Tetrahedron Letters,Vol.28,No.41,pp 4901-4904,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A NEW APPROACH TO THE SYNTHESIS OF PENTACYCLIC INDOLE DERIVATIVES RELATED TO ASPIDOSPERMA ALKALOIDS

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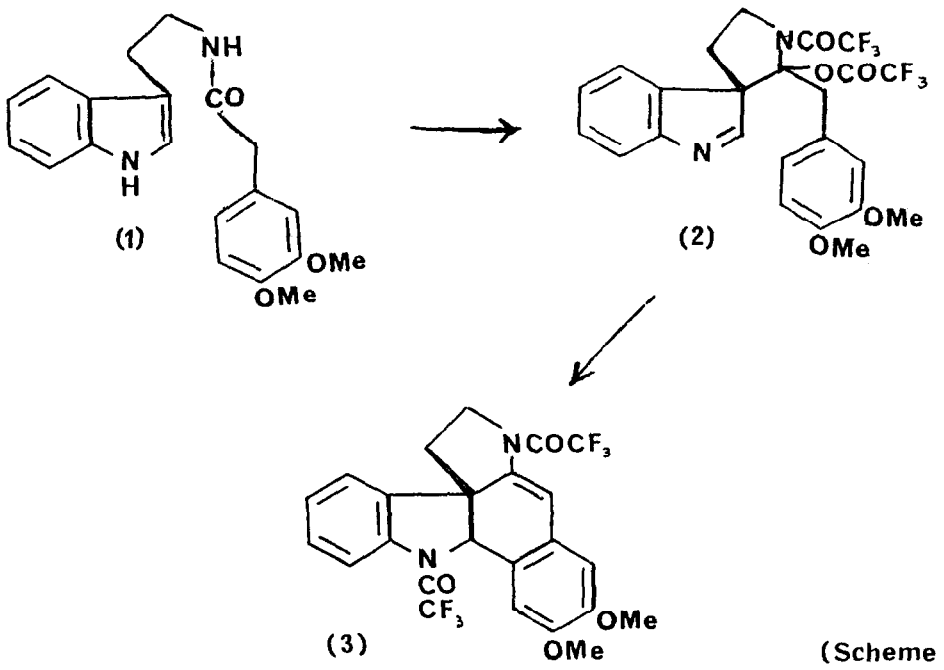
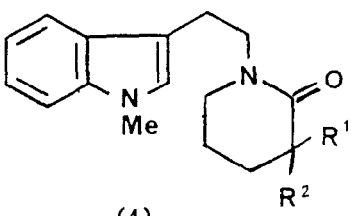
Summary: N-Indolylethyl-2-pyridones bearing appropriate β-dicarbonyl substituents in the 3-position have been cyclised to pentacyclic indoles via spirocyclic indolenines by catalysis with trifluoroacetic anhydride.

In earlier studies of electrophilic substitution in indoles, we provided evidence[1] that simple 3-alkyl indoles are acylated at the 2-position in an indirect process involving initial attack at the 3-position followed by migration of the incoming acyl substituent. More recently, we have shown that the intermediate 3-alkyl, 3-acyl-indolenines involved in these acylation reactions could be trapped by suitable nucleophilic species in both intra-[2] and inter-[3] molecular fashion. For example, N(3,4-dimethoxyphenylacetyl)-tryptamine (1) underwent trifluoroacetic anhydride catalysed cyclisation to the spiropentacyclic indoline (3) in virtually quantitative yield presumably via the intermediate spirocyclic indolenine (2). (Scheme 1).



(Scheme 1)

We now show how this approach can be extended to the synthesis of spirocyclic indolines related to the Aspidosperma series of alkaloids. The lactam (4a)[4] was first prepared by established methods[5] and converted into its lithium enolate; acylation with diketene afforded the oily amido dione (5a) in reasonable yield. On stirring the latter with trifluoroacetic anhydride at 20° for 24 hr. the crystalline spiropentacyclic indoline (6a) was obtained in 60% yield as the sole product.

