SYNTHESIS AND PROPERTIES OF CARBAMOYL DERIVATIVES OF 5-HYDROXY-3,3,5-TRIMETHYLISOXAZOLIDINE

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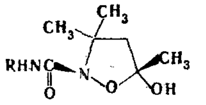
The reaction of 5-hydroxy-3,3,5-trimethylisoxazolidine with alkyl (or aryl) isocyanates gives N-alkyl(aryl)-carbamoyl-5-hydroxy-3,3,5-trimethylisoxazolidines, which react with methanol in the presence of p-toluenesulfonic acid to give 5-methoxy-1-carbamoyl derivatives of isoxazolidine. When arylcarbamoyl-5-hydroxy-3,3,5-trimethylisoxazolidines are heated in carbon tetrachloride, they are converted to O-arylcarbamoyl-N-(2-methyl-4-oxo-2-pentyl)hydroxylamines, the treatment of which with hydrogen chloride in benzene made it possible to isolate 1,2,6-oxadiazepin-7-ones along with the hydrochloride of the given compounds.

N-Carbamoyl derivatives of α-hydroxylamino oximes undergo cyclization to substituted 2-imidazolidinones under the influence of acids and alkalis [1, 2]. In the present research we investigated the carbamoylation of a representative of β-keto hydroxylamines — 4-hydroxylamino-4-methyl-2-pentanone — which exists in the 5-hydroxy-3,3,5-trimethylisoxazolidine form (I), and we also studied the effect of alkaline and acidic agents on the carbamoyl derivatives that we obtained.

The presence of two nucleophilic centers in I suggested the possible formation of two types of O- and N-mono- and O,N-disubstituted derivatives. However, the reaction of I with alkyl (or aryl) isocyanates in aprotic solvents leads to unique individual II, which, with respect to the results of analysis, correspond to the condensation of I with 1 mole of isocyanate.

Absorption bands at 1640-1680 and 1500-1540 cm^{-1}, which are characteristic for the urea fragment, are observed in the IR spectra of KBr pellets of II. Three singlets of protons of methyl groups at 1.31, 1.51, and 1.58 ppm, an AB signal of methylene protons (2.04 and 2.20 ppm, J = 12 Hz), an NCH_3 signal at 2.63, and an OH singlet at 5.62 ppm are observed in the PMR spectrum of IIa in CCl_4. A band of stretching vibrations of OH groups at 3600 cm^{-1}, which has a shoulder at 3580 cm^{-1}, is observed in the IR spectra of solutions of II in CCl_4 along with bands of stretching vibrations of NH groups at 3420-3440 cm^{-1}. This may be associated with the possible existence of II in the form of two spatial isomers, viz., A and B.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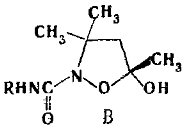
B

II a $R=CH_3$, b $R=C_2H_5$, c $R=C(CH_3)_3$, d $R=CH_2CH=CH_2$, e $R=C_6H_5$, f $R=3\text{-}NO_2C_6H_4$, g $R=4\text{-}CH_3C_6H_4$, h $R=3\text{-}CF_3C_6H_4$, i $R=2\text{-}ClC_6H_4$, j $R=3\text{-}ClC_6H_4$, k $R=4\text{-}ClC_6H_4$, l $R=3,4\text{-}Cl_2C_6H_3$, m $R=\alpha\text{-}C_{10}H_7$, n $R=\beta\text{-}C_{10}H_7$

Signals of two forms can also be observed in the PMR spectra of these compounds. Thus in the PMR spectrum of IIk the signals of three methyl groups in the 3 and 5 positions at 1.35, 1.49, and 1.58 ppm are broadened and have shoulders at 1.37, 1.51, and 1.60 ppm, respectively.

