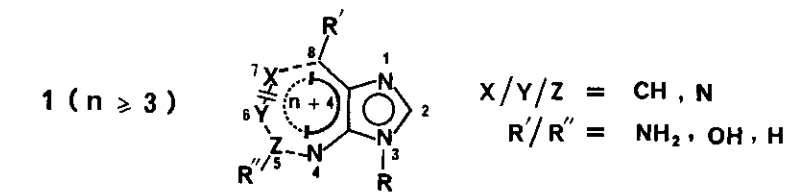
MODELS FOR "FAT" NUCLEOSIDES AND NUCLEOTIDES: SYNTHESES OF "FAT" XANTHINE (fX), "FAT" GUANINE (fG), AND "FAT" HYPOXANTHINE (fHx) ANALOGUES OF THE IMIDAZO[4,5-e][1,4]DIAZEPINE SYSTEM[1]

Ramachandra S. Hosmane,* Anila Bhan, and Michael E. Rauser
Laboratory for Chemical Dynamics, Department of Chemistry
University of Maryland Baltimore County, Catonsville, Maryland 21228, U.S.A.

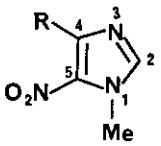
Abstract — Synthetic analogues of xanthine, guanine, and hypoxanthine, possessing the skeletal structure of imidazo[4,5-e][1,4]diazepine, are reported.

We have launched a broad and long term research program involving the synthesis and biochemical investigations of a family of nucleosides and nucleotides which we conveniently refer to as "fat" nucleosides and nucleotides. Replacement of the pyrimidine part of the purine nucleus with a bulkier seven- or higher membered ring, embedded with hetero atoms-- nitrogen and/or sulfur and/or phosphorus-- yields the "fat" nucleosides,[2] represented by the general formula 1 (R=β-D-ribofuranosyl, n≥3). By virtue of structural resemblance to their natural

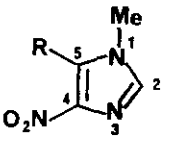


counterparts, the target "fat" nucleosides/nucleotides are potential candidates as substrates or inhibitors for various enzymes lying on the purine biosynthetic pathway and for those requiring energy cofactors. We report here our preliminary model studies relating to one such "fat" purine structure which bears the 7:5-fused imidazo[4,5-e][1,4]diazepine skeleton (1; n=3, X=N, Y=CH_2, Z=CH). The "fat" analogues of xanthine (fX: 1, R'=R''=OH), guanine (fG: 1, R'=OH, R''=NH_2), and hypoxanthine (fHx: 1, R'=OH, R''=H) reported herein contain methyl substitution at either 1- or 3-position of 1, the latter isomer representing the target nucleoside. The other regioisomeric precursors and/or final products are intended to facilitate later the structural distinction between the potential regioisomeric nucleosides resulting upon ribosidation of either the parent nucleus of 1 or of the appropriate imidazole precursor leading to 1.

The common starting materials employed in the intended syntheses were 4-cyano-1-methyl-5-nitroimidazole (2) and 5-cyano-1-methyl-4-nitroimidazole (3), whose preparation from the



2 ; R = CN
4 ; R = Me



3 ; R = CN
5 ; R = Me

respective 1,4-dimethyl-4- and 1,5-dimethyl-5-nitroimidazoles (4 and 5) have been reported by us recently.[3] The common first step in the synthesis (see Scheme) involved the hydrolysis of 2 or 3 with sodium nitrite and sulfuric acid[4] to obtain 6 or 7,[5] respectively. These latter, upon condensation with N-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide at 0°C, provided 8 or 9, respectively. Although the latter key intermediates could be characterized under strictly anhydrous conditions, they were conveniently employed in subsequent steps without further purification.

Synthesis of the "fat" xanthine (fX) analogues, 14 or 15,[5] from 8 or 9, respectively involved sequential reactions with glycine methyl ester to obtain 10 or 11,[5] reduction with Raney-Ni/H_2 to yield 12 or 13,[5] and ring closure with sodium methoxide/methanol.

