The Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part VII.[1] The Nitration of Pyridines in the α-Position and Rules for the Nitration of Substituted Pyridines

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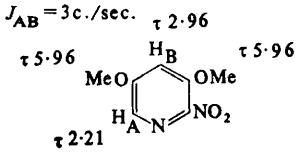
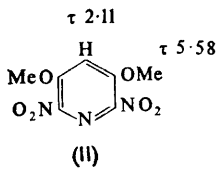
Kinetic criteria show that the nitration of 3,5-dimethoxypyridine proceeds on the conjugate acid species in the 2-position, and that the 6-nitration of 3,5-dimethoxy-2-nitropyridine occurs on the free base. Relative reactivities are compared with the corresponding benzenoid compounds. A set of rules is proposed for the nitration of substituted pyridines and their synthetic applications discussed.

To direct nitration into the α-position of pyridine, activating groups were required in the 3- and 5-positions. The 2-mono- and 2,6-di-nitration of 3,5-diethoxypyridine has been reported,[2] but to facilitate kinetic comparisons with earlier work, we wished to study the successive nitration of 3,5-dimethoxypyridine. This has been previously prepared[3] in low yield from 3,5-dibromopyridine by sodium methoxide treatment. We found the commercially available 3,5-dichloropyridine very reluctant to react with methoxide, but initial conversion to the *N*-oxide, nucleophilic replacement, and subsequent reduction gave 3,5-dimethoxypyridine in 40% overall yield.

Preparatively, mononitration was almost quantitative, but dinitration gave poor yields only, because of the instability of the product; however, kinetics could be followed using equations specially developed for a reaction in which decomposition of the product occurs simultaneously. The orientations of the mixtures were confirmed by the n.m.r. spectral data (I) and (II) in deuteriochloroform. As expected, the kinetic results confirmed that the first nitration occurred on the conjugate acid and the second on the free base.



(I)



(II)

EXPERIMENTAL

For details of the acids, and their standardisation, see ref. 1.

3,5-Dichloropyridine 1-Oxide.—3,5-Dichloropyridine was oxidised with hydrogen peroxide in glacial acetic acid, by the method of Ochiai,[4] to give the *1-oxide* (90%), which crystallised from light petroleum (b. p. 100—120°) as long needles, m. p. 109° after vacuum sublimation at 100°/15 mm. (Found: C, 36·4; H, 1·7; N, 8·3. $C_5H_3Cl_2N$ requires C, 36·6; H, 1·8; N, 8·5%).

3,5-Dimethoxypyridine 1-Oxide.— 3,5-Dichloropyridine 1-oxide (25 g.) was heated under reflux for 16 hr. with methanolic sodium methoxide [from sodium (30 g.) in 'AnalaR' methanol (300 ml.)]. The methanol was evaporated at 15 mm., and the residue was dissolved, with cooling, in a little water. Chloroform extraction of the dried (K_2CO_3) extracts gave 3,5-dimethoxypyridine 1-oxide which crystallised from light petroleum (b. p. 100—120°)–ethyl acetate as needles (15·4 g., 65%), m. p. 91° (lit.,[3] 91—93°).

3,5-Dimethoxypyridine.—3,5-Dimethoxypyridine 1-oxide (4·5 g.) in ethanol (100 ml.), was hydrogenated (4 atm. 60°) over 5% palladium on charcoal (0·5 g.). When no more hydrogen was absorbed, the solution was filtered, and the ethanol evaporated. The residual 3,5-dimethoxypyridine (2·9 g., 72%) distilled at 112°/0·22 mm. The picrate had m. p. 145—145·5° (lit.,[3] 146·5—147°).

3,5-Dimethoxy-2-nitropyridine.—Mixed nitric acid (0·72 g., 95%) and sulphuric acid (20 ml., 98%) was added to 3,5-dimethoxypyridine (1·39 g.) in sulphuric acid (30 ml., 98%) at 0°. The pale yellow mixture was stirred for 1 min. and poured on ice. The precipitated solid crystallised from aqueous ethanol and sublimed at 115°/15 mm. to give pale yellow needles (1·55 g., 84%), m. p. 117—118·5° (lit.,[3] 115·5—116·5°).

3,5-Dimethoxy-2,6-dinitropyridine.—Nitric acid (10 ml., 70%) was added, with stirring, to 3,5-dimethoxypyridine (1·39 g.) in sulphuric acid (50 ml., 98%). The mixture was heated at 40° for 18 hr., then poured on ice. The *dinitro-compound* (0·7 g., 30%) crystallised from aqueous ethanol as pale yellow needles, m. p. 181—182° (Found: C, 36·5; H, 3·0; N, 18·2. $C_7H_7N_3O_6$ requires C, 36·7; H, 3·1; N, 18·3%).

Kinetic Measurements.—(i) 3,5-Dimethoxypyridine (pK_a 4·44); the kinetics were followed under second-order conditions at room temperature, using the u.v. technique described previously.[1] (ii) 3,5-Dimethoxy-2-nitropyridine (pK_a −2·52, n = 1·1, determined as before [5]); the kinetics were complicated by the partial decomposition of the reaction product. By taking measurements at the isosbestic point (342 mμ) of the mono- and di-nitro-compounds, and also at 285 mμ, where there is a large extinction coefficient difference between the two compounds, it was possible to obtain rate constants for the nitration.

