A STUDY OF THE REDUCTIVE CLEAVAGE OF VINYL AND ALKYL PHOSPHORYL ESTERS

Thesis by
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Acknowledgments

I wish to thank Professor Robert E. Ireland for his patient guidance during the past four years. I would also like to express my appreciation to the taxpayers of the United States for providing the funds for the NDEA fellowship which served as my source of support.

Abstract

A number of alcohols and enolate anions were deoxygenated by reduction of the corresponding diethylphosphate or tetramethylphosphorodiamidate esters. Lithium-amine solutions were successful reducing agents in most cases, and, in addition, tetramethylphosphorodiamidate esters were cleaved by the adduct of lithium and biphenyl in tetrahydrofuran.

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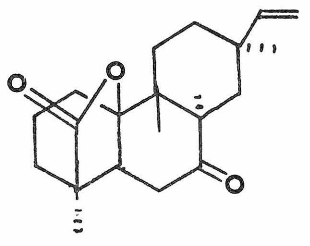
Historical

The work to be described herein had its beginning in a consideration of possible methods of constructing the skeleton needed for the total synthesis of the mold metabolite, rosenonolactone (1) (1), a diterpenoid lactone possessing an unusual trans-syn-trans system of ring fusions. While one pathway, using the oxidative cyclization of alcohol 2 to ether 3, had already been shown to be feasible (2), the



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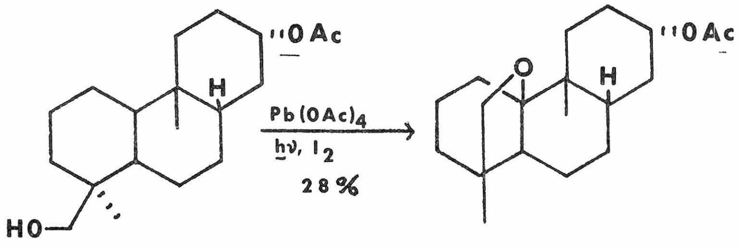
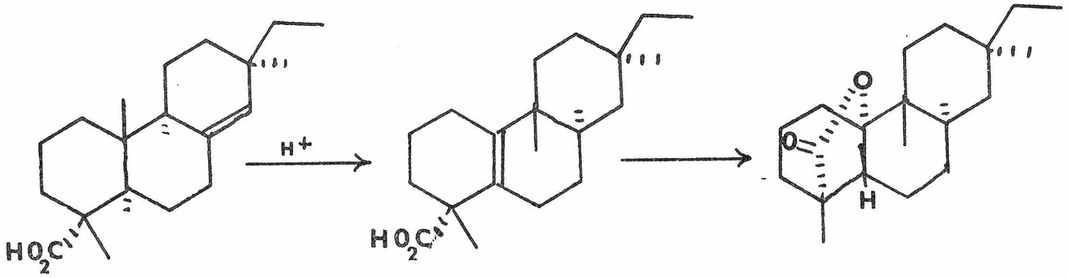
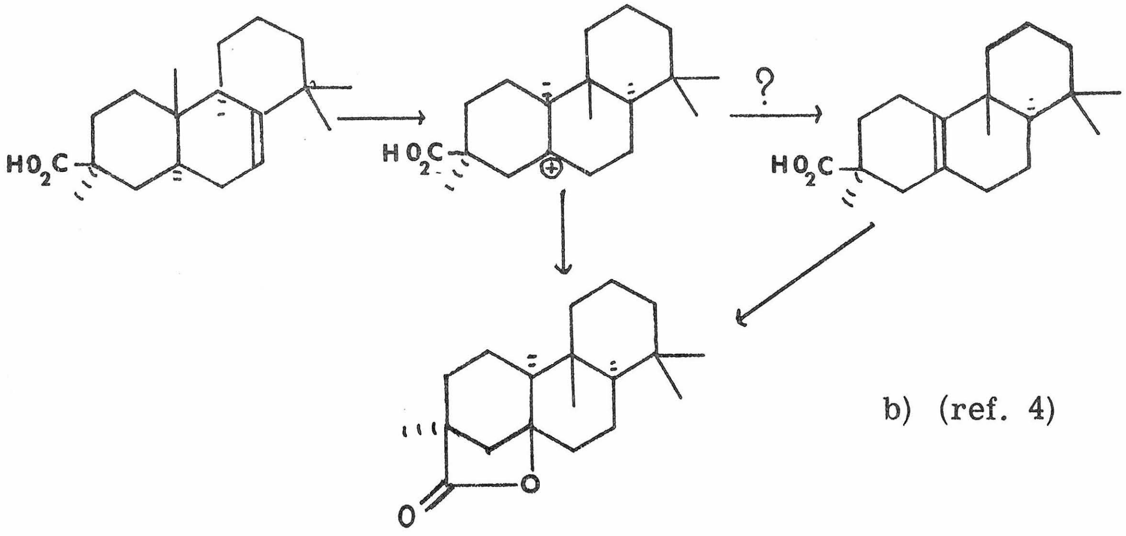


2 3

low yield of this reaction coupled with a many-step synthesis of alcohol 2 provided encouragement for the search for alternative schemes. An attractive possibility was suggested by rearrangements of the type shown in Figure 1.



a) (ref. 3)



b) (ref. 4)

Figure 1

Both of these rearrangements involve protonation of an olefinic bond, successive 1, 2-trans-diaxial hydride and methyl shifts, and closure to a γ-lactone. Similar events would lead to the desired lactone skeleton, providing that the chain of events depicted in Figure 2 could be initiated in a step in which a bond trans to the

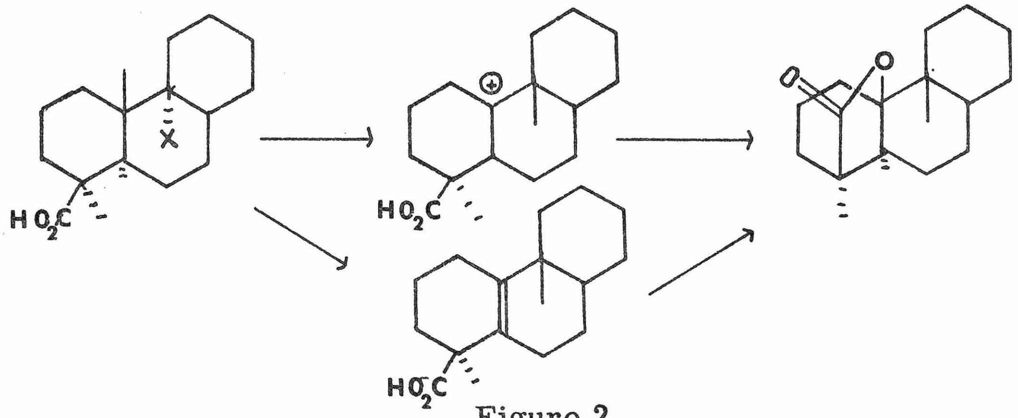
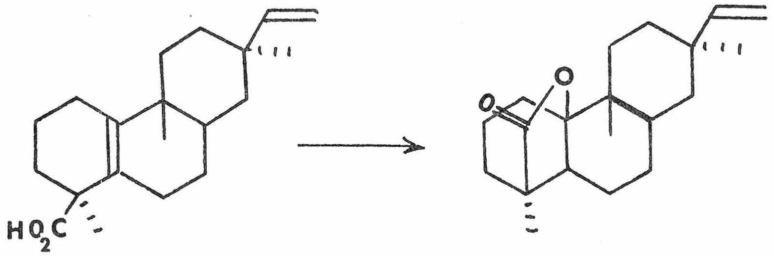
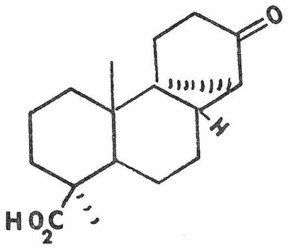


Figure 2

angular methyl is broken. As the figure shows, this rearrangement differs from those in Figure 1 in that the cyclization proceeds by attack <u>cis</u> to the departing angular methyl. However, this should present no problem if the olefinic intermediate is formed. Indeed, lactonization of a similar olefinic acid is one of the steps in an existing synthesis of rosenonolactone (5).



A procedure which might provide the necessary initiation involves the acid catalyzed opening of cyclopropyl ketone 4. Precedent for this sort of reaction has recently been reported by Stork and co-workers, who carried out the transformations illustrated in Figure 3. The formation of the bicyclic products in the first reaction shown takes place in a series of steps like the ones needed for the desired rearrangement.



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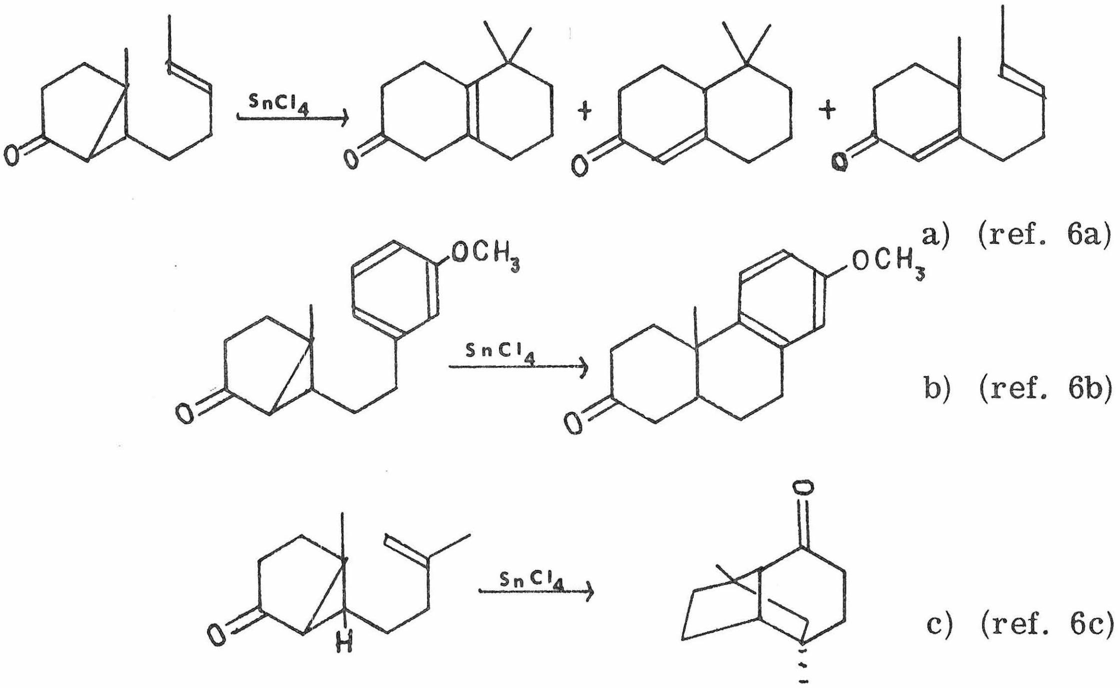
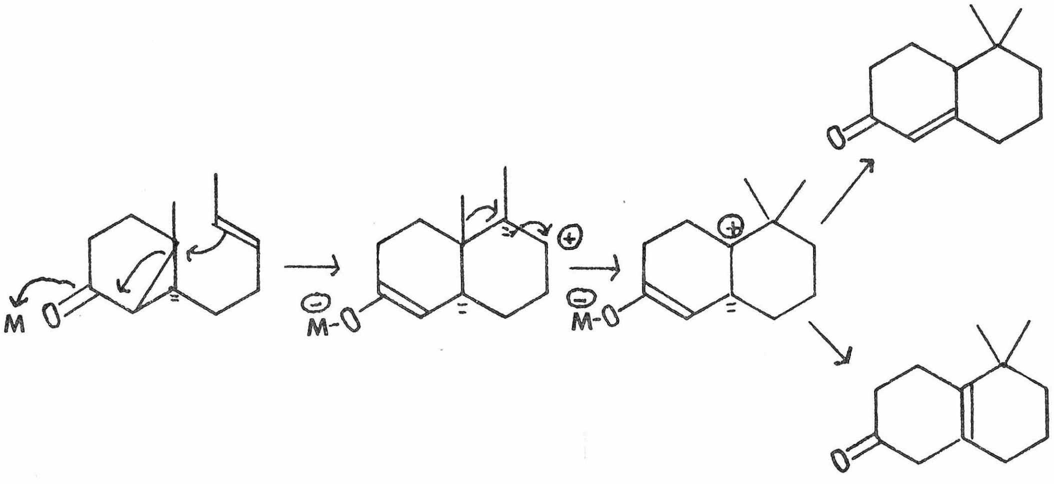


Figure 3



Although the preparation of a compound resembling cyclopropyl ketone 4 has been explored (7) (Figure 4), a simpler and more readily available model system seemed appropriate for determination

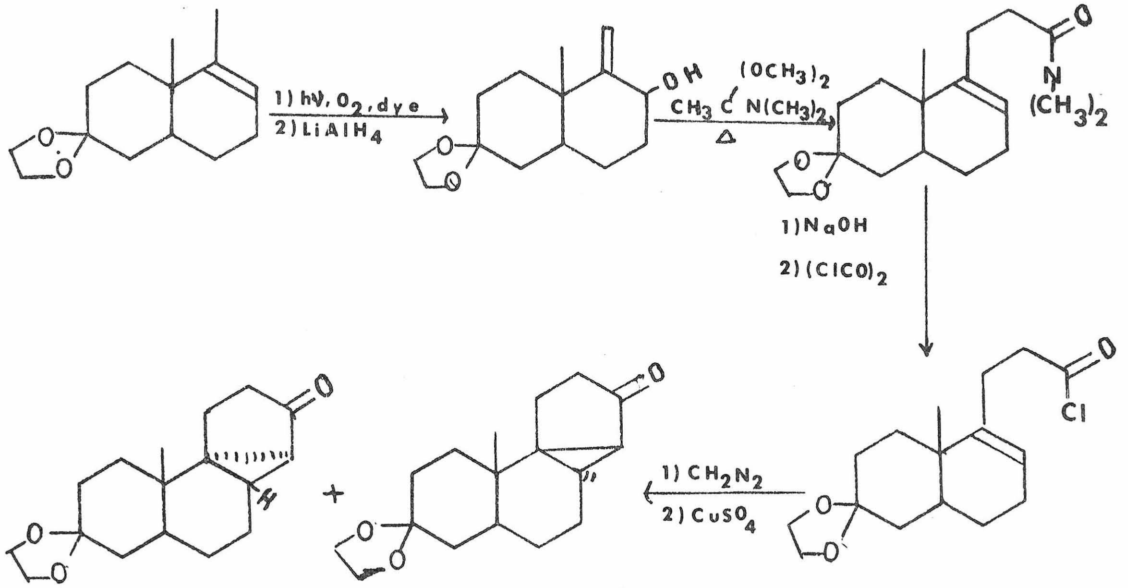
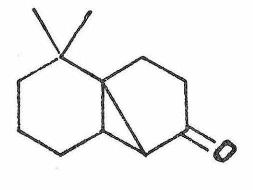


Figure 4

of the optimum conditions for the ring-opening. The tricyclic ketone 5 appeared to be a good choice for this purpose, since the proper



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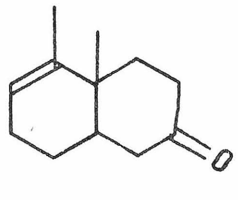

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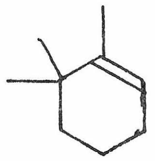

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cyclopropyl cleavage would involve a simple methyl shift, presumably resulting in formation of olefin 6, which could easily be distinguished from the starting material by spectrometric means. In order that some experience with the sequence of reactions in Figure 4 might be gained, the preparation of ketone 5 was to be carried out by a similar pathway, starting out with olefin 7.

Discussion

While the rapid preparation of olefin 7 was initially the major goal, a profitable exercise in synthetic design lay in performing this preparation in as few simple steps as possible. An additional aim would be to use reactions which could find general synthetic applications. The most straightforward of the existing procedures for synthesizing this olefin, that of Vejdelek, Rajsner, and Protiva (8), outlined in Figure 5, did not seem too satisfactory in the light of these considerations. The major objection was that the preparation of 2, 2-dimethylcyclohexanone, the starting material for this transformation, is a tedious process. It may be made by one of several techniques. One might methylate 2-methylcyclohexanone and isolate the desired material from a mixture of di-, tri-, and tetramethylated ketones via a three-step chemical process (9). Alternatively, it is possible to use blocking groups, such as the ones shown in Figure 6, which must be removed following the methylation.

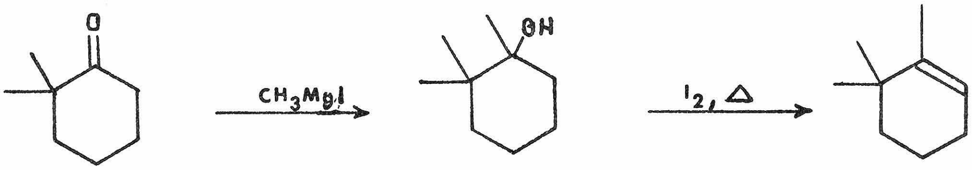
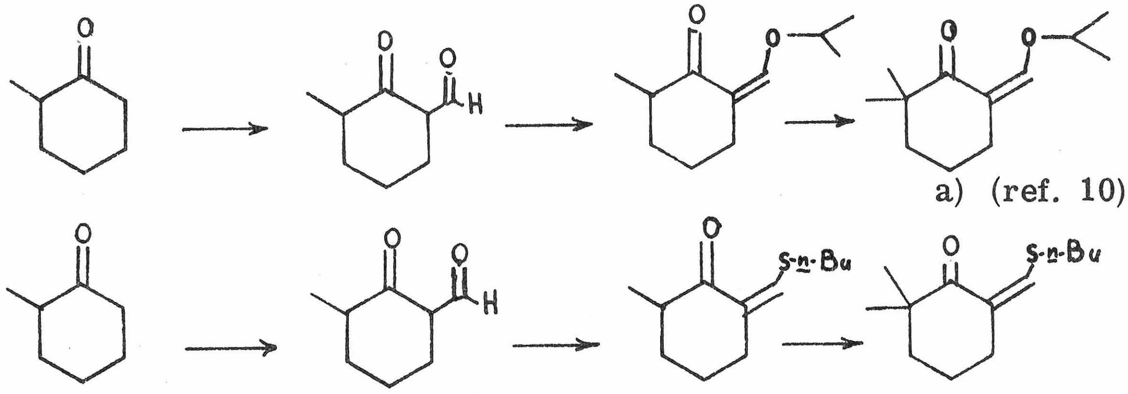


Figure 5

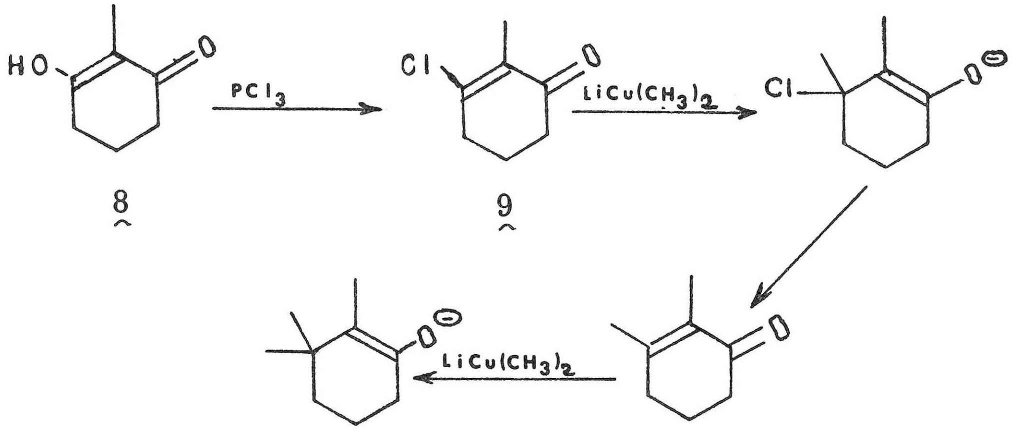


a) (ref. 10)

b) (ref. 11)

Figure 6

Because of these factors, a different pathway to olefin 7 was devised. The starting material was to be 2-methyldihydroresorcinol (8), which could be converted to chloride 9 by treatment with phosphorus trichloride (12). The chloride should be converted to enolate 10 by lithium dimethylcuprate (13). It was necessary to consider possible means by which olefin 7 might be generated from enolate 10.



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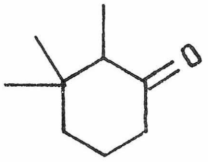
The simplest of these would involve reduction of the corresponding ketone (11) to alcohol 12, which could then be dehydrated to form 7. The use of strong acid for this dehydration would probably give only the desired olefin, but this sort of treatment is not appropriate for other alcohols, especially ones which can undergo rearrangement during olefin formation. On the other hand, elimination of an ester of alcohol 12 could give rise to the isomeric olefin, 13, since there are protons on both carbons adjacent to the hydroxyl function.



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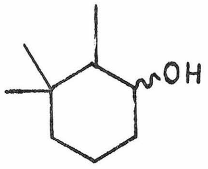

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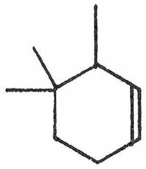

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Another prospective means of olefin formation entails treatment of the *p*-toluenesulfonylhydrazone of a ketone with an alkyllithium compound (Figure 7) (14). However, this reaction usually proceeds by abstraction of the least hindered proton, a path which in our case would lead to the unwanted olefin, 13, if not a mixture of the two products.

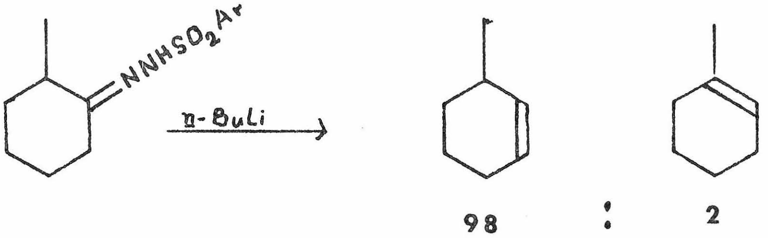
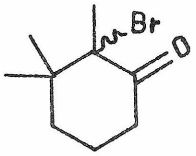


Figure 7

Alternatively, it should be possible to find a deoxygenation reaction which maintains the positional specificity of an enolate such as 10. Several techniques already existed at the time of this speculation. For example, it is known that ketones with good leaving groups adjacent to the carbonyl function are converted to olefins upon treatment with hydrazine. In our case, the most readily available ketone was the bromo-ketone, 14, which could be made by treatment of the corresponding enol acetate (15) with bromine (15). A recent investigation of the reductive elimination, however, indicated that it is necessary to use an olefinic solvent, such as cyclohexene, in order to prevent reduction of the double bond by diimide, which is formed during the reaction (16). Since it would be difficult to separate the product, 7, from most olefins which could be used as the reaction solvent, this procedure was eliminated from consideration.



