7. H. G. Heller and M. Szewczyk, J. Chem. Soc., Perkin 1, No. 12, 1487 (1974).
8. C. G. Overberger and C. W. Roberts, J. Am. Chem. Soc., 71, 3618 (1949).
9. H. Stobbe, Berichte, 1, 94 (1897).
10. P. J. Darcy, R. J. Hart, and H. G. Heller, J. Chem. Soc., Perkin 1, No. 6, 571 (1978).
11. S. P. Hiremath and R. S. Hosmane, Adv. Heterocycl. Chem., 15, 277 (1973).
12. M. D. Cohen, H. W. Kaufman, D. Sinnreich, and G. M. J. Schmidt, J. Chem. Soc., B, No. 6, 1035 (1970).
13. H. D. Ilge, H. Langbein, M. Reichenbächer, and R. Paetzold, J. Prakt. Chem., 323, 367 (1981).
14. V. I. Minkin, E. A. Medyantseva, O. G. Lyashik, A. V. Metelitsa, N. M. Andreeva, M. I. Knyazhanskii, and N. V. Volbushko, Khim. Geterotsikl. Soedin., No. 11, 1569 (1986).
15. V. M. Rodionov and T. K. Veselovskaya, Zh. Obshch. Khim., 20, 2202 (1950).

CARBOXYIMIDAZOLES IN THE MANNICH REACTION

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Depending on the reagent ratio, 5-dimethylaminomethyl-4-imidazole-4-carboxylic acid and 2,4,5-tris(dimethylaminomethyl)imidazole were obtained in the aminomethylation of imidazole-4-carboxylic and imidazole-4,5-dicarboxylic acids. The oxidation of these compounds with nitric acid leads to imidazole-4,5-dicarboxylic acid.

It is known that imidazole, inasmuch as it is a π-surplus heterocycle, readily undergoes electrophilic substitution reactions [1, p. 55] to give mono-, di-, and trisubstitution products [2]. This is also characteristic for the Mannich reaction. Thus mono- and polysubstituted Mannich bases were obtained from 2-methylimidazole and 4,5-dimethyl- and 2,4-dimethylimidazole in the reaction with formaldehyde and piperidine (or diethylamine), whereas in an acidic medium the reaction of imidazole and 2-methylimidazole led only to N-substituted reaction products [3].

We have studied the behavior in the Mannich reaction of imidazole derivatives that contain carboxy and nitro groups, viz., imidazole-4-carboxylic (I), imidazole-4,5-dicarboxylic (II), and 4-nitroimidazole-5-carboxylic acid and 4-nitroimidazole. It was found that the reaction does not take place at room temperature even in the case of a tenfold excess of the reagents and standing for a long time (72 h). When we heated acid II to 80-100°C with equimolar amounts of dimethylamine and formaldehyde we observed the formation of a mixture of three to four compounds, from which we were able to isolate part of the unchanged starting substance and the principal product, viz., 5-dimethylaminomethyl-imidazole-4-carboxylic acid (III) in the form of hydrochloride IIIa. Under the same conditions, according to TLC data, acid I gives a more complex mixture, one of the components of which is also III. Because of the low chromatographic mobilities, we were unable to isolate individual substances from the mixture.

An increase in the excess amounts of dimethylamine and formaldehyde from sevenfold to tenfold amounts at 80-100°C led to the formation from acids I and II of the same Mannich base, viz., 2,4,5-tris(dimethylaminomethyl)imidazole (IV), which was isolated in the form of mono- and trihydrochlorides IVa and IVb. Compound IVb was also obtained under the same conditions from imidazole.

