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CONVERSION OF OXINDOLE ALKALOIDS INTO INDOLE ALKALOIDS

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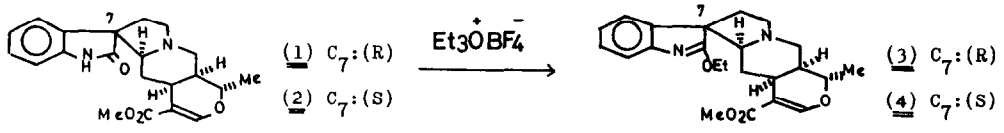
While extensive study has been made on the oxidative transformation of natural indolic alkaloids into their oxindole equivalents, and several ingenious general methods have been developed[1,2] the reverse process has not been realized. Attempts along this line[3,4,5] have shown that whereas some synthetic N-methyl-3-spirooxindoles are reduced and subsequently rearranged into the corresponding indoles by use of $LiAlH_4$ followed where necessary by treatment with acid, natural oxindole alkaloids are reduced to indolines by excess amounts of $LiAlH_4$[6]. The presence of a carbomethoxyl group in the molecule makes the use of this reagent further unprofitable.

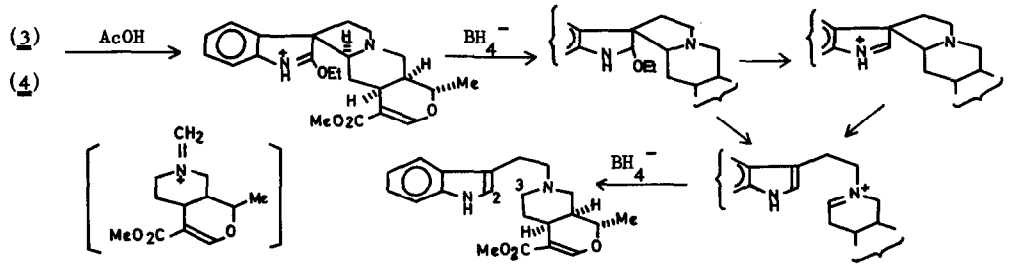
In our structural study of gardneramine,[7] we found that $NaBH_4$ in acetic acid[8] is a suitable reduction reagent for the iminoether system, which is a potential oxindole. Employing this reductive method as a key step, we have successfully accomplished the conversion of some natural oxindoles into their indole congeners.

Ethyl iminoethers were prepared from oxindoles by means of Meerwein's reagent. Thus, treatment of both pteropodine (= uncarine C)(1) and isopteropodine (= uncarine E)(2), which had been separated from Uncaria florida Vidal in this laboratory[9], with the reagent afforded the same mixture of two epimeric iminoethers, 3 and 4, in 84 % total yield. The less polar epimer (4) was obtained in a crystalline state, mp 122-124°, UV λ_{max}^{MeOH} 213(4.30) and 241(4.03) mμ, IR $\nu_{max}^{CHCl_3}$ 1692,1630 (conj. ester), 1575 (C=N) cm^{-1}. On mild acid treatment, 4 gave isopteropodine (2) as the sole oxindole, proving the stereochemical assignment. A similar preparation of epimeric iminoethers from oxindoles by use of Meerwein's reagent was recently reported by Gaskell et al.[11]



(1) C_7:(R)
(2) C_7:(S)
(3) C_7:(R)
(4) C_7:(S)

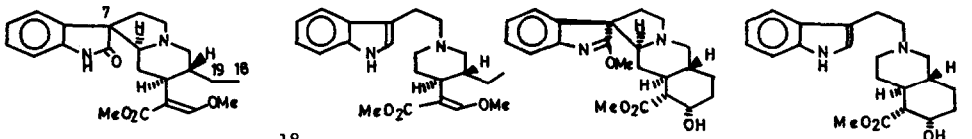
Although treatment of 4, or a mixture of 3 and 4, with excess $NaBH_4$ in ethanol resulted in recovery of the starting material, smooth reaction proceeded when acetic acid was used as the solvent. The product (5) (59 % yield) showed the characteristic UV spectrum (λ_{max}^{MeOH} 223, 283 and 291 mμ) of an indole having an α,β-unsaturated ester system, and gave a positive response to the Ehrlich test. The mass spectrum, with the molecular ion peak at m/e 354 and the base peak of particular diagnostic value at m/e 224, indicated the 2,3-seco-heteroyohimbinoid structure as shown. Its formation may be rationalized by the following mechanism.



m/e 224 (5)

Catalytic reduction of 4 with Adams' catalyst in acetic acid also afforded 5 in 30 % yield, together with unchanged 4 and isomerized oxindoles.[10]

A similar $NaBH_4$-acetic acid reduction of an iminoether mixture derived from isorhynchophylline (6) gave an amorphous indole (7). Yohimbine oxindole iminoether (8)[1a] was also reduced to give a crystalline indole (9), mp 114-116°, $[\alpha]_D$ + 48.3° (MeOH), whose perchlorate melted at 205-208°.



