Preparation of *N*, *N*′-Disubstituted Piperazines from Bis(2-anilinoethyl) Phenylphosphonites

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Preceding paper(1) describes that bis(2-anilinoethyl) phenylphosphonite (I) is prepared by the reaction of 2, 3-diphenyl-1, 3, 2-oxazaphospholidine (II, $R=C_6H_5$) with an equimolar amount of 2-anilinoethanol. A small amount of *N*, *N*′-diphenylpiperazine was always formed by the above reaction. The formation of the piperazine suggests that the phosphonite decomposes thermally into the piperazine. In this paper, the formation of *N*, *N*′-disubstituted piperazines by the thermal decomposition of various bis(2-aminoethyl) phenylphosphonites were investigated.

When bis(2-anilinoethyl) phenylphosphonite was

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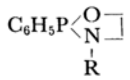
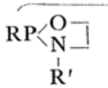
1) O. Mitsunobu, T. Ohashi, M. Kikuchi and T. Mukaiyama, This Bulletin, **39**, 214 (1966).

TABLE 1. PREPARATION OF *N*, *N*′-DISUBSTITUTED PIPERAZINE

	HO-CH$_2$ HN-CH$_2$ R′	Temp.	Time	Product							
						Yield	Mp °C or Bp °C/mmHg		Anal, %		
R	R′	°C	hr	R	R′	%			C	H	N
C_6H_5	C_6H_5	210	3	C_6H_5	C_6H_5	80*	163—165 (THF)	F	80.23	7.82	11.96
								C	80.67	7.57	11.77
p-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	180	2	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	73	186—188 (toluene)	F	81.33	8.30	10.52
								C	81.16	8.29	10.51
p-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	180	1	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	82	242—244 (anisole)	F	72.72	7.66	9.65
								C	72.45	7.43	9.39
p-ClC_6H_4	*p*-ClC_6H_4	180—200	1	*p*-ClC_6H_4	*p*-ClC_6H_4	57	238—240 (toluene)	F	62.69	5.32	9.06
								C	62.55	5.25	9.12
C_6H_5	CH_3	180—190	3	C_6H_5	CH_3	25**	105—107/5	F	74.23	9.08	15.41
								C	74.95	9.15	15.90
C_2H_5	C_2H_5	200	1	C_2H_5	C_2H_5	43	80—83/35—40	F	67.71	13.00	19.75
								C	67.55	12.76	19.70

F=Found, C=Calcd ( ); Solvent of recrystallization. * 36% of phenylphosphinic acid was obtained. ** 31% of diphenylpiperazine was obtained.

TABLE 2. PREPARATION OF 1, 3, 2-OXAZAPHOSPHOLIDINES

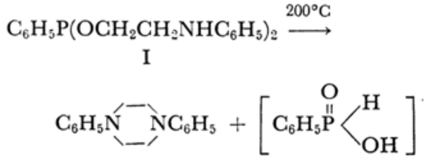
$RP(NEt_2)_2$	$HOCH_2CH_2\overset{H}{N}R'$	Temp.	Time	Product					
						Yield	Bp °C/mmHg (Mp °C)	Anal, N%	
R	R′	°C	hr	R	R′	%		Calcd	Found
C_6H_5	H	150—155	1	C_6H_5	H	61	115—118/4—5	8.38	8.62
C_6H_5	CH_3	127	2.5	C_6H_5	CH_3	25	88— 91/0.02	7.74	7.83
C_6H_5	C_2H_5	150—170	3	C_6H_5	C_2H_5	86	79— 81/1—2	7.18	7.29
C_6H_5	C_6H_5	*	2.5	C_6H_5	C_6H_5	85	130—132/0.03 (75—76)	5.76	5.88
C_6H_5	*p*-$CH_3C_6H_4$	150—170	4	C_6H_5	*p*-$CH_3C_6H_4$	48	163—165/0.1 (62—64)	5.46	5.69
C_6H_5	*p*-$CH_3OC_6H_4$	150—170	4	C_6H_5	*p*-$CH_3OC_6H_4$	91	158—162/0.05 (56—58)	5.13	5.15
C_6H_5	*p*-ClC_6H_4	150—170	3	C_6H_5	*p*-ClC_6H_4	74	154—162/0.08 (53—55)	5.04	5.03
C_2H_5O	C_6H_5	120	3	C_2H_5O	C_6H_5	84	88— 91/0.02	6.64	6.79
***	C_6H_5	**	5	C_2H_5O	C_6H_5	55	91— 92/0.02	6.64	6.70

* The reaction was carried out in refluxing xylene.

** The reaction was carried out in refluxing toluene.

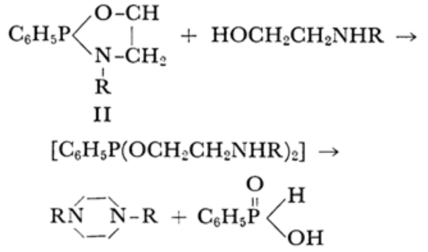
*** Ethyl *N*-phenyliminophosphite ($C_2H_5O\text{-}P{=}NC_6H_5$) was used.

heated at 200°C for 1 hr, *N, N'*-diphenylpiperazine was obtained in a 78% yield.


