filtration. An nmr spectrum in DMSO-d_6 indicated approximately 70% alkylation and that the isopropoxy group was still present. The entire sample was reexposed to the above reaction conditions. After heating for 10 min, the mixture was allowed to cool. The precipitate of about 200 mg was collected by filtration and shown by nmr to be a 1:1 mixture of **8** and **1c**. The filtrate was added to 25 ml of ether and the brownish precipitate was collected (150 mg). Tlc analysis indicated the absence of any of the free base **8**. Recrystallization of this material from methanol gave 95 mg of pure **1c**: mp >350° dec, softens at 220°; nmr[12] (DMSO-d_6) δ 3.77 (s, $-OSO_3CH_3$), 4.08 (s, OCH_3), 4.15 (s, OCH_3), 4.26 (s, OCH_3), 5.03 (s, NCH_3), 7.63 (s, H_1), 7.97 (s, H_7), 8.23 (s, H_4), 8.25 (d, J = 9 Hz, H_{12}), 8.35 (s, H_{10}), 8.85 (d, J = 9 Hz, H_{11}), 9.99 (s, H_6).

Anal. Calcd for $C_{22}H_{23}NO_8S \cdot H_2O$: C, 55.11; H, 5.22; N, 2.92. Found: C, 54.97; H, 5.04; N, 2.97.

Fagaronine Chloride (1a). The exchange of counterions was by the method of Zee Cheng and Cheng.[10] In an 8% aqueous NaCl solution (12 ml) was suspended 50 mg of **1c**. After stirring for 0.5 hr at room temperature, filtration gave 36 mg (88%) of **1a**, mp 198–200°, with resolidification and remelting at 260–261° (lit.[1] 202°, 255°). The nmr, ir, uv, and base-shifted uv were identical with those of an authentic sample.[2]

Acknowledgment. This work was supported in part by Grants CA 13648 from the National Cancer Institute and GM 15425 from the National Institute of General Medical Sciences, National Institutes of Health.

Registry No.—**1a**, 52259-64-0; **1c**, 52259-66-2; **2**, 7311-22-0; **3a**, 24309-45-3; **3b**, 52259-67-3; **4**, 52259-68-4; **5**, 52259-69-5; **6b**, 52259-70-8; **7**, 52259-71-9; **8**, 52259-72-0; *o*-bromoveratraldehyde, 5392-10-9.

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7-Hydroxymyoporone, a New Toxic Furanosesquiterpene from Mold-Damaged Sweet Potatoes

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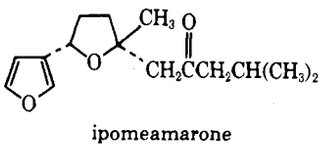
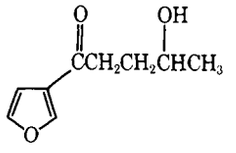
A new stress metabolite of the sweet potato has been isolated and identified as 1-(3-furoyl)-4,8-dimethyl-7-hydroxy-1,6-nonanedione (7-hydroxymyoporone). The structure assignment was based on spectral data and transformation to 3-methyl-5-(3-furoyl)pentanoic acid. The degradation product was synthesized by a reaction sequence involving the acylation of methyl 3-methyl-5-oxocyclopentanecarboxylate with 3-furoyl chloride and cleavage of the resulting diketo ester with aqueous base. The toxicity of 7-hydroxymyoporone is similar to that of the well-known sweet potato phytoalexin, ipomeamarone.

Sweet potatoes, when infected by fungus or when subjected to certain other stress conditions, elaborate numerous furanoid metabolites, all of apparent terpenoid origin.[1] Ipomeamarone was the first of these to be isolated



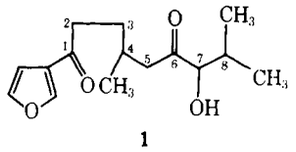
ipomeamarone



4-ipomeanol

and identified.[2] The compound is hepatotoxic and is usually the most abundant of the furan metabolites. We have been particularly interested in a group of 1,4-dioxygenated 1-(3-furyl)pentanes, also isolated from mold-damaged sweet potatoes.[3] These compounds, especially 1-(3-furyl)-4-hydroxy-1-pentanone (4-ipomeanol), show a marked specific pulmonary toxicity in laboratory animals.

