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N-Quaternary Compounds

Part VI. Pyridinium-3-oxides

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Various synthetic approaches to 2-alkyl- or aryl-thio-1-alkyl-pyridinium-3-oxides are discussed. Alkylation of 3-hydroxy-2-alkylthio or 2-bromopyridines with methyl iodide leads to *N*-alkylation. With an alkylthiopyridine some transalkylation on the sulphur occurred. *O*-Alkylation becomes the more important pathway with bulky alkylating agents such as iodoacetate. UV absorption data are discussed.

In connection with our studies of dihydrothiazolo[3,2-a]pyridinium-8-oxides[1] we have also prepared some pyridinium analogues lacking the thiazoline ring. The synthetic pathways are illustrated below. The thiolactam (I) was *S*-alkylated using an alkyl halide in aqueous alkali or in a higher boiling solvent in the absence of a base. The alkylation occurs exclusively on the sulphur atom as this is the strongest nucleophile present in the molecule. Direct *S*-arylation requires that the leaving group in the arene is highly activated towards nucleophilic substitution. Such derivatives, however, are easily obtained by treating the bromo compound (IV) with a thiophenoxide.

Treatment of the bromo compound (IV) with methyl or ethyl iodide in DMF at 70° furnished the quaternary derivative (V). On the other hand treatment of IV with diazomethane in ether/*tert* butanol at −15° resulted in *O*-methylation in 90 % yield. These results parallel the behaviour of 3-hydroxypyridine which is mainly *N*-alkylated using dimethyl sulphate or methyl iodide. With diazomethane *O*-alkylation is favoured at low temperature.[2]

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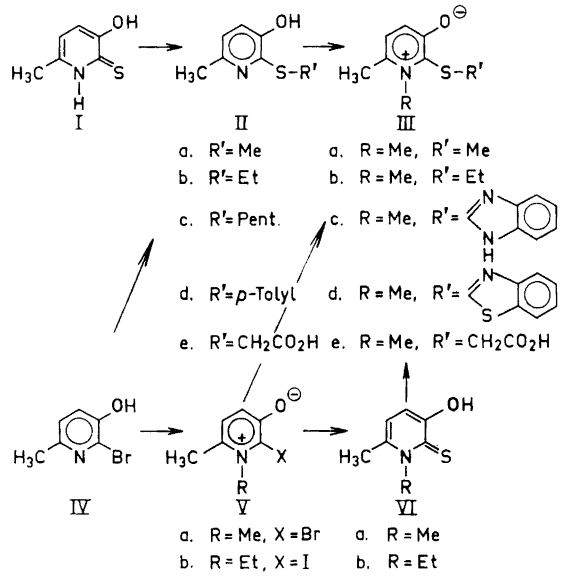
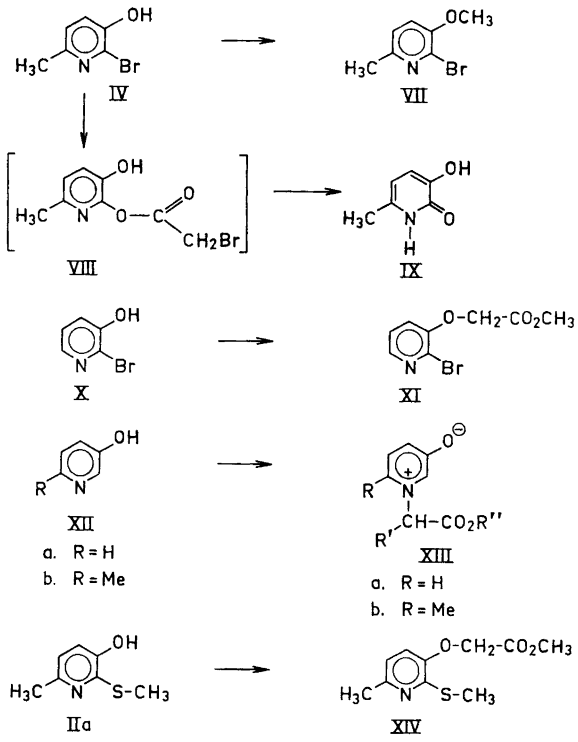


