Synthesis of Tricyclic Phospholene Oxides by Cycloaddition of Phosphorus Halides with Heterocyclic Analogs of 1-Vinyl-3,4-dihydronaphthalenes (1)

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Replacement of C-4 with a hetero substituent (NR,O,S) in the 1-vinyl-3,4-dihydronaphthalene system has provided a new type of diene for participation in the McCormack cycloaddition reaction with P(III) halides. The tricyclic phospholene oxides so obtained are the first to bear an additional heteroatom in the ring system. 1,2-Dihydro-7-methoxy-1-(*p*-toluenesulfonyl)-4-vinylquinoline is a stable solid that reacts with methylphosphonous dichloride to give, after hydrolysis of the cycloadduct, the 1,2,4,5-tetrahydro-1*H*-phospholo-[2,3-*c*]quinoline ring system. The dihydroquinoline moiety was aromatized by detosylation with potassium *t*-butoxide. The tendency of 4-vinyl-2*H*-benzopyran to dimerize was a serious complication in its use, and the cycloaddition with methylphosphonous dichloride proceeded only in low yield. The product, a 2,3,3a,4-tetrahydrobenzo[3,2-*d*]pyran derivative, was a stable, easily purified and characterized substance. 4-Vinyl-2*H*-benzo[*b*]thiopyran was more stable than the pyran, but the phospholo derivative from reaction with methylphosphonous dichloride was more difficult to purify. All products were characterized by ^{13}C-nmr spectroscopy.

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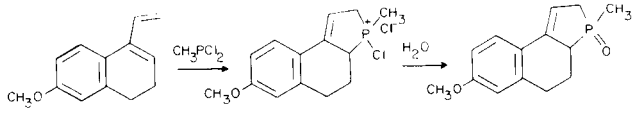
It has been shown in previous work in this laboratory that 1-vinyl-cycloalkenes (2) and some benzo derivatives (3) function well as dienes in the versatile McCormack cycloaddition with P(III) halides. This reaction stands as the most useful synthesis of the 5-membered heterocyclic system containing phosphorus (4). We have now considered the feasibility of using heterocyclic counterparts of some 1-vinylcycloalkenes as dienes in this synthesis, for if successful the reaction would make available new types of multi-ring heterocyclic systems containing two (or more) hetero atoms. The 1-vinyl-3,4-dihydronaphthalene framework (as in **1**) was used in this study, since this system (3) is quite reactive under McCormack conditions (forming **2** as the isolated product) and 4-hetero derivatives seemed especially accessible by synthesis.



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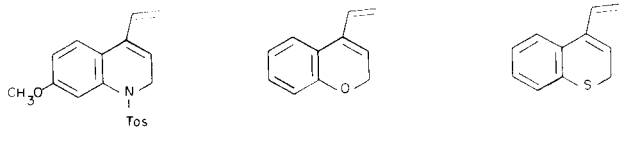
The heterocyclic counterparts that we have examined are shown as **3-5**. In the aza series, the functionality used for N is quite variable, but the tosyl derivative was chosen to reduce the electron density on N, thereby preventing interaction at this site with the phosphorus halide (5). Another advantage provided by the tosyl derivatives is that this group can undergo an elimination to generate the quinoline ring system.



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The aza-substituted diene **3** was prepared from the well-known (6) tertiary alcohol **7**, a substance of value in aza-steroid synthesis. The dehydration does not appear to have been documented previously, but it was easily accomplished (75%) by the quinoline-iodine method in refluxing benzene. The diene was a stable, recrystallizable, solid. The McCormack cycloaddition with methylphosphonous dichloride was performed at room temperature in benzene; as is typical for such cycloadditions the reaction required several days. Hydrolysis gave the solid phospholene oxide **8** in 75% yield; recrystallization from ethyl acetate provided a sample of analytical purity. It is not common (4) for the double bond to appear in the 2-phospholene position from the hydrolysis conditions used (ice water), but this was clearly indicated for **8** from the ^{1}H-nmr spectrum, which contained no olefinic proton signals (found at δ 6.07 in the carbocyclic counterpart **2** (3)). The ^{31}P-nmr signal appeared at δ + 63.0; a similar value (+ 66.4) has been found for the rearranged product from **2**. The ^{13}C-nmr spectrum (Table I) also supported the assigned structure.

