REACTION OF SUBSTITUTED 1-HYDROXY-4-HYDROXYLAMINOIMIDAZOLIDIN-2-ONE WITH ARYL ISOCYANATES

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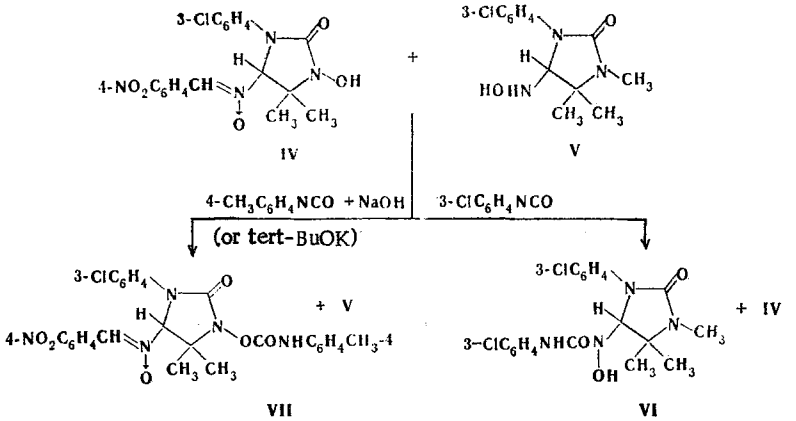
UDC 547.781.3.5'782'783'495.1.07:543.422

Various variants of reactions involving the carbamoylation of 1-hydroxy-3-(3'-chlorophenyl)-5,5-dimethyl-4-hydroxylaminoimidazolidin-2-one, which has three nucleophilic centers, viz., the N- and O-hydroxylamino groups and the O-hydroxyurea fragment of the molecule, were studied. Depending on the reaction conditions, mono-, and di-, and tricarbamoyl derivatives of substituted 4-hydroxylaminoimidazolidin-2-one were synthesized.

We have previously shown that N-carbamoyl derivatives of α-hydroxylaminooximes, under the influence of an alkali, undergo cyclization to give substituted 4-hydroxylaminoimidazolidin-2-ones [1]. In the present research we studied various variants of reactions involving the carbamoylation of 1-hydroxy-3-(3'-chlorophenyl)-5,5-dimethyl-4-hydroxylaminoimidazolidin-2-one (I), which has three nucleophilic centers, viz., the N- and O-hydroxylamino groups and the O-hydroxyurea fragment of the molecule.

As one should have expected, the reaction of I with aryl isocyanates in tetrahydrofuran (THF) leads to the corresponding N-monocarbamoyl derivatives IIa,b with the addition of acyl groups to the nitrogen atom of the hydroxylamino group as the most nucleophilic center. Subsequent carbamoylation of the II leads only to 4-[N,O-bis(4-tolylcarbamoyl)-hydroxylamino]-1-(4-tolylcarbamoyloxy)-5,5-dimethyl-3-(3-chlorophenyl)-imidazolidin-2-one (III).



