this conclusion on the fact that the smallest of the ratios mentioned above (i.e., $\leq 2.2 \times 10^{-4}$ for *tert*-butylamine) effectively sets an upper limit for the fraction of reaction that can take place from an equilibrated singlet state. Given the fact that the observed reactivity is approximately an order of magnitude higher than could be expected from such a model, we believe that the simplest explanation for the observed triplet reactivity is a direct triplet–diazo reaction leading to the product ground state, since there is no evidence for excited product (azine) formation. It should be noted however, that our conclusion in this case is based on the comparison with other systems reported earlier,[6,12–14] rather than on entirely independent evidence.

To the best of our knowledge, the rate constants reported here are the first values reported for carbene–diazo reactions.[26] Both singlet and triplet carbene states were found to react with the parent diphenyldiazomethane with rate constants of 2.3×10^{10} and 3.4×10^{7} M^{-1} s^{-2}, respectively, in acetonitrile at room temperature. The partition between singlet and triplet processes will be largely determined within the singlet manifold; i.e., at sufficiently high diazo concentrations or in the presence of other scavengers (such as the experiments using 3 M methanol discussed above) the carbenes will be trapped before they have an opportunity to undergo intersystem crossing to the triplet state.

Registry No. $PhC(=N_2)Ph$, 883-40-9; $Ph_2C=NN=CPh_2$, 983-79-9; $Ph_2C=CPh_2$, 632-51-9; $PhCH_2Ph$, 3129-17-7.

---

(26) A rough estimate of 3×10^{7} M^{-1} s^{-1} for $k_{\mathrm{diazo}}^{\mathrm{T}}$ was reported earlier[27] on the basis of a lifetime determination using dielectric loss techniques.

(27) Fessenden, R. W.; Scaiano, J. C. *Chem. Phys. Lett.* **1985**, *117*, 103.

Quaternary Ammonium Tetrakis(diperoxotungsto)phosphates(3–) as a New Class of Catalysts for Efficient Alkene Epoxidation with Hydrogen Peroxide

Carlo Venturello* and Rino D'Aloisio

Istituto G. Donegani S.p.A., Novara, Italy

Received July 8, 1987

The use of quaternary ammonium tetrakis(diperoxotungsto)phosphates(3–) in conjunction with hydrogen peroxide as the primary oxidant in an aqueous/organic biphase system provides an efficient, versatile, and synthetically valuable catalytic method for olefin epoxidation. By this method, a variety of water-insoluble unactivated alkenes, internal or terminal, open-chain or cyclic, isolated or carrying diversified functionalities, were epoxidized in high yields under mild conditions and after relatively short reaction times.

In connection with our works on the oxidation of organic substrates with hydrogen peroxide catalyzed by the tungstate–phosphate ion association,[1,2] we recently succeeded in isolating and structurally characterizing by X-ray diffraction analysis a novel tungsten peroxo complex, tetrahexylammonium tetrakis(diperoxotungsto)phosphate(3–) (**1a**).[3] Interestingly, we observed that this complex, besides being a good stoichiometric reagent for olefin epoxidation in nonprotic solvents, also acted as a catalyst for the same reaction when used in conjunction with hydrogen peroxide as the primary oxidant in an aqueous/organic biphasic system.

$$Q^{+}_{3}\left\{PO_4\left[W(O)(O_2)_2\right]_4\right\}^{3-}$$

1

$$\mathbf{a};\ Q^{+} = \left[(C_6H_{13})_4N\right]^{+}$$
$$\mathbf{b};\ Q^{+} = \left[(C_8H_{17})_3NCH_3\right]^{+}$$
$$\mathbf{c};\ Q^{+} = \left\{\left[C_{18}H_{37}(76\%) + C_{16}H_{33}(24\%)\right]_2N(CH_3)_2\right\}^{+}$$

Examples of well-defined early transition metal peroxo species displaying catalytic activity are scanty in the literature,[4] despite the number of such complexes known.[5] This prompted us to try out whether a general method for the synthesis of epoxides might be worked out, based on the above oxidizing system. In the course of this study, we had to face two main problems, the first one related to the efficiency of the catalyst complex involved and the second one concerned with the control of undesired side effects caused by the oxidizing system itself.

It is known from the phase-transfer technique that the organic structure of the catalyst cation not only influences its ability to transport an anion from the aqueous to the organic phase but also strongly affects the rate of the organic phase reaction.[6] Therefore, various onium moieties of suitable lipophilic character (other than tetrahexylammonium) were preliminarily tested as a counterion in the synthesis of **1**, in the hope of isolating some complex that might exhibit an efficiency higher than **1a** as an oxidation catalyst. This led us to single out two new terms of **1**, **1b** and **1c**, which actually appeared to fulfill our expectations.

---

(1) Venturello, C.; Alneri, E.; Ricci, M. *J. Org. Chem.* **1983**, *48*, 3831.

(2) Venturello, C.; Ricci, M. *J. Org. Chem.* **1986**, *51*, 1599.

(3) Venturello, C.; D'Aloisio, R.; Bart, J. C. J.; Ricci, M. *J. Mol. Catal.* **1985**, *32*, 107.