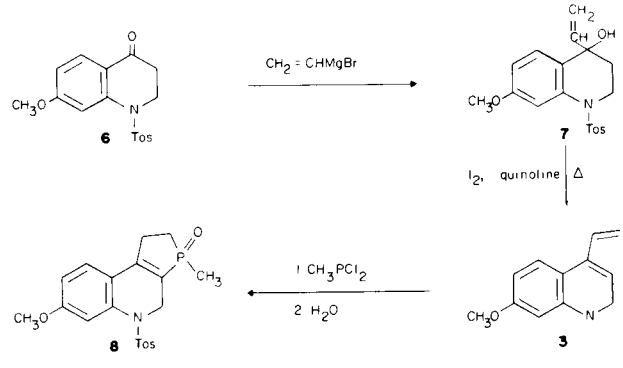

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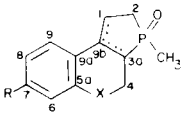
Table I

^{13}C-NMR Spectra of Tricyclic Phospholene Oxides (a)



	2, X = CH_2, R = OCH_3, Δ [9b,1]	**12**, X = O R = H, Δ [9b,1]	**15a**, X = S R = H, Δ [9b,1]	**8**, X = *N*-Tosyl R = OCH_3, Δ [3a,9b]
PCH_3	10.38 (62.3)	10.88 (62.3)	16.91 (64.1)	16.54 (68.4)
1	112.95 (8.5)	114.25 (7.9)	119.44 (6.7)	25.85 (5.9)
2	31.58 (63.5)	31.82 (71.3)	33.69 (63.5)	26.65 (70.3)
3a	41.36 (70.2)	39.45 (65.3)	40.57 (65.9)	124.15 (74.2)
4	21.50 (4.3)	64.73	26.45 (2.4)	43.55 (13.7)
5	30.56 (13.4)	—	—	—
5a	138.26 (1.2)	153.74	133.26	137.76
6	113.52 (b)	117.84	124.99	112.89
7	158.37	130.11	128.86	161.46
8	113.52 (b)	121.46	127.16	113.54
9	125.16 (1.8)	123.89	126.14 (1.2)	125.39
9a	123.98 (8.5)	(c)	129.88 (7.3)	(c)
9b	137.37 (15.9)	132.52 (12.8)	137.59 (14.0)	147.98 (29.3)

(a) In deuteriochloroform with internal tetramethylsilane as reference. Values in parentheses are ^{13}C-^{31}P coupling constants (in Hz) where observed. (b) Superimposed. (c) Not observed.

The quinoline ring was readily constructed from **8** by elimination of the elements of *p*-toluenesulfinic acid with potassium *t*-butoxide. The product **9** represents the first known quinoline derivative bearing a fused phospholane ring. This compound was easily purified by crystallization

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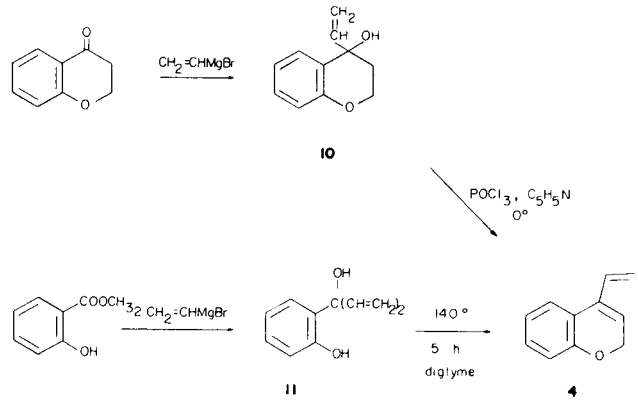
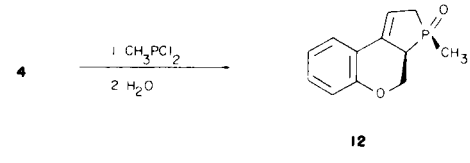
from benzene or by vacuum sublimation. It was fully characterized by spectral techniques. Of special interest is a comparison of the ^{31}P shift in the dihydro derivative **8** to the aromatized compound. Just as observed for the carbocyclic system (7), the aromatization produced an upfield shift (**8**, δ + 63.0, **9**, + 59.0). The aza-substitution did not produce significant changes in the ^{31}P shifts (*cf.* **9** to + 55.2 for the naphthalene counterpart (7)).

