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Synthesis of 3-Isothiocyanatopropion- and -butyraldehyde Diethyl Acetals and Their Reactions with N-Nucleophiles

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Abstract—A one-pot procedure was developed for the synthesis of 3-isothiocyanatopropionaldehyde and 3-isothiocyanatobutyraldehyde diethyl acetals from the corresponding α,β-unsaturated aldehydes. Reactions of 1,1-diethoxy-3-isothiocyanatobutane with aliphatic amines and hydrazines gave, respectively, substituted thioureas and thiosemicarbazides which underwent acid-catalyzed cyclization to form 6-ethoxytetrahydropyrimidine-2(1*H*)-thiones, 9,10-dimethoxy-2-methyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinoline-4-thiones, and 2-methyl-2,3,6,7,12,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole-4(1*H*)-thione.

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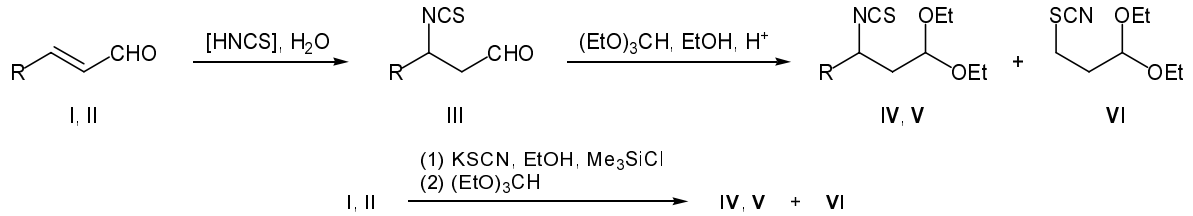
Carbonyl compounds having an isothiocyanato group in the β-position are widely used in organic synthesis [1, 2]. On the other hand, their application is limited because of their low stability on storage in basic medium. As we showed in [3], 1,1-diethoxy-3-isothiocyanatobutane (**V**) is free from the above disadvantages, and in some cases it can be used as a synthetic equivalent of the corresponding aldehyde. Acetal **V** was prepared previously from 3-isothiocyanatobutanal (**III**) which was synthesized in turn from crotonaldehyde (**II**) and thiocyanic acid [4]. In this case, the yield of **V**, calculated on the initial aldehyde **II**, did not exceed 30%. With a view to simplify the procedure for the preparation of 3-isothiocyanatoaldehyde acetals we performed a one-pot synthesis via successive addition of chlorotrimethylsilane and triethyl orthoformate to a suspension of potassium thiocyanate in ethanol, containing the corresponding α,β-unsaturated aldehyde (**I** or **II**, Scheme 1). The reaction of potassium thiocyanate with chlorotrimethylsilane in alcoholic medium generates free thiocyanic acid which adds to α,β-unsaturated aldehyde. The subsequent reaction of isothiocyanato- and thiocyanato-substituted aldehydes with alcohol in the presence of triethyl orthoformate leads to the formation of acetals **IV**–**VI** (Scheme 1). The addition of thiocyanic acid to crotonaldehyde in water was reported to give isothiocyanate **III**, while its addition to acrolein led to a mixture of the corresponding isothiocyanate and thiocyanate at a ratio of 3:1 [4]. Likewise, from aldehyde **II** we obtained isothiocyanato acetal **V** as the only product (yield 69%), whereas a mixture of 1,1-diethoxy-3-isothiocyanatopropane (**IV**) and 1,1-diethoxy-3-thiocyanatopropane (**VI**) at a ratio of 2:1 (overall yield 63%) was formed from aldehyde **I**. Presumably, the selectivity in the addition of HNCS to acrolein depends on the solvent.

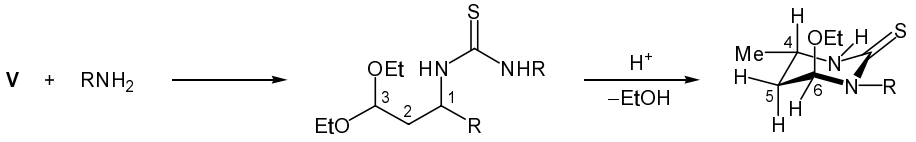
The IR spectra of acetals **IV**–**VI** (neat) contained absorption bands typical of stretching vibrations of the acetal C–H bond (a doublet at 1050–1120 cm^{-1}). The isothiocyanato group gives rise to a strong peak in the region 2000–2200 cm^{-1}. In the spectrum of isomer

Scheme 1.



I, **IV**, R = H; **II**, **III**, **V**, R = Me.

Scheme 2.



R = 2-(1*H*-indol-3-yl)ethyl (**a**), 3,4-$(MeO)_2C_6H_3(CH_2)_2$ (**b**), $Ph(CH_2)_2$ (**c**), $PhCH_2$ (**d**), 2-furoylamino (**e**), PhCONH (**f**), 3,4-$(MeO)_2C_6H_3CH_2NH$ (**g**), NH_2 (**h**), 4*H*-1,2,4-triazol-4-yl (**i**), 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl (**j**).

mixture **IV**/**VI**, stretching vibrations of the thiocyanato group appeared as a shoulder at 2180 cm^{-1} on the NCS band [4]. The ^1H NMR spectrum of acetal **V** was identical to that reported for a sample of **V** prepared by independent method [3], and its ^{13}C NMR spectrum (recorded without decoupling from protons) was fully consistent with its structure. The ^1H and ^{13}C NMR spectra of acetal mixture **IV**/**VI** contained a double set of signals with an intensity ratio of 2:1. The chemical shifts and signal multiplicities were in agreement with the structure of these compounds.

