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LETTERS TO THE EDITOR

RECYCLIZATION OF ETHYL 4-HYDROXY-2-THIOXOHEXA-HYDROPYRIMIDINE-5-CARBOXY-LATES INTO 5-ACYL-5,6-DIHYDRO-2-THIOURACILS

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We have observed previously that 5-acyl-4-hydroxyhexahydropyrimidine-2-thiones **1** under the influence of bases (NaH, NaOH) in dry acetonitrile underwent rearrangement, proceeding with clevage of the C-4–C-5 to give N-acyl-N'-(β-oxoalkyl)thioureas [1]. In a continuation of this investigation it seemed advisable to study the behavior of esters of 4-hydroxy-2-thioxohexahydropyrimidine-5-carboxylic acids with respect to bases. In this paper we present preliminary results of the study of the reaction of the previously described hydroxypyrimidines **2a,b** [2,3] with sodium hydride.

We have shown, that unlike compounds **1**, pyrimidine **2a** under the influence of an equivalent amount of NaH in anhydrous acetonitrile at room temperature in one day was converted not into the thioureide **3a** but instead underwent recyclization to form 5-benzoyl-5,6-dihydro-2-thiouracil (**4**). The latter was isolated in 91% yield after neutralization of the reaction mixture with acetic acid with subsequent removal of the solvent in vacuum, treatment of the solid residue with water and filtration of the product. Evidently the recyclization of compound **2a** occurs *via* the intermediate formation of its acyclic isomer, oxoalkylthiourea, **7a**.

Conversion of the hydroxypyrimidine **2b** (a mixture of 5*R**,6*R**- and 5*S**,6*R**-diastereomers in a 65:35 ratio) under the influence of an equivalent amount of sodium hydride occurred analogously (acetonitrile, 20°C). In this case a product was obtained in 85% yield as a mixture of dihydrothiouracil **5** (*cis* diastereomer) and the *Z*- and *E*-isomers of the enol forms of **6** in the ratio 60:30:10 respectively. We have shown that this ratio is not changed when the hydroxypyrimidine **2b** with a different isomer composition [(*5R*,6R*)*:(*5S*,6R*)* = 92:8] was used and also on recrystallization of the product.

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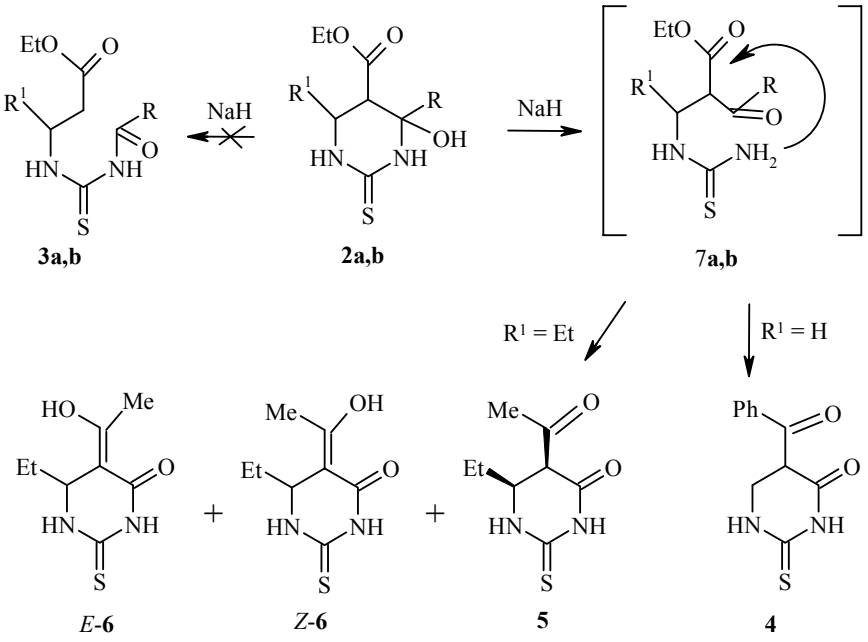
Thus we have developed a method for the synthesis of 5-acyl-5,6-dihydro-2-thiouracils based on the recyclization of readily available esters of 4-hydroxy-2-thioxohexahydropyrimidine-5-carboxylic acids under the influence of sodium hydride. The recyclization described is of a general nature which will be the basis of our future studies. It should be noted that 5-acyl-5,6-dihydrothiouracils and their 2-oxoanalogs have been a difficult class of heterocyclic compounds to obtain until now. The only previously described example of this class was obtained by the reaction of phorone with chlorosulfonyl isocyanate [4].