The oxygen-containing diene (**4**) was far less readily obtained. It has a strong tendency to undergo dimerization and this presents a major problem in both the synthesis method and the isolation procedure. The elevated temperature method of alcohol dehydration (as applied to **10**), which was used for the aza compound, was not successful, and was replaced by the phosphorus oxychloride-pyridine method at 0°. The diene product was purified only by column chromatography and never isolated in pure form, since concentration of solutions invariably caused dimerization. An alternative method of preparation (8), outlined below, was also employed but did not give substantially superior results.



Solutions of the diene from either source were used directly in the cycloaddition with methylphosphonous dichloride. The best results, though still quite modest, were obtained when the adduct that had precipitated after a few days was collected and hydrolyzed, although on some occasions no product could be isolated. Because of these difficulties, the method cannot be said to have much synthetic value, although the phospholene oxide **12** once obtained is a stable crystalline solid, obtained in analytically pure form. Its ^{1}H-nmr spectrum (δ6.23, $^3J_{PH}$ = 28 Hz)



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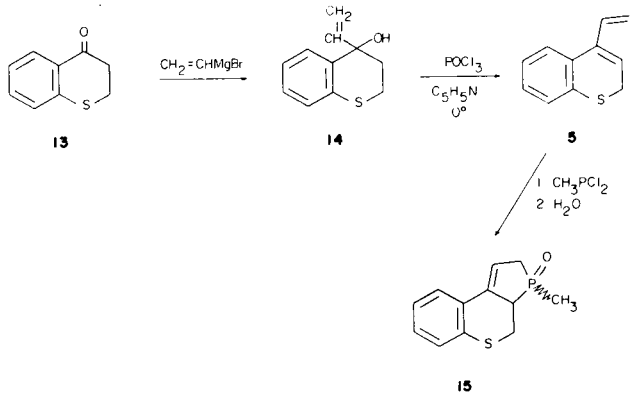
provided the proof that the double bond remained in the β, γ position with respect to P. The 2-substituted 3-phospholene ring system can exist in *cis, trans* isomeric forms due to the chirality of phosphorus. The assignment of the *cis* structure shown in **12** was based on the relatively upfield position of the ^{13}C-nmr signal for the PCH_3 group. The value is nearly coincident with that found for the *cis* isomer of **2** (Table I). The less crowded *trans* isomer has a shift that is downfield by several ppm in such systems (2).

The sulfur-containing diene (**5**) proved to be much more stable than the oxygen counterpart. It was obtained in low yield (13.2%) by dehydration with the phosphorus oxychloride-pyridine system of the tertiary alcohol **14**, itself formed from vinylmagnesium bromide addition to 4-thiochromanone (100%). The diene was isolated as an oil from chromatographic purification and had the expected nmr spectrum. The cycloaddition with methylphosphonous dichloride proceeded relatively rapidly, and the adduct collected after 2.5 days gave, after hydrolysis, a 75% yield of crude phospholene oxide (**15**).



