SYNTHESIS OF 5,6-DIHYDRO-4H-1,3-THIAZINES BASED ON SUBSTITUTED N-PHENYLTHIOUREAS

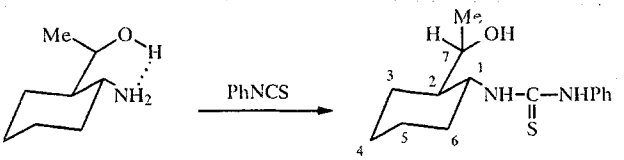
B. V. Unkovskii,* I. P. Boiko, Yu. F. Malina, T. D. Sokolova, V. F. Shchegel'skii, and L. N. Knyaz'kova

The reaction of phenyl isothiocyanate with 1,3-amino alcohols was used to synthesize substituted N-phenylthioureas, for which cyclization under the influence of mineral acids to give substituted 5,6-dihydro-4H-1,3-thiazines was studied.

In order to synthesize compounds that have properties of practical use we obtained 6-methyl- and 6-phenyl-4,5-tetramethylene-2-phenylamino-5,6-dihydro-4H-1,3-thiazines. As acyclic precursors of the 5,6-dihydro-4H-1,3-thiazines we used substituted thioureas obtained by the reaction of 1,3-amino alcohols with phenyl isothiocyanate in analogy with the known reaction of alkyl and aryl isothiocyanates with primary or secondary amines, which can lead to monosubstituted N,N-disubstituted and N,N,N′-trisubstituted thioureas [1].

In our research we used the previously described 1-(2-aminocyclohexyl)-1-ethanol (I) [2], 1-(2-aminocyclohexyl)-1-phenylmethanol (II) [3], 2-(1-aminocyclohexyl)-1-cyclohexanol (III) [3], and 2-(1-amino-1-methylethyl)-1-cyclohexanol (IV) [3]. The reaction of 1,3-amino alcohols I-IV with phenyl isothiocyanate proceeds quite smoothly in 1-3 h at 0-5°C.

N-Phenyl-N′-[2-(1-hydroxyethyl)cyclohexyl]thiourea (V) was synthesized by the reaction of purified (by distillation) 1-(2-aminocyclohexyl)-1-ethanol (I) with phenyl isothiocyanate. In addition to a band at 3080-3380 cm^{-1}, which corresponds to stretching vibrations of OH and NH groups, an intense absorption band of a thioamido group at 1530-1560 cm^{-1} is present in the IR spectra of thiourea V and the below-described thioureas VI-VIII.



I V

In connection with the fact that starting amino alcohol I is a mixture of erythro-trans and threo-trans isomers (70:30) that differ with respect to the orientation of the methyl group in the quasi-cyclic amino alcohol molecule [2], as a result of its reaction with phenyl isothiocyanate one should have expected the formation of two (erythro and threo) stereoisomers of N-phenyl-N′-[2-(1-hydroxyethyl)cyclohexyl]thiourea (V). From the reaction product we were able to isolate only one diastereomer of N-phenyl-N′-[2-(1-hydroxyethyl)cyclohexyl]thiourea (V) with a trans-diequatorial orientation of the thioureido and 2-hydroxyethyl groups relative to the cyclohexane ring. The fact that we obtained only one isomer of thiourea V instead of the expected two stereoisomers is evidently associated with the loss of the second isomer during purification of starting amino alcohol I and thiourea V itself. The stereochemical individuality of thiourea V is confirmed by data from the ^{13}C NMR spectrum. The three-dimensional structure of thiourea V was established by means of the PMR spectrum, in which the signal of a 1*a*-H proton in the form of a triplet of doublets with spin–spin coupling constants (SSCC) $J_{12} = J_{16a} \sim 10$ Hz and $J_{16e} = 3.5$ Hz is present at 4.30 ppm. (The signal is clearly seen when trifluoroacetic acid is added during recording of the spectrum.)

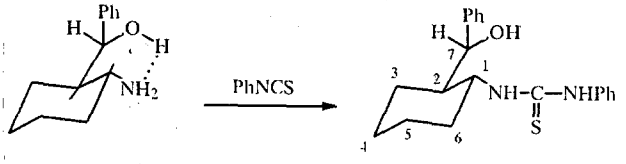
*Deceased.

M. V. Lomonosov Moscow Institute of Fine Chemical Technology, Moscow 117571. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1433-1437, October, 1992. Original article submitted May 8, 1992.

0009-3122/92/2810-1225$12.50

On the basis of these data it may be concluded that the coupling 1-H and 2-H protons are axially oriented, whereas, consequently, the thioureido and hydroxyethyl groups are equatorially oriented relative to the cyclohexane ring. The signal of a 7-H proton at 3.84 ppm with SSCC J_{72} = 4.0 Hz is also present in the PMR spectrum of thiourea V; this makes it possible to assign a trans-erythro configuration to the thiourea V molecule.

