1,2,6-Thiadiazin-3,5(2*H*,6*H*)-dione 1,1-dioxide derivatives: crystal structure, physico-chemical and biological properties

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Crystal structure, ^1H and ^{13}C nmr spectroscopy and pK_a measurements of 1,2,6-thiadiazin-3,5(2*H*,6*H*)-dione derivatives related with phenylbutazone are reported. An anomalous variation in the pK_a values of compounds **1**, **2**, and **3** has been observed. Antiinflammatory, analgesic, and antipyretic activities of these compounds have been evaluated.

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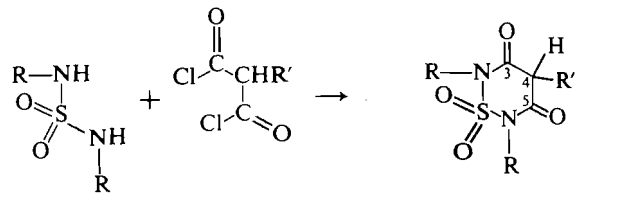
On a déterminé la structure cristalline, les spectres rmn du ^1H et du ^{13}C et les valeurs des pK_a de dérivés de la thiadiazine-1,2,6 dione-3,5(2*H*,6*H*) qui sont apparentés avec la phénylbutazone. On a observé une variation anormale dans les valeurs des pK_a des composés **1**, **2** et **3**. On a évalué les propriétés antiinflammatoire, analgésique et antipyrétique de ces composés.

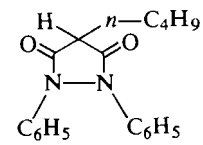
[Traduit par la revue]

Introduction

In a previous paper (1) we carried out a comparative study between the physicochemical properties of 1,2,6-thiadiazine 1,1-dioxide derivatives and related pyrazoles. We have now extended the comparison to compounds of this series with antiinflammatory activity. Thus, we now wish to report the physico-chemical properties and preliminary biological screening of 1,2,6-thiadiazin-3,5(2*H*,6*H*)-dione 1,1-dioxides **1** (2), **2** and **3** (3), structurally related to phenylbutazone **4**. Compound **3** can be considered as pyrazolidindione **4** in which an SO_2 group has been introduced between the two nitrogen atoms. Thiadiazine derivatives **1** and **2** have been chosen because the cyclohexyl moiety seems to be useful for inducing antiinflammatory activity (4–6). Thus, whilst 1,2-dicyclohexyl pyrazole derivatives have shown some activity (7), the corresponding cyclopentyl compounds turned out to be inactive (8).



1 R = C_6H_{11}, R′ = H
2 R = C_6H_{11}, R′ = *n*-C_4H_9
3 R = C_6H_5, R′ = *n*-C_4H_9



SCHEME 1

Results and discussion

Synthesis, nmr data and pK_a values

Compound **2** was prepared from *N*,*N*′-dicyclohexylsulfamide and *n*-butylmalonyl chloride following the procedure used to prepare **1** (2).

The ^1H nmr data of compounds **1**, **2**, and **3** can be found in the experimental part. The assignments have been made by chemical correlation and signal multiplicity. The spectrum of compound **1** at 300 MHz shows the signals belonging to the protons of the cyclohexyl moieties separated in six multiplets. It was therefore possible to assign most of these signals on the basis of their multiplicity and coupling constants. The multiplet, a triplet of triplets, appearing at lower field ($J_{1'a,2'a}$ = 12.36 Hz, $J_{1'a,2'e}$ = 3.85 Hz) corresponds to H1′a indicating that the heterocyclic rest is, as expected, in the equatorial position. The following signal that corresponds to H2′a, appears as a double quartet indicating that J_{gem}, $J_{H2'a,H1'a}$, and $J_{H2'a,H3'a}$ have very close values ($J \sim |12|$ Hz). In this way, the signals corresponding to the other axial protons appear like a triplet of quartets and the signals corresponding to the equatorial protons as distorted doublets ($J_{gem} = \sim -12$ Hz, and $2.5 < J_{e,e}, J_{a,e} < 4$ Hz).

The ^{13}C nmr data of compounds **1**, **2**, **3**, and phenylbutazone (**4**) (9) are gathered in Table 1.

The effect of an SO_2 group on ^{13}C nmr chemical shift can be evaluated by comparing the data of thiadiazine derivatives **1**, **2**, **3**, and those of phenylbutazone (**4**). Thus, the signal belonging to the equivalent C3 and C5 is shifted to lower field (~5 ppm) in phenylbutazone, whilst the C4 signal is shifted to higher field (~6 ppm) as can be seen from the data of **3** and **4**. The signals corresponding to the *ortho*, *meta*, and *para* carbons of phenylbutazone are separated from each other about 3 ppm, whilst in compound **3** they appear with a difference of 0.3 ppm, the one corresponding to the *p*-carbon atom being that appearing at lower field.

