Table III. Conversion of Coal-Model Methoxyl Compounds in Tetralin at 400 °C

coal-model substrate	wt % in tetralin (amt, mg)	% reaction at 20 h	K_1, s^{-1} [a]
(*o*-methoxyphenyl)-phenylmethane	4.1 (12.3) [b]	90	3.7×10^{-5}
anisole	2.2 (6.7) [b]	29	4.7×10^{-6}
p-methylanisole	5.0 (15.0)	64	1.4×10^{-5}
2-benzyl-4-methylphenol	4.7 (14.1)	57	1.2×10^{-5}

[a] Defined first-order rate constant based on disappearance of starting material. [b] Equivalent molarity in tetralin.

In summary, the scission of strong C–C and C–O bonds in (hydroxyphenyl)phenylmethanes and hydroxyphenyl phenyl ethers during reaction in tetralin at 400 °C has been shown to occur via ionic tautomerization to the respective keto forms which can undergo homolytic scission at rapid rates. In the case of the (hydroxyphenyl)phenylmethanes, the tautomerization is rapid and constitutes a preequilibrium, but in the case of hydroxyphenyl phenyl ethers, the tautomerization is slower and constitutes the principal rate-controlling step. The sometimes beneficial effects of added phenols in coal conversion processes[1c] may be due in part to increased rates of tautomerization in diphenyl ether and diphenylmethane structures analogous to those studied in this work; the effects of added phenols may be further enhanced in coal conversions due to the inherent inhibition of bimolecular self-reactions by the coal matrix.

Acknowledgment. We acknowledge the support of the U.S. Department of Energy under Contract No. DE-AC22-79-ET14855 and Dr. Ronald H. Fleming of SRI International for many helpful discussions.

Registry No. *o*-HOPPM, 28994-41-4; *p*-HOPPM, 101-53-1; *m*-HOPPM, 22272-48-6; *p*-HOPPE, 831-82-3; *o*-MeOPPM, 883-90-9; anisole, 100-66-3; *p*-methylanisole, 104-93-8; 2-benzyl-4-methylphenol, 716-96-1; $PhCH_2Ph$, 101-81-5; PhOPh, 101-84-8; $PhCH_2CH_2Ph$, 103-29-7.

Notes

D-Homo Steroids from Oxidation of 17-Methylene Steroids by Thallium(III) Nitrate

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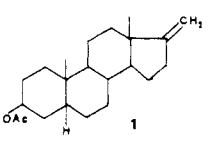
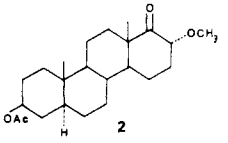
It is known that thallium(III) salts react with olefins and oxidative rearrangements generally occur. With thallium(III) nitrate, alicyclic olefins containing an endocyclic double bond undergo a ring contraction and ring-contracted aldehydes and ketones are obtained.[1] Thallium(III) perchlorate reacts with exocyclic olefins, causing a ring expansion, and the products of the oxidation are ring-enlarged ketones.[2] Recently, Ortar et al.,[3] in a study of the oxidation of a steroidal exocyclic olefin with (among other salts) thallium(III) acetate in methanol at 60 °C, obtained a ring-enlarged ketone.

This paper concerns the reaction of thallium(III) nitrate (TTN) with three 17-methylene steroids in a mixture of CH_3OH/trimethyl orthoformate (TMOF) at room temperature and the characterization of the oxidation products by means of analytical and spectroscopic data.

By treating 17-methylene-5α-androstan-3β-yl acetate (**1**)[4] with TTN[5] in CH_3OH/TMOF at room temperature, *D*-homo-17α-methoxy-17a-oxo-5α-androstan-3β-yl acetate (**2**) is obtained.



1



2

From the chemical analysis and molecular weight (376), deduced from its mass spectrum, compound **2** has molecular formula $C_{23}H_{36}O_4$. The IR spectrum exhibits an intense band at 1710 cm^{-1}, which can be ascribed to a six-membered cyclic ketone; this band does not disappear after hydrolysis of **2** with methanolic KOH.

