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The Reactions of Amido Phosphites. A New Synthesis of Oxazolidine, Imidazolidone and Thiazolidine Derivatives

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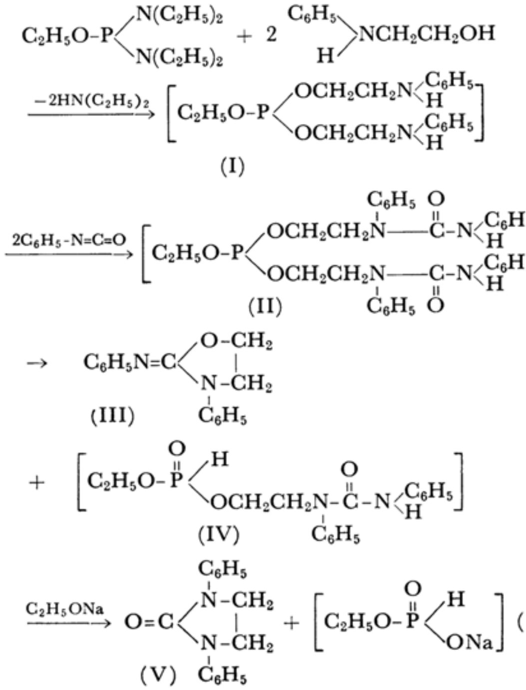
A new method for the preparation of various 2, 3-disubstituted oxazolidine, 2, 3-disubstituted thiazolidine and 1, 3-disubstituted imidazolidone derivatives from β-aminoethyl phosphites and either phenyl isocyanate or phenyl isothiocyanate has been developed. When 1 mol. of ethyl bis(β-anilinoethyl) phosphite, resulting from the reaction of ethyl bis(diethylamido) phosphite with *N*-phenyl ethanolamine, was treated with 2 mol. of phenyl isocyanate, 2-phenylimino-3-phenyl-1,3-oxazolidine was obtained in a 57% yield, along with an oily product. This oily product afforded a 36% yield of *N*, *N'*-diphenyl-2-imidazolidone when it was treated with sodium ethoxide. On the other hand, the pentavalent phosphorus compound, ethyl bis(β-*N*-phenyl-ureidoethyl) phosphate, did not afford an oxazolidine derivative but was converted to imidazolidone in the presence of sodium ethoxide. The reaction of β-anilinoethyl propylene phosphite with an equimolar amount of phenyl isocyanate gave only *N*, *N'*-diphenyl-2-imidazolidone in a 32% yield; 2-phenylimino-3-phenyl-1, 3-oxazolidine could not be obtained. These reactions were then extended to the preparation of exo-imino-thiazolidines. The reactions of β-aminoethyl phosphites with phenyl isothiocyanate resulted in the formation of 2-phenylimino-3-phenyl-1, 3-thiazolidine in fairly good yields.

It has been found in a previous paper[1] that bis(β-anilinoethyl) phenyl phosphonite reacts with phenyl isocyanate to form 2-phenylimino-3-phenyl-1, 3-oxazolidine in a fairly good yield. Exo-imino cyclic compounds, such as ethylene iminocarbonates, 2-iminotetrahydrofuranes and 2-imino-1, 3-oxazolidines, have been known to polymerize in the presence of cationic catalysts, giving polyurethanes, polyamides and polyureas respectively.[2–5]

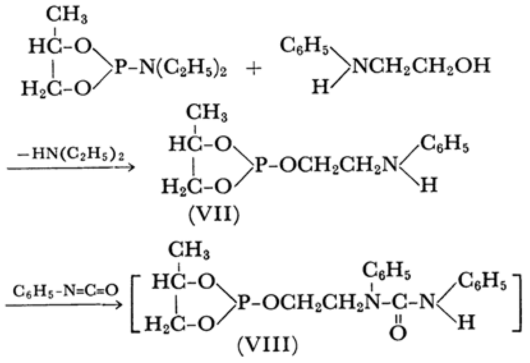
Concerning the preperation of exo-imino oxazolidine and thiazolidine, several methods have been reported.[6–10]