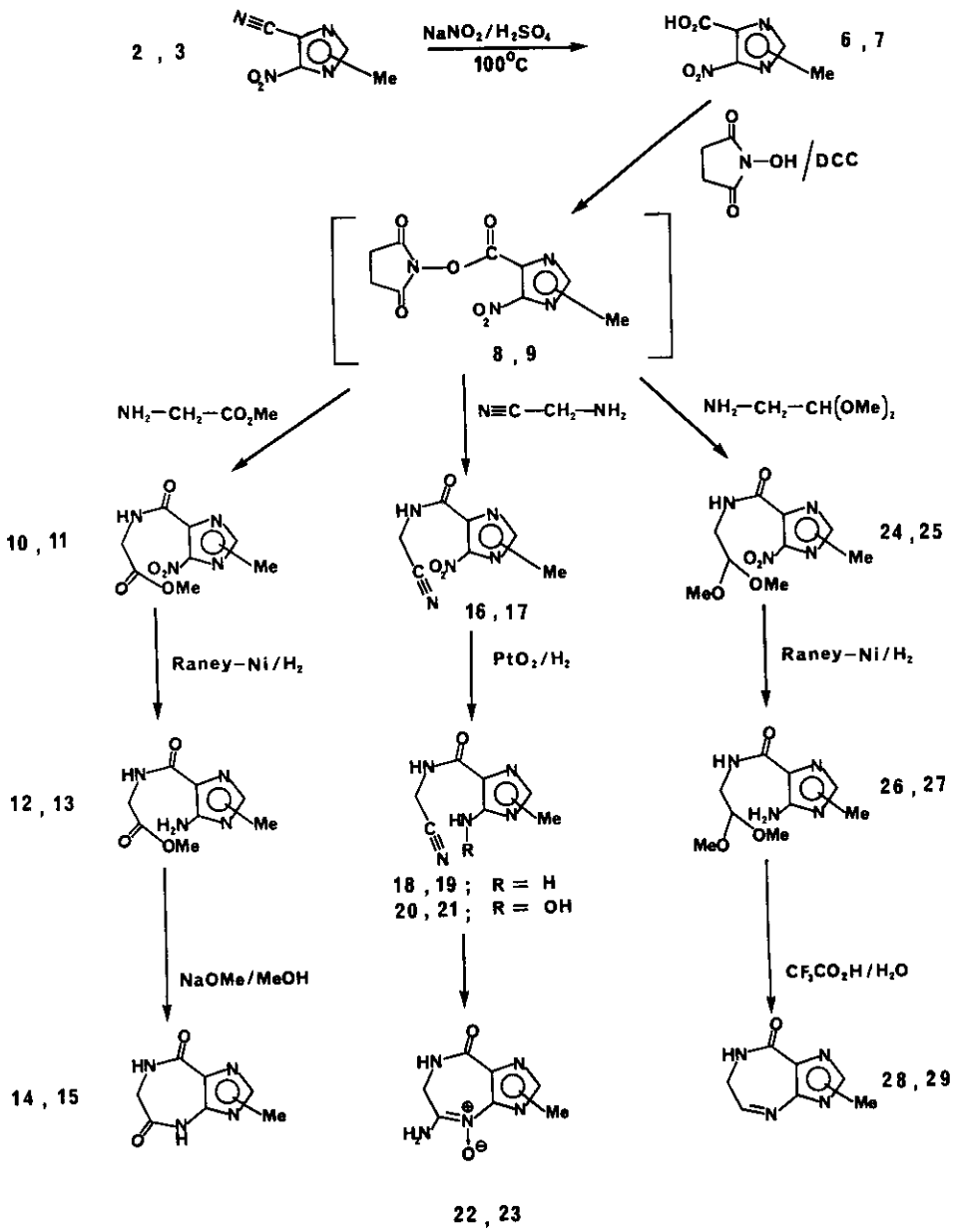
In the synthesis of the target "fat" guanines (fG), the intermediate 8 or 9 was initially reacted with aminoacetonitrile to give 16 or 17,[5] respectively. These latter, upon catalytic reduction with platinum oxide and hydrogen provided either the ring-closed fG N-oxides, 22[5] (presumably via the intermediates 20) or the ring-opened 19, respectively. The magnetic non-equivalency of the extranuclear NH_2 protons in the ^1H NMR spectrum of 22 (δ 8.97 and 8.21, respectively) can be attributed to the possible intramolecular hydrogen bonding between the amino function and the adjacent N-oxide.

The "fat" hypoxanthines (fHx) were prepared from 8 or 9 in consecutive steps which involved reaction with aminoacetaldehyde dimethyl acetal to yield 24 or 25,[5] reduction with Raney-Ni/H_2 to give 26 or 27,[5] followed by acetal hydrolysis, catalyzed by aqueous trifluoroacetic acid and concomitant ring-closure.

ACKNOWLEDGEMENTS

This research was supported by a grant from the National Institutes Health (Grant No. CA 36154), DHHS. We also express our thanks to Professor Patrick Callery and Linda Geelhaar of the School of Pharmacy, University of Maryland, Baltimore for the mass spectral data.

