Synthesis of 5-Hydroxy- and 5,6-Dihydroxy-derivatives of Spiro[indane-2,2'-pyrrolidine], Rigid Analogues of Tyramine and Dopamine Respectively

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Benzyl chloride and its 3-methoxy-, 4-methoxy-, and 3,4-dimethoxy-derivatives react with *N*-benzoylproline in the presence of lithium di-isopropylamide in THF to afford the correspondingly substituted *N*-benzoyl-2-benzylprolines (2g), (2h), (2i), and (2k), respectively. Intramolecular cyclisation of the acid chloride of (2g) with aluminium chloride afforded *N*-benzoylspiro[1-oxoindane-2,2'-pyrrolidine] (3g). Compound (2h) was cyclised in polyphosphoric acid to a mixture of the 5-methoxy- and 7-methoxy-derivatives, (3h) and (3j), of *N*-benzoylspiro[1-oxoindane-2,2'-pyrrolidine], whereas cyclisation of (2k) was best achieved in trifluoroacetic anhydride, affording the 5,6-dimethoxy-derivative (3k) in moderate yield. Compound (2i) failed to cyclise under a variety of conditions. Compound (3k) and the isomeric mixture of (3h) and (3j) were each reduced with lithium aluminium hydride, to the corresponding *N*-benzylspiro[1-hydroxyindane-2,2'-pyrrolidine] derivative followed by catalytic *N*-debenzylation and reductive dehydroxylation with diborane in THF to afford respectively, spiro[5,6-dimethoxyindane-2,2'-pyrrolidine] (1f) and a mixture of the 5-methoxy- (1d) and 4-methoxy- (1e) derivatives of (1a), from which (1d) was separated by preparative t.l.c. The mixture of spiro[1-hydroxyindane-2,2'-pyrrolidine] epimers [(5a) and (6a)] was resistant to reductive dehydroxylation. An alternative route to (1d) was *via* initial Michael condensation of 5-methoxy-2-nitroindane with methyl acrylate to give (10), which could be reductively cyclised with Raney nickel to spiro[5-methoxyindane-2,2'-(5'-oxopyrrolidine)] (11) followed by LAH reduction to give (1d). *O*-Demethylation of (1d) and (1f) in HBr afforded spiro[5-hydroxyindane-2,2'-pyrrolidine] (1b) and spiro[5,6-dihydroxyindane-2,2'-pyrrolidine] (1c), rigid analogues of tyramine and dopamine, respectively.

In the course of our studies on the pharmacological properties of rigid phenylethylamine systems, we have recently described the synthesis of the novel heterocycle spiro[indane-2,2'-pyrrolidine] (1a).[1] This compound was designed as an analogue of the analgesic, 2-aminoindane,[2] in which the rotation of the C–N bond was restricted. Recent structure–activity studies on derivatives of the opiate peptide, enkephalin,[3-5] have indicated that the presence of a rigid tyramine moiety may be an important criterion for analgesic activity in many opiate molecules. Similarly, studies on rigid dopamine analogues [6-9] have shown that dopaminergic activity may be related to a particular conformation of the dopamine molecule. In order to further examine the structure–activity relationships of certain rigid phenylethylamine systems, we have investigated new synthetic procedures designed to afford the hydroxy-substituted derivatives (1b) and (1c), which may be regarded as rigid analogues of tyramine and dopamine, respectively.

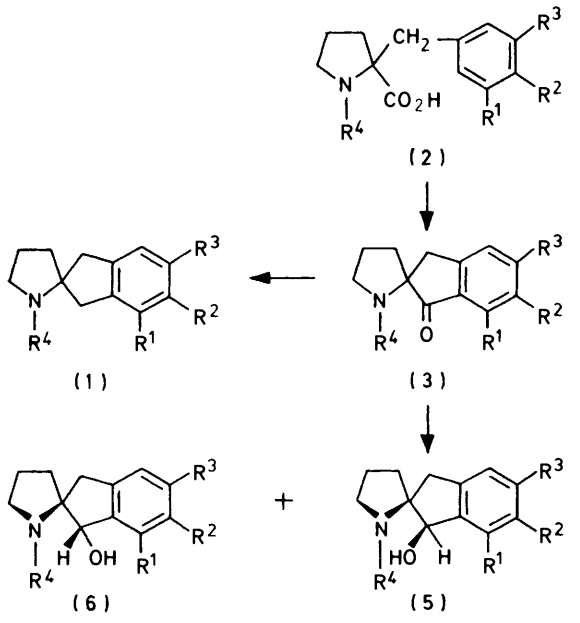
Benzyloxycarbonylproline has recently been shown [10] to undergo α-benzylation with benzyl chlorides in the presence of lithium di-isopropylamide (LDA), although concomittant Wittig rearrangement of the benzyloxycarbonyl group occurs. These results and others,[11-13] published during the course of this study, prompted us to examine a synthetic route to (1a) *via* the preparation and polyphosphoric-acid-induced cyclisation of *N*-benzoyl-2-benzylproline (2g), followed by reduction and *N*-debenzylation of the resulting cyclic ketone (3g). The availability of appropriately substituted benzyl chlorides makes this synthetic route an attractive method for the preparation of derivatives of (1a) bearing aromatic substituents.

RESULTS AND DISCUSSION

Treatment of *N*-benzoylproline [14] with benzyl chloride in the presence of LDA and NaH afforded (2g) in yields of 51—88%; the use of benzyl bromide in place of benzyl chloride in this reaction gave much lower yields of (2g).[15] The above reaction may be general for the preparation of benzyl-substituted derivatives of (2g), since compounds (2g), (2h), (2i), and (2k) were all prepared from the appropriate benzyl chloride by this procedure. Intramolecular cyclisation of the *N*-benzoyl-2-benzylprolines to the corresponding *N*-benzoylspiro[1-oxoindane-2,2'-pyrrolidine] (3) proved to be troublesome. Attempts to cyclise (2g) with PPA at 95—100 °C failed, the breakdown product, 5-benzamido-1-phenylpentan-2-one being obtained in 28% yield. The product is probably formed as a result of initial decarbonylative elimination of (2g) to the *N*-benzoyl-2-benzyl-1-pyridinium intermediate, then hydrolysis of the N(1)–C(2) double bond (*cf.* ref. 16). PPA cyclisation of (2h) afforded a 42% yield of a mixture of the positional isomers (3h) and (3j), whereas (2i) and (2k) both failed to cyclise under these conditions. Cyclisation of the acid chloride of (2g) with aluminium chloride gave a poor, but workable, yield of (3g); however, no product could be isolated when the same method was applied to the acid chlorides of (2i) and (2k). Activated benzene rings have been reported to undergo condensation with carboxylic acids in the presence of trifluoroacetic anhydride.[17] Using this procedure, cyclisation of (2k) to (3k) was achieved in 58% yield. However, under similar conditions, (2h) afforded a low yield of a mixture of (3h) and (3j), and the geometrical isomers, (4a) and (4b). The latter two products are presumably formed *via* trifluoroacetylation of the 2-pyrrolylidene intermediate (4e) and/or (4f) *via* the mechanism proposed in Scheme 2. Reaction of (2i) with trifluoroacetic anhydride afforded only 2-(*N*-benzoyl-2-pyrrolylidene)-1,1,1-trifluoro-4-(4-methoxyphenyl)butan-2-one (4c or d).

