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SYNTHESIS AND ANTICONVULSIVE ACTIVITY OF 7-AMINO-SUBSTITUTED CYCLOPENTA[4′,5′]-PYRIDO[3′,2′:4,5]FURO[3,2-*d*]PYRIMIDINES

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Methods for the synthesis of new cyclopenta[4′,5′]pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidine derivatives based on 3-oxo-derivatives of cyclopenta[*c*]pyridines were developed. O-alkylated derivatives of these latter compounds were cyclized to furo[2,3-*b*]pyridines, which were converted to furo[3,2-*d*]pyrimidin-7-ones with formamide. Subsequent chlorination and amination of 7-oxo derivatives yielded 7-amino derivatives. The anticonvulsive and predicted tranquillizer activities of the compounds synthesized here were assessed. Compounds with anticonvulsant properties were identified.

Keywords: furo[3,2-*d*]pyrimidines, cyclopenta[*c*]pyridines, synthesis, cyclization, amino derivatives, anticonvulsive activity.

Condensed furo[3,2-*d*]pyrimidines have high levels of biological activity [1 – 7]. The aim of the present work was to seek new biologically active compounds of this series. We have previously reported the synthesis of condensed furo[3,2-*d*]pyrimidines based on pyrano[3,4-*c*]pyridines and 5,6,7,8-tetrahydroisoquinolines [8, 9]. The starting compounds in the present studies were 3-oxo derivatives of cyclopenta[*c*]pyridines I, which were converted to the corresponding O-alkylated derivatives II by interaction with chloroacetic acid ethyl ester. Cyclization of the latter compounds to form furo[2,3-*b*]pyridines III occurs only in the presence of sodium ethylate in absolute ethanol (99.95%). Compounds with two active functional groups in the furan ring were prepared via cyclization by condensation with formamide. Overall, this led to synthesis of condensed furo[3,2-*d*]pyrimidin-7-ones IV, which were converted to the corresponding chloro derivatives V using phosphorus oxychloride. Further reaction of chlorides V with various amines led to the target 7-amino derivatives VI. Biological testing of these compounds showed that many have anticonvulsive activity.

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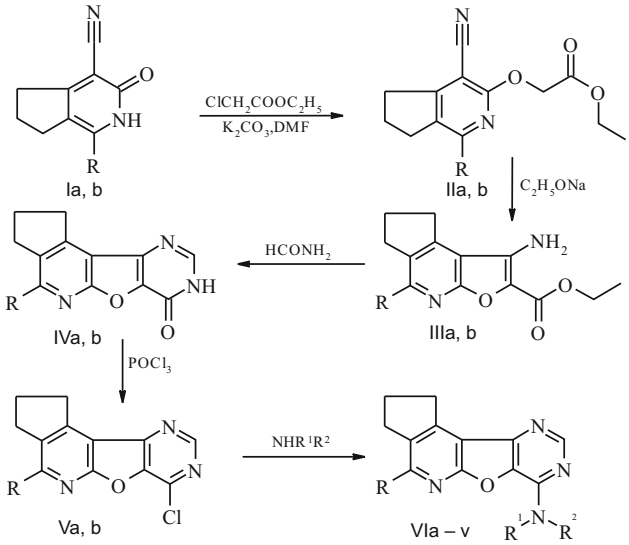
EXPERIMENTAL CHEMICAL SECTION

IR spectra were taken on a Nicolet Avatar 330 spectrometer in Vaseline grease. PMR spectra were obtained on a Mercury 300 instrument in DMSO-d_6. TLC was performed using Silufol UV-254 plates in the following solvent systems: ethanol-chloroform 1:3 (II, IIIa, b); chloroform-pyridine 3:1 (IV, Va, b); chloroform:ethanol 1:3 (VIa-v); detection was with iodine vapor. Elemental analysis results were consistent with atomic formulae.

Ethyl-2-(6,7-dihydro-1-isopropyl(isobutyl)-4-cyano-5*H*-cyclpenta[*c*]pyridin-3-yloxy)acetate IIa (IIb) (general method). Chloroacetic acid ethyl ester (13.48 g, 0.11 mol) was added dropwise with mixing to a suspension of 0.1 mol of cyclopenta[*c*]pyridine Ia (Ib) and 15 g (0.11 mol) of potash in 150 ml of dry DMF. The temperature of the reaction mix was maintained at 75 – 80°C for 2 h; the mix was cooled to room temperature and poured into cold water. The resulting crystals were collected by filtration, washed with water, dried, and recrystallized from ethanol (Table 1).

