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1,2-DIHYDROISOQUINOLINES—XVI[1]

INDENO[1,2-*c*]ISOQUINOLINE DERIVATIVES

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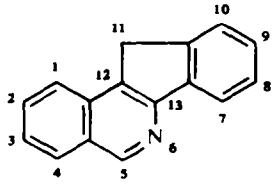
Abstract—The preparation of indeno[1,2-*c*]isoquinolines by three methods is described, and some earlier literature concerning the cyclization of 2-methyl-4-benzyl-1,2-dihydroisoquinolines corrected.

RECENTLY, in a re-investigation of some of Perkin's work[2] with the alkaloid cryptopine, we[3] showed that epicryptopirubin chloride is a derivative of 11*H*-indeno [1.2-*c*]isoquinoline (**1**), and during attempts to synthesise some benzo[*c*]phenanthrides, we[4] described a further example of this ring-system. The only other reports concerning indeno[1.2-*c*]isoquinoline derivatives are those of Chatterjea and Mukherjee[5] and of Wawzonek *et al.*[6] Since isocoumarins are easily converted into isocarbostyrils,[7] the closely related indeno[1.2-*c*]isocoumarins[7, 8] can be regarded as synthetic precursors of derivatives of **1**.



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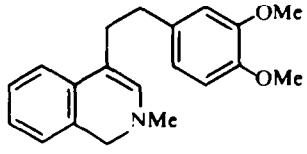

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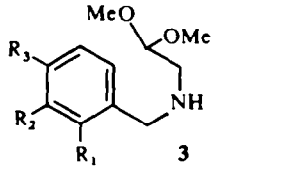
In view of our interest in indeno[1.2-*c*]isoquinolines, and of our considerable interest in 4-benzylisoquinolines,[9] we were intrigued by the report[10] that certain 2-methyl-4-benzyl-1,2-dihydroisoquinolines are cyclized to 5,6,12,13-11*H*-tetrahydroindeno[1.2-*c*]isoquinolines by acids, especially since we[11] had found that the 2-methyl-4-[β-arylethyl]-1,2-dihydroisoquinoline (**2**) undergoes disproportionation, and not ring-closure under similar conditions. Gensler *et al.*[10] reported that acid-catalysed condensation of **3**, ($R_1 = R_2 = OMe$; $R_3 = H$) with piperonal initially gave a compound formulated as **4**, in agreement with our[12] previous suggestion, and that this was converted by alkali into the 4-benzylisoquinoline **5**; hydrochloride m.p. 100–102°). A small amount of the 11-*H*-indeno[1.2-*c*]isoquinoline (**6**, $R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$) was also isolated. Gensler's structural assignments were based essentially upon NMR evidence. The methiodide of **5** was reduced with LAH to the stable 1,2-dihydroisoquinoline (**7**), which was then treated with a HCl/acetic acid mixture. The product, an oil, was allocated[10] structure **8** (R = H) on the basis of spectral data and the dehydrogenation of it with iodine to a quaternary

iodide, said to be identical with **9**, the methiodide of **6** ($R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$).

In our hands,[13] the condensation of **3** ($R_1 = R_2 = OMe$; $R_3 = H$) with piperonal gave a small amount of the hydrochloride of **6** ($R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$) as described by Gensler *et al.*, but the major product, a hydrochloride m.p. 100–102°, was found[14] to be **10** ($R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$), which is easily isomerised by base to **5**, methiodide m.p. 178–180°. When the 1,2-dihydroisoquinoline (**7**) was treated with HCl/acetic acid as previously[10] described, disproportionation, and not ring-closure, occurred. The two products, isolated in almost equal amounts, were shown to be the metho salt of **5** and the 1,2,3,4-tetrahydroisoquinoline (**11**). The latter substance, an oil, was characterized as the methiodide, an authentic sample of which was obtained by the catalytic reduction of **7** followed by treatment with methyl iodide. An authentic sample of **8** (R = H; a solid m.p. 156–157°) was prepared by reducing **9** with $NaBH_4$, and it was found not to be identical with the base obtained by treating **7** with acids.



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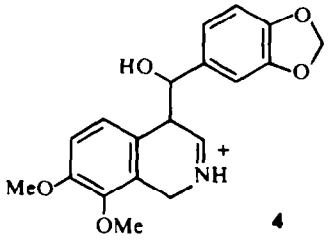

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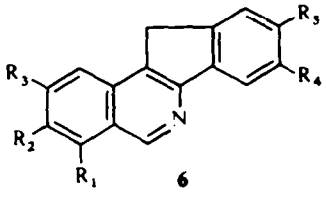

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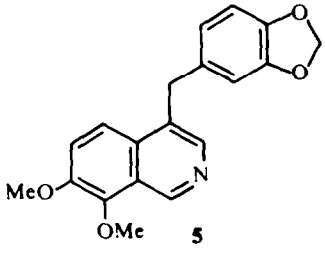