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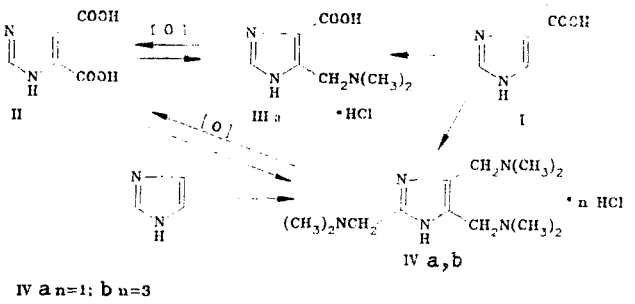

IV a n=1; b n=3

A band of stretching vibrations of a carbonyl carboxy group at 1725 cm^{-1} is present in the IR spectrum of IIIa, while signals of a proton of the imidazole ring and one dimethylaminomethyl fragment are present in the PMR spectrum. The structures of IVa, b are confirmed by the absence in their IR spectra of bands of stretching vibrations of a carboxy group; the PMR spectra of solutions in d_6-DMSO do not contain signals of protons of an imidazole ring vis-à-vis the presence of signals of protons of three dimethylaminomethyl groups; two of them are chemically equivalent. However, in CF_3COOH the protons of the dimethylaminomethyl groups resonate at different fields.

In order to additionally confirm the structures of the compounds obtained and to study the possibility of their practical use we carried out the oxidation of salts IIIa and IVb with a mixture of nitric and sulfuric acids to imidazole-4,5-dicarboxylic acid III; the intermediate in the case of the oxidation of salt IVb is evidently either the imidazole-2,4,5-tricarboxylic acid, which is decarboxylated during the reaction, or one of the 4,5-disubstituted imidazole-2-carboxylic acids formed in the successive oxidative destruction of the dimethylaminomethyl fragments.

In contrast to carboxylic acids I and II, 4-nitroimidazole-5-carboxylic acid and 4-nitroimidazole did not undergo the Mannich reaction even on treatment with a tenfold excess of the reagents at 80-100°C for 8 h; this can evidently be explained by their existence in the aci nitro form.

The results obtained show that, in contrast to alkylimidazoles, carboxy derivatives of imidazole undergo the Mannich reaction considerably more readily in the 4(5) position than in the 2 position of the ring. Even the presence of carboxy groups in the 4 and 5 positions, which in this case are replaced, despite the unoccupied 2 position, do not hinder aminomethylation. In the latter case two reaction mechanisms are possible: ipso replacement of the carboxy group by the attacking electrophile or initial thermal decarboxylation with the intermediate formation of an imidazole. Decarboxylation was not observed in the case of prolonged heating of acids I and II with dimethylamine in the absence of formaldehyde. A mechanism involving ipso substitution is evidently realized under the experimental conditions; this is known for hydroxymethylation in the imidazole series [4].

Since imidazole-4,5-dicarboxylic acid (II) is an intermediate in the synthesis of the medicinal preparation etimizole, while imidazole-4-carboxylic acid (I) is quite accessible [5], the aminomethylation of imidazole I with subsequent oxidation of Mannich base IV with nitric acid takes on practical value as an alternative method for the synthesis of the pharmaceutical intermediate II [6] from another raw material, viz., acid I.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of aqueous solutions were obtained with a Beckman UV-26 spectrophotometer. The PMR spectra were measured with a Perkin–Elmer R-12B spectrometer (60 MHz) with tetramethylsilane (TMS) as the internal standard. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in two solvent systems: n-butanol–acetic acid–water (4:1:1) (R_f) and n-propanol–3% ammonium hydroxide (3:1) (R_f'). The results of elementary analysis for C, H, N, and Cl were in agreement with the calculated values.

5-Dimethylaminomethylimidazole-4-carboxylic Acid Hydrochloride (IIIa, $C_7H_{11}N_3O_2 \cdot HCl$). A mixture of 2.0 g (12.8 mmole) of acid II, 0.46 g (15.4 mmole based on CH_2O) of paraformaldehyde, 4.66 ml (30.8 mmole) of a 33% aqueous solution of dimethylamine, and 15 ml of water was

refluxed at 80-100°C for 4 h, after which the mixture was cooled and acidified to pH 1-2 with concentrated hydrochloric acid. The precipitate was removed by filtration and washed with water to give 0.56 g (28%) of a substance that, with respect to its IR spectrum, melting point, and chromatographic mobility, was identical to starting acid II. The filtrate and wash waters were evaporated to dryness in vacuo, and the residue was crystallized twice from ethanol to give 0.4 g (16%) of salt IIIa with mp 249-251°C, R_f 0.05, and R_f^+ 0.13. IR spectrum: 1725 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 230 nm (3.92). PMR spectrum (d_6-DMSO): 7.91 (1H, s, 2-H), 4.46 (2H, s, CH_2N), 2.80 ppm (6H, s, $N(CH_3)_2$).

