SYNTHESIS OF 6,7-DIHYDRO-10-TRIDEUTEROMETHYL-6,8,8-TRIMETHYL-8H-PYRANO[3,2-g]CHROMONE-2-CARBOXYLIC ACID

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SUMMARY

Synthesis of 6,7-dihydro-10-trideuteromethyl-6,8,8-trimethyl-8H-pyrano[3,2-g]chromone-2-carboxylic acid (10) in high isotopic purity is described. The trideuteromethylation was achieved by sodium borodeuteride reduction of the ethoxycarbonyl derivative (5) of 7-hydroxy-2,2,4-trimethylchroman-8-carboxylic acid (4). This labelled compound (10) is required for use as mass spectrometric stable isotope internal standard for the study of metabolic fate of 6,7-dihydro-6,8,8,10-tetramethyl-8H-pyrano[3,2-g]chromone-2-carboxylic acid (9), which is an orally active antiallergic agent.

Key Words: Antiallergic Agent, Sodium Borodeuteride, Trideuteromethylation

In a search for the orally active antiallergic agents possessing a mode of action similar to that of disodium cromoglycate,[1] 6,7-dihydro-6,8,8,10-tetramethyl-8H-pyrano[3,2-g]chromone-2-carboxylic acid (9) was found to possess antiallergic activity in the rat passive cutaneous anaphylaxis (PCA) model and to show the activity when administered in rats.[2]

In this paper I describe the synthesis of 6,7-dihydro-10-trideuteromethyl-6,8,8-trimethyl-8H-pyrano[3,2-g]chromone-2-carboxylic acid (10), which was used as mass spectrometric stable isotope internal standard for the study of metabolic fate of 9 in animals.

2,6-Dihydroxybenzoic acid (1) was converted into the methylester (2) by refluxing with methanol in the presence of sulfuric acid. The reaction of 2 with 2-methyl-2,4-pentanediol in the presence of sulfuric acid in ethyl acetate gave methyl 7-hydroxy-2,2,4-trimethylchroman-8-carboxylate (3), and then 3 was hydrol-

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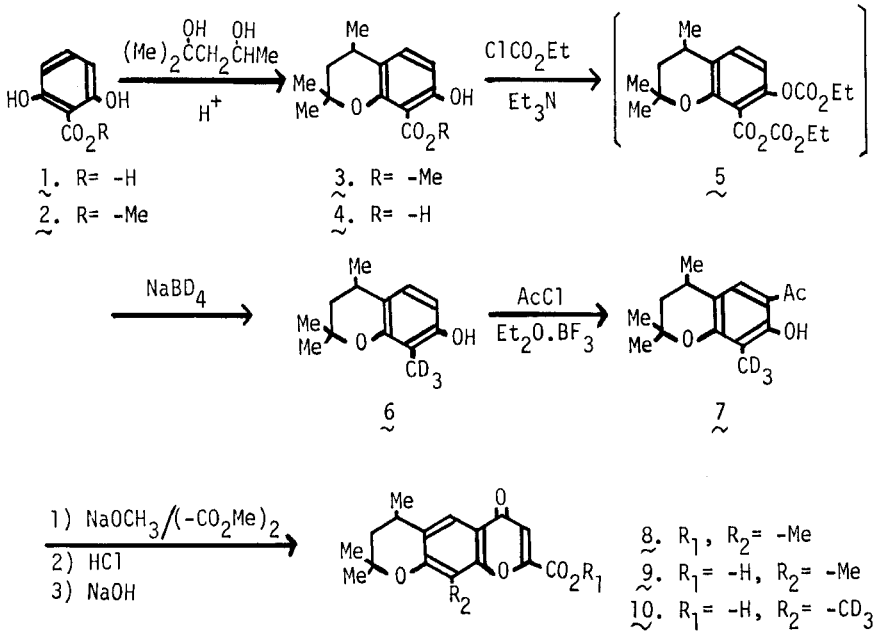
ysised to the carboxylic acid (4). In the previous paper[3] we reported that the ethoxycarbonyl derivative of salicylic acid was reduced with sodium borohydride to give o-cresol. In this case, when sodium borodeuteride ($NaBD_4$) was used instead of sodium borohydride, o-trideuteromethylphenol was obtained. The ethoxy-



