TABLE I
ANALYTICAL RESULTS FOR HETEROCYCLIC SULFENAMIDES

Compd.[a]	Yield, %	M.p., °C.	Formula	Mol. wt. Calcd.	Mol. wt. Found	Calcd., % C	H	N	S	Found, % C	H	N	S
2-Pyridinesulfenamide	55	79–80	$C_5H_6N_2S$	126	122	47.6	4.8	22.2	25.4	47.7	5.2	22.1	25.3
4-Methyl-2-pyridinesulfenamide	46	79–80	$C_6H_8N_2S$	140	145	51.4	5.7	20.0	22.9	51.2	5.8	20.1	22.7
2-Pyrimidinesulfenamide	40	110–112	$C_4H_5N_3S$	127	133	37.8	3.9	33.1	25.2	37.7	3.8	33.6	25.0
4-Methyl-2-pyrimidinesulfenamide	42	114–116	$C_5H_7N_3S$	141	149	42.6	5.0	29.8	22.7	42.7	5.0	30.2	22.5
Sodium 2-sulfenamido-6-methylpyrimidine-4-olate monohydrate	58	280–285	$C_5H_8N_3NaO_2S$	...	...	30.5	4.0	21.3	16.2	30.4	3.5	20.9	16.5
2-(Pyridyl 1-oxide)sulfenamide	40	146–148	$C_5H_6N_2OS$	142	136	42.3	4.2	19.7	22.5	42.2	4.6	20.0	22.5

[a] All of the compounds were recrystallized from benzene–petroleum ether (b.p. 65–110°) except 2-pyridinesulfenamide (isopropy alcohol–petroleum ether), sodium 2-sulfenamido-6-methylpyrimidin-4-olate monohydrate (water), and 2-(pyridyl 1-oxide)sulfenamide (methanol.)

Potential Inhibitors of Cancerous Growth. V. Substituted Benzylidene Derivatives of D-Ribose as Synthetic Intermediates

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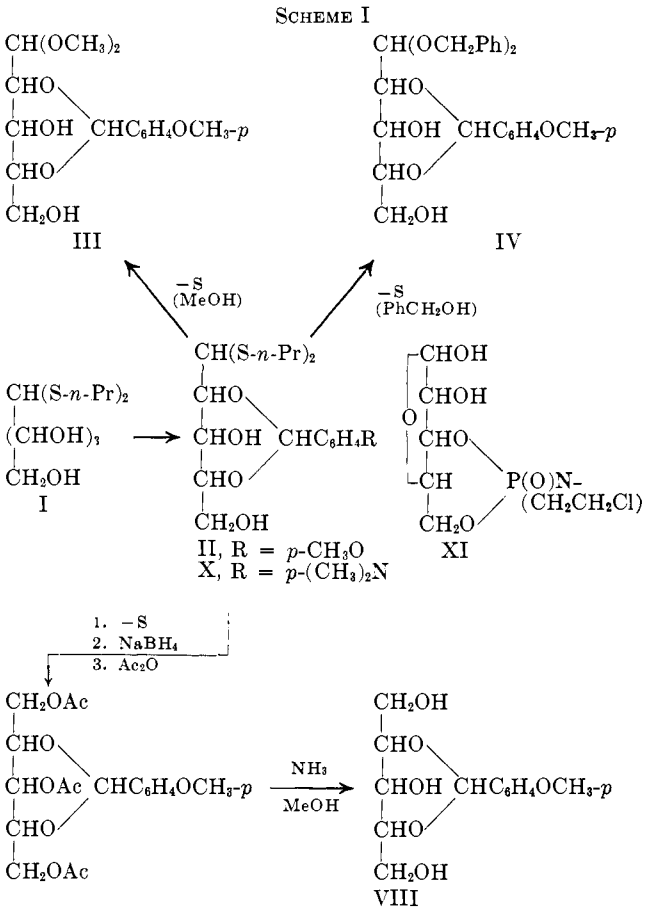
The selection of ribose as a "carrier" molecule in the design[1] of anticancer compounds with enhanced specific action (XI) is suggested by its role in cellular nucleic acid synthesis. Ribose compounds selectively phosphorylated[2] on positions 3 and 5 may be anticipated to be particularly favorable with respect to biological reactivation in actively growing cancer cells. In this respect, the anisylidene group has been found to be suitable for the selective protection of hydroxyls on positions 2 and 4 in the course of these syntheses.

