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Proton Magnetic Resonance and ^{31}P Nuclear Magnetic Resonance Studies of Substituted Phospholan-3-one 1-Oxides[1]

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A study of the pmr and ^{31}P nmr spectra of a series of 3-phospholanone 1-oxides is reported. Both types of nmr spectra and infrared analysis indicate that an enol–keto tautomerism exists in the solid state and in F_3CCO_2H solution. The following 1-oxides were investigated: 1-benzyl-2-phenylphospholan-3-one, 1-benzyl-2-phenyl-4-methylphospholan-3-one, 1-benzyl-2-phenyl-5-methylphospholan-3-one, 1-benzyl-2-phenyl-4,5-dimethylphospholan-3-one, 1-benzyl-2,5-diphenylphospholan-3-one, and also 4-oxo-2-benzyl-2-phosphabicyclo[3.3.0]octane 2-oxide. Comparison of chemical shifts and coupling constants for HH and $H^{31}P$ with model systems indicates that substituents at C-5 of the phospholan-3-one ring are cis with respect to the P→O group. For substituents at both C-5 and C-4 the relationship with the P→O group is tentatively given as cis and trans, respectively. Methylation of several of these phospholan-3-one 1-oxides gave the corresponding *O*-methyl ethers except for 1-benzyl-2-phenyl-4-methylphospholan-3-one 1-oxide, which afforded 1-benzyl-2-phenyl-2,4-dimethylphospholan-3-one 1-oxide.

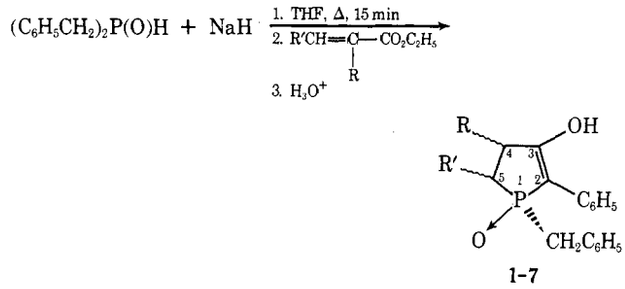
As part of a continuing study of the chemistry of saturated, polycyclic carbon–phosphorus heterocycles,[3,4] we have examined the pmr and ^{31}P nmr spectra of several substituted phospholan-3-one 1-oxides.[5] To our knowledge, no systematic spectral analysis of the molecular geometry of these systems has been published. Although our primary objective was to determine the stereochemistry of these products, it was noted that the condensation of dibenzylphosphine oxide with α,β-unsaturated esters in the presence of NaH in THF was dependent upon the concentration of NaH with respect to the yield of the corresponding cyclic 1-oxides **1–7** (Chart I), an observation not recorded in the pioneering work in this area.[5a] As will be noted in Table I, this dependence on concentration of NaH may be of a steric nature, since differences in yield were not observed until the α,β-unsaturated ester was ethyl tiglate, ethyl cinnamate, or carbethoxycyclopentene. The presence of a bulky substituent (R′) of **9** may hinder the conversion of **9** to **10** as proposed originally (Scheme I).[5a] This situation could necessitate the addition of a second equivalent of NaH to convert **9** or **10** to the dianion **11**, which may then cyclize to the desired phospholan-3-one 1-oxide. Although the conditions of the reaction were generally not meticulously optimized for each compound, it is likely with careful manipulation that excellent conversions can be expected with 2 equiv of NaH. Whether or not a dianion such as **11** participates cannot be answered unequivocally, since **12** appears to exist heavily in the enol form even in the

Table I
Yields and Physical Data for the Substituted Phospholan-3-one 1-Oxides

Compd	% yield of 1-oxide: 1 equiv NaH	2 equiv NaH	Mp, °C	Molecular formula	Anal., % (P)	
1[a,b]	49	59	207–208	$C_{17}H_{17}O_2P$	Calcd	10.89
					Found	10.54
2[a]	76	62	216–218	$C_{18}H_{19}O_2P$	Calcd	10.38
					Found	10.19
3	54	49	221.5–223	$C_{18}H_{19}O_2P$	Calcd	10.38
					Found	10.12
4	81	75	181–183	$C_{19}H_{21}O_2P$	Calcd	9.92
					Found	9.74
5[a]	45	89	217–219	$C_{23}H_{21}O_2P$	Calcd	8.59
					Found	8.31
6[a]	67	83	225–226	$C_{20}H_{21}O_2P$	Calcd	9.55
					Found	9.21
7		6[c]	225–226	$C_{23}H_{21}O_2P$	Calcd	8.59
					Found	8.57

[a] These compounds were previously reported in ref 5a. [b] Registry no., 40203-63-2. [c] A yield of 73% of the open-chain compound $(C_6H_5CH_2)_2P(O)CH(C_6H_5)CH(CO_2C_2H_5)_2$ was also obtained. *Anal.* Calcd for $C_{28}H_{31}O_5P$: P, 6.47. Found: P, 6.43. Compound **7** is believed to be the 3 isomer **12b**.

Chart I

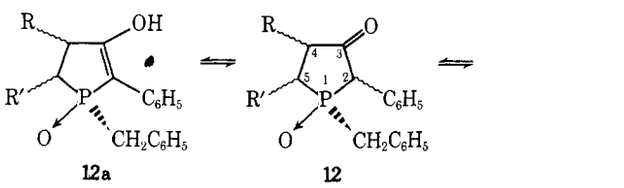


1-7

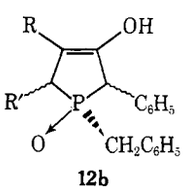
Compd	R	R′
1	H	H
2	CH_3	H
3	H	CH_3
4	CH_3	CH_3
5	H	C_6H_5
6	$-(CH_2)_3-$	
7[a]	H	C_6H_5

[a] Minor product from the above reaction utilizing diethyl benzalmalonate as the α,β-unsaturated ester, with the double bond between C-3 and C-4.

solid state. Although the double bond may be formed between C-2 and C-3 (**12a**) or C-3 and C-4 (**12b**), enolization



