Nitration of Some 3,5-Disubstituted Pyridine *N*-Oxides

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The preparation of 3-chloro-5-methoxypyridine *N*-oxide and its nitration are reported. Mononitration yields 5-chloro-3-methoxy-2-nitro-pyridine *N*-oxide while more drastic conditions give 3-chloro-5-methoxy-2,6-dinitropyridine. Removal of various substituents by base hydrolysis is also discussed.

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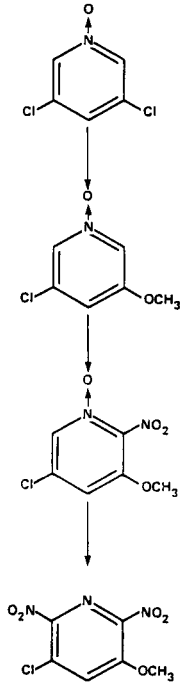
Electrophilic substitution, especially nitration, of *N*-oxides has been of great importance in the synthesis of many pyridine derivatives [1-5]. Of particular interest have been those derivatives bearing halogen and alkoxyl groups in positions 3 and 5. Nitration with mixed acids of 3-bromo-, 3-methoxy-, 3-ethoxy-, 3,5-dichloro-, and 3,5-dibromopyridine *N*-oxides leads to γ-nitro derivatives, which do not undergo further nitration [2-4]. In contrast, 3,5-dimethoxy, 3,5-diethoxy, and 3-bromo-5-ethoxypyridine *N*-oxides undergo α-nitration yielding mononitro derivatives, which on further nitration, give 2,6-dinitro derivatives usually accompanied by reduction of the *N*-oxide [2,3,5].

This difference in behavior has been attributed to dominance by the normally γ orienting *N*-oxide in the first group of compounds being overpowered in the second group by the orienting influence of the alkoxyl groups combined with steric hindrance of the γ position [2]. In all of the known cases where nitration fails to occur in the γ position, at least one of the 3,5-substituents is an alkoxyl group, and the other is fairly bulky. It was of interest, therefore, to examine nitration of 3-alkoxy-5-substituted-pyridine *N*-oxides in which the 5 substituent was smaller. We have now done this for one such compound, 3-chloro-5-methoxypyridine *N*-oxide. We have also studied the reactions of some of the mononitro compounds with a few strong bases.

Johnson, Katritzky and Viney [3] reported preparing 3,5-dimethoxypyridine *N*-oxide by treating 3,5-dichloropyridine *N*-oxide with ten-fold excess of sodium methoxide in methanol [6]. We have found that by reducing the excess methoxide to five-fold, it is possible to obtain good yields of the previously unreported 3-chloro-5-methoxypyridine *N*-oxide (Scheme 1).

Scheme 1



Nitration of 3-chloro-5-methoxypyridine *N*-oxide by the method given in reference [3] for dinitration of 3,5-dimethoxypyridine *N*-oxide gave a 20% yield of a mononitro derivative free of dinitro compounds. Yield of up to 50% of the same mononitro derivative were obtained by replacing the 70% nitric acid used by Johnson *et al* [3] with an equivalent amount of white fuming nitric acid or absolute nitric acid and reducing the reaction time to 1 hour (Scheme 1). Thin layer chromatography showed a small impurity that was readily removed by recrystallization from ethyl acetate/petroleum ether. The major product was assigned the structure 5-chloro-3-methoxy-2-nitropyridine *N*-oxide on the basis of elemental analysis and the following arguments based on nmr spectroscopy: Introduction of a nitro group causes lowfield (*i.e.*, higher δ) shifts in both ring protons and the protons of an adjacent methoxyl group. The effect on a methoxyl group across the ring from the nitro group would be expected to be negligible. The resonance that we found in the mononitro compound at 7.045 must be from the γ proton, which appears at 6.899 in the unnitrated compound. If it were from one of the other ring resonances, the shift would be a highfield

