INVESTIGATION OF THE REACTIVITIES AND TAUTOMERISM OF AZOLIDINES.

42.* 2-IMINOTHIAZOLIDIN-4-ONES IN THE MANNICH REACTION WITH SECONDARY AMINES

S. Yu. Solov'eva, S. M. Ramsh, and A. I. Ginak

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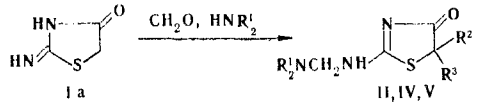
The aminomethylation of 2-iminothiazolidin-4-one with aqueous formaldehyde and piperidine gives 2-piperidinomethylamino-5-hydroxymethyl-5-piperidinomethylthiazolin-4-one, as well as a compound with an unestablished structure, rather than 3-piperidinomethyl-2-iminothiazolidin-4-one, as was previously assumed. The aminomethylation of 2-iminothiazolidin-4-one with diphenylamine and diethylamine leads to the formation of 2-monoaminomethyl derivatives. 2-Imino-5-benzylidenethiazolidin-4-one reacts with paraformaldehyde and piperidine in benzene to give 2-piperidinomethylimino-3-[(3-piperidinomethyl-4-oxo-5-benzylidenethiazolidin-2-ylidene)iminomethyl]-5-benzylidenethiazolidin-4-one.

In [2] we showed that in the reaction of 5-arylidene derivatives of 2-iminothiazolidin-4-one (Ia) with an aqueous solution of formaldehyde and piperidine the indicated compounds undergo aminomethylation at the exocyclic nitrogen atom. It seemed of interest to ascertain whether the reaction pathway depends on the nature of the solvent and how 2-iminothiazolidin-4-one (Ia), which is not substituted in the $C_{(5)}$ position, would behave in aminomethylation.

The product of the reaction of Ia with aqueous formaldehyde and piperidine was found to be identical to the compound described in [3] as 3-piperidinomethyl-2-iminothiazolidin-4-one; however, according to our data, it has a different structure. Because of its low solubility, we were unable to obtain a qualitative PMR spectrum in any of the solvents used (d_6-DMSO, d_7-DMF, and d_4-methanol). Weak broad signals of protons of NH and OH signals, which disappear when D_2O is added, and signals of methylene protons, the form of which does not change when D_2O is added, are observed in the PMR spectrum of a solution in d_6-DMSO. It follows from the integral intensities of the signals that the product contains two piperidyl groups rather than one, as was asserted in [3]. The results of elementary analysis are also in agreement with this. Assuming that the hydroxy proton belongs to the heteroxymethyl group, one must choose between two possible structures with substituents in the 2, 5, and 5 or 3, 5, and 5 positions.



II $R_2^1=(CH_2)_5$, $R^2=CH_2$-piperidyl, $R^3=CH_2OH$; IV $R^1=C_6H_5$, $R^2=R^3=H$; V $R^1=C_2H_5$, $R^2=R^3=CH_2OH$

The character of the IR spectrum in the region of stretching vibrations of double bonds constitutes evidence in favor of the 2,5,5-substituted compound: the C=O (1690 cm^{-1}) and C=N (1585 cm^{-1}) frequencies are close to the frequencies of the corresponding 2-methyl derivative of Ia rather than to the 3-methyl derivative [4]. Structure II seems most likely because of the steric hindrance when both piperidinomethyl groups are attached to the $C_{(5)}$ atom. The poorly resolved low-intensity multiplet at 4.31 ppm should be assigned to the absorption of methylene protons at the exocyclic $N_{(2')}$ atom, and the signal at 3.62 ppm should be assigned to the resonance of the methylene protons of the hydroxymethyl group [1];

*See [1] for communication 41.

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however, the multiplet of methylene protons of the piperidinomethyl group attached to the $C_{(5)}$ atom at 2.73 ppm is partially "covered" by the signals of the residual protons of the solvent and the protons of the α-methylene groups of the piperidyl group (2.55 ppm). This assignment of the signal at 4.31 ppm is in agreement with the deshielding effect of the nitrogen atoms and requires that the C=N bond is located in the ring [1].