SCHEME


2 , 3
NaNO2/H2SO4
100°C
6 , 7
N-OH/DCC
8 , 9
NH2-CH2-CO2Me
N≡C-CH2-NH2
NH2-CH2-CH(OMe)2
10 , 11
16 , 17
24 , 25
Raney-Ni/H2
PtO2/H2
Raney-Ni/H2
12 , 13
26 , 27
18 , 19 ; R = H
20 , 21 ; R = OH
NaOMe/MeOH
CF3CO2H/H2O
14 , 15
28 , 29
22 , 23

REFERENCES AND NOTES

1. (a) This paper is dedicated to Professor Nelson J. Leonard of the University of Illinois, Urbana on his 70th birthday, (b) presented in part, see: "Abstracts of Papers," 10th International Congress of Heterocyclic Chemistry, Waterloo, Canada, Aug. 11-16, 1985; Abstr. No. P5-167.

2. The term "fat" nucleoside is herein conveniently applied when the ring replacing the pyrimidine nucleus of a purine is, in addition to being bulkier, peripherally compatible with that of the natural counterpart, with suitable substituents at the appropriate positions, e.g. fX: 1, R'=R"=OH; fG: 1, R'=OH, R"=NH_2; fHx: 1, R'=OH, R"=H. A few nucleosides which fit the above general description have been recently synthesized and contain the following ring systems: a) imidazo[4,5-d][1,3]diazepine,[8] b) pyrazolo[3,4-d][1,3]diazepine,[9] and c) triazolo[4,5-d][1,3]diazepine.[9]

3. R.S. Hosmane, A. Bhan, and M.E. Rauser, J. Org. Chem., **1985**, 50, 5892.

4. F.G. Mann and J.W.G. Porter, J. Chem. Soc., **1945**, 751.

5. The physical data and chemical yields for the compounds reported in this paper are as follow:

Compound 6: colorless needles from MeOH-H_2O; 89%; mp 146-148°C; ^1H NMR (Me_2SO-d_6) δ 8.51 (br s, 1, CO_2H), 7.89 (s, 1, CH), 3.84 (s, 3, Me); IR (KBr) 3400-2700 (br, OH), 1710-1700 (C=O) cm^{-1}; Anal.[6] C, H, N; **Compound 7**: colorless needles from MeOH-H_2O; 90%; mp 165°C (lit.[4] mp 163°C); ^1H NMR (Me_2SO-d_6) δ 9.77 (br s, 1, CO_2H), 7.92 (s, 1, CH), 3.82 (s, 3, Me); IR (KBr) 3400-2700 (br, OH), 1710-1700 (C=O) cm^{-1}; **Compound 8**: pale yellow squares from CH_3CN-hexane; 62-68%; mp 178-181°C; ^1H NMR (Me_2SO-d_6) δ 8.20 (s, 1, CH), 3.92 (s, 3, Me), 2.87 (s, 4, two CH_2); **Compound 9**: white crystals from CH_3CN-hexane; 75%; mp 133-136°C; ^1H NMR (Me_2SO-d_6) δ 8.22 (s, 1, CH), 3.91 (s, 3, Me), 2.89 (s, 4, two CH_2); IR (KBr) 1780, 1750 cm^{-1}; **Compound 10**: white needles from $CHCl_3$-petroleum ether (60-80°C); 64%; mp 124-127°C; ^1H NMR (Me_2SO-d_6) δ 8.8 (t, J_{NH,CH_2} = 5.6 Hz, 1, NH, exchangeable with D_2O), 8.01 (s, 1, CH), 4.0 (d, $J_{CH_2,NH}$ = 5.6 Hz, 2, CH_2), 3.86 (s, 3, N-Me), 3.65 (s, 3, O-Me); IR (KBr) 3320, 1740, 1680 cm^{-1}; MS (70 eV) m/e 242 (M^+), 211, 183, 154; Anal.[6] C, H, N; **Compound 11**: white needles from $CHCl_3$; 65%; mp 132-134°C; ^1H NMR (Me_2SO-d_6) δ 7.80 (s, 1, CH), 4.03 (d, $J_{CH_2,NH}$ = 5.6 Hz, 2, CH_2), 3.7 (s, 3, N-Me), 3.69 (s, 3, O-Me); IR (KBr) 3300, 1740, 1640 cm^{-1}; MS (70 eV) m/e 242 (M^+), 224, 183, 154, 143; Anal.[6] C, H, N; **Compound 12**: white needles from MeOH-hexane; 77%; mp 113-115°C; ^1H NMR (Me_2SO-d_6) δ 7.64 (t, J_{NH,CH_2} = 5.6 Hz, 1, NH, exchangeable with D_2O), 7.10 (s, 1, CH), 5.72 (br s, 2, NH_2, exchangeable with D_2O), 3.91 (d, $J_{CH_2,NH}$ = 5.6 Hz, 2, CH_2), 3.62 (s, 3, Me), 3.39 (s, 3, Me); IR (KBr) 3300, 3120, 1740 cm^{-1}; MS (70 eV) m/e 212 (M^+), 143, 124, 98; Anal.[6] C, H, N;

