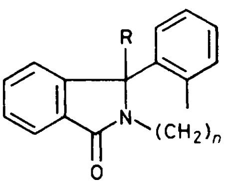
New Fused Heterocyclic Systems derived from Pyridine-2,3-dicarboximides

Gregory J. Hitchings and John M. Vernon*

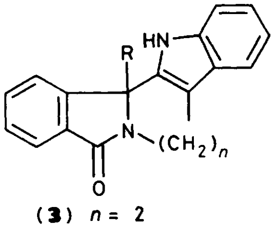
Department of Chemistry, University of York, Heslington, York YO1 5DD, U.K.

α-Hydroxylactams (**8**), formed by regioselective reduction or Grignard addition to pyridine-2,3-dicarboximides (**7**), undergo acid-catalysed cyclodehydration to give the new pyrido[2′,3′ : 3,4]-pyrrolo fused heterocyclic systems (**10**)—(**13**).

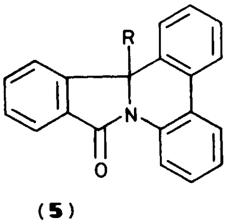
A widely used procedure for the synthesis of fused heterocyclic systems involves the cyclodehydration of α-hydroxylactams.[1] In particular, derivatives of the fused isoindole systems (**1**)—(**5**) have been obtained by acid treatment of *N*-substituted hydroxyphthalimidines (**6**)[2,3] or, in some cases, by a one-step procedure from *o*-acylbenzoic acids and the appropriate amines.[3,4] Our preparation of aza-analogues of the fused heterocyclic systems (**1**)—(**3**) and (**5**) *via* cyclodehydration of hydroxylactams derived from pyridine-2,3-dicarboximides (**7a**—**d**) represents a significant extension of the utility of this general method.



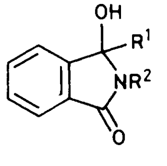
(**1**) $n = 1$
(**2**) $n = 2$



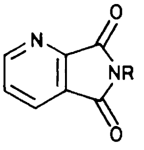
(**3**) $n = 2$
(**4**) $n = 3$

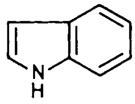


(**5**)

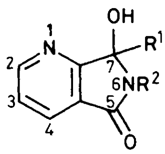


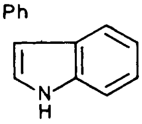
(**6**)

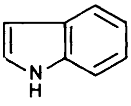


(**7**) **a**; R = $\mathrm{CH_2Ph}$
b; R = $\mathrm{CH_2CH_2Ph}$
c; R = $\mathrm{CH_2CH_2}$ 

d; R = $o\text{-}\mathrm{C_6H_4Ph}$



(**8**) **a**; $\mathrm{R^1 = H, R^2 = CH_2Ph}$
b; $\mathrm{R^1 = H, R^2 = CH_2CH_2Ph}$
c; $\mathrm{R^1 = H, R^2 = CH_2CH_2}$ 

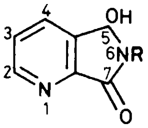
d; $\mathrm{R^1 = H, R^2} = o\text{-}\mathrm{C_6H_4Ph}$
e; $\mathrm{R^1 = Ph, R^2 = CH_2Ph}$
f; $\mathrm{R^1 = Ph, R^2 = CH_2CH_2Ph}$
g; $\mathrm{R^1 = Ph, R^2 = CH_2CH_2}$ 

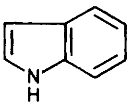
h; $\mathrm{R^1 = Ph, R^2} = o\text{-}\mathrm{C_6H_4Ph}$

Reduction of the imides (**7a**—**d**) with sodium borohydride in ethanol gave mixtures of regioisomeric hydroxylactams (**8**) and (**9**) (Table 1). These were distinguished by ^{1}H and ^{13}C n.m.r. evidence, which showed that the major product in each case was the 7-hydroxy-5-oxo-pyrrolo[3,4-*b*]pyridine (**8**) formed by attack at the more reactive carbonyl group in (**7**). For example, in the ^{1}H n.m.r. spectrum of (**9b**), irradiation at the frequency for the resonance of H-4 produced a nuclear Overhauser enhancement of the resonances due to H-3 and H-5. The corresponding experiment with the regioisomer (**8b**) showed no such interaction between H-4 and H-7.

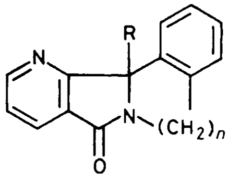
Reaction of the imides (**7a**—**d**) with a four-fold excess of phenylmagnesium bromide gave in every case only a single adduct (Table 1). Comparison of ^{13}C n.m.r. chemical shifts for the ring junction atoms C-4a and C-7a, which are distinctively different in (**8a**—**d**) and (**9a**—**d**), showed the Grignard adducts to be (**8e**—**h**). The regiospecificity observed in these reactions may be attributed to co-ordination of the pyridine nitrogen atom to magnesium, which directs the Grignard addition to the adjacent carbonyl group.

Cyclodehydration of the hydroxylactams (**8b**—**h**) occurred in refluxing trifluoroacetic acid to give the corresponding pyrido[2′,3′ : 3,4]pyrrolo fused heterocyclic products listed in

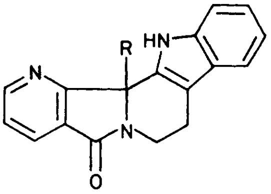


(**9**) **a**; R = $\mathrm{CH_2Ph}$
b; R = $\mathrm{CH_2CH_2Ph}$
c; R = $\mathrm{CH_2CH_2}$ 

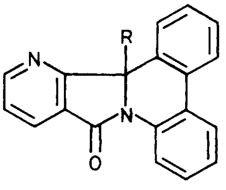
d; R = $o\text{-}\mathrm{C_6H_4Ph}$



(**10**) **a**; $n = 1$, R = H
b; $n = 1$, R = Ph
(**11**) **a**; $n = 2$, R = H
b; $n = 2$, R = Ph



(**12**) **a**; R = H
b; R = Ph



(**13**) **a**; R = H
b; R = Ph

Table 1. Hydroxylactam and fused heterocyclic products.[a]

Imide	Reducing agent	Hydroxylactam(s)	%Yield	Cyclised product	% Yield
(**7a**)	$NaBH_4$	(**8a**), (**9a**)	50, 18	(**10a**)	0
(**7b**)	$NaBH_4$	(**8b**), (**9b**)	82, 14	(**11a**)	93
(**7c**)	$NaBH_4$	(**8c**), (**9c**)	63, trace	(**12a**)	64
(**7d**)	$NaBH_4$	(**8d**), (**9d**)	58, 19	(**13a**)	88
(**7a**)	PhMgBr	(**8e**)[b]	62	(**10b**)	40
(**7b**)	PhMgBr	(**8f**)	83	(**11b**)	73
(**7c**)	PhMgBr	(**8g**)	100	(**12b**)	56
(**7d**)	PhMgBr	(**8h**)	100	(**13b**)	64

[a] All new compounds are characterised by appropriate spectroscopic evidence, including atomic composition of the molecular ion by mass spectrometry. [b] Molecular ion absent in the mass spectrum of (**8e**), but atomic composition $C_{20}H_{16}N_2O$ verified for the peak at highest *m/z* corresponding to $[M - O]^{\bullet +}$.

Table 1. Ring closure failed only in the case of (**8a**), as reported previously for the related *N*-benzylphthalimidine derivative (**6**; $R^1 = H$, $R^2 = CH_2Ph$);[2] under more forcing conditions (hot polyphosphoric acid) only tars were obtained.

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