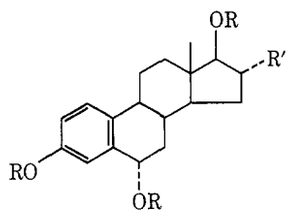
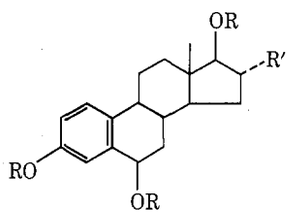


1a, R = H; R′ = OH
b, R = Ac; R′ = OAc
c, R = R′ = H
d, R = Ac; R′ = H



2a, R = H; R′ = OH
b, R = Ac; R′ = OAc
c, R = R′ = H
d, R = Ac; R′ = H

on the basis of this assignment. The ORD spectrum of **2c** was reported by Crabbé and Klyne in 1967.[5] This sample of **2c** was obtained from Wintersteiner, but no physical constants or other spectral data were given for the material.

In order to remove these uncertainties and to establish unambiguously the configurations of the 6-hydroxyestradiols, we obtained pure samples of **1c** and **2c** by the methods and criteria described for **1a** and **2a**.[2] The physical constants of these samples are in good agreement with those reported earlier,[7] and the pmr spectra of triacetates **1d** and **2d** (Table I) demonstrate that the higher melting and the lower melting triols are **1c** and **2c**, respectively, in accord with the original tentative assignments. The CD spectra of triols **1c** and **2c** (Table II) are strictly analogous to those of **1a** and **2a**. The observed consistency of the Cotton effects (both negative for **1a** and **1c**, both positive for **2a** and **2c**) suggests a reliable means of configurational identification of minute amounts of the 6-hydroxyestradiol and the 6-hydroxyestriol isolated as metabolites in rats[8] and humans.[9]

TABLE I

PMR DATA FOR 6-HYDROXYESTRADIOLS IN CHLOROFORM-*d*

Compd	δ, ppm[a] C-6 H	C-17 H[b]	C-3 CH_3CO[c]	C-6 CH_3CO[c]	C-17 CH_3CO[c]
6α-Hydroxyestradiol triacetate (1d)	6.08[d]	4.74	2.28	2.13	2.05
6β-Hydroxyestradiol triacetate (2d)	6.08[e]	4.74	2.28	2.05	2.05

[a] Chemical shift downfield from TMS. [b] Multiplet. [c] Singlet. [d] Triplet, spacing 8 Hz. [e] Doublet, spacing 3 Hz.

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Tlc systems (silica gel HF-254) were 9:1 C_6H_6–EtOAc (system 1) or 4:1 C_6H_6–MeOH (system 2). Pmr spectra were determined with a JEOL MH-100 spectrometer and uv spectra with a Cary Model 14 spectrophotometer. CD spectra were measured using a Cary Model 60 spectropolarimeter equipped with a CD Model 6001 accessory.

6-Oxoestradiol (4).—Estradiol diacetate (4.83 g, 13.6 mmol) was oxidized as described previously for estriol triacetate[2] using CrO_3 (4.08 g, 40.8 mmol) in glacial HOAc (42 ml) and H_2O (3.5 ml). The mixture of products (4.25 g) was combined with 4.77 g from a similar oxidation and chromatographed on 200 g of silica gel as described previously to give 1.13 g (10%) of crude 6-oxoestradiol diacetate (**3**), pure by tlc (R_f 0.6, system 1). A sample recrystallized from MeOH had mp 170–171° (lit.[10] mp 173–175°). A solution of **3** (1.13 g, 3.05 mmol) in 0.5 *N* 95% methanolic KOH (12 ml) was allowed to stand for 10 hr at room temperature and then was evaporated to near dryness. The residue was diluted with H_2O and acidified with 5% HCl, yielding **4** (0.77 g, 89%), pure by tlc (R_f 0.5, system 2). A sample recrystallized from MeOH had mp 267–268° (lit.[10] mp 281–283°).

6β-Hydroxyestradiol (2c).—A solution of **4** (100 mg, 0.349 mmol) in absolute EtOH (15 ml) was hydrogenated for 18 hr over Pt (from 45 mg of PtO_2). Tlc of the residue after filtration through Celite and evaporation of the filtrate to dryness revealed a major component (R_f 0.4, system 2) which was isolated by preparative tlc. This sample of **2c** (38 mg, homogeneous to tlc) would not crystallize but was converted to the readily crystalline triacetate **2d**: mp 173–176°; $[\alpha]^{25}D$ + 56° (*c* 1.05, absolute EtOH) [lit.[7] mp 176–178°; $[\alpha]^{24}D$ + 53° (*c* 0.860, $CHCl_3$)]. Alkaline hydrolysis (0.2 *N* 95% methanolic KOH) then yielded crystalline **2c**, which after recrystallization from MeOH melted at 125–135° followed by resolidification and melting at 195–200°, $[\alpha]^{25}D$ + 31° (*c* 0.64, absolute EtOH) [lit.[7] mp 126–134° followed by resolidification and melting at 191–195°, $[\alpha]^{25}D$ +29° (*c* 0.487, EtOH)].

