Synthesis and Reactivity of 3-Methylisoxazolo[4,5-*c*]pyridines

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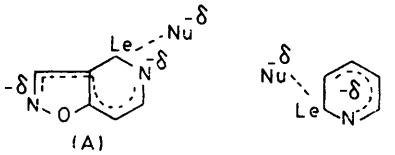
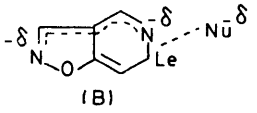
The preparation of 3-methylisoxazolo[4,5-*c*]pyridine and some derivatives is described. As expected, the 4-position of this system is the most reactive towards nucleophiles.

Of the four possible 1,2-benzisoxazole analogues with a nitrogen atom in the benzene ring, only derivatives of isoxazolo [5,4-*b*]pyridine are known.[1] We report here a synthesis of 3-methylisoxazolo[4,5-*c*]pyridine (XIV) and the reactions of some of its derivatives.

In this system, the presence of the isoxazole ring should result in reactions with nucleophiles (Nu) being faster than those of the pyridine system, owing to



(A)



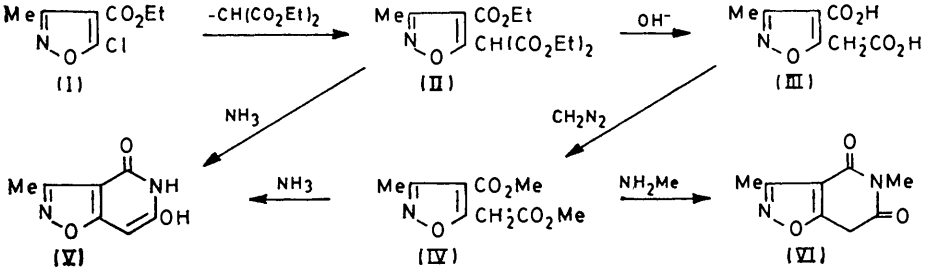
(B)

increased stabilisation of negative charge over a seven-atom system. This stabilisation should be most effective when the leaving group (Le) is at the 4-position, because the 4-substituted transition state, when written as (A), is expected to be more extensively conjugated than the 6-analogue (B).

6-Hydroxy-3-methylisoxazolo[4,5-*c*]pyridin-4(5*H*)-one was prepared from ethyl 5-chloro-3-methylisoxazole-4-carboxylate (I);[2] this was treated with diethyl sodiomalonate to give the isoxazolylmalonate (II), which, on hydrolysis (20% NaOH), gave the isoxazol-5-ylacetic acid (III). The diester (IV), obtained by the action of diazomethane, reacted with concentrated aqueous ammonia to give compound (V), whereas reaction with methylamine afforded the methyl derivative (VI). Compound (V) can be obtained in a single step by the action of concentrated aqueous ammonia on the malonate (II).

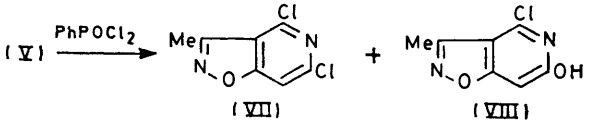
Compound (V) can exist in numerous tautomeric forms. In the solid state a hydroxy-oxo-form (ν_{CO} 1 660 cm^{-1}) is present; signals attributable to CH and CH_2 in the n.m.r. spectrum [$(CD_3)_2SO$] (Table) show the existence of an equilibrium mixture of tautomers. The methyl derivative (VI) exists in the dioxo-form in the solid state (ν_{CO} 1 690 and 1 715 cm^{-1}) and in $CDCl_3$ solution (CH_2 singlet in the n.m.r. spectrum), whereas in $(CD_3)_2SO$ a signal assignable to CH is also detectable.

By heating compound (V) with phenylphosphonic dichloride, 4,6-dichloro-3-methylisoxazolo[4,5-*c*]pyridine



(I) (II) (III) (V) (IV) (VI)

(VII) was obtained, along with a small amount of the monochloro-derivative (VIII). As predicted, compound



