ACTA CHEMICA SCANDINAVICA 23 (1969) 1975–1985

N-Quaternary Compounds

Part V.[1] Nuclear Substitution

KJELL UNDHEIM

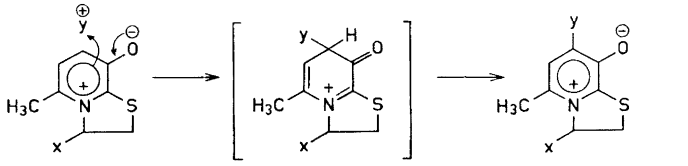
Chemical Institute, University of Oslo, Oslo 3, Norway

VEGARD NORDAL

Research Division, Nyegaard & Co. A/S, Oslo, Norway

5-Methyldihydrothiazolo[3,2-a]pyridinium-8-oxide derivatives are substituted by electrophiles in the 7-position. Diazonium salts cause arylation. A bromine or iodine atom in the 7-position is substituted by nucleophilic reagents without rupture of the dihydrothiazole ring.

Under normal reaction conditions non-substituted *N*-alkyl pyridinium salts would be resistant towards electrophilic substitution because of the π-electron deficiency caused by the quaternary annular nitrogen. The magnitude of a positive inductive effect from an alkyl substituent will not be large enough for substitution. But a strongly electron donating group such as a hydroxyl group might be expected to reduce the electron deficiency sufficiently for electrophilic substitution to occur. A hydroxyl group in the 2- or 4-position leads to a lactam structure whereby the nitrogen atom is no longer quaternary, and the ring is therefore readily substituted.[2] More interesting is a hydroxyl group in the 3-position when the quaternary character of the nitrogen is



Ia x = H
b x = CO_2H

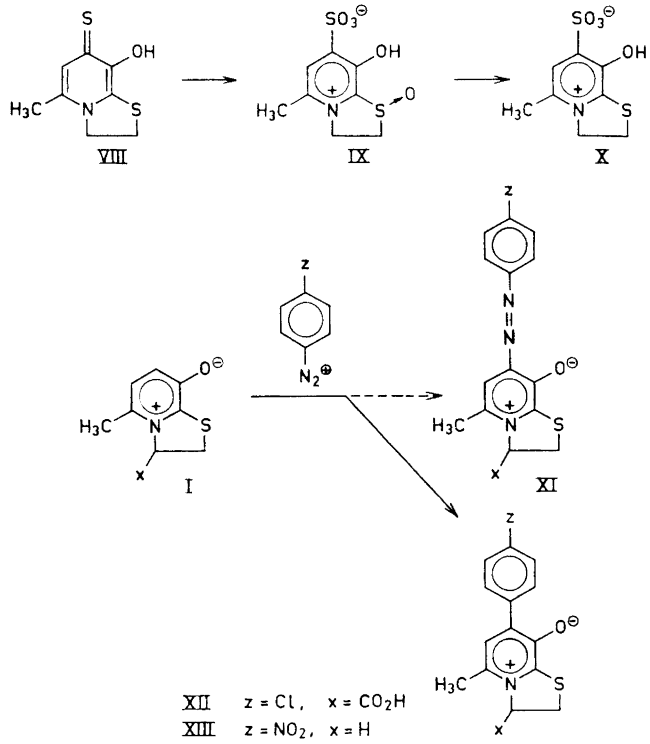
II

III x = H, y = Br
IV x = CO_2H, y = Br
V x = CO_2H, y = I
VI x = H, y = NO_2
VII x = CO_2H, y = NO_2

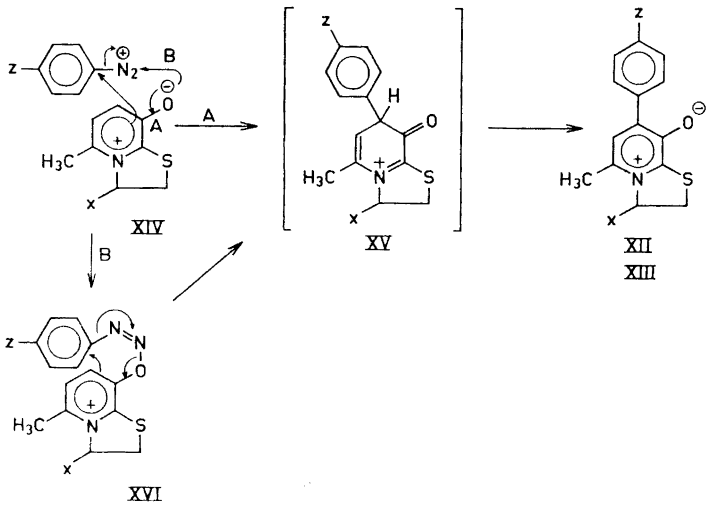
retained. But attempts to brominate or iodinate 1,6-dimethylpyridinium-3-oxide were unsuccessful. Another strongly electron donating group is required such as the thioether group present in the dihydrothiazolo[3,2-a]pyridinium-8-oxide derivative (I).

