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N-Quaternary Compounds

Part VII. *N*-Oxides of 3-Hydroxypyridines

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Electrophilic substitution in 3-hydroxypyridine 1-oxides first takes place in the 2-position, then in the 4- or 6-position. A bromine atom in the 2- or 4-position was substituted by mercaptide ions, while the nitro group was not displaced. 3-Hydroxy-1-methoxypyridinium methyl sulphate was substituted selectively in the 2-position when treated with the sodium salt of butanethiol in DMF.

In connection with our studies of *N*-quaternary structures derived from 3-hydroxypyridines [1] we have also studied corresponding pyridine *N*-oxides.

The *N*-oxidation of I was carried out with hydrogen peroxide in acetic acid at 70°. The oxidation is a result of a bond formation between the lone pair of electrons on the annular nitrogen atom and the electron deficient hydroxyl group in the peracid. Consequently, the rate of the reaction will be subject to steric hindrance and will depend on the basicity of the annular nitrogen atom besides the electron withdrawing activity of the acyl group.

I	R = H,	R′ = H	VI	R = H,	R′ = H
II	R = Me,	R′ = H	VII	R = Me,	R′ = H
III	R = H,	R′ = Me	VIII	R = H,	R′ = Me
IV	R = H,	R′ = Br	IX	R = H,	R′ = Br
V	R = Me,	R′ = Br	X	R = Me,	R′ = Br

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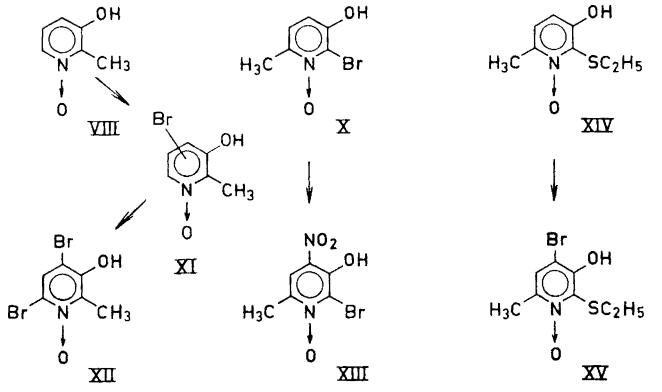
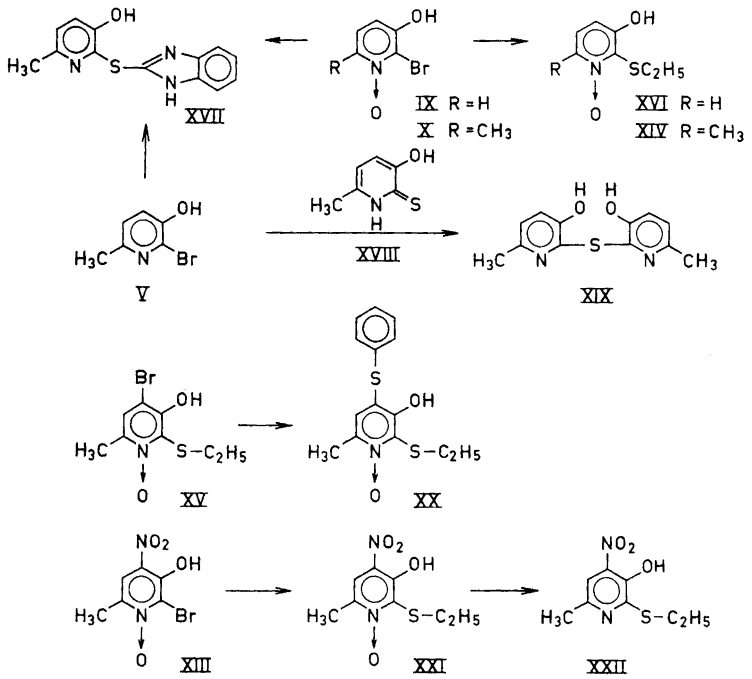
Modena and Todesco [2] have found that the electron donating properties of a methyl group in the 2-position increases the basicity of the annular nitrogen atom to such an extent that this dominates over the steric hindrance introduced and thus promotes *N*-oxidation. In agreement with this the two methyl derivatives (II and III) reacted readily with peracetic acid as above. This is not true with a bromine atom in an *ortho* position. Both the negative inductive effect of the bromine and perhaps the more important large spatial hindrance of the bromine atom introduced, would tend to make the molecule more resistant to oxidation. Thus the two bromo compounds (IV and V) resisted *N*-oxidation with hydrogen peroxide in acetic or formic acid. However, by increasing the activity of the peracid as in the case of pertrifluoracetic acid generated *in situ* from hydrogen peroxide and trifluoroacetic acid, the oxidation could readily be effected.

