The Reactions of Heterocyclic Isothiocyanates Bearing an *ortho* Ester Group with Aminoalcohols

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Heterocyclic isothiocyanates **1, 5, 9,** bearing an *o*-ester group were converted to thiourea derivatives **2a-c, 6a-b,** and **10a-b,** respectively, using β-aminoalcohols, and to the fused ring systems, *e.g.,* thieno[3,2-*d*]pyrimidine **4a-b**, pyrido[2,3-*d*]pyrimidine **8**, pteridine **11a,** thiazolo[3,2-*a*]pyrido[2,3-*d*]pyrimidine **7a-b**, and thiazolo[3,2-*a*]thieno[3,2-*d*]pyrimidine **3a-c**, derivatives.

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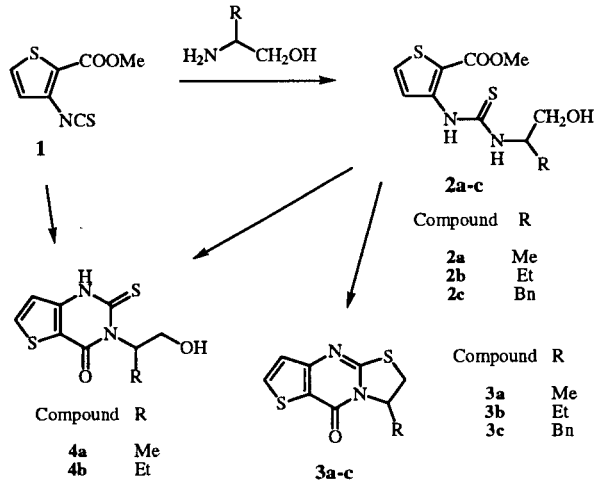
Recently, we have shown that heterocyclic isothicyanates bearing an *ortho* ester group are versatile compounds for the synthesis of heterocyclic thiourea derivatives, and different fused heterocyclic systems, *i.e.*, isomeric pyridopyrimidines, pteridines, thiazolopyridopyrimidines, etc. [1,2,3,4,5,6]. The synthesis of some thiazole condensed thienopyrimidine derivatives and their gastric antisecretory activity has also been described [7]. In the present paper, we describe the syntheses of thieno[3,2-*d*]pyrimidine, pteridine, thiazolo[3,2-*a*]pyrido[2,3-*d*]pyrimidine, and thiazolo[3,2-*a*]thieno[3,2-*d*]pyrimidine derivatives.

Treatment of methyl 3-isothiocyanatothiophene-2-carboxylate (**1**) with different β-aminoalcohols under mild reaction conditions yielded corresponding thioureido derivatives **2a-c**. At room temperature in tetrahydrofuran only the traces of the fused thienopyrimidine derivatives **4a-b** were observed upon isolation of the crude products, as determined by ^{1}H nmr spectroscopy.

The syntheses of 7-(aryl)alkyl-6,7-dihydro-9*H*-thiazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-9-ones **3a-c** were accomplished by heating the corresponding thiourea derivatives **2a-c** in methanolic hydrogen chloride at reflux temperature in good to moderate yields. (Scheme 1). This type of compound was obtained in a single reaction step using cysteamine in pyridine [6]. During this reaction course no intermediate thieno[3,2-*d*]pyrimidine derivatives were isolated, although in a separate reaction thieno[3,2-*d*]pyrimidine derivatives **4a-b** were synthesized. Compound **4a** was formed by reacting thiourea derivative **2a** under alkaline conditions, and the identical reaction product **4a** was isolated after the treatment of the isothiocyanate **1** with (*S*)-(+)-2- amino-1-propanol in the presence of potassium *tert*-butoxide at reflux temperature. Treatment of the compound **2b** with dimethylformamide dimethylacetal gave thieno[3,2-*d*]pyrimidine derivative **4b**, and no *S*-methylated product was formed during this reaction. (Scheme 1).