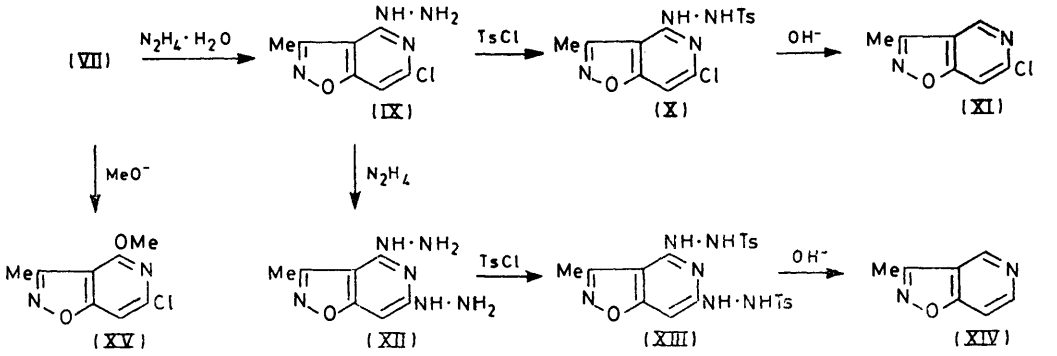
(V) (VII) (VIII)

(VII) reacted with most nucleophiles to yield the corresponding disubstituted products. The most reactive halogen is that at the 4-position. The difference in reactivity is so great that the reaction can always

[1] (*a*) K. Bowden, G. Crank, and W. J. Ross, *J. Chem. Soc.* (*C*), 1968, 172; (*b*) U.S.P. 3,381,016 (*Chem. Abs.*, 1968, **69**, 52122k); (*c*) Fr. P. 1,513,038 (*Chem. Abs.*, 1969, **70**, 106502a); (*d*) G.P. 2,215,087 (*Chem. Abs.*, 1973, **78**, 4235p); (*e*) G.P. 2,213,077 (*Chem. Abs.*, 1973, **78**, 4236q); (*f*) T. Denzel and H. Höhn, *Arch. Pharm.*, 1972, **305**, 833; (*g*) G.P. 2,213,076 (*Chem. Abs.*, 1973, **78**, 16162a); (*h*) G.P. 2,237,765 (*Chem. Abs.*, 1973, **78**, 136281k); (*i*) G.P. 2,301,267 (*Chem. Abs.*, 1973, **79**, 92212c); (*j*) A. Sammour, A. Raouf, M. Elkasaby, M. Hassan, *J. prakt. Chem.*, 1973, **315**, 1175; (*k*) G.P. 2,329,809 (*Chem. Abs.*, 1974, **80**, 82964f).

[2] G. Adembri and P. Tedeschi, *Boll. sci. Fac. Chim. ind. Bologna*, 1965, **23**, 203.

be stopped at the monosubstitution stage. Thus, by the action of hydrazine hydrate in dioxan at room temperature, we obtained the 4-hydrazino-derivative (IX), the tosyl derivative (X) of which decomposed under alkaline conditions to give the monochloroisoxazolo-[4,5-*c*]pyridine (XI). Indeed, vigorous conditions are usually necessary to obtain disubstituted products.

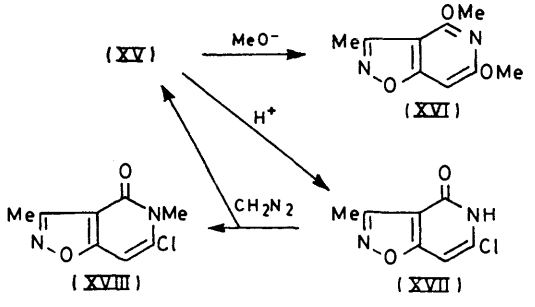


Formation of the dihydrazine (XII) needed anhydrous hydrazine and brief heating.

The structure of compound (XI) followed from its n.m.r. spectrum. The position of the protons was confirmed from the coupling constant, whose value is in agreement with $J_{2,5}$ for pyridine [3] and with $J_{4,7}$ for 3-methylisoxazolo[4,5-*c*]pyridine (XIV), obtained from the bistosylhydrazine (XIII) by alkaline degradation.

