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# *N*-Quaternary Compounds

## Part XXXIII. Reactions between Pyrid-2-thiones and Activated Acetylenes

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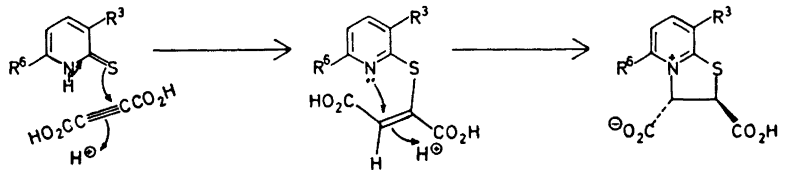
Pyrid-2-thiones with acetylenedicarboxylic acid gave *trans*-2,3-dicarboxydihydrothiazolo[3,2-a]pyridinium derivatives. Vinyl thioethers were the products from the reactions with propiolic and phenylpropiolic acids. Stereochemical assignments are based on NMR data. Bromination of the vinyl thioethers is a convenient method for the preparation of the thiazolo[3,2-a]pyridinium system.

The initial reaction between pyrid-2-thiones and bromofumaric or bromomaleic acid was found to involve HBr elimination. The pyrid-2-thione would then add to the generated acetylene.[1] This observation led us to extend Michael type addition studies of sulphur nucleophiles from electron deficient double bonds into triple bonds. With acetylenedicarboxylic acid in cold chloroform the reaction was rapid with formation of the bicyclic pyridinium derivative (III). The NMR coupling constant for the vicinal 2,3-protons was in the region 0 – 1 cps and *trans* configuration could therefore be assigned to the products.[1] NMR experiments using pyrid-2-thione showed that the same product was obtained in deuterium oxide. In trifluoroacetic acid (TFA), however, a singlet signal appeared at 5$\tau$ which, once it had reached a maximum, decreased very slowly with time. The signal may be ascribed to a vinyl proton such as in the vinyl thioether II (Scheme 1). Acid catalysis in the adduct formation seems likely, even in chloroform, since acetylenedicarboxylic acid is a relatively strong acid (p$K_a$ 1.74).[2] This would lead to a *trans*-addition product (II) as is usually found for thiol additions to triple bonds.[3,4] A further argument in favour of this configuration (II) is the *trans* configuration of the cyclised product III. The formation of the latter from the initial adduct involves nucleophilic attack from the annular nitrogen onto the double bond (Scheme 1). The *cis*-isomer, with respect to the carboxy groups, would have to be isomerised during the cyclisation or the cyclisation product rapidly epimerised to the *trans*-isomer.



