dioxane gives the ω-bromo derivative whether the hydroxyl group is protected by acylation or kept as such. This gives cupric bromide–dioxane a decided advantage over other brominating agents. Whether the hydroxyl group is protected or otherwise, bromination proceeds to take place at the carbon atom activated by the >C=O group. In compounds VI and VII, the second >C=O group in the pyrone ring has less activity owing to lactonization with oxygen, and such bromination takes place at the ω-position at the acetyl group in preference to C-3.[14,15]

Experimental

Preparation of ω-Bromo-4-methoxy-2-hydroxyacetophenone (II).—4-Methoxy-2-hydroxyacetophenone (1.7 g., 0.01 mole) and cupric bromide (4.5 g., 0.02 mole) in dioxane (50 ml.) were refluxed for 3 hr. The white cuprous bromide was filtered off at the pump and dioxane was removed under reduced pressure. The gummy greenish product was extracted with ether, the ethereal layer was dried with anhydrous sodium sulfate, and the ether was removed. The residue was crystallized repeatedly from petroleum ether–benzene to obtain shining white, hard crystals (1.1 g.), m.p. 161°.

Anal. Calcd. for $C_9H_9BrO_3$: C, 44.08; H, 3.67; Br, 32.65. Found: C, 43.98; H, 3.69; Br, 33.22.

Preparation of 6-Methoxybenzofuran-3-one (III).—II (1 g.) was dissolved in ethanol and treated with potassium hydroxide solution (10 ml., 40%). On slight warming the mixture turned rose red. After 2 hr. the mixture was acidified with hydrochloric acid. The rose red solid was filtered off and was crystallized repeatedly from methanol (0.5 g.), m.p. 170–171°. The ethanolic ferric chloride color was violet.

Anal. Calcd. for $C_9H_8O_3$: C, 65.86; H, 4.87. Found: C, 65.43; H, 4.92.

Preparation of 4′,6-Dimethoxybenzylidenecoumaran-3-one. (IV).—II (3.3 g.) was dissolved in hot ethanol (15 ml.) and anisaldehyde (3 ml.) was added to it. The mixture was heated to boiling and sodium hydroxide solution (10 ml., 40%) was added with stirring. The mixture was brought to boiling again. The yellowish shining solid was filtered off after 1 hr. and was crystallized repeatedly from 60% ethyl alcohol to obtain shining wooly crystals (1.5 g.), m.p. 135–136°. The ethanolic ferric reaction was negative.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.35; H, 4.96. Found: C, 72.08; H, 4.99.

The filtrate after removing compound IV, m.p. 135°, was diluted with water and kept overnight. It was acidified with hydrochloric acid, and the gummy yellow solid was fractionally crystallized from ethyl acetate. The first fraction gave 0.3 g. of IV, and the second fraction, m.p. 188° (acetic acid), was found to be 4′,7-dimethoxyflavonol (V).

Anal. Calcd. for $C_{17}H_{15}C_5$: C, 68.45; H, 4.7. Found: C, 68.15; H, 4.81.

Direct Formation of Flavonol V.—To II (1.5 g.) in hot ethyl alcohol (15 ml.) anisaldehyde (1.5 ml.) was added, and the mixture was boiled. After 15 min. sodium hydroxide solution (25 ml., 5%) was added with stirring and the reaction mixture was kept overnight. It was acidified with hydrochloric acid. The yellow solid was fractionally crystallized to give two fractions: one, m.p. 135° (0.2 g.), was IV; and the second, m.p. 188–189° (0.5 g.), was the flavonol V.

ω-Bromo-4-methoxy-2-hydroxyacetophenone (II). From Dimethoxyresorcinol and Bromoacetyl Chloride.—A solution of resorcinol dimethyl ether (2 g.) and bromoacetyl chloride (2.5 g., obtained from bromoacetic acid and thionyl chloride) in carbon disulfide (20 ml.) was treated with anhydrous aluminum chloride (5 g.) as described previously[11] to form ω-bromo-4-methoxy-2-hydroxyacetophenone (0.8 g.), m.p. 158–159°, identical with II obtained in the first experiment.

