[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

Chlorodehydroxylation of Nitrogen Heterocycles with Phenylphosphonic Dichloride

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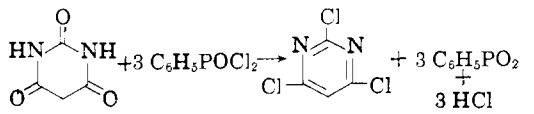
Phenylphosphonic dichloride has been found to be a useful and convenient reagent for the replacement of the elements of a hydroxyl group by chlorine in nitrogen heterocycles. The action of the substance is similar to that of phosphorus oxychloride, replacement being effected most easily when the oxygen is in a position alpha- or gamma- to a ring nitrogen. The utility and convenience of the reagent stem from its high boiling point, which makes it possible to conduct reactions in an open vessel and on a large scale, even at high temperatures. Thus the inconvenience, hazard and necessarily limited scale associated with the sealed-tube procedure for phosphorus oxychloride reactions may be avoided.

A common and fundamental reaction in the chemistry of nitrogen heterocycles is the replacement of a hydroxyl group (present on a hetero-ring as such or in the tautomeric "ketonic" form) by chlorine. The reaction is important in the synthesis of many unsubstituted ring systems and their substituted derivatives, since the hydroxy compounds are often available from ring-closure reactions and since the chlorines can usually be removed by hydrogenolysis or displaced by nucleophilic reagents to insert useful functional groups. The reagent most commonly employed for the chlorodehydroxylation reaction is phosphorus oxychloride. Although many of the reactions proceed readily at the reflux temperature of this reagent (107°), not infrequently temperatures of the order of 160–180° are required, thus necessitating the use of a sealed vessel, usually a Carius tube. Aside from the hazard and inconvenience of such a device, it is clearly ill-suited for large-scale preparations. The utility of the alternative, less-volatile phosphorus pentachloride is greatly diminished by its tendency to function also as an oxidative chlorinating agent, effecting substitution of chlorine for hydrogen at one or more carbon atoms of a reactive ring.[2] Thus a non-oxidative chlorodehydroxylating agent, similar in its action to phosphorus oxychloride but with a much lower volatility obviously would be desirable. It has been found that the inexpensive, commercially-available phenylphosphonic dichloride (dichlorophenylphosphine oxide) is, in most cases, an attractive substitute for the older reagents.

Phenylphosphonic dichloride, a liquid of "not unpleasant fruity odor," boils at 258° with only slight decomposition.[3] Its hydrolysis products, including phenylphosphonic acid and salts thereof, are easily water-soluble; thus the chlorodehydroxylation products may be separated readily from the phosphorus compounds. A typical reaction with barbituric acid may be formulated as shown in the equation



The results of a series of trial reactions carried out to investigate the activity of the reagent are shown in Table I. The hydroxy compounds were chosen from those available in this Laboratory to represent a relatively wide range of reactivities, as indicated by the conditions described in the literature for their reactions with phosphorus oxychloride. Comparison of the phosphorus oxychloride results and those obtained with the new reagent indicates that in some cases the latter is less reactive, in that somewhat higher temperatures are required to effect the transformations. Such a comparison is of limited validity, however, for indeed in other cases it was found that the phenylphosphonic dichloride reaction could be carried out at a *lower* temperature than had been reported for the $POCl_3$ process. It is possible that in these examples the $POCl_3$ reaction had been run at a temperature higher than necessary due to the impossibility of observing hydrogen chloride evolution (and hence evidence of reaction) in a sealed-tube process. The ease of observation of gas evolution may be mentioned as another advantage of the new reagent.

