# The Total Synthesis of (±) Ochrobirine

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The total synthesis of (±) ochrobirine is described.

La synthèse totale de la (±) ochrobirine est décrite.

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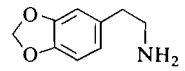
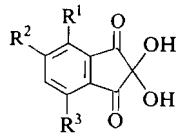
Ochrobirine was first isolated by Manske (1) in 1936 from *Corydalis sibirica* (L.) Pers. and has since been found in other species of Corydalis (2, 3). Recently (4), the spirobenzylisoquinoline structure **1** was assigned to the alkaloid almost entirely on the basis of its p.m.r. spectrum.

Since no rational degradations of ochrobirine could be found it was decided to attempt a synthesis of the alkaloid in order to confirm its structure. Many syntheses of spirobenzylisoquinoline alkaloids have been successfully achieved (5) by Pictet–Spengler condensation of suitable β-phenethylamines with various 1,2-indanediones. Consequently, it was decided to attempt the synthesis of ochrobirine by an extension of this method using 4,5-methylenedioxyindanetrione in a similar Pictet–Spengler condensation. Preliminary experiments, carried out in this laboratory, demonstrated that such a condensation between homopiperonylamine (**2**) and ninhydrin (**3**) produced a spirodione **4** in excellent yield (6) thus verifying the applicability of this route to ochrobirine. In the latter case the synthesis would entail the elaboration of the methylenedioxy ninhydrin **5**, a similar Pictet–Spengler condensation, *N*-methylation, and reduction of the resulting spirodione **6** to produce a mixture of diastereomers which should contain (±) ochrobirine.

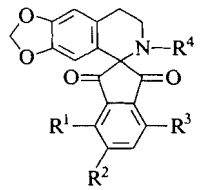
The synthesis of **5** thus becomes the major task of this undertaking and predictably enough, was tedious, time-consuming, and beset with poor yields. Two approaches were explored. The first, illustrated in Scheme 1, was based on the



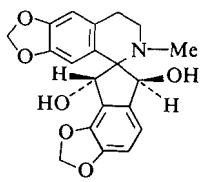
**2**



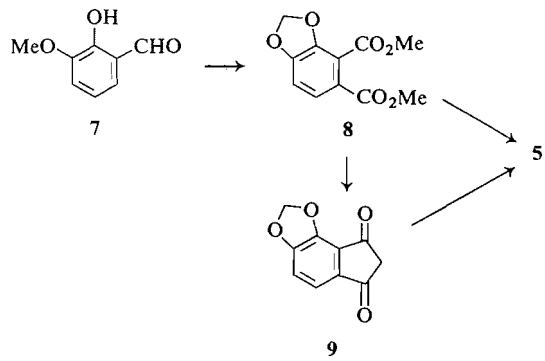
**3** $R^1 = R^2 = R^3 = H$
**5** $R^1 + R^2 = O{-}CH_2{-}O$; $R^3 = H$
**13** $R^1 + R^2 = OCH_2O$; $R^3 = Br$



**4** $R^1 = R^2 = R^3 = R^4 = H$
**6** $R^1 + R^2 = OCH_2O$; $R^3 = R^4 = H$
**16** $R^1 + R^2 = OCH_2O$; $R^3 = Br$, $R^4 = H$
**17** $R^1 + R^2 = OCH_2O$; $R^3 = Br$, $R^4 = CO_2Et$
**19** $R^1 + R^2 = OCH_2O$; $R^3 = H$, $R^4 = Me$



