Novel Heterocycles. 3. Synthesis of Fused 1,3,2-Benzodiazaphosphorin Ring Systems

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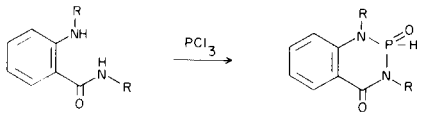
Received January 11, 1979

Novel fused tricyclic phosphorus heterocycles **9** and **11** and the tetracycle **15** were synthesized by cyclization of 1-haloalkyl (or 3-haloalkyl)-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1*H*)one 2-oxides with sodium hydride. Some spectral data of the products are also discussed.

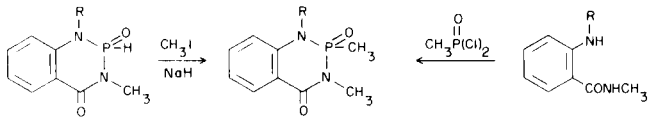
J. Heterocyclic Chem., **16**, 897 (1979).

In a recent report (1), the reaction between *N*-substituted anthranilamides and phosphorus trichloride to produce 1,3,2-benzodiazaphosphorins (**1**) was investigated.



The chemistry of the phosphorus heteroatom in various ring systems has been documented (2). In this report the reactivity of the phosphorus atom in this type ring system will be explored.

The treatment of **2** with methyl iodide in the presence of sodium hydride furnished the *P*-methylated products **4a** and **4b**.

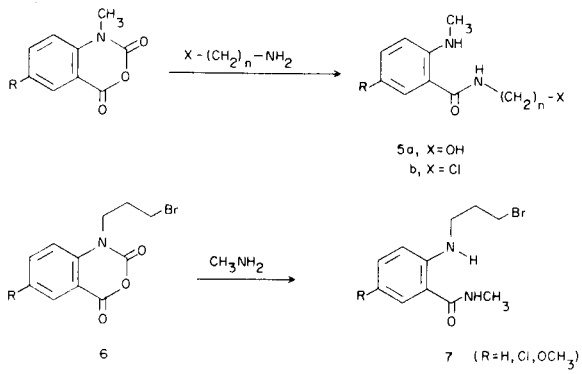


The infrared spectra of these compounds lacks the P-H absorption formerly appearing between 2400 and 2350 cm^{-1} (1) and still exhibits a moderately intense band observed at 1340 cm^{-1} (P=O stretching vibration). The nmr spectra also lacks the characteristic P-H doublet formerly seen at δ 7.8 while a P-CH_3 signal (doublet) is observed at δ 1.6 (J = 16 Hz).

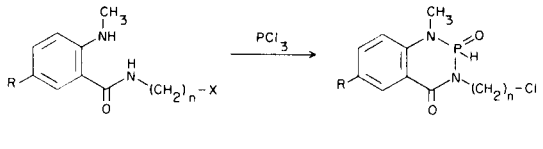
Additional proof of *P*-alkylation was furnished by the treatment of **3a** with methyl phosphonic dichloride to also yield **4a**. The spectral data of **4a** obtained by both of these methods were found to be identical.

The ease of alkylation on phosphorus prompted the investigation into the possibility of the synthesis of tricyclic phosphorus heterocycles. If either nitrogen of **1** possesses a haloaklyl functionality of suitable chain length, intramolecular alkylation may proceed to furnish the corresponding [2,1-*b*][1,3,2] or [1,2-*a*][1,3,2]benzodiazaphosphorin.

The appropriate anthranilamides (**5** and **7**) required as intermediates may readily be obtained by the treatment of an isatoic anhydride (3) with either an amino alcohol or a haloalkyl amine in dioxane (see Table 1) or by the treatment of an *N*-haloalkyl isatoic anhydride **6** with methylamine in dioxane (4).



The treatment of anthranilamides (either **5a** or **5b**) with phosphorus trichloride produced the desired 2,3-dihydro-3-chloroalkyl-1-methyl-1,3,2-benzodiazaphosphorin-4-(1*H*)one 2-oxides **8** (see Table 2). In general, this reaction proceeds in much higher yield when chloroalkyl anthranilamides (**5b**) are used instead of the corresponding hydroxyalkyl anthranilamides (**5a**).



