A NOVEL ROUTE TO A 16-SUBSTITUTED NINE-MEMBERED INDOLE ALKALOID RELATED TO QUEBRACHAMINE AND CLEAVAMINE

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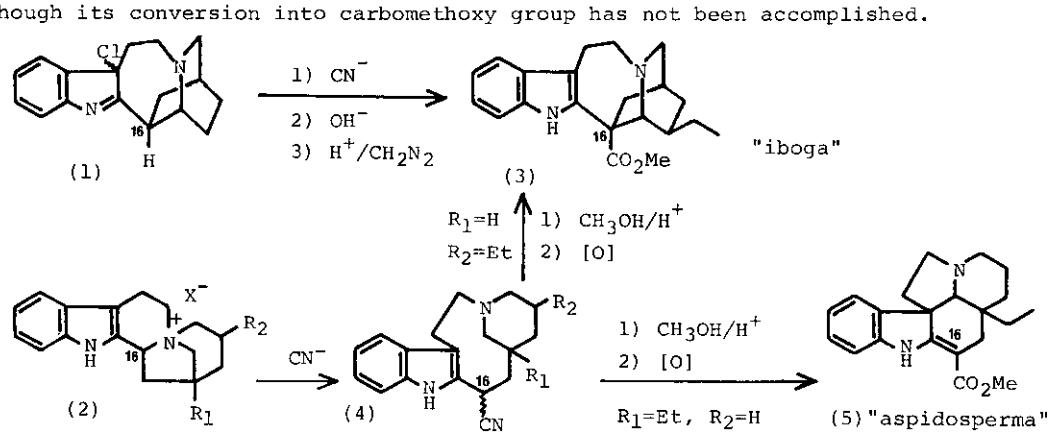
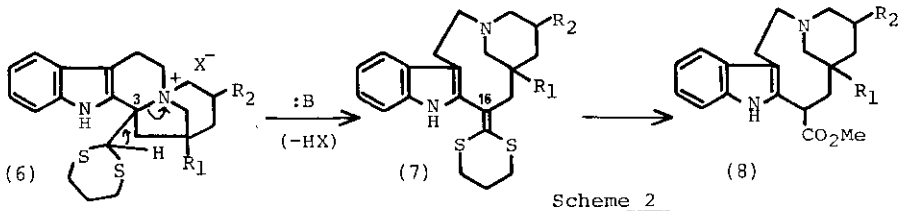
Abstract-----A novel route to a quebrachamine-cleavamine type alkaloid bearing C-16 carboxyl equivalent has been developed.

One of major subjects in the synthesis of the iboga and the aspidosperma type indole alkaloids is introduction of carbomethoxy unit on C-16 center. There have been developed two general routes for introduction of carbomethoxy group on C-16 center via a cyanide precursor through a chloroindolenine intermediate[1](1) and a quaternary base intermediate[2](2), however, they are often less satisfactory owing to low overall yield and multi-step operations(Scheme 1). Our plan for introducing a carbomethoxy group on the desired center involves the following three stages; (i) formation of a quaternary carboline base(6) bearing a dithiane group on C-3, (ii) simaltaneous formation of the quebrachamine-cleavamine framework and a carboxy equivalent at C-16 center(7), and (iii) conversion of the carboxyl equivalent into carbomethoxy group(8)(Scheme 2). Present report describes our preliminary results which could lead to introduction of a carboxyl equivalent on the appropriate center though its conversion into carbomethoxy group has not been accomplished.