The pK_a values (water) were measured using the spectrophotometric method and the data are shown in Table 2.

The substitution of a C—H (**1**) by a C-*n*-butyl group (**2**) slightly affects the acidity (+0.16 pK_a units), taking into account the statistical effect (10). On the other hand, the pK_a variation between compounds **3** and **4** can be explained by

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TABLE 1. ^{13}C nmr chemical shifts[a] (δ ppm) of **1**, **2**, **3**, and phenylbutazone (**4**) (9)

	δ									
Compd.[b]	C3,C5	C4	C1′	C2′	C3′	C4′	C7	C8	C9	C10
1	163.1	45.1	57.8	29.9	25.8	24.6	—	—	—	—
2	165.1	51.8	58.4	29.9	25.8	24.7	28.6	25.1	22.2	13.6
3	164.8	51.5	132.0	129.6[c]	128.9[c]	130.1	28.8	24.7	22.2	13.6
4	169.9	45.6	135.8	122.3	128.1	125.3	27.0	26.2	21.4	12.9

[a]DMSO-d_6 as solvent.
[b]C3, C4, C5 correspond to the heterocyclic rest, C1′, C2′, C3′, and C4′ to the cyclohexyl or phenyl rings and C7, C8, C9, and C10 to the *n*-butyl moiety.
[c]The assignments may be reversed.

TABLE 2. pK_a values of **1**, **2**, **3**, and phenylbutazone (**4**)

Compound	pK_{a_1}
1	6.04±0.11
2	6.18±0.06
3	3.92±0.04
4	4.42±0.10

the electron-withdrawing effect of the SO_2 group. The strong variation of the pK_a values between the two dicyclohexyl derivatives and the diphenyl derivative **3** is not easily explained. In related barbiturates, the presence of monooxo or dioxo tautomer forms in the salt formation accounts for changes in the pK_a values (11). However, in thiadiazine derivatives **1**, **2**, and **3** the variation in pK_a values cannot be due to the existence of different tautomers since their uv spectra are very similar and the ^1H nmr spectra of the three compounds show only the signal corresponding to the CH tautomers (dioxo form). Despite the fact that electronic and steric effects of substituents cause changes in pK_a values in barbituric acid derivatives (12), these effects do not seem to be enough to account for such strong variations in the pK_a values of the thiadiazines.

X-ray discussion

The crystal structures of **2** and **3** have been determined by single crystal X-ray diffraction techniques. Figures 1 and 2 are perspective drawings of their final X-ray models (13). A list of bond lengths and bond angles is given in Tables 3 and 4, which compare well with other thiadiazine compounds (1, 14–20), taking into account the different location of the double bonds within these molecules.

The thiadiazine rings of both compounds present boat conformations (21), $\phi 2$ = 179.8(3) and $\theta 2$ = 93.2(3) for **2**, $\phi 2$ = 0.0(2) and $\theta 2$ = 89.2(2) for **3**, with the C4 and S atoms at the flaps (see also Table 5). These structures, together with another one reported previously (22), are examples of thiadiazine rings showing boat conformations. The best planes of the cyclohexyl rings in **2** (C22, C23, C25, C26 and C62, C63, C65, C66) form similar angles, 88(1)°, with the best plane of the thiadiazine ring. The phenyl rings in **3** are also symmetrically oriented with respect to the best plane of the thiadiazine ring and make an angle of 95(1)° with it. This symmetrical orientation of the substituted rings does not occur in the analogue compound phenylbutazone (23), where the two phenyl rings make angles of ~60° and ~40°, respectively, with the main ring, this situation occurring in the two crystallographically independent molecules. The other structural difference of phenylbutazone is

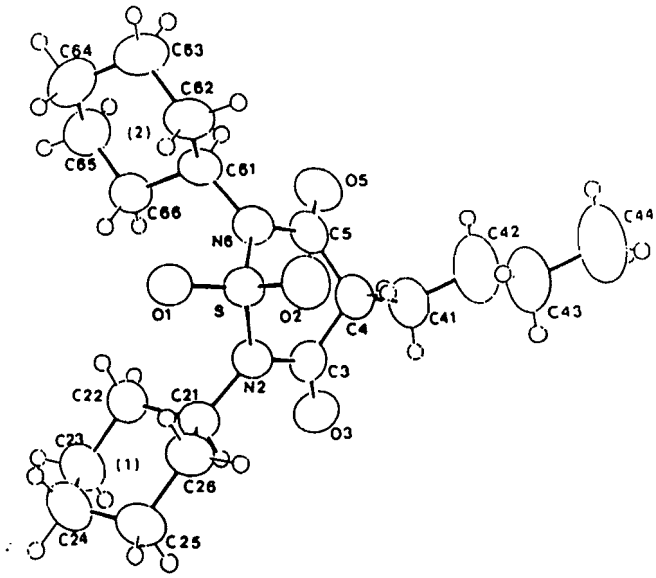

FIG. 1. A perspective view of molecule **2**.

the lack of planarity around its nitrogen atoms, which is not observed in **2** and **3**. Thus, the incorporation of the SO_2 group to phenylbutazone to produce the present thiadiazine derivatives plays an important role in determining the final molecular geometry.

