Reactivity of 4-Amino-2-benzyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-Dioxide towards Amines: Synthesis of Potential Histamine H_2-Receptor Antagonists

Vicente J. Arán,* José R. Ruiz, and Manfred Stud
Instituto de Quimica Médica (C.S.I.C.), Juan de la Cierva 3, 28006 Madrid, Spain

The reaction of the title compound (**1**) with sodium or ammonium hydroxides yielded the corresponding ring-opened derivatives (**2**) and (**3**). Reaction of compound (**1**) with amines afforded, depending on the basicity of the latter and the reaction conditions, products (**4**) or (**6**) resulting from ring opening, and/or the amino-exchange derivatives (**5**). Some of these compounds, containing a furan- or imidazole-derived chain, may be useful as new histamine H_2-receptor antagonists.

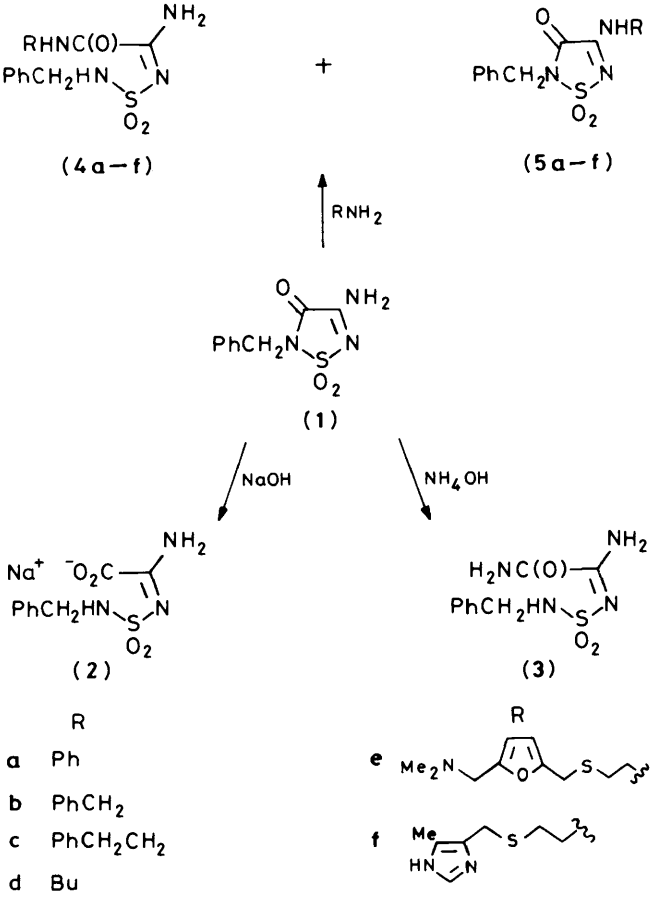
We have recently found[1] a method of synthesis of 2-substituted 4-amino-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxides by ring contraction of 2-substituted tetrahydro-3,5-dioxo-2*H*-1,2,6-thiadiazine 1,1-dioxides. The 1,2,5-thiadiazole ring has been shown to be useful as a 'urea equivalent moiety'[2,3] in the development of new histamine H_2-receptor antagonists.

