Evidence for an Ionic Mechanism for the Reaction of 2-Cyclopropylpyridine N-Oxide with Acetic Anhydride

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The rearrangement of 2-cyclopropylpyridine N-oxide with acetic anhydride afforded 2-(2-pyridyl)-2-propenyl acetate and 2-(1-acetoxycyclopropyl)pyridine as the main products; 5-acetoxy-2-cyclopropylpyridine was also isolated in moderate yield. The opening of the cyclopropyl ring provides evidence for an ionic mechanism. This was supported by experiments with ^{18}O-labeled acetic anhydride.

Reaction of 2-alkylpyridine N-oxides with acetic anhydride proceeds with rearrangement to the corresponding 2-acetoxyalkylpyridines. The mechanism is still controversial;[1-7] the results seem best accommodated by a tight ion pair mechanism but neither radical pairs nor concerted reaction paths can be entirely excluded.

The N-oxide of 2-cyclopropylpyridine (1) should lend itself particularly well for obtaining direct proof for an ionic reaction path since the cyclopropyl cation would only be expected to have a transient existence[8] while the cor-

responding radical is expected to survive the reaction conditions.[9]

When the present work was undertaken, no satisfactory method for the preparation of 2-cyclopropylpyridine was available.[10-13] The double bonds of 2-vinylpyridine (2) and 4-vinylpyridine (3) are electron deficient and might therefore react with sulfur ylids to yield the corresponding cyclopropane derivatives. Indeed both isomers 2 and 3 reacted readily with dimethylsulfonium methylide to give 2-(4) and 4-cyclopropylpyridine (5) in 63 and 60 % yields, respectively. After this work was completed Levine and Patrick[14] reported an extensive study on the same reaction with similar results. Compounds 2 and 3 reacted also with dimethyloxosulfonium methylide, but the yields of the cyclopropanes 4 and 5 were only 7 and 19 %, respectively.

Peracetic acid oxidation of 2-cyclopropylpyridine (4) afforded the N-oxide 1 in 88 % yield. When a solution of the latter in acetic
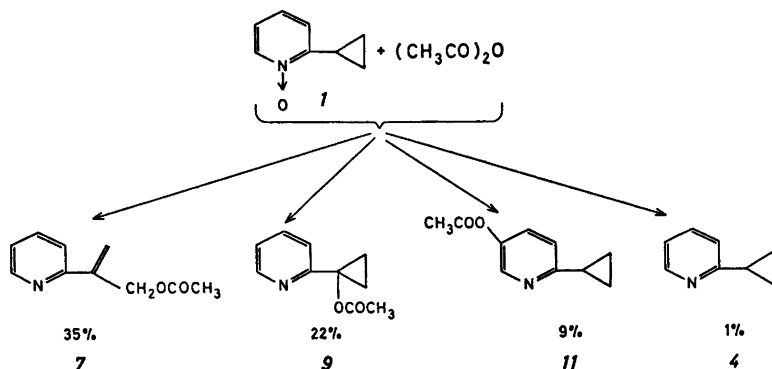
Scheme 1.
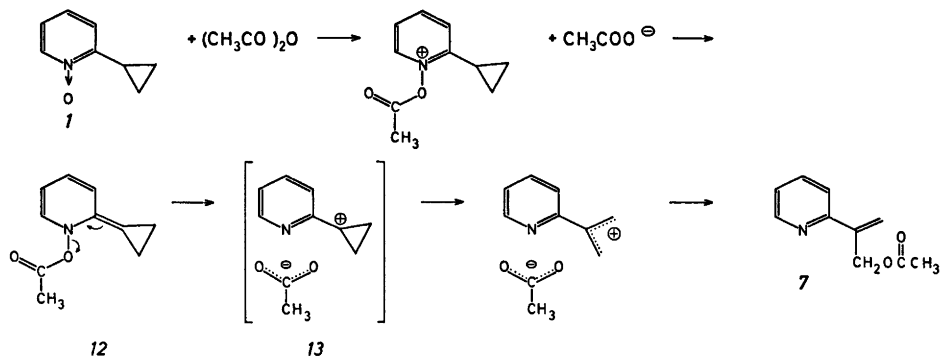
Scheme 2.

anhydride was heated to 160 °C for 2 h a product consisting of essentially three isomeric compounds was obtained in 66 % yield. They were separated by preparative gas chromatography, and identified on the basis of spectroscopic data. The major product (35 %) was shown to be 2-(2-pyridyl)-2-propenyl acetate (*7*) which on basic hydrolysis gave the corresponding alcohol *8*. The second product (22 %) was identified as 2-(1-acetoxycyclopropyl)pyridine (*9*); in this case basic hydrolysis led to the known 1-(2-pyridyl)-1-propanone (*10*).[15] The spectral properties of the minor product (9 %) were in accordance with the structure of 5-acetoxy-2-cyclopropylpyridine (*11*); the 3-acetoxy isomer could not be detected in the reaction mixture. No interconversion of the esters *7* and *9* took place under the reaction conditions. In addition to the above compounds the product mixture contained a small amount of 2-cyclopropylpyridine (1 %) which was most probably formed from the *N*-oxide *1* by a deoxygenation process.

