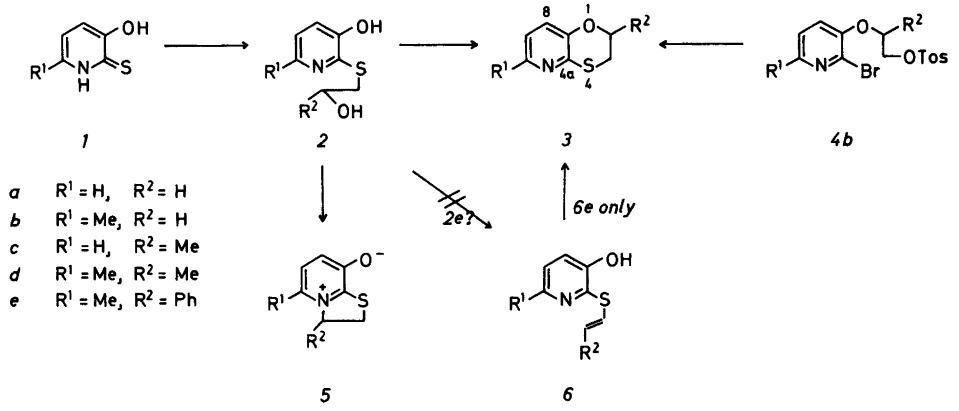
Synthesis of 2,3-Dihydro[1,4]-oxathieno[3,2-*b*]pyridines

GUNNAR A. ULSAKER, TORE LAERUM and KJELL UNDHEIM

Department of Chemistry, University of Oslo, Oslo 3, Norway

In connection with our extensive studies of the novel dihydrothiazolo[3,2-*a*]pyridinium-8-olate system we needed for comparison members of the isomeric 2,3-dihydro[1,4]oxathieno[3,2-*b*]-pyridine system.[1] Thus gas phase pyrolysis of dihydrothiazolo[3,2-*a*]pyridinium-8-olate derivatives have yielded rearranged products of the 2,3-dihydro[1,4]oxathieno[3,2-*b*]pyridine type.[2] The latter heterocyclic system has not been investigated except for our report on the synthesis of the 6-methyl derivative *3b* by thiation of 2-bromo-3-(2-tosyloxyethyloxy)-6-methylpyridine (*4b*, Scheme 1).[3] Requiring a more versatile synthesis of [1,4-oxathieno[3,2-*b*]pyridines we have reinvestigated the cyclisation reactions of 2-(2-hydroxyethylthio)-3-hydroxypyridines which can be prepared in high yields by alkylations of pyridine-2-thiones.[4,5] Previously we have reported that the cyclisation reactions of the 2-(2-hydroxyethylthio)-3-hydroxypyridines yield exclusively the dihydrothiazolo[3,2-*a*]pyridinium-8-olate derivatives.[4,5] We now report that the cyclisation reaction in very strongly acidic media can take a different course with formation of the 2,3-dihydro[1,4]-oxathieno[3,2-*b*]pyridines. The course of the reaction appears to depend on the temperature. Thus at 80 °C in polyphosphoric acid *2b* gave *ca.* 10 % of *3b*, the major product being the betaine *5b*. The yield of *3b* in concentrated sulfuric acid was raised to 26 %, and was further raised to 76 % at 110 °C and to 90 % at 150 °C. When the ethylthio group carries a β-methyl (*2c,2d*) or a β-phenyl (*2e*) substituent the best yields (67–81 %) were obtained with polyphosphoric acid at 80 °C. Initial formation of the betaine *5*, succeeded by rearrangements under the strongly acidic conditions, was excluded by subjecting *5b* to the same reaction conditions as used in the formation of *3b* from *2b*. Presumably cyclisation of *2* over the pyridine nitrogen atom is prevented by protonation of the latter in strong acid. Elimination of water from *2* with formation of *S*-vinyl derivatives *6* was not seen; furthermore, alkenylthio intermediates (*6*) in very strong acid medium are cyclised to [1,3]oxathiolo[4,5-*b*]pyridines.[6] The phenyl derivative *2e*, however, may behave differently since elimination of water can readily occur and the styrylthio derivative *6e* is cyclised almost exclusively to the thieno derivative *3e* in strong acid; this constitutes a convenient synthesis of 2-aryl derivatives of *3* since the corresponding intermediates *6* are readily available.[5] The different reaction paths for the β-aryl and β-alkyl derivatives are attributed to the relative stabilisation of carbonium ion after protonation of the double bond in *6*; in the alkyl derivatives the nucleophilic phenolic oxygen adds to the α-carbon to form [1,3]oxathiolo[4,5-*b*]pyridines,[6] in the phenyl derivative to the β-carbon to form a 2,3-dihydro[1,4]oxathieno]3,2-*b*]pyridine *3*.

