REINVESTIGATION OF THE REACTION OF NICOTINIC ACID 1-OXIDE WITH ACETIC ANHYDRIDE

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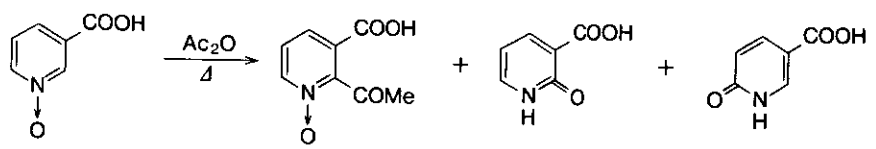
Abstract ——Reinvestigation of the reaction of nicotinic acid 1-oxide (1) with boiling acetic anhydride has revealed that the primary product is not 2-acetylnicotinic acid 1-oxide (3) but 3-acetoxy-4-aza-3-methyl-1(3H)-isobenzofuranone 4-oxide (2), the acetate of the ring tautomer of 3. Reactions of 2 and 3 with phosphorus trichloride and some related reactions are reported.

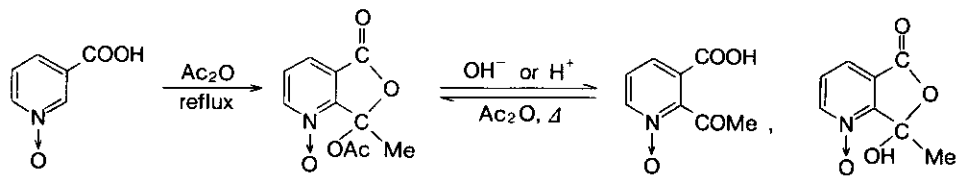
Early in 1960, Bain and Saxton[1] reported that the reaction of nicotinic acid 1-oxide (1) with boiling acetic anhydride (Ac_2O) afforded 2-acetylnicotinic acid 1-oxide (3) together with small amounts of the expected 2- and 6-pyridones.



1 3

Reactions of pyridine 1-oxides with Ac_2O are well documented and usually afford deoxygenated α- or β-acetoxylation products by nucleophilic processes.[2,3] Contrary to these reactions, the formation of 3 apparently arises from an electrophilic reaction. In order to elucidate the essential feature of this unique reaction, we first reinvestigated the reaction in some detail.

Bain and Saxton originally refluxed 1 with Ac_2O for 6 h, concentrated the reaction mixture in vacuo, and treated the residue with dil. KOH followed by acidification and isolated 3.[1] When the residue from the reaction mixture was chromatographed on silica gel prior to treatment with KOH, there was obtained 3-acetoxy-4-aza-3-methyl-1(3H)-isobenzofuranone 4-oxide (2) in 62% yield, in stead of 3, accompanied with small amounts of 2- and 6-hydroxynicotinic acids. The structure of 2 was established by elemental analysis, the ir, pmr and cmr spectroscopies, and finally by X-ray analysis (Fig. 1). Upon treatment with dil. NaOH or hydrochloric acid, 2 was easily hydrolyzed to 3. Conversely, 3 was transformed readily to 2 by heating with Ac_2O. Thus, it was evident that the primary product is not 3, but 2, that is the acetylated derivative of the ring tautomer of 3 (3'), and 3 is the hydrolysis product of 2.



1 2 3 3'

Although the ring-chain tautomerism[4] of 2-acetylnicotinic acid 1-oxide (3'⇌3) has not been explored in detail, it seems very likely that the predominant form is the chain form 3 at least in DMSO, since the cmr spectrum (DMSO-d_6) gives no signal due to C_3 of 3' and the pmr spectrum (DMSO-d_6) is well consistent with the chain form 3.[5]