The formation of compound *7* is particularly interesting because it provides evidence for an ionic mechanism as depicted in Scheme 2.

The heterolytic cleavage of the N – O bond in the anhydro base *12* affords a cyclopropyl cation *13* which undergoes ring-opening before recombining with an acetate anion.

The formation of compound *9* is surprising because the cyclopropyl ring is preserved. It cannot easily be accepted as a result of an ionic mechanism; a radical pair mechanism or a concerted rearrangement of the anhydro base would appear to be more reasonable explanations. On the other hand, compound *11* may

originate from any of the three mechanistic pathways. In an attempt to distinguish between these alternatives the reaction was carried out with ^{18}O-labeled acetic anhydride (*14*) and the products were analysed by mass spectrometry.

No molecular ion was obtained from the anhydride *14* and therefore the atom % of ^{18}O was calculated from m/e 43 and 45 and was found to be 8.1 %. The excess acetyl chloride from the preparation of the anhydride *14* contained approximately the same amount of ^{18}O (7.8 %) and equilibration of all oxygen atoms in the anhydride therefore must have occurred, e.g. 8.1 % labeling per oxygen.

The ^{18}O-content of the esters *7*, *9*, and *11* was calculated from m/e 43 – 45 for the carbonyl oxygen and m/e 134 – 136 and 135 – 137 for the ether oxygen; peaks corresponding to the molecular ions were either lacking or of too low intensity for the desired accuracy. The results are presented in Table 1 as a mean of three to eight measurements; owing to random distribution the error is estimated to be ± 0.3.

An oxy-Cope type rearrangement of the ester *7* in the mass spectrometer would result in scrambling of the labeled oxygens; however, analyses of the corresponding alcohol *8* gave the same amount of labeling as in the corresponding oxygen of ester *7*; such a rearrange-
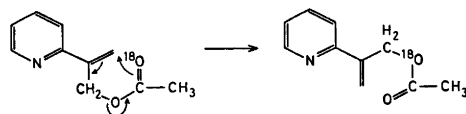
Scheme 3.

Table 1. Percentages of ^{18}O in acetyl chloride, acetic anhydride, and the pyridines studied calculated from peaks at m/e $43-45$ and m/e $134-136$ and $135-137$ in their mass spectra after correction for ^{13}C-abundance.

Compound	m/e $43-45$	m/e $134-136$ $135-137$	Total
CH₃COCl[a]	7.8		
(CH₃CO)₂O (*14*)	8.1		
CH₃COOH[b]	7.2		
7	6.3	6.1	12.4
8		6.2	
9	5.6	2.4	8.0
11	6.5	4.4	10.9
7[c]	4.8	5.2	10.0
CH₃COOH[bc]	4.9		

[a] Excess acetyl chloride distilled off from the reaction mixture from the preparation of the ^{18}O-labeled acetic anhydride (*14*). [b] Acetic acid and excess acetic anhydride distilled off from the reaction mixture after the rearrangement reaction. [c] From the control experiment starting with unlabeled ester *7* and 7.2 % labeling per oxygen in the acetic anhydride/acetic acid mixture.

ment cannot therefore have altered the isotopic distribution.

Since one acyl group adds to the *N*-oxide an intramolecular rearrangement would require a total labeling in the resulting esters of 8.1 %,* the same amount as in one oxygen atom of the anhydride. Higher ^{18}O-content in any of the esters could be due to contributing ionic intermolecular processes since the acetate anion formed from the acetic anhydride contains 16.2 % of labeled oxygen. However, an alternative explanation is possible. If an acetate exchange takes place between the labeled acetic anhydride/acetic acid and either of the esters a higher than 8.1 % content of ^{18}O would result. Such an exchange took place in the case of the allylic ester *7* (Table 1), and we can therefore not conclude that the high content of ^{18}O measured for this compound is due to an intermolecular process.

