Cyclic Homologs of Xanthines. I. Imidazo[4,5-*e*][1,4]diazepine-5,8-diones

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A useful synthetic approach to variously alkylated 4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-diones is reported. These compounds are potentially interesting cyclic homologs of pharmacologically important alkylxanthines.

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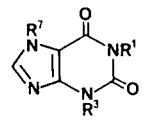
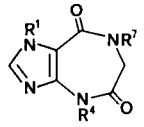
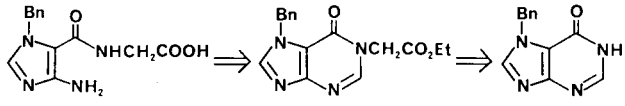
Theophylline (**1a**) has been used for some time in the treatment of asthma [1]. Other 1,3-dialkylxanthines are of biochemical significance as cyclic nucleotide phosphodiesterase inhibitors and adenosine antagonists [2,3]. As part of a program to explore structure-activity relationships in theophylline analogs we wished to prepare the cyclic homolog **2a**, and other alkylated derivatives of 4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (IDD). One example of this ring system has been reported, the caffeine homolog **2b** [4]. This compound was prepared in three steps from caffeine (**1b**), but the approach proved to be impractical for the preparation of other derivatives for reasons outlined below. We now wish to report a convenient synthesis of IDD's which allows the preparation of the parent heterocycle, 4-alkyl, and 4,7-dialkyl derivatives from a common intermediate, 1-benzyl-4,5,7,8-tetrahydro-6*H*-imidazo-[4,5-*e*][1,4]diazepine-5,8-dione (**7a**).





1a R^7 = H, R^1 = R^3 = Me
1b R^1 = R^3 = R^7 = Me
1c R^7 = Bn, R^1 = R^3 = Me
1d R^7 = R^1 = H, R^3 = Pr
1e R^7 = H, R^1 = Me, R^3 = iBu

2a R^1 = H, R^4 = R^7 = Me
2b R^1 = R^4 = R^7 = Me
2c R^1 = Bn, R^4 = R^7 = Me
2d R^1 = Bn, R^4 = R^7 = Et
2e R^1 = Bn, R^4 = iBu, R^7 = Me
2f R^1 = H, R^4 = iBu, R^7 = Me



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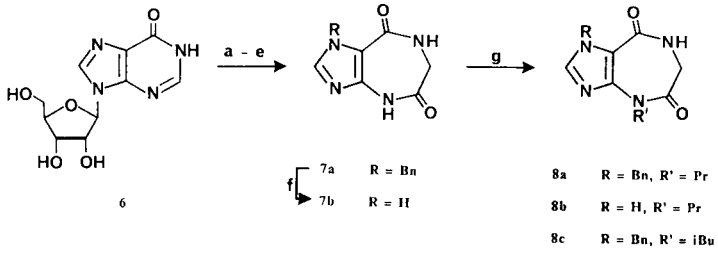
We first explored the synthesis of **2a** using the previously published approach to this ring system [4]. The series of reactions reported for the homologation of caffeine requires all three alkyl groups to be present on the xanthine nucleus. The synthesis of **2a** was achieved therefore *via* the 1-benzyl derivative **2c**, which was prepared from 7-benzyltheophylline (**1c**). Thus **1c** was treated with sodium hydroxide which opened the pyrimidine ring to give *N*-methyl-1-benzyl-5-methylaminoimidazole-4-carboxamide. This was converted to **2c** by sequential reaction with chloroacetyl chloride and sodium ethoxide. The low overall yield in this conversion, due to the poor recovery in the xanthine ring opening step, precludes this from being a generally useful method, particularly since 1,3-dialkylxanthines other than theophylline are not readily available. Another disadvantage of this approach is that it does not allow access to IDD's with less than two alkyl groups on the seven membered ring. The theophylline homolog **2a** was prepared from **2c** in good yield by hydrogenolysis over 20% palladium hydroxide on carbon, the more familiar palladium on carbon proving to be an ineffective catalyst for this reaction. While this approach allowed the preparation of **2a** and demonstrated the utility of the benzyl protecting group, we decided to explore an alternative approach to other IDD derivatives.