This method assumes that the decomposition product(s) does not absorb at the wavelengths concerned. This was shown to be approximately true by heating 3,5-dimethoxy-2,6-dinitropyridine in the reaction medium, when after a few hours there was a 90% reduction in the extinction coefficients concerned. The concentration, x, of product formed after time t sec. was calculated from,[6]

$$x = \frac{a}{D_\infty}(D_t - D_0)\left[1 - \frac{(D_{oi} - D_{ti})(D_\infty - D_0)}{D_{oi}(D_t - D_0) + D_\infty(D_{oi} - D_{ti})}\right]^{-1}$$

[1] Part VI, C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, and M. Viney, preceding Paper.
[2] H. J. den Hertog and J. W. van Weeren, *Rec. Trav. chim.*, 1948, **67**, 980.
[3] H. J. den Hertog, M. van Ammers, and S. Schukking, *Rec. Trav. chim.*, 1955, **74**, 1171.
[4] E. Ochiai, *J. Org. Chem.*, 1953, **18**, 534.
[5] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, N. Shakir, and A. M. White, *Tetrahedron*, 1965, **21**, 1055.
[6] M. Viney, Ph.D. Thesis, University of East Anglia, 1966.

where a = initial concentration of substrate, D_o = initial optical density at 285 mμ, D_t = optical density at 285 mμ after time t sec., $D_\infty = a$(extinction coefficient of product at 285 mμ), D_{oi} = initial optical density at the isosbestic point, and D_{ti} = optical density at the isosbestic point after time t sec.

Table 1 and Figure 1 show a typical kinetic run on 3,5-dimethoxy-2,6-dinitropyridine.

RESULTS AND DISCUSSION

The Arrhenius parameters for the nitrations are listed in Table 2, and the rate profiles defined in Table 3 and Figure 2. For the nitration of 3,5-dimethoxy-2-nitropyridine, the results are expressed as k(free base).

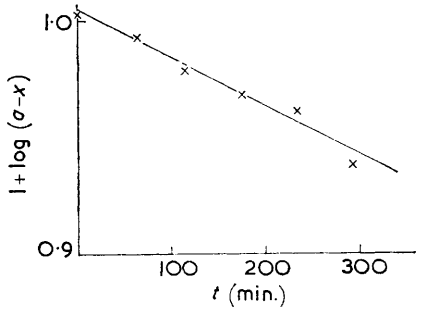


FIGURE 1 First-order plot for the nitration of 3,5-dimethoxy-2-nitropyridine

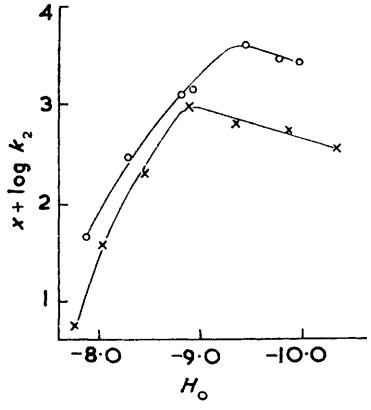


FIGURE 2 Acidity dependence of rates of nitration of 3,5-dimethoxypyridine at 25°, $x = 3$, (×—×—×), and 3,5-dimethoxy-2-nitropyridine at 51°, $x = 1$, k_2(free base) (○—○—○)

Using the criteria previously discussed,[1] we now deduce the species (free base or conjugate acid) on which reaction is proceeding.

3,5-Dimethoxypyridine.—From the shape of the rate profile [1] (Table 3, Figure 2), it is clear that 3,5-dimethoxypyridine is reacting as the conjugate acid. This is confirmed by the entropy of activation, −20·0 e.u. (Table 2), which is in agreement with the theoretical prediction for reactions of two monocharged ions.[1] The calculated encounter rate [7] for the reaction in 98% sulphuric acid is $8{\cdot}5 \times 10^8$ l./mole/sec. at 25°. Reaction *via* the free base is excluded as it would require an encounter rate of at least 3×10^{14} l./mole/sec. (from equation 4 of ref. 1).

3,5-Dimethoxy-2-nitropyridine.— The "corrected" rate profile for the nitration of 3,5-dimethoxy-3-nitropyridine for reaction proceeding on the free base (allowing for the concentration of free base following H_0) is of the typical form [1] where the concentration of the species undergoing nitration is invarient, indicating the validity of the correction made. Here, k(free base) in 98% sulphuric acid is 200 l./mole/sec. at 51°, considerably smaller than the encounter rate (even allowing for the elevated temperature), and thus entirely consistent with the existence of an appreciable energy of activation.

Relative Reactivities.—The previous work [1] on the nitration rates of 1,3-dimethoxybenzene at 22·7°, and 2,4-dimethoxynitrobenzene at 31° enables calculation of relative reactivities. For 3,5-dimethoxypyridine in 86% sulphuric acid at 25°, log k_2 is 1·05 (Figure 2).

