

AZABENZOXAZOLES: SYNTHESIS OF 3-METHYLISOXAZOLO [5,4-c]- AND
2-METHYLOXAZOLO [5,4-c] PYRIDINES

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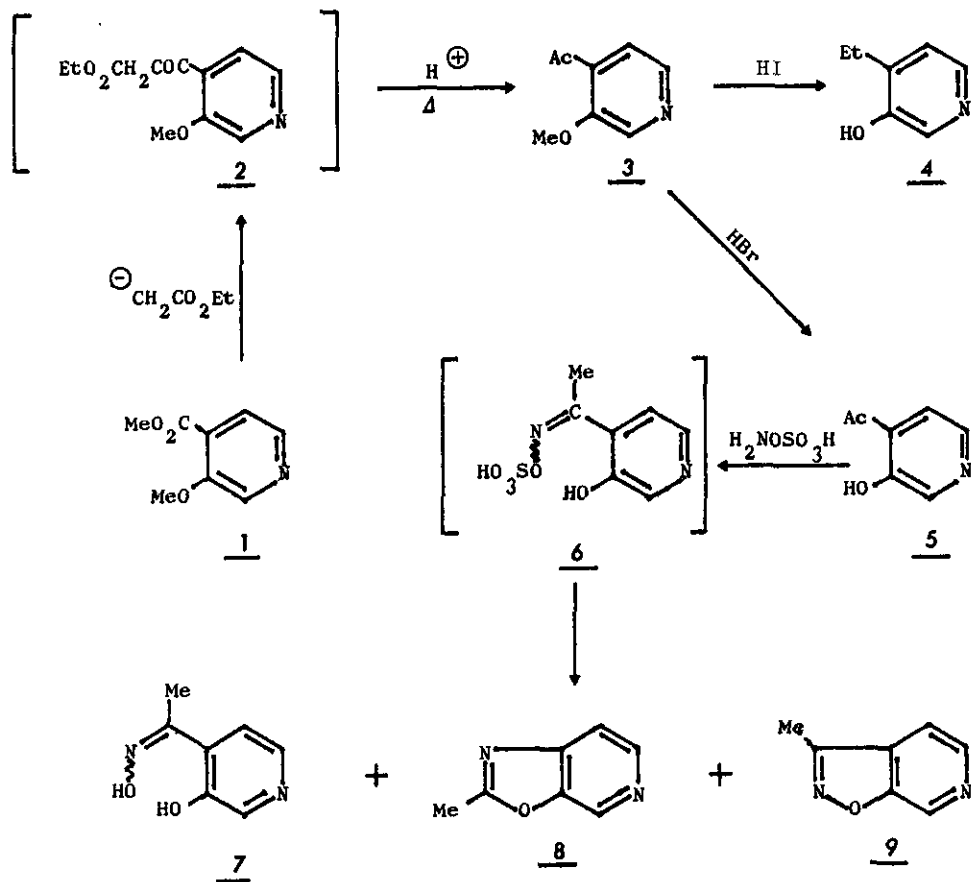
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Abstract - A convenient synthesis of 4-acetyl-3-hydroxypyridine
is reported; this compound allows the preparation of the new
isoxazolo [5,4-c]- and oxazolo [5,4-c]pyridine ring systems.

Because our interest in the chemistry of azabenzoxazoles, we previously reported
the synthesis of 3-methylisoxazolo [4,5-c]-,^{1a} [5,4-b]-,^{1b} and [4,5-b]pyridines;^{1c}
furthermore, both a study of the photochemical behaviour of some derivatives of
the first system² and a kinetic investigation on the methoxy-dehalogenation
reactions of several chloro derivatives of the three systems were also carried
out.^{1c,3}

We now describe in this paper the first synthetic approach to the hitherto unknown
title ring systems (8) and (9), which were obtained by ring closure of the suitably
3,4-disubstituted pyridine (5).

This key product was prepared in good yield by treatment of 4-acetyl-3-methoxy-
pyridine (3) with concentrated hydrobromic acid; the latter compound was synthesized
by condensation of the ester (1) with ethyl acetate in the presence of sodium
methoxide, followed by hydrolysis of the intermediate (2) with aqueous hydrochloric
acid. When the hydrolysis of the methoxyl derivative (3) was carried out with
concentrated hydriodic acid the unknown 4-ethyl-3-hydroxypyridine (4) was isolated
as major product, due to the simultaneous reduction of the starting material.
On the basis of previous findings,^{4a-e} reaction of o-hydroxyaryl ketone or
aldehyde O-sulphonyloximes with aqueous alkali appears the most suitable approach
to closure of an isoxazole system condensed to an aromatic ring. Thus, 4-acetyl-
3-hydroxypyridine (5) easily reacted with hydroxylammonium O-sulphonate in water
to give the soluble oxime O-sulphonate (6); treatment of the resulting solution
with sodium hydrogencarbonate released a mixture of the oxime (7) and the two
isomers (8) and (9), which were separated by a careful fractional sublimation