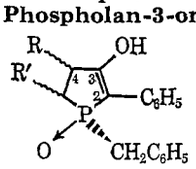
12a **12**



12b

between C-2 and C-3 would probably be favored owing to conjugation with the 2-phenyl substituent and the phosphoryl group. Table II lists the major infrared absorption maxima for the phospholan-3-one 1-oxides. The predominance of the enol form is quite apparent with the appearance of a broad OH absorption between 2445 and 2532 cm^{-1} and the olefinic absorption between 1595 and 1615 cm^{-1}.[6,7]

Table II
Major Infrared Absorption Maxima of the Substituted Phospholan-3-one 1-Oxides[a]

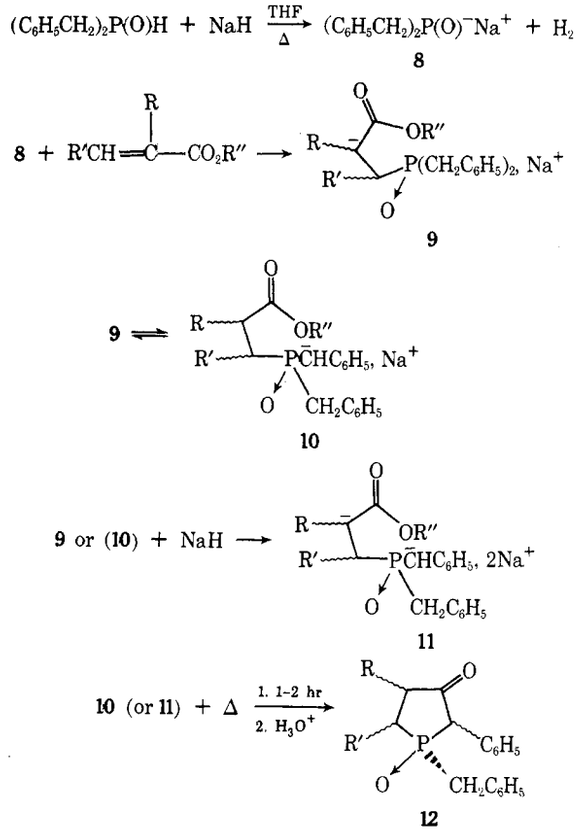


Compd	R	R′	ν, cm⁻¹ OH	ν, cm⁻¹ -C=C-	ν, cm⁻¹ P→O
1	H	H	2500	1608	1101
2	CH_3	H	2445	1600	1087
3	H	CH_3	2505	1615	1099
4	CH_3	CH_3	2489	1603	1105
5	H	C_6H_5	2532	1613	1130
6	$-(CH_2)_3-$		2483	1595	1106
7[b]	H	C_6H_5	2469	1607	1098

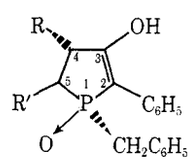
[a] The spectra were obtained on samples (4 mg) with KBr (400 mg) pellets. [b] This structure is suggested to have the double bond located between positions 3 and 4.

Assuming that **9** or **11** are the logical precursors of **12a**, it is quite reasonable that epimerization at position 4 could occur, since that carbon atom holds a negative charge and would expectedly assume the most stable configuration with respect to adjacent groups. Consequently, one isomer could well be envisioned as a final product. Deduction of the stereochemistry at positions 1, 4, and 5 for this isomer has heretofore been unreported, although it is crucial for not only understanding the mechanism of ring closure but also for making the method of further synthetic utility.

Scheme I

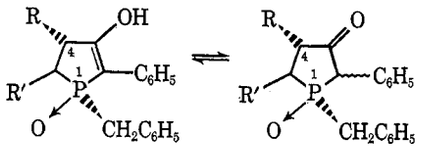


Structural models constructed from several sets of molecular models (including Courtauld models) strongly suggest a cis arrangement for P→O *vs.* R′ (C-5) and a trans arrangement for R′ *vs.* R (at C-5 *vs.* C-4) on the basis of molecular crowding in either the keto or enol form. Since



solubilities in all organic solvents tested was negligible (a few of these oxides were reported[5a] soluble in CH_3OH but we could not reproduce this observation to the extent that a signal could be detected by nmr analysis at 100 MHz), 2–3 drops of F_3CCO_2H was always added to a suspension of the compound in $DCCl_3$. Solution occurred rapidly but, of course, this process would expectedly favor enol formation. Enolization at C-2 to give a conjugated system (**12a**) involving the 2-phenyl substituent and the phosphoryl groups is preferred. This preference is supported by the observations that with varying acid concentrations, signals for

Table III
^{31}P Resonances of Enol–Keto Equilibria Relative to H_3PO_4[a]



Compd	Enol, ppm	Rel abundance, %	Registry no.	Keto, ppm	Rel abundance, %	Registry no.
1	−77.2	98	52050-76-7	−59.8	2	40203-59-6
2[b]	−74.4	34.2	52050-77-8	−55.5	11.5	52080-01-0
	−70.0	45		−53.3	9.3	
3	−77.6	91.7	52050-78-9	−62.9	8.3	52050-82-5
4[b]	−70.4	67.8	52050-79-0	−57.7	12.3	52050-83-6
	−68.4	10.2		−51.6	9.7	
5	−71.4	92.9	52050-80-3	−59.0	7.1	52080-02-1
6	−72.3	92.5	52050-81-4	−56.8	7.5	52080-03-2

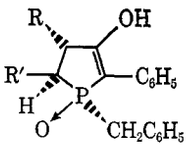
[a] The spectra were obtained on samples (1.5 g) in $DCCl_3$ (4 ml) with 4–5 drops of CF_3CO_2H added, which would favor the enol form. [b] Resonances believed to be due to cis–trans isomers involving the methyl group at C-4 with respect to the phosphoryl group in each tautomer.

the protons at C-4 (as in **1**) were not removed nor was the doublet observed for a methyl substituent at C-4 (as in **2**) converted to a singlet. These changes would be expected if enolization at the third bond in oxides **1–6** to form **12b** were to occur. Consequently, we feel that the stereochemistry at C-4 relative to that at positions 1 and 5 is unchanged.

