Preparation of some Thiopyranopyridine Derivatives

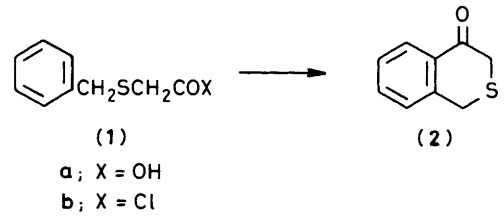
Kenneth Clarke,* John Goulding, and Richard M. Scrowston
Department of Chemistry, The University, Hull HU6 7RX

In the first systematic study of thiopyranopyridines in which the sulphur atom is separated from the pyridine ring by one carbon atom, the four isomeric enol esters, ethyl 5-hydroxy-8*H*-thiopyrano[3,4-*b*]-pyridine-6-carboxylate (**4b**), ethyl 8-hydroxy-5*H*-thiopyrano[4,3-*b*]pyridine-7-carboxylate (**5b**), and ethyl 4-hydroxy-1*H*-thiopyrano[3,4-*c*]- and [4,3-*c*]pyridine-3-carboxylate (**6b**) and (**7b**), have been synthesised. Improved methods for the preparation of their pyridine precursors are described. With phenylhydrazine, the enol esters (**4b**)—(**7b**) give condensed pyrazole derivatives (**15**)—(**18**), which have dipolar structures; with hot mineral acid they undergo decarboxylative hydrolysis, to give the corresponding oxothiopyranopyridines (**4a**)—(**7a**).

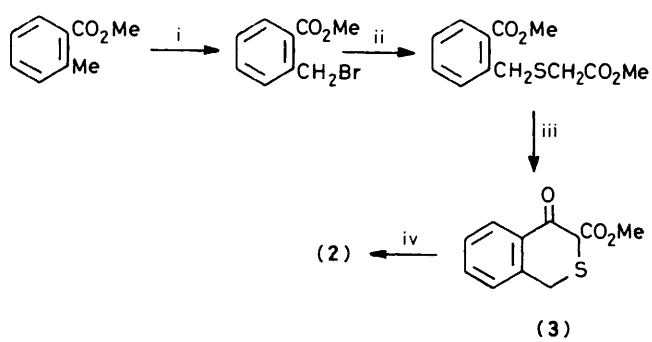
The chemistry of 1*H*-2-benzothiopyran-4(3*H*)-one (**2**) is well documented.[1,2] Surprisingly little work has been reported on the isomeric thiopyranopyridines (**4a**)—(**7a**), in which the sulphur atom of the thiopyran ring is separated from the pyridine ring by a methylene group. Up to 1962, the Ring Index recorded only the thiopyrano[4,3-*b*]pyridine system [*cf.* (**5**)], which had been prepared in a reduced form in 1925.[3] Since then, a thiopyrano[4,3-*b*]pyridine derivative with an aromatic pyridine ring has been prepared by treatment of a 1,5-dicarbonyl compound containing a preformed thiopyran ring with hydroxylamine.[4] Other thiopyranopyridines of types (**4a**), (**5a**), and (**7a**) have been obtained only as partially reduced derivatives.

The benzothiopyrans (**2**) are most commonly obtained by cyclisation of the appropriate (benzylthio)acetic acid (**1a**) with polyphosphoric acid[5] or of the corresponding acid chloride (**1b**) with aluminium chloride[6] (Scheme 1). Neither of these methods is applicable to the preparation of the pyridine analogues (**4a**)—(**7a**) because of the deactivation of the pyridine ring towards electrophilic attack. However, in 1976 we described[7] a convenient synthesis of methyl 3,4-dihydro-4-oxo-1*H*-2-benzothiopyran-3-carboxylate (**3**) from methyl *o*-toluate (Scheme 2); this was readily hydrolysed and decarboxylated to give the thiopyranone (**2**). Application of this method to the four isomeric pyridinecarboxylic esters (**8b**)—(**11b**), in which the ester group is flanked by a methyl substituent, should likewise give the thiopyranopyridines (**4**)—(**7**).

