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

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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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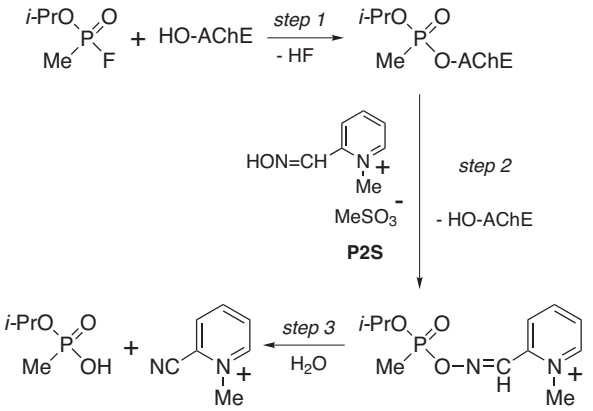


Scheme 1. Mechanism of AChE inhibition (*step 1*), reactivation by the therapeutic oxime P2S (*step 2*), and formation of non-toxic products (*step 3*).

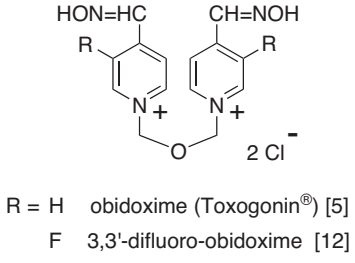


Fig. 1. Obidoxime and a difluorinated analogue.

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!

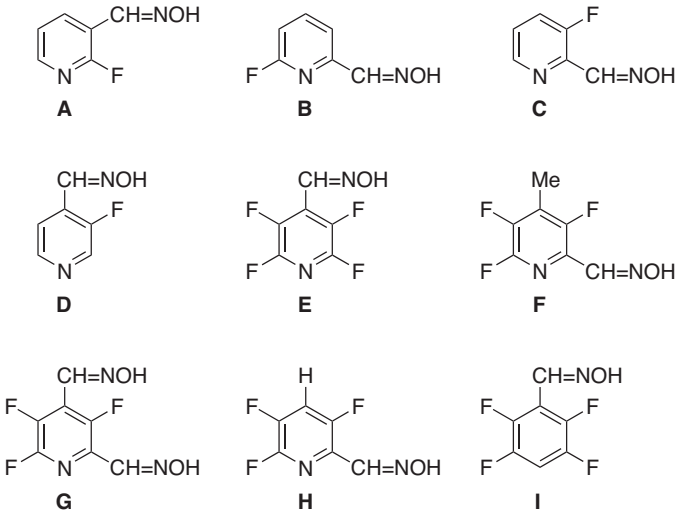


Fig. 2. UMIST-CDEE target oximes.

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

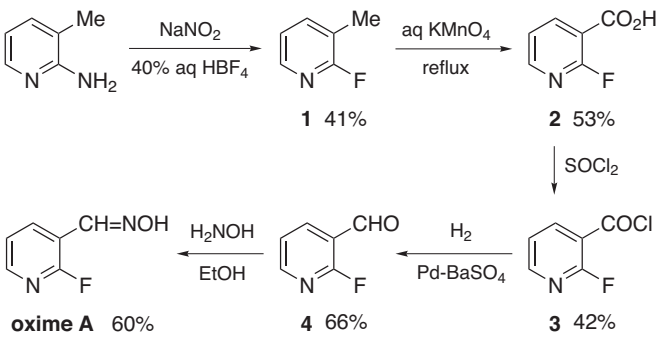
The Balz-Schiemann technique was used to convert 2-amino-3-methylpyridine into 2-fluoro-3-methylpyridine (**1**) (Scheme 2), permanganate oxidation of this to acid **2** followed by its conversion to acyl chloride **3** was conducted according to literature instructions [14–17]. Rosenmund reduction was 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%).

