steam bath for 3 hr, cooled, and filtered to give 112.4 g (83%) of **1**, mp 145–147°. Two recrystallizations (EtOH) gave an analytical sample: mp 148–149°; ir 1750 cm^{-1} (C=O); nmr (DMSO) δ 1.4 (t, 3, CH_3), 2.9 (m, 4 H), 4.35 (q, 2, OCH_2), 7.0–8.0 (m, 5 H).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.23. Found: C, 71.16; H, 5.34.

Ethyl 8-Methoxy-5,6-dihydro-2-oxo-2*H*-naphtho[1,2-*b*]pyran-3-carboxylate (2).—6-Methoxy-α-tetralone (470 g, 2.67 mol) was converted by the procedure described above to **2**, mp 141–143°. Recrystallization (DMF–H_2O) gave 550 g (68.5%) of analytically pure **2**: mp 150.5–152°; ir 1750 cm^{-1} (C=O); nmr (CF_3CO_2H) δ 0.9 (t, 3, CH_3), 2.2 (s, 4 H), 3.2 (s, 3, OCH_3), 4.0 (q, 2, OCH_2), 6.4–7.4 (m, 3 H), 8.0 (s, 1 H).

Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.76; H, 5.43.

2,3,4,4a,9,10-Hexahydro-2,4a-ethanophenanthrene-2-carboxylic Acid (7).—The pyran **1** (50 g, 0.185 mol) was allowed to react with ethylene at 3000 atm at 200° for 14 hr to give 47.3 g (91%) of **5**, mp 50–51°, ir 1730 cm^{-1} (C=O). A mixture of 7 g (24.8 mmol) of **5** an 125 ml of 2 *N* NaOH was heated at reflux for 12 hr, cooled, washed twice with Et_2O, and acidified with concentrated hydrochloric acid to give 5.77 g (92%) of **7**, mp 217–225°. One recrystallization (EtOH) gave an analytical sample: mp 227–228°; ir 1700 cm^{-1} (C=O); nmr (DMSO) δ 1.3 (m, 4 H), 2.0 (m, 4 H), 2.5 (m, 4 H), 6.2 (s, 1 H), 7.3 (m, 4 H).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.12. Found: C, 80.06; H, 6.86.

Ethyl 8-Methoxy-2,3,4,4a,9,10-hexahydro-2,4a-ethanophenanthrene-2-carboxylate (6).—Similarly, 82.5 g (0.275 mol) of the pyran **2** gave with ethylene 73 g (85%) of colorless crystals (EtOH) of **6**, mp 92–92.5°, ir 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.17; H, 7.81.

3,4,9,10-Tetrahydrophenanthrene-2-carboxylic Acid (4).—The pyran **1** (10 g, 37 mmol) was allowed to react with ethylene at 1000 atm at 200° for 14 hr to give 9 g (96%) of a reddish oil **3**, ir 1700 cm^{-1} (C=O). The oil was hydrolyzed with 2 *N* NaOH to give 6.55 g (74%) of **4**, mp 184–186°. One recrystallization (EtOH) gave an analytical sample: mp 188–189°; ir 1775 cm^{-1} (C=O); uv (EtOH) 353 nm (ε 19,600); nmr (DMSO) δ 2.5 (m, 8 H), 7.0 (s, 1 H), 7.2 (m, 4 H).

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.99; H, 6.25.

7-Methoxy-2,3,4,4a,9,10-hexahydro-2,4a-ethanophenanthrene-2-carboxylic Acid (8).—A mixture of 460 g (1.47 mol) of **6**, 80 g (2 mol) of NaOH, and 1000 ml of diethylene glycol was heated at 160° for 2 hr. The mixture was cooled, diluted with H_2O, and acidified with concentrated hydrochloric acid to give 410 g (99%) of **8**. One recrystallization (CH_3CN) gave an analytical sample, mp 213–216°, ir 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 76.03; H, 7.09. Found: C, 76.24; H, 7.07.