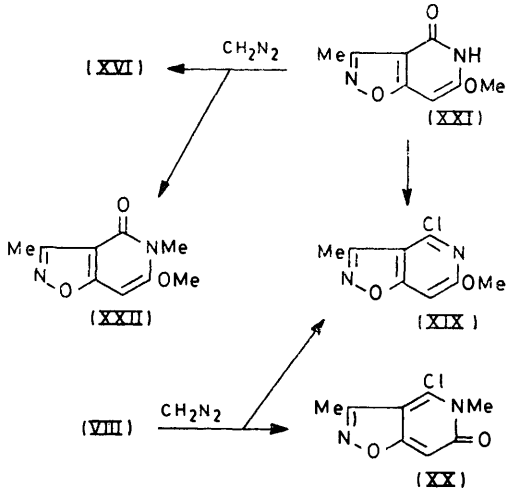
Analogously, when compound (VII) was treated for 3 h with sodium methoxide (4.5 mol. equiv), only the monomethoxy-derivative (XV) was isolated. The dimethoxyisoxazolo[4,5-*c*]pyridine (XVI) was prepared by prolonged heating of the dichloro-derivative (VII) with a larger excess of methoxide.

The structure of compound (XV) was deduced from its n.m.r. spectrum: the position of the ring proton signal is shifted by 0.4 p.p.m., in comparison with the corresponding proton of compounds (XI) and (XIV), in agreement with the presence of a *para*-methoxy-group.[4]



Demethylation by acid of compound (XV) gives the 6-chloro-compound (XVII). The isomer (VIII) must therefore be the 4-chloro-compound.

Compound (XVII) exists in the oxo-form in the solid state (ν_{CO} 1 670 cm^{-1}) and in methanolic solution, in which it shows an u.v. spectrum nearly identical with that of compound (XVIII), obtained along with the *O*-methyl isomer (XV), by treatment of the chloro-derivative (XVII) with diazomethane. On the other hand, the isomeric chloro-derivative (VIII) exists always in the hydroxy-form; in the i.r. spectrum bands at 3 050 cm^{-1} (CH) and 3 560 cm^{-1} (non-bonded OH) are present. The strong band at 1 630 cm^{-1} must be assigned to a ring vibration mode because it appears at lower frequencies



in the spectra of solutions of carbon tetrachloride. The n.m.r. spectrum shows a CH signal unaffected by D_2O: therefore there is no appreciable conversion into the $-CH_2-CO-$ form. The u.v. spectrum is very similar to that of the *O*-methyl derivative (XIX), which was prepared along with (XX) by treatment of compound (VIII) with diazomethane. The structures (XVIII) and (XX) were supported by conversion into the dione (VI) by hydrolysis.

The assignment of structure (XIX) led us to the conclusion that compound (V), when treated with diazomethane (1.3 mol. equiv.), gave the 6-methoxy-derivative (XXI), almost exclusively, since this was

[3] L. M. Jackman and S. Sternhell, in ' Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 307.

[4] H. L. Retcofsky and F. R. McDonald, *Tetrahedron Letters*, 1968, 2575.

N.m.r. data (60 MHz) (J in Hz; internal tetramethylsilane as reference)

Compd.	Solvent	δ	Assignment
(V)	$(CD_3)_2SO$	2.34s	3-Me
		4.10br,s [a]	7-H_2
		5.65s [a]	7-H
		11.20br,s [a]	6- or 4-OH and NH
(VI)	$(CD_3)_2SO$	2.40s	3-Me
		3.20br,s [b]	NMe
		4.30br,s [a]	7-H_2
		5.80br,s [a]	7-H
		11.70br,s [a]	6-OH
	$CDCl_3$	2.49s	3-Me
		3.22s	NMe
		4.04s [a]	7-H_2
(VII)	$(CD_3)_2SO$	2.66s	3-Me
		8.08s	7-H
	$CDCl_3$	2.72s	3-Me
		7.44s	7-H
(VIII)	$(CD_3)_2SO$	2.57s	3-Me
		6.74s [c]	7-H
		12.00br,s [a]	6-OH
(XI)	$(CD_3)_2SO$	2.62s	3-Me
		8.97d, 7.92d, $J_{4,7}$ 0.8	4-H, 7-H
	$CDCl_3$	2.62s	3-Me
		8.70d, 7.46d, $J_{4,7}$ 0.8	4-H, 7-H
(XIV)	$(CD_3)_2SO$	2.62s	3-Me
		9.15d, 7.72dd, 8.65d, $J_{4,7}$ 1.0, $J_{6,7}$ 6.0	4-H, 7-H, 6-H
	$CDCl_3$	2.62s	3-Me
		8.95d, 7.42dd, 8.60d, $J_{4,7}$ 1.0, $J_{6,7}$ 6.0	4-H, 7-H, 6-H
(XV)	$(CD_3)_2SO$	2.52s	3-Me
		4.03s	4-OMe
		7.49s	7-H
	$CDCl_3$	2.59s	3-Me
		4.00s	4-OMe
		7.06s	7-H
(XVI)	$(CD_3)_2SO$	2.47s	3-Me
		3.91s, 4.01s	4-, 6-OMe
		6.53s	7-H
	$CDCl_3$	2.53s	3-Me
		3.96s, 4.06s	4-, 6-OMe
		6.31s	7-H
(XVII)	$(CD_3)_2SO$	2.49s	3-Me
		6.99s	7-H
		12.75br,s [a]	4-OH and NH
(XVIII)	$(CD_3)_2SO$	2.60s	3-Me
		3.94s	6-OMe
		7.08s	7-H
	$CDCl_3$	2.67s	3-Me
		4.01s	6-OMe
		6.67s	7-H
(XIX)	$CDCl_3$	2.54s	3-Me
		3.77s	NMe
		6.26s	7-H
(XX)	$CDCl_3$	2.53s	3-Me
		3.63s	NMe
		6.62s	7-H
(XXI)	$(CD_3)_2SO$	2.40s	3-Me
		3.88s	6-OMe
		6.14s	7-H
		11.90br,s [a]	4-OH and NH
(XXII)	$(CD_3)_2SO$	2.42s	3-Me
		3.31s	NMe
		3.97s	6-OMe
		6.28s	7-H
	$CDCl_3$	2.57s	3-Me
		3.46s	NMe
		3.98s	6-OMe
		5.85s	7-H

