5,6,7,8-tetrahydroquinoline (II). A mixture of 1.74 g (0.01 mol) of compound I and 35 ml of phosphorus oxychloride was heated in a boiling water bath for 8 h. Excess phosphorus oxychloride was then evaporated in vacuo and the residue was alkalinized with aqueous sodium hydroxide with cooling using iced water; the resulting crystalline precipitate was collected by filtration, washed with water, and dried. The yield was 1.6 g (85.6%) and the melting temperature was 136 – 137°C (ethanol). R_f was 0.75. The atomic formula was $C_{10}H_9ClN_2$. The IR spectrum, ν_{max}, cm^{-1}, was: 1580, 1620 (arom.), 2240 (CN). The PMR spectrum, ppm, was: 1.84 – 2.02 (m, 4H, CH_2CH_2), 2.98-3.07 (m, 4H, 5-CH_2 and 8-CH_2), 7.73 (s, 1H, CH).

Ethyl-3-amino-5,6,7,8-tetrahydrothieno-[2,3-*b*]quinoline-2-carboxylate (III). Sodium ethylate prepared from 0.23 g (0.01 mol) of metallic sodium and 25 ml of absolute ethanol was supplemented by dropwise addition of 1.2 ml of thioglycolic acid ethyl ester and 1.92 g (0.01 mol) of compound II with mixing. The reaction mix was boiled with mixing for 6 h. Solvent was then evaporated, water was added, and the crystalline precipitate was collected by filtration. The



V, a: $R^1 = -C_5H_{11}i$; b: $R^1 = -CH_2COOCH_3$; c: $R^1 = -CH_2-C(=CH_2)-CH_3$; d: $R^1 = -(CH_2)_2-OCH_3$;

e: $R^1 = -CH_2-C(=O)-NH_2$; f: $R^1 = -CH_2-C_6H_5$; g: $R^1 = -CH_2-C(=O)-NH-C_6H_4-CH_3$;

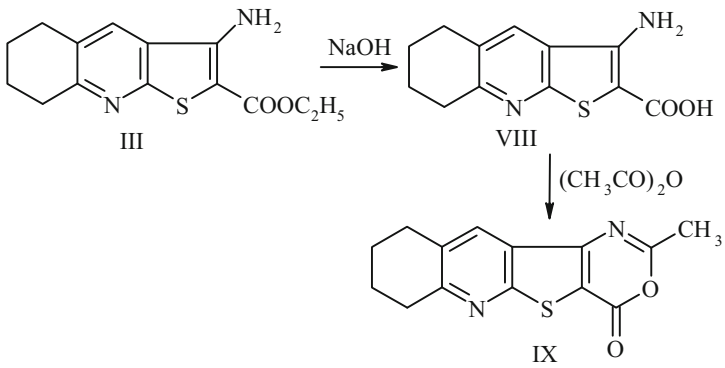
h: $R^1 = -CH_2-C(=O)-NH-C_6H_3(OCH_3)-CH_3O$; i: $R^1 = -CH_2-C(=O)-NH-C_6H_4-CH_3$;

j: $R^1 = -CH_2-C(=O)-NH-C_6H_4-OCH_3$; k: $R^1 = -CH_2-C(=O)-NH-CH(Ph)_2$;

VII, a: $R^2 = H$, $R^3 = -C_4H_9i$; b: $R^2 = H$, $R^3 = -C_6H_{13}$; c: $R^2 = H$, $R^3 = NH_2$;

d: $R^2 = H$, $R^3 = -(CH_2)_2-N(C_2H_5)_2$; e: $R^2 = H$, $R^3 = -C_6H_{13}$; f: $NR^2R^3 = -N$(C5H10);

g: $NR^2R^3 = -N$(C4H8O); h: $R^2 = H$, $R^3 = -(CH_2)_2-C_6H_5$; i: $R^2 = H$, $R^3 = -CH_2C_6H_5$.