1. R= -H
2. R= -Me
3. R= -Me
4. R= -H
5
6
7
8. R_1, R_2= -Me
9. R_1= -H, R_2= -Me
10. R_1= -H, R_2= $-CD_3$

carbonyl derivative (5) was prepared from 4 and 2 equivalents of ethyl chloroformate in the presence of 2 equivalents of triethylamine in tetrahydrofuran and was added to an aqueous solution of sodium borodeuteride. 7-Hydroxy-8-trideuteromethyl-2,2,4-trimethylchroman (6) was obtained in 47.9% yield. The presence of the trideuteromethyl group in the 8-position of 6 caused the anticipated shift of three mass units in the parent peak (206→209) and the base peak (151→154) of mass spectrum, and the peak of aromatic methyl group was hardly detected in NMR spectrum of 6. These mean that the carboxyl group of 4 was reduced to the trideuteromethyl group. Reaction of 6 with acetyl chloride in boron trifluoride etherate gave 6-acetyl-7-hydroxy-8-trideuteromethyl-2,2,4-trimethylchroman (7), and then 7 was converted to the acylpyruvate derivative by reaction with dimethyl oxalate in the presence of sodium methoxide. The acylpyruvate derivative was cyclized to methyl 6,7-dihydro-10-trideuteromethyl-6,8,8-trimethyl-8H-pyrano[3,2-g]-chromone-2-carboxylate (8) under acidic conditions, giving a 59.0% yield from

6. 8 was converted 10 in 93.0% yield by hydrolysis with sodium hydroxide in ethanol-water below 10°. The presence of the trideuteromethyl group in the 10-position of 10 gave a parent peak at m/e 305 and the base peak at m/e 250 in the mass spectrum, and hardly showed the peak of the aromatic methyl group in NMR spectrum. These mean that the desired compound 10 was obtained.

EXPERIMENTAL

All melting points are uncorrected. Infrared (IR) spectra were measured with a Hitachi-215 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured with a JEOL PS-100 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were measured with a JEOL TMS-OISG spectrometer. Sodium borodeuteride ($NaBD_4$) was purchased from E.MERCK (deuteration degree not less than 98%).

Methyl 2,6-dihydroxybenzoate (2)

A solution of 2,6-dihydroxybenzoic acid (1) (50.0g, 0.32 mol) and conc.H_2SO_4 (30 ml) in methanol (500 ml) was refluxed for 5 hr. After removal of methanol, the residue was diluted with water and extracted with ether. The organic layer was washed with water, 5% aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of solvent, the residue was recrystallized from n-hexane-ether to give 2 in 29.3% yield (16 g). mp 150°. IR (Nujol) : 3400 (-OH), 1650 (>C=O) cm^{-1}. NMR (in $CDCl_3$) δ : 4.00 (3H, s, $-OCH_3$), 6.40 (2H, d, 2 x aromatic H), 7.30 (1H, t, aromatic H), 9.50 (2H, s, 2 x -OH).

Methyl 7-hydroxy-2,2,4-trimethylchroman-8-carboxylate (3)

2-Methyl-2,4-pentanediol (8.9 g, 0.075 mol) was added to a solution of 2 (8.4 g, 0.05 mol) and conc.H_2SO_4 (3 ml) in ethyl acetate (50 ml) at 60° over a period of 30 min. After refluxing for 30 min, the reaction mixture was washed with water, 5% aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed on silica gel using n-hexane-ether (5: 1) as an eluent to provide 3 as colorless oil in 18.4% yield (2.3 g). The fractions eluted with n-hexane-ether (3: 1) afforded 4.3 g of 2 (recovery). IR (Liquid) : 1650 (>C=O) cm^{-1}. NMR (in $CDCl_3$) δ : 1.20 (3H, s, $-CH_3$), 1.25 (3H, d, $-CH_3$), 1.40 (3H, s, $-CH_3$), 1.50 -2.00 (2H, m, $>CH_2$), 2.50 - 3.00 (1H, m, $\rightarrow$CH), 6.40 (1H, d, aromatic H), 7.20 (1H, d, aromatic H), 11.20 (1H, s, -OH).

7-Hydroxy-2,2,4-trimethylchroman-8-carboxylic acid (4)

A solution of 3 (2.2 g, 8.8 m mol) in ethanol (20 ml) was mixed with 10% aqueous NaOH (20 ml) and refluxed for 30 min. The reaction mixture was diluted with water, made acidic with dil.HCl and extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. After removal of solvent, the residue was recrystallized from ether-n-hexane to give 4 in 72.2% yield (1.5 g). mp 131 - 135°. IR (Nujol) : 3300 - 2500 (-OH), 1680 (>C=O) cm^{-1}. NMR (in $CDCl_3$)δ : 1.30 (3H, d, $-CH_3$), 1.40 (3H, t, $-CH_3$), 1.55 (3H, t, $-CH_3$), 1.70 - 2.20 (2H, m, $>CH_2$), 2.60 - 3.20 (1H, m, >CH), 6.60 (1H, d, aromatic H), 7.35 (1H, d, aromatic H), 11.80 (1H, s, -OH), 12.00 (1H, s, -OH).