New crystalline anisylidene D-ribose derivatives (II–IV) that may be used in the synthesis of new anticancer compounds have been obtained (see Scheme I).

The structural proof of II was based on evidence obtained by means of acetylation and reduction studies. Demercaptalation of 3,5-di-*O*-acetyl-2,4-*O*-anisylidene-D-ribose di-*n*-propyl dithioacetal (V) in aqueous acetone in the usual manner produced an oil which was reduced with sodium borohydride, and the product then was acetylated to yield an optically inactive crystalline product VII. Upon deacetylation of this product, another optically inactive crystalline product VIII was obtained. These results may be construed as evidence of a symmetrical structure of the molecule.[3] It was therefore inferred that VII was 1,3,5-tri-*O*-acetyl-2,4-*O*-anisylideneribitol, which in turn required VIII to be 2,4-*O*-anisylideneribitol.

SCHEME I



Experimental Section

All reagents and solvents were of ordinary grade quality. When required, solvents were purified and dried according to standard methods.[4] All evaporations, unless when stated otherwise, were conducted in a rotary flash evaporator at water aspirator pressure. Melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra of the compounds prepared were obtained on a Unicam SP. 200 recording spectrophotometer, using a 3% solution in $CHCl_3$ in a 0.1-mm. NaCl cell. Ultraviolet spectra were obtained on a Beckman DK2 recording ultraviolet spectrophotometer. Elementary analyses were done by the Microanalytical Section, National Chemical Research Laboratory, C.S.I.R., Pretoria.

2,4-*O*-Anisylidene-D-ribose Di-*n*-propyl Dithioacetal (II).—Anisaldehyde (4.36 ml., 36 mmoles) was added to a solution of D-ribose di-*n*-propyl dithioacetal (8.53 g., 30 mmoles) in 20 ml. of dioxane and the solution was cooled to 5–10° in an ice bath. To this solution was added a mixture of 29 ml. of concentrated HCl (sp. gr. 1.16) and 16 ml. of water, previously cooled to 5–10°, and the mixture was shaken vigorously with intermittant cooling. Within 1 min. a precipitate formed. After 4 min. ice water (10 ml.) was added and the mixture was shaken for another min. The product was then filtered rapidly and washed with ice water (50 ml.). The precipitate was taken up in 500 ml. of ethyl acetate and successively washed with cold saturated $NaHCO_3$ and water. After drying (Na_2SO_4), the ethyl acetate was evaporated under reduced pressure to yield 11.0 g. of a crystal-

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line product. Recrystallization from 125 ml. of benzene gave 10.5 g. (85%) of pure product with m.p. 135–137°; $\nu_{max}^{CHCl_3}$ 2.74, 2.9 (OH), 3.30 μ (sh, C–H aromatic); λ_{max}^{EtOH} 271 mμ.

Anal. Calcd. for $C_{19}H_{36}O_5S_2$: C, 56.72; H, 7.51. Found: C, 56.65; H, 7.20.

2,4-*O*-Anisylidene-D-ribose Dimethyl Acetal (III).—A three-necked flask was charged with 4.02 g. (10 mmoles) of 2,4-*O*-anisylidene-D-ribose di-*n*-propyl dithioacetal, 8.66 g. (40 mmoles) of yellow mercuric oxide, 8.00 g. of anhydrous $CaSO_4$, and 200 ml. of absolute methanol. The mixture was stirred vigorously with the flask submerged in a water bath maintained at 65°. Mercuric chloride, 4.07 g. (15 mmoles), dissolved in 50 ml. of absolute methanol, was added dropwise over a period of 5 min. Stirring was continued for a further 1.5 hr. The hot reaction mixture was then filtered through a layer of Standard Supercel and the precipitate was washed with three portions of methanol. The combined filtrate and washings were cooled in ice water and an aqueous NH_3 solution was added to pH 7. After 1 hr. in the ice water, the ammonia–mercuric chloride complex was removed by filtration and the filtrate was concentrated at the pump to give an aqueous syrup, which was dissolved in 100 ml. of $CHCl_3$ and washed once with 100 ml. of cold distilled water. After drying (Na_2SO_4), the solution was evaporated to yield 3 g. of a crystalline material. Recrystallization from 15 ml. of ethyl acetate and 40 ml. of petroleum ether (b.p. 60–80°) gave 2.58 g. (82%) of pure product with m.p. 110–111.5°; $\nu_{max}^{CHCl_3}$ 2.81 (OH), 3.20 (C–H aromatic), 9.17 (broad, C–O–C); λ_{max}^{EtOH} 271 mμ.