yield was 1.6 g (59.5%) and the melting temperature was 238 – 239°C (ethanol). R_f was 0.63. the atomic formula was $C_{14}H_{16}N_2O_2S$. The IR spectrum, ν_{max}, cm^{-1}, was: 1540, 1580 (arom.); 1680 (C=O); 3180, 3280, 3410 (NH_2). The PMR spectrum, ppm, was: 1.41 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$),1.84 – 2.02 (m, 4H, CH_2CH_2), 2.97 – 3.06 (m, 4H, 5-CH_2 and 8-CH_2), 4.28 (q, 2H, J 7.1 Hz, $O\underline{CH_2}CH_3$), 5.83 (s, 2H, NH_2), 7.98 (s, 1H, CH).

3,4,7,8,9,10-Hexahydropyrimido[4′,5′:4,5]thieno[2,3-*b*]-quinolin-4-one (IV). A mixture of 2.76 g (0.01 mol) of compound III and 20 ml of formamide was heated at 195-200°C for 3 h. The reaction was then cooled, crystals were collected by filtration, washed with water and ethanol, and dried. The yield was 1.8 g (69.8%) and the melting temperature was 333-334°C (ethanol). R_f was 0.52. the atomic formula was $C_{13}H_{11}N_3OS$. The IR spectrum, ν_{max}, cm^{-1}, was: 1550, 1600, 1620 (arom., C=C, C=N); 1680 (C=O); 3110 (NH). The PMR spectrum, ppm, was: 1.84 – 2.01 (m, 4H, CH_2CH_2), 2.94 – 3.04 (m, 4H, 7-CH_2 and 10-CH_2), 8.21 (t, 1H, J 1.0 Hz, 11-CH), 8.33 (s, 1H, N=CH), 12.90 (m, 1H, NH).

