Syntheses of New Unsymmetrical and Symmetrical Diaryl-sulphides and Diarylsulphones Containing Thiazolinyl and Thiazolidinonyl Moieties Using 4,4'-Diacytldiphenylsulphide

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Abstract: Condensation of 4,4'-diacytldiphenyl sulphide (2) with variable amounts of thiosemicarbazide (3) in refluxing ethanol and in the presence of catalytic amounts of dry piperidine afforded only 4-acetylthiosemicarbazone-4'-acetyldiphenyl sulphide (5). Condensation of 2 with excess semicarbazide hydrochloride (4) in the presence of fused sodium acetate and/or piperidine yielded 4,4'-diacytldisemicarbazone diphenyl sulphide (6), whereas use of equimolar amounts of 2 and 4 afforded 4-acetyl-semicarbazone-4'-acetyldiphenyl sulphide (7). 4-Acetylsemicarbazone-4'-acetylthiosemicarbazone diphenyl sulphide (8) was also obtained via two different routes. The effect of tautomeric structure 5d is discussed. 4-(4"-phenyl-Δ³-thiazoline-2"-acetylazino)-4'-acetyldiphenyl sulphide (9), 4-(5"-carboxyethyl-4"-thiazolidinone-2"-acetylazino)-4'-acetyldiphenyl sulphide (10), 4-(4"-thiazolidinone-2"-acetylazino)-4'-acetyldiphenyl sulphide (11) and 4-(4"-methyl-Δ³-thiazoline-2"-acetylazino)-4'-acetyldiphenyl sulphide (12) were prepared by interaction of 5 with phenacylbromide, bromodiethylmalonate, chloro ethylacetate and chloroaacetone, respectively. Sulphides 9-12 were easily condensed with 3 to afford the corresponding 4-(heterocyclic moiety-2"-acetylazino)-4'-acetyldisemicarbazone diphenyl sulphides 23-26. Oxidation of the prepared sulphides 5-7, 9-12, 23 and 25-26 using H₂O₂/glacial AcOH mixtures yielded only 4,4'-diacytldiphenyl sulphone (13) as the main product in every case, besides 3 and 4 in certain cases. Unsymmetrical and symmetrical sulphones 14-22 were obtained starting from 13. The structures of the synthesized compounds are based on IR, ¹H-NMR, ¹³C-NMR and mass spectral data. A
theoretical study on some of the prepared compounds using molecular modeling was carried out.

**Keywords:** Diarylsulphides, -sulphones, thiozolinyl and thiazolidinonyl moieties.

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**Introduction**

We are interested in the chemistry of diaryl sulphides and diaryl sulphones containing different heterocyclic and other organic moieties [1-10]. Diaryl sulphide and diaryl sulphone skeletons are not only the key structural elements of the most widely employed class of antibacterial drugs [11-13], but also act as building blocks in certain polymers commonly used in mouldings, coatings, adhesive membranes, composite matrices and engineering thermoplastics [14-17]. In view of these reported applications, there is still a tremendous demand to synthesize such title molecules. During the last three decades considerable work from the laboratory of M.A. Abbady et al. has been published describing the synthesis of new diaryl sulphides, diaryl sulphones, diaryl selenides and diaryl selenones [18-19] containing varied additional moieties, as well as their evaluation as potential pharmaceuticals.

**Results and Discussion**

In this communication we describe the syntheses of a series of hitherto unreported diaryl sulphides and diaryl sulphones containing carbazone, thiazoline and thiazolidinone moieties. The starting material for these syntheses and subsequent studies is 4,4'-diacetyldiphenyl sulphide (2), which was prepared according to the literature method [4], and was also obtained during our attempts to acetylate diphenyl sulphoxide (1) using the Friedel Crafts reaction [4]. Compound 2 condensed with excess of thiosemicarbazide 3 in refluxing ethanol in the presence of a catalytic amount of piperidine as a basic catalyst to afford only 4-acetylthiosemicarbazone-4'-acetyldiphenyl sulphide (5). Attempts to prepare 4,4'-diacetylthiosemicarbazone diphenyl sulphide (5a) starting from 2 and/or 5 using the same condensation with 3 under a variety of conditions were unsuccessful. As an explanation for this unexpected behaviour the mechanism illustrated in Scheme I is suggested. Thus, it is believed that structure 5d, which has an incompletely polarized carbonyl group in 4'-acetyl group, probably represents one of the contributing charged resonance structures of 5. The positive charge of that C=O is shifted through π conjugation from the migration origin (which is its carbon atom) to the migration terminus (which is the carbon atom attached to extreme -NH₂) (with the sulphur atom acting as a relay for conjugation) [25].

The development of positive charge at that new position is rigidly localized by the +I of -SH group (according to Ingold terminology). It is believed that structure 5d affects the behaviour of the whole molecule of 5 and is responsible for the previously mentioned local incomplete polarization of its 4'-C=O group, which now has low nucleophilicity; hence this decreases to a large extent the subsequent nucleophilic attack of 3 on 5 [20,21], to a degree that prevents the second step
condensation and/or simultaneous condensation (actually an *in situ* stepwise reaction) to form the expected symmetrical sulphide 5a (Scheme II).

