Studies on Tetrahydroisoquinoline. Part 13.[1] Total Syntheses of (±)-*O*-Methylandrocymbine, (±)-Androcymbine, (±)-Kreysigine, (±)-Multifloramine, and their Related Phenethylisoquinoline Alkaloids

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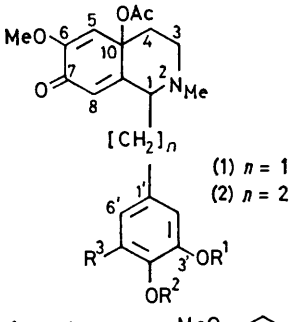
Trifluoroacetic acid treatment of *p*-quinol acetates derived from phenethylisoquinolines has led to the formation of (±)-homoaporphines, (±)-homomorphinandienones, and (±)-homoproaporphines. Thus three new (±)-homoaporphines (10g—i) possessing a hydroxy group in ring D have been synthesized. The stereostructure of (±)-homoproaporphine (4b), formed as a single spiro-isomer, has been determined by means of *X*-ray crystallographic analysis, partly for the settlement of stereochemistry on isomeric natural kreysiginone. On the basis of the above result, the steric course for the formation of (4b) has been discussed. An efficient method, consisting of oxidation with lead tetra-acetate of phenethylisoquinolines in trifluoroacetic acid–acetic acid, for the predominant formation of (±)-homomorphinandienones, has been newly developed.

RECENTLY the simple synthesis of aporphines *via* *p*-quinol acetates has been carried out in this laboratory.[1,2] Two notable developments came out of this study. First, trifluoroacetic acid (CF_3CO_2H) was found to be much superior as a cyclizing agent to concentrated sulphuric acid–acetic anhydride (Thiele's condition). Secondly, the benzyloxy-group was found to be effective for the cyclization, and debenzylation of the aporphines thus formed was straightforward.



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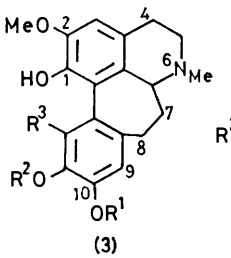

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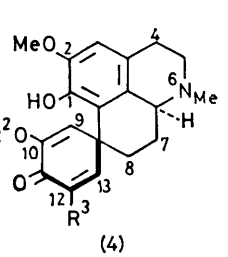

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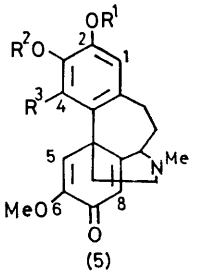

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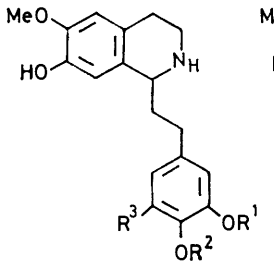

(13)
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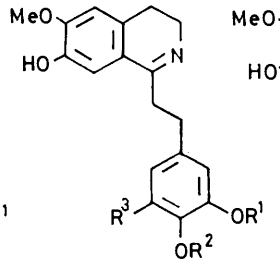
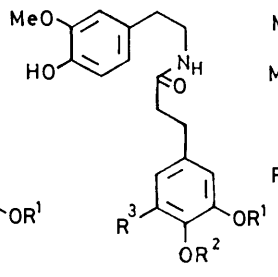
b; R^1 = R^2 = Me, R^3 = H
c; R^1 = R^2 = Me, R^3 = OMe



(12)
d; R^1 = Me, R^2 = CH_2Ph, R^3 = H
e; R^1 = CH_2Ph, R^2 = Me, R^3 = H
f; R^1 = Me, R^2 = CH_2Ph, R^3 = OMe



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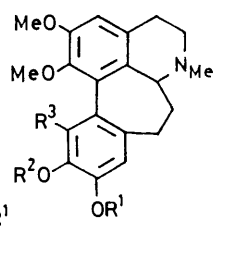

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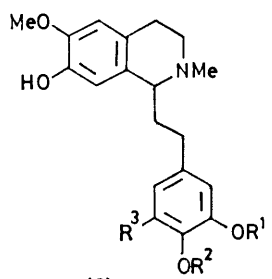


(6)
g; R^1 = Me, R^2 = R^3 = H
h; R^1 = R^3 = H, R^2 = Me
i; R^1 = Me, R^2 = H, R^3 = OMe

RESULTS AND DISCUSSION

In the light of Baldwin's rules[3] for ring closure, our successful methodology for the synthesis of aporphines was based on the favourable 6-*endo-trig* ring closure at the C-8 and C-6′ positions. According to the rules, a 6-*exo-tet* process, that is ring closure at the C-10 and C-6′ positions leading to morphinandienones, was also favoured, while 5-*endo-trig* ring closure to proaporphines was disfavoured. However, no morphinandienone was formed, probably due to a strain imposed on an intermediate giving the dienone.

In contrast with *p*-quinol acetates (1) carrying 1-benzyl groups, acid-catalysed cyclization of those (2) carrying 1-phenethyl groups was expected to obey the rules to give the homoaporphines (3) (7-*endo-trig*), homoproaporphines (4) (6-*endo-trig*), and homomorphinandienones (5) (7-*exo-tet*).