2,4,5-Tris(dimethylaminomethyl)imidazole Trihydrochloride (IVb, $C_{12}H_{25}N_5 \cdot 3HCl$). A) A mixture of 4.0 g (35.7 mmole) of acid I, 16.1 g (536 mmole) of paraformaldehyde, and 80 ml (537 mmole) of a 33% aqueous solution of dimethylamine was refluxed at 80-100°C for 4 h, after which the mixture was evaporated to dryness in vacuo. Water (40 ml) was added to the residue, and the aqueous solution was acidified to pH < 1 with concentrated hydrochloric acid. The solution was evaporated to dryness in vacuo, and the residue was crystallized twice from ethanol to give 6.7 g (54%) of a product with mp 185-186°C, R_f 0.00, and R_f^+ 0.04. PMR spectrum (d_6-DMSO): 4.38 (2H, s, CH_2N), 4.50 (4H, s, $2(CH_2N)$), 2.81 ppm (18H, s, $3N(CH_3)_2$). PMR spectrum (CF_3COOH): 4.54 (2H, s, CH_2N), 4.62 (2H, s, CH_2N), 4.77 (2H, s, CH_2N), 2.76 (6H, s, $N(CH_3)_2$), 2.83 (6H, s, $N(CH_3)_2$), 2.88 ppm (6H, s, $N(CH_3)_2$).

B) This compound was also obtained by a method similar to method A from 6.24 g (40 mmole) of acid II, 18.0 g (600 mmole) of paraformaldehyde, and 90 ml (600 mmole) of 33% aqueous dimethylamine. The yield was 9.75 g (70%). With respect to the IR and PMR spectra, melting point, and chromatographic mobility the product was identical to that obtained by method A.

C) This compound was obtained by a method similar to method A from 1.36 g (20 mmole) of imidazole, 9.0 g (300 mmole) of paraformaldehyde, and 45 ml (300 mmole) of 33% aqueous dimethylamine. The yield was 4.1 g (59%). With respect to its IR and PMR spectra, melting point, and chromatographic mobility the product was identical to the products obtained by methods A and B.

2,4,5-Tris(dimethylaminomethyl)imidazole Hydrochloride (IVa, $C_{12}H_{25}N_5 \cdot HCl$). A 3.5-g (10 mmole) sample of salt IVb was added to a solution of sodium ethoxide prepared from 20 ml of ethanol and 0.46 g (20 mmole) of sodium, and the mixture was stirred at room temperature for 6 h. The sodium chloride was removed by filtration, the filtrate was evaporated to dryness in vacuo, and the residue was dissolved in a mixture of 10 ml of ethanol and 10 ml of dioxane. The solution was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was re-evaporated twice with absolute ethanol, and the resinous product was dried in a desiccator over KOH. Upon trituration the resin crystallized to give 2.23 g (81%) of colorless crystals with mp 138-141°C. PMR spectrum (d_6-DMSO): 3.41 (2H, s, CH_2N), 3.70 (4H, s, CH_2N), 2.14 (6H, s, $N(CH_3)_2$), 2.34 ppm (12H, s, $2N(CH_3)_2$).

Imidazole-4,5-dicarboxylic Acid (II). A) A 10-ml sample of concentrated sulfuric acid was added to 3.0 g (14.6 mmole) of hydrochloride IIIa, and the mixture was heated to 105°C. It was then treated with 100 ml of 56% nitric acid, and the acidified mixture was maintained at 110-120°C until the evolution of nitrogen oxides ceased. The excess nitric acid was evaporated with stirring until the temperature of the mixture reached 140°C. The residue was diluted with water to a volume of 100 ml, and the precipitate was removed by filtration and washed with water to give 0.82 g (36%) of a substance that, with respect to its IR spectrum, melting point, and chromatographic mobility, was identical to a sample with a genuine structure [6, p. 168].

