

N-Quaternary Compounds

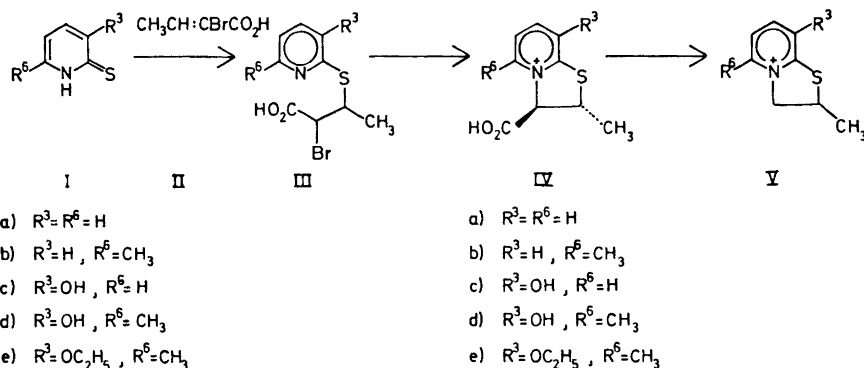
Part XXXII. Michael Addition of Pyrid-2-thiones to α -Bromo- α,β -unsaturated Acids

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In the reaction between the isomeric α -bromocrotonic acids and pyrid-2-thiones only the dihydrothiazolo[3,2-a]pyridinium derivative with 2,3-*trans* configuration was formed. The Michael adduct appears formed by *cis* addition. Hydrogen bonding to sulphur from *ortho*-phenolic hydrogen greatly reduced the reaction rate.

In Michael type additions the reaction rate depends on the properties of the nucleophile as well as on the nature of substituents attached to the electrophilic double bond.² In a previous work with a sulphur nucleophile the effect of double bond substituents was briefly discussed.³ Our systems, however, involve a concurrent cyclisation step which may complicate interpretation of the experimental results. In most cases, however, the cyclisation is so rapid that the Michael addition is the rate determining step in the overall reaction.



Scheme 1.

Reactions were tried in several solvents. The most homogeneous products were obtained in acetone and ethyl acetate. The cyclisation product (IV) as HBr salt is precipitated as formed in these solvents. The quaternary acid (IV) is readily decarboxylated due to the activating effect of the annular nitrogen. To avoid decarboxylation in the stereochemical studies the reactions were run in the cold (20°C). With the exception of Ie the reaction requires a long time and was stopped and the product isolated before the reaction had gone to completion. Based on the percent yield divided by the time in days some qualitative information on relative rates of the reaction between the isomeric 2-bromocrotonic acids and the pyrid-2-thiones (I) was obtained

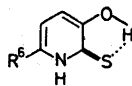
Table 1. Reaction rate expressed as percent yield of IV formed per day.^a

	IVa	IVb	IVc	IVd	IVe
<i>trans</i>	2.3	2.1	0.2	0.4	5.10
<i>cis</i>	1.0	1.2	0.1	0.3	3.60

^a Acetone was the solvent in the syntheses of IVc and IVd due to low solubility of the 3-hydroxypyrid-2-thione in ethyl acetate which was used in the case of IVa, IVb, and IVe.

(Table 1). The rate of adduct formation will depend on the electron density on the sulphur. Thus the 6-methyl derivative (Ib) reacts slightly faster than the parent pyrid-2-thione. The *ortho*-hydroxyl group in Ic might be expected to promote the reaction by its electron releasing properties. Instead a very marked rate reduction was observed. The 6-methyl group in Id again increases the rate relative to Ic but the rate is way below that of the parent pyrid-2-thione. On the other hand the 3-ethoxy derivative Ie reacts much faster than Id and faster than Ib. The electron releasing properties of the ethoxy group are therefore far more important than any steric interaction from the *ortho*-ethoxy group in the formation of the Michael adduct. The relatively low reaction rates for the hydroxy compounds are therefore attributed to hydrogen bonding with sulphur as the hydrogen acceptor. In a comparative study of hydrogen bonding ability of pyrid-2-thione and pyrid-2-one it was concluded that the former has a lower ability to form dimers through intermolecular hydrogen bonding than the oxygen analogue.⁵ The otherwise weak hydrogen bonding to sulphur,⁵ however, shows considerable strength in intramolecular phenolic hydrogen bonding to the sulphur in an *ortho*-thioether group.^{6,7} The above discussion leads to the postulation of a relatively strong hydrogen bonding between the phenolic hydrogen and the sulphur of the thione group. Intramolecular hydrogen bonding would be stabilised through a pseudo-5-membered ring (Scheme 2).