Compared with the spectrum of **1** (same solvent), the ^1H NMR spectrum of **2** shows the downfield shift of a methyl signal, the presence of a methoxy group (singlet at δ 3.40), a deshielded ethereal proton (nearly four broad signals at δ 4.07), and the disappearance of the multiplet due to methylene protons (δ 4.48). Under the same experimental conditions as for **1**, TTN oxidized 17-methylene-5-androsten-3β-yl acetate (**3**)[4] and 17-methylene-1,3,5-estratrien-3-yl acetate (**5**),[6] giving *D*-homo-17α-methoxy-17a-oxo-5-androsten-3β-yl acetate (**4**)[7] and *D*-homo-17α-methoxy-17a-oxo-1,3,5-estratrien-3-yl acetate (**6**), respectively.[8]

The spectroscopic properties of **4** and **6** (see Experimental Section) are in good agreement with the assigned structures.

(1) A. McKillop, J. D. Hunt, E. C. Taylor, and F. Kienzle, *Tetrahedron Lett.*, 5275 (1970); A. McKillop, J. D. Hunt, F. Kienzle, E. Bigham, and E. C. Taylor, *J. Am. Chem. Soc.*, **95**, 3635 (1973).
(2) P. Abley, J. E. Byrd, and J. Halpern, *J. Am. Chem. Soc.*, **95**, 2591 (1973); D. Farcasiu and P. v. R. Schleyer, D. B. Ladlie, *J. Org. Chem.*, **38**, 3455 (1973).
(3) G. Ortar and I. Torrini, *Tetrahedron*, **33**, 859 (1977).
(4) G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.*, **98**, 604 (1965).
(5) Thallium(III) nitrate has been prepared according to A. McKillop, J. D. Hunt, F. Kienzle, E. Bigham, and E. C. Taylor, *J. Am. Chem. Soc.*, **95**, 3635 (1973).
(6) Compound **5** has been prepared from 3-hydroxy-1,3,5-estratrien-17-one according to the procedure described for other 17-ketones.[4] Physical and spectroscopic properties of **5** are described in the Experimental Section.
(7) The 5,6 double bond does not react appreciably under these conditions with TTN.
(8) The reactions of **1**, **3**, and **5** with TTN give rise to complex mixtures that contain, respectively, **2**, **4**, and **6** as major products and many other unidentified products.

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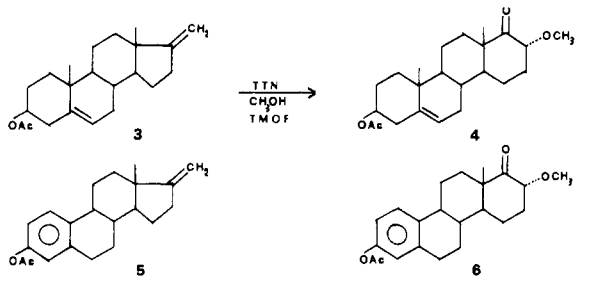


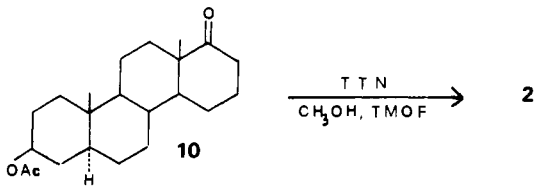
Hydrolysis of **2**, **4**, and **6** with methanolic KOH afforded the corresponding 3-hydroxy derivatives, *D*-homo-17α-methoxy-17a-oxo-5α-androstan-3β-ol (**7**), *D*-homo-17α-methoxy-17a-oxo-5-androsten-3β-ol (**8**), and *D*-homo-17α-methoxy-17a-oxo-1,3,5-estratrien-3-ol (**9**), with spectroscopic properties in agreement with expectation (see Experimental Section).

