SYNTHETIC STUDIES IN THE STRYCHNOS-TYPE ALKALOID FIELD

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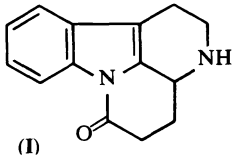
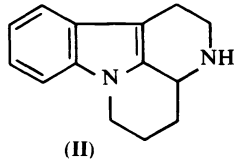
ABSTRACT

A highly general synthetic route to strychnos-type alkaloids is exemplified by the total synthesis of tubifoline, condyfoline, geissoschizoline, fluorocurarine and condylocarpine.

Our entry into the field of total synthesis of strychnos type alkaloids was initially somewhat fortuitous. Lithium aluminium hydride reduction of the lactam (**I**), obtained[1] from the reaction of tryptamine with α-ketoglutaric acid, had been reported[2] in 1965 to give the base (**II**). On re-investigation of

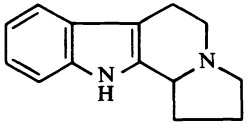


(I)

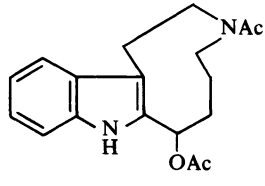


(II)

this reduction we concluded[3] that this structure assignment was incorrect and that the product was the isomeric base (**III**); this conclusion was simultaneously reached by Italian workers[4] independently. In the course of our studies we found that the base reacted very readily and quantitatively with acetic anhydride, giving a product whose structure was shown[5] to be (**IV**). This very ready formation of a compound containing an indole fused to a nine-membered ring suggested interesting synthetic possibilities which were then pursued.

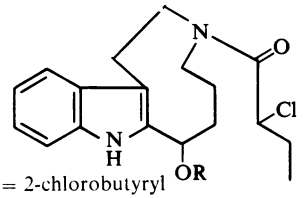


(III)

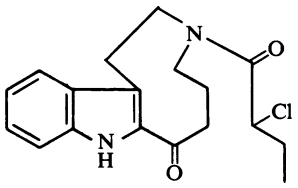


(IV)

Treatment of (**III**) with 2,2′-dichlorobutyric anhydride gave the expected product (**Va**). Hydrolysis with cold dilute alkali gave the alcohol (**Vb**), which with manganese dioxide or lead tetra-acetate was smoothly oxidized to the ketone (**VI**).

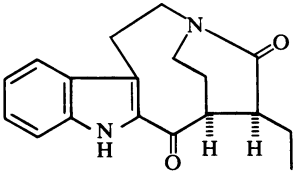


(Va) R = 2-chlorobutyryl
(Vb) R = H

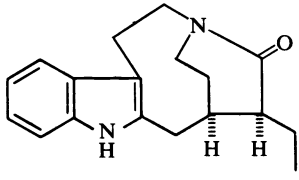


(VI)

Treatment of this ketone with sodium *t*-amyloxide in benzene gave the tetracyclic keto-lactam (**VII**) as one stereoisomer only. This key intermediate was obtained in good yield and served as the foundation for several synthetic sequences.

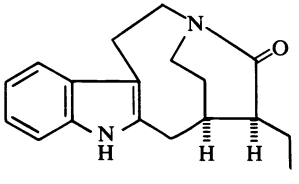


(VII)

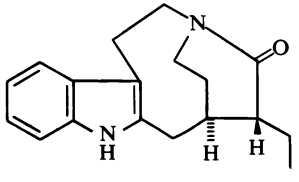


(VIII)

Wolf–Kishner reduction eliminated the ketone carbonyl to yield the lactam (**IX**): a small amount of the stereoisomeric lactam (**X**) was also obtained.

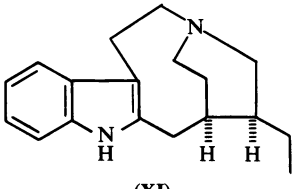


(IX)

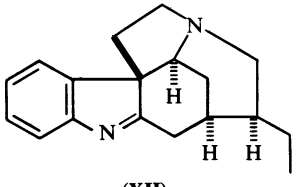


(X)

On reduction of (**IX**) with lithium aluminium hydride the tetracyclic base (**XI**) was obtained. This proved to be identical (apart from optical activity) with a degradation product previously obtained by Smith and Wröbel[6] from akuam-



(XI)

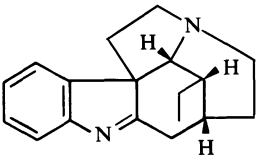


(XII)