In the present investigation, a new method for the preparation of various exo-imino oxazolidine and thiazolidine derivatives from β-aminoethyl phosphite and either phenyl isocyanate or phenyl isothiocyanate has been studied. When 1 mol. of ethyl bis(β-anilinoethyl) phosphite(I), the result of the reaction of 1 mol. of ethyl bis(diethylamido) phosphite with 2 mol. of *N*-phenyl ethanolamine, was treated with 2 mol. of phenyl isocyanate in benzene at room temperature, a considerable heat liberation was observed. After the reaction mixture had been refluxed for 3 hr., a highly viscous substance (II) was formed. Its infrared spectrum showed an absorption at 1670 cm^{-1} which was due to a carbonyl group of an urea linkage or to an exo-imino group of a five-membered ring, while the absorption peak at 2280 cm^{-1} which was due to an isocyanate group had disappeared. When this substance (II) was left to stand for a few days at room temperature, a crystalline product was obtained; this was identified as 2-phenylimino-3-phenyl-1, 3-oxazolidine (III) by a comparison of its infrared spectrum with that of an authentic sample[5] and by an elemental analysis. A 57% yield of the 2-phenylimino-3-phenyl-1, 3-oxazolidine was obtained by filtration. The infrared absorption spectrum of the filtrate showed characteristic bands attributed to P–H (2350 cm^{-1}) and to P=O (1260—1280 cm^{-1}). When the substance IV was treated with sodium ethoxide in benzene and *N, N'*-diphenyl-2-imidazolidone (V), cyclic urea was obtained in a 36% yield according to the following equation (1):


(1)

Similarly, the other substituted exo-imino oxazolidines and imidazolidones were obtained in fairly good yields (see Tables I and II).

Ethyl bis(β-anilinoethyl) phosphite, which had been obtained from the reaction of 2-ethoxy-3-phenyl-1, 3, 2-oxazaphospholidine (VI) and an equimolar amount of *N*-phenyl ethanolamine, was treated with phenyl isocyanate* to give 52.1% of the oxazolidine and 48.8% of the imidazolidone. On the other hand, the exo-imino compound could not be obtained by the reaction of β-anilinoethyl propylene phosphite (VII) with an equimolar amount of phenyl isocyanate under the same conditions. *N, N'*-Diphenyl-2-imidazolidone (V) resulted in a 40% yield when the above-mentioned reaction mixture VIII was treated with sodium ethoxide (Eq. 2):



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

2) T. Mukaiyama, T. Fujisawa, H. Nohira and T. Hyugaji, *J. Org. Chem.*, **27**, 3337 (1962).

3) T. Mukaiyama and K. Sato, This Bulletin, **36**, 99 (1963).

4) T. Fujisawa, Y. Tamura and T. Mukaiyama, ibid., **37**, 793 (1964).

5) H. Nohira, Y. Nishikawa and T. Mukaiyama, ibid., **37**, 797 (1964).

6) F. B. Dains, R. Q. Brewster, J. S. Blair and W. C. Thompson, *J. Am. Chem. Soc.*, **44**, 2637 (1922).

7) F. B. Dains, R. Q. Brewster, I. L. Malm, A. W. Miller, R. V. Maneval and J. A. Sultzaberger, *J. Am. Chem. Soc.*, **47**, 1981 (1925).

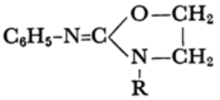
8) B. Adcock, A. Lawson and D. H. Miles, *J. Chem. Soc.*, **1961** 5120.

9) R. W. Luckenbaugh, U. S. Pat. 2902356 (1959).

10) J. T. Thurston, U. S. Pat. 2479525 (1949).

* It has been proved that the isomerization reaction of 2-phenylimino-3-phenyl-1, 3-oxazolidine to *N, N'*-diphenyl-2-imidazolidone does not occur when the oxazolidine is treated with sodium ethoxide in refluxing ethanol for 1 hr. Eighty per cent of the oxazolidine is recovered.

TABLE I. THE SYNTHESIS OF 2-PHENYLIMINO-3-ARYL-1,3-OXAZOLIDINE



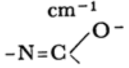
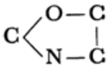
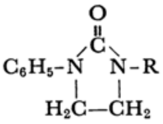
R	Yield %	M. p. °C		Analysis, % C	H	N	IR absorption cm⁻¹	
								
C_6H_5	57.0	115—116	Found	75.65	5.96	11.74	1670	1410
			Calcd.	75.63	5.88	11.76		
p-CH_3-C_6H_4	69.5	142—144	Found	76.12	6.15	11.39	1673	1410
			Calcd.	76.16	6.39	11.10		
p-CH_3O-C_6H_4	57.4	108—109	Found	71.65	6.19	11.04	1670	1415
			Calcd.	71.62	6.01	10.44		
p-Cl-C_6H_4	46.3	136—138	Found	65.95	4.77	10.00	1675	1407
			Calcd.	66.00	4.77	10.02		