Electrophilic substitution in I could in principle occur in either the 6- or 7-position. Considerations of the transition states, however, show that the best stabilisation is obtained by substitution in the *ortho* position to the hydroxyl group or rather its anion as shown (II). The directing power in the halogenations and nitrations we have carried out is such that only one isomer is formed in each case.

The brominations were done with bromine in acetic acid in the presence of potassium acetate. The bromination of Ia was also run with success in ethanol without added base. Similarly aqueous sodium iododichloride treatment of Ib furnished the iodo derivative (V).



Nitration was carried out with concentrated nitric acid on Ib dissolved in acetic acid-sulphuric acid. But our attempts to effect sulphonation simply by heating in concentrated sulphuric acid were not successful. Other conditions were not studied. Instead the sulphonic acid (X) was made by hydrogen peroxide formic acid oxidation of the thione (VIII) and the resulting sulphonic acid sulphoxide (IX) reduced catalytically over 5 % palladium on charcoal.



Diazonium salts are fairly weak electrophilic reagents. We have tried to react diazotized *p*-nitroaniline and *p*-chloroaniline with I under standard conditions. The expected azo derivative (XI), however, was not obtained. Instead arylation had occurred giving XII as was found by elementary analysis and confirmed by the mass spectrum. The apparent molecular ion was found at *m/e* 276 corresponding to M—44 due to thermal decarboxylation as previously found for the parent molecule.[3] These results would fit a free radical mechanism, but this pathway must be excluded as the reactions were carried out in aqueous media. However, these results can be interpreted by postulating a nucleophilic attack by the phenolate anion onto the electrophilic carbon carrying the diazonium group followed by evolution of nitrogen (path A). Diazonium salts are converted to covalent forms by the anions of weak acids. Therefore, it seems more likely that the electrophilic attack is initially on the phenolate oxygen with the formation of XVI (path B). This intermediate then rearranges through a six-membered transition state with expulsion of nitrogen.

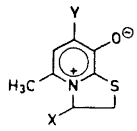
The electrophilic substitutions described have been formulated as taking place in the 7-position in I for mechanistical reasons. This conclusion is further supported by the chemical shifts in NMR. The aromatic proton in I with the lowest chemical shift is in the 7-position.[4] After bromination of Ia the remaining aromatic proton (in III) shows a downfield shift compared with the 6-proton in Ia, but it resonates at a higher field than does the 7-proton in Ia (Table 1). Therefore the substitution must have taken place in the 7-position.

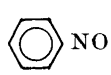
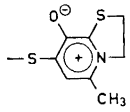
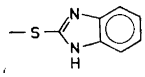
The postulated substitution pattern has also been proved by chemical means. Thus Raney nickel desulphurisation in 15 % aqueous sodium hydroxide furnished two major products (XVIII and XIX).

The pyridine (XVIII) was precipitated from the neutralized solution after the reaction while the quaternary derivative (XIX) was isolated *via* phenol extraction of the weakly acidified solution. The NMR-spectrum in

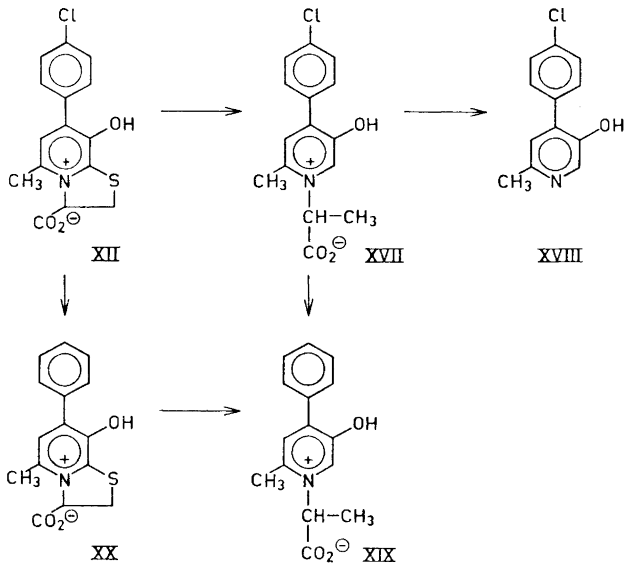
Table 1.

