A convenient entry into the rhoeadan skeleton. Total synthesis of (±)-*cis*-alpinigenine[1]

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Condensation of 4-bromoisochroman-3-one (**8***a*) with *N*-methyl-3,4-dimethoxy-β-phenethylamine (**7**) provides the aminolactone **9***a* which by diisobutylaluminum hydride reduction followed by polyphosphoric acid mediated cyclization gives the tetracyclic product **10***a*, thus constituting a convergent, short entry into the rhoeadan alkaloid skeleton. Chromium trioxide oxidation of **10***a* affords a low yield of the corresponding lactone **11***a*. A parallel series of reactions starting from 7,8-dimethoxy-4-bromoisochroman-3-one (**8***b*), prepared either via Baeyer–Villiger oxidation of 4,5-dimethoxy-2-indanone (**14**) or, more conveniently, via benzeneboronic acid assisted condensation of 3-hydroxy-4-methoxyphenylacetic acid (**18**) with formaldehyde, yields 7,8,12,13-tetramethoxy-3-methylrhoeadan (**10***b*). Oxidation of compound **10***b* with chromium trioxide gives the corresponding lactone **11***b* also in low yield. Since **11***b* has been previously converted into (±)-*cis*-alpinigenine (**11***c*) and (±)-*cis*-alpinine (**11***d*), this work constitutes total syntheses of these alkaloids.

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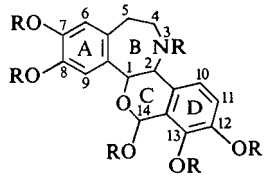
La condensation de la bromo-4 isochromanone-3 (**8***a*) sur la *N*-méthyldiméthoxy-3,4 β-phénéthylamine (**7**) conduit à l'aminolactone (**9***a*) qui, par réduction par l'hydrure de diisobutylaluminium suivie d'une cyclisation en présence d'acide polyphosphorique, donne le produit tétracyclique **10***a*. Ceci constitue une voie d'accès convergente et courte au squelette de l'alcaloide rhoéadane. L'oxydation du composé **10***a* par le trioxyde de chrome conduit, avec un faible rendement, à la lactone correspondante, **11***a*. Une série parallèle de réactions partant de la diméthoxy-7,8 bromo-4 isochromanone-3 (**8***a*), préparée soit par une oxydation de Baeyer–Villiger de la diméthoxy-4,5 indanone-2 (**14**) soit plus facilement par condensation de l'acide hydroxy-3 méthoxy-4 phénylacétique (**18**) sur le formaldéhyde en présence d'acide benzèneboronique, conduit au tétraméthoxy-7,8,12,13 méthyl-3 rhoéadane (**10***b*). L'oxydation du composé **10***b* par le trioxyde de chrome donne la lactone correspondante **11***b* également avec un faible rendement. Depuis que le composé **11***b*, a été transformé antérieurement en (±)-alpinigénine *cis* (**11***c*) et en (±)-alpinine *cis* (**11***d*), ce travail constitue une synthèse totale de ces alcaloides.

[Traduit par le journal]

The Rhoeadine–Papaverrubine class of alkaloids (**1**) (1) is comprised of about 30 bases elaborated almost exclusively within the *Papaver* genus (2, 3). Its major distinguishing structural feature, exhibited only by three other alkaloid types (*Cephalotaxus* group (**2**) (4), stepinonine, a bisbenzylisoquinoline (**3**) (5), and the recently discovered chilenine (**4**) (6)), is the benzazepine skeleton (rings A/B in **1**). This and other inherent structural and stereochemical points of interest as well as the discovery of potentially useful biological activity (1, 7) have provided the predictable stimulus for synthetic effort (1, 2, 8). Most routes (Table 1, refs. 9–13) are initiated from or proceed via intermediates of other classes of benzylisoquinoline alkaloids. The most economic route to rhoeadans reported to date employs phthalideisoquinoline alkaloids as starting materials (10). This route is rendered attractive by the recent availability of improved syntheses of the latter class of alkaloids (2, 14). An attractive synthetic method for the rhoeadan skeleton starting from *N*-benzyl-3,4-dihydroisoquinolinium salts has been developed by Shamma and Töke (12). However, this strategy appears not to have been applied to synthesis of the alkaloids themselves, owing perhaps to the lack of



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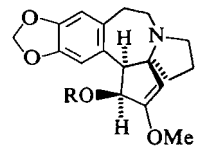

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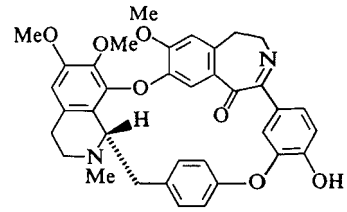

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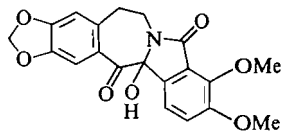

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[1]Abstracted in part from the thesis of I.A. submitted in partial fulfillment for the Ph.D. degree, University of Waterloo, 1975.

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TABLE 1. Synthesis of rhoeadan alkaloids

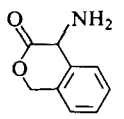
Precursor alkaloid type	Number of steps	Overall yield	Ref.
Spirobenzylisoquinoline[a]	8	~1%	9
Phthalideisoquinoline	5	24%	10
Protoberberine[b]	5	11%	11
N-Benzyl-3,4-dihydroisoquinolinium salt[c]	6	45%	12
Protoberberine[d]	8	7%	13

[a]Based on a β-phenethylamine starting material.
[b]A synthetic substance was used as starting material.
[c]Synthesis of the rhoeadan ring skeleton only was achieved.
[d]Converted into a relay benz[*d*]indeno[1,2-*b*]azepine system which was also available by total synthesis and had been transformed into a rhoeadan alkaloid.

convenient routes to contiguously substituted C/D ring precursors, a situation which has been recently rectified (15). Herein we report a new efficient and convergent entry into the rhoeadan ring system and its application to the synthesis of the (±)-*cis*-alpinigenine (**11***c*) (11, 16).

Several precedents notwithstanding (8), the amide lactone **6**, readily available from the condensation of the aminoisochroman-3-one **5** with 3,4-dimethoxyphenylacetyl chloride, could not be cyclized to a benzazepine derivative under a variety of Friedel–Crafts conditions. The aminolactone **9***a*, prepared in high yield by condensation of the *N*-methyl-β-phenethylamine **7** with 4-bromoisochroman-3-one (**8***a*) (available via Baeyer–Villiger reaction of 2-indanone) (Scheme 1), likewise failed to cyclize or suffered extensive decomposition under Lewis acid catalyzed conditions.[2] In the expectation of increasing reactivity, compound **9***a* was partially reduced with diisobutylaluminum hydride (Dibal) to give the aminolactol **9***b* in high yield. When **9***b* was exposed to neat polyphosphoric acid at 35°C, the desired rhoeadan derivative **10***a* was obtained (13% overall yield from indene).[3] The nmr and ms data of **10***a* were consistent with the tetracyclic structure showing close similarity to those observed for the rhoeadan alkaloids (1). Furthermore, the C-1 and C-2 proton doublets at δ 4.72 and 3.72 respectively showed a coupling constant, $J_{1,2}$ = 2.5 Hz, consistent with a *cis*-B/C ring juncture as expected on the basis of an α-oxo carbonium ion intermediate leading to the thermodynamically more stable stereochemistry (16).

