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Transition-Metal Peroxide Reactions. Synthesis of α-Hydroxycarbonyl Compounds from Enolates

E. Vedejs,* D. A. Engler, and J. E. Telschow

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

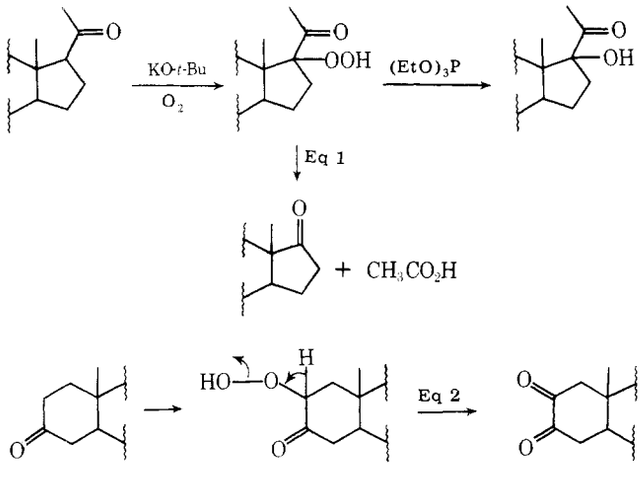
Received June 10, 1977

Enolates of ketones, esters, and lactones are oxidized by MoO_5·Py·HMPA (MoOPH) to give α-hydroxy derivatives. The reaction succeeds with carbonyl compounds having α-methylene or α-methine groups, but enolates from methyl ketones give variable results. The hydroxylation process does not afford products of oxidative C–C cleavage which might be formed from an α-hydroperoxycarbonyl intermediate. If the initial intermediate from an enolate and MoOPH is heated, further oxidation to an α-dicarbonyl compound occurs in poor yield. These results suggest an intermediate having the partial structure $R'C(=O)RCHOMoO_4L_2^-$. Hydroxylation of kinetic enolates derived from unsymmetrical cyclic ketones, cyclohexenones, and certain methyl ketones can be achieved. Acyloin regioisomers are not interconverted under the reaction conditions. Hydroxylation of relatively nonhindered ketones is complicated by aldol condensation between unreacted enolate and the oxidation intermediate. This problem can be minimized by working in dilute solution or by using an inverse addition technique (enolate added to MoOPH). Oxidation of enolate analogues prepared from oximes or *N,N*-dimethylhydrazones has been demonstrated, although yields are low. Stabilized enolates of 1,3-dicarbonyl compounds are not hydroxylated using the typical procedure, and the related dianions afford complex product mixtures.

Introduction

The synthetic problem of enolate hydroxylation has been the object of numerous studies.[1,2,5-7] Barton and co-workers achieved the direct enolate oxygenation of pregnan-20-one, and subsequent hydroperoxide reduction gave the 17α-hydroxy derivative.[1a] Gardner et al. found that modified conditions using in situ triethyl phosphite reduction of the hydroperoxides gave superior yields.[2a,b] In the absence of phosphite, oxidative α-carbon cleavage may occur (eq 1, Scheme I), a reaction which has been studied in several analogous systems.[3] The Barton oxidation cannot be used to introduce a hydroxyl group at an enolizable methyl or methylene group because a second fragmentation pathway (eq 2, Scheme I) is available to the resulting α-hydroperoxy ketone.[4] An α-dicarbonyl compound is formed initially, but further oxidation is facile and complex product mixtures are obtained.

Scheme I



Practical oxygenation of carboxylate dianions can be achieved in a number of examples without in situ peroxide reduction by triethyl phosphite.[5] The carboxylate dianion is apparently sufficiently reactive to attack the peroxide O–O bond so that peroxide does not accumulate as oxygen is introduced. If the dianion is added to excess oxygen, the hydroperoxide can be isolated in moderate yield.[5a,c] Oxidation of amide or lactam enolates by the inverse addition method is also feasible.[6] The same technique can be employed for hydroxylation of α-branched esters,[6a,7] but esters having an α-methylene group behave unpredictably.[5a,6a]

A promising method for synthesis of α-hydroxy derivatives of unbranched carbonyl compounds involves the epoxidation of enol silanes.[8] An α-trimethylsiloxycarbonyl compound can be isolated under nonhydroxylic conditions, and facile hydrolysis to the free alcohol is possible. Acetoxylation of enols with reagents such as mercuric acetate or lead tetraacetate might also be considered,[9] but hydrolysis of α-acetoxy derivatives of ketones is often complicated by interconversion of acyloin regioisomers as will be shown later in this account.

A preliminary report[10] from our laboratory described the direct hydroxylation of enolates with the molybdenum peroxide reagent MoO_5·pyridine·HMPA (MoOPH).[11] Representative ketone and ester enolates were reacted with MoOPH in tetrahydrofuran solution, and hydrolysis of the product gave α-hydroxycarbonyl compounds. The details of the oxidation procedure are the subject of this paper.

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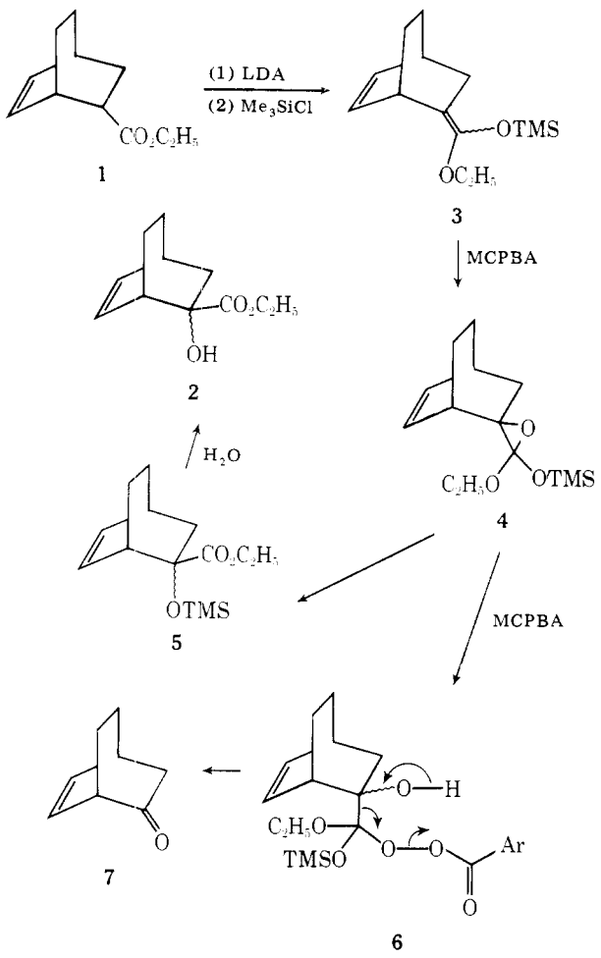
Scheme II



Our interest in enolate hydroxylation began as part of a synthetic project which required conversion of a model ester **1** into the α-hydroxy ester **2**. Small-scale attempts to hydroxylate the enolate with molecular oxygen were not promising, so we examined the oxidation of the derived ketene acetal **3**.

The reaction of **3** with $Pb(OAc)_4$ (1:1 stoichiometry, THF, 0 °C) gave at least three products, and an NMR spectrum of the crude mixture showed only traces of olefinic hydrogens remaining. This reaction was not investigated further. Oxidation with MCPBA did afford some of the desired α-trimethylsiloxy ester **5** (50–60%), but ca. 10% of the cleavage product **7** was inevitably present as well.[12] Since formation of ketone **7** can be explained by epoxidation of **3** and subsequent nucleophilic opening of **4** by a second mole of MCPBA as shown in Scheme II, we turned to the presumably nonnucleophilic epoxidizing agent MoO_5·HMPA.[13] Treatment of **3** with 1 mol of MoO_5·HMPA in methylene chloride at 20 °C resulted in an exothermic reaction, and aqueous workup gave **2** in good yield.

An obvious simplification of the oxidation procedure is to avoid the silylation step and to oxidize the enolate directly. Although this is possible with MoO_5·HMPA, the reagent is hygroscopic and must be dried thoroughly before use. A more convenient reagent for enolate hydroxylation proved to be the highly crystalline and reasonably air-stable complex MoO_5·pyridine·HMPA (MoOPH).[11] This substance reacts with typical enolates in the temperature range −70 to −20 °C, and aqueous workup affords α-hydroxycarbonyl compounds.

