Reactivity of *N'*-substituted *N*-(4-pentynoyl)- and *N*-[2-(2-propynyl)-4-pentynoyl]thioureas

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Dedicated to Professor RNDr. V. Sutoris, CSc., in honour of his 60th birthday

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Treatment of *N*-(4-pentynoyl)- and *N*-[2-(2-propynyl)-4-pentynoyl]-thioureas with sodium ethoxide and mercury(II) chloride or acetate, respectively, results in splitting-off of acyl residue under formation of *N*-substituted thioureas. On heating 4-{*N*-[2-(2-propynyl)-4-pentynoyl]thiocarbamoyl} morpholine in ethanol under catalytic action of titanium(III) chloride the reaction proceeds on the thiocarbonyl group, while the morpholine residue is replaced by ethoxy group under formation of the respective *O*-ethyl monothiocarbamate. On treatment of the studied thioureas with bromine in chloroform it was found that only the compounds with aromatic residue were reactive. While *N'*-phenyl derivatives are oxidized to the respective ureas, *N'*,*N'*-diphenylthioureas undergo intramolecular electrophilic aromatic substitution to give benzothiazoline derivatives.

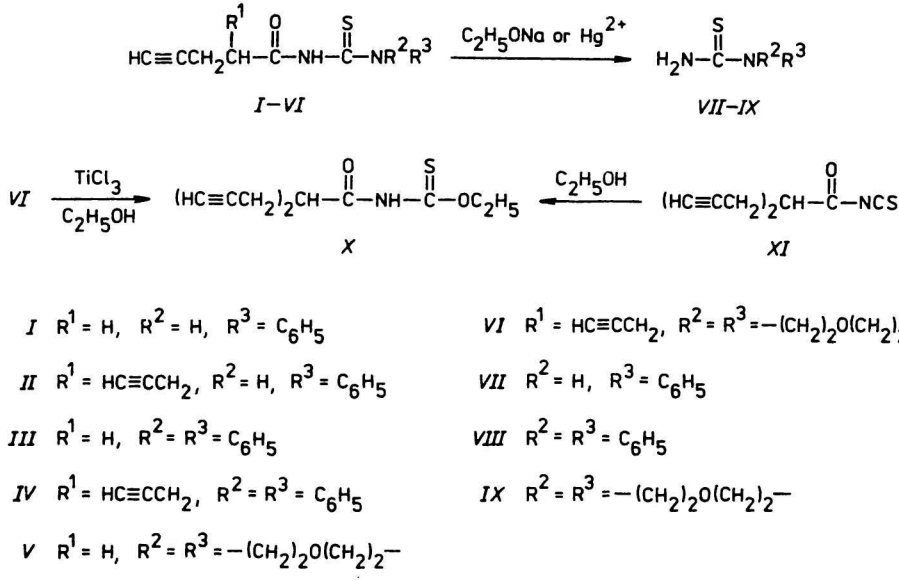
Действие этанолята натрия и хлорида или ацетата ртути(II) соответственно на *N*-(4-пентиноил)- и *N*-[2-(2-пропинил)-4-пентиноил]-тиомочевины приводит к отщеплению ацильного остатка с образованием *N*-замещенных тиомочевин. При нагревании 4-{*N*-[2-(2-пропинил)-4-пентиноил]тиокарбамоил}морфолина в этаноле при каталитическом действии хлористого титана(III) реакция проходит по тиокарбонильной группе, а остаток морфолина замещается этокси-группой с образованием соответствующего *O*-этилмонотиокарбамата. При воздействии бромом на исследуемые тиомочевины в хлороформе было обнаружено, что только соединения с ароматическими остатками были реакционноспособны. В то время как *N'*-фенил-производные окисляются в соответствующие мочевины, *N'*,*N'*-дифенилтиомочевины подвергаются внутримолекулярному электрофильному ароматическому замещению с образованием производных бензотиазолина.