7-Hydroxy-8-trideuteromethyl-2,2,4-trimethylchroman (6)

To a solution of 6 (4.72 g, 20 m mol) and triethylamine (4.45 g, 44 m mol) in tetrahydrofuran (40 ml) was added ethyl chloroformate (4.78 g, 44 m mol) at 0 - 5° over a period of 30 min, and the whole was stirred for 20 min at the same temperature. The white precipitate (triethylammonium chloride) was filtered off, washed with tetrahydrofuran, and the combined filtrate was added to a solution of sodium borodeuteride (3.35 g, 80 m mol) in water (50 ml) at 5 - 15° with stirring over a period of 30 min. After stirring at room temperature for 2 hr, the reaction mixture was diluted with water, made acidic with dil.HCl and extracted with ether. The organic layer was washed with water, 5% aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed on silica gel using n-hexane-ether (6: 1) as an eluent to provide 6 as a solid of mp 121 - 123° in 47.9% yield (2.01 g). IR (Nujol) : 3450 (-OH) cm^{-1}. NMR (in $CDCl_3$)δ : 1.20 (3H, s, $-CH_3$), 1.25 (3H, d, $-CH_3$), 1.40 (3H, s, $-CH_3$), 1.60 - 2.00 (2H, m, $>CH_2$), 2.50 - 3.10 (1H, m, >CH), 5.00 (1H, broad, -OH), 6.30 (1H, d, aromatic H), 6.90 (1H, d, aromatic H). MS (m/e) : 209 (M^+), 154 (base peak).

6,7-Dihydro-10-trideuteromethyl-6,8,8-trimethyl-8H-pyrano(3,2-g)chromone-2-carboxylic acid (10)

A mixture of 6 (1.88 g, 9.0 m mol), boron trifluoride etherate (10 ml) and acetyl chloride (0.85 g, 10.8 m mol) was heated at 60 - 70° for 1.5 hr. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with water, 2% aqueous NaOH and dried over $MgSO_4$. After removal of

solvent, the residue (1.69 g) was used in the next step without purification. IR (Nujol) : 1630 (>C=O) cm^{-1}. A solution of the crude 7 (1.69 g) and dimethyl oxalate (3.1 g, 27 m mol) in tetrahydrofuran (20 ml) was added to a solution of sodium methoxide (6.9 ml of 28% methanolic $NaOCH_3$, 35.8 m mol) in tetrahydrofuran (45 ml) at 60° over a period of 45 min. After stirring at the same temperature for 30 min, the reaction mixture was diluted with water, made acidic with dil.HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$. After removal of solvent, the residue was dissolved in methanol (25 ml) containing conc.HCl (1.0 ml) and refluxed for 1 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed on silica gel using n-hexane-ether (3: 1) as an eluent to provide 8 as a solid of mp 150 - 152° in 59.0% yield (1.70 g). IR (Nujol) : 1735 (>C=O) cm^{-1}. Aqueous NaOH (4%, 6.0 ml) was added to a solution of 8 (1.6 g, 5.0 m mol) in ethanol (50 ml) below 10° . After stirring below 10° for 2 hr, the reaction mixture was made acidic with dil.HCl and extracted with ethyl acetate. The organic layer was extracted with 5% aqueous $NaHCO_3$ and the aqueous layer was made acidic with dil.HCl and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$. After removal of solvent, the residue was recrystallized from n-hexane-ether to give 10 as crystals of mp 276 - 278° in 93.0% yield(1.42 g). IR (Nujol) : 1720 (>C=O), 1625 (>C=O) cm^{-1}. NMR (in $CDCl_3$)δ : 1.36 (3H, s, $-CH_3$), 1.44 (3H, d, $-CH_3$), 1.52 (3H, s, $-CH_3$), 1.90 - 2.20 (2H, m, $>CH_2$), 2.90 - 3.30 (1H, m, >CH), 6.94 (1H, s, =CH), 7.94 (1H, s, aromatic H). MS (m/e) : 305 (M^+), 250 (base peak). Deuteration degree of the methyl group of 10-position was found to be not less than 95% by measurement of the NMR spectrum.

REFERENCES

1. Cairns H., Hunter F.D., Johnson P.B., King J., Lee T.B., Lord G.H., Minshull R. and Cox J.S.G.-J. Med. Chem. 15: 583 (1972); Cox J.S.G.-Adv. Drug. Res. 5: 115 (1970)
2. The 99th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, Aug., 1979.
3. Minami N. and Kijima S.-Chem. Pharm. Bull. (Tokyo), 27: 816 (1979)