3a,b **2a,b** **7a,b**

E-**6** *Z*-**6** **5** **4**

2, **3**, **7** **a** R = Ph, R¹ = H; **b** R = Me, R¹ = Et

IR spectra of nujol mulls were recorded with a Bruker Equinox 55/s Fourier spectrophotometer. ^{1}H and ^{13}C NMR spectra of DMSO-d_6 solutions were recorded with Bruker DPX 300 spectrometer (300 and 75 MHz respectively). The standards were the central signal of the residual protons of the solvent, δ 2.50 ppm (for ^{1}H) and the central signal of the C atom of the solvent, δ = 39.50 ppm (for ^{13}C).

5-Benzoyl-5,6-dihydro-2-thiouracil (4). Yield 90.6%; mp 243.5-244°C (dec., ethanol). IR spectrum, ν, cm^{-1}: 3179 (w), 3107 (w, NH), 1693 (w, C=O in PhC=O), 1674 (w), 1597(w), 1580 [m, NH–C(S)–NH–C(O)]; 706 cm^{-1} (w, δ_{CH} in Ph). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.30 (1H, d, $^{4}J_{N(3)H,N(1)H}$ = 1.4, H-3); 9.72 (1H, ddd, $^{3}J_{N(1)H,Ha\text{-}6}$ =3.3, $^{3}J_{N(1)H,Hb\text{-}6}$ = 3.0, $^{4}J_{N(1)H,N(3)H}$ = 1.4, H-1); 8.02-8.07 (2H, m, H-2 and H-6 in Ph); 7.66-7.72 (1H, m, H-4 in Ph); 7.51-7.59 (2H, m, H-3 and H-5 in Ph); 4.97 (1H, dd, $^{3}J_{H\text{-}5,\ Hb\text{-}6}$ = 8.0, $^{3}J_{H\text{-}5,\ Ha\text{-}6}$ =6.2, H-5); 3.68 (1H, ddd, $^{2}J_{Ha\text{-}6,Hb\text{-}6}$ = 13.7, $^{3}J_{Ha\text{-}6,H\text{-}5}$ = 6.2, $^{3}J_{Ha\text{-}6,N(1H)}$ = 3.3, H*a*-6); 3.63 (1H, ddd, $^{2}J_{Ha\text{-}6,Hb\text{-}6}$ = 13.7, $^{3}J_{Hb\text{-}6,H\text{-}5}$ = 8.0, $^{3}J_{Hb\text{-}6,N(1H)}$ = 3.0, H*b*-6). ^{13}C NMR spectrum, δ ppm): 194.98 (C=O in PhC=O); 178.48 (C-2); 165.24 (C-4); 135.48 (C-1 in Ph); 133.95 (C-4 in Ph); 129.04 (C-2 and C-6 in Ph); 128.76 (C-3 and C-5 in Ph); 46.59 (C-5); 41.03 (C-6). Found, %: C 56.20; H 4.27; N 11.99. $C_{11}H_{10}N_2O_2S$. Calculated, %: C 56.40; H 4.30; N 11.96.

***cis*-5-Acetyl-6-ethyl-5,6-dihydro-2-thiouracil (5), *Z*-6-ethyl-5-(1-hydroxyethylidene)-5,6-dihydro-2-thiouracil (*Z*-6), and *E*-6-ethyl-5-(1-hydroxyethylidene)-5,6-dihydro-2-thiouracil (*E*-6)** (a 60:30:10 mixture). Yield 84.7%; mp 176-177.5°C (ethanol). IR spectrum, ν, cm^{-1}: 3178 (w), 3126 (s, NH), 1642 (w) 1590 [w, NH–C(S)–NH–C(O) and C=O in Ac]. ^{1}H NMR, δ, ppm (*J*, Hz): dihydrothiouracil **5** – 11.27 (1H, d, $^{4}J_{N(1)H,N(3)H}$ = 1.5, H-3); 9.81 (1H, dd, $^{3}J_{N(1)H,H\text{-}6}$ = 3.9, $^{4}J_{N(1)H,N(3)H}$ = 1.5, H-1); 3.82 (1H, d, $^{3}J_{H\text{-}5,H\text{-}6}$ = 3.9, H-5);