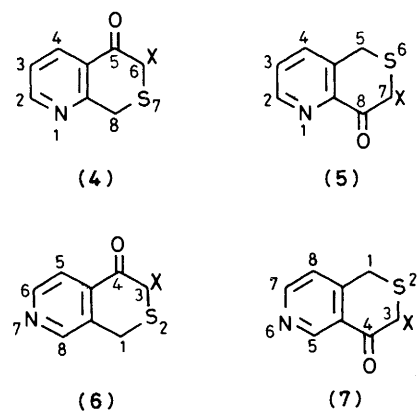
The preparation of the four isomeric pyridinecarboxylic acids (**8a**)—(**11a**) (or their esters) presented the first problem because, although all of them are known compounds, some of the published synthetic routes are lacking in detail, whilst others are unsuitable on a large scale. Ethyl 2-methylpyridine-3-carboxylate (**8b**) was obtained (47%) by Van der Stelt's method,[8] in which ethyl 3-aminocrotonate condensed with acraldehyde, and the resulting dihydropyridine derivative was dehydrogenated with sulphur. 3-Methylpyridine-2-carbonitrile, obtained by successive treatment of 3-methylpyridine *N*-oxide with dimethyl sulphate and cyanide ion (*cf.* ref. 9), was readily converted (see Experimental section) into ethyl 3-methylpyridine-2-carboxylate (**9b**) (28% overall from 3-methylpyridine). The corresponding carboxylic acid (**9a**) has been prepared more recently in better yield,[10] but the starting material is 2-amino-3-methylpyridine, which is not readily available. 3-Methylpyridine-4-carboxylic acid (**10a**) and its isomer (**11a**) were both obtained by selective oxidation of 3,4-dimethylpyridine, then esterified. With selenium dioxide (*cf.* ref. 11), the 4-methyl group was oxidised preferentially, to give the acid (**10a**) [62% (as the ester)]; with chromium trioxide (*cf.* ref. 12) the isomeric 4-methylpyridine-3-carboxylic acid (**11a**) [43% (as the ester)] was obtained. Acidic permanganate is known[12] to disrupt the pyridine ring, but treatment with aqueous potassium permanganate at room temperature for 5 days converted 3,4-dimethylpyridine into a mixture of 4-methylpyridine-3-carboxylic acid



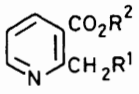
Scheme 1. *Reagents:* X = OH, polyphosphoric acid; X = Cl, $AlCl_3$



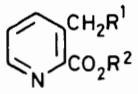
Scheme 2. *Reagents:* i, *N*-bromosuccinimide; ii, $MeO_2CCH_2S^-$; iii, MeO^-; iv, H^+



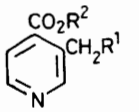
a; X = H
b; X = CO_2Et (in the enol form)



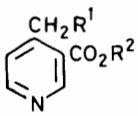
(8)



(9)



(10)



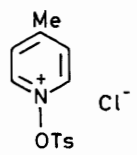
(11)

a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Et$
c; $R^1 = Br$, $R^2 = Et$
d; $R^1 = Cl$, $R^2 = Et$
e; $R^1 = SCH_2CO_2Et$, $R^2 = Et$

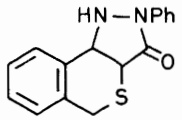
(**11a**) and 3-methylpyridine-4-carboxylic acid (**10a**) (4:1). Crystallisation of the mixture from 5M-hydrochloric acid gave the former as the hydrochloride salt; this was esterified to give the ester (**11b**) (42%). In practice, the crude oxidation product was esterified, and the resulting mixture of esters (**10b**) and (**11b**) was used directly in the next stage of the reaction, after which pure ethyl 4-chloromethylpyridine-3-carboxylate (**11d**) could be obtained.

Unlike the esters of the toluic acids,[7] the methylpyridinecarboxylic esters did not easily undergo halogenation in the side-chain, and when reaction was accomplished, the products were usually unstable and had often to be used without purification. Attempts at direct photobromination, either with or without a radical initiator, failed, probably because of the formation of pyridine–bromine addition complexes and extensive degradation. With *N*-bromosuccinimide in the presence of light, some of the required bromomethyl compound was formed (n.m.r.), but this decomposed rapidly and the formation of tars cut down the transmission of light and halted the reaction. We believed that the tar resulted from *N*-alkylation of the pyridine ring by the initially formed bromomethyl compound, and argued that deliberate protonation of the pyridine nitrogen atom might inhibit the side reaction. Indeed, in the presence of acetic acid (1 mol equiv.), the reaction was much cleaner. However, the addition of more acetic acid or the use of a stronger acid (*e.g.* trichloroacetic acid) promoted dibromination of the methyl group. Use of the acid-catalysed bromination procedure gave ethyl 2- or 4-bromomethylpyridine-3-carboxylate (**8c**) or (**11c**) (67 or 42%) and ethyl 3-bromomethylpyridine-2- or -4-carboxylate (**9c**) or (**10c**) (45 or 30%). The low yield of the last compound again seemed due to the separation of oily pyridine–bromine complexes. There is evidence[13] that the corresponding pyridine–chlorine complexes are less stable, and therefore less readily formed, so we investigated halogenation with *N*-chlorosuccinimide in the presence of acetic acid. Improved yields of the halogenomethyl compounds (**9d**) and (**10d**) (65 and 66%) were thereby obtained.

