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NEW ISOQUINOLINES AS POTENTIAL BRONCHODILATOR AGENTS

S. F. DYKE* and A. W. C. WHITE
School of Chemistry and Chemical Engineering, University of Bath, Bath, Som.

and

D. HARTLEY
Chemistry Department, Allen and Hanburys Ltd., Ware, Hertfordshire

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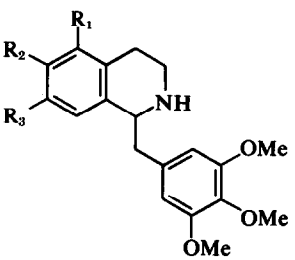
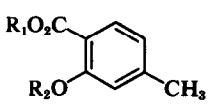
Abstract—The syntheses of 5-hydroxy-6-hydroxymethyl, 6-hydroxy-7-hydroxymethyl and 7-hydroxy-6-hydroxymethyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolines (**1d**), (**1b**) and (**1c**) respectively, are described.

Analogues of adrenaline in which the catechol nucleus is replaced by a saligenin moiety have led to an improved drug for the treatment of asthma.[1] Consequently, it was expected that similar modification of trimetoquinol (**1a**),[2] a potent but short-acting bronchodilator in man, would also lead to an improved product. We now wish to report the syntheses of the novel isoquinolines **1b**, **1c** and **1d** from the readily available *m*-cresotinic acid (**2a**).[3]

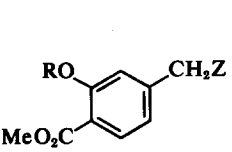


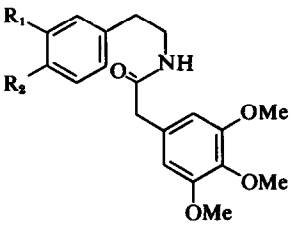


	R_1	R_2	R_3
1a	H	OH	OH
1b	H	OH	CH_2OH
1c	H	CH_2OH	OH
1d	OH	CH_2OH	H
1e	H	OH	CO_2Me
1f	H	CO_2Me	OH
1g	OH	CO_2Me	H

	R_1	R_2
2a	H	H
2b	Me	Ac

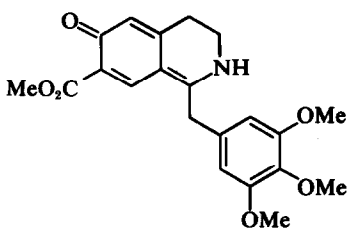
In one sequence, *m*-cresotinic acid (**2a**) was esterified and acetylated to **2b**, then reacted with N-bromosuccinimide to yield the bromide (**3a**),[4] which was converted in a standard manner, via the nitrile (**3b**) and amine (**3c**), into the β-arylethylamide (**4a**). Cyclisation of this amide gave a product, the IR and UV spectra of which are more compatible with the structure (**5**) than with the expected 3,4-dihydroisoquinoline (**6**); this feature is more usually observed for the fully aromatic 6-hydroxyisoquinoline derivatives.[5] Hydrogenation





	R	Z
3a	Ac	Br
3b	H	CN
3c	H	CH_2NH_2

	R_1	R_2
4a	OH	CO_2Me
4b	CO_2Me	OH



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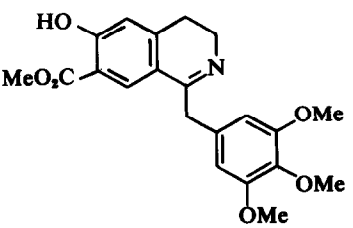

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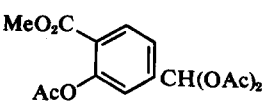
of **5** gave the required 1,2,3,4-tetrahydroisoquinoline (**1e**), which was further reduced by LAH in

THF. Continuous extraction of the reaction mixture with ethyl acetate resulted in a 56% yield of the required saligenin derivative (**1b**).

The Bischler-Napieralski reaction,[6] used above to construct the isoquinoline ring, involves an electrophilic substitution onto an aromatic ring suitably activated by an electron-donating substituent *para* to the position of ring-closure. This structural feature is not present in the amide (**4b**) that would be required for the generation of **1c**, so that a different approach is necessary. The route chosen involved the preparation of the aromatic isoquinoline (**9a**) by the Pomeranz-Fritsch method,[7] followed by alkylation at C_1 via the Reissert reaction.[8]

Thus, the ester (**2b**) was oxidised with chromium trioxide in acetic acid to the aldehyde triacetate (**7**), which, by standard procedures, was converted into the benzalamino acetal (**8**). Cyclisation of this acetal with PPA went surprisingly well to



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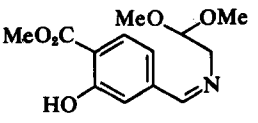

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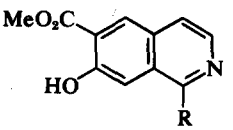
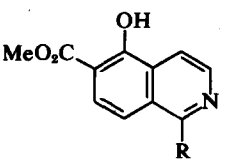


9a: R = H
9b: R = 3,4,5(OMe)$_3$C$_6$H$_2$CH$_2$

give a 90% yield of a mixture of the two isoquinolines (**9a** and **10a**). These structures follow from the diagnostic NMR spectra. The ratio of the isomers

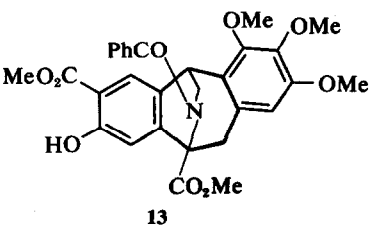


10a: R = H
10b: R = 3,4,5-(OMe)$_3$C$_6$H$_2$CH$_2$

formed, and the total yield of cyclised material varied with the experimental conditions. The isomers were separated initially by chromatography on silica plates but subsequently by seeding and crystallisation. Each isomer was taken separately through the remainder of the synthesis, which is summarised in the Scheme.

