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NOVEL SYNTHESIS AND REACTIONS OF 1,4,7-TRIMETHYL-4,5,7,8-TETRAHYDRO-6H-IMIDAZO[4,5-*e*][1,4]DIAZEPINE-5,8-DIONE — A CYCLIC CAFFEINE ANALOG

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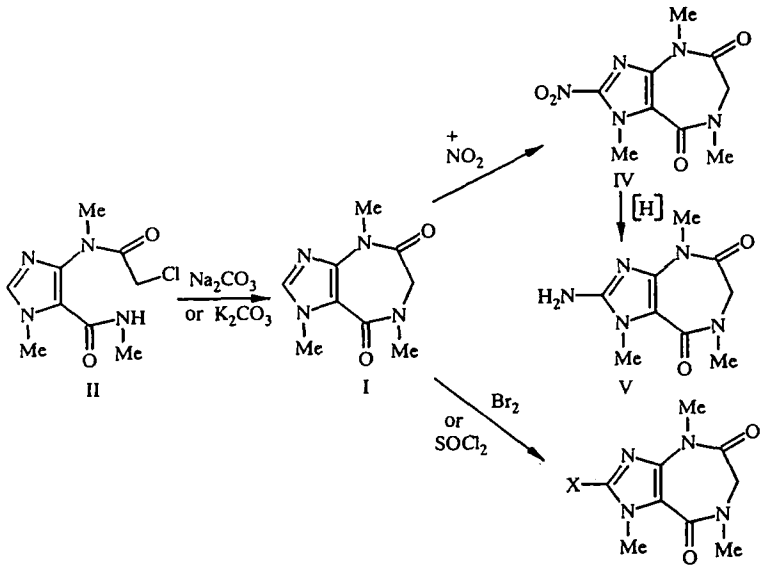
The synthesis of a cyclic homolog of caffeine is reported. Its 2-nitro- and 2-amino derivatives were obtained for the first time. It was shown that the 2-bromo and 2-chloro substituted cyclic homologs react with nucleophiles under basically identical conditions. Whereas 8-bromocaffeine can give a normal Ullman reaction product via heating with powdered copper in ethylene glycol, the homolog gives only a reduction product and does not react with potassium thiocyanate or cyanide.

The interest shown in imidazo[4,5-*e*][1,4]diazepines is mostly due to their structural analogy to 1,4-benzodiazepines on the one hand and to purines on the other. An additional reason favoring work on compounds of this class was opened up by the antitumor antibiotic azepinomycin [1-3]. The first synthesis of the cyclic homolog of caffeine was brought about by a direct cyclization of the chloroacetamido derivative II using sodium hydride in benzene or sodium methylate in methanol [4, 5].



III a X = Cl, b X = Br

We have shown that use of sodium or potassium carbonate in water as condensing agents simplifies the conditions both for carrying it out and for the separation of the desired product I directly from the reaction medium without additional purification and with an increase in yield to 97%.

We have, for the first time, carried out nitration of the cyclic homolog I using fuming nitric acid in acetic anhydride. The nitro compound IV obtained in this way is smoothly reduced by $Na_2S_2O_4$ in aqueous ethanol. The synthesis of 2-halo derivatives IIIa, b and preparation of products of nucleophilic substitution of the 2-bromo cyclic homolog IIIb [4] has previously

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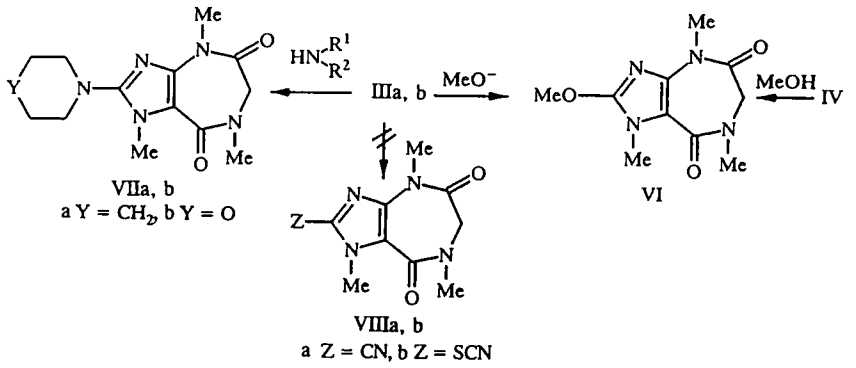
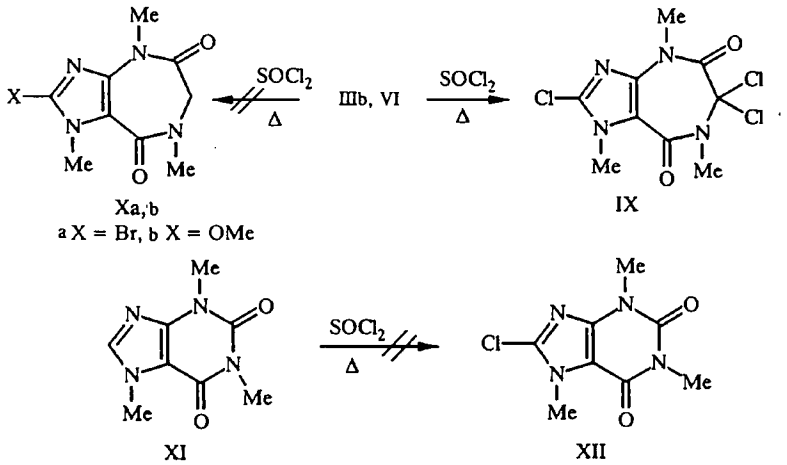
been reported [4-6]. Considering that the chemical properties of the 2-chloro derivative IIIa have not previously been studied, it was decided to compare the basic behavior of the 2-chloro and 2-bromo substituted products IIIa and IIIb respectively under nucleophilic substitution conditions and then to contrast their properties with those of the 8-halo caffeines. It was found that the bromine atoms in compounds IIIa and IIIb are exchanged for a methoxy group and amine residues under the same conditions and with virtually the same yields.

