JOURNAL OF THE
AMERICAN CHEMICAL SOCIETY

VOLUME 68 APRIL 10, 1946 NUMBER 4

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORY OF GENERAL ANILINE AND FILM CORPORATION]

Phosphazo Compounds and their Use in Preparing Amides

BY H. W. GRIMMEL, A. GUENTHER AND JACK F. MORGAN

A common method of preparing N-mono-substituted amides utilizes the reaction of primary amines with acyl chlorides. The latter compounds are often prepared by the interaction of a carboxylic acid and phosphorus trichloride. Early investigators found that the two steps could be combined successfully into one operation. A case in evidence is the preparation of anilides of 3-hydroxy-2-naphthoic acid. Patents dealing with compounds of this type usually list as syntheses the interaction of 3-hydroxy-2-naphthoyl chloride with an aromatic amine or the interaction of 3-hydroxy-2-naphthoic acid with an aromatic amine in the presence of phosphorus trichloride as condensing agent. The formation of amides by this combined process has long been assumed to proceed via the acid chloride. However, work carried out in this Laboratory casts doubt on this assumption. An alternate mechanism is proposed and data are given to substantiate it.

When phosphorus trichloride is added to a solution of a primary amine and a carboxylic acid in a non-polar solvent, such as toluene, the initial reaction consists primarily of interaction of the amine and the phosphorus trichloride to form a phosphazo[1] compound.

$$5RNH_2 + PCl_3 \longrightarrow RN{=}P{-}NHR^2 + 3RNH_2{\cdot}HCl \quad (1)$$

If heated, the phosphazo compound then reacts with the carboxylic acid as follows

$$R{-}N{=}P{-}NHR + 2RCOOH \longrightarrow 2RCONHR + HPO_2 \quad (2)$$

To verify the postulated mechanism, various primary amines were converted in toluene solution to their respective phosphazo compounds by reaction with phosphorus trichloride at temperatures of 20–115°. The phosphazo compounds were then allowed to react with carboxylic acids in boiling toluene and the resulting amides identified. Of twenty-five amines investigated, nineteen reacted successfully to form phosphazo compounds, which were in turn converted to N-substituted benzamides by subsequent reaction with benzoic acid. The results are summarized

TABLE I

N-SUBSTITUTED BENZAMIDES

	Amine used	Procedure[a] Phosphazo	Procedure[a] Amine	Crude product Yield, %	Crude product M. p., °C.
1	Aniline	1	5	85	161–162
2	*o*-Toluidine	1	5	72	143–144
3	*m*-Toluidine	1	6	80	120
4	*p*-Toluidine	1	6	50	154–156
5	*m*-Chloroaniline	1	5	75	114–116
6	*o*-Anisidine	1	6	76	61–63
7	*m*-Nitroaniline	2	5	70	156–157
8	*m*-Aminophenol	4	5	7	169–171
9	*p*-Aminodiphenylamine	3	7	30	159–160[c]
10	*m*-Phenylenediamine	1	7	11[c]	241–243[c]
11	*p*-Phenylenediamine	3	7	67	295–297
12	Benzidine	3	7	94	343–345[c]
13	4,4'-Diaminodiphenylmethane	3	7	20	246–247
14	*α*-Naphthylamine	1	5	39	157–159
15	Sulfanilic acid	2	7	90	.....
16	2-Aminopyridine	4[b]	7[b]	52	82–84
17	Cyclohexylamine	1	5	68[c]	148–149[c]
18	*n*-Butylamine	1	7	45[c]	41–42[c]
19	Dodecylamine	1	6	60	67–68
20	Dodecylamine	4	6	77[c]	66–67[c]

[a] Numbers refer to procedures given in the Experimental Section. [b] Pyridine was used as solvent. [c] Represents recrystallized material.

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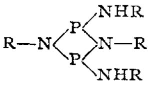
[1] The term phosphazo was first used by Michaelis and Schroeter [*Ber.*, **27**, 491–497 (1894)] in describing "*phosphazobenzolpiperidid,*" $C_6H_5N{=}P{-}NC_5H_{10}$ which they prepared by the condensation of "phosphazobenzolchloride" ($C_6H_5N{=}P{-}Cl$) and piperidine.

[2] The structure shown above perhaps should be written as



since molecular weight determinations show that these compounds exist as dimers in solution.