**1**




SCHEME 1

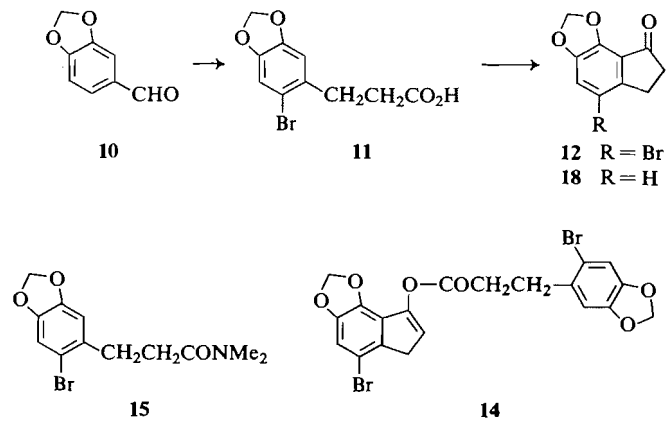
use of *o*-vanillin (7) as the starting material and on the demonstration that diethyl phthalate is readily converted into ninhydrin in high yield by condensation with dimethyl sulfoxide under basic catalysis (7). The dimethyl phthalate **8** was prepared by standard methods in an overall yield of 6% from *o*-vanillin. However, the condensation of **8** with dimethyl sulfoxide produced a red gum lacking methylenedioxy resonance in its p.m.r. spectrum but possessing a broad peak at $\delta$ 9.0 (exchangeable with $D_2O$) and providing a deep blue–black color with neutral ferric chloride. Use of irreversibly formed methylsulfinyl carbanion (8) gave similar results. An alternative method for effecting the required conversion of **8** to **5** was also investigated. This involved the sodium hydride condensation of **8** with ethyl acetate (9) to the 1,3-indanedione **9** which could be oxidized with selenium dioxide (10) to **5**. Again, a red gum was obtained in the ester condensation and only a very small amount of **9** could be isolated. It therefore appears that the methylenedioxy group is unstable under the strongly basic conditions, probably undergoing nucleophilic displacement in the course of the reaction.

An alternative starting material, piperonal (**10**), has the advantage of possessing the required methylenedioxy group, and the problem of the unsuitable meta situation of the aldehyde group could be overcome by modifying the synthetic target to the bromoindanetrione **13** so as to accommodate a blocking bromine atom. Piperonal was converted by standard procedures to the bromoacid **11** which was cyclized with phosphorus pentoxide (11) to the bromoindanone **12** (Scheme 2). This cyclization was found to be a most temperamental reaction and the yield at the best of times was only about 20%. Moreover the product was accompanied by a significant impurity, which could only be removed by several crystallizations or repeated chromatography. The nature of this impurity was investigated and it was shown to be the enol ester **14**. This structure was supported by the i.r. and p.m.r. spectra (see Experimental) and also by the fact that alkaline hydrolysis of it afforded **11** and **12**. A similar product has been identified in the PPE cyclization of a substituted phenylpropionic acid (20). In subsequent runs of this experiment the crude solid product was therefore saponified with aqueous methanolic potassium carbonate before isolation of the indanone. In this manner a purer product was obtained.

Several other methods of cyclization of this acid were also attempted. Concentrated sulfuric acid, fluorosulfonic acid, and hydrofluoric acid caused charring; the sulfur trioxide dimethylformamide complex (12) gave an excellent yield of the *N*,*N*-dimethylamide **15**, probably by amide exchange. The structure of **15** was evident from its i.r. and p.m.r. spectra and from the fact that it could be obtained by reaction between the acid chloride of **11** and dimethylamine. Attempts were made to cyclize the acid chloride. It was treated with aluminum chloride at temperatures ranging from $-15$ to $+20°$ but only traces of the desired indanone were obtained. Results were similar with stannic chloride as the catalyst.

Nonetheless, the indanone **12** was available and now had to be converted to the indanetrione **13** and here there was a choice of two methods. The first which was Ruhemann's classical synthesis of ninhydrin (13) was known to give a poor yield. The second method (14), more recent, consisted of oxidation of 1-indanone with selenium dioxide directly to ninhydrin in 79% yield, but in our case it furnished the trione **13** in only 15% yield.