Proceeding from the data on the exchange of the 5-hydroxy group in I by an alkoxy group in neutral and acidic media [3] with allowance for data on the alkaline and acidic cycliza-

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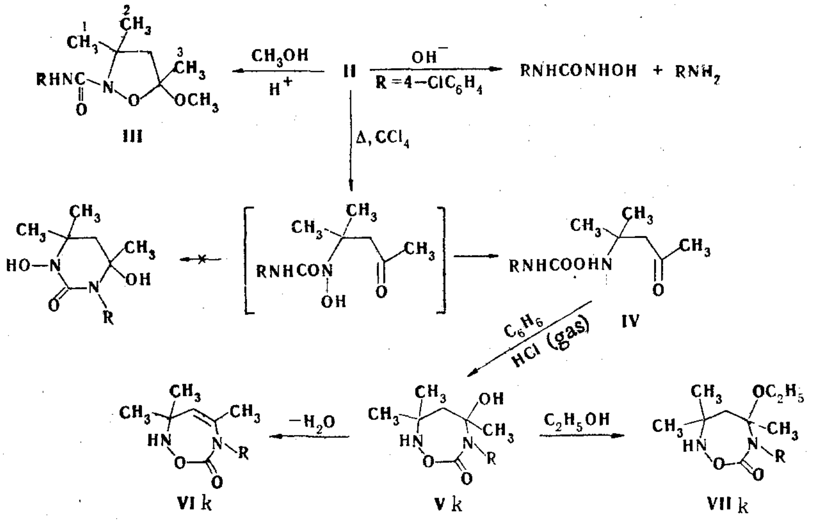
tion of N-carbamoyl derivatives of isobutylene α-hydroxylamino oxime [1], one may assume also in the case of II the probability of both the production of the corresponding alkoxy derivatives and their recyclization to give substituted 1,4-dihydroxyhexahydro-2-pyrimidinones. However, when we treated IIk with alkali, we were able to isolate only the corresponding hydroxyurea and 4-chloroaniline, which were characterized by the data from their IR and PMR spectra and qualitative reactions, from the resinified reaction mixture. However, we obtained the corresponding 5-methoxy-2-alkyl(aryl)carbamoyl-3,3,5-trimethylisoxazolidines (III) when we treated II with hydrochloric acid in methanol. The data from their IR spectra in KBr may serve as a confirmation of the structures of III: absorption of a urea fragment is present at 1650-1660 and 1500-1510 cm^{-1} and virtually coincides with the corresponding bands of starting II, and absorption of an OH group is absent. The negative test with a solution of ferric chloride excludes the formation of 1,4-dihydroxyhexahydro-2-pyrimidinone derivatives.

Three singlets of protons of methyl groups at 1.32, 1.45, and 1.52 ppm, a signal of methylene protons at 2.22 ppm, a singlet of 5-OCH_3 protons at 3.23 ppm, a multiplet of aromatic protons centered at 7.49 ppm, and, finally, an NH singlet at 8.54 ppm are observed in the PMR spectrum of IIIk in d_6-DMSO.

When we allowed II to stand in methanol at room temperature in the presence of catalytic amounts of p-toluenesulfonic acid, we were also able to observe a gradual increase in the amount of methoxy derivatives III. However, prolonged heating of this solution in the case of II*l* unexpectedly led to the isolation of N-3,4-dichlorophenylurethane.



The lack of data on the preparation of urethanes from hydroxyureas, together with data [4] on the possible conversion of N-hydroxyureas to their O-acyl isomers, makes it possible to assume that the intermediately formed N-substituted hydroxyureas undergo the same transformation with the subsequent formation of urethanes [5]. It seemed of interest to isolate O-acyl derivatives IV; we were able to accomplish this by heating II in carbon tetrachloride.

Two bands of carbonyl-group absorption (1710-1720 and 1750-1780 cm^{-1}) and NH absorption (3260 and 3310-3317 cm^{-1}) are observed in the IR spectra of IV in CCl_4, but OH vibrations are absent in the 3600 cm^{-1} region. When a solution of ferric chloride is added to IV, they do not give the blue-green coloration that is characteristic for hydroxamic acids. Singlets of protons of $< C(CH_3)_2$ groups at 1.08, of methyl protons at 1.98, and of methylene protons at 2.47, two NH singlets at 7.8 and 8.98, and a multiplet of aromatic protons at 7.25 ppm are observed in the PMR spectrum of IVk in CCl_4.

When IIa is heated in CCl_4 with 3,4-dichlorophenyl isocyanate, it is converted to O-(3,4-dichlorophenylcarbamoyl)-N-(2-methyl-4-oxo-2-pentyl)hydroxylamine, and this may serve as an indication of an intermolecular mechanism for the transcarbamoylation reaction.