^{31}P nmr analysis of compounds **1–6** confirmed this enol–keto equilibrium (Table III). At least two signals were observed in each case for these relatively concentrated solutions.[8] The resonance signal furthest downfield with respect to 85% H_3PO_4 was assigned the enol form in agreement with the infrared data (Table II), pmr spectra (Table IV), and the reported ^{31}P assignments for the enol–keto forms of 1-methylphospholan-3-one 1-oxide of −60.5 and −51.0 ppm, respectively.[6] The observation of four signals for **2** is considered to result from epimerization at C-4 during the course of the cyclization involving intermediates **9** or **11**. Thus, the possibility of cis–trans isomers at C-4 with respect to the phosphoryl group exists which would yield signals for two enol forms and for two keto forms.[9] Although a similar situation might be anticipated for the dimethyl derivative **4**, epimerization in this case may be hindered by the presence of the methyl at C-5, and the initial trans relationship of the two methyls of ethyl tiglate may be expected to be retained. This hypothesis is substantiated by the observation that 9% (by glc analysis) ethyl angelate was initially present in the commercial ethyl tiglate and could contribute to the signal at −68.4 ppm observed in only 10% relative abundance (proposed to be the *cis*-dimethyl derivative). Since none of these compounds other than **7** indicated the presence of a proton resonance for C-2 in the pmr spectra, the possibility of cis–trans isomers at C-2 in order to explain the two keto signals of **2** and **4** is not considered tenable.

Resolution of the pmr spectra was best with the substituted oxides **2, 3, 4,** and **5** (Table IV). The benzylic protons ($PCH_2C_6H_5$) are at nearly identical δ values and the J_{PCH} values are quite comparable (18 Hz). The possibility of cis–trans isomers for the methyl at C-4 of **2** discussed earlier is substantiated by the presence of two doublets, δ 0.71 and 1.25 ppm (J_{HCCH} = 7.0 Hz for both doublets), of nearly equivalent intensity. Focusing on δ positions for the methyl protons at C-5 in **3** (Figure 1) and **4**, there is very similar shielding (δ 1.19 and 1.22 ppm) and coupling (J_{PCCH_3} = 16.5 *vs.* 17 Hz and J_{HCCH} = 7.0 *vs.* 7.0 Hz) in **3** and **4**, respectively. The proton at C-5 of **3** and **4** experiences a slightly different shielding environment (δ 2.44 and 1.89 ppm); however, the couplings are comparable (J_{HCCH} = 7.0 *vs.* 7.0 Hz and J_{PCH} = 7 *vs.* 7 Hz) for **3** and **4**, respectively. Extensive homonuclear and heteronuclear decoupling (^1H and ^{31}P) confirmed these assignments. Although decoupling experiments on **5** were not as definitive as desired because of overlap of signals for the proton at C-5 and the benzylic doublet, an approximate J_{PCH} = 7 Hz was observed for the C-5 proton.

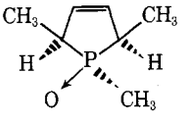
Table IV
Pmr Data for the Substituted Phospholan-3-one 1-Oxides[a]



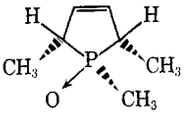
	δ, ppm					
		C-4		C-5		
Compd	$PCH_2C_6H_5$[b]	CH	CH_3	CH	CH_3	C_6H_5
1	3.43 (18.0)	2.34		2.34		7.25
2	3.49 (18.0)	1.87	0.71[c]	2.48		7.25
			1.25			
3	3.46 (17.5)	2.44		2.44[d]	1.19[e]	7.22
4	3.44 (18.0)	2.61[f]	0.91[g]	1.89[h]	1.22[i]	7.20
5	3.57 (18.0)	2.95		3.57		7.33
6[j]	3.51 (18.0)	2.80		2.80		7.25
7	3.17 (18.0)	6.51		3.67		7.20

[a] Spectra obtained on $DCCl_3$ solutions of each compound with 2–3 drops of CF_3CO_2H added. [b] Resonances were doublets due to ^{31}P coupling with $J_{PCH_2C_6H_5}$ (Hz) in parentheses. [c] Two doublets, J_{HCCH} = 7.0 Hz for each; possibility of cis–trans isomers about C-4 with respect to P→O. [d] Multiplet, J_{HCCH} = 7.0, J_{PCH} = 7 Hz. [e] Doublet of doublets, J_{HCCH} = 7.0, J_{PCCH_3} = 16.5 Hz. [f] Multiplet, J_{HCCH} = 7 Hz. [g] Doublet, J_{HCCH} = 7 Hz. [h] Multiplet, J_{HCCH} = 7, J_{PCH} = 7 Hz. [i] Multiplet, J_{HCCH} = 7, J_{PCCH_3} = 17.0 Hz. [j] $-(CH_2)_3-$ resonance at 1.80 ppm.

Model systems are rare for a comparison of J_{PCH} couplings when the P→O group is cis or trans to the C–H bond on an α carbon atom of phospholane 1-oxides. However, others[10] have found a J_{PCH} = 6.50 Hz for cis (**13**) and J_{PCH}



13 (cis)



14 (trans)