NMR Spectra in TFA



Compound	Substituents			Chemical shifts in τ values				
	X	Y		2	3	5	6	7
Ia	H	H		6.12	4.90	7.25	2.70	2.30
III	H	Br		6.07	4.87	7.27	2.40	
VI	H	NO_2		5.93	4.68	7.17	2.00	
X	H	SO_3H		6.12	4.87	7.27	2.25	
IX	H	SO_3H	Sulphoxide	5.93	4.33	6.98	1.47	
XIII	H			6.03	4.78	7.18	2.60	AA′BB′ 1.50 and 2.12
VIII	H	SH		6.15	5.00	7.33	2.70	
XXIII	H	SH	8-Ac	6.12	4.92	7.27	2.60	
XXI	H			6.08	4.87	7.30	2.73	
XXII	H			6.07	4.83	7.28	2.52	Singlet 2.20
IV	CO_2H	Br		5.72	3.73	7.25	2.30	
V	CO_2H	I		5.72	3.73	7.28	2.08	
VII	CO_2H	NO_2		5.53	3.52	7.13	1.88	
XII	CO_2H	C_6H_4Cl		5.70	3.70	7.20	2.58	Singlet 2.40
XXV	CO_2H	SH		5.82	3.87	7.35	2.62	

DMSO-d_6 of the former substance showed a three-proton singlet at 7.55 τ (Me-group), a one-proton singlet at 1.70 τ (proton in 2-position) and a one-proton singlet at 2.75 τ (proton in 5-position). The protons in the phenyl ring give rise to a four-proton AA′BB′ pattern with chemical shifts at 2.23

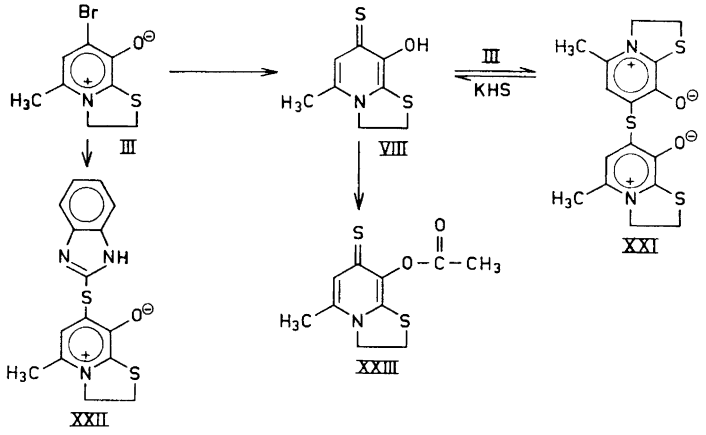


and 2.42 τ (J=9.0 cps). Therefore the chlorine atom has not been removed. Since the coupling constant between the two pyridine protons is very small, the protons appearing as singlets, these protons must be situated 1,4 to each other proving the postulated substitution pattern. This substitution pattern was further confirmed for the quaternary structure (XIX) from its NMR spectrum in TFA. The aromatic methyl group appears as a singlet at 7.07 τ while the methyl group of the side chain appears as a doublet at 7.83 τ (J=7.5 cps) and the methine proton (quartet) at 4.10 τ. The five-proton signal of the phenyl group appears as a broad singlet at 2.25 τ. The two pyridine protons resonate as singlets at 1.40 and 2.08 τ in agreement with a 1,4-arrangement. The five-proton signal of the phenyl group means that the molecule has been dehalogenated while the dealkylated product (XVIII) has retained the chlorine atom. The dehalogenation was confirmed by the mass spectrum.

The apparent molecular ion was found at *m/e* 213 corresponding to M—44 due to thermal decarboxylation. Only a very weak peak appeared at *m/e* 247, the M—44 peak for the corresponding chloro compound. XIX could arise by hydrogenolysis of the chlorine in XII followed by desulphurisation of XX. Alternatively the chlorine in XVII undergoes hydrogenolysis before cleavage of the side-chain yielding XIX. It should be pointed out that XVIII and XIX were the major components after the reaction. Other anticipated products were undoubtedly formed but in minor amounts under the experimental conditions used.