TABLE II

ANILIDES OF CARBOXYLIC ACIDS

	Acid used	Method[a] of isolation	Crude product Yield	M. p., °C.
1	Formic	5	Small	42
2	Acetic	5	74	113–114
3	Propionic	5	65^b	$107–108^b$
4	Lauric	5	74	77–78
5	Stearic	7	65^b	$97–98^b$
6	Cinnamic	5	80	148–150
7	Glycolic	7	49	$95–96^b$
8	Oxalic	5	45	248
9	Malonic	7	65^b	$226–227^b$
10	Succinic	7	41^b	$220–223^b$
11	Pimelic	5	53	154–156
12	Fumaric	7	34^b	$303–304^b$
13	Maleic	7	$16^{b,c}$	$199–200^b$
14	Tartaric	7	45	248–250
15	Benzoic	5	85	161–162
16	*p*-Nitrobenzoic	7	83	210–211
17	Salicylic	7	74	134
18	Anthranilic	5	42^b	$122–128^b$
19	Phthalic	5	73^d	205
20	Isophthalic	7	55^b	$279–281^b$
21	Terephthalic	7	25	333–334
22	3-Hydroxy-2-naphthoic	7	89–100	244–246
23	Nicotinic	5	38	124–126

[a] Numbers refer to procedures given in Experimental Section. [b] Represents recrystallized material. [c] Material isolated was maleanilic acid though the actual product of the reaction is probably maleanil which is readily hydrolyzed. [d] Product is phthalanil.

in Table I. That these results were not peculiar to benzoic acid was shown by successful preparation of anilides of twenty-two different mono- and di-carboxylic acids of the aliphatic, aromatic and heterocyclic series. They are listed in Table II. Also the preparation of six miscellaneous amides is recorded in Table III.

TABLE III

MISCELLANEOUS AMIDES

No.	Amide prepared	Procedure Phosphazo	Amide	Crude product Yield	M. p., °C.
1	*m*-Laurotoluide	1	6	88	$55–56^a$
2	*p*-Acetotoluide	1	7	58	146–148
3	3-Chloropropionanilide	1	7	77	$83–85^a$
4	N-Butylstearamide	1	6	60	
5	N-Octylpropionamide	4	6	73	$120–122^{a,b}$

[a] Represents purified material. [b] Represents boiling point at 1.5 mm.

Limitations of the Method: A. Amines.—When either *o*- or *p*-nitroaniline in toluene solution was treated with phosphorus trichloride and warmed a vigorous reaction took place and the nitroaniline was converted to a black tar. No such decomposition was encountered in the case of the more basic *meta* isomer. Neither *p*-aminoacetanilide nor 1-aminoanthraquinone appeared to form reactive phosphazo compounds under our experimental conditions. Also, aminocarboxylic acids cannot be converted to stable phosphazo compounds by the method outlined in the experimental section or by using pyridine as solvent. The carboxyl group is not protected by either of these solvents and is therefore available for reaction with any phosphazo compound as soon as it forms. However, the use of pyridine did make possible the formation of a stable phosphazo compound from sulfanilic acid which was

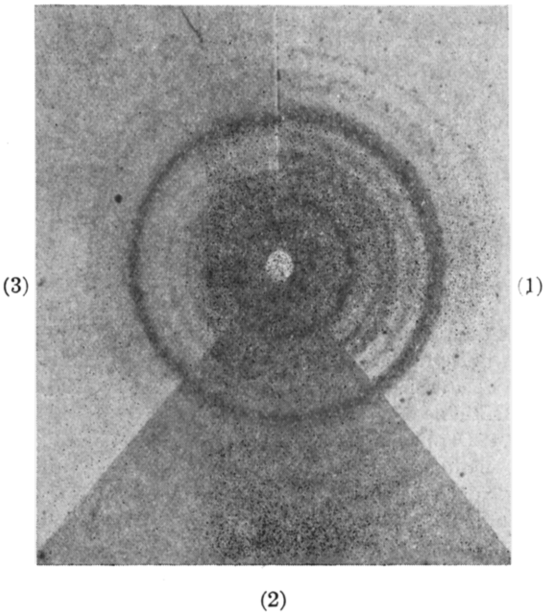


Fig. 1.—This composite pattern shows that samples 1 and 2 are identical. Recrystallization from chloroform caused a change from pattern 1 to pattern 3. This change could be produced by chloroform of crystallization, polymorphism or by chemical reaction.