Table 1

Assignment of ^{13}C NMR Peaks; the Value in Brackets is the Relative Intensity

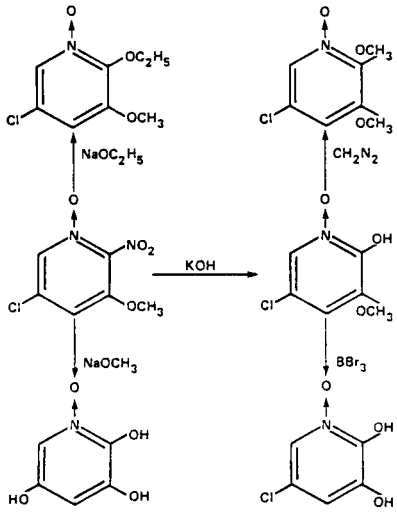
Substitution	Methoxyl	Ring carbon 2	3	4	5	6
3,5-Dimethoxy	56.001 [2.0]	121.104 [0.66]	157.724 [0.17]	100.415 [1.10]	157.724 [0.17]	121.104 [0.66]
3,5-Dimethoxy-2-nitro	57.098 (3-) [1.0]	149.693 [0.14]	157.775 [0.09]	98.847 [1.11]	157.775 [0.09]	119.810 [0.40]
3,5-Dimethoxy-2,6-dinitro	57.567 [1.0]	162.	153.165 [0.11]	107.620 [0.92]	153.165 [0.11]	162.
3-Chloro-5-methoxy	56.346 [1.0]	131.923 [0.43]	132.903 [0.37]	113.274 [1.28]	157.484 [0.28]	126.443 [0.39]
5-Chloro-3-methoxy-2-nitro	57.602 [1.0]	131.763 [0.46]	134.087 [0.17]	111.133 [1.07]	149.140 [0.12]	157.092 [0.02]
3-Chloro-5-methoxy-2,6-dinitro	58.072 [1.0]		129.407 [0.01]	120.061 [0.32]	150.482 [0.12]	

shift. Since the γ-proton is still present, the nitro group must occupy one of the two α positions. The relatively large shift in the methoxyl resonance from 3.857 to 3.995 indicates that the nitro is adjacent to the methoxyl, *i.e.*, in position 2. This assignment is further supported by comparison of ^{13}C nmr spectra. The assignments are presented in Table 1. 3,5-Dimethoxypyridine *N*-oxide shows a single methoxyl resonance. Introduction of one nitro group results in a spectrum with two unequal methoxyls with shifts relative to the unsubstituted compound of +0.738 and +1.097 ppm. The nitro group must, therefore, be in the 2 position since the symmetrical 4-nitro compound would show only one methoxyl resonance. This confirms the earlier assignment [2,3,5]. The methoxyl with the larger shift is presumed to be the one in the 3 position adjacent to the nitro group. In the 5-chloro-3-methoxy series the shift on introduction of the nitro group is +1.256 ppm, which is more consistent with an assignment of the nitro group to the 2 position adjacent to the methoxyl than to the 6 position opposite it. The carbon at position 4, which is readily assigned on the basis of relative intenstities, is little changed on nitration supporting the assignment to an α position.

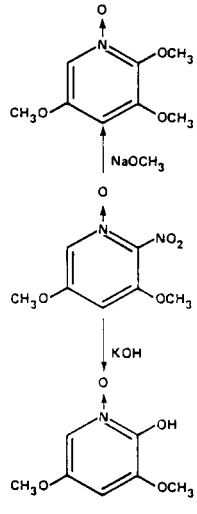
5-Chloro-3-methoxy-2-nitropyridine *N*-oxide was further nitrated in refluxing absolute nitric acid to yield a dinitro compound from which the *N*-oxide had been removed (Scheme 1). Deoxidation results from the action of nitrogen oxides on the *N*-oxide [2]. Attempts to reoxidize the dinitro compound to an *N*-oxide were unsuccessful. Comparison to the shifts in the proton nmr spectrum caused by introduction of the second nitro group with those caused by introduction of the first suggested that the second nitro had entered the 4 position. However, comparison of ^{13}C spectra indicated more strongly that it was in the 6 position. Dinitration of 3,5-dimethoxypyridine *N*-oxide gives a compound having only one methoxyl resonance; the 2,6 assignment for this compound is thus confirmed. For the two methoxyls to coincide, the shifts introduced by the second nitro group must be +0.469 for the methoxyl on the opposite side of the ring and +0.828 for the methoxyl adjacent. If the same shifts are produced in the 5-chloro-3-methoxy series, the 2,4-dinitro compound should exhibit a methoxyl resonance at +2.084 while the 2,6-dinitro isomer should show one at +1.725 ppm. The methoxyl resonance in our dinitro compound is at +1.726 ppm indicating a 2,6 assignment. Additionally, the resonance for the carbon at position 4 shows about the same (+6.787 *vs* +7.205 pmm) small shift as that in the dimethoxyl compound.

