BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 3350—3352 (1969)

Reaction of 6-Methylpicolinic Acid *N*-Oxide with Acetic Anhydride[1)]

Yukito MURAKAMI and Junzo SUNAMOTO

Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Hakozaki, Fukuoka

(Received May 21, 1969)

The reactions of picoline *N*-oxides with acetic anhydride have been studied by many workers for theoretical and practical interest.[2-9)] Recently, Ford and Swan[10)] have found that the reaction of 2-picoline *N*-oxide with acetic anhydride gave a mixture of three isomers, 3-acetoxy-2-picoline, 5-acetoxy-2-picoline, and 2-acetoxymethylpyridine in a relative proportion of 15 : 18 : 67. Meanwhile, the reaction of pyridine *N*-oxide with acetic anhydride gave 2-acetoxypyridine.[11)]

The reactions of carboxypyridine *N*-oxides with acetic anhydride also have been studied. Bain and Saxton[12)] have reported that picolinic acid *N*-oxide was converted to 2-pyridone and pyridine *N*-oxide by acetic anhydride in acetonitrile along with the quantitative evolution of carbon dioxide, where pyridine *N*-oxide was the main product. On the other hand, 2-carbomethoxypyridine *N*-oxide did not undergo decarboxylation with acetic anhydride, but normally afforded 6-acetoxy-2-carbomethoxypyridine.[13)]

It is of interest to investigate what reaction may occur in the case of 6-methylpicolinic acid *N*-oxide with acetic anhydride, where the *N*-oxide carries both electron withdrawing and donating groups at the α-positions of the pyridine ring. Baker *et al.*[14)] have reported that the reaction product of 6-methylpicolinic acid *N*-oxide with acetic anhydride was 2-acetoxymethylpyridine, only by determining its boiling point and the melting point of the corresponding picrate. However, they did not try to hydrolyze the acylated compound. From our present results we see that they mistook 6-acetoxy-2-picoline for 2-acetoxymethylpyridine because there is no considerable difference between both compounds in their physical properties. We found that the acylated compound produced during the course of the reaction of 6-methylpicolinic acid *N*-oxide with acetic anhydride was not 2-acetoxymethylpyridine, but 6-acetoxy-2-picoline. This was confirmed by the hydrolysis of the acylated intermediate which afforded 6-methyl-2-pyridone.

The results will present an interesting question as to whether decarboxylation proceeds prior to *N*-acetoxylation as indicated in the case of picolinic *N*-oxide.[12)] If decarboxylation occurred predominantly prior to acetoxylation, the principal intermediate would be 2-picoline *N*-oxide and/or 2-acetoxymethylpyridine. On the other hand, if *N*-acetoxylation and the subsequent N–O fission were predominant prior to decarboxylation, 6-acetoxymethylpicolinic acid and/or 2-acetoxymethylpyridine would be produced. When 6-methylpicolinic acid *N*-oxide was warmed to 90—98°C with acetic anhydride, a smooth evolution of carbon dioxide occurred. The main product was 6-acetoxy-2-picoline, and 6-methyl-2-pyridone was present in a very small yield. The reaction of 2-picoline *N*-oxide, which is the decarboxylation product, with acetic anhydride under the same reaction condition did not give 6-acetoxy-2-picoline and/or 6-methyl-2-pyridone, but gave 2-acetoxymethylpyridine along with a trace amount of 5-acetoxy-2-picoline, similar to the result of Ford and Swan.[10)] Therefore, decarboxylation, N–O fission, and acetoxylation at the C-2 position must take place in concert to give 6-acetoxy-2-picoline. The following reaction mechanism is put forward to

1) Contribution No. 157 from the Department of Organic Synthesis, Faculty of Engineering, Kyushu University.

2) G. Kobayashi and S. Furukawa, *Chem. Pharm. Bull. (Tokyo)*, **1**, 347 (1953).

3) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

4) O. H. Bullitt and J. T. Maynard, *ibid.*, **76**, 1370 (1954).

5) V. J. Traynelis and R. F. Martello, *ibid.*, **80**, 6590 (1958).

6) S. Oae and Y. Kitaoka, *ibid.*, **84**, 3359 (1962).

7) S. Oae, Y. Kitaoka and T. Kitao, *Tetrahedron*, **20**, 2685 (1964).