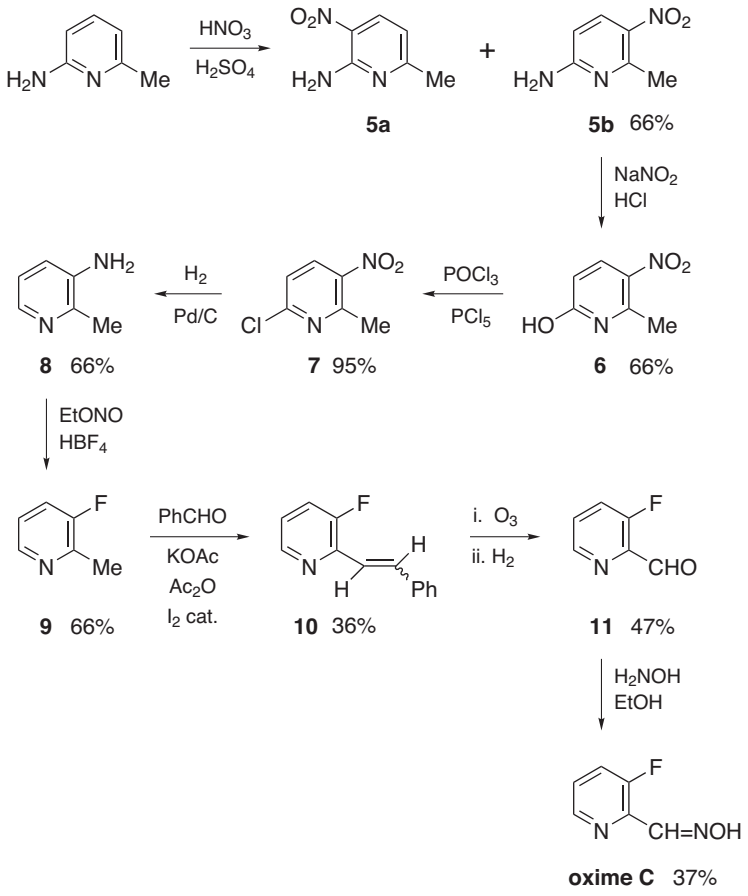
2.1.2. β-Monofluorinated pyridinealdoximes C and D

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.



Scheme 3.

2.2. Polyfluorinated oximes

2.2.1. Pyridinealdoximes E-H

Tetrafluoropyridine-4-aldoxime (**E**) and 3,5,6-trifluoro-4-methylpyridine-2-aldoxime (**F**) were reported long ago [22–24]. The favoured route (of three) to oxime (**E**) featured 4-position propenylation of pentafluoropyridine (**19**) with MeCH=CHLi [22] followed by ozonolysis of the product **20** and oximation of the carboxaldehyde **24** produced (Scheme 5) [23,24]. In like manner 2,3,5,6-tetrafluoro-4-methylpyridine (**27**) was converted to 3,5,6-trifluoro-4-methyl-2-propenylpyridine (**28**) and thence to 3,5,6-trifluoro-4-methylpyridine-2-carboxaldehyde (**29**), the precursor of oxime (**F**) (Scheme 6) [23].

Attempts to prepare formyl precursors of oximes **G** and **H** started, respectively, from pentafluoropyridine and 2,3,5,6-tetrafluoropyridine (ex. $C_5F_5N + LiAlH_4$ [22]). In both cases, propenylation featured as the chosen route to the aldehydes sought. Carried out on a larger scale and giving a better product yield (85 vs. 62%) than previously [22], this provided 3,5,6-trifluoro-2,4-dipropenylpyridine (**30**), ozonisation of which followed by reduction, yielded only an intractable tar (Scheme 7). Unchanged starting material contaminated with traces of unidentified material and 'tar' resulted when 2,3,5,6-tetrafluoropyridine (**32**) was treated with propenyl-lithium (Scheme 8).

