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N-Quaternary Compounds. XXXVI.[1] Nitro- and Diazonium-group Activation in Reactions of Pyridinium Derivatives

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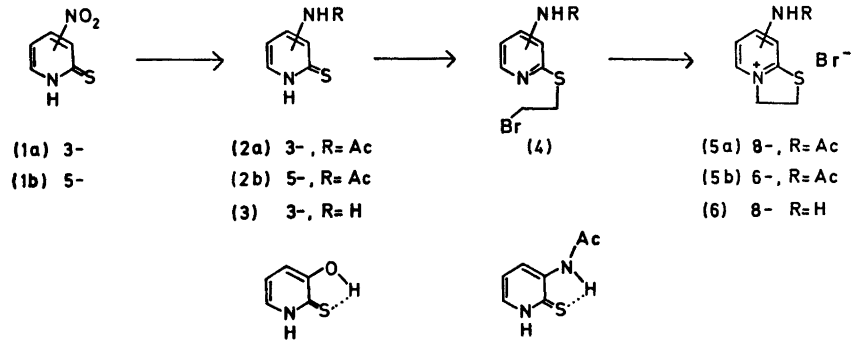
6-(8)-Nitrodihydrothiazolo[3,2-*a*]pyridinium salts as pseudo-bases are readily brominated. Diazotisation of the 8-amino derivative is followed by re-arrangement of the diazonium salt into dihydrothiazolo[2,3-*e*]*v*-triazoles.

Simple pyridinium derivatives are electron deficient and therefore not reactive towards electrophiles. The pyridinium ring in dihydro thiazolo[3,2-*a*]pyridinium-8-oxide, however, is readily substituted by electrophiles because of the activation from the oxide function.[2] In the present work we have investigated effects of other substituents on the reactivity of the pyridinium ring. Syntheses of amino derivatives are shown in Scheme 1. The acetamides (*2a*) and (*2b*) required for the syntheses were prepared by dithionite reduction [3] of the corresponding nitropyrid-2-thiones [4] and the amides isolated after acetylation. The 3-amine (*3*) was prepared from the amide (*2a*) by acid hydrolysis.

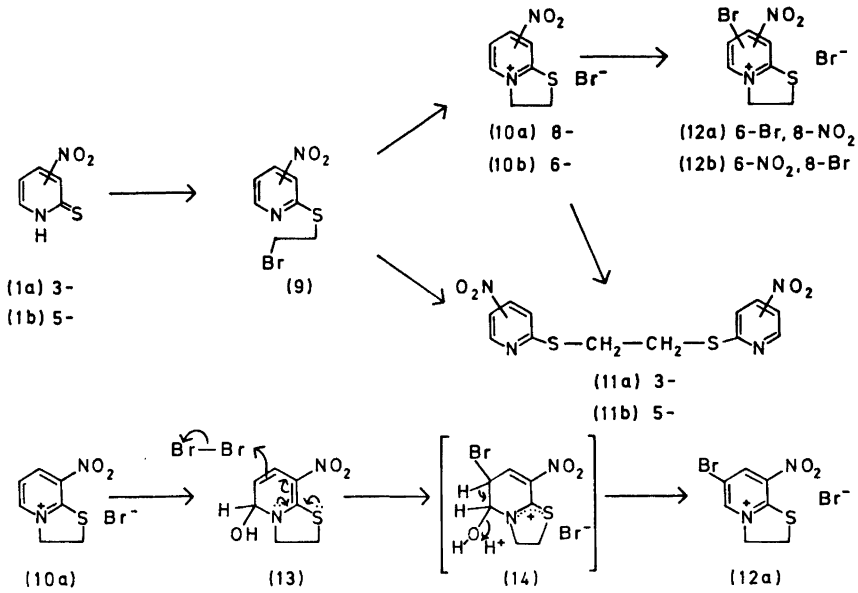
Pyrid-2-thiones are initially attacked on the sulphur atom by electrophilic carbon.[5,6] A 3-ethoxy group increases the reaction rate by virtue of its electron releasing properties while a 3-hydroxy group has the opposite effect. The latter has been attributed to intramolecular hydrogen bonding (*7*).[6] In the present work it was noticeable that the 3-acetamide was less reactive than the 5-isomer as expected on the basis of steric interference and hydrogen bonding (*8*).

