528 (15), 450 (24), 385 (10), 320 (22), 318 (15), 306 (29), 304 (31), 267 (21), 266 (35), 265 (100), 264 (22), 263 (60), 262 (24), 186 (56), 128 (62), 127 (36), 121 (45), 56 (55).

Anal. Calcd for $C_{20}H_{18}Fe_2Se_2$: C, 45.45; H, 3.41. Found: C, 45.55; H, 3.39.

**n-Butylferrocenyl Selenide (VI).** Ferrocenyl selenocyanate (291 mg, 1 mmol) stirred with 0.5 ml of n-butyllithium (2.2 M) in 10 ml of dried n-heptane at room temperature in a Schlenck reaction tube under argon for 4 h. A clear yellow solution was obtained. A drop of water was added to decompose unreacted n-butyllithium. This solution was then extracted with ether and washed with water. After drying over anhydrous $MgSO_4$ and removal of the solvent, an orange-yellow oil was obtained. After alumina dry column purification (developed with 1:1 $CH_2Cl_2$ and n-heptane), crude VI was obtained (280 mg, 87%). An analytical sample was obtained by further purification with high pressure liquid chromatography (porasil $C_{18}$ column, 15:85 ethylene chloride in n-heptane): mass spectrum (70 eV) m/e (rel intensity) 324 (14), 323 (13), 322 (75), 321 (8), 320 (41), 319 (15), 318 (17), 267 (21), 266 (19), 265 (100), 264 (11), 263 (57), 262 (20), 261 (24), 186 (11), 129 (39), 128 (17), 121 (23), 56 (20); NMR ($CDCl_3$) $\delta$ 0.83 (3 H, t, $J$ = 7 Hz), 1.4 (4 H, m), 2.5 (t, 2 H, $J$ = 7 Hz), 4.1 (5 H, s), 4.1 (2 H, t, $J$ = 2 Hz), 4.2 (2 H, t, $J$ = 2 Hz); ir ($CCl_4$, 0.1 cm ir tran) 3185 m, 2950 s, 2920 s, 2860 m, 1760 vw, 1725 vw, 1590 vw, 1460 m, 1410 w, 1385 w, 1255 m, 1195 w, 1150 m, 1100 m, 1020 s, and 1000 $cm^{-1}$ m.

Anal. Calcd for $C_{14}H_{17}FeSe$: C, 52.33; H, 5.61. Found: C, 52.28; H, 5.58.

**Acknowledgment.** Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

**Registry No.**—I, 58463-77-7; II, 58463-78-8; VI, 58463-79-9; ferrocenyl selenocyanate, 58463-80-2; chloromercuriferrocene, 1273-75-2.

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# Uvaretin, a New Antitumor Agent from *Uvaria acuminata* (Annonaceae)

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The chloroform extract of *Uvaria acuminata* Oliv. has shown inhibitory activity against the P-388 lymphocytic leukemia test system of the National Cancer Institute. The major constituent of this extract was identified as the new 3'-benzyldihydrochalcone uvaretin, 1-[2,4-dihydroxy-3-(2-hydroxybenzyl)-6-methoxyphenyl]-3-phenyl-1-propanone ($C_{23}H_{22}O_5$). The structure was proven by x-ray crystallography and other methods.

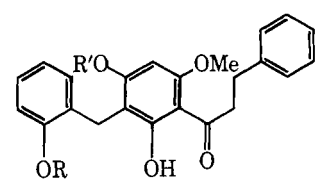
As a result of the continuing search for plants having tumor-inhibiting constituents, the chloroform extract of the roots of *Uvaria acuminata* Oliv. (Annonaceae)[17] was found to have inhibitory activity toward the P-388 (3PS) lymphocytic leukemia test system.