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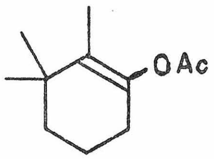

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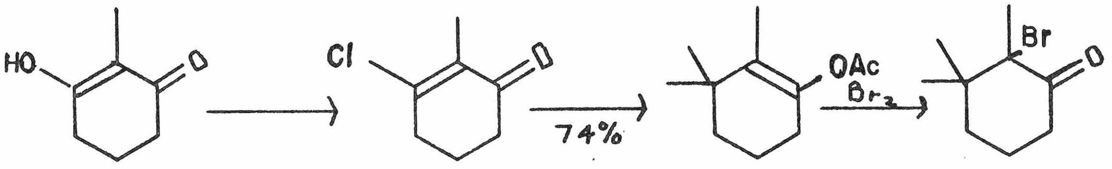
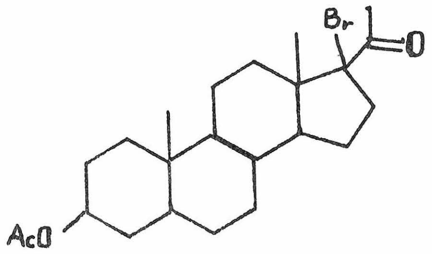
Actual experimentation was applied to the production of 7 by another possible means, involving conversion of bromoketone 14 to the corresponding bromohydrin and treatment of the latter substance with zinc metal, making use of a common method for preparing olefins (17). Unfortunately, when the sequence of reactions shown



8 9 15 14

Figure 8

in Figure 8 was carried out, several difficulties arose. Bromoketone 14 seemed to be unstable at room temperature and couldn't be isolated as a pure compound. Attempted reduction of impure ketone 14 with either lithium aluminum hydride or sodium borohydride led to mixtures of products which did not contain any bromohydrin. This last conclusion was based upon the short retention time of the major components when the mixture was analyzed by gas chromatography and upon the failure of alcoholic components to give a positive Beilstein test (18) after they had been isolated by column chromatography. A similar result was reported by Wendler, Graber, and Hazen (19), who observed the formation of a mixture of bromohydrin



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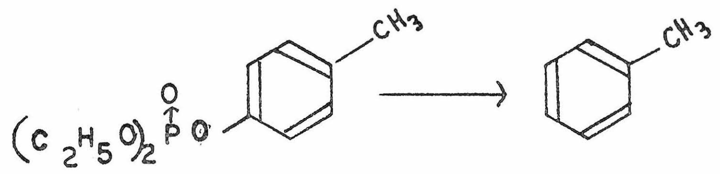
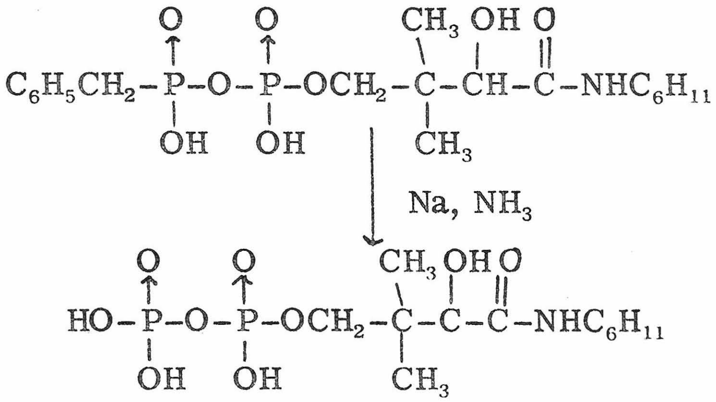
and a non-brominated alcohol in the borohydride reduction of ketone 16, which also has a bromine attached to a tertiary carbon.

An appraisal of the method for deoxygenating phenols which was developed by Kenner and Williams (20) suggested another possible direction of attack. These workers were able to convert a number of aryl diethyl phosphate esters to the corresponding hydrocarbons by treatment with sodium in ammonia liquid. An example of this reaction is the reduction of phosphate ester 17 to toluene. This



process is akin to others which have been reported. Baddiley and Thain observed the production of inorganic phosphate during the sodium-liquid ammonia reduction of diphenyl hydrogen phosphate and dibenzyl hydrogen phosphate (21). The reductive cleavage reaction has been used to remove benzyl protecting groups used in the preparation of phosphate esters such as 18 (22).



$$C_6H_5CH_2-\underset{OH}{\overset{\overset{O}{\uparrow}}{P}}-O-\underset{OH}{\overset{\overset{O}{\uparrow}}{P}}-OCH_2-\underset{CH_3}{\overset{CH_3}{C}}-\overset{OH}{CH}-\overset{\overset{O}{\|}}{C}-NHC_6H_{11}$$

$$\Big\downarrow \text{Na, } NH_3$$

$$HO-\underset{OH}{\overset{\overset{O}{\uparrow}}{P}}-O-\underset{OH}{\overset{\overset{O}{\uparrow}}{P}}-OCH_2-\underset{CH_3}{\overset{CH_3}{C}}-\overset{OH}{C}-\overset{\overset{O}{\|}}{C}-NHC_6H_{11}$$

18

A similar reaction was reported by Lipkin, Jones, and Galiano, who described their success in preparing dibutyl hydrogen phosphate by treating dibutyl p-toluyl phosphate with the sodium radical anion of naphthalene (23). Although no mention was made of the fate of the aromatic moiety, it is presumably lost as a toluyl radical or anion. The reaction requires only one mole of radical ion for each mole of ester, so it appears as if a one-electron reduction is the initial step of the fission reaction. Various possible mechanisms are outlined in Figure 9.

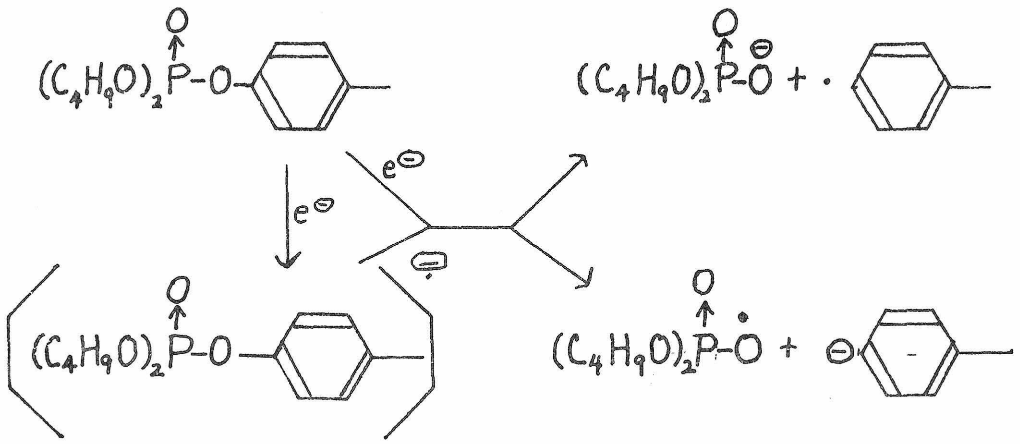


Figure 9

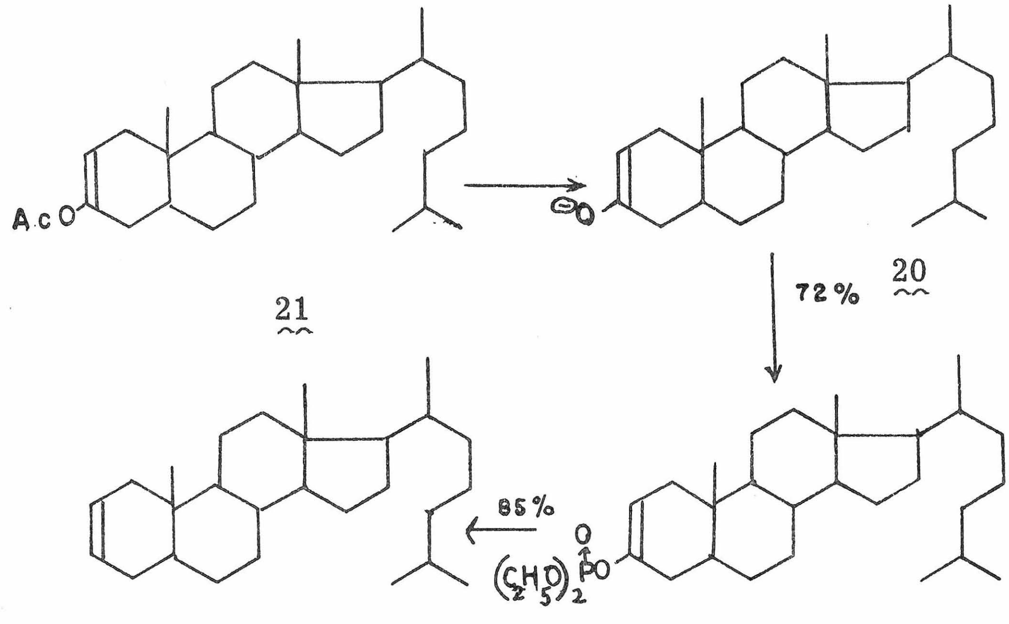
It was felt that enol phosphates would also undergo this type of cleavage were they treated with sufficiently strong reducing agents. Solutions of lithium in ethylamine and methylamine were chosen as reducing reagents for several reasons. In the first place, solutions of alkali metals in alkylamines seem to have greater reduction potentials than those of analogous solutions in ammonia (24).

Evidence for this fact was provided by Krapcho and Nadel (24b), who studied the reduction of isolated double bonds using ethylamine as the solvent. These reductions did not take place in liquid ammonia solution, except in the case of some terminal vinyl groups. The reaction in ethylamine did take place even when the temperature was lowered to -34°, the boiling point of ammonia, demonstrating that the greater reducing power of the amine solutions could not be ascribed to the higher temperatures at which they are customarily used.

Another reason for the choice of the alkylamines as solvents was that organic substrates ought to be more soluble in them than in ammonia. A third reason for this choice was that the boiling points of methyl- and ethylamine (-6° and 16°) make them more convenient than ammonia to use.

In a trial run, an attempt was made to prepare and reduce cholest-2-ene-3-yl diethyl phosphate (**19**). The ester was obtained by phosphorylation with diethylphosphorochloridate of the enolate anion **20**, which had been generated by treatment of 3-acetoxycholest-2-ene (**21**) with methyllithium in dimethoxyethane (25). This phosphate ester (**19**) was then converted to cholest-2-ene (**22**) with high yield by the action of lithium in ethylamine-tetrahydrofuran solution in the presence of *t*-butyl alcohol.

Just after the completion of the above reaction, Fetizon, Jurion, and Anh (26) reported the same reduction, in addition to the reduction of the enol phosphate from dihydrotestosterone acetate (**23**). While the reduction of ester **23** to the corresponding olefin, **24**, proceeded



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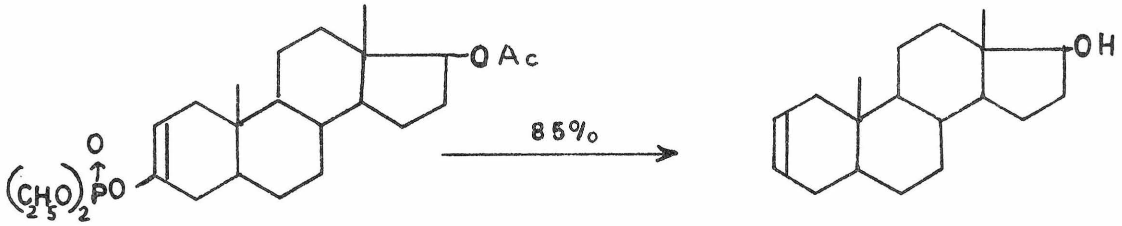

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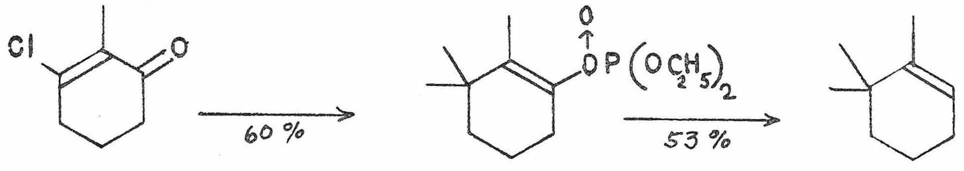
24

in good yield, the reduction of ester 19 gave only a moderate yield (65%). Since Fetizon and co-workers used ammonia as the solvent for these reductions, the difference in yield might be attributed to the differences in solubilities between the derivatives of a mono-oxygenated steroid nucleus possessing a long side chain and a smaller di-oxygenated nucleus with no side chain. The difference might not have been apparent in ethylamine, our solvent, in which the solubilities should be greater.

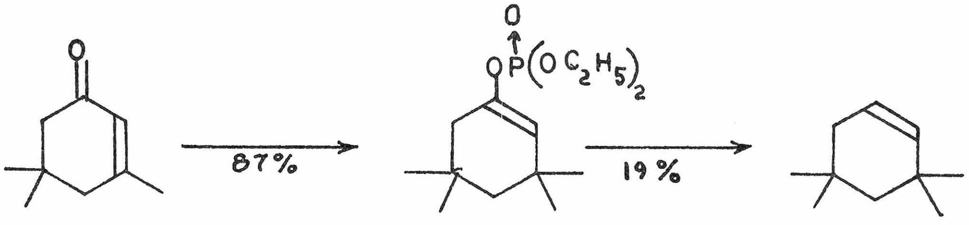
It is of note that these workers obtained their enol phosphates <u>via</u> the Perkow reaction (27) between the corresponding bromoketones and triethyl phosphite (conditions unspecified). Since earlier experiments in the present work had shown that the formation of ester 19 does not proceed when triethylphosphite and 2-bromocholestanone are mixed in either ether or ethanol, an attempt was made to make these materials react in the absence of solvent. Indeed, when a mixture of triethyl phosphite and bromocholestanone was heated until the steroid melted (140°) a 92% yield of phosphate ester 19 was obtained.

The success of the pilot reaction led directly to the preparation of enol phosphate 25, made by phosphorylation of enolate 10, which was generated by the conjugate addition to chloroketone 9. This ester (25) was reduced in methylamine instead of ethylamine to prevent excessive loss of product upon the removal of the solvent. The reductive cleavage gave the desired olefin, 7, in a pure state, albeit in a disappointingly low 53% yield.



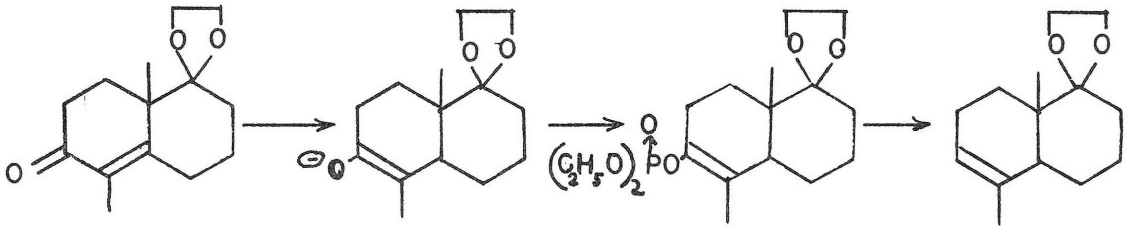
9 25 7

The conjugate addition to a less complex system, isophorone (26), resulted in formation of the enol phosphate, 27, in a more satisfactory 87% yield. However, when this substance was treated with lithium in either methylamine or ammonia, only a very small amount of the olefin, 28, could be recovered. Since success has been encountered during the formation of disubstituted olefin 22 and volatile olefin 7, it is not immediately apparent why the reduction of phosphate 27 is so unfavorable.



26 27 28

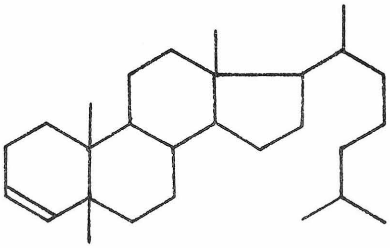
Several other enolate anions, generated by conjugate addition to unsaturated ketones, have been phosphorylated and reduced. Ireland and Pfister reported the interception of enolate 29, formed in the lithium-ammonia reduction of ketone 28, with diethylphosphorochloridate (28). The resulting ester (30) was then reduced using



28 29 30 31

lithium in ethylamine. These workers were also able to obtain moderate yields of the corresponding olefin, 31, by carrying out the lithium-ethylamine reduction without prior isolation of the intermediate phosphate. Another example in this work was the preparation of 5-methylcoprost-3-ene (32), which was obtained by reduction of phosphate 33, an ester formed by phosphorylation of the enolate from the addition of lithium dimethylcuprate to cholest-4-en-3-one (34).

To compare this new mode of deoxygenation with existing ones, the yields and melting points of cholest-2-ene, prepared by various methods from cholestanone or cholestanol, are shown in Table 1.



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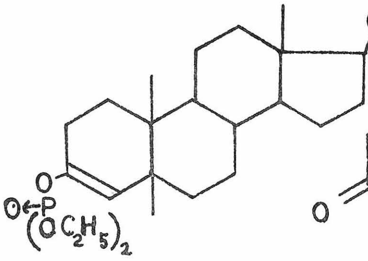

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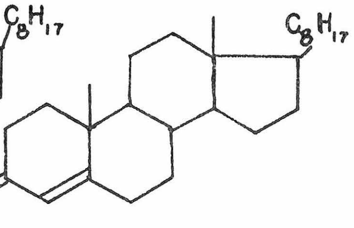

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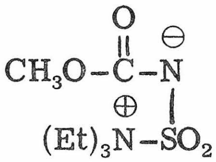
As may be seen from the table, the method described herein compares favorably with the other methods in the simple case of the preparation of 22. In such special cases as the formation of 2, 3, 3-trimethylcyclohexene or 31 it would seem to have several advantages over these other techniques. In the first place, the specificity imparted by conjugate addition to the double bond is never lost. Also, only one intermediate compound, the enol phosphate lies between the

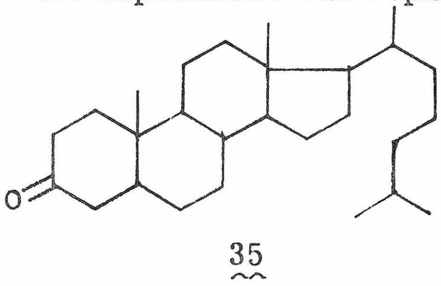
Table 1

Preparations of Cholest-2-ene

Starting material	Reagent	% yield (mp)	Ref.
2α-Bromocholestan-3β-ol	Zn, HOAc	55 (69-70°)	(29)
2α-Bromocholestan-3-one	N_2H_4, cyclohexene, KOAc	64 (72-74°)	(16)
Cholestan-3-one p-Toluenesulfonylhydrazone	CH_3OH, LiOH	81 (72°)	(30)
Cholestan-3-one p-Toluenesulfonylhydrazone	n-BuLi	78 (69°)	(31)
Cholestan-3-one p-Toluenesulfonylhydrazone	DMSO	82 (69.5-70.5°)	(32)
Cholestan-3β-ol	 $CH_3O-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{N}-SO_2-\overset{\oplus}{N}(Et)_3$	63 (73-74°)	(33)
Cholest-2-en-3-yl Diethyl phosphate (**19**)	Li, $EtNH_2$ THF, tBuOH	85 (75-76°)	
Cholest-2-en-3-yl Tetramethylphosphorodiamidate (**41**)	Li, $EtNH_2$ THF, tBuOH	83 (73-74°)	

enolate and the olefin, a feature which complies with the desire for a small number of step in the reaction sequence. Finally, if purification is necessary, it may be carried out using adsorption chromatography at the enol phosphate stage, so that separations of mixtures of olefins are not necessary. This would seem to be fairly important in the preparation of volatile compounds such as 1, in which the use of such techniques as fractional distillation or preparative vapor phase chromatography may be avoided.

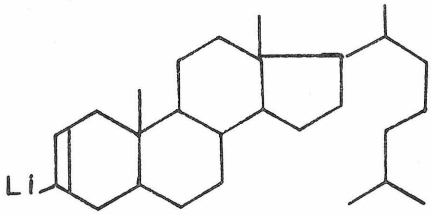
At the completion of this phase of the work, there was made a decision to explore various facets of the reductive cleavage of enol phosphates. Especially interesting was the possibility of expanding the scope of the method by using systems with smaller (more positive) reduction potentials than metal-amine solutions. Also interesting was the possibility of using aprotic solvents. Since Lipkin and co-workers (23) had used the naphthalene radical anion to reduce aromatic phosphates, attempts were made to achieve the reductive cleavage of 3-cholestenyl diethyl phosphate (19) with similar agents. When the phosphate was treated with lithium-naphthalene in dimethoxyethane, however, the only product which was found had the same infrared and gas chromatographic characteristics as cholestanone (35). Likewise, when the naphthalene was replaced with biphenyl,



35

the major product seemed to be the ketone, but the gas chromatographic trace indicated the presence of a small amount (ca. 10%) of the desired product, cholest-2-ene. It should be noted that the ketone could not have been formed by hydrolysis of the starting enol phosphate during the reaction workup, since no cleavage was observed when the ester was subjected to the conditions it would have encountered in the workup.

Several other reducing agents were tried out in an attempt to see if this competitive reaction, the formation of the ketone, could be avoided. The first of these reagents, lithium-trimesitylborane, which has been used successfully to reduce unsaturated ketones (34), had no apparent effect on the enol phosphate. On the other hand, blue solutions of lithium in hexamethylphosphoramide did reduce the ester to the olefin, 21. Since this solvent had been shown to be inert to organolithium compounds (35), there seemed to be a possibility that the product of the cleavage reaction was cholestenyllithium (36).