Attempted carbonyl reduction of (3g) and (3k) with hydrazine afforded, respectively, starting material and a

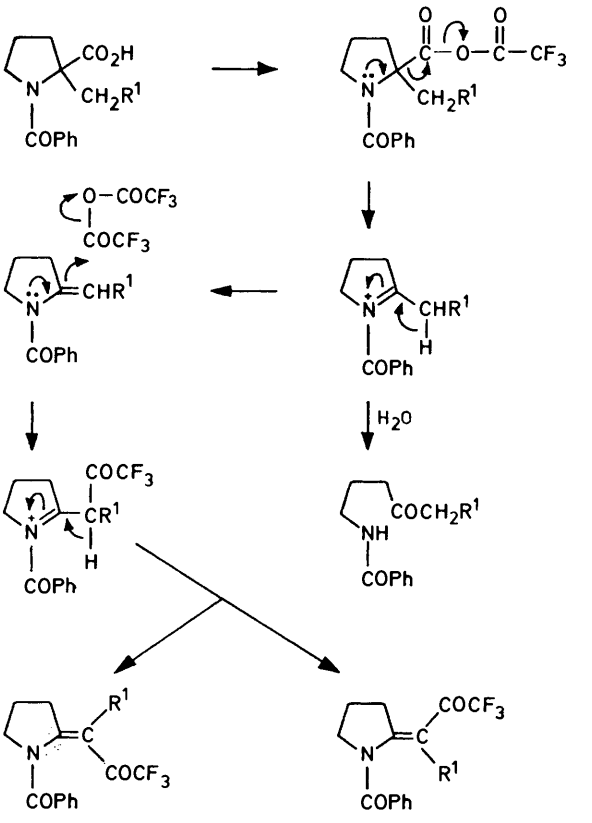
phenolic product, assigned as either (3l) or (3m), while Clemmensen reduction of (3k) gave the reduced cleavage product (7) in good yield. This latter observation is not unexpected, since *N*-methyl-2-acetylpiperidine, under Clemmensen conditions, has been shown to undergo reductive cleavage of the C(2)–N bond to give *N*-methyl-7-aminoheptan-2-one and *N*-methyl-1-heptylamine.[18] Reductions of aromatic ketones to the corresponding methylene derivative have been previously carried out



a; $R^1 = R^2 = R^3 = R^4 = H$
b; $R^1 = R^2 = R^4 = H$, $R^3 = OH$
c; $R^1 = R^4 = H$, $R^2 = R^3 = OH$
d; $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
e; $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
f; $R^1 = R^4 = H$, $R^2 = R^3 = OMe$
g; $R^1 = R^2 = R^3 = H$, $R^4 = COPh$
h; $R^1 = R^2 = H$, $R^3 = OMe$, $R^4 = COPh$
i; $R^1 = R^3 = H$, $R^2 = OMe$, $R^4 = COPh$
j; $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = COPh$
k; $R^1 - H$, $R^2 = R^3 = OMe$, $R^4 = COPh$
l; $R^1 = H$, $R^2 = OH$, $R^3 = OMe$, $R^4 = COPh$
m; $R^1 = H$, $R^2 = OMe$, $R^3 = OH$, $R^4 = COPh$
n; $R^1 = R^2 = R^3 = H$, $R^4 = CH_2Ph$
o; $R^1 = R^2 = H$, $R^3 = OMe$, $R^4 = CH_2Ph$
p; $R^1 = OMe$, $R^2 = R^3 = H$, $R^4 = CH_2Ph$
q; $R^1 = H$, $R^2 = R^3 = OMe$, $R^4 = CH_2Ph$

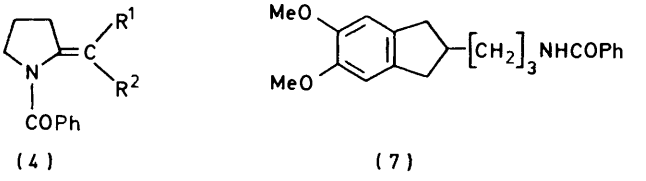
SCHEME 1

with diborane in THF,[19] and in this study it was shown that a methoxy-group, either *ortho* or *para* to the carbonyl group, activates the benzylic position, promoting facile cleavage of the initial reduction product. When ketone (3g) was reduced with diborane in THF, the formation of a 1 : 1 mixture of the epimeric alcohols (5n) and (6n) resulted. The 1α-ol (5n) was identified from its ^1H n.m.r. spectrum, which showed a low field one-proton singlet at τ 4.75, assignable to the C(1) proton. The corresponding signal in the β-isomer (6n), which was obtained pure by chromatography, resonates at τ 5.18. The relatively higher chemical shift of the C(1) proton in the β-isomer is attributed to the shielding effect of the adjacent *cis*-amino-group.[20] Compounds (5n) and (6n)



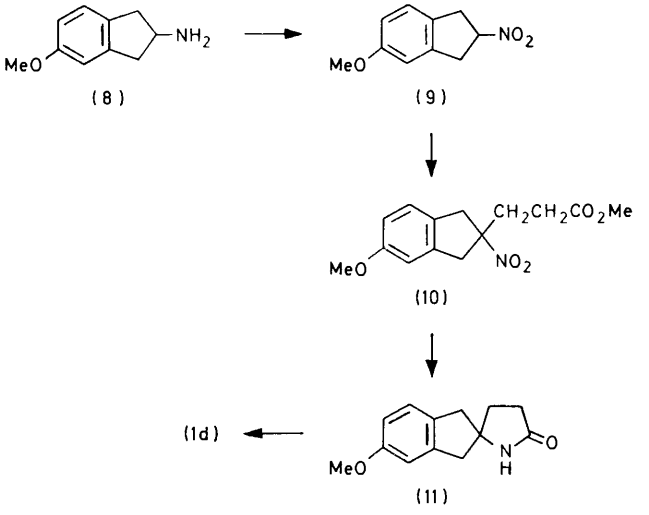
SCHEME 2

were also obtained from LAH reduction of (3g), although interestingly, the resulting epimer ratio was 4 : 1 in favour of the α-isomer; similar results were obtained from LAH reduction of (3k) and the isomeric mixture of (3h) and (3j). LAH reduction of 2-(*N*-phthalimido)-indan-1-one has analogously been reported to afford a 2 : 1 mixture of the *cis* and *trans* isomers, respectively, of 2-(*N*-isoindolyl)-1-hydroxyindane.[21] These results indicate that some steric preference in the formation of the LAH complex with *N*-acyl-2-aminoindan-1-ones and subsequent hydride ion addition exists, probably on the side of the molecule *cis* to the amido-function, and deserves further investigation. Anomalous behaviour of nitrogen-containing compounds with LAH has been observed in a number of other systems,[22] where an un-



a; $R^1 = 3\text{-}MeOC_6H_4$, $R^2 = COCF_3$
b; $R^1 = COCF_3$, $R^2 = 3\text{-}MeOC_6H_4$
c; $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = COCF_3$
d; $R^1 = COCF_3$, $R^2 = 4\text{-}MeOC_6H_4$
e; $R^1 = 3\text{-}MeOC_6H_4$, $R^2 = H$
f; $R^1 = H$, $R^2 = 3\text{-}MeOC_6H_4$

expected carbon–carbon double bond reduction was explained by a prior complexation with a relatively remote nitrogen. Attempts to reductively dehydroxylate (5n) and (6n) with palladium catalysts under a variety of conditions were unsuccessful. Diborane–THF reduction of (3k), on the other hand, resulted in formation of (1q) in good yield and similar treatment of the isomeric mixture of (3h) and (3j) afforded (1o) and (1p). Surprisingly, both (1q) and the mixture of (1o) and (1p) proved to be resistant to catalytic *N*-debenzylation with palladium catalysts under various conditions. On the other hand, catalytic *N*-debenzylation of the epimeric mixture of (5n) and (6n) proceeded at a reasonable rate, although subsequent reductive dehydroxylation with diborane in THF, or catalytically with palladium–charcoal, failed. When catalytic *N*-debenzylation of the epimeric mixture of (5q) and (6q) [obtained from LAH reduction of (3k)] was carried out, followed by reduction of the product with diborane, the



SCHEME 3

required spiro-derivative (1f) was obtained in 80% overall yield from (5q) and (6q). Similarly, *N*-debenzylation of a mixture of the two pairs of diastereoisomers, (5o) and (6o), and (5p) and (6p), followed by diborane reduction, afforded a mixture of (1d) and (1e) from which (1d) could be separated by preparative t.l.c. The resistance of structures (1o), (1p), and (1q) to catalytic *N*-debenzylation is interesting and may be a result of poor adsorption of these bladed structures onto the catalytic surface. However, the facile *N*-debenzylation of (5o), (5p), (5q), (6o), (6p), and (6q) suggests that in these compounds, the 1-hydroxy-group is either necessary for interaction at the catalyst surface, or is itself involved in the mechanism of *N*-debenzylation.