In a reaction between ethyl 2-isothiocyanatopyridine-3-carboxylate **5** with aminoalcohols thioureido derivatives **6a-b** were formed in good yield. Treatment of thiourea derivative **6a** with sodium hydroxide solution gave pyrido-[2,3-*d*]pyrimidine derivative **8**. 3-Alkyl-2-thioxo-2,3-dihydro-5*H*-pyrido [2,3-*d*][1,3]thiazolo [3,2-*a*]pyrimidin-5-ones

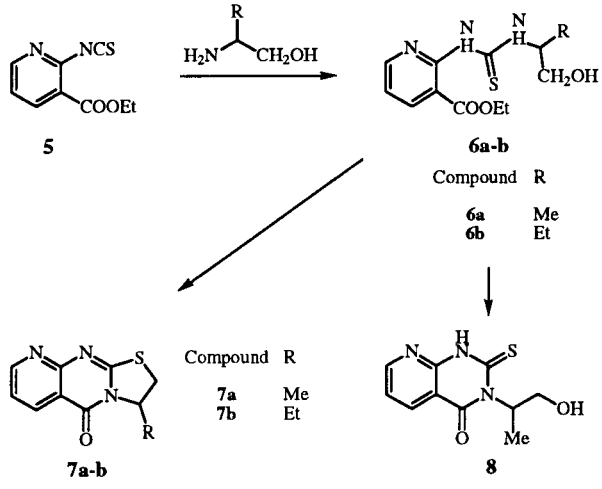
Scheme 1



7a-b were obtained by heating corresponding thioureido derivatives **6a-b** in refluxing methanolic hydrogen chloride in good to moderate yields (Scheme 2).

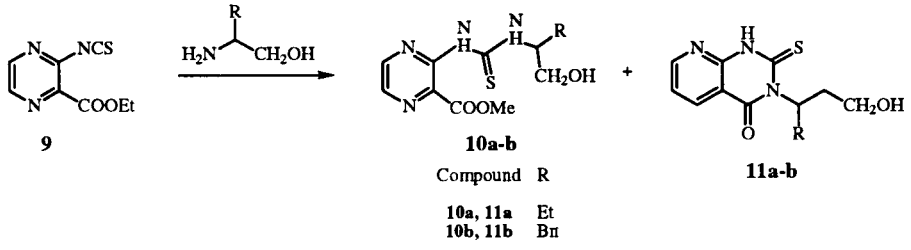
The same reactions were applied also to methyl 3-isothiocyanatopyrazine-2-carboxylate **9**, although in reaction with (*R*)-(-)-2-amino-1-butanol, methyl 3[3-[(1-(hydroxymethyl)propyl]thioureido]-2-pyrazinecarboxylate **10a** and

Scheme 2



3-[1-(hydroxymethyl)propyl]-2-thioxo-1,2-dihydropteridin-4(3*H*)-one **11a** were formed in similar amounts without the addition of the base. In reaction of isothiocyanate **9** with *R*-(+)-2-amino-3-phenyl-1-propanol the main product was methyl 3-[3-(1-benzyl-2-hydroxyethyl)thioureido]-2-pyrazinecarboxylate **10b**, and pteridinone derivative **11b** was formed only in traces under this reaction conditions, as detected by ^{1}H nmr. A multiple spin spectra for the protons of the -CH_2- groups in fused thiazole ring have been observed in all tricyclic compounds.

Scheme 3



EXPERIMENTAL

Melting points were determined on a Leitz-Cambridge hot stage and are uncorrected. The ir spectra were recorded on a Perkin Elmer FTIR 1600 instrument as potassium bromide pellets. The ^{1}H nmr spectra were measured on a Varian VXR 300 at 300 MHz using TMS as internal standard. Elemental analyses were performed on a Perkin Elmer 2400C, C, H, N analyzer. Optical rotations were measured on a Perkin Elmer 240 MC polarimeter.

The Synthesis of Methyl 3-(Hydroxyalkyl)thioureido-2-thiophenecarboxylates.

Methyl 3-[3-(2-Hydroxy-1-methylethyl)thioureido]-2-thiophenecarboxylate (**2a**).

To a stirred solution of methyl 3-isothiocyanatothiophene-2-carboxylate **1** (0.45 g, 2.26 mmoles) in 8 ml of dry tetrahydrofuran, *S*-(+)-2-amino-2-propanol (0.183 g, 2.44 mmoles) was added, and stirred at room temperature for 24 hours. After evaporation of the solvent at reduced pressure the oily residue was cooled to 0° to give 0.59 g (95%) of pale yellow crystals, mp 103-104°; ir: 3254, 2963, 1684, 1559, 1437, 1399, 1262, 1186, 1086, 1020, 800, 668 cm^{-1}; $[\alpha]_D^{20}$ = -13.62° (c = 0.501 g/100 ml of methanol); ^{1}H nmr (deuteriochloroform): δ 1.30 (d, 3H, J = 6.7 Hz, CH_3CH-), 2.94 (t, 1H, J = 5.2 Hz, -CH_2OH), 3.59-3.71 and 3.78-3.92 (2m, 1H each, -CH_2OH), 3.87 (s, 3H, -COOCH_3), 4.24-4.64 (m, 1H, NHC*H*(CH_2OH)CH_3), 7.05 (d, 1H, J = 7.9 Hz, H_4), 7.44 (d, 1H, J = 5.4 Hz, H_5), 8.52 (broad s, 1H, N*H*), 10.39 (broad s, 1H, N*H*).