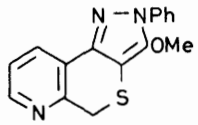
2- and 4-Methylpyridines may be converted into the corresponding chloromethyl compounds by tosylation of the *N*-oxide and treatment of the resulting *N*-(*O*-toluene-*p*-sulphonate) salt [*e.g.* (**12**)] with hydrochloric acid.[14] Ethyl 2- and



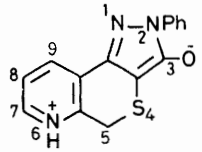
(12)



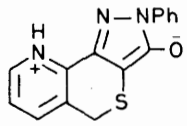
(13)



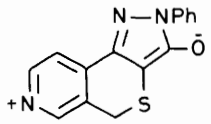
(14)



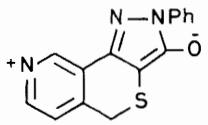
(15)



(16)



(17)



(18)

4-chloromethylpyridine-3-carboxylates (**8d**) and (**11d**) (42 and 69%) were obtained from the corresponding methyl derivative by this method. When the mixture of esters (**10b**) and (**11b**) (*vide supra*) was subjected to this sequence of reactions, ethyl 4-chloromethylpyridine-3-carboxylate (**11d**) (58%) was obtained; the minor ester (**10b**), which contained a 3-methyl group, could not be chlorinated under these conditions, and was lost during work-up.

The success of this method of chlorination led us to consider whether a suitably quaternised pyridine derivative might react with ethyl sodiomercaptoacetate, to give the sulphides (**8e**) and (**11e**). Bauer and Gardella had previously found[15] that 1-methoxy-2- or -4-methylpyridinium methosulphate reacted with thiophenoxide ion, to give the 2- or 4-CH_2SPh compounds. Unfortunately, we found that treatment of 3-ethoxycarbonyl-1-methoxy-4-methylpyridinium methosulphate with ethyl sodiomercaptoacetate merely regenerated the starting ester (**11b**) (76%), presumably because the alkanethiolate anion is more nucleophilic than the phenoxide anion. However, the halogenomethylpyridines reacted readily with ethyl mercaptoacetate at 0 °C in the presence of sodium ethoxide (1 mol equiv.), to give the required esters (**8e**)—(**11e**) (60—80%). Raising the temperature or using even a slight excess of base lowered the yields considerably, presumably in the latter case because of concomitant cyclisation. Cyclisation of the diesters (**8e**)—(**11e**) was best accomplished by use of sodium ethoxide in toluene at 0 °C. The resulting thiopyranopyridines (**4b**)—(**7b**) (60—70%) were all tautomeric systems, which existed almost entirely in the enolic form, both in the solid phase (i.r. spectrum) and in solution in deuteriochloroform (^1H n.m.r. spectrum).

We next used the isomer (**4b**) as a typical example of the enol esters (**4b**)—(**7b**) in order to compare its reactions with some carbonyl reagents with those already described for the benzo analogue (**3**).[7] In the presence of Dowex-1 (OH^-) anion exchange resin, it formed an oxime; like that of the analogue (**3**),[7] this failed to cyclise to the corresponding isoxazolone derivative. The enol ester (**4b**) condensed with phenylhydrazine and cyclised to give a product which differed markedly in properties from those of the pyrazolone derivative (**13**), obtained from the benzenoid derivative (**3**). It was insoluble in ether or chloroform and decomposed at >210 °C; its i.r. spectrum lacked carbonyl absorption, but showed a strong $\equiv\overset{+}{N}H$ band. Methylation with methyl iodide and sodium hydrox-

ide in dimethylformamide (DMF) gave solely an *O*-methyl derivative, whose spectroscopic properties were in accord with structure (**14**). Similar methylation of the pyrazolone (**13**) also gave an *O*-methyl derivative (40%) with properties similar to those of the *O*-methylated product (**14**), but in this case an *N*-methyl compound (60%) was also formed.[7] It therefore appears that the condensation product of the enol ester (**4b**) with phenylhydrazine has the dipolar structure (**15**). The ^{1}H n.m.r. spectrum, although not well resolved in the aromatic region, showed that the pyridine protons are moved to lower field strength than usual, as would be expected[16] for a protonated pyridine ring, and that the methylene group in the thiopyran ring is intact. An alternative dipolar structure, in which a nitrogen atom of the pyrazolone ring is protonated, seems unlikely in view of the fact that non-pyridine fused pyrazolones [*cf.* (**13**)] invariably exist in the oxo form. The enol esters (**5b**)—(**7b**) also reacted with phenylhydrazine, to give similar compounds for which we propose the dipolar structures (**16**)—(**18**).

