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NOVEL SYNTHESES OF 1-SUBSTITUTED-7,8-DIALKOXYISOCHROMAN-3-ONES AND 8-SUBSTITUTED-2,3,9,10-TETRAMETHOXYBERBINES

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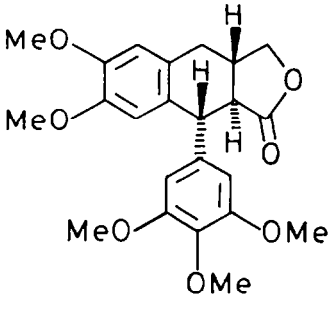
Abstract - A novel and general method for the synthesis of 1-substituted-7,8-dialkoxyisochroman-3-ones is described from 3,4-dialkoxy-N,N-dimethylbenzylamines (5a-b). 1-Methyl- and 1-phenyl-7,8-dimethoxyisochroman-3-ones (7g and 7d) have been used to synthesise 8-methyl- and 8-phenyl-tetrahydropalmatines (9a, 10a and 9b, 10b). No synthesis of these compounds have been so far reported.

Isochroman-3-ones having substituents at 1-position have been widely used for the synthesis of benzylisoquinolines[1,2], berbines[2], lignans[3] and for some heterocyclic compounds[1]. These are also used as synthons for biologically active compounds[4]. A recent[3] synthesis of deoxyisosikkimotoxin (1) utilises 1-aryl-6,7-dimethoxyisochroman-3-one as a starting material and thus demonstrates its utility. 1-Benzyl--6,7-dimethoxyisochromanone, has also been used[2] for the synthesis of 1-benzylisoquinoline 2 and for the berbine alkaloid, tetrahydropalmatine. These



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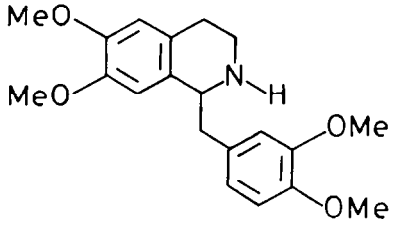

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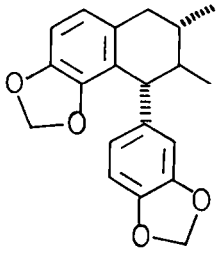

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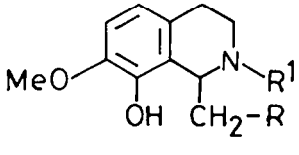

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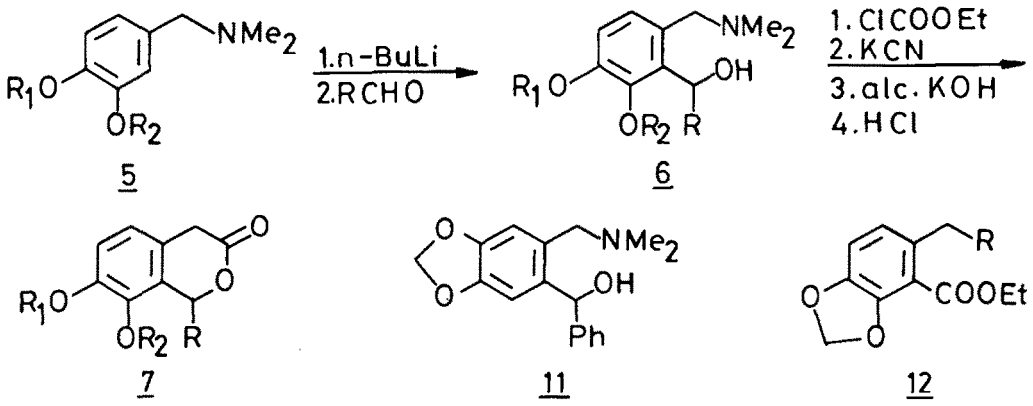
	R	R^1
4 a	Ar	Me
b	H	H

6,7-dialkoxyisochromanones which are readily available by normal acid catalysed methods[1-4] could not be used for the synthesis of lignans like otobain[5] (3) and isoquinoline alkaloids[6a] like 4a[6b] and 4b[7]. Such compounds (3, 4a,b) on the other hand could be synthesised from isochromanones having specific substitution pattern,like 1-substituted-7,8-dialkoxyisochromanones. The synthesis of these compounds have not been reported so far. Furthermore, these cannot be synthesised easily by normal acid catalysed methods[1-4] or by the recently reported methods[8,9].