Anal. Calcd. for $C_{10}H_{14}N_2O_3S_2$: C, 43.78; H, 5.14; N, 10.21. Found: C, 43.84; H, 4.60; N, 10.45.

Methyl 3-[3-[1-(Hydroxymethyl)propyl]thioureido]-2-thiophenecarboxylate (**2b**).

This compound was obtained from methyl 3-isothiocyanatothiophene-2-carboxylate (**1**) (0.45 g, 2.26 mmoles), (*R*)-(-)-2-amino-1-butanol (0.218 g, 2.45 mmoles) in 8 ml of dry tetrahydrofuran at room temperature. After evaporation of the solvent at reduced pressure the oily residue was purified using column chromatography (silica gel, chloroform:acetone = 10:1) to give white crystals which were recrystallized twice from ethanol to give 0.52 g (79%) of white crystals, mp 109-112°; ir: 3294, 2964, 1678, 1593, 1539, 1447, 1401, 1344, 1280, 1247, 1095, 1048, 778 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.02 (t, 3H, J = 7.4 Hz, CH_3CH_2-), 1.56-1.76 (m, 2H, CH_3CH_2-), 2.41 (t, 1H, J = 4.4 Hz,-CH_2OH), 3.66-3.78 and 3.80-3.93 (2m, 3H,-CH_2OH, -NHC*H*(CH_2OH)CH_2CH_3), 3.84 (s, 3H,-COOCH_3), 6.68 (d, 1H, J = 7.9 Hz, H4), 7.47 (d, 1H, J = 7.9 Hz, H5), 8.56 (broad s, 1H, NH), 10.42 (broad s, 1H, N*H*).

Anal. Calcd. for $C_{11}H_{16}N_2O_3S_2$: C, 45.81; H, 5.59; N, 9.71. Found: C, 45.68; K 5.49; N, 10.02.

Methyl 3-[3-(1-Benzyl-2-hydroxyethyl)thioureido]-2-thiophenecarboxylate (**2c**).

This compound was obtained from methyl 3-isothiocyanatothiophene-2-carboxylate (**1**) (0.45 g, 2.26 mmoles), *R*-(+)-2-amino-3-phenyl-1-propanol (0.377 g, 2.45 mmoles) in 8 ml of dry tetrahydrofuran at room temperature. After evaporation of the solvent at reduced pressure the oily residue was triturated with methanol to give white crystals which were purified using column chromatography (silica gel, dichloromethane:methanol = 90:1) to give 0.63 g (63%) of white crystals, mp 145-146°; ir: 3248, 3060, 1681, 1604, 1557, 1488, 1444, 1394, 1277, 1244, 1197, 1090, 1038, 782, 691 cm^{-1}; $[\alpha]_D^{20}$ = +111.28° (c = 0.406 g/100 ml of methanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.90 (d, 2H, J = 6.8 Hz, $C_6H_5CH_2$-), 3.40-3.52 (m, 2H,-CH_2OH), 3.83 (s, 3H,-COOCH_3),4.42-4.56 (m, 1H, -NHC*H*(CH_2OH)-CH_2Ph), 4.96 (t, 1H, J = 4.8 Hz, O*H*), 7.16-7.34 (m, 5H, Ar), 7.78 (d, 1H, J = 5.4 Hz, H_4), 8.28 (d, 1H, J = 5.4 Hz, H_5), 9.17 (d, 1H, J = 7.6 Hz, NH), 9.98 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{18}N_2O_3S_2$: C, 54.84; H, 5.18; N, 7.99. Found: C, 55.13; H, 4.97; N, 7.74.

7-Methyl-6,7-dihydro-9*H*-[1,3]thiazolo[3,2-*a*]thieno[3,2-*d*]-pyrimidin-9-one (**3a**).

