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TRANSFORMATION OF INDOLE ALKALOIDS—I

CONVERSION OF OXINDOLE ALKALOIDS INTO INDOLE ALKALOIDS[1]

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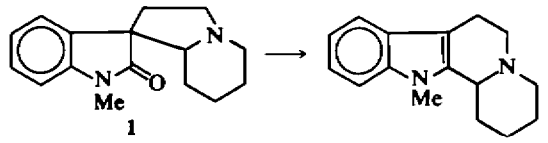
Abstract—Chemical conversion of some natural oxindoles (pteropodine, isopteropodine and isorhynchophylline) into the corresponding indole alkaloids has been made by way of a sequence of reactions which include formation of iminoethers of the natural oxindoles with Meerwein's reagent, reduction of the iminoethers to 2,3-seco-indoles and cyclization of 2,3-seco-indoles to the desired natural indole alkaloids. Sodium borohydride in acetic acid was found to be a specific reagent for the reduction of oxindole-iminoethers to 2,3-seco-indoles which were the key intermediates in these transformations. Yohimbine-oxindole iminoether was similarly converted to yohimbine and pseudoyohimbine. A number of by-products were obtained and their structures were elucidated.

The conversion of indole alkaloids into their corresponding spirooxindoles have been studied extensively and several ingeneous general methods have been reported. Thus, Finch and Taylor[2a] chlorinated the β-position of some indole alkaloids with t-butyl hypochlorite. Treatment of the resulting chlorides under basic conditions gave iminoethers which were then hydrolysed in refluxing aqueous acetic acid to the spiro oxindoles. The same authors[2b] found that lead tetraacetate oxidation of indoles followed by treatment with methanolic acetic acid was a superior method for the preparation of *cis*-DE yohimbinoid oxindole alkaloids. Zinnes and Shavel[3] found that the β-chloro-indolenines rearranged to the corresponding oxindoles when refluxed in aqueous methanol containing a small amount of acetic acid. Oxindole alkaloids often coexist with their corresponding indole alkaloids in plants and their biogenetic relationship could be interpreted in terms of analogous enzymatic oxidation.[4] From the chemical point of view, however, the reverse process, *viz* reductive transformation of spirooxindoles into the corresponding indole alkaloids, is also of great interest.

Work along this line has been successful on rather simple, synthetic N-methyl-oxindoles (for examples: **1**,[5] **3**[6] and **5**[7] in Chart 1).

A typical condition involves use of a controlled amount of LAH and subsequent treatment with a mineral acid. Application of this procedure to natural oxindoles seems to be of limited value since conventional LAH reduction is known to give unrearranged indolines,[8] and furthermore, the presence of the carbomethoxyl group in many natural oxindoles makes the control of the reduction conditions more difficult.

In 1968, an ample quantity of a Rubiaceae plant,



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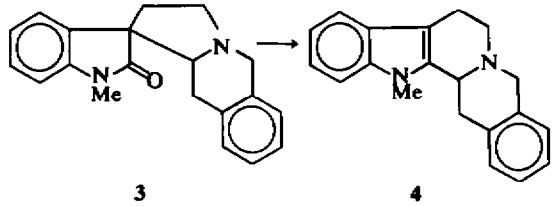

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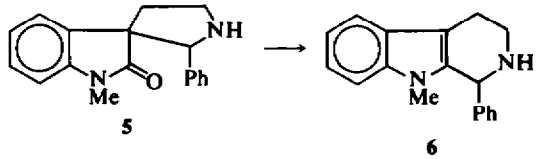
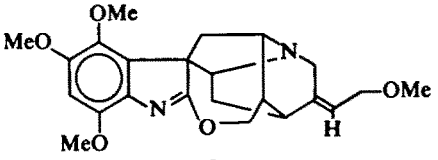


5 6 (7)

Uncaria florida, was collected in the southern part of Formosa, and subsequently the plant was found to be a rich source of oxindole alkaloids, e.g. pteropodine (uncarine C), isopteropodine (uncarine E), speciophylline (uncarine D) and uncarine F.[9] Using these oxindoles as starting materials, study for the selective reduction of oxindole carbonyl was started. First tried was Borch's method,[10] namely, sodium borohydride reduction of imminium tetrafluoroborates which had been prepared *in situ* from an oxindole and Meerwein's reagent, but no satisfactory result was obtained.

In the meantime, the unique structure of gardneramine (7), the main alkaloid of *Gardneria* spp., had been elucidated in this laboratory.[11] Gardneramine (7) has in its structure an iminoether system, which can be regarded as a potential oxindole function. It was then found that the system, though stable in a neutral condition, is susceptible to sodium borohydride reduction in acetic acid giving the dihydro derivative (8), which showed in its NMR spectrum a C_2—H signal at 5·15 δ and a N—H signal at 4·13 δ coupled with J = 4 Hz. In this case, no further reduction into a seco indole (see below) nor rearrangement into a 2,3-disubstituted indole was observed, presumably because of the bridge-head nature of N_b.