**Scheme I**

The proposed mechanism depicted in Scheme I is supported by the following evidence: (i) literature precedents [24, 25]; (ii) a molecular modeling study on the more stable structure of 2, which is not coplanar (c.f. Fig. A) [26]; (iii) the \(^1\)H-NMR of 2 (c.f. Experimental), which shows a singlet at \(\delta\) 2.55-2.59 (6H, 4,4'-dimethyl) with some splitting at the top of that signal into a doublet with a difference of \(\approx\) \(\delta\) 0.04 ppm between its two singlet peaks. This difference may be attributable to different environments of the 4,4'-diacetyl groups of 2, which may in turn be related to *cis-trans* geometrical isomerism or to the fact that the resonance structure of 2 (i.e. 2a) is not coplanar or both. Similar results were obtained from the \(^1\)H-NMR spectrum of 13 (c.f. Experimental and Fig. B) [7,23]; (iv) the lower IR stretching frequency of the remote carbonyl group in 5 due its enolization (c.f. Table III); (v) the \(^{13}\)C-NMR chemical shift of compound 5 shows a signal at \(\delta\) 55 ppm that reveals that structure 5d is the more predominant one for 5.
In contrast to the behaviour of 2 in its condensation with 3, the former compound smoothly condensed with excess semicarbazide hydrochloride (4) in the presence of a catalytic amount of fused AcONa and/or piperidine to give the expected 4,4’-diacetylsemicarbazone diphenyl sulphide (6). This formation could be interpreted via inspection of the charged contributing resonance structure 7c (Scheme I) which has comparatively less rigidly localized developed positive charge than the corresponding one 5d, clearly due to the lower basicity of the -OH group compared to that of the -SH group. As a result, the 4-acetylsemicarbazone moiety in structures 7a,b,c has a comparatively little effect on the localized polarisation of the 4’- C=O of 7, to such an extent that it permits the second step condensation of 7 with 4 and/or simultaneous condensation of 2 with excess 4 to occur, thus with forming 6 under a variety of conditions (Scheme II).
It is worth noting that two additional pieces of evidence could also clarify the previous statements. The first chemical evidence was achieved by replacing the sulphide linkage in 5 by a sulphone one to produce 4-acetylthiosemicarbzone-4'-acetyl diphenyl sulphone (14) (Scheme III) which was easily condensed (second step) with 3 in refluxing ethanol in the presence of a catalytic amount of piperidine to form 4,4'-diacetylthiosemicarbzone diphenyl sulphone (16).
Scheme III

\[
\begin{align*}
14 & \quad \text{variable amounts of 3, piperidine/ethanol reflux} \\
13 & \quad \text{excess of 4, ethanol, AcONa} \\
15 & \quad \text{equimolar amounts of 4, AcONa} \\
16 & \quad \text{2 moles of 3, piperidine, ethanol reflux} \\
17 & \quad \text{variable amounts of 3, piperidine/ethanol cold} \\
18 & \quad \text{2 moles of 3, piperidine, ethanol reflux} \\
& \quad \text{excess 4, AcONa, C}_2\text{H}_5\text{OH, cold stirring} \\
& \quad \text{14}
\end{align*}
\]
Here the sulphone group prevents the complete $\pi$ conjugation through 14, which as a result displays a rather different carbonyl group behaviour than that of 5 and even 2, and accordingly it does not experience any effects from the carbazone moiety.

Scheme IV
The second piece of chemical evidence comes from examination of the results when the part containing the thione group in the thiosemicarbazone moiety of 5 was used in assembling the heterocyclic moieties of sulphides 9-12. In these reactions the effect of the thiosemicarbazone group was totally cancelled to a degree that permits the 4'-C=O to condense easily with 3 to produce the sulphides 23-26 under the same conditions previously used (Scheme IV). It is interesting to note that sulphide 5 smoothly condensed with 4 in cold ethanol containing fused AcONa to give 4-acetylthiosemicarbazone-4'-acetylsemicarbazone diphenyl sulphide (8) which alternatively was formed by condensation of sulphide 7 with 3 using the previously mentioned method (c.f. Experimental). The two sulphides obtainable by two different routes (Scheme II) are identical (m.p., mixed m.p. and spectral data). The chemical behaviour of 5 in its condensation with 4 is different than that observed with 3. The theoretical reasoning for that difference is that it apparently depends upon the different reactivity of 3 and 4 towards addition on 4'-C=O [22].

Condensation of 4,4'-diacetyldiphenyl sulphone 13 (vide infra) with an excess of 3 in refluxing ethanol containing a catalytic amount of piperidine afforded only 4-acetylthiosemicarbazone-4'-acetyl diphenyl sulphone (14) (this condensation was not accomplished using fused AcONa). A separate second step condensation of 14 with 3 using the same conditions gave 4,4'-diacetylthiosemicarbazone diphenyl sulphone (16). The latter stepwise formation could be explained as previously discussed and also based on the fact that the energy needed for formation of 16 via simultaneous condensation (E=155.5505 kcal/mol, G=1.4838) is more than that needed for formation of 14 (which is the monothiosemicarbazone derivative of 13) via a one step condensation (E=17.7515; G=14.4536) [26]. Condensation of 13 with an equimolar amount of 4 in the presence of fused AcONa smoothly yielded 4-acetylthiosemicarbazone-4'-acetyl diphenyl sulphone (15), while using an excess of 4, it afforded 4,4'-diacetylthiosemicarbazone diphenyl sulphone (17). 4-Acetylthiosemicarbazone-4'-acetylsemicarbazone diphenyl sulphone (18) was prepared as previously mentioned either by condensation of 15 with 3 and/or 14 with 4 (Scheme III). The two sulphones obtained by the two different routes are identical (m.p, mixed m.p and spectral data). The structures of the prepared compounds 5-8 and 13-18 were established by elemental analysis, I.R, ¹H-NMR, ¹³C-NMR and mass spectral data (c.f. Experimental). It is interesting to note that the electron attracting properties of the 4,4'-diacetyl groups in 13 are nearly equal to that of the SO₂ group and that this affects the NMR data of the aromatic protons (nearly a singlet) which is completely different from the data of the corresponding protons in 2. The same environmental comparison between sulphones 6, 8 and sulphones 17, 18, respectively, is also valid. In the latter sulphones the electron attracting properties of the 4,4'-bis-azomethine groups are nearly equal to that of SO₂ groups in the same molecules (c.f. Experimental).