3-(3-Methylbutyl)-3,4,7,8,9,10-hexahydropyrimido-[4′,5′:4,5]thieno[2,3-*b*]quinolin-4-one (Va). A mixture of 2.57 g (0.01 molecule) of compound IV, 1.7 g (0.012 mol) of potash, and 10 ml of absolute DMF was boiled for 0.5 h. After cooling, the mixture was supplemented by dropwise addition of 1.28 g (0.012 mol) of isopentyl chloride and boiled for 1 h. After cooling, the mixture was supplemented with iced water and the resulting crystalline precipitate was collected by filtration, washed with water and ether, and dried. The yield was 2.3 g (61.2%) and the melting temperature was 151-152°C (ethanol). R_f was 0.57. The atomic formula was $C_{18}H_{21}N_3OS$. The IR spectrum, ν_{max}, cm^{-1}, was: Va-k: 1550, 1575, 1590 (arom., C=C, C=N conj.). The PMR spectrum, ppm, was: 1.02 (d, 6H, J 6.2 Hz, $CH(\underline{CH_3})_2$), 1.63-1.78 (m, 3H, $CHCH_2$),1.86 – 2.02 (m, 4H, CH_2CH_2), 2.96-3.08 (m, 7-CH_2 and 10-CH_2), 4.05 – 4.11 (m, 2H, NCH_2), 8.16 (t, 1H, J 1.0 Hz, 11-CH), 8.43 (s, 1H, N=CH). Compounds Vb-k were prepared by an analogous method (Table 1). PMR spectra, ppm, were: **Vb**: 1.86-2.03 (m, 4H, CH_2CH_2), 2.97-3.08 (m, 4H, 7-CH_2 and 10-CH_2), 3.79 (s, 3H, OCH_3), 4.91 (s, 2H, NCH_2), 8.20 (t, 2H, J 1.0 Hz, 11-CH), 8.48 (s, 1H, N=CH), **Vc**: 1.83 (broad s, 3H, CH_3), 1.86-2.03 (m, 4H, CH_2CH_2), 2.97 – 3.08 (m, 4H, 7-CH_2 and 10-CH_2), 4.65 (broad s, 2H, NCH_2), 4.76 – 4.78 and 4.94 – 4.96 (m, 1H and 1H, $=CH_2$), 8.17 (t, 1H, J 1.0 Hz, 11-CH), 8.34 (s, 1H, N=CH), **Vd**: 1.86 – 2.03 (m, 4H, CH_2CH_2), 2.97 – 3.08 (m, 4H, 7-CH_2 and 10-CH_2), 3.32 (s, 3H, CH_3), 3.68 (t, 2H, J 5.1 Hz, OCH_2), 4.25 (t, 2H, J 5.1 Hz, N=CH_2), 8.17 (t, 1H, J 1.0 Hz, 11-CH), 8.31 (s, 1H, N=CH), **Ve**: 1.86 – 2.03 (m, 4H, CH_2CH_2), 2.97 – 3.08 (m, 4H, 7-CH_2 and 10-CH_2), 4.71 (s, 2H, NCH_2), 7.10 (broad, 1H) and 7.65 (broad, 1H, NH_2), 8.20 (t, 1H, J 1.0 Hz, 11-CH), 8.37 (s, 1H, N=CH), **Vf**: 1.86 – 2.02 (m, 4H, CH_2CH_2), 2.96 – 3.07 (m, 4H, 7-CH_2 and 10-CH_2), 5.29 (s, 2H, NCH_2), 7.24 – 7.36 (m, 3H) and 7.42 – 7.47 (m, 2H, C_6H_5), 8.16 (t, 1H, J 1.0 Hz, 11-CH), 8.61 (s, 1H, N=CH), **Vg**: 1.85 – 2.02 (m, 4H, CH_2CH_2), 2.30 (s, 3H, CH_3), 2.97 – 3.07 (m, 4H, 7-CH_2 and 10-CH_2), 4.92 (s, 2H, NCH_2), 7.03 – 7.09 and 7.45 – 7.50 (m, 2H-2H, C_6H_4), 8.23 (t, 1H, J 1.0 Hz, 11-CH), 8.49 (s, 1H, N=CH), 10.23 (broad, 1H, NH), **Vh**: 1.86 – 2.02 (m, 4H, CH_2CH_2), 2.97 – 3.07 (m, 4H, 7-CH_2 and 10-CH_2), 3.77 (s, 3H, *n*-OCH_3) and 3.90 (s, 3H, *o*-OCH_3), 5.00 (s, 2H, NCH_2), 6.41 (dd, 1H, J_1 8.8, J_2 2.6 Hz, =CH), 6.54 (d, 1H, J 2.6 Hz, NHC=CH$\underline{CH}$), 7.83 (d, 1H, J 8.8 Hz, NHC=$\underline{CH}$), 8.23 (t, 1H, J 1.0 Hz, 11-CH), 8.47 (broad s, 1H, N=CH), 9.43 (broad, 1H, NH), **Vi**: 1.87-2.03 (m, 4H, CH_2CH_2), 2.33 (s, 3H, CH_3), 2.98-3.08 (m, 4H, 7-CH_2 and 10-CH_2), 4.93 (s, 2H, NCH_2), 6.80 – 7.46 (m, 4H, C_6H_4), 8.22 (t, 1H, J 1.0 Hz, 11-CH), 8.46 (s, 1H, N=CH), 10.19 (broad, 1H, NH), **Vj**: 1.87 – 2.03 (m, 4H, CH_2CH_2), 2.98 – 3.08 (m, 4H, 7-CH_2 and 10-CH_2), 3.76 (s, 3H, OCH_3), 4.91 (s, 2H, NCH_2), 6.77 – 6.82 (m, 2H) and 7.49 – 7.54 (m, 2H, C_6H_4), 8.22 (t, 1H, J 1.0 Hz, 11-CH), 8.46 (s, 1H, N=CH), 10.15 (broad, 1H, NH), **Vk**: 1.87 – 2.03 (m, 4H, CH_2CH_2), 2.97-3.08 (m, 4H, 7-CH_2 and 10-CH_2), 4.86 (s, 2H, NCH_2), 6.17 (d, 1H, J 8.5 Hz, NH$\underline{CH}$), 7.21 – 7.36 (m, 10H, $2C_6H_5$), 8.21 (t, 1H, J 1.0 Hz, 11-CH), 8.42 (s, 1H, N=CH), 9.19 (d, 1H, J 8.5 Hz, NH).

