Thermal Fragmentations of Nitrated 8-Quinolinols

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8-Quinolinols which are substituted in the aromatic nucleus by nitro-, chloro-, or by sulfonic acid groups underwent a neat thermal fragmentation upon heating in 75% nitric acid as reaction medium yielding 2,3-dicarboxypyridinium nitrate. The scope and the mechanism of these reactions are discussed.

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The studies directed towards the large scale preparation of 2,3-pyridindicarboxylic acid (**1**) have provoked numerous attempts over the past fifty years to use as an inexpensive starting material either quinoline or alternatively 8-quinolinol (**2**).

Although the oxidation of quinoline proceeded readily at temperatures of 180-240° using either dilute or concentrated nitric acid, the 2,3-pyridindicarboxylic acid formed as an intermediate during the oxidative process, readily underwent α-decarboxylation and thus furnished solely 3-pyridincarboxylic acid (nicotinic acid) [1a,b].

Nitrations of quinoline occurred at much lower temperature when using a mixture of oleum and nitric acid as reaction medium which afforded a mixture of 5-and 8-nitroquinoline, but no oxidative ring cleavage was observed [2].

The literature is replete with methods describing the oxidative degradations of the benzoid part of the quinoline system, however, it appears that only two methods have attracted some further attention. They rely on the oxidative power of either hydrogen peroxide [3], or of aqueous sodium hypochlorite [4]. Both reactions are performed in the presence of metal salts.

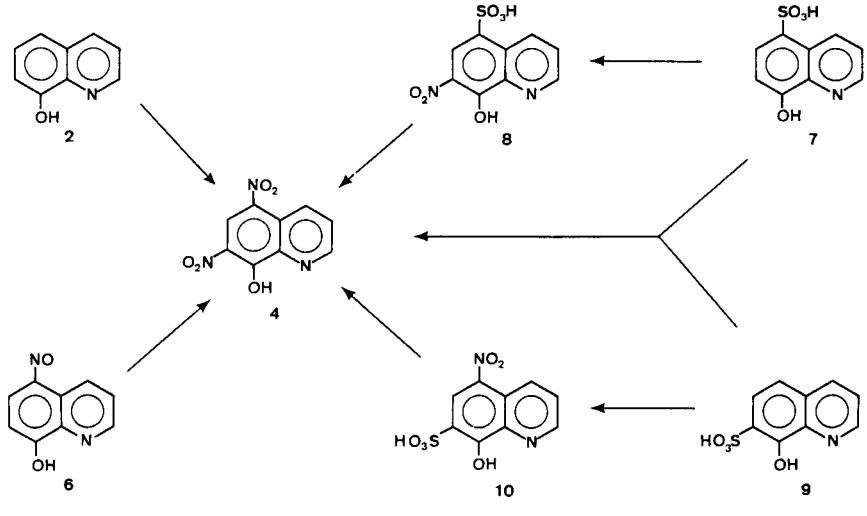
The disadvantages of these methods are largely seen as due to the extensive exothermic course of the reactions and therefore they imply again the possibility of unwanted decarboxylation with formation of nicotinic acid. Conversion of the metal salts of **1** thus obtained to the free acid appears to be a further obstacle to be dealt with in the work-up procedure of these reactions.

On the other hand, the nitration and subsequent oxidation of 8-quinolinol (**2**) using 100% nitric acid under controlled reaction conditions proffered also a convenient procedure for the synthesis of **1**, even when carried out on a large scale, thereby furnishing yields of about 93% [5]. The experimental inconvenience of adding the crystalline **2** to an excess of 100% nitric acid, as described in the previous paper [5] was circumvented in later years by using 65% nitric acid and also reversing the mode of addition of the two reactants, but otherwise the same reaction conditions and work-up procedure was used and nearly quantitative yields of **5** were realized [6].

It was stated in a recently issued patent [7] that this reaction was not reproducible and did not afford any 2,3-pyridindicarboxylic acid at all. However, as it will be seen, this statement in the patent is erroneous.