In our previous work [1] we studied the selectivity of nucleophilic addition and substitution on the isothiocyanatocarbonyl group of 4-pentynoyl- and 2-(2-propynyl)-4-pentynoyl isothiocyanate in their reactions with amines. We found that the respective thioureas were selectively formed when diphenylamine

was used with both isothiocyanates as well as in the reaction of 2-(2-propynyl)-4--pentynoyl isothiocyanate with piperidine and morpholine. In the reaction of both isothiocyanates with benzylamine and aniline and in the reaction of 4-pentynoyl isothiocyanate with piperidine and morpholine the mixture of thiourea and the substitution product of the respective amide was formed.

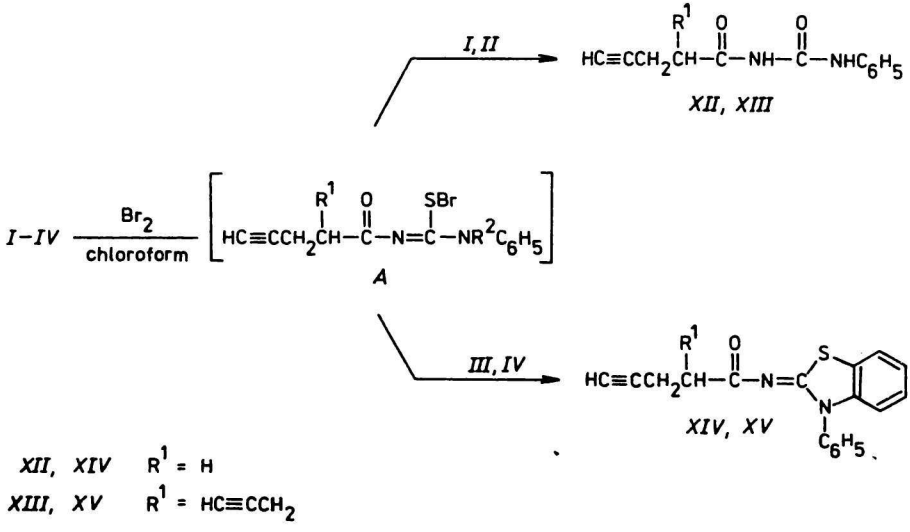
In the present work we have studied the reactivity of the obtained addition products, *i.e.* *N'*-substituted *N*-(4-pentynoyl)- and *N*-[2-(2-propynyl)-4-pentynoyl]thioureas. We wanted to know whether the triple bond of the 4-pentynoyl residue would be sufficiently reactive for intramolecular addition of sulfur or nitrogen atom [2] to give seven- and five-membered heterocycles, respectively. We found that intramolecular addition did not take place under various conditions (treatment with alkali reagents, catalysis with metal salts, and oxidation with bromine), however, other reactions proceeded on the acylthiourea grouping. In nucleophilic additions to nonactivated C≡C bond the reactivity of the nucleophile is often increased by action of alkali reagents [3, 4] or the reactivity of the C ≡ C bond is increased by catalysis with mercury(II) compounds [5—9] or other reagents, *e.g.* titanium(IV) chloride [10]. Based on this knowledge, we studied the reactions of thioureas *I—VI* (Scheme 1) with sodium ethoxide as well as with mercury(II) chloride and acetate. We found that the acyl residue was split-off under formation of *N*-substituted thioureas *VII—IX*. Though on treatment with sodium hydride in dimethylformamide or dimethyl sulfoxide the respective sodium salts were formed, as indicated by release of hydrogen, after the work-up of the reaction mixture only the starting unreacted compound was recovered. Interesting results were obtained when studying the effect of titanium chlorides on thiourea *VI*. While titanium(IV) chloride in dioxan and ethanol and titanium(III) chloride in dioxan brought about no change, on heating of thiourea *VI* in ethanol in the presence of titanium(III) chloride, the morpholine residue was replaced by ethoxy group under formation of *O*-ethyl *N*-[2-(2--propynyl)-4-pentynoyl]monothiocarbamate (*X*, Scheme 1). When this reaction was run in dioxan in the presence of 5% ethanol, the same product was obtained, but in low yield. The structure of the compound *X* was proved unambiguously by independent synthesis, namely by the reaction of 2-(2-propynyl)-4-pentynoyl isothiocyanate (*XI*) with ethanol.

