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# SYNTHESIS AND INTRAMOLECULAR CYCLIZATION OF BISTHIADIAZINYLMETHANE DERIVATIVES

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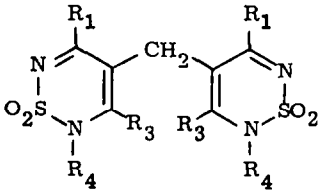
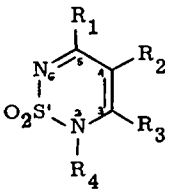
Abstract. – Bisthiadiazinylmethane derivatives obtained from 1,2,6-thiadiazine 1,1-dioxides and formaldehyde, undergo unusual intramolecular cyclizations to thiadiazino [4,3-g] [2,1,3] benzothiadiazine tetraoxides. The structures of the newly synthesized compounds are discussed on the basis of $^{1}H$ and $^{13}C$-NMR data and X-ray analysis.

The chemistry of binuclear heterocycles is an attractive subject especially in what concerns their chelating properties. In this respect, it was interesting to extend the ligand capabilities found for some 1,2,6-thiadiazines [1] to bisthiadiazinylmethane derivatives and thus, their synthesis and a study of their reactivity has been carried out. In an earlier report, Pagani [2] described 4,4'-methylenebis-(3,5-dimethyl-2H-1,2,6-thiadiazine) 1,1,1',1'-tetraoxide (1) which was obtained in an attempt to prepare the corresponding 4-chloromethylthiadiazine from 3,5-dimethyl-2H-1,2,6-thiadiazine 1,1-dioxide [3] with formaldehyde and hydrochloric acid.

The synthesis of bisthiadiazinylmethane derivatives was not easy to achieve. The first synthetic approach which involved condensation of sulfamides with suitable tetracarbonylic compounds such as 3,5-diacetylheptan-2,6-dione [4] failed. On the other hand, condensation of the thiadiazine moiety with formaldehyde was limited sterically by the nature of the substituents $R_1$ and $R_3$. However, excellent yields of 1 and 2 were obtained by treating the corresponding mononuclear thiadiazines with formaldehyde in the presence of triethylamine. In the case of 3-methyl-5-phenyl-2H-1,2,6-thiadiazine 1,1-dioxide [5] the reaction afforded the corresponding 4-hydroxymethyl derivative (3) as the main product. The use of N-alkyl and N-arylthiadiazines [6] resulted in the recovery of the starting materials, probably due to the reduced reactivity towards weak electrophiles of position 4 of the N-substituted thiadiazines as previously observed. [2]





**1** $R_1 = R_3 = CH_3$; $R_4 = H$

**2** $R_1 = CH_3$; $R_3 = R_4 = H$

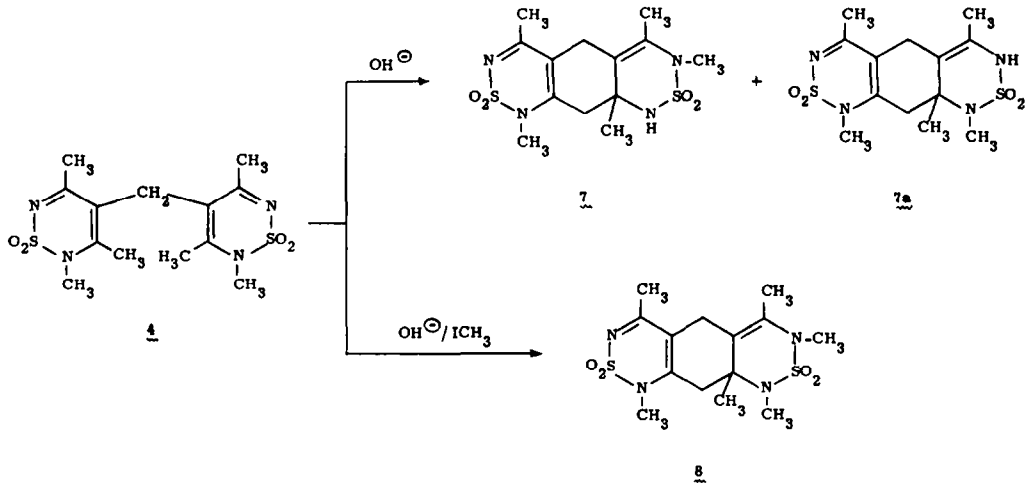
**4** $R_1 = R_3 = R_4 = CH_3$

**5** $R_1 = R_4 = CH_3$; $R_3 = H$

**3** $R_1 = Ph$; $R_2 = CH_2OH$; $R_3 = CH_3$; $R_4 = H$

**6** $R_1 = R_2 = R_3 = R_4 = CH_3$

The bisthiadiazinylmethane derivatives **1** and **2** could not be alkylated with dimethyl sulfate but with methyl iodide **4** and **5** were obtained, respectively. Compound **4** showed an unexpected behaviour in alkaline medium. Its boiling acetone solutions in the presence of sodium hydroxide or potassium carbonate underwent deep changes in colour affording the tricyclic derivatives **7** and **7a**. In the same conditions, and in the presence of methyl iodide **4** gave the corresponding N-methyl derivative **8**, the structure of which was confirmed by X-ray analysis and NMR studies.




