# 725. *The Preparation of Some 3-Substituted Rhodanines and their Thiazine Analogues.*

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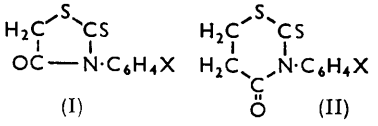
The preparation of 3-substituted rhodanines (I) and their thiazine analogues (II) has involved a new method: base-catalysed addition of thiols to aryl isothiocyanates is utilised to prepare the intermediate acids which are then cyclised. The aryl thiocarbamoylthioacetic acids cyclise too readily to be isolated but the corresponding propionic acids can be obtained pure.

3-SUBSTITUTED rhodanines (I) possess fungicidal activity,[1] but this has not been reported for the corresponding thiazine derivatives (II). These compounds were prepared by Holmberg [2] and Brown *et al.*[1] by ring-closure of the acids (III) and (IV) respectively, which have been obtained [3] by starting from dithiocarbamic acid or its derivatives. The acids (IV) were isolated but the other intermediates were cyclised *in situ*.



(I) (II)

$R\cdot NH\cdot CS\cdot S\cdot CH_2\cdot CO_2H$ (III)

$R\cdot NH\cdot CS\cdot S\cdot CH_2\cdot CH_2\cdot CO_2H$ (IV)

Our work started similarly. Ammonium *N*-aryldithiocarbamates [4] with sodium bromoacetate gave acids (III) which were not obtained pure owing to the ease of cyclisation, but the dithiocarbamates added to acrylic acid and the propionic acids (IV) could be purified. These methods are, however, limited in that weakly basic amines such as *p*-nitroaniline do not form dithiocarbamates,[5] so we then studied the use of aryl isothiocyanates.[6]

Considerable work [7] has been devoted to reaction of isothiocyanates with the hydroxyl ion, amines, and alcohols but only little [8] to that with thiols. Condensing aryl isothiocyanates with mercaptoacetic acid alone at 125° led to only a low yield of the rhodanine; and none of the thiazine analogue or the parent acid (IV) was obtained from β-mercaptopropionic acid under these conditions. However, good yields of the intermediate acids were obtained in both these reactions when they were carried out in 25—30% aqueous trimethylamine; again the propionic acids (IV), but not the acetic acids (III), were isolated.

For the cyclisation Holmberg [2] used acetic anhydride and sulphuric acid, and Brown *et al.*[1] used hydrochloric acid. We generally used acetic anhydride at 125° but for some of the rhodanines better yields were obtained by warming the acids in dilute acetic acid or acidified 95% alcohol.

The fungicidal tests are being completed and will be published elsewhere.

[1] Van der Kerk, van Os, de Vries, and Sijpesteijn, *Mededel Landbouwhogeschool en Opzoekingsstass Staat Gent*, 1953, **18**, 402; Brown, Bradsher, Morgan, Tetenbaum, and Wilder, *J. Amer. Chem. Soc.*, 1956, **78**, 384.

[2] Holmberg, *Ber.*, 1914, **47**, 159.

[3] Gresham, Jansen, and Shaver, *J. Amer. Chem. Soc.*, 1948, **70**, 1001; Jansen and Mathes, *ibid.*, 1955, **77**, 2866; Seyden-Penne, *Ann. Chim.* (*France*), 1958, **3**, 599; Holmberg, *J. prakt. Chem.*, 1910, **81**, 451.

[4] Dains, Brewster, and Olander, *Org. Synth.*, Coll. Vol. I, 1941, p. 477.

[5] Losanitch, *Ber.*, 1891, **24**, 3021; 1907, **40**, 2970.

[6] Dyson and George, *J.*, 1924, **125**, 1702.

[7] Zahradník, *Coll. Czech. Chem. Comm.*, 1959, **24**, 3407, 3422; Browne and Dyson, *J.*, 1931, 3285.

[8] Andreasch and Zipser, *Monatsh.*, 1903, **24**, 499; Benghiat, Stauffer Chemical Co., U.S.P. 2,905,689/1959.

## Experimental

The *products* and the methods by which they were obtained are listed in Tables 1—3. The following are examples of the methods.