We investigated further the course of the *Hugershoff* reaction [11], *i.e.* oxidation of the studied thioureas with bromine in chloroform. We found that the intermediate sulfenyl bromides (*A*) did not react with the C≡C bond by electrophilic addition. With thioureas having alkylamine residue no reaction took place. In the case of phenylamine residue (*I* and *II*) the thiocarbonyl group was oxidized to carbonyl group under formation of ureas *XII* and *XIII* (Scheme 2), probably by hydrolysis of the respective sulfenyl bromides, similarly as on the oxidation of *N*-phenyl-*N'*-(2-phenyl-4-thiazolylmethyl)thioureas with



Scheme 1

$K_3[Fe(CN)_6]$ [12]. On the other hand, thioureas *III* and *IV* reacted with diphenylamine residue similarly as *N*-methyl-*N*-phenyl-*N'*-(3-phenylpropenoyl)-thiourea [13] and *N*-substituted phenyl-*N'*-(3-phenylpropenoyl)thioureas with



Scheme 2

substituents activating the *o*-position of the phenyl ring [14]. Here, due to electrophility of the sulfur atom of sulfenyl bromide (*A*), intramolecular electrophilic substitution took place on the aromatic ring under formation of benzothiazoline derivatives *XIV* and *XV*. We found that in the case of the diphenylamine residue the respective urea *XVI* could be prepared by photooxidation of thiourea *IV*.

The structures of the obtained products were proved by spectral methods. In the IR spectra of *N*-acylureas *XII*, *XIII*, and *XVI* characteristic split absorption bands of the CONHCO grouping appeared with maxima at $\tilde{\nu} = 1680\ \mathrm{cm}^{-1}$ and $\tilde{\nu} = 1710\ \mathrm{cm}^{-1}$, in agreement with the data published on spectra of *N*-acylureas [15]. While in the ^{13}C NMR spectrum of thiourea *II* signals $\delta(\mathrm{C=O}) = 173$ ppm and $\delta(\mathrm{C=S}) = 178$ ppm were present, the spectrum of *N*-acylurea *XIII* showed two signals of the carbonyl carbons $\delta(\mathrm{C=O}) = 152$ ppm and 175 ppm. In the mass spectra of the compounds *II* and *XIII* peaks of molecular ions with m/z values corresponding to the expected molecular masses were present. For determination of the structure of *II* it is significant that the peak $[C_6H_5NCS]^+$ appeared in the spectrum at $m/z = 135$ ($I_r = 57\,\%$), while the spectrum of urea *XIII* revealed the similar peak $[C_6H_5NCO]^+$ at $m/z = 119$ ($I_r = 58\,\%$). The respective fragment ions can be formed in both cases from the molecular ion by hydrogen shift, followed by splitting-off of the amide residue. Their presence proves unambiguously the conversion of acylthiourea grouping of the compound *II* into acylurea grouping of the compound *XIII*.

Elemental analysis of the products *XIV* and *XV* pointed to loss of two hydrogen atoms against the starting thioureas *III* and *IV*. This, together with the significant shift of the band $\nu(\mathrm{C=O})$ from the region of $\tilde{\nu} = 1705$—$1720\ \mathrm{cm}^{-1}$ with thioureas to $\tilde{\nu} = 1620\ \mathrm{cm}^{-1}$ with benzothiazoline derivatives indicated the formation of the conjugated system O=C−N=C and proved the structures suggested for the compounds *XIV* and *XV*.

Experimental

All thioureas used and 2-(2-propynyl)-4-pentynoyl isothiocyanate were prepared according to [1]. The course of the reactions was monitored by thin-layer chromatography on Silufol plates (Kavalier).