Treatment of 5-chloro-3-methoxyl-2-nitropyridine *N*-oxide, 3,5-dichloro-4-nitropyridine *N*-oxide or 3,5-dimethoxy-2-nitropyridine *N*-oxide with potassium hydroxide or sodium methoxide in methanol in a 1 to 2 ratio results primarily in removal of the nitro group and formation of the corresponding hydroxy compound (Scheme 2). With 3,5-dimethoxy-2-nitropyridine *N*-oxide and sodium methoxide in rigidly dried methanol, we were able to obtain a moderate yield of 2,3,5-trimethoxypyridine *N*-oxide (Scheme 3), but we were not successful in obtaining the methoxy compounds in the other two cases. We did prepare 5-chloro-2-ethoxy-3-methoxypyridine *N*-oxide from 5-chloro-3-methoxy-2-nitropyridine *N*-oxide using sodium ethoxide in ethanol (Scheme 2). With 5-chloro-3-methoxy-2-nitropyridine *N*-oxide, higher ratios of potassium hydroxide result in removal of first the nitro group, then the methoxyl, and finally the chlorine. A 1 to 3 ratio gave a mixture of 5-chloro-2-hydroxy-3-methoxy- and 5-chloro-2,3-dihydroxypyridine *N*-oxides that could not be separated by crystallization. The pure dihydroxy compound could be prepared by boron tribromide cleavage of the 5-chloro-2-hydroxy-3-methoxypyridine *N*-oxide (Scheme 2). Treatment of this compound with diazomethane gave 5-chloro-2,3-dimethoxypyridine *N*-oxide (Scheme 2).

Scheme 2



Scheme 3



EXPERIMENTAL

Proton nuclear magnetic resonance (nmr) spectra were obtained in acetone-d_6 solution on a Varian EM360 instrument except as noted. In the nmr listings, S = singlet, D = doublet, M = a complex multiplet centered at the indicated δ, T = triplet, Q = quartet. Shifts (γ) are measured relative to internal tetermethylsilane and are reported in ppm. Coupling constants (J) are in Hz, and the number in parenthesis is the relative area. Infrared spectra were taken on a Perkin Elmer Model 457 grating spectrometer in potassium bromide pellets and are reported in wave numbers. Melting points were taken on a Mettler FP1 at a heating rate of 2°C/min and are corrected. Microchemical analyses were performed by Midwest Microlab Ltd., Indianapolis, Indiana.

3-Chloro-5-methoxypyridine *N*-Oxide.

3,5-Dichloropyridine *N*-oxide (7) (20 g, 0.12 mole), methanol (240 ml), and sodium methoxide (28 g, 0.52 mole) were refluxed together for 16 hours. The methanol was evaporated under a stream of argon, and the residue was dissolved in 250 ml of water. Extraction of this solution with 2 × 100 ml of chloroform, drying over anhydrous potassium carbonate, filtering and evaporating left 17.0 g (87%) of crude product melting at 155°. The analytical sample was recrystallized three times from ethyl acetate/petroleum ether and sublimed at 100° and 1 Pa, mp 156.5°; nmr: OCH_3 3.98 S (3), Hγ 7.18 T (1), Hα 8.00 D (2); (high resolution nmr in deuteriochloroform): (8) OCH_3 3.857, Hγ 6.899, Hα 7.891, Hα' 7.918, Jα,γ 1.99, Jα',γ 1.67, Jα,α' 1.60 (α' is adjacent to the methoxyl); tlc (silica gel/dichloromethane): R_f = 0.50; ir: NO stretch 1280, CCl 670.

Anal. Calcd. for $C_6H_6ClNO_2$: C, 45.16; H, 3.79; N, 8.78. Found: C, 45.27; H, 3.90; N, 9.00.

5-Chloro-3-methoxy-2-nitropyridine *N*-Oxide.

3-Chloro-5-methoxypyridine *N*-oxide (1.0 g, 6.3 mmoles), concentrated sulfuric acid (24.5 ml) and 90% nitric acid (1.0 ml) were heated at 90° for 1 hour. The cooled reaction mixture was poured over 100 g of ice, and the product was collected by filtration, washed with water, and dried overnight at room temperature and 3 Pa, weight 0.6 g (47%), mp 130°. The analytical sample was recrystallized three times from ethyl acetate/petroleum ether and sublimed at 120° and 1 Pa, mp 153°; nmr: OCH_3 4.13 S (3), Hγ 7.66 D (1), Hα 8.28 E (1); (high resolution nmr in deuteriochloroform): OCH_3 3.995; Hγ 7.045, Hα 7.955, J,γ 1.66; tlc (silica gel/dichloromethane): R_f = 0.61; ir: NO_2 asym stretch 1560, NO_2 sym stretch 1380, NO stretch 1260, CCl 645.

Anal. Calcd. for $C_6H_5ClN_2O_4$: C, 35.23; H, 2.46; N, 13.69. Found: C, 34.95; H, 2.36; N, 13.56.