6α-Hydroxyestradiol (1c), purchased from Steraloids, was homogeneous to tlc (R_f 0.4, system 2): mp 230–235°; $[\alpha]^{25}D$ +85° (*c* 1.09, absolute EtOH) [lit.[7] mp 233–246°, $[\alpha]^{23}D$ +78° (*c* 0.746, EtOH)]. Acetic anhydride–pyridine treatment gave the triacetate **1d**: mp 141–143°; $[\alpha]^{25}D$ +35° (*c* 1.05, absolute EtOH) [lit.[7] mp 143–144°, $[\alpha]^{23}D$ +40° (*c* 0.944, $CHCl_3$)].

TABLE II

SPECTRAL DATA FOR ESTRADIOL DERIVATIVES IN ABSOLUTE ETHANOL[a]

Compd	Uv max, λ, nm (ε)	CD max, λ, nm ([θ])
6α-Hydroxyestradiol (1c)	288[b] (2000)	289 (−1300)
	282 (2200)	283 (−1300)
	229[b] (5900)	230 (−3300)
	222 (7700)	
6β-Hydroxyestradiol (2c)	288[b] (1900)	288 (+500)
	282 (2100)	280 (+600)
	228[b] (5900)	228 (+20,000)
	221 (7400)	
6-Oxoestradiol diacetate (3)		366 (+850)
		352 (+4000)
		338 (+8300)
		326 (+10,000)
	298 (2100)	296 (−15,000)
	247 (10,000)	247 (−15,000)
6-Oxoestradiol (4)	327 (3000)	345 (+22,000)
		311 (−20,000)
	256 (8900)	252 (−10,000)
	222 (20,000)	223 (+26,000)

[a] *c* 0.0043–0.021 g/100 ml; *l* = 1 cm; temperature 25°. [b] Shoulder.

Registry No.—**1a**, 7291-49-8; **1c**, 1229-24-9; **1d**, 6626-42-2; **2a**, 36615-04-0; **2c**, 3583-03-7; **2d**, 6944-48-5; **3**, 3434-45-5; **4**, 571-92-6.

(8) G. C. Mueller and G. Rumney, *J. Amer. Chem. Soc.*, **79**, 1004 (1957).
(9) J. Breuer, F. Breuer, H. Breuer, and R. Knuppen, *Z. Physiol. Chem.*, **346**, 279 (1966).
(10) B. Longwell and O. Wintersteiner, *J. Biol. Chem.*, **133**, 219 (1940).

An Intramolecular Rearrangement Involving Neighboring Ether Oxygen

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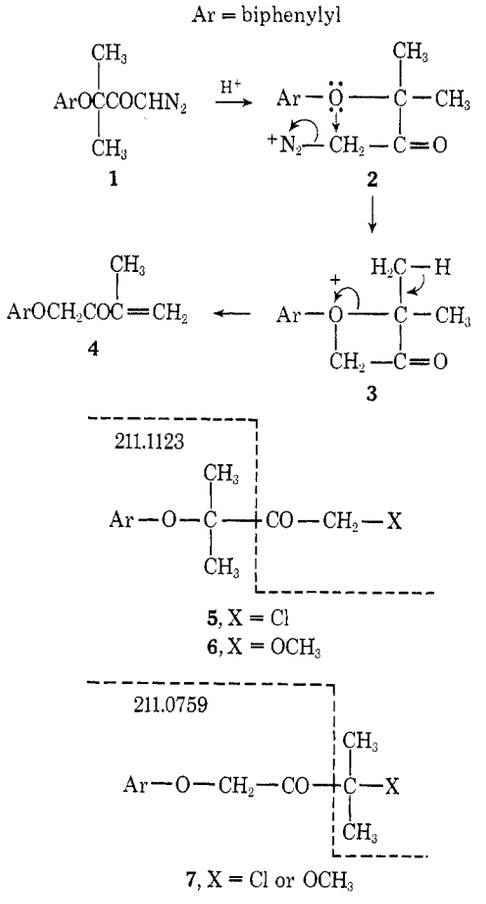
This paper describes a molecular rearrangement involving neighboring-group participation by an ether oxygen. While investigating carbenoid reactions from

