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NEW METHODS FOR THE SYNTHESIS OF OXINDOLE ALKALOIDS. TOTAL SYNTHESES OF ISOPTEROPODINE AND PTEROPODINE.

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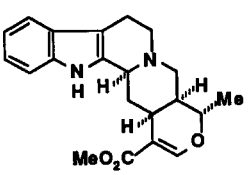
Abstract. The 2-oxindole alkaloids isopteropodine (**11**) and pteropodine (**12**) were conveniently synthesised from the known pentacycle (**9**) *via* a new and general protocol for oxidation and rearrangement of carboline lactams into 3,3-disubstituted-2-oxindoles.

During the course of a general program directed toward the design and development of new strategies for the synthesis of alkaloids, we were recently intrigued by some of the challenges presented by the oxindole alkaloids.[1] Not only is this class of alkaloids one of the major subgroups of the indole family, but oxindoles are also purported as intermediates in the biosynthetic pathway *en route* to the *Strychnos* family of alkaloids.[2] During the course of our efforts in the heteroyohimboid and corynantheoid arena, it recently occurred to us that intermediates we employed for the facile preparation of tetrahydroalstonine (**1**) and geissoschizine (**2**)[3] might also be exploited in the formulation of biogenetically-patterned syntheses of representative members of oxindole and *Strychnos* alkaloids. We now report results of some of our studies in this area, and we describe a new tactic to effect a highly stereoselective, oxidative rearrangement of carboline derivatives into 3,3-disubstituted-2-oxindoles that has resulted in a concise route to isopteropodine (**11**) and pteropodine (**12**).



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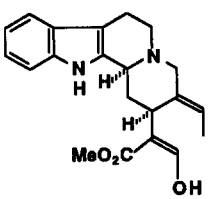
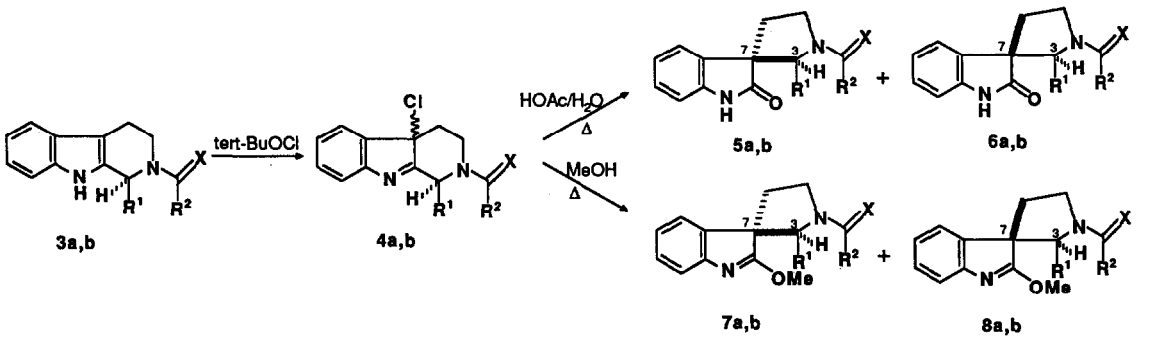


2

The oxidation of indoles of the general form **3a** with *tert*-butyl hypochlorite was first exploited as a method to effect dehydrogenation.[4] However, it was later discovered that the intermediate chloro indolenines **4a** underwent rearrangement upon heating in aqueous acetic acid to give a C(7) epimeric mixture of the 2-oxindoles **5a** and **6a** in moderate to good yields (Scheme 1).[5] Under acidic conditions at equilibrium, diastereoisomer **6a** (type B oxindole) was the major product, whereas **5a** (type A oxindole) dominated the equilibrium mixture under basic conditions; there was not a pronounced preference for either **5a** or **6a** under any conditions. In a recent and detailed study of this oxidation-rearrangement sequence in the yohimboid area,[6] it was found that chlorination of the indole ring produced a mixture of α- and β-chloro isomers **4a** and that only the major, α-chloro isomer suffered rearrangement in refluxing methanol to provide a rapidly equilibrating mixture of imidates **7a** and **8a** in which **7a** dominated slightly; the β-chloro isomer was unreactive under these conditions. The weight of the evidence in these studies suggested that α-**4a**