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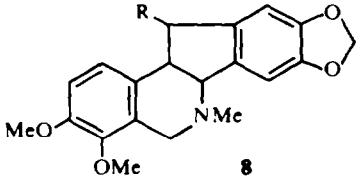

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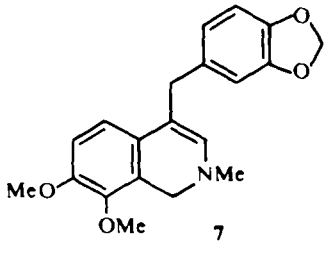

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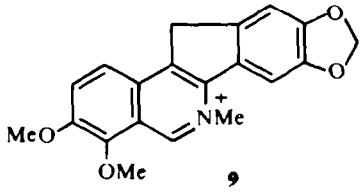
An analogous sequence of reactions has been conducted by us with **3** ($R_1 = H$; $R_2 = R_3 = OMe$) and piperonal. The indenoisoquinoline (**6**, $R_1 = H$; $R_2 = R_3 = OMe$; $R_4 + R_5 = CH_2O_2$) was obtained, in very small yield, but again the major product was the exocyclic compound **10** ($R_1 = H$; $R_2 = R_3 = OMe$; $R_4 + R_5 =$

CH_2O_2). When the aminoacetal **3** (R_1 = H; R_2 = R_3 = OMe) was condensed with veratraldehyde under slightly different conditions (Experimental) the 11*H*-indeno [1.2-*c*]isoquinoline (**6**, R_1 = H; R_2 = R_3 = R_4 = R_5 = OMe) was isolated easily in 21% yield. When piperonal and **3** (R_1 = H; R_2 = R_3 = OMe) were condensed under these same conditions **6** (R_1 = H; R_2 = R_3 = OMe; R_4 + R_5 = CH_2O_2) was recovered in 17% yield. In another variation of this potentially useful reaction, the



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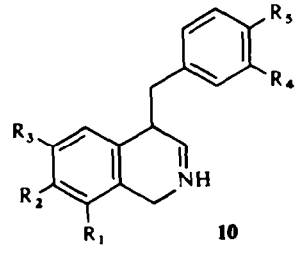

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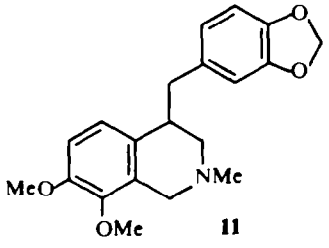

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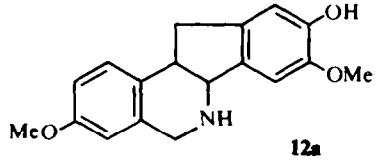
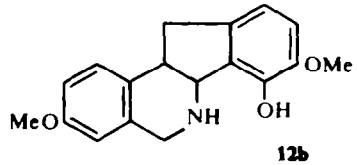


12a



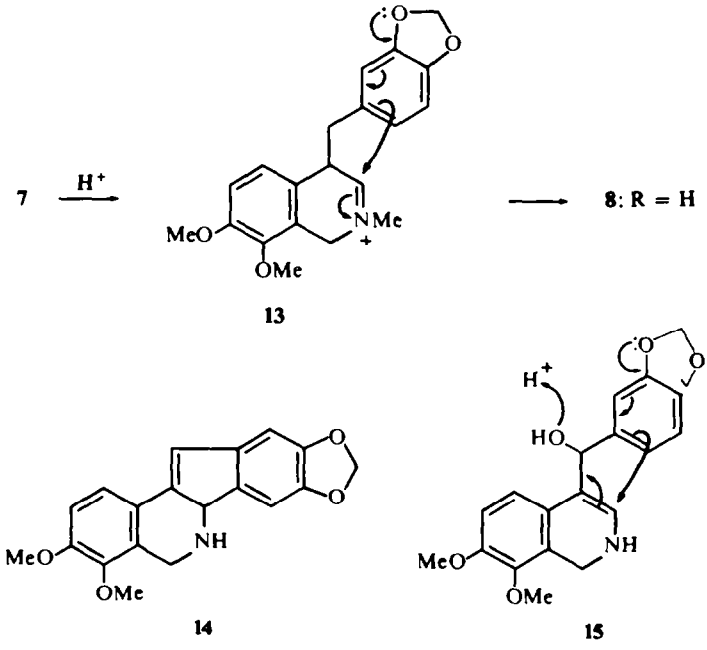
12b

compound **10** (R_1 = R_3 = H; R_2 = R_5 = OMe; R_4 = OH), obtained by condensing isovanillin with *m*-methoxybenzylaminoacetal (**3**, R_1 = R_3 = H; R_2 = OMe), was hydrogenated in glacial acetic acid solution, using Pd/C as catalyst. The product, isolated in 58% yield, proved to be the tetrahydroindeno[1.2-*c*]isoquinoline (**12a**) or (**12b**), and not the expected 1,2,3,4-tetrahydroisoquinoline. The formation of **12** probably involves initial attack by the relatively highly nucleophilic aromatic ring of **10** (R_1 = R_3 = H; R_2 = R_5 = OMe; R_4 = OH) *para* or *ortho* to the OH group at C_3 on the 1,4-dihydroisoquinolinium ring, followed by reduction of the stilbenoid double bond.