The conformation of the thiadiazine rings in **2** and **3** described above causes the H-atom bonded to C4 to get near to one of the oxygen atoms of the SO_2 group (Fig. 3). In compound **2** (pK_a = 6.18) the distance H4...O2 = 2.48 Å is less than in compound **3** (2.70 Å, pK_a = 3.92). The contact H4...O2 cannot be considered as a typical hydrogen bond, but it indicates (24) a certain attractive interaction, that produces a major structural fixation of the H4 atom in **2**.

Biological results

The antipyretic, analgesic, and antiinflammatory activity of thiadiazines **1**, **2**, and **3** has been evaluated. The preliminary results are shown in Table 6.

Compound **3**, closely related with phenylbutazone, shows an antiinflammatory activity similar to this compound, whilst **1** and **2** present much lower activity. Compound **2** presents a remarkable analgesic activity and this result is the only one that is statistically significant.

There seems to be a correlation between the pK_a values and the antiinflammatory activity since the two more active compounds are also the more acidic.

In previous reports (25, 26) a relationship between the carbon

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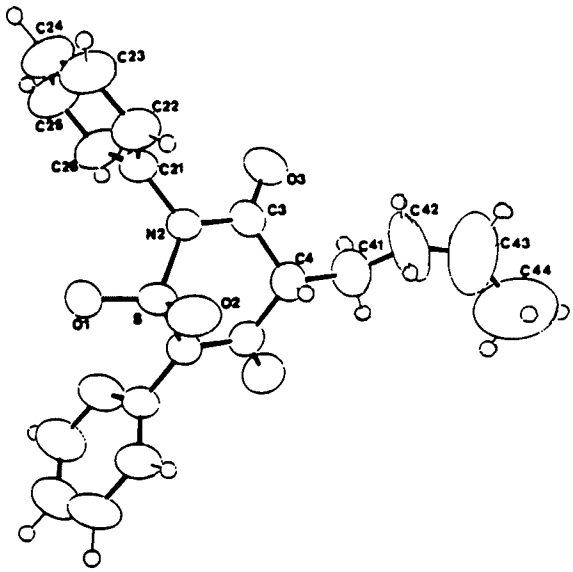

FIG. 2. A perspective view of molecule **3**. A crystallographic mirror plane passes through O1, O2, S, C4, and C41. Atoms C42, C43, and C44 are disordered.

TABLE 3. Bond lengths (Å) and bond angles (deg) for **2** with standard deviations in parentheses

Bond	Length	Bond	Length
S—O1	1.411(3)	C21—C26	1.521(6)
S—O2	1.422(3)	C22—C23	1.527(7)
S—N2	1.649(3)	C23—C24	1.527(8)
S—N6	1.653(4)	C24—C25	1.504(7)
O3—C3	1.207(5)	C25—C26	1.529(7)
O5—C5	1.209(6)	C41—C42	1.444(8)
N2—C3	1.399(6)	C42—C43	1.43 (1)
N2—C21	1.505(5)	C43—C44	1.44 (1)
N6—C5	1.395(6)	C61—C62	1.515(6)
N6—C61	1.492(5)	C61—C66	1.515(6)
C3—C4	1.519(6)	C62—C63	1.525(6)
C4—C5	1.516(6)	C63—C64	1.518(8)
C4—C41	1.530(7)	C64—C65	1.517(8)
C21—C22	1.519(5)	C65—C66	1.519(7)

