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SYNTHESIS OF CROWN CONTAINING IMIDAZO[4,5-*e*] AND -[5,4-*e*][1,4]DIAZEPINES

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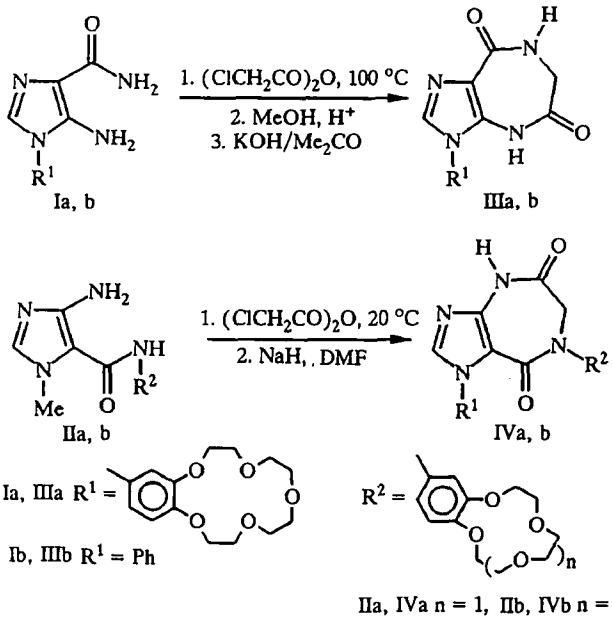
Starting from benzocrown substituted 4(5)-aminoimidazole-5(4)-carboxamides we have, for the first time, prepared benzocrown imidazo[4,5-e]- and -[5,4-e][1,4]diazepines — cyclic homologs of the corresponding xanthines.

The imidazo[4,5-*e*][1,4]diazepine nucleus is a basic structural fragment of the natural antibiotic azepinomycin [1].

Up to this time there has only been one study concerned with the synthesis of crown containing derivatives of this class [2]. At the same time, it has been shown that introduction of macrocyclic fragments changes the properties of purines in a significant way [3-5]. These circumstances encouraged us to carry out the synthesis of imidazo[4,5-*e*]- and -[5,4-*e*][1,4]diazepines (cyclic homologs of xanthines) with fragments containing the benzocrown ether nucleus. As starting materials we used crown substituted aminoimidazolecarboxamides I and IIa, b which were prepared by known methods [6]. However, compounds of type I are not acylated by chloroacetyl chloride or chloroacetic anhydride at room temperature. This caused us to use the available 1-phenyl-5-aminoimidazole-4-carboxamide Ib as model compound to fit the conditions of the acylation.



According to TLC data, heating compound Ib in a melt with chloroacetic anhydride at 100°C gives a mixture of two products (reaction A) consisting of approximately equal amounts of di- and trichloracetyl derivatives.

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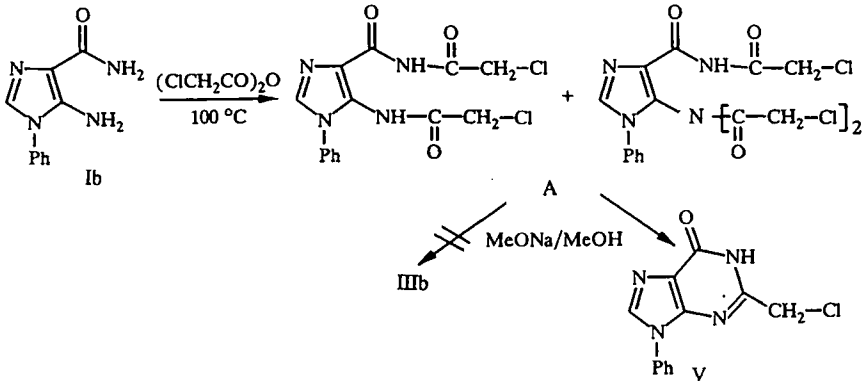
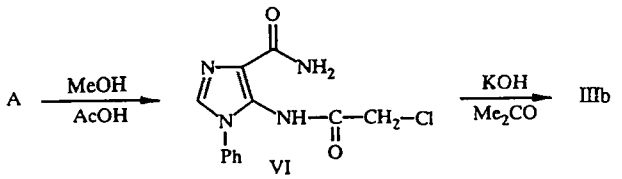


Attempts to cyclize mixture A to diazepine IIIb by heating it with sodium methylate in methanol (as used previously for the synthesis of analogous compounds [7]) resulted in the purine V.

The chloroacetyl derivative VI was prepared by refluxing mixture A in methanol in the presence of glacial acetic acid. Cyclization of VI to diazepine IIIb was performed using powdered KOH in acetone.



