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Registry No.—**1**, 13010-22-5; **2**, 13010-21-4; **3**, 54502-26-0; **4**, 69847-11-6; **5**, 69847-12-7; **6**, 69847-13-8; **7**, 24381-12-2; **8**, 61748-87-6; 2-iodo-3-hydroxy-1,3,5(10)-estratrien-17-one, 42979-88-4.

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Regiospecificity of (+)-Catechin Methylation

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Previous work on the chloranil dehydrogenation of phenolic flavans to flavylium salts[1] has shown the need to protect any *o*-dihydroxyphenyl function present in the flavan prior to the oxidation. In addition, it was shown that the oxidation involves the formation of a *p*-quinone methide intermediate, thus requiring a free phenolic OH either at $C_{4'}$ or C_7. To extend this reaction to (+)-catechin (**1**), it would be necessary to first modify the B ring, preferably through partial methylation, to protect the reactive o-dihydroxyphenyl group.

Although the exhaustive methylation of **1** with diazomethane is known to give the tetramethyl ether **2**,[2] a recent study[3] on the ionization of **1** has shown that the pK_as of the four reactive phenolic groups differ significantly, the most acidic one being present in ring B (either the 3′ or 4′ position). From this evidence, it was felt that under partial methylation conditions, the monomethylation of ring B should be expected to occur preferentially. Treatment of (+)-catechin (**1**) with 1 equiv of CH_2N_2 in Et_2O–MeOH for 30 min at room temperature gave a mixture which showed three spots on TLC (silica gel, 10% MeOH in $CHCl_3$ as eluant). These were separated as three fractions via column chromatography on silica gel 60. The first material to elute (4%, HPLC trace Figure 1a) was readily identified as 3′,4′-dimethylcatechin (**5**) from its characteristic retro-Diels–Alder MS fragment at *m/e* 180.

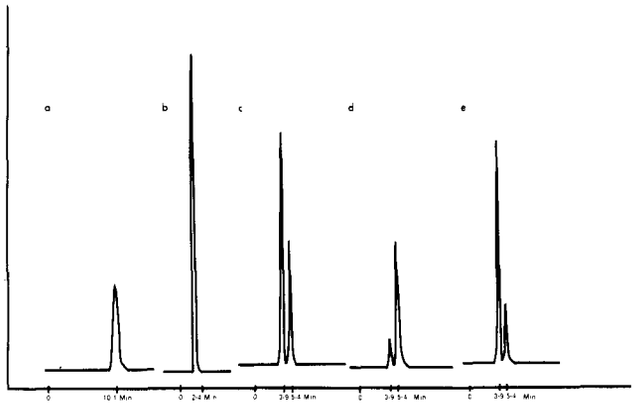


Figure 1. LC analysis of (+)-catechin methylation products: (a) compound **5**; (b) compound **1**; (c) crude mixture of **3** and **4**; (d) crystallized **4**; (e) **3** recovered from mother liquors of **4**.

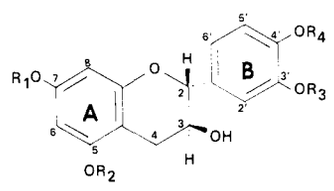
The second fraction eluted (43%) showed two peaks on LC analysis (2:1 ratio, Figure 1c) indicating a mixture of monomethyl ethers. From the MS spectrum of the mixture, it was evident that the two compounds present were the 3′- and 4′-monomethyl ethers **3** and **4**, because of the presence of a strong retro-Diels–Alder fragment at *m/e* 166 and the absence of a fragment at *m/e* 153 expected if the 5- or 7-monomethyl derivatives were present. The third fraction eluted (39%, LC trace Figure 1b) was identical to starting material **1**.

Proof of structure for the isomeric monomethyl ethers **3** and **4** was obtained by chemical degradation, as the available ^{13}C NMR data[4–7] for phenolic compounds bearing similar vanillic/isovanillic isomerism showed no appreciable differences for the chemical shifts of $C_{3'}$ and $C_{4'}$.

To that effect, the crude mixture of **3** and **4** was crystallized from MeOH–$CHCl_3$ to give one of the isomers as a white solid, mp 222–4 °C, 80% pure by LC (Figure 1d). It was shown to be the 4′-*O*-methyl isomer **4** through ethylation to **6**, which gave 4-methoxy-3-ethoxybenzoic acid upon oxidation with aqueous $KMnO_4$.

From the mother liquors of **4**, the isomer **3** (78% pure, Figure 1e) was recovered as a glassy solid that failed to crystallize. Ethylation of **3** afforded **7**, which on oxidation with $KMnO_4$ gave the expected 4-ethoxy-3-methoxybenzoic acid.

The observed exclusive methylation of (+)-catechin ring B indicates that, under the conditions adopted, its two phenolic groups are the most acidic of the four present.



