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Synthesis of isoquinoline and yohimbinoid alkaloids

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Abstract - A systematic survey of the different synthetic methodologies available for the syntheses of isoquinoline and yohimbinoid alkaloids revealed that the general approaches to these compounds involved either an A/B → C → D/→ E approach or a D/E → C/B/A approach. We have now devised a novel method for the syntheses of both the isoquinoline and indole alkaloids belonging to the tetrahydroprotoberberine and yohimbinoid skeleton. In the method developed by us a suitable 'D' ring is first chosen on which the 'C' ring is built. This bicyclic C/D ring system is then cleaved by condensing with a suitable A/B unit bearing an amine so that an overall A/B → seco C/D ring system is generated. By appropriate reactions the total synthesis of the alkaloids has been achieved in which the seco 'C' ring undergoes cyclisation.

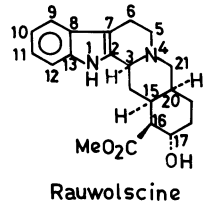
The total syntheses of two tetrahydroprotoberberine alkaloids, (±) 2,3-dimethoxyberbine and (±)-norcoralydine and three pentacyclic indole compounds, (±) decarbomethoxy dihydrogambirtannine, (±) alloyohimbine and (±) rauwolscine will be discussed.

Our method for the synthesis of these alkaloids was based on the choice of 3-isochromanone derivative as a suitable synthon for the construction of the nonnitrogenous moiety. The nitrogenous portion was derived from tryptamine. Since 3-isochromanones belong to δ-lactones they can readily be prepared from 2-indanones by Bayer-Villiger oxidation. However, the conventional method for the synthesis of 2-indanone is not a simple procedure. An improved method for 2-indenone and its derivatives has been developed by us using a diazoketone intermediate. A unique acid catalysed diazoketone cyclisation procedure yielded the desired 2-indanones in good yields.

INTRODUCTION

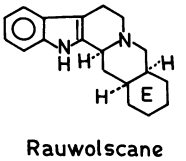
Rauwolfia comprises one of the important genera of the family Apocynaceae. For the past few decades the present author has been pursuing intensive work on Rauwolfia species (ref. 1,2). Of these Rauwolfia caneacens Linn has gained much importance as a drug plant. More than a dozen of indole alkaloids have been isolated from this natural source. These are illustrated in Table 1. Of these, rauwolscine, ajmalicine and ajmaline have a great demand in the world market for their clinical use as hypotensive, peripheral vasodilator and as antiarrythmic agents respectively.

Rauwolscine was isolated a few decades ago. The skeletal pattern could be ascertained from X-ray crystallographic analysis (ref. 3) of the parent molecule, rauwolscane, where the ring E is unsubstituted.



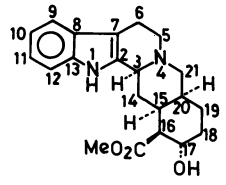
Rauwolscine

C_3-H--- α and axial
C_{15}-H---- α and axial
C_{16}-CO_2Me- β and equatorial
C_{17}-OH-- α and equatorial

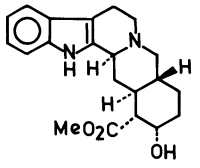


Rauwolscane

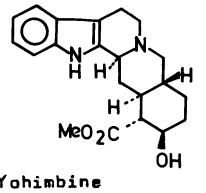
Table 1. Major indole alkaloids isolated from *Rauwolfia caneacens* Linn.