## Discussion

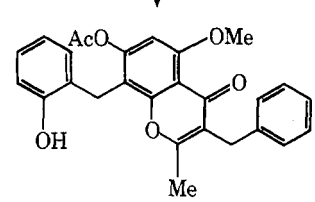
The major constituent of the chloroform extract of *Uvaria acuminata* Oliv. was found to be uvaretin, $C_{23}H_{22}O_5$. Uvaretin, subsequently shown to be I, was found to undergo the Kostanecki reaction[1] to give a 3-benzyl-2-methylchromone (II) characteristic of 2'-hydroxydihydrochalcones (e.g., phloretin).[2] In addition, the $^1H$ NMR spectrum of uvaretin shows the two 2-proton signals of an $A_2B_2$ pattern, centered at 2.90 and 3.33 ppm, expected for a $\beta$-propiophenone moiety. This $^1H$ NMR spectrum also contains a signal (13.9 ppm) for an intramolecularly hydrogen-bonded phenolic hydroxyl group.

Uvaretin (I) forms a monomethyl ether (III) with diazomethane and a dimethyl ether (IV) with dimethyl sulfate, both of which still contain the internally bonded phenolic hydroxyl group.

Uvaretin (I) demonstrated an activity of 133% test/control (T/C) at 10 mg/kg in the 3PS system. The monomethyl ether (III) of uvaretin showed an activity of 132% T/C at 1 mg/kg




I, R = R' = H
III, R = H; R' = Me
IV, R = R' = Me


II

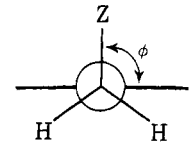
and the dimethyl ether (IV) demonstrated 144 and 141% T/C at 4 and 2 mg/kg, respectively. Activity in the 3PS system is defined as an increase in the survival of treated animals over that of controls resulting in a T/C $\geq$ 125%.[3]

**Table I. Fractional Coordinates and Estimated Standard Deviations**

| Atom | x/a | y/b | z/c |
|---|---|---|---|
| O1 | −0.2725 (2) | 0.2168 (4) | 0.3601 (2) |
| O2 | −0.4210 (2) | 0.1098 (4) | 0.2912 (2) |
| O3 | −0.5740 (2) | 0.1910 (4) | −0.0145 (2) |
| O4 | −0.2845 (2) | 0.4043 (4) | 0.1179 (2) |
| O5 | −0.5681 (2) | 0.1921 (4) | 0.3197 (2) |
| C1 | −0.0252 (3) | 0.3633 (7) | 0.3716 (3) |
| C2 | 0.0270 (3) | 0.2417 (8) | 0.3475 (3) |
| C3 | 0.1053 (4) | 0.2995 (9) | 0.3432 (4) |
| C4 | 0.1337 (3) | 0.4675 (9) | 0.3614 (4) |
| C5 | 0.0838 (4) | 0.5832 (9) | 0.3849 (4) |
| C6 | 0.0052 (3) | 0.5290 (8) | 0.3890 (3) |
| C7 | −0.1111 (3) | 0.3110 (7) | 0.3776 (3) |
| C8 | −0.1845 (3) | 0.3360 (6) | 0.2877 (3) |
| C9 | −0.2698 (2) | 0.2680 (5) | 0.2871 (2) |
| C10 | −0.2825 (3) | 0.4505 (7) | 0.0329 (3) |
| C1′ | −0.3479 (2) | 0.2579 (5) | 0.2069 (2) |
| C2′ | −0.4229 (2) | 0.1730 (5) | 0.2112 (2) |
| C3′ | −0.4986 (2) | 0.1494 (5) | 0.1388 (2) |
| C4′ | −0.5002 (2) | 0.2137 (5) | 0.0576 (2) |
| C5′ | −0.4295 (2) | 0.3000 (5) | 0.0487 (2) |
| C6′ | −0.3548 (2) | 0.3206 (5) | 0.1223 (2) |
| C7′ | −0.5734 (3) | 0.0461 (5) | 0.1472 (2) |
| C1″ | −0.6459 (2) | 0.1494 (5) | 0.1609 (2) |
| C2″ | −0.6409 (2) | 0.2125 (5) | 0.2438 (2) |
| C3″ | −0.7099 (2) | 0.2988 (6) | 0.2544 (2) |
| C4″ | −0.7863 (3) | 0.3238 (6) | 0.1815 (3) |
| C5″ | −0.7929 (3) | 0.2620 (7) | 0.0985 (3) |
| C6″ | −0.7233 (3) | 0.1751 (6) | 0.0895 (3) |
| HC2 | 0.009 (2) | 0.119 (5) | 0.334 (2) |
| HC3 | 0.140 (2) | 0.217 (5) | 0.317 (2) |
| HC4 | 0.197 (2) | 0.521 (5) | 0.363 (2) |
| HC5 | 0.101 (2) | 0.714 (5) | 0.400 (2) |
| HC6 | −0.026 (2) | 0.613 (5) | 0.408 (2) |
| H1C7 | −0.124 (2) | 0.380 (5) | 0.430 (2) |
| H2C7 | −0.103 (2) | 0.191 (5) | 0.403 (2) |
| H1C8 | −0.167 (2) | 0.285 (5) | 0.240 (2) |
| H2C8 | −0.188 (2) | 0.454 (5) | 0.270 (2) |
| H1C10 | −0.295 (3) | 0.336 (6) | −0.005 (3) |
| H2C10 | −0.336 (3) | 0.518 (6) | −0.003 (3) |
| H3C10 | −0.226 (3) | 0.506 (6) | 0.043 (3) |
| HC5′ | −0.434 (2) | 0.341 (5) | −0.014 (2) |
| H1C7′ | −0.547 (2) | −0.034 (5) | 0.195 (2) |
| H2C7′ | −0.603 (2) | −0.033 (5) | 0.088 (2) |
| HC3″ | −0.702 (2) | 0.335 (5) | 0.318 (2) |
| HC4″ | −0.836 (2) | 0.377 (5) | 0.192 (2) |
| HC5″ | −0.849 (2) | 0.281 (5) | 0.044 (2) |
| HC6″ | −0.726 (2) | 0.131 (5) | 0.029 (2) |
| HO2 | −0.365 (2) | 0.146 (5) | 0.339 (2) |
| HO3 | −0.564 (2) | 0.226 (5) | −0.063 (2) |
| HO4 | −0.519 (2) | 0.159 (5) | 0.308 (2) |

