The Synthesis of (±)-Ochrobirine. A New Route to the Spirobenzylisoquinoline System[1]

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The spirobenzylisoquinoline system has been synthesized from substituted 2-phenyl-1,3-indandiones as starting materials. Ring B of the spiro system was constructed by a modified Pomeranz–Fritsch reaction. The reaction sequence has been applied to the synthesis of an analog of ochrobirine and then to (±)-ochrobirine itself.

Le système spirobenzylisoquinoline a été synthétisé à partir des phényl-2 indanediones-1,3 substituées en tant que produits de départ. Le cycle B du système spirannique a été construit selon une réaction modifiée de Pomeranz–Fritsch. La séquence réactionnelle a été appliquée à la synthèse d'un analogue de l'ochrobirine et de l'ochrobirine (±) elle-même. [Traduit par le journal]

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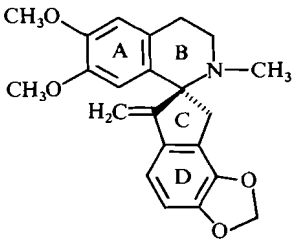
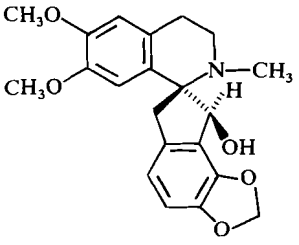
The spirobenzylisoquinoline alkaloids were first isolated some 30 years ago (1) but it was not until 1964 that a structure was assigned to ochotensimine, an alkaloid of this group (2–4). In the intervening years structures have been proposed for other related alkaloids (5–10) and the total synthesis of several of them has been realized. The alkaloids of this family vary in the nature of the substituents present on aromatic ring A and in the type and number of substituents on the spiro ring. The main structural variants are exemplified in ochotensimine, fumaricine, and ochrobirine shown below.

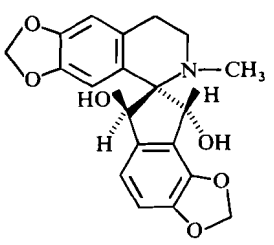
The synthesis of alkaloids related to ochotensimine and fumaricine has been realized by a route in which the key step is a Pictet–Spengler condensation of the appropriately substituted 1,2-indandione with an appropriately substituted phenylethylamine as shown in Scheme 1. The first synthesis of this type was reported by McLean *et al.* (11, 12) for ochotensimine. Several variants of this scheme have since been reported (13–17). By using ninhydrin instead of an indandione in the Pictet–Spengler condensation the groups of Manske and Ahmed (18) and Kametani *et al.* (19) synthesized model compounds in which two oxygens were incorporated into the spiro ring. Both groups have recently completed the total synthesis of (±)-ochrobirine by this method (20, 21). Other routes to the spiro system have been developed by Kametani *et al.* (22) and by Shamma *et al.* (23–25). In the former a phenylpyruvic acid is substituted for the indandione in the Pictet–Spengler reaction and the spiro ring completed by a cyclization of the acid function. In the latter a protoberberine system is rearranged to the spiro system. Here we report a new synthesis of the spirobenzylisoquinolines by a route different from those previously reported. We have used this method to synthesize (±)-ochrobirine. Our method utilizes the readily



Ochotensimine



Fumaricine



Ochrobirine

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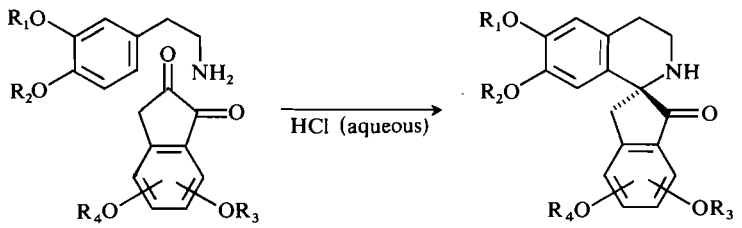


SCHEME 1

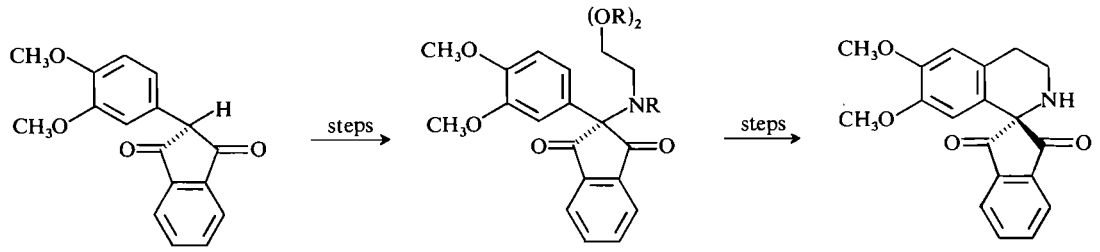
available 2-phenyl-1,3-indandiones as starting compounds and completes the synthesis of the spiro system by construction of ring **B** through a modified Pomeranz–Fritsch synthesis as shown in Scheme 2. The scheme was tested using 2-(3,4-dimethoxyphenyl)-1,3-indandione (**1**) before proceeding to the synthesis of (±)-ochrobirine.

