Synthetic Investigation on Isothiazolo-[5,4-*b*]- and -[4,5-c]-pyridines

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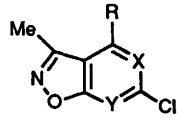
Different approaches to the title ring systems were examined, based on the cleavage of the N–O bond in the isoxazolopyridine-4-thiols (**3**) and (**4**) which afforded the hydroxy derivatives (**6**) and (**7**), respectively, in moderate to good yields. 3-Methylisothiazolo-[5,4-*b*]- and -[4,5-*c*]-pyridine (**11**) and (**18**), as well as several functionalized derivatives, were easily obtained from these key intermediates through the corresponding 4,6-dichloroisothiazolopyridines (**10**) and (**17**).

Aromatic isothiazolopyridines are extensively investigated in view of their potential biological activity.[1] Whereas different routes to several isothiazolo[5,4-*b*]pyridines have been reported in the literature,[1,2] only one procedure is known for the synthesis, in low yields, of two isothiazolo[4,5-*c*]pyridine derivatives.[3]

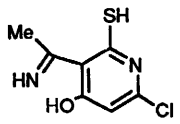
Following our interest in the chemistry of pyridines fused to five-membered heterocycles,[4] we investigated the possibility of employing the isoxazolo-[4,5-*c*]- and -[5,4-*b*]-pyridine-4-thiols (**3**) and (**4**) as building blocks for a direct entry into the above ring systems by cleavage of the N–O bond.

Results and Discussion

The starting materials (**3**) and (**4**) were obtained nearly quantitatively from compounds (**1**) and (**2**) by regiospecific substitution of the chlorine at position 4 by the thiolate anion.



(1) X = N, Y = CH, R = Cl
(2) X = CH, Y = N, R = Cl
(3) X = N, Y = CH, R = SH
(4) X = CH, Y = N, R = SH



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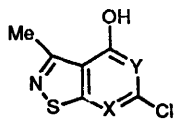
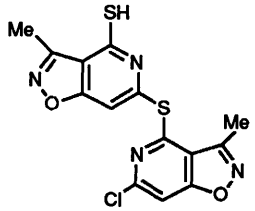


(6) X = N, Y = CH
(7) X = CH, Y = N



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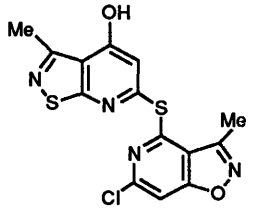

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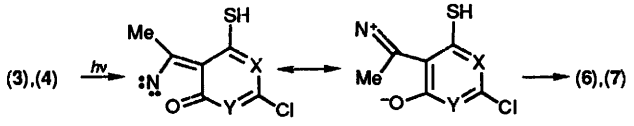
Catalytic hydrogenation of (**3**), followed by reaction of the intermediate pyridine (**5**) with hydroxylamine *O*-sulphonic acid, gave the desired product (**6**) in moderate yield; in contrast, several attempts to cleave the thiol (**4**) under similar conditions were unsuccessful. On this basis and bearing in mind the fact that 4-hydrazinoisoxazolopyridines can be advantageously converted into 1-aminopyrazolopyridine derivatives by UV irradiation,[5] we tried to extend this method to the synthesis of the above-cited ring systems. Thus, when the thiol (**3**) was irradiated in methanol, a complex mixture was obtained from which the bicyclic derivative (**6**) was isolated in 30% yield together with minor amounts of the sulphides (**8**) and (**9**); these latter compounds were also synthesized by heating the potassium salt of (**3**) with (**3**) and (**6**) (1 equiv.), respectively, in dimethylformamide. Analogously, irradiation of (**4**) under the same conditions afforded the isothiazolopyridine (**7**) in 38% yield; small amounts of sulphide-type compounds were detected in the crude product by NMR analysis.

Although this photochemical route shows some limits for synthetic purposes owing to the numerous side products, it appears nevertheless of interest from a mechanistic viewpoint; according to the reaction paths previously suggested for the above conversions,[5] the formation of compounds (**6**) and (**7**) from (**3**) and (**4**), respectively, can be accounted for on the basis of the reactions in the Scheme involving nitrene intermediates which then evolve into the final products by intramolecular attack of the SH group.



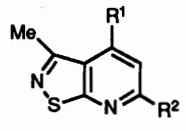
Scheme.