Interaction of 5 and/or 14 with phenacyl bromide in the presence of fused AcONa afforded 4-(4'-phenyl-Δ³-thiazoline-2'-acetylazino)-4'-acyetyl diphenyl sulphide (9) and 4-(4'-phenyl-Δ³-thiazoline-2'-acetylazino)-4'-acyetyl diphenyl sulphone (19), respectively. Similarly, reaction of 5 and/or 14 with bromo diethylmalonate in the presence of fused AcONa gave 4-(5'-carboxyethyl-4'-thiazolidinone-2'-acetylazino)-4'-acyetyl diphenyl sulphide (10) and 4-(5'-carboxyethyl-4'-thiazolidinone-2'-acetylazino)-4'-acyetyl diphenyl sulphone (20), respectively, while reaction with chloroethylacetate in the presence of fused AcONa gave 4-(4'-thiazolidinone-2'-acetylazino)-4'-acyetyl diphenyl sulphide
(11) and 4-(4"-thiazolidinone-2"-acetylazo)-4'-acetyldiphenyl sulphone (21), respectively. Finally, reactions with chloroacetone in the presence of fused AcONa gave 4-(4"-methyl-Δ³-thiazoline-2"-acetylazo)-4'-acetyldiphenyl sulphide (12) and 4-(4"-methyl-Δ³-thiazoline-2"-acetylazo)-4'-acetyldiphenyl sulphone (22) respectively (Scheme IV). The 4'-acetyltiosemicarbazono derivatives of sulphides 9-12 were used to obtain sulphides 4-(4"-phenyl-Δ³-thiazoline-2"-acetylazo)-4'-acetylthiosemicarbazono diphenyl sulphide (23), 4-(5"-carboxyethyl-4"-thiazolidinone-2"-acetylazo)-4'-acetyltiosemicarbazonediphenyl sulphone (24); 4-(4"-carboxyethyl-4"-thiazolidinone-2"-acetylazo)-4'-acetylthiosemicarbazono diphenyl sulphide (25) and 4-(4"-thiazolidinone-2"-acetylazo)-4'-acetyltiosemicarbazono diphenyl sulphide (26), respectively (Scheme IV). A shortcut to achieving that goal was by interaction of sulphides 9-12 with 3 in the presence of piperidine to afford compounds 23-26 in moderate yields.

Oxidation of the prepared sulphides 5-12 and 23-26 using glacial AcOH/H₂O₂ mixtures at room temperature for at least one week yielded only 13 as the main product from every sulphide examined, although other compounds were isolated in some cases (see Table I). The structures 19-26 were elucidated on the basis of elemental analyses, IR and NMR data (Tables II, III).

**Table I:** Oxidation products of the prepared sulphides using glacial AcOH/H₂O₂ mixtures.

| Prepared sulphides | Oxidation product(s) | Prepared sulphides | Oxidation product(s) |
|--------------------|----------------------|--------------------|----------------------|
| 5                  | 13 + 3               | 11                 | 13 + unidentified substance |
| 6                  | 13 + 4               | 12                 | 13 + 3 + unidentified substance |
| 7                  | 13 + 4               | 23                 | 13 + 3 + unidentified substance |
| 8                  | 13 + 3 + 4           | 24                 | 13 + 3 + unidentified substance |
| 9                  | 13 + unidentified substance | 25                 | 13 + 3 + unidentified substance |
| 10                 | 13 + unidentified substance | 26                 | 13 + 3 + unidentified substance |

Along with the experimental investigation and as further confirmation of the structures of the compounds synthesized, we also carried out some theoretical studies on selected prepared compounds with the help of molecular modeling software [26]. From the obtained data (Table IV) the parent compound 2 (Fig. A) has energy (E)= 15.7673 kcal, Gradient, (G)= 0.099593; compound 5 (Fig. C), the monosubstituted thiosemicarbazono derivative of 2, has E= 33.71358, G= 0.089813. By comparison of 5 with 5a (the dissubstituted dithiosemicarbazono derivative of 2, Fig. D), which has E= 24.24438, G= 0.09677 it was noted that despite the fact that 5a was not experimentally obtained in the present work under a variety of conditions for reasons were previously discussed, the theoretical values of the latter are less than that of the former, i.e. 5a is more stable than 5. Comparing 7 (the monosubstituted semicarbazono derivative of 2), which has E= 19.878, G= 0.0946 with 6, which has E= 97.59393, G= 0.09596 it was found that 7 is more stable than 6 (Figs. E, F). Furthermore, comparisons were carried out between the structures 10 (keto-form), E= 101.8926, G= 0.0957, and its
tautomeric forms 10a (OH-form), $E = 35.82579$, $G = 0.08946$ and 10b (HN-(HO)C= form), $E = 29.69458$, $G = 0.09995$. These results proved that 10 is more stable than 10a and/or 10b and are in accordance with the data obtained experimentally (IR, NMR, c.f. Table III).
On the other hand, when the same comparison was repeated between the structures 11 (keto-form), E= 27.941029, G= 0.08989 and 11a (HN-(HO)C= form), E= 35.82579, G= 0.08946, and 11b (HN-(HO)C= form), E= 29.69458, G= 0.0995, these results proved that 11 is more stable than 11a and/or 11b and are also in accordance with experimental data (IR, NMR, cf. Table III).

