NEW SYNTHESIS OF IMIDAZO[4,5-e][1,3]DIAZEPINE

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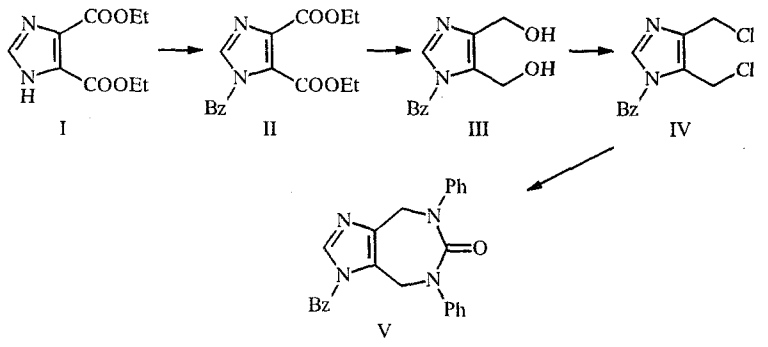
A new approach has been implemented in the synthesis of imidazo-[4,5,-e][1,3]diazepines consisting in the cyclization of 4,5-di-(cholormethyl)imidazole by urea derivatives.

The attention of chemists and biochemists has recently been drawn both to the separation from natural materials and to the synthesis of imidazo[4,5-e][1,4]diazepines and imidazo[4,5-d]-[1,3]diazepines having antiviral and antibacterial activity. [1-5]. Since until this time only one solitary investigation [6] has been devoted to the synthesis of imidazo[4,5-e][1,3]diazepines, we set ourselves the task of developing a new method of synthesis of such structures.

In analogy with [7], a fairly convenient approach to the synthesis of these compounds could be the cyclization of 4,5-di-(halomethyl)imidazoles with urea derivatives. Therefore, as a starting compound we selected the readily available diethyl ester of imidazole-4,5-dicarboxylic acid (I) [8], which was converted into compound II according to the scheme shown below.



The reduction of diester II by lithium aluminum hydride in THF leads to 1-benzyl-4,5-di(hydroxymethyl)imidazole (III), the treatment of which with thionyl chloride gave dichloride IV. By cyclization of the latter with a disodium salt of diphenyl urea in dry DMFA, 1-benzyl-5,7-diphenylimidazo[4,5-e][1,3]diazepin-6-one (V) was isolated in a 20% yield. This low yield is most likely explainable by the possible intermolecular "crosslinks" of the starting dichloride IV and the urea used.

The structure of the synthesized imidazoles II-IV and imidazo-[1,3]diazepine V was confirmed by the IR, PMR and mass spectral data. The purity was confirmed by TLC and elemental analysis data.

In the mass spectrum of compound V, in addition to the peak of molecular ions (45%), there are peaks of fragments, the formation of which is accompanied by a conventional bond cleavage. The study of the metastable transitions (unstable defocusing, PADI and the meassurement of the accurate masses of fragmentary ions makes it possible to distinguish two primary paths of the decomposition of molecular ions – the elimination of benzyl radical (the M-91$^+$ ions) (A) and the splitting of the diazepine ring with subsequent elimination of PhNCO (the M-119$^+$ ions) (B):

Together with the fragments shown in the mass spectrum, peaks of ions with m/z 119 (13%) and 91 (100%) are also observed, the formation of which is due to redistribution of the charge in accordance with the difference in the ionization potentials of particles formed according to the above fragmentation scheme.

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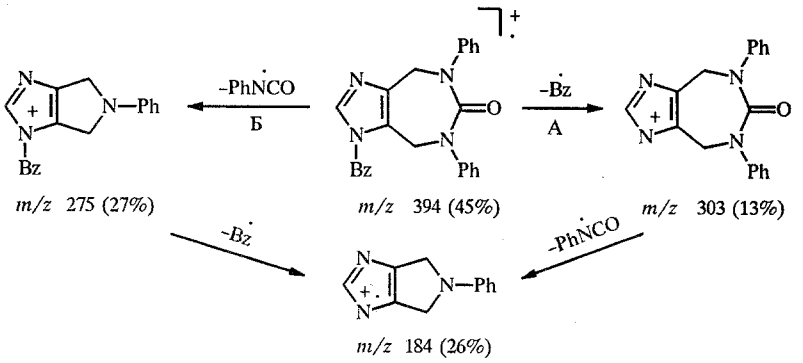