The total ^{18}O-content of the ester *9* is 8.0 % as expected for an intramolecular process and the distribution reveals that the process is

* The naturally occurring isotope in the *N*-oxide *1* is only 0.2 % which is less than the estimated error and is therefore neglected.

not concerted. In 5-acetoxy-2-cyclopropyl-pyridine (*11*), however, the total ^{18}O-content of 10.9 % is too high to originate from an intramolecular process exclusively; hence, the formation of compound *11* could partly involve an ionic intermolecular pathway. The positive charge in the 2-cyclopropylpyridine cation intermediate *13* is resonance stabilized by the pyridine ring thus giving this intermediate the possibility to exist without ring opening sufficiently for both the esters *9* and *11* to be formed through ionic intermediates (Scheme 4).
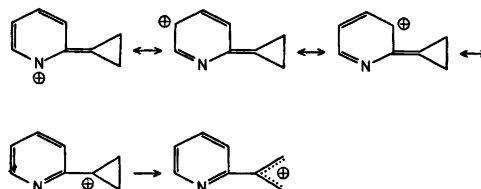
Scheme 4.

The uneven ^{18}O-distribution in the esters *9* and *11* shows that in both cases the rate of recombination and that of rotation of the acetate anion are comparable. The predominance of isotopic labeling in the carbonyl oxygen confirms the findings of Oae *et al.*[4,16]

Our work with 2-cyclopropylpyridine *N*-oxide gives ample evidence for an ionic mechanism for ~53 % of the products. There is also good reason for assuming essentially an ionic intramolecular recombination for the remaining 47 %, even if traces of a concerted reaction cannot be entirely excluded.

EXPERIMENTAL

Melting points were determined on a micro hot stage. Preparative gas chromatography was carried out on a Varian Aerograph Model 711 with 15 % SE 52 on Chromosorb W $30-60$ mesh. UV spectra were recorded on Cary 14 Spectrophotometer in ethanol, IR spectra on a Perkin-Elmer 457 Grating Infrared Spectrophotometer (film or KBr), NMR spectra on Varian A-60 and HA 100 Spectrometers with TMS as internal standard and the mass spectra on an AEI/EC MS 902 instrument with indirect inlet, 70 eV, high resolution and absolute intensities which had to be corrected for ^{13}C-abundance. All glassware used in ^{18}O-labeled work was dried at 150 °C for 20 h before use.

Elemental analyses were performed by I. Beetz, West Germany.

2-Cyclopropylpyridine (4). To sodium hydride 50 % dispersed in oil (8 g, 167 mmol) dimethyl sulfoxide (60 ml) (distilled from calcium hydride) was slowly added with stirring under nitrogen. The reaction mixture was kept at 75 °C for 30 min until evolution of hydrogen had ceased. Dry tetrahydrofuran (60 ml) was added and the solution was cooled on ice before addition of trimethylsulfonium iodide (35 g, 172 mmol) in dimethyl sulfoxide (180 ml). After 1 min 2-vinylpyridine (*2*) (17 g, 162 mmol) was added and the ice bath was removed after 45 min allowing the reaction mixture to attain room temperature. Water was added and the solution was extracted with ether. The combined extracts were dried and distillation gave 12 g (63 %) of 2-cyclopropylpyridine (*4*), b.p. 26 – 28 °C/0.05 mmHg, (lit.[14] b.p. 67 – 70 °C/20 mmHg). The UV, IR, and NMR spectra were consistent with those previously reported.[13]

2-Cyclopropylpyridine N-oxide (1). A mixture of 2-cyclopropylpyridine (*4*) (7 g, 59 mmol) and hydrogen peroxide (30 %, 10 ml, 86 mmol) in acetic acid (70 ml) was kept at 70 °C for 20 h. The acetic acid was removed and the residue distilled to give 7 g (88 %) of compound *1*, b.p. 100 – 113 °C/0.02 mmHg, m.p. ∼30 °C. NMR (CDCl$_3$): δ 0.58 – 1.37 and 2.47 – 3.98 (cyclopropyl H, complex signal), 6.72 – 7.38 and 8.13 – 8.34 (aromatic H, complex signal). IR: 1240 cm^{-1} s. MS: *m/e* 135 (M$^+$), 119, 118 (base peak) and 116. (Found: C 70.95; H 7.07. Calc. for C$_8$H$_9$NO: C 71.07; H 6.81.)

Rearrangement of 2-cyclopropylpyridine-N-oxide. The *N*-oxide *1* (6 g, 44 mmol) was dissolved in acetic anhydride (220 ml) and heated to 160 °C for 2 h. The excess anhydride was removed at reduced pressure and the residue distilled to give 4.5 g (66 %) of a mixture of three products, *7, 9,* and *11,* b.p. 100 – 103 °C/0.25 mmHg. These were separated by preparative gas chromatography.

