Total Synthesis of Spirobenzylisoquinoline Alkaloids. Part III. (±)-Ochrobirine[1]

STEWART MCLEAN AND JOHN WHELAN
Department of Chemistry, University of Toronto, Toronto, Ontario
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The route to spirobenzylisoquinoline alkaloids through a Pictet–Spengler cyclization of a suitable 1,2-indanedione has been modified, by the introduction of a 3-bromo substituent into the indanedione, with a view to providing a general synthesis of spirobenzylisoquinoline alkaloids bearing two oxygen functions on ring C. A highly stereoselective synthesis of (±)-ochrobirine has been achieved.

L'accès aux alcaloïdes du type spirobenzylisoquinoléine par une cyclisation selon Pictet–Spengler d'une indane dione-1,2 adéquate, a été modifié par l'introduction d'un substituant bromo-3 sur l'indanedione en vue d'obtenir une synthèse générale d'alcaloïdes spirobenzylisoquinoléine porteurs de deux fonctions oxygénées sur le cycle C. Une synthèse hautement stéréosélective de l'ochrobirine (±) a été réalisée.
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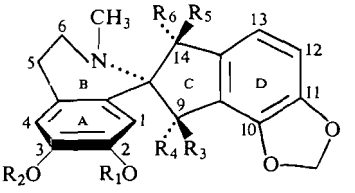
The term spirobenzylisoquinoline alkaloids has been applied to a group of alkaloids isolated from certain *Corydalis* and *Fumaria* species and having the skeleton shown in **1**. This structural class has been recognized for a relatively short time, and all members of it known at present can be described by structure **1** in which variations of substitution occur only in rings A and C (1). In ochotensimine (**1***a*) and ochotensine (**1***b*), the first members of this class to be recognized (2), ring C carries a single substituent, a methylene group at C-14; alkaloids with oxygen functions (at carbonyl or carbinol oxidation levels) at one or both of positions 9 and 14 have been described more recently. We reported in 1968 (3) the first total synthesis of a member of this class, (±)-ochotensimine, and since then the descriptions of several syntheses of this alkaloid, ochotensine, and some of the alkaloids with oxygen functions in ring C have appeared.

The synthetic plan of the majority of the successful syntheses of these alkaloids has been related to the one we used to synthesize ochotensimine: the condensation of an indanedione (such as **2**) with a phenylethylamine (such as **3**), each suitably substituted, followed by manipulation of the functionality of the intermediate to provide the target molecule. Ochrobirine (**1***c*) (4), for example, has been synthesized from the methylenedioxyindanetrione (**2** with C═O in place of C—X) and subsequent reduction of the dione intermediate (**4** with C═O in place of C—X) (5, 6); **1***c* is also an example of a spirobenzylisoquinoline alkaloid that has been synthesized by a different route proceeding, nevertheless, through the same dione intermediate (7). We recognized that our original synthetic plan could be developed into a general synthesis of those spirobenzylisoquinoline alkaloids with two oxygen functions on ring C if a suitable functional group could be introduced into position 3 of the indanedione precursor (**2**). In principle at least, this group (X), which could subsequently be converted into an oxygen function distinguishable from the aromatic ketone already present, would allow control to be maintained throughout the synthesis of both functionality and stereochemistry at the sites destined to be C-9 and -14 in the final product, and provide controlled routes to any of the target alkaloids.

We have found that the substituent X most suitable for this purpose is bromine and we have converted the methylenedioxyindanedione **2***a*, already available to us from our earlier work (3), to its monobromo derivative **2***b*. A Pictet–Spengler reaction of **2***b* with the dihydroxyphenylethylamine **3**, produced the spiro compound **4***a* which appears to be a single epimer and, although its stereochemistry is not proven at this stage, its subsequent fate can most readily be explained if it is the epimer shown in **5**.

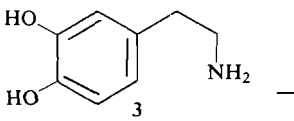
The phenolic hydroxyl groups were protected by conversion to a mixed carbonate and the

[1]Taken from the Ph.D. Thesis of John Whelan, University of Toronto. References 3*a* and *b* constitute Parts I and II, respectively.