Generally, in aminopyridines it is the pyridine nitrogen atom which is the more basic and nucleophilic. Accordingly, cyclisation of the *S*-alkylated intermediate (*4*) should occur over the pyridine nitrogen atom to the dihydrothiazolo[3,2-*a*]pyridinium derivatives (*5a-6*) even in the case of the 3-amine (*3*). This was confirmed by acid hydrolysis of the bicyclic product from (*2a*) which gave the condensation product from (*3*). The latter product contains a diazotisable amino group as discussed below.

S-Alkylation is the overall rate determining step in the reaction sequence with very rapid cyclisation of the *S*-alkylated intermediate



Scheme 1. (7) (8)

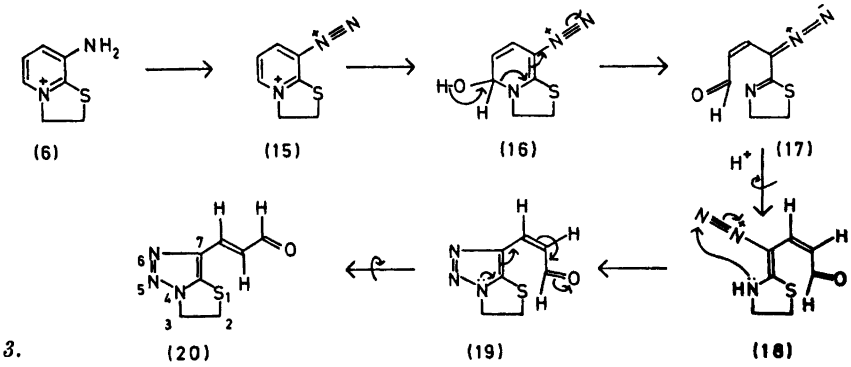


Scheme 2.

since the latter was not observed in the reaction. In the reaction of the nitro analogues (*1*), however, a dipyridyl thioether (*11*) was isolated. The nitro group serves to decrease the nucleophilicities of both the sulphur and the pyridine nitrogen atoms. The reduced cyclisation rate could account for formation of (*11*). The bicyclic product (*10*), however, is reactive towards nucleophiles and (*11*) could equally well have been formed by a nucleophilic ring-opening of (*10*). The latter path was demonstrated by addition of the parent thione (*1*) as sodium salt to the pyridinium salt (*10*) which resulted in formation of (*11*).

Dihydrothiazolo[3,2-*a*]pyridinium derivatives with a hydroxy group in 8-position are very readily substituted by electrophiles and even undergo diazo-coupling reactions.[2] The electron releasing properties of the amino group and the acetamido group, however, were not sufficient to effect direct bromination in (*5*) and (*6*) under mild conditions.[2] Contrary to deductive expectations, however, the nitro-substituted pyridinium derivatives (*10*) are readily brominated in aqueous methanol. This observation is understandable in terms of pseudo-base formation as illustrated in Scheme 2 for the 8-nitro derivative (*13*). As distinct from the amino salts (*5,6*) the electron withdrawing effect by the nitro group increases the electron deficiency of the pyridinium ring to the extent that hydroxyl addition occurs. Pseudo-base formation in pyridinium systems has been found to occur preferentially in an α-position to the heteroatom.[7] The pseudo-base thus formed can be regarded both as an *N*-vinyl and *S*-vinyl derivative activated for electrophilic substitution in 6- or 8-position, respectively (Scheme 2). The mechanistically postulated substitution pattern is further supported by the NMR spectra which show two pyridinium protons with chemical shifts less than 1 τ and coupling constants $J = 1.5 - 2.0$ Hz as expected for 1,3-coupling.

In order to prove the dihydrothiazolo[3,2-*a*]-pyridinium structure with a primary amino group, after the reaction of 3-amino-pyrid-2-thione (*3*), the condensation product was diazotised using isoamyl nitrite in aqueous acetic acid. The diazonium group is interesting since it is by far the most strongly electron-attracting group known.[8] It is an electrophilic reagent which can attack a vicinal thioether group with 1,2,3-thiadiazole formation.[9] Any appreciable product formation with opening of the dihydrothiazole ring, however, was not



Scheme 3.