The Pictet–Spengler reaction of **13** with homopiperonylamine (**2**) was now carried out to afford the spirodione **16**. It was decided to *N*-methylate this compound via the urethane **17** in view of a recent report (15) that stereospecific reduction of a carbonyl group in a closely related




SCHEME 2

*spiro* compound was achieved in a like manner. The urethane thus obtained from the reaction of **16** with ethylchloroformate was then reduced with lithium aluminum hydride to a product which was a mixture of two compounds, presumably diastereomers, of which the preponderant component was identical with natural ochrobirine (i.r., p.m.r., and t.l.c.). The hydrogenolysis of the bromide was not entirely unexpected (18) and could be regarded as a nucleophilic substitution favored by the presence of the ortho carbonyl group. Alternatively, if this carbonyl group was reduced initially, an intramolecular hydride transfer via a cyclic alkoxide intermediate may be envisaged by analogy with the earlier work (18).

A short while after the completion of this synthesis a communication claiming the total synthesis of (±) ochrobirine by a similar route appeared (16). The sodium borohydride reduction of the dione **6**, contrary to previous reports with similar systems (*5b*, *5c*, 6) and to our own experience with **17**, was claimed to take place stereospecifically to give (±) ochrobirine exclusively. Furthermore, the melting point of the product as reported was 23° lower than that of our synthetic compound. This synthesis was therefore repeated in our laboratory starting from the bromoindanone **12** which was catalytically hydrogenated (palladium–charcoal) to **18**, oxidized with selenium dioxide to **5**, and condensed with homopiperonylamine to give **6**, which was *N*-methylated with formic acid and formalin to the *N*-methyl dione **19**. Reduction of this compound by sodium borohydride in methanol yielded a mixture of two compounds of very similar $R_f$ (t.l.c.) which were separable by preparative thick-layer chromatography. The preponderant product was (±) ochrobirine identical with our previous synthetic sample. An independent synthesis of (±) ochrobirine (17) via a Pomeranz–Fritsch cyclization involved, in its penultimate stages, intermediates **6** and **19** which were identical with ours. A mixture similar to ours resulted in the final borohydride reduction of **19**.

TABLE 1. Melting points recorded for ochrobirine and some synthetic intermediates

| Compound | Melting point (°C) | | |
|---|---|---|---|
| | Present synthesis | Reference 16 | Reference 17 |
| **5** | 222 | 208–210 | — |
| **6** | 198–200 | 167–171 | 198–199 |
| **19** | 194–196 | 118–122 | 195–196 |
| **1** | 210 | 185–187 | 210–212 |

Furthermore, there were surprising discrepancies in the reported melting points of these intermediates (Table 1).

We have also observed that the melting point of synthetic (±) ochrobirine increased on standing to about 225° after *ca.* 4 months. In later preparations, the product obtained melted at 235°. As all these products were structurally identical (i.r. in chloroform solution, t.l.c.) the differences in melting point can only be attributed to the existence of two crystalline modifications of (±) ochrobirine.

## Experimental

Melting points were determined using a Fisher Meltemp unit and are uncorrected. The p.m.r. spectra, unless otherwise specified, were recorded using the frequency sweep mode of a Varian HA-100 spectrometer. Spectra at 60 MHz were recorded on a Varian T-60 instrument. Samples were dissolved in $CDCl_3$, unless otherwise specified, using TMS as the internal locking signal. Chemical shifts were measured relative to TMS. The i.r. spectra were recorded on a Perkin–Elmer 457 spectrometer and a Coleman–Hitachi EPS-3T spectrophotometer was used for the u.v. spectra.

*Dimethyl-3,4-methylenedioxyphthalate (**8**)*

3,4-Methylenedioxyphthalic acid (**19**) (0.7 g) in methanol (25 ml) was treated with excess ethereal diazomethane and the mixture allowed to stand overnight. The brownish gum obtained after removal of the solvents was purified by column chromatography (alumina, Brockman Activity I, 80–200 mesh) in methylene chloride. The colorless thick oil crystallized upon standing and was washed with ligroin (40–60°) (0.6 g) and the solid recrystallized from methylene chloride – ligroin m.p. 57–59°.