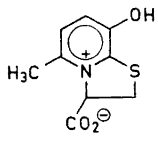
The pyridinium oxide (I) is not readily attacked by nucleophilic reagents.[3] On the other hand, dihydrothiazolo[3,2-a]pyridinium bromide suffers opening of the thiazole ring on treatment with a sulphide anion.[5] The different behaviour for these two parent structural systems towards nucleophiles can be attributed

to the electron donating properties of the hydroxyl group present in I. When the 7-bromo or 7-iodo derivatives were treated with a sulphide nucleophilic displacement of the halogen atom resulted under relatively mild conditions. Thus excess potassium hydrogen sulphide in DMF at 80—100° for 3 h furnished the corresponding thione (VIII). But when the reaction was carried out with one equivalent of potassium hydrogen sulphide at a lower temperature and shorter heating time the diaryl thioether (XXI) was obtained. Chromatographic studies of the thione formation indicated that the thioether (XXI) might in part be an intermediate. This was proved by heating the thioether (XXI) with potassium hydrogen sulphide. The thioether was all converted to the thione (VIII). The above observation means that the thione as first formed must be a better nucleophilic reagent than the sulphide anion. Similarly the sodium salt of 2-mercaptobenzimidazole with the bromo derivative (III) furnished the corresponding thioether (XXII)



The hydroxyl group of compounds of type (I) could not be readily acetylated. However, the thione reacts readily with acetic anhydride in pyridine. The IR spectrum shows ester absorption at 1760 cm^{-1} only compatible with a vinyl acetate formulation [6] as in structure XXIII.

From Table 1 it is seen that the chemical shifts in NMR depend on the electronic properties of the 7-substituent in a roughly predictable manner. The most remarkable downfield shift is seen in the case of the sulphoxide (IX). Thus the 6-proton is shifted 0.8 τ downwards as compared to the sulphonic acid (X). Similarly the methyl group is shifted about 0.3 τ to lower field. These strong downfield shifts must mean that the electron density in the heteroaromatic system is strongly reduced because the lone pair electrons on the thioether sulphur are no longer available for participation in resonance with the aromatic π-electrons due to the electronegative oxygen. In KBr the carboxylic acid group in Ib has its C—O stretching band at 1640 cm^{-1} and therefore exists as a carboxylate. The betaine formulation (XXIV)



XXIV

is also evident from pK_a measurements.[7] The value found for the carboxy group in Ib, pK_a 1.5, is relatively little affected by electronegative substituents in the 7-position. The acidity of the phenolic group, however, is increased from pK_a 4.97 (Ib) to 2.85 for the bromo derivation (IV). The C—O stretching frequency in 7- substituted derivates is spread out over the 1620—1720 cm^{-1} region, which is the region for the ionized to non-ionized carboxyl absorption. The spread of absorption could be due to increased intermolecular hydrogen-bonding between the carboxylate group and the phenolic OH-group with increasing acidity of this group.

4-Mercaptopyridines exist almost exclusively in the tautomeric pyrid-4-thione structure.[8] The 4-mercapto derivatives (VIII and XXV) have therefore been assigned a thione structure. The nitrogen in these molecules is no longer quaternary and members of this series will therefore have different properties as shown by the facile *O*-acylation of VIII.

EXPERIMENTAL

7-Bromo-5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide hydrobromide (III). a) 5-Methyldihydrothiazolo[3,2-a]pyridinium-8-oxide (0.17 g, 0.001 mole) was dissolved in a solution of potassium acetate (0.20 g, 0.002 mole) in acetic acid (20 ml). To this solution at room temperature was then added dropwise bromine (0.11 ml, 0.002 mole) in acetic acid (10 ml). An orange coloured precipitate was formed almost immediately. After stirring overnight the solid was filtered off, washed with water and dried (0.17 g, 52 %). Recrystallisation from water gave colourless needles, m.p. 258—262° (decomp.). The brominated material is nonfluorescent and gives an immediate precipitate with silver nitrate. Analysis showed it to be the hydrobromide of the desired bromo compound. (Found: C 29.52; H 3.01; N 4.25. Calc. for $C_8H_8BrNOS \cdot HBr$: C 29.38; H 2.77; N 4.28).

b) 5-Methyldihydrothiazolo[3,2-a]pyridinium-8-oxide (51.0 g, 0.3 mole) was dissolved in ethanol (1000 ml) and bromine (30 ml) added dropwise over 30 min to the stirred refluxing solution. The heating was continued for another hour, then the solution was concentrated to about 750 ml and left; white crystalline precipitate of the bromo-hydrobromide (61.1 g, 62 %).