In contrast to 8-halo caffeines [7], their cyclic analogs IIIa and IIIb do not react with potassium cyanide or thiocyanate in DMF. This is evidently due to the large electron acceptor effect of the pyrimidine ring on the imidazole and hence, their activation towards nucleophilic attack in the case of caffeine when compared with the similar effect of the 1,4-diazepine fragment in its cyclic homolog.

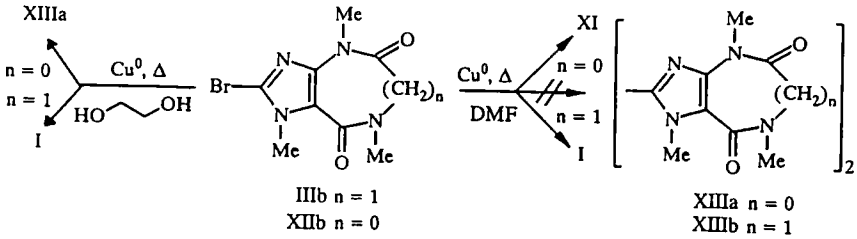


When heated in anhydrous methanol saturated with HCl, the nitro compound IV is readily converted to the 2-methoxy derivative VI [6].

We have previously reported the synthesis of the 2,6,6-trichloro derivative IX based on the caffeine homolog I [6]. Attempts to use this reaction for chlorination of IIIb and VI were not successful; in place of the expected products Xa, b there was only separated from the reaction mixture the 2,6,6-trichloro substituted cyclic homolog IX. The result obtained showed that, in refluxing $SOCl_2$, along with the chlorination of position 6 in the starting compounds IIIb and VI there occurs substitution of the bromine atom and (or) the methoxy group by chlorine.



It was of interest to find that caffeine XI is not chlorinated by refluxing $SOCl_2$. Heating the 8-bromo caffeine XIIb or its cyclic homolog IIIb in DMF in the presence of copper powder does not form the "normal" Ullman products XIIIa, b but leads to caffeine XI or its cyclic homolog I, respectively.



When DMF is exchanged in this reaction for ethylene glycol it is found that the bromocaffeine XIIb gives the bis derivative XIIIa in 72% yield but the reaction involving its homolog I results in reduction of the starting material IIIb to compound I.

Hence we have shown that the introduction of a methylene group in the pyrimidine ring of caffeine XI and the change to its cyclic homolog I is accompanied by a significant change in the chemical properties of the higher homolog series of caffeine.

EXPERIMENTAL

PMR Spectra were taken on a Bruker AM-250 instrument in CD_2Cl_2 or $(CD_3)_2CO$ using TMS as internal standard, and mass spectra on an MAT-112 with introduction of the sample at an ionization energy of 70 eV and at a temperature 40-50°C higher than the melting point of the sample. Control on the course of the reaction and the purity of the substances was carried out by TLC on Silufol UV-254 plates in an acetone–hexane (2:1) or acetone–benzene (2:1) system.

1,4,7-Trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (I). A. Sodium carbonate (2.4 g, 22 mmole) was dissolved with stirring in water (60 ml) in a chemical vessel. The solution was heated with constant stirring to 60°C and finely divided compound II (4.8 g, 20 mmole) was added in one portion without ceasing stirring. The temperature was maintained at 60°C for 30 min with stirring of the solution. The reaction mixture was cooled to room temperature and extracted with chloroform (6 × 35 ml). The chloroform extract was evaporated on a rotary evaporator to give chromatographically pure product (I) with mp 157-158°C and M^+ 208. PMR Spectrum: 7.67 (1H, s, 2-H); 3.98 (2H, s, CH_2); 3.90 (3H, s, 1-CH_3); 3.39 (3H, s, 4-CH_3); 3.14 ppm (3H, s, 7-CH_3). Found, %: C 51.8; H 5.9; N 26.8. $C_9H_{12}N_4O_2$. Calculated, %; C 51.9; H 5.8; N 26.9. Yield 4.1 g (97%).

