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# SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3, 5-DISUBSTITUTED RHODANINES. *Part -IV*

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Substituted rhodanines $(I)_{a-c}$ reacted with halo compounds, aromatic aldehydes, ketones, anhydrides and amines to afford compounds (II-V)a-c. The antibacterial activities of all the synthesized derivatives have been investigated.

***Key words:*** Synthesis, Biological activity, 3,5-Disubstituted rhodanines.

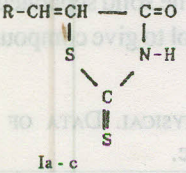
## Introduction

From the therapeutic point of view rhodanines are of considerable interest as their importance in the treatment of disease have been firmly established [1-3].

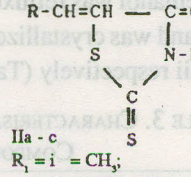
Our findings in previous reports [4,5] that some 3, 5-disubstituted rhodanines possess marked biological potency, encouraged us to extend investigation to synthesize a new series of rhodanine derivatives with a view to study the effect of different functional variations on biological activity.

## Results and Discussion

Rhodanine $(I)_{a-c}$ [6] reacted with halo compounds namely, methyl iodide, acetyl chloride, bromobenzene, benzoyl chloride and p-toluene sulphonyl chloride to afford derivatives II(a-c) i- v.

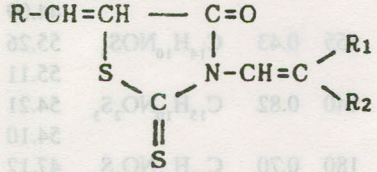


Ia - c
R = a = Thiophene
= b = Furan
= c = Pyrrole



IIa - c
$R_1$ = i = $CH_3$;
= ii = $CH_3$. CO-
= iii = $C_6H_5$ -
= iv = $SO_2$. $C_6H_4$. $CH_3$ - (p)

Reaction of compounds II(a-c)i with aromatic aldehydes and ketones yielded a number of new derivatives III (a-c) i-viii.

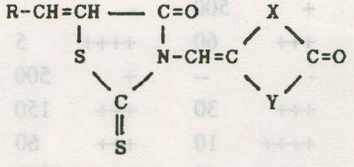


III(a-c) i-viii

R = a = Thiophene
= b = Furan
= c = Pyrrole

| | $R_1$ | $R_2$ |
|---|---|---|
| i) | H | $C_6H_5$ |
| ii) | H | $C_6H_4$. OH (p) |
| iii) | H | $C_6H_4$. $(OCH_3)$ (p) |
| iv) | H | $C_6H_4$. $NO_2$ (p) |
| v) | H | $CH_3$ |
| vi) | $CH_3$ | $C_6H_5$ |
| vii) | $C_6H_5$ | $C_6H_4$. OH (p) |
| viii) | $C_6H_5$ | |

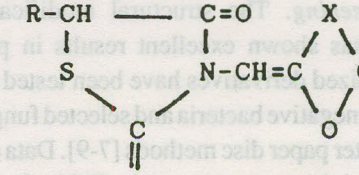
Condensation of compounds III(a-c) with anhydrides or imides afforded products IV(a-c) i-iv respectively.



IV(a-c)i-iv

| R | X | Y |
|---|---|---|
| a=Thiophene | i) $CH_2$-$CH_2$ | O |
| b=Furan | ii) CH=CH | O |
| c=Pyrrole | iii) $C_6H_4$ | O |
| | iv) $C_6H_4$ | NH |

A number of new rhodanines V (a-c) i-iii were prepared also by condensation of IV (a-c) i, ii, iv with aromatic amines.



V-(a-c) i-iii

| R | X | Ar |
|---|---|---|
| a=Thiophene | i) $CH_2$-$CH_2$ | $C_6H_5$ |
| b=Furan | ii) CH=CH | $C_6H_4$. $CH_3$ (p) |
| c=Pyrrole | iii) $C_6H_4$ | $C_6H_5$ |

The structure of the new synthesized derivatives was confirmed by: (i) elemental analysis (ii) IR spectra and (iii) NMR spectra. All the synthesized derivatives showed bands in accordance with the assigned structures (Table 1a, b).