7-Bromo-8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (IV). To 8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate semi-hydrate (44.0 g, 0.2 mole) and potassium acetate (23.4 g, 0.24 mole) suspended in acetic acid (4000 ml) was added with stirring over 2 h a solution of bromine (38.4 g, 0.24 mole) in acetic acid (1000 ml). The temperature during the addition and for another hour was kept at 50—60°. When about one 1/4 of the bromine solution had been added a clear solution resulted and when 3/4 of the bromine had been added the bromo compound started to precipitate out. There was obtained 57.6 g (98 %) of the bromo compound, m.p. 210—20° (decomp.). Recrystallization from formic acid-water gave white crystals, m.p. 230—240° (decomp.). (Found: C 37.25; H 2.89; N 4.95; Br 27.16. Calc. for $C_9H_8BrNO_3S$: C 37.24; H 2.76; N 4.83; Br 27.50).

8-Hydroxy-7-iodo-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (V). 3.3 N aq. sodium iododichloride ($NaICl_2$) (46 ml, 0.15 mole) was added dropwise (30 min) at 60° to a stirred solution of 8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-

carboxylate (22.0 g, 0.1 mole) and sodium acetate·$3H_2O$ (28.0 g, 0.2 mole) in water (2000 ml). After stirring at 60° for 2 h another 15 ml of 3.3 N $NaICl_2$ aq. (0.5 mole) was added, and the reaction stirred at 60° overnight. The precipitated iodo derivative (20.5 g, 60 %), m.p. 210—213° (decomp.) was recrystallized from formic acid-water, m.p. 216—219° (decomp.). (Found: C 32.06; H 2.33; N 4.06; I 37.76. Calc. for $C_9H_8INO_3S$: C 32.06; H 2.39; N 4.16; I 37.63).

5-Methyl-7-nitrodihydrothiazolo[3,2-a]pyridinium-8-oxide (VI). To 5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide (16.7 g, 0.1 mole) in a solution of conc. sulphuric acid (4.9 g, 0.05 mole) in acetic acid (500 ml) was added dropwise (30 min) with stirring at room temperature a solution of conc. nitric acid (10 ml, 0.2 mole) and conc. sulphuric acid (4.9 g, 0.05 mole) in acetic acid (50 ml). The sulphate first formed dissolved slowly, to give a yellowish solution before a pale yellow solid started crystallizing out. After stirring at room temperature overnight the solid (11.4 g, 44.0 %), m.p. 182—186°, was filtered off. This product was the hydrosulphate salt of the title compound. Recrystallisation from water gave the free base (barium chloride test negative), m.p. 234—236°. (Found: C 45.27; H 3.76; N 12.80. Calc. for $C_8H_8N_2O_3S$: C 45.32; H 3.80; N 13.21). IR (KBr). 1320 and 1570 cm^{-1} (NO_2).

8-Hydroxy-5-methyl-7-nitrodihydrothiazolo[3,2-a]pyridinium-3-carboxylate (VII). A solution of conc. sulphuric acid (9.8 g, 0.1 mole) and conc. nitric acid (25 g, 0.4 mole) in acetic acid (100 ml) was added dropwise with stirring at room temperature over 3 h to a suspension of 8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (44.0 g, 0.2 mole) in a solution of conc. sulphuric acid (9.8 g, 0.1 mole) in acetic acid (4000 ml). The reaction mixture was stirred for 48 h, a little undissolved material removed by filtration, the filtrate concentrated to about 100 ml and water (400 ml) added. The orange coloured nitro derivative was slowly precipitated (32.4 g, 62 %), m.p. 137° (decomp.). An analytical sample recrystallized from formic acid-water had m.p. 142° (decomp.). (Found: C 42.17; H 3.38; N 11.15. Calc. for $C_9H_8N_2O_5S$: C 42.18; H 3.15; N 10.93). IR (KBr). 1320 and 1560 cm^{-1} (NO_2).

8-Hydroxy-5-methyl-1-oxodihydrothiazolo[3,2-a]pyridinium-7-sulphonate (IX). 8-Hydroxy-5-methyldihydrothiazolo[3,2-a]pyrid-7-thione (2.0 g, 0.01 mole) was dissolved in formic acid (35 ml) and 35 % H_2O_2 (4.9 ml, 0.05 mole) added. The temperature was kept below 40° by external cooling. After standing at room temperature overnight the solution was evaporated to dryness at reduced pressure below 40—45°. The residual oily material was dissolved in the cold in water (5 ml). On standing in the cold the desired substance crystallized out (1.12 g, 43 %), m.p. 260—275° (decomp.). Recrystallization twice from water gave the white solid, m.p. 295—7° (decomp.). (Found: C 36.27; H 3.45; S 24.54. Calc. for $C_8H_9NO_5S_2$: C 36.50; H 3.44; S 24.35). IR (KBr): Strong band around 1250 cm^{-1} (SO_3^-). Strong band at 1060 (SO_3^- and sulphoxide).