Properties of MoO_5·Py·HMPA (MoOPH). Mimoun et al. have described the isolation of crystalline molybdenum peroxides having a variety of ligands.[11] A solution of $H_2Mo_2O_{11}$ is prepared by dissolving MoO_3 in 30% H_2O_2 at 40 °C, and addition of HMPA to this solution affords crystalline MoO_5·H_2O·HMPA in high yield. This operation can be performed routinely by the published method on a 50-g scale, provided that rigorous internal temperature control is maintained during dissolution of MoO_3 (see Experimental Section). Mimoun et al. converted the sparingly soluble MoO_5·H_2O·HMPA directly into MoOPH by treatment with pyridine. We prefer to first prepare MoO_5·HMPA[11] from the hydrate (vacuum desiccator). The anhydrous peroxide is easily soluble in tetrahydrofuran (THF) and addition of one equivalent of pyridine precipitates MoOPH as finely divided crystalline material. In our hands, Mimoun's procedure gave MoOPH contaminated with hydrate, and purification of the product by recrystallization failed because MoOPH decomposes slowly in solution at 25 °C or above.

All of the molybdenum peroxides are light sensitive and decompose to a significant extent after several days of (improper) storage in a clear glass container at room temperature. However, these reagents can be stored for months with no apparent decomposition in a refrigerator shielded from light. We have observed no indication that molybdenum peroxides are shock-sensitive or in any way hazardous in contact with typical organic solvents. Upon heating, small samples of MoOPH decompose with copious gas evolution. Larger samples (0.1–1 g) ignite when placed on a hot plate but do not detonate. We are aware of one instance where a sample of MoO_5·HMPA decomposed with sufficient force to break the jar and char the contents after several weeks of storage at ambient temperature without protection from light.[14] Our experience indicates that no such hazards exist with MoO_5·Py·HMPA (MoOPH) if the reagent is refrigerated between use. Nevertheless, routine precautions are appropriate when handling this high molecular weight peroxide.

Molybdenum peroxides behave as electrophilic oxygen donors and resemble organic peracids in some of their chemical properties. Anionic species such as alkyllithium reagents[15] or nitrile-stabilized carbanions[16] are attacked rapidly by MoO_5·HMPA or by MoOPH at temperatures below 0 °C, resulting in C–O bond formation. Electron-rich neutral substrates including sulfides,[17] *N*-silylamides,[18] or oximes[17] are oxidized more slowly and ambient temperatures are typically necessary. Alkenes can also be oxidized, but temperatures between 40 and 80 °C are usually employed for catalytic epoxidation (Mo catalyst + ROOH)[19] or for stoichiometric epoxidation with MoO_5·HMPA.[13]

Enolate Hydroxylation with MoOPH. The procedure for hydroxylation of carbonyl compounds consists simply of adding the ketone or ester to a 5–10% excess of lithium diisopropylamide in THF–hexane at −70 °C, followed by addition of crystalline MoOPH at a temperature between −70 and −20 °C depending on the individual case. As soon as the sparingly soluble reagent has dissolved, the reaction can be quenched with aqueous sodium sulfite and extracted to recover products. Sodium sulfite apparently reduces unreacted Mo^{VI} species, produces water-soluble salts, and facilitates recovery of organic products. A simple water workup can also be used, but this typically affords emulsions, lower material balance, and highly colored organic-soluble molybdenum-containing side products.

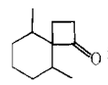
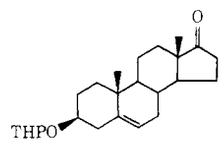
Two reaction pathways can be written for enolate oxidation with MoOPH which are consistent with the known tendency of MoO_5 chelates to transfer one of the peroxidic oxygens rather than the oxo oxygen to potential nucleophiles.[13e] The first (path a, Scheme III) involves cleavage of the O–O bond and formation of **8**, while the second (path b) cleaves an O–Mo bond to give **9**. If path b is the preferred mechanism, then one might expect to isolate α-hydroperoxycarbonyl compounds or their α-carbon cleavage products (Scheme I, eq 1). Since no such products have been detected from any MoOPH hy-

Table I. MoOPH Oxidation of Esters and Lactones[d]

Registry no.	Ester	α-Hydroxy ester	Yield
101-97-3	Ethyl phenylacetate	Ethyl mandelate	58%[a]
106-73-0	Methyl heptanoate	Methyl 2-hydroxyheptanoate	74%[a]
2021-28-5	Methyl 3-phenylpropionate	Ethyl 2-hydroxy-3-phenylpropionate	60%[a]
42858-39-9	Ethyl bicyclo[2.2.2]oct-2-ene-5-carboxylate	Ethyl 5-hydroxybicyclo[2.2.2]oct-2-ene-5-carboxylate	85%[a,c]
19340-56-8	α-Butylbutyrolactone	α-Hydroxy-α-butylbutyrolactone	73%[b]
21303-80-0	γ-Phenyl-γ-methylbutyrolactone	α-Hydroxy-γ-phenyl-γ-methylbutyrolactone	56%[a]

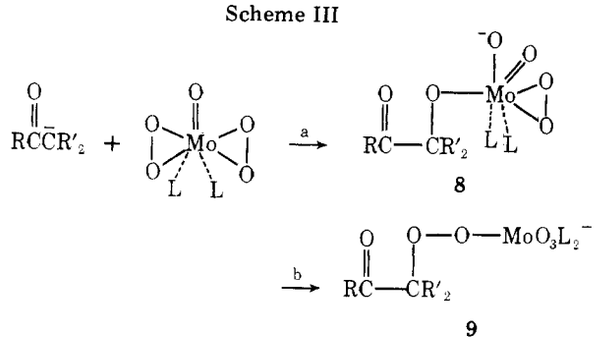
[a] Isolated yield. [b] GLPC yield. [c] Mixture of exo and endo isomers. [d] All oxidations done at −78 °C, 2 h; 1.1 mmol of MoOPH added to enolate from 1 mmol of ester + 1.05 mmol of LDA in THF–hexane.

Table II. Oxidation of Ketones[h]

Registry no.	Ketone	Oxidation temp, °C	α-Hydroxy ketone	α-Diketone
1009-14-9	Valerophenone	−22	60%	13%
		−22[a]	70%	11%
		−44[a]	62%	<2%
451-40-1	Deoxybenzoin	−44	34%	26%
611-70-1	Isobutyrophenone	−22	65%[c]	—
529-34-0	α-Tetralone	−22	48%	*b*
76-22-2	Camphor	−22	70% (endo OH)[d]	<2%
		−22; heat to 60 °C, 16 h	44%[e]	11%
4528-68-1	4,4-Diphenylcyclohexanone	−22	46%	*b*
1444-65-1	2-Phenylcyclohexanone	−44	70% (4:1, **19a–19b**)	<5%
64070-08-2		−22	81%[e]	*b*
19637-35-5		−44	75% (16α OH)[g]	*b*

[a] Inverse addition method, enolate added to MoOPH. [b] Yield of α-diketone not established. [c] For NMR data, see ref 20. [d] See ref 31 for characterization of all four possible isomers. [e] Mixture of diastereomers, stereochemistry not determined. [f] B. M. Trost, M. Preckel, and L. M. Leichter, *J. Am. Chem. Soc.*, **97**, 2224 (1975). [g] Removal of OTHP at pH 3 gave 3β,16α-dihydroxyandrost-5-en-17-one: A. Hassner and P. Catsoulacos, *J. Org. Chem.*, 31, 3149 (1966); K. Fotherby, A. Colas, S. Atherden, and G. Marrian, *Biochem. J.*, **66**, 664 (1957). [h] All oxidations performed by addition of 1.5 mmol of MoOPH to enolate from 1 mmol of ketone + 1.05 mmol of LDA unless noted otherwise, THF–hexane solution. Yields refer to pure material isolated by preparative layer chromatography.

Scheme III



droxylation, path a is considered more plausible.