Previously, treatment of (2) under Thiele's condition gave (3) as the sole product, not accompanied by (4) and/or (5).[4,5] However, this result did not fully rule out the initial generation of (4) and/or (5), leading to the formation of (3) after rearrangement under the influence of strong acid. Accordingly, it was hoped that employment of a weaker acid would give rise to (4) and/or (5) in addition to (3) and we studied the reaction of *p*-quinol acetate (2) with CF_3CO_2H.

The crude *p*-quinol acetate (2a)[5] from lead tetra-

acetate oxidation of the phenolic base (6a) [5] in acetic acid was treated with CF_3CO_2H in methylene chloride at room temperature for 2 h. Purification of the resulting reaction mixture by preparative t.l.c. gave (±)-1-hydroxy-2-methoxy-10,11-methylenedioxyhomoaporphine (3a).[5] No homomorphinandienone (5a) was found. Similar treatment of *p*-quinol acetate (2b) [4] from the phenolic base (6b) [4] afforded three compounds, (±)-demethoxy-*O*-methylandrocymbine (5b),[6] (±)-1-hydroxy-2,10,11-trimethoxyhomoaporphine (3b),[4,6] and (±)-1-hydroxy-2,10-dimethoxyhomoproaporphine (4b).[7] The yields of all products in the cyclization are shown in Table 1.

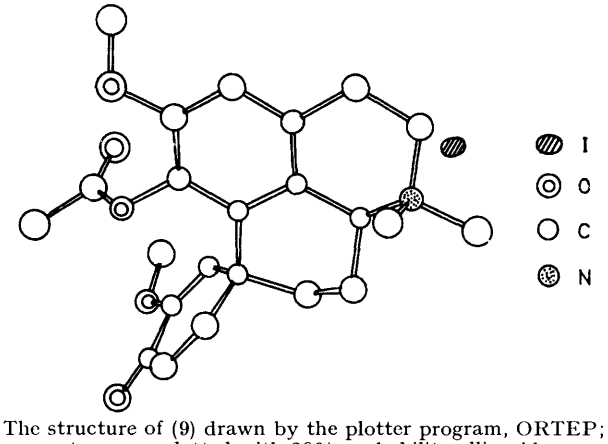
Thus we could obtain a homomorphinandienone and a homoproaporphine albeit in low yields. The m.p. and n.m.r. and i.r. spectra of (4b) were consistent with those of ' Dienone II '.[7] It was shown that the homoproaporphine (4b) was formed in a pure state not contaminated with (±)-kreysiginone (7) [7a] [the spiro-isomer of (4b)], by inspection of the n.m.r. spectrum of crude (4b).

Thus the present reaction was in marked contrast to the oxidative coupling of diphenol (6g), in which two spiro-isomers [' Dienones I and II,' (7) and (4b)] were obtained in almost equal amounts.

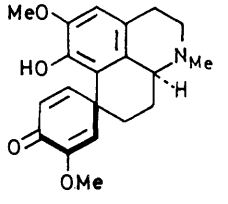
Although Kametani *et al.* have already proposed the stereostructure of ' Dienone II ' (4b) on the basis of chemical evidence,[8] more decisive evidence was desirable, both intrinsically and for a reasonable explanation of the present reaction path. Consequently, we carried out an *X*-ray crystallographic analysis on the methiodide (9) of the acetate (8) of ' Dienone II '.[9]

Crystal Data.—$C_{23}H_{28}NO_5I$, $M = 525.38$, m.p. 255—256 °C. Monoclinic, space group $C2/c$, $Z = 8$, $D_m = 1.467$ g cm^{-1}, $a = 20.435(10)$, $b = 11.899(5)$, $c = 21.379(10)$ Å, $\beta = 113.741(1)°$, $U = 4\,758$ Å^3. The final R was 0.05 for 2 852 reflections. Thus the stereostructure was determined as (4b), confirming Kametani's original postulate. This in turn constituted an indirect but unequivocal confirmation of the stereostructure of kreysiginone as being (7). An ORTEP plot of the structure of (9) is shown in the Figure.

The stereospecificity is most probably explained by the path shown in the Scheme. The carbonium ion (A) is derived from the action of acid on the *p*-quinol acetate (2b). The benzene ring of the phenethyl group in (A) could attack intramolecularly on the positive carbon (8-position) through two transition states, involving a chair (B) and a boat (C) six-membered ring; however, (B) is energetically more favourable than (C).[10] Furthermore, the transition state (B1), having the phenethyl methoxy group at the 3'-position, farthest from ring A, was favoured over another, (B2), in which it is in the 5'-position.



The structure of (9) drawn by the plotter program, ORTEP; atoms are plotted with 30% probability ellipsoids



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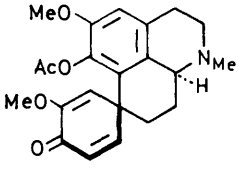

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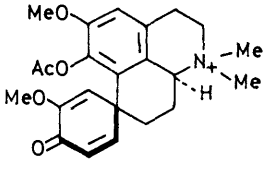


(9)

Similarly, the phenolic base (6c) [4] gave (±)-*O*-methylandrocymbine (5c),[6,11] (±)-kreysigine (3c),[4,6,7a] and (±)-12-methoxykreysiginone (4c).[7]

In addition, in order to synthesize (±)-multifloramine (3i) and (±)-androcymbine (5i), similar treatment of the corresponding *p*-quinol acetates (2d—f) from the 1-phenethyl-7-phenolic bases (6d—f), having the protected hydroxy group in ring C, was undertaken.