TABLE II. THE SYNTHESIS OF 1-PHENYL-3-ARYL-IMIDAZOLIDONE-2



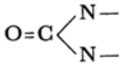
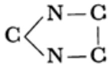
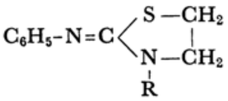
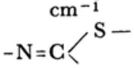
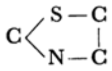
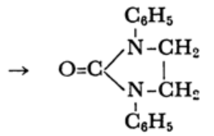
R	Yield %	M. p. °C		Analysis, % C	H	N	IR absorption cm⁻¹	
								
C_6H_5-	35.9	216—218	Found	76.06	5.97	11.86	1690	1420
			Calcd.	75.63	5.88	11.76		
p-CH_3-C_6H_4-	50.8	191—193	Found	75.86	6.58	11.15	1692	1430
			Calcd.	76.16	6.39	11.10		
p-CH_3O-C_6H_4-	69.7	212—213	Found	71.77	6.23	10.57	1690	1420
			Calcd.	71.62	6.01	10.44		1436
p-Cl-C_6H_4-	11.2	200—202	Found	65.81	4.72	10.27	1688	1427
			Calcd.	66.00	4.77	10.02		

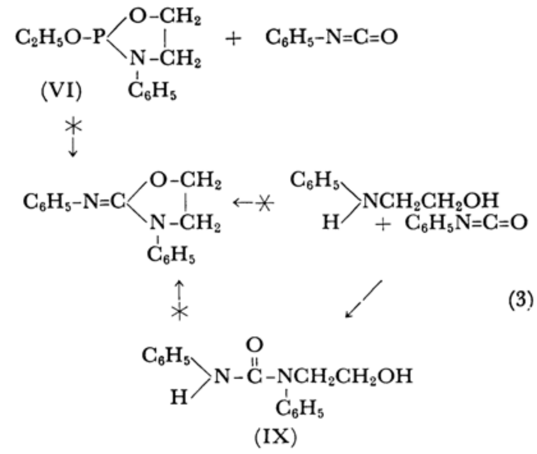
TABLE III. THE SYNTHESIS OF 2-PHENYLIMINO-3-ARYL-1,3-THIAZOLIDINE



R	Yield %	M. p. °C		Analysis, % C	H	N	IR absorption cm⁻¹	
								
C_6H_5-	70.7	134—135	Found	70.96	5.71	11.28	1617	1374
			Calcd.	70.87	5.51	11.02		
p-CH_3-C_6H_4-	81.2	122—123	Found	71.89	6.15	10.72	1630	1378
			Calcd.	71.70	5.96	10.46		
p-CH_3O-C_6H_4-	97.7	117—118	Found	67.44	5.53	10.07	1615	1388
			Calcd.	67.60	5.63	9.85		
p-Cl-C_6H_4-	56.0	105—106	Found	62.08	4.66	9.87	1615	1385
			Calcd.	62.30	4.50	9.69		


(2)

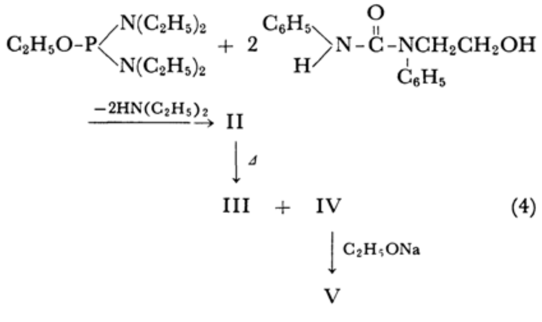
Also, it was found that 2-phenylimino-3-phenyl-1, 3-oxazolidine (III) could not be obtained by the treatment of either 2-ethoxy-3-phenyl-1,3,2-oxazaphospholidine or *N*-phenyl ethanolamine with phenyl isocyanate (Eq. 3):


(VI)