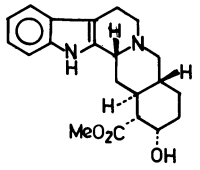
Rauwolscine
$C_{21}H_{26}O_3N_2$



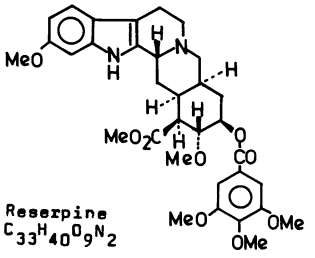
Yohimbine
$C_{21}H_{26}O_3N_2$



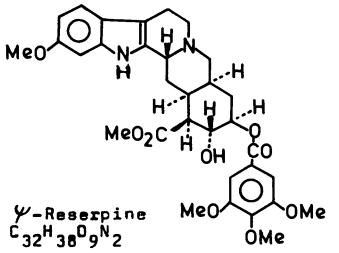
β-Yohimbine
$C_{21}H_{26}O_3N_2$



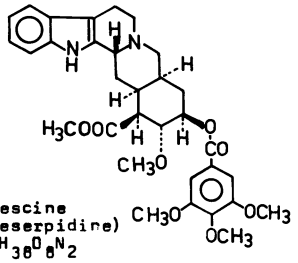
ψ-Yohimbine
$C_{21}H_{26}O_3N_2$



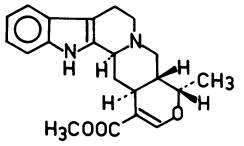
Reserpine
$C_{33}H_{40}O_9N_2$



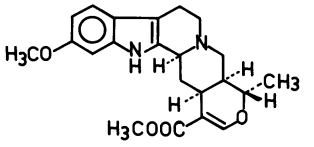
ψ-Reserpine
$C_{32}H_{38}O_9N_2$



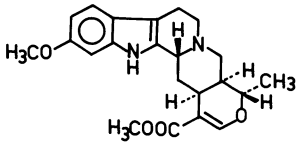
Canescine
(=Deserpidine)
$C_{32}H_{36}O_8N_2$



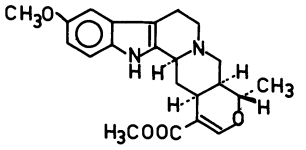
Ajmalicine
(δ-Yohimbine)
$C_{21}H_{24}O_3N_2$



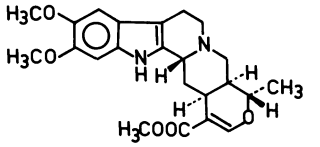
Reserpinine
$C_{22}H_{26}O_4N_2$



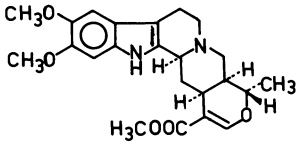
Isoreserpinine
$C_{22}H_{26}O_4N_2$



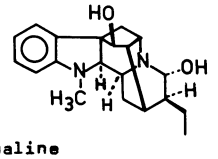
Aricine
$C_{22}H_{26}O_4N_2$



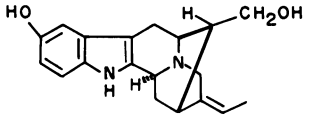
Reserpiline
$C_{23}H_{28}O_5N_2$



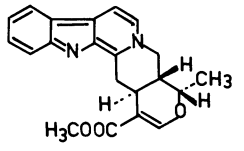
Isoreserpiline
$C_{23}H_{28}O_5N_2$



Ajmaline
$C_{20}H_{26}O_2N_2$



Sarpagine
(=Raupine)
$C_{19}H_{22}O_2N_2$

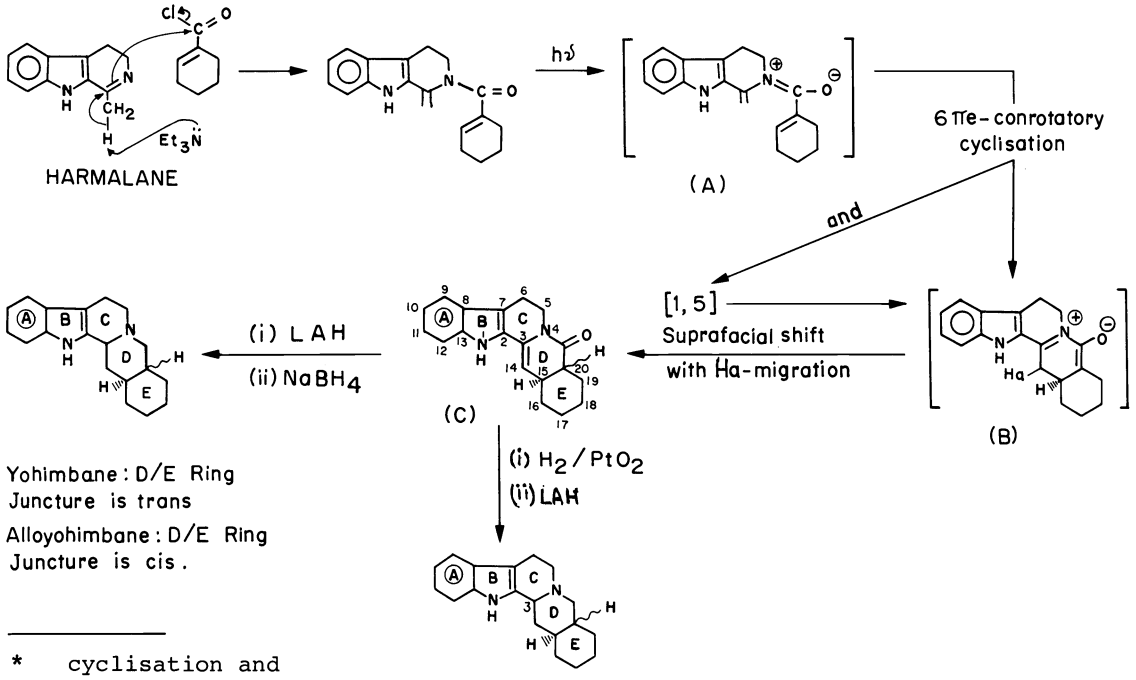


Serpentine
$C_{21}H_{20}O_3N_2$

The exact location of the hydroxyl and carbomethoxyl functionalities in ring E was settled from the following sequence of reactions.