By analogy with the synthesis of 1,4-benzodiazepine-2,5-dione the preparation of the imidazodiazepinedione ring system was envisaged as proceeding *via* an intermediate **3** suitably protected on the imidazole ring nitrogen [5]. The benzyl group was retained for this purpose not only because it seemed to have the required chemical characteristics but also because the immediate precursors to the final target compounds would then be cyclic homologs of 7-benzylxanthines which have also shown interesting biochemical properties [6]. Retrosynthetic analysis suggested that **3** could be prepared from the disubstituted hypoxanthine **4**, which could in turn be prepared from 7-benzylhypoxanthine (**5**). Several syntheses of **5** have been reported [7]. None of these is well suited to the convenient preparation of reasonable amounts of this compound. We have found that inosine (**6**) can be easily benzylated and deribosylated to give 7-benzylhypoxanthine in 40-50% yield without purification of the intermediate 7-benzylinosine. The convenience of the procedure, which quickly provides multigram quantities from readily available precursors, more than makes up for the moderate yield. We are currently exploring the generality of this reaction sequence for the preparation of other 7-alkylpurines.



a. Ph_2Br; b. HCl; c. NaH, $BrCH_2CO_2Et$; d. NaOH; e. AcOH; f. H_2, $Pd(OH)_2$; g. NaH, R'Br.

Reaction of 7-benzylhypoxanthine with ethyl bromoacetate gives the expected 1,7-disubstituted compound **4** which on treatment with sodium hydroxide undergoes ring opening to *N*-(4-amino-1-benzylimidazole-5-carbonyl)-glycine (**3**). On heating in glacial acetic acid **3** was converted to the desired key intermediate **7a** in near quantitative yield. The proton nmr spectrum of this intermediate shows two exchangeable resonances. The higher field signal appears as a triplet due to coupling with the protons on *C*-6 and can therefore be assigned to the proton on *N*-7. The lower field signal, appearing as a singlet, is thus assigned to the proton on *N*-4. Other features of the proton and carbon magnetic resonance spectra are also consistent with the assigned structure. The benzyl group was readily removed from **7a** by hydrogenolysis to give the unsubstituted heterocycle **7b**, a cyclic homolog of the purine xanthine which is an important intermediate in the catabolism of purines.

Alkylation of **7a** with slightly more than two equivalents of methyl iodide in the presence of a base gave **2c** in excellent yield. No other product was observed thus confirming the expectation that *O*-alkylation would not occur under these conditions. 1-Benzyl-4,7-diethyl-IDD (**2d**) was prepared similarly. A more significant demonstration of the utility of **7a** as an intermediate in the synthesis of alkylated IDD's is given by its selective monoalkylation. On treatment with one equivalent each of sodium hydride and 1-bromopropane **7a** was converted to a single product isolated in 89% yield. The pmr spectrum of this product differed from that of **7a** only in the presence of the propyl group resonances and the absence of the lower field exchangeable resonance. The remaining exchangeable resonance appeared as a triplet confirming that reaction had occurred at *N*-4 to give the 4-propyl derivative **8a**. The selectivity observed in this reaction can be rationalized as being due to the increased acidity of the *N*-4 proton compared to the *N*7 proton caused by extra electron delocalization through the imidazole ring and the *C*-8 carbonyl function. Debenzylation of **8a** gave **8b**, the cyclic homolog of the potential anti-asthmatic compound enprofylline (**1d**) [8]. Regiospecific alkylation of **7a** was also observed with isobutyl bromide, **8c** being isolated in 82% yield, and is anticipated to be a general property of the ring system. Further alkylation of **8c** with methyl iodide gave **2e**, which was debenzylated to **2f**. The latter compound is the cyclic homolog of 3-isobutyl-1-methylxanthine (IBMX, **1e**), a potent inhibitor of cyclic nucleotide phosphodiesterase [9].

Thus we have demonstrated that the readily available key intermediate **7a** can be conveniently elaborated to a number of mono and dialkyl imidazodiazepinediones, potentially interesting cyclic homologs of biochemically significant xanthines. The ability of these compounds to interact with adenosine receptors is currently being explored. While this work was in progress we became aware of a recently published note outlining an alternate approach to this ring system [10].

EXPERIMENTAL

Melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Proton and carbon nmr spectra were recorded on a Varian VXR300 spectrometer in DMSO-d_6 and are referenced to the solvent. Microanalyses were performed by Desert Analytics, Tucson, Arizona.

N-Methyl-1-benzyl-4-methylaminoimidazole-5-carboxamide.

7-Benzyltheophylline (**1c**, 21.6 g, 80 mmoles) was suspended in 95% ethanol (500 ml), 6*M* aqueous sodium hydroxide was added, and the mixture was heated at reflux for 16 hours. Most of the solvent was removed *in vacuo*, water was added, and the product was extracted into dichloromethane. Concentration gave the imidazole as a gum which solidified on addition of ether, yielding 7.4 g (38%). Crystallization from water gave an analytical sample, mp 113-114°; ^{1}H nmr: 2.7 (d, 3H, NCH_3), 2.8 (d, 3H, NCH_3), 5.2 (br q, 1H, NHCH$_3$), 5.4 (s, 2H, PhCH_2), 7.0 (br q, 1H, NHCH$_3$), 7.2-7.4 (m, 5H, Ph), 7.6 (s, 1H, H-2).