B) A 10-ml sample of concentrated sulfuric acid was added to 3.5 g (10 mmole) of trihydrochloride IVb, the solution was heated to 105°C and treated with 100 ml of 56% nitric acid, and the mixture was maintained at 110-120°C until the evolution of nitrogen oxides ceased. The excess nitric acid was evaporated in vacuo, the residue was diluted with water to a volume of 100 ml, and the precipitate was removed by filtration and washed with water to give 1.1 g (70%) of a substance that, with respect to its IR spectrum, melting point, and chromatographic mobility, was identical to a sample with a genuine structure [6].

LITERATURE CITED

1. A. F. Pozharskii, Theoretical Foundations of the Chemistry of Heterocycles [in Russian], Khimiya, Moscow (1985).
2. M. R. Grimett, Adv. Heterocycl. Chem., No. 12, 103 (1970).

3. F. B. Stocker, J. L. Kurtz, B. L. Gilman, and D. A. Forsyth, J. Org. Chem., 35, 883 (1970).
4. C. S. Kim, K. G. Lec, and J. B. Chac, J. Heterocycl. Chem., 20, 1417 (1983).
5. A. E. Onishik, Zh. Obshch. Khim., 25, 984 (1955).
6. M. V. Rubtsov and A. G. Baichikov, Synthetic Pharmaceutical-Chemical Preparations [in Russian], Meditsina, Moscow (1971).

1,2,4-TRIAZOLO[1,5-a]BENZIMIDAZOLES: TAUTOMERISM AND ALKYLATION

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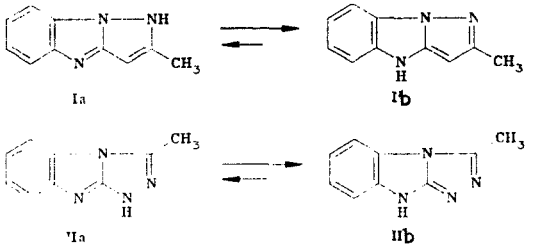
The position of the tautomeric equilibrium in unsubstituted 1,2,4-triazolo[1,5-a] benzimidazole, as well as in its 2-methyl and 2-phenyl derivatives, was investigated by UV, IR, and PMR spectroscopy and by determination of the ionization constants. In all cases the amount of the 4H tautomer in the equilibrium mixture is two to three orders of magnitude greater than the amount of the 3H tautomer, while signs of the existence of the 1 H form are not observed. The synthesis of unsubstituted triazolo [1,5-a]-benzimidazole was accomplished for the first time. The alkylation of the indicated triazolo [1,5-a]benzimidazoles was studied and a relationship between the regiospecificity of this reaction and the position of the tautomeric equilibrium was established.

In recent years the attention of researchers has been directed to condensed systems based on benzimidazole in which another zole ring is attached at the 1–2 bond of the benzimidazole molecule [1]. The principal reason for this interest is the high biological activities of some imidazo[1,2-a]benzimidazoles [2, 3], as well as the complex mutual effect of the condensed rings, the study of which is important for the development of the theoretical chemistry of heterocycles. One of the chief manifestations of this effect is the position of the tautomeric equilibrium in azolobenzimidazoles. Up until now it has been studied for 2-methylpyrazolo[1,5-a]benzimidazole (I) [4] and 3-methyl-1,2,4-triazolo[4,3-a]benzimidazole (II) [5]; it was demonstrated by PMR spectroscopy and measurement of the dipole moments that the 4H tautomer (Ib) dominates in the first case, whereas the 1H tautomer (IIa) dominates in the second case.



The aim of the present research was to study the tautomerism of 1,2,4-triazolo[1,5-a] benzimidazoles III–V. This heterocyclic system contains within itself the features of the structural properties both with I and with azoles II, but the existence of not two but rather three tautomeric forms is possible for it. From a theoretical point of view the following

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