SYNTHESIS OF DERIVATIVES OF 1,2,3,4-TETRAHYDROIMIDAZO[1,5-c]-1,2,4-TRIAZINE

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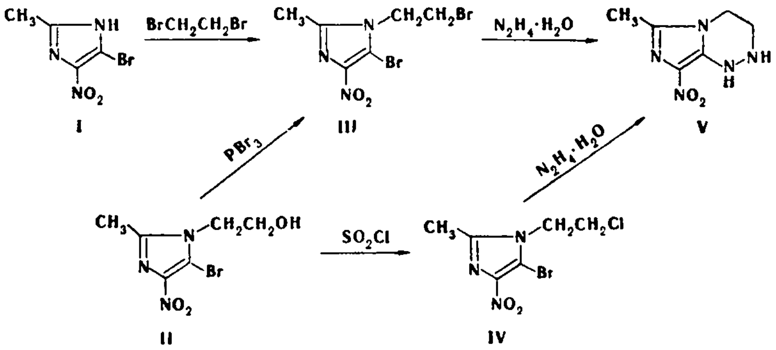
Many condensed derivatives of imidazole possess a wide spectrum of biological action, and some of the individual compounds have found extensive practical application [1]. Hence further studies are expedient on the development of new synthetic routes for heterocyclic systems in which the imidazole fragment is bound to other rings, for example with the hydrogenated triazine nucleus, which possesses high biological activity [2-4]. Up until our brief communication [5], 1,2,3,4-tetrahydroimidazo[1,5-c]-1,2,4-triazine or any of its derivatives were not known.

With the aim of preparing the 1-(β-bromoethyl)- and 1-carbethoxymethyl-2-methyl-4-nitro-5-bromoimidazoles, which are intermediates for the synthesis of derivatives of the system mentioned above, the reaction of the accessible 2-methyl-4(5)-nitro-5(4)-bromoimidazole (I) [6] with 1,2-dibromoethane and ethyl bromoacetate was studied. It was shown that reaction readily occurs in the lower alcohols or in aqueous DMF in the presence of an alkaline agent and results in the formation of 1-(β-bromoethyl)-2-methyl-4-nitro-5-bromoimidazole (III) or 1-carboethoxyethyl-2-methyl-4-nitro-5-bromoimidazole (VI).

When PBr_3 is reacted with the previously described [7] 1-(β-hydroxethyl)-2-methyl-4-nitro-5-bromoimidazole (II), a substance (III) is isolated, which from its constants and IR spectrum is identical with the corresponding compound obtained in the reaction of the initial compound I with 1,2-dibromoethane. When II is heated at the boiling point with thionyl chloride, 1-(β-chloroethyl)-2-methyl-4-nitro-5-bromoimidazole (IV) is formed, which, like III, when reacted with hydrazine hydrate in methanol in a sealed ampul at 160-180° cyclizes to 1,2,3,4-tetrahydro-6-methyl-8-nitroimidazo[1,5-c]-1,2,4-triazine (V).



The structure of compound V was confirmed by chemical and physiochemical methods. In the IR spectrum of V the intense band of the imino group was observed in the region of 3250 cm^{-1}, and in the PMR spectrum signals were present in the regions 4.40 and 3.95 ppm, characteristic for methylene group protons.

The isolated compound V does not react under various conditions with benzaldehyde and ninhydrin, which indicates the absence of amino groups in it as would be the case in the above-mentioned reaction if the isomeric product 1-aminoimidazoimidazoline was formed.

