The Syntheses of Ripariochromene A and Methylripariochromene A[1)]

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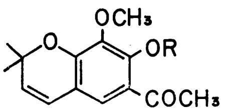
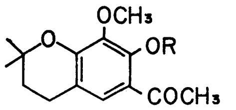
7,8-Dimethoxy-2,2-dimethylchroman was obtained from pyrogallol trimethyl ether and β,β-dimethylacrylyl chloride *via* the corresponding chroman-4-one. The Friedel-Crafts reaction of the chroman with acetyl chloride yielded 6-acetyl-7-hydroxy-8-methoxy-2,2-dimethylchroman. The dehydrogenation of the acetylchroman with DDQ in anhydrous benzene afforded ripariochromene A. Ripariochromene A was converted into methylripariochromene A

Ripariochromene A has recently been isolated, along with several chromenes, from Australian *Eupatorium riparium* Regel.[2)] Its structure has been shown to be 6-acetyl-7-hydroxy-8-methoxy-2,2-dimethylchromene (I), with an unique 1,2,3-trioxygenated pattern, on the basis of the spectral evidence.[2)] Methylripariochromene A (the methyl ether of I) (II) also has been isolated from Australian[2)] and Jamaican *E. riparium* Regel.[3)] The present paper will describe the syntheses of I[4)] and II from 7,8-dimethoxy-2,2-dimethylchroman (III).



I R=H
II R=CH_3
X R=CH_3CO



VIII R=H
IX R=CH_3CO

The condensation of pyrogallol trimethyl ether (IV) and β,β-dimethylacrylyl chloride (V) in the presence of anhydrous aluminum chloride over a 52 hr period gave 7,8-dimethoxy-2,2-dimethylchroman-4-one (VI). When the above condensation was allowed to proceed for a relatively short period of time, 2-hydroxy-3,4-dimethoxyphenyl 2-methyl-1-propenyl ketone (VII) was obtained, along with a small amount of VI. The NMR spectra of VI and VII showed the presence of one methylene group (δ 2.68 ppm) and one hydrogen-bonded hydroxyl group (δ 13.13 ppm) respectively. The ketone (VII) was easily converted into the chromanone (VI) when heated with ethanolic hydrochloric acid or acetic acid. The Clemmensen-reduction of VI or the hydrogenolysis of the thioketal of VI with Raney nickel gave the chroman (III).[5)] The hydrogenolysis afforded III in a better yield than did the Clemmensen-reduction. The Friedel-Crafts reaction of III with acetyl chloride gave 6-acetyl-7-hydroxy-8-methoxy-2,2-dimethylchroman (VIII) (δ 2.52 ppm). The dehydrogenation[6—8)] of VIII with 2,3-dichloro-5,6-dicyano-*p*-quinone (DDQ) in anhydrous benzene gave the desired chromene (I) (mp 89.5—90.5 °C),[1)] which was shown to be identical with natural ripariochromene A on the basis of a mixed-melting-point determination and by NMR, infrared, and ultraviolet spectral comparisons.

The chromene (I) was easily converted into the methyl ether (II) (colorless liquid).[2)] The properties of this synthetic chromene (II) were in full accord with those of natural methylripariochromene A.

Experimental[9)]

2-Hydroxy-3,4-dimethoxyphenyl 2-Methyl-1-propenyl Ketone (VII). With stirring and cooling at 0 °C, β,β-dimethylacrylyl chloride (5.2 g) was added, drop by drop, to a solution of anhydrous aluminum chloride (6.5 g), pyrogallol trimethyl ether (5.6 g), and anhydrous ether (100 ml). After stirring at room temperature for 6 hr, the mixture was poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate and water, dried, and evaporated. The residue was recrystallized from a mixture of acetone and *n*-hexane to give yellow needles (mp 66.5—67 °C), which gave a dark green ferric chloride reaction in ethanol; yield, 5.5 g (70%). IR: 1642 cm^{-1}. NMR: ($CDCl_3$) 2.03_s, 2.19_s ($2\times CH_3$); 3.88_s, 3.90_s ($2\times CH_3O$); 6.46_d (C_5-H), 7.55_d (C_6-H) (each J=9 Hz); 6.70_{bs} (CH=C); 13.13_s (OH).