IR spectra, ν_{max}, cm^{-1}, were: **IIa** (IIb). 2220 (CN), 1750 (C=O). PMR spectra, δ, ppm, were: **IIa**: 1.16 (d, 6H, J 6.7 Hz, $CH(\underline{CH_3})_2$), 1.28 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 2.20 (quin, 2H, J 7.5 Hz, 6-CH_2), 2.89 (t, 2H, J 7.5 Hz, 7-CH_2),



I – Va: R = *i*-C_3H_7; b: R = *i*-C_4H_9; VIa: R = *i*-C_3H_7, $R^1 + R^2$ = -$(CH_2)_4$-; b: R = *i*-C_4H_9, $R^1 + R^2$ = -$(CH_2)_4$-; c: R = *i*-C_3H_7, $R^1 + R^2$ = -$(CH_2)_2O(CH_2)_2$-; d: R = *i*-C_4H_9, $R^1 + R^2$ = $(CH_2)_2O(CH_2)_2$-; e: R = *i*-C_3H_7; R^1 = H, R^2 = -CH_2CH_2OH; f: R = *i*-C_4H_9, R^1 = H, R^2 = -CH_2CH_2OH; g: R = *i*-C_3H_7; R^1 = H, R^2 = 2-methoxyethyl; h: R = *i*-C_4H_9; R^1 = H, R^2 = methoxyethyl; i: R = *i*-C_3H_7; R^1 = H, R^2 = $CH_2CH_2N(CH_3)_2$; j: R = *i*-C_4H_9; R^1 = H, R^2 = -$CH_2CH_2N(CH_3)_2$; k: R = *i*-C_3H_7; $R^1 + R^2$ = -$(CH_2)_2NCH_3(CH_2)_2$-; l: R = *i*-C_4H_9; $R^1 + R^2$ = -$(CH_2)_2NCH_3(CH_2)_2$-; m: : R = *i*-C_3H_7; R^1 = H, R^2 = -$CH_2CH_2CH_2OH$; n: R = *i*-C_4H_9; R^1 = H, R^2 = -$CH_2CH_2CH_2OH$; o: R = *i*-C_3H_7; R^1 = H, R^2 = -$CH_2CH(CH_3)OH$; p: R = *i*-C_4H_9; R^1 = H, R^2 = -$CH_2CH(CH_3)OH$; q: R = *i*-C_3H_7; R^1 = H, R^2 = 3-pyridylmethyl; r: R = *i*-C_4H_9; R^1 = H, R^2 = 3-pyridylmethyl; s: R = *i*-C_3H_7; R^1 = H, R^2 = 2-morpholinoethyl; t: R = *i*-C_4H_9; R^1 = H, R^2 = 2-morpholinoethyl; u: R = *i*-C_3H_7; R^1 = H, R^2 = 2-furylmethyl; v: R = *i*-C_4H_9; R^1 = H, R^2 = 2-furylmethyl.

3.00 (sp, 1H, J 6.7 Hz, $\underline{CH}(CH_3)_2$), 3.06 (t, 2H, J 7.5 Hz, 5-CH_2), 4.16 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 4.88 (s, 2H, OCH_2), **IIb**: 0.91 (d, 6H, J 6.6 Hz, $CH(\underline{CH_3})_2$), 1.27 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 2.10 (m, 1H, $\underline{CH}(CH_3)_2$), 2.18 (quin, 2H, J 7.5 Hz, 6-CH_2), 2.48 (d, 2H, J 7.1 Hz, $CH\underline{CH_2}$), 2.86 (t, 2H, J 7.5 Hz, 7-CH_2), 3.07 (t, 2H, J 7.5 Hz, 5-CH_2), 4.15 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 4.89 (s, 2H, OCH_2).

1-Amino-7,8-dihydro-5-isopropyl(isubutyl)-6*H*-cyclopenta[*d*]furo[2,3-*b*]pyridin-2-carbonic acid ethyl ester IIIa (IIIb) (general method). Compound IIa (IIb) (0.1 mol) was added to a solution of sodium ethylate prepared from 2.53 g (0.11 mol) of sodium and 300 ml of absolute ethanol. The mixture was boiled for 10 – 15 min, cooled, and poured onto ice. The resulting crystals were collected by filtration, washed with water, dried, and recrystallized from ethanol (Table 1).

