Pergamon

Tetrahedron Letters, Vol. 35, No. 40, pp. 7469-7472, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01564-3

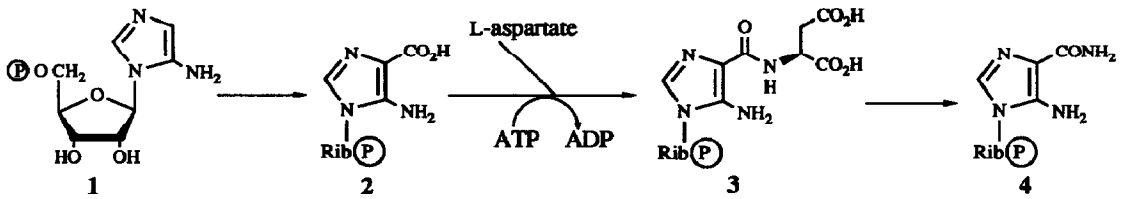
Synthesis of 5-Amino-4-sulfonamidoimidazole Nucleosides as Potential Inhibitors of Purine Biosynthesis, and of an Imidazothiadiazine Dioxide Analogue of Adenosine

A Scott Frame,[a] Grahame Mackenzie*[b] and Richard H. Wightman*[a]

[a]Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, U.K.
[b]School of Chemistry, University of Hull, Hull HU6 7RX, U.K.

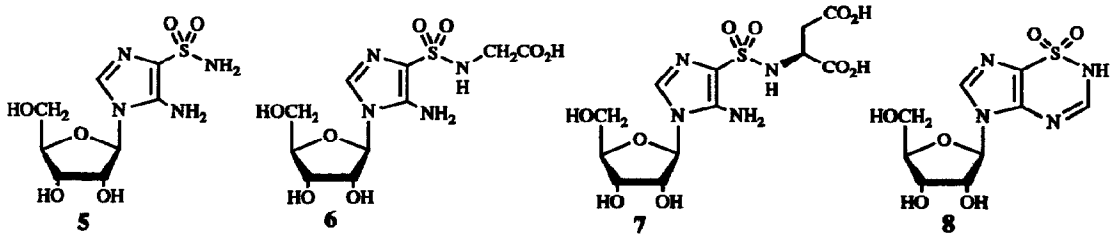
Abstract: 5-Amino-4-sulfonamido-1-(β-D-ribofuranosyl)imidazole **5** and two more complex sulfonamides **6** and **7** have been prepared as potential inhibitors of intermediate stages in the *de novo* biosynthesis of purine nucleotides; cyclization of a protected form of **5** gave 5-(β-D-ribofuranosyl)imidazo[4,5-*e*]-1,2,4-thiadiazine-1,1-dioxide **8**, a novel analogue of adenosine and inosine.

The pathway for the *de novo* biosynthesis of purines plays an essential role in rapidly proliferating tissues, and thus inhibition of the enzymes of this pathway has attracted attention in the search for new agents in anti-tumour chemotherapy.[1] The intermediate stages in purine nucleotide biosynthesis (Scheme 1) involve the enzyme-catalysed carboxylation of 5-aminoimidazole ribonucleotide (AIR, **1**) to give the 4-carboxycompound CAIR **2**,[2] the ATP-dependent linking of **2** with L-aspartate to give the *N*-succinylamide SAICAR **3**, and the subsequent elimination of fumaric acid to give the carboxamide AICAR **4**. The enzymic conversions of **1** to **2** and of **2** to **3** are closely linked in both mammalian[3] and avian tissues, with a bifunctional enzyme being involved in the latter case.[4] The conversion of **2** to **3** can be envisaged as involving the formation of an acyl phosphate by interaction of **2** with ATP, followed by reaction with L-aspartate *via* a tetrahedral intermediate. Thus this enzyme may well be susceptible to inhibition by appropriate transition state analogues.