Found: C, 65.93; H, 6.88%. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83%.

7,8-Dimethoxy-2,2-dimethylchroman-4-one (VI). The ketone (VII) (3 g) was heated under reflux with ethanol containing 2 M hydrochloric acid (100 ml) for 3 hr. After removing the ethanol under reduced pressure, the residue was poured into cold water (50 ml) and extracted with ether. The ethereal extract was washed with 5% aqueous sodium carbonate and water, dried, and evaporated. The residue was then recrystallized from aqueous ethanol to give colorless needles; mp 75—75.5 °C; yield, 2.7 g (90%). IR: 1693 cm^{-1} (Nujol). NMR: ($CDCl_3$) 1.44_s ($2\times CH_3$); 2.68_s (CH_2); 3.80_s, 3.89_s ($2\times CH_3O$); 6.55_d (C_6-H), 7.61_d (C_5-H) (each J=9 Hz).

Found: C, 66.14; H, 6.77%. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83%.

The ketone (VII) was also converted into the chroman-4-one (VI) in boiling glacial acetic acid containing a small amount of concentrated hydrochloric acid.

The chromanone (VI) was also obtained along with a small amount of the ketone (VII) by the Friedel-Crafts reaction of pyrogallol trimethyl ether with β,β-dimethylacrylyl chloride in anhydrous ether at room temperature for 52 hr. It gave a mp of 75—75.5 °C and a mixed mp of 75—75.5 °C with the above chromanone.

7,8-Dimethoxy-2,2-dimethylchroman (III). A mixture of the chromanone (VI) (2.7 g), anhydrous sodium sulfate (2 g), freshly-fused zinc chloride (2.5 g), and ethyl mercaptan (20 ml) was allowed to stand overnight in a refrigerator, and then for 3 hr at room temperature. The mixture was subsequently poured into cold water (50 ml) and extracted with ether. The ethereal layer was washed with 10% aqueous sodium hydroxide, water, dried, and evaporated. The residue gave a thioketal (colorless liquid) (3.8 g). The crude thioketal (3.8 g) was refluxed with Rany nickel (80 g) in ethanol (100 ml) for 3 hr to give III (colorless liquid) (2 g, 72%), which was purified by column chromatography on silica gel with chloroform. IR: 1498, 1582, 1613 cm^{-1} (liquid). NMR: (CDCl$_3$) 1.35$_s$ (2×CH$_3$); 1.78$_t$ (C$_3$–H), 2.72$_t$ (C$_4$–H) (each 2H, J=7 Hz); 3.80$_s$ (2×CH$_3$O); 6.40$_d$ (C$_6$–H), 6.74$_d$ (C$_5$–H) (each J=9 Hz).

The chroman (III) was also prepared by the Clemmensen-reduction described by Schwarz *et al.* (yield, 22%).⁵⁾

6-Acetyl-7-hydroxy-8-methoxy-2,2-dimethylchroman (VIII). The acetylation of the chroman (III) (2.5 g) with acetyl chloride (3 g) and anhydrous aluminum chloride (4 g) in anhydrous ether (50 ml) at room temperature gave, in the course of 6 hr, the desired acetyl chroman, VIII. It was then recrystallized from aqueous ethanol to give colorless needles (2.3 g; 45%; mp 97—98 °C) and gave a brown ferric chloride reaction in ethanol. IR: 1640 cm^{-1}. UV: $\lambda_{\max}^{\mathrm{EtOH}}$ nm(log ε); 222.5 (4.30), 238 (4.00), 288 (4.22), 327 (3.66). NMR: (CDCl$_3$) 1.40$_s$ (2×CH$_3$); 1.83$_t$ (C$_3$–H), 2.76$_t$ (C$_4$–H) (each 2H, J=7 Hz); 2.52$_s$ (CH$_3$CO); 3.84$_s$ (CH$_3$O); 7.26$_s$ (C$_5$–H); 12.40$_s$ (OH).