Synthesis of 1-substituted-7,8-dialkoxyisochromanones :

We report herein a novel method for the synthesis of 1-alkyl- and 1-aryl--7,8-dialkoxyisochromanones (Scheme I). The amino alcohols (6a-g) required for the synthesis of isochromanones (7a-g) were prepared from the corresponding 3,4-dialkoxy-N,N-dimethylbenzylamines 5a and 5b, by making use of a heteroatom



5 6 7 11 12

	R_1	R_2		R_1	R_2	R
5a	$-CH_2-$		6,7a	$-CH_2-$		$-C_6H_5$
b	Me	Me	b	$-CH_2-$		$-3,4(OMe)_2\,C_6H_3$
			c	$-CH_2-$		$-3,4(-OCH_2O-)\,C_6H_3$
			d	Me	Me	$-C_6H_5$
	R		e	Me	Me	$-3,4(OMe)_2\,C_6H_3$
12a	Cl		f	Me	Me	$-3,4(-OCH_2O-)\,C_6H_3$
b	CN		g	Me	Me	Me

Scheme I

directed metallation reaction[10,11]. Thus, lithiation[12] of 3,4-methylenedioxy-N,N--dimethylbenzylamine (5a), with n-BuLi followed by reaction with benzaldehyde gave the amino alcohol 6a. In its IR spectrum it exhibited a weak band at 3400 cm^{-1} for -OH group. Due to the presence of asymmetric carbon ortho to $-CH_2NMe_2$group, these methylene protons became nonequivalent and appeared as doublets (J=12.5 Hz) at 2.60 and 3.20 δ in its PMR spectrum. The phenyl protons appeared as a multiplet at 7.10-7.50 δ and the remaining two aromatic protons appeared as a singlet (accidental equivalence) at 6.61δ. This PMR data could not differenciate structures 6a from 11 . However, the work of Cushman and coworkers[12b] has shown that lithiation of 5a gives a 1,2,3,4-tetrasubstituted product. Furthermore, this work had also shown that methylenedioxybenzenes having substituents at C_3- and C_4- shows C_5- and C_6-protons as two proton singlets (accidental equivalence). Thus, in 12a these aromatic protons appear as a singlet at 6.93 δ. Similar results are seen in 12b (2H, s at 7.01 δ). When the C_3-, C_4-substituents are

fused into a ring[12b] these protons appear as two doublets. In view of this it was felt that structure of this product could be established in the next step (cyclisation). As expected, the product of cyclisation showed its aromatic protons as two doublets, indicating that the cyclised product had structure 7a and hence the lithiation product had structure 6a. This confirmed that compound 5a undergoes lithiation at C_2-position. The other aminoalcohols (6b-g) were similarly prepared from the amines 5a and 5b.

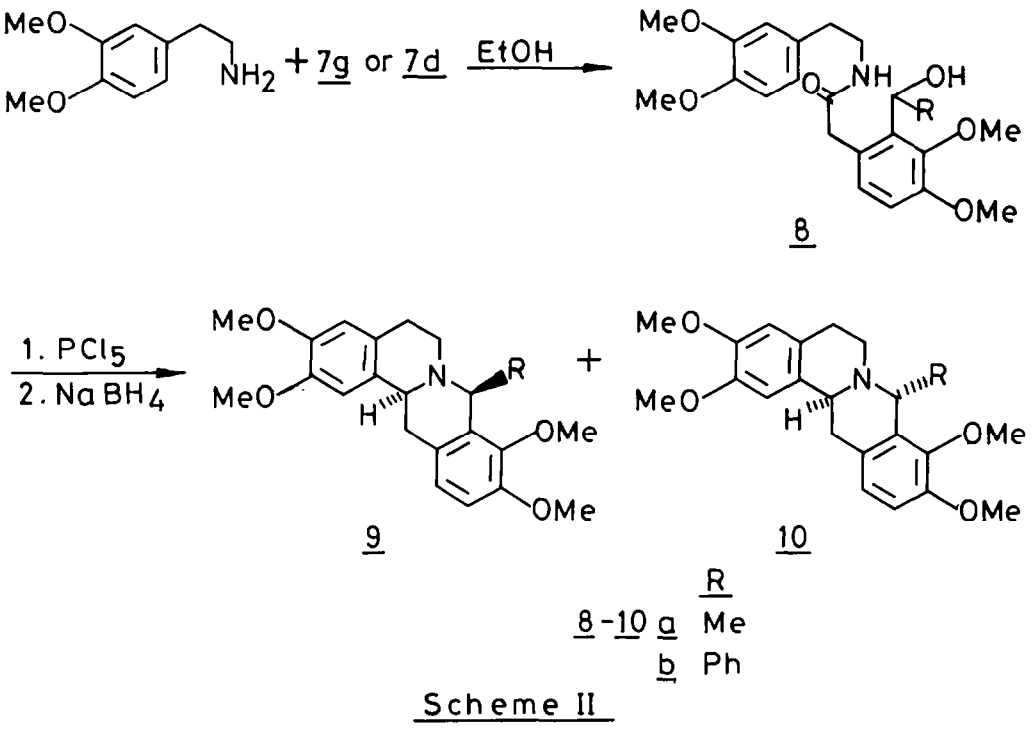
The alcohols (6a-g) on successive reactions with ClCOOEt, KCN in DMF, alcoholic KOH and finally with dil. HCl, furnished the isochroman-3-ones (7a-g) in 41-58% yield. The structures of all these isochromanones were determined on the basis of their analytical and spectral data. In IR spectra these compounds (7a-g) exhibited ν_{CO} around 1750 cm^{-1}. In PMR spectra, except in case of 7g, the C_4-methylene protons appeared as doublets. Thus, in 7a the methylene protons appeared as doublets (J=18 Hz) at 3.31 and 3.60 δ. Its C_5- and C_6-aromatic protons appeared as doublets (J=7.5 Hz) at 6.79 and 6.63 δ respectively.