**4** **7** **7a** **8**

The mechanism of this unusual intramolecular cyclization has not yet been definitely established. Nevertheless, a radical pathway is not assumed since EPR measurements did not detect the presence of radicals in the course of the reaction. An ionic mechanism seems more likely and so, the first step would be removal of an acidic proton of the activated 3-methyl group to give a carbanion that would attack an electron-defficient position of the other thiadiazine moiety with concomitant ring closure. Although both possible isomers **7** and **7a** were, in fact, detected by $^1$H-NMR in the reaction medium, only **7** could be isolated. This enhanced reactivity of methyl groups adjacent to N-methyl groups had previously been observed in the prototropic behaviour of analogous fully methylated 2-pyrimidones [7] and it can account for the fact that neither **1** nor **5** underwent this intramolecular cyclization.

In order to extend this cyclyzation to other related binuclear heterocycles, attempts to synthesize the hitherto unknown 5,5'-methylenebis (4,6-dimethyl-2(1H)-pyrimidone) were carried out. However, this compound could neither be obtained by condensation of urea with 3,5-diacetylheptan-2,6-dione nor starting from the corresponding 4,6-dimethyl-2-pyrimidone and formaldehyde. This should not be surprising if one takes into account the enhanced reactivity towards electrophiles of position 4 of the thiadiazine 1,1-dioxide in comparison to the corresponding position 5 of the pyrimidone.

## $^{1}H$ and $^{13}C$-Nuclear Magnetic Resonance Discussion

The NMR data of the newly synthesized compounds are consistent with the structures and are given in the Experimental Part.

The $^{13}C$-NMR spectrum of 1 [2], not registered before, shows the signals corresponding to the equivalent C-3 and C-5 atoms and the one of the methyl groups very broadened, due to the fact that the prototropic exchange existing in the NH thiadiazine derivatives [5] is, in this case, very slow.

The assignment of the chemical shifts of 2, 3, and 5 was straightforward [5]. In the $^{1}H$-NMR spectrum of 5 it was not possible to observe coupling between H-3 and the methylene group, whilst in other related thiadiazine derivatives similar coupling exists.[5]

The $^{1}H$-NMR chemical shifts of the methyl groups of the bisthiadiazine derivative 4 were assigned by comparison with the data of 2,3,5-trimethyl-1,2,6-thiadiazine 1,1-dioxide [5]; furthermore, the 3-methyl group is coupled with the methylene (J = 0.7 Hz). The $^{13}C$-NMR data were compared with the data of the above mentioned compound and 6.[8] The chemical shift of the 3-methyl group was confirmed by selective irradiation.

The $^{1}H$-NMR chemical shifts and coupling constants of compounds 7 and 8 are shown in Tables 1 and 2. The number assigned to each carbon atom in the Tables is the same as in the X-ray figure for a better comparison in both drawings.

The spectrum of 8 in DMSO-$d_6$ was not useful due to the fact that some signals appeared overlapped. The most appropriate solvent was $CDCl_3$ + 1% $F_3C$-COOD mixture in which all the signals could be seen. The two methyl groups ($CH_3$-14 and $CH_3$-19) in the A ring were assigned by comparison of the spectra of 4 and 8 in DMSO-$d_6$. The signals of the two other N-methyl groups ($CH_3$-16 and $CH_3$-17) appear very close and it was not possible to assign them unequivocally. The signal corresponding to $CH_3$-18 attached to an $sp^3$-hybridized carbon appears at upper field than the corresponding to $CH_3$-15 attached to an $sp^2$ carbon. Both signals appear in the resolution enhancement spectrum as doublets due to the long-range coupling between H-18, H-d and H-15, H-a. The protons corresponding to the methylene groups are not equivalent and appear in the spectrum as four doublets of an AB ($CH_2$-5) and AM ($CH_2$-11) systems. A resolution enhancement treatment shows the doublets as more complex signals. In order to assign unequivocally the chemical shifts and to measure the long-range coupling constants, double resonance experiments and computer assisted analysis were performed. These analysis were carried out considering a subsystem formed by the four methylenic protons and the two methyl groups coupled with H-a and H-d. From these studies, it was found out that $CH_3$-15 is coupled with H-a with a larger coupling constant than $CH_3$-18 with H-d, probably due to the double bond existing between the 15-methyl and the 5-methylene groups. On the other hand, $CH_3$-15 and $CH_3$-18 seem to be coupled with the other methylenic protons H-b and H-c, respectively, but the coupling constants are too small to be measured. The pairs of methylenic protons H-a, H-d and H-b, H-c are also coupled through five bonds.

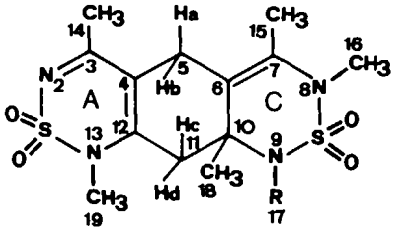



TABLE 1. $^{1}$H-NMR Chemical Shifts (ppm) of Compounds 7 and 8

| Comp. | R | Solvent | H-a | H-b | H-c | H-c | H-14 | H-15 | H-16 | H-17 | H-18 | H-19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | H | DMSO-$d_6$ | 3.11* | ~3.4* | 2.74* | 3.28* | 2.30 | 1.90 | 2.85 | 7.60 | 1.33 | 3.33 |
| 8 | $CH_3$ | $CDCl_3$ +1% $F_3C$-COOD | 3.30 | 3.50 | 2.95 | 3.41 | 2.51 | 2.11 | 3.09* | 3.08* | 1.59 | 3.60 |
| | | DMSO-$d_6$ | - | - | - | - | 2.30 | 1.90 | 2.81* | 2.83* | 1.35 | 3.38 |

