This finding suggests an examination of the differences in s_ρ. Accordingly the relative magnitudes of s_ρ (*i.e.*, s_ρ/ρ) were compared for the *meta* and *para* groups of each series. The number of series for which the relative value of s_ρ/ρ for the *meta* series was appreciably larger, appreciably smaller and approximately equal to the value for the *para* series were counted, and the results of these counts are presented in Table II. It is apparent that there is no significantly better overall precision in either series.

TABLE II

COMPARISON OF THE PRECISION OF THE HAMMETT EQUATION APPLIED SEPARATELY TO *m*- AND *p*-SUBSTITUTED COMPOUNDS (ENTRIES ARE NUMBERS OF SERIES)

	$s_\rho/\rho(meta)$ / $s_\rho/\rho(para)$			$r_{meta} - r_{para}$				
Applicable σ	>1	~1	<1	>0.15	~0.1[a]	~0	~−0.1	<−0.15
Normal								
σ	93	9	118	68	31	32	28	61
σ^-	31	3	30	18	10	13	12	11
σ^+	21	1	30	22	4	9	6	11
Total	145	13	178	108	45	54	46	83

It was further tested whether, in the series showing significant differences by the *t*-test, a systematic difference between the two types of series could be shown. Similar counts were made for the series with significant *t*-tests, and those with significant *t*- but non-significant *F*-tests. Whereas it appears that the number of series for which s_ρ/ρ (*meta*) is larger than s_ρ/ρ (*para*) is slightly larger than the number of series for which this relation is the reverse, there is no drastic difference in these numbers.

A further test of the comparative precision of the two types of series is provided by a comparison of the two types of series is provided by a comparison of the correlation coefficients. Again counts for different ranges of $r_{meta} - r_{para}$ are shown in Table II, and indicate no systematic differences in the precision attainable with *meta* or *para* compounds.

Thus it is evident that Hine's conclusion that ρ_p and ρ_m need not be measures of the same quantity is borne out statistically. This conclusion does not, however, detract greatly from the usefulness of the Hammett equation. Table I shows that, in the majority of the cases (75 to 85%, depending on the criterion chosen), *no* significant difference exists between ρ_p and ρ_m and between the intercepts. The differences that are encountered are generally quite small. Considering the approximate and empirical nature of the Hammett equation, this new limitation pointed out by Hine does not appear serious.

Calculations.—The calculations were performed on an IBM 650 MDDPM by a modification of a program now in use in this Laboratory.[5] The changes in the program consisted of successively reading the data, comparing series identification, letting the computer determine whether the substituent was a fused ring system or a heteroatom (identification number between 800 and 999, 3800 and 3999, 6800 and 6999), in which case the piece of data was by-passed, and then whether the identification number was even (*meta*) or odd (*para*). Data (σ and log k), and their squares and cross-products were accumulated separately. Since the identification number for the unsubstituted compounds is 000, they were automatically included in the *meta* series. When all data for one series were read, the computer checked whether $n \geq 3$ for both *meta* and *para* series. If either $n < 3$, no further work was done, but the computer proceeded automatically to the next series. If both $n \geq 3$, the standard program calculated the straight lines for both the *meta* and *para* series, and punched identification, ρ, s_ρ, r, S, Sy^2 and n. Then the sums, and sums of squares and cross-products for the two partial series were added together, and the total regression was performed.

The *t*- and *F*-tests were also made by the computer, using a small separate program. This program reads 3 cards (the output from the previous program for the *meta*, *para* and total series), compares identifications to ensure that cards are in order, calculates $\rho_p - \rho_m$, the average of the two s_ρ and makes the *t*-test. It further computes $S(meta)$ and $S(para) - S(\text{total})$, divides by $Sd^2(meta)$ and $Sd^2(para)$, multiples the result by $[n(\text{total})-4]/2$, and makes the *F*-test. The tests are made by comparing the values of t and F so calculated with values stored in a table on the drum of the computer. The results of the tests are punched, with the ρ-difference, the average of s_ρ, and the calculated F on a card carrying the series identification. Beyond these calculations all counts were made by hand.

(5) H. H. Jaffé, Technical Report No. 10 to the Office of Ordnance Research. A limited number of copies of this report are available for distribution by the author.

CINCINNATI, OHIO

[CONTRIBUTION FROM THE VENEREAL DISEASE EXPERIMENTAL LABORATORY, COMMUNICABLE DISEASE CENTER, U. S. PUBLIC HEALTH SERVICE, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF NORTH CAROLINA]

p-Cyanophenylphosphonic Acid and Related Compounds[1]

BY G. O. DOAK AND LEON D. FREEDMAN

RECEIVED DECEMBER 22, 1958

p-Cyanophenylphosphonic acid has been prepared from *p*-cyanobenzenediazonium fluoborate by the diazo reaction and from *p*-aminophenylphosphonic acid by the Sandmeyer reaction. Reduction with lithium aluminum hydride gives *p*-α-aminotolylphosphonic acid, the phosphonic acid analog of Marfanil. *p*-Amidinophenylphosphonic acid was prepared through the imino ethyl ether. Neither the amino nor amidino compounds possessed significant antibacterial activity against three species of microörganisms.