2.2.2. Pentafluorobenzaldoxime I

Pentafluorobenzaldoxime (**I**) was isolated in 70% yield from oximation of pentafluorobenzaldehyde (ex. $C_6F_5MgBr + HCO_2Et$ [25]) (Scheme 9). It was prepared early on in the study to demonstrate that a polyfluorinated aromatic carboxaldehyde was capable of conversion to an oxime under standard conditions, rather than undergoing ring substitution (at the time pentafluorobenzaldehyde **35** was more easily prepared than the related mono- and polyfluorinated pyridine systems and therefore a good test case). Oxime (**I**) was not screened for potential biological activity because it lacked the nitrogen atom believed to be necessary for AChE reactivation.

2.3. Porton screening data

The classical approach adopted at Porton [26,27] for screening potency of oximes as reactivators of inhibited AChE sought to correlate a relevant thermodynamic property (*e.g.* pK_a) with nucleophilicity towards a particular NA (*e.g.* sarin). Nucleophilicity towards the NA was assumed to reflect that towards inhibited AChE. Acid dissociation constants for pyridinealdoximes and their methiodides (2-, 3- and 4-PAM) [28–33] reflect the inductive and conjugative effect of the nitrogen atom. Reactivating power of inhibited enzyme decreases in the order 2-PAM (pK_a 7.8) > 4-PAM (8.5) ≫ 3-PAM (9.2) [33,34].We measured pK_a values and second-order rate constants (k_{ox-}) towards sarin of the fluorinated pyridine aldoximes and some perprotio analogues (Table 1). A fluorine atom in the 3-position barely affected the pK_a of pyridine 2- and 4-aldoxime. The correlation that increased pK_a increases reactivity [26,27] was obeyed. The k_{ox-} of 2,3,5,6-tetrafluoropyridine-4-aldoxime (**E**) approached that of P2S, but even four fluorine atoms had reduced the pK_a to only 9.1.

The suggestion that the high reactivation ability of 1-methylpyridinium-2-aldoxime salts (P2S and 2-PAM) reflects the ability of the quaternary nitrogen atom to bind to the anionic site of inhibited AChE, orientating the oxime group towards the phosphorus atom of the bound inhibitor [35], is difficult to