4-Chloro-7,8,9,10-hexahydropyrimido[4′,5′:4,5]thieno-[2,3-*b*]quinoline (VI). A mixture of 2.57 g (0.01 mol) of compound IV, 2 ml of absolute pyridine, and 30 ml of phosphorus oxychloride was heated for 3 h at 95-100°C. Excess phosphorus oxychloride was evaporated in vacuo and the residue was supplemented by dropwise addition of 20 ml of iced water with cooling. The mixture was then neutralized

TABLE 1. Properties of Compounds Vb-k, VIIb-i

Compound	Yield, %	mp, °C	R_f	Atomic formula
Vb	59.9	199 – 200	0.56	$C_{16}H_{15}N_3O_3S$
Vc	61.2	146 – 147	0.58	$C_{17}H_{17}N_3OS$
Vd	62.3	162 – 163	0.61	$C_{16}H_{17}N_3O_2S$
Ve	75.3	333 – 334	0.55	$C_{15}H_{14}N_4O_2S$
Vf	69.3	158 – 159	0.59	$C_{20}H_{17}N_3OS$
Vg	68.2	319 – 320	0.57	$C_{22}H_{20}N_4O_2S$
Vh	68.4	283 – 284	0.55	$C_{23}H_{22}N_4O_4S$
Vi	69.2	223 – 224	0.59	$C_{22}H_{20}N_4O_2S$
Vj	71.1	304 – 305	0.58	$C_{22}H_{19}N_4O_3S$
Vk	69.9	242 – 243	0.54	$C_{28}H_{24}N_4O_2S$
VIIb	58.9	156 – 157	0.63	$C_{19}H_{24}N_4S$
VIIc	65.3	191 – 192	0.52	$C_{13}H_{13}N_5S$
VIId	54.3	210 – 211	0.54	$C_{19}H_{25}N_5S$
VIIe	63.2	241 – 242	0.61	$C_{19}H_{22}N_4S$
VIIf	68.7	161 – 162	0.63	$C_{18}H_{20}N_4S$
VIIg	69.3	148 – 149	0.64	$C_{17}H_{18}N_4OS$
VIIh	71.1	218 – 219	0.62	$C_{21}H_{20}N_4S$
VIIi	69.8	271 – 272	0.61	$C_{20}H_{18}N_3S$

* Recrystallized from ethanol

with aqueous ammonia solution and the resulting crystalline precipitate was collected by filtration, washed with water, and dried. The yield was 1.8 g (65.7%) and the melting temperature was 132 – 133°C (ethanol). R_f was 0.63. The atomic formula was $C_{13}H_{10}ClN_3S$. The IR spectrum, ν_{max}, cm^{-1}, was: 1520, 1560, 1600 (arom., C=C, C=N). The PMR spectrum, ppm, was: 1.87-2.04 (m, 4H, CH_2CH_2), 2.99-3.11 (m, 4H, 7-CH_2 and 10-CH_2, 8.39 (t, 1H, J 1.0 Hz, 11-CH), 9.0 (s, 1H, N=CH).

