Imidazo[4,5-*e*][1,3]diazepine-4,6-dione. A Novel Xanthine Analogue

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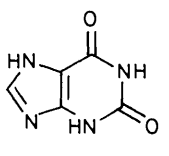
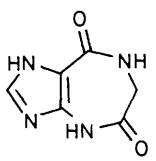
The first examples of the imidazo[4,5-*e*][1,3]diazepine ring system are reported, the compounds being diones related to xanthine.

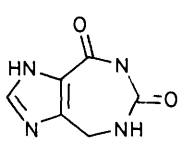
Xanthine (**1**) is an important intermediate in purine metabolism. Analogues of xanthine, and particularly its alkylated derivatives, are of significant interest in biochemistry and pharmacology due to their interaction with enzymes and receptors.[1] We recently reported the preparation of (**2**), a cyclic homologue of xanthine.[2] Alkylated derivatives of (**2**) antagonize the binding of adenosine to the A2 receptor in a manner analogous to those of xanthine.[3] We were thus encouraged to prepare other cyclic homologues of xanthine. In this communication we report the synthesis of 7,8-dihydro-3*H*,5*H*-imidazo[4,5-*e*][1,3]diazepine-4,6-dione (**3**). This compound, which is isomeric with (**2**), is the first reported example of this heterocyclic ring system.



(**1**)



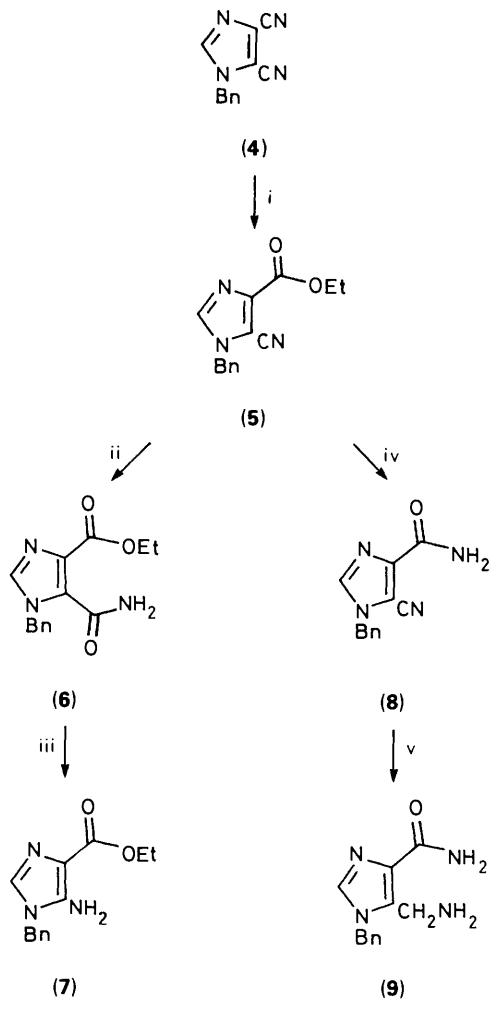
(**2**)



(**3**)

In the preparation of (**2**), the methodology used was patterned after that used for the synthesis of the corresponding 1,4-benzodiazepine-2,5-diones. The 2,4-benzodiazepine-1,3-dione related to (**3**) is unknown however, although its 2,4-dibenzyl derivative has been prepared by oxidation of 2,4-dibenzyl-2,4-benzodiazepin-3-one.[4] In an attempt to prepare the unsubstituted diazepinedione by the same method, it was reported that the only product isolated was a phthalimidine derivative presumably arising by a facile ring contraction of the intermediate 2,4-benzodiazepine-1,3-dione. A similar ring contraction of (**3**) was not expected since imidazoles with fused five-membered rings are known to be unstable and thus do not form readily.[5]