Anal. Calcd. for $C_{13}H_{16}N_4O$: C, 63.93; H, 6.56; N, 22.95. Found: C, 63.62; H, 6.61; N, 22.94.

1-Benzyl-4,7-dimethyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**2c**).

N-Methyl-1-benzyl-4-methylaminoimidazole-5-carboxamide (6.4 g, 26.2 mmoles) was dissolved in chloroform (50 ml), potassium carbonate (10 g) and chloroacetyl chloride (2.5 ml, 30 mmoles) were added, and the mixture was stirred at ambient temperature for 4 hours. Suspended solid was removed by filtration and the solution was concentrated *in vacuo*. A solution of sodium ethoxide (prepared from 0.6 g of sodium, 26.2 g-atoms) in

absolute ethanol (50 ml) was added and after stirring for 2 hours at ambient temperature the solvent was removed *in vacuo*. The residue was partitioned between water and methylene chloride, and the organic extract was dried over magnesium sulfate and concentrated. Compound **2c** (6.5 g, 86%) crystallized from 5% methanol in diethyl ether, mp 94-95°; ^{1}H nmr: 3.0 (s, 3H, NCH_3), 3.3 (s, 3H, NCH_3), 3.95 (s, 2H, NCH_2CO), 5.55 (s, 2H, PhCH_2), 7.2-7.4 (m, 5H, Ph), 8.05 (s, 1H, H-2).

Anal. Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.38; H, 5.63; N, 19.72. Found: C, 63.09; H, 5.64; N, 19.74.

7-Benzylhypoxanthine (**5**).

Inosine (20 g, 0.07 mole) was dissolved in dry DMSO (100 ml), benzyl bromide (17 ml, 0.14 mole) was added, and the solution was stirred at ambient temperature for 24 hours. The solution was poured slowly into ethyl acetate (3600 ml), the supernatant was decanted from the gummy precipitate, and the latter was dissolved in 10% hydrochloric acid (150 ml). The solution was heated at 70° for 2 hours, cooled, and neutralized by addition of 6*M* sodium hydroxide. The precipitate was collected, washed thoroughly with water, and dried *in vacuo* yielding 7.5 g (47%) of **5** as a brown solid which could be used without further purification. An analytical sample obtained on recrystallization from ethanol was identical to that previously reported [7].

Ethyl (7-Benzylhypoxanthin-1-yl)acetate (**4**).

7-Benzylhypoxanthine (5, 10 g, 44 mmoles) and sodium hydride (60% dispersion, 2 g, 47 mmoles) were dissolved in DMF (150 ml) and ethyl bromoacetate (5.3 ml, 47 mmoles) was added. After stirring at 70° for 16 hours, the DMF was evaporated *in vacuo*, the residue was triturated with water, and the mixture was chilled. The product was filtered, washed with water, and hexane, and dried yielding 10.4 g (76%). An analytical sample, mp 148-149°, was obtained by recrystallization from ethanol; ^{1}H nmr: 1.2 (t, 3H, CH_2CH_3), 4.15 (q, 2H, CH_2CH_3), 4.85 (s, 2H, NCH_2CO), 5.6 (s, 2H, PhCH_2), 7.3 (s, 5H, Ph), 8.35 (s, 1H, H-2), 8.5 (s, 1H, H-8).

Anal. Calcd. for $C_{16}H_{16}N_4O_3$: C, 61.54; H, 5.13; N, 17.95. Found: C, 61.29; H, 5.10; N, 17.91.

N-(4-Amino-1-benzylimidazol-5-carbonyl)glycine (**3**).

Compound **4** (5 g, 16 mmoles) was dissolved in hot 95% ethanol (100 ml), 6*M* aqueous sodium hydroxide (9 ml) was added, and the solution was heated under reflux for 2 hours. Solvents were removed *in vacuo* and the residue was dissolved in water (100 ml). The solution was cooled and brought to *p*H 4 by addition of concentrated hydrochloric acid. The product was filtered, washed with water, and dried *in vacuo* yielding 3.66 g (84%). Recrystallization from 95% ethanol gave an analytical sample, mp 284-286°; ^{1}H nmr: 3.85 (d, 2H, NCH_2CO), 5.4 (s, 2H, PhCH_2), 6.0 (br, 3H, -NH_3^+), 7.2-7.4 (m, 5H, Ph), 7.5 (t, 1H, NHCH$_2$), 7.6 (s, 1H, H-2).

Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.11; N, 20.44. Found: C, 56.90; H, 5.13; N, 20.21.

1-Benzyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**7a**).

Compound **3** (2 g, 7.3 mmoles) was dissolved in glacial acetic acid (20 ml) and the solution was heated under reflux for 6 hours. Solvent was evaporated *in vacuo*, the residue was triturated with water, filtered, washed with water, and dried *in vacuo* to yield 1.6 g (87%) of **7a**. Although poorly soluble the product could be recrystallized from a large volume of aqueous ethanol, mp 288-289°; ^{1}H nmr: 3.5 (d, 2H, NCH_2CO), 5.5 (s, 2H, PhCH_2), 7.2-7.4 (m, 5H, Ph), 7.9 (s, 1H, H-2), 8.0 (t, 1H, H-7), 10.8 (s, 1H, H-4); ^{13}C nmr: 46 (C-6), 49 (PhCH_2), 110 (C-8a), 127, 128, 129, 137 (Ph), 140 (C-2), 143 (C-3a), 162, 168 (C-5, C-8).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.94; H, 4.69; N, 21.88. Found: C, 60.82; H, 4.71; N, 21.75.

1-Benzyl-4,7-diethyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**2d**).

Compound **7a** (2 g, 7.8 mmoles) was suspended in dry DMF (100 ml), sodium hydride (60% dispersion, 0.64 g, 16 mmoles) and ethyl bromide (1.2 ml, 16 mmoles) were added, and the mixture was heated at 70° for 16 hours. DMF was evaporated *in vacuo* and the residue was partitioned between water and dichloromethane. The organic extract was dried over magnesium sulfate and concentrated, and the solid residue (2.1 g, 86%) was recrystallized from aqueous ethanol, mp 104-106°; ^{1}H nmr: 1.0 (t, 3H, CH_2CH_3), 1.1 (t, 3H, CH_2CH_3), 3.4 (q, 2H, NCH_2CH$_3$), 3.9 (s, 2H, NCH_2CO), 3.95 (q, 2H, NCH_2CH$_3$), 5.5 (s, 2H, PhCH_2), 7.2-7.4 (m, 5H, Ph), 8.05 (s, 1H, H-2).

Anal. Calcd. for $C_{17}H_{20}N_4O_2$: C, 65.38; H, 6.41; N, 17.95; Found: C, 65.62; H, 6.45; N, 17.82.

1-Benzyl-4-propyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**8a**).

Compound **7a** (1.52 g, 5.94 mmoles) was suspended in dry DMF (80 ml) and sodium hydride (60%) dispersion, 0.27 g, 6.83 mmoles) was added. After 15 minutes 1-bromopropane (0.62 ml, 6.83 mmoles) was added and the solution stirred at 70° for 16 hours. The solvent was evaporated *in vacuo*, the residue was partitioned between aqueous sodium bicarbonate and dichloromethane, and the organic extracts were dried over magnesium sulfate and concentrated. The product (1.59 g, 90%) crystallized from aqueous ethanol, mp 163-164°; ^{1}H nmr: 0.8 (t, 3H, CH_2CH_3), 1.55 (m, 2H, $CH_2CH_2CH_3$), 3.65 (d, 2H, NCH_2CO), 3.9 (t, 2H, NCH_2CH$_2$), 5.55 (s, 2H, PhCH_2), 7.2-7.4 (m, 5H, Ph), 8.1 (s, 1H, H-2), 8.2 (t, 1H, H-7).

Anal. Calcd. for $C_{16}H_{18}N_4O_2$: C, 64.43; H, 6.04; N, 18.79. Found: C, 64.33; H, 6.03; N, 18.69.

1-Benzyl-4-isobutyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**8c**).

Compound **7a** (1.0 g, 4.1 mmoles) was alkylated as above using sodium hydride (0.18 g, 4.5 mmoles) and isobutyl bromide (0.5 ml, 4.5 mmoles). The product (1.1 g, 86%) was crystallized from isopropyl alcohol, mp 196-198°; ^{1}H nmr: 0.8 (d, 6H, CH(CH_3)$_2$), 1.9 (m, 1H, CH$_2$CHMe$_2$), 3.65 (d, 2H, NCH_2CO), 3.8 (d, 2H, NCH_2CHMe$_2$), 5.5 (d, 2H, PhCH_2), 7.2-7.4 (m, 5H, Ph), 8.05 (s, 1H, H-2), 8.2 (t, 1H, H-7).