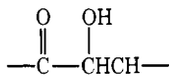
As part of our continuing investigation of the phytoalexins of the sweet potato, we have isolated a new furanosesquiterpene which has been identified as 1-(3-furyl)-7-hydroxy-4,8-dimethyl-1,6-nonanedione (7-hydroxymyoporone, **1**).[4] The compound was obtained from sweet potato slices that had been incubated with cultures of *Ceratocystis fimbriata*.[5] The isolation involved extraction into ethyl acetate and chromatography on silica gel followed by preparative glpc of the partially purified material, after treatment with a trimethylsilylating reagent. The trimethylsilyl ether was cleaved with tetra-*n*-butylammonium fluoride[6] to give the pure metabolite in a yield of 20 mg/kg of sweet potatoes (wet weight).



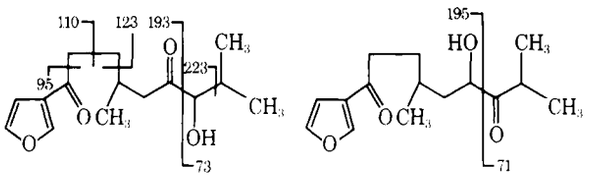
1

The empirical formula, $C_{15}H_{22}O_4$, of **1** was established from the elemental analysis and from the parent ion at *m/e* 266 in the mass spectrum. The 1-(3-furyl)-1-alkanone moiety was indicated by the characteristic pmr signals (δ 6.72, 7.41, and 8.00) for the furyl protons[7] and by the conjugated carbonyl stretching frequency (1670 cm^{-1}) and the furyl absorptions (3130, 1560, 1500, and 870 cm^{-1}) in the infrared spectrum and further substantiated by the ion at *m/e* 95 (3-furyl-C≡O$^+$) in the mass spectrum. The presence of a nonconjugated ketone and a hydroxyl group was also inferred from the infrared spectrum.

Compound **1** gave a positive test with Tollen's reagent which suggested the presence of an acyloin structure, since the spectra provided no evidence for the presence of any other easily oxidized group. Pmr spectra limited the possible locations for the acyloin group. In the spectrum of the trimethylsilyl ether of **1**, the methinyl proton appeared as a doublet at δ 3.55; after cleavage of the silyl ether this signal was transformed into a less clearly defined multiplet at δ 4.01. The partial structure

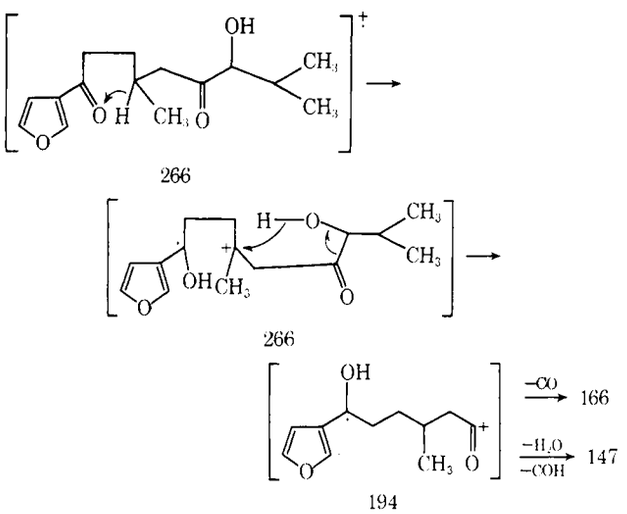


is indicated for **1**. If a normal sesquiterpene skeleton, such as that in ipomeamarone, can be assumed, then the keto and hydroxyl groups of the acyloin must respectively be at positions 2 and 3, 6 and 5, or 6 and 7. The first of these possibilities can be immediately eliminated by the presence of an intense ion at *m/e* 110 (3-furyl-C(OH)=CH_2·$^+$) in the mass spectrum. The third possibility, but not the second, was in accord with the mass spectrum. Interpretation was complicated by an apparent isomerization of **1** into acyloin **2** in the mass spectrometer. Such a rearrangement of α-ketols in the mass spectrometer has previously been observed.[8] Assignments for major fragment ions from **1** and **2** are shown below.



