Total synthesis of spirobenzylisoquinoline alkaloids: (±)-ochotensimine

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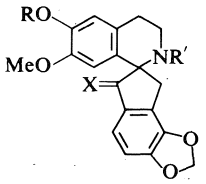
Received October 27, 1969

A synthesis of ochotensimine that can be modified to lead to related spirobenzylisoquinoline alkaloids is described.

Canadian Journal of Chemistry, **48**, 948 (1970)

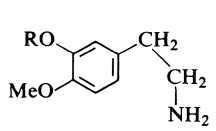
In 1940 Manske (1) reported the isolation of the alkaloids ochotensine and ochotensimine from the fumariaceous plant *Corydalis ochotensis* Turcz. A few years ago the structures **1***a* and **1***b*, respectively, were assigned to these alkaloids on the basis of chemical, spectroscopic, and X-ray crystallographic evidence (2). Ochotensine and ochotensimine were of considerable interest since they appeared to belong to a new structural class of alkaloids in which the basic benzylisoquinoline framework had been modified to incorporate a spiro union. Several further fumariaceous alkaloids have very recently been assigned structures incorporating the same type of skeleton (3).



1

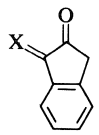
a R = H; R′ = Me; X = CH_2
b R = Me; R′ = Me; X = CH_2
c R = H; R′ = H; X = O
d R = Me; R′ = Me; X = O

In 1968 we communicated a preliminary report of the total synthesis of (±)-ochotensimine (4); since then Irie *et al.* (5) have reported a synthesis that closely parallels our own and there have been several reports of syntheses of analogs by related routes (5, 6). Very recently Shamma (7) has reported a very interesting synthesis of the spiro skeleton by a completely different route that may be related to the biosynthesis of this class of alkaloids. We now report the details of our own synthesis, some steps of which we have improved since our preliminary communication (4).



2

a R = Me
b R = H



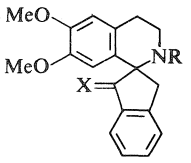
3

a X = H_2
b X = O

The Pictet–Spengler reaction (8) has found extensive use for the synthesis of tetrahydroisoquinolines, but in almost all of the vast amount of work on the reaction the carbonyl component has been an aldehyde. The literature does, however, contain a few isolated references to the use of the reaction with pyruvic acid derivatives (9) and, in one case, with cyclic ketones (10). Both classes of ketones offered potential routes to the spiro skeleton and this led us to investigate first the applicability of the method with model cyclic ketones.

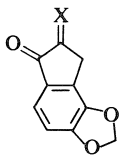
We were pleased to find conditions, utilizing hot 85% phosphoric acid, under which homoveratrylamine (**2***a*) reacted with 2-indanone (**3***a*) to form the tetracylic product **4***a* which incorporated the required skeleton. 1,2-Indanedione (**3***b*) then appeared to be ideal as the next model carbonyl component: it can be anticipated that of the two carbonyl groups present, the one at position 2 should be the more reactive in the cyclization reaction, and the second carbonyl should be retained in the product (**4***b*) at the precise position where an exocyclic methylene must eventually be introduced. When the reaction was carried out, the yield of **4***b* was, in fact, higher than that of **4***a* in the earlier case and no trace of the isomer resulting from reaction at position 1 was isolated.

Treatment of **4***b* with formic acid and formaldehyde converted it to its *N*-methyl derivative **4***c* by the Eschweiler–Clarke reaction. A



4

a R = H; X = H_2
b R = H; X = O
c R = Me; X = O
d R = Me; X = CH_2

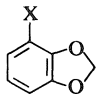


5

a X = O
b X = H_2
c X = NOH
d X = H,OAc

standard Wittig reaction employing methylenetriphenylphosphorane transformed **4***c* to **4***d*, which has all the structural features of ochotensimine except the methylenedioxy substituent. The spectroscopic characteristics of these compounds were in accord with the structural assignments made; in particular, the nuclear magnetic resonance (n.m.r.) spectrum of **4***d* was remarkably similar to that of ochotensimine except that it exhibited signals for two further aromatic protons in place of those of the methylenedioxy protons in the alkaloid.

