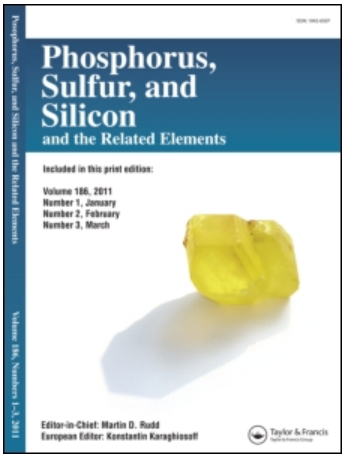

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS V[1-4]. REACTION OF 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIA DIPHOSPHETANE-2,4-DISULFIDE WITH CYCLIC AND HETEROCYCLIC KETONES

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS V[1–4]. REACTION OF 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIA DIPHOSPHETANE-2,4-DISULFIDE WITH CYCLIC AND HETEROCYCLIC KETONES

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Cyclic ketones **2** and **8a,b** reacted with Lawesson's reagent (**1**) in different molar ratios to give the oxathiaphosphole (**4**), the disulfide **7** and the dithiones **9a,b**. N-Methyl barbituric acid (**10b**) reacted with LR to produce the enethiole **11** and the sulfide **12**. Pyrazolone derivatives **13** and **17** reacted with LR in different molar ratios to form the corresponding products **15, 16** and **19**. Rohdanine (**20**) reacted with LR to give the enethiole **22** and the disulfide **23**.

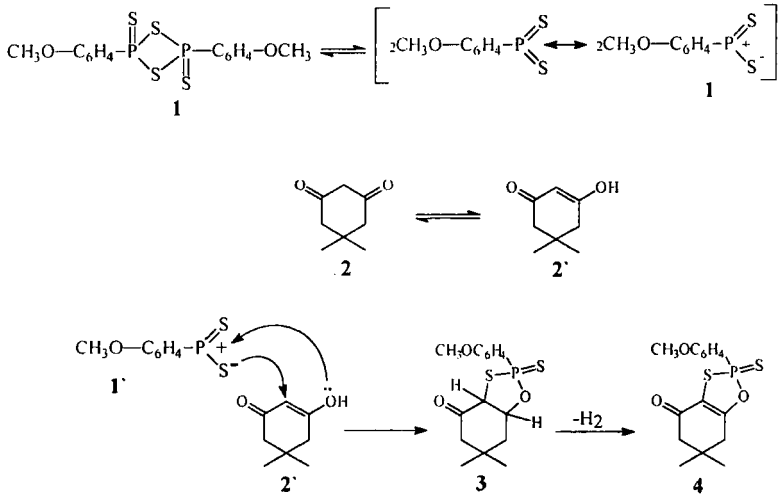
Keywords: Lawesson's reagent (LR); dimedone; pyrazolone; sulfides; disulfides

Synthesis of aliphatic thioketones from the corresponding ketones and H_2S/HCl have been attempted since the end of the last century[5,6], but this reagent somtimes is not suitable for cyclic and heterocyclic ketones. 2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, (LR), has been developed as a powerful and versatile reagent for the conversion of a wide variety of carbonyls[7]. Although Lawesson's reagent has been extensively utilized in organic synthesis[8–11], little has been reported for sulfur-containing heterocycles.

This report descreibs the reaction of Lawesson's reagent **1** with cyclic and heterocyclic ketones to form different cyclic sulfides and heterocyclic thioles. 3,3-Dimethylcyclohexane-1,5-dione (dimedone) (**2**) reacted with Lawesson's reagent **1** to produce different products depending on the

* Corresponding Author.