The structures of the 11*H*-indenoisoquinolines (**6**) were established by their characteristic UV, NMR and mass spectra.

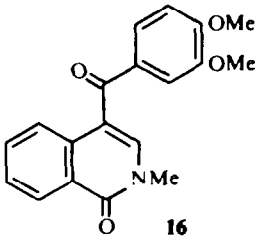
The cyclization of 4-benzyl-1,2-dihydroisoquinolines such as **7** to **8** (R = H) is most easily explained by protonation at C_4 to give the 1,4-dihydroisoquinolinium salt (**13**), followed by nucleophilic attack at C_3 by the aromatic ring of the C_4-substituent. For 1,2-dihydroisoquinolines that lack a C_4-substituent, such a protonation occurs as the

initial step as required for pavine[15] or berbine[16] formation, or rearrangement.[17] However, in a 4-benzyl-1,2-dihydroisoquinoline, it is likely that protonation occurs predominantly at nitrogen, leading to disproportionation. The formation of **6** (R_1 = R_2 = OMe; R_3 = H; R_4 + R_5 = CH_2O_2) in the original condensation of **3** (R_1 = R_2 = OMe; R_3 = H) with piperonal is easily understood because the first-formed product (**4**) already possesses the imminium ion structure required for cyclization; both dehydration to **10** (R_1 = R_2 = OMe; R_3 = H; R_4 + R_5 = CH_2O_2) and cyclization to **8** (R = OH) can then occur. Dehydration of the latter to **14** followed by isomerization and aerial oxidation completes the formation of the 11*H*-indeno [1.2-*c*]isoquinoline. A precedent for the last step already exists.[3] We were unable to cyclise **10** (R_1 = R_2 = OMe; R_3 = H; R_4 + R_5 = CH_2O_2) to **14** and thence to **6** (R_1 = R_2 = OMe; R_3 = H; R_4 + R_5 = CH_2O_2) under a variety of conditions of acid treatment, but another sequence to explain the latter's formation might involve the conversion of **4** to **15**, followed by elimination of water to give **14** and eventual oxidation to **6** as before.



We have been able to devise a new synthesis of the indeno[1.2-*c*]isoquinoline ring system based upon this last hypothesis. The 4-acylisocarbostyril[18] (**16**) was reduced with $NaBH_4$ to the alcohol (**17**, R = H; Z = O), and the derived ethyl ether (**17**, R = OEt; Z = O) was reacted with an ethanolic solution of HCl. A new, neutral compound, isolated in 88% yield, was shown by mass spectral analysis to be $C_{19}H_{17}NO_3$. The NMR spectrum of this material was found to be characteristic of the expected structure **18**. The alcohol **17** (R = H; Z = O) also cyclised to **18**, though somewhat

less readily. When an attempt was made to reduce **16** to **17** (R = H; Z = 2H) with LAH, the product was the 4-benzylidene-1,2-3,4-tetrahydroisoquinoline (**19**).



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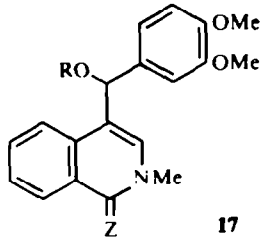

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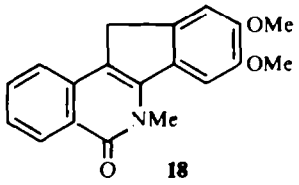

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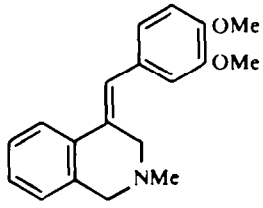

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EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined in EtOH soln. IR spectra were recorded as Nujol mulls and chemical shifts are expressed in ppm downfield from TMS as an internal standard.

3,4-*Dimethoxy*-8,9-*methylenedioxy*-11H-*indeno*[1.2-c]*isoquinoline* (**6**, $R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$)

Piperonal (3 g) in EtOH (15 ml) was added to 2,3-dimethoxybenzylacetaldehydedimethylaminoacetal (2·85 g) in conc HCl (15 ml). After heating at reflux for 30 min and cooling overnight, red crystals separated (2·0). A sample of this material was recrystallized from EtOH to yield **10** ($R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$) as prisms m.p. 100–102°.