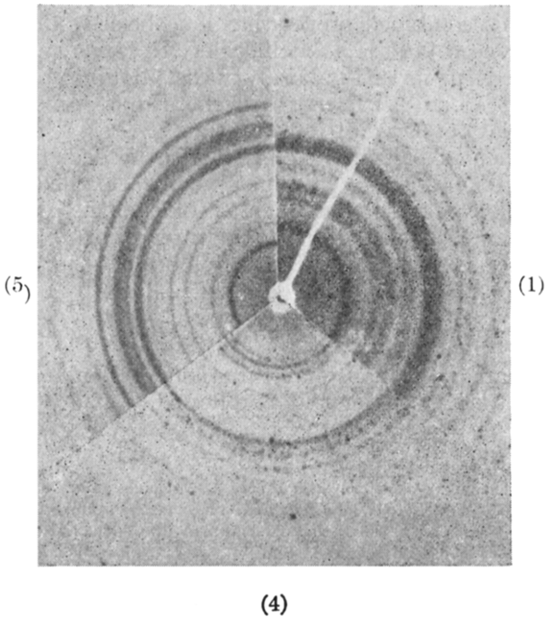


Fig. 2.—Patterns (1) and (5) have little in common and neither of these products appears to be contaminated by aniline phosphite (4) in more than negligible amounts.

converted to N-benzoylsulfanilic acid in 90% yield.

B. Acids.—A few organic acids failed to react with phosphazo compounds to form the expected amides. The aliphatic α-amino acids, glycine and *dl*-alanine, remained unchanged when treated with phenylphosphazoanilide at the temperature of boiling toluene. *p*-Aminobenzoic acid did, however, react with phenylphosphazoanilide but the product was an unidentified solid melting above 300°. In contrast to this, anthranilic acid yielded *o*-aminobenzanilide in 42% yield. Sodium salts of carboxylic acids do not react with phosphazo compounds, as evidenced by experiments with sodium benzoate and sodium 3-hydroxy-2-naphthoate. The method does not appear to be applicable to the synthesis of N-substituted sulfonamides. Treatment of phenylphosphazoanilide with *p*-chlorobenzenesulfonic acid produced none of the sulfonanilide.

When an excess of aniline was used in the initial reaction with phosphorus trichloride, ultimate yields of benzanilide were increased to 100% of the theoretical. By also using an excess of benzoic acid the yield of benzanilide was further increased to 115% based on phosphorus trichloride (equation 1). Since blank runs (omitting phosphorus trichloride) showed that aniline does not react with benzoic acid to form benzanilide when the two substances are heated for two hours in boiling toluene, it is probable that the increase (15%) is due to the presence of metaphosphorous acid.

It is also possible to prepare phosphazoanilides from phenylphosphazo chloride, $C_6H_5—N=P—Cl$,[3] though the method is less efficient and more tedious to carry out because the chloride is highly unstable with respect to moisture. In this Laboratory a small amount of phenylphosphazoanilide was prepared from phenylphosphazo chloride and aniline in boiling toluene solution. The product was identical in all respects with phenylphosphazoanilide prepared by the interaction of phosphorus trichloride and aniline. It was also found that phenylphosphazo chloride reacts with benzoic acid to yield benzanilide and benzoyl chloride as follows

$$C_6H_5—N=P—Cl + 2C_6H_5COOH \longrightarrow C_6H_5CONHC_6H_5 + C_6H_5COCl + HPO_2 \quad (3)$$

Experimental

General Procedure for Preparation of Phosphazo Compounds.—A 3-necked flask equipped with stirrer, reflux condenser and dropping funnel is mounted in an oil-bath. To the flask are added 2 moles of monoamine or 1 mole of diamine and 300–1200 ml. of toluene. Aliphatic amines and the simpler aromatic amines require no more than 300 ml. of solvent; more complex slightly soluble amines require more solvent to facilitate stirring and completion of the reaction in a reasonable time. The solution or suspension is stirred at room temperature (temperatures of 50–70° are advantageous for slightly soluble amines) and treated dropwise with a solution of 55 g. (0.4 mole) of phosphorus trichloride in 50 ml. of toluene. Separation of the amine hydrochloride usually takes place immediately, though long-chain aliphatic amine hydrochlorides are sufficiently soluble in toluene to prevent separation of the amine salt. The suspension is heated to the reflux temperature (oil-bath at 130°) and agitated for one to two hours to ensure completion of the reaction. Heating the reaction mixture is not essential except for slightly soluble amines.

From this point the procedure may be varied according to the relative solubilities of the particular amine salt and phosphazo compound. Four procedures are listed below and the one employed for each amine has been listed in Table I.

