

Nasim H. Rama and A. Saeed

Department of Chemistry, Quaid-I-Azam University, Islamabad, Pakistan

C. W. Bird\* and J. Cobb

Department of Chemistry, King's College, The Strand, London, WC2R 2LS, United Kingdom

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3,5-Dimethoxyphenylalkan-2-ols react with diethoxymethane and boron trifluoride etherate, or aqueous formaldehyde and hydrochloric acid forming bis(6,8-dimethoxychroman-5-yl)methanes.

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Recent reports [1,2] on the DDQ promoted introduction of substituents at C1 of isochromans appeared to be of particular relevance to our program of synthesis of naturally occurring derivatives [3,4,5]. The latter, by virtue of their biosynthetic origin, normally have hydroxyl or methoxyl groups at C6 and/or C8 of the isochroman nucleus whereas the aforementioned experiments have been conducted solely on the 5,8-dimethoxy derivatives.

In order to prepare appropriate 6,8-dimethoxyisochromans for our studies we attempted their preparation by the reaction of the corresponding 3,5-dimethoxyphenylalkan-2-ol with either diethoxymethane and boron trifluoride etherate or aqueous formaldehyde and hydrochloric acid. Although these conditions have been used previously for the preparation of 5,6- [6], 5,7- [7] and 6,7-dimethoxyisochromans [8], the only products that we were able to obtain in almost quantitative yield proved to be the bis-(isochroman-5-yl)methanes **1**. All attempts to promote monomeric isochroman formation by altering the proportions of reagents have proved unsuccessful.

The structures of these products were established from their spectroscopic properties. Each of the compounds **1**, **2** and **3** showed the expected molecular ion in the mass spectrum accompanied by the tropylium species **4** as the base peak. In the case of **1** the <sup>1</sup>H nmr spectrum showed in addition to the two methoxys at 3.74 and 3.78 only a single aromatic hydrogen at 6.31 and a two proton singlet

at 3.90 for the bridging methylene. The protons associated with the dihydropyran ring show the expected signals at 4.66 (s) C1, 3.82 (t) C3 and 2.58 (t) C4. Although examination of molecular models points to the occurrence of restriction of free rotation of the isochromanyl rings around the two C<sub>Ar</sub>-C axes we have been unable to detect any such effect from variable temperature nmr studies down to -50°. This is in accord with earlier observations on didurylmethane [9].

As both **2** and **3** contain chiral centers they would be expected to be formed as diastereomeric mixtures. While we have so far been unable to separate them, their <sup>1</sup>H nmr spectra display characteristic duplicate absorptions for many of the protons.

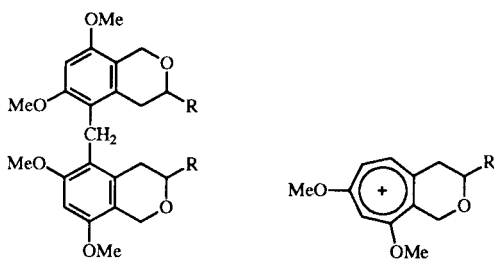
Although biosynthetic considerations suggest that such bis-isochromanylmethanes might be found in nature none have so far been reported. The only previous example of such a compound was obtained from 3,4,5-trimethoxyphenylpropan-2-ol [10].

## EXPERIMENTAL

Melting points were determined on a Meltemp MP-D apparatus and are uncorrected. The <sup>1</sup>H nmr spectra were measured on a Bruker AM400 spectrometer using tetramethylsilane as the internal standard. In the cases where a mixture of diastereomers was obtained, the frequency of the more intense of a pair of duplicate signals is listed first. Mass spectra were obtained with a Jeol AX505W spectrometer.

Bis(6,8-dimethoxyisochroman-5-yl)methane (**1**).

