INTRODUCTION OF SUBSTITUENTS TO C_3 OF YOHIMBINOID SKELETON

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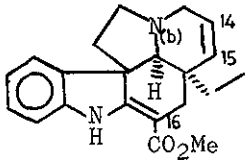
Chlorination took place at the nucleophilic centres of tabersonine (1) and yohimbine (4) when their hydrochlorides were oxidized with m-chloro perbenzoic acid. Chloroindolenine N_b-oxide (5), thus obtained from yohimbine, was susceptible to nucleophilic attack at C_3 position to give stable 3-substituted yohimbine N_b-oxides. No indication of the rearrangement to oxindole was observed.

In the course of our study on the alkaloidal constituents of Amsonia spp., tabersonine hydrochloride (1·HCl) was oxidized with m-chloro perbenzoic acid. Instead of the expected C_{16}-hydroxylated compound (2), chloride (3) was obtained as the main product, which was identified with a specimen prepared from 1 according to a procedure reported for chlorination of vincadifformine (1, 14,15-dihydro-).[1] Though precise mechanism of the above chlorination is unknown, chloronium ion or chlororadical that was formed from chloride anion on oxidation with m-chloro perbenzoic acid must have attacked the nucleophilic centre, C_{16}. When two molar equi-

valents of the peracid was used, the corresponding N-oxide (3, N_b-O) was formed.

To test the generality of this type of reaction, yohimbine hydrochloride (4·HCl) was oxidized with m-chloro perbenzoic acid. By use of 2.5 molar equivalents of the reagent, chloroindolenine N_b-oxide (5) was given as expected. 3,4,5,6-Tetradehydro yohimbine (6) was formed from 5 on treatment with hot methanol or during column chromatography over silica gel. To confirm the structure of 5, a different synthesis was made. Thus yohimbine (4) was chlorinated with tertiary butyl hypochlorite[2] and the product was then oxidized with m-chloro perbenzoic acid. The resulting compound was found to be identical with 5 by TLC and IR spectrum. Obviously four stereoisomers are possible for 5 due to the two asymmetric centres at C_7 and N_b. Though we have not succeeded in ascribing any definite stereostructure for 5, S configuration at C_7 has been suggested by the CD spectrum showing a positive Cotton effect at 268 nm.[3]



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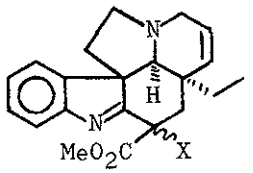
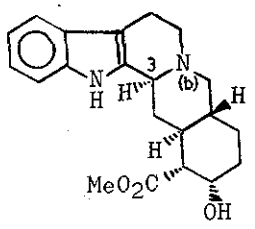


2 X= OH

3 X= Cl



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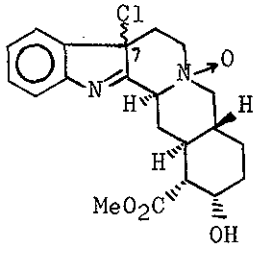

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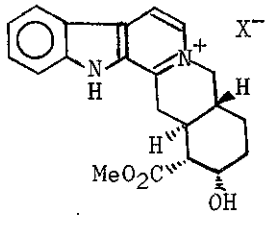

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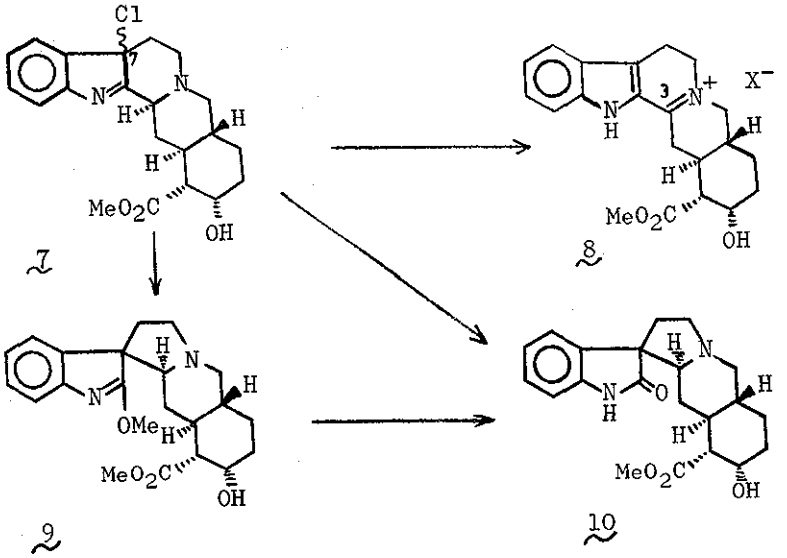
Chloroindolenine (7) has been reported to show several interesting reactions. For examples, ethanolic hydrogen chloride converts 7 to 3-dehydro salt (8). Rearrangement of the substituent from α to β position on the indole ring was observed by Finch and Taylor, who treated 7 with refluxing MeOH containing an equivalent of base.[4] The reaction product was an imidoether of oxindole (9), which gave yohimbine oxindole (10) on hydrolysis with acetic acid. The same type of rearrangement was reported by Zinnes et al.[2], who treated 7 with refluxing MeOH which had been adjusted to pH 6, and obtained yohimbine oxindole (10).

