Journal of Natural Products
Vol. 49, No. 1, pp. 122-125, Jan-Feb 1986

SYNTHESIS OF (±)-7- AND 8-HYDROXYDUNNIONE

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ABSTRACT.—The structures of two new natural products 7- and 8-hydroxydunnione have been confirmed by simple syntheses of their racemic forms.

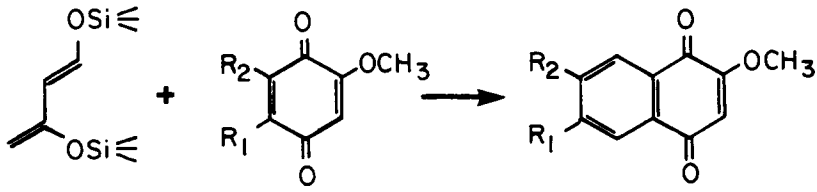
Recently, two new naphthoquinones were isolated (1) among other quinones from *Streptocarpus dunnii* Mast. and have been identified mainly on spectral grounds as 7- and 8-hydroxydunnione. The 7-hydroxy compound has been obtained in the dextrorotary modification, whereas only the racemic form was observed in the second case. These substances are of particular interest because their biosynthesis has been shown to involve a unique mode of prenylation (2).

Expeditious syntheses of these natural products can be envisioned using an approach used in the instance of trypethelones (3). The required substrates, derivatives of 2,7- and 3,5-dihydroxynaphthoquinones are, in principle, readily accessible by application of simple regiospecific procedures devised earlier (4,5). Some 2,6-isomers were also prepared for purposes of identification and comparison. These compounds or their derivatives, when known, have previously been obtained only by multi-step processes involving the appropriate tetralone (6-8) or disubstituted naphthalene (9-11).

Cycloaddition of 1,3-bistrimethylsiloxy-1,3-butadiene (**1**) (12) to 2-chloro- 5- or 6-methoxybenzoquinones (**2** or **3**) (13-15) was followed by percolating a solution of the adduct through a column of silica gel and gave the corresponding naphthoquinones (**4a** and **5a**) in nearly quantitative yield (Scheme 1). The acetylated derivative, 7-acetoxy-2-methoxynaphthoquinone (**4c**), on ether exchange with silver (I) oxide and isoprenyl bromide in HMPA, followed by Claisen rearrangement in boiling EtOH and cyclization in cold concentrated H_2SO_4, yielded 7-hydroxydunnione (**7a**), essentially in a one-flask procedure with an overall yield of 36% (along with a small amount of the rearranged β-isodunnione, **7b**).

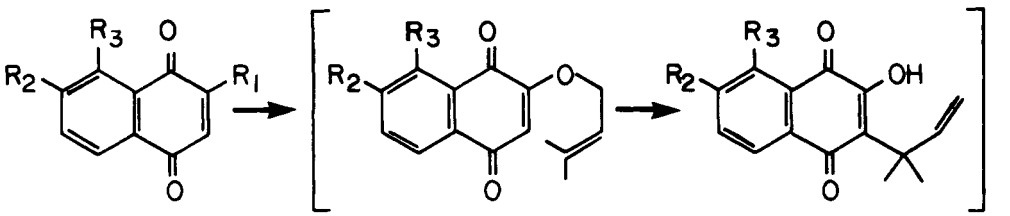
5-Acetoxy-3-methoxynaphthoquinone (**6a**) (16) was subjected to the same reaction conditions but afforded only 17% of 8-hydroxydunnione (**8a**) (and 4% of the β-iso-compound **8b**). However, when the corresponding diacetate (**6b**) (9) was carried through the same steps, a 29% yield of the desired quinone was isolated (Scheme II).

Although the natural products appear to be unavailable, comparison of the exten-

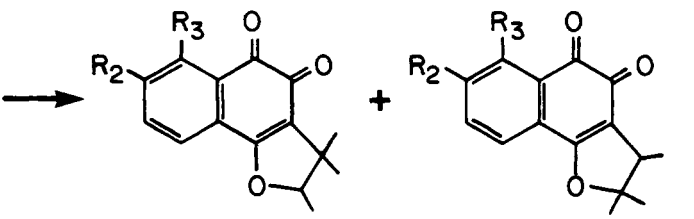


		R_1	R_2		R_1	R_2
1	**2**	Cl	H	**4a**	H	OH
	3	H	Cl	**4b**	H	OCH_3
				4c	H	OAc
				5a	OH	H
				5b	OCH_3	H
				5c	OAc	H

SCHEME I



	R_1	R_2	R_3
4c	OCH_3	OAc	H
6a	OCH_3	H	OAc
6b	OAc	H	OAc



	R_2	R_3		R_2	R_3
7a	OH	H	**7b**	OH	H
8a	H	OH	**8b**	H	OH

SCHEME II

sive data of the literature with those of the synthetic materials leaves no doubt as to their similarity.

