SYNTHESIS OF 5,6-TRIMETHYLENETETRAHYDRO-1,3-OXAZINE-4-SPIROCYCLOPENTANES AND THEIR ACYCLIC PRECURSORS

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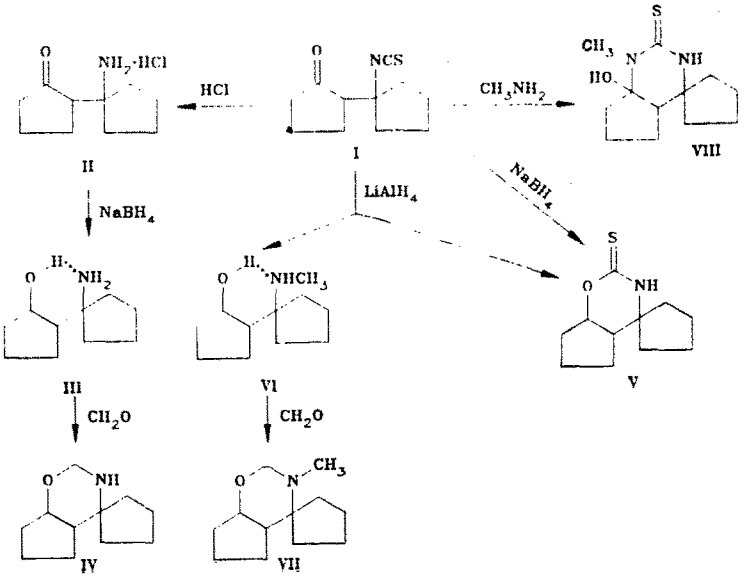
Tricyclic tetrahydro-1,3-oxazines – 5,6-trimethylenetetrahydro-1,3-oxazine-4-spirocyclopentanes IV, V, and VII – were synthesized on the basis of 2-(1-isothiocyanatocyclopentyl)cyclopentanone (I). The reductive cyclization of the latter by the action of sodium borohydride leads to oxazinethione V; the acidic hydrolysis of I with subsequent reduction of amino ketone hydrochloride II with sodium borohydride and the reaction of isothiocyanato ketone I with lithium aluminum hydride make it possible to obtain 1,3-amino alcohols III and VI, respectively, which are converted to tetrahydro-1,3-oxazines IV and VII by cyclization with formaldehyde. Pyrimidinethione VIII was synthesized from isothiocyanato ketone I and methylamine. Compounds III-VII are mixtures of stereoisomers with predominance of the cis isomer.

In developing research involving the study of the reactivities of β-isothiocyanato ketones [1] we have synthesized the previously described [2] 2-(1-isothiocyanatocyclopentyl)cyclopentanone (I) by the addition of thiocyanic acid at the moment of its generation to an α,β-unsaturated ketone – cyclopentylidenecyclopentanone [3]. Isothiocyanato ketone I was used as the starting compound for the synthesis of some heterocyclic compounds containing N, O, and S atoms in the 1 and 3 positions (IV, V, VII, and VIII), as well as their acyclic precursors III and VI. By acidic hydrolysis of ketone I with concentrated hydrochloric acid, in analogy to [4], we obtained 2-(1-aminocyclopentyl)cyclopentanone hydrochloride (II), which was reduced with sodium borohydride to 2-(1-aminocyclopentyl)cyclopentanol (III). The latter was converted to 5,6-trimethylenetetrahydro-1,3-oxazine-4-spirocyclopentane (IV) by cyclization with formaldehyde.



According to the PMR spectral data, amino alcohol III, after two recrystallizations from hexane, is an individual isomer with a cis configuration at the site of fusion of the cyclopentane ring and the quasi-cyclic part of the amino alcohol molecule;

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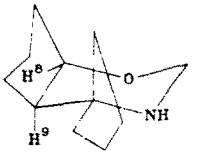
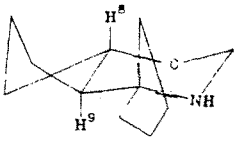
this was established in analogy with the results in [8-10]. A broad signal of a 1-H proton with a half width of ~11 Hz is present in the PMR spectrum of amino alcohol III at 4.31 ppm; this makes it possible to conclude that this proton is equatorially oriented and, consequently, that the alcohol has a cis configuration.