***N*-4-Isobutyl(7,8,9,10-hexahydropyrimido[4′,5′:4,5]-thieno[2,3-*b*]quinolin-4-yl)amine (VIIa).** A mixture of 2.76 g (0.01 mol) of compound VI, 1.44 g (0.02 mol) of isobutylamine, and 50 ml of absolute ethanol was boiled for 6 h. Solvent was then evaporated in vacuo and the residue was supplemented with 20 ml of water and the resulting crystalline precipitate was collected by filtration, washed with water, and dried. The yield was 1.8 g (58.1%) and the melting temperature was 223 – 224°C (ethanol). R_f was 0.56. The atomic formula was $C_{17}H_{20}N_4S$. IR spectra, ν_{max}, cm^{-1}, were: **VIIa-i**: 1520, 1560, 1600 (arom., C=C, C=N); 3220 (NH); **VIIc**: 3150, 3300 (NH-NH_2). The PMR spectrum, ppm, was: 0.98 (d, 6H, J 6.7 Hz,$(CH_3)_2$), 1.86 – 2.02 (m, 4H, CH_2CH_2), 1.98 – 2.12 (m, 1H, $\underline{CH}(CH_3)_2$), 2.97 – 3.07 (m, 4H, 7-CH_2 and 10-CH_2), 3.36 (dd, 2H, J 7.0, 5.8 Hz, NCH_2), 7.48 (t, 1H, J 5.8 Hz, NH), 8.22 (t, 1H, J 1.0 Hz, 11-CH), 8.40 (s, 1H, N=CH). Compounds IVb-i were prepared by an analogous method (Table 1). PMR spectra, ppm, were: **VIIb**: 0.91 (t, 3H, J 6.8 Hz, CH_3), 1.29 – 1.44 (m, 6H, $(\underline{CH_2})_3CH_3$), 1.59 – 1.70 (m, 2H,$NHCH_2\underline{CH_2}$), 1.85 – 2.01 (m, 4H, CH_2CH_2), 2.96 – 3.05(m, 4H, 7-CH_2 and 10-CH_2), 3.47 – 3.54 (m, 2H, NCH_2),7.42 (t, 1H, J 5.5 Hz, NH), 8.20 (t, 1H, J 1.0 Hz, 11-CH), 8.40 (s, 1H, N=CH), **VIIc**: 1.84 – 2.01 (m, 4H, CH_2CH_2), 2.95 – 3.05 (m, 4H, 7-CH_2 and 10-CH_2), 4.72 (broad, 2H, NH_2), 8.21 (t, 1H, J 1.0 Hz, 11-CH), 8.33 (s, 1H, N=CH), 8.87 (broad, 1H, NH), **VIId**: 1.05 (t, 6H, $N(CH_2\underline{CH_3})_2$), 1.86-2.02 (m, 4H, CH_2CH_2), 2.60-3.06 (m, 10H, 7-CH_2, 10-CH_2, NCH_2 and $N(\underline{CH_2}CH_3)_2$), 3.62 (qu, 2H, J 6.5 Hz, $NHCH_2$),8.22 (t, 1H, J 1.0 Hz, 11-CH), 8.46 (s, 1H, N=CH), **VIIe**: 1.16-1.29 (m, 1H, C_6H_{11}), 1.32 – 1.51 (m, 4H, C_6H_{11}), 1.67-2.03 (m, 9H, CH_2CH_2 and C_6H_{11}), 2.97 – 3.06 (m, 4H, 7-CH_2 and 10-CH_2), 4.09 – 4.21 (m, 1H, $NH\underline{CH}$), 7.12 (d, 1H, J 7.9 Hz, NH), 8.21 (broad s, 1H, 11-CH), 8.39 (s, 1H, N=CH), **VIIf**: 1.70 – 1.82 (m, 6H, $CH_2CH_2CH_2$), 1.86 – 2.03 (m, 4H, CH_2CH_2), 2.98 – 3.07 (m, 4H, 7-CH_2 and 10-CH_2), 3.92 – 3.97 (m, 4H, CH_2-N-CH_2), 8.25 (t, 1H, J 1.0 Hz, 11-CH), 8.47 (s, 1H, N=CH), **VIIg**: 1.86 – 2.03 (m, 4H, CH_2CH_2), 2.98 – 3.08 (m, 4H, 7-CH_2 and 10-CH_2), 3.78 – 3.82 (m, 4H) and 3.93-3.97 (m, 4H, C_4H_8NO), 8.27 (t, 1H, J 1.0 Hz, 11-CH), 8.53 (s, 1H, N=CH), **VIIh**: 1.86 – 2.02 (m, 4H, $\underline{CH_2}CH_2$), 2.95 – 3.07 (m, 6H, $\underline{CH_2}CH_2$ and $\underline{CH_2}C_6H_5$), 3.72 – 3.81 (m, 2H, NCH_2),7.12 – 7.19 (m, 1H) and 7.22 – 7.28 (m, 4H, C_6H_5), 7.60 (t, 1H, J 5.7 Hz, NH), 8.23 (t, 1H, J 1.0 Hz, 11-CH), 8.47 (s, 1H, N=CH), **VIIi**: 1.86 – 2.02 (m, 4H, CH_2CH_2), 2.96 – 3.07 (m, 4H, 7-CH_2 and 10-CH_2), 5.31 (s, 2H, NCH_2), 7.19 – 7.32 (m, 3H, H-3.4.5 C_6H_5), 7.43 – 7.47 (m, 2H, H-2,6 C_6H_5), 8.22 (t, 1H, J 1.0 Hz, 11-CH), 8.47 (s, 1H, N=CH).

