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

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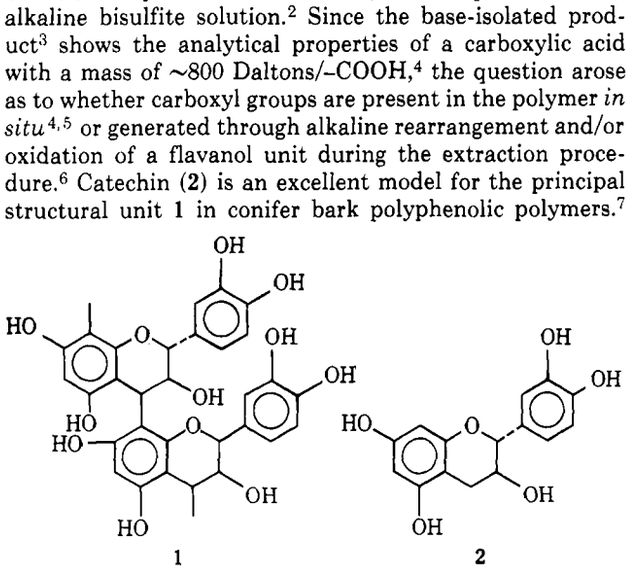
Catechinic acid, a base rearrangement product of the flavanol catechin, has been shown by both chemical and X-ray evidence to be the enol of 6-(3,4-dihydroxyphenyl)-7-hydroxy-2,4,9-bicyclo[3.3.1]nonatrione (**5**). The structure of this product is relevant to the transformation which occurs to polyflavanoids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

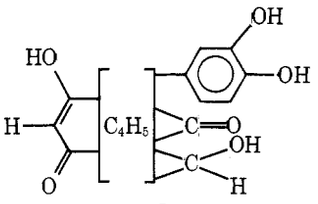
methyl ether τ 4.25, 1 H singlet). This view allowed the formulation of a partial structure of CA as **3** and additionally accounted for the formation of two very similar trimethylation products in terms of methylation at either end of an unsymmetrical anion.

The reactivity of the isolated carbonyl function was shown by the failure of diazomethane methylation of CA to give either of the trimethyl ethers described above. Instead, a permethylated product, $C_{19}H_{22}O_6$, was obtained which contained an epoxide ring resulting from methylene addition to the carbonyl. The same product was prepared upon diazomethane treatment of trimethylcatechinic acid. Similarly, mild hydrogenation of catechinic acid over palladium yielded a diol which could be trimethylated and then diacetylated.

The relationships among the six unassigned protons were deduced by examination of the nmr spectra of these derivatives. The single proton (H_D) α to the hydroxyl group appeared routinely as a six-line signal derived from a triplet (J = 11–12 Hz) and a doublet (J = 5 Hz). The spin constants correspond to the presence of one adjacent equatorial (H_C) and two axial (H_B, H_E) protons. Three 1 H signals at higher field also showed large coupling constants: H_E τ 6.90 (dd, J = 11, 4 Hz), H_C at 7.36 (ddd, J = 12, 5, 4 Hz), and H_B at 8.02 (td, J = 12, 4 Hz). The shifts and coupling constants are consistent with assignment of H_E and H_B as the axial protons adjacent to H_D, while H_C is the equatorial one, also geminally coupled to H_B. The downfield position of H_E required it to be benzylic and thus located the dimethoxyphenyl substituent.

The additional couplings of H_B, H_C, and H_E indicated the presence of other proton(s) coupled with $J \sim 4$ Hz. These could be equated with an ill-resolved two proton signal at $\tau \sim 6.6$, and, since this shifts upfield to ~ 7.2 following addition to the reactive carbonyl, it was ascribed to equatorial α,α' substituents (H_A, H_F) on the ketone. Thus the remainder of the structure could be formulated as **4**.

Consideration of the partial structures **3** and **4** leads to a final structure **5** (or its enol tautomer) for CA. This formulation accounts for all of the spectral properties of the material and is reasonably derived from **2** by any of a number of base-catalyzed routes, of which that shown is only one possibility. The fact that the relative stereochemistry of CA corresponds to that of catechin might appear to favor a concerted anionic rearrangement, but, since the product is in the most stable conformation, no firm judgement can be made. Further studies on this point are being undertaken.