It is interesting to note that in case of 7d, 7f and 7g the aromatic protons at C_5- and C_6- appear as two proton singlet. However, since the parent compounds 6d and 6g show the corresponding protons as two doublets (at 6.81 and 6.98 δ, J=8 Hz in 6d; at 6.63 and 6.80 δ, J=8 Hz in 6g) it is obvious that in 7d and 7g these protons appear as singlets due to accidental equivalence. The accidental equivalence of these protons in 7f could therefore be explained.

Use of isochromanones for 8-substitutedberbine synthesis :

The synthetic utility of these compounds has now been demonstrated by synthesising both diastereomers of 8-substituted tetrahydropalmatines, in two steps. There are some reports wherein 8-methylberbines having oxygen functions at 9- and 10-positions in ring D have been obtained[13] from the corresponding berbine methiodides having oxygen functions at 9- and 10-positions. However no synthesis of 8-substituted berbines having 9,10-oxygenation have, so far, been reported. Such berbines which have oxygen functions at 9- and 10-positions in ring D, are difficult to synthesise[6a,14] by normal methods involving Bischler--Napieralski and Mannich cyclisations. Several methods[15] are known for the total synthesis of 8-methylberbines having oxygen functions at 10- and 11-positions in ring D. However, in this case the methods used involve multistep sequences.

We have now visualised a strategy for the synthesis of 8-substituted berbines having oxygen functions at 9- and 10-positions in ring D. Our approach (Scheme II) utilises 1-substituted-7,8-dialkoxyisochromanones and homoveratrylamine and furnishes the desired 8-substituted tetrahydropalmatines (9a, 10a and 9b, 10b) in two steps. Thus, 1-methyl-7,8-dimethoxyisochroman-3-one (7g) was condensed with homoveratrylamine in ethanol to give the hydroxyamide 8a in 95% yield. Compound 8a on cyclisation with PCl_5 followed by $NaBH_4$ reduction gave a mixture of two products (TLC) in 51% yield. Chromatography over neutral alumina afforded both compounds, m.p. 111-12° and 163-64° in pure forms. From the elemental analysis, spectral data and mode of formation these compounds are obviously the isomers 9a and 10a. In 8-β-methylberbines with different oxygenation pattern, it is reported[13b,15a] that Bohlmann bands (between 2700-2900 cm^{-1}) are observed when the IR spectra are scanned in chloroform solution. The 8-α-methyl epimers do not show these bands. Since compound m.p. 163-64° shows these bands whereas compound m.p. 111-12° does not show these bands it was deduced that compound m.p. 163-64° should have structure 9a. Whereas compound m.p. 111-12° should be represented by 10a.



Scheme II

This stereochemical assignment was confirmed by looking at the PMR spectra. It is reported[13b,15a] that 8-α-methylberbine with oxygen functions at 9- and 10-positions show its C_8-proton at lower field (4.06δ) as compared to its C_8-epimer (signal at 3.6-3.8δ). Furthermore the signal of the C_8-methyl is at higher field (1.4δ) in the α-isomer than in the β-isomer (1.53δ). The compound m.p. 111-12° showed C_8-H between 4.1 and 4.45 δ and C_8-methyl at 1.4δ (d, J=6.5 Hz) whereas compound m.p. 163-64° showed these signals at 3.85-3.90 and 1.52 δ (d, J=6.5 Hz) respectively. This confirmed that compounds m.p. 111-12° and 163-64° should have structures 10a and 9a respectively. Kametani and coworkers have reported[13b] that optically active 9a (prepared from berbine methiodide) has m.p. 182.5-184°.