Attempts to prepare the ketones (**4a**)—(**7a**) by successive hydrolysis and decarboxylation of the enol esters (**4b**)—(**7b**) were unsuccessful when the hydrolysing agent was aqueous 5% sodium hydroxide. With refluxing 2M-hydrochloric acid, however, the crystalline, unstable ketones were obtained (40—80%), and characterised as the stable picrates.

Experimental

I.r. data refer to potassium chloride discs. ^{1}H N.m.r. data refer to solutions in deuteriochloroform (unless otherwise stated). Light petroleum refers to the fraction with b.p. 60—80 °C. Ether refers to diethyl ether. Compounds which were not obtained analytically pure had, unless stated otherwise, a purity of >95% (t.l.c.); they all showed the expected molecular ion peak(s) in the mass spectrum.

Ethyl 2-Methylpyridine-3-carboxylate (**8b**).—This was prepared (47%) by the method of Van der Stelt,[8] and was obtained a pale yellow oil, b.p. 120—125 °C at 20 mmHg (lit.,[8] 115—118 °C at 17 mmHg).

Ethyl 3-Methylpyridine-2-carboxylate (**9b**).—A mixture of 3-methylpyridine (50 g), glacial acetic acid (500 ml), and hydrogen peroxide (30% w/v; 160 ml) was kept at 100 °C for 3.5 h, then the solvents were removed carefully under reduced pressure. The resulting solid was kept at 80 °C and 0.5 mmHg for 0.5 h to remove the last traces of solvent, then a solution of the crude *N*-oxide (58 g) in hot (80 °C) water was treated dropwise during 3 h with dimethyl sulphate (68 g). The mixture was kept at 80 °C for 2 h, then cooled, diluted with water, and neutralised (pH 7) by the addition of solid sodium carbonate.

The neutral solution was added dropwise during 1 h under nitrogen to an ice-cold solution of sodium cyanide (75 g) in water (250 ml), then the mixture was allowed to attain room temperature overnight (nitrogen atmosphere). Cooling in ice then gave 3-methylpyridine-2-carbonitrile (24 g, 38% overall), m.p. 87—89 °C (lit.,[9] 87—90 °C) (from ethanol).

A mixture of the nitrile (23.6 g), sodium hydroxide (6 g), and water (30 ml) was heated under reflux for 4 h, then cooled, filtered, acidified with concentrated hydrochloric acid, and evaporated to dryness under reduced pressure. The residue was powdered, dried (48 h *in vacuo*), and boiled for 4 h with dry ethanol (200 ml), which had been saturated with hydrogen chloride at 0 °C. Most of the ethanol was removed under reduced pressure, then water (100 ml) was added and the mixture was neutralised with sodium carbonate. Extraction with ether and work-up gave the ester (**9b**) (22.3 g, 70%), b.p. 128—130 °C at 20 mmHg. The *hydrochloride* had m.p. 156—157 °C (needles from ethanol) (Found: C, 53.8; H, 5.85; N, 6.9. $C_9H_{12}ClNO_2$ requires C, 53.6; H, 6.0; N, 6.95%).

Ethyl 3-Methylpyridine-4-carboxylate (**10b**).—Selenium dioxide (36 g) was added in portions to a hot (155 °C), stirred solution of 3,4-dimethylpyridine (21.4 g) in diphenyl ether (200 ml). Stirring was continued at 155 °C for a further 0.5 h, then at 185 °C for 0.5 h, during which time the liberated water was distilled off. The cooled mixture was filtered, and the residue was treated with several portions of boiling water to extract the carboxylic acid. The combined aqueous extracts were washed with chloroform, then evaporated to dryness, to give crude 3-methylpyridine-4-carboxylic acid (**10a**) (26 g). This was dried, then esterified by the method just described for the acid (**9a**), to give an oil (20.6 g, 62%), b.p. 114—118 °C at 15 mmHg (lit.,[17] 116—117 °C at 14 mmHg).

Ethyl 4-Methylpyridine-3-carboxylate (**11b**).—*Method A.* Potassium permanganate (63.2 g) was added in ten equal portions during 5 days to a stirred solution of 3,4-dimethylpyridine (21.4 g) in water (200 ml) at room temperature. The precipitated manganese(IV) oxide was filtered off (Hyflo), then the colourless filtrate was acidified to congo red and evaporated to dryness. The dried (48 h *in vacuo*) residue contained inorganic salts and a mixture (4:1) of the hydrochlorides of 4-methylpyridine-3-carboxylic acid (**11a**) and 3-methylpyridine-4-carboxylic acid (**10a**); δ[$(CD_3)_2SO$] 2.43 and 2.35 respectively (s, Me). Fractional crystallisation from 5M-hydrochloric acid (2 ml g^{-1}) gave the former [(**11a**)·HCl], still contaminated with inorganic salts. Esterification by the method already described gave the ester (**11b**) as an oil, b.p. 118—122 °C at 15 mmHg (lit.,[18] 60—62 °C at 0.5 mmHg).