IR spectra, ν_{max}, cm^{-1}, were: **IIIa (IIIb).** 3370, 3500 (NH_2), 1690 (C=O). PMR spectra, δ, ppm, were, **IIIa**: 1.25 (d, 6H, J 6.7 Hz, $CH(\underline{CH_3})_2$), 1.40 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 2.23 (quin, 2H, J 7.5 Hz, 7-CH_2), 2.93 (t, 2H, J 7.5 Hz, 6-CH_2), 3.11 (sp, 1H, J 6.7 Hz, $\underline{CH}(CH_3)_2$), 3.29 (t, 2H, J 7.5 Hz, 8-CH_2), 4.32 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 5.70 (broad, 2H, NH_2), **IIIb**: 0.95 (d, 6H, J 6.6 Hz, $CH(\underline{CH_3})_2$), 1.41 (t, 3H, J 7.1 Hz, $CH_2\underline{CH_3}$), 2.19 (m, 1H, $\underline{CH}(CH_3)_2$), 2.22 (quin, 2H, J 7.5 Hz, 7-CH_2), 2.60 (d, 2H, J 7.1 Hz, $CH\underline{CH_2}$), 2.90 (t, 2H, J 7.5 Hz, 6-CH_2), 3.29 (t, 2H, J 7.5 Hz, 8-CH_2), 4.33 (q, 2H, J 7.1 Hz, $\underline{CH_2}CH_3$), 5.70 (broad, 2H, NH_2).

4-Isopropyl(isobutyl)-2,3,7,8-tetrahydro-1*H*-cyclopenta[4′,5′]pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidin-7-one IVa (IVb) (general method). A mixture of 0.1 mol of compound IIIa (IIIb) and 200 ml of formamide was boiled for 4 h. After cooling, the resulting crystals were collected by filtration, washed with water, dried, and recrystallized from DMSO (Table 1).

IR spectra, ν_{max}, cm^{-1}, were: **IVa (IVb).** 3330 (NH), 1660 (CO). The PMR spectrum, δ, ppm, was, **IVa**: 1.31 (d, 6H, J 6.7 Hz, $CH(\underline{CH_3})_2$), 2.29 (quin, 2H, J 7.5 Hz, 2-CH_2), 3.02 (t, 2H, J 7.5 Hz, 3-CH_2), 3.20 (sp, 1H, J 6.7 Hz, $\underline{CH}(CH_3)_2$), 3.37 (t, 2H, J 7.5 Hz, 1-CH_2), 7.99 (2, 1H, 9-CH), 12.80 (broad, 1H, NH), **IVb**: 0.98 (d, 6H, J 6.6 Hz,

TABLE 1. Properties of Compounds II, III, IV, Va, b, VIa – v.

