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SHORT COMMUNICATIONS

Multidentate Imidazole- and Tetrazole-Containing Ligands for Biomimetic Studies*

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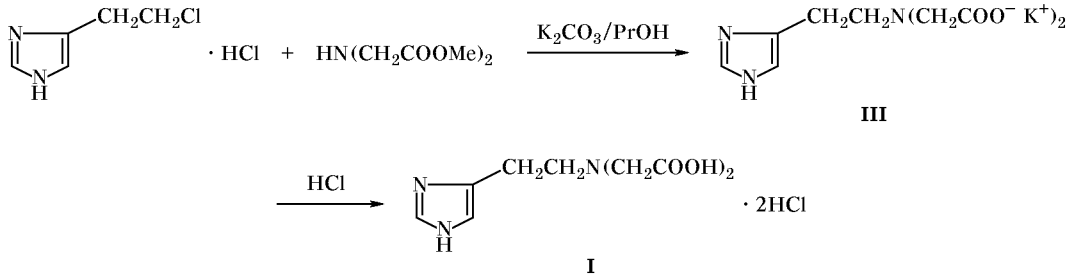
Recent advances in pharmaceutical chemistry are concerned to a considerable extent with creation of new effective drugs on the basis of compounds containing imidazole and tetrazole fragments. One of the first representatives of this class is cimetidin which has received wide application for treatment of peptic ulcer [1]. Another example demonstrating successful development of this line in the medical chemistry is losartan which is the first representative of nonpeptide blockers of angiotensin II receptors [2, 3]. Therefore, imidazole- and tetrazole-containing substrates attract increasing attention; for example, 2,2′-[2-(4-imidazolyl)ethyl]iminodiacetic acid (**I**) and 2-(5-hydroxy-2-tetrazolyl)acetic acid (**II**) can be used as multidentate ligands in biomimetic studies.

2,2′-[2-(4-Imidazolyl)ethyl]iminodiacetic acid (**I**) can be synthesized in two ways: (1) by alkylation of histamine (with preliminarily protected N–H bond in the heteroring by trityl group) with ethyl chloroacetate and subsequent acid hydrolysis of the diester thus obtained and (2) by alkylation of dimethyl iminodiacetate with 4-(2-chloroethyl)imidazole and analogous hydrolysis procedure. The first approach turned out to be ineffective, for the reaction of 4-(2-aminoethyl)-1-tritylimidazole with ethyl chloroacetate involved not only the amino nitrogen atom but also C^2 of the heteroring. As a result, an intractable mixture of substitution products was obtained. This reaction course was not surprising since formation of 2-substituted product in the alkylation of imidazoles is known to be possible [4, 5].

The second approach was more promising. By heating 4-(2-chloroethyl)imidazole with dimethyl iminodiacetate in 1-propanol in the presence of K_2CO_3 we obtained 75% of dipotassium 2,2′-[2-(4-imidazolyl)ethyl]iminodiacetate (**III**) as 2:1:2 solvate with 1-propanol and water (Scheme 1). A specific feature of this reaction is that the diester formed in the first stage undergoes hydrolysis which is catalyzed intramolecularly by imidazole, obviously in the same

Scheme 1.



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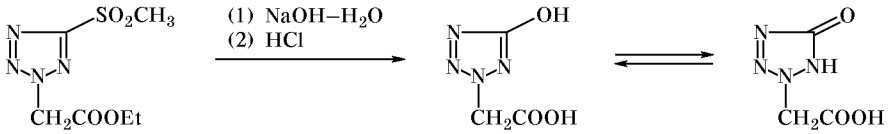
Scheme 2.



II

manner as in a number of enzymatic processes [6]. Free acid **I** was also isolated (as the corresponding dihydrochloride) by treatment of dipotassium salt **III** with 15% hydrochloric acid.

2-(5-Hydroxy-2-tetrazolyl)acetic acid (**II**) was synthesized by alkaline hydrolysis of ethyl 5-methylsulfonyltetrazol-2-ylacetic acid (Scheme 2). It should be noted that ligands like **II** can exist in two tautomeric forms [7, 8]. As shown by IR and ^{13}C NMR spectroscopy, the tautomeric equilibrium for acid **II** is displaced toward the 5-hydroxy tautomer.

4-(2-Aminoethyl)-1-tritylimidazole was synthesized by tritylation of 4-(2-aminoethyl)imidazole with subsequent selective deprotection of the amino group following the procedure described in [9]. The procedures for preparation of 4-(2-chloroethyl)imidazole and ethyl 5-methylsulfonyltetrazol-2-ylacetic acid were reported in [10, 11].