Synthesis of IIIa was achieved, as shown below, without separation of the chloroacetamido derivative of type VI in the pure state.

Acylation of the aminoamides IIa, b was carried out using chloroacetic anhydride in chloroform at room temperature and identification of the chloroacetyl derivatives was confirmed mass spectrometrically. Compounds IVa, b underwent intramolecular cyclization without additional purification using sodium hydride in anhydrous DMF. Hence we have, for the first time, developed and carried out the synthesis of cyclic homologs of xanthines containing benzocrown fragments as substitutents.

EXPERIMENTAL

Monitoring of the reaction course and the purity of the products was carried out using TLC on Silufol UV-254 plates. PMR Spectra were obtained on a Bruker AM-250 spectrometer (250 MHz) with DMSO-D_6 as solvent and TMS as internal standard. Mass spectra were recorded on an MX-1321 spectrometer with direct introduction of the sample. The temperature of the ionization chamber was 200°C and the ionization energy 70 eV.

1-Phenyl-5-aminoimidazole-4-carboxamide (Ib). A mixture of aminocyanoacetamide (1 g, 10 mmole) and orthoformic ester (1.65 ml, 10 mmole) was refluxed for 45 min in absolute acetonitrile (30 ml) and freshly distilled aniline (0.9 ml, 10 mmole) added. The product was refluxed for 7 h and solvent evaporated off *in vacuo*. Water (70 ml) was added and the precipitate was washed with water, dried, and recrystallized from methanol to give Ib (2.8 g, 70%) with mp 216-217°C. PMR Spectrum: 7.65 (5H, m, Ph); 7.42 (1H, s, 2-H); 7.04 (1H, s, NH); 6.88 (1H, s, NH), 5.83 ppm (2H, s, NH_2). M^+ 202.

1-(4-Benzo-15-crown-5)-5-aminoimidazole-4-carboxamide (Ia), was prepared by method [6].

2-Chloromethyl-9-phenylhypoxanthine (V). A mixture of Ib (2 g, 10 mmole) and chloroacetic anhydride (8 g, 40 mmole) was heated at 100°C for 4 h. The cooled reaction mass was washed three times with 100 ml portions of ether. The residue, after removal of the last portion of ether, was dried *in vacuo* and then dissolved in methanol (100 ml) containing sodium methylate (0.54 g, 10 mmole). The reaction mixture was refluxed for 30 min and solvent evaporated *in vacuo*. The residue was washed with cold water and dried. The product obtained was recrystallized from a mixture of benzene and hexane. Yield 0.8 g (62%), mp 250°C (decomp.). PMR Spectrum: 12.57 (1H, s, 1-H); 8.45 (1H, s, 8-H); 7.83-7.51 (5H, m, Ph); 4.63 ppm (2H, s, CH_2). M^+ 260:262 (3:1). Found, %: C 55.30; H 3.71; N 21.58; Cl 13.64. $C_{19}H_9ClN_4O$. Calculated, %: C 55.28; H 3.45; N 21.50; Cl 13.64.

1-Phenyl-5-chloroacetamidoimidazole-4-carboxamide (VI). A mixture of Ia and chloroacetic acid anhydride (4 g, 20 mmole) was heated at 100°C for 4 h. After cooling to 20°C, the reaction mixture was extracted three times with 50 ml portions of ether, removing them from the residue by decantation. The residue was dissolved in methanol (50 ml), acetic acid (1 ml) was added, and the product refluxed with a condenser for 18 h. The solvent was distilled off *in vacuo*. The residue was washed with water and dried in air. The product was recrystallized from a mixture of benzene and acetone, mp 206-207°C. Yield 1 g (73%). PMR Spectrum: 9.9 (1H, s, NH); 7.95 (1H, s, 2-H); 7.81-7.41 (5H, m, Ph); 7.07 (2H, s, NH_2); 4.16 ppm (2H, s, CH_2). M^+ 278:280 (3:1).

1-Phenyl-4,5,7,8-tetrahydro-6H-imidazo[5,4-*e*][1,4]diazepine-4,7-dione (IIIb). Powdered potassium hydroxide (4.1 g, 5.5 mmole) was added with stirring to a solution of VI (1.4 g, 5 mmole) in acetone (150 ml). The product was refluxed with stirring for 3 h, cooled, the acetone poured off from the precipitate, and the precipitate washed with pure acetone (30 ml) and dissolved in water (75 ml). The solution was neutralized with hydrochloric acid and refluxed with activated carbon. The carbon was filtered off and the filtrate extracted with chloroform (3 × 35 ml). The chloroform extract was separated and the aqueous layer evaporated *in vacuo*. The residue was extracted with hot DMF, the extract filtered, and the DMF removed on a rotary evaporator. The residue was washed with methanol (30 ml) and dried in air. Yield 0.6 g (50%), mp 334-338°C. PMR Spectrum: 10.56 (1H, s, 8-NH), 7.99 (1H, t, 5-NH, J = 5.3 Hz); 7.90 (1H, s, 2-H); 7.66-7.53 (5H, m, Ph); 3.79 ppm (2H, d, CH_2, J = 5.3 Hz). M^+ 242. Found, %: C 59.37; H 4.09; N 23.22. $C_{12}H_{10}N_4O_2$. Calculated, %: C 59.50; H 4.13; N 23.14.