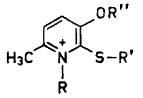
Apart from differences in the nature of the alkylating reagent, the different positional reactivities in the molecule might very well be due to variations in the ionic state of the molecule depending on temperature and polarity of solvent used.[3,4] Besides the expected differences in solubilities the methylated products (V and VII) were identified by UV and NMR data. Thus the product from methyl iodide showed a bathochromic UV shift of about 30 units (Table 2) on going from acidic to alkaline solution. The diazomethane product showed a blue shift of 15 units on going from acidic to alkaline solution.

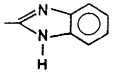
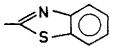
Heating IV with bromoacetic acid in chlorobenzene yielded the lactam (IX) presumably arisen *via* VIII. No *O*- or *N*-alkylated product was obtained. The failure to obtain quaternisation is largely due to the two *ortho* substituents in the pyridine and the bulkiness of the bromoacetic acid molecule. To make the access to the nucleophilic nitrogen easier the methyl group was removed. Thus X as the sodium salt in ethanol was treated with methyl iodoacetate. Preparatively only the *O*-alkylated product (XI) was obtained. Chromatography showed that only small amounts of other products were formed. The structure of the product obtained was evident from a blue shift in UV (300→285 mμ) on going from an acidic to alkaline solution. The structure was further confirmed by solubilities and by the chemical shift in NMR of the methylene protons in the acetic acid moiety. These were found at 4.83 τ as expected for an *O*-methylene group and at a higher field than when attached to a quaternary nitrogen as in XVIII. As pointed out above, dimethyl sulphate treatment of 3-hydroxypyridine in alkaline solution results almost exclusively in *N*-alkylation. Similarly both 3-hydroxypyridine and 3-hydroxy-6-methylpyridine (XII) are readily *N*-alkylated by the bulky α-bromo or iodo-carboxylic esters to furnish XIII.[5] Therefore, since IV as shown above, is *N*-



alkylated by primary alkyl halides, the *N*-deactivation observed in IV in the case of α-bromo or iodo-carboxylic esters is mainly steric in nature, *i.e.* the size of the bromine atom blocks the approach of the alkyl halide to the annular nitrogen resulting in preferential *O*-alkylation. This conclusion is further supported by alkylation experiments on the thioether IIa as discussed below. In the product obtained from the alkylation of IV with ethyl iodide the nuclear bromine had been exchanged by an iodine atom. It seems most likely that the exchange reaction occurs after the quaternisation since the bromine atom is then more activated towards nucleophilic displacement and can be replaced by a such strong nucleophile as the iodide ion. With methyl iodide as the alkylating agent the bromine was not replaced. However, such a replacement of bromine by iodide ions in the above type of reaction will always be a matter of degree depending on experimental conditions used. Thus the mass spectra of the iodo product formed (Vb) and the bromo product (Va) showed these to contain some bromo and iodo analogues, respectively. Such halogen exchange reactions are known from the literature. Thus the bromine atom in 1-ethyl-2-bromopyridinium bromide is displaced by iodide ion.[6] But when the weaker nucleophile was the anion such as in the case of 1-benzyl-2-iodopyridinium bromide the iodine was not displaced by bromide ion.[7]

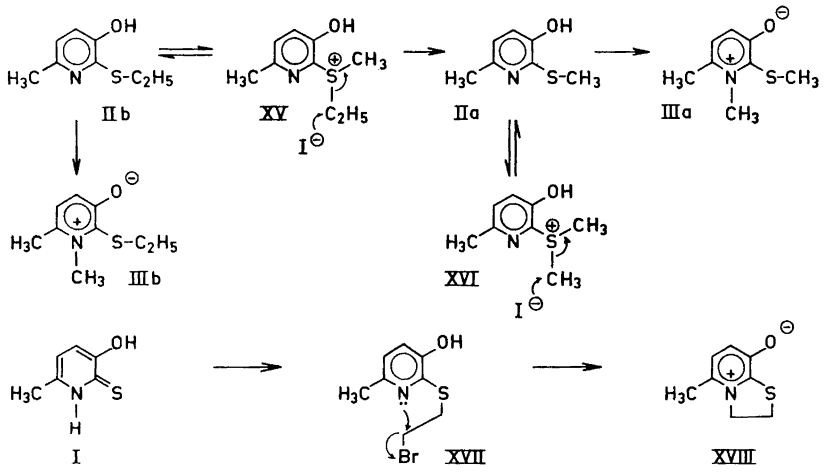
The *N*-alkylated thiolactam (VI) is available from V by potassium hydrogen sulphide treatment in DMF at 80°. *S*-Alkylation of VI will then furnish quater-