The absorption of the $C_{(5)}$—CH_2—N protons at stronger field as compared with the remaining methylene protons is explained by shielding of the $C_{(4)}$=O bond. The multiplicities of the signals of the methylene protons of the piperidinomethyl groups at 2.73 and 4.31 ppm constitute evidence that they are not equivalent.

The UV spectrum of II is similar to the UV spectrum of starting triazolidinone Ia. The absolute reproducibility of the spectral characteristics of samples obtained in different experiments guarantees the individuality and purity of II. We were unable to record its mass spectrum because of its thermal instability.

Compound III, the structure of which could not be established, was also isolated from the reaction mixture in the aminomethylation of Ia with piperidine. Its elementary composition corresponds to or is close to the empirical formula of II. Because of its very low solubility, the signals in the PMR spectrum are weak and uninformative; signals of NH and OH protons are not detected. As in the case of II, the UV spectrum of III is also similar to the UV spectrum of 2-iminothiazolidin-4-one (Ia). The IR spectrum differs from the IR spectrum of II with respect to the presence of a very broad band in the high-frequency region at ∿3270 cm^{-1} and three new bands in the region of vibrations of double bonds at 1710-1720 (sh), 1645, and 1540 cm^{-1}. The resolution of the bands is poor in the "fingerprint" region. We were unable to obtain the mass spectrum of III because of its thermal instability. According to derivatographic data, decomposition with a loss in mass commences at 30-40°C (the product "volatilizes"). The initial point of the enthalpy peak on the DTA curve corresponds to the visually observed frothing temperature of 120-125°C during determination of the melting point of the substance in a capillary, and the apex of the enthalpy peak corresponds to a temperature of ∿160°C, at which the substance melts with decomposition in the crucible of the derivatograph.

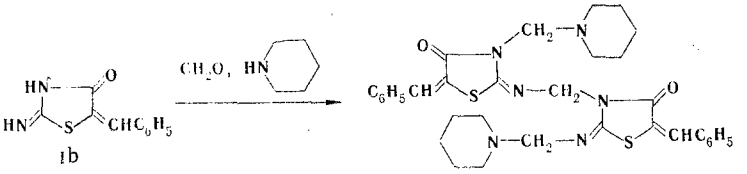
Compound III decomposes during chromatography on Silufol; among other spots, a spot of Ia is detected on the chromatograph, but a spot of II is absent. The IR spectrum of a solid sample, the visually observed melting point, and the results of elementary analysis are reproducible from experiment to experiment, and this constitutes evidence for the individuality of III.

Monoaminomethyl derivatives IV and V are formed as a result of aminomethylation with diphenylamine and diethylamine. The methylene protons of the aminomethyl group of IV absorb in the form of a multiplet signal at 4.86 ppm. We were unable to record the temperature dependence of the PMR spectrum because of the low solubility in d_6-DMSO (and in other solvents). The signal of the NH proton is not detected in the PMR spectrum. The position of the aminomethyl fragment was established on the basis of a comparison of the IR spectrum of IV with the IR spectra of the 2- and 3-methyl derivatives of Ia [4]: The observed C=O (1675 cm^{-1}) and C=N (1585 cm^{-1}) frequencies are characteristic for a 2-substituted derivative.

We were unable to select a solvent for recrystallization of V. The melting point (with decomposition), the results of elementary analysis, and the spectral characteristics of samples of this compound obtained in different experiments were reproducible, and its individuality and purity were confirmed by thin-layer chromatography (TLC) on Silufol. The bands in the IR spectrum of a solid sample of V are poorly resolvable, and it is only slightly soluble in the solvents that are usually employed for recording PMR spectra; the signals are "blurred" and indistinct when d_6-DMSO is used as the solvent. The broad signal at 4.93 ppm is due to absorption of the hydroxy protons, the multiplet at 4.78 ppm is due to absorption of the methylene protons of the N—CH_2—N fragment, and the multiplet at 3.65 ppm is due to absorption of the methylene protons of hydroxymethyl groups. The presence of two groups of CH_3 (1.13 and 0.85 ppm) and CH_2 (2.91 and 2.4-2.5 ppm) protons of ethyl groups constitutes evidence for retarded rotation about the partially double exocyclic C_2=N_2, bond, and the ratio of the intensities of the triplets of the methyl protons (∿1:0.7) indicates a different concentration of conformers. The significant degree of double bond character of the exocyclic N—C bond in IV and V leads to the observed weak-field shift of the

signals of the methylene protons attached to the exocyclic $N_{(2')}$ atom as compared with II. Compound V in the crystalline state exists in the imino form, inasmuch as the frequencies of the stretching vibrations of the C=O and C=N bonds (1740 and 1650 cm^{-1}, respectively) are close to the C=O and C=N frequencies of 2-imino-3-methylthiazolidin-4-one [4], which models the imino form of Ia.