Compound 13: white needles from MeOH-hexane; 76%; mp 128-130°C; ^{1}H NMR (Me_2SO-d_6) δ 7.45 (t, J_{NH,CH_2} = 5.6 Hz, 1, NH, exchangeable with D_2O), 7.34 (s, 1, CH), 5.14 (br s, 2, NH_2, exchangeable with D_2O), 3.94 (d, $J_{CH_2,NH}$ = 5.6 Hz, 2, CH_2), 3.64 (s, 6, OMe + N-Me); IR (KBr) 3370, 3360, 1740, 1630 cm^{-1}; MS (70 eV) m/e 212 (M^+), 143, 124, 98; Anal.[6] C, H, N; **Compound 14**: off-white solid from MeOH-petroleum ether (40-60°C); 59%; mp 292-295°C(dec); ^{1}H NMR (Me_2SO-d_6) δ 7.96 (t, J_{NH,CH_2} = 4.8 Hz, 1, NH, exchangeable with D_2O), 7.63 (s, 1, CH), 3.68 (d, $J_{CH_2,NH}$ = 4.8 Hz, 2, CH_2), 3.60 (s, 3, Me); MS (70 eV) m/e 180 (M^+), 150, 140, 123; Anal.[6] C, H, N; **Compound 15**: white solid from MeOH-hexane; 29%; mp >300°C; ^{1}H NMR (Me_2SO-d_6) δ 10.69 (br s, 1, NH, exchangeable with D_2O), 7.94 (t, J_{NH,CH_2} = 4.8 Hz, 1, NH, exchangeable with D_2O), 7.72 (s, 1, CH), 3.77 (s, 3, N-Me), 3.63 (d, $J_{CH_2,NH}$ = 4.8 Hz, 2, CH_2); IR (KBr) 3170, 1702, 1660 cm^{-1}; MS (70 eV) m/e 180 (M^+), 151, 124; Anal.[6,7] C, H, N; **Compound 16**: white needles from EtOH; 56%; mp 162-164°C; ^{1}H NMR (Me_2SO-d_6) δ 9.18 (t, J_{NH,CH_2} = 5.6 Hz, 1, NH, exchangeable with D_2O), 8.0 (s, 1, CH), 4.29 (d, $J_{CH_2,NH}$ = 5.6 Hz, 2, CH_2), 3.88 (s, 3, N-Me); IR (KBr) 3280 (NH), 2240 (C≡N), 1650 (C=O) cm^{-1}; UV (EtOH) λ_{max} = 294 nm; MS (70 eV) m/e 209 (M^+), 155, 154, 138, 115; Anal.[6] C, H, N; **Compound 17**: white needles from MeOH-petroleum ether (60-80°C); 50%; mp 173-175°C; ^{1}H NMR (Me_2SO-d_6) δ 7.9 (s, 1, CH), 4.41 (s, 2, CH_2), 3.69 (s, 3, Me); IR (KBr) 2258 (C≡N) cm^{-1}; MS (70 eV) m/e 209 (M^+), 191, 179, 161; Anal.[6] C, H, N; **Compound 19**: off-white crystals from $CHCl_3$-hexane; 20%; mp 170-172°C; ^{1}H NMR (Me_2SO-d_6) δ 7.60 (br, 1, NH, exchangeable with D_2O), 7.36 (s, 1, CH), 5.33 (br s, 2, NH_2, exchangeable with D_2O), 4.20 (d, 2, CH_2), 3.69 (s, 3, N-Me); IR (KBr) 2240 (C≡N), 1640 (C=O) cm^{-1}; MS (70 eV) m/e 179 (M^+), 151, 124, 109, 97; **Compound 22**: colorless flakes from DMF-$CHCl_3$; 27%; mp 160°C (dec); ^{1}H NMR (Me_2SO-d_6) δ 8.97 (br s, 1, NH of NH_2, exchangeable with D_2O), 8.58 (t, J_{NH,CH_2} = 5.8 Hz, 1, NHCO, exchangeable with D_2O), 8.21 (br s, 1, NH of NH_2, exchangeable with D_2O), 7.5 (s, 1, CH), 4.18 (d, $J_{CH_2,NH}$ = 5.8 Hz, 2, CH_2), 3.59 (s, 3, Me); IR (KBr) 3240-2840, 1640, 1580, 1525 cm^{-1}; UV (EtOH) λ_{max} 266 nm; Anal.[6] C, H, N; **Compound 24**: oil/low-melting solid from silica gel column [eluent: $CHCl_3$-MeOH (9:1)]; recrystallized from Et_2O; 60-69%; mp 86-88°C; ^{1}H NMR (Me_2SO-d_6) δ 8.39 (t, J_{NH,CH_2} = 5.8 Hz, 1, NH, exchangeable with D_2O), 7.98 (s, 1, imidazole CH), 4.47 (t, J_{CH,CH_2} = 5.4 Hz, 1, CH of acetal), 3.86 (s, 3, N-Me), 3.38-3.27 (dd, $J_{CH_2,CH}$ = 5.4 Hz, $J_{CH_2,NH}$ = 5.8 Hz, 2, CH_2), 3.27 (s, 6, two OMe); IR (neat) 3300, 2840, 1660 cm^{-1}; MS (70 eV) m/e 227 (M^+-OMe), 181, 154, 149, 137, 123, 110, 108, 80, 75; Anal.[6] C, H, N; **Compound 25**: white crystals from Et_2O; 90-94%; mp 68-70°C; ^{1}H NMR (Me_2SO-d_6) δ 7.83 (s, 1, imidazole CH), 4.5 (t, J_{CH,CH_2} = 5.45 Hz, 1, CH of acetal), 3.67 (s, 3, N-Me)-3.39-3.25 (dd, $J_{CH_2,CH}$ = 5.45 Hz, $J_{CH_2,NH}$ = 5.8 Hz, 2, CH_2), 3.32 (s, 6, two OMe); IR (KBr) 3260, 1640 cm^{-1}; MS (CI, 70 eV) m/e 259 (M^+ + 1), 227, 195, 167, 166, 155, 154,