(1)

As shown in the previous paper,[1] bis(2-anilinoethyl) phenylphosphonite is formed by the reaction of 2, 3-diphenyl-1, 3, 2-oxazaphospholidine with 2-anilinoethanol. Thus the direct method for the preparation of piperazines from 1, 3, 2-oxazaphospholidines and 2-aminoethanols were attempted.

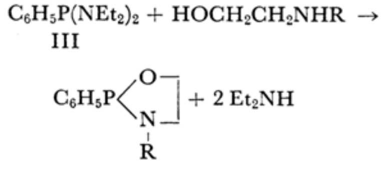
The reaction of equimolar amounts of 2, 3-diphenyl-1, 3, 2-oxazaphospholidine and 2-anilinoethanol at 210°C for 3 hr resulted in the formation of *N, N'*-diphenylpiperazine and phenyl phosphinic acid in 80% and 36% yields respectively (Eq. (2), R=C_6H_5).


(2)

Similarly, various *N, N'*-disubstituted piperazines were prepared and the results are summarized in Table 1.

It must be noted that when 2, 3-diphenyl-1, 3, 2-oxazaphospholidine and 2-methylaminoethanol were heated at 190°C for 3 hr, an unsymmetrical piperazine, *N*-phenyl-*N'*-methylpiperazine was obtained in 25% yield along with *N, N'*-diphenylpiperazine.

The starting materials, 3-substituted 2-phenyl-1, 3, 2-oxazaphospholidines were synthesized by the reaction of bis(diethylamino) phenylphosphine (III) with the corresponding *N*-substituted 2-aminoethanol as shown in the following equation (Eq. (3)). The results are summarized in Table 2.


(3)

Experimental

Preparation of 2-Phenyl-3-*p*-methoxyphenyl-1, 3, 2-oxazaphospholidine. A mixture of bis(diethylamino) phenylphosphine (III, 5.04 g, 0.02 mol) and 2-*p*-anisidinoethanol (3.34 g, 0.02 mol) was heated at 150—170°C for 4 hr. The mixture was distilled to give 2-phenyl-3-*p*-methoxyphenyl-1, 3, 2-oxazaphospholidine (5.00 g, 91.3%, bp 174—178°C/0.1—0.15 mmHg) which was solidified on standing. Recrystallization from ether gave mp 41—44°C.

Found: N, 5.15%. Calcd for $C_{15}H_{16}NO_2P$: N, 5.13%.

Similarly, several 1, 3, 2-oxazaphospholidines were prepared. The results are summarized in Table 2.

Preparation of *N, N'*-Diphenylpiperazine. A mixture of 2, 3-diphenyl-1, 3, 2-oxazaphospholidine (2.43 g, 0.01 mol) and 2-anilinoethanol (1.37 g, 0.01 mol) was heated at 180°C for 3 hr. Benzene (10 m*l*) was added to the mixture and *N, N'*-diphenylpiperazine (1.5 g) was removed by filtration. Aqueous sodium hydroxide (5%) was added to the filtrate and the solution was concentrated to give *N, N'*-diphenylpiperazine (0.41 g). Total yield of *N, N'*-diphenylpiperazine was 80% (1.91 g), mp 160—163°C. To the aqueous layer, concentrated hydrochloric was added and the solution was concentrated to give phenylphosphinic acid (36%). Recrystallization from water gave mp 71—72°C.

Similarly, some *N, N'*-diarylpiperazine were obtained as shown in Table 1.

Preparation of *N, N'*-Diethylpiperazine. A mixture of 2-phenyl-3-ethyl-1, 3, 2-oxazaphospholidine (2.48 g, 0.0127 mol) and 2-ethylaminoethanol (1.14 g, 0.0127 mol) was heated at 200°C for 1 hr. Ether and aqueous sodium hydroxide were added to the mixture. The ether layer was dried and distilled to give *N, N'*-diethylpiperadine (0.78 g, 43%, bp 80—83°C/35—40 mmHg, n_D^{25} 1.4541. Found: C, 67.71; H, 13.00; N, 19.75%).

Preparation of *N*-Phenyl-*N'*-methylpiperazine. A mixture of 2, 3-diphenyl-1, 3, 2-oxazaphospholidine (4.6 g, 0.03 mol) and 2-methylaminoethanol (2.25 g, 0.03 mol) was heated at 180—190°C for 3 hr. Benzene (10 m*l*) was added to the mixture and *N, N'*-diphenylpiperazine (0.07 g, mp 160—163°C) was removed by filtration. Aqueous sodium hydroxide (1.2 g. NaOH in 10 m*l* of H_2O) was added to the filtrate. Benzene layer was dried and distilled to give *N*-phenyl-*N'*-methylpiperazine (1.31 g, 25%, bp 100—110°C/4—6 mmHg. Redistillation gave an analytical sample, bp 105—107°C/5 mmHg. Found: C, 74.23; H, 9.08; N, 15.41%). From the residue of the distillation, *N, N'*-diphenylpiperazine was obtained (0.16 g, mp 160—163°C).

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