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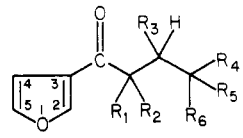
Synthesis and Analysis of Various 3-Furyl Ketones from *Perilla frutescens*

John E. Garst* and Benjamin J. Wilson

Synthesis of 3-cyanofuran from 3-bromofuran and CuCN in *N*-methylpyrrolidone or equilibration of 3-furoic acid with 1,3-dicyanobenzene gave equally good yields. The latter procedure also afforded 2-cyanofuran from 2-furoic acid, but both 3-methyl- and 5-methyl-2-furoic acid gave only methylfuran decarboxylation products. Reaction of either 2- or 3-cyanofuran with isoamylmagnesium bromide gave moderate yields of the respective isoamyl 2- or 3-furyl ketones after imine hydrolysis. 1-(3-Furyl)-2-(phenylselenenyl)-4-methylpentan-1-one, formed quantitatively by reaction of isoamyl 3-furyl ketone with phenylselenenyl chloride, gave excellent yields of isoegomaketone upon H_2O_2 oxidation. Isoegomaketone was selectively deconjugated to egomaketone by successive treatments with potassium *tert*-butoxide in dry *tert*-butyl alcohol and dilute HOAc. The isoegomaketone methanol Michael adduct 1-(3-furyl)-3-methoxy-4-methylpentan-1-one, prepared by stirring with suspended Na_2CO_3 in methanol, was found to be a likely artifact of methanol extraction rather than a true constituent of *Perilla frutescens* as previously reported; the other three 3-furyl ketones have been identified and quantitated.

Acute bovine pulmonary toxicity, caused by ingestion of moldy sweet potatoes containing 4-ipomeanol (1), led



1, $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = CH_3$; $R_6 = OH$
2, $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = R_6 = CH_3$
3, $R_1 = R_2 = H$; $R_3 = R_4$ = olefin; $R_5 = R_6 = CH_3$
4, $R_1 = R_4 = H$; $R_2 = R_3$ = olefin; $R_5 = R_6 = CH_3$
5, $R_1 = R_2 = R_6 = H$; $R_3 = OCH_3$; $R_4 = R_5 = CH_3$
6, R_1 = Br; $R_2 = R_3 = R_4 = H$; $R_5 = R_6 = CH_3$
7, R_1 = PhSe; $R_2 = R_3 = R_4 = H$; $R_5 = R_6 = CH_3$

to structure–toxicity studies of numerous 3-substituted furans in mice (Garst and Wilson, 1981). Those studies revealed a 0.99 correlation coefficient between acute murine toxicity and the 5-furan ^{13}C NMR resonance shift for divergent 3-substituted furans. A good linear relationship was also discovered between acute toxicity and an HPLC measure of the octanol–water partition coefficient of methyl through hexyl 3-furyl ketones. These studies had previously identified perilla ketone (2) as a potent and lung-selective pulmonary toxicant in mice (Wilson et al., 1977, 1978). The widespread mint plant *Perilla frutescens* is a major cause of bovine respiratory toxicity (Wilson et al., 1977, 1978) and is a natural source of 2, egomaketone (3), isoegomaketone (4), and the methyl ether 5 (Ueda and Fujita, 1962; Ito, 1964; Ina and Suzuki, 1971). Since use of the plant as a condiment in Japanese restaurants presents human health questions and existing procedures afforded unsatisfactory quantities of these agents for toxicity evaluation in large animals, a facile, moderate-scale synthesis of these agents was developed from 3-furoic acid.

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MATERIALS AND METHODS

Chemical analysis was performed with a Hewlett-Packard 1084B HPLC and a 10 cm long, 10-μm particle size, RP-8 column from Brownlee Laboratories (Santa Clara, CA). The ultraviolet absorbance signal at 204 nm was integrated for quantitation. Elution was achieved by using 2 mL min^{-1} 37% MeOH–H_2O with a column temperature of 35 °C. Typical elution times are 3.99 min for 5, 4.55 min for 3, and 5.59 min for 4. Perilla ketone elutes near 8 min, making this procedure superior to the following method used earlier for screening of ethereal *P. frutescens* extracts.