TABLE 1a.

| Comp. No. | $\gamma cm^{-1}$ | Characteristic group |
|---|---|---|
| Ia | 1705 | C=O |
| Ic | 3300 | NH |
| IIb | 1630 | C=S |
| III(a) vii | 1650 | $C_6H_5$ |
| IV (b) ii | 1745 | C=O |
| V (a)i | 1625 | C=N |

TABLE Ib.

| Comp. No. | δ | Characteristic group |
|---|---|---|
| Ib | 3.5 | NH |
| II (a)i | 2.5 | $CH_3$ |
| III (b)vii | 7.4 | $C_6H_5$ |
| IV (a)ii | 2.8 | CH |
| V (c)i | 4.0 | $CH_2$ |

*(a-c) i-viii and IV (a-c) i-iv.* A mixture of [II (a-c) i, 0.01 mole] and the aromatic aldehyde, ketone, anhydride or imide (0.015 mole) were heated in an oil bath at 200-220° for 5 hrs. After cooling, the product was crystallized from ethanol to give compounds III (a-c) i-viii and IV (a-c) i-iv respectively (Table 3).

*General procedure for the synthesis of compounds V (a-c) i- iii.* A mixture of [IV (a-c) i-iii, 0.01 mole] and the aromatic amine namely, aniline or p-toluidine (0.01 mole) in (50 ml) ethanol was refluxed for 5 hrs. The solid separated on cooling and was crystallized from ethanol to give compounds V (a-c) iii respectively (Table 3).

TABLE 2. ACTIVITY (A) AND MINIMUM INHIBITORY CONCENTRATION (MIC) FOR ACTIVE COMPOUNDS.

| Comp. No. | *Bacillus mycoids* | | *Bacillus cereus* | | *Bacillus subtilis* | | *Escherichia coli* | | *Penicilium chrysogenum* | | *Salmonella typhosa* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | MIC | A | MIC | A | MIC | A | MIC | A | MIC | A | MIC |
| $IIa_v$ | ++ | 125 | ++++ | 10 | + | 250 | +++ | 30 | - | - | +++ | 30 |
| bi | +++ | 30 | +++ | 30 | ++++ | 5 | ++ | 125 | + | 500 | ++ | 125 |
| $III_{bii}$ | + | 500 | - | - | ++++ | 10 | +++ | 30 | +++ | 30 | +++ | 60 |
| iv | +++ | 60 | ++++ | 5 | ++ | 250 | + | 500 | ++++ | 10 | ++++ | 5 |
| viii | - | -- | + | 500 | +++ | 30 | +++ | 60 | ++ | 125 | ++++ | 10 |
| aii | +++ | 30 | +++ | 150 | - | - | + | 500 | +++ | 30 | +++ | 30 |
| IV | ++++ | 10 | +++ | 60 | + | 500 | ++++ | 5 | ++ | 125 | +++ | 60 |
| bii | +++ | 60 | ++ | 250 | ++++ | 5 | ++ | 125 | ++++ | 10 | ++++ | 5 |
| ci | + | 500 | - | - | ++ | 250 | ++++ | 5 | ++++ | 5 | +++ | 30 |
| ii | ++ | 125 | ++++ | 10 | +++ | 60 | ++ | 125 | +++ | 60 | ++ | 250 |
| $V_{bii}$ | ++ | 250 | +++ | 30 | - | - | ++++ | 10 | +++ | 30 | ++++ | 10 |
| ci | ++++ | 5 | +++ | 60 | ++ | 125 | + | 500 | + | 125 | ++ | 125 |

(A): Antibacterial activity; (++++) = highly active; (+++) = moderately active; (++) and (+) = slightly active; (-) = inactive.