TABLE 2. $^{1}$H-NMR Coupling Constants of Compounds 7 and 8

| Comp. | R | Solvent | Coupling Constants, Hz |
|---|---|---|---|
| 7 | H | DMSO-$d_6$ | $^{2}J_{H\text{-}a,H\text{-}b} = -18.3$, $^{2}J_{H\text{-}c,H\text{-}d} = -17.8$ |
| 8 | $CH_3$ | $CDCl_3$ +1% $F_3C$-COOD | $^{2}J_{H\text{-}a,H\text{-}b} = -18.3$, $^{2}J_{H\text{-}c,H\text{-}d} = -17.2$, $^{4}J_{H\text{-}18,H\text{-}d} = \lvert 0.9 \rvert$, $^{5}J_{H\text{-}15,H\text{-}a} = \lvert 1.41 \rvert$; $^{5}J_{H\text{-}a,H\text{-}d} = \lvert 2.0 \rvert$, $^{5}J_{H\text{-}b,H\text{-}c} = \lvert 1.0 \rvert$ |

* Assignments may be interchanged.

TABLE 3. $^{13}$C-NMR Chemical Shifts (ppm) of Compounds 7 and 8

| Comp. | R | C-3 | C-4 | C-5 | C-6 | C-7 | C-10 | C-11 | C-12 | C-14 | C-15 | C-16 | C-17 | C-18 | C-19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | H | 173.02 | 106.75 | 26.15 | 118.65 | 132.01 | 57.46 | 39.03 | 152.54 | 23.84 | 17.10 | 36.10 | -- | 25.75 | 30.45 |
| 8 | $CH_3$ | 174.12 | 107.84 | 27.25 | 120.11 | 132.42 | 61.50 | 35.86 | 152.17 | 23.85 | 17.45 | 37.50 | 27.83 | 22.22 | 31.35 |

TABLE 4. $^{1}$H-$^{13}$C Coupling Constants (Hz) [a]

| Comp. | C-3 | C-4 | C-5 | C-7 | C-11 | C-14 | C-15 | C-16 | C-17 | C-18 | C-19 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | | | $^{1}J$ = 130.0 | | $^{1}J$ = 132.5 | $^{1}J$ = 128.6 | $^{1}J$ = 127.9 | $^{1}J$ = 140.1 | -- | $^{1}J$ = 127.3 | $^{1}J$ = 140.8 |
| 8 | $^{2}J_{H-14}$ = \|4.5\| [c] | $^{2}J_{H-a}$ = \|7.0\| [b] | $^{1}J_{H-a}$ = 130.4 | $^{2}J_{H-15}$ = \|7.2\| [b] | $^{1}J_{H-c}$ = 130.0 | $^{1}J$ = 129.7 | $^{1}J$ = 128.6 | $^{1}J$ = 142.3 | $^{1}J$ = 140.5 | $^{1}J$ = 129.7 | $^{1}J$ = 143.8 |
| | $^{3}J_{H-a}$ = 2.0* [c] | $^{2}J_{H-b}$ = \|7.0\| [b] | $^{1}J_{H-b}$ = 130.4 | | $^{1}J_{H-d}$ = 133.5 | | | $^{4}J_{H-15}$ = 1.8 | | $^{3}J_{H-c}$ = 3.0* | |
| | $^{3}J_{H-b}$ = 8.1* [c] | $^{3}J_{H-c}$ = 0.0* [b] | | | $^{3}J_{H-18}$ = 5.5 [c] | | | | | $^{3}J_{H-d}$ = 5.8* | |
| | | $^{3}J_{H-d}$ = 3.8* [b] | | | $^{4}J_{H-a}$ = 0.0* [c] | | | | | | |
| | | $^{3}J_{H-14}$ = 7.0 [b] | | | $^{4}J_{H-b}$ = 3.0* [c] | | | | | | |

a) The data with asterisk may be reversed.

b) Calculated from residual coupling constants.

c) Determined by computer assisted analyses.

The $^{1}$H-NMR spectrum of 7 in DMSO-$d_6$ shows the signal of a methylenic proton overlapped with the corresponding to $CH_3$-19; unfortunately, it was not possible to register the spectrum in the $CDCl_3$ + 1% $F_3C$-COOD mixture, because the compound decomposes in the solvent. The assignment of the chemical shifts was made by comparing the data of 7 and 8. The chemical shifts of the protons of the two methylenic groups may be reversed. The N-methyl group in the C ring was assigned to the N-8 on the basis of $^{13}$C-NMR data as can be seen below.

