Synthesis of γ-Carbolines

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THE reductive cyclization of *N*-[2-(3-indolyl)-2-oxoethyl]-pyridinium and -isoquinolinium salts with lithium aluminium hydride has found many successful applications in the preparation of quinolizine derivatives related to the yohimbine alkaloids.[1] We have new found that the similar reduction of *N*-[2-(2-indolyl)-2-oxoethyl]-pyridinium and -isoquinolinium salts is a particularly effective way of obtaining γ-carboline derivatives.[2]

Thus, conversion of bromomethyl 2-indolyl ketone (I), prepared *via* the diazoketone route,[3] into the pyridinium salts (II) occurred in good yields. Reduction of these salts with lithium aluminium hydride resulted in extremely easy ring closures to the γ-carboline derivatives (III). Analytical, molecular-weight (mass spectra), and spectral data were consistent with the formulation of these products as quinolizine derivatives. Further evidence that showed that ring closure had occurred was the iodine–potassium acetate

TABLE

Properties of the pyridinium salts and γ-carboline derivatives

Salts (II)					γ-Carbolines (III)	
R	X	m.p. (°C)	ν_{NH}(cm.$^{-1}$)	ν_{CO}(cm.$^{-1}$)	R	m.p. (°C)
H	Cl[a]	210 dec.	3278	1661	H	196—197
3-Me	Br[b]	160	3125	1667	3-Me	238
3,4-Benzo	Br[b]	269	3125	1653	2,3-Benzo[c]	200

[a] Reduction of the corresponding bromide and iodide gave the same product; [b] Reduction of the corresponding iodide gave the same product; [c] HCl, m.p. 205° dec.; OAc, m.p. 121° (ν_{CO} 1706 cm.$^{-1}$); an epimeric product, m.p. 215°, was also obtained in this instance.

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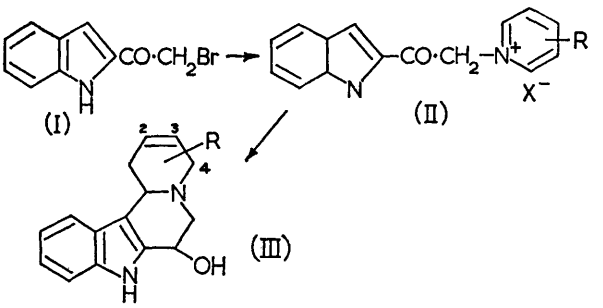
oxidation of (III) to dihydroquinolizinium salts, which underwent ready reduction with sodium borohydride to their precursors. These were not identical with the 1-[2-(2-indolyl)-2-hydroxyethyl]-1,2,5,6-tetrahydro-1-[2-hydroxy-2-(2-indolyl)ethyl]-pyridines formed by reduction of the pyridinium salts (II) with sodium borohydride.

Mineral acid was not necessary to effect ring closure of the intermediate enamine formed in the reduction. This is consistent with the greater electron density at the 3-position of the indole nucleus compared to the 2-position.



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[2] A review of synthetic methods can be found in: W. O. Kermack and J. E. McKail, "Heterocyclic Compounds". Vol. 7, ed. R. C. Elderfield, Wiley, New York, 1961, ch. 3; see also Belgian patent 669, 682 (March 15, 1966); *Chem. Abs.*, 1966, **65**, 8884.

[3] F. Weygand and H. J. Bestman, "Newer Methods of Preparative Organic Chemistry, Vol. 3", Academic Press, New York, 1964.