The i.r. spectrum: $\nu_{max}$ ($CHCl_3$) 1720 $cm^{-1}$. The 60 MHz p.m.r. spectrum ($\delta$): 3.83 (3H, s); 3.87 (3H, s); 6.40 (2H, s); 6.83 (1H, d); 7.47 (1H, d) ($J_{AB}$ = 8 Hz).

Anal. Calcd. for $C_{11}H_{10}O_6$: C, 55.47; H, 4.23. Found: C, 55.70; H, 4.26.

*3,4-Methylenedioxyindan-1,3-dione (**9**)*

A solution of **8** (0.5 g) in dry ethyl acetate (1 ml) was added to sodium hydride (0.148 g, 50% dispersion in mineral oil) contained in 5 ml round-bottomed flask fitted with a condenser and calcium chloride guard tube. The mixture was refluxed on a steam bath for 4 h, after which the dark red gum was washed with ether and filtered. It was treated with 3 *N* hydrochloric acid (8 ml) and heated on a water bath at 80–85° for 1 h. The mixture was extracted with methylene chloride, washed, and dried ($MgSO_4$). After removal of the solvent the resulting red product was chromatographed (silica gel) in ethyl acetate, and a small amount of **9** obtained and recrystallized from benzene, m.p. 198–200°.

The i.r. spectrum: $\nu_{max}$ ($CHCl_3$) 1710 and 1740 $cm^{-1}$. The 60 MHz p.m.r. spectrum ($\delta$): 3.23 (2H, s); 6.31 (2H, s); 7.27 (1H, d); 7.57 (1H, d); ($J_{AB}$ = 8 Hz).

*4-Bromo-6,7-methylenedioxyindan-1-one, (**12**) and 1-(4′,5′-Methylenedioxy-2′-bromo)hydrocinnamoyloxy-4-bromo-6,7-methylenedioxyindene (**14**)*

Compound **12** was prepared by the method of Haworth *et al.* (11). The crude solid obtained consisted of two compounds (t.l.c. silica, benzene–acetone 4:1). The faster moving component **14** was separated from the slower **12** by column chromatography using the same system and crystallized from methanol m.p. 163°.

The i.r. spectrum of **14**: $\nu_{max}$ ($CHCl_3$) 1762 $cm^{-1}$. The 60 Hz p.m.r. spectrum ($\delta$): 3.00 (4H, m); 3.33 (2H, d); 6.27 (1H, t) ($J_{AX}$ = 2 Hz); 6.00 (2H, s); 6.03 (2H, s); 6.90 (1H, s); 6.93 (1H, s); 7.07 (1H, s).

Anal. Calcd. for $C_{20}H_{14}Br_2O_6$: C, 47.16; H, 2.77. Found: C, 47.65; H, 2.85.

*Hydrolysis of **14***

Compound **14** (200 mg), potassium carbonate (100 mg), methanol (15 ml), and water (2 ml) were heated on a steam bath for 2 h. The mixture was diluted with water and extracted with ether. The ethereal extract was washed with water and dried ($Na_2SO_4$) to leave a residue which was crystallized from benzene (80 mg). The product was identical with **12** (p.m.r., i.r., and m.p.).

The aqueous extract on acidifying with concentrated HCl deposited a precipitate which was dissolved in ether, dried ($Na_2SO_4$), and evaporated to dryness to leave a residue which crystallized from chloroform (94 mg). This product was identical with 6-bromo-3,4-methylenedioxy hydrocinnamic acid (p.m.r., i.r., and m.p.).

*N,N-Dimethyl-3,4-methylenedioxy-6-bromohydrocinnamamide (**15**)*

3,4-Methylenedioxy-6-bromohydrocinnamic acid (1 g) was heated with sulfur trioxide – dimethylformamide complex (12) (20 ml) at 160° for 30 min. The solution was poured into crushed ice and the white precipitate which separated extracted with chloroform. The chloroform extract was washed (10% aqueous sodium carbonate), dried ($MgSO_4$), evaporated to dryness, and the residue crystallized from benzene (780 mg), m.p. 77°.