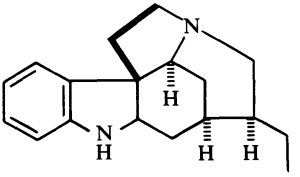
micine, which confirmed all structural and stereochemical assignments thus far. Schumann and Schmid had already[7] converted the base (**XI**) (obtained from natural sources by degradation) into a mixture of the alkaloids tubifoline (**XII**) and condyfoline (**XIII**) by aerial oxidation in the presence of platinum:

repetition of this using our synthetic base[8] gave the racemates of these two alkaloids and, furthermore, lithium aluminium hydride reduction of (±)-tubifoline gave (±)-tubifolidine (**XIV**). Thus, total synthesis of three of the simpler pentacyclic strychnos-type alkaloids had been achieved, and the way was open for further elaboration.

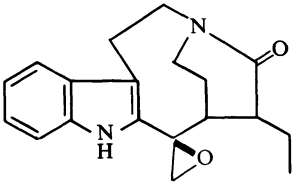
Returning to the keto-lactam (**VII**), this with dimethyl sulphonium methylide in dimethyl sulphoxide gave the epoxide (**XV**) in good yield, and the latter was smoothly isomerized to the aldehyde (**XVI**) by magnesium bromide etherate or simply by heating alone. The aldehyde was protected



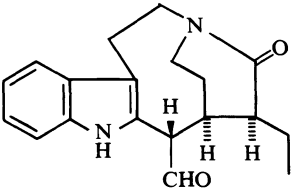
(XIII)



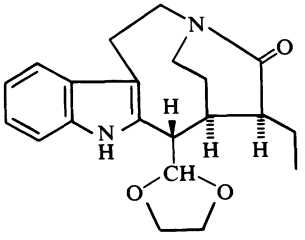
(XIV)



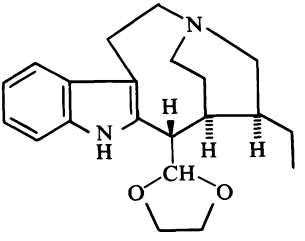
(XV)



(XVI)

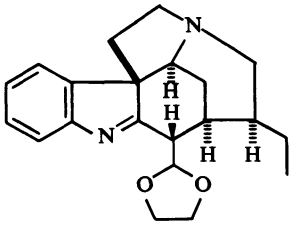


(XVII)



(XVIII)

by conversion to the ethylene acetal (**XVII**), and this with lithium aluminium hydride gave the base (**XVIII**). On aerial oxidation in the presence of platinum this gave the indolenine (**XIX**), which on hydrolysis with dilute acid gave (±)-dihydronorfluorocurarine[9] (**XX**). It is noteworthy that in this case the oxidation gives only (**XX**), in contradistinction to the oxidation of the simpler base (**XI**), which gives a mixture of two skeletal types, corresponding to oxidation at the methylene groups at each side of the basic nitrogen atom. Examination of models indicates that the extra substituent in (**XVIII**) interferes badly in the transition state required for cyclization to a condyfoline type in this



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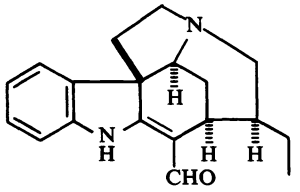
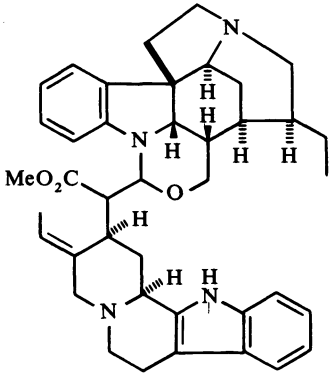
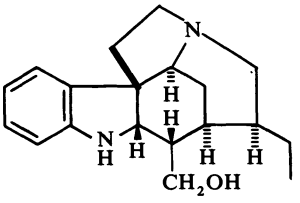


(XX)

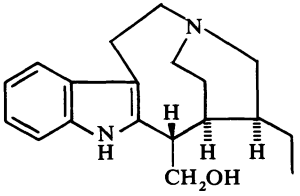
case. However, as we shall see later, it is possible to force cyclization to a condyfoline-type skeleton, even in the presence of such a substituent, by a non-oxidative process.