1 **2**

Ions at *m/e* 194, 166, and 147 are thought to result from a cleavage between carbons 6 and 7 concurrent with a hydrogen shift and followed by further fragmentation.

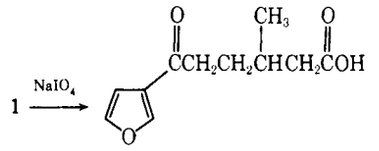


266

266

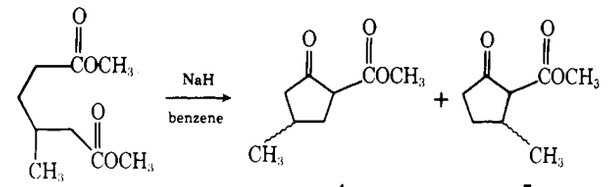
194

Further evidence for the proposed structure **1** was obtained by cleavage of the acyloin with sodium periodate. Carboxylic acid **3** obtained from the oxidation gave a parent ion at *m/e* 210 in the mass spectrum, suggesting the empirical formula $C_{11}H_{14}O_4$, as would be expected with oxidative cleavage between positions 6 and 7. The presence in **3** of the 1-(3-furyl)-1-alkanone moiety and the carboxylic acid group was substantiated by pmr and infrared spectra.

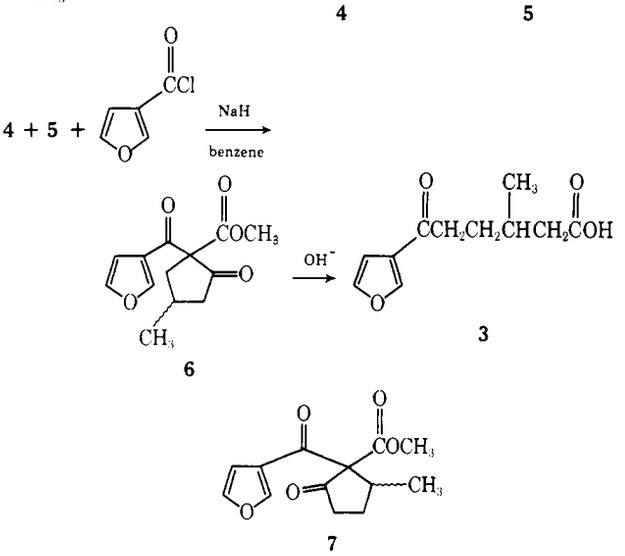


3

Unequivocal proof of the structure of **3** was obtained by independent synthesis. A Dieckmann cyclization of the dimethyl ester of 3-methyladipic acid gave a 2.5:1 mixture of keto esters **4** and **5**. Useful quantities of pure **4** could not be



4 **5**



6 **3**

7

obtained by distillation or chromatography, but acylation of the mixture with 3-furoyl chloride gave **6** which is the acylation product of **4**. A small quantity of isomer **7** may have been formed, but it was not detected. The difference in rate of acylation of **4** and **5** is ascribed to steric hindrance caused by the *C*-methyl group in **5**. The fact that the mixture of unreacted **4** and **5** recovered from the reaction was significantly enriched in **5** is consistent with this difference in reactivity. In a similar reaction sequence beginning with a Dieckmann condensation of the diethyl ester of 3-methyladipate followed by alkylation with ethyl bromoacetate, Sorm reported finding only products resulting from alkylation of the ethyl ester homolog of **4**.[9]

The pmr spectrum of **6** suggested that it was a mixture of diastereoisomers, but supported its gross structure. The mass spectrum provided further support; a strong ion at *m/e* 69 is assigned as $CH_3CH{=}CHC{\equiv}O^+$, derived from a fragmentation of the cyclopentanone ring.[10] Loss of this fragment is consistent with structure **6** but not **7**.