All the data suggest that the oxidation products of the three 17-methylene steroids examined are ring-enlarged ketones.

A two-step mechanism is shown in Scheme I to account for the oxidation of **1**, **3**, and **5** with TTN.

In the first step, the ring enlargement affords the 17a-ketone "i", which, in a second step, undergoes an enolization followed by the oxythallation of the newly formed C=C bond; methanolysis of the C—Tl bond then gives 17α-methoxy 17a-ketone "ii".

As support for the proposed mechanism, *D*-homo-17a-oxo-5α-androstan-3β-yl acetate (**10**)[9] was oxidized with TTN under the same conditions as for **1**. A crystalline compound identical in all respects (melting point, IR, ^{1}H NMR) with **2** was obtained.[10]



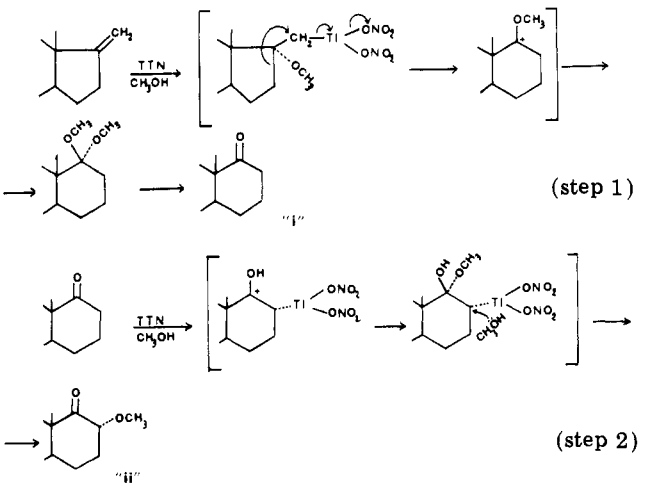
The α configuration (equatorial) is assigned to the methoxy group in **2** since its rotatory dispersion curve exhibits no Cotton effect and is similar to that of the unsubstituted *D*-homo 17a-ketone (**10**). This result is in agreement with prediction based on the octant rule and with the rotatory dispersion curve of *D*-homo-17α-methyl-17a-oxo-5α-androstan-3β-yl acetate.[11] The same C_{17} configuration is assigned to **4** and **6** since they have spectroscopic properties very similar to those of **2**.

Experimental Section

Melting points were determined with a Kofler microscope and are uncorrected. Infrared spectra were recorded in $CHCl_3$ on a Perkin-Elmer 257 Infracord spectrophotometer. ^{1}H NMR spectra were obtained on a Perkin-Elmer R-32 (90 MHz) or JEOL C-60 MHz spectrometer, using $CDCl_3$ solvent (unless otherwise stated) and Me_4Si as an internal standard; chemical shifts are reported in parts per million (δ) downfield from Me_4Si. Mass spectra were recorded on an AEI MS-12 spectrometer at 70 eV. Optical rotations were determined in $CHCl_3$ (unless otherwise stated) at room temperature, using a Perkin-Elmer 141 polarimeter with concentrations specified. Rotatory dispersion curves were measured in CH_3OH on a Cary 60 spectropolarimeter.

Yields evaluated from starting material correspond to the pure isolated product.

Scheme I



General Procedure for Oxidation of 17-Methylene Derivatives 1, 3, and 5 with Thallium(III) Nitrate (TTN). A solution of TTN (3.6 mmol) in a mixture of dry CH_3OH and trimethyl orthoformate (1:1; 5–6 mL) was added in small portions, at room temperature, to a magnetically stirred solution of the 17-methylene derivative (1.2 mmol) in a mixture of dry CH_3OH and trimethyl orthoformate (1:1; 8 mL).

The total reaction time was ~2 h; thallium(I) nitrate precipitated during the reaction.

