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## The Acylation of 2-Picoline-N-oxide and 2,6-Lutidine N-oxide (1)

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2-Picoline N-oxide and 2,6-Lutidine N-oxide have been acylated in good to high yields by reaction with a series of aliphatic, aromatic and heterocyclic esters using sodium amide in liquid ammonia as the condensing agent.

Base effected acylations have previously been reported for 2-picoline (3, 4, 5) and 2,6-lutidine (6). We now report an extension of these reactions to 2-picoline N-oxide and 2,6-lutidine N-oxide. As an orienting reaction the benzoylation of 2-picoline N-oxide in the presence of sodium amide in liquid ammonia was studied. Thus, when 2-picoline N-oxide (two equivalents) was treated with sodium amide (two equivalents) in liquid ammonia followed by methyl benzoate (one equivalent) there was isolated 2-phenacylpyridine N-oxide (83.5%). However, when a 1:1:1 molar ratio of reactants was employed, the yield of 2-phenacylpyridine N-oxide fell to (46.8%) based on the ester. These results suggest that the course of the reaction may be represented by the following scheme, which is analogous to that suggested previously for the acylation of certain other methyl substituted heterocyclic nitrogen compounds (3, 4, 7). Next, 2-picoline N-oxide and 2,6-lutidine N-oxide were condensed with a series of aliphatic, aromatic and heterocyclic esters in the presence of sodium amide in liquid ammonia, using a 2:2:1 molar ratio of tar base N-oxide to sodium amide, to ester, respectively, to give the corresponding 2-picoly ketone N-oxides and 2,6-lutidyl ketone N-oxides in good yields; the results are given in Table I.

Certain base-effected acylations, (8, 9) oximations (10, 11) and aldol-type condensations (12, 13, 14) have previously been reported for 2-picoline N-oxide and 2,6-lutidine N-oxide. For those cases in which a direct comparison can be made between the prototropic activity of the methyl groups in the parent tar bases and their N-oxides, it would appear that for base-catalyzed reactions the methyl groups of the N-oxides are the more reactive (8, 10). For example, Adams and Miyano (8) have shown that whereas 2-picoline will not condense with the active aliphatic ester, ethyl oxalate, in the presence of potassium methoxide, 2-picoline N-oxide will react to give a 35% yield of ethyl 2-pyridylpyruvate N-oxide. From the present work two further direct comparisons can be made between the relative prototropic activity of the methyl groups in tar bases and their N-oxides. Thus, when 2-picoline N-oxide and 2,6-lutidine N-oxide were condensed with methyl benzoate in the present study 85.3% and 79.4% of the corresponding ketone N-oxides were obtained

respectively, whereas 2-picoline (15) and 2,6-lutidine (16) have been condensed with methyl benzoate under comparable conditions and gave the corresponding ketones in 50.2% and 44.0%, respectively.

From these and previous results (8, 10) it would appear that contrary to an earlier report (14), the N-oxide function may produce a significant enhancement in the prototropic activity of the methyl groups in  $\alpha$ -methyl pyridyl systems.

### EXPERIMENTAL

In this section typical procedures are given for: (a) the product is water insoluble; (b) the product is water soluble; and (c) the product may be distilled.

(a) The preparation of 2-phenacylpyridine N-oxide.

To sodium amide (0.2 mole) in 250 ml. of anhydrous liquid ammonia was added 2-picoline N-oxide (0.2 mole, 21.8 g.) which had previously been melted. The resulting, deep red solution was stirred for one hr. and then methyl benzoate (0.1 mole, 13.6 g.) diluted with an equal volume of anhydrous ether was added over a ten min. period. The mixture was stirred for one hr. and the reaction quenched by the addition of solid ammonium chloride (13.0 g.). The ammonia was replaced by 200 ml. of ether by heating the reactor on a steam bath. When the ammonia was essentially completely displaced, as was indicated by the refluxing of the ether, the reaction mixture was poured onto a small amount of ice, the solution was chilled and the precipitated solid was filtered, sucked dry and then washed with several portions of ether. In this way there was obtained 18.0 g. (85.3%) of 2-phenacylpyridine N-oxide, m.p. 158° from a mixture of benzene and petroleum ether (60-70° B.P.).