Boron trifluoride etherate (0.27 ml, 2 mmoles) was added dropwise to a stirred solution of (3,5-dimethoxyphenyl)ethan-2-ol (1.82 g, 0.01 mole) and diethoxymethane (1.04 g, 0.01 mole) in 20 ml nitromethane. The mixture was stirred at 22° for 3 hours. Water was added and the organic product was isolated by ether extraction. The ether extract was dried (sodium sulfate) and evaporated. The residue was crystallized from ethyl acetate-petroleum ether to yield 1.68 g (84%), mp 180-181°; <sup>1</sup>H nmr (deuteriochloroform): δ 2.58 (t, 4H, 4-H, J = 5.6 Hz), 3.74 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.82 (t, 4H, 3-H, J = 5.7 Hz),



- 1** R = H  
**2** R = CH<sub>3</sub>  
**3** R = C<sub>11</sub>H<sub>23</sub>

3.90 (s, 2H, -CH<sub>2</sub>-), 4.66 (s, 4H, 1-H), 6.31 (s, 2H, ArH); ms: (70 eV, electron impact) m/z 400 (M<sup>+</sup>), 206 (100%), 178, 147.

*Anal.* Calcd. for C<sub>23</sub>H<sub>28</sub>O<sub>6</sub>: C, 69.0; H, 7.0. Found: C, 68.8; H, 7.1.

Bis(6,8-dimethoxy-3-methylisochroman-5-yl)methane (2).

Following the preceding method (3,5-dimethoxyphenyl)propan-2-ol was converted into (2) (87%), mp 220-221°; <sup>1</sup>H nmr (deuteriochloroform): δ 1.25 and 1.29 (d's, 6H, J = 6.1 Hz, CH<sub>3</sub>), 2.09 and 2.35 (dd, 2H, J = 10.8 and 16.7 Hz, 4-H), 2.77 and 2.74 (dd, 2H, J = 16.7 and 2.0 Hz, 4-H), 3.55-3.70 (m, 2H, 3-H), 3.75 and 3.70 (s, 3H, CH<sub>3</sub>O), 3.79 and 3.78 (s, 3H, CH<sub>3</sub>O), 3.88 (s, 2H, -CH<sub>2</sub>-), 4.57 (d, 2H, J = 15.3 Hz, 1-H), 4.85 and 4.87 (d, 2H, J = 15.3 Hz, 1-H), 6.30 (s, 2H, ArH); ms: (70 eV, electron impact) m/z 428 (M<sup>+</sup>), 220 (100%).

*Anal.* Calcd. for C<sub>25</sub>H<sub>32</sub>O<sub>6</sub>: C, 70.09; H, 7.48. Found: C, 69.9; H, 7.33.

Bis(6,8-dimethoxy-3-undecylisochroman-5-yl)methane (3).

To a stirred solution of (3,5-dimethoxyphenyl)tridecan-2-ol (1.68 g, 0.005 mole) in 10 ml of ether was added dropwise a mixture of 0.35 ml of 37% formalin (0.0045 mole) and 0.45 ml of concentrated hydrochloric acid (0.045 mole). The reaction mixture was stirred for 1 hour and 5 ml of 5% aqueous sodium bicarbonate solution was added. The ether layer was separated and the aqueous layer extracted with ether. The combined ether extracts were dried (sodium sulfate) and evaporated to leave a colorless oil which solidified on standing. This was recrystallized from ethyl acetate-petroleum ether to yield 1.37 g (77%), mp 98°; <sup>1</sup>H nmr (deuteriochloroform): δ 0.88 (t, 6H, J = 7.0 Hz, CH<sub>3</sub> x 2), 1.26 (br s, 36H, 2'-10'-H x 2), 1.63 (br s, 4H, 1'-H),

2.03 and 2.29 (dd, 2H, J = 16.8 and 10.6 Hz, 4-H), 2.65-2.80 (m, 2H, 4-H), 3.35-3.50 (m, 2H, 3-H), 3.75 and 3.72 (s, 6H, CH<sub>3</sub>O x 2), 3.78 and 3.77 (s, 6H, CH<sub>3</sub>O x 2), 3.90 (s, 2H, -CH<sub>2</sub>-), 4.54 (d, 2H, J = 15.2 Hz, 1-H), 4.84 and 4.86 (d, 2H, J = 15.2 Hz, 1-H), 6.29 and 6.28 (s, 2H, ArH); ms: (70 eV, electron impact) m/z 708 (M<sup>+</sup>), 362 (100%).

*Anal.* Calcd. for C<sub>45</sub>H<sub>72</sub>O<sub>6</sub>: C, 76.27; H, 10.17. Found: C, 76.10; H, 10.27.

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