

# REARRANGEMENT OF TERTIARY AMINE OXIDES—IX<sup>1</sup>

## THE MECHANISM OF THE REACTION OF QUINALDINE N-OXIDE WITH BENZOYL CHLORIDE

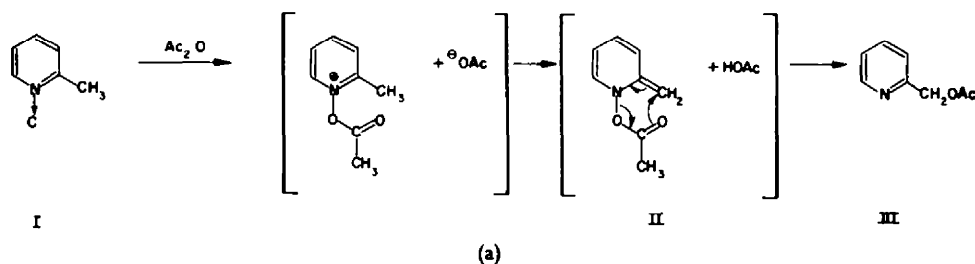
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**Abstract**—The reaction of quinaldine N-oxide with benzoyl chloride has been investigated using <sup>18</sup>O as tracer. The main product, 2-benzoyloxymethylquinoline, obtained by the reaction of quinaldine N-oxide and <sup>18</sup>O-labelled benzoyl chloride has been shown to contain an equal concentration of <sup>18</sup>O in both ether and carbonyl oxygens. In addition to the main product, this reaction gives small amounts of carbon dioxide and quinaldine, suggesting the formation of radicals in the reaction path, however the addition of radical scavenger, DPPH, fails to effect the reaction. This evidence favours a radical cage reaction, and rules out an intramolecular ionic mechanism and a free radical chain process.

THE reaction of 2-picoline N-oxide with acetic anhydride has been known to give 2-acetoxymethylpyridine,<sup>2-4</sup> and the mechanism hitherto accepted for the rearrangement is as follows,<sup>5</sup> (a):



Boekelheide and Harrington,<sup>6</sup> however, suggested instead, a free radical chain process, based on their observations that this reaction is exothermic after an initial induction period and is very little affected by the change of solvent while the reaction mixture causes polymerization of styrene, as shown in (b). Meanwhile, Traynelis and Martello<sup>7</sup> have shown that the reaction is not influenced at all by the addition of styrene or other stronger free radical scavengers and also that 2-butyroxymethylpyridine is the only product isolated from the reaction of 2-picoline N-oxide and n-butyric anhydride in the presence of sodium acetate. Based on these observations, they favour the intramolecular cyclic rearrangement as depicted under (a).

More recently, this reaction has been studied by means of <sup>18</sup>O-tracers<sup>8</sup> and the 2-acetoxymethylpyridine, obtained in the reaction of 2-picoline N-oxide and

<sup>1</sup> Paper VIII: S. Oae, T. Fukumoto, M. Yamagami, *Bull. Chem. Soc., Japan* **36**, 728 (1963).

<sup>2</sup> G. Kobayashi and S. Furukawa, *Pharm. Bull.* **1**, 347 (1953).

<sup>3</sup> V. Boekelheide and W. L. Linn, *J. Amer. Chem. Soc.* **76**, 1286 (1954).