It is seen from Table I that in most cases in which the phosphorus oxychloride or phosphorus pentachloride reaction has been effected under any but the most stringent conditions the yield of chloro compound was at least comparable and in some cases better with $C_6H_5POCl_2$. Two exceptions are to be found in 2,6-dihydroxy-3,4-lutidine and 2,6-dihydroxy-4-picoline. Yields were very low with these compounds, apparently because some condensation or oxidation reaction proceeded faster than the replacement. Theobromine and uric acid also yielded no identifiable products. These two materials require extraordinary reaction conditions with phosphorus oxychloride. In the case of compounds with the hydroxy group β- to the ring nitrogen yields were low with the new reagent. Thus 4-hydroxyisoquinoline gave a better yield of the 4-chloro compound with phosphorus oxychloride, at least when the $C_6H_5POCl_2$ reaction was run for a shorter period and with a smaller excess of reagent. A noteworthy and somewhat unexpected result, however, was the production of 3-chloropyridine in low yield from the reaction of phenylphosphonic dichloride with the extremely inert 3-hydroxypyridine. It should be noted that in most cases the trial reactions with the new material were run only once, and hence the yields were not necessarily optimum. An obvious variation would be the use of a greater excess of the chlorodehydroxylating agent, as is frequently the practice with $POCl_3$. Further, the reactions were run on a small scale, and in the cases where only

(1) Ciba Pharmaceutical Products Inc., Summit, N. J.

(2) H. S. Mosher in Elderfield's "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. 1, p. 514.

(3) A. Michaelis, *Ann.*, **181**, 301 (1876).

TABLE I

CHLORODEHYDROXYLATIONS

Hydroxy compound	Product	Molar ratio $C_6H_5POCl_2$	Temp., °C., and time, hr.	Yield, %	B.p. (mm.) or [m.p.,] °C.	Molar ratio $POCl_3$[PCl_5]	Temp., °C. and time, hr.	Yield, %
3-Methyl-2-pyridone	2-Chloro-3-picoline	1.2x	180, 4	83	188–191	[1.5x][a]	150, 1	41[b]
Citrazinic acid	2,6-Dichloroisonicotinic acid	4x	205, 3.5	45	[202–206]	3x	200, 3.5	34,[c] 75[d]
2,6-Dihydroxy-3,4-lutidine	2,6-Dichloro-3,4-lutidine	2.5x	180, 2.5	<4	[61–67]	2.25x	180, 4	79[e]
			205, 2[f]	0				
			130, 4	0				
		3x	180, 4	<4	[64.5–71]			
2,6-Dihydroxy-4-picoline	2,6-Dichloro-4-picoline	2.5x	130, 1 + 180, 4	13[g]	[62–65][g]	PBr_3, 1.5x	180, 4.5	36[h]
Chelidamic acid	4-Chloropyridine-2,6-dicarboxylic acid	4x	130, 2	52	[208.5 dec.]	[3x]	"Reflux"[i]	?
3-Hydroxypyridine	3-Chloropyridine	2x	205, 6	7.3	144–151[j]	[?]	?	?
2,4-Dihydroxy-6,7-dihydro-1,5-pyrindine	2,4-Dichloro-6,7-dihydro-1,5-pyrindine	2.5x	165, 4	69	134–136 (13)	3.7x	180, 6	82[k]
Barbituric acid	2,4,6-Trichloropyrimidine	4x	185, 4	67	94–95 (10); [19.5–21.5]	1.5x	135, 1	66[l]
						4.2x[m]	Refl., 5 min.	46[m]
Carbostyril	2-Chloroquinoline	2x	130, 3.5	98	[35–37][n]	$POCl_3$ + PCl_5	135, ?	"Almost[n] quant."
Homophthalimide	1,3-Dichloroisoquinoline	2x	160, 3	87	[120.5–121.5][o]	3x	160, 3	41[o]
		2.5x	160, 0.5	89	[119.5–120.5][o]			
4-Hydroxyisocarbostyril	1-Chloro-4-hydroxyisoquinoline	3x	205, 6	33	[194.0–195.5][p]	9x	165, 5	?[p]
	1,4-Dichloroisoquinoline			0				2.7[p]
4-Hydroxyisoquinoline	4-Chloroisoquinoline	2x	205, 6	36	[27.5–28.5][q] 127–131 (9)	6.5x	180, 22	73[q]
Theobromine	2,6-Dichloro-7-methylpurine	5x	225, 3.5	0		12x[r]	140, 3	30[r]
Uric acid	2,6-Dichloro-8-hydroxypurine	5x	215, 15.5	0		[s]	165, 6	40–50[s]