The subsequent treatment of **8** with sodium hydride afforded the tricyclic benzodiazaphosphorins **9** in low yield. The major portion of the reaction mixture was found to be the initial chloroalkyl anthranilamide (**5b**) resulting from the loss of phosphorus from **8**.

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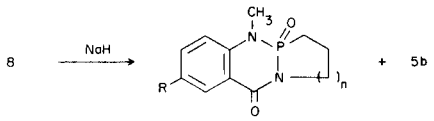
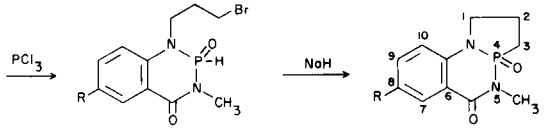


9a, R=H, n=1
b, R=H, n=2
c, R=Cl, n=1

In an analogous series of reactions, the treatment of **7** with phosphorus trichloride produced the desired 1-bromopropyl-2,3-dihydro-3-methyl-1,3,2-benzodiazaphosphorin-4(1*H*)one 2-oxides (**10**), which when treated with sodium hydride afforded the tricyclic benzodiazaphosphorins (**11**).



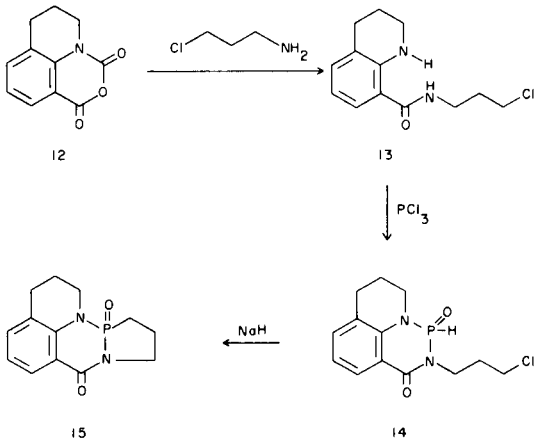
10

11a, R=H
b, R=OCH_3
c, R=Cl

Employment of tricyclic anhydride (**12**) (5) according to Scheme I furnished the tetracyclic phosphorin (**15**) in moderate yield.

The infrared spectra of **9**, **11** and **15** exhibited amide absorptions between 1675 and 1655 cm^{-1} and P=O stretching vibrations between 1340 and 1325 cm^{-1}. In the nmr,

Scheme I



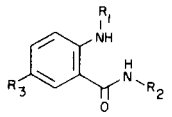
12 13 14 15

the N-CH_3 signal in **9** was observed as a doublet centered at approximately δ 3.3 with a coupling constant of 10 Hz. The N-CH_3 signal in **11** falls between δ 3.3 and 3.25 but has a J value of 8 Hz.

EXPERIMENTAL

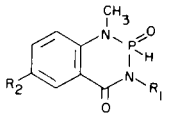
Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian T-60 and EM 360 spectrometers using tetramethylsilane as an internal reference. Chemical

Table 1



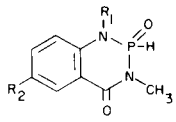
Compound No.	R_1	R_2	R_3	M.p., °C	Yield, %	Molecular Formula	Analysis Calcd. C	H	N	Cl
16	CH_3	CH_2CH_2OH	H	77-80	94	$C_{10}H_{14}N_2O_2$	61.8	7.3	14.4	
							(61.7	7.2	14.1)	
17	CH_3	CH_2CH_2Cl	H	92-95	91	$C_{10}H_{13}ClN_2O$	56.5	6.2	13.2	16.7
							(56.7	6.4	13.2	16.6)
18	CH_3	$CH_2CH_2CH_2OH$	H	68-72	80	$C_{11}H_{16}N_2O_2$	63.4	7.8	13.5	
							(63.5	7.5	13.5)	
19	CH_3	$CH_2CH_2CH_2Cl$	H	68-71	100	$C_{11}H_{15}ClN_2O$	58.3	6.7	12.4	15.6
							(58.6	6.8	12.2	16.0)
20	CH_3	$CH_2CH_2CH_2Cl$	OCH_3	oil	95	$C_{12}H_{17}ClN_2O_2$	56.1	6.7	10.9	
							(56.1	7.1	10.9)	
21	CH_3	$CH_2CH_2CH_2Cl$	Cl	90-93	100	$C_{11}H_{14}Cl_2N_2O$	56.6	5.4	10.7	27.1
							(56.5	5.5	10.8	26.9)
22	CH_3	$CH_2CH_2CH_2CH_2OH$	H	115-118	76	$C_{12}H_{16}N_2O_2$	64.8	8.2	12.6	
							(64.6	8.3	12.7)	