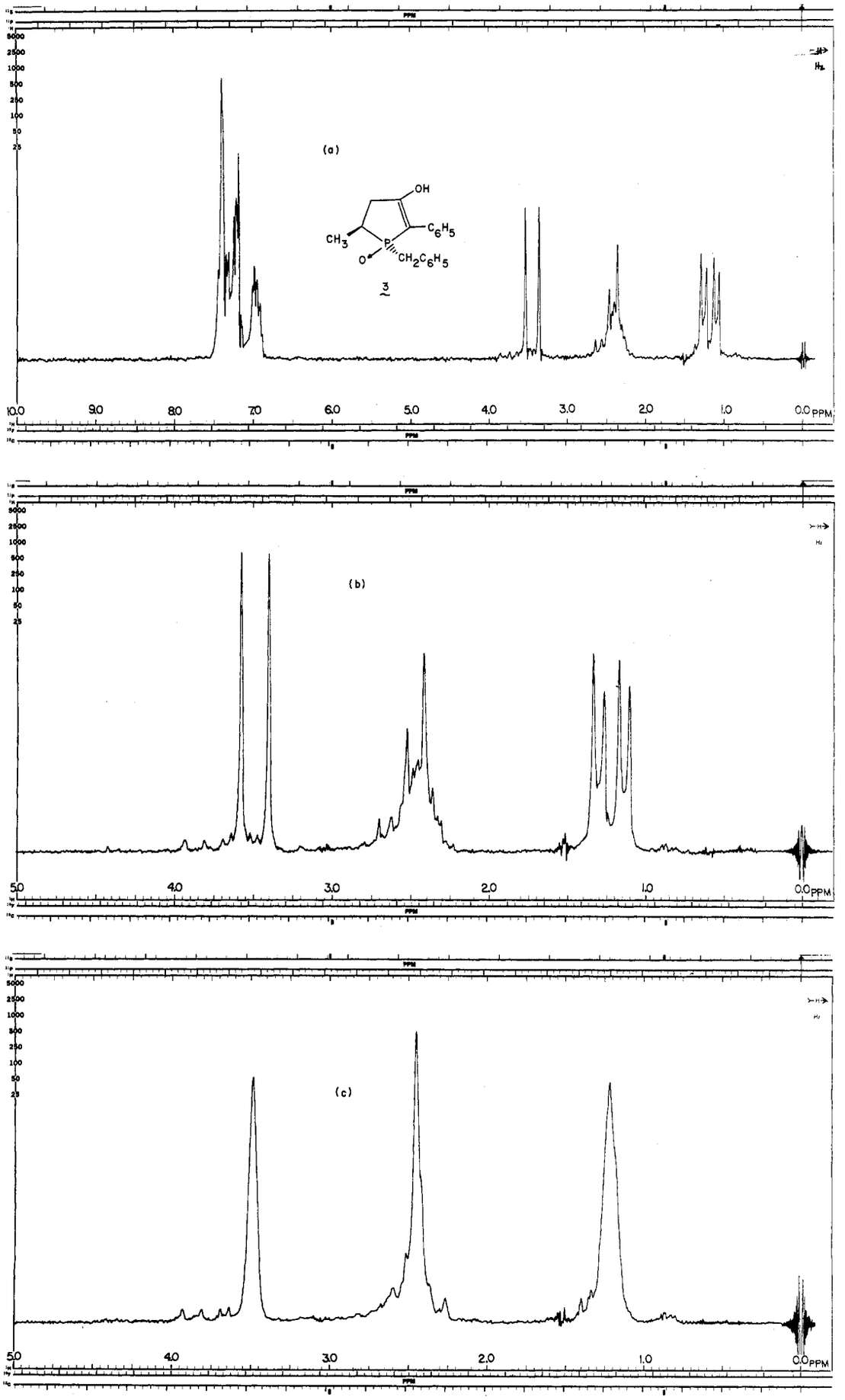
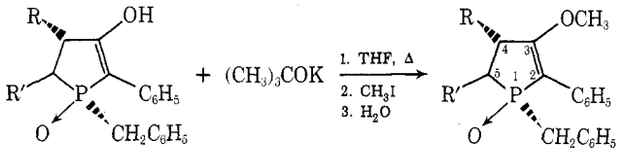


Figure 1. (a) Pmr spectrum of **3** ($DCCl_3$/3 drops of F_3CCO_2H) obtained at 100 MHz; (b) spectrum of the area 0–5.0 ppm of (a) expanded at 100 MHz; (c) ^1H spectrum for the 0–5.0 ppm area (b above) while irradiating ^{31}P (40.548 MHz). TMS is the internal standard.

Chart II



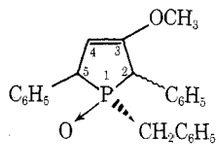
15-17

Compd	R	R′	% yield of O-methylated oxide
15	H	CH_3	86
16	H	C_6H_5	79
17	$-(CH_2)_8-$		82

= 13.5 Hz for trans (**14**) in $DCCl_3$. Thus, in the cis isomer **13** the P→O and C–H bonds are trans. Our values of J_{PCH} = 7.0 Hz for the C-5 proton for **3, 4,** and **5** strongly suggest a similar stereochemistry as in **13.** Additional support is available on this point from ^{13}C–^{31}P couplings in the *P*-phenyl analogs of **13** and **14** as well as in the *P*-methyl compounds **13** and **14.**[10b] From the ^{13}C spectra, it was concluded that with a trans relationship of the P→O group *vs.* the CCH_3 group (at the α carbon), the methyl group was more deshielded.[10b] These conclusions were based in part on similar observations with the corresponding phosphines and on the assumption that the stereochemistry is preserved in oxidation to the phosphine oxides, which is reasonable and well known in the literature.[11]

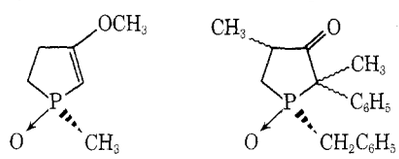
The J_{HCCH_3} = 7 Hz coupling in **3** and **4** is normal and the J_{HCCH} = 7 Hz is likewise defensible. Models imply the system may not deviate much from planarity. On this reasonable assumption, the *J* value for HCCH vicinal coupling is defensible for a trans arrangement.[12] In the case of **4,** this situation may also be defended on steric considerations in the anion **9** in that proton addition to the enolate ion will occur in such a manner that the methyl at C-4 is positioned trans to the methyl group at C-5. However, without a substituent at C-5 as in **2,** inversion may occur at C-4 prior to hydrogen exchange to give **10** or prior to closure of **11** to give, after neutralization, **12.** Epimerization may also occur with **12,** since the reaction mixture is basic ($C_2H_5O^-$ is displaced) prior to work-up. This would explain the observed signals for the protons on the cis or trans methyl group at C-4 of **2.**

Methylation of **3, 5,** and **6** in THF with $(CH_3)_3COK$ and CH_3I at room temperature or 40° gave the corresponding *O*-methyl ethers (**15–17,** Chart II) in high yield. In the case of **7** (with the alkene linkage of the enol between C-3 and C-4), methylation under identical conditions yielded (87%) the corresponding *O*-methyl ether **18.** Infrared and pmr



18

analysis of these O-methylated phospholan-3-one 1-oxides indicated that the alkylation occurred at the enolic oxygen atom. The evidence is the olefinic absorption in the ir spectrum (1575–1592 cm^{-1}) (Table V) and the presence of a sharp singlet for the *O*-methyl resonance in the pmr spectra (δ 3.58–3.74 ppm) (Table VI). This would indicate that the environment around the *O*-methyl groups was very much alike and similar to that observed (δ 3.78 ppm) for the *O*-methyl ether **19.**[6] The relationship of the C-5 substit-