The structure of uvaretin was determined to be I by x-ray crystallography. Fractional coordinates are given in Table I, and bond distances and angles in Figure 1. The average estimated standard deviations for C–C, C=O, C–O distances are 0.006, 0.005, and 0.005 Å, respectively, and for angles, 0.3°. The weighted average of C–C bond lengths in aromatic rings (C1–C6, C1′–C6′, C1″–C6″) are 1.383 ± 0.006, 1.394 ± 0.006, and 1.387 ± 0.006 Å, which differ slightly from the value 1.393 Å observed in crystalline benzene.[4] The average internal angle in the benzene rings is 120.0°. The distances between oxygens partaking in intramolecular hydrogen bonds (dashed lines) are 2.441 (O1–O2) and 2.703 (O2–O5) Å. The C–C–C angles about tetrahedral carbons C7 and C8 are slightly larger than the tetrahedral angle, while that about C7′ is enlarged to 116.4°.[5]

The molecular conformation is shown in Figure 2.[6] It is partially governed by the intramolecular hydrogen bonds shown as dashed lines; e.g., the torsion angle O1–C9–C1′–C2′ is 6.7°. The C1′–C9–C8–C7 angle is 172.2°, C9–C8–C7–C1 is 173.8°, and C10–O4–C6′–C5′ is 9.3°.[7] The remaining three carbon–carbon single bonds are of the type Aryl–$CH_2Z$; the two of these influenced by the O2–O5 hydrogen bond have torsion angles $\phi$ of 81.5 (C2″–C1″–C7′–C3′) and 87.2° (C1′–




C7′–C3′–C4′), and the third $\phi$ is 89.1° (C8–C7–C1–C2). In these three cases $\phi$ is 80–90°, but this is not generally true, since in kavain it is 18.5°,[8] in dihydrokavain 6.5°,[9] in dibenzyl 71.6°,[10] and in 4,4′-dimethyldibenzyl 72.6°.[11]

The molecular packing, shown in Figure 3, is partially controlled by the intermolecular hydrogen bond between O3 and O5 (2.845 Å, dotted line). These bonds create infinite chains of molecules in the *c* direction. Other intermolecular distances less than 3.5 Å are O1–C10 (3.118 Å), O2–C2″ (3.345 Å), O5–C6′ (3.401 Å), and O2–C3″ (3.480 Å).