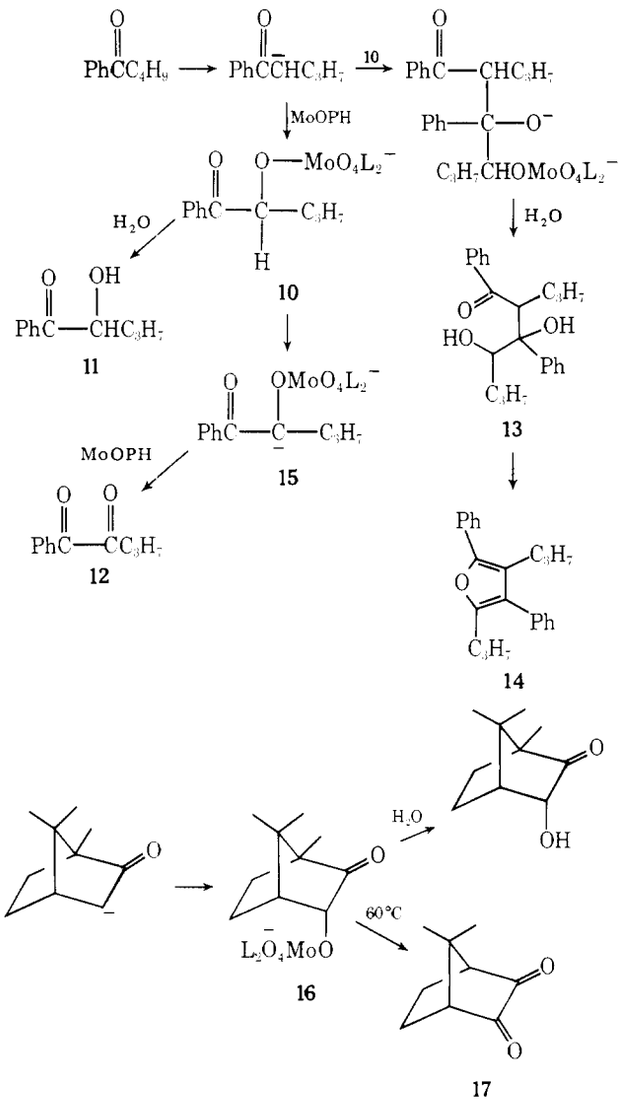
Table I lists typical ester or lactone hydroxylations performed by addition of MoOPH to the enolate at −78 °C. All esters studied were oxidized within 2 h at −78 °C, and no attempt was made to optimize individual cases. By comparison, ketone enolates (Table II) are less reactive. The representative procedure consists of MoOPH addition to the enolate at −22 °C, followed by Na_2SO_3 quenching as soon as the reagent has dissolved (2–5 min). However, results were more reproducible at −44 °C for several of the ketones examined. In general, ketone hydroxylations are more sensitive to reaction conditions, and it is advisable to optimize temperature, concentration, and stoichiometry variables to minimize side reactions.

We have examined the hydroxylation of valerophenone in some detail because this system is especially prone to side reactions under typical conditions (−22 °C, 1.05 *m* LDA, 1.5 mol of MoOPH, 15 min). Although the α-hydroxy ketone **11**[20] is still formed in reasonable yield (60%), the product mixture also contains α-diketone **12**[21] (13%), recovered valerophenone (5%), and two unstable compounds which could not be obtained in pure form. After several hours at room temperature, the unstable products decompose to a new substance (**14**) (22% based on valerophenone) which is assigned the furan structure from NMR data and the absence of carbonyl or hydroxyl absorptions in the infrared spectrum.

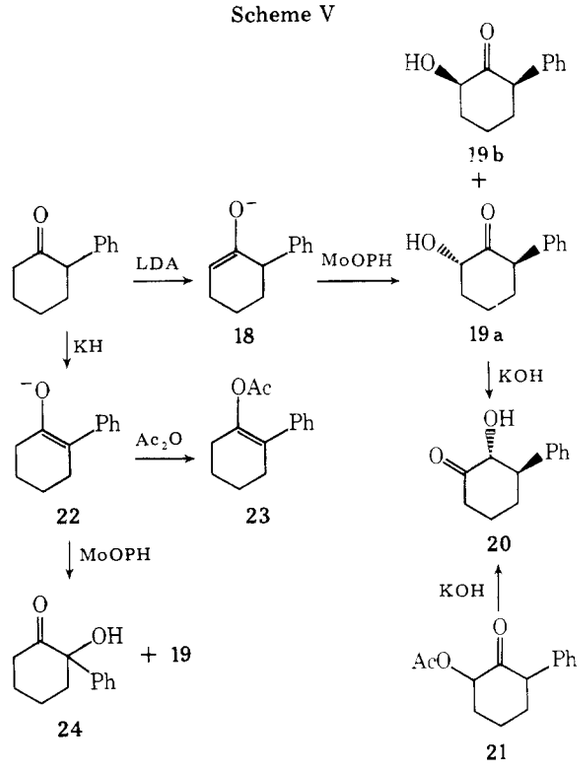
If the experiment is repeated using 1 mol of MoOPH/2 mol of enolate, the yield of **14** increases (42%) at the expense of **11** (43%) and α-diketone **12** (<2%). These conditions maximize contact between starting enolate and the hypothetical oxidation intermediate **10** and allow an aldol condensation to become important (Scheme IV). Cyclization and dehydration of the unstable adduct **13** then leads to the furan **14**. It is significant that 1 mol of MoOPH affords a total of 1.3 mol of products (**11** + **14**) derived from α-oxidation. Clearly, both peroxide rings of MoOPH must be available to some extent for enolate oxidation, and **10** or some derived species must act as the source of electrophilic oxygen after MoOPH is consumed.

Since the formation of **13** is a bimolecular process, it is possible to maximize the yield of **11** by a dilution method. Addition of the enolate to excess MoOPH at −22 °C affords 70% of **11** and 6% of **14** after the usual isolation procedure.

Scheme IV



Scheme V



There is little change in α-diketone yield at −22 °C although an inverse addition experiment at −44 °C gives only traces of **12.**

The pathway leading to α-diketone has not been established, but it seems probable that an anion such as **15** is involved. Direct fragmentation of **15** to **12** and a lower oxidation state of molybdenum is apparently not important at −22 °C since addition of excess LDA *after* addition of MoOPH to the enolate does not change the product ratio. More likely, **15** is subject to further oxidation by MoOPH. As to the origin of **15,** enolate equilibration by proton transfer from **10** to valerophenone enolate provides the simplest rationale and also accounts for the persistent recovery of unreacted starting ketone (5–10%) in spite of all precautions to dry solvents and reagents.

If the solution obtained from MoOPH and valerophenone enolate is heated to 40 °C, the ratio of **12:11** increases. However, numerous other products are formed and the material balance is poor. A more convincing case for thermal fragmentation of a MoOPH oxidation intermediate can be made in the hydroxylation of camphor. At −22 °C, this reaction affords no trace of α-diketone, but thermolysis of the intermediate **16** at 60 °C gives camphor quinone **17**[22] in 11% yield.

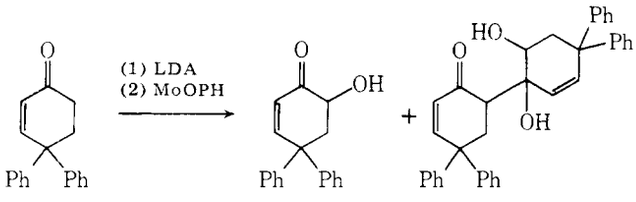
Among the major advantages of MoOPH hydroxylation of lithium enolates is the formation of that acyloin which corresponds to the kinetic enolate in regiochemistry. Thus, addition of 2-phenylcyclohexanone to LDA at −78 °C affords an enolate **18** (Scheme V) and addition of MoOPH at −44 °C gives acyloin diastereomers **19a** and **19b** (7:1) as sole products. Attempts to perform this oxidation at −22 °C result in variable yields and several minor side products. The major diastereomer **19a** is assigned trans stereochemistry on the basis of NMR evidence. One of the low-field methines (4.18 ppm) is a doublet of doublets, J = 11, 6 Hz, while the other methine proton is a broad singlet (4.03 ppm). Clearly, the 4.18 ppm methine is axial while the other is equatorial, a result which is consistent with MoOPH approach from the least hindered enolate face. Treatment of **19a** with methanolic KOH results in rapid conversion into a single acyloin isomer **20.** This substance cannot be detected in the crude MoOPH product by TLC or NMR, so interconversion of acyloin isomers does not occur during MoOPH oxidation or aqueous workup.

