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N-Quaternary Compounds

Part XIV. The [1,3]Thiazino[3,2-a]pyridinium-9-oxide System. A Rearrangement to the Thiazolo[3,2-a]pyridinium-8-oxide System

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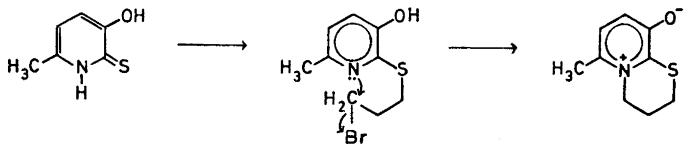
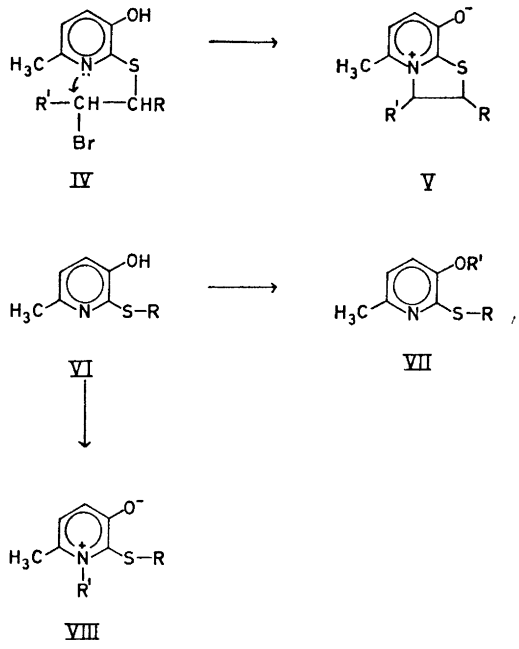
Substituted pyrid-2-thione on treatment with 1,3-dibromopropanes gave dihydro[1,3]thiazines. Bromination of a 1-(2-pyridylthio)-propen-2 resulted in immediate formation of the corresponding dihydrothiazole derivative. Elimination of water from the 3-hydroxy-dihydro[1,3]thiazine in acid solution gave the [1,3]thiazine as well as a thiazole. The thiazole is formed by rearrangement of the intermediate carbonium ion. The ratio between the products depends on reaction conditions. The structures were assigned from spectroscopic data. Of the two possible [1,3]isomers only the 4H-isomer was observed.

While the dihydrothiazolo[3,2-a]pyridinium-8-oxide system has been extensively studied recently [1] no report has so far appeared in the literature on the dihydro[1,3]thiazino[3,2-a]pyridinium cation or any betaine structure thereof. In this paper we describe studies over the thiazino-9-oxide system (III).



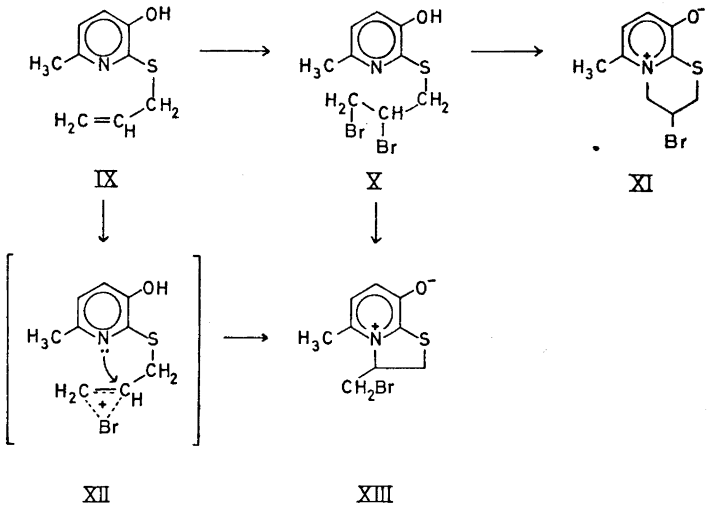
I II III

Although the thiolactam (I) contains 3 nucleophilic centres, represented by the heteroatoms N, O, and S, monoalkylation with alkyl halides has been found to occur exclusively on sulphur. Further attack is either on the annular nitrogen (VIII) or the phenolic oxygen (VII). *N*-Quaternisation is the favoured mode of reaction but this reaction is very sensitive to steric interaction in which case *O*-alkylation results.[2]