Alternatively, the crude mixture of acids was esterified in the same way to give a mixture of the esters (**10b**) and (**11b**) (23.5 g, 71%), b.p. 115—120 °C at 15 mmHg. The components could not be separated by distillation, so the mixtuure was used directly in the next stage.

Method B. Chromium trioxide (20 g) was added in portions to a stirred, ice-cold solution of 3,4-dimethylpyridine (10.7 g) in concentrated sulphuric acid (20 ml). The temperature was allowed to rise to 70 °C during the addition, and then allowed to fall. Ethanol (100 ml) was then added and the mixture was heated under reflux for 2 h, then most of the ethanol was distilled off and the cooled residue was poured on ice. After neutralisation of the mixture with solid sodium carbonate, ether extraction and work-up gave the ester (**11b**) (7.1 g, 43%), identical with that obtained by method A.

Ethyl 2-Bromomethylpyridine-3-carboxylate (**8c**).—A stirred mixture of *N*-bromosuccinimide (22.25 g), ethyl 2-methylpyridine-3-carboxylate (16.5 g), glacial acetic acid (6 ml), azobisisobutyronitrile (0.2 g), and carbon tetrachloride (200 ml) was illuminated (2 × 200 W tungsten lamps) at 60 °C until reaction was complete (n.m.r.). The cooled mixture was then neutralised with aqueous sodium hydrogen carbonate and the organic phase was washed, dried, and evaporated under reduced pressure at 40 °C. The crude bromomethyl compound (21 g, 86%) was used immediately in the next stage. It contained *ca.* 78% of the required product, δ 5.00 (s, CH_2Br), together with equal amounts of starting material, δ 2.94 (s, Me), and the dibromomethyl compound, δ 7.83 (s, $CHBr_2$). The bromomethyl compound (**8c**) was characterised as the *hydrobromide*, which formed needles, m.p. 158—159 °C (from ethanol) (Found: C, 33.5; H, 3.5; N, 4.15. $C_9H_{11}Br_2NO_2$ requires C, 33.25; H, 3.4; N, 4.3%).

Ethyl 3-Chloromethylpyridine-2-carboxylate (**9d**).—Ethyl 3-methylpyridine-2-carboxylate (16.5 g) was chlorinated with *N*-

Table. Analytical, physical, and spectral data for pyridine and condensed pyridine derivatives.

