The Oxidation of Secondary Alcohols in Diethyl Ether with Aqueous Chromic Acid. A Convenient Procedure for the Preparation of Ketones in High Epimeric Purity[1]

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Convenient procedures have been developed to convert secondary alcohols into ketones in excellent yield and high epimeric purity utilizing oxidation of the alcohol in diethyl ether with aqueous chromic acid. In one procedure (procedure A) the stoichiometric amount of sodium dichromate and sulfuric acid in water is added to the diethyl ether solution of alcohol at 25–30° and the reaction is continued for 2 hr. In the second procedure (procedure B), especially applicable to strained bicyclic alcohols, a 100% excess of the oxidation agent is used. In this case the reaction is complete in 15 min at 0°. These procedures offer especial promise for the preparation of ketones without accompanying epimerization or loss of isotopic purity.

The oxidation of secondary alcohols by hexavalent chromium derivatives is the most commonly employed method to prepare ketones. Although the oxidation with aqueous chromic acid has long been a standard method,[3] many modified procedures have been developed to simplify the isolation process, to achieve certain selectivity, and to improve the yield as well as the purity of the products.[4]

In the course of studying the direct chromic acid oxidation of organoboranes to ketones in the usual hydroboration solvents (diglyme, tetrahydrofuran, and diethyl ether),[5] it became desirable to explore the oxidation of secondary alcohols in these solvents. To our surprise, the oxidation of secondary alcohols proceeded very simply and cleanly in a two-phase system involving diethyl ether and a water solution of sodium dichromate and sulfuric acid. There appeared to be significant advantages to such an oxidation procedure. Consequently, we decided to undertake a detailed study.

In one early experiment we observed that, when a solution of cyclohexanol was contacted at 25° with an aqueous solution of the calculated quantity of sodium dichromate and sulfuric acid, the cyclohexanol disappeared almost immediately from the ether phase. Evidently, the cyclohexanol must be rapidly esterified and the chromic acid ester is extracted into the aqueous phase. Ketone then begins to appear at a moderate rate and is extracted into the ether phase as it forms. The ether phase then protects the ketone from undesirable side reactions, such as further oxidation or epimerization. Indeed, it proved possible to develop procedures which give nearly quantitative yields of ketones from a wide variety of secondary alcohols, with remarkably low epimerization for derivatives subject to this side reaction.

Results and Discussion

Since the preliminary results with diethyl ether were so promising, we decided to explore a representative range of solvents in order to see which one might be preferable for such oxidations. For these studies *l*-menthol was employed as a representative substrate to explore the relative efficacy of the different solvents. For these initial experiments we utilized the stoichiometric quantity of sodium dichromate and sulfuric acid. This had the advantage that any further oxidation of the ketone or of the solvent by the chromic acid[6,7] could readily be detected through decreased yields of the ketone. Finally, analysis of the product for isomenthone indicated the presence of undesired epimerization.

Gas chromatographic analyses revealed that the use of certain water-miscible solvents, such as diglyme or tetrahydrofuran, was undesirable because they were attacked by chromic acid, resulting in decreased yields of menthone, with considerable epimerization. Water-miscible solvents, relatively stable to chromic acid, gave almost complete oxidation to ketone, but the product contained several per cent of the epimerized ketone, isomenthone. Water-immiscible solvents, such as benzene[8] and *n*-pentane, were stable to the chromic acid but formed severe emulsions which hindered isolation of the product. Finally, we tried a number of oxygen containing solvents immiscible with the aqueous phase. Among these were solvents such as diisopropyl ether, ethyl acetate, and diethyl ketone. However, in these cases there was significant attack by the chromic acid, resulting in considerable amounts of alcohol in the ketone product.

Among the solvents examined, diethyl ether was clearly superior. In the presence of this second phase the oxidation proceeded smoothly, with no problem from emulsions. Separation of the ether layer provided for an exceptionally simple recovery of the product from the reaction mixture. Attack of the ether by aqueous chromic acid is evidently quite low, since the menthone product contained only 1.5% of residual alcohol. (Use of excess chromic acid was unfavorable, since a decrease in yield was observed, presumably arising from further oxidation of the ketone product.)

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(1) A preliminary report of a portion of this study has been published: H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

(2) Based in part on the Ph.D. Theses of C. P. Garg (1962) and K.-T. Liu (1968), Purdue University, Lafayette, Ind.

