Notes

A department for short papers of immediate interest.

Preparation of *O*-(Isopropylmethylphosphono)-4-formyl-1-methylpyridinium Iodide Oxime

BRENNIE E. HACKLEY, JR., AND OMER O. OWENS

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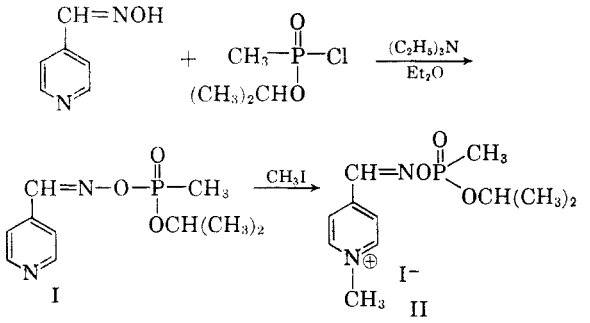
During initial screening studies of the velocity of reaction between isopropyl methylphosphonofluoridate (GB)[1] and a variety of oximes,[2] it was observed that many of the oximes reacted in two distinct acid-producing steps. The steps consisted of an initial phosphonylation of the oxime followed by breakdown of the phosphonylated oxime to secondary products.

With the discovery of the usefulness of pyridinium oximes such as 2-formyl-1-methylpyridinium iodide oxime[3] and 1,1′-trimethylenebis(4-formylpyridinium bromide) dioxime[4] in the treatment of poisoning by the organophosphorus anticholinesterases, a detailed investigation of the reaction between oximes of this general class and GB was undertaken.[5] As a part of this study, it was desirable to obtain a sample of a typical phosphonylated pyridinium oxime, *i.e.*, *O*-(isopropyl methylphosphono)-1-methyl-4-formylpyridinium iodide oxime.

We have prepared this compound by the reaction of pyridine-4-aldoxime with isopropyl methylphosphonochloridate in nonaqueous solution[6] followed by quaternization with methyl iodide according to the following scheme.



Compound II is a powerful inhibitor of eel acetylcholinesterase with a rate constant at *p*H 7.4 and 25° = 4.7–5.7 × $10^7 M^{-1}$ min.$^{-1}$. Its LD^{50} in white mice *via* the intravenous route of administration is 0.2 mg./kg. Detailed studies of the hydrolysis of this compound are in progress and will be reported later.

EXPERIMENTAL

Preparation of O-(isopropylmethylphosphono)pyridine-4-aldoxime (I). Isopropyl methylphosphonochloridate, 17.2 g. (0.11 mole), was added dropwise with stirring to a cooled solution of 12.2 (0.1 mole) of pyridine-4-aldoxime and 11.1 g. (0.11 mole) of triethylamine in 500 ml. of absolute diethyl ether (the triethylamine was distilled over KOH and the ether was dried over sodium). The temperature of the solution was maintained below 25° during the addition. After standing overnight the triethylamine hydrochloride which had precipitated was filtered from the solution and the ether was removed under vacuum, at bath temperature below 0°, leaving a light yellow viscous oil. The oil was heated to 50° (bath temperature) under high vacuum to remove the last traces of solvent. (An attempt to distill this oil at 0.2 mm. resulted in decomposition; a volatile fraction which distilled and solidified in the receiver, was found to be 4-cyanopyridine m.p. 80°C. The residue was a viscous, strongly acidic liquid believed to be isopropylmethylphosphonic acid.) A total of 23 g. (97%) of the desired product was obtained. This product was used, without further purification in the subsequent synthesis.

Anal. Calcd. for $C_{10}H_{15}N_2PO_3$ C, 49.59; H, 6.19; N, 11.57; P, 12.81. Found: C, 48.9; H, 6.4; N, 11.3; P, 12.0.

Preparation of O-(Isopropylmethylphosphono)-4-formyl-1-methylpyridinium iodide oxime (II). An excess of methyl-iodide (0.04 mole) was added to an ether solution containing 4.8 g. (0.02 mole) of I. The mixture was allowed to stand at room temperature overnight after which an orange-red oil separated from the solution. This oil was triturated with several 50 ml. portions of anhydrous diethyl ether; it solidified while drying over P_2O_5 in vacuo at room temperature. The yield of II was 7.0 g. (91%) m.p. 97° dec. The material is an extremely hydroscopic orange powder. It decomposes slowly upon standing at room temperature, even in a closed vessel, but can be stored at 0°, in a desiccator over P_2O_5 for several months with little or no decomposition. All attempts to recrystallize this material resulted in lowered antiacetylcholinesterase activity. On the basis of the phosphorus analysis the sample is 91% pure.

Anal. Calcd. for $C_{11}H_{18}N_2PI$: C, 34.4; H, 4.7; N, 7.3; P, 8.1; I, 33.1. Found: C, 34.0; H, 4.6; N, 7.1; P, 7.4; I, 34.4.

CHEMOTHERAPY BRANCH
BIOCHEMICAL RESEARCH DIVISION
U. S. ARMY CHEMICAL WARFARE LABORATORIES
ARMY CHEMICAL CENTER, MD.

(1) GB is the code designation given this compound by the U. S. Army Chemical Corps.

(2) B. E. Hackley, Jr., Ph.D. Dissertation. University of Delaware, 1956. University Microfilms, Ann Arbor, Mich., 1958.

(3) For historical references see I. B. Wilson, *Biochimica et Biophysica Acta*, **27**, 196 (1958).

(4) E. J. Poziomek, B. E. Hackley, Jr., and G. M. Steinberg, *J. Org. Chem.*, **23**, 714 (1958).

(5) To be reported elsewhere.

(6) J. H. Turnbull, *Chem. and Ind. (London)*, 350 (1956).