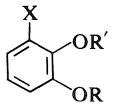
The synthesis of the model compound **4***d* indicated that it should be possible to use the same route to ochotensimine if **5***a*, the appropriate methylenedioxy derivative of **3***b*, could be obtained as the starting material for the sequence. This task required the use of a surprisingly large number of synthetic steps. Many substituted methylenedioxybenzenes are readily available as starting materials, but all of the common examples are derivatives of piperonal and it seemed inevitable that synthetic elaboration of these would lead to undesired isomers of **5***a*. It was therefore necessary to use a sequence incorporating the methylenation of a suitably substituted catechol, a reaction that frequently presents technical difficulties.



6

a X = COOH
b X = CH_2OH
c X = CHO
d X = CH=CHCOOH
e X = CH_2CH_2COOH

Perkin and Trikojus (11) have described a convenient preparation of the methylenedioxybenzoic acid **6***a* from 2,3-dihydroxybenzoic acid



7

a X = CHO; R = Me; R′ = H
b X = CHO; R = Me; R′ = Me
c X = COOH; R = Me; R′ = Me
d X = COOH; R = H; R′ = H
e X = CHO; R = H; R′ = H

(**7***d*), which is now commercially available. We have been able to repeat this and obtain **6***a* in yields of 52% for this step. They converted **6***a* to the methylenedioxycinnamic acid **6***d* by a sequence which we have modified, with a considerable improvement in convenience and yield, by the use of reagents not available to them: **6***a* was reduced with lithium aluminum hydride to the alcohol **6***b*, which was oxidized to the aldehyde **6***c* by chromium trioxide in pyridine (12). Perkin's original preparation of 2,3-dihydroxybenzoic acid (**7***d*) started with *o*-vanillin (**7***a*), which is still a very convenient starting material. However, it was unfortunately necessary to methylate **7***a* to protect the phenolic group, oxidize the aldehyde group of the *o*-veratraldehyde (**7***b*) obtained, and then remove both methyl groups from the product **7***c* in order to obtain **7***d*; furthermore the oxidation level required at **6***c*, an aldehyde, is the same as in **7***a* but it was necessary, in order to introduce the methylenedioxy group, to go through the lengthy series of oxidations and reductions described. We have now been able to devise a method for converting *o*-vanillin (**7***a*) to **6***c* in two steps and in excellent yield. The demethylation of *o*-vanillin to 2,3-dihydroxybenzaldehyde (**7***e*) by hydrobromic acid can be accomplished on a large scale by the method of Pauly *et al.* (13); yields of up to 60% were obtained. The product can then be converted directly to **6***c* in 64% yield by the method that Tomita and Aoyagi have recently described (14), where methylenation is carried out by methylene iodide in dimethylformamide in the presence of cupric oxide and potassium carbonate. The aldehyde (**6***c*) produced by this method was of a very good quality and could be converted by condensation with malonic acid under Perkin's conditions (11) to the methylenedioxycinnamic acid **6***d* in 96% yield; the yield was considerably lower if less pure starting material was used. The conversion

of **6***d* to **6***e* was effected in 92% yield by reduction with sodium amalgam.

The conversion of **6***e* to the indanone **5***b* was accomplished by a Friedel–Crafts cyclization, a reaction which has received a considerable amount of study in a wide variety of contexts. The conclusions that can be drawn from these studies are, in summary, that the optimum conditions for cyclization are remarkably dependent on the precise constitution of the substrate, and yields are liable to fall rapidly if the reaction conditions are allowed to diverge from the optimum. The cyclization of **6***e* was typical. In our original method **6***e* was heated with phosphorus pentoxide and converted to **5***b* in a yield of 25%; this result is comparable with that of Irie *et al.* (5) and, like them we observed the formation of a by-product with infrared (i.r.) absorption at 5.67 μ. We now find that **6***e* can be converted via its acid chloride to **5***b* in 76% yield, the cyclization being effected by treatment of the acid chloride with aluminum chloride in methylene chloride at −10°; the temperature used was extremely critical since at a few degrees below the optimum the rate of the reaction fell rapidly, while raising the temperature caused an appreciable increase in the formation of the by-product at the expense of **5***b*.