(4) (a) Jacobson, S. E.; Tang, R.; Mares, F. *J. Chem. Soc., Chem. Commun.* **1978**, 888. (b) Jacobson, S. E.; Muccigrosso, D. A.; Mares, F. *J. Org. Chem.* **1979**, *44*, 921. (c) Chaumette, P.; Mimoun, H.; Saussine, L.; Fischer, J.; Mitschler, A. *J. Organomet. Chem.* **1983**, *250*, 291. (d) Prandi, J.; Kagan, H. B.; Mimoun, H. *Tetrahedron Lett.* **1986**, *27*, 2617.

(5) (a) Sheldon, R. A.; Kochi, J. K. In *Metal-Catalyzed Oxidations of Organic Compounds; Academic*: New York, 1981; Chapter 4. (b) Mimoun, H. In *The Chemistry of Functional Groups, Peroxides*; Patai, S., Ed.; Wiley: New York, 1983; Chapter 15.

(6) Starks, M.; Liotta, C. In *Phase Transfer Catalysis. Principles and Techniques*; Academic: New York, 1978; Chapters 2 and 3.

0022-3263/88/1953-1553$01.50/0

A peculiar feature of the oxidizing system, which emerged from our study, concerned the presence in the reaction medium of acidity due to the heteropoly compound nature of the catalyst. Although a fairly high acidity was allowed in many cases by the biphasic conditions used, ring opening occurred with more acid-sensitive epoxides, thus seriously limiting the scope of the reaction. To solve this problem, we devised an alternative procedure, which ensured the required acidity control while preserving a satisfactory degree of activity of the catalyst.

As a result of these studies, we could develop a very efficient, versatile, and synthetically valuable catalytic epoxidation method. While further work is in progress to clarify how the onium group affects the oxidizing activity of the peroxo anion in complexes **1b** and **1c**, we address the present paper to the description of the preparation of the latter and to the illustration of the results attained with them in the epoxidation of olefins by hydrogen peroxide.

Methyltrioctylammonium and dimethyl[dioctadecyl (76%) + dihexadecyl (24%)]ammonium tetrakis(diperoxotungsto)phosphates **1b** and **1c** are easily prepared according to the general eq 1 by stirring at room temperature an aqueous solution of hydrogen peroxide, tungstic acid, and phosphoric acid with a dichloromethane solution of the commercially available methyltrioctylammonium chloride and dimethyl[dioctadecyl (76%) + dihexadecyl (24%)]ammonium chloride (Arquad 2HT), respectively.

$$4\,H_2WO_4 + H_3PO_4 + 8\,H_2O_2 + 3\,Q^+Cl^- \xrightarrow[CH_2Cl_2 \text{ or } C_6H_6]{\text{water}} 1 + 3\,HCl + 12\,H_2O \quad (1)$$

Q^+ = lipophilic onium group

Evaporation in vacuo of the resultant organic layer affords the desired complexes **1b** or **1c** in excellent yield as a syrup and a white powder, respectively. Elemental analysis, active oxygen content, molecular weight measurement, and spectral data of **1b** and **1c** are consistent with the assigned structure (see the Experimental Section).

In the presence of **1b** or **1c** as the catalyst, a variety of water-insoluble unactivated olefins, internal or terminal, open-chain or cyclic, isolated or carrying diversified functionalities, can all satisfactorily be epoxidized with dilute (16%) hydrogen peroxide. High selectivities to epoxides (80–95%) on both hydrogen peroxide and olefin at a substantially complete conversion of hydrogen peroxide are attained after relatively short reaction times and under mild conditions. The results are summarized in Table I.

As illustrated by entries 1–4 and 7–9 of Table I, the method reported here appears to be especially valuable in epoxidation of simple terminal alkenes, well-known to be poorly reactive with dilute aqueous hydrogen peroxide in the presence of catalysts based on group 5A,B and 6A,B metal oxides.[4d,7] The high-yield synthesis of epichlorohydrin from the weakly nucleophilic allyl chloride (entry 8) is indicative of the effectiveness of the current oxidizing system. In this respect, notice that epoxidation of 1-octene run in the presence of **1b** or **1c** as the catalyst (entry 4) is over in only 45 and 55 min, respectively, instead of 120 min as required with **1a**, under the same reaction conditions and with similar yields.

The method includes two variants, hereinafter called procedure A and B. In procedure A (the most general one), the reaction is conducted by simply applying vigorous stirring, usually at 60–70 °C, to a biphase mixture of water and 1,2-dichloroethane (DCE) or benzene containing hydrogen peroxide, the olefin (usually in a 50–70% molar excess over hydrogen peroxide), and catalytic amounts of **1b** or **1c** until the charged oxidant has almost completely disappeared. A molar ratio hydrogen peroxide/catalyst of ca. 200:1 is commonly employed.

As mentioned above, the aqueous phase of the biphasic system is quite acidic (pH ca. 2.3),[8] likely due to hydrolysis of the peroxo heteropolyanion ($PW_4O_{24}{}^{3-}$) of the catalyst complex. Nevertheless, with most of the substrates reported here, this is not prejudicial to stability of the formed epoxide, under the reaction conditions.