19 **20**

uents with respect to the phosphoryl group of these *O*-methyl ethers also has not changed, since the C-5 methyl of **15** (R = H; R′ = CH_3) (Figure 2) appears as a doublet of doublets, δ 1.23 ppm (J_{HCCH} = 7.0 and J_{PCCH_3} = 15 Hz) compared to a doublet of doublets, δ 1.19 ppm (J_{HCCH} = 7.0 and J_{PCCH_3} = 16.5 Hz) for the starting compound **3.**

An exception to the observed methylations to afford the *O*-methyl ethers was noted in the case of 1-benzyl-2-phenyl-4-methylphospholan-3-one 1-oxides (**2**). The major product isolated in a 67% yield was the C-2 methylated derivative 1-benzyl-2-phenyl-2,4-dimethylphospholan-3-one 1-oxide (**20**). The infrared spectrum displayed a strong band for the C=O at 1725 cm^{-1} and a shift in the P→O vibration to 1179 cm^{-1} (Table V).[13] Pmr analysis did not afford a singlet indicative of the other *O*-methyl derivatives (**15–18**) but instead a doublet appeared (δ 1.76 ppm, J_{PCCH_3} = 12 Hz) in addition to the doublet for the methyl at C-4 (δ 1.34 ppm, J_{HCCH} = 7.0 Hz).[14] Interestingly, the

Table V
Major Infrared Absorption Maxima of the *O*-Methyl Phospholan-3-one 1-Oxides[a]

Compd	Registry no.	ν, cm^{-1} –C=C–	ν, cm^{-1} P→O
15	52050-84-7	1592	1173
16	52050-85-8	1575	1159
17	52050-86-9	1583	1167
18	52050-49-4	1583	1172
20	52050-50-7	(1725)[b]	1179

[a] The spectra were obtained on samples (4 mg) with KBr (400 mg) pellets. [b] Absorption of the C=O of the C-methylated product.

Table VI
Pmr Data for the *O*-Methyl Phospholan-3-one 1-Oxides[a]

	δ values							
			C-4		C-5		C-2	
Compd	$PCH_2C_6H_5$[b]	OCH_3[c]	CH	CH_3	CH	CH_3	CH	C_6H_5
15	3.27 (17.5)	3.60	2.25		2.25	1.23[d]		7.41
16	3.22 (18.0)	3.65	2.87		3.22			7.24
17[e]	3.27 (18.0)	3.58	2.20		2.20			7.43
18	3.02 (16.0)	3.74	6.53[f]		2.42		2.42	7.35
20[g]	2.58		2.58	1.34[h]	2.58		(1.76)[i]	7.24

[a] Spectra obtained on $DCCl_3$ solutions of each compound with TMS as internal standard. [b] Resonances were doublets due to ^{31}P coupling with $J_{PCH_2C_6H_5}$ (Hz) in parentheses. [c] Resonances were intense singlets in all cases except **20.** [d] Doublet of doublets, J_{HCCH} = 7.0, J_{PCCH_3} = 15 Hz. [e] Resonances for $-(CH_2)_8-$ also appear as a broad multiplet at 2.20 ppm [f] Vinylic resonance due to –C=C– between C-3 and C-4. [g] Possible C-methylation at C-2 rather than O-methylation. [h] Doublet, J_{HCCH} = 7.0 Hz. [i] Resonance for methyl group at C-2 appearing as a doublet, J_{PCCH_3} = 12 Hz.