Methyl 3-[3-(2-hydroxy-1-methylethyl)thioureido]-2-thiophenecarboxylate (**2a**) (0.91 g, 3.32 mmoles) was dissolved in 37 ml of methanolic hydrogen chloride and stirred at reflux temperature for 24 hours, and after evaporation of the solvent under reduced pressure the brown residue was dissolved in 10 ml of water and neutralized to *p*H 7.5 with water ammonia and extracted with chloroform (3 x 30 ml). The organic layer was dried (magnesium sulfate) and evaporated to yield the solid which was recrystallized from ethanol to give 0.18 g (24%) of white crystals, mp 191-192° (lit mp 147-149°); ir: 3458, 3104, 2955, 1679, 1542, 1490, 1359, 1194, 1108, 783 cm^{-1}; ms: (124°)

m/z 224 (MH^+); $[\alpha]_D^{20}$ = +133.98° (c = 0.379 g/100 ml of methanol); ^1H nmr (deuteriochloroform): δ 1.59 (d, 3H, J = 6.4 Hz, CH_3CH-), 3.04 (dd, 1H, ABX system, J_{AX} = 0.7 Hz, J_{AB} = 11.2 Hz, H_6), 3.83 (dd, 1H, ABX system, J_{BX} = 7.6 Hz, J_{AB} = 11.2 Hz, H_6), 5.28 (m, 1H, ABX system, H_7), 7.18 (d, 1H, J = 5.4 Hz, H_3), 7.73 (d, 1H, J = 5.1 Hz, H_2).

Anal. Calcd. for $C_9H_8N_2OS_2$ x HCl x 3/2 H_2O: C, 37.55; H, 4.20; N, 9.73. Found: C, 38.01; H, 3.88; N, 10.05.

7-Ethyl-6,7-dihydro-9*H*-[1,3]thiazolo[3,2-*a*]thieno[3,2-*d*]-pyrimidin-9-one (**3b**).

Compound **3b** was obtained in a similar manner from methyl 3-[3-[1-hydroxymethyl)propyl]thioureido]-2-thiophenecarboxylate (**2b**) (0.1 g, 0.35 mmoles) in refluxing methanolic hydrogen chloride to give a crude product which was purified using column chromatography (silica gel, dichloromethane:methanol = 90:1) to give 0.05 g (60%) of white crystals, mp 108-109°; ir: 3457, 2964, 2874, 1652, 1544, 1496, 1456, 1364, 1238, 1197, 1049, 827, 782, 688 cm^{-1}; $[\alpha]_D^{20}$ = -124.4° (c = 0.357 g/100 ml of methanol); ^1H nmr (deuteriochloroform): δ 1.07 (t, 3H, J = 7.3 Hz, CH_3CH_2-), 1.90-2.08 (m, 2H, CH_3CH_2-), 3.19 (dd, 1H, ABX system, J_{AX} = 0.9 Hz, J_{AB}= 11.5 Hz, H6), 3.75 (dd, 1H, ABX system, J_{BX} = 7.8 Hz, J_{AB} = 11.5 Hz, H_6), 5.0-5.12 (m, 1H, ABX system, H_7), 7.18 (d, 1H, J = 5.4 Hz, H_3), 7.73 (d, 1H, J = 5.1 Hz, H_2).

Anal. Calcd. for $C_{10}H_{10}N_2OS_2$: C, 50.39; H, 4.24; N, 11.76. Found: C, 50.34; H, 3.93; N, 11.76.

7-Benzyl-6.7-dihydro-9*H*-[1,3]thiazolo[3,2-*a*]thieno[3,2-*d*]-pyrimidin-9-one (**3c**).

Compound **3c** was obtained in a similar manner from methyl 3-[3-(1-benzyl-2-hydroxyethyl)thioureido]-2-thiophenecarboxylate (**2c**) (0.35 g, 0.1 mmole) in refluxing methanolic hydrogen chloride for 1 hour to give a crude product which was recrystallized from 1-propanol to give 0.08 g (27%) of white crystals, mp 162-165°; ir: 3457, 3112, 2942, 1668, 1548, 1499, 1365, 1256, 1195, 1038, 790, 746, 699 cm^{-1}; $[\alpha]_D^{20}$ = -130.0° (c = 0.345 g/100 ml of methanol); ^1H nmr (deuteriochloroform): δ 3.01-3.16 (m, 2H, $C_6H_5CH_2$-), 3.38 (dd, 1H, ABX system, J_{AX} = 3.2 Hz, J_{AB} = 13.2 Hz, H_6), 3.57 (dd, 1H, ABX system, J_{BX} = 7.6 Hz, J_{AB} = 11.7 Hz, H_6), 5.23-5.38 (m, 1H, ABX system, H_7), 7.20 (d, 1H, J = 5.4 Hz, H_3), 7.26-7.42 (m, 5H, $C_6H_5CH_2$-), 7.76 (d, 1H, J = 5.1 Hz, H_2).