followed by a preparative thin-layer chromatography. Compound (7), coming from hydrolysis of the intermediate (6), was also obtained by reaction of the ketone (5) with hydroxylamine hydrochloride. Several attempts to cyclize this compound following the conditions described by Crabbé,^{4d} afforded only starting material. Whereas the formation of 3-methylisoxazolo[5,4-c]pyridine (9) can be rationalized by an intramolecular nucleophilic displacement of the (E)-oxime ester, the presence of a small amount of 2-methyloxazolo[5,4-c]pyridine (8) is certainly due to a competitive Beckmann rearrangement of the same intermediate.^{4a-d} Although compounds (8) and (9) cannot be easily distinguished spectroscopically, their structures were unambiguously determined through the photochemical behaviour of (9) which, according to a trend previously reported for isoxazolo[4,5-c]-² and [5,4-b]pyridine,⁵ isomerized into (8) by U.V. irradiation.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin Elmer 283 spectrophotometer for KBr discs.

¹H N.m.r. spectra were recorded with a Perkin Elmer R 600 instrument; chemical shifts (J in Hz) are reported in ppm downfield from internal tetramethylsilane. U.v. spectra were measured for solutions in methanol with a Cary 14 spectrophotometer. Silica-gel plates (Merck F₂₅₄) and silica-gel 60 (Merck; 230-400 mesh) were used for analytical and preparative t.l.c., and for column chromatography, respectively. Extracts were dried over sodium sulphate and solvents were evaporated in vacuo.

4-Acetyl-3-methoxypyridine (3)

A solution of 4-carbomethoxy-3-methoxypyridine (1)⁶ (4.6 g, 0.027 mol) in ethyl acetate (4.5 g, 0.051 mol) was added with stirring to anhydrous sodium methoxide (2.23 g, 0.041 mol). The mixture was then gently refluxed for 18 hr. After cooling the mass was dissolved in water (30 ml) and the resultant solution was neutralized with concentrated hydrochloric acid. The dark oil was directly dissolved by addition of a further 10 ml of concentrated hydrochloric acid and the hydrolysis completed by vigorous refluxing (3 hr). The cold solution was neutralized with solid potassium carbonate and extracted exhaustively with ether to afford a residue which, after distillation at 63-65°C and 0.025 mm Hg, gave on cooling at 0°C compound (3) as white crystals (2.5 g, y 61%); m.p. 22-24°C; I.r. 1685 (CO) cm⁻¹; U.v. max (log ε): 229(3.69) and 307 nm(3.56); N.m.r. (CDCl₃): δ 2.60 (s, Me), 4.02 (s, OMe), 7.49 (d, J 4.6, 5-H), 8.36 (d, J 4.6, 6-H), 8.49 (s, 2-H); Anal. Calcd. for C₈H₉NO₂: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.45; H, 5.98; N, 9.29%.

4-Ethyl-3-hydroxypyridine (4)

4-Acetyl-3-methoxypyridine (3) (1.45 g, 0.0096 mol) was refluxed for 16 hr in 57% hydriodic acid (15 ml). The cooled solution was washed with ether to remove iodine, then neutralized with aqueous 20% sodium hydroxide and extracted with chloroform. Evaporation of the solvent afforded an oily residue which was distilled at 82°C and 0.33 mm Hg to give compound (4) (0.5 g, y 42%) as pale yellow crystals; m.p. 95-97°C after sublimation at 80°C and 0.01 mm Hg; I.r. 3300-1700 (OH or NH) cm⁻¹; U.v. max (log ε): 276 nm (3.62); N.m.r. (CDCl₃): δ 1.26 (t, J 6.8, CH₂-CH₃), 2.75 (q, J 6.8, CH₂-CH₃), 7.15 (d, J 4.8, 5-H), 8.00 (d, J 4.8, 6-H), 8.23 (s, 2-H), 12.35 (exch. s, OH); Anal. Calcd. for C₇H₉NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.18; H, 7.28; N, 11.28%.