An analysis of the PMR spectrum of tetrahydro-1,3-oxazine IV makes it possible to arrive at a more thorough understanding of the three-dimensional structure of amino alcohol III. The cyclization of amino alcohol III to tetrahydrooxazine IV occurs without involving the asymmetric centers in the molecule, and the configuration of oxazine IV should therefore correspond completely to the configuration of amino alcohol III. For the synthesis of oxazine IV we used unrecrystallized amino alcohol III. According to the PMR spectral data, oxazine IV is a mixture of two spatial isomers with cis and trans configurations at the site of fusion of the tetrahydro-1,3-oxazine and cyclopentane rings.



cis-IVa



trans-IVb

A broad signal of an 8-H proton with a half width of 7 Hz, which indicates an equatorial orientation of the 8-H proton and its affiliation with the cis isomer (IVa) of the oxazine, is present in the spectrum at 3.96 ppm, while a signal of an 8-H proton in the form of a triplet with two spin-spin coupling constants $J_{8,8}$ and $J_{7,8}$, equal to ~10 Hz, which indicates an axial orientation of the 8-H proton and, consequently, trans-diequatorial fusion of the oxazine and cyclopentane rings, is present at 3.24 ppm. Two groups of signals of 2-CH_2 groups of two geometrical isomers of oxazines IVa and IVb, which are superimposed over one another, are present at 4.1 ppm. Broad signals of protons of two NH groups belonging to two stereoisomers are present at 8.00 and 8.04 ppm. The ratio of the areas of these signals, i.e., the ratio of the two spatial isomers of tetrahydro-1,3-oxazines IVa and IVb and amino alcohols III, is ~70:30 in favor of the cis isomer.

The reduction of isothiocyanato ketone I with sodium borohydride is accompanied by cyclization to 5,6-trimethylenetetrahydro-1,3-oxazine-4-spirocyclopentane-2-thione (V) which, according to the PMR spectral data after purification by recrystallization, is an individual stereoisomer with cis fusion of the tetrahydrooxazine and cyclopentane rings, as established from the half width of the signal of the 8-H proton (δ 4.79 ppm), which is equal to ~10 Hz. A mixture of thioxo derivative V and 2-(1-methylaminocyclopentyl)cyclopentanol (VI) in approximately equal amounts is formed in quantitative yield in the reduction of ketone I with lithium aluminum hydride in analogy with [5]. According to the IR and PMR spectral data, the oxazinethione is completely identical to thione V obtained by reduction of isothiocyanato ketone I with sodium borohydride. Amino alcohol VI was converted, without prior purification, by the action of formaldehyde, in analogy with [6], to 3-methyl-5,6-trimethylenetetrahydro-1,3-oxazine-4-spirocyclopentane (VII), in the PMR spectrum of which signals of protons of a 2-CH_2 group in the form of two doublets with geminal SSCC $J_{H_aH_e} \approx 10$ Hz are present at 4.12 and 4.21 ppm. In addition, there is a broad signal of an 8-H proton (δ 3.96 ppm) with a half width of ~10 Hz, which provides evidence for an equatorial orientation of the 8-H proton and, consequently, cis fusion of the cyclopentane and tetrahydro-1,3-oxazine rings. We studied the reaction of isothiocyanato ketone I with methylamine in analogy with [7], as a result of which we obtained 6-hydroxy-1-methyl-5,6-trimethylenehexahydropyrimidine-2-thione (VIII), which, according to the PMR spectral data, is a mixture of stereoisomers in a ratio of 9:1.

EXPERIMENTAL

The IR spectra of thin layers of the liquid substances and suspensions of the solid substances in mineral oil were recorded with a UR-10 spectrometer. The PMR spectra of 1-2% solutions of the compounds in $CHCl_3$ and DMSO were recorded with a Bruker-250 spectrometer with tetramethylsilane (TMS) as the internal standard. The purity of the compounds obtained was monitored in all cases by means of TLC on Silufol plates.

Cyclopentadienylcyclopentanone was obtained by the method in [3] in 54% yield and had bp 135-136°C (25 mm). IR spectrum (thin layer): 1645 (C=C), 1705 cm^{-1} (C=O). 2-(1-Isothiocyanatocyclopentyl)cyclopentanone (I) was obtained in 67% yield by the method in [2] and had bp 124-125°C (10 mm). IR spectrum (thin layer): 1730 (C=O), 2100 cm^{-1} (N=C=S).

2-(1-Aminocyclopentyl)cyclopentanone Hydrochloride (II). A mixture of 2.16 g (10 mmole) of I and 20 ml of concentrated HCl was heated for 2 h on a boiling-water bath with stirring, after which the mixture was cooled to 20°C, and

the neutral reaction products were extracted with ether. The aqueous solution was evaporated to dryness to give 1.02 g (48%) of salt II, which was used without purification in the reduction reaction.