Anal. Calcd. for $C_{15}H_{12}N_2OS_2$: C, 59.96; H, 4.03; N, 9.33. Found: C, 59.63; H, 3.84; N, 8.92.

3-(2-Hydroxy-1-methylethyl)-2-thioxo-1,2-dihydrothieno[3,2-*d*]-pyrimidin4(3*H*)-one (**4a**).

Method A.

A solution of methyl 3-[3-(2-hydroxy-1-methylethyl)-thioureido]-2-thiophenecarboxylate **2a** (0.100 g, 0.36 mmole) in 5 ml of 10% sodium hydroxide was stirring at room temperature for 10 minutes, acidified to *p*H 6.6 with 10% hydrochloric acid solution and the precipitated product was filtered to give 0.70 g (79%) of white crystals, mp 181-184° (lit mp 176-178°), ir: 3396, 3060, 2926, 1641, 1579, 1548, 1460, 1373, 1206, 1098, 1041, 913, 768 cm^{-1}; $[\alpha]_D^{20}$ = -22.35° (c = 0.460 g/100 ml of methanol); ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.37 (d, 3H, J = 6.2 Hz, CH_3CH-), 3.62-3.82 and 3.85-4.04 (2m, 1H each, CH_2OH), 4.82 (broad, 1H,-CH_2OH), 5.80-6.04 (m, 1H, -$CHCH_2OH$), 7.01 (d, 1H, J = 5.1 Hz, H_7), 8.15 (d, 1H, J = 5.1 Hz, H_6).

Anal. Calcd. for $C_{10}H_{12}N_2O_2S_2$: C, 44.61; H, 4.16; N, 11.56. Found: C, 44.98; H, 3.95; N, 11.87.

Method B.

To a stirred solution of methyl 3-isothiocyanatothiophene-2-carboxylate **1** (0. 10 g, 0.50 mmole) in 2 ml of dry tetrahydrofuran, *S*-(+)-2-amino-2-propanol (0.041 g, 0.54 mmole) and potassium *tert*-butoxide (0.028 g, 0.25 mmole) were added and the mixture was heated for 20 hours at reflux temperature. After the evaporation of the solvent at reduced pressure, the residue was purified using column chromatography (silica gel, chloroform: acetone = 5:1) to give 0.072 g (59%) of white crystals with the same characteristics as described above.

3-[1-(Hydroxymethyl)propyl]-2-thioxo-1,2-dihydrothieno[3,2-*d*]-pyrimidin-4(3*H*)-one (**4b**).

To a suspension of methyl 3-[3-[1-(hydroxymethyl)-propyllthioureido]-2-thiophenecarboxylate (0.089 g, 0.35 mmole) **2b** in 3 ml of dry methanol, dimethylformamide dimethylacetal (0.052 ml, 0.37 mmole) was added, and the mixture was heating at reflux temperature for 19 hours. The solvent was evaporated under reduced pressure, and the residue triturated with dichloromethane. The precipitation was filtered to give 0.036 g (45%) of white crystals, mp 181-189°; ir: 3380, 3140, 3050, 2940, 2900, 1640, 1578, 1540, 1500, 1450, 1410, 1387, 1326, 1275, 1220, 1108, 1065, 1043, 1018, 980, 825, 770, 730 cm^{-1}; $[\alpha]_D^{20}$ =-16.20° (c = 0.401 g/100 ml of methanol); ^1H nmr (dimethyl-d_6 sulfoxide): δ 0.85 (t, 3H, J = 7.4 Hz, CH_3CH_2-), 1.75-1.92 and 1.95-2.13 (2m, 1H each, CH_3CH_2-), 3.69-3.82 and 3.88-4.30 (2m, 1H each,-CH_2OH), 4.78 (t, 1H, J = 5.3 Hz, -CH_2OH), 5.9-6.10 (m, 1H, EtCH(N)CH_2OH), 7.01 (d, 1H, J = 5.2 Hz, H_7), 8.13 (d, 1H, J = 5.1 Hz, H_6).

Anal. Calcd. for $C_{10}H_{12}N_2O_2S_2$: C, 46.85; H, 4.72; N, 10.93. Found: C, 47. 10; H, 4.69; N, 11.26.

Ethyl 2-[3-(2-Hydroxy-1-methylethyl)thioureido]-3-pyridinecarboxylate (**6a**).