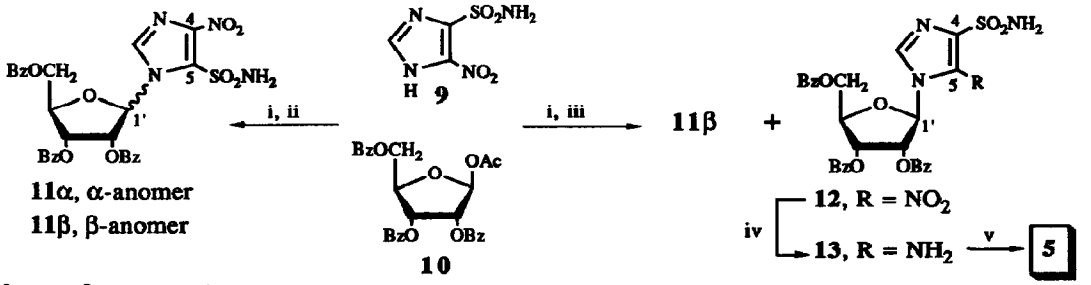


Scheme 1

We here describe the synthesis of the simple imidazole sulfonamide **5**, which can be regarded either as a substrate analogue of **2** and **4**,[5] or as a simple transition state analogue for the conversion of **2** to **3**, and also the more complex structures **6** and **7**, which incorporate wholly or partially the L-aspartyl unit. We also report the cyclization of an intermediate in the synthesis of **5**, leading to the novel imidazothiadiazine dioxide **8**, a potential inhibitor of enzymes which effect reactions at C-6 of adenosine, inosine, or their nucleotides.



When 4(5)-nitro-5(4)-sulphonamidoimidazole **9**[6] was silylated, followed by reaction of the silylated heterocycle with the D-ribose derivative **10** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) overnight, a separable mixture of the two isomers **11α** (39%) and **11β** (48%) was formed (Scheme 2). The formation of an α-anomer in such condensations is unusual, even under conditions of thermodynamic control, but it is significant that a similar condensation of **10** with 2-nitroimidazole also gives the α-product.[7] When the condensation of **9** and **10** was carried out under conditions of kinetic control, however, a mixture of **11β** (41%) and the required isomer **12** (44%) was obtained. Reduction of nitrocompound **12** gave the aminosulfonamide **13** in high yield, and this, on debenzoylation, give the triol **1**.

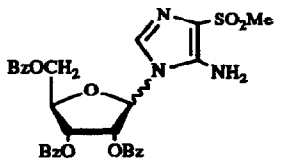


Scheme 2. i, **9**, TMSCl, HMDS, xylene, reflux; ii, add **10**, TMSOTf, MeCN, 0 °C to r.t., 16 h; iii, as ii, but 3 min.; iv, H_2, Pd/C, EtOAc; v, NH_3, MeOH.

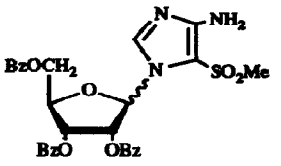
The structures of isomers such as **11α**, **11β** and **12**, and related compounds described below, are supported by a number of self-consistent NMR criteria: (a) for any α,β-pair (*e.g.* **11α** and **11β**), H-1' of the α-anomer appears at lower field, and with a larger coupling constant $J_{1',2'}$, than is the case for the β-anomer;[7,8] (b) for any regioisomeric pair (*e.g.* **11β** and **12**), reduction of the nitro group to an amino function induces a greater upfield shift for H-1' in the case of the 5-nitro isomer (*e.g.* **12**), as would be expected on the basis of the greater proximity of the nitro/amino function to H-1' in this regioisomer; (c) for any regioisomeric pair of aminosulphonamides (*e.g.* **13** and the reduction product from **11β**), the signals for C-4 and C-5 are more widely separated in the case of the 4-amino-isomer (Δδ ~50 ppm) than is found for the corresponding 5-aminocompound (Δδ ~25 ppm).[9]

These correlations, particularly the very useful criterion (c), were validated by the preparation of separate samples of the aminosulfones **14α**, **14β**, **15α** and**15β**, each of which was prepared by reduction of the corresponding nitrosulfone. Two of these nitrosulfones (the precursors of **14α** and **14β**) were synthesised by the coupling of **10** with 4(5)-methylthio-5(4)-nitroimidazole,[10] followed by oxidation to the sulfone, whilst the other pair were obtained by carrying out the coupling at the sulfone level of oxidation. We have previously

shown that, for couplings carried out using 4(5)-alkylthio-5(4)-nitroimidazoles, the regiochemistry of the products can be easily distinguished by UV measurements, and these are supported ultimately by X-ray crystallography.[10]