Experimental

General

The times required for the completion of the reactions and the purity of the prepared compounds were monitored by thin layer chromatography (TLC). Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyser and a GmbH VARIOEL V23 elemental analysis system in CHNS mode. IR spectra [27] were recorded on a Pye-Unicam SP3-100 spectrophotometer using KBr wafer technique. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on JNM-LA400-MHZ NMR spectrophotometer using the appropriate deuterated solvent and TMS as internal standard (chemical shifts expressed in $\delta$ ppm). Mass spectra were recorded on Jeol JMS-600 mass spectrometer.

4,4’-Diaacetyldiphenyl sulphide (2).

This compound was prepared according to a literature method [4], or by the following procedure: Anhydrous AlCl$_3$ (6.66 g, 0.049 mole) was added in small portions to a conical flask containing diphenylsulphoxide (1, 2.02 g, 0.01 mole) and acetyl chloride (2.8 mL, 0.04 mole) dissolved in carbon disulphide (30 mL), The reaction mixture was stirred in ice bath for 6 hr. The CS$_2$ was evaporated under vacuum, the residue poured onto a mixture of ice and conc. HCl and the resulting pale yellow precipitate was collected and recrystallized from pet. ether (60-80°C) as colourless flakes. Yield: 85%; m.p 90-92°C; IR (v, cm$^{-1}$): 1690 (C=O); $^1$H-NMR (CDCl$_3$): $\delta$ 2.57 (s, 6H, 2-COCH$_3$, split into two bands at the top with $\delta$ 2.55 and 2.59), 7.34-7.93 (m, 8H, Ar-H); Anal. Calc. for C$_{16}$H$_{14}$O$_2$S: C, 70.93; H, 5.39; S, 11.85; Found: C, 70.81; H, 5.25; S, 11.92; MS: M$^+$, m/z (%): 270 (78%).

4-Acetylthiosemicarbazone-4’-acetyldiphenyl sulphide (5).

A mixture of 2 (1.0 g, 0.0037 mole) and 3 (0.675 g, 0.0074 mole) in ethanol (30 mL) was refluxed for 7 hr in presence of two drops of piperidine. On cooling, yellow crystals separated from the reaction mixture and were recrystallized from C$_2$H$_5$OH. Yield 74.8%; m.p 190-192°C; IR (v, cm$^{-1}$): 3400, 3300, 3200 (NH and NH$_2$), 1640 (C=O, the lower frequency due to enolization of the remote carbonyl group), 1600 (C=N); $^1$H-NMR (DMSO-d$_6$): $\delta$ 3.22 (s, 6H, 2CH$_3$), 4.48 (s, 2H, NH$_2$), 7.1-7.5 (m, 8H, Ar-H), 8.62 (s, 1H, NH); $^{13}$C-NMR: $\delta$ 18.429 (CH$_3$-C=N); $\delta$ 27.010 (CH$_3$-C=O); 55.928 (-C $\delta+$); 127.109-145.571 (C-aromatic); 181.038 (-C=N-) and 197.220 (-C=O); Anal. Calc. for C$_{17}$H$_{17}$N$_3$OS$_2$:
C, 59.47; H, 4.95; N, 12.24; S, 18.65; Found: C, 59.40; H, 4.55; N, 12.11; S, 18.61; MS: M+, m/z (%): 343 (2.2).

4,4'-Diacetylsemicarbazone diphenyl sulphide (6).

To a mixture of semicarbazide hydrochloride (0.92 g, 0.00824 mole) and AcONa (1.04 g, 0.01264 mole) dissolved in water (8 mL) a solution of 2 (0.58 g, 0.00214 mole) in ethanol was added with continuous shaking. Ethanol was added if necessary to obtain a clear solution. Shaking was continued for further one hour, and the mixture was cooled in the refrigerator. The separated crystals were filtered off, washed with cold water, dried and crystallized from acetic acid. Yield 85.70%; m.p >300°C (decomp.); IR (ν, cm⁻¹): 3450, 3350, 3200 (NH, NH₂), 1680 (C=O), 1580 (C=N); ¹H-NMR (DMSO-d₆): δ 2.15 (s, 6H, 2CH₃), 6.49 (s, 4H, 2NH₂), 7.27-7.93 (m, 8H, Ar-H); 9.39 (s, 2H, 2NH). Anal. Calc. for C₁₈H₂₀N₆O₂S: C, 56.25; H, 5.20; N, 21.87; S, 8.33; Found: C, 56.20; H, 5.10; N, 21.66; S, 8.10.

4-Acetyl-4'-acetylsemicarbazone diphenyl sulphide (7).

A solution of compound 2 (0.58 g, 0.00214 mole) in ethanol was added with continuous shaking to a mixture of 4 (0.23 g, 0.00206 mole) and AcONa (0.26 g, 0.00316 mole) dissolved in water (8 mL). The reaction mixture was worked up as in the case of 6. The separated crystals were filtered off, washed with cold water, dried and crystallized from ethanol, m.p 190-191°C, yield 85%; IR (ν, cm⁻¹): 3470, 3150, 3160 (NH, NH₂), 1695, 1665 (C=O), 1580 (C=N); ¹H-NMR (DMSO-d₆): δ 2.25 (s, 3H, CH₃-CN); 2.6 (s, 3H, O=C-CH₃); 6.70 (s, 2H, NH₂); 7.30-8.20 (m, 8H, Ar-H); 9.70 (s, 1H, NH); Anal. Calc. for C₁₇H₁₇N₃O₂S: C, 63.38; H, 5.19; N, 12.84; S, 9.78; Found: C, 63.48; H, 5.13; N, 12.67; S, 9.90.

