The mixture was cooled, diluted with 50 mL of ether, and filtered to give a yellow powdery solid.

The yellow orange filtrate was evaporated to dryness to give a solid mass. Thin-layer chromatography (silica gel plate) indicated triphenylphosphine was the predominant component. Several other components were present in trace quantities.

The yellow powdery solid isolated from the reaction was identified as iodo(fluoren-9-ylidenebenzyl)bis(triphenylphosphine)palladium(II): yield 981 mg (0.970 mmol, 97.2%); mp 204–206 °C; IR (KBr) 3050, 1570, 1481, 1435, 1085, 780, 740, 730, 690 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 6.36 (d, 1 H, J = 7.5 Hz, fluorenyl H_8), 6.48 (br d, 2 H, J = 7.5 Hz, fluorenyl H_2, H_7), 6.65 (ddd, 1 H J = 7.5, 7.5, 1.0 Hz, fluorenyl H_6), 6.84–7.67 (3 sets of multiplets, 38 H, fluorenyl H_3, H_4, H_5 and all phenyl H's), 9.83–9.87 (m, 1 H, fluorenyl H_1). Anal. for $C_{56}H_{43}IP_2Pd$: C, 66.52; H, 4.29; I, 12.55. Found: C, 66.39; H, 4.29; I, 12.67.

Reaction of Phenylacetylene with Iodo(fluoren-9-ylidenebenzyl)bis(triphenylphosphine)palladium(II). A mixture of 401 mg (0.397 mmol) of iodo(fluoren-9-ylidenebenzyl)bis(triphenylphosphine)palladium(II) and 55 mg (0.54 mmol) of phenylacetylene in 10 mL of deaerated, anhydrous triethylamine (Fluka reagent grade) was heated at 100 °C under nitrogen for 10 min. At this point, the yellow complex turned black.

The mixture was cooled, diluted with 50 mL of ether, and filtered. Unreacted starting yellow complex was isolated (214 mg; i.e., the reaction was ca. 50% over in 10 min).

The black filtrate was concentrated to give a brown mass. Thin-layer chromatography (silica gel plate) indicated the presence of bright yellow 3-(fluoren-9-ylidene)-1,3-diphenylpropyne. Column chromatography through silica gel, eluting with 1:4 dichloromethane–hexane (1 L), removed a bright yellow band. Evaporation of the eluate to dryness, followed by recrystallization of the solid from hexane, gave bright yellow crystals of 3-(fluoren-9-ylidene)-1,3-diphenylpropyne: yield 30 mg (0.085 mmol, 21%); mp 114–116 °C; IR and ^1H NMR spectra were superimposable on those of an authentic sample.

Reaction of Iodine with Iodo(fluoren-9-ylidenebenzyl)bis(triphenylphosphine)palladium(II). A solution of 204 mg (0.202 mmol) of iodo(fluoren-9-ylidenebenzyl)bis(triphenylphosphine)palladium(II) in 50 mL of anhydrous dichloromethane was treated with dropwise addition of a 0.134 N solution of iodine in dichloromethane (standardized against sodium thiosulfate). At the end point, the purple color of iodine persisted. The mixture was then diluted with an equal volume of hexane and filtered to remove the orange-yellow diiodobis(triphenylphosphine)palladium(II) complex: mp 263–264 °C.

The filtrate was concentrated. Thin-layer chromatography on a silica gel plate indicated the presence of one product. Column chromatography through silica gel, eluting with hexane, yielded analytically pure needles of (α-iodobenzylidene)fluorene: 11.5 mg (0.030 mmol, 15.0%), mp. 137–138 °C; IR (KBr) weak absorptions at 3050, 1610, 1572, and strong absorptions at 1444, 778, 726 cm^{-1}; GC/MS indicated 99+% purity and a molecular ion at m/e 380; 250-MHz ^1H NMR ($CDCl_3$) δ 6.09 (dd, 1 H, J = 8.2, 0.8 Hz, fluorenyl H_8), 6.81 (ddd, 1 H, J = 8.2, 8.2, 0.8 Hz, fluorenyl H_7), 7.21 (ddd, 1 H, J = 8.2, 7.5, 0.8 Hz, fluorenyl H_6), 7.63 (dd, 1 H, J = 7.5, 0.8 Hz, fluorenyl H_5), 7.71 (m, 1 H, fluorenyl H_4), 7.33–7.73 (complex m, 7 H, fluorenyl H_2, H_3 and phenyl H's), 9.04–9.08 (m, 1 H, fluorenyl H_1); ^{13}C NMR ($CDCl_3$) δ 147.84, 142.03, 141.06, 139.68, 138.82, 138.41, 129.73, 129.38, 128.96, 128.46, 127.86, 127.16, 126.67, 125.54, 125.04, 119.80, 119.19, 99.46. Anal. Calcd for $C_{20}H_{13}I$: C, 63.18; H, 3.45; I, 33.38. Found: C, 63.25; H, 3.34; I, 33.45.