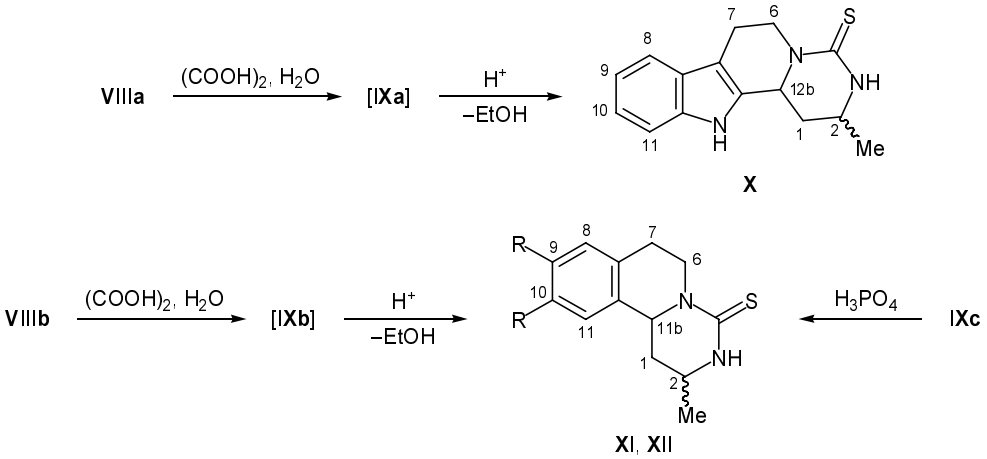
Compound **V** readily reacted with nitrogen-centered nucleophiles (primary aliphatic amines and hydrazines **VIIa**–**VIIj**) in diethyl ether. The reactions occurred at the isothiocyanato group to give substituted thioureas and thiosemicarbazides **VIIIa**–**VIIIj** in 52–98% yield (Scheme 2).

Treatment of compounds **VIIIc**–**VIIIg** with a saturated aqueous solution of oxalic acid or heating in alcohol in the presence of a catalytic amount of *p*-toluenesulfonic acid led to the formation of 37–76% of 6-ethoxy-4-methyltetrahydropyrimidine-2(1*H*)-thiones **IXc**–**IXc**. It should be noted that the pyrimidine ring closure is diastereoselective, and compounds **IXc**–**IXg** are formed as a single diastereoisomer with the ethoxy group in the axial position and methyl group in the equatorial position.

In the ^1H NMR spectra of pyrimidinethiones **IXc**–**IXg**, the coupling constants $^3J_{5\text{-}eq,\,6\text{-}eq}$ and $^3J_{5\text{-}ax,\,6\text{-}eq}$ range from 2.4 to 2.6 Hz, indicating equatorial orientation of the proton on C^6. One of the C^5H_2 protons appears as a multiplet at δ 1.28–1.41 ppm with the following coupling constants: ^2J = 13.2–13.4, $^3J_{5\text{-}ax,4\text{-}ax}$ = 13.0–13.2, and $^3J_{5\text{-}ax,\,6\text{-}eq}$ = 2.4–2.6 Hz. These values correspond to axial orientation of the 4-H proton and equatorial orientation of the methyl group at the same carbon atom. Axial orientation of the ethoxy group is typical of structurally related compounds and is determined by the anomeric effect [5].

In the reactions of thioureas **VIIIa** and **VIIIb** with a saturated aqueous solution of oxalic acid we isolated 2-methyl-2,3,6,7,12,12b-hexahydropyrimido[1',6':1,2]-pyrido[3,4-*b*]indole-4(1*H*)-thione (**X**) and 9,10-dimethoxy-2-methyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinoline-4-thione (**XI**), respectively (Scheme 3). The transformation of **VIIIa** and **VIIIb** into compounds **X** and **XI** is likely to occur as cascade cyclization, the first step of which is formation of

Scheme 3.



XI, R = MeO; **XII**, R = H.

6-ethoxypyrimidine-2-thiones **IXa** and **IXb**. Compounds **X** and **XI** were formed as mixtures of 2,11b-*cis*/*trans* and 12,12b-*cis*/*trans* isomers at ratios of 3:5 and 4:3, respectively (yield 44 and 53%). An analogous cyclization of 6-hydroxypyrimidine-2-thiones was reported by us previously [6]. The NMR spectra of **X** and **XI** were identical to those given in [6].

1-Phenylethyl-substituted pyrimidine **IXc** failed to undergo cyclization under analogous conditions. We succeeded in obtaining the corresponding cyclization product, 2-methyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinoline-4-thione (**XII**) only by heating compound **IXc** in 85% phosphoric acid. Compound **XII** was isolated as a mixture of 2,11b-*cis*/*trans* isomers at a ratio of 8:5 (overall yield 22%).

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer from neat substances or solutions in $CHCl_3$. The NMR spectra were measured on a Bruker AC-200 spectrometer at 200.13 MHz for ^1H and 50.3 MHz for ^{13}C using tetramethylsilane as internal reference. The progress of reactions and the purity of products were monitored by TLC on Sorbfil plates (STKh-1VE silica gel, layer thickness 110 μm, polyethylene terephthalate support). The melting points were determined on a Boetius melting point apparatus.