Anal. Calcd. for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.40; H, 6.95.

2,4-*O*-Anisylidene-D-ribose Dibenzyl Acetal (IV).—A dry three-necked flask was charged with 2.01 g. (5 mmoles) of II, 4.33 g. (20 mmoles) of yellow mercuric oxide, 4 g. of anhydrous $CaSO_4$, and 70 ml. of absolute benzyl alcohol. The mixture was stirred vigorously with the flask submerged in a water bath maintained at 65°. Mercuric chloride, 2.04 g. (7.5 mmoles), dissolved in 50 ml. of absolute benzyl alcohol, was added dropwise over a period of 5 min. Stirring was continued for a further 2 hr. after which time the hot reaction mixture was filtered through Standard Supercel, and the precipitate was washed twice with 50-ml. portions of anhydrous $CHCl_3$. The chloroform was then evaporated from the combined filtrate at the pump. The benzyl alcohol was removed by vacuum distillation on a boiling water bath at 0.5 mm. (It is essential that the ebullition tube should be equipped with a $CaCl_2$ tube in order to prevent moisture from coming into contact with the benzyl alcohol solution.) The solution was washed with cold distilled water until free of I⁻. After drying (Na_2SO_4), the solution was concentrated to yield a yellow oil. Addition of 25 ml. of di-*n*-butyl ether converted the oil into 1.7 g. (73%) of a colorless amorphous solid which could not be crystallized. Trituration with methanol yielded fine crystals which were, however, too soluble in methanol to be recrystallized; $\nu_{max}^{CHCl_3}$ 2.86 (OH), 3.33 μ (C–H aromatic); λ_{max}^{EtOH} 272 mμ.

Anal. Calcd. for $C_{27}H_{36}O_7$: C, 69.52; H, 6.47. Found: C, 68.89; H, 6.47.

3,5-Di-*O*-acetyl-2,4-*O*-anisylidene-D-ribose Di-*n*-propyl Dithioacetal (V).—To a cooled solution of 4.02 g. (10 mmoles) of II in 10 ml. of absolute pyridine, was added 6 ml. (63.5 mmoles) of acetic anhydride. This mixture was left at 0–5° for 10 min. and then at room temperature for 72 hr. It was then poured into crushed ice (200 g.), whereupon the acetate separated as a gummy residue. After decantation of the aqueous layer, this residue was taken up in 200 ml. of $CHCl_3$ and washed successively with cold 50-ml. portions of 1 *N* H_2SO_4, saturated $NaHCO_3$, and water, dried (Na_2SO_4), and evaporated under reduced pressure to give 4.7 g. of a syrup which could not be crystallized. After dissolving in 100 ml. of chloroform and decoloration with charcoal, a colorless syrup, 4.45 g. (91.4%), was obtained; $\nu_{max}^{CHCl_3}$ 5.78 (ester C=O), 8.33 μ (C–O stretching), no OH absorption near 2.9 μ; $\lambda_{max}^{CHCl_3}$ 271.5 mμ.

Anal. Calcd. for $C_{23}H_{34}O_7S_2$: C, 56.78; H, 7.04. Found: C, 56.70; H, 7.18.

2,4-*O*-Anisylidene-3,5-di-*O*-benzoyl-D-ribose Di-*n*-propyl Dithioacetal (VI).—A quantity of 1.61 g. (4 mmoles) of II was dissolved in 6 ml. of absolute pyridine at 0–10° and held in position above a magnetic stirrer. A buret was fitted into one of the sockets of the flask, and the other was equipped with a $CaCl_2$ tube. While stirring, freshly distilled benzoyl chloride (1.85 ml., 16 mmoles) was added from the buret to the mixture at a rate of 0.1 ml./min. Stirring was continued at 0–10° for 5 hr. The purple mixture was then poured into 150 g. of well-stirred crushed ice. The benzoate separated as a gummy precipitate which was removed by decantation of the aqueous layer. The residue was taken up in 100 ml. of chloroform and washed successively with cold 50 ml. portions of 1 *N* H_2SO_4, saturated $NaHCO_3$, and water and evaporated under reduced pressure to yield a yellow syrup. After addition of 15 ml. of methanol, 2.3 g. of a crystalline material was obtained. Recrystallization from 35 ml. of methanol gave 2.2 g. (90%) of pure product with m.p. 89–90°; $\nu_{max}^{CHCl_3}$ 5.81 μ (ester C=O), no OH absorption near 2.9 μ; λ_{max}^{EtOH} 274.5 mμ.