Table 1. UV Absorption of 

Comp.	Substituents			0.1 N NaOH						0.1 N HCl					
	R	R′	R″	λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε
IIa	—	Me	H	325	3.96			250	3.86	325	3.95			240	3.58
IIb	—	Et	H	325	3.94			250	3.85	325	3.90			240	3.55
IIc	—	Pent.	H	325	3.94			250	3.86	325	3.90			240	3.50
IId	—	*p*-Tolyl	H	325	3.86			245	4.10	330	3.75	305	3.80	240	3.91
IIe	—	CH_2CO_2H	H	325	3.95			250	3.86	325	3.94			240	3.57
I	—	H	H	370	3.80	265	3.71	245	3.76	355	4.10			260	3.78
VIa	Me	—	H	370	3.98	270	3.65	245	3.68	350	4.10			260	3.68
VIb	Et	—	H	375	4.14	270	3.81	250	3.74	355	4.11			260	3.70
IIIa	Me	Me	H	355	3.90			255	3.86	325	3.86			—	—
IIIb	Me	Et	H	355	3.90			255	3.87	325	3.85			—	—
IIIe	Me	CH_2CO_2H	H	355	3.97			255	3.89	325	3.97			—	—
IIIc	Me		H	355	4.03			275	4.17	325	4.11			280	4.09
IIId	Me		H	365[a]	3.95			280	4.11						
XIV	—	Me	CH_2CO_2Me	305	3.76			245	3.75	335	3.85			245	3.41

[a] Measured in ethanol since the compound was not soluble in 0.1 N NaOH.

nary compounds of type III. Thus 1,6-dimethyl-3-hydroxypyrid-2-thione (VIa) as the sodium salt in methanol was *S*-alkylated using ethyl iodide. This alkylation takes place under fairly mild conditions. To our knowledge no transalkylation of an alkyl group on the nitrogen in thiolactams have been recorded nor have we observed any such tendency. The above reaction, therefore, leads exclusively to *S*-alkylation in contrast to the alkylation of the thioether (II) in which case exchange on sulphur might occur. Thus when 2-ethio-3-hydroxy-6-methylpyridine (IIb) was quaternized with methyl iodide the product was found by chromatography to consist of two components in the ratio 3:2, the major component being the desired compound (IIIb). The minor component was identified as 1,6-dimethyl-3-hydroxy-2-methiopyridinium iodide (IIIa). Therefore, the thioether sulphur in II is as good a nucleophilic site as is the pyridine nitrogen in this alkylation if it is assumed that the *S*-transalkylation occurs mainly before *N*-quaternisation. This seems a reasonable assumption to make since the nucleophilicity of the sulphur should be reduced after *N*-quaternisation because of the now electron deficient pyridinium ring to which the sulphur is directly attached.



In the absence of steric effects *N*-alkylation of the thioether (II) should proceed readily due to the presence in the molecule of strongly electron donating groups. These groups will increase the electron density on the annular nitrogen and therefore the nucleophilicity. The sulphur of the thioether will be the strongest electron donor to the annular nitrogen. Despite this the quaternisation of IIb is much more difficult to effect and the reaction rate is very much decreased as compared with the desthioether pyridine (XII). This clearly shows that steric effects dominate completely over electronic effects. When the alkylating agent becomes more bulky as in the case of methyl iodoacetate, *N*-alkylation no longer occurs. The product obtained was identified by NMR and UV as the *O*-alkylated derivative (XIV).

