on a Hitachi–Perkin Elmer R-20 spectrometer with a dilute solution in deuterochloroform, and tetramethylsilane as an internal standard.

**Materials.** Commercially available xanthine, theophylline, theobromine, and adenine, as well as trimethyl and triethyl phosphates were used without further purification. Dimethyl methyl- and diethyl ethylphosphonates were prepared quantitatively *via* Arbuzov reactions using the corresponding trialkyl phosphites and alkyl iodides.[10] Methyl dimethyl- and ethyl ethylphenylphosphinates were obtained by the procedure of Reinhardt, *et al.*,[11] and Steininger,[12] respectively. Reaction conditions are listed in Table I. The following preparations are typical.

**Alkylation of Xanthine (1). A. With Trimethyl Phosphate (a).** A mixture of **1** (3.0 g, 0.02 mol) and **a** (14.0 g, 0.1 mol) was refluxed with stirring. The light-boiling substances were removed from the resulting clear solution under reduced pressure to give a residue, which was then dissolved in chloroform, and the solution was neutralized with an aqueous solution of sodium hydrogen carbonate. Evaporation of the solvent from the organic solution gave caffeine (**5**) as crystals: 1.90 g (50%); mp 223–234° (tetrahydrofuran–diethyl ether) (lit.[13] mp 235°); $\lambda_{max}$ ($H_2O$) 272 nm (log $\epsilon$ 4.04) [lit.[13] $\lambda_{max}$ ($H_2O$) 272 nm (log $\epsilon$ 4.03)].

**B. With Triethyl Phosphate (d).** Compound (1) (3.25 g, 0.02 mol) and **d** (11.68 g, 0.06 mol) afforded the following two products after preparative thin layer chromatography (2-mm thickness, Silica gel G according to Stahl, E. Merck, Darmstadt, West Germany) of the chloroform extract, which was obtained from the reaction mixture in a manner similar to that mentioned above. A mixture of ether and ethanol (15:1) was employed as a developing solvent.

**3,7-Diethylxanthine (4):** 1.1 g (25%); $R_f$ 0.5; mp 179–182° ($H_2O$) (lit.[14] mp 183°); ir (KBr) 3150 (w), 2980 (m), 1680 (s), 1540 (m), 1445 (w), 1275 (w), 1220 (w), 1030 (m), and 850 (m) $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 8.90 (s, 1, NH), 7.50 (s, 1, ring H), 4.25 (q, 2, $CH_2$), 4.10 (q, 2, $CH_2$), 1.50 (t, 3, $CH_3$), and 1.32 (t, 3, $CH_3$).

**1,3,7-Triethylxanthine (6):** 1.1 g (22%); $R_f$ 0.8; mp 108–111° ($H_2O$) (lit.[15] mp 111°); ir (KBr) 3100 (w), 2980 (w), 1700 (s), 1650 (s), 1545 (m), 1450 (m), 1230 (w), 1050 (w), 1020 (w), 875 (m), and 750 (m) $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 7.45 (s, 1, ring H), 3.7–4.5 (complex m, 6, 3 $CH_2$) and 1.0–1.6 (complex m, 9, 3 $CH_3$).

**Ethylation of Theophylline (2) with d.** A mixture of **2** (3.46 g, 0.02 mol) and **d** (10.50 g, 0.06 mol) was heated at 180° for 1.3 hr. The reaction mixture was treated in a manner similar to the methylation of **1** to give 3.12 g (79%) of 7-ethyl-1,3-dimethylxanthine (**7**): mp 148–149° (ethanol) (lit.[2] mp 152–153°); ir (KBr) 3100 (w), 2980 (w), 1700 (s), 1650 (s), 1545 (m), 1480 (m), 1220 (m), 1190 (m), 1020 (w), 970 (m), and 740 (m) $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 7.46 (s, 1, ring H), 4.35 (q, 2, $CH_2$), 3.62 (s, 3, $NCH_3$), 3.45 (s, 3, $NCH_3$) and 1.55 (t, 3, $CH_3$).

**Methylation of 3,7-Diethylxanthine (4) with a.** Compound **4** (1.0 g, 0.005 mol) was treated with excess of **a** to produce 0.8 g (72%) of 3,7-diethyl-1-methylxanthine (**8**): mp 96° (sublimed); ir (KBr) 3100 (w), 1700 (s), 1650 (s), 1545 (m), 1490 (m), 1230 (m), 1000 (m), and 750 (m) $cm^{-1}$.