## Experimental Section[19]

**Extraction Procedure.** The roots (dried and ground, 1.58 kg) of *Uvaria acuminata* were extracted exhaustively in a Lloyd-type extractor with petroleum ether (bp 30–60 °C). After removal of the solvent, the petroleum ether extraction residue weighed 4.8 g. The marc was then extracted in a like fashion with ethanol. The solvent from the ethanol extract was removed in air to provide 42.7 g of residue. The latter was partitioned between chloroform and water (1:1) and, after the layers had been separated, the chloroform was removed in air and the water lyophilized. The former yielded 22.8 g of residue and the latter 20.0 g.

**Isolation of Uvaretin (I).** The residue from the chloroform phase (above, 6.3 g) was chromatographed over silica gel 60 (900 g, 40 × 1800 mm), eluting with dichloromethane, benzene, and ethyl acetate, 3:6:1, respectively. Those fractions containing the major component based upon thin layer chromatography were combined to yield 2.24 g of an oily material, largely uvaretin. Solidification was effected with carbon tetrachloride/acetone giving 0.9 g of purified uvaretin. Recrystallization from acetonitrile gave pure material as colorless platelets, mp 162–163 °C. The infrared [(KBr) 3300, 1625, and 1590 $cm^{-1}$], ultraviolet [(EtOH) $\lambda_{max}$ 330 nm (log $\epsilon$ 4.48), 284 (sh) (4.11), and 254 (sh) (3.82)], $^1H$ NMR [(acetone-$d_6$) $\delta$ 2.90 and 3.33 (each 2 H, $A_2B_2$ pattern), 3.83 (3 H, s), 4.25 (2 H, s), 6.20 (1 H, s), 6.9 (4 H, m), 7.23 (5 H, s), 8.8 (2 H, br), and 13.9 (1 H, s)], and mass [*m/e* 378 ($M^+$ base), 273, 246, 179, 167, 140, 107, and 91] spectra were in accord with structure I.

Anal. Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.85. Found: C, 72.90; H, 5.88.

**Kostanecki Reaction Product II.** Uvaretin (100 mg) was treated with fused sodium acetate (0.2 g) and acetic anhydride (2 ml) under the usual Kostanecki conditions.[12] Following workup, the crude oily product (100 mg) was passed through an alumina (activity grade II) column and crystallized from ethyl acetate. Two recrystallizations from ethyl acetate/methanol gave pure material (22 mg) as colorless, tiny cubes, mp 256–259 °C. The alumina treatment appears to have removed the acetate moiety from C-2″. The infrared [(KBr) 3070, 1760, 1640, 1560, and 1200 $cm^{-1}$], ultraviolet [(EtOH) $\lambda_{max}$ 312 nm (log $\epsilon$ 3.75), 295 (3.77), 262 (4.30), 253 (3.27), and 237 (3.34)], $^1H$ NMR [(pyridine-$d_5$) $\delta$ 2.10 (3 H, s), 2.33 (3 H, s), 3.72 (3 H, s), 3.90 (2 H, s), 4.31 (2 H, s), 6.66 (1 H, s), 7.0 (4 H, m), and 7.2 (5 H, s)], and mass [*m/e* 444 ($M^+$), 402, 384, 207, 149, 129, 128, 107, and 91 (base)] spectra were in accord with structure II.

Anal. Calcd for $C_{27}H_{24}O_6 \cdot H_2O$: C, 70.11; H, 5.66. Found: C, 70.24; H, 5.39.

