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N-Quaternary Compounds. Part XLII.[1] Competitive Neighbouring Group Participation in Cyclisation Reactions of 2-Pyridylthioethers

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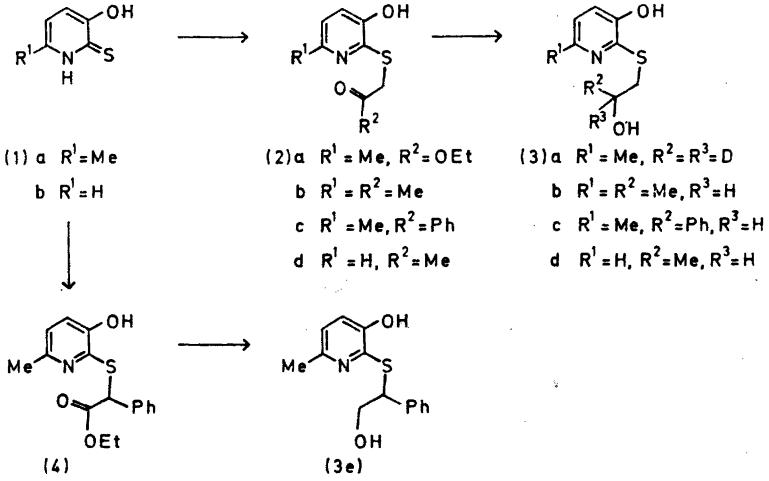
2-β-Hydroxyalkylthiopyridines in cold thionyl chloride react to yield the corresponding cyclised dihydrothiazolo[3,2-*a*]pyridinium derivative and a mixture of two 2-β-chloroalkylthiopyridine isomers. Further rearrangements may occur on cyclisation of the latter. The product compositions depend on the nature of the substituents and is in part rationalised by an episulfonium intermediate. Acid catalysed cyclisation of a 2-vinylthiopyridine, a 2-allylthiopyridine, and of 2-β-hydroxyalkylthiopyridines, however, proceeded without rearrangement.

Sulfur neighbouring group participation [2–5] has been used to explain the formation of a mixture of 2- and 3-carboxydihydrothiazolo[3,2-*a*]-pyridinium derivatives in the cyclisation of a 2-bromo-3-(2-pyridylthio)propionic acid.[6] Analogous reactions have been reported in that α-chloro-β-alkylthio- or β-arylthiopropionitrile or corresponding propionates react with nucleophiles to preferentially yield the product with the thioether group in the α-position.[2] The reaction path is more complicated on substitution of the side-chain β-carbon in 2-ethylthiopyridines since neighbouring group participation is possible from either the thioether sulfur atom or the pyridine nitrogen atom. Some ambiguity may also be attached to the role of the carboxy group in the cyclisation reaction described [6] although the carboxy group is largely un-ionised in acid solution.[3] Nevertheless, we have in the present work excluded the carboxy function from the sulfur side-chain. In the simplest example the side-chain carries only the leaving group on the β-carbon atom (Scheme 1). In order to distinguish



Scheme 1.

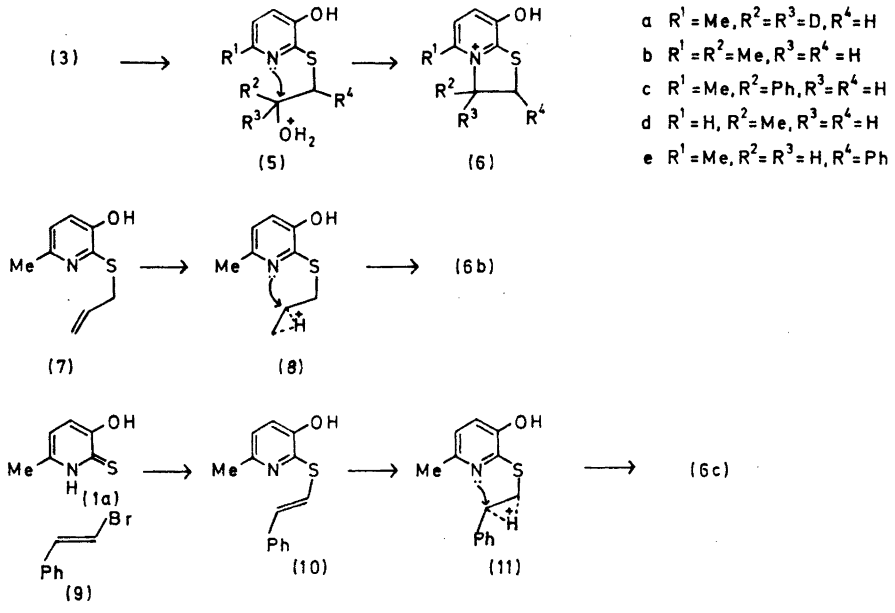
between the two methylene groups in the reaction product the terminal methylene group was deuteriated *3a*. The influences of alkyl and aryl substituents in the side-chain on the course of the cyclisation reaction of β-hydroxy derivatives have been studied.

