Anal. Calcd. for $(C_6H_5)_2P(O)CH(OH)C_6H_5$: P, 10.0. Found: P, 9.9.

Further evaporation of the benzene filtrate gave 3.20 g. of an impure white solid, melting at 125–151°. No higher melting solid such as described by Conant was found.

Reduction of α-(Dibenzylphosphinyl)-benzyl Alcohol (IIIa) to Tribenzylphosphine Oxide. (1) Direct Reaction with Red Phosphorus and Hydriodic Acid.—A mixture of 4.60 g. (0.0137 mole) of IIIa, 100 ml. of glacial acetic acid, 60 ml. of 48.3% hydriodic acid and 0.60 g. of red phosphorus was refluxed for 41 hr. On cooling, the colorless solution was filtered and poured into 1800 ml. of water. Filtration yielded 3.65 g. of a yellowish solid melting at 181–185°. Recrystallization from 100 ml. of 2:1 aqueous alcohol containing 0.5 g. of potassium hydroxide gave 1.10 g. (35.0% yield) of white needles melting at 210–212°. One recrystallization from 1:1 aqueous alcohol yielded 0.95 g. of tribenzylphosphine oxide melting at 211.5–212.1°.

Anal. Calcd. for $(C_6H_5CH_2)_3PO$: P, 9.7. Found: P, 9.5.

This product failed to depress the melting point of an authentic sample as prepared by the addition of $POCl_3$ to benzylmagnesium chloride.[14]

Acidification of the alkaline filtrate gave 1.35 g. (40.1% yield) of dibenzylphosphinic acid as shiny white plates, melting at 188.5–189.5°.

Anal. Calcd. for $(C_6H_5CH_2)_2P(O)OH$: P, 12.6; neut. equiv., 246. Found: P, 12.5; neut. equiv., 246.

A sample of the acid did not depress the melting point of an authentic sample of dibenzylphosphinic acid prepared by the oxidation of Ia.[1]

(2) Stepwise Reaction. Chlorination and Reduction.—A mixture of 5.00 g. (0.0149 mole) of IIIa, 3.10 g. (0.0149 mole) of phosphorus pentachloride and 50 ml. of benzene was refluxed under nitrogen for 1 hr. The benzene was stripped off by heating at reduced pressure to 40°, leaving a crude yellowish solid which was used without purification. The solid was dissolved in 100 ml. of glacial acetic acid and refluxed for 8 hr. with 60 ml. of concentrated hydriodic acid and 0.60 g. of red phosphorus. The mixture was treated as before to yield 2.20 g. (46.0% yield) of tribenzylphosphine oxide and 1.25 g. (34.1% yield) of dibenzylphosphinic acid.

Cleavage Reactions of α-(Dibenzylphosphinyl)-benzyl Alcohol (IIIa). (1) Acid Cleavage.—A mixture of 2.05 g. (0.0061 mole) of IIIa, 10 ml. of concentrated hydrochloric acid, 10 ml. of water and 35 ml. of alcohol was refluxed under nitrogen for 9 hr. After cooling, the clear solution was poured into 150 ml. of water, and 1.65 g. of a white solid, melting at 157–159°, was obtained. Recrystallization from 1:1 aqueous alcohol gave 1.55 g., melting at 161.4–162.5°, which did not depress the melting point of IIIa. The acidic filtrate was treated with an aqueous solution of 2,4-dinitrophenylhydrazine hydrochloride to yield 0.30 g. of a yellow product, melting at 231–233°. This substance did not depress the melting point of an authentic sample of the 2,4-dinitrophenylhydrazone of benzaldehyde.

(2) Basic Cleavage. (a) Room Temperature.—A mixture of 2.00 g. of IIIa, 3.5 g. of sodium hydroxide, 8 ml. of water and 35 ml. of alcohol was allowed to stand at room temperature for 12 hr. The mixture was poured into 100 ml. of water to give, after recrystallization, 1.70 g. of IIIa (85% recovery).

(b) Reflux Temperature.—A similar mixture was refluxed under nitrogen for 12 hr. and poured into 150 ml. of water. Filtration of the cloudy solution yielded only 0.01 g. of an impure white solid. The filtrate was acidified with 15 ml. of concentrated hydrochloric acid to give 1.40 g. of white product melting at 178–185°. Two recrystallizations from 1:1 aqueous alcohol gave 0.98 g. (66% yield) of dibenzylphosphinic acid melting at 189.4–189.9°. Treatment of the acidic filtrate with aqueous 2,4-dinitrophenylhydrazine hydrochloride gave less than 0.01 g. of a yellow-brown solid melting at 201–223°.

