Cyclisation Studies of *O*-Benzylhydroxyguanidines: Synthesis of *N*-Hydroxyimidazolines and *N*-Hydroxypyrimidones

Malcolm M. Campbell,*[a] Alexander C. Campbell,*[b] Alistair Peace,[a] Jack Pick,[b] and Gilbert F. Woods[b]

[a] *School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, U.K.*
[b] *Organon Scientific Development Group, Newhouse, Lanarkshire ML1 5SM, U.K.*

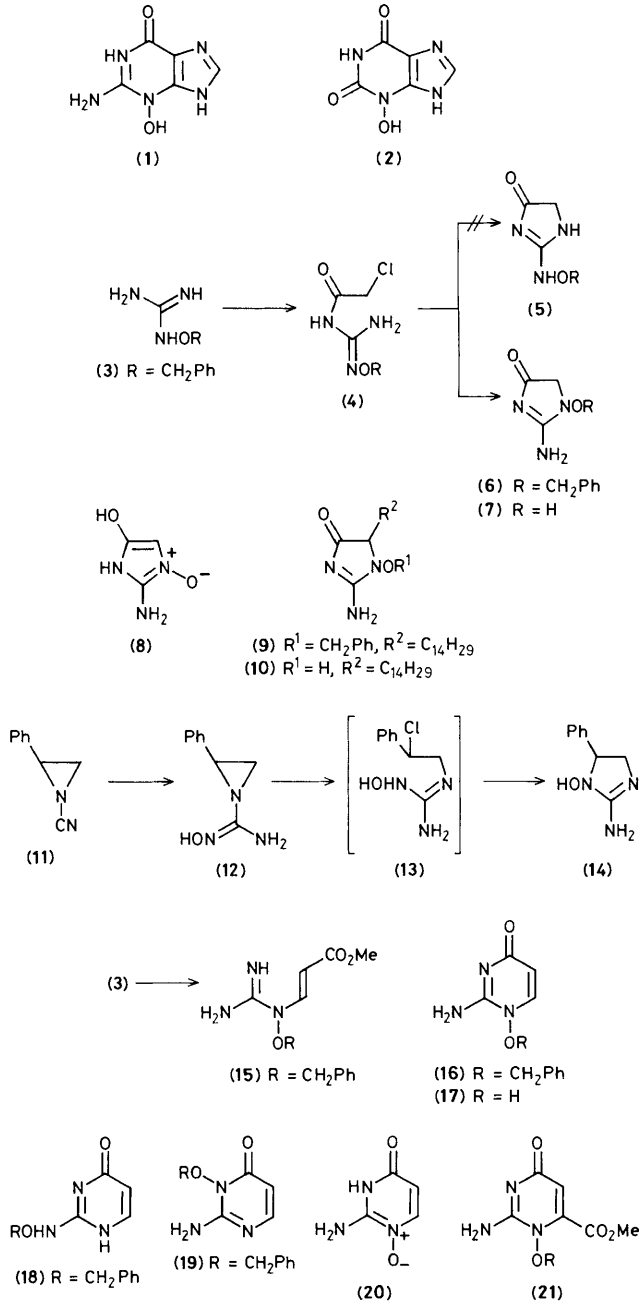
Two new classes of *N*-hydroxy heterocycles, *N*-hydroxy-2-imidazolines and *N*-hydroxypyrimidones, were synthesized by chemoselective intramolecular cyclisations.

N-Hydroxy heterocycles are relatively uncommon,[1] recent important examples of relevance to this study being *N*-hydroxypurines which are oncogenic. These include 3-hydroxyxanthine (**1**) and 3-hydroxyguanine (**2**).[2] Metabolic esterification *in vivo* is an essential step for tumour development. We therefore describe in this communication syntheses of new monocyclic *N*-hydroxy heterocycles, including an *N*-hydroxypyrimidone of particular interest.