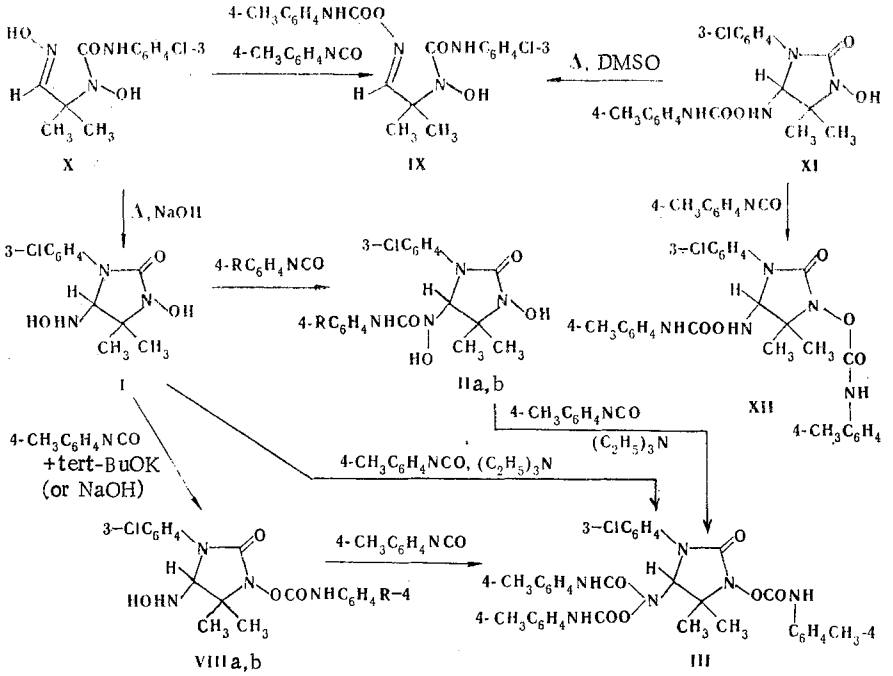
Considering the known fact of the increased nucleophilicity of the oximate anion as compared, for example, with aniline or phenylhydrazine in reactions with acylating agents [2], we assumed that the formation of a hydroxamate anion would make it possible in our case to change the direction of carbamoylation from the hydroxylamino group to the hydroxyurea fragment. For experimental clarification we introduced these groups into different but similarly constructed compounds. Treatment of a mixture of N-[1-hydroxy-3-(3-chlorophenyl)-5,5-dimethylimidazolidin-2-on-4-yl]-4-nitrophenylnitrone (IV) and 4-hydroxylamino-3-(3-chlorophenyl)-1,5,5-trimethylimidazolidin-2-one (V) with 3-chlorophenyl isocyanate leads to the production of 4-[1-hydroxy-3-(3'-chlorophenyl)ureido]-3-(3-chlorophenyl)-1,5,5-trimethylimidazolidin-2-one (VI), whereas in the presence of potassium tert-butoxide the same reaction with 4-tolyl isocyanate gives only N-[1-(4-tolylcarbamoyloxy)-3-(3-chlorophenyl)-5,5-dimethylimidazolidin-2-on-4-yl]-4-nitrophenylnitrone (VII), and V remains unchanged.

All-Union Scientific-Research Institute of Chemical Agents for the Protection of Plants, Moscow 109088. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1115-1119, August, 1983. Original article submitted October 26, 1982.

0009-3122/83/1908-0897$07.50

The carbamoylation of I in the presence of alkali or potassium tert-butoxide leads only to VIII, which do not give a qualitative reaction with an alcohol solution of ferric chloride for the presence of an unsubstituted (at the oxygen fragment) hydroxamic acid (or hydroxyurea), and, at the same time, one observes the formation of the bright-red complex with 2,3,5-triphenyltetrazolium ion that is characteristic for the HONH group [3]. A broad absorption band of carbonyl groups centered at 1730 cm^{-1} is observed in the IR spectra of the synthesized compounds; in the PMR spectrum of VIIIa, in addition to two singlets of protons of two gem-dimethyl groups at 1.34 and 1.37 ppm and a singlet of a methyl group of a tolyl grouping at 2.21 ppm, one observes two doublets of CH and NH protons at 4.91 (J = 6 Hz) and 6.75 ppm (J = 6 Hz) and a singlet of NH protons at 9.75 ppm. The 4-hydroxylamino-1-(arylcarbamoyloxy)-5,5-dimethyl-3-(3-chlorophenyl)imidazolidin-2-one structure was assigned to VIII on the basis of these data. It should be noted that VIII are unstable at room temperature, evidently because of the considerable acylating ability of the O-carbamoyl grouping. When VIIIa is maintained in solution in THF, it is converted to a mixture, in which I-III are detected in addition to the starting compound.

Acylation of VIIIa with 2 moles (3 moles in the case of I) of 4-tosyl isocyanate in the presence of catalytic amounts of triethylamine leads to III.