Basic Cleavage of Other Adducts of Disubstituted Phosphine Oxides. α-(Diphenylphosphinyl)-benzyl Alcohol (IIIc).—A mixture of 5.15 g. (0.0167 mole) of IIIc, 10.0 g. of sodium hydroxide, 25 ml. of water and 100 ml. of alcohol was refluxed under nitrogen for 9 hr. The dark red reaction mixture was poured into 300 ml. of water, filtered and acidified to give 3.25 g. of a faint yellow solid melting at 185–187.5°. After six recrystallizations from 3:1 aqueous alcohol, 1.05 g. (28.9% yield) of diphenylphosphinic acid as long white needles was obtained melting at 188.5–189.0°. The literature[15] lists melting points of diphenylphosphinic acid ranging from 188–190° to 195–196°.

Anal. Calcd. for $(C_6H_5)_2P(O)OH$: P, 14.2; neut. equiv., 218. Found: P, 14.0; neut. equiv., 220.

2-Dibenzylphosphinyl-2-butanol.—A similar basic cleavage of 2-dibenzylphosphinyl-2-butanol resulted in a 59% yield of dibenzylphosphinic acid.

Reaction of Dibenzylphosphine Oxide and Benzaldehyde in Aqueous Alcoholic Base.—A mixture of 3.80 g. (0.0165 mole) of Ia, 1.80 g. (0.0169 mole) of benzaldehyde, 10.0 g. of sodium hydroxide, 20 ml. of water and 80 ml. of alcohol was refluxed for 12 hr. under nitrogen. After dilution with water, acidification and recrystallization, 2.45 g. (60.3% yield) of dibenzylphosphinic acid was obtained. Similar treatment of Ia in the absence of benzaldehyde resulted in the isolation of dibenzylphosphinic acid in 65.0% yield.

(14) R. Sauvage, *Compt. rend.*, **139**, 674 (1904).

(15) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 170.

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[CONTRIBUTION FROM THE BOUND BROOK LABORATORIES, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

The Use of Polyphosphoric Acid in the Synthesis of 2-Aryl- and 2-Alkyl-substituted Benzimidazoles, Benzoxazoles and Benzothiazoles[1]

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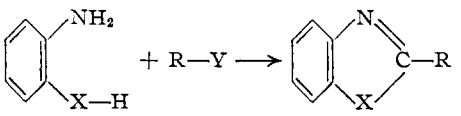
The formation of 2-aryl- and 2-alkyl-substituted benzimidazoles, benzoxazoles and benzothiazoles by the polyphosphoric acid-catalyzed condensation of a carboxylic acid, ester, amide or nitrile with an *o*-amino-, *o*-hydroxy- or *o*-mercapto-arylamine is described. The condensations proceed in good yield to give products which, in certain instances, are not readily attainable by conventional condensation techniques.

The utility of polyphosphoric acid as a remarkably effective condensing agent, particularly for intra- and intermolecular condensations, has been extensively demonstrated in recent years. Nothing has been reported, however, regarding its effectiveness in intermolecular condensations of the type found in the Phillips benzimidazole synthesis,[2] or in similar reactions leading to the benzoxazole and benzothiazole series (I). These condensations generally are carried out by thermal fusion, heating in solvents or in various concentrations of hydrochloric or sulfuric acid, or by heating under pressure in the presence of dilute hydrochloric acid.

(1) Presented at the Delaware Valley Regional Meeting, Philadelphia, Pa., February 16, 1956.

(2) J. B. Wright, *Chem. Revs.*, **48**, 406 (1951).