With certain olefins, however, whose epoxides are sensitive to a greater extent to the acid-catalyzed hydrolytic cleavage, such as cyclohexene, 2,4,4-trimethyl-2-pentene, styrene, tetramethylethylene, and 4-vinylcyclohexene (entries 5, 6, 12, 14, 15), the reaction is best performed by using procedure B, where the pH of the aqueous phase is adjusted to a higher value (around 3.3),[8] suitable to largely prevent the ring opening of the related epoxides, under the reaction conditions. This may be achieved by controlled addition of sodium hydroxide to the above two-phase system. In practice, however, it has been found easier to employ as the water phase a solution containing, besides hydrogen peroxide, tungstate and phosphate ions and adjusted in advance to pH 4 (see the Experimental Section). In this way, the required pH value (3.3) is attained all at once at the time the water and organic phase are put into contact.

It has to be emphasized that procedure B as such is less effective than procedure A, as a result of the more extensive hydrolytic alteration of the catalyst at the working pH adopted and of the presence of inorganic salts in the water phase, which have been found to slow down the reaction significantly.[9] These inconveniences, however, are usually offset by the greater reactivity of the substrates (mainly, cyclic or highly substituted open-chain alkenes) for which procedure B is required.

It is noteworthy that epoxidation of 4-vinylcyclohexene (entry 15) proceeds in quite a regioselective manner, mainly affording 1,2-epoxy-4-vinylcyclohexane (**16**) along with a small amount of the 7,8-oxide **17** and the diepoxide **18** (ratio **16**/**17**/**18** of 94.1:2.4:3.5). By use of procedure A instead of B (reaction time 30 min), the formation of **18** was considerably reduced (ratio **16**/**17**/**18** of 96.4:2.6:1). The yield in **16**, however, was about 12% less owing to diol formation.

The unusual stability of the oxirane ring in general observed with the present method, in spite of the acidic conditions under which the reaction is conducted, is ascribable to both the protective effect of the double-phase and the relatively short contact times with the water phase, which are made possible by the high efficiency of the catalysts employed and, as mentioned above, by the use of an excess of olefin. The latter is recommended in order to obtain the best yields of epoxide and to minimize side reactions which can cause destruction of the oxirane ring.

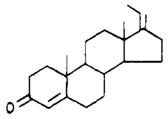
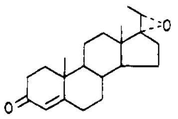
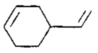
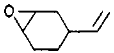
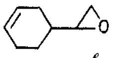
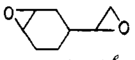
---

(7) (a) Pralus, M.; Lecoq, J. C.; Schirmann, J. P. In *Fundamental Research in Homogeneous Catalysis*; Tsutsui, M., Ed.; Plenum: New York, 1979; Vol. 3, pp 327–343 and references therein. (b) Jacobson, S. E.; Mares, F.; Zambri, P. M. *J. Am. Chem. Soc.* **1979**, *101*, 6946.

(8) Measured at room temperature and based on the reactant-to-catalyst ratios and the phase volumes indicated in Table I.

(9) As an example, in the epoxidation of 1-octene (Table I, entry 4; **1b** as the catalyst) addition of 0.93 mmol of $Na_2WO_4 \cdot 2H_2O$ and 4.65 mmol of an equimolar $NaH_2PO_4 \cdot H_2O$/40% (w/v) H_3PO_4 mixture to the biphase reaction system (with adjustment of the pH of the aqueous phase to its original value 2.3 by aqueous NaOH) led to the lowering of H_2O_2 conversion from 99 to 64%. This retarding effect has been found to be particularly remarkable with foreign salts. Thus, in the above epoxidation, addition of 1.39 mmol of Na_2SO_4 caused H_2O_2 conversion to fall to 59%. The latter dropped to 37% by the addition of 5.58 mmol of Na_2SO_4. These data suggest the occurrence of a salting-out effect, which would make the catalyst reoxidation by H_2O_2 in the water phase more difficult.

Table I. Epoxidation of Olefins with H_2O_2 Catalyzed by Tetrakis(diperoxotungsto)phosphates 1b and 1c[a]

entry	olefin (mmol)	catalyst (mmol)	solvent (mL)	procedure[b]	temp, °C	time, min	product(s)	% yield[c]
1	*O*-acetyleugenol (90)	**1b** (0.38)	DCE (10)	A[d]	60	150	*O*-acetyleugenol oxide (**2**)	94
2	*n*-butyl 3-butenoate (90)	**1b** (0.31)	DCE (10)	A	70	150	*n*-butyl 3,4-epoxybutyrate (**3**)	85
3	1-dodecene (100)	**1b** (0.31)	DCE (10)	A	70	60	1,2-epoxydodecane (**4**)	94
4	1-octene (100)	**1b** (**1c**) (0.31)	DCE (10)	A	70	45 (55)	1,2-epoxyoctane (**5**)	88[e] (89)[e]
5	cyclohexene (100)	**1c** (0.20)	C_6H_6 (20)	B	60	60	epoxycyclohexane (**6**)	88[e]
6	2,4,4-trimethyl-2-pentene (100)	**1b** (0.31)	DCE (10)	B	70	120	3-*tert*-butyl-2,2-dimethyloxirane (**7**)	91[e]
7	methallyl chloride (150)	**1b** (0.38)	C_6H_6 (15)	A[f,g]	70	60	2-chloromethyl-2-methyloxirane (**8**)	85[e]
8	allyl chloride (150)	**1b** (0.38)	C_6H_6 (15)	A[g]	reflux	150	epichlorohydrin (**9**)	85[e]
9	safrole (90)	**1b** (0.31)	DCE (10)	A[h]	60	105	safrole oxide (**10**)	77
10	 (20)[i]	**1c** (0.04)	C_6H_6 (10)	A[j]	50	45	 **11**	92
11	(*E*)-4-decene (100)	**1b** (0.31)	DCE (10)	A	70	45	(*E*)-4,5-epoxydecane (**12**)	94
12	styrene[k] (200)	**1c** (0.51)	C_6H_6 (10)	B[l]	50	120	styrene oxide (**13**)	74(81)[m]
13	(*E*)-4-octene (100)	**1b** (0.155)	DCE (10)	A	70	50	(*E*)-4,5-epoxyoctane (**14**)	91[e]
14	tetramethylethylene (100)	**1b** (0.31)	CH_2Cl_2 (10)	B[g]	40	75	tetramethyloxirane (**15**)	86[e]
15	 (100)	**1c** (0.20)	C_6H_6 (20)	B	60	60	 **16** (83%)[e,n]  **17** (2%)[e]  **18** (3%)[e]	