4-Acetylthiosemicarbazone-4'-acetylsemicarbazone diphenyl sulphide (8).

This compound was obtained by the following two methods:

Method A: To a mixture of 4 (0.08 g, 0.00582 mole) and AcONa (0.35 g, 0.0042 mole) dissolved in water (≈ 8 mL), a solution of 5 (1.0 g, 0.00291 mole) in ethanol was added with continuous shaking. The reaction mixture was worked up as in the case of 6. The crystals formed were filtered off, washed with cold water, dried and recrystallized from AcOH, m.p >300°C (decomp.), yield 75%; IR (ν, cm⁻¹): 3400, 3200, 3150 (NH, NH₂), 1680 (C=O), 1580 (C=N), 1480 (C=S); ¹H-NMR (DMSO-d₆): δ 2.15 (s, 3H, CH₃, acetyl thiosemicarbazone); 2.26 (s, 3H, CH₃, acetylsemicarbazone); 6.48 (s, 4H, 2NH₂); 7.25-8.28 (m, 8H, Ar-H); 9.36 (s, 1H, NH) and 10.26 (s, 1H, NH); Anal. Calc. for C₁₈H₂₀N₆O₂S: C, 54.00; H, 5.00; N, 21.00; S, 16.00; Found: C, 53.88; H, 4.96; N, 20.79; S, 15.93.

Method B: A mixture of 7 (1.0 g, 0.003 mole) and 3 (0.55 g, 0.0061 mole) in ethanol (30 mL) containing two drops of piperidine was refluxed for 7 hr. On cooling the crystals that separated were
filtered and recrystallized from AcOH, m.p >300°C (decomp.), yield 71%. The physical and spectral data of the two products from the two methods were identical.

4-Acetylthiosemicarbazone-4'-acetyldiphenyl sulphone (14).

A mixture of 13 (1.0 g, 0.0033 mole) and 3 (0.675 g, 0.0074 mole) in ethanol (30 mL) containing a few drops of piperidine was refluxed for 7 hr. After cooling the pale yellow crystals formed were separated and recrystallized from ethanol, m.p 185°C, yield 80.5%; IR (ν, cm⁻¹): 3380, 3280, 3200 (NH, NH₂); 1680 (C=O); 1640 (C=N); 1335, 1160 (SO₂); ¹H-NMR (DMSO-d₆): δ 2.58 (s, 6H, 2CH₃); 4.48 (s, 2H, NH₂); 7.17-8.12 (m, 8H, Ar-H) and 8.61 (s, 1H, NH); Anal. Calc. for C₁₇H₁₇N₃O₃S₂: C, 54.11; H, 4.50; N, 11.11; S, 16.97; Found: C, 54.38; H, 4.36; N, 11.35; S, 16.85.

4-Acetylsemicarbazone-4'-acetyldiphenyl sulphone (15).

To a mixture of compound 5 (0.36 g, 0.0012 mole) and AcONa (0.26 g, 0.003) dissolved in water (8 mL) a solution of 13 (1.0 g, 0.0031 mole) in ethanol was added with continuous shaking. The reaction mixture was worked up as previously mentioned in the case of 6. The separated crystals were filtered off, washed with cold water, dried and crystallized from ethanol, m.p 200°C, yield 82%; IR (ν, cm⁻¹): 3470, 3250, 3170 (NH, NH₂); 1690, 1665 (C=O); 1580 (C=N), 1340, 1160 (SO₂); ¹H-NMR (DMSO-d₆): δ 2.60 (s, 6H, 2CH₃); 4.56 (s, 2H, NH₂); 7.30-8.20 (m, 8H, Ar-H) and 8.60 (s, 1H, NH); Anal. Calc. for C₁₇H₁₇N₃O₄S: C, 56.82; H, 4.73; N, 11.69; S, 8.91; Found: C, 56.66; H, 4.59; N, 11.39; S, 8.63.

4,4'-Diacetylthiosemicarbazone diphenyl sulphone (16).

A mixture of 14 (1.0 g, 0.0026 mole) and 3 (0.972 g, 0.01 mole) in ethanol (30 mL) containing a few drops of piperidine was refluxed for 7 hr. After cooling the pale yellow crystals formed were separated, crystallized from AcOH, m.p >350 (decomp.), yield 65%; IR (ν, cm⁻¹): 3400, 3280, 3200 (NH, NH₂); 1680 (C=O); 1620 (C=N); 1510 (C=S); ¹H-NMR (DMSO-d₆): δ 2.32 (s, 6H, 2CH₃); 4.42 (s, 4H, 2NH₂); 8.22 (s, 8H, Ar-H) and 10.80 (s, 2H, 2NH); Anal. Calc. for C₁₈H₂₀N₆O₄S:C, 48.21; H, 4.46; N, 18.75; S, 7.69; Found: C, 48.11; H, 4.43; N, 18.53; S, 7.88.

4,4'-Diacetylsemicarbazone diphenyl sulphone (17).

To a mixture of 4 (1.47 g, 0.013 mole) and AcONa (0.81 g, 0.0099 mole) dissolved in water (8 mL) a solution of 13 (1.0 g, 0.00316 mole) in ethanol was added with continuous shaking. The reaction mixture was worked up as in the case of 6. The separated crystals were filtered off, washed with cold water, dried and crystallized from AcOH, m.p >350°C (decomp.), yield 65%; IR (ν, cm⁻¹): 3400, 3250, 3100 (NH, NH₂); 1680 (C=O); 1620 (C=N); 1340, 1170 (SO₂); ¹H-NMR (DMSO-d₆): δ 2.23 (s, 6H, 2CH₃); 6.68 (s, 4H, 2NH₂); 8.12 (s, 8H, Ar-H) and 11.00 (s, 2H, 2NH); Anal. Calc. for C₁₈H₂₀N₆O₄S:C, 51.92; H, 4.80; N, 20.19; S, 7.69; Found: C, 51.69; H, 4.21; N, 20.40; S, 7.88.
4-Acetylthiosemicarbazone-4'-acetylsemicarbazone diphenyl sulphone (18).