2-Phenyl-1,3-indandiones are available by two routes. For example, 3-benzylidenephthalides, prepared by a Perkin condensation of a phthalic anhydride and a phenylacetic acid (26), rearrange in base to 1,3-indandiones (27). In another method, reported by Shapiro *et al.* (28, 29), benzylidenephthalide formation and rearrangement are carried out in the same reaction vessel by interacting a phthalide with an aromatic aldehyde in the presence of an alkoxide and an ester, used as a scavenger to remove the water liberated in benzylidenephthalide formation. Both methods, outlined in Scheme 3, gave high yields of the model compound, 2-(3,4-dimethoxyphenyl)-1,3-indandione (**1**).

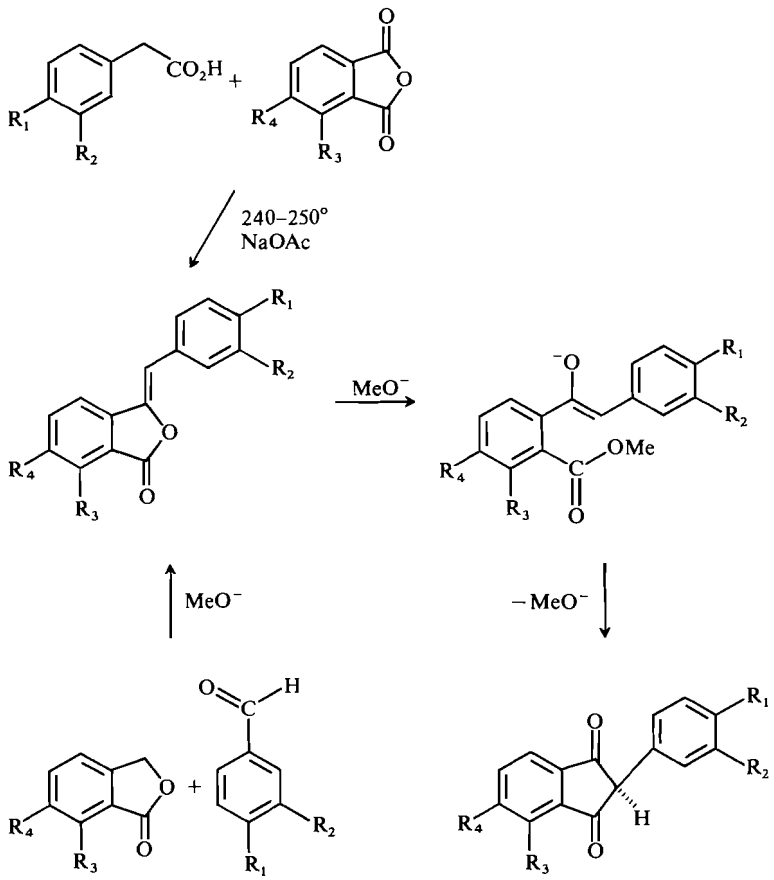
The introduction of the nitrogen and the two carbons required to complete the carbon framework was brought about by bromination followed by displacement of bromine by aminoacetaldehyde diethyl acetal. The bromination of 2-phenyl-1,3-indandiones has been studied previously (30) as has the displacement of the bromines with amines (31). Compound **1** brominated readily in glacial acetic acid to 2-bromo-2-(3,4-dimethoxyphenyl)-1,3-indandione (**2**), but the compound proved unstable to heat and light. Purification of **2** was not attempted, therefore, but it was used directly in the next step. The product, 2-(2,2-diethoxyethylamino)-2-(3,4-dimethoxyphenyl)-1,3-indandione (**3**), was obtained in 73% yield based on **1**. These and subsequent steps of the synthesis are outlined in Scheme 4.

Following the procedure of Bobbitt *et al.* (32, 33) the cyclization of **3** in 6 *M* aqueous ethanolic HCl was attempted. Instead of the expected spiroisoquinoline we obtained the dione, **1**, formed by cleavage of the C_2—N bond; glyoxal, as its bis-2,4-dinitrophenyl hydrazone was also isolated. The formation of these products and ammonia is rationalized in Scheme 5 where the driving force for the elimination is postulated to be the protonation at nitrogen. Accordingly, the nitrogen was acetylated and cyclization of the *N*-acetyl compound **4** attempted again. The reaction now proceeded normally to yield **5** (Scheme 4). Reduction of **5** to **6** was brought about with H_2 over Adams catalyst. Hydrolysis of the *N*-acetyl group yielded **7** which had previously been prepared by another route (34).