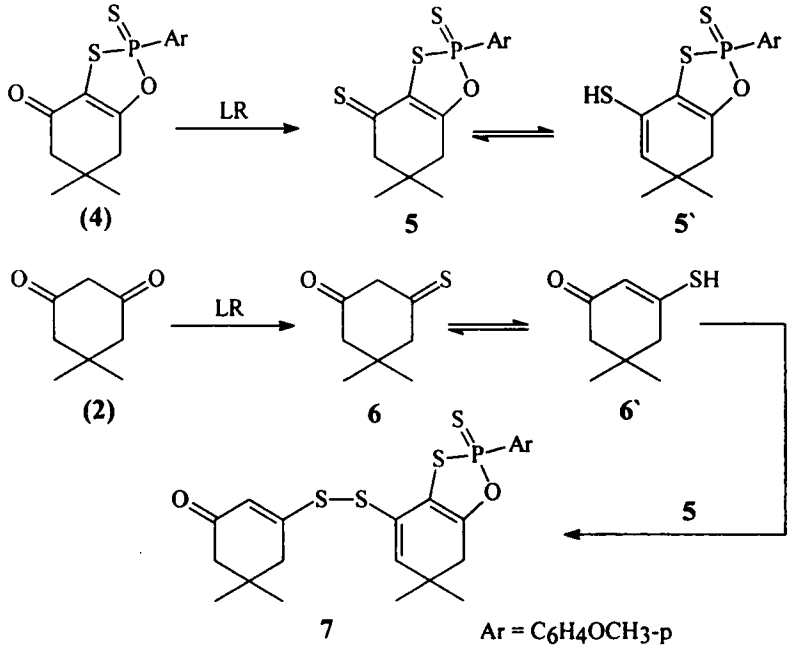
experimental conditions. Thus, when 1 mole equivalent of compound **2** was allowed to react with 0.5 mole equivalent of LR in dry toluene at 80°C, the unexpected 1,3,2-oxathiaphosphole **4** was formed in 60% yield. The structure of **4** was confirmed from its analysis and spectroscopic data. The ^{1}H-NMR spectrum of compound **4** showed signals at $\delta = 1.40$ and $\delta = 1.55$ ppm for two CH_3 protons (singlets); $\delta = 2.60$ and 2.85 ppm for two CH_2 protons (singlets); $\delta = 3.75$ ppm for the O-CH_3 protons (singlet) and $\delta = 6.80$–7.75 ppm for the aromatic protons (multiplet). The IR spectrum of compound **4** (KBr), showed two bands at 2973, 2934 cm^{-1} for the $2CH_3$ groups, band at 1670 cm^{-1} for (C=O) and band at 1604 for C=C. The MS spectrum and the microanalytical data supported the proposed structure (c.f experimental section). Compound **4** is an addition product, the mechanism of its formation is shown in scheme 1. It is based on the addition of the monomeric species of **1** to compound **2** yielding the intermediate **3** which lose hydrogen to produce **4**. (Scheme 1).



SCHEME 1

When 1 mole equivalent of dimedone was allowed to react with one mole equivalent of LR, the disulfide **7** was isolated as well as a small amount of compound **4**. The structure of **7** was based on spectroscopic evidence (c.f. experimental section). It may be assumed that LR in this experiment led to thionation of both compound **4** and compound **2** to produce

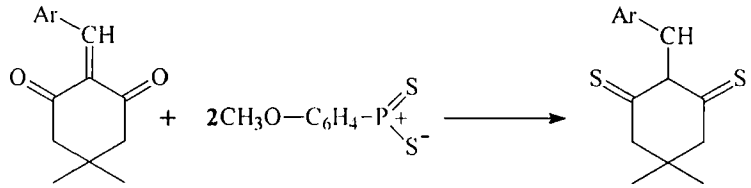
compounds **5** and **6**. The latter have the tendency to exist in the thiole form (**5'** and **6'**) which accelerate their attachment via loss of hydrogen to produce the disulfide **7** (Scheme 2). Similar disulfides were prepared previously[12]



SCHEME 2

The arylidene derivatives of dimedone (**8a,b**) were also reacted with LR in acetonitrile whereby the corresponding thione derivatives **9a,b** were isolated. The MS spectrum of **9a,b** showed an ion peak at m/z=290 $[M]^+$ and at m/z = 305 $[M]^+$, respectively. The structures of the products were also confirmed by analysis and spectroscopic data (c.f. experimental section).

The study was also extended to the effect of LR on the heterocyclic ketones. N-Substituted barbituric acid (**10a**) reacted with LR in dry toluene under reflux for 3 hrs to form the enethiole **11** and the disulfide **12**. The formation of the enethiole is in accordance with the reaction of

