Synthesis of the Aspidosperma Alkaloid Nucleus: 5-Oxode-ethylvincadifformamide

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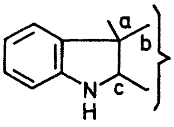
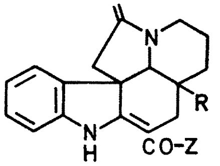
Summary Construction of the Aspidosperma alkaloid nucleus by a five-step procedure is described.

IN continuation of our studies of a c–b–a approach (I) toward the construction of alkaloids of the vincadifformine (II) type[1] a short synthesis of the Aspidosperma alkaloid skeleton has been developed.

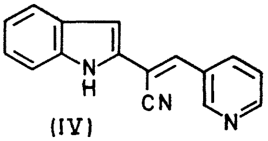
Sodium borohydride reduction of 1-(2-indolyl)-2-(3-pyridyl)acrylonitrile (IV)[1] followed by hydrolysis of the resultant oily nitrile (V) with alkaline hydrogen peroxide yielded the amide (VI), m.p. 202°. Hydrogenation of the latter in methanolic hydrogen chloride over platinum produced tetracyclic amide (VII), m.p. 252°, *m/e* 269 (*M*), 268 (*M*−1) (same intensity), λ_{max} (EtOH) 222 (log ϵ 4·56), 275 (3·87), 283 (3·38), and 291 nm (3·77), whose treatment with trifluoroacetic anhydride[2] followed by alkaline hydrolysis led to nitrile (VIII), m.p. 242°, *m/e* 251 (*M*), ν_{max} (Nujol) 4·46 μm (C≡N). Exposure of the amide (VII) to bromoacetyl bromide gave the diamide (IX). Heating a dimethylformamide solution of this unstable compound and sodium hydrogen carbonate for a short time afforded the pentacycle (III), m.p. 174°, *m/e* 309 (*M*) (*M*−1 peak absent), λ_{max} (EtOH) 224 (log ϵ 4·10), 297 (4·02), and 327 nm (4·12), ν_{max} (Nujol) 5·82 (s), 5·92 (s) (lactam C = O),[3] and 6·02 μm (s) (amide C = O).



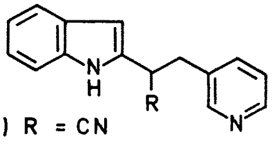
(I)



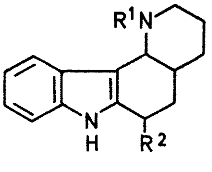
(II) R = Et, Y = H_2, Z = OMe
(III) R = H, Y = O, Z = NH_2



(IV)



(V) R = CN
(VI) R = $CONH_2$



(VII) R^1 = H, R^2 = $CONH_2$
(VIII) R^1 = H, R^2 = CN
(IX) R^1 = $BrCH_2CO$, R^2 = $CONH_2$

Two reactions of this short scheme of synthesis of the Aspidosperma alkaloid nucleus are of unusual interest.

One reaction is the reductive cyclization (VI → VII) executed in 45% yield Other examples of this new process will be reported later The second new reaction involves the construction of the ubiquitous ethanamino-bridge of the indole alkaloids by an intramolecular indole β-alkylation (IX → III) Unfortunately, its yield is only *ca* 10%, a fact ascribable at least in part to an unfavourable stereochemical environment for the reaction in the probably *trans*-C/D tetracycle (IX)

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[1] H -P Husson C Thal P Potier, and E Wenkert, *J Org Chem* , in the press

[2] L A Carpino *J Amer Chem Soc* 1960 **82**, 2725

[3] The lactam carbonyl absorption of 18-oxostrychnine is at 5 92 μm (Nujol), P J Scheuer, *J Amer Chem Soc* , 1960, **82**, 193