The application of the above model study to the synthesis of the rhoeadan alkaloid, *cis*-alpinigenine (**11***c*), required (a) a search for methods to effect oxidative functionalization at C-14 and (*b*) the



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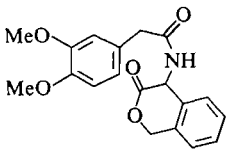

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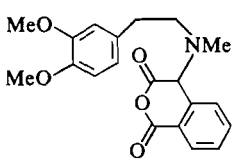
development of a route for the dimethoxyisochroman-3-one **8***b*. In order to achieve the first goal, a number of oxidations (e.g., acetoxylation using peroxyesters/Cu^+ (17), hydroxylation using Ce^{+4} (18), *t*-BuOK/*t*-BuOH/O_2/DMSO (19), Triton B/pyridine/O_2 (20))[4] were carried out on the model compound **10***a* with uniformly unsuccessful results. Finally, oxidation using CrO_3 in acetic acid (21) gave a mixture of at least six products from which the lactone **11***a* was isolated in ~10% yield by preparative thick-layer chromatography. The conversion of rhoeadan lactones analogous to **11***a* into the corresponding alkaloids (**1**), including *cis*-alpinigenine (**11***c*), is well documented (10, 13*a*). In view of this and in the hope that greater

[2]Attempts to obtain a potentially more attractive intermediate **i** by condensation of **7** with 4-bromoisochroman-1,3-dione gave instead **ii** which formed the basis of a general synthesis of phthalideisoquinoline alkaloids (ref. 14).



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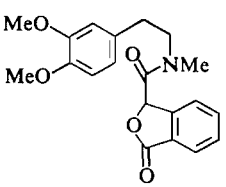
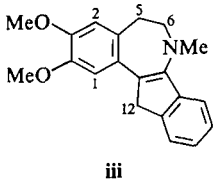


ii

[3]A number of other Lewis acid catalysts (e.g. $POCl_3$, BF_3·Et_2O, HCl) failed to yield **10***a*. Concentrated sulfuric acid furnished the indenobenzazepine **iii** in low yield (see Experimental).



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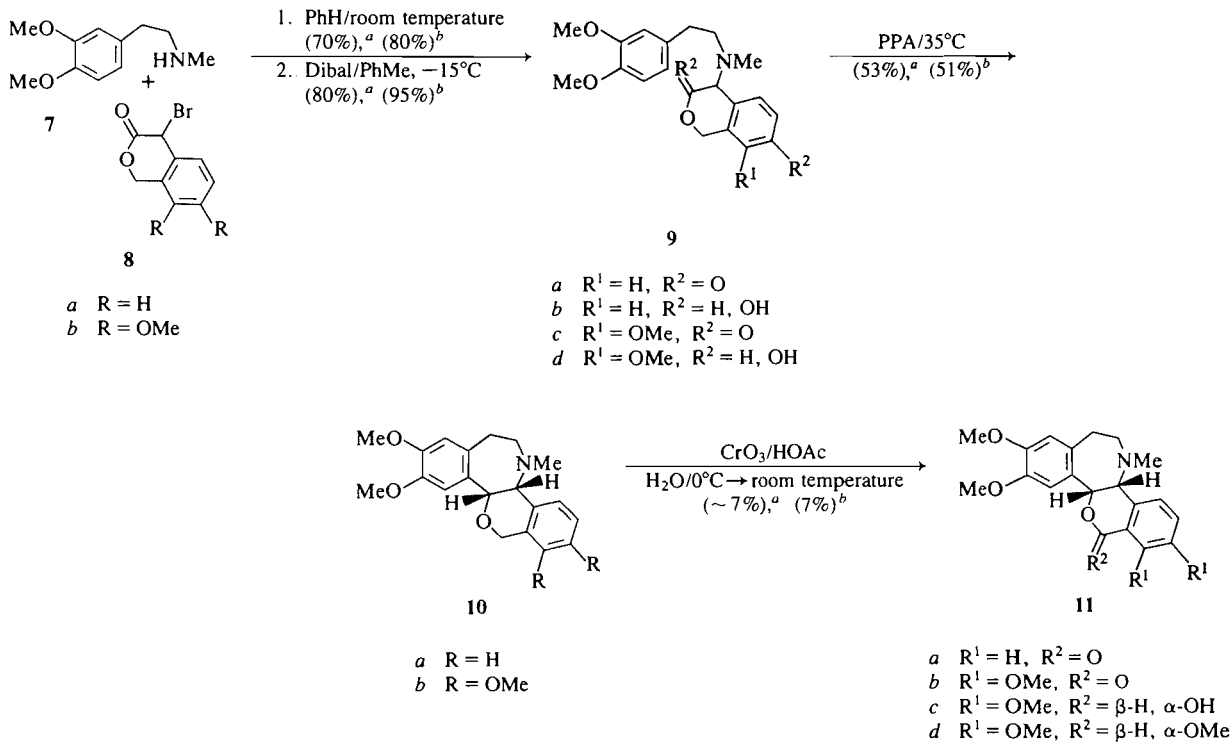
[4]These reactions are described in the Ph.D. thesis of I.A.



SCHEME 1

[a]Yields for **8***a* series.
[b]Yields for **8***b* series.

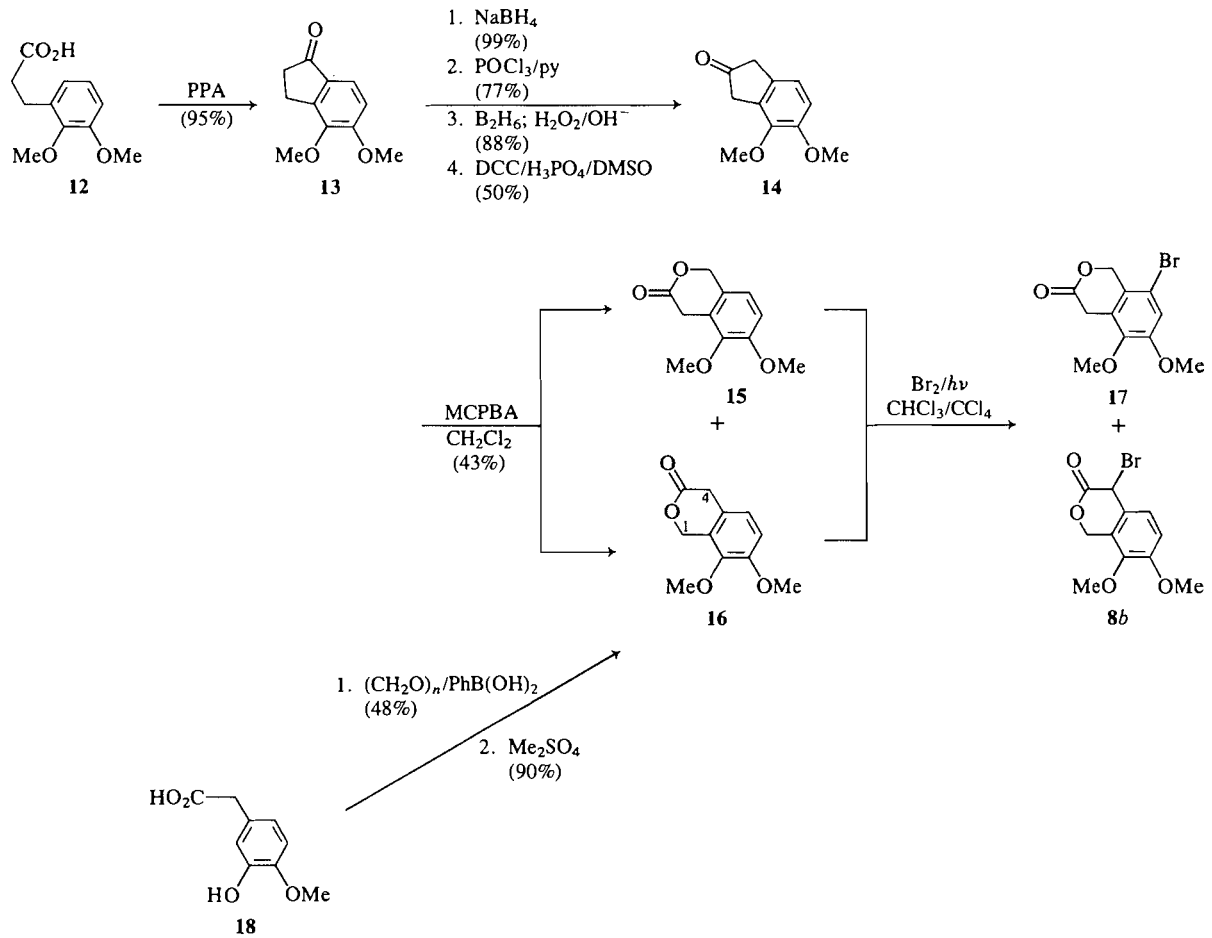
C-14 oxidative regioselectivity would be achieved in **10***b* as a result of the presence of activating ring D methoxy groups, the second task, that of synthesizing the isochroman-3-one **8***b* component required for *cis*-alpinigenine, was undertaken.