Scheme 1



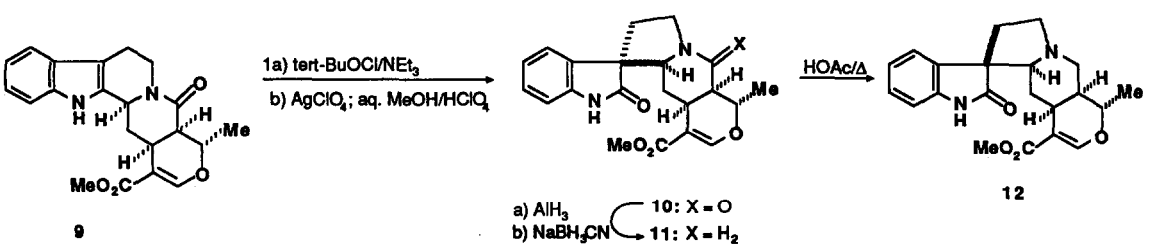
Series a: X = H_2; R^1, R^2 = alkyl
b: X = O; R^1, R^2 = alkyl

underwent preferential addition of methanol from the α-face to give an intermediate adduct that suffered stereoselective 1,2-reorganization to give **7a**, which subsequently equilibrated to a mixture of **7a** and **8a**.

Although the oxidative transformation of carbolines of general structure **3a** into products **5a** - **8a** is well documented, few examples exist for the related conversion of carbolines such as **3b** in which N_b is part of an amide function into spiro indole products. For example, forcing conditions are required to induce rearrangement of chloroindolenines related to **4b** in which N_b is incorporated in a D-ring lactam, and low yields of the desired 2-oxindoles **5b** and **6b** were obtained in these cases owing to deleterious side reactions.[7] Other *N*-acylated substrates behaved similarly.[8] When we first attempted to apply these methods to effect the conversions of heteroyohimboid and corynantheoid derivatives containing D-ring lactams into the corresponding 2-oxindoles, we were thus not surprised to discover that pathways of decomposition or oxidation at C(3) dominated. It was necessary to develop a new procedure for inducing this process for oxidation/rearrangement in more highly functionalised environments.

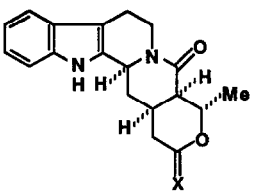
Toward this end, we reasoned that silver salts[6] might facilitate the rearrangement of chloroindolenines of general type **4b**. In order to test this hypothesis, the intermediate chloroindolenine that formed upon reaction of **9**[3] with *tert*-butylhypochlorite in the presence of triethylamine was treated with silver perchlorate in methanolic perchloric acid at room temperature to deliver the 2-oxindole **10**[9,10] in 87% yield (Scheme 2). Not only was the yield for this reaction excellent, but it proceeded with a high degree of stereoselectivity. There was no evidence of epimerization at C(3), and less than 5% of the other spiro isomer epimeric at C(7) was detectable by ^{1}H NMR and HPLC analysis of the crude reaction mixture. Thus, in contradistinction to analogous 2-oxindoles wherein N_b is basic, the lactam

Scheme 2

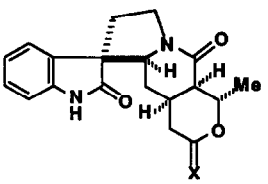


nitrogen N_b in **10** apparently does not participate in a retro-Mannich process to allow equilibration at C(3) and/or C(7). Indeed, several preliminary attempts to induce acid-catalyzed equilibration of **10** were unsuccessful. The stereochemistry at C(7) of **10**, which was initially assigned on the basis of ^{1}H n.O.e. experiments, was unequivocally established by an X-ray crystal analysis.[11] Selective hydride reduction [(a) AlH_3; THF; -50 °C; 1 h. (b) $NaBH_3CN$; MeOH/HOAc; RT; 1 h (83%)] of the lactam function in **10** was readily achieved in one pot to furnish isopteropodine (**11**),[12,13] which underwent acid-catalyzed equilibration at C(7) to furnish a mixture (3:1) of pteropodine (**12**) and isopteropodine (**11**). The **11** and **12** thus obtained were identical with authentic samples.[13]

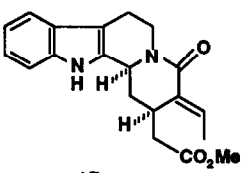
Since the conditions required for the stereoselective conversion of **9** into **10** were both mild and highly efficient, we engaged in a brief study to probe the scope and limitations of the method. Thus, the heteroyohimboid derivatives **13** and **14** and the corynantheoid analogues **17** and **19** were converted into the corresponding 3-chloroindolenines (*tert*-BuOCl; Et_3N; CH_2Cl_2; 0 °C; 30 min) that then underwent facile silver ion-induced rearrangement ($AgClO_4$; aq. MeOH; $HClO_4$; RT; 18 h) to give **15** (86%), **16** (96%), **18** (67%), and **20** (44%), respectively. In the case of 21-oxogeissoschizine (**19**), there are two reactive sites for attack by electrophilic chlorine, and the chloroacetal **20** was the major product although other unidentified substances were also obtained.



