N-Quaternary Compounds

Part III. Addition of 3-Hydroxypyrid-2-thiones to α-Bromo-α,β-unsaturated Acids

KJELL UNDHEIM

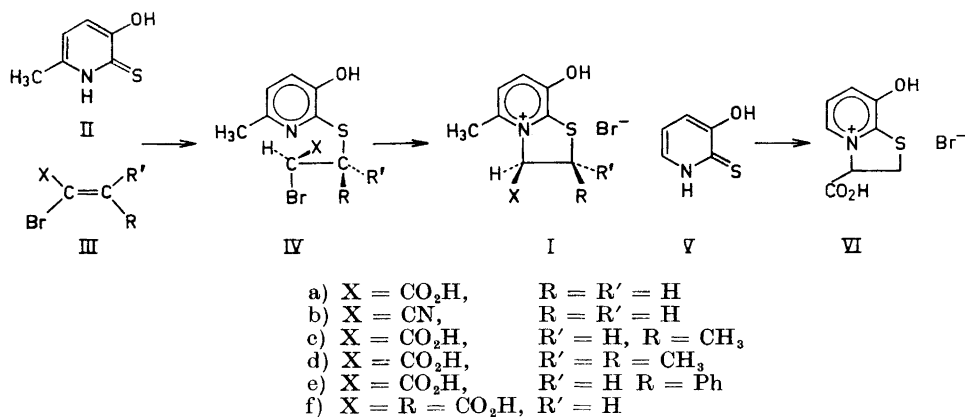*Chemical Institute, University of Oslo, Oslo 3, Norway*

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A new synthetic approach to the dihydrothiazolo[3,2-a]pyridinium ring system has been found in the addition of 3-hydroxypyrid-2-thiones to α-bromo-α,β-unsaturated carbonyl derivatives followed by cyclisation of the adducts first formed. The stereochemistry of the addition is *trans*. The rate of the reaction increases with the nucleophilicity of the sulphur atom. β-Substituents with electron donating properties such as alkyl or phenyl groups decrease the reaction rate while an electron attracting substituent had the opposite effect.

In our preceding paper [1] we have confirmed by total synthesis the postulated structure [2] of a blue fluorescent substance isolated from liver hydrolysates [3] as 8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (Ia). We now report on our search for alternative synthetic pathways to the dihydrothiazolo[3,2-a]pyridinium ring system. In the reaction between the thiolactam (II) and 2,3-dibromopropionate ester we have reported [1] that the 3-carboxy derivative (Ia) is formed in the presence of a strong base such as sodium alkoxide. A weaker base led to the corresponding 2-carboxy derivative. This difference in orientation could very well be due to a change from a simple substitution mechanism to a β-elimination-addition mechanism. The necessary elimination of HBr is caused by the strong base through abstraction of the activated proton on the α-carbon. Since the sulphur atom of thiols will add to the β-carbon in α,β-unsaturated acids [4] it seemed likely in this case that addition of the sulphur in the thiolactam to the β-carbon in the

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generated α-bromoacrylate could occur, thus leading eventually to the 3-carboxy derivative (Ia). The bromine atom on the α-carbon in the acrylate becomes a good leaving group in the adduct (IV) leading to cyclisation. The primary adduct (IV) would be expected to cyclise very readily with the formation of the 5-membered dihydrothiazolo ring in accordance with previous findings [1] for similar intermediates. The idea of the thiolactam addition was tested by heating α-bromoacrylic acid [5] with the thiolactam (II) in ethyl acetate solution. The primary adduct (IV) was cyclised as formed since the condensation product (Ia) as hydrobromide crystallised out in excellent yield without any detectable contamination by the adduct. The desmethyl thiolactam (V) similarly furnished VI. Esters and amides of α-bromo-α,β-unsaturated acids react equally well.[6] The same applies to α-bromoacrylonitrile. If the bromine atom is replaced by hydrogen, however, as in acrylic acid itself, no adduct with the thiolactam could be detected under our experimental conditions. It therefore seems that two electronegative groups on the same carbon are necessary for the addition to take place. The introduction of the more electronegative keto or aldehyde groups instead of the carboxylic acid group should enhance the reactivity.


