Some Nitropyridine Derivatives[1]

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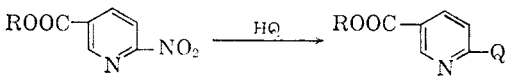
During the study of possible synthetic routes to a pyridine analog of Chloromycetin[2] several nitropyridine derivatives were prepared. 5-Nitropyridine-2-carboxaldehyde was prepared by the selenium dioxide oxidation of 2-methyl-5-nitropyridine but the yield was low and this approach was not followed further. 2-Nitropyridine-5-carboxylic acid was prepared and its esterification and subsequent use in ester-type condensations was investigated. The 2-nitro group proved to be very labile toward nucleophilic substitution. It was replaced by chloro, hydroxy, methoxy, and amino groups with ease.



R = H or CH_3
Q = Cl, OH, OCH_3, NH_2

Because of this, successful Claisen ester type condensations of methyl 2-nitropyridine-5-carboxylate were not realized.

The reaction of 2-nitropyridine-5-carboxylic acid with sulfuric acid in ethanol, or hydrochloric acid in methanol, led to the displacement of the 2-nitro group by the hydroxyl or chloro group, in addition to esterification. Displacement also occurred when 2-nitropyridine-5-carboxylic acid was heated in aqueous sulfuric or hydrochloric acid. The synthesis of methyl 2-nitropyridine-5-carboxylate was achieved by the use of diazomethane. In attempts to condense methyl 2-nitropyridine-5-carboxylate with ethyl acetate in the presence of sodium methoxide, the product obtained was methyl 2-methoxypyridine-5-carboxaldehyde.

Displacement of the 2-nitro group has been reported in the reactions of potassium hydroxide and sodium ethoxide with 2-nitropyridine,[3] hydrobromic acid with 2-nitro-5-ethoxypyridine and 2,6-dinitro-3,5-diethoxypyridine,[4] acetyl chloride and 2-nitropyridine-N-oxide,[5] and ammonia with 2-nitro-5-bromopyridine and 2-nitro-5-ethoxypyridine.[6] Similar reactions of 4-nitropyridine derivatives have been reported.[3,7] No reports of the displacement of a 3-nitro group from the pyridine ring were found.

The similarity in substitution reactions of many pyridine compounds and the corresponding nitrobenzene derivatives is well known.[8] Displacements of nitro groups from tri- and tetra-nitrobenzene under strong acidic conditions and of nitro groups from dinitro- and dinitrohalo-benzenes by basic reagents have been reviewed.[9] Such reactions are in contrast to the inert character of mononitrobenzene derivatives towards such displacement reactions. The reactivity of the 2-nitro group in the pyridine ring is readily rationalized according to the general mechanism of aromatic nucleophilic displacements.[9-11]

EXPERIMENTAL[12]

2-Methyl-5-nitropyridine.[13] To a solution of diethyl malonate (41.0 g., 0.26 mole) in anhydrous ether (500 ml.) was added sodium hydride (6.2 g., 0.26 mole) under a nitrogen atmosphere. When the evolution of hydrogen had subsided, 2-chloro-5-nitropyridine[14] (40.0 g., 0.26 mole) was added with stirring, followed by the removal of ether by distillation. The red, tarry residue was heated by an oil bath to 110° for 1 hr., then refluxed in 12 N sulfuric acid (300 ml.) for 9 hr., during which time the product was removed by continuous steam distillation. This was accomplished by placing a reflux condenser almost horizontally, allowing the solid to remain in the condenser while the water flowed back into the flask; the white crystalline product, 2-methyl-5-nitropyridine (23.1 g., 65% yield), melted at 108–110°.

5-Nitropyridine-2-carboxaldehyde. The oxidation of 2-methyl-5-nitropyridine to the aldehyde was accomplished, after extensive exploration, by a procedure similar to that of Baumgarten,[15] who reported the preparation of 3-nitropyridine-4-carboxaldehyde. 2-Methyl-5-nitropyridine (1.00 g., 0.0072 mole) and freshly prepared selenium dioxide (0.80 g., 0.0072 mole) were dissolved in ethanol (20 ml., 95%) and refluxed for 5.5 hr. Some black selenium (0.10 g.) was removed by filtration. Xylene (30 ml.) was added and the ethanol was removed by distillation over a two hour period. A tarry precipitate (0.63 g.) containing selenium was removed by filtration and the filtrate was extracted with 6*N* hydrochloric acid (3 × 15 ml.). The extract was filtered through Celite and made basic with sodium bicarbonate, filtered again to remove a small amount of red precipitate and the filtrate extracted with chloroform (3 × 20 ml.). The extract was dried over anhydrous magnesium sulfate,

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evaporated to an oily residue (0.46 g.) which was distilled at 100° and 30 mm. to give a white, crystalline solid (0.19 g., 17% yield), m.p. 54–57°. The infrared spectrum had a carbonyl band at 5.86 microns. This material stained the skin dark green.

Anal. Calcd. for $C_6H_4N_2O_3$: C, 47.38; H, 2.65; N, 18.42. Found: C, 47.31; H, 2.78; N, 18.36.

The oxime was white, m.p. 190–191°; the 2,4-dinitrophenylhydrazone was chrome yellow, m.p. 250–252° with sintering at 228–232°; the thiosemicarbazide was yellow, m.p. 177–179°.

