The Reaction Between Isatin and Some Amines

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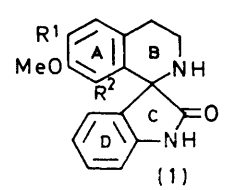
In acidic aqueous solution 2-(3,4-dimethoxyphenyl)ethylamine and isatin reacted to give 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-3'-(2'-oxoindoline) (1a): 2-(3-hydroxy-4-methoxyphenyl)ethylamine gave a mixture of the analogous 6-hydroxy-7-methoxyspiran (1b) and the isomeric 8-hydroxy-7-methoxyspiran (1c). In neither case was a derivative of 1-benzyl-1,2,3,4-tetrahydroisoquinoline detected. A mixture of 2-(3-hydroxy-4-methoxyphenyl)ethylamine and benzylamine reacted with isatin to form, in addition to the spirans, some 6-hydroxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (3b): but when a mixture of 2-(3,4-dimethoxyphenyl)-ethylamine and benzylamine was used, no 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline was detected.

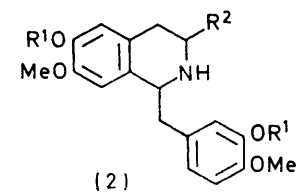
ISATIN in aqueous solution can oxidise benzylamine to benzaldehyde,[1] and can degrade some 2-amino-acids to aldehydes.[2] It seemed possible that if a suitable derivative of 2-phenylethylamine were oxidised under conditions favouring Pictet–Spengler cyclisation,[3a] then if any aldehyde were formed, this could condense with unchanged amine to produce a derivative of 1-benzyl-1,2,3,4-tetrahydroisoquinoline in a process analogous to that suggested for the biogenesis of the alkaloids related to laudanosine.[4] While this work was in progress the conversion by monoamineoxidase of 2-(3,4-dihydroxyphenyl)ethylamine into norlaudanosine was reported.[5]

The Strecker degradation is known to proceed better with 2-amino-acids than with the corresponding amines. However, we decided to use amines as the starting materials as the products would be easier to handle than the amino-acids [(2a) or (2b), but $R^2 = CO_2H$] that would be produced from derivatives of 2-(3,4-hydroxyphenyl)ethylamine. 2-(3,4-Dimethoxyphenyl)-ethylamine was first chosen. Cyclisation of Schiffs bases *para* to an MeO group requires concentrated hydrochloric acid, and, while ring closure is usual, hydrolysis may occur instead.[6] We find that even in concentrated hydrochloric acid, isatin oxidises benzylamine to benzaldehyde; estimation of this as its 2,4-dinitrophenylhydrazone gives the yield as *ca.* 35%. A different experiment showed that under these conditions benzaldehyde and 2-(3,4-dimethoxyphenyl)-ethylamine react to produce 6,7-dimethoxy-1-phenyl-



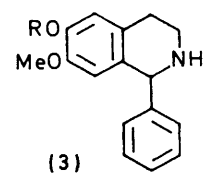
(1)

a; R^1 = MeO, R^2 = H
b; R^1 = HO, R^2 = H
c; R^1 = H, R^2 = HO



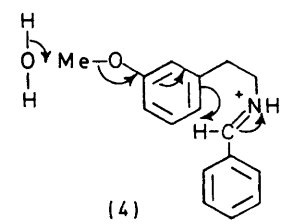
(2)

a; R^1 = Me, R^2 = H
b; R^1 = H, R^2 = H
c; R^1 = CH_2Ph, R^2 = H



(3)

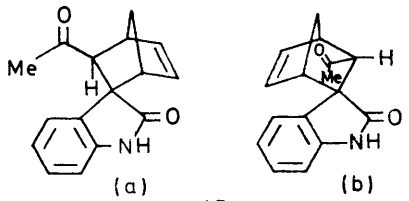
a; R = Me
b; R = H



(4)

[1] W. Traube, *Ber.*, 1911, **44**, 3145.
[2] For a review of this reaction, see A. Schonberg and R. Moubacher, *Chem. Rev.*, 1952, **50**, 261.
[3] (*a*) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, 1951, **6**, ch. 3; (*b*) ch. 2.
[4] Sir Robert Robinson, 'Structural Relations of Natural Compounds,' Oxford University Press, Oxford, 1955, p. 78.
[5] P. Holtz, K. Stock, and E. Westermann, *Nature*, 1964, **203**, 656.
[6] E. C. Weinbach and W. H. Hartung, *J. Org. Chem.*, 1950, **15**, 676.

