Journal of Fluorine Chemistry 132 (2011) 541–547

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis of some fluorine-containing pyridinealdoximes of potential use for the treatment of organophosphorus nerve-agent poisoning

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ARTICLE INFO

Article history:
Received 31 January 2011
Received in revised form 5 May 2011
Accepted 29 May 2011
Available online 28 June 2011

Keywords:
Fluoropyridines
Fluorinated pyridinecarboxaldehydes
Nerve agent
Oximes
2-PAM
Sarin

ABSTRACT

Fluoroheterocyclic aldoximes were screened as therapeutic agents for the treatment of anticholinesterase poisoning. 2-Fluoropyridine-3- and -6-aldoxime, and 3-fluoropyridine-2- and -4-aldoxime, were synthesised. Attempts to obtain 3,5,6-trifluoropyridine-2,4-bis(aldoxime) and -2-aldoxime, however, proved unsuccessful. Pentafluorobenzaldoxime was prepared by oximation of pentafluorobenzaldehyde. Acid dissociation constants (pK_a) and second-order rate constants ($k_{ox}-$) of the fluorinated pyridinealdoximes towards sarin were measured. 2,3,5,6-Tetrafluoropyridine-4-aldoxime had the best profile: its $k_{ox}-$ approached that of the therapeutic oxime P2S (310 vs. 120 l mol^{-1} min^{-1}), but its higher pK_a (9.1 vs. 7.8) fell short of the target figure of 8 required for reactivation of inhibited acetylcholinesterase *in vivo*. *N*-alkylation of the fluorinated pyridine-aldoximes may reduce their pK_a nearer to 8 and enhance their therapeutic potential.

1. Introduction

Terrorist use of sarin in a Tokyo subway in 1995 highlighted the threat from organophosphorus nerve agents (NAs) [1]. Despite an effort spanning decades, treatment of NA poisoning is still unsatisfactory and the search for improved antidotes continues [2]. Some compounds with an N–OH group can reactivate acetylcholinesterase (AChE) inhibited by NAs. An effective reactivator is 1-methylpyridinium-2-aldoxime methanesulfonate (P2S) which contains a pyridinium scaffold that binds reversibly to the anionic site of inhibited AChE [3] and a nucleophilic oxime group that ionises at physiological pH [4]. The resultant oximate ion attacks and releases the NA residue, restoring normal enzyme activity (Scheme 1) and nerve transmission.

Some bis-quaternary oximes such as obidoxime (Fig. 1) are generally more effective against a broader range of NAs than mono-quaternary oximes [5]. However none of the oximes researched to date are sufficiently efficacious against all known NAs. Finding an oxime sufficiently effective against AChE inhibited by a variety of NAs is still an important task and many institutes are interested in the synthesis of AChE reactivators and their chemical precursors.

Although a quaternary nitrogen atom is believed to be necessary for binding the inhibited enzyme anionic site [5], it limits passage of the compound through the blood-brain-barrier (BBB) where uptake is thought desirable for combating the toxic effects of NAs on the central nervous system [6,7]. The acid dissociation constant (pK_a) of the oxime group determines the concentration of oximate ion and thus the rate of reactivation. Studies by Porton scientists showed that under physiological conditions (pH 7.4, 37 °C) only oximes with a pK_a around 8 reacted satisfactorily with organophosphorus compounds [8]. Oximes having a pK_a much less than 8 did ionise but the anion was too feebly nucleophilic to enable reactivation to occur quickly. Those having a pK_a much greater than 8 did not ionise appreciably and insufficient anion was available for reactivation. Adjusting the charge on nitrogen, and hence binding to the anionic site and the pK_a, might be possible by adding fluorine atoms to the pyridine scaffold. Exchange of H for F will increase size only slightly (*respective van der Waals radii*: 1.20 and 1.47 Å) but will modulate the charge on nitrogen and the lipophilicity [9], maybe enabling the molecule to surmount the BBB.

This paper describes the synthesis of some fluorinated pyridine aldoximes and an assessment of their potential for treating NA poisoning. Synthetic work was conducted at the University of Manchester Institute of Science and Technology (UMIST) during

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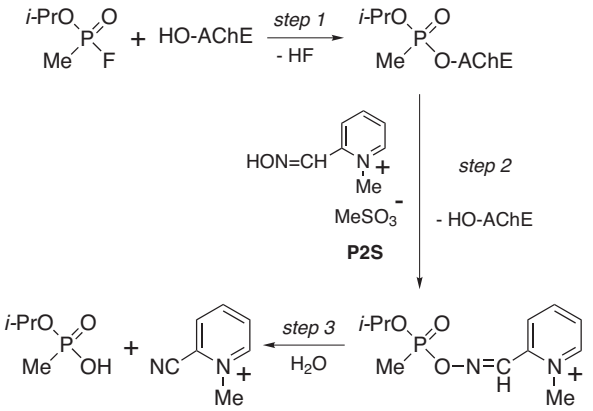
0022-1139/$ – see front matter.
doi:10.1016/j.jfluchem.2011.05.028



Scheme 1. Mechanism of AChE inhibition (*step 1*), reactivation by the therapeutic oxime P2S (*step 2*), and formation of non-toxic products (*step 3*).