In sharp contrast to the unwillingness of II to undergo *N*-quaternisation stand the corresponding reactions leading to the cyclic dihydrothiazolo[3,2-a]-

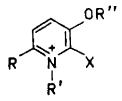
pyridinium derivatives (XVIII). In the reaction between the thione (I) with a 1,2-bifunctional ethylene derivative such as 1,2-dibromoethane, intermediates of type XVII are formed but have not been isolated as the reactions proceed all the way to XVIII. In this case, however, the alkylating agent is already present in the molecule at the right proximity for the condensation to occur and does not have to overcome the same steric hindrance on approaching the nucleophilic center as does an external reagent.

Treatment of the halopyridinium compounds (V) with alkyl or arylthioxide in methanol furnished the quaternary thioethers (III) in high yields. This constitutes the simplest method for the synthesis of type III compounds.

UV absorption data are collected in Tables 1 and 2. Simple *S*-alkyl pyridines (II) absorb at 325 mμ in 0.1 N NaOH. The position of this long-wave absorption band is not changed in acid solution. The thiolactam (I) and its *N*-alkylated derivatives (VI) have the same absorption bands as would be expected. These bands are at higher wavelengths than for the *S*-alkyl derivatives (II). When both the nitrogen and the sulphur are alkylated the long-wave absorption in alkaline solution is at 355 mμ and therefore in between the values for the *N*-alkylated and *S*-alkylated derivatives. In acid solution this band is found at 325 mμ as in the case of the *S*-alkylated derivatives, since when II is protonated on the nitrogen it becomes electronically similar to III.

The *O*-alkylated product (XIV) has different absorption bands and can therefore readily be distinguished from compounds of the quaternary type (III).

One might expect that the 5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide (XVIII) should have the same absorption bands as IIIa. But these absorptions are found at 5—15 units higher wave-lengths,[1] *viz.* at 360 and 340 mμ in alkaline and acidic solutions, respectively. This is possibly due to some form of ring current through the thiazolinium ring system.

Table 2. UV Absorption of 

Comp.	Substituents				0.1 N NaOH aq.				0.1 N HCl aq.			
	R	R′	R″	X	λ	log ε	λ	log ε	λ	log ε	λ	log ε
IV	Me	—	H	Br	310	3.77	245	4.05	300	3.97	230	3.78
VII	Me	—	CH_3	Br	285	3.82	225	3.87	300	3.91	230	3.74
XI	H	—	CH_2CO_2Me	Br	285	3.83	225	3.84	300	3.72		
Va	Me	Me	H	Br	340	4.08	—	—	310	4.09	225	4.30
Vb	Me	Et	H	I	345	4.03	225	4.39	320	4.08	220	4.27

EXPERIMENTAL

Paper chromatography and TLC in silica gel in BuOH:EtOH-NH_3:H_2O (4:1:2:1) and BuOH:HOAc:H_2O (100:22:50) were used in this work. The UV data were recorded on a Beckmann DB—G UV spectrophotometer.

2-Ethio-3-hydroxy-6-methylpyridine (IIb). a) Ethyl iodide (117 g, 0.75 mole) was added dropwise over 15 min to a stirred solution of 3-hydroxy-6-methylpyrid-2-thione (70.6 g, 0.5 mole) in 1 N NaOH aq. (750 ml, 0.75 mole) at 40°. The reaction was kept at 40° for 2 h and allowed to stand at room temperature overnight. The pH was then adjusted to 5.3 with dilute HCl and the oily suspension extracted with ether. The combined ether extracts (in all 750 ml) was washed with water, dried, evaporated and the residual oil distilled to furnish a yellowish oil, b.p. 120—130°/0.05 mm, 66.1 g (72%) which crystallized on cooling. Recrystallisation from petroleum ether (b.p. 60°) gave white crystals, m.p. 47—49°.

b) A solution of ethyl iodide (3.44 g, 0.022 mole) and 3-hydroxy-6-methylpyrid-2-thione (2.82 g, 0.02 mole) in dry benzene (75 ml) was refluxed for 48 h. A reddish-brown oil separated gradually from the solution. After cooling, the benzene layer was decanted, the semisolid dried *in vacuo*, dissolved in water (50 ml) at 70°, the solution treated with a little charcoal, and finally concentrated to about 10 ml when the hydroiodide crystallized out (2.55 g, 43 %), m.p. 124—128°. Further recrystallisation from acetic acid gave m.p. 126—128°. (Found: C 32.35; H 4.11; N 4.83; S 10.68. Calc. for $C_8H_{11}NOS \cdot HI$: C 32.32; H 4.07; N 4.71; S 10.79).