The fact of the intramolecular cyclization of IV under the influence of acidic agents is interesting. Thus, in addition to its hydrochloride, a complex mixture of substances, from which two fractions were isolated by column chromatography, was obtained when hydrogen chloride was bubbled through a benzene solution of IVk.

In addition to a broad C=O band at 1680-1710 cm^{-1} and absorption bands of an aromatic ring at 1590 and 3100 cm^{-1}, an NH absorption band at 3430, $-CH=C<$ bands at 830 and 3060 cm^{-1}, and, finally, a broad absorption band of a bonded OH group at 3230-3390 cm^{-1} are observed in the IR spectrum (CCl_4) of the first fraction. These data make it possible to assume the presence of two compounds — 5-hydroxy-6-(4'-chlorophenyl)-3,3,5-trimethyl-1,2,6-oxadiazepin-7-one (Vk) and 6-(4'-chlorophenyl)-3,3,5-trimethyl-Δ^4-1,2,6-oxadiazepin-7-one (VIk) — in this fraction.

In fact, six singlets of methyl groups at 1.29, 1.34, 1.43, 1.55, 1.57, and 1.58 ppm, a signal of protons of a methylene grouping in the 4 position of Vk in the form of an AB system (with chemical shifts at 2.21 and 2.57 ppm, J = 12 Hz), a singlet of the $>CH-$ proton of VIl at 4.82 ppm, and a multiplet of aromatic protons centered at 7.17 ppm are observed in the PMR spectrum of this fraction in CCl_4. According to the data from the PMR spectrum, the Vk:VIk ratio is close to 3:2. Facile dehydration of the Vk→VIk type has been observed [6, 7] in heterocyclic structures that have an $>NC(OH)CH_3$ fragment. When the mixture of compounds (Vk + VIk) was heated in absolute alcohol, individual crystalline VIk was obtained. However, rapid conversion to the starting mixture is observed upon attempts to record the PMR spectrum of a solution of it in d_6-DMSO.

Absorption bands of a C=O group at 1690, of a C—O—C group at 1200, and of an NH group at 3430 cm^{-1} are observed in the IR spectrum (CCl_4) of VIIk. Three singlets of methyl protons at 1.40, 1.49, and 1.63 ppm, a singlet of NH protons at 7.03 ppm, a multiplet of aromatic protons centered at 7.27 ppm, and a triplet and quartet at 1.63 and 3.56 ppm (J = 8 Hz), which were assigned to the OC_2H_5 group, are observed in its PMR spectrum. The signal of geminal hydrogen atoms in the 6 position of the ring is an AB system (with chemical shifts at 2.11 and 2.34 ppm, J = 12 Hz).

These data, together with the results of elementary analysis, make it possible to assign the 5-ethoxy-6-(4'-chlorophenyl)-3,3,5-trimethyl-1,2,6-oxadiazepin-7-one structure to VIIk. The presence of an ethoxy group in the oxadiazepine ring of VIIk is explained by ethoxylation of Vk, evidently due to the ethanol present in the chloroform eluate (see [3]). The acid hydrolysis of VIk to starting Vk serves as a confirmation of its structure.

EXPERIMENTAL

The IR spectra of KBr pellets and solutions of the compounds in carbon tetrachloride were recorded with UR-10 and Perkin-Elmer 457 spectrometers. The PMR spectra of 10% solutions of the compounds in $(CD_3)_2SO$ were recorded with Tesla BS-487 and Brucker HX-90E spectrometers with hexamethyldisiloxane as the internal standard. The mass spectrum was recorded with an LKB-2091 chromatographic mass spectrometer. The results of elementary analysis, the melting points, and the spectral characteristics of II-IV are presented in Tables 1 and 2.

N-Alkyl(aryl)carbamoyl-5-hydroxy-3,3,5-trimethylisoxazolidines (II). A solution of 2 mmole of the corresponding isocyanate in 10 ml of tetrahydrofuran (THF) was added dropwise to a solution of 2 mmole of I in 30 ml of dry THF, and the resulting solution was stirred at 25°C for 1.5 h [the reaction was monitored by chromatography on Silufol UV-254 with elution by THF—hexane (1:1)], after which the solvent was removed by evaporation in vacuo, and the residue began to crystallize in ether.