This compound was prepared by the following two methods:

Method A: To a mixture of 4 (0.59 g, 0.00533 mole) and AcONa (0.32 g, 0.004 mole) dissolved in water (≈ 8 mL), a solution of 14 (1.0 g, 0.00266 mole) in ethanol was added with continuous shaking. The reaction mixture was worked up as in the case of 6. The separated crystals were filtered off, washed with cold water, dried and crystallized from AcOH, m.p >350°C (decomp.), yield 77%; IR (ν, cm⁻¹): 3450, 3200, 3150 (NH, NH₂); 1675 (C=O), 1580 (C=N); 1485 (C=S); 1340, 1160 (SO₂); ¹H-NMR (DMSO-d₆): δ 2.23 (s, 3H, CH₃); 2.52 (s, 3H, CH₃); 6.50 (s, 4H, 2NH₂); 7.28-7.59 (m, 8H, Ar-H); 9.56 (s, 1H, NH) and 10.30 (s, 1H, NH); Anal. Calc. for C₁₈H₂₀N₆O₃S₂: C, 50.00; H, 4.62; N, 19.44; S, 14.81; Found: C, 49.98; H, 4.55; N, 19.35; S, 14.63.

Method B: A mixture of 15 (1.0 g, 0.0027 mole) and 3 (0.50 g, 0.005 mole) in ethanol (30 mL) containing a catalytic amount of dry piperidine (two drops) was refluxed for 6 hr. On cooling the separated crystals were collected, dried and recrystallized from AcOH, m.p >350°C (decomp.), yield 75%. The physical and spectral data of the two products obtainable by both methods were identical.

General procedure for the oxidation of sulphides 5-12,23-26 and preparation of 13.

A solution of diarylsulphide (0.02 mole) in glacial AcOH (≈ 20 mL) was warmed if necessary, cooled, filtered and 30% H₂O₂ (≈ 30 mL) was added. The mixture was kept at room temperature for 7 days and the deposited crystalline product from each oxidation was filtered, purified as usual and identified as 4,4'-diacetyldiphenylsulphone (13); IR (ν, cm⁻¹): 1690 (C=O); 1310, 1150 (SO₂); ¹H-NMR (DMSO-d₆): δ 2.57 (s, 6H, 2CH₃); 8.10 (s, 8H, Ar-H); MS: M⁺, m/z (%): 302 (23.5); Anal. Calc. for C₁₆H₁₄O₄S: C, 63.57; H, 4.63; S, 10.59; Found: C, 63.44; H, 4.35; S, 10.51.

Isolation of 3 and/or 4 from the oxidation mixtures of 5 and/or 6 respectively (as representative examples):

After filtration of 13 from the oxidation mixture of 5 and/or 6, the filtrate was neutralized with NaHCO₃ solution, the precipitate formed was filtered, purified and identified as 3. To a filtrate from the reaction mixture of 6, conc. HCl was added (3 mL) and the reaction mixture was evaporated to a small volume, cooled, the formed precipitate was filtered, purified and identified as 4.

General procedure for the preparation of compounds 9-12.

Compound 5 (0.5 g, 0.00145 mole) was mixed separately with (0.0014 mole) of phenacyl bromide, bromodiethylmalonate, chloroethylacetate and chloroacetone in the presence of anhydrous AcONa (3.0 g) in ethanol (30 mL). Each mixture was refluxed for 5-7 hr, then allowed to cool and poured onto
ice/water mixture. The precipitate solid product from every reaction was collected, crystallized from
the appropriate solvent. The results are given in Tables II, III.

**General procedure for the preparation of compounds 19-22.**

Compound 14 (1.0 g, 0.00266 mole) was mixed separately with (0.0026 mole) of
phenacylbromide, bromodiethylmalonate, chloroethylacetate and chloroacetone in the presence of
anhydrous sodium acetate (3.0 g) in ethanol (30 mL). Each mixture was refluxed for 5-7 hr, then
allowed to cool and poured onto ice/water mixture. The precipitated solid product of every reaction
was collected and purified from the proper solvent. The yields and characterization details for the
products of these reactions are given in Tables II-III.

**General procedure for the preparation of compounds 23-26.**

A mixture of each sulphide 9-12 (0.0011 mole) and thiosemicarbazide (0.2 g, 0.002 mole) in ethanol
(30 mL) containing two drops of piperidine was refluxed for 7 hr. On cooling yellow crystals were
separated from the reaction mixtures and recrystallized from the appropriate solvent. The results are
summarized in Tables II-III.