The free base was generated by dissolution in water and neutralization with sodium hydroxide and found to be identical with that prepared in aqueous NaOH.

3-Hydroxy-6-methyl-2-methiopyridine (IIa). Methyl iodide (25.5 g, 0.18 mole) was added dropwise (15—20 min) at room temperature to a vigorously stirred solution of 3-hydroxy-6-methylpyrid-2-thione (21.5 g, 0.15 mole) in N NaOH aq. (180 ml, 0.18 mole). After stirring for 2 h the pH of the resultant suspension (pH 10.2) was adjusted to 8.5 with dilute HCl and the solid filtered off; yield: 21.0 g (90 %). For analysis the product was further purified by vacuum sublimation or by recrystallisation from water; m.p. 127—129° (subl.). (Found: C 53.80; H 5.69; N 8.96; S 20.80. Calc. for C_7H_9NOS: C 54.18; H 5.84; N 9.03; S 20.65).

3-Hydroxy-6-methyl-2-pentylthiopyridine (IIc). 1-Iodopentane (49.5 g, 0.25 mole) and 3-hydroxy-6-methylpyrid-2-thione (28.2 g, 0.2 mole) were heated together in acetonitrile (300 ml) at 80° for 4 h, the solution evaporated at reduced pressure, water (100 ml) added, the pH of the suspension brought to 7 with 10 N NaOH (in all 25 ml) and extracted with ethyl acetate (5 × 40 ml). The dried acetate solution was evaporated and the residual oil distilled to give a pale yellow oil, b.p. 120—150°/1.5 mm Hg which solidified; yield: 26.7 g (63 %), m.p. about 34°. (Found: C 62.76; H 7.76; N 6.99. Calc. for $C_{11}H_{17}NOS$: C 62.52; H 8.10; N 6.63).

2-Carboxymethio-3-hydroxy-6-methyl-pyridinium bromide (IIe). Bromoacetic acid (16.6 g, 0.12 mole), dissolved in 50 ml dry chlorobenzene was added dropwise over 1 h at 132°C to a vigorously stirred solution of 3-hydroxy-6-methylpyrid-2-thione (11.0 g, 0.088 mole) in 250 ml dry chlorobenzene. A pale yellow solid precipitated gradually during the addition. The solution was refluxed for another 2 h under dry conditions, then allowed to stand at room temperature overnight. The precipitate was removed by filtration; 21 g crude product (94 % yield), m.p. 148—165°C. The hydrobromide thus obtained could be recrystallized from hot glacial acetic acid. An analytical sample had m.p. 168—170°. (Found: C 34.55; H 3.67; N 5.12. Calc. for $C_8H_9NO_3S$,HBr: C 34.31; H 3.60; N 5.00).

*3-Hydroxy-6-methyl-2-*p*-tolylthiopyridine (IId).* *p*-Methyl-thiophenol (14.8 g, 0.12 mole) and 2-bromo-3-hydroxy-6-methylpyridine (18.8 g, 0.1 mole) in ethanolic sodium ethoxide (500 ml; from 2.76 g of sodium (0.12 mole)) were heated at reflux for 24 h, another 2.8 g of the thiol added and the heating continued for another 24 h. The reaction mixture was then evaporated, the residue treated with water (50 ml) and the mixture acidified with acetic acid (10 ml). The greyish-white solid obtained (18.3 g, 79 %) melted at 135—137°. The analytical sample was recrystallized from ligroin, m.p. 139—141°. (Found: C 67.46; H 5.69; N 6.01. Calc. for $C_{13}H_{13}NOS$: C 67.50; H 5.66; N 6.05).

