Synthesis of 5,6,6a,7,7a,12a-Hexahydro-4*H*-benzo[*d*,*e*]benzothieno-[2,3-*g*]quinolines and of 8-Phenyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*d*,*e*]quinolines

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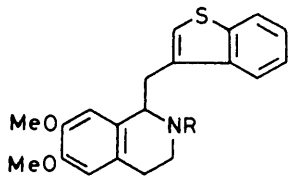
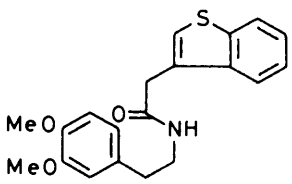
Demethylation of 1-(3-benzo[*b*]thienylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1; R = H) gives two diastereoisomeric 1,2-dihydroxy-5,6,6a,7,7a,12a-hexahydro-4*H*-benzo[*d*,*e*]benzothieno-[2,3-*g*]quinolines (4; R = H). Desulphurisation of their *N*-acetyl-di-*O*-methyl derivative (5; R^1 = Me, R^2 = Ac) gave the diastereoisomeric 1-acetyl-5,6-dimethoxy-8-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*d*,*e*]quinolines (6; R = Ac). Desulphurisation of 6-formyl-1,2-dimethoxy-5,6,6a,7,7a,12a-hexahydro-4*H*-benzo[*d*,*e*]benzothieno[2,3-*g*]quinoline (5; R^1 = Me, R^2 = CHO) gave 1-formyl-5,6-dimethoxy-8-phenyl-2,3,9,9a-tetrahydro-1*H*-benzo[*d*,*e*]quinoline (7; R = CHO) together with two separable diastereoisomers of the corresponding hexahydro-derivative (6; R = CHO); all of these were converted into the corresponding *N*-methyl derivatives (7; R = Me) and (6; R = Me) respectively. Evidence for these structures has been provided by alternative synthesis. A novel process for monophenylation of alkyl aryl ketones is described.

In connection with an investigation concerning the potential biological properties of modified 1-benzylisoquinolines of the tetrahydropapaveroline type, the tetrahydroisoquinolines (1; R = H and Me) were synthesised by routine methods with a view to their conventional demethylation in boiling hydrobromic acid. Thus, thermal condensation of methyl 3-benzo[*b*]thienylacetate with 2-(3,4-dimethoxyphenyl)-ethylamine gave the acetamide (2) which was cyclised with phosphoryl chloride to yield 1-(3-benzo[*b*]thienylmethyl)-3,4-dihydroisoquinoline (3). Reduction of the hydrochloride salt of compound (3), either catalytically or with sodium borohydride, gave 1-(3-benzo[*b*]thienylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1; R = H). On demethylation with hydrobromic acid, concurrent cyclisation occurred to form an inseparable mixture of diastereoisomeric 1,2-dihydroxy-5,6,6a,7,7a,12a-hexahydro-4*H*-benzo[*d*,*e*]-benzothieno[2,3-*g*]quinolines (4; R = H), isolated as the hydrobromides. An analogous type of cyclisation has been reported [1] for the nitrogen isostere of compound (1). Such a ring closure was originally deduced from the mass spectrum wherein the molecular ion (*m*/*e* 311) was the base peak whereas simple 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivatives normally undergo substantial fragmentation under these conditions.[2] In agreement compound (1; R = H) exhibited a relatively weak peak at *m*/*e* 339 with substantial peaks at *m*/*e* 192 (base peak) and 147, corresponding to the tetrahydroisoquinolyl and benzothienylmethyl moieties, respectively. Apart from conventional assignments the n.m.r. spectrum of compound (4; R = H) specifically showed only one proton at τ 3.4 (aromatic proton of a phenol) and a one proton doublet ($J_{7a,12a}$ 9.5 Hz) at τ 4.7. [Analogous evidence (in Experimental section) demonstrated ring closure of (1; R = Me) to (4; R = Me).] The sharp signals exhibited by the n.m.r. spectrum of compound (4; R = H) and its apparent homogeneity on t.l.c. originally suggested the presence of only one diastereoisomer, but this was disproved by subsequent transformations (see below). The product (4; R = H) was converted into the corresponding 1,2-diacetoxy-6-acetyl-5,6,6a,7,7a,12a-hexahydro-4*H*-benzo[*d*,*e*]benzothieno[2,3-*g*]quinoline (5; R^1 = R^2 = Ac), and thence to the di-*O*-methyl ether (5; R^1 = Me, R^2 = Ac). Desulphurisation of this ether (5; R^1 = Me, R^2 = Ac) with Raney nickel gave an inseparable mixture of the diastereoisomeric 1-acetyl-5,6-dimethoxy-8-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*d*,*e*]quinolines (6; R = Ac). Confirmation of the skeletal structure of (6; R = Ac) and hence that of the precursors (4) and (5), together with a partial solution to the problems associated with the difficulty of separating the pairs of diastereoisomers was achieved as follows. Thus, compound (4; R = H) was converted successively into (5; R^1 = Me, R^2 = CHO) and thence by desulphurisation into a mixture which was separated by h.p.l.c. into (i) diastereoisomer A of (6; R = CHO) obtained as a crystalline solid, (ii) diastereoisomer B of (6; R = CHO) obtained only as an oil, and (iii) 1-formyl-5,6-dimethoxy-8-phenyl-2,3,9,9a-tetrahydro-1*H*-benzo[*d*,*e*]quinoline (7; R = CHO). Reduction of both stereoisomers A and B, and of (7; R = CHO) with lithium aluminium hydride gave the corresponding *N*-methyl derivatives (6; R = Me) (A and B isomers) and (7; R = Me). The direct synthesis of comparable derivatives, and thereby the confirmation of the structures (6; isomers A and B), was achieved as follows. Cyclisation of 3-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)propionic acid (8; R = H) with oleum (*cf.* ref. 3) gave the ketone (9; R^1 = R^2 = H). Attempts to generate the requisite monophenyl derivative (9; R^1 = H, R^2 = Ph) by direct phenylation of the ketone (9; R^1 = R^2 = H) using diphenyliodonium chloride in the presence of potassium t-butoxide [4] gave only the diphenyl derivative (9; R^1 = R^2 = Ph). However, the anion of (9; R^1 = R^2 = H), now generated using lithium diisopropylamide at room temperature, was readily monosubstituted with diphenyl disulphide in tetrahydrofuran (*cf.* ref. 5) to yield compound (9; R^1 = H, R^2 = PhS); in the presence of hexamethylphosphoric amide, only the diphenylthio compound (9; R^1 = R^2 = PhS) was obtained. Being unstable (9; R^1 = H, R^2 = PhS) was dissolved immediately in methanolic potassium methoxide and arylated (diphenyl iodonium chloride) to give (9; R^1 = Ph, R^2 = PhS) of which one stereoisomer predominated. Desulphurisation of this compound (9; R^1 = Ph, R^2 = PhS) gave the phenyl derivative (9; R^1 = Ph, R^2 = H); this was reduced by the Clemmensen process to yield (7; R = Me), identical with the corresponding product obtained from desulphurisation of (5; R^1 = R^2 = Me), together with a second compound clearly