2-(1-Aminocyclopentyl)cyclopentanol (III, $C_{10}H_{19}NO$). A 0.185-g (46 mmoles) sample of sodium borohydride was added gradually in small portions to a solution of 0.76 g (37 mmoles) of salt II in 50 ml of water, and the reaction mixture was stirred for 2 h at 20°C. A 1.7-g sample of potassium hydroxide was then added, and the reaction product was extracted with ether (two 30-ml portions). The combined ether extracts were dried with anhydrous sodium sulfate, and the ether was removed by distillation to give 0.49 g (4%) of amino alcohol III with mp 50-52°C (from hexane). IR spectrum (in mineral oil): 3080-3225 cm^{-1} (OH···NH). PMR spectrum: 4.31 (1H, br.s, half width 11 Hz), 3.28 (1H, br.s, OH···NH), 1.0-2.0 ppm [14H, m, $(CH_2)_7$].

5,6-Trimethylenetetrahydro-1,3-oxazine-4-spirocyclopentane (IV). A 0.9-g (30 mmoles) sample of paraformaldehyde was added to a solution of 0.44 g (26 mmoles) of amino alcohol III in 19 ml of benzene, and the mixture was refluxed with removal of the water for 2 h. The benzene was then removed by distillation, and the residue was fractionated in vacuo to give 0.38 g (81%) of oxazine IV in the form of a mixture of stereoisomers. PMR spectrum: cis isomer: 8.04 (1H, br.s, NH), 3.96 (1H, s, 8-H, half width 7 Hz), 0.5-2.4 ppm [14H, m, $(CH_2)_7$]; trans isomer: 8.0 (1H, s, NH), 3.24 ppm (1H, t, 8-H, $J_{8,9} \approx J_{7,8} \sim 10$ Hz).

5,6-Trimethylenetetrahydro-1,3-oxazine-4-spirocyclopentane-2-thione (V, $C_{11}H_{17}NO$). A 0.53-g (14 mmoles) sample of sodium borohydride was added with stirring in small portions to a solution of 3 g (14 mmoles) of isothiocyanato ketone I in 20 ml of methanol, after which the mixture was stirred for 30 min at 20°C. The methanol was then removed by distillation, 30 ml of water was added to the residue, and the reaction product was extracted with chloroform (two 30-ml portions). After drying with anhydrous sodium sulfate, the chloroform was removed by distillation to give 1.88 g (62%) of oxazinethione V with mp 147-148°C (from alcohol). IR spectrum (in mineral oil): 1550 (thioamide II), 3100 cm^{-1} (NH). PMR spectrum: 8.4 (1H, br.s, NH), 4.79 (1H, s, 8-H, half width ~10 Hz), 1.75-2.05 ppm [14H, m, $(CH_2)_7$].

3-Methyl-5,6-trimethylenetetrahydro-1,3-oxazine-4-spirocyclopentane (VII, $C_{12}H_{21}NO$). A solution of 3.1 g (14 mmoles) of isothiocyanato ketone I in 50 ml of anhydrous ether was added with stirring and cooling with ice water to a suspension of 5.1 g (160 mmoles) of lithium aluminum hydride in 120 ml of anhydrous ether, after which the mixture was stirred and refluxed for 3 h. It was then cooled and hydrolyzed by the successive addition of 5 ml of water, 15 ml of 15% potassium hydroxide solution, and 5 ml of water. The ether layer was separated, and the precipitate was washed with chloroform. After drying of the combined extracts, the solvent was removed by distillation, and 70 ml of ether and 5 ml of dilute sulfuric acid were added to the residue until the mixture was acidic. The ether was removed, the residue was dried, and the solvent was removed by distillation to give 1.25 g (40%) of oxazinethione V with mp 147-148°C. No melting-point depression was observed for a mixture of this product with thione V obtained by the action of sodium borohydride on isothiocyanate I. The aqueous layer was treated with sodium hydroxide solution until the mixture was alkaline, after which it was extracted with ether. After drying with anhydrous sodium sulfate, the ether was removed by distillation, and the residue was fractionated to give 1.6 g (59%) of amino alcohol VI with bp 150°C (18 mm). A 0.066-g (2 mmoles) sample of paraformaldehyde was added to a solution of 0.4 g (2 mmoles) of amino alcohol VI in 10 ml of benzene, and the mixture was refluxed with a Dean–Stark adapter for 2 h. The solvent was then removed by distillation, and the residue was fractionated to give 0.32 g (75%) of oxazine VII with bp 126°C (10 mm). PMR spectrum: 4.21 and 4.12 (1H each, d, $^2J_{2a2e} = 10$ Hz, 2-CH_2), 3.96 (1H, br. s, 8-H, half width 10 Hz), 2.39 ppm (3H, s, N–CH_3).

