New Derivatives of 3-Methylisoxazolo[5,4-*b*]pyridine

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The synthesis and properties of 4,6-dichloro- (IV), 4-chloro- (XII) and 6-chloro-3-methylisoxazolo[5,4-*b*]pyridine (XI) are described. Depending on the reaction conditions compound IV with hydrazine or methoxide gave mono- or bi-substituted products. The halogen atom at the 4-position was shown to be the more mobile.

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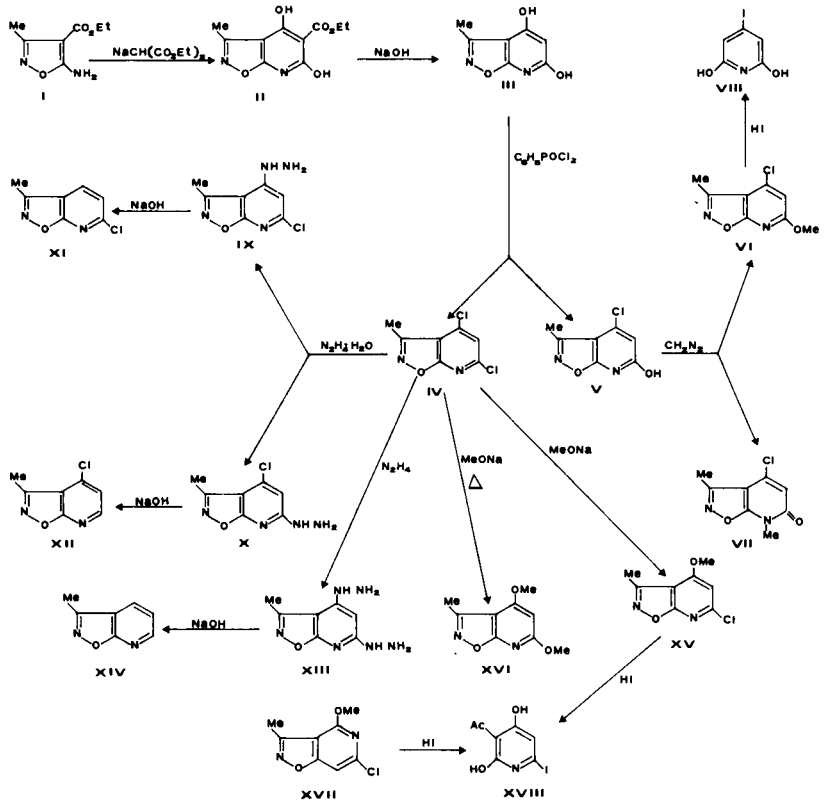
Our interest in the chemistry of isoxazolopyridines (1) prompted us to study the influence of the isoxazole ring on the reactivity in the different isoxazolopyridines. For this purpose we prepared several derivatives of 3-methylisoxazolo[5,4-*b*]pyridine. They are usually synthetized from 3-methyl-5-aminoisoxazole and β-dioxo compounds (2), or from suitable 3-acyl-2(1*H*)pyridones and hydroxylamine (3). However, no chlorinated compounds at the 4- and 6-positions are obtainable from the compounds prepared in these ways.

The synthesis of 4,6-dihydroxy-3-methylisoxazolo[5,4-*b*]pyridine (III) was achieved from ethyl 5-amino-3-methylisoxazole-4-carboxylate (I). It was treated with diethyl sodio-malonate to give the ester (II), which was



hydrolysed and decarboxylated in 15% sodium hydroxide to compound III. This can exist in numerous tautomeric forms: in the solid state a dihydroxy-form is present since the ir spectrum shows no stretching vibrations of CO group; in the nmr spectrum (DMSO-d_6) (Table) a signal attributable to CH disappears on deuteration. This behavior is consistent with the existence of an equilibrium mixture of tautomers.

By heating compound III with phenylphosphonic dichloride, 4,6-dichloro-3-methylisoxazolo[5,4-*b*]pyridine (IV) was obtained, along with a small amount of the monochloro-derivative (V).