IIa, VIIIa R=CH_3; IIb, VIIIb R=Cl

The O-arylcarbamoyl derivative at the oxygen atom of the hydroxylamino group cannot be synthesized by direct carbamoylation of I. However, heating of 1-[O-(4-tolylcarbamoyl)]-2-[N-(3-chlorophenylcarbamoyl)hydroxyamino]-2-methylpropanal oxime (IX) [obtained by the reaction of 2-[N-(3-chlorophenylcarbamoyl)hydroxyamino]-2-methylpropanal oxime (X) with 4-tolyl isocyanate] in dimethyl sulfoxide (DMSO) at 90°C gave a compound, in the IR spectrum of which one observes two absorption bands of a carbonyl group at 1700 and 1740 cm^{-1}; in addition to two singlets of gem-dimethyl groups at 1.35 and 1.5 ppm and a singlet of a methyl group of a tolyl grouping at 1.55 ppm, the PMR spectrum contains two doublets of NH and CH protons at 7.88 (J = 6 Hz) and 5.25 ppm (J = 6 Hz) and a singlet of a proton of an N–OH group at 8.51 ppm. These data make it possible to assign the O-(4-tolylcarbamoyl)-N-[1-hydroxy-3-(3-chlorophenyl)-5,5-dimethylimidazolidin-2-one-4-yl]hydroxylamine structure (XI) to the synthesized compound.

Exhaustive carbamoylation of XI leads only to XII, which does not give a qualitative reaction with $FeCl_3$ for the presence of an unsubstituted hydroxyurea fragment. A broad absorption band of three carbonyl groups centered at 1740 cm^{-1} is observed in the IR spectrum of XII. Two singlets of protons of gem-dimethyl groups at 1.35 and 1.55 ppm, two doublets of NH and CH protons at 8.25 (J = 6 Hz) and 5.32 ppm (J = 6 Hz), a singlet of protons of two methyl groups of a tolyl grouping at 2.25 ppm, and two singlets of protons of two NH groups

at 9.22 and 9.86 ppm are present in the PMR spectrum. The 4-[O-(4-tolylcarbamoyl)hydroxyamino]-1-(4-tolycarbamoyloxy)-3-(3-chlorophenyl)-5,5-dimethylimidazolidin-2-one structure was assigned to XII on the basis of these data.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Perkin-Elmer 457 spectrometer. The PMR spectra of 10% solutions in $(CD_3)_2SO$ were recorded with Brucker HX-90E (90 MHz) and Varian FT-80 (80 MHz) spectrometers with tetramethylsilane as the internal standard. Chromatographic separation of the synthesized compounds was realized by chromatography on silica gel in a THF–hexane system.

Chromatographic investigation of the compounds obtained was carried out on Silufol UV-254 plates in an acetone–hexane system (3:4).

1-Hydroxy-3-(3-chlorophenyl)-5,5-dimethyl-4-hydroxylaminoiminoimidazolidin-2-one and 2-[N-(3'-chlorophenylcarbamoyl)hydroxyamino]-2-methylpropanal oxime (X) were obtained by the method in [1].

4-[N'-Aryl-N-hydroxy-N-ureido]-1-hydroxy-3-(3-chlorophenyl)-5,5-dimethylimidazolidin-2-ones (II). A 2-mmole sample of the aryl isocyanate in 10 ml of THF was added at −30°C to a solution of 2 mmole of I in 30 ml of THF. At the end of the reaction (as monitored by TLC), the solvent was evaporated *in vacuo*, 10 ml of ether was added to the residue, and the precipitate was removed by filtration to give IIa,b. Compound IIa, with mp 198-199°C, was obtained in 96% yield. IR spectrum (KBr): 1650 and 1705 cm^{-1} (C=O). Found: Cl 8.9; N 13.8%. $C_{19}H_{21}ClN_4O_4$. Calculated: Cl 8.8; N 13.8%. Compound IIb, with mp 187-188°C, was obtained in 92% yield. IR spectrum (KBr): 1635 and 1680 cm^{-1} (C=O). Found: Cl 16.3; N 13.3%. $C_{18}H_{18}Cl_2N_4O_4$. Calculated: Cl 16.7; N 13.2%.

