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THE PHOSPHORYLATION OF 4,4′-DIAMINODIPHENYLSULFONE AND CONVERSION OF THE PRODUCTS INTO AMIDOPHOSPHORIC ACID DERIVATIVES

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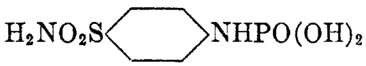
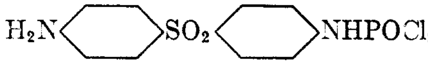
The reaction of phosphoryl chloride with sulfanilamide and related sulfonamides has been reported (1) to yield chlorophosphoryl derivatives from which could be prepared water-soluble salts of the corresponding N-phosphonic acids. The products from sulfanilamide were assigned structures I and II. The present article describes the phosphorylation of 4,4′-diaminodiphenylsulfone both in pyridine solution and by excess of phosphoryl chloride at 100°, and conversion of the products into water-soluble sodium salts.

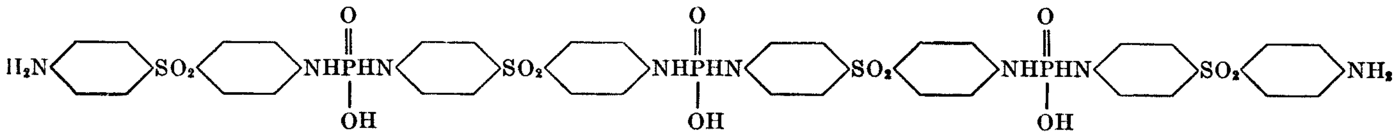

I


II

The reaction of phosphoryl chloride with the sulfone in dry pyridine solution should be capable of producing a variety of products according to the conditions, especially the proportion of the reactants and the temperature. This investigation has been limited to the reaction below room temperature and in the presence of an excess of the sulfone. Under these conditions the initial product of phosphorylation (III) would be expected to react with diaminodiphenylsulfone and intermediate chlorophosphoryl derivatives to form polymolecular condensation products. Isolation of the products was carried out after hydrolysis of the chlorophosphoryl derivatives in aqueous pyridine solution near 0°. Emphasis is placed on a water-soluble sodium salt, which was obtained in a yield of 45–50 g. from 120 g. of diaminodiphenylsulfone.

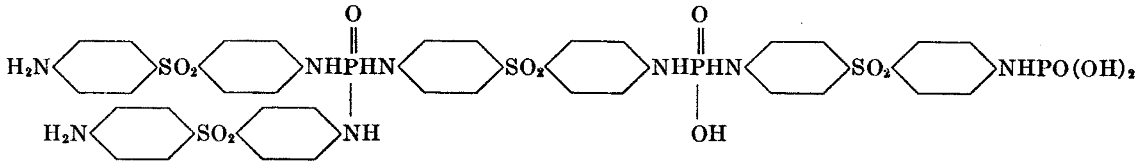

III

The proof of the homogeneity of the sodium salt and the assignment of a structure have been complicated by the failure of the salt or any of its derivatives to crystallize. However, the amorphous sodium salt has been subjected to a thorough fractional precipitation from its aqueous solution by ethanol, and the resulting purified salt used as the starting material for the preparation of the parent acid, its 2-aminoethanol salt, and *p*-dimethylaminobenzylidene derivative. The analytical data summarized in Table I are in substantial agreement with the theoretical values for the tri-diamidophosphoric acid derivative (IV), its trisodium salt, tri-2-aminoethanol salt, and di-*p*-dimethylaminobenzylidene derivative. The presence of two unsubstituted primary amino groups is shown by the formation of the di-*p*-dimethylaminobenzylidene derivative and con-

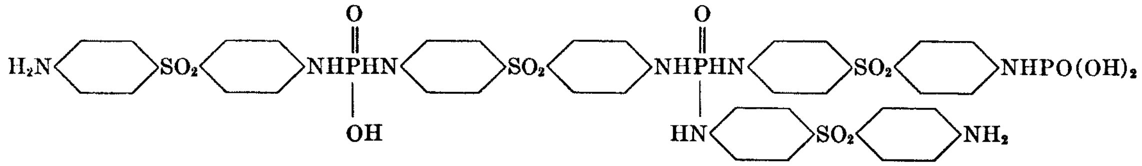


IV

N,N′-Bis(N-*p*-sulfanilylphenyl-N′-*p*-phenylsulfonylphenyldiamidophosphinico)diamidophosphoric acid



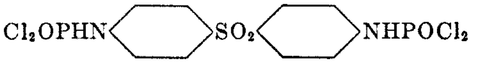
V



VI

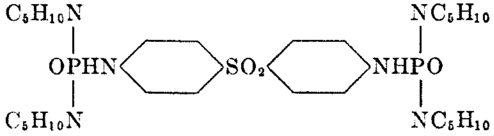
firmed by the diazotization value of both the acid and its sodium salt. The sodium content of the salt and the neutralization value of the acid correspond to the tribasicity of IV. The titration curve shown in Fig. 1 does not establish the difference in the acidic groups expected for the monoamidophosphoric acid group of V and VI which seems to justify a tentative preference for the symmetrical structure IV over the isomeric tribasic acids V and VI. In accordance with its N-phosphoryl structure the acid is hydrolyzed by *N* hydrochloric acid at 100° to produce 4,4′-diaminodiphenylsulfone, which was isolated as pure crystals in 85% yield.