Plant analyses were performed with a Waters HPLC and utilized two C-18 Bondapak reverse-phase columns in series and 50% MeOH–H_2O as the elution solvent. Quantitation was achieved by comparing the refractive index signals of plant and authentic materials.

Boiling and melting points (Thomas-Hoover apparatus) are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer, and ^1H NMR spectra were recorded on a JOEL Model JNM-MH-100 or

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Varian EM90 spectrometer using Me_4Si as the internal standard. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. In all cases spectral data were consistent with the proposed structures and elemental analyses were within 0.3% of the calculated values.

3-Cyanofuran. *Method A.* 3-Bromofuran (26.0 g, 0.177 mol) was added over several minutes to a magnetically stirred suspension of Cu_2CN_2 (28.5 g, 0.318 g-atom) in CaH-dried and distilled NMP (88.5 mL). The warm mixture was refluxed for 1.75–2.0 h; a head and condenser were attached and the liquid was distilled to bp 204 °C. The distillate was diluted 3× with Et_2O and washed with saturated NaCl (4 × 50 mL), 2 N HCl (75 mL), and H_2O (2 × 50 mL). The NaCl solution was extracted (Et_2O; 2 × 50 mL), and the Et_2O extract was washed with HCl and H_2O as before. The combined Et_2O fractions were dried ($MgSO_4$), evaporated at reduced pressure, and distilled to give 13 g (79%) of 3-cyanofuran, bp 148–153 °C [Srogl et al. (1970), 151 °C], which crystallized upon standing, mp 29 °C. Spectral data are given under Method B.

Method B: General Procedures for Conversion of Furoic Acid to Furonitrile. 3-Furoic acid (56.04 g, 0.5 mol) and 1,3-dicyanobenzene (128.13 g, 1 mol) were heated to reflux for 0.5 h; a head and condenser were attached, and crude 3-cyanofuran (47.1 g) was slowly distilled until the temperature in the distilling head reached 195 °C or until crystallization occurred in the condenser. The crude distillate, diluted 3–4-fold with Et_2O, was washed with 0.5 N NaOH to pH 11 and with saturated NaCl (3 × 60 mL). The Et_2O fraction was dried ($MgSO_4$), evaporated at room temperature under reduced pressure, and distilled to afford 3-cyanofuran: 37.7 g (81%) at bp 150–154 °C; IR (neat) 3152, 2241, 1499, 1355, 1162, and 962 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62 (d,1 H, H-4, J = 2 Hz), 7.44 (d, 1 H, H-5, J = 2 Hz), 7.90 (s, 1 H, H-2).

1-(3-Furyl)-4-methylpentan-1-one (2). 3-Cyanofuran (18.6 g, 0.2 mol) in Et_2O (20 mL) was added dropwise to isoamylmagnesium bromide [from Mg (6 g), isoamyl bromide (39 g), and Et_2O (175 mL)]; the solution was refluxed for 1 h. PhH (500 mL) was added continuously as the Et_2O was removed from distillation to bp 79–80 °C. The PhH solution was refluxed (2.5 h), decomposed under cooling with HCl (6 N, 200 mL) and H_2O (300 mL), and allowed to stand at room temperature overnight. The organic phase separated, and the H_2O fraction was extracted with Et_2O (2 × 100 mL). The combined organic fraction was washed with H_2O (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and H_2O (2 × 50 mL) and then dried ($MgSO_4$). The PhH–Et_2O was evaporated under reduced pressure and the product distilled through a short column to afford 24.7 g (74%) of **2**, bp 50–60 °C (0.3–0.1 mmHg). The product was redistilled to afford 24.2 g (73%) of colorless **2**: bp 49–50 °C (0.1 mmHg) [Ueda and Fujita (1962), bp 72–73 °C (3 mmHg)]; IR (neat) 3137, 1670, 1560, 1508, and 1465 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, 6 H, 2 CH_3), 1.62 (m, 3 H, CH_2CH), 2.74 (t, 2 H, CH_2CO), 6.75 (d, 1 H, H-4, J = 2 Hz), 7.40 (d, 1 H, H-5, J = 2 Hz), 8.02 (s, 1 H, H-2). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.25; H, 8.49. Found: C, 72.08; H, 8.50.