1,2,3,4-tetrahydroisoquinoline (3a), together with some of the corresponding 6-hydroxy-7-methoxy-compound (3b). A possible mechanism for this selective demethylation, involving hydrolysis at the transition state for ring closure, is indicated (4). The reaction between 2-(3,4-dimethoxyphenyl)ethylamine and isatin afforded only 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-3′-(2′-oxoindoline) (1a); neither tetrahydropapaverine (2a) nor its possible oxidation products were detected. The structure of the spiran follows from its analysis, equivalent weight, and the spectral data. The conformation is defined as one in which the bond C(1)–C(2′) is quasi-axial with respect to ring B. Dreiding models show that if this bond is quasi-equatorial and ring B is in a half-boat conformation, there is very close approach between the hydrogen atoms on C(4) and C(4′); while if ring B is in the half-chair form there is crowding between the hydrogen atoms on C(3) and C(4′). If the bond C(1)–C(2′) is quasi-axial there are no such close approaches, and with ring B in either conformation the bond C(8)–H is parallel to the plane of ring D, and the proton about 2 Å from this plane. This hydrogen atom is thus responsible for the one-proton signal at τ 3·92. Analogously, in the spiro-3′-(2′-oxoindoline) derivatives (5a)

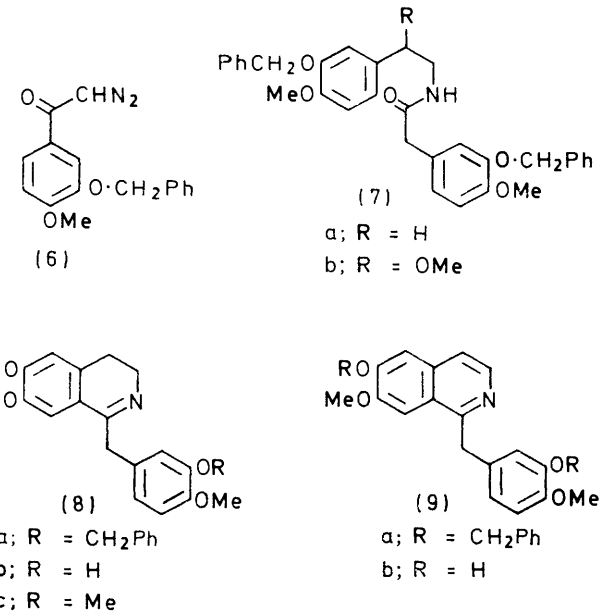


(5)

and (5b),[7] the benzene ring shields the protons of the acetyl group causing the signal to be shifted upfield by *ca.* τ 0·5. The pK_a found for this spiran, *ca.* 5·0, accords with that (*ca.* 5·0) calculated from the data of Clark and Perrin;[8] namely, 11·15 (secondary amine), +0·2 (N-atom in a ring), —(1·4 + 0·8) (ring D, acting along two paths), and —1·4 (ring A) —2·8 (–CONH– for $-CONH_2$). The formation of this spiran was unexpected. Although pyruvic acid can react in aqueous solution with suitable derivatives of 2-(2,4-dihydroxyphenyl)ethylamine to give derivatives of 1,2,3,4-tetrahydroisoquinoline,[3a] it was considered that all non-enolisable ketones and some enolisable ones required polyphosphoric acid or similarly active catalysts for ring closure.[9] Later work [10] has shown that analogous spirans are readily formed only if the product contains a free hydroxy-group in the 6-position.

Repetition of the reaction using isatin, and a mixture of 2-(3,4-dimethoxyphenyl)ethylamine and benzylamine gave the spiran (1a) as the chief product, and did not reveal any 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline.

The conversion of 2-(3-hydroxy-4-methoxyphenyl)-ethylamine into derivatives of tetrahydroisoquinoline requires less acidic conditions than are needed for the corresponding dimethoxyamine, and reaction with isatin could, in principle, give both the spirans (1b) and (1c), and 6-hydroxy-7-methoxy-1-(3-hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (2b). The latter compound was known; it had been synthesised from the amide (7a) by ring closure to the dihydroisoquinoline (8a), followed by reduction and debenzylation.[11] A new route to the amide is described in the Experimental section. In addition, the isoquinoline (9b) and its 3,4-dihydro-derivative (8b) were prepared



as possible products of the reaction. The latter compound was already known, and had been obtained by debenzylation of its ether (8a).[11] Attempts to dehydrogenate the tetrahydroisoquinoline (2c) to the isoquinoline (9a) either with palladium on charcoal, or with triphenylmethyl perchlorate failed, and the isoquinoline was prepared from the amide (7b) by a modified Bischler–Napieralski reaction [3b] involving simultaneous ring-closure and loss of methanol.

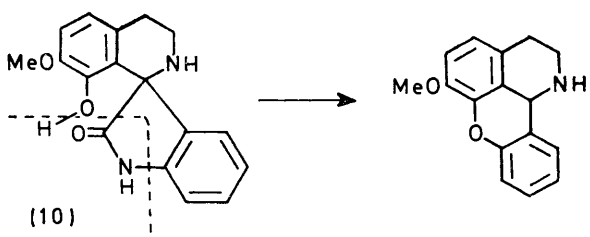
The reaction between isatin and 2-(3-hydroxy-4-methoxyphenyl)ethylamine was carried out in 0·01N-hydrochloric acid, and gave a mixture of the two spirans (1b) and (1c). Paper chromatography of the products, followed by spraying with the Folin–Ciocalteau reagent [12] and exposure to ammonia vapour

[7] C. G. Richards and M. S. F. Ross, *Tetrahedron Letters*, 1968, 4391.
[8] J. Clark and D. D. Perrin, *Quart. Rev.*, 1964, **18**, 295.
[9] E. Grundwell, *J. Chem. Soc.*, 1962, 3834, and references cited.
[10] T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasuka, and H. Ishimaru, *J. Chem. Soc.* (*C*), 1968, 112; T. Kametani, K. Kigasawa, M. Hiiragi, and H. Ishimaru, *Chem. Pharm. Bull.* (*Japan*), 1969, **17**, 2353.
[11] M. Tomita and J. Kunitomo, *Yakugaku Zasshi*, 1960, **80**, 1245 (*Chem. Abs.*, 1961, **55**, 3640f).
[12] O. Folin and V. Ciocalteau, *J. Biol. Chem.*, 1927, **73**, 627.

revealed the phenols.[13] Most phenols (and some other reducing agents) give a blue spot, but both spirans gave brown spots. None of the 1-benzyltetrahydroisoquinoline (2b) was found among the products and though the evidence is less definite, we conclude from the experiments when benzylamine was added that the more oxidised bases (8b) and (9b) were also absent.