Since metal–nitrene complexes have recently been invoked for the thermal N–O cleavage of different isoxazoles in the presence of $Mo(CO)_6$,[6] we decided to explore this new ring opening for the preparation of compounds (**6**) and (**7**). Treatment of the isoxazolopyridines (**3**) and (**4**) in boiling methanol with an equimolecular amount of $Mo(CO)_6$ afforded in good yields the desired products which were easily converted into the corresponding dichloro derivatives (**10**) and (**17**), respectively, with phenylphosphonic dichloride.

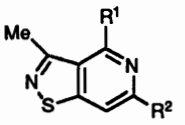
Catalytic hydrogenation of (**10**), stopped before the complete disappearance of the starting material, allowed us to obtain 3-methylisothiazolo[5,4-*b*]pyridine (**11**) together with the regioisomeric monochloro derivatives (**12**) and (**13**). The former compound arises exclusively from (**12**), since (**13**) is completely inert under the above conditions.

In contrast, the isomer (**17**) was unaffected by hydrogenation but it reacted with anhydrous hydrazine and hydrazine hydrate to give compounds (**20**) and (**21**), respectively; oxidative decomposition of the former enabled us to prepare 3-methylisothiazolo[4,5-*c*]pyridine (**18**), whereas the corresponding 6-chloro-3-methylisothiazolo[4,5-*c*]pyridine (**19**) was obtained from the latter in a similar way.

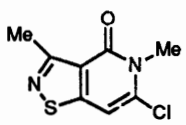
When the dichloro derivative (**10**) was treated with sodium



(10) $R^1 = R^2 = Cl$
(11) $R^1 = R^2 = H$
(12) $R^1 = Cl$, $R^2 = H$
(13) $R^1 = H$, $R^2 = Cl$
(14) $R^1 = R^2 = OMe$
(15) $R^1 = OMe$, $R^2 = Cl$
(16) $R^1 = Cl$, $R^2 = OMe$



(17) $R^1 = R^2 = Cl$
(18) $R^1 = R^2 = H$
(19) $R^1 = H$, $R^2 = Cl$
(20) $R^1 = R^2 = NHNH_2$
(21) $R^1 = NHNH_2$, $R^2 = Cl$
(22) $R^1 = R^2 = OMe$
(23) $R^1 = OMe$, $R^2 = Cl$



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methoxide (2 equiv.) in boiling methanol for 1 h, 4,6-dimethoxy-3-methylisothiazolo[5,4-*b*]pyridine (**14**) was isolated as the predominant product, together with minor amounts of the regioisomers (**15**) and (**16**). In contrast, treatment of the corresponding compound (**17**) under the same conditions afforded only the monomethoxy derivative (**23**) in 93% yield, whereas compound (**22**) was obtained in good yields by prolonged heating of (**17**) with an excess of the same reagent.

These findings clearly demonstrate that, although both the halogen atoms of (**10**) and (**17**) can be easily removed, their relative lability depends sensitively on the fusion of the isothiazole ring to the pyridine system. Compounds (**15**) and (**23**) were obtained unambiguously from the corresponding 4-hydroxy derivatives (**6**) and (**7**), respectively, and diazomethane; the *N*-methyl derivative (**24**) was also isolated from the latter reaction. All the other structures of the new products were established on the basis of the ^1H NMR values reported in the Experimental section.

In summary, the high-yield conversion of the isoxazolopyridine-4-thiols (**3**) and (**4**) with $Mo(CO)_6$ into the corresponding 4-hydroxy derivatives (**6**) and (**7**), respectively, represents a new, attractive approach to different isothiazolopyridine ring systems, owing to the ready availability of the starting materials as well as the possibility of further synthetic elaboration of the primary products.

Experimental

IR spectra were obtained for dispersions in KBr with a Perkin-Elmer 283 spectrometer. ^1H NMR spectra were recorded on a Perkin-Elmer R32 spectrometer at 90 MHz and chemical shifts are given in ppm relative to internal $SiMe_4$, coupling constants in Hz. Commercial $Mo(CO)_6$ (Fluka AG) was used. M.p.s are uncorrected. Merck Kieselgel (230–400 mesh ASTM) was employed for analytical and preparative TLC, as well as for column chromatography. Photochemical reactions were carried out with a medium-pressure mercury immersion lamp (125 W) filtered and cooled with copper(II) sulphate solution (cut off $\geqslant 300$ nm); nitrogen was constantly bubbled through the solution during the photolyses. Light petroleum refers to the fraction of b.p. 40–70 °C.