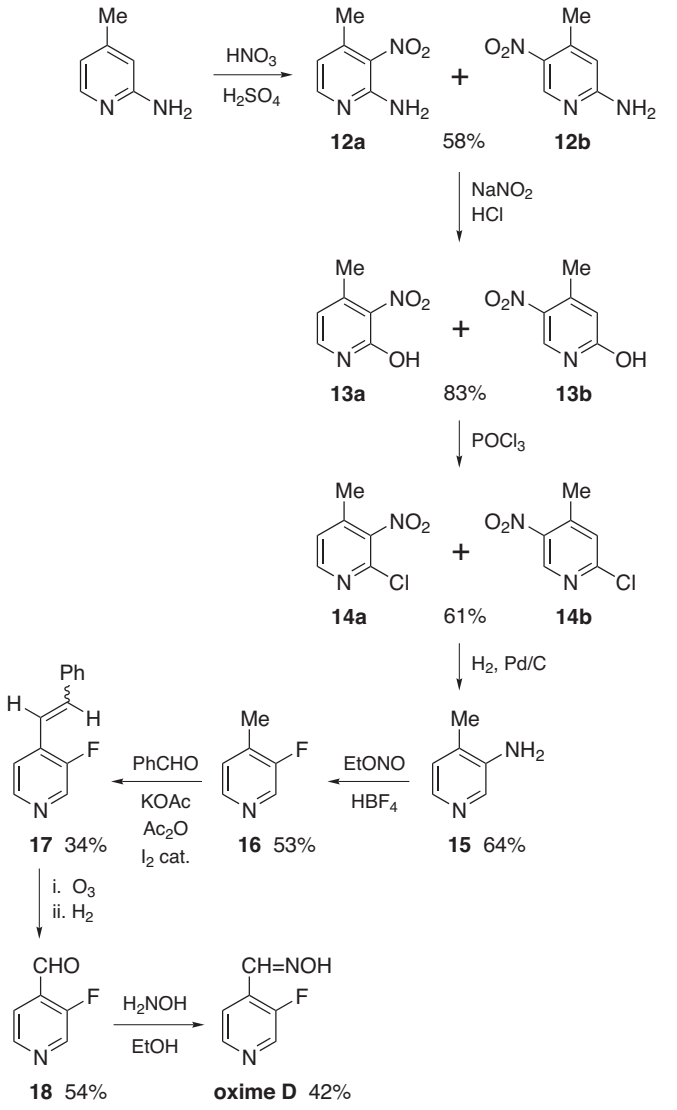
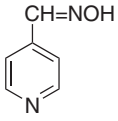
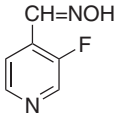
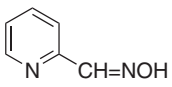
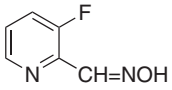
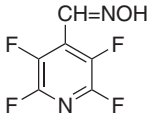
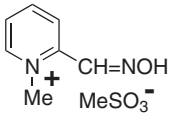
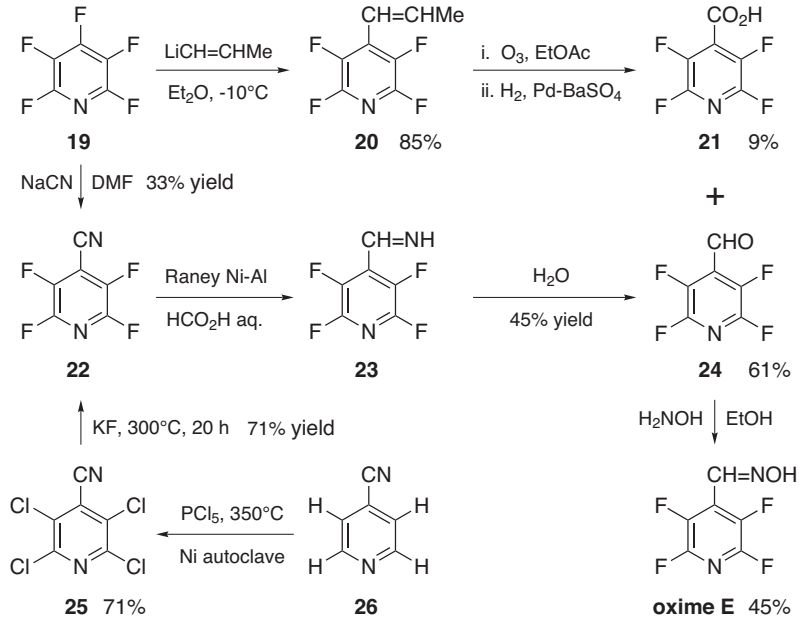


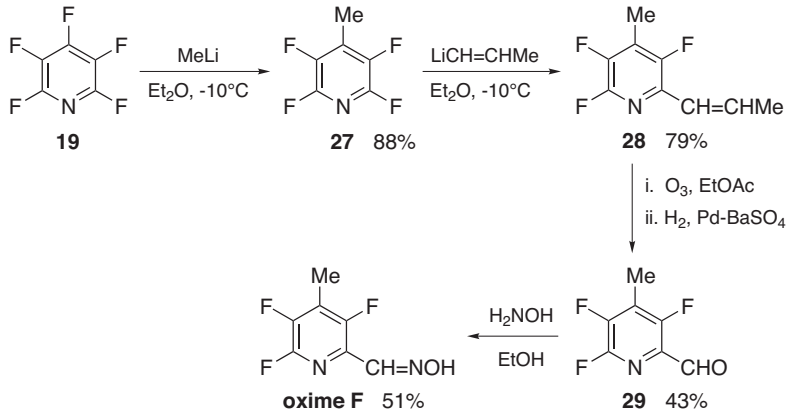
Table 1
Porton screening data.

