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THE STRUCTURE AND PROPERTIES OF PETALINE

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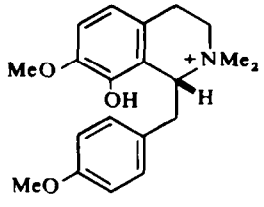
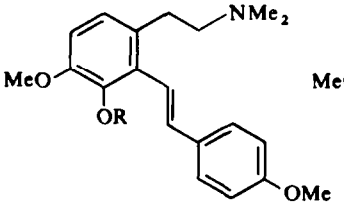
Abstract—Structural studies on petaline (I) are described.

The plant *Leontice leontopetalum* has had a checkered career in folk medicine and chemical investigations were originally undertaken on the grounds of reputed anti-epileptic activity.[1] Although no principles having anti-epileptic activity were detected, the alkaloid (−) petaline, which is unusual in being a quaternary alkaloid which produces tonic convulsions,[2] was isolated. In earlier communications,[3, 4] evidence has been presented that (−)petaline has structure I. Confirmatory evidence has recently been provided from other laboratories by syntheses.[5, 6] We here present details of our structural studies.

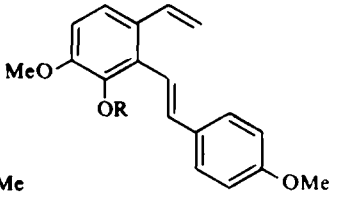
A convenient first step in these studies was conversion of petaline to its crystalline methine base II using Amberlite IRA-400 (OH form). This methine is typical of those derived from tetrahydroisoquinolinium salts since it shows the UV spectrum characteristic[7] of a stilbene with maxima at 216 and 299 mμ and also since it shows resonances corresponding to a β-dimethylaminoethyl side chain (2H multiplets at 7·1 and 7·5 τ forming an $A'_2B'_2$ system and a 6H singlet at 7·69 τ). The presence of this side chain was confirmed by Hofmann degradation to give trimethylamine and III whose NMR spectrum showed resonances typical of the olefinic protons of a styrene, forming an ABX system (τ_A 4·80, τ_B 4·51, τ_X 3·03, J_{AB} = 2 Hz, J_{AX} = 10·7 Hz, J_{BX} = 17·3 Hz). The presence of two OMe groups in petaline methine was indicated by analysis and by 3H singlets in the NMR at 6·12 and 6·17 τ. The situation of one of these in a *p*-methoxyphenyl unit was apparent from the formation of *p*-methoxybenzaldehyde following ozonolysis of the above styrene.



I



II: R = H
V. R = SO_2Me

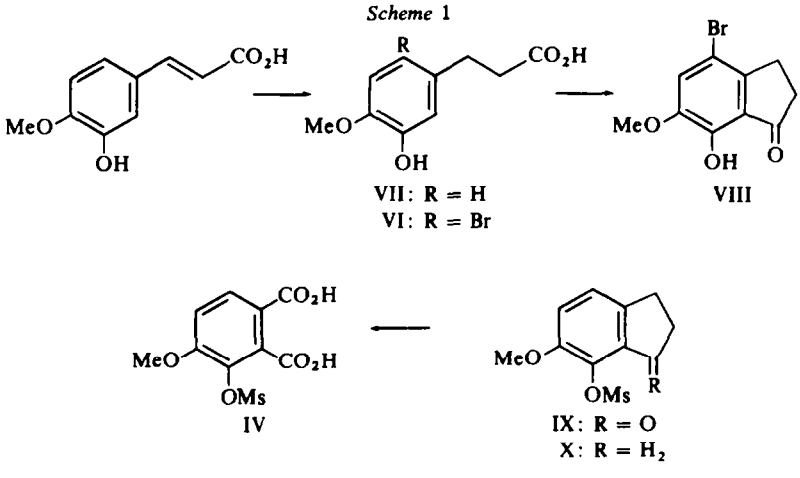


III: R = H
XIX: R = $COCH_3$

The remaining O atom was present as a phenolic OH group whose IR absorption at 3540 cm^{-1} was in accord with weak intramolecular H-bonding to an *ortho* OMe group.

The unusual orientation of substituents in the isoquinoline ring of petaline became evident from the positive Gibbs tests[8] given by petaline methine and the styrene III, indicating the absence of substituents *para* to the phenol group. This was confirmed by the formation of 3-methanesulphonyloxy-4-methoxyphthalic acid (IV) together with the expected *p*-anisic acid, upon dichromate oxidation of O-methanesulphonylpetaline methine (V). The structure of this dicarboxylic acid was established by the unambiguous synthesis indicated in Scheme 1.

