N-Quaternary Compounds. Part II.[1] Hydride Shift and Lactam Formation in Diazotisation of a β-Aminopyridinium Derivative

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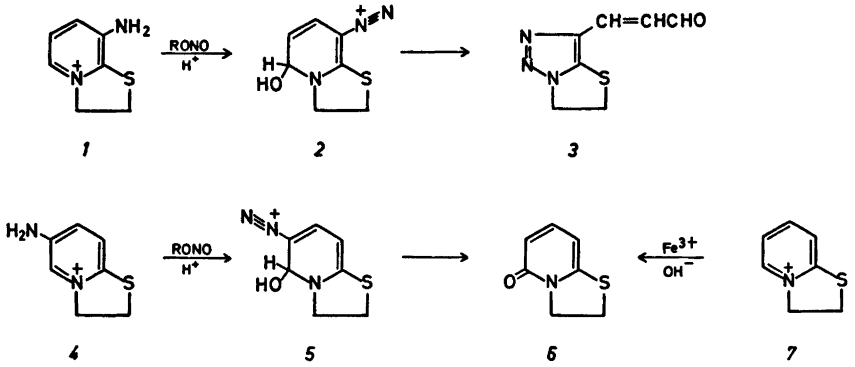
Diazotisation of 8-aminodihydrothiazolo[3,2-*a*]-pyridinium acetate *1* results in the formation of 3-(4-dihydrothiazolo[3,2-*e*]-1,2,3-triazolyl)acr-aldehyde *3* by a series of reactions involving a rearrangement.[2] The electron deficient pyridinium system in *1* is further activated on introduction of the strongly electron withdrawing diazonium group.[3] The course of the reaction is rationalised by intermediate formation of an anhydro-base through addition of solvent to the 5-position, which corresponds to the *para* position for the diazonium group.[2] In the 6-amino isomer *4*, however, the *para* position to the amino group is occupied by a sulfur substituent, and this compound was therefore diazotised for comparative studies. A relevant example of *para* substitution is available from the literature in that 1-amino-4-ethoxycarbonylquinolizinium salts[4] lead to the formation of the corresponding 1,2,3-triazole in very much the same way as diazotisation of simple 3-aminopyridinium salts may lead to 1,2,3-triazoles.[5,6] However, in the diazotisation of 6-aminodihydrothiazolo[3,2-*a*]pyridinium salts, dihydrothiazolo[3,2-*a*]-pyridin-5-one *6* was formed. The product has molecular ion *m/e* 153 (C_5H_7NOS), CO band in IR at 1660 cm^{-1} and ^1H NMR shows aromatic protons at δ 6.15 (H-6, H-8) and 7.22(H-7) with vicinal couplings *J* 7.5 and 8.5 Hz in accordance with vicinal β,γ-pyridine protons. The UV maxima at 243 and 328 nm (EtOH) correspond to the values 245 and 320 nm reported for the 4-methyl homologue and differ substantially from the values 235 and 265 nm reported for the isomer 5-methyldihydrothiazolo[3,2-*a*]pyridin-4-one.[7] The structure *6* assigned to the product was confirmed by a separate syntheses of *6*; pyridine-2-thione was condensed with 1,2-dibromoethane and the product *7* oxidised with alkaline potassium hexacyanoferrate(III)[8] to yield *6*.

Formation of the pyridinone *6* could be rationalised by a pyridynium intermediate which by analogy to pyridynes[9] would be expected to add water to the more activated α-carbon (C-5). A second possibility is a concerted reaction involving loss of nitrogen and an intramolecular hydride shift in an intermediate pseudo-base *5*. The latter path was shown to be the case by a deuteriation experiment. Thus the 6-amino derivative *4* can be deuteriated selectively in the 5-position in alkaline deuterium oxide. The deuterium was fully retained in the diazotisation reaction in accordance with an intramolecular deuteride shift to the 6-deuterio isomer *10*; ^1H NMR shows two vicinal pyridine protons at δ 6.07 (H-8) and 7.22 (H-7) and $J_{7,8}$ 7.5 Hz.

The 8-deuterio isomer *14* has also been prepared by analogy to the preparation of the non-deuteriated pyridinone *6* by photolysis.[10] Thus the betaine *11* is selectively deuteriated in the 5-position in alkaline deuterium oxide and the 5-deuterio analogue *12* is irradiated using a Hanovia medium pressure Hg-lamp. The 8-deuterio pyridinone *14* is one of the photochemical products and is presumably formed *via* the valence isomer *13*;[10] ^1H NMR shows two vicinal protons at δ 6.20 (H-6) and 7.22 (H-7) and $J_{6,7}$ 8.5 Hz.