The remainder of the crude product was stirred in water and the pH raised to > 10 by the addition of 30% KOH aq. After 1 hr the product was collected and heated with EtOH; the bulk of the solid readily dissolved, but some (~5%) remained insoluble. This was filtered off and recrystallized from pyridine to give **6** ($R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$) m.p. 242–243° (lit.,[10] 242–243·5, λ_{max} (ε) nm, 236 (35,000), 337 (24,000). ν_{max} cm^{-1}. 1620 (C=N), 1570 (C=C), NMR (CF_3CO_2H) ppm, 9·4 m [1] (C_5—H), 8·1–7·1 m [4] (aromatic protons), 6·1 s [2] (—OCH_2O), 4·1 m [8] (2 × OCH_3, —CH_2Ar.), Mass (*m/e*) 321 M^+ (100%), 306 M^+—CH_3 (36%), 278 (38%), 263 (20%), 248 (8%), 233 (10%), 220 (5%), 205 (15%), 177 (12%). [Found: C, 71·1; H, 4·8; N, 4·3; Calc. for $C_{19}H_{15}NO_4$. C, 71·0; H, 4·7; N, 4·4%]. This compound was further characterized as the methosulphate; colourless prisms m.p. 247–248° (EtOH). [Found: C, 56·3; H, 4·9; N, 3·4; S, 6·7. $C_{21}H_{21}NO_8S$ requires: C, 56·4; H, 4·7; N, 3·1; S, 7·2%]. Anion exchange yielded the methiodide **9**, which recrystallized as yellow needles from EtOH m.p. 253–254° (sinters at ~190°). [Found: C, 51·5; H, 3·4; N, 3·1; I, 28·6 $C_{20}H_{18}NO_4I$ requires: C, 51·8; H, 3·9; N, 3·1; I, 28·8%].

Reduction of the methosulphate or methiodide with $NaBH_4$ in EtOH gave **8**, (R = H) (87%) as colourless prisms m.p. 156–157°, from EtOH; NMR ($CDCl_3$) ppm, ~6·8 m [4] (aromatic protons), 5·9 s [2] (—OCH_2—O—), 4·2–2·9 complex [12] (2 × —OCH_3, —N—CH_2—, ArCH_2—, 2 × C$\underline{H}$—), 2·36 s [3] (—N—CH_3). [Found: C, 70·4; H, 6·2; N, 4·0. $C_{20}H_{21}NO_4$ requires: C, 70·8; H, 6·2; N, 4·1%].

4-(3,4-Methylenedioxybenzylidene)-7,8-dimethoxy-1,4-dihydroisoquinoline (**10**, $R_1 = R_2 = OMe$; $R_3 = H$; $R_4 + R_5 = CH_2O_2$).

On cooling the ethanolic soln, of the major component in the above reaction, colourless plates (1·3 g) of 4-(3,4-methylenedioxybenzylidene)-7,8-dimethoxy-1,4-dihydroisoquinoline were obtained which recrystallized from EtOH; m.p. 106–108°. λ_{max} (ε) nm, 255 (48,500); ν_{max} cm^{-1}, 1620 (C═N), 1600 (C═C); NMR ($CDCl_3$) ppm, 8·6 m [1] (C_3—H), 7·4–6·5 m [6] (olefinic and aromatic protons) 5·8 s [2] (—OCH_2O—), 5·0 s [2] (>N—CH_2—), 3·9 s [6] (2 × —OCH_3). [Found: C, 70·8; H, 5·4; N, 4·2 $C_{19}H_{17}NO_4$ requires: C, 70·6; H, 5·3; N, 4·3%].

4-(3,4-Methylenedioxybenzyl)-7,8-dimethoxyisoquinoline (5)

The base (1·0 g), from the previous reaction, was heated with EtOH (10 ml) containing 30% KOH aq (25 ml) for 30 min. On cooling, colourless crystals of **5** separated (0·8 g), m.p. 115–117° (lit.,[10] 124–125°). λ_{max} (ε) nm, 236 (55,000), 286 (13,800), 340 (10,500); ν_{max} cm^{-1}, 1620 (C═N), 1570, 1500 (C═C); NMR ($CDCl_3$) ppm, 9·0 s [1] (C_1—H), 8·25 s [1] (C_3—H) ~7·0 [5] (aromatic protons). 5·8 s [2] (—OCH_2O—), 4·13 s [2] (—CH_2—Ar), 4·0 s [6] (2 × —OCH_3). [Found: C, 70·0; H, 5·2; N, 4·4. Calc. for $C_{19}H_{17}NO_4$: C, 70·6; H, 5·3; N, 4·3%]. The methiodide was also prepared: m.p. 178–180° (EtOH). [Found: C, 51·9; H, 4·5; N, 3·0; I, 27·3 $C_{20}H_{20}NO_4I$ requires: C, 51·6; H, 4·3; N, 3·1; I, 27·3%].