*Anal.* Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.25; H, 6.18; 24.42.

**Alkylation of Adenine (9). A. With a.** A mixture of **9** (1.50 g, 0.01 mol) and **a** (1.40 g, 0.01 mol) in dimethylformamide (10 ml) was refluxed for 2 hr. The reaction mixture was allowed to stand overnight to yield crystals which was dissolved in aqueous sodium hydrogen carbonate and the solution was concentrated to dryness. Extraction of the residue with ethanol and evaporation of the solvent afforded 3-methyladenine (**10**) as crystals: 0.75 g (45%); mp 300° (water) (lit.[16] mp 302°); $\lambda_{max}$ ($H_2O$) 274 nm (log $\epsilon$ 4.17) [lit.[16] $\lambda_{max}$ ($H_2O$) 274 nm (log $\epsilon$ 4.21)].

**B. With d.** Adenine (1.50 g, 0.01 mol) and **d** (2.0 g, 0.01 mol) were refluxed in dimethylformamide (8 ml) for 4 hr. The solvent was evaporated under reduced pressure to give a residue, which was then dissolved in aqueous hydrogen carbonate and concentrated as much as possible. The resulting residue in ethanol was chromatographed on alumina (2 cm × 30 cm, 300 mesh, neutral). Elution with a mixture of ethyl acetate and methanol (10:1) gave 0.2 g (15%) of 9-ethyladenine (**11**): mp 193° (ethyl acetate–ether) (lit.[17] mp 194–195°); $\lambda_{max}$ ($H_2O$) 260.0 nm (log $\epsilon$ 4.13) [lit.[17] $\lambda_{max}$ ($H_2O$) 262 nm (log $\epsilon$ 4.15)].

Subsequent elution with the same solvent afforded 0.5 g (30%) of 3-ethyladenine (**12**): mp 229–232° (lit.[16] mp 233°); $\lambda_{max}$ ($H_2O$) 274.5 nm (log $\lambda$ 4.15) [lit.[16] $\lambda_{max}$ ($H_2O$) 273 nm (log $\epsilon$ 4.04)].

**Registry No.**—**1,** 69-89-6; **2,** 58-55-9; **3,** 83-67-0; **4,** 53432-04-5; **5,** 58-08-2; **6,** 31542-50-4; **7,** 23043-88-1; **8,** 53432-05-6; **9,** 73-24-5; **10,** 5142-23-4; **11,** 2715-68-6; **12,** 43003-87-8; **a,** 512-56-1; **b,** 756-79-6; **c,** 14337-77-0; **d,** 78-40-0; **e,** 78-38-6; **f,** 2227-43-2.

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## Synthesis of Furoguaiacidin Diethyl Ether


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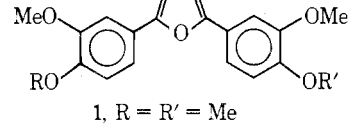
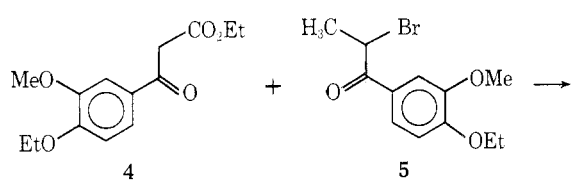
From "lignum vitae", the heartwood of *Guaiacum officinale*, King and Wilson[1] isolated and identified nine lignans including furoguaiacin [as the dimethyl ether (**1**)] and methylfuroguaiacin [as the ethyl ether (**2**)]. Until recently,




1, R = R′ = Me
2, R = Me; R′ = Et

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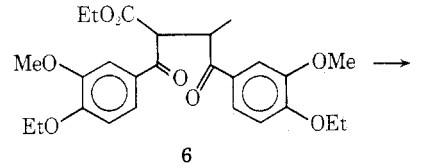


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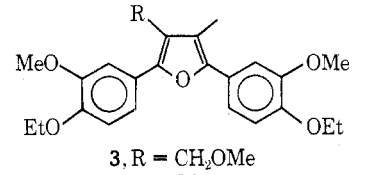


3, R = $CH_2OMe$
7, R = $CO_2Et$
8, R = $CH_2OH$

when a third member named furoguaiacidin was isolated (as the diethyl ether) by Majumder and Bhattacharyya[2] from the same source, these were the only known examples of lignans possessing the furan heterocycle system.