Compound (Formula)	Yield (%)	Solvent	M.p.(°C) [B.p.(°C/mmHg)]	I.r. $\nu_{max.}$ (cm^{-1})	δ_H (p.p.m.) SCH_2CO	$ArCH_2S$	OH	Found (Required) (%) C	H	N	M^+
(8e)	76		[143—148/0.05]	1 725 (C=O)	3.30	4.37		55.4	5.9	4.85	283
($C_{13}H_{17}NO_4S$)								(55.1)	(6.05)	(4.95)	(283)
(9e)	62		[150—158/0.05]	1 725 (C=O)	3.30	4.23		55.45	5.95	5.1	283
($C_{13}H_{17}NO_4S$)								(55.1)	(6.05)	(4.95)	(283)
(10e)	64	EtOH[a]	156—157[a]	1 730 (C=O)	3.27	4.15		49.0[a]	5.65[a]	(4.2[a]	283
($C_{13}H_{17}NO_4S$)			[150—156/0.05]					(48.8)[a]	(5.65)[a]	(4.4)[a]	(283)
(11e)	79	EtOH[a]	152—153[a]	1 730 (C=O)	3.15	4.27		48.85[a]	5.7[a]	4.25[a]	283
($C_{13}H_{17}NO_4S$)			[138—142/0.05]					(48.8)[a]	(5.65)[a]	(4.4)[a]	(283)
(4b)	61	*b*	81—82	1 638 (ester C=O)		3.92	12.38	55.45	4.65	5.75	237
($C_{11}H_{11}NO_3S$)								(55.65)	(4.7)	(5.9)	(237)
(5b)	67	*b*	54—55	1 642 (ester C=O)		3.82	12.1br	55.6	4.7	5.95	237
($C_{11}H_{11}NO_3S$)								(55.65)	(4.7)	(5.9)	(237)
(6b)	59	*b*	46—48	1 640 (ester C=O)		3.78	12.28	55.6	4.7	5.85	237
($C_{11}H_{11}NO_3S$)								(55.65)	(4.7)	(5.9)	(237)
(7b)	63	*b*	79—80	1 645 (ester C=O)		3.78	12.4br	55.6	4.75	5.9	237
($C_{11}H_{11}NO_3S$)								(55.65)	(4.7)	(5.9)	(237)
(4a)	75	*b*	51—52	1 680 (C=O)	3.45	4.11					165
(C_8H_7NOS)											(165)
($C_{14}H_{10}N_4O_8S$)[c]		EtOH	166—168 (decomp.)[c]					42.65[d]	2.45[d]	13.95[d]	
(5a)	38	*b*	78—81	1 695 (C=O)	3.67	4.05					165
(C_8H_7NOS)											(165)
($C_{14}H_{10}N_4O_8S$)[c]		EtOH	196—198 (decomp.)[c]					42.9[d]	2.45[d]	14.2[d]	
(6a)	72	*b*	78—80	1 695 (C=O)	3.62	3.95					165
(C_8H_7NOS)											(165)
($C_{14}H_{10}N_4O_8S$)[c]		EtOH	168—170 (decomp.)[c]					42.85[d]	2.5[d]	14.0[d]	
(7a)	78	*b*	76—78	1 685 (C=O)	3.57	3.85					165
(C_8H_7NOS)											(165)
($C_{14}H_{10}N_4O_8S$)[c]		EtOH	148—150 (decomp.)[c]					42.75[d]	2.45[d]	14.0[d]	
(15)	75	EtOH—DMF	*e*	2 400 ($\equiv\overset{+}{N}H$)		4.38[f]		64.1	4.0	14.9	281
($C_{15}H_{11}N_3OS$)								(64.05)	(3.95)	(14.95)	(281)
(16)	63	EtOH—DMF	*e*	2 600 ($\equiv\overset{+}{N}H$)		4.00[f]		63.9	3.9	14.9	281
($C_{15}H_{11}N_3OS$)								(64.05)	(3.95)	(14.95)	(281)
(17)	71	EtOH—DMF	*e*	2 400 ($\equiv\overset{+}{N}H$)		4.08[f]		64.0	4.05	15.0	281
($C_{15}H_{11}N_3OS$)								(64.05)	(3.95)	(14.95)	(281)
(18)	69	EtOH—DMF	*e*	2 400 ($\equiv\overset{+}{N}H$)		4.05[f]		64.05	3.9	14.9	281
($C_{15}H_{11}N_3OS$)								(64.05)	(3.95)	(14.95)	(281)

[a] HCl Salt ($C_{13}H_{18}ClNO_4S$). [b] EtOAc–light petroleum. [c] Picrate. [d] Required values for all the picrates: C, 42.65; H, 2.55; N, 14.2%. [e] Decomposed at *ca.* 200—210 °C. [f] In $(CD_3)_2SO$.

chlorosuccinimide (*ca.* 40 g) by a method analogous to that used for the bromination reaction just described, except that the chlorinating agent was added in portions during 8 h. When the reaction was complete (n.m.r.), the unstable crude product (15.5 g, 76.5%) was isolated as before. It contained *ca.* 85% of the required product (**9d**), δ 4.95 (s, CH_2Cl). The *hydrochloride* crystallised from ethanol as needles, m.p. 134—135 °C (Found: C, 45.55; H, 4.6; N, 5.8. $C_9H_{11}Cl_2NO_2$ requires C, 45.75; H, 4.7; N, 5.95%).

Similarly prepared, ethyl 3-chloromethylpyridine-4-carboxylate (**10d**) (78%), δ 4.90 (s, CH_2Cl), was *ca.* 85% pure. The *hydrochloride* had m.p. 125—127 °C (from ethanol–ether) (Found: C, 45.65; H, 4.6; N, 5.75%).

Ethyl 4-Chloromethylpyridine-3-carboxylate (**11d**).—(*a*) Ethyl 4-methylpyridine-3-carboxylate (**11b**) (16.5 g) was kept at 100 °C for 3.5 h with hydrogen peroxide (30% w/v; 40 ml) in glacial acetic acid (150 ml).

(*b*) The crude, dry *N*-oxide (18 g), obtained by the procedure already described for 3-methylpyridine *N*-oxide, was heated under reflux for 1.5 h with toluene-*p*-sulphonyl chloride (38.1 g) in dioxane (100 ml). The cooled mixture was then treated with hydrochloric acid (10% v/v; 100 ml), stirred for 15 min, and shaken with ether (4 × 50 ml) to remove the excess of the sulphonyl chloride. The aqueous phase was neutralised with sodium hydrogen carbonate and the product [13.8 g, 69% overall from (**11b**)], δ 5.0 (s, CH_2Cl), was extracted into ether. It was characterised as the *hydrochloride*, which formed needles, m.p. 131—132 °C (from ethanol) (Found: C, 45.6; H, 4.6; N, 5.85%).