The identity of the two products was established by comparison of their melting points, their i.r. and their n.m.r. spectra. *N*-methylation of **7** to **8** by the Eschweiler–Clarke procedure proceeded in very low yield



SCHEME 2



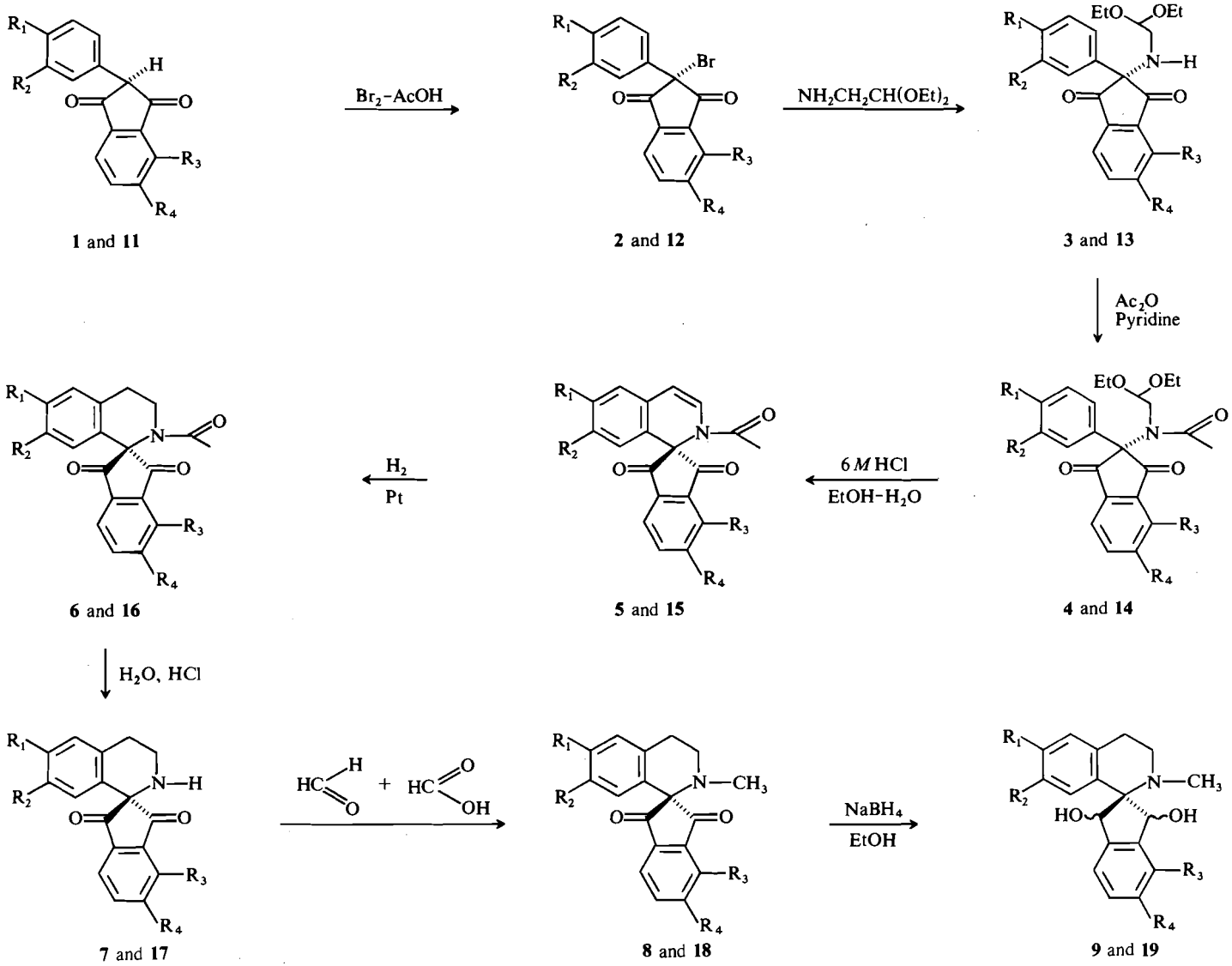
In the model synthesis: $R_1 = R_2 = OCH_3$; $R_3 = R_4 = H$.
In the ochrobirine synthesis: $R_1 + R_2 = R_3 + R_4 = OCH_2O$.

SCHEME 3

which was surprising since this reaction had already been applied successfully to similar systems (18, 34). However the reduction of **8** to the corresponding diol had already been reported (34) and we found that the diol was readily *N*-methylated with formaldehyde and sodium borohydride to **9**. The configuration of the diol was not established in this study. With the successful completion of the model synthesis attention was turned to the synthesis of (±)-ochrobirine.

The starting compounds required for the synthesis of ochrobirine are piperonal and 6,7-methylenedioxyphthalide in one case and 3,4-methylenedioxyphenylacetic acid and 3,4-methylenedioxyphthalic anhydride in the other depending upon the route chosen for the preparation of the substituted 2-phenyl-1,3-indandione. All compounds are available commercially or by procedures described in the literature but it is worthwhile to note that the preparation of the phthalic acid derivatives is lengthy and cumbersome and is a major shortcoming of this synthesis.