[a] Signal disappears on deuteriation. [b] The broad signal appears as a sharp singlet at about 60 °C; on deuteriation two signals appear at 3.07 and 3.22 which coalesce at temperatures near 60 °C and appear as a sharp singlet at *ca.* 80 °C. [c] Signal does not disappear on deuteriation after 5 h.

converted into compound (XIX) by phenylphosphonic dichloride.

With an excess of diazomethane compound (V) afforded a mixture of *OO*- and *NO*-dimethyl derivatives, (XVI) and (XXII). Compound (XXII) was also prepared from the chloro-derivative (XVIII) with sodium methoxide.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 457 spectrometer for KBr discs, unless otherwise stated. ^1H N.m.r. spectra were recorded with a Hitachi–Perkin-Elmer R20 B instrument. U.v. spectra were measured for solutions in methanol with a Cary 14 spectrophotometer. Silica gel plates (Merck F_{254}) were used for analytical and preparative t.l.c.

Diethyl (4-Ethoxycarbonyl-3-methylisoxazol-5-yl)malonate (II).—To a suspension of diethyl sodiomalonate (0.793 mol) in dry benzene, prepared from diethyl malonate (127 g) and sodium hydride (18.9 g) in benzene (850 ml), a solution of ethyl 5-chloro-3-methylisoxazole-4-carboxylate (50 g, 0.265 mol) in benzene (50 ml) was added. The mixture was refluxed for 15 h, then evaporated and the residue was dissolved in water. The solution, after extraction with ether, was acidified to pH 4 with concentrated hydrochloric acid and again extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated. The residual liquid was distilled yielding an *oil* (75 g, 90%), b.p. 134—136° at 0.15 mmHg (Found: C, 53.6; H, 6.15; N, 4.5. $C_{14}H_{19}NO_7$ requires C, 53.7; H, 6.1; N, 4.5%).

Methyl (4-Ethoxycarbonyl-3-methylisoxazol-5-yl)acetate (IV).—The ester (II) (40 g, 0.128 mol) was refluxed for 2 h in aqueous 15% sodium hydroxide (635 ml) to give the *diacid* (III) (19.8 g, 84%). A sample crystallised from water had m.p. 195—196° (decomp.) (Found: C, 45.5; H, 3.8; N, 7.8. $C_7H_7NO_5$ requires C, 45.4; H, 3.8; N, 7.6%). To a suspension of the diacid (III) (19.8 g, 0.107 mol) in ether (180 ml), ethereal diazomethane (0.321 mol) was added. The solvent was removed and the residue distilled to give a *liquid* (18.85 g, 82.5%), b.p. 89—92° at 0.05 mmHg (Found: C, 50.95; H, 5.2; N, 6.65. $C_9H_{11}NO_5$ requires C, 50.7; H, 5.2; N, 6.6%); $\nu_{max.}$ (film) 1 745 and 1 725 cm^{-1} (CO).

