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Synthesis of a novel ring-expanded purine analogue containing a 5:8-fused imidazo[4,5-*e*][1,2,4]triazocine ring system amidst opportunistic rearrangements and ring transformations

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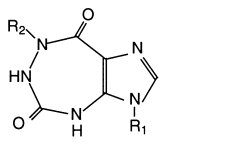
Abstract—A novel 5:8-fused heterocycle containing the imidazo[4,5-*e*][1,2,4]triazocine ring system has been synthesized in ten steps commencing from 1-benzyl-5-methyl-4-nitroimidazole. The compound is a new member of the family of ring-expanded xanthine–xanthosine analogues reported from this laboratory. The synthesis led to the unraveling of a number of novel rearrangements and ring-transformations.

1. Introduction

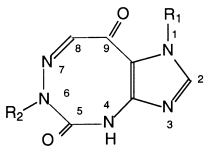
Ring-expanded purine bases as well as their nucleoside and nucleotide derivatives carry chemical, biochemical, biophysical, and medicinal significance.[1] While chemical significance concerns their synthesis and study of structure, stability, acid-base properties, aromaticity, tautomeric equilibria, etc. their biochemical significance derives from their potential substrate–inhibitory activity against a host of enzymes of purine metabolism, and enzymes that require energy cofactors such as ATP or GTP. Endowed with unique steric, electronic, and conformational characteristics, they are also potentially excellent probes for biophysical investigations of nucleic acid structure and function. From a medicinal standpoint, they can be regarded as analogues of purines with potential applications in anticancer and antiviral therapy.

Often plagued with undesired, opportunistic rearrangements, ring-expanded purine bases often present formidable challenge especially when the target ring systems are antiaromatic by Hückel standards. We have in fact reported a few such rearrangements involving the 5:7-fused imidazo[4,5-*e*][1,2,4]triazepine ring system (**1**).[2] While most of the target compounds of the latter system were found to be remarkably stable when once synthesized, the steps leading to their synthesis, more often than not, were prone to unforeseen ring transformations and rearrangements. Therefore, their structures shall only be assigned with due caution, especially since a large number of reportedly alleged seven and larger ring heterocycles were later discovered to be only 5- or 6-membered ring systems by X-ray diffraction analyses.[3] This report describes our synthetic studies on the title imidazo[4,5-*e*][1,2,4]triazocine ring system (**2**).[4] This 5:8-fused heterocyclic system proved to be just as or even more synthetically challenging than many other predecessor ring-expanded purine systems with a 5:7-fusion.



1

a; $R_1 = R_2 = H$
b; $R_1 = CH_2Ph$, $R_2 = H$
c; $R_1 = R_2 = CH_2Ph$
d; R1 = β-D-ribofuranosyl, R = H



2

a; $R_1 = R_2 = H$
b; $R_1 = CH_2Ph$, $R_2 = H$
c; $R_1 = R_2 = CH_2Ph$

2. Results and discussion

As was the case with **1**, the logical targets for initial synthetic explorations of the new heterocyclic system **2** are the benzyl analogues **2b** and **2c**. The benzyl substitutions, while being stable to both acidic and basic reaction conditions, can be conveniently cleaved by catalytic hydrogenation to produce the parent heterocycle that can later be used for constructing the corresponding nucleoside and nucleotide derivatives for eventual biological investigations. In that context, the ring-expanded analogues of

Keywords: ring-expanded purine; ring transformations; 5:8-fused heterocycles; rearrangements.

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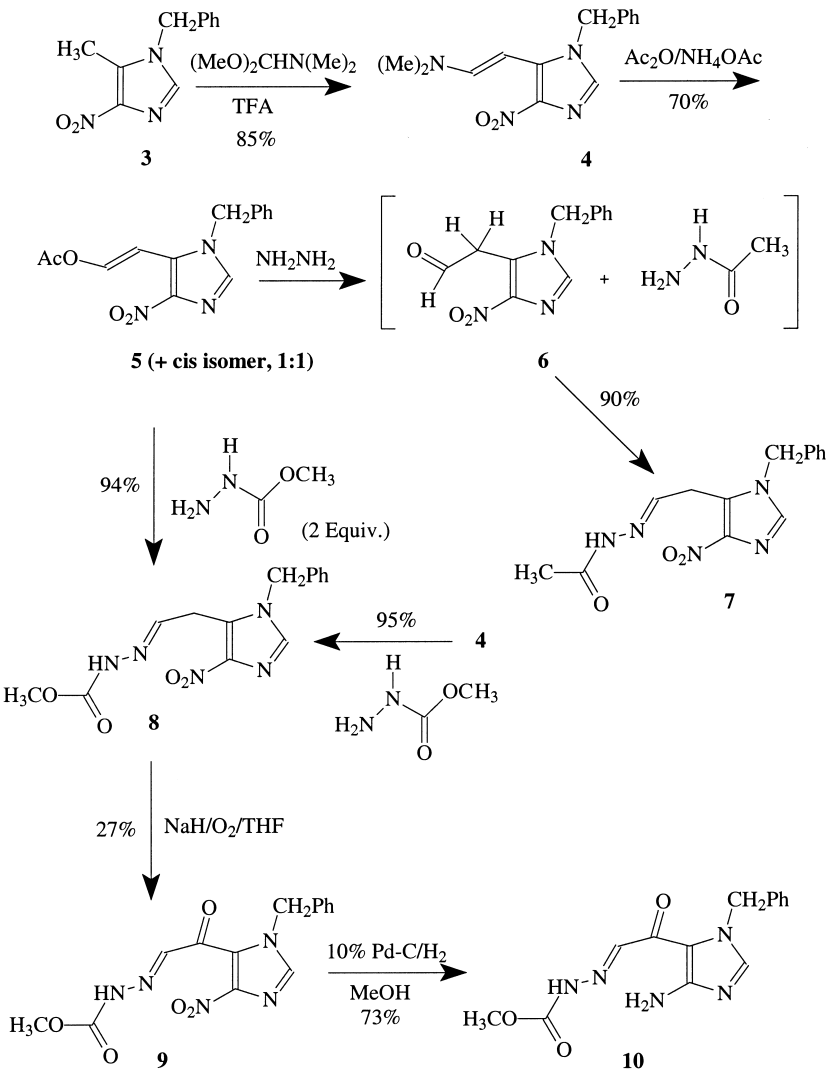


Scheme 1.

xanthine are also preferrred as they are the convenient precursors to a wide variety of other purine analogues, including adenine, guanine, isoguanine, hypoxanthine, and 2,6-diaminopurine.

The required synthetic precursor for the target **2b** is 4-amino-1-benzylimidazole-5-glyoxal (N^2-methoxycarbonyl)hydrazone (**10**) whose synthesis is outlined in Scheme 1. The synthesis commenced with 1-benzyl-5-methyl-4-

