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METHYLATION OF THE CYCLIC HOMOLOG OF XANTHINE

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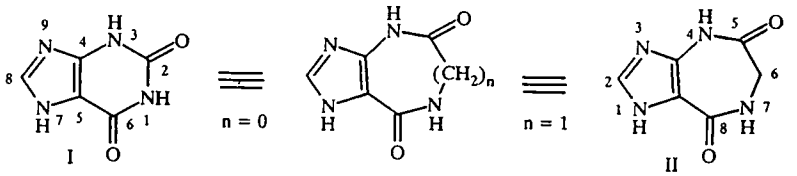
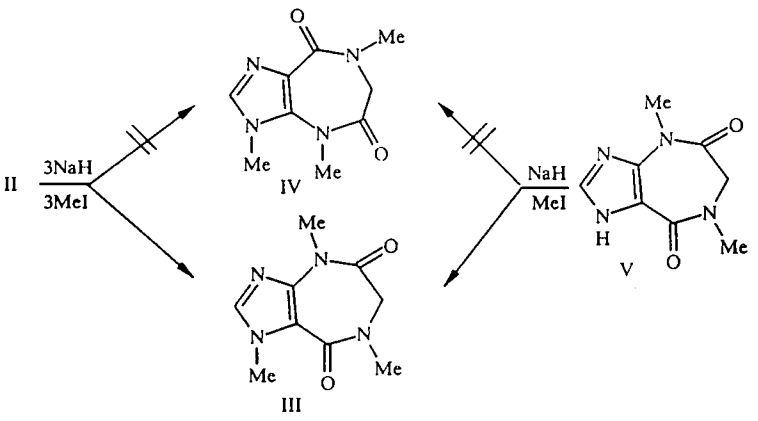
Alkylation of the cyclic homolog of xanthine in the methyl iodide–sodium hydride system as a function of the reagent–alkylating system ratio yields different products: for a 1:3 ratio of reagents, a homolog of caffeine is formed, while for a 1:2 ratio, a homolog of theobromine is formed. In contrast to xanthine, methylation of its cyclic homolog initially takes place at the imidazole ring and occurs in the sequence $N_{(1)}$, $N_{(4)}$, $N_{(7)}$.

Xanthine I is alkylated in basic medium in the order $N_{(3)}$, $N_{(7)}$, $N_{(1)}$ [1]. We investigated the sequence of methylation of the nitrogen atoms in the cyclic homolog of xanthine II.



I II

The reaction was conducted in the sodium hydride–dimethylformamide system with methyl iodide. When compound II was subsequently treated with 3 moles of sodium hydride and methyl iodide, the formation of two isomeric products III and IV is theoretically possible, but it was found in practice that caffeine homolog III, obtained previously in [2], is the only product of the reaction. The fact that not even traces of isohomolog IV were found is due to the lower energetic advantage of isomer IV because of the additional stress of the diazepine ring caused by reciprocal repulsion of the CH_3 groups at the $N_{(1)}$ and $N_{(8)}$ atoms in the molecule of compound IV [3]. This situation is probably responsible for the fact that product III is obtained in similar conditions as a result of monomethylation of the cyclic homolog of theophylline V [4].



Theobromine homolog VI, described previously in [4], is obtained with a good yield in the reaction of compound II with two equivalents of NaH and CH_3I. According to TLC data, the reaction mixture in this case contains trace amounts of starting compound II and trimethyl derivative III, in addition to basic product VI.

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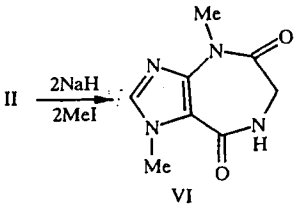
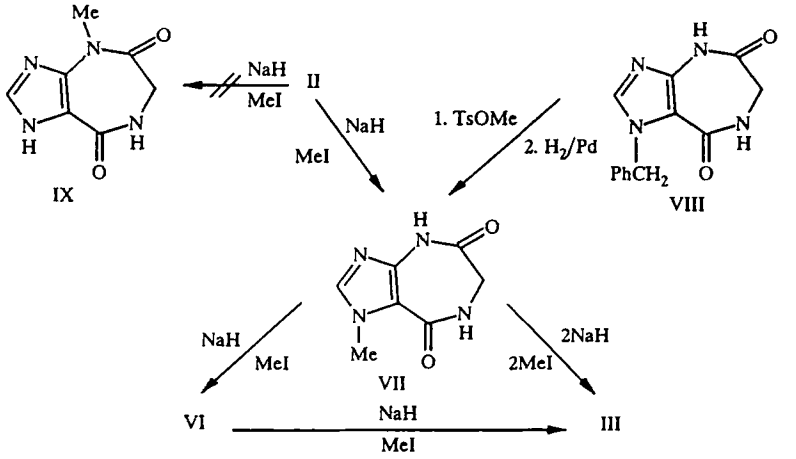


