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ELECTROPHILIC SUBSTITUTION IN INDOLES—II[1]

THE FORMATION OF 3,3-SPIROCYCLIC INDOLE DERIVATIVES FROM TRYPTAMINES AND THEIR REARRANGEMENT TO β-CARBOLINES

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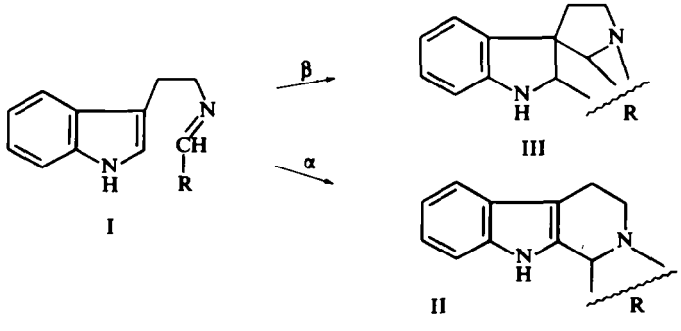
Abstract—Attempts to isolate 3,3-*spiro*-cyclicindolenines thought to be intermediates in the cyclization of benzylidenetryptamines to tetrahydro-β-carbolines are described. One such *spiro*-pyrrolidinoindolenine, prepared by an alternative route from a spirocyclic oxindole derivative, was shown to undergo an extremely facile acid catalysed rearrangement to a tetrahydro-β-carboline. In contrast two piperidino*spiro*indolenines did not rearrange to β-carbolines even under very vigorous acidic treatment. The relevance of these reactions to a new theory of electrophilic substitution in 3-substituted indoles, and the biogenesis of indole alkaloids is discussed.

THE biosynthesis of indole alkaloids has excited the interest of organic chemists for many years, and early speculations were reviewed by Robinson[2] in 1955. Since then radioactive tracer studies have shown that tryptophan is the precursor of the indole portion of the majority of indole alkaloids. Recently interest has centred on the origin of the alicyclic C_{10}-moiety in the three main classes (i.e. the yohimbine, aspidosperma and iboga types), and this has culminated in the discovery that they are derived from mevalonate.[3] Further work, in progress, is aimed at finding out the precise nature of the C_{10}-precursors, how they are derived from mevalonate, and how they are incorporated into the alkaloids.[4]

Our own work, which was started several years ago,[5] has not been concerned directly with this problem but rather with the mechanisms of condensation of tryptophan (or tryptamine) with the alicyclic moiety. By analogy with the long known biogenetic type syntheses of simple β-carbolines,[6] the initial product is presumably a Schiff's base (I) formed by condensation of the tryptamine with an

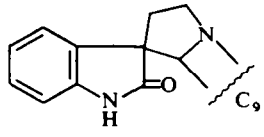


aldehyde (or α-keto acid). This Schiff's base then undergoes cyclization at either α- or β-position of the indole nucleus to yield (eventually) the "α-" (II) or the "β-" (III) types of indole alkaloids. Simple examples of the α-series are the β-carbolines, whilst more complex examples include yohimbine and its congeners; the strychnos and aspidosperma types provide many examples of the β-series.

However, whilst this hypothesis has received general acceptance in recent years, and tracer experiments have clearly shown the origin of many indole alkaloids from tryptophan and mevalonate, it is not clear what controls the direction of the initial ring closure (i.e. whether it occurs in an "α-" or "β-" sense). Admittedly one could argue that the control is essentially enzymic, and that no fruitful purpose would be served by further discussion until more was known of the nature and mode of action of the enzymes involved. However, on the other hand the mode of cyclization must be essentially similar to analogous model reactions of indoles in the laboratory, and this paper is concerned with some preliminary studies in this area.

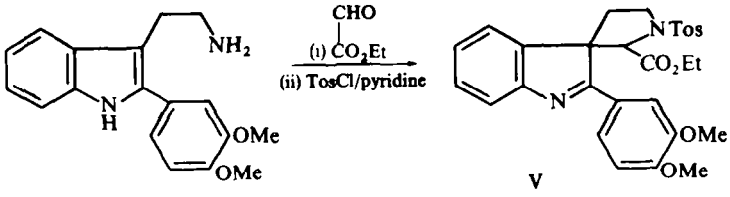
Woodward[7] originally put forward two theories for the biogenesis of strychnine, the first of which involved formation of a 3,3-*spiro*-cyclicindolenine (cf. III) intermediate which was then assumed to undergo cyclization by attack of a suitably placed nucleophilic centre in the alicyclic moiety. (Admittedly theories of the origin of the latter current at the time have since been disproved,[3] but the basic concept is still accepted.) This suggestion was later extended to include the aspidosperma group of alkaloids, and circumstantial evidence for it has since been provided by Robinson's model experiments on the condensation of ketones with indoles,[8] and by Van Tamelen's biogenetically patterned experiments[9] leading to a close relation of the Wieland-Gumlich aldehyde. Woodward's second theory[7] involved initial oxidation of the tryptamine to oxindolylethylamine, and this would readily account for the formation of 3,3-spirocyclic intermediates (which could lead to the β-indole alkaloids) because of the high anionoid activity of the 3-position in oxindoles. This suggestion has been further developed by Hendrickson,[10] but it seems somewhat less attractive than the first hypothesis for two reasons, (i) oxindole alkaloids are comparatively rare, and moreover their presence has not yet been observed in plants of the strychnos family, and (ii) the intermediate *spiro*-cyclicoxindole would have to be reduced at a later stage in the biosynthesis (thus effectively reversing the initial oxidation step) in order to account for the formation of many of the β-indole alkaloids.