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(4) For concise reviews, see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 142–147; S. R. Sandler and W. Karo, "Organic Functional Group Preparations," Academic Press, New York, N. Y., 1968, pp 169–176. For more recent work, see J. C. Collins, W. W. Hess, and T. J. Katz, *Tetrahedron Lett.*, 3363 (1968).

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(6) K. B. Wiberg, Ed., "Oxidation in Organic Chemistry," part A, Academic Press, New York, N. Y., 1965, Chapter 2.

(7) J. Rocek and A. Riehl, *J. Amer. Chem. Soc.*, **88**, 4749 (1966); **89**, 6691 (1967); *J. Org. Chem.*, **32**, 3569 (1967).

(8) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 139.

Finally, the *l*-menthone recovered was exceptionally free of isomenthone.

The effect of variations in temperature and reaction times was then explored. The reaction at room temperature (25–30°) appeared to be more favorable than reaction at lower temperatures. At 25° the reaction is essentially over in 45 min. However, longer reaction times were not deleterious. Consequently, it appeared desirable to standardize on a 2-hr reaction time to allow for less reactive alcohols. A standard procedure (procedure A) was then developed. In this procedure, a stoichiometric amount of sodium dichromate and sulfuric acid was dissolved in water and this solution was added over a 15-min period to a solution of the secondary alcohol in diethyl ether at 25–30°. After 2 hr, the organic layer was separated and the product isolated (for details, see Experimental Section). Application of this procedure to some representative alcohols gave, in general, yields of 85–97%. Only in the case of bicyclic alcohols, such as *exo*-norbornanol, were the yields significantly lower. Fortunately, as will be described later, it proved possible to overcome this difficulty through a modified procedure (procedure B). The experimental results with the above procedure are summarized in Table I.

TABLE I

OXIDATION OF ALCOHOLS IN DIETHYL ETHER WITH EQUIVALENT AQUEOUS CHROMIC ACID AT 25°

Alcohol	Yield of ketone, % Glpc	Isolated
3-Methyl-2-butanol	85	
Cyclopentanol	87	
Cyclohexanol	92	
Cyclooctanol	93	
2-Methylcyclohexanol[a]	97	87
l-Menthol[b]	97	84[d]
Isopinocampheol[c]	94	80[e]
exo-Norbornanol	61	

[a] 58% *cis*- and 42% *trans* alcohols. [b] $[\alpha]_D$ −48.7°. [c] $[\alpha]_D$ −32.4°. [d] $[\alpha]_D$ −29.9°. [e] $[\alpha]_D$ +10.04°.

It was of interest to compare the epimeric purities of the products from this procedure with those realized in other commonly utilized procedures in the literature.

TABLE II

OXIDATION OF *l*-MENTHOL AND ISOPINOCAMPHEOL BY VARIOUS PROCEDURES

Procedure[a]	Product from *l*-menthol, %[b]		
	Menthol	Isomenthone	Menthol
A	97	Trace	1.5
C	86	4	2
D	90	3	Trace
E	71	3	0
	Product from isopinocampheol, %		
	Isopino-camphone	Pinocamphone	Isopino-campheol
A	94	Trace	0
C	84	4	1
D	86	4	1
E	78	3	0

[a] Procedure A, stoichiometric amount of aqueous chromic acid with alcohol in diethyl ether. Procedure C, chromic acid in acetone: K. Bowden, I. M. Heilborn, E. R. H. Jones, and B. C. L. Weeden, *J. Chem. Soc.*, 39 (1946). Procedure D, aqueous chromic acid.[3] Procedure E, chromic acid in 90% acetic acid at 25°: B. Gastamide, *Ann. Chim. (Paris)*, 9, 257 (1954). [b] Determined by glpc.

l-Menthol and isopinocampheol were selected as test substrates. The results are summarized in Table II.

Alkyl- and aryl-substituted, and deuterium-tagged norbornanones are the necessary starting materials for synthesizing various bicyclo[2.2.1]heptyl alcohols, ester, halides, and olefins, employed in our studies of the nature of norbornyl cation. It follows that the comparatively low yield of ketone in the oxidation of norbornanol and related bicyclic alcohols by the present oxidation procedure constituted a severe handicap. Consequently, we undertook to develop an improved method which would be applicable to these strained bicyclic alcohols. We were led to a satisfactory procedure by the following considerations.