(1)



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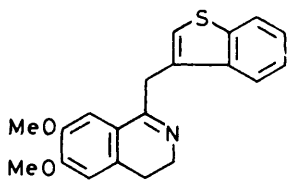

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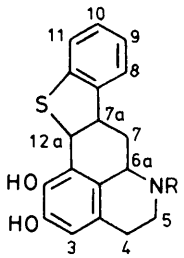

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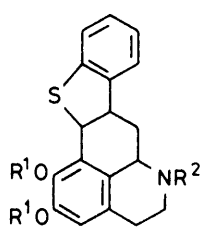

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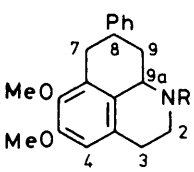

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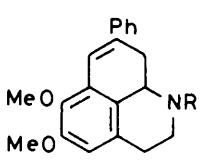

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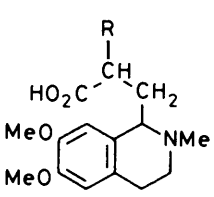

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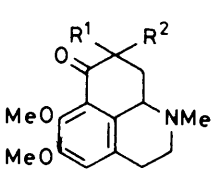
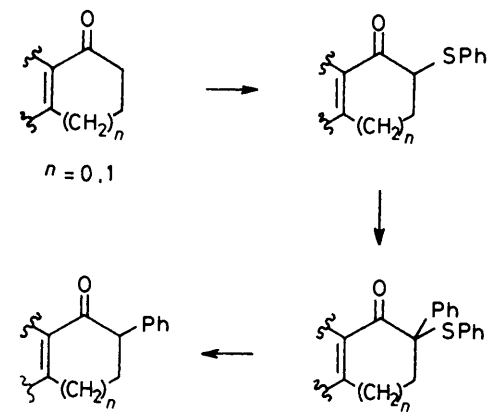
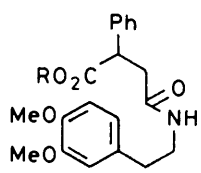


(9)

identical (n.m.r., i.r., R_F), with the diastereoisomer B of compound (6; R = Me). Although the appropriate n.m.r. spectra were not immediately superimposable because of trace impurities, the identity (homodiastereoisomerism) of the two samples was established by the n.m.r. spectrum of a 1 : 1 mixture of the two preparations. Sharp, single signals were then exhibited by the aromatic protons, methoxy, and *N*-methyl groups. By contrast, the spectrum of 'synthetic' (6; R = Me) (1 part) and the diastereoisomer A of (6; R = Me) (1 part) showed correspondence, but non-superimposability, of these signals, thus confirming that these two compounds were stereochemically different. Both the stereoisomers of (6; R = Me) were very susceptible to oxidation at room temperature and attempts to prepare crystalline derivatives were uniformly unsuccessful. Nevertheless the above confirmation of the structure of (7) and of the appropriate isomer B of (6; R = Me) substantiate the structures assigned to compound (4) and its derivatives.*



Scheme.



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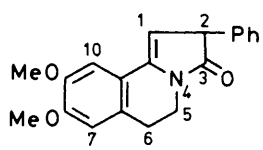

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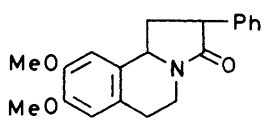

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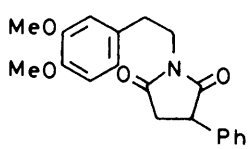

(13)

The above effectively incorporates a sequence for the monophenylation of the alkyl aryl ketone (9; $R^1 = R^2 = H$) and it was found that the same sequence could be extended to 1-tetralone and indan-1-one to yield 2-phenyl-1-tetralone and 2-phenylindan-1-one respectively (see Scheme).

In preliminary experiments to establish the structure of compound (6; R = H) by an unequivocal synthesis, attempts were made *inter alia* to cyclise *N*-[2-(3,4-dimethoxyphenyl)-ethyl]-2-phenylsuccinamic acids and esters of type (10) but derivatives of types (11), (12), and (13) were obtained.