The tosylhydrazone was prepared by refluxing a solution of **2** (2.99 g, 18 mmol) and $pTsNHNH_2$ (3.91 g, 21 mmol) in 100% EtOH for 6 h. Cooling (0 °C) gave the crystalline solid (4.4 g, 75%), mp 137.5–139 (100% EtOH). Perilla ketone (**2**) could be recovered from the solid by concentrated HCl catalyzed exchange (3 drops) with Me_2CO (Sachs and Fuchs, 1976), extraction with hexane, and high-vacuum distillation.

1-(2-Furyl)-4-methylpentan-1-one. This isomer of **2** was prepared in 64% yield from 2-cyanofuran by the Grignard method for **2**: bp 47–49 °C (0.15 mmHg) [Asahira and Murayama (1914), 119 °C (22 mmHg)]: IR (neat) 3125, 1670, 1565, and 1465 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, 6 H, 2CH_3), 1.64 (m, 3 H, CH_2CH), 2.86 (t, 2 H, CH_2CO), 6.52 (m, 1 H, H-3, J = 2 and 4 Hz), 7.24 (d, 1 H, H-2, J = 4 Hz), 7.64 (s, 1 H, H-4, J = 2 Hz). Anal. Calcd for $C_{10}H_{14}O_2$: 72.25; H, 8.49. Found: C, 72.04; H, 8.48.

1-(3-Furyl)-4-methylpent-3-en-1-one (3). *Method A (4:1 Mixture of 3–4).* To DMF (80 mL, molecular sieves, type 3A) was added LiBr (18.6 g, anhydrous), Li_2CO_3 (15.8 g, anhydrous), and **3** [1-(3-furyl)-2-bromo-4-methylpentan-1-one] (9.8 g, 0.04 mol). The mixture was refluxed with magnetic stirring for 3 h under N_2. Upon cooling the material solidified and was taken into Et_2O, washed with 400 mL of 10% HOAc and then $NaHCO_3$ (saturated) until the aqueous fraction was neutral to litmus, and dried ($MgSO_4$). The solvent was evaporated and the brown oil distilled as in method B (pure **3**) through a 25 theoretical plate Telfon spinning band column to afford 4.5 g (70%) of a 3.8:1 mixture of **3** and **4**. This ratio was based on the integrated signals of the methyl groups at 1.70 and 1.08 for **3** and **4**, respectively.

Method B (Pure 3). Pure **4** or mixtures of **3** and **4** only (4.2 g, 0.0256 mol) were added dropwise to a stirred mixture of KO-t-Bu (Aldrich, freshly opened, 30 g) in *t*-BuOH (anhydrous, 130 mL under N_2. The purple solution was warmed to 40 °C to prevent solvent crystallization. After 3 h, the mixture was treated with 500 mL of 10% HOAc, then carefully neutralized with $NaHCO_3$ (saturated), extracted with Et_2O, washed with H_2O (3 × 100 mL), dried (molecular sieves, type 3A), and distilled, bp 62–64 °C (0.25 mmHg) [Ueda and Fujita (1962), 122–126 °C (20 mmHg)] to afford 3.25 g (80%) of pure **3**: IR (neat) 3130, 1674, and 1310 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 and 1.76 (s, 6 H, 2CH_3), 3.43 (d, 2 H, CH_2CO, J = 7 Hz), 5.36 (t, 1 H, CH, J = 2 and 7 Hz), 6.73 (s, 1 H, H-4), 7.40 (s, 1 H, H-5), 8.02 (s, 1 H, H-2). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.95; H, 7.31.