The $^{13}$C-NMR chemical shifts and coupling constants of 7 and 8 are gathered in Tables 3 and 4. In compound 8, the assignments were based on the following criteria: chemical correlation, signal multiplicity, coupling constants and selective irradiation. The coupling constants belonging to the three N-methyl groups are larger ($J > 140$ Hz) than the ones ($J < 130$ Hz) corresponding to the C-methyl groups [9]. All methyl groups were assigned by selective irradiation except the two N-methyl groups at the C-ring because the frequencies of their protons are very close. However, by irradiation at H-15, the coupling between H-15 and C-16 disappeared; thus, C-16 and C-17 could be unequivocally assigned. The two methylenic groups were assigned by selective irradiation at H-c. The coupling constants of $C_{11}$, H-c and C-11, H-d were determined by application of the Pachler equation [10] to the measured residual coupling constants in the irradiated spectra. Of the signals corresponding to the quaternary carbon atoms, the one which appears at higher field was assigned to the only $sp^3$-hybridized carbon (C-10). The chemical shifts of C-3, C-4 and C-12 were assigned by comparison of the spectra of 8 and the parent compound 4. By selective irradiation at H-15 the signal corresponding to C-7 is modified since the coupling between C-7 and H-15 disappears. In this case, a long-range coupling between C-7 and H-a and H-b can be observed. Finally, by exclusion, the signal at $\delta = 120.11$ ppm must belong to C-6. The resolution enhancement coupled spectrum shows a number of long-range couplings, but, only some coupling constants could be determined either from the residual coupling constants in the irradiated spectra or by direct measurement in the coupled spectrum.

From the data of $^{3}J_{C-3,H-5} = 8.1$ Hz, it could be concluded that one of the protons of 5-methylene forms a torsion angle (C3-C4-C5-H5) of $\simeq 180°$ [11], whilst in solid state neither H-5A nor H-5B form such a torsion angle (C3-C4-C5-H5A = 54(2)° and C3-C4-C5-H5B = 53(2)°). Likewise, the values of both $^{3}J_{C-18,H-11}$ are not in agreement with the torsion angles in solid state (C18-C10-C11-H11A = 103(1)° and C18-C10-C11-H11B = 57(2)°). From these data, it is reasonable to suppose that the conformation is different in solution than in solid state and so the difference in the chemical shifts of the protons of the 11-methylene cannot be justified by the interaction between H-11A and O-4 (see Table 7) existing in the solid state.

The assignments in compound 7 were made by comparing the spectra of 7 and 8. The N-methyl group, which does not appear in the spectrum of 7 is that corresponding to $CH_3$-17 in 8. This fact is in agreement with the other data since the biggest variations in the chemical shifts between both spectra are in the neighbouring carbon atoms, i.e. C-10 ($\Delta\delta = -4.04$ ppm), C-18 ($\Delta\delta = +3.53$ ppm) and C-11 ($\Delta\delta = +3.17$ ppm).

## X-Ray Analysis

The crystal structure of compound 8 has been analyzed by X-ray diffraction. Fig. 1 shows a perspective view of the final X-ray model. The difference between the two pairs of bonds S1-01 and S2-03 vs. S1-02 and S2-04 are just below the significance of the achieved precission (Table 5). The double bonds are localized at the C3-N2, C4-C12 and C6-C7 bonds (Fig. 1).

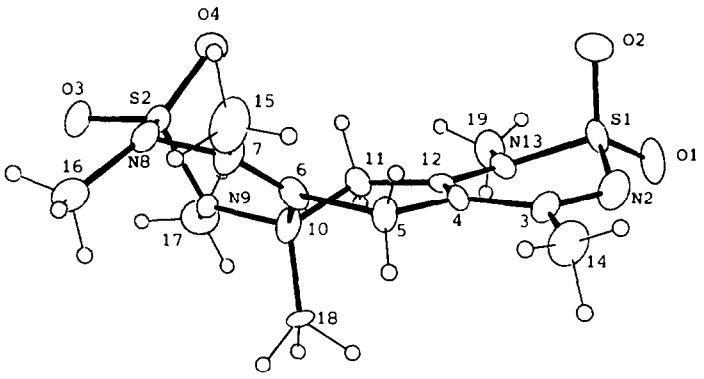



Fig. 1. ORTEP view of the molecule showing the atomic numbering [12]

This localization and the characteristics of the $SO_2N_2$ groups gives rise to the conformation of the rings: S-rings envelope flapping at S atoms, central ring half-chair at C4-C12 (see Table 6) the overall bending of the molecule being 38.1(7)° around C6-C10 and just 3.4(7)° around C4-C12. The different degree of puckering of both S-rings and the higher bending around C6-C10 could be explained in terms of the interactions involving O3 and O4 (Table 7).

TABLE 5

BOND DISTANCES (Å)

| | | | |
|---|---|---|---|
| S1-O1 | 1.404(14) | S2-O3 | 1.417(13) |
| S1-O2 | 1.430(15) | S2-O4 | 1.436(12) |
| S1-N2 | 1.622(18) | S2-N8 | 1.642(15) |
| S1-N13 | 1.688(15) | S2-N9 | 1.658(14) |
| N2-C3 | 1.336(25) | N8-C7 | 1.441(22) |
| C3-C4 | 1.407(25) | C7-C6 | 1.325(23) |
| C4-C12 | 1.370(24) | C6-C10 | 1.555(25) |
| C12-N13 | 1.385(20) | C10-N9 | 1.480(21) |
| C3-C14 | 1.484(27) | C7-C15 | 1.479(27) |
| N13-C19 | 1.463(24) | N9-C17 | 1.497(22) |
| C4-C5 | 1.493(21) | C10-C18 | 1.509(24) |
| C12-C11 | 1.478(24) | C10-C11 | 1.565(21) |
| C5-C6 | 1.516(23) | N8-C16 | 1.466(24) |