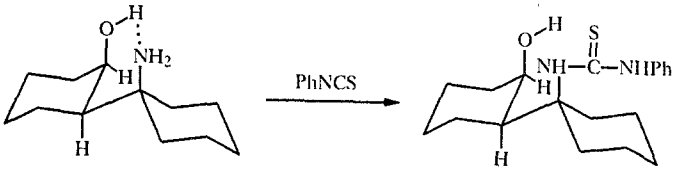
N-Phenyl-N′-[2-(1-hydroxy-1-phenylmethyl)cyclohexyl]thiourea (VI) was synthesized by the reaction of 1-(2-aminocyclohexyl)-1-phenylmethanol (II) with phenyl isothiocyanate.



II VI

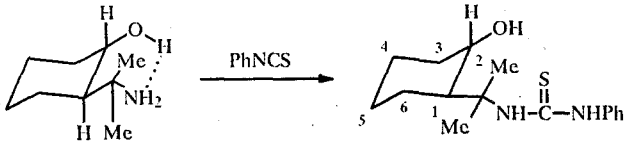
Since an erythro-trans configuration of starting amino alcohol II was previously established from PMR spectral data [3], and the reaction with phenyl isothiocyanate takes place without involvement of the asymmetric centers in the molecule, thiourea VI also has an erythro-trans configuration. The signal of the 7-H proton of the phenyl(hydroxy)methyl group in the form of a doublet with SSCC J_{72} = 4.5 Hz is present in the PMR spectrum of thiourea VI at 5.0 ppm. The magnitude of this SSCC confirms an erythro configuration of the carbinol center of the molecule.

The reaction of the cis isomer of 2-(1-aminocyclohexyl)-1-cyclohexanol (III) [4] with phenyl isothiocyanate gave N-phenyl-N′-[1-(2-hydroxycyclohexyl)cyclohexyl]thiourea (VII), the composition and structure of which were confirmed by IR spectral data and the results of elementary analysis.



III VII

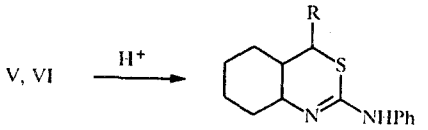
N-Phenyl-N′-[(2-hydroxycyclohexyl)-1-methylethyl]thiourea (VIII), which, after two recrystallizations from alcohol, is an individual diastereoisomer with a trans-diequatorial orientation of the hydroxy and thioureidoalkyl groups relative to the cyclohexane ring, was similarly synthesized from a mixture of the cis and trans isomers of 2-(1-amino-1-methylethyl)-1-cyclohexanol (IV), in which the trans isomer predominates (70%) [4], by reaction with phenyl isothiocyanate.



trans-IV VIII

The signal of a 1-H proton in the form of a triplet of doublets with SSCC $J_{12} = J_{16a} \sim 10$ Hz and J_{16e} = 3.5 Hz is present in the PMR spectrum of thiourea VIII at 2.05 ppm. These data make it possible to ascribe an axial orientation to the coupling 2-H and 1-H protons, and, consequently, the hydroxy and thioureidoalkyl groups are trans-diequatorially oriented.

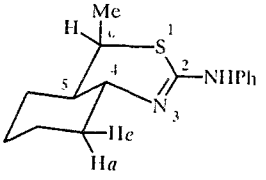
The synthesized substituted thioureas V-VIII were used to obtain some 5,6-dihydro-4H-1,3-thiazines. The cyclization of substituted N-aryl-N′-hydroxyalkylthioureas by the action of acidic catalysts, as a result of which alkyl-substituted 2-arylamino-5,6-dihydro-4H-1,3-thiazines were obtained, has been described [1, 5]. In analogy with these reports we attempted to accomplish the cyclization of thioureas V-VIII by the action of mineral acids (HCl, H_2SO_4). By refluxing with concentrated HCl for ~40 min thioureas V and VI were converted to 6-methyl-(6-phenyl)-4,5-tetramethylene-2-phenylamino-5,6-dihydro-4H-1,3-thiazines IX and X, for which it is known that the existence of amino and imino forms (amine−imine tautomerism) is possible. However, according to the available literature data, such compounds exist primarily in the amino form [5, 6].



