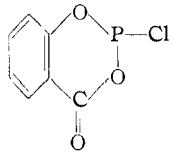
[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

A Re-examination of the Reaction Between Phosphorus Trichloride and Salicylic Acid

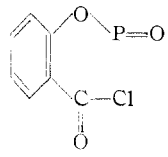
BY RICHARD W. YOUNG

The bicyclic "chlorophosphite" formulation is suggested for the product of the reaction of salicylic acid with phosphorus trichloride. Evidence is presented which suggests that a rearrangement is involved in the conversion of the chlorophosphite to salicylic acid amides.

The product (I) of the reaction between phosphorous trichloride and salicylic acid was originally formulated[1] as either Ia or Ib but later evidence was presented[2] which indicated that Ib was

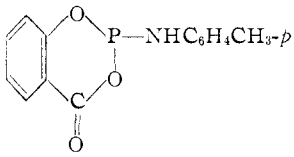


Ia

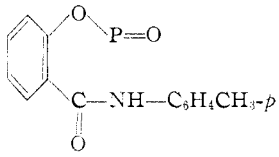


Ib

the correct formulation. This structural assignment was based on the observation that the reaction of I with *p*-toluidine produced II which afforded salicyl-*p*-toluide (III) on subsequent hydrolysis. This compound was formulated as IIb, but the present work indicates that IIa is more consistent with the properties of the compound.



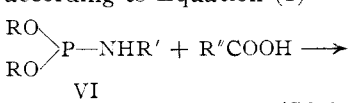
IIa



IIb

When II was treated with aniline and then hydrolyzed, only salicylanilide was obtained. When I was treated with 2 equivalents of diethylamine presumably to give IV, the N-diethyl analog of II, and the latter compound treated with *p*-toluidine, salicyl-*p*-toluide was isolated after hydrolysis; no salicyldiethylamide was detected. When I was treated with an equivalent of ethanol in the presence of triethylamine and the product (V) hydrolyzed, salicylic acid was recovered and no ethyl salicylate could be detected. These results are in accord with the hypothesis that II contains an anhydride function and no carbon–nitrogen bond.

Anderson, Welcher and Young[3] have reported the unusual reactivity of diester amidophosphites (VI) toward carboxylic acids producing amides according to Equation (1)

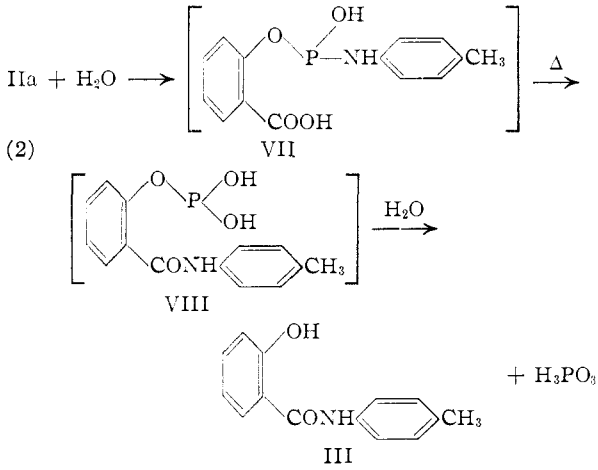


VI

$$R''CONHR' + (RO)_2POH \quad (1)$$

The similarity between VI and IIa is shown by the reaction of II with carbobenzoxyglycine ($C_6H_5CH_2OCONHCH_2COOH$) to give a 67% yield of carbobenzoxyglycine-*p*-toluide and a 2% yield of salicyl-*p*-toluide. This reaction would not be expected for structure IIb, since the reaction of carboxamides and carboxylic acids requires heating in excess of 200° to effect exchange.[4] Salicyl-*p*-toluide, for example, is completely unchanged after heating with carbobenzoxyglycine under conditions in which II reacted easily. In view of this evidence indicating the presence of a phosphorus–nitrogen bond in II, the migration of the amino group to the carbonyl carbon must be explained.

