pyranyl) ether (VI, 888 mg., 90%) as a viscous oil which resisted crystallization. The infrared spectrum showed no hydroxyl absorption, but exhibited absorption bands at 1735 cm.$^{-1}$ (acetate carbonyl), 1665 cm.$^{-1}$ (conjugated carbonyl), 1612 cm.$^{-1}$ (C=C stretching vibration) and 1225 cm.$^{-1}$ (C—O stretching vibration of the acetate group).

19-Hydroxy-4-androsten-3-one-17β-(2′-tetrahydropyranyl) Ether (VII).—To a solution of VI (875 mg.) in methanol (178 ml.), a solution of 75% methanolic 0.1 *N* potassium carbonate (670 ml.) was added and the contents were left under nitrogen for 20 hr. at room temperature. Most of the methanol was evaporated under reduced pressure at 40° and the contents were diluted with water (1500 ml.) and cooled in an ice box. The 19-hydroxy-4-androsten-3-one-17β-(2′-tetrahydropyranyl) ether (VII, 739 mg., 93%) which precipitated was filtered and crystallized from ethyl acetate to give the analytical product, m.p. 195–201°, $[\alpha]_D$ +140° (*c* 0.97), λ_{max} 243 mμ (ε 15,757); ν_{max} 3430, 1655, and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 74.19; H, 9.34. Found: C, 73.91; H, 9.45.

3,19-Dioxo-4-androstene-17β-(2′-tetrahydropyranyl) Ether (VIII).—To a cold solution (10–15°) of VII (693 mg.) in acetone (50 ml.) under nitrogen atmosphere, 8 *N* chromic acid was added dropwise until a reddish brown color persisted. After an additional 2 min. stirring, the mixture was diluted with water (500 ml.) and extracted with ethyl acetate. The extract was washed with brine, sodium bicarbonate solution, and with water until neutral, and dried over anhydrous sodium sulfate. The solvent was removed and the residue (608 mg.) was chromatographed on alumina (18 g.). Elution of the chromatographic column with benzene gave 3,19-dioxo-4-androstene-17β-(2′-tetrahydropyranyl) ether (VIII, 490 mg., 71%) which was crystallized from acetone–petroleum ether to give the analytical product, m.p. 114–118°, $[\alpha]_D$ +98° (*c* 0.57), λ_{max} 243 mμ (ε 13,426), ν_{max} 2725, 1710, 1673, and 1615 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.67; H, 9.14.

3,19-Dioxo-4-androsten-17β-ol (IX).—To a solution of VIII (439 mg.) in 90% ethanol (25 ml.), concentrated hydrochloric acid (0.4 ml.) was added and the contents were refluxed for 1 hr. in an atmosphere of nitrogen. The reaction mixture was cooled and neutralized with sodium bicarbonate solution. It was then diluted with water (500 ml.) and extracted with ethyl acetate. The ethyl acetate extract was washed with brine solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a resinous product (342 mg.) which was chromatographed on alumina (10 g.). After 3,19-dioxo-4-androsten-17β-ol (IX, 241 mg. 70%) was eluted with benzene–ether (8:2), it was crystallized (needles) from acetone–petroleum ether, m.p. 124–126°, $[\alpha]_D$ +186° (*c* 0.2), λ_{max} 246 mμ (ε 12,916), ν_{max} 3450, 2725, 1750, 1660, and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.11; H, 8.80.

The second polymorphic form was crystallized from acetone (rectangular prisms), m.p. 167–168°, $[\alpha]_D$ +195°; λ_{max} 246 mμ (ε 12,880), ν_{max} 3448, 2725, 1750, 1660, and 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.51; H, 8.69.

Acknowledgment.—We wish to thank Professor Takeshi Nakao of the Jikei University School of Medicine, Tokyo, Japan, for kindly sending us an authentic sample of 19-hydroxytestosterone (IV) and the Syntex Company, Mexico City, D. F., for providing us with a generous quantity of 19-hydroxy-4-androstene-3,17-dione (I).

Reactions of Ortho Esters with Di-*t*-butyl Peroxide

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Received August 20, 1962

In reactions induced by dialkyl peroxides, compounds having ether functions undergo fragmentation by a free radical path yielding carbonyl-containing products. For example, acetals, the class of compounds that have received the most attention in such reactions,[1] yield esters as the major products in reactions induced with di-*t*-butyl peroxide. We have extended the investigation of the free radical reactions of compounds with ether functions to a study of the di-*t*-butyl peroxide induced reactions of trimethyl orthoformate, triethyl orthoformate, and triethyl orthoacetate. The orthoformates yield both carbonate and formate esters as reaction products whereas ethyl acetate was obtained from the orthoacetate.