1,2,3,4,4a,9,10,10a-Octahydro-2,4a-ethanophenanthrene-2-carboxylic Acid (11).—The ester **5** (25 g, 88.7 mmol) was hydrogenated in EtOH with 5% Pt–C at 3 atm at room temperature. Filtration and concentration of the filtrate gave 24.15 g (96%) of **9**, mp 74–79°, ir 1730 cm^{-1} (C=O). Hydrolysis of **9** with 2 *N* NaOH gave 19.8 g (91%) of **11**, mp 205–207°. One recrystallization (EtOH) gave an analytical sample: mp 209–210.5°; λ 1700 cm^{-1}; nmr (DMSO) δ 1.8 (m, 13 H), 2.75 (t, 2 H), 7.15 (m, 4 H).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.62; H, 7.90.

Ethyl 7-Methoxy-1,2,3,4,4a,9,10,10a-octahydro-2,4a-ethanophenanthrene-2-carboxylate (10).—A mixture of 69.6 g (0.2 mol) of **6**, 200 ml of EtOAc, and 0.2 g of 10% Pd/C was hydrogenated at 50 psi and room temperature to give 70 g (100%) of **10**. One recrystallization (*i*-PrOH–H_2O) gave an analytical sample, mp 65.5–67.5°, ir 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.69; H, 8.40.

1,2,3,4,4a,9,10,10a-Octahydro-2,4a-ethanophenanthrene-2-amine Hydrochloride (12).—A solution of 6.0 g (23.4 mmol) of the acid **11** and 2.6 g (25.7 mmol) of Et_3N in 80 ml of Me_2CO was cooled to 0°. Maintaining this temperature, 2.8 g (25.8 mmol) of $ClCO_2Et$ was added, the reaction was stirred for 30 min, and then a solution of 3.1 g (47.7 mmol) of NaN_3 in 8 ml of H_2O was added. After the reaction mixture was stirred for an additional 30 min, it was poured onto ice and extracted with 4 × 50 ml of toluene. The combined extracts, after drying over $MgSO_4$, were gently heated until N_2 evolution ceased. Concentration under vacuum gave 5.75 g of the isocyanate, λ 2300 cm^{-1} (NCO). A solution of this isocyanate in 15 ml of methanol was stirred overnight and the solvent was removed under vacuum to yield the methyl carbamate, λ 1750 cm^{-1} (C=O). A solution of the carbamate in 100 ml of BuOH containing 11.2 g (0.2 mol) of KOH was heated at reflux overnight, then cooled and acidified with 4 *N* aqueous HCl. The acidic solution was concentrated under vacuum and the residue was twice recrystallized (H_2O) to give 1.8 g (29%) of **12**, λ 3300 cm^{-1} (NH_3), nmr (D_2O) δ 1.8 (m, 13 H), 2.75 (t, 2 H), 7.2 (m, 4 H).

Anal. Calcd for $C_{16}H_{21}N \cdot HCl \cdot {}^1/_2H_2O$: C, 70.18; H, 8.46; N, 5.12; Cl, 12.95. Found: C, 70.44; H, 8.46; N, 5.07; Cl, 12.94.

Registry No.—**1**, 23716-45-2; **2**, 32497-39-5; **4**, 39253-61-7; **5**, 23716-46-3; **6**, 32497-41-9; **7**, 23718-15-2; **8**, 32497-43-1; **9**, 23716-47-4; **10**, 32497-42-0; **11**, 23716-48-5; **12**, 23716-49-6; ethyl ethoxymethylenecyanoacetate, 94-05-3; α-tetralone, 529-34-0; 6-methoxy-α-tetralone, 1078-19-9.

A New Synthesis of α-Amino Acids[1]

KAZUO MATSUMOTO,* MAMORU SUZUKI, AND MUNEJI MIYOSHI

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co. Ltd., 962 Kashima-cho, Higashiyodogawa-ku, Osaka, Japan

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A number of methods for the practical chemical synthesis of α-amino acids exist,[2] among which the amination of carboxylic acids figures prominently. For example, amination of α-halogen acids[3] and unsaturated esters[4] and reductive amination of α-keto acids[5] is frequently employed. Recently, Inouye, *et al.*, reported the amination of sodiomalonate by chloramine[6] and Yamada, *et al.*, have described a similar amination of α-lithiated carboxylic acid salts by various aminating reagents.[7] However, the carboxylation of the α-carbon atom of amines has not been reported previously.

