from **2b** and **3b** to give enedione **4**.[10] Other minor products are the 6α-hydroxy Δ^4-3-ketones (**3a**) and the parent Δ^4-3-ketone (**5**). Generally the ratio between the 6β and 6α epimers was never lower than 8–10, a rather high value for a free-radical oxygenation giving as a rule comparable amounts of epimers.[7,11] Higher amounts of 6α-hydroxy compound were found only on autoxidation of cortisol 21-acetate 3-ethyl enol ether.

Also in solvents other than alcohols, for instance in benzene or tetrahydrofuran, transformation of the enol ethers was complete in a brief time, although longer than in alcohol. 6β-Hydroxy Δ^4-3-ketone **2a** could not be isolated in satisfactory yield, but it was still the major component of the reaction mixture, which contained other compounds besides those cited above and peroxides other than **2b** and **3b**.[12] The results obtained in autoxidations carried out for preparative purpose in direct sunlight and mainly without radical generators are reported in Table I. The new enol ethers employed as starting compounds have been prepared according to already described procedures.[13]

Experimental Section[14]

The following example is given to illustrate the method used to perform autoxidation and to prepare the compounds listed in Table I.

Autoxidation of 3-Ethoxyandrosta-3,5-dien-17-one.—In a 1-l. Roux bottle, 2 g of androstenedione 3-ethyl enol ether and 150 ml of ethanol were added and the bottle was placed on a suitable shaker and exposed to direct sunlight (average temperature, 30°). After about 1 hr the initially suspended product dissolved completely; after 2 hr thin layer chromatography revealed the presence of about 5% of the starting enol ether and about 85% of hydroxylated compounds, mainly 6β-hydroxyandrostenedione. Spraying of the chromatogram with potassium iodide–acetic acid visualized trace amounts of peroxides, identical with the 6-hydroperoxyandrost-4-ene-3,17-dione, prepared as an epimeric mixture from androst-5-ene-3,17-dione by benzoyl peroxide initiated autoxidation according to Fieser, *et al.*[6]

After 3 hr the solvent was evaporated under vacuum and digestion of the residue with ether yielded 1.1 g (60%) of 6β-hydroxyandrost-4-ene-3,17-dione, mp 185–192°, purity on thin layer at least 98%. Recrystallization from acetone–hexane gave the analytical sample, mp 193–195°, $[\alpha]_D$ +105°, λ_{max} 237 mμ (ϵ 14,200), identical with the product prepared according to Dusza, *et al.*[4] Evaporation of the collected mother liquors gave a residue which by thin layer chromatography was found to contain at least 50% of 6β-hydroxyandrostenedione, about 5% of androstenedione, about 10% of 6α-hydroxyandrostenedione and 1–2% of androst-4-ene-3,6,17-trione.

Besides the R_f values, the by-products were identified as follows. Androstenedione was identified by elution from the chromatogram and comparison of ultraviolet and infrared spectra with those of an authentic specimen. 6α-Hydroxyandrostenedione was eluted and compared with the product prepared from the 6β epimer by epimerization of the acetate according to Balantan and Ehrenstein.[15] Moreover, after refluxing in methanol with hydrochloric acid, the rearrangement product[16] was compared with a specimen of 5α-androstene-3,6,17-trione[15] obtained from 6β-hydroxyandrostenedione by the same treatment. Androst-4-ene-3,6,17-trione was identified by comparing the ultraviolet (λ_{max} 252 mμ) and infrared spectra of the eluted material with those of the authentic specimen, mp 229–230°, $[\alpha]_D$ +38° (acetone) [lit. mp 216–217°,[17] 220–225°[18], 223–225°;[19] $[\alpha]_D$ +42.1°,[17] +32.3°,[18] +43°[19] (acetone)], prepared by oxidation of 6β-hydroxyandrostenedione with 8 *N* chromic acid in acetone.