The construction of 7,8-dimethoxyisochroman-3-one (**8***b*) was achieved by alternative classical and modern methodologies (Scheme 2). In the classical approach, 2,3-dimethoxyphenylpropionic acid (**12**), prepared from 2,3-dimethoxybenzaldehyde by Knoevenagel technology, was subjected to Friedel–Crafts cyclization using polyphosphoric acid to give the 1-indanone **13** in high yield. Ketone transposition to the 2-indanone **14** was effected uneventfully by a four-step sequence. Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid gave a mixture of two isochromanones **15** and **16** which could not be separated by preparative tlc using multiple development and a variety of solvent systems. Examination of the integrated nmr spectrum of this mixture and comparison with authentic **15** synthesized by an alternative route (see Experimental) established that the isomers **15** and **16** were present in a 60:40 ratio in the mixture.[5] The lack of regioselectivity in the formation of **15** and **16** is perhaps expected on the basis of the similar electronic factors and lack of steric constraints operating in the Baeyer–Villiger rearrangement of the intermediate resulting from **14**.[6]

Bromination of the mixture of isochromanones **15**, **16** with one equivalent of bromine gave two major products, **17** and **8***b*, in a 1.3:1 ratio which were easily separated by taking advantage of their solubility differences in ether. Based on the 60:40 ratio of the starting isochromanones **15** and **16**, the

[5]This synthesis of **15** and **16** was first executed in 1972 by C. F. Tahk and K. R. Cuppet at Kent State University in independent synthetic work aimed at the rhoeadan alkaloids which was abruptly terminated. We are grateful to Drs. Tahk and Cuppet for allowing us to develop and use this route and for providing assistance, experimental details, spectra and samples, and for many stimulating discussions.

[6]In contrast, and as expected, Baeyer–Villiger reaction of 5,6-dimethoxy-2-indanone yields 6,7-dimethoxyisochroman-3-one, a useful intermediate for the synthesis of berberine alkaloids (22).



SCHEME 2

calculated yield of **8***b* from **14** is 14%. Their structures were assigned by nmr and ms data, in particular, comparison of such spectra for **8***b* with the model compound **8***a* (see Experimental). The formation of **17** may reflect steric interference to free radical C-4 bromination.

During the course of this work, Nagata and co-workers reported on the direct preparation of the required isochromanone **8***b* in 83% yield by treatment of homoisovanillic acid (**18**) with paraformaldehyde in the presence of benzeneboronic acid followed by conventional methylation (23). This interesting regiospecific introduction of a one-carbon unit, contrasting with normal electrophilic substitution behavior of such systems,[7] most likely involves the intermediacy of a phenoxyboronic acid which coordinates formaldehyde, thereby transferring it into the 2-position of the aromatic ring.[8,9] Unfortunately, in our hands, the reaction of **18** with paraformaldehyde gave 8-hydroxy-7-methoxyisochroman-3-one only in a reproducible 48% yield.[10] Nevertheless, this short route afforded the key intermediate **16** in gram quantities in 25% overall yield (based on commercially available isovanillin), thus showing considerable

[7]For example, the HCl-mediated reaction of 3,4-dimethoxyphenylacetic acid with formaldehyde provides 6,7-dimethoxyisochroman-3-one in 84% yield (24). See also ref. 23*b*.

[8]Intermediate boron heterocycles have been isolated in many cases (23*b*).

[9]Such *ortho*-transfer reactions via prior heteroatom to catalyst coordination have opened new strategies for regiospecific synthesis of polysubstituted aromatics (25).

[10]The yields are critically dependent on the manner of addition of paraformaldehyde and benzeneboronic acid and on the efficiency of water removal from the reaction mixture. Our yields were achieved using a Dean–Stark trap and not the special water separator employed by Nagata *et al.* (23). We are indebted to Drs. W. Nagata and K. Okada for correspondence and a photograph of the water separator and to Dr. M. T. Thomas for carrying out the experiments.

advantage in convenience and efficiency over the Baeyer–Villiger approach described above.[11,12]

The condensation of the bromoisochromanone **8***b* with two equivalents of the β-phenethylamine **7** produced the aminolactone **9***c* in high yield. Dibal reduction led smoothly and in quantitative yield to lactol **9***d* which upon treatment with PPA at steam bath temperatures produced the tetramethoxyrhoeadan **10***b*. Unfortunately, chromium trioxide oxidation of **10***b* gave a complex mixture of products from which 14-oxy-*cis*-alpinigenine (**11***c*) was isolated in low yield by preparative tlc. The identity of **11***b* was established by comparison (mp, mixture mp, tlc, ir, nmr, ms) with an authentic sample prepared by an alternative route also at the University of Waterloo (13*a*).[13] Since **11***b* has been previously converted into *cis*-alpinigenine (**11***c*) and *cis*-alpinine (**11***d*) in high yields (13*a*), our work completes total syntheses of these alkaloids.

The utility of this synthesis for the preparation of rhoeadan alkaloids is undermined by the low yield in the final oxidation step, **10***a*, **10***b* → **11***a*, **11***b*. However, it represents a convenient entry into the rhoeadan ring system (**10***a* in 13%, **10***b* in 7% overall yields) from readily available precursors. The synthesis of **10***b* is made attractive by the efficient preparation of the isochromanone **16** (23, 30).

Experimental

Microanalyses were performed by A. G. Gygli, Toronto, Ontario. Melting points were measured on a Fisher–Johns apparatus and are uncorrected. Infrared spectra were determined on a Beckmann IR-10 spectrophotometer. The nmr spectra were obtained with a Varian T-60 spectrometer using TMS as internal standard in $CDCl_3$ solution unless otherwise stated. Mass spectra (ms) were recorded on a A.E.I. MS-30 double beam, double-focussing instrument; peaks with *m/e* > 100 and % rel. intensity > 20 only are given. Silica gel 60 (70–230 mesh) and aluminum oxide (neutral, activity 1) from Brinkmann, Canada and Florisil (60–100 mesh) from Fisher Scientific were used for column chromatography; silica gel GF-254 (type 60) and aluminum oxide G (type E) obtained from Brinkmann, Canada were employed for thick-layer chromatography. The phrase standard work-up means extraction with either CH_2Cl_2 of $CHCl_3$ followed by drying over Na_2SO_4, filtration, and evaporation to dryness *in vacuo*.

4-Aminoisochroman-3-one (5)

Indan-2-one (31) was converted into *isochroman-3-one* by a literature method (32), mp 81–83°C (lit. (33) mp 80.6–81°C), ir and nmr identical with those reported (33).