**Uvaretin Monomethyl Ether (III).** Uvaretin (110 mg) in dry dioxane (20 ml) was treated in the usual manner[13] with diazomethane, generated from *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (Aldrich, 1 g). After 2 h reaction at room temperature, workup afforded 100 mg of uvaretin monomethyl ether, which was recrystallized from ethyl acetate to colorless platelets, mp 138–139 °C. Uvaretin monomethyl ether prepared in this way had infrared [($CHCl_3$) 3380, 1610, and 1590 $cm^{-1}$], ultraviolet [(EtOH) $\lambda_{max}$ 290 nm (log $\epsilon$ 4.40)], $^1H$ NMR [(acetone-$d_6$) $\delta$ 3.0 and 3.3 (each 2 H, $A_2B_2$ pattern), 3.90 (8 H, s), 6.26 (1

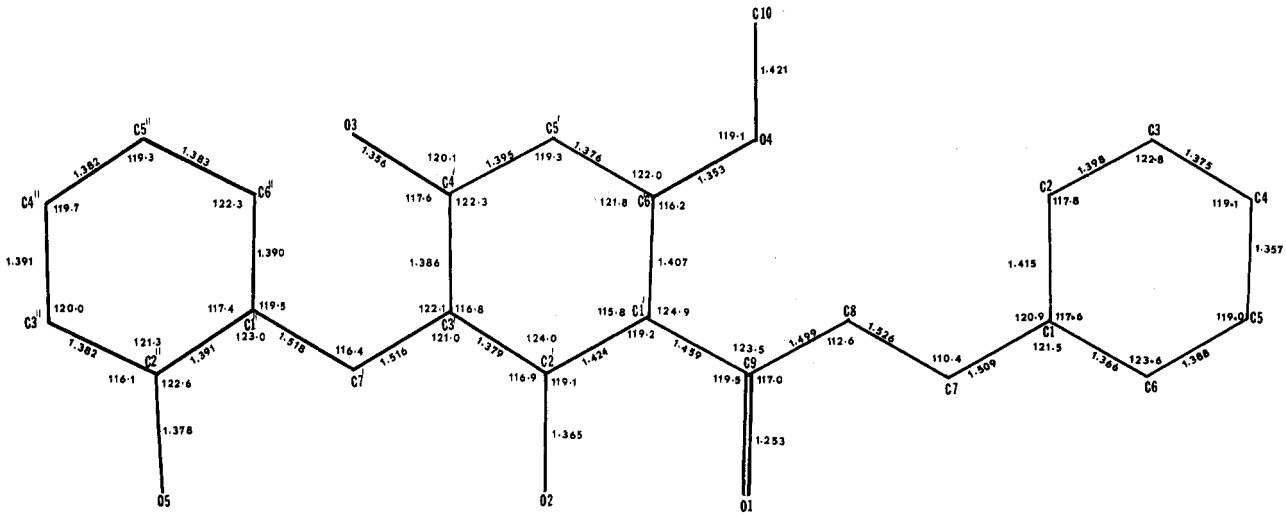


**Figure 1.** Bond lengths (Å) and angles (deg) in uvaretin (I).

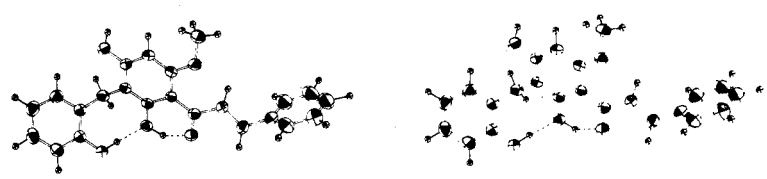


**Figure 2.** Stereoscopic view of uvaretin (I). Hydrogen atoms are shown as spheres and other atoms as 50% probability ellipsoids.

