Synthesis of the 1,3,2-Benzodiazaphosphorin Ring System

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A series of 1,3-disubstituted-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1*H*)one 2-oxides was prepared by a method involving the treatment of an appropriate anthranilamide with phosphorus trichloride. Tricyclic diazaphosphorins **24** and **28** were also prepared. Some spectral data of the products are also discussed.

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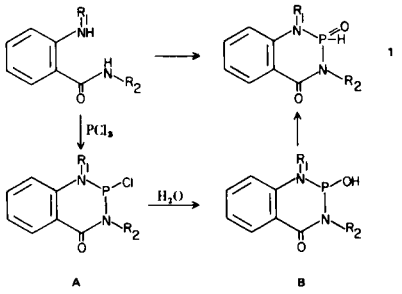
Anthranilamides have been used as intermediates in the synthesis of various heterocycles. Their treatment with dimethylformamide (1) and phosgene (2) to form quinazolinones, with thionyl chloride to produce benzothiadiazinones (3), with nitrous acid to yield benzotriazinones (4), and with dimethyl acetylenedicarboxylate to produce 1,4-benzodiazepine-3,5-diones (5) has been well documented. To our knowledge, treatment of anthranilamides with phosphorus halides has not been reported.

When *N*-substituted anthranilamides were allowed to react with phosphorus trichloride, benzodiazaphosphorins of type **1** were produced, presumably through intermediate **A** (6) (Scheme 1).

Scheme 1



Subsequent hydration of **A** yields **B**. Analysis of spectral evidence leads to the conclusion that the compounds exist predominantly in the 2-oxo form (**1**) rather than the 2-hydroxy form (**B**). This finding is compatible with the observations of Meyrick and Thompson(7) who reported that dialkyl hydrogen phosphites exist wholly in the phosphonate form.

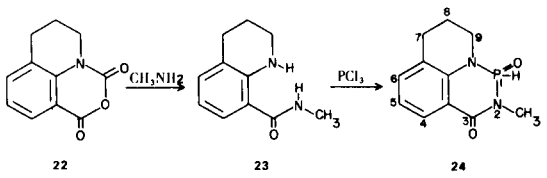
The infrared spectra of these compounds exhibit a P-H absorption of medium intensity between 2400 and 2350 cm^{-1} which is well within the normal range of P-H absorptions reported by Bellamy (8). In all compounds, a moderately intense band is observed between 1350 and 1320 cm^{-1}. This absorption is assigned to the P=O stretching vibration and is within the limit of published values (9,10), although the higher than average values may be due to the effect of the nitrogen substituents directly attached to the phosphorus atom (10,11).

The nmr spectra exhibit characteristic P-H signals seen as a doublet centered at 7.8 δ with coupling constants ranging from 636 to 654 Hz. These also are within the limits of published values (12). In addition, one can observe PNCH couplings with R groups at positions 1 and 3. For example, when R_1 and R_2 are methyl groups (compound **12**), two individual sets of doublets almost superimposable on each other are seen at 3.25 δ, one with a coupling constant of 9 Hz and the other with a J value of 8 Hz. The assignment as to which N-CH_3 group possesses which coupling constant was made by employing compounds in which the position at 1 and 3 were substituted with a functionality other than methyl (*e.g.*, **17** and **20**). It was found that the methyl at position 1 has the coupling constant of 9 Hz. These values are in accord with published PNCH constants (13).

The starting anthranilamides (Table 1) are conveniently prepared by the treatment of isatoic anhydrides (14) with amines. When gaseous amines are employed, they are bubbled through a solution of the isatoic anhydride in dioxane at room temperature. When liquid amines are used, a solution of the isatoic anhydride in dioxane is treated with 1.5 equivalents of the appropriate amine at 60°.

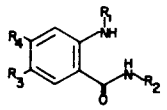
The use of tricyclic anhydrides (**22** (15) and **26**) leads to the formation of two novel ring systems **24** and **28** (Schemes 2 and 3).

Scheme 2



Anhydride **26** can readily be prepared by the treatment of 3-amino-2-naphthoic acid with ethyl chloroformate followed by alkylation of **25** with methyl iodide in the presence of sodium hydride. The naphthamide **27** is formed in good yield by the treatment of **26** with methylamine at room temperature.