Bonds	Angle	Bonds	Angle
N2—S—N6	101.0(2)	O5—C5—N6	121.0(4)
O2—S—N6	108.9(2)	N2—C21—C26	113.1(3)
O2—S—N2	109.2(2)	N2—C21—C22	112.4(3)
O1—S—N6	109.0(2)	C22—C21—C26	111.9(4)
O1—S—N2	108.4(2)	C21—C22—C23	109.1(4)
O1—S—O2	118.9(2)	C22—C23—C24	111.3(4)
S—N2—C21	122.8(3)	C23—C24—C25	111.2(4)
S—N2—C3	118.2(3)	C24—C25—C26	111.8(4)
C3—N2—C21	119.1(3)	C21—C26—C25	108.6(3)
S—N6—C61	122.3(3)	C4—C41—C42	116.1(5)
S—N6—C5	118.0(3)	C41—C42—C43	125.1(6)
C5—N6—C61	119.7(3)	C42—C43—C44	119.7(7)
O3—C3—N2	120.7(4)	N6—C61—C66	112.3(3)
N2—C3—C4	115.6(3)	N6—C61—C62	113.2(3)
O3—C3—C4	123.7(4)	C62—C61—C66	112.3(3)
C3—C4—C41	111.8(4)	C61—C62—C63	109.0(4)
C3—C4—C5	110.7(3)	C62—C63—C64	110.8(4)
C5—C4—C41	112.6(4)	C63—C64—C65	111.4(5)
N6—C5—C4	115.9(4)	C64—C65—C66	110.9(4)
O5—C5—C4	123.1(4)	C61—C66—C65	109.3(4)

TABLE 4. Bond lengths (Å) and bond angles (deg) for **3** with standard deviations in parentheses

Bond	Length	Bond	Length
S—O1	1.414(3)	C21—C26	1.369(4)
S—O2	1.420(3)	C22—C23	1.398(6)
S—N2	1.658(2)	C23—C24	1.363(7)
O3—C3	1.197(4)	C24—C25	1.365(6)
N2—C3	1.396(4)	C25—C26	1.375(6)
N2—C21	1.454(3)	C41—C42	1.47 (1)
C3—C4	1.517(4)	C42—C43	1.36 (3)
C4—C41	1.499(7)	C43—C44	1.40 (4)
C21—C22	1.367(4)		

Bonds	Angle	Bonds	Angle
N2—S—N2′	101.1(7)	N2—C21—C26	118.9(2)
O2—S—N2	109.3(1)	N2—C21—C22	120.1(3)
O1—S—N2	108.2(1)	C22—C21—C26	121.0(3)
O1—S—O2	119.2(2)	C21—C22—C23	118.2(3)
S—N2—C21	117.1(2)	C22—C23—C24	120.9(4)
S—N2—C3	121.1(2)	C23—C24—C25	119.8(4)
C3—N2—C21	121.6(2)	C24—C25—C26	120.2(4)
O3—C3—N2	120.4(3)	C21—C26—C25	120.0(3)
N2—C3—C4	115.1(2)	C4—C41—C42	115.6(5)
O3—C3—C4	124.5(2)	C41—C42—C43	120 (2)
O3—C4—C41	114.1(1)	C42—C43—C44	127 (2)

TABLE 5. Intracyclic torsional angles for **2** and **3** with standard deviations in parentheses

2		**3**	
Bonds	Angle	Angle	Bonds
S—N2—C3—C4	−2.6(5)	0.3(4)	S—N2—C3—C4
N2—C3—C4—C5	−48.4(5)	47.4(4)	N2—C3—C4—C3′
C3—C4—C5—N6	48.4(5)	−47.4(4)	C3—C4—C3′—N2′
C4—C5—N6—S	2.8(5)	−0.3(4)	C4—C3′—N2′—S
C5—N6—S—N2	−47.3(3)	40.5(1)	C3′—N2′—S—N2
N6—S—N2—C3	47.2(3)	−40.5(1)	N2′—S—N2—C3

chemical shifts of the biological active center and hypnotic activity in barbituric acid derivatives and analgesic activity in antipyrine derivatives has been described. No relationship seems to exist between the chemical shifts of C4 and the biological activities of compounds **1**, **2**, **3**, and **4**, since the pairs of compounds with similar C4 chemical shifts (**1** and **4**, **2** and **3**) do not have similar activities. No more correlations have been made due to the few data available.

Although the antiinflammatory activity found in compound **3** seems to indicate that the parallelism between pyrazole and thiadiazine derivatives (1) exists also in what biological activities are concerned, the high toxicity of **3** and the not very significant activities of **1** and **2** do not encourage further development.

Experimental

Melting points were determined in a Kofler apparatus and are uncorrected. ^{1}H nmr spectra were recorded at 90 MHz on a Varian EM-390 or at 300 MHz on a Varian XL-300 spectrometers. ^{13}C nmr spectra were recorded at 20.15 MHz on a Bruker WP-80 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophoto-