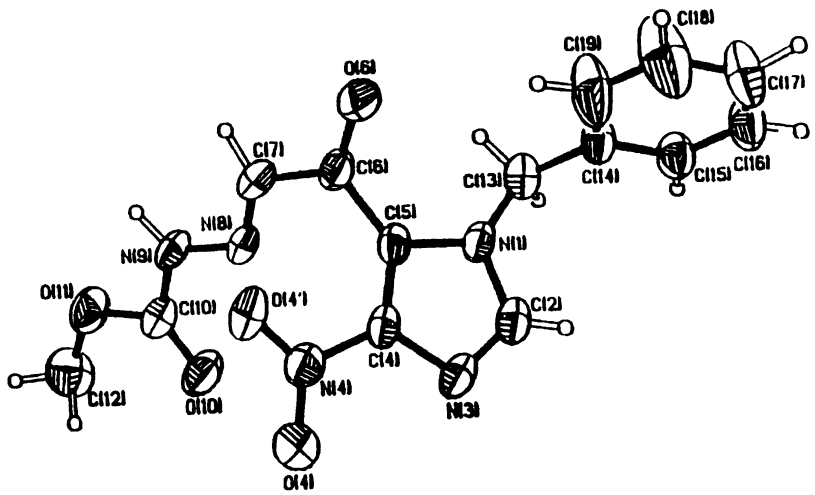
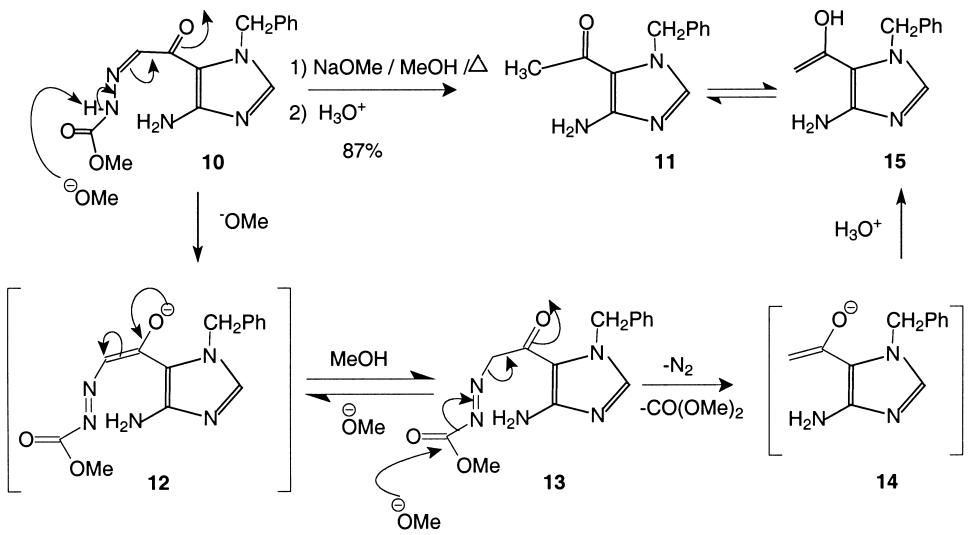
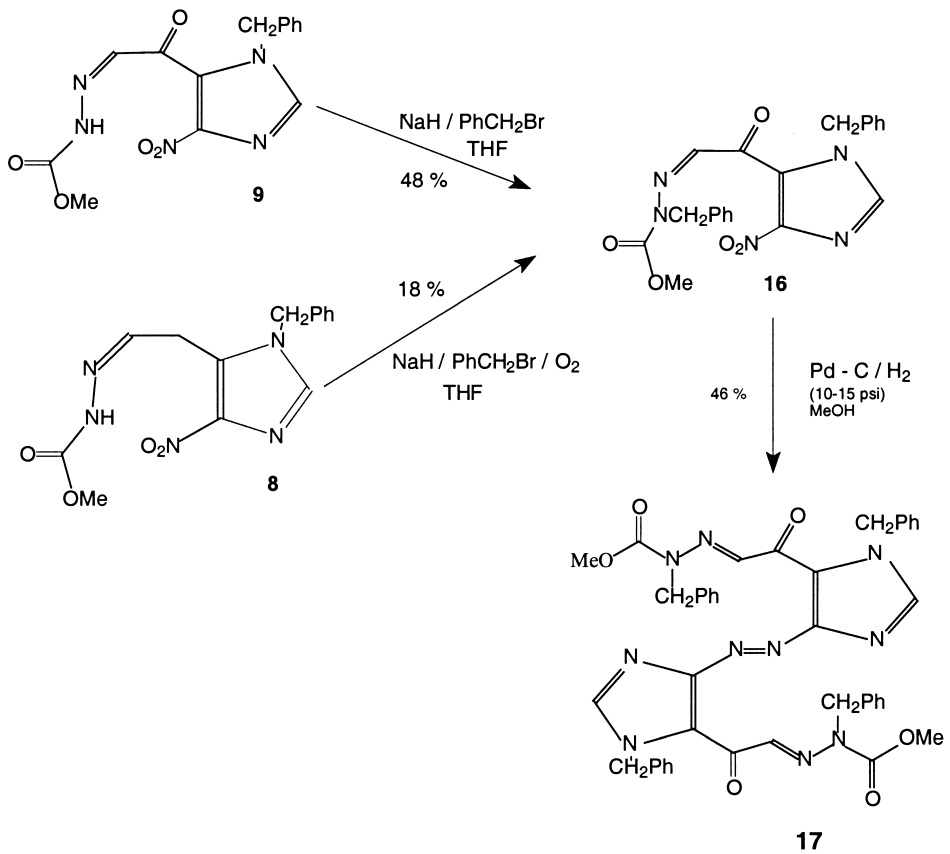


Figure 1. ORTEP view of **9** showing the atom numbering scheme that was employed.



Scheme 2.

nitroimidazole (**3**),[5] which was treated with dimethylformamide dimethyl acetal, catalyzed by trifluoroacetic acid, to form 1-benzyl-5-β-(*N*,*N*-dimethylaminoethylene-4-nitroimidazole (**4**) in 85% yield. The enamine **4** was converted to the corresponding enol-acetate **5** in 70% yield by reaction with acetic anhydride–ammonium acetate. When **5** was treated with an equivalent of hydrazine, the product isolated was the acetylhydrazone **7**. Apparently, **5** undergoes initial deacylation to form the intermediate aldehyde **6** and acetohydrazide which further reacts to form **7**. Based upon this result, the desired **8** was prepared from **5** in 94% yield by reaction with 2 equiv. or more of methylcarbazate. It was later discovered that **8** could also be prepared directly from **4** and methylcarbazate in 95% yield. The 5-methylene group of **8** was oxidized to the corresponding keto group of **9** by treatment with sodium hydride in the presence of molecular oxygen in 27% yield. In order to improve the yield of the latter reaction, various alternative methods of oxidation were attempted, including $CrO_3{\cdot}(Pyr)_2$,[6a] $MgO-KMnO_4$-(HNO_3-H_2O),[6b] DDQ–MeOH,[6c] and $NaH-O_2$–trimethyl



Scheme 3.

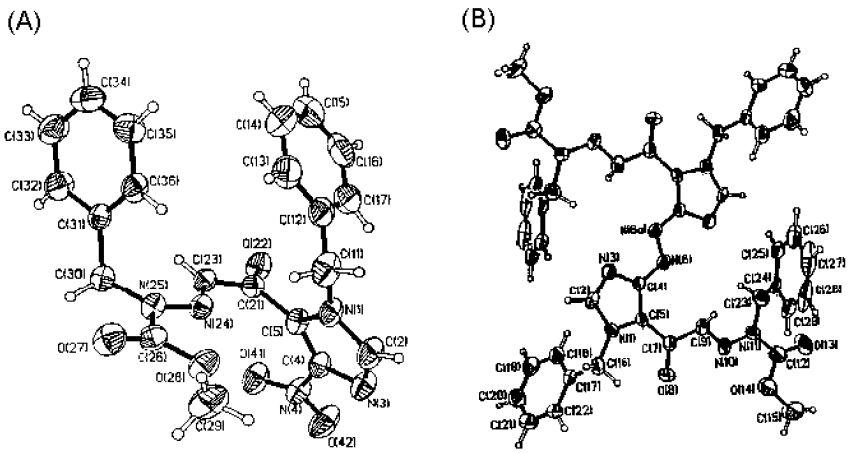
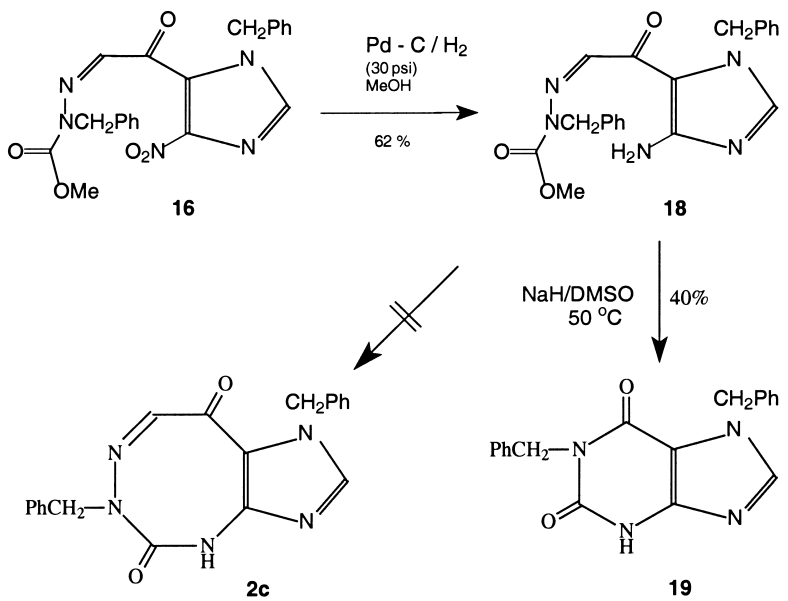


Figure 2. ORTEP view of (A) compound **16** and (B) compound **17**.

phosphite,[6d,e] but the yield in each case was less than desirable. The structure of **9** was confirmed by single-crystal X-ray diffraction analysis. An ORTEP view of the molecule along with the atom numbering scheme that we employed is shown in Fig. 1. The atomic co-ordinates with thermal motion parameters, bond lengths, bond angles, and selected torsion angles are collected in tables of the Supplementary Material. Data from the tables show that **9** contains a planar imidazole ring with 1-benzyl, 4-nitro, and 5-keto substituents that are essentially coplanar with the ring. The carbon or nitrogen atom of the substituents, directly connected to the ring, does not deviate by more than 6° from planarity (180 or 0°) as evidenced by torsion angles. The orientation of the C7–N8 double bond with respect to the C5–C6 bond is *syn*, whereas that of C6–C7 with respect to N8–N9 is *anti*. Finally, the nitro group of **9** was reduced by catalytic hydrogenation over Pd–C to obtain the desired amino compound **10** in 73% yield.

The attempted ring-closure of **10** to **2b** with sodium methoxide–methanol, followed by acid work-up, however, produced only the degradation product, 5-acetyl-4-amino-1-benzylimidazole (**11**), in 88% yield. A tentative mechanism (Scheme 2) for the formation of **11** involves the initial attack of methoxide ion at the side chain carbamate carbonyl of **10** to produce **13**. The latter, upon another attack by methoxide, eliminates a molecule of gaseous nitrogen to form **14**. The subsequent acid work-up would produce the enol **15**, which tautomerizes to the ketone **11**.