6-Hydroxy-3-Methylisoxazolo[4,5-c]pyridin-4(5H)-one (V).—A suspension of the ester (II) (50 g, 0.16 mol) in aqueous 32% ammonium hydroxide (300 ml) was kept at room temperature for 12 h and then refluxed for 6 h. The resulting solution was cooled and acidified to pH 3 with concentrated hydrochloric acid to give *compound* (V), which was filtered off, washed with ether, and dried (yield 14 g, 53%). A sample crystallised from ethanol had m.p. 227—228° (decomp.) (Found: C, 50.7; H, 3.7; N, 16.7. $C_7H_6N_2O_3$ requires C, 50.6; H, 3.6; N, 16.9%); $\nu_{max.}$ 3 300—2 400br (NH and OH) and 1660 cm^{-1} (CO); $\lambda_{max.}$ 265sh and 285 nm (log ε 3.93 and 4.11). This compound was also prepared (82%) from the diester (IV) in an analogous way.

3,5-Dimethylisoxazolo[4,5-c]pyridine-4,6(7H)-dione (VI).—(*a*) A suspension of the diester (IV) (5 g, 0.0235 mol) in aqueous 35% methylammonium hydroxide (75 ml) was refluxed for 5 h. The resulting solution was acidified (pH 3) with concentrated hydrochloric acid and kept overnight in the refrigerator to give the *N-methyl derivative* (VI), which was recrystallised from water and dried at 90°

(yield 2 g, 47%); m.p. 136—137° (Found: C, 53.45; H, 4.5; N, 15.85. $C_8H_8N_2O_3$ requires C, 53.3; H, 4.5; N, 15.55%); $\nu_{max.}$ 1 715 and 1 690 cm^{-1} (CO); $\lambda_{max.}$ 208, 250, and 289 nm (log ε 4.21, 3.51, and 3.87).

(*b*) A suspension of the chloro-derivative (XX) (0.2 g, 0.001 mol) in N-sodium hydroxide (7 ml) was heated at 50 °C for 5 min. The resulting solution was acidified to pH 3 with concentrated hydrochloric acid to give compound (VI) (0.15 g, 82.5%). The product (VI) was also obtained (25%) from the chloro-derivative (XVIII) in N-sodium hydroxide at 80—100 °C (1 h).

4,6-Dichloro-3-methyl (VII) *and 4-Chloro-6-hydroxy-3-methylisoxazolo*[4,5-c]*pyridine* (VIII).—A mixture of compound (V) (7.6 g, 0.046 mol) and phenylphosphonic dichloride (16.5 ml, 0.116 mol) was heated at 160 °C for 3 h and, after cooling, poured into ice–water (330 ml). After decomposition of the excess of phenylphosphonic dichloride, the solid was filtered off, washed with water, and treated with 0.5N-sodium hydroxide (170 ml); the insoluble *dichloro-derivative* (VII) was collected, washed with water, dried, and sublimed at 60° and 0.02 mmHg (yield 6.44 g, 69.4%); m.p. 91—92° (Found: C, 41.4; H, 1.9; Cl, 34.8; N, 13.7. $C_7H_4Cl_2N_2O$ requires C, 41.4; H, 2.0; Cl, 35.0; N, 13.8%); $\nu_{max.}$ 3 080 cm^{-1} (CH); $\lambda_{max.}$ 213, 240sh, 248, 254, and 264sh nm (log ε 4.41, 3.83, 3.94, 3.96, and 3.73).

The mother liquors were acidified to pH 3 with concentrated hydrochloric acid to afford the *monochloro-derivative* (VIII) (1.75 g, 21%), which, after sublimation at 110° and 0.02 mmHg, melted at 243° (decomp.) (Found: C, 45.3; H, 2.6; Cl, 19.2; N, 15.2. $C_7H_5ClN_2O_2$ requires C, 45.55; H, 2.7; Cl, 19.2; N, 15.2%); $\nu_{max.}$ 3 080 (CH) and 3 300—3 200br cm^{-1} (OH); $\lambda_{max.}$ 216, 247sh, 253, 258sh, and 275 nm (log ε 4.36, 3.68, 3.78, 3.77, and 3.78).