Nitration is the best studied electrophilic substitution in pyridine 1-oxides. Substitution in the 4-position is favoured.[3] But with a hydroxyl group in the 3-position the orienting effect of the latter predominates over that of the *N*-oxide group and the positions *ortho* and *para* to the hydroxyl group are nitrated as in 3-hydroxypyridine itself.[4] Similarly, bromination of 3-hydroxypyridine 1-oxide has been reported to yield the 2-bromo derivative again as in the case of 3-hydroxypyridine itself.[5] A methyl group in the 6-position (VII) would not be expected to change this substitution pattern. If the 2-position is blocked by a methyl group, however, one could have substitution in the 4- or 6-position since both these positions are activated by both the hydroxyl group and the *N*-oxide group. Instead bromination, with bromine in pyridine or acetic acid at room temperature or at −10° in pyridine, gave largely the dibromo compound (XII). With both *ortho* positions occupied as in the case of X, nitration occurs in the 4-position. Similarly the thioether (XIV) was readily brominated with bromine in cold acetic acid. The thioether (XIV) itself was prepared from the bromo compound (X) by nucleophilic displacement using the sodium salt of ethanethiol in DMF at elevated temperature. The desmethyl derivative (XVI) was similarly obtained.

With 2-mercaptobenzimidazole reduction of the *N*-oxide occurred with the formation of the deoxygenated analogue (XVII). The reaction was also



attempted in other solvents with and without added base, but similar results were obtained. The deoxygenation was confirmed by identity with the compound synthesised from V. A second product isolated in the latter reaction was found to be the thioether (XIX) whose structure was confirmed by condensing the bromo compound (V) with 3-hydroxy-6-methylpyrid-2-thione (XVIII).

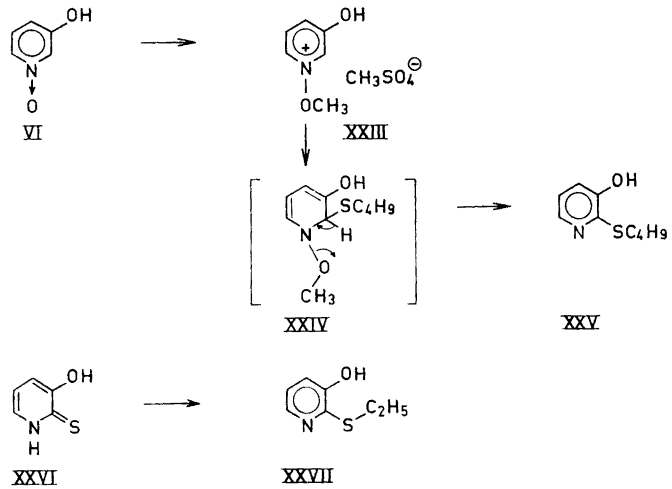


The bromine in XV, despite the presence of two strongly electron donating groups in addition to the methyl group, is sufficiently activated by the *N*-oxide group for nucleophilic displacement. Thus treatment of XV with the thiophenolate ion furnished the thioether (XX). In XIII either the 4-nitro group or the 2-bromo atom could in theory be replaced by a nucleophilic reagent. But it was found that with the sodium salt of ethanethiol in DMF the bromine was selectively replaced with the formation of XXI. With longer heating time in the presence of excess thiol partial reduction occurred with the formation of the deoxygenated compound (XXII). That this compound had mainly arisen by thiol reduction of XXI was shown chromatographically by heating the *N*-oxide (XXI) with two equivalents of the sodium salt of ethanethiol in DMF for 24 hours. About 70 % of the *N*-oxide had then been deoxygenated. This finding is perhaps surprising since the nitro group would have been expected to suffer ready displacement in the same way as the bromine in the corresponding bromo compound (XV) rather than reduction of the *N*-oxide grouping.