4-[N,O-Bis(4-tolylcarbamoyl)hydroxylamino]-1-(4-tolylcarbamoyloxy)-3-(3-chlorophenyl)-5,5-dimethylimidazolidin-2-one (III). A 2-mmole sample of 4-tolyl isocyanate was added dropwise to a solution of 1 mmole of IIa in 40 ml of THF in the presence of catalytic amounts of triethylamine, and the mixture was maintained at room temperature for 1 h. The solvent was evaporated *in vacuo*, and the residue was treated with ether and filtered to give III, with mp 176-177°C, in 70% yield. PMR spectrum [$(CD_3)_2SO$]: 1.37 (3H, s) and 1.39 [3H, s, 5-$(CH_3)_2$]; 2.17 (9H, s, Ar–CH_3); 6.15 (1H, s, 4-CH); 8.9 (1H, s, NH); 9.0 (1H, s, NH); 9.86 (1H, s, NH); 7.12 ppm (16H, m, C_6H_4). Found: C 65.9; H 5.6; Cl 5.3; N 13.2%. $C_{35}H_{35}ClN_6O_6$. Calculated: C 66.2; H 5.5; Cl 5.6; N 13.2%.

N-[1-Hydroxy-3-(3-chlorophenyl)-5,5-dimethylimidazolidin-2-on-4-yl]-4-nitrophenylnitrone (IV). A 2-mmole sample of 4-nitrobenzaldehyde was added to a solution of 2 mmole of I in 15 ml of alcohol, and the mixture was refluxed for 30 min. It was then allowed to stand overnight at room temperature, and the precipitate was removed by filtration and washed with 5 ml of ether to give yellow crystals of IV, with mp 223°C, in 82% yield. IR spectrum (KBr): 1140 (N→O), 1600 (C=N→O), and 1959 cm^{-1} (C=O). UV spectrum (in alcohol): λ^1 243 (log ε^1 4.20) and λ^2 349 nm (log ε^2 4.06). Found: C 56.7; H 5.2; Cl 8.6; N 13.9%. $C_{19}H_{19}ClN_4O_4$. Calculated: C 56.6; H 4.8; Cl 8.8; N 13.0%.

4-Hydroxylamino-3-(3-chlorophenyl)-1,5,5-trimethylimidazolidin-2-one (V). This compound, with mp 158-159°C, was obtained in 94% yield by the method in [1] by the action of 3-chlorophenyl isocyanate on 2-methylamino-2-methylpropanol oxime. IR spectrum (KBr): 1660 (C=O) and 930 cm^{-1} (N–O); (CCl_4): 3580 cm^{-1} (N–OH). Found: C 53.2; H 6.0; Cl 12.9; N 15.6%. $C_{12}H_{16}ClN_3O_2$. Calculated: C 53.4; H 6.0; Cl 13.1; N 15.6%.

Comparison of the Reactivities of the Hydroxylamino Group in the 4 Position and the N–OH Group in the 1 Position of Imidazolidin-2-one. A 1-mmole sample of 3-chlorophenyl isocyanate was added dropwise at −30°C to a solution of 1 mmole of IV and 1 mmole of V in 20 ml of THF. Compound V disappeared according to TLC, while IV remained unchanged. The solvent was evaporated, the residue was treated with diethyl ether and filtered, and the precipitate was subjected to column chromatography on silica gel [elution with acetone–hexane (1:4)] to give VI, with mp 227-229°C, in 98% yield. IR spectrum (KBr): 1670 and 1700 cm^{-1} (C=O). Found: Cl 16.5; N 13.3%. $C_{19}H_{20}Cl_2N_4O_3$. Calculated: Cl 16.8; N 13.2%.