*Biological screening.* The structural modification of rhodanine moiety has shown excellent results in pharmacology. The synthesized derivatives have been tested against gram positive, gram negative bacteria and selected fungi using the hole plate and filter paper disc methods [7-9]. Data concerening biological activities are set out in Table 2. Twelve compounds have shown characteristic activities against a number of different microorganisms.

## Experimental

All melting points are uncorrected. IR spectra were recorded on a Unicam SP-1200 spectrophotometer using KBr discs. NMR spectra were determined at 60 MHz on a Varian A-60 spectrophotometer using DMSO-d6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as δppm units.

*Reaction of 3-substituted rhodanines I (a-c) with halo compounds.* Rhodanines [I (a-c), 0.01 mole] and halo compounds namely, methyl iodide, acetyl chloride, bromobenzene, benzoyl chloride and p-toluene sulphonyl chloride (0.015 mole) were dissolved in pyridine. The reaction was refluxed for 3 hrs and the product was poured into ice-cold water and the products were crystallized from benzene to give II (a-c) i.v (Table 3).

TABLE 3. CHARACTERISATION AND PHYSICAL DATA OF COMPOUNDS (II-V)a-c.

| Comp. No. | Yield (%) | M.P. (°C) | $R_f$ | Molecular formula | Analysis Calc/Found C | H | N |
|---|---|---|---|---|---|---|---|
| IIai | 33 | 117 | 0.68 | $C_9H_8NOS_3$ | 44.62 | 3.30 | 5.78 |
| | | | | | 44.09 | 3.50 | 5.00 |
| ii | 61 | 160 | 0.55 | $C_{10}H_{10}NO_2S_3$ | 44.11 | 3.67 | 5.14 |
| | | | | | 44.09 | 3.50 | 5.00 |
| iii | 54 | 155 | 0.43 | $C_{14}H_{10}NOS_3$ | 55.26 | 3.28 | 4.60 |
| | | | | | 55.11 | 3.10 | 4.20 |
| iv | 82 | 140 | 0.82 | $C_{15}H_{10}NO_2S_3$ | 54.21 | 3.01 | 4.21 |
| | | | | | 54.10 | 3.00 | 4.11 |
| v | 50 | 180 | 0.70 | $C_{15}H_{12}NO_3S_4$ | 47.12 | 3.14 | 3.66 |
| | | | | | 47.77 | 3.25 | 3.15 |
| bi | 71 | 168 | 0.48 | $C_9H_8NO_2S_2$ | 47.78 | 3.53 | 6.19 |
| | | | | | 47.51 | 3.18 | 6.22 |
| ii | 30 | 143 | 0.56 | $C_{10}H_{10}NO_3S_2$ | 46.87 | 3.90 | 5.46 |
| | | | | | 46.09 | 3.20 | 5.20 |
| iii | 87 | 126 | 0.90 | $C_{14}H_{10}NO_2S_2$ | 58.33 | 3.47 | 4.86 |
| | | | | | 58.15 | 3.12 | 4.11 |