The marked activity of *p*-aminophenylphosphonic (phosphanilic) acid against a number of pathogenic microörganisms *in vitro*[2] has prompted us to undertake the preparation of *p*-α-aminotolylphosphonic acid, the phosphonic acid analog of Marfanil. Marathe, Limaye and Bhide have previously attempted the preparation of this compound.[3] They were unable to prepare the

(1) Presented at the Southeastern Regional Meeting of the American Chemical Society, Durham, N. C., November, 1957.

(2) J. D. Thayer, H. J. Magnuson and M. S. Gravatt, *Antibiotics & Chemotherapy*, **3**, 256 (1953).

(3) K. G. Marathe, N. S. Limaye and B. V. Bhide, *J. Sci. Ind. Research (India)*, **98**, 268 (1950).

desired intermediate, *p*-cyanophenylphosphonic acid, either from *p*-aminophenylphosphonic acid by the Sandmeyer reaction or from *p*-chlorophenylphosphonic acid by reaction with potassium cyanide. However, chlorination of *p*-tolylphosphonic acid gave *p*-α-chlorotolylphosphonic acid, which was then heated with aqueous ammonia. Acidification of the ammoniacal solution gave a product which was formulated as ammonium hydrogen *p*-α-aminotolylphosphonate. Apparently no attempt was made to prepare the free acid, nor are the analytical data on the acid ammonium salt completely unequivocal. Since other amino-substituted phosphonic acids are precipitated as the free acid when their alkaline solutions are acidified to congo red, it was surprising to us that an acid ammonium salt should precipitate under these conditions.

In view of the ease with which aromatic phosphonic acids can be prepared by the diazo reaction,[4] we first attempted the preparation of *p*-cyanophenylphosphonic acid from *p*-cyanobenzenediazonium fluoborate. Although none of the desired compound was isolated, we did obtain a small amount of *p*-carboxyphenylphosphonic acid, presumably formed by hydrolysis of the cyano derivative during the isolation step. Accordingly, conditions were modified to avoid hydrolysis of the cyano group. Steam distillation was omitted and the desired acid isolated through the magnesium salt.

We also investigated the Sandmeyer reaction. Since Kosolapoff has shown that aminophenylphosphonic acids readily undergo this reaction,[5] the failure of Marathe, Limaye and Bhide to obtain *p*-cyanophenylphosphonic acid is somewhat surprising. We have now found that this compound can be prepared from phosphanilic acid in 65% yield by the Sandmeyer reaction. We were unable to reduce the nitrile with hydrogen and Adams platinum catalyst in acetic anhydride at 30 pounds pressure.[6] After shaking for several minutes the platinum separated out in a hard resinous mass on the side of the reduction vessel. Reduction was achieved, although in small yield, with lithium aluminum hydride. *p*-α-Aminotolylphosphonic acid is precipitated from ammoniacal solution by acidification to congo red, contrary to the report of Marathe, Limaye and Bhide.[3] We also prepared *p*-amidinophenylphosphonic acid from the nitrile in the usual manner. Both the amidino- and aminotolylphosphonic acids were tested *in vitro* against *E. coli communior*, *A. aerogenes* and three strains of *M. pyrogenes var. aureus*, which were sulfa and penicillin resistant.[7] Neither phosphorus compound showed activity at a concentration of 10^{-2} molar.

Experimental

p-Cyanophenylphosphonic Acid by the Diazo Reaction.—*p*-Cyanobenzenediazonium fluoborate (32.5 g., 0.15 mole) and 150 ml. of anhydrous ethyl acetate were used. The apparatus and reaction conditions have been described previously.[4] No evolution of nitrogen occurred until the mixture was warmed. After nitrogen evolution had ceased, the reaction mixture was cooled to 5° and 125 ml. of water was added dropwise. The clear solution was now concentrated *in vacuo* to 100 ml. at <40°. The solution was filtered and solid sodium carbonate added to *p*H 6. The precipitate of copper carbonate was removed, the filtrate was made strongly alkaline with aqueous ammonia, and 600 ml. of magnesium mixture was added. After standing overnight the precipitate of magnesium ammonium phosphate was removed, and the filtrate boiled for 10 minutes with stirring. The hot mixture was filtered and the magnesium *p*-cyanophenylphosphonate washed once with 50 ml. of hot water. This salt was then treated with 150 ml. of 5% sodium hydroxide solution, and the resulting magnesium hydroxide was removed by filtration. The solution was then diluted to 500 ml. with water, stirred with 100 g. of Dowex 50, and finally passed through a Dowex 50 column.[8] The resulting solution, approximately 1 liter in volume, was taken to dryness *in vacuo* and the resulting solid dried in a desiccator. It was finally extracted in a Soxhlet with 100 ml. of ether. When the ether was cooled in a deep-freeze, 7.4 g., 27%, of pure *p*-cyanophenylphosphonic acid, m.p. 142–145°, crystallized from solution.

