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SYNTHESIS OF THE 6-METHYL AND 6,8-DIMETHYL ETHERS OF RHODOCOMATULIN

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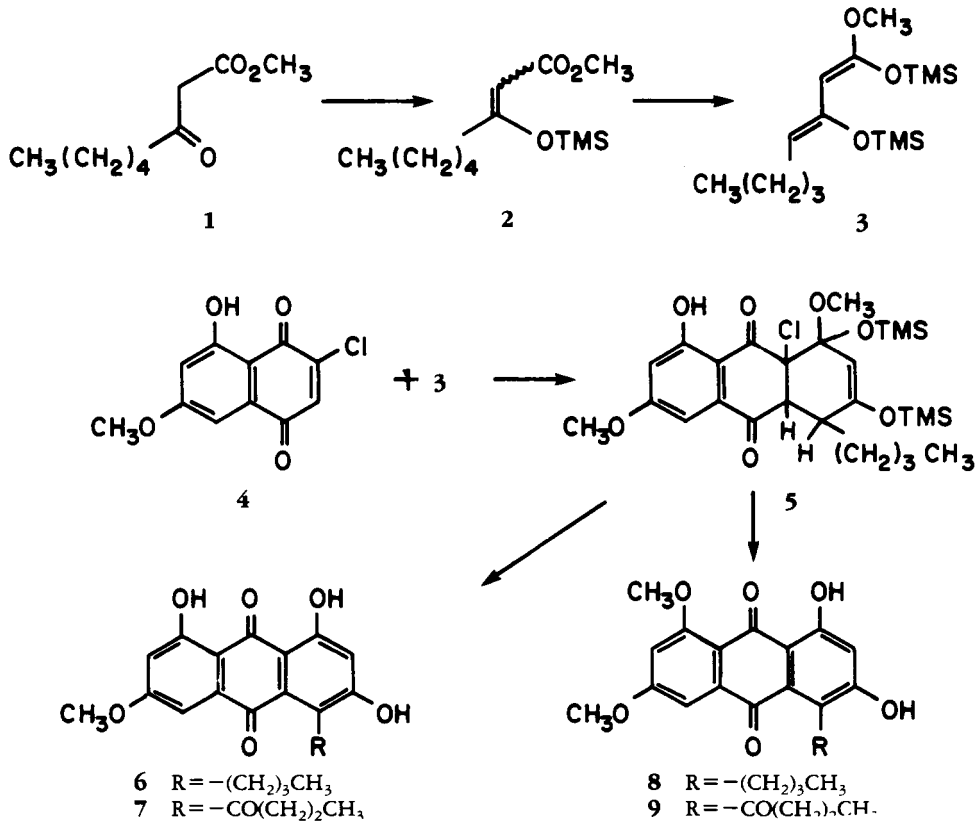
ABSTRACT.—The structures proposed for the 6-methyl and 6,8-dimethyl ethers of rhodocomatulin, two naturally occurring crinoid pigments, have been confirmed by synthesis.

The substitution pattern in the naturally occurring ethers of rhodocomatulin (1-3) has been established by an unambiguous elaboration of the permethylated product (4), but no synthesis of the actual pigments has been recorded. Inasmuch as regiospecific preparations of quinones allow simple syntheses of partially methylated derivatives of polyhydroxylated compounds (5), specific confirmation of the structures of these metabolites was sought.

The diene used in our earlier work (4), 1,1-dimethoxy-3-trimethylsiloxy-1,3-octadiene, was replaced by the more versatile 1-methoxy-1,3-bistrimethylsiloxy derivative [**3**], which is readily obtained by double enolsilylation of methyl 3-oxooctanoate [**1**] (6). Cycloaddition of diene **3** to 3-chloro-5-hydroxy-7-methoxynaphthoquinone [**4**] (7) proceeded slowly in refluxing C_6H_6 but, when carried out without solvent, was complete in 30 h at room temperature. The adduct was hydrolyzed by concentrated HCl in THF to preclude formation of the 1-methyl ether (8,9) and was aromatized by refluxing in the same medium. Photochemical oxidation (4) of the resulting 4-butylanthraquinone afforded a 69% yield of 6-*O*-methylrhodocomatulin [**7**] identical to an au-



thentic sample and established that the oxidation process is even more effective for the actual metabolite than it had been previously for the permethylated model.