Reaction of **6** with aqueous base at room temperature gave a 20% yield of racemic **3** as a crystalline product. The material could not be compared by mixture melting point

with the optically active material obtained by oxidation of **1**, but their identity was otherwise established by spectroscopic (ir, pmr, mass spectral) comparison.

In preliminary studies 7-hydroxymyoporone was found to be hepatotoxic to mice upon intraperitoneal administration of 200–250 mg/kg doses.

Experimental Section

The infrared spectra were obtained using a Perkin-Elmer Model 621 spectrophotometer. Pmr spectra were obtained using a JEOL JMN-MH-100 spectrophotometer with tetramethylsilane (TMS) as internal standard. Cmr spectra were obtained using a Varian XL-100 equipped with a Transform Technology, Inc., TT-100 Fourier transform accessory; TMS was used as the internal standard. Mass spectra were obtained using an LKB gas chromatograph–mass spectrometer, Type 9000. Ultraviolet spectra were obtained using a Cary Model 14 recording spectrophotometer. Gas–liquid phase chromatography (glpc) was carried out using a Aerograph Model A-700 gas chromatograph. Optical rotatory dispersion was measured using a Cary Model 60 spectropolarimeter. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected.

Bioproduction of 7-Hydroxymyoporone (1). Sweet potatoes (11 kg), washed with sodium hypochlorite solution, cut into 1-cm thick slices, and coated with a 15% mannitol solution, were inoculated with *Ceratocystis fimbriata* grown in a potato starch–sucrose medium. Six days after inoculation, the slices were frozen with Dry Ice and ground in a grain mill. The ground material was extracted with ethyl acetate and the ethyl acetate solution was dried and concentrated to yield 23.8 g of brown oil. The oil was placed on a 5-cm diameter column containing 125 g of silica gel (Matheson Coleman and Bell, Grade 62, 60–200 mesh) and eluted first with hexane, then with ether–hexane (1:19). The ether–hexane eluent contained 2.0 g of a yellow oil which, according to glpc, contained three major components in approximately 1:3:10 ratio. Silylation of 700 mg of the mixture with Tri-Sil/BSA (Pierce Chemical Co.) and preparative glpc using a 2.5 m × 1 cm glass column containing 10% UC-W98 on 80/100 Chromosorb Q operated at 205° and 125 ml/min helium flow produced 140 mg of the trimethylsilyl derivative of the major component: pmr (CCl_4) δ 0.10 (s, 9 H), 0.92 (m, 9 H), 1.58 (m, 2 H), 1.95 (m, 2 H), 2.37 (m, 2 H), 2.62 (t, J = 7 Hz, 2 H), 3.55 (d, J = 7 Hz, 1 H), 6.59 (m, 1 H), 7.27 (m, 1 H), and 7.82 (m, 1 H); *m/e* 338 (M^+).

The purified silyl ether (107 mg) was dissolved in tetrahydrofuran (THF) and treated with 1 ml of 1 *N* tetra-*n*-butylammonium fluoride in THF at 0° for 10 min. The THF was removed by evaporation in a stream of nitrogen and the residue was placed on a small column of deactivated silica gel and eluted with ether–hexane (1:1). Evaporation of the solvent gave 75 mg of 1 as a colorless oil: $[\alpha]^{26}D$ +12.3° (*c* 0.64, CH_3OH); ir ($CHCl_3$) 3480, 3130, 2955, 2865, 1705, 1670, 1560, 1500, 1460, 1150, and 870 cm^{-1}; pmr ($CDCl_3$) δ 0.72 (d, J = 7 Hz, 3 H, CH_3), 0.96 (d, J = 7 Hz, 3 H, CH_3), 1.12 (d, J = 7 Hz, 3 H, CH_3), 1.50–1.85 (m, 2 H, 4- and 8-CH), 1.95–2.30 (m, 2 H, 3-CH_2), 2.41 (m, 2 H, 5-CH_2), 2.78 (t, J = 7 Hz, 2 H, 2-CH_2), 3.37 (broad singlet, 1 H, OH), 4.01 (m, 1 H, 7-CH),[11] 6.72 (m, 1 H, 4-furyl), 7.41 (m, 1 H, 5-furyl), and 8.00 (m, 1 H, 2-furyl); uv (CH_3OH) 213 nm (ϵ 6600) and 253 (3000); major mass spectral peaks at *m/e* (rel intensity) 266 (2), 233 (2), 195 (60), 194 (71), 193 (27), 166 (83), 147 (85), 137 (38), 123 (77), 110 (69), 95 (100), 73 (38), 71 (19), and 55 (58); cmr (CCl_4) 15.1 (methyl at C-4), 19.8 (methyls at C-8), 28.6 (C-8), 30.8 (C-3 or C-4), 30.9 (C-4 or C-3), 37.8 (C-2), 45.1 (C-5), 81.0 (C-7), 108.8 (4-furyl), 127.7 (3-furyl), 143.9 (5-furyl), 147.0 (2-furyl), 193.4 (C-1), and 211.3 ppm (C-6).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.88; H, 8.42.