The two spirans differ markedly in their solubilities; they can easily be separated, since the hydrochloride of (1b), which is the chief crystalline product of the reaction, is only sparingly soluble in dilute hydrochloric acid, while the hydrochloride of (1c) is very soluble in this reagent. Conversely, the solubilities of the free bases in methanol are in the reverse order. The free bases can easily be distinguished as (1b) is less stable to atmospheric oxygen than (1c), and soon acquires a superficial pink colour; (1c) turns yellow. The structural assignments follow from the presence in the ^{1}H n.m.r. spectrum of (1b) of a one-proton signal at τ 3·72 that is absent from the spectrum of (1c).

The high-resolution mass spectra agree with these findings. The results are given as (measured mass of fragment, decimal digits of calculated mass, ion current as percentage of that for molecular ion, d signifies double peak of this whole-number mass), and, where appropriate, in the order for (1a), (1b), (1c). Each of these compound loses NH_3 (293·1041, 0·1052, <10 d; 279·0882, 0·0895, <10, d; 279·0877, 0·0895, <10), and the elements $C_2H_3O_2$ (251·1183, 0·1184, <130, d; 237·1027, 0·1028, 67; 237·1016, 0·1028, <25, d). Only (1a) and (1b) show ions for ready loss of CHO (281·1294, 0·1290, 377; 267·1132, 0·1133, 156), probably arising from OC(2′) + H on C(8), as (1c) shows an ion generated by loss of CHO_2 (251·1176, 0·1184, 200). Also, only (1a) and (1b) show strong peaks for ions resulting from loss of C_2H_4O, probably as $H_3COC(7)$-C(8)H (266·1053, 0·1055, 25; 252·0890, 0·0899, 89), as (1c) shows a signal for the ion generated by loss of $C_2H_4O_2$, *i.e.* $H_3COC(7)C(8)OH$ (236·0944, 0·0950, 34).



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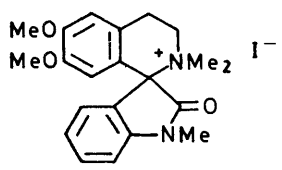

(11)

Finally, only (1c) shows a strong signal for the ion formed by loss of CH_2NO (252·1019, 0·1024, 144) that can be rationalised as HNCOH by the process (10).

Attempts to convert (1b) into (1a) with diazomethane gave low yields of unidentified material, but treatment with methyl iodide and potassium hydroxide converted both (1a) and (1b) into the methiodide (11).

When isatin was allowed to react with a mixture of 2-(3-hydroxy-4-methoxyphenyl)ethylamine and benzylamine at pH 2, 4, 6, or 8, the yield of crude basic product was highest at pH 8. Preparative t.l.c. of the products was accompanied by extensive oxidation, but a small quantity of 6-hydroxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (3b) was isolated and identified by its i.r. spectrum and mixed m.p. The compound retains hydroxylic solvents tenaciously as shown by the original analysis[14] and its behaviour when heated (see Experimental section).

Thus conversion, by a single operation, of a suitable derivative of 2-phenylethylamine into a 1,2,3,4-tetrahydroisoquinoline seems possible; but a catalyst operating by a simple dehydrogenation would be a better choice than one containing a carbonyl function which can participate in transamination.

EXPERIMENTAL

Unless otherwise stated, m.p.s were determined on a Kofler block; spectral data are given in the sequence: ^{1}H n.m.r., determined on a Perkin-Elmer R10 instrument at 40 MHz, with tetramethylsilane as internal standard, solvent deuteriochloroform unless otherwise stated, in τ units followed by [multiplicity; *J*-value; no. of protons contributing; proton assignment (s)]: u.v., (log ε), in methanol unless otherwise stated: i.r., in KCl discs. Isolation of a base means the material was, if necessary, dissolved in water, the solution made alkaline (alkali specified) and extracted (solvent specified); the extract was washed (with water if no other liquid is specified), dried (Na_2SO_4), and evaporated; paper chromatograms were run on Whatman No. 1 paper, by the ascending technique with solvent systems (all proportions by volume) (A) ethyl acetate–acetic acid–water, 75 : 9 : 9; (B) n-butanol–acetic acid–water, 4 : 5 : 1; (C) ethyl acetate–pyridine–water, 200 : 90 : 200; unless otherwise stated, system (A) was used. Thin layer chromatograms were run with Kieselgel G as adsorbent. Unless otherwise stated, paper, and thin-layer chromatograms were developed by spraying with the Folin–Ciocalteau reagent, followed by exposure to ammonia vapour.[12,13] Where appropriate, colours on paper and thin-layer chromatograms are indicated: Y (yellow), G (green), B (blue), Br (brown), D (dark); f signifies that the colour is due to fluorescence; + signifies reaction to a named reagent; enclosure in parentheses indicates a weak signal.