A solution of isochroman-3-one (6.0 g, 40 mmol) and *n*-butyl nitrite (6.2 g, 60 mmol) in a mixture of anhydrous THF (28 mL) and ether (16 mL) was added dropwise to an ice-cold, stirred solution of sodium ethoxide (from sodium metal, 1.04 g, 45 mmol) in a mixture of anhydrous ethanol (15 mL) and ether (20 mL) maintained under nitrogen. The red mixture was stirred at ice-bath temperature for 8 h, treated with water (50 mL), and the resulting solution was washed with ether (80 mL). After acidification (concentrated HCl), the aqueous layer deposited, in 20 h, colourless needles of *4-hydroxyiminoisochroman-3-one* (2.5 g) which were collected by filtration. The filtrate was concentrated *in vacuo* and extracted with chloroform to yield an additional 0.3 g of product (total yield, 39%), mp 191–193°C (EtOH–$CHCl_3$); ir (KBr) ν_{max}: 3460, 1738, 1620 cm^{-1}; nmr δ: 5.44 (s, 2H), 7.42–7.65 (m, 4H); ms *m/e* (% rel. intensity): 177 (25, M^+), 133 (37), 132 (46), 117 (70), 116 (80), 105 (31), 104 (100), 103 (30), 102 (20). *Anal.* calcd. for $C_9H_7O_3N$: C 61.02, H 3.98, N 7.91; found: C 60.97, H 3.88, N 7.84.

Hydrogenation of 4-hydroxyimino-isochroman-3-one (0.25 g, 1.4 mmol) over platinum oxide in glacial acetic acid (8 mL) at 50 psi and room temperature followed by neutralization (NH_4OH) and standard work-up gave a colorless oil which was dissolved in dry ether and subjected to a stream of dry HCl gas. The resulting precipitate was collected and dried under reduced pressure to give 0.26 g (93%) of *4-amino-isochroman-3-one hydrochloride*, mp 154–158°C; ir (KBr) ν_{max}: 3450 (br), 2880 (br), 1762 cm^{-1}, which was used without further purification.

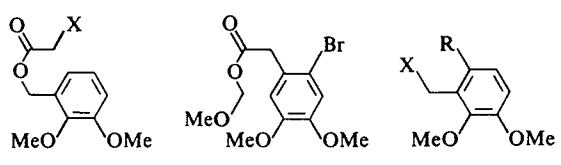
N-*4-(Isochroman-3-one)-2-(3,'4'-dimethoxyphenyl)-acetamide (6)*

A solution of 3,4-dimethoxyphenylacetyl chloride (34) (0.215 g, 1 mmol) in THF (0.8 mL) was added dropwise to a stirred mixture of 4-amino-isochroman-3-one hydrochloride (0.20 g, 1 mmol) and a few drops of a saturated solution of aqueous $NaHCO_3$ in THF (3 mL). The mixture was stirred for 15 min and treated successively with ether (15 mL) and water (10 mL). The resulting colorless precipitate was recrystallized from aqueous EtOH to give 0.28 g (82%) of compound **6**, mp 155–156.5°C; ir (KBr) ν_{max}: 1740, 1642 cm^{-1}; nmr δ: 3.80 (s, 2H), 3.93, 3.96 (2 × s, 6H), 5.20–5.83 (m, 3H), 6.4 (br s, 1H, D_2O exch.), 7.0 (br s, 3H), 7.35 (br s, 4H); ms *m/e* (% rel. intensity): 341 (4, M^+), 178 (68), 163 (28), 152 (44), 151 (100), 137 (20), 119 (42), 118 (20), 117 (26), 107 (33), 106 (23). *Anal.* calcd. for $C_{19}H_{19}NO_5$: C 66.86, H 5.61, N 4.10; found: C 67.02, H 5.68, N 4.09.

4-Bromoisochroman-3-one (8a)

A solution of isochroman-3-one (7.41 g, 50 mmol) in a mixture of spectral grade chloroform (15 mL) and carbon tetrachloride (15 mL) was placed in a two-necked flask fitted with a condenser and a dropping funnel whose lower end was drawn into a

[11]Among the other approaches attempted to achieve the synthesis of **16**, the irradiation of **iv**, X = Br or Cl (26), the acid-catalyzed reaction of **iv** and **v** (27), and the benzylic metalation and carbonation of **vi**, X = NEt_2, R = Me (28) resulted either in recovery of starting material, partial degradation, or decomposition. In addition, the selective oxidation of the non-benzylic alcohol function of **vi**, X = OH, R = CH_2CH_2OH (29) could not be achieved (footnote 4 and S. O. de Silva and M. T. Thomas, unpublished results, University of Waterloo).



[12]Recently, **16** has been prepared in high yield via **vi**, X = NMe_2, R = CH_2OH obtained by successive metalation (*n*-BuLi) and formaldehyde treatment of **vi**, X = NMe_2, R = H (30).

[13]We are grateful to Professor R. Rodrigo and Dr. K. Orito for an authentic sample of **11***b* and pertinent spectral data.

capillary. The solution was brought to reflux with an unfrosted lamp (200 W, General Electric) positioned 15–20 cm from the flask. Bromine (8 g, 50 mmol) in carbon tetrachloride (10 mL) was slowly introduced. Instant decoloration of bromine was observed. The mixture was further refluxed for 1 h, cooled, diluted with chloroform (30 mL), and washed with successive portions of 5% aqueous sodium bicarbonate solution (20 mL) and water (20 mL). Standard work-up gave 8.4 g of a yellow oil which was purified by column chromatography (Florisil, $CHCl_3$–PhH, 65:35 eluent) to give 7 g (79%) of compound **8***a* as a pale yellow oil, bp 116–117°C/0.3 Torr. Treatment with decolorizing carbon followed by crystallization from ether gave **8***a* as colorless crystals, mp 58.5–59.5°C; ir ($CHCl_3$) ν_{max}: 1740 cm^{-1}; nmr δ: 5.25, 5.72 (2 × d, 2H, J = 14 Hz), 5.50 (s, 1H), 7.40 (s, 4H); ms *m/e* (% rel. intensity): 228, 226 (17, M^+), 147 (100), 119 (58), 118 (20), 103 (32). *Anal.* calcd. for $C_9H_7BrO_2$: C 47.60, H 3.10; found: C 47.81, H 3.10.

*4-(*N*-Methyl)-β-3′,4′-dimethoxyphenylethylamino)-isochroman-3-one (***9***a)*

A solution of 4-bromoisochroman-3-one (**8***a*) (1.77 g, 10 mmol) in anhydrous benzene (14 mL) was added dropwise under nitrogen to a stirred solution of *N*-methyl-β-3,4-dimethoxyphenethylamine (**7**) (14) (3.91 g, 20 mmol) in dry benzene (20 mL). The mixture was stirred at room temperature for 2 h. The precipitated hydrobromide of **7** was collected by filtration and the filtrate was diluted with benzene (50 mL) and washed with successive portions of 50% aqueous sodium bicarbonate solution (20 mL) and water (20 mL). Standard work-up gave an oil which was purified by column chromatography (silica gel, $CHCl_3$–MeOH, 300:1 eluent) to afford 2.4 g (70%) of compound **9***a* as a colorless thick oil, ir ($CHCl_3$) ν_{max}: 1745 cm^{-1}; nmr δ: 2.46 (s, 3H), 2.87 (br s, 4H), 3.78 (s, 6H), 4.31 (s, 1H), 5.03, 5.33 (2 × d, 2H, J = 14 Hz), 6.76 (s, 3H), 7.20–7.50 (m, 4H); ms *m/e* (% rel. intensity); 341 (0.5, M^+), 190 (100), 147 (31), 119 (28). *Anal.* calcd. for $C_{20}H_{23}NO_4$: C 70.36, H 6.79, N 4.10; found: C 70.49, H 6.66, N 4.00.