We now report a short synthesis of 2,5-bis(4-ethoxy-3-methoxyphenyl)-4-methoxymethyl-3-methylfuran (**3**), the structure proposed for furoguaiacidin diethyl ether. Alkylation of ethyl 4-ethoxy-3-methoxybenzoylacetate (**4**) with α-bromo-4-ethoxy-3-methoxypropiophenone (**5**) using sodium hydride gave the diketo ester (**6**) which, without isolation, was converted to the required furan, ethyl 2,5-bis(4-ethoxy-3-methoxyphenyl)-3-methylfuran-4-carboxylate (**7**). Reduction of this ester with lithium aluminum hydride gave the alcohol (**8**) which on alkylation with methyl iodide–sodium hydride in dimethoxyethane gave the product, furoguaiacidin diethyl ether (**3**) with physical constants (mp, nmr, ir, uv) in excellent agreement with those reported.

## Experimental Section

Nmr spectra were measured in deuteriochloroform solution with tetramethylsilane as internal standard.

**Ethyl 4-Ethoxy-3-methoxybenzoylacetate (4).** A previously described procedure[3] was modified by using sodium hydride instead of sodium ethoxide and reducing the reaction time from 60 hr to 30 min: nmr δ 1.23 (t, 3 H, $J$ = 7 Hz, $-CO_2CH_2CH_3$), 1.47 (t, 3 H, $J$ = 7 Hz, $ArOCH_2CH_3$), 3.87 (s, 3 H, $OCH_3$), 3.90 (s, 2 H, $CH_2$), 4.13 (q, 2 H, $J$ = 7 Hz, $ArOCH_2CH_3$), 4.17 (q, 2 H, $J$ = 7 Hz, $-CO_2CH_2CH_3$), 6.75–7.57 (m, 3 H, ArH).

**α-Bromo-4-ethoxy-3-methoxypropiophenone (5)** was crystallized from methanol and had mp 72–73° (lit.[4] 76–77°); nmr δ 1.47 (t, 3 H, $J$ = 7 Hz, $ArOCH_2CH_3$), 1.85 (d, 3 H, $J$ = 6.5 Hz, $CH_3CHBr$), 3.88 (s, 3 H, $OCH_3$), 4.16 (q, 2 H, $J$ = 7 Hz, $ArOCH_2CH_3$), 5.29 (q, 1 H, $J$ = 6.5 Hz, $CH_3CHBrCO$), 6.78–7.62 (m, 3 H, ArH).

**Ethyl 2,5-Bis(4-ethoxy-3-methoxyphenyl)-3-methylfuran-4-carboxylate (7).** Sodium hydride (122 mg, 57% oil dispersion) was added with stirring to absolute ethanol (50 ml) under nitrogen, followed by a solution of the keto ester **4** (770 mg) in the same solvent (25 ml). This mixture was stirred for 15–20 min, and a solution of the bromo ketone **5** (830 mg) in ethanol (25 ml) was added dropwise. The flask was then stoppered and stirred at room temperature for 3 days. Hydrogen chloride gas was bubbled through the reaction mixture for 20 min at 0°, then the resulting dark solution refluxed for 1 hr, poured into water (300 ml), and extracted with chloroform. Removal of the solvent and crystallization of the dark residue from methanol gave the furan ester (**7**) as pale yellow prisms (550 mg): mp 113–115°; nmr δ 1.32 (t, 3 H, $J$ = 7 Hz, $-CO_2CH_2CH_3$), 1.47 (t, 6 H, $J$ = 7 Hz, $ArOCH_2CH_3$), 2.38 (s, 3 H, $CH_3$), 3.92 (s, 6 H, $OCH_3$), 4.14 (q, 4H, $J$ = 7 Hz, $ArOCH_2CH_3$), 4.33 (q, 2 H, $J$ = 7 Hz, $-CO_2CH_2CH_3$), 6.83–7.57 (m, 6 H, ArH).

*Anal.* Calcd for $C_{26}H_{30}O_7$: C, 68.70; H, 6.65. Found: C, 68.80; H, 6.68.