Infrared spectra were recorded in chloroform with an IR-75 (Zeiss, Jena) apparatus, ^{1}H and ^{13}C NMR spectra with a Tesla BS 487 A (80 MHz) and Tesla BS 567 A (25.25 MHz) spectrometers in deuteriochloroform (*II*, *X*, *XIII*, *XV*, *XVI*) or in the mixture of deuteriochloroform and hexadeuteriodimethyl sulfoxide (volume ratio = 1 : 1) (*VII*—*IX*, *XII*, *XIV*). Mass spectra of the compounds *II* and *XIII* were measured with an MS 902 S (AEI Manchester) apparatus at 70 eV.

N-[2-(2-Propynyl)-4-pentynoyl]-N'-phenylthiourea (II)

^{13}C NMR, δ/ppm: 20.68 (t, $-CH_2-$), 45.32 (d, $-\overset{|}{C}H-$), 71.97 (d, $\equiv CH$), 79.66 (d, $\equiv C-$), 124.15, 126.91, 128.85, 137.44 (d, d, d, s, C_6H_5-), 173.27 (s, C=O), 177.97 (s, C=S). Mass spectrum, m/z (I_r/%): M^+, 270 (5), $[M-CH\equiv CCH_2]^+$, 231 (4), $[M-(CH\equiv CCH_2)_2CONH_2]^+$, 135 (56).

N-Substituted thioureas (VII—IX)

Method A

To the solution of thiourea *I—VI* (2 mmol) in ethanol or dioxan (30 cm^3) mercury(II) chloride (2 mmol) was added, or to the solution of the respective thiourea (2 mmol) in acetic acid (20 cm^3) mercury(II) acetate (2 mmol) was added and heated at 70°C until the starting compound vanished (10—20 h). The solvent was distilled off at reduced pressure and the residue was dissolved in minimum amount of chloroform and separated on a column of silica gel 100—250 μm (40 g), using benzene—acetone (volume ratio = 7 : 1) as the eluent, to give the products *VII—IX* in 35—50% yield.

Method B

Thiourea *I—VI* (2 mmol) was dissolved in the solution of sodium (3 mmol) in anhydrous ethanol (15 cm^3) and heated at 60°C for 3 h. Ethanol was distilled off and the residue was dissolved in water (20 cm^3), neutralized with 10% hydrochloric acid, and extracted with chloroform (10 × 20 cm^3). The extract was dried with magnesium(II) sulfate, chloroform was distilled off, and the residue was crystallized to give the compounds *VII—IX* in 60—70% yield.

Physicochemical constants of *N*-phenylthiourea (*VII*) and *N,N*-diphenylthiourea (*VIII*) are correspondent with the literature data [16].

Thiocarbamoylmorpholine (*IX*): Yield = 50—70%, m.p. = 150—152 °C (chloroform—petroleum ether). For $C_5H_{10}N_2OS$ (M_r = 146.2) w_i(calc.): 41.08% C, 6.89% H, 19.16% N; w_i(found): 41.22% C, 6.82% H, 19.23% N. IR, $\tilde{\nu}$/cm^{-1}: 1500 (NHCS), 2850 and 2930 (CH_2), 3400 and 3500 (NH_2). ^{1}H NMR, δ/ppm: 3.73 (m, 8H, $-(CH_2)_2O(CH_2)_2-$), 7.04 (s, 2H, $-NH_2$).

O-Ethyl N-[2-(2-propynyl)-4-pentynoyl]monothiocarbamate (X)

Method A

To the solution of thiourea *VI* (260 mg; 1 mmol) in ethanol (35 cm^3) titanium(III) chloride (15 mg; 0.1 mmol) in the form of 15% aqueous solution was added and the solution was heated at the bath temperature 80 °C for 60 h. Ethanol was distilled off,

the residue was separated on silica gel 100—250 μm (50 g), using benzene—acetone (volume ratio = 7 : 1) as the eluent, to give 130 mg (58 %) yield. When the mixture of dioxan (33.5 cm^3) and ethanol (1.5 cm^3) was used as solvent, the yield achieved was only 5 %.

