SYNTHESIS OF HALOGEN SUBSTITUTED IMIDAZO[4,5-e][1,4]DIAZEPINE-5,8-DIONES. CYCLIC HOMOLOGS OF METHYLXANTHINES

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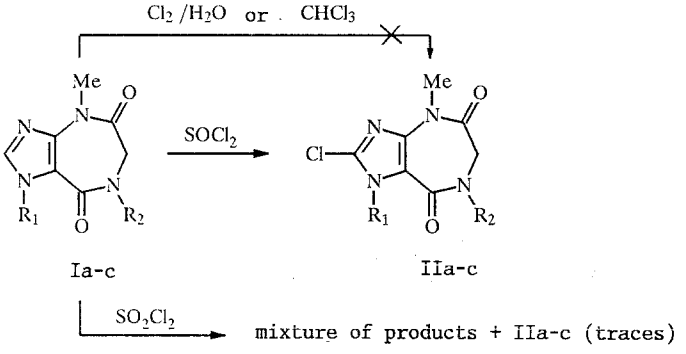
Possible routes for synthesis of 2-haloimidazo[4,5-e][1,4]diazepines are discussed. Conditions for chlorination differ for homologs of caffeine, theophylline, and theobromine. For the caffeine homolog, both the 2-chloro- and 2,6,6-trichloro products are obtained depending on the synthetic conditions.

Halogen-substituted purines have found wide usage in the synthesis of various members of this class [1]. It is likely that the halo derivatives II and VI would be valuable synthons in fine organic synthesis.

Only one derivative of this type (VIa) has so far been reported in which a bromine atom has been substituted on amine and alcohol fragments [2].

The aim of this work was to study the chlorination and bromination of the homologs of caffeine (Ia), theobromine (Ib), and theophylline (Ic) and to compare the conditions needed with those for the analogous xanthines.

Introduction of halogen into the pyrimidine ring of xanthines is well known [3] through refluxing the xanthine with $POCl_3$. In attempting to apply this reaction to Ib we could not obtain the desired 8-chloro derivative. It was not even formed upon refluxing Ib with a mixture of $SOCl_2$ and DMF, considered an optimum method for preparing imidoyl chlorides [4].



I, II a $R_1=R_2=Me$; b $R_1=Me$, $R_2=H$; c $R_1=H$, $R_2=Me$

Bearing in mind that the reported conditions for introducing a chlorine atom are practically identical for the methylxanthines [5], chlorination of Ia-c was attempted using chlorine in water or chloroform. However, in all cases mixtures of hygroscopic products were obtained which, according to chromatographic analysis, contained neither starting materials nor the substitution products IIa-c.

The latter were synthesized by treating the starting homologs Ia-c with $SOCl_2$. The caffeine homolog Ia was readily converted to the chloroderivative IIa at room temperature and to the trichloro derivative III upon refluxing. The homologous theobromine and theophylline were halogenated by refluxing in $SOCl_2$ for many hours. Even after 40 h, the reaction of Ic was not complete.

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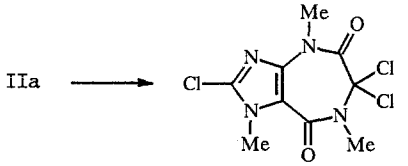
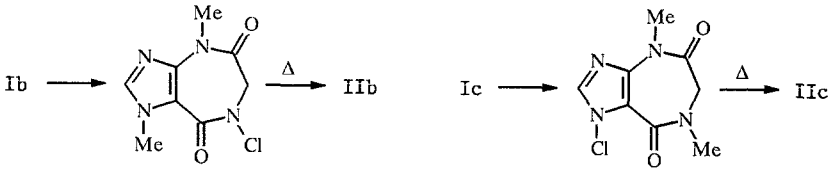


III

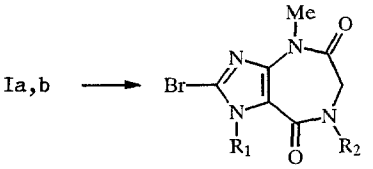
Exchanging $SOCl_2$ for SO_2Cl_2 gave a complex mixture of products containing traces of IIa-c by TLC.

The optimum route for preparing the 2-chloro derivative IIb is conversion to the N-haloamide IV which readily gives IIb upon thermolysis. Similarly, the theophylline homolog Ic gave IIc via V under the same conditions.



IV V

It has previously been shown that bromination of the caffeine homolog and of caffeine itself occur using bromine in water [6]. We have found that the yield of VIa can be increased from 56 to 73% if the reaction is carried out in chloroform in the presence of ferric bromide. However, Ib is not brominated under these conditions. VIb was obtained by refluxing Ib in glacial acetic acid in the presence of anhydrous sodium acetate and bromine.



VIa,b

VI a $R_1=R_2=Me$; b $R_1=Me$, $R_2=H$

Hence we have developed a convenient synthesis of 2-halo substituted derivatives of type II and VI. In contrast to methylxanthines, for which halogenation conditions are extremely similar, the conditions for introducing halogen into imidazo[4,5-e][1,4]diazepines Ia-c are specific for each homolog.

EXPERIMENTAL

PMR Spectra were recorded on a Bruker AM-250 instrument at 250 MHz using $CDCl_3$ solvent and TMS internal standard. Mass spectra were measured on a Varian MAT-112 using direct introduction, an ionization energy of 70 eV, and a temperature 40-50°C above the sample melting point. Reaction monitoring and compound purity were followed by TLC on Silufol UV-254 plates in acetone–hexane (2:1) or acetone–benzene (2:1).

