O'Connor[3] for benzonitrile hydrolysis diminish from +0.64 at 70° to +0.48 at 111° and crudely extrapolate to about +0.38 at 133.5°. The ϕ parameter we obtain for o-tolunitrile hydrolysis at 133.5°, namely +0.61, is considerably higher than +0.38.

From Arrhenius extrapolation of the log k_2^0 values of Hyland and O'Connor to 133.5°, we reckon k_2^0 for benzonitrile hydrolysis at that temperature to be 5.3×10^{-6} M^{-1} sec^{-1}. This compares with 1.1×10^{-5} M^{-1} sec^{-1} for o-tolunitrile from our data. The ortho methyl group approximately doubles the hydrolysis rate. This augmentation probably is to be attributed to a favorable effect of o-methyl on equilibrium protonation of the nitrile. It also suggests that there is minimal steric hindrance by o-methyl to attack of water at carbon of the protonated nitrile.

For hydrolysis of a weakly basic substrate, the ϕ parameter is composite, being the sum of ϕ_e for equilibrium protonation of the substrate and ϕ_r for the step(s) in which the protonated substrate progresses to transition state and thence to products.[5] Inasmuch as only the ϕ_r value could be related to reaction mechanism and there are no data available from which to calculate the ϕ_e value for nitrile protonation, we eschew attempting to draw mechanistic conclusions from our kinetic data.

Experimental Section

A small amount of o-tolunitrile was dissolved in a standardized solution of $HClO_4$ in distilled water. Aliquots were sealed in glass ampoules which were immersed, all at once, in a thermostat at 133.5 ± 0.2°. At measured times ampoules were removed, plunged into cold water, and opened, and 2-ml portions transferred by pipet into 10-ml volumetric flasks containing 3 ml of 6 M aqueous NaOH. The flasks were diluted to the mark with distilled water and the absorbances of the resulting solutions were immediately measured at 231 nm by means of a Beckman Model DU spectrophotometer. (Independent measurements showed that in alkaline solution o-toluamide and o-toluate ion have equal extinction coefficients at 231 nm.) Plots of ln $(A_t - A_\infty)$ were linear, and the negatives of their slopes (calculated by linear regression analysis) were taken as $k\psi$.

Registry No.—o-Tolunitrile, 529-19-1; perchloric acid, 7601-90-3.

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Nitration of the Acridizinium Ion and Its 6,11-Dihydro Derivative[1]

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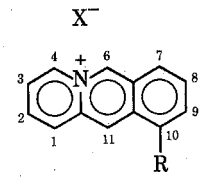
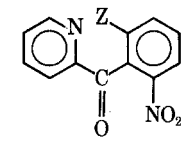
To date, the only clear-cut electrophilic substitution reaction carried out with the unsubstituted acridizinium ion 1 has been sulfonation,[2] which occurs at position 10 of the cation. The mechanism of the halogenation reaction is obscure. It was suggested[3] that at least some of the products were formed by an addition–elimination mechanism. To date, there has been no report of the nitration of the acridizinium ion.



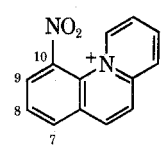
1, R = H
2, R = NO_2



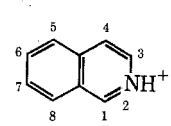
3, Z = COOH
4, Z = H

Earlier experiments showed that, when acridizinium salts are heated with nitric acid, the product is a compound formed by oxidation[4] as well as nitration. When a mixture of concentrated nitric and sulfuric acids at below −5° is used, a mononitro acridizinium salt is obtained in good yield. The product is so susceptible to nucleophilic attack that it can be crystallized satisfactorily only if acid is present. Oxidation of the new nitroacridizinium salt at 100° in concentrated nitric acid afforded a 2-(2-carboxynitrobenzoyl)pyridine which, on decarboxylation, yielded the known[5] 2-(2-nitrobenzoyl)pyridine (4). From this, it follows that the acid is 3 and the original nitration product is the 10-nitro derivative (2).

The 10 position, like the 8 position, does not bear a positive charge in any of the canonical forms contributing to the resonance hybrid. It is probable that nitration and sulfonation occur predominantly at position 10 (rather than 8) because of the greater reactivity of α positions in polycyclic systems. The observation parallels exactly that of the nitration of the benzo[c]quinolizinium ion[6] (yielding 5) in that the nitration occurs in the ring most remote from the positive charge and at that α position which does not bear a positive charge in any of the canonical forms contributing to the resonance hybrid. Another interesting parallel is the nitration of isoquinoline. In mixed acid, in which it exists as its conjugate acid 6, it affords the 5-nitro derivative in 90% yield.[7] This orientation is explicable on the same basis as that of the two benzoquinolizinium systems (2 and 5). Reduction of the nitro group of 2 is accompanied by reduction of the quinolizinium system.

