REACTIONS OF PYRIDINE N-OXIDE WITH ENAMINES OF N-SUBSTITUTED 4-PIPERIDONES IN THE PRESENCE OF AN ACYLATING AGENT

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Pyridine N-oxide reacts with enamines of N-benzoyl-, N-ethoxycarbonyl- and N-acetyl-4-piperidones in the presence of benzoyl chloride to give N-substituted 3-(2-pyridyl)-4-piperidones in fair or good yields. Enamine of N-methyl- or N-benzyl-4-piperidone resists this reaction.

Pyridine N-oxide (I) readily reacts with enamines of cyclohexanone in the presence of benzoyl chloride to give 2-(2-pyridyl)-cyclohexanone on treatment of the reactants with 20% hydrochloric acid[1]. While the reaction using 1(10)-dehydroquinolizidine as a heterocyclic enamine similarly proceeds[2], attempted reations with enamines of N-substituted 4-piperidones such as morpholine enamine of N-benzoyl-4-piperidone

(A) were described to be unsuccessful[3].

Recently we happened to find that a small amount of picolinic acid N-oxide was obtained from the reaction of I with A by oxidation of the residue from the 20% hydrochloric acid extract with 30% hydrogen peroxide and acetic acid. This fact stimulated to re-examine this reaction, and we succeeded in the isolation of N-benzoyl-3-(2-pyridyl)-4-piperidone (II) on treatment of the reaction mixture with conc. hydrochloric acid instead of the generally used 20% hydrochloric acid.

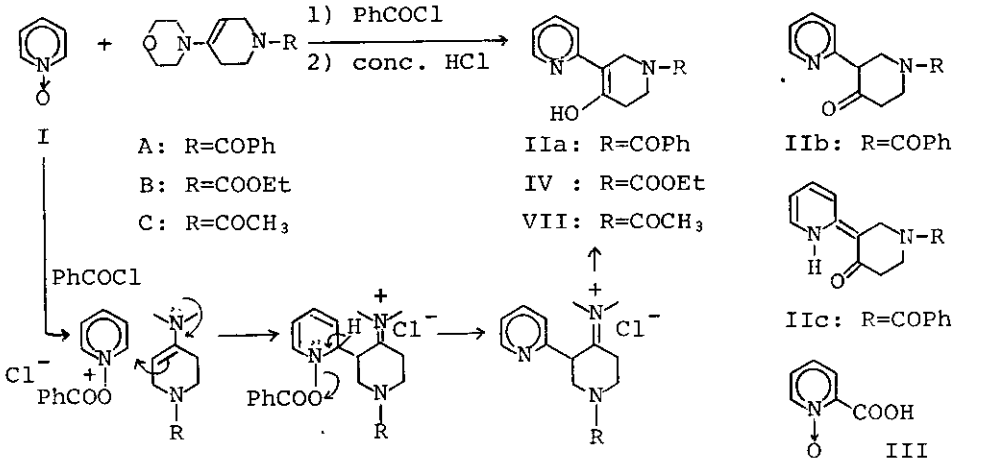
Thus, when benzoyl chloride (1.2 equiv) was added to an ice-cooled solution of I and A (3 equiv) in chloroform, an exothermic reaction occured and the solution became dark red through yellow. The reaction mixture was kept at room temperature for 2 days, followed by extracting with conc. hydrochloric acid to give II, light yellow powders, mp 114-116° (isopropyl alcohol-isopropyl ether), as a main product in 26% yield.

Structure assignment of II is based on the satisfactory elemental analysis [$C_{17}H_{16}O_2N_2$], the ir spectrum [ν_{max}^{KBr}: 2600 (a chelated hydrogen bond) and 1630 cm^{-1} (an enol C=C bond)] and nmr spectrum [δ ($CDCl_3$): 2.48 (2H, t, J=6.0 Hz, C_5-H of piperidone ring), 3.68 (2H, t, J=6.0 Hz, C_6-H of piperidone ring), 4.33 (2H, s, C_2-H of piperidone ring), 8.30 (1H, m, α-H of pyridine ring) and 15.5 (1H, s, OH); apparently II exists chiefly as the enolic form (IIa) rather than the ketonic (IIb) and the enaminic ones (IIc) in the same way with other 2-picolyl ketones[4]. Oxidation of II with 30% hydrogen peroxide-

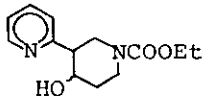
acetic acid gave picolinic acid N-oxide (III).

The reaction can be explained by the addition-elimination process of the benzoyl-adduct of I as in the case reported earlier[1], and the reported failure[3] in isolating the product II may be due to the sparing solubility of II in 20% hydrochloric acid.

It was further found that the use of morpholine enamine of N-ethoxycarbonyl-4-piperidone (B) instead of A gave the corre-



sponding product (IV), yellowish oil, bp 158-160° (0.3-0.4 mm Hg), in much better yield (85%).



V, VI

Treatment of V with sodium borohydride in ethanol afforded two isomeric alcohols (V and VI); V was isolated as a crystalline hydrochloride, mp181-184°, and VI as an oxalate, mp 140°.

Some detailed examinations of reactions with enamines of N-ethoxycarbonyl-4-piperidone revealed that there were no noticeable differences among reactions using 4-morpholino-,

4-piperidino- and 4-pyrrolidino-derivatives and the order in effectiveness of acylating agents were as follows : benzoyl chloride > tosyl chloride > acetyl chloride > acetic anhydride (see Table).

Much more remarkable is the large dependency of the ease with which the reaction occurs on the nature of the N-substituent of the piperidone; thus, the reaction of I with morpholine enamine of N-acetyl-4-piperidone (C) smoothly proceeded in the presence of benzoyl chloride to give the N-acetyl derivative (VII), bp 120-130° (bath temp.)(0.1-0.2 mm Hg), in 51.4% yield, but no definite product was obtained from the similar reaction with enamines of N-methyl- or N-benzyl-4-piperidone.

Table I

Exp. No.	(I) g	Amine of Enamine[a] g (eq)		AX g (eq)		Et_3N g(eq)	React. time	Product(IV) g (%)
1	4.75	morpholine	16.8 (1.4)	PhCOCl	8.4 (1.2)	-	48hr	10.6 (85)
2	4.75	morpholine	16.8 (1.4)	TsCl	11.4 (1.2)	-	48hr	4.7 (37.9)
3	4.75	morpholine	16.8 (1.4)	AcCl	4.7 (1.2)	-	48hr	1.9 (15.3)
4	4.75	morpholine	16.8 (1.4)	Ac_2O	6.1 (1.2)	-	48hr	0.4 (3.3)
5	4.75	piperidine	16.7 (1.4)	PhCOCl	8.4 (1.2)	-	48hr	9.8 (79)
6	4.75	pyrrolidine	15.7 (1.4)	PhCOCl	8.4 (1.2)	-	48hr	9.9 (79.8)
7	4.75	morpholine	12.0 (1.0)	PhCOCl	7.0 (1.0)	-	48hr	7.7 (62)
8	4.75	morpholine	24.0) (2.0)	PhCOCl	7.0 (1.0)	-	48hr	10.1 (81.5)
9	4.75	morpholine	12.0 (1.0)	PhCOCl	7.0 (1.0)	5.06 (1.0)	48hr	5.7 (46)

a) Enamine of N-ethoxycarbonyl-4-piperidone

Enamine B is most reactive towards this type of reaction among enamines of N-substituted 4-piperidone so far examined and reacts with various derivatives of pyridine and other aromatic *N*-oxides. The details of this study will be published shortly.

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