6-Chloro-4-hydrazino-3-methylisoxazolo[4,5-c]*pyridine* (IX).—To a solution of the dichloro-derivative (VII) (2 g, 0.009 85 mol) in dioxan (5 ml), hydrazine hydrate (1.90 ml, 0.0395 mol) was added slowly with stirring. The resultant mixture was kept at room temperature for 12 h. The white precipitate provided compound (IX) (1.55 g). Treatment of the mother liquors with water afforded a second crop (0.25 g) of the same product (total yield 92%). Crystallisation from benzene gave pure *monohydrazino-derivative* (IX), m.p. 200—201 (decomp.) (Found: C, 42.25; H, 3.35; Cl, 17.85; N, 28.2. $C_7H_7ClN_4O$ requires C, 42.3; H, 3.55; Cl, 17.85; N, 28.2%); $\nu_{max.}$ 3 320, 3 240, and 3 200—2 500br cm^{-1} (NH_2 and NH); $\lambda_{max.}$ 221, 286, and 296sh nm (log ε 4.30, 4.23, and 4.19).

4,6-Dihydrazino-3-methylisoxazolo[4,5-c]*pyridine* (XII).—To the dichloro-derivative (VII) (5 g, 0.0246 mol), anhydrous hydrazine (15 ml) was added dropwise with cooling (ice–water bath). The mixture was then heated at 100—110 °C for 15 min, cooled, and diluted with water (30 ml). The precipitate was filtered off, washed with cold methanol, and recrystallised from methanol to give *compound* (XII) (4.3 g, 90%), m.p. 227—228° (decomp.) (Found: C, 43.4; H, 5.2; N, 43.1. $C_7H_{10}N_6O$ requires C, 43.3; H, 5.2; N, 43.3%); $\nu_{max.}$ 3 360—2 700br cm^{-1} (NH_2 and NH); $\lambda_{max.}$ 232 and 295 nm (log ε 4.29 and 4.14).

The Tosylhydrazino-derivatives (X) *and* (XIII).—To a suspension of the hydrazino-derivative (IX) or (XII) (0.01 mol) in anhydrous pyridine (15 ml), cooled in ice, tosyl chloride (1.2 mol. equiv. for each $NH{\cdot}NH_2$ group) was added. After 12 h the solution was poured onto crushed ice. The oily product was washed with cold water and solidified on rubbing to a brown mass.

6-Chloro-3-methyl-4-tosylhydrazinoisoxazolo[4,5-c]*pyridine* (X) (75%) was obtained after three crystallisations from ethanol; m.p. 175—176° (decomp.) (Found: C, 47.8; H, 3.7; Cl, 10.05; N, 16,0; S, 9.0. $C_{14}H_{13}ClN_4O_3S$ requires C, 47.7; H, 3.7; Cl, 10.05; N, 15.9; S, 9.1%); $\lambda_{max.}$ 220, 267, and 285 nm (log ε 4.40, 3.96, and 3.88).

3-Methyl-4,6-bistosylhydrazinoisoxazolo[4,5-c]*pyridine* (XIII) (75%) was obtained by two crystallisations from benzene–ethanol (1 : 4) (charcoal) and two further crystallisations from ethanol; m.p. 186—187° (decomp.) (Found: C, 50.4; H, 4.45; N, 16.8; S, 12.7. $C_{21}H_{22}N_6O_5S_2$ requires C, 50.2; H, 4.4; N, 16.7; S, 12.8%); $\lambda_{max.}$ 227 and 285 nm (log ε 4.64 and 4.16).

Alkaline Decomposition of the Tosylhydrazines (X) *and* (XIII).—The hydrazine (X) or (XIII) (0.008 mol) and ethylene glycol (16 ml) was heated to 160 °C. To the hot solution anhydrous sodium carbonate (2.5 mol. equiv. for each $NH{\cdot}NHTs$ group) was added. Heating was continued for an additional 60—120 s and the solution was then rapidly cooled to about 100 °C and diluted with hot water (150 ml). The mixture was extracted with ether and the extracts were dried (Na_2SO_4) and evaporated. The crystalline residue was purified by sublimation at 60° and 0.05 mmHg.

6-Chloro-3-methylisoxazolo[4,5-c]*pyridine* (XI) melted at 106—108° (yield 58.5%) (Found: C, 49.7; H, 3.0; Cl, 21.2; N, 16.4. $C_7H_5ClN_2O$ requires C, 49.9; H, 3.0; Cl, 21.0; N, 16.6%); $\nu_{max.}$ 3 100 and 3 090 cm^{-1} (CH); $\lambda_{max.}$ 210 and 241 nm (log ε 4.40 and 3.89).