Heating a mixture of an ortho ester and di-*t*-butyl peroxide at 135° results in the formation of the liquid and gaseous products in the quantities listed in Table I. Both the qualitative identifications and the quantitative determinations of these products were made by gas chromatographic analyses of the reaction mixtures and the gases evolved.

These products and their distribution suggest that the following sequence of free radical processes may be involved in these reactions.

$$((CH_3)_3CO)_2 \longrightarrow 2(CH_3)_3CO\cdot \quad (1)$$

$$(CH_3)_3CO\cdot \longrightarrow CH_3COCH_3 + CH_3\cdot \quad (2)$$

$$(CH_3)_3CO\cdot \text{ (or } CH_3\cdot) + \underset{\text{I}}{(RCH_2O)_3CH} \longrightarrow (CH_3)_3COH \text{ (or } CH_4) + \underset{\text{A}\cdot}{(RCH_2O)_3C\cdot} \quad (3)$$

$$(CH_3)_3CO\cdot \text{ (or } CH_3\cdot) + \text{I} \longrightarrow (CH_3)_3COH \text{ (or } CH_4) + \underset{\text{B}\cdot}{(RCH_2O)_2CHO\overset{\cdot}{C}HR} \quad (4)$$

$$\text{A}\cdot \longrightarrow (RCH_2O)_2C{=}O + \underset{\text{C}\cdot}{RCH_2\cdot} \quad (5)$$

$$\text{B}\cdot \longrightarrow RCHO + \underset{\text{D}\cdot}{(RCH_2O)_2\overset{\cdot}{C}H} \quad (6)$$

$$\text{D}\cdot \longrightarrow RCH_2OCHO + \text{C}\cdot \quad (7)$$

$$\text{D}\cdot + \text{I} \longrightarrow (RCH_2O)_2CH_2 + \text{A}\cdot \text{ or B}\cdot \quad (8)$$

$$\text{C}\cdot + \text{I} \longrightarrow RCH_3 + \text{A}\cdot \text{ or B}\cdot \quad (9)$$

R = H or CH_3

According to this proposed reaction scheme, certain quantitative relationships should exist

(1) L. P. Kuhn and C. Wellman, *J. Org. Chem.*, **22**, 774 (1956); E. S. Huyser, *ibid.*, **25**, 1820 (1960); C. L. Aldrich, J. B. Zachry, and E. A. Hunter, *ibid.*, **27**, 47 (1962); E. S. Huyser and Z. Garcia, *ibid.*, **27**, 2716 (1962).

TABLE I

REACTIONS OF ORTHO ESTERS WITH DI-*t*-BUTYL PEROXIDE FOR 18 HR. AT 135°

Ortho ester (mmoles)	Mmoles of peroxide	Products	Mmoles
Trimethyl orthoformate (500)	30	Methyl carbonate	29
		Formaldehyde	1.7
		Methyl formate	1.5
		Methylal	0.7
		Acetone	41
		Methane	84
		t-Butyl alcohol	None
		Ethane	None
Triethyl orthoformate (500)	30	Ethyl carbonate	21
		Acetaldehyde	10
		Ethyl formate	20
		Acetone	[a]
		t-Butyl alcohol	[a]
		Diethoxyethane	None
		Ethane	35[b]
		Methane and carbon monoxide	[a]
Triethyl orthoacetate (210)	80	Ethyl acetate	110
		Acetaldehyde	54
		t-Butyl alcohol	[a]
		Acetone	None
		Acetal	None
		Ethane	100[b]
		Methane and carbon monoxide	[a]

[a] Observed as a product but amount not determined. [b] Trace of ethylene also present.

among the products found in these reactions. Some of these expected relationships can be demonstrated to occur within the experimental uncertainty of our quantitative measurements. In the triethyl orthoformate reaction, the amount of ethane (35 mmoles) should be the same as the combined amounts of ethyl carbonate and ethyl formate (41 mmoles). The amount of acetaldehyde, which should be equal to the amount of ethyl formate, is low. This could be accounted for, in part, if the aldehyde undergoes decarbonylation producing methane and carbon monoxide *via* the following chain sequence.[2]

$$CH_3\cdot + CH_3CHO \longrightarrow CH_4 + CH_3\dot{C}O$$

$$CH_3\dot{C}O \longrightarrow CH_3\cdot + CO$$

Unfortunately, the gas chromatographic technique employed for the gas analyses did not separate methane and carbon monoxide. In the trimethyl orthoformate reaction, the amount of methane (84 mmoles) produced should be equivalent to the sum of the amounts of methyl formate, methyl carbonate, and acetone (72 mmoles). Very little, if any, carbon monoxide resulting from the decarbonylation of formaldehyde could have been present in this reaction. The total amount of formaldehyde formed (1.7 mmoles detected) could not have been greater than the sum of the amounts of methyl formate and methylal (2.2 mmoles).