The removal of the cyano and benzoyl groups from alkylated Reissert compounds, has in the past[8] been achieved by treating them with alcoholic KOH solution. 1-Benzylisoquinoline has thus been obtained in 78% yield. We have now found that the conversion reaches 95% when the Reissert compound is treated with NaOMe in MeOH *at room temperature*. These latter conditions, when applied to **11** and **12** (Scheme), gave the isoquinolines (**9b** and **10b**) in 81% and 90% yields, respectively. Catalytic hydrogenation of **9b** and **10b** gave the 1,2,3,4-tetrahydroisoquinolines (**1f** and **1g**), respectively, and further reduction with LAH yielded the required compounds **1c** and **1d**.

On one occasion when the alkylated Reissert compound (**11**) was reacted with NaOMe, followed by aqueous HCl (to re-esterify the carboxyl group at C_6), the expected isoquinoline (**9b**) was accompanied by a small amount (15%) of a second component which analysed for $C_{30}H_{29}NO_9$. On the basis of NMR and mass spectral data, structure **13** or **14** is allotted to this material, but it has not proved possible to distinguish between them. Although the mass spectral fragmentations of alkaloids based upon the isopavine and pavine skeleta are known[9] and characteristic, the structures **13** and **14** contain several CO groups which may well alter these fragmentation patterns.



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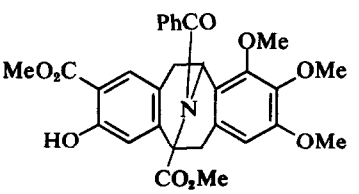

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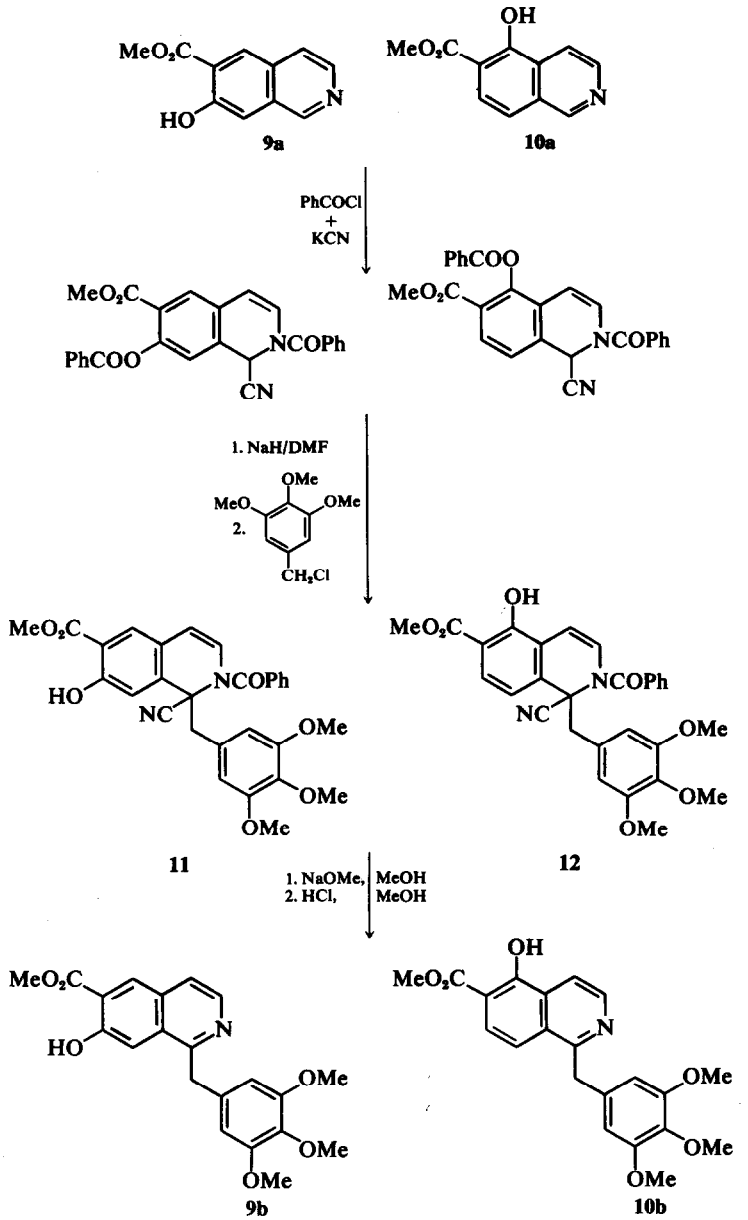
None of the compounds described have any useful pharmacological action. The absence of bronchodilator activity in the saligenins **1b**, **1c** and **1d** questions the validity of structure-activity interrelationships between trimetoquinol and other β-adrenergic stimulants such as isoprenaline and salbutamol.[10] In particular, the inactivity of the saligenin (**1b**) does not support the proposal made by Larsen for the mechanism of action of trimetoquinol at adrenergic receptors.[11]

EXPERIMENTAL

M.p's are uncorrected. UV data refer to 95% EtOH soln and absorption maxima are expressed in nm. IR spectra were measured in nujol mulls unless otherwise stated and absorption maxima are expressed in cm^{-1}. NMR spectra were determined at 60 MHz and chemical shifts are expressed as ppm downfield from internal TMS.