8-(Bromoacetyl)-7-hydroxy-4-methylcoumarin (VIII).—8-Acetyl-7-hydroxy-4-methylcoumarin (VI, 3.38 g.) and cupric bromide (9.2 g.) were dissolved in dioxane (100 ml.) in a round-bottom flask (250 ml.), and the contents of the flask were refluxed for 4–5 hr. The white cuprous bromide was filtered off at the pump and the solvent was removed under reduced pressure. A greenish yellow solid was extracted with ethyl acetate and dried over anhydrous sodium sulfate. The solvent was removed and the yellow solid was crystallized from ethyl alcohol to yield 3.0 g. of yellowish white shining crystals, m.p. 135°. It gave a positive test for halogen and a phenolic group. It gave a depression of mixture melting point with 8-acetyl-7-hydroxy-4-methyl-3-bromocoumarin, m.p. 210°.

Anal. Calcd. for $C_{12}H_9BrO_4$: C, 48.49; H, 3.03; Br, 26.94. Found: C, 48.25; H, 3.12; Br, 26.98.

6-(Bromoacetyl)-5-hydroxy-4-methylcoumarin (IX).—6-Acetyl-5-hydroxy-4-methylcoumarin (VII, 3.38 g.) and cupric bromide (9.2 g.) were dissolved in dioxane (100 ml.) and treated as above. The solid was crystallized fractionally from ethyl alcohol to yield yellowish white crystals (2.5 g.), m.p. 146°. It showed a depression of mixture melting point with 6-acetyl-5-hydroxy-4-methyl-3-bromocoumarin, m.p. 226°, and also with 8-bromo-6-acetyl-5-hydroxy-4-methylcoumarin, m.p. 204°.

Anal. Calcd. for $C_{12}H_9BrO_4$: C, 48.49; H, 3.03; Br, 26.94. Found: C, 48.15; H, 3.21; Br, 27.24.

Action of Alcoholic Alkali on Compounds VIII and IX.—VIII (1.5 g.) was dissolved in hot ethyl alcohol and potassium hydroxide (10 ml., 40%) was added to it with stirring. The mixture was heated for 5 min. and was kept overnight. The red-colored mixture on acidification with dilute hydrochloric acid gave a red solid. It was crystallized from ethyl alcohol to yield red shining crystals (0.8 g.) of X, m.p. 153–154°.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.7. Found: C, 66.26; H, 3.75.

IX on similar treatment as above gave a reddish crystalline compound (XI), m.p. 157–159°.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.7. Found: C, 66.22; H, 3.76.

Action of Zinc Dust and Water on Compound II.—A mixture of II (0.5 g.), zinc dust (1 g.), and water (20 ml.) was refluxed for 8 hr. The mixture was extracted with ether and dried over anhydrous sodium sulfate. The ether was removed and a gummy residue obtained on crystallization with 60% ethyl alcohol gave 0.3 g. of shining white crystals, m.p. 50°, which remained undepressed when mixed with 4-methoxy-2-hydroxyacetophenone.

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(15) When this article was under revision a paper by E. R. Glazier was published [*ibid.*, **27**, 4397 (1962)], dealing with bromination of a steroidal ketone in the presence of an olefinic bond using cupric bromide in tetrahydrofuran instead of in dioxane, effecting a similar bromination at the acetyl group.

The Rate of Oxidation of Alicyclic Ketones with Perbenzoic Acid[1a]

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The oxidation of ketones with peracids to obtain esters or lactones has been thoroughly studied from the preparative[1b] kinetic and mechanistic points of view. The results of Criegee,[3] Friess,[2] and Doering[4,5] on the mechanism were explained on the basis of a slow, rate-controlling addition of the peracid to the ketone group. This is followed by cleavage of the oxygen–oxygen bond leaving an electron-deficient atom to which the more appropiate alkyl group shifts with a concerted release of the proton. In the steroid field the oxidation

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(3) von R. Criegee, *Ann.*, **560**, 127 (1948).