observed for (*6*). Nor was the diazotised pyridinium molecule sufficiently stabilised from the thiother group for heterolytic reactions with water in which N_2 is the leaving group. Instead the highly electron deficient pyridinium system adds a hydroxyl ion similar to the observation for the nitro derivatives (*10*) discussed above. The pseudo-base then re-arranges to two main products identified as the v-thiazoles (*19*) and (*20*). The *trans*-acraldehyde (*20*) is the more stable and is readily formed from the *cis*-isomer by isomerisation about the double bond. The formyl group in IR absorbs at 1670 cm^{-1}. Both isomers have UV absorption maxima at 314 and 239 nm. High resolution mass spectrometry shows molecular ion at *m/e* 181 with the presented elemental compositions. The fragmentation is characterised by $[M-N_2]$ being the major intermediate for lower mass fragments. The coupling constant between the α-(3.8 τ) and the β-proton (2.2 τ) is $J=16$ Hz for the *trans*-isomer. Between the α-proton and the formyl proton (0.4 τ) the coupling constant is $J=8$ Hz. The vicinal vinyl coupling between the α- (4.0 τ) and the β-proton (2.7 τ) in the *cis*-isomer is $J=12$ Hz, the coupling between the α-proton and the formyl proton being as in the *trans*-isomer. The chemical shift for the formyl proton in the *cis*-isomer, however, has been moved downfield to -0.7 τ. A similar observation for *cis*-3-(v-triazolo[1,5-*a*]pyridyl)acraldehydes relative to their *trans*-isomers has been attributed to the vicinal nitrogen lone-pair in the triazole.[10] The isomer shifts in the present case are of the same order which could mean that the lone pairs on the sp^3-hybridised sulphur atom have little influence in this respect.

X-Ray analysis of the *trans*-isomer (*20*) shows that the acraldehyde side-chain has a conformational preference.[11] It lies with its substituents in the ring-plane and has the α-hydrogen atom close to the sulphur atom (*20*). The triazole ring is planar. The dihydrothiazole ring has the envelope conformation with the 1- and 3-atoms nearly coplanar with the triazole ring and the C-2 atom 0.4 Å out of plane.[11] The envelope conformation corresponds to that found in dihydrothiazolo-pyridines.[12]

The crude product after the diazotisation reaction is an almost equimolar mixture of the *cis*- and *trans*-isomers. In weak acid solution the *cis*-isomer is converted to the *trans*-isomer. Warming a solution of the 1:1 isomer mixture in deuterium oxide also led to the *trans*-isomer. No deuterium was incorporated in the molecule. Isomerisation therefore occurs without any exchange of vinyl protons.

The re-arrangement leading to the *v*-triazoles is explained by initial hydroxyl addition to the carbon next to the hetero-atom followed by re-arrangement as indicated in Scheme 3. The reaction appears general in that simple 1-alkyl- and 1-aryl-3-aminopyridinium salts are convertible into 3-(1-alkyl or aryl-4-v-triazolyl)-acraldehydes.[13,14] Similar re-arrangements to v-triazoles have also been observed from a number of 1-aminoquinolizinium salts in aqueous nitrous acid.[10]

No attempts have been made to study the intermediate diazonium salts (Scheme 3). In simple 3-aminopyridinium salts, however, a transient and quickly disappearing diazo-coupling ability was observed supporting the formulation of an initial diazonium salt.[13,14]

The cyclisation corresponds to the well established formation of benzotriazoles by diazotisation of *o*-phenylenediamine.[15]

The exocyclic double bond in the initially formed triazole would be expected to have retained the *cis*-configuration. The presence in the reaction product of almost equal amounts of the *cis*- and *trans*-isomers is presumably due to the ease of isomerisation of the *cis*-isomer under the experimental conditions used.

EXPERIMENTAL

All NMR spectra were determined on a 60 MHz Varian A-60A spectrometer.

3-Acetamidopyrid-2-thione (2a) was prepared by sodium dithionite reduction of 3-nitropyrid-2-thione [4] followed by acetylation as described for 5-acetamidopyrid-2-thione (*2b*).[3] Yield 38 %, m.p. 196–197 °C (H_2O). (Found: N 16.85; S 18.94. Calc. for $C_7H_8N_2OS$: N 16.65; S 19.06).

8-Acetamidodihydrothiazolo[3,2-a]pyridinium bromide (5a). 3-Acetamidopyrid-2-thione (0.85 g, 0.005 mol), potassium carbonate (0.35 g, 0.0025 mol) and 1,2-dibromoethane (0.94 g, 0.005 mol) were stirred together in anhydrous dimethylformamide (30 ml) in the cold. Chromatography showed the reaction to be over after 3 h. The reaction mixture was then evaporated at reduced pressure and the residue dissolved by heating in dilute methanol. The title compound was precipitated on cooling; yield 38 %, m.p. 269–270 °C (decomp.) (dilute MeOH). (Found: C 38.85; H 3.98; N 10.36. Calc. for $C_9H_{11}BrN_2OS$: C 39.28; H 4.03; N 10.18), τ (TFA) 6.0 (2 H-2), 4.6 (2 H-3), 1.3 (H-5), 2.3 (H-6), 1.3 (H-7), 7.5 ($COCH_3$); $J_{5,6}$ 6.0, $J_{6,7}$ 8.0, $J_{5,7}$ 2.0 Hz.