**Table II: Yields and Physical data of compounds 9-12, 19-26.**

| Compd. No. | M.p. recrystallization solvent | Yield % | Molecular formulae (Mol. wt.) | Elemental analysis Calcd/Found % |
|------------|--------------------------------|---------|------------------------------|--------------------------------|
| 9          | 160°C, decomp. EtOH/H2O (1:1)  | 54      | C_{25}H_{21}N_{3}OS_{2} (443) | C 67.72 H 4.74 N 9.48 S 14.44 |
|            |                                |         |                              | H 67.90 N 4.52 S 9.70           |
| 10         | 260°C, decomp. EtOH/H2O (1:1)  | 53      | C_{22}H_{21}N_{3}O_{4}S_{2} (455) | C 58.02 H 4.61 N 9.23 S 14.06 |
|            |                                |         |                              | H 58.12 N 4.52 S 9.32           |
| 11         | 160°C EtOH                      | 53      | C_{19}H_{17}N_{3}O_{2}S_{2} (383) | C 59.53 H 4.43 N 10.96 S 16.71 |
|            |                                |         |                              | H 59.40 N 4.32 S 10.80          |
| 12         | 120°C, EtOH                     | 52.5    | C_{20}H_{19}N_{3}O_{2}S_{2} (381) | C 62.99 H 4.98 N 11.02 S 16.79 |
|            |                                |         |                              | H 62.81 N 4.80 S 11.11          |
| 19         | >300°C AcOH                     | 62      | C_{25}H_{21}N_{3}O_{2}S_{2} (475) | C 63.15 H 4.42 N 8.84 S 13.47 |
|            |                                |         |                              | H 63.11 N 4.32 S 8.71           |
| 20         | >300°C AcOH                     | 65      | C_{22}H_{21}N_{3}O_{4}S_{2} (487) | C 54.20 H 4.31 N 8.62 S 13.11 |
|            |                                |         |                              | H 54.10 N 4.22 S 8.51           |
| 21         | >300°C AcOH                     | 61.5    | C_{19}H_{17}N_{3}O_{4}S (415)  | C 54.93 H 4.09 N 10.12 S 15.42 |
|            |                                |         |                              | H 54.12 N 4.01 S 10.11          |
| Compd. No. | X₂   | X₁   | Ar             | Spectral data                                                                 |
|-----------|------|------|----------------|-----------------------------------------------------------------------------|
| 22        |      |      | C₅₂H₉₂N₂O₃S₂  | >300°C AcOH                                                                 |
| 23        | 300°C, EtOH/H₂O (1:1) | 70   | Cₓ₂Hₓ₂Nₓ₆Sₓ₃  | 60.46 50.31 4.65 4.55 16.27 16.11 18.60 18.40 |
| 24        | 300°C, EtOH | 75   | Cₓ₃Hₓ₄Nₓ₆Oₓ₃Sₓ₃ (528) | 52.27 52.17 4.54 4.06 15.90 15.80 18.18 18.11 |
| 25        | 300°C, EtOH | 73   | Cₓ₂Hₓ₂Nₓ₆Oₓ₃Sₓ₃ (456) | 52.63 52.61 4.38 4.10 18.42 18.22 21.05 20.75 |
| 26        | 300°C, EtOH-water (1:1) | 71   | Cₓ₁Hₓ₂Nₓ₆Sₓ₃ (455) | 55.38 55.14 5.05 4.84 18.46 18.40 21.09 20.93 |

Table III: Spectral data of compounds 9-12.

X₁-X₂-N-N=Ar

| Compd. No. | X₂   | X₁   | Ar             | Spectral data                                                                 |
|------------|------|------|----------------|-----------------------------------------------------------------------------|
| 9          | -S-  | Acetyl | N=Ph            | IR (ν, cm⁻¹): 1660 (C=O), 1600 (C=N); ¹H-NMR (DMSO-d₆): δ 2.27 (s, 3H, CH₃-C=N), 2.30 (s, 3H, CH₃CO), 4.35 (s, 2H, CH₃ of thiazoline), 7.27-7.94 (m, 13H, Ar-H). |
| 10         | -S-  | Acetyl | CO₂C₂H₅        | IR (ν, cm⁻¹): 3400 (NH), 1700 (ester C=O), 1680 (C=O), 1580 (C=N); ¹H-NMR (DMSO-d₆): δ 1.13 (t, 3H, CH₂ ester), 2.25 (s, 3H, CH₂-C=N), 2.52 (s, 3H, COCH₃), 4.02 (q, 2H, CH₂ ester), 5.36 (s, 1H, -CH of thiazoline ring), 7.30-7.99 (m, 8H, Ar⁻H), 8.28 (s, 1H, NH). |
| 11         | -S-  | Acetyl | NH-C=O          | IR (ν, cm⁻¹): 3450 (NH), 1700, 1705 (C=O), 1605 (C=N); ¹H-NMR (DMSO-d₆): δ 2.24 (s, 3H, CH₃-C=N), 2.40 (s, 3H, CH₃CO), 3.92 (s, 2H, CH₂ of thiazolidenone ring), 7.00-8.00 (m, 8H, Ar⁻H), 8.25 (s, 1H, NH). |
| 12         | -S-  | Acetyl | N=CH₃          | IR (ν, cm⁻¹): 1670 (C=O), 1590 (C=N); ¹H-NMR (CDCl₃): δ 2.25 (s, 6H, CH₃ of thiazoline, CH3=C=N), 2.45 (s, 3H, CH₃CO), 6.20 (s, 2H, CH₃ of thiazoline ring), 7.30-7.85 (m, 8H, Ar⁻H). |
Table III: (Continued) Spectral data of compounds 19-26.