The mixture was diluted with water and extracted several times with ether; the ether layers were washed to neutrality with saturated aqueous $NaHCO_3$ and water. After drying (Na_2SO_4) and solvent evaporation, the residue was chromatographed on silica gel (Merck, 70–230 mesh ASTM).

By use of mixtures of benzene–ether as eluent, **2**, **4**, and **6** were isolated from their corresponding reaction mixtures, containing other unidentified products.

The product **2** (yield 30%), after crystallization from benzene–petroleum ether (40–70 °C), had the following: mp 160–162 °C; $[\alpha]_D$ +15.7° (*c* 1.0); IR ν_{max} 1710 (C=O) cm^{-1}; ^{1}H NMR 0.80 (3 H, s, C_{10}-CH_3), 1.10 (3 H, s, C_{13}-CH_3), 2.00 (3 H, s, CH_3C=O), 3.40 (3 H, s, OCH_3), 4.07 (1 H, nearly four broad signals, $J \simeq 12$, 7.5 Hz, $CHOCH_3$), 4.55 (1 H, br signal, CHOAc); mass spectrum, *m/e* 376 (M^+, base), 348, 346, 316, 215. Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.12; H, 9.63.

The product **4** (yield 40%), after crystallization from benzene–petroleum ether (40–70 °C), had the following: mp 200–205 °C dec; $[\alpha]_D$ −69.7° (*c* 1.9); IR ν_{max} 1710 (C=O) cm^{-1}; ^{1}H NMR 1.03 (3 H, s, C_{10}-CH_3), 1.13 (3 H, s, C_{13}-CH_3), 2.01 (3 H, s, CH_3C=O), 3.42 (3 H, s, OCH_3), 4.13 (1 H, br signal, $CHOCH_3$), 4.60 (1 H, br signal, CHOAc), 5.38 (1 H, br signal, CH=); mass spectrum, *m/e* 314 (M^+ − 60, base), 299, 282. Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.37; H, 9.14.

The product **6** (yield 50%), after crystallization from benzene–petroleum ether (40–70 °C), had the following: mp 186–189 °C; $[\alpha]_D$ +80.7° (*c* 1.3); IR ν_{max} 1720 (C=O), 1750 ($OCOCH_3$) cm^{-1}; ^{1}H NMR 1.14 (3 H, s, C_{13}-CH_3), 2.26 (3 H, s, CH_3C=O), 3.40 (3 H, s, OCH_3), 4.15 (1 H, nearly four broad signals, $J \simeq 12$, 7.5 Hz, $CHOCH_3$), 6.88 (2 H, 2 br signals) and 7.31 (1 H, 2 br signals) (aromatic protons); mass spectrum, *m/e* 356 (M^+), 314 (base), 279. Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.75; H, 7.80.

Hydrolysis of 2, 4, and 6. **2** (**4** or **6**) (0.18 mmol) was dissolved, by gentle warming, in a methanolic solution (1.5 mL) of KOH (5–7% w/v) and allowed to stand at room temperature for 4 h. The mixture, worked up in the usual way, gave a residue from which **7** (**8** or **9**) was isolated by chromatography on silica gel, using benzene–ethyl acetate as eluent.

After crystallization from benzene–petroleum ether (40–70 °C), the product **7** had the following: mp 149–152 °C; $[\alpha]_D$ +30.4° (*c* 1.2); IR ν_{max} 3580, 3410 (OH), 1710 (C=O) cm^{-1}; ^{1}H NMR 0.79 (3 H, s, C_{10}-CH_3), 1.09 (3 H, s, C_{13}-CH_3), 3.40 (3 H, s, OCH_3), 3.45 (1 H, br signal, CHOH), 4.07 (1 H, br signal, $CHOCH_3$); mass spectrum, *m/e* 334 (M^+, base), 306, 304, 274, 233, 217, 215. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.60; H, 10.30.