In the model series 1,2-indanedione (**3***b*) was conveniently prepared by nitrosation of 1-indanone and hydrolysis of the product with hydrochloric acid in the presence of formaldehyde (15). The methylenedioxyindanone **5***b* was readily converted to the oximino ketone **5***c* by *n*-butyl nitrite as in the model series, but we were unable to obtain useful amounts of **5***a* by acid-catalyzed hydrolysis of **5***c*; our conditions were either too gentle and **5***c* was recovered, or too vigorous and extensive degradation resulted. Although Irie and his co-workers (5) have now reported that they have found conditions under which this hydrolysis can be carried out, the very marked difference in behavior of **5***c* and the analogous compound in the model series gives evidence that the reactions at the 2 position of an indanone can be markedly influenced by the presence or absence of a methylenedioxy group on the aromatic ring, an observation that is unexpected, unexplained, and an ill omen for the next stage of the synthesis. We did, in fact, succeed in converting **5***c* to **5***a* by Eistert's method (16) which required the methylation of **5***c* with diazomethane and acid-catalyzed hydrolysis of the product, but in our most convenient synthesis of **5***a*, **5***b* was acetoxylated with lead tetraacetate (17) and the product, **5***d*, was hydrolyzed to the corresponding hydroxyketone and then oxidized to **5***a* by the Jones reagent; when this sequence was carried out rapidly and with care to avoid the degradation of the somewhat unstable intermediates, yields of 70% were achieved.

With **5***a* available we turned our attention to completing the synthesis of ochotensimine (**1***b*) by the route established in the synthesis of the model compound **4***d*. However, as the results of the attempted acid-catalyzed hydrolysis of **5***c* had led us to fear, the Pictet–Spengler reaction of **5***a* with homoveratrylamine (**2***a*) under the conditions used in the model series led to no recognizable product. Since one potential source of difficulty was the methylenedioxy group which may not have survived the strongly acid conditions, we sought less vigorous conditions for the reaction. It soon became apparent that a more reactive phenylethylamine was required, so we turned to the phenolic compound **2***b* and found that this reacted with **5***a* in the presence of dilute hydrochloric acid and that excellent yields of the spiro compound **1***c* could be obtained by careful control of the concentration of acid and temperature. The product (**1***c*) was *O*-methylated with diazomethane and *N*-methylated by the Eschweiler–Clarke reaction as in the model series, the product, **1***d*, being obtained in excellent yield. The final step to (±)-ochotensimine (**1***b*), the Wittig reaction, was also carried out under the same conditions as in the model series. The product was non-crystalline, as is natural ochotensimine, and the identity of the two materials in every respect but optical activity was established by i.r., ultraviolet (u.v.), and n.m.r. spectroscopy as well as by their mass spectrometric fragmentation patterns and their behavior in thin-layer chromatography (t.l.c.). Intermediate **1***c* has also been converted to (±)-ochotensine (**1***a*) by Irie *et al.* (5) and by Beckett and Kelly (6).

We have carried out a number of unsuccessful attempts to resolve our synthetic products; the resolving agents *d*-10-camphorsulfonic acid, the 2′-chloro, 2′-bromo, and 2′-nitro derivatives of (2*R*,3*R*)- and (2*S*,3*S*)-tartranilic acid (18) were used with **1***b*, **1***c*, and **1***d*, the toluenesulfonate

esters of D- and L-leucine were used with **1***b*, and the di-*p*-toluoyl derivatives of D- and L-tartaric acids (19) were used with **1***c* and **1***d*.

Experimental

Melting points were determined on a Thomas–Kofler micro hot stage. Spectrometers used were: Beckman IR 8 for i.r. spectra, Bausch and Lomb Spectronic 505 and Unicam SP. 800 for u.v. spectra, and Varian A-60 and HA-100 for n.m.r. spectra. Unless otherwise indicated, i.r. spectra were obtained with chloroform solutions, u.v. spectra with methanol solutions, and n.m.r. spectra with chloroform-*d* solutions.