p-Cyanophenylphosphonic Acid by the Sandmeyer Reaction.—Phosphanilic acid (17.3 g., 0.1 mole) was dissolved in 50 ml. of 6 *N* hydrochloric acid and diazotized at 0°. The cold solution was neutralized with solid sodium carbonate and then added dropwise to a cold solution of cuprous cyanide. This latter solution was prepared from 32 g. of cupric sulfate.[9] Nitrogen was evolved from the reaction mixture. It was allowed to stand overnight, then warmed on the steam-bath for 15 minutes. After cooling again to room temperature, the mixture was acidified to congo red with hydrochloric acid and the heavy precipitate which formed was removed by filtration and discarded. The clear filtrate was made alkaline with ammonia, 400 ml. of magnesia mixture was added, and the mixture boiled and stirred for 10 minutes. The subsequent isolation was identical with that described above. The yield was 69%, m.p. 143–144°.

Anal. Calcd. for $C_7H_6NO_3P$: N, 7.65; P, 16.92; neut. equiv., 91.55. Found: N, 7.74; P, 16.82; neut. equiv., 92.4.

p-α-Aminotolylphosphonic Acid.—*p*-Cyanophenylphosphonic acid (5.4 g., 0.03 mole) was dissolved in 700 ml. of ether which had previously been distilled from lithium aluminum hydride. The solution was added dropwise to a solution of 2.4 g. of lithium aluminum hydride in 200 ml. of dry ether. The reaction was conducted in a 3-necked flask equipped with a sealed stirrer, dropping funnel and reflux condenser. A stream of dry nitrogen was passed over the reaction mixture during the addition and all outlets were protected with soda lime tubes. The mixture was refluxed gently during the addition and for 1 hour thereafter; 25 ml. of ethyl acetate was then added followed by 200 ml. of water. The mixture was filtered and the aqueous layer evaporated to 75 ml., and acidified with acetic acid. The desired compound crystallized from solution. It was washed with cold water and dried. The yield was 17%, m.p. >300°.

Anal. Calcd. for $C_7H_{10}NO_3P$: N, 7.49; P, 16.55. Found: N, 7.45; P, 16.06.

The nitrogen analysis of this compound was unchanged within experimental error when it was dissolved in aqueous ammonia and reprecipitated by acidification to congo red.

p-Amidinophenylphosphonic Acid.—A solution of 6.25 g. of *p*-cyanophenylphosphonic acid in 20 ml. of dry ether and 2.5 ml. of absolute alcohol was cooled to 0° and saturated with dry hydrogen chloride. The mixture was allowed to stand for 7 days. The crystalline precipitate of the imino ether hydrochloride was removed by filtration, washed with cold ether and dried. The yield was 84%; the material softened at approximately 220° without melting to a clear liquid.

(4) G. O. Doak and L. D. Freedman, THIS JOURNAL, **73**, 5658 (1951).

(5) G. M. Kosolapoff, *ibid.*, **70**, 3465 (1948).

(6) W. H. Carothers and G. A. Jones, *ibid.*, **47**, 3051 (1925).

(7) We are grateful to Dr. J. D. Thayer of our bacteriology section for testing these compounds.

(8) It is difficult to remove all of the anions from a phosphonic acid salt except at high dilutions because cation exchange resins have only a limited capacity at low *p*H values.

(9) H. T. Clark and R. R. Read, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., (941, p. 514.

Anal. Calcd. for $C_6H_{13}ClNO_4P$: N, 5.27; P, 11.66; neut. equiv., 88.55. Found: N, 5.29; P, 11.48; neut. equiv., 88.9.

Five grams of the above **ethyl *p*-phosphonobenzamidate hydrochloride** was added to 50 ml. of alcoholic ammonia (11.5%) in a pressure bottle. The mixture was heated to 60° for 3 hours and allowed to cool overnight. The crystalline precipitate was removed and recrystallized from hot water. The yield was 81%, m.p. >300°.

Anal. Calcd. for $C_7H_9N_2O_3P$: N, 14.00; P, 15.48. Found: N, 14.05; P, 15.14.

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CHAPEL HILL, N. C.