The assignment of structure V was based on the formation of compound VIII from VI. Methylation of V with diazomethane afforded a mixture of the methyl derivatives VI and VII. Compound VI, heated in hydroiodic acid, yielded 4-iodo-2,6-dihydroxypyridine (VIII), whose structure followed from elemental analysis and the nmr spectrum in DMSO-d_6. It shows a singlet at δ 6.14 and a broad signal at δ 6.3-7.3 (in the ratio 1:1), which both disappear on deuteration. Whereas the former was attributed to the two protons at the 3,5-positions, the latter was assigned to the two protons bonded to the heteroatoms.

Compound V exists in the hydroxy structure in the solid state since no CO stretching band is present in the ir spectrum.

In the dichloro derivative IV, the chlorine atom at the 4-position is the more mobile. In fact it was displaced by sodium methoxide or hydrazine hydrate at room temperature to give, respectively, the methoxy derivative XV and a mixture of 4-hydrazino- (IX) and 6-hydrazino derivative (X), where the former predominated. More vigorous conditions are necessary to obtain the disubstituted products XVI and XIII.

The structure of the methoxy derivative XV was substantiated by its conversion with hydroiodic acid into the acetylpyridine XVIII, which was also obtained from 6-chloro-4-methoxy-3-methylisoxazolo[4,5-*c*]pyridine (XVII) (1).

The assignment of structures IX and X was supported by conversion into the monochloro derivatives XI and XII respectively, by oxidative decomposition in alkaline medium. A comparison of the coupling constants (Table) of compounds XI and XII with those of 3-methylisoxazolo[5,4-*b*]pyridine (XIV) enabled us to assign the correct structures to the above chloro derivatives. Compound XIV was obtained from the dihydrazino derivative XIII by alkaline oxidative degradation.

Kinetic studies on the mobility of halogens in the isoxazolo[4,5-*c*]pyridines and isoxazolo[5,4-*b*]pyridines are in progress.

Table

Proton Magnetic Resonance Spectra of 3-Methylisoxazolo[5,4-*b*]pyridine Derivatives

Compound	Solvent	Signals (intensity, multiplicity (with coupling constants), assignment)
II	DMSO-d_6	1.30 (3, t (J 7), CH_3), 2.44 (1, s, 3-CH_3), 3.50 (2, br s, NH and/or OH) (a), 4.35 (2, q (J 7), CH_2)
III	DMSO-d_6	2.44 (3, s, 3-CH_3), 5.93 (1, s, 5-H) (a), 11.70 (2, br s, 4-OH and 6-OH or 7-H) (a)
IV	$CDCl_3$	2.68 (3, s, 3-CH_3), 7.32 (1, s, 5-H)
V	DMSO-d_6	2.53 (3, s, 3-CH_3), 6.74 (1, s, 5-H)
VI	$CDCl_3$	2.61 (3, s, 3-CH_3), 4.02 (3, s, 6-OCH_3), 6.71 (1, s, 5-H)
VII	$CDCl_3$	2.51 (3, s, 3-CH_3), 3.60 (3, s, 7-CH_3), 6.44 (1, s, 5-H)
IX	DMSO-d_6	2.55 (3, s, 3-CH_3), 4.63 (2, s, NH_2) (a), 6.86 (1, s, 5-H), 8.48 (1, s, NH) (a)
X	DMSO-d_6	2.46 (3, s, 3-CH_3), 4.50 (2, s, NH_2) (a), 6.78 (1, s, 5-H), 8.75 (1, s, NH) (a)
XI	$CDCl_3$	2.59 (3, s, 3-CH_3), 7.36 (1, d (J 8), 5-H), 8.05 (1, d (J 8), 4-H)
XII	$CDCl_3$	2.71 (3, s, 3-CH_3), 7.30 (1, d (J 5), 5-H), 8.50 (1, d (J 5), 6-H)
XIII	DMSO-d_6	2.41 (3, s, 3-CH_3), 4.21 (4, br s, NH_2) (a), 6.20 (1, s, 5-H), 7.42 (1, s, NH) (a), 7.74 (1, s, NH) (a)
XIV	$CDCl_3$	2.58 (3, s, 3-CH_3), 7.33 (1, dd ($J_{4,5}$ 8, $J_{5,6}$ 4.75), 5-H), 8.08 (1, dd ($J_{4,5}$ 8, $J_{4,6}$ 1.7), 4-H), 8.60 (1, dd ($J_{5,6}$ 4.75, $J_{4,6}$ 1.7) 6-H)
XV	$CDCl_3$	2.55 (3, s, 3-CH_3), 4.05 (3, s, 4-OCH_3), 6.68 (1, s, 5-H)
XVI	$CDCl_3$	2.49 (3, s, 3-CH_3), 3.92 (3, s, 4- or 6-OCH_3), 3.98 (3, s, 4- or 6-OCH_3), 6.01 (1, s, 5-H).