Preparation of the 6,8-dimethyl ether can result from the addition of the foregoing reagent, **3**, to 3-chloro-5,7-dimethoxy naphthoquinone. However, in view of the low reactivity of such substrates and of the fact that this quinone had previously given a small amount of the "wrong" regioisomer even under favorable conditions (7), it was deemed prudent to avoid such a starting material. At this point a novel modification was introduced that allows for a significant increase in the flexibility of the approach. It was observed that unprotected hydroxyl groups in an adduct such as **5** could be methylated readily by MeI in the presence of Ag_2O without affecting other sensitive features of the molecule. In this way adduct **5** was selectively methylated in the 8-position, and after hydrolysis, aromatization, and photoxidation, an unambiguous synthesis of rhodocomatulin 6,8-dimethyl ether [**9**] was provided.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mps were taken in capillary tubes with a Thomas-Hoover apparatus and are not corrected. The uv spectra were determined on a Hewlett-Packard 8450A spectrophotometer; the ir spectra on a Beckman model IR-4250 instrument calibrated with a film of polystyrene. ^{1}H-nmr spectra were recorded with a Varian XL-200 spectrometer using TMS as internal standard. Mass spectra were obtained with a Hewlett-Packard 5995A spectrometer. Merck Si gel $60F_{254}$ for dry column chromatography was used throughout in a product-to-adsorbent ratio of 1:50-100. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN.

METHYL 3-TRIMETHYLSILOXYOCT-2-ENOATE [**2**].—To a fine suspension of anhydrous $ZnCl_2$ (600 mg) in dry triethylamine (33.4 g; 0.33 mol) were added successively methyl 3-oxooctanoate (25.8 g; 0.15 mol) in dry C_6H_6 (50 ml) (40 min) and chlorotrimethylsilane (32.6 g; 0.30 mol) (1 h) (10). The mixture was stirred at 25° for 2 h, warmed to 40° for 16 h, cooled, and diluted with petroleum ether, bp 35-60° (250 ml). After filtration, the volatile fractions were evaporated, and the last operation was repeated until salts no longer precipitated. Distillation of the residue under vacuum gave methyl 3-trimethylsiloxyoct-2-enoate (32.6 g; 89%), bp 79-83°/0.45 mmHg, as a 3.3:1 mixture of *E*- and *Z*-isomers; ir ν max (KBr) cm^{-1} 1720, 1625, 1255, 845; ^{1}H nmr ($CDCl_3$) δ 0.26 (s, *Z*-3-OTMS), 0.27 (s, *E*-3-OTMS), 0.89 (t, J=6.7 Hz, 8-H), 1.27-1.37 (m, 6,7-H), 1.45-1.59 (m, 5-H), 2.09 (t, J=7.5 Hz, *Z*-4-H), 2.70 (t, J=7.5 Hz, *E*-4-H), 3.66 (s, 1-OCH_3), 5.07 (s, *E*-2-H), 5.12 (s, *Z*-2-H). *Anal.* calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 59.20; H, 9.89.

1-METHOXY-1,3-BIS(TRIMETHYLSILOXY)-1,3-OCTADIENE [**3**].—To a solution of LDA prepared at 0° from dry diisopropylamine (11.1 g; 0.11 mol) in anhydrous THF (100 ml) and a 1.6 M solution of *n*-butyllithium in hexane (73 ml; 0.12 mol), stirred for 15 min and then cooled to −78°, were added methyl 3-trimethylsiloxyoct-2-enoate [**2**] [24.4 g; 0.10 mol, in THF (30 ml)] (70 min). After 30 min chlorotrimethylsilane (16.3 g; 0.15 mol) in the same solvent (30 ml) was added over a period of 2 h. The mixture was allowed to warm to room temperature, concentrated, diluted with petroleum ether bp 30-60° (300 ml), filtered, and evaporated. This operation was repeated until salts were no longer precipitated. Distillation of the residue gave the octadiene **3**, bp 101-108°/0.5 mm Hg (30.2 g; 96%) as a mixture of stereoisomers of which one (ca. 70%) was largely predominant; ir ν max (KBr) cm^{-1} 1655, 1615, 1250, 845; ^{1}H nmr ($CDCl_3$) (principal isomer) δ 0.18 (9H, s, 3-OTMS), 0.23 (9H, s, 1-OTMS), 0.89 (3H, t, J=7.0 Hz, 8-H), 1.26-1.37 (4H, m, 6,7-H), 2.06 (2H, q, J=7.0 Hz, 5-H), 3.52 (3H, s, 1-OCH_3), 3.89 (1H, s, 2-H), 4.88 (1H, t, J=7.0 Hz, 4-H). Elemental analyses were not attempted on this product.