It is pertinent to note that in the presence of bases, xanthine is methylated by two equivalents of CH_3I into theobromine, and, with an excess, into caffeine [5].

The product of monomethylation VII was obtained from diazepine II using one equivalent of base and methylating agent in the reaction. No product of type IX was found in the reaction mixture. The structure of compound VII was confirmed by back synthesis from derivative VIII with the well-known method in [6].



As a result of monomethylation of diazepine VII, theobromine homolog VI was obtained. The use of two equivalents of sodium hydride and methyl iodide in this reaction resulted in trimethyl derivative III.

The order of methylation of nitrogen atoms with methyl iodide in the presence of a base in cyclic homolog II thus differs from the order for xanthine itself. Methylation of compound II, in contrast to xanthine, begins from the imidazole nucleus and takes place in the sequence $N_{(1)}$, $N_{(4)}$, $N_{(7)}$.

EXPERIMENTAL

The evolution of the reactions was monitored and the individuality of the substances was assessed with TLC on Silufol UV-254 plates in acetone–benzene, 2:1; acetone–hexane, 2:1; and chloroform–ethanol, 5:1 systems. The PMR spectra were made on a Bruker AM-250 spectrometer in $CDCl_3$ with TMS as internal standard. The mass spectra were recorded on a Varian MAT-112. The results of elemental analysis for C, N, and H corresponded to the calculated results.

1,4,7-Trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (III). A mixture of 1 g (6 mmole) of xanthine homolog II and 0.48 g (18 mmole) of sodium hydride with addition of 10% paraffin in 100 ml of anhydrous DMF was mixed at room temperature until evolution of hydrogen stopped. Then, while constantly stirring, 1.2 ml (19.2 mmole) of methyl iodide was added by drops, heated to boiling, and boiled while stirring for 30 min. After cooling of the reaction mixture, the solvent was eliminated in a vacuum, and the sediment was dissolved in water and extracted with chloroform. After evaporation of the chloroform, the dry residue was recrystallized from toluene. Mp = 157-158°C. According to the data in [2], mp = 157-159°C. M^+ 208. Yield of 0.94 g (75%). PMR spectrum ($CDCl_3$): 7.36 (1H, s, 2-H), 3.92 (2H, s, 6-H), 3.85 (3H, s, 1-CH_3), 3.38 (3H, s, 4-CH_3), 3.12 ppm (3H, s, 7-CH_3). Found, %: C 51.80; H 5.94; N 26.80. $C_9H_{12}N_4O_2$. Calculated, %: C 51.90; H 5.80; N 26.93.

Compound III based on derivatives V-VII was synthesized in similar conditions.

1,4-Dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (VI). Prepared from compound II or VII with a similar method. Mp = 218-220°C. M^+ 194. According to the data in [4], the melting point is 218-220°C. Yield of 69%. Found, %: C 49.25; H 5.52; N 28.73. $C_8H_{10}N_4O_2$. Calculated, %: C 49.58; H 5.15; N 28.87.

1-Methyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (VII). Synthesized from compound II by a similar method. Mp = 340°C. M^+ 180. PMR spectrum (DMSO-D_6): 10.76 (1H, br. s, 4-NH), 8.02 (1H, t, J = 5.3, 7-NH), 7.77 (1H, s, 2-H), 3.92 (3H, s, 1-CH_3), 3.68 ppm (2H, J = 5.3, 6-H). The mass spectra and PMR spectra of samples of compound VII obtained by methylation of the cyclic homolog of xanthine and synthesized by the method in [6] were totally identical. Found, %: C 46.53; H 4.38; N 31.00. $C_7H_8N_4O_2$. Calculated, %: C 46.67; H 4.44; N 31.11.

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