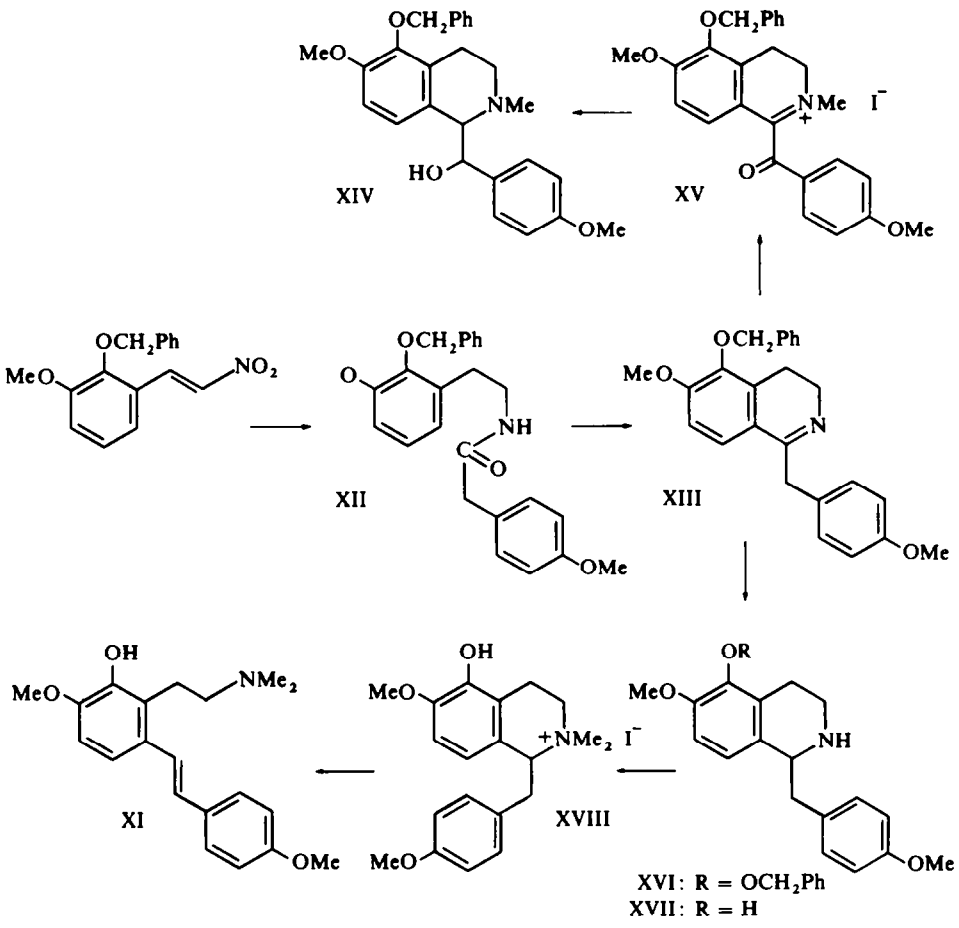
Scheme 1



In this synthesis, the desired orientation of substituents was achieved by cyclodehydration of the 3-hydroxy-4-methoxyphenylpropionic acid VI in which the 6-position is blocked by means of a Br atom. The desired monobromo acid was obtained by bromination of the hydrocinnamic acid VII under controlled conditions. The location of the Br atom in the 6-position followed firstly from the absence of coupling shown by the two aromatic protons in the NMR spectrum of the corresponding ethyl ester, which appeared as 1H singlets at 3·00 (H-5) and 3·18 τ (H-2), and secondly by the formation upon cyclization, of a bromoindanone VIII with the properties expected of a 7-hydroxyindanone. This product gave a blue coloration with ethanolic $FeCl_3$ and a yellow-green chelate with $Cu(OAc)_2$ in acetone. It also showed a red shift of its long wavelength UV absorption band upon basification of 41 mμ (7-hydroxyindanone itself gives a shift of 47 mμ). Debromination of the bromoindanone VIII was effected by hydrogenation over Pd-C and the oily product was converted directly to its crystalline mesylate IX. In one experiment, as a result of overreduction, this sequence gave the indane X. Dichromate oxidation of either mesylate gave a phthalic acid identical to that derived from O-mesylpetaline methine.

It follows from the above that the structure of petaline methine is either I or XI. The latter compound was synthesized from 2-benzyloxy-3-methoxy-β-nitrostyrene as indicated in Scheme 2. Bischler-Napieralski cyclization of the intermediate amide XII gave an oily product XIII which showed the UV spectral characteristics of a 3,4-dihydroisoquinoline, having a max at 278 mμ which underwent a bathochromic

Scheme 2



shift of 49 mμ upon acidification. Reaction of this product with methyl iodide, followed by borohydride reduction and quaternization with methyl iodide gave, not the desired methiodide but the hydroxy analogue XIV. The intermediate leading to this compound was shown to be the keto methiodide XV its formation following the tendency of 1-benzyl-3,4-dihydroisoquinolines to oxidize in air to 1-benzoyl derivatives.[9] This side reaction was avoided by borohydride reduction of the intermediate 3,4-dihydroisoquinoline. After removal of the benzyl group by catalytic reduction, further catalytic reduction in the presence of formaldehyde followed by treatment with methyl iodide gave the N,N-dimethyl quaternary salt XVIII ("pseudopetaline iodide").

Since neither m.ps nor solid state IR spectra allowed a distinctive comparison of this racemic compound with a sample of petaline iodide, initially these compounds were distinguished by the contrasting properties of the corresponding methines, XI, m.p. 173° and II, m.p. 123° respectively. The more crowded environment of the stilbene system in the latter is reflected in the position of its long wavelength band (299 mμ as compared with 317 mμ in XI).