copper-catalyzed decompositions of diazo ketones, we had occasion to prepare the diazo ketone **1**. In one preparation of **1**, the diazo ketone was contaminated (as deduced by subsequent events) by its precursor, 2-(4-biphenylyloxy)-2-methylpropionyl chloride. An attempt to recrystallize the crude diazo ketone from methanol resulted in its complete destruction and formation of four major products which were separated by chromatography. Three of the products were those to be expected, namely, methyl 2-(4-biphenylyloxy)-2-methylpropionate (from reaction of the above-mentioned acid chloride with methanol), the chloro ketone **5** (from reaction of the diazo ketone **1** with hydrogen chloride), and the methoxy ketone **6** (from acid-catalyzed reaction of the diazo ketone **1** with methanol).

Analytical and spectroscopic data indicate that the fourth product was 1-(4-biphenylyloxy)-3-methyl-3-buten-2-one (**4**). Hydrogenation of this substance afforded the expected dihydro compound, 1-(4-biphenylyloxy)-3-methyl-2-butanone, the identity of which was confirmed by analytical and spectroscopic means. The unsaturated ketone **4** was obtained in higher yield by subjecting the diazo ketone **1** to perchloric acid cat-



alyzed rearrangement under essentially aprotic conditions (tetrahydrofuran with a trace of water from the acid).

While no kinetic studies of this rearrangement have been undertaken, it is possible to construct a likely mechanistic course of reaction. Protonation of the diazo ketone can lead to intermediate **2** which, on loss of nitrogen and ring closure, would afford the oxonium ion **3**.[1-3] Loss of a proton and scission of the four-membered ring, as indicated in **3**, would lead to the observed product **4**. Ion **2** is the probable precursor of products **5** and **6**; however, it should be recognized that attack of chloride ion or methanol on the methylene carbon of **3** may account for a portion of these products.[4]

The possibility of chloride ion or methanol attacking the quaternary carbon of **3**, while less likely, could lead to products of type **7**, which would not be readily distinguishable (by nmr) from the actual products **5** and **6**. Low resolution mass spectra of the chloro ketone and methoxy ketone are reasonably consistent for structures of type **5** and **6**. However, compounds **5**, **6**, or **7** should all suffer significant fragmentation on electron impact to give ions of mass 211. In the case of the methoxy ketone (assumed to be representative), a high resolution mass spectrum ruled in favor of structure **6** when a single ion peak of nominal mass 211 was observed at 211.1116.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. The nmr spectra were obtained with a Varian A-60 spectrometer and significant signals are located in parts per million (δ) downfield from internal TMS. Low resolution mass spectra were obtained with an Atlas MAT CH4 spectrometer and the high resolution mass spectrum was obtained with a CEC 21-110 spectrometer; data are reported as m/e for M^+ and significant fragment ions.

Products from the Reaction of 2-(4-Biphenylyloxy)-2-methylpropionyl Chloride and 3-(4-Biphenylyloxy)-1-diazo-3-methyl-2-butanone (1) in Methanol.—A solution of 10 g of 2-(4-biphenylyloxy)-2-methylpropionyl chloride[5] in 100 ml of dry benzene was added to ethereal diazomethane prepared from 25 g of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. The mixture was stirred overnight at room temperature and then concentrated *in vacuo*. Attempted recrystallization of the crude diazo ketone residue from methanol[6] afforded 8 g of a mixture consisting of four major products as detected by thin layer chromatography on silica gel with 10% ethyl acetate in cyclohexane. The mixture was chromatographed in a column prepared by wet packing 1400 g of silica gel (E. Merck) with 10% ethyl acetate in cyclohexane. Elution of the column with 4 l. of the same solvent followed by 4 l. of 15% ethyl acetate in cyclohexane gave the following products.

A. 3-(4-Biphenylyloxy)-1-chloro-3-methyl-2-butanone (5).—Band 1 afforded 1 g of material which, on recrystallization from methanol, gave 0.41 g of **5**, mp 135–136°. The analytical sample of chloro ketone was crystallized from methanol and had mp 136–137°; nmr ($CDCl_3$) δ 4.63 (s, 2, $COCH_2Cl$), 1.53 [s, 6, $C(CH_3)_2$]; mass spectrum (70 eV) 288 and 290 (ratio 3:1, M^+), 211 $[C_6H_5C_6H_4O{=}C(CH_3)_2]^+$, and other ions at 170, 153, and 152.

Anal. Calcd for $C_{17}H_{17}ClO_2$: C, 70.70; H, 5.94. Found: C, 70.46; H, 6.06.

