equatorial), 4.6 (m, 3-CH, axial), 5.18 (broad d, 6-olefinic C-H).

3β-Acetoxy-16α,17α-methylene-5-pregnen-20-ols (3 and 4). To a solution of 557.0 mg of **2** in 10 mL of dry tetrahydrofuran and 30 mL of 2-propanol was added 557.0 mg of sodium borohydride. The rapidly stirred suspension was reacted at room temperature for 3 h. After being cooled to 0 °C, the reaction mixture was diluted with 10 mL of methanol and allowed to proceed for an additional 2 h at 25–27 °C. The reaction mixture was cautiously treated with saturated aqueous potassium dihydrogen phosphate and extracted with ether. The combined extracts were washed with water and saturated salt solution and dried over magnesium sulfate; the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on eight 20 × 20 silica plates (1000 μm) using 95:5 benzene/ether as eluent to give the fast moving alcohol **3** which crystallized from chloroform as white needles (173 mg, 30.89% yield): mp 149–151 °C; IR (Nujol mull) 3448, 1727, 1266, 1089, 1044 cm^{-1}; CI-MS (CH_4) *m/e* 373 $(M + H)^+$; ^1H NMR (EM-390) ($CDCl_3$) δ 0.3–0.73 (m, cyclopropyl methylene), 0.92 (s, 18-CH_3), 1.03 (s, 19-CH_3), 1.2 (d, J = 6 Hz, 21-CH_3), 2.03 (s, $CH_3C(O)OC_3$, equatorial), 4.25 (q, J = 6 Hz, 20-CH), 4.6 (m, 3-CH, axial), 5.4 (broad d, 6-olefinic CH).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.42; H, 9.15. Found: C, 77.52; H, 9.20.

The slow moving alcohol **4** crystallized from chloroform as white needles (139.0 mg, 24.8%): mp 140–144 °C; IR (Nujol mull) 3571, 1709, 1259, 1036 cm^{-1}; CI-MS (CH_4) *m/e* 373 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.3–0.8 (m, cyclopropyl methylene), 0.92 (d, 21-CH_3, half of the doublet obscured), 0.97 (s, 18-CH_3), 1.03 (s, 19-CH_3), 2.02 (s, $CH_3C(O)OC_3$, equatorial), 4.37 (q, J = 6 Hz, 20-CH), 4.5 (m, 3-CH, axial), 5.3 (broad doublet, 6-olefinic CH).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.42; H, 9.15. Found: C, 77.40; H, 9.11.

(17a*E*)-*D*-Homo-5,17a(20)-pregnadien-3β,16α-diyl Diacetate (5). (a) From the Fast Moving Alcohol. A solution of 40 mg of the fast moving alcohol derivative in 2.0 mL of glacial acetic acid was heated at 110–112 °C (oil-bath temperature) under nitrogen for about 2 h. After being cooled to room temperature, the reaction mixture was diluted with cold water and brought to pH 8 with sodium bicarbonate. The aqueous mixture was extracted with ether. The ethereal solution was washed with water and saturated salt solution, dried over magnesium sulfate, and filtered; the filtrate was evaporated under reduced pressure. The residue was chromatographed on a 20 × 20 silica plate (1000 μm) using 95:5 benzene/ether as eluent to give **5** as a white foam (39 mg, 88%) homogeneous on a TLC analysis: R_f = 0.54 (95:5 benzene/ether); IR (Nujol mull) 1739, 1242, 1136, 1030 cm^{-1}; MS *m/e* 354 $(M - CH_3COOH)^+$; CI-MS (isobutane as gas carrier) *m/e* 415, $(M + H)^+$; ^1H NMR (SC-300) ($CDCl_3$) δ 0.92 (s, 18-CH_3), 1.01 (s, 19-CH_3), 1.55 (d, J = 6 Hz, 21-CH_3), 1.99 (s, $CH_3C(O)OC_{16}$), 2.03 (s, $CH_3C(O)OC_3$), 4.6 (m, 3-CH, axial), 5.13 (quintet, 16-CH, equatorial), 5.28–5.4 (m, 2 H, vinyl H at C-6 and C-20).