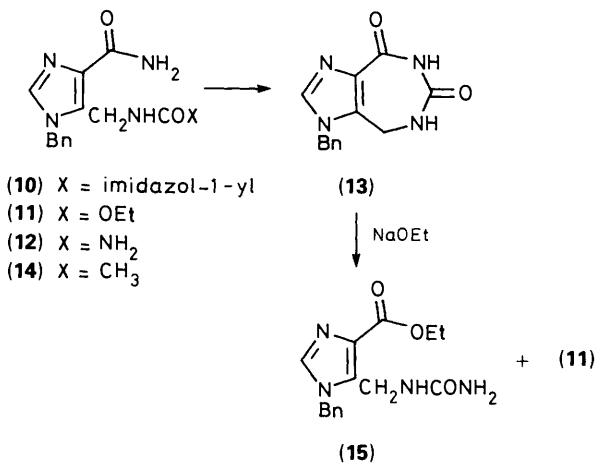
The ready formation of phthalimidine from *o*-aminomethyl-



Scheme 1. *Reagents:* i, NaOEt; ii, H_2O_2, Na_2MoO_4; iii, NaOCl; iv, NH_3; v, H_2/Pd.

benzamide makes the use of a conventional ring-closure approach to the 2,4-benzodiazepines impractical and accounts for the relative scarcity of reports of these compounds. Since a similar ring closure was not expected for 5-aminomethylimidazole-4-carboxamide,[5] a suitably protected derivative of this compound was envisioned as a precursor to (**3**). The benzyl group was chosen to protect the imidazole ring nitrogen since it had been used successfully in the preparation of (**2**). 5-Aminomethyl-1-benzylimidazole-4-carboxamide (**9**) was prepared from 1-benzyl-4,5-dicyanoimidazole (**4**) as shown in the Scheme.* Treatment of (**4**) with sodium ethoxide gave a single monoester in good yield, along with a small amount of the diester. The monoester was shown to be (**5**) by reaction with hydrogen peroxide, and treatment of the resulting amide (**6**) with sodium hypochlorite to give the amine (**7**), identical with material synthesized by an unambiguous route.[6] Reaction of (**5**) with ammonia gave 1-benzyl-5-cyanoimidazole-4-carboxamide (**8**), which was easily reduced to the desired amine (**9**) by catalytic hydrogenation in acetic acid. As predicted (**9**) showed no tendency to eliminate ammonia and undergo ring closure to an imidazo[4,5-*c*]pyrrole.

On reaction with excess carbonyl di-imidazole in pyridine at ambient temperature, (**9**) was converted to the imidazolide (**10**).



The product was isolated in 65% yield after precipitation by the addition of a large volume of water to the reaction mixture. Treatment of (**10**) with sodium ethoxide in ethanol or with ammonia in aqueous ethanol led to the carbamate (**11**) and the urea (**12**), respectively. After prolonged heating in anhydrous dioxan, (**10**) was recovered unchanged. Ring closure of (**10**) was accomplished by heating in a 10:1 mixture of dioxan and acetic anhydride. 1-Benzyl-7,8-dihydro-1*H*,5*H*-imidazo[4,5-*e*][1,3]-diazepine-4,6-dione (**13**) was isolated in 40% yield, along with an equal amount of the acetyl derivative (**14**).