Periodate Oxidation of 1. Sodium periodate (75 mg, 0.35 mmol) dissolved in 4 ml of 1 *N* sulfuric acid was added to 90 mg (0.33 mmol) of 1 in 5 ml of methanol. After heating at 40° for 15 min, the solution was cooled and extracted with ether. Extraction of the ether with sodium bicarbonate, followed by acidification and ether extraction of the aqueous phase, then drying and concentrating the ether solution gave 3-methyl-5-(3-furoyl)pentanoic acid (**3**). Recrystallization from hexane gave colorless needles: mp 47–48°; ir (CCl_4) 3360–2790, 3145, 2965, 1710, 1680, 1560, 1510, 1455, 1410, 1390, 1380, 1295, 1160, and 875 cm^{-1}; pmr ($CDCl_3$) δ 1.01 (d, J = 7 Hz, 3 H, CH_3), 1.54–2.20 (m, 3 H), 2.31 (three-line multiplet with 6 Hz separation between lines, 2 H, 2-CH_2), 2.78 (t, J = 7 Hz, 2 H, 5-CH_2), 6.76 (m, 1 H, 4-furyl), 7.40 (m, 1 H, 5-furyl), 8.02 (m, 1 H, 2-furyl), and 9.60 (broad singlet, 1 H, CO_2H); major mass spectral peaks at *m/e* (rel intensity) 210 (2), 164 (2), 151 (1), 150 (1), 123 (3), 111 (1), 110 (28), 96 (6), 95 (100), and 67 (9). The optical rotatory dispersion was obtained in the 275–400-nm region: $[\alpha]_{325}$ −70° (*c* 0.039, CH_3OH).

Synthesis of 3. Dimethyl 3-methyladipate (5 g, 27 mmol), sodium hydride (50% oil dispersion, 5 g, 104 mmol), benzene (75 ml), and 5 drops of methanol were heated at reflux for 1 hr. After this time the mixture was cooled and poured into 100 g of ice and 15 ml of acetic acid. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water, saturated sodium bicarbonate, and saturated sodium chloride, then dried and concentrated. The residue was distilled to give 2.9 g (70% yield) of a colorless liquid: bp 110–111° (14 Torr) [lit.[12] bp 110° (16 Torr)]; pmr (CCl_4) δ 1.1–1.3 (m, apparently a pair of doublets superimposed on a doublet, 3 H), 1.6–2.8 (m, 5 H), 3.0–3.4 (m, 1 H), and 3.70–3.85 (m, 3 H). On the basis of integration of the signals at δ 1.1–1.3 the material was estimated to be a 2.5:1 mixture of methyl 3-methyl-5-oxocyclopentanecarboxylate (**4**) and methyl 2-methyl-5-oxocyclopentanecarboxylate (**5**).