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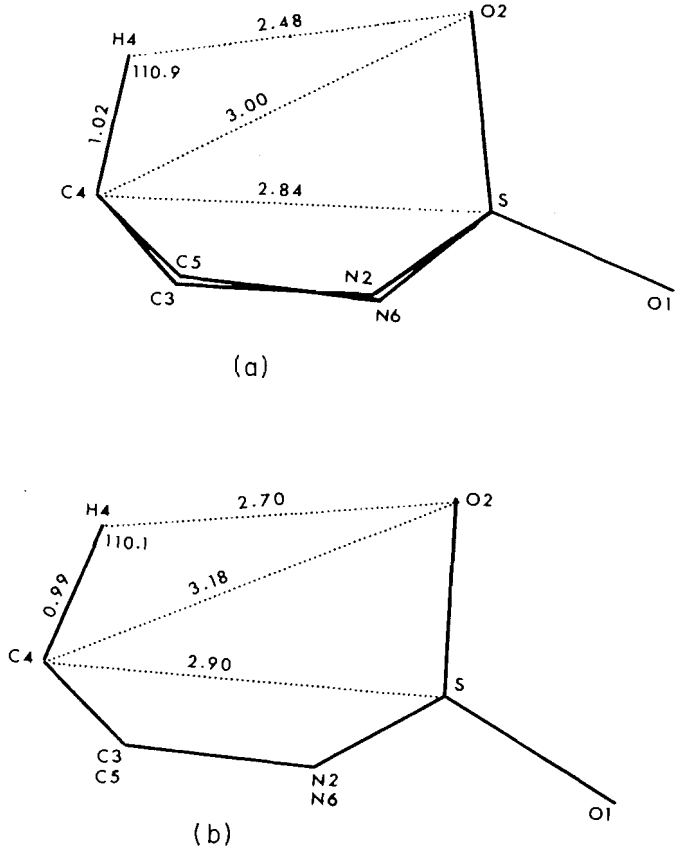

FIG. 3. Projection of a fragment of the molecule onto a plane normal to the best ring plane: (*a*) for **2**, (*b*) for **3**.

TABLE 6. Antipyretic (AP), analgesic (AN), antiinflammatory (AI) activities (in %) and LD_{50} of thiadiazines

Compound[a]	AP[b]	AN[c]	AI[d]	LD_{50} (mg/kg)
1	55	41	30	300–1000
2	28	67[e]	10	300–1000
3	—	—	100	100
4	—	—	100	500

[a]All compounds have been tested at the same dose as the standard.
[b]Aminopyrine as standard (100% activity, dose 50 mg/kg).
[c]Acetylsalicylic acid as standard (100% activity, dose 100 mg/kg).
[d]Phenylbutazone (**4**) as standard (100% activity, dose 50 mg/kg).
[e]Significant difference: $0.02 < p < 0.05$.

meter. Ultraviolet spectra were registered on a Perkin-Elmer 402 spectrophotometer.

Crystal data for **2** are as follows:

$C_{19}H_{32}N_2O_4S$ m.w. = 384.53
Triclinic, $P\bar{1}$, a = 11.45(1), b = 15.678(2), c = 5.7669(2) Å, α = 90.22(1), β = 99.35(2), γ = 93.62(1), Z = 2, V = 1019.4(2) Å^3, D_x = 1.25 Mg m^{-3}, μ(CuKα) = 1.58 mm^{-1}, F(000) = 416.

Crystal data for **3** are as follows:

$C_{19}H_{20}N_2O_4S$ m.w. = 372.23
Orthorhombic, *Pnma*, a = 9.9891(3), b = 13.3077(4), c = 13.9982(2) Å, Z = 4, V = 1860.8(1) Å^3, D_x = 1.32 Mg m^{-3}, μ(CuKα) = 1.56 mm^{-1}, F(000) = 784.

Needle shaped colourless crystals, mounted on a PW1100 four circle diffractometer. Intensities were recorded in the $\omega/2\theta$ scan mode with θ between 2° and 65°. Graphite monochromatized CuKα radiation (λ = 1.54178 Å) was used. A total of 3710, for **2**, and 1659, for **3**, independent reflexions were measured, of which 2933 (for **2**) and 1200 (for **3**) were flagged as observed with $I > 2\sigma(I)$. Intensity data were corrected by Lorentz and polarization effects. No absorption correction was applied. Lattice parameters were determined by least-squares fit of the θ values for 45 and 32 reflexions respectively ($15° < \theta < 30°$) measured at 295 K for both positive and negative Bragg angles (gravity centres of the peaks), using only the most accurate circle (ω) of the diffractometer. Scattering factors for neutral atoms and anomalous dispersion corrections for S and O atoms were taken from International tables for X-ray crystallography (27). The structures were solved using MULTAN (28). Atoms C42, C43, and C44 of compound **3** are disordered as they do not lie on the mirror plane passing through O1, O2, S, C4, and C41, and so they have been assigned to a population parameter of 0.5. The structures were refined by full-matrix least-squares analysis using anisotropic temperature coefficients (H atoms as isotropic fixed contributors). All H atoms were located in a difference map, except those attached to C42, C43, and C44 in compound **3** which were calculated geometrically. A convenient weighting scheme of type $w = w_1 w_2$, with $w_1 = k/(a + b|F_o|)^2$ and $w_2 = 1/(c + d \sin\theta/\lambda)$, was used to obtain flat dependence in $\langle w\Delta^2 F\rangle$ vs. $\langle F_o\rangle$ and vs. $\langle \sin\theta/\lambda\rangle$ (29); the coefficients used for **2** are a = 0.9, b = −0.2 for $F_o < 11$, a = 0.3, b = 0 for $F_o > 11$, c = 1.85 and k = 0.6, d = −1.9 for all reflexions; the coefficients used for **3** are a = 1.4, b = −0.2 for $F_o < 12$, a = 0.5, b = 0 for $F_o > 12$, k = 0.4, c = 2.5, d = −5.0 for all reflexions. The unweighted and weighted final R values were 0.066 and 0.080 for **2** and 0.047 and 0.051 for **3**. Most calculations were performed with the XRAY76 System (30). Tables 7 and 8 show the final atomic parameters.[2]