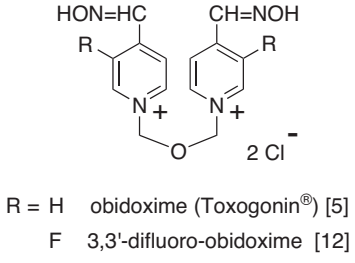


Fig. 1. Obidoxime and a difluorinated analogue.

the period 1963–1966 [10] and compounds submitted to the then Chemical Defence Experimental Establishment (CDEE) at Porton Down (UK) for biological testing. Owing to British national security restrictions at the time, which have now been lifted, neither the synthetic work nor the screening results could be published; the purpose of this paper is to remedy this situation. Note that the first communications concerning fluorinated pyridinium aldoximes as antidotes for nerve-agent poisoning appeared in the open literature only recently (2009–2010) [11–13], derivatives of 3-fluoropyridine-4-aldoxime (*e.g.* 3,3′-difluoro-obidoxime, Fig. 1) being described. 3-Fluoropyridine-4-aldoxime was one of the targets (**A**–**I**; Fig. 2) involved in our researches initiated 48 years ago!

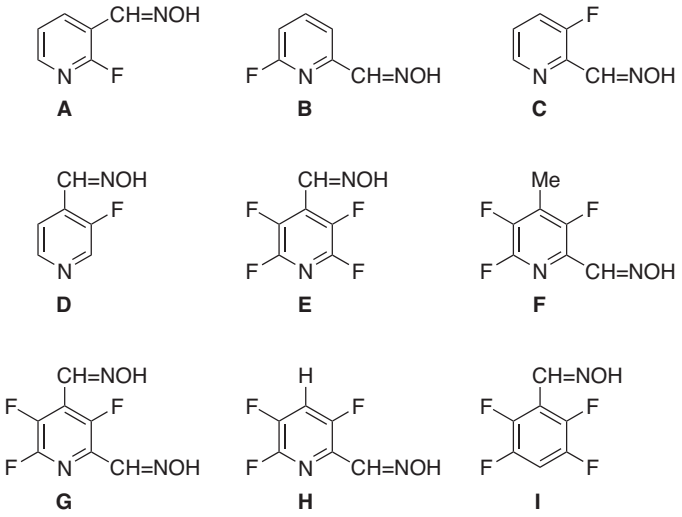


Fig. 2. UMIST-CDEE target oximes.

Acid dissociation constants and rates of reaction with sarin of three of the fluorinated pyridinealdoximes were compared at Porton with those obtained with P2S and some non-quaternized analogues. These data have been mentioned briefly before [1], but experimental details and a discussion of the results are now presented for the first time.

2. Results and discussion

2.1. Monofluorinated pyridinealdoximes

2.1.1. α-Fluorinated pyridinealdoximes A and B

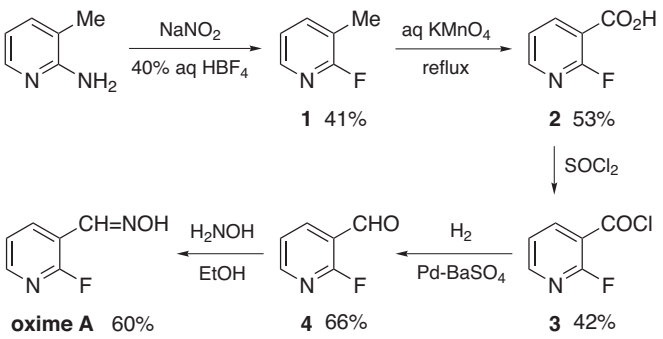
The Balz-Schiemann technique was used to convert 2-amino-3-methylpyridine into 2-fluoro-3-methylpyridine (**1**) (Scheme 2), permanganate oxidation of this to acid **2** followed by its conversion to acyl chloride **3** was conducted according to literature instructions [14–17]. Rosenmund reduction was used to transform the acyl chloride into carboxaldehyde **4**. Previously this technique was reported to give poor yields with heterocyclic acid chlorides [18], yet homocyclic acid chlorides gave good yields if nuclear halogen substituents were present. Our conversion of acid chloride **3** to carboxaldehyde **4** in satisfactory yield (66%) demonstrated that fluoroheterocyclic compounds could undergo facile catalytic reduction by hydrogen in boiling xylene. Carboxaldehyde **4** reacted smoothly with hydroxylamine produced *in situ* from hydroxylamine hydrochloride (15 min reflux in ethanolic NaOH aq) to provide oxime **A** in 60% yield.

2-Fluoropyridine-6-aldoxime (**B**) was prepared similarly from 2-amino-6-methylpyridine (→ 2-fluoro-6-methylpyridine 39% → -6-carboxylic acid 50% → -6-carboxylic acid chloride 72% → -6-carboxaldehyde 68% → **B** 71%).

2.1.2. β-Monofluorinated pyridinealdoximes C and D

Literature routes were adapted for transforming 2-amino-6-methylpyridine into 3-fluoro-2-methylpyridine [19,20] (Scheme 3). Conversion of the β-nitro compound **5b** (isolated by steam distillation [19]) to its 6-chloro analogue (**7**), followed by reductive dechlorination then Balz–Schiemann fluorodediazoniation [20] of the resulting aminopicoline **8**, provided 3-fluoro-2-methylpyridine (**9**). Condensation of **9** with benzaldehyde, as described for its non-fluorinated analogue [21], followed by ozonolysis of the benzylidine derivative **10** produced gave 3-fluoropyridine-2-carboxaldehyde (**11**) and hence access to oxime **C**.

The sequence used to obtain oxime **C** (Scheme 3) was applied to 2-amino-4-methylpyridine, the only difference being that the products of nitration (3- and 5-isomers) were not separated but jointly processed to provide 3-amino-4-methylpyridine **15** and thence 3-fluoropyridine-4-aldoxime (**D**) (Scheme 4).



Scheme 2.