Experimental

Light petroleum refers to the fraction of b.p. 40—60 °C. N.m.r. spectra were determined in deuteriochloroform unless otherwise stated.

* Since this work was completed, it has been reported [6] that benzo[*b*]thiophen and substituted benzo[*b*]thiophens [7] react with aromatic hydrocarbons in the presence of certain Lewis acids to give 2- or 3-aryl-2,3-dihydrobenzo[*b*]thiophens (as well as other products) This reaction is facilitated by the presence of protons and may be related to the ring closure here reported.

1-(3-*Benzo*[b]*thienylmethyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (1; R = H) *Hydrochloride*.—A solution of 3-cyanomethylbenzo[*b*]thiophen [8] (2.5 g) in methanol (25 ml) was saturated with hydrogen chloride, with the temperature maintained below 10 °C. After 40 h the solution was heated under reflux for 8 h, when the solvent was removed under reduced pressure; water (20 ml) was added and the residue was extracted with ethyl acetate (3 × 20 ml). Methyl 3-benzo[*b*]thienylacetate (2.8 g) had b.p. 120—130 °C/0.3 mmHg (Found: C, 63.9; H, 5.2. Calc. for $C_{11}H_{10}SO_2$: C, 64.1; H, 4.9%). An alternative synthesis has been reported.[9]

A mixture of this ester (2 g) and 3,4-dimethoxyphenylethylamine (1.8 g) was maintained at 180 °C for 2 h. Purification of the product from isopropyl alcohol–light petroleum gave N-[2-(3,4-*dimethoxyphenyl*)*ethyl*]-3-*benzo*[b]*thioenylacetamide* (2) (2.1 g) in small prisms, m.p. 110—112 °C (Found: C, 67.7; H, 6.1; N, 3.9. $C_{20}H_{21}NO_3S$ requires C, 67.6; H, 6.0; N, 4.0%).

A solution of this amide (10 g) in toluene (60 ml) containing phosphoryl chloride (24 ml) was refluxed for 30 min. Purification of this product from methanol gave 1-(3-*benzo*[b]*thienylmethyl*)-6,7-*dimethoxy*-3,4-*dihydroisoquinoline* (3) *hydrochloride* (8.6 g) as pale yellow needles, m.p. 177—180 °C (Found: C, 63.9; H, 5.3; Cl, 9.8; N, 3.6; S, 9.4. $C_{20}H_{20}ClNO_2S$ requires C, 64.3; H, 5.4; Cl, 9.5; N, 3.8; S, 8.6%).

Reduction of a solution of this hydrochloride (0.75 g) in methanol (40 ml) containing platinic oxide (50 mg) until hydrogen (45 ml = 1 mol equiv.) had been absorbed gave 1-(3-*benzo*[b]*thienylmethyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (1; R = H) *hydrochloride* (0.5 g), m.p. 210—212 °C (Found: C, 63.9; H, 5.9; N, 3.8%; M^+ 339. $C_{22}H_{22}ClNO_2S$ requires C 63.9; H, 5.9; N, 3.7%; M^+ 339), τ 0.35 (2 H, bs), 2.0—2.3 (2 H, m), 2.5—2.8 (2 H, m), 2.78 (1 H, s), 3.43 (1 H, s), 4.17 (1 H, s), 5.2 (1 H, bs), 6.20 (3 H, s), 6.72 (3 H, s), and 5.8—7.0 (6 H, m); *m/e* 339 (0.15), 193 (13), 192 (100), 177 (3), 176 (7), 148 (4.5), 147 (6.5), 131 (2), and 118 (1.5).

Reduction of compound (3) hydrochloride (3.7 g) in ethanol (50 ml) with sodium borohydride (2 g) during ½ h, gave the same (i.r., n.m.r., m.p. and mixed m.p.) tetrahydro-derivative (1) hydrochloride (3.1 g).

1-(3-*Benzo*[b]*thienylmethyl*)-6,7-*dimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (1; R = Me).—The free base (3) (2 g) was treated in the usual manner with methyl iodide to give 1-(3-*benzo*[b]*thienylmethyl*)-6,7-*dimethoxy*-2-*methyl*-3,4-*dihydroisoquinolinium iodide* (1 g), as yellow needles, m.p. 203—205 °C (Found: C, 52.5; H, 4.5; N, 2.7. $C_{21}H_{22}NO_2IS$ requires C, 52.6; H, 4.6; N, 2.9%).

Reduction of a solution of this iodide (2.6 g) in ethanol (30 ml) with sodium borohydride (1 g) during ½ h, gave 1-(3-benzo[*b*]thienylmethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1; R = Me) (1.9 g) which was characterised as the *hydriodide*, yellow needles, m.p. 197—198 °C (Found: C, 52.1; H, 5.2; N, 2.7. $C_{21}H_{24}INO_2S$ requires C, 52.2; H, 5.0; N, 2.8%); τ 2.0—2.4 (2 H, m), 2.5—2.8 (2 H, m), 3.02 (1 H, s), 3.42 (1 H, s), 2.5—3.5 (1 H, b), 4.30 (1 H, s), 6.20 (3 H, s), 6.71 (3 H, s), 7.27 (3 H, s), and 5.7—7.5 (7 H, m).