The Phillips benzimidazole synthesis, which involves heating the carboxylic acid with the *o*-phenylenediamine in aqueous hydrochloric acid, is thought to involve the formation of the monoacyl derivative of the free arylamine[3] followed by ring



I

X = NH, O, S
Y = COOH, COOR', $CONH_2$, CN
R = alkyl, aryl

closure involving dehydration,[4] and the catalytic action of dilute mineral acids has been established.[5] While conventional methods of condensation work well for the preparation of 2-alkyl-substituted derivatives, they frequently fail or give low yields in the preparation of certain 2-aryl-substituted compounds. For example, the Phillips synthesis of 2-phenylbenzimidazole gives only a trace yield of the desired product.[6] If the aqueous hydrochloric acid condensation is carried out in a sealed tube at 180°, however, the 2-phenylbenzimidazole may be obtained in high yield.[5] A few other 2-arylbenzimidazoles have been obtained in fair to poor yield by this method.[7] *o*-Diamines which are either more basic or less basic than *o*-phenylenediamine, such as the 4-chloro- or 4-methyl-*o*-phenylenediamines, react less readily with carboxylic acids in aqueous hydrochloric acid under pressure.[8] We have found that polyphosphoric acid is a highly effective, convenient, and very general catalyst for promoting condensations of this type, and also for promoting similar condensations leading to the benzoxazole and benzothiazole series. The reagent is especially valuable since high yields of products may be obtained without the use of elevated pressure.

It has been reported[9] that anthranilic acid gives only a dyestuff upon condensation with *o*-phenylenediamine, and our attempts to prepare 2-(*o*-aminophenyl)-benzimidazole in refluxing 50 and 70% sulfuric acids, in refluxing 85% orthophosphoric acid, or in anhydrous orthophosphoric acid at 250° were unsuccessful. Porai-Koshits and coworkers have also reported[7] that this condensation fails to take place under pressure, even with hydrochloric acid concentrations as high as 35%. The desired condensation product, 2-(*o*-aminophenyl)-benzimidazole (III), was obtained readily in 75% yield by the use of polyphosphoric acid at 250°.

The catalyst, which also serves as a suitable solvent for the reaction, is equally effective for the condensation of carboxylic acids, amides, esters or nitriles with aromatic diamines, *o*-aminophenols and *o*-aminothiophenols. The nature or position of inert substituents, such as chlorine or methyl, on the ring of the aromatic acids did not appear critical except for the fact that the presence of an *o*-nitro group resulted in the carbonization of the reaction mixture upon heating. The latter result, due to the oxidative effect of the nitro group at elevated temperatures, has also been encountered in other methods of condensation.[10] Arylamines having inert substituents such as chlorine also react satisfactorily, and heterocyclic or aliphatic acids may be employed as well as aromatic acids.

The condensation reaction involving aromatic carboxylic acids, or their derivatives, generally required temperatures of 200–250°. In the preparation of 2-(*o*-aminophenyl)-benzimidazole, raising the reaction temperature to 300° lowered the yield slightly (62%), while lowering the temperature to 175° led to the formation of a mixture consisting of considerable amounts of by-products and gave only a 21% yield of the benzimidazole. The preparation of 2-alkyl derivatives proceeds at much lower temperatures than 2-aryl derivatives.

In addition to the simplicity of the method and the high yields, the products are obtained in a higher state of purity than by conventional procedures since side reactions, such as sulfonation, which may occur to a considerable extent at the temperatures required for many of the condensations, are avoided.

Experimental

General.—The compounds were prepared by four general procedures which differed from each other only in the method of isolating the crude reaction product. The procedures are described below, and the data on the preparation of the compounds are summarized in Table I. Commercially available polyphosphoric acid (Victor Chemical Works) was employed in this investigation, and the reaction mixtures were protected from moist air by means of a calcium chloride drying tube and stirred mechanically.

Two of the compounds prepared, 2-*m*-tolylbenzimidazole (II) and 2-(*o*-aminophenyl)-benzothiazole (XIII), showed a considerable variation from the melting points ascribed to these structures in the literature.

Procedure A.—Equimolar amounts of *o*-phenylenediamine and the carboxylic acid (or its corresponding ester, amide or nitrile) were mixed with a sufficient quantity of polyphosphoric acid to give a stirrable paste. The mixture was heated slowly to 250°, and the resulting solution was stirred at 250° (±3°) for four hours, permitted to cool to about 100°, and poured in a thin stream into a large volume of rapidly stirred water. The insoluble residue was collected by filtration, washed with a small amount of water and reslurried in an excess of 10% sodium carbonate solution. The alkaline slurry was filtered and the product washed thoroughly with water and dried at 60°. The crude product was recrystallized from alcohol or an aqueous alcohol mixture subsequent to treatment with a small amount of activated charcoal.