BOND ANGLES (°)

| | | | |
|---|---|---|---|
| N2-S1-N13 | 103.4(7) | N8-S2-N9 | 101.4(7) |
| O2-S1-N13 | 107.9(8) | O4-S2-N9 | 110.8(7) |
| O2-S1-N2 | 110.7(8) | O4-S2-N8 | 109.3(7) |
| O1-S1-N13 | 108.2(8) | O3-S2-N8 | 107.3(8) |
| O1-S1-N2 | 109.4(9) | O3-S2-N9 | 108.7(7) |
| O1-S1-O2 | 116.5(8) | O3-S2-O4 | 118.0(7) |
| S1-N2-C3 | 118.3(15) | S2-N8-C16 | 114.3(12) |
| N2-C3-C14 | 114.2(17) | S2-N8-C7 | 113.8(11) |
| N2-C3-C4 | 125.6(18) | C7-N8-C16 | 115.4(14) |
| C4-C3-C14 | 120.2(18) | S2-N9-C17 | 113.2(11) |
| C3-C4-C12 | 120.2(15) | S2-N9-C10 | 115.3(11) |
| C3-C4-C5 | 119.0(16) | C10-N9-C17 | 118.5(13) |
| C5-C4-C12 | 120.5(14) | N8-C7-C6 | 120.4(16) |
| C4-C12-C11 | 123.8(14) | C6-C7-C15 | 126.8(16) |
| N13-C12-C11 | 114.3(14) | N8-C7-C15 | 112.7(14) |
| N13-C12-C4 | 121.7(15) | N9-C10-C6 | 112.1(12) |
| S1-N13-C19 | 114.2(10) | C6-C10-C18 | 108.7(14) |
| S1-N13-C12 | 118.7(12) | C6-C10-C11 | 107.0(14) |
| C12-N13-C19 | 124.9(14) | N9-C10-C18 | 108.1(13) |
| C4-C5-C6 | 115.2(14) | N9-C10-C11 | 110.1(13) |
| C10-C11-C12 | 114.2(13) | C11-C10-C18 | 110.8(13) |
| C5-C6-C10 | 112.1(13) | C7-C6-C10 | 126.5(15) |
| C5-C6-C7 | 121.3(16) | | |

TABLE 6

TORSION ANGLES (°)

| | | | |
|---|---|---|---|
| N2-S1-N13-C12 | 36(1) | N8-S2-N9-C10 | -58(1) |
| N13-S1-N2-C3 | -35(2) | N9-S2-N8-C7 | 57(1) |
| S1-N2-C3-C4 | 18(3) | S2-N8-C7-C6 | -30(2) |
| S1-N13-C12-C4 | -17(2) | S2-N9-C10-C6 | 31(2) |
| N2-C3-C4-C12 | 10(3) | C7-C6-C10-N9 | 4(2) |
| C3-C4-C12-N13 | -8(3) | C10-C6-C7-N8 | -4(3) |
| C5-C4-C12-C11 | -1(3) | O2-S1-N2-C3 | 81(2) |
| C12-C4-C5-C6 | -12(2) | O1-S1-N2-C3 | -150(2) |
| C4-C5-C6-C10 | 43(2) | O4-S2-N9-C10 | 59(1) |
| C5-C6-C10-C11 | -59(2) | O3-S2-N9-C10 | -171(1) |
| C6-C10-C11-C12 | 46(2) | C7-C8-C10-C11 | 125(2) |
| C10-C11-C12-C4 | -18(2) | C7-C8-C10-C18 | -118(2) |

* S1N2-C4C12-C6C10-S2N8 35(15)

EXPERIMENTAL AND CALCULATED CREMER AND POPLE PARAMETERS

| | Q2 | Q3 | $\Phi$ | $\theta$ |
|---|---|---|---|---|
| S1-RING: | | | | |
| Exp. | 0.34(1) | -0.17(2) | 118(3) | 116(3) |
| Cal. envelope | Q2 | Q3 | 120 | 125.3 |
| CENTRAL RING: | | | | |
| Exp. | 0.38(2) | 0.31(2) | 157(3) | 51(2) |
| Cal. half chair | Q2 | Q3 | 150 | 50 |
| S2-RING: | | | | |
| Exp. | 0.47(1) | 0.31(1) | 0(2) | 124(2) |
| Cal. envelope | Q2 | Q3 | 0 | 125.3 |

PLANES AND LINES ANGLES

| | | |
|---|---|---|
| N2,C3,C4,C5,C11,C12,N13 | - N2,S1,N13 | 32.9(6) |
| N2,C3,C4,C5,C11,C12,N13 | - C6,C10,N9,N8,C7 | 38.2(5) |
| C6,C10,N9,N8,C7 | - N8,S2,N9 | 50.4(6) |
| * S1N2,C4C12 | - C4C12,C6C10 | 3.4(7) |
| * C4C12,C6C10 | - C6C10,S2N8 | 38.1(7) |

* S1N2, C4C12, C6C10 are the midpoints of S1-N2, C4-C12 and C6-C10 bonds respectively.