The protection of the side-chain hydrazino moiety with an alkyl or aralkyl group was anticipated to lower the likelihood of degradation of **10** to **11** as the two nitrogen atoms could no longer be eliminated as the entropy-favored nitrogen gas. To this end, we aimed to prepare the dibenzyl analogue **16** (Scheme 3). Compound **16** was prepared either from **10** using benzyl bromide–sodium hydride (48% yield) or directly from **8** in a one-pot reaction using the same reagents plus molecular oxygen (18%). However, the attempted catalytic hydrogenation of **16** in order to reduce its nitro group into the corresponding amino group, using Pd–C–H_2, only afforded the dimer **17** in 46% yield. The structures of both **16** and **17** were confirmed by single-crystal X-ray diffraction analysis (Fig. 2). Apparently, under



Scheme 4.

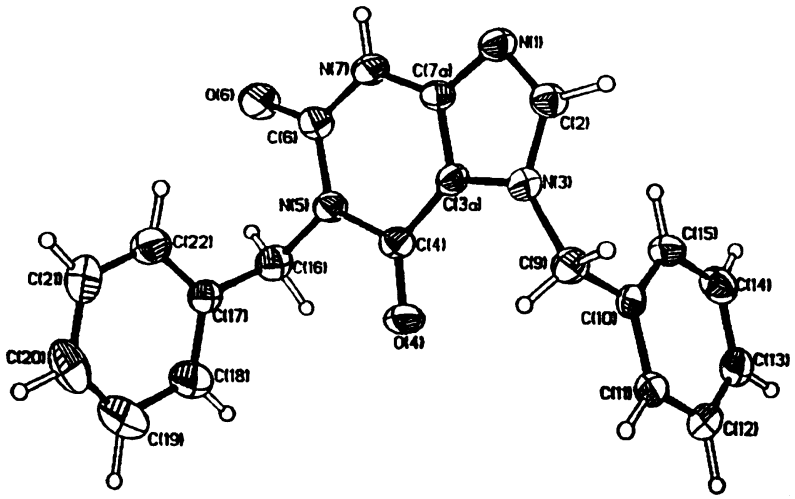
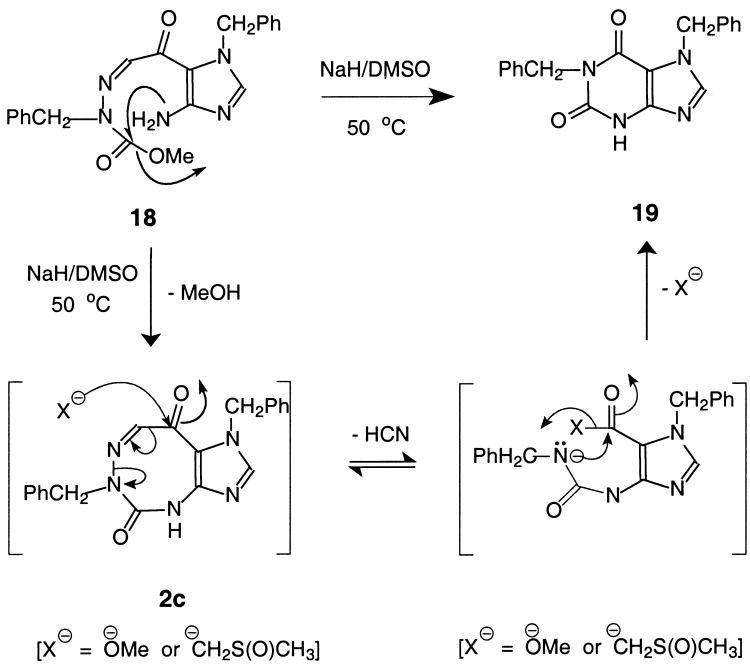


Figure 3. ORTEP view of compound **19**.

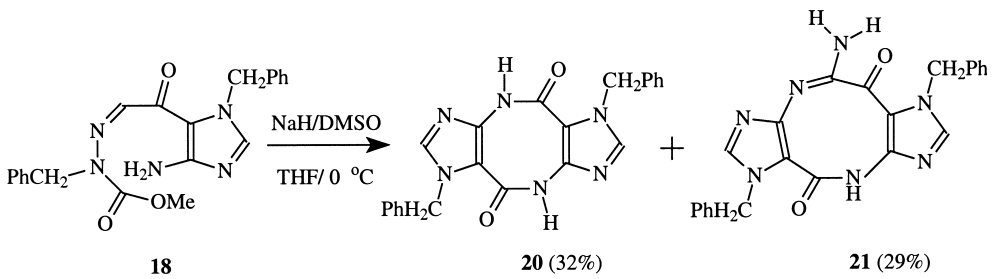
low pressure of hydrogen that was employed, the partially formed amino group of the target compound reacts with the intermediate nitroso compound to form the observed dimer **17**.

The problem of dimer formation during catalytic reduction was overcome by doubling the pressure of hydrogen gas, which was anticipated to enhance the rate of reduction and minimize the amount of unreacted nitroso species during the course of reduction. Thus, at 30 psi of H_2, **16** was reduced to form the desired **18** in 62% yield. However, the attempted ring-closure of **18** in sodium hydride–dimethyl sulfoxide at 50–60°C gave only the rearranged 5:6-fused system (Scheme 4), a xanthine derivative **19** instead of the desired 5:8-fused **2c**. The structure of **19** was confirmed by single-crystal X-ray diffraction analyses (Fig. 3). A tentative mechanism for the transformation of **18** to **19** is outlined in Scheme 5. As shown, the observed rearrangement might proceed by way of the desired 5:8-fused system **2c** as an intermediate. The base-catalyzed ring-opening of **2c** with concomitant elimination of hydrogen cyanide, followed by ring-closure would yield the observed 1,7-dibenzylxanthine (**19**). The attempted ring-closure of **18** with sodium methoxide in methanol at room temperature only resulted in a product that lacked the methoxycarbonyl functionality (see below).

It was thought that the reaction conditions were too drastic for the desired ring-closure of **18** to **2c**, and that the milder reaction conditions were believed necessary. Therefore, the same reaction was carried out at 0°C. This time, two new products were isolated from the reaction mixture, whose FAB mass spectra exhibited the M+1 peaks at *m/z* 399 and 426. The determination of elemental composition of these peaks by high resolution FAB pointed to molecular formulae of $C_{22}H_{18}N_6O_2$ and $C_{23}H_{19}N_7O_2$, respectively.



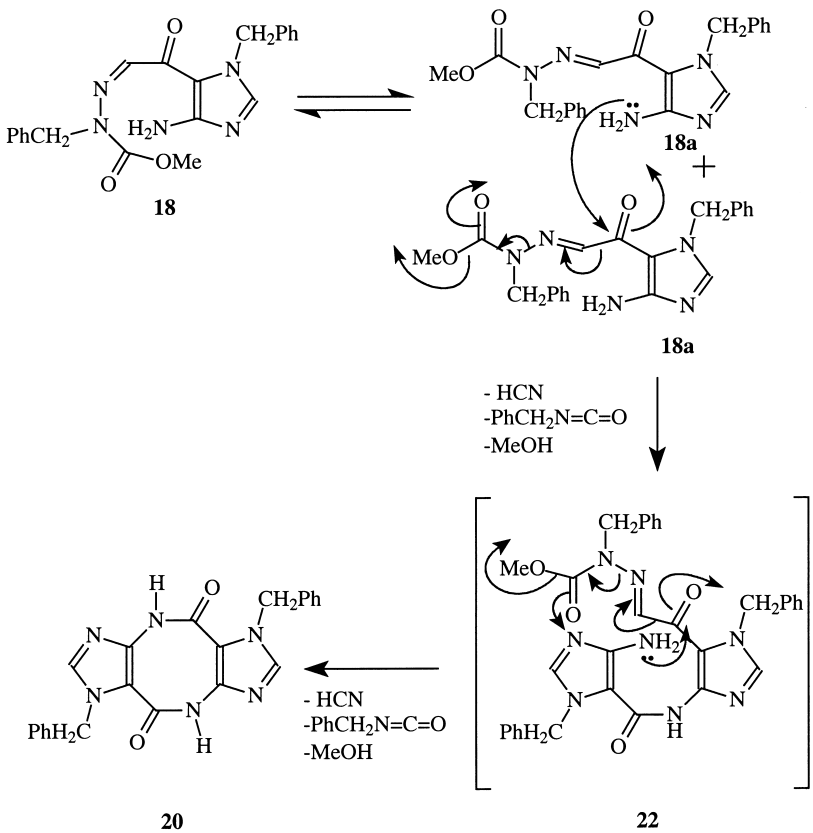
Scheme 5.



