

Synthesis of the Alkaloids Escholamine and Takatonine *via* a Modified Pomeranz–Fritsch Reaction

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Treatment of the Schiff's base formed from piperonal and aminoacetaldehyde dimethyl acetal with benzylmagnesium chloride gave 1-(3,4-methylenedioxyphenyl)-2-phenylethylaminoacetaldehyde dimethyl acetal (4; $R^1 = R^2 = H$), the tosylate of which was cyclised under acidic conditions to 1-benzyl-1,2-dihydro-6,7-methylenedioxy-2-tosylisoquinoline (5; $R = H$) and *trans*-3,4-methylenedioxy-stilbene (6). Further acid treatment of (5; $R = H$) gave 1-benzyl-6,7-methylenedioxyisoquinoline (7; $R = H$) and 6,7-methylenedioxyisoquinoline. Similar results were obtained using *p*-methoxybenzylmagnesium chloride with the same Schiff's base (from piperonal). 6,7-Methylenedioxy-1-(3,4-methylenedioxybenzyl)isoquinoline (10) (escholamine free base) was prepared from 6,7-methylenedioxyisoquinoline and 3,4-methylenedioxybenzyl chloride *via* a Reissert compound in 60% yield. Similarly 5,6,7-trimethoxyisoquinoline and *p*-methoxybenzyl chloride gave 5,6,7-trimethoxy-1-(4-methoxybenzyl)isoquinoline (11) (takatonine free base) in 75% yield.

THE isoquinoline-based alkaloids have been synthesised by a variety of methods.¹ Although the majority of

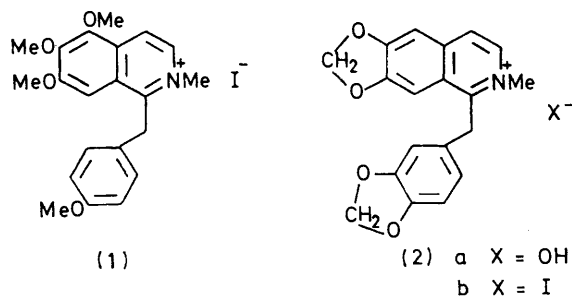
¹ W. M. Whaley, T. R. Govindachari, and W. J. Gensler, *Org. Reactions*, 1951, **6**, 74.

these compounds are tetrahydroisoquinolines, naturally occurring isoquinolines are also known² and in general

² T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Elsevier, Amsterdam, 1969.

their syntheses have involved acid catalysed cyclisations of appropriate *N*-substituted benzylamines or phenylethylamines followed by high temperature dehydrogenations of the intermediate tetrahydroisoquinolines.

Two aromatic isoquinoline alkaloids are takatonine³ and escholamine.⁴ Takatonine (1), an active constituent of the crude drug takato-gusa is found in the species *Thalictrum thunbergii* (minus) and was eventually correctly identified⁵ as 5,6,7-trimethoxy-1-(4-methoxybenzyl)isoquinoline methiodide. The only previous synthesis, by Kupchan *et al.*,⁵ highlighted the chemical difficulties; the

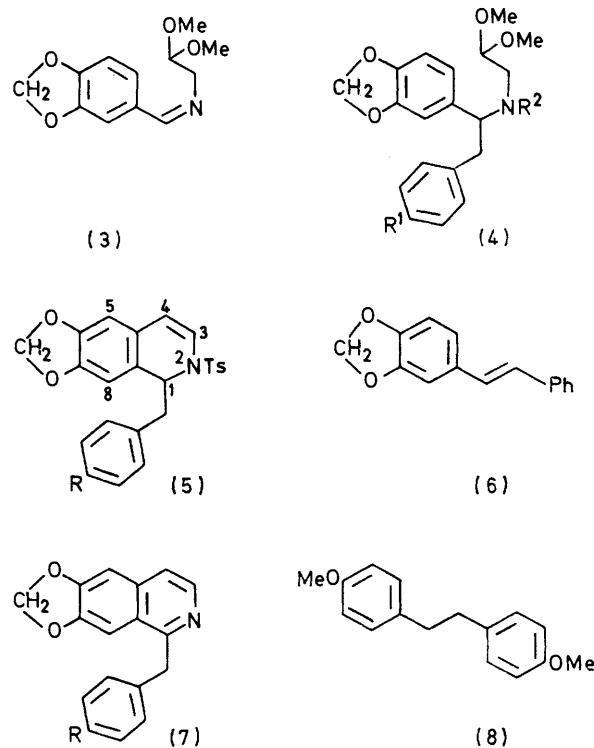


route included an initial Bischler-Napieralski cyclisation to a 3,4-dihydroisoquinoline, borohydride reduction of the latter to a tetrahydroisoquinoline, and subsequent dehydrogenation with palladium black at 180–240°.