**2,5-Bis(4-ethoxy-3-methoxyphenyl)-4-hydroxymethyl-3-methylfuran (8).** A solution of the ester **7** (149 mg) in ether (15 ml) was added with stirring to lithium aluminum hydride (*ca.* 0.5 g) in ether (30 ml) at 0° under nitrogen. The mixture was allowed to reach room temperature on standing overnight, then decomposed by addition of ethyl acetate, then water until coagulation occurred. The solution was decanted, dried ($MgSO_4$), and evaporated to yield the alcohol **8**, crystallized from methanol as colorless needles: mp 147–148°; nmr δ 1.45 (t, 6 H, $J$ = 7 Hz, $ArOCH_2CH_3$), 2.03 (br s, 1 H, –OH), 2.25 (s, 3 H, $CH_3$), 3.88 (s, 6 H, $OCH_3$), 4.09 (q, 6 H, $J$ = 7 Hz, $ArOCH_2CH_3$), 4.62 (s, 2 H, $CH_2OH$), 6.80–7.52 (m, 6 H, ArH).

*Anal.* Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.80; H, 6.90.

**Furoguaiacidin Diethyl Ether (3).** To a stirred solution of the alcohol **8** (547 mg) in dry 1,2-dimethoxyethane (25 ml) was added methyl iodide (10 drops) and sodium hydride (*ca.* 10 mg, 57% oil dispersion) under nitrogen. More methyl iodide (25 drops) was then added and the mixture stirred overnight at room temperature. Removal of the solvent under reduced pressure gave a yellow-green crystalline residue, which was dissolved in chloroform, washed with water, and dried. Removal of the colored impurity was effected by preparative tlc (silica gel, Merck PF 254+366) using benzene–acetone (9:1) to give furoguaiacidin diethyl ether (**3**) as colorless prisms (290 mg) from methanol: mp 133.5–135° (lit.[2] mp 135°); λ($C_2H_5OH$) 258 nm (log 4.47) and 324 (4.16); nmr δ 1.45 (t, 4 H, $J$ = 7 Hz, $ArOCH_2CH_3$), 2.27 (s, 3 H, $CH_3$), 3.45 (s, 3 H, $-CH_2OCH_3$), 3.92 (s, 6 H, $ArOCH_3$), 4.12 (q, 4 H, $J$ = 7 Hz, $ArOCH_2CH_3$), 4.40 (s, 2 H, $CH_2OCH_3$), and 6.83–7.37 (m, 6 H, ArH).

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**Registry No.**—**3**, 52465-56-2; **4**, 53293-05-3; **5**, 721-42-6; **7**, 53293-06-4; **8**, 53293-07-5.

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# Anomalous Reaction of Selenium and Carbon Disulfide with Sodium Acetylide. Synthesis of Selenium Analogs of 1,3-Dithiole-2-thione[1]

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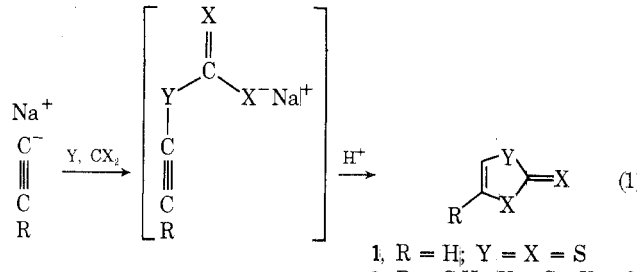
In 1964, Mayer and Gebhardt[2] reported a simple one-step synthesis of 1,3-dithiole-2-thione (**1**) which involved the addition of sulfur and carbon disulfide to sodium acetylide (eq 1). This procedure was subsequently extended with




(1)

**1**, R = H; Y = X = S
**2**, R = $C_6H_5$; Y = Se; X = S
**3**, R = $CH_3$; Y = Se; X = S

the preparation of 5-phenyl-1,3-thiaselenole-2-thione (**2**).[3] We report here the anomalous reaction that occurs in the attempt to prepare the parent compound of **2** by this method.

Treatment of sodium acetylide with selenium and carbon disulfide gave, in addition to the expected product, 1,3-thiaselenole-2-thione (**4**), four other related compounds identified as **1**, 1,3-dithiole-2-selone (**5**), 1,3-thiaselenole-2-selone (**6**), and 1,3-diselenole-2-thione (**7**). In a similar reaction, sulfur and carbon diselenide reacted with sodium acetylide to give the same products as well as 1,3-diselenole-2-selone (**8**). Table I lists the relative percentages of the products formed in these two reactions. The products were easily separated by chromatography on silica gel (5% $CHCl_3$ in $CCl_4$). Relative to **1**, the introduction of selenium into the ring reduces the retention time on the column, while replacement of the thiocarbonyl in **1** with a selenocarbonyl increases it. In a compound such as **6**, the selenium in the carbonyl has a greater effect on the retention time than in the ring, and this material is eluted after **1**.