*6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-2′-indane (**4a**)*

Homoveratrylamine (**2***a*) (5.4 g; 30 mmoles), 2-indanone (**3***a*) (20) (4.2 g; 32 mmoles), and 11 ml 85% phosphoric acid were heated together at 80–90° under nitrogen for 21 h. The dark suspension that resulted was poured into 60 ml water, extracted with chloroform, made basic with sodium hydroxide, and then extracted with ether. The ether afforded a residue (1.4 g) which failed to crystallize from common solvents. Treatment with acetic anhydride and a little pyridine at room temperature overnight converted the residue to the crystalline *N*-acetyl derivative of **4***a* (1.3 g; 4 mmoles), which had, after recrystallization from methanol, m.p. 152–153°.

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.80; H, 6.91; N, 4.22.

The i.r.: λ_{max} 6.11 μ; u.v.: λ_{max} 232 (inflect. ε 8300), 266 (ε 2600), 272 (ε 3900), 278 (ε 3400), 282 (ε 3400), and 288 mμ (inflect.); n.m.r. (τ; A-60): 2.85 (4H; s), 3.42 (1H; s), 3.57 (1H; s), 6.19 (3H; s), 6.58 (3H; s), 7.81 (3H; s), 5.92, 6.86 (2H each; apparently AB quartet, *J* 16 Hz), 6.31, 7.17 (2H each; apparently components of A_2B_2 multiplet).

*6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1-spiro-2′-indanone-1′ (**4c**)*

Homoveratrylamine (**2***a*) (1.6 g; 9 mmoles), 1,2-indanedione (**3***b*) (15) (1.4 g; 9.5 mmoles), and 10 ml 85% phosphoric acid were subjected to the treatment just described. The product, **4***b*, (0.83 g) (5.84 μ peak in i.r.), which failed to crystallize, was acetylated as in the previous case. The *N*-acetyl derivative was crystalline, m.p. 177–179°, but appeared to be hygroscopic and gave unreproducible microanalytical results ("best values" are quoted).

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.79, H, 6.02; N, 3.99. Found: C, 72.02; H, 6.34; N, 3.94.

The i.r. λ_{max} 5.80, 6.10 μ; u.v.: λ_{max} 239 (ε 18 300) and 286 mμ (ε 6100); n.m.r. (τ; A-60): 2.10–2.71 (4H; complex); 3.33 (1H; s), 3.84 (1H; s), 6.17 (3H; s), 6.60 (3H; s), 6.00–7.18 (6H; complex), 7.82 (3H; s).

A mixture of **4***b* (6.2 g; 20 mmoles), 7 ml 85% formic acid, and 5 ml 40% formaldehyde was heated on a steam-bath for 10 h and then evaporated under reduced pressure to a syrup. The syrup was diluted with 30 ml water, made basic with 1 *N* sodium hydroxide, and thoroughly extracted with chloroform. The chloroform extract afforded **4***c* as a brown solid (6.4 g; 20 mmoles) which, after chromatography on alumina (Brockmann activity I) with ether elution and recrystallization from methanol–ether, was obtained as yellow crystals, m.p. 136–138°.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.11; H, 6.57; N, 4.34.

The i.r.: λ_{max} 5.85 μ; u.v. λ_{max} 246 (ε 15 600), 287 (ε 5400), and 301 mμ (inflect.); n.m.r. (τ; A-60): 2.10–2.68 (4H; complex), 3.37 (1H; s), 3.92 (1H; s), 6.18 (3H; s), 6.50 (3H; s), 6.53–7.20 (6H; complex), 7.70 (3H; s). Methiodide, m.p. 145–148°.

Anal. Calcd. for $C_{21}H_{24}NO_3I$: C, 54.19; H, 5.16; N, 3.01. Found: C, 54.17; H, 5.66; N, 3.04.