Since thiol compounds, sulphide and thiourea can be used for deoxygenation of aromatic *N*-oxides,[6] competitive deoxygenation as observed would be expected where the substitution rate is slow.

The order of the reactivity of a displaceable ring substituent [7] in the activated *ortho* or *para* positions in pyridine is $\equiv N^+-Me > \equiv N\rightarrow O > \equiv N$. Thus *N*-alkyl pyridinium salts are attacked by strong nucleophilic reagents in the *ortho* position.[8] The polarisation of the *N*-oxide group is not strong enough for such a nucleophilic attack on an unsubstituted *ortho* position. However, the *N*-quaternary structure is easily arrived at by *O*-acylation or *O*-alkylation of the *N*-oxide. Therefore 3-hydroxypyridine 1-oxide was *O*-methylated by heating with dimethyl sulphate. The 3-hydroxyl group did not react under the experimental conditions used. When the 1-methoxypyridinium derivative (XXIII) was treated with the sodium salt of butanethiol in DMF at 70—90° a homogeneous product was obtained. Therefore only one positional isomer was obtained. Bauer *et al.*[9] have reported that the product from the reaction of 1-alkoxypyridinium salts with propyl- and octylmercaptide ions consisted of pyridine and a mixture of 3- and 4-alkylthiopyridines, predominantly the 3-isomer.

Similarly, the 3-picoline *N*-oxides with propanethiol in the presence of benzenesulfonyl chloride produced a number of isomeric propyl mercaptopicolines.[10] Entry of the sulphide group took place in α- and β-positions and the methyl group seemed to exert little directive influence on this substitution. With 3-picoline 1-oxide about 50 % of the product obtained was substituted in the 2-position. These results stand in contrast to the total directive power found for the 3-hydroxyl group above.



The NMR spectrum of the isolated compound in TFA showed aromatic protons resonating at 1.82, 2.12, and 2.35 τ in an ABX system, the coupling constants being 2.0, 5.5, and 8.5 cps. The presence of only one low field proton

shows that the substitution must have taken place in an α-position to the annular nitrogen. The coupling constants are only compatible with the 2,3-disubstituted pyridine (XXV) indicated. This was further confirmed by the near identity in the aromatic region of the NMR spectra of XXVII synthesized by alkylation of the thiolactam (XXVI). The aromatic protons were found at 1.77 (H_6), 2.08 (H_4), and 2.30 τ (H_5), the couplings being 2.0 ($J_{4,6}$), 5.5 ($J_{5,6}$), and 8.5 cps ($J_{4,5}$).

The selective nucleophilic substitution in the 2-position can perhaps be explained by the 2-position being the position where the negative inductive effect of the annular nitrogen atom and the phenolic oxygen is most strongly felt and therefore the more activated of the *ortho* positions. If the reaction is formulated as an addition of the mercaptide ion (XXIV) followed by loss of methanol in a cyclic transition state, *para* substitution would be excluded.

EXPERIMENTAL

3-Hydroxy-6-methylpyridine 1-oxide (VII). 35 % Hydrogen peroxide (3 ml, 0.031 mole) was added to a solution of 3-hydroxy-6-methylpyridine (3.3 g, 0.03 mole) in acetic acid (18 ml) and the resultant solution heated at 70° for 3 h. Then another 3 ml of hydrogen peroxide was added and the heating at 70° continued for another 15 h. As chromatography showed the reaction was not complete, another 3 ml of hydrogen peroxide was added and the heating continued for another 2 h. The solution was then concentrated to about 10 ml, water (10 ml) added, the solution again concentrated and diluted with water. The *N*-oxide slowly crystallized on leaving the solution in the cold; yield 3.0 g (80 %), m.p. 189–191°. Recrystallisation from ethanol gave m.p. 195–196°. (Found: C 57.75; H 5.51; N 11.09. Calc. for $C_6H_7NO_2$: C 57.95; H 5.64; N 11.19).