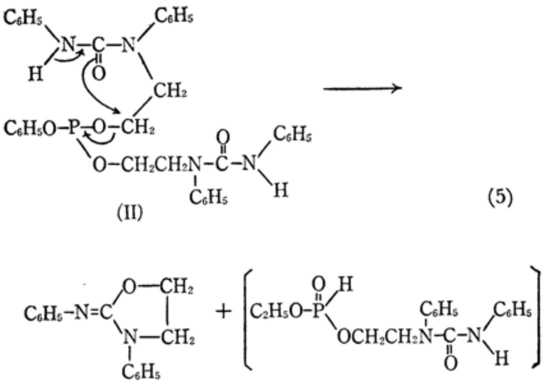
(IX)

(3)

These results suggest that ethyl bis(β-*N*-phenylureidoethyl) phosphite (II) may be a necessary intermediate for the formation of oxazolidine. The proposed intermediate (II) may be expected to be analogously formed by the reaction of *N*-(β-hydroxyethyl)-*N*, *N'*-diphenyl urea (IX) with amido phosphite. Indeed, when the urea alcohol was treated with ethyl bis(diethylamido) phosphite, nearly quantitative yields of 2-phenylimino-3-phenyl-1, 3-oxazolidine and an oily product were formed. The oily product gave a 26.9% yield of *N*, *N'*-diphenyl-2-imidazolidone upon treatment with sodium ethoxide (Eq. 4):

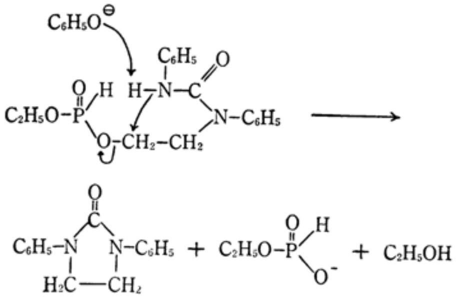

(4)

On the basis of these results, it can be considered that the reaction proceeds through a key intermediate II, which, on heating, is decomposed into IV and oxazolidine by an internal nucleophilic displacement of carbonyl oxygen to α-carbon (as is shown in Eq. 5):

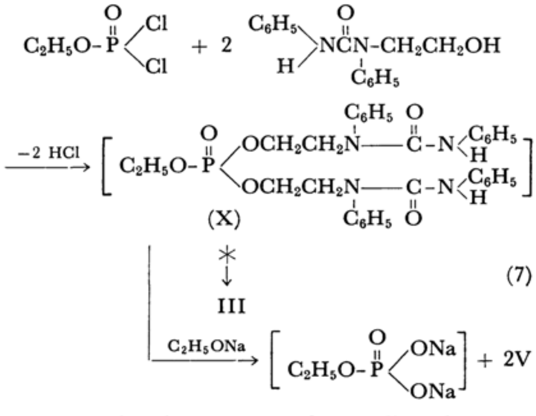

(II)

(5)

On the other hand, imidazolidone was formed by an internal nucleophilic attack of nitrogen on α-carbon when IV or VIII was treated with sodium ethoxide, as is shown in the following equation (Eq. 6):


(6)

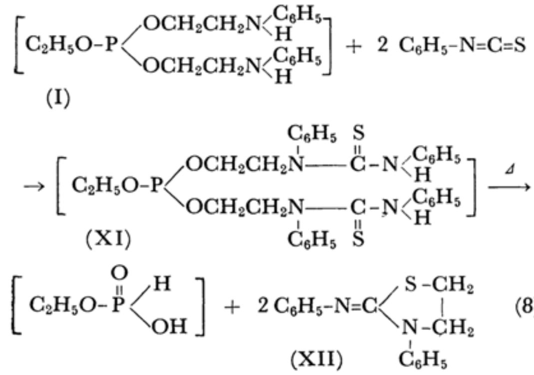
It must be noted that when ethyl bis(β-*N*-phenylureidoethyl) phosphate (X) was used in place of the trivalent phosphorus compound, exo-imino oxazolidine could not be obtained, but a 85.7% yield of imidazolidone was obtained by treatment with sodium ethoxide (Eq. 7):


(X)

(7)

