Communications TO THE EDITOR

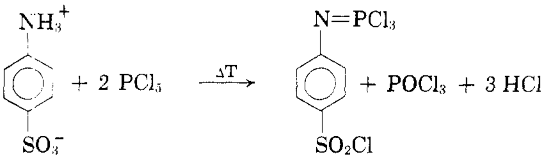
A New Synthesis of Sulfanilamides

Sir:

Sulfanilic acid is the logical starting material for the synthesis of sulfanilamides, but the known[1,2] methods for this conversion are hardly satisfactory. An experimentally simple method will now be described.

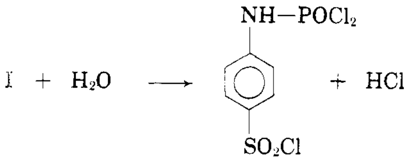
N-(*p*-Chlorosulfonylphenyl)phosphoramidic dichloride (II), obtained by Laar[3] in unspecified yield from the reaction of potassium sulfanilate and phosphorus pentachloride, serves as intermediate in this synthesis. II has now been prepared in practically quantitative yield by heating sulfanilic acid with at least two molar equivalents of phosphorus pentachloride with or without a diluent (such as phosphorus oxychloride, phosphorus trichloride, or carbon tetrachloride) and finally pouring the reaction mixture onto ice. The preparation proceeds according to equations A and B.

(A)



I

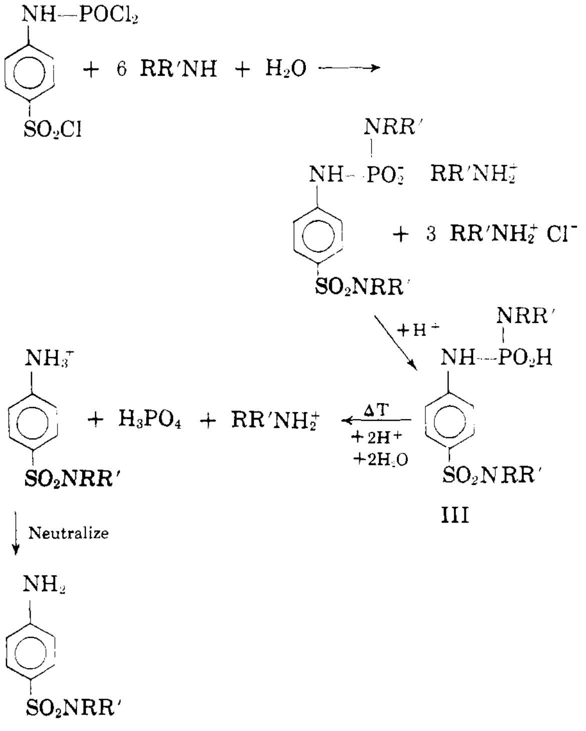
(B)



II

This reaction sequence was proved by the isolation of N-(*p*-chlorosulfonylphenyl)phosphorimidic trichloride (I). Phosphorus oxychloride and excess phosphorus pentachloride were removed by heating under reduced pressure from a reaction mixture containing no diluent (final temperature of bath: 140°; final pressure: 7 mm.). The residue was analytically pure I, m.p. 108–111°. Calc'd for $C_6H_4Cl_4NO_2PS$: C, 22.04; H, 1.23; Cl, 43.38; N, 4.28; P, 9.47; S, 9.80. Found:[4] C, 22.24; H, 1.43; Cl, 43.57; N, 4.36; P, 9.44; S, 9.95. I, being very sensitive to moisture, required handling in a dry box. Substances containing the phosphorimidic trichloride group are generally highly reactive towards water.[5,6]

II was ordinarily used for the synthesis of sulfanilamides immediately after filtration from water and without drying. II is gradually decomposed on standing with water. In one instance II was purified by drying *in vacuo* over potassium hydroxide and recrystallizing twice from boiling toluene. M.p. 155°. Calc'd for $C_6H_5Cl_3NO_3PS$: C, 23.36; H, 1.63; Cl, 34.48; N, 4.54; P, 10.04; S, 10.39. Found: C, 23.23; H, 1.95; Cl, 33.70; N, 4.54; P, 10.48; S, 9.98.



III

IV

(a) $R = R' = H$
(b) $R = H, R' = CH_3$
(c) $R = R' = CH_3$
(d) $R = R' = C_2H_5$
(e) R = H, R' = Cyclohexyl
(f) R = H, R' = Benzyl
(g) R = H, R' = Phenyl
(h) R = H, R' = *2*-Pyridyl (sulfapyridine)
(i) $R = H, R' = H_2N—C{=}NH$ (sulfaguanidine)

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(1) P. Gelmo, *J. prakt. Chem.*, [2], **77**, 369 (1908).

(2) B. P. H. Wiesner and E. Katscher, British Patent 536,216 (May 7, 1941) [*Chem. Abstr.*, **36**, 1332 (1942)]; U. S. Patent 2,284,461 (May 26, 1942) [*Chem. Abstr.*, **36**, 6755 (1942)].

(3) C. Laar, *J. prakt. Chem.*, [2], **20**, 250 (1879).

(4) The analyses in this paper are by W. Manser, E. T. H., Zurich, Switzerland, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(5) J. E. Gilpin, *Am. Chem. J.*, **19**, 354 (1897).

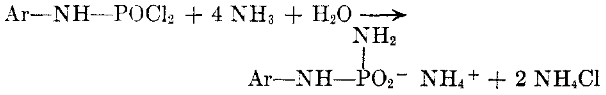
(6) A. V. Kirsanov and E. A. Abrazhanova, *Sbornik Stateĭ Obshcheĭ Khim.*, **2**, 1048 (1953) [*Chem. Abstr.*, **49**, 3052 (1955)]; A. V. Kirsanov and V. P. Molosnova, *Zhur. Obshcheĭ Khim.*, **25**, 772 (1955); A. V. Kirsanov and R. G. Makitra, *Zhur. Obshcheĭ Khim.*, **26**, 905 (1956).