The u.v. spectrum: $\lambda_{max}$ (MeOH) 238 and 294 nm (log $\varepsilon$ 3.63 and 3.63). The i.r. spectrum: $\nu_{max}$ ($CHCl_3$) 1630 $cm^{-1}$. The 60 MHz p.m.r. spectrum ($\delta$): 7.0 (1H, s); 6.8 (1H, s); 5.97 (2H, s); 2.97 (6H, s); 2.9–3.2 (2H, m).

Anal. Calcd. for $C_{12}H_{14}BrNO_3 \cdot \frac{1}{2}H_2O$: C, 46.60; H, 4.54; N, 4.54. Found: C, 46.43; H, 4.89; N, 4.53.

*4-Bromo-6,7-methylenedioxyindan-1,3-dione-2,2-diol (**13**)*

Compound **12** (5.3 g) was added to a solution of selenium dioxide (4.4 g) in peroxide free dioxane (60 ml) and water (0.5 ml). The mixture was heated at 95–100° for 6 h. The black precipitate of selenium was filtered. The red filtrate was concentrated under reduced pressure to half its volume. Water (50 ml) was added, and the solution was brought to boiling and filtered. The hot filtrate was decolorized (charcoal), and on cooling deposited pale yellow prisms (800 mg), recrystallized from water, m.p. 230–233°.

The u.v. spectrum: $\lambda_{max}$ (MeOH) 253, 315, and 358 nm (log $\varepsilon$ 4.37, 3.70, and 3.63). The i.r. spectrum: $\nu_{max}$ ($CHCl_3$) 1728, 1753 $cm^{-1}$. The p.m.r. spectrum (acetone-$d_6$, $\delta$): 6.37 (2H, s); 7.47 (1H, s).

Anal. Calcd. for $C_{10}H_5BrO_6 \cdot \frac{1}{2}H_2O$: C, 39.35; H, 1.97. Found: C, 39.43; H, 2.03.

*6,7-Methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2′-(4′bromo-6′,7′-methylenedioxy-1′,3′-indanedione) (**16**)*

A solution of homopiperonylamine (**2**) (200 mg), in absolute ethanol (5 ml) was placed in a 100 ml two-necked flask equipped with a magnetic stirrer, pressure-equalizing dropping funnel, and a calcium chloride guard tube. The flask was cooled in an ice bath and a solution of **13** (200 mg) in absolute ethanol (20 ml) was added dropwise over a period of 15 min. The solution was stirred for another 25 min. The solution on further cooling (Dry Ice – acetone) deposited a white precipitate which dissolved to an orange solution when dry hydrogen chloride was bubbled through the mixture (15 min). The temperature was now raised to 25° and the solution poured into crushed ice, basified with concentrated ammonia solution, and extracted with ether. The ether was removed to yield a yellow residue which crystallized from acetone–methanol (180 mg), m.p. 219–221°.

The u.v. spectrum: $\lambda_{max}$ (MeOH) 251, 304, 352 nm (log $\varepsilon$ 4.38, 3.86, 3.78). The i.r. spectrum: $\nu_{max}$ ($CHCl_3$) 1714 and 1743 $cm^{-1}$. The p.m.r. spectrum ($\delta$): 1.78 (1H, s exchangeable with $D_2O$); 2.78 (2H, t); 3.4 (2Ht) ($J_{AX} = 6$ Hz); 5.84 (2H, s); 6.02 (1H, s); 6.32 (2H, s); 6.62 (1H, s); 7.36 (1H, s).

Anal. Calcd. for $C_{19}H_{12}BrNO_6$: C, 53.04; H, 2.81; N, 3.25. Found: C, 52.48; H, 2.81; N, 3.21.

Mol. Wt. Calcd. for $C_{19}H_{12}{}^{79}BrNO_6$: 428.985. Found (h.r.m.s.): 428.987.