SCHEME 1

Mass spectra were measured with AEI MS 12 instrument.

Methyl 4-cyanomethyl-2-hydroxybenzoate (**3b**). KCN (10 g) in water (50 ml) was added to **3a** (28·7 g) in dioxan (200 ml) and the mixture was heated under reflux for 2 hr. The soln was concentrated under reduced pressure, poured into water and extracted with ether. The ethereal extracts were dried ($MgSO_4$) and concentrated to give the *nitrile* **3b** (6·7 g, 35%) as colourless flat rods, m.p. 100·9° (from ether); NMR ($CDCl_3$), 7·6 d [1] $J = 7·5$ Hz (C_6—H), 6·75–6·65 m [2] (C_3 and C_5—H), 3·84 s [3] ($COOCH_3$), 3·72 s [2] (—CH_2CN); ν max, 3220, 2255 and 1685; λ max (ϵ), 242 (10,400) and 310 (4,390). (Found: C, 62·8; H, 4·7; N, 7·4. $C_{10}H_9NO_3$ requires: C, 62·8; H, 4·75; N, 7·3%).

Methyl 4-(2-aminoethyl)-2-hydroxy benzoate (**3c**). The nitrile **3b** (5·73 g) in MeOH (100 ml) was added to a pre-reduced suspension of PtO_2 (0·5 g) in EtOH (50 ml) containing MeOH saturated with HCl (16 ml) and hydrogenated until uptake of gas ceased (48 hr). The catalyst was removed and the filtrate evaporated *in vacuo*. Trituration of the residue with ether gave the hydrochloride salt of the *amine* **3c** (5·5 g, 80%) as white crystals, m.p. 209°; NMR (D_2O) 7·7 d [1] $J = 8·5$ Hz (C_6—H), 7·08–6·91 m [2] (C_3 and C_5—H), 4·11 s [3] ($COOCH_3$), 3·7–2·91 [4] ($CH_2CH_2NH_2$); ν max, 3180–3000 (bonded OH), 2800–2400 and 2070 ($^{\oplus}NH_3$), 1680 (C 0·0); λ max (ϵ), 243 (12,480) and 309 (4,800). (Found: C, 51·6; H, 6·4; N, 5·9. $C_{10}H_{13}NO_3$.HCl requires: C, 51·8; H, 6·1; N, 6·0%).

Methyl 2-hydroxy-4-[2-[2-(3,4,5-trimethoxyphenyl)-acetamido]ethyl]benzoate (**4a**). 3,4,5-Trimethoxyphenylacetyl chloride (2·44 g) in benzene (40 ml) was added slowly with stirring to the above amine hydrochloride (2·31 g) in pyridine (20 ml) and the mixture was left overnight at room temp. After acidification with cold dilute HCl, the mixture was extracted with benzene. The extracts were dried ($MgSO_4$) and evaporated and the residue was triturated with ether to give the *amide* **4a** (2·6 g, 64%) m.p. 141·6° (from MeOH); NMR ($CDCl_3$), 7·67 d [1] J = 8 Hz (C_6—H), 6·8–6·42 m [2] (C_3 and C_5—H), 6·37 s [2] ($C_6\underline{H}_2(OMe)_3$), 5·55 s [1] (N—H), 3·92 s [3] (—$COOC\underline{H}_3$), 3·79 s [9] (3 x—$OC\underline{H}_3$), 3·41 s [2] ($ArC\underline{H}_2CO$—), 3·40 t [2] and 2·92 t [2] (AA′BB′ pattern, —CH_2CH_2—); ν_{max}, 3340, 3300, 1695 (CO.O), 1650 and 1560 (CO.N); λ_{max} (ϵ), 244 (16,120), 310 (4,130). (Found: C, 62·3; H, 6·2; N, 3·4. $C_{21}H_{25}NO_7$ requires: C, 62·5; H, 6·25; N, 3·5%).

Methyl 3,4-dihydro-6-hydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline-7-carboxylate (**5** or **6**). A mixture of the amide **4a** (407 mg) and $POCl_3$ (1·1 g) in acetonitrile (10 ml) was heated under reflux for 1 hr and then evaporated *in vacuo*. The residue was dissolved in benzene-ethyl acetate (1:1) and washed with sat Na_2CO_3aq, and then with saturated brine. The organic extracts were dried ($MgSO_4$) and treated with ethereal HCl to give an orange gum, which crystallised on trituration with EtOAc containing a few drops of MeOH to give a methanolate of the required *hydrochloride* **4a** (240 mg, 53%) as yellow needles, m.p. 122·6°; NMR ($CDCl_3$), 8·53 s broad [1] (C_8—H), 6·93 s broad [1] (C_5—H), 6·8 s [2] ($C_6\underline{H}_2(OMe)_3$), 4·58 s [2] ($ArC\underline{H}_2$—), 3·91 s [3] ($C_4'$—$OC\underline{H}_3$), 3·85 s [6] ($C_3'$ and C_5'—$OC\underline{H}_3$), 3·77 s [3] (—$COOC\underline{H}_3$), 3·95–3·1 m [4] (—CH_2-CH_2—); ν_{max} ($CHBr_3$), 1740, 1690; λ_{max} (ϵ), 315 (9,910), 235 (32,760). (Found: C, 57·9; H, 6·1; N, 3·2. $C_{22}H_{27}NO_7$. HCl requires: C, 58·2; H, 6·2; N, 3·2%).

