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# *N*-Quaternary Compounds

## Part XVII. Addition of Thioamides to α-Bromo-α,β-unsaturated Acids

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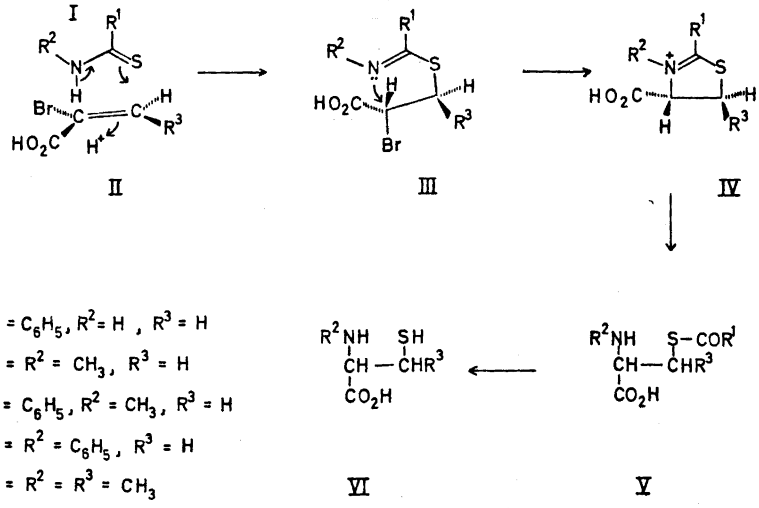
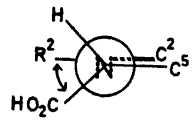
Thioamides have been found to form adducts with α-bromo-α,β-unsaturated acids. The adducts formed are at once cyclised to thiazolinium derivatives. For steric reasons the reaction rate decreases with increasing number and size of substituents. *N*-Cysteine derivatives are formed on acid hydrolysis.

Pyrid-2-thiones and α-bromo-α,β-unsaturated acids readily form adducts which immediately are cyclised with the formation of dihydrothiazolo-[3,2-a]pyridinium-3-carboxylates.[2] Pyrimidines react similarly.[3] We now report that thioamides with α-bromo-α,β-unsaturated acids undergo the same sequence of reactions leading to the corresponding thiazolinium derivates.



The thioamides were heated with α-bromoacrylic acid in ethyl acetate for various lengths of time depending on reactivity of the thioamide. The reactivity depends on both electronic and steric factors. Electron donating substituents in the thioamide will increase the nucleophilicity of both the sulphur and the nitrogen and thereby increase the reactivity. Attachment of electronegative substituents to the double bond in the unsaturated acid will act in the same direction. This rate promotion, however, will be counteracted by steric effects through the size of the substituents introduced. From the results below and from previous work [2] it must be concluded that steric effects are generally more important.

After the initial addition of the sulphur nucleophile to the electrophilic double bond, the adduct (III) must be able to assume a *cis* configuration over the ylidene double bond for the lone pair electrons on the nitrogen to attack and displace the bromine as a bromide ion. The *cis* configuration, however, rapidly becomes less favourable with increasing size of the substituents $R^1$ and $R^2$ due to non-bonded interaction. Therefore the rate of the reaction will decrease. Furthermore, in the cyclic structure (IV) there is also considerable steric interaction between the substituents $R^1$ and $R^2$. No doubt these substituents will be twisted out of the $R^1-C^2-N-R^2$ plane. This high energy state confers great instability on the molecule as shown by the ease with which it undergoes hydrolysis by water attack at the C-2 carbon. The high energy state caused by the $R^1-R^2$ interaction is further increased by interaction between the carboxy group and the $R^2$ substituent. This is best seen in the Newman projection VII in which the molecule for illustrative purposes is assumed to be planar through $C^2$ to $C^5$. In actual fact the molecule no doubt will assume an envelope conformation in which the interacting groups are as far apart as possible relative to their sizes.




VII

Experimentally it was found that thiobenzamide and *N*-methylthioacetamide on heating with α-bromoacrylic acid for 1 h furnished the 2-phenylthiazoline (IVa) and the 2,3-dimethylthiazolinium derivative (IVb) in 80–90 % yield. Therefore the steric repulsion between the phenyl group and the *N*-H proton ($R^1=C_6H_5$, $R^2=H$) or between the two methyl groups ($R^1=R^2=CH_3$) in III is not important for the course of the reaction. On the other hand, the interaction between a phenyl group and a methyl group ($R^1=C_6H_5$, $R^2=CH_3$) is stronger. Thus the expected product (IVc) was only formed in 54 % yield after heating for 24 h. With both $R^1$ and $R^2$ equal to phenyl groups the yield of IVd after 48 h was 40 %.