[a] O. Seide, *Ber.*, **57**, 1802 (1924). [b] Yield not reported in ref.; above yield obtained this Laboratory by PCl_5 method. [c] W. H. Levelt and J. P. Wibaut, *Rec. trav. chim.*, **48**, 466 (1929). [d] This yield is the acid chloride, reported by J. Buchi, P. Labhart and L. B. Ragaz, *Helv. Chim. Acta*, **30**, 507 (1947). [e] J. P. Wibaut and E. C. Kooyman, *Rec. trav. chim.*, **63**, 235 (1944). [f] This reaction carried out in a nitrogen atmosphere. [g] Compound not reported in literature; *vide infra*. [h] The dibromo compound has been reported by J. Bernstein, *et al.*, THIS JOURNAL, **69**, 1156 (1947). [i] No details of yield or procedure reported by L. Orthner, *Ann.*, **456**, 246 (1927); E. Koenigs and W. Jaeschke, *Ber.*, **54**, 1351 (1921), reported a 75% yield of the corresponding ethyl ester. [j] Preparation with PCl_5 reported by K. Tamari and K. Morino, *C. A.*, **46**, 5143[d] (1952); no details of yield or procedure given in abstract. [k] V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **28**, 1684 (1945); the isolation in the $C_6H_5POCl_2$ reaction was the same as that of the reference except that the crude mixture was steam distilled for preliminary purification. Final product $n^{25.5}D$ 1.5728; product prepared by Prelog's method $n^{25.5}D$ 1.5715. [l] S. Gabriel, *Ber.*, **33**, 3666 (1900). [m] J. Baddiley and A. Topham, *J. Chem. Soc.*, 678 (1944); this reaction proceeded at the lower temperature in the presence of dimethylaniline. [n] Melting point undepressed on admixture with authentic 2-chloroquinoline; ref., P. Friedlaender and H. Ostermaier, *Ber.*, **15**, 332 (1882). [o] Melting point undepressed on admixture with sample prepared by method of ref., S. Gabriel, *Ber.*, **19**, 2354 (1886); the latter also obtained a small yield of 1-chloro-3-hydroxyisoquinoline. In this Laboratory a 69% yield of the dichloro derivative was obtained by Gabriel's method. [p] Melting point undepressed on admixture of product with sample prepared by method of ref., S. Gabriel and J. Colman, *Ber.*, **33**, 980 (1900); in this Laboratory the yield of crude 1-chloro-4-hydroxyisoquinoline prepared by Gabriel's method was 88%; when the period of heating was extended to 22 hours at 180°, an 80% yield of the dichloro product was obtained. [q] M. M. Robison and B. L. Robison, THIS JOURNAL, **80**, 3443 (1958). [r] E. Fischer, *Ber.*, **30**, 2400 (1897). [s] E. Fischer and L. Ach, *ibid.*, **30**, 2208 (1897); this product was prepared from the potassium salt of uric acid.

1–2 g. of liquid product was obtained, mechanical losses in distillation were considerable.

It seems probable that the close resemblance between the properties of phenylphosphonic dichloride and phosphoryl chloride, together with the much higher boiling point of the former, may make it an attractive reagent in other kinds of chlorodehydroxylations and in different types of reactions such as the dehydration of amides and other functional groups.

