Products **2** and **9** were readily identified in the reaction mixtures by their GC–mass spectra. The isolated isoxazoles **9a–d** were identical in all respects with the authentic products (Table I) prepared from DMADC and the corresponding α-chloro oximes and triethylamine in ether.

Table I

6	R	Yield, % 9[a]	Mp, °C
a	C_6H_5–	46	52–54 (lit.[12] 62–63)
b	4-$CH_3OC_6H_4$–	73	72.5–73.5
c	4-$O_2NC_6H_4$–	45	103–105
d	3,4-$Cl_2C_6H_3$–	45	112.5–114
f	2,4,6-$(CH_3)_3C_6H_2$–	82	65.5–67

[a] Isolated yields of pure products from α-chloro oximes. All products gave satisfactory combustion analyses (C, H, N) and ir, NMR, and mass spectra.

Thermolysis of **3a** in excess ethyl propiolate **10** produced phenyl isocyanate and a mixture of the isomeric esters **11** and **12** (40% yield) in a mole ratio of 25:75 (Scheme II). The preponderant formation of isomer **12** is difficult to explain by ionic mechanisms and is strong evidence in support of the intermediate formation of benzonitrile oxide in this reaction. Treatment of excess **10** with benzonitrile oxide generated from α-chlorobenzaldoxime produced **11** and **12** in a mole ratio of 30:70, whereas the ratio of the corresponding methyl esters obtained from methyl propiolate is reported[13] to be 28:72. Esters **11** and **12** were easily separated by gas chromatography and identified by comparison of their spectra (ir, NMR, mass) with authentic materials.[14,15] Finally, the decomposition of **3a** in the presence of the more active dipolarophile norbornene produced adduct **13**[16] (mp 97–100 °C, mmp 98–100°) in good yield (Scheme II).

In contrast to **3a** and **3c** the dibenzohydroxamates **1a** and **1c** and excess DMADC did not yield 1,3-dipolar adducts when heated at the reflux temperature in chlorobenzene. The primary product in each case was the corresponding isocyanate.

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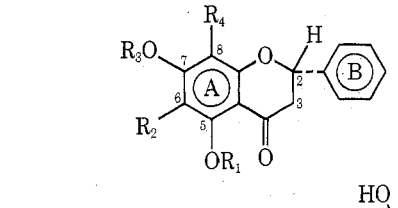
Uvaretin and Isouvaretin. Two Novel Cytotoxic *C*-Benzylflavanones from *Uvaria chamae* L.

Summary: Two cytotoxic principles, uvaretin (**1**) and isouvaretin (**2**), have been isolated from the stem bark of *Uvaria chamae* L. (Annonaceae) and their structures have been established as novel *C*-benzylflavanones.

Sir: An ethanolic extract of the stem bark of *Uvaria chamae* L. (Annonaceae) was found to show activity in vivo against P-388 leukemia in the mouse and in vitro against cells derived from human carcinoma of the nasopharynx (KB).[1] Fractionation of the ethanol extract was guided by assay against KB. The activity was concentrated in the ethyl acetate soluble fraction of an ethyl acetate–water partition. Chromatography of the ethyl acetate fraction over silicic acid afforded uvaretin and isouvaretin.

Uvaretin, $C_{22}H_{18}O_5$,[2] mp 210–211 °C, $[\alpha]^{25}D$ −52° (*c* 0.122, MeOH), gave a positive test (red) with magnesium–hydrochloric acid and formed a trimethyl ether upon treatment with excess ethereal CH_2N_2 for 4 days at room temperature. The uv spectrum of uvaretin showed λ_{max} (MeOH) 324 nm (ϵ 15 400) and 289 (10 500) and showed considerable bathochromic shifts with aluminum chloride (24 nm) sodium acetate[3] (36 nm) which are consistent with a flavanone nucleus with hydroxyl groups present at positions 5 and 7. The ir spectrum (KBr) showed broad hydroxyl bands at 3100 cm^{-1} and a carbonyl absorption at 1630 cm^{-1} which are in accord with the presence of a hydroxyl group at C-5 in a flavanone. The mass spectrum showed a parent peak at *m/e* 362 (100%) and fragment ions at *m/e* 285 (M^+ − 77, 16%), 258 (M^+ − 104, 37%), and 104 (9%) which indicated an unsubstituted B ring.[4,5]

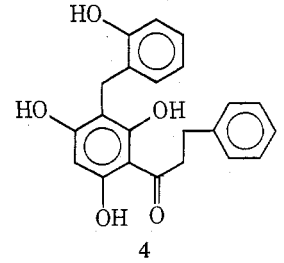


1 and 2, $R_1 = R_2 = R_3 = H$; $R_4 =$ —CH_2—(HO-phenyl)

(or $R_1 = R_3 = R_4 = H$; $R_2 =$ —CH_2—(HO-phenyl))

3, $R_1 = R_2 = R_3 = R_4 = H$

5, $R_1 = R_3 = H$; $R_2 = R_4 =$ —CH_2—(HO-phenyl)



4

The NMR spectrum (60 MHz, acetone-d_6) clearly showed an ABX pattern characteristic of the protons at H-3 (AB) and H-2 (X) of a flavanone nucleus,[3] a 1 H singlet for H-6 (or H-8) at δ 6.10, a 5 H broad singlet for the five protons of ring B at δ 7.5, and a 1 H singlet at δ 12.60

for OH at C-5 (exchanges with D_2O). These features of the NMR spectrum are characteristic of flavanones like pinocembrin (**3**).[6] Additional peaks in the NMR spectrum of uvaretin include a 2 H singlet at δ 3.91, a 4 H multiplet near δ 6.8, and two other exchangeable protons located near the protons of the aromatic rings.