Table 1



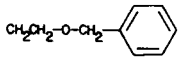
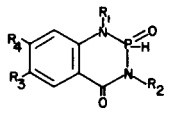
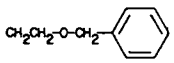
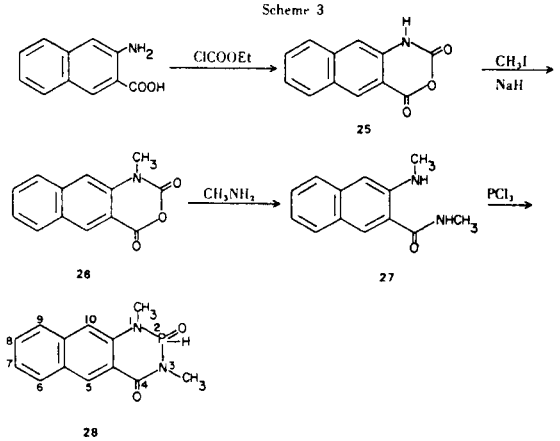
Compound No.	R_1	R_2	R_3	R_4	M.p., °C	Procedure, Yield	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl
2	CH_3	CH_3	H	H	88-91	A, 100	$C_9H_{12}N_2O$	65.8 (65.6)	7.4 (7.3)	17.1 (16.8)	
3	CH_3	CH_3	Cl	H	99-102	A, 100	$C_9H_{11}ClN_2O$	54.4 (54.6)	5.6 (5.7)	14.1 (14.4)	17.8 (18.0)
4	CH_3	CH_3	H	Cl	89-92	A, 100	$C_9H_{11}ClN_2O$	54.4 (54.2)	5.6 (6.0)	14.1 (14.0)	17.8 (17.9)
5	CH_3	CH_3	$O\text{-}CH_2\text{-}O$		155-157	A, 97	$C_{10}H_{12}N_2O_3$	57.7 (57.4)	5.8 (5.8)	13.5 (13.2)	
6	CH_3	CH_2CH_3	H	H	86-89	A, 100	$C_{10}H_{14}N_2O$	67.4 (67.4)	7.9 (7.9)	15.7 (16.1)	
7	CH_3	$CH_2CH{=}CH_2$	H	H	70-73	B, 100	$C_{11}H_{14}N_2O$	69.4 (69.2)	7.4 (7.4)	14.7 (14.7)	
8	CH_3		H	H	60-62	B, 99	$C_{17}H_{20}N_2O_2$	71.8 (71.9)	7.1 (7.0)	9.9) (9.9)	
9	CH_2CH_3	CH_3	H	H	60-62	A, 100	$C_{10}H_{14}N_2O$	67.1 (67.1)	7.9 (8.1)	15.7 (15.6)	
10	$CH_2CH{=}CH_2$	CH_3	H	H	60-63	A, 100	$C_{11}H_{14}N_2O$	69.4 (69.6)	7.4 (7.4)	14.7 (14.9)	
11		CH_3	H	H	75-78	A, 72	$C_{14}H_{14}N_2O$	74.3 (73.9)	6.2 (6.6)	12.4 (12.4)	

Table 2



Compound No.	R_1	R_2	R_3	R_4	M.p., °C	Yield	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl
12	CH_3	CH_3	H	H	124-126	60	$C_9H_{11}N_2O_2P$	51.4 (51.7)	5.3 (5.5)	13.3 (13.1)	
13	CH_3	CH_3	Cl	H	175-176	64	$C_9H_{10}ClN_2O_2P$	44.2 (44.0)	4.1 (4.5)	11.5 (11.6)	14.5 (14.8)
14	CH_3	CH_3	H	Cl	168-170	56	$C_9H_{10}ClN_2O_2P$	44.2 (43.8)	4.1 (4.2)	11.5 (11.0)	14.5 (14.9)
15	CH_3	CH_3	$O\text{-}CH_2\text{-}O$		190-192	48	$C_{10}H_{11}N_2O_4P$	47.4 (47.3)	4.0 (4.5)	11.1 (11.2)	
16	CH_3	CH_2CH_3	H	H	113-116	59	$C_{10}H_{13}N_2O_2P$	53.6 (53.3)	5.9 (6.2)	12.5 (12.5)	
17	CH_3	$CH_2CH{=}CH_2$	H	H	102-105	66	$C_{11}H_{13}N_2O_2P$	55.9 (56.0)	5.6 (5.8)	11.9 (12.0)	
18	CH_3		H	H	64-67	75	$C_{17}H_{19}N_2O_3P$	61.8 (61.7)	5.8 (5.5)	8.5 (8.4)	
19	CH_2CH_3	CH_3	H	H	91-93	49	$C_{10}H_{13}N_2O_2P$	53.6 (53.9)	5.9 (5.7)	12.5 (12.8)	
20	$CH_2CH{=}CH_2$	CH_3	H	H	89-92	51	$C_{11}H_{13}N_2O_2P$	55.9 (56.1)	5.6 (5.3)	11.9 (12.1)	
21		CH_3	H	H	140-142	58	$C_{14}H_{13}N_2O_2P$	61.8 (61.9)	4.8 (4.9)	10.3 (10.2)	

Scheme 3



Investigations into the formation and chemical reactivity of additional novel heterocycles derived from phosphorus trihalides are in progress.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian A-60 and T-60 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

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

Procedure for the Preparation of Anthranilamides (Table 1).

A. Gaseous Amines.

Into a suspension of 0.1 mole of the corresponding isatoic anhydride (14) in 200 ml. of dioxane was bubbled the appropriate amine for 15 minutes. After the introduction of the amine was stopped the reaction mixture was stirred at room temperature an additional 30 minutes. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride. After drying over sodium sulfate, the solvent was removed under reduced pressure to furnish the product. Analytical samples were recrystallized from ether.

B. Liquid Amines.

A suspension of 0.1 mole of the corresponding isatoic anhydride and 0.15 mole of the appropriate amine in 200 ml. of dioxane was stirred at 60° for 3 hours. The solvent was removed under reduced pressure to furnish the product. Analytical samples were recrystallized from ether.