The solvent has a substantial effect on the reaction pathway when several reaction centers are present in the nucleophilic compound [6]. According to the data in [7], the 3-NH group of 2-imino-5-benzylidenethiazolidin-4-one (Ib) undergoes aminomethylation when the reaction is carried out in an aprotic solvent (benzene) and in the case of an equimolar reagent ratio.* We were unable to obtain the 3-aminomethyl derivative of Ib by the method in [7]. We isolated VI from the reaction mixture when we used a twofold excess of piperidine.



The IR spectrum of a solid sample of the compound obtained does not contain bands of vibrations of an NH bond, and the C=O (1710 cm^{-1}) and C=N (1645 cm^{-1}) frequencies are close to the corresponding frequencies of the stretching vibrations of 2-imino-3-methyl-5-benzylidenethiazolidin-4-one (1715 and 1620 cm^{-1}) [2]. A multiplet of the protons of the 5-benzylidene grouping at 7.22-7.75 ppm, signals of three methylene groups at 5.42, 4.83, and 4.12 ppm, and two multiplets of piperidyl protons at 2.60 and 1.45 ppm are present in the PMR spectrum; the ratio of the intensities of the signals is 6:1:1:1:4:6. These spectral characteristics are possible only for the VI structure; the signals at 4.83 and 4.12 ppm should be assigned to the absorption of $N_{(2')}$—CH_2 and $N_{(3)}$—CH_2 protons of piperidinomethyl groupings [8], and the resonance at 5.42 ppm should be assigned to the absorption of a "bridged" methylene group that links two iminothiazolidine fragments. The molecular mass (630 amu) of VI determined by reverse ebullioscopy in dichloroethane is in agreement with the calculated value (614.82 amu).

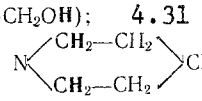
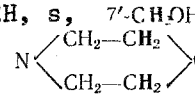
The PMR spectrum of VI has one peculiarity: The signals of the methylene protons have slight asymmetrical broadening at the base of the peak, and shifted (to weak field), diffuse, low-intensity signals at 3.17 and 2.00 ppm are adjacent to two intense multiplets of the protons of piperidyl groups. On the basis of the available data one cannot with certainty assert whether this peculiarity is due to Z,E isomerism involving the C=N bonds or is due to repeated isomerism involving rotation about the CH_2—N bonds.

EXPERIMENTAL

The PMR spectra were recorded with Perkin—Elmer R-12, Tesla BS-467 (60 MHz), and Tesla BS-487C (80 MHz) spectrometers with hexamethyldisiloxane as the internal standard. The IR spectra of suspensions of the compounds in mineral oil and perfluorinated mineral oil were obtained with an IKS-29 spectrometer. The UV spectra of solutions in ethanol were recorded with an SF-16 spectrophotometer. The derivatogram was recorded with the derivatograph of the Paulik—Paulik—Erdey system; the sample weight was 20 mg, the time required for one revolution of the drum was 100 min, the DTA, DTG, and TG sensitivities were 1/3, 1/30, and 50 mg, respectively, the heating rate was 8 deg/min, and the standard was Al_2O_3. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates by elution with ethanol—chloroform (1:4 for II-V and 1:10 for VI).

2-Piperidinomethylamino-5,5-hydroxymethylpiperidinomethylthiazolin-4-one (II). A mixture of 4.6 g (0.04 mole) of 2-iminothiazolidin-4-one (Ia), 7.6 g (0.09 mole) of piperidine, and 14.4 ml (∿0.18 mole) of formalin was stirred for ∿1 h until a viscous yellow oil formed, after which the mixture was decanted, and the oil was dissolved in ethanol. After several hours, II precipitated and was crystallized from ethanol to give 3.9 g (28%) of a product with 175-177°C (173°C [3]). IR spectrum: 3200 (OH); 3030 (NH); 2940, 2860 (CH_2); 1690 (C=O); 1585 (C=N); 1505 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 221 (4.29) and 250 nm (3.91). PMR spectrum (d_6-DMSO, 80 MHz, cyclohexane as the internal standard): 9.28 (1H, s,

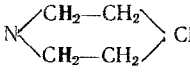
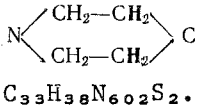
*Formaldehyde was introduced into the reaction in the form of paraformaldehyde.