Anal. Calcd. for $C_{33}H_{36}O_7S_2$: C, 64.91; H, 6.26. Found: C, 64.79; H, 6.26.

1,3,5-Tri-*O*-acetyl-2,4-*O*-anisylideneribitol (VII). A.—To a vigorously stirred mixture of acetone (75 ml.), water (10 ml.), yellow mercuric oxide (7.7 g., 36 mmoles), and 4.37 g. (9 mmoles) of II, while being heated on a water bath at 60°, was added 7.33 g. (27 mmoles) of $HgCl_2$ dissolved in 25 ml. of acetone, over a period of 5 min. Stirring was then continued for 1 hr. after which time the solids were removed by filtration through Standard Supercel at the pump and thoroughly washed with acetone. A little yellow mercuric oxide was added to the combined filtrate and washings and the mixture finally was concentrated at 45°. The residue was then extracted with two 50-ml. portions of $CHCl_3$. The $CHCl_3$ solution was washed twice with 50-ml. portions of cold 10% KI and finally three times with 100-ml. portions of cold distilled water (until free of I⁻). After drying (Na_2SO_4) the solution was concentrated to a syrup which weighed 3 g. This corresponds to a yield of 94% of 3,5-di-*O*-acetyl-2,4-*O*-anisylidene-D-ribose. The infrared spectrum of this syrup revealed that some of the acetyl groups had probably been hydrolyzed during the reaction in view of the fact that OH as well as C=O absorption appeared at 2.9 and 5.78 μ, respectively.

B.—The syrup was dissolved in 30 ml. of ethanol and a solution of 0.34 g. (9 mmoles) of $NaBH_4$ in 3 ml. of water was added slowly. The mixture was left at room temperature until the evolution of H_2 had ceased. The solids were then removed by filtration and washed with ethanol, and the combined filtrate and washings were concentrated. The residue was dehydrated by repeated evaporation with anhydrous acetone and finally dried for 5 hr. at room temperature under high vacuum. The residue thus obtained was dissolved in 6 ml. of anhydrous pyridine and was cooled for 10 min. at 0–5°, while adding 5 ml. (52.9 mmoles) of acetic anhydride. The mixture was then left at room temperature for another 72 hr. The acetate, which crystallized as a white solid on pouring this mixture into 150 g. of well-stirred crushed ice, was removed by filtration. This was taken up in 100 ml. of $CHCl_3$ which was washed and worked up as usual. It was evaporated to a syrup which crystallized. Recrystallization from 15 ml. of 2-propanol yielded 2.47 g. of a colorless crystalline compound with m.p. 101–102° (over-all yield 69.2%), $\alpha^{24}D$ 0 ± 0.23° (*c* 3, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3.33 (C–H aromatic), 5.78 (ester C=O), 8.03 μ (C–O stretching), no OH absorption 2.9 μ; $\lambda_{max}^{CHCl_3}$ 273 mμ.

Anal. Calcd. for $C_{25}H_{32}O_9$: C, 57.57; H, 6.09. Found: C, 57.97; H, 6.19.

2,4-*O*-Anisylideneribitol (VIII).—A quantity of 0.594 g. (1.5 mmoles) of VII was dissolved in 30 ml. of absolute methanol, and the solution was cooled to 0° and saturated with dry NH_3. The solution was left at room temperature for 3 hr. after which time the solvent was evaporated under reduced pressure. A colorless syrup, which crystallized readily, was obtained. Recrystallization from $CHCl_3$ gave 0.35 g. (86.3%) of fine, colorless needles with m.p. 119–120°; $\alpha^{24}D$ 0 ± 0.20° (*c* 3, methanol); ν_{max}^{Nujol} 2.90 μ (OH), no C=O absorption near 5.75 μ.

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.41; H, 6.71.

