[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY OF WESTERN RESERVE UNIVERSITY]

Thiophosphoric Amides: Aminolysis

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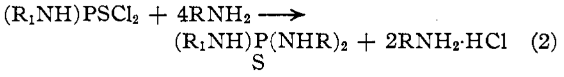
Mixed thiophosphoric triamides of the type $(RNH)_2PS(NHR_1)$ where R is an aromatic radical and R_1 an aliphatic radical have been prepared by Michaelis[1] by the stepwise aminolysis of thiophosphoryl chloride

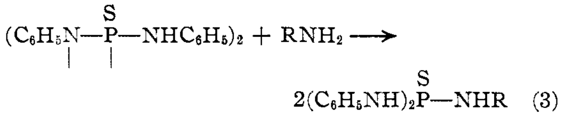
$$2R_1NH_2 + PSCl_3 \longrightarrow (R_1NH)PSCl_2 + R_1NH_2{\cdot}HCl \quad (1)$$



$$(R_1NH)PSCl_2 + 4RNH_2 \longrightarrow (R_1NH)\overset{S}{P}(NHR)_2 + 2RNH_2{\cdot}HCl \quad (2)$$

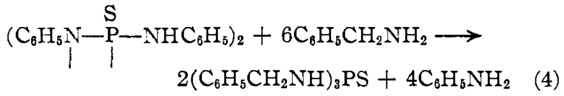
Michaelis could not use this method to prepare mixed triamides in which both radicals were aromatic since the intermediate, $RNHPSCl_2$, lost hydrogen chloride to give $RN{=}PSCl$.

A new approach to the preparation of mixed thiophosphoric triamides was suggested by the addition of aniline to dimeric thiophosphoric anil anilide.[2] The addition of amines to dimeric thiophosphoric anil anilide could yield mixed thiophosphoric triamides



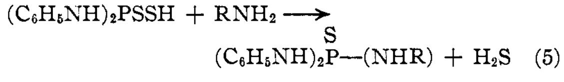
$$(C_6H_5N\text{—}\overset{S}{P}\text{—}NHC_6H_5)_2 + RNH_2 \longrightarrow 2(C_6H_5NH)_2\overset{S}{P}\text{—}NHR \quad (3)$$

When RNH_2 in equation (3) was benzylamine, in excess, the product at temperatures of 30 and 60° was a mixture containing triamides of both benzylamine and aniline. No pure mixed triamide could be isolated. When the reaction temperature was raised to 130° tribenzylthiophosphoric amide was isolated in good yield. This product could have formed only through the addition of benzylamine to dimeric thiophosphoric anil anilide and the replacement of aniline by benzylamine



$$(C_6H_5N\text{—}\overset{S}{P}\text{—}NHC_6H_5)_2 + 6C_6H_5CH_2NH_2 \longrightarrow 2(C_6H_5CH_2NH)_3PS + 4C_6H_5NH_2 \quad (4)$$

A second approach to the preparation of mixed thiophosphoric triamides appeared to be possible through the reaction of dithiophosphoric dianilide with amines according to the equation



$$(C_6H_5NH)_2PSSH + RNH_2 \longrightarrow (C_6H_5NH)_2\overset{S}{P}\text{—}(NHR) + H_2S \quad (5)$$

This reaction has already been carried out with aniline to give thiophosphoric trianilide. When dithiophosphoric dianilide was treated with benzylamine, tribenzyl thiophosphoric amide rather than a mixed triamide was obtained. Tribenzylthiophosphoric amide must have resulted from the concurrent formation of a mixed triamide by loss of hydrogen sulfide between dithiophosphoric dianilide and benzylamine and displacement of aniline by benzylamine

$$(C_6H_5NH)_2PSSH + 3C_6H_5CH_2NH_2 \longrightarrow (C_6H_5CH_2NH)_3PS + 2C_6H_5NH_2 + H_2S \quad (6)$$

The displacement of aniline by benzylamine with the formation of benzylamine triamide in each of these cases suggested the possibility of a similar reaction occurring also with a triamide. The reaction of triamides with primary aliphatic amines and with primary aromatic amines was therefore studied. This reaction could lead to mixed triamides $(RNH)_2\overset{S}{P}(NHR')$ and $(RNH)\overset{S}{P}(NHR')_2$ by partial displacement or to $(RNH)_3PS$ by complete displacement. The results of this study are shown in Table I.

