SYNTHESIS AND PROPERTIES OF 1-(2-HYDROXYETHYL)TETRAZOLE

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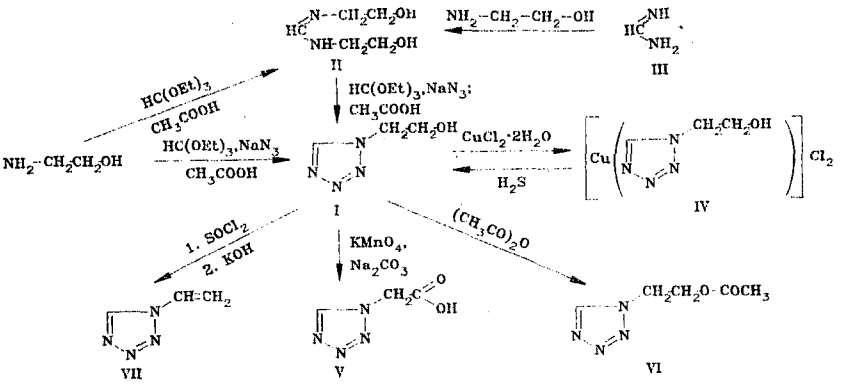
The heterocyclization of monoethanolamine with ethyl orthoformate and sodium azide in acetic acid was studied. It was shown that the reaction proceeds through a step involving the formation of a disubstituted formamidine and leads to the production of 1-(2-hydroxyethyl)tetrazole in high yield. A method for the purification of 1-(2-hydroxyethyl)tetrazole by complexing with cupric chloride was developed, and its physicochemical properties and some chemical transformations were investigated.

As one of the simplest derivatives of tetrazole, 1-(2-hydroxyethyl)tetrazole (I) is of interest for the synthesis of various substituted derivatives of this heterocycle that have found application in medicine, biology, agriculture, and some other fields [1-3]. The preparation of a difficult-to-separate mixture of tetrazole I with its 2-(2-hydroxyethyl) isomer by means of prolonged alkylation of tetrazole with 2-chloroethanol in the presence of alkali has been described [4]. However, tetrazole I was not isolated and has not yet been described in the literature.

After analyzing methods for the synthesis of tetrazole derivatives [1, 2, 5], we assumed that I can be obtained by a known (in individual instances [6-8]) but little-investigated method for the synthesis of the tetrazole ring by heterocyclization of ammonia or a primary amine with an ortho ester and an inorganic azide. In order to develop a convenient synthesis of tetrazole I via this method we studied the reaction of monoethanolamine, ethyl orthoformate, and sodium azide in acetic acid. The reaction commences even at room temperature, but a temperature of 80-90°C is necessary for a complete and directed reaction. The order of introduction of the reagents also affects the course of the reaction. The optimal procedure is the addition of acetic acid to a mixture of the azide and amine in the ortho ester. Under these conditions the reaction proceeds smoothly and is complete in 3 h (tetrazole I is obtained in greater than 80% yield). It was found that the reaction commences with the formation of N,N'-disubstituted amidine II, which was isolated from the reaction mixture in the form of the acetate. This amidine is also formed in high yield under the conditions of the synthesis of tetrazole I in the absence of sodium azide. The structure of amidine II was established by IR and PMR spectroscopy and by alternative synthesis from formamidine (III) and monoethanolamine. A special experiment showed that amidine II reacts with sodium azide and the ortho ester in acetic acid to give tetrazole I in 80% yield. We were unable to carry out this reaction



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without the ortho ester, since the amidine grouping is resistant to attack by the azide ion. When amidine II is heated in the presence of the ortho ester, it is evidently converted to an imido ester [9]; the latter reacts with sodium azide to give an azidoazomethine, which undergoes cyclization to the corresponding tetrazole.

The tetrazole I (a viscous light-brown liquid) obtained by this method contains a certain amount of impurities (5-10%) and is difficult to purify by ordinary methods. We studied the possibility of its purification by complexing with cupric chloride on the basis of the fact that 1-alkyltetrazoles in organic solvents form readily separable solid complexes with $CuCl_2$ [10]. We found that tetrazole I precipitates from alcohol solutions of cupric chloride in virtually quantitative yield in the form of complex IV, which is readily decomposed by the action of a number of reagents (for example, H_2S and NaOH). Recrystallization of the complex or repeated complexing is required for the purification of the markedly impure product. Pure tetrazole I is a colorless, low-melting, crystalline product. Absorption bands at 3363 cm^{-1} (OH), 2959 and 2885 cm^{-1} (CH_2), and 3133 cm^{-1} (CH), as well as a series of absorption bands of stretching and stretching-deformation vibrations of the tetrazole ring at 1171, 1108, and 1067 cm^{-1}, are present in the IR spectrum of I. Two singlets at 9.36 and 5.06 ppm (5-H and OH, respectively) and two triplets of methylene protons at 4.82 and 4.14 ppm (J = 5.0 Hz) are observed in the PMR spectrum.