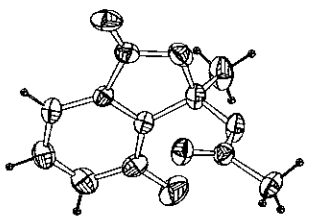


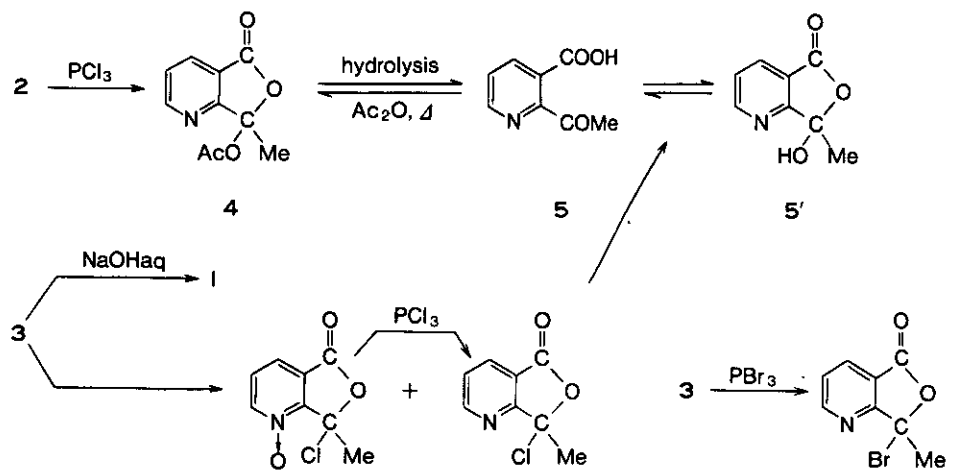
Fig. 1 ORTEP drawing of 2

Deoxygenation of 2 with phosphorus trichloride (PCl_3) proceeded smoothly to give the 3-acetoxy-4-azaisobenzofuranone (4) in 80% yield. While 4 was hydrolyzed in NaOH solution to furnish 2-acetylnicotinic acid (5), heating 4 with water on a steam bath for 1 h gave 5 in 20% yield only with a 70% recovery of 4. Compound 5 was identical with a sample obtained by hydrogenating 2 over palladium-charcoal according to the literature procedure,[1] and converted to 4 with hot Ac_2O. In contrast to 3, the equilibrium between the chain form 5 and the ring form 5' was evident from the cmr spectrum (DMSO-d_6) which exhibited signals due to an acetyl carbonyl-carbon of 5 and a quaternary carbon (C_3) of 5' at δ 200.4 and 106.5, respectively. The ratio of 5 to 5' was estimated to be

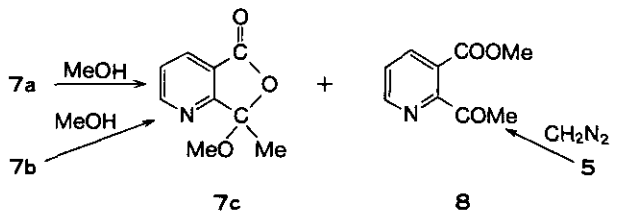
2:1 from the relative intensities of methyl-carbon signals of 5 and 5' at δ 27.6 and 24.1, respectively.

Deacetylation of 3 occurred very easily; thus, 1 was obtained in 90% yield when a 20% NaOH solution of 3 was warmed at 50-60°C for 5 min. Treatment of 3 with 1 eq PCl_3 gave the 3-chloro-4-azaisobenzofuranone (7a) and its 4-oxide (6a) in practically equal yields of 30%; 6a was easily deoxygenated with PCl_3 to 7a. When 2 eq PCl_3 was used, only 7a was formed in 75% yield. Further it was found that the reaction of 3 with thionyl chloride in the presence of a catalytic amount of DMF[6] gave 6a in 71.6% yield and that with 1 eq PBr_3 afforded the 3-bromo-4-azaisobenzofuranone (7b) as a sole product in 51% yield. Such a predominant formation of cyclic halides has been well noticed also in the cases of 2-acetylbenzoic acid and its analogues.[4]

Hydrolysis of 7a to 5 was readily effected by warming with water or acids. When 7a was treated with methanol at room temperature for 1 h followed by warming on a steam bath for 30 min, the normal methyl ester (8) and the cyclic methoxy deivative (7c) were formed in the ratio of 4:1. On the other hand, methanolysis of 7b afforded only 7c, and methylation of 5 with diazomethane gave only 8. Attempted reactions of 6a and 7a with sodium acetate in tetrahydrofuran did not give cyclic acetate, 2 and 4. These reactions are formulated below.