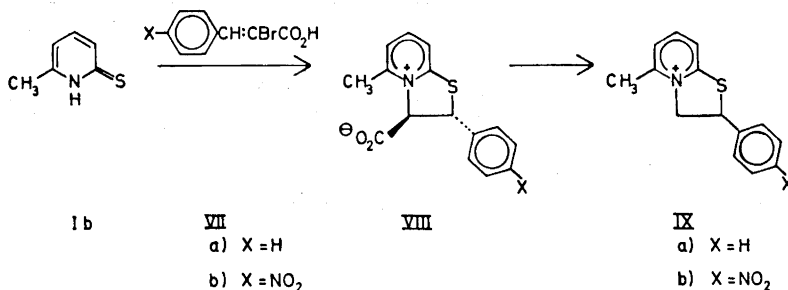
The β -methyl group in crotonic acid, due to both steric and electronic effects, strongly reduces the reaction rate relative to acrylic acid.³ The same was found for β -phenyl derivatives. Thus the two stereoisomeric cinnamic acids did not react to any degree with 6-methylpyrid-2-thione in the cold. The reaction required heating for several days and led only to decarboxylated



VI

Scheme 2.

material. A *para*-nitro group in the cinnamic acid should promote the reaction by its electron withdrawing properties and have no steric influence. The electronic effect of the nitro group, however, was not sufficient for making the reaction go in the cold. Heating led only to decarboxylated material. These experiments showed no difference in reaction rates between the *cis*- and *trans*-cinnamic acids.



Scheme 3.

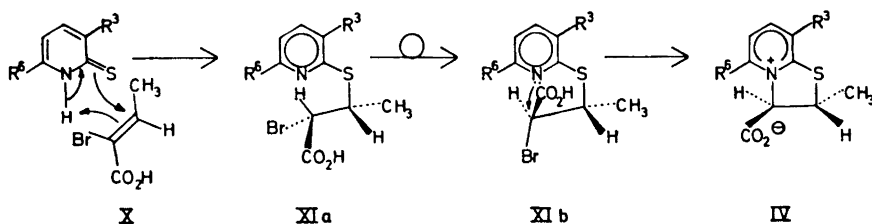
The low reactivity in the cinnamic acid series led us to restrict the stereochemical studies to the stereoisomeric crotonic acids. Experimentally both *cis*- and *trans*- α -bromocrotonic acid gave the *trans*-product (IVa) with pyridin-2-thione. The structural assignment follows from the NMR spectrum recorded in trifluoroacetic acid (TFA). The Karplus relationship⁸ between dihedral angle and coupling constant is affected by electronegative substituents and their configuration.⁹ Despite the uncertainties introduced by the electronegative substituents as to the exact value of the dihedral angle the experimentally observed coupling constant between the vicinal 2,3-methine protons, $J_{2,3} = 1.0$ cps, is so small that *trans* assignment must be concluded. This assignment is also in agreement with X-ray data for a closely related compound.¹⁰

Since both the *cis*- and *trans*-crotonic acids give a cyclic product IV with *trans* stereochemistry, isomerisation must have occurred. A different addition mechanism for the isomeric acids seems unlikely. Isomerisation could occur in one of the acids prior to reaction, in the Michael adduct (III) or in the cyclic product first formed (Scheme 4). The reaction of Ib was therefore carried out in deuteriated acetone and the reaction progress studied by NMR. In this way it was found that the *cis*-acid was isomerised to the *trans*-acid before any

addition product was seen by NMR. The *trans*-acid was not isomerised. The isomerisation was readily demonstrated to be HBr catalysed. The intermediate Michael adduct was not observed spectroscopically or by chromatography. This confirms the rate limiting step in the overall reaction to be adduct formation. Very rapid isomerisation in the highly reactive Michael adduct seems unlikely since an optically active analogue of the adduct has been cyclised with high optical yield.¹