In fact Woodward's first scheme[7] can be readily extended to include the oxindole alkaloids for it has long been known that hydration of the double bond in an indolenine, followed by oxidation affords the corresponding oxindole,[11,12] e.g. III could give IV. This type of oxidation has been carried out in the laboratory with such mild reagents as ferricyanide, and silver oxide.[11,12]



IV

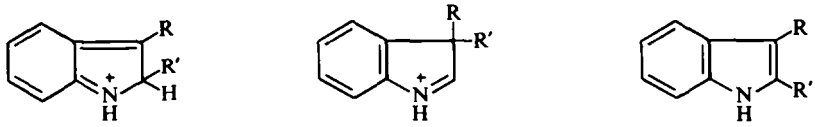
Woodward's first suggestion[7] is also supported by his own extremely elegant synthesis[13] of strychnine since one of the initial stages involved the formation of a *spiro*-cyclicindolenine (V) from 2-veratryltryptamine and glyoxylic ester. Admittedly



V

the 2-position is blocked in this case, whereas 2-unsubstituted tryptamines condense with aldehydes to give β-carbolines under neutral or mildly acidic conditions[6] and thus apparently provide examples of direct substitution at the 2-position. Indeed it has been suggested that the 2-position in skatole and other 3-alkylindoles is the most favoured for electrophilic attack.[14] However in indole itself the 3-position is the most reactive, and UV and NMR studies clearly show that protonation of indole and 3-substituted indoles in strongly acidic media occurs at the 3-position, to give 3-[H]—indolium salts.[15,16] Moreover studies in deuterated acids have indicated that hydrogen exchange at the 2-position is extremely slow compared with that at the 1- and 3-positions,[15] and alkylation of the Grignard derivatives of 3-alkylindoles also affords 3,3-disubstituted indolenines.

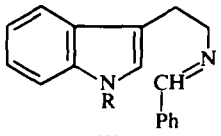
Consideration of the mechanisms of these reactions indicates that direct electrophilic substitution at the 2-position of the indole nucleus is energetically unfavourable (compared with attack at position-3) because it involves primary formation of an intermediate of general structure VI in which the π-electron system of the benzene ring has been disturbed.[17] Substitution at the 3-position in contrast gives an intermediate of type VII without involving the benzene ring, and, insofar as one may regard indole as an enamine derived from aniline, this is also consistent with the normal mode of attack of electrophiles at the β-position of an enamine.[18] Indolenines of type VII, synthesized by alkylation of indole Grignard reagents, readily rearrange



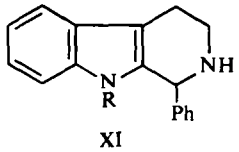
VI VII VIII

under acidic conditions to 2,3-disubstituted indoles (VIII),[1,19] and we have also shown that which substituent migrates depends on their relative migratory aptitudes.[1,5,20] We suggested,[1] therefore, that formation of many 2,3-disubstituted indoles (VIII) by electrophilic substitution in 3-substituted indoles involves initial formation of an indolenine (VII), followed by rearrangement, rather than direct substitution at the 2-position. This view has received strong support in subsequent work,[20,21] but the present paper is concerned with earlier model experiments aimed at the synthesis of indolenines thought to be intermediates in the formation of tetrahydro-β-carbolines.