I II III

a) $R^3 = R^6 = H$

b) $R^3 = H$, $R^6 = CH_3$

c) $R^3 = OH$, $R^6 = H$

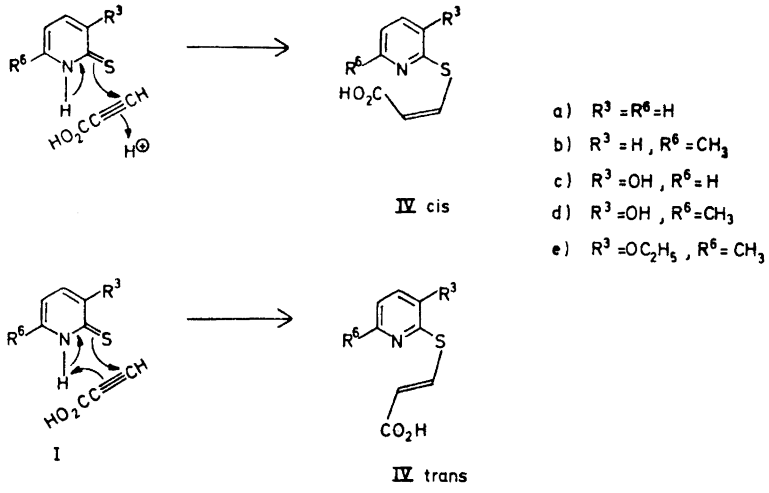
d) $R^3 = OH$, $R^6 = CH_3$

e) $R^3 = OC_2H_5$, $R^6 = CH_3$

*Scheme 1.*

Propiolic acid is less active towards nucleophiles than acetylenedicarboxylic acid. Even so it reacted readily with pyrid-2-thiones in cold chloroform. The phenolic pyrid-2-thiones (1c, d) were found less reactive, due to intramolecular hydrogen bonding between the phenolic-OH group and the sulphur,[1] but the reaction for all pyrid-2-thiones was complete after 1 day without heating. Two products were formed in each case and were shown by NMR and MS to be the stereoisomeric vinyl ethers IV (Scheme 2). In no case did the vinyl thioether cyclise to the dihydrothiazolo[3,2-a]pyridinium system as was the case in the acetylenedicarboxylic acid series. The NMR spectra (TFA) contain the two vinyl protons in two AB patterns in the 3.2 to 3.8 $\tau$ and 1.7 to 2.5 $\tau$ regions, the vicinal coupling constant being 10.0 cps and 15.5 – 15.9 cps, respectively. The magnetic and stereochemical relationships around the double bond in the above series should be very similar to those in $\beta$-phenylthioacrylic acid. For the latter the coupling constants were 15.3 and 10.0 cps, the former being assigned to the *trans*-isomer and the latter to the *cis*-isomer.[5] The isomer IV with the higher coupling constants, in its IR spectrum shows out of plane deformation at 960 $cm^{-1}$ for its olefin hydrogen pair compared to 680 $cm^{-1}$ for the other isomer. These data correlate well with the values 965 $cm^{-1}$ and 675 – 730 $cm^{-1}$ quoted for *trans*- and *cis*-olefins, respectively.[6] For structural assignments by NMR, however, it is important to have the stereochemistry of one member of an analogues series determined by an absolute method. Therefore the isomer of IVb with the larger coupling constant was subjected to X-ray analysis and the structure found to be *trans*.[7] The *cis*/*trans*-isomer ratio was variable but the *trans*-isomer was the major component.

The stereoisomeric mixture (IV) can arise either by two competing reaction pathways or by isomerisation of the first formed isomer. NMR studies of the reaction between 6-methylpyrid-2-thione and propiolic acid in deuteriated chloroform showed the product *cis*/*trans* ratio (1:8) to be independent of time. The *trans*-isomer would on stereochemical grounds be expected to be thermodynamically the more stable isomer as has been established in equilibration studies in the analogous $\beta$-phenylthioacrylic acid series.[8,9] Epimerisation




*Scheme 2.*

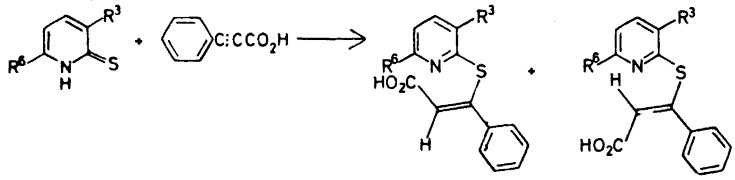
studies of IV in various solvents and conditions did not change the isomer ratio. Isomerisation to an equilibrium mixture under the mild reaction conditions is therefore excluded.

This leaves two competing reaction pathways to be considered. The acid strength of propiolic acid ($pK_a$ 1.85)[10] is of the same order as that of acetylenedicarboxylic acid. A similar *trans*-addition mechanism is therefore reasonable to assume (Scheme 2). A reasonable explanation for the competitive formation of the *trans* product is suggested by a favourable set up for *cis*-addition if the sulphur nucleophile can be assumed to react as the thione tautomer (Scheme 2) which is by far the more important tautomeric form.

Phenylpropiolic acid showed reduced reactivity towards pyrid-2-thiones. After 10 days in cold chloroform the reaction between phenylpropiolic acid and the most reactive nucleophile (Ie) was only half completed, which is to be compared with the reaction between propiolic acid and Ie which was over in less than one day. Qualitatively the relative rates of addition for the pyrid-2-thiones to phenylpropiolic acid were established from the reaction in 0.1 M solutions in cold deuteriochloroform in tubes used for NMR recordings. The relative rates were found to follow the previously established pattern Ie > Ib > Ia > Id > Ic.[1]