Results and Discussion

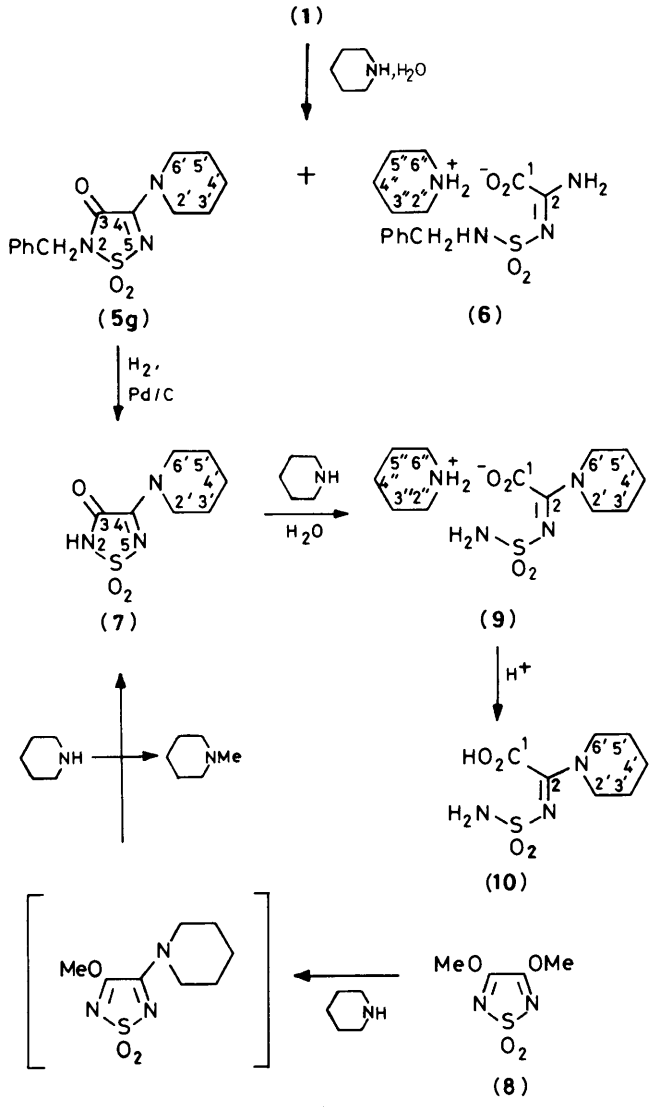
The 3-oxo-1,2,5-thiadiazole ring present in the title compound is very sensitive towards nucleophiles; *e.g.* compound (1) reacted easily at room temperature with aqueous sodium or ammonium hydroxide to yield the corresponding ring-opened derivatives (**2**) and (**3**). Reaction with primary amines in 96% ethanol, depending on their basicity, yielded ring-opening (**4**) and/or amino-exchange (**5**) products. With aniline, only the corresponding amino-exchange derivative (**5a**) was obtained with no trace of the anilide (**4a**), but other amines of intermediate basicity yielded a mixture of both compounds (**4**) and (**5**), which were easily separated by preparative t.l.c. (p.l.c.) (Scheme 1). The more basic piperidine reacted with compound (**1**), with results which depended on the experimental conditions. When the reaction was carried out in water, only the piperidinium salt (**6**) was produced; nevertheless, if anhydrous ethanol was used as solvent, a complex mixture, from which only compound (**5g**) could easily be isolated, was obtained. When moisture was not rigorously excluded from the reaction, the main isolable product was the salt (**6**) and only a small amount of compound (**5g**) was formed (Scheme 2).

The structures of all new compounds have been established on the basis of analytical and spectral data. In the i.r. spectra, compounds (**5**) showed a single NH stretching band [except (**5g**)], and a carbonyl band at *ca.* 1 750 cm^{-1}; compounds (**3**) and (**4**) exhibited a more complex NH stretching zone, and amide carbonyl bands at lower frequencies (1 700—1 725 cm^{-1}). In the ^1H n.m.r. spectra, the characteristic benzylic methylene protons appeared as singlets in compounds (**5**), and at higher field and as doublets (which collapsed to singlets with deuterium oxide) in compounds (**3**) and (**4**). The sodium and piperidinium salts (**2**) and (**6**) did not show carbonyl absorption up to 1 700 cm^{-1}; furthermore, a low-intensity structured broad band at 2 300—3 000 cm^{-1}, which can be attributed to the substituted ammonium ion stretching, is also present in the i.r. spectrum of salt (**6**). In the ^1H n.m.r. spectra of salts (**2**) and (**6**) the behaviour of the benzylic protons is similar to that of compounds (**3**) and (**4**).