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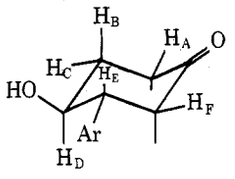

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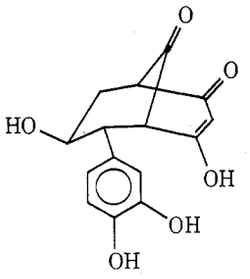
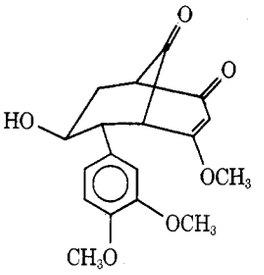


5

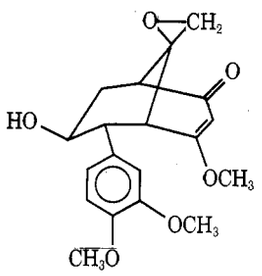
Methylation of the enolizable β diketone system may potentially occur on either oxygen, as is shown by the concurrent formation of two trimethyl derivatives. An assignment of the structures may be made by noting that the nmr shifts of the enol ether protons are strikingly different in the two compounds. Examination of models suggests that the higher field signals (trimethylcatechinic acid, τ 6.41; *cf.* trimethylisocatechinic acid, τ 6.17) correspond to the structure in which the methoxyl is on the same side of the bridged ring as the aromatic substituent. This is oriented by steric forces so that the methoxyl lies above the aromatic plane and is embedded in the shielding cone produced by the ring current. Thus trimethyl catechinic acid has been assigned the structure **6**. Methylation by diazomethane



6

gives predominantly products with the high-field ether, and these have been assigned the corresponding structure.

The direction of addition to the bridge carbonyl and thus the stereochemistry of the products has not been proved unambiguously. We favor the structure **7** for permethylcatechinic acid, however, on the basis of the nmr spectrum of the diacetate prepared from the diol **8** formed by reduction



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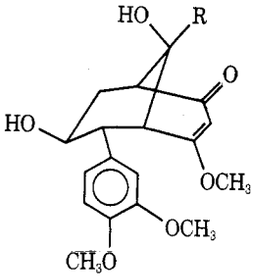


8, R = CH_3
9, R = H

of **7**. In this product the secondary acetate, like all the acetates in this series, shows its methyl signal at the high value of τ 8.2. This, like the corresponding upfield shift of the enol methyl ether, undoubtedly reflects the position of the methyl in the shielding cone of the phenyl group. The tertiary acetate, however, appears at τ 7.77, *i.e.*, has a significant downfield shift. This may be ascribed both to its axial orientation with respect to the cyclohexane ring[11] and to the fact that the mean position of the methyl is in the plane of the aromatic ring and is thus deshielded. The alternative orientation for the hydroxyl would place the acetate methyl above the plane of the enolic system and so should lead to increased rather than decreased shielding. The diacetate derived from the diol **9** obtained by hydrogenation and methylation of **5** shows the same shifts and presumably has the same stereochemistry.

To confirm the proposed structure a single-crystal X-ray structure determination on trimethyl catechinic acid (**6**) has been carried out. This study, the details of which will be reported elsewhere,[12] confirmed our deductions in all respects and showed the molecule represented in Figure 1. In particular, the phenyl ring is oriented approximately normal to the plane of the cyclohexanone, with the enol ether lying above it, as suggested above.

Although no studies have yet been carried out to com-

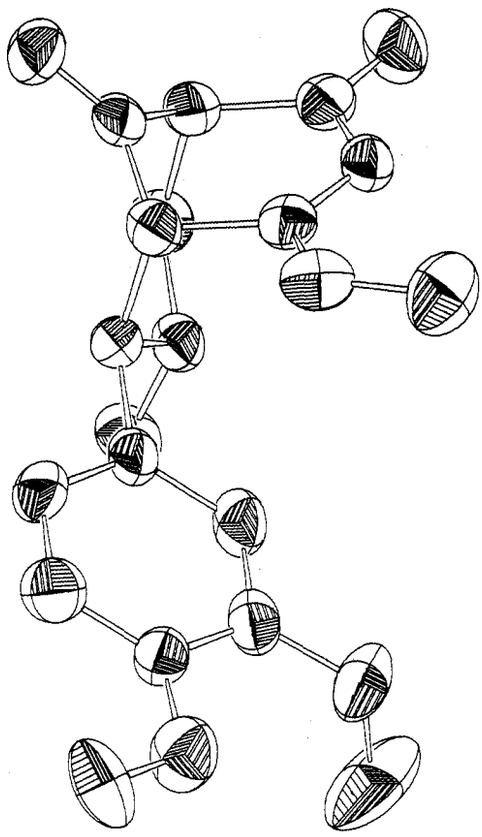
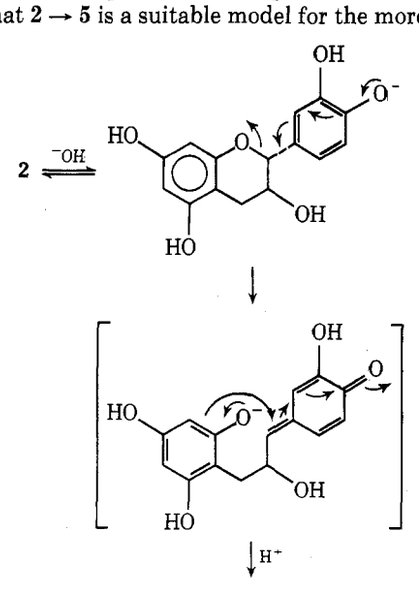