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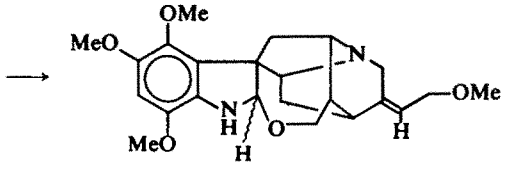

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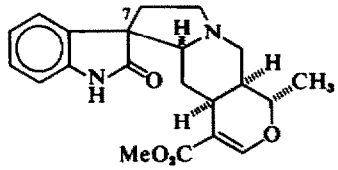
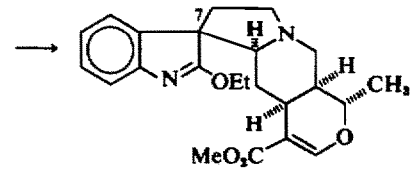
Iminoethers were prepared from some natural oxindoles and were reduced in a similar manner as above. In these cases the reduction gave rise to the corresponding seco-indoles, which were then oxidatively cyclized to the natural indole alkaloids. Thus, the conversion of natural oxindole into the indole congeners was attained, some examples of which will now be described.

Ethyl iminoethers were prepared from oxindoles by use of Meerwein's reagent. Thus, pteropodine (uncarine C, 9) and isopteropodine (uncarine E, 10), when treated with the reagent, gave rise to the same mixture of two iminoethers, regardless of the starting material. From a column of Al_2O_3, the faster moving epimer (12) was obtained as colorless prisms, m.p. 122–124°, having UV absorption maxima at 213 (4·30) and 241 (4·03) mμ and IR absorption maxima at 1692, 1630 (conj ester), and 1575 (C=N—) cm^{-1}. On mild acid treatment, 12 gave isopteropodine (10) as the sole oxindole, thereby proving the C_7 configuration as S. Though not obtained in a crystalline state, the slower moving product obtained from the column was evidently the C_7 epimer of 12. Gaskell *et al.*[12] reported a similar preparation of the epimeric iminoethers from a synthetic oxindole by use of Meerwein's reagent.



9: $C_{(7)}$: R
10: $C_{(7)}$: S

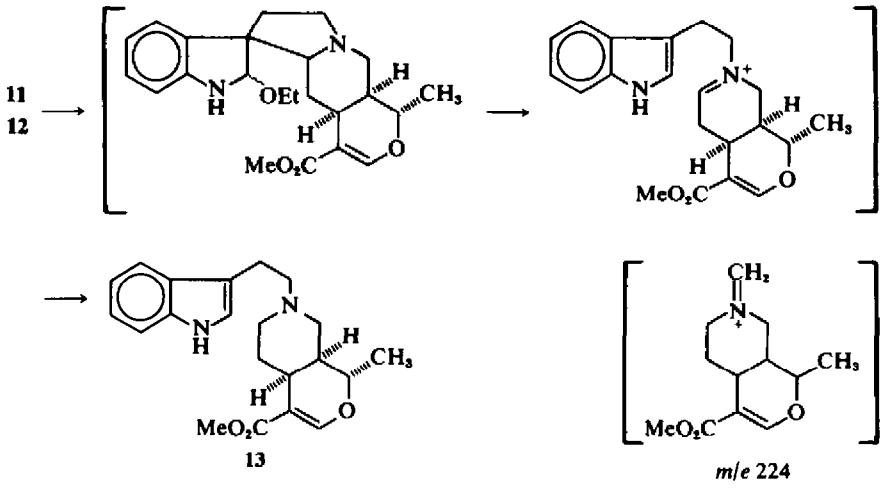


11: $C_{(7)}$: R
12: $C_{(7)}$: S

Although treatment of 12, or a mixture of 11 and 12, with excess sodium borohydride in boiling ethanol resulted in recovery of the starting material, reaction was induced when acetic acid was used as the solvent. Thus, an excess of sodium borohydride (10 molar equivs) was added portionwise to a stirred solution of 12 in acetic acid, and after vigorous effervescence ceased, the solution was kept stirring at room temperature for 3 hr. Al_2O_3 column chromatography of the product afforded prisms (13), m.p. 99–101°, which showed a characteristic UV spectrum (λ_{max}^{MeOH} mμ: 223, 283 and 291) of an indole in addition to a β-alkoxy acrylic ester system. The mass spectrum, with the molecular ion peak at *m/e* 354 and the base peak, of particular diagnostic value, at *m/e* 224 (Chart 4), strongly indicated the 2,3-seco heteroyohimbinoid structure (13) of the product. In addition, the structural assignment was supported by a positive reaction to the Ehrlich test and the presence of a NMR signal due to the α-H of the indole nucleus (6·99 δ, 1 H, d., J = 2·5 Hz). Catalytic reduction of 12 with Adams' catalyst in AcOH resulted in the formation of 13 in 40% yield. Soon after our preliminary communication[1] was published, a different synthesis of the same compound (13), though in racemic form, was reported independently by Ushoković *et al.*[13]