6-Hydroxy-1-methyl-5,6-trimethylenehexahydropyrimidine-4-spirocyclopentane-2-thione (VIII, $C_{12}H_{20}N_2O$). A 0.867-g (28 mmoles) sample of methylamine in the form of a 32% aqueous solution was added with stirring at 10°C to a mixture of 4.57 g (22 mmoles) of isothiocyanato ketone I and 1 ml of water. The precipitated crystals were separated and washed with water, ether, and cold acetone to give 4.3 g (83%) of pyrimidinethione VIII which, according to the PMR spectral data, was a mixture of stereoisomers in a ratio of 7:1 and had mp 199-200°C (from alcohol). IR spectrum (in mineral oil): 1460-1530 (thioamide II), 3050-3200 cm^{-1} (OH···NH). PMR spectrum: first isomer: 8.11 (1H, br.s, NH), 3.39 (1H, br.s, OH), 3.12 (3H, s, N–CH_3), 2.21 ppm (1H, t, 9-H); other isomer: 8.09 (1H, br.s, NH), 3.31 (1H, br.s, OH), 3.22 (3H, s, N–CH_3), 2.11 ppm (1H, m, 9-H).

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SYNTHESIS OF PYRAZOLE, 1,3,4-THIADIAZOLE, AND 1,2,4-TRIAZOLE DERIVATIVES BY CONDENSATOIN OF 1,3-DIOXO COMPOUNDS WITH THIOSEMICARBAZIDE DERIVATIVES

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The reaction of β-diketones with 2-unsubstituted thiosemicarbazides leads to the formation of the corresponding 1-thiocarbamoyl-5-hydroxy-2-pyrazolines, which readily undergo aromatization to give pyrazoles, while the reaction of benzoylacetaldehyde leads to the formation of the corresponding hydrazone. Acetylacetone 2-methyl- and 2,4-dimethylthiosemicarbazones are inclined to undergo tautomerization and, depending on the conditions, can exist in enehydrazine, hydrazone, 1,2,4-triazoline, and 1,3,4-thiadiazoline forms or mixtures of these forms. Upon heating these substances are converted to mixtures of the 1,3,5-trimethylpyrazole and the corresponding 1,2,4-triazoline-5-thione. The structures of the compounds were studied by means of IR and ^1H, ^{13}C, and ^{15}N NMR spectroscopy and mass spectrometry.

The reaction of thiosemicarbazide derivatives (four reaction centers) with 1,3-dioxo compounds (two reaction centers) is a typical example of the condensation of polyfunctional reagents that is used for the synthesis of various heterocycles. The primary products (I) of condensation due to the participation of the amino $N_{(1)}$ atom [which are capable, like other hydrazines of β-dicarbonyl compounds, of existing in hydrazone (A) or enehydrazine (B) forms [1, 2]] upon subsequent cyclization can, in principle, be converted to pyrazole [3, 4], 1,2,4-triazole, 1,3,4-thiadiazepine [6, 7], and 1,2,4-triazepine [8] derivatives (see scheme on following page).

On the basis of the information set forth above, a detailed study of the reaction under discussion is necessary.

For this we again examined the structures of the products of condensation of thiosemicarbazide and 4-methylthiosemicarbazide with acetylacetone and of thiosemicarbazide with dibenzoylmethane [3, 4], and we additionally synthesized products of the reaction of 4-methylthiosemicarbazide with dibenzoylmethane and of thiosemicarbazide with benzoylacetaldehyde and benzoylacetone (Ia-f, respectively). The characteristics of Ia-c were published previously [3, 4, 6], and data on Id-f are presented in the Experimental section of the present paper. These results provide unambiguous evidence that Ia-d have a cyclic structure; thus tautomeric or isomeric forms A and B should be excluded. Furthermore, for them it is not necessary to take into account structures F and I·HX, since the IR spectra of Ia-d do not contain absorption of a carbonyl group at 1650-1800 cm^{-1}, while the ^{13}C NMR spectra do not contain signals above 190 ppm. Compounds Ib, d also cannot exist in forms D' and E, since in their PMR spectra the signal of the methyl group attached to the nitrogen atom is a doublet, which constitutes evidence in favor of the presence of an $NHCH_3$ fragment, and since the spectral characteristics of all Ia-d are completely analogous, the possibility of the existence of Ia, c also in the same forms is doubtful.

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