PCl_3	1 eq	30%	30%
PCl_3	2 eq	—	75%
$SOCl_2$		71.6%	—



7c 8

Further studies are in progress to elucidate the mechanism, and the results will be reported in a subsequent paper.

EXPERIMENTAL

All melting points are uncorrected. Spectral data were recorded on the following instruments. Uv: Varian Cary 118 spectrophotometer. Ir: Hitachi Infrared spectrophotometer 260-30 or Nicolet FT-IR spectrometer MX-1. Ms: Shimadzu LKB 9000, Hitachi-Perkin Elmer RMU-6D or Finnigan Mass spectrometer. Pmr and cmr: JEOL FX-200, Nicolet NT-360 or Bruker CXP-180 spectrometer. X-Ray diffraction data were obtained with a Enraf-Nonius four-circle X-ray autodiffractomer by using Cu Kα (λ=1.54178Å) radiation. Column chromatography was carried out on Wakogel C-200, 100-200 mesh or Baker chemical's silica gel, 60-200 mesh.

Reaction of Nicotinic Acid 1-Oxide (1) with Ac_2O —The N-Oxide (1, 10 g) was refluxed in Ac_2O (15 ml) for 6 h. The mixture was concentrated in vacuo, and the residue was chromatographed on silica gel with $CHCl_3$ and $CHCl_3$-MeOH (1-3%) to give 9.92 g (62%) of 3-acetoxy-4-aza-3-methyl-1(3H)-isobenzofuranone 4-oxide (2), pale yellow prisms, mp 126°C (iso-PrOH-hexane). Anal. Calcd for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.54; H, 4.03; N, 6.07. Ms m/z: 223 (M^+). Uv (H_2O) nm (log ε): 262 (3.0), 212 (3.25). Ir (Nujol) νcm^{-1}: 1800, 1765 (strong CO). Pmr ($CDCl_3$) δ: 2.08 (3H, s, C_3-CH_3), 2.11 (3H, s, $COCH_3$), 7.45 (1H, dd, H_6), 7.72 (1H, dd, H_7), 8.30 (1H, dd, H_5) ($J_{5,6}$=6.0, $J_{6,7}$=7.2, $J_{5,7}$=0.6 Hz). Cmr (DMSO-d_6) δ: 20.8 (q, C_3-$\underline{C}H_3$), 21.6 (q, $CO\underline{C}H_3$), 101.3 (s, C_3), 122.2 (d, C_6), 126.7 (d, C_{7a}), 127.9 (d, C_7), 144.4 (d, C_5), 152.3 (s, C_{3a}), 163.0 (s, CO), 168.6 (s, CO). Crystal Data: $C_{10}H_9NO_5$, MW=223.19, monoclinic, space group Pz_1/a, a=24.782, b=8.1006, c=10.1260 Å, β=90.75, V=913.18 $Å^3$, Z=8, Dc=1.462, R=8.6%, 3460 independent reflections.

Continued elution with $CHCl_3$-MeOH (6-30%) gave 0.54 g (5.4%) of 2-hydroxynicotinic acid, mp 260-262°C,[1] and then 0.15 g (1.5%) of 6-hydroxynicotinic acid, mp 318-320°C.[1]

Reactions of 3-Acetoxy-4-aza-3-methyl-1(3H)-isobenzofuranone 4-Oxide (2) —1) A mix-

ture of 2 (0.4 g) and 2% NaOH (40 ml) was heated on a steam bath for 0.5 h. The solution was acidified to pH 3 with conc. HCl, concentrated in vacuo, and the residue was chromatographed on silica gel with $CHCl_3$-MeOH(1:1) to give 0.227 g (70%) of 2-acetylnicotinic acid 1-oxide (3), colorless needles, mp 247-249 °C (decomp.)(H_2O). Anal. Calcd for $C_8H_7NO_4$: C, 53.04, H, 3.89; N, 7.73. Found: C, 52.90; H, 3.81; N, 7.75. Ms m/z: 181 (M^+). Uv (H_2O) nm (log ε): 260 (3.52), 214 (3.13). Ir (KBr) ν cm^{-1}: 1880-1750 (br), 1725 (strong CO). Pmr (DMSO-d_6) δ: 2.41 (3H, s, CH_3), 7.57 (1H, dd, H_5), 7.83 (1H, dd, H_4), 8.47 (1H, dd, H_6) ($J_{4,5}$=7.8, $J_{5,6}$=6.0, $J_{4,6}$=1.2 Hz). Cmr (DMSO-d_6)δ: 29.5 (q, CH_3), 124.9 (d, C_5), 126.7 (d, C_4), 136.4(s, C_3), 138.9 (d, C_6), 147.9 (s, C_2), 165.2 (s, COOH), 196.0 (s, COMe).