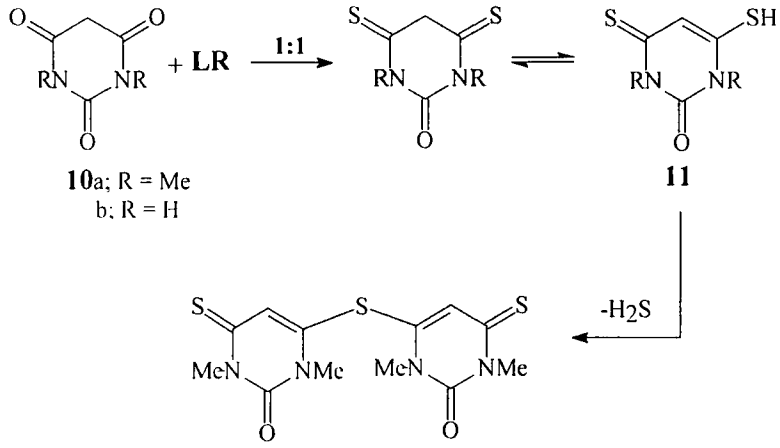


8a, Ar = C_6H_4-OCH_3-p
b, Ar = C_6H_4-NO_2-p

9a,b

SCHEME 3

aliphatic ketones with LR[9,13] and the formation of compound **12** is due to the dimerization of the enethiole **11** by loss of H_2S. Similar sulfides was reported before in Lawesson's reagent reactions[14].



10a; R = Me
b; R = H

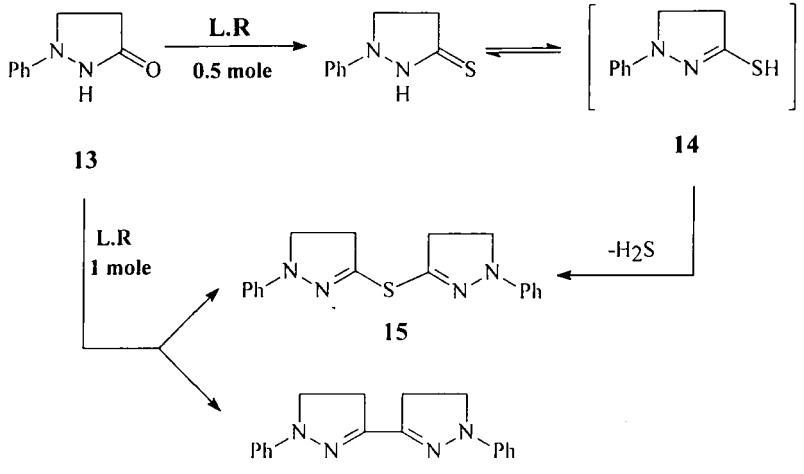
11

12

SCHEME 4

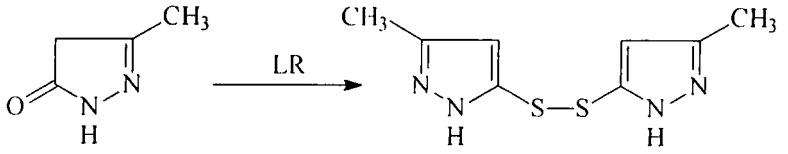
On the other hand, attempted reaction of 1,3-dihydrobarbituric acid (**10b**) with LR under different conditions failed. The starting compound **10b** was recovered practically unchanged. The study was also concerned with the effect of LR on pyrazolone derivatives. 1-Hydro-2-phenyl-pyrazol-5-one (**13**) reacted readily with 0.5 mole of LR to yield the sulfide derivative (**15**). The reaction is believed to proceed via intermediate **14**.

The same sulfide product **(15)** produced when one mole equivalent of LR reacted with one mole equivalent of the pyrazolone **13** under the same conditions beside the formation of the pyrazole dimer **16** (Scheme 5). The dimeric structure was supported by spectroscopic and analytical data. (c.f. expermintal section). Similar demeric product was obtained before[14].