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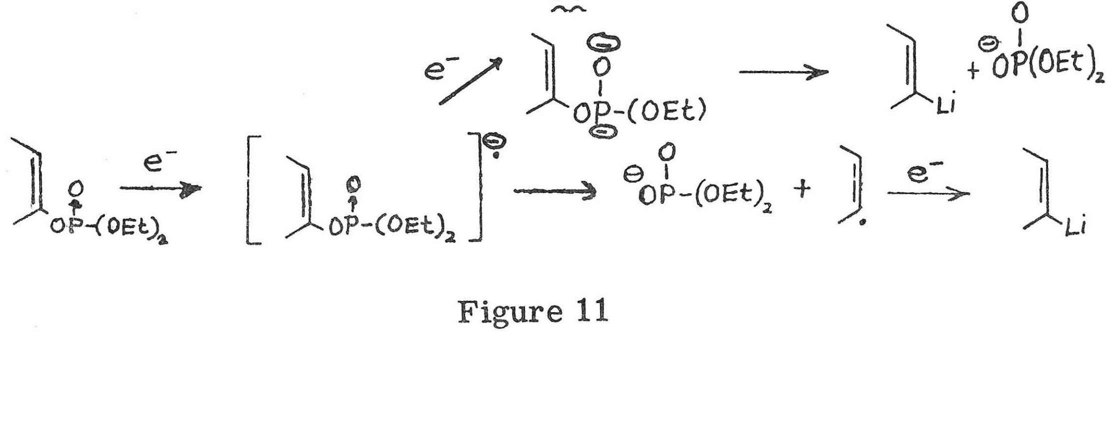
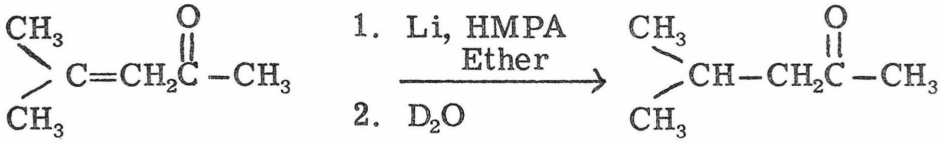


Figure 11

The pathways by which this intermediate might have arisen are shown in Figure 11.

When, however, the reaction mixture from this reduction was quenched with deuterium oxide, there was no deuterium incorporated into the molecule, as determined by the absence of a C-D band in the infrared spectrum. This would indicate either that some component in the medium was able to protonate any cholestenyllithium that was formed or that the organo-lithium compound was never formed. This behavior is like that of alkyl halides, which form "Wurtz products" (35) instead of alkyllithiums when they are added to blue solutions of lithium in hexamethylphosphoramide. A similar result was observed by Angibeaud, Larcheveque, Normant, and Tchoubar when they attempted to incorporate deuterium at the β carbon of ketone 37 during the reduction of 38 with lithium in hexamethylphosphoramide (36).



38 37

The use of hexamethylphosphoramide as a solvent suggested another direction in which the investigation might be taken. Normant and co-workers have also shown that hexamethylphosphoramide slowly decomposes in the presence of alkali metals to form the corresponding dimethylamide ion. Their proposed mechanism is shown in Figure 12.

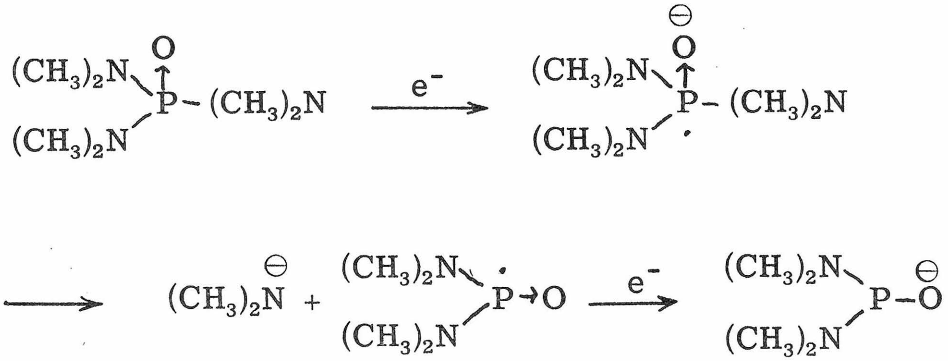


Figure 12

If an ester moiety were substituted for one of the amide groups then the fission could take place following any of three pathways (Figure 13). The amide could be displaced, an oxygen anion could be displaced, or, as is the case with enol dialkylphosphates, a carbon-oxygen cleavage could occur. Another property of hexamethylphosphoramide which might be displayed by a diamidate ester would be the ability to dissolve lithium metal, a property which would facilitate the direct reaction between the ester and the metal, without the

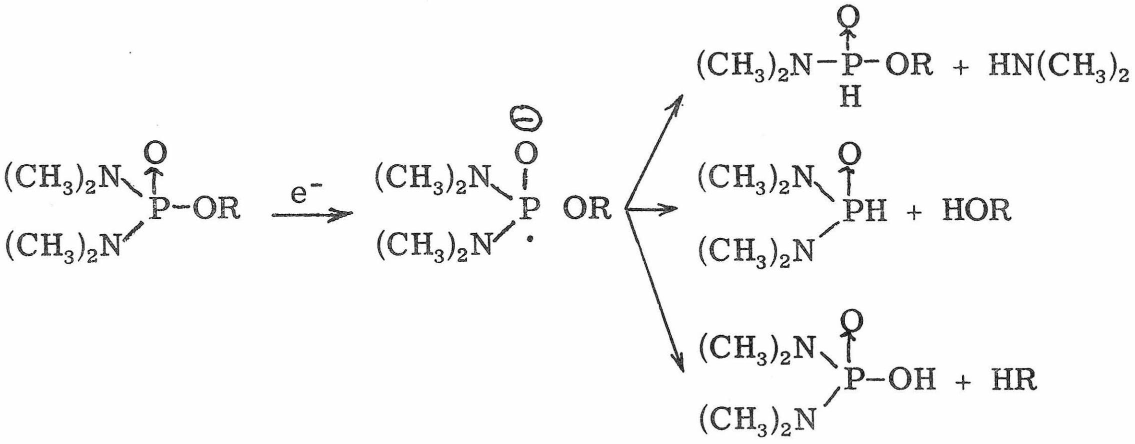
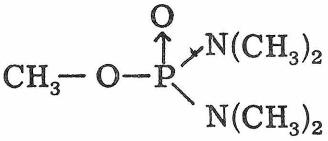


Figure 13

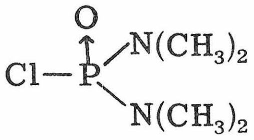
intervention of electrons solvated in a reactive solvent such as an alkyl amine or hexamethylphosphoramide.

For the testing of these ideas, two phosphorodiamidate esters were prepared. The first, methyl tetramethylphosphorodiamidate (37), 39, was prepared by the reaction of the corresponding phosphorochloridate, 40, with sodium methoxide. The second ester, cholestenyl phosphorodiamidate 41 was obtained *via* the phosphoroylation of the enolate generated by treatment of cholestenone with sodium hydride in dimethyoxyethane. The behavior of these compounds toward lithium metal was investigated under a variety of conditions.



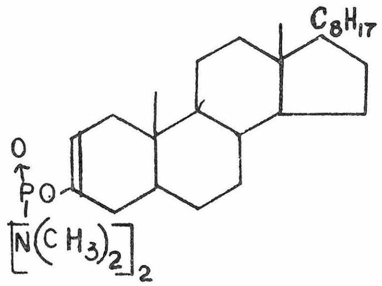
$CH_3{-}O{-}P(\rightarrow O)[N(CH_3)_2]_2$

39



$Cl{-}P(\rightarrow O)[N(CH_3)_2]_2$

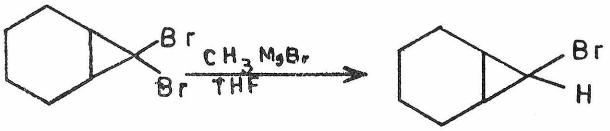
40



41

Unlike hexamethylphosphoramide, the neat methyl diamidate ester, 39, would not by itself dissolve lithium which had been taken out of a mineral oil dispersion. However, when small amounts of biphenyl were added to such a mixture, the suspension turned green, indicating formation of the aromatic radical ion; then it turned blue, which seemed to indicate the interaction of electrons with the ester. This mixture also exploded, possibly because of the decomposition of phosphorodiamidate 39.

When the cholestenyl ester, **41**, was dissolved in tetrahydrofuran and treated with the lithium dispersion, no reaction was observed, even when small portions of dibromoethane were added to form a more reactive metal surface (38). On the other hand, when biphenyl was used to "entrain" electrons, a reaction took place in hexane, benzene, and tetrahydrofuran. Use of the first two solvents produced hydrocarbons, indicating that the C–O fission had occurred. These did not seem to be practical solvents, however, since the reactions resulted in mixtures of products from which cholestene, a minor product, could not be separated. Reductions with the lithium-biphenyl system (39) in tetrahydrofuran seemed to be more promising, since cholestene appeared to be the only product. Here, again, no deuterium was incorporated into the product when the reaction mixture was treated with deuterium oxide. This means that the intermediate must have obtained either a proton or a hydrogen atom from some component of the medium. One possible source of these would be molecules of unreacted starting material, which ought to resemble hexamethylphosphoramide in this aspect. However, unless the product resulting from this abstraction could also be reduced, then the recovery of hydrocarbon should not have been greater than 50% (the yield was 84%). Another possibility is that the phosphoryl fragment from the cleavage can donate a hydrogen or a proton. A third possibility is that the solvent, tetrahydrofuran, acts as a source of one of these. Since this solvent is stable to vinyllithium compounds (vinyllithium is available commercially in tetrahydrofuran solution), then any abstraction from it would have to be of hydrogen atoms. Seyferth has apparently observed a similar phenomenon during the treatment of dibromonorcarane (42) with methyl magnesium bromide (40).



42

It is of interest to note that the reduction of ester 41 using lithium-biphenyl in hexamethylphosphoramide did not take place. It has been shown that radical ions have high stability in this solvent (41), so perhaps the biphenyl radical ion's potential was reduced to the point that electron transfer to the phosphoryl ester would not take place. Reduction also did not occur when lithium-trimesitylborane was tested as a reducing agent, nor did it occur when the di-lithium dianion of nickel tetraphenylporphin (NiTPP), which has been used as a selective two-electron reducing agent by Corey and Kuwajima (Figure 14) (42), was tried. The results of all the trials in aprotic

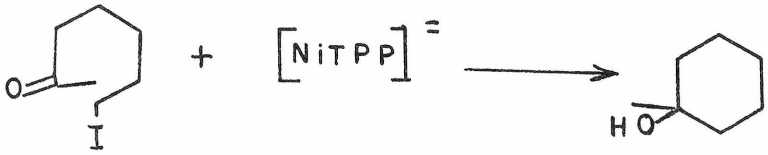


Figure 14

Table 2

Reductions of Phosphoryl Esters in Aprotic Solvents

Reagent	Yield of cholest-2-ene	mp °	
A. Reduction of cholest-2-en-3-yl diethylphosphate			
Li, Naphthalene Dimethoxyethane	0		
Li, Biphenyl, THF	Trace		
Li, TMB[d], THF	0		a
1) Li, HMPA[e] 2) D_2O	76%	69.5-70.5	b
1) Li, HMPA, LiBr 2) D_2O	70%	70 -72.5	b
B. Reduction of cholest-2-en-3-yl tetramethylphosphorodiamidate			
Li, THR	0		a
Li, Biphenyl Hexane	unknown		c
Li, Biphenyl Benzene	unknown		c
Li, Biphenyl THF	84%	70.5-71.5	
1) Li, Biphenyl, THF 2) D_2O	70%	64 -65	b
Li, TMB, THF	0		a
Li, NiTPP[f], THF	0		a
Li, Biphenyl, HMPA	0		a

[a] Starting material was recovered.

[b] No deuterium was incorporated into the molecule.

[c] The product was a mixture of hydrocarbons.

[d] Trimesitylborane.

[e] Hexamethylphosphoramide.

[f] Tetraphenylporphin.

media are summarized in Table 2.

No advantage seems to have been gained through use of the tetramethylphosphorodiamidate ester (41) in place of the diethylphosphate ester (19) when the reductive fission was carried out in ethylamine. However, several features of the diamidate could serve to make such a compound a valuable intermediate. When ester 41 was treated with sodium borohydride in ethanol, no loss of starting material was observed. Likewise, this material did not react with ethereal lithium aluminum hydride, methyllithium, lithium dimethyl cuprate, or ethanolic potassium hydroxide, which indicates that many operations might be performed upon a molecule possessing an enol phosphorodiamidate moiety.

The overall success encountered in the use of phosphoryl esters as intermediates in the deoxygenation of enolate anions led to a consideration of the potential of this sort of procedure as a means of deoxygenation to form saturated centers, even though there exist numerous standard procedures for accomplishing this task, starting with either ketones and aldehydes or with alcohols. The carbonyl compounds, for example, have been reduced by three major methods (43). The Clemmensen reduction, which makes use of zinc in strong acid, has not worked well with ketones which are not activated by some kind of unsaturation (43). The next type, which includes the various modifications of the Wolff-Kishner reaction (Figure 15), has been used with success in a great number of cases, and seems to be the best way of reducing ordinary ketones and aldehydes. The third

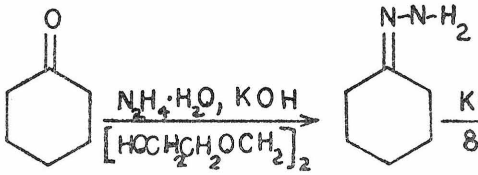
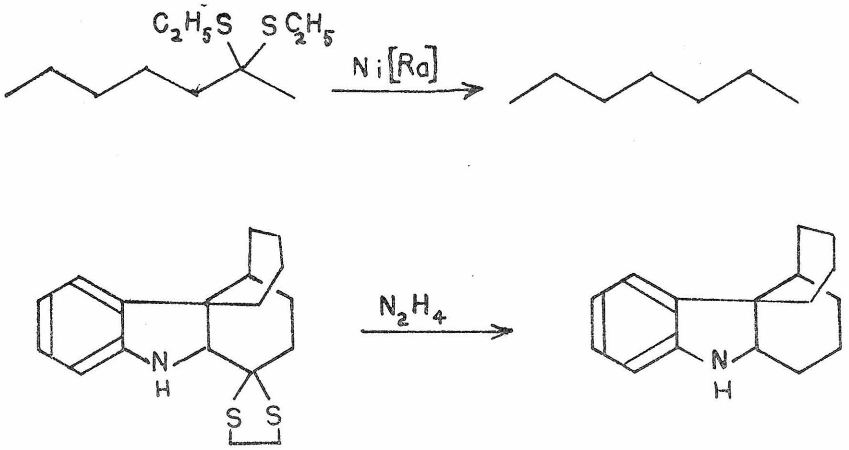


Figure 15 (ref. 44)

method involves desulfurization of dithioketal derivatives of carbonyl compounds with Raney nickel (45), or hydrazine (46) (Figure 16).

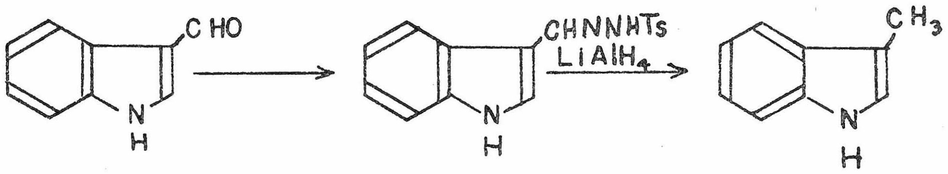


a) (ref. 45)

b) (ref. 46)

Figure 16

An additional procedure which works well in few cases utilizes hydride reduction of a p-toluenehydrazone (Figure 17).

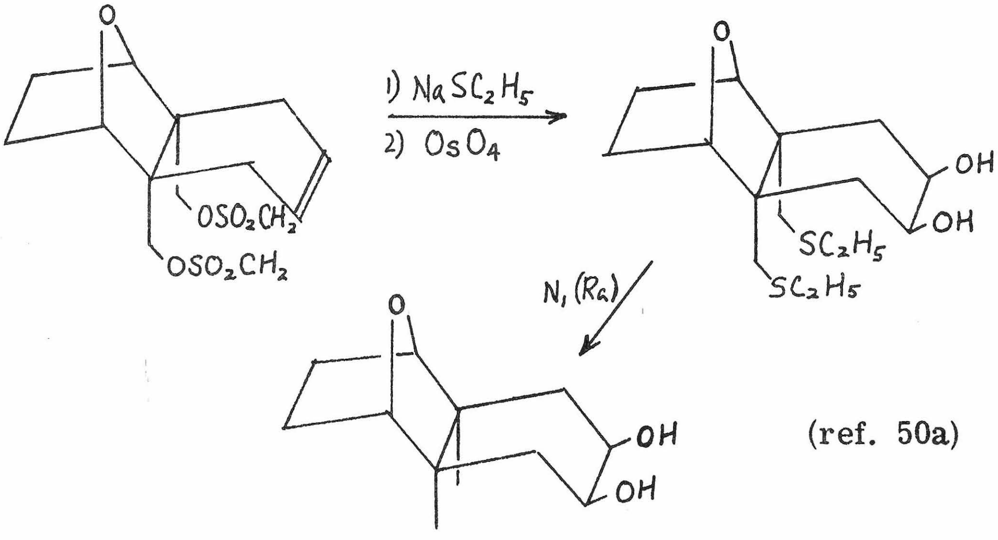


(ref. 47)

Figure 17

There are also several methods for deoxygenation of alcohols which are not activated by nearby unsaturation. Sulfonate esters of primary and secondary alcohols have been cleaved by lithium aluminum hydride (48) or lithium in ammonia (49). These esters have also been converted to thioethers, which may be desulfurized with Raney nickel (Figure 18) (50). Alcohols may also be changed into halides, and there are numerous procedures for conversion of these into hydrocarbons. Of course, there is the additional possibility of forming an olefin by one of the methods previously discussed and then of hydrogenating it.

So that a comparison of the phosphoryl ester cleavage reaction with these methods might be made, phosphoryl esters of various alcohols were prepared and reduced. Although many methods of converting alcohols to such esters have been developed (51), only several were here investigated.



(ref. 50a)

Figure 18

The most simple procedure, treatment of the alcohol with a phosphorylating agent in dry pyridine at room temperature, was quite satisfactory for preparation of diethylphosphate esters of the primary and secondary alcohols. This method did not work as well when the unreactive tetramethyldiamidophosphorochloridate was used as the phosphorylating agent. However, more successful procedures for the preparation of tetraalkyl diamidophosphate esters using tertiary amine solvents have been worked out (52), so this method is available if other methods are inappropriate.

A more successful general procedure entailed generation of a lithium alcoholate with n-butyllithium in dimethoxyethane, and then treatment of this intermediate with a solution of the phosphorylating agent in triethylamine. While both the bidentate Lewis base, dimethoxyethane, and the triethylamine may have increased the reactivity of the oxygen anion toward the phosphoryl center by coordination of the lithium cation (53), the amine served the more visible function of removing any hydrogen chloride from the chloridate through precipitation of the amine hydrochloride salt. Table 3 summarizes the results of the phosphorylation of the alcohols which were used.

The conversion of 3β-methylcholestan-3α-yl diethylphosphate (**44**) to 3β-methylcholestane (**56**) using lithium-ethylamine proceeds with a 91% yield. Thus, this method compares favoraby with the procedure of Barton, Campos-Neves, and Cookson (54), who made the halides **61**, a and b from alcohol **43** in about 75% yield. Their reduction, utilizing lithium in ammonia, led to 3β-methylcholestane

Table 3

Phosphorylation of Alcohols *

Alcohol	Reagents	Product	% Yield	mp°
43	1) C_4H_9Li, ether 2) $(C_2H_9O)_2POCl$	44	82	oil
45	$(C_2H_5O)_2POCl$, pyridine	46	94	76-79
47	$(C_2H_5O)_2POCl$, pyridine	48	94	67-71
47	$[(CH_3)_2N]_2POCl$, pyridine	49	40	144.5-146.5
47	1) CH_3Li, ether 2) $[(CH_3)_2N]_2POCl$	49	94	147-150
47	1) C_4H_9Li, dimethoxyethane 2) $[(CH_3)_2N]_2POCl$, triethylamine	49	38	143-145
50	1) C_4H_9Li, ether 2) $(C_2H_5O)_2POCl$	51	60	oil
50	1) C_4H_9Li, dimethoxyethane 2) $[(CH_3)_2N]_2POCl$, triethylamine	52	93	oil
53	$(C_2H_5O)_2POCl$, pyridine	54	64	oil
53	1) C_4H_9Li, dimethoxyethane 2) $[(CH_3)_2N]_2POCl$, triethylamine	55	92	102-104

* The alcohols and phosphoryl esters are shown in Figure 19.