Rapid epimerisation at C-3 in an initially formed *cis*-cyclisation product has not been experimentally excluded. 8-Hydroxy-5-methyldihydrothiazolo-[3,2-a]pyridinium-3-carboxylate, however, is optically stable under these conditions, although the C-3 methine proton is readily exchangeable.¹¹ Since the reaction of 3-hydroxy-6-methylpyrid-2-thione (Id) with both *cis*- and *trans*-crotonic acid gave the same *trans*-cyclic product, rapid isomerisation at this stage seems less likely. It should be pointed out, however, that the effect of a *cis*-methyl group on the rate of epimerisation at C-3 remains to be tried. So far such a compound has not been available. It does not seem unreasonable, however, to assume that the non-bonded interaction between the 2-methyl group and the 3-carboxy group in a *cis*-product is not sufficient to cause immediate epimerisation at C-3.

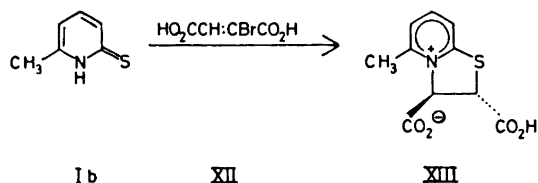
The HBr generated in the cyclisation would almost certainly exclude a free radical mechanism in the adduct formation. Support for this view follows from separate experiments carried out in the presence of hydroquinone, or benzoyl peroxide or without any external agent, which showed no detectable rate differences or different product composition.



Scheme 4.

Cyclisation of the α -bromo-acid has been found to proceed by inversion of the configuration.¹ It therefore follows from the above discussions that adduct formation proceeds by a *cis* mechanism rather than the usual *trans* pathway observed in acid catalysed thiol addition and base induced thioxide additions. Free radical additions are less stereospecific.^{12,13} *trans*-Addition was originally suggested, however, working with *cis*- α -bromocrotonic acid since isomerisation to the *trans*-acid had not been realised.

Pyrid-2-thione exists almost entirely in this form rather than as the tautomeric 2-mercaptopyridine.¹⁴ The substituted derivatives should behave similarly. If these molecules are assumed to react as thiones the *cis* addition can be explained by a concerted reaction involving 6-atoms in the transition state as indicated in Scheme 4 (X).



Scheme 5.

To increase the reactivity of the α,β -unsaturated acid an electron attracting substituent was introduced onto the β -carbon, the compounds studied being bromomaleic and bromofumaric acid, respectively. Additions of the pyrid-2-thione (Ib) to these acids in cold ethyl acetate immediately led to precipitation of a product identified as the hydrobromide of the pyrid-2-thione. After two further days the pyrid-2-thione was fully converted into the cyclic product XIII (Scheme 5). The HBr arises through rapid elimination and generation of acetylenedicarboxylic acid. The pyrid-2-thione then adds to the triple bond followed by cyclisation of the resultant vinyl ether. The reason for HBr elimination lies in high activation of the vinyl proton.

The cyclic product XIII was assigned a *trans* configuration since the coupling constant between the vicinal 2,3-methine protons was close to zero. The configurational assignment has also been confirmed by X-ray work.¹⁵ The X-ray studies show that the dihydrothiazolo ring in the solid state has an envelope conformation with the 1- and 3-atoms nearly coplanar with the pyridine ring and the C-2 carbon 0.5 Å out of the plane. The angle between the 2,3-substituents was 160° corresponding to a dihedral angle between the two vicinal hydrogens of about 80° explaining the small coupling constant in NMR. The zwitterions form infinite chains through intermolecular hydrogen bonding between the 2- and 3'-carboxyl groups in adjacent molecules. The O to H distance is larger in the 3-carboxyl group than in the 2-carboxyl group. The 3-carboxyl group has therefore a larger degree of carboxylate character as would be expected on electronic grounds.