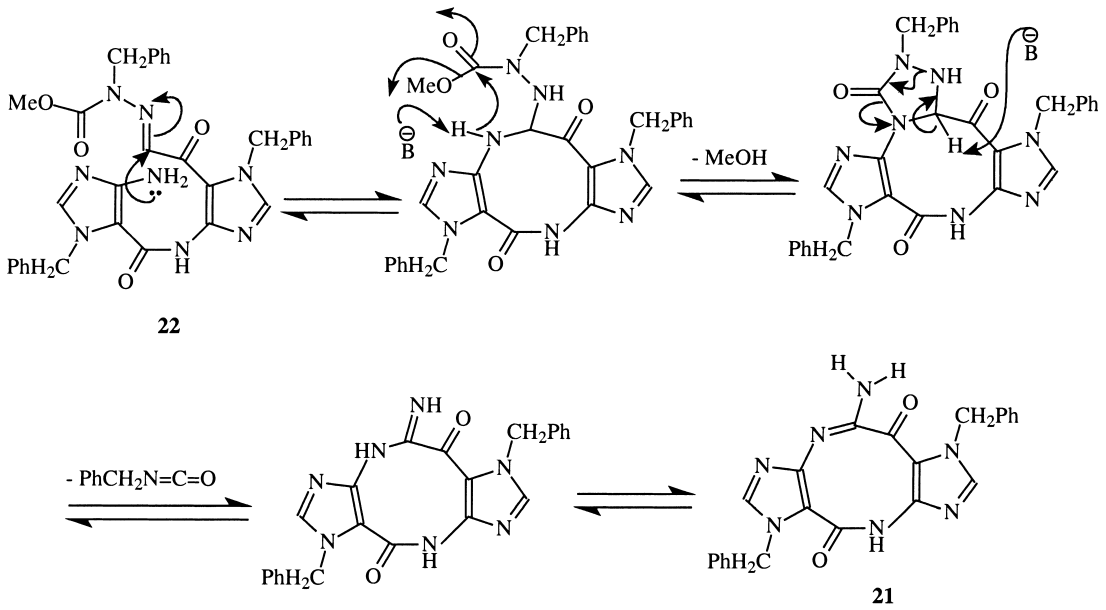
Scheme 6.

These mass spectral data, coupled with their NMR data, led to the proposed structures **20** and **21** for these two products (Scheme 6). Tentative reaction pathways for the formation of the **20** and **21** have been outlined in Schemes 7 and 8, respectively. Apparently, at a low temperature, compound **18** could preferably exist in a sterically less crowded form **18a**. The latter is likely to undergo intermolecular condensation, rather than intramolecular, with a loss of molecules of hydrogen cyanide, methanol, and *N*-benzyl isocyanate, to form the dimeric intermediate **22**. Subsequent intramolecular condensation of **22** with a loss of second molecule each of hydrogen cyanide, methanol, and *N*-benzyl isocyanate would produce the observed novel bis-imidazodiazocinedione (**20**). The reaction pathway for the formation of **21** is similar, with the exception that the final intramolecular ring-closure of **22** occurs at the hydrazone junction, instead of carbonyl, of the side-chain (see Scheme 8).

The above results led us to the following conclusions: (a) The employed 0°C is too low for effecting the desired intramolecular condensation of **18** to form **2c**, and (b) the electrophilicity of the concerned side-chain carbonyl group where the ring-closure is supposed to take place, is inadequate for nucleophilic attack as it is flanked by two electron-donating methoxy and hydrazino functionalities (viz a carbonate or a urea). To make the matter worse, the concerned amino nucleophile attached to the imidazole ring is also deactivated as it is conjugated to the carbonyl group (viz amide). Accordingly, we decided to replace the methoxycarbonyl group with the highly electrophilic *p*-nitrophenoxycarbonyl functionality. Thus, compound **18** was treated with excess sodium methoxide in methanol to form **23** (Scheme 9), which was further reacted with *p*-nitrobenzene chloroformate to obtain the desired **24** in 84% yield. Finally, the latter was ring-closed at room temperature in the presence of 4-dimethylaminopyridine (DMAP) to afford the target **2c** as a yellow solid in low



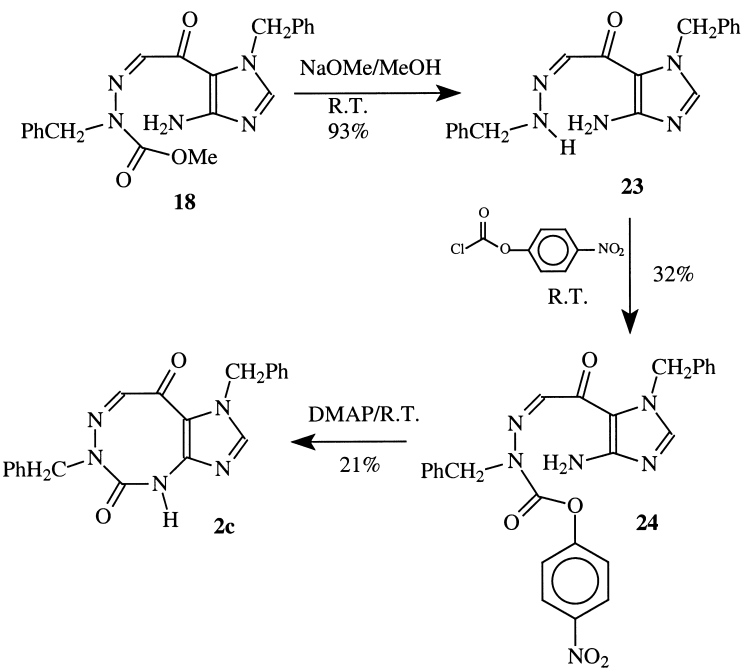
Scheme 7.



Scheme 8.

yield (21%). A TLC of the initial reaction mixture showed the presence of a number of other side products besides the target **2c**, one of which had an identical R_f as that of the authentic xanthine analogue **19** isolated earlier. No further attempts were made to isolate or purify these other products. The ^1H and ^{13}C NMR, mass spectral, and microanalytical data of **2c** are consistent with the structure as assigned. Further attempts to increase the yields of **2c** as well as its conversions into the corresponding nucleoside–nucleotide analogues by sequential debenzylation, and ribosylation–phosphorylation procedures that are well established in this lab,[1] are currently in progress.

Finally, in an attempt to confirm the intermediacy of **2c** in the earlier observed rearrangement of **18** to **19** (see Scheme 5), compound **2c** was heated in a mixture of sodium hydride and dimethyl sulfoxide at 50°C. A TLC comparison in three different solvents showed complete conversion of **2c** into **19** in less than an hour. The ^1H NMR of the product was identical to that of **19** obtained from **18**.



Scheme 9.

3. Conclusion

A novel ring-expanded congener of purine containing a 5:8-fused imidazo[4,5-*e*][1,2,4]triazocine ring system has been synthesized in 10 steps starting from an imidazole derivative. The compound undergoes facile base-catalyzed rearrangement to form a 5:6-fused xanthine analogue. The undertaken synthetic approach unravelled a number of interesting ring transformations.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 80, 300 or 500 MHz on an IBM NR/80, a GE QE-300, or a GE GN-500 spectrometer, respectively. ^{13}C NMR spectra were run on the GE QE-300 spectrometer operating at 75 MHz. The reported spectral data are relative to Me_4Si as an internal reference standard. Multiplicity is designated by the abbreviation, s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet, m=multiplet, br=broad, and ap=apparent. Deuterium oxide was used to verify the presence of exchangeable protons. Electron impact (EI) or chemical ionization (CI) mass spectra were recorded at 70 eV on a Hewlett Packard 5988A mass spectrometer. The fast atom bombardment (FAB) mass spectra were recorded at the Mass Spectral Facility, Department of Biochemistry, Michigan State University, East Lansing, MI. Infrared spectra were obtained on a Perkin–Elmer 1420 ratio recording instrument. Ultraviolet spectra were recorded on a Gilford Response UV–VIS spectrophotometer. X-Ray diffraction analyses were carried out at the Department of Chemistry, Southern Methodist University, Dallas, TX on an automatic Nicolet R3m/V diffractometer. Elemental Microanalyses were performed by Atlantic Microlab, INC., Norcross, Georgia. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Dry solvents were prepared as follows: toluene was distilled over sodium; tetrahydrofuran was first dried over CaH_2 and then distilled over sodium. Dry solvents were stored over 4 Å molecular sieves.

4.1.1. 1-Benzyl-5-β-(dimethylamino)ethylene-4-nitroimidazole (4). To a 250 mL three-neck, round-bottom flask equipped with a condenser and guard tube was placed **3** (10.0 g, 0.046 mol). The solid was dissolved by the addition of DMF (100 mL) before adding DMF–DMA (6.00 g, 0.0504 mol) by a syringe. The reaction mixture was stirred at room temperature and trifluoroacetic acid (TFA) (0.1 mL) was added. The mixture was heated to reflux for 5–24 h until complete formation of a slower moving, UV-absorbing compound as observed by TLC (silica gel, $CHCl_3$–acetone, 1:1). The mixture was then evaporated to dryness resulting in a dark red oil. The oil was covered with toluene and refrigerated overnight to form a crystalline solid. The solid was recrystallized from toluene to give red crystals; yield 10.6 g (85%): mp 148.5–149.5°C; ^{1}H NMR (DMSO-d_6) δ 7.82 (d, 1H, J=13.51 Hz, side-chain β-CH), 7.72 (s, 1H, imidazole CH), 7.32 (m, 5H, PhH's), 5.31 (s, 2H, CH_2), 5.13 (d, 1H, J=13.20 Hz, sidechain α-CH), 2.83 (s, 6H, $N(CH_3)_2$; MS (EI) m/z 272 (M^+), 255, 217, 181, 134, 107, 91, 65. Anal. calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.83; H, 5.96; N, 20.46.