(2) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, p. 277.

Abstraction of a formyl hydrogen (reaction 3) is not possible in the reaction of triethyl orthoacetate. This limits the products expected to those that can arise from a radical such as B· in the reaction scheme; namely, acetaldehyde, ethyl acetate, ethane, and possibly acetal. The amounts of ethyl acetate (110 mmoles) and ethane (100 mmoles) should be equivalent. According to the reaction scheme, the amount of acetaldehyde should be the same as the amount of ethane or the amount of ethyl acetate. The fact that the aldehyde content is low may be due to the decarbonylation reaction of acetaldehyde under these conditions.

The relative amounts of formation of the radicals resulting from the abstraction of the formyl hydrogens of the orthoformates (reaction 3) with respect to those radicals which are formed by abstraction of an α-hydrogen from the alkyl groups (reaction 4) can be determined from the data in Table I. The relatively large amount of methyl carbonate with respect to formaldehyde formed in the trimethyl orthoformate reaction indicates a greater reactivity of the formyl hydrogen than the methyl hydrogens toward attack by the chain carrying free radicals. The very nearly equivalent amounts of ethyl carbonate and ethyl formate show, assuming the same reactivity of the formyl hydrogen as that in trimethyl orthoformate, that the α-hydrogens of the ethyl groups in triethyl orthoformate are far more reactive than the hydrogens of the methyl groups in trimethyl orthoformate.

The absence of *t*-butyl alcohol as a reaction product in the trimethyl orthoformate reaction is also indicative of the low reactivity of the hydrogens in this ortho ester toward abstraction. The rate of breakdown of the *t*-butoxyl radical to acetone and methyl radicals (reaction 2) is faster than abstraction of a hydrogen from trimethyl orthoformate (reactions 3 and 4). In the triethyl orthoformate case, the presence of *t*-butyl alcohol as a reaction product shows that the hydrogen abstraction reactions by the *t*-butoxyl radicals (reactions 3 and 4) compete favorably with the breakdown of this radical (reaction 2). The absence of acetone as a reaction product in the triethyl orthoacetate reaction suggests that hydrogen abstraction proceeds even more readily in this case.

Our data also indicate that ethyl radicals are more easily eliminated from an acetal radical (type D· in the reaction scheme) than are methyl radicals. The presence of methylal as a reaction product in the trimethyl orthoformate reaction shows that the hydrogen abstraction reaction of the acetal radical (reaction 8) competes favorably with the elimination reaction (reaction 7) to form methyl formate. Although an acetal radical of the same type is formed in both the triethyl orthoformate and triethyl orthoacetate reactions, none of the cor-

responding acetals were formed as reaction products. This would indicate that the elimination of the ethyl radical (reaction 7) from the acetal radical proceeds to the complete exclusion of any hydrogen abstractions by this radical (reaction 8) even though hydrogen abstraction is apparently more facile than in the trimethyl orthoformate.

These free radical fragmentation reactions of ortho esters have short kinetic chain lengths. They are, however, reactions that might lead to the formation of by-products in other free radical reactions of ortho esters, for example, Kharasch additions to olefins.[3]

Experimental

Trimethyl orthoformate and triethyl orthoformate (Matheson, Coleman and Bell) were distilled before using. Triethyl orthoacetate was obtained as a research sample from Kay-Fries Chemicals, Inc., and was used without further purification as was the di-*t*-butyl peroxide (Lucidol). The compounds used as references for the gas chromatographic analyses were stock items which were purified when necessary to give a single chromatographic peak.

Trimethyl Orthoformate and Di-*t*-butyl Peroxide.—A reaction mixture consisting of trimethyl orthoformate (53 g., 0.50 mole) and di-*t*-butyl peroxide (4.4 g., 0.03 mole) was heated for 18 hr. at 135° in a stainless steel autoclave. After cooling, the gas formed in the reaction was released, passed through a Dry Ice trap and its volume (1.97 l. corrected to standard conditions) measured by means of a wet test meter. A sample of the gas was analysed on an 8-ft. silicon gel column (column temperature 77°, helium used as carrier gas) and proved to be 95% methane. Some of the formaldehyde produced in the reaction was condensed in the Dry Ice trap. The liquid portion of the reaction mixture was distilled and the fraction boiling up to 100° collected. Gas chromatographic analysis on an 8-ft. column packed with 15% di-2-ethylhexyl sebacate on Chromosorb P (column temperature 50°, helium used as carrier gas) indicated peaks with retention times identical with those of authentic samples of formaldehyde, methyl formate, methylal, acetone, and methyl carbonate as well as unchanged trimethyl orthoformate. The amounts of these components were determined by comparison of their peak areas, necessary correction factors having been previously determined from the chromatograms of known mixtures of these materials.