*4-(*N*-Methyl-β-3′,4′-dimethoxyphenylethylamino)-isochroman-3-ol (***9***b)*

A solution of diisobutylaluminum hydride (Alfa Products) (3 mL, 20% *n*-hexane solution) in dry toluene (5 mL) was added dropwise to a stirred solution of compound **9***a* (0.15 g, 0.4 mmol) in toluene (20 mL) at −15°C (ice–salt bath) under nitrogen. The mixture was stirred for 1 h and treated successively with a 2 *M* solution of isopropyl alcohol in toluene (5 mL) and water (0.2 mL). The mixture was stirred at room temperature for 2 h, chloroform (15 mL) and anhydrous sodium sulfate (0.75 g) were added, and the whole was subjected to filtration. The filtrate was concentrated under reduced pressure to give crude material which was purified by column chromatography (silica gel, $CHCl_3$–MeOH, 98:2 eluent) to furnish 120 mg (80%) of compound **9***b* as a colourless oil; ir ($CHCl_3$) ν_{max}: 3270 (br) cm^{-1}; nmr δ: 2.31 (s, 3H, NCH_3), 2.67–3.15 (m, 4H, $—CH_2CH_2$), 3.60 (d, 1H, J = 3 Hz, C-4 H), 3.82, 3.87 (2 × s, 6H, 2 × OCH_3), 4.80 (s, 2H, C-1 H), 4.83 (d, 1H, J = 3 Hz, C-3 H), 5.40 (br s, 1H, OH, D_2O exch.) 6.80 (s, 3H, A ring H), 7.08–7.50 (m, 4H, D ring H); ms *m/e* (% rel. intensity): 343 (< 0.5, M^+) 192 (100), 174 (25), 165 (27), 152 (25), 151 (35), 149 (25), 133 (27), 131 (25), 121 (35), 119 (34), 103 (28). *Anal.* calcd. for $C_{20}H_{25}NO_4$: C 69.96, H 7.34, N 4.08; found: C 70.07, H 7.24, N 4.23.

*7,8-Dimethoxy-3-methylrhoeadan (***10***a)*

A mixture of compound **9***b* (1.0 g, 2.9 mmol) and polyphosphoric acid (15 g) (35) was mechanically stirred at 35°C for 24 h. The resulting reddish brown syrup was poured into a stirred ice–water mixture (40 g), basified with ammonium hydroxide, and subjected to standard work-up to give 0.70 g of crude material. Preparative tlc separation (aluminum oxide, activity 1, $CHCl_3$ eluent) followed by recrystallization from chloroform–ethanol afforded 0.5 g (53%) of compound **10***a*, mp 158.5–159°C; nmr δ: 2.38 (s, 3H, NCH_3), 2.60–3.50 (m, 4H, $—CH_2CH_2$), 3.72 (d, 1H, J = 2.5 Hz, C-2 H), 3.88, 3.90 (2 × s, 6H, 2 × OCH_3), 4.72 (d, 1H, J = 2.5 Hz, C-1 H), 4.97, 5.30 (2 × d, 2H, J = 14 Hz, C-14 H), 6.73, 6.86 (2 × s, 2H, A ring H), 7.10–7.50 (m, 4H, D ring H); ms *m/e* (% rel. intensity): 325 (54, M^+), 296 (57), 206 (100), 193 (39), 164 (25), 146 (30). *Anal.* calcd. for $C_{20}H_{23}NO_3$: C 72.82, H 7.12, N 4.30; found: C 72.42, H 7.08, N 4.33.

*7,8-Dimethoxy-3-methylrhoeadan-14-one (***11***a)*

A solution of chromium trioxide (0.8 g) in a mixture of water (1 mL) and glacial acetic acid (4 mL) was added dropwise to an ice-cold, stirred solution of compound **10***a* (1 g, 3.1 mmol) in glacial acetic acid (20 mL). The mixture was stirred at ice-bath temperatures for 15 min, at room temperature for 30 min, treated with an equal volume of water, and extracted with chloroform (6 × 50 mL). The organic extract was washed successively with 5% aqueous sodium bicarbonate solution (30 mL) and water (30 mL) and subjected to standard work-up to give a brown syrup which was resolved into six fractions by preparative tlc (silica gel, $CHCl_3$–MeOH, 100:8). One of the high R_f fractions gave 73 mg (7%) of compound **11***a* as a colourless solid, mp 203–205°C; ir (KBr) ν_{max}: 1718 cm^{-1}; nmr δ: 2.21 (s, 3H, NCH_3), 2.40–3.40 (m, 4H, $—CH_2CH_2$), 3.51 (d, 1H, J = 2 Hz, C-2 H), 3.82, 3.90 (2 × s, 6H, 2 × OCH_3), 5.38 (d, 1H, J = 2 Hz, C-1 H), 6.72, 6.77 (2 × s, 2H, A ring H), 7.40–8.40 (m, 4H, D ring H); ms *m/e* (% rel. intensity): 339 (10, M^+), 206 (100), 193 (33) 146 (34). *Anal.* calcd. for $C_{20}H_{21}NO_4$: C 70.37, H 6.24, N 4.13; found: C 70.11, H 6.30, N 4.19.

*5,6,7,12-Tetrahydro-7-methyl-2,3-dimethoxybenz[*d*]indeno-[1,2-*b*]azepine (iii)*

A solution of compound **9***b* (300 mg, 0.8 mmol) in concentrated sulfuric acid (1 mL) was stirred in an ice–water bath for 20 min, treated with ice-water (5 g), and neutralized with ammonium hydroxide solution. Standard work-up gave an oil which was resolved by preparative tlc (silica gel, $CHCl_3$–MeOH, 100:1.5) into three major components one of which (R_f ~0.75) yielded 72 mg (27%) of a colorless oil, nmr δ: 2.90–3.35 (m, 4H, C-5, C-6 H), 3.02 (s, 3H, NCH_3), 3.84 (s, 2H, C-12 H), 3.89, 3.95 (2 × s, 6H, 2 × OCH_3), 6.74, 7.14 (2 × s, 2H, A ring H), 7.20–7.60 (m, 4H, D ring H); ms *m/e*: 307 (M^+). The nmr spectrum was very similar to spectra of analogous more highly substituted benz[*d*]indeno[1,2-*b*]azepine derivatives (9, 13*a*, 36). The instability of compound **iii** precluded its further characterization.

*3-(2,3-Dimethoxyphenyl)propionic acid (***12***)*

Hydrogenation of 2,3-dimethoxycinnamic acid (21.17 g, 102 mmol) (37) over 10% Pd/C (0.164 g) in glacial acetic acid (270 mL) at 65°C and 30 psi gave a solid which upon recrystallization from pentane–cyclohexane afforded 20.15 g (94%) of compound **12**, mp 64–66°C (lit. (38) mp 69–70°C); ir ($CHCl_3$) ν_{max}: 1705 cm^{-1}; nmr δ: 2.78 (m, 4H), 3.81 (s, 6H), 6.80 (m, 3H).

*4,5-Dimethoxyindan-1-one (***13***)*

A mixture of compound **12** (11.56 g, 55 mmol) and freshly prepared (35) polyphosphoric acid (100 g) was stirred mechanically at steam bath temperatures for 10 min. The dark red mixture was poured into a stirred ice–water mixture (360 g) and extracted with methylene chloride (4 × 60 mL). The organic extract was washed successively with 10% aqueous sodium bicarbonate (ca. 50 mL) and water (50 mL), and subjected to standard work-up to give 10 g (95%) of compound **13** as a colourless solid, mp 74–76°C (lit. (39) mp 74°C); ir (KBr) ν_{max}:

1705 cm^{-1}; nmr δ: 2.62–3.10 (m, 4H), 3.95 (s, 3H), 3.98 (s, 3H), 7.04 (d, 1H, J = 9 Hz), 7.55 (d, 1H, J = 9 Hz).

This reaction was previously effected in low yield using P_2O_5 (38).