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES, VICTOR CHEMICAL WORKS]

Conversion of Tertiary Phosphites to Secondary Phosphonates. Diphenyl Phosphonate[1]

BY E. N. WALSH

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A method of preparing diphenyl phosphonate is described in which triphenyl phosphite is caused to react with phosphorous acid at above 60°. Several of the reactions of diphenyl phosphonate are presented including the reactions with chlorine, alcohols, aldehydes or ketones, and the condensation reaction with secondary amines and aldehydes. The conversion of the tertiary esters of phosphorous acid, obtained from the action of phosphorus trichloride on ethylene oxides, to secondary esters, is also described.

The preparation of diphenyl phosphonate was first described by Milobendzki and Szulgin.[2] These authors used a process in which diphenyl propyl phosphite is treated with anhydrous hydrogen chloride to yield propyl chloride and diphenyl phosphonate. The use of diphenyl phosphonate as an intermediate for diphenyl phosphoramidate has been described by Atherton and Todd[3] and, subsequent to this present work, Kabachnik and Polikarper[4] have reported the preparation of diphenyl phosphonate from the hydrolysis of diphenyl phosphorochloridite.

It was found in this Laboratory that when triphenyl phosphite is heated in the presence of an oxy acid, the acidity of the mixture rapidly decreases. This effect is attributable to the phenylation of the acid by the triphenyl phosphite with the simultaneous formation of diphenyl phosphonate in accord with equation 1.

$$(C_6H_5O)_3P + HOX \longrightarrow (C_6H_5O)_2\overset{\overset{O}{\|}}{P}H + C_6H_5OX \quad (1)$$

Since, at this time, our primary interest was in a rather simple preparation of diphenyl phosphonate, a process was devised in which the acidic compound was phosphorous acid, and thus the sole product would be diphenyl phosphonate, as illustrated in equation 2. When this reaction was conducted at temperatures above 60°, good yields of diphenyl phosphonate were obtained.

$$2(C_6H_5O)_3P + H_3PO_3 \longrightarrow 3(C_6H_5O)_2\overset{\overset{O}{\|}}{P}H \quad (2)$$

The reaction of triphenyl phosphite with phosphorous acid was observed to occur in two stages. The first stage entails the reaction of one mole of phosphorous acid with one mole of triphenyl phosphite to form one mole of diphenyl phosphonate and one mole of phenyl phosphonate; equation 3. This stage of the reaction is rapid at 70°,

$$(C_6H_5O)_3P + H_3PO_3 \longrightarrow C_6H_5OPO_2H_2 + (C_6H_5O)_2\overset{\overset{O}{\|}}{P}H \quad (3)$$

and it occurs simultaneously with the disappearance from the reaction mixture of the phosphorous acid phase. The second stage of the reaction consists of the action of a second mole of triphenyl phosphite with phenyl phosphonate to form two moles of diphenyl phosphonate, as shown in equation 4,

$$(C_6H_5O)_3P + C_6H_5OPO_2H_2 \longrightarrow 2(C_6H_5O)_2\overset{\overset{O}{\|}}{P}H \quad (4)$$

This second stage is a much slower reaction, requiring five hours to approach completion at 70°.

A series of diaryl phosphonates was prepared in order to determine the scope of the synthesis.

The action of phosphorus trichloride on three moles of alcohol, in the absence of a basic condensation agent, usually leads to the formation of dialkyl phosphonates and alkyl chloride.[5] However, when the alcohol is substituted with strong electronegative groups, as in the case of the 2-nitro alcohols, α-cyano alcohols,[6] and 2,2,2-trichloroethanol,[7] the tertiary phosphite is usually obtained, and little or no dialkyl phosphonate can be isolated. Similarly, the action of phosphorus trichloride on the ethylene oxides leads directly to the formation of the tris-(2-chloroalkyl) phosphite.[8] In preparations where the tertiary phosphite is obtained more readily than the dialkyl phosphonate, the reaction of the tertiary phosphite with phosphorous acid presents a satisfactory method of preparing the corresponding dialkyl phosphonate,

(1) Presented before the Division of Organic Chemistry, 133rd National A.C.S. Meeting, San Francisco, Calif., April, 1958.

(2) T. Milobendzki and K. Szulgin, *Chem. Polsk.*, **15**, 166 (1917); *C. A.*, **13**, 2867 (1919).

(3) F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 677 (1947).

(4) M. I. Kabachnik and Yu. M. Polikarper, *Doklady Akad. Nauk S.S.S.R.*, **115**, 512 (1957).

(5) A. Sacks and N. Levitsky, *J. Russ. Phys. Chem. Soc.*, **35**, 211 (1903).

(6) A. Chrzaszczewska and W. Sobieranski, *Roczniki Chem.*, **7**, 470 (1927).

(7) M. Delacre, *Bull. soc. chim.*, **48**, 787 (1887).

(8) M. I. Kabachnik and P. A. Rossiiskaya, *Izvestiya Akad. Nauk S.S.S.R.*, 295 (1946).