The mixture of keto esters **4** and **5** (2.5 g, 16 mmol) was added slowly to 0.5 g (21 mmol) of sodium hydride suspended in benzene and then stirred at room temperature for 30 min. After this time 3-furoyl chloride, prepared from 2.0 g (18 mmol) of 3-furoic acid and 5 ml of oxalyl chloride, was added and the reaction mixture was refluxed for 1 hr. The mixture was allowed to cool and then filtered. Chromatography (silica gel, ether–hexane, 1:49) of the residue obtained from concentration of the filtrate produced 1.0 g of unreacted **4** and **5** and 1.4 g of 2-(3-furoyl)-2-carbomethoxy-4-methylcyclopentanone (**6**): ir (neat) 3150, 2960, 1765, 1730, 1670, 1560, 1510, 1455, 1435, 1305, 1285, 1265, 1240, 1160, 1145, 1035, 875, 865, and 735 cm^{-1}; pmr ($CDCl_3$) δ 0.96 (d, J = 6 Hz, 3 H, 4-CH_3), 1.85–3.10 (m, H), 3.71 (s, 3 H, OCH_3), 6.71 (m, 1 H, 4-furyl), 7.39 (m, 1 H, 5-furyl), and 8.08 (m, 1 H, 2-furyl); major mass spectral peaks at *m/e* (rel intensity) 250 (5), 181 (20), 149 (17), 95 (100), 69 (9), and 39 (18).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.63. Found: C, 62.30; H, 5.43.

Diketo ester **6** (1.1 g, 4.4 mmol) was suspended in 10 ml of water containing 0.6 g (10 mmol) of sodium hydroxide and stirred at 40°. After 3 hr the mixture was extracted with ether, then acidified and again extracted with ether. The second ether extract was dried and concentrated to give 0.92 g of acidic material. Two recrystallizations from hexane produced 0.19 g (20% yield) of **3** as white needles: mp 58–59°; ir ($CHCl_3$) 3370–2850, 3150, 2965, 2935, 1710, 1680, 1560, 1510, 1460, 1410, 1390, 1380, 1295, 1160, and 875 cm^{-1}; pmr ($CDCl_3$) δ 1.02 (d, J = 7 Hz, 3 H, CH_3), 1.40–2.20 (m, 3 H), 2.31 (three-line multiplet with 6 Hz separation between lines, 2 H, 2-CH_2), 2.82 (t, J = 7 Hz, 2 H, 5-CH_2), 6.75 (m, 1 H, 4-furyl), 7.41 (m, 1 H, 5-furyl), 8.03 (m, 1 H, 2-furyl), and 10.9 (broad singlet, 1 H, CO_2H); major mass spectral peaks at *m/e* (rel intensity) 210 (3), 164 (2), 151 (1), 150 (2), 123 (4), 111 (4), 110 (53), 96 (6), 95 (100), and 67 (5).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.02; H, 6.58.

About 20 mg of 3-furoic acid (mp 118–121°) was obtained from the hexane-insoluble material by recrystallization from benzene.

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Registry No.—**1**, 52259-61-7; **3**, 52259-62-8; **6**, 52259-63-9.

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The Structure of Catechinic Acid. A Base Rearrangement Product of Catechin

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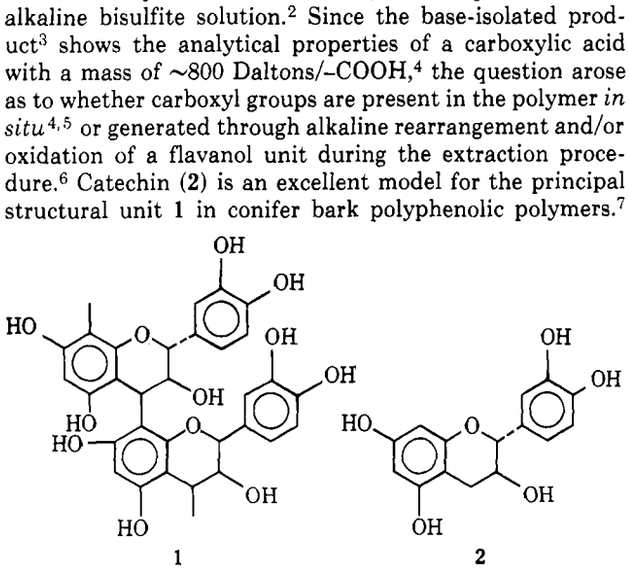
Catechinic acid, a base rearrangement product of the flavanol catechin, has been shown by both chemical and X-ray evidence to be the enol of 6-(3,4-dihydroxyphenyl)-7-hydroxy-2,4,9-bicyclo[3.3.1]nonatrione (**5**). The structure of this product is relevant to the transformation which occurs to polyflavanoids in wood and bark when similarly treated with base to give "bark phenolic acids."