Compound (1d) was also synthesised *via* an alternative route (see Scheme 3). Oxidation of 2-amino-5-methoxyindane (8) with peracetic acid afforded the previously unreported 5-methoxy-2-nitroindane (9). Michael condensation of (9) with methyl acrylate gave (10), which could be reductively cyclised with Raney nickel to the spiro-amide (11). LAH reduction of (11) gave (1d) in 7% overall yield from (8). *O*-Demethylation of (1d) and (1f) to (1b) and (1c) respectively, was satisfactorily carried out in 47% HBr.

EXPERIMENTAL

M.p.s were measured on a Reichert hot-stage microscope. Recrystallisation solvents are designated in parentheses. Yields of solids refer to products obtained prior to recrystallisation, unless otherwise stated. I.r. spectra were recorded on a Perkin-Elmer model 237 grating spectrophotometer and ^{1}H n.m.r. spectra were recorded on a Perkin-Elmer R24 spectrometer. Mass spectra were recorded on a A.E.I. MS12 spectrometer operating at a probe temperature of 200 °C. Microanalyses were conducted by Mr. M. Hart, Department of Chemistry, Manchester University.

Arylalkylation of Benzoylproline.—*N*-Benzoylproline [14] (0.04 mol) dissolved in THF (40 ml), was added slowly to a mechanically stirred mixture of NaH (0.09 mol), diisopropylamine (0.06 mol), and THF (50 ml) under nitrogen. The mixture was brought to reflux for 15 min and then cooled with an ice–salt bath until the internal temperature was 5 °C. n-Butyl-lithium (20% in heptane, 26 ml) was added in three equal portions, the ice-bath removed, and the mixture heated at 40 °C (internal temperature) for 30 min. The appropriate benzyl chloride (0.03 mol) was dripped slowly into the deep red solution and the reaction brought to reflux temperature. A further addition of the benzyl chloride (0.02 mol) was made and the mixture refluxed for 3 h. The resulting pale yellow solution was cooled and dilute HCl (10% v/v, 100 ml) added. The mixture was made alkaline with dilute NaOH solution (10% w/v) and the aqueous layer separated. The organic layer was diluted with water (50 ml) and ether (75 ml), acidified with dilute HCl (10% v/v), and extracted with ethyl acetate (3 × 100 ml). The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was triturated with ethyl acetate to afford the appropriate *N*-benzoyl-2-benzylproline as an off-white crystalline solid.

N-Benzoyl-2-benzylproline (2g). This compound was obtained as a white crystalline solid (70%), m.p. 169—172.5 °C; $\nu_{max.}$ (Nujol) 1 735 (carboxylic acid C=O) and 1 600 (NC=O) cm^{-1}, τ($CDCl_3$) −0.64 (1 H, s, OH), 2.53 (5 H, s, NCOPh), 2.70 (5 H, s, CPh), 5.98 (1 H, d, *J* 13.5 Hz, one of benzylic CH_2), 6.36—7.37 (2 H, m, proline 5-H_2), 6.82 (1 H, d, *J* 13.5 Hz, one of benzylic CH_2), and 7.45—8.92 (4 H, m, proline 3- and 4-H_2); *m/e* 309 (0.4%), 218 (15), 159 (4), 146 (3), and 105 (100) (Found: C, 74.2; H, 6.3; N, 4.3. $C_{19}H_{19}NO_3$ requires C, 73.8; H, 6.2; N, 4.5%).

N-Benzoyl-2-(3-methoxybenzyl)proline (2h). This compound was obtained as white crystals (60%), m.p. 160—163 °C; $\nu_{max.}$ (Nujol) 1 735 (carboxylic acid C=O) and 1 600 (NCO) cm^{-1}; τ($CDCl_3$) −0.42 (1 H, s, CO_2H), 2.20—2.90 (7 H, m, NCOPh and methoxybenzyl 5- and 6-protons), 2.95—3.28 (2 H, m, methoxybenzyl 2- and 4-protons), 6.01 (1 H, d, *J* 13.5 Hz, one of benzylic CH_2), 6.28 (3 H, s, OMe), 6.41—7.30 (2 H, m, proline 5-H_2), 6.85 (1 H, d, *J* 13.5 Hz, one of benzylic CH_2), and 7.42—8.80 (4 H, m, proline 3- and 4-H_2); *m/e* 339 (8%), 295 (45), 294 (20), 218 (89), 190 (28), 121 (30), 106 (48), and 105 (100) (Found: C, 71.0; H, 6.25; N, 3.9. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 4.1%).

N-Benzoyl-2-(4-methoxybenzyl)proline (2i). This compound was obtained as white prisms (61%), m.p. 185—187 °C; $\nu_{max.}$ (Nujol) 1 740 (carboxylic acid C=O) and 1 605 (NC=O) cm^{-1}; τ($CDCl_3$) −0.60 (1 H, s, CO_2H), 2.47 (5 H, s, NCOPh), 2.74 (2 H, d, *J* 8 Hz, 2- and 6-protons of methoxybenzyl group), 3.08 (2 H, d, *J* 8 Hz, 3- and 5-protons of methoxybenzyl group), 6.03 (1 H, d, *J* 13.5 Hz, one of benzylic CH_2), 6.15 (3 H, s, OMe), 6.42—7.15 (2 H, m, proline 5-H_2), 6.84 (1 H, d, *J* 13.5 Hz, one of benzylic CH_2), and 7.41—8.82 (4 H, m, proline 3- and 4-H_2); *m/e* 339 (11%), 295 (21), 219 (15), 218 (98), 121 (55), and 105 (100) (Found: C, 70.4; H, 6.1; N, 4.0. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 4.1%).

N-Benzoyl-2-(3,4-dimethoxybenzyl)proline (2k). This compound was obtained as white crystals (51%), m.p. 178—185 °C; $\nu_{max.}$ (Nujol) 1 735 (carboxylic acid C=O) and 1 595 (NCO) cm^{-1}; τ($CDCl_3$) 1.24 (1 H, s, CO_2H), 2.59 (5 H, s, NCOPh), 3.23 (3 H, m, aromatic dimethoxybenzyl protons), 6.07 (1 H, d, *J* 13.5 Hz, one of benzylic CH_2), 6.15 (3 H, s, OMe), 6.29 (3 H, s, OMe), 6.47—7.17 (2 H, m, proline 5-H_2), 6.80 (1 H, d, *J* 13.5 Hz, one of benzylic CH_2), and 7.45—8.87 (4 H, m, proline 3- and 4-H_2); *m/e* 369 (14%), 218 (29), 151 (26), and 105 (100) (Found: C, 68.0; H, 6.4; N, 3.5. $C_{21}H_{23}NO_5$ requires C, 68.3; H, 6.3; N, 3.8%).

Intramolecular Cyclisation of N-Benzoyl-(2-benzylproline (2g).—*Method* (*a*). Phosphorus pentaoxide (5.0 g) and orthophosphoric acid (5.0 g) were mixed together in a round-bottom flask and heated with a naked flame until a clear liquid was obtained. On cooling, *N*-benzoyl-2-benzylproline (1.0 g) was added and the mixture heated at 95—100 °C on an oil-bath with stirring. The initial rapid effervescence diminished after 10 min, and heating was continued for 1 h. The mixture was then cooled, poured into ice–water (75 ml) and the resulting aqueous mixture extracted into ethyl acetate (3 × 50 ml). The combined organic layers were washed with water (1 × 50 ml), sodium bicarbonate solution (10% w/v, 1 × 75 ml), dried ($MgSO_4$), and the solvent evaporated to afford a yellow oil which on refrigeration afforded *5-benzamido-1-phenylpentan-2-one* as a buff solid (28%), m.p. 68—72 °C [ether–light petroleum (b.p. 40—60 °C)]; $\nu_{max.}$ (Nujol) 1 715 (C=O), 1 635 and 1 600 (NC=O) cm^{-1}; τ($CDCl_3$) 2.05—2.40 (2 H, m, benzoyl 2- and 6-H), 2.40—2.99 (3 H, m, benzoyl 3-, 4-, and 5-H), 2.78 (5 H, s, Ph), 3.29 (1 H, d, *J* 6 Hz, exchangeable with D_2O, NH), 6.34 (2 H, s, 1-CH_2), 6.65 (2 H, q, collapses to t with D_2O, *J* 6 Hz, 5-CH_2), 7.43 (2 H, t, *J* 6.2 Hz, 3-CH_2), and 8.17 (2 H, m, 4-CH_2); *m/e* 281 (15%), 190 (23), 105 (100), and 77 (37) (Found: C, 76.8; H, 6.7; N, 4.9. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%).