Found: C, 67.19; H, 7.03%. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

Acetate (IX). The acetic anhydride–pyridine method; mp 143—144 °C (colorless needles from aqueous ethanol); a negative ferric chloride reaction. IR: 1670, 1762 cm^{-1}. NMR: (CDCl$_3$) 1.39$_s$ (2×CH$_3$); 1.83$_t$ (C$_3$–H), 2.83$_t$ (C$_4$–H) (each 2H, J=7 Hz); 2.37$_s$, 2.48$_s$ (2×CH$_3$CO); 3.80$_s$ (CH$_3$O); 7.38$_s$ (C$_5$–H).

Found: C, 65.92; H, 6.97%. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90%.

6-Acetyl-7-hydroxy-8-methoxy-2,2-dimethylchromene (Ripariochromene A) (I). The chroman (VIII) (0.3 g) and DDQ (0.32 g) in anhydrous benzene (60 ml) were heated under reflux for 3 hr, and then the benzene was removed under reduced pressure. The residue was purified by column chromatography on silica gel with petroleum ether–ethyl acetate (9: 1) to give the desired chromene. It was recrystallized from petroleum ether to give colorless needles (mp 89.5—90.5 °C, not depressed by mixture with nautral riperiochromene A (lit, mp 88.5 °C²⁾)) and gave a light blue ferric chloride reaction in ethanol; yield, 0.11 g (37%). IR: 1635 cm^{-1}. UV: $\lambda_{\max}^{\mathrm{EtOH}}$ nm(log ε); 258 (4.57), 293 (3.89), 348 (3.64). NMR: (CDCl$_3$) 1.47$_s$ (2×CH$_3$); 2.52$_s$ (CH$_3$CO); 3.88$_s$ (CH$_3$O); 5.58$_d$ (C$_3$–H), 6.27$_d$ (C$_4$–H) (each J=9 Hz); 7.10$_s$ (C$_5$–H); 12.80$_s$ (OH).

Found: C, 67.65; H, 6.35%. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%.

6-Acetyl-7,8-dimethoxy-2,2-dimethylchromene (Methylripariochromene A) (II). The chromene (I) (49 mg) was refluxed with dimethyl sulfate (0.4 g) and anhydrous potassium carbonate (0.6 g) in anhydrous acetone (30 ml) for 24 hr, and then the acetone was removed. The mixture was extracted with ether, and the ethereal extract was washed with dilute hydrochloric acid and water, dried, and evaporated. The residue was purified by column chromatography on silica gel with chloroform to give the methyl ether²⁾ (colorless liquid) (48 mg, 92%), which gave a negative ferric chloride reaction. IR: 1673 cm^{-1} (CCl$_4$). UV: $\lambda_{\max}^{\mathrm{EtOH}}$ nm(log ε); 255 (4.24), 290 (3.68). NMR: (CDCl$_3$) 1.47$_s$ (2×CH$_3$); 2.57$_s$ (CH$_3$CO); 3.85$_s$, 3.94$_s$ (2×CH$_3$O); 5.57$_d$ (C$_3$–H), 6.28$_d$ (C$_4$–H) (each J=9 Hz); 7.20$_s$ (C$_5$–H).

Found: C, 68.60; H, 7.22%. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.93%.

Acetate (X). The acetic anhydride–pyridine method; colorless liquid; a negative ferric chloride reaction. IR: 1676, 1767 cm^{-1}. NMR: (CDCl$_3$) 1.48$_s$ (2×CH$_3$); 2.35$_s$, 2.45$_s$ (2×CH$_3$CO); 3.82$_s$ (CH$_3$O); 5.63$_d$ (C$_3$–H), 6.30$_d$ (C$_4$–H) (each J=9 Hz); 7.29$_s$ (C$_5$–H).

Found: C, 66.26; H, 6.26%. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25%.

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9) All the melting points are uncorrected. The NMR spectra were measured with a Hitachi R-20 spectrometer (60 MHz), using tetramethylsilane as the internal standard (δ, ppm): s, singlet; d, doublet; t, triplet; b, broad; bs, broad singlet.