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Registry No. **4a**, 52026-22-9; **4b**, 61837-21-6; **5**, 61837-22-7; **6a**, 87682-41-5; **7a**, 87682-42-6; **7a**-d_{10}, 87682-43-7; **8**, 87682-44-8; **9a**, 56150-56-2; **10**, 25837-46-1; **11**, 7142-76-9; **12**, 87682-45-9; **16**, 87682-40-4; **17**, 10271-61-1; **18**, 87682-46-0; PhC≡CH, 536-74-3; HC≡CSiMe$_3$, 1066-54-2; 1,2-dibromobenzene, 583-53-9; 2,2′-dibromobiphenyl, 13029-09-9; 2,2′-diiodobiphenyl, 2236-52-4; 2,2′-dibromo-3,5′-dinitrobiphenyl, 87682-47-1; copper(I) phenylacetylide, 13146-23-1; 9-bromophenanthrene, 573-17-1; 9-iodophenanthrene, 17024-12-3; (3-phenyl-1,2-propadienyl)triphenylphosphonium bromide, 64934-32-3; 9-fluorenone, 486-25-9; 9-(1-butylidene)fluorene, 29754-40-3; bromobenzene-d_5, 4165-57-5; (phenyl-d_5-ethynyl)trimethylsilane, 87682-48-2; 1,3-diphenylpropyn-3-one, 7338-94-5.

A Convenient Synthesis of (Acyloxy)alkyl α-Ethers of Phenols

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(Acyloxy)alkyl α-ethers (1) of phenols, thiophenol, and catechols have been prepared in good yield by their alkylation with (acyloxy)alkyl α-chlorides or iodides in acetone in the presence of K_2CO_3. In addition, one example of an (acylthio)alkyl α-ether was prepared. Either partial or complete acylation rather than alkylation on oxygen took place if the α-iodide was not used except for reactions of 3-chloro-1(3*H*)-isobenzofuranone with phenol or catechol or the reaction of (benzoylthio)methyl chloride with β-estradiol. It is suggested that more alkylation takes place with iodide as a leaving group because of the tighter transition state that develops with the better nucleofuge. The alkylation reaction sequence has two advantages for the synthesis of 1: (1) the mildness of the reaction conditions and (2) the wide variety of acyl and alkyl groups that can be incorporated into the product through the (acyloxy)alkyl α-halides.

Background

(Acyloxy)alkyl α-ethers of phenols (1) have been studied because of their similarity to proposed intermediates in enzymatic reactions[1] and because of their potential use as pesticides.[2,3] However, the fact that (acyloxy)alkyl de-

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[‡] University of Florida.
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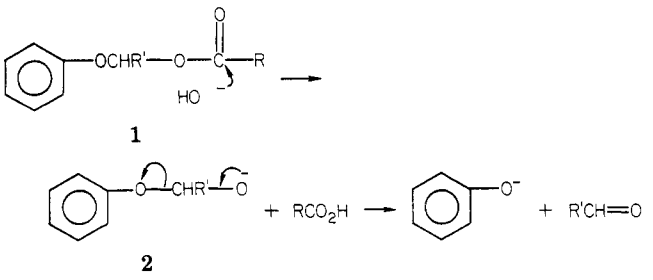
(1) Fife, T. H.; De, N. C. *J. Am. Chem. Soc.* **1974**, *96*, 6158.
(2) Tabbache, S.; Loubinoux, B. *Synthesis* **1982**, 665.
(3) Barber, H. J.; Fuller, R. F.; Green, M. B.; Zwartouw, H. T. *J. Appl. Chem.* **1953**, *3*, 266.

0022-3263/83/1948-5280$01.50/0

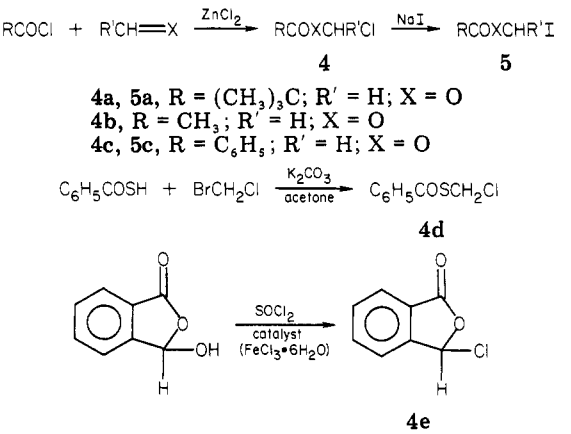
Scheme I



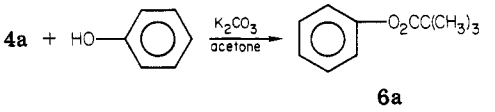
rivatives of phenols are alkyl ethers and yet are hydrolytically reversible (Scheme I) because of the inherent instability of the intermediate aldehyde–phenol adduct **2** (a hemiacetal) suggested that (acyloxy)alkyl groups might also be useful as protecting groups for phenols and catechols in complex syntheses. By analogy the (acyloxy)alkyl group has been employed for some time as an amino-protecting and as a substitution-steering group in heterocycle syntheses in situations similar to that envisaged for phenol where normal acyl derivatives were too labile and alkyl derivatives were not labile enough.[4] In addition, the (acyloxy)alkyl derivatives of phenols are potentially useful as prodrugs of phenols where the derivative transiently protects the phenols from premature glucuronidation and sulfation[5] and then hydrolyzes in a timely manner to release the biologically active phenol. Thus, (acyloxy)alkyl prodrug derivatives of carboxylic acids—(acyloxy)alkyl α-esters—have already proven quite useful for improving the biological availability of the parent carboxylic acid.[6,7] Therefore, the synthesis of (acyloxy)alkyl α-ethers of phenols and catechols was undertaken as a first step toward determining the synthetic and biological utility of **1**.