6-Acetamidodihydrothiazolo[3,2-a]pyridinium bromide (5b) was prepared as (*5a*) in 60 % yield, m.p. 320–323 °C (decomp.) (dil. MeOH). Reaction time 30 min. (Found: S 11.33; Br 29.24. Calc. for $C_9H_{11}BrN_2OS$: S 11.65; Br 29.04). τ (TFA) 6.1 (2 H-2), 4.7 (2 H-3), 0.5 (H-5), 1.6 (H-7), 2.2 (H-8), 7.6 ($COCH_3$); $J_{7,8}$ 9.0, $J_{5,7}$ 2.0 Hz.

8-Nitrodihydrothiazolo[3,2-a]pyridinium bromide (10a) was synthesised as (*5a*). The reaction time was 1 day. The solid residue after evaporation of the reaction mixture was extracted with hot dilute methanol (4:1) and the yellow, insoluble material crystallised from acetone. The product thus obtained in 15 % yield, m.p. 148–149 °C, has been identified as *1,2-di-(3-nitro-2-pyridylthio)ethane* (*11a*); molecular ion composition by high resolution MS: $C_{12}H_{10}N_4O_4S$; τ (TFA) 6.1 (4 H-2 CH_2), 0.8 (H-4), 2.0 (H-5), 0.8 (H-6).

The title compound was precipitated from the dilute ethanol solution on cooling; yield 38 %, m.p. 300 °C (decomp.). (Found: C 32.26; H 2.68; S 11.95. Calc. for $C_7H_7BrN_2O_2S$: C 31.95; H 2.68, S 12.19), τ (TFA) 6.1 (2 H-2), 4.5 (2 H-3), 0.8 (H-5), 2.1 (H-6), 0.8 (H-7); $J_{5,6}$ 6.0, $J_{6,7}$ 8.0, $J_{5,7} < 1$ Hz.

6-Nitrodihydrothiazolo[3,2-a]pyridinium bromide (10b) was prepared as (*10a*). The reaction time was 4 h. The yield of co-formed *1,2-di-(5-nitro-2-pyridylthio)ethane* (*11b*) was 18 %, m.p. 153–156 °C (acetone); molecular ion composition by high resolution MS: $C_{12}H_{10}N_4O_4S_2$; τ (TFA) 6.4 (4 H-2 CH_2), 1.9 (H-3), 1.0 (H-4), 0.5 (H-6).

The yield of the title compound (*10b*) was 60 %; no melting point due to gradual decomposition on heating (dil. MeOH). (Found: C 31.93; H 2.66; S 12.17. Calc. for $C_7H_7BrN_2O_2S$: C 31.95; H 2.68; S 12.19), τ (TFA) 5.8 (2 H-2), 4.4 (2 H-3), 0.3 (H-5), 1.0 (H-7), 1.9 (H-8); $J_{7,8}$ 9.0, $J_{5,7}$ 2.0 Hz.

8-Aminodihydrothiazolo[3,2-a]pyridinium bromide (6). (a) 3-Acetamidopyrid-2-thione (4.8 g, 0.04 mol) was dissolved in a solution of conc. HBr (5 ml) and ethanol (50 ml) and the resultant solution heated under reflux for 4 h. The precipitated 3-aminopyrid-2-thione (*3*) as hydrobromide was filtered off from the cold reaction mixture and reacted further with 1,2-dibromoethane in DMF as described for (*2a*) using an additional equivalent of potassium carbonate for neutralisation of the hydrobromide. The reaction time was 15 min; yield 59 %, m.p. 155–157 °C (dil. EtOH). (Found: C 33.48; H 4.43; N 11.20. Calc. for $C_7H_9BrN_2S.H_2O$: C 33.48; H 4.41; N 11.15), τ (TFA) 5.9 (2 H-2), 4.6 (2 H-3), 1.4 (H-5), 2.3 (H-6), 1.6 (H-7); $J_{5,6}$ 6.0, $J_{6,7}$ 8.0, $J_{5,7} < 1$ Hz.