Registry No.—6β-Hydroxyandrost-4-ene-3,17-dione, 63-00-3; 6β,17β-dihydroxyandrost-4-en-3-one, 62-99-7; 17β-acetoxy-6β-hydroxyandrost-4-en-3-one, 13096-48-5; 17α-methyl-6β,17β-dihydroxyandrost-4-en-3-one, 13096-49-6; 17α-ethynyl-17β-acetoxy-6β-hydroxyestr-4-en-3-one, 6856-27-5; 6α-methyl-6β,17α-dihydroxypregn-4-ene-3,20-dione, 13096-50-9; 21-acetoxy-6β,-17α-dihydroxypregn-4-ene-3,20-dione, 13096-51-0; 21-acetoxy-6β,17α-dihydroxypregn-4-ene-3,11,20-trione, 13096-52-1; 21-acetoxy-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione, 13096-53-2; 6β-hydroxycholest-4-en-3-one, 570-89-8; 6β-hydroxypregn-4-ene-3,30-dione, 604-19-3.

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[10] For a complete review on autoxidation inhibiton, see K. U. Ingold, *Chem. Rev.*, **61**, 563 (1961).

[11] A. Nickon, N. Schwartz, J. B. Di Giorgio, and D. A. Widdowson, *J. Org. Chem.*, **30**, 1711 (1965).

[12] Preliminary experiments on photosensitized oxygenation of enol ethers, carried out according to A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961), showed that in these conditions too 6β-hydroxy Δ^4-3-ketones (**2a**) were the main products.

[13] A. Ercoli and R. Gardi, *J. Am. Chem. Soc.*, **82**, 746 (1960).

[14] Rotations are in dioxane unless otherwise indicated. Thin layer chromatographies have been carried out in the following systems, according to the polarity of the compounds: ethyl ether–chloroform (1:9), benzene–ethyl acetate (1:1), benzene–ethyl acetate (1:4). We are indebted to Dr. Sergio Cairoli for the microanalyses and to Dr. Cesare Pedrali for the infrared spectra.

[15] C. P. Balantan and M. Ehrenstein, *J. Org. Chem.*, **17**, 1587 (1952).

[16] B. Ellis and V. A. Petrow, *J. Chem. Soc.*, 1078 (1939).

[17] A. Butenandt and B. Riegel, *Ber.*, **69**, 1163 (1936).

[18] D. H. Peterson, S. H. Eppstein, P. D. Meister, B. J. Magerlein, H. C. Murray, H. M. Leigh, A. Weintraub, and L. M. Reineke, *J. Am. Chem. Soc.*, **75**, 412 (1953).

[19] C. Amendolla, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954).

Autoxidative Cleavage of Isopropyl Mesityl Ketone

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In the course of some other studies[3] with isopropyl mesityl ketone (I), a colorless, crystalline compound was frequently observed to form in the liquid ketone which gradually turned dark on standing or following various manipulations. The phenomenon with this ketone has not been previously reported to our knowledge. The compound was identified as mesitoic acid (II) by its neutralization equivalent and comparison of the melting point and the infrared curve with those of authentic mesitoic acid. Although acetone was the expected product from the 3-carbon fragement, conclusive evidence for its presence was difficult to obtain from the original liquid mixtures. However, when oxidation was carried out under controlled conditions by bubbling oxygen gas into the liquid ketone and passing the exit gas through a 2,4-dinitrophenylhydrazine solution, a 2,4-dinitrophenylhydrazone was obtained which was identified as the acetone derivative from its melting point and mixture melting point with authentic material and its R_f value on thin layer chromatography compared with the R_f of 2,4-dinitrophenylhydrazone of acetone. Further identification was made by condensing a liquid from the exit gas in a low-temperature trap and comparing the infrared spectrum with acetone's. By this means, water was also found to be a product of the oxidation, the mole ratio of acetone–water being