Table 2



Compound No.	R_1	R_2	M.p., °C	Procedure Yield, %	Molecular Formula	Analysis Calcd. C	H	N	(Found) Cl
23	CH_2CH_2Cl	H	137-139	A, 70	$C_{10}H_{12}ClN_2O_2P$	46.4	4.7	10.8	
				B, 41		(46.4	4.8	10.6)	
24	$CH_2CH_2CH_2Cl$	H	96-98	A, 76	$C_{11}H_{14}ClN_2O_2P$	48.4	5.2	10.3	13.0
				B, 38		(48.6	5.6	10.2	13.4)
25	$CH_2CH_2CH_2CH_2Cl$	H	96-99	B, 43	$C_{12}H_{16}ClN_2O_2P$	50.3	5.6	9.8	12.4
						(50.5	5.7	9.9	12.8)
26	$CH_2CH_2CH_2Cl$	Cl	120-123	A, 64	$C_{11}H_{13}ClN_2O_2P$	43.0	4.3	9.1	23.1
						(43.1	4.5	9.2	23.2)
27	$CH_2CH_2CH_2Cl$	OCH_3	106-108	A, 25	$C_{12}H_{16}ClN_2O_3P$	47.6	5.3	9.3	
						(47.2	5.0	9.6)	

Table 3



Compound No.	R_1	R_2	M.p., °C	Yield, %	Molecular Formula	Analysis Calcd. C	(Found) H	N
28	CH_2CH_2Br	H	154-156	45	$C_{10}H_{12}BrN_2O_2P$	39.6	4.0	9.2
						(39.9	4.3	9.4)
29	$CH_2CH_2CH_2Br$	H	oil	96	$C_{11}H_{14}BrN_2O_2P$	No Analysis		
30	$CH_2CH_2CH_2Br$	Cl	oil	64	$C_{11}H_{13}BrClN_2O_2P$	No Analysis		
31	$CH_2CH_2CH_2Br$	OCH_3	oil	67	$C_{12}H_{16}BrN_2O_3P$	No Analysis		

shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrometer.

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

2,3-Dihydro-1,2,3-trimethyl-1,3,2-benzodiazaphosphorin-4-(1*H*)one 2-Oxide (**4a**).

Method A.

To a cooled solution of 1.0 g. of **2a** (1) in 60 ml. of dioxane was added 0.23 g. of sodium hydride (50% in mineral oil, pentane washed) in portions (the internal temperature of the reaction mixture was kept below 15°). After addition, the reaction mixture was allowed to warm to room temperature then 0.7 g. of methyl iodide was added, and the mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and water was added to the residue. The aqueous solution was acidified with 2*N* hydrochloric acid and was extracted into methylene chloride. The solvent was removed under reduced pressure and the resulting oil was crystallized from ether to yield 0.35 g. of **4a** (33%), m.p. 123-126°; ir (chloroform): 1670, 1340 cm^{-1}; nmr (deuteriochloroform): δ 8.2 (m, 1), 7.7-6.9 (m, 3), 3.25 (d, 3, J = 8 Hz), 3.25 (d, 3, J = 7 Hz), 1.6 (d, 3, J = 16 Hz).

Anal. Calcd. for $C_{10}H_{13}N_2O_2P$: C, 53.6; H, 5.9; N, 12.5. Found: C, 54.0; H, 5.9; N, 12.3.

Method B.

A solution of 1.6 g. of **3a** and 1.3 g. of methyl phosphonic dichloride in 40 ml. of benzene was refluxed for 48 hours. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a column of silica gel using a solution of 1% methanol/chloroform to elute the product which was crystallized from ether to yield 0.35 g. of **4a** (16%), m.p. 123-126°.