B. Powdered copper (1.45 g) was added to a solution of IIIb (1.44 g, 5 mmole) in DMF (2.35 ml). The mixture was refluxed for 2 h, filtered, washed on the filter with DMF (2 × 5 ml), and the combined filtrate evaporated to dryness *in vacuo*. The residue was washed with water and dried to give compound I (0.77 g, 75%) with mp 157-158°C and M^+ 208.

Mixed samples of the compound I formed obtained by methods A and B and by methods A and [4], respectively, did not show a depression of melting point.

1,3,7-Trimethylxanthine (caffeine) (XI) was obtained similarly (method B). mp 235-237°C. Yield 72%. A mixed sample of XI and known caffeine did not show a depression of melting point.

2-Chloro-, 2-bromo-, and 2,6,6-trichloro-1,4,7-trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4]diazepine-5,8-diones IIIa, IIIb, and IX, respectively, were obtained by method [7].

2-Nitro-1,4,7-trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (IV). Concentrated nitric acid (d = 1.5 g/cm^3, 5 ml) was added dropwise with cooling and stirring to acetic anhydride (30 ml) at such a speed as to keep the temperature below 15°C. The solution of acetyl nitrate obtained was rapidly poured into a solution cooled to 15°C which contained I (5.2 g, 25 mmole) in glacial acetic acid (75 ml) and allowed to stand at room temperature for 24 h. The reaction mixture was poured into water (500 ml) and after decomposition of the acetic anhydride was extracted with chloroform (7 × 50 ml) and purified by column chromatography on silica gel. The eluent was chloroform. mp 163-165°C; M^+ 253. PMR Spectrum: 4.03 (2H, s, CH_2); 4.14 (3H, s, 1-CH_3); 3.41 (3H, s, 4-CH_3); 3.18 ppm (3H, s, 7-CH_3). Found, %: C 42.5; H 4.5; N 23.6. $C_9H_{11}N_5O_4$. Calculated, %: C 42.7; H 4.3; N 23.7. Yield 1.58 g (25%).

2-Amino-1,4,7-trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (V). A solution of IV (0.5 g, 0.2 mmole) in ethanol (60 ml) was slowly added with constant stirring to a solution of $Na_2S_2O_4$ (1.8 g, 1 mmole) in water (10 ml). After 40 min the reaction mixture was extracted with ether (6 × 20 ml) and the ether extracts dried and treated with carbon. Distillation of the ether then gave amine V with mp 181-182°C and M^+ 223. PMR Spectrum: 4.34 (2H, s, NH_2); 3.96 (2H, s, CH_2); 3.60 (3H, s, 1-CH_3); 3.31 (3H, s, 4-CH_3); 3.08 ppm (3H, s, 7-CH_3). Found, %: C 48.2; H 5.6; N 31.6. $C_9H_{13}N_5O_4$. Calculated, %: C 48.4; H 5.8; N 31.4. Yield 0.32 g (71%).

2-(Piperid-1-yl)- and 2-(morpholin-4-yl)-1,4,7-trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4]diazepine-5,8-diones VIIa and VIIb, respectively, were prepared from compound IIIa by method [4].

2-Methoxy-1,4,7-trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-*e*][1,4][diazepine-5,8-dione (VI). A solution of nitro derivative IV (1.12 g, 5 mmole) in anhydrous methanol (100 ml) saturated with dry HCl was refluxed with a condenser for 30 min. The solvent was evaporated *in vacuo*, the residue neutralized with dilute ammonia, and dried, mp 224-226°C and M^+

238. PMR Spectrum 3.58 (3H, s, OCH_3); 3.94 (2H, s, CH_2); 4.05 (3H, s, 1-CH_3); 3.34 (3H, s, 4-CH_3); 3.09 ppm (3H, s, 7-CH_3). Found, %: C 50.5; H 5.9; N 24.1. $C_{10}H_{14}N_4O_2$. Calculated, %: C 50.4; H 5.9; N 23.9. Yield 0.95 g (80%).

8,8'-Bis-(1,3,7-trimethylxanthine) (XIIIa). Compound XIIb (1.43 g, 5 mmole), copper powder (1.5 g), and ethylene glycol (50 ml) were mixed in a round bottomed flask. The mixture was refluxed with a condenser for 15 h, the copper filtered off, and poured into a solution of sodium sulfide (2 g) in water (200 ml). The precipitate was filtered off, washed on the filter with water, and refluxed with acetone (30 ml). The aqueous phase was extracted with chloroform (5 × 35 ml). The chloroform solution was washed with water and combined with the acetone solution The combined extract was dried over anhydrous sodium sulfate, treated with carbon, and evaporated *in vacuo* to give XIIIa with mp 222-224°C (CH_3OH) and M^+ 386. PMR Spectrum in $(CD_3)_2CO$: 4.25 (6H, s, CH_3); 3.54 (6H, s, CH_3); 3.31 ppm (6H, s, CH_3). Found, %: C 49.8; H 5.1; N 29.7. $C_{16}H_{18}N_8O_4$. Calculated, %: C 50.0; H 4.9; N 29.9. Yield 0.69 g (72%).

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