Various α-isocyanoacetic acid derivatives (**5**, R′ = Et) were prepared by the same conditions and procedure. The yields, ir, and nmr spectra of these compounds are summarized in Table I.

Hydrolysis of the ethyl α-isocyanoacetate derivatives (**5**, R′ = Et) was carried out as follows: 1.89 g (0.01 mol) of the ethyl α-isocyanophenylacetate was dissolved in a mixture of hydrochloric acid (6 ml) and methanol (30 ml), and the mixture was heated at 50° for 30 min to convert the isonitrile group to the amino group. After the reaction was complete, the solvent and the excess hydrochloric acid were removed *in vacuo*. The resulting hydrochloride was dissolved without purification in 20 ml of 2 *N* sodium hydroxide and allowed to stand for 3 hr at room temperature. The reaction mixture was washed with ether and decolorized with activated charcoal. Subsequently, the alkaline solution was adjusted to pH 6.5 with concentrated hydrochloric acid and the mixture was allowed to stand overnight in an ice box. The precipitate was collected by filtration and dried; 1.36 g of phenylglycine was obtained (90% yield). The compound showed a single spot on PPC, R_f 0.40 (*n*-BuOH:AcOH:H_2O, 3:1:1).

Anal. Calcd for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.43; H, 6.11; N, 9.18.

Part of the ethyl α-isocyanoacetate derivatives (**5**, R′ = Et) was converted to the amino acid ethyl ester hydrochlorides (**6**, R′ = Et) by partial acid hydrolysis in the same way as above. For example, from 0.95 g (0.005 mol) of ethyl α-isocyanophenylacetate, 1.04 g of phenylglycine ethyl ester hydrochloride was obtained (97% yield), mp 203° dec (lit.[19] mp 197° dec).

B. Reaction of Benzyl Isocyanide with Dimethyl Carbonate.—A mixture of 2.34 g (0.02 mol) of benzyl isocyanide and 1.80 g (0.02 mol) of dimethyl carbonate in 10 ml of dimethylformamide was gradually added to a suspension of 0.84 g (0.002 mol) of sodium hydride (63% in oil) in 15 ml of dimethylformamide at 15° over a period of 15 min under stirring. Stirring was continued for 1 hr at room temperature, the treatment was carried out according to method A, and 2.45 g of methyl α-isocyanophenylacetate was obtained (70% yield): ir (film) 2130 (NC), 1750 cm^{-1} (COOMe); nmr (CCl_4) δ 7.40 (s, 5, ArH), 5.29 (s, 1, CH), 3.70 (s, 3, OMe).

C. Reaction of Benzyl Isocyanide with Carbon Dioxide.—To a solution of 2.34 g (0.02 mol) of benzyl isocyanide in 15 ml of tetrahydrofuran was added dropwise a mixture of 13 ml of *n*-butyllithium (15% in hexane) in 8 ml of tetrahydrofuran at −60° over a period of 30 min under stirring. Stirring was continued for 1 hr at the same temperature, 1.76 g (0.04 mol) of Dry Ice was added to the reaction mixture, and the mixture was gradually warmed to 0°. Hydrochloric acid was added to the mixture to bring the pH to about 2 and the mixture was heated at 50° for 30 min and then evaporated under reduced pressure. To the residue was added water, and the solution was washed with ether and subsequently concentrated *in vacuo*. The hydrolyzed products were dissolved in 15 ml of water and treated with a Dowex 50 column (H^+ form) and the acidic components, but not the amino acids, were eluted with water. The amino acid was eluted with 5% ammonia. The solution was concentrated to dryness under reduced pressure and 1.21 g of phenylglycine identical with an authentic specimen was obtained (40% yield).