2-(2-Pyridyl)-2-propenyl acetate (7). The yield was 35 % of a colourless liquid. NMR (CCl$_4$): δ 2.07 (s, Ac), 5.15 (CH$_2$), 5.52 and 5.96 (olefinic H), 7.00 – 7.73 and 8.90 (aromatic H, complex signal). IR: 1732 cm^{-1}. MS: *m/e* 135, 134 (base peak) and 118. UV: λ_{max} 234.5 nm (log ε 3.8) and 275 (log ε 3.6). (Found: C 67.90; H 5.85. Calc. for C$_{10}$H$_{11}$NO$_2$: C 67.73; H 6.26.)

2-(2-Pyridyl)-2-propenol (8). The acetate *7* (100 mg) was refluxed in a 10 % sodium hydroxide solution (3 ml) for 1 h, the mixture was extracted with ether, dried with sodium sulfate and the ether evaporated to give 60 mg (79 %) of compound *8*; NMR (CCl$_4$): δ 4.16 (s, OH), 4.58 (methylene H), 5.78 and 5.50 (olefinic H), 7.06 – 7.71 and 8.33 – 8.67 (aromatic H, complex signal). IR: 3300 cm^{-1} broad and strong relationship in the fingerprint region to the IR spectrum of compound *7.* MS: *m/e* 135 (M$^+$),

134, 106 (base peak), 104, and 78. UV: λ_{max} 233.5 nm (log ε 3.2) and 275 nm (log ε 3.5).

2-(1-Acetoxycyclopropyl)pyridine (9). The yield was 22 % of a while solid, m.p. 34 – 36 °C. NMR (CCl$_4$): δ 1.34 and 1.58 (m, cyclopropyl H), 2.15 (s, Ac), 6.90 – 7.70 and 8.01 (aromatic H, complex signal). IR: 1750 cm^{-1} s. MS: *m/e* 135, 134 (base peak), 79, and 78. UV: λ_{max} 268 nm (log ε 3.5). (Found: C 68.23; H 6.14. Calc. for C$_{10}$H$_{11}$NO$_2$: C 67.73; H 6.26.)

1-(2-Pyridyl)-1-propanone (10). The ester *9* (100 mg) was refluxed in a 10 % sodium hydroxide solution (3 ml) for 4 h, the solution was extracted with ether, dried with sodium sulfate and the ether evaporated to give 50 mg (65 %) of compound *10.* NMR (CDCl$_3$): δ 1.27 (t) and 3.23 (q, *J* 7.5 Hz, ethyl H), 7.01 – 8.33 (aromatic H, complex signal). IR: 1689 cm^{-1} s. Phenylhydrazone: m.p. 128 – 129 °C. (lit.[15] m.p. 129 – 131 °C).

5-Acetoxy-2-cyclopropylpyridine (11). The yield was 9 % of a colourless liquid. NMR (CDCl$_3$): δ 1.00 (d, methylene cyclopropyl H), 2.20 (q, *J* 6 Hz, methine cyclopropyl H), 2.33 (s, Ac), 7.12 (d, H3), 7.33 (2d, H4), 8.14 (d, H6); $J_{3,4}$ 8.5 Hz and $J_{4,6}$ 3 Hz. IR: 1760 cm^{-1} s, 1040 m, 1020 m. MS: *m/e* 177 (M$^+$), 135, 134 (base peak) and 59. UV: λ_{max} 226.5 nm (log ε 3.8) and 275.5 nm (log ε 3.8)

^{18}O-Labeled acetic anhydride (14). From a pressure equalized dropping funnel placed on top of a reflux condenser acetyl chloride (1.24 g, 15.8 mmol) was carefully added to H$_2$^{18}O (0.6 g, 31.6 mmol) of 50 % enrichment (Norsk Hydro) and refluxed for 20 h. With ice cooling sodium ethoxide, prepared from sodium (0.8 g) and ethanol (10 ml), was added dropwise through the same dropping funnel until the reaction mixture was just basic to phenolphthalein. The ethanol was distilled off and the residue dried (0.03 mmHg) over phosphorus pentoxide for 20 h. Acetyl chloride (2.8 g, 35.7 mmol) was added to the dry sodium acetate and the mixture heated at 140 °C (oil bath) for 6 h. The excess of acetyl chloride (1.6 g) was removed and subsequent distillation gave 0.54 g (34 %) of ^{18}O-labeled acetic anhydride (*14*) b.p. 139 °C.

Reaction of 2-cyclopropylpyridine N-oxide in ^{18}O-labeled acetic anhydride. The procedure was as described previously using 2-cyclopropylpyridine *N*-oxide (*1*) (0.61 g, 4.5 mmol) and ^{18}O-labeled acetic anhydride (*14*) (0.52 g, 5.1 mmol).

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