In connection with attempts to obtain a reliable synthesis for the prepartion of the otherwise elusive 2-car-

SCHEME 1



boxy-3-pyridineglyoxylic acid (**3**) - often suspected to be an intermediate in the formation of **1** - the oxidative nitration has been somewhat modified [8a-c], in particular the work-up procedure, which led to **3** in a yield of 26% [8a]. However, the predominant product in this modified process was still the quinolinic acid. On the other hand, it proved to be a convenient way to prepare **3** which was subsequently used as starting material in the synthesis of pyrido[2,3-*d*]pyridazines [8c].

Since it was presumed that nitration of the benzoid part of **2** represented the initiating step in the synthesis of **1**, we undertook a study of the thermal behaviour of 5,7-dinitro-8-quinolinol (**4**) which is formed in the nitration process of **2**. It soon became apparant that a thermally initiated fragmentation of **4** was the responsible step in the formation of **5**.

There are numerous references describing various syntheses of **4** starting from either **2** or from its sulfonated derivatives as precursors (Scheme 1).

Generally, the dinitro compound **4** has been prepared by addition of **2** to dilute aqueous nitric acid of various concentrations, claiming yields of 65-87% of **4** [9a,b]. Similarly, nitration of **2** in acetic acid as solvent furnished also **4**, although in unspecified yield [10].

For synthetic purposes, however, one of the best methods appeared to be nitration of **2** in a solution of concentrated sulfuric acid at 5° yielding **4** in 86% yield [11]. Some attention has also been paid to the stepwise nitration of **2**. Thus nitrosation of **2** yielded 5-nitroso-8-quinolinol (**6**) which upon treatment with nitric acid furnished **4** in high yield [9a,12]. A small yield of **4** was also realized by nitration of **2** in acetic acid, however, the major product isolated proved to be 7-nitro-8-quinolinol [13,14].

The facile displacement of a sulfonic acid moiety by a nitro group offered alternative routes leading to nitrated derivatives of **2** (Scheme 1). The sulfonation of **2** in 15% oleum proceeded smoothly and with excellent yield, and the subsequent nitration of 8-quinolinol-5-sulfonic acid (**7**) [15] thus obtained with nitric acid at 5-10° is known to give 7-nitro-8-quinolinol-5-sulfonic acid (**8**) [16]. Both compounds **7** and **8**, respectively, yielded **4** on treatment with either concentrated or dilute (32%) nitric acid, although the latter one required extended reaction time. Similarly, while the controlled nitration of 8-quinolinol-7-sulfonic acid (**9**) furnished the mono-nitrated product **10** [17], treatment of either **9** or of **10** with a large excess of nitric acid again gave **4**. It may be presumed that under some of the reaction conditions used during the nitration, in particular the ones which proceeded at elevated temperature, the simultaneously occurring ring cleavage of **4** may never be wholly excluded which thus contributes to a considerably lower yield of **4**.

It may be mentioned that the oxidation of **7** in an aqueous solution with sodium chlorate in the presence of catalytic amounts of vanadium salts proceeded smoothly with evolution of carbon dioxide, and represents an excellent method to prepare **1** in good yield [18].

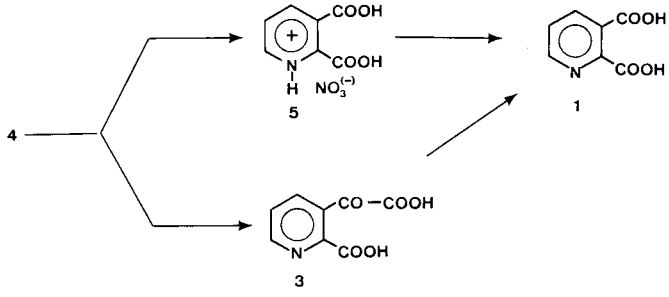
The direct oxidation of **11** using concentrated nitric acid in the presence of catalytic amounts of vanadium salts proceeded with exothermic violence at 85° and yielded **1** in excellent yield [19]. This catalytic oxidation does not involve isolation of any nitrated quinoline as an intermediate, although nitrated products are very likely to be precursors in the catalytic ring opening process.

The oxidative degradation of **11** with nitric acid or alternatively a mixture of nitric acid and hydrochloric acid has also been reported in a patent [20].