*Des(methylenedioxy)ochotensimine (**4d**)*

Methyltriphenylphosphonium bromide (2.15 g; 6 mmoles) and 4.2 ml of 14.9% butyl lithium (6 mmoles) were stirred together under nitrogen at room temperature for 2 h. A solution of **4***c* (646 mg; 2.0 mmoles) in 30 ml tetrahydrofuran was added, and the reaction mixture was refluxed 9 h, and then poured into 100 ml water. Extraction with chloroform afforded a product (1.54 g) which was chromatographed on 45 g neutral alumina (Brockmann activity I) with elution first with benzene – petroleum ether and then benzene. The benzene fractions afforded **4***d* as a noncrystalline residue (285 mg; 0.89 mmoles): i.r. λ_{max} 6.22 (m)μ; u.v. λ_{max} 227 (ε 37 700), 281 (ε 6300), 289 (ε 6100), and 300 mμ (ε 4000); n.m.r. (τ; A-60): 2.10–2.76 (4H; complex), 3.41 (1H; s), 3.65 (1H; s), 4.19 (1H; s), 4.95 (1H; s), 6.15 (3H; s), 6.40 (3H; s), 6.68 (2H; AB quartet, *J*, 18 Hz, internal chemical shift 27 Hz), 7.04–7.42 (4H; complex), 7.88 (3H; s). Treatment of **4***d* with methyl iodide in acetone–ether converted it to its methiodide which was obtained crystalline, m.p. 130–134°, after recrystallization from acetone–ether.

Anal. Calcd. for $C_{22}H_{26}NO_2I$: C, 56.92; H, 5.61; N, 3.02. Found: C, 56.77; H, 5.92; N, 2.95.

*2,3-Methylenedioxybenzaldehyde (**6c**)*

Method A

o-Vanillin (**7***a*) was converted into 2,3-dihydroxybenzaldehyde (**7***e*) in 60% yield by the method of Pauly *et al.* (13). A mixture of **7***e* (10.0 g; 72.5 mmoles), methylene iodide (31.4 g; 117 mmoles), potassium carbonate (30.0 g; 218 mmoles), cupric oxide (1.0 g) and 85 ml dimethylformamide was heated to 100–110° under nitrogen and vigorously stirred for 3½ h (14). The reaction mixture was cooled, diluted with 1400 ml ice-water, and thoroughly extracted with ether. The ether extract, after it had been washed successively with 3% hydrochloric acid, 10% aqueous potassium carbonate, and water, yielded crystalline **6***c* (7.0 g; 47 mmoles), m.p. 32–34° (lit. (11) 34°).

Method B

2,3-Methylenedioxybenzoic acid (**6***a*) (19.8 g; 119 mmoles), prepared from 2,3-dihydroxybenzoic acid (11), in 600 ml tetrahydrofuran was added dropwise to a suspension of lithium aluminum hydride (4.75 g; 125 mmoles) in 600 ml ether under nitrogen. The reaction mixture was refluxed 4 days, cooled, treated with ice, and made acid with 10% sulfuric acid. The aqueous layer was thoroughly extracted with ether, and the combined ether extracts yielded a brown oil (18.9 g) from which **6***b*, (16.3 g; 108 mmoles) m.p. 34–35° (lit. (21) 34–35°) was obtained as tan needles.

A solution of **6***b* (12.4 g; 81.5 mmoles) in 50 ml pyridine was added in one portion to a chilled, well-stirred suspension of chromium trioxide (24.4 g; 244 mmoles) in 600 ml pyridine. The suspension, which immediately turned greenish brown, was stirred for 20 min and then allowed to stand at room temperature 22 h. The solution was diluted with 250 ml ether and the precipitate removed by filtration. The filtrate was diluted with 600 ml water and thoroughly extracted with ether and the combined ether extracts, after they had been washed successively with 10% hydrochloric acid, 4% aqueous sodium carbonate, and water, yielded yellowish crystals of **6***c* (7.95 g; 53 mmoles), m.p. 32–34°.

2,3-Methylenedioxydihydrocinnamic Acid (6e)

The aldehyde **6***c* was converted in 96% yield by Perkin's method (11) into 2,3-methylenedioxycinnamic acid (**6***d*), m.p. 190–194°; recrystallization from methanol gave material m.p. 194–196°; i.r.: λ_{max} 3–4, 5.92, 6.12 μ; u.v.: λ_{max} 230 (ε 20 600), 275 (ε 20 300), and 335 mμ (ε 4240); n.m.r.: (τ; A-60; acetone-d_6): 2.15–2.78 (3H; complex), 2.85 (2H; AB quartet, *J*, 16 Hz, internal chemical shift 59 Hz), 3.86 (2H; s).