The preparation of the 2-phenyl-1,3-indandione in the model series proceeded in high yield by both methods but such was not the case when the methylenedioxy compounds were used. Yields of less than 10% were obtained in both routes. The starting materials were not recovered and the desired product was accompanied by polymeric material. The reasons for the failure in these condensations were not established. However, we found that, when the phenylacetic acid was treated with acetic anhydride, presumably to give an anhydride, prior



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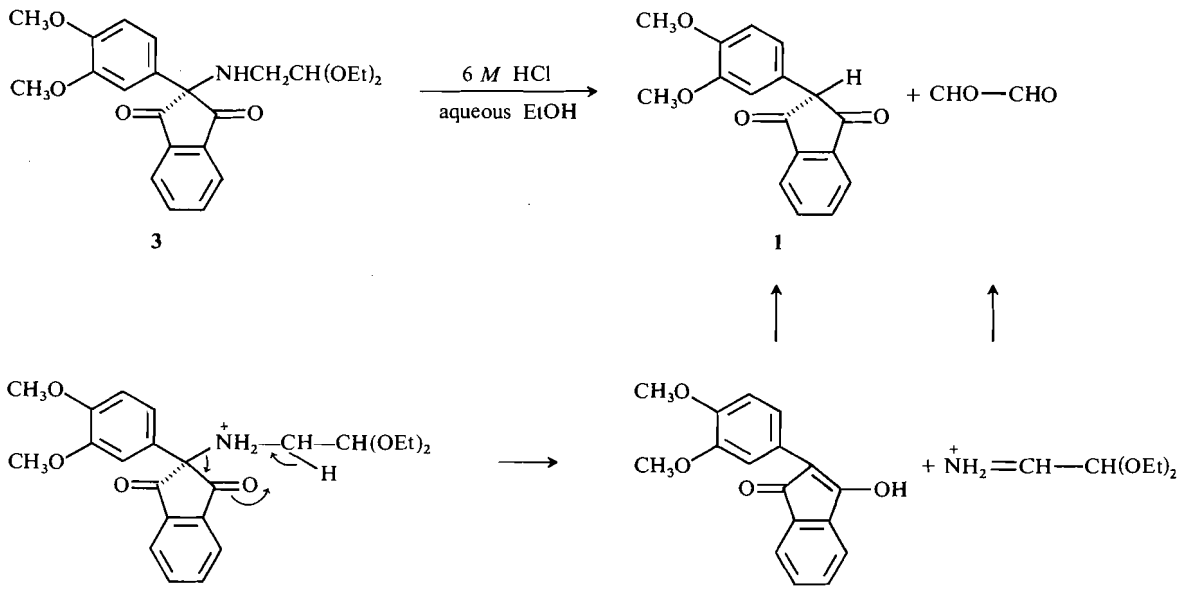
SCHEME 4



SCHEME 5

to addition of the phthalic anhydride and fused sodium acetate, a satisfactory yield (60–65%) of the benzylidenephthalide (**10**) was obtained. Rearrangement to the dione (**11**) proceeded in nearly quantitative yield. The remainder of the synthesis proceeded in a manner analogous to that in the model series (see Scheme 4) and in satisfactory yield. It was possible, however, to methylate the secondary amine (**17**) by the Eschweiler–Clarke method in satisfactory yield. Compounds **17** and **18** isolated by us have melting points identical with those found by Nalliah *et al.* (21) but considerably higher than those reported by Kametani *et al.* (20 *a*, *b*). Our (±)-ochrobirine melted at nearly the same temperature as that reported for the lower melting modification of Nalliah *et al.* (21). The spectral properties (i.r. and mass spectrum) of synthetic (±)-ochrobirine are identical with those of the natural base. The high degree of specificity found in the borohydride reduction of **18** to **19** was unexpected but has been observed by others (20, 21).

The absolute configuration of (±)-ochrobirine and other alkaloids of this family (35) has recently been established and conforms to that in the formulas.

Experimental

Apparatus, Methods, and Materials

Melting points were recorded on a Köfler micro hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann IR5 or a Perkin–Elmer 337 spectrophotometer in chloroform solution unless otherwise stated. The p.m.r. spectra were recorded on a Varian A60 or a T60 spectrophotometer in solution in $CDCl_3$ using tetramethylsilane as an internal standard. Chemical shifts are reported in p.p.m. (δ) from TMS. The symbols s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet are used in reporting spectra. Mass spectra were routinely run on all samples to check their molecular weights either on a Hitachi RMU 6A mass spectrometer or on a C.E.C. 21-110B double focusing instrument. High resolution mass spectrometry was used to confirm the composition of several compounds and mass measurements were made by procedures described elsewhere (34).

The microanalyses were performed by Gygli Microanalytical Laboratory, Toronto, Ontario.

3-(3,4-Dimethoxybenzylidene)-phthalide

A mixture of 3,4-dimethoxyphenylacetic acid (0.025 mol), phthalic anhydride (0.021 mol), and freshly fused sodium acetate (150 mg) was rapidly heated in an oil bath to 240–245° and the temperature maintained there until the reaction was complete (1–2 h). The reaction mixture was cooled, dissolved in the minimum amount of hot methanol, and the solution filtered. Upon cooling, yellow crystals of the phthalide were deposited melting at 133–134°; yield, 78%.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.35; H, 4.97. Found: C, 72.13; H, 4.98.

I.r.: ν_{max} 1775 cm^{-1}; p.m.r.: 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.24 (1H, s, benzylic H), and 6.74–6.90 (7H, m, aromatic H's).

