[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL]

THE SYNTHESIS OF DIMETHYLAMINOETHYL ESTERS OF AROMATIC PHOSPHONIC ACIDS[1]

RALPH W. BOST,[2] LOUIS D. QUIN,[3] AND ARTHUR ROE

Received August 7, 1952

The well-known local anesthetic properties and other pharmacological activity of carboxylic acid esters of amino alcohols prompted us to attempt the preparation of some esters of aromatic phosphonic acids and amino alcohols for pharmacological evaluation. Such compounds have not been previously described in the literature. This paper reports the synthesis of the dimethylaminoethyl esters of certain aromatic phosphonic acids.

Some exploratory experiments on the synthesis of this type of ester by reaction of a phosphonyl dichloride with an amino alcohol indicated that this was not a particularly satisfactory method for preparation of these compounds. The ester hydrochlorides obtained from these reactions could not be crystallized and were apparently somewhat unstable. Conversion of these to the free bases gave impure, noncrystallizing, undistillable oils. An alternate method of synthesis of phosphonic acid esters involves reaction of a silver phosphonate with an alkyl halide (1, 2). This method has not been widely used, but it was found to work satisfactorily for the synthesis of bis(dimethylaminoethyl) phosphonates using 2-chloroethyldimethylamine as the halide. The reaction is best conducted in anhydrous ethanol as solvent at 50° for several hours; yields of about 30–40% of pure ester were obtained by this method. Use of a higher reaction temperature is unfavorable as the products so obtained were difficultly purified. The compounds prepared, as well as their properties, are recorded in Table I. In addition, bis(2-dimethylaminoethyl) *p*-nitrobenzenephosphonate was reduced catalytically to give the corresponding ester of phosphanilic acid. The esters were obtained in the crude state as oils which could be crystallized from an anhydrous ethanol-ethyl acetate mixture. These esters are extremely hygroscopic and very soluble in water and alcohols; they are insoluble in nonpolar solvents. After standing several weeks in a desiccator at room temperature, there was evidence of some decomposition in certain cases; the originally white material became slightly tan and a strong amine odor developed.

The recently described (3) reaction of diazonium fluoborates and phosphorus trichloride was used to prepare the unavailable phosphonic acids needed in this research. The acids prepared by this method are recorded in Table II. The procedure as described by Doak and Freedman was used, except that a different method of isolation of the products was employed; it was found to be more

[1] Taken from a portion of the dissertation submitted by Louis D. Quin to the Graduate School of the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree.

[2] Deceased.

[3] Tennessee Eastman Fellow, 1951–1952; present address: Westvaco Chemical Division, South Charleston, West Virginia.

expedient for the purpose of this research to isolate the acids through their *p*-toluidine salts rather than their hemi-sodium or potassium salts. The advantage of the *p*-toluidine salt method was that the free phosphonic acids were not needed here, but solutions of their sodium salts, easily obtained from the *p*-toluidine

TABLE I

BIS(DIMETHYLAMINOETHYL) ESTERS OF AROMATIC PHOSPHONIC ACIDS

SUBSTITUENT IN PHENYL GROUP OF ESTER	YIELD,[a] %	M.P.,[b] °C.	FORMULA	P ANALYSES		N ANALYSES	
				Calc'd	Found	Calc'd	Found
H	38.6	145–147 d.	$C_{14}H_{25}N_2O_3P$	10.31	10.71[c]	9.33	9.19
p-NO_2	41.2	158–159	$C_{14}H_{24}N_3O_5P$	8.97	8.96	12.17	12.01
p-F	31.8	158–160 d.	$C_{14}H_{24}FN_2O_3P$	9.73	10.49[c]	8.80	8.62
p-Cl	40.7	185–186 d.	$C_{14}H_{24}ClN_2O_3P$	9.25	9.92[c]	8.37	8.52
p-CH_3O	38.9	160–162 d.	$C_{15}H_{27}N_2O_4P$	9.38	9.78[c]	8.48	8.35
3,4-CH_2(O—)(O—)	16.3	154–156 d.	$C_{15}H_{25}N_2O_5P$	9.00	9.30	8.14	7.99
p-$C_2H_5SO_2$	29.5	173–175 d.	$C_{16}H_{29}N_2O_5PS$	7.89	7.96	7.14	6.81
p-NH_2	58.4[d]	180–182 d.	$C_{14}H_{26}N_3O_3P$	9.82	9.71	13.33	13.09