Method (*b*). *N*-Benzoyl-2-benzylproline (4.0 g) was dissolved in redistilled thionyl chloride (15 ml) and the mixture heated under reflux for 2 h. Dry dichloromethane (50 ml) was added to the cooled reaction mixture and the solvent evaporated; this procedure was repeated twice. The resulting oil was dissolved in dry dichloromethane (100 ml) and cooled in ice. Freshly sublimed aluminium chloride (5.0 g) was added in two equal portions to the stirred dichloromethane solution during 30 min, the ice-bath removed, and the mixture stirred for a further 1.5 h. The reaction mixture was poured into a water–dilute hydrochloric acid–ice mixture (100 ml), and the organic layer separated. The aqueous layer was extracted with dichloromethane (1 × 50 ml), the combined organic liquors washed with water (1 × 50 ml), potassium carbonate solution (10% v/v, 2 × 50 ml), and water (1 × 50 ml), and dried ($MgSO_4$). On evaporation of the solvent, a gum was obtained which, when triturated with ether–light petroleum (b.p. 40—60 °C) afforded *N-benzoyl-spiro*[*1-oxoindan-2,2′-pyrrolidine*] (3g) as a light brown solid (37%), m.p. 110—111.5 °C (ether); $\nu_{max.}$ (Nujol) 1 720 (C=O) and 1 620 (NC=O) cm^{-1}; τ($CDCl_3$) 2.00—2.77 (9 H, m, aromatic protons), 6.09—6.47 (2 H, m, pyrrolidine 5-H_2), 6.14 (1 H, d, *J* 16 Hz, indane 3-H *cis* to nitrogen), 6.93 (1 H, d, *J* 16 Hz, indane 3-H *trans* to nitrogen), and 7.68—8.22 (4 H, m, pyrrolidine 3- and 4-H_2); *m/e* 291 (40%), 186 (43), 170 (35), 122 (11), and 105 (100) (Found: C, 78.5; H, 5.9; N, 4.7. $C_{18}H_{17}NO_2$ requires C, 78.3; H, 5.9; N, 4.8%).

Intramolecular Cyclisation of N-Benzoyl-2-(3-methoxybenzyl)proline (2h).—*Method* (*a*). Reaction of (2h) with polyphosphoric acid, in the manner described above, gave a white solid (42%), m.p. 122—136 °C, which was shown to be a mixture of *N-benzoylspiro*[*(5-methoxy-1-oxoindane)-2,2′-pyrrolidine*] (3h) and *N-benzoylspiro*[*(7-methoxy-1-oxoindane)-2,2′-pyrrolidine*) (3*j*), respectively; $\nu_{max.}$ (Nujol) 1 710 (C=O) and 1 615 (NC=O) cm^{-1}; τ($CDCl_3$) 2.13—2.86 (6 H, m, aromatic protons), 2.98—3.37 (2 H, m, aromatic protons), 5.98—6.66 (3 H, m, pyrrolidine 5-H_2 and indane 3-H *cis* to nitrogen), 6.12 (1 H, s, 7-OMe), 6.21 (2 H, s, 5-OMe), 7.04 (1 H, d, *J* 16 Hz, indane 3-H *trans* to nitrogen), 7.55—8.38 (4 H, m, pyrrolidine 3- and 4-H_2); *m/e* 321 (33%), 216 (48), 201 (14), 200 (76), 188 (17), 175 (16), and 105 (100); t.l.c. of the above product on silica gel sheets (Eastman chromagram) using ethyl acetate–benzene (1 : 1 v/v) as developing solvent, showed two u.v. detectable spots at R_F 0.59 and 0.38 (Found: C, 75.2; H, 6.2; N, 4.2. $C_{20}H_{19}NO_3$ requires C, 74.7; H, 6.0; N, 4.4%).

Method (*b*). Reaction of (2h) with thionyl chloride and attempted cyclisation of the crude acid chloride with aluminium chloride as described previously, afforded a resinous product from which no identifiable product could be isolated.

Method (*c*). A mixture of (2h) (2.0 g) and trifluoroacetic anhydride (1.5 ml) in dry benzene (20 ml) was heated under reflux for 4 h. The cooled reaction mixture was poured into saturated sodium carbonate solution (20 ml) and the organic phase separated. The aqueous layer was washed with benzene (1 × 50 ml) and acidified to give a white precipitate of starting material (0.5 g). The combined organic liquors were washed with water (1 × 50 ml), dried ($MgSO_4$), and the solvent evaporated to yield an oil, which was separated into two fractions on a silica gel column (Fisons, 80—200 mesh, 2 × 30 cm) with ether as eluant. The first fraction afforded an oil on evaporation of solvent, and was refractionated on a silica gel column (1 × 15 cm) with light petroleum (b.p. 30—40 °C)–ether (1 : 1 v/v) as eluant to yield a yellow solid (9%), m.p. 116—124 °C, identified as a mixture of the geometrical isomers, (4a) and (4b), of 3-(*N*-benzoyl-2-pyrrolylidene)-1,1,1-trifluoro-4-(3-methoxyphenyl)butan-2-one; $\nu_{max.}$ (Nujol) 1 720 (CF_3C=O) and 1 600 (N−C=O) cm^{-1}; τ($CDCl_3$) 2.40—3.20 (9 H, aromatic protons), 6.20 (0.5 H, s, OMe of one of geometrical forms), 6.43 (0.5 H, s, OMe of other geometrical form), 6.10—6.25 (2 H, m, pyrrolidine 5-H_2), 6.80—7.35 (2 H, m, pyrrolidine 3-H_2), and 7.82—8.80 (2 H, m, pyrrolidine 4-H_2); *m/e* 389 (12%), 293 (12), 292 (49), and 106 (100) [Found: M^+ 389.123 10. $C_{21}H_{18}F_3NO_3$ requires *M* 389.123 87. Found: (*M* − CF_3CO), 292.133 45. $C_{19}H_{18}NO_2$ requires 292.133 75]; t.l.c. on silica gel sheets, using light petroleum (b.p. 40—60 °C)–ether (1 : 1 v/v) as developing solvent, showed two u.v.-detectable spots at R_F 0.46

and 0.66 (Found: C, 65.3; H, 4.8; N, 3.6; F, 14.4. $C_{21}H_{18}NO_3F_3$ requires C, 64.8; H, 4.7; N, 3.6; F, 14.6%). The second fraction from the initial silica gel column yielded an oil after evaporation of solvent. On trituration of the oil with dry ether, a white solid was obtained (10.5%), m.p. 122—138 °C, shown to be a mixture of (3h) and (3j).

Attempted Intramolecular Cyclisation of N-*Benzoyl*-2-(4-*methoxybenzyl*)*proline* (2i).—No isolable products could be obtained on reaction of (2i) with either polyphosphoric acid or thionyl chloride followed by aluminium chloride [see methods (a) and (b) above]. Attempted cyclisation of (2i) with trifluoroacetic anhydride [method (c)] afforded only 3-(*N*-benzoyl-2-pyrrolylidene)-1,1,1-trifluoro-4-(4-methoxyphenyl)butan-2-one [(4c) and/or (4d)] (14%), m.p. 145—151 °C; $\nu_{max.}$ (Nujol) 1 720 (CF_3C=O) and 1 610 (NC=O) cm^{-1}; τ($CDCl_3$) 2.51 (5 H, s, COPh), 2.75 (2 H, d, *J* 8.5 Hz, methoxyphenyl 2- and 6-H), 3.08 (2 H, d, *J* 8.5 Hz, methoxyphenyl 3- and 5-H), 5.94—6.38 (2 H, m pyrrolidine 5-H_2), 6.18 (3 H, s, OMe), 6.82—7.51 (2 H, m, pyrrolidine 3-H_2), and 7.81—8.10 (2 H, m, pyrrolidine 4-H_2); *m/e* 389 (14%), 292 (76), 188 (18), 172 (24), 106 (20), and 105 (100); no satisfactory elemental analysis figures could be obtained for this product.