The phosphorylation of diaminodiphenylsulfone with excess of phosphoryl chloride at 100° yields a crystalline chlorophosphoryl derivative. Warnat (3) has reported the preparation of a chlorophosphoryl derivative to which he ascribed structure VII but presented no analytical data. This structure has now been confirmed by the preparation of pure crystalline 4,4′-bis(dipiperidylphosphorosoamino)diphenylsulfone (VIII) through reaction of the chlorophosphoryl derivative with piperidine. The piperidyl derivative was isolated as dimorphic forms melting at 190–191° and 221–222°.



VII

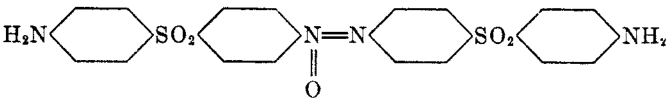
4,4′-Bis(dichlorophosphorosoamino)-diphenylsulfone



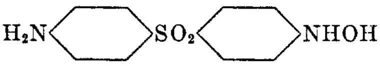
VIII

Through reaction with cold aqueous sodium bicarbonate solution the chlorine is eliminated from the molecule of the chlorophosphoryl derivative (VII) to produce an aqueous solution of sodium salts. This reaction is accompanied by cleavage of the phosphorus from a considerable portion of the phosphorylation product, as shown by the formation of diaminodiphenylsulfone. Acidification of the aqueous solution of sodium salts precipitates the phosphorylation product mixed with smaller amounts of diaminodiphenylsulfone and 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene (IX). The azoxy derivative was isolated as nearly colorless crystals melting at 245–246° (uncor.). It was characterized by an elementary analysis, determination of its diazotization value, and reduction by stannous chloride to yield 4,4′-diaminodiphenylsulfone. The compound probably is formed from 4-amino-4′-hydroxylaminodiphenylsulfone (X) in the course of the splitting of the phosphorylation product in aqueous sodium bicarbonate solution.

The phosphorylation product, after two precipitations by acidification of the aqueous solution of the sodium salt and extraction with acetone, is obtained as an amorphous powder in a yield of 20–25 g. from 100 g. of diaminodiphenyl-



IX



X

sulfone. This material, previously designated "N-phosphoryl derivative of 4,4′-diaminodiphenylsulfone," has been shown to possess antibacterial activity (4). It can be prepared regularly with approximately the same composition and properties. The substance, however, is not a pure compound. Although its sodium salt in neutral aqueous solution is substantially stable at room temperature, heating the solution at 100° liberates 25–30% of the material as a mixture composed principally of 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene and diaminodiphenylsulfone. The portion of the material stable in aqueous solution at 100° yields the sulfone and azoxy derivative through hydrolysis by *N* hydrochloric acid at 100°. The azoxy derivative, obtained in this way, may owe its origin to initially formed 4-amino-4′-hydroxylaminodiphenylsulfone, a possibility suggested by the known conversion of 4-hydroxylaminobenzenesulfonamide (5) into azoxybenzene-4,4′-disulfonamide and *p*-aminophenol by hot hydrochloric acid. The results indicate that either 4-amino-4′-hydroxylaminodiphenylsulfone or 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene is an integral part of the molecule of the phosphoryl derivative. Although the "N-phosphoryl derivative" is not a pure compound, directions for its preparation and data on its composition (see formulas XI and XII) are included on account of its antibacterial activity.

EXPERIMENTAL

Phosphorylation of 4,4′-diaminodiphenylsulfone in pyridine solution. Synthesis of the tri-diamidophosphoric acid derivative (IV). To a mechanically stirred solution of 120 g. of diaminodiphenylsulfone (1.5 molecular equivalents) in 560 cc. of anhydrous pyridine at 2–5° was added dropwise during one hour 49.6 g. of phosphoryl chloride (1.0 molecular equivalent). The ice-bath was removed and the red solution, which contained a gel in suspension, was stirred for forty-five minutes. The mixture was added gradually in the course of thirty minutes to an efficiently stirred solution of 100 cc. of pyridine in 500 cc. of ice water, the reaction flask being washed first with 15 cc. of pyridine and then with a solution of 10 cc. of pyridine in 25 cc. of water. The stirring at about 5° was continued for an additional thirty minutes, the solution left overnight at room temperature, then filtered and neutralized by sodium hydroxide solution. In order to remove pyridine, the solution was concentrated *in vacuo* (bath, 45–50°) virtually to dryness. To the thick, red sirup was added 1500 cc. of water. After being mixed thoroughly, the insoluble solid was filtered off and washed with 300 cc. of cold water. The air-dried solid weighed 87 g. This material is a mixture, the constituents of which have not yet been identified. A considerable part of it is soluble in a large volume of cold acetone. The portion insoluble in acetone consists mostly of aqueous alkali soluble material, probably IV or an unidentified amidophosphoric acid derivative. Extraction of 5 g. of the mixture with 35 cc. of cold 5% hydrochloric acid, filtration, and neutralization of the filtrate by sodium hydroxide yielded 1.7

g. of diaminodiphenylsulfone. Part of the material insoluble in 5% hydrochloric acid was soluble in sodium hydroxide solution due to the presence of an amidophosphoric acid derivative.