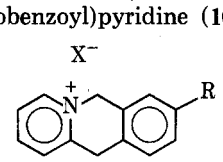


5

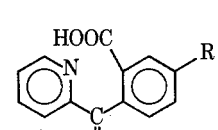


6

As was reported earlier,[8] acridizinium salts can be reduced over a palladium catalyst to yield the 6,11-dihydro product (7). Nitration of 7 afforded a 70% yield of 8-nitro-6,11-dihydroacridizinium salt (8), the identity of which was established by oxidation to the known[4] 2-(2-carboxy-4-nitrobenzoyl)pyridine (10). The discovery that this oxidation could be carried out by the use of permanganate prompted a reinvestigation of the oxidation of acridizinium bromide. In the first paper[9] dealing with acridizinium salts, the statement was made that the crude permanganate oxidation product, obtained in 81% yield, was impure phthalic acid. This statement, based only on a



7, R = H
8, R = NO_2



9, R = H
10, R = NO_2

melting point and on sublimation experiments which were discontinued after a few milligrams of phthalic anhydride was obtained, is obviously in error. Oxidation of acridizinium bromide with potassium permanganate has now been found to afford a 36% yield of 2-(2-carboxybenzoyl)-pyridine (9).

Our nitration experiments make it clear that, in the oxidative nitration which converts the acridizinium ion into 2-(2-carboxy-4-nitrobenzoyl)pyridine (10), oxidation must precede nitration or else the product would be 3. It has now been shown that 9 is not an intermediate since it is recovered unchanged when subjected to the conditions of the oxidative nitration.

Experimental Section

10-Nitroacridizinium Perchlorate (2, X = ClO_4). To a mechanically stirred solution containing 50 ml of concentrated sulfuric acid and 50 ml of concentrated nitric acid, cooled to −5 to −10°, 5 g of acridizinium bromide[10] was added in small portions. After an additional 15 min, the mixture was poured into 400 ml of ice–water. The resulting solution was allowed to come to room temperature and filtered to remove some reddish solid. Addition of 100 ml of 35% perchloric acid to the filtrate and cooling gave 4.2 g of yellow needles. Recrystallization from water containing perchloric acid afforded 3.8 g (65.5%) of pure yellow needles, mp 197–198°.

Anal. Calcd for $C_{13}H_9ClN_2O_6$: C, 48.07; H, 2.77; N, 8.63. Found: C, 48.19; H, 2.70; N, 8.65.

The **bromide** was prepared by suspending 1 g of the perchlorate salt (2) in 25 ml of methanol which had been saturated with potassium bromide. After the slurry had been warmed and stirred for 2 hr, the potassium perchlorate was filtered off, the solution concentrated, and crystallization induced by addition of ethyl acetate. The bromide consisted of yellow platelets, mp 225–227°.

Anal. Calcd for $C_{13}H_9N_2O_2Br$: C, 48.29; H, 3.40; N, 8.67. Found: C, 48.19; H, 3.38; N, 8.79.

2-(2-Carboxy-6-nitrobenzoyl)pyridine (3). A solution of 2 g of 10-nitroacridizinium perchlorate in 20 ml of concentrated nitric acid was heated for 6 hr on a steam bath. The solution was cooled and diluted with 50 ml of water; solid sodium bicarbonate was added in small portions. At a pH ~2, 0.7 g (42%) of a colorless solid, mp 203–207°, precipitated. Recrystallization from acetic acid–water afforded a product, mp 224–225°.

Anal. Calcd for $C_{13}H_8N_2O_5$: C, 57.36; H, 2.96; N, 10.29. Found: C, 56.99; H, 3.05; N, 10.40.

2-(2-Nitrobenzoyl)pyridine (4). A mixture of 0.5 g of 3 with 0.1 g of copper powder was heated for 30 min at 180°. The solid was thoroughly extracted with boiling ethanol, and the extract filtered and concentrated, causing the crystallization of 0.25 g of tan needles, mp 117–118° (lit.[4] 117–118°).

Anal. Calcd for $C_{12}H_8N_2O_3$: C, 63.15; H, 3.53; N, 12.28. Found: C, 62.67; H, 3.52; N, 12.06.