[a] Unless otherwise stated, all reactions were performed in an aqueous/organic biphase system using 60 mmol of H_2O_2 (12.5 mL of aqueous solution). [b] A, only H_2O_2 present in the aqueous phase; B, $Na_2WO_4{\cdot}2H_2O$ and H_3PO_4 (3 and 15 mol/mol of catalyst, respectively) also present along with H_2O_2 in the aqueous phase (adjusted apart to pH 4 by aqueous NaOH). [c] Unless otherwise noted, the yield (based on H_2O_2 charged) is of product isolated by elution on a column (56 cm × 45 mm) of silica gel (70–230 mesh, 400 g). Elution conditions [(entry), eluant, $R_{f(\mathrm{epoxide})}$, $R_{f(\mathrm{olefin})}$]: (1 and 10), Et_2O/*n*-hexane (7:3), 0.45, 0.80 and 0.43, 0.68; (9), id. (3:7), 0.36, 0.71; (3), id. (1:9), 0.53, 0.92; (12), Et_2O/*n*-pentane (5:95), 0.50, 0.92; (2), id. (3:7), 0.38, 0.68†; (11), *n*-pentane (to eluate the olefin) and then Et_2O/*n*-pentane (3:7), 0.50*, 0.85*. †Determined in Et_2O/*n*-heptane (3:7). *Determined in Et_2O/*n*-heptane (5:95). Product purity [determined by GLC or, for **11**, by HPLC (25 cm × 4 mm i.d. Lichrosorb Si 60 column, 98.5:1.5 *n*-hexane/*i*-PrOH, 1.5 mL/min flow rate)] was in all cases ≥97% except for **4** (93%), which was contaminated by isomeric epoxydodecanes due to the presence (~3%) of internal dodecenes (more reactive) in the starting olefin (GLC/MS analysis). [d] To have a good phase separation, at the end of the reaction Et_2O (50 mL) was added to the reaction mixture. For column chromatography of the organic phase (after removal of Et_2O), 500 g instead of 400 g of silica gel was used. [e] Yield determined by GLC on the organic phase (internal standard). [f] Good phase separation occurs under warm conditions. [g] At the end of the reaction, the aqueous phase was salted out (NaCl) and extracted with Et_2O, and the ethereal extract was added to the organic phase. [h] Dark brown organic phase. [i] Reaction performed with 12 mmol of H_2O_2 (2.5 mL of aqueous solution). [j] Before phase separation, benzene (10 mL) was added to the reaction mixture to dissolve some of the product that precipitated. For column chromatography of the organic phase (after removal of benzene), 240 g instead of 400 g of silica gel was used. [k] At the end of the reaction, only little amounts (<2%) of polymerized styrene was found. [l] The organic phase was eluted on a column (64 cm × 45 mm) of Florisil (100–200 mesh, 440 g) instead of silica gel. [m] Yield determined by titration of the organic phase, after addition of anhydrous Na_2SO_4 (3.8 g) and MgO (0.05 g): Sully, B. D. *Analyst (London)* **1960**, *85*, 895. [n] Cis/trans ~ 1:1 mixture [determined by GLC on a 30 m × 0.32 mm i.d. SPB-1 fused silica capillary column (1.0 μm film) (Supelco); *T*, 70 °C.

The extent of this excess depends on the reactivity of the substrate and the related epoxide and also on the amount of catalyst used. The excess olefin is found substantially unchanged at the end of the reaction. When the olefin was used in a stoichiometric quantity with respect to hydrogen peroxide, a substantial reduction (20–70%) in yield of epoxide was observed.

The reaction appears to be stereospecific, as evidenced by the formation of only (*E*)-4-decene oxide from (*E*)-4-decene and of only (*E*)-4-octene oxide from (*E*)-4-octene (entries 11 and 13) (GLC analysis). Analogously, when subjected to epoxidation, pregna-4(*Z*),17(20)-dien-3-one (entry 10) gave only (*Z*)-17α,20-epoxypregn-4-en-3-one (**11**), within the limits of ^1H NMR detection. The α-attack at C-17 is well established.[10] It is noteworthy that, while epoxidation of pregna-4(*E*),17(20)-dien-3-one with organic peracids has been reported,[11] to the best of our knowledge epoxidation of the *Z* isomer does not seem to have been hitherto described.