Although (acyloxy)alkyl α-esters are relatively easy to prepare from the corresponding acid salt and an (acyloxy)alkyl α-halide,[6,7] (acyloxy)alkyl α-ethers have been obtained only in low yields or by way of intermediates that are difficult to obtain. For example, the reaction of carboxylic acids with chloromethyl ethers of phenol (**3**) has recently been described[2] as a convenient synthesis of **1**. However, the available methods for preparation of chloromethyl ethers of phenol are quite limited. **3** can be obtained by rhodium-catalyzed ($(C_6H_5P)_3RhCl$) decarbonylation of phenoxyacetyl chlorides at 150–180 °C (above 200 °C without the catalyst)[8] or with $AlCl_3$ at 50 °C (but only with electron-withdrawing substituents on the phenoxy ring),[9] by a series of molten NaOH and PCl_5 reactions,[3] or by free-radical halogenation of a methyl ether (preferably with an electron-withdrawing Cl substituent in the 4-position).[10] None of these reaction sequences was considered to be amenable to complex molecules. Similarly, the other reported syntheses of **1** describe the use of a strong acid to catalyze the (acyloxy)alkylation of nitrophenol and thiophenol with 3-hydroxy-1(3*H*)-isobenzofuranone[1] and the decarboxylation of (aryloxy)acetic acid with lead(IV) acetate;[11] neither of these syntheses is generally applicable to selective reactions with sensitive substrates.

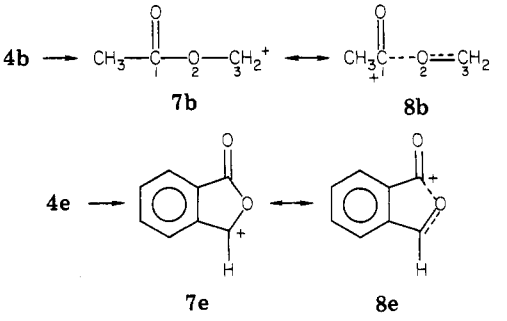
Scheme II



Scheme III



Scheme IV



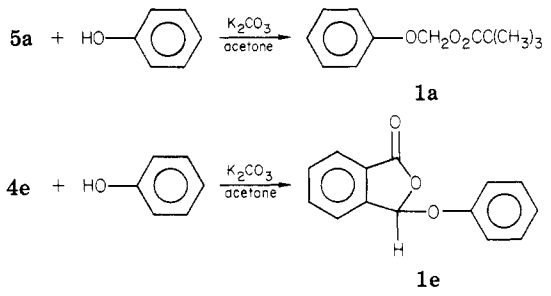
Results and Discussion

(Acyloxy)alkylation with (acyloxy)alkyl α-halides (**4**) appeared to offer an attractive alternative for the synthesis of a wide range of **1**. A large number of **4** can be prepared from the reaction of acyl halides with aldehydes alone or in the presence of $ZnCl_2$[12,13] (Scheme II for the synthesis of all **4**), and theoretically the alkylation of phenol with **4** can be carried out under mild conditions.[14] However, when **4a** was allowed to react with selected phenols and catechols of biological interest, acylated products (i.e., **6a**) instead of alkylated products (i.e., **1a**) were obtained as the major products (Scheme III).[15]

MINDO/3 SCF MO calculations[16] on the carbenium ions **7b** and **7e** generated from the ionization of representative acyclic and cyclic **4** (**4b** and **4e**) (Scheme IV) showed that significantly more positive charge was found to reside on the carbonyl atom (atom 1, **8b** and **8e**) than on the alkyl halide carbon atom (atom 3, **7b** and **7e**).[17] Thus, the MO calculations suggested that it was not surprising that an acylated (**6a**) rather than an alkylated (**1a**) product predominated from the reaction of **4a** with phenolate anion.

(4) Rasmussen, M.; Leonard, N. J. *J. Am. Chem. Soc.* **1967**, *89*, 5439.
(5) Rance, M. J.; Shillingford, J. S. *Xenobiotica* **1977**, *7*, 529.
(6) Bodor, N.; Zupan, J.; Selk, S. *Int. J. Pharm.* **1980**, *7*, 63.
(7) Deehne, W. V.; Frederiksen, E.; Gundersen, E.; Lund, F.; Morch, P.; Petersen, H. J.; Roholt, K.; Tybring, L.; Godtfredsen, W. O. *J. Med. Chem.* **1970**, *13*, 607.
(8) Benneche, T.; Undheim, K. *Acta Chem. Scand. B.* **1982**, *36*, 409.
(9) Palmer, M. H.; McVie, G. J. *Tetrahedron Lett.* **1966**, 6405.
(10) Gross, H.; Burger, W. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 221.
(11) McClelland, R. A., unpublished results.
(12) Adams, R.; Vollweiler, E. H. *J. Am. Chem. Soc.* **1918**, *40*, 1732.
(13) Bodor, N.; Kaminski, J. J. *J. Med. Chem.* **1980**, *23*, 566.
(14) McKillop, A.; Fiaud, J. C.; Hug, R. P. *Tetrahedron* **1974**, *30*, 1379.
(15) Zupan, J. U.S. Patent 4 275 219, June 23, 1981, and U.S. Patent 4 338 454, July 6, 1982.
(16) Bodor, N.; Pearlman, R. *J. Am. Chem. Soc.* **1978**, *100*, 4946.
(17) Bodor, N.; Kaminski, J. J., unpublished results.