D. Reaction of Benzyl Isocyanide with Ethyl Chloroformate.—To a solution of 2.34 g (0.02 mol) of benzyl isocyanide in 15 ml of tetrahydrofuran was added dropwise a mixture of 13 ml of *n*-butyllithium (15% in hexane) in 8 ml of tetrahydrofuran at −60° over a period of 30 min under stirring. After stirring was continued for 1 hr at the same temperature, 2.17 g (0.02 mol) of ethyl chloroformate was added to the reaction mixture and then the mixture was gradually warmed to 0°. The mixture was neutralized with acetic acid and the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate, and the extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The product was purified by column chromatography of silica gel (80 g, Kieselgel 0.2–0.5 mm, E. Merck); 1.17 g of ethyl α-isocyanophenylacetate was obtained by elution with benzene (35% yield).

E. Reaction of Methyl Isocyanide with Diethyl Carbonate.—To a solution of 0.82 g (0.02 mol) of methyl isocyanide in 15 ml of tetrahydrofuran was added dropwise a mixture of 13 ml of *n*-butyllithium (15% in hexane) in 8 ml of tetrahydrofuran at −60° over a period of 30 min under stirring. After stirring was continued for 1 hr at the same temperature, 2.36 g (0.02 mol) of diethyl carbonate was added to the reaction mixture and then the mixture was gradually warmed to 0°. The treatment was carried out according to method D; 0.79 g of ethyl α-isocyanoacetate was obtained (35% yield). Glycine was prepared from this compound by the usual hydrolysis in 32% overall yield.

Registry No.—**3** (R = Ph), 10340-95-7; **3** (R = H), 593-75-9; **3** (R = 4-CH_3OPh), 1197-58-6; **3** (R = 4-CH_3Ph), 39495-97-1; **3** (R = 4-ClPh), 39546-47-9; **3** (R = 3,4-methylenedioxy Ph), 39533-29-4; **3** (R = 2-furyl), 2920-07-2; **5** (R = Ph; R′ = Et), 39533-31-8; **5** (R = Ph; R′ = Me), 39533-32-9; **5** (R = 4-CH_3OPh; R′ = Et), 39533-33-0; **5** (R = 4-CH_3Ph; R′ = Et), 39533-34-1; **5** (R = 4-ClPh; R′ = Et), 39533-35-2; **5** (R = 3,4-methylenedioxy Ph; R′ = Et), 39533-36-3; **5** (R = 2-furyl; R′ = Et), 39533-37-4; **5** (R = H; R′ = Et), 2999-46-4; **6** (R = Ph; R′ = Et), 879-48-1; **7** (R = Ph), 69-91-0; **7** (R = 4-CH_3OPh), 2540-53-6; **7** (R = 4-CH_3Ph), 13227-01-5; **7** (R = 4-ClPh), 6212-33-5; **7** (R = 3,4-methylenedioxy Ph), 39533-43-2; **7** (R = 2-furyl), 17119-54-9; **7** (R = H), 56-40-6; diethyl carbonate, 105-58-8; dimethyl carbonate, 616-38-6; carbon dioxide, 124-38-9; ethyl chloroformate, 541-41-3.

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An Improved Synthesis of 4-Methyl- and 4,5-Dimethyl-3-pentadecylcatechol

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Interest in the synthesis of various ring derivatives and homologs of 3-pentadecylcatechol, the saturated component of the poison ivy allergenic principle, has recently developed as the result of clinical observations concerning the immunologic and toleragenic activity of such compounds.[1-3] Because of their potential effectiveness in blocking nucleophilic reactions of the quinone of 3-pentadecylcatechol, the several ring-substituted methyl derivatives of 3-pentadecylcatechol have been of particular interest. Their syntheses, recently reported from these laboratories,[2,3] have involved in several instances multistep routes leading to low overall yields (in the range of 10–15%). We wish now to report a much improved method (three-step, overall yield about 50–55%) for the synthesis of 4-methyl- and 4,5-dimethyl-3-pentadecylcatechol (**2a** and **2b**).

The improved route starts with the benzylation of 3-pentadecylcatechol[4] according to the procedure of

(1) H. Baer, C. R. Dawson, J. S. Byck, and A. P. Kurtz, *J. Immunol.*, **104**, 178 (1970).

