remove all the [$^{14}$C]-HBA. An aliquot was counted by liquid scintillation and showed that a yield of 55% of [$^{14}$C]-HBA was obtained. The purity of the HBA from fusion was tested by tlc in three additional systems: 1-propanol:$H_2O$:$NH_4OH$ (8:1:1), benzene:methanol (1:4), and benzene:methanol:acetic acid (90:16:8). In all three systems, only one radioactive peak was detected by a Dünnschicht-Scanner, LB2721 (Berthold), and each had the same $R_f$ value as reference HBA. Pauly's reagent was used to detect the areas of reference HBA.

**Registry No.**—[$^{14}$C]-*p*-Hydroxybenzoic acid, 33875-99-9; [$^{14}$C]tyrosine, 18875-48-4.

**Acknowledgment.**—We are grateful to The Robert A. Welch Foundation and to the Muscular Dystrophy Association of America, Inc., for their respective support of this research.

## Nitriles from Aldoximes. A New Reaction of Phosphonitrilic Chloride[1]

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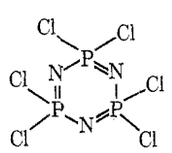
In previous work[2] we have reported that hexachlorocyclotriphosphazatriene (phosphonitrilic chloride) (**1**) can be used as an activator of the type RCOOX=Y[3] in the conversion of the carboxylic functions into amides and hydrazides in high yields and under very mild conditions.

Continuing the study of the chemical behavior of phosphonitrilic halides, we have examined the response of aliphatic, aromatic, and olefinic aldoximes toward phosphonitrilic chloride.[4]



**1**

We found that nitriles are produced at room temperature in a process that is exceptionally mild, comparable to procedures recently reported, which involve dehydration of aldoximes.[5]

The method involves addition of a solution of triethylamine (3 mol) to a solution of phosphonitrilic chloride (1 mol) and oxime (1 mol) followed by isolation of the nitrile after 2–24 hr, usually by chromatography. Some results given by our process are shown in Table I,

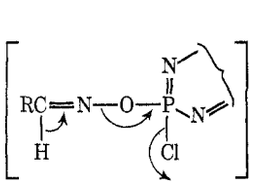
TABLE I

| Oxime[a] | Yield of nitrile, % | Time of reaction, hr |
|---|---|---|
| (*E*)-Benzaldoxime | 72 (88)[d] | 24 |
| (*Z*)-Benzaldoxime | 74 | 24 |
| (*E*)-*p*-Chlorobenzaldoxime | 76 (60.8)[e] | 18 |
| (*Z*)-*p*-Chlorobenzaldoxime | 78 (42.4)[e] | 20 |
| (*E*)-Cinnamaldoxime | 98 (95)[d] | 12 |
| (*Z*)-Cinnamaldoxime | 97 | 12 |
| Undecaldoxime[b] | 95 | 8 |
| Heptaldoxime[b] | 93 (42.7)[e] | 8 |
| (*Z*)-Furaldoxime | 89 (60)[d] | 18 |
| *p*-Phenylbenzaldoxime | 69 | 24 |
| Pyridine-2-aldoxime | 95 | 12 |
| 3,7-Dimethyl-2,6-octadienaldoxime | 98 | 12 |
| 3-Indolecarboxaldehyde[c] | 98 | 2 |

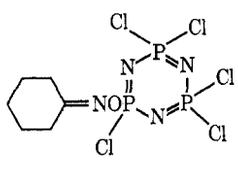
[a] Nomenclature of J. E. Blackwood, C. L. Gladys, K. L. Leoning, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968). [b] Stereochemistry unknown. [c] Reaction performed in THF. [d] Reference 5b. [e] Reference 5a.

in which the yields refer to analytically pure products obtained from reactions performed in diethyl ether. The yields given using other mild procedures are also reported.

Aldoximes react with phosphonitrilic chloride at room temperature to give nitriles, and no *O*-phosphonitrilic chloride derivative of type **2** has been observed during the reaction, whereas the cyclohexanone oxime reacts with compound **1** under the same conditions to give the compound **3** in 63% yield.



**2**



**3**

This fact induced us to hypothesize that aldoximes also react with phosphonitrilic chloride in the presence of triethylamine to give intermediates of type **2** that successively undergo 1,4 fast elimination of hydrogen chloride to form the corresponding nitriles.

Tlc analysis (silica gel, benzene as eluent) revealed the formation of nitrile and the disappearence of oxime during the time of the reaction, which was longer for the conversion of aromatic aldoximes (10–24 hr) than for the aliphatic and olefinic ones (2–8 hr). The stereochemistry of aldoximes (*E*, *Z*) has little effect on the reaction. The reaction can be performed in a variety of solvents (benzene, ethyl acetate, chloroform, THF) in very good yields.

