RESEARCH ON AMINOMETHYLENE DERIVATIVES OF AZOLES

XV.* SYNTHESIS AND STRUCTURE OF AMINOETHYLIDENE AND AMINOMETHYLENE DERIVATIVES OF 5-IMIDAZOLONE

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Aminomethylene and aminoethylidene derivatives of 5-imidazolone, the structures of which were studied by means of their UV, IR, and PMR spectra, were synthesized. It is shown that they exist in an enamine structure, primarily in the cis form stabilized by an intramolecular hydrogen bond.

In an attempt to reproduce the results in [2] in order to obtain 1, 2-dimethyl-5-imidazolone (II) from the Schmidt ester (I) and methylamine we obtained a crystalline precipitate corresponding to II with respect to its melting point and the results of elementary analysis. However, we found that the precipitate was a mixture of substances, the structure of each of which did not correspond to II. The mixture was separated with a column filled with aluminum oxide and two substances (IIIa and IVa) were isolated. The reaction of the Schmidt ester with ethylamine [2] proceeded similarly to also give two compounds (IIIb and IVb), and the latter remained in the filtrate under the reaction conditions [2].

The reaction can be directed to favor the formation of either III or IV by varying the reaction conditions.

An examination of the UV, IR, and PMR spectra (Table 1) of each of these reactions products (III and IV) and a determination of their elementary compositions and molecular weights, enabled us to assign to them the structure of 4-aminoethylidene derivatives of 5-imidazolone.

The reactivity of the methylene group of the 1,2-alkyl-5-imidazolone formed as a result of reaction of the Schmidt ester and primary amines is apparently very high, and the latter readily undergoes reaction with an imino ester to give III,† which subsequently reacts with excess primary amine to give IV. In fact, IIIa and IIIb react readily with methyl- or ethylamine in ethanol to give compounds of the IV type. This method was used to obtain IVc from IIIb.

Another possible method for the synthesis of 5-imidazolone is cyclization of glycyl anilide with ethyl orthoformate. However, this reaction also did not give the expected 1-phenyl-5-imidazole (V).

According to the results of elementary analysis and the melting point, the reaction product corresponded to the product described in [4]. However, an examination of the spectral characteristics and a determination of the molecular weight (337) showed that this compound is the 4-aminomethylene derivative of 1-phenyl-5-imidazolone (VI).

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* See [1] for communication XIV.

† Attention was directed to the possibility of the formation of this type of compound in the preparation of N-unsubstituted 5-imidazolones in [3], but the structure of these compounds was not established.

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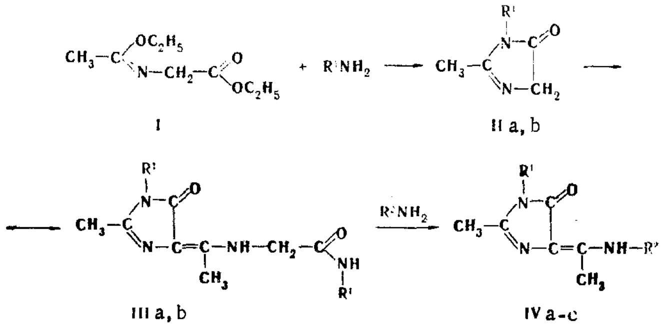
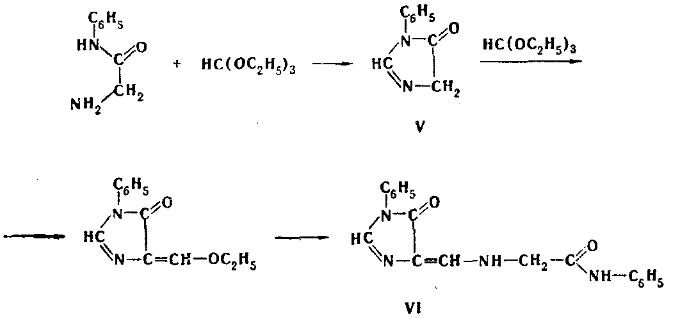