Structure **19** has been reported previously by Treibs and Weisenfels as the product obtained from 2-acetoxy-6-phenylcyclohexanone (**21**) by saponification.[23] However, the physical data reported are clearly those of **20** and not of **19a** or **19b.** We have repeated the published sequence (mercuric acetate oxidation of 2-phenylcyclohexanone; KOH saponification) and find that the assigned structure **21** is consistent with NMR data. However, the conditions used to saponify the acetate **21** result in acyloin tautomerization and formation of **20.**

When 2-phenylcyclohexanone is treated with potassium hydride, the more highly delocalized enolate **22** is formed. Enolate trapping by acetic anhydride gives 95% of the tetrasubstituted enol acetate **23.** If the potassium enolate is generated at 20 °C and then treated with 1.05 mol of MoOPH at −44 °C, the acyloin isomer **24**[24] is formed (30%), but the product mixture also contains **19** (24%). Apparently potassium enolate equilibration occurs under these conditions and the less stable enolate **18** is more reactive than **22** toward MoOPH capture. In an attempt to improve conversion to **24,** the enol acetate **23** was treated with methyllithium to form the lithio enolate corresponding to **22** which should be more resistant to enolate equilibration. However, this experiment gave only traces of acyloin products and considerable recovered starting material. Gas evolution was apparent during the experiment,

apparently due to decomposition of MoOPH by the lithium *tert*-butoxide which is present as a product of enol acetate cleavage.

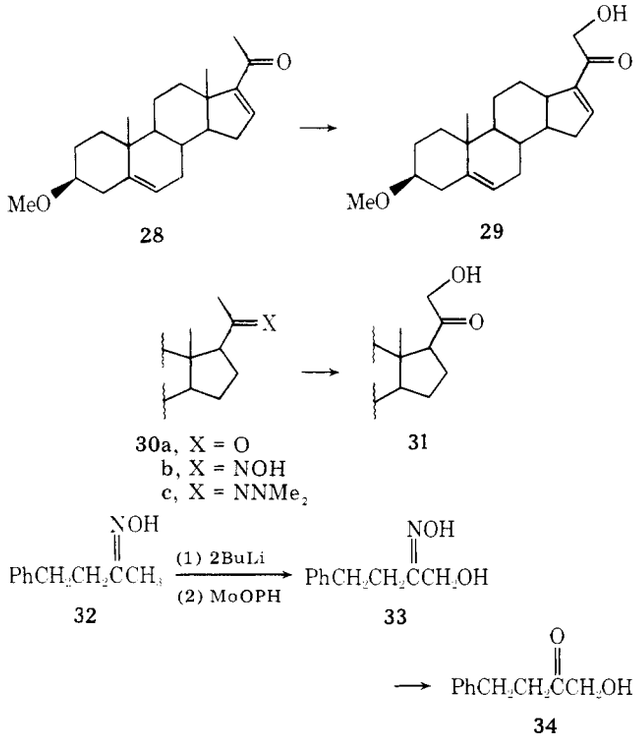
Hydroxylation of cyclohexenone derivatives is unexpectedly difficult according to the standard method (MoOPH added to enolate, −22 °C). Thus, 4,4-diphenylcyclohex-2-enone (**25**)



25 **26** **27**

gives only 17% of acyloin **26**. A crystalline substance **27** corresponding to 1:1 condensation of **25** and acyloin **26** is formed in 61% yield. The aldol condensation structure **27** is consistent with the ^{13}C NMR and ^{1}H NMR evidence, and is further supported by the efficient cleavage of **27** to equimolar amounts of **25** and **26** upon LDA treatment. As in the valerophenone case, aldol condensation can be minimized by inverse addition to give **26** (53%), **27** (7%), and recovered starting material (17%).

The aldol condensation problem is most serious for relatively unhindered enolates. As a result, methyl ketone hydroxylation is often difficult to achieve. Unstable high molecular weight products are formed under all conditions examined, and decomposition (presumably to furans) occurs if the crude products are allowed to stand at room temperature. Inverse addition is essential for the isolation of significant yields of acyloin products. Thus, 3-β-methoxypregna-5,16-dien-20-one (**28**)[25] can be converted into the C-21 hydroxylation product **29** in acceptable yield (52% of **29** + 26% recovered starting material). However, the closely analogous α,β-saturated ketone **30a**[26] suffers extensive aldol condensation and affords only ca. 20% of acyloin **31**. One must resort to LDA-induced retro-aldol fragmentation of the crude mixture to raise the isolated yield of **31** to 58% (36% recovered **30a**).



28 **29**

30a, X = O
b, X = NOH
c, X = $NNMe_2$

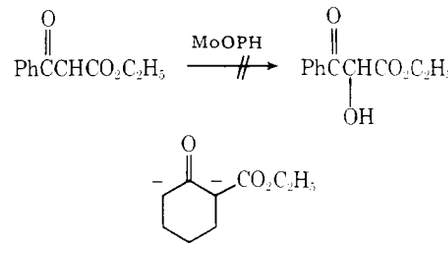
31

32 **33**

34

Unhindered 2-alkanone enolates cannot be hydroxylated with MoOPH in practical yield. Thus, 4-phenyl-2-butanone affords a hopeless mixture of at least eight products (TLC analysis) according to the usual method (LDA; MoOPH at −22 °C). However, the α-hydroxy derivative **34** can be obtained in 30–40% yield by MoOPH treatment of the oxime dianion,[27] followed by oxime hydrolysis via the bisulfite adduct.[28] If desired, the α-hydroxy oxime **33** can be isolated prior to hydrolysis in 36% yield, along with recovered **32**, 41%. Numerous attempts to improve the percent conversion failed, even though complete dianion formation could be demonstrated by sulfenylation. Similar hydroxylation and hydrolysis can be used to convert pregnenone oxime **30b** into **31**, but the yield is only ca. 20% and the percent conversion is again quite low. Oxidation of the *N,N*-dimethylhydrazone anion[29] obtained from **30c** with LDA was also examined briefly. Hydroxylation occurred to form a new substance having CH_2OH NMR signals at δ 4.1, but the product could not be purified. Attempts to cleave the crude hydrazone to **31** using published conditions[29] failed, so this approach was not pursued.

One last attempt at hydroxylation of methyl ketones deserves brief consideration. Enolizable β-keto esters might serve as acyloin precursors by hydroxylation and subsequent decarboxylation. Accordingly, the anion of ethyl benzoylacetate was reacted with MoOPH at 25 °C. Although some reaction took place as evidenced by dissolution of the MoOPH, workup with sodium sulfite gave only recovered ethyl benzoylacetate. We assume that a 1,3-dicarbonyl chelate of Mo^{VI} is formed which resists oxidation. Hydroxylation of the dianion **35** of 2-carboethoxycyclohexanone was also attempted.



35

However, the product mixture was exceedingly complex and the experiment was not pursued.

Conclusions

The MoOPH oxidation procedure is the only direct method for hydroxylation of α-methylene ketone enolates which is successful in typical examples. Hydroxylation of kinetic enolates derived from α,β-unsaturated ketones or methyl ketones is also possible, but complications due to enolate attack upon the initial oxidation intermediate are common. Hydroxylation of branched ketones or branched and unbranched esters and lactones is easily accomplished from the corresponding enolate.

By comparison with the only other direct enolate hydroxylation procedure (enolate + O_2), MoOPH hydroxylation is superior in all cases involving kinetically generated ketone enolates. Based on more limited literature comparisons, we also believe that MoOPH hydroxylation is superior with enolates from unbranched esters or lactones. However, direct oxygenation of branched ester enolates or carboxylate dianions remains the method of choice for suitable substrates due to the high yields and the obvious advantage in using molecular oxygen as the source of hydroxyl.

Experimental Section

Oxodiperoxymolybdenum(aquo)(hexamethylphosphoric triamide). The procedure of Mimoun et al.[11] was used with additional precautions to maintain temperature control. Thus, a 500-mL three-neck flask was charged with MoO_3 (30 g, 0.2 m) and 30% H_2O_2 (150 mL). The mixture was stirred vigorously with a paddle stirrer and the internal temperature was monitored throughout. An oil bath preheated to 40 °C was used to heat the mixture until a mild exo-

thermic reaction was observed. As soon as the internal temperature reached 35 °C, the heating bath was removed and the reaction temperature was maintained between 35 and 40 °C by cooling with a water bath as necessary. After the initial exothermic period, the mixture was heated at 40 °C for a total of 3.5 h with stirring throughout. Failure to maintain internal temperature control results in formation of amorphous side products.