Compound	Yield, %	Melting temperature, °C	R_f	Atomic formula
IIa	87	89 – 91	0.62	$C_{16}H_{20}N_2O_3$
IIb	85	72 – 74	0.65	$C_{17}H_{22}N_2O_3$
IIIa	83	148 – 150	0.58	$C_{16}H_{20}N_2O_3$
IIIb	89	165 – 166	0.69	$C_{17}H_{22}N_2O_3$
IVa	78	348 – 350	0.72	$C_{15}H_{15}N_3O_2$
IVb	79	> 360	0.70	$C_{16}H_{17}N_3O_2$
Va	75	130 – 132	0.68	$C_{15}H_{14}ClN_3O$
Vb	76	131 – 133	0.64	$C_{16}H_{16}ClN_3O$
VIa	81	223 – 224	0.68	$C_{19}H_{22}N_4O$
VIb	86	204 – 205	0.59	$C_{20}H_{24}N_4O$
VIc	76	208 – 210	0.61	$C_{19}H_{22}N_4O_2$
VId	81	170 – 172	0.58	$C_{20}H_{24}N_4O_2$
VIe	83	202 – 203	0.49	$C_{17}H_{20}N_4O_2$
VIf	85	214 – 215	0.50	$C_{18}H_{22}N_4O_2$
VIg	73	138 – 140	0.58	$C_{18}H_{22}N_4O_2$
VIh	91	128 – 130	0.56	$C_{19}H_{24}N_4O_2$
VIi	84	136 – 138	0.64	$C_{19}H_{25}N_5O$
VIj	78	122 – 124	0.67	$C_{20}H_{27}N_5O$
VIk	81	179 – 181	0.72	$C_{20}H_{25}N_5O$
VIl	93	160 – 161	0.58	$C_{21}H_{27}N_5O$
VIm	85	206 – 208	0.61	$C_{18}H_{22}N_4O_2$
VIn	89	196 – 198	0.52	$C_{19}H_{24}N_4O_2$
VIo	76	194 – 195	0.69	$C_{18}H_{22}N_4O_2$
VIp	90	117 – 118	0.70	$C_{19}H_{24}N_4O_2$
VIq	89	218 – 219	0.51	$C_{21}H_{21}N_5O$
VIr	76	211 – 213	0.54	$C_{22}H_{23}N_5O$
VIs	87	175 – 177	0.58	$C_{21}H_{27}N_5O_2$
VIt	89	115 – 116	0.61	$C_{22}H_{29}N_5O_2$
VIu	72	158 – 160	0.62	$C_{20}H_{20}N_4O_2$
VIv	85	175 – 177	0.54	$C_{21}H_{22}N_4O_2$

CH($\underline{CH_3}$)$_2$), 2.26 (m, 1H, $\underline{CH}$(CH$_3$)$_2$), 2.28 (quin, 2H, J 7.5 Hz, 2-CH), 2.69 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 3.00 (t, 2H, J 7.5 Hz, 3-CH_2), 3.38 (t, 2H, J 7.5 Hz, 1-CH_2), 7.98 (s, 1H, 9-CH), 12.81 (broad, 1H, NH).

2,3-Dihydro-4-isopropyl(isobutyl)-7-chloro-1*H*-cyclopenta[4′,5′]pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidine Va (Vb) (general method). A mixture of 0.1 mol of compound IVa (IVb) and 250 ml of phosphorus oxychloride was boiled for 4 h. Excess phosphorus oxychloride was evaporated to dryness; iced water was added, and the resulting crystals were collected by filtration, washed with water, dried, and recrystallized from ethanol (Table 1).

The IR spectrum, ν_{max}, cm^{-1}, was: **Va (Vb).** 1580 (C=Car). The PMR spectrum, δ, ppm, was, **Va**: 1.34 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.36 (quin, 2H, J 7.5 Hz, 2-CH_2), 3.08 (t, 2H, J 7.5 Hz, 3-CH_2), 3.25 (sp, 1H, J 6.7 Hz, $\underline{CH}$(CH$_3$)$_2$), 3.46 (t, 2H, J 7.5 Hz, 1-CH_2), 8.88 (s, 1H, 9-CH), IVb: 1.00 (d, 6H, J 6.6 Hz, CH(CH$_3$)$_2$), 2.30 (m, 1H, $\underline{CH}$(CH$_3$)$_2$), 2.35 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.75 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 3.05 (t, 2H, J 7.5 Hz, 3-CH_2), 3.47 (t, 2H, J 7.5 Hz, 1-CH_2), 8.89 (s, 1H, 9-CH).

2,3-Dihydro-4-isopropyl(isobutyl)-7-pyrrolidin-1-yl-7-tetrahydro-1*H*-cyclopenta[4′,5′]pyrido[3′,2′:4,5]furo[3,2-*d*]pyrimidine VIa (VIb). A mixture of 0.01 mol of chloride Va (Vb) and 0.022 mol of the corresponding amine in 50 ml of absolute ethanol was boiled for 10 h. The reaction mix was cooled, 100 ml of water was added, and the resulting crystals were collected by filtration, washed with water, dried, and recrystallized from ethanol (Table 1).

Compounds VIc-v were prepared in the same way (Table 1).

