N-Quaternary Compounds. Part 53.[1] Vinylation Reactions of Pyridine-2-thiones

By **Gunnar Arnfinn Ulsaker, Harald Breivik,** and **Kjell Undheim,*** Department of Chemistry, University of Oslo, Oslo 3, Norway

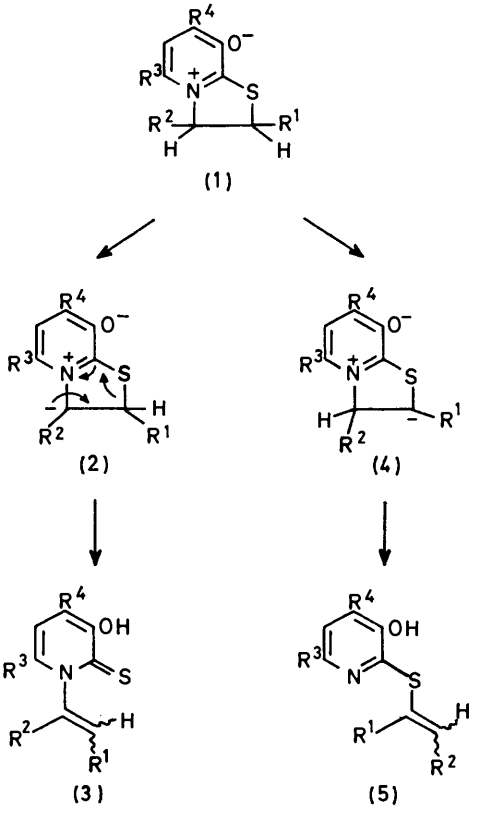
N-Vinyl derivatives of pyridine-2-thiones can be prepared by initial synthesis of dihydrothiazolo[3,2-*a*]pyridinium derivatives which are ring-opened by a strong base such as potassium t-butoxide in dimethylformamide. The product ratios of the separable *N*- and *S*-vinyl isomers formed depend largely on the nature and positions of their substituents. The major pathways in the ring-opening reactions of the dihydrothiazolo[2,3-*a*]pyridinium intermediates have been elucidated by deuterium labelling experiments. Syntheses of a number of selectively deuteriated compounds are described.

THE preparation of *N*-vinyl derivatives of pyridine-2-thiones by direct alkylation procedures is hampered by the preferential reactivity of the sulphur atom with the electrophilic reagent; *S*-vinyl derivatives are thus formed. *S*,*N*-Disubstitution, however, proceeds readily, and especially when both functions are involved in a cyclisation reaction.[2] Hence we have investigated ring-opening reactions of the dihydrothiazole ring in dihydrothiazolo[3,2-*a*]pyridinium derivatives as a pathway to vinylation.[3,4] Dihydrothiazolo[3,2-*a*]pyridinium derivatives are readily available from pyridine-2-thiones.[2]

The *N*-vinylation reaction from the dihydrothiazolo-[3,2-*a*]pyridinium derivatives (1) (Scheme 1) requires initial generation of a carbanion (2) at C-3. Thus *N*-vinylation has been achieved after decarboxylation of 3-carboxy-betaine analogues [Scheme 1; (1; $R^2 = CO_2H$)], under anhydrous conditions; in aqueous solution the decarboxylation was succeeded by protonation to yield (1).[3] Deprotonation of the betaines (1) under pyrolysis and in the presence of a solid base furnished a mixture of the *N*- and *S*-vinyl isomers; the isomer ratios were largely dependent on the nature of the substituents.[4] In the work herein described ring-opening reactions of (1) by means of potassium t-butoxide in dimethylformamide (DMF) solution have been investigated.

The reactivities of derivatives with a 2-, 3-, or 5-methyl substituent, a 5-isopropyl substituent, and derivatives with a 5- or 7-chloro-substituent were compared. Ring-opening reactions through nucleophilic substitution were not observed. The *N*- : *S*-vinyl isomer ratios were determined by g.l.c. or by ^1H n.m.r. analyses of crude isomer mixtures. The isomers could be separated by fractional crystallisation from methanol, in which the *N*-vinyl isomer is less soluble, and by thick-layer chromatography on silica gel.