Analysis of the NMR spectra of the above methines provides further evidence of the respective orientations of substituents. Deshielding by the stilbene double bond in the *ortho* position accounts for the low field position of two of the *p*-methoxyphenyl aromatic protons (2·55τ) in petaline methine, and of the phenolic ring proton in pseudopetaline methine which appears at 2·96τ and shows *ortho* coupling to the other at 3·21τ. While the phenolic ring protons in petaline methine give rise to a singlet at 3·28τ in $CDCl_3$, they appear as doublets, $J = 9$ Hz at 3·20τ and 3·35τ in acetone, as would be expected for two *ortho* coupled protons neither of which is *ortho* to the stilbene double bond. On the other hand one of these protons is shifted down to 2·95τ in the styrene III showing that it is *ortho* to the styrene double bond.

It may also be seen that the stilbene olefinic protons in petaline methine appear at 0·26 and 0·30 ppm downfield from those in pseudopetaline methine, evidently due to the presence of the oxygen substituent in the *ortho* position in petaline methine. An analogous deshielding of the α and β protons in *ortho*-coumaric acid (doublets, $J = 16$ Hz at 3·41 and 1·98τ) occurs relative to those in its *para* isomer (doublets, $J = 15{\cdot}7$ Hz at 3·72 and 2·38τ). These values suggest that in petaline methine and ortho-coumaric acid, there is a distribution of rotamers in which either the α or β olefinic proton is near to the phenolic OH group. It may be seen from the data in Table 1 (cf Nos 1 and 2 and cf Nos 4 and 5) that esterification of the 8-OH group as in O-mesylpetaline methine(V) or in the O-acetylstyrene XIX removes the shielding effect of the OH group on the dioxygenated ring protons and its deshielding effect on the stilbene olefinic protons.

Since the ORD curve is clearly that of a benzyl tetrahydroisoquinolinium salt[4] it follows that the structure of petaline is I. It may be noted that the chemical shift

TABLE I. τ VALUES (J IN Hz UNIT) OF OLEFINIC PROTONS IN PETALINE AND PSEUDOPETALINE DERIVATIVES.

		RO—C_6H_4—	$\begin{matrix}R_1O\\R_2O\end{matrix}\Big\}C_6H_2\diagup$	$Ar_1CH{=}CHAr_2$
1. Petaline methine	$CDCl_3$	3·08 (8·5) 2·51	3·28	2·92 (16·5) 2·61
	d_6-DMSO	3·05 (8·5) 2·55	3·35 (9) 3·20	2·98 (16·5) 2·77
	acetone	3·11 (8·5) 2·54	3·34 (9) 3·22	2·90 (16·5) 2·62
2. O-Mesyl petaline methine	$CDCl_3$	3·07 (9) 2·51	3·13 (8·5) 2·83	3·04
3. Pseudopetaline methine	$CDCl_3$	3·07 (9) 2·55	3·21 (9) 2·96	3·22 (16) 2·87
4. Styrene III	$CDCl_3$	3·16 (9) 2·59	3·28 (8·5) 3·04	2·96
	dioxan	3·16 (8) 2·60	3·25 (8) 3·05	3·10 (16·5) 2·93
5. O-Acetylstyrene XIX	$CDCl_3$	3·08 (9) 2·55	3·10 (9) 2·58	3·15
6. Petaline perchlorate	d_6-DMSO	3·13 (9) 2·76	3·26 (8·5) 2·98	
7. Pseudopetaline iodide	d_6-DMSO	3·20 (9) 2·97	4·20 (8·5) 3·37	

(4·96τ) of the proton at C—1 and of the two anisyl aromatic protons *meta* to the OMe group (2·76τ) are 0·3 and 0·21 ppm respectively downfield from those in pseudopetaline (XVIII), again reflecting the presence of the 8-OH group in petaline.

The upfield position (4·20τ) of one of the phenolic ring protons in pseudopetaline can be attributed to shielding by the anisyl ring in the preferred rotamer, in which the anisyl ring is remote from the N-Me groups.[10]

In experiments kindly carried out by Dr. R. Buckett, Organon Laboratories, petaline methine was found to be 6 times less effective than petaline in producing tonic convulsions in the mouse and did not show significant neuromuscular blocking activity. Pseudopetaline iodide showed neuromuscular blocking activity comparable to that of petaline iodide.

EXPERIMENTAL

M.ps are uncorrected. Unless otherwise stated, NMR spectra were determined at 60 MHz. Chemical shifts are given in τ using TMS as internal reference and coupling constants (*J*) in Hz unit. Abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. UV spectra were determined in EtOH.