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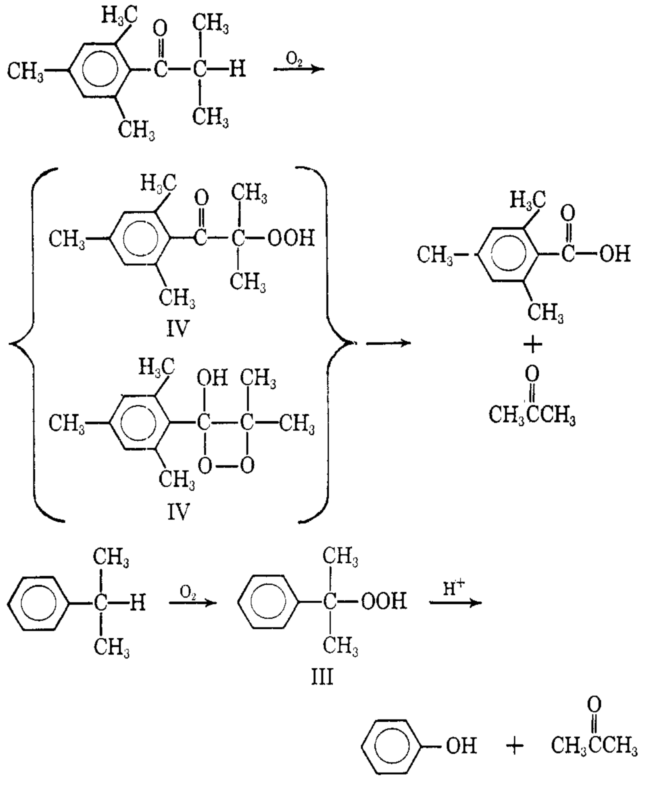
[1] Research Corp. Predoctoral Fellow.

[2] Welch Foundation Predoctoral Fellow.

[3] A. G. Pinkus and W. C. Servoss, presented at the Kansas City Chemical Conference, Nov 16, 1962.

1.85 in 15 hr and 2.00 in 21 hr as found by proton nmr. The sample from the 15-hr experiment was also analyzed for acid content, 0.478 equiv being found (based on starting ketone = 1.000 equiv) compared with 0.709 and 0.393 equiv of acetone and water, respectively. These results indicate that the water results mainly from the oxidation of the methyl groups of the aromatic ring since the relative amount of acetone formed (0.709 equiv) is greater than the amount of acid (0.478 equiv). According to the stoichiometry of Scheme I, the amounts of acetone and acid formed would be expected to be equivalent in the absence of side reactions. The interesting question arises as to whether the source of the oxygen for the formation of water is from the excess oxygen used in the oxidation or from some other source. Unfortunately the present experimental evidence does not permit a conclusive decision on this.

SCHEME I



Since a stable hydroperoxide (III) is formed from the autoxidation of cumene, the possible presence of an analogous peroxide (IV) was investigated for isopropyl mesityl ketone.[4] Although a positive iodide test for peroxide was obtained in the present case, several attempts at isolation of the intermediate were unsuccessful even though a separation could be obtained by thin layer chromatography on alumina. Of two possible formulations for the peroxide (IVa and b), the keto hydroperoxide structure (IVa) would seem to be favored. Infrared curves on reaction mixtures showed a broad absorption band *ca.* 2.99 μ which increased with time of oxidation. A band at 2.90 μ (3450 cm^{-1}) is generally assigned to the hydroxyl stretching mode for hydroperoxides in solution.[5] The infrared spectrum of a solution of cumene hydroperoxide in cumene prepared in the present investigation showed an O–H stretching band at 2.94 μ. The possibility that the band from the ketone autoxidation might have resulted from mesitoic acid was excluded by obtaining the spectrum of a solution of mesitoic acid in isopropyl mesityl ketone; the spectrum showed no absorption at 2.8–3.0 μ.

In addition, the spectra of the oxidized samples showed the development of a shoulder at 5.77 μ on the strong carbonyl stretching band of the unoxidized ketone at 5.90 μ. Although Kohler[6] formulated stable peroxides first obtained by him analogous to structure IVb, Fuson and Jackson[7] showed that peroxides of this type had infrared carbonyl stretching bands. Rigaudy[8] had earlier demonstrated that Kohler's peroxides showed ultraviolet absorption in the carbonyl region.