4.1.2. 5-(2-Acetoxy)ethylene-1-benzyl-4-nitroimidazole (5). To a dry 250 mL three-neck flask equipped with a magnetic stirring bar, a condenser, and a guard tube, was added **4** (2.00 g, 7.34 mmol). The solid was dissolved by the addition of acetonitrile (100 mL). Added to this solution was acetic anhydride (40.0 mL, 0.424 mol), followed by ammonium acetate (0.85 g, 11.0 mmol). The reaction mixture was refluxed for 10.5 h. The mixture was then rotary evaporated to dryness and the residue was adsorbed onto silica gel (40–63 μm particle size), using acetonitrile (100 mL). This was loaded onto a flash silica gel column (42 g) and eluted with chloroform. The combined fractions were evaporated to dryness to give a golden yellow oil. The ^{1}H NMR of the oil indicated the presence of *cis* and *trans* isomers (1:1). The oil was covered with ethyl acetate and allowed to stand in a refrigerator overnight to get the *trans* isomer as a yellow crystalline solid. Evaporation of the filtrate resulted in an oil which was covered with ethanol to give the *cis* isomer as a yellow solid. Combined yield 1.47 g (70%): *cis* isomer mp 82–84°C; ^{1}H NMR (DMSO-d_6) δ 8.01 (s, 1H, imidazole CH), 7.44 (d, 1H, J=7.02 Hz, CH), 7.07–7.34 (m, 5H, PhH's), 6.00 (d, 1H, J=6.96 Hz, CH), 5.27 (s, 2H, CH_2), 2.01 (s, 3H, CH_3); *trans* isomer mp 129–130°C; ^{1}H NMR (DMSO-d_6) δ 8.07 (d, 1H, J=12.8 Hz, CH), 8.03 (s, 1H, imidazole CH), 7.07–7.34 (m, 5H, PhH's), 6.52 (d, 1H, J=12.8 Hz, CH), 5.41 (s, 2H, CH_2), 2.21 (s, 3H, CH_3); MS (EI) m/z 287 (M^+). Anal. calcd for $C_{14}H_{13}N_3O_4$ (mixture of *cis* and *trans*): C, 58.53; H, 4.56; N, 14.63. Found: C, 58.53; H, 4.61; N, 14.61.

4.1.3. 1-Benzyl-4-nitroimidazole-5-acetaldehyde (N^2-acetyl)hydrazone (7). To a 100 mL two-neck round-bottomed flask was added **5** (0.54 g, 1.88 mmol) and acetonitrile (15 mL). The mixture was stirred until the solid completely dissolved. The solution was cooled in an ice-water bath, and hydrazine monohydrate (0.117 mL, 2.26 mmol) was added, when the color of the reaction mixture turned reddish brown. The pale green solid that separated after about 15–20 min was filtered out, and the filtrate was allowed to stand in a refrigerator for about 6–7 h. The colorless solid that separated was recrystallized from acetonitrile to obtain **7** (0.51 g, 90%): mp 168–169.5°C; ^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1H, ex. w/D_2O), 7.95 (s, 1H), 7.50–7.16 (m, 6H), 5.34 (s, 2H), 3.96 (s, 2H), 1.81 (s, 3H); IR (KBr) 3420 (NH), 1680 (CO), 1555 (N=CH), 1480 (NO_2), 1420 (CH_2), 1345 (NO_2) cm^{-1}. Anal. calcd for $C_{14}H_{15}N_5O_3$: C, 55.81; H, 5.02; N, 23.24. Found: C, 55.53; H, 5.12; N, 23. 28.

4.1.4. 1-Benzyl-4-nitroimidazole-5-acetaldehyde (N^2-carbomethoxy)hydrazone (8). *Method A*. To an oven-dried 100 mL two-neck roundbottom flask equipped with a magnetic stirrer, a condenser, and a guard tube, was added **5** (1.50 g, 5.22 mmol), followed by acetonitrile (50 mL). To the resulting yellow solution was added methyl carbazate (1.18 g, 13.1 mmol), and the reaction mixture was heated to reflux for 46 h. The mixture was allowed to cool, extracted with chloroform (3×50 mL), and washed with water (2×25 mL). The combined extracts were dried over $MgSO_4$, filtered through an acrodisc filter (0.45 mm), and

the filtrate was rotary evaporated to dryness, affording a reddish-orange oil. The oil was further dried using a vacuum pump (10 mm Hg) to obtain **8** as a foam; yield 1.56 g (94%): ^{1}H NMR (DMSO-d_6) δ 10.08 (s, 1H, ex. w/D_2O, NH), 7.91 (s, 1H, CH), 7.25–7.34 (m, 6H, PhH's and CH), 5.32 (s, 2H, benzyl CH_2), 3.93 (d, 2H, J=4.3 Hz, CH_2), 3.60 (s, 3H, OCH_3); IR (KBr) 3420 (NH), 1735 (C=O), 1495 (NO_2), 1350 (NO_2), 1030 (C–N) cm^{-1}. Anal. calcd for $C_{14}H_{15}N_5O_4$: C, 52.99; H, 4.76; N, 22.07. Found: C, 52.92; H, 4.80; N, 21.98.

Method B. A flame-dried 250 mL-flask was charged with **4** (8.0 g, 0.029 mol) and to this solid was added acetonitrile (150 mL). After allowing the solid to dissolve, methyl carbazate (2.48 g, 0.018 mol) was added, and the dark red solution was heated to reflux for 5 days. The mixture was diluted with water (150 mL) and extracted with $CHCl_3$ (2×100 mL). The combined organic extracts were then washed with water (2×50 mL), dried over $MgSO_4$, filtered, and the filtrate evaporated in vacuo (10 mm Hg) to give **8** as a foam in 95% yield. Spectral data and TLC behavior of this compound were identical to that of **8** obtained by Method A described above.

4.1.5. 1-Benzyl-4-nitroimidazole-5-glyoxal (N^2-methoxycarbonyl)hydrazone (9). In a flame-dried 50 mL two-neck round-bottom flask was placed sodium hydride (0.15 g, 5.0 mmol). The solid was washed twice with dry toluene (2 mL) before adding dry tetrahydrofuran (THF) (20 mL) to the reaction flask. To this suspension was added a solution of **8** (0.202 g, 0.636 mmol) in THF (5 mL). The suspension went from a reddish orange color to dark red. While stirring, O_2 gas was passed through the reaction mixture for 3–5 h. The mixture was allowed to stir overnight. It was neutralized with 1N HCl, diluted with 30 mL of water, and extracted with chloroform (3×25 mL). The combined extracts were dried over anhydrous $MgSO_4$ and then purified by flash chromatography, using a 30 g flash silica gel column. The product was eluted with chloroform–acetone (9:1). The oil obtained from evaporation of the appropriately combined fractions was crystallized from acetone–petroleum ether (bp 35–60°C) to yield white needles or from methanol overnight to give a white crystalline solid; yield 116 mg (27%): ^{1}H NMR (DMSO-d_6) δ 11.9 (s, 1H, NH, ex. w/D_2O), 8.17 (s, 1H, imino CH), 7.63 (s, 1H, imidazole CH), 7.12–7.59 (m, 5H, PhH's), 5.32 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3); IR (KBr) 3180 (NH), 1755 (C=O), 1665 (C=O), 1550, 1520, 1440 (NO_2), 1390, 1345 (NO_2), 1245, 1215, 1180, 1090, 960, 910, 835, 750, 700 cm^{-1}; MS (CI, w/*i*-butane) m/z 332 (MH^+, 14), 285 (1.9), 256 (2.3), 218 (100), 204 (46). Anal. calcd for $C_{14}H_{13}N_5O_5$: C, 50.75; H, 3.95; N, 21.14. Found: C, 50.64; H, 4.00; N, 21.00.

4.1.6. 4-Amino-1-benzylimidazole-5-glyoxal (N^2-methoxycarbonyl)hydrazone (10). To a 100 mL round-bottom flask was added **9** (0.186 g, 0.548 mmol) and the solid was covered with methanol (50 mL). The flask was warmed to form a uniform solution, and Pd–C (0.10 g) was added and the resulting slurry was stirred for 0.5 h and filtered. The filtrate was transferred to a hydrogenation bottle and Pd–C (0.15 g) was added before hydrogenation at 30 psi for 21 min. The mixture was filtered in vacuo and the filtrate was evaporated to dryness onto flash silica gel (1 g, 40–63 μm particle size). The residue was suspended in $CHCl_3$ and the resulting slurry was loaded onto a flash chromatography column packed with 10.0 g of flash silica gel. The column was eluted using a mixture of $CHCl_3$–acetone (4:1) and the appropriately combined fractions were rotary evaporated to dryness. The resulting yellow solid was triturated with a mixture of petroleum ether (bp 35–60°C) and MeOH (10:1) and filtered to yield **10**; yield 123 mg (73%): mp 193.5–195°C (dec.); ^{1}H NMR (DMSO-d_6) δ 11.56 (s, 1H, NH), 7.80 (s, 1H, imino CH), 7.45 (s, 1H, imidazole CH), 7.07–7.33 (m, 7H, PhH's and NH_2), 5.44 (s, 2H, CH_2), 3.73 (s, 3H, OCH_3); IR (KBr) 3450 (NH_2), 3390 (NH_2), 3280 (NH), 3250, 1720 (C=O), 1650 (C=O), 1560, 1550, 1460, 1445, 1430, 1255, 1231, 1135 (C–O), 1080 cm^{-1}; UV λ_{max} (MeOH) 254.0, 377.0 nm; MS (CI, w/*i*-butane) m/z 302 (MH^+, 100). Anal. calcd for $C_{14}H_{15}N_5O_3$: C, 55.81; H, 5.02; N, 23.24. Found: C, 55.82; H, 5.06; N, 23.15.