3-Methylisoxazolo[4,5-c]*pyridine* (XIV) melted at 111° (yield 40%) (Found C, 62.9; H, 4.55; N, 20.7. $C_7H_6N_2O$ requires C, 62.7; H, 4.5; N, 20.9%); $\nu_{max.}$ 3 075 cm^{-1} (CH); $\lambda_{max.}$ 232 and 265sh nm (log ε 3.82 and 2.93).

Reaction of the Dichloro-derivative (VII) *with Sodium Methoxide.*—The dichloro-derivative (VII) (2 g, 0.009 85 mol) was added to a solution of sodium (1 g, 0.043 5 g atom) in dry methanol (200 ml). The mixture was refluxed for 3.5 h and was evaporated to dryness *in vacuo*. The residue, treated with water, collected by filtration, and dried, yielded chromatographically pure *6-chloro-4-methoxy-3-methylisoxazolo*[4,5-c]*pyridine* (XV) (1.85 g, 94.6%). A sample obtained by sublimation at 60° and 0.02 mmHg had m.p. 90—91° (Found: C, 48.6; H, 3.6; Cl, 17.65; N, 14.1. $C_8H_7ClN_2O_2$ requires C, 48.4; H, 3.55; Cl, 17.9; N, 14.1%); $\nu_{max.}$ 3 110 cm^{-1} (CH); $\lambda_{max.}$ 211, 248sh, 252.5, 267, and 273sh nm (log ε 4.34, 4.02, 4.04, 3.84, and 3.78).

The above reaction, carried out with more sodium (5.66 g, 0.246 g atom) in methanol (100 ml) at reflux temperature for 16 h, gave *4,6-dimethoxy-3-methylisoxazolo*[4,5-c]*pyridine* (XVI) (1.76 g, 92%) as the only product (t.l.c.). This compound, after crystallisation from light petroleum (b.p. 75—120°), melted at 96—97° (Found: C, 55.5; H, 5.1; N, 14.2. $C_9H_{10}N_2O_3$ requires C, 55.7; H, 5.2; N, 14.4%); $\nu_{max.}$ 3 115 cm^{-1} (CH); $\lambda_{max.}$ 212 and 265 nm (log ε 4.33 and 4.15).

6-Chloro-3-methylisoxazolo[4,5-c]*pyridin-4*(5H)*-one* (XVII).—A suspension of compound (XV) (1 g, 0.005 mol) in concentrated hydrochloric acid (85 ml) was refluxed for 2 h and poured into water (200 ml). A crystalline white precipitate was collected which yielded the *chloro-derivative* (XVII) (0.6 g, 65%), m.p. 293° (decomp.) (from ethanol) (Found: C, 45.5; H, 2.8; Cl, 19.2; N, 15.1. $C_7H_5ClN_2O_2$ requires C, 45.5; H, 2.7; Cl, 19.2; N, 15.2%); $\nu_{max.}$ 3 100 (CH), 3 000—2 100br (NH) and 1 670 cm^{-1} (CO); $\lambda_{max.}$ 208, 253, and 290 nm (log ε 4.12, 3.83, and 3.95).

6-*Methoxy*-3-*methylisoxazolo*[4,5-c]*pyridin*-4(5H)-*one* (XXI).—Ethereal diazomethane (0.008 mol) was added to a suspension of compound (V) (1 g, 0.006 mol) in ether (25 ml). After 12 h the solid was filtered off [t.l.c. of the ethereal solution showed the presence of small amounts of compounds (XVI) and (XXII)] and recrystallised from ethanol (charcoal) to give the *methoxy-derivative* (XXI) (0.8 g, 74%), m.p. 250° (decomp.) (Found: C, 53.5; H, 4.5; N, 15.45. $C_8H_8N_2O_3$ requires C, 53,3; H, 4.5; N, 15.55%); $\nu_{max.}$ 3 135 (CH), 3 050—2 300br (NH) and 1 665 cm^{-1} (CO); $\lambda_{max.}$ 257 and 282 nm (log ε 3.99 and 4.07).