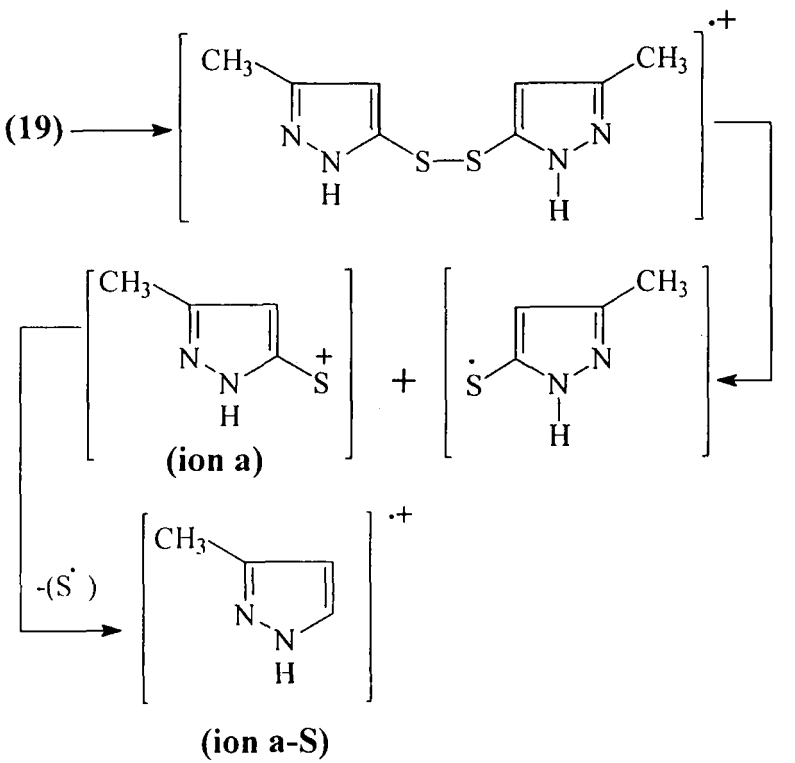


SCHEME 5

The investgation was also concerned with the behavior of 3-methylpyrazol-5-one **(17)** towards LR. When 1 mole equivalent of compound **(17)** was allowed to react with 1 mole equivalent of LR, the disulfide **19** was formed in high yield.



The MS spectrum of the disulfide **(19)** revealed ion peaks at m/z = 226 $[M]^+$, m/z = 113 $[1/2M]^+$ (ion a) and at m/z = 81 (ion a-S).

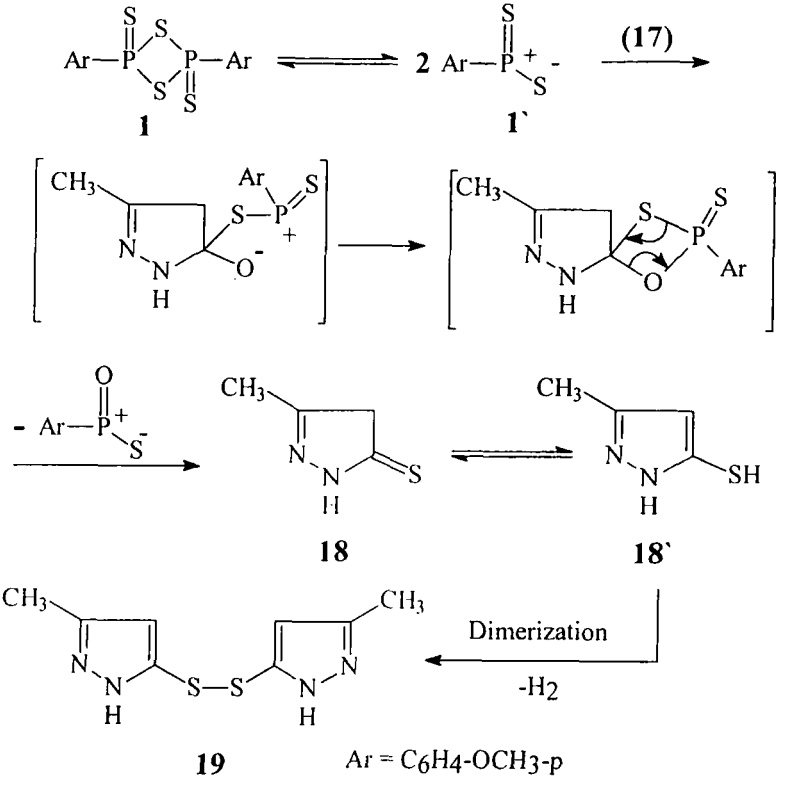


The disulfide **19**, however, may be formed via the thione form **18** which is formed first by a betaine mechanism. This is not surprising since the thione form would likely be present in the thiole from **18'** due to the lower stabilization of the thiocarbonyl group reflecting more pronounced tendency to undergo tautomeric changes. The formation of the disufides from thioles via thiyl radical was reported[10].

In a similar manner rohdanine **(20)** reacted with LR in dry toluene to produce the enethiole **22** and the disulfide **23** (Scheme 7). The identity of compounds **21** and **23** was verified by spectroscopic and elemental analysis (c.f expermintal section).