(XXI)



(XXII)

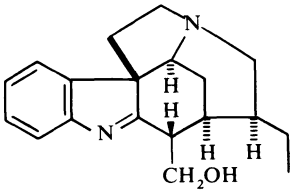


(XXIII)

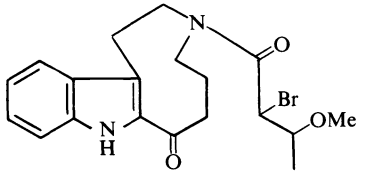
Inspection of the structure of geissoschizoline (**XXII**), a hydrolysis product of the binary alkaloid geissospermine (**XXI**), shows that it should be readily accessible from the aldehyde (**XVI**), and this indeed proved to be the case[9]. Lithium aluminium hydride reduction of (**XVI**) gave the alcohol (**XXIII**), which on oxidation as before gave the indolenine (**XXIV**). This, on treatment with diborane, gave (±) geissoschizoline identical in all respects (apart from optical activity) with a specimen of the material obtained by hydrolysis of geissospermine. Thus, the stereoselective synthesis of a strychnos-type alkaloid containing six asymmetric centres had been achieved. We also established an alternative[10], though longer and less satisfactory, conversion of the keto-lactam (**VII**) to (±)-geissoschizoline.

So far we had been confined to synthesis of alkaloid types containing an ethyl group, and further progress required replacement of this by an ethylidene

group. To achieve this it was necessary to return to the beginning. In the sequence **(III)** → **(V)** → **(VI)** the anhydride of 2-bromo-3-methoxybutyric acid was employed instead of 2,2′-dichlorobutyric anhydride. This led in an exactly analogous fashion to the keto-amide **(XXV)**. This, on treatment with

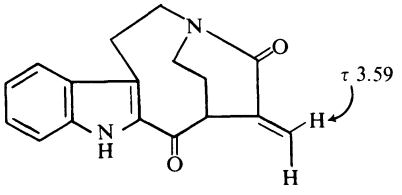


(XXIV)

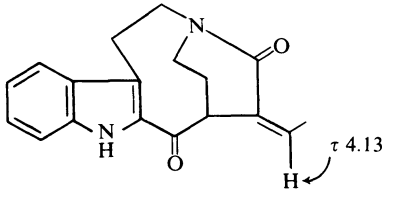


(XXV)

excess of sodium *t*-amyloxide in tetrahydrofuran, underwent a *double* elimination process, giving a mixture (60:40) of *cis* and *trans* keto-lactams **(XXVI)** and **(XXVII)**. These are readily separable, and distinguishable by their n.m.r. spectra as shown: in the case of the desired material the one vinyl proton is strongly deshielded by the neighbouring amide carbonyl group. Fortunately,

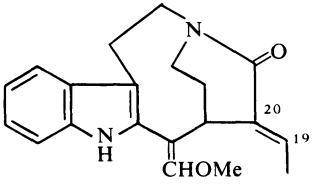


(XXVI)

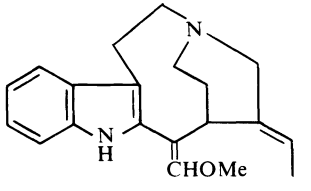


(XXVII)

the unnatural isomer is not wasted, since it can be equilibrated with the natural one on treatment with methoxide ion (clearly an addition–elimination process occurs). The keto-lactam **(XXVI)** reacts readily with dimethylsulphonium methylide to give an epoxide, as did the saturated material **(VII)**.



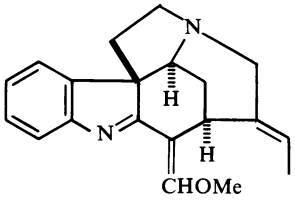
(XXVIII)



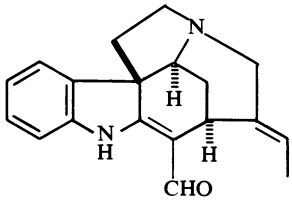
(XXIX)

But on treatment with electrophilic reagents this epoxide does *not* isomerize to an aldehyde, but instead gives the ring-enlarged ketone. Thus, an alternative route must be found in the present case, and attention was turned to a Wittig-type process. Reaction of **(XXVI)** with methoxymethylenetriphenyl-

phosphorane gave the enol ether (**XXVIII**). Reductive removal of the lactam carbonyl proved difficult, since concomitant reduction of the 19,20-double bond occurred very readily. Eventually, aluminium hydride was employed,



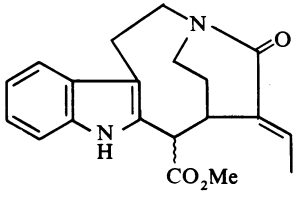
(XXX)



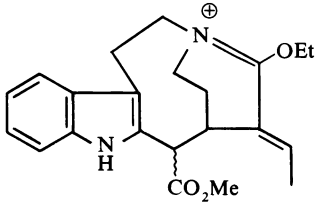
(XXXI)

although even this reagent gave some of the 19,20-dihydro compound together with the desired amine (**XXIX**). The mixture was oxidized as before to the indolenine (**XXX**) (together with some 19,20-dihydro compound), which with cold dilute acid gave a mixture of (±)-norfluorocurarine (**XXXI**) and (±)-dihydronorfluorocurarine (**XX**). The mixture was separated on an alumina column, yielding crystalline (±)-norfluorocurarine identical in all respects (apart from optical activity) with a specimen of the natural material. Quaternization with methyl iodide yielded (±)-fluorocurarine iodide, the first Calabash-curare alkaloid to be synthesized[11].