In conclusion, we believe the results reported here adequately illustrate the fact that the catalytic use of complexes **1b** and **1c** in conjunction with hydrogen peroxide may provide an efficient and simple route for epoxide synthesis.

Experimental Section

IR spectra were run on a Perkin-Elmer Model 983 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. Mass spectra were obtained on a Varian

---

(10) (a) Fieser, L. F. *Experientia* **1950**, *6*, 312. (b) *Steroid Reactions*; Djerassi, C., Ed.; Holden-Day: San Francisco, 1963. (c) Matthews, G. J.; Hassner, A. In *Organic Reactions in Steroid Chemistry*; Fried, J., Edwards, J. A., Eds.; Van Nostrand Reihold: New York, 1972; Vol. 2, Chapter 9. (d) Oliveto, E. P. *Ibid.*; Vol. 2, Chapter 11.

(11) Batres, E.; Rosenkranz, G.; Sondheimer, F. *J. Am. Chem. Soc.* **1955**, *77*, 4155 and references therein. The olefin used by the authors (mp 136–138 °C) has been identified later as the *E* isomer: (a) Lee, H.; Wolff, M. E. *J. Org. Chem.* **1967**, *32*, 192. (b) Krieger, B.; Kaspar, E. *Chem. Ber.* **1967**, *100*, 1169.

MAT 112 S instrument. GLC analyses were performed on a Varian 3700 instrument, using a 2 m × 2 mm i.d. 5% UCC-W 980 on 60-80 Chromosorb G glass column or a 25 m × 0.32 mm i.d. OV1 bonded-phase, fused silica capillary column (0.1–0.15-μm film) (Carlo Erba Strumentazione), with column temperature programming. TLC were performed on precoated silica gel 60F-254 plates (Merck), and spots were detected by observation under a 254-nm source, by spraying with a potassium permanganate solution, or by exposure to iodine fumes, according to the substrate. The pH measurements were performed by using a Metrohom (E 532) digital pH meter. Molecular weight measurements of tetrakis(diperoxotungsto)phosphates **1b** and **1c** were performed by vapor-phase osmometry (35 °C). Products were identified by combustion analysis and spectral data (when isolated) or by GLC/MS analysis in comparison with authentic samples. Melting points were determined by the Kofler method and are uncorrected.

Materials. Tungstic acid (Merck), sodium tungstate dihydrate (Carlo Erba), and methyltrioctylammonium chloride (Fluka) were used as received. Dimethyl[dioctadecyl (76%) + dihexadecyl (24%)]ammonium chloride (Arquad 2HT) (obtained from AKZO Chemie Italia S.p.A. as a paste containing 75% of active substance) was purified by washings with acetone before use, obtaining a white powder, which was filtered and dried over a porous plate. Phosphoric acid (85%, Carlo Erba) and hydrogen peroxide (40% w/v, Fluka) were used after appropriate dilution. *O*-Acetyleugenol[12] and pregna-4(*Z*),17(20)-dien-3-one[13] were prepared according to literature procedures. *n*-Butyl 3-butenoate was prepared from crotonoyl chloride and 1-butanol following the procedure used by Boots and Boots for preparing the *tert*-butyl isomeric ester:[14] bp 72–73 °C (20 mm); IR (neat) 3085, 3020, 2962, 2936, 2876, 1740, 1643, 1466, 1328, 1254, 1176, 993, 921 cm^{-1}. Anal. Calcd for $C_8H_4O_2$: C, 67.57; H, 9.92. Found: C, 67.70; H, 10.02. All other olefins used in this work were commercial products (Fluka) and were purified by distillation before use. Samples for comparison of noncommercial epoxides were prepared from the corresponding olefins with *m*-chloroperbenzoic acid (MCPBA, Aldrich) following conventional procedures.[15]

Preparation of $[(C_8H_{17})_3NCH_3]^+_3[PO_4[W(O)(O_2)_2]_4]^{3-}$ (1b). A suspension of tungstic acid (2.50 g, 10 mmol) in 7 mL of 30% aqueous H_2O_2 was stirred and heated to 60 °C until a colorless solution was obtained. To this solution, filtered and cooled at room temperature, was added 40% w/v H_3PO_4 (0.62 mL, ca. 2.5 mmol), and the whole was diluted to 30 mL with water. To the resultant solution, 2.09 g of methyltrioctylammonium chloride (97% pure, equivalent to 2.027 g, 5 mmol) in dichloromethane (40 mL) was added dropwise with stirring over about 2 min. Stirring was continued for an additional 15 min. The organic phase was then separated, dried over Na_2SO_4, filtered, and gently evaporated on a rotary evaporator under reduced pressure at 40–50 °C (bath) to give 3.70 g (98.4%, based on the quaternary ammonium salt charged) of an almost colorless syrup: IR (neat, KBr plates) 1088, 1058,[16] and 1035[16] (sh) (P—O), 975 (W=O), 856 and 846 (O—O), 591 and 523 cm^{-1} $(\overline{\text{W—O—O}})_{\text{as,s}}$,[17] other bands at 725, 651,[18] 576,[19] and 549[19] cm^{-1}; molecular weight ($CHCl_3$) M_r(calcd) 2256.7, M_r(obsd) 2190. Anal. Calcd for $C_{75}H_{162}N_3PW_4O_{24}$: C, 39.91; H, 7.24; N, 1.86; W, 32.6; P, 1.37; O (active), 5.68. Found: C, 40.30; H, 7.39; N, 1.84; W, 31.0; P, 1.31; O (active),[20] 5.66.