Reaction between Isatin and Benzylamine (*see ref.* 1).—Benzylamine (1·00 g) and isatin (2·74 g) were refluxed with 2N-hydrochloric acid (25 ml) for 1·5 h. The benzaldehyde was removed by steam distillation and converted into its 2,4-dinitrophenylhydrazone (1·03 g, 37%). When concentrated hydrochloric acid was used, the yield of benzaldehyde dinitrophenylhydrazone was 32%.

6,7-*Dimethoxy*-1-*phenyl*-1,2,3,4-*tetrahydroisoquinoline* (3a)

[13] *Cf.* D. A. A. Kidd and J. Walker, *J. Chem. Soc.*, 1954, 669.
[14] T. Kametani and M. Shio, *J. Heterocyclic Chem.*, 1965, **2**, 222.

and 6,7-*Dimethoxy*-1-*phenyl*-3,4-*dihydroisoquinoline*.—The tetrahydroisoquinoline was prepared from 2-(3,4-dimethoxyphenyl)ethylamine and benzladehyde in refluxing concentrated hydrochloric acid; the reaction yielded both 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (3a), crystals from benzene–light petroleum, m.p. 114°, $\lambda_{max.}$ 288 nm (3·52) [lit.,[15] m.p. 112—113°, $\lambda_{max.}$ 286 nm (3·25)], and 6-hydroxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline, crystals from ethanol, m.p. 185° (lit.,[14] 184·5—185·5) *m/e* 255·1250; calc. for $C_{16}H_{17}NO_2$, 255·1259. Dehydrogenation of (3a) with iodine in ethanolic solution gave crude 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline, purified as its picrate m.p. (from methanol) 195° (lit.,[16] 195—196·5); the free base, after crystallisation from benzene, had m.p. 122° (lit.,[16] 122—123°).

3,4-*Dihydropapaverine* (8c) *and* 1,2,3,4-*Tetrahydropapaverine* (2a).—These compounds were prepared from 3,4-dimethoxyphenylacetic acid and 2-(3,4-dimethoxyphenyl)ethylamine by a route similar to that of Battersby *et al.*[17] through the amide [as (7a) but with Me for $PhCH_2$), m.p. 123° (lit., 125—126°). 3,4-Dihydropapaverine was isolated as its hydrochloride. Its behaviour when heated is more complex than is reported in the literature; from methanol, it forms large, deep yellow tablets, m.p. *ca.* 136° (efferv. sintering from 126°); from dilute hydrochloric acid, very pale yellow prisms, m.p. *ca.* 125° (slight efferv. sintering from *ca.* 100°). The crystals from dilute hydrochloric acid were dissolved in ethanol, water was removed by azeotropic distillation with benzene, and the residue was crystallised from methylene chloride. On being heated these partly melted at *ca.* 130°, partly solidified and remelted at 167°, partly solidified and finally melted at 184° [lit.,[18a] not very sharply at 180° (decomp.); [18b] 186—187°]. Reduction of this hydrochloride with sodium borohydride gave 1,2,3,4-tetrahydropapaverine, isolated as its hydriodide, m.p. 245° (decomp.); [lit.,[17] 247° (decomp.)].

Reaction between Isatin and 2-(3,4-*Dimethoxyphenyl*)-*ethylamine*.—2-(3,4-Dimethoxyphenyl)ethylamine (4·47 g) and isatin (3·63 g) were refluxed with a mixture of concentrated hydrochloric acid (20 ml), water (20 ml), and benzene (40 ml) for 11 h. The liquid was basified (Na_2CO_3) and the bases were passed successively into methylene chloride, 2N-sulphuric acid, and then isolated (Na_2CO_3; methylene chloride) giving 5·79 g of granular product. Recrystallisation from methanol gave the 6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*-1-*spiro*-3′-(2′-*oxoindoline*) (1a) as white needles (3·63 g, 49%), m.p. 200° (Found: *m/e*, 310·1315; C, 69·2; H, 6·0; N, 9·1. $C_{18}H_{18}N_2O_3$ requires *m/e*, 310·1317; C, 69·7; H, 5·9; N, 9·0%); ^{1}H n.m.r.: 0·60 [s, broad; 1; HN(1′)], 2·6—3·2 [m; 4; HC(Ar), ring D], 3·31 [s; 1; HC(5)], 3·92 [s; 1; HC(8)], 6·15, 6·42 [2 × (s; 3; OCH_3)], 6·8—7·5 [m; poor resolution, 4; $H_2C(3) + H_2C(4)$], 7·9 [s, broad; 1; HN(2)]; u.v., 285 nm (3·76); ν— 333·0 and ν— 172·0 mm^{-1}. Equivalent weight (pK_a) by titration in water containing *ca.* 5% of ethanol; 327 (4·8) and 322 (5·2) (theory, 310). The *diacetyl derivative* (acetic anhydride, sodium acetate) formed white needles from methanol, m.p. 166° (Found: C, 67·0; H, 5·6; N, 7·1. $C_{22}H_{22}N_2O_5$ requires C, 67·0; H, 5·6; N, 7·1%), ν_{CO} 177·0, 170·0, and 167·0 mm^{-1}. A paper chromatogram of the products of the reaction between isatin and 2-(3,4-dimethoxyphenyl)ethylamine (and some controls), was examined successively in daylight; u.v. light for fluorescent, and for absorbing material (dark spot when the paper is backed by material fluorescing in u.v. light); and sprayed with platinum iodide (colour of spot specified if not black). These processes revealed spots with R_F values and characteristics: 0·18, Bf (not identified); 0·33, Y, Yf (not identified); 0·63, + (yellow spot) [spiran (1a), 0·64, + (yellow spot); papaverine, 0·77, Y-Gf, +; 3,4-dihydropapaverine, 0·58, Y, D, +; tetrahydropapaverine, 0·65, ++].