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

2-Chloro-1,4,7-trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e]-[1,4]diazepine-5,8-dione (IIa, $C_9H_{11}N_4O_2Cl$). A solution of Ia [2] (2.08 g, 10 mmole) in $SOCl_2$ (20 ml) was held at 20°C for 36 h. Thionyl chloride was distilled off under reduced pressure. The dry residue was dissolved in a minimum volume of $CHCl_3$ and chromatographed on a SiO_2 column (L 100/250, 2 × 30 cm) using chloroform eluent. The solvent was evaporated and the residue recrystallized from toluene to give product with mp 142°C and M^+ 242:244 (3:1). PMR Spectrum: 3.94 (2H, s, CH_2); 3.81 (3H, s, 1-CH_3); 3.35 (3H, s, 4-CH_3); 3.12 ppm (3H, s, 7-CH_3). Yield 1.04 g (43%).

2,6,6-Trichloro-1,4,7-trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (III, $C_9H_9N_4O_2Cl_3$). A solution of Ia (2.08 g, 10 mole) in $SOCl_2$ (20 ml) was refluxed for 20 h. The mixture was treated similarly to the above to give product with mp 216-218°C and M^+ 310:316 (3:1). PMR Spectrum: 3.44 (3H, s, 1-CH_3); 3.19 (3H, s, 4-CH_3); 3.17 ppm (3H, s, 7-CH_3). Yield 1.52 g (48%).

7-Chloro-1,4-dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (IV, $C_8H_9N_4O_2Cl$). Compounds Ib [7] (1.94 g, 10 mmole) was dissolved with heating in water (150 ml). The solution was cooled to 20°C and sodium hypochlorite (30 ml, active concentration of chlorine 71-100% g/liter [8]) was added in one portion. After 2 min, sodium bicarbonate was added to pH 7-8. After a further 10 min the precipitate was filtered off, washed with cold water, and dried in air. PMR Spectrum: 7.40 (1H, s, CH_{imid}); 4.33 (2H, s, CH_2); 3.41 ppm (3H, s, 4-CH_3). Yield 2 g (87.5%).

2-Chloro-1,4-dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (IIb, $C_8H_9N_4O_2Cl$). A. A suspension of IV (2.3 g, 10 mmole) in decane (50 ml) was slowly heated to reflux with stirring. After refluxing for 10 min it was cooled and the precipitate filtered, washed with hexane, and recrystallized from ethanol. mp 256-258°C. Yield 2 g (90%).

B. Compound Ib (1.94 g, 10 mmole) was suspended in $SOCl_2$ (50 ml) and refluxed for 48 h. The mixture was treated as for IIa to give product with mp 256-258°C (from ethanol) and M^+ 228:230 (3:1). PMR Spectrum: 7.00 (1H, t, NH, J = 5.8 Hz); 3.93 (2H, d, CH_2, J = 5.8 Hz); 3.87 (3H, s, 1-CH_3); 3.41 ppm (3H, s, 4-CH_3). Yield 1.1 g (50%).

2-Chloro-4,7-dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (IIc, $C_8H_9N_4O_2Cl$). A suspension of Ic [7] (1.94 g, 10 mmole) in $SOCl_2$ (50 ml) was refluxed for 40 h. The mixture was treated as for IIa to give product with mp 228-230°C with M^+ 228:230 (3:1). PMR Spectrum: 3.99 (2H, s, CH_2); 3.39 (3H, s, 4-CH_3); 3.17 ppm (3H, s, 7-CH_3). Yield 0.5 g (21%).

2-Bromo-1,4,7-trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (VIa). Bromine (16 g) was added dropwise over 20 min to a suspension of Ia (2.08 g, 10 mmole) and chloroform (50 ml) in the presence of a catalytic amount of iron filings. The mixture was refluxed for 20 h, cooled, and diluted with stirring with water ($\simeq$ 100 ml) until the precipitate had fully dissolved. The chloroform layer was separated, washed with $NaHCO_3$ solution (3%) to pH 7, with sodium thiosulfate solution (5%), dried over anhydrous $MgSO_4$, and evaporated to dryness on a rotary evaporator. The product had mp 168-170°C and M^+ 286:288 (1:1). PMR Spectrum: 4.11 (2H, s, CH_2); 3.91 (3H, s, 1-CH_3); 3.38 (3H, s, 4-CH_3); 3.17 ppm (3H, s, 7-CH_3). Yield 2.09 g (73%).

2-Bromo-1,4-dimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (VIb, $C_8H_9N_4O_2Br$). Anhydrous sodium acetate (3 g) was added to a refluxing solution of Ib (1.94 g, 10 mmole) in glacial acetic acid (50 ml). After dropwise addition of bromine (6.4 g) over $\simeq$ 10 min the mixture was refluxed until the color disappeared ($\simeq$ 8 h). The mixture was filtered hot and the filtrate evaporated at reduced pressure, and the dry residue washed with cold water and dried. The product had mp 270°C (air) and M^+ 272:274 (1:1). PMR Spectrum: 5.97 (1H, br s, NH); 3.87 (2H, d, CH_2, J = 5.9 Hz); 3.83 (3H, s, 1-CH_3); 3.37 ppm (3H, s, 4-CH_3). Yield 1.2 g (43%).

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