(b) From the Slow Moving Alcohol. A solution of 40 mg of slow moving alcohol in 2.0 mL of glacial acetic acid was heated at 110–112 °C (oil bath temperature) under nitrogen for about 2 h. Workup as described above (39.3 mg, 88.3%) gave material homogeneous on TLC analysis, R_f = 0.54 (95:5 benzene/ether), whose spectral data are identical in all respects with those of the above described product **5**.

The combined products from (a) and (b) experiments were analyzed by ^{13}C NMR ($CDCl_3$) and showed δ_c 13.04 (C-19), 17.74 and 19.19 (C-21 and C-18), 20.54 (C-11), 21.93 (2 CH_3CO_2), 27.73, 28.12, and 29.26 (C-2, C-15, and C-17), 31.87 (C-7 and C-8), 35.93 (C-12), 36.63 (C-1), 36.82 (C-10), 37.85 (C-4), 38.67 (C-13), 45.85 (C-14), 49.50 (C-9), 70.89 (C-16), 73.83 (C-3), 115.48 (C-20), 122.31 (C-6), 139.35 (C-5), 143.06 (C-17a), 170.46 and 170.75 (2 CH_3CO_2).

Subsequently, the compound **5** was crystallized from methanol, mp 158–159 °C (effervesces), and analyzed as a dimethanol solvate.

Anal. Calcd for $C_{26}H_{34}O_4 \cdot (2CH_3OH)$: C, 70.26; H, 9.60. Found: C, 70.38; H, 9.87.

Acknowledgment. N.G.S. sincerely thanks Drs. L. Z. Pollara and A. K. Bose for their encouragement and for very helpful discussions during his stay at Stevens Institute of Technology and Dr. Alan Douglas for his helpful collaboration with the ^{13}C NMR studies. We are also indebted to Mr. B. Pramanik of the Stevens Institute of Technology for the chemical ionization mass spectrum measurements. The mass spectrum was measured by Mr. Jack Smith at Merck Sharp and Dohme Research Laboratories. The authors wish to thank Dr. B. Arison for determination and interpretation of ^1H NMR spectra (Varian SC-300).

Registry No.—**1**, 979-02-2; **2**, 6173-60-0; **3**, 69867-42-1; **4**, 69867-43-2; **5**, 69867-44-3; dimethylsulfoxonium methylide, 5367-24-8; trimethylsulfoxonium iodide, 1774-47-6; dimethyl sulfoxide, 67-68-5.

References and Notes

(1) A major part of this work was done at Stevens Institute of Technology, Hoboken, N.J., by N.G.S. while on sabbatical leave from Merck Sharp and Dohme Research Labs, Rahway, N.J. 07065.
(2) Ajay K. Bose and N. G. Steinberg, *J. Org. Chem.*, **36**, 2400 (1971).
(3) N. G. Steinberg, Ph.D. Thesis, Stevens Institute of Technology, 1969.
(4) N. G. Steinberg, G. H. Rasmussen, G. H. Reynolds, J. P. Springer, and B. H. Arison, manuscript in preparation.
(5) (a) Hans G. Lehmann, German Patent 1 183 500 (1964); *Chem. Abstr.*, **62**, 6540 (1965); (b) W. F. Johns and K. W. Salamon, *J. Org. Chem.*, **36**, 1952 (1971); (c) H. Laurent and R. Weichert, "Organic Reactions in Steroid Chemistry", Vol. 2, Van Nostrand-Reinhold, Princeton, N.J., 1972, p 115.
(6) G. E. Arth, G. F. Reynolds, G. H. Rasmusson, A. Chen, and A. A. Patchett, *Tetrahedron Lett.*, 291–294 (1974).
(7) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
(8) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, 1959, p 337.
(9) W. D. Closson and G. T. Kwiatkowski, *Tetrahedron*, **21**, 2779 (1965).
(10) S. Winstein and E. M. Kosower, *J. Am. Chem. Soc.*, **81**, 4399 (1959).
(11) (a) R. R. Ernst, *J. Chem. Phys.*, **45**, 3845 (1966); (b) M. Tanabe, T. Hamasaki, D. Thomas, and L. Johnson, *J. Am. Chem. Soc.*, **93**, 274 (1971).
(12) E. Wenkert, A. O. Clouse, D. W. Cochran, and D. Doddrell, *J. Am. Chem. Soc.*, **91**, 6879 (1969).
(13) J. W. Blunt and J. B. Stothers, *Org. Magn. Reson.*, **9**, 439 (1977).
(14) There are, in fact, three methylene carbons at 27.7, 28.1, and 29.3 ppm, one of which is assigned to C-2 (28.1 ppm) based on comparison with the model cholest-5-en-3β-yl acetate. C-2 could be assigned to either of the other two signals without changing the arguments in the structure elucidation.
(15) H. J. Schneider and V. Hoppen, *J. Org. Chem.*, **43**, 3866 (1978).
(16) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972, p 60.
(17) Sheves, Sialom, and Mazur have described an analogous rearrangement in the Vitamin D_3 field, *J. Chem. Soc., Chem. Commun.*, 554 (1978), and references therein.