Freshly prepared 2% sodium amalgam (88 g; 77 mmoles Na) was added to a well-stirred solution of **6***d* (7.68 g; 40.0 mmoles) in 18 ml 2.5 *N* sodium hydroxide over 1 h. The mixture was filtered and the filtrate was acidified with dilute hydrochloric acid. The acid **6***e* (7.11 g; 37 mmoles), m.p. 80–82°, was precipitated.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.65; H, 5.01.

The i.r.: λ_{max} 3–4, 5.84 μ; u.v.: λ_{max} 233 (ε 2900) and 282 mμ (ε 2700); n.m.r. (τ; A-60): 3.30 (3H; m), 4.09 (2H; s), 6.99–7.45 (4H; complex).

4,5-Methylenedioxy-1-indanone (5b)

Method A

A solution of **6***e* (2.0 g; 10.3 mmoles) in 4 ml purified thionyl chloride was stirred with the exclusion of moisture for 2 h at room temperature. The excess thionyl chloride was evaporated under reduced pressure and the amber oil which resulted was dissolved in 5 ml dry methylene chloride and added dropwise over 7 min to a vigorously stirred suspension of finely powdered aluminum chloride (1.8 g; 13.7 mmoles) in 125 ml methylene chloride at −10°. The reaction was stopped by the addition of 30 ml 10% hydrochloric acid, and the aqueous layer was separated and extracted with further methylene chloride; the combined organic layers were washed successively with water, 2% sodium hydroxide, and water. The organic extract afforded a white solid which was recrystallized from acetone–ether and **5***b* (1.3 g; 7.6 mmoles), m.p. 165–168°, was obtained.

Method B

Phosphorus pentoxide (6 g) was added in small portions with shaking to a boiling solution of **6***e* (1.1 g; 5.6 mmoles) in 30 ml benzene. After the mixture had been refluxed with occasional agitation for 5 h, it was poured on to 100 g crushed ice and successively extracted with ether and ethyl acetate. The combined extracts, after they had been washed with saturated aqueous sodium bicarbonate and water, afforded a residue (0.66 g) which consisted of **5***b* and an impurity which showed i.r. absorption at 5.67 μ. Pure **5***b* (effective yield ~25%) m.p. 165–168°, was obtained by repeated recrystallization of the residue from acetone–ether.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.38; H, 4.39.

The i.r.: λ_{max} 5.88, 6.12 μ; u.v.: λ_{max} 235 (ε 24 800), 286 (ε 7300), and 305 mμ (inflect., ε 5500); n.m.r. (τ; A-60): 2.87 (2H; AB quartet, *J*, 8 Hz, internal chemical shift 31 Hz), 3.92 (2H; s), 6.84–7.46 (4H; complex).

4,5-Methylenedioxy-1,2-indanedione (5a)

Method A

A solution of **5***b* (0.35 g; 2.0 mmoles) in 25 ml glacial acetic acid containing 7 ml of acetic anhydride was heated to 78° with stirring and red lead oxide (Pb_3O_4; 2.75 g; 4.0 mmoles) was added in portions over 1 h (care was taken that each portion of lead oxide had completely reacted before the next was added). The solution was kept at 78° for a further $3\frac{3}{4}$ h and 10 ml methanol were then added and the stirring was continued for a further 15 min. The solution was cooled to room temperature and added to 225 ml of cold water. The aqueous solution was thoroughly extracted with methylene chloride, and the extract was filtered through Celite and washed with water until the wash water was neutral. The extract afforded a yellow solid from which the acetoxyindanone **5***d* (0.3 g; 1.35 mmoles), m.p. 129–131° was isolated by recrystallization from hexane – carbon tetrachloride.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.77; H, 4.51.

The i.r.: λ_{max} 5.75, 5.82 μ; u.v. λ_{max} 238 (ε 22 500) 294 (ε 7400), and 309 mμ (inflect.): n.m.r. (τ; HA-100) 2.85 (2H; AB quartet, *J*, 8.0 Hz, internal chemical shift 54 Hz), 3.91 (2H; narrow multiplet), 4.60, 6.40, 7.10 (1H each; AMX pattern, J_{AM} 5Hz, J_{AX} 9 Hz, J_{MX} 18 Hz), 7.84 (3H; s).