A 1-mmole sample of 4-tosyl isocyanate was added dropwise at −30°C to a solution of 1 mmole of IV and 1 mmole of V in 20 ml of THF in the presence of catalytic amounts of potassium tert-butoxide. According to TLC, IV vanished, but V remained unchanged. The solvent

was evaporated, and the residue was subjected to column chromatography on silica gel [elution with acetone–hexane (1:4)] to give VII, with mp 115-116°C, in 89% yield. IR spectrum (KBr): 1750, 1780 (C=O); 1135 (N→O); 1520, 1350 cm^{-1} (NO_2). Found: C 58.3; H 4.4; Cl 6.6; N 13.0%. $C_{26}H_{24}ClN_3O_6$. Calculated: C 58.0; H 4.5; Cl 6.6; N 13.0%.

4-Hydroxylamino-1-(arylcarbamoyloxy)-3-(3-chlorophenyl)-5,5-dimethylimidazolidin-2-ones (VIIIa,b). A solution of 1 mmole of 4-tolyl isocyanate in 10 ml of THF was added dropwise at −40°C to a solution of 1 mmole of I in 20 ml of THF in the presence of catalytic amounts of NaOH. At the end of the reaction (according to chromatographic monitoring), the reaction mass was poured into 100 ml of cooled (to −30°C) pentane. The precipitate was removed by filtration to give VIIIa,b. Compound VIIIa, with mp 100-101°C, was obtained in 66% yield. Found: C 52.9; H 4.2; Cl 8.7; N 13.5%. $C_{18}H_{17}ClN_4O_5$. Calculated: C 53.4; H 4.2; Cl 8.8; N 13.8%. Compound VIIIb was obtained in 45% yield. Found: Cl 16.4; N 13.1%. $C_{18}H_{18}Cl_2N_4O_4$. Calculated: C 16.7; N 13.2%.

1-[O-(4-Tolylcarbamoyl)]-2-[N'-3-chlorophenylcarbamoyl)hydroxyamino]-2-methylpropanal Oxime (IX). A solution of 1 mmole of 4-tolyl isocyanate in 15 ml of THF was added dropwise to a solution of 1 mmole of X in 40 ml of THF, after which the mixture was maintained at room temperature for 24 h (with chromatographic monitoring). The solvent was evaporated *in vacuo*, the precipitate was treated with 10 ml of ether, and the solid material was removed by filtration to give IX, with mp 148-150°C, in 54% yield. IR spectrum (KBr): 1660, 1700 cm^{-1} (C=O). PMR spectrum [$(CD_3)_2SO$]: 1.5 [6H, s, $(CH_3)_2$], 7.95 (1H, s, CH), 8.59 (1H, s, NH), 8.96 (1H, s, NH). Found: C 56.6; H 5.3; Cl 8.6; N 13.9%. $C_{19}H_{21}ClN_4O_4$. Calculated: C 56.4; H 5.2; Cl 8.8; N 13.8%.

O-(4-Tolylcarbamoyl)-N-[1-hydroxy-3-(3-chlorophenyl)-5,5-dimethylimidazolidin-2-on-4-yl]hydroxylamine (XI). A solution of 1 mmole of IX in 10 ml of DMSO was heated to 80°C, after which it was poured into 100 ml of water, and the aqueous mixture was extracted with 100 ml of ether. The extract was dried over $MgSO_4$, the ether was evaporated, and the precipitate was removed by filtration to give a product with mp 154-155°C in 86% yield. Found: C 56.8; H 5.3; Cl 8.7; N 13.5%. $C_{19}H_{21}ClN_4O_4$. Calculated: C 56.4; H 5.2; Cl 8.8; N 13.8%.

4-[O-(4-Tolylcarbamoyl)hydroxyamino]-1-(4-tolylcarbamoyloxy)-3-(3-chlorophenyl)-5,5-dimethylimidazolidin-2-one (XII). A solution of 4-tolyl isocyanate in 20 ml of THF was added dropwise to a solution of 1 mmole of XI in 50 ml of THF in the presence of a catalytic amount of triethylamine. At the end of the reaction, the solvent was evaporated, and the residue was treated with ether to give XII, with mp 120-121°C, in 70% yield. Found: C 63.4; H 5.0; Cl 6.4; N 11.1%. $C_{29}H_{28}ClN_5O_5$. Calculated: C 63.1; H 5.1; Cl 6.4; N 10.9%.

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