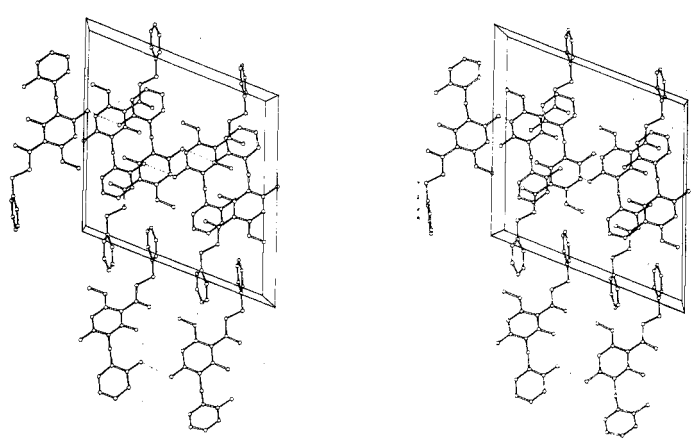


**Figure 3.** Stereoscopic view of a unit cell, *b* axis projection, with the *a* axis vertical.

H, s), 6.9 (4 H, m), 7.20 (5 H, s), 7.9 (1 H, br), and 14.5 (1 H, s)], and mass [*m/e* 392 ($M^+$), 287, 260, 193, 181, 154, 107, 91 (base), and 87] spectra in accord with structure III.

Anal. Calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 73.07; H, 6.27.

**Uvaretin Dimethyl Ether (IV).** Uvaretin (200 mg) was methylated with sodium hydroxide (0.5 g) and dimethyl sulfate (1.2 g) in the usual way.[14] After workup, the crude semisolid product (170 mg) was recrystallized twice from hexane/benzene to provide pure material as colorless, tiny needles, mp 122–123 °C. The uvaretin dimethyl ether prepared in this way had infrared [($CHCl_3$) 3400, 1610, and 1590 $cm^{-1}$], ultraviolet [(EtOH) $\lambda_{max}$ 291 nm (log $\epsilon$ 4.40)], $^1H$ NMR [($CDCl_3$) 3.0 and 3.3 (each 2 H, $A_2B_2$ pattern), 3.75 (3 H, s), 3.81 (6 H, s), 3.91 (2 H, s), 5.96 (1 H, s), 6.8 (4 H, m), 7.20 (5 H, s), and 13.9 (1 H, s)], and mass [*m/e* 406 ($M^+$), 301, 274, 193, 181, 166, 121 (base), 91, 77, and 65] spectra in accord with structure IV.

Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.44. Found: C, 74.27; H, 6.44.

**Crystallographic Study of Uvaretin (I).** Colorless crystals were grown from chloroform/benzene. A needle 0.2 × 0.2 × 0.4 mm was mounted with the *b* axis parallel to the goniostat $\phi$ axis. The space group was determined by film methods to be $P2_1/c$. The cell parameters were found using eight reflections on a Picker-FACS-I diffractometer (Cu K$\alpha$, $\lambda$ = 1.54178 Å, graphite monochromator) to be $a$ = 16.499 (6), $b$ = 7.723 (2), $c$ = 16.055 (6) Å, and $\beta$ = 111.11° (1). The crystal density was measured by flotation as 1.316 g/ml, agreeing well with a calculated density of 1.317 g/ml assuming four molecules in the unit cell. Intensity data were collected up to $2\theta$ = 120° using a scintillation counter with pulse-height analyzer, $\theta$–$2\theta$ scan technique, 2°/min scan rate, 10-s background counts, attenuators when the count rate exceeded $10^4$ counts/s, and 2° scan range with a dispersion factor allowing for $\alpha_1$–$\alpha_2$ splitting at large $2\theta$ values. Of 2676 independent reflections measured, $2343 > 3\sigma(I)$ were considered observed. Three standard reflections were monitored every 50 measurements to check the crystal alignment and the stability; no decrease in the intensity of standards was observed. Lorentz and polarization corrections were applied to the data, but no correction was made for absorption.