2) A mixture of 2 (0.1 g) and conc. HCl was boiled for 1 h. The reaction mixture was cooled and deposited crystals of 3 (0.047 g, 54%) were filtered. Evaporation of the filtrate gave an additional 0.021 g (26%) of 3.

3) To an ice-cooled solution of 2 (446 mg) in AcOEt (5 ml) was added dropwise PCl_3 (0.3 ml, 1.7 eq), and the mixture was stirred at 5-15 °C for 1 h, poured on ice-water and extracted with ether. The extract was washed successively with dil. $NaHCO_3$ and water. Removal of the ether left 0.47 g of crude 3-acetoxy-4-aza-3-methyl-1(3H)-isobenzofuranone (4) as a pale yellow oil, which was purified by chromatography on silica gel with $CHCl_3$ to give 0.331 g (80%) of pure 4, an oil. Ms m/z: 207 (M^+). Ir (neat) ν cm^{-1}: 1790, 1750 (strong CO). Pmr ($CDCl_3$) δ: 1.91 (3H, s, CH_3), 2.01 (3H, s, CH_3), 7.43 (1H, dd, H_6), 8.12 (1H, dd, H_7), 8.75 (1H, dd, H_5) ($J_{5,6}$=5.0, $J_{6,7}$=7.8, $J_{5,7}$=1.8 Hz). Cmr ($CDCl_3$) δ: 21.2 (q, CH_3), 24.0 (q, CH_3), 103.8 (s, C_3), 121.0 (s, C_{7a}), 124.9 (d, C_6), 133.8 (d, C_7), 155.0 (d, C_5), 165.5 (s, C_{3a}), 166.5 (s, CO), 168.4 (s, CO).

Treatment of 4 with excess ether-HCl in MeOH followed by evaporation of the solvent gave 4 hydrochloride as somewhat unstable crystals, which was washed with iso-PrOH-ether, mp 123.4 °C. Anal. Calcd for $C_{10}H_9NO_4 \cdot HCl$: C, 49.30; H, 3.72; N, 5.75. Found: C, 49.59; H, 4.04; N, 5.73.

Reactions of 2-Acetylnicotinic Acid 1-Oxide (3)—1) A solution of 3 (181 mg) in 20% NaOH (1.4 ml) was warmed at 50-60 °C for 5 min. The mixture was acidified with conc. HCl to pH 1-2 and concentrated in vacuo. The residue was heated with DMF (100 ml) and insoluble materials were filtered. The residue from the filtrate was chromatographed on silica gel with $CHCl_3$-MeOH to give 125 mg of 1, mp 260-262 °C (H_2O).

2) A mixture of 3 (181 mg) and Ac_2O (2 ml) was heated at 75 °C for 1 h, then at 105 °C

for 6 h. The mixture was concentrated in vacuo to give 223 mg (100%) of 2.