1,1-Diethoxy-3-isothiocyanatobutane (V). Chlorotrimethylsilane, 15.4 ml (13.2 g, 0.12 mol), was added dropwise to a mixture of 10.0 ml (8.48 g, 0.12 mol) of freshly distilled crotonaldehyde (**II**) and 1.75 g (0.12 mol) of potassium thiocyanate in 28 ml of anhydrous ethanol EtOH under stirring at 0°C with protection from atmospheric moisture. The mixture was stirred for 2 h, 20.0 ml (17.8 g, 0.12 mol) of triethyl orthoformate was added, and the mixture was stirred for 48 h at room temperature and neutralized with a 5% aqueous solution of sodium carbonate. The organic layer was separated, the aqueous layer was treated with diethyl ether (3×15 ml), the extracts were combined with the organic phase and dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was distilled in a vacuum. Yield 17.0 g (69%), bp 130–132°C (22). IR spectrum, ν, cm^{-1}: 1050–1110 (C–O), 2000–2200 (NCS). The ^1H NMR spectrum of **V** coincided with that described previously [3]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm ($^1J_{CH}$, Hz): 15.4 q ($OCH_2C\mathbf{H}_3$, J = 126.1), 22.2 q (3-CH_3, J = 128.9), 41.5 t (C^2, J = 128.5), 50.8 d (C^3, J = 146.1), 61.9 t ($O\mathbf{C}H_2CH_3$, J = 141.3), 100.2 d (C^1, J = 158.1), 131.2 s (NCS).

1,1-Diethoxy-3-isothiocyanatopropane (IV) was synthesized in a similar way using acrolein (**I**) as initial compound. The product was isolated as a mixture with 1,1-diethoxy-3-thiocyanatopropane (**VI**) at a ratio of 2:1. Overall yield 63%, bp 121–122°C (15 mm). IR spectrum, ν, cm^{-1}: 1050–1120 (C^1–H), 2000–2200 (NCS, SCN). ^1H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): **IV**: 1.21 t (6H, $OCH_2C\mathbf{H}_3$, ^3J = 7.0), 1.97 d.t (2H, C^2H_2, ^3J = 5.6, 6.6), 3.44–3.75 m (6H, $OC\mathbf{H}_2CH_3$, C^3H_2), 4.62 t (1H, 1-H, ^3J = 5.6); **VI**: 1.20 t (6H, $OCH_2C\mathbf{H}_3$, ^3J = 7.0), 2.11 d.t (2H, C^2H_2, ^3J = 5.3, 7.3), 3.06 t (2H, C^3H_2, ^3J = 7.3), 3.44–3.75 m (4H, $OC\mathbf{H}_2CH_3$), 4.61 t (1H, 1-H, ^3J = 5.3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: **IV**: 15.3 ($OCH_2\mathbf{C}H_3$), 34.2 (C^2), 41.2 (C^3), 62.2 ($O\mathbf{C}H_2CH_3$), 100.2 (C^1), 112.5 (NCS); **VI**: 15.3 ($OCH_2\mathbf{C}H_3$), 29.6 (C^3), 34.2 (C^2), 62.2 ($O\mathbf{C}H_2CH_3$), 100.8 (C^1), 113.8 (SCN).

***N*-(3,3-Diethoxy-1-methylpropyl)-*N'*-[2-(1*H*-indol-3-yl)ethyl]thiourea (VIIIa).** A solution of 1.915 g (0.012 mol) of 2-(1*H*-indol-3-yl)ethan-1-amine (**VIIa**) in 20 ml of diethyl ether was added dropwise under stirring to a solution of 2.434 g (0.012 mol) of acetal **V** in 20 ml of diethyl ether. The mixture was stirred for 5 h, the solvent was removed under reduced pressure, and the residue was washed with cold petroleum ether and dried under reduced pressure at 50°C. Yield 3.960 g (91%), oily substance. IR spectrum, ν, cm^{-1}: 1040–1100 (C–O); 1520 (C=S); 3390, 3450, 3500 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.11 t (6H, $OCH_2C\mathbf{H}_3$, ^3J = 7.0), 1.15 d (3H, 1-CH_3, ^3J = 3.7), 1.69 d.d (2H, C^2H_2, ^3J = 5.5, 5.0), 3.00 t (2H, CH_2, indole, ^3J = 6.5), 3.40 t (2H, NCH_2, ^3J = 6.5), 3.56 q (4H, $OC\mathbf{H}_2CH_3$, ^3J = 7.0), 4.05 m (1H, 1-H), 4.50 t (1H, 3-H, ^3J = 5.0), 6.30 s (1H, NH), 6.38 s (1H, N'H), 6.94 s (1H, 2'-H), 7.07 d.d (1H, 6'-H, ^3J = 7.2, 7.0), 7.16 d.d (1H, 5'-H, ^3J = 7.2, 7.0), 7.33 d (1H, 7'-H, ^3J = 7.0), 7.57 d (1H, 4'-H, ^3J = 7.0), 8.63 s (1H, 1'-H). Found, %: C 62.85; H 8.01. $C_{19}H_{29}N_3O_2S$. Calculated, %: C 62.78; H 8.04.