The starting materials (6d—f) were prepared according to the method described in a previous paper.[1] Lead tetra-acetate oxidation of (6d) in AcOH led readily to the *p*-quinol acetate (2d). The same treatment as above of crude (2d) afforded (±)-3-benzyloxy-2,6-dimethoxyhomomorphinandienone (5d), (±)-11-benzyloxy-1-hydroxy-2,10-dimethoxyhomoaporphine (3d), and ' Dienone II ' (4b).

Similarly, the phenolic bases (6e) or (6f) gave three compounds, *i.e.* from (6e) (±)-2-benzyloxy-3,6-dimethoxyhomomorphinandienone (5e), (±)-10-benzyl-

TABLE 1

Cyclization products from reactions *via* *p*-quinol acetates

Starting phenol	Product [yield (%)] Homomorphinandienone	Homoaporphine	Homoproaporphine
(6a)		(3a) [55.0]	
(6b)	(5b) [3.3]	(3b) [44.2]	(4b) [6.9]
(6c)	(5c) [23.1]	(3c) [35.2]	(4c) [31.3]
(6d)	(5d) [6.1]	(3d) [39.3]	(4b) [15.5]
(6e)	(5e) [0.3]	(3e) [29.6]	(4e) [11.4]
(6f)	(5f) [12.2]	(3f) [27.3]	(4c) [15.9]

oxy-1-hydroxy-2,11-dimethoxyhomoaporphine (3e), and (±)-10-benzyloxy-1-hydroxy-2-methoxyhomoproaporphine (4e); from (6f) (±)-*O*-benzylandrocymbine (5f),[12] benzylmultifloramine (3f), and homoproaporphine (4c), respectively. The stereostructure of (4e) was presumed to be the same as that of ' Dienone II ' (4b).

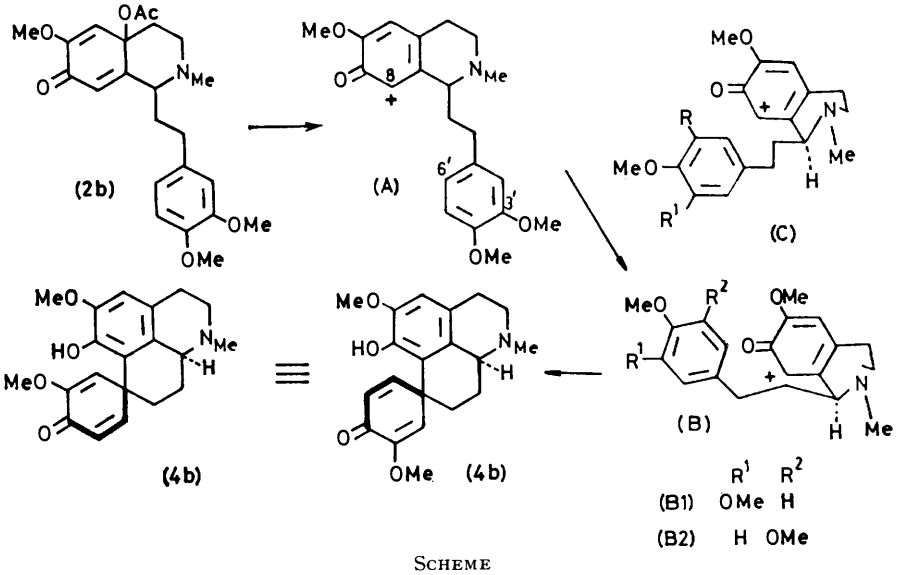
Since Kametani *et al.*[12] had already converted (5f) to (±)-androcymbine (5i), the formation of (5f) constituted a total synthesis of (5i).

The yield of (5) was dependent on both the number and effectiveness of the electron-donating groups in ring C. That methylenedioxy- and benzyloxy-groups were not very effective as electron-donors was reflected in the yields of (5a) and (5e), that of the former being nil, and that of the latter very low.

to try the $Pb(OAc)_4$ oxidation of (6) in the presence of CF_3CO_2H. To a mixture of (6c) in AcOH–CF_3CO_2H (4 : 1) was added $Pb(OAc)_4$ in one portion, and the whole was stirred at room temperature for 1 h. The usual work-up gave (±)-*O*-methylandrocymbine (5c) (26%), (±)-kreysigine (3c) (7.5%), and (±)-12-methoxykreysigine (4c) (15%).

On the basis of this favourable result, we carried out the oxidation of other phenolic bases (6a, b, d, e, f) in a similar manner, and each product, together with its yield, is shown in Table 2. Apparently, the yield of (5) was slightly greater than that given by the method *via* *p*-quinol acetate (2), while that of (3) was considerably decreased, and that of (4) was almost unaltered.

To obtain some mechanistic information, *p*-quinol



SCHEME

Catalytic debenzylation (palladium–carbon, methanol) of (3d), (3e), and (3f) afforded (±)-1,11-dihydroxy-2,10-dimethoxyhomoaporphine (3g),[8] (±)-1,10-dihydroxy-2,11-dimethoxyhomoaporphine (3h),[8] and (±)-multifloramine (3i),[7a] respectively.