The amide 8b was similarly prepared in 86% yield by condensing 7d with homoveratrylamine. This product 8b on cyclisation (PCl_5) followed by reduction ($NaBH_4$) gave a mixture of two products. Careful chromatographic separation of this mixture, over silica gel, provided pure products m.p. 151-52° and 170-72° in 25 and 11% yields respectively. From the elemental analysis and mode of formation, one of these compounds must be 9b and the other 10b. The IR spectrum (in $CHCl_3$) of compound m.p. 170-72° showed Bohlmann bands whereas that of compound m.p. 151-52° did not show these bands. It was then deduced that compounds m.p. 170-72° and 151-52° should be represented by structures 9b and 10b respectively. In agreement with this assignment the C_8-proton of compound m.p. 151-52° appeared at lower field (5.41δ) than that of compound m.p. 170-72° (4.65δ). This confirms the structures of 9b and 10b.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra were measured as nujol mulls on a Beckmann IR-20 spectrophotometer. UV spectra in MeOH (λ_{max} in nm, log ϵ values in parenthesis) on a Shimadzu UV-300 spectrophotometer, and PMR spectra in $CDCl_3$ on a Perkin-Elmer R-32, 90 MHz instrument; chemical shifts are expressed in δ(ppm) downfield from TMS as an internal standard.

Synthesis of amino alcohols 6a-c :

(a) Lithiation of N,N-dimethyl-3,4-methylenedioxybenzylamine (5a)

A stirred soln of N,N-dimethyl-3,4-methylenedioxybenzylamine (4.475 g, 0.025 mol) in ether (50 ml) was treated with n-BuLi (0.075 mol, prepared from 1.4 g of Li and 11.4 ml of BuBr in 100 ml of ether) at room temp. The metallated mixture was stirred at room temp for 2 hr to give a green coloured lithio-derivative.

(b) Treatment of the above lithioderivative with various aldehydes

(i) Treatment with benzaldehyde

A soln of freshly distilled benzaldehyde (0.075 mol) in ether (30 ml) was added to the metallated mixture. It was stirred at room temp for 2 hr and then decomposed with water (100 ml). The organic phase was separated and the aqueous layer extracted with ether (2 x 50 ml). The combined ether extract was treated with 1:1 HCl (2 x 50 ml). The acidic layer was basified with 2 N NaOH and extracted with ether (2 x 60 ml). The ether layer was dried (Na_2SO_4) and evaporated to give a solid which was purified by column chromatography over neutral alumina using n-hexane-ethyl acetate (9:1) as eluent to give a solid. It was recrystallised from hexane to give the amino alcohol 6a (1.5 g, 21%), m.p. 126°, IR : 3400 cm^{-1}, PMR : 2.1 (s, 6H, $-NMe_2$), 2.6 (d, J=12.5 Hz, 1H, $-HCH-NMe_2$), 3.20 (d, J=12.5 Hz, 1H, $-HCH-NMe_2$), 6.0 (ill resolved d, 2H, $-OCH_2O-$), 6.15 (s, 1H, ArCH-O), 6.61 (s, 2H, Ar-H), 7.1-7.5 (m, 5H, -Ph), 8.65 (bs, 1H, -OH, exchangeable with D_2O). (Found : C, 71.85; H, 6.74%. Calc ($C_{17}H_{19}NO_3$) : C, 71.56; H, 6.71%).

(ii) Treatment with veratraldehyde

Similar treatment of the metallated mixture with a soln of veratraldehyde (0.075 mol) in ether (50 ml) and workup as above gave 6b (1.8 g, 23%); m.p. 121° (from n-hexane); IR : 3350 cm^{-1}; PMR : 2.12 (s, 6H, $-NMe_2$), 2.55 (d, J=12 Hz, 1H, $-HCH-NMe_2$), 3.3 (d, J=12 Hz, 1H, $-HCH-NMe_2$), 3.84 (s, 6H, 2 x -OMe), 6.0 (narrow dd, 2H, $-CH_2O-$), 6.03 (s, 1H, ArCHOH), 6.59 (s, 2H, Ar-H), 6.7 (s, 2H, Ar-H), 7.05 (s, 1H, Ar-H), 8.2-8.5 (bs, 1H, -OH, exchangeable with D_2O). (Found : C, 66.42; H, 6.47%. Calc ($C_{19}H_{23}NO_5$) : C, 66.07; H, 6.71%).