2,3-Dihydro-2,3-dimethyl-1-phenyl-1,3,2-benzodiazaphosphorin-4(1*H*)one 2-Oxide (**4b**).

The reaction, using 5.5 g. of **2b**, 1.0 g. of sodium hydride, and 3.0 g. of methyl iodide, was performed similar to the one described for the preparation of **4a** and the product, **4b**, was isolated in 48% yield, m.p. 164-166°; ir (chloroform): 1670, 1340 cm^{-1}; nmr (deuteriochloroform): δ 8.25 (m, 1), 7.7-6.9 (m, 7), 6.5 (m, 1), 3.3 (d, 3, J = 8 Hz), 1.7 (d, 3, J = 16 Hz).

Anal. Calcd. for $C_{15}H_{15}N_2O_2P$: C, 62.9; H, 5.3; N, 9.8. Found: C, 62.9; H, 5.6; N, 9.8.

General Procedure for Preparation of **5** (Table 1).

Amino Alcohols.

A mixture of 0.1 mole of the isatoic anhydride (3) and 0.11 mole of the amino alcohol in 250 ml. of dioxane was stirred at 60° for 1.5 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a solution of 5% methanol/chloroform to elute the product. These products were crystallized from ether or ether/pentane.

Chloroalkyl Amines.

A mixture of 0.1 mole of the isatoic anhydride (3) and 0.11 mole of the chloroalkyl amine in 250 ml. of dioxane was stirred at 60° for 3 hours. The solvent was removed under recuded pressure and the residue was crystallized from either ether or ether/pentane to furnish the product **5b**.

General Procedure for the Preparation of 2,3-Dihydro-3-chloroalkyl-1-methyl-1,3,2-benzodiazaphosphorin-4(1*H*)one 2-Oxides (**8**) (Table 2).

Procedure A.

A mixture of 0.09 mole of **5b** and 0.091 mole of phosphorus trichloride in 250 ml. of benzene was refluxed for 5 hours. Ethyl acetate was added to the reaction mixture and it was washed with cold dilute sodium bicarbonate. The solvent was removed under reduced pressure and the resulting oil was crystallized from ether to yield **8**.

Procedure B.

A mixture of 0.04 mole of **5a** and 0.085 mole of phosphorus trichloride was refluxed for 18 hours. The solvent was removed under reduced pressure and cold dilute sodium bicarbonate was added. The mixture was extracted into methylene chloride. The solvent was removed under reduced pressure and the resulting oil was crystallized from ether to yield **8**.

1,2,3,4,4,5-Hexahydro-5-methyl-10*H*[1,2]azaphospholo[2,1-*b*][1,3,2]-benzodiazaphosphorin-10-one 4-Oxide (**9a**).

To a cooled solution of 13.0 g. of **24** in 250 ml. of dioxane was added 2.3 g. of sodium hydride (50% in mineral oil, pentane washed) in portions and the mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and cold water was added to the residue. The mixture was acidified with 2*N* hydrochloric acid and was extracted into methylene chloride. The solvent was removed under reduced pressure and the resulting solid was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product which was crystallized from methylene chloride/ether to yield 3.8 g. of **9a** (34%), m.p. 155-158°; ir (chloroform): 1655, 1355, 1340 cm^{-1}; nmr (deuteriochloroform): δ 8.1 (m, 1), 7.7-6.9 (m, 3), 3.9 (m, 2), 3.25 (d, 3, J = 10 Hz), 2.8-1.9 (m, 4); ms: (70 eV) m/e 236 (M+).

Anal. Calcd. for $C_{11}H_{13}N_2O_2P$: C, 55.9; H, 5.6; N, 11.9. Found: C, 56.2; H, 5.5; N, 11.7.

1,2,3,4,5,5-Hexahydro-6-methyl[1,2]azaphosphorino[2,1-*b*][1,3,2]benzodiazaphosphorin-11(6*H*)one 5-Oxide (**9b**).

The reaction using 6.0 g. of **25** and 1.0 g. of sodium hydride was performed similar to the one described for the preparation of **9a** and the product, **9b**, was isolated in 5% yield, m.p. 153-156°; ir (chloroform): 1650, 1340 cm^{-1}; nmr (deuteriochloroform): δ 8.15 (m, 1), 7.7-6.8 (m, 3), 5.3-4.6 (m, 1), 3.8-3.0 (m, 1), 3.2 (d, 3, J = 9 Hz), 2.7-1.3 (m, 6); ms: (70 eV) m/e 250 (M+).