Chromic acid oxidation of secondary alcohol has been considered to proceed *via* the following sequence.[6,9–13]

$$Cr_2O_7^{2-} + H_2O \rightleftharpoons 2HCrO_4^-$$

$$HCrO_4^- + HA + H^+ \rightleftharpoons HCrO_3A + H_2O$$

$$R_2CHOH + HCrO_3A \rightleftharpoons R_2CHOCrO_2A + H_2O$$

$$R_2CHOCrO_2A \xrightarrow{\text{slow}} R_2CO + Cr(IV)$$

$$Cr(IV) + Cr(VI) \xrightarrow{\text{fast}} 2Cr(V)$$

$$R_2CHOH + Cr(V) \xrightarrow{\text{fast}} R_2CO + Cr(III)$$

The Cr(V) species is more powerful than Cr(VI) in the oxidation reaction. Under ordinary conditions it may be responsible for as much as two-thirds of the total oxidation and may lead to unwanted side reactions, such as C–C bond cleavage of secondary alcohols.[6,14] On the other hand, recent findings have

$$(CH_3)_3CCH(OH)C_6H_5 \longrightarrow (CH_3)_3COH + C_6H_5CHO$$

indicated that Cr(IV) may be responsible for the cleavage reaction.[15–17] Consequently, the strained norbornyl derivatives might be easily cleaved by Cr(V) or Cr(IV). Such a side reaction might be decreased in the presence of excess Cr(VI). However, the previous results (*vide supra*) indicated that the use of excess chromic acid decreased the yield of ketone. It appeared that this difficulty might be overcome by running the reaction at lower temperatures and/or shorter time.

Indeed, a series of experiments based on our standard procedure revealed that the yield of norbornanone from *exo*-norbornanol increased when excess chromic acid was used at lower temperature and the reaction was run for shorter periods. The most suitable conditions adopted for such oxidations appeared to be the use of 0°. The oxidizing agent is added to the diethyl ether solution of alcohol over a period of 10 min, the reaction mixture is stirred for 5 min, and the product is recovered by separating the ether layer

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(10) K. B. Wiberg and H. Schäfer, *ibid.*, **89**, 455 (1967); **91**, 927, 933 (1969).
(11) R. Stewart and D. G. Lee, *Can. J. Chem.*, **42**, 439 (1964).
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(14) J. J. Cawley and F. H. Westheimer, *Chem. Ind. (London)*, 656 (1960).
(15) J. Roček and A. E. Radkowsky, *J. Amer. Chem. Soc.*, **90**, 2986 (1968).
(16) W. A. Mosher and G. L. Driscoll, *ibid.*, **90**, 4189 (1968).
(17) P. M. Nave and W. S. Trahanovsky, *ibid.*, **92**, 1120 (1970).

and removing the ether (for details, see Experimental Section).

This modified procedure not only gives excellent yields in the oxidation of bicyclo[2.2.1]heptyl alcohols (Table III), but also is applicable to many other

TABLE III

OXIDATION OF ALCOHOLS IN DIETHYL ETHER WITH 100% EXCESS AQUEOUS CHROMIC ACID AT 0°

Alcohol	Yield of ketone, % Glpc	Isolated
Cyclohexanol	98	
exo-Norbornanol[a]	85	80
endo-Norbornanol	90	
1-Methyl-*exo*-norbornanol	76	70
1-Methyl-*endo*-norbornanol	89	81
1-Phenyl-*exo*-norbornanol	74	68
7,7-Dimethyl-*exo*-norbornanol[b]	90	80
Isoborneol	99	
Borneol	99	
endo-Fenchyl alcohol	95	

[a] *exo*-3-*d*-*exo*-Norbornanol yielded *exo*-3-*d*-norbornanone retaining over 98% isotopic purity. [b] *exo*-3-*d*-7,7-Dimethyl-*exo*-norbornanol yielded *exo*-3-*d*-7,7-dimethylnorbornanone retaining over 98% isotopic purity.

strained or labile systems, such as bicyclo[3.2.0]heptan-2-ol[18] and 2-isocaranol,[19] for which other oxidation methods proved unsatisfactory, as well as to the more usual alcohols for which the previous procedure is applicable (Table I). More important, no epimerization[19] or loss of isotopic purity has been observed. The yield of ketone is, in general, higher than that realized from other commonly used procedures. A comparison of representative cases is summarized in Table IV.