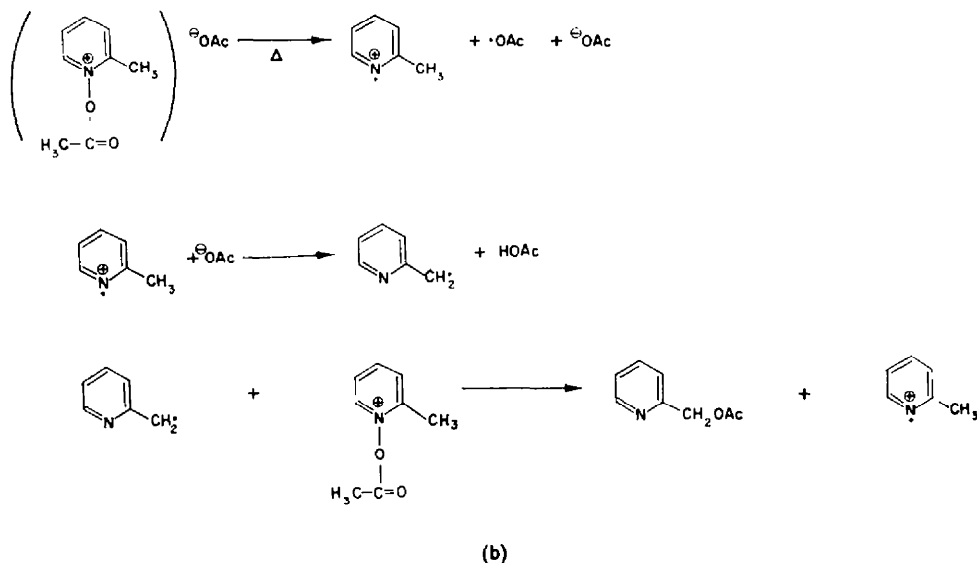
<sup>4</sup> O. H. Bullit and J. T. Maynard, *J. Amer. Chem. Soc.* **76**, 1370 (1954).

<sup>5</sup> I. J. Pachter, *J. Amer. Chem. Soc.* **75**, 3026 (1953).

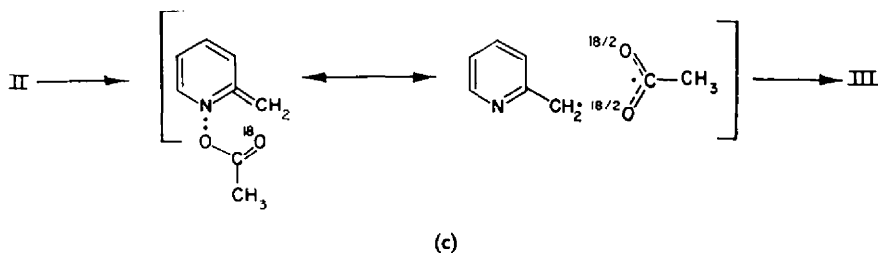
<sup>6</sup> V. Boekelheide and D. L. Harrington, *Chem. & Ind.* 1423 (1955).

<sup>7</sup> V. J. Traynelis and R. F. Martello, *J. Amer. Chem. Soc.* **80**, 6590 (1958).

<sup>8</sup> S. Oae, T. Kitao, and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3359 (1962).



$^{18}\text{O}$ -labelled acetic anhydride, of which all three oxygens were equally enriched, has been shown to contain an equal concentration of  $^{18}\text{O}$  in both the ether and the carbonyl oxygens, while the  $^{18}\text{O}$  enrichment of both oxygens is exactly a half of that of  $^{18}\text{O}$ -labelled acetic anhydride originally employed. The reaction was also shown to be unaffected either by changing the amount of solvent or by the addition of a strong radical scavenger, DPPH. Based on these observations, it was suggested<sup>8</sup> that the reaction proceeds through a "radical pair" process which involves a homolytic cleavage of the nitrogen-oxygen bond of the anhydrobase(II), as follows, (c):



While the reaction between 4-picoline N-oxide and acetic anhydride apparently proceeds through a different path, an ionic intermolecular rearrangement,<sup>9</sup> the  $^{18}\text{O}$ -tracer experiments suggest that the reaction of N,N-dimethylaniline N-oxide with acetic anhydride to form *o*-acetoxy-N, N-dimethylaniline also proceeds via a similar free radical cage process.<sup>10</sup>

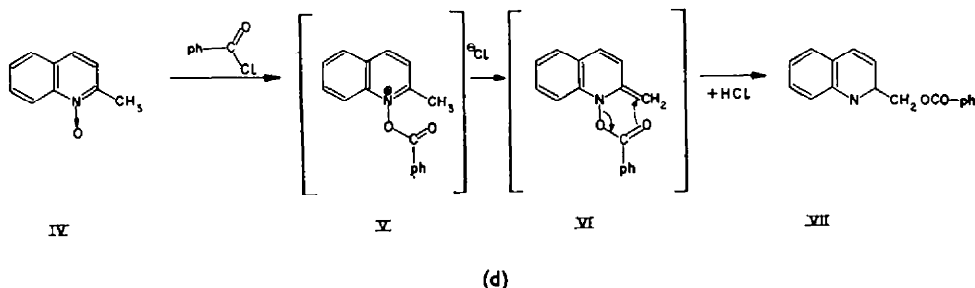
The reaction of quinaldine N-oxide with benzoyl chloride appears to be a similar reaction type. Earlier, Henze<sup>11</sup> suggested that the product is N-benzoyloxyquinoline-2-methide, which upon hydrolysis is converted to N-hydroxyquinoline-2-methide.