Reaction of benzyloxyguanidine (**3**)[3] with equivalent amounts of chloroacetyl chloride and triethylamine in tetrahydrofuran (THF) at 0 °C gave the *N*-chloroacetyl adduct (**4**), m.p. 130—131 °C, in 85% yield. Cyclisation was achieved with sodium hydride in THF to give a product of possible structure (**5**) or (**6**), in 80% yield, m.p. 165—167 °C; i.r. $\nu_{max.}$(KCl) 3250, 1660, 1630, and 1295 cm^{-1}; n.m.r. δ_H 3.60 (s, 2H, NCH_2CO), δ_C [$^2H_6$]dimethyl sulphoxide, DMSO, 56.5 (t, NCH_2CO), 175.5 (s, C=N), and 181.2 (s, C=O).† Structure elucidation was not possible on the basis of spectroscopic data or chemical reactivity, but was achieved by *X*-ray crystallography, and structure (**6**) established for the product. It is noteworthy that in the formation of (**4**) the amine group was more nucleophilic, whereas in the cyclisation step to (**6**) the *N*-benzyloxyamino group was preferred, illustrating differences in chemoselectivity in benzyloxyguanidine reactions.[4] The chemistry of (**6**) was complicated by rapid extrusion of benzyl alcohol in most reactions, but debenzylation was achieved by hydrogenation over 5% Pd–C giving the novel *N*-hydroxyimidazoline (**7**)† in 95% yield, m.p. 164 °C (violent decomp.). Alternative tautomeric structures for (**7**) include the *N*-oxide (**8**), but spectroscopic similarities to (**6**) point firmly to the *N*-hydroxide structure; i.r. $\nu_{max.}$ (KBr) 3350, 1655, 1640, and 1280 cm^{-1}; n.m.r. δ_H ([$^2H_6$]DMSO) 3.80 (s, 2H, NCH_2CO), δ_C ([$^2H_6$]DMSO) 57.75 (t, NCH_2CO), 175.96 (s, C=N), and 181.66 (s, C=O). Substituted variants such as (**9**) and (**10**) were prepared in a similar manner although freshly re-sublimed potassium t-butoxide had to be used for cyclisation.† [These could not be prepared by alkylation of (**6**), since most bases caused elimination of benzyl alcohol and decomposition of the residual heterocycle.]

In a different synthetic stratagem, *N*-cyanophenylaziridine (**11**) was treated with hydroxylamine, giving the new structure (**12**).† Ring expansion was effected by triethylamine hydrochloride, giving specifically the *N*-hydroxyimidazoline (**14**) presumably *via* intermediate (**13**). Again cyclisation involved the *O*-substituted nitrogen preferentially, presumably in consequence of the α-effect. Structure (**14**), rather than the isomeric alternatives, was strongly supported by significant anisotropic shielding effects on the *O*-acetyl derivative in the ^1H n.m.r. spectrum.†

Six-membered ring variants were also synthesized. For example, benzyloxyguanidine (**3**) was treated with methyl propiolate to give, directly, (**16**) in 60% yield. The intermediacy of (**15**) was indicated by its isolation (20%) from the reaction mixture, and subsequent conversion into (**16**) upon exposure to similar reaction conditions.† Alternative structures (**18**) and (**19**) were excluded, following *X*-ray crystallographic structure elucidation. This reaction therefore proceeds by initial Michael addition by the benzyloxyamino



† All new compounds were characterised spectroscopically, and by elemental analysis with the exception of (**12**) which exhibited correct n.m.r. data for the aziridine structure, but which was highly unstable and had to be progressed immediately to (**14**).

group, followed by intramolecular cyclisation by the amino group, in contrast to the sequence of events in the five-membered ring cases. Deprotection (H_2, Pd–10% C) gave the *N*-hydroxypyrimidone (**17**), 69%, m.p. 270—272 °C, whose i.r., n.m.r., and u.v. spectroscopic properties were more compatible with structure (**17**) than alternative *N*-oxide tautomers such as (**20**). [$\nu_{max.}$ (KCl) 3600—3240, 1701, and 1660 cm^{-1}; $\lambda_{max.}$ (EtOH) 270 nm (ε 3800); δ_H ([$^2H_6$]DMSO) 6.15 (1H, d, *J* 9 Hz), 8.15 (1H, d, *J* 9 Hz); δ_C ([$^2H_6$]DMSO) 103.07(NC=C), 145.50 (NC=C), 152.14 (C=N), 163.10 (C=O).] Similarly prepared from dimethyl acetylenedicarboxylate was (**21**) (90%).

Cyclisation methods have thus been established for new 5- and 6-membered monocyclic *N*-hydroxy heterocycles. *N*-Hydroxypyrimidone (**17**) is a particularly interesting member of this group, being an *N*-hydroxylated variant of the pyrimidine bases, and therefore comparable with *N*-hydroxypurines.[2]

We thank Dr. D. Williams, Department of Chemistry, Imperial College, for the *X*-ray crystal structures of (**6**) and (**16**).

Received, 28th May 1985; Com. 726

References

1 H. S. Roberts, in 'Comprehensive Organic Chemistry,' vol. 2, ed. D. H. R. Barton and W. D. Ollis, Pergamon Press, 1979, p. 190.
2 J. A. Parham and M. A. Templeton, *J. Org. Chem.*, 1982, **47**, 652, and references cited therein.
3 D. G. Martin, E. L. Schumann, W. Veldkamp, and M. Keasting, *J. Med. Chem.*, 1965, **8**, 456.
4 For the synthesis of 2-hydroxyiminoimidazolidine, see: C. Belzecki and J. Trojnar, *Bull. Acad. Pol. Sci., Serp. Sci. Chim.*, 1970, **18**, 379.