Escholamine (2a) was first isolated from *Eschschultzia* (probably *E. Oregana*) in 1965^{6,7} although the free base 3,4:6,7-bismethylenedioxyprotopapaverine was synthesised by Perkin⁸ in 1925 and by Schlittler⁹ in 1949. In the latter case, the compound was an intermediate in the synthesis of an aporphine alkaloid by a modified Bischler-Napieralski reaction, but was obtained in unspecified yield.

The work in the preceding paper indicated the possibility of using our new mild and high yield route to isoquinolines for the syntheses of these two alkaloids. As in our earlier curarine synthesis¹⁰ insertion of a benzylic substituent at the 1-position of the isoquinoline system was required. Although this could be achieved through a Reissert compound from the appropriate isoquinoline and a benzyl halide,^{10,11} a more efficient alternative lay, in theory, in the addition¹² of a Grignard reagent to the Schiff's base prior to the isoquinoline cyclisation. In a model experiment benzylmagnesium chloride (prepared from benzyl alcohol) was added to 3,4-methylenedioxybenzylideneaminoacetaldehyde dimethyl acetal (3) to form 1-(3,4-methylenedioxyphenyl)-2-phenylethylaminoacetaldehyde dimethyl acetal (4; R¹ = R² = H), in very good yield. Treatment of the latter with toluene-*p*-sulphonyl chloride in dry pyridine gave the tosylate (4;

R¹ = H, R² = Ts) in high yield, which on refluxing in dilute hydrochloric acid in dioxan gave 1-benzyl-6,7-methylenedioxy-2-tosyl-1,2-dihydroisoquinoline (5; R = H) (85%). *trans*-6,7-Methylenedioxy-stilbene (6) was also formed in low yield, presumably as a result of competitive protonation and elimination of the sulphonamide group. The dihydroisoquinoline (5; R = H) isolated as an oil, did not give a molecular ion but gave the expected M⁺ - 91 fragment ion at *m/e* 328.064 (C₁₇H₁₄NO₄S) and showed in its n.n.r. spectrum the C-3 olefinic proton as a doublet at τ 3.45 (*J* 8 Hz) together with the C-4 proton doublet [τ 4.2 (*J* 8 Hz)] and 5- and 8-aromatic proton singlets (τ 3.62 and 4.15). Attempted detosylation of (5; R = H) by strong base failed, presumably due to the steric and/or electronic effects of the benzyl substituent, but conversion into the desired isoquinoline (7; R = H) was achieved by treatment with stronger acid than was used in the original cyclisation of (4; R¹ = H, R² = Ts) to (5; R = H). An appreciable amount (20%) of 6,7-methylenedioxyisoquinoline (see preceding paper), formed by loss of the 1-benzyl substituent in preference to the



proton, was also obtained. Both takatonine and escholamine contain 1-alkoxybenzyl substituents so a more appropriate experiment was the addition of the 4-methoxybenzyl group to the Schiff's base (3). Initially

³ E. Fujita and T. Tomimatsu, *J. Pharm. Soc. Japan*, 1959, **79**, 1082.

⁴ L. Slavikova and J. Slavik, *Coll. Czech. Chem. Comm.*, 1966, **31**, 3362.

⁵ S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, 1966, **31**, 516.

⁶ H. Furukawa, T.-H. Yang, and T. J. Lin, *J. Pharm. Soc. Japan*, 1965, **85**, 472.

⁷ J. Kunitome, E. Yuge, and Y. Nagai, *J. Pharm. Soc. Japan*, 1966, **86**, 456.

⁸ J. S. Buck, W. H. Perkin, and T. S. Stevens, *J. Chem. Soc.*, 1925, 1462.

⁹ E. Schlittler and A. Lindenmann, *Helv. Chim. Acta*, 1949, **32**, 1881.