1 $R_1 = R_2 = R_3 = R_4 = H$
2 $R_1 = R_2 = R_3 = R_4 = CH_3$
3 $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$
4 $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$
5 $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$
6 $R_1 = R_2 = R_3 = C_2H_5$; $R_4 = CH_3$
7 $R_1 = R_2 = R_4 = C_2H_5$; $R_3 = CH_3$

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ unless otherwise stated. Chemical shifts are given in ppm downfield from Me_4Si. Abbreviations: s = singlet; b s = broad singlet; b d = broad doublet; d = doublet; t = triplet; m = multiplet. All reagents were used as received from the supplier and were reagent grade. Silica gel 60 was supplied by E. Merck, Darmstadt, West Germany. Microanalyses were performed by Gailbraith Laboratories, Knoxville, Tenn. LC analyses were performed on a Waters liquid chromatograph using a 300 × 4 mm μBondapak/C_{18} column and a Schoeffel SF 770 UV/Vis detector set at 280 nm. A flow rate of 2 mL/min was maintained employing a mixture of water–acetic acid–methanol (90:10:10 by volume) as eluant.

Methylation of (+)-Catechin. To a solution of 2.0 g of (+)-catechin (K&K) in 100 mL of 10% MeOH–Et_2O was added 1 equiv of CH_2N_2 in Et_2O (~70 mL, solution titrated vs. benzoic acid). After standing for 30 min at room temperature, one drop of HOAc was added and the solution was evaporated. The resulting light brown oil

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was chromatographed on a 2.5 × 50 cm silica gel column using 3, 4, and 8% MeOH in $CHCl_3$ as eluant. Fractions were combined after TLC analysis to give 102 mg (4%) of **3′,4′-dimethyl-(+)-catechin (5)**: mp 247–8 °C (MeOH–$CHCl_3$); IR (KBr) 2.96, 6.67, 6.90, 8.04, 8.85, and 9.90 μm; MS *m/e* (rel intensity) 318 (39), 180 (100), 165 (18), 152 (20), 151 (35), 139 (38), and 43 (54); NMR (Me_2SO-d_6) δ 6.95 (3 H, b s, C_2′H, C_5′H, and C_6′H), 5.82 (2 H, b d, C_6H and C_8H), 4.58 (1 H, b d, C_2H), 3.75 (7 H, b s, OCH_3 and C_3H), and 2.50 (2 H, m, C_4H). Anal. Calcd for $C_{12}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 63.89; H, 5.88. In addition to starting material (780 mg, 39%), there was obtained a mixture of monomethyl catechins (857 mg, 43%) as an oil. Crystallization of the oil from MeOH–$CHCl_3$ gave 345 mg (17%) of white solid, mp 222–4 °C (recrystallized mp 228–30 °C). From the spectral data and its chemical reactions, this material was identified as 4′-methyl-(+)-catechin (**4**): IR (KRr) 2.98, 6.25, 6.65, 7.05, 8.04, 9.03, and 9.71 μm; MS *m/e* (rel intensity) 304 (50), 167 (17), 166 (100), 151 (13), 139 (82), 138 (25), and 137 (38); NMR (Me_2SO-d_6) δ 6.82 (3 H, b s, C_2′H, C_5′H, and C_6′H), 5.85 (2 H, b d, C_6H and C_8H), 4.55 (1 H, d, C_2H), 3.75 (4, H, b s, OCH_3 and C_3H), and 2.50 (2 H, m, C_4H). Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.48; H, 5.47.

3′,5,7-Triethyl-4′-methyl-(+)-catechin (6). A mixture of 200 mg of 4′-methyl-(+)-catechin (**4**) and 2.5 g of granular K_2CO_3 in 10 mL of acetone was heated to reflux, and 1.4 mL of diethyl sulfate was added in 0.2-mL aliquots through the condenser every 10 min. After the addition was completed, the reflux was continued overnight. The mixture was then filtered, and the precipitated was washed with 2 × 10 mL of acetone. Evaporation of the combined filtrate gave a liquid which solidified on stirring with 0.5% KOH solution overnight. Crystallization from EtOAc–hexane afforded 192 mg (75%) of **3′,5,7-triethyl-4′-methyl-(+)-catechin (6)**: mp 104–5 °C (recrystallized mp 108–9 °C); IR (KBr) 2.90, 6.34, 7.00, 7.25, 8.00, 8.78, 8.96, 9.80, and 12.6 μm; MS *m/e* (rel intensity) 388 (28), 196 (14), 195 (100), 194 (25), 167 (12), 166 (10), and 139 (11); NMR δ 6.96 (3 H, b s, C_2′H, C_5′H, and C_6′H), 6.12 (2 H, s, C_6H and C_8H), 4.60 (1 H, d, C_2H), 3.7–4.3 (10 H, m, OCH_2CH_3, OCH_2, and C_3H), 2.4–3.3 (2 H, m C_4H), 1.95 (1 H, m, OH), and 1.2–1.6 (9 H, m, OCH_2CH_3). Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.10; H, 7.16.