8) V. J. Traynelis and P. L. Pacini, *J. Am. Chem. Soc.*, **86**, 4917 (1964).

9) T. Cohen and J. H. Fager, *ibid.*, **87**, 5701 (1965).

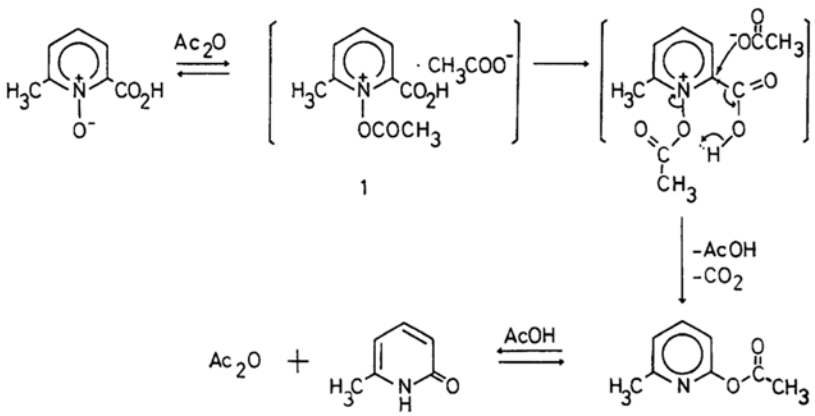
10) P. W. Ford and J. M. Swan, *Australian J. Chem.*, **18**, 867 (1965).

11) J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr and R. G. Peterson, *J. Am. Chem. Soc.*, **85**, 958 (1963).

12) B. M. Bain and J. E. Saxton, *J. Chem. Soc.*, **1961**, 5216.

13) V. Boekelheide and W. L. Lehn, *J. Org. Chem.*, **26**, 428 (1961).

14) W. Baker, K. M. Bruggle, J. F. W. McOmie and D. A. M. Watkins, *J. Chem. Soc.*, **1958**, 3594.



explain the present result.

Picolinic acid *N*-oxide undergoes rapid decarboxylation to pyridine *N*-oxide at room temperature upon addition of benzoyl chloride.[13] Therefore, it is evident that the formation of the *N*-acetoxypyridinium ion **1** is necessary for the ease of decarboxylation. 6-Acetoxy-2-picoline may further react with acetic acid during the reaction and/or distillation to give 6-methyl-2-pyridone, because the pyridone was usually obtained from the distillation residue. When the hydrolysis was carried out without isolating the acetoxylated intermediate, 6-methyl-2-pyridone was obtained in a yield of 84%. Thus, it seems that the present reaction is an improved synthetic method of 6-methyl-2-pyridone from 2,6-lutidine, differing from the conventional method *via* diazotization and the subsequent hydrolysis of 6-methyl-2-aminopyridine.[15]

Experimental

All infrared spectra were measured on a Koken Model DS-301 spectrophotometer equipped with sodium chloride optics. Nuclear magnetic resonance spectra were taken on a Varian A-60 using TMS as an internal standard. Mass spectra were measured on a JEOL JMS-01SG mass spectrometer. The ultraviolet spectra were recorded on a Hitachi Model EPS-2 recording spectrometer.

2,6-Lutidine *N*-Oxide. 2,6-Lutidine *N*-oxide was obtained by the reaction of 2,6-lutidine (53 g) with 30% hydrogen peroxide (50 m*l*) in glacial acetic acid, according to the method described in literature:[3] yield 36 g; bp 125—128°C/18 mmHg; lit., 131°C/22 mmHg,[16] 115—119°C/18 mmHg.[3] IR (neat): 1566 cm^{-1} (ring C=C, C=N str.); 1249 cm^{-1} (N–O str.); 766, 841 cm^{-1} (C–H def.).

6-Methylpicolinic Acid *N*-Oxide. 6-Methylpicolinic acid *N*-oxide was prepared by the oxidation of 2,6-lutidine *N*-oxide (22 g) with aqueous potassium permanganate solution, according to the method of Suszko and Szafran:[17] yield 9.0 g after recrystallization from methanol, mp 197—197.5°C (decomp.); lit,[18] mp 177°C. The melting point determined in the present work was not identical with that given in literature,[14,18] but infrared spectra of the sample prepared in this work was completely consistent with that reported by Szafran;[19,20] IR (KBr): 1680, 1615 cm^{-1} (C=O str.); 768, 818, 831 cm^{-1} (C–H def.). In mass spectroscopy, a molecular radical ion M^+ (*m/e* 157) was present, corresponding to the molecular formula $C_7H_7O_3N$.