EXPERIMENTAL

All melting points were taken for samples in capillary tubes with a Thomas-Hoover Apparatus and are not corrected. The uv spectra were determined on a Hewlett-Packard 8450A spectrophotometer and 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 silica 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, Tenn. Exact masses were provided by the Laboratoire de spectrométrie de masse, Université de Sherbrooke, Sherbrooke, Québec.

PREPARATION OF NAPHTHOQUINONES.—*General method.*—A solution of the benzoquinone (2.0 mmol) and bistrimethylsiloxybutadiene (12) (2.5 mmol) in dry C_6H_6 (10 ml) was heated to reflux for ca. 18 h, cooled, and poured onto a column of silica gel (60 g). Slow elution with a mixture of C_6H_6-EtOAc (2:1) provided the corresponding naphthoquinone.

7-HYDROXY-2-METHOXYNAPHTHOQUINONE (**4a**).—A reaction carried out with 2-chloro-5-methoxybenzoquinone (**2**) (13-15) gave **4a** (99%), mp 246.0-246.5° (MeOH); ir ν max (KBr) cm^{-1} 3340 br, 1670, 1640, 1613, 1590, and 1573; uv λ max (MeOH) nm (log ϵ) 263 (4.29), 289 (4.04), and 336 (3.34); ^{1}H nmr (DMSO-d_6) δ 3.83 (3H, s, 2-OCH_3), 6.22 (1H, s, 3-H), 7.16 (1H, dd, J=8.6, 2.5 Hz, 6-H), 7.30 (1H, d, J=2.5 Hz, 8-H), and 7.84 (1H, d, J=8.6 Hz, 5-H); ms *m/z* 204 (M^+). Anal. calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.72; H, 4.10.

2,7-DIMETHOXYNAPHTHOQUINONE (**4b**).—This derivative was prepared from **4a** by the usual method (MeI-Ag_2O-$CHCl_3$) and in nearly quantitative yield, mp 214.0-214.5° ($CHCl_3$/MeOH) [lit. (6) mp 217-218°]; ir ν max (KBr) cm^{-1} 1680, 1642, 1609, 1590, and 1573; uv λ max (MeOH) nm (log ϵ) 261 (4.39), 288 (4.12), and 333 (3.47); ^{1}H nmr ($CDCl_3$) δ 3.90 (3H, s, 2-OCH_3), 3.95 (3H, s, 7-OCH_3), 6.11 (1H, s, 3-H), 7.22 (1H, dd, J=8.6, 2.5 Hz, 6-H), 7.57 (1H, d, J=2.5 Hz, 8-H), and 8.03 (1H, d, J=8.6 Hz, 5-H).

7-ACETOXY-2-METHOXYNAPHTHOQUINONE (**4c**).—Acetylation of **4a** (Ac_2O-H_2SO_4) afforded the acetate **4c** (87%), mp 206.5-207.5° ($CHCl_3$/petroleum ether, bp 60-80°); ir ν max (KBr) cm^{-1} 1762, 1679, 1645, 1607, 1596, and 1583; uv λ max (MeOH) nm (log ϵ) 249 (4.33), 272 sh (4.13), 279 (4.15),

and 328 (3.49); ^{1}H nmr ($CDCl_3$) δ 2.35 (3H, s, 7-OAc), 3.91 (3H, s, 2-OCH_3), 6.18 (1H, s, 3-H), 7.47 (1H, dd, J=8.5, 2.4 Hz, 6-H), 7.85 (1H, d, J=2.4 Hz, 8-H), and 8.13 (1H, d, J=8.5 Hz, 5-H); ms *m/z* 246 (M^+). Anal. calcd for $C_{13}H_{10}O_5$: C, 63.42; H, 4.09. Found: C, 63.11; H, 4.30.

6-HYDROXY-2-METHOXYNAPHTHOQUINONE (**5a**).—Application of the general method to 2-chloro-6-methoxybenzoquinone (**3**) (13-15) gave naphthoquinone **5a** in nearly quantitative yield, mp 292-293° (MeOH) [lit. (8) mp 285-295°]; ir ν max (KBr) cm^{-1} 3330 br, 1662, 1648, 1610, 1584, and 1570; uv λ max (MeOH) nm (log ε) 268 (4.21), 290 (4.19), and 332 (3.45); ^{1}H nmr (DMSO-d_6) δ 3.84 (3H, s, 2-OCH_3), 6.26 (1H, s, 3-H), 7.12 (1H, dd, J=8.6, 2.5 Hz, 7-H), 7.27 (1H, d, J=2.5 Hz, 5-H), and 7.89 (1H, d, J=8.6 Hz, 8-H).