The crude tri-diamidophosphoric acid derivative (IV) was precipitated from the thoroughly stirred filtrate from the 87 g. of solid by the dropwise addition of 260 cc. of 19% hydrochloric acid. It was filtered immediately and washed with cold water. To a suspension of the substance in 250 cc. of water was added, with stirring, sufficient 10% sodium hydroxide solution to yield a solution of the sodium salt neutral to litmus paper. The amorphous tri-diamidophosphoric acid derivative was precipitated from the filtered solution by the addition of hydrochloric acid in amount known to be equivalent to the sodium hydroxide used for neutralization of the crude product. After the substance had been filtered off and washed with cold water, an aqueous solution of the sodium salt, neutral to litmus, was again prepared; it was kept at room temperature for twenty-four to forty-eight hours and filtered to remove a little solid material. The solution was concentrated *in vacuo* with the bath at 50° to a volume of 100 cc. and poured slowly into 1100 cc. of vigorously stirred commercial absolute ethanol, the residual sirup being transferred with the use of 25 cc. of water. The air-dried, solid sodium salt, thus precipitated, weighed 47 g. In case high humidity prevails, the substance should be dried in an evacuated desiccator over calcium chloride. An additional 2.8 g. of sodium salt was obtained by evaporation of the filtrate *in vacuo* (bath, 40–45°) to dryness, extraction of the residue with 35 cc. of cold water in portions, filtration after twenty hours to remove 1.7 g. of insoluble solid, and concentration of the aqueous solution, followed by precipitation of the salt with ethanol. A solution of the 47 g. of sodium salt in 65 cc. of water, to which had been added 135 cc. of ethanol, was kept at room temperature for several hours, and then separated from some sirup by decantation. The sodium salt was precipitated by the addition of this solution to 625 cc. of thoroughly stirred absolute ethanol. The salt, after being filtered, washed with cold absolute ethanol, and dried for several days in an evacuated desiccator over calcium chloride, weighed 34 g. The powder lost 3.6% in weight at 100° *in vacuo* and then showed: P, 8.19; S, 9.80; diazotization as compared, with diaminodiphenylsulfone (2), 17%. The analytical data recorded in Table I for the trisodium salt of the tri-diamidophosphoric acid derivative were obtained after the material had been subjected to a thorough fractional precipitation from its aqueous solution by ethanol, to yield 11 g. of amorphous, slightly yellow, solid sodium salt. The salt in dilute aqueous solution apparently is stable at 100°; 0.1 g. in 2 cc. of solution in water, after being kept at 100° for thirty minutes and cooled, yielded upon addition of 2.3 cc. of 0.1 *N* hydrochloric acid 0.07 g. of the parent acid showing a neutralization value in virtual agreement with that recorded in Table I. Evidence, supplementary to the analytical data, on the purity and structure of the sodium salt was obtained by the preparation and analysis (Table I) of the parent tri-diamidophosphoric acid derivative, its 2-aminoethanol salt, and di-*p*-dimethylaminobenzylidene derivative.

The tri-diamidophosphoric acid derivative was precipitated as an amorphous solid by the addition of 4.5 cc. of *N* hydrochloric acid to a solution of 2 g. of the above carefully fractionated sodium salt in 20 cc. of water. The acid was filtered promptly and washed free of chlorine ions by cold water. The washing is facilitated by allowing the product, after being washed partially, to dry overnight at room temperature before removal of the last traces of chlorine ions. After being dried in an evacuated desiccator over calcium chloride, the slightly yellow powder weighed 1.6 g. and melted at 181–182° (uncor.). The melting point varies with the moisture content of the sample. The melting points of this amorphous acid and its two derivatives herein described are not regarded as reliable criteria of purity. The substance lost 1.8% in weight at 100° *in vacuo*; it showed no change in appearance and neutralization value as a result of the heating. The acid is soluble in cold 2-aminoethanol; it is only slightly soluble in water and the usual organic solvents. Hydrolysis by *N* hydrochloric acid at 100° yielded 4,4′-diaminodiphenylsulfone (0.1 g. of substance, suspended in 10 cc. of *N* hydrochloric acid and kept at 100° for one hour, gave a

TABLE I

TRI-DIAMIDOPHOSPHORIC ACID (IV) AND DERIVATIVES

SUBSTANCE	EMPIRICAL FORMULA	ANALYSES, %													
		Calc'd							Found[a]						
		C	H	N	P	S	Na	Diazotization	C	H	N	P	S	Na	Diazotization[b]
Tri-diamidophosphoric acid[c] (IV)	$C_{48}H_{45}N_8O_{14}P_3S_4$	48.89	3.85	9.51	7.88	10.88	—	21.1	48.41	3.94	9.38	7.77	11.07	—	24[d]
Trisodium salt	$C_{48}H_{42}N_8Na_3O_{14}P_3S_4$	—	—	9.00	7.46	10.30	5.54	19.9	—	—	8.96	7.63	10.26	5.41	16
Tri-2-aminoethanol salt	$C_{54}H_{66}N_{11}O_{17}P_3S_4$	47.60	4.88	11.31	6.82	9.41	—	—	47.15	5.05	11.30	6.99	9.50	—	—
Di-*p*-dimethylaminobenzylidene derivative[e]	$C_{66}H_{63}N_{10}O_{14}P_3S_4$	54.99	4.41	9.72	6.45	8.90	—	—	—	—	—	—	—	—	—
	$C_{66}H_{63}N_{10}O_{14}P_3S_4$ + 1.1% Cl	54.39	4.36	9.61	6.38	8.80	—	—	53.87	4.39	9.80	6.31	9.00	—	—

[a] With the exception specified, all samples were dried to constant weight at 100° *in vacuo*.