The phospholene oxide was difficult to purify; a sample placed through Norite treatment, chromatography on alumina, and several recrystallizations from both ethyl acetate and acetone still retained a yellow color. Nevertheless, the sample gave the correct elemental analysis for a monohydrate, and its nmr spectra were proper for a mixture of *cis, trans* isomers of **15**. The isomers gave ^{31}P-nmr shifts of + 61.8 and + 69.6. These values are similar to those obtained for the *trans* and *cis* isomers of the carbocyclic model 2 (+ 62.5 and + 70.5, respectively (3)). Further proof that the isomer (designated **15a**) of δ ^{31}P + 61.8 has the *trans* structure came from its ^{13}C-nmr spectrum; a pure sample of this isomer was eluted from alumina with ethyl acetate shortly before the other (obtained only in mixture form), and had the expected downfield position for PCH_3 of δ 16.54.

Summary.

This work has established that the McCormack cycloaddition reaction can be applied to dienes where one double bond is incorporated in a heterocyclic ring. The *N*-tosyl group is especially well tolerated as the hetero component, and quite good yields of intermediates and final phosphorus-containing products were obtained. The diene with a sulfur ring-component was obtained in lower yield, but it reacted well with methylphosphonous dichloride and gave a solid product in high yield. A problem with purification of the sample was not completely solved, however. The oxygen-substituted diene gave very poor results; its tendency to dimerize is very great, and it was inconsistent in its behavior in the cycloaddition reaction. At best, only poor yields were obtained. The final heterocyclic product is, however, stable and purifiable. The use of P(III) halides other than methylphosphonous dichloride may lead to different characteristics in this and the other cycloadditions and in their final products, but these possibilities are left open for exploration.

EXPERIMENTAL

1,2-Dihydro-7-methoxy-1(*p*-toluenesulfonyl)-4-vinylquinoline (**3**).

To a solution of 18.7 g (0.052 mole) of alcohol **7**, prepared as described in the literature (6) from ketone **6**, in 200 ml of benzene was added 5 drops of quinoline and a crystal of iodine. The mixture was refluxed for 8 hours, collecting the water formed (nearly the theoretical amount) in a Dean-Stark trap. The reaction mixture was washed with 150 ml of saturated sodium bicarbonate and sodium chloride solutions, and the organic layer was then dried (sodium sulfate). Removal of the solvent left a yellow oil which solidified overnight. Recrystallization from absolute ethanol gave 13.9 g (78%) of diene **3**, mp 104-106° (sealed tube); ^{1}H-nmr (deuteriochloroform): δ 2.31 (s, CH_3-C_6H_4), 3.87 (s, CH_3O), 4.34 (d, $^3J_{HH}$ = 5.5 Hz, CH_2N), 4.8-6.2 (ABX pattern, CH_2=CH), 5.42 (t, $^3J_{HH}$ = 5.5 Hz, HC-3), 6.6-7.3 (m, aromatic H).

Anal. Calcd. for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10; S, 9.39. Found: C,66.61; H, 5.76; N, 4.07; S, 9.44.

7-Methoxy-3-methyl-3-oxo-1,2,4,5-tetrahydro-*N*-(*p*-toluenesulfonyl)-1*H*-phospholo[2,3-*c*]quinoline (**8**).

A mixture of 3.41 g (10 mmoles) of diene **3** and 1.35 g (11.5 mmoles) of freshly distilled methylphosphonous dichloride in 12 ml of benzene, with a small amount of copper stearate as polymerization inhibitor, started to precipitate a solid after 4 hours. The mass was broken up with 11 ml of benzene after 24 hours, and allowed to stand for 8 days. The mixture was then poured onto 16 g of ice, neutralized with 3 g of sodium bicarbonate, and extracted with 3 30-ml portions of chloroform. The extracts were dried (magnesium sulfate) and evaporated to leave an oil. Trituration with pentane gave a tan solid (2.9 g, 75%), mp 172-176° dec. Recrystallization from ethyl acetate gave a sample of **8** of mp 189-192°; ^{1}H-nmr (deuteriochloroform): δ 1.56 (d, $^2J_{PH}$ = 13.5 Hz, PCH_3), 1.62-2.8 (m, CH_2-CH_2P), 2.37 (s, CH_3-C_6H_4), 3.94 (s, CH_3O), 4.1-5.1 (m, CH_2N), 6.8-7.8 (m, aromatic H); ^{31}P-nmr (deuteriochloroform): + 63.0; ^{13}C-nmr, Table I.