A solution of **5***d* (95 mg; 0.405 mmoles) in 35 ml methanol was kept at 0° under nitrogen and a solution of 1.2 ml of 2% aqueous sodium hydroxide in 15 ml methanol was added dropwise over about 15 min. The solution was poured into 100 ml of ice-water and immediately acidified with 10% hydrochloric acid. The solution was thoroughly extracted with methylene chloride, and, after the extract had been washed with water, it yielded an unstable yellow solid (75 mg) [Mol. Wt. Calcd. for $C_{10}H_8O_4$: 192.0422. Found (mass spectrometry): 192.0423] which was immediately dissolved in 5 ml acetone at 10° and the Jones reagent (22) was added until an orange–brown color persisted (~0.25 ml reagent was required). The solution was diluted with 40 ml water and thoroughly extracted with methylene chloride. The extract afforded **5***a* (73 mg; 0.385 mmoles) m.p. 158–168° (value strongly dependent on rate of heating; material appeared to decompose near its m.p.).

Anal. Calcd. for $C_{10}H_6O_4$: C, 63.16; H, 3.18. Found: C, 63.33; H, 3.27.

The i.r.: λ_{max} 5.66, 5.82 μ; u.v.: λ_{max} 239 (ε 20 500), 294 (ε 7400), and 311 mμ (ε 6600); material too insoluble for useful n.m.r. spectrum.

Method B

To an ice-cooled, well-stirred solution of **5***b* (3.02 g; 17.1 mmoles) in 300 ml methanol were added *n*-butyl nitrite (2.1 g; 20.3 mmoles) and 2 ml concentrated hydrochloric acid. The mixture was stirred 1 h and then left

at room temperature 20 h. The precipitate of **5***c* (2.95 g; 14.4 mmoles), m.p. 257–260°, which formed was recrystallized from acetone–tetrahydrofuran and obtained as crystals m.p. 258–260°.

Anal. Calcd. for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.67; H, 3.60; N, 6.70.

The i.r.: λ_{max}(KBr) 5.89, 6.17 μ; u.v.: λ_{max} 253 (ε 10 900), 313 (inflect.), and 340 mμ (ε 4800); n.m.r. (τ; A-60; DMSO-d_6): −2.79 (1H; s), 2.78 (2H; AB quartet, *J*, 8 Hz, internal chemical shift 21 Hz), 3.77 (2H; s), 6.38 (2H; s).

A suspension of **5***c* (112 mg; 0.54 mmole) in 100 ml tetrahydrofuran containing a few drops of methanol was stirred for 21 h with 25 ml ethereal diazomethane (~ 8.3 mmoles). The residue (120 mg), m.p. 185–186°, recovered after evaporation of the solvent, was recrystallized from acetone–ether and obtained as yellow crystals, m.p. 188–189°, showing i.r. absorption at 5.92 and 6.38 μ. Hydrolysis of this material (55 mg) in 9% hydrochloric acid at room temperature for 7 days converted it to a product (43 mg), m.p. 150–173°, which consisted largely of **5***a*, but which could be purified by recrystallization from acetone–ether only with difficulty and with poor recovery of material.

*6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1-spiro-2′-(4′,-5′-methylenedioxy-1′-indanone) (**1***d*)*

A suspension of finely powdered **5***a* (380 mg; 2.0 mmoles) and β-(3-hydroxy-4-methoxyphenyl)ethylamine hydrochloride (**2***b*) (500 mg; 2.0 mmoles) in 15 ml 2.5% hydrochloric acid was stirred vigorously at 49–52° for 4 days. Unchanged **5***a* (237 mg; 1.25 mmoles) was recovered by extraction of the reaction mixture with methylene chloride. The reaction mixture was then made slightly basic with saturated aqueous sodium bicarbonate and re-extracted with methylene chloride. The extract afforded an amber oil (310 mg) which was purified by preparative layer chromatography on silica gel G. Crystalline **1***c* (230 mg; 0.68 mmoles), m.p. 104–107°, was then obtained from acetone. This material corresponds to that obtained by Kelly and Beckett (6) and we thank Professor Kelly for a sample of his material for direct comparison with ours; the material obtained by Irie *et al.* (5) is apparently a different crystalline modification. The material we obtained gave erratic analytical results, probably because of tenacious retention of variable amounts of solvent.

