

1-Chloroethyl-4-methyl-6,7-dimethoxyisochroman

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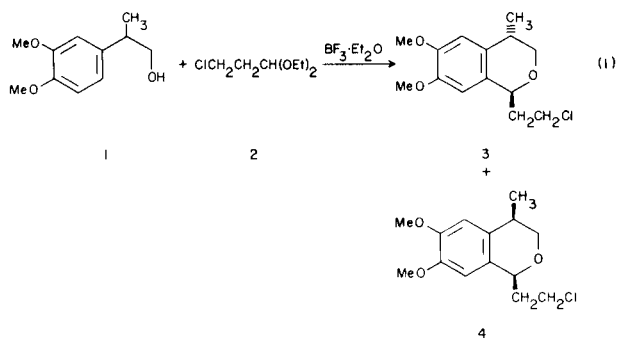
The boron trifluoride catalyzed reaction of 2-methyl-2-(3,4-dimethoxyphenyl)ethanol and chloropropionaldehyde diethyl acetal yields a mixture of *cis* and *trans* 1-chloroethyl-4-methyl-6,7-dimethoxyisochroman. The structure of the *trans* compound was established by X-ray analysis. The *trans* compound equilibrates to a mixture of the *cis* and *trans* when exposed to boron trifluoride catalyst.

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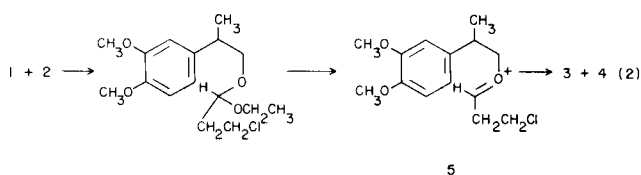
The preparation of 1-haloalkyl-6,7-dimethoxyisochromans has been reported by Humber (1). Such isochromans are conveniently prepared from 3,4-dimethoxyphenyl-ethanol and halosubstituted aldehydes under acid catalyzed conditions.

We have examined the stereochemical course of the boron trifluoride catalyzed condensation of 2-methyl-2-(3,4-dimethoxyphenyl)ethanol and an equimolar amount of the diethyl ketal of 3-chloropropionaldehyde (Equation 1). The reaction was run in nitromethane. Under the conditions of the reaction, isochromans **3** and **4** are formed in a ratio of 1.65 to 1 in an overall, isolated yield of 78%.

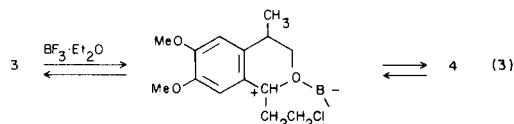
Isochromans **3** and **4** co-crystallize after chromatography. We were unable to separate the two by adsorption chromatography on silica gel. However, they can be separated by reverse phase chromatography on RP18® or by gas chromatography on OV17®. The *trans* isomer can be isolated pure by fractional crystallization from ethyl acetate and Skelly Solve B®.



Presumably, a mixed acetal of 3-chloropropionaldehyde and 2-methyl-2-(3,4-dimethoxyphenyl)-1-ethanol is first formed. Boron trifluoride and the mixed acetal can then generate an oxonium ion which cyclizes in two possible orientations of intermediate **5** via a 6-endotrigrinal reaction (3) to yield the *cis* and *trans* products (Equation 2).

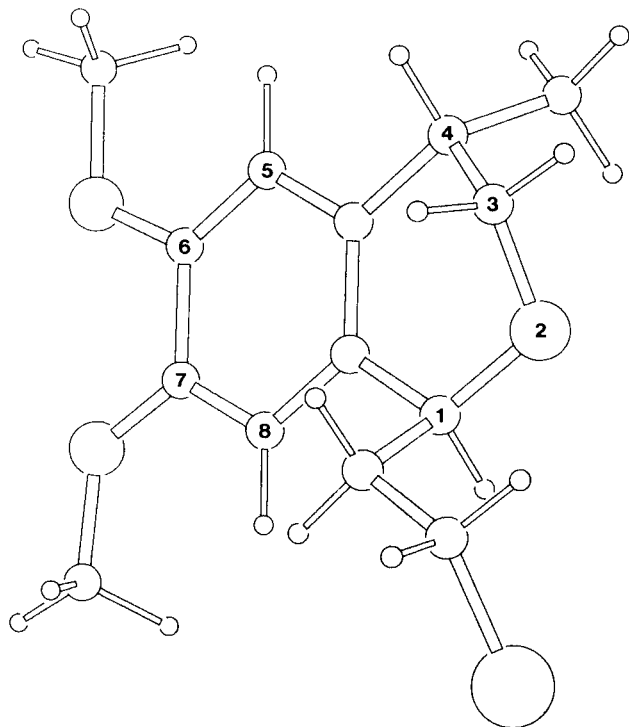


The pure *trans* isochroman **3** undergoes facile Lewis acid mediated conversion to the *cis* compound **4**. When the *trans* isomer was dissolved in nitromethane and was treated with 0.25 equivalents of boron trifluoride etherate, an equilibrium mixture which was 44% *trans* and 56% *cis* was established within 2 hours. Presumably, this isomerization is initiated by boron trifluoride catalyzed cleavage of the isochroman ring followed by closure (Equation 3).



