SYNTHESIS OF IMIDAZO[4,5-e][1,4]DIAZEPINE-8-ONE

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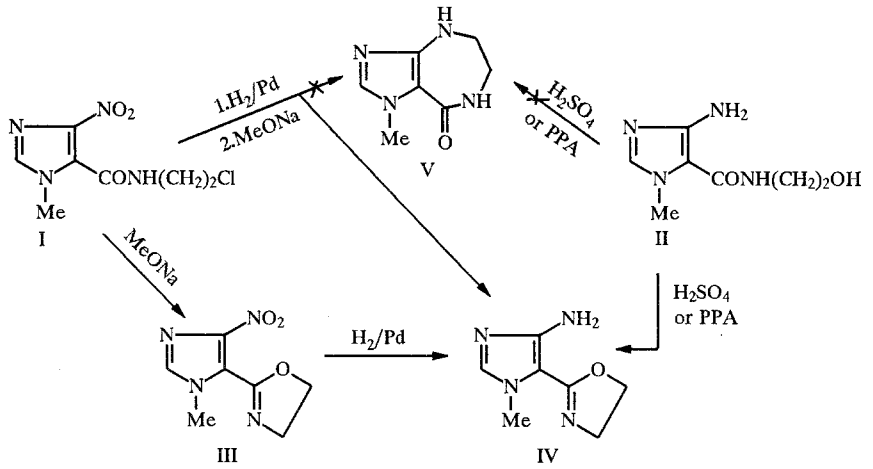
We have developed a method for synthesis of 1-methyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepin-8-one. We have shown that in intramolecular cyclization of N-(2-hydroxyethyl)- or N-(2-chloroethyl)amides of 1-methyl-4-aminoimidazolyl-5-carboxylic acids it is not the corresponding tetrahydroimidazo[4,5-e][1,4]diazepin-8-ones which are formed but rather the isomeric 4-amino-5-(oxazolin-2-yl)imidazoles.

Earlier we reported the synthesis of imidazo[4,5-e][1,4]diazepine-8-ones by intramolecular cyclodehydrogenation of N-(2-hydroxyethyl)amides of 4-aminoimidazolyl-5-carboxylic acids in concentrated H_2SO_4 or polyphosphoric acid (PPA) or by reductive cyclization of N-(2-chloroethyl)amides of 4-nitroimidazolyl-5-carboxylic acids [1].

In an attempt to reproduce this scheme, we established that instead of the imidazo[4,5-e][1,4]diazepine-8-ones described by the authors, the isomeric 4-amino-5-(oxazolin-2-yl)imidazoles are formed. This result is quite consistent with known data [2] and was described earlier by us for analogous derivatives of 1,2,3-triazole [3].



Formation of imidazooxazoline IV is supported by the presence in the PMR spectrum ($CDCl_3$) of a signal from the primary amino group and by the nature of the spin—spin coupling of the protons in the CH_2 group (two triplets, erroneously assumed by the authors as support for the formation of a diazepine ring).

We carried out an alternate synthesis in order to rigorously prove the formation of imidazooxazoline IV under the described conditions. This essentially involved initial cyclization of the corresponding N-(2-chloroethyl)amide of 4-nitroimidazolyl-5-carboxylic acid I to 1-methyl-4-nitro-5-(oxazolin-2-yl)imidazole III [in the PMR spectrum ($CDCl_3$) of which there are two triplets for the CH_2 groups] with subsequent reduction of the nitro group. The compound synthesized by such a route proved to be identical to samples obtained upon cyclization of compound I or II under the conditions described by the authors.

We know that primary amines are alkylated by alcohols upon boiling in the presence of Raney nickel [4]. It is assumed that this process includes oxidation of the alcohol to the aldehyde and formation of a Schiff's base with its subsequent reduction. We considered that this reaction is useful in the synthesis of azolo[4,5-e][1,4]diazepines.

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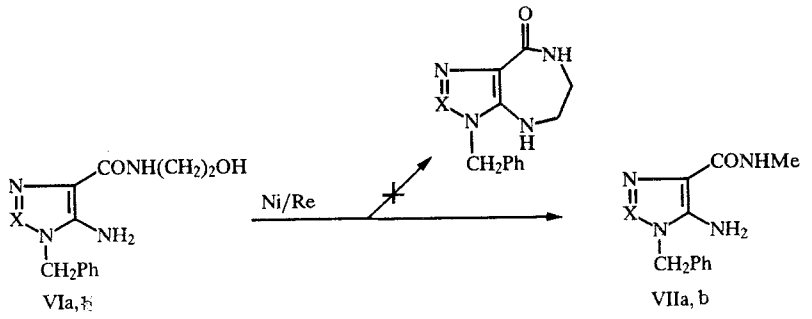
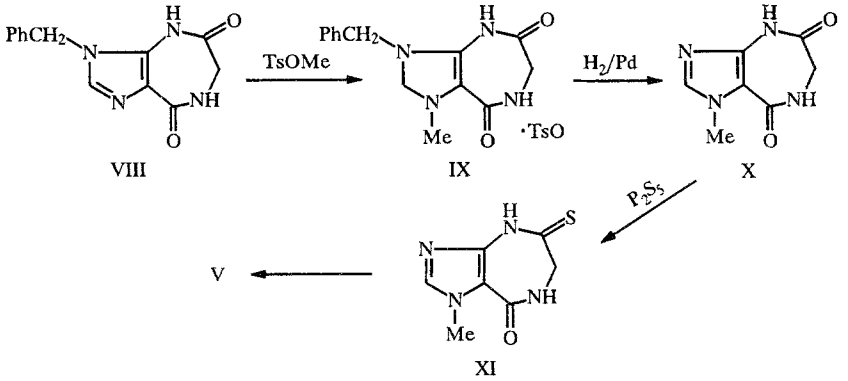