Anal. Calcd. for $C_{20}H_{22}NO_4PS$: C, 59.54; H, 5.50; N, 3.47; P, 7.68. Found: C, 59.33; H, 5.53; N, 3.36; P, 7.99.

1,2-Dihydro-7-methoxy-3-methyl-3-oxo-1*H*-phospholo[2,3-*c*]quinoline (**9**).

A mixture of 3.0 g of tosyl derivative (**8**), 8.25 g of potassium *t*-butoxide, and 150 ml of tetrahydrofuran was refluxed for 1 hour. The resulting red-brown solution was cooled and poured into 250 ml of cold water. The solution was extracted with 3 100-ml portions of chloroform. The quinoline was then extracted from the chloroform solution with 5 50-ml portions of 10% hydrochloric acid. The acid was neutralized with solid sodium bicarbonate, and the quinoline extracted with 4 75-ml portions of chloroform. The combined extracts were dried over magnesium sulfate, and the colorless solution stripped to give 1.40 g (78%) of white solid, mp 183.5-184.5°. Recrystallization from benzene gave a sample of **9** with mp 184-185°; ^{1}H-nmr (deuteriochloroform): δ 1.81 (d, $^2J_{PH}$ = 13.5 Hz, P-CH_3), 2.35 (m, CH_2P), 3.36 (m, CH_2CH_2P), 3.92 (s, CH_3O), 7.03 (d of d, $^3J_{ortho}$ = 9 Hz, $^4J_{meta}$ = 2.5 Hz, *H*C-8), 7.26 (d, $^4J_{meta}$ = 2.5 Hz, *H*C-6), 7.53 (d, $^3J_{ortho}$ = 9 Hz, *H*C-9), 8.80 (d, $^3J_{PH}$ = 3 Hz, *H*C-4); ^{31}P-nmr (deuteriochloroform): δ + 59.0; uv (absolute ethanol): λ max 333 nm (log ϵ 3.54), 321 (3.53), 281 shoulder (3.65), 272 (3.70), 243 (4.76); ms: m/e calcd. 247.0762 (M+), found, 247.0758.

Anal. Calcd. for $C_{13}H_{14}NO_2P$: C, 63.14; H, 5.71; N, 5.67; P, 12.54. Found: C, 63.26; H, 5.61; N, 5.43; P, 12.71.

4-Vinyl-2*H*-benzopyran (**4**) from 4-Chromanone.

A solution of 27.9 g (0.19 mole) of 4-chromanone in THF was treated with 0.21 mole of vinyl magnesium bromide (10). After hydrolysis, the alcohol product (**10**) was extracted and the extracts concentrated. The product was unstable and was not isolated. It was dissolved in 100 ml of pyridine, cooled to 0°, and treated with 23 ml (0.245 mole) of phosphorus oxychloride dissolved in 100 ml of pyridine. The mixture was stirred overnight at room temperature, and then was poured onto ice. The deep purple aqueous solution was extracted with 4 100-ml portions of pentane. The yellow extract was washed with small portions of 10% hydrochloric

acid to remove the pyridine, and then with saturated sodium bicarbonate solution. After decolorization with Norite A, the extract was dried (magnesium sulfate), and partly concentrated (to 50 ml) for use in the cycloaddition reaction. A small portion was rapidly freed of solvent so that a ^{1}H-nmr spectrum (deuteriochloroform) of **4** could be taken: δ 4.7 (d, J = 4 Hz, -CH_2O), 5.2-5.5 (m, CH=CH_2), 5.75 (t, J = 4 Hz, =CH-CH$_2$-), 6.3-6.7 (poorly resolved d of d, CH=CH$_2$), 6.9-7.3 (aromatic H).