Reaction between Benzylamine, 2-(3,4-*Dimethoxyphenyl*)-*ethylamine, and Isatin*.—A mixture of benzylamine (0·57 g), 2-(3,4-dimethoxyphenyl)ethylamine (1·00 g), isatin (1·50 g), and concentrated hydrochloric acid (20 ml) was refluxed for 4 h, cooled, extracted with ether; it was then basified with sodium carbonate and volatile materials were removed by steam distillation. The residue was acidified with hydrochloric acid, and a further quantity of non-basic material was removed by shaking with methylene chloride. The basic product was isolated (Na_2CO_3; $CHCl_2$) to give a pale yellow oil (0·2 g) which solidified when set aside. Recrystallisation from methanol gave the spiran (1a) above, m.p. 199—201°, i.r. spectrum identical with that of an authentic sample. Paper chromatography of the mixed bases (and some controls), followed by examination first under u.v. light, then after spraying the chromatogram with a solution of iodine in chloroform showed spots with R_F values; 0·17, Bf, (not identified); 0·38, Of (not identified); 0·51 [spiran (1a), 0·50; 2-(3,4-dimethoxyphenyl)-ethylamine, 0·30; benzylamine, 0·34; 6·7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline, 0·50, Gf; 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline, 0·56, Bf].

3-*Benzyloxy*-4-*methoxyphenyl Diazomethyl Ketone* (6).—The preparation of this compound (yield, 58%) followed a literature procedure,[19] but the m.p. found, 108—109° was lower than the reported value, 114—115°. The analysis was satisfactory (Found: C, 68·5; H, 5·2; N, 9·3. Calc. for $C_{16}H_{14}N_2O_3$: C, 68·1; H, 5·0; N, 9·4%), and the spectral data regular: ^{1}H n.m.r.: 2·4—3·3 [m; 8; HC(Ar)], 4·22 (s; 1; HCN_2), 4·84 (s; 2; OCH_2Ar), and 6·11 (s; 3; OCH_3); $\nu_{C=N=N}$ 210·0 and ν_{CO} 168·0 mm^{-1}.

3-*Benzyloxy*-4-*methoxyphenyl*-N-[2-(3-*benzyloxy*-4-*methoxyphenyl*)*ethyl*]*acetamide* (7a).—A solution containing 2-(3-benzyloxy-4-methoxyphenyl)ethylamine (3·6 g) and the diazoketone above (3·3 g) in *o*-dichlorobenzene (50 ml) was added during 15 min to refluxing *o*-dichlorobenzene (50 ml); heating was continued for a further 15 min. Concentration of the mixture on a steam-bath under reduced pressure gave brown crystals of the crude product. Recrystallisation, first from benzene then from methanol, gave the amide (2·3 g, 45%) as white needles, m.p. 114—115° (lit.,[11] m.p. 113·5—115°) (Found: C, 75·0; H, 6·7; N, 3·0. Calc. for $C_{32}H_{33}NO_5$: C, 75·1; H, 6·5; N, 2·7%); ^{1}H n.m.r. 2·62 (s, broad; 10; 2 × C_6H_5); 3·0—3·6 [m; 6; HC(Ar)]; 4·91 (s; 4; 2 × OCH_2Ar); 6·15, 6·18 (2 × (s; 3; OCH_3); 6·4—7·0 [m, unresolved; 3 including 7·37 (d; *J* 7 Hz; 2); $ArCH_2{\cdot}CH_2{\cdot}NH$].

[15] J. Knabe and H. Roloff, *Arch. Pharm.*, 1965, **298**, 561.
[16] M. Lora-Tamayo, R. Madroñero, and G. G. Muñoz, *Chem. Ber.*, 1960, **93**, 289.
[17] A. R. Battersby, R. Binks, R. J. Francis, D. J. McCaldin, and H. Ramuz, *J. Chem. Soc.*, 1964, 3600.
[18] (*a*) A. Dobrowsky, *Monatsh.*, 1951, **82**, 122; (*b*) T. Kametani and K. Fukumoto, *Yakugaku Zasshi*, 1963, **83**, 1031 (*Chem. Abs.*, 1964, **60**, 10,731h).
[19] K. W. Gopinath, T. R. Govindachari, and N. Visnawathan, *Chem. Ber.*, 1959, **92**, 1657.