(a) Signal disappears on deuteration.

EXPERIMENTAL

All melting points are uncorrected. Unless otherwise stated, the infrared spectra were measured for potassium bromide discs with a Perkin-Elmer 457 spectrometer and the ultraviolet spectra were taken in methanol with a Cary 14 spectrophotometer. ^1H nmr spectra were recorded with a R32 Perkin Elmer instrument (90 MHz); chemical shifts (J in Hz) are reported in ppm downfield from internal TMS. Silica gel plates (Merck F_{254}) were used for analytical and preparative tlc.

5-Ethoxycarbonyl-4,6-dihydroxy-3-methylisoxazolo[5,4-*b*]pyridine (II).

To a solution of diethyl sodio-malonate (21.2 mmoles) in dry ethanol, prepared from sodium (0.49 g.), dry ethanol (25 ml.) and diethyl malonate (3.4 g.), ethyl 5-amino-3-methylisoxazole-4-carboxylate (1.5 g., 8.82 mmoles) was added. The resultant mixture was refluxed for 6 hours and then cooled. The insoluble sodium

salt of II was collected by filtration, dissolved in water and acidified (*p*H 2-3) with concentrated hydrochloric acid to yield compound II (2 g., 95%), m.p. 229° dec. (from ethanol); ir: 3160-2000 (NH or OH) and 1670 (C=O) cm^{-1}; uv: 227 (log ε 4.43), 245 sh and 298 (log ε 4.00) nm.

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.64; H, 4.28; N, 11.75.

4,6-Dihydroxy-3-methylisoxazolo[5,4-*b*]pyridine (III).

The ester II (3.7 g.) was refluxed for 6 hours in aqueous 15% sodium hydroxide (130 ml.). The resulting solution was acidified to *p*H 3 with concentrated hydrochloric acid to give the dihydroxy derivative III which was filtered off, washed with water, ethanol, ether and dried at 100°, m.p. 252° dec. (2.1 g., 81.3%); ir: 3350-2100 (OH) cm^{-1}; uv: 208 (log ε 4.30), 244 (log ε 3.91) and 275 (log ε 3.99) nm.

Anal. Calcd. for $C_7H_6N_2O_3$: C, 50.61; H, 3.64; N, 16.86. Found: C, 50.43; H, 3.72; N, 16.64.

4,6-Dichloro- (IV) and 4-Chloro-6-hydroxy-3-methylisoxazolo-[5,4-*b*]pyridine (V).

A mixture of compound III (22 g., 132 mmoles) and phenylphosphonic dichloride (94.2 ml., 664 mmoles) was heated at 160° for 3 hours and, after cooling, poured into ice water (2000 ml.). After decompositon of the excess of phenylphosphonic dichloride, the solid was filtered off, washed with water and treated with 0.5 *N* sodium hydroxide (510 ml.). The insoluble dichloro derivative (IV) was collected, washed with water, dried and sublimed at 100° and 0.05 mm Hg, m.p. 128° (14.6 g., 54.5%); ir: 3080 (CH) cm^{-1}; uv: 247 (log ε 3.82), 286 (log ε 3.95), 291 sh and 295 (log ε 3.90) nm.

Anal. Calcd. for $C_7H_4Cl_2N_2O$: C, 41.42; H, 1.99; N, 13.80; Cl, 34.91. Found: C, 41.45; H, 1.98; N, 13.96; Cl, 34.81.