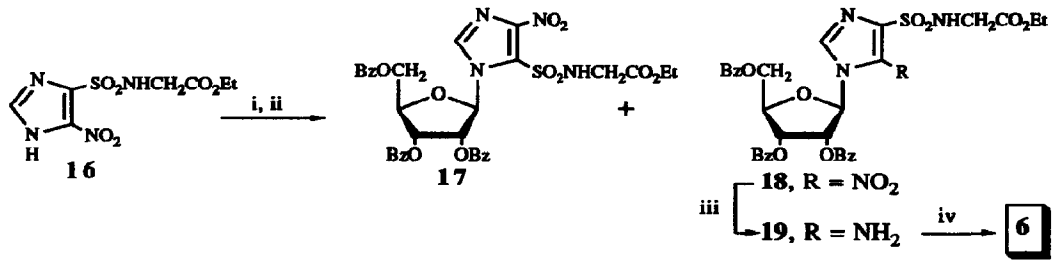


14α, α-anomer
14β, β-anomer



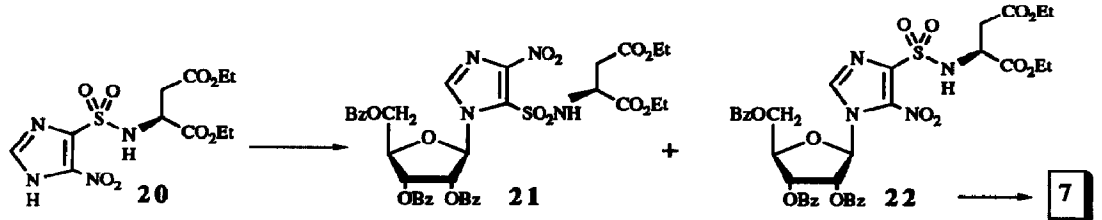
15α, α-anomer
15β, β-anomer

The more complex analogues **6** and **7** were prepared in a similar way. Thus, when the sulfonamide **16**, prepared by reaction of the sulfonyl chloride[6] with ethyl glycinate hydrochloride (Et_3N, DMF, 56%), was condensed with **10** under conditions of kinetic control, the two readily-separable products **17** (33%) and **18** (34%) were produced (Scheme 3) [under conditions of thermodynamic control, **17** (32%), its α-anomer (27%) and the α-anomer of **18** (14%) were the products]. Reduction of the correct regioisomer **18** gave aminosulfonamide **19** (δ_C 141.1 and 116.6, Δδ 24.5; reduction product of **17**, δ_C 102.4 and 154.2, Δδ 51.8) quantitatively, and deprotection gave the triol **6**.



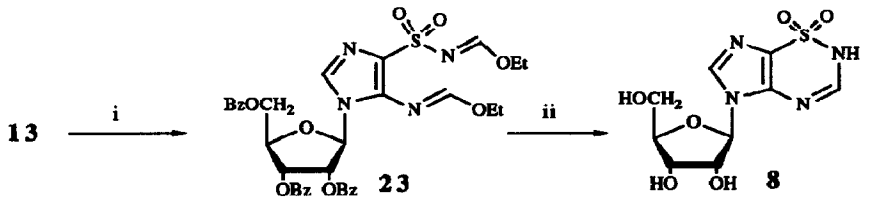
Scheme 3. i, TMSCl, HMDS, xylene, reflux, 2 h; ii, **10**, TMSOTf, MeCN, 0 °C, 3 min; iii, H_2, Pd/C, EtOAc; iv, NaOMe (cat.), MeOH, then NaOH aq.

A very similar sequence (3 min reaction time) was used (Scheme 4) to convert the sulfonamide **20** (from the sulfonyl chloride and diethyl L-aspartate in DMF and Et_3N) into an easily separable mixture of the 4-nitro-β-isomer **21** (38%), and its regioisomer **22** (29%); under thermodynamic control a mixture of **21** and its α-anomer were obtained. Reduction of **22** to the aminosulfonamide (δ_C 140.7 and 117.7, Δδ 23.0; reduction product of **21**, δ_C 103.0 and 154.0, Δδ 51.0), and deprotection gave the *N*-sulfonylaspartate **7**.