EXPERIMENTAL

The NMR data were recorded on a Varian A-60A instrument and the UV data on a Perkin-Elmer 137-UV instrument.

trans-2-Methyldihydrothiazolo[3,2-*a*]pyridinium-3-carboxylate (IVa). A solution of α -bromocrotonic acid (*cis*¹⁶ and *trans*¹⁷) (1.65 g, 0.01 mol) and pyrid-2-thione (1.11 g, 0.01 mol) in ethyl acetate (90 ml) was left in the cold. The hydrobromide of the title compound was slowly precipitated. The yield from *trans*-acid after 22 days was 1.38 g (50 %); from *cis*-acid 0.55 g (20 %), m.p. 180–185°C (decomp.).

The zwitterion was generated by passage of an aqueous solution of the hydrobromide through a column of Amberlite IR-45(OH) followed by elution with water. Any coprecipitated pyrid-2-thione remained on the column. The eluates were freeze-dried and the solid residue crystallised as white needles from aqueous acetone; m.p. 138°C (decomp.). (Found: C 55.43; H 4.94; N 7.43. Calc. for C₉H₈NO₂S: C 55.39; H 4.65; N 7.21.) UV in 0.1 N NaOH: 353 nm (log ϵ 3.95), 277 nm (4.04), 222 nm (4.08); in 0.1 N HCl: 325 nm (log ϵ 3.84), 250 nm (3.96), 212 nm (4.01). NMR in TFA: 8.18 τ (2-CH₃, doublet, J = 7.0 cps), 5.23 τ (2-H, octet, $J_{2,3}$ = 1.0 cps), 3.84 τ (3-H, doublet), 1.1–2.3 τ (pyridyl-H).

*trans-2,5-Dimethyldihydrothiazolo[3,2-*a*]pyridinium-3-carboxylate (IVb)*. The hydrobromide was prepared as above from 6-methylpyrid-2-thione in 32 % yield from *trans*-acid after 15 days and 24 % yield from *cis*-acid after 20 days. The zwitterion, generated over Amberlite IR-45(OH) as above, was slightly contaminated with decarboxylated material (Vb). Elemental analysis was obtained for Vb. UV in 0.1 N NaOH: 355 nm ($\log \epsilon$ 3.86), 275 nm (3.81), 222 nm (3.88); in 0.1 N HCl: 329 nm ($\log \epsilon$ 4.08), 242 nm (4.04), 210 nm (4.10). NMR in TFA: 8.20 τ (2-CH₃, doublet, $J_{2-CH_3} = 7.0$ cps), 5.27 τ (2-H, quartet, $J_{2,3} < 1$ cps), 3.92 τ (3-H, singlet), 7.10 τ (5-CH₃), 1.4–2.8 τ (pyridyl-H).

*trans-2-Methyl-8-hydroxydihydrothiazolo[3,2-*a*]pyridinium-3-carboxylate (IVc)* was prepared from 3-hydroxypyrid-2-thione in acetone. The yield of HBr salt from *trans*-acid after 40 days was 9 %; from *cis*-acid 6 %.

The HBr salt, m.p. 175–180°C (decomp.), was converted to the zwitterion over Amberlite IR-45(OH) as above. It was partly decarboxylated (Vc). The elemental analysis was carried out on Vc. UV in 0.1 N NaOH: 355 nm ($\log \epsilon$ 4.04), 250 nm (3.99), 224 nm (3.86). NMR in TFA: 8.20 τ (2-CH₃, doublet, $J = 7.0$), 5.28 τ (2-H, octet), 4.11 τ (3-H, doublet, $J_{2,3} = 1.0$ cps), 1.6–2.5 τ (pyridyl-H).