<sup>9</sup> S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3362 (1962).

<sup>10</sup> S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3366 (1962).

<sup>11</sup> M. Henze, *Ber. Dtsch. Chem. Ges* **69**, 534 (1936).

However, Pachter proved that the product is 2-benzoyloxymethylquinoline by showing that the hydrolysis product is identical with the reduction product of quinoline-2-carboxylic acid with lithium aluminium hydride.<sup>5</sup> Consequently, it was suggested that the reaction proceeds through an internal cyclic rearrangement as follows: (d)



The mechanism of this reaction has been investigated using  $^{18}\text{O}$ , the labelled benzoyl chloride being prepared by the initial alkaline hydrolysis of benzonitrile with  $^{18}\text{O}$ -enriched water and subsequent chlorination of the resulting  $^{18}\text{O}$ -enriched sodium benzoate with phosphorous pentachloride. According to Henze, an aqueous sodium hydroxide solution of quinaldine N-oxide is treated with a slight excess of the  $^{18}\text{O}$ -labelled benzoyl chloride (enriched with 1.42 atom % of  $^{18}\text{O}$ ), resulting in 2-benzoyloxymethylquinoline. In order to determine the distribution of  $^{18}\text{O}$ , the 2-benzoyloxymethylquinoline was hydrolysed to 2-quinolinemethanol in alcoholic sodium hydroxide solution. Under similar conditions there was no exchange between 2-quinolinemethanol and  $^{18}\text{O}$ -enriched water containing sodium hydroxide.

The intramolecular cyclic rearrangement, which involves shifts of an electron pair in VI, requires all the excess  $^{18}\text{O}$  in the ester to be incorporated in the ether group and the carbonyl oxygen to be natural. The formation of 2-benzoyloxymethylquinoline via a "free radical cage" provides a product in which both oxygen atoms contain an average concentration of a natural and an excess  $^{18}\text{O}$ .

The analytical values of  $^{18}\text{O}$  for 2-benzoyloxymethylquinoline are shown in Table 1.

TABLE 1

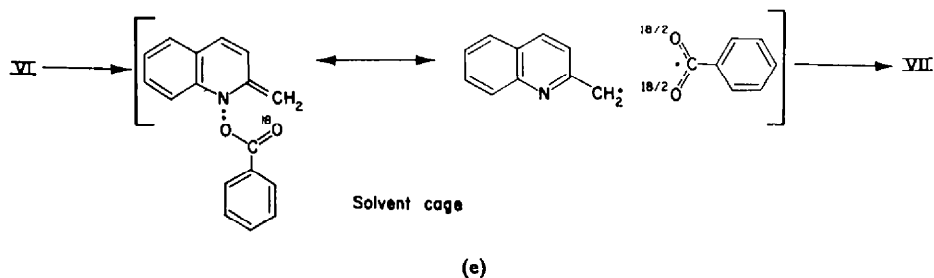
Compound	Atom % $^{18}\text{O}$
$\text{C}_6\text{H}_5\text{COCl}$	1.42
$\text{C}_6\text{H}_5\text{N}-\text{CH}_2\text{OCOC}_6\text{H}_5$	0.81
$\text{C}_6\text{H}_5\text{N}-\text{CH}_2\text{OH}$	0.83

These results favour the free radical cage process and clearly exclude the intramolecular cyclic rearrangement since the latter mechanism requires the  $^{18}\text{O}$  value to be 1.42 for quinolinemethanol.