Scheme V

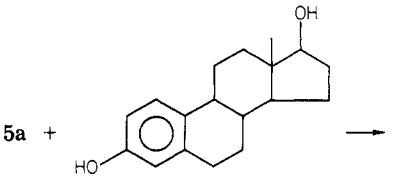


Although, the results of the MINDO/3 calculation and the product distribution results from the reaction of **4a** with phenols and catechols suggested that **1** could not be obtained by that route, the fact that compounds **1** are accessible by alternate routes and are stable, isolable entities was convincing evidence that conditions for the reaction in Scheme III had not been optimized and that **1** could still be obtained by a modification of Scheme III. Therefore, a systematic study of all the possible reaction variables was undertaken. Variations in the gegenion associated with the phenolate anion as well as in the polarity of the aprotic solvent used did not change the results. However, when the leaving group was changed to iodide—(**4a** → **5a**) a better leaving group—or the (acyloxy)methylene portion of the halide to an (acyloxy)benzyl α-halide (**4a** → **4e**), excellent yields of the desired **1a** or **1e**, respectively, were obtained (Scheme V). These results were unexpected because both changes tended more toward conditions favoring an S_N1 type reaction, which should have favored more rather than less contribution by (**7**↔**8**) to the transition state and ultimately should have led to more rather than less acylation according to most interpretations[18] of the effect of such changes.

A similar dichotomy in the predicted and observed results from the reactions of amines with **4** has been rationalized in terms of increased leaving-group ability and decreased nucleophilicity, leading to the formation of tighter S_N2 transition states.[19] A complete evaluation of the effect of leaving-group ability and nucleophilicity on the product distribution from the reaction of **4** with phenols and other oxygen nucleophiles has been presented elsewhere.[20]

The scope of the reaction of phenols and catechols with **4** or **5** to give **1** can be illustrated by the examples that follow. **5a** and **5c** were prepared from the chloride by using the Finkelstein reaction.[19] The subsequent reactions of **5a** with phenol,[21] β-estradiol (**9**),[21] and the protected catecholamines (**11**–**13**)[22] gave the corresponding ethers **1a**, **10**, **14**, **15**, and **16** (Scheme V and eq 1–6). The reactions of **5a** and **5c** with β-estradiol (**9**) to give **10** and **22** and **5a** with **12** and **13** to give **15** and **16** show that under carefully controlled conditions phenols can be alkylated in the presence of unprotected alcohols. Apparently, if the reaction is run under heterogeneous conditions in the presence of a relatively weak base such as K_2CO_3, only the more weakly nucleophilic phenolate anion is generated and reacts with iodide. On the other hand, amines must be protected during the preparation of (acyloxy)alkyl α-ethers.

The preparation of the deprotected catecholamine ethers **17**–**19** shows that it is possible to alkylate the N-protected catecholamines and then selectively cleave the *N-tert*-butoxycarbonyl group without cleaving the (pivalyloxy)methyl group. Thus, the (acyloxy)alkyl ether group can be introduced selectively and exhibits selective stability towards standard cleavage conditions.



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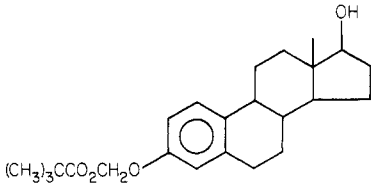

(1)

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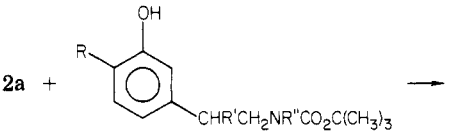
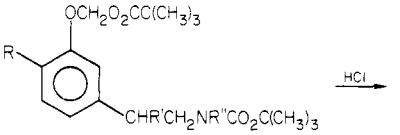
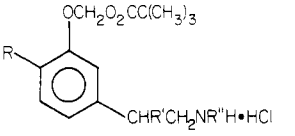


11, R = OH; R′ = H; R″ = H
12, R = OH; R′ = OH; R″ = CH_3
13, R = H; R′ = OH; R″ = CH_3

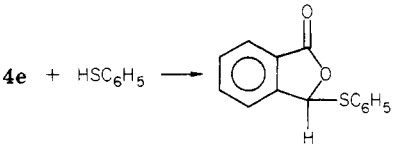


14, R = $OCH_2O_2CC(CH_3)_3$; R′ = H; R″ = H
15, R = $OCH_2O_2CC(CH_3)_3$; R′ = OH; R″ = CH_3
16, R = H; R′ = OH; R″ = CH_3