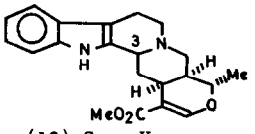
(20) C_7:(R) (21) C_7:(R), Δ^{18}

(6) C_7:(S) (22) C_7:(S), Δ^{18}

(7) (8) (9)

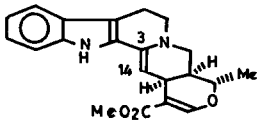
The 2,3-seco-indoles, thus obtained, were then subjected to oxidative cyclization.[12] A solution of 5 in dilute acetic acid was heated with excess $Hg(OAc)_2$, then treated with hydrogen sulfide. Extraction with benzene afforded a mixture (25 % yield) which consisted of approximately equal amounts of two indoles, 10 and 11. The less polar component (10), mp 221-223°, $[\alpha]_D$ - 110° ($CHCl_3$), was identified with natural tetrahydroalstonine by mixed fusion and comparison of optical rotation, TLC and UV, IR and mass spectra. Amorphous 11, $[\alpha]_D$ - 45° (EtOH), was shown to be akuammigine on the basis of comparison of optical rotation, TLC behaviour in three

solvent systems, and UV, IR and mass spectra. Furthermore, 11 underwent epimerization at C_3 in hot acetic acid to give crystalline 10, confirming the structural assignment. The aqueous layer, after pH adjustment to 6 - 7, was then extracted with methylene chloride to yield a minor product (12), mp 180-198°, to which the enamine structure, depicted below, was ascribed on the basis of spectral data and conversion to 10 on $NaBH_4$ reduction. An additional amount of 10 was obtained through $NaBH_4$ treatment of the concentrated aqueous layer.

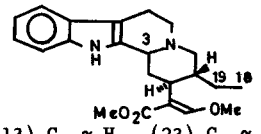


(10) C_3-α H

(11) C_3-β H



(12)



(13) C_3-α H (23) C_3-α H, Δ^{18}

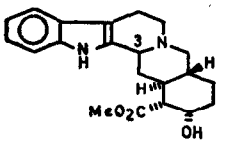
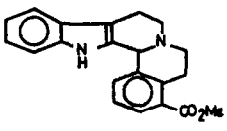
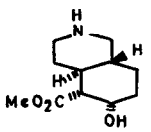
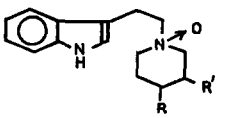
(14) C_3-β H (24) C_3-β H, Δ^{18}

Similar treatment of 7 with $Hg(OAc)_2$ led to the formation of a complex mixture of products from which hirsutine (14)** was isolated by means of preparative TLC and identified with an authentic specimen. At the same time, the presence of expected dihydrocorynantheine (13) in the mixture was confirmed by TLC analysis.

Morrison et al.[13] described the preferential formation of (±)-pseudoyohimbane by $Hg(OAc)_2$ oxidation of (±)-2,3-seco-yohimbane. Our result using 2,3-seco-yohimbine (9), however, was less straightforward. Thus, both yohimbine (15) and pseudoyohimbine (16) were isolated and identified with authentic samples by direct comparison. Moreover, an inside yohimbane derivative (17), mp 112-117°, and a decahydroisoquinoline derivative (18), mp 139-144°, were obtained and characterized by their spectral data.

Quite recently, Husson et al.[14] reported a new type of C ring formation through piperidine N-oxides (19). We investigated application of their procedure to 2,3-seco-akuammigine (5).

** In our reinvestigation of the constituents of Uncaria rhynchophylla Mig., besides the hitherto reported rhynchophylline (20) and isorhynchophylline (6), two indoles, hirsutine (14) and its 18,19-dehydro analogue (24), mp 92-94°, $[\alpha]_D$ + 68.5° ($CHCl_3$), were newly isolated. The latter was a new base and we have since learned that the same alkaloid was recently isolated from a Mitragyna sp. and named as hirsuteine by Shellard et al., independently.[15] Furthermore, the presence of four additional bases in the same plant has been demonstrated; corynoxeine (21), isocorynoxeine (22), corynantheine (23) and dihydrocorynantheine (13). This part of the work has been accomplished by Mr. Nobuo Shinma in this laboratory.

(15) C_3-α H (17) (18) (19)

(16) C_3-β H

Hydrogen peroxide oxidation of 5 in methylene chloride gave a mixture of epimeric N-oxides, which without further purification was treated with trifluoroacetic anhydride containing trifluoroacetic acid in methylene chloride. Akuammigine (11) was isolated and identified with an authentic specimen ; in contrast to the oxidation with mercuric acetate, no detectable formation of tetrahydroalstonine (10) was observed.

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