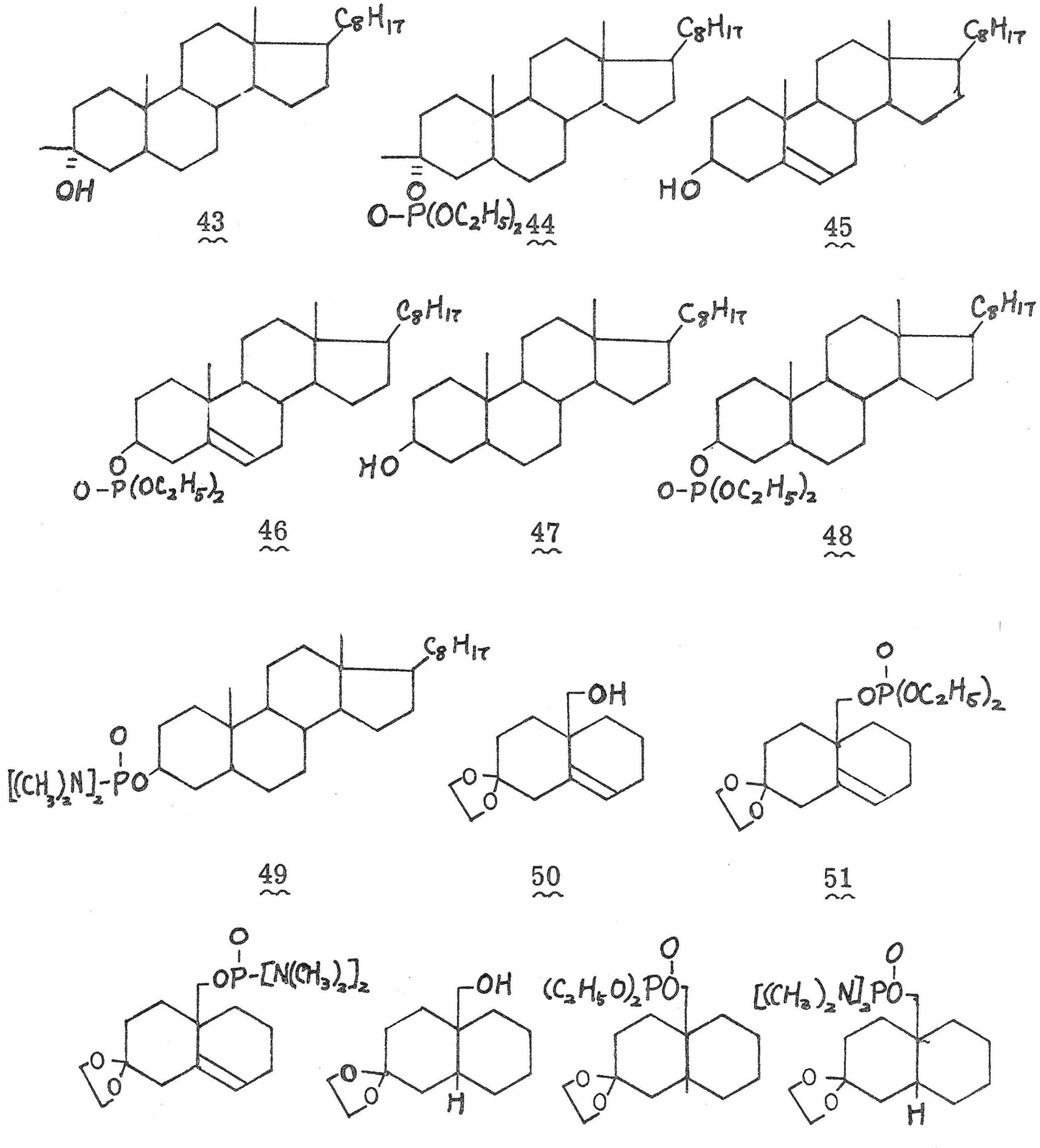
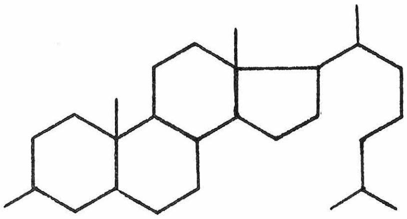
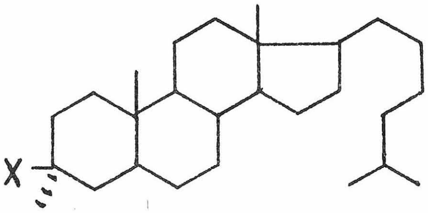

C_8H_{17}
OH
43
C_8H_{17}
O
O-P(OC$_2$H$_5$)$_2$
44
C_8H_{17}
HO
45
C_8H_{17}
O
O-P(OC$_2$H$_5$)$_2$
46
C_8H_{17}
HO
47
C_8H_{17}
O
O-P(OC$_2$H$_5$)$_2$
48
C_8H_{17}
O
[(CH$_3$)$_2$N]$_2$-PO
49
OH
O
O
50
O
OP(OC$_2$H$_5$)$_2$
O
O
51
O
OP-[N(CH$_3$)$_2$]$_2$
O
O
52
OH
O
O
H
53
O
(C$_2$H$_5$O)$_2$PO
O
O
54
O
[(CH$_3$)$_2$N]$_2$PO
O
O
H
55

Figure 19



56

in 78% and 75% from the chloride and bromide respectively. Some recent work (55) has indicated that the configuration at C-3 of the tertiary halides is not as shown (40), but the opposite (62). This would mean that reduction of these halides takes place without



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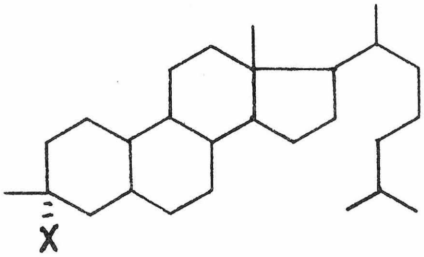


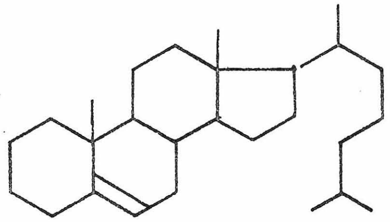
62

a) X = Cl
b) X = Br

inversion of the center which is reduced, which makes the result identical to that of the reduction of tertiary phosphate ester 44.

When the reductive cleavage was tested with the secondary esters, the results proved to be less straightforward. While reduction of cholesteryl p-toluenesulfonate with lithium aluminum hydride produced a mixture of cholest-5-ene (57) and cyclocholestane (63)

(48), reduction of the diethylphosphate ester of this alcohol (46) with lithium-ethylamine afforded only the former. This result is comparable to the one reported by Ireland, Wrigley, and Young, who reduced cholesteryl chloride (64) to the olefin, 57, with a 72% yield by treating it with sodium in ammonia (56). A similar 75% yield was



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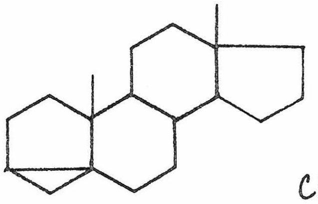

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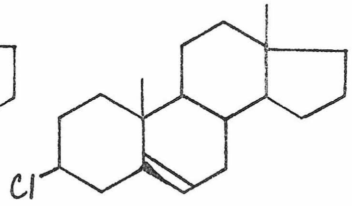
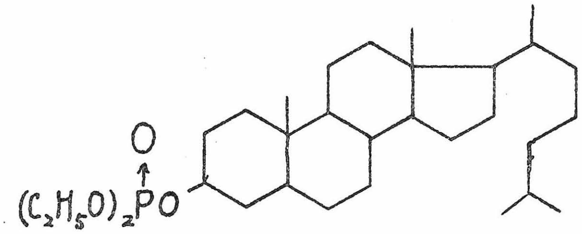
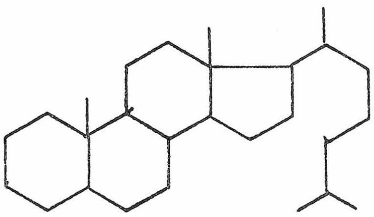


64

obtained by Cristol and Barbour when they treated the chloride with sodium-biphenyl in dimethoxyethane (57). The analogous fully saturated ester, cholestan-3-yl diethylphosphate 48, proved to be a poor substrate for the reductive cleavage with lithium-ethylamine, since only a 12% yield of cholestane (58) was realized. The major product seemed to be a white, flocculent solid which was insoluble in both



48



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organic solvents and water. The difference in yield of hydrocarbon between the examples of cholestanyl diethylphosphate (**48**) and cholesteryl diethylphosphate (**46**) indicates that the double bond of the latter compound somehow exerted an influence upon the course of the reaction. Specifically, the presence of the double bond supressed the formation of a competitive product, the white precipitate.

While the diethylphosphate ester of cholestanol was of little synthetic use, the same was not true of the analogous phosphorodiamidate, which was reduced by both lithium-ethylamine and lithium-biphenyl to cholestane in high yield. These cases are compared with other means of deoxygenation to form cholestane in Table 4.

Several other experiments were performed to investigate the properties of phosphorodiamidate ester **49**. As in the case of the analogous vinyl ester, **41**, this ester was not affected by treatment with dilithium nickel tetraphenylporphin or with ethereal lithium aluminum hydride. This material was not hydrolyzed in refluxing aqueous ethanol under acidic (pH 1) or strongly basic (10% potassium hydroxide) conditions. Hydrolysis did take place when a solution of ester **49** and cupric acetate in 2*M* hydrochloric acid and acetic acid was heated at 90° for 60 hours.

Finally, the esters of the primary alcohols were tested. Alcohol **50** (61) was chosen because it resembles the alcohol **63** which Marshall, Faubl, and Warne were able to deoxygenate by treatment of the methanesulfonate ester (**64**) with lithium in ammonia (49). In their case, the only product from lithium aluminum hydride reduction

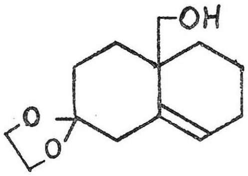
Table 4

Preparation of Cholestane

Starting material	Reagent	% Yield (mp)	Ref.
Cholestanone Hydrazone	Hydrazine	93 (81)	(58)
Cholestanone Ethylenedithioketal	Ni(Ra)	100[a] (–)[b]	(59)
Cholestanone *p*-Toluenesulfonylhydrazone	$NaBH_4$	82[a] (–)[b]	(30)
Cholestan-3-yl *p*-Toluenesulfonate	$LiAlH_4$	80 (78-79)	(60)
Cholestan-3-yl Tetramethylphosphorodiamidate (49)	Li, $C_2H_5NH_2$	90 (79-81)	
Cholestan-3-yl Tetramethylphosphorodiamidate (49)	Li, Biphenyl, Tetrahydrofuran	75 (79-80)	

[a] The yield was estimated by gas chromatography.

[b] Not Reported.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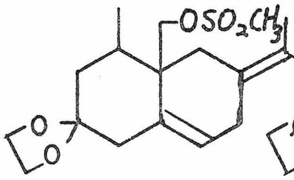
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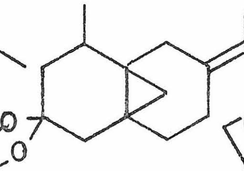
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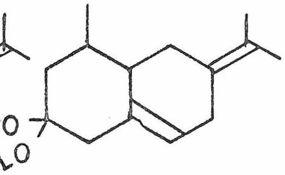
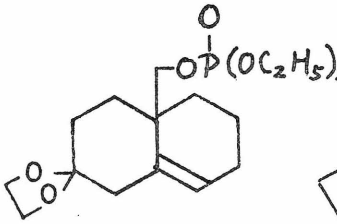

66

of the sulfonate was the cyclopropyl ketal, 65, while the lithium-ammonia reduction produced the desired product 66 accompanied by some of the starting alcohol.

The experience with the phosphoryl esters which had been tested so far indicated that reduction of the phosphoryl esters 51 and 52 would not produce any of the starting alcohol and, indeed, none of alcohol 50 was detected in the products. However, reduction of these two esters did produce a mixture of two ketals. These were shown to be the desired products, ketal 58, and the cyclopropyl ketal, 59, by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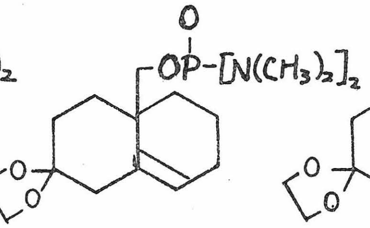
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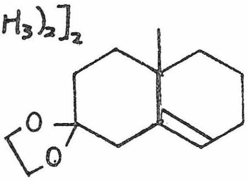
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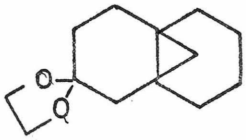
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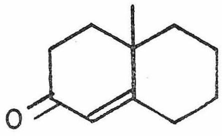
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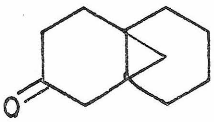
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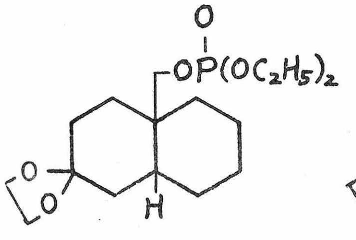
hydrolysis to the respective ketones 67 and 68 and characterization of these as the 2, 4-dinitrophenylhydrazone derivatives (62).

In an attempt to produce either ketal 58 or ketal 59 exclusively, the reduction of phosphorodiamidate ester 52 was performed at bath temperatures of -78° and 25°. At the former temperature, a one-to-one mixture was obtained, but at the latter, only a trace of the cyclopropyl ketal was detected by the presence of absorption in the nuclear magnetic resonance spectrum due to the cyclopropyl protons. Reactions at intermediate temperatures resulted in production of these two compounds in ratios between these two extremes. These results are summarized in Table 5. It should be noted that no reduction was observed when lithium-ammonia was used as the reaction medium.

The reactions of the esters of the fully saturated alsohol, 53, (61) were like those of the esters of cholestanol in the sense that the diethylphosphate ester, 54, produced a white precipitate upon treatment with lithium in ethylamine, apparently to the exclusion of any of the desired ketal, 60 (63). On the other hand, reduction of the phosphorodiamidate ester, 55, proceeded in 97% yield. As in the case of



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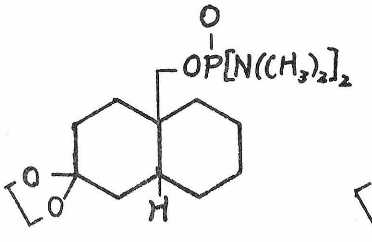

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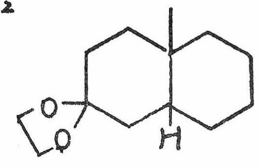

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Table 5

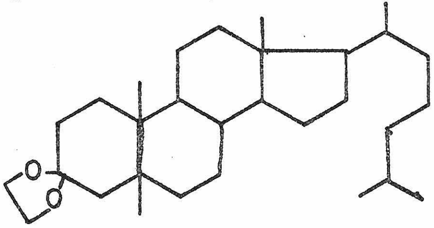
Reduction of Esters of Alcohol 50 at Different Temperatures

Ester	Bath Temperature °	% Yield	Ratio of 58 to 59*
52	25	93	9:1
51	0	91	3:1
52	-10	97	2:1
52	-30	81	1.5:1
52	-78	92	1:1

* This approximate ratio was determined by comparing the integrals of the vinyl and cyclopropyl protons in the nmr spectrum (Appendix A).

the unsaturated ester, **52**, this reduction did not occur in lithium-ammonia, but did occur in lithium-ethylamine at -78°. At this point, an opportunity was taken to test whether or not the *t*-butyl alcohol which had been used in the reductive fission reactions was necessary. The cleavage of phosphorodiamidate ester **61** did take place with nearly as high a yield as was obtained in the presence of the alcohol, but the nuclear magnetic resonance spectrum of the crude product possessed many extraneous absorptions. While this phenomenon may not be too important if the product is to be purified by distillation or chromatography, it might cause trouble with involatile hydrocarbons such as the steroids which have been prepared *via* this technique.

Angular methyl groups have previously been introduced through deoxygenation using several procedures. For example, Nagata, Hirai, Itazaki, and Takeda made use of a modified Huang-Minlon technique to produce ketal **69** from the corresponding aldehyde, **70**, with a 90% yield (64). While, more recently, Marshall and Ruden employed the same reaction to reduce aldehyde **71** to diketal **72** as part of the synthetic route to nootkatone (65).



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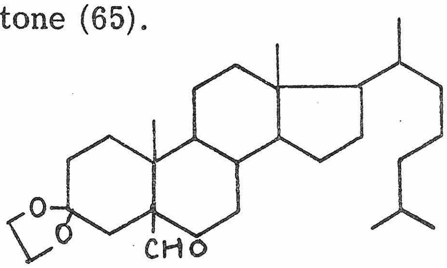

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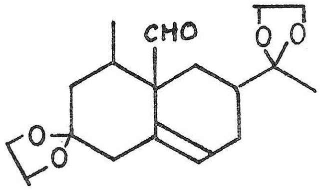

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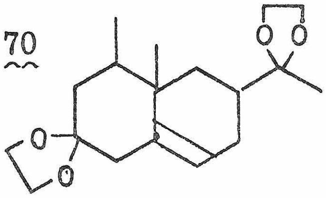

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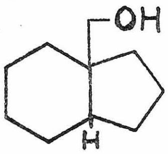
Other examples were provided by the work of Kronenthal and Becker, who were able to deoxygenate the indyl methanol 73 and the decalyl methanol 74 (66). The cis-indane-methyl p-toluene sulfonate, 75, was reduced by lithium aluminum hydride. While use of this procedure resulted in a 68% yield of the cis-methylindane, 76, the trans-decalin-methyl p-toluenesulfonate, 77, was not affected by this treatment. In order to make the trans-ketal, 78, these workers converted the sulfonate to a benzyl thioether (79) and desulfurized this derivative with Raney nickel to afford the desired product. A similar cis ketal, 81, was formed using the same method by Hussey, Liao, and Baker (50b), who had obtained only the diol, 82, upon lithium aluminum hydride reduction of the p-toluenesulfonate ester, 83.



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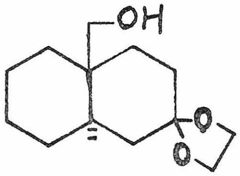

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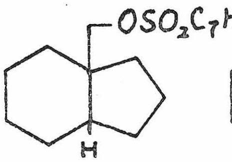

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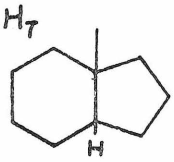

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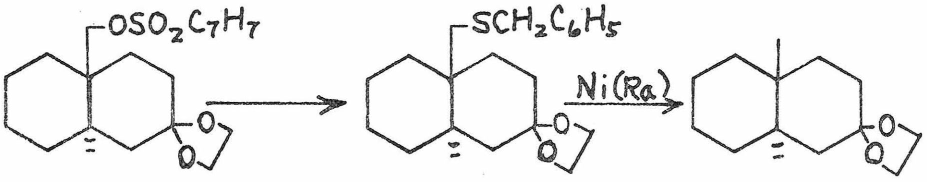

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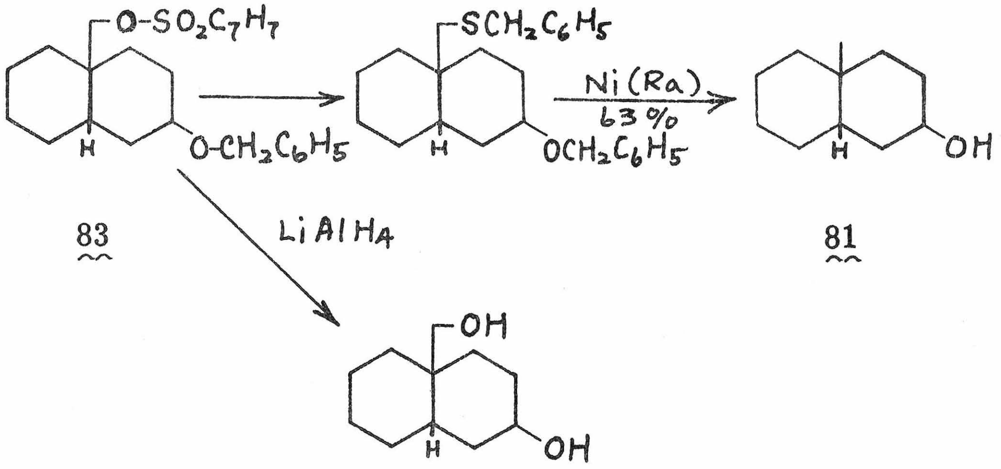
The reduction of phosphoryl esters in lithium-ethylamine solutions as a means of deoxygenation suffers from a large number of limitations. Many other functional groups are reduced under the



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reaction conditions (67). These include terminal and conjugated olefinic bonds, various aromatic groups, acetylenes, halides, benzylic and allylic ethers and esters, ordinary esters, and others. Use of the deoxygenation of phosphorodiamidate esters by the milder reducing agent, lithium-biphenyl, ought to extend the scope of the technique, since isolated olefinic bonds, and simple aromatic structures should be stable to this reagent under the conditions needed for reductive fission of the phosphoryl ester. Even terminal olefins, which are rapidly reduced by lithium-ethylamine solutions, but are not reduced by lithium-ammonia, ought to be stable to lithium-biphenyl, since biphenyl does accept electrons from lithium in ammonia. Aromatic ethers are cleaved by lithium-biphenyl, but only through use of elevated temperatures and extended reaction times (39).

Experimental Section

(a) Melting points (mp) were determined on a micro hot stage and are uncorrected.

(b) Infrared spectra (ir) were determined on a Perkin-Elmer 237B grating infrared spectrophotometer. Solution spectra were observed in 0.2 mm cavity cells using chloroform as solvent and polystyrene calibration bands (2850. and 1601.4 cm^{-1}).

(d) Nuclear magnetic resonance spectra (nmr) were determined on a Varian A-60A or a T-60 spectrometer. Resonances are recorded in ppm (δ) downfield from tetramethylsilane.

(e) Gas chromatographic (gc) analyses were performed on an F & M Model 810 Research Chromatograph equipped with hydrogen flame detectors. The column dimensions were $6' \times 1/8''$, the packing was 4% SE 30 on "diatoport S" and the carrier gas (helium) flow rate was maintained at 60 ml/min.

(f) Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

(g) Anhydrous solvents were purified by the designated method just before use. Ether, tetrahydrofuran, and dimethoxyethane were distilled from lithium aluminum hydride; pyridine, triethylamine, and <u>t</u>-butyl alcohol were distilled from calcium hydride; hexamethylphosphoramide was distilled from Linde 13X molecular sieves at 1 mm and 85-90° and was stored over the seives. Pentane was distilled using no precautions for the exclusion of moisture; petroleum ether refers to the fraction of boiling point (bp) 30-60° as supplied by J. T. Baker Chemical Company.

(h) Unless otherwise indicated, reductions were carried out under a positive argon pressure (mineral oil bubbler). Other reactions were run under a positive nitrogen pressure (mercury bubbler).