Preparation of $[[C_{18}H_{37}(76\%) + C_{16}H_{33}(24\%)]_2N(CH_3)_2]^+_3$-$[PO_4[W(O)(O_2)_2]_4]^{3-}$ (1c). The procedure used was the same as for **1b**, except that dimethyl[dioctadecyl (76%) + dihexadecyl (24%)]ammonium chloride [96% pure (~4% H_2O), 2.98 g, 5 mmol[21]] instead of methyltrioctylammonium chloride was used. A white solid (4.33 g, 94%, based on the quaternary ammonium salt charged) was obtained: IR (Nujol, KBr plates) 1087, 1059,[16] and 1035[16] (sh) (P—O), 988 and 970 (W=O), 857 and 846 (O—O), 591 and 524 cm^{-1} $(\overline{\text{W—O—O}})_{\text{as,s}}$,[17] other bands at 721, 651,[18] 575,[19] and 548[19] cm^{-1}; average molecular weight (DCE) $\bar{M}_r$(calcd) 2761.7, $\bar{M}_r$(obsd) 2940. The product softened around 100 °C and melted completely at between 150 and 155 °C with decomposition. Anal. Calcd for $C_{111}H_{234}N_3PWO_{24}$: C, 48.27; H, 8.54; N, 1.52; W, 26.63; P, 1.12; O (active), 4.63. Found: C, 48.52; H, 8.56; N, 1.53; W, 26.75; P, 1.14; O (active),[20] 4.60.

Epoxidation Procedures. A 100-mL glass reactor equipped with a mechanical stirrer, thermometer, and reflux condenser was charged with 1,2-dichloroethane (benzene or dichloromethane) (10–20 mL), the appropriate olefin (90–200 mmol), and tetrakis(diperoxotungsto)phosphate **1b** or **1c** (0.155–0.51 mmol) (see Table I). Then, 12.75 mL of 16% w/v H_2O_2 (60 mmol) (procedure A) or of an aqueous solution containing $Na_2WO_4{\cdot}2H_2O$, H_3PO_4 (3 and 15 mol/mol of **1b** or **1c**, respectively[22]), H_2O_2[23] (60 mmol), and the required amount of NaOH to adjust the pH to 4 (procedure B) was introduced. The resultant biphase mixture was heated with vigorous stirring to the prescribed temperature for the required time (see Table I). The water and organic layers were then separated, and the amount of unreacted H_2O_2 was determined by iodometric titration. In entries 1–3 and 9–12 (Table I), the organic layer was chromatographed over silica gel (or Florisil), with Et_2O/*n*-hexane(-pentane) as the eluant (for details, see Table I). Evaporation of the respective fractions on a rotavapor at atmospheric pressure (entries 2, 11, 12)[24] or under reduced pressure (entries 1, 3, 9, 10) afforded the desired epoxide and led to recovered excess olefin.[25] In the other cases (entries 4–8 and 13–15, Table I), the organic layer was directly analyzed by GLC.

Notice. In the initial stage, the reaction is in general quite exothermic. Operating at a larger scale (>0.2 mol, as H_2O_2), a thermal control is required.

***O*-Acetyleugenol oxide (2)** was obtained by procedure A as an oil, which solidified on standing or by scratching: mp 49–51 °C [Et_2O/petroleum ether (bp 40–70 °C)] (lit.[26] mp 50–51 °C). It had spectra identical with those of an authentic sample prepared by a reported procedure.[26] Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.80; H, 6.30.

***n*-Butyl 3,4-epoxybutyrate (3)** was prepared by procedure A: bp 111–112 °C (20 mm); IR (neat) 3055, 2962, 2936, 2876, 1739, 1466, 1409, 1325, 1265, 1180, 841 cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.94 (t, J = 7.3 Hz, 3 H), 1.39 (sextet, $J \simeq$ 7.3 Hz, 2 H), 1.64 (quintet, $J \simeq$ 6.7 Hz, 2 H), 2.45–2.65 (m, 3 H), 2.84 (dd, $J_1 \simeq J_2$ = 4.9 Hz, 1 H), 3.29 (m, 1 H), 4.14 (t, J = 6.7 Hz, 2 H); MS, *m/e* (relative intensity) M$^+$ absent, 115 (1.5), 103 (14), 102 (13),

---

(12) Tieman, F.; Nagai, N. *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 201.

(13) Bastard, J.; Fetizon, M. R.; Gramain, J. C. *Tetrahedron* **1973**, *29*, 2867.

(14) Boots, S. G.; Boots, M. R. *J. Pharm. Sci.* **1975**, *64*(7), 1262.

(15) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, pp 137–139.

(16) The presence of an absorption in the 1050 cm^{-1} region has been observed with "unsaturated tungstophosphates": Massart, R.; Contant, R.; Fruchart, J.-M.; Ciabrini, J. P. *Inorg. Chem.* **1977**, *16*, 2916.