TABLE IV

COMPARISON OF YIELD OF BICYCLO[2.2.1]HEPTANONES FROM VARIOUS OXIDATION PROCEDURES

Procedure[a]	Yield of ketone,[b] % *exo*-Norbornanol	*endo*-Norbornanol	1-Methyl-*exo*-norbornanol	1-Phenyl-*exo*-norbornanol
A	61[c]	76[c]	59[d]	
B	85[c]	90[c]	70[d]	68[d]
C		85[e,f]	67[d,f]	51[d,g]
D		79[d,h]		
F		74[e]		

[a] Procedures A, C, and D are described in Table II. Procedure B, 100% excess aqueous chromic acid with alcohol in diethyl ether. Procedure F, chromium trioxide and alcohol in pyridine [Sarett's reagent, see G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 722 (1953)]. [b] Present work unless otherwise mentioned. [c] Determined by glpc. [d] Isolation. [e] Crude product. [f] Reference 23. [g] Reference 25. [h] H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **82**, 1209 (1960).

In applying this procedure to 5,6-dehydronorbornanol, the yield dropped to approximately 60%. Consequently, it would appear that for the oxidation of such acid-sensitive structures this procedure may not be so satisfactory as the application of Sarett's reagent.[20]

(18) W. J. Hammer, Ph.D. Thesis, Purdue University, Lafayette, Ind., 1967.

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(20) J. G. Atkinson, M. H. Fisher, D. Horley, A. T. Morse, R. S. Stuart, and E. Synnes, *Can. J. Chem.*, **43**, 1614 (1965).

Experimental Section

Glpc Analysis.—All analyses were carried out on a Perkin-Elmer Model 154 vapor fractometer equipped with appropriate columns.

Materials.—Cyclooctanol was obtained by the reduction of cyclooctanone with sodium borohydride. Isopinocampheol was synthesized from the hydroboration–oxidation of α-pinene,[21] and the isopinocamphone prepared by chromic acid oxidation of the alcohol. Isomerization of isopinocamphone gave a mixture of pinocamphone and isopinocamphone.[21] The reduction with lithium trimethoxyaluminohydride[22] yielded 98% pure *endo*-norbornanol, 99% pure 1-methyl-*endo*-norbornanol, and 97% pure *endo*-fenchyl alcohol, respectively, from the corresponding ketones. 1-Methyl-*exo*-norbornanol was prepared by modified procedures of Berson and coworkers.[23,24] Direct oxidation of *exo*-2-methyl-*endo*-norbornanol gave 1-methylnorbornanone.[24] 1-Phenyl-*exo*-norbornanol and 1-phenylnorbornanone were synthesized by modified procedures of Kleinfelter and Schleyer.[24,25] 7,7-Dimethylnorbornanone was prepared *via* hydroboration and oxidation.[26] From *cis*-*exo*-3-acetoxy-7,7-dimethyl-2-norbornylmercuric chloride[26] 7,7-dimethyl-*exo*-norbornanol was obtained from reduction with 2% sodium amalgam in sodium hydroxide and the 3-*exo*-*d* isomer was obtained from reduction with 2% sodium amalgam in sodium deuterioxide.[24] Similarly, 3-*exo*-*d*-*exo*-norbornanol was prepared from *cis*-*exo*-3-hydroxy-2-*exo*-norbornylmercuric chloride.[24] Other alcohols and ketones utilized were commercial samples used without further treatment.

Chromic Acid Solution.—The chromic acid solution used for the oxidation was prepared from the appropriate amount of sodium dichromate and sulfuric acid as indicated by the following equation.

$$3R_2CHOH + Na_2Cr_2O_7 + 4H_2SO_4 \longrightarrow 3R_2CO + Na_2SO_4 + Cr_2(SO_4)_3 + 7H_2O$$

The chromic acid solution is prepared by dissolving 100 g (0.33 mol) of sodium dichromate dihydrate in 300 ml of water. The sulfuric acid (97%), 136 g (1.34 mol), was then added. The solution was then diluted to 500-ml total volume. This solution will oxidize 1.00 mol of secondary alcohol by procedure A or 0.05 mol of secondary alcohol by procedure B.