4-(3,4-Methylenedioxybenzyl)-7,8-dimethoxy-2-methyl-1,2-dihydroisoquinoline (7)

4-(3,4-Methylenedioxybenzyl)-7,8-dimethoxy-2-methylisoquinolinium iodide (2 g) was suspended in dry ether (20 ml) under N_2. LAH (1·5 g) was added portionwise, and the mixture stirred at RT for 3 hr. After this time excess LAH was destroyed by the cautious addition of 30% aqueous sodium potassium tartrate soln, and the solvent layer then decanted from the gelatinous ppt which had formed. Evaporation of the solvent yielded **7** as a crystalline residue which recrystallized from EtOH as colourless needles (1 g), m.p. 97–98° (lit.,[10] 97–98°); λ_{max} (ε) nm, 297 (10,000), 325 (18,000); ν_{max} cm^{-1}, 1640 (C═C), 1250 (—OCH_2O—), NMR ($CDCl_3$) ppm, 6·8 m [5] (aromatic protons), 5·8 s [3] (—OCH_2O— and C_3—H), 4·2 s [2] (—CH_2—N—), ~3·7 two s [6] (2 × —OCH_3), 3·3 s [2] (—CH_2— Ar), 2·67 s [3] (═N—CH_2). [Found: C, 70·4; H, 5·8; N, 4·5 Calc. for $C_{20}H_{21}NO_4$: C, 70·8; H, 6·2; N, 4·1%].

The same product (**7**) was also obtained when the above isoquinolinium salt was reduced with $NaBH_4$ in boiling absolute EtOH soln, yield 70% m.p. 97–98°.

Action of acids upon **7**

(a) *Perchloric acid.* The 1,2-dihydroisoquinoline (1 g) in EtOH soln (20 ml) containing perchloric acid (2 ml) was heated under reflux for 30 min. On cooling yellow crystals of 4-(3,4-methylenedioxybenzyl)-7,8-dimethoxy-2-methylisoquinolinium perchlorate (0·6 g) separated, m.p. 187°; λ_{max} (ε) nm, 257 (35,000); ν_{max} cm^{-1}, 1650 (C═N), 1080 $(ClO_4)^-$. NMR (CF_3CO_2H) ppm, 9·5 s [1] (C_1—H), 8·05 s [2] (C_5—H, C_6—H), 7·9 s [1] (C_3—H), 6·8 s [3] (aromatic protons), 5·9 s [2] (—OCH_2O—), 4·5 s [5] (—CH_2—Ar, —N⁺—CH_3), 4·3, 4·2 s [6] 2 × —OCH_3). [Found: C, 54·6; H, 4·5; N, 3·8; Cl, 8·9. $C_{20}H_{20}NO_8Cl$ requires: C, 54·8; H, 4·6; N, 3·2; Cl, 8·1%].

Basification of the mother liquor with NH_4OH aq, followed by extraction with $CHCl_3$ yielded, after removal of the solvent, **11** (0·3 g) as an oil. The methiodide of this substance was prepared, affording pale yellow needles m.p. 216° (EtOH); λ_{max} (ε) nm, 288 (4830), ν_{max} cm^{-1}, 1600 (C═C); NMR (CF_3CO_2H) ppm, 7·33 q [2] $J = 8$ Hz (C_5—H, C_6—H); 6·8 s [3] (aromatic protons); 6·0 s [2] (—OCH_2O—); 4·67 broad s [2] (—N⁺—CH_2—); 4·1–2·67 complex [17] (2 × —OCH_3, 2 × —N⁺—CH_3, —CH_2—CH—CH_2—Ar). [Found: C, 52·2; H, 5·3; N, 3·1; I, 26·6. $C_{21}H_{26}NO_4I$ requires: C, 52·3; H, 5·4; N, 2·9; I, 26·3%].

This product was identical with a sample prepared by the catalytic reduction of **7** in EtOH solution at 1 atm pressure, catalyst 10% Pd/C, followed by treatment with MeI.

Oxidation of the 2-methyl-1,2,3,4-tetrahydroisoquinoline with I_2/KOAc in ethanol gave 4-(3,4-methylenedioxybenzyl)-7,8-dimethoxy-2-methylisoquinolinium iodide m.p. 180–181° identical with an authentic sample.

(b) *Hydrochloric acid/acetic acid.* The 1,2-dihydroisoquinoline (1 g) was heated under reflux with glacial

AcOH (30 ml) and conc HCl (1·5 ml) under N_2. The reaction mixture was cooled and basified with ammonia soln; extraction with $CHCl_3$ yielded **11** (50%) as an oil, which was subsequently characterized as the methiodide. The aqueous phase after $CHCl_3$ extraction was treated with 60% aq $HClO_4$ (5 ml); on cooling 4-(3,4-methylenedioxybenzyl)-7,8-dimethoxy-2-methylisoquinolinium perchlorate (44%) separated.