Sulfanilamides IVa–i were prepared by the following procedure, with minor modifications in individual cases. II was allowed to react with at least six equivalents of ammonia or of a primary or secondary amine in the presence of water. Since ammonia or the amine also serves as acceptor for the acid liberated in the reaction, it may be partially replaced by an inorganic base (such as sodium carbonate or sodium bicarbonate) or by a tertiary amine. After the initial reaction had subsided, heat was usually applied. The reaction mixture then was acidified and briefly warmed. On neutralization the sulfanilamide precipitated. The approximate yields, based on sulfanilic acid, obtained in our experiments are as follows: 70% for IVa and IVb, 60% for IVf, 50% for IVc, IVd and IVg, 30% for IVe, IVh and IVi. These yields do not include additional quantities of sulfanilamides obtainable by the hydrolysis of side-products which were formed in some of the reactions and are to be discussed later.

The formation of sulfanilamides is rationalized as proceeding by way of phosphorodiamidic acids (III).

The following facts support such a path:

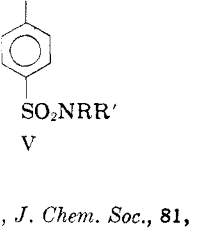
1. The —$POCl_2$ group of N-phenylphosphoramidic dichloride and of N-(*p*-chlorophenyl)phosphoramidic dichloride is partly amidated and partly hydrolyzed by aqueous ammonia.[7,8]



$$\mathrm{Ar{-}NH{-}POCl_2 + 4\,NH_3 + H_2O \longrightarrow Ar{-}NH{-}\overset{\displaystyle NH_2}{\overset{|}{P}}O_2^-\ NH_4^+ + 2\,NH_4Cl}$$

2. Phosphorodiamidic acids, while stable to alkali, undergo acid hydrolysis very readily.[9] The free phosphate content of our reaction mixtures increased greatly during the acid treatment. No sulfanilamides were isolated when the reaction mixtures were neutralized without prior acid treatment. Phosphoric triamides, frequently obtained as side-products (see below), are only difficultly hydrolyzable by acid or alkali.

Some of the reactions yielded acid-insoluble side-products which were removable just before the final neutralization. They were phosphoric triamides (V) resulting from complete amidation of II.



V

Vd. R = R′ = C_2H_5. M.p. 152–153°. Calc'd for $C_{18}H_{35}N_4O_3PS$: C, 51.65; H, 8.43; N, 13.39; P, 7.40 S, 7.66. Found: C, 51.32; H, 8.59; N, 13.76; P 7.49; S, 7.54.

Ve. R = H, R′ = cyclohexyl. M.p. 205°. Calc'd for $C_{24}H_{41}N_4O_3PS$: C, 58.04; H, 8.32; N, 11.28; P, 6.24; S, 6.46. Found: C, 58.37; H, 8.08; N, 11.18; P, 6.08; S, 6.43.

Vf. R = H. R′ = benzyl. M.p. 179°. Calc'd for $C_{27}H_{29}N_4O_3PS$: C, 62.29; H, 5.62; N, 10.76; P, 5.91; S, 6.16. Found: C, 62.11; H, 5.47; N, 10.91; P, 6.09; S, 6.12.

Vg. R = H, R′ = phenyl. M.p. 257° (dec.). Calc'd for $C_{24}H_{23}N_4O_3PS$: C, 60.24; H, 4.84; N, 11.71; P, 6.47; S, 6.70. Found: C, 60.05; H, 4.86; N, 11.57; P, 6.38; S, 6.75.

Compounds of type V could be converted to the corresponding sulfanilamides by acid or alkaline hydrolysis under vigorous conditions. The sulfonamide group is thus more resistant to hydrolysis than is the phosphoric triamide group.

Phosphoric triamides in general are converted by alkaline hydrolysis to phosphorodiamidates, *i.e.*, only one P—N bond is cleaved, further hydrolytic break-down requiring a mild treatment with acid.[10] There are two ways in which the phosphoric triamide group of V can be cleaved by alkali. It appears that both possible modes of alkaline cleavage occur side by side, since a quantity of the corresponding sulfanilamide (IV) is obtained without acid treatment and an additional quantity after acid treatment.

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(7) R. M. Caven, *J. Chem. Soc.*, **81**, 1367 (1902).

(8) K. Rorig, *J. Am. Chem. Soc.*, **71**, 3561 (1949).

(9) A. Michaelis and H. v. Soden, *Ann.*, **229**, 339 (1885).

(10) T. I. Bieber and H. M. Gladstone, to be published.

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Mercury Derivatives of Fluorocarbon Carboxylic Acid Amides

Sir:

We have found that mercury derivatives of fluorocarbon carboxylic acid amides can be prepared readily by heating a small amount of the amide with an excess of red mercuric oxide to 150–170° for about five minutes. The mixture then is cooled, 10 ml. of 95% ethanol is added, and the

TABLE I

MERCURY DERIVATIVES OF FLUOROCARBON AMIDES

$(RCONH)_2Hg$ R	M.P., °C.	Mercury, % Theory	Mercury, % Found	Nitrogen, % Theory	Nitrogen, % Found
CF_3—	219	47.17	47.05	6.60	6.67
CF_3CF_2—	244	38.16	37.92	5.34	5.44
$CF_3CF_2CF_2$—	286	32.05	31.88	4.48	4.59