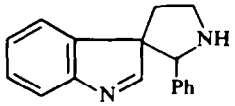
Our initial idea was that it might be possible to isolate such an indolenine intermediate X in the cyclization of N-benzylidenetryptamine (IX: R = H) which had earlier been shown to afford 1-phenyl-tetrahydro-β-carboline (XI; R = H) under mildly acidic conditions.[22] However even under such mild conditions as treatment with dry hydrogen chloride in dry ether an immediate quantitative yield of the β-



IX

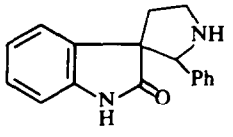


XI

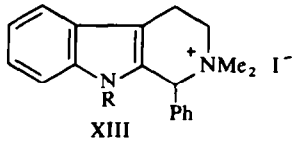


X

carboline was obtained. Similarly the *ind*-N-methyl derivative (IX R = Me) gave the 9-methyltetrahydro-β-carboline (XI; R = Me). Benzylidene tryptamine (IX; R = H) was recovered unchanged after warming in aqueous solution at pH8 for several hours but on heating more strongly at higher pH hydrolysis occurred. It is conceivable that a small amount of the *spiro*-cyclicindolenine (X) is formed under these conditions (in equilibrium with the benzylidenetryptamine), and if so hydration and oxidation might be expected to lead irreversibly to the formation of the corresponding *spiro*-cyclicoxindole (XII) (cf. our speculations above concerning the biogenetic origin of the oxindole alkaloids). However attempts to effect this type of reaction by ferricyanide oxidation under neutral and alkaline conditions in both one, and two, phase systems did not, unfortunately meet with success.



XII



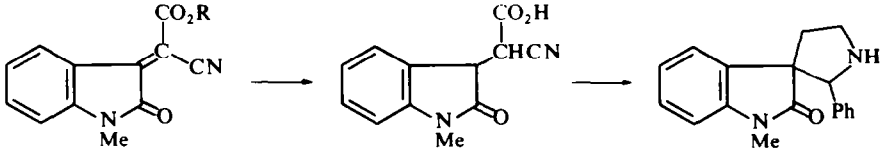
XIII

On heating benzylidenetryptamine with methyl iodide at 100° in a sealed tube for 2 hr, Hoshino and Kotake[22] obtained the tetrahydro-β-carboline methiodide (XIII; R = H); we also obtained the same product by brief warming with methyl iodide in methanol, and the *ind*-N-methylbenzylidenetryptamine (IX; R = Me) similarly gave the methiodide XIII (R = Me). Next bearing in mind the formation of the spirocyclic indolenine (V) in Woodward's strychnine synthesis we treated benzylidenetryptamine (IX; R = H) with *p*-toluene sulphonyl chloride in pyridine at room temperature but unfortunately the only product was the N-tosyl-tetrahydro-β-carboline. Another possibility investigated was the activation of the indole nucleus in benzylidenetryptamine by reaction with methyl magnesium iodide to give the Grignard derivative; however, no evidence of cyclization was obtained (spectroscopically) and starting material was quantitatively recovered on work-up.

In view of Woodward's successful synthesis of a *spiro*-cyclicindolenine from a 2-substituted tryptamine, we also attempted to cyclize 2-methylbenzylidenetryptamine in the same manner as above. However, spectroscopic examination of the reaction mixtures showed that only indolic materials were present (Experimental). Clearly cyclization is energetically unfavourable in this case, whereas Woodward's

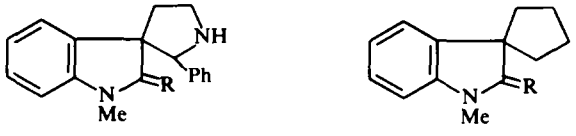
success may perhaps be attributed to greater stability induced by the stilbene like conjugation of his veratryl-indolenine product V.

We were therefore faced with two possibilities in considering the cyclization of benzylidenetryptamines to give tetrahydro-β-carbolines, (i) that direct electrophilic attack at the 2-position is involved, or (ii) that an intermediate indolenine (e.g. X), if formed, rearranges extremely easily to the β-carboline. In order to follow up the latter possibility we set out to synthesize a *spiro*-cyclicindolenine intermediate of this type by an alternative route via the *spiro*-cyclicoxindole (XVI) shown below. The latter was synthesized by essentially the same route as that developed by Harley-Mason and Ingleby,[23] although a more convenient method of preparing one of the intermediates was devised. Condensation of N-methylisatin with benzyl cyanoacetate gave the isatylidene cyanoacetate (XIV; R = Bzl) which was readily hydrogenolysed and reduced to the oxindolyl-cyanoacetic acid (XV). (In the original method[23] ethyl cyanoacetate was used and the conditions of the subsequent

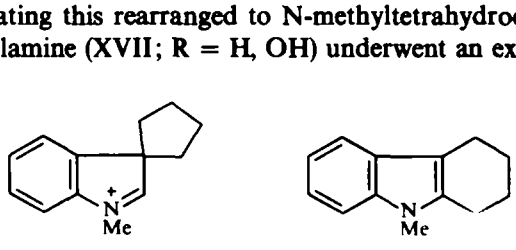


reduction and hydrolysis of the isatylidene cyanoacetate (XIV; R = Et) were quite critical in order to avoid undesirable side reactions). Decarboxylation of the cyanoacetic acid (XV) followed by catalytic reduction of the nitrile and condensation with benzaldehyde then afforded the desired *spiro*-cyclicoxindole (XVI).