*trans-2,5-Dimethyl-8-hydroxydihydrothiazolo[3,2-*a*]pyridinium-3-carboxylate (IVd)*. The HBr salt was prepared from 3-hydroxy-6-methylpyrid-2-thione in acetone. The yield of HBr salt from *trans*-acid was 15 % after 40 days; from the *cis*-acid 12 %. The title compound has previously been described.³ UV in 0.1 N NaOH: 364 nm ($\log \epsilon$ 4.06), 250 nm (4.00), 224 nm (3.92); in 0.1 N HCl: 346 nm ($\log \epsilon$ 3.93), 240 nm (3.77), 216 nm (4.00). NMR in TFA: 8.20 τ (2-CH₃, doublet, $J = 7.0$ cps), 5.27 τ (2-H, quartet), 3.95 τ (3-H, singlet, $J_{2,3} < 1$ cps), 7.20 τ (5-CH₃), 2.1–2.6 τ (pyridyl-H).

*trans-2,5-Dimethyl-8-ethoxydihydrothiazolo[3,2-*a*]pyridinium-3-carboxylate (IVe)* was prepared from 3-ethoxy-6-methylpyrid-2-thione¹⁸ in ethyl acetate. The yield of HBr salt after 4 h was 85 % from the *trans*-acid and 60 % from the *cis*-acid, m.p. 180–183°C (decomp.).

The zwitterion, liberated on an Amberlite IR-45(OH) column as above, was recrystallised from aqueous acetone, m.p. 93°C (decomp.) (Found: C 52.96; H 6.38; N 5.01. Calc. C₁₂H₁₆NO₃S.H₂O: C 53.11; H 6.32; N 5.16.) UV in 0.1 N NaOH: 357 nm ($\log \epsilon$ 3.86), 242 nm (3.72), 220 nm (3.73); in 0.1 N HCl: 346 nm ($\log \epsilon$ 3.90), 243 nm (3.81), 215 nm (3.89). NMR in TFA: 8.24 τ (2-CH₃, doublet, $J = 7.0$ cps), 5.30 τ (2-H, quartet), 3.95 τ (3-H, singlet, $J_{2,3} = 0$ cps), 7.20 τ (5-CH₃), 2.4–2.5 τ (pyridyl-H), 8.44 and 5.62 τ (OC₂H₅).

*2-Methyldihydrothiazolo[3,2-*a*]pyridinium-8-oxide (Vc)*. A solution of 3-hydroxypyrid-2-thione (3.81 g, 0.03 mol) and *trans*- α -bromocrotonic acid (4.85 g, 0.03 mol) in ethyl acetate (80 ml) was heated under reflux for 6 days. The title compound was precipitated as hydrobromide; yield 0.74 g (9 %), m.p. 142–151°C (decomp.).

The betaine was generated by passage of an aqueous solution through a column of Amberlite IR-45(OH) and evaporation of the eluates. Recrystallisation from acetone gave white needles, m.p. 84–85°C (decomp.) (Found: C 51.62; H 6.00; N 7.71. Calc. for C₈H₉NOS.H₂O: C 51.85; H 5.99; N 7.56.) UV in 0.1 N NaOH: 353 nm ($\log \epsilon$ 3.98), 263 nm (3.85), 246 nm (3.86), 221 nm (3.53); in 0.1 N HCl: 336 nm ($\log \epsilon$ 3.93), ~245 sh. nm, 234 nm (3.71), 212 nm (4.14). NMR in TFA: 8.30 τ (2-CH₃, doublet, $J = 7.0$ cps), 5.5 τ (2-H, multiplet), 4.9 τ (3-H, multiplet), 1.7–2.6 τ (pyridyl-H).

*2,5-Dimethyldihydrothiazolo[3,2-*a*]pyridinium bromide (Vb)*. The title compound was prepared in 35 % yield by heating 6-methylpyrid-2-thione in ethyl acetate with *trans*- α -bromocrotonic acid for 20 h. The product was recrystallised from acetone, containing a drop of HBr, in white needles; m.p. 199–200°C. (Found: C 43.60; H 4.96; N 5.67. Calc. for C₈H₁₂BrNS: C 43.91; H 4.92; N 5.69.) UV in 0.1 N NaOH: 327 nm ($\log \epsilon$ 3.88), 252 nm (3.88), ~225 sh. nm; in 0.1 N HCl: 327 nm ($\log \epsilon$ 3.99), 252 nm (3.88), 210 nm (4.13). NMR in TFA: 8.30 τ (2-CH₃, doublet, $J = 6.5$ cps), 5.5 τ (2-H, multiplet), 5.0 τ (2H, multiplet), 7.22 τ (5-CH₃), 1.8–2.6 τ (pyridyl-H).