Methyl 1,2,3,4-tetrahydro-6-hydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline-7-carboxylate (**1e**). The hydrochloride **6** (450 mg) in EtOH (25 ml) was hydrogenated over PtO_2 (120 mg) until uptake ceased (24 cc in 10 min). The filtrate from the catalyst was evaporated. The residue solidified on trituration with ether to yield the required *tetrahydroisoquinoline hydrochloride* (330 mg, 73%) as colourless crystals m.p. 138·5 (from benzene); NMR ($CDCl_3$), 7·27 s [1] (C_8—H), 6·75 s [1] (C_5—H), 6·43 s [2] ($C_6\underline{H}_2(OMe)_3$), 4·8 broad [1] ($C_1$—H), 3·87 s [3] (—$COOCH_3$) 3·82 s [3] ($C_4'$—$OCH_3$), 3·76 s [6] ($C_3'$ and C_5'—OCH_3), 2·9–3·6 complex [6] (—CH_2—CH_2— and $ArCH_2$—); ν_{max} ($CHBr_3$), 3200, 2800–2500, 1687; λ_{max} (ϵ), 313 (4000), 235–240 sh (16,600), 216 (49,900). (Found: C, 59·1; H, 6·3; N, 3·1. $C_{21}H_{25}NO_6$. HCl requires: C, 59·5; H, 6·2; N, 3·3%).

1,2,3,4-Tetrahydro-7-hydroxy-6-hydroxymethyl-1-(3,4,5-trimethoxybenzyl)isoquinoline (**1b**). The hydrochloride **1e** (650 mg) in THF (25 ml) was added with stirring to LAH (120 mg) in THF (20 ml). The stirred mixture was heated under reflux for 0·5 hr, allowed to cool, and the excess of hydride decomposed with water. After evaporating the THF *in vacuo* the residue was dissolved in dilute HCl and then basified with $NaHCO_3$aq. Continuous extraction with EtOAc gave the *diol* **1b** (310 mg, 56%) as glistening plates m.p. 174·5° [from benzene-methanol (trace)]; NMR ($CDCl_3$/DMSO), 7·08 s [1] (C_8—H), 6·52 s [1] (C_5—H), 6·47 s [1] ($C_6\underline{H}_2(OMe)_3$), 4·62 s [2] (—$C\underline{H}_2$—OH), 4·1 s [1] ($C_1$—H), 3·75 s [3] ($C_4'$—$OCH_3$), 3·35–2·2 m [4] (—$CH_2$—$CH_2$—), 2·2 s [2] ($ArCH_2$—); ν_{max}, 3200–3000 (bonded-OH), 2800–2400 (bonded-NH); λ_{max} (ϵ), 282 (3000). (Found: C, 66·7; H, 7·1; N, 3·5. $C_{20}H_{25}NO_5$ requires: C, 66·8; H, 7·0; N, 3·9%).

Methyl 2-acetoxy-4-(diacetoxymethyl)benzoate (**7**). Glacial AcOH (500 ml) was added to a soln of CrO_3 (90 g) in Ac_2O (750 ml), the soln was cooled to 0° and conc H_2SO_4 (50 ml) added cautiously. This mixture was added dropwise over 4 hr to a stirred soln of **2b** (50 g) in Ac_2O (500 ml) maintained between −10° and −15°. After stirring for a further 2 hr, the soln was allowed to reach 0° over 1 hr, and isopropanol (600 ml) cautiously added, keeping the temp below 15°. The resulting dark green soln was evaporated to low bulk under reduced pressure at 35° and ice (500 g) was added. The soln was left for 1 hr, then extracted with $CHCl_3$ (4 × 100 ml). The combined $CHCl_3$ extracts were washed with sat $NaHCO_3$aq, and water and dried ($MgSO_4$). Removal of the $CHCl_3$ afforded a golden oil which solidified on standing (42 g, 54%). Recrystallisation from MeOH afforded white crystals, m.p. 95°; NMR ($CDCl_3$), 8·01 d [1] J = 8·7 Hz (C_5—H), 7·68 s [1] (Ar—C$\underline{H}$), 7·4 d [1] J = 8·7 Hz (C_6—H), 7·26 s [1] (C_2—H), 3·83 s [3] ($COOCH_3$), 2·3 s [3] (Ar—O—$COC\underline{H}_3$), 2·1 s [6] ($OCOCH_3$)$_2$; ν_{max}, 1765 broad, 1710, 1628; λ_{max} (ϵ), 283 (1,100), 232 (13,000). (Found: C, 55·7; H, 4·9. $C_{15}H_{16}O_8$ requires: C, 55·6; H, 5·0%).