Preparation of Starting Materials

Cholestanone. -- Cholestan-3-one, mp 124-128° [lit 128-130° (68)], was prepared *via* the lithium-ammonia reduction of cholest-4-en-3-one, mp 80-82°, which had been made using the procedure of Fieser (69).

3-Acetoxycholest-2-ene. -- The enol acetate of cholestanone was made from cholestanone, mp 124-128°, using acetyl chloride and acetic anhydride. The enol ester melted from 92-95° [lit 93-98° (70)].

2-Bromocholestan-3-one. -- Bromocholestanone, mp 166.5-167° [lit 169-170° (71)], was prepared by the method of Djerassi and Scholz (72).

3β-Cholestanol. -- Cholestanol, mp 140-142° [lit 142-143° (73)], was prepared by the reduction of cholestanone with lithium *tris* *t*-butoxy-aluminum hydride. Cholestanol, mp 139-141°, was also obtained from Matheson, Coleman, and Bell.

3β-Methylcholestan-3α-ol (**43**) (54). -- A solution of 390 mg (1 mmole) of cholestanone, mp 124-128°, dissolved in 10 ml ether was added to a solution of 1 ml of 1.7 *M* (1.7 mmole) of methyllithium in 40 ml of ether. After 6 hours at room temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride, diluted with 50 ml of ether and washed with 100 ml of water and 100 ml of brine. The solution was then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was separated into the two components on a 20 × 20 cm × 2.5 mm silica gel plate using 7:1 benzene/ether as eluent. The material in the faster moving band, R_f *ca*. .45, consisted of 200 mg (50%) of the white crystalline alcohol, mp 120-124° [lit mp 126-127° (54)]: ir ($CHCl_3$) 3600 cm^{-1} (–OH); nmr ($CDCl_3$) δ 2.5-0.5 (complex).

(2, 2-Ethylenedioxy-1, 2, 3, 4, 4a, 5, 6, 7-octahydronaphthy-4a-methanol (**50**) (61). --

a) **4a-Methoxycarbonyl-3, 4, 4a, 5, 6, 7-hexahydro-(1H)-naphthalenone** (74). -- A method similar to one used by Marshall, Faubl, and Warne (49) was used in the preparation of this compound. A solution of 10 g (0.44 mole) of methyl vinyl ketone, obtained from a freshly opened bottle, and 10 ml of methanol was added over a period of 1 hour to a mixture of 20 g (*ca*. 0.13 mole) of ethyl cyclohexanone-2-carboxylate (40% of methyl ester), 0.50 g (0.013 mole) of sodium methoxide, and 500 ml of methanol which was cooled in a bath kept at 0°. After an additional 0.5 hour, 30 g (0.75 mole) of sodium methoxide was added, and the solution was stirred at room temperature for 22 hours. At the end of this time, the reaction mixture was poured into a mixture of 900 g of ice and 250 ml of concentrated aqueous hydrochloric acid, and the resulting slurry was extracted with three 300 ml portions of benzene. The combined organic layers were washed with 200 ml of 10% aqueous sodium bicarbonate and 200 ml of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was then fractionally distilled, the fraction boiling from 130-150° (1 mm) being retained. The ketone thus obtained consisted of a colorless oil weighing 17 g (67%): ir 1725 cm^{-1} (acetate), 1670 (ketone), 1623 (C=C); nmr δ 5.95 (s, 1, vinyl), δ 3.78 (OCH_3).

b) (2, 2-Ethylenedioxy1, 2, 3, 4, 4a, 5, 6, 7-octahydronaphthyl-4a-methanol (**50**). -- The method of Minckler, Hussey, and Baker (74) was used to prepare the ketal of the keto ester, **75**. Thus, a solution of 17 g of ketone **75** (0.082 mole), 80 ml of ethylene glycol, 1.2 g (0.0063 mole) of p-toluenesulphonic acid-monohydrate, and 1.4 ℓ of benzene were heated at reflux, with provision for the removal of water, for 14 hours, and then poured into a mixture of equal portions of ice and sodium bicarbonate. The layers were separated, the aqueous layer was extracted with two 200 ml portions of benzene, and the combined organic phases were washed with 600 ml of water and 600 ml of brine. The solvent was removed in vacuo, leaving 20.3 g of residue: ir 1725 cm^{-1} (C=O), 1658 (C=C); nmr ($CDCl_3$) δ 5.6 (vinyl), δ 3.94 (ketal), δ 3.70 ($O-CH_3$).

Of this material, 19.4 g (0.077 mole) was dissolved in 100 ml of ether and added to a slurry of 7 g (0.2 mole) of lithium aluminum hydride in 400 ml of ether. After the mixture had been stirred for three hours, sodium sulphate-decahydrate was added cautiously until no gray color remained, anhydrous sodium sulphate was added, and the resulting suspension was stirred for 10 hours. Then, the solids were filtered off, and the solvent was removed in vacuo, leaving

17.5 g (103%) of an off-color oil. This material was triturated with a small portion of pentane, and the crystalline substance thus obtained was recrystallized from ether/hexane, giving 10.1 g (57%) of white crystalline alcohol **50**, mp 89.5-91.5° [lit 90.6-92.0° (61)]; ir ($CHCl_3$) 3600 cm^{-1} (OH), 1565 (C=C); nmr ($CDCl_3$) δ 5.64 (s, 1, vinyl), δ 4.00 (s, 4, ketal), δ 3.67 (s, 2, hydroxymethylene).

(2, 2-Ethylenedioxy-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydronaphthyl)-4a-methanol (**54**) (74). -- Catalytic hydrogenation of 800 mg (3.6 mmoles) of alcohol **50** in 10 ml of ethanol, using 30 mg of 5% palladium on charcoal, afforded 800 mg of saturated alcohol after 20 hours of reaction time at atmospheric pressure and uptake of 55 ml (uncorrected -83%) of hydrogen. This represents a 97% yield. The alcohol, a colorless oil, was not purified further [lit mp 65.3-67° (74)]: ir ($CHCl_3$) 3600 cm^{-1} (OH); nmr ($CDCl_3$) δ 3.94 (s, 4, ketal), δ 3.55 (s, 2, hydroxymethylene), δ 2.96 (s, 1, –O–H).

Phosphorylating Agents

Diethylphosphorochloridate, bp 105-107° (40 mm) [lit 93-95 (18 mm) (75)], was prepared by the method of McCombie, Saunders, and Stacey (75).

N, N, N′, N′-Tetramethyldiamidophosphorochloridate, bp 96-98° (4 mm) [lit 98 (15 mm) (76)], was prepared by the procedure of Crunden and Hudson (76).

Preliminary Experiments

3-Chloro-2-methyl-cyclohex-2-enone (9). -- The procedure of Zav'yalov and Kondratieva (12) was followed. To a stirred suspension of 5.0 g (0.04 mole) of 2-methyl-1,3-hexanedione (**8**) (mp 204-207°) in 30 ml of chloroform was added 1.2 ml (0.013 mole) of phosphorus trichloride. This mixture was heated at reflux for period of 4 hours, poured into ice-water, and extracted with two 20 ml portions of ether. The combined ethereal layers were washed successively with 20 ml of 10% aqueous potassium hydroxide, 20 ml of water, and 20 ml of brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was evaporatively distilled at 170° (bath temp) and 24 mm [lit bp 83-84 (7mm) (12)] The resulting chloroketone, **9**, amounted to 4.98 g (87%); ir ($CHCl_3$) 1675 cm^{-1} (C=C) 1625 (C=C); nmr ($CDCl_3$) δ 1.92 (t, 3, J = 0.6 Hz. CH_3), n_D^{25} 1.5105 (lit n_D^{20} 1.5172).

1-Acetoxy-2,3,3-trimethylcyclohexene (15). -- A solution of lithium dimethyl cuprate (13) was prepared by the addition of 75 ml of 2.0 *M* (0.15 mole) of methyllithium to a stirred slurry of 14.60 g (0.075 mole) of cuprous iodide in 50 ml of ether. After the initial yellow precipitate had disappeared, a solution of 5.0 g (0.035 mole) of chloro-enone **9** in 10 ml of ether was added dropwise during a 25 minute period. The mixture, which slowly deposited a green precipitate, was stirred for an additional 2.5 hours, cooled to 0°, and treated with 10 ml (*ca.* 0.1 mole) of acetic anhydride. Following another 2.5 hour's reaction time, 5 ml more of acetic anhydride was added. The reaction mixture, after an additional hour, was poured into a slurry of ice and ammonium chloride, and the resulting slush was extracted with three 100 ml portions of ether. The combined ethereal layers were washed with 100 ml each of saturated aqueous sodium bicarbonate, water, and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was evaporatively distilled at 100° (bath temp) and 5 mm and give 4.62 g (74%) of enol acetate as a colorless oil: ir ($CHCl_3$) 1743 cm^{-1} (C=O) 1664 (C=C–O); nmr ($CDCl_3$) δ 2.11 (s, 3, acetyl), δ 1.04 (S, 2 × 3, *gem*-dimethyl). This material was suitable for combustion analysis.

Anal. Calcd for $C_{11}H_{18}O$: C, 72.49; H, 9.95; Found: C, 72.33; H, 9.95.

Bromination of Enol Acetate 15. -- A solution of 74 $\mu\ell$ (1.35 mmole) of bromine in 15 ml of chloroform was added during a 30 minute period to a solution of 246 mg (1.35 mmole) of ester **15** in 30 ml of carbon tetrachloride. The temperature was maintained at about 0° by an ice-water bath during the addition. After 30 more minutes' stirring, the volatile components of the mixture were removed on a rotary evaporator. The residue consisted of off-color oily crystals which turned to an oil upon standing at room temperature for two hours. The gc trace of this substance (130°, rt 3.9 min) showed it to be different from the starting material (rt 2.7 min), and the ir spectrum indicated the presence of a haloketone (1720 cm^{-1}). Attempted evaporative distillation of this material led to a complex mixture (gc). The bromoketone from another 380 mg (2 mmoles) of enol acetate was dissolved in 15 ml of methanol and treated with 180 mg of sodium borohydride, and the resulting mixture was diluted with 40 ml of pentane and 60 ml of water, the layers were separated, and the aqueous layer was extracted with four 30 ml portions of pentane. The combined organic layers were washed with 10 ml of water and 20 ml of brine, dried (Na_2SO_4), and concentrated in vacuo. The gc trace of the residue showed only two low-boiling components (130°, rt 1.4 and 1.8 min) and the infrared spectrum indicated the presence of an alcohol (3600 cm^{-1}). This material was chromatographed on 15 g of activity III neutral alumina (Woelm). The fractions representing the higher boiling substance was eluted with 1% ether in petroleum ether. The infrared spectrum indicated the presence of an alcohol (3600 cm^{-1}), but no green coloration appeared when a copper wire which had been dipped in this alcohol was held above a Bunsen burner (Beilstein test).

Phosphorylation

Cholest-2-en-3-yl diethyl phosphate (19). --

A. The general procedure of House and Trost was used to generate the enolate (25). Thus, a solution of 340 mg (0.82 mmole) of cholest-2-en-3-yl acetate (**21**), mp 92-95°, in 4 ml of dimethoxyethane was added to a solution of 0.90 ml of 2.1 *M* (1.8 mmole) of methyllithium in 4 ml of dimethoxyethane. The mixture was stirred for thirty minutes at room temperature, treated with 0.8 ml (*ca.* 5 mmoles) of diethylphosphorochloridate and stirred for an additional 5 hours. Then, the reaction mixture was poured into a slurry of ice-sodium bicarbonate and extracted with three 60 ml portions of ether. The combined ethereal phases were washed with 60 ml of saturated aqueous sodium bicarbonate and 60 ml of brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue, which amounted to about 500 mg, was chromatographed on a 2 × 18 cm column containing 30 g of silica gel. The fraction containing the desired product appeared after the column had been eluted with 150 ml of a 25% solution of ethyl acetate in benzene. The enol phosphate recovered amounted to 310 mg (72%) and consisted of white prisms, mp 46-48°: ir ($CHCl_3$) 1690 cm^{-1} (C=C=O), 1265 ($P \rightarrow O$), 1030 (P–O–C sat), 970 (P–O–C vinyl); nmr ($CDCl_3$) δ 5.28 (broad, s, 1, vinyl), δ 4.1 (quint., 4, apparent J = 7 Hz, phosphate methylene). A portion of the material from method "B" was used as the analytical sample without further purification.

Anal. Calcd for $C_{31}H_{55}O_4P$: C, 71.22; H, 10.60; P, 5.92. Found: C, 71.25; H, 10.55; P, 5.92.

B. A flask containing a mixture of 830 mg (18 mmoles) of 2-bromocholestan-3-one, mp 163-165, and 0.50 ml of carefully distilled triethyl phosphite was immersed in an oil bath, which was then heated to 140°. After the solid had disappeared, the bath was cooled to 120° and the reaction mixture was stirred for 3.5 hours. The mixture was then dissolved in ethyl acetate and filtered through a 2 × 15 cm column containing 17 g of silica gel. The phosphate recovered amounted to 840 mg (92%) and consisted of white needles, mp 49-51°. The spectral characteristics (ir, nmr) were identical to those of the ester prepared by method "A".

Treatment of 2-bromocholestanone with triethyl phosphite in ethanol. -- A mixture 93 mg (0.2 mmole) of 2-bromocholestanone, 33 mg (0.2 mmole) of triethyl phosphite, and 5 ml of ether was stirred at room temperature for 2 hours, and the volatile components were removed on a rotary evaporator. The infrared spectrum of the crystalline residue indicated that it was starting material.

Treatment of 2-bromocholestanone with triethyl phosphite in ether. -- The proportions of reactants used above was heated at reflux for a period of 2 hours in 5 ml of ether. Again, the infrared spectrum of the residue after evaporation of the solvent showed the presence of only starting material.

Diethyl 2, 3, 3-trimethylcyclohexen-1-yl phosphate (25). -- The enolate anion from 500 mg (3.5 mmole) of chloroketone **9** was generated in 10 ml of ether according to the procedure used for the preparation of enol acetate **15**. The resulting mixture was treated with 4 ml (*ca.* 30 mmole) of diethylphosphorochloridate, stirred for 3 hours at room temperature, and poured onto a slurry of sodium bicarbonate and ice. The layers were separated, and the aqueous layer was extracted with 30 ml of ether. The combined organic phases were washed with two 20 ml portions of water and 20 ml of brine, dried, and concentrated *in vacuo*. The residue was dissolved in a small portion of 30% ether in petroleum ether, and chromatographed on a 2.5 × 22 cm column of 75 g of silica gel. The column was eluted with about 440 ml of 30% ether in petroleum ether and 120 ml of pure ether. The enol phosphate appeared in the latter portion. The recovered phosphate was evaporatively distilled at 100° (bath temp) and 4 mm. The distillate, a colorless oil amounted to 590 mg (62%): ir ($CHCl_3$) 1685 cm^{-1} (C=C–O), 1260 (P→O), 1030 (P–O–C sat), 972 (P–O–C vinyl); nmr ($CDCl_3$) δ 4.09 (quint, 4, apparent J = 7 Hz, phosphate methylene), δ 1.32 (t, 6, J = 7 Hz, phosphate methyl), δ 1.00 (S, 2 × 3, *gem*-dimethyl). The material used for analysis was obtained directly from a similarly prepared portion of ester **25**.

Anal. Calcd for $C_{13}H_{25}O_4P$: C, 56.51; H, 9.12; P, 11.21. Found: C, 56.34; H, 9.17; P, 11.16.

Diethyl 2,2,5,5-tetramethylcyclohexen-1-yl phosphate (27). -- Lithium dimethyl cuprate was generated at 0° from 9.6 g (0.05 mole) of cuprous iodide and 50.0 ml (0.10 mole) of 2.0 M methyllithium in a three-necked flask equipped with a mechanical stirrer and a dropping funnel. A solution of 5.54 g (0.04 mole) of isophorone in 30 ml of ether was added dropwise over a period of 30 minutes. This mixture was stirred for 2 hours at 0°, and then the dropping funnel was replaceed by another which had a small glass wool plug above the stopcock. A 50 ml portion of triethylamine and 34.4 g (0.2 mole) of diethyl phosphorochloridate were added to this funnel, and the resulting solution was added rapidly to the reaction mixture. The funnel was washed through with 20 ml of ether, and the yellow slurry was stirred for 1 hour at room temperature. At the end of this time, the residual organo-copper compounds were decomposed with a small portion of saturated aqueous sodium bicarbonate. The reaction mixture was washed with two 500 ml portions of cold 1 M aqueous ammonium hydroxide, 100 ml of water, and 100 ml of brine. Each wash was extracted with 200 ml of ether, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in ether and filtered through 600 g of silica gel (Merck). The residue from the evaporation of the ether was evaporatively distilled at 100° (air bath temp) and 0.1 mm, affording 10.1 g (87%) of enol phosphate 27: ir ($CHCl_3$) 1678 cm^{-1} (C=C), 1267 (P–O), 1030 (P–O–C sat), 980 (P–O–C vinyl); nmr ($CDCl_3$) δ 5.23 (broad, 1, vinyl), δ 4.10 (quint, 4, apparent J = 7 Hz, phosphate methylene) δ 1.99 (s, 2, allylic), δ 1.04 (s, 2×3, methyl), δ 1.00 (s, 2×3, methyl). This material was suitable for combustion analysis.

Anal. Calcd for $C_{14}H_{27}O_4P$: C, 57.91; H, 9.36; P, 10.67. Found: C, 57.80; H, 9.26; P, 10.49.

Methyl tetramethylphosphorodiamidate (16) (37). -- A mixture of 10 g (0.19 mole), of sodium methoxide, 10 g (0.059 mole) of tetramethyldiamidophosphorochloridate, and 180 ml of ether was stirred at room temperature in a nitrogen atmosphere for 48 hours. The resulting suspension was filtered, and the filtrate was concentrated on a rotary evaporator and distilled. The product, **16**, was collected from 72-74° at 6 mm [lit 60° at 1 mm (37)], amounted to 7.8 g (86%): ir ($CHCl_3$) 1300 cm^{-1} (P–N), 1180 ($P \rightarrow O$), 983 ($P{-}O{-}CH_3$); nmr (neat) δ 2.56 (d, 4, $J = 10$ Hz), δ 3.52 (d, 1, $J = 9$ Hz).

Cholest-2-en-3-yl tetramethylphosphorodiamidate (41). -- A mixture of 1.3 g (3.4 mmole) of cholestanone, mp 124-128°, 190 mg (4.6 mmole) of 58% NaH dispersion, 30 $\mu\ell$ of *t*-butyl alcohol, and 70 ml of dimethoxyethane was heated at reflux for 13 hours. After the mixture had been allowed to cool, 0.8 ml (*ca*. 5 mmole) of tetramethyoxydiamidophosphorochloridate was added from a syringe, and this mixture was stirred for 10 hours at room temperature. The reaction mixture was poured into 100 ml of 10% aqueous hydrochloric acid and an equal portion of ice, and the resulting suspension was extracted with two 100 ml portions of ether. The combined organic layers were washed with two 50 ml portions of water and 100 ml of brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, applied to a 2.5 × 20 cm column containing 95 mg of silica gel, and eluted with ethyl acetate. The enol phosphoroamidate was contained in the fractions following the first 400 ml of eluent, and amounted to 1.28 g (73%) of white needles, mp 93-103°: ir ($CHCl_3$) 1680 cm^{-1} (C=C–O), 1300 (P–N), 990 (P–O–C vinyl); nmr δ 2.63 (d, 12, J = 9 Hz, N-methyls), δ 5.3 (broad s, 1, vinyl). The analytical sample was prepared by recrystallization of a portion of this material from pentane at -5° and melted at 95-105° (needles).

Anal. Calcd for $C_{31}H_{60}N_2O_2P$: C, 71.08; H, 11.54; N, 5.35; P, 5.91. Found: C, 71.17; H, 11.34; N, 5.32; P, 5.82.

Diethyl 3β-methylcholestan-3α-yl phosphate (44). -- A solution of 70 mg (0.17 mmole) of alcohol **43** in 10 ml of ether was treated successively with 0.1 ml of 2.4 *M* *n*-butyllithium (0.24 mmole) in hexane and 0.6 ml (*ca.* 3 mmole) of diethylphosphorochloridate. The mixture was stirred for 10 hours and then poured into a slurry of equal portions of ice and sodium bicarbonate. After the aqueous layer had been separated, the organic layer was washed with 20 ml of water and 20 ml of brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was streaked onto a 20 × 20 cm × 2.5 mm silica gel plate, which was developed twice with benzene. The desired ester, **26**, was recovered from a band of R_f 0.1 and amounted to 76 mg (82%). This material would not crystallize: ir ($CHCl_3$) 1300 cm^{-1} (C–N–), 1190 (P→O), 990 (C–O–P); nmr ($CDCl_3$) δ 4.2 (apparent quint, 4, J = 9 Hz, phosphate methylene). A portion of this material was used directly as the analytical sample.

Anal. Calcd for $C_{32}H_{59}O_4P$: C, 71.33; H, 11.04. Found: C, 71.05; H, 11.33.

Cholesteryl diethyl phosphate (46). -- A mixture of 1.0 g (2.6 mmole) of cholesterol, mp 149-152, 2 ml (*ca.* 10 mmoles) of diethylphosphorochloridate, and 50 ml of pyridine was stirred at room temperature during a 50 minute period, poured into a mixture of equal portions of 85% lactic acid and ice, and extracted with three 40 ml portions of ether. The combined organic layers were washed with two 200 ml portions of ice-cold 5% aqueous potassium hydroxide and 200 ml of brine, dried (Na_2SO_4), and concentrated *in vacuo*. The cholesteryl diethyl phosphate (46) thus obtained amounted to 1.3 g (94%), and consisted of white platelets, mp 76-79°: ir ($CHCl_3$) 1668 cm^{-1} (C=C), 1255 (P–O), 1023 (P–O–C); nmr ($CDCl_3$) δ 5.4 (broad, 1, vinyl), δ 4.1 (quint, 5, apparent J = 7 Hz, phosphate methylene, phosphate methinyl). The analytical sample was prepared by further purifying a portion of the material on a 20 × 20 cm × 2.5 mm silica gel plate, using ether as eluent (R_f 0.1). This substance was recrystallized twice from pentane at 0°C to a melting point of 75-76.5°.