The *N*-vinyl isomer (3a) constituted 98% of the isomer product from the parent compound (1a). The *N*-vinyl isomer (3b) alone was obtained from the 2-methyl derivative (1b), whereas the 3-methyl derivative (1c) gave the *S*-vinyl isomer (5c) as the major product (70%). With the methyl group in the 5-position, compound (1d), *N*-vinyl formation is again favoured to the extent of 95%. An increase in the size of the 5-substituent to the isopropyl group, compound (1e), decreased the relative yield of the *N*-vinyl isomer to 55%. From the 5-chloro-derivative (1f) the relative yield of the

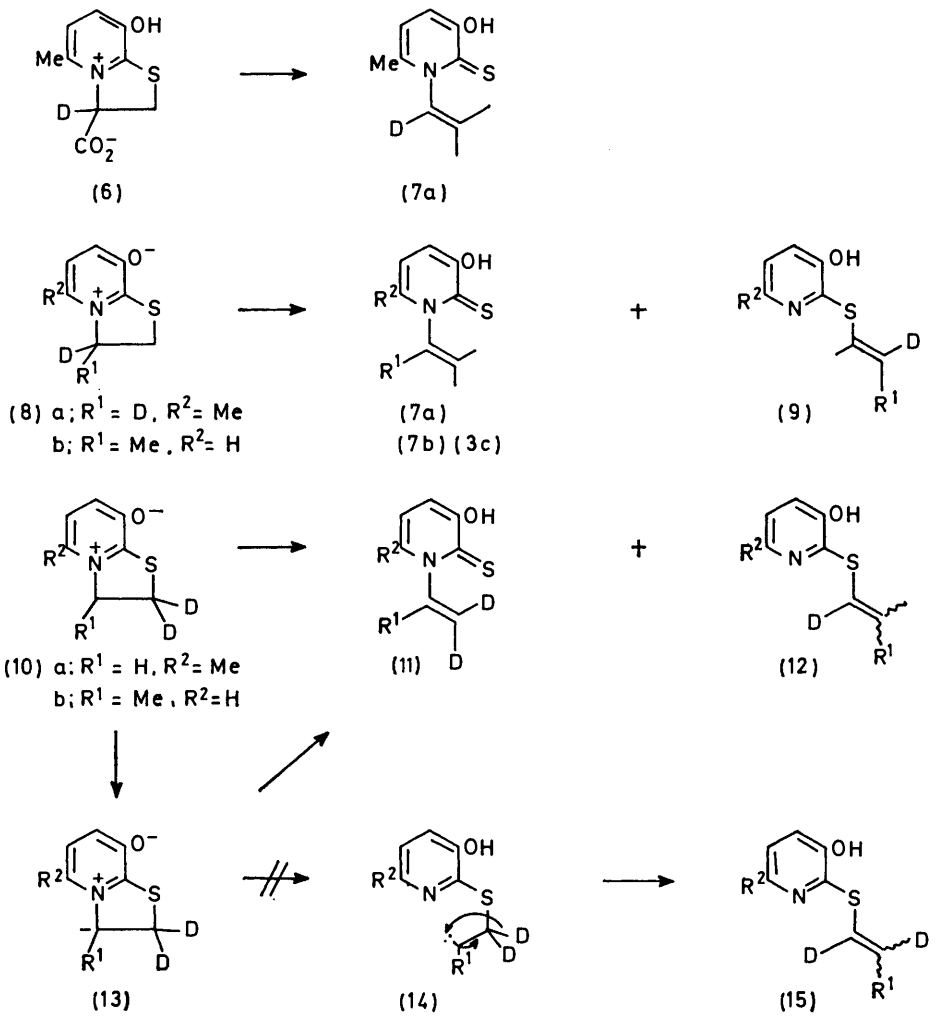


	R^1	R^2	R^3	R^4
a;	H	H	H	H
b;	Me	H	H	H
c;	H	Me	H	H
d;	H	H	Me	H
e;	H	H	Pr^i	H
f;	H	H	Cl	H
g;	H	H	H	Cl

SCHEME 1

N-vinyl isomer (3f) was 77%, whereas *N*-vinyl formation was strongly favoured (98%) from the 7-chloro-derivative (1g) as in the case of the parent compound (1a).