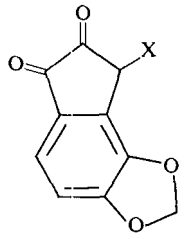


1

	R_1	R_2	R_3	R_4	R_5	R_6
a Ochotensimine	CH_3	CH_3	H	H	$=CH_2$	
b Ochotensine	CH_3	H	H	H	$=CH_2$	
c Ochrobirine	$-CH_2-$		H	OH	OH	H

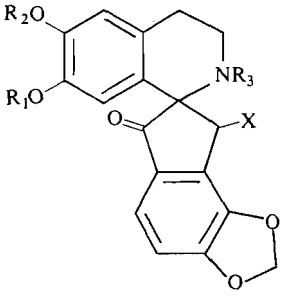


3



2

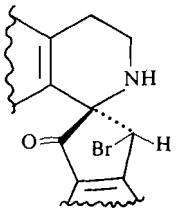
a X = H
b X = Br



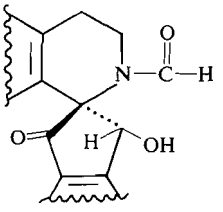
4

a $R_1 = R_2 = H; R_3 = H; X = Br$
b $R_1 = R_2 = CH_3OCO; R_3 = CHO; X = Br$
c $R_1 = R_2 = CH_3OCO; R_3 = CHO; X = OH$
d $R_1 + R_2 = CH_2; R_3 = CHO; X = OH$

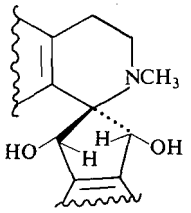
nitrogen was then formylated with acetic–formic anhydride. The product **4***b* was treated with aqueous acetic acid containing silver acetate in order to replace the bromine with a hydroxyl group and form **4***c*. This reaction appears to have taken place with net inversion at the reaction site and produced the alcohol **4***c* with the same configuration at C-9 as ochrobirine (as illustrated in **6**). The alcohol **4***c* was protected as its tetrahydropyranyl ether and the protecting groups were removed from the catechol system, which was then methylenated to provide an intermediate possessing the methylenedioxybenzene moiety found in ochrobirine (**1***c*) and several other spirobenzylisoquinoline alkaloids.



5

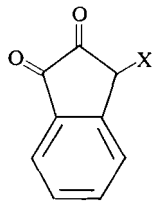


6



7

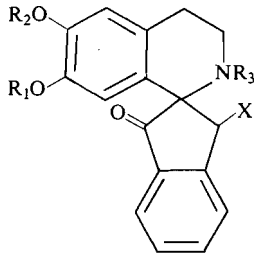
The alcohol function was regenerated by hydrolysis of the tetrahydropyranyl ether, the ketonic and amide carbonyl functions were reduced with lithium aluminum hydride, and (±)-ochrobirine (**1***c*) (the stereochemistry is illustrated by **7**) was isolated. This material formed crystals, m.p. 237–241°, identical in spectroscopic and t.l.c. characteristics with the authentic alkaloid; comment has been made previously (6, 7) on the variation in the values reported for the melting point of ochrobirine,



8

a X = H

b X = Br



9

a $R_1 = R_2 = H; R_3 = H; X = Br$

b $R_1 = R_2 = CH_3OCO; R_3 = CHO; X = Br$

c $R_1 = R_2 = CH_3OCO; R_3 = CHO; X = OH$

d $R_1 + R_2 = CH_2; R_3 = CHO; X = OH$

and our value is in accord with that reported by Manske and coworkers (6).

This route was explored first starting with the unsubstituted parent 1,2-indanedione (**8***a*) because of its greater accessibility, and the details of the reactions in the exploratory model series and in the main series (leading to alkaloids) can conveniently be discussed together. The reaction sequence produced a series of highly functionalized intermediates, most of which were fairly unstable and resisted isolation and purification by standard procedures; none was obtained crystalline. It was, therefore, generally necessary to carry forward to the next step material in as pure a condition as could be obtained in the circumstances; in each case a reference sample was purified until it appeared to be homogeneous by t.l.c. (or a mixture of epimers in the case of tetrahydropyranyl ethers), and characterized by spectroscopic methods. Our description of the details of the reaction steps, including their stereochemical features, is based on these data, a reasonable expectation for the predictability of recognized processes, and the successful outcome of the synthetic sequence, which has led to an alkaloid of established structure and stereochemistry (4); consequently, this synthesis of **1***c* does not serve in the usual sense to confirm the structure and stereochemistry assigned to the alkaloid, instead the assignments made to the alkaloid show the most probable course, particularly with respect to stereochemistry, followed by the synthesis.