3-Chloro-5-methoxy-2,6-dinitropyridine.

5-Chloro-3-methoxy-2-nitropyridine *N*-oxide (4.0 g, 20 mmoles) was added to cold absolute nitric acid (20 ml) at a rate slow enough to keep the temperature below 10°. The reaction mixture was then refluxed for 18-20 hours, cooled to room temperature and poured over 100 g of ice. The product was collected by filtration, washed with water and dried overnight at room temperature and 3 Pa, weight 1.6 g (34%), mp 110°. The analytical sample was twice recrystallized from ethyl acetate/petroleum ether and sublimed at 140° and 1 Pa, mp 115°; nmr: OCH_3 4.30 S (3), Hγ 8.54 S (1); tlc (silica gel/dichloromethane): R_f = 0.75; ir: NO_2 asym stretch 1550, NO_2 sym stretch 1350, NO stretch 1280, CCl 645.

Anal. Calcd. for $C_6H_4ClN_3O_5$: C, 30.85; H, 1.73; N, 17.99. Found: C, 30.91; H, 1.84; N, 17.94.

5-Chloro-2-hydroxy-3-methoxypyridine *N*-Oxide.

A solution of 1.14 g (5.6 mmoles) of 5-chloro-3-methoxy-2-nitropyridine *N*-oxide and 0.63 g (11.2 mmoles) of potassium hydroxide in 40 ml of methanol was refluxed for 15 hours. After cooling, the solvent was removed on a rotary evaporator, and the residue was dissolved in 20 ml of water. Continuous extraction for 24 hours with methylene chloride yielded 0.33 g of recovered starting material. The aqueous solution was adjusted to a *p*H of less than 2 with 1*N* hydrochloric acid and reextracted to yield 0.67 g (82%) of slightly yellow solid, mp 154°. After three recrystallizations from ethyl acetate/ethanol and sublimation at 100° and 0.1 Pa it melted at 161°; nmr: OCH_3 3.89 S (3), Hγ 6.78 D(1), Hα 7.54 D(1), OH 8.9 broad S (1).

Anal. Calcd. for $C_6H_6ClNO_3$: C, 41.05; H, 3.45; N, 7.98; Cl, 20.10. Found: C, 41.01; H, 3.69; N, 8.11; Cl, 20.46.

A similar hydrolysis of 1.56 g (7.65 mmoles) of 5-chloro-3-methoxy-2-nitropyridine *N*-oxide with 15.3 mmoles of sodium methoxide in 40 ml of methanol gave 0.71 g (64%) of the same material.

5-Chloro-2,3-dihydroxypyridine *N*-Oxide.

A solution of 0.5 ml (1.32 g, 5.3 mmoles) of boron tribromide in 2 ml of methylene dichloride was added dropwise over about 2 minutes at room temperature to a stirred solution of 0.26 g (1.6 mmoles) of 5-chloro-2-hydroxy-3-methoxypyridine *N*-oxide in 10 ml of methylene dichloride, and the mixture was stirred at room temperature for 25 hours. Water (20 ml) was slowly added from a pipet, and the resulting aqueous solution was continuously extracted for 25 hours with methylene dichloride. Evaporation and drying at room temperature and 16 kPa left 0.19 g (73%) of

nearly colorless product melting at 206°. Recrystallization from absolute ethanol and sublimation at 100° and 0.1 Pa raised the melting point to 230° (lit mp, 180° [8]); nmr: 1:1 deuteriochloroform/perdeuteriomethanol): Hγ 6.80 D (1), Hα 7.36 D (2); ir: NO stretch 1260.

Anal. Calcd. for $C_5H_4ClNO_3$: C, 37.17; H, 2.50; N, 8.67; Cl, 21.95. Found: C, 37.21; H, 2.54; N, 8.59; Cl, 22.24.

5-Chloro-2,3-dimethoxypyridine *N*-Oxide.

A suspension of 0.16 g (1.14 mmoles) of 5-chloro-2,3-dihydroxypyridine *N*-oxide in 2 ml of ethyl acetate was treated at 0° with the diazomethane generated from 0.93 g (6.3 mmoles) of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. After stirring at room temperature for 18 hours, the solvent was evaporated under a stream of argon to leave 0.18 g (85%) of a slightly brown oil that was purified by thin layer chromatography using a silica gel plate and 1% methanol in methylene dichloride as the eluent to yield a colorless solid melting at 91°; nmr (deuteriochloroform): OCH_3, 3.94 S (3) and 4.17 S (3), Hγ 6.87 D (1). Hα 7.95 D (1), J = 3.