When II was treated with approximately a 20-fold excess of water, only 35–50% of III was produced, but when II was first refluxed with 1 mole of water for a short time and then completely hydrolyzed, a 90% yield of the toluide was isolated. These facts are consistent with the mechanism (Equation 2)



(2)

VII

VIII

III

Hydrolytic cleavage of the very reactive anhydride may give rise to VII which can rearrange intramolecularly to VIII by the reaction of the amidophosphite with the carboxylic acid.[5] Subsequent treatment with water may decompose the monophenylphosphorous acid (VIII), thereby forming III and probably phosphorous acid, but the presence of this acid in the reaction mixture was not demonstrated Support for the mechanistic hypothesis is given by the fact that VII reacted with carbobenzoxyglycine to give a 24% yield of carbobenzoxyglycine-*p*-toluide and a 52% yield of III; in this case, an intermolecular reaction may compete with the intramolecular migration.

Although these reactions suggest that II is a bicyclic amidophosphite, they do not offer any direct evidence concerning the structure of I. In view of the possible rearrangement of IIa to III, the structure Ia must be reconsidered. Its low boiling point and the failure of *m*- and *p*-hydroxyben-

(1) R. Anschütz and W. O. Emery, *Ann.*, **239**, 301 (1887).

(2) L. Anschütz, *ibid.*, **439**, 265 (1924).

(3) G. W. Anderson, A. D. Welcher and R. W. Young, THIS JOURNAL, **73**, 501 (1951), and unpublished data.

(4) J. Biehringer and W. Borsunn, *Ber.*, **39**, 3348 (1906).

(5) The intimate mechanism of this migration is not known. The mechanism of the general reaction of phosphite amides with carboxylic acids is being investigated.

zoic acids to give analogous products[2] favor the cyclic hypothesis.

Experimental[6]

2-Chloro-5,6-benzo-1,3,2-dioxaphosphorin-4-one[7] (**"Salicylchlorophosphite"**) (I).—A solution of 138 g. (1 mole) of salicylic acid, 150 g. of phosphorus trichloride and 150 cc. of toluene was refluxed for 3 hours, after which time the evolution of hydrogen chloride had practically ceased. Excess phosphorus trichloride and solvent were removed under reduced pressure on the steam-bath and the residue distilled. Crystallization of the product in the condenser caused difficulty and two fractions were obtained; 71 g., b.p. 132–133° at 12 mm., and 67 g., b.p. 117–118° at 5 mm. These fractions were combined and redistilled to give 120 g. (60%); b.p. 127–128° at 11 mm.; m.p. 36–37°; reported[1] b.p. 127° at 11 mm., m.p. 36–37°.

Anal. Calcd. for $C_7H_4ClO_3P$: Cl, 17.51. Found: Cl, 17.31, 17.45.

This material reacts vigorously with water to give salicylic acid in 90% yield after recrystallization from water.

2-*p*-Methylanilino-5,6-benzo-1,3,2-dioxaphosphorin-4-one (II). **A. Reaction with Water.**—II was prepared according to the method of Anschütz[2] or by treatment of I in cold benzene with equivalent quantities of *p*-toluidine and triethylamine. Following filtration of triethylamine hydrochloride the compound was employed *in situ*. The compound polymerizes on prolonged heating, presumably to form polyamides. The N-diethyl analog of II decomposed violently on attempted molecular distillation, producing an intractable resin. It is known from related work[3] that phosphite amides react with anhydrides, which may account for the failure to isolate II. When treated with approximately a 20-mole excess of water, salicyl-*p*-toluide was obtained in 35–50% yield; m.p. 155–156°, reported[2] m.p. 155.5–156.5°. When II was refluxed for 1 hour with 1 molar equivalent of water and then treated with excess water, a 90% yield of salicyl-*p*-toluide (III) was obtained; m.p. 153.5–155°, mixed m.p. 153–155°.

B. Reaction with Aniline.—II was prepared from 4.6 g. of I by reaction with triethylamine and *p*-toluidine in 50 cc. of chilled benzene. The solution after filtration of triethylamine hydrochloride was treated with 2.2 g. of aniline and warmed on the steam-bath for 30 minutes. The reaction mixture was washed with 25 cc. of saturated sodium bicarbonate, 10 cc. of water and finally with 20 cc. of 6 *N* hydrochloric acid. After concentration the solid was twice recrystallized from 50% alcohol; yield 2.6 g. (53%); m.p. 133–134°, identified as salicylanilide by mixed m.p. with an authentic sample, m.p. 134–135°, literature m.p. 131–132°.[8]

Neutralization of the hydrochloric acid extract with sodium hydroxide afforded 1.4 g. (66%) of *p*-toluidine; m.p. 44–46°, mixed m.p. 43–45°.