To a solution of ethyl 2-isothicyanatopyridine-2-carboxylate **5** (0.4 g, 1.92 mmoles) in 7 ml of dry tetrahydrofuran, *S*-(+)-2-amino-1-propanol was added, stirred at room temperature for 1 hour and the solvent was evaporated under reduced pressure to give white crystals, 0.26 g (48%), mp 132-133°; ir: 3446, 3264, 2965, 1688, 1601, 1558, 1506, 1424, 1365, 1280, 1199, 1146, 1088, 1053, 781, 720 cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.25 (d, 3H, J = 6.6 Hz, CH_3CH-), 1.37 (t, 3H, J = 7.1 Hz, CH_3CH_2-), 3.38-3.50 (m, 1H, CH_3CH-), 4.22-4.51 (m, 4H, CH_3CH_2-, -$CH(CH_3)CH_2OH$), 7.20 (dd, 1H, $J_{4,5}$ = 7.6 Hz, $J_{5,6}$ = 4.9 Hz, H_5), 8.44 (d, 1H, $J_{4,5}$ = 7.8 Hz, H_4), 8.50 (d, 1H, $J_{5,6}$ = 4.8 Hz, H_6), 11.16 (s, 1H, N*H*), 11.73 (d, 1H, J = 7.6 Hz, N*H*).

Anal. Calcd. for $C_{12}H_{17}N_3O_3S$: C, 50.87; H, 6.05; N, 14.83. Found: C, 51.36; H, 5.63; N, 15.28.

Ethyl 2-[3-[1-(Hydroxymethyl)propyl]thioureido]-3-pyridinecarboxylate (**6b**).

Compound **6b** was obtained in a similar manner as compound **6a** from ethyl 2-isothicyanatopyridine-3-carboxylate **5** (0.4 g, 1.92 mmoles) in 7 ml of dry tetrahydrofuran, and *R*-(-)-2-amino-1-butanol in 3 hours at room temperature. The solvent was evaporated under reduced pressure to give white crystals, 0.03 g (6%), mp 100-104°; ir: 3264, 2966, 2864, 1690, 1599, 1559, 1507, 1422, 1279, 1182, 1142, 1085, 1051, 777 cm^{-1}; $[\alpha]_D^{20}$ = +33.28° (c = 0.357 g/100 ml of methanol); ^1H nmr (deuteriochloroform): δ 1.04 (t, 3H, J = 7.3 Hz, CH_3CH_2CH-), 1.43 (t, 3H,

J = 7.3 Hz,CH_3CH$_2$O-), 1.66-1.84 (m, 2H, CH$_3$CH_2CH-), 3.72-3.84 and 3.87-4.0 (2m, 1H each, -CHCH_2OH), 4.43 (q, 2H, J = 7.3 Hz, CH$_3$CH_2O-), 4.55-4.70 (m, 1H, -NHC*H*CH$_2$), 7.02 (dd, 1H, $J_{4,5}$ = 7.8 Hz, $J_{5,6}$ = 4.9 Hz, H_5), 8.31-8.46 (m, 2H, H_4, H_6), 11.45 (broad s, 1H, N*H*), 11.79 (broad d, 1H, J = 7.3 Hz, N*H*).

Anal. Calcd. for $C_{13}H_{19}N_3O_3S$: C, 52.49; H, 6.45; N, 14.13. Found: C, 52.82; H, 6.25; N, 13.72.

3-Methyl-2,3,10,10a-tetrahydro-5*H*-pyrido[2,3-*d*][1,3]thiazolo-[3,2-*a*]pyrimidin-5-one (**7a**).

Ethyl 2-[3-(2-hydroxy-1-methylethyl)thioureido]-3-pyridinecarboxylate **6a** (0.2 g, 0.71 mmole) was dissolved in 7 ml of methanolic hydrogen chloride and stirred at reflux temperature for 19 hours, and after evaporation of the solvent under reduced pressure the brownish residue was triturated with 3 ml of chloroform and the precipitated product was filtered, dissolved in 4 ml of water and neutralized to *p*H 7.5 with water ammonia and extracted with chloroform (2 x 30 ml). The organic layer was dried (magnesium sulfate). After filtration, the solvent was removed under reduced pressure to give 0.12 g (78%) of white crystals, mp 213-215°; ir: 3464, 1682, 1558, 1424, 1358, 1295, 1244, 1172, 1109, 1030, 802, 727 cm^{-1}; $[\alpha]_D^{20}$ +155.59° (c = 0.367 g/100 ml of methanol); ^{1}H nmr (deuteriochloroform): δ 1.59 (d, 3H, J = 6.3 Hz, CH_3CH-), 3.05 (dd, 1H, ABX system, J_{AX} = 0.7 Hz, J_{AB}= 11.2 Hz, H_2), 3.80 (dd, 1H, ABX system, J_{BX} = 7.8 Hz, J_{AB} = 11.2 Hz, H_2), 5.20-5.35 (m, 1H, ABX system, H_3), 7.34 (dd, 1H, $J_{6,7}$ = 8.1 Hz, $J_{7,8}$ = 4.4 Hz, H_7), 8.51 (dd, 1H, $J_{6,8}$ = 1.9 Hz, $J_{6,7}$ = 8.1 Hz, H_6), 8.9 (dd, 1H, $J_{6,8}$ =1.9 Hz, $J_{7,8}$ = 4.6 Hz, H_8).
Anal. Calcd. for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16. Found: C, 54,98; H, 3.88; N, 19.45.

