SYNTHESIS OF 7- AND 8-NITRO DERIVATIVES OF 4-OXO-1,2,4-TRIAZINO[4,5-a]BENZIMIDAZOLE

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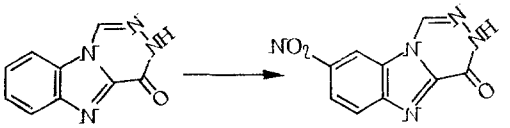
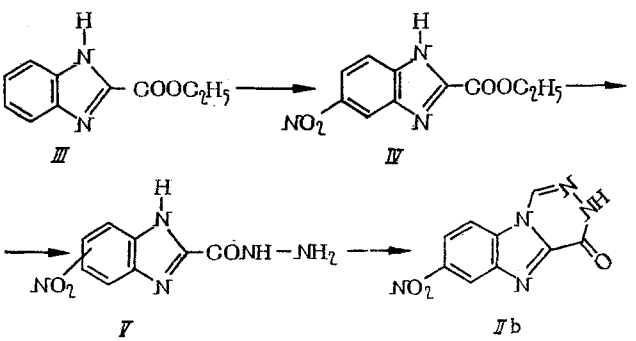
The preparation of nitro derivatives of 4-oxo-1,2,4-triazino[4,5-a]benzimidazole (I) was of interest in the search for medicinal compounds, since in the series of 1,2-di-substituted benzimidazoles the presence of a nitro group in the benzene ring is associated with high pharmacological activity. For example, clonitazene and etonitazene exhibit analgesic activity [1]. The present work was devoted to the study of the reaction of nitration of I. It was established by us that when the nitration reaction is carried out at a temperature not higher than 25°C and by using a nitrating mixture, the nitro group enters the benzene ring. In the mononitro derivative thus prepared (IIa), the nitro group was found, by PMR spectroscopy, to be at position 7 or 8:



I IIa

To establish the exact position of the nitro group, the mononitro derivative IIb was synthesized by us according to the following scheme:



III IV V IIb

The ethyl ester of benzimidazole-2-carboxylic acid (III) was nitrated with a mixture of nitric and sulfuric acids, and the ethyl ester of 5(6)-nitrobenzimidazole-2-carboxylic acid produced (IV) was converted, by the action of hydrazine hydrate, into the hydrazide of 5(6)-nitrobenzimidazole-2-carboxylic acid (V). The latter was cyclized to IIb by the action of orthoformic ester. It can be assumed that the cyclization takes place around the nitrogen atom para to the nitro group to form 7-nitro-4-oxo-1,2,4-triazino[4,5-a]benzimidazole, as occurs in the case of 2-(γ-hydroxypropyl)-5(6)nitrobenzimidazole [2]. According to IR and PMR spectra, this compound is not identical with compound IIa. Examination of the PMR spectra of IIa and IIb showed that the structure of the signals in the spectra of these compounds is analogous: there

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TABLE 1. Experimental (b) and Calculated (a) Values of the Chemical Shifts of 4-Oxo-1,2,4-triazine[4,5-a]benzimidazole and Its 7- and 8-Nitro Derivatives (δ-scale)

Compound	Solvent	H−C_6		H−C_7		H−C_8		H−C_9	
		a	b	a	b	a	b	a	b
I	Dimethyl-sulfoxide	–	7.97	–	7.60	–	7.60	–	8.30
IIb	Dimethyl-formamide	8.94	8.78	–	–	8.56	8.42	8.49	8.50
Shape of signal		Singlet split		–		Doublet split		Doublet	
IIa	Dimethyl-formamide	8.16	8.17	8.56	8.48	–	–	9.26	9.43
Shape of signal		Doublet		Doublet split		–		Singlet split	

Note. Spectra run on INMI-4H100 instrument with working frequency 100 MHz. Internal standard was tetramethylsilane.

is a singlet signal, simply attributed to a proton at C_1; a split singlet with J ~ 2-2.3 Hz, which, depending on the position of the nitro group, can be attributed to a proton at C_6 or C_9; and two doublets with J ~ 8.8-10 Hz, the weak doublet being split with J ~ 2-2.3 Hz. The last signals are caused by the neighboring protons at C_8 and C_9 (nitro group in position 7) or by the protons at C_7 and C_6 (the nitro group in position 8).