III, IV a $R^1 = R^2 = CH_3$; b $R^1 = R^2 = C_2H_5$; c $R^1 = C_2H_5$, $R^2 = CH_3$

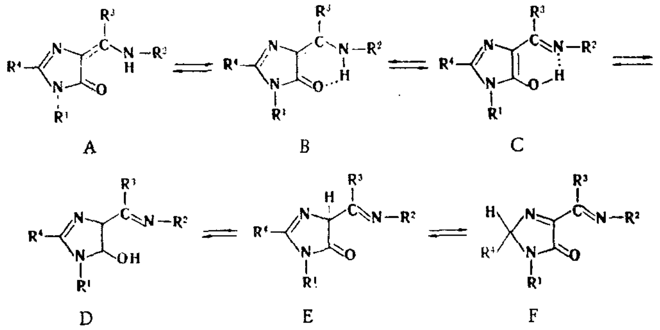
In this case also, the 1-phenyl-5-imidazolone evidently undergoes a number of transformations leading to VI under the reaction conditions.



The 4-methylaminomethylene (VII), 4-phenylaminomethylene (VIII), and 4-piperidinomethylene (IX) derivatives of 1-phenyl-5-imidazolone were obtained from VI by transamination.

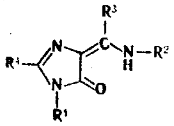
The aminomethylene and aminoethylidene derivatves of 5-imidazolone can exist in several forms.

A broad signal of the proton of an NH group at 9.1-9.5 ppm is observed in the PMR spectra of $CDCl_3$ solutions of III and IV (Table 1). The location of the proton at the nitrogen atom of the aminoethylidene group can be judged from the magnitude of the J_{NH,CH_3} spin–spin coupling constant (5 Hz) and the presence of the doublet of a CH_3 group. In the case of VI, δ_{NH} is found at 10 ppm. Thus the PMR spectral data make it possible to assign enamine structures (structures A and B) to the investigated compounds. The enamine structures differ with respect to the spatial orientation of the R^3 group and the NHR^2 group, and structure B is stabilized by an intramolecular hydrogen bond (IMHB). An examination of the PMR spectra of IVa, particularly the signals of the protons of the aminoethylidene group (CH_3 and $NHCH_3$), immediately after preparation of the solutions and after they have stood for some time shows that the signals of two structures are initially observed (Table 1, IVa* and IVa). On standing, the amount of one of the structures decreases, and the intensity of the signals of the protons of the other more stable structure, which has a broad signal of an NH group at 9.2 ppm, i.e., a compound with an IMHB (structure IVb), increases.



The IR spectra of $CHCl_3$ solutions of IVa, b and IVa-c in the region of stretching vibrations of the NH group contain two absorption bands (Table 1), which can be assigned to the vibrations of the $-C(=O)-C=C(CH_3)-NHR$ amidovinyl group, unconnected and connected by an IMHB. In addition, there are intense absorption bands at 1660-1670, 1630-1640, and 1570 cm^{-1}, which can be assigned to the absorption of the CO

TABLE 1. Spectral Characteristics of 5-Imidazolone Derivatives



Compound	PMR spectra, δ, ppm					Principal bands in IR spectra at 1500-1700 and 3000-3500 cm^{-1}	UV spectra in ethanol, λ_{max}, (log ε)
	NR^1	NR^2[a]	R^3	R^4	NH		
IIIa	3,10	4,13 2,88	2,30	2,20	9,46	1670, 1640, 1540; 3220—3350, 3430—3470	225 (4,16); 245[b] (3,93); 327 (4,34)
IIIb	1,17m[c]	4,07 3,56m 1,25m	2,33	2,25	9,50	1670, 1638, 1538; 3210—3310, 3420—3460	225 (4,10); 245[b] (3,94); 327 (4,20)
IVa	3.15	3,07	2,35	2,24	9,20	1660, 1630, 1570; 3150—3315; 3390—3420	225 (4,19); 245[b] (3,94); 327 (4,46)
IVa*[d]	3,15 3,20	3,07 3,02	2,35 2,52	2,24 2.20	9,20 6,63		
IVb	1,22m 3,46m	3,54m 1,30m	2,30	2,20	—	1655, 1625, 1569; 3150—3300; 3400—3410	225 (4,06); 245[b] (3,82); 327 (4,46)
IVc	1,30m 3,70m	3,05	2,40	2,30	9,10	1655, 1630, 1570; 3150—3315; 3390—3420	226 (4,07); 245[b] (3,85); 327 (4,26)
VI[e]					10	1700, 1612—1632; 1556	237[b] 250; 326
VII							226 (4,24); 255 (4,26); 331 (4,72)