NMR spectra of the addition product show the latter to consist almost entirely of one stereoisomer, the vinyl proton signal in NMR (TFA) appearing in the 3.4 – 3.5 $\tau$ region. A weak signal from the vinyl proton of the minor isomer may be seen at some 0.2 $\tau$ lower field. The second signal was strongest for Va, in which case integration of the spectrum indicated 5 – 10 % of the minor stereoisomer, while only one vinyl proton signal was seen for Vd. The configurational assignment in this case is more uncertain. The acid strength relatively to propiolic acid is decreased ($pK_a$ 2.23).[10] The above results indicate that any correlation between the $pK_a$ of the acetylenecarboxylic acid, because

of difference in acidity or as a measure for the reactivity of the conjugated triple bond, and the reaction mixtures would indicate an even higher proportion of product formed by *cis*-addition than in the case of propiolic acid. The suggested *cis* configuration (Scheme 3) for the major product would appear to be supported from calculations of the chemical shifts for the vinyl protons in the stereoisomers V through the use of additive shielding parameters for olefinic protons.[11] The calculations for a *trans* structure gave the value 387 cps, for a *cis* structure 343 cps. The experimental values for the two vinyl protons recorded in $CDCl_3$ were 370 – 385 cps in the minor product and 360 – 370 cps in the major product.



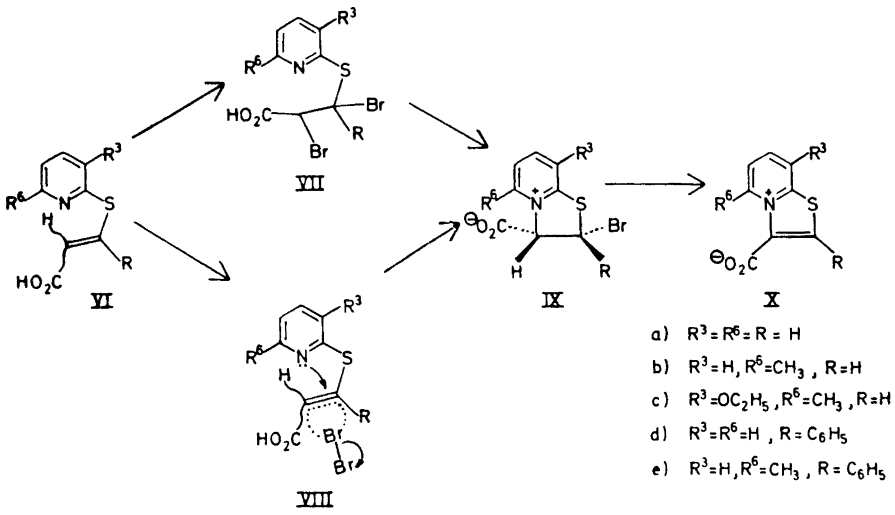

I V trans V cis

a) $R^3 = R^6 = H$
b) $R^3 = H$, $R^6 = CH_3$
c) $R^3 = OH$, $R^6 = H$
d) $R^3 = OH$, $R^6 = CH_3$
e) $R^3 = OC_2H_5$, $R^6 = CH_3$

*Scheme 3.*

The double bond in the vinyl thioethers prepared is activated towards electrophiles. By the reaction with bromine a very convenient synthesis to the thiazolo[3,2-a]pyridinium system is available (Scheme 4) as distinct from proton addition which led to the dihydrothiazolo[3,2-a]pyridinium system (Scheme 1). Thus bromine addition to a cold chloroform solution of the vinyl thioether gave immediate precipitation of a product which on isolation was found to be a thiazolo[3,2-a]pyridinium derivative (X). Thus the NMR spectra for the products from the phenylvinyl thioethers contained only aromatic protons, the structures assigned therefore being Xd and Xe. The products without a 2-substituent have a proton signal at low field (1.4 $\tau$) as previously reported for such derivatives.[12]

The reaction to the bicyclic product IX may go *via* two different paths. The initial attack by bromine may be followed by back-side attack by the pyridine nitrogen (VIII) with direct formation of the dihydrothiazole (IX). Alternatively IX is formed *via* the dibromide VII. Presumably both pathways would be operative depending on substituent effects. In the present case, however, the absence of VII in the reaction product would appear to favour direct addition of the pyridine nitrogen as indicated in VIII (Scheme 4). Irrespective of the original stereochemistry in IX the HBr elimination would be expected to occur very readily because of the activation of the 3-methine




*Scheme 4.*

proton by both the carboxy and the ammonium groups. The same groups will stabilise the corresponding carbanion whereby the correct stereochemistry for E2 elimination can be introduced. Perhaps even more likely in this case, however, would be the two-step E1cB elimination which involves a carbanion intermediate.