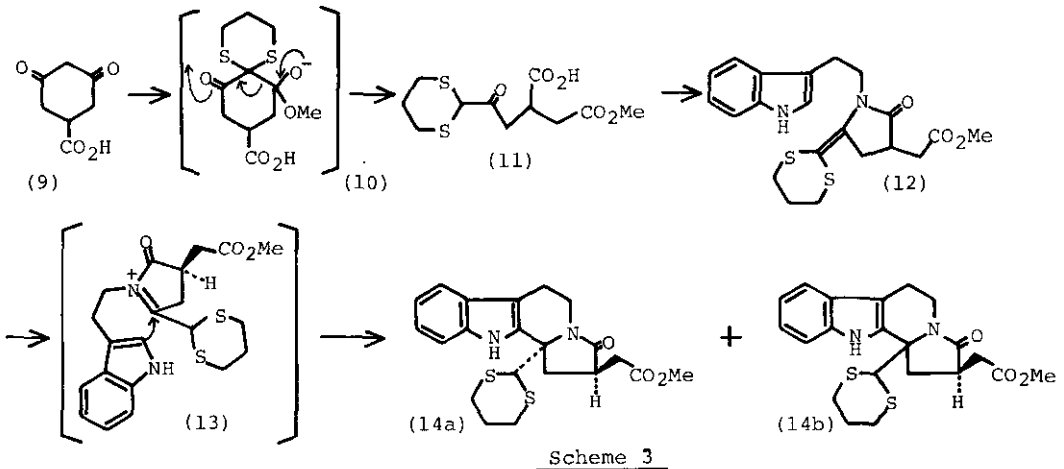
Scheme 1



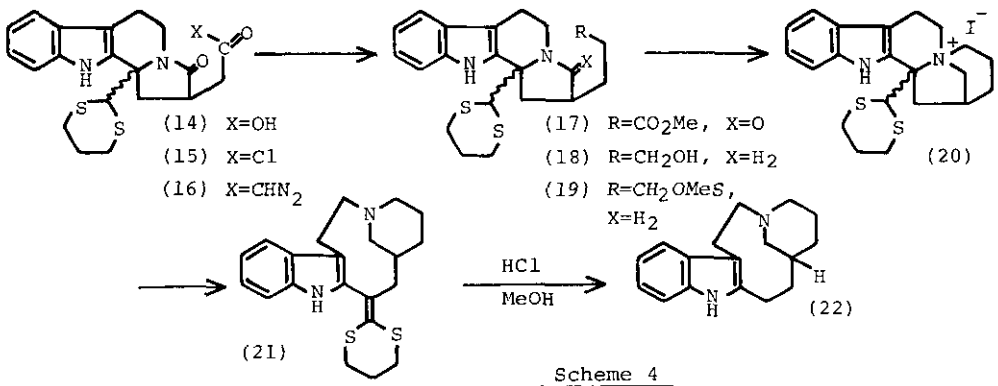
Scheme 2

Treatment of 1,3-cyclohexadione-5-carboxylic acid[3](9) with trimethylene dithiotosylate in the presence of potassium acetate in boiling methanol initiated a concurrent thioketalization and ring cleavage[4] to give the α-diketone monothioketal[5](11), mp 108∿110 °C, in 50.3 % yield via (10). Condensation of (11) with equimolar amount of tryptamine in boiling benzene by removing water azeotropically using a Dean-Stark apparatus, gave the exo-olefin(12), mp 142∿143 °C, in 85 % yield. Acid catalyzed cyclization of (12) in boiling benzene in the presence of catalytic amount of p-toluenesulfonic acid afforded the carboline(14a,b) mp 214∿216 °C, in 93.0 % yield as an inseparable mixture of two epimers α-oriented-dithianyl(14a) and β-oriented-dithianyl(14b) isomers, of which ratio(2:5) could be readily discernible by NMR peak intensities of the methine proton of the dithiane group at 4.70 and 4.63 ppm(2:5) and the ester methyl group at 3.70 and 3.60 ppm(5:2). Predominant formation of the β-isomer(14b) could be due to steric interaction of the acetic acid residue which allows preferential cyclization from the α-side of the intermediate(13) as shown (Scheme 3). Hydrolysis of (14a,b) with 10 % methanolic potassium hydroxyde gave the carboxylic acid(14), mp 246 °C(decomp), which was transformed into the homoester(17), mp 115∿118 °C, as a inseparable mixture of epimers in 70.5 % overall yield by Arndt-Eistert reaction via the acid chloride(15) and the diazoketone(16). Reduction of (17) with lithium alminum hydride in tetrahydrofuran at room temperature afforded the amino-alcohol(18) in 82.4 % yield as an inseparable mixture of epimers. Mesylation of (18) with methanesulfonyl chloride in the presence of triethylamine in boiling chloroform, followed by treatment with sodium iodide in boiling methyl ethyl ketone gave the pentacyclic quaternary iodide(20), which, without purification, was exposed to potassium tert.butoxide in tetrahydrofuran at 0 °C to furnish the expected nine-membered amine(21), mp 217∿220 °C, bearing carboxyl equivalent at C-16 center through a smooth regioselective fragmentation. The overall yield of (21) was 32.7 % from the amino-alcohol(18). Conversion of the ketene thioacetal group of (21) into the carbomethoxy group using a mercuric salt[6] as catalyst failed to give the expected C-16 ester(8; R_1=R_2=H). Desethylquebrachamine(of desethyldihydrocleavamine)[7](22) gum, was obtained in 34.6 % yield with some recovery of the starting material(18 %)

when (21) was refluxed in methanolic hydrogen chloride(43 %).



Scheme 3



Scheme 4

References and Notes

1) G. Büchi and R.E. Manning, J. Amer. Chem. Soc., 88, 2532 (1966).

2) (a) J. Harley-Mason, Atta-ur-Rahman and J.A. Beisler, Chem. Commun., 743 (1966). (b) G.H. Foster, J. Harley-Mason and W.R. Waterfield, Chem. Commun., 21 (1967).

3) M.E. Kuehne and B.F. Lambert, J. Amer. Chem. Soc., 81, 4278 (1959).

4) Cf. R.J. Bryant and E. McDonald, Tetrahadron Lett., 3841 (1975).

5) All new compound reported in this work gave satisfactory spectral and analytical data(± 0.3 %) or correct high resolution mass spectral values.

6) Cf. L. Field, Synthesis, 713 (1978).

7) Identical with the authentic material prepared by a different route: Cf. S. Takano, M. Hirama, T. Araki, and K. Ogasawara, J. Amer. Chem. Soc., 98, 7084 (1976).

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