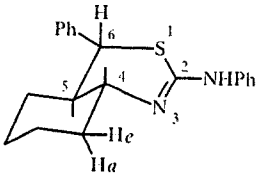
IX, X

V, IX R = Me; VI, X R = Ph

After purification by recrystallization, thiazines IX and X are individual diastereoisomers, the three-dimensional structures of which were established by means of the PMR spectra. The trans configuration of dihydrothiazine IX at the site of fusion of the cyclohexane and dihydrothiazine rings is predetermined by the trans-diequatorial orientation of the substituents in starting thiourea V. In the PMR spectrum of thiazine IX one can isolate at 3.0 ppm the signal of a 6-H proton with SSCC J_{65} = 3.6 Hz and $J_{6,CH3}$ = 7.0 Hz, which makes it possible to ascribe an equatorial orientation to the 6-H proton, and, consequently, the methyl group is axially oriented.



IX



X

The signal of a 4-H proton in the form of a characteristic triplet of doublets with $J_{45} = J_{4a} = 10.8$ Hz and $J_{4e} = 4.2$ Hz is present in the PMR spectrum of 4,5-tetramethylene-6-phenyl-2-phenylamino-5,6-dihydro-4H-1,3-thiazine (X) at 3.2 ppm; this makes it possible to ascribe an axial orientation to the 4-H and 5-H protons, and, consequently, the X molecule has trans fusion of the cyclohexane and 1,3-thiazine rings, which corresponds to a trans-diequatorial orientation of the substituents in starting thiourea V. The signal of a 6-H proton in the form of a doublet with J_{56} = 10.8 Hz is present at 4.05 ppm, which indicates an axial orientation of the 5-H and 6-H protons, and, consequently, the phenyl group attached to the ring $C_{(6)}$ atom is equatorially oriented. Attention is directed to the fact that starting 1,3-amino alcohol II had an erythro configuration with an axially oriented phenyl group in the quasi-cyclic amino alcohol molecule [3]. The corresponding thiourea VI had the same erythro configuration. The change in the orientation of the phenyl group as a result of the cyclization reaction can be explained by the formation of an intermediate stabilized (by the phenyl group) carbonium ion, the subsequent cyclization of which leads to the energetically more favorable diastereoisomer of thiazine X with an equatorially oriented phenyl group.

We were unable to accomplish the cyclization of thioureas VII and VIII to the corresponding 5,6-dihydro-4H-1,3-thiazines, although the reaction was carried out under various conditions: with hydrogen chloride, concentrated HCl in the cold and with heating, and with concentrated H_2SO_4. However, according to the TLC and PMR spectral data, destruction of the molecule to give phenylthiourea and unidentified substances was observed in all cases. This is evidently associated with steric factors that hinder cyclization.

EXPERIMENTAL

The IR spectra of thin layers of the liquid substances and suspensions of the solid substances in mineral oil were recorded with a Shimadzu IR-435 spectrometer. The ^1H NMR spectra of 2-3% solutions in $CDCl_3$ and the ^{13}C NMR spectra of 20% solutions in $CDCl_3$ or DMSO were recorded with an AC-200 P spectrometer with tetramethylsilane (TMS) as the internal standard. Thin-layer chromatography was carried out on Silufol plates in chloroform—methanol (9.5:0.5).

The results of elementary analysis were in agreement with the calculated values.

N-Phenyl-N′-[2-(1-hydroxyethyl)cyclohexyl]thiourea (V, $C_{15}H_{22}N_2OS$). A mixture of 1 g (0.007 mole) of 1-(2-aminocyclohexyl)-1-ethanol (I) in 15 ml of anhydrous ether and 1.1 ml (0.01 mole) of phenyl isothiocyanate was maintained at 3°C for 3 h, after which the resulting crystalline precipitate was removed by filtration to give 1.42 g (73%) of crude thiourea V with mp 160-161°C (alcohol) and R_f 0.36. ^{13}C NMR spectrum: 179.5 (C=S); 139.5 (quaternary carbon atom); 128.5, 124,

and 123 (m-, p-, and o-carbon atoms of the phenyl ring); 65.5 (OCH); 54.5 [$C_{(1)}$]; 48 [$C_{(2)}$]; 33, 31, 25.5, 24, and 18 ppm [$C_{(3)}$–$C_{(6)}$ atoms of the cyclohexane ring and carbon atom of the CH_3 group].

Thioureas VI-VIII were similarly obtained.

N-Phenyl-N′-[2-(1-hydroxy-1-phenylmethyl)cyclohexyl]thiourea (VI, $C_{20}H_{24}N_2OS$). The reaction of 3.0 g (0.015 mole) of 1-(2-aminocyclohexyl)-1-phenylmethanol (II) in 20 ml of anhydrous ether and 1.8 ml (0.015 mole) of phenyl isothiocyanate gave 3.5 g (70%) of thiourea VI with mp 159-160°C (alcohol) and R_f 0.36. ^{13}C NMR spectrum: 179.5 (C=S); group of signals at 123-144.5 (C atoms of the phenyl ring); 70.06 (C–OH); 54.43 [$C_{(1)}$]; 49.0 [$C_{(2)}$]; 32.4, 30.8, 25.0, and 22.9 ppm [$C_{(3)}$–$C_{(6)}$ atoms of the cyclohexane ring].