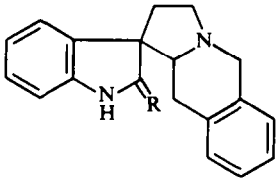
The latter was reduced to the corresponding carbinolamine (XVII; R = H, OH) by treatment with the calculated quantity of LAH in ether; the use of excess hydride



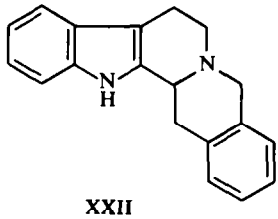
led to the formation of the indoline (XVII R = H_2). Similar results were obtained in the reduction of the cyclopentyloxindole (XVIII; R = O) whereas Witkop and Patrick[24] had only obtained the carbinolamine (XVIII; R = H, OH) using excess hydride. In cold 6N HCl the UV spectrum indicated only formation of the indolenine salt XIX, but on heating this rearranged to N-methyltetrahydrocarbazole (XX). In contrast the carbinolamine (XVII; R = H, OH) underwent an extremely facile acid



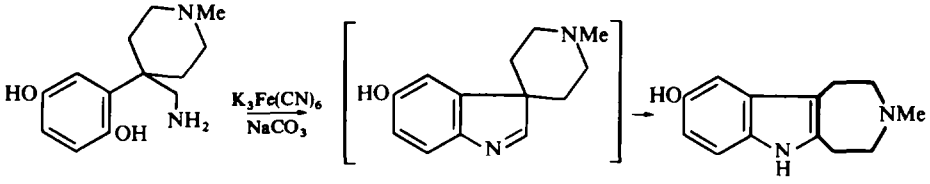
catalysed rearrangement to *ind*-N-methyl-1-phenyltetrahydro-β-carboline (XI; R = Me). Even spectroscopic grade ethanol (unless basified) was sufficiently acidic to cause rearrangement, and it was essential to work up the LAH reduction mixture entirely under alkaline conditions. UV studies even under the mildest acidic conditions did not detect the formation of the intermediate indolenine (*ind*-N-methosalt of X). The latter must therefore rearrange very easily to the β-carboline and it is not surprising that we failed to isolate or detect such an intermediate in the cyclization of benzylidenetryptamines. It seems very likely that both the Ph group and the side-chain amino-function assist in facilitating the rearrangement because (i) later work has shown that the benzyl group in 3-benzyl-3-methylindolenine rearranges very readily under mild acidic conditions to give 2-benzyl-3-methylindole,[20] and (ii) the pentacyclicindolinol (XXI; R = H, OH) is presumably an intermediate in the reduction of the oxindole (XXI, R = O) with LAH to give the yohimbine derivative XXII[25,26] and rearrangement of the aminomethyl grouping presumably occurs



XXI



XXII

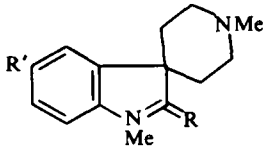


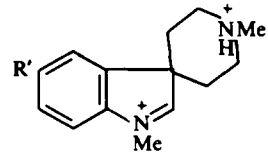
XXIII XXIV XXV

under the mild acidic conditions used in the work-up (not thermally or spontaneous as suggested by Belleau[26]). (A rearrangement, in the reverse direction, of a 1-benzyltetrahydro-β-carboline to a *spiro*-cyclicindoline in hot concentrated hydrochloric acid has been described by Harley-Mason and Waterfield,[27] but the vigorous conditions used and the fact that the rearrangement product is stabilized by a further ring closure vitiates direct comparison with the examples discussed above).

An analogous rearrangement of an intermediate indolenine XXIV presumably also occurs in the formation of the azepindole derivative XXV on oxidative cyclization[28] of the dihydroxyphenylethylamine (XXIII). In order to test this hypothesis we prepared the spirocyclicoxindole[29] (XXVI; R = O R′ = H) from N-methyloxindole and 2,2′-dichlorodiethylmethylamine, and reduced it to the corresponding carbinolamine (XXVII; R = H, OH, R′ = H). However the latter proved to be

extremely stable under acidic conditions (Experimental) and was not rearranged even by heating with polyphosphoric acid at 180° for 4 hr, starting material being recovered in good yield on basification. In 0·5N HCl the UV spectrum was identical


XXVI


XXVII

with that of the free base, whereas in stronger acid (6N) the spectrum was typical of an indolenine salt (Table 1); (The dipicrate of the indolenine salt XXVII also showed a tendency to dissociate on recrystallization). It is thus clear that protonation of the aliphatic amino group precedes indolenine (XXVII) formation, and the positive charge on the spirocyclicpiperidine ring inhibits rearrangement by reducing its migratory aptitude. The facile rearrangement involved in the transformation of the