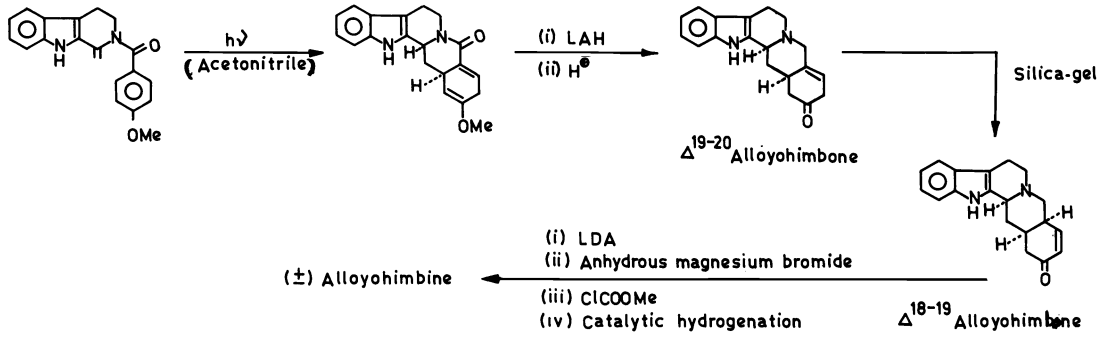
The synthetic strategy developed for the synthesis of (±) rauwolscine in our laboratory will be discussed. The key compound selected for the purpose was 17-oxoalloyohimbane. This one regiospecific functionalisation at C_{16}-with-CO_2Me followed by stereospecific reduction of the C_{17}-ketone to the α-hydroxyl would allow the completion of the C_{17}-epimer of rauwolscine. This alkaloid on base catalysed epimerisation would furnish (±) rauwolscine. The synthesis of the key compound i.e. 17-oxoalloyohimbane thereby is a crucial one. Efforts have been made to construct this pentacyclic ring system and have proved successful.

Among the methods developed in recent years mention may be made, on Professor I. Ninomiya's novel procedure for the synthesis of pentacyclic indole alkaloid (ref. 4) of the yohimbinoid series. The procedure is simple. It involves an enamide photocyclisation via six π electron conrotatory cyclisation to give a trans cyclic intermediate (B). The photocyclised product would be obtained from (B) depending upon the reaction condition, either oxidative or non-oxidative. An interesting example of Ninomya's method illustrated in the synthesis of yohimbane, epiyohimbane and alloyohimbane from harmalane is cited herein: Harmalane was acetylated using 1-cyclohexene-1-carbonyl chloride to yield the enamide. It was irradiated with a low pressure Hg ← lamp at room temperature under nonoxidative conditions to yield the dehydrolactam (C). This photocyclisation can be explained to occur via an electrocyclic reaction in a conrotatory manner. This leads to the intermediate (A) which on* 1, 5 suprafacial shift of hydrogen generates the lactam (B). On keeping in solution it readily changed to the dehydrolactam (C). Successive reduction of the lactam with LAH and $NaBH_4$ furnished (±) yohimbane and (±) alloyohimbane in 3:2 ratio. However, catalytic hydrogenation with PtO_2/H_2 of the lactam followed by reduction with LAH afforded yohimbane, epiyohimbane and alloyohimbane in 2:1 ratio (racemic).