4-*Chloro*-6-*methoxy*-3-*methylisoxazolo*[4,5-c]*pyridine* (XIX).—A mixture of the methoxy-derivative (XXI) (0.5 g, 0.0028 mol) and phenylphosphonic dichloride (0.51 ml, 0.003 58 mol) was heated at 160 °C for 3 h and, after cooling, poured into ice–water (30 ml). After decomposition of the excess of phenylphosphonic dichloride, the solid was filtered off, washed with aqueous 5% sodium hydrogen carbonate and then with water, dried, and sublimed at 50° and 0.03 mmHg to give the *chloro-derivative* (XIX) (0.36 g, 64.8%), m.p. 117—118° (Found: C, 48.6; H, 3.5; Cl, 17.9; N, 14.1. $C_8H_7ClN_2O_2$ requires C, 48.4; H, 3.55; Cl, 17.9; N, 14.1%); $\nu_{max.}$ 3 110 cm^{-1} (CH); $\lambda_{max.}$ 216, 247sh, 254, 258sh, and 277 nm (log ε 4.43, 3.77, 3.85, 3.83, and 3.83).

Treatment of the Methoxy-derivative (XXI) *with Diazomethane.*—Ethereal diazomethane (0.0347 mol) was added to a solution of the methoxy-derivative (XXI) (2.5 g, 0.0139 mol) in methanol (80 ml). After 12 h the solution was evaporated and the residue (2.4 g) separated into two components by preparative layer chromatography with light petroleum (b.p. 30—50°)–chloroform (2 : 1 v/v) as developer. The fastest running band gave the dimethoxy-derivative (XVI) (1 g, 37.1%), identical (m.p. and i.r. spectrum) with the material described above. The second band yielded 6-*methoxy*-3,5-*dimethylisoxazolo*[4,5-c]*pyridin*-4(5H)-*one* (XXII) (0.9 g, 33.4%), m.p. 163—164° [from light petroleum (b.p. 75—120°)] (Found: C, 55.5; H, 5.15; N, 14.4. $C_9H_{10}N_2O_3$ requires C, 55.7; H, 5.2; N, 14.4%); $\nu_{max.}$ 3 090 (CH) and 1 690 cm^{-1} (CO); $\lambda_{max.}$ 204, 257, and 283 nm (log ε 4.22, 3.93, and 4.06). This product (20%) was also obtained from the chloro-derivative (XVIII) (0.001 mol) and sodium methoxide (0.004 mol) in methanol (10 ml) at reflux temperature (10 h).

Treatment of the Chloro-derivative (VIII) *with Diazomethane.*—Ethereal diazomethane (0.007 58 mol) was added to a suspension of the chloro-derivative (VIII) (0.7 g, 0.0038 mol) in ether (20 ml). After 12 h the solid was filtered off, washed with a small amount of ether, and recrystallised from carbon tetrachloride to give 4-*chloro*-3,5-*dimethylisoxazolo*[4.5-c]*pyridin*-6(5H)-*one* (XX) (0.2 g, 26.3%), m.p. 223—224° (decomp.) (Found: C, 48.4; H, 3.4; Cl, 18.1; N, 14.0. $C_8H_7ClN_2O_2$ requires C, 48.4; H, 3.5; Cl, 17.9; N, 14.1%); $\nu_{max.}$ 3 060 (CH) and 1 670 cm^{-1} (CO): $\lambda_{max.}$ 225, 257sh, 263, and 336 nm (log ε 4.45, 3.56, 3.63, and 3.76). The mother liquors were evaporated and the resulting solid sublimed to give the methoxy-derivative (XIX) (0.450 g, 59.6%), identical (m.p. and i.r. spectrum) with the material described above.

Treatment of the Chloro-derivative (XVII) *with Diazomethane.*—Ethereal diazomethane (0.0065 mol) was added to a suspension of the chloro-derivative (XVII) (0.6 g, 0.003 25 mol) in ether (20 ml). After 12 h the solid was filtered off and crystallised from light petroleum (b.p. 75—120°) to give 6-*chloro*-3,5-*dimethylisoxazolo*[4,5-c]*pyridin*-4(5H)-*one* (XVIII) (0.2 g, 31%), m.p. 162—163° (Found: C, 48.2; H, 3.5; Cl, 18.0; N, 14.2. $C_8H_7ClN_2O_2$ requires C, 48.4; H, 3.5; Cl, 17.9; N, 14.1%); $\nu_{max.}$ 3 080 (CH) and 1 675 cm^{-1} (CO); $\lambda_{max.}$ 212, 252, and 295 nm (log ε 4.1, 3.74, and 3.98). The mother liquors were evaporated to give a mixture which was sublimed at 50° and 0.05 mmHg to afford the methoxy-derivative (XV) (0.20 g, 31%). The residue (0.17 g, 26%) was compound (XVIII).

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