Methyl 4-formyl-2-hydroxy-benzoate. The above **7** (42·0 g) was heated under reflux with MeOH (300 ml) and H_2SO_4 (10 ml; 98%) for 3 hr. After removal of the MeOH under reduced pressure, ice (200 g) was added and the soln extracted with $CHCl_3$ (4 × 100 ml). The combined $CHCl_3$ extracts were washed with $NaHCO_3$ (3 × 100 ml), water (2 × 100 ml) and dried ($MgSO_4$). Removal of the solvent afforded a solid which recrystallised as white florets from 60–80 petrol (23·4 g, 85%) m.p. 76–77°; NMR ($CDCl_3$), 10·82 s [1] (—OH, removed by D_2O), 10·01 s [1] (—CHO), 7·98 d [1] J = 8·0 Hz (C_5—H), 7·36 d [1] J = 8·0 Hz (C_6—H), 7·43 s [1] (C_2—H), 3·96 s [3] (—$COOCH_3$); ν_{max}, 3250, 1700 broad, 1625, 1580; λ_{max} (ϵ), 340 (3,200), 264 sh (11,300), 258 (12,000), 250 (10,600). (Found: C, 59·9; H, 4·5. $C_9H_8O_4$ requires: C, 60·0; H, 4·5%).

Methyl 4-[[(2,2-dimethoxyethyl)imino]methyl]-2-hydroxy benzoate (**8**). A mixture of methyl 4-formyl-2-hydroxy benzoate (60 g) and aminoacetaldehydedimethylacetal (35 g) in benzene (500 ml) was heated under reflux for 4 hr. The solid product obtained after removal of the solvent was recrystallised from petrol (60–80), (80 g, 90%), m.p. 64–65°; NMR ($CDCl_3$), 10·77 s [1] (—OH, removed by D_2O), 8·0–7·2 complex [3] (Aromatic H), 8·25 s [1] (Ar—CH=N—), 4·70 t [1] J = 5·0 Hz (—$C\underline{H}$—$(OMe)_2$), 3·93 s [3] ($COOCH_3$), 3·42 s [6] (2 × OCH_3), 3·7–3·9 m [2] (N—CH_2—CH—); ν_{max}, 3130, 1680, 1652, 1623; λ_{max} (ϵ), 334 (4,600), 265 (22,800), 272 sh (20,000). (Found: C, 58·4; H, 6·4; N, 5·3. $C_{13}H_{17}NO_5$ requires: C, 58·4; H, 6·4; N, 5·3%).

Methyl 7-hydroxy-isoquinoline-6-carboxylate (**9a**) *and methyl 5-hydroxyisoquinoline-6-carboxylate* (**10a**). (See Table.) The Schiff's base **8** (12·0 g) was stirred at 70–80° in freshly prepared polyphosphoric acid (orthophosphoric acid (90 ml), P_2O_5 (120 g)) for 5 hr. After dilution with water (1 litre) the soln was basified with $NaHCO_3$ and extracted with $CHCl_3$ (4 × 150 ml). The combined $CHCl_3$ extracts were washed with water (2 × 100 ml), dried ($MgSO_4$) and evaporated to leave a yellow solid (8·6 g, 94%). Chromatographic separation of 200 mg on silica, eluting with C_6H_6/$CHCl_3$ (50:50) afforded *methyl 7-hydroxyisoquinoline-6-carboxylate* (**7**) 40 mg, m.p. 120–121°; NMR ($CDCl_3$) 9·1 s [1] (C_1—H), 8·36 d [1] J = 6·0 Hz (C_3—H), 7·49 d [1] J = 6·0 Hz (C_4—H), 8·34 s [1] (C_5—H), 7·34 s [1] (C_8—H), 4·00 s [3] ($COOCH_3$); ν_{max} (solution in $CHCl_3$), 3270, 1692, 1640, 1258; λ_{max} (ϵ), 380 (2,860), 270 (5,700), 235 (51,800); mass *m/e* 203 (M^+).

Table 1. Cyclisation of Schiff's base (8)

Conditions			Crude yield	Ratio of isoquinolines
				10a 9a
H_2SO_4 (86% w/w)	RT	20 hr	40%	3 : 5
H_2SO_4 (76% w/w)	RT	1 wk	45%	1 : 1
PPA	RT	24 hr	Poor	1 : 3
PPA	45°	24 hr	40%	1 : 2
PPA	50°	24 hr	60%	1 : 1
PPA	70–100°	5 hr	95%	3 : 1

[65%], 171 (100%). (Found: C, 64·9; H, 4·5; N, 7·0. $C_{11}H_9NO_3$ requires: C, 65·0; H, 4·5; N, 6·9%). Also from the chromatographic separation was obtained *methyl 5-hydroxyisoquinoline-6-carboxylate* (**10a**) 120 mg, m.p. 137–138°; NMR ($CDCl_3$), 12·8 s [1] (—OH, removed by D_2O), 9·1 s broad [1] (C_1—H), 8·58 d broad [1] $J = 6$ Hz (C_3—H), 8·05 d [1] $J = 6$ Hz (C_4—H), 7·77 d [1] $J = 8·8$ Hz (C_7—H), 7·28 d [1] $J = 8·8$ Hz (C_8—H), 3·96 s [3] ($COOCH_3$); ν_{max} (soln in $CHCl_3$), 2800–3520, 1676, 1642, 1260; λ_{max} (ϵ), 365 (5,200), 351 (5,600), 275 sh (5000), 254 (25,000); mass *m/e* 203 (M^+) [50%], 171 [100%]. (Found: C, 65·2; H, 4·6; N, 7·1. $C_{11}H_9NO_3$ requires: C, 65·0; H, 4·5; N, 6·9%).

Subsequently isomers **9a** and **12a** were separated by fractional crystallisation using petrol (60–80).