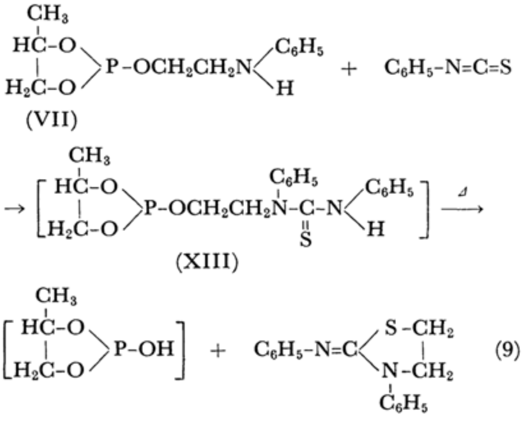
Further, for the purpose of extending the reaction to the preparation of exo-imino thiazolidine derivatives, 3.48 g. of ethyl bis(β-anilinoethyl) phosphite (I) was treated with 2.70 g. of phenyl isothiocyanate; 3.59 g. of 2-phenylimino-3-phenyl-1, 3-thiazolidine (**XII**) was thus obtained. Similarly, the other exo-imino thiazolidine derivatives were obtained in good yields by the treatment of *N*-substituted ethanolamines with amido phosphite and phenyl isothiocyanate (see Table III).

Contrary to the case of ethyl bis(β-*N*-phenylureidoethyl) phosphite (II), this result shows that the decomposition of 1 mol. of ethyl bis(β-*N*-phenylthioureidoethyl) phosphite (XI) affords 2 mol. of thiazolidine (Eq. 8):



(I) (XI) (XII) (8)

In this connection, it is interesting to note that the reaction of β-anilinoethyl propylene phosphite (VII) with an equimolar amount of phenyl isothiocyanate resulted in the formation of exo-imino thiazolidine (XII) in a fairly good yield (Eq. 9):



(VII) (XIII) (9)

The predominant formation of thiazolidine from mono or bis(β-*N*-phenylthioureidoethyl) phosphite (XIII or XI) may be attributed to the high nucleophilicity of the sulfur.

Experimental

Materials. — Commercially - available *N* - phenyl ethanolamine, phenyl isocyanate and phenyl isothiocyanate were purified by distillation. *p*-Tolyl ethanolamine, *p*-anisyl ethanolamine and *p*-chlorophenyl ethanolamine were prepared from the corresponding aromatic amines, ethylenechlorohydrine and triethylamine. Ethyl bis(diethylamido) phosphite (b. p. 81—83°C/9 mmHg) was prepared in a manner analogous to that reported by Burgada.[11] *N*-(β-Hydroxyethyl)-*N, N'*-diphenyl urea[12] and ethyl phosphorodichloridate[13] were prepared according to literature procedures. Bis(β-anilinoethyl) phenyl phosphonite, ethyl bis(β-anilinoethyl) phosphite and β-anilinoethyl propylene phosphite were prepared as has been previously described.[1] The purification of ethyl bis(β-anilinoethyl) phosphite was difficult since it decomposes into *N, N'*-diphenyl piperazine during distillation. Therefore, the reaction mixture resulting from the reaction of 1 mol. of ethyl bis(diethylamido) phosphite with 2 mol. of *N*-phenyl ethanolamine was used as the starting material, ethyl bis(β-anilinoethyl) phosphite, in the following experiments.

The Reaction of Ethyl Bis(β-anilinoethyl) Phosphite with Phenyl Isocyanate.—A solution of phenyl isocyanate (2.38 g.; 0.02 mol.) in 10 ml. of dry toluene was added, drop by drop, into a solution of ethyl bis(β-anilinoethyl) phosphite, which had resulted from the reaction of 2.20 g. (0.01 mol.) of ethyl bis(diethylamido) phosphite with 2.74 g. (0.02 mol.) of *N*-phenyl ethanolamine, in 20 ml. of dry toluene at room temperature. After an exothermic reaction had ceased, the reaction mixture was refluxed for 3 hr. The solvent was then removed under reduced pressure, and a viscous oily substance was obtained. When the substance had been left standing for several days at room temperature, a small amount of a colorless crystalline compound appeared. After 5 ml. of 99.5% ethanol had been added to the mixture, a colorless crystalline compound, 1.35 g. (57%), m. p. 111-116°C, was obtained by filtration. After recrystallization from ethanol, the melting point rose to 115—116°C.

The infrared spectrum of the product was identical with that of authentic 2-phenylimino-3-phenyl-1, 3-oxazolidine.[5] (Found: C, 75.65; H, 5.96; N, 11.74%).