The β-hydroxy derivatives were prepared as shown in Scheme 1. The thiolactams *1* are selectively alkylated on the sulfur atom.[7] Sodium borohydride reduction of the ketones *2b – d* thus prepared furnished the α-substituted derivatives *3b – d*; lithium aluminium hydride reduction of the ester *4* yielded the α-substituted derivative *3e*. The ester *2a* was reduced by lithium aluminium deuteride to the β,β-dideuterio derivative *3a*.

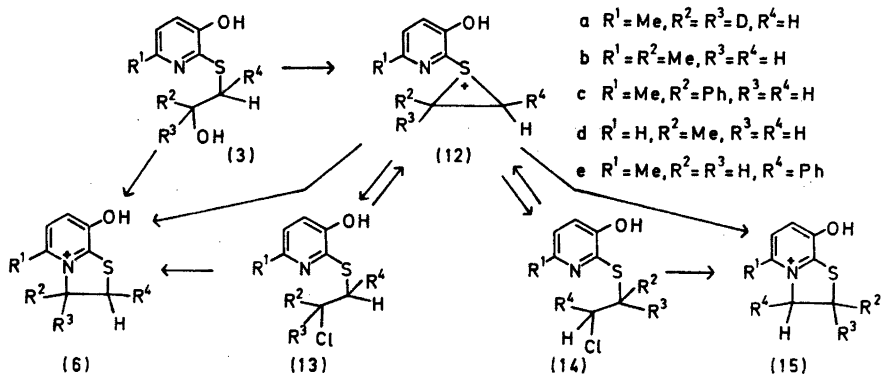
It has been found that direct substitution of the hydroxy group in *3* can be effected by heating in acetic acid or formic acid. In strong hydrochloric acid, however, little cyclisation took place presumably because the pyridine is protonated in strong acid solution. The product formed corresponds to a direct cyclisation reaction of 3; in no case was the rearranged isomer *15* (Scheme 3) seen (NMR). It is conceivable,[2–4] however, that some of the cyclic product may have been formed by acid catalysed cyclisation of a vinyl intermediate generated initially by water elimination. Therefore the synthesis of a suitable *S*-vinyl compound was developed by heating the thiolactam *1a* and β-bromostyrene together in acetic acid at 80 °C. The *S*-vinyl product *10* was indeed cyclised to *6c* on heating in acetic acid at elevated temperatures which shows that *S*-vinyl intermediates are possible. The vinylation reaction (*9→10*) corresponds to an overall nucleophilic displacement of the bromine atom; the substitution pattern is governed by the electron accepting properties of the phenyl ring.

In a related acid catalysed reaction the allyl derivative *7* was cyclised to *6b* without rearrangement (NMR) by heating in acetic acid. This reaction is analogous to our previously reported preferential five-ring cyclisation of *7* by bromination.[7] The generally more rapid formation of five- than six-membered rings [3] may be ascribed to the more negative activation entropy for the latter process.[8]

In contrast to the acid catalysed cyclisation reactions which proceeded without isomerisations, the reactions in thionyl chloride have yielded mixtures of isomeric products (Scheme 3). The compositions of the crude reaction products were determined by NMR. The



Scheme 2.