VI, VII a X = CH, b X = N

However, upon boiling 1-benzyl-4-(β-hydroxyethylaminocarbonyl)-5-aminoimidazole (VIa) or 1-benzyl-4-(β-hydroxyethyl-aminocarbonyl)-5-amino-1,2,3-triazole (VIb) in dioxane over Raney nickel, we obtained the corresponding methylamides of the imidazole VIIa or the 1,2,3-triazole VIIb. This result obviously is explained by the fact that the intermediate aldehyde derivatives under the reaction conditions, minus the Schiff's base, are rapidly oxidized to the corresponding carboxylic acids with subsequent decarboxylation.

We synthesized the imidazodiazepine V according to the scheme



The diazepine VIII [5] upon heating in a medium of the methyl ester of p-toluenesulfonic acid is converted to the quaternary imidazolium salt IX. Its debenzylation over palladium black led to imidazodiazepine X. By substitution of the amide oxygen by sulfur in the reaction with P_2S_5 we obtained the corresponding tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5-thion-8-one, which is smoothly desulfurized over Raney nickel to the diazepine V.

EXPERIMENTAL

The course of the reactions was monitored and the purity of the substances was assessed using TLC on Silufol UV-254 plates in the acetone—benzene (1:2), acetone—hexane (2:1), and chloroform—ethanol (5:1) systems. The IR spectra were taken on the Specord IR-75 spectrometer in chloroform. The PMR spectra were taken on the Bruker AM-250 (250 MHz) in $CDCl_3$; internal standard TMS. The mass spectra were taken on the Varian MAT-112.

1-Methyl-4-nitro-5-(β-chloroethylaminocarbonyl)-imidazole (I, $C_7H_9N_4O_3Cl$) and 1-methyl-4-amino-5-(β-hydroxy-ethylaminocarbonyl)imidazole (II, $C_7H_{12}N_4O_2$) were synthesized as in [1].

1-Methyl-4-nitro-5-(oxazolin-2-yl)imidazole (III, $C_7H_8N_4O_3$). 0.1 g (4.35 mmoles) sodium was dissolved in 20 ml absolute methanol. 0.5 g (2.15 mmoles) compound I was added to the sodium methylate solution formed. The reaction mixture was boiled for 1 h; the methanol was driven off to dryness in a rotary evaporator. 50 ml H_2O was added to the residue and it was extracted with chloroform (2 × 25 ml). The combined extracts were evaporated on a rotary evaporator to dryness. The residue was recrystallized from an acetone—hexane mixture. Yield 0.3 g (71%), T_{mp} 154-155°C. PMR spectrum ($CDCl_3$): 7.50 (1H, s, 2-H), 4.51 (2H, t, J = 9.5 Hz, CH_2), 4.16 (2H, t, J = 9.5 Hz, CH_2), 3.86 ppm (3H, s, 1-CH_3). IR spectrum ($CHCl_3$): 1660 (C=N), 1540-1500 (NO_2 split), 1340-1320 cm^{-1} (NO_2 split).

1-Methyl-4-amino-5-(oxazolin-2-yl)imidazole (IV, $C_7H_{10}N_4O$). A. Compound II was subjected to intramolecular cyclodehydrogenation in concentrated H_2SO_4 [1]. Yield of compound IV, 40%.

B. 0.2 g (1 mmole) compound III was dissolved in 50 ml methanol. An equal mass of Raney nickel was introduced and it was hydrogenated at 20°C and atmospheric pressure until absorption of hydrogen ceased (1 h). The catalyst was filtered off and it was washed with 25 ml ethanol. The methanol solution was evaporated to dryness. The residue was recrystallized from an acetone—hexane mixture. Yield 0.12 g (71%). T_{mp} 154-155°C.

A mixed sample of the compounds obtained using methods **A** and **B** did not give a depression in the melting point. PMR spectrum ($CDCl_3$): 7.09 (1H, s, 2-H), 4.78 (2H, br.s, NH_2), 4.31 (2H, t, J = 9.0 Hz, CH_2), 3.97 (2H, t, J = 9.0 Hz, CH_2), 3.75 ppm (3H, s, 1-CH_3). IR spectrum ($CHCl_3$): 3450 and 3370 (NH_2), 1650-1600 cm^{-1} (C=N, split).