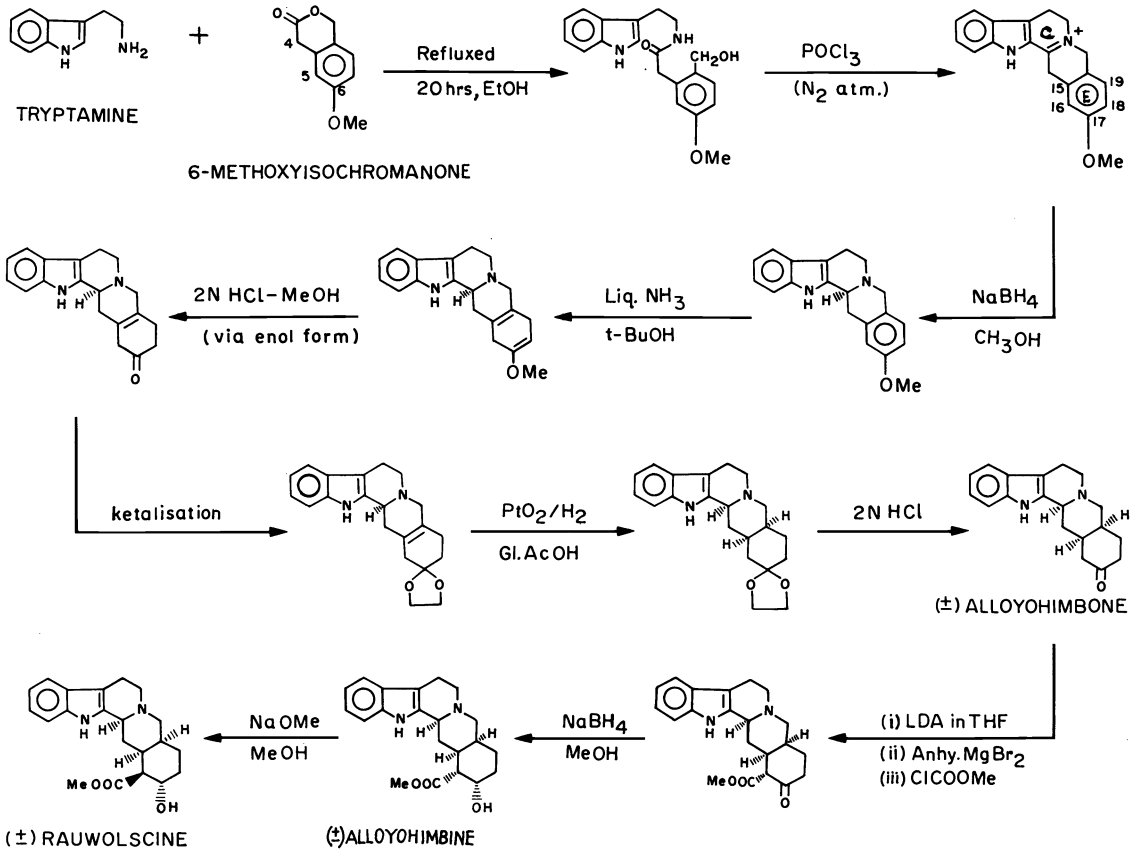
* cyclisation and

Using the same sequence of reactions didehydroyohimbone (or didehydro-alloyohimbone) was also synthesised from harmalane (ref. 4).

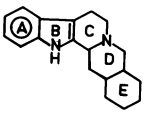


A novel method developed in our laboratory for the synthesis of (±) rauwolscine will now be elaborated.

SYNTHESIS OF (±) RAUWOLSCINE

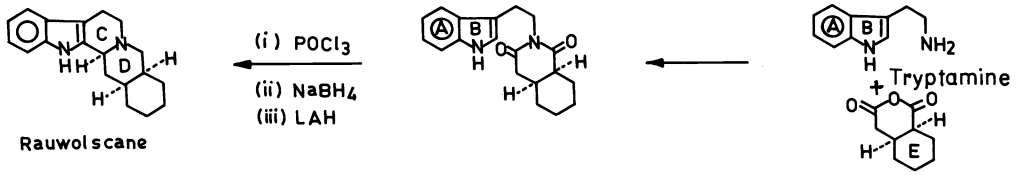


In this context it deserves mention that several approaches have been made to build up the pentacyclic skeleton of the indolic base to which rauwolscine belongs. Synthetic procedures developed so far require a lot of ingenuity and skill to construct the actual molecular frame work with the desired chirality at the assymetric centres. Starting from tryptamine which provides A & B ring system rauwolscane could be prepared. Kametani, Kaziwaro and Fukumoto group (ref. 5) have developed a new synthetic methodology based on thermal cyclisation. The formation of the gross skeleton of E-hexadehydroyohimbine could be explained from the



Basic skeleton of Pentacyclic indole alkaloid of Rauwolfia species

sequence of reactions as methioned below: Tryptamine and 1-carboxybenzocyclobutene were subjected to Bischler-Napieralski reaction. Δ^3-dehydroharman derivative on thermal cycloaddition produced a quaternary base opening in a conrotatory fashion to generate the orthoquinodimethide species.