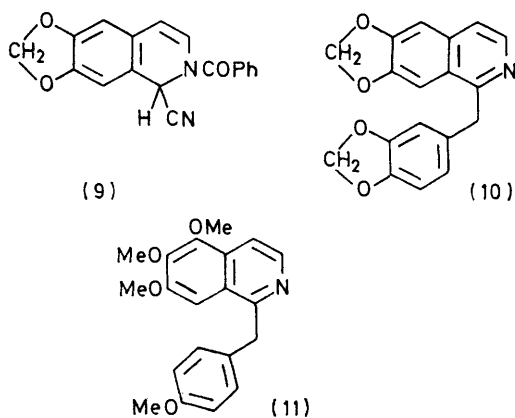
¹⁰ A. H. Jackson and G. W. Stewart, *Chem. Comm.*, 1971, 149; S. A. Charnock, A. H. Jackson, J. A. Martin, and G. W. Stewart, *J.C.S. Perkin I*, 1974, 1911.

¹¹ B. C. Uff and J. R. Kershaw, *J. Chem. Soc. (C)*, 1969, 666.

¹² R. B. Moffett and W. M. Hoehn, *J. Amer. Chem. Soc.*, 1947, **69**, 1792.

attempts to prepare the corresponding Grignard reagent failed, the main isolable product presumably being 1,2-bis-*p*-methoxyphenylethane (8), formed by ready reaction of the reagent with unchanged benzyl halide in preference to its attack on the Schiff's base. However, by use of a twenty molar excess of magnesium, 4-methoxybenzylmagnesium chloride was successfully prepared,¹³ and addition to the Schiff's base (3) then gave 1-(3,4-methylenedioxyphenyl)-2-(4-methoxyphenyl)ethylaminoacetaldehyde dimethyl acetal (4; R¹ = OMe, R² = H) as a yellow oil. This was converted into the oily tosylate (4; R¹ = OMe, R² = Ts) and cyclisation under the usual dilute acid conditions then gave 1-(4-methoxybenzyl)-6,7-methylenedioxy-2-tosyl-1,2-dihydroisoquinoline (5; R = OMe); no detosylation was observed under these conditions. When (5; R = OMe) was boiled under reflux in a stronger hydrochloric acid-dioxan mixture (2*N*) the required 1-(4-methoxybenzyl)-6,7-methylenedioxyisoquinoline (7; R = OMe) was produced in low yields and the major product was 6,7-methylenedioxyisoquinoline (16%); presumably the extra stability of the 4-methoxybenzyl fragment is responsible for the reversal in product distribution when compared with the benzyl analogue.

The difficulty in the preparation of reactive Grignard reagents, and the enhanced tendency for loss of the 1-substituent during detosylation suggested that a more promising approach to alkaloids like escholamine and takatonine would use the Reissert procedure for the isoquinoline unsubstituted in the 1-position as a basis for *substituent* 1-substitution *via* the Reissert compounds. Accordingly 6,7-methylenedioxyisoquinoline was synthesised as described in the preceding paper, and treatment with benzoyl chloride and potassium cyanide gave 2-benzoyl-1-cyano-6,7-methylenedioxy-1,2-dihydroisoquinoline (9).¹⁴ 3,4-Methylenedioxybenzyl chloride



(from piperonal) reacted smoothly with the anion of (9) (formed with sodium hydride in dimethylformamide), and alkaline decomposition of the cyano-intermediate afforded 6,7-methylenedioxyisoquinoline-1-(3,4-methylenedioxybenzyl)isoquinoline (10). Escholamine (2) was characterised as the methiodide salt, m.p. 266–267°, in 60.5%

¹³ R. C. Elderfield and V. B. Meyer, *J. Amer. Chem. Soc.*, 1954, **76**, 1883.

¹⁴ S. F. Dyke and A. C. Ellis, *Tetrahedron*, 1972, **28**, 3999.

yield from the starting isoquinoline. This procedure is likely to give improved yields as a result of a recent¹⁵ alternative method of decomposing the Reissert intermediate. By an analogous sequence of reactions 5,6,7-trimethoxyisoquinoline¹⁶ afforded the free base (11) as a brown oil. Treatment with methyl iodide then gave takatonine (1) in 75% overall yield from the 1-unsubstituted isoquinoline.