C. Reaction with Carbobenzoxyglycine.—A solution of II in 175 cc. of benzene prepared from 10.1 g. of I was refluxed with 10.45 g. of carbobenzoxyglycine for 30 minutes. Upon cooling, 12 g. of crude carbobenzoxyglycine-*p*-toluide, m.p. 150–165°, crystallized. After the addition of 100 cc. of ether the filtrate was first extracted with saturated sodium bicarbonate, which, upon acidification, gave 7.5 g. of a mixture of salicylic acid and carbobenzoxyglycine; m.p. 120–140°. Extraction of the filtrate with 20 cc. of 4 *N* sodium hydroxide afforded, after acidification, 0.2 g. (2%) of III; m.p. and mixed m.p. 154–156°. Concentration of the organic layer left a small amount of solid which was combined with the crude carbobenzoxyglycine-*p*-toluide obtained above; the combined fractions were recrystallized from alcohol to give 10.3 g. (67%), m.p. 159–161°.

An authentic sample of carbobenzoxyglycine-*p*-toluide was prepared by the reaction of *p*-toluidine with the mixed anhydride of carbobenzoxyglycine and diethyl phosphite[3] and was recrystallized from alcohol; m.p. 160–161°.

Anal.[9] Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.48, 68.62; H, 6.17, 5.82; N, 9.55, 9.66.

When II, prepared from 5.05 g. (0.025 mole) of I in 100 cc. of benzene, was first heated with 0.45 g. (0.025 mole) of water for 15 minutes then refluxed with carbobenzoxyglycine for 30 minutes, III was obtained in 52% yield (3.0 g., m.p. 153–156°), carbobenzoxyglycine-*p*-toluide was obtained in 24% yield (1.8 g., m.p. 158.5–160°), and a mixture (4.7 g., m.p. 100–150°) containing salicylic acid and carbobenzoxyglycine was recovered.

Reaction of 2-Diethylamino-5,6-benzo-1,3,2-dioxaphosphorin-4-one (IV) with *p*-Toluidine.—To a solution of 3.09 g. of I in 50 cc. of benzene was added a solution of 1 equivalent each of diethylamine and triethylamine in benzene. Following filtration of triethylamine hydrochloride, the solution was concentrated and excess *p*-toluidine was added. After warming on the steam-bath for 10 minutes, 50 cc. of ether was added, the solution was extracted successively with water, dilute sodium bicarbonate and concentrated. III was obtained in 74% yield (2.5 g.); m.p. 158–160°, mixed m.p. 158–160°.

Reaction of 2-Ethoxy-5,6-benzo-1,3,2-dioxaphosphorin-4-one (V) with Water.—A solution of 5.05 g. of I in 25 cc. of benzene was chilled during the dropwise addition of 1.05 g. of absolute ethanol and 2.5 g. of triethylamine in 50 cc. of benzene. Following filtration of triethylamine hydrochloride (3.4 g., 100%), the solution was concentrated *in vacuo*, the residue being treated with cold water and extracted with ether. The ether layer was extracted with saturated sodium bicarbonate and acidified to give 2.7 g. (78%) of salicylic acid; m.p. and mixed m.p. 154–156°. No material was found in the organic layer upon concentration.

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(6) All melting points are corrected and were taken on a Fisher–Johns melting point block.

(7) This nomenclature is adopted from that employed by *Chemical Abstracts* for heterocyclic phosphorus compounds. The parent of I and II is 1,3,2-dioxaphosphorinane (*C. A. Decennial Index*, 1937–1946, p. 5463).

(8) C. F. H. Allen and J. Van Allan, *Org. Syntheses*, **26**, 92 (1946).

(9) Analysis performed by the Microanalytical Laboratory under the direction of Dr. J. A. Kuck.