A-Ring Iodination of Estradiol

Frederick Sweet,* Timothy B. Patrick, and Jackquline M. Mudd

Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Missouri 63110, and Department of Chemistry, Southern Illinois University at Edwardsville, Edwardsville, Illinois 62026

Received January 18, 1979

Contrary to the earlier reports, A-ring monoiodination of estradiol was found not to be a selective process in the present work. Unambiguous syntheses of 2-iodo- and 4-iodoestradiols are described here for the first time.

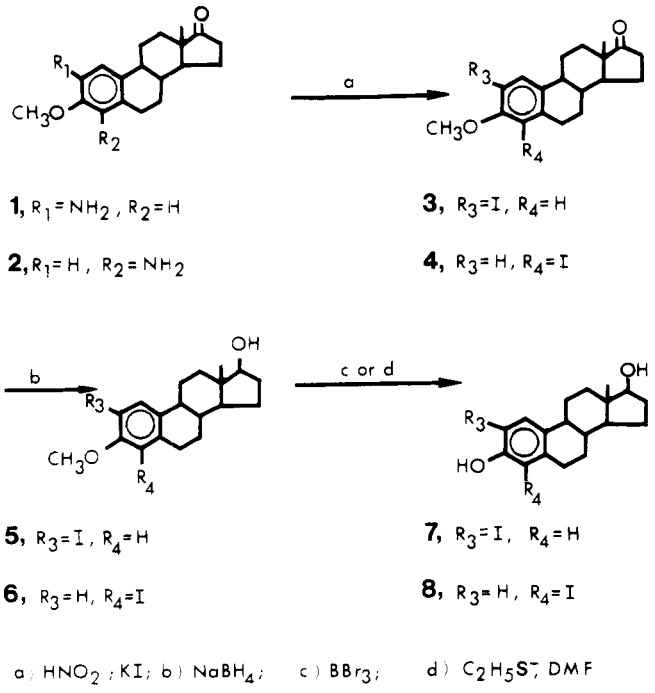
Iodination of estradiol was explored to extend our synthesis and to investigate the biological activity of A-ring substituted estrogen derivatives.[1] Thirty years ago it was reported that 2 equiv of *N*-iodoacetamide or molecular iodine under alkaline conditions reacts with estradiol to give 2,4-diiodoestradiol, a mixture of monoiodinated steroids, and unreacted starting material.[2] Four years later Hillmann-Elias and co-workers reported that mercuric acetate catalyzed iodination of estradiol gave a 90% yield of 2-iodoestradiol.[3] The remarkably selective monoiodination reaction remained a standard for the preparation of 2-iodoestradiol for over two decades.[4-7] Although selective monobromination of estradiol has also been reported,[8] this reaction was unequivocally shown to give an isomeric mixture of 2- and 4-bromoestradiols.[9] Thus, it seemed that the earlier reported selective monoiodination of estradiol was questionable.

We repeated the mercuric acetate catalyzed iodination of estradiol[3] and consistently obtained mixtures of four or five components. Therefore, we attempted to obtain direct monoiodination of estradiol by employing different reaction conditions. Iodination of estradiol in the presence of sodium

* Address correspondence to Washington University School of Medicine.

0022-3263/79/1944-2296$01.00/0 © 1979 American Chemical Society

Scheme I



hydride in dimethoxyethane[10] or thallium(I) acetate[11] produced similar complex reaction mixtures. Analysis by thin-layer chromatography of the reaction mixtures from mercuric acetate catalyzed iodination of estradiol showed that these mixtures mainly contained 2-iodo- and 4-iodoestradiols. We prepared these compounds by well-established synthetic methods to provide authentic materials for comparison. The close R_f values of the two isomers (0.44 and 0.41 in chloroform containing 5% acetonitrile[9]) precluded their precise quantitative analysis in the reaction mixtures. Minor amounts of 2,4-diiodoestradiol (R_f 0.71) and unreacted starting material (R_f 0.30) were also identified in the mixtures from the mercuric acetate catalyzed iodination reaction.