The reaction of thiophosphoric trianilide with tributylamine and with dimethylaniline was tried to determine the effect of tertiary amines, which could not enter into displacement reactions.

When thiophosphoric trianilide was heated at 130° in a large excess of tributylamine, hydrogen sulfide was continuously evolved for twenty hours. Aniline and the phosphate ion were identified as decomposition products. Dimethylaniline promoted a similar decomposition, but required a much longer reaction time. In neither case could any thiophosphoric trianilide be recovered.

It is apparent that this decomposition not only resulted in the rupture of nitrogen–phosphorus bonds, but that the rate at which these bonds were broken was related to the basicity of the tertiary amine used. It would follow that thiophosphoric triamides heated in excess primary aliphatic or aromatic amines would have nitrogen-phosphorus bonds severed in an analogous fashion. In this case, however, a new triamide could form from the excess amine present. Thus is it possible that displacement reactions involving primary amines and thiophosphoric triamides with primary amine residues attached to phosphorus be expressed as a mobile equilibrium

$$(RNH)_3PS + 3R'NH_2 \longleftrightarrow (R'NH)_3PS + 3RNH_2 \quad (7)$$

The position of equilibrium would depend upon the relative stability of the phosphorus–nitrogen bond of the two triamides. The relative rates at which tertiary amines decomposed thiophosphoric acid trianilide indicated that the aliphatic amines would sever nitrogen–phosphorus bonds more rapidly than the less basic aromatic amines. It would follow in equation (7), that the nitrogen–phosphorus bonds of an aliphatic amine would be more stable than that of an aromatic amine. Under the conditions used with the triamides of primary

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(1) Michaelis, *Ann.*, **326**, 129–258 (1903).

(2) Buck, Bartleson and Lankelma, THIS JOURNAL, **70**, 744 (1948).

TABLE I

	Triamide $(RNH)_3PS$	Amine	Temp., °C.	Time, hr.	Product
1	$(C_6H_5NH)_3PS$	$C_6H_5CH_2NH_2$	30–60	2	No reaction
2	$(C_6H_5NH)_3PS$	$C_6H_5CH_2NH_2$	*130*	*2*	*A mixture of triamides of aniline and benzylamine*
3	$(C_6H_5NH)_3PS$	$C_6H_5CH_2NH_2$	180	2	$(C_6H_5CH_2NH)_3PS$ 80% yield
4	$(n\text{-}C_3H_7NH)_3PS$	$C_6H_5CH_2NH_2$	150–160	4	$(C_6H_5CH_2NH)_3PS$ 84% yield
5	$(C_5H_{10}N)_3PS$[a]	$C_6H_5CH_2NH_2$	170	4	No reaction
6	$(C_6H_5NH)_3PS$	$p\text{-}ClC_6H_4NH_2$	130	2	A mixture of triamides of aniline and *p*-chloroaniline
7	$(C_6H_5NH)_3PS$	$p\text{-}ClC_6H_4NH_2$	180	2	$(p\text{-}ClC_2H_4NH)_3PS$ 40% yield
8	$(C_6H_5{\cdot}CH_2NH)_3PS$	$C_6H_5NH_2$	130 and 180		A mixture of triamides of benzylamine and aniline
9	$(n\text{-}C_3H_7NH)_3PS$	$C_6H_5NH_2$	180	8	$(C_6H_5NH)_3PS$, 40% yield
10	$(C_5H_{10}N)_3PS$[a]	$C_6H_5NH_2$	180	4	No reaction

[a] Piperidyl.

amines, the nitrogen–phosphorus bond of the triamide of a secondary amine, piperidine, was not severed by tertiary amines, either aliphatic or aromatic. Primary amines also would not be expected to sever these bonds under comparable reaction conditions. The establishment of an equilibrium and therefore displacement reactions could not occur. This was verified; Table I, number 5.