Figure 1. X-Ray structure of trimethylcatechinic acid.

pare **5** directly with "bark phenolic acids," the similarities of their physical properties, the known presence of catechin-derived units (**1**) in bark,[7] and the similarity of the conditions used to produce acidic products, all lead us to believe that **2** → **5** is a suitable model for the more complex



reaction. It may thus be suggested that the polymeric bark phenolic acids contain an enolic hydroxyl rather than a carboxyl group as previously postulated.[4]

Experimental Section

Ir spectra were taken on a Perkin-Elmer Model 21 or on a Beckman Model IR-120 instrument. Nmr data were obtained from Sadtler Research Laboratories, Inc. (Varian A-60A or HA-100D) or were taken on a Varian T-60. The 220-MHz spectra were measured by the Varian Corporation as a courtesy. Uv spectra were measured on a Cary 11 MS. Mass spectral data were obtained by Morgan Schaffer Corp. on a Hitachi Perkin-Elmer RMU-6D. Combustion analyses were performed by A. Bernhardt, Elbach uber Engelskirchen, West Germany.

Column chromatography was carried out on Mallinckrodt silica gel, 200–325 mesh, and tlc on Brinkman silica gel G. Three solvent systems were used: A, 5:4:1 toluene–EtOAc–HCO_2H; B, 200:47:15:1 benzene–EtOH–H_2O–HOAc—upper phase; C, 9:1 EtOAc–MeOH + 1% HOAc.

Preparation of Catechinic Acid (5). (+)-Catechin (2.0 g) was added to a refluxing solution NaOH (1.0 g) in 200 ml of H_2O in a three-necked flask supplied with a continual N_2 flush. After 45 min the reaction was cooled in ice, treated with IR-120 resin (H^+ form, 35 ml), and stirred for 1 hr. The resin was filtered off and the solution evaporated to dryness to give a light brown resinous product. This was dissolved in acetone (200 ml) and the solution concentrated *in vacuo* until precipitation occurred. The precipitate was filtered off to give 1.37 g of catechinic acid–acetone complex as a white crystalline solid: mp 168–170°; ir (KBr) 1745 (s), 1695 (s), 1610 (s), 1535 (m) cm^{-1}; uv (H_2O) 285 nm (ϵ 19,300). Evaporation of the acetone mother liquor gave 0.44 g of unsolvated catechinic acid, essentially the same on tlc comparison (solvent C).

A sample of catechinic acid purified by repeated precipitation from acetone with ether and dried at 75° (0.02 Torr) was a white amorphous powder, charring at 200–220°.

Anal. Calcd for $C_{15}H_{14}O_6 \cdot H_2O$: C, 58.44; H, 5.23; mol wt, 308. Found: C, 58.82, 58.87; H, 5.16, 5.28; mol wt, 311 (neut equiv).

Trimethylation of Catechinic Acid. Catechinic acid (500 mg), acetone (60 ml), Me_2SO_4 (1.4 ml), and K_2CO_3 (8.0 g) were refluxed overnight. Tlc (solvent B) showed predominantly two products. These were separated by multiple elution tlc to give 211 mg of trimethylcatechinic acid (more mobile) and 88 mg of the isomer.