*3-(3,4-Methylenedioxybenzylidene)-6,7-methylenedioxyphthalide (**10**)*

The method described above for the preparation of the 3-(3,4-dimethoxybenzylidene)-phthalide gave very low yields when applied to the preparation of the methylenedioxy compound. It was found, however, that the following procedure was satisfactory. A mixture of 3,4-methylenedioxyphenyl acetic acid (0.025 mol) and freshly distilled acetic anhydride (0.05 mol) was heated on a steam bath for 15 min. 3,4-Methylenedioxyphthalic anhydride (0.021 mol) and freshly fused sodium acetate (200 mg) were added and the mixture was heated rapidly to 170–180° until the distillation of acetic acid and other volatile components was complete (45–60 min). The solid was dissolved in hot methanol, the solution filtered and cooled. The bright yellow crystals which separated melted at 259–261°; yield, 60–62%. I.r.: ν_{max} 1772 cm^{-1}.

Anal. Calcd. for $C_{17}H_{10}O_6$: C, 65.80; H, 3.23. Found: C, 65.70; H, 3.33.

*2-(3,4-Dimethoxyphenyl)-1,3-indandione (**1**) from 3-(3,4-Dimethoxybenzylidene)-phthalide (Method A)*

The benzylidenephthalide (0.025 mol) in boiling absolute methanol (200 ml) was treated with a solution of sodium methoxide freshly prepared from sodium (750 mg) and absolute methanol (25 ml). The bright red solution so obtained was heated under reflux for 1 h, cooled, and the solvent removed under vacuum. The red residue was dissolved in water and extracted with ether. The aqueous layer was separated, acidified to p*H* 4 with 10% sulfuric acid and extracted several times with chloroform. The extract was washed several times with water, dried over anhydrous sodium sulfate and evaporated to dryness. The white solid residue was recrystallized from benzene and melted at 196–197°; yield, 92–95%.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.35; H, 4.97. Found: C, 72.51; H, 4.83.

I.r.: ν_{max} 1710, 1745 cm^{-1}; p.m.r.: 3.79 (6H, s, 2 × OCH_3), 4.17 (1H, s, benzylic H), 6.69 (3H, m, aromatic H), 7.73–8.10 (4H, m, aromatic H's).

*2-(3,4-Dimethoxyphenyl)-1,3-indandione (**1**) from 3,4-Dimethoxybenzaldehyde and Phthalide (Method B)*

A boiling mixture of phthalide (0.025 mol), aldehyde (0.025 mol) and freshly distilled methyl formate (12 ml) was treated with a solution of sodium methoxide in methanol prepared from sodium (1.95 g) in anyhydrous methanol (24 ml). The solution, which became red immediately upon addition of the methoxide, was boiled for 1 h under reflux and then worked-up as in the procedure above. Compound **1** was obtained in 95% yield.

*2-(3,4-Methylenedioxyphenyl)-4,5-methylenedioxy-1,3-indandione (**11**)*

This compound was prepared from the phthalide (**10**) by the procedure outlined previously (method A) for the rearrangement of 3-(3,4-dimethoxybenzylidene)-phthalide. Like its analog, this compound was recrystallized from benzene and then melted at 209–210°; yield, 93%. When its preparation from piperonal and 6,7-methylenedioxyphthalide (method B above) was attempted only 5–10% of the desired product was obtained.

Anal. Calcd. for $C_{17}H_{10}O_6$: C, 65.81, H. 3.23. Found: C, 65.66; H, 3.11.

I.r.: ν_{max} 1708, 1740 cm^{-1}; p.m.r.: 4.17 (1H, s, benzylic H), 5.88 (2H, s, OCH_2O), 6.16 (2H, s, OCH_2O), 6.89, 7.46 (2H, AB quartet, $J = 8$ Hz, C-6 and C-7 H's), 6.70–7.42 (3H, m, aromatic H's).

*2-Bromo-2-(3,4-dimethoxyphenyl)-1,3-indandione (**2**)*

A stirred solution of dione **1** (0.005 mol) in glacial acetic acid (100 ml) under an atmosphere of oxygen-free nitrogen at room temperature was treated rapidly with a solution of bromine (0.005 mol) in glacial acetic acid (15 ml). The absorption of bromine was instantaneous but the reaction was stirred for 5 min before removing the glacial acetic acid under vacuum. It was necessary to keep the temperature below 20° at this stage to avoid decomposition of the bromo compound. The residue was a yellow crystalline material melting at 133–134°. In most cases it was used directly in the next step because attempts to recrystallize it resulted in its decomposition. I.r.: ν_{max} 1710, 1745 cm^{-1}; p.m.r.: 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.70–8.3 (7H, m, aromatic H's).

*2-Bromo-2-(3,4-methylenedioxyphenyl)-4,5-methylenedioxy-1,3-indandione (**12**)*

Compound **11** was brominated by a procedure identical with that used for the preparation of **2**. The crude product melted at 176–178°. I.r.: ν_{max} 1708, 1745 cm^{-1}; p.m.r.: 5.90 (2H, s, OCH_2O), 6.16 (2H, s, OCH_2O), 7.03, 7.57 (AB quartet, $J = 8$ Hz, C-6 and C-7 H's), 6.6–7.3 (3H, m, aromatic H's).