(iii) Treatment with piperonal

The above metallation mixture was treated with a soln of piperonal (0.075 mol) in ether (50 ml) at 0°. The reaction mixture was stirred at room temp for 2 hr, then decomposed with water and worked up as above to give 6c (3g, 34%); m.p. 140° (from n-hexane); IR : 3080 cm^{-1}, PMR : 2.12 (s, 6H, $-NMe_2$), 2.57 (d, J=13 Hz, 1H, $-HCH-NMe_2$), 3.34 (d, J=13 Hz, 1H, $-HCH-NMe_2$), 5.87-6.15 (m, 5H, 2 x $-OCH_2O-$ and CHOH), 6.58-6.95 (m, 5H, Ar-H). (Found : C, 65.79; H, 5.75%. Calc ($C_{18}H_{19}NO_5$) : C, 65.64; H, 5.82%).

Synthesis of amino alcohols 6d-g :

(a) Lithiation of N,N-dimethyl-3,4-dimethoxybenzylamine (5b)

A soln of N,N-dimethyl-3,4-dimethoxybenzylamine (1.95 g, 0.01 mol) in ether (30 ml) was lithiated using n-BuLi (0.03 mol, prepared from 0.56 g Li and 4.56 ml BuBr in 70 ml ether) as described in case of 5a. The metallated mixture was stirred at room temp for 1 hr.

(b) Treatment of the above lithioderivative with various aldehydes

(i) The metallated mixture was treated with soln of benzaldehyde, veratraldehyde and piperonal as described earlier[16] to give amino alcohols 6d-f in 93, 90 and 88% yields respectively.

(ii) Treatment with acetaldehyde

The above metallated mixture was treated with acetaldehyde (6 ml) at 0°. The reaction mixture was stirred at 0° for 1 hr and decomposed with water (50 ml).

On usual workup as above gave an oily product which on distillation under reduced pressure gave the amino alcohol 6g (1.25 g, 52%), b.p. 140-45°/2 mm; IR (neat) : 3150 and 3300 cm^{-1}; PMR : 1.47 (d, J=7 Hz, 3H, $-CH(CH_3)-O$), 2.22 (s, 6H, $-NMe_2$), 3.04 (d, J=12 Hz, 1H, HCH-NMe_2), 3.79 (s, 3H, -OMe), 3.82 (s, 3H, -OMe), 4.02 (d, J=12 Hz, 1H, HCH-NMe_2), 5.35 (q, J=7 Hz, $O-CHCH_3$), 6.1 (bs, exchangeable with D_2O, -CH-OH), 6.63 (d, J=8 Hz, 1H, Ar-H), 6.8 (d, J=8 Hz, 1H, Ar-H). (Found : C, 65.19; H, 8.93% . Calc ($C_{13}H_{21}NO_3$) : C, 65.24; H, 8.85%).

Synthesis of isochroman-3-ones (7a-c) :

General Procedure : A soln of ethyl chloroformate (2.5 ml) in benzene (5 ml) was added to a vigorously stirred soln of amino alcohol 6a-c (0.5 g) in benzene (15 ml) containing $NaHCO_3$ (1 g). The stirring was continued further for a period of 1 hr. Filtration and removal of the solvent at low pressure, left the crude chlorocompound as a thick liquid, which was dissolved in dry DMF (5 ml). KCN (1 g) and KI (0.050 g) were added to it and the reaction mixture was stirred at room temp for 12, 10 and 8 hr during the reaction of 6a, 6b and 6c respectively Water (50 ml) was added to the reaction mixture and extracted with ether (3 x 50 ml). The combined ether extract was washed with water (50 ml). Drying (Na_2SO_4) and evaporation of the ether layer afforded the crude nitrile, as a thick liquid, which was dissolved in MeOH (10 ml) and an alcoholic soln of KOH (0.3 g KOH in 1 ml water and 2 ml MeOH) was added to it. It was refluxed on water bath for the period of 8, 6 and 4 hr in the reactions of 6a, 6b and 6c respectively. MeOH was removed in vacuo. Water (50 ml) added to the residue and it was extracted with ether. The aqueous layer was acidified with 1:1 HCl and left aside for 2 hr. It was extracted with ether (2 x 50 ml). The ether layer was dried (Na_2SO_4) and evaporated to give an oily product, which was purified by chromatography over silica gel using n-hexane-ethyl acetate (9:1) as eluent to give a solid. It was recrystallised from $CHCl_3$-n-hexane to give isochroman-3-one (7a-c) having the following properties.