3-Hydroxypyridine 1-oxide (VI) [11] was prepared as above in 71 % yield, m.p. 186–192°.

3-Hydroxy-2-methylpyridine 1-oxide (VIII) was prepared as above in 64 % yield, m.p. 230–231° after recrystallisation from dilute ethanol. (Found: C 57.84; H 5.51; N 11.04. Calc. for $C_6H_7NO_2$: C 57.59; H 5.64; N 11.19).

2-Bromo-3-hydroxypyridine 1-oxide (IX). 35 % Hydrogen peroxide (30 ml, 0.31 mole) was added to 2-bromo-3-hydroxypyridine (52.2 g, 0.3 mole) in trifluoroacetic acid (40 ml) and acetic acid (300 ml). The solid was gradually dissolved. After 3 days at room temperature another 30 ml of hydrogen peroxide was added, the solution left for another day when the oxide started crystallising out. The mixture was concentrated to about 150 ml and the solid filtered off; yield 21.2 g, m.p. 189–191°. Another 30 ml of hydrogen peroxide was added to the filtrate as chromatography showed this still to contain some unreacted pyridine base. After another day the solution was concentrated to half its volume when another crop (20.7 g, total yield 73 %) crystallised out, m.p. 185–188°. The analytical sample, recrystallised from water and acetic acid, melted at 188–193°. (Found: C 31.82; H 2.25; N 7.52. Calc. for $C_5H_4BrNO_2$: C 31.61; H 2.12; N 7.37).

2-Bromo-3-hydroxy-6-methylpyridine 1-oxide (X). 35 % Hydrogen peroxide (20 ml, 0.21 mole) was added to 2-bromo-3-hydroxy-6-methylpyridine (37.6 g, 0.2 mole) in trifluoroacetic acid (30 ml) and acetic acid (200 ml). The solid was gradually dissolved. After 3 days at room temperature another 20 ml of hydrogen peroxide were added, the solution left for another 3 days to complete the reaction, the solution concentrated at reduced pressure to about 50 ml and diluted with water (100 ml). A white crystalline solid (21.0 g), m.p. 196–197°, was deposited on standing. Concentrating the solution gave another 8.6 g (total yield 73 %). The white solid melted at 194–196° after recrystallisation from acetic acid and ethanol. (Found: C 35.67; H 3.00; N 7.00. Calc. for $C_6H_6BrNO_2$: C 35.32; H 2.96; N 6.86).

4,6-Dibromo-3-hydroxy-2-methylpyridine 1-oxide (XII). Bromine (1.76 g, 0.011 mole) in pyridine (20 ml) was added dropwise over 45 min at room temperature to a stirred solution of 3-hydroxy-2-methylpyridine 1-oxide (1.25 g, 0.01 mole) in pyridine (60 ml). The

reaction was kept at this temperature for another 2 h, evaporated at reduced pressure, the residue dissolved in water (10 ml) and the solution acidified with HCl. A greyish white solid was precipitated (0.80 g), m.p. 168—172°. Recrystallisation from ethanol gave m.p. 170—174°. (Found: C 25.24; H 1.96; N 4.96. Calc. for $C_6H_5Br_2NO_2$: C 25.60; H 1.78; N 4.96).

When the bromination was run at −10° or in acetic acid the same product was obtained.