3-Ethyl-2,3,10,10a-tetrahydro-5*H*-pyrido[2,3-*d*][1,3]thiazolo-[3,2-*a*]pyrimidin-5-one (**7b**).

Ethyl 2-[3-[1-(hydroxymethyl)propyl]thioureido]-3-pyridinecarboxylate **6b** (0.09 g, 0.3 mmole) was dissolved in 3 ml of methanolic hydrogen chloride and stirred at reflux temperature for 24 hours, and after evaporation of the solvent under reduced pressure the residue was triturated with 3 ml of chloroform and the precipitated product was filtered, dissolved in 4 ml of water and neutralized to *p*H 7.5 with water ammonia and extracted with chloroform (2 x 30 ml). The organic layer was dried using magnesium sulfate. After filtration, the solvent was removed under reduced pressure and the product recrystallized from toluene-hexane to give 0.03 g (42%) of white crystals, mp 168-170°; ir: 3456, 2980, 1674, 1558, 1428, 1245, 1036, 802 cm^{-1}; $[\alpha]_D^{20}$ = -181.5° (c = 0.340 g/100 ml of methanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 0.97 (t, 3H, J = 7.3 Hz, CH_3CH$_2$-), 1.72-1.98 (m, 2H, CH$_3$CH_2-), 3.40 (dd, 1H, ABX system, J_{AX} = 0.9 Hz, J_{AB} = 11.5 Hz, H_2), 3.80 (dd, 1H, ABX system, J_{BX} = 7.8 Hz, J_{AB} = 11.5 Hz, H_2), 4.92-5.05 (m, 1H, ABX system, H_3), 7.47 (dd, 1H, $J_{6,7}$ = 7.8 Hz, $J_{7,8}$ = 4.6 Hz, H_7), 8.47 (dd, 1H, $J_{6,8}$ = 1.9 Hz, $J_{6,7}$ = 7.8 Hz, H_6), 8.87 (dd, 1H, $J_{6,8}$ = 1.9 Hz, $J_{7,8}$ = 4.6 Hz, H_8).
Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.62; H, 4.76; N, 18.01. Found: C, 56.33; H, 5.01; N, 17.79.

3-(2-Hydroxy-1-methylethyl)-2-thioxo-1,2-dihydropyrido-[2,3-*d*]pyrimidin-4(3*H*)-one (**8**).

Ethyl 2-[3-(2-hydroxy-1-methylethyl)thioureido]-3-pyridinecarboxylate **6a** (1.49 g, 5.29 mmoles) was dissolved in 65 ml of 10% (w/w) sodium hydroxide solution and reaction mixture was stirred for 20 minutes at room temperature. It was acidified with 10% hydrogen chloride solution to *p*H 6.5 and of the precipitated product was filtered and recrystallized from 1-propanol to give 0.18 g (37%) white crystals, mp 214-215°; ir: 3464, 3107, 2926, 1702, 1678, 1602, 1525, 1455, 1402, 1296, 1255, 1185, 1108, 1038, 773 cm^{-1}; $[\alpha]_D^{20}$ = -41.44° (c = 0.340 g/100 ml dimethyl sulfoxide); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.36 (d, 3H, J = 6.8 Hz, CH_3CH-), 3.64-3.76 and 3.91-4.05 (2m, 1H each, -CH_2OH), 4.80 (t, 1H, J = 6.4 Hz, -CH$_2$O*H*), 5.83-6.30 (m, 1H, -C*H*(CH$_3$)CH$_2$OH), 7.63 (dd, 1H, $J_{5,6}$ = 7.8 Hz, $J_{6,7}$ = 4.8 Hz, H_6), 8.29 (dd, 1H, $J_{5,7}$ = 1.9 Hz, H_5), 8.68 (dd, 1H, H_7).
Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71. Found: C, 50.57; H, 4.40; N, 18.05.

