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REACTION OF FUNCTIONALLY 4-SUBSTITUTED HEXAHYDROPYRIMIDINE-2-THIONES WITH SODIUM TETRAHYDROBORATE. SYNTHESIS OF SIX-MEMBERED CYCLIC THIOUREAS

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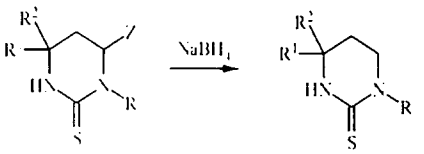
A new method was developed for the production of six-membered cyclic ureas based on the reaction of readily obtainable 4-azido-, 4-acetoxy-, or 4-phenylsulfonylhexahydropyrimidine-2-thiones with sodium tetrahydroborate.

Six-membered cyclic thioureas (hexahydro-2-pyrimidinethiones) are an extremely useful class of organic compounds, which attract attention in connection with their great practical significance [1] and high synthetic potential [1-5]. The main method for the production of these compounds is the reaction of 1,3-diaminoalkanes with such compounds as carbon disulfide, thiophosgene, etc. [1]. A substantial limitation of this method is the fact that many of the initial diamines are difficult to obtain.

Recently [6] we developed a simple general method for the synthesis of six-membered cyclic thioureas based on the reduction of readily obtainable 4-hydroxy- or 4-alkoxyhexahydro-2-pyrimidinethiones and 1,2,3,4-tetrahydro-2-pyrimidinethiones with the sodium borohydride–trifluoroacetic acid system in inert solvents. A disadvantage of this method is the use of toxic and aggressive trifluoroacetic acid and also the high acidity of the reaction medium, which is required for the generation of the reactive immonium intermediates from the initial heterocyclic compounds [6]. In the absence of trifluoroacetic acid or in the presence of the weaker acetic acid, the six-membered cyclic thioureas are not formed [6]. In [7-10] we showed that substituted hexahydro-2-pyrimidinethiones containing azide, acetoxy, or arylsulfonyl groups at the $C_{(4)}$ atom exhibit high activity in reactions with nucleophilic reagents, leading to the formation of the corresponding products from substitution at the indicated atom. In a development of these investigations and with the aim of developing a new gentle method for the production of hexahydro-2-pyrimidinethiones it seemed expedient to study the reactions of the indicated functionally 4-substituted hexahydro-2-pyrimidinethiones with an H-nucleophile such as sodium tetrahydroborate.

We showed that 4-azidotetrahydro-2-pyrimidinethiones (Ia-d) react readily with sodium tetrahydroborate in acetonitrile at 20°C for 6-7 h, giving 89-100% yields of the products from substitution of the azide group by a hydrogen atom, i.e., the corresponding hexahydro-2-pyrimidinethiones (IIa-d). The optimum amount of the reducing agent is a twofold molar excess in relation to the initial azidopyrimidine (I). As solvent it is possible to use DMFA, as we demonstrated in the case of the reaction of the azidopyrimidine (Ib) with sodium tetrahydroborate in DMFA, leading to the formation of compound (IIb) with a yield of 95%.



Ia-d, Ia, b, IV IIa-d

I Z = N_3, III Z = OAc, IV Z = SO_2Ph; Ia, IIa R = R^1 = R^2 = H; Ib, IIb, IIIa, IV R = R^2 = H, R^1 = Me; Ic, IIc, IIIb R = R^1 = Me, R^2 = H, Id, IId R = H, R^1 = R^2 = Me

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4-Acetoxy- and 4-arylsulfonylhexahydro-2-pyrimidinethiones can also be used as starting compounds. Thus, in the reaction of 4-acetoxy-2-pyrimidinethiones (IIIa, b) with sodium tetrahydroborate in acetonitrile (20°C, 5-8 h) compounds (IIb, c) are obtained with yields of 97-98%. In the reaction of 4-phenylsulfonyl-2-pyrimidinethione (IV) with sodium tetrahydroborate under analogous conditions, the pyrimidine (IIb) is formed with a yield of 85%.

Thus, on account of the realization of the reactions under mild practically neutral conditions, the method described in the present work for the production of six-membered cyclic thioureas may provide a useful alternative to the synthesis of these compounds by the usual method [6].

In the IR spectrum of compound (IId), all the main features of the spectra of other six-membered cyclic thioureas appear [6]. Thus, there is a broad absorption band for the stretching vibrations of the N–H groups at 3195 cm^{-1}, there are two strong "thioamide-II" bands at 1572 and 1544 cm^{-1}, and there is also a characteristic strong band at 1187 cm^{-1}, due to the deformation vibrations of the N–H bonds.