Monobromination of the indanedione **8***a* under controlled conditions provided an excellent yield of **8***b*; care was required to prevent dibromination and other unwanted reactions from occurring, and the methylenedioxy derivative (**2***a*) appeared to be even more sensitive to the reaction conditions, but essentially quantitative conversion could be achieved under the correct conditions. The Pictet–Spengler reaction of **8***b* with the hydrochloride of dihydroxyphenylethylamine **3** provided the spiro compound **9***a* in good yield (50%); in the main series the yield of **4***a* was even better (>70%). In both series the appearance in the n.m.r. spectrum of a single peak in the range characteristic of the proton at the C-Br position pointed to the production of a single epimer at C-9. The bromo ketones were readily degraded by base, but the bromine resisted displacement under a wide range of conditions that used external nucleophiles that were not strong bases. Attempts to introduce an oxygen function directly at an earlier stage by acetoxylation of **8***a* did not lead to the desired isomer. We turned, therefore, to an approach which would introduce a substituent capable of providing intramolecular assistance in the displacement of the bromine. To this end the *N*-formyl derivative **9***b* was prepared by the action of acetic–formic anhydride on the derivative of **9***a* in which the phenolic hydroxyl groups had been protected as mixed carbonates; these conversions were carried out in excellent yields both in the model series and in the main series where **4***b* was obtained. Treatment of **9***b* with silver acetate in hot aqueous acetic acid now led to a clean replacement of the bromine by a hydroxyl group. It seems probable, therefore, that the *N*-formyl group has served, as intended, to provide intramolecular assistance in the displacement of the bromine (8), and this appears to be possible only when these groups have the *trans*-relationship depicted in **5**; furthermore, the solvolysis must then have taken place with net inversion of configuration at C-9 since parallel results were obtained (with a yield of 90% under slightly milder solvolysis conditions) in the main series and the product obtained (**4***c*) can be assigned the *cis*-configuration shown in **6** because it led ultimately, under conditions where no further stereochemical change at C-9 would be expected, to ochrobirine, which has been assigned this configuration at C-9 (4).

Careful basic hydrolysis of the carbonate **9***c* regenerated the catechol in ring A and this was methylenated by treatment with methylene iodide and base in dimethylformamide in the

presence of a copper catalyst (3, 9). An acceptable but not good yield of the desired methylenedioxybenzene derivative (**9***d*) was obtained, but several by-products were also isolated; in the main series the situation was even worse and the yield of desired product (15%) from **4***c* was considered to be unacceptably low. Since it appeared probable that the β-hydroxy ketone of ring C was largely responsible for the difficulty encountered in the methylenation reaction, in the main series the hydroxyl function was protected as its tetrahydropyranyl derivative prior to methylenation. The methylenation reaction was now highly successful and an excellent yield of the methylenedioxy compound was obtained. (Spectroscopic evidence indicated that the tetrahydropyranyl derivatives existed as pairs of epimers differing in configuration in the tetrahydropyran ring; this was of no consequence with respect to the development of the stereochemistry of the alkaloidal skeleton.) We have commented previously (3) on the desirability of carrying out the formation of a methylenedioxybenzene moiety early in a synthesis and before sensitive functional groups are present because of the vigorous conditions required to effect methylenation of a catechol; in the present synthesis, however, the activated phenolic character of **3** was required to obtain an acceptable yield of product in the Pictet–Spengler step, and the recent description of a relatively mild methylenation reaction (8) was of critical value to our synthetic plan.

In the model series, after the formyl group had been removed by hydrolysis, it was found that the presence of the hydroxyl group prevented successful completion of the Eschweiler–Clarke *N*-methylation reaction. Consequently, in the main series hydrolysis was carried out under conditions that removed only the tetrahydropyranyl group and formed **4***d* (the sequence from **4***c* was carried out with an over-all yield greater than 85%), and both the ketone and the amide carbonyl groups were reduced by addition of lithium aluminum hydride. (±)-Ochrobirine (**1***c*) uncontaminated by the epimeric diol was obtained (in 53% yield); the stereoselectivity of this reduction is most readily attributed, as has been proposed by others (5, 6), to internal delivery of hydride to the carbonyl group at C-14 from an aluminum hydride complex formed first at the C-9 hydroxyl group. Under the conditions we used some *N*-demethylochrobirine was also isolated, resulting from reductive removal of the *N*-formyl group by the lithium aluminum hydride; however, this yielded further (±)-ochrobirine (19% from **4***d*) on re-formylation and lithium aluminum hydride reduction.