a) X = CO₂H,   R = R' = H
b) X = CN,   R = R' = H
c) X = CO₂H,   R' = H, R = CH₃
d) X = CO₂H,   R' = R = CH₃
e) X = CO₂H,   R' = H R = Ph
f) X = R = CO₂H, R' = H

A methyl substituent on the β-carbon in α-bromoacrylic acid markedly decreases the rate of the reaction. Thus to effect a preparative yield of Ic a solution of α-bromoisocrotonic acid [7] and the thiolactam (II) in ethyl acetate was refluxed for 13 days as compared with 10—15 h for α-bromoacrylic acid. The product obtained contained about 50 % of decarboxylated material (IXa). With a second β-methyl group such as in α-bromo-β,β-dimethylacrylic acid no reaction took place even under drastic conditions. With a phenyl group on the β-carbon such as in α-bromoisocinnamic acid [8] prolonged reflux in the higher boiling chlorobenzene was necessary. However, the product obtained under these conditions had been completely decarboxylated. At lower temperatures in more polar aqueous solvent systems some of the expected condensation product was formed as shown by chromatography. The thermal decarboxylation in these cases, especially in chlorobenzene, was not unexpected

in view of the ease with which Ia is thermally decarboxylated.[2] The intermediate anion (VIII) is strongly stabilized by the neighbouring quaternary nitrogen atom. A second less likely explanation for the formation of IXb would be decarboxylation of α-bromocinnamic acid giving β-bromostyrene which then could undergo addition and condensation. This possibility was ruled out by treating β-bromostyrene with the thiolactam (II) in a separate experiment under the same experimental conditions used for the cinnamic acid. No reaction occurred. The ease with which the decarboxylation occurs in this class of compounds makes the thiolactam addition approach a potentially useful synthetic pathway for selectively preparing 2-substituted mono-alkyl or aryl derivatives.

VII
a. R = CH$_3$
b. R = Ph

VIII

IX
a. R = CH$_3$
b. R = Ph
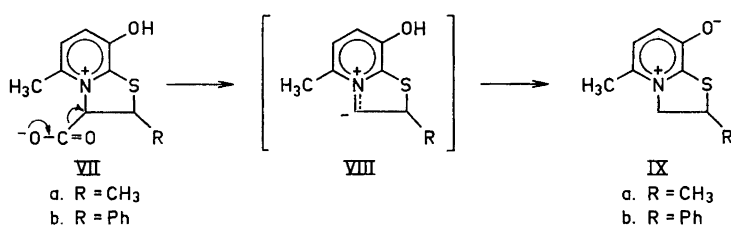
Acid catalyzed additions to α,β-unsaturated acids are initiated by electrophilic attachment of a proton to the double bond or to the oxygen of the carbonyl group, the latter being favoured in the literature. To visualize the stereochemistry in the addition process, we have attached the proton to the double bond. The partial positive charge developed on the β-carbon after proton addition will be reduced by electron donating alkyl or aryl substituents. On the other hand an electron attracting group should enhance the positive character and therefore increase the rate of the addition. In agreement with this it was found that α-bromomaleic anhydride reacted in the cold with the thiolactam (II) in ethyl acetate solution. These results would suggest that the electronic factor is the more important. The difference in reaction rates of the crotonic and cinnamic acids is largely explained by the difference in magnitude of the positive inductive and mesomeric effects of the alkyl and aryl groups, respectively. But steric factors undoubtedly play an important part in interfering with the addition since α-bromo-β,β-dimethylacrylic acid failed to react under our conditions. The rate of a nucleophilic attack by sulphur onto the β-carbon of the unsaturated acid should depend on the electron availability on the sulphur atom. In agreement with this, 3-hydroxy-6-methylpyrimid-2-thione [9] was found to react very sluggishly with α-bromoacrylic acid. However, it is not possible to reduce the electron density on the sulphur atom without at the same time reducing the electron density on the neighbouring annular nitrogen. Nucleophilic attack by the annular nitrogen onto the α-carbon carrying the leaving group therefore becomes less likely. Furthermore, the cyclisation reaction of the adduct must no doubt compete with the reverse β-elimination reaction because of the activated hydrogen on the α-carbon and because of the stability of the thiophenoxide ion liberated.