[b] Diazotization values were obtained by comparison of the samples with 4,4′-diaminodiphenylsulfone according to the method of Bratton and Marshall (2).

[c] Calc'd for IV: 2.54 cc. of 0.1 *N* NaOH solution per 100 mg. Found: 2.47 cc. (phenolphthalein).

[d] The substance, which had been dried in an evacuated desiccator over calcium chloride, was known to lose 1.8% in weight at 100° *in vacuo*.

[e] The sample contained 1.1% chlorine.

solution which, upon being cooled, filtered, and neutralized by sodium hydroxide solution, deposited crystals of the sulfone; the yield was increased to 0.072 g., or 85% by concentration of the filtrate *in vacuo* to dryness and separation of the sulfone from inorganic crystals by extraction with acetone; m.p. 175–176°, not depressed by authentic sulfone).

The titration curve for the tri-diamidophosphoric acid derivative is shown in Fig. 1. A solution of the sodium salt was prepared by the addition of 14.13 cc. of 0.1 N sodium hydroxide solution to an aqueous suspension of 0.5600 g. of the acid, which had been dried in an evacuated desiccator over calcium chloride; the solution finally was diluted with water to a volume of 35 cc. at 28°. Solutions for the *p*H determinations were prepared in one case by dilution of 2 cc. of the sodium salt solution with 3 cc. of water and for the other points by the addition of various amounts of 0.02 N hydrochloric acid or of 0.01 N sodium hydroxide solution to 2 cc. aliquots of the sodium salt solution with sufficient water to make 5 cc. (c, 0.0054 M). The *p*H of each solution was determined[1] at 28° with the use of

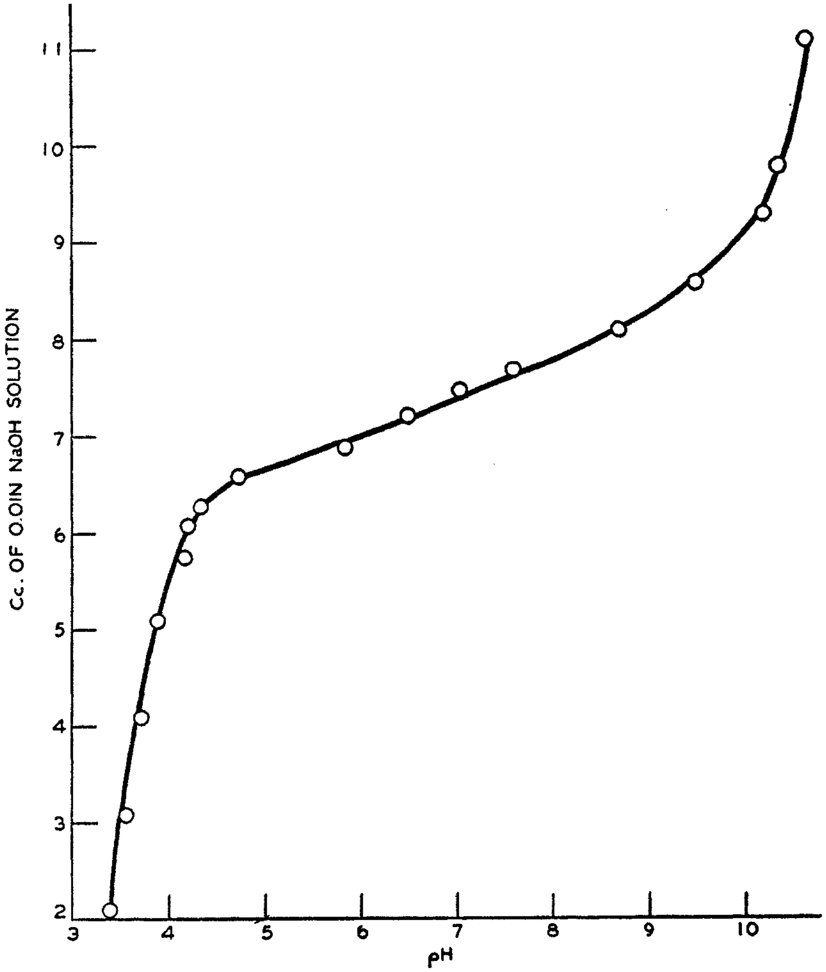


FIG. 1. TITRATION CURVE OF THE TRI-DIAMIDOPHOSPHORIC ACID DERIVATIVE

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[1] Indebtedness is expressed to Dr. E. W. Emmart for the *p*H readings.

the glass electrode of a Beckman *p*H meter. A slight turbidity was observed in the solution having *p*H 4.8; the turbidity increased progressively as the *p*H became smaller.

For the preparation of the 2-aminoethanol salt the tri-diamidophosphoric acid derivative, prepared as described from 1 g. of sodium salt, was dissolved in a mixture of 4 cc. of water and 4 g. of 2-aminoethanol (b.p. 167–170°). To this solution was added, with stirring, 100 cc. of absolute ethanol. The amorphous, virtually colorless, solid precipitate was filtered, washed with absolute ethanol, and dried in an evacuated desiccator over calcium chloride; weight, 0.3 g. Additional material can be obtained from the filtrate by evaporation of the solvent *in vacuo* and precipitation by the addition of the aqueous solution of the residue to ethanol. The 0.3 g., after being dried to constant weight at 100° *in vacuo*, was used for analyses; m.p. 175–176°. Acidification of the aqueous solution of a sample which had been kept at 100° *in vacuo* for three hours precipitated the parent tri-diamidophosphoric acid derivative; m.p. 179–180°. This result confirms the salt structure of the compound dried at 100°.