Anal. Calcd for $C_{31}H_{55}O_4P$: C, 71.22; H, 10.61; P, 5.93. Found: C, 71.02; H, 10.61; P, 5.72.

Cholestanyl diethyl phosphate (48). A mixture of 310 mg (0.81 mmole) of 3β-cholestanol, mp 140-142°, 1.2 ml (*ca.* 7 mmoles) of diethylphosphorochloridate, and 25 ml of pyridine was treated exactly as was the mixture used for the preparation of cholesteryl diethyl phosphate (**46**). This procedure afforded 410 mg (94%) of cholestanyl diethyl phosphate (**48**), which existed as white, waxy prisms, mp 67-71°: ir ($CHCl_3$) 1260 cm^{-1} ($P \rightarrow O$), 1025 (P–O–C); nmr ($CDCl_3$) δ 4.1 (quint, 5, apparent J = 7 Hz, phosphate methylene and phosphate methinyl). For the analytical sample, a portion of this material was recrystallized two times from pentane at -30° to give white prisms, mp 66.5-69.5°.

Anal. Cacd for $C_{31}H_{57}O_4P$: C, 7095; H, 10.95; P, 5.90. Found: C, 71.15; H, 10.89; P, 5.72.

Cholestanyl tetramethylphosphorodiamidate (49).

A. A mixture of 200 mg (0.52 mmole) of 3β-cholestanol, mp 140-142°, 2 ml (*ca.* 10 mmoles) of tetramethyl diamidophosphorochloridate, and 25 ml of pyridine was stirred at room temperature for a period of 10 hours. The reaction mixture was then diluted with 30 ml of ether and poured into a mixture of 60 ml of water, 60 ml of ether, and 10 ml of 10% aqueous hydrochloric acid. The layers were separated, and the ethereal layer was washed with 50 ml of water, two 50 ml portions of saturated aqueous copper sulfate, 50 ml of water, and 50 ml of brine. The solution was dried (Na_2SO_4), concentrated *in vacuo*, dissolved in ethyl acetate, and chromatographed on a 2 × 18 cm column filled with 30 g of silica gel. The phosphorodiamidate was eluted after 200 ml of solvent and afforded 110 mg (40%) of white platelets, mp 144.5-146.5°, upon concentration: ir ($CHCl_3$) 1305 cm^{-1} (P–N), 985 (P–O–C); nmr ($CDCl_3$) δ 2.7 (d, 12, $J = 9$ Hz, N-methyls). For the analytical sample, a portion of the purified reaction product was recrystallized from ethyl acetate to give white needles, mp 144.5-146.5°.

Anal. Calcd for $C_{31}H_{62}O_2N_2P$: C, 70.81; H, 11.88; N, 5.33; P, 5.89. Found: C, 11.01; H, 11.65; N, 5.42; P, 5.74.

B. A solution of 400 mg (1.0 mmoles) of cholestanol, mp 140-142°, in 400 ml of ether was treated with 0.5 ml (1.1 mmole) of 2.16 *M* methyllithium, the resulting mixture was stirred for one hour at room temperature, and 1 ml (*ca.* 6 mmoles) of tetramethyldiamidophosphorochloridate was added. After 16 hours stirring, this mixture was poured into 100 ml of water and extracted with two 50 ml portions of ether. The combined ethereal layers were washed with two 40 ml portions of water and 40 ml of brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed according to the procedure in A, affording 202 mg (38%) of ester **31**. This sample melted from 143 to 145° and had the same spectral properties (ir) as the material from A.

C. A solution of 428 mg (1.11 mmole) of 3β-cholestanol, mp 139-141°, and 2 mg of 1,10-phenanthroline-hydrate in 20 ml of dimethoxyethane was treated with 2.4 *M* butyllithium solution until a purple color persisted, the volume added being 0.5 ml (1.2 mmole).

Then, a solution containing 1 ml (*ca.* 6 mmole) of tetramethyldiamidophosphorochloridate and 6 ml of triethylamine was added by syringe. The mixture was stirred for two hours at room temperature, poured into a slurry of 100 ml of aqueous 10% potassium hydroxide and an equal portion of ice, and extracted with three 50 ml portions of ether. The combined organic phases were washed with 30 ml of 10% aqueous potassium hydroxide and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue, upon trituration with a small amount of pentane, afforded 5.45 mg (94%) of ester **49**. The material prepared by this method had a melting point of 147-150° and spectral characteristics (ir, nmr) essentially identical to those of the product from the above preparation.

Diethyl (2, 2-ethylenedioxy-1, 2, 3, 4, 4a, 5, 6, 7-octahydronaphthyl)-4a methyl phosphate (51). -- A solution of 300 mg (1.34 mmoles) of alcohol **50** in 10 ml of ether was treated with 0.7 ml of 2.4 *M* (1.7 mmole) *n*-butyllithium followed by 0.5 ml (*ca.* 3 mmoles) of diethylphosphorochloridate. After 10 hours, the reaction mixture was diluted with additional ether and filtered through a short column of alumina (Activity III). This procedure afforded a colorless oil which was evaporatively distilled at 140° (bath temp) and 0.1 mm, to give 280 mg (60%) of ester **51**: ir ($CHCl_3$) 1670 cm^{-1} (C=C), 1260 ($P \rightarrow O$), 1025 (–P–O–C–); nmr ($CDCl_3$) δ 5.60 (s, 1, vinyl), δ 4.1 (mult, 10, $-OCH_2-$), δ 1.33 (t, 6, J = 7 Hz, phosphate methyls). This material was suitable for combustion analysis.

Anal. Calcd for $C_{17}H_{29}O_6P$: C, 56.66; H, 8.11; P, 8.59. Found: C, 56.48; H, 8.22; P, 8.65.

(2,2-Ethylenedioxy-1,2,3,4,4a,5,6,7-octahydronaphthyl)-4a-methyl Tetramethylphosphorodiamidate (52). -- The general method used in the preparation of 49(B) was used in this esterification. A solution of 2.0 ml of 2.4 *M* (4.8 mmoles) of *n*-butyllithium in hexane was added to a solution of alcohol 50 in 45 ml of glyme. Then, 4 ml (*ca.* 20 mmoles) of tetramethyldiamidophosphorochloridate was added, and the mixture was stirred for two hours at room temperature. The reaction mixture was worked up according to the described procedure, and the residue was vaporatively distilled at 150° (bath temp) and 0.1 mm. The distillate, weighing 1.6 g, represented a 93% yield of the desired ester (52): ir ($CHCl_3$) 1665 cm^{-1} (–C=C) 1035 (–P–N), 1180 (P→O), 980 (P–O–C); nmr ($CDCl_3$) δ 5.57 (s, 1, vinyl), δ 3.94 (apparent s, 6, $-O-CH_2-$), δ 2.66 (d, 12, J = 9 Hz, N-methyls). A portion of the material from a similar preparation was used as the analytical sample.

Anal. Calcd for $C_{17}H_{31}N_2O_4P$: C, 56.96; H, 8.72; N, 7.82; P, 8.64. Found: C, 56.94; H, 8.92; N, 7.71; P, 8.56.

Diethyl(2,2-ethylenedioxy-1,2,3,4,4aβ,5,6,7,8,8aβ-decahydronaphthyl)-4aβ-methyl phosphate (54). -- A solution of 800 mg (35 mmoles) of alcohol 53 in 12 ml of pyridine was cooled to 0° and treated with 3 ml (*ca.* 20 mmoles) of diethylphosphorochloridate, and the resulting mixture was allowed to stand for ten hours at -16°.

The reaction mixture was then diluted with 30 ml of ether and filtered through a short column of alumina (Activity III). The resulting colorless oil was evaporatively distilled at 140° (bath temp) and 0.1 mm. The distillate, ester 54, amounted to 830 mg (64%): ir ($CHCl_3$) 1260 cm^{-1} (P→O), 1030 (P–O–C); nmr ($CDCl_3$) δ 4.1 (mult, 10, –O–CH_2–). A portion of this material was used directly as the analytical sample.

Anal. Calcd for $C_{17}H_{31}O_6P$: C, 56.34; H, 8.62; P, 8.55. Found: C, 56.44; H, 8.78; P, 8.48.

(2,2-Ethylenedioxy-1,2,3,4,4aβ,5,6,7,8,8aβ-decahydronaphthyl)-4aβ-methyl phosphorodiamidate (55). -- The alcoholate from 1.10 g (4.87 mmoles) of alcohol 53 was generated in 50 ml of glyme with 2.3 ml of 2.4 *M* (5.5 mmoles) *n*-butyllithium and was phosphorylated with a solution of 2.6 ml (*ca.* 14 mmoles) of tetramethyldiamidophosphorochloridate in 5 ml of triethylamine according to the procedure used in preparation of 31(B). The crude ester, consisting of oily crystals, mp 90-95°, was triturated with a small amount of pentane to afford 1.62 g (92%) of 42 as white prisms, mp 102-104°: ir ($CHCl_3$) 1305 (P–N), 1185 (P→O), 990 (P–O–C); nmr ($CDCl_3$) δ 3.94 (mult, 6, –O–CH_2–), δ 4.34 (d, 12, $J = 9$ Hz, N-methyls). A portion of this material was evaporatively distilled at 150° (bath temp) and 0.1 mm and was submitted for elemental analysis.

Anal. Calcd for $C_{17}H_{33}N_2O_4P$: C, 56.65; H, 9.23; N, 7.77; P, 8.60. Found: C, 56.57; H, 9.48; N, 7.55; P, 8.38.

Reductions

The general method for reductions in ethylamine. -- Ethylamine was distilled from the tank through a drying tower that contained potassium hydroxide pellets and was collected in a three-necked round bottom flask which was equipped with an argon inlet, a magnetic stirring bar, and a rubber septum. The lithium wire was cleaned before use by rapid wash in methanol and a rinse in pentane. A solution of the designated amount of lithium in ethylamine was prepared, the bath temperature was adjusted to that indicated, and the phosphoryl ester and alcohol dissolved in tetrahydrofuran were added dropwise from a syringe. The reaction was allowed to continue for the designated time before it was quenched.

Reduction of cholestenyl diethyl phosphate (**19**). -- The reaction was carried out using 160 mg (0.31 mmole) of the ester (**19**), 40 mg (5.0 mmoles) of lithium, 25 ml of ethylamine, 80 ml (0.86 mmole) of *t*-butyl alcohol, and 10 ml of tetrahydrofuran. The reaction time was 1.5 hour, and the reaction mixture was quenched with ethanol. After the ethylamine had been driven off, the mixture was poured into 50 ml of water and extracted with two 60 ml portions of petroleum ether. The combined organic layers were washed with 20 ml of brine and dried (Na_2SO_4). Removal of solvent left 116 mg (100%) of white crystals, mp 68.5-69°. Recrystallization from ether/acetone provided 97 mg (85%) of needles, mp 75-76° [lit 74-75 (70)]:

ir ($CHCl_3$) 1655 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.54 (s, 2, vinyl).

Reduction of phosphorodiamidate (41). -- This reduction employed 335 mg (0.64 mmoles) of the ester, 70 mg (10 mmoles) of lithium, 64 mg (0.86 mmole) of t-butyl alcohol, 25 ml of ethylamine, and 10 ml of tetrahydrofuran. The work up was carried out according to the procedure in the previous reduction and afforded 217 mg of white crystals, mp 67-68°. This material was filtered through a short plug of alumina (Woelm neutral), a procedure which resulted in the recovery of 195 mg (83%) of cholest-2-ene, mp 73-74°. The spectral properties (ir) of this sample are the same as those of that from the preceding reduction.

Reduction of ester (44). -- The procedure was performed using 30.0 mg (0.058 mmole) of the ester, 44, 10 mg (1.4 mmole) of lithium, 10 $\mu\ell$ (0.1 mmole) of t-butyl alcohol, 5 ml of tetrahydrofuran, and 12 ml of ethylamine. The mixture was stirred at -25° for 40 minutes and then was quenched with saturated aqueous ammonium chloride. The ethylamine was allowed to evaporate, and the residue was diluted with 15 ml of pentane and washed with 20 ml of water. The aqueous layer was extracted with an additional 20 ml of pentane, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The 20.2 mg (91%) of residue had a melting range of 99-100°, α_D^{25} + 26.9° (c 1.38). This material was recrystallized from chloroform/methanol, affording 18 mg (80%) of crystals, mp 100-101°. A second recrystallization left clear crystals, mp 101-102°. The highest reported melting point for 3β-methylcholestane (**56**) is 105-106°, α_D + 28° (54) ir ($CHCl_3$) (hydrocarbon); nmr ($CDCl_3$) (hydrocarbon).

Reduction of cholesteryl diethyl phosphate (46). -- This reduction was carried out with 100 mg (0.192 mmole) of the ester, **46**, 50 mg (7.2 mmoles) of lithium, 40 $\mu\ell$ (0.42 mmole) of *t*-butyl alcohol, 12 ml of tetrahydrofuran, and 30 ml of ethylamine. The procedure as used in the previous reduction resulted in the recovery of 54 mg (80%) of white crystals, mp 90.5-93°. The reported melting point is 91-92° (78). ir ($CHCl_3$) 1660 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.22 (s, 1, vinyl).

Reduction of cholestanyl diethyl phosphate (48). -- In this case, 142 mg (0.27 mmoles) of the ester, **48**, 70 mg (11 mmoles) of lithium, 60 $\mu\ell$ of *t*-butyl alcohol, 12 ml of tetrahydrofuran, and 20 ml of ethylamine were used. The reaction mixture was quenched with saturated aqueous ammonium chloride after 30 minutes of reaction time at 0°. The mixture was worked up according to the procedure used for the reduction of **46**. The residue was filtered through a short plug of alumina, giving 14 mg of white crystals, mp 77-79.5° trituration with about 0.5 ml of acetone afforded 13 mg (12%) of cholestane mp 78-79.5° [lit, see Table 4]: ir ($CHCl_3$) (only saturated hydrocarbon); nmr ($CDCl_3$) (hydrocarbon).

Reduction of diamidate (49). -- The procedure was used for the reduction of 85 mg (0.165 mmole) of ester **44** with 100 mg (14 mmoles) of lithium and 90 µℓ of *t*-butyl alcohol in 20 ml of tetrahydrofuran and 30 ml of ethylamine. The reduction was allowed to proceed for three hours at 0°, and then isopropyl alcohol was added. After the amine had been allowed to evaporate, the reaction mixture was diluted with 40 ml of petroleum ether and poured into a separatory funnel layered with 70 ml of water and 40 ml of petroleum ether. The organic layer was washed with 10% aqueous potassium hydroxide and brine, dried (Na_2SO_4), and concentrated *in vacuo*. In this fashion there was obtained 55 mg (90%) of cholestane as white crystals, mp 79-79.5°. The spectra (ir, nmr) are identical to previous spectra of cholestane.

Reduction of diethyl phosphate 51. -- A solution of 250 mg (0.69 mmoles) of the ester, **51**, in 10 ml of tetrahydrofuran was added to a mixture of 80 mg (12 mmoles) of lithium, 80 µℓ (0.85 mmoles) of *t*-butyl alcohol, 5 ml of tetrahydrofuran, and 25 ml of ethylamine. After the mixture had stirred for 25 minutes at 0°, it was treated with saturated aqueous ammonium chloride, and the amine was allowed to distill away through a 15 cm Vigreux column. The residue was poured into 30 ml of saturated aqueous sodium bicarbonate and extracted with two 30 ml portions of pentane. The combined organic fractions were washed with 20 ml of brine, dried (Na_2SO_4), and concentrated at atmospheric pressure. The residue was evaporatively distilled at 120° (bath temp) and 0.5 mm to afford 135 mg (91%) of the mixture of ketals: nmr ($CDCl_3$) δ 5.38 (s, 0.76, vinyl), δ 0.40 (mult, 0.52; cyclopropyl). The ratio of products is about 3:1. This mixture was dissolved in 6 ml of acetone, treated with 3 mg of para-toluenesulfonic acid, and stirred at room temperature for 3 hours. Then, the reaction mixture was poured into 50 ml of saturated aqueous sodium bicarbonate and extracted with two 30 ml portions of isopentane. The combined organic layers were washed with 30 ml of brine, dried (Na_2SO_4), and concentrated at atmospheric pressure. The residue was chromatographed on a 1 cm × 8 cm containing 10 g of silica gel, the eluent being 9:1 petroleum ether/ether. After 120 ml of solvent had gone through, 20 mg (16%) of the cyclopropyl ketone (**68**) was eluted in 30 ml, while 80 mg (64%) of the unsaturated ketone, **67**, was eluted in 20 ml after an initial 200 ml. The compounds were characterized as the 2,4-DNP derivatives. The cyclopropyl ketone-2,4-DNP was obtained as yellow needles from ethanol, mp 158-160.5° [lit 155-157° (62)]. The unsaturated 2,4-DNP exists as red-orange crystals, mp 171.5-172.5° (ethanol) [lit 168-169° (62)].

Reduction of phosphorodiamidate 52. --

A. The reduction was carried out by the usual manner at -10°, using 330 mg (0.92 mmole) of ester **52**, 60 mg (8.5 mmoles) of lithium, 100 $\mu\ell$ (1.1 mole) of t-butyl alcohol, 20 ml of tetrahydrofuran, and 30 ml of ethylamine. After 40 minutes, ammonium chloride solution was added, and the mixture, after the amine had been distilled off, was poured into saturated aqueous sodium bicarbonate and extracted with two 25 ml portions of pentane. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated at atmospheric pressure. The residue was evaporatively distilled at 120° (bath temp) and 0.5 mm, giving 183 mg (97%) of distillate. The spectral characteristics of the product indicated that it was a mixture of **58** and **59**: ir ($CHCl_3$) 3050 cm^{-1} (cyclopropyl), 1660 (C=C); nmr ($CDCl_3$) δ 5.38 (s, 0.66, vinyl), δ 0.40 (mult, 0.74, cyclopropyl).

B. The reduction was performed at -30° (dry-ice, acetone, water) using 110 mg (0.31 mmole) of ester **52**, 30 mg (4.2 mmoles) of lithium, 50 $\mu\ell$ (0.5 mmole) of t-butyl alcohol, 5 ml of tetrahydrofuran, and 10 ml of ethylamine. The product mixture, after distillation amounted to 52 mg (81%), and contained ketals **58** and **59** in a ratio of about 1.5 to 1 (nmr): nmr ($CDCl_3$) δ 5.38 (s, 0.6, vinyl), δ 0.40 (mult, 0.8, cyclopropyl).

C. The reduction was carried out at -78° with the same proportions of materials as were used in A. The mixture of ketals amounted to 178 mg (92%). The nmr spectrum indicated the ratio of products was one to one. nmr ($CDCl_3$) δ 5.38 (s, 0.5, vinyl), δ 0.40 (mult, 1, cyclopropyl).

D. The reduction was also performed with 130 mg (0.36 mmole) of ester **52**, 30 mg (4.3 mmoles) of lithium, 40 $\mu\ell$ (0.42 mmole) of t-butyl alcohol, 10 ml of tetrahydrofuran, and 20 ml of ethylamine at reflux. These conditions resulted in recovery of 71 mg

(93%) of the ketal **58**, which contained about 5% of the cyclopropyl ketal, **59**: nmr ($CDCl_3$) δ 5.38 (s, 1, vinyl), δ 0.40 (mult, 0.1, cyclopropyl).

Stability of the products, 38 and 39, to the reaction conditions. -- The product mixture from example C above, was subjected to the same treatment as the starting material of that reaction. The nmr spectrum of the material recovered did not differ from that of the original mixture.

Attempted reduction of phosphorodiamidate ester 52 with lithium-ammonia. -- A solution of 330 mg (0.92 mmole) of diamidate ester **52** and 15 ml of tetrahydrofuran was added to a refluxing solution of 60 mg (8.5 mmoles) of lithium in 30 ml of ammonia which had been prepared in the same manner as the lithium-ethylamine solutions. After a workup analogous to the preceding experiment, the residue was 280 mg of a substance with the same nmr spectrum as the starting material.

Attempted reduction of diethyl phosphate 54. -- The standard procedure was applied to the reduction of 430 mg (1.24 mmole) of ester **54**, using 130 mg (19 mmoles) of lithium, 170 μℓ (1.8 mmole) of *t*-butyl alcohol, 25 ml of tetrahydrofuran, and 45 ml of ethylamine. The reaction was allowed to proceed for two hours at 0° and was then quenched with saturated aqueous ammonium chloride. The amine was allowed to distill away through a 15 cm Vigreux column, and the residue was poured into 100 ml of water and extracted with two 40 ml portions of pentane. The combined organic layers were washed with 40 ml of brine, dried (Na_2SO_4), and concentrated at atmospheric pressure. There was no residue. It should be noted that the workup to this reaction was accompanied by formation of large quantities of insoluble flocculent white precipitate.

Reduction of phosphorodiamidate 55. -- The same procedure as used above was utilized to reduce 170 mg (0.47 mmole) of the analogous ester, **55**. In this instance, the reaction was carried out using 60 mg (8.7 mmoles) of lithium, 60 μl (0.63 mmole) of *t*-butyl alcohol, 7 ml of tetrahydrofuran, and 20 ml of ethylamine. The oil thus obtained was evaporatively distilled at 120° (oven temp) and 0.5 mm, to afford 96 mg (97%) of the desired product, ketal **43** (63): nmr ($CDCl_3$) δ 3.96 (s, 4, ketal), δ 1.0 (s, 3, methyl). This material was converted to the ketone in the same manner as were ketals **58** and **59**. The material melted from 46-48° and had a mixed melting point of 48-50° with a sample , mp 50-52° from another source (63).

Attempted reduction of phosphorodiamidate ester 55 with lithium-ammonia. -- A solution of 350 mg (0.97 mmole) of diamidate **55**, 100 μl (1.1 mmole) of *t*-butyl alcohol, and 10 ml of tetrahydrofuran was added to a refluxing solution of 10 mg (10 mmoles) of lithium in 35 ml ammonia. The mixture was allowed to reflux for two hours and was quenched with saturated aqueous ammonium chloride. The ammonia was driven off, and the residue was diluted with 50 ml of water and extracted with two 30 ml portions of ether. The ethereal layers were washed with brine, dried (Na_2SO_4), and concentrated at atmospheric pressure. The nmr spectrum of the residue showed that only starting material was present.