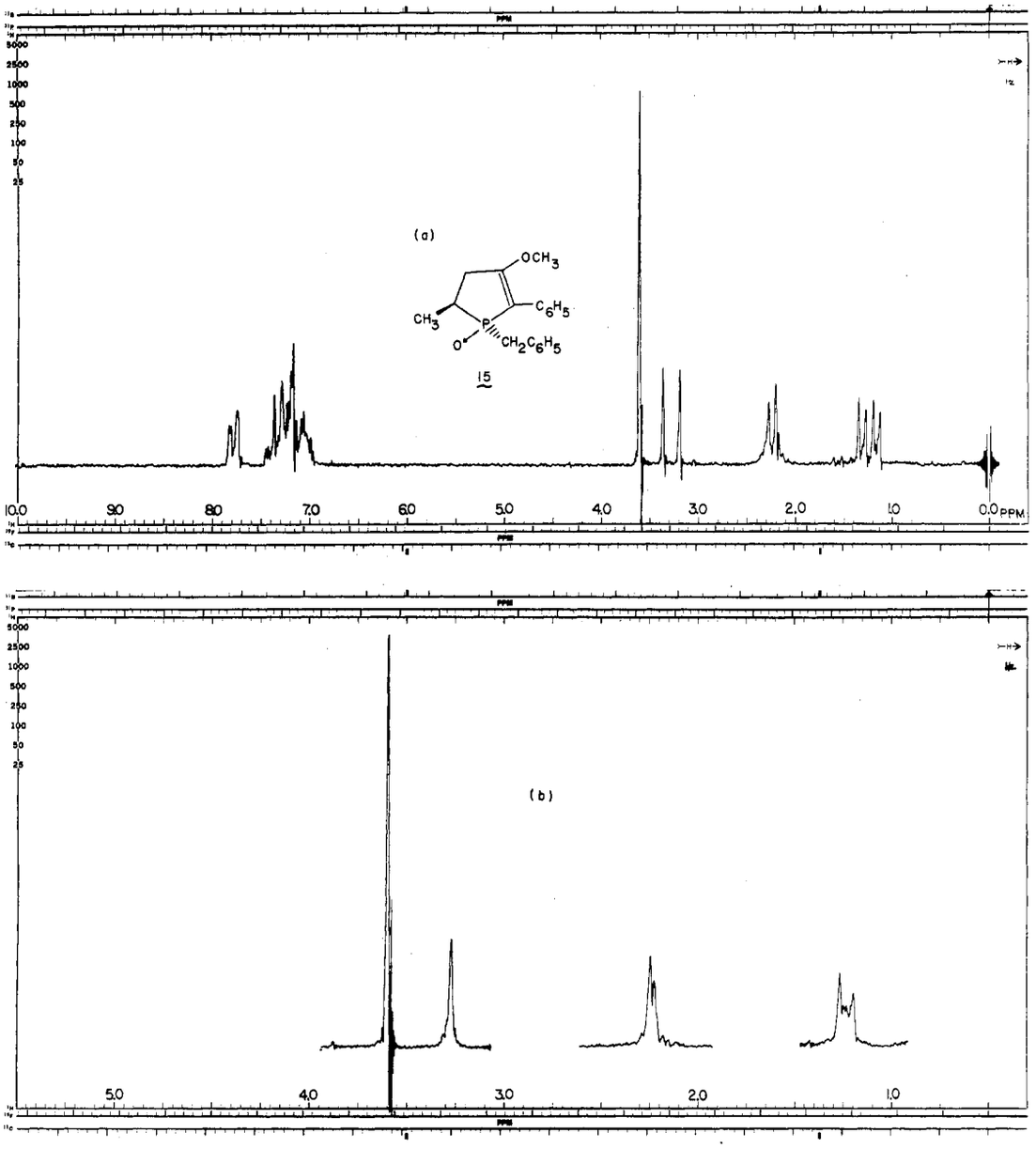


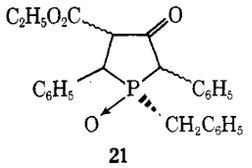
Figure 2. (a) Pmr spectrum of **15** ($DCCl_3$) obtained at 100 MHz; (b) ^1H spectrum for the 0–5.0 ppm area of (a) while irradiating ^{31}P (40.548 MHz). TMS is the internal standard.

two doublets observed for the isomers (cis–trans C-4 methyl group) of **2** (Table IV) afforded only the one doublet (Table VI) in the methylated product indicating a possible interconversion of one to the other. Also it was noted that the benzylic protons are no longer equivalent, appearing as two doublets (J_{HCH} = 7.0 and $J_{PCH_2C_6H_5}$ = 16.0 Hz). Extensive homonuclear and heteronuclear decoupling (^1H and ^{31}P) supported these assignments. The mass spectral and elemental analysis supported the hypothesis that methylation had occurred (Table VII).[15]

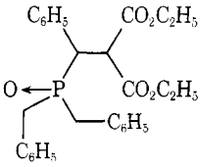
Table VII
Physical Properties for Products from Methylations of Phospholan-3-one 1-Oxides

Compd	Mp, °C	Molecular formula	Anal., % (P)	
15	150–151	$C_{19}H_{21}O_2P$	Calcd	9.92
			Found	9.89
16	177–179	$C_{24}H_{23}O_2P$	Calcd	8.27
			Found	8.27
17	148.5–150	$C_{21}H_{23}O_2P$	Calcd	9.15
			Found	9.19
18	142–144	$C_{24}H_{23}O_2P$	Calcd	8.27
			Found	8.14
20	154–155.5	$C_{19}H_{21}O_2P$	Calcd	9.92
			Found	9.97

In attempting to extend the condensation of dibenzylphosphine oxide with α,β-unsaturated esters (eq 1) to α,β-unsaturated diesters, such as diethyl benzalmalonate, the reaction did not afford 1-benzyl-2,5-diphenyl-4-carbethoxyphospholan-3-one 1-oxide (**21**), even with 2 equiv of NaH in THF and 18 hr at reflux. Instead, **22** was isolated (73%)



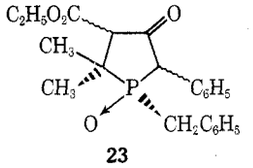
21



22

along with **7** (6%). The structure of **22** is based upon ir, pmr, mass spectral, and elemental analysis. The formation of **7**, which is believed to be isomeric with **5**, with the dou-

ble bond between C-3 and C-4 rather than C-2 and C-3, may arise from very slow cleavage of the residual ester group of **21** (perhaps during work-up) to give a carboxyl group β to the keto group. Decarboxylation could then occur to give the oxide **7** with the enol in the observed position. This assignment is based on the observed differences in infrared absorption [2469 (OH), 1607 (–C=C–), and 1098 cm^{-1} (P→O) for **7** *vs.* 2532 (OH), 1613 (–C=C–), and 1130 cm^{-1} (P→O) for **5**] and the presence of a vinylic multiplet (δ 6.51 ppm) for the C-4 proton of **7** and broad doublets for the protons at C-2 and C-5 (δ 3.67 ppm) in the pmr spectrum. The mass spectral[15] and elemental analysis (Table I) also support this structure. Methylation of **7** gave a product with the alkene linkage retained between C-3 and C-4 and was designated as the *O*-methyl ether **18** [ir 1583 (–C=C–) and 1172 cm^{-1} (P→O) for **18** *vs.* 1575 (–C=C–) and 1159 cm^{-1} (P→O) for **16** (R = H; R′ = C_6H_5) derived from **5** (Table V)]. The vinylic signal for the C-4 proton is also retained in the pmr spectrum of **18** (Table VI). The mass spectral and elemental analysis support an *O*-methyl structure for **18** and isomerism with **16** (Table VII). The inability to undergo cyclization observed for the diester diethyl benzalmalonate does not appear to be general, since utilizing diethyl isopropylidenemalonate and 3 equiv of NaH in the condensation with dibenzylphosphine oxide afforded 1-benzyl-2-phenyl-5,5-dimethyl-4-carbethoxyphospholan-3-one 1-oxide (**23**) as the major product.



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Infrared, pmr, mass spectral, and elemental analysis again argue for the structure assigned. An extension of this synthetic procedure to other α,β-unsaturated systems is currently under study.

Experimental Section

General Procedure. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A unit as KBr pellets. Pmr and ^{31}P nmr spectra were obtained with a XL-100 (15) Varian spectrometer in $DCCl_3$ with 3–4 drops of CF_3CO_2H added in the case of the substituted phospholan-3-one 1-oxides. Mass spectral analysis was performed on a CEC Model 21 HR unit. Anhydrous THF was obtained fresh for each run by distillation from NaH immediately before use.

Starting Materials. Dibenzylphosphine oxide was prepared by a literature procedure.[16] Carbethoxycyclopentene was also prepared by a published route[17] with the modification that reduction of 2-carbethoxycyclopentanone to 2-carbethoxycyclopentanol was achieved with $NaBH_4$. All other esters were either commercially available or were prepared in routine fashion from esterification of commercial acids.

