NOVEL SYNTHESIS OF 4,5,7,8-TETRAHYDRO-6H-IMIDAZO[4,5-e]-[1,4]DIAZEPINE-5,8-DIONE. A CYCLIC XANTHINE HOMOLOG

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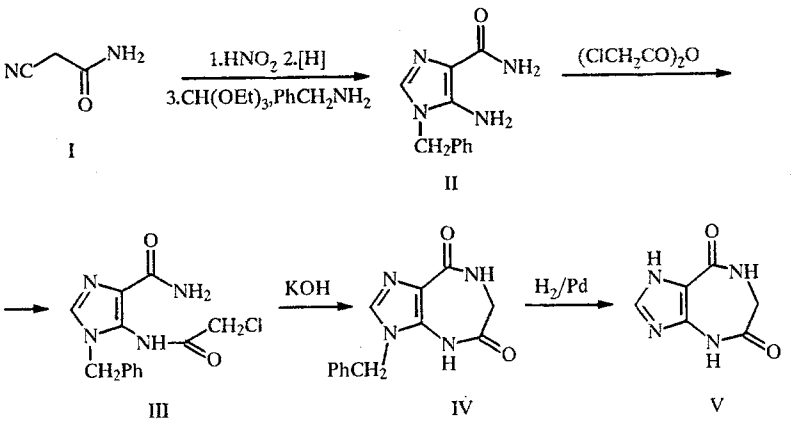
The xanthine homolog 4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione has been synthesized in four stages from cyanoacetamide.

We have previously synthesized the cyclic xanthine homolog 4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione and its methyl derivatives from natural purines [1-3].

This xanthine homolog has now been synthesized from cyanoacetamide (I) which is converted by a known method to 1-benzyl-5-aminoimidazole-4-carboxamide II [4]. Compound II could not be acylated by chloroacetyl chloride in dioxane or acetic acid. Use of chloroacetic anhydride gave the chloroacetyl derivative III which could be readily cyclized to IV by refluxing in KOH-acetone. Attempted cyclization using the previously reported MeONa—methanol [2] system was not successful. The xanthine homolog V was obtained by hydrogenolysis of IV over palladium black.



EXPERIMENTAL

TLC on Silufol UV-254 plates (acetone—hexane, 2:1 or methanol—water, 1:1) was used to monitor the reaction course and product purities. Mass spectra were recorded on a Varian-MAT 112 instrument using direct introduction and ionization energy of 70 eV. The molecular weights derived from the mass spectrum agreed with those calculated. PMR spectra were taken on a Bruker AM-250 instrument at 250 MHz using DMSO-d_6 solvent and TMS internal standard.

Elemental analytical data for C, H, N, and Cl agreed with those calculated.

1-Benzyl-5-chloroacetamidoimidazole-4-carboxamide (III, $C_{13}H_{13}N_4O_2Cl$). Chloroacetic anhydride (3.4 g, 0.02 mole) was added to a suspension of amide II (2.16 g, 0.01 mole) in absolute dioxane (50 ml). The reaction mixture was stirred at 20°C until full solution of the starting product (about 10 h) and poured into water. After 0.5 h, the precipitate was filtered, washed with water, and dried. Recrystallization from a methanol—toluene mixture gave analytically pure product with mp 184-186°C. PMR spectrum: 4.11 (2H, s, CH_2Cl); 5.18 (2H, s, CH_2Ph); 5.55 (1H, s, NH_2); 6.90 (1H, s, NH_2); 7.12-7.32 (6H, m, Ph and H-2); 9.48 ppm (1H, s, NH). Yield 2.2 g (75%).

1-Benzyl-4,5,7,8-tetrahydro-6H-imidazo[5,4-e][1,4]diazepine-4,7-dione (IV, $C_{13}H_{12}N_4O_2$). Powdered potassium hydroxide (1.7 g, 0.03 mole) was added to a suspension of amide III (2.9 g, 0.01 mole) in acetone (100 ml). The reaction mixture was refluxed using a reflux condenser for 3 h. The precipitate was filtered, washed with acetone, dissolved in a minimum volume of water, and acidified with concentrated HCl to pH 7. After 20 min, the precipitate was filtered and washed with cold water and a small volume of acetone. Recrystallization from ethanol gave an analytically pure sample with mp 322-323°C. PMR spectrum:

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3.62 (2H, d, H-6, J = 5.5 Hz); 5.33 (2H, s, $PhCH_2$); 7.19-7.44 (5H, m, Ph); 7.75 (1H, s, H-2); 7.91 (1H, t, H-5, J = 5.5 Hz); 10.98 ppm (1H, s, H-8). Yield 2.2 g (85.7%).

4,5,7,8-Tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (V, $C_6H_6N_4O_2$). Palladium black (about 50 mg) was added to a solution of diazepine IV (2.6 g, 0.01 mole) in glacial acetic acid (100 ml) and hydrogenated using hydrogen at atmospheric pressure and room temperature. At the end of the reaction (TLC) the catalyst was filtered off and washed with acetic acid. The solution was evaporated to dryness in vacuo and the residue recrystallized from water to give product with mp 340°C. PMR spectrum: 3.82 (2H, d, H-6, J = 5.0 Hz); 7.74 (1H, s, H-2); 7.93 (1H, t, H-7, J = 5.0 Hz); 10.83 (1H, s, H-4); 12.93 ppm (1H, s, H-1). Yield 1.25 g (75%).

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