SYNTHESIS AND STUDY OF THE RATE OF AMINOLYSIS OF O-(ACYLAMINOACYL)OXIMES OF FORMYLPYRIDINES AND PYRIDYL METHYL KETONES*

P. Ya. Romanovski, T. Plucinski, and G. Kupryszewski

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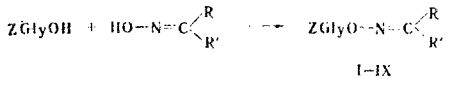
A number of O-(benzyloxycarbonylglycyl) derivatives of alkyl-, phenyl-, and pyridyl-substituted oximes were synthesized, and their chemical properties and reactivities under aminolysis conditions were studied. The principal factor that determines the reactivities of the investigated compounds during the formation of a peptide bond is the presence of a weakly acidic catalyst; the different reactivities of the compounds under the same conditions are due to the influence of the electron-acceptor effects of the substituents attached to the carbon atom of the oxime group.

The possibilities for the application of O-acylaminoacyl derivatives of oximes as activated esters for the synthesis of peptides have been investigated in several laboratories [1-5]. The acylating capacity of these relatively inactive compounds increases markedly in the presence of carboxylic acid [6, 7]. Recently in a study of the peculiarities of the aminolysis of O-acyl derivatives of 4-pyridinealdoxime the reason for the observed catalytic effect was ascribed to the influence of acetic acid in the role of a coordinate bifunctional catalyst, but we also did not exclude the transmission of the catalytic effect through the conjugated system of 4-pyridinealdoxime in the case of direct protonation of the basic nitrogen atom of the pyridine ring [8-10].

To investigate the effect of substituents attached to the carbon atom of the oxime group on the reactivities of O-(acylaminoacyl) derivatives of oximes and to more clearly ascribe the observed catalytic effect to one of the reasons cited above we synthesized a numer of model compounds – O-(benzyloxycarbonylglycyl) derivatives of various oximes [syn-benzaldoxime (I), syn-2-, 3-, and 4-pyridinealdoximes (II-IV, respectively), acetoxime (V), acetophenoneoxime (VI), and 2-, 3-, and 4-pyridyl methyl ketoximes (VII-IX)] – and compared the acylating abilities of these compounds on reaction with primary amines.†

The synthesis of model compounds I-IX (see Table 1) was carried out with the use of dicyclohexylcarbodiimide or 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline as the condensing agents.



I–IX

The ester bond of I-IX is unstable under the conditions of removal of the benzyloxycarbonyl protective group and is cleaved by the action of hydrogen bromide in glacial acetic acid or by catalytic hydrogenation.

As a model reaction for the study of the relative reactivities of O-acylaminoacyl derivatives I-IX with primary amines we selected their reaction with an equivalent amount of benzylamine in dioxane both in the absence of acetic acid or in the presence of an equivalent amount of acetic acid as the catalyst.‡

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†See [11] for our prelimnary communication.

‡Benzyloxycarbonylglycine benzylamide was isolated in 70-90% yield when the corresponding experiments were carried out on a preparative scale.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006. Institute of Chemistry, Gdansk University, Poland 80216. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1336-1339, October, 1977. Original article submitted January 4, 1977.

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TABLE 1. O-Benzyloxycarbonylglycine Derivatives of Aldoximes and Ketoximes

Compound	R	R′	mp, °C	R_f (system)	Found, %			Empirical formula	Calc., %			IR spectrum, ν_{CO}, cm-1		Yield, %	
					C	H	N		C	H	N	ester	urethane	A	B
I	H	C_6H	103—105	0,40 (A)	65,2	5,2	9,0	$C_{17}H_{16}N_2O_4$	65,4	5,2	9,0	1770	1700	90	—
II	H	2-Pyridyl	120,5—122	0,48(B)	61,4	5,0	13,3					1770	1700	90	—
III	H	3-Pyridyl	109—110	0,25(B)	61,3	4,9	13,0	$C_{16}H_{15}N_3O_4$	61,4	4,8	13,4	1785	1685	75	50
IV	H	4 -Pyridyl	115—116,5	0,23(B)	61,4	5,0	13,8					1770	1685	80	—
V	CH_3	CH_3	109—111	0,35(A)	58,9	5,9	10,7	$C_{13}H_{16}N_2O_4$	59,1	6,1	10,7	1785	1720	90	—
VI	CH_3	C_6H_5	80—82	0,45(A)	66,3	5,6	8,5	$C_{18}H_{18}N_2O_4$	66,2	5,6	8,5	1780	1680	90	—
VII	CH_3	2-Pyridyl	60—71	0,52(B) 0,65 (c)	62,4	5,3	12,7					1785	1680	80	60
VIII	CH_3	3-Pyridyl	87—89	0,27(B)	62,7	5,3	12,8	$C_{17}H_{17}N_3O_4$	62,4	5,2	12,8	1770	1680	85	70
IX	CH_3	4-Pyridyl	82—83	0,25(B)	62,3	5,2	12,7					1780	1685	90	65