## EXPERIMENTAL

The NMR data were recorded on a Varian A-60A instrument.

trans-*2-Carboxydihydrothiazolo[3,2-a]pyridinium-3-carboxylates (III).* Acetylenedicarboxylic acid (1.14 g, 0.01 mol) dissolved in anhydrous ethyl acetate (20 ml) was added dropwise to a solution of a pyrid-2-thione (I) (0.01 mol) in anhydrous ethyl acetate (70 ml). A yellowish-white solid was rapidly precipitated. The crude product of the 5-desmethyl analogues was sensitive to moisture, the 5-methyl analogues insensitive.

The 5-desmethyl analogues were absorbed onto charcoal in boiling ethanol (100 ml) from which they were desorbed in formic acid (50 ml). The formic acid on standing precipitated the zwitterionic material. This could be recrystallised by dissolution in a minimum volume of formic acid and addition of some water when the material slowly crystallised out. The crude product from the 5-methyl analogues could be recrystallised directly from dilute formic acid. Physical data are given in Table 1.

*Table 1.*

| III | M.p. °C (Decomp.) | Yield % | React. time | Empirical formulae | Found C | Found H | Found N | Calc. C | Calc. H | Calc. N |
|---|---|---|---|---|---|---|---|---|---|---|
| a | 190 | 35 | 20 min | $C_9H_7NO_4S$ | 48.29 | 3.17 | 6.32 | 48.00 | 3.13 | 6.22 |
| b | 180 | 80 | 1 d | $C_{10}H_9NO_4S$ | 50.05 | 3.70 | 5.88 | 50.20 | 3.79 | 5.85 |
| c | 180 | 30 | 30 min | $C_9H_7NO_5S.H_2O$ | 41.69 | 3.77 | 5.70 | 41.70 | 3.50 | 5.40 |
| d | 187 | 86 | 1 d | $C_{10}H_9NO_5S.H_2O$ | 43.68 | 4.01 | 5.35 | 43.93 | 4.07 | 5.15 |
| e | 157 | 88 | 1 d | $C_{12}H_{13}NO_5S$ | 50.76 | 4.43 | 5.24 | 50.77 | 4.60 | 4.93 |

NMR in TFA: a; 4.55 τ (2H, $J_{2,3}=1.0$), 3.27 (3H). b; 4.65 τ (2H, $J_{2,3}<1$), 3.28 (3H), 7.02 (5-$CH_3$). c; 4.62 τ (2H, $J_{2,3}=1.2$), 3.30 (3H), d; 4.70 τ (2H, $J_{2,3}<1$), 3.33 (3H), 7.15 (5-$CH_3$). e; 4.65 τ (2H, $J_{2,3}<1$), 3.27 (3H), 7.15 (5-$CH_3$).

*β-2-Pyridylthiopropenic acids (IV).* Propiolic acid (0.70 g, 0.01 mol) in chloroform (30 ml) was added to a pyrid-2-thione (0.01 mol) dissolved in chloroform (40 ml). The phenolic derivatives came out of solution, the others were soluble. After one day at room temperature the chloroform was distilled off and the residual material crystallised from dilute ethanol. Physical data are given in Table 2. In one case (IVb) the *trans* isomer was selectively precipitated on crystallisation of the *cis/trans* mixture from dilute ethanol. This was the sample subjected to X-ray analysis.[7]

NMR in TFA: The chemical shift for the pyridyl hydrogens or the pyridyl methyl group is not affected by the double bond stereochemistry. The vinyl protons appear in two AB patterns due to *cis/trans* isomerism. The chemical shifts are (a): 3.17, 2.37 τ ($J=10.0$); 3.48, 1.87 ($J=15.3$). (b): 3.52, 2.38 τ ($J=10.0$); 3.57, 1.72 ($J=15.5$). (c): 3.27, 2.47 τ ($J=10.0$); 3.70, 1.91 ($J=15.5$). (d): 3.65, 2.55 τ ($J=10.0$); 3.87, 2.00 ($J=15.9$). (e): 3.65, 2.50 τ ($J=10$); 3.77, 1.90 ($J=15.5$).