EXPERIMENTAL SECTION

All melting points are uncorrected. Solvents used were dried. IR spectra were taken in KBr on a OK 9712 IR spectrometer. ^{1}H-NMR were recorded



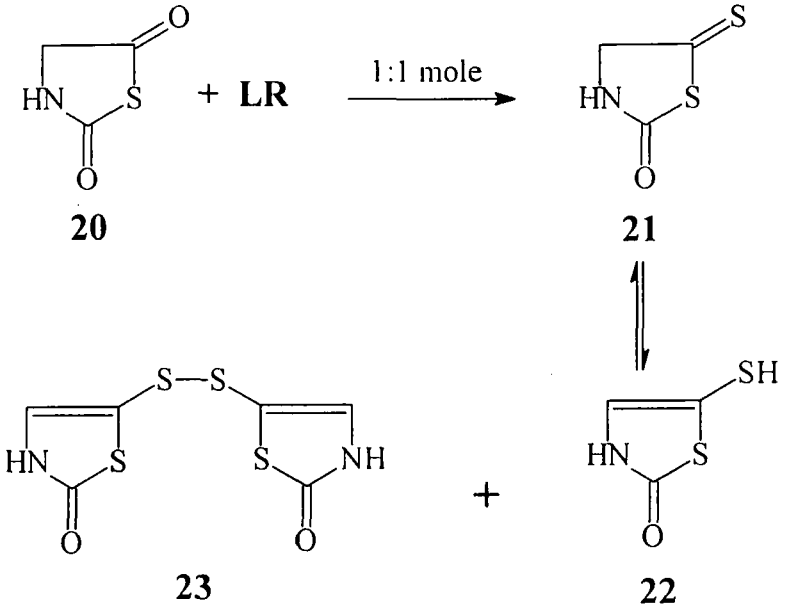
SCHEME 6

on Varian EM-360–60 MHz spectrometer with DMSO and $CDCl_3$ as solvents and TMS as internal reference.

Chemical shifts are experessed as δ units (ppm). The mass spectra were recorded on kratos (75 ev) MS equipment. Analytical data were obtained from the Microanalytical data unit at the National Research Centre.

Reaction of LR with 3,3-dimethylcyclohexan-1,5-dione (4,7)

(a) To a suspension of **2** (0.01 mole) in dry toluene (30 ml), **1** (0.005 mole) was added. The reaction mixture was heated at 80°C for 3 hrs. The solvent was evaporated under vaccum and the residue that was left behind was



SCHEME 7

applied to a column prepared by packing a slurry of silica gel in n-hexane. Ethyl acetate-n-hexane (2:8, v:v) eluted 1,3,2-oxathiaphosphole **4**: as yellow crystals, m.p. 115°C, recrystallized from n-hexane. Yield 2.21g (65%). IR: $\nu = 2973, 2934$ ($2CH_3$), 1670 (C=O), 1604 (C=C); ^{1}H-NMR (DMSO-d_6): $\delta = 1.40$ (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.60 (s, 2H, CH_2), 2.85 (s, 2H, CH_2), 3.75 (s, 3H, O-CH_3), 6.80–7.75 (m, 4H, aromatic protons); MS: m/z = 340 (M^+, 29%). Anal. found C: 52.90, H: 5.02, S: 18.80 P: 9.10; Calcd for $C_{15}H_{17}O_3S_2P$ (340) C: 52.94, H: 5.00, S: 18.82, P: 9.11.

(b) Similarly compound **2** (0.01 mole) reacted with LR (0.01 mole) under the same previous conditions. The reaction mixture was worked up in the same way as in (a). The column was developed first with n-hexane-ethylacetate (9:1; v:v) which progressively changed to 7:3, 5:5, 3:7 and finally ethylacetate, at 250 ml internals. Fractions of 50 ml were collected. The first material eluted from the column, was purified by recrystallization from n-hexane, m.p. 115°C and shown to be compound **4** (mixed m.p. with authntic sample).

