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SYNTHESIS OF ISOCHROMANS VIA THE TITANIUM TETRACHLORIDE ASSISTED CYCLIZATION OF ACETALS OF PHENETHYL ALCOHOLS

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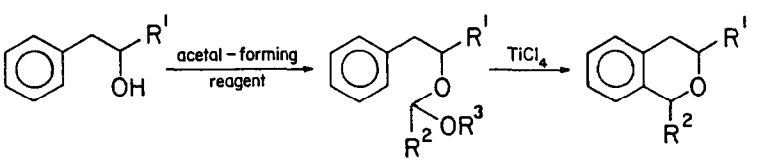
Summary: This paper reports the preparation of five 3,4-dihydro-1H-2-benzopyrans in good yields via the $TiCl_4$ promoted cyclization of acetals derived from phenethyl alcohols.

The isochroman (3,4-dihydro-1H-2-benzopyran) and isochromene (1H-2-benzopyran) nuclei have a meager place among natural product structures. However,the 1-oxo derivatives, isochroman-1-one (3,4-dihydroisocoumarin or 3,4-dihydro-1H-2-benzopyran-1-one) and isochromen-1-one (isocoumarin or 1H-2-benzopyran-1-one), are present in a significant cadre of naturally occurring lactones.[1] Both the isocoumarin and the 3,4-dihydroisocoumarin structures can often be obtained from isochromans since the 1-carbon is readily oxidized to the carbonyl,[2] and the 4-carbon in 3,4-dihydroisocoumarins can be brominated followed by elimination to give the isocoumarin structure.[3]

It appears that isochromans, a relatively little studied class of compounds, are commonly synthesized by the carbon-oxygen bond-forming cyclization of 2-(2-hydroxymethylphenyl)ethanols (homophthalyl alcohols)[4,5] or closely related compounds such as 2-(2-bromoethyl)benzyl bromide,[6] 1-acetoxymethyl-2-(2-chloroethyl)benzene,[7] and selected amino alcohols.[8] Additionally, several workers[9-14] have reported that the reaction of phenethyl alcohols with paraformaldehyde or paraldehyde in the presence of acid leads to good yields of isochromans. The most extensive work in this area has been done by Thibault.[14] These later syntheses are carbon-carbon bond-forming cyclizations and proceed through α-chloroethers or half-acetals. A related reaction occurring via an α-iodoether has also been reported by Jung and coworkers.[15]

We wish to report an approach to the synthesis of isochromans under very mild conditions which involves the prior preparation of acetals derived from phenethyl alcohols followed by cyclization to isochromans utilizing a Lewis acid (Scheme I). Since there are a



Ia (R' = H)
b (R' = CH_3)

IIa (R' = H, R^2 = H, R^3 = OCH_2CH_2OMe)
b (R' = H, R^2 = CH_3, R^3 = C_2H_5)
c (R' = CH_3, R^2 = H, R^3 = $OCH_2CH_2OCH_3$)
d (R' = CH_3, R^2 = CH_3, R^3 = C_2H_5)

III

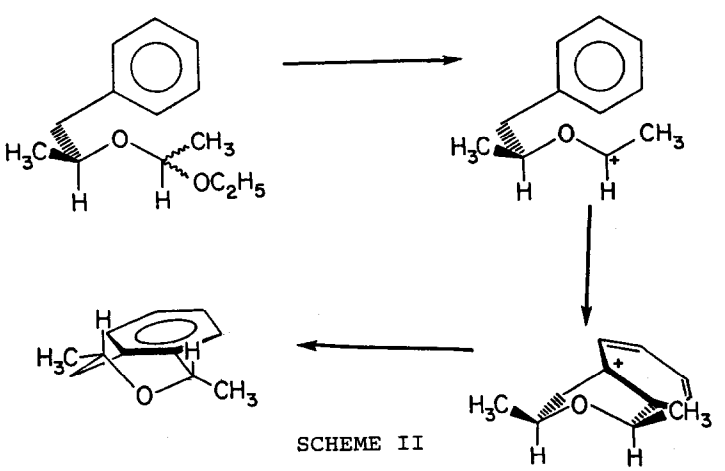
SCHEME I

variety of acetal-forming reagents available,[16] we believe that this approach may have general merit for isochroman synthesis. To our knowledge there are only two reports[17-19] of a few isochromans synthesized via a phenethyl alcohol-acetal intermediate. In both cases phenethyl alcohols were reacted with chloromethyl methyl ether in the presence of zinc chloride at room temperature to presumably give intermediate acetals (II-R^2=H,R^3=Me) which immediately cyclized to the isochroman structures.

In this work we have prepared four acetals (II a-d) from 2-phenylethanol and 3-phenyl-2-propanol and the acetal-forming reagents ethyl vinyl ether and methoxyethoxymethyl chloride (MEM chloride). These reactions are routine and give the acetals in excellent yields.[16] The four acetals were in turn subjected to treatment with titanium tetrachloride in methylene chloride to form isochromans (vide infra).

The two MEM acetals were readily cyclized in excellent yield by reaction with an equimolar quantity of titanium tetrachloride in methylene chloride at 0°C for only 30 minutes. The cyclization of the ethyl vinyl ether-based acetals was best accomplished by reaction with twice the stoichiometric amount of titanium tetrachloride in methylene chloride at -63°C for 4 h. The products are readily isolated by short path distillation and preparative GLC. The cis and trans-1,3-dimethyl-3,4-dihydro-1H-2-benzopyrans are isolable by preparative GLC.