2-Bromo-3-methoxy-6-methylpyridine (VII). A solution of 2-bromo-3-hydroxy-6-methylpyridine (4.0 g, 0.021 mole) in *tert.*-butanol (100 ml) was added dropwise over

5½ h to a stirred solution of diazomethane (3.5 g) in ether (150 ml) at −15°. After stirring for another 20 min the solution was evaporated at reduced pressure, the residue dissolved in ether (50 ml), a little insoluble material removed by filtration, the ether evaporated, and the residue crystallized from water; yield: 3.8 g (90 %), m.p. 54°. (Found: C 41.52; H 4.02; N 6.84. Calc. for C_7H_8BrNO: C 41.78; H 4.01; N 6.96).

2-Bromo-1,6-dimethyl-3-hydroxypyridinium iodide (Va). 2-Bromo-3-hydroxy-6-methylpyridine (54.6 g, 0.3 mole) was dissolved in dry DMF (250 ml) and methyl iodide (57.0 g, 0.4 mole) added. The solution, in a thick-walled sealed 500 ml flask, was heated in an oil bath at 70° for 2 days. The precipitated solid was removed by filtration, washed well with MeOH yielding the desired product (73 g, 74 %), m.p. 231−233°, which was used directly in successive syntheses without further purification. An analytical sample recrystallized from water had m.p. 234−235°. (Found: N 4.34. Calc. for C_7H_9BrINO: N 4.24).

A similar synthesis in MeOH instead of DMF with 3 equivalents of methyl iodide furnished 64 % of the desired product

1-Ethyl-3-hydroxy-2-iodo-6-methylpyridinium iodide (Vb). A solution of 2-bromo-3-hydroxy-6-methylpyridine (18.8 g, 0.1 mole) and ethyl iodide (23.5 g, 0.15 mole) in dry DMF (120 ml) was heated in a pressure bottle (500 ml) at 90° for 48 h. More ethyl iodide (15.6 g, 0.1 mole) was added and the heating resumed for another 24 h. The solution was then evaporated to dryness and the residue dissolved in ethanol (20 ml). A greyish-brown solid (9.2 g, 27 %) crystallized out, m.p. 182−185°. Recrystallisation twice from methanol (charcoal treatment) gave the white crystalline pyridinium salt, m.p. 187−192°. (Found: C 24.97; H 3.04; N 3.29. Calc. for $C_8H_{11}I_2NO$: C 24.57; H 2.83; N 3.58).

Attempted quaternisation using bromoacetic acid: formation of 3-hydroxy-6-methyl-pyrid-2-one (IX). 2-Bromo-3-hydroxy-6-methyl-pyridine (5 g, 0.026 mole) was dissolved in chlorobenzene (190 ml) and 15 ml of the solution distilled off to remove any moisture before bromoacetic acid (5.39 g, 0.039 mole) was added and the solution refluxed for 26 h. A fine crystalline solid was slowly formed which was found to be the hydrobromide of the bromopyridinol. Concentration of the filtrate to 35 ml furnished a second crop, in all 3.1 g. Evaporation of the filtrate to 10 ml furnished 130 mg of a material which after 2 recrystallisations from ethanol had m.p. 192−194°. This substance has been identified as 2,3-dihydroxy-6-methylpyridine. (Found: C 57.39; H 5.75; N 10.93. Calc. for $C_6H_7NO_2$: C 57.58; H 5.64; N 11.20).

1,6-Dimethyl-3-hydroxypyrid-2-thione (VIa). 2-Bromo-1,6-dimethyl-3-hydroxypyridinium iodide (25 g, 0.075 mole) was added in small portions to a stirred solution of potassium hydrogen sulphide (13.5 g, 0.19 mole) in dry DMF (500 ml) at 80°. After 1 h the DMF was distilled off at reduced pressure at about 80°. The residual brown solid was triturated with water (100 ml) and the pH brought to 6.5 with acetic acid. The pale grey solid, after filtering, washing and drying, weighed 10.9 g (94 %), m.p. 140−150° with sublimation occurring from 110°. This substance was chromatographically homogeneous. An analytical sample, recrystallized twice from methanol, melted at 151−154° with sublimation occurring from 105°. (Found: C 53.70; H 5.72; N 9.01. Calc. for C_7H_9NOS: C 54.17; H 5.84; N 9.02).