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

To a solution of 0.1 mole of the appropriate anthranilamide in 300 ml. of benzene was added 0.1 mole of phosphorus trichloride and the mixture was refluxed for 5 hours. The mixture was cooled and 300 ml. of ethyl acetate was added. This mixture was washed with cold dilute sodium bicarbonate solution and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished the product. Analytical samples were recrystallized from methylene chloride/ether.

8,9-Dihydro-2-methyl-1*H*,7*H*-[1,3,2]diazaphosphorino[5,6,1-*ij*]-quinolin-3(2*H*)one 1-Oxide (**24**).

To a solution of 8.0 g. of *N*-methyl-1,2,3,4-tetrahydroquinoline-8-carboxamide (15) in 200 ml. of benzene was added 5.6 g. of phosphorus trichloride (precipitation occurs). The mixture was refluxed for 18 hours during which time a solution was formed. The reaction mixture was cooled and poured into cold water. Dilute sodium bicarbonate solution was added and the organic phase was separated, washed with brine and dried over sodium sulfate. Removal of the solvent under reduced pressure yielded 8.0 g. of crude product. This was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product. Recrystallization from methylene chloride/ether yielded 4.2 g. (44%) of **24**, m.p. = 104-106°; ir (chloroform): 2360, 1675 cm^{-1}; nmr (deuteriochloroform): δ 7.9 (m, 1), 7.8 (d, 1, J = 642 Hz), 7.0 (m, 2), 3.7 (m, 2), 3.2 (d, 3, J = 9 Hz), 2.85 (t, 2), 2.0 (m, 2).

Anal. Calcd. for $C_{11}H_{13}N_2O_2P$: C, 55.9; H, 5.6; N, 11.9. Found: C, 56.1; H, 5.5; N, 11.8.

2*H*-Naphth[2,3-*d*][1,3]oxazine-2,4(1*H*)dione (**25**).

A mixture of 30.0 g. of 3-amino-2-naphthoic acid and 135 ml. of ethyl chloroformate was refluxed for 24 hours. The reaction mixture was cooled and the resulting precipitate was filtered and washed with ethanol then ether to yield 19.5 g. (57%) of **25**, m.p. >300°; this material was used without further purification in subsequent reactions.

1-Methyl-2*H*-naphth[2,3-*d*][1,3]oxazine-2,4(1*H*)dione (**26**).

To a suspension of 15.0 g. of **25** in 250 ml. of DMA was added 3.5 g. of sodium hydride (50% in mineral oil, pentane washed) in portions. When the evolution of hydrogen ceased, the mixture was stirred at room temperature for one hour then 12.0 g. of methyl iodide was added and stirring was continued for 18 hours. The reaction mixture was concentrated to one half volume and was poured onto cold water. The resulting precipitate was filtered and recrystallized from methylene chloride/ethyl acetate to yield 6.2 g. (39%) of **26**, m.p. = 230-232°; ir (chloroform): 1785, 1730, 1640 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 8.6 (s, 1), 8.2-7.4 (m, 5), 3.7 (s, 3).

Anal. Calcd. for $C_{13}H_9NO_3$: C, 68.7; H, 4.0; N, 6.2. Found: C, 68.7; H, 4.0; N, 5.8.

N-Methyl-3-methylamino-2-naphthamide (**27**).

Into a suspension of 6.0 g. of **26** in 200 ml. dioxane was bubbled methyl amine for 30 minutes. After the introduction of the amine was stopped, the reaction mixture was stirred at room temperature an additional 30 minutes. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride and dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting solid was recrystallized from ether/pentane to yield 5.2 g. (80%) of **27**, m.p. = 124-126°; ir (chloroform): 3460, 3380, 1660 cm^{-1}; nmr (deuteriochloroform): δ 7.6-6.3 (m, 8), 2.7 (m, 6).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.9; H, 6.6; N, 13.1. Found: C, 72.9; H, 7.0; N, 13.2.

2,3-Dihydro-1,3-dimethylnaphtho[2,3-*d*]-1,3,2-diazaphosphorin-4(1*H*)one 2-Oxide (**28**).

A mixture of 5.2 g. of **27** and 3.5 g. of phosphorus trichloride in 150 ml. of benzene was refluxed for 24 hours. The solvent was removed under reduced pressure, then cold water was added to the residue. The mixture was made basic by the addition of dilute sodium bicarbonate solution and then was extracted into methylene chloride. Removal of the solvent under reduced pressure and recrystallization of the residue from ethyl acetate yielded 4.6 g. (73%) of **28**, m.p. = 187-189°; ir (potassium

bromide) 2380, 1670 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 8.6 (s, 1), 8.0-7.2 (m, 5), 7.7 (d, 1, J = 654 Hz), 3.2 (d, 3, J = 9 Hz), 3.1 (d, 3, J = 8 Hz).

Anal. Calcd. for $C_{13}H_{13}N_2O_2P$: C, 60.0; H, 5.0; N, 10.8. Found: C, 60.0; H, 4.9; N, 10.8.

Acknowledgement.

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