With 1,2-bifunctional ethane derivatives the bicyclic dihydrothiazolo-[3,2-a]pyridinium system (V) is obtained.[3] In the intermediate (IV) the bromine on the β-carbon is favourably spaced in the molecule for substitution by the annular nitrogen. In fact, the cyclisation of the β-bromothioether (IV) takes place so readily that it has not been isolated even when the β-carbon carries such bulky carbonyl functions as carboxy, carbethoxy, carbomenthoxy, carbamoyl or nitrile groups.[1,3,4] No *O*-alkylation, which would result in the formation of the corresponding 6-membered ring, has been observed. On the other hand when the simple thioether (VI) is treated with haloacetic acid esters exclusive *O*-alkylation takes place.[2]

3-Hydroxypyrid-2-thiones on treatment with 1,3-difunctional propane derivatives have now been found to undergo *S*-alkylation followed by *N*-quaternisation rather than cyclisation by *O*-alkylation. Qualitatively 1,3-dibromopropane reacts with the thiolactam (I) at the same rate as 1,2-dibromoethane. The allylic thioether (IX), from the treatment of the thiolactam with allyl bromide, was prepared in order to look at a possible competition between 5- and 6-membered ring formation. Thus if X is an intermediate in the bromination of IX a mixture of the two isomers (XI and XIII) would be formed, the ratio reflecting the relative rates of cyclisation. From the above discussion it is obvious that X would be very reactive. Its synthesis was therefore attempted under mild conditions such as the addition of bromine to a cold solution of the allyl thioether (IX) in carbon tetrachloride. This, however, resulted in spontaneous precipitation of a homogeneous, crystalline solid, identified as XIII. It is therefore very doubtful if X was ever formed.



IX X XI

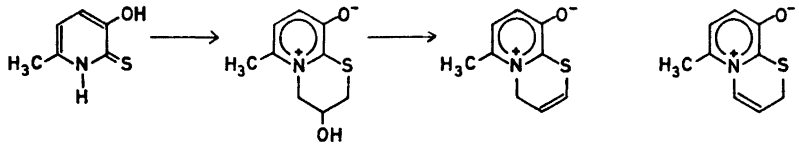
XII XIII

Further evidence against the intermediate compound X comes from our isolation of the mesyl derivative of the β-hydroxyethyl thioether of I[3] and also corresponding α-bromo-β-2-pyridylthiopropionic and α-bromo-β-2-pyridylthiobutyric acids which on cyclisation lead to 5- and 6-membered rings.[5] Thus the mechanism in the above reaction must involve initial electrophilic attack of the bromine on the double bond followed by nucleophilic attack on the intermediate onium adduct by the annular nitrogen rather than attack by the bromide ion. The reaction is specific. Only one product was seen. The carbon attacked, is the one favoured by electronic arguments in addition reactions, and by the statistical cyclisation factor.

The structure of the reaction product was evident from spectroscopic properties. Quaternary compounds of the dihydrothiazolo-pyridinium-8-oxide type have the major long-wave absorption band at about 345 mμ in acid solution.[3] In alkaline solution this band is shifted about 15 units upwards. The corresponding bands for the simple thioether (VI) are at 325 mμ in both acid and alkaline solution.[2] The reaction product has absorption maxima at 348 mμ (N HCl) and 362 mμ (N NaOH) and therefore must be *N*-quaternary. The distinction between a 5- or a 6-membered ring follows from the NMR data in TFA. The four protons of the two methylene groups are overlapping in the 6.3 – 5.1 τ region. The signals from the methine proton are centred around 4.1 τ. In the NMR spectra of the other dihydrothiazino derivatives (III and XIV) the signals from the methylene groups are about 100 cps apart. The observed chemical shifts for the four methylene protons correspond roughly to that of the *S*-CH_2 protons in III. This would agree with a *S*-CH_2 group and a $-CH_2-Br$ group. Finally the low chemical shift of the methine proton is in agreement with the values previously found for the $\equiv CH-N^+\equiv$ group.

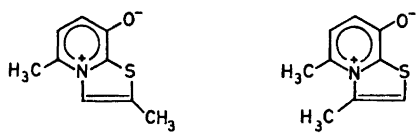
For studies of [1,3]thiazines (XV) a 3-substituted dihydro[1,3]thiazine was required. As the bromination of the allyl thioether, discussed above, did

not furnish any of the 3-bromo derivative (XI), the obvious choice for a condensation reagent would be a 1,3-difunctional propane derivative carrying a potential leaving group on the C-2 carbon. Thus 1,3-dibromoisopropanol was condensed with the thiolactam to give the 3-hydroxy derivative (XIV). Water elimination should give the thiazine isomers (XV), the ratio of which would in the end depend on the relative stabilities as discussed below. Experimentally, the introduction of the double bond was first attempted by tosylation of XIV followed by treatment with a tertiary amine or with tertiary butoxide. In the former case no elimination occurred while the strong alkaline medium caused extensive destruction of the molecule. Since the pyridinium compounds are very acid stable [3] attention was then turned to acid catalyzed dehydration of XIV. The reaction was run in warm orthophosphoric acid or in cold sulphuric acid. Chromatography showed that in the phosphoric acid two products were formed in the ratio 1:1 while the ratio in sulphuric acid was 3:1. Preparatively the two products from the reaction in phosphoric acid