Although the preparation of some of these oxides was reported while our work was in progress[5a] (except for ethyl crotonate, ethyl tiglate, diethyl benzalmalonate, and diethyl isopropylidenemalonate), experimental details were not included. Therefore, our general procedure will be described. Standard apparatus used was a 500-ml, three-necked, round-bottomed flask equipped with mechanical stirrer, additional funnel, condenser, and N_2 inlet. The preparation of 1-benzyl-2,5-diphenylphospholan-3-one 1-oxide (**5**) will be described using 1 and 2 equiv of NaH.

1-Benzyl-2,5-diphenylphospholan-3-one 1-Oxide (5). A. From 1 Equiv of NaH. A slurry of 1.7 g (55.6% in mineral oil, 0.04 mol) of NaH in 50 ml of anhydrous THF at room temperature was treated with 9.2 g (0.04 mol) of dibenzylphosphine oxide in 50 ml of THF. The resulting mixture was heated at reflux for 15 min with vigorous evolution of a gas (presumed H_2) and with formation of a clear, pale-yellow solution. This solution heated to reflux was treated (dropwise) with a solution of 7.05 g (0.04 mol) of ethyl cinnamate in 75 ml of THF. After addition, the dark yellow mixture was boiled (2 hr), cooled to room temperature, and hydrolyzed (25 ml of 1.6 *N* ammonium chloride solution). Two layers separated upon saturation (NaCl) and the aqueous layer was extracted (2 × 100 ml) with THF. The dried ($MgSO_4$) organic extracts were evaporated *in vacuo* to give a pale yellow powder. Recrystallization of this powder from C_2H_5OH–H_2O (1:1) afforded 6.5 g (45%) of a white solid, mp 217–219° (lit.[5] mp 217–219°). Infrared, nmr, and analytical data are found in Tables I–IV.

B. From 2 Equiv of NaH. A slurry of 1.3 g (55.6% dispersion in mineral oil, 0.03 mol) of NaH in 50 ml of anhydrous THF at room temperature was treated with 6.9 g (0.03 mol) of dibenzylphosphine oxide in 50 ml of THF. Again the mixture was boiled for 15 min with much evolution of a gas and with formation of a clear, pale-yellow solution. While boiling, the solution was treated with 5.3 g (0.03 mol) of ethyl cinnamate in 75 ml of THF. When addition was complete, the mixture was boiled for 2 hr and treated with another slurry of 1.3 g (0.03 mol) of NaH in 50 ml of THF. After another 2 hr at reflux (much gas evolved), the solution was cooled to room temperature and hydrolyzed with 30 ml of 2 *N* acetic acid. Two layers resulted upon saturation (NaCl) and the aqueous layer was extracted (2 × 100 ml) with THF. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to leave a white powder. Recrystallization (C_2H_5OH–H_2O) gave 9.6 g (89%) of the desired phospholan-3-one 1-oxide, mp 217–219°. Infrared, nmr, and analytical data for the other substituted phospholan-3-one 1-oxides prepared by the above procedures are given in Tables I–IV.

***O*-Methyl Derivative of 1-Benzyl-2,5-diphenylphospholan-3-one 1-Oxide (16).** A mixture of 1.0 g (2.7 mmol) of the oxide **5** in 25 ml of anhydrous THF was treated with 0.34 g (3 mmol) of $(CH_3)_3COK$ in 25 ml of THF at room temperature. After 1 hr the yellow solution was treated with 0.5 g (3.5 mmol) of CH_3I in 25 ml of THF. After complete addition, the orange mixture was stirred for 1 hr at room temperature and hydrolyzed (25 ml H_2O), and the resulting mixture was extracted (1 × 50 ml of THF). The organic extracts were dried ($MgSO_4$) and the THF was removed by evaporation to afford a yellow powder. Two recrystallizations (C_6H_6–C_6H_{12}) gave 0.8 g (79%) of the *O*-methyl ether **16**, mp 177–179°, mass spectrum (70 eV) *m/e* 374 (M^+). Infrared and nmr data are given in Tables V and VI.

Anal. Calcd for $C_{24}H_{23}O_2P$: C, 76.99; H, 6.19; P, 8.27. Found: C, 77.16; H, 6.20; P, 8.27.

Physical data for other O-methylated phospholan-3-one 1-oxides prepared by a similar procedure are listed in Table VII.

1-Benzyl-2-phenyl-2,4-dimethylphospholan-3-one 1-Oxide (20). A mixture of 2.0 g (6.7 mmol) of the oxide **2** in 25 ml of anhydrous THF was treated with 1.0 g (8.9 mmol) of $(CH_3)_3COK$ in 25 ml of THF at room temperature. After 1 hr, the yellow solution was treated with 10.0 g (7 mmol) of CH_3I in 25 ml of THF. After complete addition, the orange mixture was stirred for 1 hr at room temperature and hydrolyzed (15 ml H_2O), and the resulting mixture was extracted [2 × 75 ml of $(C_2H_5)_2O$]. The organic extracts were dried ($MgSO_4$) and the solvent was removed by evaporation to afford a yellow powder. Two recrystallizations from cyclohexane–chloroform (4:1) gave 1.4 g (67%) of **20**, mp 154–155.5°. Infrared, nmr, and analytical data are given in Tables V–VII.

Anal. Calcd for $C_{19}H_{21}O_2P$: P, 9.92. Found: P, 9.97.

Dibenzylphosphine Oxide with Diethyl Benzalmalonate. A slurry of 1.3 g (55.6% dispersion in mineral oil, 0.03 mol) of NaH in 50 ml of anhydrous THF at room temperature was treated with 6.9 g (0.03 mol) of dibenzylphosphine oxide in 50 ml of THF. The resulting mixture was heated at reflux for 15 min with vigorous evolution of gas (presumed H_2) and with formation of a clear, pale-yellow solution. This solution heated to reflux was treated (dropwise) with a solution of 7.5 g (0.03 mol) of diethyl benzalmalonate[18] in 100 ml of THF. When addition was complete, the mixture was boiled for 2 hr with the appearance of a white precipitate and then treated with another slurry of 1.3 g (0.03 mol) of NaH in 50 ml of THF. After an additional 3 hr at reflux (gas evolved), the now dark-orange mixture was cooled to room temperature and hydrolyzed (30 ml of 2 *N* acetic acid). Two layers resulted upon saturation (NaCl) and the aqueous layer was extracted (2 × 150 ml) with THF. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to leave a yellow oil. Titration of this oil with boiling cyclohexane followed by a hot filtration yielded a yellow, insoluble powder. Recrystallization of this powder from ethyl acetate–ethanol gave 0.65 g (6%) of 1-benzyl-2,5-diphenylphospholan-3-one 1-oxide (**7**), mp 225–226°. Infrared, nmr, and analytical data are given in Tables I, II, and IV.