6-Chloro-3-methylisoxazolo[4,5-c]*pyridine-4-thiol* (**3**).—4,6-Dichloro-3-methylisoxazolo[4,5-*c*]pyridine (**1**)[7] (5.3 g, 26 mmol) in anhydrous ethanol (80 ml) was added to a freshly prepared solution of potassium hydrosulphide[8] (4.69 g, 65 mmol) in the same solvent (25 ml); the mixture was refluxed for 1 h and kept overnight at room temperature. Removal of the solvent left a residue which was dissolved in the minimum amount of water; acidification of the solution with hydrochloric acid (6M; pH 4) afforded *compound* (**3**) (4.7 g, 90%), m.p. 210–211 °C (decomp.) [from EtOH–H_2O (2:1 v/v)] (Found: C, 42.1; H, 2.5; N, 13.9. $C_7H_5ClN_2OS$ requires C, 41.9; H, 2.5; N, 14.0%); ν_{max} 3 200–2 500vbr, 1 585, 1 210, and 1 025 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 2.65 (3 H, s, 3-Me), 7.48 (1 H, s, 7-H), and 14.08 (1 H, br s, exch., NH).

6-Chloro-3-methylisoxazolo[5,4-b]*pyridine-4-thiol* (**4**).—Operating as above, the dichloro derivative (**2**)[9] (5.3 g, 26 mmol) gave the *thiol* (**4**) (4.6 g, 88%), m.p. 145 °C (decomp.) [from EtOH–H_2O (2:1 v/v)] (Found: C, 42.2; H, 2.6; N, 13.8%); ν_{max} 3 080, 2 440, and 1 590 cm^{-1}; $\delta_H(CDCl_3)$ 2.69 (3 H, s, 3-Me), 4.09 (1 H, br s, exch., SH), and 7.12 (1 H, s, 5-H).

6-Chloro-3-(1-iminoethyl)-2-mercaptopyridin-4-ol (**5**).—A mixture of the thiol (**3**) (5 g, 25 mmol) and Pd/C (10%; 0.5 g) in aqueous sodium hydroxide (1M; 200 ml) was shaken for 15 h in a Parr apparatus under a hydrogen pressure of 50 psi. The catalyst was filtered off and the solution was neutralized with hydrochloric acid (6M) to give *compound* (**5**) (2.9 g, 57%), m.p. 330 °C (from MeCN) (Found: C, 41.7; H, 3.2; N, 13.9. $C_7H_7ClN_2OS$ requires C, 41.5; H, 3.5; N, 13.8%); ν_{max} 3 100–2 300vbr, 1 600, 1 555, and 1 450 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 2.82 (3 H, s, 3-Me), 6.03 (1 H, s, 5-H), 10.55 (1 H, br s, exch., SH/NH/OH), 12.20 (1 H, br s, exch., NH/OH/SH), and 13.65 (1 H, br, s, exch., OH/SH/NH).

6-Chloro-3-methylisothiazolo[5,4-b]*pyridin-4-ol* (**6**).—Hydroxylamine *O*-sulphonic acid (2.8 g, 25 mmol) in water (50 ml) was added to a solution of (**5**) (5 g, 25 mmol) and sodium hydroxide (2 g, 50 mmol) in ethanol (95%; 250 ml), and the mixture was stirred at room temperature for 16 h. After dilution with water (150 ml) the solution was acidified with concentrated hydrochloric acid (pH 1) to precipitate *compound* (**6**) (3 g, 61%). An analytical sample, obtained by sublimation at 130 °C and 0.05 mmHg, melted at 234–235 °C (Found: C, 41.6; H, 2.4; N, 13.7. $C_7H_5ClN_2OS$ requires C, 41.9; H, 2.5; N, 14.0%); ν_{max} 3 300–2 300vbr, 1 595, and 1 550 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 2.71 (3 H, s, 3-Me), 6.82 (1 H, s, 5-H), and 13.65 (1 H, br s exch., OH/NH).

Irradiation of Compounds (**3**) *and* (**4**).—A solution of the thiol (0.5 g, 2.5 mmol) in methanol (350 ml) was irradiated for 3–4 h and the solvent was removed under reduced pressure.