4-BUTYL-1,3-8-TRIHYDROXY-6-METHOXYANTHRAQUINONE [**6**].—A mixture of 3-chloro-5-hydroxy-7-methoxynaphthoquinone [**4**] (119 mg; 0.50 mmol) and diene **3** (475 mg; 1.50 mmol) was stirred at room temperature for 30 h and diluted with THF (10 ml) and 12 N HCl (1.0 ml). The resultant solution was stirred at 25° for 1 h, refluxed for 1 h, cooled, poured into Et_2O (150 ml), and washed with H_2O (3×50 ml). The residue was triturated with petroleum ether, bp 30-60° and, upon purification by chromatography (CH_2Cl_2 then CH_2Cl_2-EtOAc, 20:1), gave the anthraquinone **6** (157 mg; 92%), mp 201° ($CHCl_3$); uv λ max (EtOH 95%) nm (log ϵ) 225 (4.49), 258 sh (4.28), 264 (4.30), 298 (4.28), 458 (4.08); ir ν max (KBr) cm^{-1} 3270 br, 1620, 1600, 1560; ^{1}H nmr [$(CD_3)_2CO$)] δ 0.97 (3H, t, J=7.0 Hz, 4′-H, 1.43-1.56 (4H, m, 2′,3′-H), 3.07 (2H, t, J=7.4 Hz, 1′-H), 3.96 (3H, s, 6-OCH_3), 6.65 (1H, s, 2-H), 6.66 (1H, d, J=2.7 Hz, 7-H), 7.14 (1H, d, J=2.7 Hz, 5-H), 12.20 and 12.84 (2×1H, 2s, 1,8-OH); ms *m/z* 342 $[M]^+$ (30), 300 $[M-C_3H_6]^+$ (59), 299 $[M-C_3H_7]^+$ (100). *Anal.* calcd for $C_{19}H_{18}O_6$: C, 66.67; H, 5.30. Found: C, 66.42; H, 5.47.

4-BUTANOYL-1,3,8-TRIHYDROXY-6-METHOXYANTHRAQUINONE (RHODOCOMATULIN 6-METHYL ETHER) [7].—Oxygen was slowly bubbled into a boiling solution of butylanthraquinone **6** (50 mg; 0.15 mmol) in absolute EtOH (20 ml) that was simultaneously irradiated (110 min) with a 500 watt lamp (Sylvania Superflood EbW). Purification of the crude product by chromatography (CH_2Cl_2-EtOAc, 10:1 then 5:1) afforded rhodocomatulin 6-methyl ether [7] (36 mg; 69%), mp 250.5-251.5° (absolute EtOH) [lit. (1) 250-252° (dec)] indistinguishable (ir, mmp, tlc in four solvent systems) from an authentic sample; uv λ max (EtOH 95%+1% HOAc) nm (log ε) 228 (4.30), 256 (4.18), 263 (4.19), 293 (4.37), 318 (3.90), 366 (3.43), 456 (3.98); ir ν max (KBr) cm^{-1} 3060 br, 1680, 1670, 1630, 1600, 1550; ^1H nmr [$(CD_3)_2CO$] δ 1.02 (3H, t, J=7.3 Hz, 4′-H), 1.80 (2H, sex, J=7.3 Hz, 3′-H), 2.71 (2H, t, J=7.3 Hz, 2′-H), 3.99 (3H, s, 6-OCH_3), 6.73 (1H, s, 2-H), 6.77 (1H, d, J=2.6 Hz, 7-H), 7.19 (1H, d, J=2.6 Hz, 5-H), 12.21 and 12.46 (2×1H, 2s, 1,8-OH); ms *m/z* 356 $[M]^+$ (15), 314 $[M-C_3H_6]^+$ (10), 313 $[M-C_3H_7]^+$ (100). *Anal.* calcd for $C_{19}H_{16}O_7$: C, 64.04; H, 4.53. Found: C, 63.77; H, 4.35.