N-Alkyl(aryl)carbamoyl-5-methoxy-3,3,5-trimethylisoxazolidines (III). Hydrochloric acid (20 ml) was added to a solution of 2 mmole of II in 20 ml of methanol, and the mixture was maintained at 25°C with stirring for 4 h (with chromatographic monitoring). It was then neutralized, after which the methanol was removed by evaporation, and the precipitate was removed by filtration.

O-Arylcarbamoyl-N-(2-methyl-4-oxo-2-pentyl)hydroxylamines (IV). A solution of 2 mmole of II in carbon tetrachloride was refluxed for 3 h (with chromatographic monitoring), after which it was cooled, and the unchanged II was removed by filtration. The filtrate was evaporated, as a result of which an oily product was obtained.

Conversion of IVk Under the Influence of HCl. Hydrogen chloride was bubbled into a solution of 2 mmole of IVk in benzene, and the resulting precipitate was removed by filtration and recrystallized from THF to give the hydrochloride of IVk, with mp 114-115°C, in 70% yield. Found: C 48.5; H 5.7; Cl 21.9; N 8.8%. $C_{13}H_{17}N_2O_3 \cdot HCl$. Calculated: C 48.6; H 5.6; Cl 22.1; N 8.7%.

TABLE 1. Compounds II-IV

Compound	R	T, mp, °C	IR spectrum, cm^{-1}		Found,%				Empirical formula	Calculated, %				Yield, % *
			C=O	NH	C	H	Cl	N		C	H	Cl	N	
II a	CH_3	98—99	1620	3480 †	51,0	8,6	—	14,9	$C_8H_{16}N_2O_3$	51,0	8,4	—	14,8	90
IIb	C_2H_5	70—71	1650	3440 †	53,3	8,8	—	14,0	$C_9H_{18}N_2O_3$	53,4	8,9	—	13,9	95
II c	$(CH_3)_3C$	104—106	1630	3430 †	57,3	9,2	—	12,2	$C_{11}H_{22}N_2O_3$	57,4	9,6	—	12,2	80
II d	$CH_2{=}CHCH_2$	59—60	1620	3420 †	56,1	8,5	—	13,3	$C_{10}H_{18}N_2O_3$	56,0	8,5	—	13,1	91
II e	C_6H_5	118—120	1640	—	62,5	7,5	—	11,3	$C_{13}H_{18}N_2O_3$	62,4	7,2	—	11,2	89
II f	3-$NO_2C_6H_4$	126—128	1650	3420	52,9	5,9	—	14,2	$C_{13}H_{17}N_3O_5$	52,9	5,8	—	14,2	98
II g	4-$CH_3C_6H_4$	137	1670	—	63,5	7,6	—	10,3	$C_{14}H_{20}N_2O_3$	63,6	7,6	—	10,6	75
II h	3-$CF_3C_6H_4$	135—136	1660	3430	52,7	5,3	—	8,7	$C_{14}H_{17}F_3N_2O_3$	52,8	5,4	—	8,8	75
II i	2-ClC_6H_4	110—112	1660	3450 †	54,9	6,0	12,1	10,0	$C_{13}H_{17}ClN_2O_3$	54,8	6,0	12,4	9,8	58
II j	3-ClC_6H_4	133—134	1640	3420	54,9	6,1	12,2	10,0	$C_{13}H_{17}ClN_2O_3$	54,8	6,0	12,4	9,8	95
II k	4-ClC_6H_4	129—131	1680	3430 †	54,8	5,8	12,6	9,9	$C_{13}H_{17}ClN_2O_3$	54,8	6,0	12,4	9,8	89
II l	3,4-$Cl_2C_6H_3$	134—136	1670	3430 †	48,8	4,9	22,1	8,7	$C_{13}H_{16}Cl_2N_2O_3$	48,9	5,0	22,2	8,8	83
II m	α-$C_{10}H_7$	133—134	1660	3440	67,9	6,8	—	9,3	$C_{17}H_{20}N_2O_3$	68,0	6,7	—	9,3	53
II n	β-$C_{10}H_7$	139—140	1665	3430	67,8	6,8	—	9,2	$C_{17}H_{20}N_2O_3$	68,0	6,7	—	9,3	44
III a	CH_3	72—75	1650	—	53,3	9,0	—	14,0	$C_9H_{18}N_2O_3$	53,4	8,9	—	13,8	70
III c	$(CH_3)_3C$	57—60	1660	—	58,8	9,9	—	11,4	$C_{12}H_{14}N_2O_3$	59,0	9,9	—	11,5	70
III d	$CH_2{=}CHCH_2$	47—50	1640	—	57,8	8,8	—	12,2	$C_{11}H_{20}N_2O_3$	57,9	8,8	—	12,3	70
III k	4-ClC_6H_4	126—128	1650	—	56,4	6,2	12,0	9,5	$C_{14}H_{19}ClN_2O_3$	56,3	6,4	11,8	9,4	70
III 1	3,4-$Cl_2C_6H_3$	145—146	1660	—	50,4	5,4	21,2	8,3	$C_{14}H_{18}Cl_2N_2O_3$	50,4	5,4	21,3	8,4	75
IV e	C_6H_5	—	1710 1765	3320 3360	62,4	7,4	—	11,3	$C_{13}H_{18}N_2O_3$	62,4	7,2	—	11,2	80
IVh	3-$CF_3C_6H_4$	—	1725 1780	3310 3260	52,6	5,2	—	8,6	$C_{14}H_{17}F_3N_2O_3$	52,8	5,4	—	8,8	82
IVk	4-ClC_6H_4	—	1710 1750	3310 3260	54,7	5,9	12,4	9,8	$C_{13}H_{17}ClN_2O_3$	54,8	6,0	12,4	9,8	79
IV1	3,4-$Cl_2C_6H_3$	—	1700 1770	3310 3260	48,7	4,9	22,1	8,6	$C_{13}H_{16}Cl_2N_2O_3$	48,9	5,0	22,2	8,8	78