2,6-DIMETHOXYNAPHTHOQUINONE (**5b**).— The diether **5b** was obtained from **5a** (MeI-Ag_2O-$CHCl_3$) in nearly quantitative yield, mp 229-230° ($CHCl_3$/MeOH) [lit. (6) mp 232-233°]; ir ν max (KBr) cm^{-1} 1672, 1650, 1601, 1592, and 1572; uv λ max (MeOH) nm (log ε) 265 (4.27), 290 (4.23), and 328 (3.54); ^{1}H nmr ($CDCl_3$) δ 3.90 (3H, s, 2-OCH_3), 3.95 (3H, s, 6-OCH_3), 6.13 (1H, s, 3-H), 7.16 (1H, dd, J=8.6, 2.5 Hz, 7-H), 7.53 (1H, d, J=2.5 Hz, 5-H), and 8.08 (1H, d, J=8.6 Hz, 8-H).

6-ACETOXY-2-METHOXYNAPHTHOQUINONE (**5c**).—Acetylation of **5a** (Ac_2O-H_2SO_4) gave a 95% yield of the acetate **5c**, mp 187.5-188.0° ($CHCl_3$/petroleum ether, bp 60-80°) [lit. (8) mp 187°]; ir ν max (KBr) cm^{-1} 1768, 1687, 1648, 1637, 1610, 1598, and 1578; uv λ max (MeOH) nm (log ε) 251 (4.27), 280 (4.22), and 328 (3.51); ^{1}H nmr ($CDCl_3$) δ 2.36 (3H, s, 6-OAc), 3.91 (3H, s, 2-OCH_3), 6.19 (1H, s, 3-H), 7.44 (1H, dd, J=8.4, 2.2 Hz, 7-H), 7.80 (1H, d, J=2.2 Hz, 5-H), and 8.17 (1H, d, J=8.4 Hz, 8-H).

PREPARATION OF HYDROXYDUNNIONES.—*General method.*—A mixture of the methoxynaphthoquinone (2.0 mmol), freshly prepared Ag_2O (3.6 g; 16 mmol), and redistilled isoprenyl bromide (3.0 g; 20 mmol) in dry HMPA (15 ml) was stirred for 20 h, diluted with Et_2O (300 ml), filtered, washed several times with H_2O, dried, and evaporated (1.8 g of Ag_2O and 1.5 g of isoprenyl bromide in the case of 2-acetoxynaphthoquinones). The residue was dissolved in absolute EtOH (50 ml), refluxed for 20 h and again evaporated. Cold concentrated H_2SO_4 (5 ml) was then added, the mixture was stirred for 10 min at 0°, poured into ice H_2O (300 ml), and extracted with Et_2O.

(±)-7-HYDROXYDUNNIONE (2,3,4,5-TETRAHYDRO-7-HYDROXY-2,3,3-TRIMETHYLNAPHTHO[1,2-b]FURAN-4,5-DIONE) (**7a**).—Application of the foregoing method to quinone **4c** and separation of the crude product by chromatography (C_6H_6-EtOAc, 2:1) gave 7-hydroxydunnione (**7a**) (186 mg; 36%), mp 206° (C_6H_6) [lit. (1) mp (+)-isomer 217-219°]; ir ν max (KBr) cm^{-1} 3180 br, 1700, 1640, 1630, 1600, 1550, 1500, 1414, 1303, 1219, 1158, 1090, 1060, 1029, and 822; uv λ max (MeOH) nm (log ε) 270 (4.47), 277 (4.50), 303 (3.79), and 496 (3.31); ^{1}H nmr ($CDCl_3$) δ 1.27 (3H, s, 3-CH_3), 1.45 (3H, s, 3-CH_3), 1.46 (3H, d, J=6.6 Hz, 2-CH_3), 4.66 (1H, q, J=6.6 Hz, 2-H), 7.13 (1H, dd, J=8.4, 2.6 Hz, 8-H), 7.53 (1H, br s, 7-OH), 7.54 (1H, d, J=8.4 Hz, 9-H), and 7.62 (1H, d, J=2.6 Hz, 6-H); ms *m/z* 258 (M^+). Anal. calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.90; H, 5.65.