(4) W. von E. Doering and L. Speers, *J. Am. Chem. Soc.*, **72**, 5515 (1950).

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of 20-keto steroids[6] to produce androstane derivatives is of particular value. In preparative work, Δ^5-3-ketones and 3-,[7,9] 7-,[8] 17-,[9,10] and 20-ketones[6] have been oxidized to the corresponding lactones, but no kinetic study measuring the rate of oxidation of these ketones has been reported.

Therefore, the rates of oxidation of some simple alicyclic ketones were measured in order to investigate the effect of alkyl substituents located at different sites in the ring. Compounds examined included substituted cyclopentanones and cyclohexanones, α-halo ketones, and steroid ketones. The results obtained are reported in Table I.

TABLE I

OXIDATION OF KETONES WITH PERBENZOIC ACID

Cyclopentanones	$k_2 \times 10^4$ l. mole^{-1} sec.$^{-1}$
Cyclopentanone	2.15 ± 0.1
3-Methylcyclopentanone	1.39 ± 0.01
Camphor	0.245 ± 0.05
Fenchone	0.198 ± 0.07
1-Indanone	0.17 ± 0.04
5-Methoxyindanone	0.917 ± 0.04
Cyclohexanones	
Cyclohexanone	15.8 ± 0.04
2-Methylcyclohexanone	7.53 ± 0.08
2,2-Dimethylcyclohexanone	5.04 ± 0.1
3-Methylcyclohexanone	12.2 ± 0.03
4-Methylcyclohexanone	19.2 ± 0.05
4-*t*-Butylcyclohexanone	27.7 ± 0.09
1-Tetralone	0.11 ± 0.06
6-Methoxy-1-tetralone	0.65 ± 0.01
α-Halo and steroid ketones	
2-Chlorocyclohexanone	0.425 ± 0.001
2-Bromocholestan-3-one	1.26 ± 0.03
2,2-Dibromocholestan-3-one	33.2 ± 0.08
Cholestan-3-one	16.2 ± 0.05
3β-Hydroxyandrostan-17-one	0.352 ± 0.01
3β-Acetoxyestrone	0.22 ± 0.009
17α-Methyl-17β-hydroxy-androstan-3-one	10.0 ± 0.01
3β-Acetoxypregnan-20-one	0.119 ± 0.005
Cyclodecanone	0.145 ± 0.002

Experimental

The oxidation study was made at 25 ± 0.02° using a thermoregulated constant temperature bath. The concentration ratio of perbenzoic acid to ketone was 1.25 (0.05 *M* for ketone and 0.0625 *M* for the perbenzoic acid). Each experiment was started by mixing a measured volume of the perbenzoic acid solution of known concentration with chloroform in a dark volumetric flask and allowing it to reach the working temperature. The ketone dissolved in chloroform was added to the mixture and the volume was brought up to 100 ml. At convenient times aliquots were withdrawn and treated with an excess of potassium iodide in acid medium. The iodine liberated was titrated with 0.1 *N* sodium thiosulfate. At the same time a blank reaction was run to measure the autodecomposition of perbenzoic acid.[11]

All the samples used were purified specimens but, since all of them are known, only their physical constants are reported here, together with a brief description of the preparation of some of them.

