Biogenetically Patterned Synthesis of the Spiro[indoline-3,4′-proline] System

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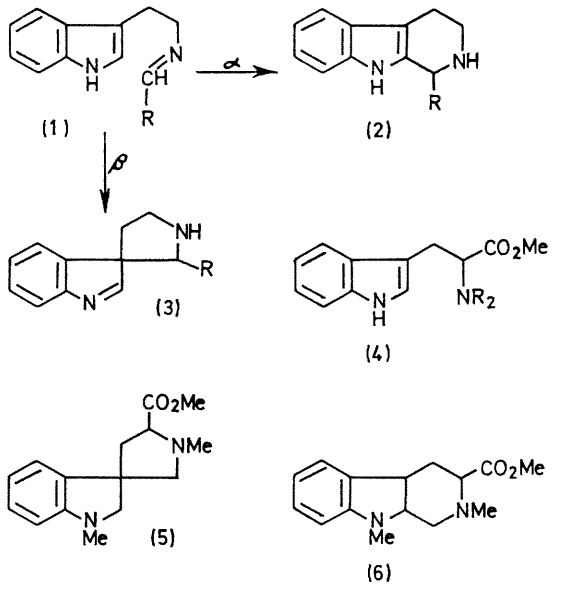
Summary Reaction of tryptophan with dry formaldehyde under reducing conditions yielded spiro-[*N*-methylindoline-3,4′-*N*-methylproline methyl ester].

RECENTLY, workers in the field of indole alkaloid biosynthesis have been concerned with the biosynthetic pathway immediately after the condensation of tryptophan (or tryptamine) with the C_{10} alicyclic moiety.[1,2] The initial product is presumably a Schiff base (**1**) which can then undergo cyclization at either the α- or β-position of the indole nucleus to form (**2**) or (**3**), respectively, the precursors of the three major families of indole alkaloids. Intramolecular attack of various Schiff bases has been reported at both the α- and β-positions.[1,3] We now report a technique for trapping the unstable spiroindolenine intermediate formed after β-attack. This method involves formation of the spiro[indoline-3,4′-proline] system, (**5**).

Reaction of tryptophan methyl ester (**4**; R = H) with a large excess of dry formaldehyde and hydrogen in the presence of Raney nickel or 5% palladium on charcoal, afforded a mixture of products. Chromatography over aluminium yielded *N*(b), *N*(b)-dimethyltryptophan methyl ester (**4**; R = Me) together with a new compound (**5**), the amount of which ranged from 0—52% depending upon reaction conditions.†

The spectroscopic properties of (**5**) [ν($CHCl_3$) 1735 cm^{-1} (CO_2Me); u.v. λ_{max} (EtOH) 252 (ε 9600) and 297 nm (ε 3200) (indoline chromophore);[4] n.m.r. ($CDCl_3$) δ 2·44 (s, 3H, NCH_3), 2·74 (s, 3H, NCH_3), 3·90 (s, 3H, CO_2CH_3), 2·5 (m, 3H), 3·35 (m, 4H), and 6·3—7·5 (m, 4H, arom.)] are consistent with an indoline structure. The base formed a red monopicrate, m.p. 181—183°, but a dipicrate could not be prepared.

Upon acidification, the u.v. absorption spectrum was only slightly changed with maxima at 253 nm (ε 10,300) and 304 nm (ε 3100) indicating the indoline chromophore had been retained.[4] However, when concentrated hydrochloric acid was used as a solvent the indoline absorption changed to a benzenoid type with λ_{max} 252 nm (ε 960). During their studies on toxiferine[5] and folicanthine,[6] Hodson and his co-workers have noted that the spectra of

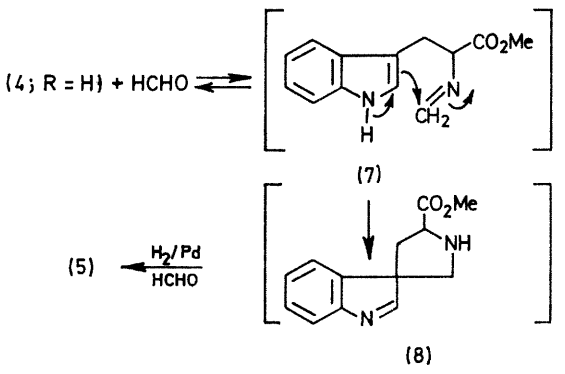


many simple indolines are affected by the pH of the solution. Where more than three carbon atoms separate N(a) and N(b), the indoline absorption changes to benzenoid upon acidification with 0·1N-hydrochloric acid, due to protonation of both N(a) and N(b).[6] In the hexahydro-β-carboline system where three carbon atoms separate N(a) and N(b), this shift does not occur, since N(a) is not protonated under these conditions owing to the field effect of the closely placed positively charged N(b) nitrogen atom.[5] When N(a) and N(b) are separated by one carbon atom, as in physostigmine, acidification causes a blue shift of about

† The yield of product depended on a large number of variables, such as activity of Raney nickel, reaction temperature, dryness and excess of formaldehyde. Satisfactory analyses were obtained for all new compounds reported.

10 nm in the u.v. spectrum.[6] Consequently, in the present case where there was only a slight change in the u.v. spectrum upon acidification, the nitrogen atoms are separated by two or three carbon atoms, *i.e.*, the reaction with formaldehyde has brought the nitrogen atoms closer together.

Structures (**5**) and (**6**) satisfy all the chemical and spectral data so far. To distinguish between these two possibilities the n.m.r. spectrum was run at 220 MHz. The presence of an ABX system [AB centred at δ 2·33 ($\Delta\nu_{AB}$ 0·12 p.p.m., J_{AB} 13·0Hz), X centred at δ3·22 (t, $J_{AX} = J_{BX}$ = 8·0 Hz)] an AB system [δ 2·92 (ν_{AB} 0·78 p.p.m., J_{AB} 9·5 Hz) and an AA′ system [δ 3·18 (s, 2H)] establishes (**5**) as the correct structure. The C-2 indoline proton signals, which give rise to the AA′ system in $CDCl_3$, change to an AB quartet when the 220 MHz spectrum is run in benzene.



SCHEME

The formation of (**5**) may readily be explained by the mechanism shown in the Scheme. The Schiff base (**7**) formed by reaction of (**4**; R = H) with dry formaldehyde,[7] attacks at the β-position of the indole nucleus to form the unstable indolenine (**8**). Reduction of (**8**) produces a stable indoline. However, because both nitrogens are now secondary and basic, they are *N*-methylated by the excess of formaldehyde under the reducing conditions to yield the spiro-[*N*-methylindoline-3,4′-*N*-methylproline methyl ester] (**5**).

Tryptamine was used in the same reaction but no spiroindoline was isolated, only *N*(b),*N*(b)-dimethyltryptamine. The reaction conditions were varied greatly but no spiroindoline could be obtained. When tryptamine hydrochloride was reacted with paraformaldehyde in 95% ethanol, a tetrahydro-β-carboline (**2**; R = H) was produced, *i.e.*, the product from α-attack.[7] Running the above reaction under reducing conditions again afforded (**2**; R = H), indicating that β-attack followed by rearrangement had not occurred during the formation of (**2**; R = H). In conclusion, it is interesting to note that tryptamine has been specifically incorporated into several alkaloids of *Vinca rosea* with considerable variation in efficiency suggesting that decarboxylation of tryptophan may be delayed until after its incorporation into some indole alkaloids.[8]

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