2-Hydroxy-3,4'-dimethoxy-6-(β-dimethylaminoethyl)-trans-stilbene (*Petaline methine*) (II)

Petaline reineckate (5 g), isolated from dry powdered *Leontice leontopetalum* extractives as previously described, was introduced in acetone (20 ml) to a column of Amberlite IRA—400 (OH) (250 g), and washed through with dry EtOH. Evaporation gave the *methine* which crystallized from acetone in colourless needles, m.p. 121–123°, UV λ_{max} mμ (ε): 216 (28,400), 299 (21,100), UV $\lambda_{max}^{EtOH-NaOH}$ mμ (ε): 218 (26,700), 256 (17,200) 296 (15,200), 360 (8,400), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3540 (OH), IR ν_{max}^{CS} cm^{-1}: 969 (double bond), NMR ($CDCl_3$): 6H s at 7·69 (—NMe_2), two 3H s at 6·17, 6·12 (—OMe), two 2H m at 7·1 and 7·5 $A'_2B'_2$ system, —CH_2·CH_2·N), 1H s at 4·05 (disappearing upon deuteration, OH), 2H s at 3·28 (phenolic ring H), two 2H d at 2·51 and 3·08 (AA'BB' system, J_{AB} = 9, *p*-MeO-C_6H_4—), two 1H d at 2·61 and 2·92 (AB quartet, *J* = 16, stilbene olefinic H). (Found: C, 73·6; H, 7·75; N, 4·6; OMe, 19·4; active H, 0·33; M^+ at *m/e* 327. $C_{20}H_{25}NO_3$ requires C, 73·4; H, 7·7; N, 4·3; two OMe, 19·0; one active H, 0·31%; M.W. 327).

Hofman degradation of petaline methine. Petaline methine (3·1 g) was refluxed with MeI (4 ml) in acetone (50 ml) for 2·5 hr. The *methiodide*, which separated, crystallized from acetone, m.p. 169–171°, UV λ_{max} mμ (ε): 217 (63,000), 297 (24,200). (Found: C, 53·7: H, 6·9; N, 3·1 $C_{21}H_{28}INO_3$ requires C, 53·7; H, 6·3; N, 3·0%).

The methiodide (3·6 g), in MeOH was passed through a column of Amberlite IRA-400 (OH) (60 g.). Evaporation of the MeOH gave the corresponding methohydroxide (m.p. 150–155°) which was heated under N_2 in 5% ethanolic NaOEt (67 ml) for 2·5 hr. The effluent gas was passed through saturated ethanolic picric acid. The resulting picrate crystallized from EtOH in yellow needles, m.p. 209–211°. (Found: C, 37·85; H, 4·2; N, 19·25. Calc. for $C_9H_{12}N_4O_7$; C, 37·5; H, 4·2; N, 19·45%. Identity with an authentic sample of trimethylamine picrate was established by mixed m.p. and by comparison of IR spectra.

The non-volatile reaction mixture was acidified with dilute aqueous AcOH and then exhaustively extracted with benzene to give *2-hydroxy-3,4'-dimethoxy-6-vinyl*-trans-*stilbene* (III), which crystallized from ether-light petroleum (b.p. 40–60°) in orange needles (1·68 g, 78%), m.p. 111–113°, UV λ_{max} mμ(ε): 209 (27,000), 269 (23,900), 305 (21,100), UV λ_{max}^{N-KOH} mμ(ε): 254 (21,800), 272 (21,700), 365 (9,300), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3545 (OH), NMR ($CDCl_3$): two 3H s at 6·20, 6·11 (—OMe), three 1H m, H_A at 4·82, H_B at 4·51 and H_X at 3·03 (ABX system, J_{AX} = 10·7, J_{BX} = 17·3, J_{AB} = 2, vinyl group), two 1H d at 3·04, 3·28 (AB quartet, *J* = 8·5, phenolic ring H), two 2H d at 2·59, 3·16 (AA'BB' system, J_{AB} = 9, *p*-MeO—C_6H_4—), 2 H s at 2·96 (stilbene olefinic H). (Found: C, 76·7; H, 6·8; M^+ at *m/e* 282. $C_{18}H_{18}O_3$ requires: C, 76·6; H, 6·4%; M.W. 282).

The corresponding O-acetyl derivative showed the following NMR resonances in $CDCl_3$: 3H s at 7·7 (—O·CO·Me), two 3H s at 6·17, 6·18 (—OMe), three 1H m, H_A at 4·77, H_B at 4·43 and H_c at 3·05 (ABX system, J_{AX} = 10, J_{BX} = 17, J_{AB} = 2, vinyl group), two 1H d at 2·58, 3·10 (AB quartet, *J* = 9, dioxygenated aromatic ring H), two 2H d at 2·55, 3·08 (AA'BB' system, J_{AB} = 9, *p*-MeO—C_6H_4—), 2H s at 3·15 (stilbene olefinic H).

Treatment of the phenolic vinyl stilbene (1·1 g) with 10% BF_3—MeOH (35 ml) at 100° for 20 min gave

the corresponding *methyl ether* (0·84 g, 80%), m.p. 168–170° from benzene—light petroleum (b.p. 40–60°). (Found: C, 77·3; H, 6·6, $C_{19}H_{20}O_3$ requires: C, 77·0; H, 6·8%).