[a] The signal of the NH group present in R^2 was not observed in the spectra of IIIa and IIIb.

[b] Shoulder.

[c] The letter m denotes a multiplet.

[d] The PMR spectrum was recorded immediately after preparation of the solution.

[e] The PMR spectrum was obtained from a solution in d$_6$-DMSO, and the IR spectrum was obtained from KBr pellets.

group [5], the deformation vibrations of the NH bond, and the stretching vibrations of the $-C=C-$ bond. The similar character of the UV spectra of the investigated compounds confirms their close structures.

Thus the reaction of the Schmidt ester with primary amines and of glycyl anilide with ethyl orthoformate gives, instead of 5-imidazolone, 4-aminoethylidene and 4-aminomethylene derivatives of 5-imidazolone, respectively, which exist in nonpolar solvents in an enamine structure, primarily in the cis form stabilized by an IMHB. The problems of the ratio between the cis and trans forms, the possibilities of interconversion in solvents and during synthesis, and the tautomeric transformation of these compounds require additional study.

EXPERIMENTAL

The IR spectra of 2-5% solutions of the compounds in CHCl$_3$ were recorded with a UR-20 spectrometer at a layer thickness of 0.5 mm. The UV spectra were recorded with an SF-8 spectrophotometer. The PMR spectra of 3-10% solutions in CDCl$_3$ were recorded with an RYa-2306 spectrometer (60 MHz)* with hexamethyldisiloxane as the internal standard. The molecular weight was determined osmometrically with a V-PO 302B apparatus.

The Schmidt ester (I) was obtained by the method in [2].

1,2-Dimethyl-4-(methylamidocarbonyl)methylaminoethylidene-5-imidazolone (IIIa). This compound was obtained by the method in [2]; the yield of a mixture with mp 165-173° was 37%. Separation with a chromatographic column filled with Al$_2$O$_3$ (elution by chloroform) gave IIIa with mp 178° (from ethyl acetate) and R$_f$ 0.16-0.20 in 3% yield. Found: N 25.3%; M 212 (in chloroform). C$_{10}$H$_{16}$N$_4$O$_2$. Calculated: N 25%; M 224. The remainder of the mixture separated with the chromatographic columns was IVa (see below).

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Compound IIa could be obtained in 29% yield by 10 min refluxing of the reaction mixture described in [2] and subsequent standing at room temperature for 20 h.

1,2-Dimethyl-4-methylaminoethylidene-5-imidazolone (IVa). A) This compound, with mp 182° (from ethyl acetate) and Rf 0.65-0.70, was obtained in 29% yield by chromatographic separation of the mixture as described in the preceding experiment. Found: N 24.7%; M 163.5 (in chloroform). $C_7H_{13}N_3O$. Calculated: N 25.2%; M 167.

B) A 2-g (8.9 mmole) sample of IIIa was heated in 10 ml of ethanol with 6.2 g (200 mmole) of methylamine (a 33% solution in ethanol) at 40-50° for 2-3 h.* The yellow solution was evaporated, and the oily residue was treated with hot ethyl acetate. The ethyl acetate solution was cooled to precipitate 0.8 g (50%) of colorless crystals. No melting-point depression was observed for a mixture of this product with the sample obtained in experiment A.

