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Short Communications

N-Quaternary Compounds. Part L.* Elimination Reactions in Dihydrothiazolo[3,2-*a*]pyridinium Derivates

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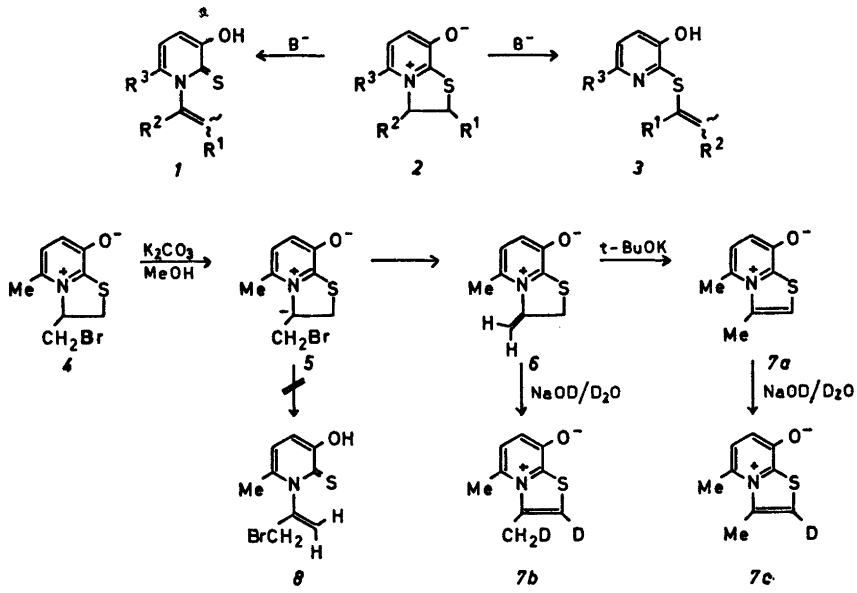
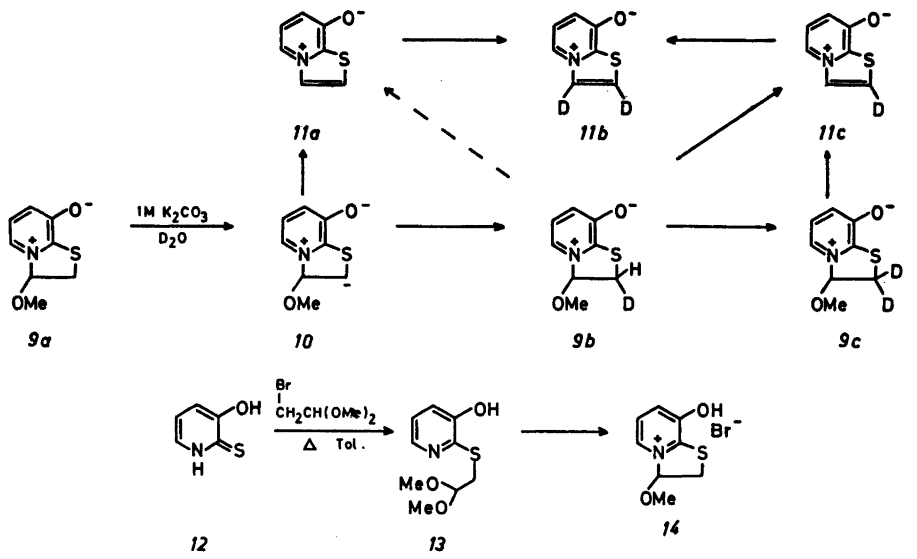
Members of the dihydrothiazolo[3,2-*a*]pyridinium-8-olate series under basic conditions can be rearranged to the corresponding *N*-vinylpyridine-2-thione *1* and the isomeric 2-vinylthiopyridine *3*; the product ratio depends on the nature of the substituents.[2,3] Presumably *N*-vinyl formation *1* is initiated by deprotonation at C-3. In the 3-bromomethyl derivate *4*, however, carbanion formation at C-3 may be envisaged to be succeeded by cleavage of either the C–Br or C–S bond (Scheme 1, *6* or *8*); instead the thiazolo derivate *7a* was isolated after treatment of *4* with 0.5 potassium *t*-butoxide. Its formation is rationalized by initial bromide expulsion to the methylene derivative *6* which is succeeded by a prototropic shift to the fully aromatic isomer *7a*. Intermediate formation of the methylene derivative *6* was demonstrated using milder basic conditions; treatment of *4* with potassium carbonate at room temperature and careful work-up of the reaction mixture yielded *6*. The latter was isomerised to *7a* using potassium *t*-butoxide. The rearrangement of *6* was also run in 0.8 M NaOD in an NMR tube and was complete after 3 h at room temperature. The signal intensity of H-6, which is in a non-activated pyridine position, was used as internal integration standard in the NMR measurements. The intensity ratio for the proton signals from the 3- and 5-methyl groups was 2:3, and there was no deuterium incorporated into the 5-methyl group. In addition the product *7b* was deuteriated in the 2-position. In a separate experiment under similar conditions it was shown that H-2 was rapidly exchanged with deuterium and there was no deuterium incorporation into the methyl groups. Hence, from the above findings, it is