Methyl 2-benzoyl-7-benzoyloxy-1-cyano-1,2-dihydroisoquinoline-6-carboxylate. A mixture of **9a** (10 g), CH_2Cl_2 (60 ml), KCN (16 g) and water (30 ml) was stirred whilst benzoyl chloride (28 g) in CH_2Cl_2 (20 ml) was added during 2 hr. After stirring for a further 24 hr the layers were separated and the CH_2Cl_2 layer washed with water, 2N NCl, water, 2N NaOH and water. The soln was dried ($MgSO_4$) and evaporated to give a red oil which crystallised from *n*-BuOH. Recrystallisation from MeOH gave white needles (5·5 g, 24%) m.p. 203–3°; NMR (DMSO), 8·3–7·4 complex [12] (Aromatic H), 7·04 s broad [1] (C_1—H), 6·83 d [1] $J = 8·0$ Hz (C_3—H), 6·33 d [1] $J = 8·0$ Hz (C_4—H), 3·70 s [3] ($COOCH_3$); ν_{max}, 1758, 1710, 1670, 1640, 1626; λ_{max} (ϵ), 330 sh (6,200), 291 (15,000), 239 (39,000); mass *m/e* 438 (M^+) [18%], 105 [100%]. (Found: C, 71·0; H, 4·1; N, 6·3. $C_{26}H_{18}N_2O_5$ requires: C, 71·2; H, 4·1; N, 6·4%).

About 30% of the starting material was recovered as the O-benzoate from the 2N HCl washings by basification ($NaHCO_3$) and extraction with $CHCl_3$, and could be recycled. The *hydrochloride salt* was recrystallised from EtOH, m.p. 196–197°; NMR (DMSO), 9·93 s [1] (C_1—H), 8·97 s [1] (C_5—H), 8·57 s [1] (C_8—H), 8·83 d [1] $J = 6·0$ Hz (C_3—H), 8·63 d [1] $J = 6·0$ Hz (C_4—H), 8·4–7·6 complex [5] (O—CO—C_6H_5), 3·86 s [3] ($COOCH_3$); ν_{max}, 2350–1960 several bands, 1740, 1721; λ_{max} (ϵ), 338 (2,900), 230 (61,600); mass *m/e* 307 (M^+) [25%], 105 [100%]. (Found: C, 63·0; H, 4·0; N, 4·1; Cl, 10·0. $C_{18}H_{13}NO_4HCl$ requires: C, 62·9; H, 4·1; N, 4·1; Cl, 10·3%).

In an analogous experiment *methyl 2-benzoyl-5-benzoyloxy-1-cyano-1,2-dihydroisoquinoline-6-carboxylate* was prepared (18%) from **10a**. It crystallised as white needles from MeOH, m.p. 194–195°; NMR (DMSO), 8·4–7·4 complex [12] (Aromatic H), 7·15 s [1] (C_1—H), 6·86 d [1] $J = 8·0$ Hz (C_3—H), 6·19 d [1] $J = 8·0$ Hz (C_4—H), 3·7 s [1] ($COOCH_3$); ν_{max}, 1740, 1680, 1635, 1603; λ_{max} (ϵ), 330 sh (6,300), 293 (13,600), 238 (39,000); mass *m/e* 438 (M^+) [8%], 105 [100%]. (Found: C, 71·2; H, 4·1; N, 6·6. $C_{26}H_{18}N_2O_5$ requires: C, 71·2; H, 4·1; N, 6·4%).

Again, starting material was recovered in about 30% yield as O-benzoate from the HCl washings and could be recycled. Methyl 5-benzoyloxyisoquinoline-6-carboxylate was recrystallised from petrol (60–80), m.p. 116–117°; NMR ($CDCl_3$), 9·34 s broad [1] (C_1—H), 8·60 d [1] $J = 6·0$ Hz (C_3—H), 8·4–7·4 complex [8] (Aromatic H plus C_4—H), 3·70 s [1] ($COOCH_3$); ν_{max}, 1744, 1730, 1602, 1585; λ_{max} (ϵ), 338 (3,600), 268 sh (6,500), 228 (54,500); mass *m/e* 307 (M^+) [10%], 105 [100%]. (Found: C, 70·6; H, 4·3; N, 4·5. $C_{18}H_{13}NO_4$ requires: C, 70·4; H, 4·3; N, 4·6%).

Methyl 2-benzoyl-1-cyano-1,2-dihydro-7-hydroxy-1-(3,4,5-trimethoxybenzyl)-6-carboxylate (**11**). A soln of methyl 2-benzoyl-7-benzyloxy-1-cyano-1,2-dihydroisoquinoline-6-carboxylate (4·0 g) in dry DMF (40 ml) was added to a stirred suspension of sodium hydride (0·4 gm) in dry DMF (5 ml) at 0° under N_2. When no more H_2 was evolved (10 min), 3,4,5-trimethoxybenzylchloride (2·2 g) in DMF (10 ml) was added over 30 min. Stirring was continued for 4 hr, raising to room temp after 90 min. After excess sodium hydride had been decomposed by the addition of MeOH, the solvent was removed at 40° under reduced pressure to give a yellow solid which was recrystallised from MeOH as white plates (2·86 g, 61%) m.p. 205°; NMR (DMSO), 7·59 s [5] (N—COC_6H_5), 7·53 s [1] (C_5—H), 6·83 s [1] (C_8—H), 6·10 s [2] ($C_6H_2(OMe)_3$), 6·23 d [1] $J = 8·0$ Hz (C_3—H), 5·72 d [1] $J = 8·0$ Hz (C_4—H), 3·87 s [3] (—$COOCH_3$), 3·45–3·67 complex (—CH_2—Ar and 3 × Ar (OCH_3)); ν_{max}, 3050 1673, 1640, 1616, 1592, 1137; λ_{max} (ϵ), 305 (13,700), 238 (3,070); mass *m/e* 514 (M^+) [1·0%], 105 [100%]. (Found: C, 67·5; H, 5·2; N, 5·4. $C_{29}H_{26}N_2O_7$ requires: C, 67·7; H, 5·1; N, 5·4%).