3) To a mixture of 3 (181 mg) and DMF (5 ml)-AcOEt (5 ml) was added PCl_3 (0.1 ml, 1.15 eq) at -10 °C, and the mixture was stirred at -5 ~ -10 °C for 1 h, poured on ice, shaken with saturated NaCl solution and extracted with ether. The extract was washed twice with saturated NaCl solution, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$-ether to give 55 mg (30%) of 4-aza-3-chloro-3-methyl-1(3H)-isobenzofuranone (7a) and then 60 mg (30%) of its 4-oxide (6a). 7a: colorless needles, mp 74-75 °C (ether-hexane). Anal. Calcd for $C_8H_6ClNO_2$: C, 52.34; H, 3.29; N, 7.63. Found; C, 52.32; H, 3.14; N, 7.58. Ir (KBr) ν cm^{-1}: 1790 (CO). Pmr ($CDCl_3$) δ : 2.28 (3H, s, CH_3), 7.58 (1H, dd, H_6), 8.24 (1H, dd, H_7), 8.98 (1H, dd, H_5) ($J_{5,6}$=5.0, $J_{6,7}$=7.8, $J_{5,7}$=1.6 Hz). Cmr ($CDCl_3$) δ : 28.3 (q, CH_3), 98.0 (s, CH_3), 117.8 (s, C_{7a}), 125.5 (d, C_6), 134.6 (d, C_7), 156.3 (d, C_5), 164.8 (s, C_{3a}), 168.3 (s, CO). 6a: colorless needles, mp 147 °C (decomp.) ($CHCl_3$-hexane). Anal. Calcd for $C_8H_6ClNO_3$: C, 48.14; H, 3.03; N, 7.02. Found: C, 48.16; H, 2.92; N, 6.96. Ir (KBr) ν cm^{-1}: 1800 (CO). Pmr ($CDCl_3$) δ : 2.40 (3H, s, CH_3), 7.32-7.80 (2H, m, H_6, H_7). 8.41 (1H, dd, H_5) ($J_{5,6}$=6.0, $J_{5,7}$=1.8 Hz). Cmr ($CDCl_3$) δ : 26.2 (q, CH_3), 95.3 (s, C_3), 121.9 (s, C_{7a}), 124.2 (d, C_6), 128.5 (d, C_7), 145.4 (d, C_5), 154.0 (s, C_{3a}), 162.5 (s, CO).

Treatment of 6a (199.6 mg) with PCl_3 (0.1 ml) in DMF (5 ml)-AcOEt (5 ml) at 0 °C for 10 min and then at room temperature for 30 min gave 150 mg (82.3%) of 7a.

4) A mixture of 3 (181 mg), PCl_3 (0.2 ml, 2.3 eq) and DMF (5 ml)-AcOEt (5 ml) was stirred at 0 °C for 10 min and then at room temperature for 30 min. The mixture was worked up as described in 3) to give 137.7 mg (75%) of 7a.

5) A mixture containing 3 (181 mg), $SOCl_2$ (1 ml) and 3-4 drops of DMF[6] was stirred at room temperature for 5 h, and then concentrated in vacuo. The residue was diluted with crushed ice and extracted with THF. The extract was washed three times with saturated NaCl solution and concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$-ether to give 143 mg (71.6 %) of 6a.

6) A mixture of 3 (181 mg), PBr_3 (0.19 ml, 1.2 eq) and DMF (15 ml)-AcOEt (5 ml) prepared at -10 °C was stirred at -10 ~ -5 °C for 1 h, poured on crushed ice and NaCl, and extracted with ether. The extract was washed with saturated NaCl solution and concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$-ether to give 114 mg of 4-aza-3-bromo-3-methyl-1(3H)-isobenzofuranone (7b), colorless needles, mp 73-74 °C (ether-hexane). Anal. Calcd for $C_8H_6BrNO_2$: C, 42.14; H,

2,65; N, 6.14. Found: C, 42.88, H, 2.56; N, 6.20. Ir (Kbr) νcm^{-1}: 1785 (CO). Pmr ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 7.51 (1H, dd, H_6), 8.20 (1H, dd, H_7), 8.95 (1H, dd, H_5) ($J_{5,6}$=5.0, $J_{6,7}$=7.8, $J_{5,7}$=1.8 Hz). Cmr ($CDCl_3$) δ: 30.2 (q, CH_3), 89.1 (s, C_3), 117.3 (s, C_{7a}), 125.1 (d, C_6), 134.6 (d, C_7), 156.3 (d, C_5), 164.7 (s, CO), 169.8 (s, CO).