Trimethylcatechinic Acid (6). Trimethylcatechinic acid crystallized from hexane–CH_2Cl_2 as white crystals: mp 193–194°; ir 3580 (w), 1740 (s), 1660 (s), 1600 (s), 1520 (s) cm^{-1}; uv (95% EtOH) 232 nm (ϵ 12,300), 260 (14,000); $[\alpha]^{25}D$ ($CHCl_3$, *c* 1.18 g/100 ml) +202°; nmr ($CDCl_3$ 220 MHz) τ 3.14 (d, 1), 3.30 (m, 2), 4.25 (s, 1), 5.55 (td, 1, J = 11.5, 5.5 Hz), 6.11 (s, 3), 6.12 (s, 3), 6.41 (s, 3), 6.63 (m, 2), 6.90 (dd, 1, J = 11, 4 Hz) 7.36 (ddd, 1, J = 12, 5.5, 3.5 Hz), 8.02 (dd, 1, J = 12, 4 Hz); mass spectrum (rel intensity) 332 (96), 288 (6), 260 (5), 257 (6), 191 (10), 181 (20), 165 (18), 151 (100), 137 (25).

Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07; *m/e* 332 (100), 333 (20.01), 334 (3.09). Found: C, 65.21, 65.19; H, 6.20, 5.95; *m/e* 332 (100), 333 (20.13), 334 (2.95).

Acetylation with Ac_2O and NaOAc overnight in refluxing benzene yielded after preparative tlc (solvent B) the monoacetate: ir ($CHCl_3$) 1730 (s), 1650 (s), 1590 (s) cm^{-1}; uv (95% EtOH) 232, 259 nm; nmr ($CDCl_3$) τ 3.25 (s, 1), 3.34 (q, 2), 4.21 (s, 1), 4.28 (m, 1), 6.14 (s, 3), 6.16 (s, 3), 6.44 (s, 3), 6.65 (m), 7.20–8.15 (m), 8.21 (s, 3).

Trimethylisocatechinic Acid. Trimethylisocatechinic acid did not crystallize: ir ($CHCl_3$) 3570 (w), 1735 (s), 1655 (s), 1602 (s), 1515 (s) cm^{-1}; uv (95% EtOH) 230, 256 nm; nmr ($CDCl_3$) τ 3.23 (s, 1), 3.33 (m, 2), 4.28 (s, 1), 5.61 (td, 1, J = 11.5, 5.5 Hz), 6.17 (s, 9), 6.60 (m, 2), 6.95 (dd, 1, J = 11, 4 Hz), 7.35 (m), 8.00 (m); mass spectrum (rel intensity) 332 (100), 288 (29), 266 (29), 260 (16), 245 (11), 217 (15), 191 (27), 181 (9), 162 (11), 151 (86).

Anal. Calcd for $C_{18}H_{20}O_6$: *m/e* 332 (100), 333 (20.01), 334 (3.09). Found: *m/e* 332 (100), 333 (19.98), 334 (3.08).

Acetylation overnight with Ac_2O–NaOAc in refluxing benzene yielded the amorphous monoacetate: ir ($CHCl_3$) 1736 (s), 1660 (s), 1605 (s) cm^{-1}; uv (95% EtOH) 232, 255 mn; nmr ($CDCl_3$) τ 3.22 (s, 1), 3.35 (dd, 2), 4.16 (s, 1), 4.30 (td, 1) 6.12 (s, 3), 6.16 (s, 6), 6.63 (m, 3), 7.35 (ddd, 1), 8.03 (m, 1), 8.20 (s, 3).

Dihydrotrimethylisocatechinic Acid. Trimethylisocatechinic acid (50 mg) was hydrogenated at 50 psi overnight in MeOH (20 ml) with platinum oxide (40 mg). Preparative tlc (solvent B) gave recovered starting material (8.5 mg) and product (14 mg): ir ($CHCl_3$) 3580 (w), 1640 (s), 1598 (s), 1510 (s) cm^{-1}; uv (95% EtOH) 232, 252 nm; mass spectrum (rel intensity) 334 (96), 316 (4), 273 (34), 193 (20), 164 (19), 151 (100), 137 (30).

Anal. Calcd for $C_{18}H_{22}O_6$: *m/e* 334 (100), 335 (20.04), 336 (3.10). Found: *m/e* 334 (100), 335 (20.13), 336 (10.6).