1-Ethyl-2-methyl-4-(ethylamidocarbonyl)methylaminoethylidene-5-imidazolone (IIIb). This compound, with mp 194° (from ethyl acetate), was obtained in 51% yield by the method in [2]. Found: C 58.1; H 8.9; N 22.2%; M 267 (in chloroform). $C_{12}H_{20}N_4O_2$. Calculated: C 57.1; H 8.0; N 22.2%; M 252.

1-Ethyl-2-methyl-4-ethylaminoethylidene-5-imidazolone (IVb). A) Compound IVb was isolated in low yields from the filtrate after separation of IIIb (see the preceding experiment).

B) A 6-g (23.8 mmole) sample of IIIb was heated in 60 ml of ethanol with 16.2 g (360 mmole) of ethylamine at 40-60° for 8-10 h, after which the solvent was evaporated, and the oily residue was treated with hot n-heptane. Cooling of the heptane solution yielded 2.4 g (50%) of colorless crystals with mp 70-71° (from n-heptane). Found: N 20.8%; M 203 (in chloroform). $C_{10}H_{17}N_3O$. Calculated: N 21.6%; M 195.

1-Ethyl-2-methylaminoethylidene-5-imidazolone (IVc). This compound was obtained by the method used to prepare IVb by heating 4 g of IIIb with methylamine for 3-4 h. The yield of colorless crystals with mp 123° (from n-heptane) was 2.3 g (80%). Found: N 22.6%; M 178 (in chloroform). $C_9H_{15}N_3O$. Calculated: N 23.2%; M 181.

1-Phenyl-4-(anilidocarbonyl)methylaminomethylene-5-imidazole (VI). A 3-g (8.3 mmole) sample of glycyl anilide carbonate was dissolved in 70 ml of refluxing absolute ethanol, after which 1.36 g (9.2 mmole) of ethyl orthoformate was added, and the mixture was refluxed for 2 h. It was then cooled and worked up to give 1.19 g (43.4%) of light-yellow crystals with mp 227° (from n-butanol). Found: C 68; H 5.8; N 17.4%; M 337 (in dioxane). $C_{18}H_{16}N_4O_2$. Calculated: C 67.5; H 5.0; N 17.5%; M 320.

1-Phenyl-4-methylaminomethylene-5-imidazolone (VII). A 0.9-g (2.8 mmole) sample of imidazolone VI was refluxed with 1.9 g (60 mmole) of methylamine (a 33% solution in ethanol) for 6 h, after which the mixture was cooled, and the unchanged VI was removed by filtration. The filtrate was evaporated, and the residue was treated several times with ether, after which the residue was dissolved in chloroform. The chloroform solution was filtered and passed through a column filled with aluminum oxide with elution by chloroform to give 0.17 g (30%) of a cream-colored product with Rf 0.65-0.70. Crystallization from petroleum ether–benzene (2 : 1) gave colorless needles with mp 188.5-189°. Found: N 21.2%. $C_{11}H_{11}N_3O$. Calculated: N 20.9%.

1-Phenyl-4-phenylaminomethylene-5-imidazolone (VIII). A solution of 0.25 g (0.78 mmole) of VI in 50 ml of butanol was refluxed for 8 h with 1.1 g of aniline, after which the solvent was removed by distillation, and the residue was dissolved in ether. The unchanged VI was removed by filtration, the filtrate was evaporated, and the residue was dissolved in chloroform and passed through a column filled with aluminum oxide with elution by chloroform to give 0.1 g (50%) of yellow needles with mp 168-169° (from benzene) and Rf 0.7-0.8. Found: N 15.9%; M 254 (in dioxane). $C_{16}H_{13}N_3O$. Calculated: N 16%; M 263.

1-Phenyl-4-piperidinomethylene-5-imidazolone (IX). This compound was obtained by the method used to prepare VII (with exclusion of treatment of the residue with ether) from 0.4 g (1.25 mmole) of VI in 20 ml of ethanol and 1.3 g (16.4 mmole) of piperidine. The yield of product with Rf 0.8 was 0.2 g (67%). Crystallization from petroleum ether–benzene (2.5 : 1) gave colorless needles with mp 189°. Found: N 15.9%; M 256 (in chloroform). $C_{15}H_{17}N_3O$. Calculated: N 16.5%; M 255.