1,2-*Dihydroxy*-5,6,6a,7,7a,12a-*hexahydro*-4H-*benzo*[d,e]-*benzothieno*[2,3-g]*quinoline* (4; R = H) *Hydrobromide*.—A mixture of (1; R = H) (2.5 g) and constant b.p. hydrobromic acid (25 ml) was refluxed (nitrogen) for 8 h. Next day the precipitate was collected, washed with acetone and dried to yield the title *compound* (4; R = H) (1.8 g) which formed prisms, m.p. 263—265 °C (from acetone) (Found: C, 55.2; H, 4.6; N, 3.5%; M^+ 311. $C_{18}H_{18}BrNO_2S$ requires C, 55.1; H, 4.6; N, 3.6%; M^+ 311); τ(Me_2SO) 0.41 (1 H, s), 1.09 (1 H, s), 0.3—1.3 (2 H, b), 2.84 (4 H, bs), 3.43 (1 H, s), 4.70 (1 H, d, *J* 9.5 Hz), and 5.6—7.5 (8 H, m); *m/e* 311 (88), 278 (1), 202 (38), 188 (100), and 177 (1).

Prepared from this hydrobromide (2 g) by the pyridine–acetic anhydride method was 1,2-*diacetoxy*-6-*acetyl*-5,6,6a,-7,7a,12a-*hexahydro*-4H-*benzo*[d,e]*benzothieno*[2,3-g]*quinoline* (5; $R^1 = R^2 =$ Ac) (1.7 g) as prisms, m.p. 202—205 °C (from ethyl acetate) (Found: C, 65.9; H, 5.3; N, 3.2%; M^+ 437. $C_{24}H_{23}NO_5S$ requires C, 65.9; H, 5.3; N, 3.2%; M^+ 437); τ 2.85 (4 H, bs), 3.03 (1 H, s), 4.3—5.2 (2 H, b), 5.8—6.2 (1 H, b), 7.63 (3 H, s), 7.72 (3 H, s), and 6.5—8.4 (9 H, m); *m/e* 437 (15), 395 (17), 394 (55), 353 (13), 352 (37), 310 (29), 303 (51), 261 (48), 230 (13), 219 (32), 188 (18), and 43 (100).

A solution of this acetate (1.3 g) in acetone (65 ml) and 25% aqueous sodium hydroxide (3.25 ml) was refluxed for 1 h; methyl iodide (13 ml) was then added and the mixture boiled for a further 15 min. Isolated in the normal manner, 6-*acetyl*-1,2-*dimethoxy*-5,6,6a,7,7a,12a-*hexahydro*-4H-*benzo*-[d,e]*benzothieno*[2,3-g]*quinoline* (5; R^1 = Me, R^2 = Ac) (0.5 g) formed plates, m.p. 162—164 °C (from ethyl acetate–light petroleum) (Found: C, 69.2; H, 5.9; N, 3.5%; M^+ 381. $C_{22}H_{23}NO_3S$ requires C, 69.3; H, 6.1; N, 3.7%; M^+ 381); τ 2.87 (4 H, bs), 3.37 (1 H, s), 4.0—4.5 (1 H, b), 4.5—5.3 (2 H, b), 6.08 (3 H, s), 6.14 (3 H, s), and 6.5—8.4 (9 H, m); *m/e* 381 (24), 339 (16), 338 (67), 310 (17), 248 (17), 247 (100), 232 (29), 216 (38), 190 (20), and 43 (36).

1-*Acetyl*-5,6-*dimethoxy*-8-*phenyl*-2,3,7,8,9,9a-*hexahydro*-1H-*benzo*[d,e]*quinoline* (6; R = Ac).—A solution of (5; R^1 = Me, R^2 = Ac) (0.5 g) in methanol (50 ml) containing Raney nickel (W2) [10] (10 g) and concentrated hydrochloric acid (2 drops) was refluxed for 1 h. The product was purified from ethyl acetate–light petroleum to give a mixture of the diastereoisomers of the title *compound* (6; R = Ac) (0.3 g) as needles, m.p. 167—169 °C (Found: C, 74.8; H, 7.1; N, 4.0%; M^+ 351. $C_{22}H_{25}NO_3$ requires C, 75.2; H, 7.2; N, 4.0%; M^+ 351); τ 2.5—3.0 (5 H, m), 3.42 (1 H, s), 4.5—5.5 (2 H, b), 6.17 (3 H, s), 6.25 and 6.38 (3 H), 6.0—7.7 (8 H, m), and 7.83 (3 H, s); *m/e* 352 (23), 351 (92), 308 (22) 292 (13), 273 (17), 260 (20), 247 (47), 232 (48), 218 (15), 217 (12), 216 (13), 204 (18), 190 (100), 115 (17), and 91 (45).

1,2-*Dihydroxy*-6-*methyl*-5,6,6a,7,7a,12a-*hexahydro*-4H-*benzo*[d,e]*benzothieno*[2,3-g]*quinoline* (4; R = Me) *Hydrobromide*.—A mixture of crude (1; R = Me) (1.9 g) and constant b.p. hydrobromic acid (25 ml) was refluxed (nitrogen) during 8 h. Next day the precipitate was collected, and washed with acetone to yield the title *compound* (4; R = Me) (2 g) as a microcrystalline solid, m.p. 255—260 °C (Found: C, 55.6; H, 4.9; N, 3.3. $C_{19}H_{20}BrNO_2S$ requires C, 56.1; H, 4.9; N, 3.4%); τ(Me_2SO) −0.8 (1 H, b), 0.0 (1 H, b), 2.4—3.1 (4 H, m), 3.41 (1 H, s), 4.65 (1 H, d, *J* 10 Hz), 5.5—7.6 (9 H, m), and 7.02 (3 H, d).