Permethylcatechinic Acid (7). Catechinic acid (500 mg) in MeOH was treated with an excess of diazomethane in ether at 4° for 2 days. Evaporation gave a viscous oil which was purified by preparative tlc (solvent B) to give a white amorphous solid (310 mg): ir 3528 (w), 1652 (s), 1602 (s), 1521 (s) cm^{-1}; uv (95% EtOH) 233 (11,400), 254 (12,800) nm; nmr ($CDCl_3$, 220 MHz) τ 3.16 (d, 1),

3.31 (m, 2), 4.40 (s, 1) 5.75 (td, 1, J = 11, 5 Hz), 6.14 (s, 3), 6.15 (s, 3), 6.46 (s, 3) 6.83 (dd, 1, J = 11, 4 Hz), 7.14 (s, 2), 7.71 (m, 4), 8.00 (td, 1, J = 12, 4 Hz); mass spectrum (rel intensity) 346 (52), 274 (4), 193 (24), 180 (27), 167 (51), 162 (30), 151 (100).

Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88, H, 6.40; *m/e* 346 (100), 347 (21.1), 348 (3.32). Found: C, 65.71; H, 6.36; *m/e* 346 (100), 347 (21.1), 348 (3.88).

Treatment of trimethylcatechinic acid with CH_2N_2 gave a product which was identical by tlc and ir.

Acetylation of permethylcatechinic acid with NaOAc and Ac_2O in benzene gave the acetate as a viscous oil: ir ($CHCl_3$) 1735 (s), 1660 (s), 1605 (s), 1522 (s) cm^{-1}; uv (95% EtOH) 237, 252 nm; nmr ($CDCl_3$) τ 3.25 (s, 1), 3.35 (m, 2), 4.35 (s, 1), 4.46 (m, 1), 6.15 (s, 3), 6.17 (s, 3), 6.49 (s, 3), 6.56 (m, 1), 7.14 (s, 2), 7.69 (m), 7.80–8.15 (m), 8.21 (s, 3); mass spectrum (rel intensity) 388 (26), 328 (100), 313 (7), 299 (12), 193 (46), 180 (25), 151 (60), 137 (22).

Anal. Calcd for $C_{21}H_{24}O_7$: *m/e* 388 (100), 389 (23.3), 390 (4.00). Found: *m/e* 388 (100), 385 (23.7), 390 (4.09).

Dihydropermethylcatechinic Acid (8). Permethylcatechinic acid (50 mg) was hydrogenated for 5 hr at 50 psi with 5% Pd/C (100 mg) in MeOH (30 ml). Preparative tlc (solvent B) gave 30 mg of amorphous product: ir ($CHCl_3$), 3620 (w), 3440 (w), 1647 (s), 1605 (s), 1522 cm^{-1}; uv (95% EtOH) 230, 258 nm; nmr ($CDCl_3$) τ 3.30 (m, 3), 4.55 (s, 1), 5.87 (m, 1), 6.16 (s, 3), 6.17 (s, 3), 6.55 (s, 3), 6.85 (br s), 7.45 (m), 7.9 (m), 8.65 (s, 3); mass spectrum (rel intensity) 348 (34), 193 (7), 181 (12), 179 (26), 164 (13), 151 (100), 138 (17).

Anal. Calcd for $C_{19}H_{24}O_6$: *m/e* 348 (100), 349 (21.1), 350 (3.32). Found: *m/e* 348 (100), 349 (21.1), 350 (3.35).

Acetylation with NaOAc and Ac_2O in benzene gave the diacetate as a white solid: ir ($CHCl_3$) 1732 (s), 1655 (s), 1608 (s), 1523 (s) cm^{-1}; uv (95% EtOH) 233, 255 nm; nmr ($CDCl_3$) τ 3.35 (m, 3), 4.48 (s, 1), 4.52 (m, 1), 6.14 (s, 3), 6,16 (s, 3), 6.52 (s, 3), 6.65 (m), 7.6–8.02 (m), 7.78 (s, 3), 8.17 (s, 3), 8.38 (s, 3).

Trimethyldihydrocatechinic Acid (9). Catechinic acid (400 mg) in MeOH was hydrogenated for 5 hr at 50 psi over 5% Pd/C (500 mg). The filtered reaction mixture was evaporated to dryness and then treated with excess CH_2N_2 at 4° for 3 days. Evaporation *in vacuo* gave a viscous oil which was purified by preparative tlc (solvent B) to give the major product (90 mg): ir ($CHCl_3$), 3620 (w), 3420 (w), 1649 (s), 1602 (s), 1520 (s) cm^{-1}; uv (95% EtOH) 232, 254 nm; nmr ($CDCl_3$) τ 3.42 (m, 3), 4.54 (s, 1), 5.94 (m), 6.17 (s, 3), 6.20 (s, 3), 6.34 (m), 6.54 (s, 3), 6.70 (dd, 1), 7.27 (m, 2), 7.93 (m); mass spectrum (rel intensity) 334 (55), 316 (4), 304 (8), 273 (4), 193 (10), 183 (11), 179 (15), 167 (27), 165 (28), 151 (100), 137 (81).