Presumably the cyclization of the acetals proceeds via the abstraction of alkoxide by the Lewis acid leaving a stabilized oxocarbocation which then undergoes electrophilic attack on the aromatic ring. Finally, elimination of a proton gives the dihydrobenzopyran nucleus (see Scheme II). This pathway is supported by the cyclization of the acetal derived from 1-phenyl-2-propanol and ethyl vinyl ether which was isolated as a 52:48 mixture of two diastereomers. Cyclization of this ca. 50:50 diastereomeric mixture gives cis and trans-1,3-dimethyl-3,4-dihydro-1H-2-benzopyran in an 80:20 ratio, respectively. This product distribution supports an oxocarbocationic intermediate in which the acetal carbon becomes trigonal losing its chirality. The cis isomer is favored presumably because of the methyl groups tending to adopt a pseudo-equational conformation so as to minimize 1,3-diaxial interaction across the oxygen; this effect has been observed previously in pyran chemistry.[20]



SCHEME II

The MEM ethers were prepared from the phenethyl alcohols, MEM chloride and diisopropylethylamine according to the procedure of Corey, Gras, and Ulrich.[21] Both acetals were isolated by fractional distillation at ca. 140° at 0.7 torr. The acetals derived from ethyl vinyl ether were prepared by allowing the phenethyl alcohols to react at 30° with a three-fold excess of ethyl vinyl ether using 85% phosphoric acid as the catalyst. The acetals were isolated by distillation at 95-100° at 0.3 torr. ^{13}C-NMR ($CDCl_3/Me_4Si$) data are listed below.

1-(2-methoxyethoxy)methoxy-2-phenylethane: 36.8, 58.1, 66.9, 68.8, 71.9, 95.6, 126.9, 129.4, 129.8, 139.4

2-(2-methoxyethoxy)methoxy-1-phenylpropane: 19.9, 43.3, 58.3, 66.4, 71.5, 73.5, 83.6, 126.3, 128.5, 130.0, 139.2

1-(1-ethoxyethoxy)-2-phenylethane: 15.4, 19.9, 36.7, 60.4, 65.8, 99.7, 126.6, 128.7, 129.6, 139.5

2-(1-ethoxyethoxy)-1-phenylpropane: 15.2, 20.2, 20.9, 43.7, 59.0, 73.2, 98.8, 126.4, 128.6, 130.0, 139.2 (All non-aromatic peaks occur in pairs with separations ranging from 0.1 to 1.6 ppm.)

The isochromans were prepared from the acetals using a 250-mL three-necked round bottom flask equipped with a magnetic stirring bar, rubber spectum, and a nitrogen inlet vented to a safety bubbler. Under a nitrogen flow the flask was charged with methylene chloride (10 mL per mmole of acetal) and titanium tetrachloride (2 mmole per mmole acetal). The reaction flask was cooled to the appropriate temperature whereupon the acetal was added dropwise via syringe. (Reactions were run with 10-20 mmol of acetal.) The reaction was quenched by adding methanol (0.2 mL per mmole of acetal) and 50 mL of 3 N hydrochloric acid saturated with sodium chloride. After warming to room temperature the organic layer was separated and the aqueous layer extracted with diethyl ether. The benzopyran products were isolated by short path distillation or preparative GLC.

3,4-Dihydro-1H-2-benzopyran: ^{1}H (84% isolated and ^{13}C) NMR ($CDCl_3/Me_4Si$) δ 2.80(t,2,4-CH_2), 3.92(t,2,3-CH_2), 4.72(s,br,2,1-CH_2), ~7.1(m,4, aromatic); δ 68.5 and 66.5 C_1, and C_3, 28.2 C_4; aromatic - 125.0, 127.0, 127.5, 129.8, 132.7, 133.7.

3-Methyl-3,4-dihydro-1H-2-benzopyran: (81% isolated) ^{1}H and ^{13}C NMR ($CDCl_3/Me_4Si$) δ 1.35(d,3,CH_3), 2.67(d,2,4-CH_2), 3.69(m,1,3-C<u>H</u>(CH_3)), 4.79(s,br,2,1-CH_2), ~7.0(m,4,aromatic); δ 68.7 C_1, 71.2 C_3, 36.1 C_4, 22.0 1,3-CH_3; aromatic - 124.8, 126.5, 127.0, 129.2, 134.0, 135.1.

1-Methyl-3,4-dihydro-1H-2-benzopyran: (70% glc) ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.55(d,3,CH_3), ~2.75 and ~3.75 (complex m, 3 and 4-CH_2), 4.82(q, 1, C<u>H</u>(CH_3)), ~7.1(m,4,aromatic); δ 72.7 C_1, 63.9 C_3, 29.7 C_4, 22.1 1,3-CH_3; aromatic - 125.7, 126.9, 127.1, 129.7, 134.1, 140.2.

1,3-Dimethyl-3,4-dihydro-1H-2-benzopyran(cis): (64% glc) ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.25(d,3,3-CH_3), 1.54(d,3,1-CH_3), 2.75(m, 2,4-CH_2), 3.94 and 5.00 (m,1,3, and 1-C<u>H</u>(CH_3)), ~7.1 (m,4,aromatic); δ 73.2 and 70.7 C_1 and C_3, 37.2 C_4, 22.4 1,3-CH_3; aromatic - 125.0, 127.0, 127.1, 129.3, 134.5, 140.2.

1,3-Dimethyl-3,4-dihydro-1-H-2-benzopyran(trans): (16% glc) ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.31, 1.56, 2.75, 3.63, 4.75, and ~7.1 (descriptions similar to the cis isomer); δ 71.0 and 64.1 C_1 and C_3, 36.5 C_4, 21.6 and 22.5 1,3-CH_3; aromatic - 126.0, 126.7, 126.9, 129.6, 133.8, 139.8.

The ease with which a variety of acetals can be prepared with phenethyl alcohols, the many available Lewis acids, and the mild reaction conditions suggest that this approach to isochroman structures may have reasonable applicability.[22]

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