The structure of compound **3** was unambiguously assigned by X-ray analysis (2). Based on X-ray data, C-1, C-4, and the aromatic ring are very nearly coplanar. The geometry of substituents at C-1 and C-4 can thus be evaluated by consideration of their distances from the plane of the aromatic system. The bond to the chloroethyl substituent at C-1 makes an angle of 59° with the plane, whereas the hydrogen at C-1 branches at an angle of 47°. The methyl group at C-4 has an angle of 64° with the plane, whereas the hydrogen at C-4 has a 41° angle (see Figure 1). The oxygen bearing ring, itself, exists in a conformation with the oxygen and the CH₂ on opposite sides of the plane defined by C-1, C-4 and the aromatic ring. The alkyl substituents are more axial than equatorial, presumably because of the unfavorable *peri* interaction with the aromatic hydrogens at C-5 and C-8.

FIGURE 1



EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nmr spectra were recorded on a Varian HFT-80 spectrophotometer. Preparative chromatography was performed on a medium pressure liquid chromatograph which included a Milton Roy D pump[®] 1 x 40" LDC glass columns which were packed with 40-60 μ silica gel 60[®], and a nitrogen pressure injection system. The analytical high pressure liquid chromatograph included a Milton Roy minipump[®], a liquid capacitor pulse dampening system, a Valco injector[®] and an Altex uv detector[®]. Detailed plans are available from the authors for either the medium pressure preparative or the high pressure analytical liquid chromatographs.

cis- and *trans*-1-(2-Chloroethyl)-4-methyl-6,7-dimethoxyisochromans (**3** and **4**).

A mixture of 2.48 g. (0.0126 mole) of 2-methyl-2-(3,4-dimethoxyphenyl)-1-ethanol and 2.25 g. (0.0126 mole) of 3-chloropropionaldehyde diethyl acetal in 30 ml. of nitromethane was treated at room temperature with 0.18 g. (0.00126 mole) of boron trifluoride etherate. After stirring for two hours at room temperature, the mixture was partitioned between methylene chloride and aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate, concentrated *in vacuo* and chromatographed on silica gel (5 to 15% ethyl acetate in Skelly B) to yield 2.64 g. (78%) of a mixture of isomers **3** and **4** in a ratio of 1.65 to 1.0 (gc, hplc, and proton nmr). This mixture readily crystallized, m.p. 71-75[°], and gave good elemental analysis.

Anal. Calcd. for C₁₄H₁₉ClO₃: C, 62.21; H, 7.09; Cl, 13.31. Found: C, 62.46; H, 7.22; Cl, 13.09.

The mixture of **3** and **4** could be separated analytically by gas chromatography (OV 17[®], 150[°]) where the *cis* isomer moves faster. Resolution was also achieved by high pressure liquid chromatography (4 m x 50 cm RP18[®], 10 μ particle size, 60% methanol/40% water). The *trans* isomer moves faster than the *cis* isomer. The *trans* isomer was isolated most simply by fractional crystallization from ethyl acetate and Skelly Solve B, m.p. 81.5-83[°]; nmr (deuteriochloroform) (compound **3**): δ 6.72 (s, 1), 6.51 (s, 1), 4.85 (5, 1), 3.87 (s, 3), 3.85 (s, 3), 3.25-4.1 (m, 4), 3.7-4.0 (m, 1), 2.05-2.35 (m, 2), 1.22 (d, 3, J = 6.8 Hz, CH₃); nmr (deuteriochloroform) (compound **4**): δ 1.30 (d, 3, J = 6.9 Hz, CH₃).

Isomerization of **3** to **4**.

A 0.21 g. (0.78 mmole) sample of pure **3** was dissolved in 3 ml. of nitromethane and treated under nitrogen at room temperature with 0.034 g. (0.24 mmole) of boron trifluoride etherate. At intervals of 1, 2, and 18 hours, aliquots were removed, partitioned with methylene chloride and aqueous sodium bicarbonate, and assayed by gc (OV 17, 150[°]) at these intervals; *trans* (**3**) to *cis* (**4**) ratios of 0.90, 0.79, and 0.79 were obtained.

REFERENCES AND NOTES

- (1) T. A. Dobson and L. J. Humber, *J. Heterocyclic Chem.*, **12**, 591 (1975).
- (2) C. Chidester, to be published.
- (3a) J. E. Baldwin, J. Cutting, W. DuPont, L. I. Kruse, J. Silberman, and R. C. Thomas, *ibid.*, 736 (1976).