***N*-(3,3-Diethoxy-1-methylpropyl)-*N'*-[2-(3,4-dimethoxyphenyl)ethyl]thiourea (VIIIb)** was synthesized in a similar way from acetal **V** and 2-(3,4-dimethoxyphenyl)ethan-1-amine (**VIIb**). Yield 96%, oily substance. IR spectrum, ν, cm^{-1}: 1010–1120 (C–O); 1490 (C=S); 3350, 3420 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.17 t (3H, $OCH_2C\mathbf{H}_3$, ^3J = 7.0), 1.18 t (3H, $OCH_2C\mathbf{H}_3$, ^3J = 7.0), 1.23 d (3H, 1-CH_3, ^3J = 6.4), 1.80 d.d (2H, C^2H_2, ^3J = 5.7, 5.5), 2.87 t (2H, $C\mathbf{H}_2Ar$, ^3J = 7.0), 3.44 q (2H, $OC\mathbf{H}_2CH_3$, ^3J = 7.0), 3.49 q (2H, $OC\mathbf{H}_2CH_3$, ^3J = 7.0), 3.65 m (2H, NCH_2), 3.84 s (6H, OCH_3), 4.02 m (1H, 1-H),

4.58 t (1H, 3-H, ^3J = 5.5), 6.46 s (1H, NH), 6.50 s (1H, N'H), 6.73–6.82 m (3H, H_{arom}). Found, %: C 59.39; H 8.38. $C_{19}H_{32}N_2O_4S$. Calculated, %: C 59.35; H 8.39.

***N*-(3,3-Diethoxy-1-methylpropyl)-*N'*-(2-phenylethyl)thiourea (VIIIc)** was synthesized in a similar way from acetal **V** and 2-phenylethan-1-amine (**VIIc**). Yield 98%, oily substance. IR spectrum, ν, cm^{-1}: 1030–1100 (C–O); 1510 (C=S); 3350, 3450 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.14 t (3H, OCH_2CH_3, ^3J = 7.0), 1.17 t (3H, OCH_2CH_3, ^3J = 7.0), 1.22 d (3H, 1-CH_3, ^3J = 6.8), 1.80 d.d (2H, C^2H_2, ^3J = 5.7, 5.5), 2.92 t (2H, CH_2Ph, ^3J = 7.0), 3.44 m (2H, $NHCH_2$), 3.52–3.70 m (4H, OCH_2CH_3), 4.06 m (1H, 1-H), 4.56 t (1H, 3-H, ^3J = 5.5), 6.57 s (1H, NH), 6.61 s (1H, N'H), 7.19–7.23 m (5H, H_{arom}). Found, %: C 62.90; H 8.67. $C_{17}H_{28}N_2O_2S$. Calculated, %: C 62.93; H 8.70.

***N*-Benzyl-*N'*-(3,3-diethoxy-1-methylpropyl)thiourea (VIIId)** was synthesized in a similar way from acetal **V** and benzylamine (**VIId**). The product separated from the reaction mixture and was filtered off and washed with cold petroleum ether. Yield 94%, mp 73–74°C. IR spectrum, ν, cm^{-1}: 1040–1110 (C–O); 1500 (C=S); 3320, 3420 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.07 t (3H, OCH_2CH_3, ^3J = 7.0), 1.13 t (3H, OCH_2CH_3, ^3J = 7.0), 1.25 d (3H, 1-CH_3, ^3J = 6.6), 1.81 d.d (2H, C^2H_2, ^3J = 5.7, 5.6), 3.40 q (2H, OCH_2CH_3, ^3J = 7.0), 3.55 q (2H, OCH_2CH_3, ^3J = 7.0), 4.06 m (1H, 1-H), 4.56 t (1H, 3-H, ^3J = 5.6), 4.68 m (2H, CH_2Ph), 6.38 d (1H, NH, ^3J = 7.9), 6.74 s (1H, N'H), 7.32 m (5H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.2 (OCH_2CH_3), 15.3 (OCH_2CH_3), 21.1 (1-CH_3), 40.4 (C^2), 46.8 (C^1), 48.8 (CH_2Ph), 61.1 (OCH_2CH_3), 62.4 (OCH_2CH_3), 100.5 (C^3), 127.7 ($C^{4'}$), 127.8 ($C^{3'}$, $C^{5'}$), 128.7 ($C^{2'}$, $C^{6'}$), 137.5 ($C^{1'}$), 180.8 (C=S). Found, %: C 61.89; H 8.40. $C_{16}H_{26}N_2O_2S$. Calculated, %: C 61.90; H 8.44.

***N*-(3,3-Diethoxy-1-methylpropyl)-2-(2-furylcarbonyl)hydrazine-1-carbothioamide (VIIIe)** was synthesized as described above for compound **VIIIa** from acetal **V** and furan-2-carbohydrazide (**VIIe**). Yield 65%, oily substance. IR spectrum, ν, cm^{-1}: 1050–1120 (C–O); 1510 (C=S); 1680 (C=O); 3300, 3440 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.10 t (3H, OCH_2CH_3, ^3J = 7.0), 1.24 t (3H, OCH_2CH_3, ^3J = 7.0), 1.26 d (3H, 1-CH_3, ^3J = 6.6), 1.88 d.d (2H, C^2H_2, ^3J = 5.7, 5.7), 3.50 m (2H, OCH_2CH_3), 3.55 m (2H, OCH_2CH_3), 4.58 m (1H, 1-H, ^3J = 5.7), 4.68 t (1H, 3-H, ^3J = 5.7), 7.35 d (1H, NH, ^3J = 8.1), 8.89 s (1H, N'H), 6.54 d.d (1H, 4'-H, ^3J = 3.4, 1.8), 7.22 d (1H, 3'-H, ^3J = 3.4), 7.54 s (1H, 5'-H), 9.24 s (1H, NHCO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.7 (OCH_2CH_3), 16.0 (OCH_2CH_3), 20.7 (1-CH_3), 40.1 (C^2), 48.5 (C^1), 62.0 (OCH_2CH_3), 63.0 (OCH_2CH_3), 101.3 (C^3), 113.0 ($C^{4'}$), 117.1 ($C^{3'}$), 131.2 ($C^{5'}$), 146.1 ($C^{2'}$), 170.8 (C=O), 181.1 (C=S). Found, %: C 51.16; H 7.03. $C_{14}H_{23}N_3O_4S$. Calculated, %: C 51.05; H 7.04.