Furthermore, methylation with diazomethane of (3d), (3e), and (3f) gave (±)-11-benzyloxy-1,2,10-trimethoxy- (10d), (±)-10-benzyloxy-1,2,11-trimethoxy- (10e), and (±)-11-benzyloxy-1,2,10,12-tetramethoxy-homoaporphine (10f), respectively. Successive debenzylation of (10d), (10e), and (10f) afforded (±)-11-hydroxy-1,2,10-trimethoxy- (10g), (±)-10-hydroxy-1,2,11-trimethoxy-homoaporphine (10h), and (±)-1-*O*-methylmultifloramine (10i), respectively.

As expected, treatment with CF_3CO_2H of *p*-quinol acetate carrying a 1-phenethyl group [except (2a)] yielded three types of products; homoaporphine (3), homoproaporphine (4), and homomorphinandienone (5). However, the reaction was by no means satisfactory for the efficient synthesis of (5).

Schwartz's recent report [11] that (±)-*O*-methylandrocymbine (5c) could be synthesized in fair yield (20%) by thallium trifluoroacetate oxidation of (6c) prompted us acetate (2c), derived from (6c), was dissolved in AcOH followed by treatment with CF_3CO_2H, with stirring, at room temperature for 1 h. The distribution pattern of the three products in this reaction (entry 7 in Table 2) was clearly distinguished from that in the original reaction above (entry 3) as shown in Table 2. Accordingly, a reaction path involving direct coupling rather than *p*-quinol acetate (2) * contributed largely to the cyclization (entries 1—6), although details for the mechanism are still uncertain.

EXPERIMENTAL

All melting points were measured on a Buchi melting point measuring apparatus. N.m.r. spectra were recorded on a JEOL model JNR-4H-100 spectrometer (100 MHz) in $CDCl_3$ solution (5—10%) using $SiMe_4$ as internal standard, unless otherwise noted; mass spectra were measured with a Hitachi model RMU-6E mass spectrometer; and i.r. spectra were run on Hitachi model 215 ($CHCl_3$) and 225 (KBr) spectrometers. Preparative t.l.c. was performed over silica gel GF_{254} (Merck). Microanalytical data for all new compounds are shown in Table 3.

* A trace of (2) was observed on t.l.c. in some reactions.

TABLE 2

Cyclization products from reactions in the presence of CF_3CO_2H

Entry	Starting phenol	Product [yield (%)] Homomorphinandienone	Homoaporphine	Homoproaporphine
1	(6a)		(3a) [19]	
2	(6b)	(5b) [16]		(4b) [31]
3	(6c)	(5c) [26]	(3c) [7.5]	(4c) [15]
4	(6d)	(5d) [14]		(4b) [18]
5	(6e)	(5e) [5]		(4e) [16]
6	(6f)	(5f) [13]	(3f) [10]	(4c) [10]
7	(6c)	(5c) [13]	(3c) [15]	(4c) [3]

TABLE 3

Microanalytical data for new compounds

Compound	Formula	Molecular weight	Calc. % C	Calc. % H	Calc. % N	Found % C	Found % H	Found % N
(3d)	$C_{27}H_{29}NO_4$	431.51	75.15	6.77	3.25	75.22	6.85	3.17
(3e)	$C_{27}H_{29}NO_4$	431.51	75.15	6.77	3.25	75.09	6.68	2.97
(3f)	$C_{28}H_{31}NO_5$	461.54	72.86	6.77	3.04	72.62	6.82	3.11
(3g)	$C_{20}H_{23}NO_4 \cdot H_2O$	359.406	66.83	7.01	3.90	67.25	7.23	3.50
(4e)	$C_{26}H_{27}NO_4 \cdot 0.25H_2O$	421.984	74.00	6.57	3.32	74.22	6.78	3.31
(5c)	$C_{22}H_{27}NO_5$	385.44	68.55	7.06	3.63	68.49	7.05	3.38
(5d) *	$C_{27}H_{29}NO_4 \cdot CH_3I \cdot H_2O$	591.47	56.85	5.79	2.36	57.10	5.64	2.12
(5f)	$C_{28}H_{31}NO_5$	461.54	72.86	6.77	3.04	72.92	6.89	2.63
(6d) *	$C_{27}H_{31}NO_4 \cdot CH_3I$	575.48	58.43	5.91	2.43	58.21	6.01	2.21
(6e) *	$C_{27}H_{31}NO_4 \cdot CH_3I$	575.48	58.43	5.91	2.43	58.34	5.95	2.45
(6f)	$C_{28}H_{33}NO_5$	463.55	72.54	7.18	3.02	72.51	7.12	3.02
(8)	$C_{22}H_{25}NO_5$	383.43	68.91	6.57	3.65	68.64	6.51	3.92
(9)	$C_{23}H_{28}NO_5I$	525.38	52.58	5.37	2.67	52.35	5.32	2.86
(10d) *	$C_{28}H_{31}NO_4 \cdot CH_3I$	587.484	59.29	5.83	2.38	59.09	5.88	2.08
(10e) *	$C_{28}H_{31}NO_4 \cdot CH_3I$	587.484	59.29	5.83	2.38	59.03	5.61	2.24
(10f) *	$C_{29}H_{33}NO_5 \cdot CH_3I \cdot 0.5H_2O$	642.514	56.08	5.80	2.18	55.96	5.55	2.00
(10g) *	$C_{21}H_{25}NO_4 \cdot CH_3I$	497.36	53.12	5.67	2.82	52.87	5.69	2.55
(10h)	$C_{21}H_{25}NO_4$	355.42	70.96	7.09	3.94	70.83	7.25	3.91
(10i)	$C_{22}H_{27}NO_5$	385.44	68.55	7.06	3.63	68.32	7.23	3.65
(12d)	$C_{26}H_{29}NO_5$	435.50	71.70	6.71	3.22	71.94	6.60	3.10
(12e)	$C_{26}H_{29}NO_5$	435.50	71.70	6.71	3.22	71.53	6.63	3.05
(12f)	$C_{27}H_{31}NO_6 \cdot H_2O$	483.546	67.06	6.87	2.90	67.30	6.77	2.79
(13d)	$C_{26}H_{29}NO_4 \cdot C_6H_6$	497.61	77.23	7.09	2.82	76.88	7.00	2.99
(13e)	$C_{26}H_{29}NO_4$	419.50	74.44	6.97	3.34	74.07	6.97	3.35