Experimental Section[9]

Isopropyl Mesityl Ketone (I).—Isopropyl mesityl ketone was prepared[10] by the Friedel–Crafts reaction of isobutyryl chloride and mesitylene in carbon disulfide using aluminum chloride: 55% yield; bp 99–102° (2 mm); $n^{25}D$ 1.5054.

Isolation and Identification of Mesitoic Acid (II).—Varying yields of the acid were obtained depending on the length of time the sample of isopropyl mesityl ketone had been standing and the particular conditions. For example, *ca.* 4 g of crystals were obtained from 125 g of the ketone after storage in the dark for 18 months. The crystals were collected by filtration and washed with several small portions of *n*-hexane, mp 150.5–151.5°. After two recrystallizations from benzene, the material had mp[11] 154.0–155.0°. The neutralization equivalent (determined in 1:1 (v/v) ethanol–water by potentiometric titration with sodium hydroxide standardized against potassium acid phthalate also in 1:1 aqueous ethanol) was 166 (calcd 164.2 for mesitoic acid). A mixture melting point with mesitoic acid synthesized[12] by the carbonation of mesityl magnesium bromide was undepressed. Comparison of the infrared spectra of the two samples also confirmed their identity.

Detection and Attempted Isolation of Peroxide.—The filtrate from the mesitoic acid precipitate was tested for peroxide by dissolving a few drops in several milliliters of alcohol, acidifying with hydrochloric acid, and adding alcoholic potassium iodide. A reddish brown color formed, whereas no color appeared in a control test with freshly prepared ketone; a confirmatory test was obtained using alcoholic sodium iodide–starch solution.

The presence of peroxide was also demonstrated by thin layer chromatography. A sample of the reaction mixture in chromatography on alumina or on Eastman chromatographic film poly(ethylene terephthalate) bearing silica gel bound with polyvinyl alcohol containing a fluorescent indicator of lead–manganese–

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[4] In the autoxidation of cumene it should be pointed out that the decomposition of cumene hydroperoxide (III) to phenol and acetone occurs in a separate acid-catalyzed step, whereas, in the autoxidation of isopropyl mesityl ketone, mesitoic acid is formed without added acid.

[5] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 122; A. V. Karyakin, V. A. Nikitin, and K. I. Ivanov, *Zh. Fiz. Khim.*, **27**, 1856 (1953) [*Chem. Abstr.*, **49**, 5126 (1955)]. C. Walling and L. D. Heaton [*J. Am. Chem. Soc.*, **87**, 48 (1965)] reported that the infrared spectrum of *t*-butyl hydroperoxide shows a sharp O–H stretching band at 3554 cm^{-1} in dilute carbon tetrachloride solutions which shifts to lower frequencies at higher concentrations or with addition of aromatic solvents.

[6] E. P. Kohler, *Am. Chem. J.*, **36**, 177, 529 (1906); **37**, 369 (1907). E. P. Kohler, F. H. Westheimer, and M. Tishler, *J. Am. Chem. Soc.*, **58**, 264 (1936). E. P. Kohler and R. B. Thompson, *ibid.*, **59**, 887 (1937).

[7] R. C. Fuson and H. L. Jackson, *ibid.*, **72**, 1637 (1950).

[8] J. Rigaudy, *Compt. Rend.*, **226**, 1993 (1948).

[9] Melting points were taken with total immersion thermometers; boiling points are uncorrected.

[10] R. C. Fuson and C. H. McKeever, *J. Am. Chem. Soc.*, **62**, 999 (1940).

[11] A. Claus, *J. Prakt. Chem.*, [2], **41**, 506 (1890). F. K. Beilstein ["Handbuch der organischen Chemie," 4th ed, Vol. 9, 1926, p 553] reported mp 155°. Other Beilstein references list lower melting points ranging from 147 to 152°.