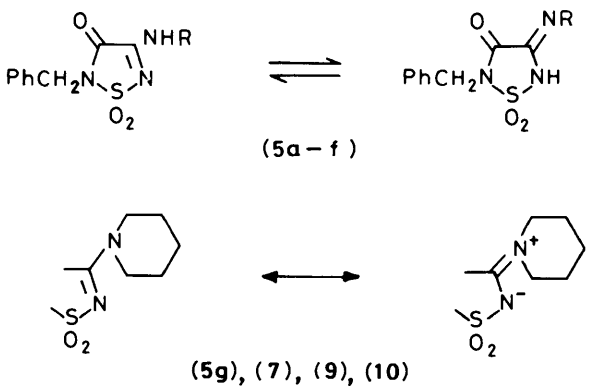
Hydrogenolysis of compound (**5g**) afforded the debenzylated product (**7**), the preparation of which by another procedure has been claimed by Carmack and co-workers.[4] Nevertheless, we think that the compound obtained by these authors from piperidine and 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (**8**) has the open structure (**9**), which results from the reaction of the initially formed compound (**7**) with water and piperidine (Scheme 2). Although the spectral data of compound (**7**) are in agreement with the structure proposed by us, in the i.r. spectrum of the compound prepared by the above mentioned authors there is no carbonyl absorption up to 1 700 cm^{-1}, and therefore it cannot have a cyclic structure as proposed. Furthermore, the structured broad band found in compound (**6**), and attributed to the substituted ammonium ion stretching, is also present in the i.r. spectrum of the salt (**9**). In its ^1H n.m.r. spectrum, signals for two different piperidine rings can be detected. In one of them, the methylene protons adjacent to the nitrogen appear as two different signals [as in compounds (**5g**) and (**7**), see below], and in the other as a single signal at higher field [as in compound



Scheme 1.



Scheme 2.

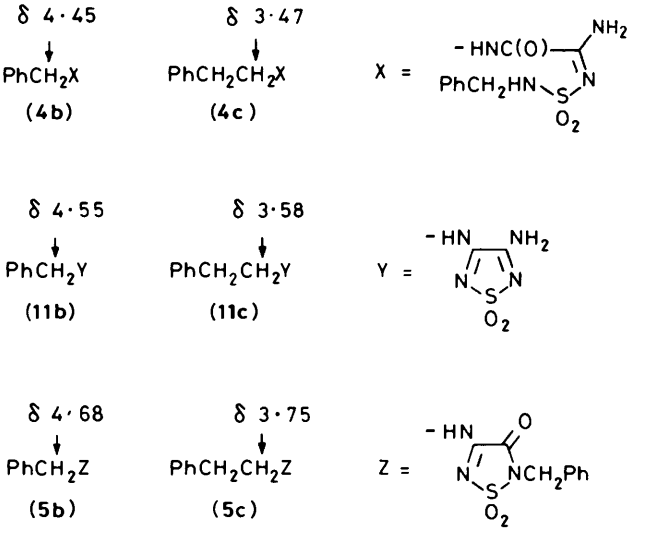


Scheme 3.

(6)]. The ^{13}C n.m.r. spectrum of compound (**9**) also confirms the presence of two piperidine rings. Fragmentation of the salt (**9**) in mass spectrometry is very similar to that of compound (**7**), the apparent molecular peak (*m/z* 217) being the same. As in the case of salt (**6**), easy elimination of water and piperidine must take place in compound (**9**), and then the real molecular peak (*m/z* 302) cannot be detected.

Since compound (**9**) is a very hygroscopic syrup, a satisfactory analysis could not be obtained, either by the above mentioned authors or by us. Nevertheless, treatment of compound (**9**) with a strongly acidic ion-exchange resin afforded the free acid (**10**), which has been completely characterized. Furthermore, compound (**9**) has also been prepared by us from pure compound (**7**) or acid (**10**) and piperidine in water, thus confirming the proposed structure.

A considerable 'imino' character can be attributed to compounds (**5**), having a secondary nitrogen atom bonded to position 4, according to Carmack and co-workers[4] (Scheme 3). Furthermore, compounds (**5g**) and (**7**) showed, in their ^1H n.m.r. spectra, two different signals for the methylene protons adjacent to the piperidine tertiary nitrogen bonded to C-4. ^{13}C N.m.r. spectra of these compounds showed that the five carbon atoms of the piperidine ring are different, thus implying that there is no free rotation through the C-4–N-1′ bond. The rigidity of the linked piperidine ring, also found in the open-chain derivatives (**9**) and (**10**), may be explained by considering the contribution to the structure of these products of the depicted zwitterionic structure (Scheme 3). A similar feature can



be inferred for some related morpholino compounds, also prepared by Carmack and co-workers,[4] according to the reported spectral data. The strong electron-withdrawing properties of the SO_2 group may perhaps explain this behaviour.