(b) The preparation of 2,6-lutidyl 3-pyridyl ketone N-oxide.

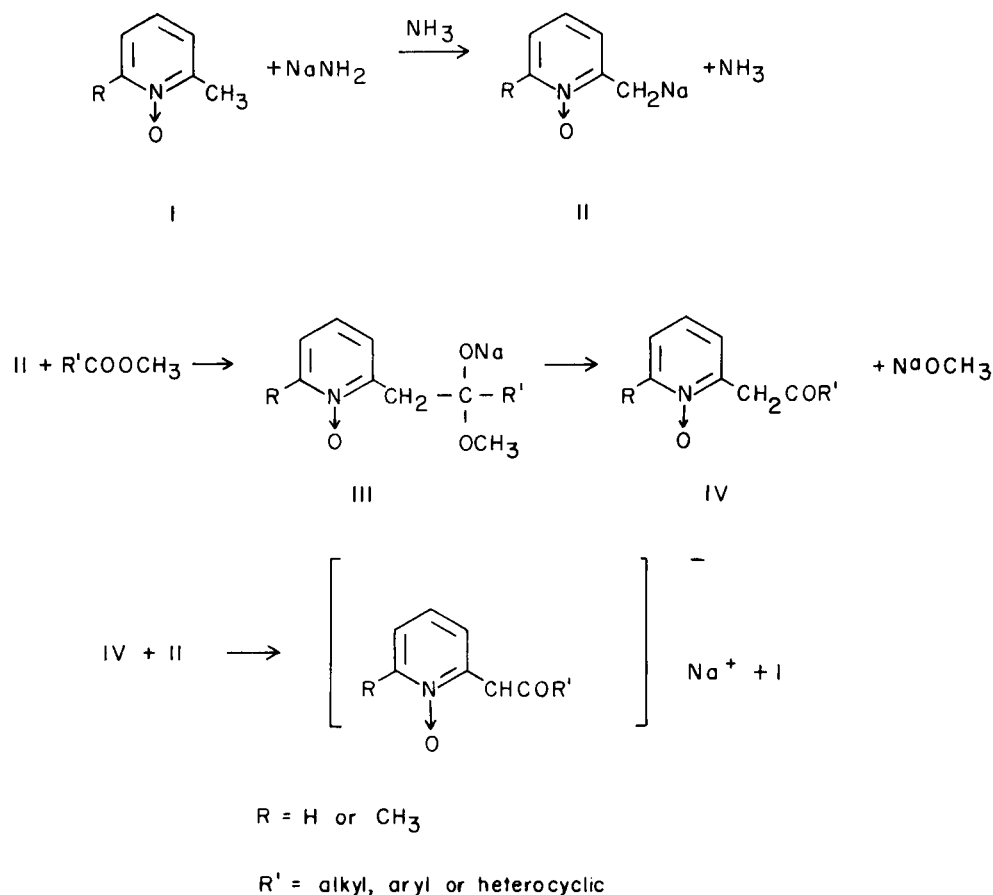
Sodium amide (0.4 mole) in 400 ml. of anhydrous liquid ammonia; 2,6-lutidine N-oxide (0.4 mole, 49.2 g.) and methyl nicotinate (0.2 mole, 30.3 g.) were allowed to react as described in section (a). After pouring the reaction mixture over ice, the pH of the solution was brought to 7 and the solution was extracted with several portions of chloroform. The combined solvent extracts were dried over sodium sulphate. As much of the chloroform as possible was then removed from the extracts and anhydrous ether was added to the residue. The 2,6-lutidyl 3-pyridyl ketone N-oxide which separated, was filtered and washed with several portions of ether. In this way there was obtained 22.8 g. (50.0%) of 2,6-lutidyl 3-pyridyl ketone N-oxide, m.p. 133-134° from a mixture of benzene and petroleum ether (60-70° B.P.).

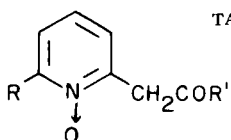
(c) The preparation of 2,6-lutidyl isopropyl ketone N-oxide.