The addition of Grignard reagents to an appropriate Schiff's base, prior to *N*-tosylation and dilute acid-catalysed cyclisation, seems to be an efficient route to simple 1-benzylisoquinolines, but not to the related alkoxybenzyl compounds. In the latter cases, preparation of the appropriate isoquinoline followed by benzylation of its Reissert derivative leads to a highly efficient overall synthesis. This is exemplified by the above synthesis of takatonine free base in 59% overall yield from 3,4,5-trimethoxybenzaldehyde.

EXPERIMENTAL

N.m.r. spectra were measured at 100 MHz on a Perkin-Elmer R.14 spectrometer in CDCl₃ unless stated otherwise; u.v. spectra were determined in spectroscopic grade ethanol on a Unicam SP 800 spectrophotometer and i.r. spectra on a Unicam SP 200G grating i.r. spectrometer. Mass spectra were obtained at 70 eV on a Varian CH5-D instrument fitted with a Varian 620i data system and Statos 21 fast printer. M.p.s were corrected. Petroleum refers to that of boiling range 40–60°.

1-(3,4-Methylenedioxyphenyl)-2-phenylethylaminoacetaldehyde Dimethyl Acetal (4; R¹ = R² = H).—Magnesium turnings (1.83 g, 0.075 mol) were added to dry ether (50 ml) and benzyl chloride (9.5 g, 0.075 mol) in ether (30 ml) was added slowly under nitrogen after initiation of the reaction with iodine (0.5 g). The solution was stirred for 15 min and heated under reflux for 0.5 h. 3,4-Methylenedioxybenzylideneaminoacetaldehyde dimethyl acetal (7.14 g, 0.03 mol) in ether (50 ml) was then added dropwise to the stirred solution. A transitory red colouration occurred and after refluxing for 1 h the solution was cooled and the Grignard complex destroyed with saturated ammonium chloride. The ether layer was separated and the solid residue washed with ether (50 ml). The ether extracts were combined, washed with water (2 × 50 ml), dried, and the ether removed under vacuum to yield the required amine as a yellow oil (9.3 g, 90%), τ 2.78, 3.10, and 3.28 (8H, m, ArH), 4.08 (2H, s, OCH₂O), 5.63 (1H, t, *J* 6 Hz, CHOMe), 6.23 (1H, t, *J* 7 Hz, CHN), 6.75 (6H, s, OMe), 7.10 (2H, d, *J* 7 Hz, CH₂Ar), 7.43 (2H, d, *J* 6 Hz, CH₂N), and 8.33 (1H, s, NH), ν_{\max} 3330 (NH) cm⁻¹; 3,5-dinitrobenzoyl derivative, m.p. 126–127° (Found: C, 59.7; H, 5.0; N, 7.95. C₁₉H₂₃NO₄ requires C, 59.6; H, 4.8; N, 8.05%).

N-[1-(3,4-Methylenedioxyphenyl)-2-phenylethyl]-*N*-tosylaminoacetaldehyde Dimethyl Acetal (4; R¹ = H, R² = Ts).—The dimethyl acetal (4; R¹ = R² = H) (5.1 g, 0.015 mol) was dissolved in dry pyridine (25 ml) and toluene-*p*-sulphonyl chloride (2.9 g, 0.016 mol) was added. The solution was stirred at 20° for 2 days and poured into water (100 ml). The aqueous solution was extracted with ether

¹⁵ S. F. Dyke, A. W. C. White, and D. Hartley, *Tetrahedron*, 1973, **29**, 857.

¹⁶ M. P. Cava and M. V. Lakshmikantham, *J. Org. Chem.*, 1970, **35**, 1867.

(3 × 75 ml) and the ether extract washed with 0.5M-hydrochloric acid (2 × 75 ml), water (2 × 75 ml), dried, and the solvent removed under vacuum to yield a dark brown oil. Chromatography on grade V alumina and elution with petroleum-ether (1:4) yielded the *tosylate* (4; R¹ = H, R² = Ts) as a light yellow oil (5 g, 68%) which crystallised, m.p. 90–90.5°, τ 2.43, 2.80–2.90, and 3.41 (12H, ArH), 4.20 (2H, s, OCH₂O), 4.9 and 5.65 (2H, 2m, CHN, CH–O), 6.65 (4H, m, CH₂N, CH₂Ar), 6.74 (6H, s, OMe), and 7.64 (3H, s, ArMe) (Found: *M* – 91, 392.116. C₁₈H₂₂NO₆S requires *m/e* 392.116), *M*⁺ 483 by field-ionisation mass spectrometry.