After cooling to 20 °C, the reaction mixture was filtered to remove solids, and the yellow solution was cooled to 10 °C. Hexamethylphosphoric triamide (37.3 g) was added with stirring, and the crystalline precipitate was collected on a Büchner funnel. Recrystallization from methanol (40 °C maximum temperature) gave MoO_5·H_2O·HMPA as yellow needles (50 g, 67%).

Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)(MoOPH). The anhydrous complex MoO_5·HMPA was prepared as described by Mimoun et al.[11] (vacuum desiccator, 0.2 mm, 24 h over P_2O_5). A solution of 18 g (51.9 mmol) of MoO_5·HMPA in dry THF (40 mL) was stirred magnetically and cooled with a water bath (20 °C) while pyridine (4.11 g, 51.9 mmol, distilled from BaO) was added dropwise. The yellow crystalline precipitate was collected, washed with a small amount of THF (5–10 mL), anhydrous ether (ca. 100 mL), and dried under vacuum to give MoOPH as finely divided, free-flowing crystalline material. The MoOPH was placed in a dark glass bottle and stored in a larger container over Drierite in the refrigerator.

Exposure to sunlight or fluorescent light causes gradual darkening of the crystals. After several days of such exposure at 25 °C, the smell of HMPA and pyridine is apparent and the crystals become "sticky". Use of partially decomposed MoOPH gives lower yields and results in gummy precipitates during aqueous workup of hydroxylation mixtures.

Lithium Diisopropylamide (LDA). A stock solution of LDA was prepared in the following way. A 50-mL Erlenmeyer flask was fused to a high vacuum three-way stopcock as the sole outlet. After flame drying, the stopcock was greased, the flask flushed with nitrogen, and 20 mL of commercial *n*-butyllithium (ca. 1.5 M in hexane) was introduced by syringe through a septum placed over the vertical stopcock inlet. Nitrogen flow was maintained through the stopcock ports by means of syringe needles connected to a nitrogen tank and a mineral oil bubbler. The flask was then cooled to −70 °C and dry diisopropylamine (4.6 mL, 33 mmol, distilled from BaO) was added by syringe while gently swirling the mixture in a dry ice bath. To the gelatinous LDA–hexane mixture was then added dry THF (20 mL, distilled from benzophenone–sodium ketyl). After addition of the first milliliter or so of THF, the LDA crystallized and then slowly redissolved. The solution was then allowed to reach ambient temperature under a slow nitrogen stream throughout. A small amount of flocculent precipitate did not interfere with subsequent use and eventually settled to the bottom of the flask. The LDA solution could be stored for 2–3 weeks at ambient temperature (stopcock closed) without deterioration. However, accidental introduction of air resulted in darkening of the solution from pale yellow (depending on the batch of C_4H_9Li) to brown.

Titration of LDA. A variation of the method of Watson and Eastham[30] was used. Thus, commercial menthol (0.312 g, 2 mmol) was dissolved in dry THF (5 mL) under nitrogen at −70 °C and a few crystals of anhydrous phenanthroline were added. The stock solution of LDA was then added dropwise by syringe until the pale yellow color of lithium menthoxide phenanthroline changed to the characteristic rust color of LDA–phenanthroline. The end point comes with little warning, but is easily detected within ±1 drop from a typical syringe needle. At temperatures above −22 °C, the end point is more difficult to detect, and gradual darkening throughout the LDA addition makes titration at 20 °C impossible. The titration was repeatable to ±2% using a 5-mL syringe; identical results were obtained on a 10-mmol scale, and concentrations of 0.6–0.7 M LDA were typical.

General Procedure for MoOPH Oxidation (Method A). Titrated LDA solution (1.5 mL, 0.7 M, 1.05 mmol) was transferred to a flame-dried, nitrogen-purged 50-mL three-neck flask. The LDA was cooled in a dry ice–acetone bath, and a solution of the carbonyl compound (1.0 mmol) in 10 mL of dry THF was added dropwise over 2–3 min. A slow nitrogen flow was maintained through the system at all times. After 15 min stirring at −78 °C, the solution was brought to the desired temperature for oxidation (−78 °C for esters and lactones, −44 to −22 °C for ketones; see Tables I and II). An excess of MoOPH (0.65 g, 1.5 mmol) was then added at once by means of an L-shaped tube sealed at one end and fitted with a male ground-glass joint at the other. The tube was filled with the calculated amount of MoOPH at the start of the experiment and attached to one neck of the reaction vessel. Rotation of the addition tube into the vertical position resulted in addition of MoOPH over a few seconds to the stirred enolate. If the temperature was sufficient for reaction, the mixture rapidly became orange to red and the MoOPH slowly dissolved. Depending on the substrate and temperature, the color remained red or turned various shades of green-blue. After the crystalline reagent had dissolved (typically to form a slightly opaque solution) the reaction mixture was quenched with saturated sodium sulfite solution (5 mL), warmed to 20 °C, and sufficient water was added to give two homogeneous layers. This mixture was stirred 15 min or until no further color change in the organic layer was evident. The layers were then separated, organic products were extracted with a suitable solvent (usually ether), and the organic extracts were washed with 5% HCl to remove pyridine. After drying ($MgSO_4$) and evaporation, the products were isolated by preparative layer chromatography or other means as appropriate.

Inverse Addition Procedure for MoOPH Oxidation (Method B). The enolate was prepared as above at −78 °C in a single-neck flask stoppered with a septum and flushed with nitrogen via syringe needle inlet and exit. A second flask was charged with MoOPH (1.5–2 mol/mol of enolate) and dry THF (10 mL). This flask was connected through septa to the enolate flask by a U-shaped cannula which could be raised or lowered through the septum caps. With the cannula raised above the liquid levels, nitrogen was swept from the enolate flask through the cannula and vented from the MoOPH flask. After the stirred MoOPH suspension was cooled to the desired temperature, the enolate was introduced dropwise by repeatedly dipping the top of the cannula below the level of enolate solution under *gentle* nitrogen pressure. After enolate transfer was complete, the reaction was allowed to proceed as before and was worked up in the same way.

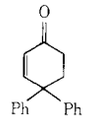
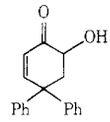
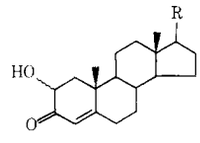
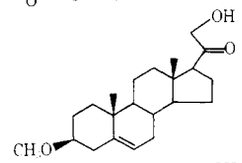
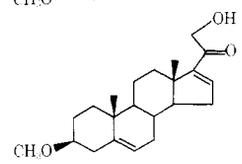
Hydroxylation of Valerophenone Using Method A. The enolate from valerophenone (0.324 g, 2 mmol) was oxidized at −22 °C as described above, with 15 min total oxidation time. After workup with sodium sulfite, the crude product was analyzed by thin-layer chromatography on silica gel, 20% CH_2Cl_2–hexane, two developments. Spots were noted at R_f 0.55, 0.5 (valerophenone), 0.4, 0.25, and 0.2 (major). After 1 h at room temperature in ether solution, a new spot, R_f 0.8, was apparent. After 24 h, the R_f 0.8 spot was intense and the spots of 0.4 and 0.25 had nearly disappeared. Preparative TLC separation gave **14** (0.077 g, 22%, R_f 0.8), diketone **12**[21] (0.043 g, 12%, R_f 0.55), valerophenone (0.015 g, 5%, R_f 0.5), and acyloin **11**[20] (0.195 g, 60%, R_f 0.2). Both **11** and **12** were identified by comparison of NMR spectra with authentic material. The furan **14** was obtained as a colorless oil which darkened slowly upon exposure to oxygen: ^1H NMR ($CDCl_3$, δ) 7.6 (2 H, d, J = 8 Hz), 7.1–7.5 (8 H, m), 2.6 (4 H, br t, J = 7 Hz), 1.2–1.8 (4 H, m), 0.95 (3 H, t, J = 7 Hz), 0.82 (3 H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$,δ) 151, 146.3, 133.9, 132, 129.6, 128.2, 128, 126.5, 126.2, 125.1, 124.3, 121.6, 28.3, 26.2, 22.9, 21.8, 13.9, 13.6; IR (neat, cm^{-1}) 2960 (s), 2930 (s), 2870 (s), 1595 (m), 1495 (s), 1130 (m), 1070 (m), 990 (m); (no absorptions at <3100, or between 1650 and 1800). Anal. Calcd for $C_{22}H_{24}O$: C, 87.80; H, 7.32. Found: C, 87.91; H, 7.30.