1-Ethyl-3-hydroxy-6-methylpyrid-2-thione (VIb). 2-Bromo-1-ethyl-3-hydroxy-6-methylpyridinium iodide (25.8 g, 0.075 mole) was added portionwise at 80° to a stirred solution of potassium hydrogen sulphide (16.2 g, 0.225 mole) in dry DMF (1000 ml). After stirring for 2 h at 80° the DMF was distilled off at reduced pressure and the residue triturated with water (100 ml) the pH being adjusted to 6.5 with acetic acid. The pale grey solid weighed 11.2 g (88 %), m.p. 89−94°, and was chromatographically homogeneous. The very pale yellow analytical sample, recrystallized twice from ligroin, had m.p. 91−93°. (Found: C 56.81; H 6.39; N 8.17. Calc. for $C_8H_{11}NOS$: C 56.75; H 6.55; N 8.34).

1,6-Dimethyl-2-ethio-3-hydroxypyridinium iodide (IIIb). a) 2.4 N Sodium methylate (28.7 ml, 0.066 mole) was added to a solution of 1,6-dimethyl-3-hydroxypyrid-2-thione (8.55 g, 0.055 mole). To the resultant solution was added ethyl iodide (10.3 g, 0.066 mole) and the solution refluxed for 3 h when more ethyl iodide (1.0 g, 0.0064 mole) was added and the heating continued for another hour. The methanol was then evaporated, the residue dissolved in water (25 ml) and the pH adjusted to 1 with hydrochloric acid. The hydroiodide (12.4 g, 73 %) slowly crystallized out, m.p. 180−181°. Recrystallization from water gave m.p. 184−186°. (Found: C 34.79; H 4.43; N 4.71. Calc. for $C_9H_{13}NOS \cdot HI$: C 34.73; H 4.53; N 4.50).

b) A solution of 2-ethio-3-hydroxy-6-methylpyridine (22 g, 0.13 mole) in methyl iodide (100 ml) was refluxed for 44 h. The precipitated solid (22.1 g) was found chromatographically to consist of two compounds in the ratio 3:2, the major product being the desired compound, the minor product being 1,6-dimethyl-3-hydroxy-2-methiopyridinium iodide (IIIa). This was less soluble in ethanol than the title compound and was obtained in pure form after three recrystallizations from ethanol, m.p. 190—193°. (Found: C 32.48; H 4.20; N 4.80. Calc. for $C_8H_{11}NOS \cdot HI$: C 32.44; N 4.08; N 4.73).

1,6-Dimethyl-2-(2-thiobenzimidazolyl)pyridinium-3-oxide (IIIc). 2.2 N Methanolic sodium methoxide (17 ml, 0.039 mole) was added to 2-bromo-1,6-dimethyl-3-hydroxypyridinium iodide (13.6 g, 0.043 mole) in dry methanol (200 ml). Similarly 2.2 N methanolic sodium methoxide (19 ml, 0.043 mole) was added to 2-mercaptobenzimidazole (6.19 g, 0.043 mole) in methanol (50 ml). The benzimidazole solution was then added dropwise (30 min) with stirring to the boiling solution first prepared. The reaction mixture was then refluxed for 5 h and the yellow solid formed (9.2 g, 82 %) filtered from the cooled (35—40°) solution, m.p. 239—240° (decomp.). An analytical sample recrystallized from ethanol had m.p. 252—253°. (Found: C 61.81; H 5.12; N 15.41; S 11.82. Calc. for $C_{14}H_{13}N_3OS$: C 61.97; H 4.83; N 15.49; S 11.81).