(*i*) Treatment of the residue obtained from (**3**) with methanol (10 ml) gave 6-(*6-chloro-3-methylisoxazolo*[4,5-c]*pyridin-4-ylthio*)-3-*methylisoxazolo*[4,5-c]*pyridine-4-thiol* (**8**) (0.025 g) which was separated by filtration. An analytical sample, obtained by crystallisation from MeOH, melted at 204–205 °C (decomp.) (Found: C, 45.9; H, 2.4; N, 15.6. $C_{14}H_9ClN_4O_2S_2$ requires C, 46.1; H, 2.5; N, 15.4%); ν_{max} 3 080–2 680br, 1 595, and 980 cm^{-1}; $\delta_H(CDCl_3)$ 2.79 (3 H, s, Me), 2.81 (3 H, s, Me), 3.50 (1 H, vbr s, exch., SH/NH), 6.98 (1 H, s, 7-H), and 7.48 (1 H, s, 7′-H).

The filtrate was evaporated to dryness and the residue was resolved into three components by flash chromatography [$CHCl_3$–MeOH (9:1 v/v) as eluant]. The first band gave a further crop of compound (**8**) (0.025 g, total yield 11%). The second band afforded 6-(*6-chloro-3-methylisoxazolo*[4,5-c]*pyridin-4-ylthio*)-3-*methylisothiazolo*[5,4-b]*pyridin-4-ol* (**9**) (0.11 g, 22%), m.p. 128–130 °C (from MeOH) (Found: C, 45.2; H, 3.1; N, 14.4. $C_{14}H_9ClN_4O_2S_2 \cdot CH_3OH$ requires C, 45.4; H, 3.3; N, 14.1%); ν_{max} 3 080–2 680br, 1 595, 1 570, and 1 550 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 2.54 (3 H, s, Me), 2.68 (3 H, s, Me), 3.15 (3 H, s, MeOH), 3.8 (1 H, br s, exch., OH/NH), 6.82 (1 H, s, 5-H), and 7.99 (1 H, s, 7′-H).

The slowest moving band gave compound (**6**) (0.15 g, 30%), identical (IR and ^1H NMR spectrum) with the material obtained from compound (**5**).

(*ii*) The crude product was treated with boiling methanol

(30 ml) and the insoluble material was filtered off; evaporation to dryness of the filtrate left a residue which was subjected to flash chromatography (ether as eluant) to give 6-*chloro*-3-*methylisothiazolo*[4,5-c]*pyridin*-4-*ol* (**7**) (R_f 0.73; 0.19 g, 38%), m.p. 300 °C (decomp) (from ethanol) (Found: C, 42.1; H, 2.5; N, 13.8. $C_7H_5ClN_2OS$ requires C, 41.9, H, 2.5; N, 14.0%); ν_{max} 3 200–2 200br, 1 665, 1 590, and 1 185 cm^{-1}; δ_H[$(CD_3)_2SO$] 2.69 (3 H, s, Me), 7.20 (1 H, s, 7-H), and 12.62 (1 H, br s exch., NH/OH).

Synthesis of the Sulphides (**8**) *and* (**9**).—The potassium salt of the thiol (**3**) (0.1 g, 0.4 mmol) was heated with an equimolar amount (0.085 g) of compounds (**3**) and (**6**), respectively, in dimethylformamide (4 ml) at 110 °C for 10 h. The cooled reaction mixture was diluted with water (50 ml) and the solid was filtered off, dried, and treated as follows.

(*i*) Crystallization from methanol afforded compound (**8**) (0.11 g, 72%), identical (IR and ^1H NMR spectrum) with the product just described.

(*ii*) PLC [$CHCl_3$–MeOH (95:5 v/v) as eluant] gave compound (**9**) (0.05 g, 30%), identical (IR and ^1H NMR spectrum) with material obtained as above.

Reactions of Compounds (**3**) *and* (**4**) *with Hexacarbonylmolybdenum.*—$Mo(CO)_6$ (5 g, 19 mmol) was added to a solution of the bicyclic thiol (3.84 g, 19 mmol) in boiling methanol (380 ml) and the stirred mixture was refluxed for 1 h and filtered hot; after addition of SiO_2 (5 g) to the filtrate, the solvent was slowly removed by rotary evaporation. Soxhlet extraction of the residue (ether and ethyl acetate as solvents) afforded compound (**6**) (2.92 g, 76%) and compound (**7**) (3.2 g, 84%), respectively, identical (IR and ^1H NMR spectra) with materials obtained as above.