(2)

17, R = $OCH_2O_2CC(CH_3)_3$; R′ = H; R″ = H
18, R = $OCH_2O_2CC(CH_3)_3$; R′ = OH; R″ = CH_3
19, R = H; R′ = OH; R″ = CH_3



(3)

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The reactions of **4e** with phenol and catechol to give **1e** and **21** illustrate that R′ can be varied in the preparation of **1**, while the reaction of **4d** with estradiol to give **23** shows that, in addition to (acyloxy)alkyl ethers, (acylthio)alkyl ethers are also accessible by this general synthetic scheme. Furthermore, the reaction of **4e** with thiophenol to give **20** shows that thiophenols can be alkylated with **4** and can produce (acyloxy)alkyl α-thiophenols by an alternative route to the reaction of 3-hydroxy-1(3*H*)-isobenzofuranones with thiophenols in the presence of acid catalysts.

Although it was clear from the elemental composition of the products (**1a** and **6a**) from the reactions of acyclic **4** (**4a**) with phenols whether, in fact, acylated or alkylated products had been obtained, the course of the reaction of

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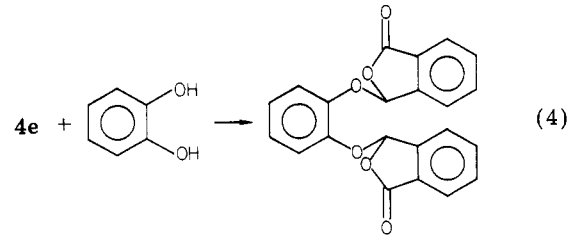

(4)

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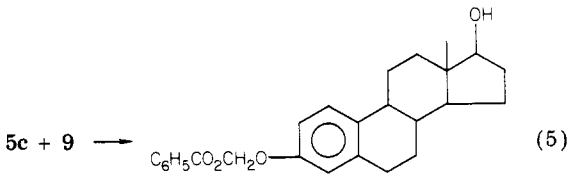

(5)

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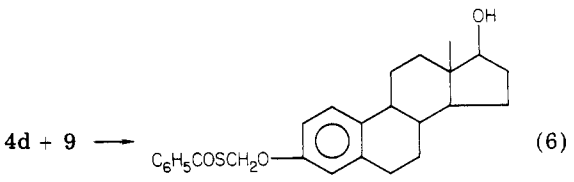

(6)

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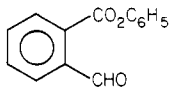
cyclic 4 (**4e**) with phenol and thiophenol was not clear from the elemental analysis of the products since the acylated (e.g., **1e'**) and alkylated (e.g., **1e**) products have identical



1e'

compositions. However, the products from the reaction of **4e** exhibit only one C=O absorption in their IR spectra, while the corresponding acylated products should exhibit two C=O absorptions in their spectra.[23-25] In addition, an acylated product should exhibit a CH=O absorption in its ^{1}H NMR spectrum, which should appear at about δ 10.1–10.6 on the basis of the reported chemical shifts of CH=O in analogous compounds.[19,26,27] No absorptions below δ 8.5 are observed in the NMR spectra of the crude reaction mixtures from which **1e** and **20** were isolated. Finally, the ^{13}C NMR spectra of **1a** and **1e** show only one carbon absorption due to a carbonyl carbon (atom 1) and one carbon absorption due to the atom-3 carbon.[28] Thus, it is clear that, in the case of the reaction of **4e** with phenol and thiophenol, the product is the alkylated product.

Experimental Section

^{1}H NMR spectra were recorded on a Varian 1-60 instrument and the ^{13}C NMR spectra on a Bruker WP-80 instrument. The IR spectra were obtained with a Beckman Acculab 4 spectrophotometer. Melting points (uncorrected) were determined on a Thomas-Hoover capillary apparatus. Microanalyses were performed by Atlantic Microlab, Inc. of Atlanta, GA, or by Midwest Microlab, Ltd., Indianapolis, IN. Unless otherwise specified the chemicals were obtained from Aldrich or Sigma except for the bulk solvents, which were obtained from Fisher. TLC analyses were run on Brinkman Polygram Sil G/UV 254. The anhydrous NaI and K_2CO_3 were stored in a vacuum desiccator until immediately before use, and the acetone was stored over 4A 8–12-mesh molecular sieves before it was used. The silica gel used for chromatography was Mallinckrodt SilicAR CC-7.

Reaction of (Pivalyloxy)methyl Iodide (5a) with Phenol.[21] (Pivalyloxy)methyl chloride (0.0068 mol, 1.02 g) was allowed to react with anhydrous NaI (1.02 g, 0.0068 mol) in 15 mL of dry acetone overnight in a tightly sealed flask. The suspension was then allowed to react with 0.94 g (0.0068 mol) of anhydrous K_2CO_3 and 0.64 g (0.0068 mol) of phenol overnight at room temperature. The suspension was diluted to 150 mL with ether and filtered. The filtrate was concentrated to give 1.15 g (82%) of **1a** as a colorless oil, which was identical with an analytical sample[21] by NMR spectroscopy: ^{1}H NMR ($CDCl_3$) δ 7.4–6.6 (m, 5, aromatic H), 5.73 (s, 2, OCH_2O_2C), 1.20 (s, 9, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$) δ 177.5 (C=O), 156.8 (aromatic CO), 128.8, 122.8, 115.8 (aromatic C), 86.0 (OCH_2O), 38.9 ($C(CH_3)_3$), 26.9 ($(CH_3)_3C$).