8-Hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-7-sulphonate (X). 8-Hydroxy-5-methyl-1-oxodihydrothiazolo[3,2-a]pyridinium-7-sulphonate (0.30 g, 0.0014 mole) dissolved in formic acid (30 ml) was hydrogenated over 5 % palladium on charcoal at 2 kg/cm² for 5 h. Chromatography then showed the reaction to be complete and the product to be homogeneous. The catalyst was then removed by filtration, the colourless filtrate evaporated to dryness and the white residual solid recrystallized from formic acid-water (1:5), m.p. 343—346°. (Found: C 38.76; H 3.77; N 5.82; S 25.93. Calc. for $C_8H_9NO_4S_2$: C 38.86; H 3.67; N 5.67; S 25.93). IR (KBr). Strong band around 1230 cm^{-1} (SO_3^-). Weaker, sharp band at 1060 cm^{-1} (SO_3^-).

3-Carboxy-8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyrid-7-thione (XXV). 7-Bromo-8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (21.6, 0.075 mole) was added in portions over 10 min to a stirred suspension of potassium hydrogen sulphide (11.8 g, 0.165 mole) in anhydrous DMF (500 ml) at 80°. After stirring for 1½ hour the dark green solution was evaporated to dryness at reduced pressure and the residue dissolved in water (150 ml) at 50°. The solution was treated with a little charcoal, the pH brought to 2.5 with HCl when the pale grey thione was precipitated (12.2 g, 67 %), m.p. 188—190°. Recrystallization from methanol, or methanol-DMF gave m.p. 193—197°. (Found: C 44.44; H 4.00; N 5.86; S 25.95. Calc. for $C_9H_9NO_3S_2$: C 44.43; H 3.73; N 5.73; S 26.36).

A similar synthesis from the iodo derivative instead of the bromo compound gave 78 % yield of the desired thione. IR (KBr): Strong band at 1735 cm^{-1} (carboxyl group).

8-Hydroxy-5-methyldihydrothiazolo[3,2-a]pyrid-7-thione (VIII). 7-Bromo-5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide hydrobromide (48.9, 0.15 mole) was added in portions (5 min) to a stirred suspension of potassium hydrogen sulphide (35.5 g, 0.49 mole) in dry DMF (500 ml) at 100—105°. The addition completed, the greenish suspension was stirred at this temperature for 3½ h before the insoluble material was filtered from the hot reaction mixture and the filtrate concentrated to about 100 ml. The thione (21.0 g, 70.0 %) crystallized out on standing in the cold, m.p. 250—255°. Recrystallization from DMF or large water volume gave m.p. 252—258° (decomp.). (Found: C 48.17; H 4.30; N 7.25; S 32.61. Calc. for $C_8H_9NOS_2$: C 48.20; H 4.55; N 7.03; S 32.18).

7,7'-Bis(5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide) thioether (XXI). 7-Bromo-5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide hydrobromide (3.3 g, 0.01 mole) was added in small portions to a stirred suspension of KHS (0.8 g, 0.011 mole) in dry DMF (50 ml) at 65—70°. A new yellowish substance was slowly precipitated. The reaction was stirred at this temperature for 2 h, allowed to cool and the solid collected by filtration. The solid (2.3 g), m.p. about 290°, was contaminated with a little inorganic salt, and was recrystallised twice from 5 % aqueous HBr, m.p. 300—307°. Finally an aqueous solution was adjusted to pH 7.5 with dilute NaOH and the solution left in the cold; pale yellow needles slowly crystallised out. On drying at 80° *in vacuo* the colour changed to deeper yellow-brown but on dissolution the pale yellow colour was regained. The substance melted at 267—269°. (Found: C 51.21; H 4.63; N 7.86; S 26.01. Calc. for $C_{16}H_{16}N_2O_2S_3 \cdot \frac{1}{2}H_2O$: C 51.45; H 4.59; N 7.50; S 25.76).