Scheme 3.

magnetic non-equivalence of the methylene protons on the α-carbon atom in the *S*-side-chain in the substituted chloro derivatives *13* and *14* and in the corresponding dihydro-thiazolo[3,2-*a*]pyridinium derivatives often complicated the spectral analyses due to overlap of the proton signals. Fortunately the chemical shifts of the protons in the methyl and phenyl substituents differ slightly before and after cyclisation and have also been used in the composition analyses. The structural assignments of the isomeric quaternary products are ascertained by comparison with authentic 2-substituted isomers previously prepared by non-ambiguous methods.[9,10] In the case of the deuteriated derivative *3a* identification of the *N*-quaternary product formed was evident from the relative chemical shifts of the methylene protons.[11]

Analogues of the β-halides *13* and *14* are readily cyclised.[6] The reactions in thionyl chloride were therefore run in the cold; the reaction time was 12–14 h. The deuteriated hydroxy derivative *3a* yielded a mixture of the *N*-quaternary compound *6a* and the chlorinated derivative *13a* in the ratio 6:1; no rearranged isomer (*14* or *15*) was seen (NMR). Heating the crude product mixture in ethyl acetate for 5 h, however, gave the quaternary isomers *6* and *15* in the ratio 20:1. Consequently some of the chloro compound *13a* has been cyclised *via* an episulfonium intermediate *12*. From the β-methyl derivative *3b* the amount of cyclised *N*-quaternary product was almost negligible while the 6-desmethyl analogue *3d* yielded about 10 % of the cyclised product *6d*. The major products in both these cases were the chloro isomers *13* and *14* which were formed in the approximate ratio 3:2. It seems likely that steric retardation of the cyclisation reaction is a major reason for the formation of the chloro isomers. The β-phenyl derivative reacted similarly with 20 % cyclisation to the 3-isomer *6c*; the major products were the chloro isomers *13c* and *14c* in the ratio 2:1. The α-phenyl derivative (*3e*) yielded about 20 % of the cyclised isomer *6e*. The reaction in this case yielded several products but the major components were the chloro isomers *13e* and *14e* in the ratio 1:2; on heating the mixture of the chloro compounds in ethyl acetate cyclisation occurred almost exclusively to the 3-phenyl isomer *15e*. The same product *6c* was obtained from the chloro isomer mixture derived from the β-phenyl derivative *3c*. The isomer ratios in the β-methyl series (*b* and *d*) were little affected on cyclisation of the chloro isomer mixture (*13* and *14*).

The product compositions are interpreted in terms of reaction paths which may not, or may go partially or almost completely through an episulfonium intermediate *12*. The formation of an episulfonium intermediate shows that sulfur neighbouring group participation is involved in the reaction. The possibility also exists for neighbouring group participation from the pyridine nitrogen atom. Participation from either heteroatom in its initial stage leads to partial bonding to the reaction centre with the formation of an internally solvated ion pair. Collapse of such a five-membered ring structure leads directly to the stable dihydrothiazolo-

pyridinium system in which case no rearranged isomer is formed. Collapse of the ion pair bonding with the thioether sulfur atom, however, leads to the highly reactive episulfonium intermediate which may suffer addition of the pyridine nitrogen atom to either episulfonium carbon atom and thus give rise to two structural isomers. Chloride ion addition to the reactive intermediates, however, will compete with the cyclisation reactions. The chlorine atom in the cyclisation of *13* and *14* may be displaced by the same type of mechanisms. The episulfonium intermediate *12* formed in the cyclisation of the deuteriated chloro isomer *13a* is symmetrical neglecting the deuterium isotope effect. The intermediate *12* is therefore expected to react with almost the same probability at either carbon atom resulting in an 1:1 product isomer ratio. The small fraction of rearranged product *15a* observed points to effective competitive neighbouring group participation from the pyridine nitrogen atom. In the reaction of the episulfonium carbon atom the nitrogen nucleophile must add *cis* to the sulfur which appears possible if the carbon-sulfur bond is stretched or almost broken so that the sulfur holds the partially charged carbon atom from some distance.