Intramolecular Cyclisation of N-*Benzoyl*-2-(3,4-*dimethoxybenzyl*)*proline* (2k).—No isolable products could be obtained when (2k) was reacted with either polyphosphoric acid or thionyl chloride followed by aluminium chloride [see methods (a) and (b) above]. Reaction of (2k) with trifluoroacetic anhydride [see method (c)] afforded N-*benzoylspiro*[5,6-*dimethoxy*-1-*oxoindane*)-2,2′-*pyrrolidine*] (3k) as a pale yellow solid (58%), m.p. 183—185 °C; $\nu_{max.}$ (Nujol) 1 705 (C=O) and 1 605 (NC=O) cm^{-1}; τ($CDCl_3$) 2.21—2.78 (6 H, m, COPh and indane 7-H), 3.16 (1 H, s, indane 4-H), 5.88—6.62 (3 H, m, pyrrolidine 5-H_2 and indane 3-H *cis* to nitrogen), 6.10 (3 H, s, OMe), 6.14 (3 H, s, OMe), 7.04 (1 H, d, *J* 16 Hz, indane 3-H *trans* to nitrogen), and 7.61—8.25 (4 H, m, pyrrolidine 3- and 4-H_2); *m/e* 351 (42%), 246 (22), 230 (100), 204 (22), and 105 (91) (Found: C, 71.9; H, 6.0; N, 3.9. $C_{21}H_{21}NO_4$ requires C, 71.8; H, 6.0; N, 4.0%).

Wolff–Kishner Reduction of N-*Benzoylspiro*[1-*oxoindane*-2,2′-*pyrrolidine*] (3g).—Compound (3g) (105 mg) was dissolved in absolute ethanol (10 ml), hydrazine hydrate (0.2 ml), and triethylamine (0.3 ml) were added, and the mixture heated under reflux for 1 h. The cooled mixture was evaporated to dryness, and the residue shown to be unchanged starting material (m.p., i.r., and ^1H n.m.r. spectra). Similar results were obtained when potassium hydroxide in diethylene glycol was utilised in place of triethylamine and ethanol.

Wolff–Kishner Reduction of N-*Benzoylspiro*[(5,6-*dimethoxy*-1-*oxoindane*)-2,2′-*pyrrolidine*] (3k). A mixture of (3k) (0.75 g), hydrazine hydrate (0.75 ml), and potassium hydroxide (0.36 g) in diethylene glycol (25 ml) was heated under reflux (oil bath) for 2 h. The cooled reaction mixture was poured into dilute HCl (10% v/v, 40 ml) and the resulting solid filtered off and dissolved in dichloromethane (20 ml). The filtrate was extracted with dichloromethane and the combined organic liquors washed with sodium carbonate solution (10% w/v, 20 ml). Evaporation of the organic layer afforded a negligible residue. Acidification of the aqueous layer, extraction with dichloromethane (2 × 75 ml), and evaporation of the combined organic extracts, afforded a white solid (28%), m.p. 289—293 °C (with decomposition), assigned as either N-*benzoylspiro*[(5-*hydroxy*-6-*methoxy*-1-*oxoindane*)-2,2′-*pyrrolidine*] (31) or N-*benzoyl*-*spiro*[(6-*hydroxy*-5-*methoxy*-1-*oxoindane*)-2,2′-*pyrrolidine*] (3m); $\nu_{max.}$ (Nujol) 3 400—3 350 (OH), 1 715 (C=O), and 1 600 (NC=O) cm^{-1}; τ(CF_3CO_2H) 1.72—2.81 (5 H, m, Ph), 2.54 [1 H, s, indane 4- (or 7-) H], 3.01 [1 H, s, indane 7- (or 4-) H], 6.05 (3 H, s, OMe), 6.05—6.49 (3 H, m, pyrrolidine 5-H_2 and indane 3-H *cis* to nitrogen), 6.89 (1 H, d, *J* 16 Hz, indane 3-H *trans* to nitrogen), and 7.82 (4 H, m, pyrrolidine 3- and 4-H_2); *m/e* 337 (62%), 232 (30), 216 (90), 150 (38), 149 (44), and 105 (100) (Found: C, 71.5; H, 5.7; N, 4.5. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.6; N, 4.2%).

Clemmensen Reduction of N-*Benzoylspiro*[(5,6-*dimethoxy*-1-*oxoindane*)-2,2′-*pyrrolidine*] (3k).—Zinc wool (1.5 g) was covered with sodium hydroxide solution (15% w/v) and the mixture warmed until hydrogen gas was evolved. The solution was then decanted off, the zinc wool washed with water (5 × 25 ml) and then covered with mercuric chloride solution (1% w/v, 25 ml) for 30 min. After decanting off the mercuric chloride solution, the zinc amalgam was rinsed with water (2 × 25 ml), and then covered with a mixture of water (0.5 ml), concentrated HCl (2.0 ml), and toluene (5.0 ml). Compound (3k) (0.75 g) was added to the amalgam and the mixture vigorously heated under reflux for 2 h. Additional concentrated HCl (1.0 ml) was then added and the refluxing was continued for a further 4 h. The cooled reaction mixture was poured into a mixture of benzene (50 ml) and water (50 ml) and the aqueous layer was separated and extracted with benzene (1 × 25 ml); the combined organic layers were then washed with water (1 × 25 ml), dried ($MgSO_4$), and the solvent evaporated off. Trituration of the resulting residue with ether–light petroleum (b.p. 30—40 °C) afforded N-*benzoyl*-3-[2-(5,6-*dimethoxyindanyl*)]*propylamine* (7) as a white crystalline solid (69%), m.p. 107—113 °C; $\nu_{max.}$ (Nujol) 1 640 and 1 610 (NC=O) cm^{-1}; τ($CDCl_3$) 2.02—2.37 (2 H, m, benzoyl 2- and 6-H), 2.40—2.66 (3 H, m, benzoyl 3-, 4-, and 5-H), 3.32 (2 H, s, indane 4- and 7-H), 3.50 (1 H, s, exchangeable with D_2O, NH), 6.04—7.73 (7 H, m, indane 1-H_2, 2-H, 3-H_2, and CH_2N), 6.20 (6 H, s, 2 × OMe), and 7.91—8.60 (4 H, m, C-CH_2CH_2); *m/e* 339 (21%), 135 (13), 134 (16), and 105 (100) (Found: C, 74.5; H, 7.2; N, 4.4%; M^+ 339.182 40. $C_{21}H_{25}NO_3$ requires C, 74.3; H, 7.4; N, 4.1%; *M* 339.183 4).

Attempted Preparation of N-*Benzylspiro*[*indane*-2,2′-*pyrrolidine*] (1n).—Compound (3g) (0.3 g) was dissolved in THF (50 ml) and diborane (prepared by the action of boron trifluoride–ether on a suspension of sodium borohydride in diglyme) bubbled through the solution until an aliquot showed the presence of an excess of diborane (a positive reaction is when an effervescence with ethanol is observed). The solution was then heated at reflux temperature for 40 h. Excess of diborane was destroyed by the addition of a few drops of sodium hydroxide solution (10% w/v) to the cooled reaction mixture, which was then poured into a mixture of water (30 ml) and ether (75 ml). The organic layer was separated and the aqueous layer extracted with ether (1 × 50 ml). The combined ethereal extracts were washed with hydrochloric acid (10% v/v, 2 × 15 ml), and the acid washings basified and then extracted with dichloromethane (2 × 20 ml) and then chloroform (1 × 25 ml). The combined organic layers were evaporated to yield an oil (81%), which was shown to consist of a 1 : 1 mixture of the α- and β-epimers of N-*benzylspiro*[1-*hydroxyindane*-2,2′-*pyrrolidine*] (5n) and (6n) respectively; $\nu_{max.}$ (Nujol) 3 600—3 200 (OH) cm^{-1}; τ($CDCl_3$) 2.35—2.95 (9 H, m, aromatic