Procedure 1: For Soluble Phosphazo Compound and Insoluble Amine Hydrochloride.—The hot reaction mixture is filtered for quantitative removal of the amine hydrochloride. This precipitate is washed with hot toluene (300 ml.) and the combined filtrate and washings used directly for reaction with a carboxylic acid. In some cases the filtrate and washings may be evaporated to dryness at reduced pressure and the residue washed thoroughly with alcohol to obtain a relatively pure phosphazo compound.

Procedure 2: For Soluble Phosphazo Compound and Soluble Amine Hydrochloride.—Long-chain aliphatic amines fall in this class. A complete separation of the hydrochloride and phosphazo compound appears to be impractical. Therefore such toluene solutions are used directly in condensations with carboxylic acids.

Procedure 3: Both Products Insoluble.—The reaction mixture is filtered and the solid is washed with toluene and dried. The solid is ground in a mortar and extracted several times with cold water to remove all the amine hydrochloride. Traces of free amine are then removed from the remaining solid by similar extraction with cold alcohol. The remaining insoluble product is in some cases a relatively pure phosphazo compound.

Procedure 4: Both Products Insoluble.—The reaction mixture is used directly for reaction with a carboxylic acid.

Phenylphosphazoanilide.—This white crystalline solid was isolated as suggested in procedure 1 in a yield of 67.5%; m. p. 251–253°.

Anal. Calcd. for $C_{12}H_{11}N_2P$: C, 67.27; H, 5.17; N, 13.08. Found: C, 67.54; H, 4.99; N, 13.11. Molecular weight in dioxane by the freezing point depression method: Calcd. for dimer, $C_{24}H_{22}N_4P_2$: 428.5. Found: 420 (average).

4,4′-Dimethylphenylphosphazoanilide.—This compound was isolated as suggested in procedure 1 in 42% yield; m. p. 197–200° (preheated bath).

Anal. Calcd. for $C_{14}H_{15}N_2P$: C, 69.39; H, 6.24; N, 11.56. Found: C, 69.28; H, 5.98; N, 11.18.

2,2′-Dimethoxyphenylphosphazoanilide.—The pure compound was isolated as suggested in procedure 1 in 32% yield; m. p. 138–140°.

Anal. Calcd. for $C_{14}H_{15}N_2O_2P$: C, 61.30; H, 5.51; N, 10.21. Found: C, 61.26; H, 5.64; N, 10.12. Molecular weight in bromoform by freezing point depression method: Calcd. for dimer, $C_{28}H_{30}N_4O_4P_2$: 548.6. Found: 534 (average).

General Properties of Aromatic Phosphazo Compounds.—The three phosphazo compounds listed above are soluble in toluene, xylene, chloroform and aniline; somewhat soluble in benzene, very slightly soluble in alcohol or acetone; insoluble in water or petroleum ether. Phenylphosphazoanilide is readily recrystallized from chloroform but the resultant crystals are not identical with the origi-

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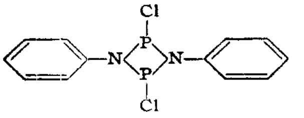
[3] This compound may have the structure



which agrees with molecular weight determinations made by Michaelis and Schroeter (ref. 1).

nal as shown by X-ray diffraction patterns. Prolonged exposure to light or heat (100° or above) causes slow decomposition though the compounds are stable for months at room temperature in the dark. Phosphazo compounds are hydrolyzed very slowly by water or dilute alkalies but the reaction is rapid in warm dilute acids.

$$R—N{=}P—NHR + 2HCl + 3H_2O \longrightarrow 2RNH_2{\cdot}HCl + H_3PO_3$$

General Procedure for Preparation of Amides.—A 3-necked flask equipped with stirrer and reflux condenser is mounted in an oil-bath. To the flask is added 0.2 mole of a monocarboxylic acid or 0.1 mole of a dicarboxylic acid and a phosphazo compound (equivalent to 0.2 mole of a monoamine or 0.1 mole of a diamine) dissolved in 150–200 ml. of toluene. This mixture is stirred, heated to boiling (oil-bath at 130°) and agitation continued at this temperature for two hours. The reaction proceeds readily at the reflux temperature with the separation of metaphosphorous acid (HPO_2) as an orange gummy precipitate. In most cases, the desired amide is soluble in the hot toluene and can be conveniently separated from the orange precipitate by decantation or filtration. The crude amide is then isolated by one of three methods, as follows.