1-Phenyl-7,8-methylenedioxyisochroman-3-one (7a) : (0.215 g, 49%); m.p. 109°, IR : 1740 cm^{-1} ; PMR : 3.31 (d, J=18 Hz, 1H, HCH-CO), 3.60 (d, J=18 Hz, 1H, H-CHCO), 5.92-6.10 (m, 2H, $-OCH_2O-$), 6.59 (s, 1H, -OCH-Ph), 6.63 (d, J=7 Hz, 1H, Ar-H), 6.79 (d, J=7 Hz, 1H, Ar-H), 7.28 (s, 5H, Ar-H). (Found : C, 72.01; H, 4.59% . Calc ($C_{16}H_{12}O_4$) : C, 71.63, H, 4.51%).

1-(3,4-Dimethoxyphenyl)-7,8-methylenedioxyisochroman-3-one (7b) : (0.190 g, 41%); m.p. 165-66°, IR : 1730 cm^{-1}; PMR : 3.36 (d, J=18 Hz, 1H, HCH-CO), 3.62 (d, J=18 Hz, 1H, -H-CHCO), 3.87 (s, 6H, 2 x -OMe), 6.0 (narrow dd, 2H, $-OCH_2O-$), 6.5-6.93 (m, 6H, Ar-H and Ar-CH-O) . (Found : C, 65.59%; H, 4.94% . Calc ($C_{18}H_{16}O_6$) : C, 65.85; H, 4.91%).

1-(3,4-Methylenedioxyphenyl)-7,8-methylenedioxyisochroman-3-one (7c) : (0.215 g, 46%), m.p. 120°; IR : 1740 cm^{-1}; PMR : 3.36 (d, J=18 Hz, 1H, -HCHCO), 3.61 (d, J=18 Hz, 1H, -HCHCO), 5.88-6.15 (m, 4H, 2 x $-OCH_2O-$), 6.49 (s, 1H, ArCHO-), 6.58-6.90(m, 5H, Ar-H). (Found : C, 65.14; H, 3.62% .Calc ($C_{17}H_{12}O_6$) : C, 65.38; H, 3.87%).

Synthesis of isochroman-3-ones (7d-g) :

General procedure : The amino alcohol 6d-g (2 g) on similar reaction with ethyl chloroformate in presence of $NaHCO_3$ gave the chlorocompound as a thick liquid. It was dissolved in dry DMF (10 ml) and KCN (4 g) was added to it. The reaction mixture was stirred at room temp for 6 hr. Water (75 ml) was added to the reaction mixture and extracted with ether (3 x 75 ml). Combined ether extract was washed with water (50 ml). Drying (Na_2SO_4) and evaporation of the ether extract gave the crude nitrile as a thick liquid. It was dissolved in MeOH (20 ml). Alcoholic soln of KOH (1 g KOH in 10 ml water and 10 ml MeOH) was added to it and refluxed on water bath for the period of 4, 0.5, 0.5 and 6 hr in the reactions of 6d, 6e, 6f and 6g respectively. MeOH was removed in vacuo and water (50 ml) was added to the residue. On workup as above gave a thick liquid which was chromatographed over silica gel using n-hexane-ethyl acetate (9:1) as eluent to give a solid. It was recrystallised from $CHCl_3$-n-hexane to give white crystals of isochroman-3-one.

1-Phenyl-7,8-dimethoxyisochroman-3-one (7d) : Yield 53%; m.p. 63°; IR: 1770 cm^{-1} PMR : 3.3 (d, J=18 Hz, 1H, -HCHCO), 3.6 (d, J=18 Hz, 1H, -HCHCO), 3.82 (s, 3H, -OMe), 3.90 (s, 3H, -OMe), 6.84 (s, 1H, ArCH-O), 6.94 (s, 2H, Ar-H), 7.28 (s, 5H, -Ph). (Found : C, 71.63; H, 5.75% . Calc ($C_{17}H_{16}O_4$) : C, 71.82; H, 5.67%).

1-(3,4-Dimethoxyphenyl)-7,8-dimethoxyisochroman-3-one (7e) : Yield 58%; m.p. 118-20°, IR : 1740 cm^{-1} ; PMR : 3.3 (d, J=18 Hz, 1H, -HCHCO), 3.6 (d, J=18 Hz, 1H, -HCHCO), 3.85 (s, 9H, 3 x OMe), 3.92 (s, 3H, -OMe), 6.50-6.95 (m, 6H, 5 x ArH and ArCH-O-). (Found : C, 66.21; H, 5.74%. Calc ($C_{19}H_{20}O_6$) : C, 66.27; H, 5.85%)

1-(3,4-Methylenedioxyphenyl)-7,8-dimethoxyisochroman-3-one (7f) : Yield 53%, m.p. 92-94°; IR : 1740 cm^{-1} ; PMR : 3.35 (d, J=18 Hz, 1H, -HCHCO), 3.61 (d, J=18 Hz, 1H, -HCHCO), 3.82 (s, 3H, -OMe), 3.90 (s, 3H, -OMe), 5.91 (s, 2H, $-OCH_2O-$), 6.6-6.80(m, 4H, 3 x Ar-H and ArCH-O-), 6.92 (s, 2H, Ar-H). (Found : C, 65.81; H, 4.86%. Calc ($C_{18}H_{16}O_6$) : C, 65.85; H, 4.91%).