3,5-Di-*O*-acetyl-2,4-*O*-anisylidene-D-ribose 2,4-Dinitrophenylhydrazone (IX).—A quantity of 4.37 g. (9 mmoles) of II was demercaptalated in the presence of acetone and water as described previously. The syrup obtained failed to crystallize from ethyl acetate–petroleum ether (b.p. 60–80°). However, after being dissolved in 50 ml. of methanol and evaporated under reduced pressure, a solid mass was obtained. After several recrystallizations from ethyl acetate–petroleum ether (b.p. 60–80°), a fraction consisting of a fine crystalline material, m.p. 94–96°, was obtained which was presumably 3,5-di-*O*-acetyl-2,4-*O*-anisylidene-D-ribose containing 1 mole of methanol of crystallization. This material (0.0704 g., 0.2 mmole) was converted into the DNP derivative in the usual manner. A yellow crystalline product (0.061 g., 57%) with m.p. 162–164° was obtained. Re-

crystallization from 25 ml. of methanol gave fine yellow crystals with m.p. 182.5–184°; $\nu_{max}^{CHCl_3}$ 3.03 μ (N–H stretching), 5.76 μ (ester C=O).

Anal. Calcd. for $C_{23}H_{24}N_4O_{11}$: C, 51.88; H, 4.54; N, 10.52. Found: C, 51.86; H, 4.79; N, 10.21.

2,4-*O*-*p*-Dimethylaminobenzylidene-D-ribose Di-*n*-propyl Dithioacetal (X).—D-Ribose di-*n*-propyl dithioacetal (1.136 g., 4 mmoles) was added to a solution of *p*-dimethylaminobenzaldehyde (0.672 g., 4.5 mmoles) in 3 ml. of dioxane, and the solution was cooled to 5–10°. To this was added a mixture of 2 ml. of concentrated HCl (sp. gr. 1.16) and 5 ml. of water, previously cooled to 5–10°, and the resulting mixture was shaken vigorously with intermittant cooling for 20 min. A yellow solution was obtained which was poured into a separating funnel containing 100 ml. of ethyl acetate as well as 120 ml. of saturated aqueous $NaHCO_3$ solution. The ethyl acetate solution was then washed twice with 50 ml. of cold water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure yielded 1.4 g. of a yellow oil. Crystallization was accomplished with the aid of a mixture of 2 ml. of ethyl acetate and 8 ml. of petroleum ether (b.p. 60–80°), yielding 0.73 g. (4.4%) of a crystalline material with m.p. 125–127°; $\nu_{max}^{CHCl_3}$ 2.82, 2.94 μ (OH).

Anal. Calcd. for $C_{20}H_{33}NO_4S_2$: C, 57.84; H, 7.95; N, 3.37. Found: C, 57.41; H, 7.88; N, 3.07.

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Some New Arylphosphonic and Diarylphosphinic Acids

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In earlier papers[1,2] we have reported that some arylphosphonic ($ArPO_3H_2$) and diarylphosphinic (Ar_2PO_2H) acids have appreciable *in vitro* activity against *Treponema pallidum*, the causative agent of syphilis. The preparation of eleven of the acids tested[2] has not yet been described. Nine of these were new compounds while two were known compounds which we prepared by methods different from those used previously. The present note describes the preparation and chemical properties of these eleven compounds. Their analyses, yields, and melting points are listed in Table I. Ultraviolet absorption data for some of the compounds are given in Table II.

Experimental Section

***p*-Iodophenylphosphonic Acid.**—Dry *p*-iodobenzenediazonium fluoroborate was suspended in isopropyl acetate and treated with PCl_3 and CuBr in the usual manner.[3] After the reaction mixture was hydrolyzed and steam distilled, the residual liquid in the distilling flask was filtered while hot in order to remove a brown oil. The filtrate was evaporated on the steam bath to incipient crystallization and then cooled. The crude phosphonic acid thus obtained was recrystallized from water.

***p*-Acetylphenylphosphonic Acid. A. From the Diazonium Fluoroborate and PCl_3.**—*p*-Nitroacetophenone (Eastman) in ethyl acetate was reduced with Raney nickel and hydrogen at 3.5 kg./cm.^{2} (50 lb.). After the catalyst was removed, the amine was isolated by evaporating the solvent *in vacuo* and purified by recrystallization from 95% ethanol. The yield of pure *p*-aminoacetophenone was 82%, m.p. 105–107° (lit.[4] m.p. 106–107°).

p-Acetylbenzenediazonium fluoroborate was prepared from the above amine and allowed to react with PCl_3 and CuBr in ethyl acetate. The phosphonic acid was isolated in the usual manner and was purified by procedure A as previously described.[3] Before analysis, it was dried *in vacuo* at 100°.