*Table 2.*

| IV | M.p. °C | Yield % | React. time | Emp. form. | Found C | Found H | Found N | Calc. C | Calc. H | Calc. N |
|---|---|---|---|---|---|---|---|---|---|---|
| a | 152–153 | 94 | 1 d | $C_8H_7NO_2S$ | 52.83 | 3.84 | 7.48 | 53.03 | 3.89 | 7.73 |
| b | 125 | 99 | » | $C_9H_9NO_2S$ | 55.34 | 4.55 | 7.17 | 55.37 | 4.65 | 7.18 |
| c | 153–154 | 86 | » | $C_8H_7NO_3S.\frac{1}{2}H_2O$ | 46.89 | 4.03 | 6.98 | 46.60 | 3.91 | 6.79 |
| d | 174–175 | 95 | » | $C_9H_9NO_3S$ | 50.98 | 4.40 | 6.66 | 51.16 | 4.29 | 6.63 |
| e | 189–190 | 93 | » | $C_{11}H_{13}NO_3S$ | 55.50 | 5.29 | 5.81 | 55.21 | 5.48 | 5.85 |

*β-2-Pyridylthiocinnamic acids (V).* Phenylpropiolic acid (1.46 g, 0.01 mol) in chloroform (40 ml) was added dropwise to a pyrid-2-thione (0.01 mol) in chloroform (50 ml). In some cases the product formed was slowly precipitated. After 10 days in the cold the chloroform was distilled off and the residual material crystallised from ethanol, or in the case of Ve from dilute methanol. Physical data are given in Table 3.

NMR in TFA: The vinyl proton appears as a singlet at 3.28 τ (a), 3.40 (b), 3.47 (c), 3.50 (d), 3.52 (e). The phenyl group falls in the 2.65–2.60 τ region, the 6-methyl group 7.45–7.35 τ.

*Table 3.*

| V | M.p. °C | Yield % | Emp. form. | Found C | Found H | Found N | Calc. C | Calc. H | Calc. N |
|---|---|---|---|---|---|---|---|---|---|
| a | 169 | 46 | $C_{14}H_{11}NO_2S$ | 65.24 | 4.51 | 5.58 | 65.34 | 4.31 | 5.45 |
| b | 141–142 | 57 | $C_{15}H_{13}NO_2S$ | 66.64 | 5.04 | 5.28 | 66.42 | 4.83 | 5.18 |
| c | 188 | 32 | $C_{14}H_{11}NO_3S$ | 61.61 | 4.17 | 4.84 | 61.53 | 4.06 | 5.13 |
| d | 198 | 40 | $C_{15}H_{13}NO_3S$ | 62.50 | 4.83 | 4.79 | 62.72 | 4.56 | 4.88 |
| e | 189 | 30 | $C_{17}H_{17}NO_3S$ | 64.19 | 5.55 | | 64.59 | 5.43 | |

*Thiazolo[3,2-a]pyridinium-3-carboxylates (X) as HBr salts.* Bromine (0.005 mol) in chloroform (10 ml) was added dropwise to a solution of the β-2-pyridylthiocinnamic or -propenic acid (0.05 mol) in chloroform (40 ml). The hydrobromides were precipitated at once as a crystalline material or as an oil which solidified with time. After one day the chloroform was distilled off and the residual material recrystallised from dilute ethanol, methanol, or acetone to which had been added 1–2 drops of HBr. Physical data are given in Table 4.

*Table 4.*

| X | M.p. °C (decomp.) | Yield % | Emp. form. | Found C | Found H | Found N | Calc. C | Calc. H | Calc. N |
|---|---|---|---|---|---|---|---|---|---|
| a | 297 | 63 | $C_8H_5NO_2S.HBr$ | 37.17 | 2.61 | 5.45 | 36.91 | 2.33 | 5.41 |
| b | 188 | 73 | $C_9H_7NO_2S.HBr$ | 39.83 | 3.17 | 5.33 | 39.43 | 2.94 | 5.11 |
| c | 271 | 49 | $C_{11}H_{11}NO_3S.HBr$ | 41.89 | 4.10 | 4.56 | 41.52 | 3.80 | 4.40 |
| d | 185 | 75 | $C_{14}H_9NO_3S.HBr$ | 49.73 | 2.97 | 4.19 | 50.00 | 3.00 | 4.17 |
| e | 210 | 63 | $C_{15}H_{11}NO_2S.HBr$ | 51.82 | 3.30 | 3.67 | 51.46 | 3.46 | 4.02 |

NMR in TFA: a; 1.37 τ (2H), 1.1 – 2.1 (Pyr.-H). b; 1.40 τ (2H), 1.32 – 2.2 (Pyr.-H), 7.05 ($CH_3$). c; 1.37 τ (2H), 1.9 – 2.2 (Pyr.-H), 7.12 ($CH_3$). d; 2.65 τ (2-Phenyl), 1.1 – 2.1 (Pyr.-H). e; 2.63 τ (2-Phenyl), 1.8 – 2.6 (Pyr.-H), 3.25 ($CH_3$).

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