4,5-Dimethoxyindan-1-ol

Powdered sodium borohydride (2.27 g, 60 mmol) was added in portions to a stirred solution of compound **13** (10 g, 52 mmol) in ethanol (65 mL). The mixture was stirred for 30 min, refluxed for 20 min, diluted with water (300 mL), and extracted with methylene chloride (3 × 100 mL). Standard work-up afforded 10 g (99%) of 6,7-dimethoxyindan-1-ol, mp 91–92°C; ir (KBr) ν_{max}: 3300 cm^{-1}; nmr δ: 1.9 (br s, 1H, D_2O exch.), 1.95–3.20 (m, 4H), 5.15 (t, 1H, J = 6.5 Hz), 6.76, 7.06 (2 × d, 2H, J = 9 Hz) which was used in the next reaction without further purification.

6,7-Dimethoxyindene

Freshly distilled phosphorus oxychloride (25 g, 163 mmol) was added dropwise to a stirred, ice-cold solution of 4,5-dimethoxyindan-1-ol (10 g, 52 mmol), in anhydrous pyridine (75 mL). The solution was allowed to stand for 45 min, refluxed for 35 min, cooled, and poured slowly into a stirred ice–water mixture (400 mL). 6 *N* Hydrochloric acid (80 mL) was added and the whole was extracted with methylene chloride (5 × 50 mL). Standard work-up followed by steam distillation and extraction of the distillate with methylene chloride gave 7 g (77%) of 6,7-dimethoxyindene as a colourless oil, bp 88–93°C/0.55–0.9 Torr; ir (neat) ν_{max}: 1613 cm^{-1}; nmr δ: 3.10–3.50 (m, 2H), 3.85, 3.95 (2 × s, 6H), 6.20–7.30 (m, 4H). *Anal.* calcd. for $C_{11}H_{12}O_2$: C 74.98, H 6.86; found: C 74.89, H 6.83.

4,5-Dimethoxyindan-2-ol

Under a dry nitrogen atmosphere, a solution of 6,7-dimethoxyindene (6.86 g, 39 mmol) in anhydrous THF (15 mL) was added dropwise to a magnetically stirred 1 *M* solution of diborane in THF (Aldrich) (19.5 mL, 19.5 mmol) at a rate so as to keep the temperature below 30°C. The resulting solution was stirred 2 h and treated successively with water (0.5 mL), 3 *N* aqueous sodium hydroxide (13.6 mL), and 30% hydrogen peroxide (4.8 mL, 47 mmol) during which time the temperature of the mixture was maintained below 35°C. The reaction mixture was stirred for 16 h, diluted with ether (25 mL), and treated with saturated solid sodium chloride. Standard work-up followed by distillation afforded 6.68 g (88%) of 4,5-dimethoxyindan-2-ol, bp 116–122°C/0.1 Torr; mp 54–56°C; ir (KBr) ν_{max}: 3497 cm^{-1}; nmr δ: 2.24 (s, 1H, D_2O exch.), 2.50–3.40 (m, 4H), 3.84 (s, 6H), 4.40–4.80 (m, 1H), 6.73, 6.93 (2 × d, 2H, J = 9 Hz). *Anal.* calcd. for $C_{11}H_{14}O_3$: C 68.02, H 7.27; found: C 68.19, H 7.35.

4,5-Dimethoxyindan-2-one (14)

To a stirred solution of 4,5-dimethoxyindan-2-ol (6.6 g, 36 mmol) and dicyclohexylcarbodiimide (22.25 g, 108 mmol) in a mixture of benzene (100 mL) and dry dimethyl sulfoxide (10 mL), was added 0.7 mL of a 5 *M* solution of orthophosphoric acid in dry dimethyl sulfoxide. The mixture was stirred under nitrogen for 20 h and the resulting precipitate was collected by filtration and washed with benzene (75 mL). The combined filtrate was treated with 5% aqueous sodium bicarbonate solution (100 mL) and the mixture was stirred for 1 h. Standard work-up gave a brown oil which was dissolved in absolute ethanol (30 mL) and the resulting solution was cooled to −20°C to deposit 3.7 g of brown crystalline solid. Recrystallization from absolute ethanol gave 3.43 g (50%) of compound **14** as pale yellow needles, mp 91.5–93°C; ir ($CHCl_3$) ν_{max}: 1746 cm^{-1}; nmr δ: 3.47 (s, 4H), 3.83 (s, 6H), 6.82, 7.0 (2 × d, 2H, J = 9 Hz). *Anal.* calcd. for $C_{11}H_{12}O_3$: C 68.73, H 6.29; found: C 68.77, H 6.20.

5,6-Dimethoxyisochroman-3-one (15) and 7,8-dimethoxyisochroman-3-one (16) by Baeyer–Villiger reaction

A solution of compound **14** (5 g, 26 mmol) and *m*-chloroperbenzoic acid (8.2 g, 40.4 mmol) in chloroform (100 mL) was stirred with the exclusion of air for 2 days. The resulting precipitate was collected by filtration and the filtrate was concentrated *in vacuo* to give 9.0 g of solid which was redissolved in chloroform (150 mL) and shaken with 5% aqueous sodium bicarbonate solution (100 mL) until gas evolution ceased. Standard work-up gave 5.5 g of a light brown solid which upon two recrystallizations from ether–pentane at −20°C provided 2.31 g (43%) of a mixture of the isomeric compounds **15** and **16**, mp 40–45°C; ir (KBr) ν_{max}: 1752 cm^{-1}; nmr δ: 3.65 (s, 0.6 H), 3.77 (s, 1.4 H), 3.87, 3.90 (2 × s, 6H), 5.26 (s, 1.4 H), 5.44 (s, 0.6 H), 6.90 (s, 2H); ms *m/e*: 208 (M^+). *Anal.* calcd. for $C_{11}H_{12}O_4$: C 63.45, H 5.81; found: C 63.56, H 5.84.

Comparison of the integrated nmr spectrum of the mixture of **15** and **16** with that of pure **15**, synthesized independently as described below, allowed the assignments of the resonances at δ 3.65 (s, —CH_2CO), 3.87 (s, OCH_3), 5.26 (s, —CH_2O) to compound **16**. Therefore the mixture consists of a 60:40 ratio of the isomeric isochroman-3-ones **15** and **16**.

Since attempts to separate this mixture by fractional crystallization and repeated tlc on silica gel and alumina using a variety of solvent systems failed, it was subjected to bromination as described below.

5,6-Dimethoxyisochroman-3-one (15)

2,3-Dimethoxybenzaldehyde was converted into 2,3-dimethoxyphenylacetic acid by the following reactions and intermediates: (*1*). $NaBH_4$/EtOH/room temperature/20 h → 2,3-dimethoxybenzyl alcohol (99%), mp 49–51°C (lit. (38) mp 46–48°C); (*2*). $SOCl_2$/PhH/ɲ/1.5 h → 2,3-dimethoxybenzyl chloride (99%), used without purification; (*3*). NaCN/H_2O (40) → 2,3-dimethoxybenzyl cyanide (85%), used without purification; (*4*). 20% aqueous KOH/ɲ/4 h → 2,3-dimethoxyphenylacetic acid (87%), mp 80–82°C (lit. (41) mp 84°C).