In the ^{13}C NMR spectra recorded for *3a*, *3b* and *3d* the chemical shift for C6 in *3a* is ascribed to the signal with the highest short range coupling; 142.3 ppm, $^{1}J_{CH}$ 182 Hz. The 6-methyl substituent in *3b* and *3d* results in 8–9 ppm shift for C6 towards lower field in accordance with the shifts for the α-



Scheme 1.

0302-4369/80/080619-02$02.50

carbons in 2-picoline.[7] Further assignments of pyridine signals are based on Gated-(1) decouplings.

The UV absorption with long-wave band at 305 – 310 mm, which is shifted *ca.* 30 units towards higher wavelength in acid solution, parallels the absorption of the five-membered ring [1,3]-oxathiolo[4,5-*b*]pyridine analogues.[6]

*Experimental. Synthesis of 2,3-dihydro[1,4]-oxathieno[3,2-*b*]pyridines* 3. The 2-(2-hydroxyethylthio)-3-hydroxypyridine[3] (*2*, 1 mmol) was dissolved in concentrated sulfuric acid (2.0 g), and the solution heated at 150 °C for 30 min. The cold mixture was poured onto ice-water (10 ml) and neutralised with sodium bicarbonate. Subsequently the mixture was extracted with chloroform, (3 × 5 ml), and the dried ($MgSO_4$) chloroform solution evaporated; the residue was *3*. Compounds *3a* – *3c* were oils and were converted into hydrogen fluoroborates before elemental analysis by dissolution of the oil in ether (3 ml) and addition of etheral HBF_4 until precipitation of the salt was complete. The salt was triturated with ether before analysis.

When polyphosphoric acid was used in the cyclisation the weight ratio between the pyridine and the reagent was 1:20. The reactions were run at 80 °C and were worked up as above. The products were analysed by TLC and GLC.

3a. Yield 83 % (30 min at 150 °C in conc. sulfuric acid); m.p. 154 °C (HBF_4-salt). Anal.: $C_7H_7NOS \cdot HBF_4$: C, H. UV [EtOH (log ε)]: 306 (3.86), 251 (3.65) nm; [0.1 N HCl in EtOH]: 333 (3.95), 254 (3.52) nm. ^{1}H NMR ($CDCl_3$): δ 3.2 (2 H-3, m), 4.35 (2 H-2, m), 6.85 – 6.95 (2 H-7, 8), 7.95 – 8.05 (H-6). ^{13}C NMR [25.2 MHz, $CDCl_3$ (J_{CH} Hz)]: δ 26.6 (C3, 141), 64.9 (C2, 150), 120.6 (C7, 163), 124.7 (C8, 166), 142.3 (C6, 182), 144.3 (C8a), 149.3 (C4a); Gated-(1) decoupling[J_{CH} Hz]: $^2J_{C6,H7}$ 3.9, $^3J_{C6,H8}$ 6.9, $^2J_{C7,H6}$ 8.8, $^3J_{C8,H6}$ 6.8.