(9) C. R. Engel and L. Ruest, *Can. J. Chem.*, **48**, 3136 (1970).
(10) The reaction mixture of **1** with TTN does not contain *D*-homo-17a-oxo-5α-androstan-3β-yl acetate (**10**).
(11) D. K. Fukshima, S. Dobriner, and R. S. Rosenfeld, *J. Org. Chem.*, **26**, 5025 (1961).

After crystallization from benzene–petroleum ether (40–70 °C), the product **8** had the following: mp 132–138 °C dec; $[\alpha]_D$ −69.9° (*c* 1.0); IR ν_{max} 3600, 3420 (OH), 1720 (C=O) cm^{-1}; ^1H NMR 1.00 (3 H, s, C_{10}-CH_3), 1.12 (3 H, s, C_{13}-CH_3), 3.42 (3 H, s, OCH_3), 3.60 (1 H, br signal, CHOH), 4.15 (1 H, nearly four broad signals, $J \simeq 12$, 8 Hz, $CHOCH_3$), 5.35 (1 H, br signal, CH=); mass spectrum, *m/e* 332 (M^+, base), 271, 239, 201. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.70; H, 9.85.

After crystallization from CH_3OH, the product **9** had the following: mp 207–215 °C dec; $[\alpha]_D$ + 103.1° (*c* 0.8, dioxane); IR ν_{max} 3600, 3300 (OH), 1720 (C=O) cm^{-1}; ^1H NMR (dioxane-d_8, sparingly soluble) 1.10 (3 H, s, C_{13}-CH_3), 3.30 (3 H, s, OCH_3), 4.05 (1 H, br signal, $CHOCH_3$), 6.45 (2 H, 2 br signals) and 7.08 (1 H, 2 br signals) (aromatic protons); mass spectrum, *m/e* 314 (M^+, base), 213, 160. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.35; H, 8.50.

Preparation of 17-Methylene-1,3,5-estratrien-3-yl Acetate (5) and Its 3-Hydroxy Derivative. Compound **5** was prepared from 3-hydroxy-1,3,5-estratrien-17-one according to the procedure described for other 17-ketones,[4] yield 80%.

After crystallization from CH_3OH, the product **5** had the following: mp 80–82 °C; $[\alpha]_D$ +51.8° (*c* 1.5); IR ν_{max} 1760 (OC-OCH_3), 880 (C=CH_2) cm^{-1}; ^1H NMR 0.82 (3 H, s, C_{13}-CH_3), 2.22 (3 H, s, CH_3C=O), 4.69 (2 H, br signal, C=CH_2), 6.84 (2 H, 2 br signals) and 7.29 (1 H, 2 br signals) (aromatic protons); mass spectrum, *m/e* 310 (M^+), 268 (base), 269, 160, 133. Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.50; H, 8.64.

The 3-hydroxy derivative of **5** (17-methylene-1,3,5-estratrien-3-ol) was obtained by treating **5** with methanolic KOH (5–7% w/v) solution, following the same procedure used for the hydrolysis of **2**, **4**, and **6**. The product was then crystallized from benzene–petroleum ether (40–70 °C) and had the following: mp 134–137 °C; $[\alpha]_D$ 49.9° (*c* 0.7); IR ν_{max} 3490, 3310 (OH), 8.75 (C=CH_2) cm^{-1}; ^1H NMR 0.84 (3 H, s, C_{13}-CH_3), 4.70 and 4.95 (2 H, 2 br signals, C=CH_2), 6.63 (2 H, 2 br signals) and 7.17 (1 H, 2 br signals) (aromatic protons); mass spectrum, *m/e* 260 (M^+, base), 160, 133. Anal. Calcd for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 84.80; H, 9.01.

Registry No. **1**, 1164-94-9; **2**, 77257-04-6; **3**, 853-22-5; **4**, 77257-05-7; **5**, 77257-06-8; **6**, 77257-07-9; **7**, 77257-08-0; **8**, 77257-09-1; **9**, 77257-10-4; 3-hydroxy-1,3,5-estratrien-17-one, 53-16-7; 17-methylene-1,3,5-estratrien-3-ol, 34111-53-0; TTN, 13746-98-0.