***trans*-1-(3-Furyl)-4-methylpent-2-en-1-one (4).** The crystalline intermediate **7** (58.8 g) was dissolved in THF (anhydrous, 400 mL) and EtOAc (anhydrous, 400 mL) and cooled to 5 °C. Glacial HOAc (3 mL) was added followed by the dropwise addition of H_2O_2 (30%, 56 mL), whose exothermic reaction requires keeping the temperature below 35 °C. After 4 h, the magnetically stirred solution was washed with $NaHCO_3$ and NaCl solutions (saturated, 3 × 200 mL each), dried ($MgSO_4$), and evaporated under reduced pressure to afford 27.6 g (92%) of crude isoegomaketone. One impurity, indicated by the peak at 1700 cm^{-1}, does not readily elute from silica gel with CH_2Cl_2; a bright yellow, but trace, contaminant elutes just prior to the isoegomaketone. The pure, water-white elution product was distilled, bp 58 °C (0.08 mmHg), to give 24.6 g (81%) of **4** [Massy-Westropp and Reynolds (1966), 70 °C (1 mmHg)]: IR (neat) 3130, 2960, 1665, 1618, and 1556 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, 6 H, 2CH_3, J = 7 Hz), 2.48 (m, 2 H, CH, J = 7 Hz), 6.46 (d, 1 H, COCH, J = 16 Hz), 6.98 (d, 1 H, CH-*i*-Pr, J = 7 and 16 Hz), 6.76 (s, 1 H, H-4), J = 2 Hz), 7.40 (s, 1 H, H-5, J = 2 Hz), 8.06 (s, 1 H, H-2). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.97; H, 7.49.

1-(3-Furyl)-3-methoxy-4-methylpentan-1-one (5). *Initial Experiment.* Compound **4** (1 g, 6.1 mmol) in MeOH (anhydrous, 10 mL) containing Na_2CO_3 (anhydrous, 0.2 g) was magnetically stirred for 48 h at room temperature under N_2, during which time the mixture became

yellow. After 48 h, H_2O (20 mL) was added and 0.5 g (25%) of solid **8** was collected. Extraction of the aqueous fraction with Et_2O (3 × 20 mL) afforded 0.5 g of an oil: IR (neat) 3128 and 1665 cm^{-1}; ^1H NMR (CCl_4) indicated a 3:1 ratio of **5** to **4**, with the following positions for *5*, δ 0.94 (d, 6 H, $2CH_3$), 2.5–3.1 (m, 2 H, CH_2CO), 3.24 (s, 3 H, OCH_3), 3.66 (m, 1 H, CHOMe), 6.78 (s, 1 H, H-4), 7.49 (s, 1 H, H-5), 8.14 (s, 1 H, H-2). The ratio was based on integration of signals for the aliphatic methyl groups at 0.94 and 1.08 for **5** and **4**, respectively in CCl_4.

Second Experiment. Repetition of the above procedure using compound **4** (3.88 g, 23.7 mmol) in MeOH (anhydrous, 233 mL) and Na_2CO_3 (anhydrous, 0.81 g) afforded solid **8** (0.31 g, 8%) and 3.57 g of oil containing 17% unreacted **4**, 18% unsaturated ketone **3**, and a 57% yield of methyl ether **5** after 25 h, as determined by HPLC.

1-(3-Furyl)-2-bromo-4-methylpentan-1-one (6). When literature bromination procedures for 3-acetylfuran (Massy-Westropp and Reynolds, 1966) were used, **2** (11.0 g, 66.6 mmol) in CS_2 (90 mL) and Br_2 (11.2 g, 69 mmol) in CS_2 (15 mL) afforded 13.6 g (86%) of **6**: bp 76 °C (0.15 mmHg); IR (neat) 3130, 2950, and 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (2 d, 6 H, $2CH_3$), 1.4–2.1 (m, 3 H, CH_2CH), 4.85 (t, 1 H, CHBr), 6.91 (s, 1 H, H-4), 7.55 (s, 1 H, H-5), 8.30 (s, 1 H, H-2). Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 48.99; H, 5.30. Found: C, 48.86; H, 5.43.