2-Iodoestradiol (**7**) and 4-iodoestradiol (**8**) were prepared from the corresponding aminoestrone 3-methyl ether derivatives[12] represented by equations in Scheme I. Demethylation of **5** and **6** was difficult. Boron tribromide demethylation[13] of **3** followed by reduction gave **7**, but this method did not succeed with **4**. Sodium ethylmercaptide demethylation[14] of **5** or **6** gave **7** or **8**, respectively, in satisfactory yields. Structural assignments for all of the new compounds were supported by elemental and spectral analyses, described in the Experimental Section.

Experimental Section

Temperature readings are reported uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded on a Beckman IR-33 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian T-60 (^{1}H) with tetramethylsilane as an internal standard (δ 0.0). Thin-layer chromatography was performed with Eastman silica gel G (200-μm thickness) plates containing a fluorescent indicator.

2-Iodo-3-methoxy-1,3,5(10)-estratrien-17-one (3). A solution of 500 mg (1.67 mmol) of 2-amino-3-methoxy-1,3,5(10)-estratrien-17-one (**1**)[12] in 10 mL of 6 N sulfuric acid was treated at 5 °C with a solution of 0.3 g of sodium nitrite in 5 mL of water. After 0.5 h, the stirred mixture was treated with 1.3 g of potassium iodide in 5 mL of water. A thick red precipitate formed which was dissolved by addition of 10 mL of dioxane. Excess iodine was reduced by adding aqueous sodium bisulfite. The resulting mixture was extracted with ether. The ethereal extract was dried (Na_2SO_4), filtered, and concentrated to a yellow oil. Chromatography of the oil on a 2.5 × 20 cm column of alumina (eluted with benzene–chloroform, 2:1) furnished a white solid which was recrystallized from 2-propanol to give 300 mg (44%) of pure **3**: mp 158–159 °C; R_f 0.40 (benzene–$CHCl_3$, 1:1); IR (KBr) 1745 (C=O), 1250 (C–O), 1065 (C–O) cm^{-1}; UV ($CHCl_3$) 246, 289, 298 nm; ^{1}H NMR ($CDCl_3$) δ 8.1 (s, 18-CH_3), 1.2–3.2 (br, aliphatic), 3.85 (s, OCH_3), 6.6 (s, aromatic), 7.7 (s, aromatic).

Anal. Calcd for $C_{19}H_{23}O_2I$: C, 55.61; H, 5.61; I, 30.98. Found: C, 55.78; H, 5.72; I, 30.68.

4-Iodo-3-methoxy-1,3,5(10)-estratrien-17-one (4). A procedure similar to that described above for the preparation of **3** was used starting with 1.0 g (3.3 mmol) of 4-amino-3-methoxy-1,3,5(10)-estratrien-17-one (**2**).[12] Recrystallization of the crude product from 2-propanol furnished 0.72 g (53%) of pure **4**: mp 209–212 °C; R_f 0.91 (benzene–chloroform, 1:1); IR (KBr) 1730 (C=O), 1270, 1065 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9 (s, 18-CH_3), 1.0–3.0 (aliphatic), 3.85 (s, OCH_3), 6.7 (d, J = 10 Hz, aromatic), 7.3 (d, J = 10 Hz, aromatic).

Anal. Calcd for $C_{19}H_{23}O_2I$: C, 55.61; H, 5.61; I, 30.98. Found: C, 55.71; H, 5.58; I, 30.70.

2-Iodo-3-methoxy-1,3,5(10)-estratrien-17β-ol (5). A solution of 300 mg (0.73 mmol) of **3** in 10 mL of ethanol was treated at room temperature with 200 mg of sodium borohydride. After standing overnight, the mixture was acidified and extracted with ether, and the ethereal extract was concentrated. Recrystallization from 2-propanol furnished **5** as white plates: 260 mg (86%); mp 162–165 °C; IR (KBr) 3200 (broad OH), 1180, 970 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.8 (s, 18-CH_3), 1.0–3.0 (broad, aliphatic), 3.7 (m, 17-CH), 3.8 (s, OCH_3), 6.5 (s, aromatic), 7.6 (s, aromatic).