4-(2-Aminoethyl)-1-tritylimidazole. mp 110°C (from butyl acetate). IR spectrum, ν, cm^{-1}: 830, 870, 920, 990, 1000, 1040, 1140, 1160, 1190, 1240, 1290, 1330, 1390, 1450, 1500, 1600, 2860, 2940, 3040, 3070, 3380. ^1H NMR spectrum, δ, ppm: 2.66 t (2H, CH_2N), 2.94 t (2H, CH_2), 6.57 s (1H, 5-H), 7.12–7.35 m (16H, 2-H and H_{arom}). Found, %: C 81.49; H 6.69; N 11.81. $C_{24}H_{23}N_3$. Calculated, % C 81.59; H 6.52; N 11.89.

2,2′-[2-(4-Imidazolyl)ethyl]iminodiacetic acid (I). Dipotassium salt **III**, 1.1 mmol, was dissolved in 10 ml of 15% hydrochloric acid, the solution was evaporated to dryness, and the residue was treated with anhydrous methanol (2 × 10 ml). The precipitate of KCl was filtered off, and the filtrate was evaporated under reduced pressure. Acid **I** was purified by reprecipitation from 10 ml of anhydrous methanol with dry diethyl ether. The product was dried at 100°C. Yield 0.34 g (83%), light brown powder, mp 180–185°C. IR spectrum, ν, cm^{-1}: 910, 1090, 1250, 1440, 1630, 1750, 2870, 2980. ^1H NMR spectrum (D_2O), δ, ppm: 3.27 m (2H, CH_2), 3.76 m (2H, CH_2N), 4.15 s (4H, $2CH_2COOH$), 7.28 s (1H, 5-H), 8.6 s (1H, 2-H). Found, %: C 34.00; H 4.95; N 13.24. $C_9H_{13}N_3O_4 \cdot 2HCl \cdot H_2O$. Calculated, %: C 33.96; H 5.34; N 13.20.

2-(5-Hydroxy-2-tetrazolyl)acetic acid (II). A mixture of 0.01 mol of ethyl 5-methylsulfonyltetrazol-2-ylacetic acid and 25 ml of 10% aqueous sodium hydroxide was stirred for 6 h at 95–100°C. The mixture was cooled to 15°C, acidified to pH 1 with concentrated hydrochloric acid, and extracted with ethyl acetate (4 × 15 ml). The combined extracts were dried over magnesium sulfate and evaporated. Yield 1.29 g (90%), mp 172–173°C (from heptane–ethyl acetate, 1 : 2). IR spectrum, ν, cm^{-1}: 960, 1025, 1110, 1180, 1238, 1287, 1395, 1436, 1457, 1590, 1730, 2688, 2930, 2985, 3020. ^1H NMR spectrum, δ, ppm: 5.27 s (2H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 53.85 (CH_2), 167.91 (COOH), 170.88 (C^5). Found, %: C 25.29; H 2.68; N 38.87. $C_3H_4N_4O_3$. Calculated, %: C 25.00; H 2.78; N 38.89.

Dipotassium 2,2′-[2-(4-imidazolyl)ethyl]iminodiacetate (III). To a solution of 3 mmol of 4-(2-chloroethyl)imidazole hydrochloride in 30 ml of anhydrous 1-propanol at 20°C we added 0.01 mol of calcined potassium carbonate. The mixture was stirred for 20 min at 50–60°C, 3.2 mmol of dimethyl iminodiacetate was added, the mixture was heated for 20 h at 96–97°C and cooled to 20°C, and the precipitate was filtered off. The filtrate was evaporated under reduced pressure at 20°C. Yield 0.68 g (75%). Very hygroscopic substance. After reprecipitation from 1-propanol with dry diethyl ether and drying over P_2O_5 in a vacuum, its melting point was 84–85°C. IR spectrum, ν, cm^{-1}: 950, 990, 1030, 1060, 1140, 1160, 1215, 1260, 1335, 1410, 1595. ^1H NMR spectrum (D_2O), δ, ppm: 0.86 s (3H, CH_3), 1.52 s (2H, CH_2), 2.80–2.90 d (4H, C_2H_4), 3.35 s (4H, $2CH_2COO^- K^+$), 3.54 s (2H, CH_2), 6.83 s (1H, 5-H), 7.62 s (1H, 2-H). Found, %: C 35.63; H 5.66; N 12.04. $2C_9H_{11}K_2N_3O_4 \cdot C_3H_7OH \cdot 2H_2O$. Calculated, %: C 35.87; H 6.26; N 11.95.

The IR spectra were recorded on a UR-20 spectrometer in KBr. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AC-200 instrument in DMSO-d_6 using TMS as internal reference.

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