1-(3-Furyl)-2-(phenylselenenyl)-4-methylpentan-1-one (7). To phenylselenenyl chloride (Aldrich Chemical Co.) (51 g, 0.266 mol) was added EtOAc (1000 mL) and **2** (37 g, 36.3 mL, 0.233 mol). Concentrated HCl (4 mL) was added and the solution stirred magnetically for 60 h at room temperature. After this time, the light yellow to orange solution was washed with H_2O (3 × 200 mL), $NaHCO_3$ (saturated, 2 × 200 mL) and dried (molecular sieves, type 3A), and the solvent was removed under reduced pressure. Several crystallizations from minimal cold (0 °C) petroleum ether afforded 65 g (92%) of white crystalline **7** product: mp 59–60 °C; IR (Nujol) 3120 and 1640 cm^{-1}; ^1H NMR (CCl_4) δ 0.85 (2 d, 6 H, $2CH_3$), 1.70 (m, H, $CHMe_2$), 3.95 (t, H, CHCO), 6.60 (s, H, H-4), 7.23 (m, 6 H, H-5 and PhSe), 7.67 (s, H, H-2). The chemical ionization mass spectrum M + 1 peak occurred at 323, but peaks corresponding to the other selenium isotopes were also observed. Anal. Calcd for $C_{16}H_{17}SeO_2$: C, 60.00; H, 5.35; Se, 24.65. Found: C, 59.82; H, 5.56; Se, 24.41.

1-(3-Furyl)-3-isopropyl-4-(3-furoyl)-6-methyl-5-hepten-1-one (8). To MeOH (10 mL) containing NaOMe (0.33 g, 72 mmol) was added **4** (1 g, 6.1 mmol). The mixture was refluxed 1 h and crystallized upon cooling. Collection afforded 0.7 g (70%) of the dimer: mp 170–171 °C (MeOH); IR (Nujol) 3125, 1655, 1640, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (2 d, 6 H, $2CH_3$), 1.42 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.74 (m, H, $CHMe_2$), 2.54 (m, 2 H, CH_2), 2.88 (m, H, CH-*i*-Pr), 3.70 (t, H, CHCO, J = 7 Hz); 4.86 (d, H, CH=C, J = 7 Hz), 6.52 (s, 2 H, H-4); 7.16 (s, 2 H, H-5), 7.70 and 7.76 (2 s, 2 H, H-2); chemical ionization mass spectra M + 1 ion = 329, scission products at 219 and 165. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.39. Found: C, 73.09; H, 7.49.

RESULTS AND DISCUSSION

Efforts to reproduce literature reactions between 3-furoyl chloride and disobutylcadmium (Matsuura, 1957) or diethylisobutyl malonate (Arata and Achiwa, 1958) led initially to an improved synthesis of 3-furoyl chloride. Since 3-furoic acid is insoluble in refluxing $SOCl_2$, a catalytic amount of *N,N*-dimethylformamide (DMF) was used to expedite the reaction, but an adduct was formed that codistilled. Substitution of *N,N*-diphenylformamide enabled separation of the pure acid chloride. However, sufficient pure **2** for toxicity evaluation was obtained only via the organocadmium procedure and then only after Girard's carbonyl purification (Ueda and Fujita, 1962). As a result a new approach to these compounds was sought.