10-Aminobenzo[*b*]quinolizidine Methiodide. A suspension of 2 g of 10-nitroacridizinium perchlorate (2) with 0.2 g of platinum oxide in 100 ml of ethanol was hydrogenated at atmospheric pressure. After absorption of the theoretical amount of hydrogen, the catalyst was removed and the solution concentrated under reduced pressure. The salt was converted into the free base from which the methiodide was prepared. The tan solid was recrystallized from methanol–ethyl acetate to give 0.7 g (32%) of tan needles, mp 254–256°.

Anal. Calcd for $C_{14}H_{21}IN_2 \cdot \frac{1}{2}H_2O$: C, 47.60; H, 6.28; N, 7.93. Found: C, 47.94; H, 6.13; N, 7.72.

8-Nitro-6,11-dihydroacridizinium Perchlorate (8). A mixture of 15 ml of concentrated sulfuric acid and 15 ml of concentrated nitric acid was cooled to 0° and 1.5 g of 6,11-dihydroacridizinium bromide (7)[8] was added over a period of 15 min. After an additional 1 hr, the mixture was poured into 200 ml of ice–water. The solution was filtered and 25 ml of 35% perchloric acid added to the filtrate. The mixture was refrigerated overnight and then collected and recrystallized from water containing a few drops of perchloric acid. The yield was 1.3 g (70%) of tan needles, mp 190–193°.

Anal. Calcd for $C_{13}H_{11}ClN_2O_6$: C, 47.79; H, 3.39; N, 8.58. Found: C, 47.70; H, 3.43; N, 8.48.

2-(2-Carboxy-4-nitrobenzoyl)pyridine (10). A. By Oxidation with Nitric Acid. A 1-g sample of 8-nitro-6,11-dihydroacridizinium perchlorate (8) in 25 ml of concentrated nitric acid was heated overnight on a steam bath. The nitric acid was removed under reduced pressure and the residue extracted with sodium bicarbonate solution. The extract was filtered and acidified, affording the crude product. Recrystallization from acetic acid–water afforded 0.3 g (36%) of product, mp 215–217°.

B. By Oxidation with Permanganate. A 1-g sample of 8 was suspended in 25 ml of hot water on a steam bath and the solution stirred while powdered potassium permanganate was added. When the color was no longer immediately discharged, the hot solution was filtered to remove manganese dioxide and then acidified. Upon cooling, 0.3 g (36%) of product, mp 217–218°, crystallized. Both products were shown to be identical by mixture melting point and ir spectra and were shown to be identical with an authentic specimen.[4]

2-(2-Carboxybenzoyl)pyridine (9). A 1-g sample of acridizinium bromide was oxidized with permanganate essentially as in the case of 8 except that acidification of the alkaline solution with dilute hydrochloric acid was carefully done to pH 5. The product consisted of colorless needles, mp 225–227°; yield, 0.3 g (36%).

Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.97; N, 6.17. Found: C, 68.54; H, 3.87; N, 6.13.

A sample of the keto acid (9), dissolved in concentrated nitric acid and heated on the steam bath for 12 hr, was recovered unchanged.

Registry No.—1 (X = Br), 7547-88-8; 2 (X = ClO_4), 50585-79-0; 2 (X = Br), 50585-80-3; 3, 50678-82-5; 4, 50678-83-6; 7 (X = Br), 15757-24-1; 8 (X = ClO_4), 50585-82-5; 9, 27693-49-8; 10, 50585-83-6; 10-aminobenzo[*b*]quinolizidine methiodide, 50678-84-7.

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Biological Probes. I. Carbon-6-Labeled Nicotinamide

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Recent interest in studies using nonradioactive labels for tracing metabolic pathways and as general biological probes has led us to develop new methods for labeling the internal ring positions of nicotinamide (1). The following describes an efficient method for preparing gram quantities of specifically labeled 1 containing ^{13}C at the C-6 position. The incorporation of this base into the coenzyme NAD^+ (2) using biosynthetic techniques can be and has been readily accomplished.[1]

The ease with which quinolines can be prepared and then oxidized to pyridinecarboxylic acids suggested that an attractive synthetic scheme could be developed incorporating these transformations as key steps. Specifically, a high yield of 2-methylquinoline-2-^{13}C (3) was obtained from *o*-aminobenzaldehyde and acetone-2-^{13}C under Friedlander reaction conditions, as is shown in Scheme I. Preliminary experiments had shown that the attempted direct oxidative degradation of 3 to a pyridinecarboxylic acid under a variety of conditions resulted in only partial