(17) Due to the presence of four bands in the 500–600-cm^{-1} region (see ref 19) instead of the two expected ones for the tungsten–peroxide stretching,[5b] identification of the latter was made on the basis of the shifts observed for them in the IR spectrum of the complex when prepared with $H_2{}^{18,18}O_2$ (50% atom ^{18}O).

(18) A band near 650 cm^{-1} has been observed in other molybdenum and tungsten peroxo complexes: Mimoun, H.; Seree de Roch, I.; Sajus, L. *Bull. Soc. Chim. Fr.* **1969**, 1481 and references therein.

(19) The 548(9)- and 575(6)-cm^{-1} bands are likely ascribable to the heteropolyanion, analogous to those exhibited by 12-tungstophosphates in the 500–600-cm^{-1} region: Rocchiccioli-Deltcheff, C.; Thouvenot, R.; Franck, R. *Spectrochim. Acta, Part A* **1976**, *32A*, 587.

(20) The product failed to give a satisfactory active oxygen value by normal iodometric methods due to the observed interference of the onium moiety. Active oxygen was determined as follows. An aliquot of the product was treated with a known excess of Na_2SO_3 in 5% aqueous NaOH. The resultant solution was extracted with CH_2Cl_2 in the presence of ClO_4^- ions (to remove the onium group) and then titrated iodometrically ($I_2/Na_2S_2O_3$).

(21) Calculated on the basis of an average molecular formula $C_{37}H_{78}$-NCl as resulting from the given composition (Anal. Calcd for $C_{37}H_{78}NCl$: C, 77.62; H, 13.73; N, 2.45; Cl, 6.19. Found: C, 77.16; H, 13.94; N, 2.46; Cl, 6.34).

(22) No attempt was made to determine the minimum $WO_4{}^{2-}$ ($PO_4{}^{3-}$)/catalyst molar ratio required for obtaining the prescribed pH value (3.3) of the aqueous phase of the resultant biphasic system.

(23) In order to prevent a little decomposition of the oxidant, H_2O_2 should be added only after $Na_2WO_4{\cdot}2H_2O$ has been completely dissolved and acidified with H_3PO_4.

(24) A moderate vacuum [100–150 mm at 50–60 °C (bath)] was applied only at the end in order to ensure complete removal of the solvent.

(25) Under the conditions adopted for the workup, excess styrene (entry 12) could not be wholly recovered.

(26) Schopf, C.; Brass, E.; Jacobi, E.; Jorde, W.; Mocknik, W.; Neuroth, L.; Salzer, W. *Justus Liebigs Ann. Chem.* **1940**, *544*, 30.

85 (100), 74 (13), 57 (56), 56 (62), 43 (20), 41 (57). The product was identical in all respects with a specimen prepared by epoxidation with MCPBA. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.52; H, 8.76.

Safrole oxide (10) was obtained by procedure A as a yellowish oil, which by distillation gave a colorless product: bp 111–112 °C (2 mm) [lit.[27] bp 116–118 °C (4 mm)]. It had spectra identical with those of an authentic sample prepared by a reported procedure.[27] Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.17; H, 5.74.

(*Z*)-17*α*,20-Epoxy-4-pregnen-3-one (11) was prepared by procedure A: mp 178–179 °C (EtOAc); $[\alpha]^{25}_D$ +105° (*c* 2, $CHCl_3$); IR (CH_2Cl_2) 3013, 2945, 2880, 1666, 1615, 1469, 1452, 1434, 1420, 1380, 1270, 1228, 889, 867 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.93 (s, 3 H, C-18 Me), 1.19 (s, 3 H, C-19 Me), 1.37 (d, *J* = 5.7 Hz, 3 H, C-21 Me), 2.98 (q, *J* = 5.7 Hz, 1 H, C_{20}-H), 5.73 (s, 1 H, C_4-H); MS, *m/e* (relative intensity) 314 M^+ (22), 270 (90), 149 (50), 122 (60), 95 (100), 93 (66), 79 (41), 67 (25), 55 (32), 43 (64). The product was identical in all respects with a specimen prepared by epoxidation with MCPBA. Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.25; H, 9.63.

By treatment with $LiAlH_4$ and subsequent oxidation with MnO_2,[11] **11** was converted to 17*α*-hydroxy-pregn-4-en-3-one (17-ethylepitestosterone): mp 151–153 °C (lit.[11] mp 152–153 °C); $[\alpha]^{20}_D$ +81° ($CHCl_3$) [lit.[11] $[\alpha]^{20}_D$ +81° ($CHCl_3$)].

(*E*)-4,5-Epoxydecane (12) was prepared by procedure A: bp 59–60 °C (1 mm); IR (neat) 2962, 2936, 2876, 2860, 1466, 1430, 1380, 1120, 951, 903, 879 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (m, 3 H), 0.96 (m, 3 H), 1.20–1.38 (m, 4 H), 1.38–1.64 (m, 8 H), 2.60–2.73 (m, 2 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.97, 19.44, 22.67, 25.83, 31.78, 34.33, 58.64, 58.80; MS, *m/e* (relative intensity) 156 M^+ (0.75), 138 (10), 113 (20), 99 (6), 95 (18), 85 (10), 71 (18), 67 (40), 57 (84), 55 (100), 43 (76), 41 (62). The product was identical in all respects with a specimen prepared by epoxidation with MCPBA. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 77.18; H, 13.16.