Reaction of Thallium Thiophenoxide with 3-Chloro-1-(3*H*)-isobenzofuranone (4e). Thallium thiophenoxide was prepared by allowing thallium ethoxide to react with thiophenol in hexane and filtering the resulting precipitate. Then, a DMF solution of 2.13 g (0.013 mol) of the chloride[19,29] was added to a cold (0 °C) DMF (75 mL) suspension of 3.13 g (0.01 mol) of the thallium salt. The mixture was warmed to room temperature and stirred overnight. The suspension was filtered and the DMF evaporated. The residue was redissolved in benzene and the benzene was washed with water (2 × 25 mL) and dried over Na_2SO_4. The benzene was evaporated and the residue recrystallized from CCl_4 to give 2.1 g [87% yield, mp 98–100 °C (lit.[30] mp 102–103 °C)] of 3-(phenylthio)-1(3*H*)-isobenzofuranone: TLC (silica gel, benzene) R_f 0.54; IR (KBr) 1740 (s, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.0–8.0 (m, 9, aromatic H), 6.73 (s, 1, OCHS). Anal. Calcd for $C_{14}H_{10}O_2S$: C, 69.40; H, 4.16; S, 13.24. Found: C, 69.25; H, 4.46; S, 13.34.

Reaction of Thallium Phenoxide with 3-Chloro-1(3*H*)-isobenzofuranone (4e). To a DMF solution of 1.68 g (0.01 mol) of **4e**[19,29] at 0 °C was added dropwise with stirring a suspension of 2.97 g (0.01 mol) of thallium phenoxide prepared as in the previous preparation of thallium thiophenoxide. After the addition was complete, the reaction mixture was allowed to warm to room temperature and to stir overnight. The suspension was filtered and the DMF evaporated. The residue was redissolved in benzene and the solution was washed with water and then dried over Na_2SO_4. The benzene was evaporated and the residue was crystallized from CCl_4 to give 1.9 g (85% yield, mp 117–120 °C) of 3-phenoxy-1(3*H*)-isobenzofuranone (**1e**): TLC (silica gel, benzene) R_f 0.53; IR (KBr) 1770 (s, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.0–7.45 (m, 4, aromatic H), 7.45–7.0 (m, 5, aromatic H), 6.8 (s, 1, OCHO); ^{13}C NMR ($CDCl_3$) δ 168.1 (C=O), 156.7 (aromatic CO), 144.6 (aromatic CCH(O)O), 99.8 (OCHO). Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.21; H, 4.51.

Preparation of (Benzoylthio)methyl Chloride (4d). To a well-stirred suspension of anhydrous K_2CO_3 (1.0 g, 0.0073 mol) in 150 mL of dry acetone were added bromochloromethane (1.87 g, 0.0145 mol) and thiobenzoic acid (1.0 g, 0.0073 mol). The suspension was stirred at room temperature under N_2 for 1 h, and then the acetone was evaporated in vacuo. The residue was extracted with ether, and the ether and residual bromochloromethane were evaporated to give the crude product, which was used as such: ^{1}H NMR (CCl_4) δ 7.9–7.3 (m, 5, aromatic H), 5.01 (s, 2, SCH_2Cl).

Preparation of (Pivalyloxy)methyl Iodide (5a). (Pivalyloxy)methyl chloride (10 g, 0.067 mol) and 12 g (0.08 mol) of anhydrous NaI were allowed to react in 75 mL of anhydrous acetone for 5 h at room temperature. The acetone was evaporated and ether was added to the residue. The suspension that resulted was filtered. The filtrate was washed with sodium thiosulfate and water and then dried over $MgSO_4$. The ether was evaporated and the residue was purified by column chromatography, using silica gel and 60% hexane–benzene as the eluent, to give a 60% yield of the desired product: ^{1}H NMR ($CDCl_3$) δ 5.91 (s, 2, ICH_2O_2), 1.2 (s, 9, $(CH_3)_3CCO_2$).

Reaction of 17β-Estradiol with (Acylhetero)alkyl α-Halides: Reaction with (Benzoyloxy)methyl Iodide. 17β-Estradiol (0.5 g, 0.0018 mol) was dissolved in 30 mL of dry acetone,

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and the solution was allowed to react at reflux for 24 h with anhydrous K_2CO_3 (0.5 g, 0.0037 mol) and 15 mL of a dry acetone solution of (benzoyloxy)methyl iodide formed from the reaction of (benzoyloxy)methyl chloride (0.29 g, 0.0019 mol) and 0.85 g (0.0057 mol) of anhydrous NaI for 30 min. The acetone was removed in vacuo. The residue was extracted with ether (200 mL) and filtered. The filtrate was dried over Na_2SO_4 and concentrated, and that residue was chromatographed on silica gel with 10% ethyl acetate–$CHCl_3$ to give a 67% yield of the desired 1,3,5(10)-estratriene-3,17β-diol 3-(benzoyloxy)methyl ether (**22**) as a yellow oil: IR (KBr) 1735 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 8.1–6.6 (m, 8, aromatic H) 5.89 (s, 2, OCH_2O_2), 0.79 (s, 3, CH_3). Anal. Calcd for $C_{26}H_{30}O_4$: C, 76.84; H, 7.39. Found: C, 77.10; H, 7.50.