The second material eluted, proved to be **7**, recrystallized from n-hexane orange crystals, m.p. 314°C, IR: ν = 2975, 2930–2844 ($4CH_3$), 1678 (C=O), 1599 (C=C); ^{1}H-NMR (DMSO-d_6): δ = 1.20 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.10 (s, 6H, $2CH_3$), 2.65 (s, 2H, CH_2), 2.75 (s, 2H, CH_2), 3.20 (s, 2H, CH2), 3.80 (s, 3H, O-CH3), 6.80 (s, 1H, CH), 6.85 (s, 1H, CH), 6.95–7.70 (m, 4H, aromatic protons); MS: m/z = 510 (M^+, 23%). Anal. found C: 54.20, H: 5.25 S: 25.00 P: 6.07; Calcd for $C_{23}H_{27}O_3S_4P$ (510) C: 54.11 H: 5.29, S: 25.09, P: 6.07

Reaction of LR with 2-aryldine-5,5-dimethylcyclohexa-1,5-dione (9a,b)

General Procedure

To a solution of each **8a,b** (0.01 mole) in dry acetonitrile (20 ml), LR (0.005 mole) was added. The reaction mixture was stirred overnight. The solvent was evaporated under vaccum, the remaining residue was treated with cyclohexane. The solid product formed was collected by filteration and recrystallized from methanol.

2-Aryldine-5,5-dimethylcyclohexa-1,3-dithione (9a,b)

9a: red crystals, yield 2.32g (80%), m.p. 226°C. IR: ν = 2973, 2950–2930 ($3CH_3$), 1220 (C=S). ^{1}H-NMR ($CDCl_3$): δ = 0.9 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 2.10 (s, 2H, CH_2), 2.35 (s, 2H, CH_2), 3.70 (s, 3H, O-CH_3), 6.65–6.75 (d, 2H, aromatic protons), 6.95–7.10 (d, 2H, aromatic protons). MS: m/z = 290 (M^+, 24%), Anal. found C: 66.00, H: 6.25 S: 22.02; Calcd for $C_{16}H_{18}OS_2$ (290) C: 66.20, H: 6.20, S: 22.06.

9b: red crystals, m.p. 206°C, yield 2.37g (78%),. IR: ν = 2970, 2955 ($2CH_3$), 1602 (C=C), 1210 (C=S). MS: m/z=305 (M^+, 28%), ion peak at m/z = 272 (M^+-SH, 10%). Anal. found C: 59.00, H: 4.88, N: 4.54, S: 20.90; Calcd for $C_{15}H_{15}NO_2S_2$(305) C: 59.01, H: 4.91, N: 4.59, S: 20.98.

Reaction of LR with barbituric acid (11, 12)

To a solution of **10a** (0.01 mole) in toluene (25 ml), LR (0.005 mole) was added. The reaction mixture was refluxed for 3 hrs. After cooling, a yellow solid ppt formed, filtered and recrystallized from benzene to give com-

pound **11**. Compound **11** yellow crystals, m.p. 196°C, yield 0.37g (20%). IR: ν = 2986, 2931 ($2CH_3$), 1697 (C=O), 1068 (C=S). ^{1}H-NMR (DMSO-d_6): δ = 3.15 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 6.55 (s, 2H, CH_2). MS: m/z = 188 (M^+, 100%), ion peak at m/z = 155 (M^+-SH, 35%). Anal. found C: 38.25, H: 4.25, N: 14.85, S: 34.00; Calcd for $C_6H_8N_2OS_2$ (188) C: 38.29, H: 4.25, N: 14.89, S: 34.04.

The filtrate of the previous reaction was left for several days whereby the disulfide **12** was precipitated.

Compound 12: red crystals, m.p. 322°C, yield 2.12g (62%),. IR: ν = 2989, 2966–2903 ($4CH_3$), 1692, 1662 (2C=O), 1109, 1060 (2C=S). ^{1}H-NMR (DMSO-d_6): δ = 3.25 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 6.70 (s, 2H, CH), 6.85 (s, 2H, CH). MS: m/z = 342 (M^+, 37%). Anal. found C: 42.00, H: 4.02, N: 16.30, S: 28.00; Calcd for $C_{12}H_{14}N_4O_2S_3$(342) C: 42.10, H: 4.09, N: 16.37, S: 28.07.