1,6-Dimethyl-2-(2-thiobenzothiazolyl)pyridinium-3-oxide (IIId). 2-Mercaptobenzothiazole (5.0 g, 0.03 mole) was dissolved in dry methanol (50 ml) containing one equivalent of sodium methoxide. This solution was added slowly with stirring to a refluxing suspension of 2-bromo-1,6-dimethyl-3-hydroxypyridinium iodide (9.9 g, 0.03 mole) and methanol (160 ml) containing 0.03 mole of sodium methoxide. The reaction was refluxed for 4 h, allowed to cool and the solid collected by filtration. A second crop was obtained by concentration of the filtrate. The combined solid fractions were triturated with warm water (3×20 ml), yield 5.8 g (67 %), m.p. 220—225°. An analytical sample recrystallized from ethanol melted at 233—237°. (Found: C 58.10; H 4.35; N 9.69; S 22.20. Calc. for $C_{14}H_{12}N_2OS_2$: C 58.30; H 4.20; N 9.71; S 22.24).

2-Carboxymethio-1,6-dimethylpyridinium-3-oxide (IIIe). The disodium salt of mercapto acetic acid was prepared by adding 2 N methanolic sodium methoxide (50 ml, 0.1 mole) to an ethanolic (20 ml) soluton of mercapto acetic acid (4.6 g, 0.05 mole). Another solution was prepared by adding 2-bromo-1,6-dimethyl-3-hydroxypyridinium iodide (16.5 g, 0.05 mole) to dry ethanol (670 ml) and then 2 N methanolic sodium methoxide (22.5 ml, 0.045 mole). The first solution was added dropwise with stirring to the pyridinium solution and the reaction refluxed for 6 h. The reaction mixture was then evaporated, the residual material dissolved in water (70 ml) and the pH adjusted to 4.0 with 2 N HCl when the desired compound was precipitated mainly as the hydroiodide (7.5 g, 34 %), the hydroiodic acid obviously coming from the sodium iodide when treated with HCl.

The free base was obtained by dissolving the hydroiodide salt (1.0 g) in water (100 ml), adjusting the pH to 5.0 and extracting with 90 % phenol (3×20 ml). The phenol extracts were washed several times with water until the washings were free from halide ions. The phenol was then diluted with ether (120 ml) when a water layer was formed. The water phase was separated and the phenol layer extracted with water (3×25 ml). The combined water layer and extracts was washed with ethyl ether (3×20 ml) to remove any phenol and then lyophilized yielding the desired solid (0.69 g) which after recrystallisation from ethanol had m.p. 179—180°. (Found: C 50.89; H 5.32; N 6.63; S 15.40. Calc. for $C_9H_{11}NO_3S$: C 50.69; H 5.20; N 6.57; S 15.03).

3-Methylcarboxymethoxy-2-methio-6-methylpyridine (XIV). Methanolic sodium methoxide (24 ml, 0.053 mole) was added to a solution of 3-hydroxy-2-methio-6-methylpyridine (7.2 g, 0.048 mole) and methyl iodoacetate (10.1 g, 0.050 mole) in dry methanol (180 ml). The solution was refluxed for 72 h. Paper chromatography showed a nearly homogeneous product. The reaction mixture was evaporated, the residue extracted with boiling methyl acetate (2×20 ml), the extracts evaporated and the residue crystallized by trituration with water. White needles from dilute methanol; yield 6.8 g (62 %), m.p. 74—75°. (Found: C 52.84; H 5.95; N 6.20; S 14.14. Calc. for $C_{10}H_{13}NO_3S$: C 52.85; H 5.76; N 6.16; S 14.11). NMR (TFA): 7.22 τ (S—Me), 7.15 τ (6—Me), 5.97 τ (OMe), 4.92 τ (OCH_2), 2.28 τ and 2.51 τ (H_4 and H_5, AB, J=9.0 cps). IR (KBr): No OH-band. Ester carbonyl at 1730 cm^{-1}.

The acid was obtained by hydrolysis in N HCl and heating for 1 h. Evaporation, dissolution in water, the passage of the aqueous solution through DEAE-sephadex and elution with aqueous formic acid furnished the acid of the pyridine base. The analytical sample, recrystallized from water, melted at 96—97°. (Found: C 50.67; H 5.21; N 6.93. Calc. for $C_9H_{11}NO_3S$: C 50.69; H 5.20; N 6.57).

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