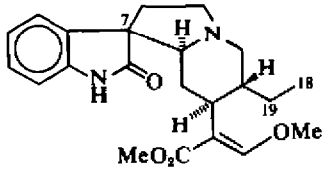
The second oxindole chosen by us as a starting material was isorhynchophylline (14), which is the main constituent of *Uncaria rhynchophylla* Miq. together with its $C_{(7)}$ epimer, rhynchophylline (15).[14] In our reinvestigation, however, both "rhynchophylline" and "isorhynchophylline" in the above plant were found to be contaminated by their $\Delta^{18,19}$ congeners, namely corynoxeine (16) and isocorynoxeine (17), respectively. In addition, four known indole alkaloids were newly found in the same plant. Details will be described elsewhere.[15]

Isorhynchophylline (14) was converted to an epimeric mixture of iminoethers (18) by Meerwein's

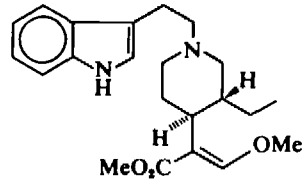


reagent. In this case, however, considerable formation of a quarternary salt (**19**) was observed. The iminoether (**18**), without further purification, was then submitted to $NaBH_4$/AcOH reduction and the corresponding seco-indole was obtained as an amorphous powder (**20**).

Yohimbine oxindole iminoether (**21**), prepared from yohimbine according to Taylor's method,[2a] was similarly reduced to a crystalline 2,3-seco-indole (**22**), m.p. 117–118°, $[\alpha]_D$ +48·3°, which forms a well characterized perchlorate (**23**), m.p. 205–208°. On acetylation with acetic anhydride and pyridine, **22** gave the acetate (**24**), m.p. 88–91°, NMR 2·05 δ (3H, s., —OAc).



14: $C_{(7)}$: R
15: $C_{(7)}$: S
16: $C_{(7)}$: R, Δ^{18}
17: $C_{(7)}$: S, Δ^{18}



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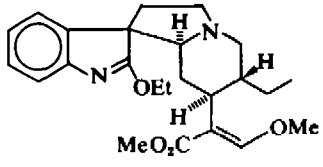
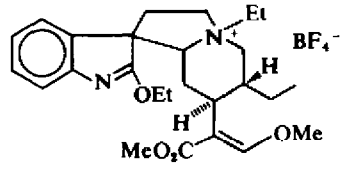


18: $C_{(7)}$: R and S



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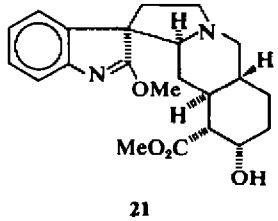

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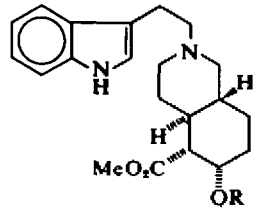
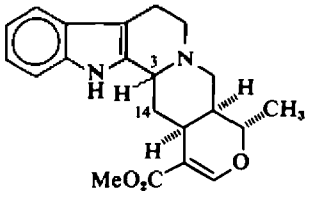


22: R = H
24: R = Ac

2,3-Seco-indoles, thus obtained, were then submitted to oxidative cyclization[16] to form the corresponding indole alkaloids. A solution of **13** in dilute acetic acid was heated with an excess of mercuric acetate and then was treated with sodium borohydride. Extraction of the basified solution with $CHCl_3$ afforded a mixture consisting of approximately equal amounts of two indoles (**25** and **26**). The less polar component (**25**), m.p. 221–224°, $[\alpha]_D$ −110°, was identified as tetrahydroalstonine by mixture m.p. determination with an authentic sample and by comparison of their physical properties including optical rotation, TLC, UV, IR and mass spectrum. Amorphous (**26**), $[\alpha]_D$ −45·0°, was



25: $C_{(3)}$ αH
26: $C_{(3)}$ βH
27: $\Delta^{3,14}$

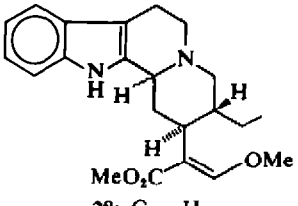
shown to be akuammigine on the basis of comparison with an authentic material in optical rotation, TLC behaviour in three solvent systems, UV, IR and mass spectrum. Furthermore, **26** underwent epimerization at $C_{(3)}$[17] in hot acetic acid to give crystalline **25**, confirming the correctness of the structural assignment.