The mother liquors were acidified to *p*H 3 with concentrated hydrochloric acid to afford the monochloro derivative V which, after sublimation at 150° and 0.05 mm Hg, melted at 220° dec. (4.7 g., 19.3%); ir: 3200-2200 (OH) cm^{-1}; uv: 218 (log ε 4.05), 243 (log ε 3.78), 250 (log ε 3.71), 288 (log ε 3.97), 295 (log ε 3.97) and 310 sh nm.

Anal. Calcd. for $C_7H_5ClN_2O_2$: C, 45.55; H, 2.73; N, 15.18; Cl, 19.20. Found: C, 45.40; H, 2.77; N, 14.95; Cl, 19.00.

Reaction of the Chloro Derivative V with Diazomethane.

Ethereal diazomethane (0.8 g., 19 mmoles) was added to a suspension of the chloro derivative (V) (1 g., 5.4 mmoles) in ether (25 ml.). After 12 hours the solution was evaporated to give a mixture (1 g.) of compounds VI (55%) and VII (45%) (nmr), which was resolved into two components by preparative layer chromatography with ligroin (75-120° b.p.) as developer. The fastest moving band gave 4-chloro-6-methoxy-3-methylisoxazolo[5,4-*b*]pyridine (VI) (0.55 g., 51.3%), m.p. 98° (after sublimation at 50° and 0.05 mm Hg); ir: 3100 and 3080 (CH) cm^{-1}; uv: 218 (log ε 4.08), 234 (log ε 3.77), 240 (log ε 3.75), 248 (log ε 3.59), 285 (log ε 4.03) and 292 (log ε 3.99) nm.

Anal. Calcd. for $C_8H_7ClN_2O_2$: C, 48.38; H, 3.55; N, 14.11; Cl, 17.84. Found: C, 48.16; H, 3.51; N, 13.99; Cl, 18.05.

The second band yielded 4-chloro-3,7-dimethylisoxazolo[5,4-*b*]pyridin-6(7*H*)one (VII) which, after sublimation at 70° and 0.05 mm Hg, melted at 125° (0.45 g., 42%); ir: 3060 (CH) and 1685 (C=O) cm^{-1}; uv: 223 (log ε 4.11), 245 (log ε 3.81), 300 sh, 307 (log ε 3.97) and 315 sh nm.

Anal. Calcd. for $C_8H_7ClN_2O_2$: C, 48.38; H, 3.55; N, 14.11; Cl, 17.84. Found: C, 48.55; H, 3.47; N, 14.03; Cl, 17.62.

Reaction of the 4-Chloro-6-methoxy-3-methylisoxazolo[5,4-*b*]-pyridine (VI) with Hydroiodic Acid.

A suspension of compound VI (0.5 g., 2.5 mmoles) in concentrated (57%) hydroiodic acid (5 ml.) was heated at 100° for 3.5 hours. The resulting solution kept at room temperature for 12 hours gave a brown precipitate which, after addition of water, was filtered off and dissolved in the minimum amount of 1 *N* sodium hydroxide. This solution, after extraction with ether, was acidified to *p*H 3 with concentrated hydrochloric acid to give 4-iodo-2,6-dihydroxypyridine (VIII) (0.45 g., 75.9%), m.p. 235° dec. (from ethanol); ir: 3200-2000 (OH and/or NH) cm^{-1}; uv: 215 sh, 226 (log ε 4.31) and 317 (log ε 3.96) nm.

Anal. Calcd. for $C_5H_4INO_2$: C, 25.34; H, 1.70; N, 5.91; I, 53.55. Found: C, 25.22; H, 1.73; N, 6.14; I, 53.18.

Reaction of the 4,6-Dichloro-3-methylisoxazolo[5,4-*b*]pyridine (IV) with Hydrazine Hydrate.