4,6-*Dichloro*-3-*methylisothiazolo*[5,4-b]*pyridine* (**10**).—Compound (**6**) (2 g, 10 mmol) and phenylphosphonic dichloride (3.6 ml, 25 mmol) were heated at 160 °C for 3 h and, after cooling, ice–water (50 ml) was added. The solid separated by filtration was repeatedly treated with aqueous sodium hydroxide (0.5M) and washed with water to afford the *dichloro derivative* (**10**) which was purified by sublimation at 100 °C and 0.02 mmHg (1.9 g, 87%), m.p. 140–141 °C (Found: C, 38.4; H, 1.7; N, 12.9. $C_7H_4Cl_2N_2S$ requires C, 38.4; H, 1.8; N, 12.8%); ν_{max} 3 090, 1 550, and 1 530 cm^{-1}; $\delta_H(CDCl_3)$ 2.92 (3 H, s, Me) and 7.40 (1 H, s, 5-H).

4,6-*Dichloro*-3-*methylisothiazolo*[4,5-c]*pyridine* (**17**).—Operating as above, chlorination of (**7**) (2 g, 10 mmol) gave compound (**17**) (1.75 g, 80%), m.p. 122–123 °C (after sublimation at 100 °C and 0.02 mmHg) (Found: C, 38.1; H, 1.9; N, 13.1%); ν_{max} 3 070, 1 565, and 1 560 cm^{-1}; $\delta_H(CDCl_3)$ 2.95 (3 H, s, Me) and 7.78 (1 H, s, 7-H).

Catalytic Hydrogenation of Compound (**10**).—A mixture of (**10**) (0.6 g, 2.7 mmol), Pd/C (10%; 0.2 g), and triethylamine (0.39 ml, 2.7 mmol) in ethanol (300 ml) was shaken in a Parr apparatus under a hydrogen pressure of 75 psi for 24 h. The catalyst was filtered off and the solution was evaporated to dryness to give a residue that was resolved into four components by flash chromatography with ether–light petroleum (1:2 v/v) as eluant.

After some starting material (0.04 g) had been recovered from the fastest running fractions, the second band afforded 4-*chloro*-3-*methylisothiazolo*[5,4-b]*pyridine* (**12**) [(0.04 g, 8%, based on compound (**10**) which had reacted], m.p. 118–119 °C after sublimation at 80 °C and 0.02 mmHg (Found: C, 45.8; H, 2.8; N, 14.8. $C_7H_5ClN_2S$ requires C, 45.5; H, 2.7; N, 15.2%); ν_{max} 3 080, 3 060, 1 560, and 1 535 cm^{-1}; $\delta_H(CDCl_3)$ 2.97 (3 H, s, Me), 7.34 (1 H, d, *J* 5.0 Hz, 5-H), and 8.58 (1 H, d, *J* 5.0 Hz, 6-H).

The third band gave 6-*chloro*-3-*methylisothiazolo*[5,4-b]*pyridine* (**13**) (0.25 g, 53%, based on compound (**10**) which had reacted), m.p. 106–108 °C after sublimation at 80 °C and 0.02 mmHg and crystallisation from cyclohexane (Found: C, 45.6; H, 2.8; N, 15.0%); ν_{max} 3 050, 1 570, and 1 535 cm^{-1}; $\delta_H(CDCl_3)$ 2.72 (3 H, s, Me), 7.36 (1 H, d, *J* 8.4 Hz, 5-H), and 8.12 (1 H, d, *J* 8.4 Hz, 4-H).

Finally, the slowest moving fractions afforded 3-methylisothiazolo[5,4-*b*]pyridine (**11**) [(0.043 g, 11% on the basis of compound (**10**) which had reacted], identical (m.p. and ^1H NMR spectrum) with an authentic sample.[10]

3-*Methylisothiazolo*[4,5-c]*pyridine* (**18**).—Anhydrous hydrazine (5 ml, 155 mmol) was added with cooling to the dichloro derivative (**17**) (1 g, 4.6 mmol); the mixture was heated at 100 °C for 1 h, cooled, diluted with water (8 ml), and filtered to give a solid (0.94 g), m.p. 245–250 °C (decomp.) containing, together with a very small amount of compound (**21**) (see below), 4,6-dihydrazino-3-methylisothiazolo[4,5-*c*]pyridine (**20**) as the predominant component; ν_{max} 3 330, 3 310, 3 270, 3 180, 1 635, and 1 595 cm^{-1}.