Tetrazole I can be readily converted to 1-tetrazolylacetic acid (V), 1-(2-acetoxyethyl)-tetrazole (VI), and 1-vinyltetrazole (VII); this confirms the structure of the product obtained. Considering the practical value and the relative inaccessibility [4, 11, 13] of 1-vinyltetrazole (VII), the proposed method can be used to obtain it preparatively.

EXPERIMENTAL

Commercial-grade reagents were used in our research. The ethyl orthoformate was freshly distilled. The IR spectra of thin layers (I, II, VI, and VII) and KBr pellets (IV, V) were obtained with a Specord IR-75 spectrometer. The PMR spectra of 7-10% solutions of I, II, and V (in d_6-DMSO) and VI and VII (in $CDCl_3$) were recorded with a Jeol JNM-PS-100 spectrometer (100 MHz) with hexamethyldisiloxane as the internal standard.

1-(2-Hydroxyethyl)tetrazole (I). A) Acetic acid (60 ml) was added with stirring to a mixture of 12.2 g (0.2 mole) of monoethanolamine, 14.3 g (0.22 mole) of NaN_3, and 60 ml of ethyl orthoformate, and the mixture was heated at 80-90°C for 3 h. It was then cooled and treated with 22 ml of concentrated HCl, and the mixture was filtered. The filtrate was evaporated in vacuo to give 21.3 g of crude tetrazole I, which was dissolved in 50 ml of ethanol. The ethanol solution was heated to the boiling point, and a solution of 17.1 g (0.1 mole) of $CuCl_2 \cdot 2H_2O$ in 50 ml of boiling ethanol was added to it. The solution was cooled to 0-5°C, and the IV complex that crystallized out was separated, washed with cold ethanol, and dried to give 29.8 g (83%) of complex IV with mp 163-165°C (decomp.). The crystals were then dissolved in 50 ml of water, and H_2S was passed into the solution until the copper had precipitated completely. The solution was filtered, the filtrate was evaporated in vacuo, and the residue was extracted with tetrahydrofuran (THF). The extract was dried with molecular sieves, and the solvent was removed by distillation to give 18.0 g (79%) of a product with mp 36-38°C that was soluble in water, alcohols, and THF but insoluble in ethyl acetate, chloroform, and ether. Found: C 31.2; H 5.0; N 48.6%. $C_3H_6N_4O$. Calculated: C 31.6; H 5.3; N 49.1%.

B) Acetic acid (60 ml) was added to a mixture of 18.9 g (0.1 mole) of amidine II acetate and 14.3 g (0.22 mole) of NaN_3 in 20 ml of ethyl orthoformate, and the mixture was heated at 80-90°C for 2 h. It was then cooled and treated with 22 ml of concentrated HCl. The mixture was filtered, and the filtrated was evaporated in vacuo. Purification of the product by complexing (see above) gave 17.9 g (78%) of tetrazole I.

N,N'-Bis(2-hydroxyethyl)formamidine (II) Acetate. A mixture of 12.2 g (0.2 mole) of monoethanolamine, 45 ml of ethyl orthoformate, and 60 ml of acetic acid was heated at 80-90°C for 2 h, after which it was evaporated in vacuo, and the residue was dissolved in 50 ml of ethanol. The product was precipitated with 150 ml of ethyl acetate. The precipitated viscous oil was separated and dried in vacuo to give 16.4 g (87%) of product.