[a] From silver phosphonate. [b] Corrected. [c] Analysis was run after compound was a few weeks old and slight decomposition had occurred. [d] Prepared by reduction of corresponding nitro compound.

TABLE II

ARYL PHOSPHONIC ACIDS FROM DIAZONIUM FLUOBORATES AND PCl_3

-BENZENEPHOSPHONIC ACID	YIELD OF *p*-TOLUIDINE, SALT %[a]	M.P.[b] OF ACID, °C.	FORMULA	P ANALYSES, %		NEUTRAL EQUIVALENT[c]	
				Calc'd	Found	Calc'd	Found
p-Fluoro-	48.1	125–127	$C_6H_6FO_3P$	17.59	17.53	88.1	88.3
3,4-Methylenedioxy-	36.8	160–161	$C_7H_7O_5P$	15.33	15.48	101.1	101.8
p-Ethylmercapto-	—[d]	159–160	$C_8H_{11}O_3PS$	13.87	14.08	109.1	108.7
p-Nitro-	46.1[e, f]	—[g, h]	—	—	—	—	—
p-Methoxy-	18.0	—[g, i]	—	—	—	—	—
p-Ethoxy-	29.3	—[g, i]	—	—	—	—	—

[a] Based on di-*p*-toluidine salt. [b] Corrected. [c] The indicator used was thymolphthalein. [d] Isolated as free acid; yield 41.2%. [e] Based on a single run where product was recrystallized from water; this solvent gave a poor recovery of product. [f] M.p. 217–218° d. Calc'd for $C_{20}H_{24}N_3O_5P$: N, 10.07. Found: N, 10.27. [g] The *p*-toluidine salt was not converted to the free acid. [h] Previously prepared in reference (3). [i] Previously prepared by Michaelis, *Ann.*, **293**, 193; **294**, 1 (1896).

salts, sufficed for the preparation of the silver salts required in the ester synthesis. The *p*-toluidine salts were insoluble in water and precipitated in a state of good purity. They could be recrystallized from ethanol, but in some cases an analytically pure salt could not be obtained; this was due to the fact that the product was a mixture of the mono- and di-*p*-toluidine salts. The composition of the

product was related to the strength of the particular phosphonic acid. Acids of high ionization constants—those having a *meta*-directing group in the *para* position—gave analytically pure di-*p*-toluidine salts, whereas weaker acids—those having an *ortho-para*-directing group in the *para* position—gave salts of mixed composition; this fact did not affect the usefulness of this method of isolation. Only in cases where the phosphonic acid had not been reported in the literature were the *p*-toluidine salts converted to the free acids. This was accomplished by first forming the di-sodium salts by adding the calculated amount of sodium hydroxide, removing the liberated *p*-toluidine by steam-distillation or by extraction with ether, and passing the solution through a column of a cation exchange resin. The resulting solution of the free acid was then evaporated to crystallization. The reason for adopting this cation exchange technique was that it was found to be very difficult to remove sodium completely from the products obtained by mere acidification of the sodium salt solutions; this was due to the fact that the rather insoluble hemi-sodium salts sometimes precipi-

TABLE III

DIARYL PHOSPHINIC ACIDS

-PHOSPHINIC ACID	YIELD, %	M.P., °C.	FORMULA	P ANALYSES, %		NEUTRAL EQUIVALENT[a]	
				Calc'd	Found	Calc'd	Found
Bis(*p*-ethoxyphenyl)-	6.1	158–159	$C_{16}H_{19}O_4P$	10.11	10.30	306.3	306.7
Bis(*p*-fluorophenyl)-	7.2	116–118	$C_{12}H_9F_2O_2P$	12.19	12.57	254.2	252.5
Bis(3,4-methylenedioxyphenyl)-	2.9	234–235 dec.	$C_{14}H_{11}O_6P$	10.12	10.13	306.2	305.0

[a] The indicator used was phenolphthalein.

tated in preference to the highly soluble free acids, even in solutions of high acidity.