O-*Methanesulphonylpetaline methine* (V)

Petaline methine (0·55 g) in pyridine (10 ml) was treated at 0° with $MeSO_2Cl$ (2 ml) in pyridine (2 ml). After 12 hr at 0°, ice and sat Na_2CO_3 aq were added and the mixture allowed to stand for 24 hr at 0°. The oil which separated was allowed to stand with fresh water and then gave the *mesylate* as colourless needles (0·5 g, 74%), m.p. 102–103° (from EtOAc–light petroleum, b.p. 60–80°), IR ν_{max}^{Nujol} cm^{-1}: 1150 (—OSO_2R), NMR ($CDCl_3$): 6H sat 7·7 (—NMe_2), two 3H sat 6·11, 6·18 (—OMe), 3H sat 6·79 (—OSO_2Me), two 2H m at 7·2, 7·4 ($A'_2B'_2$ system, —CH_2CH_2·N), two 1H d at 2·85, 3·12 (AB quartet, J = 9, dioxygenated aromatic ring H), two 2H d at 2·52, 3·08 (AA'BB' system, J_{AB} = 9, *p*-MeO—C_6H_4—), 2H s at 3·05 (stilbene olefinic H). (Found: C, 62·2; H, 6·8; N, 3·5. $C_{21}H_{27}NO_5S$ requires: C, 62·2; H, 6·7; N, 3·5%).

3-*Methanesulphonyloxy-4-methoxyphthalic acid* (IV)

A. *By oxidation of* O-*mesylpetaline methine.* O-Mesylpetaline methine (0·15 g) was refluxed for 30 min with $K_2Cr_2O_7$ (1·33 g) and H_2SO_4 (4 ml) in water (20 ml). After cooling, SO_2 was passed through the soln until it was bright green. $CHCl_3$ extraction (3 × 25 ml) gave anisic acid (4 mg) (identified by mixed m.p. and comparison of IR spectrum with an authentic sample). The aqueous mother liquor was continuously extracted overnight with $CHCl_3$ to give 3-*methanesulphonyloxy-4-methoxyphthalic acid* (16 mg 11%) as a colourless powder, m.p. 179–194°, identical (mixed m.p. and comparison of IR spectrum) with a sample synthesized as in B or C. Further proof of identity was provided by comparison (mixed m.p. and IR spectra) of the corresponding anhydrides (see below).

B. *By oxidation of* 7-*methanesulphonyloxy-6-methoxyindan*-1-*one* (IX). Oxidation of 7-methanesulphonyloxy-6-methoxyindan-1-one (0·2 g) with $K_2Cr_2O_7$ (1 g) and H_2SO_4 (3 ml) in water (15 ml), carried out as in the preceding experiment (A), gave 3-methanesulphonyloxy-4-methoxyphthalic acid as a colourles solid (74 mg, 34%), m.p. 180–194°, IR ν_{max}^{Nujol} cm^{-1}: 1720 and 1690 (>C=O), 1160 (—OSO_2Me). Sublimation at 160°/0·02 mm gave the *anhydride* as colourless crystals, m.p. 170°, IR ν_{max}^{Nujol} cm^{-1}: 1850 and 1775 (—CO·O·CO—), 1160 (—OSO_2Me). (Found: C, 44·3; H, 3·1. $C_{10}H_8O_7S$ requires: C, 44·0; H, 2·8%).

C. *By oxidation od* 3-*methanesulphonyloxy-4-methoxyindane.* Oxidation of the indane under the conditions described in B for the indanone gave the same phthalic acid in similar yield.

3-*Hydroxy-4-methoxycinnamic acid*

A mixture of isovanillin (50 g) and malonic acid (77·5 g) in pyridine (300 ml) containing piperidine (5 ml) was heated at 100° for 1 hr and then refluxed for 5 min. The cooled solution was poured into water and acidified with 6N HCl. Crystallization of the resulting cinnamic acid gave colourless plates, (55 g, 88%), m.p. 233–234°, IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH), 1660 (CO_2H), 973 (*trans* double bond), UV λ_{max} mμ (ε): 220 (12,000), 243 (10,700), 295 (13,200), 324 (14,800), NMR (acetone): 3H m at 2·8–3·15 (Ar—H), two 1H d at 2·4, 3·68 (AB quartet, J = 15·5, β and α olefinic H). (Found: C, 61·9; H, 5·2. $C_{10}H_{10}O_4$ requires: C, 61·9; H, 5·2%).

3-*Hydroxy-4-methoxyphenylpropionic acid* (VII)

3-Hydroxy-4-methoxycinnamic acid (52·6 g), dissolved in 12% KOH aq (200 ml) was hydrogenated at atm temp and press over 10% Pd-C (2·2 g), until 1 mole of H_2 had been absorbed. After removal of the catalyst, acidification with 6N HCl gave the *hydrocinnamic acid*, which crystallized from benzene in colourless prisms (51·5 g, 97%), m.p. 146–150°, IR ν_{max}^{Nujol} cm^{-1}: 3350 (OH); 1700 (CO_2H). (Found: C, 61·4; H, 5·9. $C_{10}H_{12}O_4$ requires: C, 61·2; H, 6·2%).

γ-(2-*Bromo-5-hydroxy-4-methoxyphenyl*) *propionic acid* (VI)

A soln of Br_2 (1·55 ml) in HOAc (25 ml) was added during 20 min to a stirred soln of 3-hydroxy-4-methoxyphenylpropionic acid (5 g) in HOAc (100 ml) at 18°. After a further 12 hr, the solvent was evaporated under reduced press giving the *bromoacid*, which crystallized from benzene in colourless needles (6·5 g, 93%), m.p. 142–144°, IR ν_{max}^{Nujol} cm^{-1}: 3350 (OH), 1700 (CO_2H). (Found: C, 43·8; H, 4·4. $C_{10}H_{11}BrO_4$ requires: C, 43·6; H, 4·0%).