TABLE 1. UV SPECTRA of 2-HYDROXYINDOLINES

Hydroxyindoline	In 95% Ethanol		In 6N Ethanolic HCl	
	λ_{max} (mμ)	log ε_{max}	λ_{max} (mμ)	log ε_{max}
XVII R = H, OH	248	4·11	(rearranges)	
	293	3·64		
XVIII R = H, OH	250	3·96	235	3·60
	300	3·44	240	3·60
			280	3·50
XXVI R = H, OH;	250	4·04	234	3·88
R′ = H	299	3·49	240	3·86
			286	3·72
XXVII R = H, OH;	248	4·04	254	3·48
R′ = OMe	318	3·56	334	3·51

phenylethylamine (XXIII) to the azepindole (XXV) however occurs at neutral pH, and may well be facilitated by favourable energy factors in the steps preceding rearrangement. The indolic N-Me group in the carbinolamine (XXVI; R = H, OH, R′ = H) may be partly responsible for the different results in the two reactions but the effect is presumably a minor one, and the preparation of the N-desmethyl analogue would present considerable problems. The other difference between the two series of compounds is the 5-OH group in XXIII, XXIV and XXV; however the 5-OMe analogue in the other series (XXVI; R = H, OH; R′ = OMe) behaves in exactly the same way as the unsubstituted compound by forming an indolenine salt (XXVII; R′ = OMe) in acidic media which does not rearrange. An interesting feature of the UV spectra of these two compounds (Table 1) is the bathochromic shift of the long wavelength band compared with the other carbinolamines and indolenines; this parallels other observations on 5-hydroxy- and 5-alkoxyindolenines.[16,30] Further work on the factors influencing these rearrangements is in progress.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined with a Unican SP500 instrument. Light petrol refers to the fraction b.p. 60–80° (unless otherwise stated).

N(b)-*Benzylidenetryptamine.* Tryptamine (1·6 g) and freshly distilled benzaldehyde (1·06 g) in benzene (30 ml) were heated under reflux in a flask attached to a Dean and Stark separator for 30 min. After evaporation of the benzene the residual yellow gum was crystallized from light petrol to give the benzylidenetryptamine (1·5 g; 61%) as needles, m.p. 118° (lit.[17] 120–121°). (Found: C, 82·3; H, 6·4; N, 11·4. Calc. for $C_{17}H_{10}N_2$: C, 82·2; H, 6·5; N, 11·3%); λ_{max} (log ε_{max}) in 95% EtOH: 223 (4·55), 246 (4·24), 281 (3·88%) mμ.

3-(*Benzylideneaminoethyl*)-1-*methylindole. Ind*-N-methyltryptamine (1·74 g) and benzaldehyde (1·06 g) were condensed in boiling benzene as in the analogous example above. The red oil, obtained on evaporation of the benzene, was distilled at 160°/l. mm to give 3-(benzylideneaminoethyl)-1-methylindole (1·2 g; 46%) as a pale yellow oil, which darkened rapidly on exposure to air. (Found: C, 82·0; H, 7·2. $C_{18}H_{18}N_2$ requires: C, 82·4; H, 6·9%); λ_{max} (log ε_{max}) in 95% EtOH: 226 (4·60), 244 (4·24), 284–286 (3·88) mμ.

3-(*Benzylideneaminoethyl*)-2-*methylindole.* 2-methyltryptamine (1·74 g) and benzaldehyde (1·06 g) were condensed together as in the foregoing preparations, and gave the corresponding *benzylidinetryptamine* (1·6 g; 61%) as pale cream plates, m.p. 93–94° from light petrol. (Found: C, 82·5; H, 7·0; N, 10·6. $C_{18}H_{18}N_2$ requires: C, 82·4; H, 6·9; N, 10·7%); λ_{max} (log ε_{max}) in 95% EtOH: 227 (4·56), 245 (4·25), 281 (3·96), 290 (3·91) mμ.

Cyclization of benzylidenetryptamines

(a) Dry HCl was passed into a soln of benzylidenetryptamine (0·10 g) in dry ether (5 ml), and the yellow gummy product formed rapidly solidified. The latter crystallized from EtOH–AcOEt to give phenyl-1,2,3,4-tetrahydro-β-carboline hydrochloride (0·10 g; 87%) as tiny prisms, m.p. 258–260° (lit.[18] 258°); λ_{max} (log ε_{max}): 221 (4·55), 272 (3·86), 281 (3·85), 291 (3·70) mμ. The free base crystallized from light petrol as prisms m.p. 168–169° (lit.[17] 168°).