138; Anal.[6] C, H, N; **Compound 26**: Transparent crystals from MeOH-Et_2O; 45%; mp 106-109°C; ^1H NMR (Me_2SO-d_6) δ 7.07 (br s, 2, NH + imidazole CH); 5.67 (br, 2, NH_2, exchangeable with D_2O), 4.44 (t, J_{CH,CH_2} = 5.2 Hz, 1, CH of acetal), 3.38 (s, 3, N-Me), 3.33-3.26 (d+s, 8, CH_2 + two OMe); IR (neat) 3300, 2840, 1660 cm^{-1}; MS (70 eV) m/e 228 (M^+), 196, 165, 149, 124, 75; Anal.[6] C, H, N; **Compound 27**: off-white crystals from MeOH-Et_2O; 79%; mp 99-101°C; ^1H NMR (Me_2SO-d_6) δ 7.3 (s, 1, imidazole CH), 7.13 (t, J_{NH,CH_2} = 5.7 Hz, 1, NH, exchangeable with D_2O), 4.97 (br s, 2, NH_2, exchangeable with D_2O), 4.47 (t, J_{CH,CH_2} = 5.4 Hz, 1, CH of acetal), 3.68 (s, 3, N-Me), 3.39-3.27 (dd, $J_{CH_2,NH}$ = 5.7 Hz, $J_{CH_2,CH}$ = 5.4 Hz, 2, CH_2), 3.29 (s, 6, two OMe); IR (KBr) 3320, 1655 cm^{-1}; MS (70 eV) m/e 228 (M^+), 196, 165, 151, 124; Anal.[6] C, H, N; **Compound 29**: white powder; 45%; mp 170°C; ^1H NMR (Me_2SO-d_6) δ 8.75 (br s, Diazepine CH), 8.21-7.57 (br, 1, NH, exchangeable with D_2O), 7.77 (s, 1, imidazole CH), 6.93-6.1 (br, H_2O, exchangeable with D_2O), 3.88 (s, 3, N-Me), 4.0-3.59 (m, 2, CH_2); IR (KBr) 3240, 1640 cm^{-1}; MS (70 eV) m/e 164 (M^+), 95, 78, 69.

6. The elemental microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. The analyses were within ±0.3% of the calculated values.

7. The elemental microanalyses of compounds **15** and **19** each showed the presence of 0.25 mole of adventitious water.

8. E. Chan, S.R. Putt, H.D.H. Showalter, and D.C. Baker, J. Org. Chem., **1982**, 47, 3457 and the references cited therein.

9. O.L. Acevedo, S.H. Krawczyk, and L.B. Townsend, J. Org. Chem., **1986**, 51, 1050 and the references cited therein.

Received, 29th May, 1986