Oxime	pK_a	k_{ox-} ($l\,mol^{-1}\,min^{-1}$)
	10.1	–
 **D**	9.8	1800
 **P2A**	10.1	1690
 **C**	10.1	1300
 **E**	9.1	310
 **P2S**	7.8	120

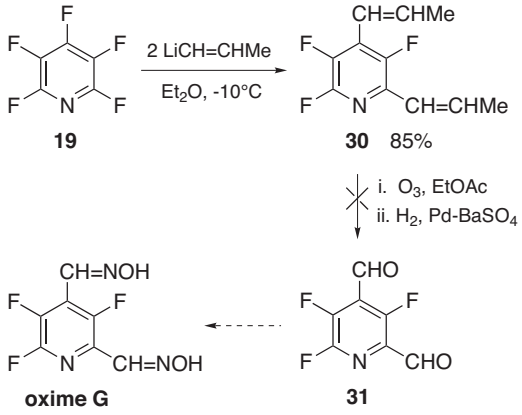
Scheme 4.



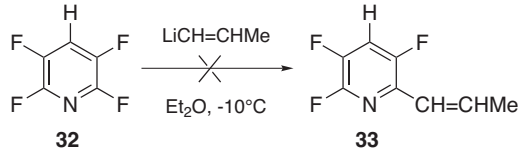
Scheme 5.



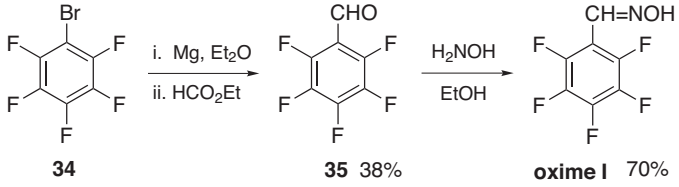
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

evaluate relative to the basicity and nucleophilicity of the oxime group, because in most instances the inductive effect of the quaternary nitrogen atom influences profoundly these properties. Aldoximes with a pK_a of 7.6–8.0 will be the best reactivators *in vivo* regardless of oximate nucleophilicity or the presence of a quaternary nitrogen atom. A recent study comparing oxime pK_a with reactivity towards sarin confirmed that reactivity tails off as the pK_a exceeds 9 [36]. Although the fluorinated oximes screened did not appear promising antidotes, *N*-alkylation, which seems feasible [37], might reduce the pK_a to a value useful for reactivation (*cf.* P2A 10.1 → P2S 7.8) and impart beneficial activity. Supporting this idea is the finding that 3-fluoro-4-PAM reactivated $(EtO)_2$-P(O)OAChE *in vitro* much more efficiently than 4-PAM [12].

Although the screening method reported here was used in the past at Porton to select compounds for *in vivo* evaluation, direct reaction between an oxime and an organophosphorus inhibitor is not relevant *in vivo* – reactivation of inhibited AChE is the major mechanism of therapeutic action. To evaluate novel oximes it is now common practice to investigate the kinetics of reactivation of inhibited AChE before moving to *in vivo* models. Caution must be exercised however, as the merit of reactivation experiments lies not in their ability to predict the effectiveness of treatment *in vivo*, but as an adjunct to such studies [38]. Also, the pK_a and formation of oximates is only one factor responsible for the reactivating potency of oximes. The pK_a value for P2S is the same as that measured for obidoxime, which reactivates more efficiently AChE inhibited by a broader range of organophosphorus compounds [5,7]. Evidence has accumulated to suggest that reversible π-bonding of oximes to tryptophan residues [3] in the AChE active site may help manoeuvre the oximate anion towards the bound phosphorus residue. This would suggest an improvement in reactivation with increasing positive charge on the oxime ring; this effect may contribute to the greater efficacy of 1-alkylpyridinium salts over their unquaternized counterparts. Fluorine atoms should cause the ring to become more electron-deficient and able to π-bond better (note that benzene (mp 6 °C) and hexafluorobenzene (mp 4 °C) form a stable 1:1 complex (mp 24 °C) when mixed [39]). Other oxime selection criteria are summarised elsewhere [40].