It will be recalled that all the direct cyclisation reactions have occurred without isomerisation. In thionyl chloride initial esterification is expected and the chlorosulfite ester group is then intramolecularly displaced or substituted by a chloride ion in an intra- or intermolecular process. The amount of chloro compound formed seems to increase with β-substitution (*3b – d*) possibly because the rate of cyclisation is decreased due to increase in non-bonded interaction although chain-branching often promotes cyclisation.

Ring opening of the substituted episulfonium intermediate either by the pyridine nitrogen atom or by the chloride ion is expected to occur in such a way that the nucleophile adds to the more stabilised incipient carbonium ion; the product ratio for the β-methyl chloro isomers *13* and *14* were about 3:2. Phenyl group stabilisation (*3c*) increased this ratio to about 2:1 while the ratio for the α-phenyl analogue (*3e*) was about 1:2. Cyclisation of the mixture of chloro derivatives from the phenyl isomers *3c* and *3e* gave only the 3-phenyl substituted cyclised product in accordance with an episulfonium intermediate. The isomer ratios in the chloro compounds, however, indicate that chlorine substitution occurs both by direct substitution and *via* an episulfonium intermediate.

It has been the purpose of this work to show that neighbouring group participation from the thioether sulfur atom is to be expected in the cyclisation of 2-ethylthiopyridines with a suitable leaving group on the β-carbon of the S-side-chain. The extent to which the sulfur participation in the reaction leads to an episulfonium intermediate or to direct cyclisation appears to depend on the nature of the leaving group besides on substituent and solvent stabilisation of the incipient carbonium ion.

EXPERIMENTAL

The NMR spectra were recorded with a Varian A-60A or a Varian A-100 instrument.

Ethyl (3-hydroxy-6-methyl-2-pyridylthio)acetate (2a).*HCl*. Thionyl chloride (7 ml) was added slowly with stirring to ethanol (70 ml) at −70 °C before 3-hydroxy-6-methyl-2-pyridylthioacetic acid (1.0 g, 0.005 mol) was added. The reaction mixture was allowed to reach room temperature overnight. The ethanol was evaporated, the residue triturated with ether and the residue crystallised from ethanol/acetone; yield 0.92 g (70 %), m.p. 155 °C. (Found: C 45.49; H 5.72. Calc. for $C_{10}H_{13}NO_3S.HCl$: C 45.60; H 5.32); δ(TFA) 2.8(Me), 1.3 and 4.5 (OEt), 4.1(*S*-CH_2), 7.6 and 8.0 (AB, 2 H-Py).

The free base, required for the synthesis of *3a*, was isolated by extraction of a neutralised aqueous solution with ether.

Ethyl 2-(3-hydroxy-6-methyl-2-pyridylthio)-phenylacetate (4) was prepared as above from 2-(3-hydroxy-6-methyl-2-pyridylthio)-phenylacetic acid.[12] The isolated free base was crystallised from toluene; yield 88 %, m.p. 131 °C. (Found: C 63.12; H 5.94. Calc. for $C_{16}H_{17}NO_3S$: C 63.36; H 5.65); δ($CDCl_3$) 2.4(Me), 1.2 and 4.1(OEt), 5.4(CH), 6.8 and 7.0(AB, 2 H-Py).

2-Phenacylthio-3-hydroxy-6-methylpyridine (2c). Potassium carbonate (20.0 g, 0.145 mol) was added to a solution of 3-hydroxy-6-methylpyrid-2-thione (16.4 g, 0.116 mol) in dimethylformamide (150 ml) followed by slow addition of ω-bromoacetophenone (26.4 g, 0.133 mol). The reaction mixture was stirred at room temperature overnight before filtration. The title compound was precipitated on dilution of the filtrate with water and pH adjustment to *ca.* 5; yield 29.1 g (95 %), m.p. 145 °C after recrystallisation from toluene. (Found: C 64.75;

H 5.19. Calc. for $C_{14}H_{13}NO_2S$: C 64.86; H 5.05); δ(TFA) 2.9(Me), 4.8(CH_2), 7.5–8.2(5 H-Ph, 2 H-Py).