I XIV XVa XVb

were separated on DEAE-Sephadex. The minor, yellow compound was eluted with water while the major, white component came off with 0.1 N formic acid. The mass spectra showed molecular ion *m/e* 179 (C_9H_9NOS) for both components corresponding to loss of water but their fragmentation patterns were different. The white product in N NaOH had absorption maxima at 246, 260, and 362 mμ compared to 254, 260, and 363 mμ in the starting material (XIV) and can therefore be assigned structure XV. The postulated structure was confirmed by NMR data as discussed below. The UV spectra of the yellow substance had major absorption bands in the normal regions for the dihydrothiazolo system but in addition it had a number of bands between 260 and 280 mμ reminiscent of naphthalene. This would suggest a fully aromatized thiazolo-pyridinium system and this was confirmed by the NMR data in TFA. Thus two methyl groups are found in the aromatic methyl region (7.09–7.20 τ). Besides the two pyridine protons at 2.04 τ, a third aromatic proton

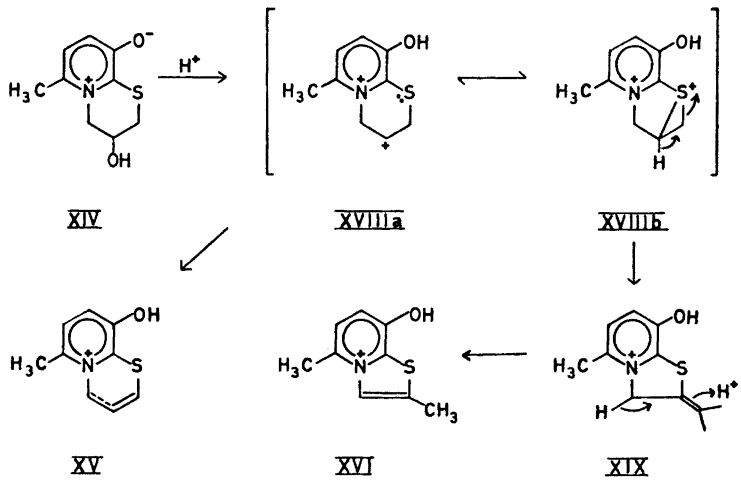


XVI XVII

is found at 1.84 τ. The latter is weakly coupled ($J = 1.5$ cps) to the methyl group at 7.20 τ, presumably part of the thiazole ring. The above isomeric structures therefore will have to be considered.

A decision between these possibilities could not be made with certainty on the basis of the available spectroscopic data alone. However, the third aromatic proton in XVI is next to the charged nitrogen while in XVII it is next to the sulphur. A direct comparison with the chemical shifts in the respective methyl thiazoles would not be valid due to the unknown effect of the quaternary nitrogen and the attached aromatic system but it was felt that the low chemical shift (1.84 τ) of the observed proton would agree better with structure XVI and this structure would also be in agreement with the postulated reaction mechanism. The original structural assignment was later confirmed by non-ambiguous syntheses of both isomers by acid catalyzed cyclisation of the corresponding β-carbonyl sulphides.[6] The possibility that the thiazine could be an intermediate in the rearrangement to the thiazole was tested by treating the thiazine (XV) separately with phosphoric acid under the original reaction conditions. No reaction took place.

The formation of these two products is readily understood through the postulated reaction mechanism.



XIV XVIIIa XVIIIb

XV XVI XIX

Secondary alcohols are said to be dehydrated by strong acids according to an E1 mechanism. In this case the acid induced elimination of water will be assisted by sulphur participation favouring even more strongly a kind of an E1 mechanism. According to this postulate the intermediate, resonance stabilized carbonium ion (XVIII) is sufficiently long-lived for extensive rearrangement to occur in competition with simple proton elimination. Only one thiazine isomer was formed in the acid catalyzed dehydration of XIV. *A priori* one would expect both isomers to have been formed since the protons on both methylene groups are activated by the neighbouring hetero atoms and the aromatic ring system, and that these isomers could be easily interconverted.