Reaction with (Benzoylthio)methyl Chloride. The reaction of 17β-estradiol (5.0 g, 0.018 mol) in 300 mL of dry acetone with 7.6 g (0.055 mol) of anhydrous K_2CO_3 and (benzoylthio)methyl chloride (10.3 g, 0.055 mol) was allowed to proceed for 2 days under N_2 at room temperature. The mixture was processed as above with 25% ethyl acetate–hexane to give 1.3 g (mp 48–50 °C, 17% yield) of 1,3,5(10)-estratriene-3,17β-diol 3-(benzoylthio)methyl ether (**23**) as a foam: IR (KBr) 1720 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ 8.15–6.6 (m, 8, aromatic H), 5.85 (s, 2, SCH_2O), 0.85 (s, 3, CH_3). Anal. Calcd for $C_{26}H_{30}SO_3$: C, 73.96; H, 7.10; S, 7.59. Found: C, 73.96; H, 7.27; S, 7.67.

Preparation of 3,4-Bis[(pivalyloxy)methyl]dopamine Hydrochloride (17).[22] First the catecholamine was protected from reactions with the amine group using the *tert*-butylcarbonyl group. Dopamine hydrobromide (7.8 g, 0.033 mol) was dissolved in 25 mL of 70% aqueous triethylamine. The mixture was stirred in an ice bath under N_2, and a solution of 5 mL (0.050 mol) of *tert*-butoxy azidoformate[31] in 15 mL of dioxane was added. The mixture was stirred for 5 h at room temperature under N_2. The mixture was then evaporated. The residue was dissolved in 40 mL of 5% HCl solution, and the aqueous solution was immediately extracted with ether (2 × 200 mL). The ether layers were combined, washed with a saturated $NaHCO_3$ solution, and dried over $MgSO_4$. The ether was evaporated to give 8.0 g *N*-(*tert*-butoxycarbonyl)dopamine **11** as white crystals [mp 136–138 °C, 94% yield, from benzene (lit.[32] mp 137–138 °C)]. The amine protected dopamine (1.11 g, 0.0044 mol) was allowed to react with an excess of preformed iodomethyl pivalate (2.5 mL) in dry acetone (20 mL), using anhydrous K_2CO_3 (1.45 g, 0.01 mol) as an acid scavenger. The suspension was stirred at room temperature for 6 h and then the acetone was evaporated. The residue was suspended in $CHCl_3$ and filtered. The filtrate was dried over Na_2SO_4 and concentrated to give *N*-(*tert*-butoxycarbonyl)-3,4-bis[(pivalyloxy)methyl]dopamine (**14**) as white crystals: 1.9 g, 88% yield, mp 71–73 °C from hexane; ^1H NMR ($CDCl_3$) δ 6.89 (m, 3, aromatic H), 5.72 (s, 4, OCH_2O_2C), 4.15 (m, 1, NH), 3.35 (m, 2), 2.79 (m, 2), 1.42 (s, 9, $(CH_3)_3CO$), 1.18 (s, 18, $(CH_3)_3CCO_2$); IR (neat) 3410 (NH), 1760 and 1726 (C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{39}NO_8$: C, 62.35; H, 8.16; N, 2.91. Found: C, 62.60; H, 8.30; N, 2.69. The N-protected O-alkylated dopamine was deprotected by dissolving the protected dopamine (1.2 g, 0.0025 mol) in 20 mL of ethyl acetate. Anhydrous HCl was bubbled through the solution for 10 min at 0 °C and then the solution was evaporated to give a residue, which was crystallized from hexane–benzene to give 0.98 g (90% yield, mp 100–101 °C) of the desired product as needle crystals: ^1H NMR ($CDCl_3$) δ 8.40 (s, 3, $^+NH_3$), 7.00 (m, 3, aromatic H), 5.73 (s, 4, OCH_2O_2C), 3.13 (m, 4, aromatic $CH_2CH_2NH_3^+$), 1.18 (s, 18, $(CH_3)_3CCO_2$); IR (KBr) 3410 (NH), 1740 (C=O) cm^{-1}. Anal. Calcd for $C_{20}H_{32}ClNO_6$: C, 57.47; H, 7.73; N, 3.35. Found: C, 57.37; H, 7.85; N, 3.16.