Found: C, 55.12; H, 4.58; N, 9.16%. Calcd for $C_7H_7O_3N$: C, 54.90; H, 4.61; N, 9.15%.

A sample prepared through the *N*-oxidation of 6-methylpicolinic acid was also identical with the above product.

Reaction of 6-Methylpicolinic Acid *N*-Oxide with Acetic Anhydride. A mixture of 5 m*l* of acetic anhydride and 3.2 g of 6-methylpicolinic acid *N*-oxide was placed in a 50 m*l* conical flask equipped with a reflux condenser and a calcium tube, and warmed on a steam bath at 96—98°C. After about 1 hr, the color of the reaction mixture began to turn to a transparent brownish orange along with continuous evolution of carbon dioxide. The evolution of carbon dioxide lasted about one hour and half. The reaction mixture was distilled under reduced pressure after a period of 6 hr on a steam bath; 1.88 g of colorless oil (sample I), bp 107°C/18 mmHg, mp of the picrate, 165—167°C. Prism-like crystals (sample II) were isolated from the distillation residue; yield 280 mg, mp 163.5—164°C.

Hydrolysis of Sample I. A mixture of 1.0 g of sample I and 10 m*l* of concentrated hydrochloric acid was heated under reflux for 7 hr. The resulting solution was evaporated quickly by the introduction of dried air at room temperature, poured into chloroform, and then neutralized by an aqueous carbonate. The chloroform layer was dried over sodium sulfate overnight, and con-

15) R. Adams and A. W. Schrecker, *J. Am. Chem. Soc.*, **71**, 1186(1949).

16) D. Jerchel and J. Jacobs, *Angew. Chem.*, **66**, 298 (1954).

17) J. Suszko and M. Szafran, *Roczniki Chem.*, **38**, 1793 (1964); *Chem. Abstr.*, **62**, 10403g (1965).

18) W. Mathes, W. Sauermilch and T. Klein, *Chem. Ber.*, **86**, 584 (1953).

19) M. Szafran, *Bull. Acad. Poln. Sci., Ser. sci. chim.*, **10**, 479 (1962).

20) M. Szafran, *ibid.*, **13**, 245 (1965).

centrated to isolate crystals. The crystals were washed with ether; yield 230 mg, mp 163.5—164.0°C. An admixture with sample II indicated no mp depression. The product was identified as 6-methyl-2-pyridone.

IR (KBr): 2400—3200 cm^{-1} (H-bonded N–H str.); 1660 cm^{-1} (C=O str.); 1608, 1552 cm^{-1} (ring C=C, C=N str.); 733, 795, 810 cm^{-1} (C–H def.). NMR (0.5M in $CDCl_3$): 2.34 ppm (3 protons singlet, CH_3); 6.00—6.11 ppm (1 proton broad doublet, H-5), 6.33—6.48 ppm (1 proton broad doublet, H-3); 7.25—7.52 ppm (1 proton multiplets of an X-part in an ABX system, H-4 with $J_{3,4}=9.3$ cps, $J_{4,5}=6.7$ cps). UV (10^{-4}M in EtOH); λ_{max} 229.5 mμ ($\varepsilon=8700$), 288.1 mμ ($\varepsilon=8100$).

Found: C, 65.65; H, 6.51; N, 12.63%. Calcd for C_6H_7ON: C, 66.04; H, 6.46; N, 12.83%.

In another experiment, a mixture of 15 g of the *N*-oxide and 26 g of acetic anhydride was warmed at 60—65°C for 18 hr with stirring. The mixture was then directly hydrolyzed with 230 m*l* of 6N hydrochloric acid at 90—100°C for 5 hr. The resulting solution was concentrated to 100 m*l* and extracted with benzene. The benzene solution was concentrated to give crystalline mass; 9.0 g (84%) of 6-methyl-2-pyridone was obtained.

Thanks are due to Mr. Akira Iwamitsu for his assistance in part of the experimental work, also to the Research Institute of Yoshitomi Seiyaku Co., Ltd., for the measurements of mass spectra.