3-Amino-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-2-carboxylic acid (VIII). A mixture of 2.76 g (0.01 mol) of compound III and 50 ml of 5% aqueous sodium hydroxide solution was boiled for 4 h. After cooling, the mixture was supplemented with acetic acid to pH 6. The resulting crystalline precipitate was collected by filtration, washed with water and ethanol, and dried. The yield was 1.5 g (61.4%) and the melting temperature was 162 – 163°C (ethanol). R_f was 0.50. The atomic formula was $C_{12}H_{12}N_2O_2S$. The IR spectrum, ν_{max}, cm^{-1}, was: 1560, 1590, 1610 (arom.), 1660 (C=O), 3200, 3340, 3430 (NH_2, OH). The PMR spectrum, ppm, was: 1.84-2.02 (m, 4H, CH_2CH_2), 2.96 – 3.06 (m, 4H, 5-CH_2 and 8-CH_2), 6.81 (broad, 2H, NH_2), 11.22 (broad, 1H, OH).

2-Methyl-7,8,9,10-tetrahydrothieno-4*H*-[1,3]oxazino-[4′,5′:4,5]thieno[2,3-*b*]quinolin-4-one (IX). A mixture of 2.48 g (0.01 mol) of compound VIII and 20 ml of acetic anhydride was boiled for 1 h. The reaction mix was cooled and the resulting crystalline precipitate was collected by filtration, washed with ether and water, and dried. The yield was 1.5 g (59.4%) and the melting temperature was 190-191°C (ethanol). R_f was 0.62. The atomic formula was $C_{14}H_{12}N_2O_2S$. The IR spectrum ν_{max}, cm^{-1}, was: 1560, 1590, 1620 (arom., C=C, C=N), 1750 (C=O, lactone). The PMR

TABLE 2. Comparative Anticorasol and Exploratory Activity of Compounds Vb, VIIa, and Diazepam

Compound	Corasol antagonism (ED_{50}, mg/kg)	Number of		
		horizontal movements	vertical movements	cell sniffings
Control for compounds (emulsifer)		21 *(17.3 – 24.7)	5.3 (3.03 – 7.57)	4.2 (3.0 – 5.4)
Vb	36 *(24.0 – 54.0)	27 (19.4 – 34.6)	6.5 (2.2 – 10.08)	2.4 (1.1 – 3.7)
VIIa	41 (22.5 – 74.6)	9.3 (3.4 – 15.2)	3.2 (2.8 – 3.6)	–
Control for diazepam (emulsifier)		18.6 (13.7 – 23.5)	1.1 (0.7 – 1.5)	2.1 (1.0 – 3.2)
Diazepam	0.5 (0.4 – 0.7)	33.6 (29.4 – 37.8)	6.4 (5.4 – 7.4)	5.0 (3.7 – 6.3)

* Significance interval at a probability level of $p = 0.05$.

spectrum, ppm, was: 1.84 – 2.01 (m, 4H, CH_2CH_2), 2.55 (s, 3H, CH_3), 2.94 – 3.04 (m, 4H, 7-CH_2 and 10-CH_2), 8.21 (t, 1H, J 1.0 Hz, 11-CH), 8.32 (s, 1H, N=CH).