Improved Synthesis of Cyanofurans and Furyl Ketones. Srogl and co-workers reported 3-cyanofuran preparation from 3-bromofuran and CuCN–KCN (Srogl et al., 1970). Reaction of the nitrile with Grignard reagents affords good to excellent yields of various simple 3-furyl ketones (Srogl et al., 1970). In order to exploit the latter reaction, we reexamined their preparation of 3-cyanofuran. Substitution of CuCN in dry *N*-methylpyrrolidone for their CuCN–KCN–quinoline procedure increased the 3-cyanofuran yield, as previously observed (Newman and Boden, 1961). In addition, the procedure of Toland and Ferstandig for converting acids to nitriles was explored (1958). Double distillation of the molten mixture of 3-furoic acid and 1,3-dicyanobenzene consistently, and far more conveniently, gave 80% yields of the lower boiling 3-cyanofuran in up to 1-mol batches. The facility of this reaction prompted examination of its utility for the preparation of other cyanofurans. Under these same conditions 3-methyl-2-furoic acid (Burness, 1963) and 5-methyl-2-furoic acid, the latter obtained from 5-methylfurfural by alkaline $AgNO_3$ oxidation (Campaign and LeSuer, 1963), afforded 19% and 39% yields of the corresponding 3- and 2-methylfurans. Only traces of the nitrile remained. Cyanofuran yields from this procedure appear to be inversely related to the previously reported tendency of the furoic acid to decarboxylate (Burness, 1963; Deady and Shanks, 1972). Reaction of 2- and 3-cyanofuran with isoamylmagnesium bromide afforded 64% and 68–74% yields of the 2- and 3-furyl isoamyl ketones, respectively, after hydrolysis of the intermediate imine.

Synthesis of Isoegomaketone, Egomaketone, and 1-(3-Furyl)-3-methoxy-4-methylpentan-1-one. Isoegomaketone (**4**) has been previously synthesized by condensing bromomethyl 3-furyl ketone with isobutyraldehyde in 60% overall yield (Massy-Westropp and Reynolds, 1966). The furan was prepared by α-bromination of 3-acetylfuran, a difficult-to-obtain and exceedingly sublimable lung toxic furan (Garst and Wilson, 1981). Our route to isoegomaketone affords an 86% yield of the intermediate 1-(3-furyl)-2-bromo-4-methylpentane-1-one (**6**) simply by titrating **2** with Br_2 in CS_2, as reported for the preparation of bromomethyl 3-furyl ketone (Massy-Westropp and Reynolds, 1966). The furan ring remains unaffected by the liberated gaseous HBr as long as the reaction is protected from water vapor.

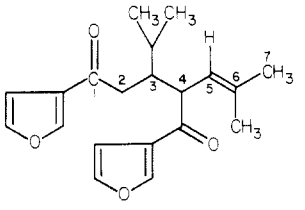
Both triethylamine (TEA) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) are reported to affect dehydrobromination reactions in refluxing diethyl ether (Price and Judge, 1973; Oediger et al., 1972). However, both reagents failed to dehydrohalogenate **6** under these conditions. This reaction was finally achieved in 70% yield by refluxing **6** with LiBr–Li_2CO_3 in dry DMF (Joly et al., 1958), but this procedure afforded a 3.8:1 ratio of unconjugated ketone **3** to conjugated ketone **4**. Spinning band distillation did not separate the olefins. This ratio, which favors the unconjugated ketone, is contrary to expectations. Perhaps it stems either from a greater stability of the trisubstituted olefin or from kinetic factors, but no effort was made to discern which is the case.

Failure of DBU and TEA to effect dehydrohalogenation may reside in the conformation of the α-bromo ketone. The IR spectrum of neat α-bromo ketone **6** displays a carbonyl stretch at 1672 cm^{-1}, virtually unchanged from

the 1670-cm^{-1} value for perilla ketone. On this basis the bromine atom resides exclusively out of the plane of the 3-furoyl group (Bellamy, 1966). Molecular models suggest that the trans β carbon hydrogen resides in a depression between the isopropyl substituent and the furan ring. Perhaps this arrangement sufficiently diminishes access to the DBU or TEA nitrogen that this dehydrohalogenation requires the higher temperatures associated with refluxing DMF, as opposed to refluxing ether.

Pure *trans*-isoegomaketone (4) was finally obtained in 81% yield by hydrogen peroxide oxidation of the α-phenylselenide 7, obtained by the method of Sharpless et al. (1973), providing a high overall yield of 4 from commercially available 3-furoic acid. Pure egomaketone (3) was obtained in 80% yield by deconjugation of isoegomaketone (4) to the dark purple conjugated enolate by using commercial potassium *tert*-butoxide in warm anhydrous *tert*-butyl alcohol, followed by acidification with excess 10% HOAc (Ringold and Malhotra, 1962). In our hands both pure olefins 3 and 4 seem to undergo bond migration, resulting in an equilibrium mixture after a few months storage at 0 °C. In retrospect, our inability to separate these isomers by spinning band distillation may have a basis in this observation. No effort has been made, however, to investigate this bond migration problem.