TABLE 7

MAIN HYDROGEN INTERACTIONS (Å) AND (°) WITH SYMMETRY OPERATIONS

| | | | |
|---|---|---|---|
| O3...H16B | 2.54(1) | O3...H16B-C16 | 96(1)i |
| O3...H17B | 2.56(1) | O3...H17B-C17 | 98(1)i |
| N8...H15B | 2.65(1) | N8...H15A-C15 | 67(1)i |
| N8...H15A | 2.63(1) | N8...H15A-C15 | 67(1)i |
| O4...H11A | 2.50(1) | O4...H11A-C11 | 128(1)i |
| N9...H11A | 2.61(1) | N9...H11A-C11 | 72(1)i |
| O2...H18C | 2.67(1) | O2...H18C-C18 | 132(1)ii |
| O4...H14C | 2.66(1) | O4...H14C-C14 | 135(1)iii |
| O4...H15C | 2.63(1) | O4...H15C-C15 | 166(1)iii |
| O4...H19A | 2.31(1) | O4...H19A-C19 | 169(1)iv |
| O2...H11B | 2.64(1) | O2...H11B-C11 | 145(1)ii |

i = x,y,z
ii = -x,1/2+y,1/2-z
iii = x,1/2-y,z-1/2
iv = -x,-y,z

TABLE 8. Crystal analysis parameters at room temperature

| | |
|---|---|
| **Crystal data :** | |
| Formula | $C_{14}H_{22}N_4O_4S_2$ |
| Crystal habit | Yellow trapezoidal plate |
| Crystal size (mm) | 0.13 x 0.10 x 0.02 |
| Symmetry | Orthorrombic, Pbca |
| Unit cell determination: least-squares fit to | 47 reflexions, $\theta(Cu) < 45°$ |
| Unit cell dimensions (Å) | 25.2814(11), 12.1977(3), 11.0033(4) |
| Packing: V(Å$^3$), Z | 3393.1(2), 8 |
| D(g cm-3), M, F(000) | 1.466, 374.47, 1584 |
| **Experimental data :** | |
| Radiation & technique | CuKα , PW1100 diffractometer bisecting geometry |
| Monochromator | Graphite oriented |
| Collection mode | $\omega/2\theta$ , $\theta < 65°$, 1 x 1 det. apertures 1.3 min/ref., 1.2 scan width |
| Total independent data | 2892 |
| Observed data | 833, $F > 2\sigma$ |
| Stability | Two reflexions every 90 min.,no variation |
| μ(cm-1) | 30.37 |
| **Solution and refinement :** | |
| Solution | XRAY76 [13], VAX 11/750 |
| Refinement | Least-squares on F's, observed reflexions One block |
| Final shift/error | 0.04 |
| Number of variables | 217 (hydrogen fixed) |
| Degrees of freedom | 616 |
| Ratio of freedom | 3.8 |
| Weisthing scheme | Empirical as to give no trends in $\langle w\Delta^2F \rangle$ vs. $\langle Fo \rangle$ or $\langle \sin\theta/\lambda \rangle$ |
| Max. thermal values (Å$^2$) | U22(O1)=0.10(1) |
| Final ΔF peaks | 0.46 eÅ-3 near the Rh atoms |
| Final R, Rw | 0.082, 0.082 |
| Atomic factors | International Tables for X-Ray Crystallography [14] |

TABLE 9. Atomic Coordinates and Thermal Parameters AS: $UEQ=(1/3).SUM\left[UIJ.AI^*.AJ^*.AI.AJ.COS(AI,AJ)\right]$

| Atom | X/A | Y/B | Z/C | UEQ |
|---|---|---|---|---|
| S1 | 0.0493( 2) | 0.1074( 5) | 0.3295( 5) | 44( 2) |
| S2 | -0.1899( 2) | 0.0224( 4) | 0.0154( 4) | 37( 2) |
| O1 | 0.0956( 2) | 0.0511(12) | 0.3620(14) | 75( 6) |
| O2 | 0.0554( 5) | 0.1974(10) | 0.2475(14) | 69( 6) |
| O3 | -0.2246( 4) | -0.0295(11) | -0.0677(11) | 57( 5) |
| O4 | -0.1458( 4) | 0.0823( 9) | -0.0329(10) | 44( 5) |
| N2 | 0.0185( 6) | 0.1458(12) | 0.4516(16) | 55( 6) |
| N8 | -0.2247( 5) | 0.1033(12) | 0.1041(13) | 37( 5) |
| N9 | -0.1698( 5) | -0.0721(11) | 0.1129(12) | 32( 5) |
| N13 | 0.0072( 5) | 0.0169(12) | 0.2655(13) | 37( 6) |
| C3 | -0.0342( 8) | 0.1536(14) | 0.4479(18) | 49( 8) |
| C4 | -0.0870( 6) | 0.1080(15) | 0.3580(16) | 30( 6) |
| C5 | -0.1251( 6) | 0.1303(15) | 0.3623(15) | 40( 7) |
| C6 | -0.1564( 6) | 0.0875(14) | 0.2548(15) | 33( 6) |
| C7 | -0.1954( 6) | 0.1454(16) | 0.2063(16) | 43( 7) |
| C10 | -0.1393( 6) | -0.0304(15) | 0.2180(15) | 36( 6) |
| C11 | -0.0791( 6) | -0.0250(15) | 0.1857(17) | 38( 6) |
| C12 | -0.0467( 6) | 0.0361(13) | 0.2746(15) | 30( 6) |
| C14 | -0.0576( 7) | 0.2133(17) | 0.5524(18) | 60( 9) |
| C15 | -0.2142( 7) | 0.2546(16) | 0.2460(20) | 63( 8) |
| C16 | -0.2779( 8) | 0.0628(15) | 0.1319(18) | 55( 8) |
| C17 | -0.1516( 7) | -0.1754(14) | 0.0525(17) | 47( 8) |
| C18 | -0.1487( 6) | -0.1062(14) | 0.3241(15) | 34( 6) |
| C19 | 0.0319( 7) | -0.0569(15) | 0.1776(19) | 48( 7) |