The di-*p*-dimethylaminobenzylidene derivative was precipitated upon addition of 1 cc. of 24% hydrochloric acid to a homogeneous solution prepared by mixing a solution of 0.25 g. of *p*-dimethylaminobenzaldehyde in 4 cc. of absolute ethanol with a solution of 1.0 g. of the sodium salt in 2 cc. of water. The orange-colored, amorphous solid was filtered, washed first with cold water, then with absolute ethanol, and dried in an evacuated desiccator over calcium chloride; yield, 1.1 g. The substance contained 1.1% chlorine, probably retained as hydrochloride. After being dried at 100° *in vacuo*, it melted at 218–219° (uncor.). The compound is only slightly soluble in water and the usual organic solvents.

4,4′-Bis(dipiperidylphosphorosoamino)diphenylsulfone. A mixture of 10 g. of 4,4′-diaminodiphenylsulfone and 50 g. of phosphoryl chloride was heated at 100° under a reflux condenser for four and one-half hours with occasional shaking. The dark red solution, which in occasional experiments contained some solid reaction product in suspension, was kept at room temperature for a short time and then poured into 40 cc. of benzene. The sirup which was precipitated crystallized readily upon being stirred or after nucleation with crystals of the chlorophosphoryl derivative. The crystals were filtered and washed with cold benzene to remove excess phosphoryl chloride. The chlorophosphoryl derivative is only slightly soluble in benzene, chloroform, carbon tetrachloride, and petroleum ether. Although it reacts rapidly with water and consequently is unstable in the air, it can be kept for several days in an evacuated desiccator over solid sodium hydroxide with little apparent decomposition.

The freshly prepared chlorophosphoryl derivative was added in small portions, with stirring, to 100 cc. of piperidine, cooled in ice-water. After thorough mixing had been accomplished, the thick paste was left overnight at room temperature with exclusion of atmospheric moisture. The solid was then separated by filtration, washed first with 35 cc. of piperidine and finally with dry diethyl ether. It was mixed with 30 cc. of cold water, the insoluble solid filtered off, and washed with 20 cc. of water; air-dried weight, 18 g. Some unidentified amorphous material was precipitated by addition of the piperidine mother liquor to 600 cc. of water, followed by acidification with hydrochloric acid. Acidification of the water extract of the 18 g. of solid also precipitated amorphous material. The 18 g. of solid was found to contain some piperidine hydrochloride, which probably could have been removed advantageously by further extraction with water. By fractional recrystallization from mixtures of absolute ethanol and ether 9.5 g. of slightly impure 4,4′-bis(dipiperidylphosphorosoamino)diphenylsulfone melting near 180° was isolated. After completion of purification by recrystallization from a mixture of chloroform and ether the colorless, short, slender rods, dried for twenty hours in an evacuated desiccator over calcium chloride, melted at 180–181° (uncor.). The crystals lost 14.5% in weight at 100° *in vacuo* and then melted at 190–191° (uncor.). The compound is soluble in cold chloroform, ethanol, and methanol; difficultly soluble in cold acetone; slightly soluble in ether; and virtually insoluble in water.

Anal. Calc'd for $C_{32}H_{50}N_6O_4P_2S$: C, 56.78; H, 7.45; P, 9.15; S, 4.74.
Found (dried at 100° *in vacuo*): C, 56.44; H, 7.21; P, 9.20; S, 4.86.

With the use of absolute ethanol-ether as the solvent the piperidyl derivative was observed to crystallize sometimes as a second modification, prismatic needles melting at 221–222° (cor.). The pure crystals, after being dried in an evacuated desiccator over calcium chloride, lost 1.5% in weight at 100° *in vacuo* without change in the melting point. Found (dried at 100° *in vacuo*): C, 56.53; H, 7.23; P, 9.05; S, 4.88.

Reactions of 4,4'-bis(dichlorophosphorosoamino)diphenylsulfone with aqueous sodium bicarbonate solution. The reaction of 100 g. of diaminodiphenylsulfone with 500 g. of phosphoryl chloride at 100° was carried out as described. The following hydrolysis was started immediately after filtration of the crystals of the chlorophosphoryl derivative. The crude substance was added gradually during about one and one-half hours to a mechanically stirred mixture of 600 g. of sodium bicarbonate and 1400 cc. of distilled water contained in an 8-liter glass jar cooled in ice-water. After all of the substance had been added, the stirring was continued for one hour, and the mixture left overnight at room temperature to assure completion of the hydrolysis of the chlorophosphoryl derivative. The mixture was then stirred for thirty minutes, the solid thrown down by centrifugation, and a clear solution finally obtained by filtration. With the aid of centrifugation the solid was washed twice with 300 cc. portions of cold water, the washings being kept separate from the principal solution. The solid was shown to be a mixture of sodium bicarbonate and diaminodiphenylsulfone which, in one experiment, weighed 28 g. after purification. The crude phosphoryl derivative was precipitated from the principal solution by the addition of 160 cc. of 38% hydrochloric acid and from the aqueous washings by the addition of the acid in amount, usually about 120 cc., sufficient to precipitate the substance completely. The phosphoryl derivative was filtered and washed with cold water. Neutralization of the filtrate with sodium hydroxide solution precipitated some diaminodiphenylsulfone; m.p. 174–176°.