Derivatives of 2-Acetylnicotinic Acid (5) — 1) A mixture of 4 (207 mg) and NaOH·(80 mg)-H_2O (5 ml) was heated on a steam bath for 30 min. The mixture was cooled, acidified to pH 3 with conc. HCl and extracted with THF. The extract was washed twice with saturated NaCl solution and concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$-MeOH to give 127 mg (77%) of 5, colorless needles, mp 127-128 °C (MeOH-ether-hexane). Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.06; H, 4.25; N, 8.50. Ir (KBr) ν cm^{-1}: 1755 (CO). Pmr ($CDCl_3$-DMSO-d_6) δ: 2.35 (3H, br, CH_3), 7.53 (1H, dd, H_5), 8.15 (1H, dd, H_4), 8.77 (1H, dd, H_6) ($J_{4,5}$=7.8, $J_{5,6}$=5.0, $J_{4,6}$=1.8 Hz), 9-12 (1H, br-s, OH). Cmr (DMSO-d_6) δ : 24.1 (q, CH_3 in 5'), 27.6 (q, CH_3 in 5), 106.5 (s, C_3 in 5'), 119.5 (s), 125.3 (d), 125.4 (d), 126.5 (s), 133.6 (d), 137.2 (d), 150.7 (d), 155.3 (s), 155.5 (d), 166.2 (s), 167.3 (s), 200.4 (s, $\underline{C}OCH_3$ in 5).

2) A mixture of 4 (207 mg) and H_2O (2 ml) was heated on a steam bath for 1 h. The solvent was evaporated in vacuo, and the residue was chromatographed on silica gel with $CHCl_3$-MeOH to give 123.7 mg (75%) of unchanged 4 and then 33 mg (20%) of 5.

3) A mixture of 5 (165 mg) and Ac_2O (2 ml) was warmed at 75 °C for 1 h, and then the temperature was gradually raised to 105 °C during 6 h. The mixture was concentrated in vacuo, and the residue was chromatographed on silica gel with $CHCl_3$ to give 165.6 mg (80%) of 4.

4) A mixture of 7a (183.6 mg) and H_2O (5 ml) was heated on a steam bath for 1 h to give 132 mg (80%) of 5, mp 127-128 °C.

5) A solution of 7b (114 mg) in MeOH (5 ml) was stirred at room temperature for 1 h, then heated on a steam bath for 10 min. The solvent was removed in vacuo, and the residue was chromatographed on a silica gel with $CHCl_3$-MeOH to give 76 mg (85%) of 4-aza-3-methoxy-3-methyl-1(3H)-isobenzofuranone (7c), colorless prisms, mp 144 °C. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.28; H, 4.96; N, 7.84. Ir (KBr) νcm^{-1}: 1760. Pmr ($CDCl_3$) δ: 1.88 (3H, s, CH_3), 3.14 (3H, s, OCH_3), 7.51 (1H, dd, H_6), 8.16 (1H, dd, H_7), 8.90 (1H, dd, H_5) ($J_{5,6}$=5.0, $J_{6,7}$=8.0, $J_{5,7}$=1.8 Hz). Cmr ($CDCl_3$) δ:23.1 (q, CH_3), 51.7 (q, OCH_3), 108.9 (s, C_3), 121.2 (s, C_{7a}), 125.2 (d, C_6), 134.0 (d, C_7), 155.65 (s, C_{3a}), 155.7 (d, C_5), 166.1 (s, CO).

6) To a solution of 5 (500 mg) in MeOH (5 ml) was added excess CH_2N_2-ether at 0 °C, and the mixture was kept at 0 °C for 12 h to give methyl 2-acetylnicotinate (8), a pale yellow oil. Pmr ($CDCl_3$) δ: 2.65 (3H, s, $COCH_3$), 3.89 (3H, s, $COOCH_3$), 7.45 (1H, dd, H_5), 8.01 (1H, dd, H_4), 8.69 (1H, dd, H_6) ($J_{4,5}$=8.0, $J_{5,6}$=5.0, $J_{4,6}$=1.8 Hz).

7) A solution of 7a (184 mg) in MeOH (5 ml) was stirred at room temperature for 1 h, then heated on a steam bath for 30 min. The solvent was removed, and the residue was chromatographed on silica gel with $CHCl_3$-MeOH to give 170 mg of a mixture of 7c and 8. The ratio of 7c to 8 was roughly estimated as 1:4 by pmr spectroscopy.

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3. The representative examples of deoxygenative α- and β-acetoxylations are as follows. α-Acetoxylation: the formation of 2-acetoxypyridine or 2-pyridone from pyridine 1-oxide. β-Acetoxylation: the formation of 2-pyridylmethyl acetate, and 3- and 5-acetoxy-2-picolines from 2-picoline 1-oxide. cf. Ref. 2 and also S. Oae and K. Ogino, Heterocycles, 1977, 6, 583.
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