* Part IL, see Ref. 1.



Scheme 1.



Scheme 2.

concluded that the 3-methylene group in *6* receives its hydrogen by an intermolecular process.

Deprotonation of the 3-methoxy derivative *9a* (Scheme 2) at C-2 or C-3 might be envisaged to yield either an *N*-vinyl (*1*, $R^1=R^3=H$, $R^2=$ OMe) or *S*-vinyl (*3*, $R^1=R^3=H$, $R^2=OMe$) derivative or a mixture thereof. Base treatment of *9a*, however, yielded the thiazole *11a*. The latter was also obtained from *9a* using cold concentrated sulfuric acid, which is a reagent previously used for cyclization of 2-β-oxoalkylthiopyridines to homologues of *11a*.[4]

Formation of the thiazole *11a* with base is rationalized by proton abstraction from C-2 followed by elimination of the methoxy group in preference to the Hofmann elimination with *S*-vinyl formation (*3*, $R^1=R^3=H$, $R^2=OMe$).

The transformation of *9a* to *11a* was investigated using ^1H NMR spectrometry. H-6 was used as internal integration standard as discussed above. *9a* in 1 M K_2CO_3 solutions in deuterium oxide was used. No exchange of H-7 and *ca.* 5 % exchange of H-5 had occurred after heating at 90 °C for 6 h or heating at 60 °C for 95 h. Heating at 90 °C for 6 h gave complete elimination to the thiazole. Exchange of H-3 in *9a* was not seen during the reaction, whereas the H-2 protons were exchangeable. Thus about 50 % of *9a* had reacted to the thiazole *11b* after 95 h at 60 °C whereas the other part of *9a* was deuteriated to the extent of 70 % in the 2-position (Scheme 2). Evaporation and heating of this mixture in water for 2 h gave the mono and dideuteriated thiazoles *11c* and *11b* in the ratio 1:2 (NMR). Complete deuteriation at C-2 resulted on further heating with 1 M K_2CO_3 in deuterium oxide. In the reactions of *9a* as discussed above, the non-deuteriated thiazole *11a* was not seen, presumably because H-2 and H-3 in *11a* are readily exchangeable.

The NMR data show that proton abstraction at C-2 is faster than elimination of the methoxy group which suggests an E1cB elimination mechanism. Preferential anion formation at C-2 is attributed to the stabilising interaction between the carbanion and the sulfur atom,[5,6] which presumably is enhanced because the sulfur atom is part of a thiopyridinio system.

The 3-methoxy derivative *9a* was synthesized from the corresponding pyridine-2-thione by heating the latter together with bromoacetaldehyde dimethylacetal in toluene. Cyclization over the phenolic hydroxy group to the corresponding methyl 3-pyridyl acetal was not seen under these conditions,[4] the product being the pyridinium derivative *9a*.

Experimental. 3-Methylene-5-methyldihydrothiazolo[3,2-a]pyridinium-8-olate 6. Potassium carbonate (0.28 g, 0.002 mol) was added to a solution of 3-bromomethyl-5-methyl-8-hydroxydihydrothiazolo[3,2-*a*]pyridinium bromide[7] (0.30 g, 0.001 mol) in methanol (50 ml) and the reaction mixture stirred at room temperature for 1 h. The reaction mixture was then acidified with acetic acid and evaporated almost to dryness at reduced pressure. The residual mixture was dissolved in water (20 ml) and the aqueous solution was extracted with aq. phenol (90 % phenol, 3 x 10 ml). The combined phenol extracts were washed with water (10 ml), ether (100 ml) added, and the separated water layer collected. The ether – phenol layer was washed