To a thoroughly stirred suspension of the phosphoryl derivative in 400 cc. of water was added sufficient 10% sodium hydroxide solution to produce a *p*H of about 9 (phenolphthalein). After being kept at room temperature for two hours, the insoluble solid was removed by filtration or centrifugation, and washed with cold water. The solid, 15–18 g., is a mixture containing diaminodiphenylsulfone and 4,4'-bis(*p*-aminobenzenesulfonyl)-azoxybenzene, the isolation of which is described below. To the light red solution was added 20% hydrochloric acid in amount known to be equivalent to the sodium hydroxide used for neutralization of the phosphoryl derivative. After the precipitate had been filtered and washed with cold water, the above described process for neutralization of the substance to *p*H 9 was repeated. The solution was kept at room temperature for an hour to allow complete separation of some fine solid. The suspension was cleared by the addition of 250 cc. of 95% ethanol, the light red solution filtered, and the phosphoryl derivative precipitated in amorphous condition as previously described. The substance was filtered, washed with 15 cc. of cold 40% ethanol, then with cold water, and dried thoroughly at room temperature. To assure freedom of the substance from diaminodiphenylsulfone and 4,4'-bis(*p*-aminobenzenesulfonyl)azoxybenzene, the product was suspended in 100 cc. of dry acetone, mixed thoroughly, filtered, and washed with acetone. The weight of the residue left by concentration of the acetone solution to dryness usually was about 1% of the weight of the substance extracted; in case, however, the phosphoryl derivative is not dried prior to the acetone extraction, a considerable proportion of the material is dissolved by the acetone-water mixture. After the substance had been extracted with acetone, it was dried in an evacuated desiccator over calcium chloride. In an atmosphere of excessive humidity the product should be placed in the desiccator immediately following the washing with acetone to avoid some coloration and slight gumming. The yield of gray, amorphous, hygroscopic powder was 20–25 g. This is the material used for chemotherapeutic tests (4).

The melting point of the powder, usually between 160° and 170°, was somewhat variable in different preparations. It lost 2.7% in weight at 100° *in vacuo*. Its diazotization value was about 20% compared with diaminodiphenylsulfone (2). The following analytical data[2]

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[2] Thanks are expressed to Dr. B. B. Westfall, of this Laboratory, for carrying out the colorimetric phosphorus determinations.

are representative of the results of analyses of samples (dried at 100° *in vacuo*) from several preparations: C, 45.0–46.5; H, 3.9; N, 8.8; P, 9.5; S, 10.2. The substance is only slightly soluble in water and the usual organic solvents; it is more soluble in mixtures of water with acetone, ethanol, or dioxane. An aqueous solution of the sodium salt is prepared conveniently by the addition of *N* sodium hydroxide solution (1.8–2.0 cc. per g. of substance usually produces a *p*H of 6–7) to the dry powder with prompt stirring until a clear solution results; this solution can be diluted with water to any desired concentration.

The sodium salt in neutral aqueous solution, upon being heated at 100°, liberated 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene and diaminodiphenylsulfone. A 10% solution, prepared by stirring 18 cc. of *N* sodium hydroxide solution with 10 g. of the dry phosphoryl derivative followed by dilution with 82 cc. of water, was kept at 100° for thirty minutes. A precipitate separated and after the mixture had been kept overnight at room temperature, 1.7 g. of solid was filtered off. By extraction of the solid with cold 5% hydrochloric acid, removal of the insoluble material by filtration, and neutralization of the filtrate with sodium hydroxide solution, 0.4 g. of diaminodiphenylsulfone was obtained; m.p. 175–176°, not depressed by authentic sulfone. Purification of the insoluble material as described later under 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene yielded 0.5 g. of somewhat impure azoxy derivative, which in pure condition melted at 245–246° (uncor.) alone or mixed with the authentic compound. Calc'd for $C_{24}H_{20}N_4O_5S_2$: S, 12.61. Found: S, 12.41. To the filtrate from the 1.7 g. of solid, containing the portion of the sodium salt stable in aqueous solution at 100°, was added 18 cc. of *N* hydrochloric acid. The amorphous precipitate, after being filtered, washed with water, and dried in an evacuated desiccator over calcium chloride, weighed 7.5 g. A concentrated neutral aqueous solution of the sodium salt of this material was added to 175 cc. of vigorously stirred absolute ethanol. The amorphous sodium salt, thus obtained, was precipitated four times from its aqueous solution by ethanol and dried in an evacuated desiccator over calcium chloride; weight, 3.5 g.[3] The combined filtrates from all the precipitations were concentrated *in vacuo* to dryness, and the residue extracted several times with cold water to separate the sodium salt from 1.5 g. of insoluble material from which was isolated 0.5 g. of pure diaminodiphenylsulfone. The sodium salt was isolated from the aqueous solution by concentration and precipitation by ethanol; after another precipitation 0.5 g. of sodium salt was obtained.