Experimental

Melting points were determined on a Thomas-Kofler micro hot stage. Spectrometers used were a Perkin–Elmer 237B or 257 for i.r. spectra, a Unicam SP800 for u.v. spectra, a Varian T-60 for n.m.r. spectra, a CEC 21-490 for mass spectra, and an AEI MS-902 for accurate mass measurements. Unless otherwise indicated, chloroform solutions were used to obtain i.r. spectra and the wavelengths of significant absorptions are reported in μ, and chloroform-*d* solutions (with tetramethylsilane as internal standard) were used to obtain n.m.r. spectra and chemical shifts are reported on the τ scale followed in parentheses with an indication of the multiplicity of the signal (singlet, doublet, etc. are abbreviated to their initial letters) and the number of protons associated with it. Since the intermediates obtained were non-crystalline and generally unstable, they could not be characterized by microanalysis; some were too unstable to provide satisfactory mass spectra, the parent-molecule ion frequently being absent and ions indicative of thermal degradations being present, but the *m/e* values of the more abundant ions (followed in parentheses by an indication of their relative abundance) and the accurate mass measurements of certain significant ions are reported for key intermediates where these values could be obtained.

*The 3-Bromo-1,2-indanediones (**8***b*, **2***b*)

(a) Model Series

Pyridinium bromide perbromide (800 mg; 2.5 mmol) was added to a solution of 1,2-indanedione (3) (290 mg; 2.0 mmol) in 25 ml of glacial acetic acid and the mixture was heated on a steam bath with vigorous swirling. As soon as the red color faded (5–10 min), the reaction mixture was poured into 400 ml of ice-water and thoroughly extracted with methylene chloride. The extract, after it had been washed with water until neutral, afforded 3-bromo-1,2-indanedione (**8***b*) (390 mg; 1.7 mmol) as an unstable amber oil. Spectroscopic characteristics: i.r. 5.64, 5.77; n.m.r. 1.8–2.4 (complex; 4), 4.34 (s; 1); mass spectrum 226, 224 (equal intensity; mol. ions corresponding to $C_9H_5BrO_2$).

(b) Methylenedioxy Series

4,5-Methylenedioxy-1,2-indanedione (3) (190 mg; 1.0 mmol) was brominated with pyridinium bromide perbromide (400 mg; 1.25 mmol) under the same conditions, and the bromo derivative **2***b* (280 mg; 1.0 mmol) was obtained as an unstable amber oil. Spectroscopic characteristics: i.r. 5.65, 5.81; n.m.r. 2.65 (AB q, J = 8 Hz, int. chem. shift 33 Hz; 2), 3.67 (narrow m; 2), 4.46 (s; 1).

The Spiro Skeletons (Pictet–Spengler Cyclization)

(a) Model Series

A mixture of the bromo dione **8***b* (390 mg; 1.7 mmol) and β-(3,4-dihydroxphenyl)ethylamine hydrochloride (429 mg; 2.25 mmol) in 30 ml of absolute ethanol was heated at 68–70° with vigorous stirring under nitrogen

for 24.5 h. The reaction mixture was cooled, diluted with 250 ml of 3% hydrochloric acid, and extracted with methylene chloride. The aqueous solution was cooled to 0°, very carefully neutralized (to Fisher short range Alkacid ribbon) by the addition of solid sodium bicarbonate, and thoroughly extracted with methylene chloride. This extract afforded the bromospiroisoquinoline **9***a* (300 mg; 0.83 mmol) as a dark unstable oil. Spectroscopic characteristics: i.r. 2.75, 2.81, 3.05 (broad), 5.80; n.m.r. ($CDCl_3$–CH_3OD): 1.9–2.8 (complex; 4), 3.29 (s; 1), 3.95 (s; 1), 4.24 (s; 1) (remainder of the spectrum obscured by solvent).

Methyl chloroformate (*ca.* 2.4 mmol) was added dropwise to a stirred solution of **9***a* (300 mg; 0.83 mmol) in 25 ml of pyridine cooled to 0°. The reaction mixture was allowed to warm up to room temperature and stirring was continued for 20 h. Solvent was removed by vacuum distillation at room temperature, and the residue was taken up in methylene chloride, washed with water, and recovered in the usual manner as an amber oil (i.r. 5.65, 5.79).