Experimental[4,5]

After the reaction mixtures had been heated with exclusion of moisture as indicated in Table I, they were cooled and added to water (usually about 30 ml. per 8 g. of phenylphosphonic dichloride used). The decomposition of excess reagent and of phenylphosphonic anhydride is not as vigorous as that of phosphorus oxychloride, and since almost all of the reactions were run on a 0.01-mole scale (hydroxy compound), external cooling was seldom necessary. Indeed, in a few cases it was found to be advantageous to initiate decomposition by mild warming of the aqueous mixture. It is probable, however, that in large-scale reactions the decompositions would have to be moderated. After hydrolysis of the phosphorus compounds the product was isolated and purified by an appropriate method, usually that reported in the literature for the corresponding phosphoryl chloride reaction. Thus, if necessary, the aqueous mixture was neutralized with ammonia, after which the product might be separated directly in a pure state by filtration (2-chloroquinoline), by extraction and distillation (2-chloro-3-picoline), or by steam distillation, extraction and distillation (3-chloropyridine). The reaction temperatures referred to in the table both for the $C_6H_5POCl_2$ reactions and for the literature methods usually varied ±5°.

2,6-Dichloroisonicotinic Acid.—After decomposition of the reaction mixture with water it was made basic with potassium carbonate and filtered to remove insoluble tars. The solution then was acidified and the precipitate and liquid extracted with ether. After drying, the extract was filtered through a bed of Darco and evaporated to yield a solid composed of product and some starting material. This was recrystallized from 1:2 ethanol–water and the product again taken up in ether to remove the less-soluble citrazinic acid.

(4) We wish to express our sincere appreciation to Dr. Diether G. Markees of the Biological Laboratory, Amherst College, who provided generous samples of a number of the hydroxy compounds used in this study.

(5) (a) Eastman "yellow label" phenylphosphoric dichloride was used. (b) Nitrogen analysis by a semi-micro Kjeldahl technique, this Laboratory.

Repetition of the Darco treatment and of the recrystallization afforded the product referred to in the table.

2,6-Dichloro-4-picoline.—In this reaction, as in that with the corresponding 3,4-lutidine, the reaction mixture was difficult to decompose, and warming of the aqueous mixture was necessary. Steam distillation afforded a white, crystalline solid, as indicated in the table. For analysis the substance was sublimed at 60° (8 mm.), recrystallized from low-boiling petroleum ether and sublimed again to produce shiny white blades, m.p. 65.0–66.0°.

Anal. Calcd. for $C_6H_5NCl_2$: N, 8.65. Found: N, 8.61.

When the reaction was carried out at 155° or at 205° the yields were negligible.

4-Chloropyridine-2,6-dicarboxylic Acid.—The reaction mixture was heated as indicated, decomposed with water and made basic. The dark solution was filtered through Darco and the product precipitated and dried at 135° to produce a 79% yield of crude, anhydrous product. Recrystallization from acetic acid, a repetition of the Darco treatment of a basic solution, and redrying produced the cream-colored, anhydrous material referred to in the table. It was identified by its melting point, a positive qualitative test for chlorine, and its neutral equivalent.

Anal. Calcd. for $C_7H_4NO_4Cl$: neut. equiv., 100.8. Found: neut. equiv., 102.8, 103.0.

Theobromine Reaction.—When the reaction mixture was heated as indicated in the table, then decomposed with cold water, an oily mass was formed. This produced an amorphous solid of indefinite melting range on partial neutralization. Its behavior on attempted recrystallization indicated a mixture and when it was found that the substance was completely soluble in 5% sodium bicarbonate solution it was not investigated further.

Uric Acid Reaction.—Decomposition of the dark reaction mixture with water gradually produced an amorphous, tarry solid. Since extraction with ether and evaporation produced only a small quantity of solid, whose melting point was well above that reported for 2,6,8-trichloropurine,[6] and since the ether-insoluble material, unlike 2,6-dichloro-8-hydroxypurine[6], was completely soluble in concentrated nitric acid, the reaction was not investigated further.

(6) E. Fischer, *Ber.*, **30**, 2220 (1897).

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[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, ST. LOUIS RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

Adiponitrile—a Novel Self-condensation Sequence

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Adiponitrile was cyclized under heterogeneous conditions by a molecular equivalent of sodium *t*-butoxide in toluene to give the expected product 2-amino-1-cyano-1-cyclopentene (III). However, under homogeneous conditions in *t*-butyl alcohol with a catalytic amount of potassium *t*-butoxide, a dimeric substance found to have structure VII was the major product. Compound VII was converted smoothly to 4-amino-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2-valeronitrile (VIb) by aqueous mineral acids. The structure of VIb was proved by synthesis. Derivatives of III and various pyrimidines related to VIb were prepared.