Anal. Calcd. for $C_{17}H_{20}N_4O_2$: C, 65.38; H, 6.41; N, 17.95. Found: C, 65.66; H, 6.51; N, 18.04.

1-Benzyl-4-isobutyl-7-methyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]-diazepine-5,8-dione (**2e**).

Compound **8c** (0.25 g, 0.8 mmoles) was alkylated as above using sodium hydride (40 mg, 1 mmole) and methyl iodide (0.06 ml, 1 mmole). The product (0.25 g, 96%) was crystallized from ethyl acetate, mp 159-160°; ^{1}H nmr: 0.8 (d, 6H, CH(CH_3)$_2$), 1.9 (m, 1H, CH$_2$CHMe$_2$), 3.0 (s, 3H, NCH_3), 3.8 (d, 2H, NCH_2CHMe$_2$), 3.95 (s, 2H, NCH_2CO), 5.5 (s, 2H, PhCH$_2$), 7.2-7.4 (m, 5H, Ph), 8.05 (s, 1H, H-2).

Anal. Calcd. for $C_{18}H_{22}N_4O_2$: C, 66.26; H, 6.75; N, 17.18. Found: C, 66.28; H, 6.81; N, 17.04.

General Procedure for Hydrogenolysis.

Substrate was dissolved in glacial acetic acid (10-20 ml/mmole), 20% palladium hydroxide on carbon (0.2 g/mmole) was added, and the mixture was shaken at ambient temperature under hydrogen (40 psi) for 16 hours in a Parr apparatus. Catalyst was removed by filtration and washed with acetic acid, and the solution was evaporated to dryness *in vacuo*. Purification of the individual products is detailed below.

4,7-Dimethyl-4,5,7,8-tetrahydroimidazo[4,5-*e*][1,4]diazepine-5,8-dione (**2a**).

Compound **2a** (82%) crystallized from water, mp 258-260°; ^{1}H nmr: 3.0 (s, 3H, NCH_3), 3.35 (s, 3H, NCH_3), 4.05 (s, 2H, NCH_2CO), 7.8 (s, 1H, H-2), 13.1 (br, 1H, H-1); ^{13}C nmr: 31, 35 (Me), 54 (C-6), 112 (C-8a), 136 (C-2), 143 (C-3a), 160, 166 (C-5, C-8).

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.15; N, 28.87. Found: C, 49.29; H, 5.11; N, 28.97.

4,5,7,8-Tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**7b**).

The residue was dissolved in water. Evaporation *in vacuo* to a small volume gave the product (72%) as a white crystalline solid. Recrystal-

lization from water gave an analytical sample, mp >340°; ^{1}H nmr: 3.7 (d, 2H, NCH_2CO), 7.7 (s, 1H, H-2), 7.8 (t, 1H, H-7), 10.7 (s, 1H, H-4), 12.8 (br s, 1H, H-1); ^{13}C nmr: 46 (C-6), 112 (C-8a), 136 (C-2), 143 (C-3a), 162, 168 (C-5, C-8).

Anal. Calcd. for $C_6H_6N_4O_2 \cdot H_2O$: C, 39.13; H, 4.38; N, 30.42. Found: C, 39.50; H, 4.30; N, 30.19.

4-Propyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**8b**).

The residue was crystallized from ethyl acetate-ethanol, in a yield of 79%, mp 220-222°; ^{1}H nmr: 0.8 (t, 3H), 1.5 (m, 2H), 3.75 (d, 2H), 3.9 (t, 2H), 7.8 (s, 1H), 8.1 (t, 1H), 12.6 (br s, 1H).

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.92; H, 5.77; N, 26.92. Found: C, 51.85; H, 5.76; N, 26.69.

4-Isobutyl-7-methyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**2f**).

The residue was dissolved in a minimum amount of ethanol. Addition of ether gave a crystalline product, mp 159-160°, in 91% yield; ^{1}H nmr: 0.8 (d, 6H, CH(CH_3)$_2$), 1.9 (m, 1H, CH_2CHMe$_2$), 3.05 (s, 3H, NCH_3), 3.8 (d, 2H, CH_2CHMe$_2$), 4.0 (s, 2H, NCH_2CO), 7.8 (s, 1H, H-2), 13.0 (br s, 1H, H-1).

Anal. Calcd. for $C_{11}H_{16}N_4O_2$: C, 55.93; H, 6.78; N, 23.73. Found: C, 55.96; H, 6.65; N, 23.45.

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* Author to whom correspondence should be addressed.

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