Use of the mixture of esters (**10b**) and (**11b**) in this reaction gave a comparable yield of ethyl 4-chloromethylpyridine-3-carboxylate (**11d**), uncontaminated with the isomer (**10d**).

Reaction of 3-Ethoxycarbonyl-1-methoxy-4-methylpyridinium Methosulphate with Ethyl Sodiomercaptoacetate.—(*a*) A mixture of the *N*-oxide of the ester (**11b**) (1.8 g) and dimethyl sulphate (1.26 g) was kept at 100 °C for 3 h, then cooled and triturated with dry ether, to give 3-ethoxycarbonyl-1-methoxy-4-methylpyridinium methosulphate as a white powder (2.2 g).

(*b*) Ethyl mercaptoacetate (1.2 g) and a solution of the foregoing crude methosulphate (2 g) in dry ethanol (25 ml) were successively added dropwise to a stirred, cold (0 °C) solution of sodium ethoxide [from sodium (0.23 g)] in dry ethanol (25 ml), then the mixture was heated under reflux for 0.5 h. The usual work-up gave only ethyl 4-methylpyridine-3-carboxylate (**11b**) (0.9 g, 76%), identical with authentic material.

Ethyl (3-*Ethoxycarbonyl*-2-*pyridylmethylthio*)*acetate* (**8e**).—An ice-cold, stirred solution of sodium (0.58 g) in dry ethanol (25 ml) was treated slowly and successively with ethyl mercaptoacetate (3.0 g) and freshly prepared ethyl 2-bromomethylpyridine-3-carboxylate (**8c**) (78% pure; 5.1 g), then the coolant was removed. When the mixture had attained room temperature it was carefully acidified with glacial acetic acid, then the solvent was distilled off and the residue was treated with ether–water. The ethereal phase was separated and the aqueous phase was shaken with ether (3 × 25 ml). The combined ethereal extracts were washed (aqueous $NaHCO_3$), dried, and evaporated, to give a pale yellow *oil*. Details of this and of *ethyl* (2-*ethoxycarbonyl*-3-*pyridylmethylthio*)*acetate* (**9e**), *ethyl* (4-*ethoxycarbonyl*-3-*pyridylmethylthio*)*acetate* (**10e**), and *ethyl* (3-*ethoxycarbonyl*-4-*pyridylmethylthio*)*acetate* (**11e**), which were prepared similarly, are shown in the Table.

Ethyl 5-*Hydroxy*-8H-*thiopyrano*[3,4-b]*pyridine*-6-*carboxylate* (**4b**).—The diester (**8e**) (2.83 g) was added to an ice-cold, stirred suspension of powdered sodium ethoxide [from sodium (0.48 g)] in dry toluene (50 ml), and the mixture was stirred at 0 °C for 1 h. The mixture was shaken with water (3 × 25 ml) and the combined aqueous extracts were acidified with glacial acetic acid, then shaken with ether (3 × 25 ml). The combined ethereal extracts were shaken with 2M-hydrochloric acid (3 × 25 ml) and the resulting combined acidic extracts were treated first with solid sodium hydrogen carbonate until just neutral, then with a few drops of glacial acetic acid. Ether extraction in the usual way gave an oily product which was crystallised with difficulty from ethyl acetate–light petroleum as bright yellow *needles*.

Details of this product, and of the similarly prepared enol esters (**5b**)—(**7b**), are given in the Table.

Oxime of the Enol Ester (**4b**).—A mixture of ethyl 5-hydroxy-8*H*-thiopyrano[3,4-*b*]pyridine-6-carboxylate (**4b**) (2.4 g), hydroxylamine hydrochloride (0.5 g), Dowex 1 (OH^-) anion-exchange resin (0.5 g), and methanol (50 ml) was stirred at room temperature for 10 days; further portions of hydroxylamine hydrochloride (0.2 g) and resin (0.2 g) were added at 2 day intervals. The resin was filtered off, then the filtrate was evaporated to dryness, and a solution of the residue in chloroform–methanol (9:1) was filtered through silica gel. The product formed *needles* (1.1 g, 44%), m.p. 149—150 °C (decomp.) (from methanol) (Found: C, 52.35; H, 4.8; N, 11.0%; M^+, 252. $C_{11}H_{12}N_2O_3S$ requires C, 52.35; H, 4.8; N, 11.1%; *M*, 252); $\nu_{max.}$ 2 700br (OH) and 1 725 cm^{-1} (C=O); δ 3.75, 4.15 (AB quartet, *J* 16 Hz, 8-CH_2), 5.00 (s, 6-H), and 12.27 (br s, OH).