* Methiodide.

N-(4-*Hydroxy*-3-*methoxyphenyl*)*ethyl*-4-*benzyloxy*-3-*methoxyphenylpropionamide* (11d).—A mixture of β-(4-hydroxy-3-methoxyphenyl)ethylamine [1] (0.84 g, 5 mmol) and 4-benzyloxy-3-methoxyphenylpropionic acid (1.43 g, 5 mmol) was heated at 190—200 °C (bath temperature) for 3 h, and the product was taken up in CH_2Cl_2. The CH_2Cl_2 extract was washed successively with 5% HCl, brine, saturated $NaHCO_3$, and brine, and evaporation of the solvent then gave brown crystals of (11d) (1.95 g, 89.4%), m.p. 98—105 °C, which were recrystallized from benzene–n-hexane to yield colourless fine needles (1.61 g, 73.9%), m.p. 107—109 °C; the analytical sample had m.p. 110—112 °C; δ 2.37 (2 H, t, *J* 7.5 Hz, $COCH_2CH_2Ph$), 2.63 (2 H, t, *J* 7.5 Hz, $NHCH_2CH_2Ph$), 2.85 (2 H, t, *J* 7.5 Hz, $COCH_2CH_2Ph$), 3.41 (2 H, q, *J* 7.5 Hz, $NHCH_2CH_2Ph$), 3.77, 3.80 (each 3 H, s, OMe), 5.08 (2 H, s, OCH_2Ph), and 5.50 and 5.80 (each 1 H, br s, OH or NH); $\nu_{max.}$ (KBr) 3 455, 3 310 (OH and NH), and 1 640 cm^{-1} (CONH).

N-(4-*Hydroxy*-3-*methoxyphenyl*)*ethyl*-3-*benzyloxy*-4-*methoxyphenylpropionamide* (11e).—A mixture of β-(4-hydroxy-3-methoxyphenyl)ethylamine (0.84 g, 5 mmol) and 3-benzyloxy-4-methoxyphenylpropionic acid (1.43 g, 5 mmol) was heated at 160—165 °C (bath temperature), and the same work-up as described above gave an amorphous mass (1.91 g), which was crystallized from benzene–n-hexane to yield colourless prisms of (11e) (1.80 g, 82.6%), m.p. 92—95 °C; an analytical sample had m.p. 94—96 °C; δ 2.31 (2 H, t, *J* 7.5 Hz, $COCH_2CH_2Ph$), 2.62 (2 H, t, *J* 7.5 Hz, $NHCH_2CH_2Ph$), 2.82 (2 H, t, *J* 7.5 Hz, $COCH_2CH_2Ph$), 3.39 (2 H, q, *J* 7.5 Hz, $NHCH_2CH_2Ph$), 3.80 (6 H, s, 2 × OMe), 5.09 (2 H, s, OCH_2Ph), and 5.35, 5.70 (each 1 H, s, OH and NH); $\nu_{max.}$ (KBr) 3 470, 3 320 (OH and NH), and 1 645 cm^{-1} (CONH).

N-(4-*Hydroxy*-3-*methoxyphenyl*)*ethyl*-4-*benzyloxy*-3,5-*dimethoxyphenylpropionamide* (11f).—A mixture of β-(4-hydroxy-3-methoxyphenyl)ethylamine (1.67 g, 0.01 mol) and 4-benzyloxy-3,5-dimethoxyphenylpropionic acid (3.16 g, 0.01 mol) was heated at 170 °C (bath temperature) for 2 h. The same work-up as described above gave a dark brown oil (4.48 g), which was chromatographed on silica gel with benzene–MeOH (100 : 1) to give colourless crystals of (11f) (2.86 g, 59.2%), m.p. 111—113 °C. Recrystallization from benzene–ether afforded colourless prisms (2.52 g, 52.1%), m.p. 111—114 °C; an analytical sample had m.p. 114—116 °C; δ [$(CD_3)_2SO$] 3.72 (9 H, s, 3 × OMe), 4.87 (2 H, s, OCH_2Ph), 6.55 (2 H, s, ArH), 7.88 (1 H, t, *J* 5.0 Hz, NH), and 8.71 (1 H, s, OH); $\nu_{max.}$ (KBr) 3 565, 3 500 (OH and NH), and 1 640 cm^{-1} (CONH).