2-Benzoyl-*N*-(3,3-diethoxy-1-methylpropyl)hydrazine-1-carbothioamide (VIIIf) was synthesized as described above for compound **VIIIa** from acetal **V** and benzohydrazide (**VIIf**). Yield 86%, mp 104–105°C. IR spectrum, ν, cm^{-1}: 1050–1120 (C–O); 1520 (C=S); 1650 (C=O); 3240, 3300 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.10 t (3H, OCH_2CH_3, ^3J = 6.8), 1.13 t (3H, OCH_2CH_3, ^3J = 6.8), 1.23 d (3H, 1-CH_3, ^3J = 6.4), 1.84 d.d (2H, C^2H_2, ^3J = 5.5, 5.3), 3.50 q (2H, OCH_2CH_3, ^3J = 6.8), 3.58 q (2H, OCH_2CH_3, ^3J = 6.8), 4.54 m (1H, 1-H, ^3J = 5.3), 4.67 t (1H, 3-H, ^3J = 5.5), 7.42–7.91 m (6H, NH, H_{arom}), 9.49 s (1H, N'H), 9.82 s (1H, NHCO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.8 (OCH_2CH_3), 16.0 (OCH_2CH_3), 21.1 (1-CH_3), 40.5 (C^2), 48.4 (C^1), 62.0 (OCH_2CH_3), 62.7 (OCH_2CH_3), 101.2 (C^3), 128.0 ($C^{2'}$, $C^{6'}$), 129.5 ($C^{3'}$, $C^{5'}$), 131.9 ($C^{1'}$), 133.3 ($C^{4'}$), 171.2 (C=O), 180.3 (C=S). Found, %: C 56.72; H 7.38. $C_{16}H_{25}N_3O_3S$. Calculated, %: C 56.61; H 7.42.

***N*-(3,3-Diethoxy-1-methylpropyl)-2-(3,4-dimethoxybenzyl)hydrazine-1-carbothioamide (VIIIg)** was synthesized as described above for compound **VIIId** from acetal **V** and 1-(3,4-dimethoxyphenyl)hydrazine (**VIIg**). Yield 52%, mp 78–79°C. IR spectrum, ν, cm^{-1}: 1020–1120 (C–O); 1510 (C=S); 3330, 3420 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.18 t (3H, OCH_2CH_3, ^3J = 7.2), 1.21 t (3H, OCH_2CH_3, ^3J = 7.2), 1.28 d (3H, 1-CH_3, ^3J = 6.8), 1.90 d.d (2H, C^2H_2, ^3J = 5.7, 5.5), 3.46–3.76 m (6H, OCH_2CH_3, NHNH), 3.86 s (6H, OCH_3), 4.60 m (1H, 1-H), 4.68 t (1H, 3-H, ^3J = 5.5), 5.21 d (1H, $CH_2C_6H_3$, ^2J = 14.5), 5.38 d (1H, $CH_2C_6H_3$, ^2J = 14.5), 6.84 m (2H, 5'-H, 6'-H), 7.00 s (1H, 2'-H), 8.28 d (1H, NH, ^3J = 8.3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.3 (OCH_2CH_3), 15.4 (OCH_2CH_3), 20.4 (1-CH_3), 39.8 (C^2), 48.0 (C^1), 55.9 (OCH_3), 57.2 ($CH_2C_6H_3$), 60.8 (OCH_2CH_3), 62.2 (OCH_2CH_3), 100.9 (C^3), 111.2 ($C^{5'}$), 111.4 ($C^{2'}$), 120.8 ($C^{6'}$), 128.5 ($C^{1'}$), 148.8 ($C^{4'}$), 149.4 ($C^{3'}$), 180.9 (C=S). Found, %: C 56.03; H 8.14. $C_{18}H_{31}N_3O_4S$. Calculated, %: C 56.08; H 8.10.

***N*-(3,3-Diethoxy-1-methylpropyl)hydrazinecarbothioamide (VIIIh)** was synthesized as described above for compound **VIIIa** from acetal **V** and hydrazine (**VIIh**). Yield 94%, oily substance. IR spectrum, ν, cm^{-1}: 1050–1120 (C–O); 1520 (C=S); 3200, 3320,

3400 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.20 t (3H, OCH_2CH_3, ^3J = 7.0), 1.24 t (3H, OCH_2CH_3, ^3J = 7.0), 1.28 d (3H, 1-CH_3, ^3J = 6.8), 1.90 d.d (2H, C^2H_2, ^3J = 5.9, 5.7), 3.44–3.62 m (2H, OCH_2CH_3), 3.65–3.77 m (2H, OCH_2CH_3), 3.81 s (2H, NH_2), 4.57 m (1H, 1-H, ^3J = 7.8, 6.8), 4.69 t (1H, 3-H, ^3J = 5.9), 7.79 d (1H, NH, ^3J = 7.8), 7.89 s (1H, N'H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.3 (OCH_2CH_3), 15.4 (OCH_2CH_3), 20.5 (1-CH_3), 39.7 (C^2), 46.9 (C^1), 61.1 (OCH_3), 62.2 (OCH_3), 100.9 (C^3), 181.0 (C=S). Found, %: C 46.20; H 8.95. $C_9H_{21}N_3O_2S$. Calculated, %: C 45.93; H 8.99.