H), 4.75 (0.5 H, s, epimer with indane 1-H *cis* to nitrogen), 5.15 (0.5 H, s, epimer with indane 1-H *trans* to nitrogen), 5.95—8.45 (11 H, complex overlapping multiplets, reduces to 10 H with D_2O, indane 3-H_2, pyrrolidine 3-, 4-, and 5-H_2, CH_2Ph and OH). A sample of the above epimeric mixture (0.5 g) was chromatographed on an alumina column (Laporte Industries, type H, 5.6 × 1.4 cm) with ether–light petroleum (b.p. 40—60 °C) (1 : 10 v/v). An initial fraction was obtained which on evaporation of solvent afforded the pure β-isomer (6n) as white crystals, sensitive to light, m.p. 80—82.5 °C; τ($CDCl_3$) 2.36—3.01 (4 H, m, indane aromatic H), 2.81 (5 H, s, Ph), 5.18 (1 H, s, indane 1-H *trans* to nitrogen), and 5.50 (1 H, s, exchangeable with D_2O, OH), 6.32—8.47 (10 H, complex overlapping multiplets, indane 3-H_2, pyrrolidine 3-, 4-, and 5-H_2, and NCH_2Ph); *m/e* 279 (68%), 261 (10), 248 (27), 188 (58), 160 (82), and 91 (100) (Found: C, 81.65; H, 7.55; N, 4.9. $C_{19}H_{21}NO$ requires C, 81.7; H, 7.6; N, 5.0%).

Lithium Aluminium Hydride Reduction of N-*Benzoylspiro*[1-*oxoindane*-2,2′-*pyrrolidines*].—The appropriate *N*-benzoylspiro[1-oxoindane-2,2′-pyrrolidine] (3.6 mmol) was added to a mixture of THF (75 ml) and LAH (0.9 g), and the reaction mixture heated under reflux for 12 h. Work-up in the usual manner afforded the corresponding *N*-benzylspiro[1-hydroxyindane-2,2′-pyrrolidine] as an epimeric mixture of the 1α-ol (5) and 1β-ol (6) isomers. LAH reduction of (3 g) gave a 4 : 1 mixture of the α- and β-epimers (5n) and (6n), respectively. LAH reduction of the isomeric mixture of (3h) and (3i) gave a clear oil (93%), which consisted of a four-component mixture of the epimers of N-*benzylspiro*[5-*methoxy*-1-*hydroxyindane*)-2,2′-*pyrrolidine*] (5o and 6o) and N-*benzylspiro*[(7-*methoxy*-1-*hydroxyindane*)-2,2′-*pyrrolidine*] (5p and 6p); τ($CDCl_3$) 2.46—2.97 (6 H, m, aromatic H), 3.03—3.36 (2 H, m, aromatic H), 4.84 (0.15 H, s, indane 1-H *cis* to nitrogen in 5- and 7-methoxy-isomers), 5.23 (0.85 H, s, indane 1-H *trans* to nitrogen in 5- and 7-methoxy-isomers), 6.21 (1 H, s, 7-OMe), 6.24 (2 H, s, 5-OMe), and 6.31—8.50 (11 H, complex overlapping m, indane 3-H_2, pyrrolidine 3-, 4-, and 5-H_2, NCH_2Ph, and OH). No attempt was made to separate these isomers. LAH reduction of (3k) afforded N-*benzylspiro*[5,6-*dimethoxy*-1-*hydroxyindane*-2,2′-*pyrrolidine*] as white crystals, m.p. 112—114.5 °C (85%), shown to be an epimeric mixture of (5q) and (6q); τ($CDCl_3$) 2.85 (5 H, s, Ph), 3.04 (1 H, s, indane 7-H), 3.34 (1 H, s, indane 4-H), 4.90 (0.15 H, s, indane 1-H *cis* to nitrogen), 5.27 (0.85 H, s, indane 1-H *trans* to nitrogen), 6.17, (3 H, s, Me), 6.20 (3 H, s, OMe), 5.62—6.42 (1 H, broad s, exchangeable with D_2O, OH), and 6.27—8.50 (10 H, complex overlapping m, indane 3-H_2, pyrrolidine 3-, 4-, and 5-H_2, and NCH_2Ph); *m/e* 340 (8%), 339 (31), 248 (31), 160 (100), and 91 (59) (Found: C, 74.3; H, 7.4; N, 4.1. $C_{21}H_{25}NO_3$ requires C, 74.3; H, 7.4; N, 4.1%).

N-*Benzylspiro*[5-(*and* 4-)*methoxyindane*-2,2′-*pyrrolidine*] (1o *and* 1p).—The isomeric mixture of (3h) and (3j) was reduced with diborane in THF under conditions identical to those employed for the attempted reduction of (3g) and afforded a mixture of the 4- *and* 5-*methoxy-derivatives* of N-*benzylspiro*[*indane*-2,2′-*pyrrolidine*] (1o) and (1p), respectively, as a clear oil (55%); τ($CDCl_3$) 2.58—3.11 (6 H, m, aromatic H), 3.12—3.55 (2 H, m, aromatic H), 6.27 (1 H, s, 4-OMe), 6.34 (2 H, s, 5-OMe), 6.61 (2 H, s, NCH_2Ph), 6.67—7.60 (6 H, complex overlapping m, indane 1- and 3-H_2, and pyrrolidine 5-H_2), and 7.95—8.51 (4 H, m, pyrrolidine 3- and 4-H_2).

N-*Benzylspiro*[5,6-*dimethoxyindane*-2,2′-*pyrrolidine*] (1q).—Reduction of (3k) with diborane in THF afforded N-*benzylspiro*[5,6-*dimethoxyindane*-2,2′-*pyrrolidine*] (1q) as a clear oil (66%); τ($CDCl_3$) 2.78 (5 H, s, Ph), 3.30 (2 H, s, indane 4- and 7-H), 6.85 (2 H, d, *J* 16 Hz, indane 1- and 3-H *cis* to nitrogen), 7.08—7.56 (4 H, overlapping m, indane 1- and 3-H *trans* to nitrogen and pyrrolidine 5-H_2), and 8.12 (4 H, m, pyrrolidine 3- and 4-H_2); *m/e* 232 (97%), 308 (61), 241 (100), 232 (36), 201 (48), 165 (32), and 98 (39); the fumaric acid salt was obtained as a white crystalline solid, m.p. 184—190 °C (Found: C, 68.8; H, 6.9; N, 3.0. $C_{25}H_{29}NO_6$ requires C, 68.3; H, 6.7; N, 3.2%).

Attempted Catalytic N-*Debenzylation of* N-*Benzylspiro*[*indane*-2,2′-*pyrrolidines*].—Compound (1q) (0.32 g) was dissolved in absolute ethanol (50 ml) containing four drops of perchloric acid (70% w/v). Palladium–charcoal catalyst (5%, 0.4 g) was then added and the mixture shaken under hydrogen at atmospheric pressure and ambient temperature for 15 h. No uptake of hydrogen was observed during this period, and quantitative recovery of starting material was obtained after filtering off the catalyst and evaporating the filtrate. The use of glacial acetic acid in place of ethanol, or the substitution of palladium black in place of palladium–charcoal, had no beneficial effect on the reaction. Similar attempts to *N*-debenzylate the isomeric mixture of (1o) and (1p) were also unsuccessful.