Anal. Calcd. for $C_7H_8ClNO_3$: C, 44.34; H, 4.25; N, 7.39. Found: C, 44.16; H, 4.04; N, 7.13.

2,3,5-Trihydroxypyridine *N*-Oxide.

A solution of 13.5 mmoles of freshly prepared sodium methoxide and 0.75 g (3.7 mmoles) of 3-chloro-5-methoxy-6-nitropyridine *N*-oxide in 15 ml of carefully dried toluene was refluxed for 15 hours. After cooling to room temperature, 25 ml of water was added, and the aqueous solution was continuously extracted for 25 hours with methylene dichloride. Evaporation and drying left a trace of starting material. The aqueous phase was adjusted to *p*H 2 with concentrated hydrochloric acid and continuously extracted as before. Evaporation left 0.57 g (105%) of an orange solid, mp 138°. After 3 recrystallizations from ethyl acetate/petroleum ether and subliming at 120° and 0.1 Pa it melted at 161°; nmr (deuteriochloroform): OH 3.88 S (3), Hγ 6.78 D (a), Hα 7.55 D (1); ir: NO stretch 1260.

Anal. Calcd. for $C_5H_5NO_4 \cdot 0.2H_2O$: C, 40.94; H, 3.71; N, 9.55. Found: C, 40.92; H, 3.52; N, 9.53.

5-Chloro-2-ethoxy-3-methoxypyridine *N*-Oxide.

A solution of 1.21 g (5.94 mmoles) of 5-chloro-3-methoxy-2-nitropyridine *N*-oxide in 40 ml of absolute ethanol containing 11.9 mmoles of freshly prepared sodium ethoxide was refluxed for 15 hours. The ethanol was removed on a rotary evaporator at aspirator pressure, and the residue was dissolved in 20 ml of water. The aqueous solution was continuously extracted for 25 hours with methylene dichloride. Evaporation and drying left 0.29 g (24%) of tan solid melting at about 82°. After 4 recrystallizations from petroleum ether and sublimation at 125° and 1 Pa, it melted at 113°; nmr (deuteriochloroform): CH_3 1.48 T (3) J = 7, OCH_3 3.80 S (3), OCH_2 4.41 Q (2) J = 7, Hγ 6.92 D (1), Hα 7.87 D (1) J = 3; IR NO stretch 1260.

Anal. Calcd. for $C_8H_{10}ClNO_3$: C, 47.19; H, 4.95; N, 6.88; Cl, 17.41. Found: C, 47.19; H, 5.02; N, 6.99; Cl, 17.26.

2-Hydroxy-3,5-dimethoxypyridine-*N*-Oxide.

Hydrolysis of 0.76 g (3.80 mmoles) of 3,5-dimethoxy-2-nitropyridine *N*-oxide by the procedure used for preparation of 5-chloro-2-hydroxy-3-methoxypyridine *N*-oxide yielded 0.41 g (63%) of solid product melting at 149°. After two recrystallizations from ethyl acetate/petroleum ether and sublimation at 70° and 1 Pa, it melted at 160° with decomposition; nmr (deuteriochloroform): OCH_3 3.71 S (3) 3.83 S (3), Hγ 6.53 D (1), Hα 6.98 D (1), OH 7.30 S (1); ir: NO stretch 1277.

Anal. Calcd. for $C_7H_9NO_4$: C, 49.12; H, 5.50; N, 8.18. Found: C, 48.92; H, 5.52; N, 7.89.

2,3,5-Trimethoxypyridine *N*-Oxide.

A solution of 0.69 g (3.45 mmoles) of 3,5-dimethoxy-2-nitropyridine *N*-oxide in 20 ml of absolute methanol containing 3.43 mmoles of freshly prepared sodium methoxide was refluxed for 15 hours. The methanol was removed on a rotary evaporator, and the residue was dissolved in 20 ml of water. Continuous extraction for 25 hours with methylene dichloride followed by evaporation and drying left 0.31 g (49%) of tan solid melting at 104°. After three recrystallizations from ethyl acetate/petroleum ether and sublimation at 150° and 1 Pa, it melted at 109°; nmr (deuteriochloroform): OCH_3 3.82 S (3) 3.98 S (3) 4.10 S (3), Hγ 6.60 D (1), Hα 7.70 D (1); ir: NO stretch 1280.

Anal. Calcd. for $C_8H_{11}NO_4 \cdot 25H_2O$: C, 50.66; H, 6.11; N, 7.38. Found: C, 50.92; H, 6.05; N, 7.33.

Acknowledgements.

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