IR spectra, ν_{max}, cm^{-1}, were: VIa (VIb)**.** 1580 (C=Car). PMR spectra, δ, ppm, were, **VIa**: 1.30 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.08 (m, 4H, C_4H_8N), 2.30 (quin, 2H, J 7.5 Hz, 2-CH_2), 3.02 (t, 2H, J 7.5 Hz, 3-CH_2), 3.19 (sp, 1H, J 6.7 Hz, $\underline{CH}$(CH$_3$)$_2$), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 3.94 (broad, 4H, C_4H_8N), 8.32 (s, 1H, 9-CH), **VIb**: 0.98 (d, 6H, J 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.08 (m, 4H, C_4H_8N), 2.26 (m, 1H, $\underline{CH}$(CH$_3$)$_2$), 2.29 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.67 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 2.99 (t, 2H, J 7.5 Hz, 3-CH_2), 3.42 (t, 2H, J 7.5 Hz, 1-CH_2), 3.93 (broad, 4H, C_4H_8N), 8.22 (s, 1H, 9-CH), **VIc**: 1.30 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.31 (quin, 2H, J 7.5 Hz, 2-CH_2), 3.03 (t, 2H, J 7.5 Hz, 3-CH_2), 3.20 (sp, 1H, J 6.7 Hz, $\underline{CH}$(CH$_3$)$_2$), 3.42 (t, 2H, J 7.5 Hz, 3 2 1-CH_2), 3.82 (m, 4H, C_4H_8NO), 4.08 (m, 4H, C_4H_8NO), 8.41 (s, 1H, 9-CH), **VId**: 0.98 (d, 6H, J 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.27 (m, 1H, $\underline{CH}$(CH$_3$)$_2$), 2.30 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.68 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 3.00 (t, 2H, J 7.5 Hz, 3-CH_2), 3.43 (t, 2H, J 7.5 Hz, 1-CH_2), 3.82 (m, 4H, C_4H_8NO), 4.08 (m, 4H, C_4H_8NO), 8.40 (s, 1H, 9-CH), **VIe**: 1.30 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.31 (quin, 2H, J 7.5 Hz, 2-CH_2), 3.03 (t, 2H, J 7.5 Hz, 3-CH_2), 3.20 (sp, 1H, J 6.7 Hz, $\underline{CH}$(CH$_3$)$_2$), 3.41 (t, 2H, J 7.5 Hz, 3 2 1-CH_2), 3.60 – 3.70 (m, 4H, NH$\underline{CH_2CH_2}$), 4.45 (broad, 1H, OH), 7.52 (broad, 1H, NH), 8.34 (s, 1H, 9-CH), **VIf**: 0.98 (d, 6H, J 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.23 (m, 1H, $\underline{CH}$(CH$_3$)$_2$), 2.29 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.68 (d, 2H, J 7.1 Hz, 2 $\underline{CH}CH_2$), 2.99 (t, 2H, J 7.5 Hz, 3-CH_2), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 3.60 – 3.70 (m, 4H, NH$\underline{CH_2CH_2}$), 4.44 (broad, 1H, OH), 7.51 (broad, 1H, NH), 8.34 (s, 1H, 9-CH), **VIg**: 1.29 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.30 (quin, 2H, J 7.5 Hz, 2-CH_2), 3.03 (t, 2H, J 7.5 Hz, 3-CH_2), 3.20 (sp, 1H, J 6.7 Hz, $\underline{CH}$(CH$_3$)$_2$), 3.35 (s, 3H, OCH_3), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 3.58 (m, 2H, OCH_2), 3.72 (m, 2H, NH$\underline{CH_2}$), 7.62 (t, 1H, J 5.4 Hz, NH), 8.34 (s, 1H, 9-CH), **VIh**: 0.97 (d, 6H, J 6.6 Hz, CH(CH$_3$)$_2$), 2.25 (m, 1H, $\underline{CH}$(CH$_3$)$_2$), 2.28 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.67 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 2.98 (t, 2H, J 7.5 Hz, 3-CH_2), 3.35 (s, 3H, OCH_3), 3.40 (t, 2H, J 7.5 Hz, 1-CH_2), 3.58 (t, 2H, J 5.8 Hz, OCH_2), 3.72 (m, 2H, NH$\underline{CH_2}$), 7.62 (t, 1H, J 5.2 Hz, NH), 8.33 (s, 1H, 9-CH), **VIi**: 1.29 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.28 (s, 6H, N(CH$_3$)$_2$), 2.30 