Experimental. 6-Aminodihydrothiazolo[3,2-a]-pyridinium chloride 4. A strong anion exchange resin (OH^-) was added to an aqueous solution (100 ml) of 6-acetamidodihydrothiazolo[3,2-*a*]-



Scheme 1.

pyridinium [2] bromide (9.0 g, 0.033 mol) and the mixture stirred at room temperature for 3 h. The ion exchange resin was then removed, conc. HCl (100 ml) was added, and the solution heated under reflux for 1 h before evaporation. The residual solid was crystallised from dilute ethanol; yield 5.0 g (80 %), m.p. 235 – 238 °C (decomp.). Anal. $C_7H_9N_2SCl$: C, H. ^{1}H NMR (TFA): δ 3.96 (CH_2-S), 5.30 (CH_2-N), 7.90 (H-8, $J_{7,8}$ 9 Hz), 8.43 (H-7, $J_{5,7}$ 2 Hz) 9.05 (H-5).

Dihydrothiazolo[3,2-a]pyridin-5-one 6 *by diazotisation of* 4. An aqueous, saturated solution of sodium nitrite was added in excess to an aqueous solution (10 ml) of 6-aminodihydrothiazolo[3,2-*a*]pyridinium hydroxide (0.5 g, 0.0026 mol) and the resultant solution cooled to *ca.* – 5 °C before addition of 4 drops of conc. sulfuric acid. After 1 h at – 5 °C, the reaction mixture was neutralised and extracted with chloroform (3 × 20 ml). Evaporation of the dried chloroform extracts left a solid, yield 30 – 35 %, which was recrystallised from tetrachloroethylene, m.p. 77 °C. Anal. C_7H_7NOS: C, H. ^{1}H NMR ($CDCl_3$): δ 3.35 (CH_2-S), 4.46 (CH_2-N), 6.15 (H-6, H-8), 7.20 [(H-7), *J* 7.5, 8.5].

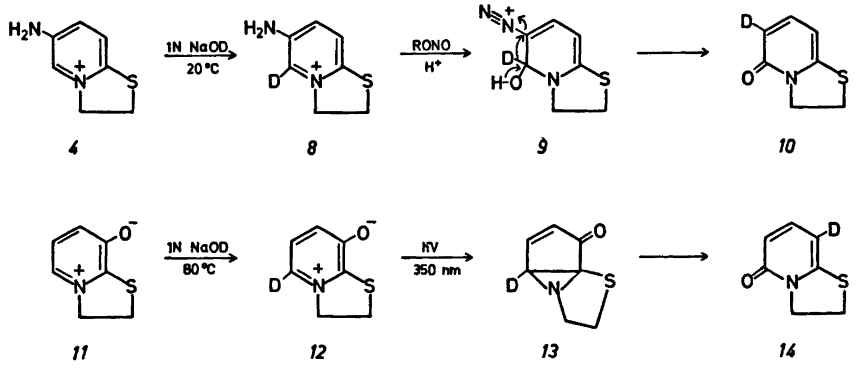
Dihydrothiazolo[3,2-a]pyridin-5-one 6 *by oxidation of* 7. Pyridine-2-thione (2.2 g, 0.02 mol), 1,2-dibromoethane (5.6 g, 0.03 mol) and potassium carbonate (3.0 g, 0.022 mol) were stirred together overnight in methanol (50 ml) at room temperature. The reaction mixture was then evaporated, the residue was dissolved in water (50 ml) and the pH was adjusted to 7 before the solution was extracted twice with chloroform. The aqueous solution contains the dihydrothiazolo[3,2-*a*]pyridinium bromide [8] which was oxidised by simultaneous, dropwise addition of aqueous potassium hexacyanoferrate(III) (13.1 g, 0.04 mol; 60 ml) and aqueous potassium hydroxide (4.5 g, 0.08 mol; 40 ml) to the ice-cold solution; the potassium hydroxide was added at twice the rate of the hexacyanoferrate(III) solution. The reaction mixture was then allowed to reach room temperature, neutralised with 6 N HCl and extracted with chloroform. Evaporation of the dried chloroform extracts left the title compound, 0.8 g (26 %), with physical properties as previously described.