The PMR spectrum of compound (IId) in deuterochloroform contains a singlet signal for the protons of the methyl groups at 1.25 ppm, multiplets for the 5-H and 6-H protons at 1.70 and 3.01 ppm respectively, and two broad singlets for the protons of the NH groups at 6.63 and 7.05 ppm. As a result of the rapid inversion of the pyrimidine ring, the 5-H, 6-H, and $N_{(1)}H$ protons of compound (IId) form a five-spin AA'BB'X system. Analysis of this system by means of the SIMNMR program for the calculation of theoretical PMR spectra made it possible to obtain the average values of the vicinal spin–spin coupling constants for J_{56} (*trans*) = 7.9, J_{56} (*cis*) = 4.5, and $J_{6\text{-H,NH}}$ = 2.5 Hz.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu IR-435 instrument for suspensions in Vaseline oil. The PMR spectra were recorded on a Bruker MSL-200 spectrometer (200.13 MHz) for solutions of the samples in deuterochloroform. The chemical shifts were calibrated against the signal of the solvent with reference to TMS (δ 7.25 ppm for chloroform). The reactions and the purity of the products were monitored by TLC on Silufol plates in the 20:1 chloroform–methanol and 4:1 ether–acetone systems, and the spots were developed with iodine vapor.

The initial 4-azido-, 4-acetoxy-, and 4-phenylsulfonylhexahydro-2-pyrimidinethiones (Ia-d, IIIa, b, IV) were obtained by the reaction of 4-hydroxyhexahydro-2-pyrimidinethiones [9, 11, 12] with hydrazoic acid in water, as described in [7, 9, 8] respectively. The *trans* isomers of compounds (Ic, d, IIa, b) or a mixture (97:3) of the *trans* and *cis* isomers of compound (III) and Aldrich sodium tetrahydroborate were used in the reduction reactions.

Hexahydro-2-pyrimidinethione (IIa). A mixture of 0.179 g (1.14 mmole) of 4-azidohexahydro-2-pyrimidinethione (Ia), 0.086 g (2.28 mmole) of finely ground sodium tetrahydroborate, and 6 ml of dry acetonitrile was stirred at 20°C for 7 h. The solvent was distilled under vacuum, 4 ml of water was added to the solid residue, and the mixture was carefully acidified to pH 2-3 with hydrochloric acid. The reaction product was extracted with chloroform (7 × 5 ml), the extract was dried over magnesium sulfate, the solvent was removed under vacuum, and the residue was kept under vacuum to constant weight. We obtained 0.118 g (89.4%) of compound (IIa) in the chromatographically pure form. A sample was completely identical with the compound obtained by the method in [6].

4-Methylhexahydro-2-pyrimidinethione (IIb). The product (IIb) was obtained similarly to compound (IIa) in the chromatographically pure form by the reaction of *trans*-4-azido-6-methylhexahydro-2-pyrimidinethione (Ib) with sodium tetrahydroborate in acetonitrile (yield 97.0%) or in DMFA (yield 94.7%). A sample was completely identical with the compound obtained by the method in [6].

Compound (IIb) was synthesized by the method described above also from *trans*-4-acetoxy-6-methylhexahydro-2-pyrimidinethione (IIIa) or 6-methyl-4-phenylsulfonylhexahydro-2-pyrimidinethione (IV) with yields of 98.3 and 84.6% respectively. In the last case, for further purification the product was washed with ether cooled to −5°C.

1,4-Dimethylhexahydro-2-pyrimidinethione (IIc). The product (IIc) was obtained similarly to compound (IIa) in the chromatographically pure form with a yield of 98.9% by the reaction of *trans*-4-azido-3,6-dimethylhexahydro-2-pyrimidinethione (Ic) with sodium tetrahydroborate in acetonitrile. A sample was identical with the compound obtained by the method in [6].

The thione (IIc) was also synthesized with a yield of 97.4% by the method described above from *trans*-4-acetoxy-3,6-dimethylhexahydro-2-pyrimidinethione (IIIb).

4,4-Dimethylhexahydro-2-pyrimidinethione (IId). The product (IId) was obtained similarly to compound (IIa) in the chromatographically pure form with a quantitative yield by the reaction of 4-azido-6,6-dimethylhexahydro-2-pyrimidinethione (Id) with sodium tetrahydroborate in acetonitrile; mp 209-209.5°C (alcohol). IR spectrum, cm^{-1}: 3195 b, 1572, 1544, 1341, 1240, 1208, 1187, 712 b, 635. PMR spectrum, ppm: 7.05 (1H, bs, $N_{(1)}-H$); 6.63 (1H, bs, $N_{(3)}-H$); 3.01 (2H, m, $J_{56}(trans)$ = 7.9, $J_{56}(cis)$ = 4.5, $H_{6\text{-}H,NH}$ = 2.5 Hz, 6-H); 1.70 (2H, m, 5-H); 1.25 (5H, s, CH_3). Found %: C 50.41; H 8.41; N 19.62. $C_6H_{12}N_2S$. Calculated %: C 49.96; H 8.39; N 19.42.

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