Electron attracting substituents in the aryl system should increase the stability of the thiophenoxide ion and at the same time reduce the nucleophilicity of the annular nitrogen. The reversibility of the addition is thus favoured and the overall reaction rate is decreased as observed.
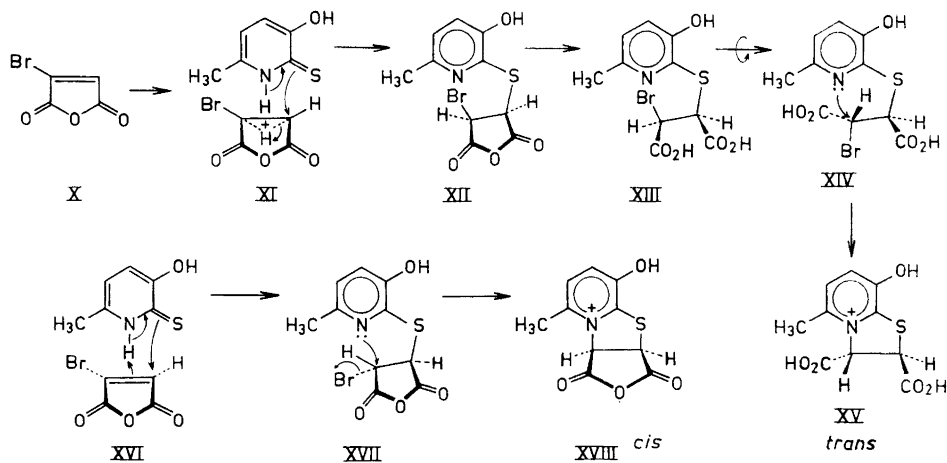
The formation of the adduct could take place by a concerted *cis* addition mechanism (XVI) leading to the *cis* derivative (XVIII) or by a polar synchronous or nearly synchronous *trans* addition mechanism (XI). The answer to this problem lies in the stereochemistry of the condensation product with bromomaleic anhydride. Only one dicarboxylic acid was found in the reaction mixture and was assigned the *trans* configuration on the basis of its NMR-spectrum (Table 1) for the following reasons. The two $C_3—C_2$ vicinal methine protons resonate as singlets at 3.35 and 4.70 τ, respectively. The vicinal spin-spin coupling constant according to the Karplus relationship [10] is related to the dihedral angle but the magnitude of the coupling constant can be greatly reduced with increased electronegativity of a substituent and with increasing number of such substituents. The configuration of electronegative substituents is also important.[11] Despite the uncertainty introduced by the electronegative substituents as to the exact value of the dihedral angle the fact that the vicinal coupling constant in the above case is close to zero for the two vicinal protons attached to a nearly planar 5-membered ring must lead to the assignment of a *trans* configuration.

The *trans* addition mechanism postulated requires that the intermediate anhydride adduct (XII) must be opened up to be able to assume the conformation (XIV) necessary for nucleophilic displacement of the bromine atom by the annular nitrogen atom. The anhydride (XII) could be opened up by moisture present or possible by HBr to an acid-acyl bromide intermediate hydrolysed during the work up of the reaction.

