# Synthesis of Spiropentacyclic Indolines by Cyclisation of 3,4-Dimethoxyphenylacetyltryptamine

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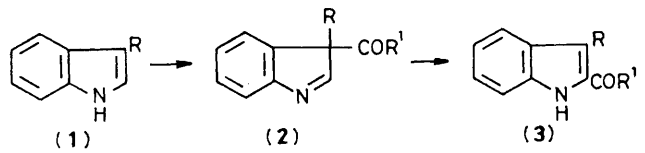
Cyclisation of *N*-(3,4-dimethoxyphenylacetyl)tryptamine (**4**) with either phosphorus trichloride, or phosphoryl chloride, affords the spirocyclic indoline (**12**) together with small amounts of β-carboline derivatives, whereas with trifluoroacetic anhydride as reagent the spirocyclic indoline (**13**) is formed in quantitative yield.

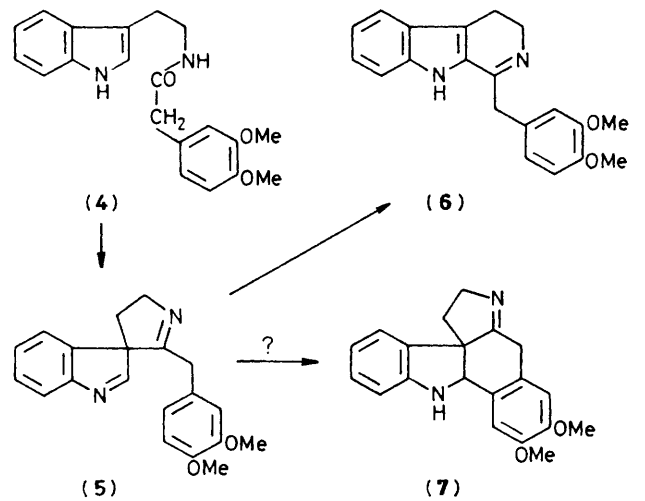
We have recently shown that acylation of 3-alkylindoles (**1**) (like other electrophilic substitution reactions) involves initial attack at the 3-position, to give 3-acylindolenines (**2**), followed by rearrangement to give 2-acyl-3-alkylindoles (**3**) (Scheme 1).[1,2] In the present communication we show how the intermediate indolenines can undergo intramolecular cyclisation if a suitable nucleophilic side-chain is available, to give spirocyclic indolines structurally related to indole alkaloids.

Initially we re-investigated a report[3] that phosphorus trichloride-catalysed cyclisation of *N*-(3,4-dimethoxyphenylacetyl)tryptamine (**4**) in boiling benzene afforded the dihydro-β-carboline (**6**). In the light of our studies of the acylation of indoles referred to above we thought that the latter might be formed *via* an intermediate spirocyclic indolenine (**5**), and that under suitable conditions it might undergo a further cyclisation to give a spirocyclic indoline (**7**) by intramolecular attack of the nucleophilic dimethoxyphenyl-residue (Scheme 2).

We were encouraged in this speculation by another study[4] of the rearrangement of the dihydroxybenzyl-β-carboline (**8**) in boiling concentrated hydrochloric acid to the spirocyclic indoline (**10**) which was thought to occur *via* the intermediacy of a spirocyclic indolenine (**9**) (Scheme 3).