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.57 (t, 2H, J 6.6 Hz, NCH_2), 3.02 (t, 2H, J 7.5 Hz, 3-CH_2), 3.19 (sp, 1H, J 6.7 Hz, $\underline{CH}$(CH$_3$)$_2$), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 3.65 (m, 2H, $\underline{CH_2}$NH), 7.37 (t, 1H, J 5.0 Hz, NH), 8.76 (s, 1H, 9-CH), **VIj**: 0.97 (d, 6H, J 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.24 (m, 1H, $\underline{CH}$(CH$_3$)$_2$), 2.28 (s, 6H, N(CH$_3$)$_2$), 2.28 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.57 (t, 2H, J 6.6 Hz, NCH_2), 2.67 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 2.98 t, 2H, J 7.5 Hz, 3-CH_2), 3.40 (t, 2H, J 7.5 Hz, 1-CH_2), 3.64 (m, 2H, $\underline{CH_2}$NH), 7.37 (broad t, 1H, J 5.2 Hz, NH), 8.33 (s, 1H, 9-CH), **VIk**: 1.31 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.30 (s, 3H, NCH_3), 2.31 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.54 (m, 4H, ($\underline{CH_2}$)$_2$NCH$_3$), 3.03 (t, 2H, J 7.5 Hz, 3-CH_2), 3.20 (sp, 1H, J 6.7 Hz, CH(CH$_3$)$_2$), 3.42 (t, 2H, J 7.5 Hz, 1-CH_2), 4.09 (m, 4H, (CH$_2$)$_2$N), 8.37 (s, 1H, 9-CH), **VIl**: 0.98 (d, 6H, J 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.27 (m, 1H, $\underline{CH}$(CH$_3$)$_2$), 2.29 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.30 (s, 3H, NCH_3), 2.53 (m, 4H, ($\underline{CH_2}$)$_2$NCH$_3$), 2.68 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 3.00 (t, 2H, J 7.5 Hz, 3-CH_2), 3.42 (t, 2H, J 7.5 Hz, 1-CH_2), 4.08 (m, 4H, ($\underline{CH_2}$)$_2$N), 8.37 (s, 1H, 9-CH), **VIm**: 1.29 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 1.81 (quin, 2H, J 7.5 Hz, NHCH$_2\underline{CH_2}$), 2.30 (quin, 2H, J 7.5 Hz, 2-CH_2), 3.03 (t, 2H, J 7.5 Hz, 3-CH_2), 3.20 (sp, 1H, J 6.7 Hz, $\underline{CH}$(CH$_3$)$_2$), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 3.56 (m, 2H, $\underline{CH_2}$OH), 3.64 (m, 2H, NH$\underline{CH_2}$), 4.24 (t, 1H, J 5.3 Hz, OH), 7.67 (broad t, 1H, J 5.2 Hz, NH), 8.33 (s, 1H, 9-CH), **VIn**: 0.97 (d, 6H, J 6.6 Hz, CH($\underline{CH_3}$)$_2$), 1.81 (quin, 2H, J 6.3 Hz, NHCH$_2\underline{CH_2}$), 2.24 (m, 1H, $\underline{CH}$(CH$_3$)$_2$), 2.29 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.68 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 2.99 (t, 2H, J 7.5 Hz, 3-CH_2), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 3.56 (m, 2H, $\underline{CH_2}$OH), 3.64 (m, 2H, NH$\underline{CH_2}$), 4.24 (broad, 1H, OH), 7.66 (t, 1H, J 5.2 Hz, NH), 8.33 (s, 1H, 9-CH), **VIo**: 1.17 (d, 3H, J 6.2 Hz, CH($\underline{CH_3}$)OH), 1.29 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.30 (quin, 2H, J 7.5 Hz, 2-CH_2), 3.03 (t, 2H, J 7.5 Hz, 3-CH_2), 3.20 (sp, 1H, J 6.7 Hz, $\underline{CH}$(CH$_3$)$_2$), 3.38 (ddd, 1H, J 13.2, J 7.3, J 5.0 Hz, NH$\underline{CH_2}$), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 3.63 (ddd, 1H, J 13.2, J 6.2, J 4.1 Hz, NH$\underline{CH_2}$), 3.91 (m, 1H, $\underline{CH}$(CH$_3$)OH), 4.53 (d, 1H, J 3.9 Hz, OH), 7.43 (dd, 1H, J 5.0, J 4.1 Hz, NH), 8.33 (s, 1H, 9-CH), **VIp**: 0.98 (d, 6H, J 6.6 Hz, CH(CH$_3$)$_2$), 1.17 (d, 3H, J