1-(4-Benzo-15-crown-5)-4,5,7,8-tetrahydro-6H-imidazo[5,4-*e*][1,4]diazepine-4,7-dione (IIIa). A mixture of Ia (1.96 g, 5 mmole) and chloroacetic acid anhydride (4 g, 20 mmole) was heated at 100°C for 4 h. The reaction mixture was cooled and washed three times with ether. The dry residue was dissolved in methanol (100 ml) containing acetic acid (2 ml) and refluxed with a condenser for 18 h. The solvent was evaporated *in vacuo*. Cyclization and separation of the cyclization product was carried out similarly to IIIb. The moist product IIIa was additionally purified by column chromatography on silica gel using chloroform–methanol eluent (1:1). Yield 0.95 g (44%), mp 289-290°C. PMR Spectrum: 10.30 (1H, s, 8-NH); 7.96 (1H, t, 5-NH, J = 5.4 Hz); 7.83 (1H, s, 2-H); 7.18-7.04 (3H, m, Ar); 4.14 (4H, m, $ArOCH_2$); 3.83 (4H, m, $ArOCH_2CH_2$); 3.77 (2H, d, 6-CH_2, J = 5.4 Hz); 3.67 ppm (8H, s, OCH_2). M^+ 432. Found, %: C 56.0; H 5.13; N 13.04. $C_{20}H_{24}N_4O_7$. Calculated, %: C 55.5; H 5.55; N 12.96.

1-Methyl-5-[N-(4-benzo-12-crown-4)-carboxamido]-4-aminoimidazole (IIa) and 1-methyl-5-[N-(4-benzo-15-crown-5)-carboxamido]-4-aminoimidazole (IIb) were synthesized by method [8].

1-Methyl-7-(4-benzo-12-crown-4)-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (IVa). A solution of IIa (2.85 g, 8 mmole) and chloroacetic acid anhydride (1.55 g, 9 mmole) in chloroform (150 ml) was stirred at room temperature for 24 h. Water (50 ml) was added and stirring continued for a further 1 h. The chloroform layer was separated, washed with water (4 × 30 ml), and dried over sodium sulfate. After evaporation of chloroform *in vacuo*, the residue was dried for 6 h in a vacuum desiccator over KOH, then dissolved in anhydrous DMF (70 ml). It was then added to a solution of sodium hydride (0.5 g, 20 mmole) under a stream of nitrogen. The reaction mixture was left overnight. After neutralization with a 5% solution of hydrochloric acid the DMF was distilled off on a rotary evaporated. The residue was washed with hexane and then water. Yield 0.96 g (35%), mp 266-267°C (DMF). PMR Spectrum ($CDCl_3$): 10.13 (1H, s, 4-NH); 7.53 (1H, s, 2-H); 7.06-6.99 (3H, m, Ar); 4.35 (2H, s, 6-CH_2); 4.19 (4H, m, $ArOCH_2$); 3.95 (3H, s CH_3); 3.85 (4H, m, $ArOCH_2CH_2$); 3.79 ppm (4H, s, OCH_2). M^+ 402. Found, %: C 56.71; H 6.09; N 12.51. $C_{19}H_{22}N_4O_6$. Calculated, %: C 56.72; H 5.47; N 13.93.

1-Methyl-7-(4-benzo-15-crown-5)-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (IVb). Prepared similarly. Yield 30%, mp 291-292°C. PMR Spectrum ($CDCl_3$); 8.73 (1H, s, 4-NH); 7.47 (1H, s, 2-H); 6.96-6.90 (3H, m, Ar); 4.35 (2H, s, 6-CH_2); 4.14 (4H, m, $ArOCH_2$); 3.95 (3H, s, CH_3); 3.91 (4H, m, $ArOCH_2CH_2$); 3.76 ppm (8H, s, OCH_2). M^+ 446. Found, %: C 56.63, H 6.09; N 12.51. $C_{21}H_{26}N_4O_7$. Calculated, %: C 56.66; H 5.82; N 12.56.

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