Anal. Calcd for $C_{18}H_{22}O_6$: *m/e* 334 (100), 335 (20.04), 336 (3.11). Found: *m/e* 334 (100), 335 (20.02), 336 (4.35).

Acetylation with Ac_2O, NaOAc, and benzene at reflux gave the diacetate as an amorphous white solid: ir ($CHCl_3$) 1738 (s), 1660 (s) 1605 (s), 1523 (s) cm^{-1}; uv (95% EtOH) 237, 252 nm; nmr ($CDCl_3$) τ 3.35 (m, 3), 4.43 (s, 1), 4.50 (m, 1), 4.80 (t, 1), 6.14 (s, 3), 6.16 (s, 3), 6.53 (s, 3), 6.65 (dd, 1), 7.06 (m, 2), 7.77 (s, 3), 8.02 (m), 8.20 (s, 3); mass spectrum (rel intensity) 418 (19), 358 (31), 298 (30), 283 (9), 266 (100), 255 (12), 251 (11), 239 (11), 214 (19), 193 (44), 180 (12), 165 (20), 151 (75), 137 (67).

Anal. Calcd for $C_{22}H_{26}O_8$: *m/e* 418 (100), 419 (24.4), 420 (4.5). Found: *m/e* 418 (100), 419 (24.7), 420 (4.6).

Acknowledgment. We thank Dr. F. W. Herrick, ITT Rayonier Inc., Shelton, Wash., for helpful discussions.

Registry No.—**2,** 154-23-4; **5,** 52484-79-4; **6,** 52358-31-3; **6** monoacetate, 52358-32-4; **7,** 52358-33-5; **7** monoacetate, 52358-34-6; **8,** 52358-35-7; **8** diacetate, 52358-36-8; **9,** 52358-37-9; **9** diacetate, 52358-38-0; trimethylisocatechinic acid, 52358-39-1; trimethylisocatechinic acid monoacetate, 52358-40-4; dihydrotrimethylisocatechinic acid, 52358-41-5; diazomethane, 334-88-3.

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(8) Compare dimedone ethyl ether (1642, 1603 cm^{-1}): K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 69.
(9) A. J. Scott, "Ultraviolet Spectra of Natural Products," Macmillan, New York, N.Y., 1964, pp 69–71. Compare dimedone, 258 nm (ε 12,000), and its anion, 282.
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A Novel Synthesis of 4α- and 4β-Methylcholest-5-en-3β-ol from 6β-Bromo-4-methylcholest-4-en-3-one[1]

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The reduction of 6β-bromo-4-methylcholest-4-en-3-one with a large excess of lithium aluminum hydride (19 equiv of H^-) in ether results in the formation of 4α-methylcholest-5-en-3β-ol in high yield (~84%). Reduction of the bromide with lithium aluminum deuteride under similar conditions gives [3α,4β-$^2H_2$]-4α-methylcholest-5-en-3β-ol. Unexpectedly, reduction of 6β-bromo-4-methylcholest-4-en-3-one with lithium aluminum hydride at a lower molar ratio (3 equiv of H^-) gave good (~31%) yields of 4β-methylcholest-5-en-3β-ol (in addition to 4α-methylcholest-5-en-3β-ol and a third compound which was not identified). The 4β-methylcholest-5-en-3β-ol formed under these conditions by reduction of the bromide with lithium aluminum deuteride was labeled in the 3α and 4α positions.

The C-4 demethylation of sterol precursors of cholesterol is an important process which has received considerable attention.[2] The initial demethylation of 4,4-dimethyl precursors has been reported to proceed with initial removal of the equatorial 4α-methyl group with subsequent inversion of the axial 4β-methyl group to the equatorial position.[3–5] We have been interested in the stereochemical fate of the C-4 hydrogen in the demethylation of 4α-monomethyl intermediates. Preliminary studies of the conversion of [2,2,4-$^3H_3$]-4α,14α-dimethylergosta-8,24(28)-dien-3β-ol into [2,2,4-$^3H_3$]-(24*R*)-24-ethylcholesta-5,22-dien-3β-ol by the Chrysophyte *Ochromonas malhamensis* have indicated that during the second demethylation the axial 4β hydrogen appears to be inverted to the equatorial 4α position.[6] We have now directed our efforts at developing a synthetic route to give a 4α-methyl-4β-tritio substrate which can be