1-Benzyl-4-methylaminocarbonyl-5-aminoamidazole (VIIa, $C_{12}H_{14}N_4O$). A mixture of 0.1 g (0.4 mmoles) compound VIa and 0.2 g Raney nickel was boiled in 50 ml dioxane for 4 h. The catalyst was filtered off and it was washed with hot methanol (20 ml). The combined filtrates were evaporated on a rotary evaporator. The residue was an oil which gradually crystallizes when held in a desiccator over KOH. M^+ 230. PMR spectrum ($CDCl_3$): 7.39-7.12 (5H, m, Ph); 7.04 (1H, s, 2-H), 6.71 (1H, br.s, NH), 4.98 (2H, s, CH_2), 4.70 (2H, br.s, NH_2), 2.91 ppm (3H, d, J = 5.1 Hz, CH_3).

1-Benzyl-4-methylaminocarbonyl-5-aminotriazole (VIIb, $C_{11}H_{13}N_5O$). A mixture of 0.5 g (2 mmoles) compound VIb and 1 g Raney nickel in 50 ml dioxane was boiled for 4 h. The catalyst was filtered and it was washed with hot methanol (2 × 25 ml). The combined filtrates were evaporated to dryness on a rotary evaporator. The residue was recrystallized from ethanol. T_{mp} 155-156°C. M 231. PMR spectrum ($CDCl_3$): 7.39-7.20 (5H, m, Ph), 6.87 (1H, br.s, NH), 5.38 (2H, s, CH_2), 4.84 (2H, br.s, NH_2), 2.96 ppm (3H, d, J = 5.1 Hz, CH_3).

1-Methyl-3-benzyl-4,5,7,8-tetrahydro-6H-imidazolium[4,5-e][1,4]diazepin-5,8-dione Tosylate (IX, $C_{21}H_{22}N_4O_5$). A mixture of 1 g (4 mmoles) compound VIII and 3.5 g (20 mmoles) of the methyl ester of p-toluenesulfonic acid was heated for 45 min at 140°C. This was cooled and carefully stirred with 50 ml THF. The residue was filtered off and it was washed on the filter with acetone. Yield 1.7 g (98%), T_{mp} 237-238°C. PMR spectrum (DMSO-d_6): 11.81 (1H, br.s, 4-H), 9.23 (1H, s, 2-H); 8.80 (1H, t, J = 5.5 Hz, 7-H), 7.54-7.15 (9H, m, Ph), 5.48 (2H, s, $-CH_2Ph$), 4.00 (3H, s, 1-CH_3), 3.84 (2H, d, J = 5.5 Hz, 6-H), 2.43 ppm (3H, s, CH_3Ar).

1-Methyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (X, $C_7H_8N_4O_2$). 0.9 g (2 mmoles) compound IX was dissolved in 100 ml methanol, 0.1 g palladium black was introduced, and it was hydrogenated at 20°C and atmospheric pressure until absorption of hydrogen ceased (about 6 h). The mixture was filtered, and the residue on the filter was carefully washed with hot water (4 × 25 ml). The filtrates were combined and 0.12 g (2 mmoles) KOH was introduced. Then it was evaporated on a rotary evaporator. The dry residue was washed with cold water (25 ml). Yield 0.3 g (82%), T_{mp} > 340°C (from H_2). M^+ 180. PMR spectrum (DMSO-d_6): 10.76 (1H, br.s, 4-H), 8.02 (1H, t, J = 5.2 Hz, 7-H), 7.77 (1H, s, 2-H), 3.92 (3H, s, 1-CH_3), 3.68 ppm (2H, d, J = 5.2 Hz, 6-H).

1-Methyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5-thion-8-one (XI, $C_7H_8N_4OS$). A mixture of 0.27 g (1.5 mmoles) diazepine X and 0.33 g (1.5 mmoles) P_2S_5 in 50 ml absolute pyridine was boiled for 10 h. The pyridine was driven off on a rotary evaporator. The residue was ground with 50 ml H_2O, filtered, and recrystallized from a mixture of ethanol with water. Yield 0.18 g (61%), T_{mp} > 350°C (with decomposition). M^+ 196. PMR spectrum (DMSO-d_6): 12.78 (1H, s, 4-H), 8.31 (1H, t, J = 5.5 Hz, 7-H), 7.85 (1H, s, 2-H), 4.08 (2H, d, J = 5.5 Hz, 6-H), 3.85 ppm (3H, s, 1-CH_3).

1-Methyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepin-8-one (V, $C_7H_{10}N_4O$). A mixture of 0.2 g (1 mmole) compound XI and 0.5 g Raney nickel was boiled in 50 ml acetone for 5 h. The Raney nickel was filtered off, and it was washed on the filter with hot methanol. The filtrates were combined and evaporated on a rotary evaporator. The residue was crystallized from a methanol—benzene—heptane mixture. Yield 0.1 g (59%), T_{mp} > 200°C (subl.). M^+ 166. IR spectrum ($CHCl_3$): 3420 (NH), 1630 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 7.17 (1H, s, 2-H), 5.74 (1H, br.s, 7-H), 4.82 (1H, br.s, 4-H), 3.47 ppm (4H, coalesced multiplet, CH_2—CH_2).

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