1-Benzyl-6,7-methylenedioxy-2-tosyl-1,2-dihydroisoquinoline (5; R = H).—The *tosylate* (4; R¹ = H, R² = Ts) (1.3 g) in dioxan (31.5 ml) and 6M-hydrochloric acid (2.4 ml) was heated under reflux in an atmosphere of nitrogen overnight, and the solution was poured into water (100 ml) and extracted with ether (3 × 50 ml). The ether was washed with water (2 × 50 ml), dried, and solvent removed under vacuum to yield the crude dihydroisoquinoline (5; R = H) as a yellow foamy oil (85%). Chromatography on grade V alumina and elution with petroleum-ether (3:2) yielded first the *dihydroisoquinoline* (5; R = H) as an oil, τ 2.50 and 2.80–3.20 (5H, ArH), 3.45 (1H, d, *J* 8 Hz, 3-H), 3.62 (1H, s, 8-H), 4.15 (1H, s, 5-H), 4.20 (1H, d, *J* 8 Hz, 4-H), 4.26 (2H, s, OCH₂O), 4.91 (1H, t, *J* 7 Hz, CH), 7.09 (2H, d, *J* 7 Hz, CH₂), and 7.74 (3H, s, ArMe), λ_{max} 316 (ε 10,500), 244 (11,500), and 224 nm (27,800) [Found: *M* – 91, 328.064 (100%). C₁₇H₁₄NO₄ requires *m/e* 328.064]. *trans*-3,4-Methylenedioxy-stilbene (6) was eluted second as a white solid (5%), m.p. 92–93° (lit.¹⁷ 93–94°), *M*⁺ 244, τ 2.60–3.30 (10H, m, ArH, CH=CH) and 4.11 (2H, s, OCH₂O), ν_{max} 1488 and 1515 (C=C) cm⁻¹.

1-Benzyl-6,7-methylenedioxyisoquinoline (7; R = H).—The foregoing *N*-tosyl-dihydroisoquinoline (5; R = H) (40 mg) was dissolved in 15 ml of a solution of potassium (1 g) in *t*-butyl alcohol (150 ml) and the solution was heated under reflux for 8 h. No reaction was observed. Similarly no reaction occurred with a solution of sodium (1 g) in methanol (150 ml) or with sodium hydride in ether. A solution of (5; R = H) (240 mg) in ethanol (18 ml) and concentrated hydrochloric acid (18 ml) was heated under reflux for 5 h and then poured into water (130 ml). The solution was extracted with ether (3 × 50 ml) and the aqueous phase made alkaline with ammonium hydroxide solution before re-extraction with ether (3 × 50 ml). After drying and removal of solvent under vacuum the second extract gave a brown oil (120 mg) for which t.l.c. showed two components. P.l.c., eluting with petroleum-ether (3:2), gave 6,7-methylenedioxyisoquinoline (18 mg), m.p. 118–119° (lit.¹⁸ 124°) and the required 1-benzyl-6,7-methylenedioxyisoquinoline (80 mg, 55%) as a white solid, m.p. 89–90° (lit.¹⁹ 94°), τ 1.72 (1H, d, *J* 5 Hz, 3-H), 2.86 (8H, m, ArH), 4.14 (2H, s, OCH₂O), and 5.52 (2H, s, CH₂), λ_{max} 334 (ε 4300), 317 (3830), 291 (3070), 270 (3860), and 240 nm (36,800) (Found: *M*⁺, 263.092. Calc. for C₁₇H₁₃NO₂: *M*, 263.094); picrate, m.p. 200–205°.

4-Methoxybenzyl Chloride.—4-Methoxybenzyl alcohol (31 g, 0.02 mol) in dry benzene (330 ml) was cooled to 0°. Dry hydrogen chloride gas was passed through the solution for 6 h until no more absorption occurred. The water formed was separated and the green solution dried (CaCl₂). The benzene then removed under reduced pressure to give a green

oil (21 g, 80%), b.p. 91° at 32 mmHg (lit.²⁰ 95° at 5 mmHg), τ 2.80 (2H, d, *J* 9 Hz, ArH), 3.22 (2H, d, *J* 9 Hz, ArH), and 5.50 (2H, s, OMe).