Scheme 4

The availability of the imidazole nucleoside **5** and its precursors opened the way for the preparation of 5-(β-D-ribofuranosyl)imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide **8**, a potentially interesting analogue of adenosine and/or inosine. The 7-(β-D-ribofuranosyl)-regioisomer of **8** was reported some years ago as the sole product of direct ribosylation of the bicyclic heterocycle.[11] Treatment of **13** with triethylorthoformate did not lead directly to the bicyclic system, but to the bis-(ethoxymethylene) compound **23** (Scheme 5); it had been found earlier that the presence of an alkyl group adjacent to the amine markedly slowed similar cyclizations.[11] However, when a methanolic solution of **23** was maintained at pH 8[11] and subsequently at pH 10, cyclization and debenzoylation occurred readily to give the imidazothiadiazine dioxide **8**[12] in 71% yield.



Scheme 5. i, $HC(OEt)_3$, 120 °C, 4 h; ii, MeOH, NaOH aq to pH 8, 2 h, then adjust to pH 10, 2 h

We hope to report elsewhere on the enzyme inhibitory properties of **5-8** and their 5'-phosphates, but initial cytotoxic testing proved disappointing, none of these compounds displaying significant cytotoxicity against the MAC 15A cell line at concentrations below 10μg. cm^{-3}.

Acknowledgements

We thank Wellcome Trust for financial support, EPSRC for access to central facilities for high-field NMR and for mass spectrometry, and Professor J.A. Double and Dr M.C. Bibby (Clinical Oncology Unit, University of Bradford) for the cytotoxicity data.

References and Notes

1. Christopherson, R.I.; Lyons, S.D. *Med. Res. Rev.*, **1990**, *10*, 505.
2. For recent interesting observations concerning this process in bacterial cells see: Mueller, E.J.; Meyer, E.; Rudolph, J.; Davisson, V.J.; Stubbe, J. *Biochemistry*, **1994**, *33*, 2269.
3. Patey, C.A.H.; Shaw, G. *Biochem. J.*, **1973**, *135*, 543.
4. Chan, Z.; Dixon, J.E.; Zalkin, H. *Proc. Natl. Acad. Sci. U.S.A.*, **1990**, *87*, 3097.
5. For a substrate analogue of **2** as an inhibitor of AIR carboxylase see: Firestine, S.M.; Davisson, V.J. *J. Med. Chem.*, **1993**, *36*, 3484.
6. Fisher, M.H.; Nicholson, W.H.; Stuart, R.S. *Can. J. Chem.*, **1961**, *39*, 501.
7. Prisbe, E.J.; Verheyden, J.P.H.; Moffatt, J.G. *J. Org. Chem.*, **1978**, *43*, 4784.
8. *e.g.*, Cook, P.D.; Rousseau, R.J.; Mian, A.M.; Rea, P.; Meyer, R.B. Jr.; Robins, R.K. *J. Am. Chem. Soc.*, **1976**, *98*, 1492.
9. A similar correlation has been observed previously for 4/5-aminoimidazole-5/4-carboxamides and carboxylates: Ewing, D.F.; Holy, A.; Votruba, I.; Humble, R.W.; Mackenzie, G.; Hewedi, F.; Shaw, G. *Carbohydr. Res.*, **1991**, *216*, 109.
10. Buchanan, J.G.; McCaig, A.E.; Wightman, R.H. *J. Chem. Soc., Perkin Trans. 1.*, **1990**, 955. In this present work we have found that coupling of 4(5)-methylthio-5(4)-nitroimidazole with **10** under conditions of thermodynamic control gives 4-methylthio-5-nitro-1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)imidazole (precursor to **14α**) as a minor product.
11. Huang, B.-S.; Parham, J.C. *J. Org. Chem.*, **1979**, *44*, 4046.
12. $[\alpha]_D$ -60.0° (*c* 0.3, H_2O); λ_{max} (H_2O, pH 8) 228 and 273 nm; δ_H (D_2O) 5.85 (1H, d, *J* 6.40, H-1'), 7.63 (1H, s, H-6), 7.96 (1H, s, H-3); δ_C [50 MHz, $(CD_3)_2SO$] 62.2 (C-5'), 71.7, 74.8 (C-2', C-3'), 87.2 (C-4'), 90.2 (C-1'), 120.9 (C-7a), 134.3 (C-4a), 135.8 (C-6), 145.9 (C-3).

(*Received in UK* 15 *July* 1994; *accepted* 12 *August* 1994)