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N-Quaternary Compounds. Part LI.* Deuterium Labelling of Thiazolo[3,2-*a*]pyridinium Betaines

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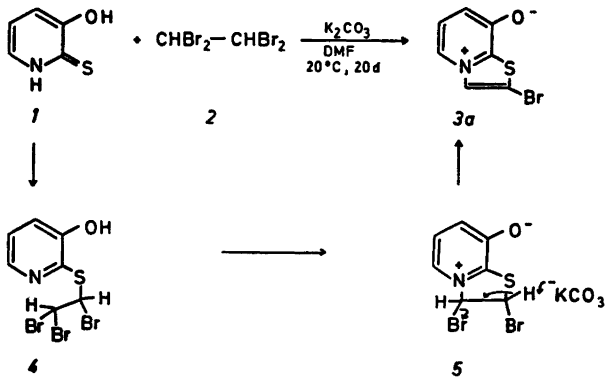
Reaction between 1,1,2,2-tetrabromoethane and 3-hydroxypyridine-2-thione has yielded 2-bromothiazolo[3,2-*a*]pyridinium-8-olate. The bromo derivative allows selective deuteriation on C-2 and C-3. The ^{13}C NMR spectra are discussed.

Simple pyridinium systems are resistant towards electrophilic substitution. The thiazolo- and dihydrothiazolo[3,2-*a*]pyridinium systems are activated by an 8-hydroxy group for electrophilic substitution in the pyridine ring.[2,3] The thiazole ring in thiazolo]3,2-*a*[pyridinium-8-olates is not activated for direct electrophilic substitution thus excluding direct halogenation.[3] We herein report a method for the synthesis of a bromo-substituted thiazole derivative. The latter also allows regioselective deuteriations in the thiazole ring (Scheme 2). Deuteriations in the pyridine ring have previously been reported.[3]

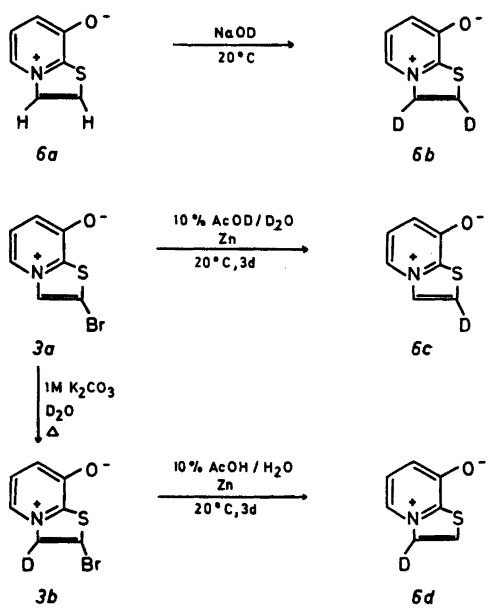
* Part L, see Ref. 1.

The bromo derivative was synthesised by allowing the pyridine-2-thione *1* and 1,1,2,2-tetrabromoethane to react together in the presence of a base in the cold. Attempts to increase the slow reaction (20 days) by increase in temperature lowered the yields. The monobromo derivative obtained has been identified as the 2-bromo isomer *3a* by ^1H NMR analysis. No intermediates have been isolated and hence the reaction path has not been elucidated. Intermediates like *4* and *5*, however, are feasible. The latter would require selective proton abstraction from C-2 as in the case of the methanol elimination from 3-methoxydihydrothiazolo[3,2-*a*]pyridinium-8-olate.[1]

Proton-deuteron exchange at C-2 and C-3 in thiazolo[3,2-*a*]pyridinium-8-olates occurs readily using NaOD such as in the formation of the 2,3-dideuterio derivative *6b* from *6a* (Scheme 2).[1,3] Deuteriation in the thiazole ring has also been found to occur readily under acidic con-



Scheme 1.



Scheme 2.

ditions; *6a* in cold trifluoroacetic acid-d_1 was completely deuteriated in the thiazole ring and partly deuteriated in the pyridine ring after 5 min. Deuteriation in acetic acid-d_1 was much slower, and in 10 % acetic acid-d_1 solution no appreciable deuteriation was seen in *6a* after one week in the cold. Hence the bromine atom in *3a* could be selectively replaced by deuterium through reduction with zinc powder in 10 % acetic acid-d_1 solution. Basically the same approach has been used to synthesise the 3-deuterio isomer *6d*. The bromo derivative *3a* in the presence of potassium carbonate in deuterium oxide was deuteriated at C-3 to furnish *3b* which was hydrogenolysed with zinc powder in 10 % acetic acid to the 3-deuterio isomer *6d*.