The following compounds were prepared by the same general sequence. **3,4-Bis[(pivalyloxy)methyl]epinephrine Hydrochloride (18).**[22] Epinephrine was converted to its *N*-*tert*-butoxycarbonyl derivative **12**, which was then alkylated with preformed iodomethyl pivalate in dry acetone with anhydrous K_2CO_3 as the acid scavenger to give *N*-(*tert*-butoxycarbonyl)-3,4-bis-[(pivalyloxy)methyl]epinephrine (**15**) as a clear syrup after purification on a silica gel column, using 20% ethyl acetate–benzene as the eluent: ^1H NMR ($CDCl_3$) δ 7.0–7.1 (m, 3, aromatic H), 5.73 (s, 4, OCH_2O_2C), 4.85 (m, 1, CHOH), 3.40 (m, 2, CH_2N), 2.79 (s, 3, CH_3N), 1.46 (s, 9, $(CH_3)_3CO$), 1.18 (s, 18, $(CH_3)_3CCO_2$); IR (neat) 3430 (OH), 1750 and 1680 (C=O) cm^{-1}. Anal. Calcd for $C_{28}H_{41}NO_9$: C, 61.04; H, 8.08; N, 2.74. Found: C, 60.68; H, 8.07; N, 2.46.

The N-protected epinephrine derivative was deprotected as above to give the desired product as a clear syrup: ^1H NMR ($CDCl_3$) δ 7.15 (m, 3, aromatic H), 5.76 (s, 4, OCH_2O_2C), 5.30 (m, 1), 3.30 (m, 2, CH_2N), 2.86 (s, 3, CH_3N), 1.16 (s, 18, $(CH_3)_3CCO_2$); IR (neat) 3300 (OH), 1750 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{34}ClNO_7$: C, 56.30; H, 7.66; N, 3.12. Found: C, 56.08; H, 7.85; N, 2.88.

3-[(Pivalyloxy)methyl]phenylephrine Hydrochloride (19).[22] Phenylephrine was converted to its *N*-*tert*-butoxycarbonyl derivative **13**, which was then alkylated with preformed iodomethyl pivalate in dry acetone with anhydrous K_2CO_3 as the acid scavenger to give *N*-(*tert*-butoxycarbonyl)-3-[(pivalyloxy)-methyl]phenylephrine (**16**) as a clear syrup after chromatography on silica gel, using 20% ethyl acetate–benzene as the eluent: ^1H NMR ($CDCl_3$) δ 6.80–7.45 (m, 4, aromatic H), 5.75 (s, 2, OCH_2O_2C), 4.90 (m, 1, CHOH), 3.44 (m, 2, CH_2N), 2.81 (s, 3, CH_3N), 1.44 (s, 9, $(CH_3)_3CO$), 1.18 (s, 9, $(CH_3)_3CCO_2$): IR (neat) 3430 (OH), 1750 and 1675 (C=O) cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_6$: C, 62.97; H, 8.19; N, 3.67. Found: C, 63.00; H, 8.31; N, 3.41.

The N-protected phenylephrine derivative was deprotected as above to give the desired product: ^1H NMR ($CDCl_3$) δ 6.8–7.2 (m, 4, aromatic H), 5.69 (s, 2, OCH_2O_2C), 5.3 (m, 1, CHOH), 3.12 (m, 2, CH_2N), 2.77 (s, 3, CH_3N), 1.16 (s, 9, $(CH_3)_3CCO_2$); IR (neat) 3300 (OH), 1740 (C=O) cm^{-1}. Satisfactory elemental analyses could not be obtained.

Reaction of 3-Chloro-1(3*H*)-isobenzofuranone (4e) with Catechol. A dry acetone (15 mL) suspension of 0.70 (0.005 mol) of anhydrous K_2CO_3 containing 0.84 g (0.005 mol) of the chloride and 0.27 g (0.0025 mol) of catechol was allowed to react at room temperature for 48 h. The suspension was diluted with CH_2Cl_2 (100 mL) and filtered. The filtrate was concentrated to give 0.90 g (96% yield) of white solid. The crude product was crystallized from hot $CHCl_3$ layered with ether (10:10 mL) to give 0.60 g (mp 188–190 °C, 65% yield) of 1,2-bis(1-oxo-(3*H*)-isobenzofuran-3-yl)catechol (**21**): IR (KBr) 1785 (s, C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0–7.0 (m, 12, aromatic H), 6.81 and 6.71 (2 s, 1, OCHO); analytical sample, mp 189–191 °C; TLC (silica gel, ether) R_f 0.02. Anal. Calcd for $C_{22}H_{14}O_6$: C, 70.58; H, 3.77. Found: C, 70.42; H, 3.83.

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Registry No. **1a**, 82212-47-3; **1e**, 61133-42-4; **4a**, 18997-19-8; **4d**, 30216-81-0; **4e**, 6295-21-2; **5a**, 53064-79-2; **5c**, 13943-33-4; **9**, 50-28-2; **11**, 37034-31-4; **12**, 87697-27-6; **13**, 82212-44-0; **14**, 81653-62-5; **15**, 87697-28-7; **16**, 82212-45-1; **17**, 81653-63-6; **18**, 87697-29-8; **19**, 82212-46-2; **20**, 51287-54-8; **21**, 87116-23-2; **22**, 87697-30-1; **23**, 87697-31-2; phenol, 108-95-2; thallium thiophenoxide, 57340-80-4; thallium phenoxide, 25491-50-3; bromochloromethane, 74-97-5; thiobenzoic acid, 98-91-9; dopamine hydrobromide, 645-31-8; epinephrine, 51-43-4; phenylephrine, 59-42-7; catechol, 120-80-9.

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