The stability of the isolated isomer, however, was such that attempts to isomerize it in alkaline solution met with no success. On the other hand both the corresponding 2H- and 4H-1-benzothiopyrans are stable.[7]

The thiazine product has been assigned structure XVa on the basis of the NMR spectrum in TFA. The four protons of the thiazine ring are overlapping in the 4.5–5.5 τ region. In the dihydrothiazines (III, XIV) the protons of the S-CH_2 group vibrate in the 6.3–6.8 τ region. The signals from the methylene group in 2H-1-benzothiopyran and 4H-1-benzothiopyran are also found in this region, *viz.*, at 6.65 and 6.76 τ (CCl_4), respectively.[7] The methylene protons of the $\equiv N^+-CH_2-$ group in III and XIV, however, are found at 5.0–5.6 τ. Therefore the thiazine must have the $\equiv N^+-CH_2$-group and is the 4H-[1,3]thiazine isomer (XVa).

EXPERIMENTAL

Paper chromatography and TLC on silica gel GF_{254} in BuOH:EtOH:NH_3:H_2O (4:1:2:1) and BuOH:HOAc:H_2O (100:22:50) were used. The spots are blue fluorescent in UV light. The UV data were recorded on a Perkin-Elmer model 137-UV spectrophotometer and the NMR data on a Varian A-60A spectrophotometer.

1-(3-Hydroxy-6-methyl-2-pyridylthio)propen-2 (IX). 3-Hydroxy-6-methylpyrid-2-thione [8] (2.8 g, 0.02 mole) was added to a methanolic solution (50 ml) of sodium methoxide (0.02 mole). Allyl bromide (2.4 g, 0.02 mole) in methanol (10 ml) was then added dropwise. After 1 h in the cold the solvent was evaporated, the residual oily material suspended in water (25 ml), the desired material extracted with chloroform (3 × 25 ml), dried over $MgSO_4$, evaporated and the residual oil distilled; b.p. 97–99° (0.3–0.4 mmHg). After solidification the product melted at 39–42°; yield 3.0 g (83 %). (Found: C 59.89; H 6.27; N 8.10; S 17.39. Calc. for $C_9H_{11}NOS$: C 59.66; H 6.12; N 7.75; S 17.62).

NMR in TFA: 7.20 τ (singlet, 6-CH_3), 6.15 τ (doublet, S-CH_2), 4.87 τ (triplet, $=CH_2$), 3.7–4.3 τ (multiplet, $=CH$), 2.03, 2.39 τ (AB quartet, 4–5 CH–CH).

3-Bromomethyl-5-methyl-8-hydroxydihydrothiazolo[3,2-a]pyridinium bromide (XIII). Bromine (2.4 g, 0.015 mole) in carbon tetrachloride (10 ml) was added dropwise to a stirred solution of 1-(3-hydroxy-6-methyl-2-pyridylthio)propen-2 (1.8 g, 0.01 mole) in carbon tetrachloride (50 ml) at 0–5°. A yellow solid was precipitated immediately. Recrystallization from ethanol/acetone gave a white crystalline product; yield 3.1 g (91 %), m.p. 239–241° (Found: C 31.82; H 3.46; N 4.57; S 8.99. Calc. for $C_9H_{11}NOSBr$: C 31.72; H 3.23; N 4.12; S 9.29). UV absorption: λ_{max} in N HCl at 348 (3.62), 250 sh (3.39) and 240 mμ (3.43); in N NaOH at 362 (3.16), 310 (3.37) and 252 mμ (3.18).

NMR in TFA: 7.14 τ (singlet, 5-CH_3), 5.7–6.3 τ (multiplet, CH_2S and CH_2Br), 4.15 τ (multiplet, 3-H), 2.19, 2.62 τ (AB quartet, 6–7 CH–CH).

6-Methyldihydro[1,3]thiazino[3,2-a]pyridinium-9-oxide (III). 3-Hydroxy-6-methylpyrid-2-thione (6.32 g 0.045 mole) was dissolved in methanolic (75 ml) sodium methoxide (from 1.05 g of sodium, 0.045 mole) and a methanolic solution (10 ml) of 1,3-dibromopropane (10.2 g, 0.045 mole) added dropwise to the stirred solution. The reaction mixture was left in the cold for 1 h, evaporated, the residue suspended in chloroform, the desired substance extracted into water (3 × 25 ml) and the water solution evaporated. Most of the inorganic salt was removed by extraction of the hydrobromide into boiling ethanol (50 ml). The hydrobromide crystallized out on cooling. The zwitterion was obtained by passing an aqueous solution of the hydrobromide through a DEAE-Sephadex A-25 column in the amine form. The whitish solid had m.p. 168–170° after recrystallization from ethanol-ethyl acetate (1:3); yield 4.8 g (66 %). (Found: C 59.64; H 6.43; N 7.71; S 17.88. Calc. for $C_9H_{11}NOS$: C 59.70; H 6.12; N 7.74; S 17.69). UV absorption: λ_{max} in N HCl at 342 (3.86) and 251 mμ (3.31); in N NaOH at 363 (3.71), 265 sh (3.61) and 247 mμ (3.72).