In a similar manner the *ind*-N-methyl analogue gave 9-*methyl*-1-*phenyl*-1,2,3,4-*terahydro*-β-*carboline hydrochloride* as tiny prisms (from EtOH–AcOEt) m.p. 275–277° (dec). (Found: N, 9·4; $C_{18}H_{18}N_2 \cdot HCl$ requires: N, 9·4%); λ_{max} (log ε_{max}) in 95% EtOH: 224 (4·65), 276 (3·93), 284 (3·92) mμ. The *free base* crystallized from light petrol as rhombs m.p. 120°.

The 2-methylbenzylidenetryptamine also gave a yellow gummy product on treatment with dry HCl in ether, but this proved to be very unstable and decomposed on exposure to air to a red oil which smelt of benzaldehyde.

(b) Benzylidenetryptamine (0·20 g) and MeI (2 ml) in MeOH (5 ml) were heated together under reflux for 1 hr. On cooling 2-methyl-1-phenyl-1,2,3,4-tetrahydro-β-carboline methiodide (0·26 g; 81%) crystallized as pale yellow needles, m.p. 217° (lit.[18] 218–219°); λ_{max} (log ε_{max}) in 95% EtOH: 220 (4·76), 271 (3·91), 281 (3·89), 290 (3·82) mμ.

Ind-N-methylbenzylidenetryptamine similarly gave 2,9-*dimethyl*-1-*phenyl*-1,2,3,4-*tetrahydro*-β-*carboline methiodide* (78%) as pale yellow needles, m.p. 252°. (Found: C, 57·1; H, 5·6; N, 6·2. $C_{20}H_{23}N_2I$ requires: C, 57·4; H, 5·5; N, 6·7%); λ_{max} (log ε_{max}) in 95% EtOH: 222 (4·78), 278 (3·91), 284 (3·93) mμ.

Treatment of 2-methylbenzylidenetryptamine with MeI in MeOH gave an intractable gummy material which could not be crystallized. However, its UV spectrum (λ_{max} 224, 285 mμ) was clearly indolic indicating that the gum may be a mixture of N-methylated derivatives and not a spirocyclic indolenine.

(c) N-Benzylidenetryptamine in aqueous EtOH at pH 7–8 was kept at 60° for 5 hr and recovered unchanged on work-up, as shown by mixed m.p. and IR comparisons.

(d) N-Benzylidenetryptamine (1·0 g) in dry ether was treated with EtMgI (0·9 g; 1·1 equivs) in ether (10 ml) and after standing for a short while the complex was decomposed with 5% Rochelle salt soln. The organic product was extracted into ether, dried (K_2CO_3) and the ether evaporated to dryness to yield starting material (0·95 g) identified by m.p. and IR comparisons.

(e) N-Benzylidenetryptamine (0·50 g) in dry pyridine (3 ml) was treated with freshly recrystallized *p*-toluenesulphonyl chloride (0·33 g) and the mixture kept overnight at 20°. On removal of the pyridine *in vacuo* a hygroscopic yellow solid was obtained, and crystallized from EtOH to give 1-phenyl-2-tosyl-1,2,3,4-*tetrahydro*-β-*carboline* (0·52 g; 64%) as colourless needles, m.p. 192°. (Found: C, 71·8; H, 5·4; N, 6·8. $C_{24}H_{22}O_2N_2S$ requires: C, 71·6; H, 5·5; N, 7·0%); λ_{max} (log ε_{max}) in 95% EtOH: 225, 275 and 290 mμ. The same product was also formed by direct tosylation of 1-phenyl-1,2,3,4-tetrahydro-β-carboline.

1-*Methyl*-3,3-spiro-*cyclopentylindoline*. 1-Methyl-3,3-*spiro*-cyclopentyloxindole (0·20 g) in dry ether (30 ml) was heated under reflux for 1 hr with a suspension of LAH (0·057 g). After decomposition of the complex with water the product was extracted with ether and dried (K_2CO_3). Removal of the ether gave a colourless oil, (UV spectrum—see Table 1) which was characterized as its orange *picrate* m.p. 176° from EtOH. (Found: C, 54·8; H, 5·0; N, 13·4. $C_{13}H_{17}N \cdot C_6H_3O_7N_3$ requires: C, 54·8; H, 4·8; N, 13·5%).

2-*Hydroxy*-1-*methyl*-3,3-spiro-*cyclopentylindoline*. 1-Methyl 3,3-*spiro*-cyclopentyloxindole (0·20 g; 1·0 mmole) was added to a suspension of LAH (0·019 g; 0·5 mmole) in dry ether (30 ml), and the mixture heated under reflux for 1 hr. The complex was cautiously decomposed with water, and the product extracted with ether and dried (K_2CO_3). Evaporation of the ether gave the desired hydroxyindoline as a reddish oil. This product was characterized by its UV spectra (Table 1) and its IR spectrum (film): ν_{max} 3·10 μ (OH), no absorption in the carbonyl region (5·7–6·1 μ). Distillation of this material gave a colourless oil the IR spectrum of which showed that some re-oxidation to oxindole had occurred (ν_{max} (film): 3·10 (OH) and 5·85 (CO) μ).