Registry No. **1b**, 112421-56-4; **2**, 69017-35-2; **3**, 112399-92-5; **4**, 2855-19-8; **5**, 2984-50-1; **6**, 286-20-4; **7**, 96-06-0; **8**, 598-09-4; **9**, 106-89-8; **10**, 7470-44-2; **11**, 14928-97-3; **12**, 56740-10-4; **13**, 96-09-3; **14**, 1689-70-9; **15**, 5076-20-0; **16**, 106-86-5; **17**, 5116-65-4; **18**, 106-87-6; H_3PO_4, 7664-38-2; $Na_2WO_4 \cdot H_2O$, 10213-10-2; *O*-acetyleugenol, 93-28-7; *n*-butyl 3-butenoate, 14036-56-7; 1-dodecene, 112-41-4; 1-octene, 111-66-0; cyclohexene, 110-83-8; 2,4,4-trimethyl-2-pentene, 107-40-4; methallyl chloride, 563-47-3; allyl chloride, 107-05-1; safrole, 94-59-7; (*Z*)-pregna-4,17(20)-dien-3-one, 51154-62-2; (*E*)-4-decene, 19398-89-1; styrene, 100-42-5; (*E*)-4-octene, 14850-23-8; tetramethylethylene, 563-79-1; 4-ethenyl-1-cyclohexene, 100-40-3; tungstic acid, 7783-03-1.

---

[27] Noller, C. R.; Kneeland, P. D. *J. Am. Chem. Soc.* **1946**, *68*, 201.

Notes

Regioselective Synthesis of 2- and 3-(Phenylthio)juglone Derivatives

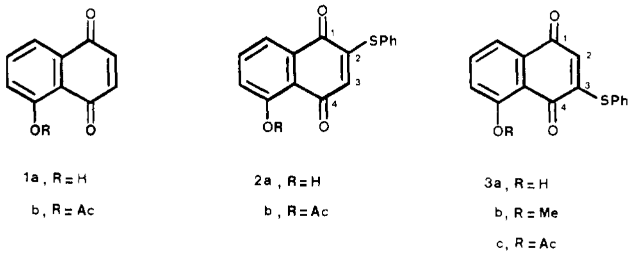
Sylvain Laugraud, André Guingant, Claude Chassagnard, and Jean d'Angelo*

Unité de Chimie Organique Associée au CNRS No. 476, ESPCI, 75231 Paris Cedex 05, France

Received July 20, 1987

Regioisomeric (phenylthio)juglone derivatives **2**, **3**, and related compounds are useful synthons in several approaches to anthracyclinones.[1,2] Indeed, the utility of the phenylthio group (and corresponding sulfoxide) in this field of chemistry is well established, as an element directing the regiochemistry of the Diels–Alder reaction of such unsymmetrically substituted naphthoquinones,[2–4] and as a moiety temporarily preventing aromatization (through tautomerization) of the resulting adducts.[2] An efficient, highly regioselective method for the preparation of target compounds **2** and **3** is therefore required.

Scheme I



In 1951, Thomson claimed that the addition of thiophenol to juglone derivatives proceeds regioselectively, juglone (**1a**) giving the *3-substituted* product **3a**, and juglone acetate (**1b**), the *2-substituted* regioisomeric derivative **2b**.[5,6] However, in constrast with this early communication, the same author noted in 1960:[7] "The addition of toluene-*p*-thiol to juglone acetate is peculiar. As reported some years ago, it leads to the formation of 2-(*p*-tolylthio)juglone acetate. This has been successfully repeated, but recently this reaction has given predominantly the 3-isomer on several occasions!" More recently, Boeckman[1,4] and Kraus[2,3] applied the addition reaction of aromatic thiols on juglone (**1a**) and on juglone acetate (**1b**) to secure regiochemistry in approaches to anthracyclinone systems; in both cases the original observation of Thomson was confirmed.

In connection with our research in the anthracyclinone field,[8] we recently repeated Thomson's work. Surprisingly, these additions proved to be very erratic in our hands! Thus, when the addition reaction of thiophenol on juglone acetate (**1b**) was repeated 13 times, the 3-substituted isomer **3c** was predominantly obtained nine times and the 2-substituted regioisomer **2b**, four times; similarly the addition reaction of thiophenol on juglone (**1a**) was found to be nonreproducible (Scheme I) (see Experimental Section).

---

[1] Boeckman, R. K., Jr.; Delton, M. H.; Dolak, T. M.; Watanabe, T.; Glick, M. D. *J. Org. Chem.* **1979**, *44*, 4396.

[2] Kraus, G. A.; Walling, J. A. *Tetrahedron Lett.* **1986**, *27*, 1873.

[3] Kraus, G. A.; Woo, S. H. *J. Org. Chem.* **1986**, *51*, 114.

[4] Boeckman, R. K., Jr.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.

[5] Thomson, R. H. *J. Chem. Soc.* **1951**, 1237.

[6] Thomson, R. H. *J. Org. Chem.* **1951**, *16*, 1082.

[7] MacLeod, J. W.; Thomson, R. H. *J. Org. Chem.* **1960**, *25*, 36.

[8] Guingant, A.; d'Angelo, J. *Tetrahedron Lett.* **1986**, *27*, 3729.

0022-3263/88/1953-1557$01.50/0