(±)-1-(4-*Benzyloxy*-3-*methoxyphenethyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxyisoquinoline* (13d).—A solution of the amide (11d) (1.0 g, 2.3 mmol) and $POCl_3$ (1.2 ml, 13 mmol) in dry CH_2Cl_2 (15 ml) was refluxed for 2.5 h. Evaporation of the solvent under reduced pressure afforded an oil, which was washed with n-hexane. To the residue was added ice–water and the whole was basified with concentrated aqueous ammonia. The product was taken up in

TABLE 4

I.r. spectral data of the *p*-quinol acetates (in $CHCl_3$)

	OAC (cm^{-1})	Dienone
(2a) [5]	1 740	1 665, 1 645, 1 630
(2b) [4]	1 745	1 670, 1 650, 1 630
(2c) [4]	1 740	1 670, 1 640, 1 630
(2d)	1 740	1 675, 1 645, 1 630
(2e)	1 740	1 665, 1 640, 1 625
(2f)	1 740	1 670, 1 645, 1 630

CH_2Cl_2, and the CH_2Cl_2 extract was washed with brine, dried ($MgSO_4$) and the solvent removed to yield a pale brown amorphous mass of (12d) (0.94 g, quantitative) [$\nu_{max.}$ ($CHCl_3$) 3 550 (OH) and 1 580 cm^{-1} (C=N)]. To an ice-cooled, stirred solution of the dihydroisoquinoline (12d) in MeOH (20 ml) was added $NaBH_4$ (86 mg, 2.26 mmol) portion by portion, and the whole was stirred at room temperature for 20 min. After evaporation of the solvent under reduced pressure, the residue was basified with 5% $NaHCO_3$ solution and the product taken up in CH_2Cl_2. The usual work-up gave colourless crystals of (13d) (0.95 g, quantitative), m.p. 80—100 °C, which were recrystallized from benzene–n-hexane to afford colourless prisms (0.77 g, 81.5%), m.p. 100—114 °C; an analytical sample had m.p. 107—109 °C.

(±)-1-(4-*Benzyloxy*-3-*methoxyphenethyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methylisoquinoline* (6d).—To an ice-cooled, stirred solution of (13d) (0.67 g, 1.6 mmol) in MeOH (10 ml), 37% HCHO (0.65 ml, 8 mmol) was added, and stirring was continued at room temperature for 35 min. To this stirred mixture was added $NaBH_4$ (0.3 g, 8 mmol) during 5 min with ice-cooling, followed by stirring at room temperature for 1 h. The usual work-up gave a colourless amorphous mass of (6d) (0.53 g, 76.8%); δ 2.43 (3 H, s, NMe), 3.79 and 3.80 (each 3 H, s, OMe), and 5.09 (2 H, s, OCH_2Ph); $\nu_{max.}$ ($CHCl_3$) 3 530 cm^{-1} (OH); the methiodide (from MeOH) had m.p. 139—143 °C (decomp.).

(±)-1-(3-*Benzyloxy*-4-*methoxyphenethyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxyisoquinoline* (13e).—A solution of the amide (11e) (435 mg, 1 mmol) and $POCl_3$ (0.5 ml, 5.5 mmol) in dry CH_2Cl_2 (10 ml) was refluxed for 2.5 h. The usual work-up gave a pale brown amorphous mass of (12e) (400 mg, 95.9%) [$\nu_{max.}$ ($CHCl_3$) 3 530 (OH), 1 620, and 1 580 cm^{-1} (C=C and C=N)]. To a water-cooled, stirred solution of the dihydroisoquinoline (12e) in MeOH (10 ml) was added $NaBH_4$ (36 mg, 0.95 mmol) portion by portion, and stirring was continued at room temperature for 30 min. Work-up as usual gave colourless crystals of (13e) (320 mg, 81%), m.p. 90—91 °C (decomp.), which were recrystallized from benzene–n-hexane yielding colourless prisms (255 mg, 64.6%), m.p. 103—110 °C (decomp.); an analytical sample had m.p. 112—114 °C (decomp.).

(±)-1-(3-*Benzyloxy*-4-*methoxyphenethyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methylisoquinoline* (6e).—The amine (13e) (838 mg, 2 mmol) was treated with 37% HCHO (0.84 ml, 10 mmol) in MeOH (15 ml) for 45 min, followed by treatment with $NaBH_4$ (0.38 g, 10 mmol), according to the procedure given above, to afford a yellowish brown amorphous mass of (6e) (823 mg, 95.0%); δ 2.40 (3 H, s, NMe), 3.80 (6 H, s, 2 × OMe), and 5.11 (2 H, s, OCH_2Ph); $\nu_{max.}$ ($CHCl_3$) 3 550 (OH) cm^{-1} [the methiodide (from acetone–AcOEt) had m.p. 156—158 °C].