The diazepine (**13**) was characterized initially on the basis of its n.m.r. spectra and microanalysis. The imide proton appears as a singlet at δ 9.6 p.p.m. in contrast to the amide protons of (**10**) which appear as separate singlets at 7.3 and 7.6 p.p.m. The only other exchangeable resonance appears as a broad triplet at 7.8 p.p.m. The doublet assigned to the methylene group of the diazepine ring resonates at 4.2 p.p.m., significantly upfield from the 4.8 p.p.m. observed for (**10**) and even the 4.4 p.p.m. observed for (**12**). In the ^{13}C n.m.r. spectrum, the C-4 resonance is at 160.4 p.p.m., in sharp contrast to the 165 p.p.m. observed for the amide carbonyl in compounds (**10**), (**11**), (**12**), and (**14**). The C-6 resonance appears at 154.9 p.p.m. in contrast to the 158.5 p.p.m. observed for the urea carbonyl in (**12**). These features are consistent with the formation of the cyclic imide. The structure of (**13**) was confirmed by its reaction with sodium ethoxide in ethanol, which resulted in two products in an approximately 2:1 ratio. The reaction was complete in 3 h at ambient temperature. The major product was identical to the carbamate (**11**) and presumably arises by attack of ethoxide on the urea carbonyl of the diazepine ring. The minor product was characterized as the urea (**15**). This could only arise by reaction of ethoxide at the amide carbonyl of diazepine (**13**). The structure of (**15**) was confirmed by its unambiguous preparation from (**5**) by a series of reactions analogous to the preparation of (**12**) from (**8**). Removal of the benzyl group from (**13**) was achieved by hydrogenolysis over 20% palladium hydroxide on carbon. The reaction was complete in 2 h and (**3**) was isolated in near quantitative yield. The ^1H n.m.r. spectrum of (**3**) was almost identical to that of (**13**) except for the absence of the benzyl group resonances.

In conclusion, we have demonstrated the synthesis of a novel imidazodiazepine. It is expected that the methods developed here will also be applicable to the synthesis of 2,4-diazepinones fused to other five-membered heterocycles, and that these compounds will be relatively stable, in sharp contrast to 2,4-benzodiazepin-1-ones. The synthesis of cyclic homologues of theophylline and caffeine based on the imidazo[4,5-*e*][1,3]diazepine ring system is currently being explored.

* Satisfactory spectroscopic and analytical data have been obtained for all new compounds reported.

Experimental

1-*Benzyl*-7,8-*dihydro*-1H,5H-*imidazo*[4,5-e][1,3]]*diazepine*-4,6-*dione* (**13**).—Compound (**10**) (1.85 g, 5.7 mmol) was suspended in anhydrous dioxan (50 ml). Acetic anhydride (5 ml) was added, and the solution was heated under reflux for 2 h. After cooling, the precipitate was collected by filtration, washed with dioxan, and dried to give (**13**) (0.58 g, 40%). An analytical sample, m.p. 252—253 °C, was obtained on crystallization from ethanol (Found: C, 60.95; H, 4.63; N, 21.86. $C_{13}H_{12}N_4O_2$ requires C, 60.94; H, 4.72; N, 21.86%); $\delta_H[(CD_3)_2SO]$ 4.2 (d, 2 H, CH_2NH), 5.3 (s, 2 H, $PhCH_2$), 7.3—7.5 (m, 5 H, Ph), 7.8 (br t, 1 H, CH_2NH), 7.9 (s, 1 H, 2-H), and 9.5 (s, 1 H, CONHCO); $\delta_C[(CD_3)_2SO]$ 33.4, 47.4, 126.8, 127.8, 128.9, 131.7, 136.0, 136.5, 138.7, 154.9, and 160.4.

After hydrogenolysis of (**13**) in acetic acid, 7,8-*dihydro*-1H,5H-*imidazo*[4,5-e][1,3]*diazepine*-4,6-*dione* (**3**) was crystallized from DMSO–water, m.p. 287—289 °C (Found: C, 43.11; H, 3.66; N, 33.44. $C_6H_6N_4O_2$ requires C, 43.37; H, 3.64; N, 33.72%); $\delta_H[(CD_3)_2SO]$ 4.2 (d, 2 H, CH_2NH), 7.8 (br t and s, 2 H, CH_2NH and 2-H), 9.7 (s, 1 H, CONHCO), and 13.2 (br, 1 H, 1-H); $\delta_C[(CD_3)_2SO]$ 38.2, 121.2, 138.8, 145.9, 154.7, and 158.2.

Acknowledgements

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