Within the framework of our studies on the synthesis of amino acids, we have studied the reaction of isocyano compounds with various electrophiles.[8–10] In the present paper, we wish to report a new synthesis of α-amino acids by α-carboxylation of isocyano compounds, which are easily prepared from the corresponding amines.[11]

(1) Synthesis of Amino Acids and Related Compounds. 4. Part 3: ref 10. The present study was presented at the 22nd Meeting of the Kinki Branch of the Pharmaceutical Society of Japan, Hyogo, Nov. 12, 1972.

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(9) M. Suzuki, T. Iwasaki, K. Matsumoto, and K. Okumura, *Syn. Commun.*, **2**, 237 (1972).

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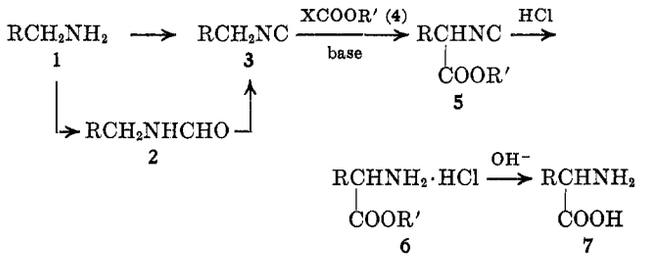
(11) After the work described in this note was completed, we became aware of a report by W. Vaalburg, J. Strating, M. G. Woldring, and H. Wynberg, *Syn. Commun.*, **2**, 423 (1972), who prepared α-phenylglycine by the same method.

The α-carboxylation of isocyano compounds was carried out according to the following scheme. The isocyano compounds (**3**) were prepared according to an improved Hofmann carbylamine reaction[12] or the Ugi reaction, which consists of the dehydration of N-monosubstituted formamides (**2**) using phosgene in the presence of tertiary amines.[13]



When the various isocyanides (**3**) reacted with diethyl carbonate in the presence of sodium hydride in dimethylformamide, ethoxycarbonylation proceeded easily at the α carbon of the isocyanides, and the corresponding ethyl α-isocyanoacetate derivatives (**5**, R′ = Et) were obtained in 59–63% yields as listed in Table I.[14–17] The ir spectra of these compounds

TABLE I
FORMATION OF α-AMINO ACIDS[a]

3	5 (R′ = Et) Ir, cm⁻¹	Nmr,[b]	Yield,	7[c]	Yield,[d]
R	NC, COOEt	δ	%	Mp, °C	%
Ph	2130, 1752	5.22	63	256 sub[e,f]	57
4-CH3OPh	2135, 1755	5.19	60	264–267 sub[g]	54
4-CH3Ph	2145, 1750	5.20	59	268–270 sub[h]	51
4-ClPh	2130, 1740	5.25	62	267–270 dec[i]	56
3,4-Methylenedioxy Ph	2140, 1750	5.16	63	227–229 sub[j]	60
2-Furyl	2130, 1745	5.31	61	209–211	55
H[k]	2150, 1755		35	235–237 dec[l]	32

[a] Reaction of isocyano compounds with diethyl carbonate in the presence of NaH. [b] Methine (s) in CCl_4. [c] Analyses agreed with the calculated values within ±0.3%. [d] Total yield from **3**. [e] sub: sublimation. [f] Lit.[14] reports sub without melting at 256°. [g] Lit.[15] mp 264–266° sub. [h] Lit.[15] mp 260–265° sub. [i] Lit.[15] mp 269–271° dec. [j] Lit.[16] mp 210°. [k] BuLi was used. [l] Lit.[17] mp 237° dec.

showed the characteristic absorption of the isonitrile group at 2130–2145 cm^{-1} and of the ester group at 1740–1755 cm^{-1}, respectively, and the nmr spectra showed one proton signal for the methine near δ 5.20. The isonitrile group of the ethyl α-isocyanoacetate derivatives was converted to the amino group by partial hydrolysis with dilute hydrochloric acid, giving the amino acid ester hydrochlorides (**6**, R′ = Et). Subsequently, the resulting compounds were hydrolyzed in sodium hydroxide solution and the corresponding free amino acids (**7**) were obtained by adjusting the pH to the isoelectric point with concentrated hydrochloric acid or by treatment with an ion exchange resin. The amino acids obtained were homogeneous by paper partition chromatography (PPC) and electrophoresis (EP) criteria and possessed the physicochemical properties of an authentic specimen.