B. Methyl 2-(4-Biphenylyloxy)-2-methylpropionate.—Band 2 afforded 3 g of material, mp 83.5–85°, which is identical with an authentic sample of methyl 2-(4-biphenylyloxy)-2-methylpropionate prepared by treatment of 2-(4-biphenylyloxy)-2-methylpropionic acid with diazomethane and recrystallization of the product from ether–hexane: mp 84–85°; nmr ($CDCl_3$) δ 3.73 (s, 3, OCH_3), 1.62 [s, 6, $C(CH_3)_2$].

(1) Analogous ions are formed from MeO-4 participation in solvolysis reactions; see P. G. Gassman and J. L. Marshall, *Tetrahedron Lett.*, 2429 (1968).

(2) For a recent leading reference on stereochemical aspects of ether oxygen participation, see L. A. Paquette, I. R. Dunkin, J. P. Freeman, and P. C. Storm, *J. Amer. Chem. Soc.*, **94**, 8124 (1972).

(3) The carbonium ion character of acid-catalyzed reactions of diazo compounds has been reviewed: R. A. More O'Ferrall, *Advan. Phys. Org. Chem.*, **5**, 331 (1967).

(4) *Cf.* L. A. Paquette and R. W. Begland, *J. Amer. Chem. Soc.*, **87**, 3784 (1965), and references contained therein.

(5) Prepared from 2-(4-biphenylyloxy)-2-methylpropionic acid [A. Buttini, G. Carminati, P. Galimberti, V. Gerosa, and M. Melandri, *Boll. Chim. Farm.*, **101**, 354 (1962)] by the method of Merck and Co., Inc. Neth. Appl: 6,500,136 (Aug. 2, 1965); *Chem. Abstr.*, **64**, P3422*g* (1966).

(6) In later work, the diazo ketone was crystallized from acetonitrile and had mp 131° dec.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.60; H, 6.48.

C. 1-(4-Biphenylyloxy)-3-methyl-3-buten-2-one (4).—Band 3 afforded 1.8 g of material which, on recrystallization from methanol, gave 1.23 g of **4**, mp 79–82°. The analytical sample of **4** was crystallized from methanol and had mp 81–82.5°; nmr ($CDCl_3$) δ 6.77–7.60 (m, 9), 6.02 (m, 1, A portion of AMX_3 pattern for isopropenyl), 5.83 (m, 1 M portion of the AMX_3 pattern), 4.97 (s, 2, OCH_2CO), 1.90 (m, 3, X_3 portion of the AMX_3 pattern); mass spectrum (70 eV) 252 (M^+), 183 ($C_6H_5C_6H_4O{=}CH_2^+$), and other ions at 169, 153, 152, 83, and 69.

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.00; H, 6.54.

D. 3-(4-Biphenylyloxy)-1-methoxy-3-methyl-2-butanone (6).—Band 4 afforded 0.8 g of material which was recrystallized from methanol to give 0.25 g of **6**, mp 93–94°. The analytical sample of **6** was crystallized from methanol and had mp 94–95°; nmr ($CDCl_3$) δ 4.55 (s, 2, OCH_2CO), 3.42 (s, 3, OCH_3), 152 [s, 6, $C(CH_3)_2$]; mass spectrum (70 eV) 284 (M^+), 211 [$C_6H_5C_6H_4O{=}C(CH_3)_2^+$], and other ions at 170, 153, 152 and 45. High resolution peak matching at mass 211 for this product showed a single ion at m/e 211.1116 (calcd for $C_{15}H_{15}O$: 211.1123).

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.12; H, 7.18.

1-(4-Biphenylyloxy)-3-methyl-3-buten-2-one (4).—To a mixture of 20 g **1** and 300 ml of tetrahydrofuran at 0° was added a solution of 1 ml of 70% perchloric acid in 25 ml of tetrahydrofuran. The mixture was stirred at room temperature for 2 hr at which time 2 ml of pyridine was added and the mixture was concentrated *in vacuo*. An ethereal solution of the residue was washed with dilute acid, dilute base, and water and then dried. The crude product was chromatographed in a column prepared by wet packing 2 kg of silica gel (E. Merck) with 15% ethyl acetate in cyclohexane. Elution of the column with the same solvent and concentration of appropriate fractions (as determined by thin layer chromatography) gave material which, on recrystallization from methanol, yielded 8.4 g of product **4**, mp 80.5–82°, identical with this substance described above.