2-Bromo-3-hydroxy-6-methyl-4-nitropyridine 1-oxide (XIII). To 2-bromo-3-hydroxy-6-methylpyridine 1-oxide (66.3 g, 0.33 mole) in acetic acid (500 ml) at 45° was added slowly with stirring a solution made from acetic anhydride (30 ml, 0.33 mole), conc. nitric acid (55 ml, 1.3 mole), conc. sulphuric acid (26 ml, 0.50 mole) and acetic acid (80 ml). The reaction was kept at 45° overnight, another 30 ml of nitric acid added slowly. When the gas evolution had ceased the reaction was heated at 60° for 2 h before evaporation at reduced pressure to a small volume. Dilution with water precipitated a yellow solid (22.5 g, 28 %), m.p. 159—163°. Recrystallisation from methanol gave m.p. 170—173°. (Found: C 28.87; H 2.16; N 11.05. Calc. for $C_6H_5BrN_2O_4$: C 28.95; H 2.02; N 11.25).

4-Bromo-2-ethio-3-hydroxy-6-methylpyridine 1-oxide (XV). Bromine (17.6 g, 0.11 mole) dissolved in acetic acid (200 ml) was added dropwise over 90 min at room temperature to a stirred solution of 2-ethio-3-hydroxy-6-methylpyridine 1-oxide (18.5 g, 0.10 mole) in acetic acid (150 ml). The resultant solution was stirred for another 2 h, evaporated at reduced pressure, the residue dissolved in water (100 ml) and the pH adjusted to 3.2 with 10 N NaOH aq. On standing in the cold, a white solid slowly crystallised out; yield 22.2 g (84 %), m.p. 122—125°. The analytical sample, recrystallised from ethanol and ethyl acetate, melted at 125—126°. (Found: C 36.54; H 3.66; N 5.54. Calc. for $C_8H_{10}BrNO_2S$: C 36.38; H 3.82; N 5.30).

2-Ethio-3-hydroxypyridine 1-oxide (XVI). 2 M Methanolic sodium methoxide (45 ml, 0.09 mole) was added to dry DMF (400 ml), excess alcohol evaporated, ethylmercaptan (3.72 g, 0.06 mole) and 2-bromo-3-hydroxypyridine 1-oxide (5.7 g, 0.03 mole) added and the reaction mixture stirred at 100° for 4 h. After evaporation at reduced pressure the oily residue was dissolved in water (40 ml), the solution acidified with acetic acid (5 ml) and excess ethylmercaptan removed by having the solution attached to a water pump. A whitish crystalline solid was precipitated on standing in the cold; yield 3.6 g (70 %), m.p. 105—108°. Recrystallisation twice from ethyl acetate gave m.p. 113—114°. (Found: C 49.46; H 5.09; N 8.09. Calc. for $C_7H_9NO_2S$: C 49.10; H 5.29; N 8.18).

2-Ethio-3-hydroxy-6-methylpyridine 1-oxide (XIV). 2 M Methanolic sodium methoxide (113 ml, 0.225 mole) was added to dry DMF (900 ml), excess alcohol evaporated, ethyl mercaptan (9.3 g, 0.15 mole) and 2-bromo-3-hydroxy-6-methylpyridine 1-oxide (15.3 g, 0.075 mole) added and the reaction mixture stirred at 110° for 4 h. After evaporation at reduced pressure the oily residue was dissolved in water (90 ml) and the solution acidified with acetic acid (11 ml). A greyish-white solid crystallised out on standing; yield 12.25 g (88 %), m.p. 137—139°. Recrystallisation from water or ethyl acetate gave white crystalline solid, m.p. 140—141°. (Found: C 51.82; H 5.80; N 7.46. Calc. for $C_8H_{11}NO_2S$: C 51.87; H 5.98; N 7.56).

3-Hydroxy-6-methyl-2(2-thiobenzimidazolyl)pyridine (XVII). 2-Bromo-3-hydroxy-6-methylpyridine (37.6 g, 0.2 mole) was dissolved in propylene glycol (300 ml) by heating to 120° and 2-mercaptobenzimidazole (32.0 g, 0.22 mole) added. The resultant solution was heated at 120° for 5 h and then allowed to cool down. The greyish-white solid was filtered off, washed with acetone and dried; weight 5.8 g, m.p. 240—275.