The substitution of an *o*-aminophenol or an *o*-aminothiophenol for the *o*-phenylenediamine yielded the corresponding benzoxazole or benzothiazole, respectively. In general, a 0.2-mole quantity of the carboxylic acid (or its corresponding ester, amide or nitrile) was employed with about 10 to 20 parts by weight of polyphosphoric acid, and the reaction mixture was poured into two liters of water.

Procedure B.—The reaction was carried out as in procedure A except that the product, which was soluble in the strongly acid drowning mixture, was precipitated by treating the clarified drowning mixture with 50% sodium hydroxide solution until the slurry was alkaline to phenolphthalein indicator paper. During the basification ice was added as required to prevent an excessive rise in temperature, but the mixture was not cooled sufficiently to cause the precipitation

(3) M. A. Phillips, *J. Chem. Soc.*, 1409 (1930).

(4) C. H. Roeder and A. R. Day, *J. Org. Chem.*, **6**, 25 (1941).

(5) B. A. Porai-Koshits, O. F. Ginzburg and L. S. Efros, *Zhur. Obshchei Khim.*, **17**, 1768 (1947); *C. A.*, **42**, 5903c (1948).

(6) M. A. Phillips, *J. Chem. Soc.*, 2395 (1928).

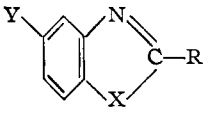
(7) B. A. Porai-Koshits and G. M. Kharkharova, *Zhur. Obshchei Khim.*, **25**, 2138 (1955).

(8) B. A. Porai-Koshits, O. F. Ginzburg and L. F. Efros, *ibid.*, **19**, 1545 (1949); *C. A.*, **44**, 1100b (1950).

(9) S. von Niementowski, *Ber.*, **30**, 3065 (1897).

(10) R. Walther and T. von Pulawski, *J. prakt. Chem.*, [2] **59**, 249 (1899).

TABLE I



No.	X	R	Y	Procedure[a]	Temp. °C.	Time hr.	Crude yield[g] %	Recryst.[h] yield %	M.p., °C (cor.)	Literature M.p., °C.	Ref.[n]	Ultraviolet absorption λmax, mμ	ε × 10⁻⁴
I	NH	Phenyl	H	A	175	2	95	81	294.5–295.5[i]	294	11	303	2.48
II	NH	*m*-Tolyl	H	A	250	3.5	99	85	217.0–219.0	112–113	20	304	2.45
III	NH	*o*-Aminophenyl	H	B	250	3.5	72	60	213.5–214.0	211	9	340, 292, 298, 251	1.20, 1.26, 1.27, 1.53
IV	NH	*o*-Chlorophenyl	H	B	250	4	90	51	231.4–232.9	234	12	292	1.43
V	NH	*o*-Hydroxyphenyl	H	C[b]	250	4	86	29	241.6–242.2	242	13	319	1.73
VI	NH	3,4-Dichlorophenyl	H	A	250	4	99	62	236.2–236.7[i]	...	..	312	2.78
VII	NH	3-Hydroxy-2-naphthyl	H	C[b]	250	4.5	37	13	301.0–304.0	305–308	14	332, 317	2.87, 2.88
VIII	NH	*o*-Carboxyphenyl	H	A[b,c]	250	4	111	58[i]	264.0–264.5[k]	277–278	15	297	1.31
IX	NH	β-Pyridyl	H	B	250	4	18	11	253.6–254.0	245	16	307	2.21
X	O	Phenyl	H	A	250	4	93	75	102.5–103.9	103	17	298	2.39
XI	O	Phenyl	Cl	C	250	4	52	30	101.1–102.1	...	..	305	2.37
XII	S	Phenyl	H	A	250	4	103	90	112.7–113.9[i]	115	18	298	1.86
XIII	S	*o*-Aminophenyl	H	A	250	4	81	52	126.7–127.7	156	21	304	2.30
XIV	NH	Phenyl	H	A[d]	250	4	100	69	293 –294[l]	294	11	..	..
XV	NH	Phenyl	H	A[e]	250	4	100	72	293 –294[l]	294	11	..	..
XVI	NH	Phenyl	H	A[f]	175	2	97	67	293 –294[l]	294	11	..	..
XVII	NH	Methyl	H	D	125	4	100	69	177.0–177.7[m]	175	19	281	0.74