The filtrate was then concentrated to give an oily substance. A slurry of sodium ethoxide (from 0.23 g. of sodium) in 10 ml. of dry benzene was added to the oily substance, and the mixture was stirred at room temperature until it became homogeneous. After it had stood for a few days, a crystalline compound, *N, N'*-diphenyl-2-imidazolidone, was precipitated. This precipitate was filtered and washed well with benzene, 0.86 g. (35.9%); m. p. 208—211°C. After it had been recrystallized from ethyl acetate, the melting point rose to 216—218°C. The infrared absorption bands are at 1690 (s), 1420(s), 1230(s), 1100(m) and 893(m) cm^{-1}.

Found: C, 76.07; H, 5.97; N, 11.86. Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.76%.

By an analogous procedure, the other oxazolidines and the corresponding imidazolidones were obtained. Their yields, melting points, analyses and infrared absorptions are summarized in Tables I and II.

The Reaction of 2-Ethoxy - 3 - Phenyl-1, 3, 2-Oxazaphospholidine with *N*-Phenyl Ethanolamine and Phenyl Isocyanate.—A mixture of 2-ethoxy-3-phenyl-1, 3, 2-oxazaphospholidine (2.11 g., 0.01 mol.) and *N*-phenyl ethanolamine (1.37 g., 0.01 mol.) in 5 ml. of dry toluene was refluxed for 3 hr. Then a solution of phenyl isocyanate (2.38 g., 0.02 mol.) in 15 ml. of dry toluene was added, drop by drop, into

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[11] R. Burgada, *Ann. Chim.*, 347 (1963).

[12] H. C. Beachell and C. P. Ngoc Son, *J. Polymer Sci.*, Part A, **2**, 4773 (1964).

[13] B. C. Saunders, G. J. Stacey, F. Wild and I. G. E. Wilding, *J. Chem. Soc.*, **1948**, 699.

the reaction mixture at room temperature. When the reaction mixture was treated as in the above experiments, 2-phenylimino-3-phenyl-1, 3-oxazolidine 1.24 g. (52.1%); m. p. 111—114°C (after recrystallization from ethanol, the melting point rose to 116—118°C) and *N, N'*-diphenyl-2-imidazolidone 1.16 g. (48.8%); m. p. 208—210°C (after recrystallization from ethyl acetate, the melting point rose to 215—217°C) were obtained.

The Reaction of *N*-Phenyl Ethanolamine with Phenyl Isocyanate.—A solution of phenyl isocyanate (1.19 g.; 0.01 mol.) in 10 ml. of dry toluene was added, drop by drop, into a solution of *N*-phenyl ethanolamine (1.37 g., 0.01 mol.) in 10 ml. of dry toluene at room temperature. A slight heat liberation was observed. The reaction mixture was then refluxed for 3 hr. After the solvent had been completely removed under reduced pressure, the residue was solidified, 2.76 g.; m. p. 80—83°C. The infrared spectrum of this solid was identical with that of an authentic *N*-(β-hydroxyethyl)-*N, N'*-diphenyl urea.[12] Recrystallization from ethyl actate gave 1.50 g. (58.7%); m. p. 88—89°C. (Found: C, 69.92; H, 6.42; N, 11.23%).

The Reaction of Ethyl Bis(diethylamido) Phosphite with *N*-(β-Hydroxyethyl)-*N, N'*-diphenyl Urea.—A of ethyl bis(diethylamido) phosphite mixture (2.20 g.; 0.01 mol.) and *N*-(β-hydroxyethyl)-*N, N'*-diphenyl urea (5.12 g., 0.02 mol.) in 20 ml. of dry toluene was refluxed for 3 hr., by which time the theoretical amount of diethylamine had been distilled off. Then the reaction mixture was refluxed for an additional 7 hr. After the solvent had been completely removed, the residue was almost solidified. When 5 ml. of 99.5% ethanol was added to the mixture, a white crystalline compound was precipitated 2.31 g. (97%); m. p. 111—114°C. Recrystallization from ethanol gave 2-phenylimino-3-phenyl-1, 3-oxazolidine, m. p. 115—116°C. *N, N'*-Diphenyl-2-imidazolidone was obtained from the oily residue by treating it with sodium ethoxide as in the foregoing experiment, 0.56 g. (23.4%); m. p. 202—206°C. After recrystallization from ethyl acetate, the melting point rose to 217—218°C.