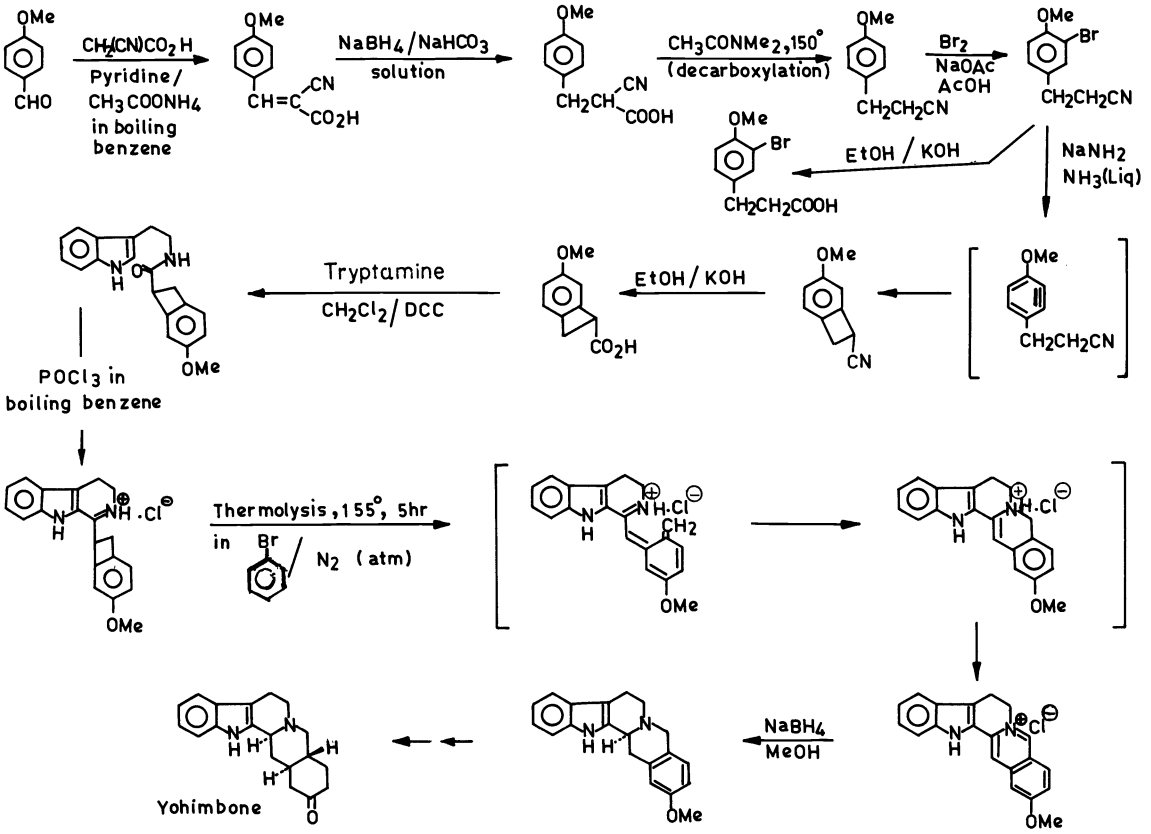
Rauwolscane

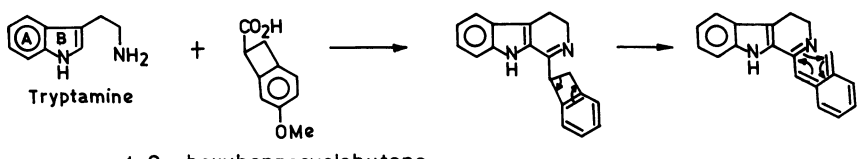
C and D ring have been generated through a sequence of reactions with hexahydrohomophthalic anhydride.

Hexahydrohomophthalic anhydride

It then underwent the Diels-Alder type cyclisation. The pentacyclic indole on reduction with $NaBH_4$ generated the pentacyclic indole skeleton having a tetrahydro- β -carboline miety as the nitrogenous unit.

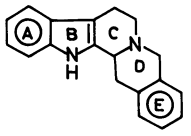
It deserves mention in this connection that an elegant synthesis of alloyohimbone has been described in Manske's Book (Vol. VIII) (ref. 6) on Alkaloids Chemistry and Pharmacology. While going through the original literature it came to our notice that the paper which Manske has referred to describes the synthesis of the 18-oxoanalcgue reported by Naito and his collaborator. Erroneously this compound has been referred to as the 17-oxoderivative. This created further interest to study the total synthesis of rauwolscine. Our strategy for this synthesis was based on the choice of a suitable synthon, viz. 6-methoxy-3-isochromanone, for the construction of the non-nitrogenous moiety, the nitrogenous moiety being developed from tryptamine.