Oxidation of Camphor; Thermolysis of the Intermediate to Give Camphorquinone. Camphor was oxidized according to method A, −22 °C, 10 min total reaction time. After the usual workup, preparative layer chromatography (40% ether–hexane) over silica gel gave *endo*-3-hydroxycamphor, 70% (R_f 0.2), identified by comparison with published NMR data of the possible hydroxycamphor isomers.[31] No other hydroxycamphor isomer was detected; the only other significant zone (R_f 0.5) was recovered camphor, 15%.

The experiment was repeated, but after oxidation at −22 °C the solution from enolate + MoOPH was heated for 18 h at 60 °C under a static nitrogen atmosphere. After the usual workup, preparative layer chromatography gave a yellow zone at R_f 0.45, 11%, which solidified after extraction and evaporation. The yellow solid was identical with camphorquinone by direct NMR and TLC comparison with an authentic sample.[22] Hydroxycamphor was isolated in 44% yield from this experiment, but the isomer ratio was not examined.

Hydroxylation of 2-Phenylcyclohexanone. Oxidation according to method A at −44 °C was performed using 0.348 g (2 mmol) of ketone, 3 mL (2.1 mmol) of LDA solution, and 1.3 g of MoOPH (3 mmol). After 1.5 h at −44 °C only traces of MoOPH crystals remained, and the opaque solution was quenched with Na_2SO_3 and worked up as usual. Preparative layer chromatography (20% ether–hexane, 2 developments) gave recovered 2-phenylcyclohexanone (R_f 0.6, 0.035 g, 10%), *trans*-2-hydroxy-6-phenylcyclohexanone (**19a**) (R_f 0.35, 0.236 g, 62%), and **19b** (R_f 0.2, 0.028 g, 8%). After standing under ca. 1 mL of hexane, **19a** slowly solidified. Recrystallization from hexane gave a sample: mp 88 °C; NMR ($CDCl_3$, δ) 7.28 (5 H, br, s), 4.18 (1 H, dd, J = 11, 6 Hz), 4.03 (1 H, br, s), 3.7 (1 H, br s, exchanged by D_2O), 1.4–2.6 (6 H, m). The minor isomer **19b** did not crystallize: NMR

Table III. Oxidation of Enones and Methyl Ketones; Inverse Addition Method

Registry no.	Ketone	α-Hydroxy ketone	
4528-64-7			(53%)
601-57-0	Cholestenone		(40%)[a]
511-26-2	3β-Methoxypregn-5-en-20-one[d]		(20%)[b] (58%)[c]
64045-69-8	3β-Methoxypregna-5,16-dien-20-one[e]		(52%)

[a] M. Tomoeda, M. Ishizaki, H. Kobazashi, S. Kamatomo, T. Koga, M. Inuzuka, and T. Furuta, *Tetrahedron*, 21, 733 (1965). [b] Yield by inverse addition estimated by NMR. [c] Isolated yield after retro-aldol fragmentation by addition of excess LDA to crude hydroxylation mixture. [d] Reference 26. [e] Reference 25.

($CDCl_3$, δ) 7.3 (5 H, m), 4.21 (1 H, m), 3.5–3.7 (2 H, m; one D_2O exchanged), 1.5–2.7 (6 H, m). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.8; H, 7.47. Found: C, 76.0; H, 7.45.

Conversion of 19a to 20. A solution of *trans*-2-hydroxy-6-phenylcyclohexanone (0.1 g) in methanol (1 mL) was added to a solution of KOH (0.1 g) in methanol (5 mL). After 15 min (20 °C) the mixture was diluted with water and extracted with ether. After drying ($MgSO_4$) and evaporation of ether, a crystalline residue was obtained. Recrystallization from ether–hexane gave colorless needles: mp 118–119 °C, identified as **20** from the NMR spectrum ($CDCl_3$, δ) 7.24 (5 H, br, s), 4.28 (1 H, dd, J = 12, 1.5 Hz; 1.5-Hz coupling disappears after shaking with D_2O), 3.6 (1 H, d, J = 1.5 Hz; D_2O exchangeable), 1.5–2.9 (7 H, m). The same substance (**20**) was obtained by saponification of 2-acetoxy-6-phenylcyclohexanone using KOH–CH_3OH according to the literature procedure[23] claimed to afford **19**. No **19a,b** could be detected by TLC analysis (20% ether–hexane).

Oxidation of the Potassium Enolate of 2-Phenylcyclohexanone. A solution of 0.348 g (2 mmol) of 2-phenylcyclohexanone in dry THF (5 mL) was stirred with ca. 3 mmol of KH (Pressure Chemical Co.) at 20 °C under nitrogen. After 20 min the solution was cooled to −44 °C (acetonitrile–dry ice) and MoOPH (0.91 g, 2.1 mmol) was added at once. The mixture was stirred for 10 min at −44 °C, 20 min at −22 °C, and then quenched and worked up as usual. Preparative layer chromatography gave recovered 2-phenylcyclohexanone (0.09 g, 26%), 2-hydroxy-2-phenylcyclohexanone (**24**)[24] (R_f 0.4, 0.118 g, 30%), and a zone containing ca. 80% **19b** by NMR (R_f 0.2, 0.115 g, yield of **19b** ca. 24%) and contaminated by unknown products. The trans isomer **19a** could not be detected in the crude product by NMR or TLC.

Enol Acetate 23 from the Potassium Enolate. A solution of 2-phenylcyclohexanone (0.076 g) in dry THF (2 mL) was stirred with KH (20 mg) for 30 min. Acetic anhydride (50 μL) was added, and after 10 min the solution was diluted with ether, extracted rapidly with water, dried ($MgSO_4$), and evaporated. The colorless residue was analyzed by NMR (CCl_4): 0.3 H at δ 3.5 (unreacted 2-phenylcyclohexanone), relative integral assuming aromatics = 5 H; methyl singlet at δ 1.8 overlapping CH_2 envelope; no signals between δ 3.6 and 7 which might be due to less substituted enol acetate.

MoOPH Oxidation of the Enolate of 4,4-diphenylcyclohex-2-en-1-one. Method A. The oxidation was performed as usual using 4,4-diphenylcyclohex-2-en-1-one (0.248 g, 1.0 mmol), LDA (1.51 mL, 0.73 N, 1.1 mmol), and MoOPH (565 mg, 1.3 mmol). PLC of the residue with 30% ether in hexane gave starting material (38 mg, 15%, R_f = 0.5) and a mixture of 6-hydroxy-4,4-diphenylcyclohex-2-en-1-one **26** and **27**. A second preparative layer separation of the mixture using 10% ethyl acetate in benzene gave **26** (38 mg, 17%): R_f = 0.48; mp 182–183 °C; NMR ($CDCl_3$, δ) 2.56 (1 H, t, J = 12 Hz), 3.01 (1 H, ddd, J = 2.0 Hz), 3.60 (1 H, OH), 4.17 (1 H, ddd, J = 2.5, 5.0, 12 Hz), 6.20 (1 H, d, J = 10 Hz), 7.0–7.4 (11 H, m); IR (cm^{-1}, $CHCl_3$) 3470 (s), 2985 (m), 1667 (s), 1582 (m), 1440 (m), 1429 (m), 1242 (m), 1136 (w), 1103 (s), 1008 (m), 901 (m), 887 (m), 826 (m), 690 (s), 658 (w); exact mass determined, 264.11493; calcd for $C_{18}H_{16}O_2$, 264.11455; ^{13}C NMR ($CDCl_3$, ppm) 44.03 (td, J = 4, 135 Hz), 51.06 (s), 70.21 (dq, J = 5, 142 Hz), 125.78 (d, J = 167 Hz), 126.96 (dt, J = 7, 161 Hz), 127.01 (dt, J = 6.5, 156 Hz), 127.25 (dt, J = 7, 162 Hz), 127.74 (dt, J = 6.5, 157 Hz), 128.70 (dd, J = 7.0, 161 Hz), 128.74 (dd, J = 7.0, 160 Hz), 142.85 (s), 147.06 (s), 157.19 (dd, J = 7.9, 16 Hz), 200 (s), and the condensation product **27** (160 mg, 61%): R_f = 0.6; mp 153–155 °C; NMR ($CDCl_3$, δ) 2.02–3.1 (6 H, m), 3.65 (1 H, dt, J = 2.0, 10 Hz), 5.90 (1 H, s, OH), 5.85 (1 H, d, J = 11 Hz), 6.20 (1 H, d, J = 10.5 Hz), 7.0–7.5 (22 H, m); IR (cm^{-1}, $CHCl_3$) 3440 (m), 3010 (m), 2960 (w), 1653 (s), 1595 (m), 1492 (s), 1445 (s), 1375 (m), 1230 (s), 1070 (m), 1060 (m), 1037 (w), 932 (m), 840 (w), 691 (s); ^{13}C NMR ($CDCl_3$, ppm) 37.80 (tm, J = 131 Hz), 39.85 (tm, J = 131 Hz), 46.26 (dm, J = 128.5 Hz), 49.34 (s), 50.95 (s), 66.18 (dm, J = 142.5 Hz), 73.39 (s), 126.13 (dt, J = 2.0, 85 Hz), 126.29 (dt, J = 2.0, 8.0 Hz), 126.76 (dt, J = 7, 159 Hz), 127.11 (dt, J = 7, 159 Hz), 127.16 (dt, J = 7, 155 Hz), 127.61 (dt, J = 6.4, 157 Hz), 128.04 (dd, J = 6, 157 Hz), 128.24 (dd, J = 7, 160 Hz), 128.35 (dd, J = 5, 156 Hz), 128.59 (dd, J = 8, 162 Hz), 128.76 (dd, J = 7.8, 161 Hz), 129.32 (d, J = 165.5 Hz), 139.08 (dd, J = 4.6, 157 Hz), 142.13 (sq, J = 65 Hz), 146.23 (sq, J = 8 Hz), 147.66 (sm), 148.06 (sm), 157.16 (dd, J = 7.8, 161 Hz), 204.25 (sm). Anal. Calcd: C, 84.41; H, 6.39. Found: C, 84.41; H, 6.40.