Besides the ether formed above a little thione (VIII) is formed. Using 3 equivalents of potassium hydrogen sulphide gave the same yield of the thioether if the heating was stopped after 2 h. If the heating was continued the thioether was converted into the thione (VIII) as shown by chromatography. This was preparatively confirmed by taking isolated thioether and heating it with potassium hydrogen sulphide in DMF as above. The thione (VIII) was formed.

8-Acetoxy-5-methyldihydrothiazolo[3,2-a]pyrid-7-thione (XXIII). Acetic anhydride (1 ml, 0.01 mole) was added dropwise to a stirred solution of 3-hydroxy-5-methyldihydrothiazolo[3,2-a]pyrid-7-thione (1.0 g, 0.006 mole) in pyridine (50 ml) at 60°. The heating was continued for 2 h and the solution allowed to cool when pale yellow flakes crystallized out; yield 0.6 g (51 %), m.p. 240—245°. The analytical sample, recrystallised from pyridine, showed change of crystal structure from about 215° and melted at 245°. (Found: C 49.66; H 4.79; N 6.00; S 26.51. Calc. for $C_{10}H_{11}NO_2S$: C 49.78; H 4.60; N 5.81; S 26.59). IR (KBr): Ester carbonyl group at 1760 cm^{-1}.

7-p-Chlorophenyl-8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (XII). An ice-cold solution of diazotized *p*-chloraniline prepared from *p*-chloraniline (12.8 g, 0.1 mole), 2 N HCl (125 ml), and sodium nitrite (6.9 g, 0.1 mole) in water (100 ml) was added dropwise with stirring at 0° to a solution prepared from 8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (21.2 g, 0.1 mole) and sodium bicarbonate (16.4 g, 0.2 mole) in water (200 ml). After 20 min when half of the diazonium solution had been added 2 N sodium carbonate (25 ml) was added to the reaction mixture. The addition of the diazonium salt was complete after another 25 min. Gas evolution (N_2) occurred during the addition and reddish brown solid precipitated out. The reaction was kept in the cold overnight and the solid (12.8 g), m.p. ~130° (decomp.) filtered off. Chromatography showed this to be a mixture of 3 major substances and has not been further studied. The filtrate, pH 6.3, was adjusted to pH 4.2 with hydrochloric acid when a yellowish solid crystallised out (13.7 g), m.p. 158—164°. Chromatography showed that about 80 % of this material was the title compound. The product was found insoluble in solvents tried and was finally purified by dissolution to give a 10 % sodium salt solution and reprecipitation with acetic acid. This was repeated once more. The yellowish compound then had m.p. 167—171°. (Found: C 56.05; H 3.71; N 4.31. Calc. for $C_{15}H_{12}ClNO_3S$: C 55.98; H 3.76; N 4.35).

5-Methyl-7-p-nitrophenyldihydrothiazolo[3,2-a]pyridinium-8-oxide (XIII). An ice-cold solution of diazotized *p*-nitroaniline, prepared from *p*-nitroaniline (20.7 g, 0.15 mole), 2 N HCl (188 ml, 0.38 mole) and sodium nitrite (10.3 g, 0.15 mole) in water (150 ml) was added dropwise with stirring at 0° to a solution prepared from 5-methyldihydro-, thiazolo[3,2-a]pyridinium-8-oxide (25.0 g, 0.15 mole) and sodium bicarbonate (25.2 g. 0.3 mole) in water (600 ml). Half of the diazonium salt had been added after one hour

At this point 2 N sodium carbonate solution (38 ml) was added and the rest of the diazonium solution added over the next hour. A reddish brown solid precipitated out. After stirring for another 2 h at 0—5°, the stirring was continued at room temperature overnight. The pH (7.3) was then adjusted to 5.2 with HCl and the reddish brown solid collected by filtration (35.3 g), m.p. 160—72° (decomp.). Chromatography showed that about 70 % of this material was the title compound. This material was extracted with boiling ethanol (800 ml), the insoluble material removed by filtration, the filtrate concentrated to about 150 ml when dark red needles were precipitated (11.9 g), m.p. 210—220°. After recrystallizing twice from ethanol the substance melted at 237—252°. (Found: C 58.28; H 4.15; N 9.73. Calc. for $C_{14}H_{12}N_2O_3S$: C 58.32; H 4.20; N 9.72).

Diazotized aniline and *p*-methylaniline reacted very slowly under the above conditions.