In an analogous experiment *methyl 2-benzoyl-1-cyano-1,2-dihydro-5-hydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline-6-carboxylate* (**12**) was prepared (72%). Recrystallisation from MeOH afforded white plates, m.p. 202–203°; NMR (DMSO), 7·70 d [1] $J = 8·7$ Hz, 6·92 d [1] $J = 8·7$ Hz (C_7—H and C_8—H), 7·59 s [5] (—N—COC_6H_5), 6·07 s [2] (—C_6H_2—$(OMe)_3$), 6·41 d [1] $J = 8·0$ Hz (C_4—H), 5·86 d [1] $J = 8·0$ Hz (C_3—H), 3·94 s [3] ($COOCH_3$), 3·7–3·4 complex [11] (—CH_2—Ar and 3 × Ar (OCH_3); ν_{max}, 3060, 1675, 1640, 1598, 1135; λ_{max} (ϵ), 367 (7,800), 260 (27,600), 239 (28,600); mass *m/e* 514 (M^+) [0·9%], 105 [100%]. (Found: C, 67·5; H, 5·1; N, 5·4. $C_{29}H_{26}N_2O_7$ requires: C, 67·7; H, 5·1; N, 5·4%).

Methyl 7-hydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline-6-carboxylate (**9b**). The alkylated Reissert compound **13** (1·8 g) was stirred at room temp for 30 hr under N_2 in NaOMe soln (2 gm Na in 150 ml MeOH). The mixture was cautiously acidified with dry HCl gas and still under HCl gas, was heated under reflux for 3 hr. The cooled soln was filtered, the solvent removed the residue basified ($NaHCO_3$), and extracted with $CHCl_3$ (3 × 50 ml). The combined $CHCl_3$ extracts were washed with water (3 × 50 ml) dried ($MgSO_4$) and evaporated to yield a pale yellow solid. Recrystallisation from MeOH afforded white crystals, m.p. 152–153° (1·09 gm, 81%); NMR ($CDCl_3$) 10·47 s [1] (—OH, removed by D_2O), 8·40 s [1] (C_5—H), 7·63 s [1] (C_8—H), 8·38 d [1] $J = 6·0$ Hz (C_3—H), 6·52 s [2] (—$C_6H_2(OMe)_3$), 4·49 s [2] (—CH_2—Ar), 4·00 s [3] ($COOCH_3$), 3·77 s [9] (3 × Ar—OCH_3); ν_{max}, 3180 broad, 1683, 1632, 1598, 1132; λ_{max} (ϵ), 383 (3,800), 240 (53,000), 270 sh (8,000); mass *m/e* 383 (M^+) [100%]

(Found: C, 65·9; H, 5·5; N, 3·8. $C_{21}H_{21}NO_6$ requires: C, 65·8; H, 5·5; N, 3·7%).

In an analogous experiment *methyl 5-hydroxy*-1-(3,4,5-*trimethoxybenzyl)isoquinoline-6-carboxylate* (**10b**) was prepared (90%) from **12** as pale yellow crystals from MeOH, m.p. 182–183°; NMR ($CDCl_3$), 11·86 s [1] (—OH, removed by D_2O), 8·60 d [1] $J = 6·0$ Hz (C_5—H), 8·08 d [1] $J = 8·0$ Hz (C_4—H), 7·83 d [1] $J = 8·8$ Hz (C_7—H), 7·55 d [1] $J = 8·8$ Hz (C_8—H), 6·50 s [2] (—$C_6H_2(OMe)_3$), 4·56 s [2] (—CH_2—Ar), 3·98 s [3] ($COOCH_3$), 3·76 s [9] (3 × Ar—OCH_3); ν_{max} 3200–3000, 1665, 1635, 1598, 1132; λ_{max} (ε), 354 (4,800), 368 (4,800), 300 sh (5,400), 290 sh (6,300), 256 (22,900); mass *m/e* 383 (M^+) [100%]. (Found: C, 66·0; H, 5·6; N, 3·6. $C_{21}H_{21}NO_6$ requires: C, 65·8; H, 5·5; N, 3·7%).

Isolation of **13** *or* **14**. On one occasion preparative layer chromatography on silica ($C_6H_6/CHCl_3$ 50/50) afforded 15% of a white crystalline solid, m.p. 264° (from MeOH); NMR ($CDCl_3$), 10·48 s [1](—OH, removed by D_2O), 7·45 complex [6] (Aromatic —H); 7·0 s [1] (Aromatic H), 6·3 s [1] (Aromatic H), 5·35 doublet of doublets [1] (methine), 3·70 complex [12] ($COOCH_3$ plus 3 × Ar—OCH_3), 4·3–2·7 complex [4] (Aliphatic —H); ν_{max}, 3100 broad, 1745, 1685, 1655, 1625; λ_{max} (ε), 322 (3,400), 245 (12,600); mass *m/e* 547 (M^+) [37%], 426 [100%]. (Found: C, 65·90; H, 5·3; N, 2·4. $C_{30}H_{29}NO_9$ requires: C, 65·8; H, 5·3; N, 2·6%).