(±)-1-(4-*Benzyloxy*-3,5-*dimethoxyphenethyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methylisoquinoline* (6f).—A solution of the amide (11f) (1.0 g, 2.06 mmol) and $POCl_3$ (1.5 ml, 16.3 mmol) in CH_2Cl_2 (14 ml) was refluxed for 3 h. The usual work-up gave a yellow amorphous mass of (12f) (905 mg, quantitative), to a water-cooled, stirred solution of which in MeOH (20 ml) was added $NaBH_4$ (80 mg, 2.11 mmol) yielding a yellow amorphous mass of (13f) (800 mg, 86.5%) [$\nu_{max.}$ ($CHCl_3$) 3 530 (OH) cm^{-1}]. Crude (13f) was treated with 37% HCHO (1.4 ml, 17.3 mmol) in MeOH (20 ml) for 30 min, followed by treatment with $NaBH_4$ (338 mg, 8.89 mmol), according to the procedure given above, to give a yellowish brown oil (682 mg). Crystallization from ether yielded colourless crystals of (6f) (436 mg, 43.8%), m.p. 64—66 °C, which were recrystallized from the same solvent to afford colourless prisms, m.p. 65—67 °C; δ 2.44 (3 H, s, NMe), 3.75 (6 H, s, 2 × OMe), 3.80 (3 H, s, OMe), 4.96 (2 H, s, OCH_2Ph), 6.38 (2 H, s, 2′- and 6′-H), and 6.54, 6.67 (each 1 H, s, Ar-H); $\nu_{max.}$ ($CHCl_3$) 3 530 cm^{-1} (OH).

General Procedure for $Pb(OAc)_4$ *Oxidation and Subsequent Acid Treatment of* (6).—To a stirred solution of (6) in AcOH [1—2 ml per 100 mg of (6)] was added $Pb(OAc)_4$ (1.1—1.2 equiv.) in one portion and stirring was continued at room temperature for 30 min. The reaction mixture was basified with 5% $NaHCO_3$ solution and the product was taken up in CH_2Cl_2, washed with brine, and dried over K_2CO_3.

TABLE 5

I.r. ($CHCl_3$) (cm^{-1}) and n.m.r. spectral data of homoaprophines

		δ							
Compound	ν(OH)	NMe	1-OMe	12-OMe	OMe	OCH_2Ph	OCH_2O	3-H and 9-H	12-H
(3a)	3 540	2.39			3.88		5.96	6.62, 6.75	7.04
(3b)	3 540	2.37			3.87, 3.90, 3.92			6.62, 6.78	7.12
(3c)	3 530	2.42		3.64	3.88, 3.90 (6 H)			6.65, 6.69	
(3d)	3 520	2.42			3.86, 3.89	5.12		6.60, 6.78	7.17
(3e)	3 525	2.34			3.80 (6 H)	5.15		6.57, 6.79	7.14
(3f)	3 530	2.42		3.60	3.87 (6 H)	5.11		6.63, 6.67	
(3g) *	3 525	2.20			3.75 (6 H)			6.65, 6.78	6.89
(3h) *	3 525	2.23			3.71, 3.78			6.64, 6.66	7.01
(3i)	3 520	2.35		3.53	3.85 (6 H)			6.58, 6.65	
(10d)		2.33	3.29		3.81, 3.88	5.13		6.63, 6.77	7.14
(10e)		2.35	3.42		3.82, 3.84	5.18		6.67, 6.82	7.13
(10f)		2.39	3.47	3.61	3.81, 3.83	5.03, 5.16 (each 1 H, d) *J* 11.5 Hz)		6.53, 6.68	
(10g)	3 530	2.34	3.43		3.84, 3.86			6.66, 6.72	7.00
(10h)	3 530	2.38	3.40		3.80, 3.85			6.67, 6.74	7.08
(10i)	3 520	2.38	3.46	3.48	3.82, 3.87			6.53, 6.68	

* N.m.r. in $(CD_3)_2SO$.

TABLE 6

I.r. ($CHCl_3$) and n.m.r. spectral data of homoproaporphines

Compound	I.r. (cm^{-1}) OH	OAc	Dienone	N.m.r. (δ) (*J* in Hz) NMe	OMe	3-H	9-H (d)	12-H (d)	13-H (dd)	OCH_2Ph	OAc
(4b)	3 510		1 650, 1 630, 1 605	2.43	3.62, 3.75	6.57	5.84 (2.5)	6.24 (10)	7.03 (2.5, 10)		
(4c)	3 510		1 650, 1 620	2.53	3.57, 3.63, 3.78	6.56	5.84 * (2.0)		6.02 * (2.0)		
(4e)	3 515		1 650, 1 630, 1 605	2.40	3.72	6.50	5.86 (2.0)	6.21 (10)	6.94 (2.5, 10)	4.88	
(8)		1 760	1 660, 1 635, 1 605	2.46	3.62, 3.73	6.68	5.83 (2.5)	6.29 (10)	7.07 (2.5, 10)		1.98

* Assignments could be reversed.