A similar mercuric acetate oxidation was carried out omitting the subsequent $NaBH_4$ reduction. The resulted solution was treated with hydrogen sulfide and the filtrate was concentrated *in vacuo*. The residue was extracted with benzene and the solvent was evaporated yielding about equal amounts of **25** and **26**. The residual aqueous layer, after pH adjustment to 6–7, was extracted with CH_2Cl_2 to give a minor product (**27**), m.p. 180–198°. From the characteristic UV spectrum (λ_{max}^{MeOH} mμ: 232, 309 and 321), mass spectral evidence (*m/e* 350, M^+) and the fact that **25** was given on $NaBH_4$ reduction, the enamine structure (**27**) was ascribed to this product.

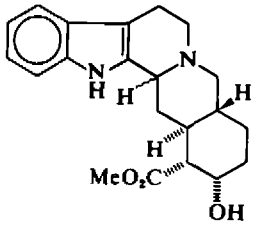
The seco-compound derived from isorhynchophylline was subjected to the oxidative cyclization with mercuric acetate followed by hydrogen sulfide treatment and $NaBH_4$ reduction. From the complex mixture of products, hirsutine (**29**) was isolated by means of preparative TLC and was identified through the agency of an authentic specimen. At the same time, the presence of the expected dihydrocorynantheine (**28**) was confirmed by TLC analysis.

When 2,3-seco-yohimbine (**22**) was treated with mercuric acetate in a similar way as above, both yohimbine (**30**) and pseudoyohimbine (**31**) were isolated and the structures were confirmed by the direct comparison with the authentic samples. In addition, an inside yohimbane derivative (**32**), m.p. 112–117°, was obtained and characterized by the physical data. Further, a decahydroisoquinoline derivative (**33**), m.p. 139–144°, which showed no absorption in the UV, was obtained. These products indicate that the dehydrogenation by mercuric acetate occurred in all of the three possible directions.[16] Morrison *et al.*[18] obtained only pseudoyohimbane in crystalline state from a similar cyclization using 2,3-seco-yohimbane. In the present case with functional groups on the E ring, the selectivity was not high both in the stereochemistry of the cyclization and in the direction of the dehydrogenation.

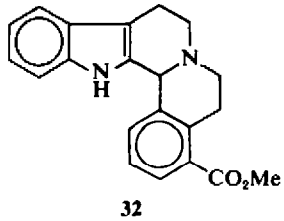
Uskokovic *et al.*[13] made use of mercuric acetate



28: $C_{(3)}$ αH
29: $C_{(3)}$ βH



30: $C_{(3)}$ αH
31: $C_{(3)}$ βH



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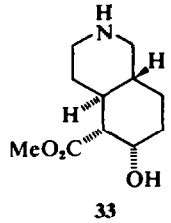

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and EDTA in similar cyclization of 2,3-seco-indoles in their recent synthetical work. Improvement was observed in the yields of **30** and **31** when the same reagents were used for the cyclization of **22**. Thus, **22** was treated with mercuric acetate (3 molar equivs) and EDTA·2Na (3 mol eq) in 1% aqueous acetic acid at 95–100°. Reduction with sodium borohydride gave yohimbine (**30**; 32%) and pseudoyohimbine (**31**; 7%).*[1]

Recently, Husson *et al.*[19] reported a unique C-ring formation by way of N-oxides of 2,3-seco compounds. Application of their procedure to the present study was attempted. Thus, seco-compound (**13**) was oxidized by hydrogen peroxide in methylene chloride-ethanol and the resulted mixture of epimeric N-oxides, without further purification, was then treated in methylene chloride solution with trifluoroacetic anhydride containing a trace of trifluoroacetic acid. Akuammigine (**26**) was isolated and identified by comparison with an authentic specimen. Only a small amount of tetrahydroalstonine (**25**) was observed by TLC.