1-(4-Biphenylyloxy)-3-methyl-2-butanone.—A mixture of 100 mg of **4**, 50 ml of tetrahydrofuran, and 100 mg of 10% palladium on carbon was shaken in a Parr hydrogenation apparatus at an initial hydrogen pressure of 15 psi. After the hydrogen uptake ceased (1 hr), the catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue was crystallized from methanol and gave 72 mg of 1-(4-biphenylyloxy)-3-methyl-2-butanone: mp 62–63°; nmr ($CDCl_3$) δ 4.62 (s, 2, OCH_2CO), 2.93 (septuplet, 1, J = 7 Hz, A portion of AX_6 pattern for isopropyl), 1.13 (d, 6, J = 7 Hz, X_6 portion of the AX_6 pattern); mass spectrum (70 eV) 254 (M^+), 183 ($C_6H_5C_6H_4OCH_2^+$), and other ions at 153, 152, 71 and 43.

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.44; H, 6.91.

Acknowledgment.—Appreciation is expressed to our analytical section for elementary analyses and especially to L. Baczynskyj, M. F. Grostic, L. M. Humphrey, and R. J. Wnuk for mass spectral measurements and helpful discussions.

Registry No.—**1**, 41507-63-5; **4**, 41507-64-6; **5**, 41507-65-7; **6**, 41507-66-8; 2-(4-biphenylyloxy)-2-methylpropionyl chloride, 4878-10-8; diazomethane, 334-88-3; methyl 2-(4-biphenylyloxy)-2-methylpropionate, 41507-68-0; 1-(4-biphenylyloxy)-3-methyl-2-butanone, 41507-69-1.

Dehydrobromination by *N*-Phenylbenzamidine

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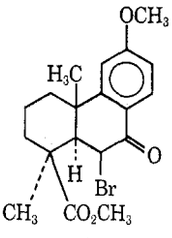
In connection with the synthesis of diterpenoid intermediates an improved yield of lactone **2** from bromo ketone **1** was required. The transformation of bromo ketone **1** to a mixture of lactone **2** (47% yield) and ester **3** (40% yield) by refluxing in collidine has been previously reported[2] along with the observation that treatment of bromo ketone **1** with sodium methoxide yields only elimination product **3**. The suggestion was offered that a major factor in the contrasting behavior of sodium methoxide and collidine might be the steric requirements of the bases for proton abstraction.[2] Thus we initiated an investigation into the improvement of the yield of lactone **2** by utilizing a variety of bases[3,4] that have greater steric requirements than collidine. As a result of this study, we now wish to report that the base *N*-phenylbenzamidine is useful for inducement of dehydrobromination.



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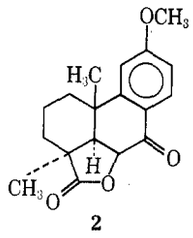

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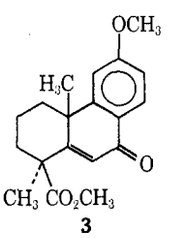
Reaction of bromo ketone **1** with 3.5 equiv of *N*-phenylbenzamidine in 25 equiv of *o*-xylene at reflux (148°) for 3 hr gave product **3** in 91% yield in the form of a white, crystalline solid, mp 175–177°. The infrared spectrum showed absorptions at 1725, 1645, 1600, and 1575 cm^{-1} for the ester, α,β-unsaturated ketone, and aromatic functional groups. The nmr spectrum exhibited resonance signals for singlets at δ 1.56 and 1.76 for the two tertiary methyl groups, singlets at δ 4.33 and 4.58 for the two methoxy groups, a singlet at δ 7.71 for the vinylic proton, a multiplet at δ 8.15 for the C-13 and C-14 protons, and a doublet (J = 8 Hz) at δ 9.58 for the C-11 proton. Neither lactone **2** nor decarbomethoxylation product **4** were found in the reaction mixture.



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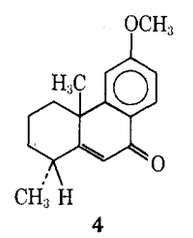

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The same reaction could be effected in approximately the same yield under milder conditions. Reaction of bromo ketone **1** with 3.5 equiv of *N*-phenylbenzamidine in 35 equiv of benzene at reflux (83°) for 48 hr gave product **3** in 90.5% yield.

Significantly, *N*-phenylbenzamidine gives much higher yields of **3** than the stronger base sodium methoxide[2] and without the concomitant *O*-alkyl cleavage

(1) National Defense Education Act Graduate Fellow, 1971–1973.

(2) E. Wenkert, *et al.*, *Can. J. Chem.*, **41**, 1924 (1963).
(3) D. H. Miles and E. J. Parish, *Tetrahedron Lett.*, 3987 (1972).
(4) E. J. Parish and D. H. Miles, *J. Org. Chem.*, **38**, 1223 (1973).