Bioorganic & Medicinal Chemistry Letters, Vol.2, No.5, pp. 421-422, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

Facile Rearrangement of 5-Carbomethoxymethyl-2-cyanoiminoimidazolones. Synthesis of 6-Carboxyhexahydropyrimidines, Potential Dihydroorotate Dehydrogenase Inhibitors

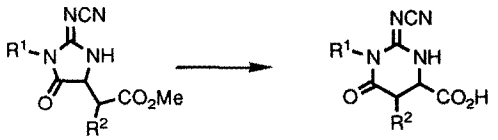
Vern M. Delisser, Peter J. Garratt and Simon N. Thorn
Department of Chemistry, University College London, 20 Gordon Street London WC1H 0AJ

Roger Wrigglesworth
Sandoz Institute for Medical Research, Gower Place, London WC1E 6BN

(*Received* 25 *February* 1992)

Abstract: 5-Carbomethoxymethyl-2-cyanoiminoimidazolones, readily prepared from diphenyl N-cyanocarbonimidate, rearrange rapidly on treatment with base at room temperature to give 6-carboxyhexahydropyrimidines.

Dihydroorotic acid is an intermediate on the *de novo* biosynthetic pathway leading to the pyrimidine bases, uracil, thymine and cytosine, structural components of DNA, RNA and the nucleotide coenzymes. Dihydroorotate dehydrogenase, the enzyme that converts dihydroorotic acid to orotic acid, is probably the least studied of the enzymes of this pathway but it appears to be a suitable target for interfering with nucleic acid metabolism.[1,2,3] Most laboratory syntheses of pyrimidines bypass the oxidation state equivalent to dihydroorotic acid, but we have recently reported a method of preparation of hexahydropyrimidines in this oxidation state.[4] Problems arose in attempting to incorporate the 6-carboxy substituent and, as we have previously reported, 5-membered imidazolones rather than 6-membered pyrimidones are preferentially formed in the intramolecular cyclisation of amines to esters where there is a choice.[5] This preference can be partially overcome by differentially substituting the competing ester groups,[6] but both systems are formed even in the most favourable case. We now find, as we had previously surmised,[5] that 2-cyanoimino-5-carbomethoxymethyl substituted imidazolones rearrange smoothly with base under very mild conditions to give the corresponding 6-carboxyhexahydropyrimidines.

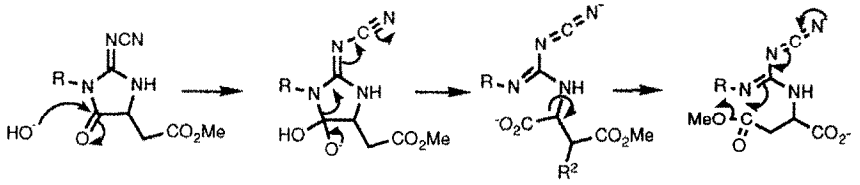


1 **2**

a $R^1 = R^2 = H$, **b** $R^1 = CH_3CH_2CH_2$, $R^2 = H$, **c** R^1 = cyclohexyl, $R^2 = H$, **d** $R^1 = CH_3(CH_2)_6$, $R^2 = H$, **e** R^1 = cyclopentyl, $R^2 = H$, **f** $R^1 = PhCH_2$, $R_2 = PhCH_2$, **g** $R^1 = PhCH_2$, $R^2 = CH_3CH_2CH_2$, **h** $R^1 = PhCH_2$, $R^2 = H$

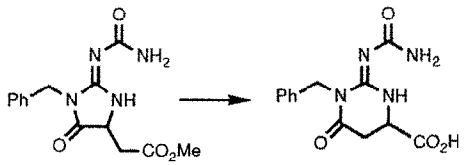
In a typical procedure, the imidazolone **1e** was added to 2M NaOH at room temperature, the mixture stirred for 10 min and then diluted with water, extracted with ether and the aqueous solution acidified with conc.HCl to pH1. The resulting precipitate was collected and washed with ether to give **2e**, mp 225-227 °C, 68%.[6, 7, 8]

Previously, the rearrangement of imidazolones to pyrimidines was reported to take much more vigorous conditions (typically, KOH, 100 °C, hours) [10] We believe that the above rearrangement involves nucleophilic addition to the carbonyl group with C-N bond cleavage being facilitated by the NCN substituent, followed by reclosure on to the remaining ester group (Scheme)



Scheme

We have also found that the urea **3**, derived from the corresponding cyanoimine **1h** by acid hydrolysis, also undergoes facile rearrangement with base to the 6-membered derivative **4**. The urea moiety presumably again allows the dispersion of charge and suggests that a range of compounds with the potential for extended conjugation should readily undergo this rearrangement



3 **4**

The major disadvantage with this synthesis of hexahydropyrimidines is that racemization occurs on formation of the 5-membered imidazolone [6] The N-cyano group is readily transformed into other functional entities to provide a group of compounds as potential dihydroorotate dehydrogenase inhibitors.

Acknowledgement. SNT thanks the Science and Engineering Research Council (UK) for a studentship.

References and Footnotes

1 Singer, T ; Gutman, M , Massey, V In *Iron-Sulfur Proteins*, W Lovenberg, Ed , Academic Press: New York, 1973; Vol. 1, p 285
2 Levine, R L , Hoogenraad, N J , Kretchmer, N. *Pediat. Res.* **1974**, *8*, 724.
3 Kensler, T W , Cooney, D In *Design of Enzyme Inhibitors as Drugs*; M Sandler and H. J Smith, Ed , Oxford Scientific Publications Oxford, 1989
4 Garratt, P. J.; Hobbs, C J ; Wrigglesworth, R. *J. Org. Chem.* **1989**, *54*, 1062
5 Besse, R.; Garratt, P J , Hobbs, C J , Rogers, H. M , Sueleiman, A M ; Walpole, C. S J., Wrigglesworth, R *Tetrahedron* **1990**, *46*, 7803
6 Garratt, P. J ; Thorn, S N., Wrigglesworth, R *Tetrahedron Letters* **1991**, *32*, 691
7 **2a**, mp 192 - 194°C, 65%; **2b**, mp 214 - 216 °C, 55%; **2c**, mp 227 - 228 °C, 65%; **2d**, mp 122 - 123 °C, 55%; **2f**, mp 145 - 147 °C, 50%, **2g**, mp 165 - 167 °C, 72%; **2h**, mp.167 - 171 °C, 89%.
8 Satisfactory analytical and/or mass spectral data were obtained for all new compounds
9 In the IR spectra, the imidazolones show the ring carbonyl group stretch at ca υ 1760 cm^{-1}, while in the pyrimidones the ring carbonyl stretch is at ca υ 1715 cm^{-1} The CN stretching frequency is about 15 cm^{-1} higher in the pyrimidone than in the corresponding imidazolone The ^{13}C NMR spectra also show the expected shift differences (refs 5, 6)
10 Mitchell, H K , Nyc, J F *J Am Chem Soc* **1947**, *69*, 674