Phases for reflections with normalized structure factor $E > 1.5$ were generated using the direct method program of Long.[15] Although normally the solution with highest consistency index and least number of cycles is correct, in the present case the correct solution was third highest in consistency index and second lowest in number of cycles. All nonhydrogen atoms were located on an $E$ map using calculated phases as coefficients. Full matrix least-squares refinement in which positional and isotropic thermal parameters were varied reduced $R$ to 0.122. Two more cycles of least-squares refinement using anisotropic thermal parameters reduced $R$ to 0.087. A difference map at this stage revealed all the hydrogen atoms. One more cycle of least-squares refinement using anisotropic temperature factors for nonhydrogen atoms and isotropic temperature factors (of nonhydrogen atoms to which they were attached) for hydrogen atoms reduced $R$ to 0.060. The refinement was terminated at this stage since

the ratios of shifts in parameters to estimated standard deviations were all less than 0.2. The refinement was based on $F_o$, the quantity minimized being $\Sigma w(F_o - F_c)^2$. Unit weights were used. The scattering factors used were those of Hanson, Herman, Lea, and Skillman.[16]

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**Registry No.**—I, 58449-06-2; II, 58449-07-3; III, 58449-08-4; IV, 58449-09-5.

**Supplementary Material Available.** Tables of temperature factors and bond distances and angles involving hydrogens (3 pages). Ordering information is given on any current masthead page.

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(17) Identification was confirmed by Dr. Robert E. Perdue, Medicinal Plant Resources Laboratory, Agricultural Research Center, Beltsville, Md. A reference specimen was deposited in that herbarium. The plant was collected in Kenya, in October 1971.
(18) Of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Md.
(19) Carbon and hydrogen analyses were performed by Chemalytics, Inc., Tempe, Ariz. $^1$H NMR, ir, uv, and mass spectra were determined using a Varian T-60 spectrometer, a Beckman IR-33, a Beckman DBG, and a Hitachi Perkin-Elmer double focusing spectrometer (Model RMU-6-E), respectively. The melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

# Antitumor Agents from *Jatropha macrorhiza* (Euphorbiaceae). II. Isolation and Characterization of Jatrophatrione[1]

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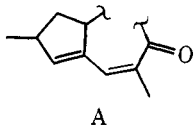
As a result of the continuing search for plants having tumor-inhibiting constituents, the chloroform extract of the roots of *Jatropha macrorhiza* Benth. (Euphorbiaceae)[2] was found to possess inhibitory activity toward the P-388 (3PS) lymphocytic leukemia test system.

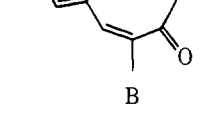
## Discussion

One constituent of the chloroform extract of *Jatropha macrorhiza* Benth. roots is the new diterpene jatrophatrione, $C_{20}H_{26}O_3$, subsequently shown to be I. The initial spectral data (ir, uv, $^1$H NMR) of jatrophatrione immediately led to the conclusion that jatrophatrione was structurally related to jatrophone (II, $C_{20}H_{24}O_3$), previously isolated from *Jatropha gossypiifolia*.[4] Specifically, the partial structure A appeared to be a common feature of the two diterpenes. Table I shows the nearly identical spectral data for jatrophatrione (I) and jatrophone (II) generated by partial structure A.



A

Assuming a close biogenetic and structural relationship to jatrophone (II), the rest of the constitution of jatrophatrione (I) was deduced. The two double bonds in partial structure A accounted for all of the vinylic carbon atoms ($^{13}$C NMR), and with two more carbonyl groups (ir, $^{13}$C NMR) there had to be one more ring. That the latter is five membered could be seen in the infrared spectrum at 1746 cm$^{-1}$ (cyclopentanone) and a quaternary methyl group in the $^1$H NMR spectrum ($\delta$ 1.47) dictated that the closure of this ring be as shown in partial structure B. The downfield position of this angular



B

methyl group suggested that it is flanked by both remaining carbonyl groups, as in structure I. Scheme I shows how the tricyclic structures I (jatrophatrione) and II (jatrophone) may be derived in nature from bicyclic precursor III; steps to this precursor from geranylgeranyl pyrophosphate via casbene oxidation product IV are readily imagined (cf. ref 5).

An x-ray study on jatrophatrione (I) confirmed the proposed constitution and showed the relative configurations to be as depicted. The absolute configuration was not determined crystallographically but is based on the assumption that jatrophatrione (I) and jatrophone (II) possess the same configuration at C2.[4] Bond distances are given in Table II and bond angles in Table III.