| Compd. No. | X₂ | X₁ | Ar | **Spectral data** |
|------------|----|----|----|-------------------|
| 19 | \(\text{SO}_2\) | Acetyl | | IR (\(\nu\), cm⁻¹): 1670 (C=O), 1600 (C=N), 1340, 1160 (SO₂); \(^1\)H-NMR (DMSO-d₆): \(\delta\) 2.28 (s, 3H, \(\text{CH}_3\text{-CN}\)), 2.35 (s, 3H, \(\text{CH}_3\text{CO}\)), 6.30 (s, 2H, \(\text{CH}_2\) of thiazoline ring). 7.85–7.99 (m, 13H, Ar-H). |
| 20 | \(\text{SO}_2\) | Acetyl | | IR (\(\nu\), cm⁻¹): 3450 (NH), 1710 (ester C=O), 1680 (C=O), 1340, 1160 (SO₂); \(^1\)H-NMR (DMSO-d₆): \(\delta\) 1.30 (t, 3H, \(\text{CH}_3\) ester), 2.65 (s, 3H, \(\text{CH}_3\text{CO}\)), 4.40 (q, 2H, \(\text{CH}_2\) ester), 7.99–8.35 (m, 8H, Ar-H), 8.80 (s, 1H, CH of thiazolidinone), 9.95 (s, 1H, NH). |
| 21 | \(\text{SO}_2\) | Acetyl | | IR (\(\nu\), cm⁻¹): 3450 (NH), 1710, 1700 (C=O), 1600 (C=N); \(^1\)H-NMR (CDCl₃): \(\delta\) 2.20, 2.30 (s, 6H, \(\text{CH}_3\) of thiazoline ring and \(\text{CH}_3\text{-C=N}\)), 2.60 (s, 3H, \(\text{CH}_3\text{CO}\)), 6.20 (s, 2H, CH₂ of thiazoline ring), 7.85–7.90 (m, 8H, Ar-H). |
| 22 | \(\text{SO}_2\) | Acetyl | | IR (\(\nu\), cm⁻¹): 1680 (C=O), 1580 (C=N); \(^1\)H-NMR (DMSO-d₆): \(\delta\) 2.3 (s, 6H, \(\text{CH}_3\) of thiazoline ring and \(\text{CH}_3\text{-C=N}\)), 2.60 (s, 3H, \(\text{CH}_3\text{CO}\)), 6.20 (s, 2H, CH₂ of thiazoline ring), 7.85–7.90 (m, 8H, Ar-H). |
| 23 | -S- | Acetyl-thiosemi-carbazone | | IR (\(\nu\), cm⁻¹): 3450, 3260, 3150 (NH₂, NH), 1600 (C=N); \(^1\)H-NMR (DMSO-d₆): \(\delta\) 2.3 (s, 6H, \(\text{CH}_3\) of thiazoline ring and \(\text{CH}_3\text{-C=N}\)), 4.7 s, 2H, NH₂), 6.30 (s, 2H, CH₂ of thiazoline ring), 7.00–7.44 (m, 19H, Ar-H), 8.85 (s, 1H, NH). |
| 24 | -S- | Acetyl-thiosemi-carbazone | | IR (\(\nu\), cm⁻¹): 3420, 3300, 3170 (NH, NH₂), 1700 (C=O), 1600 (C=N); \(^1\)H-NMR (DMSO-d₆): \(\delta\) 1.3 (t, 3H, \(\text{CH}_3\) ester), 2.56 (s, 6H, \(\text{CH}_3\)), 4.40 (q, 2H, \(\text{CH}_2\) ester), 5.14 (s, 2H, NH₂), 5.40 (s, 1H, CH of thiazolidinone ring), 7.24–8.90 (m, 8H, Ar-H), 9.14 (s, 1H, NH). |
| 25 | -S- | Acetyl-thiosemi-carbazone | | IR (\(\nu\), cm⁻¹): 3450, 3250, 3200 (NH, NH₂), 1720 (C=O), 1600 (C=N); \(^1\)H-NMR (DMSO-d₆): \(\delta\) 2.24 (s, 6H, \(\text{CH}_3\)), 3.92 (s, 2H, CH₂ of thiazolidinone), 4.86 (s, 2H, NH₂), 7.00–8.00 (m, 8H, Ar-H), 8.3 (s, 1H, NH), 9.7 (s, 1H, NH). |
| 26 | -S- | Acetyl-thiosemi-carbazone | | IR (\(\nu\), cm⁻¹): 3450, 3250, 3170 (NH, NH₂), 1600 (C=N); \(^1\)H-NMR (DMSO-d₆): 2.3 (s, 6H, \(\text{CH}_3\text{-C=N}\)), 2.50 (s, 3H, \(\text{CH}_3\) of thiazoline ring), 4.7 (s, 2H, NH₂), 6.20 (s, 2H, CH₂), 7.20–7.90 (m, 8H, Ar-H), 8.7 (s, H, NH). |
Table IV: Theoretical data of compounds 2, 5, 5a, 6-11.

| Compd. No. | Structure | Energy (ΔE) kcal/mole | Gradient (G) |
|------------|-----------|------------------------|--------------|
| 2          | ![Structure](image1) | 15.7673                | 0.099593     |
| 5          | ![Structure](image2) | 33.71358               | 0.089813     |
| 5a         | ![Structure](image3) | 24.244285              | 0.09677      |
| 6          | ![Structure](image4) | 62.47798               | 0.15902      |
| 7          | ![Structure](image5) | 20.97924               | 0.28384      |
| 8          | ![Structure](image6) | 24.35765               | 0.094893     |
| 9          | ![Structure](image7) | 36.33211               | 0.098009     |
| 10         | ![Structure](image8) | 101.8926               | 0.0957       |
| 10a        | ![Structure](image9) | 114.4389               | 0.09619      |
| 10b        | ![Structure](image10) | 111.42201              | 0.09985      |
Table IV: Continued

| Compd. No. | Structure | Energy (ΔE) kcal/mole | Gradient (G) |
|------------|-----------|-----------------------|--------------|
| 11         | ![Structure](image1) | 27.94028              | 0.08989      |
| 11a        | ![Structure](image2) | 35.82579              | 0.08946      |
| 11b        | ![Structure](image3) | 29.69458              | 0.09995      |

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