Anal. Calcd for $C_{19}H_{25}O_2I$: C, 55.34; H, 6.07; I, 30.83. Found: C, 55.12; H, 6.22; I, 31.01.

4-Iodo-3-methoxy-1,3,5(10)-estratrien-17β-ol (6). Sodium borohydride was used to reduce 0.3 g of **4** under the above conditions. Pure **6** was obtained in 99% yield (300 mg) after recrystallization from 2-propanol: mp 153–156 °C; IR (KBr) 3200 (OH, 1380, 950 (C–O) cm^{-1}; ^{1}H NMR δ 0.78 (s, 18-CH_3), 1.0–3.0 (broad, aliphatic), 3.76 (m, 17-H), 3.85 (s, OCH_3), 6.64 (d, J = 13 Hz, aromatic), 7.2 (d, J = 13 Hz, aromatic).

Anal. Calcd for $C_{19}H_{25}O_2I$: C, 55.34; H, 6.07; I, 30.83. Found: C, 55.64; H, 5.93; I, 30.66.

2-Iodo-1,3,5(10)-estratriene-3,17β-diol (7). A. To a solution containing 0.4 g (0.98 mmol) of **3** in 25 mL of anhydrous chloroform was added dropwise 1.5 g of boron tribromide at 0 °C. The mixture was stirred for 1 h, and then it was poured into an ice and ammonium hydroxide mixture. The chloroform layer was separated and filtered through a column of Florisil. Concentration of the filtrate gave 60 mg (16%) of the crude light yellow product 2-iodo-3-hydroxy-1,3,5(10)-estratrien-17-one: mp 176–178 °C; IR (KBr) 3350 (OH), 1720 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 18-CH_3), 1.1–3.1 (broad, aliphatic), 5.4 (OH), 6.96 and 7.75 (s, aromatic); R_f 0.22 (1:1 benzene–chloroform).

The crude product was reduced with sodium borohydride (see procedure above for **3** → **5**), which gave 50 mg (13% overall from **3**) of **7**, mp 176–178 °C dec (ether–hexane).

B. A mixture of 300 mg (0.73 mmol) of **5** in 20 mL of anhydrous dimethylformamide was treated with 0.3 g of sodium ethylthiolate (ethyl mercaptan and sodium hydride) in 15 mL of dimethylformamide. The resulting mixture was heated under gentle reflux for 6 h and then poured into ice water. The aqueous mixture was made alkaline with potassium hydroxide solution and then extracted several times with chloroform. The remaining aqueous solution was acidified and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and concentrated. The residue was chromatographed on a silica gel column (0.6 × 5 cm, $CHCl_3$) to give pure **7** as a light yellow powder: 110 mg (38%); mp 177–178 °C dec; IR (KBr) 3400 (OH), 1410, 1200, 1000 (s) cm^{-1}; R_f 0.44 ($CHCl_3$–CH_3CN, 95:5); UV λ_{max} ($CHCl_3$) 248, 287 nm; ^{1}H NMR ($CDCl_3$) δ 0.82 (18-CH_3), 1.1–2.6 (broad, aliphatic), 2.95 (m, 17-H), 3.9 (m, OH), 6.9 and 7.7 (s, aromatic)

Anal. Calcd for $C_{18}H_{23}O_2I$: C, 54.27; H, 5.78; I, 3.91. Found: C, 54.33; H, 5.63; I, 3.80.

4-Iodo-1,3,5(10)-estratriene-3,17β-diol (8). A solution containing 300 mg (0.73 mmol) of **6** in 25 mL of anhydrous dimethylformamide was treated with sodium ethylmercaptide as described above. The crude product was chromatographed on a silica gel column (0.6 × 5 cm, chloroform) to give 100 mg (35%) of pure **8**: mp 78–80 °C; IR (KBr) 3350 (OH), 1465, 1260, 1030 (s) cm^{-1}; UV λ_{max} ($CHCl_3$) 288, 303 nm; ^{1}H NMR ($CDCl_3$) δ 0.8 (s, 18-CH_3), 1.0–3.0 (broad, aliphatic), 3.5 (m, 17-H), 6.6 and 7.1 (d, J = 6.8 Hz, aromatic); R_f 0.41 ($CHCl_3$–CH_3CN, 95:5).