In an attempt to prepare the purported methyl ether *P. frutescens* constituent 5 by this procedure, NaOMe–HOMe was substituted for the *tert*-butoxide-*tert*-butyl alcohol. Instead, the solid dimer 8 was obtained. Possibly,



8

partial conversion of 4 via the strong base treatment to 3 was followed by Michael condensation to afford the adduct 8. However, methyl ether 5 was obtained in 59% yield along with a 25% yield of dimer 8 and recovered 4 by simply stirring 4 with Na_2CO_3 in MeOH at room temperature for 48 h. High-performance liquid chromatography (HPLC) chemical analysis of 4 during a modification of this reaction revealed a half-life of 2.5 h. The overall initial rate constant for disappearance of 4 was 7.83×10^{-5} s^{-1} (±12.7%). After about 10 half-lives some 17% of 4 remained, indicating that Michael reaction equlibrium had been attained. That analysis also revealed formation of a 10% yield of 3 and only a 57% yield of the methyl ether 5 during the reaction. Although there was no HPLC analytical evidence for the dimer 8 being formed during the reaction, an 8% yield of 8 was isolated upon addition of water. This yield was reduced from the earlier 25% yield by the increased volume of methanol used.

Thus far, HPLC analysis of etherial extracts of *P. frutescens* samples have failed to demonstrate any presence of 5, although 2–4 have been detected and quantitated in the leaf, stem, and flower. Facile chemical formation of 5 suggests this substance may be an artifact of methanol extraction of *P. frutescens* rather than a true consistuent as previously reported (Ina and Suzuki, 1971). Overall leaf, stem, and flower concentrations in micrograms per gram of plant for 22 plant samples with standard deviations for each compound are as follows: 2, 275 ± 283, 2 ± 4, and 164 ± 221; 3, 486 ± 531, 1 ± 3, and 47 ± 99; 4, 61 ± 88, 0.3 ± 3, and 6 ± 16. The high variation of the constituent furans reflects in part an overall average without regard to plant age from the onset of study. Complex growth data (not shown) suggest that isoegomaketone is the major furan present in leaves in very early summer, but perilla ketone seems to be the major furan present in late summer and before frost. This would make perilla ketone the agent of greatest toxicological concern, as poisoning of livestock usually occurs at these times.

Perilla ketone, egomaketone, and isoegomaketone have received considerable attention as model compounds for the demonstration of somewhat exotic synthetic methods or as reagents for furan ring synthesis and/or side chain elaboration (Kondo and Matsumota, 1976; Zamojski and Kozluk, 1977; Kitamura et al., 1977; Inomata et al., 1979; Abdulla and Fuhr, 1978; Hoppmann and Weyerstahl, 1978; Gosselin et al., 1979; Pillot et al., 1980). The method offered here differs in that it affords a convenient and often higher yield synthetic route for medium- to large-scale preparation of several otherwise difficult to obtain 3-furyl ketones, utilizing the preformed ring in readily available 3-furoic acid. It also eliminates the need for photochemical equipment often required by other proceudres (Kondo and Matsumota, 1976; Zamojski and Kozluk, 1977; Kitamura et al., 1977). This chemical procedure also circumvents problems often encountered by increasing the scale in photochemical reactions. However, caution is urged when working with any of these agents. The acute toxicity of perilla ketone to an animal appears to increase with the lung cytochrome P-450 content in that species (Garst et al., 1984). Although human lung contains little cytochromes P-450 (Philpot, 1983), the high turnover rates for these furans may still make them hazardous in unexpected ways.