Catalytic N-*Debenzylation of* N-*Benzylspiro*[1-*hydroxyindane*-2,2′-*pyrrolidines*].—The appropriate *N*-benzylspiro-[1-hydroxyindane-2,2′-pyrrolidine] (1.0 mmol) was dissolved in a mixture of absolute ethanol (30 ml), glacial acetic acid (5.0 ml), and perchloric acid (70% v/v, 0.6 ml). Palladium–charcoal (5%, 0.5 g) was added and the mixture shaken under hydrogen at room temperature and atmospheric pressure until hydrogen uptake was complete. The mixture was then filtered, the filtrate evaporated to low bulk, and water (50 ml) and hydrochloric acid (10% v/v, 5 ml) added. The aqueous solution was washed with ether (50 ml), strongly basified with sodium hydroxide solution, and extracted into ether (3 × 50 ml). The combined ether extracts were washed with water (50 ml), dried, filtered, and evaporated to dryness to yield the corresponding spiro[1-hydroxyindane-2,2′-pyrrolidine]. The epimeric mixture of (5n) and (6n) on catalytic debenzylation afforded *spiro*[1-*hydroxyindane*-2,2′-*pyrrolidine*] (5a and 6a) as white prisms (51%), m.p. 111—114 °C (hexane); τ($CDCl_3$) 2.42—2.94 (4 H, m, aromatic protons), 5.13 (0.15 H, s, indane 1-H *cis* to nitrogen), 5.50 (0.85 H, s, indane 1-H *trans* to nitrogen), 6.70—7.31 (6 H, reducing to 4 H on addition of D_2O, m, indane 3-H_2, pyrrolidine 5-H_2, OH, and NH), and 7.95—8.30 (4 H, m, pyrrolidine 3- and 4-H_2); *m/e* 189 (21%), 170 (79), 128 (21), 115 (33), and 91 (36) (Found: C, 76.3; H, 8.0; N, 7.6. $C_{12}H_{15}NO$ requires C, 76.2; H, 8.0; N, 7.4%). Catalytic *N*-debenzylation of the two pairs of epimers (5o and 6o) and (5p and 6p) afforded a clear gum (84%) consisting of a mixture of the epimers of *spiro*[(5-*methoxy*-1-*hydroxyindane*)-2,2′-*pyrrolidine*] (5d and 6d) and *spiro*[(7-*methoxy*-1-*hydroxyindane*)-2,2′-*pyrrolidine*] (5e and 6e); τ($CDCl_3$) 2.54—2.94 (1 H, m, aromatic H), 3.07—3.43 (2 H, m, aromatic H), 5.12 (0.05 H, s, indane 1-H *cis* to nitrogen in 7-methoxy-isomer), 5.26 (0.1 H, s, indane 1-H *cis* to nitrogen in 5-methoxy-isomer), 5.52 (0.28 H, s, indane 1-H *trans* to nitrogen in 7-methoxy-isomer), 5.62 (0.56 H, s, indane 1-H *trans* to nitrogen in 5-methoxy-isomer), 6.19 (1 H, s, 7-OMe), 6.29 (2 H, s, 5-OMe), 6.65—7.42 (4 H, m, indane 3-H_2 and pyrrolidine 5-H_2), 6.87

(broad s, disappears on addition of D_2O, OH, and NH), and 7.90—8.47 (4 H, complex m, pyrrolidine 3- and 4-H_2). *N*-Debenzylation of a mixture of the isomers (5q) and (6q) afforded *spiro*[(5,6-*dimethoxy*-1-*hydroxyindane*)-2,2′-*pyrrolidine*], (5f) and (6f), as an epimeric mixture. The product was obtained as a clear oil (93%); τ($CDCl_3$) 3.03 (1 H, s, indane 7-H), 3.31 (1 H, s, indane 4-H), 5.20 (0.15 H, s, indane 1-H *cis* to nitrogen), 5.55 (0.85 H, s, indane 1-H *trans* to nitrogen), 6.18 (3 H, s, OMe), 6.20 (3 H, s, OMe), 6.98 (2 H, disappears on addition of D_2O, broad s, OH, and NH), 7.09 (4 H, m, indane 3-H_2 and pyrrolidine 5-H_2), 8.13 (4 H, m, pyrrolidine 3- and 4-H_2) (Found: C, 67.7; H, 7.5; N, 5.6. $C_{14}H_{19}NO_3$ requires C, 67.5; H, 7.6; N, 5.6%).

Reductive Dehydroxylation of Spiro[1-*hydroxyindane*-2,2′-*pyrrolidine*] *Derivatives*.—Diborane gas was passed through a solution of the epimeric mixture of (5a) and (6a) (2.0 mmol) in THF (32 ml) until an aliquot of the reaction mixture showed rapid effervescence when added to ethanol. Work-up in the usual manner resulted in quantitative recovery of starting material. Attempts to dehydroxylate (5a) and (6a) catalytically, with palladium–charcoal (5%) in glacial acetic acid containing 1% perchloric acid, at 70 °C and 3 atm hydrogen pressure, were also unsuccessful. Dehydroxylation of the two sets of epimers (5d) and (6d), and (5e) and (6e) gave a clear oil (97%) consisting of the 4- *and* 5-*methoxy-derivatives* of *spiro*[*indane*-2,2′-*pyrrolidine*] (1e) and (1d) respectively; τ($CDCl_3$) 2.96 (1 H, d, *J* 8 Hz, aromatic H), 3.16—3.50 (2 H, complex m, aromatic protons), 6.27 (1 H, s, 4-OMe), 6.30 (2 H, s, 5-OMe), 6.82—7.36 (7 H, complex m, indane 1- and 3-H_2, pyrrolidine 5-H_2, and NH), and 7.82—8.60 (4 H, complex m, pyrrolidine 3- and 4-H_2). Chromatographic separation of the above isomers (0.1 g) was achieved on preparative t.l.c. plates of silica gel using s-butyl alcohol–isopropyl alcohol–benzene–formic acid–water (7.5 : 6.0 : 6.0 : 1.5 : 1.2) as developing solvent. On this system, (1d) (major band) had an R_F of 0.56, whereas (1e) (minor band) showed an R_F of 0.59. The sample of (1d) obtained from the above separation was slightly contaminated with (1e) but conversion to the fumarate salt, and recrystallisation from ethanol–ether, afforded (1d) as a white crystalline hemifumarate, m.p. 196—201 °C (Found: C, 68.7; H, 7.2; N, 5.1. $C_{15}H_{19}NO_3$ requires C, 68.9; H, 7.3; N, 5.4%). The regenerated base from the above salt showed τ($CDCl_3$) 2.97 (1 H, d, *J* 8 Hz, indane 7-H), 3.16—3.51 (2 H, m, indane 4- and 6-H), 6.30 (3 H, s, OMe), 6.80—7.41 (6 H, complex m, indane 1- and 3-H_2 and pyrrolidine 5-H_2), 7.83—8.48 (4 H, complex m, pyrrolidine 3- and 4-H_2), and 8.07 (1 H, broad s, NH); *m/e* 203 (100%), 202 (15), 189 (12), 188 (81), 160 (10), and 135 (35). The sample of (1e) obtained from the above preparative t.l.c. separation was contaminated with (1d) and was not purified further. Dehydroxylation of the epimeric mixture of (5f) and (6f) with diborane in THF afforded *spiro*[5,6-*dimethoxyindane*-2,2′-*pyrrolidine*] (1f) as a light pink oil (85%); τ($CDCl_3$) 3.21 (2 H, s, indane 4- and 7-H), 6.16 (6 H, s, 2 × OMe), 6.76—7.26 (6 H, complex m, indane 1- and 3-H_2 and pyrrolidine 5-H_2), 7.69 (1 H, broad s, disappears on addition of D_2O, NH), and 7.85—8.49 (4 H, complex m, pyrrolidine 3- and 4-H_2); *m/e* 233 (79%), 232 (24), 218 (100), 174 (33), 165 (21), 115 (21), and 99 (31). The hydrobromide salt was obtained as white prisms, m.p. 207—209.5 °C (ethanol–ether); τ(C_5D_5N–D_2O) 3.23 (2 H, s, indane 4- and 7-H), 5.93—6.40 (4 H, complex m, indane 1- and 3-H *cis* to nitrogen, and pyrrolidine 5-H_2), 6.28 (6 H, s, 2 × OMe), 6.81 (2 H, d, *J* 16 Hz, indane 1- and 3-H *trans* to nitrogen), and 7.62—7.96 (4 H, m, pyrrolidine 3- and 4-H_2) (Found: C, 53.6; H, 6.6; N, 4.4. $C_{14}H_{20}NO_2Br$ requires C, 53.5; H, 6.4; N, 4.4%).