EXPERIMENTAL

All m.ps were determined in glass capillary tubes using a H_2SO_4 bath and are uncorrected. IR spectra were measured by a Model EPI-G3 Spectrophotometer (Hitachi Co) and UV spectra by a Model EPS-3T Spectrophotometer (Hitachi Co). NMR spectra were run using a JNM 4H-100 NMR Instrument (Japan Electron Optics Co) in $CDCl_3$ with TMS as an internal reference unless otherwise stated. Mass spectra were taken with a Model RMU-6E Mass Spectrometer (Hitachi Co). A JASCO DIP-SL Polarimeter (Japan Spectroscopic Co) was used for the measurement of optical rotations. For column chromatography, the following adsorbents were used: Al_2O_3 according to Brockmann, activity 2–3 (Merck) and Silicic Acid AR-100 (Mallinckrodt). For TLC, Silica gel GF_{254} (Merck) was used.

$NaBH_4$/AcOH *Reduction of gardneramine* (**7**). To gardneramine **7** (0·3 g) in AcOH (6 ml), 150 mg of $NaBH_4$ was added portionwise. After vigorous effervescence ceased, the soln was poured into ice-water. Extraction of the basified soln with $CHCl_3$ followed by the usual work-up afforded colorless prisms of **8** (0·23 g), which on recrystallization from Et_2O gave an analytical sample, m.p. 144–145°; UV λ_{max}^{MeOH} mμ (log ε): 212·5 (4·57), 241·5 (inf, 3·90) and 303·5 (3·56); NMR δ: 3·31 (3H, s, aliph—OMe); 3·78, 3·80 and 3·82 (each 3H, s, 3xArom —OMe); 4·13 (1H, d, J = 4 Hz, N—H); 5·15 (1H, d, J = 4 Hz, $C_{(2)}$—H) and 6·40 (1H, s, Ar —H); mass spectrum *m/e* 414 (M^+). (Found: C, 66·37; H, 7·23; N, 6·54. $C_{23}H_{31}N_2O_5$ requires: C, 66·64; H, 7·30; N, 6·76%).

Preparation of iminoether from pteropodine (**9**). Pteropodine (uncarine C; **9**) (4·374 g, 11·9 mM) was added portionwise to a well stirred soln of Meerwein's reagent (triethyloxonium tetrafluoroborate; 9·295 g, 49 mM) in dry CH_2Cl_2 (45 ml) at room temp. After stirring overnight, the soln was basified with ammoniacal ice-water. Extraction with CH_2Cl_2 followed by drying over Na_2SO_4 afforded a syrup (4·386 g), from which **12** was obtained as fine prisms (1·288 g). The mother liquor was chromatographed over Al_2O_3 (150 g) and an additional amount (236 mg) of **12** was obtained from the n-hexane/benzene and benzene elution fractions. Further elution with benzene and benzene/$CHCl_3$ afforded a syrup (1·957 g), which contained roughly equal amounts of **12** and its epimer (**11**). Compound (**12**) showed the following physical properties: m.p. 122–124°, $[\alpha]_D$ −69·0° (*c* = 1·0, $CHCl_3$), mass spectrum: *m/e* 396 (M^+), UV λ_{max}^{MeOH} mμ (log ε): 213 (4·30) and 246 (4·03), IR ν_{max}^{KBr} cm^{-1}: no OH or NH; 2790 (Bohlmann band); 1710 (CO_2Me); 1635, 1620 (C=C) and 1578 (C=N), NMR δ: 1·40 (3H, d, J = 7 Hz, $C_{(19)}$—Me); 1·43 (3H, t, J = 7 Hz, $-CH_2CH_3$); 3·56 (3H, s, $-CO_2Me$); 4·47 (2H, q, J = 7 Hz, $-CH_2CH_3$) and 7·37 (1H, s, $C_{(17)}$—H). (Found: C, 69·78; H, 6·90; N, 6·99. $C_{23}H_{28}N_2O_4$ requires: C, 69·67; H, 7·12; N, 7·07%).

Treatment of **12** *with hydrochloric acid.* The iminoether **12** (25 mg) was dissolved in 2N HCl (2 ml) and the soln was stirred at room temp for 3 hr. TLC of the product in a cyclohexane/AcOEt (1/1) solvent system showed exclusive formation of **10**. Crystallization from benzene gave 6 mg of crystals, m.p. 198–209°, whose IR spectrum indicated an identity with isopteropodine (**10**). No change of **9** into **10** was observed under the same conditions.

Attempted reduction of the iminoethers (**11** *and* **12**) *with* $NaBH_4$. The iminoether mixture (30 mg) was dissolved in 5 ml EtOH, and 150 mg $NaBH_4$ was added. After refluxing for 18 hr, the starting material was recovered unchanged from the reaction.