A mixture of this compound (1.5 g, 7.6 mmol), concentrated hydrochloric acid (2 mL), glacial acetic acid (3.5 mL), and 30% aqueous formalin solution (0.8 g, 8 mmol) was heated at steam bath temperatures for 2 h. Water (15 mL) was added and the mixture was extracted with chloroform (3 × 40 mL). Standard work-up gave 1.2 g of a thick oil which was resolved by preparative tlc (silica gel, $CHCl_3$–MeOH, 100:1) into the following: *band 1* (R_f = 0.4): 5,6-dimethoxyisochroman-3-one (**15**), 0.12 g (7.5%), mp 153–155°C; ir ($CHCl_3$) ν_{max}: 1740 cm^{-1}; nmr δ: 3.78 (s, 2H, —CH_2), 3.88, 3.90 (2 × s, 6H, 2 × OCH_3), 5.24 (s, 2H, —CH_2CO), 6.83, 7.0 (2 × d, 2H, J = 8 Hz, aromatic H); ms *m/e* (% rel. intensity): 208 (7, M^+), 193 (71), 164 (100). *Anal.* calcd. for $C_{11}H_{12}O_4$: C 63.45, H 5.81; found: C 63.30, H 5.83; *band 2*: (R_f = 0.1): 5,6-dimethoxy-8-methylenehydroxyisochroman-3-one, 0.6 g (38%), mp 110–112°C; ir ($CHCl_3$) ν_{max}: 3620, 1740 cm^{-1}; nmr δ: 2.10 (br s, 1H, OH, D_2O exch.), 3.70 (s, 2H, —CH_2O), 3.80, 3.87 (2 × s, 6H, 2 × OCH_3), 4.64 (s, 2H, —CH_2OH), 5.33 (s, 2H, —CH_2CO), 6.87 (s, 1H, aromatic H); ms *m/e* (% rel. intensity): 238 (100, M^+), 220 (46), 192 (21), 179 (24), 177 (31), 123 (29). *Anal.* calcd. for $C_{12}H_{14}O_5$: C 60.50, H 5.92; found: C 60.32, H 5.90.

4-Bromo-7,8-dimethoxyisochroman-3-one (8b) and 5,6-dimethoxy-8-bromoisochroman-3-one (17)

A mixture of the dimethoxyisochroman-3-ones **15** and **16** (1.04 g, 5 mmol) was brominated according to the procedure used for the preparation of **8***a*. Evaporation to dryness followed by treatment of the residue with ether (5 mL) gave compound **17**, mp 170–172°C; ir (KBr) ν_{max}: 1704 cm^{-1}; nmr δ: 3.86, 3.90 (2 × s, 6H), 3.97 (s, 2H), 4.70 (s, 2H), 7.14 (s, 1H). *Anal.* calcd. for $C_{11}H_{11}BrO_4$: C 46.01, H 3.86; found: C 45.80, H 3.90.

The above filtrate was evaporated *in vacuo* at room temperature to give a pale yellow oil which upon column chromatography (silica gel, $CHCl_3$ eluent) yielded 0.55 g (38%) of compound **8***b* as a colourless oil which crystallized upon refrigera-

tion, mp 122–123°C; ir (KBr) ν_{max}: 1750 cm^{-1}; nmr δ: 3.88, 3.98 (2 × s, 6H, 2 × OCH_3), 5.15, 5.60 (2 × d, 2H, J = 14 Hz, C-1 H), 5.80 (s, 1H, C-4 H), 6.98 (s, 2H, aromatic H); ms *m/e* (% rel. intensity): 288, 286 (7, M^+), 208 (26), 207 (100), 179 (31), 151 (31). *Anal.* calcd. for $C_{11}H_{11}BrO_4$: C 46.01, H 3.86; found: C 45.84, H 4.01.

*7,8-Dimethoxyisochroman-3-one (**16**) from homoisovanillic acid (**18**)*

The Nagata procedure (23) was adapted. A mixture of homoisovanillic acid (**18**) (42) (1.82 g, 10 mmol), benzeneboronic acid (2.0 g), and benzene (100 mL) was stirred and refluxed with azeotropic removal of water (Dean–Stark trap) for 1 h. Paraformaldehyde (1.0 g) was added and the reflux was continued as before for a total of 9 h during which time paraformaldehyde (2 g) was added at 2 h intervals. Next day reflux was resumed using a new condenser after addition of benzeneboronic acid (1 g). Paraformaldehyde was added as before. After 28 h of reaction extending over 4 days, benzene was removed *in vacuo*, water (30 mL) was added to the oily residue, and the mixture was heated at 90–100°C for 1.5 h. The solid which formed was collected by filtration without cooling the mixture and was dissolved in methylene chloride. The organic extract was washed with water, dried (Na_2SO_4), and evaporated to dryness to yield 0.939 g (48%) of *8-hydroxy-7-methoxyisochroman-3-one*, mp 180–183°C (lit. (23*a*) mp 183–185°C). Methylation according to Nagata and co-workers (23*a*) gave compound **18** in 90% yield, mp 97–99°C (lit. (23*a*) mp 98–100°C).

*4-(N-Methyl-β-3′,4′-dimethoxyphenylethylamino)-7,8-dimethoxyisochroman-3-one (**9**c)*

The condensation of compound **8***b* (0.29 g, 1 mmol) with *N*-methyl-3,4-dimethoxy-β-phenethylamine (**7**) (0.39 g, 2 mmol), carried out according to the procedure described for the preparation of **9***a*, gave a yellow oil which was chromatographed (silica gel, $CHCl_3$–EtOAc, 2:1 eluent) to give 0.35 g (88%) of compound **9***c* as a colourless oil, ir ($CHCl_3$) ν_{max}: 1740 cm^{-1}; nmr δ: 2.33 (s, 3H), 2.72 (br s, 4H), 3.81, 3.83, 3.87 (3 × s, 12H), 4.48 (s, 1H), 4.80, 5.55 (2 × d, 2H, J = 14 Hz), 6.60–6.73 (m, 3H), 6.90 (s, 2H); ms *m/e* (% rel. intensity): 401 (0.5, M^+), 250 (80), 207 (100), 179 (20), 151 (21). *Anal.* calcd. for $C_{22}H_{27}NO_6$: C 65.82, H 6.78, N 3.49; found: C 65.64, H 6.71, N 3.45.

*4-(N-Methyl-β-3′,4′-dimethoxyphenylethylamino)-7,8-dimethoxyisochroman-3-ol (**9**d)*

Dibal reduction of compound **9***c* (0.35 g, 0.87 mmol) according to the procedure used to obtain compound **9***b* gave 0.30 g (99%) of oily product which was chromatographed (silica gel, $CHCl_3$–MeOH, 100:2.5 eluent) to give the lactol **9***d* as a colorless oil, ir ($CHCl_3$) ν_{max}: 3300 cm^{-1}; nmr δ: 2.33 (s, 3H, NCH_3), 2.70–3.10 (m, 4H, —CH_2CH_2—), 3.71 (d, 1H, J = 3 Hz, C-4 H), 3.81, 3.85, 3.87, 3.90 (4 × s, 12H, 4 × OCH_3), 4.70 (d, 1H, J = 3 Hz, C-3 H), 4.76 (s, 2H, C-1 H), 5.60 (br s, 1H, OH, D_2O exch.), 6.60–7.0 (m, 4H, aromatic H), 7.2 (s, 1H, aromatic H); ms *m/e* (% rel. intensity): 403 (< 0.5, M^+), 252 (100), 209 (68), 181 (53), 179 (21), 165 (23), 152 (27). *Anal.* calcd. for $C_{22}H_{29}NO_6$: C 65.49, H 7.24, N 3.47; found: C 65.58, H 7.39, N 3.45.

*7,8,12,13-Tetramethoxy-3-methylrhoeadan (**10**b)*

A mixture of the lactol **9***d* (0.35 g, 0.86 mmol) and polyphosphoric acid (10 g) was mechanically stirred and heated at steam bath temperatures for 3.5 h. Standard work-up (see preparation of **10***a*) followed by preparative tlc (alumina, $CHCl_3$ eluent) gave 0.17 g (51%) of compound **10***b* as a colorless oil which crystallized, mp 164–166°C; ir ($CHCl_3$) ν_{max}: 1605 cm^{-1}; nmr δ: 2.33 (s, 3H, NCH_3), 2.60–3.60 (m, 4H, —CH_2CH_2—), 3.86 (br s, 12H, 4 × OCH_3), 4.04 (d, 1H, J = 2 Hz, C-2 H), 4.50 (d, 1H, J = 2 Hz, C-1 H), 4.87, 5.30 (2 × d, 2H, J = 14 Hz, C-14 H), 6.72, 6.80 and 6.88 (3 × s, 4H, aromatic H); ms *m/e* (% rel. intensity): 385 (47, M^+), 370 (25), 357 (31), 356 (98), 354 (41), 343 (28), 342 (100), 326 (20), 207 (22), 206 (100), 204 (22), 194 (22), 193 (56), 192 (59), 191 (31), 190 (22), 179 (28), 178 (47), 177 (22), 176 (28), 165 (37), 164 (44), 163 (36), 162 (25), 161 (25), 151 (34), 150 (34), 149 (34), 148 (34), 147 (22), 135 (28), 134 (31), 133 (22), 121 (31), 119 (22), 118 (25), 107 (25), 103 (22). *Anal.* calcd. for $C_{20}H_{27}NO_5$: C 68.52, H 7.06, N 3.63; found: C 68.31, H 7.20, N 3.52.