2-β-Hydroxy-α-propylthio-3-hydroxy-6-methylpyridine (3b). Sodium borohydride (10.0 g, 0.26 mol) was added to a solution of 2-acetonylthio-3-hydroxy-6-methylpyridine [7] (10.0 g, 0.05 mol) in methanol (200 ml). The solution was left at room temperature for 1 h before evaporation of most of the methanol. Water was then added and the pH adjusted to *ca.* 5 before chloroform extraction. Evaporation of the washed and dried chloroform extracts left the title compound (9.1 g, 90 %); m.p. 117 °C after recrystallisation from toluene (Found: 53.88; H 6.49. Calc. for $C_9H_{13}NO_2S$: C 54.26; H 6.58); δ(TFA) 1.5(d, *J* 6.5 Hz, *Me*–CH), 2.7(Me–6), 3.4(S-CH_2), 4.5(m, CH), 7.5 and 7.8(AB, 2 H-Py).

2-β-Hydroxy-β-phenylethylthio-3-hydroxy-6-methylpyridine (3c).*HCl* was prepared from 2-phenacylthio-3-hydroxy-6-methylpyridine as above. The product was crystallised as the HCl-salt from a small volume of ethanol at −20 °C; yield 80 %, m.p. 183 °C. (Found: C 57.18; H 5.41. Calc. for $C_{14}H_{15}NO_2S$.HCl: C 57.48; H 5.37); δ(TFA) 2.7(Me), 3.6(d, CH_2), 5.3(t, CH), 7.4(5 H-Ph), 7.8 and 7.4(AB, 2 H-Py).

2-β-Hydroxy-α-propylthio-3-hydroxypyridine (3d) was prepared from 2-acetonylthio-3-hydroxypyridine [7] in 91 % yield, m.p. 101 °C (diisopropylether). (Found: C 52.27; H 6.11. Calc. for $C_8H_{11}NO_2S$: C 51.88; H 5.99); δ(TFA) 1.5(d, Me), 4.6(m, CH), 3.2–3.5(S-CH_2), 7.5–8.2(2 H-Py).

2-β-Hydroxy-α-phenylethylthio-3-hydroxy-6-methylpyridine (3e). Lithium aluminium hydride (0.75 g, 0.02 mol) was added gradually to a solution of ethyl 2-(3-hydroxy-6-methyl-2-pyridylthio)phenylacetate (1.52 g, 0.005 mol) in anhydrous ether (100 ml). The reaction was stopped by ethyl acetate addition after 1 h. After addition of water and neutralisation the title compound was extracted into ethyl acetate which was washed and dried before evaporation. The residual crystalline material weighed 1.10 g (77 %) and had m.p. 135 °C. (Found: C 64.60; H 5.89. Calc. for $C_{14}H_{15}NO_2S$: C 64.36; H 5.79); δ($CDCl_3$) 2.4(Me), 4.1(d, *J* 6.5 Hz, CH_2), 4.6(t, CH), 7.2(5 H, Ph) 6.8 and 7.0(AB, 2 H-Py).

2-β,β-Dideuterio-β-hydroxyethylthio-3-hydroxy-6-methylpyridine (3a) was prepared as above from ethyl (3-hydroxy-6-methyl-2-pyridylthio)-acetate using lithium aluminium hydride-d_4; the non-deuteriated material has previously been described.[13]

3,5-Dimethyldihydrothiazolo[3,2-a]pyridinium-8-oxide (6b).*HCl by acid cyclisation of* 7. 2-Allylthio-3-hydroxy-6-methylpyridine [7] (1.82 g, 0.01 mol) was dissolved in acetic acid (150 ml) and the solution heated in a pressure vessel at 145 °C overnight. The solution was then evaporated, the residue triturated with ether and the remaining solid heated in 6 N HCl for 30 min before evaporation. Recrystallisation of the solid residue furnished the title compound; yield 1.17 g (54 %), m.p. 277 °C (decomp.). (Found: C 49.87; H 5.59. Calc. for $C_9H_{11}NOS$.HCl: C 49.65; H 5.56); δ(TFA) 1.7(d, *J* 6.5 Hz, Me-3), 2.8(Me-5), 3.5 and 4.1(AB of ABX, *J* 12,7, *J* 1 Hz, CH_2), 5.7(X of ABX, –CH), 7.3 and 7.6(AB, 2H-Py).