A second band consisted of (±)-7-hydroxy-β-isodunnione (2,3,4,5-tetrahydro-7-hydroxy-2,2,3-trimethylnaphtho[1,2-b]furan-4,5-dione) (**7b**) (24 mg; 5%), mp 203-204° (Et_2O/petroleum ether, bp 60-80°); ir ν max (KBr) cm^{-1} 3135 br, 1700, 1642, 1629, 1610, 1580, 1566, 1554, 1505, 1447, 1303, 1260, 1118, 1078, and 801; uv λ max (MeOH) nm (log ε) 269 (4.38), 277 (4.41), 298 (3.80), and 496 (3.18); ^{1}H nmr ($CDCl_3$) δ 1.27 (3H, d, J=7.0 Hz, 3-CH_3), 1.49 (3H, s, 2-CH_3), 1.53 (3H, s, 2-CH_3), 3.19 (1H, q, J=7.0 Hz, 3-H), 7.13 (1H, dd, J=8.3, 2.5 Hz, 8-H), 7.53 (1H, d, J=8.3 Hz, 9-H), 7.62 (1H, d, J=2.5 Hz, 6-H), and 8.15 (1H, br s, 7-OH). Hrms, calcd for $C_{15}H_{14}O_4$: 258.0891. Found: 258.0891.

(±)-8-HYDROXYDUNNIONE (2,3,4,5-TETRAHYDRO-6-HYDROXY-2,3,3-TRIMETHYLNAPHTHO[1,2-b]FURAN-4,5-DIONE) (**8a**).—a) A similar reaction involving 5-acetoxy-3-methoxynaphthoquinone (**6a**) (16) afforded 8-hydroxydunnione (**8a**) (88 mg; 17%) after chromatography (C_6H_6/EtOAc, 5:1), mp 148.5-149.0° (MeOH) [lit. (1) mp 151-152°]; ir ν max (KBr) cm^{-1} 1645, 1613, 1588, 1450, 1401, 1383, 1310, 1230, 1155, and 1035; uv λ max (MeOH) nm (log ε) 238 sh (4.19), 259 (4.30), 291 (3.76), and 412 (3.72); ^{1}H nmr ($CDCl_3$) δ 1.26 (3H, s, 3-CH_3), 1.44 (3H, s, 3-CH_3), 1.46 (3H, d, J=6.6 Hz, 2-CH_3), 4.64 (1H, q, J=6.6 Hz, 2-H), 7.10 (1H, dd, J=8.8, 1.1 Hz, 7-H), 7.19 (1H, dd, J=7.3, 1.1 Hz, 9-H), 7.53 (1H, dd, J=8.8, 7.3 Hz, 8-H), and 11.93 (1H, s, 6-OH); ms *m/z* 258 (M^+). Anal. calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.62; H, 5.71.

A slower-moving zone yielded (±)-8-hydroxy-β-isodunnione (2,3,4,5-tetrahydro-6-hydroxy-2,2,3-trimethylnaphtho[1,2-b]furan-4,5-dione) (**8b**) (23 mg; 4%), mp 116-117° (petroleum ether, bp 65-110°); ir ν max (KBr) cm^{-1} 1638, 1612, 1586, 1497, 1449, 1400, 1367, 1323, 1225, 1191, and 1164; uv λ max (MeOH) nm (log ε) 239 sh (4.26), 255 (4.31), 290 (3.86), and 414 (3.76); ^{1}H nmr ($CDCl_3$) δ 1.27 (3H, d, J=7.0 Hz, 3-CH_3), 1.49 (3H, s, 2-CH_3), 1.51 (3H, s, 2-CH_3), 3.20 (1H, q,

J=7.0 Hz, 3-H), 7.11 (1H, dd, J=8.4, 1.1 Hz, 7-H), 7.18 (1H, dd, J=7.3, 1.1 Hz, 9-H), 7.52 (1H, dd, J=8.4, 7.3 Hz, 8-H), and 11.95 (1H, s, 6-OH). Hrms, calcd for $C_{15}H_{14}O_4$: 258.0891. Found: 258.0891.

b) A reaction carried out with 3,5-diacetoxynaphthoquinone (**6b**) (9) gave a 29% yield of **8a** (151 mg) and 6% of **8b** (32 mg).

ACKNOWLEDGMENTS

We gratefully acknowledge financial support and bursaries (to VG) from the Natural Sciences and Engineering Research Council of Canada and the Fonds F.C.A.C. (Gouvernement du Québec).

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Received 10 July 1985