Raney nickel desulphurisation of 7-p-chlorophenyl-8-hydroxy-5-methyl dihydrothiazolo-[3,2-a]pyridinium-3-carboxylate (XII). To the title compound (0.64 g, 0.002 mole) dissolved in 15 % NaOH aq. (20 ml) was added at 80° a small teaspoon full of Raney nickel. The reaction was vigorously stirred at 80° for 1½ h. The colour changed gradually from yellow to green. The insoluble inorganic material was filtered off and washed with water (25 ml). Chromatography of the combined washings and filtrate (colourless) showed 2 major blue fluorescent spots in the ratio 2:3 ($R_F=0.4$ and $R_F=0.9$). The pH of the solution was then adjusted to 7.1 with HCl when white solid material was precipitated. This was extracted with methanol (40 ml) and the insoluble inorganic material removed by filtration. The aqueous filtrate was extracted with ether (5×80 ml), the ether extracts dried and together with the methanol extract evaporated to dryness. The residual solid (0.10 g, 22.5 %) sublimed as long thin needles on heating from 120°, m.p. 190—200°. Chromatography showed this product only to consist of the substance with $R_F=0.9$. Recrystallization from aqueous ethanol gave m.p. 201—203°. (The crystals changed from between 145—150° and partly sublimed to needles). Recrystallization from ligroin raised the m.p. to 203—208°.)Found: C 66.4; H 5.19; N 6.37. Calc. for $C_{12}H_{10}ClNO$: C 65.7; H 4.66; N 6.38). The high carbon value is due to very slight contamination of dechlorinated material. This substance was identified as *4-p-chlorophenyl-3-hydroxy-6-methylpyridine (XVIII).* The aqueous solution after removal of the above component was brought to 3.8, extracted with 90 % phenol (3×25 ml), ether (225 ml) added to the phenol extracts, the aqueous layer which separated was collected, the phenol-ether layer extracted with water (2×30 ml), the combined water layer and washings washed with ether and evaporated. There remained a white solid (0.13 g, 25 %), m.p. 140—46°, which had m.p. 144—146° after recrystallizing twice from methanol. (Found: C 69.35; H 5.92; N 5.26. Calc. for $C_{15}H_{15}NO_3$: C 70.03; H 5.88; N 5.45). This substance was identified as *2-(3-hydroxy-6-methyl-4-phenylpyridinium)propionate (XIX).* The low carbon value is due to very low contamination by the corresponding *p*-chlorophenyl derivative. Apparent $m/e=213$ ($C_{14}H_{15}NO$), *i.e.* $C_{15}H_{15}NO_3-CO_2$ (257—44). IR (KBr). Broad band 1600—1700 cm^{-1} due to carboxylate group.

5-Methyl-7-(2-thiobenzimidazolyl)-dihydrothiazolo[3,2-a]pyridinium-8-oxide (XXII). To a mixture made from 7-bromo-5-methyldihydrothiazolo[3,2-a]pyridinium-8-oxide hydrobromide (0.98 g, 0.003 mole) and 2 N methanolic sodium methoxide (1.5 ml, 0.003 mole) was added a solution of the sodium salt of 2-mercaptobenzimidazole (0.45 g, 0.003 mole) in methanol (50 ml). The reaction was refluxed for 50 h, then allowed to stand in the cold when the yellowish condensation product crystallized out (0.10 g), m.p. 276° (decomp.). Recrystallization from aqueous acetic acid gave m.p. 278—279° (decomp.). (Fou nd: C 55.42; H 4.38; N 13.27; S 19.75. Calc. for $C_{15}H_{13}N_3OS_2\cdot\frac{1}{2}H_2O$: C 55.53; H 4.53; N 12.95; S 19.77).

REFERENCES

1. Undheim, K. and Nordal, V. Part IV. *Acta Chem. Scand.* **23** (1969) 1966.
2. Meislich, H. In Klingsberg, E. *Pyridines and Derivatives*, Interscience 1962, Part III, p. 662.
3. Undheim, K. and Nordal, V. Part I. *Acta Chem. Scand.* **23** (1969) 371.

4. Undheim, K., Nordal, V. and Tjonneland, K. Part II. *Acta Chem. Scand.* **23** (1969) 1704.
5. Balsiger, R. W., Montgomery, J. A. and Johnston, T. P. *J. Het. Chem.*, **2** (1965) 97.
6. Bellamy, L. J. *The Intrared Spectra of Complex Molecules*, Methuen 1958, p. 182.
7. Undheim, K. and Grønneberg, T. *Unpublished.*
8. Katrizky, A. R. and Lagowski, J. M. *Advan. Heterocyclic Chem.* **1** (1963) 396.

Received October 30, 1968.