TABLE 1

Data for a typical nitration run with 3,5-dimethoxy-2,6-dinitropyridine (3,5-dimethoxy-2,6-dinitropyridine = 0·0039M, HNO_3 = 0·093M, H_2SO_4 = 84·0%, temp. = 51·0°, D_∞ = 0·697)

Time (min.)	Wt. of soln. removed (g.)	D_t	D_{ti}	$a - x$	$1 + \log(a - x)$
0	3·46	0·2700	0·6580		
60	3·44	0·2727	0·6560	0·9816	0·992
120	3·45	0·2735	0·6520	0·9507	0·978
180	3·43	0·2760	0·6475	0·9285	0·968
240	3·46	0·2795	0·6475	0·9120	0·960
300	3·42	0·2814	0·6470	0·8675	0·938
360	3·44	0·2830	0·6370	0·8452	0·927

$k_2 = 8{\cdot}565 \times 10^{-5}$ l./mole/sec.

TABLE 2

Activation parameters

3,5-Dimethoxypyridine (89·98% H_2SO_4)

Temp.	$1 + \log k_2$	E_A (kcal.)	log A	ΔS (e.u.)
0·0°	0·133			
10·0	0·513	12·44 ± 0·4	8·84 ± 0·3	−20·0
17·0	0·740			
22·6	0·894			

3,5-Dimethoxy-2-nitropyridine (89·75% H_2SO_4)

Temp.	$5 + \log k_2$	E_A (kcal.)	log A	ΔS (e.u.)
39·9°	0·894			
51·0	1·384	22·67 ± 1·1	17·5 *	+15·9 *
54·7	1·610			
59·9	1·850			

* Free base.

TABLE 3

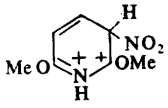
Acidity dependence of rates of nitration

3,5-Dimethoxypyridine (25°)		3,5-Dimethoxy-2-nitropyridine (51°)			
			$5 + \log k_2$		log k_2
$-H_0$	$3 + \log k_2$	$-H_0$	(stoich)	$pK_a - H_0/1{\cdot}1$	(free base)
7·79	0·745	7·87	0·814	4·68	0·674
8·06	1·684	7·97	0·933	4·95	0·883
8·45	2·306	8·28	1·245	5·24	1·480
8·88	3·020	8·82	1·424	5·72	2·144
9·36	2·857	8·91	1·384	5·80	2·184
9·90	2·752	9·45	1·326	6·30	2·626
10·36	2·591	9·78	0·899	6·60	2·499
		9·98	0·711	6·78	2·491

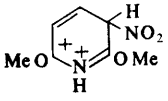
[7] M. W. Austin, J. R. Blackborrow, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1965, 1051.

Neglecting the slight temperature difference, log [k_2-(dimethoxybenzene)/k_2(3,5-dimethoxypyridine)] is 6·7. The corresponding value for 2,6-dimethoxypyridine is 6·9 at 22·7°. The close similarity of the reactivities of the two symmetrical dimethoxypyridines is surprising. Evidently, the expected greater deactivation of the α-positions by the nitrogen atom is offset by the unfavourable canonical forms (III) and (IV) in 2,6-dimethoxypyridine which reduce the activating effect of the methoxy-groups.

Comparison of the rate of nitration of 3,5-dimethoxy-2-nitropyridine as the free base with that of 2,4-dimethoxynitrobenzene gives log [k_2(2,4-dimethoxynitrobenzene)/k_2(3,5-dimethoxy-2-nitropyridine)] as 3·17 at 31°. This is calculated from the Arrhenius parameters for 3,5-dimethoxy-2-nitropyridine in 89·75% sulphuric acid, assuming that the shape of the rate profile does not change between 31 and 50°. The corresponding value for 2,6-dimethoxy-3-nitropyridine is 2·73 at 31°.



(III)



(IV)

Rules for the Nitration of Pyridines.—The qualitative results of this and the preceding Paper may be summarised in the following rules for nitration in sulphuric acid solution; (*a*) basic pyridines (p$K_a > +1$) will be nitrated as cations slowly, unless strongly electron-donating groups are present (nitration does not occur with solely electron-accepting substituents). The orientation will be to the α- or β-positions depending on the positions of the activating groups; (*b*) very weakly basic pyridines (p$K_a < -2{\cdot}5$) undergo nitration as the free bases; α or β orientations and relative reactivities being controlled by substituents in the normal way. (Somewhere in the range of pK_a +1 to −2·5 a changing-over in reactivity must occur; we are at present investigating this.)

These rules may be usefully applied in the preparative nitration of reactive pyridines. Thus, to prepare a pure mononitro-compound, the nitration should be carried out in oleum, where the extent of protonation of the mononitro product is much greater than in 90% sulphuric acid, and hence the rate of any further nitration as a free base is drastically reduced. Conversely, to obtain a good yield of dinitro-compound, it is advisable to work in 90% sulphuric acid, at the maximum activity of nitronium ion.

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