[12] The authors express appreciation to Mr. H. C. Custard, Jr., for this preparation. The synthesis was by the method of R. P. Barnes, *Org. Syn.*, **21**, 77 (1941).

activated calcium silicate using chloroform as the eluent showed separation into several spots (*via* ultraviolet light). On spraying with a reagent consisting of an aqueous solution of *ca.* 10–15% sodium iodide acidified with acetic acid or hydrochloric acid and containing *ca.* 0.2–0.5% starch, one of the spots (R_f 0.6–0.7; 0.60 on the Eastman film) formed a reddish brown to purple color. Mesitoic acid did not migrate under these conditions; isopropyl mesityl ketone showed R_f 0.78 (Eastman film). Attempts were made to isolate the peroxide by collecting the scrapings from several plates and extracting with various solvents. No material containing peroxide could be eluted with the solvents tried, although the alumina still gave a peroxide test; thus, material was eluted with methylene chloride which showed an infrared carbonyl stretching band at *ca.* 5.83 μ and no hydroxyl stretching band, but this material gave a negative test for peroxide.

Identification and Isolation of Acetone.—Oxygen gas was passed through a fresh sample of liquid ketone using a sintered-disk arrangement and the exit gases were bubbled through a 2,4-dinitrophenylhydrazine solution. At room temperature the reaction proceeded very slowly, but it took place at a faster rate on heating the ketone (to *ca.* 110° in most of the experiments). The orange 2,4-dinitrophenylhydrazone precipitate was collected by filtration and recrystallized from 95% ethanol, mp 123.5–125.0°. A sample of the hydrazone prepared from authentic acetone was yellow and melted at 124.0–125.5°, mmp 123.5–125.0°. Both samples of hydrazone migrated at the same rate on a thin layer chromatogram on aluminum oxide G using a 1:2 nitrobenzene–cyclohexane solution for development. The R_f values ranged from 0.77 to 0.87 depending on various factors such as time of standing of the sample, size of sample, etc. The sample from the cold trap showed in addition a second smaller spot with R_f 0.43 (see below).

When the exit gases from the oxidation were passed through a Dry Ice–acetone trap, a colorless liquid condensed which formed a 2,4-dinitrophenylhydrazone precipitate. Since this precipitate gave only one spot in a thin layer chromatogram, it would appear that the second spot (R_f 0.43) observed above may be a product formed from oxidation of the 2,4-dinitrophenylhydrazone. However, this was not further investigated.[13]

Analysis of Autoxidation Cold-Trap Condensate.—The infrared absorption spectrum of the liquid from above, however, did not exactly match the spectrum of a sample of pure acetone, the main differences being a strong broad absorption band centered *ca.* 3.1 μ and a broader band than acetone in the carbonyl stretching region. It was suspected that water might also be present, causing the difference in the spectra. A similar spectrum was obtained from a *ca.* 2:1 acetone–water mixture (molar ratio). Further experiments were performed on the oxidation to establish conclusively that the water was actually formed in the oxidation and not introduced from the atmosphere or other sources. Thus, the oxygen was passed through a drying train at a flow rate of *ca.* 3 l./hr before being passed through the ketone and a phosphorous pentoxide drying tube protected the cold trap from moisture at the exit. A more accurate determination of the acetone–water ratio was made from the proton nmr curve using the integrated peaks[14] at δ 2.12 and 4.13 (acetone and water peaks, respectively) which showed a molar ratio of 1.85 in 15 hr[15] and 2.00 in 21 hr, the reaction still not being complete in the reaction times. The acid content in the 15-hr experiment was determined by titration of the reaction mixture in an aqueous dioxane solution.[16] In addition to the two main nmr peaks, several small peaks were present of which one was identified as coming from a trace of the starting ketone; some of these peaks evidently originated from a peroxide, since the material from the low-temperature trap was found to give a peroxide test. Thin layer chromatography showed that the peroxide was different than the one (IVb) observed above in the reaction mixture; this one did not move under the chromatographic conditions used. It was suspected that the peroxide might be formed from the oxidation of acetone in the low-temperature trap; however, in a control experiment, no peroxide was formed after passing oxygen through acetone in the low-temperature trap for 22.5 hr. Furthermore, no material was condensed in the cold trap when the oxygen was bubbled through isopropyl mesityl ketone at room temperature for the same period of time. No further study of this was made since the peroxidic material formed only a very small part of the total amount of material in the Dry Ice trap as evidenced by the nmr curve.