6.2 Hz, CH($\underline{CH_3}$)OH), 2.24 (m, 1H, $\underline{CH}(CH_3)_2$), 2.29 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.69 (d, 2H, J 7.1 Hz, 2 CH$\underline{CH_2}$), 3.00 (t, 2H, J 7.5 Hz, 3-CH_2), 3.36 (m, 1H, NCH_2), 3.42 (t, 2H, J 7.5 Hz, 1-CH_2), 3.64 (m, 1H, NH$\underline{CH_2}$), 3.91 (m, 1H, $\underline{CH}(CH_3)$OH), 4.52 (broad, 1H, OH), 7.44 (broad, 1H, NH), 8.33 (s, 1H, 9-CH), **VIq**: 1.29 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.30 (quin, 2H, J 7.5 Hz, 2-CH_2), 3.03 (t, 2H, J 7.5 Hz, 3-CH_2), 3.20 (sp, 1H, J 6.7 Hz, $\underline{CH}(CH_3)_2$), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 4.77 (d, 2H, J 6.1 Hz, $\underline{CH_2}$NH), 7.22 (dd, 1H, J 7.8, J 4.8 Hz, H-5′), 7.76 (dt, 1H, J 7.8, J 1.8 Hz, H-6′), 8.36 (s, 1H, 9-CH), 8.39 (dd, 1H, J 4.8, J 1.8 Hz, H-4′), 8.48 (t, 1H, J 6.0 Hz, NH), 8.60 (d, 1H, J 1.8 Hz, H-2′), **VIr**: 0.97 (d, 6H, J 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.25 (m, 1H, $\underline{CH}(CH_3)_2$), 2.29 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.69 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 3.00 (t, 2H, J 7.5 Hz, 3-CH_2), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 4.77 (d, 2H, J 6.1 Hz, $\underline{CH_2}$NH), 7.22 (dd, 1H, J 7.8, J 4.8 Hz, 2 H-5′), 7.77 (ddd, 1H, J 7.8, J 1.8, J 1.6 Hz, H-6′), 8.37 (s, 1H, 9-CH), 8.39 (dd, 1H, J 4.8, J 1.6 Hz, H-4′), 8.47 (t, 1H, J 6.1 Hz, NH), 8.60 (d, 1H, J 1.8 Hz, H-2′), **VIs**: 1.29 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.30 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.50 (m, 4H, N($\underline{CH_2}$)$_2$), 2.62 (t, 2H, J 6.6 Hz, $\underline{CH_2}$N(CH_2)$_2$), 3.03 (t, 2H, J 7.5 Hz, 3-CH_2), 3.20 (sp, 1H, J 6.7 Hz, $\underline{CH}(CH_3)_2$), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 3.61 (m, 4H, O($\underline{CH_2}$)$_2$), 3.68 (m, 2H, NH$\underline{CH_2}$), 7.52 (t, 1H, J 5.2 Hz, NH), 8.33 (s, 1H, 9-CH), **VIt**: 0.97 (d, 6H, J 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.24 (m, 1H, $\underline{CH}(CH_3)_2$), 2.29 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.50 (m, 4H, N($\underline{CH_2}$)$_2$), 2.61 (t, 2H, J 6.6 Hz, $\underline{CH_2}$N(CH_2)$_2$), 2.68 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 2.99 (t, 2H, J 7.5 Hz, 3-CH_2), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 3.61 (m, 4H, O($\underline{CH_2}$)$_2$), 3.67 (m, 2H, NH$\underline{CH_2}$), 7.51 (t, 1H, J 5.3 Hz, NH), 8.33 (s, 1H, 9-CH), **VIu**: 1.29 (d, 6H, J 6.7 Hz, CH($\underline{CH_3}$)$_2$), 2.30 (quin, 2H, J 7.5 Hz, 2-CH_2), 3.03 (t, 2H, J 7.5 Hz, 3-CH_2), 3.20 (sp, 1H, J 6.7 Hz, $\underline{CH}(CH_3)_2$), 3.41 (t, 2H, J 7.5 Hz, 1-CH_2), 4.76 (d, 2H, J 5.9 Hz, NH$\underline{CH_2}$), 6.26 (dd, 1H, J 3.2, J 0.9 Hz, H-3′), 6.29 (dd, 1H, J 3.2, J 1.8 Hz, H-4′), 7.37 (dd, 1H, J 1.8, J 0.9 Hz, H-5′), 8.21 (t, 1H, J 5.9 Hz, NH), 8.38 (s, 1H, 9-CH), **VIv**: 0.97 (d, 6H, J 6.6 Hz, CH($\underline{CH_3}$)$_2$), 2.24 (m, 1H, $\underline{CH}(CH_3)_2$), 2.29 (quin, 2H, J 7.5 Hz, 2-CH_2), 2.69 (d, 2H, J 7.1 Hz, CH$\underline{CH_2}$), 3.00 (t, 2H, J 7.5 Hz, 3-CH_2), 3.42 (t, 2H, J 7.5 Hz, 1-CH_2), 4.75 (d, 2H, J 5.9 Hz, NH$\underline{CH_2}$), 6.26 (dd, 1H, J 3.2, J 1.0 Hz, H-3′), 6.28 (dd, 1H, J 3.2, J 1.8 Hz, H-4′), 7.37 (dd, 1H, J 1.8, J 1.0 Hz, H-5′), 8.20 (t, 1H, J 5.9 Hz, NH), 8.38 (s, 1H, 9-CH).