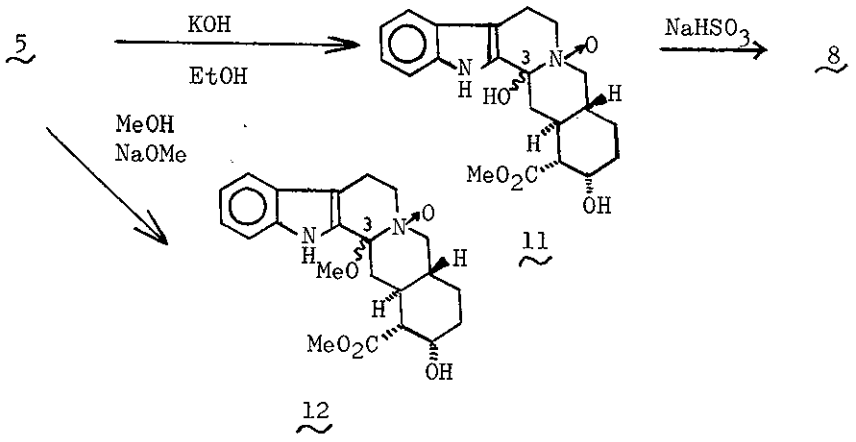


7 8 9 10

We found that $N_{(b)}$ oxidized chloroindolenine (5) showed a different type of reactivity. Thus when treated with ethanolic potassium hydroxide, 5 gave 3-hydroxy yohimbine $N_{(b)}$-oxide (11). The UV spectrum of 11 was indolic having the absorption maxima at 223(4.61), 275(3.89), 282.5 (3.91) and 292(3.83) nm. No molecular ion peak was observed in its mass

spectrum but the characteristic peaks were observed at m/e 368 ($M^+-[H_2O]$, 4%), 352($M^+-[H_2O]-[O]$,64%) and 293($M^+-[H_2O]-[O]-[CO_2Me]$,100%). Further observation that supported the assigned structure was the fact that 3-dehydroyohimbinium salt (8) was obtained when 11 was reduced with sodium bisulfite.

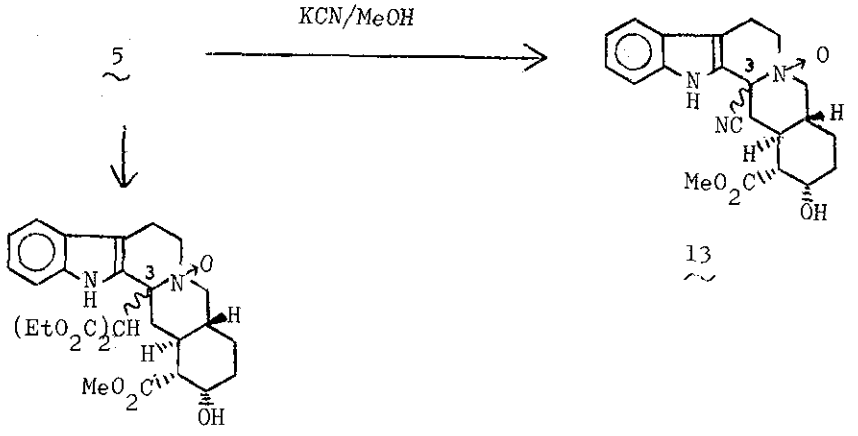
The same type of reaction occurred when the chloroindolenine $N_{(b)}$-oxide (5) was treated with methanolic sodium methoxide, the product being 3-methoxyyohimbine $N_{(b)}$-oxide (12), mp 215-216°. NMR spectrum of 12 showed the signal due to 3-methoxyl group at δ 3.20 besides the signal of carbomethoxyl group at δ 3.77.



It is interesting to note here that 5 did not give oxindole or the equivalent under the conditions specified by Zinnes[2] or Taylor.[4]

In the literature , introduction of a cyano group into C_3 position of yohimbine (4) has been realized by treatment of 3-dehydro salt (8)

with potassium cyanide[5]. When 5 was treated with methanolic potassium cyanide, 3-cyanoyohimbine $N_{(b)}$-oxide (13), mp 207-208°, was obtained in a good yield. Mass spectrum of 13 showed the molecular ion peak at m/e 395 (5%). IR absorption band due to the nitril group was weak but distinctly discernible at 2230 cm^{-1}. $N_{(b)}$-Oxidized 3-cyanoyohimbine (13) was fairly stable and the unchanged material was recovered when 13 was treated with methanolic hydrogen chloride. Three stereoisomeric structures are possible for 13 and the same is true for 11 and 12. No definite assignment of the stereo structure, however, has been made.



Finally, reactivity of 5 towards a carbanion was tested using diethyl malonate in tertiary butanol in the presence of potassium tertiary butoxide. A smooth reaction occurred to give the expected 3-diethylmalonyl yohimbine $N_{(b)}$-oxide (14). The structure of 14 was proved by the follow-

physical data. The UV spectrum was indolic and two carbonyl absorption bands were shown in the IR spectrum at 1750 (malonyl) and 1725 (carbomethoxyl) cm^{-1}. Molecular ion peak was observed at m/e 528(1%) in the mass spectrum of 14. NMR signals due to the methyl groups of the diethylmalonate residue were observed at δ 0.97 (t., J=7.4Hz) and 1.24 (t., J=6.8Hz) besides the other expected signals, e.g., COOMe, δ3.81(s.); NH, δ8.43(s.); $-CH<^{COOEt}_{COOEt}$, δ4.21(s.).

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