The Diastereoisomeric 6-*Formyl*-1,2-*dimethoxy*-5,6,6a,7,7a,-12a-*hexahydro*-4H-*benzo*[d,e]*benzothieno*[2,3-g]*quinolines* (5; R^1 = Me, R^2 = CHO).—A solution of (4; R = H) hydrobromide (7.8 g) in chloroform (100 ml) containing triethylamine (20 ml) was cooled to 0 °C and formic–acetic anhydride [11] (10 ml) added with stirring during 10 min: after 30 min 6-*formyl*-1,2-*diformyloxy*-5,6,6a,7,7a,12a-*hexahydro*-4H-*benzo*[d,e]*benzothieno*[2,3-g]*quinoline* (5; $R^1 = R^2$ = CHO) was isolated as an oil (7.3 g); τ 1.68 (1 H, s), 1.75 (2 H, s), 2.84 (4 H, bs), 3.03 (1 H, s), 4.5—5.1 (2 H, m), and 5.7—8.0 (7 H, m). The crude product (7.2 g) was dissolved in acetone (50 ml) containing methyl iodide (10 ml) and 20% aqueous potassium carbonate (50 ml), and the mixture refluxed for 2 h.

The product was initially purified by chromatography from ethyl acetate on silica to yield a mixture of the diastereoisomeric 4H-*benzo*[d,e]*benzothieno*[2,3-g]*quinolines* (5; R^1 = Me, R^2 = CHO) which separated as needles, m.p. 137—139 °C from ethyl acetate, though a satisfactory analysis could not be obtained; τ 1.81 (1 H, bs), 2.86 (4 H, m), 3.43 (1 H, bs), 4.2—4.7 (1 H, m), 5.0—5.4 (2 H, m), 6.04 (½/3 H), and 6.07 (½/3 H), 6.15 (3 H, s), and 5.7—8.1 (6 H, m).

Reduction of a solution of this mixture of diastereoisomers (5.4 g) in boiling methanol (200 ml) with Raney nickel (30 g) during 1 h, gave a mixture (3.9 g) which was partially separated by h.p.l.c. using a Waters Associates Preparative 5000 LC instrument with a 5.7 × 6.0-cm silica column with 1—2% methanol in dichloromethane as eluant, and a flow rate of 250 ml min^{-1}; detection was by a differential refractometer. Three partially resolved fractions, (a) (0.2 g), (b) (2.4 g), and (c) (0.8 g), were obtained. Fraction b was rechromatographed to yield fraction d (1.5 g): fractions c and d were combined and further repeatedly fractionated to yield fractions h (0.5 g), j (0.5 g), and k (0.2 g).

Purification of fraction a from ethyl acetate–light petroleum gave 1-*formyl*-5,6-*dimethoxy*-8-*phenyl*-2,3,9,9a-*tetrahydro*-1H-*benzo*[d,e]*quinoline* (7; R = CHO) as needles, m.p. 169—170 °C (Found: C, 75.3; H, 6.5; N, 4.0%; M^+ 335. $C_{21}H_{21}NO_3$ requires C, 75.2; H, 6.3; N, 4.2%; M^+ 335); τ 1.58 and 1.70 (total, 1 H), 2.3—2.9 (6 H, m), 3.41 (1 H, s), 4.6—5.1 (1 H, m), 5.3—5.8 (1 H, m), 6.16 (6 H, s), and 6.4—7.6 (6 H, m); *m/e* 335 (16), 334 (61), 290 (14), 278 (33), 277 (87), 263 (17), 233 (18), 87 (58), 85 (100), 84 (19), 83 (86), and 82 (22).

Reduction of this quinoline (0.05 g) during 15 min by lithium aluminium hydride (0.015 g) in tetrahydrofuran (2 ml) gave 5,6-*dimethoxy*-1-*methyl*-8-*phenyl*-2,3,9,9a-*tetrahydro*-1H-*benzo*[d,e]*quinoline* (7; R = Me) (0.035 g) as yellow needles, m.p. 135—137 °C (from diethyl ether–light petroleum) (Found: M^+ 321.1727. $C_{21}H_{23}NO_2$ requires M^+ 321.1728). Elemental analysis was not possible due to the poor stability of this compound on drying. τ 2.3—2.9 (6 H, m), 3.45 (1 H, s), 6.15 (3 H, s), 6.18 (3 H, s), 7.49 (3 H, s), and 6.2—7.6 (7 H, m); *m/e* 321 (68), 320 (100), 319 (32), 306 (17), 304 (21), 290 (18), 278 (29), 263 (21), 247 (37), 202 (15), 191 (12), 189 (13), 165 (11), 122 (19), 115 (18), 108 (53), and 94 (89).

Purification of fraction h from methanol gave the 1-*formyl*-5,6-*dimethoxy*-8-*phenyl*-2,3,7,8,9,9a-*hexahydro*-1H-*benzo*[d,e]*quinoline* (6; R = CHO; isomer A) as prisms, m.p. 131—132 °C (Found: C, 74.7; H, 6.9; N, 4.1%; M^+ 337. $C_{21}H_{23}NO_3$ requires C, 74.8; H, 6.9; N, 4.2%; M^+ 337); τ 1.61 and 1.74 (total, 1 H), 2.4—2.8 (5 H, m), 3.36 (1 H, s), 4.5—5.0 (1 H, m), 6.12 (3 H, s), 6.19 and 6.21 (total, 3 H), and 6.4—8.4 (9 H, m); *m/e* 338 (12), 337 (100), 336 (11), 323 (11), 306 (15), 260 (14), 246 (29), 245 (12), 233 (27), 231 (29), 219 (22), 218 (83), 205 (12), 190 (20), 108 (22), 93 (35), and 91 (35).