MoOPH Oxidation of 4,4-Diphenylcyclohex-2-en-1-one Using Inverse Addition. Method B. 4,4-Diphenylcyclohex-2-en-1-one (124 mg, 0.5 mmol) was dissolved in dry THF (6 mL) and added to LDA (0.79 mL, 0.70 N, 0.55 mmol) at −23 °C. After 5 min, this solution was added via cannula to MoOPH (282 mg, 0.65 mmol) in THF (10 mL) at −22 °C. An additional amount of THF (2 mL) was used to ensure complete transfer of enolate solution. The light yellow MoOPH solution turned olive green during the addition of the enolate solution. After 5 min, the reaction was quenched with cold saturated sodium sulfite (3 mL). The usual workup and PLC as described previously gave 6-hydroxy-4,4-diphenylcyclohex-2-en-1-one (**26**) (70 mg, 53%), starting material (21 mg, 17%), and self-condensation product **27** (17 mg, 7%).

Retro-aldol Fragmentation of the Condensation Product 27 from MoOPH Oxidation of 4,4-Diphenylcyclohex-2-en-1-one. The condensation product **27** (150 mg, 0.29 mmol) was dissolved in THF (3 mL) and added to LDA (0.93 mL, 0.65 mmol, 0.7 N) at −78 °C. After 5 min at −78 °C, the mixture was stirred at ambient temperature for 30 min. The reaction was quenched with water (5 mL) and extracted with ether (3 × 15 mL), and the combined ether extracts were dried over Na_2SO_4 and evaporated. PLC of the residue as before gave 6-hydroxy-4,4-diphenylcyclohex-2-en-1-one (**26**) (66 mg, 86%) and 4,4-diphenylcyclohex-2-en-1-one (**25**) (64 mg, 89%).

Preparation of 21-Hydroxy-3β-methoxypregna-5,16-dien-20-one (29). Prepared using method B from 3β-methoxypregna-5,16-dien-20-one[25] (164 mg, 0.5 mmol), LDA (0.78 mL, 0.70 N, 0.55 mmol) and MoOPH (283 mg, 0.65 mmol) at −22 °C. PLC of the residue on silica gel using 20% ethyl acetate in hexane as eluent gave colorless needles of **29** (90 mg, 52%, R_f 0.4): mp 138–139 °C (from ether–hexane); NMR ($CDCl_3$, δ) 0.98 (3 H, s), 1.08 (3 H, s), 0.8–2.6 (18 H, m), 3.08 (1 H, m), 4.48 (2 H, AB, J = 21 Hz), 5.37 (1 H, m), 6.68 (1 H, m); IR (cm^{-1}, $CHCl_3$) 3480 (m), 2940 (s), 1664 (s), 1582 (m), 1450 (m), 1432 (m), 1370 (s), 1338 (m), 1322 (s), 1085 (s), 968 (m), 950 (m), 940 (m), 915 (m), 877 (w), 840 (w), 655 (w); exact mass determined, 344.23514; calcd for $C_{22}H_{32}O_3$, 344.23443; starting material (70 mg, R_f = 0.6, 42%).

Preparation of 21-Hydroxy-3β-methoxypregn-5-en-2-one. 3β-Methoxypregn-5-en-20-one[26] (330 mg, 1.0 mmol) in dry THF (6 mL) was added to LDA (1.72 mL, 1.2 mmol, 0.70 N) at −22 °C. The resulting yellow solution was stirred for 10 min at −22 °C and MoOPH (693 mg, 1.6 mmol) was added all at once. After 5 min, the light orange homogeneous mixture was quenched with saturated Na_2SO_3 (6 mL) and the aqueous solution was extracted with chloroform (2 × 20 mL) and with ether (2 × 20 mL). The combined extracts were dried over Na_2SO_4, evaporated, and further dried under vacuum (0.30 mm) over P_2O_5 for 2 h. The crude material (a mixture of acyloin and condensation product) was then dissolved in THF (8 mL), cooled to −22 °C, and LDA (4.3 mL, 3.0 mmol, 0.70 N) was added. The mixture was stirred at ambient temperature for 30 min and quenched with water (10 mL). Extraction with ether (3 × 25 mL) gave an oily solid. PLC of the residue using 30% ether in hexane gave the acyloin **31** (199 mg, 58%): R_f = 0.31; mp 140–141 °C (from acetone); NMR ($CDCl_3$, δ) 0.69 (3 H, s), 3.36 (3 H, s), 0.8–2.5 (21 H, m), 3.02 (1 H, m), 4.15 (1 H, AB, J = 20 Hz), 5.35 (1 H, m); IR (cm^{-1}, CHCl) 3480 (m), 3008 (s), 1702 (s), 1520 (m), 1470 (m), 1432 (m), 1385 (m), 1215 (s), 1020 (s), 1060 (m), 928 (m), 750 (s), 660 (s), 621 (w); exact mass determined, 346.25079; calcd for $C_{22}H_{34}O_{31}$ 346.25079. Starting material (124 mg, R_f = 0.6, 36%) was also isolated.

Preparation of 3β-Methoxypregn-5-en-20-one Oxime (30b). The oxime was prepared by the method of Rao and Price[32] and was recrystallized from acetone: mp 220–222 °C (lit. mp 224–225 °C); NMR ($CDCl_3$, δ) 0.65 (3 H, s), 1.02 (3 H, s), 1.90 (3 H, s), 3.10 (1 H, m), 2.26 (3 H, s), 5.35 (1 H, m), 8.0 (1 H, broad OH), 0.8–2.8 (20 H, m).

Hydroxylation; Hydrolysis of 4-Phenylbutanone Oxime (32). The dianion[27] of **32** was prepared from 0.326 g (2 mmol) of oxime and 4.1 mmol of n-butyllithium (dropwise addition, −22 °C) in THF (10 mL), nitrogen atmosphere. After addition of MoOPH (0.87 g, 2 mmol) at −78 °C, the brown mixture was stirred for 1 h at −78 °C and 20 min at −22 °C, and the resulting green solution was quenched with 5% HCl (10 mL). Sufficient water was added to dissolve precipitated solids (ca. 75 mL), the products were extracted with ether (2 × 25 mL) and dried ($MgSO_4$), and the solvent was removed (aspirator). In an identical run, 1-hydroxy-4-phenyl-2-butan-2-one oxime (**33**) was isolated by preparative TLC (silica gel, 1:1:2 ether–methylene chloride–hexane, R_f 0.3), 0.132 g (36%), together with unreacted **32** (0.134 g, 41%). Traces of **34** were also present, R_f 0.5, ca. 10 mg. The hydroxy oxime **33** was recrystallized from ether: mp 37–41 °C; NMR ($CDCl_3$, δ) 2.45–2.60 (2 H, m), 2.60–2.95 (2 H, m), 4.33 (2 H, s), 5.8 (2 H, broad), 7.2 (5 H, s); IR (cm^{-1}, CHCl) 3600 (m), 3360 (m, broad), 2930 (m), 1601 (w), 1494 (m), 1452 (s), 1369 (s), 1078 (m), 1030 (m), 938 (s), 695 (s); exact mass determined 179.09463; calcd for $C_{10}H_{13}NO_2$ 179.09463.