2-(4-Methoxyphenyl)-1-(3,4-methylenedioxyphenyl)ethyl-aminoacetaldehyde Dimethyl Acetal (4; R¹ = OMe, R² = H).—Magnesium turnings (5.65 g) in dry ether (25 ml) were stirred under dry nitrogen and 4-methoxybenzyl chloride (0.4 g) was added. The reaction was initiated with iodine and heated under reflux for 10 min. 4-Methoxybenzyl chloride (1.42 g) in ether (11 ml) was added over 1.5 h and the solution was heated under reflux for a further 0.75 h. The ether layer was decanted and 3,4-methylenedioxybenzylideneaminoacetaldehyde dimethyl acetal (0.71 g) added over 15 min under nitrogen before the solution was again heated under reflux for 1 h. The Grignard complex was destroyed with ammonium chloride solution and the ether layer decanted. The residue was washed with ether (2 × 40 ml), the combined extracts were dried, and removal of solvent gave the crude amine as a yellow oil. Chromatography on 'H' grade V alumina and elution with petroleum-ether (2:3) yielded the amine (4; R¹ = OMe, R² = H) as an oil (0.92 g, 90%), τ 3.05 and 3.38 (4H, 2d, *J* 8 Hz, *p*-MeOC₆H₄), 3.30 (3H, m, ArH), 5.68 (1H, d, *J* 6 Hz, CHN), 6.30 (3H, s, ArOMe), 6.34 (1H, t, *J* 7 Hz, CHOMe), 6.80 (6H, s, OMe), 7.23 (2H, d, *J* 7 Hz, CH₂N), 7.50 (2H, d, *J* 6 Hz, ArCH₂), and 8.30 (1H, s, NH); 3,5-dinitrobenzoyl derivative, m.p. 139–140° (Found: C, 58.3; H, 5.0; N, 7.4. C₂₀H₂₅NO₃ requires C, 58.6; H, 4.9; N, 7.5%).

N-[2-(4-Methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-ethyl]-*N*-tosylaminoacetaldehyde Dimethyl Acetal (4; R¹ = OMe, R² = Ts).—Toluene-*p*-sulphonyl chloride (290 mg) was added to the foregoing amine (4; R¹ = OMe, R² = H) (540 mg) in dry pyridine (5 ml). The solution was stirred at 20° for 2 days and worked up in the usual way. Chromatography on 'H' grade V alumina and elution with petroleum-ether (1:1) gave the *tosylate* (4; R¹ = OMe, R² = Ts) as a yellow oil (300 mg, 45%), τ 2.40 and 2.80 (4H, 2d, *J* 8 Hz, ArH) 2.98 and 3.30 (4H, 2d, *J* 8 Hz, ArH), 3.27 (3H, m, ArH), 4.10 (2H, s, OCH₂O), 4.92 (1H, m, CHN), 5.62 (1H, m, CHOMe), 6.30 (3H, s, ArOMe), 6.72 (2H, obscured, CH₂Ar), 6.72 (3H, s, OMe), 6.78 (3H, s, OMe), 6.76 (2H, obscured, CH₂N), and 7.68 (3H, s, ArMe), λ_{max} 334 (ε 10,400) and 228 nm (29,200). The *tosylate* was used without further purification.

1-(4-Methoxybenzyl)-6,7-methylenedioxy-2-tosyl-1,2-dihydroisoquinoline (5; R = OMe).—To the foregoing *tosylate* (4; R¹ = OMe, R² = Ts) (150 mg) in dioxan (3.8 ml), 6M-hydrochloric acid (0.5 ml) was added under nitrogen in the dark. The solution was heated under reflux for 1.5 h and worked up as for the previous cyclisation to yield a yellow foam, which crystallised (90 mg). Recrystallisation from ethanol-water gave the *dihydroisoquinoline* (5; R = OMe), m.p. 96–98°, τ 2.50 and 2.94 (4H, 2d, *J* 8 Hz, ArH), 3.7 and 4.19 (8H, 2m, ArH, OCH₂O), 4.99 (1H, t, *J* 7 Hz, CH), 6.30 (3H, s, MeO), 6.16 (2H, d, *J* 7 Hz, CH₂), and 7.76 (3H, s, ArMe), λ_{max} 318 (ε 10,800) and 228 nm (29,500) (Found: C, 66.5; H, 5.05; N, 3.15. C₂₅H₂₅NO₅S requires C, 66.8; H, 5.15; N, 3.1%).