The parent acid was prepared from the 3.5 g. of five-times precipitated sodium salt. To a solution of the salt in 15 cc. of water was added, with stirring, 8.3 cc. of *N* hydrochloric acid. The amorphous precipitate was filtered and washed free of chlorine ions by cold water. The washing is accomplished with less loss of the product by allowing the substance, after being washed partially, to dry overnight at room temperature before removal of the last traces of chlorine ions. After being dried in an evacuated desiccator over calcium chloride, it weighed 2.3 g. and melted at 192–194° (uncor.); diazotization value as compared with diaminodiphenylsulfone (2), 19%; neutralization value (phenolphthalein), 2.37 cc. of 0.1 *N* NaOH solution per 100 mg. of substance. This material lost 2.7% in weight at 100° *in vacuo*. Found (dried at 100° *in vacuo*): C, 46.75; H, 3.79; N, 9.03; P, 7.95; S, 10.41. A sample of the acid prepared from the above 0.5 g. of sodium salt, which was isolated from the mother liquors from the 3.5 g., showed (dried at 100° *in vacuo*): C, 46.82; H, 3.74; P, 7.93; S, 10.78. The acid yields through hydrolysis by hot *N* hydrochloric acid diaminodiphenylsulfone and 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene. A suspension of 0.2 g. of the acid in 20 cc. of *N* hydrochloric acid, after being heated at 100° under a reflux condenser for one hour, gave a solution, which was filtered hot and left at room temperature. The gelatinous solid which separated was filtered, washed with 5% hydrochloric acid, then suspended in water and neutralized by sodium hydroxide solution. The solid, after being filtered, washed with water, and air-dried, weighed 0.026 g. It was

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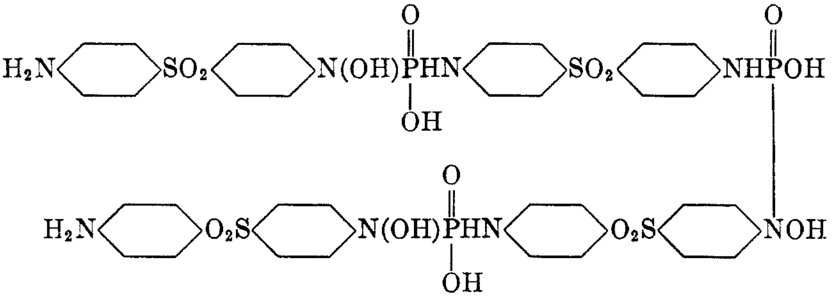
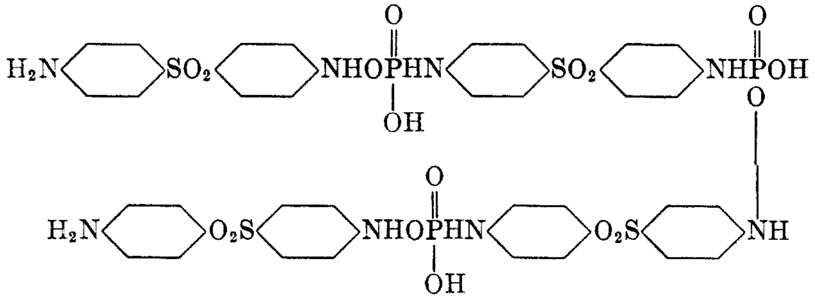
[3] In a preliminary test by Dr. E. W. Emmart this sodium salt in a concentration of 10 mg. % showed a partial inhibition of the growth of tubercle bacilli (human strain A 27) on a Difco beef medium containing 5% glycerol.

identified, after purification, as 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene by melting-point and mixed-melting-point determinations, also by resemblance to the authentic compound in appearance of the crystals and solubility. The filtrate from the crude azoxy derivative yielded 0.088 g. of diaminodiphenylsulfone, isolated by neutralization with sodium hydroxide, removal of crystals of the sulfone, concentration of the filtrate to dryness, and extraction of the residue with acetone.

Regarding the structure of the acid just described, a formula is not proposed because of the uncertain homogeneity of the material. It is noted, however, that several possible isomeric structures, illustrated by formulas XI and XII, correspond fairly well to the analytical data. Calc'd for $C_{48}H_{45}N_8O_{17}P_3S_4$: C, 46.98; H, 3.70; N, 9.13; P, 7.57; S, 10.45; diazotization, 20.2%; neutralization, 2.44 cc. of 0.1 *N* NaOH solution per 100 mg. of substance.