***N*-(3,3-Diethoxy-1-methylpropyl)-*N'*-(4*H*-1,2,4-triazol-4-yl)thiourea (VIIIi)** was synthesized as described above for compound **VIIId** from acetal **V** and 4*H*-1,2,4-triazol-4-amine (**VIIi**). Yield 64%, mp 107–108°C. IR spectrum, ν, cm^{-1}: 1050–1120 (C^3–H), 1520 (C=S), 3210 (N–H). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 1.19 t (6H, OCH_2CH_3, ^3J = 7.0), 1.23 d (3H, 1-CH_3, ^3J = 6.4), 1.70–1.99 m (2H, C^2H_2), 3.31 s (1H, NH), 3.48–3.73 m (4H, OCH_2CH_3), 4.60 t (1H, 3-H, ^3J = 5.1), 4.89 m (3H, 1-H, 3'-H, 5'-H), 8.58 s (1H, N'H). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 15.6 (OCH_2CH_3), 20.3 (1-CH_3), 40.9 (C^2), 46.9 (C^1), 62.4 (OCH_3), 63.7 (OCH_3), 84.2 ($C^{2'}$, $C^{5'}$), 102.3 (C^3), 184.5 (C=S). Found, %: C 46.20; H 7.45. $C_{11}H_{21}N_5O_2S$. Calculated, %: C 45.97; H 7.37.

***N*-(3,3-Diethoxy-1-methylpropyl)-*N'*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)thiourea (VIIIj)** was synthesized as described above for compound **VIIId** from acetal **V** and 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**VIIj**). Yield 70%, mp 122–123°C. IR spectrum, ν, cm^{-1}: 1050–1120 (C–O); 1490 (C=S); 1630 (C=O); 3290, 3410 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.95–1.30 m (9H, OCH_2CH_3, 1-CH_3), 1.62 m (1H, 2-H), 1.87 m (1H, 2-H), 2.24 s (3H, 5'-CH_3), 3.13 s (3H, 1'-CH_3), 3.39–3.73 m (4H, OCH_2CH_3), 4.49 m (1H, 1-H), 4.58 m (1H, 3-H), 7.31–7.52 m (5H, C_6H_5), 7.85 s (1H, NH), 8.41 s (1H, N'H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.8 (5'-CH_3); 15.3 (OCH_2CH_3); 15.4 (OCH_2CH_3); 20.4 (1-CH_3); 35.6 (1'-CH_3); 40.2 (C^2); 48.2 (C^1); 60.6 (OCH_3); 62.2 (OCH_3); 100.9 (C^3); 110.3 ($C^{4'}$); 124.9, 127.5, 129.4, 134.1 (C_6H_5); 134.2 ($C^{5'}$); 162.5 (C=O); 181.9 (C=S). Found, %: C 59.04; H 7.35. $C_{20}H_{30}N_4O_3S$. Calculated, %: C 59.09; H 7.44.

6-Ethoxy-4-methyl-1-(2-phenylethyl)tetrahydropyrimidine-2(1*H*)-thione (IXc). A mixture of 8.750 g (0.027 mol) of compound **VIIIc** and 80 ml of a saturated aqueous solution of oxalic acid was stirred for 24 h at room temperature. The precipitate was filtered off, washed with water, and recrystallized from ethanol. Yield 5.697 g (76%), mp 127–128°C. IR spectrum, ν, cm^{-1}: 1510 (C=S), 3450 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.18 t (3H, OCH_2CH_3, ^3J = 7.0), 1.21 d (3H, 4-CH_3, ^3J = 6.4), 1.28 m (1H, 5-H_{ax}), 1.90 m (1H, 5-H_{eq}), 2.98–3.24 m (2H, CH_2Ph), 3.47 q (2H, OCH_2CH_3, ^3J = 7.0), 3.56–3.72 m (2H, 4-H, 1-CH_2,), 4.22 d.d (1H, 6-H, ^3J = 2.4, 2.4), 4.49–4.62 m (1H, 1-CH_2), 6.92 s (1H, NH), 7.25–7.30 m (5H, C_6H_5). Found, %: C 64.60; H 7.88. $C_{15}H_{22}N_2OS$. Calculated, %: C 64.71; H 7.96.