Reduction of the iminoethers (**11** *and* **12**) *with* $NaBH_4$/AcOH. To a soln of the iminoether mixture **11** and **12** (3·20 g, 8 mM) in 40 ml of AcOH, 2·80 g (70 mM) $NaBH_4$ was added portionwise. After vigorous effervescence ceased, the soln was kept stirring at room temp for 3 hr. The soln was diluted with ice-water, basified with NH_4OH and extracted with $CHCl_3$. Removal of the solvent afforded a syrup (3·36 g), which was subjected to Al_2O_3 (130 g) column chromatography. From the eluates with n-hexane containing increasing amounts of AcOEt, **13** (1·567 g, 55%) was obtained as a syrup. Crystallization from AcOEt/n-hexane gave prisms (0·92 g), m.p. 99–101°, $[\alpha]_D^{27}$ −55·0° (*c* = 0·67, $CHCl_3$), which showed a positive reaction to Ehrlich's reagent; IR ν_{max}^{KBr} cm^{-1}: 3345 (NH); 1690, 1620 (conj. ester); UV λ_{max}^{MeOH} mμ (log ε): 224 (4·62), 245 (sh, 4·10), 284 (3·75) and 292 (3·57); NMR δ: 1·31 (3H, d, J = 7 Hz, $C_{(19)}$—Me); 3·68 (3H, s, CO_2Me); 4·45 (1H, m, $C_{(19)}$—H); 6·99 (1H, d, J = 2·5 Hz, $C_{(2)}$—H); 7·51 (1H, s, $C_{(17)}$—H) and 7·97 (1H, br, NH); mass spectrum: *m/e* 354 (M^+) and 224 (base peak). (Found: C, 70·90; H, 7·41; N, 7·71. $C_{21}H_{26}N_2O_3$ requires: C, 71·16; H, 7·39; N, 7·90%).

Catalytic reduction of **12**. Crystalline **12** (0·300 g) was reduced catalytically with Adams' catalyst (150 mg) in AcOH. The crude product (274 mg) was subjected to column chromatography over Al_2O_3 (15 g), from which 106 mg (40%) of **13** was obtained along with unchanged starting **12** (14 mg) and 128 mg of the diastereomeric mixture of oxindoles (pteropodine, isopteropodine, speciophylline and uncarine F).

Isorhynchophylline iminoether (**18**). Meerwein's reagent (5·2 g, 3M eq) was added to a soln of **14** (3·47 g) in

*[1]After our work was completed, Stork *et al.*, *J. Am. Chem. Soc.* **94**, 5109 (1972) reported a synthesis of racemic **22** and its transformation into yohimbine (**30**) and pseudoyohimbine (**31**). In the latter reactions, though the conditions employed therein are similar to ours, there seems to be some discrepancy between their results and ours in regard to the product ratios and the occurrence of minor products.

dry CH_2Cl_2 (30 ml), and the resulting soln was kept stirring at room temp overnight. Purification *via* Al_2O_3 (120 g) chromatography gave a syrup (2·99 g), whose TLC showed two spots of nearly equal size; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1575 (C=N). This mixture of the epimeric iminoethers was used for the next reaction without further purification. From the MeOH eluate of the above chromatography, a quarternary salt **19** (88 mg) was obtained. Recrystallization from acetone/n-hexane gave colorless prisms, m.p. 230–235°; IR ν_{max}^{KBr} cm^{-1}: 1694, 1640 (conj ester); 1585 (C=N); UV λ_{max}^{MeOH} mμ (log ε): 213 (4·46), 216·5 (4·47), 243 (4·19) and 274 (3·41). (Found: C, 58·99; H, 7·19; N, 4·94. $C_{26}H_{37}N_2O_4 \cdot BF_4$ requires: C, 59·10; H, 7·06; N, 5·30%).

$NaBH_4$/AcOH *Reduction of* **18**. $NaBH_4$ (850 mg) was added to an AcOH (20 ml) soln of **18** (1·141 g) during 10 min. The soln was stirred for an additional 20 min after the addition to give **20** as a syrup (342 mg), which showed a single spot with TLC (solvent system, $CHCl_3$/Me_2CO (1/1)) and a positive reaction to Ehrlich's reagent; UV λ_{max}^{MeOH} mμ: 222, 283 and 290·5; mass spectrum: *m/e* 370 (M^+) and 240 (base peak).