2,5-*Dihydro*-2-*phenylpyrazolo*[3′,4′:5,6]*thiopyrano*[3,4-b]-*pyridin*-6-*ium*-3-*olate* (**15**).—A mixture of the enol ester (**4b**) (2.37 g) and phenylhydrazine (1.9 g) was kept at 100 °C until the vigorous reaction had ceased, then the cooled product was triturated with chloroform. The residual solid formed cream *needles*. Details of this, and of the similarly prepared 2,5-*dihydro*-2-*phenylpyrazolo*[3′,4′:5,6]*thiopyrano*[4,3-b] or [3,4-c] or [4,3-c]*pyridin*-6-*ium*-3-*olates* (**16**)—(**18**), are shown in the Table.

3-*Methoxy*-2-*phenyl*-5H-*pyrazolo*[3′,4′:5,6]*thiopyrano*[3,4-b]-pyridine (**14**).—Oil-free sodium hydride (0.24 g) and methyl iodide (0.42 g) were added successively to an ice-cold solution of the oxide (**15**) (0.8 g) in dry DMF (15 ml). After 5 min, water (35 ml) was added and the product was isolated by ether extraction. It formed pale pink *needles* (0.45 g, 53.5%), m.p. 146–147 °C (Found: C, 65.1; H, 4.55; N, 14.0%; M^+, 295. $C_{16}H_{13}N_3OS$ requires C, 65.05; H, 4.45; N, 14.2%; *M*, 295); no $\equiv\overset{+}{N}H$ absorption; δ (C_6D_6) 3.49 (s, OMe) and 4.00 (s, 5-CH_2).

8H-*Thiopyrano*[3,4-b]*pyridin*-5(6H)-*one* (**4a**).—A solution of the enol ester (**4b**) (2.37 g) in 2M-hydrochloric acid (25 ml) was heated under reflux for 3 h, then cooled and neutralised with solid sodium hydrogen carbonate. Extraction with ether, passage of the dried ethereal solution through a short column of alumina, and evaporation of the solvent, gave cream *needles* (1.24 g, 75%) (from ethyl acetate–light petroleum). The *oxime* had m.p. 193—195 °C (decomp.) (from ethanol–water). Details of ketone (**4a**), and of the related compounds (**5a**)—(**7a**), are shown in the Table.

Acknowledgements

We warmly thank the S.E.R.C. for a Studentship (to J. G.).

References

1 D. S. Tarbell in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, 1951, vol. 2, ch. 14.
2 S. W. Schneller, *Adv. Heterocycl. Chem.*, 1975, **18**, 59.
3 O. Mumm, K. Behrens, A. von Fischer-Treuenfeld, G. Hingst, W. Lund, O. Mrozek, J. Sönksen, and O. Tonn, *Justus Liebigs Ann. Chem.*, 1925, **443**, 272.
4 M. R. Barkhudaryan, D. O. Sapondzhyan, and S. A. Vartanyan, *Arm. Khim. Zh.*, 1974, **27**, 56 (*Chem. Abstr.*, 1974, **81**, 49594).
5 A. K. Kiang and F. G. Mann, *J. Chem. Soc.*, 1951, 1909.
6 *E.g.* P. Cagniant and C. Cagniant, *Bull. Soc. Chim. Fr.*, 1959, 1998.
7 R. M. Scrowston and D. C. Shaw, *J. Chem. Soc., Perkin Trans. 1*, 1976, 749.
8 C. Van der Stelt, P. S. Hofman, A. B. H. Funcke, and W. Th. Nauta, *Arzneim.-Forsch.*, 1968, **18**, 756 (*Chem. Abstr.*, 1968, **69**, 86780).
9 W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, 1959, **81**, 4004.
10 G. E. Dunn and H. F. Thimm, *Can. J. Chem.*, 1977, **55**, 1342.
11 D. J. Cook and R. S. Yunghans, *J. Am. Chem. Soc.*, 1952, **74**, 5515.
12 M. Delépine, *Bull. Soc. Chim. Fr.*, 1927, **41**, 390.
13 K. Schofield, 'Hetero-aromatic Nitrogen Compounds. Pyrroles and Pyridines,' Butterworths, London, 1967, ch. 5.
14 F. A. Daniher, B. E. Hackley, and A. B. Ash, *J. Org. Chem.*, 1966, **31**, 2709.
15 L. Bauer and L. A. Gardella, *J. Org. Chem.*, 1963, **28**, 1323.
16 I. C. Smith and W. G. Schneider, *Can. J. Chem.*, 1961, **39**, 1158.
17 Y. Suzuki, *Pharm. Bull. (Tokyo)*, 1957, **5**, 78 (*Chem. Abstr.*, 1958, **52**, 1167).
18 J. M. Bobbitt and D. A. Scola, *J. Org. Chem.*, 1960, **25**, 560.

Received 23*rd November* 1983; *Paper* 3/2079