The methyl analogue (Ic) from the α-bromoisocrotonic acid condensation was separated from the decarboxylated material by crystallisation from water. The relative configuration was assigned on the basis of the NMR-
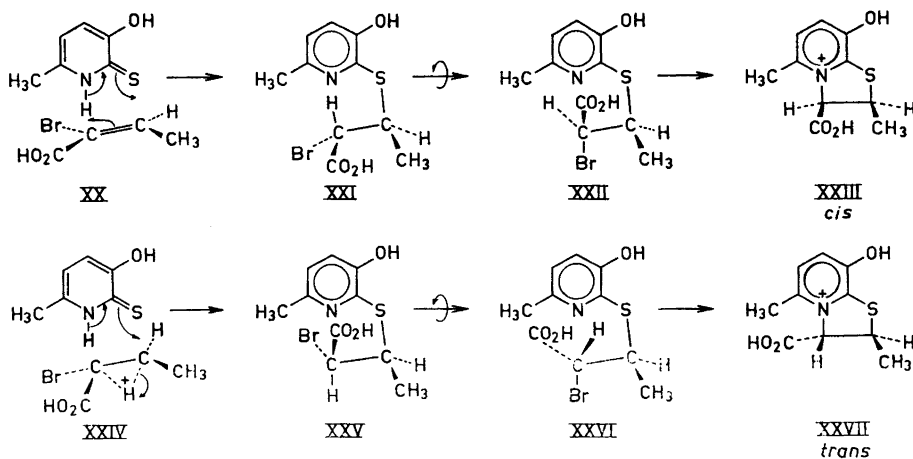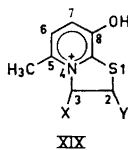
Table 1. NMR-spectra at 60 Mc/s in trifluoracetic acid (TFA).

XIX

Substance	Substituents		Chemical shifts in τ-values						Coupling constants in cps		
	x	y	2	3	5	6	7		$J_{2,3}$	J_{CH_3-2}	$J_{6,7}$
Ia	CO_2H	H	[b]5.73	[b]3.67	7.22	[a]2.58	[a]2.15		—		8.5
Ib	CN	H	5.82 5.58	3.20	7.05	2.53	2.07		7.5 2.0	$J_{2,2}$ =13.0	8.0
Ic	CO_2H	CH_3	[c]5.30	[d]4.05	7.22	2.53	2.20	[e]8.25	≈0	7.0	8.5
VII	H	CH_3	[f]5.6	[f]4.6	7.23	2.67	2.20	[e]8.30	—	7.0	8.5
IX	H	C_6H_5	[b]5.0	[b]4.2	7.28	2.65	2.15	[g]2.51			8.5
If	CO_2H	CO_2H	[d]4.20	[d]3.35	7.13	2.50	2.17		0		85.

[a] The aromatic protons resonate in an AB system.
[b] Not resolved.
[c] Quartet.
[d] Singlet.
[e] Doublet of methyl group in 2-position. Protons on carbon 2 and 3 overlap.
[g] Singlet due to phenyl group.

spectrum (Table 1). The methine proton next to the quaternary nitrogen resonates as a singlet at 4.05 τ. The methine proton next to the sulphur atom is coupled to the methyl group on the same carbon and therefore resonates as a quartet at 5.30 τ. Since the vicinal methine protons do not couple to any detectable extent they must have a *trans* configuration.

Since only the *trans* stereoisomer is obtained, the addition must be pure *cis* or *trans*. Furthermore, the addition must be synchronised or nearly synchronised since an intermediate with some lifetime would be expected to yield a mixture of the two geometric isomers produced by free rotation about the single bond. It can further be concluded that the *addition* must proceed in the *trans*-sense since *cis* addition (XX) would eventually lead to the *cis* isomer (XXIII). In the cyclisation we have then postulated a S_N2 displacement of the bromine by the annular nitrogen. This i sin agreement with our findings [12] in studies of the Menschutkin reaction between α-bromocarboxylic acids and 3-hydroxy-pyridines where we find a net inversion of the configuration at the asymmetric carbon.