*2-(2,2-Diethoxyethylamino)-2-(3,4-dimethoxyphenyl)-1,3-indandione (**3**)*

A stirred solution of compound **2** (0.01 mol) in anhydrous ether (75 ml) was cooled in an ice bath and to it was added dropwise a solution of freshly distilled aminoacetaldehyde diethyl acetal (0.02 mol) in anhydrous ether (15 ml). The resulting solution was stirred for a total of 15 h under an atmosphere of dry nitrogen. The reaction mixture, containing suspended solids, was washed twice with water, the ether layer separated, dried over anhydrous sodium sulfate, and evaporated to dryness. The yellow gum that resulted was used directly in the next step; yield, 74%. I.r.: ν_{max} 1715, 1750 cm^{-1}; p.m.r.: 1.08 (6H, t, $J = 7$ Hz, 2 × OCH_2CH_3), 2.68 (2H, d, $J = 5$ Hz, N—CH_2—CH), 3.24–3.74 (4H, m, 2 × OCH_2CH_3), 3.72 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.54 (1H, t, $J = 5$ Hz, N—CH_2—CH), 6.7–8.2 (7H aromatic H's).

*2-(2,2-Diethoxyethylamino)-2-(3,4-methylenedioxyphenyl)-4,5-methylenedioxy-1,3-indandione (**13**)*

Compound **13** was prepared from **12** in a manner identical with the preparation of **3** from **2** above; yield, 71–73%. I.r.: ν_{max} 1710, 1748 cm^{-1}; p.m.r.: 1.14 (6H, t, $J = 6$ Hz, 2 × OCH_2CH_3), 2.64 (2H, d, $J = 5$ Hz, N—CH_2CH), 2.30 (1H, broad s, NH), 3.27–3.74 (4H, complex m, 2 × O—CH_2—CH_3), 4.57 (1H, t, $J = 5$ Hz, N—CH_2—CH), 5.87 (2H, s, OCH_2O), 6.15 (2H, s, OCH_2O), 6.87, 7.44 (AB quartet, $J = 8$ Hz, C-6 and C-7 H's), and 6.70–7.00 (3H, m, aromatic H's).

Treatment of **3** *with 6 M Aqueous Ethanolic Hydrochloric Acid*

A solution of 0.005 mol of **3** in 75 ml of 6 *M* aqueous ethanolic hydrochloric acid was stirred for 16 h at room temperature. The resulting mixture contained a white precipitate. The solvent was removed under vacuum and the white residue so obtained was washed with water and filtered. Recrystallization from benzene afforded 1.35 g of needle-like crystals, m.p. 194–196°. A mixture melting point of the product and compound **1** showed no depression. The i.r. spectrum in $CHCl_3$ and the p.m.r. spectrum in $CDCl_3$ were superimposable on those of compound **1**.

The filtrate was concentrated to about 10 ml and was treated with a solution of 2,4-dinitrophenylhydrazine in ethanol and allowed to stand at room temperature for 15 min. The reddish precipitate that formed was filtered, washed with water, and air dried. Recrystallization from aqueous ethanol gave orange crystals which melted at 328–330°. Authentic glyoxal bis-2,4-dinitrophenylhydrazone is reported to melt at 328° (36).

*N-Acetyl-2-(2,2-diethoxyethylamino)-2-(3,4-dimethoxyphenyl)-1,3-indandione (***4***)*

A mixture of amine **3** (0.001 mol) in anhydrous pyridine (1 ml) and freshly distilled acetic anhydride (3 ml) was stirred at room temperature for 48 h. The solution was added to water and the mixture extracted several times with chloroform. The chloroform extract was washed several times with cold aqueous hydrochloric acid and with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was adsorbed on basic alumina and the column eluted with chloroform. After removal of chloroform from the eluant a crystalline residue was obtained which, after recrystallization from ethanol, melted at 132–133°; yield, 83%.

Anal. Calcd. for $C_{25}H_{29}NO_7$: C, 65.94; H, 6.37; N, 3.08. Found: C, 66.02; H, 6.63; N, 3.12.

I.r.: ν_{max} 1635 (amide), 1712, 1748 cm^{-1}; p.m.r.: 0.97 (6H, t, $J = 6$ Hz, $2 \times OCH_2CH_3$), 2.09 (3H, s, $COCH_3$), 3.04–3.60 (6H, m, $2 \times OCH_2—CH_3 + N—CH_2—CH$), 3.61 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 4.37 (1H, t, $J = 5$ Hz, $N—CH_2—CH$), 6.6–7.9 (7H, m, aromatic H's).

*N-Acetyl-2-(2,2-diethoxyethylamino)-2-(3,4-methylenedioxyphenyl)-4,5-methylenedioxy-1,3-indandione (***14***)*

Compound **14** was prepared from **13** in a manner analogous to the preparation of **4** above. After recrystallization from ethanol it melted at 172–174°; yield, 80%.

Anal. Calcd. for $C_{25}H_{25}NO_9$: C, 62.12; H, 5.18; N, 2.90. Found: C, 62.37; H, 5.30; N, 3.08.

I.r.: ν_{max} 1640, 1710, 1740 cm^{-1}; p.m.r.: 1.13 (6H, t, $J = 6$ Hz, $2 \times OCH_2CH_3$), 2.24 (3H, s, $COCH_3$), 3.27, 3.74 (6H, complex m, $2 \times OCH_2CH_3 + N—CH_2CH$), 4.47 (1H, t, $J = 5$ Hz, $N—CH_2—CH$), 5.90 (2H, s, OCH_2O), 6.17 (2H, s, OCH_2O), 6.87, 7.44 (2H, AB quartet, $J = 8$ Hz, C-6 and C-7 H's), and 6.97–7.10 (3H, m, aromatic H's).