The analgesic activity was tested following the Siegmund, Cadmus, and Lu method (31), using acetylsalicilic acid as standard. The antiinflammatory activity was measured by the Winter method (32)

TABLE 7. Atomic parameters for **2**

Atom	x/a	y/b	z/c	U_{eq}[a]
S	0.0728(1)	0.2489(1)	0.5502(2)	54
O1	0.1948(2)	0.2560(2)	0.5357(5)	60
O2	−0.0110(3)	0.2430(2)	0.3389(5)	78
O3	−0.0826(3)	0.1007(2)	0.9251(6)	74
O5	−0.0930(3)	0.3785(2)	0.9191(6)	79
N2	0.0477(3)	0.1667(2)	0.7167(6)	55
N6	0.0418(3)	0.3288(2)	0.7128(6)	56
C3	−0.0573(4)	0.1617(3)	0.8119(7)	58
C4	−0.1354(4)	0.2363(3)	0.7585(8)	63
C5	−0.0631(4)	0.3207(3)	0.8071(7)	60
C21	0.1334(4)	0.0978(2)	0.7718(7)	54
C22	0.2432(4)	0.1282(3)	0.9437(7)	64
C23	0.3174(5)	0.0521(4)	1.0152(9)	80
C24	0.3486(5)	0.0068(4)	0.8006(10)	84
C25	0.2390(5)	−0.0196(3)	0.6283(8)	72
C26	0.1649(4)	0.0564(3)	0.5532(7)	63
C41	−0.2423(4)	0.2293(4)	0.8873(9)	80
C42	−0.3501(5)	0.2624(6)	0.7659(13)	121
C43	−0.4063(5)	0.2382(5)	0.5326(13)	115
C44	−0.5159(7)	0.2737(8)	0.4341(19)	169
C61	0.1251(4)	0.4056(2)	0.7730(7)	56
C62	0.1581(4)	0.4509(3)	0.5589(7)	65
C63	0.2305(5)	0.5339(3)	0.6378(9)	78
C64	0.3391(5)	0.5166(3)	0.8158(10)	86
C65	0.3052(5)	0.4691(3)	1.0262(9)	79
C66	0.2330(4)	0.3863(3)	0.9494(7)	65

[a]$U_{eq} = (1/3)\Sigma[U_{ij}a_i^* a_j^* a_i a_j \cos(a_i, a_j) \times 10^3]$.

[2]Lists of observed and calculated structure factors, atomic parameters for H-atoms and anisotropic thermal coefficients are included as supplementary material. Complete set of data may be purchased from the Depository of Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Ont., Canada K1A 0S2.

TABLE 8. Atomic parameters for **3**

Atom	x/a	y/b	z/c	U_{eq}[a]
S	0.0349(1)	0.2500(—)	0.1810(1)	52
O1	−0.0153(4)	0.2500(—)	0.0865(2)	68
O2	0.1755(3)	0.2500(—)	0.1958(3)	72
O3	−0.0937(3)	0.0842(2)	0.3788(2)	75
N2	−0.0327(2)	0.1538(1)	0.2388(2)	50
C3	−0.0475(3)	0.1552(2)	0.3379(2)	54
C4	0.0015(5)	0.2500(0)	0.3868(3)	63
C21	−0.0701(3)	0.0665(2)	0.1822(2)	51
C22	0.0252(3)	−0.0012(3)	0.1546(3)	73
C23	−0.0146(5)	−0.0826(3)	0.0981(3)	93
C24	−0.1447(5)	−0.0934(3)	0.0704(3)	89
C25	−0.2379(4)	−0.0247(3)	0.0990(3)	93
C26	−0.2008(3)	0.0556(3)	0.1548(3)	74
C41	−0.0166(8)	0.2500(—)	0.4930(4)	102
C42	0.0865(13)	0.1954(9)	0.5477(6)	145
C43	0.1012(28)	0.2117(25)	0.6431(17)	269
C44	0.1704(26)	0.2906(14)	0.6864(13)	214

[a] $U_{eq} = (1/3)\Sigma[U_{ij}a_i^*a_j^*a_ia_j \cos(a_i, a_j) \times 10^3]$.

with phenylbutazone as standard and the antipyretic activity by the Bianchi method (33) using aminopyrine as standard.