This intermediate was redissolved in 10 ml of methylene chloride cooled to 0°, and 1 ml of acetic–formic anhydride was added dropwise to the stirred solution. The solution was allowed to warm up to room temperature and stirring was continued for 20 h. Solvent was removed at reduced pressure, the residue was dissolved in methylene chloride which, after it had been washed with water, afforded the formylated product **9***b* (382 mg; 0.76 mmol) as an amber oil. Spectroscopic characteristics: i.r. 5.63, 5.77, 5.96; n.m.r. 1.76 (s; 1), 1.9–2.6 (complex; 4), 2.78 (s; 1), 3.49 (s; 1), 4.38 (s; 1), 6.10 (s; 3), 6.20 (s; 3), 5.6–7.2 (complex; 4).

(b) Methylenedioxy Series

3-Bromo-4,5-methylenedioxy-1,2-indanedione (**2***b*) (280 mg; 1.0 mmol) and β-(3,4-dihydroxyphenyl)ethylamine hydrochloride (221 mg; 1.16 mmol) in 15 ml of absolute ethanol formed, under the conditions described above, the spiro compound **4***a* (286 mg; 0.71 mmol) which was isolated as an unstable yellow solid. (N.m.r. ($CDCl_3$–CH_3OD): 2.66 (AB q, J = 8 Hz, int. chem. shift 26 Hz; 2), 3.38 (s; 1), 3.76 (narrow m; 2), 4.00 (s; 1), 4.39 (s; 1) remainder of spectrum obscured by solvent.) This intermediate was immediately treated with methyl chloroformate and then acetic–formic anhydride under the conditions used in the model series, and the intermediate **4***b* (322 mg; 0.58 mmol) was isolated as an amber foam. Spectroscopic characteristics: i.r. 5.64, 5.79, 5.96; n.m.r. 1.78 (s; 1), 2.75 (AB q, J = 8 Hz, int. chem. shift 30 Hz), 2.81 (s; 1), 3.47 (s; 1), 3.85 (narrow m; 2), 4.43 (s; 1), 6.16 (s; 3), 6.22 (s; 3), 5.8–7.2 (complex; 4); mass spectrum 468(3), 364(10), 350(30), 349(100), 348(29), 334(13), 305(13), 293(15), 277(27), 276(28), 248(20), 220(14), 191(19), 190(20), 177(16), 164(17), 163(22), 123(14), 117(17); mass measurements 468.09020 (P-Br, $C_{23}H_{18}O_{10}N$, 468.09307), 349.05639 ($C_{16}H_{13}O_9$, 349.05596; $C_{19}H_{11}O_6N$, 349.05864).

Displacement of Bromine

(a) Model Series

Silver acetate (490 mg; 3.0 mmol) was added to a solution of the protected bromo spiro compound **9***b* (382 mg; 0.75 mmol) in 25 ml of 90% aqueous acetic acid, and the mixture was vigorously stirred at 100–105° under nitrogen with exclusion of light for 10 h. The reaction mixture was cooled, diluted with 400 ml of ice-water, and thoroughly extracted with methylene chloride. The extract, after it had been washed with water, afforded the hydroxy compound **9***c* (200 mg; 0.45 mmol) as an amber oil. Spectroscopic characteristics: i.r. 5.63, 5.77, 6.03; n.m.r. ($CDCl_3$–CH_3OD) 1.76 (s; 1), 2.0–2.6 (complex; 4), 2.80 (s; 1), 3.62 (s; 1), 4.80 (s; 1), 6.10 (s; 3), 6.21 (s; 3) (remainder of spectrum obscured by solvent).

(b) Methylenedioxy Series

The same reaction was carried out with **4***b* (254 mg; 0.59 mmol), carrying the methylenedioxy group in ring D, and the hydroxy compound **4***c* (210 mg; 0.53 mmol) was isolated as a brown solid after a reaction time of 8 h. Spectroscopic characteristics: i.r. 5.64, 5.79, 6.03; n.m.r. 1.78 (s; 1), 2.78 (AB q, J = 8 Hz, int. chem. shift 28 Hz; 2), 2.82 (s; 1), 3.55 (s; 1), 3.86 (narrow m; 2), 4.78 (broadened s, sharpened on addition of D_2O; 1), 6.12 (s; 3), 6.18 (s; 3), 5.8–7.4 (complex; 4); mass spectrum 467(37), 440(40), 439(57), 424(34), 412(36), 380(38), 366(34), 350(75), 349(91), 336(65), 334(74), 322(100), 321(62), 320(35), 293(46), 279(47), 277(72), 262(46), 249(32), 222(34), 221(36), 220(55), 219(40), 192(37), 191(47), 190(38), 178(38), 177(72), 165(47), 163(90), 151(35), 137(42); mass measurements 467.08433 (P-H_2O, $C_{23}H_{17}O_{10}N$, 467.08525), 349.05606 ($C_{16}H_{13}O_9$, 349.05596; $C_{19}H_{11}O_6N$, 349.05864), 322.07087 ($C_{18}H_{12}O_5N$, 322.07154).