NMR in TFA: 7.23 τ (singlet, 6-CH_3), 7.3–7.7 τ (multiplet, 3-CH_2), 6.60 (triplet, 2-CH_2), 5.40 τ (triplet, 4-CH_2) 2.28, 2.63 τ (AB quartet, 7–8 CH–CH).

3-Hydroxy-6-methyldihydro[1,3]thiazino[3,2-a]pyridinium-9-oxide (XIV). The hydrobromide was prepared in the above manner from 3-hydroxy-6-methylpyrid-2-thione (2.8 g, 0.02 mole) and 1,3-dibromopropanol-2 [8] (4.0 g, 0.02 mole) in methanolic sodium methoxide (0.02 mole). The zwitterion was obtained by the use of a DEAE-Sephadex-A25 column. The m.p. was 265° after recrystallization from ethanol/water (9:1); yield 3.0 g (74 %). (Found: C 55.16; H 5.57; N 7.23; S 16.42. Calc. for $C_9H_{11}NO_2S$: C 54.95; H 5.65; N 7.12; S 16.29). UV absorption: λ_{max} in N HCl at 343 (4.00) and 251 mμ (3.47); in N NaOH at 363 (3.91), 260 sh (3.68) and 255 mμ (3.68).

NMR in TFA: 7.2 τ (singlet, 6-CH_3), 6.45 τ (triplet, 2-CH_2), 5.1—5.6 τ (multiplet, 4-CH_2), 4.82 τ (multiplet, 3H), 2.27, 2.58 τ (AB quartet, 7—8 CH—CH).

6-Methyl-4H-[1,3]thiazino[3,2-a]pyridinium-9-oxide (XVa). The hydrobromide of 3-hydroxy-6-methyldihydro[1,3]thiazino[3,2-a]pyridinium-9-oxide (2.9 g, 0.01 mole) was dissolved in orthophosphoric acid (10 ml) and the solution heated at 140° for 3 h. Chromatography showed that 2 major products were formed. Water (10 ml) was added to the cold reaction mixture and the resultant solution applied on a DEAE-Sephadex-A25 column. Elution with water furnished a yellow solid; m.p. 206—207°, yield 0.7 g (39 %). This substance has been identified as *2,5-dimethyl-thiazolo[3,2-a]pyridinium-8-oxide (XVI).* (Found: C 60.30; H 5.06; N 7.81. Calc. for C_9H_9NOS: C 60.33; H 5.06; N 7.82). Elution of the column with 0.1 N formic acid furnished the title compound as the hydrophosphate salt. The analytical sample was recrystallized from dilute ethanol; m.p. 275° (decomp.), yield 1.0 g (36 %). (Found: C 38.61; H 4.27; N 5.19. Calc. for $C_9H_{12}NO_5SP$: C 39.00; H 4.34; N 5.06). UV absorption of zwitterion: λ_{max} in N HCl at 340 (3.92), 343 mμ (3.68); in N NaOH at 362 (3.83), 260 sh (3.65) and 246 mμ (3.74).

NMR in TFA: 7.2 τ (singlet, 6-CH_3), 5.4 τ (broad singlet, 4-CH_2), 4.8 τ (multiplet, 2—3 CH_2—CH), 2.32, 2.66 τ (AB quartet, 7—8 CH—CH).

In a second experiment the dihydrothiazine (2.9 g, 0.01 mole) was dissolved in conc. sulphuric acid (10 ml) and the solution left in the cold for 5 h. The solution was then poured into water (10 ml), the pH brought to 3.5 with 6 N NaOH, the solution extracted with phenol-water (9:1) (3×25 ml), the combined phenol extracts washed with water (50 ml), ether (500 ml) added to the phenolic solution, the separated aqueous layer collected, the ethereal solution washed with water (50 ml), the aqueous solution and the water washing combined, washed with a little ether and evaporated at reduced pressure. The two products (ratio 3:1) can be separated on the ion exchange column above or simply by repeated extractions with ethanol in which the thiazole is soluble but not the 4H-thiazine. The yield of the title compound in this procedure was 1.7 g (61 %) and of the other component 0.35 g (20 %).

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