Toluene (20 ml) was added to a suspension of this crude product (0.9 g) in aqueous sodium hydroxide (2M; 20 ml) and air was gently bubbled into the stirred mixture for 3 days. The organic layer was removed and evaporated to dryness to yield a residue which was subjected to flash chromatography with ether–light petroleum (2:1 v/v) as eluant. The first fractions gave the chloro derivative (**19**) (0.03 g), identical (IR and ^1H NMR spectrum) with the material reported below; the second band afforded *compound* (**18**) [0.16 g, 23% from (**17**)], m.p. 69–70 °C after sublimation at 50 °C and 0.02 mmHg (Found: C, 55.8; H, 4.2; N. 18.5. $C_7H_6N_2S$ requires C, 56.0; H, 4.0; N, 18.7%); ν_{max} 3 035, 2 955, 2 915, and 1 577 cm^{-1}; $\delta_H(CDCl_3)$ 2.70 (3 H, s, Me), 7.71 (1 H, dd, $J_{6,7}$ 5.9, $J_{4,7}$ 1.2 Hz, 7-H), 8.45 (1 H, d, $J_{6,7}$ 5.9 Hz, 6-H), and 9.15 (1 H, d, $J_{4,7}$ 1.2 Hz, 4-H).

6-*Chloro*-3-*methylisothiazolo*[4,5-c]*pyridine* (**19**).—A solution of compound (**17**) (1.5 g, 6.8 mmol) and hydrazine hydrate (98%; 2 ml, 40 mmol) in dioxane (8 ml) was heated at 90 °C for 3 h. After cooling, the mixture was diluted with water (50 ml) and 6-chloro-4-hydrazino-3-methylisothiazolo[4,5-*c*]pyridine (**21**) was filtered off (1 g, 63%), m.p. 217–220 °C (decomp.); ν_{max} 3 400, 3 300, 3 090, 3 080, 1 620, and 1 560 cm^{-1}. Treatment of this product as for (**20**) afforded a residue which was purified by flash chromatography with ether–light petroleum (1:2 v/v) as eluant, to give the *chloro derivative* (**19**) [R_f 0.64; 0.5 g, 59% from (**21**)], m.p. 145–147 °C (after sublimation at 100 °C and 0.02 mmHg) (Found: C, 45.3; H, 2.6; N, 15.0. $C_7H_5ClN_2S$ requires C, 45.5; H, 2.7; N, 15.2%); ν_{max} 3 105, 3 080, 3 020, and 1 565 cm^{-1}; $\delta_H(CDCl_3)$ 2.82 (3 H, s, Me), 7.86 (1 H, d, *J* 1 Hz, 7-H), and 9.02 (1 H, d, *J* 1 Hz, 4-H).

Reaction of Compounds (**10**) *and* (**17**) *with Sodium Methoxide.*—Unless otherwise stated, the dichloro derivative (2.19 g, 10 mmol) and sodium methoxide (1.08 g, 20 mmol) were refluxed in methanol (200 ml) for 1 h; removal of the solvent left a solid which was treated with water, filtered and dried.

(*i*) The residue from the reaction of (**10**) was resolved into three components by flash chromatography with light petroleum–ethyl acetate (7:1 v/v) as eluant; the first band gave 4-*chloro*-6-*methoxy*-3-*methylisothiazolo*[5,4-b]*pyridine* (**16**) (0.14 g, 6.5%), m.p. 129–130 °C (after sublimation at 80 °C and 0.02 mmHg) (Found: C, 45.1; H, 3.4; N, 13.0. $C_8H_7ClN_2OS$ requires C, 44.8; H, 3.3; N, 13.05%); ν_{max} 3 070, 3 050, 1 580, and 1 160 cm^{-1}; $\delta_H(CDCl_3)$ 2.85 (3 H, s, Me), 4.02 (3 H, s, OMe), and 6.76 (1 H, s, 5-H).