The possibility of using a variety of solvents for the reaction, the simplicity of the operations involved, the high yields together with the mild conditions, and the ready availability of the reagent **1** recommend this new route to nitriles.

(1) This work was done with financial support from the Italian National Research Council (C. N. R.).

(2) L. Caglioti, M. Poloni, and G. Rosini, *J. Org. Chem.*, **33**, 2979 (1968); M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis," Vol. 2, Wiley-Interscience, New York, N. Y., 1969, p 206.

(3) J. Rudinger, *Pure Appl. Chem.*, **7**, 335 (1963).

(4) See, for recent reviews, R. A. Shaw, *Chem. Ind. (London)*, 1737 (1967); M. L. Paddock, *Quart. Rev., Chem. Soc.*, **18**, 168 (1964); R. A. Shaw, B. W. Fitzsimmons, and B. C. Smith, *Chem. Rev.*, **62**, 247 (1962).

(5) (a) D. L. J. Clive, *Chem. Commun.*, 1014 (1970); (b) P. J. Foley, Jr., *J. Org. Chem.*, **34**, 2805 (1969); (c) T. J. Bentley, J. F. McGhie, and D. H. R. Barton, *Tetrahedron Lett.*, 2497 (1965).

Work is in progress to extend the study of the chemical behavior of phosphonitrilic chloride toward ketoxime and amides.

### Experimental Section

**Materials.**—Hexachlorocyclotriphosphazatriene (1) was purchased from Albright and Wilson, England, and used after purification by crystallization from petroleum ether (bp 30–60°). The oximes were prepared by standard methods. The nitriles were identified by comparison of their ir spectra and glc retention times with those of authentic samples and by their melting points in the case of solids. Pure-grade solvents were used without further purification.

**General Procedure.**—Triethylamine ($3.0 \times 10^{-2}$ mol) was added to a solution of the oxime ($1.0 \times 10^{-2}$ mol) and compound 1 ($1.0 \times 10^{-2}$ mol). The solution was allowed to stand at room temperature and the reaction was followed by tlc analysis (silica gel and benzene or cyclohexane–ethyl acetate as eluents). When the aldoxime had almost completely disappeared, triethylamine hydrochloride was removed by filtration and the filtrate was concentrated under reduced pressure. The mixture was taken up in 20 ml of benzene and the resulting nitrile was purified by chromatography on a silica gel column using benzene as eluent. Typical preparations follow.

**Heptanenitrile.**—To a solution of heptanealdoxime (1.29 g, $1.0 \times 10^{-2}$ mol) and phosphonitrilic chloride (3.47 g, $1.0 \times 10^{-2}$ mol) in 50 ml of diethyl ether in a 100-ml flask was added triethylamine (3.03 g, $3.0 \times 10^{-2}$ mol) in 10 ml of diethyl ether. The solution was stirred for 8 hr at room temperature. The triethylamine hydrochloride was removed by filtration and the filtrate was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel using benzene as eluent. Heptanenitrile (1.3 g), bp 54° (8 mm), was obtained in 93% yield; spectroscopic data are in agreement with those recorded on an authentic sample.

*Anal.* Calcd for $C_7H_{13}N$: C, 75.61; H, 11.79; N, 12.60. Found: C, 75.84; H, 11.62; N, 12.52.

**3-Indolecarbonitrile.**—To a solution of 3-indolecarboaldoxime (1.6 g, $1.0 \times 10^{-2}$ mol) and phosphonitrilic chloride (3.47 g, $1.0 \times 10^{-2}$ mol) in 50 ml of tetrahydrofuran in a 100-ml flask was added triethylamine (3.03 g, $3.0 \times 10^{-2}$ mol). The solution was stirred for 2 hr at room temperature. The triethylamine hydrochloride was removed by filtration and the filtrate was evaporated under reduced pressure. The resulting mixture was chromatographed on silica gel using benzene–ethyl acetate (7:3) as eluent. 3-Indolecarbonitrile (1.25 g, 98% yield) had mp 180–182° (lit.[6] mp 182–184°): spectroscopic data are in agreement with those recorded on a sample independently prepared.[6]

*Anal.* Calcd for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.71. Found: C, 75.89; H, 4.12; N, 19.54.