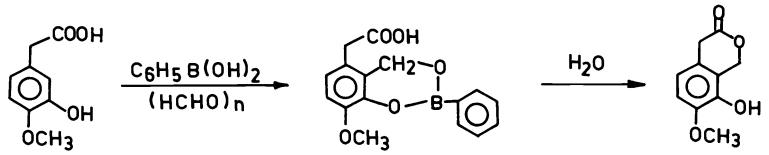
Prior to the discussion on the condensation of tryptamine with 6-methoxy-3-isochromanone and the subsequent reactions culminating in the synthesis of (±) rauwolscine it would be necessary to describe the synthesis of 6-methoxy-3-isochromanone.

Of the various approaches for the synthesis of pentacyclic indolic base of the yohimbinoid series 3-isochromanone derivatives constitute one of the important and potential synthons. The use of this compound offers a brilliant feasibility of constructing rings C and D of the yohimbinoids practically in one pot experiment.

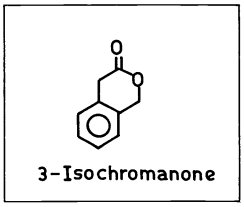


Ring E-hexadehydroyohimbane

The usual method for the construction of the 3-isochromanone system calls for the utilisation of a boron complex. This lactone (3-isochromanone) could be prepared through the cyclisation with boronic acids (ref. 7).



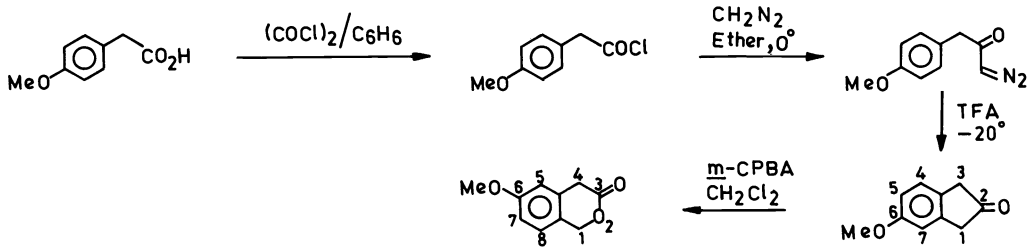
This method has certain limitations. If the phenyl nucleus lacks reactivity failing to steer the hydroxymethyl group in the desired position the method will not prove successful. Since this method possesses practical problems, the synthesis of 3-isochromanone systems which are essentially δ-lactone derivatives could be elegantly solved by using a more direct approach.



3-Isochromanone

As mentioned earlier 3-isochromanone and its derivatives belong to a δ-lactone system. They can readily be prepared by Bayer-Villiger oxidation of a suitable ketone.

Bayer-Villiger oxidation of 1-indanones has been utilised for the synthesis of oxygen heterocycles viz. coumarins. However, the synthesis of properly substituted 2-indanone always possesses a difficult task. The usual method for this is the conversion of the corresponding 1-indanone derivative to 2-indanone. An improved method has been devaloped by us via a unique diazoketone cyclisation using TFA (ref. 8). This intermediate diazoketone has been obtained from the appropriate phenyl acetic acid through a sequence of reactions discussed in the sequel:



6-Methoxy-3-isochromanone

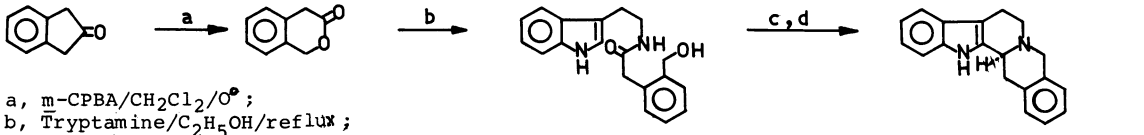
Tryptamine was made to react with 6-methoxy-3-isochromanone to generate the rings C & E of the corresponding pentacyclic base. The hydroxyamide on double cyclisation with $POCl_3$ furnished the pentacyclic skeleton with the formation of the imminium species. Sodium borohydride reduction of the corresponding enamine produced ring E-hexadehydroyohimbine.