1-Benzyl-6-ethoxy-4-methyltetrahydropyrimidine-2(1*H*)-thione (IXd) was synthesized in a similar way from compound **VIIId**. Yield 66%, mp 163–164°C. IR spectrum, ν, cm^{-1}: 1490 (C=S), 3420 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.19 t (3H, OCH_2CH_3, ^3J = 7.0), 1.23 d (3H, 4-CH_3, ^3J = 6.6), 1.41 m (1H, 5-H_{ax}), 2.03 m (1H, 5-H_{eq}), 3.44–3.56 m (2H, OCH_2CH_3), 3.69–3.80 m (1H, 4-H), 4.42 d (1H, CH_2Ph, ^2J = 15.4), 4.43 d.d (1H, 6-H, ^3J = 2.4, 2.4), 6.17 d (1H, CH_2Ph, ^2J = 15.4), 6.93 s (1H, NH), 7.26–7.35 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.4 (OCH_2CH_3), 20.5 (4-CH_3), 27.8 ($C^{3'}$, $C^{5'}$), 33.9 (C^5), 37.3 ($C^{1'}$), 43.1 (C^4), 54.7 (CH_2), 64.1 (OCH_2CH_3), 82.0 (C^6), 127.4 ($C^{4'}$), 128.6 ($C^{2'}$, $C^{6'}$), 179.0 (C=S). Found, %: C 63.80; H 7.61. $C_{14}H_{20}N_2OS$. Calculated, %: C 63.60; H 7.62.

***N*-(6-Ethoxy-4-methyl-2-thioxohexahydropyrimidin-1-yl)furan-2-carboxamide (IXe)** was synthesized in a similar way from compound **VIIIe**. Yield 40%, mp 128–129°C. IR spectrum, ν, cm^{-1}: 1490 (C=S); 1670 (C=O); 3200, 3400 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.19 t (3H, OCH_2CH_3, ^3J = 7.0), 1.20 m (1H, 5-H_{ax}), 1.24 d (3H, 4-CH_3, ^3J = 6.8), 1.93–2.10 m (1H, 5-H_{eq}), 3.59 m (1H, 4-H), 3.84 m (2H, OCH_2CH_3), 4.93 d.d (1H, 6-H, ^3J = 2.5, 2.5), 6.55 d.d (1H, 4'-H, ^3J = 3.5, 1.8), 7.28 d.d (1H, 3'-H, ^3J = 3.5, 0.8), 7.49 s (1H, NH), 7.59 d.d (1H, 5'-H, ^3J = 1.8, 0.8), 9.26 s (1H, NHCO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.3 (OCH_2CH_3), 20.3 (4-CH_3), 34.6 (C^5), 43.9 (C^4), 45.5 ($C^{5'}$), 65.0 (OCH_2CH_3), 86.9 (C^6), 112.2 ($C^{4'}$), 116.5 ($C^{3'}$), 146.1 ($C^{2'}$), 158.3 (C=O), 179.1 (C=S). Found, %: C 50.74; H 6.07. $C_{12}H_{17}N_3O_3S$. Calculated, %: C 50.87; H 6.05.

***N*-(6-Ethoxy-4-methyl-2-thioxohexahydropyrimidin-1-yl)benzamide (IXf)** was synthesized in a similar way from compound **VIIIf**. Yield 65%, mp 137–138°C. IR spectrum, ν, cm^{-1}: 1500 (C=S); 1680 (C=O); 3200, 3420 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.19 t (3H, OCH_2CH_3, ^3J = 7.0), 1.24 d

(3H, 4-CH_3, ^3J = 6.6), 1.31 m (1H, 5-H_{ax}), 1.86–2.10 m (1H, 5-H_{eq}), 3.53–3.68 m (2H, OC**H**$_2$$CH_3$), 3.73–3.92 m (1H, 4-H), 4.99 d.d (1H, 6-H, ^3J = 2.6, 2.6), 7.11 s (1H, NH), 7.45–7.98 m (5H, C_6H_5), 9.15 s (1H, NHCO). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.3 (OCH_2**C**H_3), 20.4 (4-CH_3), 34.5 (C^5), 43.9 (C^4), 65.1 (OCH_2CH_3), 86.5 (C^6), 127.7 ($C^{3'}$, $C^{5'}$), 128.8 ($C^{2'}$, $C^{6'}$), 132.1 ($C^{1'}$), 132.5 ($C^{4'}$), 167.8 (C=O), 179.1 (C=S). Found, %: C 57.25; H 6.70. $C_{14}H_{19}N_3O_2S$. Calculated, %: C 57.32; H 6.53.

1-(3,4-Dimethoxybenzylamino)-6-ethoxy-4-methyltetrahydropyrimidine-2(1*H*)-thione (IXg) was synthesized in a similar way from compound **VIIIg**. Yield 37%, mp 111–112°C. IR spectrum, ν, cm^{-1}: 1490 (C=S), 3420 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.21 t (3H, OCH_2C**H**$_3$, ^3J = 7.0), 1.26 d (3H, 4-CH_3, ^3J = 6.6), 1.38 m (1H, 5-H_{ax}), 2.03 m (1H, 5-H_{eq}), 3.46–3.57 m (2H, OC**H**$_2$$CH_3$), 3.68–3.79 m (1H, 4-H), 3.87 s (6H, OCH_3), 4.33 d (1H, C**H**$_2$$C_6H_3$, ^2J = 14.9), 4.45 d.d (1H, 6-H, ^3J = 2.4, 2.4), 6.12 d (1H, C**H**$_2$$C_6H_3$, ^2J = 14.9), 6.83–7.02 m (5H, C_6H_3, 3-H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.4 (OCH_2**C**H_3), 20.5 (4-CH_3), 34.0 (C^5), 43.0 (C^4), 54.3 (CH_2), 56.0 (OCH_3), 64.0 (O**C**H_2CH_3), 81.7 (C^6), 111.1 ($C^{5'}$), 111.4 ($C^{2'}$), 120.4 ($C^{6'}$), 129.9 ($C^{1'}$), 148.7 ($C^{4'}$), 149.3 ($C^{3'}$), 178.8 (C=S). Found, %: C 57.20; H 7.39. $C_{16}H_{25}N_3O_3S$. Calculated, %: C 56.61; H.42.