As the nitrogen approaches the electrophilic carbon in the cyclisation step (III→IV) steric repulsion between the nitrogen substituent ($R^2$) and the carboxy group has to be overcome. This can be verified by using esters

*Table 1.*

| Substituents | | | Reaction time h | Solvent for recrystallisation | M.p.° | Yield % | Molecular formula | Elementary analysis | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Found | | | | Calc. | | | |
| $R^1$ | $R^2$ | $R^3$ | | | | | | C | H | N | X | C | H | N | X |
| $C_6H_5$ | H | H | 1 | EtOH | 198–199 | 84 | $C_{10}H_{10}NO_2SBr$ | 41.94 | 3.77 | 4.81 | [a]27.76 | 41.68 | 3.50 | 4.86 | [a]27.73 |
| $CH_3$ | $CH_3$ | H | 1 | EtOH | 194–195 | 87 | $C_9H_{10}NO_2SBr$ | 30.43 | 4.28 | 6.08 | [a]34.51 | 30.01 | 4.20 | 5.83 | [a]33.28 |
| $C_6H_5$ | $CH_3$ | H | 24 | isoPrOH-EtOH (3:1) | 209–211 | 54 | $C_{11}H_{12}NO_2SBr$ | 44.05 | 4.08 | 4.59 | [b]10.63 | 43.72 | 4.00 | 4.64 | [b]10.61 |
| $C_6H_5$ | $C_6H_5$ | H | 48 | isoPrOH | 206–208 | 40 | $C_{16}H_{14}NO_2SBr$ | 52.39 | 3.97 | 3.66 | [b] 8.66 | 52.75 | 3.87 | 3.85 | [b] 8.80 |
| $CH_3$ | $CH_3$ | $CH_3$ | 3 | Acetone-EtOAc | 185–186° | 84 | $C_7H_{12}NO_2SBr$ | 33.36 | 4.96 | 5.43 | | 33.07 | 4.76 | 5.51 | |

[a] Bromine. [b] Sulphur.

prepared from alcohols of increasing size. We found that menthyl α-bromoacrylate failed to react with *N*-methylthioacetamide under the above conditions.

A substituent on the β-carbon in the acrylic acid should sterically affect the rate of sulphur addition to the double bond (I + II → III). Experimentally it was found that the reaction time for *N*-methylthioacetamide was increased from 1 h in the case of α-bromoacrylic acid to 3 h in the case of *cis* α-bromocrotonic acid (IVe).

The NMR spectra of the products were recorded in TFA. The C-4 and C-5 methine protons in IVe are at 4.40 and 5.25 τ, respectively, the coupling constant being $J = 2$ cps. The low coupling constant means that these protons have a *trans* configuration as found in the corresponding dihydrothiazolo-[3,2-a]pyridinium series.[2] Only the *trans* isomer (IVe) was obtained in the reaction. In the other derivatives (IVa – d) the thiazoline ring protons form a partially resolved ABX system with the methine proton in the region 4.0 – 4.3 τ and the methylene protons in the region 5.5 – 5.8 τ. The lower values come from the 2-phenyl derivatives. The chemical shifts for the corresponding protons in the product (V, $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = H$) arisen by hydrolysis of IVc, are at 5.3 and 6.1 τ, respectively.

As direct *N*-alkylation of 2-substituted-4-carboxymethyl-$\Delta^2$-thiazoline is difficult to effect because of steric hindrance from the 2- and 4-substituents,[1] the above addition reaction seems the best way for making such compounds. Furthermore, because of the extreme ease with which the thiazolinium compounds undergo hydrolysis the above reaction sequence is well suited for the preparation of cysteine derivatives (VI).[1]

## EXPERIMENTAL

*Synthesis of 2-substituted 4-carboxy-$\Delta^2$-thiazolinium bromide* (IV). A solution of the respective thioamides (0.02 mol), (thiobenzamide, *N*-methylthiobenzamide, and *N*-phenylthiobenzamide), and α-bromoacrylic acid (0.03 mol) or *cis* α-bromocrotonic acid (0.03 mol) in ethyl acetate (30 ml) was heated under reflux. The solid precipitate formed was then recrystallised as given in Table 1.

## REFERENCES

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