^{1}H N.m.r. data showed that both the *N*-vinyl derivative (3b) (*J* 14 Hz) and the *S*-vinyl derivative (5c) (*J* 15 Hz) had the *trans*-configuration. On heating (1c) in solid sodium carbonate mainly the *cis*-isomer of (5c) (*J* 9 Hz) was obtained,[4] and a *trans–cis* mixture of (3b) was obtained by decarboxylation of the 3-carboxy-analogue of (1b).[3]



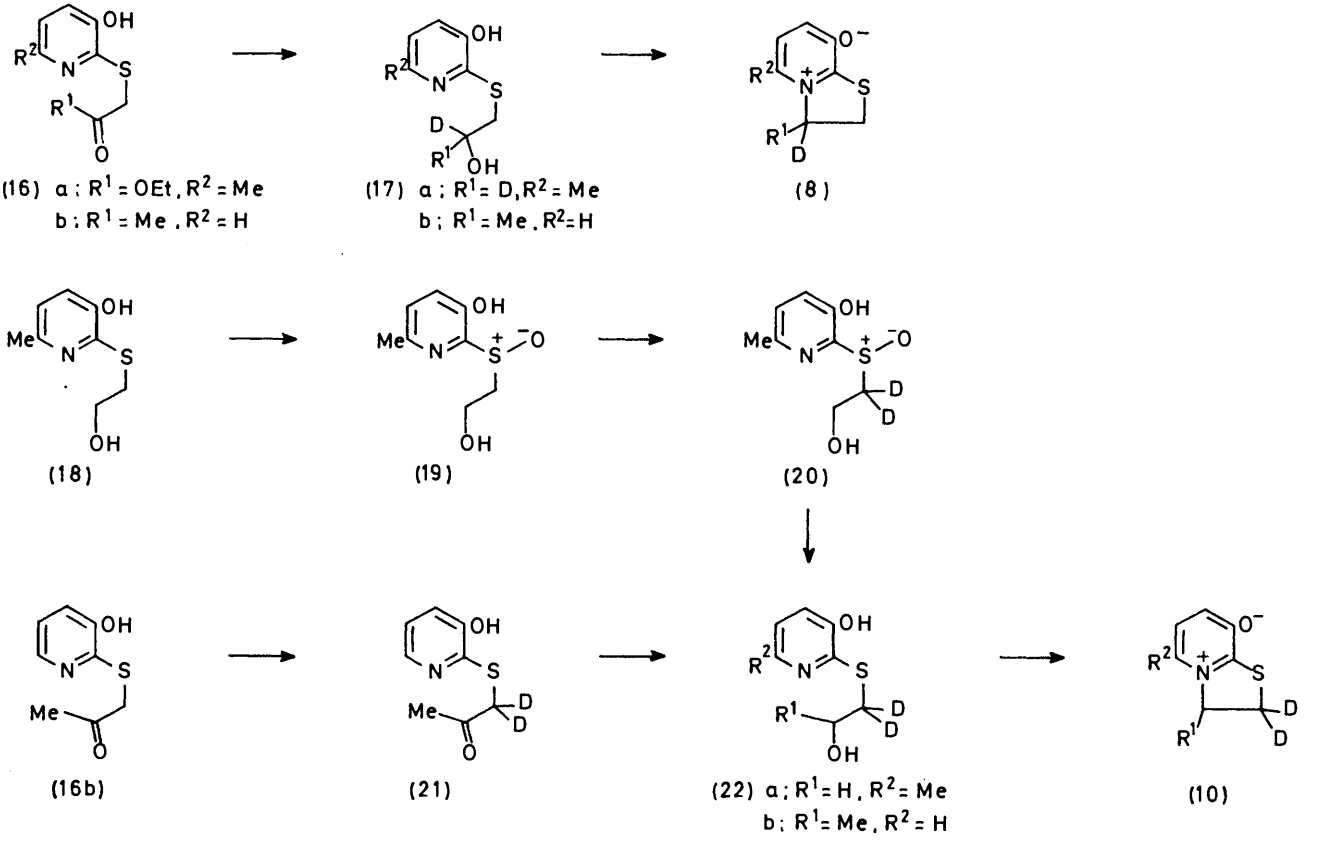
SCHEME 2

The *N*- : *S*-vinyl isomer ratios may be rationalised from considerations of relative carbanion stabilisation at C-2 and -3. Deuterium labelling experiments, discussed below, support the formation of intermediate carbanions at C-2 or -3 as major pathways in the formation of *S*- or *N*-vinyl isomers, respectively. An anion at C-3 is inductively stabilised by the quaternary nitrogen atom whereas an anion at C-2 is stabilised by interaction with the sulphur atom, and this interaction is presumably enhanced through the attachment of the sulphur to the electron-deficient pyridinium system. The better stabilisation is apparently at C-3 since (1a) gave 98% relative yield of the *N*-vinyl isomer. The change in isomer ratios for (1b and c) is attributed to the methyl group. Steric effects presumably cause the relative decrease in *N*-vinyl formation from the 5-methyl to the 5-isopropyl derivative because of increase in the non-bonded interaction when the bulky base approaches for proton abstraction at C-3, and also in the transition state from the carbanion to the *N*-vinyl product. The relative yield of the *N*-vinyl isomer is also decreased from the 5-methyl to the 5-chloro-derivative (1f). Since the effective bulkiness of these substituents are similar the difference may be caused in part by electrostatic repulsion between the lone pair of electrons on the chlorine atom and the negatively charged base.