Cyclopentanone, cyclohexanone, 3-methylcyclohexanone, 4-methylcyclohexanone, 4-*t*-butyl-cyclohexanone, 1-indanone, 1-tetralone, camphor, and fenchone were Eastman Kodak samples purified by distillation or through their semicarbazones. Hydrolysis of the latter and further distillation gave samples possessing the following constants: cyclopentanone, n^{25}D 1.4356; cyclohexanone, b.p. 143° (585 mm.), n^{20}D 1.4501; semicarbazones, m.p. 164–165°; 3-methylcyclohexanone, n^{25}D 1.4473; 4-methylcyclohexanone, n^{25}D 1.4454; 4-*t*-butylcyclohexanone, m.p. 66.5°; 1-indanone, m.p. 41°; semicarbazone, m.p. 241–242°; 1-tetralone, n^{26}D 1.5679; semicarbazone, m.p. 220–222°; camphor, m.p. 179°; fenchone, b.p. 82–84° (25 mm.), n^{26}D 1.4610; cholestan-3-one, m.p. 130–131°; eq. 2-methylcyclohexanone, prepared by oxidation of 2-methylcyclohexanol with sodium dichromate in acid medium had b.p. 63–66 (23 mm.), n^{26}D 1.4442; semicarbazone, m.p. 188°; 3-methylcyclopentanone was obtained by oxidation of 4-methylcyclohexanone with nitric acid and pyrolysis of the resultant methyladipic acid with barium hydroxide for 5 hr. at 300° and had b.p. 46–49° (15 mm.), n^{25}D 1.4320; 2,2-dimethylcyclohexanone, b.p. 153–155° (585 mm.), n^{26}D 1.4453, was prepared from 2-methylcyclohexanone by treatment of the latter with sodamide and methyl iodide. Ring enlargement of cyclononanone by the action of diazomethane and purification of the product through the semicarbazone, m.p. 210–211°, gave after hydrolysis the desired cyclodecanone, b.p. 85–87° (10 mm.).

2-Chlorocyclohexanone was prepared by direct chlorination of cyclohexanone at 0° and had b.p. 87–89° (14 mm.).

2-bromocholestan-3-one, from bromination of cholestan-3-one in acetic acid at 15° was recrystallized from chloroform and had m.p. 168–170°. 2,2-Dibromocholestan-3-one was prepared by the same procedure, m.p. 143.5–145°.

Δ^5-Cholesten-3-one, m.p. 124–124.5°, was obtained by oxidation of 5,6-dibromocholesterol followed by debromination with zinc.

3β-Acetoxy-Δ^5-cholesten-7-one, m.p. 158–160°, was prepared by oxidation of cholesteryl acetate with *t*-butyl chromate.

5-Methoxyhydrindanone, m.p. 106–107°, was obtained by the Bachman method, and 6-methoxytetralone, m.p. 77°, by oxidation of the corresponding alcohol with chromium trioxide–acetic acid. 3β-Acetoxy-Δ^5-pregnen-20-one, m.p. 142–144°, was obtained by catalytic hydrogenation (Pd–C) of Δ^5-pregnenolone acetate in ethyl acetate solution in acid medium. Other steroids were obtained as gifts from the Syntex Laboratories.

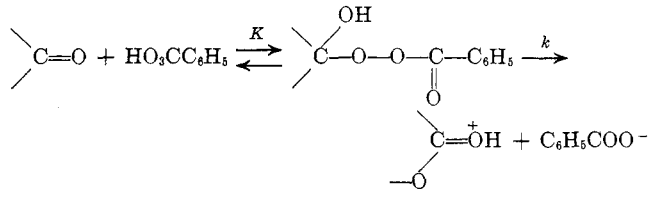
The perbenzoic acid was prepared by the method of Kergomar and Bigow[12] in almost quantitative yield. By difference of iodometric and base titration there was found to be 0.35% of benzoic acid present in the perbenzoic acid which was used in chloroformic solution for the kinetic experiments.

Results

The results obtained are given in Table I. In all cases a modified second-order rate equation was applied to take into consideration the amount of perbenzoic acid that autodecomposes slowly during the reaction.[11] Only the data for the first 30% of the reaction was considered since after this the per cent of reaction deviations from the modified second-order rate equation rises.

Discussion

Most of the results of Table I can be explained with the following mechanism.



In the first group of ketones (cyclopentanones), it is

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clear that the steric effects of the alkyl groups have a direct influence on the approach of the peracid to the carbonyl. This will affect mainly K and not k, and the over-all result is a lower rate. The rate constant of 3-methylcyclopentanone is lower than that for cyclopentanone, and the bicyclic ketones, camphor and fenchone, in which the keto group is surrounded by the methyl groups and the carbon skeleton, have much lower values.

Indanone has a lower rate constant than cyclopentanone as is expected due to the restriction in the polarization of the carbonyl which implies a lowering in resonance energy of this compound, going to the addition product (C). A methoxy group at C-5 increases the rate of oxidation in indanone and probably this is due to a higher migration capability of the aromatic group that increases k in comparison with the unsubstituted ketone.