The corresponding *ethyl ester*, prepared by refluxing the acid in EtOH containing a trace of mineral acid, crystallized from light petroleum (b.p. 80–100°) in colourless needles, m.p. 58–62°, IR ν_{max}^{Nujol} cm^{-1}: 3350 (OH), 1725 (CO_2Et), NMR ($CDCl_3$): 2H q at 5·89 and 3H t at 8·78 (J = 6, —CO·OEt), two 2H m at 7·08, 7·45 (α and β CH_2 groups), 3H s at 6·18 (OMe), two 1H s at 3·00, 3·18 (Ar—H). (Found: C, 47·2; H, 5·3. $C_{12}H_{15}BrO_4$ requires: C, 47·4; H, 5·0%).

If Br_2 was added rapidly (e.g. during 5 min) in the above bromination, a second product separated from the reaction mixture. Crystallization from EtOH gave the *dibromoacid* as colourless needles, m.p. 211–212°. (Found: C, 33·3; H, 3·0. $C_{10}H_{10}Br_2O_4$ requires: C, 33·9; H, 2·8%).

4-Bromo-7-hydroxy-6-methoxyindan-1-one (VIII)

A soln of γ-(2-bromo-5-hydroxy-4-methoxyphenyl)-propionic acid (11·8 g) in conc H_2SO_4 (100 ml) was heated at 100° under N_2 for 10 min and then poured on to crushed ice (ca. 500 g). $CHCl_3$ extracts of the resulting soln were washed with $NaHCO_3$ aq and then evaporated to give the *indanone*, which crystallized from EtOH in colourless prisms (8·3 g, 70%), m.p. 132–133°, UV λ_{max}^{MeOH} mμ (ε): 226 (17,000), 262 (6,200), 343 (2,800), UV $\lambda_{max}^{MeOH\ KOH}$ mμ (ε): 241 (18,600), 267 inf., 384 (4,800), IR ν_{max}^{Nujol} cm^{-1}: 3250 (OH), 1665 (>C=O), NMR ($CDCl_3$): two 2H m at 7·05, 7·28 ($A'_2B'_2$ system, indanone ring H), 3H s at 6·13 (OMe), 1H s at 2·79 (Ar-H), 1H br s at 1·00 (OH). (Found: C, 46·7; H, 3·8. $C_{10}H_9BrO_3$ requires: C, 46·7; H, 3·5%). The indanone gave a blue colouration with ethanolic $FeCl_3$, formed an orange 2,4-dinitrophenylhydrazone and formed sparingly soluble Na, K and Li salts.

7-Methanesulphonyloxy-6-methoxyindan-1-one (IX)

A soln of 4-bromo-7-hydroxy-6-methoxyindan-1-one (5 g) in MeOH (150 ml) was hydrogenated over 10% Pd–C (0·6 g) at atm temp and press until one mole of H_2 had been taken up (several hrs). After removal of the catalyst, evaporation gave an oil, which, without further purification was dissolved in pyridine (25 ml) and treated at 0° with $MeSO_2Cl$ (2·5 ml) in pyridine (2·5 ml). After 12 hr at 0°, the mixture was poured into water. Crystallization of the resulting ppt from MeOH (charcoal) gave the *mesyloxyindanone* as stout colourless prisms (2·4 g, 48%), m.p. 162·5–127·5°, IR ν_{max}^{Nujol} cm^{-1}; 1712 (5-membered ring aryl ketone), 1160 (—OSO_2R), NMR ($CDCl_3$): two 2H m at 6·9, 7·25 ($A'_2B'_2$ system, cyclopentenone ring H), 3H s at 6·53 (—OSO_2Me), 3H s at 6·03 (OMe), 2H s at 2·62 (Ar—H). (Found: C, 51·9; H, 4·95. $C_{11}H_{12}O_5S$ requires: C, 51·6; H, 4·7%).

3-Methanesulphonyloxy-4-methoxyindane (X)

4-Bromo-7-hydroxy-6-methoxyindan-1-one (5 g) was reduced as above but using a different batch of catalyst, until uptake of H_2 ceased. Mesylation as described above gave the *indane* as colourless needles (from light petroleum, b.p. 60–80°) (2·4 g, 51%), m.p. 102–103°, IR ν_{max}^{Nujol} cm^{-1}: 1160 (—OSO_2R), NMR ($CDCl_3$): 2H t of t at 7·95 ($J_1 = J_2 = 7$, —CH_2 β to aromatic ring), 2H broadened t at 7·22 (J = 7, benzylic CH_2), 2H t at 6·96 (J = 7, benzylic CH_2 *ortho* to OMs), 3H s at 6·77 (—OSO_2Me), 3H s at 6·17 (—OMe), 1H d at 3·20 (J = 8·5, Ar—H *ortho* to MeO), 1H broadened d at 2·90 (J = 8·5, Ar—H, *ortho* to benzylic CH_2). (Found: C, 54·7; H, 5·9. $C_{11}H_{14}O_4S$ requires: C, 54·5; H, 5·8%).