EXPERIMENTAL

The course of the reaction and the evaluation of the purity of the compounds was monitored by TLC on Silufol UV-254 plates in an acetone-hexane (1:1) or a chloroform-ethanol (5:1) system; for column chromatography silica gel 100/250 was used. The IR spectra were run on a Specord-75 IR spectrophotometer in chloroform, and the mass spectra on a Varian MAT 112 spectrometer in a direct introduction mode with the energy of the ionizing radiation of 70 eV, and at a temperature 40-50°C higher than the melting points of the samples. The PMR spectra were obtained on a Bruker AM-250 spectrometer with a working frequency of 250 MHz in $CDCl_3$, using TMS as an internal standard.

The elemental analysis data for C, H, N and Cl correspond to the calculated values.

Diethyl Ester of 1-benzylimidazole-4,5-dicarboxylic Acid (II, $C_{16}H_{18}N_2O_4$). A 21.2 g portion (0.1 M) of diethyl ester of imidazole-4,5-dicarboxylic acid (I) was dissolved in 50 ml of dry DMFA, 2.4 g (0.1 M) of sodium hydride was added, and a solution of 15.2 g (0.12 M) of benzyl chloride in 25 ml of a dry DMFA was added dropwise with stirring. The reaction mixture was heated for 4 h at 70-80°C, then was cooled, and the precipitate was filtered off. The solvent was distilled off on a rotary evaporator, and the residue was recrystallized from acetone. Yield, 27 g (90%), mp 43°C, M^+ 302. IR spectrum: 1700 cm^{-1} (C = 0). PMR spectrum: 7.23 (5H, m, Ph); 5.30 (2H, s, CH_2N); 4.29, 4.20 (2H, q, CH_2O); 1.30, 1.17 ppm (3H, t, CH_3).

1-Benzyl-4,5-di-(hydroxymethyl)imidazole (III, $C_{12}H_{14}N_2O_2$). A 35 g portion (0.115 M) of diester II in 250 ml of dry THF was added at 0.5°C to 16.5 g (0.345 M) of lithium aluminum hydride in 700 ml of dry THF. The reaction mixture was boiled for 3 h, then was cooled, held for 1 h at room temperature, and 13 ml of water, 13 ml of 15% solution of sodium hydroxide, and 40 ml of water were successively added. The precipitate was filtered off, and extracted with THF in a Soxhlet apparatus in the course of 24 h. The filtrate and the extract were combined, the solvent was distilled off, and the residue was recrystallized from ethanol. Yield, 18.8 g (75%), mp 134°C, M^+ 218. IR spectrum: 3450 cm^{-1} (OH). PMR spectrum: 7.36 (6H, m, =CH); 5.76 (2H, s, CH_2N); 5.51, 5.12 (1H, s, OH); 4.83, 4.46 (2H, d, CH_2O).

1-Benzyl-4,5-di(chloromethyl)imidazole (IV, $C_{12}H_{12}Cl_2N_2$). A 6 g portion (0.05 mole) of thionyl chloride was added dropwise to a solution of 2.18 g (0.01 M) of alcohol III in 100 ml of dry chloroform. The reaction mixture was stirred at room temperature for 3-4 h. The chloroformic layer was washed several times with water, and dried over sodium sulfate. The solvent was distilled off. Yield, 1.7 g (68%), mp 88-90°C. M^+ 255.

1-Benzyl-5,7-diphenyl-4,5,7,8-tetrahydroimidazo[4,5-e][1,3]-diazepin-6-one (V, $C_{25}H_{22}N_4O$). A solution of 2.12 g (0.01 M) of diphenylurea in 25 ml of dry DMFA was added to 0.48 g (0.02 M) of sodium hydride in 50 ml of dry DMFA, and the mixture was stirred for 30 min. Then, 2.55 g (0.01 M) of dichloride IV in 25 ml of dry DMFA was added. The reaction mixture was stirred at room temperature for 3-4 h and 10 ml of water was added. The solvent was distilled off and the residue was chromatographed on a column Yield, 0.8 g (20%), mp 176°C. M^+ 394. PMR spectrum: 7.42-7.12 (16H, m, =CH); 5.33, 4.92 (2H, s, C^8H_2); 4.63, 4.57, 4.45, 4.39 (2H, q, C^4H_2); 3.88, 3.82, 3.80, 3.76 ppm (2H, q, CH_2Ph).

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