After standing for 2 days at room temperature, the cyclohexane filtrate gave a white powder. Recrystallization (hexane) of this powder afforded 7.0 g (73%) of ethyl 2-carbethoxy-3-dibenzylphosphoryl-3-phenylpropionate (**22**): mp 85–86°; ir (KBr pellet) ν 1715 (C=O), 1228 (C–O), 1153 cm^{-1} (P→O); pmr ($DCCl_3$) δ 0.90 (t, CH_3, 3 H), 1.30 (t, CH_3, 3 H), 2.60 (m, HCCH, 2 H), 3.24 (d, $^{31}PCH_2C_6H_5$, 2 H), 3.88 (quartet, CH_2, 2 H), 4.30 (m, $^{31}PCH_2C_6H_5$ and CH_2, 4 H), 7.20 (m, 3 C_6H_5, 15 H); mass spectrum (70 eV) *m/e* (rel intensity) 433 ($M^+ - C_2H_5O\cdot$, 9.0), 388 (71.0), 387 (75.6), 313 (13.2), 230 (63.8), 203 (25.3), 176 (13.2), 139 (78.2), 131 (100.0), 103 (37.9), 92 (29.5), 91 (75.2), 77 (21.1), 65 (27.7), 45 (15.6).

Anal. Calcd for $C_{28}H_{31}O_5P$: P, 6.47. Found: P, 6.43.

1-Benzyl-2-phenyl-4-carbethoxy-5,5-dimethylphospholan-3-one 1-Oxide (23). A slurry of 1.3 g (55.6% in mineral oil, 0.03 mol) of NaH in 50 ml of anhydrous THF at room temperature was treated with 6.9 g (0.03 mol) of dibenzylphosphine oxide in 50 ml of THF. The resulting mixture was heated at reflux for 15 min with vigorous evolution of a gas (presumed H_2) and with formation of a clear, pale-yellow solution. This solution heated to reflux was treated (dropwise) with a solution of 6.0 g (0.03 mol) of diethyl isopropylidenemalonate[19] in 75 ml of THF. After addition, the mixture was boiled for 2 hr and then treated with a slurry of 2.6 g (0.06 mol) of NaH in 50 ml of THF.

After an additional 3 hr at reflux (much gas evolved), the solution was cooled to room temperature and hydrolyzed (45 ml of 2 *N* acetic acid). The solution was concentrated to ~50 ml volume and extracted (3 × 75 ml) with $HCCl_3$. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to a thick yellow oil. Dissolution of this oil in boiling diethyl ether and standing for 2 days at room temperature deposited a white powder. Recrystallization of this powder from cyclohexane–chloroform (5:1) yielded 6.5 g (56.4%) of **23**: mp 171–173°; ir (KBr) ν 2540 (OH), 1717 (C=O), 1608 (–C=C–), 1107 cm^{-1} (P→O); pmr ($DCCl_3$) δ 1.28 (m, CH_3, 9 H), 2.16 (m, CH, 1 H), 3.22 (m, $^{31}PCH_2C_6H_5$, OH, 3 H), 4.20 (m, CH_2, 2 H), 7.24 (m, 2 C_6H_5, 10 H); mass spectrum (70 eV) *m/e* (rel intensity) 384 (M^+, 18.0), 312 (19.9), 221 (20.9), 155 (22.3), 118 (28.1), 91 (100.0), 90 (18.0), 89 (14.4), 83 (32.4), 65 (14.4), 31 (16.2).

Anal. Calcd for $C_{22}H_{25}O_4P$: P, 8.06. Found: P, 8.21.

Registry No.—**22**, 52050-51-8; **23**, 52050-52-9; dibenzylphosphine oxide, 13238-16-9; ethyl cinnamate, 103-36-6; diethyl benzalmalonate, 5292-53-5; diethyl isopropylidenemalonate, 6802-75-1.

References and Notes

(1) We gratefully acknowledge partial support of this work by the Public Health Service, National Cancer Institute, Grant CA 11967-10. We also acknowledge the National Science Foundation Institution grant to purchase the XL-100 nmr unit, Grant NSF GP-17641.
(2) Research Associate, 1973–1975.
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(5) (a) Some of the oxides were reported while our work was in progress; see R. Bodalski and K. Pietrusiewicz, *Tetrahedron Lett.*, 4209 (1972). (b) D. G. Smith and D. J. H. Smith, *ibid.*, 1249 (1973).
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(13) This value is in good agreement with that band at 1730–1740 cm^{-1} observed for the carbonyl of 1-methylphospholan-3-one 1-oxide depending upon the medium (solution or a KBr pellet); see ref 6.
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Purine *N*-Oxides. LVII. 9-Hydroxyhypoxanthine, Xanthine, and Guanine[1]

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By direct application of the Shaw synthesis 8-methyl-9-hydroxypurines were successfully synthesized *via* the condensation of benzyloxyamine with the acetimidate from aminocyanoacetamide and triethyl orthoacetate. This condensation failed with triethyl orthoformate. In a modified sequence of reactions, the cyclization of the condensation product of *N*-benzyloxyformimidate and aminocyanoacetate to the imidazole was found to be catalyzed by HCl. The use of benzyloxyamine hydrochloride and the formimidate from aminocyanoacetamide also yielded the requisite imidazole. From the imidazole the title 9-hydroxypurines were obtained.

A recent synthesis of 9-hydroxy-8-methylpurines[2] involved an application of the Shaw route to 9-alkylpurines.[3] In the initial steps the condensation of triethyl orthoacetate with 2-amino-2-cyanoacetamide (**1**) to yield **2**, R = CH_3, was followed by condensation with benzyloxyamine to yield 5-amino-1-benzyloxy-2-methylimidazole-4-carbox-