with water (2 × 10 ml) and the washings combined with the water layer. The aqueous solution was washed with ether (10 ml) and then freeze-dried. The residual hydroacetate of the title compound was recrystallized from isopropanol by preparing a saturated solution at room temperature from which the product crystallized at −20 °C; yield 0.11 g (46 %). The elemental analysis was performed on the hydrofluoroborate which was prepared from the hydroacetate by dissolution of the latter in ethanol followed by addition of etheral HBF_4. The precipitate was dried over NaOH *in vacuo*, redissolved in ethanol and reprecipitated by slow addition of ether. The product started to melt at 132 °C; the gradual melting point is due to isomerization to the thiazolo analogue *7a* on heating. Anal. $C_9H_9NOS.HBF_4$: C, H. ^{1}H NMR (D_2O): δ 2.67 (5-Me), 4.22 (H-2), 5.67 and 5.77 (CH_2-3), 7.07 (H-6, H-7).

3,5-Dimethylthiazolo[3,2-a]pyridinium-8-olate 7a. 3-Bromomethyl-5-methyl-8-hydroxydihydrothiazolo[3,2-*a*]pyridinium bromide [7] (0.68 g, 0.002 mol) was added to 0.5 M potassium *t*-butoxide in *t*-butyl alcohol (20 ml, 0.01 mol) and the mixture was stirred at room temperature overnight. After acidification with acetic acid, the mixture was evaporated to dryness at reduced pressure, the residue dissolved in water and the aqueous solution passed through a column of a strong cation exchange resin (Amberlite IR-120(H^+)). After washing with water, the title compound was eluted with aq. 0.3 M ammonia. Evaporation of the eluates left the title compound in 56 % yield (0.20 g); physical properties as previously reported.[4] Treatment of 3-methylene-5-methyldihydrothiazolo[3,2-*a*]pyridinium-8-olate *6* as hydroacetate with potassium *t*-butoxide as above also yielded *7a*.

Thiazolo[3,2-a]pyridinium-8-olate 11a. *Base treatment of* 9a. Potassium *t*-butoxide, 0.5 M, in *t*-butyl alcohol (5 ml, 0.0025 mol), was added dropwise over 5 min to a solution of 3-methoxy 8-hydroxydihydrothiazolo[3,2-*a*]pyridinium bromide (0.26 g, 0.001 mol) in DMF (10 ml) at room temperature. After stirring for another 15 min, water (10 ml) was added to the reaction mixture and the pH was adjusted to 2 with HCl. The resultant mixture was extracted with ether, and the aqueous solution was passed through a strong cation exchange column (Amberlite IR-120(H^+)). After washing the column with water, the title compound was eluted with *aq.* 0.3 M ammonia. The compound obtained after evaporation was chromatographically homogenous, yield 0.11 g (73 %). For elemental analyses the compound was converted into the hydrofluoroborate by dissolution in methanol followed by dropwise addition of ethereal HBF_4 when the hydrofluoroborate was precipitated; m.p. 181 °C (decomp.). Anal. $C_7H_5NSO.HBF_4$: C,H. ^{1}H NMR(TFA): δ 7.8–8.0 and 8.8–9.1 (Pyr), 8.31 (H-2, $J_{2,3}$ 4Hz), 8.67 (H-3).

Acid treatment of 9a. 3-Methoxy-8-hydroxydihydrothiazolo[3,2-*a*]pyridinium bromide (0.4 g, 0.016 mol) was added to conc. H_2SO_4 (2 ml) at 5 °C and the reaction mixture kept at this temperature for 48 h. Ethyl ether (100 ml) was then added and the mixture left in the cold before the ethereal supernatant was decanted from the precipitate. The latter was the hydrosulfate of the title compound; yield 0.4 g (94 %).

3-Methoxy-8-hydroxydihydrothiazolo[3,2-a]-pyridinium bromide 14. A solution of 3-hydroxypyridine-2-thione (1.3 g, 0.01 mol) and bromoacetaldehyde dimethylacetal (3.4 g, 0.02 mol) in toluene (75 ml) was heated under reflux for 10 h. After cooling, the toluene was decanted from the precipitated oily material, and the latter crystallized from isopropanol: ethanol; yield 1.3 g (49 %), m.p. 222 °C (decomp.). Anal. $C_8H_8NSO_2.HBr$: C,H. ^{1}H NMR (TFA): δ 3.6 (OMe), 5.3 (H-2), 5.9 (H-3), 7.4–8.1, 8.3–8.5 (Pyr.).

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