A soln of the hydroxyindoline (0·1 g) in 6N-HCl (5 ml) was warmed at 80° for 10 min and the turbid soln formed was basified with dil NaOH aq. 9-Methyl-1,2,3,4-tetrahydrocarbazole (0·08 g; 80%) separated out, and crystallized from MeOH as plates, m.p. 50°, not depressed on admixture with an authentic sample.

Benzyl α-*cyano*-1-*methyl*-3-*oxindolylideneacetate*. 1-Methylisatin (16·1 g), benzyl cyanoacetate (17·5 g) and piperidine (0·2 ml) in EtOH (70 ml) were heated under reflux for 4 hr. After keeping overnight at 0° the brown solid product was filtered, washed with cold EtOH and re-crystallized from EtOH to give the *benzyloxindolylidenecyanoacetate* (27·7 g; 87%) as purple needles, m.p. 136°. (Found: C, 71·4; H, 4·4; N, 8·9. $C_{19}H_{14}N_2O_3$ requires: C, 71·7; H, 4·4; N, 8·8%.)

α-*Cyano*-1-*methyl*-3-*oxindolylacetic acid*. The foregoing cyanoacetate (10·0 g) in EtOH (100 ml) was hydrogenated at 20° and 1 atm. over Pd–C (0·2 g; 5%). After 1 hr the soln became colourless and 1 mole of H_2 had been absorbed indicating that reduction of the double bond had occurred. Hydrogenolysis of the benzyl ester was complete after a further 9 hr, and then removal of catalyst and solvent gave oxindolylcyanoacetic acid (5·7 g; 81%) as prisms, m.p. 113° (lit.[23] 115°) from hot water.

This product was then converted into 1-methyloxindolyl ethylamine by Harley-Mason and Ingleby's method.[23]

2-*Hydroxy*-1-*methyl*-2'-*phenylindoline*-3-spiro-3'-*pyrrolidine*. The condensation product (0·28 g; 1·0 mmole) from 1-methyloxindolylethylamine and benzaldehyde, in dry ether (30 ml) was heated under reflux with LAH (0·019 g; 0·5 mmole) for 1 hr. The complex was destroyed by addition of a few drops of 0·5N NaOH and the inorganic solids removed by filtration. The ether extract was dried (K_2CO_3), evaporated to small bulk and cooled to 0°. The *hydroxindoline* (0·14 g; 51%) crystallized as fibrous needles, and was recrystallized from ether (which had been previously shaken with solid K_2CO_3 to remove traces of acidic impurities), m.p. 108–110°. (Found: C, 76·8; H, 7·3. $C_{18}H_{20}N_2O$ requires: C, 77·1; H, 7·2%); UV spectrum—see Table 1. ν_{max} (Nujol): broad band 3·1–4·5 μ indicated hydrogen bonded OH group, perhaps partly internally bonded to the N of the pyrrolidine ring.

In a similar manner, but using excess LAH (1·5 mmoles) the corresponding 1-*methyl*-2'-*phenylindoline*-3-spiro-3'-*pyrrolidine* was prepared in 95% yield, as a colourless oil, which slowly solidified and on recrystallization from ether gave clusters of needles, m.p. 105°. The *monopicrate* formed orange fibrous needles, m.p. 186° from EtOH. (Found: C, 58·6; H, 4·6. $C_{18}H_{20}N_2 \cdot C_6H_3O_7N_3$ requires: C, 58·4; H, 4·7%.)

9-*Methyl*-1-*phenyl*-1,2,3,4-*tetrahydro*-β-*carboline*. The foregoing 2-hydroxyindoline (50 mg) in ether was treated with dry HCl and gave a brown gum which crystallized from EtOH–AcOEt as tiny prisms m.p. 275° (dec). This was identical (m.p., mixed m.p., IR and UV spectra) with the product from cyclization of *ind*-N-methylbenzylidenetryptamine.

The same product was also obtained in quantitative yield by treating the hydroxyindoline with very dilute mineral acid.

1,1'-*Dimethyl*-2-*hydroxyindoline*-3-spiro-4'-*piperidine*. The corresponding oxindole[29] (0·23 g; 1·0 mmole) in dry ether (30 ml) was heated under reflux with LAH (0·019 g; 0·5 mmole) for 1 hr. After decomposing the complex with water the ether extracts were dried (K_2CO_3) and evaporated to give the *hydroxyindoline*-spiro-*piperidine* (0·10 g; 44%) as cubes, m.p. 164–166° from ether. (Found: C, 72·3; H, 8·9; N, 12·2. $C_{14}H_{20}ON_2$ requires: C, 72·4; H, 8·7; N, 12·1%); UV spectra are recorded in Table 1, ν_{max} (Nujol) 2·9–4·0 μ (bonded OH), no absorption in the carbonyl region.