Analysis of Kinetic Isotope Effects on Complex Reactions Utilizing the Concept of the Virtual Transition State

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Kinetic isotope effects are observed when reaction rates are compared for molecules differing only in isotopic composition and originate from the different sensitivities of the reactant and transition state vibrational force fields to the isotopic substitution.[1,2] Interpretation of an observed isotope effect ultimately results in the assignment of structures, having vibrational modes of the appropriate isotopic sensitivity, to the transition state and reactant. Problems in interpretation may arise for reactions having more than a single transition state. Reactions having several transition states, "complex" reactions, are those which proceed through at least one intermediate and/or by way of at least two pathways. For such reactions in which more than a single transition state is kinetically significant, any experiment designed to probe the structure of the rate-limiting transition state will yield information not about a single, real transition state, but rather about a "virtual" transition state whose structure is a weighted average of structures of the several rate-determining, real transition states.[3] Here the problem becomes one of dissecting structures of real transition states out of the composite structure experimentally accessible. If the experimental probe of transition-state structure is the kinetic isotope effect, then this problem can, in principle, be solved by first determining the rate constants for all terms of the rate law for both isotopically labeled substrates and then dividing corresponding rate constants to produce isotope effects on the inidividual reaction steps. Such a procedure is, in fact, of limited applicability. Very high precision in the determination of reaction rates is required for the exact determination of individual rate constants and will be quite difficult to achieve for most complex reactions of interest. Even if precise data can be obtained, fitting of the data to a rate law by curve-fitting procedures to get rate constants for all terms of the rate law may prove mathematically or computationally impossible.[4] Under certain circumstances, however, a procedure not requiring the precise determination of the individual terms of a rate law is available for the quantitative analysis of kinetic isotope effect data.

We begin with the idea that the observed kinetic isotope effect on a complex reaction can be expressed as a weighted average of isotope effects on the individual reaction steps (k_m/k_m^*). The weighting factors (C_m) are the contribu-

$$k_0/k_0^* = C_1(k_1/k_1^*) + C_2(k_2/k_2^*) + ...C_m(k_m/k_m^*) \quad (1)$$

tions from the transition state of each step to determining the structure of the virtual transition state. Note that the rate constant, k_m, for the *m*th step reflects the free-energy difference between the ground state and the *m*th transition state, TS-*m*; that is, k_m is equal to the product of equilibrium constants for all steps leading to TS-*m* multiplied by the rate constant for reaction over TS-*m*.[5]

The weighting factors, C_m, can be calculated in a straightforward way. For a reaction having consecutive transition states, it can be shown that

$$C_m = (e^{\Delta G_m\dagger/RT}/e^{\Delta G\dagger_0/RT}) \quad (2)$$

or

$$C_m = k_0/k_m \quad (3)$$

where the apparent activation energy ($\Delta G_0^\dagger$) is the free-energy difference between the reactants and the virtual transition state. Similarly, for a reaction proceeding through competitive, parallel pathways

$$C_m = (e^{-\Delta G_m\dagger/RT}/e^{-\Delta G_0\dagger/RT}) \quad (4)$$

or

$$C_m = k_m/k_0 \quad (5)$$

Note that in this case the *lowest* free-energy transition

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(1) Collins, C. J., Bowman, N. S., Eds. "Isotope Effects in Chemical Reactions"; Van Nostrand-Reinhold: Princeton, NJ, 1970.
(2) Melander, L.; Saunders, W. H. "Reaction Rates of Isotopic Molecules"; John Wiley and Sons: New York, 1980.
(3) Schowen, R. L. In "Transition States of Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978.
(4) Kreshner, L. D.; Schowen, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 2014.
(5) This treatment, as derived here, applies only to those reactions having intermediates of insignificant lifetime. Similar, but more complex, equations can be derived which apply to reactions having intermediates of appreciable lifetime.

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