2,3-*Seco-yohimbine* (**22**). $NaBH_4$ (390 mg) was added to an AcOH (10 ml) soln of **21** (507 mg) which was prepared from commercial yohimbine according to Taylor's procedure.[2a] After stirring for 1 hr at room temp the mixture was worked up in the usual manner to give 476 mg of a product. Chromatography over silicic acid (60 g) gave 210 mg of a pure syrup, from which prisms of **22** (101 mg), m.p. 117–118° (from $CHCl_3$), $[\alpha]_D^{21}$ +48·3° (*c* = 1·49, MeOH), were obtained; UV λ_{max}^{MeOH} mμ (log ε): 221 (4·52), 282 (3·73) and 290 (3·65); IR ν_{max}^{KBr} cm^{-1}: 3400, 3240 (NH, OH); 1743, 1153 (ester), NMR δ (CD_3OD): 3·88 (3H, s, CO_2Me); 4·20 (1H, m, $C_{(17)}$—H); 7·01 (1H, s, $C_{(2)}$—H); mass spectrum *m/e*: 356 (M^+) and 226 (base peak). Perchlorate (**23**), micro needles from EtOH, m.p. 205–208°. (Found: C, 55·01; H, 6·48; N, 6·09. $C_{21}H_{28}N_2O_3 \cdot HClO_4$ requires: C, 55·20; H, 6·40; N, 6·13%).

Acetylation of **22**. A soln of **22** (600 mg) in a mixture of 12 ml pyridine and 8 ml Ac_2O was left standing overnight. After warming at 60° for 1 hr, the volatile materials were removed *in vacuo*. Chromatography over Al_2O_3 (15 g) gave 529 mg (80%) of **24** as a pure syrup. Crystallization from EtOAc/n-hexane afforded prisms, m.p. 88–91°; IR ν_{max}^{KBr} cm^{-1}: 3550 (NH); 1742 (OAc); 1730 (CO_2Me); 1260 (OAc); NMR δ: 2·05 (3H, s, —OAc); 3·65 (3H, s, CO_2Me); 5·40 (1H, m, $C_{(17)}$—H); 6·98 (1H, d, J = 2 Hz, $C_{(2)}$—H); 8·14 (1H, br, s, NH). Mass spectrum *m/e*: 398 (M^+); 268 (base peak).

Oxidative cyclization of **13**. 2,3-Seco-akuammigine (**13**) (0·712 g, 2·01 mM) was heated with 6·699 g (21 mM) of $Hg(OAc)_2$ in 5% AcOH (30 ml) at 100°. After 3 hr, H_2S was bubbled through the soln for 1·5 hr, and the soln was filtered through a layer of celite. The concentrated filtrate was brought to pH 6 with $NaHCO_3$ and was added to an equal volume of EtOH, $NaBH_4$ (420 mg) was added, and the soln was stirred overnight. Extraction with $CHCl_3$ gave a syrup (447 mg) which was chromatographed on silicic acid (30 g). The fractions eluted with n-hexane and n-hexane/AcOEt (1/1) were combined (106 mg) and crystallized from MeOH to give colorless plates of **25**, m.p. 220–225° (dec), $[\alpha]_D^{27}$ −110° (*c* = 0·5, $CHCl_3$); UV λ_{max}^{MeOH} mμ: 227, 284 and 290·5; mass spectrum *m/e*: 352 (M^+, base peak); IR ν_{max}^{KBr} cm^{-1}: 3380 (NH); 2790, 2740 (Bohlmann bands); 1702, 1625 (conj ester). Another recrystallization gave a sample of m.p. 221–223°, which showed the same IR spectrum as authentic **25** and showed no depression of m.p. on admixture.

Elution with n-hexane/AcOEt (1/4) and AcOEt gave an amorphous powder (103 mg), whose IR spectrum showed no Bohlmann band; UV λ_{max}^{MeOH} mμ: 225·5, 283·5 and 290·5; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH); 1695, 1630 (conj ester); mass spectrum *m/e*: 352 (M^+, base peak) $[\alpha]_D^{25}$ −45·0° (*c* = 1·0, EtOH). Comparison of the IR spectra and TLC behaviours in the following three solvent systems showed it to be **26**; system A, cyclohexane/AcOEt (1/1), R_f = 0·23, system B, acetone/$CHCl_3$ (4/5), R_f = 0·50, system C, acetone/Et_2O (5/4), R_f = 0·71.

Compound **26** (30 mg) was heated with 10 ml AcOH in a sealed tube under reflux for 24 hr. Chromatography over Al_2O_3 gave plates, m.p. 222–224°, which were identified as tetrahydroalstonine by a mixture m.p. determination.

Enamine (**27**). Oxidative cyclization was carried out using 166 mg of **13** and 146 mg of $Hg(OAc)_2$ in a similar manner as described above. After H_2S treatment, the filtrate was extracted with benzene to give a syrup (35 mg), TLC of which showed the presence of **25** and **26** in a roughly 1 : 1 ratio. (Solvent system, cyclohexane/AcOEt (1/1)). The pH of the remaining aqueous soln was adjusted to 6–7. Extraction with CH_2Cl_2 followed by chromatography over Al_2O_3 afforded 5 mg of crystalline **27**, m.p. 180–198°; mass spectrum *m/e*: 350 (M^+); UV λ_{max}^{MeOH} mμ: 232, 309 and 321; UV $\lambda_{max}^{MeOH+dil\,HCl}$ mμ: 241 and 357; IR ν_{max}^{KBr} cm^{-1}: 3410 (NH); 1709, 1625 (conj ester); no Bohlmann band. When reduced with $NaBH_4$, **25** was formed as evidenced by a TLC analysis. (Solvent system, cyclohexane/AcOEt (1/1)).