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*In CCl_4.

†The absorption of the OH group is found at 3580-3600 cm^{-1}.

TABLE 2. Data from the PMR spectra of II-IV

Compound	Chemical shifts, ppm							
	$1\text{-}CH_3$	$2\text{-}CH_3$	$3\text{-}CH_3$	OCH_3	CH_2	OH	NH	Ar or CH_3
II a	1,31	1,51	1,58	—	2,04 2,20	5,62	—	2,63
II k	1,35	1,49	1,58	—	2,15	6,35	8,24	7,40
II l	1,36	1,40	1,46	—	2,17	6,39	8,49	7,66
III k	1,32	1,45	1,52	3,23	2,22	—	8,54	7,49
III l	1,36	1,46	1,54	3,26	2,26	—	8,68	7,59
IV k	1,08		1,98	—	2,47	—	7,80 8,98	7,25
IV l	1,10		1,98	—	2,46	—	7,27 8,90	7,30

The mother liquor was evaporated, and the residual oil was subjected to column chromatography on silica gel (elution with chloroform) to give a mixture of Vk and VIk, with mp 169-171°C [after thin-layer chromatography (TLC) on Silufol UV-254, elution with chloroform, R_f 0.68 and 0.60], and VIIk (TLC on Silufol UV-254, elution with chloroform, R_f 0.86). Found: C 57.6; H 6.9; Cl 11.1; N 9.0%. $C_{15}H_{21}ClN_2O_3$. Calculated: C 57.6; H 6.8; Cl 11.3; N 8.9%.

6-(4'-Chlorophenyl)-3,3,5-trimethyl-Δ^4-1,2,6-oxadiazepin-7-one (VIk). A mixture of 50 mg of Vk and VIk was refluxed in 20 ml of absolute alcohol for 4 h, after which the alcohol was removed by evaporation to give 25 mg of VIk with mp 166°C (TLC on Silufol UV-254, elution with chloroform, R_f 0.68). Mass spectrum [M 266], m/e: 251, 237, 153, 98, 44, 43, 42, 41. Compound Vk (TLC on Silufol UV-254, elution with chloroform, R_f 0.60) was obtained by heating a solution of 10 mg of VIIk in a mixture of concentrated hydrochloric acid and THF (1:1).

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