In seeking additional evidence for the free radical cage mechanism, the reaction was carried out in other solvents with or without a free radical scavenger, DPPH, and the products were carefully analysed. The reaction has been found to proceed smoothly in refluxing non-polar solvents such as benzene or ether, even without the addition of base. In ether solution, the reaction yields not only substantial amounts of 2-benzoyloxymethylquinoline (49%) but also small amounts of quinaldine and benzoic acid, while the evolution of carbon dioxide was detected, though the amount

was very small. Quinaldine is apparently formed by the homolytic fission of the N—O bond of the anhydrobase VI, while the benzoyloxy radical, another homolytic fission fragment, either loses carbon dioxide to give a phenyl radical that eventually becomes benzene or hydrogen is abstracted to form benzoic acid or both these reactions take place simultaneously. The formation of these by-products also favours the initial homolytic cleavage of the N—O bond of the anhydrobase, VI.

The addition of DPPH to the reaction mixture in both aqueous and ether solutions has no effect, the yield of 2-benzoyloxymethylquinoline remaining almost unchanged. The  $^{18}\text{O}$ -tracer experiments together with these product analyses suggest that the only conceivable mechanism for this reaction is a solvent caged radical pair intramolecular rearrangement, as follows: (e)



Since the mechanism of this reaction is similar to that of 2-picoline N-oxide with acetic anhydride,<sup>8</sup> it must be decided whether the reaction of 2-methyl substituted *ar*-t-amine N-oxide with acid anhydride or acid halide proceeds via a free radical cage process, while that of 4-picoline N-oxide with acetic anhydride undergoes an intermolecular rearrangement. In the case of 2-picoline and quinaldine N-oxide with acyl anhydride or halide, the resulting anhydrobases would be sterically more strained than the corresponding anhydrobase from 4-picoline N-oxide, and hence the homolytic cleavage of the N—O bond in the former compounds could take place more readily without the assistance of the nucleophilic attack of acylate ion or other anion. The cleavage of the N—O bond of the anhydrobase from 4-picoline N-oxide could occur with the assistance of the nucleophilic attack of acetate ion either at C-3 or the methylene group. The facile homolytic cleavage of the N—O bond is undoubtedly associated with the bond strength of the particular linkage. N,N-Dimethylaniline N-oxide, which has its N—O stretching frequency of  $960\text{ cm}^{-1}$  corresponding to a rather small force constant of  $4.05 \times 10^{-5}\text{ dyne/cm}$  was found to react violently with acetic anhydride even at  $-30^\circ$  and the reaction was found to proceed via a "radical pair" process.<sup>10</sup>

The substantially high yield of the reaction product in these "radical pair" reactions may be ascribed to the homolytically cleaved species, even the very short-lived acetoxy radical, can find its own partner for the recombination in the close vicinity. Even in the case of 4-picoline N-oxide, a small portion of the anhydrobase would be cleaved homolytically in view of the reaction products, such as methane, carbon dioxide and 4-picoline, however the life of an acetoxy radical is so short that it perhaps decomposes before shifting to either C-3 or the methylene group. If the life of an acyloxy radical is a little longer, one may find a case where a portion of the resulting anhydrobase from 4-picoline N-oxide undergoes the solvent caged radical pair

reaction. In fact, such a case has been found in the reaction of 4-picoline N-oxide with n-butyric anhydride.<sup>12</sup> If the radical which forms by homolytic fission of the N—O bond of the anhydrobase, has a longer lifetime than that of the butyloxy radical, the reaction path may incline more towards a "radical pair" process. Since the benzoyloxy radical is known to be substantially more stable than the acetoxy radical and probably more stable than the butyloxy radical, one would expect the reaction with the benzoylating agent to proceed through a radical cage process. In fact, the preliminary experiment of lepidine N-oxide with benzoyl chloride suggests that the reaction proceeds via a radical cage process.

The IR spectra of the anhydrous quinaldine N-oxide has its N—O bond stretching frequency  $1210\text{ cm}^{-1}$  corresponding to a force constant of  $6.44 \times 10^{-5}\text{ dyne/cm}$ . In comparison with other N-oxides which had been studied, this value is almost identical to that of 2-picoline N-oxide<sup>8</sup> which has been shown to react with acetic anhydride through a "radical pair" process to give 2-acetoxymethylpyridine. Although the anhydrobase could not be isolated, and hence the force constant of the N—O bond could not be determined, it would be much lower than that of the N-oxide, because there is no positive charge on nitrogen in the anhydrobase and the reacting centre of anhydrobase is isoelectronic to the allylic benzoate which is much more reactive than the primary alkyl benzoate. These considerations and the stability of benzoyloxy radical together with the observations of <sup>18</sup>O experiments suggest that the reaction of quinaldine N-oxide with benzoyl chloride proceeds *via* radical pair path.