On Birch reduction with Na/Liq. ammonia in t-BuOH followed by hydrolysis at room temperature 15,20-dehydro-17-ketoyohimbane. This was subjected to ketalization. The ketal on reduction with Adams catalyst in glacial acetic acid followed by hydrolysis afforded alloyohimbone (17-oxoalloyohimbone). The desired chirality at C_3, C_{15} & C_{20} could be achieved. Regioselective functionalisation i.e. incorporation of carbomethoxyl at C_{16} would culminate

in the synthesis of 16-carbomethoxy rauwolscone. The procedure developed by van Tamelen for the insertion of $-CO_2Me$ at C_{16} in a stereospecific manner in yohimbone did not prove successful in alloyohimbone. Thereby an alternative approach through metallation reaction had to be made for the purpose. Alloyohimbone with LDA in THF at low temperature under conditions of kinetic control formed the lithium enolate (ref. 9). In situ it was converted to magnesium enolate with anhydrous magnesium bromide. On subsequent treatment with methylchloroformate regioselective functionalisation (axial) could be accomplished resulting in the synthesis of (±) alloyohimbinone in 60% yield purified by chromatography. Model experiments demonstrated that incorporated, carbomethoxyl at C_{16} having axial orientation would be favoured. Base catalysed epimerisation with NaOH/MeOH followed by catalytic reduction completed the synthesis of (±) rauwolscine.

Following the same methodology (±) decarbomethoxy dihydrogambirtannine has been synthesized. The appropriate 3-isochromanone on refluxing with tryptamine in ethanol gave a hydroxyamide which was further cyclised and reduced with sodium borohydride to generate the desired base, (±) decarbomethoxy dihydrogambirtannine in 30% yield (ref. 10).

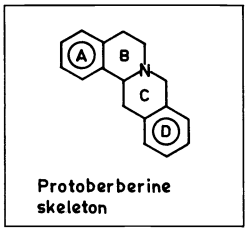
Synthesis of (+)-Decarbomethoxy Dihydrogambirtannine



a, m-CPBA/CH_2Cl_2/0°;
b, Tryptamine/C_2H_5OH/reflux;
c, $POCl_3/C_6H_6$/reflux;
d, $NaBH_4/CH_3OH$/0°.

(+) Decarbomethoxy dihydrogambirtannine

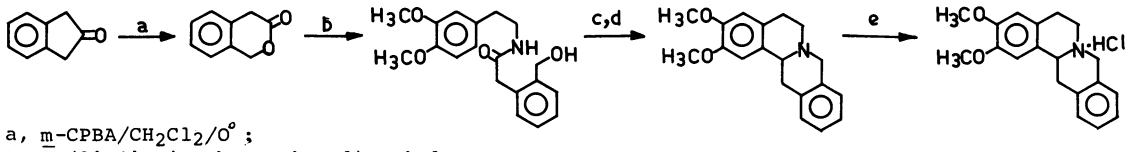
So far as the synthesis of (±) 2,3-dimethoxyberbine and (±) norcoralydine is concerned the strategy was to prepare an appropriate 3-isochromanone derivative. This method offered a feasibility of constructing B and C rings practically in one pot experiment.



Protoberberine skeleton

The starting material for the synthesis of (±) 2,3-dimethoxy berbine was readily available 2-indanone. The latter was converted to the lactone by Bayer-Villiger oxidation with meta-chloroperbenzoic acid. The lactone when condensed with 2-(3',4'-dimethoxy phenyl)-ethyl amine in ethanol under refluxing condition afforded a hydroxyamide. The hydroxyamide was then cyclised to the desired base, (±) 2,3-dimethoxy berbine by treatment with phosphorous oxychloride in dry benzene followed by reduction with sodium borohydride. The free base was an oil and its hydrochloride derivative was isolated in 30% yield (Ref. 10).

Synthesis of (+) 2,3-Dimethoxy Berbine



a, m-CPBA/CH_2Cl_2/0°;
b, 2-(3',4'-Dimethoxy phenyl)-ethyl amine/C_2H_5OH/reflux;
c, $POCl_3/C_6H_6$/reflux:
d, $NaBH_4/CH_3OH$/0°;
e, HCl/acetone.