***O*-(Pentachlorocyclotriphosphazatriene)cyclohexanone Oxime (3).**—The reaction between cyclohexanone oxime and compound 1 was performed in diethyl ether as depicted in the general procedure and gave a compound (mp 74–75°, white crystals from pentane) in 63% yield, to which the structure of *O*-(pentachlorocyclotriphosphazatriene)cyclohexanone oxime (3) was assigned: ir (KBr) 2900 (w), 1470 (vw), 1430 (w), 1375 (m), 1360 (m), 1340 (m), 1325 (m), 1310 (m), 1280 (m), 1250 (s, shoulder), 1230 (vs, shoulder), 1200 (vs, broad), 1160 (vs, shoulder), 1122 (vs), 1095 (m), 1020 (w), 960 (m), 917 (m), 870 $cm^{-1}$ (m).

*Anal.* Calcd for $C_6H_{10}Cl_5N_4OP_3$: C, 16.95; H, 2.37; Cl, 41.77; N, 13.23. Found: C, 16.70; H, 2.47; Cl, 41.81; N, 13.12.

**Registry No.**—1, 940-71-6; 3, 37709-15-2; heptanenitrile, 629-08-3; heptanealdoxime, 629-31-2; 3-indolecarbonitrile, 5457-28-3; 3-indolecarboaldoxime, 2592-05-4; cyclohexanone oxime, 100-64-1.

**Acknowledgment.**—The authors express their appreciation to Professor Luciano Caglioti for his interest in this project.

(6) H. M. Blatter, H. Lukaszewski, and G. de Stevens, *J. Amer. Chem. Soc.*, **83**, 2203 (1961); *Org. Syn.*, **43**, 58 (1963).



## The Synthesis of 1,3,5-Trimethylbicyclo[4.4.1]undecan-11-one by Intramolecular Alkylation[1]

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In our approach toward the synthesis of molecules resembling the methymycin antibiotics, we recently reported the low yields found thus far in the acid-catalyzed cyclization–dehydration of 2,4,6-trimethyl-7-(4′-hydroxybutyl)cycloheptanone (**1**) to **2**.[2]

In an attempt to overcome this problem, the following alternate pathway to **2** was developed. The alkylation of *cis,cis*-2,4,6-trimethyl-7-carbethoxycycloheptanone (**3**)[2] *via* its sodium enolate with 1,4-dibromobutane (**4**) gives a 60:40 mixture of the desired 2,4,6-trimethyl-7-carbethoxy-7-(4′-bromobutyl)cycloheptanone (**5**, as a mixture of stereoisomers) and the O-alkylated product **6**. Since **3** is a highly hindered β-keto ester,[2] it had been anticipated that some O-alkylation might occur.[3] The corresponding alkylation of the sodium enolate of carbethoxycycloheptanone (**7**) with **4** occurs mainly on carbon.[4] Treatment with acid results in the hydrolysis of **6** to leave **5**, which is then internally alkylated (with sodium hydride in hexamethylphosphoramide) to give a 60:40 mixture of the desired enol ether **9** and the bridged keto ester **8**. Decarboxylation of this mixture with lithium iodide–collidine gives 1,3,5-trimethylbicyclo[4.4.1]undecan-11-one (**10**), a mixture of the enol ethers **2**, and a small amount of 2,4,6-trimethyl-7-(3′-butenyl)cycloheptanone (**11**, derived from **2** with lithium iodide). Ketone **10** (and a minor amount of **11**) is obtained by acid hydrolysis, which converts **2** to the easily separable **1**.

The intramolecular alkylation of **5a** had been expected to occur at the presumably less hindered oxygen site of the enolate ion, especially in highly polar hexamethylphosphoramide as solvent. Indeed, the sodium enolate of 2-carbethoxy-2-(4′-bromobutyl)cycloheptanone (i) gives 9:1 O/C intramolecular alkylation (ii, iii) in the less polar medium toluene–dimethylformamide.[4] The unexpected C-alkylation in **5a** may be due to enhancement of the normally greater nucleophilicity of the enolate carbon by the 2-methyl[5a] and possibly by inhibition of solvation at the crowded enolate carbon.[6]

(1) This investigation was supported by Public Health Service Research Grant AI 07455 from the National Institute of Allergy and Infectious Diseases.

(2) I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco, and R. D. G. Rigby, *J. Org. Chem.*, **37**, 581 (1972).

(3) The related alkylation of the sodium enolate of **3** with 1-bromo-4-acetoxybutane also gives some O-alkylation.[2]

(4) Professor John Wiseman, University of Michigan, private communication.

(5) (a) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 560; (b) pp 586–595.

(6) Keto ester **5** may represent a borderline system wherein various factors can cause C- or O-intramolecular alkylation to predominate. The sodium enolate of 2-carbethoxy-2-(4′-bromobutyl)cyclododecanone (a large ring system approaching the behavior of acyclic enolates) gives intramolecular C-alkylation only.[7]

(7) H. Nozaki, H. Yamamoto, and T. Mori, *Can. J. Chem.*, **47**, 1107 (1969).