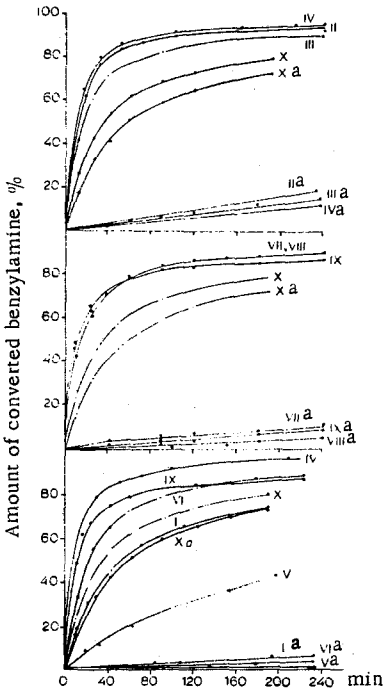
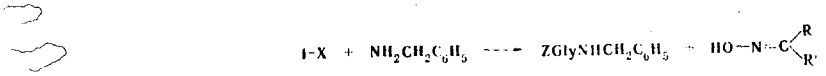


Fig. 1. Dependence of the amount of converted benzylamine on the time in the aminolysis of benzyloxycarbonylglycine esters in the absence (a) and in the presence of an equivalent amount of acetic acid (the numbers of the curves correspond to the numbers of the compounds in Table 1 and in the text).



The reaction was carried out by the method in [12], which is based on the determination of the amount of unchanged benzylamine. Benzyloxycarbonylglycine p-nitrophenyl ester (X) [13] was used as the standard compound for comparison of the results with the results described in the literature.

It follows from Fig. 1 that in the absence of a weakly acidic catalyst the rate of aminolysis of all of the investigated O-acylaminoacyl derivatives I-IX is very low and, in conformity with the ratio of the pK_a values of hydroxyl-containing components (10.0 for 4-pyridinealdoxime [14] and 7.14 for p-nitrophenol [15]), is much lower than the rate of aminolysis of ester X. In this case, despite the higher apparent activity of derivatives of pyridinealdoximes and pyridyl methyl ketoximes, we were unable to establish any definite principles. However, in the presence of acetic acid the reactivities of all of the investigated derivatives I-IX increase sharply, whereas the reactivity of standard X changes only relatively slightly. Compounds I-X are arranged in the order: II ≈ IV > III ≈ VII ≈ VIII ≈ IX > VI > X > I > V with respect to the rate of aminolysis in the presence of an equivalent amount of acetic acid.

When the curves of the conversion of model compounds I and II and III and IV, as well as VI and VII and VIII and IX (Fig. 1), are compared, it is seen that the principal portion of the catalytic effect is provided by the reaction of the exocyclic oxime group and acetic acid, whereas the differences in the reactivities of I-IX in the presence of a weakly acidic catalyst are due to the influence of the electron-acceptor effects of the substituents attached to the carbon atom of the oxime group. Thus, despite the increased activities of derivatives of heterocyclic oximes II-IV and VII-IX as compared with the corresponding derivatives of benzaldoxime I and acetophenoneoxime VI, the protonation of the heterocyclic nitrogen atom is not the principal reason for the catalytic effect. The main reason for the catalytic effect should evidently be ascribed to the influence of acetic acid as a coordinate bifunctional catalyst.

EXPERIMENTAL

The melting points (uncorrected) were determined in open capillaries. The individuality of the compounds was monitored by thin-layer chromatography (TLC) on Merck kieselgel G in a hexane–ether–acetone system (2:1:1) (A), hexane–ether–acetone (1:1:1) (B), 1-butanol–acetic acid–water (4:1:1) (C), and benzene–ethyl acetate (2:3) (D) systems; the chromatograms were developed in iodine vapors with ninhydrin as the reagent, whereas they were developed with a 0.5% solution of ferric chloride in 50% methanol in the case of 2-pyridinealdoxime and 2-pyridyl methyl ketoxime derivatives. Electrophoretic analysis was carried out on Whatman No. 1 paper in 1 N acetic acid at a potential gradient of 11 V/cm; the mobilities of the compounds were expressed with respect to histidine. The spots on the electrophoregrams were detected in UV light at 254 nm and with ninhydrin as the reagent. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 257 spectrometer. The solvents were purified by the method in [16]. The pyridinealdoximes and pyridyl methyl ketoximes were obtained by the method in [17] from the corresponding aldehydes and ketones and hydroxylamine hydrochloride.