4-(3,4-Methylenedioxybenzyl)-6,7-dimethoxyisoquinoline

Piperonal (3 g) in EtOH (15 ml) was added to a soln of N-3,4-dimethoxybenzylaminoacetaldehyde dimethylacetal (2·85 g) in conc HCl (15 ml). After heating under reflux for 30 min the soln was cooled and allowed to stand for 12 hr. The red crystals which had separated were collected and a sample (1 g) recrystallized from EtOH, to yield **10** (R_1 = H; R_2 = R_3 = OMe; R_4 + R_5 = CH_2O_2) (0·9 g) m.p. 140–142°; λ_{max} (ε) nm, 278 (15,300), 360 (15,300); ν_{max} cm^{-1}, 1645 (C=$\overset{+}{N}$), 1610 (C=C). NMR (CF_3CO_2H) ppm, 9·0 m [1] (C_3—H), 8·3 m [1] (CH—Ar), 7·4–6·9 [5] aromatic protons). 6·1 s [2] (—OCH_2O—), 5·2 s [2] (—N—CH_2—), 4.0 s [6] (2 × —OCH_3). [Found: C, 62·7; H, 5·9; N, 3·4; $C_{19}H_{17}NO_4$ requires: C, 62·1; H, 6·0; N, 3·4%]. The remainder of the crude product (3·5 g) was suspended in water (300 ml) and the pH raised to 10 by the addition of 30% NaOH aq. After stirring for 1 hr at RT the solid material was collected, and then recrystallized from EtOH* to yield 4-(3,4-methylenedioxybenzyl)-6,7-dimethoxyisoquinoline (1·8 g) as colourless needles m.p. 139–140°; λ_{max} (ε) nm, 243 (10,400), 293 (1650); ν_{max} cm^{-1}, 1620 (C=N); NMR ($CDCl_3$) ppm, 8·93 s (C_1—H) [1]; 8·25 s (C_3—H) [1]; 7·1–6·5 m [5] (aromatic protons); 5·8 s [2] (—OCH_2O—), 4·1 s [2] ($ArCH_2$—); 3·93, 3·83 s [6] (2 × —OCH_3). [Found: C, 70·4; H, 5·2; N, 4·5. $C_{19}H_{17}NO_4$ requires: C, 70·6; H, 5·3; N, 4·3%].

2,3-Dimethoxy-8,9-methylenedioxy-11H-indeno[1,2-c]isoquinoline (**6**, R_1 = H; R_2 = R_3 = OMe; R_4 + R_5 = CH_2O_2).

In the above preparation at the stage of recrystallization of the 4-(3,4-methylenedioxybenzyl)-6,7-dimethoxyisoquinoline*, whilst the bulk of the impure product dissolved in the hot EtOH, some material (0·2 g) was found to be insoluble. This compound was subsequently recrystallized from pyridine to yield the corresponding indenoisoquinoline, as pale yellow micro crystalline prisms m.p. 266–268°; λ_{max} (ε) nm, 243 (33,400), 276 (33,400), 330 (23,000), ν_{max} cm^{-1}; 1620, 1590 (C=C) NMR (CF_3CO_2H) ppm, 9·0 d [1] (C_5—H), 7·6, 7·5 s [2] (C_1—H, C_4—H), 7·37 and 7·2 s [2] (C_7—H, C_{10}—H), 6·1 s [2] (—OCH_2O—), 4·2 broad s [8] (2 × —OCH_3, $ArCH_2$—). [Found: C, 71·2; H, 4·7; N, 4·5. $C_{19}H_{15}NO_4$ requires: C, 71·0; H, 4·7; N, 4·4%].

4-(3,4-Methylenedioxybenzyl)-6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline

This compound was prepared in the usual way from the corresponding methiodide (91%). Recrystallization from EtOH afforded colourless needles m.p. 82–84°; λ_{max} (ε) nm, 295 (11,300), 335 (22,600); γ_{max} cm^{-1}, 1645 (C=C), 1600 (C=C); NMR ($CDCl_3$) ppm, 6·8 m [5] (aromatic protons); 5·8 s [3] (—OCH_2O + C_3—H); 4·0 s [2] (—CH_2—N=); 3·7 s [6] (2 × —OCH_3); 3·33 s [2] ($ArCH_2$—); 2·67 s [3] (—N—CH_3). [Found: C, 70·6; H, 6·2; N, 4·2. $C_{20}H_{21}NO_4$ requires: C, 70·8; H, 6·2; N, 4·1%].