(b) 8-Acetamidodihydrothiazolo[3,2-*a*]pyridinium bromide (*5a*) (9.0 g, 0.033 mol) was dissolved in water (100 ml) and Amberlite IRA-400 (OH^-) ion exchanger added. The ion exchanger was filtered off after stirring for 3 h, conc. HCl (100 ml) added to the filtrate and the solution heated under reflux for 1 h. Evaporation gave the amine (*6*) as chloride in 91 % yield (5.6 g).

6-Bromo-8-nitrodihydrothiazolo[3,2-a]pyridinium bromide (12a). Bromine (0.32 g, 0.002 mol) in methanol (2 ml) was added dropwise to an ice-cold solution of (*10a*) (0.52 g, 0.002 mol) in MeOH:H_2O (4:1) (10 ml). The bromine was decolourised at once. The precipitated bromo compound was recrystallised from methanol; yield 0.45 g (66 %), m.p. 303 °C (decomp.). (Found: C 24.61; H 2.06. Calc. for $C_7H_6Br_2N_2O_2S$: C 24.58; H 1.77), τ (TFA) 6.0 (2 H-2), 4.4 (2 H-3), 0.8 (H-5), 0.9 (H-7); $J_{5,7}$ 2.0 Hz.

8-Bromo-6-nitrodihydrothiazolo[3,2-a]pyridinium bromide (12b) was prepared as (*12b*) in 80 % yield, m.p. 300 °C (decomp.) (MeOH). (Found: C 24.72; H 1.85; N 8.31; Calc. for $C_7H_6Br_2N_2O_2S$: C 24.58; H 1.77, N 8.19), τ (TFA) 5.8 (2 H-2), 4.3 (2 H-3), 0.3 (H-5), 0.9 (H-7); $J_{5,7}$ 1.5 Hz.

trans-*3-(7-Dihydrothiazolo[2,3-*e]v-*triazolyl)-acraldehyde. (20).* 8-Aminodihydrothiazolo[3,2-*a*]pyridinium chloride (5.60 g, 0.03 mol) in water solution (125 ml) was stirred with Amberlite IRA-400 (OH^-) ion exchanger for 2 h. The ion exchanger was then removed by filtration and acetic acid (125 ml) added to the filtrate. Isoamyl nitrite (4.00 g, 0.034 mol) dissolved in acetic acid (20 ml) was added dropwise to the ice-cold solution over 3 h. At the end of this period the solution was evaporated almost to dryness at reduced pressure, a little water added, the pH adjusted to 7 with sodium carbonate and the solution extracted several times with ethyl acetate. The dried ethyl acetate extracts were evaporated and the residual material crystallised from water or chloroform; yield 1.4 g (25 %), m.p. 200 °C (Found: C 46.40; H 4.12; N 23.40. Calc. for $C_7H_7N_3SO$: C 46.41; H 3.90; N 23.20), τ (DMSO-d_6) 5.8 (2 H-2), 5.3 (2 H-3), 3.8 (H-2, quartet, $J_{2,3}$ 16 Hz, $J_{2,CHO}$ 8 Hz), 2.2 (H-3, doublet), 0.4 (H-CHO, doublet), λ_{max} (MeOH) 239, 314 nm (log *E* 4.03 and 4.11); *m/e* 181 (M^+) 58 %, [M−N_2] 22, [M−N_2H] 18, [M−N_2CO] 10, [M−$N_2C_2H_4$] 23, [M−N_2CHO] 20, and *m/e* 60 [C_2H_4S] 100.

The data refer to the *trans*-isomer. NMR of the crude reaction product showed this to contain the *cis-(19)* and *trans-(20)* isomers in the ratio 1:1. Warming the crude product for a short time in acetic acid led to complete isomerisation to the *trans*-form *(20)*.

NMR of the *cis*-isomer *(19)*, as it appears in the crude reaction mixture, shows the methylene protons as in *(20)* with the following shifts for the side-chain protons: τ (DMSO−d_6) 4.0 (H-2, quartet, $J_{2,3}$ 12 Hz, $J_{2,CHO}$ 8 Hz), 2.7 (H-3, doublet), −0.7 (H−CHO).

In an isomerisation experiment the crude mixture of the isomers (1:1) (45 mg) was heated in deuterium oxide (10 ml) for 2 ½ h. The NMR spectrum of the quantitatively recovered product showed only the *trans*-isomer present with no deuterium incorporation.

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