The spectra of IIa and IIb differ in the chemical shifts of the signals, which permits a determination of the character of the substitution. The triazine ring is practically an aromatic system, the presence of which affects the magnitudes of the chemical shifts of the protons of the benzene ring. Thus, the proton at C_9, spatially positioned closer to this ring, will, other things being equal (the presence of the nitro group ortho to the proton being studied), be more deshielded than the proton at C_6.

Since in compound IIa this singlet is found at δ 9.43 ppm, and in IIb at δ 8.78 ppm, it can be concluded that in IIa the nitro group occupies position 8 (singlet at C_9) and in IIb position 7 (singlet at C_6). This point of view is confirmed by calculation of the chemical shifts of the protons of the benzene ring for 7- and 8-mononitro derivatives carried out on the basis of the chemical shifts of the protons of unsubstituted I and of a calculation of the effect of the nitro group. Such an estimate of the chemical shifts of the protons of two isomeric molecules is quite rough, since the aromatic systems of a free benzene ring and of a benzene ring attached to a condensed heterocyclic system can differ significantly. Furthermore, the corresponding increments of effect of the nitro group can differ, depending on the solvent (in our case dimethylformamide and dimethylsulfoxide, tabulated data [3] is for the solvents $CDCl_3$ and CCl_4). However, since the increments for the nitro are very great and differ strongly for the o and m positions, it may be thought that such a rough estimate is sufficient to identify the isomers by the spectra. The results of the calculations of the values of the chemical shifts for the 7- and 8-nitro derivatives agree with experimental results for compounds IIb and IIa, respectively (see Table 1).

EXPERIMENTAL

8-Nitro-4-oxo-1,2,4-triazino[4,5-a]benzimidazole (IIa). To a solution of 0.3 g of I in 3 ml of concentrated sulfuric acid was added, with cooling, the nitrating mixture (0.7 ml of nitric acid, sp. gr. 1.4, and 0.2 ml of concentrated sulfuric acid) at a temperature not above 25°C; the mixture was agitated 30 min, poured on ice, and 0.5 ml of dilute (1 : 1) nitric acid was added. The precipitate was filtered, washed with ice water, dissolved in water, and worked up with 25% aqueous ammonia solution. Yield was 0.26 g (70%), mp 338°C (decomp., from dimethylformamide). Found %: C 47.04; H 2.29; N 30.40. $C_9H_5N_5O_3$. Calculated %: C 46.75; H 2.18; N 30.29.

Ethyl Ether of 5(6)-Nitrobenzimidazole-2-carboxylic Acid (IV). To a solution of 1 g of III in 4 ml of concentrated sulfuric acid was added a mixture of 1.6 ml of nitric acid and 0.7 ml of sulfuric acid at a temperature not above 10°C; the mixture was agitated 30 min and poured on ice. The precipitate was washed with ice water, dissolved in the minimum amount of water, and neutralized with 10% sodium bicarbonate solution. The precipitate was filtered, washed with water, and dried. Yield was 0.75 g (61%), mp 159-161°C

(decomp., from 50% alcohol). Found %: C 51.28; H 3.74; N 18.15. $C_{10}H_9N_3O_4$. Calculated %: C 51.06; H 3.86; N 17.91.

Hydrazide of 5(6)-Nitrobenzimidazole-2-carboxylic Acid (V). To a suspension of 0.5 g of IV in 6 ml of alcohol was added gradually 1.5 ml of hydrazine hydrate. The precipitate dissolved and then reprecipitated. The mixture was agitated 30-40 min; the precipitate was filtered and washed with water. Yield was 0.39 g (85%), mp 282°C (decom., from a 1:1 dimethylformamide-benzene mixture). Found %: C 43.49; H 3.16; N 31.99. $C_8H_7N_5O_3$. Calculated %: C 43.44; H 3.19; N 31.66.

7-Nitro-4-oxo-1,2,4-triazine[4,5-a]benzimidazole (IIb). A mixture of 2 g of V and 5 ml of freshly-distilled orthoformic ester was boiled for 6 h, as the temperature was raised gradually from 140 to 230°C. Thus the alcohol and orthoformic ester were distilled off. The residue was worked with ether. There was obtained 1.52 g of a crystalline substance which was recrystallized from alcohol, and then from a 1:1 dimethylformamide-benzene mixture. Yield was 0.3 g (14.5%), mp 305°C (decomp.). Found %: C 46.79; H 2.36; N 30.33. $C_9H_5N_5O_3$. Calculated %: C 46.75; N 2.18; N 30.29.

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