O-(Benzyloxycarbonylglycyl)oximes (I-IX) (Table 1). A) A solution of 2.26 g (11 mmole) of dicyclohexylcarbodiimide in 15 ml of methylene chloride was added in the course of 30 min to a cooled (to 0°C) solution of 2.09 g (10 mmole) of benzyloxycarbonylglycine and 12 mmole of the appropriate oxime in 150-200 ml of methylene chloride, and the reaction mixture was then allowed to stand at room temperature for 12 h. The precipitated dicyclohexylurea was removed by filtration, and the filtrate was evaporated. The residual oil was washed with ether and crystallized from ethyl acetate or a mixture of ethyl acetate with ether or petroleum ether.

B) A solution of 0.395 g (1.6 mmole) of 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in 10 ml of methylene chloride was added to a solution of 0.313 g (1.5 mmole) of benzyloxycarbonylglycine and 1.6 mmole of the appropriate oxime in 50 ml of methylene chloride, and the mixture was allowed to stand at room temperature for 12 h. The solvent was then evaporated, and the residue was worked up as in Method A.

Aminolysis of O-(Benzyloxycarbonylglycyl)-2-pyridyl Methyl Ketoxime (VII) with Benzylamine. A 0.050-g (0.5 mmole) sample of benzylamine was added to a solution of 0.165 g (0.5 mmole) of oxime ester VII in 5 ml of benzene, and the mixture was allowed to stand at room temperature for 2 h. The resulting precipitate was removed by filtration and washed with benzene to give 0.11 g (75%) of benzyloxycarbonylglycine benzylamide with mp 118-119°C (from ethanol) (mp 117-118°C [18]) and R_f 0.46 (system D).

Catalytic Hydrogenation of O-(Benzyloxycarbonylglycyl) Derivative VII. A 10-mg sample of catalyst (5% Pd on active charcoal) was added to a solution of 0.02 g of VII in methanol–acetic acid–water (6:1:1), and hydrogen was bubbled through the suspension at room temperature and atmospheric pressure. The reaction mixture was analyzed after 90 min by TLC (system C): R_f 0.17 (glycine) and 0.38 (amine). It was also subjected to electrophoretic analysis: E_{His} 0.61 (glycine) and 1.15 (amine).

Action of Hydrogen Bromide in Acetic Acid on O-(Benzyloxycarbonylglycyl) Derivative VII. A 1-ml sample of a 36% solution of hydrogen bromide in acetic acid was added to a solution of 0.02 g of VII in 1 ml of acetic acid. The reaction mixture was analyzed by TLC (system C) after 30 min: R_f 0.17 (glycine) and 0.70 (2-pyridyl methyl ketoxime). It was also subjected to electrophoretic analysis after 120 min: E_{His} 0.59 (glycine).

Investigation of the Dependence of the Aminolysis of O-(Benzyloxycarbonylglycyl)oximes on Time. A solution of 0.25 mmole of the oxime ester in 20 ml of dioxane was placed in a 50 ml volumetric flask (in the case of catalytic aminolysis 1 ml of a 0.25 N solution of acetic acid in dioxane was added). The solution was thermostatted at 20.0 ± 0.1°C, 25 ml of a 0.01 N solution of benzylamine in dioxane was added, and the mixture was diluted to the mark with dioxane. Every 15-30 min, 5-ml samples of the solution were selected and added to 5 ml of glacial acetic acid, and the amount of unchanged benzylamine was determined by titration with 0.01 N perchloric acid in the presence of Crystal Violet indicator. The end point of the titration was determined from the change in the color of the indicator from violet to blue. The results of the determinations are presented in Fig. 1.

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ORGANIC COMPOUNDS OF SELENIUM AND TELLURIUM

II.* SYNTHESIS OF BENZO[b]SELENOPHENE DERIVATIVES BY REACTION OF DIBENZAL- AND BENZALACETONE WITH SELENIUM TETRABROMIDE

V. L. Lendel, Yu. V. Migalina, S. V. Galla, A. S. Koz'min, and N. S. Zefirov

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2,3-Disubstituted 2,3-dihydrobenzo[b]selenophenes were obtained in the form of trans isomers by the action of selenium tetrabromide on dibenzal- and benzalacetone in benzene.

It has been previously shown [1] that the addition of selenium tetrahalides to 1,5- and 1,6-diolefins and their derivatives is accompanied by the formation of unique products – heterocyclic compounds containing selenium in the ring. It might have been assumed that dibenzalacetone, as a 1,4-diolefin derivative, would behave like the indicated dienes in the reaction with selenium tetrabromide. However, the high selectivity of electrophilic addition could be disrupted owing to competitive substitution in the aromatic ring [2].

A study of the reaction of selenium tetrabromide with dibenzalacetone showed that the only products are benzo[b]selenophene derivatives IIa and IIIa. The structures of the isolated compounds were confirmed by IR, PMR, and UV spectral data and the results of analysis. Benzoselenophene derivatives are evidently formed

*See [1] for communication I.

Uzhgorod State University, Uzhgorod 294000. M. V. Lomonosov Moscow State University, Moscow 117234.
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