Reaction of LR with pyrazolon derivatives (15, 16 and 19)

(a) To a solution of compound **13** (0.01 mole) in dry toluene (30 ml), LR (0.005 mole) was added. The reaction mixture was refluxed for 3 hrs. The solvent was evaporated under vaccum and the remaining residue was applied to column chromatography. The eluent used ethyl acetate-n-hexane (1:9, v:v) then (2:8, v:v), the sulfide product **(15)** was isolated as yellow crystals, m.p. 177°C, yield 2.41g (75%). IR: ν = 1666 (C=N), 1599 (C=C); ^{1}H-NMR ($CDCl_3$): δ = 3.10–3.25 (t, 4H, $2CH_2$), 3.75–3.90 (t, 4H, $2CH_2$), 6.70–7.10 (m, 5H, aromatic protons), 7.15–7.35 (m, 5H, aromatic protons); MS: m/z = 322 (M^+, 26%), Anal. found C: 67.00, H: 5.55, N: 17.20, S: 9.91. Calcd for $C_{18}H_{18}N_4S$ (322) C: 67.08, H: 5.59, N: 17.39, S: 9.93.

(b) Similarly compound **13** (0.01 mole) reacted with LR (0.01 mole) under the same previous conditions. The reaction mixture was worked up in the same way as in (a). The column was developed first with n-hexane-ethylacetate (1:9; v:v) which progressively changed to 2:8; 4:6; 5:5; v:v). The first material eluted from the column was purified by recrystallization from n-hexane, m.p. 177°C and shown to be compound **15** (mixed m.p. with authntic sample). The second matrial eluted, proved to be **16**, recrystallized from benzene; yellow crystals, m.p. 233°C, yield 0.58g (20%), IR: 1652 (C=N), 1600 (C=C); ^{1}H-NMR (DMSO-d_6): δ = 3.20–3.35 (t, 4H, $2CH_2$), 3.75–3.90 (t, 4H, $2CH_2$), 6.70–7.05 (m, 5H, aromatic

protons), 7.20–7.35 (m, 5H, aromatic protons). MS: m/z = 290 (M^+, 85%). Anal. found C: 74.43, H: 6.10, N: 19.30; Calcd for $C_{18}H_{18}N_4$ (290) C: 74.48, H: 6.20, N: 19.31.

(c) To a solution of compound **(17)** (0.01 mole) in dry toluene (25 ml), LR (0.01 mole) was added. The reaction was carried out under the same previous conditions. The remaining residue was worked up similarly by the use of column. The eluent ethylacetate-n-hexane gradually changed (1:9, 2:8, v:v), the sulphide **(19)** was isolated and recrystallized from benzene. yellow crystals, m.p. 190°C, yield 1.35g (60%). IR: ν = 3420–3179 (2NH), 2992, 2974 ($2CH_3$), 1664 (C=N); ^{1}H-NMR (DMSO-d_6): δ = 2.40 (s, 6H, $2CH_3$), 6.40 (s, 2H, CH), 12.80 (s, 2H, 2NH). MS: m/z = 226 (M^+, 97%), m/z = 113 ($1/2M^+$, 56%). Anal. found C: 42.44, H: 4.40, N: 24.70, S: 28.29. Calcd for $C_8H_{10}N_4S_2$ (226) C: 42.47, H: 4.42, N: 24.77, S: 28.31.

Reaction of LR with Rohdanine (21, 23)

To a suspension of compound **20** (0.01 mole) in dry toluene (30 ml), LR (0.01 mole) was added. The reaction mixture was refluxed for 5 hrs. The solvent was evaporated under vaccum, the remaining residue was separated into its components by column chromatography on silica gel using n-hexane-ethylacetate mixture in suitable combination as an eluent. n-Hexane-ethylacetate (8:2, v:v) eluted compound **21** as yellow crystals, recrystallized from n-hexane. m.p. 122°C, yield 0.39g (30%). IR: ν = 3190 cm^{-1} (NH), 1710 (C=O), 1174 (C=S). MS: m/z = 133 (M^+, 100%), m/z = 100 (M^+-SH, 27%). Anal. found C: 27.00, H: 2.20, N: 10.50, S: 48.11. Calcd for $C_3H_3NOS_2$ (133) C: 27.06, H: 2.25, N: 10.52, S: 48.12. n-hexane-ethylacetate (4:6; v:v) eluted compound **23** as brown crystals, recrystallized from methanol. m.p. 95°C, yield 1.05g (40%), IR: 3220–3110 (NH), 1730, 1690 (2C=O). ^{1}H-NMR (DMSO-d_6): δ = 4.20 (s, 2H, 2CH), 11.90 (s, 2H, 2NH). MS: m/z = 264 (M^+, 18%); Anal. found C: 27.20, H: 15.15, N: 10.45, S: 48.44. Calcd for $C_6H_4N_2O_2S_4$ (264) C: 27.27, H: 15.15, N: 10.60, S: 48.48.

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