This equilibrium could also be shifted by mass action. This is shown by the reaction between thiophosphoric trianilide and benzylamine. Using a large excess of benzylamine, tribenzyl thiophosphoric amide was formed in high yield; Table I, number 3. The reverse displacement could not be accomplished under comparable reaction conditions. Since the boiling points of benzylamine and aniline lie close together, selective removal of the aniline could not be used to displace the equilibrium. However, this was accomplished by using tri-*n*-propylthiophosphoric amide. In this case the triamide with the weaker nitrogen–phosphorus bonds was formed due to the selective removal of the low boiling *n*-propylamine from the equilibrium mixture, Table I, number 9.

The displacement of aniline from thiophosphoric acid trianilide by *p*-chloroaniline, Table I, number 7, was accomplished by the addition of an excess of *p*-chloroaniline to the equilibrium mixture. The displacement of *n*-propylamine from tri-*n*-propylthiophosphoric amide by benzylamine, Table I, number 4, was accomplished with the use of excess benzylamine and the continuous removal of the low boiling *n*-propylamine displaced.

Experimental

Action of Benzylamine on Dimeric Thiophosphoric Anil Anilide.—Six grams of dimeric thiophosphoric acid anil anilide and 15 g. of benzylamine were heated at 180° for three hours. Crystallization of the product from alcohol gave 4 g. of tribenzyl thiophosphoric amide, m. p. 120–123°, a 44% yield. It was identified by a mixed melting point.

At a temperature of 30 and 60° a product melting at 70–80° was obtained. It could not be purified by crystallization from alcohol. It was shown to be a mixture of triamides by cleavage with acetic acid.[2] Acetanilide, benzylamine and phosphoric acid were identified in the cleavage products. At a temperature of 130° a 50% yield of the tribenzyl thiophosphoric amide was obtained.

Action of Benzylamine on Dithiophosphoric Dianilide.—Six grams of benzylamine and 5.6 g. of dithiophosphoric dianilide were heated to 140–150° for four hours. The product was washed with dilute hydrochloric acid and crystallized from alcohol; 1.5 g. of tribenzyl thiophosphoric amide melting at 123–125° was obtained. Aniline was identified in the acid washings by conversion to acetanilide.

Action of Tertiary Amines on Thiophosphoric Trianilide.—Three grams of thiophosphoric trianilide and 20 g. of tributylamine were heated at 130° in an atmosphere of nitrogen. The evolution of hydrogen sulfide was detectable for twenty hours. The mixture was made alkaline with sodium hydroxide solution and steam distilled. The distillate was extracted with ether and the amines recovered by evaporation of the ether. The aniline was separated and identified as the benzenesulfonamide. The aqueous solution from the steam distillation gave a strong test for phosphate ion with ammonium molybdate solution.

Action of Amines on Thiophosphoric Triamides.—The combinations of amine and triamide employed, with the reaction conditions and results, are shown in Table I. The triamides employed were prepared as follows: thiophosphoric acid trianilide from aniline and phosphorus pentasulfide[2]; tribenzyl, tri-*n*-propyl, and tripiperidyl thiophosphoric amides from the amine and thiophosphoryl chloride by the method of Michaelis[1] in yields of 57, 84 and 25%, respectively. The triamide formed in each case was identified by a mixed melting point and the displaced amine was identified as an acyl derivative. In two of the cases where a mixture of triamides was obtained, Table I, numbers 2 and 8, cleavage of the amides with acetic acid yielded a mixture of acetanilide and benzylamine.

Summary

The preparation of mixed thiophosphoric triamides by the addition of amines other than aniline to dimeric thiophosphoric anil anilide was prevented by aminolysis reactions. Similarly, the reaction of amines other than aniline with dithiophosphoric dianilide failed to yield mixed thiophosphoric triamides due to aminolysis reactions.

The primary amine thiophosphoric triamides underwent complete aminolysis reactions upon heating with other primary amines. The thiophosphoric triamide of the secondary amine, piperidine, did not undergo this reaction.

An interpretation of the aminolysis reactions has been presented.

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