In order to synthesize the 3-oxo derivative of the described bicyclic system the reaction was studied of 1-carbethoxymethyl-2-methyl-4-nitro-5-bromoimidazole (VI) with hydrazine hydrate, and it was established that when the reaction is carried out under mild conditions (at 18-20°) the hydrazide of 2-methyl-4-nitro-5-bromoimidazolyl-1-acetic acid (VII) is formed. The latter when heated in boiling DMF cyclizes to 1,2,3,4-tetrahydro-3-oxo-6-methyl-

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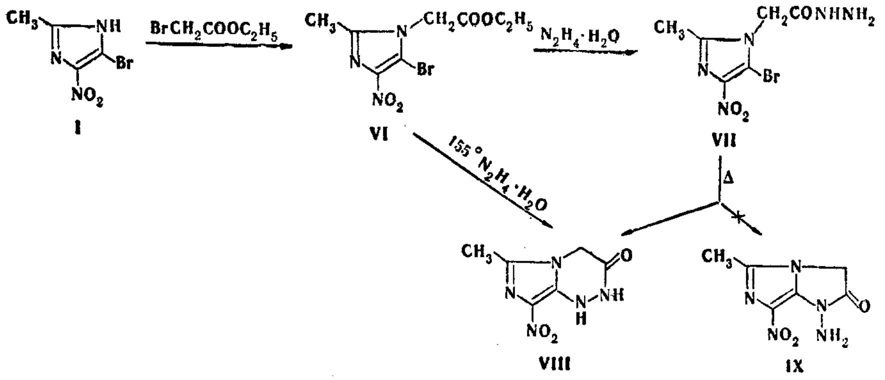
8-nitroimidazo[1,5-c]-1,2,4-triazine (VIII). The bicyclic oxo compound VIII can also be readily prepared in one stage by heating the ester VI in DMF with hydrazine hydrate in the presence of pyridine.



Cyclization of the hydrazide VII can theoretically occur in two directions, with formation of 1,2,3,4-tetrahydro-3-oxo-6-methyl-8-nitroimidazo[1,5-c]-1,2,4-triazine (VIII) or its isomeric compound 1-aminoimidazo[1,5-a]imidazolin-2-one (IX). The individual nature of the isolated product was confirmed by thin-layer chromatography (TLC), and the structure by the spectroscopic data. In the IR spectrum of VIII strong absorption bands were observed in the regions of 3200 and 1600 cm^{-1} which are characteristic of the NH and CO group of six-membered heterocyclic amines [8]. The studied reaction can be attributed to a type of intramolecular alkylation of a monoacylhydrazine, which as known occurs due to the nonacylated nitrogen atom of the hydrazino group [9].

EXPERIMENTAL

IR spectra of the compounds were recorded on a UR-20 instrument as mulls in Vaseline oil. PMR spectra were measured on a Tesla BS-467 spectrometer using DMSO solutions and HMDS as internal standard. TLC was conducted on Silufol UV-254 plates.

1-(β-Bromoethyl)-2-methyl-4-nitro-6-bromoimidazole (III). A) to a solution of 6.4 g (0.03 mole) I and 1.2 g (0.03 mole) sodium hydroxide in 100 ml of 50% aqueous DMF was added 11.3 g (0.06 mole) 1,2-dibromoethane. The mixture was heated at boiling for 10 h, poured into water, neutralized with sodium bicarbonate, the precipitate filtered off and washed with water. Yield 3.9 g (41%), mp 148-149° (from aqueous DMF), R_f 0.40 (chloroform—ethyl acetate—ethanol, 5:5:1). Found: C 23.4; H 2.0; Br 51.3; N 13.1%. $C_6H_7Br_2N_3O_2$. Calculated: C 23.0; H 2.2; Br 51.1; N 13.1%.

B) To a solution of 2.5 g (0.01 mole) II in 30 ml of anhydrous DMF was added gradually 8.1 g (0.03 mole) of phosphorus tribromide, the mixture left for 24 h at room temperature, carefully poured into water, and neutralized with sodium bicarbonate. The precipitate was filtered off and washed with water. Yield 2.0 g (58%). A test mixture of compounds III obtained by methods (A) and (B) showed no depression in melting point.