1-Methyl-7,8-dimethoxyisochroman-3-one (7g) : Yield 54%, m.p. 78-80°; IR : 1750 cm^{-1} ; PMR : 1.5 (d, J=7 Hz, 3H, Ar-CH(CH_3)-O), 3.48 (s, 2H, $-CH_2CO$), 3.80 (s, 3H, -OMe), 3.83 (s, 3H, -OMe), 5.65 (q, J=7 Hz, 1H, ArCH(CH_3)-O), 6.71 (s, 2H, Ar-H). (Found : C, 65.03; H, 6.29%. Calc ($C_{12}H_{14}O_4$) C, 64.85; H, 6.35%).

Synthesis of hydroxyamide (8a) :

A soln of 7g (0.350 g, 0.0016 mol) and homoveratrylamine (0.700 g) in abs EtOH (10 ml) was stirred and refluxed for 8 hr. Ethanol was removed under reduced pressure and the residual thick liquid obtained was purified by flash chromatography over silica gel using ethyl acetate as eluent to give 8a (0.6 g, 94.6%); IR (neat) : 1650, 3250-3400 (br) cm^{-1}; PMR (CCl_4) : 1.43 (d, J=7 Hz, 3H, CH(CH_3)-OH), 2.63 (t, J=7 Hz, 2H, $ArCH_2CH_2N$), 3.2-3.5 (m, 4H, $ArCH_2CH_2N$ and $ArCH_2CO$), 3.76, 3.79, 3.83 and 3.85 (s, 3H each, 4 x -OMe), 5.12 (q, J=7 Hz, 1H, CH(CH_3)-OH), 6.06 (bs, exchangeable with D_2O, -CHOH), 6.5-6.9 (m, 5H, Ar-H).

Synthesis of hydroxyamide (8b) :

A soln of 7d (0.1 g, 0.003 mol) and homoveratrylamine (0.1 g) in abs EtOH (5 ml) was stirred at room temp for 24 hr. Ethanol was removed in vacuo. The residual thick liquid was dissolved in benzene and washed with dil HCl (10 ml). Benzene layer was dried and evaporated in vacuo to give a crude product. It was purified by chromatography over silica gel using benzene as eluent to give a thick liquid (low melting solid) 8b (0.158 g, 87%); IR ($CHCl_3$) : 1645, 3240-3400 (br) cm^{-1}; PMR (CCl_4 + $CDCl_3$) : 2.64 (t, J=7 Hz, 2H, $ArCH_2CH_2N$), 3.2-3.5 (m, 4H, $ArCH_2CH_2N$ and $ArCH_2CO$), 3.56, 3.8, 3.82 and 3.84 (s, 3H each, 4 x -OMe), 5.85 (bs, -OH, exchangeable with D_2O), 6.23 (s, 1H, ArCH(Ph)-OH), 6.58-6.82 (m, 5H, Ar-H), 7.23 (s, 5H, -Ph). (Found : C, 69.37; H, 6.69%. Calc ($C_{27}H_{37}NO_6$) : C, 69.66; H, 6.71%).

(±)8-Methyltetrahydropalmatines(9a and 10a)

To a cooled and well stirred soln of amide 8a (0.4 g) in dry $CHCl_3$ (30 ml), PCl_5 (0.8 g) was added and the reaction mixture was stirred at room temp for 3 hr. The solvent was removed in vacuo and crushed ice added to the residue. It was washed with ether and then extracted with $CHCl_3$. The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated in vacuo to get a foamy yellow solid. It was dissolved in MeOH (30 ml) and $NaBH_4$ (0.5 g) was added to it in lots, at 0° during 15 min. It was stirred at room temp for 1 hr and MeOH was removed in vacuo. Water (30 ml) was added to the residue and it was extracted with ether (3 x 50 ml). Drying (Na_2SO_4) and evaporation of ether layer gave a thick liquid which was purified by chromatography over neutral alumina using n-hexane-ethyl acetate (95:5) as eluent. Pale yellow solid was obtained in the initial fractions. It was recrystallised from MeOH to give 9a (0.060 g, 16%). Further elution with the same solvent gave faint yellow solid. It was recrystallised from n-hexane to give 10a (0.070 g, 19%). Mixture of 9a and 10a (0.070 g, 19%) was obtained before getting pure 10a (total yield 54%).