Oxidation of *l*-Menthol in Diethyl Ether with Stoichiometric Amount of Chromic Acid. A Representative Procedure A.—Diethyl ether, 20 ml, and 7.80 g (50 mmol) of *l*-menthol were placed in a 100-ml three-necked flask fitted with a stirrer, a condenser, and an addition funnel. Chromic acid solution (25 ml) was added to the stirred solution over 15 min, maintaining the temperature at 25–30°. After 2 hr at room temperature, the upper ether layer was separated and the aqueous phase was extracted with two 10-ml portions with ether. The combined ether extracts were washed with saturated sodium bicarbonate and then water. Gas chromatographic analysis on a Carbowax 4000 column indicated 97% *l*-menthone, a trace of isomenthone, and 1.5% menthol. Vacuum distillation through a short Vigreux column gave 6.45 g, 84% yield, of *l*-menthone, bp 66–67° (4 mm), $n^{20}D$ 1.4500, $[\alpha]D$ −29.9° (lit. $n^{20}D$ 1.45038,[27] $[\alpha]D$ −29.6°[28]). Other alcohols listed in Table I were oxidized in the same manner.

Oxidation of 1-Phenyl-*exo*-norbornanol in Diethyl Ether with 100% Excess of Chromic Acid. A Representative Procedure B.—Diethyl ether, 25 ml, and 9.43 g (50 mmol) of 1-phenyl-*exo*-norbornanol were placed in a 300-ml three-necked flask fitted with a stirrer, a condenser, and an addition funnel. This flask was chilled in an ice bath for about 30 min. Chromic acid solution (50 ml) was also cooled in an ice bath for 30 min. This chilled chromic acid solution (25 ml) was added to the stirred solution of alcohol over 5 min while the other portion of chromic acid was still kept in ice bath. Then the second 25 ml of chromic acid was added in another 5 min. After the completion of addi-

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(23) J. A. Berson, *et al.*, *ibid.*, **83**, 3986 (1961).

(24) K.-T. Liu, Ph.D. Thesis, Purdue University, Lafayette, Ind., 1968.

(25) D. C. Kelinfelter and P. v. R. Schleyer, *J. Org. Chem.*, **26**, 3740 (1961).

(26) H. C. Brown, J. H. Kawakami, and S. Misumi, *ibid.*, **35**, 1360 (1970).

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tion, vigorous stirring was continued for an additional 5 min. Then the upper layer was separated, and the lower aqueous layer was extracted with two 15-ml portions of ether. The combined ether extracts were washed once with 5% sodium carbonate and then four times with water. Gas chromatographic analysis on a Carbowax 20M column with benzil as internal standard showed 74% yield of 1-phenylnorcamphor in the absence of any starting alcohol. After the solvent was removed, the remaining oil was carefully fractionally distilled through a 10-cm Vigreux column and the ketone, bp 132–135° (1.5 mm), solidified in the receiver. The yield of this glpc homogeneous 1-phenylnorboranone, mp 41–42° (lit.[25] 40.2–41.0), was 6.37 g (68%).

Other alcohols listed in Table III were oxidized in the same way.

Registry No.—3-Methyl-2-butanol, 598-75-4; cyclopentanol, 96-41-3; cyclohexanol, 108-93-0; cyclooctanol, 696-71-9; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; *l*-menthol, 2216-51-5; isopinocampheol, 1196-00-5; *exo*-norbornanol, 497-37-0; *endo*-norbornanol, 497-36-9; 1-methyl-*exo*-norbornanol, 766-25-6; 1-methyl-*endo*-norbornanol, 3588-21-4; 1-phenyl-*exo*-norbornanol, 14182-93-5; 7,7-dimethyl-*exo*-norbornanol, 26908-71-4; isoborneol, 124-76-5; borneol, 507-70-0; *endo*-fenchyl alcohol, 14575-74-7; chromic acid, 7738-94-5.