*2-Carbethoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2′-(4′-bromo-6′,7′-methylenedioxy-1′,3′-indanedione) (**17**)*

A solution of ethyl chloroformate (200 mg) in chloroform (10 ml) was added to a stirred suspension of **16** (150 mg) in 20% aqueous sodium carbonate solution (20 ml) maintained between 0 and 10°. The mixture was stirred for 1 h, the chloroform layer was separated and washed with 1 *M* hydrochloric acid, dried ($Na_2SO_4$), and the chloroform removed under reduced pressure. The residue was crystallized from methanol (120 mg), m.p. 225–226°.

The u.v. spectrum: $\lambda_{max}$ (MeOH) 251, 303, and 362 nm (log $\varepsilon$ 4.51, 3.93, 3.80). The i.r. spectrum: $\nu_{max}$ ($CHCl_3$) 1681, 1726, 1758 $cm^{-1}$. The p.m.r. spectrum ($\delta$): 1.26 (3H, t); 4.10 (2H, q) ($J_{AX} = 8$ Hz); 3.0 (2H, t); 3.90 (2H, t) ($J_{A'X'} = 5$ Hz); 5.88 (2H, s); 6.18 (1H, s); 6.30 (2H, d) (2′,3′-O—$CH_2$—O); 6.68 (1H, s); 7.36 (1H, s).

Anal. Calcd. for $C_{22}H_{16}BrNO_8$: C, 52.61; H, 3.21; N, 2.78. Found: C, 52.42; H, 3.26; N, 2.88.

The molecular formula was confirmed by h.r.m.s.

Mol. Wt. Calcd. for $C_{22}H_{16}{}^{79}BrNO_8$: 501.006. Found (h.r.m.s.): 500.999.

Mol. Wt. Calcd. for $C_{22}H_{16}{}^{81}BrNO_8$: 503.004. Found (h.r.m.s.): 503.002.

*(±) Ochrobirine (**1**)*

A solution of the urethane, **17** (200 mg) and lithium aluminum hydride (150 mg) in dry tetrahydrofuran (40 ml) was refluxed for 13 h. The excess reagent was decomposed with water and the mixture extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue on t.l.c. (silica gel) showed two spots of similar $R_f$, from which (±) ochrobirine the major component, was isolated by column chromatography (silica gel; benzene, acetone, methanol (65:15:20)) and crystallized from methanol (52 mg), m.p. 210°. In subsequent preparations the product melted at 235°.

All these samples had identical i.r., p.m.r. spectra with natural ochrobirine and on t.l.c. (silica gel) had similar $R_f$ values in the following solvent systems: benzene, acetone, methanol (65, 15, 20); benzene, ethyl acetate, methanol (30, 10, 10); benzene, ether, methanol (30, 10, 10).

*4,5-Methylenedioxyindan-1,3-dione-2,2-diol (**5**)*

6,7-Methylenedioxyindan-1-one (5*c*) (3.5 g) was added to a solution of selenium dioxide (4.4 g) in peroxide free dioxane (50 ml) and water (0.5 ml). The mixture was heated at 95–100° for 6 h. The black precipitate of selenium was filtered. The red filtrate was concentrated under reduced pressure to 20 ml, water (50 ml) was added, and the solution was brought to boiling and filtered. The hot filtrate was decolorized (charcoal), and on cooling deposited pale yellow prisms (850 mg), crystallized from water, m.p. 221–222°.

The u.v. spectrum: $\lambda_{max}$ (MeOH) 247, 295, and 347 nm (log $\varepsilon$ 4.48, 3.73, 3.64). The i.r. spectrum: $\nu_{max}$ ($CHCl_3$) 1710 and 1740 $cm^{-1}$. The 60 MHz p.m.r. spectrum in MeOH ($\delta$): 6.01 (2H, s); 7.07 (1H, d); 7.27 (1H, d) ($J_{AX} = 8$ Hz).

Anal. Calcd. for $C_{10}H_6O_6$: C, 54.05; H, 2.70. Found: C, 54.00; H, 2.97.