4-Acetyl-3-hydroxypyridine (5)

A solution of compound (3) (1.37 g, 0.009 mol) in 48% hydrobromic acid (35 ml) was refluxed for 24 hr. After cooling the reaction mixture was made alkaline (pH 11) with aqueous 20% sodium hydroxide and washed with chloroform to eliminate

the unreacted starting material (0.68 g). The alkaline solution was neutralized with concentrated hydrochloric acid and extracted exhaustively with chloroform to yield a red oil; purification by column chromatography with ether as eluant afforded 4-acetyl-3-hydroxypyridine (5) (0.46 g, y 73%) as pale yellow crystals; m.p. 52-54°C after sublimation at room temperature and 0.01 mm Hg (dinitrophenylhydrazones m.p. 236-237°C, lit. ⁷ 248-249°C); I.r. 3500-2500 (OH), 1660 (CO) cm^{-1} ; U.v. max (log ϵ): 230 (3.72) and 325 nm (3.56); N.m.r. (CDCl_3): δ 2.69 (s, Me), 7.52 (d, J 4.8, 5-H), 8.30 (d, J 4.8, 6-H), 8.54 (s, 2-H), 11.50 (exch. s, OH); Anal. Calcd. for $\text{C}_7\text{H}_7\text{NO}_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.28; H, 5.31; N, 10.28%.

Treatment of 4-acetyl-3-hydroxypyridine (5) with hydroxylammonium O-sulphonate

A solution of hydroxylammonium O-sulphonate (0.75 g, 0.0066 mol) in water (11 ml) was combined with compound (5) (0.75 g, 0.0055 mol). After a few minutes of vigorous stirring the ketone dissolved and ether (15 ml) was introduced: the mixture was stirred vigorously and cooled in an ice-bath as sodium hydrogen-carbonate (1.8 g, 0.021 mol) was added in small portions. When the addition was completed, the reaction mixture was stirred for 5 hr at room temperature; whereupon the layers were separated, and the aqueous phase was exhaustively extracted with ether. Evaporation of the solvent yielded a solid which afforded a mixture of compounds (8) and (9) by sublimation at room temperature and 0.01 mm Hg. Compound (7) (0.28 g, y 33%) was obtained by increasing the temperature to 110°C. This compound was also obtained by keeping overnight at room temperature a solution of the ketone (5) (0.137 g, 0.001 mol) and hydroxylamine hydrochloride (0.139 g, 0.002 mol) in water (5 ml): neutralization with solid potassium carbonate and extraction with ether gave the oxime (7) (0.100 g, y 66%); m.p. 223-225°C; I.r. 3300-1700 (OH) cm^{-1} ; U.v. max (log ϵ): 208 (4.31), 245 (3.88) and 309 nm (3.60); N.m.r. (DMSO-d_6): δ 2.29 (s, Me), 7.45 (d, J 5.5, 5-H), 8.17 (d, J 5.5, 6-H), 8.30 (s, 2-H), 11.29, 12.00 (exch. 2 s, 2 OH); Anal. Calcd. for $\text{C}_7\text{H}_8\text{N}_2\text{O}_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.10; H, 5.30; N, 18.35%. Compounds (8) and (9) were separated by preparative layer chromatography with ether-light petroleum (b.p. 30-50°C) (2:1 v/v) as developer. The fastest running band gave 3-methylisoxazolo[5,4-c]pyridine (9) (0.200 g, y 27%); m.p. 98-101°C; I.r. 3080 and 3040 (CH) cm^{-1} ; U.v. max (log ϵ): 228 (3.66) and 286 nm (3.64); N.m.r. (CDCl_3): δ 2.63 (s, Me), 7.60 (dd, J_{4,5} 5.1, J_{4,7} 1.2, 4-H), 8.55 (d, J_{4,5} 5.1, 5-H), 9.05 (d, J_{4,7} 1.2, 7-H); Anal. Calcd. for $\text{C}_7\text{H}_6\text{N}_2\text{O}$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.37; H, 4.57; N, 20.88%. The second band yielded 2-methyloxazolo[5,4-c]pyridine (8) (0.060 g, y 8%); m.p. 46-48°C; I.r. 3045 (CH) cm^{-1} ; U.v. max (log ϵ): 229 (3.95), 260 (3.43), 264 (3.44) and 273 nm (3.34); N.m.r. (CDCl_3): δ 2.71 (s, Me), 7.61 (d, J 5.1, 4-H), 8.53 (d, J 5.1, 5-H), 8.87

(s, 7-H); Anal. Calcd. for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.90; H, 4.57; N, 20.69%.

Irradiation of 3-methylisoxazolo[5,4-c]pyridine (9)

A solution of 3-methylisoxazolo[5,4-c]pyridine (9) (0.500 g, 0.0037 mol) in methanol (10 ml) was irradiated with an unfiltered low pressure mercury lamp. N_2 was bubbled through the solution and the progress of the reaction was monitored by t.l.c. Irradiation was stopped when about half of (9) was converted to (8). The solvent was removed and the residue separated as above by preparative layer chromatography to give starting material (0.220 g) and 2-methyloxazolo[5,4-c]pyridine (9) (0.180 g, y 36%).

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