Anal. Calcd. for $C_{12}H_{15}N_2O_2P$: C, 57.6; H, 6.1; N, 11.2. Found: C, 57.3; H, 6.4; N, 11.1.

8-Chloro-1,2,3,4,4-5-hexahydro-10*H*-[1,2]azaphospholo[2,1-*b*][1,3,2]benzodiazaphosphorin-10-one 4-Oxide (**9c**).

The reaction using 8.0 g. of **26** and 1.3 g. of sodium hydride was performed similar to the one described for the preparation of **9a** and the product, **9c**, was isolated in 9% yield, m.p. 226-229°; ir (chloroform): 1675, 1340 cm^{-1}; nmr (detueriochloroform): δ 8.05 (d, 1), 7.5 (m, 1), 6.9 (m, 1), 3.9 (m, 2), 3.25 (d, 3, J = 10 Hz), 2.9-1.8 (m, 4).

Anal. Calcd. for $C_{11}H_{12}ClN_2O_2P$: C, 48.8; H, 4.5; N, 10.4; Cl, 13.1. Found: C, 48.5; H, 4.6; N, 10.1; Cl, 12.9.

General Procedure for the Preparation of 1-Bromoalkyl-2,3-dihydro-3-methyl-1,3,2-benzodiazaphosphorin-4(1*H*)one 2-Oxides (**10**) (Table 3).

A mixture of 0.25 mole of **7** (4) and 0.026 mole of phosphorus trichloride in 100 ml. of benzene was refluxed for 5 hours. The solvent was removed under reduce pressure and cold dilute sodium bicarbonate was added to the residue. The mixture was extracted into methylene chloride and the solvent was removed under reduced pressure. The product (if crystalline) was crystallized from ether to furnish **10**.

2,3-Dihydro-1*H*-[1,2]azaphospholo[1,2-a][1,3,2]benzodiazaphosphorin-6-(5*H*)one 4-Oxide (**11a**).

The reaction using 12.2 g. of **29** and 1.9 g. of sodium hydride was performed similar to the one described for the preparation of **9a** and the product, **11a**, was isolated in 48% yield, m.p. 182-185°; ir (chloroform): 1670, 1340 cm^{-1}; nmr (deuteriochloroform): δ 8.1 (m, 1), 7.6-6.9 (m, 3), 4.1 (m, 1), 3.25 (m, 1), 3.25 (d, 3, J = 8 Hz), 2.9-1.8 (m, 4); ms: (70 eV) m/e 236 (M+).

Anal. Calcd. for $C_{11}H_{13}N_2O_2P$: C, 55.9; H, 5.6; N, 11.9. Found: C, 56.4; H, 5.4; N, 12.1.

2,3-Dihydro-8-methoxy-1*H*-[1,2]azaphospholo[1,2-**a**][1,3,2]benzodiazaphosphorin-6(5*H*)one 4- Oxide (**11b**).

The reaction using 3.8 g. of **31** and 0.55 g. of sodium hydride was performed similar to the one described for the preparation of **9a** and the product, **11b**, was isolated in 24% yield, m.p. 178-181°; ir (chloroform): 1675, 1330 cm^{-1}; nmr (deuteriochloroform): δ 7.65 (m, 1), 7.3-7.0 (m, 2), 4.2 (m, 1), 3.85 (s, 3), 3.3 (m, 1), 3.3 (d, 3 J = 8 Hz), 2.9-1.8 (m, 4).

Anal. Calcd. for $C_{12}H_{15}N_2O_3P$: C, 54.1; H, 5.7; N, 10.5. Found: C, 54.3; H, 5.3; N, 10.3.

8-Chloro-2,3-dihydro-1*H*-[1,2]azaphospholo[1,2-*a*][1,3,2]benzo diazaphosphorin-6(5*H*)one 4-Oxide (**11c**).