(2) J. S. Byck and C. R. Dawson, *J. Org. Chem.*, **32**, 1084 (1967).

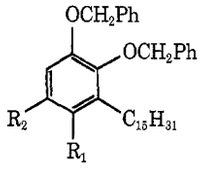
(3) J. S. Byck and C. R. Dawson, *J. Org. Chem.*, **33**, 2451 (1968).

(4) The 3-pentadecylcatechol was obtained according to the method of Kurtz and Dawson, *J. Med. Chem.*, **14**, 729 (1971).

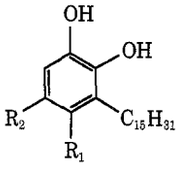
Loev and Dawson[5] and then chloromethylation of the dibenzyl ether **1a**. Earlier exploratory studies by Byck had indicated that chloromethylation leads to the formation of a monochloromethylated product.[6] In the present investigation we have thoroughly studied this reaction and have found that depending upon the proper conditions, either one or two chloromethyl groups can be introduced on the aromatic nucleus.

If the chloromethylation of **1a** is carried out with the passage of hydrogen chloride for 2 hr at 0° the product is 4-chloromethyl-3-pentadecylcatechol dibenzyl ether (**1b**). If, however, hydrogen chloride is allowed to pass through the reaction mixture for 6 hr at room temperature, then dichloromethylation is achieved, and the resulting product is 4,5-bis(chloromethyl)-3-pentadecylcatechol dibenzyl ether (**1c**). Infrared and nmr spectra have indicated that partial debenzylation occurs in the latter reaction. Since this does not interfere with the final step, no attempt was made to purify **1c**.

Both the mono- and dichloromethylated products can now be conveniently converted to 4-methyl-3-pentadecylcatechol (**2a**) and 4,5-dimethyl-3-pentadecylcatechol (**2b**), respectively, by hydrogenation with a 10% palladium on carbon catalyst. The structure of the hydrogenolysis products, as documented in the Experimental Section, verifies that the chloromethylation of **1a** can be made to give either **1b** or **1c**. This scheme thus provides a much simplified route of synthesis and an improved yield of several methylated analogs of 3-pentadecylcatechol.



1a, $R_1 = R_2 = H$
b, $R_1 = CH_2Cl$; $R_2 = H$
c, $R_1 = R_2 = CH_2Cl$



2a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = R_2 = CH_3$

Experimental Section[7]

4-Chloromethyl-3-pentadecylcatechol Dibenzyl Ether (1b).—A sample of 10.0 g (0.02 mol) of benzylated 3-pentadecylcatechol (**1a**), mp 51.0–52.0° (lit.[5] mp 52.4–53.0°), 7.4 g of paraformaldehyde, 54 ml of benzene, and 54 ml of acetic acid were cooled in an ice bath, and dry hydrogen chloride was passed through the mixture with continuous stirring. After 45 min the solution became clear, and the hydrogen chloride passage was continued for an additional 2 hr. Water and ether were added, the phases were separated, and a conventional work-up was performed. The residue was recrystallized twice from hexane to give 8.2 g (75%) of a white solid (**1b**): mp 50.0–51.0°; nmr (CCl_4) τ 2.7 (s, 10 H, C_6H_5–), 3.1 (q, 2 H, aromatic), 4.9 (s, 4 H, OCH_2–), 5.5 (s, 2 H, $-CH_2Cl$), 7.4 (t, 2 H, benzylic), 8.7 (broad s, CH_2), 8.9–9.1 (t, terminal Me), signals at 8.6–9.2 integrated for 29 H; mass spectrum m/e 549 (M^+).