XI



XII

4,4′-Bis(p-*aminobenzenesulfonyl*)*azoxybenzene.* A mixture (15–18 g.) of the azoxy derivative with diaminodiphenylsulfone and other material was obtained as described under the reactions of 4,4′-bis(dichlorophosphorosoamino)diphenylsulfone with aqueous sodium bicarbonate solution. The mixture was stirred thoroughly with 75 cc. of 5% hydrochloric acid at room temperature. The insoluble solid was filtered off, washed first with 5% hydrochloric acid and finally with water. Neutralization of the filtrate by sodium hydroxide solution precipitated about 7 g. of crystalline diaminodiphenylsulfone. The insoluble solid, after being suspended in 75 cc. of water, neutralized by sodium hydroxide, filtered, washed with water, and air-dried, weighed 7–8 g. The azoxy derivative crystallized readily as needles or elongated plates from a solution of this material in pyridine to which water had been added to turbidity; yield, 1.5 g.; the remainder of the material was amorphous. The compound was purified by several recrystallizations from a mixture of pyridine and water, activated carbon being used when needed to assist in decolorization. The air-dried crystals retain pyridine, which is not removed by washing the crystals with water. Crystals of the pure azoxy derivative are almost colorless, and melt at 245–246° (uncor.) either in the air-dried condition or after being dried to constant weight at 100° *in vacuo*. Prolonged heating at 100° *in vacuo* was found to lower the melting point in the case of certain samples which were shown by diazotization to be somewhat impure, although the air-dried material had a melting point near that of the pure compound. Samples for analysis were dried at 100° *in vacuo*. The compound is readily soluble in cold pyridine, soluble in acetone and 2-ethoxyethanol, and somewhat soluble in methanol; it is virtually insoluble in water and only slightly soluble in the majority of the common organic solvents. It failed to dissolve completely in molten camphor (1:20). On account of its slight solubility in hydrochloric acid the azoxy derivative reacts with nitrous acid only slowly under customary conditions of diazotization with starch-potassium iodide indicator. For analysis sufficient acetone was added to yield a homogenous solution (0.0810 g. of substance dissolved in 21 cc. of acetone, to which was added 31 cc. of water and 4.5 cc. of 19% hydrochloric acid, required at 2–5° 6.10 cc. of sodium nitrite solution, or 48.2% of the amount, 12.65 cc., consumed under the same conditions by 0.0810 g. of diaminodiphenylsulfone); calculated, 48.8%.

Anal. Calc'd for $C_{24}H_{20}N_4O_5S_2$: C, 56.68; H, 3.96; S, 12.61.
Found: C, 56.70, 57.03; H, 3.99, 4.10; S, 12.44.

4,4′-Diaminodiphenylsulfone is a product of the reduction of the azoxy derivative by stannous chloride. To a suspension of 0.345 g. of air-dried crystals, or 0.277 g. calculated to the dry basis, in 5 cc. of 50% aqueous acetic acid was added 0.9 cc. of 38% hydrochloric acid. After the crystals had been dissolved at steam-bath temperature, 0.8 g. of stannous chloride dihydrate was added, and the mixture kept at 100° under a reflux condenser for three hours. The nearly colorless solution upon being cooled to room temperature deposited some gelatinous solid, which was filtered, washed first with 50% acetic acid containing some hydrochloric acid, and finally with 5% hydrochloric acid. The solid in aqueous suspension was neutralized by sodium hydroxide, filtered, washed with water, and air-dried. This substance, 0.16 g. melting near 220°, was identified after recrystallization as unreacted azoxy derivative. An additional 0.03 g. was obtained from the reduction solution by dilution with an equal volume of water; the total starting material recovered was thus about 50% of the amount used. The reduction solution was treated with hydrogen sulfide, the tin sulfide filtered, and washed with water. After removal of excess hydrogen sulfide by aeration, the solution was concentrated *in vacuo* to about 5 cc., then diluted with 15 cc. of absolute ethanol, and the concentration *in vacuo* continued to dryness. The residue was transferred to a funnel with the aid of absolute ethanol. 4,4′-Diaminodiphenylsulfone was isolated both from the insoluble crystals, 0.04 g., and from the ethanol filtrate. The latter was concentrated *in vacuo* to dryness, the residue (0.2 g.) dissolved in 7 cc. of water, and the solution neutralized by sodium hydroxide, 0.02 g. of 4,4′-diaminodiphenylsulfone melting at 174–175° being precipitated. The 0.04 g. of crystals was suspended in 2 cc. of water and the mixture neutralized by sodium hydroxide, 0.03 g. of 4,4′-diaminodiphenylsulfone melting at 175–176° being produced. The identification was confirmed by the determination of the diazotization value of the product. The yield of the sulfone was about 37% on the basis of the azoxy derivative reacting.

Indebtedness is expressed to Dr. G. W. Raiziss, of the Dermatological Research Laboratory, Division of Abbott Laboratories, for the gift of some diaminodiphenylsulfone.

SUMMARY

The phosphorylation of 4,4′-diaminodiphenylsulfone in pyridine solution under specified conditions, followed by hydrolysis of the chlorophosphoryl derivative, yields an amorphous tribasic acid. The elementary composition of the acid and of three amorphous derivatives, its trisodium salt, tri-2-amino-

ethanol salt, and di-*p*-dimethylaminobenzylidene derivative, indicates the condensation of four moles of diaminodiphenylsulfone with three moles of phosphoryl chloride. The acid is represented as a tri-diamidophosphoric acid derivative. Confirmation of the amidophosphoric acid type of structure results from hydrolysis of the compound by hot hydrochloric acid to produce diaminodiphenylsulfone in high yield.

The crystalline chlorophosphoryl derivative, prepared by Warnat by phosphorylation of the sulfone with excess of hot phosphoryl chloride, is shown to be 4,4′-bis(dichlorophosphorosoamino)diphenylsulfone through its reaction with piperidine to yield crystalline 4,4′-bis(dipiperidylphosphorosoamino)diphenylsulfone, isolated as dimorphic forms melting at 190–191° and 221–222°.

4,4′-Bis(dichlorophosphorosoamino)diphenylsulfone is converted by aqueous sodium bicarbonate solution into a mixture of products consisting principally of the sodium salt of an amorphous phosphoryl derivative (4), diaminodiphenylsulfone, and crystalline 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene having the melting point 245–246°. Evidence is presented which indicates that the molecule of the phosphoryl derivative is constructed of 4-amino-4′-hydroxylaminodiphenylsulfone combined through phosphorus with 4,4′-diaminodiphenylsulfone.

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