3-*Phenylrhodanine* (*Method A*).—Bromoacetic acid (2·8 g.), dissolved in water (20 ml.), was neutralised with 2N-sodium hydroxide, and ammonium phenyldithiocarbamate (3·8 g.) in water (40 ml.) was added. The solution was warmed on a water-bath for 5 min., then cooled and filtered. The filtrate was acidified with hydrochloric acid and the precipitate filtered off. The precipitate was dissolved in a minimum volume of hot alcohol to which a few drops of dilute hydrochloric acid had been added. The rhodanine was deposited, on cooling, as pale orange needles.

Table 1. 3-*Substituted rhodanines* (I).

| X in (I) | Method of prep. | M. p. | Yield (%) | Formula | Found: N (%) | Reqd.: N (%) |
|---|---|---|---|---|---|---|
| H | A | 195—197° | 10 | $C_9H_7NOS_2$ | 6·8 | 6·7 |
| *p*-Me | B & C | 168·5—169·5 | 50 & 90 | $C_{10}H_9NOS_2$ | 6·3 | 6·3 |
| *o*-Cl | B & C | 125—126 | 12 & 45 | $C_9H_6ClNOS_2$ | 5·9 | 5·7 |
| *m*-Cl | B | 165—166 | 12 | ,, | 5·65 | 5·7 |
| *p*-Cl | A & B | 125—127 | 5 & 17 | ,, | 5·5 | 5·7 |
| 2,4-$Cl_2$ | B | 141—142 | 47 | $C_9H_5Cl_2NOS_2$ | 5·2 | 5·0 |
| *m*-$NO_2$ | C | 195—196 * | 33 | $C_9H_6N_2O_3S_2$ | 10·8 | 11·0 |
| *p*-$NO_2$ | B & C | 229—230 * | 15 & 33 | ,, | 11·1 | 11·0 |
| *p*-$CO_2Me$ | C | 146—147·5 | 38 | $C_{11}H_9NO_3S_2$ | 5·3 | 5·2 |
| *p*-OH | C | 147—149 | 45 | $C_9H_7NO_2S_2$ | 6·3 | 6·2 |
| *p*-OMe | C | 156—158 | 50 | $C_{10}H_9NO_2S_2$ | 5·7 | 5·9 |

* With decomp.

Table 2. β-(N-*Arylthiocarbamoylthio*)*propionic acids* (IV; R = $C_6H_4X$).

| X | Method of prep. | M. p.* | Yield (%) | Formula | Found: N (%) | Reqd.: N (%) |
|---|---|---|---|---|---|---|
| H | D & E | 159—160° | 46 & 33 | $C_{10}H_{11}NO_2S_2$ | 6·0 | 5·8 |
| *p*-Me | D | 155—156 | 10 | $C_{11}H_{13}NO_2S_2$ | 5·3 | 5·5 |
| *o*-Cl | E | 128·5—129·5 | 5 & 8 | $C_{10}H_{10}ClNO_2S_2$ | 5·1 | 5·1 |
| *m*-Cl | E | 121—122 | 29 | ,, | 5·4 | 5·1 |
| *p*-Cl | D & E | 151—152 | 10 & 29 | ,, | 5·1 | 5·1 |
| 2,4-$Cl_2$ | E | 103—104 | 10 | $C_{10}H_9Cl_2NO_2S_2$ | 4·6 | 4·5 |
| *m*-$NO_2$ | E | 147—148 | 21 | $C_{10}H_{10}N_2O_4S_2$ | 10·0 | 9·8 |
| *p*-$NO_2$ | E | 173—174 | 25 | ,, | 9·95 | 9·8 |
| *p*-$CO_2Me$ | E | 161—162 | 40 | $C_{12}H_{13}NO_4S_2$ | 4·9 | 4·8 |
| *p*-OH | E | 147—148 | 19 | $C_{10}H_{11}NO_3S_2$ | 5·3 | 5·45 |
| *p*-OMe | E | 156—157 | 44 | $C_{11}H_{13}NO_3S_2$ | 5·2 | 5·2 |

* With decomp.