The nitrated compound **4** was best recrystallized from dimethylformamide, without any apparant decomposition, yielding bright yellow crystals. Attempts to use other solvents such as dimethyl sulfoxide or nitrobenzene proved equally successful, but purification of the crystals was somewhat hampered by the final removal of traces of solvent.

Although **4** did not decompose below 320° it proved to be unstable upon heating in a solution of nitric acid. Thus, when a solution of **4** in 75% nitric acid was heated for 22 hours, an evolution of nitric oxide commenced at 70-75° (Scheme 2). Subsequent distillation of the nitric acid solution to dryness under reduced pressure furnished 2,3-dicarboxypyridinium nitrate (**5**) in nearly a quantitative

SCHEME 2



yield. The compound was identified by its analytical data and by comparison with an authentic specimen prepared by one of the procedures described earlier [6]. The dicarboxylic acid **1** was obtained from the salt either by dissolving it in water [5,6], or by addition of an equivalent amount of a base to an aqueous solution of **5**.

Similarly, the same type of fragmentation was observed on heating 5-chloro-7-nitro-8-quinolinol (**12**) in nitric acid.

Attempts to perform the reaction in dilute nitric acid (20-40%) yielded only small quantities of **1** along with mixtures of unidentified products. Likewise failed experiments using other mineral acids, either because of ex-

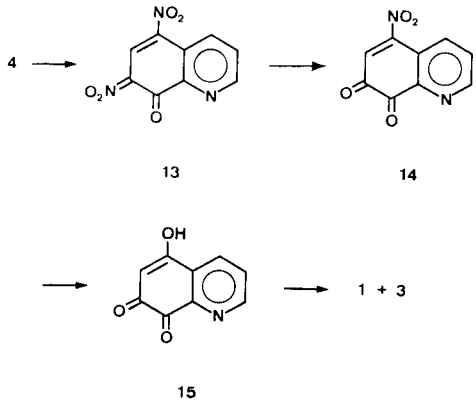
tensive decarboxylation or of other unknown side reactions. Generally, all compounds pictured in Scheme 1 may be good precursors for the synthesis of **1** when yields of the previous steps leading to **4** are satisfactory.

However, this neat thermal fragmentation yielded **5** in quantitative yield only when the solution was heated for an extended period of time (approximately 22-25 hours) which is necessary to complete the decarboxylation of the intermediately formed ketocarboxylic acid (**3**). It has been shown earlier that reduction of the heating period to one hour during the preparation of **1** reduced considerably the yield of **5** and **1**, respectively, and on the other hand improved the yield of the keto acid **3**.

The slow fragmentation of **4** becomes further obvious when Sucharda's method of preparation [5] is employed and the reaction temperature is kept below 50°. When this reaction mixture is then poured into an excess of water, a yield of only 44% of **4** was isolated.

The mechanism of this reaction has not been studied in detail, but it may be pictured in terms of an initial oxidation of the phenolic group of **4** yielding **13**, presumably followed by expulsion of the nitro group which is attached to the carbon atom C-7 yielding **14** (Scheme 3). This transient species is further oxidized to **15** which undergoes

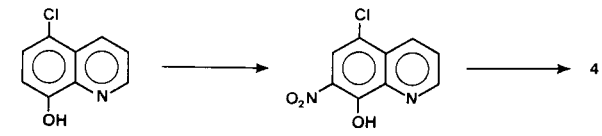
SCHEME 3



fragmentation to **3** and **1**, respectively, with concurrent evolution of nitrous oxide and of carbon dioxide.

The reaction course of this fragmentation which proffers an example from the heterocyclic series is particularly interesting in connotation with analogous fragmentations which are known to occur with nitrated 1-hydroxynaphthols [21a,b]. Related ring cleavages have also been effected by concentrated sulfuric acid [22a-d].

The oxidative cleavage of **12** proceeded at a very slow rate, and heating for 48 hours was required so as to obtain a thoroughly crystalline product of **5**.