The second band afforded 4,6-*dimethoxy*-3-*methylisothia*-

zolo[5,4-b]*pyridine* (**14**) (1.44 g, 66.6%) m.p. 149 °C (after sublimation at 100 °C and 0.02 mmHg) (Found: C, 51.6; H, 4.6; N, 13.2%. $C_9H_{10}N_2O_2S$ requires C, 51.4; H, 4.8; N, 13.3%); ν_{max} 3 080, 3 060, 1 585, 1 565, 1 210, and 1 185 cm^{-1}; $\delta_H(CDCl_3)$ 2.70 (3 H, s, Me), 3.92 (3 H, s, OMe), 3.99 (3 H, s, OMe), and 6.00 (1 H, s, 5-H).

The slowest running fractions yielded 6-*chloro*-4-*methoxy*-3-*methylisothiazolo*[5,4-b]*pyridine* (**15**) (0.40 g, 18.6%), m.p. 165 °C (after sublimation at 80 °C and 0.02 mmHg) (Found: C, 45.0; H, 3.4; N, 12.7. $C_8H_7ClN_2OS$ requires C, 44.8; H, 3.3; N, 13.05%); ν_{max} 3 080, 1 565, and 1 300 cm^{-1}; $\delta_H(CDCl_3)$ 2.76 (3 H, s, Me), 4.05 (3 H, s, OMe), and 6.69 (1 H, s, 5-H).

(*ii*) The solid obtained from (**17**) was sublimed at 60 °C and 0.02 mmHg to give 6-*chloro*-4-*methoxy*-3-*methylisothiazolo*-[4,5-c]*pyridine* (**23**) (2.0 g, 93%), m.p. 105–107 °C (Found: C, 44.8; H, 3.3; N, 13.0. $C_8H_7ClN_2OS$ requires C, 44.8; H, 3.3; N, 13.05%); ν_{max} 3 100, 3 080, 1 575, and 1 550 cm^{-1}; $\delta_H(CDCl_3)$ 2.81 (3 H, s, Me), 4.15 (3 H, s, OMe), and 7.37 (1 H, s, 7-H).

(*iii*) Treatment of compound (**17**) (0.55 g, 2.5 mmol) with sodium methoxide (2.02 g, 37.5 mmol) in methanol (45 ml) for 5 days, afforded 4,6-*dimethoxy*-3-*methylisothiazolo*[4,5-c]*pyridine* (**22**) (0.46 g, 87%), m.p. 86–87 °C (after sublimation at 60 °C and 0.02 mmHg) (Found: C, 51.7; H, 4.8; N, 13.4. $C_9H_{10}N_2O_2S$ requires C, 51.4; H, 4.8; N, 13.3%); ν_{max} 3 100, 1 590, and 1 310 cm^{-1}; $\delta_H(CDCl_3)$ 2.77 (3 H, s, Me), 3.99 (3 H, s, OMe), 4.10 (3 H, s, OMe), and 6.65 (1 H, s, 7-H).

Methylation of Compounds (**6**) *and* (**7**) *with Diazomethane.*—Ethereal diazomethane (1 g, 24 mmol) was added to a suspension of the hydroxy derivative (3 g, 15 mmol) in the same solvent (100 ml); the mixture was set aside overnight and then evaporated to dryness.

(*i*) Sublimation of the residue obtained from the reaction of (**6**) at 80 °C and 0.02 mmHg afforded the 4-methoxy derivative (**15**) (3 g, 93%), identical (IR and ^1H NMR spectrum) with material obtained as above.

(*ii*) The solid obtained from (**7**) was resolved into two components by flash chromatography with light petroleum as eluant; after the first fractions gave compound (**23**) (0.8 g, 25%), identical (IR and ^1H NMR spectrum) with the product reported above, the second band yielded 6-*chloro*-3,5-*dimethylisothiazolo*[4,5-c]*pyridin*-4(5H)-*one* (**24**) (1.77 g, 55%), m.p. 169 °C (after sublimation at 100 °C and 0.02 mmHg) (Found: C, 44.9; H, 3.3; N, 13.3. $C_8H_7ClN_2OS$ requires C, 44.8; H, 3.3; N, 13.05%); ν_{max} 3 120, 3 095, 3 065, and 1 670 cm^{-1}; $\delta_H(CDCl_3)$ 2.87 (3 H, s, Me), 3.74 (3 H, s, NMe), and 6.86 (1 H, s, 7-H).

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