Methyl 1,2,3,4-*tetrahydro-7-hydroxy*-1-(3,4,5-*trimethoxybenzyl)isoquinoline-6-carboxylate* (**1f**). Catalytic reduction of **9b** (600 mg) in EtOH (150 ml) using Adams catalyst at 60 lb/sq in for 24 hr gave a pale yellow oil; NMR ($CDCl_3$), 7·62 s [1] (C_5—H), 6·80 s [1] (C_8—H), 6·52 s [2] ($C_6H_2(OMe)_3$), 4·49 t broad [1] $J = 7$ Hz (C_1—H), 3·94 s [3] ($COOCH_3$), 3·82 s broad [9] (3 × Ar—OCH_3), 3·6–2·6 complex [6] (aliphatics); ν_{max} ($CHCl_3$), 2800–2300, 3120, 1680, 1595, 1130. The *hydrochloride* was obtained as an off-white solid from benzene (575 mg, 80%) m.p. 186–188°; λ_{max} (ε), 320 (4,050), 243 (12,800). (Found: C, 59·2; H, 6·4; N, 3·1. $C_{21}H_{25}NO_6$.HCl requires: C, 59·5; H, 6·2; N, 3·3%).

Similarly *methyl* 1,2,3,4-*tetrahydro-5-hydroxy*-1-(3,4,5-*trimethoxybenzyl)isoquinoline-6-carboxylate* (**1g**) was prepared from **10b**. The free base was obtained as an oil, NMR ($CDCl_3$), 7·64 d [1] $J = 8·7$ Hz (C_7—H), 6·60 d [1] $J = 8·7$ Hz (C_8—H), 6·5 s [2] (—$C_6H_2(OMe)_3$), 4·55 t [1] ($J = 7$ Hz) (C_1—H), 3·93 s [3] $COOCH_3$), 3·86–3·70 s broad [9] (3 × Ar—OCH_3), 3·65–2·5 complex [6] (aliphatics); ν_{max} (oil film), 2800–2500 several bands, 1680, 1597, 1132. *The hydrochloride* was obtained as a white crystalline solid from benzene (80%) m.p. 213–215°; λ_{max} (ε), 312 (3900), 248 (12,700). (Found: C, 59·3; H, 6·3; N, 3·2; $C_{21}H_{25}NO_6HCl$ requires: C, 59·5; H, 6·2; N, 3·3%).

1,2,3,4-*Tetrahydro-7-hydroxy-6-hydroxymethyl*-1-(3,4,5-*trimethoxybenzyl)isoquinoline* (**1c**). LAH (0·15 g) was added portionwise over 0·5 hr to a soln of the hydrochloride of **1f** (700 mg) in dry THF (30 ml). The stirred mixture was heated under reflux for 2 hr and stirred at room temp overnight. The excess LAH was carefully destroyed with a few drops of water and the THF removed under reduced pressure at room temp. The residue was dissolved in 2N HCl, basified ($NaHCO_3$), and extracted $CHCl_3$ (5 × 20 ml). The combined $CHCl_3$ extracts were washed with brine (3 × 20 ml) dried ($MgSO_4$) and evaporated to yield a yellow oil, which on standing with benzene solidified. Recrystallisation afforded a white crystalline solid (300 mg, 51%), m.p. 129–130°; NMR ($CDCl_3$), 6·63 s broad [2] (Aromatic H), 6·43 s [2] (Aromatic H), 5·5 s broad [3] (removed by D_2O), 4·65 s [2] (CH_2—OH), 3·78 s [9] (3 × Ar OCH_3), 4·4–3·6 complex [3] (—CH—CH_2—Ar) 3·3–2·4 complex [4] (Aliphatics); ν_{max}, 3280 sharp, 3500–3200, 1592, 1130; λ_{max} (ε), 285 (3000); mass *m/e* 355–359 cluster (M^+) [1%], 178 [100%]. (Found: C, 67·0; H, 6·9; N, 3·8. $C_{20}H_{25}NO_5$ requires: C, 66·8; H, 7·0; N, 3·9%).

In an analogous experiment 1,2,3,4-*tetrahydro-5-hydroxy-6-hydroxymethyl*-1-(3,4,5-*trimethoxybenzyl)isoquinoline* (**1d**) was obtained in 48% yield from the hydrochloride salt of **1g**. The white crystalline solid m.p. 175–177° was obtained from benzene; NMR ($CDCl_3$), 6·7 doublet of doublets [2] (C_7—H and C_8—H), 6·47 s [2] (C_6H_2 $(OMe)_3$), 4·76 s [2] (—CH_2—OH), 3·82 s [9] (3 × Ar OCH_3), 4·5–3·7 complex [3] (—CH—CH_2—Ar), 3·4–2·4 complex [4] (4 × aliphatic H); ν_{max}, 3300 sharp, 3200–2600 broad 1598, 1140; λ_{max} (ε), 278 (2000); mass *m/e* 355–359 cluster (M^+) [1%], 178 [100%]. (Found: C, 66·8; H, 7·0; N, 3·9; $C_{20}H_{25}NO_5$ requires: C, 66·8; H, 7·0; N, 3·9%).

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