Further studies of these thiolactam addition reactions are in progress and will be reported later.

EXPERIMENTAL

8-Hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate   *(Ia)*. α-Bromoacrylic acid [5] (6.8 g, 0.045 mole) in ethyl acetate (25 ml) was added dropwise to a solution of 3-hydroxy-6-methylpyrid-2-thione [1] (4.23 g, 0.03 mole) in ethyl acetate (130 ml). A solid precipitate was slowly formed. The reaction mixture was heated with stirring overnight, the volume reduced to about 50 ml by evaporation and the solid (8.9 g) collected by filtration, m.p. > 300°. For further purification this material was dissolved in water by the addition of a little sodium hydroxide to pH 7. Adjustment of the slightly warm solution to pH 3.8 with dilute hydrochloric acid precipitated a little unchanged thiolactam. On standing in the cold the chromatographically pure condensation product crystallised out in 83 % yield, m.p. 158—159°. A further recrystallisation from water gave m.p. 160°.

This product was the racemic modification of the compound isolated from liver hydrolysates [3] and identical with the compound previously synthesized.[1]

8-Hydroxydihydrothiazolo[3,2-a]pyridinium-3-carboxylate (VI). Prepared as above from 3-hydroxypyrid-2-thione,[1] m.p. 180° (decomp.). This product was identical with the compound previously synthesized.[1]

3-Cyano-8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium bromide (Ib). A solution of α-bromoacrylonitrile (26.4 g, 0.2 mole) in ethyl acetate (30 ml) was added dropwise over 20 min to a boiling solution of 3-hydroxy-6-methylpyrid-2-thione (23.2 g, 0.165 mole). Solid precipitate was formed during the addition. The reaction was completed by refluxing the reaction mixture overnight. On filtering the cold reaction mixture 33.0 g (73 %) of the hydrobromide was obtained, m.p. 230—40° (decomp.). A sample for analysis was recrystallized from water, m.p. 240—42° (decomp.). (Found: N 9.91. Calc. for $C_9H_8N_2OS-HBr$: N 10.26).

trans-*2,5-Dimethyl-8-hydroxydihydrothiazolo[2,3-a]pyridinium-3-carboxylate (Ic)*. 2,3-Dibromobutyric acid, prepared by bromine addition to crotonic acid, was converted to 2-bromoisocrotonic acid by alkali treatment.[7]

A solution of 2-bromoisocrotonic acid (16.0 g, 0.096 mole) and 3-hydroxy-6-methylpyrid-2-thione (11.4 g, 0.08 mole) in ethyl acetate) 320 ml) was refluxed for 13 days. Every day 1—2 g of the precipitated reaction product was collected by hot filtration. The total weight of solid hydrobromide collected was 21.6 g. Paper chromatography in BuOH:EtOH:NH$_3$:H$_2$O (4:1:2:1) showed the condensation product to consist of two

substances with R_F at 0.27 and 0.65. The higher R_F value would indicate decarboxylation.

The crude product was triturated with water (125 ml) at 25° for 10 min. The insoluble material (9.0 g) was filtered off and found to consist almost entirely of the title compound. Crystallisation from hot water yielded the liberated zwitterion, m.p. 142−143°, after drying at 50° at reduced pressure. When dried at 80° it partially lost water and melted at 120−130°. Decarboxylation had also occurred to some extent in the latter case. Elementary analysis was therefore carried out on the monohydrate. (Found: C 49.44; H 5.32; N 5.99; S 13.41. Calc. for $C_{10}H_{11}NO_3$ H_2O: C 49.39; H 5.38; N 5.76; S 13.18). IR spectrum in KBr; strong absorption bands at 1630−1660 cm⁻¹ due to carboxylate group.