## EXPERIMENTAL

M. ps were determined on a capillary apparatus and are uncorrected. Mass spectra were recorded on a Varian Mat-711 instrument. Column chromatography was performed on Merck silica gel 60 (70-230 mesh) and preparative layer chromatography was performed on 20x 20 cm glass plates coated with a 2 mm layer of silica gel $PF_{254}$ (Merck). Compounds were detected with U.V. light (254 nm). 3,5-Disubstituted-2H-1,2,6-thiadiazine 1,1-dioxides were prepared from the corresponding diketones and sulfamides.[3,5,6,8]

$^1H$ spectra were obtained at 298º K in DMSO-$d_6$, unless otherwise stated, on a Varian XL-300 instrument operating at 300MHz. The use of a spectral width of 3KHz with a data memory of 32 K gave a digital resolution of 0.2 Hz. The pulse width used was 8$\mu$s (53°). TMS was used as internal reference. Assignments were done using double resonance experiments. $^{13}C$ spectra were obtained at 298 K in DMSO-$d_6$ on the same instrument operating at 75 MHz. The use of a spectral width of 16KHz with a memory of 32K gave a digital resolution of 0.6 Hz. The pulse width used was 5.5$\mu$s (42°). Assignments were done using selective proton irradiation and coupled carbon spectra. Selective proton irradiation spectra were obtained under the following conditions: the spin system was broadband irradiated during 3s to build NOE. After this time period a short delay of 50 ms was introduced before the observed pulse. Adquisition time was performed under selective proton irradiation. Either $^1H$ or $^{13}C$ Fid's were weighted in order to enhance resolution. Either $^1H$ or $^{13}C$ coupled spectra were analyzed by computer simulation using the PANIC [15] program.

The main characteristics of the X-ray analysis are given in Table 8. Due to the rather small crystal size, the number of unobserved reflexions, as well as the corresponding criterion, left just about four reflexions per parameter in the refinement, leaving the H-atoms fixed. No absorption correction was done. Table 9 presents the final atomic coordinates according to the numbering given in Fig. 1. A list of structure factors, thermal parameters and hydrogen coordinates are available from the authors on request (Instituto Rocasolano, Dept. Cristalografía).

### 4,4'-Methylenebis-(3,5-dimethyl-2H-1,2,6-thiadiazine) 1,1,1',1'-tetraoxide (1)

A solution of 3,5-dimethyl-2H-1,2,6-thiadiazine 1,1-dioxide [3] (0.3 g, 0.002 mol) in methanol (50 ml) was treated with 35-40% formaldehyde (0.6 g, 0.02 mol) and triethylamine (0.04 ml) was added. The reaction mixture was refluxed for 4 h. The white crystalline solid which appeared after cooling was filtered and recrystallized from ethanol (2.9 g, 94%); m.p. 217-218° C (lit. [2] 218° C); U.V. (MeOH) $\lambda_{max}$ ($\varepsilon$): 212 nm (11600), 330 nm (8500); $^{13}C$-NMR (DMSO-$d_6$) $\delta$: 161.3 (b) (C-3, C-5), 110.8 (C-4), 24.5 ($CH_2$), 20.9 (b) ($CH_3$-3, $CH_3$-5).

### 4,4'-Methylenebis-(5-methyl-2H-1,2,6-thiadiazine) 1,1,1',1'-tetraoxide (2)

3-Methyl-2H-1,2,6-thiadiazine 1,1-dioxide [6] (1.5 g, 0.011 mol) was dissolved in methanol (50 ml) and treated with 35-40% formaldehyde (0.46 g, 0.014 mol) in the presence of triethylamine (0.06 ml). The reaction mixture was refluxed for 6 h, and the solvent removed at reduced pressure. The oily residue was purified through silica gel column chromatography with chloroform-ethanol (4:1) as eluent to yield an hygroscopic yellow foam (1.2 g, 83 %); U.V. (MeOH) $\lambda_{max}$ ($\varepsilon$): 210 nm (5500), 328 nm (5500); $^1H$-NMR (DMSO-$d_6$) $\delta$: 7.4 (s, 2H, H-3), 3.4 (s, 2H, $CH_2$), 2.2 (s, 6H, $CH_3$). (Found: C, 32.43; H, 4.17; N, 16.55. $C_9H_{12}N_4O_4S_2 \cdot 1\,1/2\ H_2O$ requires: C, 32.62; H, 4.53; N, 16.91%).

3-Methyl-4-hydroxymethyl-5-phenyl-2H-1,2,6-thiadiazine 1,1-dioxide (3)

To a solution of 3-methyl-5-phenyl-2H-1,2,6-thiadiazine 1,1-dioxide [5] (1.5 g, 0.007 mol) in methanol (50 ml) 35-40% formaldehyde (0.46 g, 0.014 mol) and triethylamine (0.04 ml) were added. The reaction mixture was refluxed for 4 h and then stirred overnight at room temperature. The white solid which appeared was filtered and recrystallized from water (0.3 g, 19%); m.p. 174-176° C (dec.) U.V. (MeOH) $\lambda_{max}$ ($\varepsilon$): 222 nm (4300), 260 nm (3500), 337 nm (4600); $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.6-7.3 (m, 5H, Ar-H), 3.5 (s, 2H, $CH_2$), 1.9 (s, 3H, $CH_3$). (Found: C, 52.46; H, 5.19; N, 11.54; S, 12.11. $C_{11}H_{12}N_2O_3S$ requires: C, 52.38; H, 4.76; S, 11.11; S, 12.69%).