1-(4-Methoxybenzyl)-6,7-methylenedioxyisoquinoline (7; R = OMe).—To the foregoing 1,2-dihydroisoquinoline (5; R = OMe) (3 g) in dioxan (40 ml) was added 6M-hydrochloric acid (20 ml). The solution was heated under reflux

¹⁷ B. H. Alexander and W. F. Barthel, *J. Org. Chem.*, 1958, **23**, 389.

¹⁸ B. Fritsch, *Annalen*, 1895, **1**, 286.

¹⁹ C. Mannich and O. Walther, *Arch. Pharm.*, 1927, **265**, 1.

²⁰ M. Sommelet and I. Marszak, *Compt. rend.*, 1934, **198**, 2256.

for 5 h, poured into water (200 ml), and extracted with ether (3 × 60 ml). The aqueous layer was made alkaline with ammonia and re-extracted with ether (3 × 60 ml). The second extract was washed with water (3 × 50 ml), dried, and solvent removed under vacuum to yield a yellow oil (410 mg). P.l.c., eluting with petroleum-ether (1:1), then yielded 6,7-methylenedioxyisoquinoline¹⁸ (25 mg) and 1-(4-methoxybenzyl)-6,7-methylenedioxyisoquinoline (11 mg). Repeating the experiment using the unchanged dihydroisoquinoline (5; R = OMe) from the first ether extraction (2 g), several times, gave the required *isoquinoline* (7; R = OMe) (4%), m.p. 120–120.5°, τ 1.67 (1H, d, *J* 5 Hz, 3-H), 2.30 (7H, m, ArH), 4.00 (2H, s, OCH₂O), 5.56 (2H, s, CH₂), and 6.28 (3H, s, MeO), λ_{\max} 330 (ϵ 3910), 317 (3180), 287 (4480), 275 (6350), 275 (6100), and 240 nm (34,200) (Found: C, 73.3; H, 4.6; N, 4.9%; M^+ , 293.103. C₁₈H₁₅NO₃ requires C, 73.7; H, 5.15; N, 4.8%, M , 293.105).

3,4-Methylenedioxybenzyl Chloride.—Piperonal (15 g) was dissolved in 25% aqueous methanol (400 ml) and sodium borohydride (4 g) in water (50 ml) and 2M-sodium hydroxide (3 ml) was added slowly. The solution was stirred for 2 h, acidified with 2M-hydrochloric acid, and the methanol removed under vacuum. The aqueous layer was extracted with ether (3 × 200 ml), the ether extracts were dried, and solvent was removed to give the alcohol as a solid which crystallised from petroleum (11 g), m.p. 51–52° (lit.,²¹ 52–53°), τ 3.17 (3H, m, ArH), 4.05 (2H, s, OCH₂O), and 5.46 (2H, s, CH₂), ν_{\max} 3300 (OH) cm⁻¹. 3,4-Methylenedioxybenzyl alcohol (11 g) in dry ether (200 ml) was stirred vigorously and thionyl chloride (24 g) was added over 15 min. The solution was stirred for 2 h and solvents and excess of thionyl chloride were removed to yield a black oil which on distillation under reduced pressure gave the chloride as an unstable oil (9 g, 72%), b.p. 91–94° at 2 mmHg.

2-Benzoyl-1-cyano-6,7-methylenedioxy-1,2-dihydroisoquinoline (9).—6,7-Methylenedioxyisoquinoline (6.6 g) was dissolved in methylene chloride (140 ml) and a solution of potassium cyanide (18 g) in water (80 ml) was added. Benzoyl chloride (freshly distilled; 18 g) was added over 0.5 h under nitrogen at 20°. The solution was kept for 1 h and potassium cyanide (9 g) in water (40 ml) was added. After a further 4 h the methylene chloride was separated, washed with water (2 × 200 ml), 2M-hydrochloric acid (200 ml), 1M-sodium hydroxide (200 ml), water (2 × 100 ml), and dried. Removal of solvent yielded the Reissert compound (9) as a brown solid which crystallised from methanol as a colourless solid (10.7 g, 93%), m.p. 134–135° (lit.,¹⁴ 137–138°), τ 2.42, 3.15, and 3.47 (8H, 3m, ArH) and 3.96 (2H, s, OCH₂O) (Found: C, 71.1; H, 4.1; N, 8.9. Calc. for C₁₈H₁₂N₂O₃: C, 71.0; H, 4.0; N, 9.2%).