*2-Acetyl-6,7-dimethoxy-1,2-dihydroisoquinoline-1-spiro-2'-(1',3'-indandione) (***5***)*

A mixture of **4** (0.003 mol) in 6 *M* aqueous ethanolic hydrochloric acid (50 ml) was stirred at room temperature for 18 h. The ethanol was removed under vacuum, the aqueous acid solution neutralized with ammonia, and the solution extracted twice with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and then evaporated to give a reddish brown residue which was purified by chromatography over basic alumina using chloroform as eluant. Evaporation of the chloroform gave an orange solid which crystallized readily from hot ethanol, m.p. 263–264°; yield, 47–52%.

Anal. Calcd. for $C_{21}H_{17}NO_5$: C, 69.42; H, 4.68; N, 3.86. Found: C, 69.39: H, 5.02; N, 3.96.

I.r.: ν_{max} 1642 ($N—COCH_3$), 1668 ($\geq C{=}C \leq$), 1715, 1750 cm^{-1}; p.m.r.: 2.26 (3H, s, $COCH_3$), 3.37 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.64, 6.77 (2H, AB quartet, $J = 8$ Hz, C-3 and C-4 H's), 5.90 (1H, s, C-8 H),[2] 6.60 (1H, s, C-5 H), 7.80–8.15 (4H, m, aromatic H's).

*2-Acetyl-6,7-methylenedioxy-1,2-dihydroisoquinoline-1-spiro-2'-(4',5'-methylenedioxy-1',3'-indandione) (***15***)*

This compound was prepared from **14** in a manner analogous to the preparation described above of **5** from **4**. After recrystallization from hot ethanol the compound melted at 305–308°; yield, 57–61%.

Anal. Calcd. for $C_{21}H_{13}NO_7$: C, 64.44; H, 3.33; N, 3.58. Found: C, 64.33; H, 3.30; N, 3.49.

I.r.: ν_{max} 1640 ($N—COCH_3$), 1675 ($\geq C{=}C \leq$), 1715 and 1745 cm^{-1}; p.m.r.: 2.17 (3H, s, $N—COCH_3$), 5.54, 6.71 (2H, AB quartet, $J = 8$ Hz, C-3 H and C-4 H's), 5.81 (2H, s, OCH_2O), 6.24 (2H, s, OCH_2O), 6.05 (1H, s, C-8 H), 6.54 (1H, s, C-5 H), 7.21, 7.61 (2H, AB quartet, $J = 8$ Hz, C-6' H and C-7' H's).

*2-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'-(1',3'-indandione) (***6***)*

Compound **5** (0.001 mol) dissolved in acetic acid (20 ml) was shaken with hydrogen at 35 p.s.i.g., in the presence of Adams catalyst (25 mg) for 1 h. The catalyst was removed by filtration and the acetic acid evaporated under vacuum. The pale yellow residue was recrystallized from ethanol and melted at 238–240°; yield, 95%.

Anal. Calcd. for $C_{21}H_{19}NO_5$: C, 69.23; H, 5.22; N, 3.85. Found: C, 69.40; H, 5.37; N, 3.85.

I.r.: ν_{max} 1640 ($N—COCH_3$), 1718 and 1750 cm^{-1}; p.m.r.: 2.35 (3H, s, $COCH_3$), 3.15, 3.94 (4H, A_2B_2m, C-3 and C-4 H's); 3.55 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.01 (1H, s, C-8 H), 6.85 (1H, s, C-5 H), 7.85–8.1 (4H, m, aromatic H's).

*2-Acetyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'-(4',5'-methylenedioxy-1',3'-indandione) (***16***)*

This compound was prepared from **15** in the same way that **6** was prepared from **5**. Recrystallization from ethanol gave yellow crystals melting at 300–301°, yield, 91%.

Anal. Calcd. for $C_{21}H_{15}NO_7$: C, 64.27; H, 3.87; N, 3.56. Found: C, 64.33; H, 3.76; N, 3.56.

I.r.: ν_{max} 1640 ($N—COCH_3$), 1715 and 1740 cm^{-1}; p.m.r.: 2.13 (3H, s, $N—COCH_3$), 3.01, 3.85 (4H, A_2B_2m, C-3 and C-4 H's), 5.82 (2H, s, OCH_2O), 6.20 (2H, s, OCH_2O), 6.18 (1H, s, C-8 H), 6.67 (1H, s, C-5 H), 7.16, 7.55 (2H, AB quartet, $J = 8$ Hz, C-6 H and C-7' H's).

[2]Assignment of the high field aromatic singlet of ring A to C-8 H is based on analogy with other spirobenzylisoquinoline systems (6, 7, 8). Moreover, the signal assigned to C-8 H is sharper than that assigned to C-5 H because the para benzylic coupling between C-8 H and the protons at C-4 is smaller than the ortho benzylic coupling between C-5 H and the protons at C-4.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'-(1',3'-indandione) (7)

The amide **6** (0.5 mmol) was boiled under reflux with 6 *M* ethanolic-aqueous HCl (25 ml) for 2 h. The mixture was taken to dryness, water added, the solution basified, and extracted with chloroform. The extract was washed, dried, and evaporated to a residue which crystallized from ether–hexane and melted at 180–182°; yield, 80%.