Methylenation

The hydroxy compound **4***c* (146 mg; 0.30 mmol) in 5 ml of dry methylene chloride was refluxed with 0.04 ml of dihydropyran and a trace of *p*-toluenesulfonic acid for 1.5 h under nitrogen. The mixture of epimeric tetrahydropyranyl derivatives (182 mg), which showed two spots on t.l.c., was isolated in the usual manner, and then dissolved in 15 ml of methanol. A solution of sodium bicarbonate (100 mg; 1.2 mmol) in 10 ml of water was added over a period of 10 min to the stirred methanol solution, which was kept at room temperature and under nitrogen. After a further 4 h, the solution was diluted with 150 ml of water and extracted with methylene chloride. The phenolic material (128 mg) obtained from the extract was dissolved in 30 ml of dimethylformamide containing methylene iodide (50 mg; 1.8 mmol), potassium carbonate (300 mg; 2.3 mmol), and cupric oxide (200 mg). The reaction mixture was blanketed with nitrogen, stirred vigorously, and heated to 120–125° for 1.5 h. It was then cooled, diluted with 350 ml of ice-water, and thoroughly extracted with methylene chloride. The extract afforded a residue (129 mg), a mixture of epimeric tetrahydropyranyl derivatives, which was dissolved in 12 ml of 0.5 *N* hydrochloric acid; the reaction mixture was stirred at room temperature under nitrogen for 2.5 h, diluted with 200 ml of water and thoroughly extracted with methylene chloride. After it had been washed with water, the extract was evaporated and the methylenedioxy compound **4***d* (100 mg; 0.26 mmol) was obtained as an amber solid. Spectroscopic characteristics: i.r. 5.81, 6.05; n.m.r. 1.70 (s; 1), 2.74 (AB q, J = 8 Hz, int. chem. shift 29 Hz; 2), 3.34 (s; 1), 3.80 (s; 2), 3.95 (s; 1), 4.13 (narrow m; 2), 4.78 (broadened s, sharpened on addition of D_2O; 1), 5.6–7.5 (complex; 4).

(±)-Ochrobirine

Lithium aluminum hydride (0.35 mmol) as an 0.05 *M*

solution in ether was added dropwise to a stirred solution of the keto amide **4***d* (32 mg; 0.084 mmol) in 40 ml of dry tetrahydrofuran at 0° under nitrogen. Stirring was continued for a further 2.5 h while the reaction mixture was allowed to warm up to room temperature; solid lithium aluminum hydride (30 mg; 0.8 mmol) was then added and the solution was refluxed for 30 min. The solution was cooled to 0°, and excess lithium aluminum hydride was carefully decomposed by dropwise addition of cold 5% hydrochloric acid. The solution was diluted with 25 ml of water, made basic with solid sodium bicarbonate, and thoroughly extracted with methylene chloride. After it had been washed with water, the extract afforded a residue which was subjected to preparative layer chromatography on silica gel G with elution by 85:14:1 methylene chloride – methanol – concentrated ammonium hydroxide. This provided (±)-ochrobirine (16 mg; 0.044 mmol) and its *N*-demethyl analog (8 mg; 0.022 mmol). The latter was *N*-formylated under the conditions described above, and then reduced with lithium aluminum hydride (15 mg; 0.40 mmol) in refluxing tetrahydrofuran to provide a further supply of (±)-ochrobirine (6 mg; 0.016 mmol). The (±)-ochrobirine was recrystallized from acetone–hexane and obtained as cream-colored prisms, m.p. 237–241° (lit. 235 (6), 210–212 (7), 185–187° (5)). The t.l.c. behavior (three systems) and n.m.r., i.r., u.v., and mass spectra were identical to those of an authentic sample of the alkaloid and the spectroscopic values corresponded to those reported (5–7) for natural and synthetic materials.

We thank the National Research Council of Canada for financial support of this work; fellowship support to J. Whelan from his source and from Kodak Canada Ltd., is also gratefully acknowledged. Professor D. B. MacLean of McMaster University provided friendly encouragement and the reference samples and spectra.

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