4′,5,7-Triethyl-3′-methyl-(+)-catechin (7). The oily mother liquors from the preparation of **5** (500 mg) were reacted in 20 mL of acetone with 2.8 mL of diethyl sulfate and 5 g of K_2CO_3 as described above. The crude product was crystallized from MeOH–H_2O to give 413 mg (2 crops, 65%) of **4′ 5,7-triethyl-3′-methyl-(+)-catechin (7)**: mp 118–120 °C (recrystallized from EtOAc–hexane mp 125–6 °C); IR (KBr) 2.94, 6.30, 7.00, 7.25, 7.94, 8.70, 9.00, 9.74, and 12.6 μm; MS *m/e* (rel intensity) 388 (34), 195 (100), 71 (37), 57 (59), 45 (38), 43 (46), and 41 (29); NMR δ 6.95 (3 H, b s, C_2′H, C_5′H, and C_6′H), 6.10 (2 H, s, C_6H and C_8H), 4.62 (1 H, d, C_2H), 3.7–4.3 (~10 H, m, OCH_2CH_3 and C_3H), 2.4–3.3 (2 H, m, C_4H), 2.10 (1 H, bs, OH), and 1.1–1.6 (9 H, m, OCH_2CH_3). Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.94; H, 7.47.

Permanganate Oxidation of 3′,5,7-Triethyl-4′-methyl-(+)-catechin (6).[10] A suspension of 200 mg of **6** in 10 mL of H_2O was heated to 100 °C with stirring, then 1.0 g of $KMnO_4$ were added in small portions over the course of 1 h. The solution was stirred at 100 °C for an additional hour then filtered hot. The MnO_2 was washed with 5 mL of hot 1% KOH solution, and the combined filtrates were cooled and acidified to pH 2 with concentrated HCl. Extraction with 2 × 10 mL of $CHCl_3$ followed by drying and evaporating the $CHCl_3$ gave a light yellow solid. Recrystallization from MeOH–H_2O afforded 13 mg of white solid, mp 159–162 °C. The solid was identical by MS comparison with an authentic sample of 3-ethoxy-4-methoxybenzoic acid (lit.[8] mp 163–4 °C, mmp 161–3.5 °C).

Permanganate Oxidation of 4′,5,7-Triethyl-3′-methyl-(+)-catechin (7). Ethylated catechin 7 was oxidized with 1 g of $KMnO_4$ at H_2O at 100 °C as described above. Recrystallization of the crude product from MeOH–H_2O gave 9 mg of white solid, mp 195–6 °C, identical by MS comparison with an authentic sample of 4-ethoxy-3-methoxybenzoic acid (lit.[9] mp 193–4 °C, mmp 195–6 °C).

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Simple Preparations of *N*-(*tert*-Butyloxycarbonyl)-*O*-methyl-L-serine and *N*-(*tert*-Butyloxycarbonyl)-*O*-methyl-L-threonine by Direct Methylation

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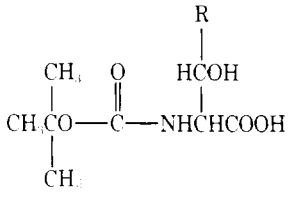
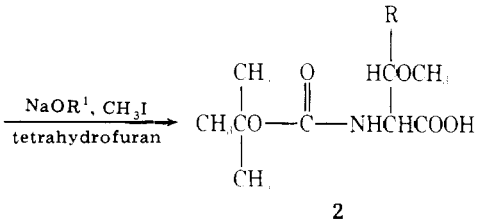
O-Methyl-L-serine[2] and *O*-methyl-L-threonine[3,4] are of interest for incorporating into peptides for structure–function relationship studies and in the search for useful analogues of biologically active molecules. *O*-Methyl-L-threonine is also an antagonist of isoleucine, inhibiting protein synthesis by ascites tumour cells.[5] The *N*-*tert*-butyloxycarbonyl (Boc) derivative of *O*-methyl-L-serine, which is useful for synthetic work, is best obtained by a five-step synthesis from L-serine of the *O*-methylamino acid, followed by acylation with *tert*-butyloxycarbonyl azide.[6] We describe in this paper a method of preparing *N*-(*tert*-butyloxycarbonyl)-*O*-methyl-L-serine (**2a**) in one step from *N*-(*tert*-butyloxycarbonyl)-L-serine (**1a**). Since the Boc group can be removed readily,[6] this provides the simplest access to the free *O*-methylamino acid as well. An analogous preparation of crystalline *N*-(*tert*-butyloxycarbonyl)-*O*-methyl-L-threonine (**2b**) is also described. Inefficient preparations of the latter[4] and the benzyloxycarbonyl derivative[3] using silver oxide and methyl iodide as reagents have been reported.



1



2

a, R = H; R^1 = CH_3
b, R = CH_3; R^1 = $CH(CH_3)_2$

Further to our studies on the N-methylation of *N*-(benzyloxycarbonyl)-[7] and *N*-(butyloxycarbonyl)amino acids[8] using methyl iodide and sodium hydride in tetrahydrofuran, the methylation of the O-unprotected derivatives of serine and threonine was examined.[9] The reaction proved complex due to partial selectivity and decomposition. We have now found that by using a sodium alkoxide as base, methylation of the butyloxycarbonyl derivatives takes place exclusively at the hydroxyl group without any decomposition occurring. The alkylation is incomplete; however, the products (**2**) can be

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