4-Vinyl-2*H*-benzo[*b*]pyran (**4**) from 3-Hydroxy-3-(*o*-hydroxyphenyl)-1,4-pentadiene (**11**).

Following the procedure of Hug, *et al.* (8), 50 g (0.33 mole) of methyl salicylate was reacted with 1 mole of vinylmagnesium bromide in tetrahydrofuran. Following stirring for 2 hours, the solution was hydrolyzed with saturated ammonium chloride. The organic layer was separated and combined with four ether extracts (200 ml each) of the aqueous solution. The organic solutions were washed (100 ml each of saturated sodium bicarbonate and sodium chloride), dried (magnesium sulfate) and concentrated. The product (**11**) was purified by column chromatography; impurities were eluted first with pentane, and **11** with ether. This provided 27.7 g (48%) of **11** in crude form. A 13 g (0.074 mole) sample in 700 ml of diglyme was heated at 140° for 5 hours. The mixture was diluted with 800 ml of water and extracted with 4 100-ml portions of petroleum ether (30-60°). These were freed of diglyme by water extraction (4 100-ml portions), and the product from partial removal of solvent then purified by chromatography on silica gel (petroleum ether as eluent). The eluted fraction containing **4** was concentrated to 25 ml, filtered to remove some of the precipitated dimer, and used directly in the cycloaddition reaction.

3-Methyl-2,3,3a,4-tetrahydrobenzo[*b*]phospholo[3,2-*d*]pyran-3-oxide (**12**).

The soluton of diene **4** obtained from cyclization of 13 g of **11** was mixed with 0.11 mole of methylphosphonous dichloride and 0.1 g of copper stearate. After 3 days at room temperature, the liquid was decanted from the solid adduct on the walls of the vessel. The solid was treated with ice and saturated sodium bicarbonate. The resulting solution was extracted several times with chloroform, the extracts were dried (magnesium sulfate) and stripped to dryness. The residue was recrystallized several times from acetone, yielding 1.8 g (11.1% from **11**), mp 160° dec; ^{1}H-nmr (deuteriochloroform): δ 1.52 (d, $^2J_{PH}$ = 12.5 Hz, PCH$_3$), 2.73 (d of d, $^2J_{PH}$ = 13 Hz, $^3J_{HH}$ = 3 Hz, HC-2), 3.45 (d, $^2J_{PH}$ = 13 Hz, HC-3a), 3.6-4.2 and 4.6-5.0 (both m, 1H, H$_A$H$_B$C-4), 6.23 (broad d, $^3J_{PH}$ = 28 Hz, HC-1), 6.70-7.70 (aromatic H); ^{13}C-nmr, Table I.

Anal. Calcd. for $C_{12}H_{13}O_2P$: C, 65.45; H, 5.95; P, 14.07. Found: C, 65.41; H, 5.95; P, 14.18.

3,4-Dihydro-4-hydroxy-4-vinyl-2*H*-benzo[*b*]thiopyran (**14**).

Thiochroman-4-one (**13**, 30 g, 0.18 mole) was reacted with vinylmagnesium bromide (0.36 mole) in tetrahydrofuran. Hydrolysis and workup as described for **10** gave 35.1 g (100%) of **14**; ^{1}H-nmr (deuteriochloroform): δ 2.1 (m, H$_2$C-3), 2.8-3.3 (m, H$_2$C-2), 5.1-5.4 (m, -CH=CH_2), 5.8-6.2 (m, -CH=CH$_2$), 6.9-7.6 (m, aromatic).

4-Vinyl-2*H*-benzo[*b*]thiopyran (**5**).