## EXPERIMENTAL

### <sup>18</sup>O-Labelled benzoyl chloride

To a mixture of 14.5 g <sup>18</sup>O-enriched water (ca. 1.5 atom % <sup>18</sup>O) and 80 ml absolute alcohol, 9.2 g metallic Na was added piece by piece with stirring and cooling, then 41 g benzonitrile was added dropwise and the mixture refluxed for 5 hr. After evaporation of the solvent, the residual mass was crushed in a mortar and thoroughly dried. (150°, 3 hr). The sodium benzoate (56 g) was treated with 90 g PCl<sub>5</sub> and refluxed for 7 hr. The mixture was filtered and the filtrate fractionally distilled under red. press., yielding <sup>18</sup>O-labelled benzoyl chloride b.p., 112–3°/65 mm Hg, 42 g (over-all yield 75%)  $n_D^{20}$ : 1.5537. <sup>18</sup>O content was 1.42 atom %.

### Quinaldine N-oxide

The preparation of quinaldine was according to the usual procedure<sup>13</sup> and the oxidation according to Ochiai for the preparation of pyridine N-oxide<sup>14</sup>.

### The reaction of quinaldine N-oxide with labelled benzoyl chloride in aqueous sodium hydroxide solution

The procedure similar to that reported by Henze<sup>11</sup> was as follows: From 4.0 g quinaldine N-oxide with 4.0 g labelled benzoyl chloride, 4.2 g (56%) 2-benzoyloxymethylquinolinium hydrochloride was obtained, (m.p., 109°–110° further repeated recrystallization from acetone gave mp. 111°–112°, lit.<sup>11</sup> 112°). By neutralization with dil. NaOH aq, this hydrochloride was converted to 2-benzoyloxymethylquinoline (m.p., 51.5–52°, lit.<sup>11</sup> 52°) and crystallized as colourless needles. (Found: C<sub>17</sub>H<sub>13</sub>NO, C, 77.77 N, 5.27 H, 5.06. calc. C, 77.55 N, 5.32 H, 4.97%). <sup>18</sup>O analysis of the ester: 0.81 atom %

### Hydrolysis of the labelled 2-benzoyloxymethylquinoline

The labelled ester (0.5 g) was dissolved in 3 ml methanol containing 0.2 g NaOH and kept a few hr at room temp. The mixture was evaporated and the residue was extracted with ether. 2-Quinolinemethanol, 0.2 g, was obtained from this extract as light yellow crystalline needles, m.p., 65°–66°. Recrystallization from hexane gave colourless crystalline needles, m.p., 67°–67.5°, lit.<sup>11</sup> 66°.

<sup>12</sup> S. Oae, Y. Kitaoka and T. Kitao, *Tetrahedron*.

<sup>13</sup> M. Murakami and Y. Yukawa, *Jinmeiyukihannoshu* pp. 80. Asakura, Tokyo (1958).

<sup>14</sup> E. Ochiai, *J. Org. Chem.* **18**, 534 (1953).

(Found.  $C_{10}H_8NO$ ; C, 75.31, N, 8.61, H, 5.77, calc; C, 75.46, N, 8.80, H, 5.69%).  $^{18}O$  analysis of 2-quinolinemethanol; 0.83 atom %.

*Exchange reaction between 2-benzoyloxymethylquinoline and  $^{18}O$  labelled sodium hydroxide*

2-Benzoyloxymethylquinoline (0.3 g), was hydrolysed in 2 ml methanolic solution containing 0.2 g  $^{18}O$ -labelled NaOH (ca. 1.5 atom %). The isolated 2-quinolinemethanol revealed no incorporation of excess  $^{18}O$ .  $^{18}O$  analysis of 2-quinolinemethanol; 0.20 atom %.