The picrate formed orange needles, m.p. 200–202° from ethanolic picric acid, the analysis of which corresponded to the *indolenine* (XXVII; R = H) *dipicrate*. (Found: C, 46·6; H, 3·7; N, 15·9. $C_{14}H_{19}N_2 \cdot C_6H_2O_7N_3 \cdot C_6H_3O_7N_3$ requires: C, 46·4; H, 3·6; N, 16·5%.) On recrystallization from EtOH the m.p.

was 198–200° and analysis indicated that the dipicrate had largely dissociated into the monopicrate of the hydroxyindoline (XXVI; R = H, OH, R' = H). (Found: C, 53·7; H, 5·8; N, 13·6. $C_{14}H_{20}N_2O \cdot C_6H_3N_3O_7$ requires: C, 52·1; H, 5·0; N, 15·2%.)

A selection of attempts to effect rearrangement of this hydroxyindoline to the corresponding azepindole is given below.

(a) Treatment with 6N methanolic HCl at 80° for 5 hr followed by basification and work-up by ether extraction etc gave starting material only in 90% yield.

(b) The 2-hydroxyindoline (50 mg) was heated in polyphosphoric acid (150 mg) at 180° under N_2 for 4 hr. The dark brown mixture formed was diluted with water, basified and ether extracted etc to give starting material (28 mg; 56%).

(c) The hydrobromide salt (150 mg) (prepared by passing dry HBr into an ether soln of the indoline) was heated under reflux in water (10 ml) for 4 hr. Basification and work-up however gave only starting material.

(d) The hydroxyindoline (50 mg) was heated at 200° *in vacuo* for 2 hr. On cooling the yellow viscous oil produced was dissolved in ether (1·0 ml) and starting material (32 mg; 64%) crystallized and was identified by mixed m.p. and spectral comparisons. The ethereal mother liquors gave a yellow gum on evaporation, which was identified as the corresponding oxindole by means of its IR and UV spectra, thus indicating that some oxidation had occurred during heating.

TABLE 2. UV SPECTRA OF OXINDOLES AND INDOLINES IN 95% ETHANOL

Oxindoles	λ_{max} (mμ)	log ε_{max}	Indolines	λ_{max} (mμ)	log ε_{max}
XVII R = O	258	3·77	XVII R = H_2	253	3·85
				302	3·40
XVIII R = O	255	3·88	XVIII R = H_2	251	3·91
				298	3·44
XXVI R = O; R' = H	254	3·89			
XXVI R = O; R' = OMe	263	3·96			
	301	3·29			

5-Methoxy-1,1'-dimethyloxindole-3-spiro-4'-piperidine. To 5-methoxy-1-methyloxindole (4·6 g) in dry toluene (30 ml) was added powdered 2,2'-dichlorodiethylmethylamine hydrochloride (5·0 g) with stirring. Sodamide (3·04 g) was then added in small portions and the temp of the mixture kept at 35–45° by external cooling. After addition was complete the mixture was stirred and heated under reflux for 2 hr, cooled and poured into water (50 ml). Basic material was extracted from the toluene layer with 2N HCl (4 × 25 ml), and the extracts were then basified, and extracted with benzene (3 × 25 ml). The dried (K_2CO_3) benzene soln was evaporated to give a dark oil, which distilled at 200°/0·2 mm to give the *oxindole-spiro-piperidine* (2·6 g; 38%) as a viscous yellow oil which slowly solidified. It was recrystallized from ether to give cream plates, mp. 100–102°. (Found: C, 69·5; H, 7·9; N, 10·6. $C_{15}H_{20}N_2O_2$ requires: C, 69·2; H, 7·7; N, 10·8%.)

2-Hydroxy-5-methoxy-1,1'-dimethylindoline-3-spiro-4'-piperidine. The foregoing *spiro*-oxindole was reduced with LAH (0·5 molar equiv) in ether in the usual manner, and the desired *hydroxyindoline* obtained in 42% yield, as rosettes of needles, m.p. 130–132° from ether. (Found: C, 68·3; H, 8·3; N, 10·7. $C_{15}H_{22}N_2O_2$ requires: C, 68·7; H, 8·4; N, 10·7%); ν_{max} (Nujol) 3·1–4·0 μ (bonded OH).

Attempts to rearrange this material by the methods described above for the 5-desmethoxy analogue all failed. Starting material being recovered in each case.

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