Sodium amide (0.2 mole), 2,6-lutidine N-oxide (0.2 mole, 24.6 g.) and ethyl isobutyrate (0.1 mole, 11.6 g.) were allowed to react as described above in section (b). The residue from the chloroform extracts was vacuum distilled and gave in addition to recovered 2,6-lutidine N-oxide, 2,6-lutidyl isopropyl ketone N-oxide 11.3 g. (58.0%), b.p. 140-146° at 0.5 mm; m.p. 91-92° from a mixture of benzene and petroleum ether (60-70° B.P.).

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Ketones of the Type  TABLE I  
Prepared by the Acylation of 2-picoline N-oxide and

2,6-Lutidine N-oxide with Esters in the Presence of Sodium Amide in Liquid Ammonia

R	R'	Yield Ketone %	m. p.	Analysis (m)				Picrate m. p. (n)	Analysis			
				% Carbon		% Hydrogen			% Carbon		% Hydrogen	
				Calcd.	Found	Calcd.	Found		Calcd.	Found	Calcd.	Found
H	C <sub>6</sub> H <sub>5</sub>	85.3 (46.8) (a)	158	73.20	73.56	5.16	5.21	162-163	51.58	51.82	3.17	3.36
H	2-C <sub>10</sub> H <sub>7</sub> (b)	83.9	163-164	77.60	77.75	4.94	5.17	176-177	56.10	56.55	3.25	3.61
H	2-C <sub>4</sub> H <sub>3</sub> S (c)	83.0	153-154	60.40	60.62	4.11	4.41	131-132	45.54	45.84	2.70	2.78
H	3-C <sub>5</sub> H <sub>4</sub> N (d)	74.7	141-142	67.27	66.93	4.71	4.89	202-203	48.76	49.19	2.96	3.32
H	2-C <sub>4</sub> H <sub>3</sub> O (e)	65.0	152-153	65.00	64.87	4.43	4.45	140-141	47.23	47.55	2.80	3.18
H	<i>iso</i> -C <sub>3</sub> H <sub>7</sub>	55.5	53-54 (f)	66.95	66.65	7.26	7.25	98.2-99.2	47.06	47.34	3.92	3.87
CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	79.5	141-142 (g)	73.99	73.65	5.76	6.06	---	---	---	---	---
CH <sub>3</sub>	2-C <sub>4</sub> H <sub>3</sub> S (c)	73.0	117-118	61.79	61.49	4.76	4.72	158-159	46.76	47.10	3.06	3.36
CH <sub>3</sub>	3-C <sub>5</sub> H <sub>4</sub> N (d)	50.0	133-134	68.40	68.80	5.31	5.45	196-197	49.89	50.16	3.31	3.57
CH <sub>3</sub>	<i>iso</i> -C <sub>3</sub> H <sub>7</sub>	58.0	91-92 (h)	68.36	68.60	7.77	8.03	--- (i)	---	---	---	---
CH <sub>3</sub>	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	41.1	96-97 (j)	69.57	69.66	8.21	8.42	--- (k)	---	---	---	---

(a) When a 1:1:1 molar ratio of reactants was employed. (b) 2-C<sub>10</sub>H<sub>7</sub> = 2-Naphthyl radical. (c) 2-C<sub>4</sub>H<sub>3</sub>S = 2-Thienyl radical. (d) 3-C<sub>5</sub>H<sub>4</sub>N = 3-Pyridyl radical. (e) 2-C<sub>4</sub>H<sub>3</sub>O = 2-Furyl radical. (f) Recrystallized from petroleum ether (30-60° B. P.); b. p. 153-155 at 1.0 mm. (g) R. Adams and W. J. Reifschneider, *J. Am. Chem. Soc.*, **79**, 2236 (1957), report 143-145° from an ethanol-ether mixture. (h) B. p. 140-146° at 0.5 mm. (i) The compound would not readily form a picrate or oxime derivative. (j) B. p. 135-140° at 0.5-1.0 mm. (k) The compound forms an oxime derivative, m. p. 189-191 from an ethanol-water mixture. *Anal.* Calcd. C, 64.87; H, 8.11. Found: C, 64.64; H, 8.12. (l) Recrystallized from a benzene-petroleum ether mixture. (m) The analyses were performed at the microanalytical laboratory of Mellon Institute, Pittsburgh, Pennsylvania. (n) Recrystallized from absolute ethanol.

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