Thorpe and Best[1] first prepared 2-cyano-1-iminocyclopentane (II) by methods which involved as the initial step the base-catalyzed cyclization of diethyl α,α'-dicyanoadipate (I). Shortly thereafter Thorpe[2] claimed to have prepared II in 84% yield by cyclizing adiponitrile in alcohol with a catalytic amount of sodium ethoxide. Ziegler, *et al.*,[3] prepared II from adiponitrile using magnesium–diethylamide in molecular amounts to effect ring closure. The material also has been obtained as a by-product in the hydrogenation of adiponitrile,[4] from the reaction of adiponitrile with Grignard reagents,[5] in the commercial preparation of adiponitrile[6] and by high temperature catalytic methods.[7] Hammer and Hines[8] recently showed that II is more correctly represented by its enolized or enamine structure III.

All attempts in this Laboratory to repeat Thorpe's cyclization[2] of adiponitrile with catalytic amounts[9] of sodium ethoxide have failed. Essentially no cyclization occurred even when the heating time was considerably extended. On the other hand, adiponitrile was readily cyclized to III by Ziegler's procedure[3] or better by a molecular equivalent of sodium *t*-butoxide suspended in toluene.

The use of a molecular amount of sodium ethoxide with other conditions essentially the same as in the original Thorpe procedure[2] yielded two crystalline products and a recovery of adiponitrile in 35% yield. The crystalline material was found to be a mixture of III in 39% over-all yield and a new compound (dimer 1), $C_{12}H_{16}N_4$, m.p. 129.5–130.5°, λ_{max}^{alc} 263 mμ, ε 14,400, obtained in 25% yield. Extension of the reflux time to 20 hours resulted in essentially complete conversion of adiponitrile to a mixture of III and the dimeric product with the latter predominating. Preparation of the dimeric substance was effected more conveniently (76% yield) by refluxing adiponitrile in *t*-butyl alcohol with a catalytic amount of potassium *t*-butoxide.

Dimer 1 was a labile basic compound. Determination of molecular weight by cryoscopic methods gave uncertain results, but ebullioscopic determination in ethylene dibromide clearly indicated a C_{12}-compound. Acetylation or benzoylation in pyridine gave low yields of an acetate (Va) and benzoate (Vb) identical with the respective derivatives obtained directly from III. When a hot pyridine solution of the dimer was quenched in ice-water, a mixture of III (about 30%) and dimer was recovered. Conversion of III back to the di-

(1) S. R. Best and J. F. Thorpe, *J. Chem. Soc.*, 685 (1909).

(2) J. F. Thorpe, *ibid.*, 1901 (1909).

(3) K. Ziegler, H. Ahlinger and E. Eberle, German Patent 591,269; *cf. Frdl.*, **20**, 537 (1934).

(4) O. Riobe and L. Gouin, *Compt. rend.*, **234**, 1889 (1952).

(5) A. Compere, *Bull. soc. chim. Belg.*, **44**, 523 (1935).

(6) R. H. Halliwell, U. S. Patent 2,768,132; see also British Patent 728,522, and L. H. Smith, "Synthetic Fiber Development in Germany"; Textile Research Institute, New York 16, N. Y., 1946, p. 589.

(7) W. A. Lazier and B. W. Howk, U. S. Patent 2,292,949.

(8) C. F. Hammer and R. A. Hines, THIS JOURNAL, **77**, 3649 (1955).

(9) Thorpe mixed 5 g. of adiponitrile and 20 ml. of absolute ethanol and dissolved in this solution a piece of sodium the size of a grain of wheat. After one hour at reflux, 4.2 g. of III, m.p. 147°, was claimed to have crystallized from the reaction mixture on cooling.