The crude 4-vinylthiochroman-4-ol (**14**) synthesized above (35.1 g, 0.18 mole) was dissolved in 150 ml of pyridine, cooled to 0°, and treated slowly with a solution of 23 ml (38.2 g, 0.25 mole) of phosphorus oxychloride and 100 ml of pyridine, so that the temperature did not rise above 2°. The solution was allowed to warm slowly to room temperature and was stirred for 18 hours. The dark solution was cooled in ice and hydrolyzed slowly with ice-water, with the temperature held below 20°. The aqueous solution was extracted with 4 200-ml portions of petroleum ether. The extracts were washed with small portions of 10% hydrochloric acid and then with saturated sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to 6.7 g of an orange-brown oil. This oil was chromatographed on alumina with a 20:80 benzene-petroleum ether eluent to give 4.4 g (13.2%) of **5** as an impure oil; ^{1}H-nmr (deuteriochloroform): δ 3.4 (d, ^3J = 6 Hz, H$_2$C-2), 5.25-5.7 (m, -CH=CH_2), 6.25 (t, ^3J = 6 Hz, HC-3), 6.5-6.8 (m, -CH=CH$_2$), 7.1-7.7 (m, aromatic).

3-Methyl-2,3,3a,4-tetrahydrobenzo[*b*]phospholo[3,2-*d*]thiopyran 3-oxide (**15**).

The 4.4 g (0.025 mole) of diene **5** was combined with 0.1 g of copper stearate, 10 ml of hexane, and 3 ml (3.9 g, 0.033 mole) of methylphosphonous dichloride. The mixture was allowed to stand for 4.5 days at room temperature. The liquids were then decanted and put aside for futher reaction, and the crumbly solid adduct was hydrolyzed with ice and sodium bicarbonate solution. The suspension of brown-pink crystals was filtered and the residue air-dried to give 5.9 g of a still moist, pasty solid. The solid was dissolved in methanol, treated with Norite-A, filtered, and reconcentrated. Recrystallization from ethyl acetate gave brown crystals. A portion of the solid was chromatographed on alumina using ethyl acetate as the eluent; **15a** was eluted first, followed by a mixture of **15a** and **15b**, both as light brown solids. Much color was retained on the column. Repeated recrystallization of these solids from acetone reduced the color to a yellow shade; the best sample, mp 103-105°, was used for an elemental analysis, which suggested a hydrate; ^{1}H-nmr (deuteriochloroform): for **15a**, δ 1.78 (d, $^2J_{PH}$ = 12 Hz, PCH$_3$), 2.5-3.5 (m, other aliphatic), 6.3 (d, $^3J_{PH}$ = 29 Hz, =CH-), 6.9-7.4 (m, aromatic); for **15b**, δ 1.57 (d, $^2J_{PH}$ = 12 Hz, PCH$_3$), 6.4 (d, $^3J_{PH}$ = 29 Hz, =CH-); ^{31}P-nmr (deuteriochloroform): δ + 61.8 (**15a**) and + 69.6 (**15b**); ^{13}C-nmr data for **15a**, Table I.

Anal. Calcd. for $C_{12}H_{13}OPS\cdot H_2O$: C, 57.15; H, 5.99; P, 12.14. Found: C, 56.81; H, 5.86; P, 12.34.

REFERENCES AND NOTES

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(5) Some exploratory experiments were performed with a tertiary amine, 1-methyl-4-vinyl-1,2,5,6-tetrahydropyridine, but were unsuccessful due to competing reactions of complexation and protonation at nitrogen.

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(9) Melting points were taken on a Mel-temp apparatus and are corrected; boiling points are uncorrected. The nmr spectra were taken as follows: ^{1}H, JEOL MH-100 spectrometer, internal TMS reference, deuteriochloroform solutions; ^{31}P, Bruker HFX-10 at 36.43 MHz, FT proton decoupled, 85% phosphoric acid external reference with positive signs downfield, negative upfield, deuteriochloroform solutions; ^{13}C, JEOL FX-60 at 15.0 MHz, FT proton decoupled, internal TMS as reference in deuteriochloroform solutions as lock. Elemental analyses were performed by MHW Laboratories, Phoenix, Arixona.

(10) G. DeStevens and B. Smolinsky, *J. Med. Chem.*, **9**, 954 (1966).