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*The completion of the reaction in this case and in all of the subsequent transamination reactions could be monitored by means of thin-layer chromatography on Al_2O_3 with chloroform as the solvent. The Rf values of the transamination products were higher than the Rf values of the starting compounds.

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2-FORMYLIMIDAZO[4,5-b]-AND 2-FORMYLIMIDAZO[4,5-c]PYRIDINES

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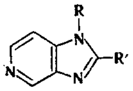
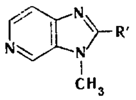
The corresponding aldehydes were obtained by oxidation of N-substituted 2-methylimidazo-[4,5-b]- and 2-methylimidazo[4,5-c]pyridines with selenium dioxide. Some of their properties and transformations were studied.

The preparation of unsubstituted 2-formylimidazo[4,5-b]pyridine and 2-formylimidazo[4,5-c]pyridine from 2,3- and 3,4-diaminopyridines and ethyl diethoxyacetate was described in [1].

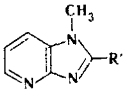
The present paper is devoted to the preparation of N^1- and N^3-substituted 2-formylimidazo[4,5-b]-pyridines and 2-formylimidazo[4,5-c]pyridines (I-III, XII, XVII, XIX, and XX) and to a study of some of their transformations with participation of the aldehyde group.



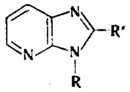
I-XI



XII-XVI



XVII, XVIII



XIX-XXVI

I R=CH$_3$, R'=CHO; II, XIX R=CH$_2$C$_6$H$_5$, R'=CHO; III, XX R=C$_6$H$_5$, R'=CHO; IV R==R'=CH$_3$; V, XXI R=CH$_2$C$_6$H$_5$, R'=CH$_3$; VI, XXII R=C$_6$H$_5$, R'=CH$_3$; VII R=CH$_3$, R'=CH=CHCOOH; VIII R=CH$_3$, R'=CN; IX, XXIV R=CH$_2$C$_6$H$_5$, R'=CN; X R=CH$_3$, R'=CONH$_2$; XI R=CH$_2$C$_6$H$_5$, R'=CONH$_2$; XII, XVII R'=CHO; XIII, XVIII R'=CH$_3$; XIV R'=CH=CHCOOH; XV R'=CN; XVI R'=CONH$_2$; XXIII R=C$_6$H$_5$, R'=CH==CHCOOH; XXV R=C$_6$H$_5$, R'=CN; XXVI R=C$_6$H$_5$, R'=CONH$_2$

Aldehydes I-III, XII, XVII, XIX, and XX were prepared by oxidation of 2-methylimidazopyridines (IV-VI, XIII, XVIII, XXI, and XXII) with selenium dioxide as in [2, 3]. The reaction was carried out in toluene, dioxane, aqueous dioxane, water, trifluoroacetic acid, and acetic anhydride; in the last two solvents the oxidation proceeds extremely slowly. The best results were achieved when dioxane was used as the solvent [4]. The action of an equivalent amount of selenium dioxide on bases IV and XIII gives, in addition to aldehydes I and XII, a certain amount (up to 18%) of 2-unsubstituted 1-methyl-1H- and 3-methyl-3H-imidazo-[4,5-c]pyridines; this may be associated with the more extensive oxidation of the starting compounds to the corresponding 2-carboxylic acids and their subsequent decarboxylation under the reaction conditions.

Aldehydes of the c series (I-III and XII) tend to add water to give monohydrates that are completely stable at room temperature and have IR spectra (KBr pellets) that do not contain carbonyl absorption. Carbonyl absorption can be observed in CCl$_4$ solution at 1705-1720 cm^{-1} after vacuum drying of the sample at 105-110° (5-10 mm) for 2 h. These results constitute evidence for the ability of aldehydes I-III and XII to

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