6-Amino-5-deuteriodihydrothiazolo[3,2-a]pyridinium chloride 8. A solution of 6-aminodihydrothiazolo[3,2-*a*]pyridinium chloride (0.3 g) was dissolved in 1 M NaOD (5 ml) and the solution left at room temperature for 15 min The solution was then neutralised with HCl and evaporated to dryness at reduced pressure. The residue was repeatedly extracted with dry methanol and the residue after evaporation of the methanol extracts, was crystallised from dilute ethanol; 55 % yield. ^{1}H NMR spectra as for *4* except for the absence of the signal at δ 9.05 and associated couplings.

6-Deuteriodihydrothiazolo[3,2-a]pyridin-5-one 10 was prepared from the deuterio analogue *8* as described for *6*. ^{1}H NMR ($CDCl_3$): δ 3.35 and 4.46 (CH_2-S and CH_2-N), 6.07 (H-8) and 7.22 [(H-7), $J_{7,8}$ 7.5 Hz].

5-Deuteriodihydrothiazolo[3,2-a]pyridinium-8-olate 12. A solution of dihydrothiazolo[3,2-*a*]pyridinium-8-olate [11] (1.0 g) in 1 M NaOD (15 ml) was heated at 80 °C for 2 h. The pH of the cold reaction mixture was adjusted to *ca.* 4 with HCl and the mixture passed over a strong cation exchange resin (Dowex 50W, H^+). The resin was washed with water until the eluate was free from chloride ions and the deuteriated betaine was eluted with 0.3 M aq. ammonia. Evaporation left the title compound [11] in 65 % yield. ^{1}H NMR (TFA): δ 3.35 (CH_2-S), 4.46 (CH_2-N), 6.2 (H-6), 7.2 [(H-7), $J_{6,7}$ 8.5 Hz].

8-Deuteriodihydrothiazolo[3,2-a]pyridin-5-one 14. 5-Deuteriodihydrothiazolo[3,2-*a*]pyridinium-8-olate (0.5 g) in ethyl acetate (400 ml) was irradiated with a Hanovia medium pressure Hg-lamp for 4 h.[10] The reddish-brown reaction mixture was evaporated at reduced pressure and room temperature. The residue was ex-



Scheme 2.

tracted with chloroform, and the chloroform extracts subjected to preparative TLC using benzene – EtOAc 1:1; yield 5 %. ^{1}H NMR ($CDCl_3$): δ 3.35 (CH_2-S), 4.46 (CH_2-N), 6.20 (H-6), 7.22 [(H-7), $J_{6,7}$ 8.5 Hz].

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Reaction of D-Glucose with Phenol and with Pyrogallol under Acidic Conditions

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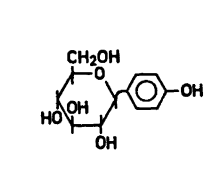
Phenols are formed when carbohydrates are degraded in aqueous weak acid [1,2] or in alkali,[3] and phenolic compounds have also been isolated from the reaction of glucose with methylamine [4] or glycine [5] (the Maillard reaction). As the phenols are isolated in lower yields in the presence of amines, it is reasonable to assume that amines, besides favouring the formation of other reaction products, catalyze the further reactions of the phenols. The phenols may react to some extent with the large excess of unreacted carbohydrates present in the reaction mixture.

In acidic media, glucose may attack phenol at oxygen or carbon. The former reaction yields phenyl glucosides,[6] while the latter (Friedel-Crafts) reaction yields phenylglucitol derivatives. Thus, *2* has been isolated from the reaction mixture of phenol and glucose in hydrogen fluoride.[7] In an early investigation of the reaction between glucose and phenol in hydrogen chloride-acetic acid or in concentrated hydrochloric acid, one water-soluble (A), one water- and benzene-insoluble (B) and one benzene-soluble (C) reaction product were isolated.[8] This investigation has now been repeated, using chromatographic and spectroscopic techniques.



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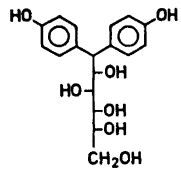

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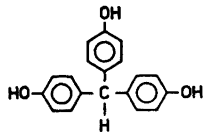

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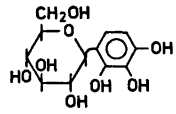

4

Product A was a complex mixture, while B seemed to be a polymeric material. Product C was pure leucoaurin (*3*). Product A was fractionated on silica gel columns and phenyl α- and β-D-glucopyranoside and *1* and *2* were isolated. The molecular formula of *1* was