Reduction of this derivative (0.05 g) with lithium aluminium hydride (0.015 g) in boiling tetrahydrofuran (2 ml) during 15 min, gave 5,6-*dimethoxy*-1-*methyl*-8-*phenyl*-2,3,7,8,9,9a-*hexahydro*-1H-*benzo*[d,e]*quinoline* (6; R = Me; isomer A) (0.03 g) as an oil (Found: M^+ 323. $C_{21}H_{25}NO_2$ requires M^+ 323). *Inter alia* the n.m.r. spectrum showed the signals τ 2.75 (5 H, s), 3.49 (1 H, s), 6.16 (3 H, s), 6.24 (3 H, s), and 7.60 (3 H, s).

Further purification of fraction k gave an oil (0.1 g) which appeared to consist predominantly of the diastereoisomeric quinoline (6; R = CHO; isomer B); τ 1.55 and 1.73 (1 H), 2.5—2.9 (5 H, m), 3.36 (1 H, s), 4.8—5.3 (1 H, m), 6.15 (6 H, s), and 6.5—8.4 (9 H, m).

Reduction of this derivative as for the isomer A gave the diastereoisomeric 1H-*benzo*[d,e]*quinoline* (6; R = Me; isomer B) as an oil (Found: M^+ 323.1880. $C_{21}H_{25}NO_2$ requires M^+ 323.1885). *Inter alia*, the n.m.r. spectrum exhibited signals at τ 2.70 (5 H, bs), 3.45 (H, s), 6.18 (3 H, s), 6.27 (3 H, s), and 7.51 (3 H, s).

Direct synthesis of Compounds (6; R = Me) *and* (7; R = Me).—A solution of 5,6-dimethoxy-1-methyl-1,2,3,8,9,9a-hexahydrobenzo[*d,e*]quinolin-7-one (9; R^1 = R^2 = H) [12,13] (0.5 g) in tetrahydrofuran was added slowly to a solution of lithium di-isopropylamide, prepared from 1.6M-n-butyllithium (1.2 ml) in hexane and di-isopropylamine (0.4 g) in tetrahydrofuran (5 ml). After ½ h the solution of the resultant lithium enolate was added dropwise during 15 min to a solution of diphenyl disulphide (0.84 g) in tetrahydrofuran (5 ml) under nitrogen. After a further 3 h the product was isolated and purified by chromatography from ethyl acetate on silica to give 5,6-*dimethoxy*-1-*methyl*-8-*phenylthio*-1,2,3,-8,9,9a-*hexahydrobenzo*[d,e]*quinolin*-7-*one* (9; R^1 = PhS, R^2 = H) (0.4 g) as a mixture of diastereoisomers (Found: M^+ 369. $C_{21}H_{23}NO_3S$ requires M^+ 369); τ 2.3—2.6 (2 H, m), 2.6—2.8 (3 H, m), 3.14 and 3.18 (total, 1 H), 5.7—6.0 (1 H, m), 6.12 and 6.18 (6 H), 6.7—7.7 (7 H, m), and 7.60 (3 H, s).

This very unstable thio-derivative (0.2 g) was dissolved immediately in methanol (5 ml) under nitrogen and a solution of potassium (0.04 g) in methanol (1 ml) added: after 15 min diphenyliodonium chloride (0.18 g) was added and the resultant mixture refluxed for 30 min. The product was purified by chromatography (on silica) with ethyl acetate–light petroleum (b.p. 40—60 °C) (1 : 1) as eluant to yield predominantly one diastereoisomer of 5,6-*dimethoxy*-1-*methyl*-8-*phenyl*-8-*phenylthio*-1,2,3,8,9,9a-*hexahydrobenzo*[d,e]*quinolin*-7-*one* (9; R^1 = PhS, R^2 = Ph) (0.17 g) as orange needles, m.p. 128—130 °C (from ethyl acetate–light petroleum) (Found: M^+ 445. $C_{27}H_{27}NO_3S$ requires M^+ 445); τ 2.2—2.5 (2 H, m), 2.5—2.9 (8 H, m), 3.22 (1 H, s), 5.9—6.3 (1 H, m), 6.24 (6 H, s), 6.7—7.8 (6 H, m), and 7.72 (3 H, s). Extreme sensitivity to oxidation precluded an elemental analysis.

A solution of this quinolin-7-one (1.3 g) in ethanol (50 ml) containing Raney nickel (*ca.* 10 g) was refluxed for 30 min, to yield 5,6-*dimethoxy*-1-*methyl*-8-*phenyl*-1,2,3,8,9,9a-*hexahydrobenzo*[d,e]*quinolin*-7-*one* (9; R^1 = H, R^2 = Ph) (0.7 g) as an oil, after purification from ethyl acetate–light petroleum on Florisil; τ 2.81 (5 H, bs), 3.19 (1 H, s), 6.21 (6 H, s), 5.9—6.5 (1 H, m), 6.6—7.9 (7 H, m), and 7.56 (3 H, s).

Reduction of this ketone (0.7 g) in refluxing alcohol (35 ml) during 10 min with zinc amalgam (3 g) and hydrochloric acid (10M; 35 ml), followed by addition of more zinc amalgam (3 g) and refluxing for a further 30 min, gave a mixture of compounds (i) and (ii). Compound (i) was purified with ethyl acetate–light petroleum on Florisil and shown to be the 1*H*-benzo[*d,e*]quinoline (7; R = Me), as needles (0.1 g). This material was identical (m.p. mixed m.p., i.r., m.s., and n.m.r.) with the specimen previously obtained from (5; R^1 = R^2 = CHO). The second fraction was compound (6; R = Me) (0.2 g) which crystallised as white needles, which were easily oxidised off, m.p. 85—90 °C (from methanol) (Found: *M*, 323.188 04. $C_{21}H_{25}NO_2$ requires M^+ 323.188 52). *Inter alia* the n.m.r. spectrum exhibited signals at τ 2.71 (5 H, s), 3.47 (1 H, s), 6.18 (3 H, s), 6.28 (3 H, s), and 7.56 (3 H, s). A 1 : 1 mixture of compound (6; R = Me), prepared by this latter route, and the product (isomer B) obtained by reduction of (6; R^1 = Me, R^2 = CHO) (isomer B) showed clearly defined singlet resonances for the aromatic, *O*-methyl, and *N*-methyl protons.