3-Benzyloxy-4-methoxyphenyl-N-[*2-methoxy-2-(3-benzyloxy-4-methoxyphenyl)ethyl*]*acetamide* (7b).—A solution of 1-amino-2-methoxy-2-(3-benzyloxy-4-methoxyphenyl)-ethane [20] (4·3 g) and 3-benzyloxy-4-methoxyphenyldiazomethylketone (4·3 g) in *o*-dichlorobenzene (75 ml) was added during 15 min to refluxing *o*-dichlorobenzene (25 ml), and refluxing was continued for a further 15 min. Evaporation under reduced pressure left a brown oil which after treatment with charcoal in hot methanol, deposited white crystals. Two further recrystallisations from methanol gave the *acetamide* (7b) (3·7 g, 45%) as white needles, m.p. 112° (Found: C, 73·2; H, 6·5; N, 2·6. $C_{33}H_{35}NO_6$ requires C, 73·2; H, 6·5; N, 2·6%); ^{1}H n.m.r. 3·63 (s, broad; 10; 2 × C_6H_5); 3·1 [m, unresolved, as broad s; 4; HC(Ar)]; 4·84, 4·88 [2 × (s; 2; $-OCH_2Ar$)]; 6·11 (s; 3; CH_3OAr); 6·82 [s; 3; $CH_3OC(2')$]; the region from 5·4—7·0 integrated for 11 protons, but only the two *O*-methyl groups gave identifiable signals; $\lambda_{max.}$ 233 (4·48) and 280 nm (3·92); ν_{NH} 330·0 and ν_{CO} 164·0 mm^{-1}.

6-Benzyloxy-7-methoxy-1-(3-benzyloxy-4-methoxybenzyl)-isoquinoline (9a).—A solution of the amide above (1·95 g) in phosphoryl chloride (40 ml) was refluxed for 3 h; after evaporation of the phosphoryl chloride under reduced pressure, the residue was partitioned between 2N-sodium hydroxide and chloroform. After the solution had been dried (Na_2SO_4), the chloroform was evaporated, leaving a brown solid (1·40 g). Two recrystallizations from methanol gave the *isoquinoline* (9a) (0·9 g, 50%) as white crystals, m.p. 148° (Found: C, 78·1; H, 6·0; N, 2·9. $C_{32}H_{29}NO_4$ requires C, 78·2; H, 5·9; N, 2·9%); ^{1}H n.m.r. 1·65 [d; *J* 7 Hz; HC(3)]; 2·62, 2·78 [2 × (s, broad; 5; C_6H_5)]; 2·95 [s, broad; 1; HC(6')]; 3·22 [s; 4; HC(5, 8, 2', 5')], 4·76, 5·01 [2 × (s; 2; OCH_2Ar)]; 6·20 (s; 6; 2 × CH_3O); the region between 2·30 and 3·40 integrated for 16 protons, but the signal for H(C4) was not resolved; $\lambda_{max.}$ 240 (5·10), 253 (infl) (4·08), 315 (3·80), and 328 nm (3·83).

1-(3-Hydroxy-4-methoxybenzyl)-6-hydroxy-7-methoxyisoquinoline (9b).—A solution of the dibenzyl ether above (0·8 g) in ethanol (15 ml) and 5N-hydrochloric acid (15 ml) was refluxed for 2 h; the mixture was concentrated under reduced pressure, and water (50 ml) was added, followed by 2N-sodium hydroxide until the solution was strongly alkaline. Extraction with ether removed some starting material. Excess of ammonium chloride was added, and the phenolic material was isolated with ether. Recrystallisation from methanol gave the *isoquinoline* (9b) (0·4 g, 80%) as white needles, m.p. 196—197° (Found: C, 69·6; H, 5·9; N, 4·4. $C_{18}H_{17}NO_4$ requires C, 69·4; H, 5·5; N, 4·5%), $\lambda_{max.}$ in 0·1N-hydrochloric acid: 250 (4·80), 285 (3·84), and 313 nm (3·95); in 0·1N-sodium hydroxide, 253 (4·72), 299 (4·07), 317 (infl, 3·98), and 333 nm (3·99); in methanol, 239 (4·77), 285 (3·77), 315 (3·39), and 328 nm (3·44); ν_{OH} 340·0 mm^{-1}. The *diacetyl derivative* (acetic anhydride, sodium acetate) separated from methanol as white crystals, m.p. 88—89° (Found: C, 66·4; H, 6·0; N, 3·5. $C_{22}H_{21}NO_6$ requires C, 66·8; H, 5·4; N, 3·5%); ^{1}H n.m.r. 1·62 [d; *J*, 6 Hz; 1; HC(3)], 2·4—3·2 [m; 6; HC(Ar)], 5·45 (s; 2; $ArCH_2Ar$), 6·17, 6·24 [2 × (s; 3; OCH_3)]; 7·66, 7·75 [2 × (s; 3; $COCH_3$)]; $\lambda_{max.}$ in 0·1N-hydrochloric acid 243 (4·61), 275 (3·81), and 345 nm (3·67); ν_{CO} 176·0 mm^{-1}.