Spectroscopic results: i.r.: λ_{max} 2.83, 5.85 μ; u.v.: λ_{max} 237 (ε 27 600), 292 (ε 11 800), and 310 mμ (inflect., ε 8000); n.m.r. (τ; CD_3OD: HA-100): 2.79 (2H; AB quartet, *J*, 8.0 Hz, internal chemical shift 46 Hz), 3.45 (1H; s), 3.88 (3H; probably 2 superimposed singlets), 6.45 (3H; s), remainder of spectrum confused by partially exchanged solvent, etc.

Treatment of **1***c* (251 mg) in 2 ml methanol with an excess of diazomethane in ether converted it quantitatively to its methyl ether which, after purification by t.l.c. (9:1 methylene chloride – methanol on silica gel G) and recrystallization from acetone–hexane, afforded crystals m.p. 179–181°.

Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.85; H, 5.49; N, 4.13.

The i.r.: λ_{max} 5.85 μ; u.v.: λ_{max} 237 (ε 37 600), 292 (ε 11 800), and 310 mμ (inflect., ε 10 500); n.m.r. (τ; HA-100): 2.78 (2H; AB quartet, *J*, 8.0 Hz, internal chemical shift 59 Hz), 3.41 (1H; s), 3.84 (1H; s), 3.90 (2H; AB quartet, $J \sim 1.5$ Hz; internal chemical shift ~ 3.5 Hz), 6.18 (3H; s), 6.40 (3H; s), 6.2–7.3 (6H; complex), 7.86 (1H; s; removed by D_2O).

A mixture of the methyl ether (180 mg; 0.53 mmole), 5 ml 91% formic acid and 0.2 ml 40% formaldehyde was heated on a steam-bath for 9½ h. The solution, when cool, was poured into 50 ml water, made basic with saturated aqueous sodium bicarbonate, and thoroughly extracted with methylene chloride. The extract afforded **1***d* (155 mg; 0.44 mmole), m.p. 162–165°, after recrystallization from acetone–hexane.

Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.88; H, 5.69; N, 3.70.

The i.r.: λ_{max} 5.86 μ; u.v.: λ_{max} 237 (ε 32 000), 292 (ε 12 600), and 310 mμ (inflect., ε 9600); n.m.r. (τ; HA-100): 2.80 (2H; AB quartet, *J*, 8.0 Hz, internal chemical shift 58 Hz), 3.41 (1H; s), 3.88 (3H; probably 1H singlet superimposed on very narrow 2H multiplet), 6.19 (3H; s), 6.44 (3H; s), 6.60 (2H; AB quartet; *J*, 18 Hz; internal chemical shift 23 Hz), 6.8–7.3 (4H; m), 7.71 (3H; s).

*(±)-Ochotensimine (**1***b*)*

Methyltriphenylphosphonium bromide (152 mg; 0.42 mmoles) and *n*-butyl lithium (0.37 mmoles) in 1.6 ml hexane were stirred together under nitrogen at room temperature for 2 h. A solution of **1***d* (45 mg; 0.125 mmoles) in 4 ml tetrahydrofuran was added and the reaction mixture was refluxed 7.5 h, and, when cool, poured into 60 ml water. Extraction with methylene chloride afforded a material which was purified by t.l.c. (11:1 ether–methanol on silica gel G). The product (26.5 mg; 0.073 mmoles) was a pale yellow oil which showed the same behavior on t.l.c. (6 systems) as natural ochotensimine and the n.m.r., i.r., u.v., and mass spectra of the synthetic and natural materials were identical in all significant characteristics.

We thank the National Research Council of Canada for financial support of this work and for a Graduate Fellowship (J.W.); a Province of Ontario Department of University Affairs Graduate Fellowship (M.-S.L.) is also gratefully acknowledged.

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