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HALLERIDONE, A CYTOTOXIC CONSTITUENT FROM *CORNUS CONTROVERSA*

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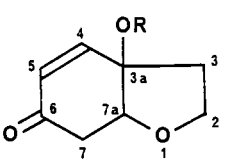
In our search for biologically active compounds in Japanese garden plants (1), a cytotoxic compound **1** was isolated from *Cornus controversa* Hamsley (Cornaceae). Several plants of this family are used in Japan to treat swellings. The spectral data of **1** were identical with those of halleridone (2) and rengyolone (3), which were, respectively, isolated from *Halleria lucida* (Scrophulariaceae) and *Forsythia suspensa* (Oleaceae). The isolated compound **1** has a *cis* ring junction as does halleridone (2) because a W-coupling ($J = 1.5$ Hz) was observed between H-4 and H-7a in the ^{1}H-nmr spectrum. Halleridone [**1**] was active against P-388 (mouse lymphocytic leukemia) and HeLa (human uterine carcinoma) cells. Derivatives **2–15** of **1** were prepared and tested for cytotoxicity against the above cells by the assay methods of Mirabelli *et al.* (4) (Table 1).

EXPERIMENTAL

PLANT MATERIAL, EXTRACTION, AND ISOLATION.—*C. controversa* was collected from the garden of our Institute (Machida, Tokyo) in July 1987; a voucher specimen is deposited at the Koishikawa Botanical Garden. The leaves (4.3 kg) of the plant were extracted with MeOH (18 liters) for 1 month at room temperature. The isolation procedure was monitored by cytotoxicity against P-388. The MeOH extract (91 g) was chromatographed using 5 columns (90 cm length × 6 cm diameter) of Si gel (900 g per column). Each column was eluted with mixtures of C_6H_6-EtOAc (100:0, 60:40, 40:60 and 0:100) which was followed by mixtures of EtOAc-MeOH (95:5, 90:10, 80:20 and 60:40) (2 liters each). Active fractions [EtOAc-MeOH (95:5 and 90:10)] (4.4 g) were chromatographed on Si gel (300 g in column of 60 cm length × 4 cm diameter) and eluted with EtOAc (30-ml fractions). A pool of active fractions (no. 25–36) (2.7 g) was purified by hplc [column, 250 mm length × 10 mm diameter packed with Develosil 30-3; eluent, EtOAc; flow rate, 3.5 ml/min; uv (252 nm) detection] to give an active compound **1** (963 mg); $[\alpha]^{25}D$ −1.5° ($c = 0.5$, MeOH); *m/z* $[M]^+$ ($C_8H_{10}O_3$) 154; whose uv, ir, ^{1}H nmr, ^{13}C nmr, and ms were identical with those of halleridone (2) and rengyolone (3).

DERIVATIVES.—Compounds **2–5** (48, 77, 104, and 131 mg, respectively) were made from **1**



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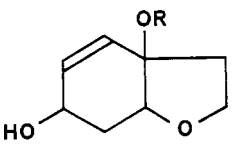
6 R= 

7 R= 

8 R= 

9 R= 



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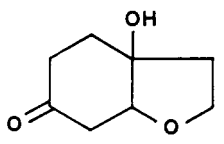

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TABLE 1. Cytotoxicity of Halleridone [**1**] and Its Derivatives.

Compound	IC_{50} (μg/ml)		Compound	IC_{50} (μg/ml)	
	P-388	HeLa-S_3		P-388	HeLa-S_3
1	2.1	2.8	**9**	0.7	0.9
2	0.5	4.1	**10**	40.8	>100
3	0.6	2.7	**11**	>100	>100
4	0.3	1.8	**12**	>100	8.8
5	0.3	0.8	**13**	38.5	5.3
6	0.5	1.6	**14**	8.4	3.5
7	0.4	1.0	**15**	43.0	>100
8	<0.1	1.2			

(50 mg) on treatment with $(RCO)_2O$ (R = Me to C_7H_{15}) (100 mg) in pyridine (0.2 ml) (room temperature, 12 h). Compounds **6–9** (25, 29, 32, and 31 mg, respectively) were prepared from **1** (16 mg) with benzoyl, *o*-, *m*-, and *p*-benzoyl chlorides (44 mg each) in pyridine (0.2 ml), respectively (room temperature, 8 h). $NaBH_4$ (4 mg) reduction of **2–5** (25 mg each) in MeOH (1 ml) (0°, 3 min) gave the corresponding enols (**11–14**) (24 mg each). On hydrolysis with saturated $Ba(OH)_2$ in a mixture of H_2O and MeOH (0.5 ml) (room temperature, 2.5 h), **11** (29 mg) gave **10** (18 mg). A mixture of **1** (30 mg) and EtOH (1 ml) was stirred with 10% Pd/C (10 mg) at room temperature for 2 h under H_2 gas to give **15** (28 mg). Derivatives are new compounds, except for **2** (2), and showed expected spectra (uv, ir, ^1H nmr, ^{13}C nmr, and ms) that are available upon request to the major author.

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