6-Hydroxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline.—The hydrochloride, prepared from benzaldehyde and 2-(3-hydroxy-4-methoxyphenyl)ethyl amine formed colourless needles from ethanol, m.p. 257—258° (lit.,[21] 257—258°). Isolation (sodium hydroxide, then excess of ammonium chloride; methylene chloride, brine) of the base and recrystallisation from ethanol gave 6-hydroxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline as white needles, m.p. 186° (Found: C, 75·2; H, 6·8; N, 5·3. $C_{16}H_{17}NO_2$ requires C, 75·3; H, 6·7; N, 5·5%); $\nu_{max.}$ 340·0 mm^{-1}. Use of methanol instead of ethanol gave crystals, m.p. *ca.* 167° resolidifying and remelting 183—184° (capillary).

Reaction Between 2-(3-Hydroxy-4-methoxyphenyl)ethylamine and Isatin.—A solution of the hydrochloride of the amine (1·00 g) and isatin (0·61 g) in 0·01N-hydrochloric acid (320 ml) was refluxed for 72 h; an excess of sodium carbonate was then added to the mixture which was shaken with methylene chloride (6 × 100 ml); the mixture of bases was taken up in 2N-sulphuric acid (4 × 50 ml) and isolated (sodium carbonate; methylene chloride, 6 × 50 ml) to give 1·34 g of crude product. This was taken up in warm 1N-hydrochloric acid (5 ml per g of crude basic product) and the solution was stored for 48 h at 5 °C; the crystals (C) (0·50 g, 33%) were collected, and the mother liquor (ML) was retained.

Isolation of the base (sodium carbonate, methylene chloride) from the crystals (C) above gave *6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-3'-(2'-oxoindoline* (1b). This compound retains hydroxylic solvents tenaciously. Recrystallisation from ethanol gave white crystals, m.p. 146—149° (Found: *m/e* 296·1159; C, 67·1; H, 5·9; N, 9·00. $C_{17}H_{16}N_2O_3$ requires *m/e*, 296·1161; $C_{17}H_{16}N_2O_3$, 0·5 C_2H_5OH requires C, 67·7; H, 6·0; N, 8·8%); ^{1}H n.m.r. (CF_3CO_2H) *ca.* 0·26 (s, broad; 1; HNCO), *ca.* 1·5 [broad; 2; $H_2N(2)$], 2·0—2·8 [m; 4; HC(Ar)]; 3·00 [s; 1; HC(5)]; 3·72 [s; 1; HC(8)]; 6·38 (s; 3; OCH_3), and 5·0—7·2 (diffuse; 6 or 7 not including signal at 6·38), and 8·51 (t; *J* 7 Hz; 1 or 2; CH_3 of ethanol); ν_{CO} 173·0 mm^{-1}; from methanol, white crystals, m.p. 168—176 (efferv., decomp., giving a dark red melt); $\lambda_{max.}$ (in 0·1N-hydrochloric acid) 285 nm (3·68). Crystallisation of the *hydrochloride* from a mixture of ethanol and water (2 : 1, v/v) gave colourless crystals, m.p. 226—232° (Found: C, 61·0; H, 5·3. $C_{17}H_{17}ClN_2O_3$ requires C, 61·3; H, 5·1%); ν_{CO} 173·0 mm^{-1}.

Isolation (sodium hydrogen carbonate; $CHCl_3$) of the base from the filtrate (ML) above and crystallisation from ethanol gave *8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-3'-(2'-oxoindoline*) (1c) as white needles (yield, in a different run, 20%), m.p. 224—230° (decomp., yellow melt) (Found: *m/e*, 296·1170; C, 69·1; H, 5·5; N, 9·4. $C_{17}H_{16}N_2O_3$ requires *m/e*, 296·1161; C, 68·9; H, 5·4; N, 9·5%); ^{1}H n.m.r. (DCl + D_2O) 2·4—3·3 [m; 6; HC(Ar)], 5·8—7·4 [diffuse 6·37 (s; OCH_3) including], the range 5·8—7·4 integrates for 7 protons; $\lambda_{max.}$ (0·1N-hydrochloric acid), 250infl. (3·52) and 288 nm (3·37); ν_{CO} 173·0 mm^{-1}. From methanol the base forms white crystals, m.p. *ca.* 134° (efferv.), solidifying in the range 135—170°, and remelting 225—235° (decomp.). The hydrochloride of this base is very soluble in water.

Paper chromatography of the crude basic product (system B) gave a single brown spot R_F 0·80; other relevant values and spot colours were: spiran (1b), brown 0·82; 2-(3-hydroxy-4-methoxyphenyl)ethylamine, blue, 0·62;

[20] K. W. Merz and J. Fink, *Arch. Pharm.*, 1956, **289**, 347.

[21] D. Beke and Cs. Szantay, *Acta Chim. Acad. Sci. Hung.*, 1958, **14**, 325 (*Chem. Abs.*, 1959, **53**, 11,275c).

tetrahydroisoquinoline (2b), blue 0·75; dihydroisoquinoline (8b), blue, 0·90; and isoquinoline (9b), blue 0·86.