In the cyclohexanones, 2-methyl-, 2,2-dimethyl-, and 3-methylcyclohexanones are less reactive than cyclohexanone owing to steric considerations; their rate constants can be easily explained on these grounds, since the oxidation slows as the groups get nearer and more bulky. In the 4-methyl- and 4-*t*-butylcyclohexanones it is at first sight surprising to find an increase in the rate, which is higher in the *t*-butylcyclohexanone.

We can consider the peracid oxidation as an addition reaction in which the anion attacks the tertiary carbonium ion of the polarized carbonyl group. Any factor stabilizing this ion in the transition state will favor the rate of oxidation.

There are several previous cases of 1:4 interactions in the cyclohexane. Owen[13] suggested the formation of a 1,4-oxygen bridge in the reaction of halohydrins with base. Bennett[14] suggested the presence of a cyclic halogenonium ion in the dehalogenation reactions of 1,4-dihalocyclohexanes and Goering[15] proposed a 1,4-bromonium ion bridge in the rearrangement of dibromocyclohexanes with ferric bromide. More conclusive was the solvolysis of *trans*-4-methoxycyclohexyl tosylate studied by Noyce.[16,17] This author and his co-workers suggested that anchimeric assistance is possible through an intermediate cyclic nonclassical ion in which the cyclohexane adopts the boat form, when the electrons on oxygen can stabilize the positive charge on the carbon. In the 4-methyl- and 4-*t*-butylcyclohexanones some type of 1,4-interaction must be operating which promotes reaction.[18]

Tetralone oxidation is 144 times slower than cyclohexanone and this result can be explained as being due to the decrease in resonance energy. A 6-methoxy group increases the migration capability of the aromatic ring and therefore k and the observed rate are higher.

In the halo ketones, it is of note that 2-chlorocyclohexanone and 2-bromocholestan-3-one are less reactive than cyclohexanone. In the chlorocyclohexanone the halogen is mainly equatorial[19] in the equilibrium mixture, and in the 2-bromocholestan-3-one it is known that bromine is α-equatorial. In both cases the dipole of the halogen and the carbonyl are in the same plane and this makes more difficult the polarization of the carbonyl with development of a positive charge on the carbonyl carbon. As a consequence these two halo ketones have a lower rate than cyclohexanone. A second bromine atom increases 26 times the rate in comparison with the monobromo ketone. This second bromine is axial and the increase in rate should be due to participation of the bromine atom and stabilization of the positive charge by formation of a bromonium ion.

Cholestan-3-one has a rate similar to that of cyclohexanone. The keto group at C-17 is oxidized at a rate that can be compared with the one of camphor and is in agreement for a 2,2,3-trisubstituted cyclopentanone. The C-20 keto group is still less reactive than the C-17 keto group.

The obtained results allow us to establish the following order of oxidation for keto steroids: 3-keto > 17-keto > 20-keto.[21]

Acknowledgment.—The authors thank Dr. A. Cross for improving the writing of the manuscript, and Dr. K. Kopecky for helpful comments.

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Synthesis of α-(Ferrocenylmethyl) Ketones by the Enamine Method[1]

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Many aldehydes and ketones can be α-alkylated *via* C-alkylation of their enamines.[3-6] N-Alkylation of enamines, which occurs to a considerable extent when simple alkyl halides are used as alkylating agents, leads to ultimate recovery of starting carbonyl compounds and is, of course, undesirable. The desired C-alkylation occurs to the exclusion of N-alkylation when the alkylating agents are reactive halides like allyl halides, benzyl halides and α-halo esters, or conjugated olefins like acrylonitrile and acrylic esters. By analogy with benzyl halides, the ferrocenylmethyl

(1) (a) Supported in part by a grant from the Research Corporation; (b) abstracted from the M.S. thesis (University of Mississippi, Aug., 1963) of M. T. Dorsett; (c) a preliminary report was presented at the 14th Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov., 1962.
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