On comparison of the chemical shifts of the methylene protons attached to the exocyclic nitrogen atoms in compounds (**5b** and **c**), and in the corresponding amino-exchange derivatives of 3,4-diamino-1,2,5-thiadiazole 1,1-dioxide (**11b** and **c**),[5] a higher electron-withdrawing power can be deduced for the 3-oxo-1,2,5-thiadiazole ring. On the same basis, the electron-withdrawing power of the 3-oxo-1,2,5-thiadiazole ring-opening-derived chain present in compounds (**4**) is only slightly lower than that of the diaminothiadiazole 1,1-dioxide ring. Since the activity of histamine H_2-receptor antagonists depends on the electron-withdrawing power of the 'urea equivalent moiety',[3] compounds (**4e** and **f**) and (**5e** and **f**) may be interesting candidates for gastric acid antisecretory drugs.

Experimental

M.p.s were determined in a Gallenkamp capillary apparatus, and are uncorrected. I.r. spectra were obtained on a Perkin-Elmer 257 spectrophotometer. ^1H N.m.r. spectra were recorded

at 90 MHz on a Varian EM-390 spectrometer, and ^{13}C n.m.r. spectra at 20 MHz on a Bruker WP-80 spectrometer, using tetramethylsilane as internal standard. Atomic numbering used in the description of ^{13}C n.m.r. spectra is given in Scheme 2. Mass spectra were obtained at 70 eV on a VG-12-250 spectrometer. 2-[5-(Dimethylaminomethyl)furfurylthio]ethylamine and 2-[(5-methylimidazol-4-yl)methylthio]ethylamine dihydrochlorides were generous gifts from Dr. J. J. Baldwin (Merck Sharp & Dohme Reserach Laboratories). Free amines were obtained by the literature method.[6]

2-Amino-2-[(N-benzylsulphamoyl)imino]acetic Acid, Sodium Salt (**2**).—A solution of 4-amino-2-benzyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide (**1**) (2.4 g, 0.01 mol) in 2M-sodium hydroxide (25 ml) was stirred for 2 h at room temperature, and then acidified with acetic acid. The precipitated solid was filtered off, and was recrystallized from water to give white crystals (83%), m.p. 236—238 °C (decomp.) (Found: C, 38.8; H, 3.7; N, 15.25; S, 11.2. $C_9H_{10}N_3NaO_4S$ requires C, 38.7; H, 3.6; N, 15.05; S, 11.5%); $\nu_{max.}$(Nujol) 3 420, 3 340, 3 300, 1 675, and 1 625 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 4.02 (2 H, d, CH_2Ph) and 7.32 (5 H, s, Ph).

2-Amino-2-[(N-benzylsulphamoyl)imino]acetamide (**3**).—A mixture of compound (**1**) (1.2 g, 0.005 mol), water (20 ml), and conc. (25%) ammonium hydroxide (4 ml) was stirred for 1 h at room temperature, and then the solid was filtered off, and recrystallized from propan-1-ol to give the *amide* as white plates (71%), m.p. 194—196 °C (decomp.) (Found: C, 42.0; H, 5.0; N, 21.6; S, 12.7. $C_9H_{12}N_4O_3S$ requires C, 42.2; H, 4.7; N, 21.9; S, 12.5%); $\nu_{max.}$(Nujol) 3 440, 3 400, 3 330, 3 240, 1 725, 1 690, and 1 620 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 4.13 (2 H, d, CH_2Ph) and 7.30 (5 H, s, Ph).