Method B

Isothiocyanate *XI* (360 mg; 2 mmol) was dissolved in anhydrous ethanol (5 cm^3) and the solution was allowed to stand at room temperature for 45 min. Ethanol was distilled off and the residue was crystallized to give 250 mg (55 %) yield. M.p. = 92—94 °C (n-hexane). For $C_{11}H_{13}NO_2S$ (M_r = 223.3) w_i(calc.): 59.17 % C, 5.87 % H, 6.27 % N; w_i(found): 58.90 % C, 6.17 % H, 6.16 % N. IR, $\tilde{\nu}/cm^{-1}$: 1495 (NHCS), 1728 (C=O), 2120 (C≡C), 3308 (≡C−H), 3400 (N−H). ^{1}H NMR, δ/ppm: 1.38 (t, J = 7 Hz, 3H, CH_3-), 2.10 (t, J = 3 Hz, 2H, ≡CH), 2.60 (m, 4H, $-C\underline{H}_2-\underset{|}{C}H-C\underline{H}_2-$), 2.95 (m, 1H, $-\underset{|}{C}H-$), 4.55 (q, J = 7 Hz, 2H, $-CH_2O$), 9.13 (s, 1H, −NH−).

N-(4-Pentynoyl)-N'-phenylurea (XII)

To the solution of thiourea *I* (210 mg; 0.87 mmol) in chloroform (10 cm^3) bromine (138 mg; 0.044 cm^3; 0.87 mmol) was added under stirring and ice-cooling and the solution was stirred at room temperature for 11/2 h. Chloroform was distilled off and the residue was separated on silica gel 100—250 μm (50 g), using benzene—acetone (volume ratio = 7 : 1) as the eluent. Yield = 120 mg (60 %), m.p. = 150—152 °C (chloroform—petroleum ether). For $C_{12}H_{12}N_2O_2$ (M_r = 216.2) w_i (calc.): 66.67 % C, 5.59 % H, 12.96 % N; w_i (found): 66.52 % C, 5.71 % H, 13.09 % N. IR, $\tilde{\nu}/cm^{-1}$: 1680 and 1710 (C=O), 2120 (C≡C), 3308 (≡C−H), 3410 (N−H). ^{1}H NMR, δ/ppm: 2.01 (t, J = 3 Hz, 1H, ≡CH), 2.63 (m, 4H, $-CH_2CH_2-$), 7.33 (m, 5H, C_6H_5-), 10.35 and 10.53 (s, s, 1H, 1H, −NH−).

N-[2-(2-Propynyl)-4-pentynoyl]-N'-phenylurea (XIII)

The compound *XIII* was obtained from thiourea *II* in the similar way as in the preceding case. Yield = 80 %, m.p. = 152—154 °C (chloroform—petroleum ether). For $C_{15}H_{14}N_2O_2$ (M_r = 254.3) w_i (calc.): 70.85 % C, 5.55 % H, 11.02 % N; w_i (found): 70.68 % C, 5.69 % H, 11.09 % N. IR, $\tilde{\nu}/cm^{-1}$: 1680 and 1710 (C=O), 2120 (C≡C), 3309 (≡C−H), 3410 (N−H). ^{1}H NMR, δ/ppm: 2.10 (t, J = 3 Hz, 2H, ≡CH), 2.68 (m, 5H, $-CH_2\underset{|}{C}HCH_2-$), 7.31 (m, 5H, C_6H_5-), 10.19 and 10.55 (s, s, 1H, 1H, −NH−). ^{13}C NMR, δ/ppm: 20.46 (t, $-CH_2-$), 45.47 (d, $-\underset{|}{C}H-$), 71.22 (d, ≡CH), 80.10 (d, ≡C−), 120.42, 124.60, 129.08, and 136.99 (d, d, d, s, C_6H_5-), 152.17 and 174.69 (s, s, C=O). Mass spectrum, m/z (I_r/%): M^+ 254 (19), $[M - HC{\equiv}CCH_2]^+$ 215 (2), $[M - (CH{\equiv}CCH_2)_2CONH_2]^+$ 119 (58).