4.1.7. 5-Acetyl-4-amino-1-benzylimidazole (11). Compound **10** (59 mg, 0.196 mmol) was placed into a flame-dried 100 mL two-neck flask equipped with a magnetic stirrer, a condenser, and a guard tube. The solid was partially dissolved by the addition of MeOH (5 mL). Freshly prepared solution of NaOMe in MeOH (0.051 g of Na (2.21 mg.atom) in 10 mL MeOH) was added slowly and the dark yellow solution was heated to reflux. A TLC (silica gel, $CHCl_3$–acetone, 1:1) of the reaction mixture after 16 h indicated complete conversion of the starting material into a new UV-absorbing spot with a lower R_f. The reaction mixture was neutralized with 1N HCl and extracted with $CHCl_3$ (2×15 mL). The combined extracts were dried over $MgSO_4$, filtered, and the filtrate was evaporated to obtain a brown solid. The solid was dissolved in MeOH and the solution was treated with decolorizing carbon. Filtration and evaporation of the solvent left a solid residue which upon trituration with ether afforded an off white solid; yield 37 mg (87%): mp 161–163°C; ^{1}H NMR (DMSO-d_6) δ 7.66 (s, 1H, imidazole CH), 7.09–7.33 (m, 5H, PhH's), 5.90 (s, 2H, NH_2, ex. w/D_2O), 5.34 (s, 2H, CH_2); IR (KBR) 3430 (NH_2), 3390, 3320 (NH_2), 1615 (C=O), 1530, 1470 (NO_2), 1380 (NO_2), 1310, 1235, 1085, 1070, 1030, 955 cm^{-1}; MS (CI, w/*i*-butane) m/z 216 (MH^+, 100).

4.1.8. 1-Benzyl-4-nitroimidazole-5-glyoxal (N^2-benzyl-N^2-methoxycarbonyl)hydrazone (16). *Method A*. To a flame-dried 50 mL two-neck round-bottom flask equipped with a condenser, a magnetic stirrer, and a guard tube, was added sodium hydride (0.0362 g, 1.51 mmol). The solid was washed with dry toluene (2×2 mL) to remove the adhering oil before adding dry THF (20 mL), followed by benzyl bromide (0.216 mL, 1.81 mmol). The solution was cooled with an ice bath. Compound **10** (0.205 g, 0.604 mmol) was placed into a separate vial, and the vial was flushed with N_2. The solid was dissolved in THF (5 mL) and the resulting yellow solution was cooled in an ice bath. The cold solution was then added dropwise to the flask, using a syringe drive (flow rate=0.06 mL min^{-1}). The reaction mixture was stirred at room temperature for 24 h, neutralized with 0.67N HCl, diluted with 30 mL of water, extracted with $CHCl_3$ (3×30 mL), and the combined extracts were dried over $MgSO_4$. After filtration and evaporation, the product

was purified by flash chromatography by first eluting the column with $CHCl_3$ and then with $CHCl_3$–acetone (19:1). The yellow oil obtained after evaporation of the appropriately combined fractions was crystallized from toluene–petroleum ether (bp 35–60°C) to yield **16** as a white solid; yield 0.123 g (48%): mp 128–130°C; ^{1}H NMR ($CDCl_3$) δ 7.04–7.43 (m, 12H, imidazole CH, imino CH, PhH's), 5.19 (s, 3H, OCH_3); IR (KBr) 1725 (C═O), 1670 (C═O), 1560, 1510, 1445 (NO_2), 1390, 1340 (NO_2), 1310, 1280, 1275, 1175 (C–O), 1080 cm^{-1}; MS (CI, w/*i*-butane) *m*/*z* 422 (MH^+, 23), 390 (3.2). Anal. calcd for $C_{21}H_{19}N_5O_5$: C, 59.85; H, 4.54; N, 16.62. Found: C, 59.95; H, 4.57; N, 16.58.

Method B. In a flame-dried 50 mL two-neck flask equipped with a guard tube and a magnetic stirrer, was placed sodium hydride (11 mg, 0.454 mmol). The solid was washed with dry toluene (2×2 mL) to remove the adhering oil before covering with dry THF (30 mL). Benzyl bromide (0.357 mL, 3.15 mmol) was added and the mixture was cooled in an ice bath. To the cold solution was added **8** (0.100 g, 0.315 mmol) at which point the colorless solution became red. The solution was allowed to come to room temperature and O_2 gas was passed through the solution for 3–5 h. The reaction mixture was stirred for an additional 10 h, neutralizing with 1N HCl, and diluted with water (25 mL). The resulting bilayered solution was extracted with $CHCl_3$ (3×30 mL), and the combined extracts were dried over MgSO4. After filtration, the compound was directly adsorbed onto flash silica gel (40–63 μm particle size) and then loaded onto a 25-g flash silica gel column. The column was eluted with hexanes–ethyl acetate (2:1) to give a yellow oil, which was crystallized by dissolving in ethyl acetate and adding hexanes until the solution became turbid. After allowing this solution to stand for some time, a white crystalline solid was formed; yield 24 mg (18%). Spectral data, melting point, and TLC behavior of this solid were identical to that of **16** obtained by Method A described above.

4.1.9. *N*,*N*′-Bis[(1-benzylimidazole-5-glyoxal (N^2-benzyl-N^2-methoxycarbonyl)hydrazone)-4-yl]-diimide (17). Compound **16** (0.9 g, 2.14 mmol) was dissolved in MeOH (150 mL), and to this solution was added 10% Pd–C (0.20 g). This suspension was allowed to stir for 0.5 h and the Pd–C was filtered off. The filtrate was placed into a hydrogenation bottle over Pd–C (0.40 g) and the mixture was hydrogenated at 10–15 psi for 1 h. A TLC (silica gel, $CHCl_3$–acetone, 4:1) of the reaction mixture showed the formation of a UV-absorbing, slower moving compound as compared to the starting material. The suspension was transferred to a 250 mL beaker and heated while stirring for 20–25 min. The color of the suspension changed from yellow to orange and the TLC (silica gel, $CHCl_3$–acetone, 4:1) at this point showed a single spot that had an approximately equal R_f as compared to the starting material, but a higher R_f as compared to the intermediate spot observed before heating. The suspension was filtered, concentrated, and allowed to crystallize while standing in the refrigerator overnight. Orange-red needles were recovered after filtration which could be recrystallized from toluene–petroleum ether (35–60°) or acetonitrile–MeOH to give orange needles; yield 0.380 g (46%): mp 212–214°C; ^{1}H NMR (DMSO-d_6) δ 8.57 (s, 2H, two CH), 8.44 (s, 2H, two CH), 7.17–7.34 (m, 20H, PhH's), 5.60 (s, 4H, two CH_2), 5.42 (s, 4H, two CH_2), 3.74 (s, 6H, two OCH_3); IR (KBr) 1720 (C═O), 1650 (C═N), 1550, 1515, 1495, 1440, 1400, 1330, 1160, 1125, 1060, 1010, 945, 905, 900, 885, 795, 765, 735, 695 cm^{-1}; UV λ_{max} (MeOH): 274.5, 391.0 nm. Anal. calcd for $C_{42}H_{38}N_{10}O_6$: C, 64.77; H, 4.91; N, 17.98. Found: C, 64.77; H, 4.92; N, 17.97.

4.1.10. 4-Amino-1-benzylimidazole-5-glyoxal (N^2-benzyl-N^2-methoxycarbonyl)hydrazone (18). Compound **16** (0.403 g, 0.956 mmol) was dissolved in methanol (125 mL) with gentle warming and to this was added 10% Pd–C (0.10 g). This suspension was allowed to stir for 0.5 h and the Pd–C was filtered off. The filtrate was placed into a hydrogenation bottle over Pd–C (0.15 g) and the mixture was hydrogenated at 30 psi for 20–40 min. The suspension was filtered in vacuo and the filtrate was evaporated to dryness to obtain a yellow solid. The solid was triturated with methanol and recrystallized from an excess of methanol to give yellow crystals; yield 0.231 g (62%): mp 176–177°C; ^{1}H NMR (DMSO-d_6) δ 7.81 (s, 1H, imino CH), 6.99–7.40 (m, 13H, PhH's+imidazole CH+NH_2 ex. w/D_2O), 5.38 (s, 2H, amide benzyl CH_2), 5.16 (s, 2H, imidazole benzyl CH_2), 3.89 (s, 3H, OCH_3); IR (KBr) 3370 (NH_2), 3290 (NH_2), 1725 (C═O), 1625, 1610, 1605,1565, 1535, 1450, 1435, 1405, 1375, 1305, 1210 (C–O), 1175, 1135, 765, 740, 695 cm^{-1}. Anal. calcd for $C_{21}H_{21}N_5O_3$: C, 64.44; H, 5.41; N, 17.89. Found: C, 64.34; H, 5.43; N, 17.77.