The crude hydroxylation product from the first run was refluxed with 0.6 g of $NaHSO_3$ in 10 mL of 50% ethanol, 3 h (Pines et al.).[28] Ethanol was then evaporated and the white crystalline suspension was stirred with 10% HCl (10 mL) and ether (20 mL) until no solids remained, ca. 20 min. Extraction with ether (2 × 20 mL), drying ($MgSO_4$), and evaporation gave an oil which contained two major spots by TLC (ether–methylene chloride–hexane, 1:1:2) and traces of two other products. Preparative layer separation gave **34** (1-hydroxy-4-phenylbutan-2-one), 0.125 g (38%), as a crystalline solid: mp 43–44 °C (needles, from ether) (lit.[33] mp 44–45 °C); NMR ($CDCl_3$, δ) 3.68 (2 H, m), 2.93 (2 H, m), 3.5 (1 H, OH), 4.10 (2 H, s), 7.17 (5 H, m); IR (cm^{-1}, $CHCl_3$) 3400 (s), 3020 (m), 2970 (m), 1730 (s), 1608 (m), 1505 (m), 1460 (m), 1070 (s), 1085 (s), 750 (s), 700 (s); exact mass determined, 164.08373; calcd for $C_{10}H_{12}O_2$, 164.08383.

MoOPH Oxidation of 3β-Methoxypregn-5-en-20-one Oxime. To 3β-methoxypregn-5-en-20-one oxime (**30b**) (150 mg, 0.44 mmol) in THF (5 mL) at −78 °C was added n-BuLi (0.590 mL, 1.49 M, 0.90 mmol). The cloudy solution was warmed to 0 °C, stirred for 30 min, and MoOPH (189 mg, 4.35 mmol) was added all at once. With the addition of MoOPH, the mixture turned orange and then quickly cleared up to a homogeneous light yellow solution. The mixture was quenched with dilute HCl (4 mL) and was extracted with chloroform (2 × 15 mL) and with ether (2 × 15 mL). After drying the combined extracts over Na_2SO_4 and evaporation of the solvents, the crude oxime mixture was hydrolyzed according to the procedure of Pines et al.,[28] as described for preparation of **34**. PLC of the residue as described previously gave 3β-methoxypregn-5-en-20-one (63 mg, 42%) and 21-hydroxy-3-methoxypreg-5-en-20-one (30 mg, 20%).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—**11**, 20907-23-7; **12**, 20895-66-3; **14**, 64045-70-1; **19a**, 53474-94-5; **19b**, 64045-71-2; **20**, 64045-72-3; **26**, 64045-73-4; **27**, 64045-74-5; **29**, 64045-75-6; **30b**, 64045-76-7; **31**, 64045-77-8; **32**, 6944-54-3; **33**, 64045-78-9; **34**, 20296-07-5; MoOPH, 23319-63-3; MoO_5·H_2O·HMPA, 23319-56-4; pyridine, 110-86-1; *endo*-3-hydroxycamphor, 21488-68-6; camphorquinone, 465-29-2; **24**, 4829-02-1; MoO_5·HMPA, 25377-12-2.

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Studies on the Selective Preparation of Aromatic Compounds. 14. An Attempt to Prepare All the Possible Deuterated Phenols by the Reductive Dehalogenation of the Corresponding Halophenols with Raney Alloys in an Alkaline Deuterium Oxide Solution[1]

Masashi Tashiro,* Akio Iwasaki, and Gouki Fukata

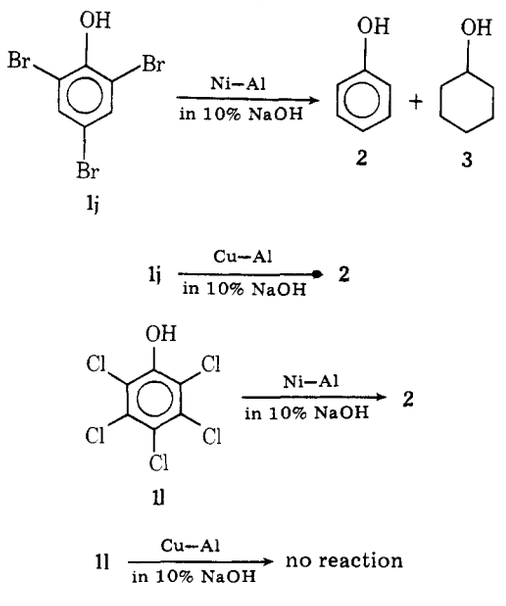
Research Institute of Industrial Science, Kyushu University 86, Hakozaki, Higashi-ku, Fukuoka 812 Japan
Received April 13, 1977

The reductive dehalogenation of the 19 halophenols **1a–s** was carried out with Raney alloys such as Ni–Al and Cu–Al in 10% NaOD–D_2O solution in order to obtain all the possible deuterated phenols. It was found that the reaction of the bromophenols with Raney Cu–Al alloy gives fairly selectively the corresponding deuterated phenols, but chlorophenols and bromochlorophenols give extensive further exchange of phenyl hydrogen atoms. 2-Bromophenoxyacetic acid (**6**) was reduced with Raney Ni–Al alloy to afford phenoxyacetic-2-*d* acid (**8**) in high purity without the further exchange of hydrogen atoms.

It has been known that[2-7] some halophenol derivatives could be reduced with Raney Ni–Al alloy in alkaline solution to afford the corresponding phenols. However, we recently found that[8] (i) the reduction of 2,4,6-tribromophenol (**1j**) with Raney Ni–Al alloy in 10% NaOH solution at 80 °C afforded phenol (**2**) with the formation of cyclohexanol (**3**) as a by-product, (ii) Raney Cu–Al alloy gave only **2** without any amount of **3**, and (iii) the former alloy was active for the reduction of chlorophenols as well as bromophenols; however, the latter alloy could reduce only bromophenols but not chlorophenols (Scheme I).

These results suggest that the desired deuterated phenols may be prepared by the reduction of the corresponding halophenols with the Raney alloys in an alkaline deuterium oxide solution.

Scheme I

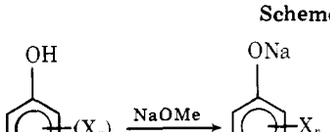


We wish to report the use of the Raney alloys for the reduction of halophenols (**1a–s**) in 10% NaOD–D_2O solution.

Results and Discussion

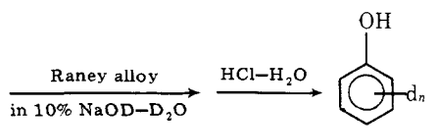
There are 19 possible isomers of the deuterated phenols. In order to obtain all of the possible deuterated phenols, the corresponding halophenols **1a–s** were reduced with Raney alloys such as Ni–Al and Cu–Al in 10% NaOD–D_2O solution which was prepared from D_2O (99.8%) and the calculated amount of NaOMe. To keep the D_2O solution in high isotopic purity, the halophenols **1** were converted to their sodium salts

Scheme II



1 **4**

a, 2-Br	g, 3,5-Br_2
b, 3-Br	h, 2,4-Cl_2, 3-Br
c, 4-Br	i, 2,4,5-Br_3
d, 2,3-Cl_2	j, 2,4,6-Br_3
e, 2,4-Br_2	k, 2,3,4,5-Br_4
f, 2,6-Br_2	l, 2,3,4,5,6-Cl_5



5

a, 2-*d*	g, 3,5-d_2
b, 3-*d*	h, 2,3,4-d_3
c, 4-*d*	i, 2,4,5-d_3
d, 2,3-d_2	j, 2,4,6-d_3
e, 2,4-d_2	k, 2,3,4,6-d_4
f, 2,6-d_2	l, 2,3,4,5,6-d_5

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