*6,7-Methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2′-(4′,5′-methylenedioxy-1′,3′-indanedione) (**6**)*

A solution of homopiperonylamine (**2**) (200 mg), in absolute ethanol (5 ml) was placed in a 100 ml, two-necked flask equipped with a magnetic stirrer, pressure-equalizing dropping funnel, and a calcium chloride guard tube. The flask was cooled in an ice bath and a solution of **5** (200 mg) in absolute ethanol (35 ml) was added dropwise over a period of 15 min and the solution stirred for another 45 min. The solution on cooling (Dry Ice – acetone) deposited a white precipitate which dissolved to an orange solution when dry hydrogen chloride was bubbled through the mixture (15 min). The temperature was raised to 40°, the solution was poured into crushed ice, basified with concentrated ammonia solution, and extracted with ether. The yellow residue obtained on removal of the ether crystallized from methanol–chloroform (230 mg), m.p. 199–201°.

The u.v. spectrum: $\lambda_{max}$ (MeOH) 245, 297, and 348 nm (log $\varepsilon$ 4.55, 3.97, and 3.80). The i.r. spectrum: $\nu_{max}$ ($CHCl_3$) 1711 and 1743 $cm^{-1}$. The p.m.r. spectrum ($\delta$): 1.95 (1H, s); 2.81 (2Ht); 3.42 (2Ht); ($J_{AX} = 6$ Hz); 5.83 (2H, s); 6.03 (1H, s); 6.31 (2H, s); 6.63 (1H, s); 7.27 (1H, d) 7.67 (1H, d) ($J_{AB} = 8$ Hz).

Anal. Calcd. for $C_{19}H_{13}NO_6$: C, 64.91; H, 3.70; N, 3.99. Found: C, 65.17; H, 3.91; N, 3.80.

*2-Methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2′-(4′,5′-methylenedioxy-1′,3′-indanedione) (**19**)*

A solution of the amine **6**, (100 mg), in 90% formic acid (1.5 ml) and 37% formaldehyde (1.5 ml) was heated on a steam bath for 6 h. The solution was poured into crushed ice and basified with concentrated ammonia solution. The mixture was extracted with ether, dried ($MgSO_4$), and evaporated to dryness. The yellow residue crystallized from methanol (60 mg), m.p. 194–196°.

The u.v. spectrum: $\lambda_{max}$ (MeOH) 245, 297, and 348 nm (log $\varepsilon$ 4.57, 3.96, and 3.80). The i.r. spectrum: $\nu_{max}$ ($CHCl_3$) 1710 and 1741 $cm^{-1}$. The p.m.r. spectrum ($\delta$): 2.39 (3H, s); 2.99 (2H, m); 3.31 (2H, m); 5.81 (2H, s); 5.96 (1H, s); 6.32 (2H, s); 6.63 (1H, s); 7.30 (1H, d); 7.64 (1H, d) ($J_{AB} = 8$ Hz).

Anal. Calcd. for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.11. Found: C, 65.81; H, 4.28.

*(+) Ochrobirine (**1**)*

Sodium borohydride (150 mg) was added to a solution of **19** (60 mg) in methanol (20 ml). The solution was stirred for 24 h. The solution was acidified with acetic acid and solvent was removed under reduced pressure. The residue was basified with concentrated ammonia solution and was extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated to dryness. The residue on t.l.c. (silica gel) showed two spots of similar $R_f$, from which (±) ochrobirine the major component, was isolated by preparative t.l.c. (silica gel; benzene, acetone, methanol (65:15:20)) and crystallized from methanol (31 mg), m.p. 235°.

The i.r. and p.m.r. spectra were identical with that of the natural ochrobirine and on t.l.c. (silica gel) had similar $R_f$ values in the same solvent systems as before.

We wish to thank Prof. D. B. MacLean for the high resolution mass spectra of **16** and **17**. Generous support from the National Research Council of Canada is gratefully acknowledged.

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