*(Contd. Table 3.)*

*(Table 3, Continue)*

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| iv | 56 | 130 | 0.33 | $C_{15}H_{12}NO_3S_2$ | 56.96 | 3.16 | 4.43 | iii | 48 | 177 | 0.84 | $C_{17}H_5N_2O_2S_2$ | 59.47 | 4.37 | 8.16 |
| | | | | | 56.11 | 3.30 | 4.11 | | | | | | 59.77 | 4.22 | 8.19 |
| v | 75 | 149 | 0.74 | $C_{15}H_{12}NO_4S_3$ | 49.18 | 3.27 | 3.82 | iv | 69 | 124 | 0.82 | $C_{16}H_{12}N_3O_3S_2$ | 53.63 | 3.35 | 11.73 |
| | | | | | 49.22 | 3.62 | 3.40 | | | | | | 53.60 | 3.32 | 11.55 |
| ci | 80 | 122 | 0.41 | $C_9H_9N_2OS_2$ | 48.00 | 4.00 | 12.44 | v | 34 | 167 | 0.42 | $C_{18}H_{18}N_3OS_2$ | 60.67 | 5.05 | 11.79 |
| | | | | | 48.03 | 4.14 | 12.40 | | | | | | 60.54 | 4.98 | 11.81 |
| ii | 46 | 103 | 0.81 | $C_{10}H_{11}N_2O_2S_2$ | 47.05 | 4.31 | 10.98 | vi | 65 | 133 | 0.73 | $C_{12}H_{13}N_2OS_2$ | 54.33 | 4.90 | 10.56 |
| | | | | | 47.00 | 4.22 | 10.53 | | | | | | 54.62 | 4.83 | 10.42 |
| iii | 70 | 152 | 0.37 | $C_{14}H_{11}N_2OS_2$ | 58.53 | 3.83 | 9.75 | vii | 49 | 172 | 0.66 | $C_{22}H_{17}N_2OS_2$ | 67.86 | 4.37 | 7.19 |
| | | | | | 58.12 | 3.51 | 9.17 | | | | | | 67.92 | 4.25 | 7.11 |
| iv | 90 | 194 | 0.64 | $C_{15}H_{11}N_2O_2S_2$ | 57.14 | 3.49 | 8.88 | viii | 81 | 119 | 0.70 | $C_{22}H_{17}N_2O_2S_2$ | 65.18 | 4.19 | 6.91 |
| | | | | | 57.09 | 3.41 | 8.72 | | | | | | 65.25 | 4.19 | 6.94 |
| v | 61 | 203 | 0.80 | $C_{15}H_{13}N_2O_3S_3$ | 49.31 | 3.56 | 7.67 | IVai | 57 | 166 | 0.46 | $C_{13}H_{10}NO_3S_3$ | 48.14 | 3.08 | 4.32 |
| | | | | | 49.27 | 3.33 | 7.18 | | | | | | 48.09 | 3.05 | 4.11 |
| IIIai | 46 | 180 | 0.47 | $C_{16}H_{12}NOS_3$ | 58.18 | 3.63 | 4.24 | ii | 47 | 139 | 0.65 | $C_{13}H_8NO_3S_3$ | 48.44 | 2.48 | 4.34 |
| | | | | | 58.04 | 3.51 | 4.11 | | | | | | 48.33 | 2.50 | 4.17 |
| ii | 58 | 191 | 0.55 | $C_{16}H_{12}NO_2S_3$ | 55.49 | 3.46 | 4.04 | iii | 68 | 180 | 0.86 | $C_{17}H_{10}NO_3S_3$ | 54.83 | 2.68 | 3.76 |
| | | | | | 55.27 | 3.30 | 4.00 | | | | | | 54.90 | 2.54 | 3.88 |
| iii | 94 | 188 | 0.72 | $C_{17}H_{14}NO_2S_3$ | 56.66 | 3.88 | 3.88 | iv | 44 | 161 | 0.69 | $C_{17}H_{11}N_2O_2S_3$ | 54.98 | 2.96 | 7.54 |
| | | | | | 56.17 | 3.72 | 3.79 | | | | | | 55.02 | 2.99 | 7.54 |
| iv | 83 | 194 | 0.81 | $C_{16}H_{11}N_2O_3S_3$ | 51.20 | 2.93 | 7.47 | bi | 80 | 128 | 0.41 | $C_{13}H_{10}NO_4S_2$ | 50.64 | 3.24 | 4.54 |
| | | | | | 51.20 | 2.88 | 7.09 | | | | | | 50.57 | 3.18 | 4.66 |