**Scheme 1**




**Scheme 2**

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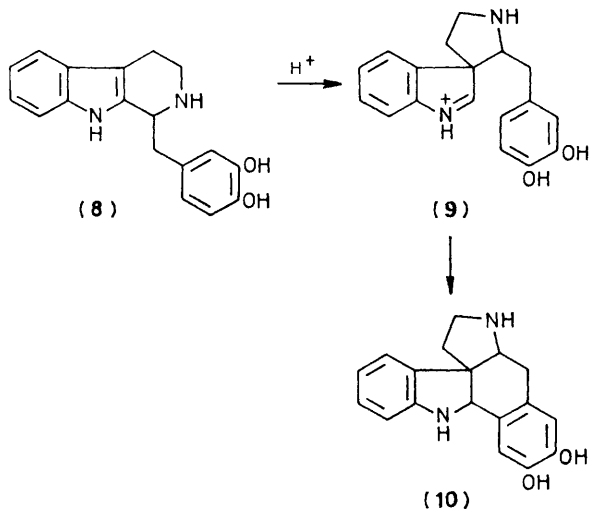
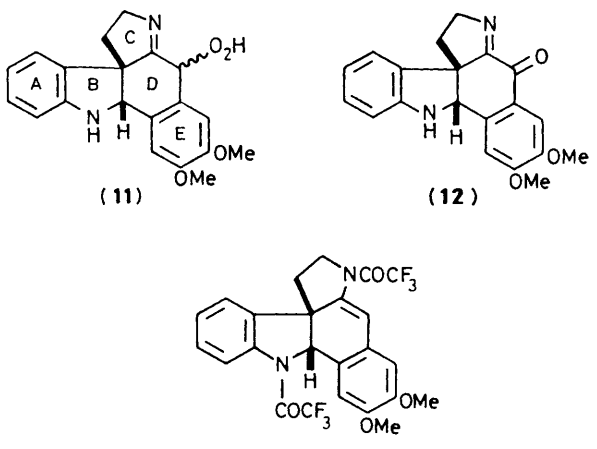
In our hands, however, the cyclisation of (**4**) with phosphorus trichloride gave a crude product from which, after chromatographic purification, the spirocyclic indoline (**12**), m.p. 241—244 °C, was isolated in 46% yield. Small amounts of β-carboline derivatives and of the hydroperoxide (**11**), m.p. 273—274 °C, were also isolated. Similar results were obtained using phosphoryl chloride as cyclising reagent. The structures of the products were elucidated by elemental analyses, and by spectroscopic methods (u.v., mass, and n.m.r.). The overall sequence of reactions involved in the formation of the spirocyclic indoline (**12**) presumably follows the route shown in Scheme 2 as far as (**7**), but autoxidation of this species by molecular oxygen then affords the hydroperoxide (**11**), which subsequently breaks down by loss of water.




**Scheme 3**



Whilst this work was in progress a report[5] appeared that a similar cyclisation of a related arylacetyltryptamine had given a mixture of two spirocyclic indolines after reduction of the initial product; the total yield, however, was only 26%.

As the foregoing reactions had given mixtures of products we sought other cyclising reagents, and found that trifluoroacetic anhydride treatment of (**4**) in benzene solution for 3 h at 0 °C, followed by 1 h at 20 °C, afforded the bis-trifluoroacetyl spirocyclic indoline (**13**), m.p. 271 °C, in quantitative yield. This was presumably formed *via* the spirocyclic indolenine (**5**) and the indoline (**7**). Hydrolysis of (**13**) with aqueous ammonia afforded the oxo-derivative (**12**) in 95% yield after work-up. This product proved to be identical in all respects with that obtained by the phosphorus trichloride cyclisations and reflects the ease with which the enamine-imine system of the intermediate spirocyclic indoline undergoes autoxidation.[6] Rings B and D in all the spirocyclic products described in this paper are presumed to be *cis* to one another (as shown) because a *trans*-ring junction would be highly strained as shown by studies of molecular models, and other considerations; the stereochemistry of the hydroperoxy-group in (**11**) is not known but the 360 MHz $^1$H n.m.r. spectrum shows that only one stereoisomer is formed.

These results provide confirmation that acetylation of 3-alkyl indoles involves initial attack at the 3-position, and show that intramolecular type cyclisation of suitable *N*-acyltryptamines (*cf.* compound **2**) has considerable potential in the synthesis of complex indolines structurally related to indole alkaloids.

We are grateful to the S.E.R.C. for support of this work.

*Received, 11th October 1982; Com. 1192*

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