4.1.11. 1,7-Dibenzylxanthine (19). A 50-mL three-neck flask, equipped with a reflux condenser, a thermometer, a guard tube, and a magnetic stirring bar, was charged with 60% NaH (7.66 mg, 0.319 mmol). After washing the NaH with dry toluene (1.5 mL), DMSO (15 mL) was added to the reaction flask through a syringe. In a separate 50-mL flask was placed **18** (50 mg, 0.13 mmol), and after flushing the flask with a stream of nitrogen, the solid was dissolved in DMSO (15 mL). The yellow solution was transferred to the reaction flask using a syringe, and added dropwise over a 50-minute period. The reaction mixture was heated to 50°C and maintained at less than 60°C for about 2 h. The reaction mixture became reddish brown in color and eventually changed back to a light yellow color. The work-up consisted of adding 1N HCl until neutral. The resulting solution was poured into ice-water, and extracted with EtOAc (4×50 mL). The combined organic extract was washed with water (8×75 mL), and dried over anhydrous $MgSO_4$. The solution was filtered in vacuo and the filtrate was evaporated to dryness, and the resulting solid was triturated with MeOH to give an off-white solid. The solid was recrystallized from MeOH to afford nearly colorless crystals of 19; yield 17 mg (40%): mp 223.5–225°C; ^{1}H NMR (DMSO-d_6) δ 12.02 (s, 1H, NH, exchangeable with D_2O), 8.19 (s, 1H, CH), 7.21–7.32 (m, 10H, Ph-H's), 5.45 (s, 2H, CH_2), 4.99 (s, 2H, CH_2); IR (KBr) 3440 (NH), 1710 (C═O), 1555, 1485, 1445, 1415, 1380, 1345, 1310, 1255, 1205, 1110, 1050, 760, 745, 720, 705, 690, 630 cm^{-1}; UV (MeOH) λ_{max} 270.5 nm. Anal. calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.85. Found: C, 68.66; H, 4.90; N, 16.91.

4.1.12. 1,6-Dibenzyl-4,5,9,10-tetrahydroimidazo[4,5-*b*:4′,5′-*f*][1,5]diazocine-5,10-dione (20) and 10-amino-1,6-dibenzyl-4,5,11-trihydrodiimidazo[4,5-*f*:4′,5′-*b*]-[1,5]diazocine-5,11-dione (21). A 25-mL two-neck

round-bottomed flask, equipped with a stirring bar and a guard tube, was charged with NaH (24 mg, 1.04 mmol) (1.5 equiv., 60%). After washing the solid with dry toluene (1.5 mL), a mixture of DMSO (2 mL)–THF (2 mL) was added to the flask by a syringe. The reaction flask was cooled to 0°C. In a separate 25 mL flask was placed **18** (160 mg, 0.41 mmol) and this flask was then flushed with a stream of nitrogen gas before dissolving the solid by the addition of a mixture of DMSO (6 mL)–THF (6 mL). The yellow solution of **18** was transferred by a syringe to the reaction flask containing NaH–DMSO by a syringe drive at a rate of 3.9 mL h^{-1}. After the addition of the starting material was complete, the temperature of the reaction mixture was allowed to reach room temperature very slowly. The color of the reaction mixture changed from yellow to orange, and then to dark red. After 16 h, a TLC (silica gel) showed two slower moving, UV-absorbing spots as compared with the starting material, which was no longer present. The reaction solution was transferred to another flask, and evaporated to dryness on a Kügelrohr apparatus at a temperature lower than 35°C. Ice water was added to the residue, and to this aqueous solution was added 1N HCl dropwise until the solution became neutral (litmus). The resulting aqueous solution was extracted with EtOAc(4×25 mL). The combined organic layer was washed with water (3×50 mL), and dried over anhydrous $MgSO_4$. The organic layer was concentrated to near dryness, which resulted in an orange precipitate. The filtration of the precipitate yielded 52 mg (32%) of **20**, mp 197–200°C (dec.); ^{1}H NMR (DMSO-d_6) δ 8.04 (s, 1H, CH), 7.92 (s, 1H, CH), 7.66 (s, 1H, NH, ex. w/D_2O), 7.39–7.06 (m, 10H, Ph H=s), 5.56 (s, 2H, CH_2), 5.50 (s, 2H, CH_2); IR (KBr) 3405 (NH), 1660 (C=O), 1640, 1605, 1530, 1525, 1500, 1450, 1365, 1340, 1110, 995, 690 cm^{-1}; UV (MeOH) λ_{max} 441 nm; HRMS (FAB) *m/z*: MH^+ calcd for $C_{22}H_{19}N_6O_2$, 399.1569; found, 399.1568; Anal. calcd for $C_{22}H_{18}N_6O_2$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.48, H, 4.68; N, 21.23.

The remaining filtrate was further purified by column chromatography (silica gel, 40–63 μm particle size), eluting with ($CHCl_3$–MeOH, 14:1). The corresponding UV-absorbing fractions were pooled and evaporated to dryness. The resulting yellow solid was recrystallized from EtOAC-petroleum ether (bp 40–60°C) to yield 50 mg (29%) of **21** as a bright yellow solid, mp 277–279°C; ^{1}H NMR (DMSO-d_6) δ 12.03 (s, 1H, NH, ex. w/D_2O), 8.52 (s, 1H, CH), 7.96 (s, 1H, CH), 7.51–6.93 (m, 12H, Ph H=s and NH_2 ex. w/D_2O), 5.58 (s, 2H, CH_2), 5.43 (s, 2H, CH_2); IR (KBr) 3490 (NH), 3420 (NH_2), 3390 (NH_2), 1685 (C=O), 1670, 1565, 1550, 1520, 1445, 1380, 1215, 1140, 1130, 880, 870, 740, 710, 695, 685, 665 cm^{-1}; UV (MeOH) λ_{max} 377, 327, 312, 256.5 nm; (pH 1) λ_{max} 360.5 nm; (pH 12) λ_{max} 329, 273.5, 243 nm; HRMS (FAB) *m/z*: MH^+ calcd for $C_{23}H_{20}N_7O_2$, 426.1678; found, 426.1697; Anal. calcd for $C_{23}H_{19}N_7O_2$: C, 64.93; H, 4.50; N, 23.05. Found: C, 65.14, H, 4.63; N, 23.18.

4.1.13. 4-Amino-1-benzylimidazole-5-glyoxal (N^2-benzyl)hydrazone (23). A solution of NaOMe–MeOH was prepared by dissolving Na (6.8 mg, 0.296 mg.atom) in MeOH (7 mL). Compound **18** (20 mg, 0.0516 mmol) was placed in a separate vial and flushed with a stream of N_2 before dissolving it in a minimum quantity of MeOH. This solution was added dropwise to the reaction flask by a syringe, and the reaction mixture was stirred at room temperature. A TLC (silica gel, $CHCl_3$–acetone, 4:1) taken after 5.5 h showed complete conversion to a new spot with a lower R_f as compared to the starting material. The reaction was neutralized with 1N HCl and extracted with ethyl acetate (2×15 mL). The organic extracts were dried over $MgSO_4$, filtered, and the filtrate evaporated to dryness. The residue was triturated with ethyl acetate–petroleum ether (35–60°C) to give **23** as a solid, yield 16 mg (93%): mp 152–154.5°C; ^{1}H NMR (DMSO-d_6) δ 8.91 (t, 1H, NH ex. w/D_2O), 7.66 (s, 1H, imidazole CH), 7.00–7.47 (m, 11H, PhH's and hydrazone–CH=), 6.23 (s, 2H, NH_2 ex. w/D_2O), 5.37 (s, 2H, imidazole benzyl CH_2) 4.37 (d, 2H, CH_2); MS (FAB) 334 (MH^+); Anal. calcd for $C_{19}H_{19}N_5O$: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.30; H, 5.83; N, 20.88.

4.1.14. 4-Amino-1-benzylimidazole-5-glyoxal (N^2-benzyl-N^2-*p*-nitrophenoxycarbonyl)-hydrazone (24). To a solution of *p*-nitrophenyl chloroformate (72 mg, 0.36 mmol) in dry acetonitrile (40 mL), contained in a 50-mL three-neck flask maintained under N_2 atmosphere, was added **23** (96 mg, 0.29 mmol). A precipitate began to form in the yellow solution in 5–10 min. The reaction mixture was stirred at room temperature for 24 h, neutralized with 2% aq.$NaHCO_3$, and extracted with EtOAc (2×50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated to dryness on a rotary evaporator. The residual golden brown oil was adsorbed onto flash silica gel (40–63 μm particle size) by coevaporation with EtOAc (25 mL), and loaded onto a flash silica gel column (6 g). The column was eluted with a 2:1 mixture of EtOAc–hexanes (bp 68–69°C), and the appropriate UV-absorbing fractions with an approximate R_f=0.2 were pooled and evaporated. The yellow residue was triturated with a mixture of EtOAc–petroleum ether (bp 30–65°C) to yield a bright yellow solid which was recrystallized from the same solvent system to give **24**; yield 39 mg (32%): mp 139–141°C; ^{1}H NMR (DMSO-d_6) δ 8.35 (d, 2H, *J*=8.5 Hz, NO_2PhH's), 7.83 (s, 1H, imidazole CH), 7.66 (d, 2H, *J*=8.5 Hz, NO_2PhH's), 7.38–7.02 (m, 13H, PhH's+–N=CH of side-chain, +NH_2 ex. w/D_2O), 5.39 (s, 2H, CH_2), 5.31 (s, 2H, CH_2); IR (KBr) 3400 (NH_2), 3280 (NH_2), 1730 (C=O), 1605, 1560 cm^{-1}; MS (FAB) *m/z* 499 (MH^+); Anal. calcd for $C_{26}H_{22}N_6O_5{\cdot}0.5H_2O$: C, 61.48; H, 4.53; N, 16.48. Found: C, 61.07; H, 4.68; N, 16.26.