General synthetic method

To a stirred solution of the corresponding *N,N'*-disubstituted sulfamide (0.01 mol) in dry toluene (50 mL) a solution of malonyl or *n*-butylmalonyl chloride (0.01 mol) in dry toluene (10 mL) was added dropwise. The mixture was heated at 50°C for 30 min and then at 70°C for 4 h. On cooling, the resulting solution was evaporated to dryness *in vacuo* and the residue crystallized from ethanol. With this procedure, the following compounds were obtained.

*2,6-Dicyclohexyl-4*H*-1,2,6-thiadiazin-3,5(2*H*,6*H*)-dione 1,1-dioxide (1)*

Yield 70%, mp 152°C (lit. (2) 152°C); uv λ_{max} (MeOH): 213 (ε, 1400), 277 nm (ε, 850); ^{1}H nmr ($CDCl_3$) δ: 1.18 (m, 2H, H4'a, $J_{gem} \sim J_{a,a} = |12|$ Hz), 1.33 (m, 4H, H3'a, $J_{gem} \sim J_{a,a} = |12|$ Hz), 1.66 (m, 2H, H4'e, $J_{gem} = -12.4$ Hz), 1.80[3] (m, 4H, H3'e), 1.85[3] (m, 4H, H2'e), 2.16 (d.q, 4H, H2'a, $J_{gem} \sim J_{1'a,2'a} \sim J_{2'a,3'a} = |12|$ Hz, $J_{2'a,3'e} =$ 3.36 Hz), 3.91 (s, 2H, H4), 4.48 (tt, 2H, H1'a, $J_{1'a,2'a} = 12.36$ Hz, $J_{1'a,2'e} = 3.85$ Hz), ir (Nujol) ν: 1760 cm^{-1} (C=O).

*4-*n*-Butyl-2,6-dicyclohexyl-1,2,6-thiadiazin-3,5-(2*H*,6*H*)-dione 1,1-dioxide (2)*

Yield 66%, mp 96°C; uv λ_{max} (MeOH): 225 (ε, 6650), 291 nm (ε, 3650); ^{1}H nmr ($CDCl_3$) δ: 0.9 (t, 3H, CH_3), 1.0–2.2 (m, 26H, H2', H3', H4', $3CH_2$ butyl moiety), 3.9 (t, 1H, H4, $J = 4.5$ Hz), 4.3 (tt, 2H, H1'a, $J_{1'a,2'a} = 12$ Hz, $J_{1'a,2'e} = 4$ Hz); ir (Nujol) ν: 1700, 1740 cm^{-1} (C=O). *Anal.* calcd. for $C_{19}H_{32}N_2O_4S$: C 59.35, H 8.38, N 7.28; found: C 59.44, H 8.49, N 6.97.

*4-*n*-Butyl-2,6-diphenyl-1,2,6-thiadiazin-3,5-(2*H*,6*H*)-dione 1,1-dioxide (3)*

Yield 65%, mp 177–178°C (lit. (3) 177–178.5°C); uv λ_{max} (MeOH): 215 (ε, 1050), 289 nm (ε, 450); ^{1}H nmr ($CDCl_3$) δ: 1.0 (t, 3H, CH_3), 1.2–1.8 (m, 4H, CH_2-8, CH_2-9), 2.2 (m, 2H, CH_2-7), 4.5 (t, 1H, H4, $J = 6$ Hz), 7.4–7.7 (m, 10H, arom.); ir (Nujol) ν: 1720, 1760 cm^{-1} (C=O).

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[3] Assignments may be reversed.