Three new diaryl phosphinic acids were obtained as byproducts from the reaction of diazonium fluoborates with phosphorus trichloride. These were isolated and purified as described in the procedure of Doak and Freedman (3). They are listed in Table III.

Since completion of this paper, an article describing some closely related compounds has appeared (3A).

EXPERIMENTAL[4]

2-Chloroethyldimethylamine. This compound was prepared by the procedure of Bost and Shealy (4) by reaction of 2-dimethylaminoethanol with thionyl chloride. It was stored in the refrigerator and freshly distilled before use.

Diazonium fluoborates. General procedure IIA described by Roe (5) was used for the preparation of all diazonium fluoborates required in the synthesis of the phosphonic acids.

Phosphonic acids. p-Chlorobenzenephosphonic acid was prepared by acid hydrolysis of diethyl *p*-chlorobenzenephosphonate, obtained from the Monsanto Chemical Company.

[4] All melting points are corrected.

Benzenephosphonic acid was prepared by hydrolysis of benzenephosphonyl dichloride obtained from the Victor Chemical Works.

p-Ethylsulfonylbenzenephosphonic acid was prepared as follows: a solution of 7.0 g. (0.0321 mole) of *p*-ethylmercaptobenzenephosphonic acid in 40 ml. of glacial acetic acid was treated with 12.9 ml. of 30% hydrogen peroxide (4.36 g., 0.128 mole) and heated on the steam-bath for four hours. The solution was slowly evaporated to dryness, giving 8.0 g. (99.6%) white powder. This crude product was recrystallized from ethanol-benzene to give white needles, m.p. 177–178°.

Anal. Calc'd for $C_8H_{11}O_5PS$: P, 12.38; Neut. eq., 125.1.
Found: P, 12.68; Neut. eq., 125.3.

The phosphonic acids listed in Table II were prepared from the corresponding diazonium fluoborates and phosphorus trichloride by the procedure of Doak and Freedman (3) using ethyl acetate as solvent and cuprous chloride as catalyst. The procedure as described was followed through the point where the crude by-product diaryl phosphinic acid separated. The filtrate from this was then treated with 30% sodium hydroxide to *p*H 8.5–9 and filtered to remove the precipitated copper hydroxide. The filtrate was heated to 60–70° and treated with a hot concentrated solution of 2 equivalents (based on diazonium fluoborate) of *p*-toluidine hydrochloride. The slurry was chilled and the precipitated *p*-toluidine salt was filtered off, washed with water, pressed as dry as possible, and washed several times with ether to remove free *p*-toluidine.

The above procedure could not be used to isolate *p*-ethylmercaptobenzenephosphonic acid, as this compound is relatively insoluble in water and precipitated along with the crude bis(*p*-ethylmercaptophenyl)phosphinic acid. To separate these acids, the procedure employed by Doak and Freedman (3) for a similar situation encountered with *p*-chlorobenzenephosphonic acid was used. The mixture of acids was dissolved in 20% sodium hydroxide, treated with Norit, and filtered. The filtrate was acidified to Congo Red, precipitating the phosphinic acid and the hemi-sodium salt of the phosphonic acid. The residue was extracted three times with boiling 6 *N* hydrochloric acid, which dissolved the phosphonic acid and left the phosphinic acid as a black oil from which a pure product could not be obtained. The phosphonic acid crystallized from the hydrochloric acid extracts and was recrystallized from 6 *N* hydrochloric acid.