Hydrolysis of the enol-ether (**XXVIII**) with dilute acid gave the corresponding aldehyde, which with hydroxylamine gave the oxime. This was dehydrated with titanium tetrachloride to the cyanide, which on methanolysis gave a stereoisomeric mixture of esters (**XXXII**). This mixture on treatment

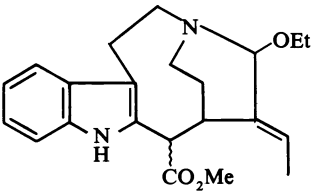


(XXXII)

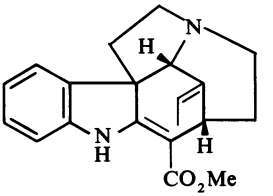


(XXXIII)

with triethyl oxonium borofluoride gave the iminoether quaternary salt (**XXXIII**). Normally, such salts on treatment with borohydride undergo complete reduction, with elimination of ethoxide to give a tertiary amine. However, in this case the reaction stops at the half-way stage, giving the carbinolamine ether (**XXXIV**), and increasing the severity of the conditions leads only to reduction of the ester group. We believe that this unusual behaviour is due to the partial 'bridgehead character' of the amides under study. All of our tetracyclic lactams have the amide group at the bridgehead of a six-membered and nine-membered ring. Examination of models shows clearly that for the amide to achieve complete co-planarity considerable strain would be involved and that consequently there is partial uncoupling of the conjuga



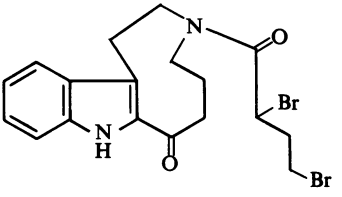
(XXXIV)



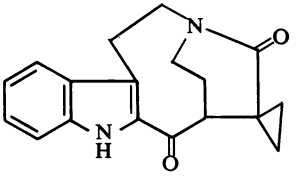
(XXXV)

tion between the carbonyl and the nitrogen lone pair. This is confirmed by the infra-red spectra, in which the carbonyl group in all of our cases appears at an unusually high frequency for a six-membered lactam. Of course, the fact that reduction of (**XXXIII**) stops at (**XXXIV**) may be put to good use. It will be noted that the carbinolamine ether is at the same oxidation level as the iminium ions assumed to be intermediates in the oxidative cyclizations discussed above, so that a *directed* cyclization to give a condyfoline type should here be possible. Indeed, this is the case, and treatment of (**XXXIV**) with boron trifluoride leads to the formation of (±)-condylocarpine[12], identical in all respects (apart from optical activity) with the natural material.

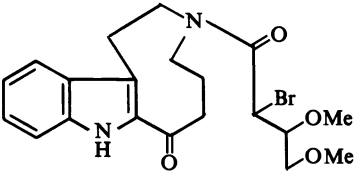
In retrospect, it will be seen that a very flexible and generalized synthetic route to strychnos-type alkaloids has been developed. The initial cleavage of the hexahydroindolopyrrocoline (**III**) may be performed with a very wide variety of acid anhydrides. I will give two more cases, leading to tetracyclic keto-lactams which it is hoped will be of synthetic value. In the first, use of the anhydride of 2,4-dibromobutyric acid leads to the keto-amide (**XXXVI**),



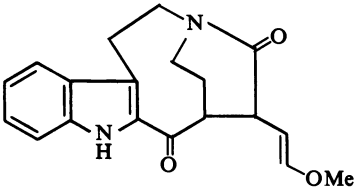
(XXXVI)



(XXXVII)



(XXXVIII)



(XXIX)

which with sodium *t*-amyloxide gives the interesting cyclopropane[13] (**XXXVII**). In the second, use of the anhydride of 2-bromo-3,4-dimethoxybutyric acid leads to the keto-amide (**XXXVIII**), which with sodium

t-amyloxide gives the keto-lactam[14] (**XXXIX**), in which it will be noted that, surprisingly, the double bond has moved out of conjugation with the carbonyl to give an enol-ether.

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