1. J. ELGUERO, C. OCHOA, M. STUD, C. ESTEBAN-CALDERON, M. MARTINEZ-RIPOLL, J. P. FAYET, and M. C. VERTOUT. J. Org. Chem. **47**, 536 (1982).
2. A. M. PAQUIN. Angew. Chem. **60**, 316 (1948).
3. H. TEUFEL. U.S. Patent 2, 956, 997 (1960).
4. J. GIELDANOWSKI, B. BOBRANSKI, J. DECKERT, and B. SZAGA. Il Farmaco, Ed. Sc. **29**, 81 (1974).
5. H. SLADOWSKA. Il Farmaco, Ed. Sc. **32**, 866 (1977).
6. J. GIELDANOWSKI, B. BOBRANSKI, J. DECKERT, B. SZAGA, and B. TEODOCZYK. Arch. Immun. Ther. Exp. **21**, 517 (1972).
7. E. WAGNER, B. BOBRANSKI, J. KUPRINSKA, B. CEBO, and T. LIBROWSKI. Il Farmaco, Ed. Sc. **35**, 1039 (1980).
8. A. BURGER and R. T. STANDRIDGE. J. Med. Chem. **6**, 221 (1963).
9. S. P. SINGH, S. S. PARMAR, V. I. STENBERG, and S. A. FARNUM. J. Heterocycl. Chem. **15**, 13 (1978).
10. R. P. BELL. The proton in chemistry. Cornell University Press, New York. 1959.
11. M. WOLFF (*Editor*). Burger's medicinal chemistry. John Wiley and Sons, New York. 1981. p. 795.
12. R. H. MC. KEOWN. J. Chem. Soc. Perkin II, 515 (1980).
13. C. K. JOHNSON. ORTEP. Report ORNL-3794. Oak Ridge National Laboratory, TN. 1965.
14. M. D. CABEZUELO, F. H. CANO, C. FOCES-FOCES, and S. GARCIA-BLANCO. Acta Crystallogr. B**33**, 3598 (1977).
15. C. ESTEBAN-CALDERON, M. MARTINEZ-RIPOLL, and S. GARCIA-BLANCO. Acta Crystallogr. B**35**, 2795 (1979).
16. C. ESTEBAN-CALDERON, M. MARTINEZ-RIPOLL, and S. GARCIA-BLANCO. Acta Crystallogr. B**38**, 1128 (1982).
17. C. ESTEBAN-CALDERON, M. MARTINEZ-RIPOLL, and S. GARCIA-BLANCO. Acta Crystallogr. B**38**, 1340 (1982).
18. C. ESTEBAN-CALDERON, M. MARTINEZ-RIPOLL, and S. GARCIA-BLANCO. Acta Crystallogr. B**38**, 2296 (1982).
19. C. ESTEBAN-CALDERON, M. MARTINEZ-RIPOLL, and S. GARCIA-BLANCO. Acta Crystallogr. B**39**, 440 (1983).
20. C. ESTEBAN-CALDERON, M. MARTINEZ-RIPOLL, and S. GARCIA-BLANCO. Acta Crystallogr. B**40**, 80 (1984).
21. D. CREMER and J. A. POPLE. J. Am. Chem. Soc. **97**(6), 1354 (1975).
22. P. BROUANT, M. PIERROT, A. BALDY, C. OCHOA, P. GOYA, J. C. SOYFER, and J. BARBE. Acta Crystallogr. In press.
23. T. P. SINGH and M. VIJAYAN. J. Chem. Soc. Perkin II, 693 (1977).
24. R. TAYLOR and O. KENNARD. J. Am. Chem. Soc. **104**(19), 5063 (1982).
25. J. OKADA and T. ESAKI. Chem. Pharm. Bull. **22**, 1580 (1974).
26. J. OKADA, T. ESAKI, and K. FUJIEDA. Chem. Pharm. Bull. **24**, 61 (1976).
27. International tables for X-ray crystallography. Vol. IV, Birmingham, Kynoch Press. 1974.
28. P. MAIN, S. J. FISKE, S. E. HULL, L. LESSINGER, G. GERMAIN, J. P. DECLERCQ, and M. M. WOOLFSON. MULTAN. A system of computer programs for the automatic solution of crystal structures from X-ray diffraction data. University of York, England and Louvain, Belgium. 1980.
29. M. MARTINEZ-RIPOLL and F. H. CANO. PESOS. A computer program for the automatic treatment of weighting schemes. Instituto Rocasolano, CSIC, Serrano 119, 28006 Madrid, Spain. 1975.
30. J. M. STEWART, F. A. KUNDELL, and J. C. BALDWIN. The XRAY 76 System. Tech. Rep. TR-446. Computer Science Center, University of Maryland, College Park, Maryland. 1976.
31. E. SIEGMUND, R. CADMUS, and G. LU. Proc. Soc. Exp. Biol. Med. **95**, 729 (1957).
32. C. A. WINTER, E. A. RISLEY, and C. W. NUSS. Proc. Soc. Exp. Biol. Med. **111**, 544 (1962).
33. C. BIANCHI, B. LUMACHI, and L. PEGRASSI. Arztneim.-Forsch. **17**, 246 (1967).

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