2-Fluoropyridine *N*-Oxide in Peptide Chemistry

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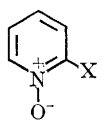
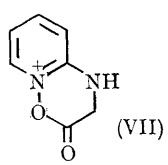
2-FLUOROPYRIDINE *N*-OXIDE[1] (I) has been prepared by the oxidation of 2-fluoropyridine with trifluoroperacetic acid in methylene dichloride.[2] It is an unstable, hygroscopic solid, darkening rapidly on exposure to air, which can best be stored at 0° in methylene chloride or as its crystalline hygroscopic hydrochloride. It is also stable for days in aqueous sodium bicarbonate. The oxide (I) reacts readily with glycine-*N*-cyclohexylamide[3] in aqueous sodium bicarbonate to give the stable amino-compound (II) which can be degraded with hot 98% formic acid to the acid (III) identical with the product obtained by condensation of the oxide (I) with glycine. The virtually quantitative yields in the condensation and fission reactions and the ease of detection and identification of the amino-acid derivatives[4] of the *N*-oxide by t.l.c. suggest that the reaction might be useful in *N*-terminal analysis of peptides. The acid (III) can also be obtained under similar conditions from the glycylglycine (IV) ($t_{\frac{1}{2}}$ 10 min.), glycylglycine ethyl ester (V), and glycine ethyl ester (VI) derivatives of the oxide. We have no conclusive evidence for the mechanism of the fission reaction but stronger acids (trifluoroacetic and hydrogen chloride in acetic) have no effect (other than salt formation) upon (II) while the fission is slower in trifluoroacetic–formic acid (1 : 1) than in 98% formic. The amide (II) is also stable to refluxing acetic acid. Accepting that these are not dielectric effects and knowing that 2-aminopyridine *N*-oxides are protonated on oxygen[5] they suggest that oxide-protonated (II) will not undergo the fission reaction and that the rate of fission depends on the concentration of carbonyl-protonated (II) which cyclises to (VII) the precursor of (III).

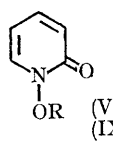
prior carboxyl activation, has been described. However the oxide (I) reacts with benzoic acid–triethylamine or tetraethylammonium benzoate in acetonitrile to give *N*-benzoyloxypyridone (IX) in 19 and 24% yield respectively. These disappointing yields were improved somewhat by treating benzoic acid with the oxide (I) in methylene dichloride to give 40% of the ester.[8] In agreement with Paquette[6] we find that the pyridone esters of simple amino-acid derivatives *e.g.*, hippuric and *N*-ethoxycarbonylglycine esters, are unstable and difficult to isolate pure. The high reactivity in *N*-acylation of the pyridone esters compared to esters of simple hydroxamic acids can be seen from the Table which also shows the expected activating effect of electron-withdrawing groups in the simple diacylhydroxylamines. *N*-Phenyl has a large accelerating effect presumably due to delocalisation of the nitrogen lone-pair reducing the electron density in the N–O–C=O system. A similar effect would explain the high reactivity of the pyridone



(I) X=F
(II) X=NH·CH$_2$·CO·NH·cyclo C$_6$H$_{11}$
(III) X=NH·CH$_2$·CO$_2$H
(IV) X=NH·CH$_2$·CO·NH·CH$_2$·CO$_2$H
(V) X=NH·CH$_2$·CO·NH·CH$_2$·CO$_2$Et
(VI) X=NH·CH$_2$·CO$_2$Et



(VII)



(VIII) R=H
(IX) R=CO·Ph

TABLE. *Half-lives of the esters with two equivalents of amine in methylene dichloride at* 20°[10]

Ester (IX)	Amine $H_2NCH_2·CONH·cyclo C_6H_{11}$	Half-life (min)
PhCON(Ph)OCOPh	,,	<1
PhCON(Ph)OCOCH$_2$NHCO$_2$Et	,,	3720
PhCON(Ph)OCOPh	cyclo$C_6H_{11}NH_2$	9
PhCON(Me)OCOPh	,,	<1
p-O$_2$NC$_6$H$_4$CON(Me)OCOPh	,,	720
p-MeOC$_6$H$_4$CON(Me)OCOPh	,,	360
	,,	1030

Recently it has been shown[6,7] that esters of *N*-hydroxypyridone (VIII) are efficient acylating agents but no method for their synthesis, without

esters. Thus it appears that from the standpoint of reactivity, and stability and ease of purification, esters of *N*-phenylhydroxamic acids offer most

promise of those hydroxamic acid esters so far investigated although at present there is no way of preparing them without prior carboxyl activation.

Finally the stability of 2-chloro- and 2-iodopyridine *N*-oxides under the conditions where the fluoro-compound reacts suggests that the nucleophilic displacements occur by an addition–elimination mechanism as found in the halogeno-2,4-dinitrobenzene series.[9]

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[1] M. Bellas and H. Suschitzky, *J. Chem. Soc.*, 1965, 2096, mention that they were unable to prepare the oxide by the method claimed in BP 847,701/1958.

[2] W. D. Emmons, *J. Amer. Chem. Soc.*, 1954, **76**, 3468.

[3] The amide was prepared by reaction of *N*-toluene-*p*-sulphonylglycine acid chloride with cyclohexylamine, followed by reductive removal of the sulphonyl group with sodium in liquid ammonia.

[4] 2-Pyridyl *N*-oxide derivatives of phe, val, asp, ala, met, and pro have been prepared.

[5] J. N. Gardener and A. R. Katritzky, *J. Chem. Soc.*, 1957, 4375.

[6] L. A. Paquette, *J. Amer. Chem. Soc.*, 1965, **87**, 5186.

[7] J. K. Sutherland and D. A. Widdowson, *J. Chem. Soc.*, 1964, 4651.

[8] This may be an example of acid catalysis of nucleophilic substitution since we have shown that (I) hydrochloride or (I) toluene-*p*-sulphonate in methanol readily gives the 2-methoxypyridine *N*-oxide. *O*-Protonation of (I) would be expected to increase the rate of nucleophilic attack at position 2.

[9] J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, *J. Amer. Chem. Soc.*, 1957, **79**, 385.

[10] All esters were prepared by reaction of hydroxamic acid, carboxylic acid, and *NN*-dicyclohexylcarbodi-imide in methylene dichloride. $t_{\frac{1}{2}}$-Values were determined by measuring the rate of disappearance of the 1800—1760 cm.$^{-1}$ absorptions on 0·005M-solutions.