The filtrate and acetone washings were combined, concentrated to 150 ml at reduced pressure and acetone (100 ml) added. The solid precipitated after standing for a few hours at −20°, weighed 43.8 g (65 %), m.p. 232—238°. The hydrobromide of the desired substance thus obtained could be recrystallized from methanol; white crystalline solid, m.p. 235—244°. The free base was obtained by dissolution of the hydrobromide (3.4 g, 0.01 mole) in methanol (100 ml), dilution with water (10 ml) and adjustment of the pH of the solution from 2.5 to 5.8 with 2 N NaOH aq.

The white solid precipitate (2.5 g) melted at 238—240°. Recrystallisation from DMF or DMF/MeOH gave m.p. 235—240°. (Found: C 60.36; H 4.38; N 16.35. Calc. for $C_{13}H_{11}N_3O$: C 60.36; H 4.38; N 16.35).

The solid first isolated (5.8 g) was recrystallised from 90 % DMF (170 ml); white crystalline solid (2.1 g), m.p. 278—284°. The free base was obtained by dissolving the

hydrobromide (1.7 g) in hot methanol (20 ml) and water (2 ml), the pH adjusted to about 7, a little insoluble material removed by filtration, the solution allowed to cool and left at −20° for a few hours. A very pale yellow crystalline solid was precipitated (0.89 g), m.p. 203−206°. Recrystallisation from methanol gave m.p. 206−208°. (Found: C 58.45; H 4.92; N 11.60. Calc. for $C_{12}H_{12}N_2O_2S$: C 58.06; H 4.87; N 11.29). This compound has been identified as bis-(3-hydroxy-6-methyl-2-pyridyl) thioether (XIX) as synthesized below.

From the N-*oxide*. A solution of 2-bromo-3-hydroxy-6-methylpyridine 1-oxide (1.02 g, 0.005 mole) and 2-mercaptobenzimidazole (1.05 g, 0.007 mole) in ethanol (50 ml) was refluxed for 24 h. The solution was then evaporated, the residue dissolved in water (20 ml) and the pH brought to 4.5 with dilute NaOH. A sticky solid was precipitated. This material was partially dried and then triturated with ethyl acetate. The solid obtained weighed 0.40 g. Chromatography and spectroscopy showed this product to be the title compound as prepared above.

The reaction was also attempted in other solvents both with the thiol itself or its sodium salt. But chromatography invariably showed that the major product was the title compound.

Bis-(3-hydroxy-6-methyl-2-pyridyl)thioether (XIX). 2-Bromo-3-hydroxy-6-methylpyridine (1.88 g, 0.01 mole) and 3-hydroxy-6-methyl-pyrid-2-thione (1.41 g, 0.01 mole) were heated together in propylene glycol (50 ml) at 120° for 5 h. The greyish-white solid precipitate was filtered off from the cold reaction mixture; yield (2.05 g, 62 %), m.p. 228−260°. The hydrobromide was added to hot methanol (20 ml) and dissolved by addition of 2 N NaOH to pH 6.5−7.0, decolorized with charcoal and the filtrate allowed to cool; pale yellow crystalline solid m.p. 200−206°. The physical chemical data are the same as for the substance above.

2-Ethio-3-hydroxy-6-methyl-4-phenylthiopyridine 1-oxide (XX). A solution of 4-bromo-2-ethio-3-hydroxy-6-methylpyridine 1-oxide (1.32 g, 0.005 mole) and thiophenol (1.1 g, 0.01 mole) in DMF (25 ml) was heated at 100° for 3½ hours. The solution was evaporated at reduced pressure, the residue dissolved in dilute ethanol, the pH adjusted to 4.5 with 2 N NaOH aq., the solution evaporated to dryness at reduced pressure and the residue dried well *in vacuo*. Extraction with boiling ligroin (2×50 ml) of the oily residue and cooling the extracts at −20° for several hours furnished a white crystalline solid; yield 0.55 g (37 %), m.p. 128−147°. Recrystallisations from ethyl acetate gave m.p. 145−151°. (Found: C 57.21; H 5.09; N 4.46. Calc. for $C_{14}H_{15}NO_2S_2$: C 57.31; H 5.15; N 4.77).