N-Phenyl-N′-[1-(2-hydroxycyclohexyl)cyclohexyl]thiourea (VII, $C_{19}H_{28}N_2OS$). The reaction of 3.0 g (0.015 mole) of 2-(1-aminocyclohexyl)-1-cyclohexanol (III) in 20 ml of anhydrous ether and 2.06 g (0.015 mole) of phenyl isothiocyanate gave 3.4 g (68%) of thiourea VII with mp 135-136°C (isopropyl alcohol) and R_f 0.54.

N-Phenyl-N′-[1-(2-hydroxycyclohexyl)-1-methylethyl]thiourea (VIII, $C_{16}H_{24}N_2OS$). The reaction of 2 g (0.013 mole) of 2-(1-amino-1-methylethyl)-1-cyclohexanol (IV) in 20 ml of anhydrous ether and 1.8 g (0.014 mole) of phenyl isothiocyanate gave 2.9 g (80%) of thiourea VIII with mp 137-138°C (alcohol) and R_f 0.5. ^{13}C NMR spectrum: 178.4 (C=S); 139.3 (quaternary carbon atom of the phenyl ring); 128.6 (C_m); 123.9 (C_p); 123.3 (C_o); 71.2 [$C_{(2)}$]; 59.0 (NH–C); 50.9 [$C_{(1)}$]; 37.1 [$C_{(3)}$]; 26.0 and 25.9 [$C_{(4)}$ and $C_{(5)}$]; 22.9 [$C_{(6)}$]; 25.1 ppm (CH_3).

6-Methyl-4,5-tetramethylene-2-phenylamino-5,6-dihydro-4H-1,3-thiazine (IX, $C_{15}H_{20}N_2S$). A mixture of 1 g (0.003 mole) of N-phenyl-N′-[2-(1-hydroxyethyl)cyclohexyl]thiourea (V) and 10 ml of concentrated HCl was refluxed for 40 min, after which it was poured over ice, and the aqueous mixture was neutralized with potassium carbonate and extracted with ether (3 × 20 ml). The ether extract was dried with anhydrous sodium sulfate, and the ether was removed by distillation to give 0.48 g (52%) of thiazine IX with mp 215-216°C (from acetone) and R_f 0.33. ^{13}C NMR spectrum: 122.2-138.6 (carbon atoms of two phenyl groups); 77.0, 57.6, 51.9, 44.5, 34.3, 28.8, 25.6, and 24.5 ppm (eight carbon atoms).

4,5-Tetramethylene-6-phenyl-2-phenylamino-5,6-dihydro-4H-1,3-thiazine (X, $C_{20}H_{22}N_2S$). Similarly, the reaction of 1 g (0.003 mole) of N-phenyl-N′-[2-(1-hydroxy-1-phenylmethyl)cyclohexyl]thiourea (VI) and 10 ml of concentrated HCl gave 0.6 g (55%) of dihydrothiazine X with mp 222-223°C (acetone) and R_f 0.33. ^{13}C NMR spectrum: 122.2-138.6 (signals of two phenyl groups); 77.0, 57.6, 51.9, 44.5, 34.3, 28.8, 25.6, and 24.5 ppm (signals of eight carbon atoms).

REFERENCES

1. *General Organic Chemistry* [in Russian], Vol. 5, Khimiya, Moscow (1983), p. 718.
2. I. P. Boiko, Yu. F. Malina, O. I. Zhuk, Yu. Yu. Samitov, and B. V. Unkovskii, *Zh. Org. Khim.*, **11**, 605 (1975).
3. B. V. Unkovskii, I. P. Boiko, Yu. F. Malina, T. O. Sashina, A. V. Peretokin, T. D. Sokolova, and L. N. Knyaz'kova, *Zh. Org. Khim.* (in press).
4. B. V. Unkovskii, T. O. Sashina, I. P. Boiko, Yu. F. Malina, and O. I. Danilova, *in: Summaries of Papers on the Nucleophilic Reactions of Carbonyl Compounds* [in Russian], Saratov (1985), p. 29.
5. P. L. Ovechkin, L. A. Ignatova, A. E. Gekhman, and B. V. Unkovskii, *Khim. Geterotsikl. Soedin.*, No. 3, 357 (1974).
6. H. Nayer, R. Giudecelli, and J. Menin, *Bull. Soc. Chim. France*, **7**, 2120 (1965).