4-BUTYL-1,3-DIHYDROXY-6,8-DIMETHOXYANTHRAQUINONE [8].—A mixture of naphthoquinone **4** (119 mg; 0.50 mmol) and diene **3** (475 mg; 1.50 mmol) was stirred at room temperature for 35 h, and the adduct thus formed was dissolved in dry $CHCl_3$ (15 ml). Freshly prepared silver (I) oxide (1.2 g; 5.2 mmol) and iodomethane (0.5 ml; 80 mmol) were then added, and the suspension was stirred in the dark at 25° for 45 h (equal portions of the iodide were introduced after 12 and 25 h). The mixture was diluted with Et_2O (150 ml), washed with H_2O, dried, and freed of solvent. After triturating with petroleum ether, bp 30-60°, the crude product was purified by chromatography (C_6H_6-EtOAc, 5:1) and yielded the anthraquinone **8** (150 mg; 84%), mp 220-220.5° (dec) (C_6H_6); uv λ max (EtOH 95%) nm (log ε) 224 (4.54), 259 sh (4.30), 266 (4.32), 292 (4.32), 358 (3.55), 450 (4.01); ir ν max (KBr) cm^{-1} 3320, 1670, 1625, 1595, 1545; ^1H nmr [$(CD_3)_2CO$] δ 0.96 (3H, t, J=7.0 Hz, 4′-H), 1.41-1.60 (4H, m, 2′,3′-H), 3.05 (2H, t, J=7.0 Hz, 1′-H), 3.95 and 3.97 (2×3H, 2s, 6,8-OCH_3), 6.64 (1H, s, 2-H), 6.85 (1H, d, J=2.8 Hz, 7-H), 7.22 (1H, d, J=2.8 Hz, 5-H), 9.74 (1H, br s, 3-OH), 14.05 (1H, s, 1-OH); ms *m/z* 356 $[M]^+$ (40), 314 $[M-C_3H_6]^+$ (23), 313 $[M-C_3H_7]^+$ (100). *Anal.* calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.41; H, 5.79.

4-BUTANOYL-1,3-DIHYDROXY-6,8-DIMETHOXYANTHRAQUINONE (RHODOCOMATULIN 6,8-DIMETHYL ETHER) [9].—In a procedure similar to the one used for the preparation of quinone **7**, rhodocomatulin 6,8-dimethyl ether [9] was obtained from anthraquinone **8** (50.0 mg; 0.14 mmol) (100 min). Purification of the crude product by chromatography (CH_2Cl_2-EtOAc, 5:1) gave the desired substance **9** (33 mg; 63%), mp 208.5-209° which solidifies and melts again at 226.5-228° (dec.) [lit. (1) 208.5-209° and 229.5-230.5°] identical (ir, mmp and tlc in four solvent systems) to a sample of the natural product; uv λ max (EtOH 95%+1% HOAc) nm (log ε) 229 (4.42), 253 (4.17), 266 sh (4.23), 287 (4.45), 314 sh (3.98), 361 (3.59), 380 (3.54), 448 (3.94); ir ν max (KBr) cm^{-1} 3600, 3530, 3090 br, 1675, 1665, 1625, 1590, 1550; ^1H nmr [$(CD_3)_2CO$] δ 1.02 (3H, t, J=7.3 Hz, 4′-H), 1.80 (2H, sex, J=7.3 Hz, 3′-H), 2.72 (2H, t, J=7.3 Hz, 2′-H), 4.00 and 4.01 (2×3H, 2s, 6,8-OCH_3), 6.71 (1H, s, 2-H), 6.99 (1H, d, J=2.6 Hz, 7-H), 7.27 (1H, d, J=2.6 Hz, 5-H), 13.73 (1H, s, 1-OH); ms *m/z* 370 $[M]^+$ (13), 328 $[M-C_3H_6]^+$ (20), 327 $[M-C_3H_7]^+$ (100). *Anal.* calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 64.18; H, 5.16.

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