[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Diethyl *N*-Arylsulfonylphosphoramidates

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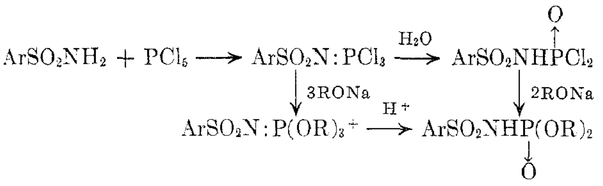
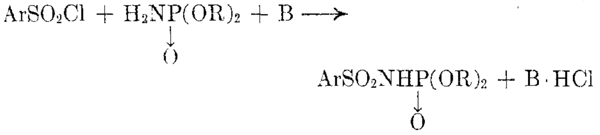
Diethyl ester of *N*-arylsulfonylphosphoramidic acids were synthesized by condensation of various sulfonamide sodium salts and diethyl phosphorochloridate. The chemical behavior of this new type of phosphorus compounds is that of monobasic acids. Tetraethyl *N*-arylsulfonyliminodiphosphates could be isolated as by-product.

The synthesis of dialkylesters of *N*-arylsulfonylphosphoramidic acids, a new class of organic phosphorus compounds, was reported previously by A. V. Kirsanov and V. I. Shevchenko[2] by the following method:



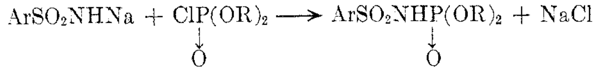
$$\begin{tikzcd} ArSO_2NH_2 + PCl_5 \arrow[r] & ArSO_2N{:}PCl_3 \arrow[r, "H_2O"] \arrow[d, "3RONa"] & ArSO_2NH\overset{O}{\overset{\uparrow}{P}}Cl_2 \arrow[d, "2RONa"] \\ & ArSO_2N{:}P(OR)_3{}^{+} \arrow[r, "H^+"] & ArSO_2NH\underset{O}{\underset{\downarrow}{P}}(OR)_2 \end{tikzcd}$$

The direct sulfonylation of the amidogroup in diethylphosphoramidate with aromatic sulfonylchlorides according to the equation was tried unsuccessfully earlier by B. C. Saunders and coworkers.[1]



$$ArSO_2Cl + H_2N\underset{O}{\underset{\downarrow}{P}}(OR)_2 + B \longrightarrow ArSO_2NH\underset{O}{\underset{\downarrow}{P}}(OR)_2 + B \cdot HCl$$

We found that dialkyl *N*-arylsulfonylphosphoramidates can be obtained in satisfactory yields by the following reaction:



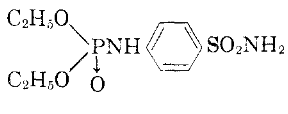
$$ArSO_2NHNa + Cl\underset{O}{\underset{\downarrow}{P}}(OR)_2 \longrightarrow ArSO_2NH\underset{O}{\underset{\downarrow}{P}}(OR)_2 + NaCl$$

The condensation of arylsulfonamide-sodium and dialkylphosphorochloridate is carried out at elevated temperatures in an inert solvent. The dialkyl arylsulfonylphosphoramidates formed are crystalline compounds, which must be isolated from oily by-products. They behave as monobasic acids which can be titrated with 0.1*N* alkali solution. The presence of one H atom attached to the nitrogen atom is responsible for the acid character. They dissolve also in sodium bicarbonate solution evolving carbon dioxide. Addition of dilute hydrochloric acid to the alkaline solution reprecipitates the arylsulfonyl phosphates unchanged. The alkali salts of dialkyl arylsulfonylphosphoramidates can be isolated from the aqueous solution by evaporation at room temperature. Most of them are crystalline, nonhygroscopic, and stable when exposed to air. These salts show considerable stability when heated in alkaline solution over a long period. They are suitable as starting materials for further reactions with halogen-containing compounds.