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Frangomeric and Anchimeric Processes in the Preparation and Reactions of α,β-Epoxy Ketones[1]

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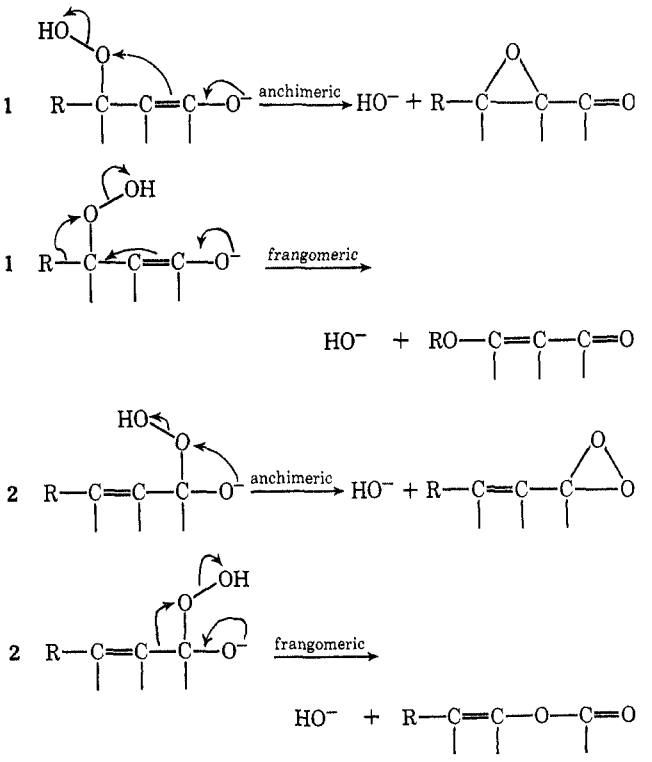
Four pathways are considered for the reaction of the hydrogen peroxide anion with α,β-unsaturated ketones. One of these pathways leading to α,β-epoxy ketones is well known. Examples of a second pathway, Baeyer–Villiger oxidation, are described with 2-arylmethylene-3-quinuclidinones. The reactions of hydrazine with α,β-epoxy ketones yield either hydroxypyrazolines or allylic alcohols depending on whether the intermediate epoxyhydrazones follow an anchimeric process or a frangomeric process. The former is shown to be preferred with α,β-epoxy ketones in which the β-carbon atom is benzylic and in which a cisoidal conformation of epoxide and ketone functions is accessible.

Heterolytic processes involving interaction between two functional groups may formally proceed by either of two pathways. Electron pairs may shift through an existing framework of chemical bonds or they may move through space, forming a new bond in the process. These two pathways have been described as frangomeric and anchimeric processes, respectively,[2] as an extension of the concept of frangomeric[3] and anchimeric[4] effects. In a formal sense, four reaction pathways could be defined for the reaction of alkaline hydrogen peroxide[5] with an α,β-unsaturated ketone.[6] The hydrogen peroxide anion could add in either the conjugate or direct mode giving either intermediate **1** or **2** and each of these could collapse to products *via* an anchimeric or a frangomeric process (Scheme I).

The first of these pathways leading to α,β-epoxy ketones is familiar and clearly preferred in most systems. The second pathway corresponds to a vinylogous Baeyer–Villiger oxidation but has never, to our knowledge, been observed. The migration of the group R formally entails heterolysis of the R—C bond whence the analogy with the generalized frangomeric process is valid. The third pathway leading to a dioxirane is unknown. The fourth pathway is a normal Baeyer–Villiger oxidation which virtually never occurs under these conditions.[7] However, one possible exception and some low-yield Baeyer–Villiger oxidations of simple ketones under these conditions have been reported.[8] The pathway is

SCHEME I



(1) Synthetic Quinine Analogs. III. Supported by the U. S. Army Medical Research and Development Command, Contract DADA-17-68-C-80-45. Part II: D. L. Coffen and T. E. McEntee, *J. Org. Chem.*, **35**, 503 (1970).

(2) J. W. Wilt and W. J. Wagner, *J. Amer. Chem. Soc.*, **90**, 6135 (1968).

(3) C. A. Grob, *Bull. Soc. Chim. Fr.*, 1360 (1960); *Angew. Chem., Int. Ed. Engl.*, **8**, 535 (1969).

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(5) (a) E. Weitz and A. Scheffer, *Chem. Ber.*, **54**, 2327 (1921); (b) for recent discussion, see R. D. Temple, *J. Org. Chem.*, **35**, 1275 (1970).

(6) With care the reagent can be used to epoxidize base sensitive unsaturated aldehydes: G. B. Payne, *J. Amer. Chem. Soc.*, **81**, 4901 (1959).

(7) C. H. Hassall, *Org. React.*, **9**, 81 (1957).

(8) H. O. House and R. L. Wasson, *J. Org. Chem.*, **22**, 1157 (1957).