2'-NH); 5.19 (1H, s, 7'-CH_2OH); 4.31 (2H, m, 2'-$NHCH_2$); 3.62 (2H, s, 7'-CH_2OH); 2.73 (2H, m, 7'-CH_2N); 2.55 (8H, m, ); and 1.40 ppm (12H, m, ). Found: N 16.9; S 9.2%. $C_{16}H_{28}N_4O_2S$. Calculated: N 16.4; S 9.4%.

Compound III. The viscous yellow oil that was formed in the preparation of II was extracted with benzene, and the benzene-insoluble residue (II) was removed by filtration. Compound III was precipitated from the benzene extract by means of hexane, washed with hexane, and dried *in vacuo* to give 0.97 g (7%) of a product with mp 122-125°C. IR spectrum: 3270, 3210, 3035, 2970, 2940, 2865, 2815, 1720, 1710, 1690, 1645, 1570, 1540, and 1500 cm^{-1}. UV spectrum, λ_{max} (log ε): 221 nm (4.30). PMR spectrum (d_6-DMSO, 60 MHz): 4.25 (m), 3.60 (s), 2.50 (m), and 1.40 ppm (m). Found: N 15.9; S 9.1%. $C_{16}H_{28}N_4O_2S$ (?). Calculated: N 16.4; S 9.4%.

2-Diphenylaminomethyliminothiazolidin-4-one (IV). A mixture of 4.6 g (0.04 mole) of Ia, 6.8 g (0.04 mole) of diphenylamine, and 16 ml (∼0.20 mole) of formalin in 60 ml of ethanol was refluxed for ∼1 h with vigorous stirring until Ia had dissolved completely, after which the ethanol was removed by distillation, and the precipitated IV was crystallized from benzene to give 5.2 g (44%) of a product with mp 133°C. IR spectrum: 3210 (NH), 1675 (C=O), and 1585 cm^{-1} (C=N + Het). UV spectrum, λ_{max} (log ε): 226 (4.39) and 240 nm (4.37). PMR spectrum (d_6-DMSO, 80 MHz): 7.05 (10H, arom.), 4.86 (2H, m, 2'-NCH_2), and 3.63 ppm (2H, 5-CH_2). Found: N 14.0; S 11.0%. $C_{16}H_{15}N_3OS$. Calculated: N 14.2; S 10.8%.

2-Diethylaminomethylimino-5,5-dihydroxymethylthiazolidin-4-one (V). A mixture of 2.3 g (0.02 mole) of Ia, 1.5 g (0.02 mole) of diethylamine, and 8 mg (∼0.10 mole) of formalin in 30 ml of ethanol was stirred for ∼1 h until Ia disappeared, after which the ethanol was removed by distillation, and the residue was extracted with three 20-ml portions of benzene. The benzene extract was dried with sodium sulfate, the benzene was removed by distillation and a white viscous oil, which solidified upon trituration, was precipitated by means of hexane. The precipitated V was removed by filtration, reprecipitated from solution in benzene by means of hexane, and dried *in vacuo* to give 2.6 g (49%) of a product with mp 260°C (dec.). IR spectrum: 3270-3300 (NH, OH), 1740 (C=O), and 1650 cm^{-1} (C=N). UV spectrum, λ_{max} (log ε): 226 (4.24) and 250 nm (4.09). PMR spectrum (d_6-DMSO, 80 Mhz): 4.93 (2H, s, OH); 4.78 (2H, m, 2'-NCH_2); 3.65 (4H, m, 5'-CH_2); 2.91, 2.4-2.5 [4H, q, $N(CH_2CH_3)_2$]; 1.13, 0.85 ppm [6H, t, $N(CH_2CH_3)_2$]. Found: N 16.2; S 12.7%. $C_{10}H_{19}N_3O_3S$. Calculated: N 16.1; S 12.3%.