To a solution of the dichloro derivative IV (10 g., 49.26 mmoles) in dioxan (80 ml.), hydrazine hydrate (9.52 ml., 197.8 mmoles) was added slowly with stirring. The resultant mixture was kept at room temperature for 12 hours and then treated with water. The white solid was filtered off to give a crude product containing (nmr spectrum) the two isomers IX and X in a ratio 3:1. Extraction with hot benzene yielded 4-chloro-6-hydrazino-3-methylisoxazolo[5,4-*b*]pyridine (X) (2.4 g., 24.5%), m.p. 223-224° dec. (from ethanol); ir: 3300, 3270 (NH_2 and NH) and 3060 (CH) cm^{-1}; uv: 210 sh, 231 (log ε 4.01), 259 (log ε 4.00) and 319 (log ε 4.13) nm.

Anal. Calcd. for $C_7H_7ClN_4O$: C, 42.33; H, 3.55; N, 28.21; Cl, 17.84. Found: C, 42.33; H, 3.54; N, 28.50; Cl, 17.62.

The residue was crystallised from ethanol to afford 6-chloro-4-hydrazino-3-methylisoxazolo[5,4-*b*]pyridine (IX) (6.9 g., 70.5%), m.p. 223-224° dec.; ir: 3350, 3250 (NH_2 and NH) and 3100 (CH) cm^{-1}; uv: 227 (log ε 4.43), 258 (log ε 3.99), 263 (log ε 3.99) and 299 (log ε 4.00) nm.

Anal. Calcd. for $C_7H_7ClN_4O$: C, 42.33; H, 3.55; N, 28.21; Cl, 17.84. Found: C, 42.45; H, 3.51; N, 28.14; Cl, 18.00.

The tosylhydrazino derivatives were obtained by treatment of IX or X with tosyl chloride in anhydrous pyridine. 6-Chloro-3-methyl-4-tosylhydrazinoisoxazolo[5,4-*b*]pyridine melted at 224° dec. (from ethanol).

Anal. Calcd. for $C_{14}H_{13}ClN_4O_3S$: C, 47.66; H, 3.71; N, 15.88; Cl, 10.04; S, 9.09. Found: C, 47.68; H, 3.73; N, 15.87; Cl, 10.23; S, 9.15.

4-Chloro-3-methyl-6-tosylhydrazinoisoxazolo[5,4-*b*]pyridine melted at 204° dec. (from ethanol).

Anal. Calcd. for $C_{14}H_{13}ClN_4O_3S$: C, 47.66; H, 3.71; N, 15.88; Cl, 10.04; S, 9.09. Found: C, 47.58; H, 3.72; N, 15.91; Cl, 10.19; S, 8.98.

4,6-Dihydrazino-3-methylisoxazolo[5,4-*b*]pyridine (XIII).

To the dichloro derivative IV (5 g., 24.6 mmoles), anhydrous hydrazine (15 ml.) was added dropwise with cooling (ice-water bath). The mixture was then heated at 100° for 15 minutes, cooled and diluted with water (30 ml.). The precipitate was filtered off, washed with cold ethanol and recrystallized from ethanol to give compound XIII (4.8 g., quantitative yield), m.p. 261° dec.; ir: 3400-3100 (NH_2 and NH) cm^{-1}; uv: 234 (log ε 4.35), 280 sh and 289 (log ε 4.23) nm.

Anal. Calcd. for $C_7H_{10}N_6O$: C, 43.29; H, 5.19; N, 43.28. Found: C, 42.98; H, 5.30; N, 43.49.

3-Methyl-4,6-bistosylhydrazinoisoxazolo[5,4-*b*]pyridine, obtained by treatment of XIII with tosyl chloride in anhydrous pyridine, melted at 230° dec. (from ethanol).

Anal. Calcd. for $C_{21}H_{22}N_6O_5S_2$: C, 50.19; H, 4.41; N, 16.72; S, 12.76. Found: C, 49.92; H, 4.56; N, 16.59; S, 12.50.

Oxidative Decomposition of the Hydrazino Derivatives IX, X and XIII.

Toluene (40-80 ml.) was added to a suspension of the hydrazino derivatives IX, X or XIII (10 mmoles) in 2 *N* sodium hydroxide (40 ml. for each $NHNH_2$ group). Air was bubbled into the reaction mixture vigorously shaked in a Parr apparatus until the solid disappeared. The organic layer was separated, washed with water and dried (calcium chloride), then rotary evaporated to give a solid which was sublimed.