Polyphenolic polymers derived from substituted flavan-3-ols or flavan-3,4-diols occur in all species of coniferous bark investigated thus far and in the heartwood and bark of a significant number of deciduous trees.[1] Part of this polymeric material cannot be extracted from wood or bark by inert solvents such as ethanol or hot water but can only be isolated by extraction with hot, dilute aqueous base or alkaline bisulfite solution.[2] Since the base-isolated product[3] shows the analytical properties of a carboxylic acid with a mass of ~800 Daltons/–COOH,[4] the question arose as to whether carboxyl groups are present in the polymer *in situ*[4,5] or generated through alkaline rearrangement and/or oxidation of a flavanol unit during the extraction procedure.[6] Catechin (**2**) is an excellent model for the principal structural unit **1** in conifer bark polyphenolic polymers.[7]



1 **2**

Treatment of **2** with base could be expected to provide insight into any corresponding reactions taking place in the polymer.

Treatment of (+)-catechin (**2**) with refluxing 0.5% NaOH for 45 min gave a >90% yield of an optically active amorphous acidic material which we have named catechinic acid (CA). Combustion analyses suggested the formula $C_{15}H_{16}O_7$, *i.e.*, a hydrated catechin, but analyses of derivatives favored $C_{15}H_{14}O_6$, with a mole of water of hydration. Similarly, crystalline material obtained from acetone contained acetone of crystallization. Titration showed behavior consistent with a monocarboxylic acid ($pK_a \sim 4.3$).

Methylation of CA with Me_2SO_4 in acetone yielded two neutral derivatives, $C_{18}H_{20}O_6$. Both displayed nmr signals indicating three methoxyl groups, and the names trimethylcatechinic acid (TMC) and trimethylisocatechinic acid (TMIC) were assigned.

The nmr spectrum of TMC showed three aromatic proton signals as a multiplet τ 3.1–3.4. In a 220-MHz spectrum these appeared as two doublets ($J \sim 10$ Hz) and a singlet. This observation, together with the appearance of two of the methoxyl signals at a normal aromatic ether value of τ 6.14, indicated that the 3,4-dihydroxyphenyl ring of catechin had survived intact. The remainder of the spectrum, however, was inconsistent with the presence of a phloroglucinol system or indeed with any additional aromatic protons. The analysis of KOH fusion products from CA showed the absence of phloroglucinol and the presence of pyrocatechol and protocatechuic acid. Thus, an extensive modification of the parent structure was indicated.

Of the six oxygen atoms, two can be assigned as above to phenolic groups. One was found to be a reactive carbonyl (discussed below) with an ir absorption at 1740 cm^{-1} in TMC, and a fourth is a secondary hydroxyl as shown by an –OH stretch in the ir (3580 cm^{-1}) and by an α-proton signal at τ 5.55 which shifts to 4.28 on acetylation. The remaining oxygens were presumably associated with the acid function and in TMC led to a methoxyl signal at τ 6.41 and a carbonyl band at 1650 cm^{-1}.

Although it has been generally assumed that the acidity of bark phenolic acids reflects the presence of carboxyl groups, the carbonyl absorption at 1650 cm^{-1} is inconsistent with a simple methyl ester. The value agrees, however, with those reported for enol ethers derived from β diketones. Comparison with literature values for model systems showed excellent agreement in the ir[8] (1650 *and* 1600 cm^{-1}), uv[9] [CA enolate anion at 285 nm (ϵ 19,300), methyl ether at 232 (12,300) and 260 (14,000)], and nmr[10] (α H of