N-[2-(2'-*Benzyloxy-3'-methoxyphenyl)ethyl*]-*4-methoxyphenyl-acetamide* (XII)

A soln of 2-benzyloxy-3-methoxy-β-nitrostyrene (1·75 g) in ether (40 ml) was added during 15 min to a stirred soln of LAH (1·6 g) in refluxing ether (200 ml). After a further hr, the excess of reagent was destroyed by means of EtOAc and the complex was decomposed with the minimum volume of water. The product, isolated in ether, was purified by extraction into 6N HCl and recovery in ether after neutralization with conc NH_4OH. The resulting oily β-phenylethylamine (1·25 g) in ether (10 ml), was stirred with 0·5 N NaOH (10 ml) and homoanisoyl chloride (1 g) for 1 hr. The solid which separated was washed successively with dil aqueous alkali, dil aqueous acid and water. Crystallization from diisopropyl ether gave the *amide* as colourless needles (1·74 g, 78%), m.p. 85–87·5°, IR ν_{max}^{Nujol} cm^{-1}: 1645, 1552 (—CO·NH—), 710, 790 (Ph—), NMR ($CDCl_3$): two 2H t at 7·33 and 6·6 (J = 6, $ArCH_2{\cdot}CH_2N<$), 2H s at 6·66 ($Ar'CH_2{\cdot}CO$—), two 3H s at 6·12 and 6·22 (OMe), 2H s at 5·02 (—OCH_2Ph), 5H m at 2·61 (Ph—), 7H m at 2·95–3·3 (oxygenated aromatic H). (Found: C, 74·15; H, 6·7; N, 3·3. $C_{25}H_{27}NO_4$ requires: C, 74·05; H, 6·7; N, 3·45%).

5-Benzyloxy-6-methoxy-1-(4'-methoxybenzyl)1,2,3,4-tetrahydroisoquinoline (XVI)

A mixture of $POCl_3$ (5 ml) and benzene (10 ml) was added under a stream of N_2 to the amide (2 g).

After refluxing the mixture for 30 min, light petroleum (b.p. 40–60°) (100 ml) was added. The oil which separated was washed with light petroleum, dissolved in 2% aqueous MeOH (100 ml) and treated with $NaBH_4$ (0·5 g) in portions. The soln was then basified with 4N NaOH and treated with more $NaBH_4$ (0·5 g) in portions. After 1 hr, the flow of N_2 which had been maintained throughout all the above operations was discontinued. The product was recovered, using ether, as a colourless oil which was treated in dry ether with gaseous HCl. The resulting *amine hydrochloride* crystallized from MeOH in colourless plates (1·37 g, 65%), m.p. 200–217° unchanged by further crystallization, IR ν_{max}^{Nujol} cm^{-1}: 712, 775 (Ph—). (Found: C, 70·2; H, 6·5; N, 3·3. $C_{25}H_{28}NO_3^+Cl^-$ requires: C, 70·5; H, 6·6; N, 3·3%).

The free *amine* crystallized from light petroleum (b.p. 60–80°) in colourless needles, m.p. 82–84°, IR ν_{max}^{Nujol} cm^{-1}: 700, 785 (Ph—), NMR ($CDCl_3$): 6H m at 6·8–7·4 (anisyl CH_2 and $—CH_2·CH_2·N$), two 3H s at 6·26, 6·18 (OMe), 2H s at 5·03 ($—OCH_2·Ph$), 5H m at 2·65 (Ph—), 6H m at 2·75–3·3 (oxygenated aromatic H). (Found: C, 76·9; H, 6·8; N, 3·6. $C_{25}H_{27}NO_3$ requires: C, 77·1; H. 7·0; N, 3·6%).

5-*Hydroxy*-6-*methoxy*-1-(4′-*methoxybenzyl*)1,2,3,4-*tetrahydroisoquinoline* (XVII)

5-Benzyloxy-6-methoxy-1-(4′-methoxybenzyl)1,2,3,4-tetrahydroisoquinoline hydrochloride (0·87 g), suspended in water (25 ml) was hydrogenated at atm press and temp over 10% Pd–C (0·2 g). After the absorption of 1 mole of H_2, the catalyst was removed, the soln was basified with conc NH_4OH. The *phenolic amine*, isolated by $CHCl_3$ extraction, crystallized from $MeNO_2$ in colourless needles (0·33 g, 50%), m.p. 157–158°. (Found: C, 71·9; H, 7·3. $C_{18}H_{21}NO_3$ requires: C, 72·2; H, 7·1%). The *pictate* crystallized from MeOH as yellow prisms, m.p. 205–215° (Found: C, 54·7; H, 4·7; H, 4·7; N, 10·3. $C_{24}H_{26}N_4O_{10}$ requires C, 54·55; H, 4·6; N, 10·6%).