We have also studied various carboxylating reagents other than diethyl carbonate, *e.g.*, dimethyl carbonate, carbon dioxide, ethyl chloroformate, and diethyl oxalate. In the case of dimethyl carbonate, the methoxycarbonylation proceeded in 70% yield under the same conditions as diethyl carbonate. Although the reaction with carbon dioxide or ethyl chloroformate did not proceed in the presence of sodium hydride, the use of *n*-butyllithium as a base promoted the carboxylation of benzyl isocyanide in 35–40% yield. However, the carboxylation with diethyl oxalate did not occur under the same conditions described above. These results are summarized in Table II. This procedure was extended to the alkyl isocyanide. Glycine was obtained from methyl isocyanide (Table I) but the expected product was not obtained from *n*-butyl isocyanide.

TABLE II
CARBOXYLATIONS WITH VARIOUS REAGENTS

$$PhCH_2NC + XCOOR \xrightarrow{base} PhCH(NC)COOR$$

X	R	Base	Reaction conditions			Yield, %
EtO	Et	NaH	DMF	b	1 hr	63
MeO	Me	NaH	DMF	b	1 hr	70
CO_2		BuLi	THF	−50°	1 hr	40[a]
Cl	Et	BuLi	THF	−50°	1 hr	35
COOEt	Et	BuLi	THF	−50°	1 hr	0

[a] Total yield of phenylglycine by hydrolysis. [b] Room temperature.

It appears that this synthetic method will be practically useful on a large scale when easily obtainable primary amines are used.

Experimental Section[18]

Materials.—Isocyanides (**3**) were prepared according to the method described by Weber, *et al.*,[12] or Ugi, *et al.*:[13] benzyl isocyanide, bp 92–93° (11 mm); 4-methoxybenzyl isocyanide, bp 114–115° (5 mm); *p*-xylyl isocyanide, bp 80–81° (3 mm); 4-chlorobenzyl isocyanide, bp 79–80° (5 mm); 3,4-methylenedioxybenzyl isocyanide, bp 120–121° (4 mm); 2-furylmethyl isocyanide, bp 85–87° (50 mm); methyl isocyanide, bp 25–30° (150 mm).

General Procedure of α-Carboxylations. A. Reaction of Isocyano Compounds with Diethyl Carbonate.—A mixture of 2.34 g (0.02 mol) of benzyl isocyanide and 2.36 g (0.02 mol) of diethyl carbonate in 10 ml of dimethylformamide was gradually added to a suspension of 0.84 g (0.022 mol) of sodium hydride (63% in oil) in 15 ml of dimethylformamide at 15° over a period of 15 min under stirring. After stirring was continued for 1 hr at room temperature, the reaction mixture was neutralized with acetic acid under cooling with an ice bath and the solvent was removed under reduced pressure below 50°. The residue was extracted with ethyl acetate, and the extract was washed with water and dried over magnesium sulfate. After the solvent was evaporated *in vacuo*, the product was purified by column chromatography on silica gel (80 g, Kieselgel 0.2–0.5 mm, E. Merck). After the paraffin included in sodium hydride was removed by elution with *n*-hexane, 2.38 g of ethyl α-isocyanophenylacetate was eluted with benzene (63% yield): ir (film) 2130 (NC), 1752 cm^{-1} (COOEt); nmr (CCl_4) δ 7.40 (s, 5, ArH), 5.22 (s, 1, CH), 4.18 (q, 2, CH_2), 1.23 (t, 3, CH_3).

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(18) Melting points and boiling points are uncorrected. Melting points were measured by the use of the Yamato melting point apparatus. Infrared spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. Nmr spectra were obtained using a Hitachi Perkin-Elmer R-20A high-resolution nmr spectrometer with tetramethylsilane as internal standard. The R_f value on PPC was recorded using Toyo filter paper No. 51.

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.

Acknowledgment.—We wish to express our thanks to Drs. T. Takayanagi and I. Chibata for their encouragement in this study.

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

DAVID I. LERNER AND CHARLES R. DAWSON*

Department of Chemistry, Columbia University, New York, New York 10027

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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

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