Triethyl Orthoformate and Di-*t*-butyl Peroxide.—A solution consisting of triethyl orthoformate (74 g., 0.50 mole) and di-*t*-butyl peroxide (4.4 g., 0.03 mole) was heated at 135° for 18 hr. in a flask equipped with a reflux condenser. The gases evolved during the course of the heating were passed through a Dry Ice trap and the volume (1.35 l. corrected to standard conditions) measured with a wet test meter. Gas chromatographic analysis of a sample of these gases on a silicon gel column (same conditions as in previous experiment) indicated the presence of ethane, a trace amount of ethylene, and a peak corresponding in retention time to that of methane and carbon monoxide. Some of the acetaldehyde formed was found in the Dry Ice trap (m.p. of 2,4-dinitrophenylhydrazone, 144–146°, reported, 147° [4]). The liquid portion of the reaction mixture was distilled and the fraction boiling up to 135° was collected. Gas chromatographic analysis on a 10-ft. column packed with 10% polyethylene succinate on Chromosorb W (column temperature, 53°, helium used as carrier gas) showed peaks with retention times the same as those of authentic samples of ethyl formate, *t*-butyl alcohol, and ethyl carbonate. Trace amounts of acetone and acetaldehye were also present. No peak with a retention time corresponding to diethoxymethane was found. The quantitative determination of the major components was made by comparison of their peak areas using toluene as an internal chromatographic standard. The necessary correction values of the mole ratios to area ratios of the reaction products with respect to toluene were determined from known mixtures.

Triethyl Orthoacetate and Di-*t*-butyl Peroxide.—A reaction mixture consisting of triethyl orthoacetate (33.9 g., 0.21 mole) and di-*t*-butyl peroxide (11.9 g., 0.08 mole) was heated for 18 hr. at 135°. The gas produced was passed through a Dry Ice trap and collected over water (2.89 l. corrected to standard conditions). Analysis of the gas by gas chromatography on a 50-ft. column packed with propylene carbonate on alumina (column temperature, 0°, helium used as carrier gas) showed the presence of ethane in the amount shown in Table I and a peak corresponding in retention time to that of methane and carbon monoxide. Most of the acetaldehyde formed was collected in the Dry Ice trap. Gas chromatographic analysis of the materials in the liquid portion boiling up to the boiling point of the orthoacetate on the di-2-ethylhexyl sebacate column showed peaks with retention times identical with those of ethyl acetate and *t*-butyl alcohol. No peaks with retention times the same as those of acetone and acetal were found. Quantitative determination of ethyl acetate was made from its peak area using benzene as an internal chromatographic standard. The mole ratio to peak area ratio for the internal standard to ethyl acetate was previously determined from known mixtures of these components.

Acknowledgment.—We wish to thank Mr. Y. N. Tang for performing the chromatographic analyses of the gaseous products. Also, we gratefully wish to acknowledge the support of this work by the National Science Foundation.

(3) T. M. Patrick, U.S. Patent 2,716,660 (1955).

(4) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley & Sons, Inc., New York, N. Y., 1959, p. 283.

Aromatic Hydroxylation by the Model Peroxidase System[1]

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Received May 18, 1962

The "Model Peroxidase System," first investigated by Udenfriend and co-workers[3a,b] and later by Grinstead,[4] is capable of hydroxylating aromatic compounds at specific sites on the ring. This system uses oxygen or hydrogen peroxide in the presence of ascorbic acid, ferrous ion, and a complexing agent ethylene diamine tetraacetic acid (EDTA) in

(1) We acknowledge with gratitude the support of this investigation by a grant from the National Science Foundation.

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(3)(a) S. Udenfriend, C. T. Clark, J. Axelrod, and B. B. Brodie *J. Biol. Chem.*, **208**, 731 (1954); (b) B. B. Brodie, J. Axelrod, P. A. Shore, and S. Udenfriend, *ibid.*, **208**, 741 (1954).

(4)(a) R. R. Grinstead, *J. Am. Chem. Soc.*, **82**, 3464 (1960); (b) R. R. Grinstead *ibid.*, **82**, 3472 (1960).