3. Conclusions

The pK_a values of 3-fluoropyridine-2- and -4-aldoxime (**C**) and (**D**) are too high for reactivation of inhibited AChE to occur *in vivo*. Tetrafluoropyridine-4-aldoxime (**E**) has a $k_{ox}-$ value approaching that of the good reactivator P2S, but suffers from the disadvantage that even four fluorine atoms reduce the pK_a to only 9.1. It seems clear, however, that *N*-alkylation or the introduction of powerful electron-attracting groups (*e.g.* CF_3, CF_2H, SF_5, NO_2, CN, CF_3SO_2 and perhaps CF_3CH_2) as well as fluorine may lower the pK_a to around the desired value of 8 while maintaining or improving the $k_{ox}-$ figure. The historical data discussed herein should stimulate further research into fluorinated oximes as countermeasures to NA poisoning. Lines of development awaiting exploitation include quaternization of the oximes described and investigation of their ability to reactivate human AChE inhibited by a variety of nerve agents.

4. Experimental details

The carboxaldehydes featured in Schemes 2–9 have become commercially available in recent years, so only procedures to the oximes are described.

4.1. 2-Fluoropyridine-3-aldoxime (A)

A solution of 2-fluoropyridine-3-carboxaldehyde (5.1 g, 40.8 mmol) in ethanol (10 ml) was added to hydroxylamine hydrochloride (5.0 g, 71.9 mmol) in water (20 ml) basified with 2 M NaOH (5 ml). The mixture was heated under reflux for 15 min and the product collected by filtration and sublimed (60 °C/1 mmHg; 3.4 g, 60%). Mp 123 °C. Calcd. for $C_6H_5FN_2O$: C, 51.4; H, 3.6; N, 20.0. Found: C, 51.1; H, 3.0; N, 19.8%.

4.2. 2-Fluoropyridine-6-aldoxime (B)

2-Fluoropyridine-6-carboxaldehyde (0.5 g, 4.0 mmol), hydroxylamine hydrochloride (1.2 g, 17.3 mol) and 1 M NaOH (12 ml) were heated under reflux for 20 min. The product that precipitated upon cooling was collected by filtration and sublimed (60 °C/1 mmHg, 0.4 g, 71%). Mp 153 °C. Calcd. for $C_6H_5FN_2O$: C, 51.4; H, 3.6; N, 20.0. Found: C, 51.5; H, 3.6; N, 20.0%.

4.3. 3-Fluoropyridine-2-aldoxime (C)

3-Fluoropyridine-2-carboxaldehyde (0.7 g, 5.6 mmol) was converted to oxime **C** with difficulty using the technique described in the previous section (0.3 g, 37%). Mp 85 °C. IR ν_{max} 3070 (m), 2809 (m), 2789 (m), 1586 (m), 1495 (s), 1445 (s), 1318 (s), 1236 (m), 1152 (w), 1110 (w), 986 (m), 980 (m) and 803 (m) cm^{-1}. Calcd. for $C_6H_5FN_2O$: C, 51.4; H, 3.6; N, 20.0. Found: C, 51.3; H, 3.6; N, 20.0%.

4.4. 3-Fluoropyridine-4-aldoxime (D)

3-Fluoropyridine-4-carboxaldehyde (1.5 g, 12 mmol) in ethanol (5 ml) was added to hydroxylamine hydrochloride (1.5 g, 21.7 mmol) in water (15 ml) basified with 2 M NaOH aq. The mixture was warmed to 60 °C for 20 min, cooled, and the resulting precipitate collected and sublimed several times to provide oxime **D** (0.7 g, 42%). Mp 115 °C. IR ν_{max} 2788 (s), 1590 (m), 1525 (m), 1430 (s), 1380 (s), 1300 (s), 1449 (m), 1220 (m), 1188 (m), 1046 (m), 1000 (s), 894 (m), 836 (s), 821 (s) cm^{-1}. Calcd. for $C_6H_5FN_2O$: C, 51.4; H, 3.6; N, 20.0. Found: C, 51.1; H, 3.1; N, 18.9%.