The ^{1}H NMR spectra (D_2O) are in accordance with structure *3a* assigned to the bromo isomer. Thus H-3 (*6c*, δ 8.30) resonates at lower field than H-2 (*6d*, δ 7.94); which is the same relative order of the chemical shifts as for the thiazole protons in isomeric 2,5- and 3,5-dimethyl homologues of *6a*,[3] and therefore supports the structural assignment. A bromine substituent in benzene has little effect on the chemical shifts of the α-protons,[4] which is also apparent in the present series by comparison of the chemical shift for H-3 in the bromo derivative (δ 8.35) and *6c* (δ 8.30).

Gated-(1) decoupled spectra [5] were useful in the relative assignment of ^{13}C chemical shifts (Fig. 1). The signals for C-8 and C-9 were identified by the lack of one-bond coupling and by the high chemical shifts. C-8 is long-range coupled with H-6, $^3J_{CH}$ 8.6 Hz. The *meta* coupling for C-9 to H-7 was not resolved in agreement with previous observation that pyridines without the lone pair of electrons are poorly resolved, which has been attributed to ^{14}N—^{13}C couplings.[6] Similarly the signals from the α-carbons in the pyridine ring in dihydrothiazolo[3,2-*a*]pyridinium derivatives are unresolved.[7] C-7 is *meta* coupled to H-5, $^3J_{CH}$ 7.2 Hz, and C-6 is *ortho* coupled to H-5, $^2J_{CH}$ 4.2 Hz. The size of the latter coupling corresponds closely to the values (*ca*, 4 Hz) reported for $^2J_{CH\alpha}$ in other pyridinium-olates.[7,8] The *ortho* couplings between the β,γ-positions in the pyridine ring were too small to be seen under the recording conditions.[7]

The one-bond carbon-hydrogen coupling $^1J_{CH}$ is highest for the α-carbons on pyridines, and is further increased on protonation or quaternisation.[6] The broad signals with $^1J_{CH}$ *ca*. 200 Hz can therefore be assigned to C-3 and

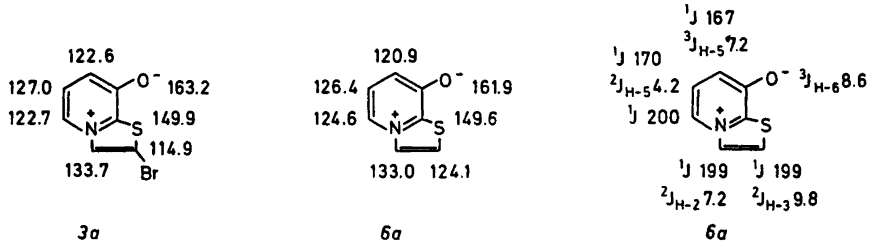


Fig. 1. ^{13}C NMR spectral data.

C-5. Further differentiation, besides the magnitude of the long range couplings, follows from comparison with the spectra of the 2- and 3-deuterio derivatives *6c* and *6d*. The relative chemical shifts of C-2 and C-3 follow the order in thiazole itself.[9] The increase *ca.* 10 Hz in the one-bond coupling can perhaps be compared with the increase $^1J_{CH}$ for the α-carbons in pyridine when the heteroatom carries a positive charge as discussed above. The increase in $^1J_{CH}$ for both C-2 and C-3 may indicate that both heteroatoms in the thiazole ring in *6* are partially charged. The *ortho* coupling for C-2 $^2J_{CH}$ 9.8 Hz is considerably less than the corresponding coupling *ca.* 16 Hz in thiazole,[9] and is reminiscent of the decrease in $^2J_{CH}$ between C-α and H-β in pyridines when the heteroatom is charged.[6-8] The *ortho* coupling $^2J_{CH}$ 7.2 Hz for C-3, however, corresponds closely to the corresponding coupling in thiazole.[9] The effect on the chemical shifts of the bromine atom in *3a* is almost as in the corresponding 5-bromothiazole, *viz.* *ca.* 10 ppm shielding at C-2 and *ca.* 1 ppm deshielding at C-3.[9]

EXPERIMENTAL

^{1}H NMR spectra were recorded in D_2O on a 60 MHz spectrometer. The ^{13}C NMR spectra were recorded in D_2O (1.5–2.0 g in 2 ml) by means of a Yeol FX60 Fourier transform spectrometer operating at 25.2 MHz. The temperature was *ca.* 30 °C. Proton-noise decoupled and gated-(1) decoupled spectra were obtained. The shifts are related to TMS.