6-Chloro-3-methylisoxazolo[5,4-*b*]pyridine (XI), after sublimation at 50° and 0.05 mm Hg, melted at 105° (yield 75%); ir: 3095 and 3060 (CH) cm^{-1}; uv: 210 sh, 235 (log ε 3.67), 284 (log ε 3.99), 289 (log ε 4.00) and 295 (log ε 3.89) nm.

Anal. Calcd. for $C_7H_5ClN_2O$: C, 49.88; H, 2.98; N, 16.62; Cl, 21.02. Found: C, 49.95; H, 3.08; N, 16.46; Cl, 20.95.

4-Chloro-3-methylisoxazolo[5,4-*b*]pyridine (XII), after sublimation at 100° and 0.05 mm Hg, melted at 110° (yield 71%); ir: 3095 (CH) cm^{-1}; uv: 240 (log ε 3.84), 282 (log ε 3.78), 286 (log ε 3.74) and 291 (log ε 3.70) nm.

Anal. Calcd. for $C_7H_5ClN_2O$: C, 49.88; H, 2.98; N, 16.62; Cl, 21.02. Found: C, 49.60; H, 2.96; N, 16.58; Cl, 20.84.

3-Methylisoxazolo[5,4-*b*]pyridine (XIV), after sublimation at 50° and 0.05 mm Hg, melted at 86° [lit. 82-84° (2e)] (yield 70%); ir: 3065 (CH) cm^{-1}; uv: 232 (log ε 3.71), 280 (log ε 3.84), 284 (log ε 3.86) and 291 (log ε 3.74) nm.

Reaction of the Dichloro Derivative (IV) with Sodium Methoxide.

The dichloro derivative IV (1 g., 4.926 mmoles) was added to a solution of sodium (0.23 g., 0.01 g.-atom) in dry methanol (50 ml.). The reaction mixture was kept at room temperature for 1 hour, then rotary evaporated. The solid residue, treated with water, collected by filtration and dried, yielded chromatographically pure 6-chloro-4-methoxy-3-methylisoxazolo[5,4-*b*]pyridine (XV) (0.9 g., 92%), m.p. 150° (from ethanol); ir: 3075 (CH) cm^{-1}; uv: 208 (log ε 4.38), 250 (log ε 4.07) and 270 sh nm.

Anal. Calcd. for $C_8H_7ClN_2O_2$: C, 48.38; H, 3.55; N, 14.11; Cl, 17.84. Found: C, 48.42; H, 3.55; N, 14.13; Cl, 17.73.

The above reaction, carried out at reflux temperature for 2 hours, gave 4,6-dimethoxy-3-methylisoxazolo[5,4-*b*]pyridine (XVI) (0.95 g., quantitative yield), m.p. 146° (from water); ir: 3070 (CH) cm^{-1}; uv: 205 (log ε 4.33), 243 (log ε 3.99) and 269 (log ε 3.96) nm.

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.39; H, 5.15; N, 14.38.

Reaction of 6-Chloro-4-methoxy-3-methylisoxazolo[5,4-*b*]pyridine (XV) or 6-Chloro-4-methoxy-3-methylisoxazolo[4,5-*c*]pyridine (XVII) with Hydroiodic Acid.

This reaction was carried out from XV or from XVII (1) by the procedure described for the treatment of VI with hydroiodic acid. The crude product was recrystallized from ethanol to give 2-iodo-5-acetyl-4,6-dihydroxypyridine (XVIII) (54%), m.p. 270-271° dec.; ir: 3200-2300 (OH) cm^{-1}; uv: 228 (log ε 4.12), 273 (log ε 3.59) and 334 (log ε 4.20) nm; nmr (DMSO-d_6: δ 2.57 (s, 3H, CH_3), 6.42 (s, 1H, CH), 12.20 (deuterium oxide exchangeable, broad s, 1H, NH or OH), 15.53 (deuterium oxide exchangeable, broad s, 1H, NH or OH).

Anal. Calcd. for $C_7H_6INO_3$: C, 30.13; H, 2.17; N, 5.02; I, 45.48. Found: C, 29.85; H, 2.19; N, 5.26; I, 45.76.

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