2-Methyl-2,3,6,7,12,12b-hexahydropyrimido[1',6':1,2]pyridino[3,4-*b*]indole-4(1*H*)-thione (X) was synthesized as described above for compound **IXc** from compound **VIIIa**. Yield 44%, mp 266–267°C. IR spectrum, ν, cm^{-1}: 1495 (C=S); 3420, 3480 (NH). The ^{1}H NMR spectrum of **X** coincided with that reported in [6]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: *trans* isomer: 20.0 (C^7), 20.7 (2-CH_3), 31.9 (C^1), 43.0 (C^2), 47.0 (C^6), 49.0 (C^{12b}), 107.6 (C^{7a}), 110.4 (C^{11}), 117.0 (C^8), 118.0 (C^{10}), 120.4 (C^9), 125.7 (C^{7b}), 132.2 (C^{12a}), 135.5 (C^{11a}), 176.5 (C=S); *cis* isomer: 20.0 (C^7), 20.7 (2-CH_3), 31.9 (C^1), 44.5 (C^2), 47.0 (C^6), 52.1 (C^{12b}), 107.6 (C^{7a}), 110.4 (C^{11}), 117.0 (C^8), 118.0 (C^{10}), 120.4 (C^9), 125.7 (C^{7b}), 132.2 (C^{12a}), 135.5 (C^{11a}), 176.5 (C=S). Found, %: C 66.12; H 6.41. $C_{15}H_{17}N_3S$. Calculated, %: C 66.39; H 6.31.

9,10-Dimethoxy-2-methyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinoline-4-thione (XI) was synthesized as described above for compound **IXc** from compound **VIIIb**. Yield 53%, mp 197–198°C. IR spectrum, ν, cm^{-1}: 1495 (C=S), 3425 (NH). The ^{1}H NMR spectrum of **XI** coincided with that reported in [6]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: *trans* isomer: 20.4 (2-CH_3), 28.0 (C^7), 34.5 (C^1), 45.7 (C^2), 46.0 (C^6), 51.3 (C^{11b}), 55.5 (OCH_3), 55.8 (OCH_3), 109.3 (C^{11}), 111.6 (C^8), 126.7 (C^{7a}), 128.2 (C^{11a}), 147.4 (C^{10}), 147.5 (C^9), 176.3 (C=S); *cis* isomer: 21.8 (2-CH_3), 28.2 (C^7), 34.5 (C^1), 44.0 (C^2), 46.4 (C^6), 51.3 (C^{11b}), 55.5 (OCH_3), 55.8 (OCH_3), 109.3 (C^{11}), 111.6 (C^8), 126.7 (C^{7a}), 128.2 (C^{11a}), 147.4 (C^{10}), 147.5 (C^9), 176.6 (C=S). Found, %: C 61.62; H 6.87. $C_{15}H_{20}N_2O_2S$. Calculated, %: C 61.62; H 6.89.

2-Methyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrimido[6,1-*a*]isoquinoline-4-thione (XII). A solution of 5.090 g (15.7 mmol) of compound **VIIIc** in 10 ml of 85% H_3PO_4 was heated for 1.5 h under reflux, cooled to room temperature, and poured onto ice. The precipitate was filtered off, washed with cold water, and recrystallized from ethanol. Yield 0.803 g (22%), mp 161–162°C. IR spectrum, ν, cm^{-1}: 1495 (C=S), 3430 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): *trans* isomer: 1.33 d (3H, 2-CH_3, ^3J = 6.6), 2.15–2.21 m (2H, C^1H_2), 2.76 m (1H, 7-H_{eq}, ^2J = 15.8, ^3J = 5.1, ^3J = 2.8), 3.00–3.21 m (1H, 7-H_{ax}), 3.32 m (1H, 6-H_{ax}, ^2J = 12.2, ^3J = 12.2, ^3J = 2.8), 3.53–3.62 m (1H, 2-H), 4.70–4.80 m (1H, 11b-H), 5.42–5.54 m (1H, 6-H_{eq}), 6.95 s (1H, NH), 7.13–7.21 m (4H, H_{arom}); *cis* isomer: 1.26 d (3H, 2-CH_3, ^3J = 6.6), 1.67 m (1H, 1-H_{ax}, ^2J = 13.2, ^3J = 11.2, 11.2), 2.53 m (1H, 1-H_{eq}, ^2J = 13.2), 2.76 m (1H, 7-H_{eq}, ^2J = 15.8, ^3J = 5.1, 2.8), 3.00–3.21 m (1H, 7-H_{ax}), 3.32 m (1H, 6-H_{ax}, ^2J = 12.2, ^3J = 12.2, 2.8), 3.65–3.76 m (1H, 2-H), 4.70–4.80 m (1H, 11b-H), 5.42–5.54 m (1H, 6-H_{eq}), 6.60 s (1H, NH), 7.13–7.21 m (4H, H_{arom}). Found, %: C 67.35; H 6.94. $C_{13}H_{16}N_2S$. Calculated, %: C 67.20; H 6.94.

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