5,6-*Dimethoxy*-1-*methyl*-8,8-*diphenylthio*-1,2,3,8,9,9a-*hexahydrobenzo*[d,e]*quinolin*-7-*one* (9; R^1 = R^2 = PhS).—A solution of compound (9; R^1 = R^2 = H) (0.5 g) in tetrahydrofuran (1.25 ml) was added at 0 °C to a solution, under

nitrogen, of lithium di-isopropylamide, prepared from 1.6M-n-butyl-lithium (1.2 ml) in hexane and di-isopropylamine (0.4 g) in hexamethylphosphoramide (4 ml) and tetrahydrofuran (1.5 ml). After 2 h solid diphenyl disulphide (0.42 g) was added: after a further 1 h the product was isolated to yield the 8,8-*diphenylthio-benzo*[d,e]*quinolin-7-one* (9; R^1 = R^2 = PhS) (0.2 g) which formed yellow needles, m.p. 129—131 °C (from ethyl acetate) (Found: C, 67.7; H, 5.7; N, 2.9. $C_{27}H_{27}NO_3S_2$ requires C, 67.9; H, 5.7; N, 2.9%); τ 2.0—2.8 (10 H, s), 3.22 (1 H, s), 6.08 (3 H, s), 6.17 (3 H, s), 7.90 (3 H, s), and 6.5—7.9 (7 H, m).

5,6-*Dimethoxy*-1-*methyl*-8,8-*diphenyl*-1,2,3,8,9,9a-*hexahydrobenzo*[d,e]*quinolin*-7-*one* (9; R^1 = R^2 = Ph).—Phenylation of 5,6-dimethoxy-1-methyl-1,2,3,8,9,9a-hexahydrobenzo[*d,e*]quinolin-7-one (9; R^1 = R^2 = H) (1 g) in t-butyl alcohol (20 ml), under nitrogen, containing 1M-potassium t-butoxide in t-butyl alcohol (4 ml) with diphenyliodonium chloride (1.2 g) at the b.p. during 2 h gave the 8,8-*diphenylbenzo*[d,e]*quinolin*-7-*one* (9; R^1 = R^2 = Ph) (0.44 g), as unstable prisms, m.p. 124—127 °C (from ethyl acetate–light petroleum); τ 2.7—2.8 (10 H, m), 3.17 (1 H, s), 6.10 (3 H, s), 6.16 (3 H, s), 6.0—7.5 (7 H, m), and 7.54 (3 H, s).

8,9-*Dimethoxy*-2-*phenyl*-1,5,6,10b-*tetrahydropyrrolo*[2,1-a]*isoquinolin*-3(2H)-*one* (12).—Prepared by the interaction of phenylsuccinic anhydride (9 g) with 3,4-dimethoxyphenylethylamine (10 g) in diethyl ether (220 ml) at 0 °C, N-[2-(3,4-*dimethoxyphenylethyl*]-2-*phenylsuccinamic acid* (10; R = H) (12 g) formed small prisms, m.p. 122—123 °C (from ethyl acetate) (Found: C, 67.4; H, 6.5; N, 4.0. $C_{20}H_{23}NO_5$ requires C, 67.2; H, 6.5; N, 3.9%). Prepared in the normal manner (almost quantitatively) by the Fischer–Speier method, the *methyl ester* (10; R = Me) formed needles, m.p. 101—102 °C (from ethyl acetate–light petroleum) (Found: C, 67.8; H, 6.6; N, 3.6: $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.8%).

Cyclisation of this ester (5 g) during 7 h in a mixture of boiling toluene (100 ml) and polyphosphoric acid (5 g), followed by chromatography of the product on silica with ethyl acetate–light petroleum as eluant, gave 8,9-*dimethoxy*-2-*phenyl*-5,6-*dihydropyrrolo*[2,1-a]*isoquinolin*-3(2H)-*one* (11) (2.6 g), as needles, m.p. 168 °C from ethyl acetate–light petroleum (M^+ 321. $C_{20}H_{19}NO_3$ requires *M* 321); τ 2.0—2.4 (2 H, m), 2.5—2.7 (4 H, m), 2.92 (1 H, s), 3.38 (1 H, s), 5.5—5.9 (1 H, m), 6.08 (3 H, s), 6.15 (3 H, s), and 6.2—7.5 (4 H, m); *m/e* 321 (38), 320 (100), 274 (24), and 246 (12).

Compound (11) was also prepared by reaction of the acid (10; R = H) (2.0 g) with phosphorus pentachloride (1.2 g) in benzene (40 ml) at room temperature during 15 min: aluminium chloride (2.5 g) was then added and this final mixture heated at 60 °C during 4 h. The crude product (identical with that prepared as above) was not isolated but was reduced with sodium borohydride (1.0 g) in methanol (50 ml) during 1 h at ambient temperature to give a mixture of diastereoisomers; this mixture was separated by chromatography on silica, with ethyl acetate–light petroleum as eluant, to yield (i) the [2,1-a]*isoquinolin*-3(2H)-*one* (12) (0.2 g), in prisms, m.p. 145—147 °C (from ethyl acetate–light petroleum) (Found: C, 74.2; H, 6.5; N, 4.3%; M^+ 323. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.5; N, 4.3%; M^+ 323); τ 2.68 (5 H, s), 3.36 (1 H, s), 3.42 (1 H, s), 5.09 (1 H, t, *J* 8 Hz), 5.67 (1 H, m), 6.15 (6 H, s), and 6.5—7.9 (6 H, m); *m/e* 323 (100), 322 (93), 308 (13), 292 (10), 191 (21), 190 (11), 176 (11), and 91 (15); and (ii) the second diastereoisomer of (12) (0.3 g), as an oil; τ 2.73 (5 H, s), 3.33 (1 H, s), 3.40 (1 H, s), 5.25 (1 H, q, *J* 9 and 7 Hz), 5.64 (1 H, q, *J* 13 and 7 Hz), 6.15 (3 H, s), 6.17 (3 H, s), 6.6—7.3 (4 H, m), and 7.7—8.2 (2 H, m).