The stability of diethyl *N*-arylsulfonyl phosphoramidates in acid solution seems to be remarkable. Thus diethyl *N*-*p*-nitrophenylsulfonylphosphoramidate may be crystallized from hot concentrated hydrochloric acid without change. However, prolonged boiling in acid solution gave *p*-nitrophenylsulfonamide as a product of hydrolysis. In general, diethyl *N*-arylsulfonylphosphoramidates are hydrolyzed almost quantitatively to the corresponding arylsulfonamide and ethyl phosphate when heated for 20 hr. in 2*N* aqueous or 2*N* alcoholic–aqueous mineral acid.

The following diethyl *N*-arylsulfonylphosphoramidates (I–IV), listed in Table I, were prepared by the condensation between the sodium salt of the corresponding arylsulfonamide and diethylphosphorochloridate.

Compound V, diethyl *N*-sulfanilylphosphoramidate was obtained by catalytic hydrogenation of diethyl *N*-*p*-nitrophenylsulfonylphosphoramidate (IV) with platinum dioxide in 100% yield. This is a new type of a phosphorylated sulfanilamide. Only those with the phosphorus atom attached to the amine nitrogen of sulfanilamide



were reported earlier.[4]

In addition to the diethyl *N*-arylsulfonylphosphoramidates oily by-products, which could not be distilled or crystallized, were obtained. Free arylsulfonamide was also isolated in a yield which varied with the amount of oily by-products obtained. Analysis of the crude oily by-products suggests that these are compounds of the type:

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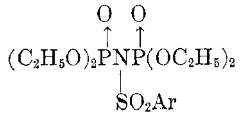
(1) This article is based on work performed in 1953 under project 116-B of the Ohio State University Research Foundation, sponsored by the Olin Mathieson Chemical Corp., Baltimore, Md. Patent applications are pending. Compounds described in this article have been subjected to pharmacological study and general screening tests as agricultural chemicals. Results will be published later.

(2) A. V. Kirsanov, V. I. Shevchenko. *Zhur. Obshchei. Khim*, **24**, 882 (1954).

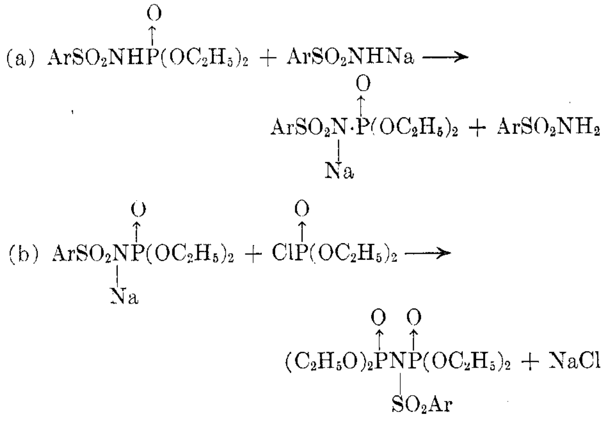
(3) B. C. Saunders, G. J. Stacey, F. Wild, I. G. E. Wilding, *J. Chem. Soc.*, 700 (1948).

(4) Brit. Patent **531,590**, Swiss Patent **206,549**, Ger. Patent **713,079**.



$\mathrm{(C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}\underset{\underset{SO_2Ar}{|}}{N}\overset{\overset{O}{\uparrow}}{P}(OC_2H_5)_2}$

A suggested mechanism for the formation of these compounds is as follows:



(a) $\mathrm{ArSO_2NH\overset{\overset{O}{\uparrow}}{P}(OC_2H_5)_2 + ArSO_2NHNa \longrightarrow ArSO_2\underset{\underset{Na}{|}}{N}\cdot\overset{\overset{O}{\uparrow}}{P}(OC_2H_5)_2 + ArSO_2NH_2}$

(b) $\mathrm{ArSO_2\underset{\underset{Na}{|}}{N}\overset{\overset{O}{\uparrow}}{P}(OC_2H_5)_2 + Cl\overset{\overset{O}{\uparrow}}{P}(OC_2H_5)_2 \longrightarrow (C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}\underset{\underset{SO_2Ar}{|}}{N}\overset{\overset{O}{\uparrow}}{P}(OC_2H_5)_2 + NaCl}$

Some of the formed diethyl *N*-arylsulfonylphosphoramidate reacts with unconverted arylsulfonamidesodium under formation of diethyl *N*-sodium-*N*-arylsulfonylphosphoramidate, which undergoes further phosphorylation by reacting with diethylphosphorochloridate. The final oily products are derivatives of the iminodiphosphoric acid.