Anal. Calcd for $C_{18}H_{23}O_2I$: C, 54.27; H, 5.78; I, 31.91. Found: C, 54.51; H, 5.97; I, 32.06.

Acknowledgments. This work was supported by research grants AM 16854 and HD 12533-01 and the Petroleum Research Fund, administered by the American Chemical Society.

F.S. is a recipient of the U.S. Public Health Service Research Career Development Award HD 70788. The authors gratefully acknowledge the technical assistance of R. Michael Judd.

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.

References and Notes

(1) Rao, K. N.; Sweet, F.; Warren, J. C. *Steroids* **1974**, *22*, 63.
(2) Albert, S.; Heard, R. D. H.; Lebland, C. P.; Saffran, J. *J. Biol. Chem.* **1949**, *157*, 247.
(3) Hillmann-Elias, A.; Hillman, G.; Scheidt, U. *Z. Naturforsch., B* **1953**, *8*, 436.
(4) Brown, W.; Turner, A. B. *J. Chromatogr.* **1967**, *26*, 518.
(5) Stefanovic, M.; Krstic, L.; Mladenovic, S. *Glas. Hem. Drus., Beograd* **1973**, *38*, 463.
(6) Exley, D.; Dutton, A. *Steroids* **1969**, *14*, 575.
(7) Thakur, M. L.; Waters, S. L. *Int. J. Appl. Radiat. Isot.* **1976**, *27*, 585.
(8) Slaunwhite, W. R.; Neely, L. *J. Org. Chem.* **1962**, *27*, 1749.
(9) Utne, T.; Jobson, R. B.; Landfraf, F. W. *J. Org. Chem.* **1968**, *33*, 1654.
(10) DeLue, R.; Brown, H. C. *Synthesis* **1976**, 114.
(11) Cambie, R. C.; Rutledge, P. S.; Smith-Palmer, T.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1160.
(12) Utne, T.; Jobson, R. B.; Babson, R. D. *J. Org. Chem.* **1968**, *33*, 2469.
(13) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.
(14) Feutrill, G. I.; Mirrington, R. W. *Tetrahedron Lett.* **1970**, 1327.

Regiospecificity of (+)-Catechin Methylation

James G. Sweeny and Guillermo A. Iacobucci*

Corporate Research and Development Department, The Coca-Cola Company Atlanta, Georgia 30301

Received January 19, 1979

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.

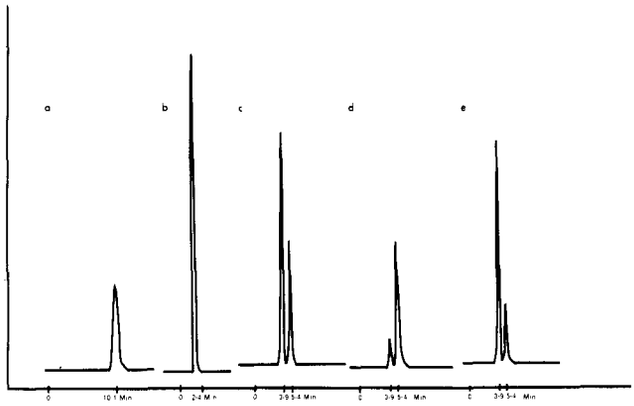


Figure 1. LC analysis of (+)-catechin methylation products: (a) compound **5**; (b) compound **1**; (c) crude mixture of **3** and **4**; (d) crystallized **4**; (e) **3** recovered from mother liquors of **4**.

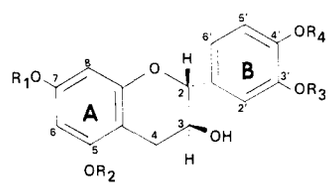
The second fraction eluted (43%) showed two peaks on LC analysis (2:1 ratio, Figure 1c) indicating a mixture of monomethyl ethers. From the MS spectrum of the mixture, it was evident that the two compounds present were the 3′- and 4′-monomethyl ethers **3** and **4**, because of the presence of a strong 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

0022-3263/79/1944-2298$01.00/0 © 1979 American Chemical Society