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.60; H, 5.26; N, 4.64. Found: C, 70.52; H, 5.30; N, 4.50.

I.r.: ν_{max} 1715 and 1750 cm^{-1}; p.m.r.: 2.79, 3.48 (4H, A_2B_2m, C-3 and -4 H's), 3.50 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.92 (1H, s, C-8 H), 6.71 (1H, s, C-5 H), 7.8–8.2 (4H, m, aromatic H's).

6,7-Methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'-(4',5'-methylenedioxy-1',3'-indandione) (17)

The amide **16** was hydrolyzed in the same way that **6** was converted to **7**. The resulting amine was recrystallized from ether–hexane and melted at 198–199°; yield, 82–84%.

Anal. Calcd. for $C_{19}H_{13}NO_6$: mol. wt. 351.074; C, 64.95; H, 3.70; N, 3.99. Found: mol. wt. 351.071 (high resolution mass spectrum); C, 64.91; H, 3.91; N, 4.04.

I.r.: ν_{max} 1715 and 1748 cm^{-1}; p.m.r.: 2.74, 3.37 (4H, A_2B_2m, C-3 and -4 H's), 5.78 (2H, s, OCH_2O), 6.28 (2H, s, OCH_2O), 5.99 (1H, s, C-8 H), 6.60 (1H, s, C-5 H), 7.20, 7.64 (2H, AB quartet, $J = 8$ Hz, C-6' and C-7' H's).

2-Methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'-(4',5'-methylenedioxy-1',3'-indandione) (18)

Amine (**17**) (100 mg), 92% formic acid (2 ml), and formaldehyde (2 ml) were heated on a steam bath for 10 h. Water was added to the mixture which was then basified with sodium bicarbonate solution and extracted twice with chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and evaporated to dryness. The yellow residue after recrystallization from ether–hexane melted at 195–196°; yield, 79%.

Anal. Calcd. for $C_{20}H_{15}NO_6$: mol. wt. 365.090; C, 65.75; H, 4.10; N, 3.84. Found: mol. wt. 365.089 (high resolution mass spectrum); C, 65.52; H, 4.03; N, 3.88.

I.r.: ν_{max} 1705 and 1737; p.m.r.: 2.41 (3H, s, N—CH_3), 2.97–3.47 (4H, complex m, C-3 and -4 H's), 5.81 (2H, s, OCH_2O), 6.31 (2H, s, OCH_2O), 5.96 (1H, s, C-8 H), 6.62 (1H, s, C-5 H), 7.24, 7.64 (2H, AB quartet, $J = 8$ Hz, C-6' and C-7' H's).

2-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'-(1',3'-indandiol) (9)

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2'-(1',3'-indandiol) (410 mg) obtained by reduction of **7** with sodium borohydride (34) was treated without purification with 2.5 ml of formalin (37%) at reflux for 2 h. The mixture was taken to dryness under vacuum, the residue so obtained was dissolved in methanol (5 ml), the solution cooled in ice, and then treated with 200 mg of $NaBH_4$. The mixture was stirred for 30 min, the solvent removed under reduced pressure, water added, and the resulting mixture extracted with methylene chloride. The dry methylene chloride solution was evaporated to dryness and crystallized from benzene–petroleum ether gave an analytical sample melting at 161–162°.

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.29; H, 6.73; N, 4.10. Found: C, 70.57; H, 6.81; N, 3.99.

P.m.r.: 2.04 (2H, broad s, 2 × O*H*); 2.65 (3H, s, N—CH_3), 2.78 (2H, t, N—CH_2), 3.48 (2H, t, Ar—CH_2), 3.27 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.35 (2H, broad s, 2 × C*H*—OH), 5.92 (1H, s, C-8 H), 6.67 (1H, s, C-5 H), 7.4 (4H, m, aromatic H's). The two proton singlet at 2.04 δ disappeared in the presence of D_2O.

(±)-Ochrobirine (19)

Compound **18** (32 mg) in absolute ethanol (35 ml) was treated with sodium borohydride (90 mg) and the mixture was stirred at room temperature for 15 h. The solvent was then removed under reduced pressure, the residue taken up in H_2O, and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and evaporated to dryness giving 26 mg of white residue. Examination by t.l.c. showed the presence of two components, one of which (the major one) had the same R_f value as natural ochrobirine. Crystallization from benzene–hexane gave 21 mg of crystalline product melting at 210–212° which on t.l.c. showed only traces of the minor component noted above. Recrystallization from methanol removed the traces of impurity without altering the melting point. The i.r. spectrum in chloroform, the p.m.r. spectrum in $CDCl_3$, and the mass spectrum of the synthetic sample were identical with those of natural ochrobirine.

Mol. Wt. Calcd. for $C_{20}H_{19}NO_6$: 369.121. Found (high resolution mass spectrum): 369.120.

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