Action of acid upon 4-(3,4-methylenedioxybenzyl)-6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline

The 1,2-dihydroisoquinoline was treated with AcOH and HCl as previously described, yielding 4-(3,4-methylenedioxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (46%), as an oil, together with 4-(3,4-methylenedioxybenzyl)-6,7-dimethoxy-2-methylisoquinolinium perchlorate (40%) m.p. 179–181°. [Found: C, 54·4; H, 4·6; N, 3·6; Cl, 8·7. $C_{20}H_{20}NO_8Cl$ requires: C, 54·8; H, 4·6; N, 3·6; Cl, 8·1%]. The tetrahydroisoquinoline was characterised as the methiodide m.p. 248–250° (EtOH). [Found: C, 52·4; H, 5·4; N, 2·9; I, 26·0 $C_{21}H_{26}NO_4I$ requires: C, 52·3; H, 5·4; N, 2·9; I, 26·3%]. It was further oxidised with iodine/KOAc in ethanol to 4-(3,4-methylenedioxybenzyl-6,7-dimethoxy-2-methylisoquinolinium iodide (m.p. and mixed m.p. with authentic sample 203–205°), yield 90%. [Found: C, 51·6; H, 4·5; N, 3·2; I, 26·9. $C_{20}H_{20}NO_4I$ requires: C, 51·6; H, 4·3; N, 3·0; I, 27·3%].

3,4,8,9-Tetramethoxy-11H-indeno[1,2-c]isoquinoline (**6**, R_1 = H, R_2, R_3, R_4, R_5 = OCH_3)

The aminoacetal **3** (R_1 = H, R_2 = R_3 = OCH_3), (5·1 g) and veratraldehyde (6·6 g) were treated with conc HCl (30 ml) and heated at 100° for 3 hr. After cooling the mixture was washed with ether (3 × 50 ml) and basified with 2N NH_4OH. The liberated basic material was extracted into chloroform (3 × 50 ml) and the combined extracts evaporated to yield a gum. This material in ether was treated with HCl and the solid hydrochloride which formed was collected and recrystallized from MeOH pale cream needles m.p. 268–270°, yield 21%; λ_{max} (ε) nm, 235 (32,200), 275 (36,400), 327 (20,500). ν_{max} cm^{-1}, 1620, 1580. [Found: C, 64·3;

H, 5·4; N, 3·75; Cl, 9·5. $C_{20}H_{20}NO_4Cl$ requires: C, 64·3; H, 5·4; N, 3·8; Cl, 9·5%]. Under similar conditions piperonal and the acetal (3, R_1 = H, R_2 = R_3 = OCH_3) gave a solid product; this was recrystallized from pyridine to give 6, (R_1 = H, R_2 = R_3 = OMe, R_4 + R_5 = CH_2O_2) as pale yellow prisms, m.p. 266–268°. (Yield 17%, identical with the material obtained earlier.)

4-(3-Hydroxy-4-methoxybenzylidene)-7-methoxy-1,4-dihydroisoquinoline

The acetal 3, (R_1 = R_3 = H; R_2 = OCH_3; 5 g) in 50% HCl aq (25 ml) and EtOH (10 ml) were heated to 60° and isovanillin (5 g) in EtOH (10 ml) was added. The temp of reaction was then increased to 90° and was maintained for 2 hr. After this time the volume was decreased to 50% by distillation under reduced pressure; the mixture was then allowed to cool and the solid product collected. This material (10, R_1 = R_3 = H; R_2 = R_5 = OMe; R_4 = OH) was virtually insoluble in all common solvents except glacial AcOH and pyridine. Recrystallization was not achieved. The free base was liberated by treating a fine suspension of the hydrochloride salt in water with ammonia. This material was recrystallized with difficulty from EtOH as colourless prisms m.p. 197–198°; λ_{max} nm, 266, 343, ν_{max} cm^{-1}, 3550 (w), 3250 (s), 2500 (w), 1610; NMR (CF_3CO_2H) ppm. 9·2–8·6 m [1]; 7·8 d [1]. J = 10 Hz (C_4—H); 7·2–6·9 m [6] (olefinic and aromatic protons); 5·1–4·7 m [2] ($ArCH_2$—), 3·95 s [6] (2 × —OCH_3). Mass (*m/e*) 295 M^+ (100%), 280 M^+—15 (25%). [Found: C, 73·0; H, 5·6; N, 4·3. $C_{18}H_{17}NO_3$ requires: C, 73·2; H, 5·8; N, 4·7%].

3,10-Dimethoxy-9-hydroxy-5,6,12,13-tetrahydro-11H-indeno[1.2-c]isoquinoline (12)

The base (10 g), prepared as in the above experiment, in glacial AcOH (150 ml) was hydrogenated at 4 atm pressure over 10% Pd/C (0·2 g) for 12 hr. Solvent and catalyst were removed to yield a yellow solid. This material crystallized from N,N'-dimethylformamide as colourless prisms (6 g) m.p. 238–239° (dec). Further purification was achieved by sublimation (200–210°; 0·2 mm); λ_{max} nm; 220, 285; ν_{max} cm^{-1}, 3500–3100; NMR (CF_3CO_2H) ppm, 7·3 d [2], J = 9·5 Hz (C_5—H); 7·1 – 6·8 m [4] (aromatic protons); 5·3–3·0 m [6] (aliphatic protons); 4·0 s [6] (2 × OCH_3). Mass (*m/e*) 297 M^+ (80%), 296 M^+—1 (100%), 280, (50%), 265 (30%). [Found: C, 72·7; H, 6·4; N, 4·7. $C_{18}H_{19}NO_3$ requires: C, 72·7; H, 6·4; N, 4·7%].