The *p*-toluidine salts were converted to the di-sodium salts by treating them with a slight excess of dilute sodium hydroxide. The liberated *p*-toluidine was removed either by steam-distillation or by extraction with ether. The solution was then warmed with Norit and filtered.

When it was desired to isolate the free phosphonic acids from these solutions of their sodium salts, the solution was passed slowly through a 12″ by 1″ column of Dowex 50 (150–300 mesh) cation exchange resin. The column was washed thoroughly and the solution and washings evaporated to crystallization of the free acids.

Silver salts of phosphonic acids. When the free phosphonic acid was to be converted to the silver salt, it was dissolved in water and treated with 2 equivalents of sodium acetate and then with 2 equivalents of silver nitrate. The precipitated salt was filtered, washed with water, and dried at 105° to constant weight. When a solution of a di-sodium salt, prepared as above from the *p*-toluidine salt, was used, the excess sodium hydroxide was first neutralized by adding a few drops of thymolphthalein and then dilute nitric acid until the solution was colorless. If the solution were colored initially, this procedure could not be followed and the end point used was *p*H 9–9.5 as determined with test paper. A slight excess of silver nitrate was then added, and the precipitated salt was washed and dried as above.

Dimethylaminoethyl esters of phosphonic acids. A one-liter 3-necked flask fitted with a Hershberg stirrer, thermometer, and reflux condenser protected with a drying tube, was charged with 0.03 mole of the silver phosphonate, 100 ml. of anhydrous ethanol, and 0.06 mole of freshly distilled 2-chloroethyldimethylamine. The slurry was stirred at 50° for 5–6 hours. The mixture was then filtered through a layer of infusorial earth and the filtrate was stripped of solvent under reduced pressure at room temperature. The residual oil was

dissolved in the minimum amount of hot anhydrous ethanol, treated with hot anhydrous ethyl acetate until the solution could not quite appear turbid, treated with Norit, and filtered. More hot ethyl acetate was then added to a definite turbidity. On standing two to three days in a stoppered flask, the product separated as a crystalline solid. To insure complete separation, the mixture was again treated with ethyl acetate. The product was recrystallized in the same manner, and dried in a vacuum over phosphorus pentoxide at room temperature. Since the esters are extremely hygroscopic, they must be protected from atmospheric moisture during their handling. The esters prepared by this procedure are listed in Table I.

Bis(2-dimethylaminoethyl) *p*-aminobenzenephosphonate was prepared as follows: a solution of 3.0 g. of bis(2-dimethylaminoethyl) *p*-nitrobenzenephosphonate in 50 ml. of anhydrous ethanol was treated with 0.5 g. of 10% palladium on charcoal, and the mixture was hydrogenated at room temperature at 50 p.s.i. for two hours. The catalyst was filtered off and the filtrate stripped of solvent to leave an oil which was crystallized by the procedure outlined above.

Analysis. The analysis for *phosphorus* was carried out by a modified version of the semimicro procedure described by Shriner (6), involving digestion of the sample in a concentrated sulfuric acid-30% hydrogen peroxide mixture. *Nitrogen* analyses were carried out by the micro Dumas method.

CHAPEL HILL, NORTH CAROLINA

REFERENCES

(1) MARIE, *Compt. rend.*, **135**, 1118 (1902).
(2) MICHAELIS, *Ann.*, **181**, 261 (1871).
(3) DOAK AND FREEDMAN, *J. Am. Chem. Soc.*, **73**, 5658 (1951).
(3A) ANDREWS, ATHERTON, BERGEL, AND MORRISON, *J. Chem. Soc.*, 780 (1952).
(4) BOST AND SHEALY, *J. Am. Chem. Soc.*, **73**, 24 (1951).
(5) ROE, in *Org. Reactions*, **5**, 193 (1949).
(6) SHRINER, in *Quantitative Analysis of Organic Compounds*, Ann Arbor, Michigan, Edwards Bros., Inc., 1946, p. 29.