3.77 (1H, ddt, $^3J_{H\text{-}6,CHa}$ = 7.2, $^3J_{H\text{-}6,CHb}$ = 5.4, $^3J_{H\text{-}6,H\text{-}5}$ = $^3J_{H\text{-}6,N(1)H}$ =3.9, H-6); 2.24 (3H, s, CH_3 in Ac); 1.30-1.60(2H, signal overlap with signals of analogous protons in other isomers, CH_2 in Et); 0.86 (3H, t, ^3J = 7.4, CH_3 in Et); dihydrothiouracil *Z*-**6** – 14.01 (1H, s, OH); 11.06 (1H, d, $^4J_{N(3)H,N(1)H}$ = 1.7, H-3); 9.79 (1H, dd, $^3J_{N(1)H,\ H\text{-}6}$ = 4.0, $^4J_{N(1)H,N(3)H}$ = 1.7, H-1); 4.17 (1H, dt, $^3J_{H\text{-}6,CHa}$ = $^3J_{H\text{-}6,CHb}$ = 5.5, $^3J_{H\text{-}6,N(1)H}$ = 4.0, H-6); 2.00 (3H, s, CH_3–C=); 1.30-1.60 (2H, m, signals overlapping with signals of analogous protons for other isomers, CH_2 in Et); 0.79 (3H, t, ^3J =7.3, CH_3 in Et); dihydrothiouracil *E*-**6** – 10.28 (1H, d, $^4J_{N(3)H,N(1)H}$ = 1.7, H-3); 9.49 (1H, dd, $^3J_{N(1)H,H\text{-}6}$ =4.4, $^4J_{N(3)H,N(1)H}$ = 1.7, H-1); 4.28 (1H, dt, $^3J_{H\text{-}6,CHa}$ = $^3J_{H\text{-}6,CHb}$ = 6.0, $^3J_{H\text{-}6,N(1)H}$ = 4.4, H-6); 2.33 (3H, CH_3–C=); 1.30-1.60 (2H, signal overlap with signals of analogous protons of other isomers, CH_2 in Et); 0.77 (3H, t, ^3J = 7.3, CH_3 in Et). ^{13}C NMR spectra, δ, ppm: dihydrothiouracil, **5** – 201.98 (C=O in Ac); 177.45 (C-2); 164.34 (C-4); 56.90 (C-5); 52.33 (C-6); 29.07 (CH_3 in Ac); 26.12 (CH_2 in Et); 9.55 (CH_3 in Et); dihydrothiouracil *Z*-**6** – 176.94 (C-2); 174.28 (C–OH); 167.12 (C-4); 95.29 (C-5); 52.21 (C-6); 30.48 (CH_2 in Et); 18.43 (CH_3–C=); 8.45 (CH_3 in Et); dihydrothiouracil *E*-**6** – 177.12 (C-2); 166.40 (C–OH); 162.66 (C-4); 98.87 (C-5); 51.42 (C-6); 28.77 (CH_2 in Et); 19.64 (CH_3 in CH_3–C=); 9.25 (CH_3 in Et). Found, %: C 47.81; H 6.32; N 13.68. $C_8H_{12}N_2O_2S$. Calculated, %: C 47.98; H 6.04; N 13.99.

REFERENCES

1. A. D. Shutalev, E. A. Kishko, and S. G. Alekseeva, *Khim. Geterotsikl. Soedin.,* 839 (1999). [*Chem. Heterocycl. Comp.,* **35**, 750 (1999)].
2. A. D. Shutalev and V. A. Kuksa, *Khim. Geterotsikl. Soedin.,* 97 (1995). [*Chem. Heterocycl. Comp.,* **31**, 86 (1995)].
3. A. D. Shutalev and V. A. Kuksa, *Khim. Geterotsikl. Soedin.,* 105 (1997). [*Chem. Heterocycl. Comp.,* **33**, 91 (1997)].
4. K. Clauss, H.-J. Friedrich and H. Jensen, *Liebigs Ann. Chem.,* 561 (1974).