The Reaction of β-Anilinoethyl Propylene Phosphite with Phenyl Isocyanate.—A solution of phenyl isocyanate (1.19 g.; 0.01 mol.) in 10 ml of dry toluene was added drop by drop to a solution of β-anilinoethyl propylene phosphite (2.41 g.; 0.01 mol.) in 10 ml. of dry toluene at room temperature. After an initial slight exothermic reaction had ceased, the reaction mixture was refluxed for 3 hr. When the solvent was then removed under reduced pressure, an oily substance was obtained. The infrared absorption bands of the substance are at 3420(w), 1655(s), 1070(m) and 990(m) cm^{-1}. Although this oily substance was kept standing in a refrigerator for a few days, 2-phenylimino-3-phenyl-1, 3-oxazolidine could not be obtained. Then a solution of sodium ethoxide (from 0.23 g. of sodium) in 10 ml. of ethanol was added to the oily subtance and the mixture was refluxed for one hour. After the reaction mixture had cooled, a crystalline compound was precipitated, 0.77 g. (32.2%), m. p. 185—190°C. The crystalline compound was recrystallized from ethyl acetate, m. p. 218—219°C. The infrared spectrum and elemental analysis of this crystalline compound were identical with those of *N, N'*-diphenyl-2-imidazolidone.

Found: C, 75.76; H, 6.10; N, 11.76%.

The Reaction of Ethyl Phosphorodichloridate with *N*-(β-Hydroxyethyl)-*N, N'*-diphenyl Urea.—A solution of ethyl phosphorodichloridate with (1.63 g., 0.01 mol.) in 20 ml. of dry benzene was vigorously added, drop by drop, into a solution of *N*-(β-hydroxyethyl)-*N, N'*-diphenyl urea (5.12 g., 0.02 mol.) in 30 ml. of dry benzene at room temperature. After the addition had been completed, the mixture was refluxed for 7 hr. Hydrogen chloride was evolved copiously. When the solvent was removed under reduced pressure, an oily residue was obtained. When 99.5% of ethanol was added to the mixture, as has been mentioned in the above experiments, oxazolidine could not be obtained. On the other hand, when sodium ethoxide (0.46 g. of sodium in 15 ml. of ethanol) was added to the mixture, it was solidified with an evolution of heat, 4.66 g., m. p. 208—243°C. This solid was then recrystallized from ethyl acetate, 3.99 g. (84.0%), m. p. 209—210°C. The infrared spectrum of this crystalline compound was identical with that of authentic *N, N'*-diphenyl-2-imidazolidone (see Experimental Section, Part 1).

The Reaction of Ethyl Bis(β-anilinoethyl) Phosphite with Phenyl Isothiocyanate.—A solution of phenyl isothiocyanate (2.70 g.; 0.02 mol.) in 10 ml. of dry toluene was added, drop by drop, into a solution of ethyl bis(β-anilinoethyl) phosphite (3.48 g.; 0.01 mol.) in 10 ml. of dry toluene at room temperature. In this case an exothermic reaction was not observed. When the reaction mixture was refluxed for 3 hr., a red liquid was obtained. After the solvent had been removed, a yellow crystalline compound was precipitated, 3.59 g. (70.7%), m. p. 126—128°C. Recrystallization from ethanol gave white needles, m. p. 134—135°C. Its infrared spectrum shows 1620(s), 1375(m), 1307(s), 1140(m) and 1080(m) cm^{-1}. This crystalline compound was found to be identical with 2-phenylimino-3-phenyl-1, 3-thiazolidine by means of elemental analysis.

Found: C, 70.96; H, 5.71; N, 11.28. Calcd. for $C_{15}H_{14}N_2S$: C, 70.78; H, 7.51; N, 11.02%.

By a similar procedure, the other thiazolidines were obtained. Their yields, melting points, analyses and infrared absorptions are listed in Table III.

The Reaction of β-Anilinoethyl Propylene Phosphite with Phenyl Isothiocyanate.—A solution of phenyl isothiocyanate (1.35 g., 0.01 mol.) in 10 ml. of dry toluene was added drop by drop to a solution of β-anilinoethyl propylene phosphite (2.14 g., 0.01 mol.) in 10 ml. of dry toluene at room temperature. After the reaction mixture had been refluxed for 5 hr., a red color, accompanied by a slight isonitrile smell, appeared. The solvent was removed under reduced pressure, and a crystalline compound was precipitated.

The precipitate was filtered off, giving 1.0 g. (39.4%) m. p. 126—128°C of 2-phenylimino-3-phenyl-1, 3-thiazolidine. After recrystallization from ethanol, the melting point rose to 131—132°C.

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