The filtrate from the trituration was brought to pH 7.5 with ammonia, extracted with ether several times to remove any unreacted thiolactam and readjusted to pH 3.5 with HCl. Some more of the title compound crystallized out. By further fractional crystallisation by slow concentration of the solution in all 7.1 g was obtained. The last fractions contained practically pure decarboxylated material as HCl−HBr salt, m.p. 283−285°. The decarboxylated zwitterion, 2,5-dimethyldihydrothiazolo[3,2-a]pyridinium-8-oxide, could be obtained by passing an aqueous solution through a column of Amberlite IR−45 resin in the amine form, (Found: C 59.48; H 6.21; N 7.51. Calc. for $C_9H_{11}NOS$: C 59.65; H 6.11; N 7.72).

IR spectrum. No strong absorption in the carbonyl region. The reaction in acetonitrile is much faster but a number of byproducts are formed.

8-Hydroxy-5-methyl-2-phenyldihydrothiazolo[3,2-a]pyridinium bromide (IXb). Solutions of 2-bromocinnamic acid (17.0 g, 0.086 mole) in chlorobenzene (300 ml) and 3-hydroxy-6-methylpyrid-2-thione (9.9 g, 0.07 mole) in chlorobenzene (500 ml) were mixed and the resultant solution refluxed for 50 h. The hydrobromide of the condensation product slowly precipitated during the reaction. There was thus obtained 17.7 g (78 %), m.p. 220−225°, shown by chromatography to be essentially homogeneous. Recrystallisation from ethanol (charcoal treatment) gave white crystals, m.p. 259−260° (decomp.). (Found: C 51.72; H 4.45; N 4.40; S 10.23. Calc. for $C_{14}H_{13}NOS \cdot HBr$: C 51.87; H 4.35; N 4.32; S 9.89).

IR in KBr showed no strong absorption band in the 1580−1750 cm⁻¹ region.

Due to the high temperature necessary to effect the reaction decarboxylation of the 3-carboxy derivative of the title compound results. Attempts to carry out the reaction in boiling ethyl acetate, methanol or in DMF at 70° gave no condensation product. In aqueous methanol a fluorescent spot, due to the 3-carboxy derivative, was seen on the chromatograms. Similar results were obtained in acetonitrile.

To prove that the decarboxylation occurs after condensation and not before to give β-bromo-styrene solutions of the thiolactam and β-bromostyrene in ethyl acetate or aqueous methanol or sodium ethoxide were refluxed for about one day. No sign of condensation could be found. Therefore the decarboxylation must occur after the condensation.

trans-2,3-Dicarboxy-8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium bromide (If). 3-Hydroxy-6-methylpyrid-2-thione (20 g, 0.2 mole) and bromomalic anhydride (37.6 g, 0.214 mole) were dissolved in cold ethyl acetate (350 ml) and the solution stirred for 18 h at room temperature. In order to complete the reaction another equivalent of bromomaleic anhydride was added and the reaction stirred for another 2 h. Water (200 ml) was then added and the mixture stirred for 6 h, the ethyl acetate removed by distillation at reduced pressure and the precipitated dark coloured solid filtered off from the aqueous residue; 12.8 g, m.p. 205−220°. Concentration of the filtrate to a small volume furnished another 9 g. The combined materials were further purified by dissolution of the above crude hydrobromide in hot water by adjusting the pH to 7.0, decolorizing with charcoal, and readjusting the pH to 2.8; white crystalline precipitate. Recrystallisation from water gave m.p. 181−184°. (Found: C 46.67; H 3.57; N 5.64; S 12.16. Calc. for $C_{10}H_9NO_5S$: C 47.06; H 3.55; N 5.49; S 12.56).

If was difficult to remove the water of crystallisation completely by drying since heating lead to partial decarboxylation as shown by chromatography.

IR spectrum in KBr. Strong carboxyl-carboxylate absorption bands at 1710 and 1650 cm⁻¹.

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