3b.[1] Yield 90 % (30 min at 150 °C in conc. sulfuric acid. UV [EtOH (log ε)]: 310 (3.84), 250 (3.55) nm; [0.1 N HCl in EtOH]: 340 (4.03), 256 (3.52). ^{1}H NMR ($CDCl_3$): δ 2.38 (6-Me), 3.1 (2 H-3, m), 4.35 (2 H-2, m), 6.72 and 6.91 (2 H-7, 8; *J* 8 Hz). ^{13}C NMR 25.2 MHz, $CDCl_3$ (J_{CH} Hz): δ 22.9 (6-Me), 26.4 (C3, 142), 64.4 (C2, 150), 119.1 (C7, 162), 124.0 (C8, 161), 140.6 (C8a), 146.6 (C4a), 150.4 (C6); Gated-(1) decoupling [J_{CH} Hz]: $^3J_{C6,H8}$ 6.9, $^3J_{C7,6Me}$ 3.9.

3c. Yield 67 % (105 min at 80 °C in polyphosphoric acid); m.p. 82 °C (HBF_4-salt). Anal.: $C_8H_9NOS \cdot HBF_4$; C, H. UV [EtOH (log ε)]: 307 (3.84), 250 (3.62) nm; [0.1 N HCl in EtOH]: 332 (3.94), 253 (3.50) nm. ^{1}H NMR ($CDCl_3$): δ 1.47 (2-Me, d), 3.1 (2 H-3, m) 4.35 (H-2, m), 6.75 – 7.1 (2 H-7, 8), 7.85 – 8.1 (H-6).

3d. Yield 70 % (90 min at 80 °C in polyphosphoric acid); m.p. 66 °C (CCl_4 at 0 °C). Anal.: $C_9H_{11}NOS$: C, H. UV [EtOH (log ε)]: 311 (3.89), 249 (sh, 3.61) nm; [0.1 N HCl in EtOH]: 341 (4.05), 254 (3.57) nm. ^{1}H NMR ($CDCl_3$): δ 1.46 (2-Me, d), 2.40 (6-Me), 3.05 (2 H-3, m), 4.3 (H-2, m), 6.72 and 6.92 (2 H-7, 8). ^{13}C NMR [25.2 MHz, $CDCl_3$ (J_{CH} Hz)]: δ 20.8 (2-Me), 23.3 (6-Me), 32.3 (C3, 145), 70.5 (C2, 153), 120.1 (C7, 163), 125.1 (C8, 162), 140.6 (C8a), 146.9 (C4a), 151.1 (C6); Gated-(1) decoupling [J_{CH} Hz]: $^3J_{C6,H8}$ Å6, $^3J_{C7,6Me}$ 3.9.

3e. Yield 81 % (60 min at 80 °C in polyphosphoric acid); m.p. 78 °C (CCl_4 at 0 °C). Anal.: $C_{14}H_{13}NOS$: C,H. UV [EtOH (log ε)]: 311 (385), 250 (sh, 3.50); [0.1 N HCl in EtOH]: 340 (3.99), 255 (3.56). ^{1}H NMR ($CDCl_3$): δ 2.41 (6-Me), 7.33 (2-Ph, s), 2.95 – 3.6 (2 H-3, m), 5.10 (H-2, m), 6.74 and 6.98 (2 H-7,8), *J* 8 Hz).

*2-Phenyl-2,3-dihydro[1,4]oxathieno[3,2-*b*]pyridine* 3e *by cyclisation of* 6e. 2-Styrylthio-3-hydroxypyridine[3] (70 mg) was stirred into polyphosphoric acid (1.9 g) and the mixture heated at 80 °C for 1 h. Water was added to the cold mixture and the aqueous solution neutralised with sodium bicarbonate and extracted with chloroform. Evaporation of the dried ($MgSO_4$) chloroform solution left a pale yellow oil; yield 77 % (54 mg) which by GLC analysis was found to be pure *3e*.

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Received August 6, 1980.