*5-Methyl-2-phenyldihydrothiazolo[3,2-*a*]pyridinium bromide (IXa)*. 6-Methylpyrid-2-thione (1.25 g, 0.01 mol) and α -bromocinnamic acid (*cis*¹⁹ and *trans*¹⁹) (2.27 g, 0.01 mol) in ethyl acetate solution (80 ml) was heated under reflux for 1 day. The yield of precipitated material from the *trans*-acid was 0.70 g (23 %) and 0.61 g (20 %) from the *cis*-acid. After 7 days the yield was 53 %. Recrystallisation from ethanol containing a drop of HBr gave a whitish material, m.p. 201°C (decomp.) (Found: C 54.46; H 4.73; N 4.75. Calc. for C₁₄H₁₄BrNS: C 54.53; H 4.56; N 4.52.) UV in 0.1 N NaOH: 330 nm ($\log \epsilon$ 3.99),

249 nm (4.08), 224 nm (3.74); in 0.1 N HCl: 330 nm (log ϵ 3.90), 249 nm (3.97), 209 nm (4.30). NMR in TFA: 2.37 τ (2-C₆H₅, singlet), 4.1–4.9 τ (2-H, 3H multiplet), 7.13 τ (5-CH₃), 1.7–2.7 τ (pyridyl-H).

5-Methyl-2-p-nitrophenyldihydrothiazolo[3,2-a]pyridinium bromide (IXb). 6-Methylpyrid-2-thione (1.25 g, 0.01 mol) and α -bromo-*p*-nitrocinnamic acid (*cis*²⁰ and *trans*²⁰) (2.72 g, 0.01 mol) in ethyl acetate solution (90 ml) was heated under reflux for 1 day. The yield of precipitated material from the *trans*-acid was 1.30 g (37 %); from the *cis*-acid 1.12 g (31 %). Recrystallisation from ethanol containing a drop of HBr gave whitish material, m.p. 252°C (decomp.). (Found: C 47.33; H 3.64; N 7.96. Calc. for C₁₄H₁₃BrN₂OS: C 47.61; H 3.54; N 7.93.) UV in 0.1 N NaOH: 460 nm (log ϵ 3.41), 322 nm (4.18), 270 nm (4.02), 223 nm (4.13); in 0.1 N HCl: 328 nm (log ϵ 4.08), ~270 sh. nm, 253 nm (4.19), 208 nm (4.33). NMR in TFA: 1.59 and 2.12 τ (AB quartet of C₆H₄NO₂), 4.1–5.0 τ (2H, 3H-multiplet), 7.10 τ (5-CH₃), 1.6–2.5 τ (pyridyl-H).

trans-2-Carboxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (XIII). Bromomaleic acid²¹ and bromofumaric acid,²² respectively, (0.1 mol) in ethyl acetate (20 ml) was added to a solution of 6-methylpyrid-2-thione (1.25 g, 0.01 mol) in ethyl acetate (70 ml). The hydrobromide of the pyrid-2-thione was immediately precipitated. After stirring in the cold for 2 days chromatography showed that the initially formed material had gradually been dissolved with precipitation of the new cyclic product.

The zwitterion was obtained by crystallisation from its HBr salt in water, m.p. 180°C (decomp.). (Found: C 50.05; H 3.70; N 5.88. Calc. for C₁₀H₉NO₄S: C 50.20; H 3.79; N 5.85.) UV in 0.1 N NaOH: 337 nm (log ϵ 3.80), 242 nm (3.86), 227 nm (3.86); in formic acid: 330 nm (log ϵ 3.87), 262 nm (3.08). NMR in TFA: 4.65 τ (2-H, singlet), 3.28 τ (3-H, singlet, $J_{2,3} < 1$ cps), 7.02 τ (5-CH₃), 1.5–2.3 τ (pyridyl-H).

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