(±) 2,3-Dimethoxy berbine

(±) 2,3-Dimethoxy berbine hydrochloride

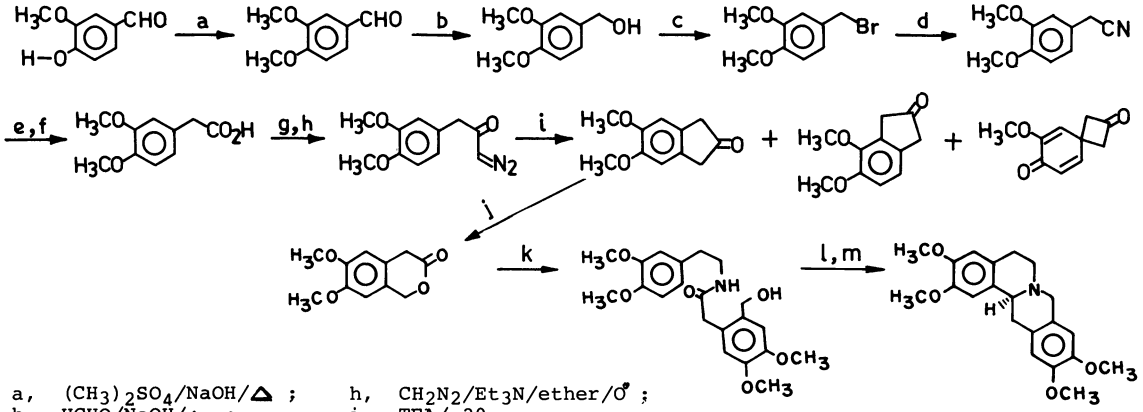
The synthesis of (±) norcoralydine, a symmetrically substituted tetrahydro-protoberberine alkaloid was achieved following the same basic principle (condensation of an amine with a lactone). The lactone 6,7-dimethoxy-3-isochromanone was condensed with 2-(3',4'-dimethoxy phenyl)-ethylamine in ethanol and the tetramethoxy hydroxyamide was cyclised with phosphorous oxychloride in dry benzene. The imine so generated was reduced with sodium borohydride and the desired base, (±) norcoralydine was obtained in 40% yield. The lactone was as before obtained from the suitable 5,6-dimethoxy-2-indanone by Beyer-Villiger oxidation with m-CPBA (Ref. 10).

In this connection it is worth mentioning that the synthesis of 5,6-dimethoxy-2-indanone had been achieved by a unique diazoketone cyclization procedure. Thus, when 3,4-dimethoxy benzyldiazomethyl ketone is treated with trifluoroacetic acid at -20°C, the indanone m.p.120° (dec.) is obtained in 69% yield in addition to two other minor products, 4,5-dimethoxy-2-indanone and spirocyclobutanone. In contrast to previous observations we believe this is a very useful synthetic route to the formation of substituted 2-indanones.

The isolation of the spiro-cyclobutanone and the confirmation of its structure from spectral and analytical measurements throw a definite light on the mechanism of the formation of 2-indanones via Ar^1-4 participation of the aromatic nucleus.

Finally, 3,4-dimethoxy benzyldiazomethyl ketone was obtained from 3,4-dimethoxy phenyl acetic acid by converting the acid first to its acid chloride derivative by means of oxalyl chloride followed by the treatment with diazomethane at 0°. The acid was, however, synthesized from vanillin.

Synthesis of (+) Norcoralydine



a, $(CH_3)_2SO_4/NaOH/\Delta$;
b, $HCHO/NaOH/\Delta$;
c, $PBr_3/Et_3N/CCl_4$;
d, $NaCN/C_2H_5OH/0°$;
e, aq. $NaOH/\Delta$;
f, HCl;
g, $(COCl)_2/C_6H_6$;
h, $CH_2N_2/Et_3N/ether/0°$;
i, TFA/-20 ;
j, m-CPBA/$CH_2Cl_2/0°$;
k, 2-(3',4'-Dimethoxyphenyl)-ethylamine/C_2H_5OH/reflux;
l, $POCl_3/C_6H_6$/reflux;
m, $NaBH_4/CH_3OH/0°$.

(±)-Norcoralydine

The new approach to the synthesis of the aforesaid indolic bases could be extended to the synthesis of reserpine and related biologically active alkaloids. The attractive feature of this synthesis is the ready availability of the starting materials and the simplicity of the methodology without involving any expensive materials.

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REFERENCES

1. A.Chatterjee, Fortschritte der Chemie Organischer Naturstoffe, 10, p. 390-422, Springer-Verlag, Wien (1953).
2. A.Chatterjee, S.C.Pakrashi and G.Werner, Fortshritte der Chemie Organischer Naturstoffe, 13, p. 346-443, Springer-Verlag, Wien (1956).
3. L.Ray, Science & Culture, India 20, 507 (1955).
4. I.Ninomiya, Heterocycles 2, 105 (1974): T.Naito, Y.Tada, Y.Nishiguchi and I.Ninomya, Heterocycles 18, 213 (1982).
5. T.Kametani, M.Kajwara and K.Fukumoto, Tetrahedron 30, 1053 (1974).
6. T.Naito and O.Nagase, J.Pharm.Soc. Japan 80, 629 (1960).
7. H.G.Peer, Rec. Trav. Chim. Pays-Bas 79, 825 (1960).
8. D.J.Beames, T.R.Klose and L.N.Mander, Aust.J.Chem., 1264 (1974).
9. O.Miyata, Y.Hirata, T.Naito and I.Ninomiya, J.Chem.Soc.Chemical Communications, 1231 (1983).
10. A.Chatterjee and S.Ghosh, Synthesis, 818 (1981).