Reaction between Benzylamine, 2-(3-Hydroxy-4-methoxyphenyl)ethylamine and Isatin: at Different pH *Values.*—A solution of the hydrochloride of the phenylethylamine (*ca.* 0·09 g; 1 mol. equiv.), benzylamine (*ca.* 0·06 g; 1 mol. equiv.) and isatin (*ca.* 0·14 g, 2 mol. equiv.) in a buffer solution (50 ml) were refluxed for 48 h; the solution was then acidified and extracted with ether. From the aqueous phase the crude basic product was isolated ($NaHCO_3$; $CHCl_3$), and the ratio, *R* (weight of crude product/weight of phenylethylamine hydrochloride) was determined. These were (pH, *R*): 2, 1·16; 4, 0·87; 6, 0·66; and 8, 1·32. Paper chromatography (system A) showed, in each case, a brown spot at R_F *ca.* 0·45 [(1b) + (1c)], and a blue one at R_F *ca.* 0·57 (3b).

The crude products obtained from the run at pH 8 were examined in more detail. Paper chromatography with system B showed spots (controls): brown, 0·74 [(1b), brown, 0·78] and blue, 0·86 [(3b) blue, 0·80]; the tetrahydroisoquinoline (2b), blue, 0·71; the dihydroisoquinoline (8b), blue, 0·83; the isoquinoline (9b), blue, 0·82. With solvent system (D) the spots revealed were: blue, 0·91 [(3b), blue, 0·91] and brown, 0·97 [(1b), brown, 0·97; (2b), (8b) (9b), each blue, 0·97]. Thin-layer chromatography, with solvent chloroform–methanol (4 : 1) showed spots: blue, 0·57 [(3a), blue, 0·57] and brown 0·84 [(1b), brown, 0·84; (2b), blue, 0·36; (8b), blue, 0·86; (9b), blue, 0·82].

Isolation of 6-Hydroxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline.—A solution of 2-(3-hydroxy-4-methoxyphenyl)ethylamine hydrochloride (7·50 g), benzylamine (4·02 g), and isatin (10·35 g) in a phosphate–citrate buffer (pH 8) was refluxed 3 days and then basified ($NaHCO_3$) and extracted with chloroform. This extract was shaken with 2N-sulphuric acid; isolation ($NaHCO_3$; $CHCl_3$; brine) gave a mixture of bases as a light yellow solid (3·0 g). Paper chromatography showed the presence of 6-hydroxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline. Crystallisation from ethanol removed the spiran (1b), m.p. 145—148°, identified by its i.r. spectrum. The mixture of bases (1·04 g) from the mother liquor was applied as a streak to a preparative t.l.c. plate; at intervals the streak was interrupted and some authentic 6-hydroxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline was applied. The plate was developed by two passes through it of a mixture of methanol and chloroform (1 : 9 v/v); at least six coloured bands were revealed. The 1-phenylisoquinoline marker gave a colourless spot appearing dark under u.v. light, R_F 0·25. The adsorbents for bands 2 (R_F 0·14—0·21; yellow, no colour under u.v.), 3 (R_F 0·21—0·27, colourless, dark under u.v.), and 4 (R_F 0·27—0·34, faint yellow, no colour under u.v.) were collected and extracted with methanol; the methanol was evaporated, and the residue was taken up in 2N-hydrochloric acid which was washed with ether. Isolation ($NaHCO_3$, ether; brine) of the basic products, and recrystallisation from methanol gave, from bands 2 and 3, an unidentified material, as white crystals, m.p. 120—121°; from band 4, 6-hydroxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline, identified by m.p. (capillary), 162°, solidifying and remelting 183° (mixed with an authentic sample, m.p. 162°, solidifying and remelting 183°); and by its i.r. spectrum.

6,7-Dimethoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinoline-1-spiro-3′-(1′-methyl-2′-oxoindolinium)iodide (11).—*From the hydroxyspiran* (1b). A solution of the spiran (0·20 g) in 5N-methanolic potassium hydroxide (6 ml) and methyl iodide (3 ml) was refluxed for 0·5 h; further methanolic potassium hydroxide (3 ml) and methyl iodide (1·5 ml) were added, and refluxing was continued for a further 0·5 h. The mixture was evaporated to dryness, and the residue was extracted with boiling isopropyl alcohol (25 ml × 5). The solid that separated from the cool solution (0·57 g) was recrystallised from methanol (2 ml) to give *6,7-dimethoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinoline-1-spiro-3′-(1′-methyl-2′-oxoindolinium) iodide* as white needles (0·12 g), m.p. 205° (decomp.) (Found: C, 52·6; H, 5·5; N, 5·9. $C_{21}H_{25}IN_2O_3$ requires C, 52·5; H, 5·3; N, 6·0%); ^1H n.m.r. (D_2O), 2·51 [s; HC(Ar)], 2·86 [s; HC(5)], 4·05 [s; HC(8)], 6·07 (s; OCH_3), 6·2—6·8 [many; OCH_3 + $(CH_3)_2N(2)$ + $H_2C(3)$ + $H_2C(4)$], and 6·87 [s; $H_3CN(1)$]; the signal strengths fit these assignments, but the compounds low solubility did not permit reliable integral values: ν_{CO} 172·0 mm^{-1}.

From the dimethoxyspiran (1a). The spiran (1a) (1·06 g) was treated with the proportionate quantities of reagents as described above to give the indolinium iodide (11) (0·45 g) as white needles, m.p. 208° (decomp.). The iodides from the two spirans had identical i.r. spectra, and showed no depression of m.p. in a mixed m.p.

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