The pathways in the vinylation reactions have been investigated using deuterium labelling. Pyrolytic decarboxylation of the 3-deuterio-carboxylate (6) gave retention of the deuterium label in the *N*-vinyl product (7a).[5] Ring-opening of the 3,3-dideuterio derivative (8a) with potassium t-butoxide in DMF gave only *ca.*

30% retention of the deuterium label, compound (7a). Because of the small amount of *S*-vinyl isomer formed and overlap of the ^1H n.m.r. signals, the degree of deuterium label retention (9a) could not be satisfactorily estimated. The *N*-vinyl isomer from the 3-deuteriated 3-methyl derivative contained no deuterium label, whereas *ca.* 30% of the deuterium label was retained [compound (9b)] in the *S*-vinyl isomer. There was no sign in any of the products of 1,2-deuterium shifts. The extensive loss of the deuterium label from the 3-deuteriated compounds can be attributed to a faster protonation than ring-opening of an intermediate carbanion on C-3. In the *N*-vinyl derivatives prepared from the 2,2-dideuterio-analogues (10), no significant loss of deuterium was seen. The *S*-vinyl isomer from the 3-methyl derivative (10b) was monodeuteriated, compound (12b). The low relative yield of *S*-vinyl isomer from (10a) precluded determination of deuterium labelling. There was a noticeable isotope effect in the ring-opening reactions in that the *N*- : *S*-vinyl isomer ratios were decreased slightly on deuteriation at C-3 and increased slightly on deuteriation at C-2. The labelling experiments exclude an initial carbanion at either C-2 or -3, respectively, as a common source for both the *N*- and *S*-vinyl isomers. This conclusion is apparent from Scheme 2 which shows the labelling requirement for a *S*-vinyl isomer (15) formed *via* a carbenoid intermediate (14).