(±)9a : m.p. 163-64°; IR ($CHCl_3$) : 2800-2700 cm^{-1} (transquinolizidine bands); UV (MeOH) : λ_{max} 237.5 (3.595); 280.5 (3.594); PMR : 1.52 (d, J=6.5 Hz, 3H, 8-Me), 2.4-3.77 (m, 7H, methylene protons and 13a-H), 3.85-3.90 (merged singlets, 13H, 4 x -OMe and 8-H), 6.6-7.0 (m, 4H, Ar-H), MS : m/z 369 (M^+), 352, 192, 178, 163. (Found : C, 71.51; H, 7.52%. Calc ($C_{22}H_{27}NO_5$) : C, 71.52; H, 7.37%).

(±)10a : m.p. 111-12°; IR ($CHCl_3$). No bands in 2800-2700 cm^{-1} region; UV (MeOH) : λ_{max} 238 (3.586), 279.5 (3.578); PMR : 1.4 (d, J=6.5 Hz, 8-Me), 2.7-3.15 (m, 6H, methylene protons), 3.85-3.9 (4 merged singlets, 4 x -OMe), 4.1-4.45 (m, 2H, 8-H and 13a-H), 6.62 (s, 1H, Ar-H), 6.71 (s, 1H, Ar-H), 6.81 (s, 2H, Ar-H). MS : m/z 369 (M^+), 354, 192, 178, 163. (Found : C, 71.88; H, 7.44%. Calc ($C_{22}H_{27}NO_4$) : C, 71.52; H, 7.37%).

(±)8-Phenyltetrahydropalmatines (9b and 10b) :

PCl_5 (0.5 g) was added to a well stirred and cooled (0°) soln of amide 8b (0.4 g) in $CHCl_3$ (30 ml) and the reaction mixture was stirred for 3 hr. The solvent was removed in vacuo. Crushed ice was added to the residue and it was washed with ether (2 x 25 ml). The aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated in vacuo to give the foamy solid. It was dissolved in MeOH (30 ml) and $NaBH_4$ (0.4 g) was added in lots to this stirred soln at 0° during 15 min. After stirring for 1 hr at room temp, MeOH

was removed in vacuo. Water (50 ml) was added to the residue and extracted with ether (3 x 50 ml). The ether layer was dried (Na_2SO_4) and evaporated to give a foamy solid which was chromatographed over silica gel using benzene-ethyl acetate (9:1) as eluent. Pale yellow solid was obtained in the initial fractions. It was recrystallised from hexane-$CHCl_3$ to give 9b (0.040 g, 11%). Further elution with the same solvent gave faint yellow solid. It was recrystallised from hexane-$CHCl_3$ to give 10b (0.095 g, 25%).

(+)9b : m.p. 170-72°, IR ($CHCl_3$) : 2800-2700 cm^{-1} (transquinolizidine bands); UV (MeOH) λ_{max} 239.5 (3.610), 280.2 (2.594); PMR : 2.2-3.2 (m, 10H, methylene protons, 13a-H and -OMe), 3.77, 3.84 and 3.89 (s, 3H each, 3 x -OMe) , 4.65 (s, 1H, 8-H), 6.51 (s, 1H, Ar-H), 6.75 (d, J=9 Hz, 1H, Ar-H), 6.81 (d, J=9 Hz, 1H, Ar-H), 7.1-7.5 (m, 6H, Ar-H and -Ph); MS : m/z, 431 (M^+), 430, 352, 192, 240, 209. (Found : C, 75.14; H, 6.65%. Calc ($C_{27}H_{29}NO_4$) : C, 75.15; H, 6.77%).

(+)10b : m.p. 151-52°, IR ($CHCl_3$) : No bands in 2800-2700 cm^{-1} region; UV (MeOH) : λ_{max} 240 (3.63), 281 (3.601); PMR : 2.4-3.25 (m, 7H, methylene protons and 13a-H), 3.29 and 3.83 (s, 3H each, 2 x -OMe), 3.86 (s, 6H, 2 x -OMe), 5.41 (s, 1H, 8-H) , 6.55 (s, 1H, Ar-H), 6.65 (s, 1H, Ar-H), 6.85 (d, J=9 Hz, 1H, Ar-H), 6.95 (d, J=9 Hz, 1H, Ar-H), 7.1-7.4 (m, 5H, -Ph). MS : m/z 431, 352, 240, 209, 192. (Found : C, 75.10; H, 6.75%. Calc ($C_{27}H_{29}NO_4$) : C, 75.15; H, 6.77%).

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