EXPERIMENTAL BIOLOGICAL SECTION

Experiments with 22 compounds (VIa – v) were performed on 225 white mice weighing 18 – 24 g; each group consisted of five animals of both genders.

Anticonvulsive and predicted tranquillizer activities were studied in terms of the effects of the agents on the clonic component of convulsions induced by s.c. corasol (90 mg/kg) in mice [10, 11]. Side effects were also studied in mice - impairments to coordination, movement, and muscle relaxation using the rotating bar test [10, 11].

TABLE 2. Comparative Anticorasol and Myorelaxant Activity of compounds VIu, VIo, VIg, and Diazepam.

Compound	Corasol antagonism (ED_{50}, mg/kg)	Myorelaxation (TD_{50}, mg/kg)
VIg	22 (18.9 – 25.5)*	45 (38.8 – 52.2)*
VIo	28 (24.3 – 32.2)*	> 50
VIu	35 (30.4 – 40.3)*	52 (21.7 – 59.8)*
Reference agent – diazepam	0.5 (0.4 – 0.63)*	2.8, (2.5 – 3.2) **

* Statistically significant differences, $p < 0.05$, between reference agent diazepam and study compounds (VIu, VIo, and VIg.

The compounds synthesized here were given i.p. at doses of 25 – 50 mg/kg as suspensions in tween-80 (Ferak Berlin) 45 min before administration of corasol and the rotating bar test. Control animals received emulsifying agent. The reference agent was diazepam (Polfa) as substance, and was given i.p. at doses of 0.1, 0.3, and 1 mg/kg. Results were analyzed statistically. Compounds VIa-v at doses of 50 mg/kg were given in three repeat experiments and the proportions of animals showing protection from clonic corasol convulsions were determined. ED_{50} values (50% effective doses) were determined in relation to the anticonvulsant effects, and *p* values were also determined [11].

Analysis of data on the anticorasol effects showed that most compounds (VIa – VIf, VIh – n, VIp – t, VIv) at 50 mg/kg showed some degree of antagonism of corasol convulsions in 20 – 60% of animals. At this dose, study compounds induced muscle relaxation. However, the results presented in Table 2 show that compounds VIg, VIo, and VIu had strong anticonvulsant activity. Thus, at a dose of 50 mg/kg, these compounds prevented corasol convulsions in almost all (80%) experimental animals and their ED_{50} values were 22 – 35 mg/kg, which not only demonstrates anticonvulsive activity, but may also be a predictor of a tranquilizing effect. The reference tranquilizer diazepam was more effective, showing anticorasol activity in 50% of mice at the lower dose of 0.5 mg/kg, which was statistically significantly different from the study compounds (Table 2).

Thus, furo[3,2-*d*]pyrimidine derivatives showed anticonvulsive and predicted tranquilizing effects similar to those of diazepam. However, like diazepam, these compounds produced muscle relaxation. It should be noted that the most active of the compounds synthesized here were 4-isopropyl-substituted derivatives.

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