The course of the ring cleavage again is presumably analogous to the one observed during the oxidation of phenols and of naphthols which are substituted by a halogen atom, and which have been shown to yield 1,2- and 1,4-quinones as the respective reaction products. Many representative examples of those reactions are compiled in the literature [23]. The quinones formed are easily oxidized further to dicarboxylic acids.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The ir spectra were recorded with a Perkin Elmer spectrometer in potassium bromide discs. Literature procedures were followed in the preparation of 8-quinolinol-5-sulfonic acid (**7**) [15], 7-nitro-8-quinolinol-5-sulfonic acid (**8**) [15,16], 8-quinolinol-7-sulfonic acid hydrate (**9**) [17], 5-nitro-8-quinolinol-7-sulfonic acid (**10**) [17] and 5,7-dinitro-8-quinolinol (**4**) [11]. 5-Chlor-8-quinolinol (**11**) was obtained from Fluka, Inc., Buchs, Switzerland.

2,3-Pyridindicarboxylic Acid (**1**).

A suspension of **5** (6 g, 0.025 mole) in 1.45 ml of 30% aqueous ammonia was stirred for 30 minutes. The crystals were filtered and washed with 3 ml of ice water, yielding 4.2 g (96.4%) of **1**, mp 184° (lit 190° [6]).

5,7-Dinitro-8-quinolinol (**4**). General Procedures.

A. Preparation from 8-Quinolinol-5-sulfonic Acid (**7**) with dilute Nitric Acid.

A suspension of **7** in 40 ml of nitric acid (32%) was stirred for 60 hours. Subsequent dilution with 100 ml of water furnished 2.63 g (64%) of **4**, mp 318° (lit 312-314° [9a]).

B. Preparation from **7** with Concentrated Nitric Acid.

To 50 ml of nitric acid were added **7** (11.25 g, 0.05 mole). The temperature rose to 60° and was maintained for 30 minutes. Then the solution was added to 250 ml of water and crystals collected by filtration, yielding 7.25 g (62%) of **4**.

C. Preparation from 7-Nitro-8-quinolinol-5-sulfonic Acid (**8**).

A solution of **8** (4.05 g, 0.015 mole) in 20 ml of nitric acid (64%) was allowed to stand for 24 hours. The yellow suspension was added to 120 ml of water and after filtration furnished 3.1 g (88%) of **4**.

D. Preparation from 8-Quinolinol-7-sulfonic Acid Hydrate (**9**).

To 10 ml of nitric acid (64%) was added **9** (2.43 g, 0.001 mole) and the temperature allowed to rise to 50° and was maintained for 15 minutes. Work-up in a manner identical with that for the above example yielded 1.55 g (66%) of **4**.

E. Preparation from 5-Nitro-8-quinolinol-7-sulfonic Acid (**10**).

The suspension of **10** (2.7 g, 0.01 mole) in 15 ml of nitric acid (64%) was stirred for 24 hours and worked up as reported above, yielding 2.07 g (88%) of **4**.

2,3-Dicarboxypyridinium Nitrate (**5**).

A solution of 5,7-dinitro-8-quinolinol (**4**) (15 g, 0.064 mole) in a mixture

of 60 ml of nitric acid (64%) and 20 ml of nitric acid (100%) was heated at 90° for 20 hours. There was an initial exothermic reaction with evolution of nitrous oxides which subsided after 15 minutes. Then a current of nitrogen was introduced for 30 minutes and the light yellow solution diluted with 50 ml of water. The solution was evaporated to dryness in a rotating evaporator, and the off-white crystals placed *in vacuo* in a desiccator (over solid potassium hydroxyde), yielding 14.9 g (100%). Recrystallization from 40% nitric acid furnished white crystals, mp 156-158° dec with gas evolution (lit 154° [6]).

Anal. Calcd. for $C_7H_6N_2O_4$: C, 36.53; H, 2.63; N, 12.17. Found: C, 36.48; H, 2.55; N, 12.21.

5-Chloro-7-nitro-8-quinolinol (**12**).

A solution of 5-chloro-8-quinolinol (**11**) (8.98 g, 0.05 mole) in 50 ml of nitric acid (64%) and 50 ml of water was stirred at 15° for 2 hours. The suspension was poured into 400 ml of water and stirred for 20 minutes. Crystals were filtered and washed with 250 ml of water yielding 8.2 g (73%) of **12**. A sample was recrystallized from methyl cellosolve to furnish orange needles, mp 198° (lit 197-199° [14]); ir: 2780, 1635, 1605, 1570, 1330, 1290, 1272, 812 cm^{-1}.

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