| v | 36 | 202 | 0.96 | $C_{18}H_{17}N_2OS_3$ | 57.90 | 4.55 | 7.50 | ii | 37 | 116 | 0.87 | $C_{13}H_8NO_4S_2$ | 50.98 | 2.61 | 4.57 |
| | | | | | 57.84 | 4.17 | 7.32 | | | | | | 51.04 | 2.72 | 4.40 |
| vi | 57 | 188 | 0.63 | $C_{12}H_{12}NOS_3$ | 51.06 | 4.25 | 4.96 | iii | 45 | 133 | 0.55 | $C_{17}H_{10}NO_4S_2$ | 57.30 | 2.80 | 3.93 |
| | | | | | 51.00 | 4.11 | 4.88 | | | | | | 57.21 | 2.82 | 4.04 |
| vii | 83 | 149 | 0.69 | $C_{22}H_{16}NOS_3$ | 62.02 | 3.94 | 3.44 | iv | 73 | 178 | 0.67 | $C_{17}H_{11}N_2O_3S_2$ | 57.46 | 3.09 | 7.88 |
| | | | | | 62.00 | 3.88 | 3.57 | | | | | | 57.33 | 3.00 | 7.93 |
| viii | 46 | 197 | 0.81 | $C_{22}H_{16}NO_2S_3$ | 62.55 | 3.79 | 3.31 | ci | 66 | 123 | 0.84 | $C_{13}H_{11}N_2O_3S_2$ | 50.81 | 3.58 | 9.12 |
| | | | | | 62.57 | 3.62 | 3.17 | | | | | | 50.77 | 3.61 | 9.00 |
| bi | 70 | 205 | 0.55 | $C_{16}H_{12}NO_2S_2$ | 61.14 | 3.82 | 4.45 | ii | 74 | 185 | 0.72 | $C_{13}H_9N_2O_3S_2$ | 51.14 | 2.95 | 9.18 |
| | | | | | 61.72 | 3.56 | 4.44 | | | | | | 51.09 | 2.90 | 9.19 |
| ii | 55 | 180 | 0.72 | $C_{16}H_{12}NO_3S_2$ | 58.18 | 3.63 | 4.24 | iii | 52 | 121 | 0.48 | $C_{18}H_{11}N_2O_3S_2$ | 57.46 | 3.09 | 7.88 |
| | | | | | 58.05 | 3.12 | 4.17 | | | | | | 57.40 | 3.00 | 7.91 |
| iii | 89 | 117 | 0.33 | $C_{17}H_{14}NO_3S_2$ | 59.30 | 4.06 | 4.06 | iv | 78 | 136 | 0.57 | $C_{17}H_{12}N_2O_3S_2$ | 57.62 | 3.38 | 11.86 |
| | | | | | 59.15 | 4.00 | 4.00 | | | | | | 57.44 | 3.26 | 11.88 |
| iv | 62 | 163 | 0.86 | $C_{16}H_{11}N_2O_4S_2$ | 53.48 | 3.06 | 7.79 | | | | | | | | |
| | | | | | 53.40 | 3.00 | 7.82 | | | | | | | | |
| v | 79 | 140 | 0.64 | $C_{18}H_{17}N_2O_2S_2$ | 60.50 | 4.76 | 7.84 | | | | | | | | |
| | | | | | 60.52 | 4.92 | 7.90 | | | | | | | | |
| vi | 45 | 185 | 0.75 | $C_{12}H_{12}NO_2S_2$ | 54.13 | 4.51 | 5.26 | | | | | | | | |
| | | | | | 54.09 | 4.62 | 5.21 | | | | | | | | |
| vii | 52 | 185 | 0.59 | $C_{22}H_{16}NO_2S_2$ | 67.69 | 4.10 | 3.50 | | | | | | | | |
| | | | | | 67.38 | 4.08 | 317 | | | | | | | | |
| viii | 33 | 156 | 0.63 | $C_{22}H_{16}NO_3S_2$ | 65.02 | 3.94 | 3.44 | | | | | | | | |
| | | | | | 65.00 | 3.99 | 3.12 | | | | | | | | |
| ci | 70 | 142 | 0.56 | $C_{16}H_{13}N_2OS_2$ | 61.34 | 4.15 | 8.94 | | | | | | | | |
| | | | | | 61.55 | 4.13 | 9.00 | | | | | | | | |
| ii | 55 | 111 | 0.62 | $C_{16}H_{13}N_2O_2S_2$ | 58.35 | 3.95 | 8.51 | | | | | | | | |
| | | | | | 58.70 | 4.02 | 8.70 | | | | | | | | |

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