3-Phenyl-5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide (6c).*HBr by acid catalysed cyclisation of* 10. A solution of 2-β-styrylthio-3-hydroxy-6-methylpyridine.HBr (13.0 g, 0.04 mol) in acetic acid (400 ml) was heated at 150 °C in a pressure bottle overnight. The acetic acid was then distilled off at reduced pressure and the solid residue triturated with acetone before recrystallisation from isopropanol; yield 9.1 g (70 %), m.p. 264 °C (decomp.). (Found: C 52.04; H 4.41. Calc. for $C_{14}H_{13}NOS$.HBr: C 51.86; H 4.35); δ(TFA) 2.5(Me), 3.6 and 4.5(AB of ABX, *J* 12,8 < 1 Hz), 6.6(X of ABX, CH), 7.0–7.5(5 H-Ph, 1 H-Py), 7.8(H-Py).

3-Methyldihydrothiazolo[3,2-a]pyridinium-8-oxide (6d).*HCl. Cyclisation of β-hydroxy derivatives in acetic acid.* A solution of 2-β-hydroxy-α-propylthio-3-hydroxypyridine (1.85 g, 0.01 mol) in acetic acid (30 ml) was heated under reflux overnight. The acetic acid was then evaporated and the residue refluxed for 1 h in 6 N HCl to hydrolyse any acetate formed in the cyclisation reaction. The HCl solution was next evaporated and the solid residue recrystallised from isopropanol; yield 1.10 g (54 %), m.p. 255 °C (decomp.). (Found: C 47.24; H 4.83. Calc. for C_8H_9NOS.HCl: C 47.17; H 4.95); δ(TFA) 1.9(d, *J* 6.5 Hz, Me), 3.5 and 4.1(AB of ABX, *J* 12,7, 6 Hz), 5.5(X of ABX,CH), 7.3–8.3(3 H-Py).

All the 2-β-hydroxyethylthiopyridines (*3*) were found to react in the same way and the products were purified by recrystallisations from isopropanol; yields 50–70 %. NMR analyses of the crude cyclised products showed the rearranged isomer *15* to be absent.

Reactions of 2-β-hydroxyethylthiopyridines (3) *in thionyl chloride solution; formation of* 6/15 *and* 13/14. The 2-β-hydroxyethylthiopyridine (0.05 mol) was dissolved in cold thionyl chloride (30 ml) and the solution left at room temperature for 12–14 h. The reaction mixture was then evaporated at reduced pressure to avoid heating. The residual solid was analysed by NMR in TFA solution.

The mixture of the cyclised product *6* and the chlorinated products *13* and *14* were then heated in ethyl acetate under reflux for 5 h and the solution evaporated before NMR analysis as above.

trans-*2-β-Styrylthio-3-hydroxy-6-methylpyridine* (10).*HBr*. A solution of β-bromostyrene (25.0 g, 0.14 mol) and 3-hydroxy-6-methylpyrid-2-thione (10.0 g, 0.07 mol) in acetic acid (150 ml) was heated at 80 °C for 10 h. The product crystallised from the cold solution and

was recrystallised from acetic acid; yield 15.0 g (66 %), m.p. 200 °C. (Found: C 51.84; H 4.54. Calc. for $C_{14}H_{13}NOS.HBr$: C 51.86; H 4.35); δ(DMSO-d_6) 2.6(Me), 6.9(d, J 16 Hz, $-CH=$), 7.2 – 7.8 ($-CH=$, 5 H-Ph, 3 H-Py).

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