*7,8,12,13-Tetramethoxy-3-methylrhoeadan-14-one (14-oxo-cis-alpinigenine) (**11**b)*

The procedure for the oxidation of compound **10***a* to **11***a* was closely followed. From the rhoeadan **10***b* (0.5 g, 1.29 mmol) there was obtained 0.48 g of a crude material which was subjected to preparative tlc (silica gel, $CHCl_3$–MeOH, 100:2 eluent) and was thereby resolved into eight bands, one of which (R_f ~0.6) yielded 35 mg (7%) of compound **11***b*, mp 194–196°C (lit. (13*a*) mp 195–196°C), whose tlc, mixture mp, ir, and ms were shown to be identical with a sample of synthetic material kindly provided by Professor Rodrigo and Dr. Orito (13*a*).

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1. M. Shamma. The isoquinoline alkaloids. Academic Press, New York. 1972. p. 399.
2. M. Shamma and J. L. Moniot. Isoquinoline alkaloids research, 1972–1977. Plenum Press, New York. 1978. p. 337.
3. F. Stermitz. Recent Adv. Phytochem. **1**, 161 (1968).
4. J. A. Finlay. Int. Rev. Sci. Org. Chem. Ser. 2, **9**, 23 (1976).
5. T. Ibuka, T. Konoshima, and Y. Inubushi. Chem. Pharm. Bull. Jpn. **23**, 114 (1975); **23**, 133 (1975).
6. V. Fajaro, V. Elango, B. K. Cassels, and M. Shamma. Tetrahedron Lett. 39 (1982).
7. S. Kasparek. Adv. Heterocycl. Chem. **17**, 45 (1974).
8. T. Kametani and K. Fukomoto. Heterocycles, **3**, 931 (1975).
9. H. Irie, S. Tani, and H. Yamane. J. Chem. Soc. Perkin Trans. I, 2986 (1972).
10. (*a*) W. Kloetzer, S. Teitel, and A. Brossi. Helv. Chim. Acta, **55**, 228 (1972); (*b*) W. Kloetzer, S. Teitel, J. Blout, and A. Brossi. Monatsh. Chem. **103**, 435 (1972); (*c*) R. Hohlbrugger and W. Kloetzer. Chem. Ber. **112**, 849 (1979).
11. S. Prabhakar, A. M. Lobo, M. R. Tavares, and I. M. C. Oliveira. J. Chem. Soc. Perkin Trans. I, 1273 (1981).
12. M. Shamma and L. Töke. Tetrahedron, **31**, 1991 (1975).
13. (*a*) K. Orito, R. H. Manske, and R. Rodrigo. J. Am. Chem. Soc. **96**, 1944 (1974); (*b*) B. Nalliah, R. H. Manske, and R. Rodrigo. Tetrahedron Lett. 2853 (1974).
14. S. O. de Silva, I. Ahmad, and V. Snieckus. Can. J. Chem. **57**, 1598 (1979).
15. S. O. de Silva, J. N. Reed, and V. Snieckus. Tetrahedron Lett. 5099 (1978).
16. H. Ronsch, A. Guggisberg, M. Hesse, and H. Schmid. Helv. Chim. Acta, **60**, 2402 (1977).
17. D. J. Rawlinson and G. Sosnovsky. Synthesis, 1 (1972); 567 (1973).
18. V. K. Grover and Y. K. Gupta. Aust. J. Chem. **23**, 757

(1970); D. M. PIATAK and L. S. EICHMEIER. J. Chem. Soc. Chem. Commun. 772 (1971).
19. J. GUTZWILLER and M. USKOKOVIC. J. Am. Chem. Soc. **100**, 576 (1978).
20. Y. SPRINZAK. J. Am. Chem. Soc. **80**, 5449 (1958).
21. J. N. SRIVASTAVA and D. N. CHAUDHURY. J. Org. Chem. **27**, 4337 (1962).
22. A. CHATTERJEE and S. GHOSH. Synthesis, 818 (1981).
23. (*a*) W. NAGATA, H. ITAZAKI, K. OKADA, T. WAKABAYASHI, K. SHIBATA, and N. TOKUTAKE. Chem. Pharm. Bull. Jpn. **23**, 2867 (1975); (*b*) W. NAGATA, K. OKADA, and T. AOKI. Synthesis, 365 (1979).
24. J. FINKLESTEIN and A. BROSSI. J. Heterocycl. Chem. **4**, 315 (1967).
25. G. CASIRAGHI, G. CASNATI, G. PUGLIA, G. SARTORI, and G. TERENGHI. J. Chem. Soc. Perkin Trans I, 1862 (1980); T. TOYODA, K. SASAKURA, and T. SUGASAWA. J. Org. Chem. **46**, 189 (1981), and references cited therein.
26. M. IKEDA, K.-I. HIRAO, Y. OKUNO, and O. YONEMITSU. Tetrahedron Lett. 1181 (1974).
27. T. A. BRYSON. Synth. Commun. **3**, 173 (1973).
28. R. L. VAUX, F. N. JONES, and C. F. HAUSER. J. Org. Chem. **29**, 1387 (1964).
29. S.-I. MURAHASHI, K.-I. ITO, T. NAOTA, and Y. MAEDA. Tetrahedron Lett. 5327 (1981).
30. N. S. NARASIMHAN, R. S. MALI, and B. S. KULKARNI. Tetrahedron Lett. 2797 (1981).
31. J. E. HORAN and R. W. SCHIESSLER. Org. Synth. Coll. Vol. V, 647 (1973).
32. G. A. SWAN. J. Chem. Soc. 1720 (1949).
33. J. H. MARKGRAF and S. J. BASTA. Synth. Commun. **2**, 139 (1972).
34. M. S. GIBSON, G. W. PRENTON, and J. M. WALTHEW. J. Chem. Soc. C, 2234 (1970).
35. A. J. BIRCH, R. JAEGER, and R. ROBINSON. J. Chem. Soc. 582 (1945).
36. T. KAMETAMI, M. S. PREMILA, S. HIRATA, H. SETO, H. NEMOTO, and K. FUKUMOTO. Can. J. Chem. **53**, 3824 (1975).
37. J. KOO, M. S. FISHER, G. N. WALKER, and J. BLAKE. Org. Synth. Coll. Vol. IV, 327 (1963).
38. W. H. PERKIN, JR. and R. ROBINSON. J. Chem. Soc. **105**, 2376 (1914).
39. J. W. HUFFMAN and C. E. OPLIGER. J. Org. Chem. **36**, 111 (1971).
40. R. ADAMS and A. F. THAL. Org. Synth. Coll. Vol. I, 107 (1932).
41. G. TSATSAS. Ann. Pharm. Fr. **7**, 733 (1949); Chem. Abstr. **44**, 5370d (1950).
42. R. GREWE and H. FISCHER. Chem. Ber. **96**, 1520 (1963); K. C. RICE and A. BROSSI. J. Org. Chem. **45**, 592 (1980).