Synthesis of the deuteriated betaines (8) and (10) are outlined in Scheme 3. Lithium aluminium [$^2H_4$]hydride reduction of the ester (16a) furnished the corresponding deuteriated alcohol (17a) which was cyclised to the 3,3-dideuterio-derivative (8a) in acetic [^2H]acid. Likewise the acetonyl derivative (16b) [2] was reduced to (17b) by means of sodium [$^2H_4$]borohydride and cyclised in acetic [^2H]acid. The synthesis outlined for the preparation of the 2,2-dideuterio-derivative (10a) from (18) had sulphoxide activation of the adjacent methylene protons as the key intermediate. Compound (18) was oxidised to the sulphoxide (19) by means of performic acid. The sulphoxide could be selectively deuteriated on the adjacent methylene carbon atom using 10% NaOD in deuterium oxide at 50 °C. Dithiophosphoric acid *OO*-diethyl ester [6] smoothly reduced (20) to the sulphide (22a) without loss of deuterium, and (22a) was cyclised to (10a) in acetic acid. The 3-methyl-2,2-dideuteriated derivative (10b) was prepared from the acetonyl sulphide (16a). Selective deuteriation of the methylene group was possible using deuterium oxide at room temperature. In weakly alkaline media deuterium was also incorporated into the pyridine ring. An ice-cold solution of (21) in deuterium oxide could be reduced to the alcohol (22b) using sodium borohydride. With a relatively short reaction time (*ca.* 20 min) the incorporation of deuterium into the pyridine ring is insignificant. Reduction in methanol or water solution resulted in partial loss of



SCHEME 3

the deuterium. The subsequent cyclisation was run in acetic acid; the use of a strong acid to catalyse the cyclisation may also result in partial rearrangements whereby the relative positions of C-2 and -3 are interchanged.[2]

EXPERIMENTAL

^{1}H N.m.r. spectra were obtained with a 60 or 100 MHz spectrophotometer.

Vinylation Reactions by Ring-opening of Dihydrothiazolo[3,2-a]*pyridinium-8-olates* (1).—A solution of potassium t-butoxide in t-butyl alcohol (75 ml, 0.038 mol) was added dropwise over 3 h at room temperature to a stirred mixture of the dihydrothiazolo[3,2-*a*]pyridinium-8-olate (0.03 mol) in DMF (400 ml). The mixture was stirred for another 30 min before it was acidified with acetic acid and evaporated to dryness under reduced pressure. The residue was triturated with water, dried, and then extracted by heating in methanol; the *N*-vinyl isomer crystallised out from the solution on cooling. The mother-liquor, which contains the *S*-vinyl isomer and remaining *N*-vinyl isomer, was evaporated to dryness under reduced pressure. The isomers were separated by chromatography on 0.5-mm thick layers of silica gel. First the plates were semi-developed in BuOH–EtOH (4 : 1). The air-dried plates were then developed in MeCN–HOAc–MePh (10 : 1 : 10). The desired chromatographic bands on the plates were scraped off and the compounds extracted into boiling methylene chloride (15 h) using a Soxhlet extraction apparatus.

The isomers could also be separated by column chromatography on neutral silica gel with BuOH–EtOAc (4 : 1); the *S*-vinyl isomer is first eluted.

Analyses of Vinyl Isomer Mixtures.—For analysis of the isomer ratios the reactions were run on a smaller scale. Thus potassium t-butoxide in t-butyl alcohol (0.5N, 0.002 5 mol) was added dropwise over 10 min to (1) (0.001 mol) dissolved in DMF (25 ml). The mixture was acidified with acetic acid after 30 min and evaporated almost to dryness at reduced pressure. Water (25 ml) was added to the residue before extraction with ether (3 × 15 ml) and the ether solution analysed for the isomer ratio. The g.l.c. analysis was carried out with a Varian-3700 instrument equipped with flame-ionisation detectors. For the relative quantitative evaluation the peak width at half height was multiplied by the peak height. The column (2 mm i.d. × 1.8 m) was made up of 3% SE-30 on Supelcoport 80—100 Mesh, and the flow rate was 30 ml N_2 min^{-1}. The temperature of the injector and the detector was 220 °C. The sample was injected isothermally at 110 °C. The instrument after 1 min was programmed for +10 °C min^{-1} up to 210 °C.

Vinyl Isomer Compositions.—The percentage composition of the vinyl isomer mixtures and g.l.c. retention times (s) were: for the products from (1a), 98% (3a) (309) and 2% (5a) (196); from (1b), 100% (3b) (determined by t.l.c.); from (1c), 30% (3c) and 70% (5c) (by ^{1}H n.m.r.); from (1d), 95% (3d) (418) and 5% (5d) (223); from (1e), 55% (3e) and 45% (5e) (by ^{1}H n.m.r.); from (1f), 77% (3f) (369) and 23% (5f) (309); from (1g), 98% (3g) (436) and 2% (5g) (322).