2-Piperidinomethylimino-3-[(3-piperidinomethyl-4-oxo-5-benzylidenethiazolidin-2-ylidene)iminomethyl]-5-benzylidenethiazolidin-4-one (VI). A mixture of 2.0 g (0.01 mole) of 2-imino-5-benzylidenethiazolidin-4-one (Ib), 1.7 g (0.02 mole) of piperidine, and 0.3 g (0.01 mole) of paraformaldehyde in 50 ml of benzene was refluxed for 4 h, after which the hot mixture was filtered to remove the undissolved material. The benzene was removed from the filtrate by distillation, and the VI was precipitated from the residue by means of ether or acetone and was crystallized from benzene–hexane (1:4) to give 1.2 g (59% with respect to formaldehyde) of a product with mp 152-153°C. IR spectrum: 1710 (C=O) and 1645 cm^{-1} (C=N). UV spectrum, λ_{max} (log ε): 239 (4.21), 289 (4.36), and 331 nm (4.60). PMR spectrum ($CDCl_3$, 60 MHz): 7.22-7.75 (12H, m, CHC_6H_5); 5.42 [2H, $N_{(2')}$–CH_2–$N_{(3)}$]; 4.83 [2H, $N_{(2')}$–CH_2-piperidyl]; 4.12 (2H, N_3–CH_2-piperidyl); 3.17, 2.60 (8H, m, ); 2.00, 1.45 ppm (12H, m, ). Found: N 13.6; S 10.8%; M 630 (inverse ebullioscopic, dichloroethane). $C_{33}H_{38}N_6O_2S_2$. Calculated: N 13.7; S 10.4%; M 614.82.

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SYNTHESIS AND SEPARATION OF DIASTEREOMERS OF THIOMORPHOLINE-CARBOXYLIC ACID ESTERS

A. V. Eremeev, R. Nurdinov,
É. É. Liepin'sh, and F. D. Polyak

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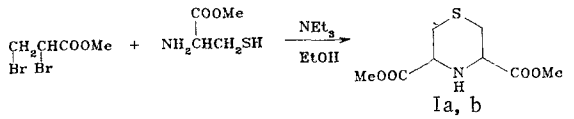
It is shown that the reaction of methyl 2,3-dibromopropionate with aminoethanethiol and L-cysteine methyl ester leads to the formation of esters of thiomorpholine-3-carboxylic and thiomorpholine-3,5-dicarboxylic acids; the latter ester was separated into individual diastereomers.

It has been previously shown that the reaction of methyl 2,3-dibromopropionate with methyl esters of natural amino acids, including S-substituted cysteine methyl ester, leads to the formation of aziridine-2-carboxylic acid derivatives [1]. In order to obtain aziridines that contain an SH group we attempted to study the reaction of methyl 2,3-dibromopropionate with L-cysteine methyl ester. As a result of the study we showed that the reaction leads to the formation of dimethylthiomorpholine-3,5-dicarboxylates rather than aziridine-2-carboxylic acid derivatives.

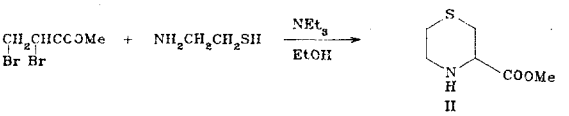


Ia, b

Analysis of the final products by high-performance liquid chromatography (HPLC) makes it possible to conclude that two compounds (in a ratio of 7:3), which were separated by preparative HPLC, are present in the product.

Data from the PMR and mass spectra prove unambiguously that these compounds are diastereomers that differ with respect to the configuration of the C_3 atom.

In order to confirm the general character of the reaction of 2,3-dibromopropionic acid with 2-mercapto-substituted amines we investigated the reaction with 2-mercaptoethylamine, in which the formation of methyl thiomorpholine-3-carboxylate (II) and the formation of methyl thiomorpholine-2-carboxylate are equally likely. The literature data, which are based only on the results of elementary analysis [2], do not make it possible to solve this problem unambiguously.



II

The product of the reaction of 2,3-dibromopropionic acid with 2-mercaptoethylamine was isolated by preparative gas–liquid chromatography (GLC). According to the PMR and mass-spectral data, the final product is methyl thiomorpholine-3-carboxylate.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
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