Methyl 3-[3-[1-(Hydroxymethyl)propyl]thioureido]-2-pyrazine-carboxylate (**10a**) and 3-[1-(Hydoxymethyl)propyl]-2-thioxo-1,2-dihydropteridin-4(3*H*)-one (**11a**).

To a stirred solution of methyl 3-isothiocyanatopyrazine-2-carboxylate **9** (0.400 g, 2.05 mmoles) in 8 ml of dry tetrahydrofuran, (*R*)-(-)-2-amino-1-butanol (0.198 g, 2.22 mmole) was added, and stirred at room temperature for 24 hours. After evaporation of the solvent to one third of the starting volume, the precipitated product was washed with a small quantity of dry tetrahydrofuran. This product was purified using column chromatography (silica gel, dichloromethane:acetone = 4:1) and the first fraction gave after recrystallization from 1-propanol 0. 113 g (22%) of **11a**, mp 202-204°, ir: 3370, 2860, 1685, 1595, 1560, 1550, 1445, 1393, 1377, 1280, 1270, 1225, 1190, 1080, 1040, 990, 720 cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 0.89 (t, 3H, J = 7.3 Hz, CH_3CH$_2$-), 1.74-1.94 and 1.94-2.14 (2m, 1H each, CH$_3$CH_2-), 3.66-3.83 and 3.90-4.12 (2m, 1H each, HOCH_2-), 4.78 (broad t, J = 5.5 Hz, *H*OCH$_2$-), 5.84-6.04 (m, 1H, CH$_3$CH$_2$C*H*(CH$_2$OH)-), 8.64 and 8.76 (2d, 1H each, J = 1.5 Hz, H_6 and H_7)
Anal. Calcd. for $C_{10}H_{12}N_4O_2S$: C, 47.61; H, 4.79; N, 22.21. Found: C, 47.39; H, 4.32; N, 22.71.
The second fraction after column chromatography yielded 0.151 g (26%) of **10a**, mp 178-180°, ir: 3438, 2961, 1695, 1576, 1507, 1436, 1384, 1295, 1231, 1175, 1078, 1046, 854, 814, 716 cm^{-1}; $[\alpha]_D^{20}$ + 18.72° (c = 0.376 g/100 ml of methanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.03 (t, 3H, J = 7.2 Hz, CH_3CH$_2$CH-), 1.63-1.80 (m, 2H, CH$_3$CH_2CH-), 3.72-3.83 and 3.85-4.02 (2m, 1H each, -CHCH_2OH), 3.94 (s, 3H, -COOCH$_3$), 4.54-4.72 (m, 1H, -NHC*H*CH$_2$), 8.41 and 8.54 (2d, 1H each, J = 2.5 Hz, H_5 and H_6), 11.03 (s, 1H, NH), 11.14 (d, 1H, J = 7.9 Hz, N*H*).
Anal. Calcd. for $C_{11}H_{16}N_4O_3S$: C, 46.47; H, 5.67; N, 19.70. Found: C, 46.49; H, 5.57; N, 19.78.

Methyl 3-[3-(1-benzyl-2-hydroxyethyl)thioureido]-2-pyrazine-carboxylate (**10b**).

Prepared in the same manner as compound **10a** from methyl 3-isothiocyanatopyrazine-2-carboxylate **9** and *R*-(+)-2-amino-3-phenyl-1-propanol, to give after column chromatography (silica gel, dichloromethane:acetone = 4:1) and recrystallization from 1-propanol 0.408 g (57%) of **10b**, mp 179-182°, ir: 3299, 2944, 1696, 1585, 1560, 1509, 1440, 1289, 1159, 1101, 1040, 812, 757, 704 cm^{-1}; $[\alpha]_D^{20}$ = + 100.04° (c = 0.409 g/100 ml of methanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.94 (dd, 1H, J = 7.6 Hz, -CHCH_2OH), 3.06 (dd, 1H, J = 7.6 Hz, -CHCH_2OH), 3.93 (s, 3H, -COOCH_3), 3.52 (d, 2H, J = 4.1 Hz, -CH_2C$_6$H$_5$), 4.44-4.57 (m, 1H, -NHC*H*CH$_2$), 7.18-7.37 (m, 5H, phenyl), 8.42 and 8.54 (2d, 1H each, J = 2.5 Hz, H_5 and H_6), 11.07 (s, 1H, N*H*), 11.23 (d, 1H, J = 7.8 Hz, NH).
Anal. Calcd. for $C_{16}H_{18}N_4O_3S$: C, 55.48; H, 5.24; N, 16.17. Found: C, 55.86; H, 4.96; N, 16.55.

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