2-Bromo-8-hydroxythiazolo[3,2-a]pyridinium fluoroborate 3a·*HBF*$_4$. A mixture of 3-hydroxypyridine-2-thione (1.27 g, 0.01 mol), 1,1,2,2-tetrabromoethane (20 ml) and potassium carbonate (6.0 g) in DMF (100 ml) was stirred at room temperature. The progress of the reaction was monitored by TLC. (Silica gel; n-BuOH:EtOH:NH_3 1:1:1). At 4-day intervals, further additions of 1,1,2,2-tetrabromoethane (10 ml) and potassium carbonate (3.0 g) were carried out. All the pyridine-2-thione had been consumed after 20 days. The reaction mixture was then filtered and the filtrate diluted with water (200 ml) before extraction with chloroform (2 × 50 ml). The aqueous solution was next passed over a strong cation exchanger [Amberlite IR-120 (H^+)]; the salts were washed out with water and the bromo derivative *3a* eluted with *aq.* 0.3 M ammonia, yield 0.40 g (17 %). For elemental analysis the product was converted to its hydrofluoroborate by addition of borofluoric acid in ether to a methanolic solution of the product. The hydrofluoroborate of *3a* was precipitated by addition of ether; m.p. 244 °C (EtOH/EtOAc). Anal. for $C_7H_4BrNSO \cdot HBF_4$: C, H. ^{1}H NMR of *3a* (D_2O): δ 8.35 (H-3), 8.11 (d, H-5, $J_{5,6}$ 6 Hz), 7.43 (dd, H-6, $J_{6,7}$ 8 Hz), 6.95 (d, H-7).

2-Deuteriothiazolo[3,2-a]pyridinium-8-olate 6c. 2-Bromothiazolo[3,2-*a*]pyridinium-8-olate (100 mg) was dissolved in 10 % acetic acid-d_1 in D_2O (1 ml) and a little zinc dust added. The progress of the reduction was monitored on silica TLC (n-BuOH:EtOH:NH_3 1:1:1). The reaction required 3 days to go to completion. The reaction mixture was then filtered and the filtrate evaporated to dryness at reduced pressure in the cold. ^{1}H NMR on the mixture (D_2O): δ 8.30 (H-3), 8.27 (d, H-5), 7.44 (d, d, H-6), 6.95 (d, H-7).

Both *6c* and *6d* (see below) can be isolated from the reaction mixtures as follows: The residue after evaporation of the reduction mixture was dissolved in water (5 ml) and the pH adjusted to *ca.* 3.5. The solution was then extracted with 90 % *aq.* phenol (3 × 5 ml) and the combined phenol extracts washed with water (2–3 ml). Ether (150 ml) was next added to the phenolic solution whereby an aqueous and an organic layer resulted. The aqueous layer was collected and the organic layer washed with water (5 × 5 ml). The combined aqueous layer and washings were extracted with ether (2 × 5 ml) before the solution was evaporated leaving the desired thiazolo[3,2-*a*]pyridinium-8-olate derivative.

3-Deuteriothiazolo[3,2-a]pyridinium-8-olate 6d. 2-Bromothiazolo[3,2-*a*]pyridinium-8-olate (100 mg) was dissolved in 1 M sodium carbonate in D_2O and the solution warmed to *ca.* 60 °C. ^{1}H NMR showed that H-3 was fully exchanged in the course of a few minutes. The solution which contains *2-bromo-3-deuteriothiazolo[3,2-a]pyridinium-8-olate* was then evaporated, the residue redissolved in water and the solution neutralised with 10 % acetic acid before evaporation. The precipitate was redissolved in water and the solution evaporated before the material was dissolved in 10 % aq. acetic acid (1 ml) and a little zinc dust added. The reaction required 3 days at room temperature to go to completion. The mixture was then filtered and the solution evaporated in the cold at reduced pressure to yield the title compounds admixed with salts. ^{1}H NMR (D_2O): δ 7.94 (H-2), 8.24 (d, 5-H), 7.46 (dd, H-6), 6.94 (d, H-7).

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