4[Hydroxy-(3,4-dimethoxyphenyl)-methyl]-2-methylisocarbostyril (17, R = H; Z = O)

4-(3,4-Dimethoxybenzoyl)-2-methylisocarbostyril[18] (2 g) in EtOH (100 ml) was treated with $NaBH_4$ (1 g). After 3 hr at reflux the solvent was removed and water added. Chloroform extraction yielded 17 (R = H; Z = O) as a colourless crystalline mass (1·7 g) which recrystallized from MeOH, m.p. 220–221°; λ_{max} (ε) nm, 295 (14,000); ν_{max} cm^{-1}, 3410 (—OH), 1635 (N—CO—), 1610, 1590 (C=N); NMR (CD_3SOCD_3) ppm, 8·1 m [1] (C_8—H), 7·7–6·7 complex [6] (aromatic protons), 5·8 s [2] (—CH(OH)Ar), 3·7 s [6] (2 × —OCH_3). [Found: C, 69·9; H, 6·0; N, 4·1 $C_{19}H_{19}NO_4$ requires: C, 70·1; H, 5·9; N, 4·3%].

5-Keto-6-methyl-8,9-dimethoxy-11H-indeno[1,2-c]isoquinoline (18)

(a) A soln of the isocarbostyril alcohol (1 g) (prepared in the previous experiment) in EtOH (50 ml) containing conc HCl (5 ml) was heated under reflux for 6 hr. After this time the soln was poured into water (50 ml) basified with 2N NaOH and extracted with $CHCl_3$ (3 × 40 ml). Evaporation of the solvent from the combined extract yielded a yellow oil, which upon trituration with MeOH gave 18 as a colourless solid. Recrystallization from MeOH afforded needles, yield 0·83 g (88%), m.p. 204–205°; λ_{max} (ε) nm, 295 (11,750); ν_{max} cm^{-1}, 1625 (C=O), 1605 (C=C); NMR ($CDCl_3$) ppm, 8·3 m [1] (C_4—H, 7·6–7·3 m [3] (aromatic protons) 7·0–7·2 s [2] (C_7—H, C_{10}—H), 3·9 s [6] (2 × OCH_3), 3·4 s [2] (—CH_2Ar). [Found: C, 74·5; H, 5·6; N, 4·7 $C_{19}H_{17}NO_3$ requires: C, 74·3; H, 5·6; N, 4·6%].

(b) The isocarbostyril alcohol (1 g) in chloroform (30 ml) was saturated with HCl during 15 min. Evaporation of the solvent gave a gum, which when treated with EtOH formed 17 (R = Et. Z = O) as colourless plates (0·9 g) m.p. 55–56°; λ_{max} (ε) nm, 285 (12,500). ν_{max} cm^{-1}, 1640 (C=O), 1620, 1590 (C=C); NMR ($CDCl_3$) ppm, 8·4 s [1] (C_8—H); 7·7–6·8 m [7] (); 3·6 q [2], J = 7 Hz (—CH_2—CH_3); 3·4 s [6] (2 × —OCH_3); 3·5 s [3] (—N—CH_3); 1·25 t [3], J = 7 Hz (CH_3—CH_2—). [Found: C, 71·1; H, 6·3; N, 4·3. $C_{21}H_{23}NO_4$ requires: C, 71·4; H, 6·6; N, 4·0%]. This compound when heated with ethanolic HCl soln, as in (a) above gave (18) in 72% yield.

4-(3,4-Dimethoxybenzylidene)-2-methyl-1,2,3,4-tetrahydroisoquinoline (19)

4-(3,4-Dimethoxybenzoyl)-2-methylisocarbostyril (1 g) in benzene (50 ml) was treated with LAH (1 g) in

small portions; after the addition of this reagent, the suspension was heated under reflux for 2 hr. The mixture was then cooled and the excess reagent decomposed in the usual way; decantation and evaporation of the solvent gave a gum, which crystallized upon trituration with EtOH. Recrystallization from this solvent yielded **19** as colourless needles (0·58 g) m.p. 112–113°; λ_{max} (ε) nm, 315 (21,000), ν_{max} cm^{-1}, 1630, 1600, 1575 (C=C); NMR ($CDCl_3$) ppm, 7·8 m [1] (C_5—H), 7·3–6·8 complex [7] (aromatic protons), 3·9 s [6] (2 × —OCH_3), ~3·6 complex [4] (2 × —CH_2—N—), 2·4 s [3] (—N—CH_3). [Found: C, 76·8; H, 7·2; N, 4·7. $C_{19}H_{21}NO_2$ requires: C, 77·3; H, 7·2; N, 4·7%].

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