The reaction using 5.7 g. of **30** and 0.8 g. of sodium hydride was performed similar to the one described for the preparation of **9a** and the product, **11c**, was isolated in 18% yield, m.p. 210-212°; ir (chloroform): 1675, 1330 cm^{-1}; nmr (deuteriochloroform): δ 7.65 (m, 1), 7.3-6.8 (m, 2), 4.3-3.5 (m, 4), 3.25 (d, 3, J = 9 Hz), 2.4-2.0 (m, 2).

Anal. **Calcd. for** $C_{11}H_{12}ClN_2O_2P$: C, 48.8; 4.5; N, 10.4; Cl, 13.1. Found: C, 49.0; H, 4.2; N, 10.4; Cl, 13.3.

N-(3-Chloropropyl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (**13**).

A mixture of 15.0 g. of **12** (5) and 1-amino-3-chloropropane in 200 ml. of dioxane was stirred at 60° for 1.5 hours. The solvent was removed under reduced pressure to yield 21.3 g. of **13** (100%). An analytical sample was crystallized from ether, m.p. 89-92°; ir (chloroform): 3470, 3360, 1650 cm^{-1}; nmr (deuteriochloroform): δ 7.6 (s, 1 (broad)), 7.3-6.9 (m, 2), 6.4 (m, 1), 6.4 (s, 1 (broad)), 3.5 (m,6), 2.75 (m, 2), 1.9 (m, 4).

Anal. Calcd. for $C_{13}H_{17}ClN_2O$: C, 61.8; H, 6.8; N, 11.1; Cl, 14.0. Found: C, 61.5; H, 7.1; N, 11.1; Cl, 13.9.

2-(3-Chloropropyl)-8,9-dihydro-1*H*,7*H*-[1,3,2]diazaphosphorino[5,6,1-*ij*]-quinolin-3(2*H*)one 1-Oxide (**14**).

A mixture of 17.0 g. of **13** and 9.5 g. of phosphorus trichloride in 250 ml. of benzene was refluxed for 5 hours. The solvent was removed under reduced pressure and cold dilute sodium bicarbonate was added to the residue. The mixture was extracted into methylene chloride and the solvent was removed under reduced pressure. The resulting solid was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 15.0 g. of **14** (75%). An analytical sample was recrystallized from ether, m.p. 127-130°; ir (chloroform): 2380, 1675, 1330 cm^{-1}; nmr (deuteriochloroform): δ 8.05 (m, 1), 7.85 (d, 1 J = 638 Hz, P-H) 7.4-6.9 (m, 2), 4.3-3.4 (m, 6), 2.85 (m, 2), 2.2 (m, 4).

Anal. Calcd. $C_{13}H_{16}ClN_2O_2P$: C, 52.3; H, 5.4; N, 9.4. Found: C, 52.4; H, 5.4; N, 9.1.

2,3,9,10,11,12-Hexahydro-1*H*,7*H*,12*H*-[1,2]azaphospholo[2,1-*a*]pyrido-[3,2,1-*ij*][1,3,2]diazaphosphorin-7-one 12-Oxide (**15**).

To a cooled solution of 10.0 g. of **14** in 250 ml. of dioxane was added 1.6 g. of sodium hydride (50% in mineral oil, pentane washed) in portions. The mixture was stirred at 10° for 30 minutes. Stirring was continued at room temperature for 18 hours. The solvent was removed under reduced pressure and then cold 1N hydrochloric acid was added to the residue. The mixture was extracted into methylene chloride and the solvent was removed under reduced pressure. The resulting solid was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 4.6 g. of **15** (52%). An analytical sample was crystallized from ether, m.p. 179-182°; ir (chloroform): 1670, 1340 cm^{-1}; nmr (deuteriochloroform): δ 7.9 (m, 1), 7.4-6.8 (m, 2), 4.1-3.3 (m, 4), 3.0-1.7 (m, 8); ms: (70 eV) m/e 262 (M+).

Anal. Calcd. $C_{13}H_{15}N_2O_2P$: C, 59.5; H, 5.8; N, 10.7. Found: C, 59.9; H, 6.1; N, 10.5.

Acknowledgement.

The author wishes to thank Dr. Sandor Barcza and his associates for running all ir and nmr spectra, Mr. William Bonkoski and associates for performing the microanalyses, and Mr. Robert Clark and Mrs. Bertha Owens for running the mass spectra.

REFERENCES AND NOTES

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