EXPERIMENTAL BIOLOGICAL SECTION

Experiments were performed using 185 white mice weighing 18 – 24 g and 40 rats weighing 120 – 130 g of both genders. Studies of anticonvulsant activity were performed for 17 compounds – VIIa-c, g, h, f and Va-h. The anticonvulsant activity of compounds was assessed in terms of the prevention of the clonic component of convulsions elicited in mice by s.c. administration of corasol (90 mg/kg), with replacement by clonic twitches or the complete absence of convulsions. Undesirable side effects in these animals – a central myorelaxant effect and impairment to motor coordination – were studied using a "rotating bar" method [5, 6]. These tests and the doses of each compound, monitoring, and comparison with diazepam were performed in five experiments.

The sedative, arousing, and anxiolytic actions of the most active compounds, i.e., Vc and VIIa, as well as diazepam, were assessed in terms of motor and exploratory behavior in rats using a modified open field model. An apparatus with a floor divided into squares with openings ("cells") was used. Experiments were performed in the daytime with natural illumination. Indicators of sedation and aroused behavior were assessed during the 5 min of the test, i.e., the number of horizontal movements (square crossings) and rearings onto the hindlimbs (vertical displacements), along with measures of anxiolytic behavior – sniffing of cells – in the experimental and control groups of animals [7 – 9]. Eight experiments with this model were run with each compound, with controls for compounds, and separate controls for diazepam. Open field experiments were run on different days for study compounds and diazepam. Results were compared with the corresponding controls.

The reference agent was the known anxiolytic diazepam, which was given i.p. to mice at doses of 0.1, 0.3, and 1 mg/kg and to rats at a dose of 2 mg/kg. Control animals received emulsifier. Results were analyzed statistically. ED_{50} values were determined for the anticonvulsant effect with the arithmetic mean and significant intervals for study compounds, and differences were identified at a probability level of $p = 0.05$. Study compounds and diazepam were given i.p. as suspensions with tween-80 and methylcarboxycellulose 45 min before administration of corasol to mice and the beginning of open field tests in rats.

Analysis of results on anticonvulsant activity in mice showed that all the new condensed derivatives (VIIa-c, g, h, f and Va-h) at the test dose of 50 mg/kg had some degree of anticorasol activity, apparent as protection from convulsions in 10 – 40% of animals. However, the most active compounds were Va, b and VIIa. These compounds at a dose of 50 mg/kg protected 60% of experimental mice from clonic corasol convulsions (ED_{50} values were 36 mg/kg for Vb, 41 mg/kg for VIIa, and 41 (22.5 – 74.6) mg for Va). Reference agent diazepam displayed 50% anticorasol activity in mice at a dose of 0.5 mg/kg (Table 2).

Undesirable side effects – impairments to motor coordination and myorelaxation – were not seen with study compounds at a dose of 50 mg/kg.

In open field experiments, rats given emulsifier (control for test compounds and diazepam) produced around 18.6 – 21.0 horizontal movements, 1.1 – 5.3 vertical movements, and 2.1 – 4.2 cell sniffing reactions. Comparison of the effects of the most active compounds, Vb and VIIa, at a dose of 50 mg/kg, with diazepam showed low levels of both horizontal and vertical movement activity and cell sniffing intensity. Thus, values for compound Vb were 27, 6.5, and 2.4 respectively, and showed statistically minor differences from control values, i.e., evidencing sedative and depressive effects.

Thus, a number of new condensed hexahydropyrimidoquinolinones (VIIa and Va, b) were found to have neurotropic properties. The new compounds, although less active than diazepam, were able to prevent clonic corasol convulsions in animals although, in contrast to the tranquilizer diazepam, sedative effects were seen in the complex open field model. Analysis of these results indicates that the nature of the radicals did not have any significant influence on the activity of the compounds. It should be emphasized that like the reference tranquilizer, the new substances did not elicit central myorelaxation at the anticonvulsive doses used. These data suggest that these agents have potential as hypnosedatives rather than activatory tranquilizers, emphasizing the potential for further studies of the spectrum of neurotropic activity in this new series of compounds.

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