3-Phenyl-2-(4-pentynoylimino)benzo[d]thiazoline (XIV)

To the solution of thiourea *III* (268 mg; 0.87 mmol) in chloroform (10 cm^3) bromine (138 mg; 0.87 mmol) was added under stirring and ice-cooling, and stirring was continued at room temperature for 45 min. Chloroform was distilled off, the residue was dissolved in methanol (15 cm^3) and water was added until occurrence of turbidity. The precipitate was sucked and dried. Yield = 213 mg (80 %), m.p. = 168—170 °C (methanol). For $C_{18}H_{14}N_2OS$ (M_r = 306.3) w_i(calc.): 70.58 % C, 4.60 % H, 9.15 % N; w_i(found): 70.30 % C, 4.42 % H, 9.31 % N. IR, $\tilde{\nu}/cm^{-1}$: 1620 (C=O), 2120 (C≡C), 3315 (≡C−H). ^{1}H NMR, δ/ppm: 1.88 (t, J = 3 Hz, 1H, ≡CH), 2.60 (m, 4H, $-CH_2CH_2-$), 7.25 (m, 9H, C_6H_5- and $-C_6H_4-$).

3-Phenyl-2-[2-(2-propynyl)-4-pentynoylimino]benzo[d]thiazoline (XV)

The compound *XV* was obtained from thiourea *IV* in the similar way as in the preceding case. Yield = 87 %, m.p. = 183—185 °C (methanol). For $C_{21}H_{16}N_2OS$ (M_r = 344.5) w_i(calc.): 73.23 % C, 4.68 % H, 8.13 % N; w_i(found): 72.98 % C, 4.66 % H, 8.13 % N. IR, $\tilde{\nu}/cm^{-1}$: 1620 (C=O), 2120 (C≡C), 3310 (≡C−H). ^{1}H NMR, δ/ppm: 1.98 (t, J = 3 Hz, 2H, ≡CH), 2.73 (m, 5H, $-CH_2\underset{|}{C}H\underset{|}{C}H_2-$), 7.38 (m, 9H, C_6H_5- and $-C_6H_4-$).

N-[2-(2-Propynyl)-4-pentynoyl]-N′,N′-diphenylurea (XVI)

The solution of thiourea *IV* (1 g; 2.8 mmol) in acetone (250 cm^3), air-bubbled through quartz, was irradiated for 5 h with a high-pressure mercury discharge lamp, type TQ 150 (Original Hanan) in an immersion apparatus with the discharge lamp placed in quartz, water-cooled jacket. After filtration with charcoal, acetone was distilled off and the residue was separated on a column of silica gel 100—250 μm (100 g), using benzene—acetone (volume ratio = 12 : 1) as the eluent. Yield = 170 mg (18 %), m.p. = 107—109 °C (chloroform—petroleum ether). For $C_{21}H_{18}N_2O_2$ (M_r = 330.4) w_i(calc.): 76.34 % C, 5.49 % H, 8.48 % N; w_i(found): 76.53 % C, 5.26 % H, 8.44 % N. IR, $\tilde{\nu}/cm^{-1}$: 1680 and 1700 (C=O), 2120 (C≡C), 3310 (≡C−H), 3375 (N−H). ^{1}H NMR, δ/ppm: 1.98 (t, J = 3 Hz, 2H, ≡CH), 2.66 (m, 4H, $-C\underline{H}_2-\underset{|}{C}H-C\underline{H}_2-$), 3.85 (m, 1H, $-\underset{|}{C}H-$), 7.28 (m, 10H, $(C_6H_5-)_2$).

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