B. From *p*-Aminophenylphosphonic Acid and Acetaldoxime.—*p*-Aminophenylphosphonic (phosphanilic) acid[5] (43.3 g.) in 200 ml. of 3.4 *N* H_2SO_4 was diazotized at 0–5°. The resulting solution was neutralized to congo red and then allowed to react with acetaldoxime under conditions similar to those described for the conversion of *p*-chloroaniline to *p*-chloroacetophenone.[6] After the reaction mixture was acidified to congo red and made even more strongly acidic by the addition of 230 ml. of concentrated HCl, the solution was evaporated on the steam bath to 100 ml. and cooled, whereupon crude *p*-acetylphenylphosphonic acid crystallized. It was purified by extraction with absolute alcohol in a Soxhlet apparatus, evaporation of the resulting solution to dryness, and recrystallization of the residue from 6 *N* HCl. The infrared spectra of samples of *p*-acetylphenylphosphonic acid made by both methods were identical.

***m*-Phenoxyphenylphosphonic Acid.** ***m*-Bromophenylphosphonic acid**[7] (5.0 g.) was allowed to react with phenol, K_2CO_3, and copper powder under conditions similar to those described for conversion of *o*-bromophenylphosphonic acid to the corresponding phenoxy compound.[8] When the reaction mixture was steam distilled (to remove excess phenol) and then acidified, the hemipotassium salt[3] of *m*-phenoxyphenylphosphonic acid crystallized from solution. This salt was added to 100 ml. of boiling 6 *N* HCl, and sufficient 95% ethanol was added to dissolve the suspended solid. The solution was cooled and extracted with three 30-ml. portions of benzene. The benzene layers were combined and evaporated to dryness. Recrystallization of the residue from a mixture of heptane–toluene (1:2) yielded pure material.

***p*-Phenoxyphenylphosphonic Acid.**—The method used to prepare and isolate the hemipotassium salt of *p*-phenoxyphenylphosphonic acid was similar to that described for the *ortho* and *meta* isomers. The free acid was obtained by recrystallization of the salt from a mixture of 1 vol. of 95% ethanol to 3 vol. of 6 *N* HCl.

2-(*p*-Tolyloxy)phenylphosphonic Acid and 2-(*p*-Tolyloxy)-*p*-tolylphosphonic Acid.—*o*-Bromophenylphosphonic acid[5] and 2-bromo-*p*-tolylphosphonic acid[9] were allowed to react with redistilled *p*-cresol under conditions similar to those used in the preparation of the phenoxy derivatives. The hemipotassium salts obtained were converted to the free acids by recrystallization from a mixture of 1 vol. of 95% ethanol to 2 vol. of 6 *N* HCl.

Bis(*p*-phenoxyphenyl)phosphinic Acid.—An intimate mixture of 8.0 g. of bis(*p*-bromophenyl)phosphinic acid,[7] 20 ml. of redistilled phenol, 10.0 g. of anhydrous K_2CO_3, and 0.2 g. of copper powder was heated under reflux for 16 hr. After the excess phenol was removed by steam distillation, the reaction mixture was filtered and then acidified to congo red. The crude phosphinic acid thus obtained was purified by recrystallization from acetone–absolute alcohol (1:2).

2-Nitro-5-bromophenylphosphonic Acid.—A solution of *m*-bromophenylphosphonic acid[7] (10.0 g.) in 50 ml. of fuming HNO_3 (*d* 1.5) was evaporated to dryness, and the residue was recrystallized from 3 *N* HCl. The structure of this phosphonic acid was not established unequivocally, but it is probably 2-nitro-5-bromophenylphosphonic acid for the following reasons. (1) The compound does not form a water-insoluble magnesium salt either at room temperature or when heated. This behavior is characteristic of arylphosphonic acids containing bulky *ortho* substituents such as the nitro group.[10] (2) The nitration of *m*-bromobenzenearsonic acid yields 2-nitro-5-bromobenzenearsonic acid,[11] and the nitration of *m*-bromobenzoic acid yields mainly 2-nitro-5-bromobenzoic acid.[12] Since the electronic structure of the phos-

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