4.5. Pentafluorobenzaldoxime (I)

Pentafluorobenzaldehyde (0.4 g, 2.0 mmol) in ethanol (5 ml) was added to a solution of hydroxylamine hydrochloride (1.0 g, 14.5 mmol) in water (4 ml) basified with 2 M NaOH (4 ml). The mixture was refluxed for 15 min. The crude precipitate was filtered off and sublimed several times to give oxime **I** (60 °C/1 mmHg; 0.3 g, 70%). Mp 129 °C. Calcd. for $C_7H_2F_5NO$: C, 39.8; H, 0.9; N, 6.6. Found: C, 40.2; H, 1.4; N, 6.4%.

4.6. Acid dissociation constants (pK_a)

These were determined by potentiometric titration of the oxime (about 0.01 M) with NaOH (0.1 M) in aqueous KCl (0.1 M) at 25 °C according to a literature method [26]. Briefly, potassium chloride was used to maintain an approximately constant ionic strength. The pK_a values were calculated by the Henderson–Hasselbalch equation from pH values around the half-neutralisation point.

4.7. Second-order rate constants ($k_{ox}-$)

The reaction between aromatic aldoximes and sarin in aqueous solution occurs by rate-controlling attack of the oxime anion at the phosphorus centre with loss of HF, followed by rapid splitting of the oxime phosphonate to give isopropyl methylphosphonic acid. Second-order rate constants ($k_{ox}-$) were derived using a literature method [26] by measuring the rate of acid production in KCl aq. (0.1 M) at 25 °C by continuous titration to constant pH with sodium hydroxide. In the presence of a large excess of oxime, and using equipment already described [26,27], the observed rate of total acid-production was first order and proportional to the oxime concentration and degree of ionisation (i) of the oxime calculated from the Henderson–Hasselbalch equation, *i.e.* $-d[sarin]/dt = d[nH^+]/dt = k_{ox}- \; i[oxime][sarin]$ where n was the number of moles of acid obtained per mole of sarin decomposed (*i.e.* 2).