5-*Methoxy*-2-*nitroindane* (9).—Hydrogen peroxide solution (87% v/v, 2.5 ml) was added dropwise to a magnetically stirred solution of 1,2-dichloroethane (30 ml) contained in a three-necked round-bottom flask fitted with reflux condenser, calcium chloride drying tube, and surrounded by an ice–salt bath. Concentrated sulphuric acid (3 drops) was then added, followed by a slow, dropwise addition of acetic anhydride (10.5 g or 11 ml) (**CARE !**) to the cooled and rapidly stirred mixture. The mixture was then diluted with 1,2-dichloroethane (15 ml) and heated rapidly to reflux. A solution of 2-amino-5-methoxyindane (8) (3.3 g) in dichloroethane (25 ml) was added, dropwise, during 30 min and the mixture heated under reflux for a further 1.5 h. The resulting red-brown solution was cooled and washed with a mixture of 0.88 ammonia solution (40 ml) and water (40 ml) and the organic layer separated. The aqueous portion was made just acid to litmus with dilute hydrochloric acid and then extracted with 1,2-dichloroethane (1 × 50 ml). The combined organic layers were washed with dilute hydrochloric acid (1 × 50 ml), sodium bicarbonate solution (10% w/v, 1 × 50 ml), dried, and the solvent evaporated to yield a brown oil. Distillation of the above crude product afforded 5-*methoxy*-2-*nitroindane* (9) as a yellow oil (15.5%), b.p. 142—148 °C at 0.8 mmHg, which crystallised slowly on standing, m.p. 39—43 °C (dichloromethane); τ($CDCl_3$) 2.95 (1 H, d, *J* 9 Hz, aromatic 7-H), 3.15—3.45 (2 H, m, aromatic 4- and 6-H), 4.82 (1 H, m, indane 2-H), 6.1—6.95 (4 H, overlapping m, indane 1- and 3-H_2), and 6.30 (3 H, s, OMe); *m/e* 193 (29%), 147 (100), 131 (29), 115 (23), 103 (23), and 91 (16) (Found: C, 61.9; H, 5.8; N, 7.1. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.3%).

Methyl 3-[2-(5-*methoxy*-2-*nitroindanyl*)]*propionate* (10).—Freshly distilled methyl acrylate (2.0 ml) was added to a magnetically stirred, refluxing mixture of (9) (1.0 g), redistilled t-butyl alcohol (30 ml) and benzyltrimethylammonium methoxide (0.25 ml), contained in a three-necked flask fitted with reflux condenser and calcium chloride drying tube. The reaction was heated under reflux for 18 h, cooled, dilute hydrochloric acid (40 ml) added, and the mixture extracted with dichloromethane (3 × 75 ml). The combined organic layers were washed with water (1 × 50 ml), dried, and the solvent evaporated to give an oily residue. Chromatographic separation of the residue on alumina (Type H, 1.8 × 8.5 cm) using light petroleum (b.p. 40—60 °C)–ether (2 : 1) as eluant afforded an initial major band, which on evaporation of solvent gave a clear oil (76%) identified as *methyl* 3-[2-(5-*methoxy*-2-*nitroindanyl*)]*propionate* (10); $\nu_{max.}$ 1 745 (C=O) cm^{-1}; τ($CDCl_3$) 2.89 (1 H, d, *J* 9 Hz, aromatic 7-H), 3.13—3.40 (2 H, m, aromatic 4- and 6-H), 5.91—6.41 (2 H, overlapping m, indane 1- and 3-H *cis* to nitro group), 6.25 (3 H, s, OMe), 6.35 (3 H, s, OMe), 6.85 (2 H, d, *J* 17 Hz, indane 1- and 3-H *trans* to nitro-group), and 7.58 (4 H, s, CH_2CH_2); *m/e* 279 (7%), 232 (100), 218 (24), 172 (28), 160 (52), 159 (93), 158 (90), 144 (35), 129 (35), and 115 (38) (Found: C, 60.2, H, 6.0: N, 4.9. $C_{14}H_{17}NO_5$ requires C, 60.2; H, 6.1; N, 5.0%).

Spiro[5-*methoxyindan*-2,2′-(5′-*oxopyrrolidine*)] (11).—A mixture of (10) (1.1 g) and Raney nickel (3.2 g, moist) in absolute ethanol (150 ml) was hydrogenated at ambient

temperature and atmospheric pressure until absorption of hydrogen ceased. The catalyst was then filtered off through Celite, the filtrate evaporated to dryness, and the residue dissolved in ether (30 ml). Light petroleum (b.p. 30—40 °C) was added, the solution cooled, and the resulting precipitate filtered at the pump to afford *spiro*[5-*methoxyindan*-2,2′-(5′-*oxopyrrolidine*] (11) as a light grey solid, m.p. 128—130 °C; $\nu_{max.}$ 1 695 (NC=O) cm^{-1}; τ($CDCl_3$) 2.96 (1 H, d, *J* 8.5 Hz, aromatic 7-H), 3.12—3.48 (3 H, reduces to 2 H on addition of D_2O, m, aromatic 4- and 6-H and NH), 6.29 (3 H, s, OMe), 7.02 (4 H, m, indane 1- and 3-H_2), and 7.41—8.10 (4 H, overlapping m, pyrrolidine 3- and 4-H_2); *m/e* 217 (100%), 202 (29), 188 (15), 174 (22), 135 (15), and 91 (15) (Found: C, 71.4; H, 6.9; N, 6.2. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.4%).

Preparation of Spiro[5-*methoxyindane*-2,2′-*pyrrolidine*] (1d) *by LAH Reduction of* (11).—A suspension of (11) (0.45 g) in dry ether (75 ml) containing LAH (0.45 g) was stirred magnetically at reflux temperature for 18 h. The reaction mixture was then cooled and the excess of LAH destroyed by dropwise addition of water. The organic layer was dried, and the solvent evaporated off to give *spiro*[5-*methoxyindane*-2,2′-*pyrrolidine*] (1d) as a colourless oil (83%). This product was identical (i.r., n.m.r., and mass spectrum, and t.l.c. characteristics on silica gel) to (1d) obtained from reductive dehydroxylation of the two sets of epimers, (5d) and (6d), and (5e) and (6e).

O-*Demethylation of* (1d) *and* (1f).—The appropriate spiro[indane-2,2′-pyrrolidine] (0.1 mmol) was refluxed under nitrogen for 1 h in 45% aqueous HBr (1.0 ml). The resulting yellow-brown solution was evaporated to dryness under nitrogen and the residue taken up in absolute ethanol. On addition of ether and refrigeration, buff crystals of the crude *O*-demethylated product were obtained. Recrystallisation from ethanol–ether afforded a purer product. The hydrobromide salt of *spiro*[5-*hydroxyindane*-2,2′-*pyrrolidine*] (1b) was obtained from (1d) by the above procedure in 71% yield after recrystallisation, m.p. 235—241 °C; τ(C_5D_5N–D_2O) 2.88—3.16 (3 H, m, aromatic H), 6.01—6.42 (4 H, complex m, indane 1- and 3-H *cis* to nitrogen, and pyrrolidine 5-H_2), 6.79 (2 H, d, *J* 16 Hz, indane 1- and 3-H *trans* to nitrogen), and 7.60—7.94 (4 H, m, pyrrolidine 3- and 4-H_2) (Found: C, 53.6; H, 6.2; N, 5.3. $C_{12}H_{16}BrNO$ requires C, 53.4; H, 6.0; N, 5.2%). *Spiro*[5,6-*dihydroxyindane*-2,2′-*pyrrolidine*] *hydrobromide* (1c) was obtained from (1f) in 79% yield after recrystallisation, m.p. 252—260 °C; τ (C_5D_5N–D_2O) 3.12 (2 H, s, indane 4- and 7-H), 5.96—6.39 (4 H, complex m, indane 1- and 3-H *cis* to nitrogen, and pyrrolidine 5-H_2), 6.76 (2 H, d, *J* 16 Hz, indane 1- and 3-H *trans* to nitrogen), and 7.58—7.97 (4 H, m, pyrrolidine 3- and 4-H_2) (Found: C, 52.2; H, 6.0; N, 4.5. $C_{12}H_{16}NO_2Br$ requires C, 52.0; H, 6.0; N, 4.7%).

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