2-Ethio-3-hydroxy-6-methyl-4-nitropyridine 1-oxide (XXI). 2.2 M Methanolic sodium methoxide (14 ml, 0.03 mole) was added to dry DMF (200 ml), the methanol evaporated, ethanethiol (1.24 g, 0.02 mole) added, the reaction heated to 100° and 2-bromo-3-hydroxy-6-methyl-4-nitropyridine 1-oxide (2.5 g, 0.01 mole) added. TLC indicated a fairly fast reaction with the appearance of a by-product which increased with time. The reaction was therefore stopped after 3 h, evaporated at reduced pressure, the residue dissolved in water (70 ml), acidified with acetic acid, precipitated impurities and a little of the desired product removed by filtration and the filtrate adjusted to pH 2.8 when the title compound was precipitated (1.5 g, 68 %), m.p. 108−112°. Recrystallisation from ethanol gave m.p. 110−114°. (Found: C 41.64; H 4.54; N 12.07. Calc. for $C_8H_{10}N_2O_4S$: C 41.74; H 4.38; N 12.17).

With longer heating time and excess ethanethiol the by-product observed chromatographically in the above experiment became the major product.

After evaporation the solid was triturated with water when the *N*-oxide dissolved. The insoluble material after crystallisation from ethanol had m.p., 97−99° and can be identified as 2-ethio-3-hydroxy-6-methyl-4-nitropyridine (XXII). (Found: C 44.93; H 4.69; N 13.21. Calc. for $C_8H_{10}N_2O_3S$: C 44.85; H 4.70; N 13.08).

When the *N*-oxide prepared as above was heated with 2 equivalents of the sodium salt of ethanethiol in DMF at 100° chromatography showed that 70 % of the *N*-oxide had been reduced after 24 h. Heating the *N*-oxide without the thiol had no effect.

2-Butylthio-3-hydroxypyridine (XXV). 3-Hydroxypyridine 1-oxide (11.1 g, 0.1 mole) was added in portions to dimethyl sulphate (15.1 g, 0.12 mole) with stirring and the reaction mixture warmed slowly to 140°. After heating for 2 h at this temperature the reaction mixture was allowed to cool, the brown oil extracted with ethyl acetate (3×25 ml) to remove excess dimethylsulphate and the residual oil dried well *in vacuo;* yield

18 g. Chromatography indicated about 10 % unchanged *N*-oxide, but otherwise a homogeneous product.

The 3-hydroxy-1-methoxypyridinium methylsulphate thus prepared (12.0 g, 0.05 mole) was dissolved in DMF (20 ml) and added dropwise to the stirred sodium salt of butylmercaptan (1.13 g, 0.1 mole) in DMF (100 ml) at 70°. The temperature during the addition rose to 105°. The reaction was stirred at 90° for 2 h, the insoluble salt removed by filtration, the filtrate evaporated at reduced pressure and the residual oil triturated with water (30 ml). The greyish-white solid formed (5.9 g, 64 %), m.p. 86—92°, furnished a white crystalline solid on recrystallisation from ligroin, m.p. 92—95°. (Found: C 59.31; H 6.92; N 7.32. Calc. for $C_9H_{13}NOS$: C 58.98; H 7.15; N 7.64).

2-Ethio-3-hydroxypyridine (XXVII). 3-Hydroxypyrid-2-thione (25.4 g, 0.2 mole) and ethyl iodide (39.0 g, 0.25 mole) were heated together in acetonitrile (300 ml) at 80° for 5 h, the solution evaporated at reduced pressure, water (200 ml) and 10 N NaOH aq. (in all 25 ml) added to the residue until pH about 7, and the suspension extracted with ethyl acetate (5 × 60 ml). The dried extracts were evaporated and the residual oil distilled, b.p. 100—104°/2 mm Hg. The colourless oil gave a white solid on cooling, m.p. 88—90°. (Found: C 53.87; H 5.74; N 9.14. Calc. for C_7H_9NOS: C 54.17; H 5.84; N 9.02).

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