B) A 10.4-g (0.1 mole) sample of formamidine acetate [13] and 12.2 g (0.2 mole) of monoethanolamine were mixed. After the vigorous evolution of ammonia had ceased, the mixture was heated at 80-90°C for 1 h. It was then dissolved in 50 ml of ethanol, and the product was precipitated with 150 ml of ethyl acetate. The precipitated oil was separated and dried in

vacuo to give 18.1 g (96%) of a product with n_D^{20} 1.4980. IR spectrum: 1553 (N–H), 1692 (C=N), and 3231 cm^{-1} (OH, NH). PMR spectrum: 7.87 (1H, s, CH), 4.32 (4H, t, J = 4.4 Hz, CH_2–N), 3.15-3.60 (6H, m, CH_2–O, OH), and 1.88 ppm (3H, s, CH_3COO). Found: C 44.0; H 7.3; N 14.4%. $C_5H_{12}N_2O_2 \cdot CH_3COOH$. Calculated: C 44.4; H 6.9; N 14.8%.

1-Tetrazolylacetic Acid (V). A mixture of 6.3 g of crude tetrazole I, 11.4 g (0.04 mole) of $Na_2CO_3 \cdot 10H_2O$, and 17.4 g of $KMnO_4$ in 350 ml of water was refluxed for 2 h, after which the solution was cooled and filtered. The filtrate was acidified to pH 2 with 50% H_2SO_4 and evaporated in vacuo, and the residue was extracted with hot acetone. The solvent was removed by distillation, and the residue was recrystallized from isopropyl alcohol to give 26 g (37%) of white crystals with mp 125-127°C. IR spectrum: 1725 (C=O) and 2500-3050 cm^{-1} (OH). PMR spectrum: 9.46 (1H,s, CH) and 5.45 ppm (2H, s, CH_2). Found: C 27.7; H 3.3; N 43.2%. $C_3H_4N_4O_2$. Calculated: C 28.1; H 3.1; N 43.7%.

1-(2-Acetoxyethyl)tetrazole (VI). Two drops of concentrated H_2SO_4 were added to a mixture of 14.1 g of crude tetrazole I and 10.2 g (0.1 mole) of acetic anhydride, and the mixture was heated on a boiling-water bath for 2 h. It was then cooled and poured into 50 ml of ice water, and the aqueous mixture was extracted with methylene chloride (four 40-ml portions). The extract was washed successively with sodium carbonate solution and water and dried over $MgSO_4$. The solvent was removed by distillation, and the residue was distilled *in vacuo* to give 11.1 g (71%) of a colorless liquid with bp 131-132°C (1.9 hPa) and n_D^{20} 1.4547. IR spectrum: 1739 cm^{-1} (C=O). PMR spectrum: 8.58 (1H, s, CH), 4.90 (2H, t, J = 6.0 Hz, CH_2–N), 4.58 (2H, t, J = 6.0 Hz, CH_2–O), and 1.91 ppm (3H, s, CH_3). Found: C 38.1; H 5.0; N 35.4%. $C_5H_8N_4O_2$. Calculated: C 38.5; H 5.1; N 35.9%.

1-Vinyltetrazole (VII). A 41.6-g (0.35 mole) sample of thionyl chloride was added with vigorous stirring and cooling (≤20°C) to 22.8 g of crude tetrazole I in 60 ml of chloroform, and the mixture was allowed to stand at room temperature for 24 h, after which it was refluxed for 2 h. The solution was evaporated, and the residual 22.0 g of crude 1-(2-chloroethyl)tetrazole was dissolved in 40 ml of methanol. Hydroquinone (0.1 g) was added, a solution of 11.2 g (0.2 mole) of KOH in 40 ml of methanol and 25 ml of water was added dropwise, and the mixture was refluxed for 2 h. It was then filtered, and the methanol was removed from the filtrate by distillation. The residue was extracted with methylene chloride (four 40-ml portions), and the extract was dried over $MgSO_4$. The solvent was removed by distillation, and the residue was distilled in vacuo to give 10.2 g (53%) of a product with mp 15-16°C, bp 94-96°C (1.3 hPa), and n_D^{20} 1.5005. IR spectrum: 1639 cm^{-1} (C=C). PMR spectrum: 9.42 (1H, s, CH), 7.50 (1H, q, J_1 = 8.8 Hz, J_2 = 15.0 Hz, –CH=), 6.09 (1H, q, J_{vic} = 8.8 Hz, J_{gem} = 2.2 Hz, $=CH_2$ cis), and 5.46 ppm (1H, q, J_{vic} = 15.0 Hz, J_{gem} = 2.2 Hz, $=CH_2$ trans). Found: C 37.0; H 4.1; N 57.9%. $C_3H_4N_4$. Calculated: C 37.5; H 4.2; N 58.3%.

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