2, 3, 3-Trimethylcyclohexene (7) (8). -- A solution of 1.50 g (5.4 mmole) of enol phosphate **25** and 0.5 ml of *t*-butyl alcohol (5.4 mmole) was added by syringe to a stirred mixture of 100 mg (15 mmoles) of lithium in 20 ml of anhydrous methylamine which was cooled in a bath kept at -30°. After two hours, the methylamine was removed by distillation through 6 inch Vigreux column, and the remaining material was flash distilled at 4 mm into a trap cooled in a dry-ice-acetone bath. The distillate a colorless oil, amounted to 407 mg (53%). Only one peak appeared on the gas chromatographic trace of this material (oven temp 40°, rt 2.9 min): ir ($CHCl_3$) 3025 cm^{-1} (C=C-H), 1653 (C=C), 1380 and 1374 (*gem*-dimethyl); nmr (neat) δ 5.3 (s, 1, vinyl), δ 0.96 (s, 2 × 3, *gem*-dimethyl), n_D^{25} 1.5439 [lit n_D^{20} 1.546 (8)].

3, 3, 5, 5-Tetramethylcyclohexene (28) (79). --

A. A 10.1 g (0.035 mole) portion of enol phosphate 27 was added by syringe to a refluxing solution of 1 g (0.15 mole) of lithium in 400 ml of ammonia. After a 30 minute reaction time, 4 ml of triethylene glycol was added, and the ammonia was allowed to distill off over a 60 cm Vigreux column. The entire system was connected to a trap immersed in a dry-ice-acetone bath, and the product was flash distilled at 0.5 mm with no heating. The tetramethylcyclohexene obtained in this fashion was distilled from sodium, bp 154-156° [lit 147.4-9° (79)] and amounted to 940 mg (19%): ir ($CHCl_3$) 1650 cm^{-1} (C=C); nmr (neat) δ 5.43 (s, 2, vinyl), δ 1.73 (s, 2, alyllic), δ 1.32 (s, 2, methylene), δ 1.04 (s, 3 × 3, methyl), δ 1.00 (s, 3, methyl), n_D^{25} 1.4410 [lit n_D^{20} 1.4450 (79)].

B. The procedure used to prepare trimethylcyclohexene 7 was performed using 11.0 g (0.038 mole) of enol phosphate 27, 3.5 ml (0.038 mole) of t-butyl alcohol, 800 mg (0.11 mole) of lithium, and 400 ml of methylamine. After the methylamine had evaporated, 500 ml of water was added, and the hydrocarbon was steam distilled into a cooled graduated cylinder. No more hydrocarbon was brought over after the first 200 ml of water was collected. The layers were separated, and the hydrocarbon layer was distilled from sodium to afford 870 mg (17%) of a colorless liquid, bp 154-158°. The nmr spectrum of this material was the same as that of the hydrocarbon prepared by method A.

Attempted reduction of enol phosphate 19 with lithium-naphthalene. -- A solution of 100 mg (0.19 mmole) of enol phosphate 19, 100 mg (0.77 mmole) of naphthalene and 20 ml of dimethoxyethane was treated with 7 mg (1 mmole) of freshly cut lithium wire. A green color appeared after 5 minutes, but the reaction was allowed to proceed for 1 hour. The mixture was treated with saturated aqueous ammonium chloride, poured into 150 ml of ice water, and extracted with four 50 ml portions of petroleum ether and three 50 ml portions of ether. The organic extracts were combined and concentrated *in vacuo*. The naphthalene was sublimed off, and the residue was chromatographed on a 20 × 20 cm × 2.5 ml silica gel plate (petroleum ether) to give 41 mg (55%) of a ketone (ir) as the only steroidal product. This material had the same gc characteristics as cholestanone (oven temp 260°, rt 4.2 min): ir ($CHCl_3$) 1704 cm^{-1} (C=O).

*Attempted reduction of enol phosphate **19** with lithium-biphenyl.* -- A solution of biphenyl radical anion was prepared by stirring a mixture of 500 mg (3.8 mmoles) of biphenyl and 20 mg (2.9 mmoles) of lithium wire in tetrahydrofuran at 0° for 2 hours. A solution of 100 mg (0.19 mmole) of enol phosphate **19** in 3 ml of tetrahydrofuran was added by syringe, and the mixture was stirred at room temperature for 1.5 hours. It was worked up as in the preceding experiment to afford 50 mg of an oil after the bicyclic materials had been removed by sublimation. The infrared spectrum indicated that this oil was a ketone, and the gc trace indicated that the material was probably cholestanone mixed with a small amount of cholestene (oven temp 260°, rt 4.2, 2.2 min, respectively).

*Base treatment of **19**.* -- Water was added to a mixture of 30 mg (4.4 mmoles) of lithium and 10 ml of tetrahydrofuran until the lithium had disappeared and 40 mg (0.077 mmole) of enol phosphate was added. This mixture was stirred for 20 minutes, poured into 50 ml of water, and extracted with three 30 ml portions of ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The infrared spectrum of the 40 mg of residue was identical to that of the starting material.

Attempted reduction of enol phosphate 19 with lithium-trimesitylborane. -- A solution of the radical anion was prepared by stirring 4 mg (0. 6 mmole) of lithium wire with 18. 0 mg (0. 5 mmoles) of trimesitylborane in 3. 5 ml of tetrahydrofuran for 10 hours at room temperature. Then, 65 mg (0. 12 mmole) of the enol phosphate (**19**) dissolved in 0. 5 ml of tetrahydrofuran was added by syringe. The mixture was stirred for 2 hours and poured into a mixture of 20 ml of petroleum ether and 25 ml of ice-water. The layers were separated, and the aqueous layer was extracted with 30 ml of petroleum ether. The combined organic phases were washed with three 30 ml portions of water and 30 ml of brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in 5 ml of ether, and the trimesitylborane was precipitated out by the addition of 0. 5 ml of ethanol. The supernatant was concentrated and chromatographed on a 20 × 20 cm × 2. 5 ml silica gel plate (petroleum ether then ether), affording 60 mg of a substance whose infrared spectrum indicated that it was starting material.

Reduction of enol phosphate 19 with lithium in hexamethylphosphoramide. -- A mixture of 0. 5 ml of tetrahydrofuran and 2. 0 ml of hexamethylphosphoramide was treated with 20 mg (2. 9 mmoles) of lithium wire and stirred for 1. 5 hour at -5°. The enol phosphate, **19**, dissolved in 3 ml of tetrahydrofuran was added. After the mixture had stirred for 45 minutes at -5°, the reaction was quenched with deuterium oxide, poured into 50 ml of ice-water, and extracted with two 30 ml portions of petroleum ether. The combined organic phases were washed with five 30 ml portions of water and 30 ml of brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was filtered through a short plug of alumina (Activity III) to give 55 mg (76%) of white crystals, mp 69.5-71.5°. A 10% solution of this substance in chloroform exhibited no infrared absorption near 2200 cm^{-1}.

Reduction of 19 with lithium in hexamethylphosphoramide in the presence of excess lithium bromide. -- A saturated solution of lithium bromide in 8 ml of tetrahydrofuran was added to a solution of 20 mg (2.9 mmoles) of lithium, 0.3 ml of tetrahydrofuran, and 1.3 ml of hexamethylphosphoramide which had been formed over 1.5 hour at -10°. Then, the enol phosphate **19** in 0.7 ml of tetrahydrofuran was introduced by syringe. The reaction was allowed to proceed for 45 minutes, and then 1 ml of deuterium oxide was added. The reaction mixture was worked up as in the previous reaction, resulting in the recovery of 52 mg (70%) of non-deuterated cholestene, mp 71.5-72.5°. The infrared spectrum of a 10% solution of this material showed no absorption around 2150 cm^{-1}.

Experiments with lithium metal dispersion. -- The metal used was obtained in the form of a 30% dispersion in paraffin oil. It was prepared for use in the following way. The dispersion was weighed into the reaction vessel, which was equipped with a magnetic stirrer bar, an argon inlet, and a serum stopper. Then a small amount of the solvent to be used in the reaction was introduced, and the suspension was stirred for a few minutes. After the lithium had all come to the surface, the solvent was withdrawn from the bottom of the flask with a syringe and hypodermic needle. This procedure was performed two additional times.

Attempt to dissolve lithium dispersion in methyl tetramethylphosphorodiamidate. -- About 90 mg of lithium metal dispersion was stirred for 40 minutes in 1.6 ml of methyl tetramethylphosphorodiamidate with no appearance of coloration. Therefore, 3 mg of biphenyl was added. The mixture turned to a pale green color, then green with blue streaks, and finally entirely blue-green. During this latter stage, the lithium started to disappear. After 25 minutes of stirring, this mixture detonated.

Reduction of phosphorodiamidate 41 with lithium metal dispersion. --

A. In hexane: A mixture of 300 mg (0.58 mmole) of ester **41**, 240 mg (35 mmole) of lithium dispersion, 550 mg (3.6 mmole) of biphenyl, and 1.5 ml of hexane was stirred for 8 hours at room temperature, treated with deuterium oxide and stirred another 15 minutes. After this time, the resulting suspension was diluted with 15 ml of hexane and washed with successive 20 ml portions of 10% aqueous hydrochloric acid, 10% aqueous potassium hydroxide, and brine. The solution was then dried (Na_2SO_4) and concentrated *in* vacuo. The residue was fractionated on a 1.5 cm × 15 cm Sephadex LH 20 column (4:1 chloroform/ether), and the non-aromatic filtrate was separated on a 20 × 20 cm silica gel plate (petroleum ether) to give 170 mg of a mixture of non-crystalline hydrocarbon. The only component discernable in the gc trace was cholestene. The nmr spectrum had two resonances in the vinyl region, at δ 5.6 (cholestene) and δ 5.4. The infrared spectrum had no absorption at 2100-2200 cm^{-1}.

B. In benzene: The procedure was repeated in 1.2 ml of benzene, with 200 mg (0.38 mmole) of the ester, 17, 150 mg (22 mmoles) of lithium dispersion, and 350 mg (2.3 mmoles) of biphenyl. The mixture was stirred for 6 hours and quenched and worked up as in A. The first 4 ml of effluent from the LH 20 column contained traces of a white, crystalline material. The bulk of the material in the next 10 ml was non-crystalline. This substance was separated on a 20 × 20 cm × 2.5 ml silica gel plate, affording 112 mg of non-crystalline material (R_f 0.95) which was again chromatographed in the same fashion, only the center of the band being retained. In this fashion, 80 mg of crystals were recovered. A portion recrystallized from benzene melted at 145-150°: ir ($CHCl_3$) 1650 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.4 (s, 1, vinyl).

Reduction of enol diamidate 41 with lithium biphenyl in tetrahydrofuran. -- A mixture of 500 mg (22 mmole) of lithium dispersion and 200 mg (1.3 mmole) of biphenyl in 2 ml of tetrahydrofuran was stirred for 40 minutes, and 194 mg (0.37 mmole) of the ester, **41**, in 1.5 ml of tetrahydrofuran was added dropwise over a period of one hour. The addition funnel was rinsed through with an additional 1.5 ml of the solvent, and the solution was stirred for another hour. After the excess metal had been destroyed by the cautious addition of isopropyl alcohol, the reaction mixture was diluted with 50 ml of petroleum ether, and washed with 40 ml portions of 10% aqueous potassium hydroxide and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The oily residue was filtered through a 1 × 40 cm LH 20 column in 4:1 chloroform/ether. The desired product, cholestene, appeared in the seventh and eighth 2 ml fractions. This substance was recrystallized from ether-acetone to give 115 mg (84%) of white needles, mp 70.5-71.5°. The spectral characteristics are those of other samples of 2-cholestene.

Attempted formation of deuterocholestene. -- A solution of 110 mg (0.21 mmole) of ester **41** in 2 ml of tetrahydrofuran was added dropwise during a 45 minute interval to a suspension of 18 mg (0.12 mmole) of biphenyl and 50 mg (7.2 mmoles) of lithium metal dispersion in 2 ml of tetrahydrofuran. After an additional 45 minutes, 1 ml of deuterium oxide was added, and the mixture was worked up as in the previous experiments. The 90 mg of crude residue was chromatographed on a 20 cm × 20 cm × 2.5 mm silica gel plate (petroleum ether, R_f 0.95), affording 72 mg (92%) of white crystals, mp 64-65°. Recrystallization from ether-acetone did not result in recovery of material with a higher melting point. The material was not deuterated (ir), and the spectra seemed to be identical to those of other samples of cholest-2-ene.

Attempted reduction of enol phosphorodiamidate 41 with lithium in tetrahydrofuran. -- A mixture of 130 mg (0.24 mmoles) of the ester, **41**, lithium from 200 mg of dispersion, and 3 ml of tetrahydrofuran was treated with 18 μℓ portions of dibromoethane initially, after 6 hours, and after 12 hours. After an additional 6 hours, the reaction mixture was quenched with water, poured into 20 ml of water, and extracted with two 10 ml portions of ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The material recovered had the spectral (ir) characteristics of the starting material, **41**.

Attempted reduction of phosphorodiamidate ester 41 with lithium-biphenyl in hexamethylphosphoramide. -- A 1 *M* solution of lithium-biphenyl was prepared by adding 70 mg (10 mmoles) of lithium wire to a solution of 1.54 g (10 mmoles) of biphenyl in 10 ml of tetrahydrofuran. Of this solution, 10 μℓ (0.01 mmole) was added to a solution of 27 mg (0.05 mmole) of ester **41** and 1 ml of hexamethylphosphoramide contained in an nmr tube which was equipped with a capillary to provide a constant flow of helium gas over the surface of the liquid. The green color did not fade, even after 1 hour. An additional 50 μℓ of radical ion solution was added, helium was bubbled through the solution briefly to mix the contents, and the tube was allowed to stand for 4 hours. The contents of the tube were poured into 10 ml of water and extracted with 10 ml of ether. The ethereal layer was washed with two 50 ml portions of water, 5 ml of brine, dried (Na_2SO_4) and concentrated in vacuo. The residue possessed the spectral characteristics (ir) of the starting material enol ester, **41**.

Treatment of enol diamidate **41** with dilithium-nickel tetraphenylporphin. -- A 0.5 M solution of lithium-naphthalene was prepared by mixing 140 mg (20 mmoles) of lithium wire, 260 mg (20 mmoles) of naphthalene, and 40 ml of tetrahydrofuran, and by stirring this mixture for 4 hours at 0°. A solution of 300 mg (0.43 mmole) of nickel tetraphenylporphin in 10 ml of tetrahydrofuran was cooled to 0° and treated with 1.7 ml (0.86 mmole) of the above solution. The dark purple color of the porphin was slowly replaced by a deep green coloration. After this mixture had stirred for 20 minutes, 100 mg (0.18 mmole) of ester **41**, dissolved in 5 ml of tetrahydrofuran, was added. The stirring was continued for 7 hours at 0°, and the mixture was treated with 3 ml of deuterium oxide, poured into 100 ml of 10% aqueous hydrochloric acid, and extracted with two 60 ml portions of ether. The combined organic layers were washed with three 100 ml portions of water and with 100 ml of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in about 5 ml of ether, and the porphin was made to precipitate by the addition of about 1 ml of methanol. The supernatant was concentrated and applied to a 20 × 20 cm silica gel plate. Development with ethyl acetate afforded 96 mg of starting material (ir).

Treatment of enol diamidate 41 with lithium-trimesitylborane. -- This experiment was carried out in the same manner as the attempted reduction of enol phosphate **19** with the trimesitylborane radical ion, with the exception that an excess of lithium metal dispersion was used in place of the lithium wire. Thus, the radical anion was formed in 6 ml of tetrahydrofuran using 200 mg (8.7 mmoles) of the dispersion and 180 mg (0.5 mmole) of the boron compound. A solution of 90 mg (0.17 mmole) of ester **41** in 4 ml of tetrahydrofuran was added to this, and then the rest of the experiment was performed as described. The only steroidal material recovered was 90 mg of the starting material (ir).

Reduction of diamidate 49 with lithium-biphenyl in tetrahydrofuran. -- The reducing agent was prepared by stirring 200 mg (2.6 mmole) of lithium metal dispersion and 80 mg (0.45 mmole) of biphenyl in 4 ml of tetrahydrofuran for 40 minutes. A solution of 90 mg (0.18 mmole) of ester **49** dissolved in 4 ml of tetrahydrofuran was added dropwise over a period of 2 hours. After an additional hour's stirring, the reaction mixture was treated with isopropyl alcohol, poured into 60 ml of aqueous potassium hydroxide, and extracted with 60 ml of petroleum ether. The ethereal layer was washed with 40 ml of water and 40 ml of brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was streaked onto a 20 cm × 20 cm × 2.5 mm silica gel plate, which was developed with petroleum ether. The desired product, cholestane (R_f 0.95), amounted to 48 mg (75%), mp 79-80°. The spectral characteristics of this material were the same as those of the cholestane produced by lithium-ethylamine reduction of esters **48** and **49**.

Treatment of diamidate 49 with dilithium-nickel tetraphenylporphin. -- This experiment was performed according to the procedure used in the attempted reduction of enol ester **41**. Thus, 90 mg (0.17 mmole) of ester **49** was added to 0.2 mmole of the dianion in the presence of 60 mg of cyclohexanone. The mixture was stirred at room temperature for 16 hours, and was treated with 10% aqueous potassium hydroxide. The workup, carried out as in the previous case, gave starting material as the only steroid component (ir).

Miscellaneous

Treatment of 41 with methyllithium. -- A mixture of 90 mg (0.17 mmole) of ester **41**, 0.5 ml of 1.7 *M* (0.9 mmole) of methyllithium solution, and 10 ml of ether was stirred for 10 hours at room temperature and was then poured into 20 ml of water. The layers were separated, and the organic layer was washed with 20 ml of brine. After the solution had dried (Na_2SO_4), the solvent was removed *in vacuo*, leaving 90 mg of starting material (ir).

Treatment of 41 with lithium dimethylcuprate. -- The above experiment was repeated using the complex from 85 mg (0.45 mmole) of cuprous iodide and 0.5 ml of methyllithium. The result was the same (ir).

Treatment of phosphorodiamidate 41 with ethanolic potassium hydroxide. -- A mixture of 100 mg (0.19 mmole) of ester **41**, 1 g of potassium hydroxide, 0.5 ml of water, and 10 ml of ethanol was heated at reflux for 18 hours, diluted with 50 ml of water, and extracted with two 40 ml portions of ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The 100 mg of residue exhibited the spectral chracteristics (ir) of the starting material.

Treatment of phosphorodiamidate 49 with ethanolic hydrochloric acid. -- A solution of 10 ml of ethanol and 55 mg (0.1 mmole) of phosphorodiamidate ester **49** was treated with 10% aqueous hydrochloric acid until the pH was lowered to 1 ("Accutint"). This solution was heated in a stoppered flask at 50° for 18 hours, poured into 30 ml of water, and extracted with two 30 ml portions of ether. The organic layers were treated as above, and the result was the same.

Treatment of phosphorodiamidate 49 with ethanolic potassium hydroxide. -- The procedure used for ester **41** was repeated with 85 mg (0.16 mmoles) of diamidate ester **49**. The only material which was recovered was starting material (ir).

Treatment of diamidate 41 with lithium aluminum hydride. -- A mixture of 100 mg (0.19 mmoles) of the ester, **41**, 500 mg (15 mmoles) of lithium aluminum hydride, and 10 ml of ether was stirred for 4 hours at room temperature, treated with sodium sulfate decahydrate and anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The infrared spectrum of the 95 mg of crystalline reside revealed only starting material.

Treatment of diamidate 49 with lithium aluminum hydride. -- The above treatment was given 70 mg of the ester, **49**, resulting in the recovery of 68 mg of starting material.

Treatment of phosphorodiamidate 49 with lithium aluminum hydride. -- The same procedure was applied to 80 mg (0.22 mmole) of the ester, with a similar result, 80 mg of starting material being recovered.

Hydrolysis of phosphorodiamidate ester 49. -- A solution consisting of 80 mg (0.15 mmole) of the ester, **49**, 20 mg of cupric acetate, 5 ml of acetic acid, and 5 ml of concentrated hydrochloric acid was heated in a stoppered flask at 90° for 60 hours, diluted with 150 ml of water, and extracted with two 50 ml portions of ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in ether and filtered through a short plug of alumina (Activity I). This procedure resulted in the recovery of 45 mg (77%) of cholestanol, mp 135-138°: ir ($CHCl_3$) 3600 cm^{-1} (–OH).