6,7-Methylenedioxy-1-(3,4-methylenedioxybenzyl)isoquinoline (10).—Sodium hydride (1.1 g of a 50% suspension in oil) was washed with petroleum and suspended in dimethylformamide (50 ml). The foregoing Reissert compound (9) (6.02 g) in dimethylformamide (50 ml) was added over 10 min at –10° under nitrogen. The dark red solution was

left for 10 min and 3,4-methylenedioxybenzyl chloride (3.8 g) in dimethylformamide (40 ml) was added over 20 min at –10°. The resulting solution was stirred at 0° for 2 h and left at 20° overnight. Excess of sodium hydride was destroyed with ethanol and the solvents were removed. The residue was dissolved in benzene (300 ml), washed with water (2 × 100 ml), and the benzene was removed and the residue dissolved in ethanol (200 ml). Sodium hydroxide (55 g) in water (80 ml) was added and the solution heated under reflux for 4 h. The ethanol layer was separated, the aqueous layer extracted with benzene (2 × 100 ml), and the organic extracts combined and evaporated under vacuum. The residue was redissolved in benzene (200 ml), washed with water (2 × 100 ml), dried, and the solvent removed to yield the crude isoquinoline (10) as a brown oil which crystallised from petroleum-ether as needles, m.p. 168–169° (lit.,⁸ 170–172°, lit.,⁹ 168–170°), τ 1.72 (1H, d, *J* 6 Hz, 3-H), 2.68 (1H, d, *J* 6 Hz, 4-H), 2.70, 3.00, 3.32, and 4.00 (6H, 4s, ArH), 4.18 (2H, s, OCH₂O), and 5.60 (2H, s, CH₂), λ_{\max} 331 (ϵ 7450), 317 (596), 290 (1010), 284 (1010), 274 (8450), and 239 nm (68,200), M^+ 307.

Escholamine Methiodide (2b).—The isoquinoline (10) (300 mg) in methanol (9 ml) was treated with methyl iodide (5 ml). The solution was heated under reflux for 2.5 h and the solvent was removed to yield a brown solid which crystallised from ethanol giving the methiodide, m.p. 266–267° (lit.,² 265–266°), τ 1.40 (1H, d, *J* 6 Hz, 3-H), 1.75 (1H, d, *J* 6 Hz, 4-H), 1.95, 2.30, 3.20 and 3.60 (5H, 4s, ArH), 4.10 (2H, s, OCH₂O), 5.08 (2H, s, CH₂), and 5.67 (3H, s, NMe) (Found: C, 50.8; H, 3.5; N, 3.5. Calc. for C₁₉H₁₆INO₄: C, 50.8; H, 3.6; N, 3.1%).

2-Benzoyl-1-cyano-5,6,7-trimethoxy-1,2-dihydroisoquinoline.—This Reissert compound was formed from 5,6,7-trimethoxyisoquinoline (8 g) as in the previous experiment. The product was isolated as a solid which recrystallised from methanol (11.2 g, 93%), m.p. 166–167° (lit.,¹⁶ 165°), τ 2.50, 3.38, 3.57, and 3.68 (8H, m, s, s, d, *J* 8 Hz, ArH) and 6.16 (9H, s, OMe) (Found: C, 68.2; H, 5.2; N, 7.9. Calc. for C₂₀H₁₈N₂O₄: C, 68.6; H, 5.2; N, 8.0%).

Takatonine (1).—The foregoing isoquinoline (280 mg) was heated under reflux in methanol (9 ml) and methyl iodide (5 ml) for 2.5 h. Removal of solvent yielded a bright yellow solid which crystallised from methanol-benzene, m.p. 178–180° (lit.,³ 181–182°), τ 1.18 (1H, d, *J* 7 Hz, 3-H), 1.74 (1H, d, *J* 7 Hz, 4-H), 2.58 (1H, s, ArH), 2.98 and 3.23 (4H, 2d, *J* 9 Hz, *p*-MeOC₆H₄), 4.89 (2H, s, CH₂), 5.40 (3H, s, NMe), and 5.89, 5.92, 5.99, and 6.27 (12H, 4s, 4 × OMe) (Found: C, 52.7; H, 5.2; N, 2.9. Calc. for C₂₁H₂₄INO₄: C, 52.4; H, 5.0; N, 2.9%).

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²¹ W. H. Carothers and R. Adams, *J. Amer. Chem. Soc.*, 1924, **46**, 1675.