Registry No. 2, 553-84-4; 2 (2-furyl isomer), 78072-59-0; 3, 59204-74-9; 4, 34348-59-9; 5, 34359-72-3; 6, 90605-43-9; 7, 90605-42-8; 8, 90605-44-0; 3-cyanofuran, 30078-65-0; 3-bromofuran, 22037-28-1; 3-furoic acid, 488-93-7; 1,3-dicyanobenzene, 626-17-5.

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Toxicity and Bitterness in Australian *Dioscorea bulbifera* L. and *Dioscorea hispida* Dennst. from Thailand

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Underground tubers of bitter yams (*Dioscorea bulbifera* L. commonly known as var. *rotunda*), which are eaten after complex processing by Australian aborigines, were analyzed for acute toxicity and for the toxic alkaloid dioscorine. Results demonstrated that these tubers were not toxic, so they were extracted and the extracts were analyzed by thin-layer chromatography in order to determine the cause of bitterness. A major bitter component was found to be diosbulbin D (0.07 mg/g), a furanoid norditerpene previously isolated by Ida et al. (1978). Traditional aboriginal food processing techniques were found to be very efficient in removing diosbulbin D, thus making the bitter yams palatable. The alkaloid and bitter principle content of raw samples of this variety was compared with that of a dioscorine-containing yam from Thailand (*Dioscorea hispida* Dennst.), which is also used as food.

Yams of the genus *Dioscorea* are a staple subsistence food in some tropical regions of the world. The dorman underground tubers and the aerial tubers of both wild and cultivated varieties are harvested as a starch source in West Africa, parts of southeast Asia, the Pacific Islands, India, and Central America (Coursey, 1967).

Some species and varieties, particularly wild forms, are toxic and/or unpalatable. Of the 59 species recorded from southeast Asia, 8 are known to be bitter and/or poisonous if eaten raw (Burkill, 1954). The local people prepare the tubers before consumption to make them edible. Toxic alkaloids previously isolated from varieties of *Dioscorea hispida* Dennst. and *Dioscorea dumetorum* (Kunth.) Pax. are dioscorine and dihydrodioscorine, respectively. To date, other classes of bitter compounds recorded are (1) saponins and sapogenins in Central American, South African, and Indian species, (2) tannins and polyphenols in Indo-Chinese varieties, and (3) furanoid norditerpenes (diosbulbins), which have been isolated only from varieties of *Dioscorea bulbifera* L. (Martin, 1979; Telek et al., 1974).

Three species of yam are indigenous to Australia, but their botanical nomenclature is currently under review (Yen, 1984). One of these, *D. bulbifera*, commonly known as var. *rotunda*, is a bush food of northern Australian aboriginal people. Only the underground tuber is eaten, not the small aerial tuber (bulbil). Other varieties of *D. bulbifera* occur widely as food plants, both in Africa and in other parts of Asia (Alexander and Coursey, 1969). In Australia today, it is mainly eaten by those who are returning to their traditional homelands. In the raw state, it is described in aboriginal English as "cheeky", by which is meant bitter or poisonous. Treatment practices vary but commonly involve baking, followed by leaching of the sliced tubers in running water, overnight. The resultant food is then eaten without further preparation. These Australian techniques are very similar to those used in other parts of the world for preparing bitter yams (Alexander and Coursey, 1969).

Since no prior analysis of the pharmacologically active components of Australian yam varieties have been carried out, the aims of the following experiments were to identify the nature of the toxic and/or bitter components of this yam variety and to examine the effectiveness of traditional food processing methods in removing these substances.

The composition of the extracts of the cheeky yam were compared throughout with that of an authentic dioscorine-containing yam, *D. hispida* Dennst. (from Thailand). This toxic yam is also prepared as a vegetable in southeast Asia (Burkill, 1954).

The findings are of interest not only to chemotaxonomists in tracing species differences but also to workers in Australian aboriginal communities.

EXPERIMENTAL SECTION

Plant Material. Underground tubers of *D. bulbifera* were collected by aboriginal people from two locations in northeast Arnhem Land, NT, Australia, during April–September (dry season and middle of dormant stage), in 1981, 1982, and 1983. Underground tubers of *D. hispida*

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