Procedure 5.—Direct crystallization from the toluene on cooling.

Procedure 6.—Treatment with 150 ml. of a 20% solution of sodium carbonate and removal of the toluene by steam-distillation. If the amide is a solid, it is separated by filtration and washed with water; if a liquid, it is extracted with ether, the ether is then evaporated, and the residue is distilled at reduced pressure.

Procedure 7.—Procedure 6 is followed without first decanting the toluene from the orange precipitate.

If purification of the amide is desired, the product can be recrystallized from 95% alcohol, dilute alcohol or other suitable solvent. In many cases the crude products are sufficiently pure to render recrystallization unnecessary.

X-Ray Diffraction Patterns.—Diffraction patterns obtained from powdered samples of phenylphosphazoanilide and related products were made in order to characterize the pure powders and to prove identity of samples prepared by different procedures. A brief history of the material used for each pattern follows.

Pattern (1).—Phenylphosphazoanilide (m. p. 251–253°) prepared by the interaction of aniline and phosphorus trichloride.

Pattern (2).—Phenylphosphazoanilide (m. p. 248–253°) prepared from aniline and phenylphosphazo chloride, $C_6H_5N{=}P—Cl$.

Pattern (3).—Same material as used in pattern (1) but recrystallized from chloroform; hard, translucent crystals melting at somewhat lower temperature and with more pronounced decomposition than product (1).

Pattern (4).—Pure aniline phosphite, $C_6H_5NH_2{\cdot}H_3PO_3$; a hydrolysis product of phenylphosphazoanilide.

Pattern (5).—Hydrate of phenylphosphazoanilide, $(C_6H_5NH_2)POH$, previously described by Michaelis and Schroeter.

Summary

1. The interaction of carboxylic acids and primary amines in the presence of phosphorus trichloride to form N-substituted amides is given a new interpretation. An intermediate formation of phosphazo compounds is proposed and substantiated by experiment.

2. Phosphazo compounds of the general formula, R—N=P—NHR, are described for the first time. They are prepared by the interaction of phosphorus trichloride and primary amines in inert solvents such as toluene.

3. This new class of phosphazo compounds can be used to prepare N-substituted amides by treatment with carboxylic acids in boiling toluene.

Easton, Pennsylvania Received September 22, 1945

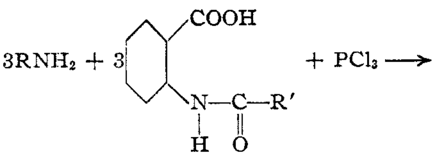
[Contribution from the Central Research Laboratory of General Aniline and Film Corporation]

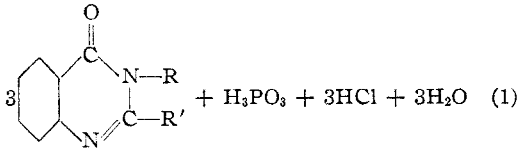
A New Synthesis of 4-Quinazolones

By H. W. Grimmel, A. Guenther and Jack F. Morgan

Methods previously employed to prepare 4-quinazolones include, among others, the heating of N-acylanthranilanilides at 200°[1] and the interaction of primary amines with the moisture sensitive acylanthranils at low temperatures.[2]

A new synthesis of 4-quinazolones has been found which allows the preparation of these compounds in one simple operation at moderate temperatures from stable starting materials. When primary amines are condensed with N-acylanthranilic acids in toluene or other suitable solvents with the aid of phosphorus trichloride, 4-quinazolones are formed, generally in good yields. This reaction is illustrated by the following equation.





It will be noted that, according to equation (1), the formation of three moles of quinazolone is accomplished by one mole of phosphorus trichloride whereas the employment of two moles of this condensing agent might normally have been expected for this condensation. Quinazolone yields were not increased when two moles of phosphorus trichloride were employed.

It was also found that 4-quinazolones could be prepared from organic phosphazo compounds.[3] For example, an 82% yield of 2-methyl-3-phenyl-4-quinazolone resulted from the interaction of phenylphosphazoanilide and N-acetylanthranilic acid in boiling toluene. This reaction may be illustrated as

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(1) Körner, *J. prakt. Chem.*, [2] **36**, 165 (1900).

(2) Original paper, Bogert and Chambers, This Journal, **27**, 649 (1905).

(3) H. W. Grimmel, A. Guenther and Jack F. Morgan, *ibid.*, **68**, 539 (1946).