2-Halogenopyridine *N*-Oxides in Peptide Chemistry: Reactions of 2-Chloro-3- and -5-nitropyridine *N*-oxides with Benzoic Acid

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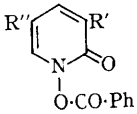
RECENTLY it has been shown that *N*-hydroxypyridone esters (Ia) can acylate amines under mild conditions: the acyloxypyridones such as (Ia) have been obtained from the reaction of an acid chloride either on *N*-hydroxypyridone (IIa)[1] or on 2-ethoxypyridine *N*-oxide (IIIa).[2] By using instead 2-fluoropyridine *N*-oxide (IIIb), *N*-benzoyloxypyridone (Ia) has been isolated in 20 and 40% yield from the reactions with tetraethylammonium benzoate and benzoic acid respectively.[3]

Such methods for the preparation of acyloxypyridones have the disavdantage of requiring as starting material either an acid halide which already therefore contains an activated carboxyl function or the 2-fluoropyridine *N*-oxide which, although it reacts with benzoic acid directly, gives benzoyloxypyridone with poor yield and is an unstable product.

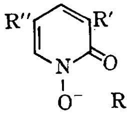
In order to overcome these inconveniences, different pyridine *N*-oxide derivatives have been considered: 2-chloro-3-nitropyridine (IIIc) and 2-chloro-5-nitropyridine *N*-oxide (IIId) have been prepared by the oxidation of the corresponding halogenonitropyridines with trifluoroperacetic acid.[4]

The compounds (IIIc) and (IIId) are stable and can be easily purified by crystallisation; they react with benzoic acid in acetonitrile or methylene dichloride to give *N*-benzoyloxypyridones (Ib) and (Ic) which can be isolated in 70% yield.[5]

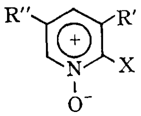
The compounds (Ib) and (Ic) react with amines in acetonitrile to give immediately the benzamides and the hydroxynitropyridone salts (IIb, IIc, IId, IIe) which are insoluble in the reaction medium and soluble in water, so that they are easily removed.


(I)

a; R′=R″ =H
b; R′=NO_2, R″ =H
c; R′=H, R″ =NO_2


(II)

a; R=R′=R″ =H
b; R′=NO_2, R″ =H, R=NH_3·cyclo-C_6H_{11}
c; R′=H, R″ =NO_2, R=NH_3·cyclo-C_6H_{11}
d; R′=NO_2, R″ =H, R=NH_3·CH_2·CO·NH·cyclo-C_6H_{11}
e; R′=H, R″ =NO_2, R=NH_3·CH_2·CO·NH·cyclo-C_6H_{11}


(III)

a; R′=R″ =H, X=OEt
b; R′=R″ =H, X=F
c; R′=NO_2, R″ =H, X=Cl
d; R′=H, R″ =NO_2, X=Cl

The presence of an electron-withdrawing group on the pyridine ring besides making the chlorine atom in (IIIc) and (IIId) more reactive and facilitating the purification of the benzoyloxypyridones (Ib) and (Ic), increases their reactivity towards amines which are acylated at 0°C. Moreover the hydroxynitropyridones formed in the reaction with amines give stable salts which can be isolated and purified.

From the reaction of (Ib) and (Ic) with cyclohexylamine, glycine *N*-cyclohexylamide, and glycine methyl ester hydrochloride the corresponding benzamides, identical with pure samples, have been obtained in quantitative yield.[6]

Phthaloyl-L-alanine reacts with (IIIc) and (IIId); the crude products[7] treated with cyclohexylamine give phthaloyl-L-alanine *N*-cyclohexylamide (40% yield).

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[1] J. K. Sutherland and D. A. Widdowson, *J. Chem. Soc.*, 1964, 4651.
[2] L. A. Paquette, *J. Amer. Chem. Soc.*, 1965, **87**, 5186.
[3] D. Sarantakis, J. K. Sutherland, C. Tortorella, and V. Tortorella, *Chem. Comm.*, 1966, 105.
[4] The oxidation of 2-chloro-3,5-dinitropyridine was unsuccessful.
[5] *N*-Benzoyloxypyridones were prepared from *N*-oxides (1 mole) and benzoic acid (1 mole) dissolved in acetonitrile or methylene dichloride under reflux for 2 hours. Yield better than that indicated has been obtained in methylene dichloride under reflux for 20 hours. 2-Chloro-5-nitropyridine *N*-oxide reacts with benzoic acid at room temperature as well: the required time to obtain 50% yield is about a week.
[6] In the first two reactions one mole of amine and one mole of *N*-benzoyloxypyridone were used; in the third one, twice the amount of triethylamine was added to equimolecular amounts of the reagents.
[7] It has been shown that the acyloxypyridones from benzoic acid and its derivatives are more stable than those from *N*-protected amino-acids since they decompose during purification (refs. 2 and 3).