2-Nitropyridine-5-carboxylic acid. 2-Nitro-5-methylpyridine, m.p. 93–95°, (average yield 66%) was prepared from 2-amino-5-methyl pyridine,[16] and oxidized by permanganate[17] to 2-nitropyridine-5-carboxylic acid, m.p. 178–180°, yield 41–89% (average 66%) based on unrecovered starting material.

Methyl 2-nitropyridine-5-carboxylate. 2-Nitropyridine-5-carboxylic acid (8.3 g., 0.0494 mole) was dissolved in refluxing absolute ether (1000 ml.), cooled to 25°, and treated with diazomethane in ether. Evaporation left a residue of white crystalline methyl 2-nitropyridine-5-carboxylate (8.3 g., 92% yield) m.p. 130–131°, strong carbonyl band at 5.85 μ.

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.27; H, 3.45; N, 15.15.

Ethyl 2-hydroxypyridine-5-carboxylate. Concentrated sulfuric acid (25 ml.) was added with cooling to a solution of 2-nitropyridine-5-carboxylic acid (20.0 g., 0.119 mole) in absolute ethanol (50 ml.). The solution was heated on a steam bath for 3 hr., cooled, poured on ice (about 300 g.), made basic with ammonium hydroxide (70 ml.), and chilled. The solid which precipitated was collected by filtration, combined with the residue from chloroform extraction of the filtrate, and recrystallized from ethyl acetate to give white crystalline ethyl 2-hydroxypyridine-5-carboxylate (14.4 g., 72%) m.p. 149–151° (lit.[18] m.p. 149–150°), strong hydroxyl band at 2.90 μ and carbonyl band at 5.89 μ.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.58; H, 5.54; N, 8.48.

2-Hydroxypyridine-5-carboxylic acid. 2-Nitropyridine-5-carboxylic acid (0.75 g.) was refluxed 1 hr. in a solution of 6*N* sulfuric acid (10 ml.) and ethanol (5 ml.); crystalline 2-hydroxypyridine-5-carboxylic acid, m.p. 300° *dec.* (lit.[16] m.p. 301–302° *dec.*), precipitated on cooling.

Methyl 2-chloropyridine-5-carboxylate. 2-Nitropyridine-5-carboxylic acid (26.5 g., 0.158 mole) was dissolved in absolute methanol (265 ml.), and a slow stream of hydrogen chloride was introduced with stirring and chilling during 90 min. and then kept at 0° for 12 hr. The solution became golden yellow after 1 hr., indicating the formation of nitric oxide. The reaction mixture was evaporated under reduced pressure, neutralized with sodium carbonate at 0° and the white precipitate which formed was collected by filtration and combined with the residue from the chloroform extract of the filtrate. The product was recrystallized from benzene-petroleum ether to give a white crystalline chlorine containing compound shown to be methyl 2-chloropyridine-5-carboxylate (17.5 g., 65% yield) m.p. 86–87° (lit.[19] m.p. 86–89°). The infrared spectrum indicated the absence of nitro or hydroxyl functions.

2-Chloropyridine-5-carboxylic acid. A mixture of 2-nitropyridine-5-carboxylic acid (0.75 g.) and concentrated hydrochloric acid (5 ml.) was boiled for 5 min.; nitric oxide was evolved. Evaporation to dryness gave white crystalline 2-chloropyridine-5-carboxylic acid (0.70 g.) m.p. 195–200° (lit.[20] m.p. 199° *dec.*). Esterification according to the previous experiment gave the methyl ester, m.p. 86–87°; a mixture melting point with sample prepared in the previous experiment was undepressed.

Methyl 2-methoxypyridine-5-carboxylate. Methyl 2-nitropyridine-5-carboxylate (0.14 g.) and methanol (0.10 ml.) were dissolved in benzene (10 ml.). Sodium hydride (0.14 g.) was added, and the mixture was refluxed 4 hr. A solid was collected by filtration which gave brown fumes on acidification, and a positive "brown ring test" with ferrous sulfate and concentrated sulfuric acid, indicating the presence of nitrite ion. The filtrate residue was sublimed to long white needles of methyl 2-methoxypyridine-5-carboxylate (0.09 g.) m.p. 48–49° (lit.[21] m.p. 42°).

Anal. Calcd. for $C_8H_{10}O_3N$: OCH_3 37.1. Found: 36.5.

Under the same conditions, but without the addition of methanol, sodium hydride was recovered by filtration and methyl 2-nitropyridine-5-carboxylate by evaporation of the filtrate. With sodium methylate in methanol the same product was obtained on sublimation but the yield was lower.

2-Aminopyridine-5-carboxylic acid. Methyl 2-nitropyridine-5-carboxylate (0.60 g.) was added to a sodium amide suspension prepared by the addition of sodium (0.08 g.) to liquid ammonia (50 ml.). The mixture immediately became deep purple, then slowly faded to brown. Evaporation of the ammonia left an amorphous gray water-soluble powder, which evolved nitric oxide upon acidification with 3*N* hydrochloric acid. From the acid solution, a small amount (10 mg.) of crystalline 2-aminopyridine-5-carboxylic acid was obtained, m.p. 290–310° dec. (lit.[22] 312° dec.).

Attempted condensations with ethyl acetate using sodium hydride, sodium amide or sodium triphenylmethyl in inert solvents were unsuccessful.

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The Synthesis of 5-Azaindole[1]

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Since 7-azaindole and 7-azatryptophan[3] have exhibited interesting biological activity in a number of systems,[4] a synthesis of 5-azaindole and deriva-

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