TABLE 7

I.r. ($CHCl_3$) and n.m.r. spectral data of homomorphinandienones

Compound	I.r. (cm^{-1}) dienone	N.m.r. (δ) NMe	OMe	4-OMe	5-H	8-H	4-H	1-H	OCH_2Ph
(5b)	1 660, 1 635, 1 610	2.37	3.63, 3.81, 3.88		6.07	6.33	6.48	6.91	
(5c)	1 660, 1 630, 1 610	2.37	3.66, 3.85 (6 H)	4.04	6.31	6.36		6.83	
(5d)	1 660, 1 635, 1 615	2.33	3.37, 3.85		5.67	6.28	6.49	6.81	5.11, 5.30 (each 1 H, d *J* 13 Hz)
(5e) *	1 660, 1 635, 1 610								
(5f)	1 660, 1 630, 1 610	2.37	3.62, 3.78	4.00	6.28	6.32		6.79	4.98

* Insufficient material for n.m.r. spectrum.

Removal of the solvent under reduced pressure gave the oily *p*-quinol acetate (2), which was treated with CF_3CO_2H [0.5 ml per 100 mg of (6)] in CH_2Cl_2 [10 ml per 100 mg of (6)] at room temperature for 2 h. Each residue obtained on the usual work-up was subjected to preparative t.l.c. Elution of the upper, middle, and lower zones gave a homomorphinandienone (5), a homoaporphine (3), and a homoproaporphine (4), respectively.

The spectral data and m.p. of each compound are shown in Tables 4—8.

General Procedure for Methylation with Diazomethane.—The phenolic base (100—140 mg) in MeOH (6—10 ml) was treated with an excess of diazomethane–ether at room temperature for 2—4 d to give an oily methyl ether (10); n.m.r. spectral data are in Table 5, yield and m.p. (methiodide) are shown in Table 9.

General Procedure for Catalytic Debenzylation.—A mixture of the benzyl ether (54—100 mg), 2% $PdCl_2$ (0.6—1 ml), and active carbon (30—50 mg) in MeOH (15—20 ml) was shaken in an atmosphere of H_2 at room temperature, until the uptake of H_2 ceased. Work-up as usual afforded the pure phenol; spectral data are in Table 5; yield and m.p. are shown in Table 10.

TABLE 8

Melting points of cyclization products

Starting phenol	Product	M.p. (°C)
(6a)	(3a) [5]	146—148 (benzene-n-hexane)
(6b)	(5b) [6]	Oil, 251—252 * (MeOH)
	(3b) [4,6]	200—201 (Pr^iOH)
	(4b) [7]	199—200 (acetonitrile–ether)
(6c)	(5c) [6,11]	172—173.5 (ether–Pr^iOH)
	(3c) [4,7a]	184—186 (benzene–n-hexane)
	(4c) [7]	176—179 (benzene–$CHCl_3$)
(6d)	(5d)	Oil, 184—187 * (MeOH)
	(3d)	184—185 (ether)
	(4b) [7]	197—199 (ether)
(6e)	(5e)	Oil
	(3e)	117—120 (benzene)
	(4e)	164—165 (benzene–n-hexane)
(6f)	(5f)	128—129 (ether–n-hexane) 245—248 * (MeOH)
	(3f)	141—142 (ether–n-hexane)
	(4c)	173—175 (acetonitrile–ether)

* Methiodide.

TABLE 9

Yields and m.p.s of methylation product

Starting phenol	Product	Yield (%)	M.p. (°C)
(3d)	(10d)	91.3	Oil, 231—233 (MeOH) *
(3e)	(10e)	100	Oil, 220—222 (decomp.) (MeOH) *
(3f)	(10f)	95.1	Oil, 214—216 (ether–MeOH) *

* Methiodide.

TABLE 10

Yields and m.p.s of debenzylation products

Starting ether	Product	Yield (%)	M.p. (°C)
(3d)	(3g) [8]	100	143—147, 184—185 (decomp.) (acetone)
(3e)	(3h) [8]	80	242—243 (benzene–MeOH)
(3f)	(3i) [7a]	87.4	190—192 (decomp.) (EtOH)
(10d)	(10g)	71.4	Amorphous mass, 284—286 (decomp.) (MeOH) *
(10e)	(10h)	84	189—191 (Pr^iOH)
(10f)	(10i)	86.4	168—169 (acetone–ether)

* Methiodide.

(±)-1-O-*Acetyl-'Dienone II'* (8) *and its Methiodide* (9).—A mixture of 'Dienone II' (4b) (79 mg), acetic anhydride (0.5 ml), and pyridine (0.5 ml) was allowed to stand at room temperature overnight. The usual work-up gave colourless crystals of (8) (80 mg), m.p. 99—102 °C (decomp.), which were recrystallized from benzene to afford fine needles, m.p. 197—199 °C (decomp.) [the methiodide (9), colourless prisms from MeOH, had m.p. 255—256 °C (decomp.)].

General Procedure for $Pb(OAc)_4$ *Oxidation of* (6) *in the Presence of* CF_3CO_2H.—To a stirred mixture of (6) (100 mg) in AcOH (2 ml) and CF_3CO_2H (0.5 ml) was added $Pb(OAc)_4$ (1.5 equiv.) in one portion at room temperature, and stirring was continued for 1 h at the same temperature. The reaction mixture was basified with 5% $NaHCO_3$ solution and the product was taken up in $CHCl_3$, washed with brine, and dried over K_2CO_3. Each residue obtained on evaporation of the solvent was subjected to preparative t.l.c., and each product was identical with an authentic sample, by comparison of i.r. and t.l.c.

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