4,5-Bis(chloromethyl)-3-pentadecylcatechol Dibenzyl Ether (1c).—Samples of 10.0 g of **1a**, 7.4 g of paraformaldehyde, 54 ml of benzene, and 54 ml of acetic acid were mixed in an ice bath and hydrogen chloride was passed through the mixture for 0.5 hr. The ice bath was removed and passage of hydrogen chloride was continued for 6 hr at room temperature. Water and ether were added, the phases were separated, and a conventional work-up was performed. The residue was recrystallized from hexane to yield 8.36 g (70%) of a white solid (**1c**): mp 79.0–81.0°; ir (CCl_4) 2.86 μ (w, OH, indicating partial debenzylation had occurred); nmr (CCl_4) τ 2.6 (s, 8 H, C_6H_5–), 3.2 (s, 1 H, aromatic), 4.3 (broad s, minor, OH, resulting from partial debenzylation), 4.9 (s, 3 H, OCH_2–), 5.2–5.3 (d, 4 H, $-CH_2Cl$), 7.4 (t, 2 H, benzylic), 8.7 (broad s, CH_2), 8.9–9.1 (t, terminal Me), signals at τ 8.6–9.2 integrated for 29 H.

4-Methyl-3-pentadecylcatechol (2a).—A sample of 5.5 g (0.01 mol) of **1b** was dissolved in 100 ml of ethyl acetate containing 2 drops of sulfuric acid, and the solution was hydrogenated in a Parr pressure reaction apparatus for 6 hr over 0.3 g of 10% palladium on carbon catalyst at an initial hydrogen pressure of 60.0 psi and at room temperature. The catalyst was then removed by filtration, and the solution was diluted with ether and washed with 10% sodium bicarbonate followed by water. The residual oil obtained after drying the solution and removal of solvent was recrystallized several times from ligroin to give 3.18 g (95%) of **2a**. This compound was identical in melting point (55.0–56.0°) and spectra (ir and nmr) with an authentic sample of 4-methyl-3-pentadecylcatechol.[3]

4,5-Dimethyl-3-pentadecylcatechol (2b).—An identical hydrogenolysis procedure was performed on 6.0 g (0.01 mol) of **1c**. The residual oil obtained after the work-up was recrystallized from hexane to yield 3.17 g (91%) of **2b**. This compound was identical in melting point and spectra (ir and nmr) with an authentic sample of 4,5-dimethyl-3-pentadecylcatechol.[2]

Registry No.—**1a**, 2792-00-9; **1b**, 39533-51-2; **1c**, 39533-52-3; **2a**, 16273-11-3; **2b**, 7771-22-4.

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(6) J. S. Byck, laboratory notes, Columbia University, 1967.
(7) Melting points were measured on a Thomas-Hoover apparatus and are corrected. The infrared spectra were recorded on a Perkin-Elmer Infracord Model 137. The nmr spectra were run on a Varian T-60 instrument and employing 20–50% solutions in CCl_4 with a drop of TMS as internal standard. Mass spectra were obtained using a Perkin-Elmer Hitachi RMU-6d instrument.

The Reaction of Trimethylsilyl Enol Ethers with Simmons–Smith Reagent. A Facile Synthesis of Trimethylsilyl Cyclopropyl Ethers and Cyclopropanols

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The reaction of trimethylsilyl enol ethers,[1] (**1**) with Simmons–Smith reagent[2] followed by cold, rapid work-up (method A) affords a mixture of trimethylsilyl cyclopropyl ethers (**2**) and cyclopropanols (**3**) enriched in **2**. Work-up at ambient conditions with no emphasis placed on rapid manipulation (method B) leads to a mixture of **2** and **3** enriched in **3**. The ether **2** upon treatment with aqueous acid gives **3** in good yield. These findings are outlined below in Scheme I, and representative yields are given in Table I.

Structural proof for the ethers **2** rests mainly on the spectral data of the compounds. Each ether **2** shows a characteristic nmr peak at *ca.* δ 0.05 representing the $Si(CH_3)_3$ moiety. The ir of **2** indicates that no OH grouping is present, and absorptions at 1250 and

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(2) (a) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959); (b) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).