Acknowledgements

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References

[1] C.M. Timperley, Highly-toxic fluorine compounds, in: R.E Banks (Ed.), Fluorine Chemistry at the Millennium: Fascinated by Fluorine, Elsevier, Oxford UK, 2000, pp. 499–537 (Chapter 29).
[2] F. Worek, R. Widmann, O. Knopff, L. Szinicz, Arch. Toxicol. 72 (1998) 237–243.
[3] P.I. Hammond, C. Kern, F. Hong, T.M. Kollmeyer, Y.P. Pang, S. Brimijoin, J. Pharmacol. Exp. Ther. 307 (2003) 190–196.
[4] F. Hobbiger, Reactivation of phosphorylated acetylcholinesterase, in: Handbuch der Experimentellen Pharmakologie Bd 15, Springer, Berlin, 1963, pp. 921–988 (Chapter 21).
[5] K. Kuca, D. Jun, K. Musilek, Mini-Rev. Med Chem. 6 (2006) 269–277.
[6] J.Z. Karasova, M. Pohanka, K. Musilek, F. Zemek, K. Kuca, Toxicol. Vitro 24 (2010) 1838–1844.
[7] V.A. Voicu, J. Bajgar, A. Medvedovici, F.S. Radulescu, D.S. Miron, J. Appl. Toxicol. 30 (2010) 719–729.
[8] D.R. Davies, A.L. Green, Br. J. Ind. Med. 16 (1959) 128–134.
[9] D.A. Smith (Ed.), Metabolism, Pharmacokinetics and Toxicity of Functional Groups – Impact of the Building Blocks of Medicinal Chemistry on ADMET, RSC Drug Discovery Series, Cambridge UK, 2010.
[10] I.M. Young, Studies of Fluorinated Pyridine Derivatives, Ph.D. Thesis, UMIST, Manchester, 1966.
[11] H.C. Jeong, N.J. Park, C.H. Chae, K. Musilek, J. Kassa, K. Kuca, Y.S. Jung, Bioorg. Med. Chem. 17 (2009) 6213–6217.
[12] H.C. Jeong, N.S. Kang, N.J. Park, E.K. Yum, Y.S. Jung, Bioorg. Med. Chem. Lett. 19 (2009) 1214–1217.
[13] J. Kassa, J.Z. Karasova, F. Caisberger, K. Musilek, K. Kuca, Y.S. Yung, J. Enz. Inhib. Med. Chem. 25 (2010) 480–484.
[14] A. Roe, G.F. Hawkins, J. Am. Chem. Soc. 69 (1947) 2443–2444.
[15] G.F. Hawkins, A. Roe, J. Org. Chem. 14 (1949) 328–332.
[16] A. Roe, P.H. Cheek, G.F. Hawkins, J. Am. Chem. Soc. 71 (1949) 4152–4153.
[17] J.T. Minor, G.F. Hawkins, C.A. Van der Werf, A. Roe, J. Am. Chem. Soc. 71 (1949) 1125–1126.
[18] E. Mosettig, R. Mozingo, Org. React. 4 (1957) 362–377.
[19] H.E. Baumgarten, H.C. Su, J. Am. Chem. Soc. 74 (1952) 3828–3831.
[20] A. Roe, R.B. Seligman, J. Org. Chem. 20 (1955) 1729–1732.
[21] J. Stanek, M. Horak, Coll. Czech. Chem. (1950) 1037–1045.
[22] R.E. Banks, J.E. Burgess, W.M. Cheng, R.N. Haszeldine, J. Chem. Soc. (1965) 575–581.
[23] R.E. Banks, R.N. Haszeldine, I.M. Young, J. Chem. Soc. (C) (1967) 2089–2091.
[24] R.N. Haszeldine, R.E. Banks, US patent 3,317,542, 2 May 1967.
[25] E. Nield, R. Stephens, J.C. Tatlow, J. Chem. Soc. (1959) 166–171.
[26] A.L. Green, B. Saville, J. Chem. Soc. (1956) 3887–3892.
[27] A.L. Green, G.L. Sainsbury, B. Saville, M. Stansfield, J. Chem. Soc. (1958) 1583–1587.
[28] S. Ginsburg, I.B. Wilson, J. Am. Chem. Soc. 79 (1957) 481–485.
[29] F. Hobbiger, M. Pitman, P.W. Sadler, Biochem. J. 75 (1960) 363–372.
[30] S.F. Mason, J. Chem. Soc. (1960) 22–26.
[31] Y. Ashani, S. Cohen, J. Med. Chem. 13 (1970) 471–474.
[32] Y. Ashani, S. Cohen, J. Med. Chem. 14 (1971) 621–626.

[33] R.L. Salvador, M. Saucier, D. Simon, R. Goyer, J. Med. Chem. 15 (1972) 646–650.
[34] F. Hobbiger, D.G. O'Sullivan, P.W. Sadler, Nature (London) 182 (1958) 1498–1499.
[35] I.B. Wilson, S. Ginsburg, C. Quan, Arch. Biochem. Biophys. 77 (1958) 286–296.
[36] F. Terrier, P. Rodriguez-Dafonte, E. Le Guéval, G. Moutiers, Org. Biomol. Chem. 4 (2006) 4352–4363.
[37] C.M. Timperley, M. Bird, S.C. Heard, S. Notman, R.W. Read, J.E.H. Tattersall, S.R. Turner, J. Fluorine Chem. 126 (2005) 1160–1165.
[38] B. Harvey, D.J. Sellers, P. Watts, Biochem. Pharm. 33 (1984) 3499–3501.
[39] P. Kirsch, Modern Fluoroorganic Chemistry, Wiley-VCH, Weinheim, 2004.
[40] M. Jokanović, M.P. Stojiljković, Eur. J. Pharmacol. 553 (2006) 10–17.