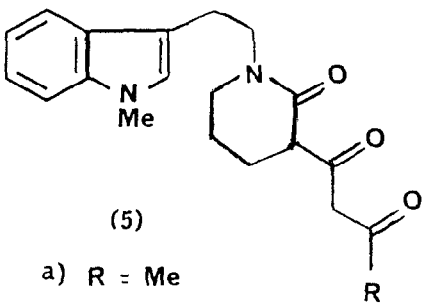


(4)

a) $R^1 = R^2 = H$

b) $R^1 = CO_2CH_2Ph$ $R^2 = H$

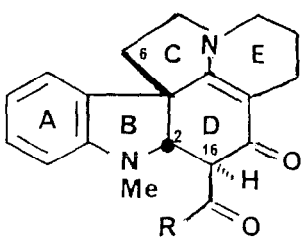
c) $R^1 = CO_2CH_2Ph$
$R^2 = COCH_2CO_2Me$



(5)

a) R = Me

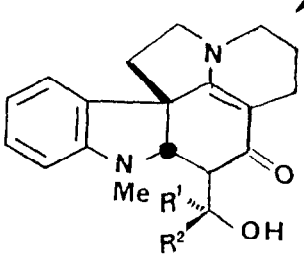
b) R = OMe



(6)

a) R = Me

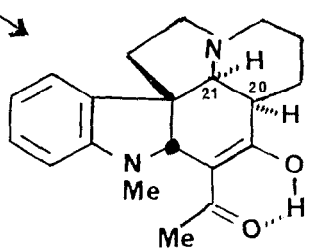
b) R = OMe



(8)

a) $R^1 = H$, $R^2 = Me$

b) $R^1 = Me$, $R^2 = H$



(7)

(Scheme 2)

The ketoester (5b) could not be prepared by direct acylation of the lactam (4a) but when the lithium enolate of the latter was treated with benzylchloroformate the benzyl ester (4b) was obtained in excellent yield. The enolate of the latter was then readily acylated with methoxycarbonylacetylchloride to give the diester (4c) which underwent hydrogenolysis and decarboxylation in presence of palladium/charcoal and ammonium formate cf.[6]. The oily ketoester (5b) obtained in this manner was treated with trifluoroacetic anhydride and afforded the pentacyclic indoline (6b) in 51% yield as a crystalline solid, m.p. 204-206°.

The B/D ring junction in both spirocyclic indolines (6a) and (6b) was assumed to be cis because of steric constraints imposed by the benzene ring A, which would enforce coplanarity of the indole nitrogen and β-carbon atoms with the benzene ring. This was confirmed by n.O.e. difference spectra which showed that irradiation of the 2-H resonance caused a 5.5% enhancement of the 6β-H resonance. The n.m.r. spectra of both compounds showed that the 2-H resonance was a doublet (J=8Hz) due to coupling with the 16-H; this indicated that the 2- and 16- protons were trans to each other and hence the assignment of configuration at C-16 is that shown in the structural formula (6). This assignment is supported by n.m.r. spectral studies of similar pentacyclic indolines in which coupling constants of 3Hz were observed for cis 2-H, 16H and 10Hz for trans 2-H, 16H[7].

Attempts to hydrogenate the double bond in the D ring of the acetyl derivative (6a) proved unsuccessful, presumably because of steric hindrance. However, use of sodium cyanoborohydride as reducing agent cf.[8] afforded the amine (7) (17%) as well as the two diastereoisomeric alcohols (8a) and (8b) in 21% and 37% yields respectively.

The n.m.r. spectrum of the amine (7) manifested a sharp singlet at δ 16.27 integrating for one proton thus showing that it existed entirely in the enol form (as illustrated in the structure) in $CDCl_3$ solution. The D/E ring junction was assigned the cis configuration as shown as the coupling constant between H-20 and H-21 was only 3Hz.

These results show that tricyclic lactams (5) with suitably placed acyl side-chains can be converted into pentacyclic indolines related to Aspidosperma alkaloids. Further work on related compounds is in progress.

Acknowledgements

We thank the S.E.R.C. and Roche Products Limited for award of a CASE studentship (to David J. Wilkins) and Dr. G. Thomas of Roche for helpful discussions.

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(Received in UK 4 August 1987)