$Hg(OAc)_2$ *Oxidation of* 2,3-*seco-hirsutine* (**20**). 2,3-Seco-hirsutine (**20**) (180 mg) and $Hg(OAc)_2$ (1·5 g) were heated in 5% AcOH (12 ml) at 100° for 1 hr. The usual work-up gave 55 mg of syrup, which was chromatographed over silica gel (10 g). Eluates with $CHCl_3$/MeOH (97/3) and $CHCl_3$/MeOH (9/1) were submitted to preparative TLC in a solvent system of benzene/$CHCl_3$/MeOH (4/1/1). Hirsutine **29** (4 mg) was obtained as a semicrystalline mass, whose IR spectrum was superimposable with that of an authentic specimen.

$Hg(OAc)_2$ *Oxidation of* 2,3-*seco-yohimbine* (**22**). 2,3-Seco-yohimbine (**22**) (300 mg) was heated with 2·7 g $Hg(OAc)_2$ in 20 ml 5% aqueous AcOH at a bath temp of 114–117° for 4·5 hr. The mixture was treated with H_2S, filtered through a layer of celite and concentrated *in vacuo*. The pH of the solution was brought to *ca* 6 by addition of $NaHCO_3$ and the soln was stirred with 350 mg of $NaBH_4$ overnight at room temp. Basification with NH_4OH followed by $CHCl_3$ extraction gave 165 mg of the crude product, which was subjected to chromatography on Al_2O_3 (10 g). Elution with benzene/$CHCl_3$ (3/1) gave 19 mg of **31**, m.p. 262–263°, $[\alpha]_D^{22}$ +29·1° (*c* = 0·55, pyridine). The m.p. showed no depression on admixture with an authentic specimen. The IR spectrum (KBr tab) was identical to that of the authentic sample.

From the eluate with benzene/$CHCl_3$ (3/1) and $CHCl_3$, 35 mg of **30**, m.p. 224–227°, was obtained. No depression of m.p. was observed on admixture with an authentic specimen, and comparison of the IR spectra confirmed the identity.

From the eluate with benzene/$CHCl_3$, a small amount of **32** was obtained, m.p. 112–117° (trom EtOH); mass spectrum *m/e*: 332 (M^+); UV λ_{max}^{MeOH} mμ: 226, 282 and 291; IR ν_{max}^{KBr} cm^{-1}: 3510 (NH); 1700, 1153 (CO_2Me).

From the eluate with $CHCl_3$/MeOH (97/3), **33** was obtained, m.p. 139–144° (from AcOEt); IR ν_{max}^{KBr} cm^{-1}: 3400, 3260 (OH, NH); 1732 (CO_2Me). The UV spectrum showed no absorption maximum; mass spectrum *m/e*: 213 (M^+, base peak).

N-*Oxide* (**34**) *from* 2,3-*seco-akuammigine* (**13**). 30% H_2O_2 (1·7 ml, 7 mM) was added to a soln of **13** (507 mg) in 30 ml CH_2Cl_2/EtOH (1/1). The soln was stirred for 48 hr at 60–65° (bath temp) and excess oxidizing agent was decomposed by addition of Pd—C. Filtration, basification with NH_4OH, and extraction with $CHCl_3$ afforded a syrup (483 mg) from which a mixture (**34**) of two N-oxides was obtained after purification by Al_2O_3 chromatography. The mixture regenerated the starting material (**13**) on reduction with $NaHSO_3$ (TLC analysis, solvent system; benzene/EtOH/Et_2NH (8/1·5/0·5)).

Akuammigine (**26**). The mixture of N-oxides (**34**) (276 mg, 0·74 mM) was dissolved in dry CH_2Cl_2 (12 ml), and under ice-cooling, 2 ml of $(CF_3CO)_2O$ containing a few drops of CF_3CO_2H was added. After stirring for 7 hr at room temp the soln was basified with $NaHCO_3$ and extracted with CH_2Cl_2. Elution with n-hexane/AcOEt (1/1) from a column of Al_2O_3 (30 g) gave an amorph powder (50 mg), which was shown to be akuammigine by comparison of the IR and mass spectra with those of an authentic specimen and by TLC analysis (solvent system; cyclohexane/AcOEt (1/1)). Tetrahydroalstonine (**25**) was not obtained in pure form.

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