The tetraethyl *N*-arylsulfonyliminodiphosphates are more water-soluble than the diethyl *N*-arylsulfonylphosphoramidates. Because of their structure they are unable to form salts and can be extracted with diethyl ether from alkaline aqueous solution. According to this fact the separation of crystalline and oily reaction products was possible.

EXPERIMENTAL[5]

Diethyl N-p-toluenesulfonylphosphoramidate. Dry *p*-toluenesulfonamide sodium salt (96.5 g. 0.5 mole) was suspended in 400 ml. of dry benzene and 86.25 g. (0.5 mole) of diethyl phosphorochloridate was added dropwise with stirring at 70°. The mixture was refluxed for 3 hr. and then cooled to 10°. A mixture of *p*-toluenesulfonamide and sodium chloride was removed by filtration. The benzene filtrate was washed twice with 50 ml. portions of water and dried over anhydrous sodium sulfate. The dried solution was filtered and the solvent distilled, leaving as residue 120 grams of an almost clear, colorless oil. Analysis showed that it was a mixture of approximately equal weights of diethyl *N*-*p*-toluenesulfonylphosphoramidate and tetraethyl *N*-*p*-toluenesulfonyliminodiphosphate. The oil was stirred at room temperature with saturated aqueous sodium hydrogen carbonate solution for 0.5 hr. and extracted with ether to remove the iminodiphosphate. Acidifying the aqueous portion with dilute hydrochloric acid liberated 35 g. of an almost colorless oil which crystallized upon standing for several weeks. The product melts at 104° after recrystallization from carbon tetrachloride or water.

Tetraethyl N-p-toluenesulfonyliminodiphosphate was isolated as a crude product by drying the ether extract with sodium sulfate and removing the solvent by distillation. The residual nearly colorless oil did not crystallize and could not be purified by distillation in 0.1 mm. vacuum.

Anal. Calcd. for $C_{15}H_{27}NO_8P_2S$: N, 3.16, P, 13.99. Found: N, 3.01, P, 12.90.

Diethyl N-phenylsulfonylphosphoramidate. Dry sodium salt of benzene sulfonamide (17.9 g., 0.100 mole) was dispersed in 200 cc. absolute benzene and diethyl phosphorochloridate (17.25 g., 0.100 mole) was added dropwise with stirring at 50° within 1 hr. The mixture was refluxed for 4 hr. After standing overnight a mixture of 5.7 g. NaCl and 4.3 g. benzenesulfonamide was filtered off. The benzene in the filtrate was removed by vacuum distillation and from the remaining oily residue diethyl-*N*-phenylsulfonylphosphoramidate, m.p. 111/112° from CCl_4, was separated from noncrystalline oily by-products with the aid of the above described procedure. Yield 40%.

Diethyl N-p-chlorophenylsulfonylphosphoramidate. Finely powdered *p*-chlorobenzenesulfonamide sodium salt (21.35 g., 0.1 mole) was suspended in 300 ml. of anhydrous benzene. During a period of 40 min., 17.25 g. (0.1 mole) of diethyl phosphorochloridate was added dropwise with stirring. The reaction temperature was maintained at 60–80°. After complete addition of the phosphorochloridate, the mixture was refluxed for 4 hr. and cooled. *p*-Chlorobenzenesulfonamide, m.p. 143°, together with sodium chloride was removed by filtration. From the filtrate the benzene was removed by vacuum distillation leaving 26 g. of an almost colorless oil. Separation from oily iminodiphosphate was possible by crystallization at 0° over a period of several weeks, filtering the crystals on a Buchner funnel with a sintered glass plate. More effective is the foregoing described separation method with $NaHCO_3$ solution. After recrystallization from an ethanol–petroleum ether mixture, colorless crystals, m.p. 141/142°, were obtained. Yield 18.4 g. = 56.3%.

