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

Michio Nakanishi and Masahiro Yatabe
Research Laboratories, Yoshitomi Pharmaceutical Industries Ltd.,
Koiwai, Yoshitomi-cho, Chikujiyo-gun, Fukuoka, Japan

Masatomo Hamana*
Faculty of Pharmaceutical Sciences, Kyushu University
Maidashi, Higashi-ku, Fukuoka, Japan

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. While the reaction using l(10)-dehydroquinolizidine as a heterocyclic enamine similarly proceeds, attempted reactions 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 occurred 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 \([v^\text{KBr}_{\text{max}}: 2600 \text{ cm}^{-1} \,(\text{a chelated hydrogen bond}) \text{ and } 1630 \text{ cm}^{-1} \,(\text{an enol C=C bond})]\) and nmr spectrum \([\delta \,(\text{CDCl}_3): 2.48 \,(2H, t, J=6.0 \text{ Hz, } C_5-H \text{ of piperidone ring}), 3.68 \,(2H, t, J=6.0 \text{ Hz, } C_6-H \text{ of piperidone ring}), 4.33 \,(2H, s, C_2-H \text{ of piperidone ring}), 8.30 \,(1H, m, \alpha-H \text{ of pyridine ring}) \text{ 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. 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, and the reported failure 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 corresponding product (IV), yellowish oil, bp 158-160° (0.3-0.4 mm Hg), in much better yield (85%).

Treatment of V with sodium borohydride in ethanol afforded two isomeric alcohols (V and VI); V was isolated as a crystalline hydrochloride, mp 181-184°, 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

<table>
<thead>
<tr>
<th>Exp. (I)</th>
<th>Amine of Enamine(a)</th>
<th>AX (eq)</th>
<th>Et(_3)N (eq)</th>
<th>React. time</th>
<th>Product (IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 4.75</td>
<td>morpholine 16.8 (1.4)</td>
<td>PhCOCl 8.4 (1.2)</td>
<td>-</td>
<td>48hr</td>
<td>10.6 (85)</td>
</tr>
<tr>
<td>2 4.75</td>
<td>morpholine 16.8 (1.4)</td>
<td>TsCl 11.4 (1.2)</td>
<td>-</td>
<td>48hr</td>
<td>4.7 (37.9)</td>
</tr>
<tr>
<td>3 4.75</td>
<td>morpholine 16.8 (1.4)</td>
<td>AcCl 4.7 (1.2)</td>
<td>-</td>
<td>48hr</td>
<td>1.9 (15.3)</td>
</tr>
<tr>
<td>4 4.75</td>
<td>morpholine 16.8 (1.4)</td>
<td>Ac(_2)O 6.1 (1.2)</td>
<td>-</td>
<td>48hr</td>
<td>0.4 (3.3)</td>
</tr>
<tr>
<td>5 4.75</td>
<td>piperidine 16.7 (1.4)</td>
<td>PhCOCl 8.4 (1.2)</td>
<td>-</td>
<td>48hr</td>
<td>9.8 (79)</td>
</tr>
<tr>
<td>6 4.75</td>
<td>pyrrolidine 15.7 (1.4)</td>
<td>PhCOCl 8.4 (1.2)</td>
<td>-</td>
<td>48hr</td>
<td>9.9 (79.8)</td>
</tr>
<tr>
<td>7 4.75</td>
<td>morpholine 12.0 (1.0)</td>
<td>PhCOCl 7.0 (1.0)</td>
<td>-</td>
<td>48hr</td>
<td>7.7 (62)</td>
</tr>
<tr>
<td>8 4.75</td>
<td>morpholine 24.0 (2.0)</td>
<td>PhCOCl 7.0 (1.0)</td>
<td>-</td>
<td>48hr</td>
<td>10.1 (81.5)</td>
</tr>
<tr>
<td>9 4.75</td>
<td>morpholine 12.0 (1.0)</td>
<td>PhCOCl 7.0 (1.0)</td>
<td>5.06</td>
<td>48hr</td>
<td>5.7 (46)</td>
</tr>
</tbody>
</table>

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.

REFERENCES

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