These data can be accommodated by a hydroxybenzyl substituent at C-6 (or C-8) in a 5,7-dihydroxyflavanone nucleus. The 4 H multiplet near δ 6.8 closely resembles the pattern found in *o*-hydroxybenzyl alcohol.[7]

Isouvaretin, $C_{22}H_{18}O_5$,[2] mp 215–217 °C, $[\alpha]^{25}D$ −15° (*c* 0.108, MeOH), also formed a trimethyl ether and had spectral data[8] very similar to that of uvaretin which led to the conclusion that isouvaretin and uvaretin were isomeric and differed only in the location of the hydroxybenzyl substituent. Catalytic hydrogenation of isouvaretin and uvaretin using H_2–Pd/C in ethanol containing KOH gave the same dihydrochalcone (**4**)[9] confirming the isomeric relationship.

C-Benzylation of (±)-pinocembrin (**3**)[10] using *o*-hydroxybenzyl alcohol and boron trifluoride etherate in dioxane[11] produced the two monobenzyl products (**1** and **2**) which were found to be identical[12] with uvaretin and isouvaretin and a dibenzyl product (**5**).[13]

The absolute stereochemistry of **1** and **2** follow from CD data which allows assignment of the 2*S* configuration.[14] Uvaretin and isouvaretin are the first reported examples of *C*-benzylflavanones.[15]

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(1) Tumor-inhibitory activity and cytotoxicity were assayed under the auspices of the National Cancer Institute by procedures described in *Cancer Chemother. Rep., Part 3*, **3**, 1 (1972). Uvaretin showed cytotoxicity (ED 50) against KB cell culture at 5.2 μg/ml and against PS cell culture at 17 μg/ml while isouvaretin was active at 2.7 μg/ml (KB) and 2.2 μg/ml (PS).

(2) The molecular formula was established by high resolution mass spectral data and supported by elemental analysis. For uvaretin and isouvaretin calculated *m/e* was 362.1154, found *m/e* 362.1169 and 362.1138, respectively.

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(7) The 60-MHz NMR spectra of *o*-, *m*-, and *p*-hydroxybenzyl alcohols were run in acetone-d_6 for comparison.

(8) Spectra: uv λ_{max} (MeOH) 324 nm (ε 12 500), 296 (9000), (NaOAc) 324; ir ν_{max} (KBr) 3030, 1650 cm^{-1}; NMR (60 MHz, acetone-d_6) δ 13.33 (1 H, s, exchanges D_2O) 7.50–7.84 (5 H), 6.67–7.50 (4 H), 6.26 (1 H, s), 5.68 (1 H, X of ABX), 4.00 (2 H, s), 2.67–3.60 (2 H, AB of ABX); *m/e* (rel abundance) 362 (100), 361 (9), 285 (13), 258 (22), 104 (13).

(9) **4** ($C_{22}H_{20}O_5$) had mp 207–208 °C; the formula was supported by high resolution MS. The products from the separate reductions were compared and found to be identical (melting points, mixture melting point, NMR, TLC, ir).

(10) Prepared according to the procedure described by S. Huzise and H. Tatsita, *Ber.*, **74B**, 275 (1941).

(11) Adopted from a similar procedure involving C-prenylation of a phloroglucinol nucleus by A. C. Jain, S. M. Jain, and J. Singh, *Tetrahedron*, **30**, 2485 (1974); the products were separated by chromatography over silica gel.

(12) Melting point, mixture melting point (no depression), TLC, superimposible ir spectra.

(13) **5** had mp 118–120 °C; the formula ($C_{29}H_{24}O_6$) was supported by high resolutions MS. The spectral data was in accord with that expected for **5**.

(14) CD: **1**, $[\theta]_{355}$ +2260, $[\theta]_{314}$ +5080, $[\theta]_{288}$ −40 000, $[\theta]_{242}$ +3620, $[\theta]_{219}$ +34 600; **2**, $[\theta]_{328}$ +3800, $[\theta]_{289}$ −24 500, $[\theta]_{251}$ −2410, $[\theta]_{219}$ +29 600. The signs of the Cotton effects in the CD spectra of flavanones have been correlated with absolute stereochemistry: W. Gaffield, *Tetrahedron*, **26**, 4093 (1970).

(15) Studies are in progress to determine the location of the hydroxybenzyl substituent for each.

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