N-Vinyl-3-hydroxypyridine-2-thione [3] (3a) had yield 70%, m.p. 84 °C (EtOH). 2-*Vinylthio*-3-*hydroxypyridine* (5a) had m.p. 97 °C ($CHCl_3$ by cooling) (Found: C, 54.75; H, 4.45. C_7H_7NOS requires C, 54.9; H, 4.6%), δ($CDCl_3$) 5.45 (*J* 9.5 Hz) and 5.4 (*J* 17 Hz) (CH_2, *J* 1 Hz) and 6.9 (CH).

trans-N-*Propenyl*-3-*hydroxypyridine*-2-*thione* (3b) had yield 68%, m.p. 98—100 °C (MeOH). Elemental analysis was carried out on a *cis–trans* mixture,[3] δ($CDCl_3$) 1.9 (Me, *J* 7 and 1.5 Hz), 5.9 (C*H*Me), and 6.7 (NCH, *J* 14 Hz). *N*-Isopropenyl-3-hydroxypyridine-2-thione [4] (3c) was formed in 15% yield. *trans*-2-Propenylthio-3-hydroxypyridine (5c) had m.p. 152 °C ($CHCl_3$), δ($CDCl_3$) 1.8 (Me, *J* 5.5 and <1 Hz), 5.9 (C*H*Me, *J* 15 and 5.5 Hz), and 6.2 (CHS, *J* 15 and <1 Hz). 2-*Vinylthio*-3-*hydroxy*-6-*methylpyridine* (5d), yield 3%, had m.p. 86 °C (CCl_4) (Found: C, 57.4; H, 5.6. C_8H_9NOS requires C, 57.5; H, 5.4%), δ($CDCl_3$) 2.5 (Me), 5.3 (*J* 9 Hz) and 5.2 (*J* 17 Hz) (CH_2, J_{gem} <1 Hz), 6.6 (CHS), and 6.8 and 7.0 (*J* 8 Hz, ArH). *N*-Vinyl-3-hydroxy-6-isopropylpyridine-2-thione [3] (3e) was formed in 31% yield, 2-vinylthio-3-hydroxy-6-isopropylpyridine [4] (6e) in 25% yield. N-*Vinyl*-3-*hydroxy*-6-*chloropyridine*-2-*thione* (3f), yield 45%, had m.p. 100 °C (MeOH) (Found: C, 44.9; H, 3.4. C_7H_6ClNOS requires C, 44.9; H, 3.2%), δ($CDCl_3$) 5.4 (*J* 16 Hz) and 5.8 (*J* 8 Hz) (CH_2, J_{gem} 1.5 Hz), 6.9 (CHN), and 6.7 and 6.9 (*J* 8 Hz, ArH). 2-*Vinylthio*-3-*hydroxy*-6-*chloropyridine* (5f), yield 10%, had m.p. 98 °C ($CHCl_3$) (Found: C, 44.8; H, 3.2. C_7H_6ClNOS requires C, 44.8; H, 3.2%), δ($CDCl_3$) 5.5 (*J* 9 Hz) and 5.45 (*J* 17 Hz) (CH_2, J_{gem} 1 Hz), 6.8 (CHS), and 7.1 (ArH). N-*Vinyl*-3-*hydroxy*-4-*chloropyridine*-2-*thione* (3g), yield 65%, had m.p. 132 °C (MeOH) (Found: C, 44.6; H, 3.15. C_7H_6ClNOS requires C, 44.8; H, 3.2%), δ($CDCl_3$) 5.3 (*J* 8.5 Hz) and 5.4 (*J* 16 Hz) (CH_2, J_{gem} 1.5 Hz), 7.7 (CHN), and 6.7 and 7.3 (*J* 7 Hz, ArH). 2-*Vinylthio*-3-*hydroxy*-4-*chloropyridine* (5g) had m.p. 127 °C ($CHCl_3$) (Found: C, 44.6; H, 3.2. C_7H_6ClNOS requires C, 44.8; H, 3.2%), δ($CDCl_3$) 5.4 (*J* 9 Hz) and 5.45 (*J* 17 Hz) (CH_2, J_{gem} <1 Hz), 7.0 (CHS), and 6.9 and 7.9 (*J* 6 Hz, ArH).