Diethyl N-p-nitrophenylsulfonylphosphoramidate. To a suspension of 22.4 g. (0.1 mole) of finely divided carefully dried *p*-nitrobenzenesulfonamide sodium salt in 400 ml. of dry benzene was added 17.25 grams (0.1 mole) of diethyl phosphorochloridate. The mixture was refluxed for 4 hr. and filtered to give a mixture of sodium chloride and 5.1 grams of *p*-nitrobenzenesulfonamide. The solvent from the filtrate was removed by vacuum distillation to give 17 grams of a clear yellowish oil. On addition of 10 ml. ethyl ether to the oil, slightly yellowish crystals separated which were recrystallized from a mixture of ethanol and petroleum ether, m.p. 139°. Yield 9 g. = 36%. Diethyl *N*-*p*-nitrophenylsulfonylphosphoramidate is readily soluble in benzene, chloroform, dioxane, ethanol, and $NaHCO_3$ solution. From its alkaline solution it is recovered unchanged on acidification.

The ethereal filtrate from diethyl *N*-*p*-nitrophenylsulfonylphosphoramidate contains mainly tetraethyl *N*-*p*-nitrophenylsulfonyliminodiphosphate and to a minor extent diethyl *p*-nitrophenylsulfonylphosphoramidate. The latter can be removed by washing the etheral solution twice with 10 ml. saturated $NaHCO_3$ solution. After drying the solution with Na_2SO_4 the solvent was removed by distillation. The residue was a clear yellow oil. Yield 50%.

Anal. Calcd. for $C_{14}H_{24}N_2O_{10}P_2S$: P, 13.07. Found: P, 13.59.

Tetraethyl *N*-*p*-nitrophenylsulfonyliminodiphosphate was also prepared by condensation of diethyl *N*-sodium *N*-*p*-nitrophenylsulfonylphosphoramidate with diethyl phosphorochloridate:

Diethyl *N*-*p*-nitrophenylsulfonylphosphoramidate (1.016 g.) was dissolved in 3.01 ml. of 1.005*N* NaOH solution. After evaporation at room temperature over P_4O_{10} the slightly yellowish sodium salt of diethyl *N*-*p*-nitrophenylsulfonylphosphoramidate was obtained.

Anal. Calcd. for $C_{10}H_{14}NaN_2O_7PS$: P, 8.62. Found: P 9.00.

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(5) All melting points are determined with the Fisher-Johns apparatus. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn. and Spang Microanalytical Laboratory, Ann Arbor, Mich.

TABLE I

	Compound	Empirical and Structural Formula	M.P. °C.	ANALYSES Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found	Phosphorus Calcd.	Phosphorus Found	Chlorine Calcd.	Chlorine Found
I	Diethyl *N*-phenylsulfonylphosphoramidate	$C_6H_5SO_2NH\underset{\underset{O}{\downarrow}}{P}(OC_2H_5)_2$ $C_{10}H_{16}NO_5PS$	111/112	40.93	40.99	5.49	5.45	4.78	4.71	10.93	10.93	10.58	10.58		
II	Diethyl *N*-*p*-tolylsulfonylphosphoramidate	$p\text{-}CH_3C_6H_4SO_2NH\underset{\underset{O}{\downarrow}}{P}(OC_2H_5)_2$ $C_{11}H_{18}NO_5PS$	104	42.96	42.53	5.90	6.04	4.56	4.71	10.44	10.16	10.10	10.07		
III	Diethyl *N*-*p*-chlorophenylsulfonylphosphoramidate	$p\text{-}ClC_6H_4SO_2NH\underset{\underset{O}{\downarrow}}{P}(OC_2H_5)_2$ $C_{10}H_{15}NO_5PSCl$	141/142	36.62	35.92	4.61	4.44	4.28	4.33	9.78	10.16	9.47	9.13	10.82	10.53
IV	Diethyl *N*-*p*-nitrophenylsulfonylphosphoramidate	$p\text{-}NO_2C_6H_4SO_2NH\underset{\underset{O}{\downarrow}}{P}(OC_2H_5)_2$ $C_{10}H_{15}N_2O_7PS$	139	35.48	35.51	4.47	4.78	8.28	8.28	9.48	9.57	9.17	9.10		
V	Diethyl *N*-sulfanilylphosphoramidate	$p\text{-}NH_2C_6H_4SO_2NH\underset{\underset{O}{\downarrow}}{P}(OC_2H_5)_2$ $C_{10}H_{17}N_2O_5PS$	157.5/ 158.5	38.93	39.05	5.56	5.63	9.09	8.94	10.40	9.77	10.06	9.91		