4,4'-Methylenebis-(2,3,5-trimethyl-1,2,6-thiadiazine) 1,1,1',1'-tetraoxide (4)

A stirred solution of 1 (0.45 g, 0.001 mol) in anhydrous acetone (50 ml) was treated with potassium carbonate (0,1 g) and methyl iodide (1 g, 0.006 mol). The mixture was refluxed for 6 h and the precipitate was filtered off. The solvent was removed "in vacuo" and the residue recrystallized from ethanol to give white crystals (0.2 g, 44%); m.p. 180° C; U.V.(MeOH) $\lambda_{max}$ ($\varepsilon$): 212 nm (11200), 333 nm (11500); $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.39 (s, 6H, N-$CH_3$), 3.68 (b.s., 2H, $CH_2$), 2.26 (b.s., 6H, $CH_3$-3), 2.14 (s, 6H, $CH_3$-5); $^{13}$C-NMR (DMSO-$d_6$) $\delta$: 172.7 (C-5), 154.7 (C-3), 112.6 (C-4), 31.2 ($^1J_{C-H}$ = 143.3 Hz, N-$CH_3$), 26.1 ($^1J_{C-H}$ = 129.3 Hz, $CH_2$), 23.0 ($^1J_{C-H}$ = 130.1 Hz, $CH_3$-5), 15.9 ($^1J_{C-H}$ = 129.0 Hz, $CH_3$-3); M.S. 360 ($M^+$). (Found: C, 43.76; H, 5.97; N, 15.30; S, 17.80. $C_{13}H_{20}N_4O_4S_2$ requires: C, 43.33; H, 5.55; N, 15.55; S, 17.77%).

4,4'-Methylenebis-(2,5-dimethyl-1,2,6-thiadiazine) 1,1,1',1'-tetraoxide (5)

Methyl iodide (0.85 g, 0.006 mol) was added to a solution of 2 (0.7 g, 0.002 mol) in anhydrous acetone (60 ml) and potassium carbonate (0.5 g). The reaction mixture was refluxed for 2 h and, once cooled, the solid was removed by filtration. The filtrate was evaporated "in vacuo", and the white solid that was left was recrystallized from methanol (0.3 g, 30%); m.p. 226-228° C, U.V. (MeOH) $\lambda_{max}$: 209 nm, 335 nm; $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.38 (s, 2H, H-3), 3.37 (s, 6H, N-$CH_3$), 3.35 (s, 2H, $CH_2$), 2.21 (s, 6H, $CH_3$); $^{13}$C-NMR (DMSO-$d_6$) $\delta$: 173.9 (C-5), 148.4 (C-3), 109.0 (C-4), 36.0 (N-$CH_3$), 27.7 ($CH_2$), 23.4 ($CH_3$-5). (Found: C, 39.77; H, 4.98; N, 16.41; S, 19.32. $C_{11}H_{16}N_4O_4S_2$ requires: C, 39.75; H, 4.81; N, 16.86; S, 19.47 %).

3,4,6,9,10a-pentamethyl-5,10-dihydro-1H-1,2,6-thiadiazino [4,3-g] [2,1,3]benzothiadiazine 2,2,8,8-tetraoxide (7)

Compound 4 (0.5 g, 0.001 mol) was dissolved in dry acetone (50 ml) and potassium carbonate (0.1 g) was added. On refluxing, the reaction colour turned to dark blue. The mixture was kept heating for 4 h and, a change in colour from blue to deep yellow could be observed. The solid was filtered off and the solvent evaporated to dryness. The residue was purified by t.l.c. with chloroform-ethanol (100:1) as eluent (0.1 g, 20%); m.p. 186-188° C; U.V. (MeOH) $\lambda_{max}$ ($\varepsilon$): 220 nm (4500), 345 nm (3300). (Found : C, 43.15; H, 5.67; N, 15.21; S, 17.72. $C_{13}H_{20}N_4O_4S_2$ requires: C, 43.33; H, 5.55; N, 15.55; S, 17.77%).

1,3,4,6,9,10a-hexamethyl-5,10-dihydro-1,2,6-thiadiazino [4,3-g] [2,1,3] benzothiadiazine 2,2,8,8-tetraoxide (8)

Methyl iodide (1 g, 0.006 mol) was added to a solution of 4 (0.45 g, 0.001 mol) in acetone (50 ml) and potassium carbonate (0.1 g). The reaction mixture became deep yellow and was refluxed for 6 h. After cooling, the solid was removed by filtration. The filtrate was evaporated to dryness "in vacuo" and the residue was recrystallized from methanol to give yellow plates (0.3 g, 65%); m.p. 176-178°C; U.V. (MeOH) $\lambda_{max}$ ($\varepsilon$): 215 nm (5400), 334 nm (3500); M.S. 374 ($M^+$). (Found: C, 44.87; H, 6.13; N, 15.13; S, 16.82. $C_{14}H_{22}N_4O_4S_2$ requires: C, 44.9; H, 5.88; N, 14.97; S, 17.11 %).

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