Infrared and Nmr Spectra.—Infrared spectra were taken with a KM-1 Baird-Atomic instrument. The acetone–water spectra were taken in IRTRAN-2 cells. Other spectra were taken in matched 0.1-mm sodium chloride cells in the concentration range of 3–5% (wt/vol) or in a sodium chloride sandwich cell for neat samples. All spectra were calibrated against polystyrene bands run on the same chart. The spectrum of mesitoic acid was obtained in carbon tetrachloride; the oxidation mixture and acetone–water were neat samples. The nmr spectra were obtained with a Varian Associates DP-60 spectrometer. Tetramethylsilane was used as an internal standard.

Registry No.—I, 2040-22-4; II, 480-63-7.

Acknowledgment.—The support of this work by Robert A. Welch Foundation and Research Corp. grants is gratefully acknowledged. The authors express appreciation to Mr. James G. Lindberg for assistance with nmr spectra.

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[13] In a recent paper, autoxidation products of phenylhydrazones were prepared and characterized as hydroperoxides: H. C. Yao and P. Resnick, *J. Org. Chem.*, **30**, 3832 (1965). For earlier related work, see R. Criegee and G. Lohaus, *Ber.*, **84**, 219 (1951); M. Busch and W. Dietz, *ibid.*, **47**, 3277 (1914).

[14] The analysis was based on synthetic acetone–water mixtures which showed two sharp singlets at the same positions as the condensate.

[15] The total amount of condensate was 2.380 g starting with 9.391 g of ketone. The integration curve showed 50 units for the acetone protons and 9.0 units for the hydroxyl protons. Thus, the ratio acetone–water = (50/6)/(9/2) = 1.85 (acetone having six protons and water having two).

[16] The reaction mixture was dissolved in purified dioxane and the solution diluted to 100 ml in a volumetric flask. A 5-ml aliquot was diluted with 30 ml of dioxane and 15 ml of distilled water and titrated with standard sodium hydroxide (0.04906 *N*) using a Beckman pH meter with glass and calomel electrodes. The average amount of acid calculated for three runs was 23.57 mequiv. Since the amount of starting ketone was 49.35 mmoles (9.391 g), the relative amount of acid calculated is 0.478 equiv based on ketone = 1 000 equiv.

Allene Chemistry. VII.[1] Reaction of Chlorine with Allene under Ionic Conditions

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The noncatalyzed addition of chlorine to allene in the dark and in inert solvents was reported[2] to produce, in moderate over-all yields (approximately 50%), an almost equimolar mixture of 2,3-dichloropropene and propargyl chloride (Table I).

$$H_2C{=}C{=}CH_2 + Cl_2 \longrightarrow \underset{20\text{–}25\%}{H_2C{=}CClCH_2Cl} + \underset{30\text{–}35\%}{HC{\equiv}CCH_2Cl}$$

The present work was undertaken in an attempt to optimize the selectivity of the reaction toward the monoadduct, 2,3-dichloropropene. At first glance it might seem that this goal should be easily attained simply by using more strongly ionic reaction conditions. For it was intimated[2] that formation of the yield-limiting by-product, propargyl chloride, was due to imperfect dissociation of chlorine in the initial π complex.

The application of ionic conditions could, however, *a priori* open the route for another side reaction, *viz.*,

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[1] Paper VI in this series: W. H. Mueller and K. Griesbaum, *J. Org. Chem.*, **32**, 856 (1967).

[2] H. G. Peer, *Rec. Trav. Chim.*, **81**, 13 (1962).