13: X = O
14: X = H, OMe



15: X = O
16: X = H, OMe



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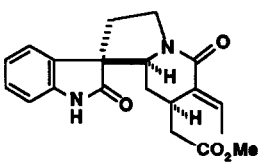

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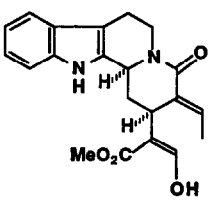

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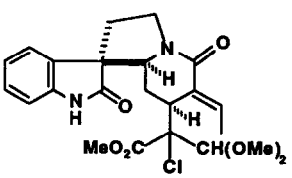

20

In conclusion, we have developed a mild, efficient, and highly stereoselective procedure to effect the conversion of indoles in which N_b is incorporated into a D ring lactam to the corresponding 2-oxindoles. Extensions of this methodology to the synthesis of other indole alkaloids are the subjects of active investigations in our laboratory, the results of which will be reported in due course.

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8. See: (a) Hollinshead, S. P.; Grubisha, D. S.; Bennett, D. W.; Cook, J. M. *Heterocycles* **1989**, *29*, 529. (b) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327.
9. All yields refer to products isolated by column chromatography and judged to be >95% pure. The compounds are assigned structures that are consistent with their spectral properties (IR, ^{1}H NMR, ^{13}C NMR, high resolution mass spectra and/or elemental analysis).
10. Spectral details for **10**: m.p. 246.5-247 °C (dec.); IR ν 3400, 3180, 3040, 2960, 2940, 1710, 1630, 1470, 1440, 1220 cm^{-1}; ^{1}H NMR (d-5 pyridine, 500 MHz) δ 12.07 (s, 1 H), 7.59 (s, 1 H), 7.33 (dt, *J* = 1.2, 7.7 Hz, 1 H), 7.14 (d, *J* = 7.7 Hz, 1 H), 7.09 (dt, *J* = 0.8, 7.6 Hz, 1 H), 7.02 (d, *J* = 7.1 Hz, 1 H), 4.18 (dd, *J* = 11.4, 4.4 Hz, 1 H), 4.08 (ddd, *J* = 12.5, 9.4, 9.1 Hz, 1 H), 3.91 (dq, *J* = 10.3, 6.2 Hz, 1 H), 3.83 (distorted t, *J* = 10.6 Hz, 1 H), 3.55 (s, 3 H), 3.04 (ddd, *J* = 12.5, 4.7, 3.11 Hz, 1 H), 2.60 (m, 1 H), 2.52 (dd, *J* = 10.2, 5.0 Hz, 1 H), 2.19 (dt, *J* = 13.0, 3.3 Hz, 1 H), 1.97 (ddd, *J* = 12.6, 8.4, 1.9 Hz, 1 H), 1.73 (d, *J* = 6.2 Hz, 3 H), 0.96 (dt, *J* = 12.6, 11.8 Hz, 1 H); ^{13}C NMR (75 MHz) δ 177.6, 167.0, 167.0, 155.4, 140.8, 130.0, 128.8, 122.8 (2 carbons), 110.8, 107.4, 71.7, 64.2, 57.0, 51.2, 44.3, 44.1, 32.5, 29.4, 27.4, 27.6, 19.8; mass spectrum, *m/z* 382.15139 ($C_{21}H_{22}N_2O_5$ requires 382.15287), 350.12630 ($C_{20}H_{18}N_2O_4$ requires 350.12666), 382, 350 (base), 324, 281, 205, 159 , 146, 130. Anal. Calcd. for $C_{21}H_{22}N_2O_5$. 0.5 H_2O: C, 64.44; H, 5.88; N, 7.16: Found: C, 64.83; H 5.58; N 7.23.
11. Lynch, V. M.; Mortimore, M.; Martin, S. F.; Davis, B. E. *Acta Cryst.* submitted for publication.
12. For previous syntheses of **11**, see: (a) Chan, K. C. *Phytochem.* **1969**, *8*, 219. (b) Borges del Castillo, J.; Manresa Ferrero, M. T.; Martin Ramon, J. L.; Rodriguez Luis, F.; Vazquez Bueno, P. *Anales de Quim.* **1980**, *76*, 295.
13. We thank Prof. M. Alam (University of Houston) for a generous sample of natural isopteropodine.

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