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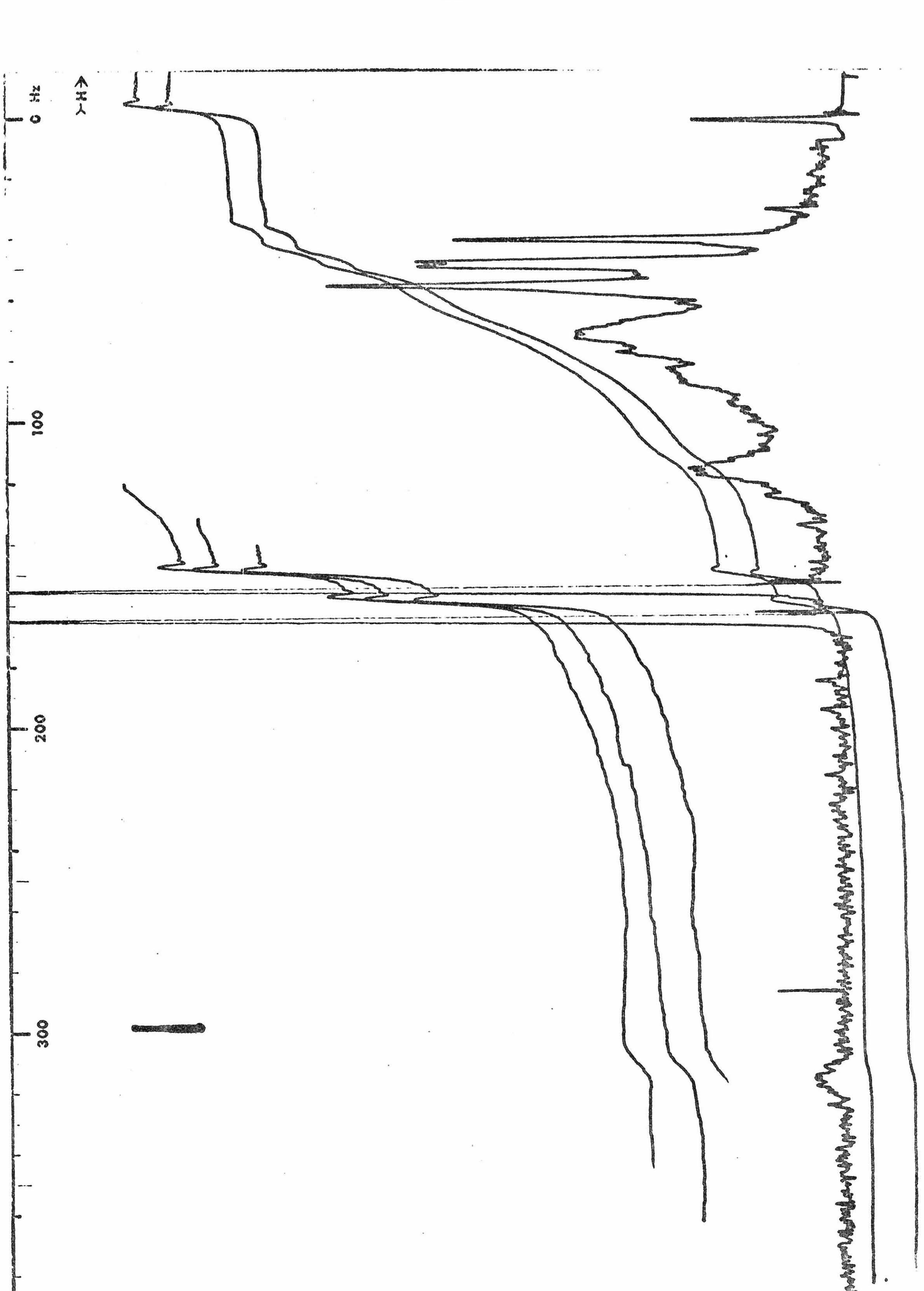
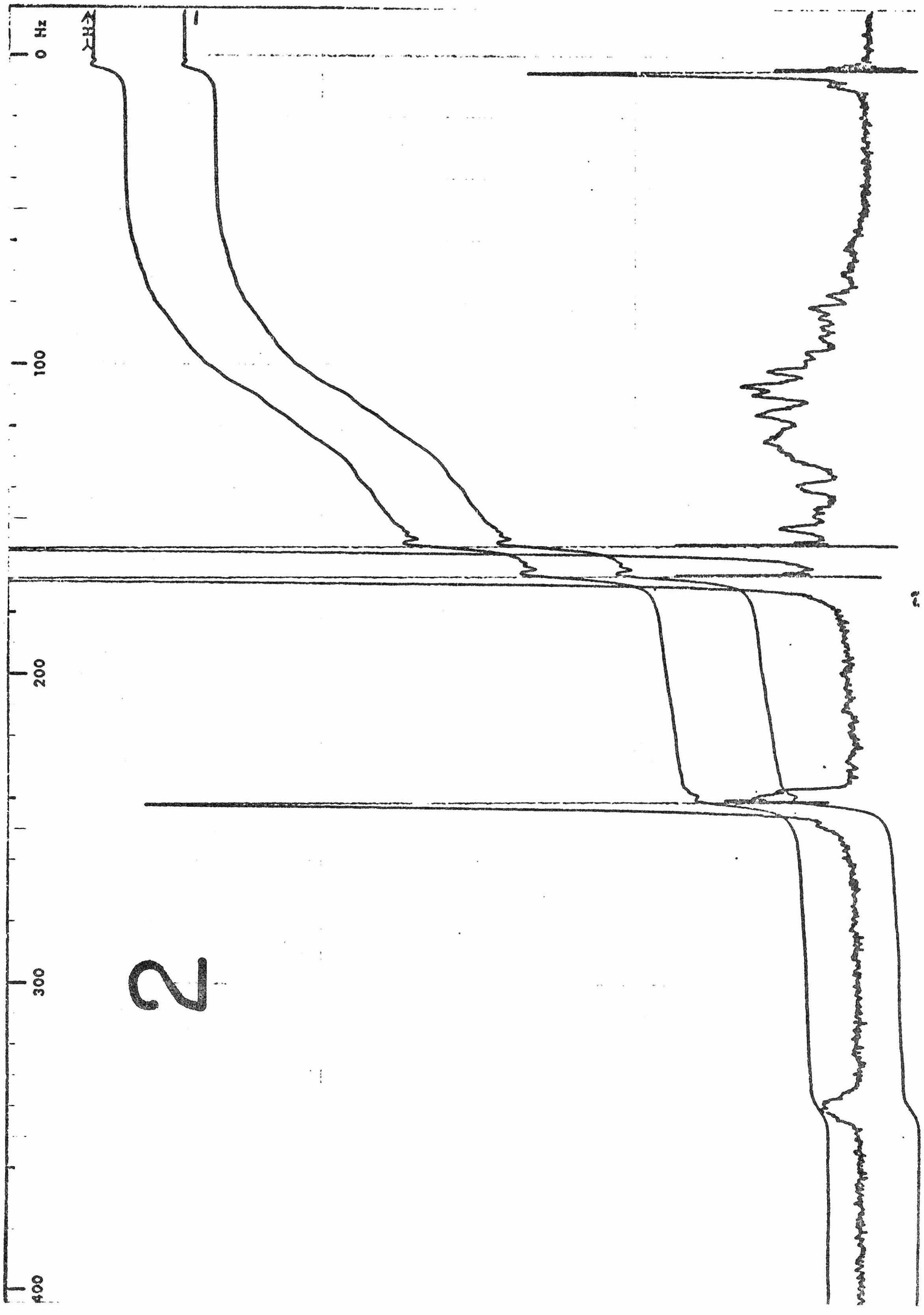
Appendix A

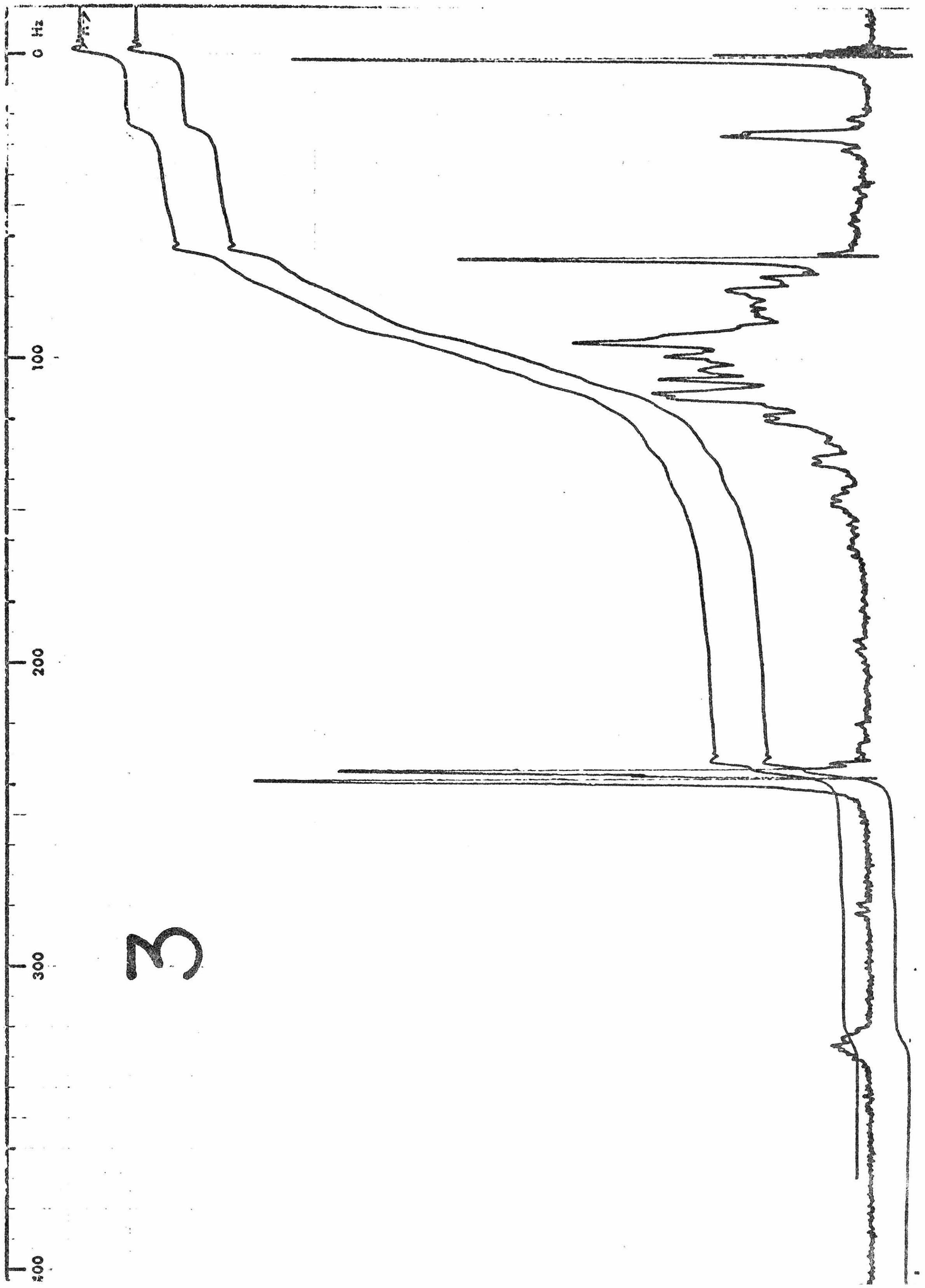
Nuclear Magnetic Resonance Spectra

1. Cholest-2-en-3-y Tetramethylphosphorodiamidate (**41**), a Representative Enol Phosphorodiamidate.
2. (2, 2-Ethylenedioxy-1, 2, 3, 4, 4a, 5, 6, 7-octahydronaphthyl)-4a-methyl Tetramethylphosphorodiamidate.
3. Product Mixture from Reduction of **52** at -78°.
4. Product Mixture from Reduction of **52** at +16°.


0 Hz
H →
100
200
300
400



0 Hz
100
200
300
400
2


0 Hz
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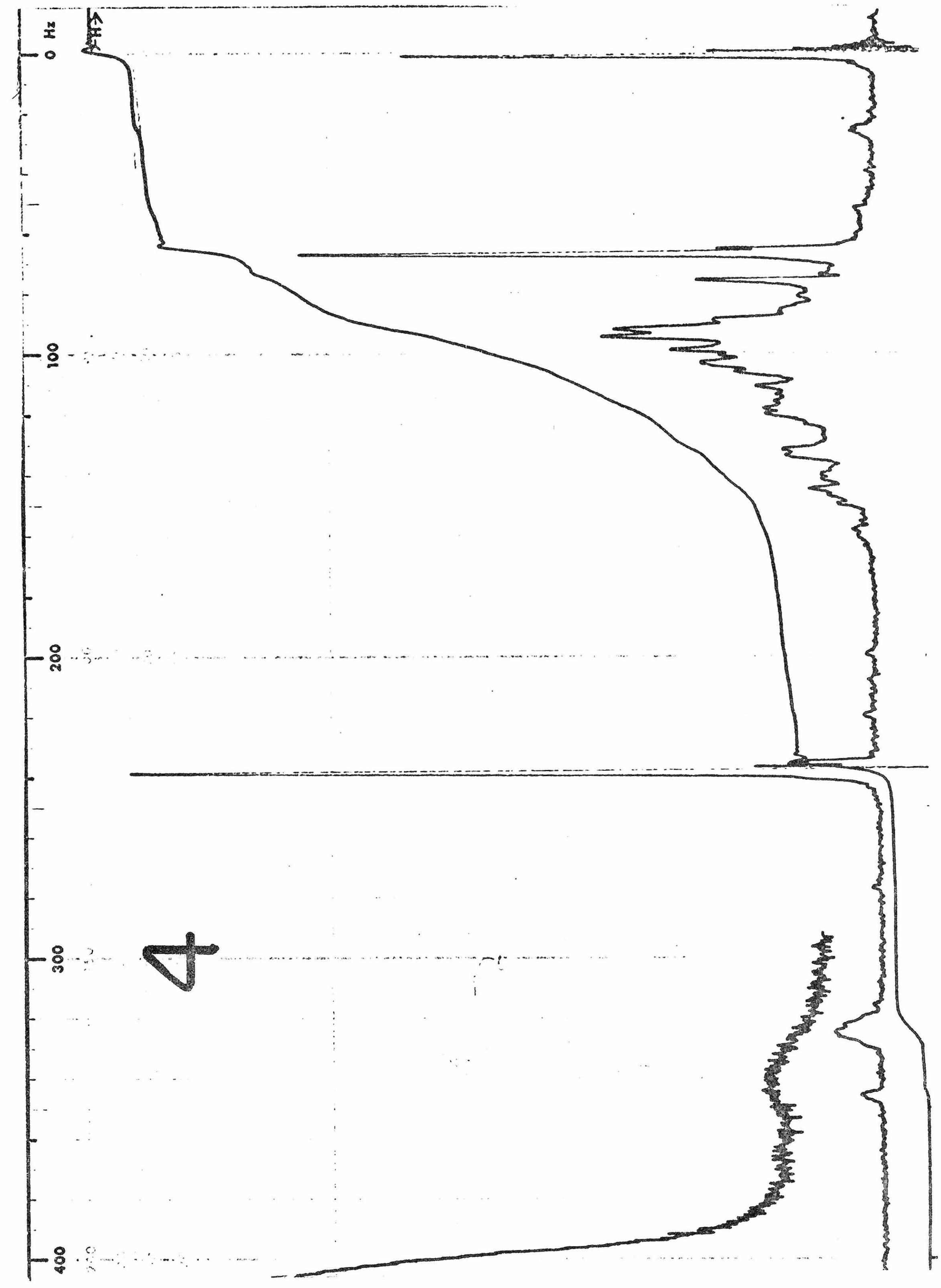
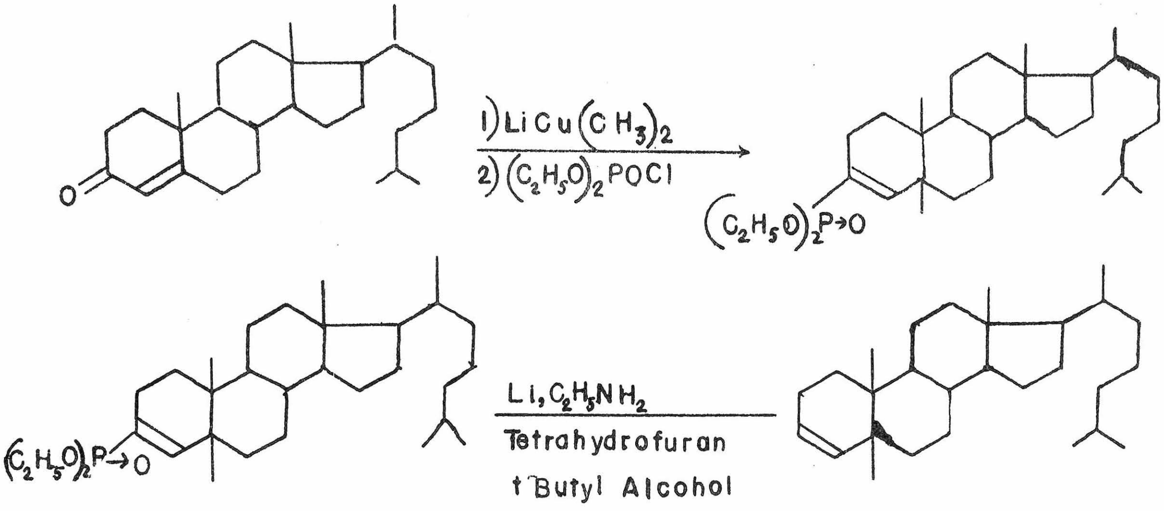
200
300
400
3


0 Hz
100
200
300
400
4

Appendix B

(A Copy of a Procedure to be Submitted to Organic Syntheses)

5-Methylcoprost-3-ene



Submitted by D. C. Muchmore[1]

1. Procedure

A. Diethyl 5-Methylcoprosten-3-en-3-yl Phosphate.[2] A suspension of 384 mg (2 mmoles) of cuprous iodide in 20 ml of ether (Note 1) is prepared in a 100 ml flask equipped with a magnetic stirring bar, a dropping funnel, a nitrogen inlet and a rubber septum. This flask is immersed in an ice-water bath, stirring is started, and 2.0 ml (4 mmoles) of 2.0 ethereal methyllithium (Note 2) is added from a hypodermic syringe. A solution of 576 mg (1.5 mmole) of cholest-4-en-3-one mp 80-82° (Note 3) in 20 ml of ether is added dropwise over a period of 20 minutes to the solution of lithium dimethylcuprate[3] which is thus formed, and the bath is removed. After 2 hours at room temperature, the dropping funnel is replaced by one with a small glass-wool plug just above the stopcock, and the flask is again immersed in the ice-water bath. A mixture of 4 ml of triethylamine (Note 4), 2 g (11.5 mmole) diethylphosphorochloridate (Note 5) and 10 ml of ether are then added from the funnel as rapidly as possible, the bath is removed, and the mixture is stirred for 1 hour. Saturated aqueous $NaHCO_3$ is added to decompose residual organocopper compounds. The contents of the flask are transferred to a separatory funnel and washed with two 50 ml portions of ice-cold 1 M ammonium hydroxide and a 50 ml portion of water. The washes are each, in turn, extracted with a 30 ml portion of ether. The combined organic layers are washed with 50 ml of brine, dried for 1 hour over Na_2SO_4 and concentrated on a rotary evaporator. The residue is dissolved in 3 ml of ether and applied to a 2.5 × 15 cm chromatographic column packed with 50 g of silica gel (Note 6) suspended in ether, and the column is eluted with ether. The first 70 ml of effluent are discarded and the next 120 ml portion is evaporated on a rotary evaporator, leaving 420-480 mg of the phosphate ester as a colorless oil of sufficient purity for the next step. The nmr spectrum ($CDCl_3$; tetramethylsilane as internal standard) of this compound exhibits absorptions at δ 5.13 (s, 1H) and δ 4.17 (apparent quintet, 4H, J = 7 cps).

B. 5-Methylcoprost-3-ene.[2] A 100 ml three-necked flask is equipped with a polyethylene-coated magnetic stirring bar, an argon inlet, another gas inlet, and a dropping funnel and is immersed in a cooling bath which is maintained at -15°. Then 50 ml of ethylamine is distilled into the flask from a cylinder through a tower filled with sodium hydroxide pellets. A 70 mg (10 mmole) piece of lithium wire is cleaned by dipping it successively into methanol and pentane and is then added to the ethylamine. The mixture is stirred for ten minutes to dissolve the lithium, and a solution of the above phosphate ester and 0.5 ml (5.5 mmole) of t-butyl alcohol (Note 7) in tetrahydrofuran is added over a period of 15 minutes to this deep blue solution. After an additional 15 minutes, 1 ml of saturated aqueous NH_4Cl is added to discharge the blue color due to excess lithium, and the ethylamine is driven off by a gentle warming of the flask. The residue is poured into 90 ml of 10% aqueous NaOH and extracted with two 30 ml portions of pentane. The combined organic layers are washed with 50 ml of brine, allowed to stand over Na_2SO_4, and reduced to dryness on a rotary evaporator. The viscous liquid which is obtained in this manner is evaporatively distilled at 0.05 mm and 150° from a 25 ml flask into a male joint (Figure). The product, 5-methylcoprost-3-ene amounts to 260-295 mg (48-53%), n_D^{25}, 1.5115. The vinylic region of the nmr spectrum ($CDCl_3$; tetramethylsilane as internal standard) shows a complex multiplet centered about 5.4 (2H), while the methyl region has five sharp absorptions from δ 0.92 to δ 0.67. Treatment of the olefin with excess ozone, followed by oxidation, results in formation of 3,4-seco-5-methylcoprostan-3,4-dioic acid, mp 168-172° (Note 8).

2. Notes

1. Reagent grade ether and reagent grade tetrahydrofuran should be distilled from lithium aluminum hydride immediately prior to use.

2. Methyllithium is available from Alfa Inorganics, Inc., Beverly, Massachusetts.

3. The preparation of cholest-4-en-3-one is described in Organic Syntheses, Coll. Vol. IV, p. 192.

4. Reagent grade triethyl amine should be distilled from calcium hydride before use.

5. Commercially available diethylphosphorochloridate is of insufficient purity for this step. It must be distilled prior to use in the acylation reaction; bp 60-62° (1.5 mm).

6. A good grade of silica gel, such as that available from E. Merck, Darmstadt, is appropriate for the column chromatography.

7. Tertiary butyl alcohol is distilled from calcium hydride before use in the reductive cleavage reaction.

8. Ozonolysis may be carried out at -10° in a 1:1 mixture of ethyl acetate and acetic acid. Hydrogen peroxide (30%) is added, and the mixture is allowed to stand for 20 hours at room temperature. Neutralization, extraction of any neutral components, and reacidification results in the formation of the diacid; softening point 130°,

mp 168-172° (ethyl acetate).

3. Discussion

The conjugate addition of lithium dimethylcopper and other organocopper reagents to α,β-unsaturated ketones is a reaction which has had wide application and which has been fairly well studied.[3a,b] In order that the positional specificity which has been conferred upon the enolate anions generated by such additions might be maintained, these intermediates have been intercepted with acetic anhydride,[3a] chlorotrimethylsilane,[4] and diethyl phosphorchloridate.[2,7]

The reductive fission of enol phosphates is a modification of the procedure used by Kenner and Williams[5] to deoxygenate phenols. The enol phosphates which have been reduced by the action of lithium in ammonia or alkylamines have been prepared by treatment of α-bromoketones with triethyl phosphiate,[6,7] by interception of enolates generated by the addition of lithium dimethylcuprate to α,β-unsaturated ketones,[2,7] and by interception of enolates resulting from treatment of unsaturated ketones with lithium in ammonia.[2]

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