4.1.15. 1,6-Dibenzylimidazo[4,5-*e*][1,2,4]triazocine-5,9-dione (2c). A mixture of **24** (390 mg, 0.78 mmol) and DMAP (200 mg, 1.6 mmol) in dry toluene (20 mL) was stirred at room temperature under N_2 atmosphere for 3 h. The solid precipitate that separated was filtered and purified by flash chromatography on a column of silica gel (20 g, 40–63 μm particle size), packed with $CHCl_3$, eluting with a mixture of $CHCl_3$–acetone (1:1). The appropriate UV-absorbing fractions were pooled and evaporated to obtain a bright yellow solid which was recrystallized from aceto-nitrile–petroleum ether (bp 30–65°C) to obtain yellow crystals of **2c**; yield 59 mg (21%): mp>250°C; ^{1}H NMR (DMSO-d_6) δ 11.84 (s, 1H, ex. w/D_2O, NH), 8.15 (s, 1H), 7.30–7.82 (m, 11H, PhH+CH), 5.53 (s, 2H, CH_2), 5.14 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 184.62 (C=O), 156.71 (C=O), 153.87, 150.19, 138.45, 134.52, 134.15, 132.62,

129.25, 128.43, 128.1, 127.71, 127.41, 115.73, 56.58, 55.23; MS (FAB) 360 (MH^+); Anal. calcd for $C_{20}H_{17}N_5O_2$: C, 66.85; H, 4.73; N, 19.50. Found: C, 66.70; H, 4.67; N, 19.38.

4.2. Single-crystal X-ray diffraction analyses

An appropriate crystal was mounted on a Nicolet R3m/V diffractometer. Final unit cell parameters were obtained by a least-squares fit of the angles of 24 accurately centered reflections ($16<2\theta<26°$). Intensity data were collected in the range of $3.5\leq2\theta\leq42.0°$ at −43°C using graphite monochromated Mo Kα (λ=0.71073 Å) radiation. The scan was $\theta/2\theta$, 2117 reflections were collected with 1916 unique with R_{int}=0.023. Three standard reflections monitored after every 150 reflections did not show any significant change in intensity during the data collection. The data were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct-methods with SHELXTL-Plus package.[7] Bloc-diagonal least-squares refinement was performed. Scattering factors were taken from the International Tables for X-ray Crystallography.[8] Hydrogen atoms, except those for methyl, were located on DF maps and refined with fixed isotopic temperature factors (U=0.08 Å^2). Details of analyses for each compound are given in the supplementary material.

Crystallographic data for ***9***. $C_{14}H_{13}N_5O_5$, M_r=363.3, P_1, a=9.387(4), b=9.898(4), c=11.265(5) Å, α=103.80(3)°, β=112.75(3)°, γ=101.42(3)°, V=886.8(7) Å^3, Z=2, ρ=1.36 g cm^{-3}, (Mo Kα)=0.71073 Å, μ=1.00 cm^{-1}. Final R=0.057 for 1494 reflections ($I>3.0\sigma(I)$).

Crystallographic data for ***16***. $C_{21}H_{19}N_5O_5$, M_r=421.4, $P2(1)/c$, a=14.122(3), b=8.560(2), c=17.710(4) Å, β=103.76(2)°, V=2079.6(7) Å^3, Z=2, ρ=1.37 g cm^{-3}, (Mo Kα)=0.71073 Å, μ=1.00 cm^{-1}. Final R 0.039 for 1428 reflections ($I>3.0\sigma(I)$).

Crystallographic data for ***17***. $C_{42}H_{40}N_{10}O_6$, M_r=780.8, $P2_1/n$, a=14.932(4), b=5.806(1), c=21.992(5) Å, β=95.40(2)°, V=1898.8(8) Å^3, Z=2, ρ=1.37 g cm^{-3}, (Mo Kα)=0.71073 Å, μ=0.88 cm^{-1}. Final R=0.053 for 1148 reflections ($I>3.0\sigma(I)$).

Crystallographic data for ***19***. $C_{19}H_{16}N_4O_2$, M_r=332.4, $C2/c$, a=24.665(6), b=5.749(2), c=23.010(4) Å, β=103.94(2)°, V=3167(2) Å^3, Z=8, ρ=1.394 g cm^{-3}, (Mo Kα)=0.71073 Å, μ=0.094 cm^{-1}. Final R=0.028 for 1346 reflections ($I>3.0\sigma$ (I)).

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References

1. (a) Hosmane, R. S. Ring-Expanded (Fat) Nucleosides as Broad-Spectrum Anticancer and Antiviral Agents. *Current Topics in Medicinal Chemistry: Recent Developments in Antiviral Nucleosides, Nucleotides, and Oligonucleotides*, Hosmane, R. S., Ed.; Bentham Science, 2002; Vol. 2, pp 1093–1109. (b) Sood, R. K.; Bhadti, V. S.; Fattom, A. I.; Naso, R. B.; Korba, B. E.; Kern, E.; Hosmane, R. S. *Antiviral Res.* **2002**, *53*, 159. (c) Wang, L.; Hosmane, R. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2893. (d) Chen, H.-M.; Hosmane, R. S. *Molecules* **2001**, *6*, 203. (e) Gill, J.; Bretner, M.; Newman, R.; Kyprianou, N.; Hosmane, R. S. *Nucleosides Nucleotides* **2001**, *20*, 1043. (f) Chen, H.-M.; Hosmane, R. S. *J. Heterocycl. Chem.* **2000**, *37*, 951. (g) Bretner, M.; Beckett, D.; Sood, R.; Hosmane, R. S. *Bioorg. Med. Chem.* **1999**, *7*, 2931. (h) Rajappan, V. P.; Hosmane, R. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3649. (i) Hosmane, R. S.; Hong, M. *Biochem. Biophys. Res. Commun.* **1997**, *236*, 88.
2. (a) Hosmane, R. S.; Lim, B. B.; Burnett, F. N. *J. Org. Chem.* **1988**, *53*, 382. (b) Hosmane, R. S.; Lim, B. B.; Summers, M. F.; Siriwardane, U.; Hosmane, N. S.; Chu, S. C. *J. Org. Chem.* **1988**, *53*, 5309. (c) Hosmane, R. S.; Lim, B. B. *Heterocycles* **1988**, *27*, 31. (d) Hosmane, R. S.; Lim, B. B. *Synthesis* **1988**, 242. (e) Afshar, C.; Berman, H. M.; Sawzik, P.; Lessinger, L.; Lim, B. B.; Hosmane, R. S. *J. Crystallogr. Spectrosc. Res.* **1987**, *17*, 533.
3. (a) Freedman, J.; Huber, E. W. *J. Heterocycl. Chem.* **1990**, *27*, 343. (b) Peet, N. P. *Synthesis* **1984**, 1065. and the references cited therein. (c) Scheiner, P.; Frank, L.; Giusti, I.; Arwin, S.; Pearson, S. A.; Excellent, F.; Harper, A. P. *J. Heterocycl. Chem.* **1984**, *21*, 1817. (d) Bridson, P. K.; Davis, R. A.; Renner, L. S. *J. Heterocycl. Chem.* **1985**, *22*, 753. (e) Peet, N. P.; Sunder, S. *J. Heterocycl.Chem.* **1984**, *21*, 1807.
4. A preliminary account of this work was presented at the 11th International Round Table on Nucleosides Nucleotides, and Their Biological Applications, Katholieke Universiteit Leuven, Belgium, September 7–11, 1994 (Abstr. No. P-41); see the proceedings of the Round Table: Burnett, F. N.; Lim, B.; Hosmane, R. S. *Nucleosides Nucleotides* **1995**, *14*, 325.
5. Hosmane, R. S.; Bhan, A.; Rauser, M. E. *J. Org. Chem.* **1985**, *50*, 5892.
6. (a) Dauben, W. G.; Lorber, M.; Fullerton, C. S. *J. Org. Chem.* **1969**, *34*, 3587. (b) Hoston, J. R.; Pitts, E. H. *J. Org. Chem.* **1961**, *26*, 4151. (c) Naidu, M. V.; Rao, G. S. K. *Synthesis* **1979**, 144. (d) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576. (e) Floyd, D. M.; Moquin, R. V.; Atwal, K. S.; Ahmed, S. Z.; Spergel, S. H.; Gorgoutas, J. Z.; Malley, M. F. *J. Org. Chem.* **1990**, *55*, 5572.
7. Sheldrick, G. M. *SHELXTL-Plus*, Siemens Analytical X-Ray Instruments, Inc. USA, 1990.
8. *International Tables for X-ray Crystallography*; Kynock: Birmingham, 1974; Vol. 4.