Table 3. 3-*Aryl-substituted tetrahydro-4-oxo-2-thiothiazines* (II).

| X in (II) | Method of prep. | M. p. | Yield (%) | Formula | Found: N (%) | Reqd.: N (%) |
|---|---|---|---|---|---|---|
| H | F | 172—174° | 54 | $C_{10}H_9NOS_2$ | 6·4 | 6·3 |
| *p*-Me | F | 147·5—148·5 | 50 | $C_{11}H_{11}NOS_2$ | 6·1 | 5·9 |
| *o*-Cl | F | 99—100 | 22 | $C_{10}H_8ClNOS_2$ | 5·8 | 5·4 |
| *m*-Cl | F | 214—215 * | 29 | ,, | 5·4 | 5·4 |
| *p*-Cl | F | 156—157·5 | 31 | ,, | 5·4 | 5·4 |
| 2,4-$Cl_2$ | F | 148—150 * | 32 | $C_{10}H_7Cl_2NOS_2$ | 5·0 | 4·8 |
| *m*-$NO_2$ | F | 192—193 * | 82 | $C_{10}H_8N_2O_3S_3$ | 10·4 | 10·4 |
| *p*-$NO_2$ | F | 212 * | 61 | ,, | 10·2 | 10·4 |
| *p*-$CO_2Me$ | F | 203—204 | 36 | $C_{12}H_{11}NO_3S_2$ | 5·0 | 5·0 |
| *p*-OH | F | 186—188 * | 20 | $C_{10}H_9NO_2S_2$ | 5·75 | 5·9 |
| *p*-OMe | F | 157—158 | 37 | $C_{11}H_{11}NO_2S_2$ | 5·4 | 5·5 |

* With decomp.

3-p-*Tolylrhodanine* (*Method B*).—*p*-Tolyl isothiocyanate (1·5 g.) and mercaptoacetic acid (1·4 ml.) were heated for 1½ hr. at 125°, then poured into water. The precipitated *rhodanine* was filtered off and recrystallised from alcohol as pale yellow needles.

3-p-*Nitrophenylrhodanine* (*Method C*).—*p*-Nitrophenyl isothiocyanate (0·9 g.) and mercaptoacetic acid (0·7 ml.) were shaken in 25—30% trimethylamine solution (10 ml.) for ½ hr. The clear solution was diluted and acidified and the precipitate filtered off, washed, and dried. The crude acid (1·0 g.) was heated with acetic anhydride (5·0 ml.) at 125° for ½ hr., poured into water and left for several hours. The solid *rhodanine* was filtered off and recrystallised from glacial acetic acid, as light orange needles.

β-(N-*Phenylthiocarbamoylthio*)*propionic Acid* (*Method D*).—To a suspension of ammonium phenyldithiocarbamate (1·9 g.) in ethyl acetate (30 ml.), at 0°, acrylic acid (1·4 ml.) was added with stirring. The whole was shaken for 1 hr., an equal volume of ether added, and the precipitate of ammonium acrylate filtered off. The filtrate was evaporated with a stream of air at room temperature, water added to the residue, and the insoluble *acid* filtered off. It (1·3 g.) was four times recrystallised from 40% aqueous acetic acid, forming colourless plates.

β-(N-p-*Nitrophenylthiocarbamoylthio*)*propionic Acid* (*Method E*).—25—30% Aqueous trimethylamine (10 ml.) was added to a mixture of *p*-nitrophenyl isothiocyanate (1·8 g.) and β-mercaptopropionic acid (1·4 g.), and the whole was shaken for ½ hr., then diluted with water, and acidified. The crude acid (2·2 g.) was filtered off and recrystallised twice from 75% aqueous acetic acid, forming yellow needles.

*Tetrahydro*-3-p-*nitrophenyl*-4-*oxo*-2-*thiothiazine* (II; R = *p*-$NO_2 \cdot C_6H_4$) (*Method F*).—β-(N-*p*-Nitrophenylthiocarbamoylthio)propionic acid (1·5 g.) and acetic anhydride (15 ml.) were heated at 125° for ½ hr., then poured into water and left several hours. The yellow solid *thiazine* derivative was filtered off, washed, and recrystallised from glacial acetic acid.

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