From the listed compounds, I and II were also prepared by A. V. Kirsanov and V. I. Shevchenko.[2] The melting points given by the Russian authors are in perfect agreement with our observations.

This sodium salt (0.856 g.) was suspended in 15 ml. dry benzene and 0.41 g. diethyl phosphorochloridate added. After 2 hr. refluxing, the formed NaCl was filtered off and the solvent removed by distillation in vacuum. The oily residue was maintained for 1 hr. under 1 mm. at 90°, whereby 0.8 g. of a clear yellow undistillable oil remained.

Anal. Calcd. for $C_{14}H_{24}N_2O_{10}P_2S$: N, 5.91, P, 13.07. Found: N, 5.59, P, 14.09.

Stability of diethyl N-p-nitrophenylsulfonylphosphoramidate against hydrolysis. Diethyl *N*-*p*-nitrophenylsulfonylphosphoramidate (0.152 g.) and 5 ml. 1*N* HCl were refluxed for 2 hr. Concentration in vacuum at 25° followed by cooling and filtering gave a mixture of 40% *p*-nitrobenzenesulfonamide and 60% unsaponified ester. Separation of both compounds was achieved by addition of 1*N* NaOH to the solids until the *p*H was 8.5. The undissolved sulfonamide was removed by filtration, the dissolved sulfonylphosphoramidate reprecipitated from the filtrate by acidifying with concentrated mineral acid.

Diethyl *N*-*p*-nitrophenylsulfonylphosphoramidate (0.152 g.) and 5 ml. 1*N* HCl refluxed for 24 hr. gave *p*-nitrobenzenesulfonamide, m.p. 178°, in almost 90% yield.

No saponification occurred when a solution of 0.1203 g. of diethyl *p*-nitrophenylsulfonylphosphoramidate in 0.75 ml. of 1*N* sodium hydroxide (*p*H 12.0) was heated for 96 hr. at 50°.

Diethyl N-sulfanilylphosphoramidate. A solution of 10 grams diethyl *N*-*p*-nitrophenylsulfonylphosphoramidate was dissolved in 125 ml. of absolute ethanol and 1.4 grams of platinum dioxide was added. The solution was hydrogenated at 30° and 745 mm. pressure. The theoretical quantity of hydrogen was absorbed within 30 min. The catalyst was removed by filtration and the solvent by distillation in vacuum. The solid residue was recrystallized by dissolving it in acetone and adding benzene until the solution became turbid. On standing, an almost colorless powder, m.p. 157.5–158.5°, crystallized. This compound is insoluble in CCl_4, ethyl acetate, benzene, $CHCl_3$, diethyl ether, but is readily soluble in dioxane, acetone, glacial acetic acid, dimethylformamide, methanol, ethanol, water, and pyridine.

Anal. Calcd. for $C_{10}H_{17}N_2O_5PS$: N, 9.09, P, 10.06, S, 10.40. Found: N, 8.94, P, 9.91, S, 9.77.

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Columbus 10, Ohio