5-*Hydroxy*-6-*methoxy*-1-(4′-*methoxybenzyl*)2,2-dimethyl-1,2,3,4-*tetrahydroisoquinolinium iodide* (XVIII)

5-Hydroxy-6-methoxy-1-(4′-methoxybenzyl)1,2,3,4-tetrahydroisoquinoline (0·28 g) in EtOH (25 ml) was hydrogenated at atm temp and press over 10% Pd–C (0·13 g) in the presence of 33% aqueous HCHO (4 ml) until one mole of H_2 had been absorbed (ca. 4 hr). After removal of the catalyst, the soln was concentrated to ca. 5 ml. The resultant tertiary base was then taken up in dil HCl aq and washed with ether. After neutralization with conc NH_4OH, $CHCl_3$ extraction gave the tertiary base as an oil which was allowed to stand overnight in EtOH (10 ml) containing MeI (5 ml). Evaporation and crystallization of the residue from EtOH gave the *base methiodide* as colourless hygroscopic needles (0·3 g, 69%), m.p. 188–198°, NMR ($CD_3·SO·CD_3$): 6H sat 6·95 ($—NMe_2^+$), 6H sat 6·27 (—OMe), 6H at 6·3–6·8 (benzylic CH_2 and $—CH_2N^+$), 1H br m at 5·3 (benzylic $CH·N^+$), two 1H d at 3·37, 4·20 (AB quartet, $J = 8·5$, dioxygenated aromatic H), two 2H d at 2·97, 3·20 (AB quartet, $J = 9$, *p*-MeO—C_6H_4—). (Found: C, 49·3; H, 6·1; N, 2·9. $C_{20}H_{26}INO_3·2H_2O$ requires: C, 48·9; H, 6·15; N, 2·85%).

3-*Hydroxy*-4,4′-*dimethoxy*-2-(β-*dimethylaminoethyl*)trans-*stilbene* (XI)

The above methiodide (0·3 g), in EtOH (25 ml) was placed on a column of Amberlite IRA-400 (OH) anion exchange resin (6 g) and eluted with EtOH. The resulting oily quaternary hydroxide was refluxed with 10% ethanolic NaOEt (15 ml) for 2 hr under N_2. The cooled soln was acidified with aqueous HOAc and then rebasified with NH_4OH. The *stilbene*, isolated by $CHCl_3$ extraction, crystallized from EtOH in colourless plates (92 mg., 44%), m.p. 170–172·5°, UV λ_{max} mμ (ε): 223 (28,700), 257 (23,400), 309 (19,300), UV $\lambda_{max}^{EtOH-NaOH}$ mμ (ε): 218 (16,000), 257 (9,500), 317 (23,400), IR ν_{max}^{Nujol} cm^{-1}: 975 (stilbene double bond), NMR ($CDCl_3$): 6H s at 7·6 ($—NMe_2$), two 3H s at 6·19, 6·11 (—OMe), two 2H m at 7·3 and 7·03 ($A'_2B'_2$ system, $—CH_2·CH_2·N$), two 1H d at 2·87, 3·22 (AB quartet, $J = 16$, stilbene olefinic H), two 1H d at 2·96, 3·21 (AB quartet, $J = 9$, phenolic ring H), two 2H d at 2·55, 3·07 (AA′BB′ system, $J_{AB} = 9$, p—MeO—C_6H_4—). (Found: C, 73·2; H, 7·75; N, 4·2. $C_{20}H_{25}NO_3$ requires: C, 73·4; H, 7·7; N, 4·3%).

5-*Benzyloxy*-6-*methoxy*-1-(4′-*methoxybenzoyl*)2-*methyl*-3,4-*dihydroisoquinolinium iodide* (XV)

A mixture of N-[2-(2′-benzyloxy-3′-methoxyphenyl)ethyl]4-methoxyphenylacetamide (0·1 g), $POCl_3$ (0·75 ml, and benzene (5 ml) was refluxed for 30 min, cooled and then added to light petroleum (b.p. 40–60°) (ca. 30 ml). The oil which separated was dissolved in $CHCl_3$ and washed with dil NaOH aq. The resultant crude oily 3,4-dihydroisoquinoline (80 mg) was treated directly with MeI (1 ml) in EtOH (1 ml). After 3 days, yellow needles (18 mg) had separated and a further 23 mg were obtained from the mother liquors. Crystallization from MeOH–ether gave the *anisoyl methiodide* as yellow needles, m.p. 164–169°. (Found: C, 56·6; H, 4·8. $C_{26}H_{26}NO_4^+I^-·\frac{1}{2}H_2O$ requires: C, 56·5; H, 4·9%).

5-Benzyloxy-(α-hydroxy-4'-methoxybenzyl)6-methoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide (XIV)

The above anisoyl methiodide (23 mg) in MeOH (1 ml) and water (1 drop) was treated with $NaBH_4$ (45 mg) in portions during 5 min. After refluxing for 1 hr, the MeOH was evaporated and water (5 ml) was added. $CHCl_3$ extraction gave a colourless oil (17 mg) which reacted with MeI (0·5 ml) in EtOH (3 ml) in 1½ hr to give a colourless solid. Crystallization from MeOH—ether gave the *tetrahydroisoquinolinium iodide* as fine needles (16 mg, 68%), m.p. 128–138°. (Found: C, 57·4; H, 5·7; M^+ at *m/e* 434. $C_{27}H_{32}NO_4^+I^-$ requires: C, 57·8; H, 5·7; M^+ = 434).

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