T.l.c. analyses of the deuteriated pyridines below were run on silica gel plates. The systems were: for the betaines aqueous NH_3–Bu^nOH–EtOH–H_2O (2 : 4 : 1) and for the uncharged pyridines MeCN–HOAc–PhMe (10 : 1 : 10).

Analyses of Deuteriated Vinyl Isomer Mixtures.—The deuteriated pyridiniumolates as HCl salts (0.5 mmol) were treated with t-butoxide (1.25 mmol) in DMF (15 ml) and the mixtures worked-up as described for the non-deuteriated compounds above. The crude vinyl isomer mixtures were analysed as above with ^{1}H n.m.r. and t.l.c.

3-*Methyl*-3-*deuteriodihydrothiazolo*[3,2-a]*pyridinium*-8-*olate* (8b) *Hydrochloride.*—Sodium [$^2H_4$]borohydride (0.29 g, 0.008 mol) was added to a solution of 2-(2-oxopropylthio)-3-hydroxypyridine [2] (0.92 g, 0.005 mol) in methanol (25 ml). The mixture was stirred at room temperature for 30 min before concentration under reduced pressure to a small volume to which water (25 ml) was added. The pH of the mixture was adjusted to *ca.* 5 and the mixture extracted with chloroform (6 × 25 ml). Evaporation of the washed and dried chloroform extracts yielded 2-(2-hydroxy-2-deuteriopropyl)-3-hydroxypyridine (17b) (0.80 g, 86%) [n.m.r. and t.l.c. as for parent compound; [2] δ($CDCl_3$) 1.3 (Me, s) and 3.1 and 3.3 (SCH_2, AB, *J* 15 Hz)].

The crude product (17b) was dissolved in acetic [^{2}H]acid (15 ml) and the solution was heated under reflux for 30 h. The solution was next concentrated to *ca.* 5 ml and ether (15 ml) was added. This mixture was stirred at room temperature for 2 h and the ether layer containing some 2,3-dihydroxypyridine impurity removed. A solution of the residue in 6N-HCl (10 ml) was heated under reflux for 30 min to hydrolyse any acetate present. Evaporation left

the title compound which was recrystallised from propan-2-ol, yield 0.42 g (51%) [n.m.r. and t.l.c. as for (1c); [2] $\delta(CF_3CO_2H)$ 1.85 (Me, s) and 3.5 and 4.05 (SCH_2, AB, J 12 Hz)].

5-*Methyl*-2,2-*dideuteriodihydrothiazolo*[3,2-a]*pyridinium*-8-*olate* (10a) *Hydrochloride*.—A solution of 2-(2-hydroxyethylsulphinyl)-3-hydroxy-6-methylpyridine (0.50 g, 0.002 5 mol) in 10% NaOD in D_2O (0.02 mol) was heated at 50 °C for 5 days. The pH of the cold mixture was adjusted to *ca.* 7 with acetic acid and the precipitated solid removed. The precipitate was extracted with methanol, and the combined methanol extracts and the filtrate were evaporated to dryness. The product was essentially 2-(2-hydroxy-1,1-dideuteriosulphinyl)-3-hydroxy-6-methylpyridine (20) [n.m.r. and t.l.c. as for (19); δ (10% NaOD) 3.95 (CH_2O, s)]. The crude product was used in the subsequent reaction without further purification.

The crude product (20) was added to absolute ethanol (45 ml), a little insoluble material removed by filtration, and dithiophosphoric acid *OO*-diethyl ester (3.5 ml) added dropwise with stirring. The mixture was stirred at room temperature overnight and then evaporated. Water (25 ml) was added to the residue and the pH adjusted to *ca.* 7.0 with sodium carbonate. The mixture was next extracted with chloroform (6 × 25 ml), and the washed and dried chloroform solution evaporated. The residual product was essentially 2-(2-hydroxy-1,1-dideuterioethylthio)-3-hydroxy-6-methylpyridine (22a) [n.m.r. and t.l.c. as for (18) [2]]. The product was contaminated with some reagent.