*The reaction of quinaldine N-oxide with benzoyl chloride in benzene*

To a solution of 2.2 g quinaldine N-oxide in 10 ml benzene, 1.8 g benzoyl chloride was added dropwise in about 1 min with refluxing. The 2-benzoyloxymethylquinolinium hydrochloride separated at the bottom of the flask together with an insoluble tarry substance. To separate this tar, the hydrochloride was made alkaline and extracted with ether. From the ethereal layer the hydrochloride was obtained and recrystallized from acetone (2.5 g; 65%), m.p., 109°–110°.

*The reaction of quinaldine N-oxide with benzoyl chloride in ether*

To a solution of 4.10 g (0.0258 M) quinaldine N-oxide in 10 ml ether, 3.70 g (0.0263 M) benzoyl chloride was added dropwise under a  $N_2$  atm., using a flask connected to a trap filled with  $Ba(OH)_2$  aq. Immediately a white precipitate appeared in the trap. After addition of the benzoyl chloride (about 2 min), the mixture was refluxed for an additional 8 min. A few drops of HCl aq. were added and the ethereal layer separated from the red tarry precipitate by decantation and the precipitate washed with ether, then made alkaline with dil. NaOH aq. before extracting with chloroform. The chloroform layer was dried ( $Na_2CO_3$ ) and distilled under red. press. After removal of the solvent, a fraction boiled at 75°–85°/1.5 mm Hg was obtained (0.27 g). The IR spectra of this fraction was identical with quinaldine, and the picrate of this fraction had m.p., 189.5°–190.5° (lit. 191°–194°) and the mixed m.p., with the authentic sample was also identical (0.0019 M, 7.4% yield). The remaining residue, a black tarry substance, was taken up in ether (black insoluble tar was separated) and a few ml HCl aq. added. 2-Benzoyloxymethylquinoline was isolated as the hydrochloride and recrystallization from acetone gave 3.65 g (0.0127 M, 49%) of the hydrochloride, m.p., 111°–112°. The white precipitate which appeared in the  $Ba(OH)_2$  aq. was measured after washing and drying, (9 mg, 0.05 mM, 0.2%). Benzoic acid was isolated from the ethereal layer by extracting with aqueous alkali and acidifying with dil. HCl aq. (0.58 g, 0.0048 M; m.p., 121°–121.5°). The benzoic acid was identical with an authentic sample in IR spectra and mixed m.p.

*The reaction of quinaldine N-oxide with benzoyl chloride in the presence of DPPH*

(1) *In aqueous solution.* To a mixture of 1.00 g (0.0063 M) quinaldine N-oxide, 0.4 g NaOH and 30 ml water, a solution of 0.88 g (0.0063 M) benzoyl chloride and 40 mg (0.1 mM) DPPH was added dropwise. By a similar procedure, 0.97 g (0.0033 M, 52%) 2-benzoyloxymethylquinolinium hydrochloride was isolated, m.p., 109°–110°.

(2) *In ether solution.* Quinaldine N-oxide (0.79 g; 0.0050 M) and 40 mg (0.1 mM) DPPH was dissolved in 5 ml ether and treated with an equimolar amount of benzoyl chloride during reflux and the mixture refluxed for an additional 10 min. After cooling, the reaction mixture was treated with dil. alkali and the ethereal layer separated. From this layer 2-benzoyloxymethylquinolinium hydrochloride was obtained by adding a few drops HCl aq. then recrystallized from acetone, m.p., 109°–110° (0.81 g; 0.0028 M; 57%).

*Infrared spectra and force constant calculation of the N—O bond of quinaldine N-oxide*

IR spectrum of quinaldine N-oxide was taken on a JASCO model IR-2 auto-recording spectrophotometer equipped with NaCl optics. A band at  $1210\text{ cm}^{-1}$  was found to shift to  $1198\text{ cm}^{-1}$  by dissolving the N-oxide in methanol, undoubtedly caused by the formation of hydrogen bonding. Therefore, this band was assigned as the N—O stretching frequency band as in the cases of other N-oxides.<sup>10</sup> From this value, the force constant (k) was calculated using the following equation,<sup>11</sup> where  $\nu$  is the

$$k = 4\pi^2\nu^2m$$

oscillating frequency and m is the mean average reduced mass of the two terminal atoms of the bond.

<sup>11</sup> C. C. Price and S. Oae, *Sulfur Bonding*, pp. 81. Ronald Press, New York (1962).