[a] Product prepared from carboxylic acid unless otherwise noted; a 10% molar excess of *o*-phenylenediamine was employed in the preparation of II, IV, V, VI, VII, VIII, IX, XIV and XV. [b] Treatment with sodium carbonate omitted and product washed acid free with water and dried. [c] From phthalic anhydride. [d] From benzonitrile. [e] From benzamide. [f] From methyl benzoate. [g] The yields in many examples represent a single run and are not optimum values. [h] All crudes were recrystallized once from aqueous alcohol (*ca.* 70%) using activated charcoal unless otherwise noted. [i] The crude was twice purified by dissolution in 10% Na_2CO_3 solution, treating with activated charcoal and reprecipitation by acidification with dilute HCl; m.p. 261–262°. [j] Recrystallized twice from aqueous alcohol. [k] Recrystallized from absolute alcohol. [l] Uncorrected m.p.; mixed m.p. with authentic sample showed no depression. [m] Recrystallized from water. [n] Satisfactory microanalyses were obtained for each compound, I through XVII. The analytical data on those compounds for which no ascribed melting point could be found are given below. *Anal.* Calcd. $C_{14}H_{12}N_2$ (II): C, 80.7; H, 5.81; N, 13.4. Found: C, 80.5; H, 5.97; N, 13.2. Calcd. for $C_{13}H_8N_2Cl_2$ (VI): C, 59.4; H, 3.06; N, 10.6; Cl, 26.9. Found: C, 59.6; H, 3.26; N, 10.9; Cl, 27.0. Calcd. for $C_{13}H_8ONCl$ (XI): C, 67.9; H, 3.50; N, 6.08; Cl, 15.4. Found: C, 68.1; H, 3.94; N, 6.10; Cl, 15.1. Calcd. for $C_{13}H_{10}N_2S$ (XIII): C, 69.2; H, 4.47; N, 12.4; S, 14.2. Found: C, 69.2; H, 4.32; N, 12.3; S, 14.6. [o] Ultraviolet absorption spectra determined at solution concentrations of 10 mg./l. in 3A alcohol; the solution of sample VII contained 0.4% dimethylformamide and that of IX was buffered with 0.4% ammonium acetate.

of inorganic salts. The crude product was collected by filtration, washed free of alkali and inorganic salts, dried and recrystallized.

Procedure C.—The reaction was carried out as in procedure A except that the isolation was accomplished by extracting the product from the carbonate-washed residue with successive portions of boiling ethanol. After treatment of the combined alcoholic extracts with a small amount of activated charcoal, the boiling filtrate was treated with hot water until crystallization was imminent. The product crystallized from the solution upon cooling and was collected by filtration.

Procedure D.—The reaction was carried out as in procedure A, except that solution obtained upon drowning the reaction mixture was treated with concd. ammonium hydroxide to neutralize the acid present. After removal of the voluminous white inorganic precipitate, the alkaline solution was evaporated to dryness on the steam-bath, and the residue extracted with three 500-ml. portions of boiling absolute alcohol. Evaporation of the extracts on the steam-bath gave the crude product.

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BOUND BROOK, N. J.

(11) C. Gastaldi and F. Cherchi, *Gazz. chim. ital.*, **431**, 303 (1913).
(12) M. Rope, R. Isensee and L. Joseph, THIS JOURNAL, **74**, 1095 (1952).
(13) J. L. Walter and H. Freiser, *Anal. Chem.*, **25**, 127 (1953).
(14) French Patent 760,944 (1934); *Chem. Zentr.*, **105**, I, 3926 (1934).
(15) H. Lieb, *Monatsh. Chem.*, **39**, 874 (1918).
(16) A. Lecco and V. Ivkovic, *Chem. Zentr.*, **103**, I, 1100 (1932).
(17) H. Hübner and H. Morse, *Ber.*, **7**, 1319 (1874).
(18) T. Zincke and G. Siebert, *ibid.*, **48**, 1251 (1915).
(19) O. Hinsberg and F. Funcke, *ibid.*, **27**, 2189 (1894).
(20) F. Montanari and R. Passerini, *Boll. sci. facolta chim. ind. Bologna*, **11**, 42 (1953); *C. A.*, **48**, 6436h (1954).
(21) M. Meyer, N. Molomut, M. Nowak and M. Ogur, *Rec. trav. chim.*, **53**, 37 (1934); *Chem. Zentr.*, **105**. I, 2129 (1934).