1-(β-Chloroethyl)-2-methyl-4-nitro-5-bromoimidazole (IV). A solution of 2.5 g (0.01 mole) II in 50 ml thionyl chloride was heated at boiling for 5 h, the excess thionyl chloride distilled off under vacuum, the residue decomposed with water, and neutralized with sodium bicarbonate. The precipitate which formed was filtered and washed with water. Yield 1.5 g (55%), mp 90-91° (from aqueous DMF). R_f 0.63 (chloroform). Found: C 26.9; H 2.9; Cl 13.4; N 15.7%. $C_6H_7BrClN_3O_2$. Calculated: C 26.8; H 2.6; Cl 13.2; N 15.6%.

1,2,3,4-Tetrahydro-6-methyl-8-nitroimidazo[1,5-c]-1,2,4-triazine (V). A mixture of 0.01 mole III or IV and 0.05 mole 85% hydrazine hydrate in 20 ml methanol was heated in a sealed ampul or in an autoclave of capacity 50 ml for 5 h at 160-180°, cooled, the precipitate filtered off and washed with water. Yield 53-60%, mp 161-163° (from aqueous DMF). IR spectrum: 3250 cm^{-1} (NH). R_f 0.71 (butanol—methanol—water, 1:10:1). Found: C 39.3; H 5.2; N 38.1%. $C_6H_9N_5O_2$. Calculated: C 39.3; H 4.9; N 38.2%.

1-Carbethoxymethyl-2-methyl-4-nitro-5-bromoimidazole (VI). To a solution of 0.01 mole of sodium ethoxide in 50 ml of anhydrous ethanol was added 2.1 g (0.01 mole) I and 2.5 g (0.015 mole) of ethyl bromoacetate. The mixture was heated at boiling for 3 h, cooled and poured into water, the precipitate filtered off and washed with water. Yield 1.15 g (39%), mp 118-120° (from aqueous ethanol). R_f 0.63 (butanol—methanol—water, 1:10:12). Found: C 32.7; H 3.5; N 14.2%. $C_8H_{10}BrN_3O_4$. Calculated: C 32.9; H 3.4; N 14.4%.

Hydrazide of 2-Methyl-4-nitro-5-bromoimidazolyl-1-acetic Acid (VII). To a suspension of 2.9 g (0.01 mole) VI in 30 ml ethanol was added 0.75 g (0.015 mole) 85% hydrazine hydrate. The reaction mixture was kept at room temperature for 48 h. The precipitate was filtered off and washed with water. Yield: 2.0 g (72%), mp 208-209° (dec.) (from water). R_f 0.66 (chloroform—ethanol, 5:1). IR spectrum: 3280 (NH), 1670 cm^{-1} (CO). Found: C 26.1; H 2.9; Br 28.8; N 25.3%. $C_6H_8BrN_5O_3$. Calculated: C 25.9; H 4.9; Br 28.7; N 25.2%.

1,2,3,4-Tetrahydro-3-oxo-6-methyl-8-nitroimidazo[1,5-c]-1,2,4-triazine (VIII). A) To a solution of 2.9 g (0.01 mole) VI in 20 ml DMF was added 0.5 g (0.01 mole) 85% hydrazine hydrate and 1 ml pyridine. The mixture was heated at boiling for 2 h, cooled, the precipitate filtered off and washed with water. Yield 1.6 g (78%), mp 268-269° (from DMF). R_f 0.51 (chloroform). IR spectrum: 3200 (NH), 1680 cm^{-1} (CO). Found: C 36.5; H 3.5; N 35.5%. $C_6H_7N_5O_3$. Calculated: C 36.5; H 3.6; N 35.5%.

B) To a solution of 2.8 g (0.01 mole) VII in 20 ml DMF was added 2 ml pyridine. The mixture was heated at boiling for 3 h, cooled, the precipitate filtered off and washed with water. Yield 1.7 g (85%). A test mixture of sample VIII, obtained by methods (A) and (B) showed no depression in melting point.

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