N-[2-(3,4-*Dimethoxyphenyl*)*ethyl*]-2-*phenylsuccinimide* (13).—Methyl *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-phenylsuccinamate (10; R = Me) (1 g) was dissolved in toluene (20 ml) containing phosphorus pentachloride (0.34 g): after 30 min titanium tetrachloride (0.8 g) was added. Next day the product was isolated and purified from ethyl acetate–light petroleum to yield N-[2-(3,4-*dimethoxyphenyl*)*ethyl*]-2-*phenylsuccinimide* (13) (0.7 g) as needles, m.p. 100—101 °C (Found: C, 70.8; H, 6.2; N, 4.2. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 4.1%. M^+ 339); τ 2.6—3.1 (5 H, m), 3.24 (3 H, s), 6.20 (3 H, s), 6.22 (3 H, s), 6.0—6.3 (1 H, m), and 6.6—7.7 (6 H, m); *m/e* 339 (6), 338 (27), 165 (13), 164 (100), 151 (32), and 149 (8).

2-*Phenyl*-1-*tetralone* [2-*Phenyl*-3,4-*dihydronaphthalen*-1(2H)-*one*].—A solution of diphenyl disulphide (20.0 g) in tetrahydrofuran (50 ml) was added at −70 °C under nitrogen to the anion generated from 1-tetralone (7.3 g) and lithium di-isopropylamide (1 equiv.) in tetrahydrofuran (50 ml). After 1 h at −70 °C the reaction mixture was evaporated under reduced pressure and the product purified from ethyl acetate–light petroleum (1 : 12) on silica to yield 2-*phenylthio*-1-*tetralone* (11.4 g) as an unstable, yellow oil; τ 1.97 (1 H, dd, *J* 7 and 2 Hz), 2.3—2.9 (8 H, m), 5.92 (1 H, dd, *J* 5 and 6 Hz), 6.4—7.1 (2 H, m), and 7.2—7.9 (2 H, m); *m/e* 254 (19), 145 (100), 144 (39), 118 (30), and 115 (31). This phenylthio-derivative (2.5 g) was added to a solution of potassium (0.4 g) in methanol (20 ml), followed by diphenyliodonium chloride (3.1 g): after ½ h the product was isolated and purified from ethyl acetate–light petroleum (1 : 25) on silica to yield 2-*phenyl*-2-*phenylthio*-1-*tetralone* as an oil (2 g); τ 1.86 (1 H, m), 2.5—3.1 (13 H, m), and 6.9—7.7 (4 H, m); *m/e* 330 (16), 221 (100), 220 (50), 118 (40), 115 (47), and 91 (60).

A solution of this derivative (1.2 g) in ethanol (2 ml) and acetic acid (1 ml) was added during 15 min to a mixture of zinc (1.3 g), ethanol (4 ml), and acetic acid (2 ml).[11] The mixture was stirred for 2 h at room temperature to yield 2-phenyl-1-tetralone (0.6 g) as plates, m.p. 75 °C (lit.,[14] m.p. 76 °C) (Found: C, 86.4; H, 6.3. Calc. for $C_{16}H_{14}O$: C, 86.5; H, 6.4%); τ 1.85 (1 H, m), 2.4—2.9 (8 H, m), 6.17 (1 H, t, *J* 8 Hz), 6.91 (2 H, m), and 7.52 (2 H, dd, *J* 6 and 8 Hz).

2-*Phenylindan*-1-*one*.—Sulphenylation of indan-1-one (4 g), as for 1-tetralone, gave 2-phenylthioindan-1-one (4 g) as plates, m.p. 62 °C (lit.,[15] 66 °C) (from ether–light petroleum) (Found: C, 75.0; H, 5.0. Calc. for $C_{15}H_{12}OS$: C, 75.0; H, 5.0%); τ 2.1—2.9 (9 H, m), 5.94 (1 H, dd, *J* 3.5 and 7 Hz), 6.37 (2 H, dd, *J* 7 and 17 Hz), and 6.95 (2 H, dd, *J* 17 and 3.5 Hz).

Prepared from this phenylthioindan-1-one (0.5 g), 2-*phenyl*-2-*phenylthioindan*-1-*one* (0.5 g) formed prisms, m.p. 97—99 °C (from ethyl acetate–light petroleum) (Found: C, 79.9; H, 5.1. $C_{21}H_{16}OS$ requires C, 79.7; H, 5.1%); τ 2.1—2.9 (14 H, m) and 6.29 (2 H, s).

Desulphurisation of this indanone (0.6 g) as for the tetralone gave 2-phenylindan-1-one (0.35 g) as prisms, m.p. 68—70 °C (lit.,[16] m.p. 76 °C (Found: C, 86.4; H, 5.8. Calc. for $C_{15}H_{12}O$: C, 86.5; H, 5.8%); τ 2.2—3.0 (9 H, m) and 5.9—7.0 (3 H, m).

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