The crude product (22a) was added to acetic acid (15 ml) and the solution heated under reflux for 20 h. The solvent was then removed under reduced pressure, the residue dissolved in water (15 ml), and the solution extracted with ether (3 × 15 ml) to remove residual reagent. The aqueous solution was evaporated almost to dryness, 6N-HCl (10 ml) was added, and the solution was heated under reflux for 1 h. Evaporation left the title compound (0.3 g) in overall yield 61% from the sulphoxide (19) [n.m.r. and t.l.c. as for (1d),[2] $\delta(CF_3CO_2H)$ 5.1 (2 H-3, s)].

3-*Methyl*-2,2-*dideuteriodihydrothiazolo*[3,2-a]*pyridinium*-8-*olate* (10b) *Hydrochloride*.—2-(2-Oxopropylthio)-3-hydroxypyridine (1.0 g) was suspended in D_2O (3.0 ml) and the suspension stirred at room temperature. The progress of the reaction was monitored by n.m.r.; the conversion to 2-(2-oxo-1,1-dideuteriopropylthio)-3-hydroxypyridine (21) was complete after 3 days [n.m.r. and t.l.c. as for (16b), δ(10% NaOD) 1.9 (Me)].

The filtered solution of (21) in D_2O was cooled in an ice–water-bath and sodium borohydride (0.3 g) was added portionwise over 5 min. After a total of 20 min the mixture was acidified with acetic acid, diluted with water, and extracted with ether. Evaporation of the washed and dried ether solution left 2-(2-hydroxy-1,1-dideuteriopropylthio)-3-hydroxypyridine (22b) (70%) [n.m.r. and t.l.c. as for parent compound,[2] $\delta(CDCl_3)$ 1.3 (Me, d), 4.15br (CH, s)].

A solution of the crude product (22b) in acetic and (15 ml) was cyclised to (10b) as described for the synthesis of (8b); yield 55% [n.m.r. and t.l.c. as for (1c),[2] $\delta(CF_3CO_2H)$ 1.85 (Me, d, J 6.5 Hz), 5.5 (H-3, m)].

2-(2-*Hydroxyethylsulphinyl*)-3-*hydroxy*-6-*methylpyridine* (19).— 2-(2-Hydroxyethylthio)-3-hydroxy-6-methylpyridine [2] (9.3 g, 0.05 mol) was dissolved in formic acid (60 ml), the solution cooled in an ice–water bath, and 30% hydrogen peroxide (5.7 ml) added. The mixture was left in the cold overnight and the mixture evaporated almost to dryness before addition of water. The aqueous solution was evaporated to dryness at reduced pressure and the solid residue (8.2 g, 80%) recrystallised from ethyl acetate, m.p. 105 °C (Found: C, 47.85; H, 5.5. $C_8H_{11}NO_3S$ requires C, 47.75; H, 5.5%), δ (10% NaOD) 2.4 (6-Me, s), 3.2 (S-CH_2, t), 3.95 (OCH_2, m), and 6.95 and 7.1 (H-4, -5, AB, J 8.5 Hz).

[8/2096 *Received*, 5*th December*, 1978]

REFERENCES

[1] Part 52, T. Laerum and K. Undheim, *J.C.S. Perkin I*, 1979, 1150.
[2] G. A. Ulsaker and K. Undheim, *Acta Chem. Scand.*, 1975, **B29**, 853.
[3] G. A. Ulsaker and K. Undheim, *Acta Chem. Scand.*, 1977, **B31**, 917.
[4] G. A. Ulsaker and K. Undheim, *Acta Chem. Scand.*, 1978, **32B**, 66.
[5] K. Undheim and T. Hurum, *Acta Chem. Scand.*, 1972, **26**, 2385.
[6] A. Nakanishi and S. Oae, *Chem. and Ind.*, 1971, 960.