N-Substituted 2-Amino-2-[(N-benzylsulphamoyl)imino]-acetamides (**4b—f**), *and 4-Substituted 2-Benzyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-Dioxides* (**5b—f**).—A mixture of compound (**1**) (1.2 g, 0.005 mol) and ethanol (10 ml) was slightly warmed until solution, and then a solution of an excess (0.006 mol) of the corresponding amine in the same solvent (5 ml) was added. The solution was stirred until a solid crystallized out, and then the mixture was kept at room temperature overnight. The solid was filtered off and was shown to be a mixture of compounds (**4**) and (**5**) which were separated by p.l.c. on silica-gel, with chloroform–ethanol mixtures as developing solvent. The preparation of compounds (**4e** and **f**) and (**5e** and **f**) was carried out with 0.001 mol of each reagent, and the reaction mixture was directly applied onto the preparative plates. Yields are given in Table 1. M.p.s and analytical data are in Table 2 [compounds (**4**)] and Table 3 [compounds (**5**)]. ^1H N.m.r. and i.r. spectral data are in Table 4 [compounds (**4**)] and Table 5. [compounds (**5**)].

$\delta_C[(CD_3)_2SO]$ (**4c**) 34.62 (t, CH_2CH_2Ph), 40.79 (t, CH_2CH_2Ph), 46.39 (t, $NHCH_2Ph$), 126.18 (d), 127.02 (d), 127.67 (d), 128.15 (d), 128.33 (d), 128.55 (d), 138.14 (s), and 138.95 (s) (Ph), and 152.54 and 159.49 [both s, C-2 and -1 (or *vice versa*)]; (**5c**) 33.15 (t, CH_2CH_2Ph), 44.03 (t, CH_2CH_2Ph and $NHCH_2Ph$), 126.41 (d), 127.99 (d), 128.42 (d), 128.51 (d), 134.37 (s), and 138.12 (s) (Ph), and 154.45 and 155.50 [both s, C-3 and -4 (or *vice versa*)]; *m/z* (**4c**) 360 (M^+, 2%), 269 ($M^+ - SO_2$, 15), 190 (45), 106 (29), 105 (25), 104 (47), 100 (17), 91 (100), 77 (16), and 65 (14); (**5e**) 436 (M^+, 3%), 421 (2), 392 (3), 391 (3), 238 (3), 169 (3), 138 (82), 137 (100), 125 (14), 124 (20), 110 (28), 94 (34), 91 (82), 81 (7), and 65 (9).

Reaction of Compound (**1**) *with Piperidine.*—(a) *In water.* To a solution of piperidine (1.28 g, 0.015 mol) in water (50 ml) was slowly added compound (**1**) (2.4 g, 0.01 mol). The mixture was stirred until solution, and then evaporated to dryness. The residue was recrystallized from propan-1-ol, and was shown to be *2-amino-2-[(N-benzylsulphamoyl)imino]acetic acid, piperidinium salt* (**6**) as white plates (93%), m.p. 138—140 °C (decomp.) (Found, C, 49.3; H, 6.4; N, 16.3; S, 9.7. $C_{14}H_{22}N_4O_4S$ requires C, 49.1; H, 6.5; N, 16.4; S, 9.4%); $\nu_{max.}$(Nujol) 3 310, 3 080, 2 620, 2 520, 2 420, and 1 625 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.60 (6 H, br s, $C[CH_2]_3C$), 3.17 (4 H, br s, CH_2NCH_2), 4.00 (2 H, d, CH_2Ph), and 7.30 (5 H, m, Ph); $\delta_C[(CD_3)_2SO]$ 21.87 (t, C-4″), 22.16 (t, C-3″ and -5″), 43.65 (t, C-2″ and -6″), 46.27 (t, CH_2Ph), 126.90 (d), 127.56 (d), 128.10 (d), and 138.45 (s) (Ph), and 159.77 and 162.81 [both s, C-2 and -1 (or *vice versa*)]; *m/z* 239 ($M^+ - C_5H_{11}N - H_2O$, 0.5%), 175 (4), 107 (28), 106 (53), 91 (21), 85 (53), 84 (100), 77 (21), 70 (14), and 56 (63).

(b) *In ethanol.* A mixture of compound (**1**) (2.4 g, 0.01 mol) and 96% ethanol (25 ml) was slightly warmed until solution, and then piperidine (0.85 g, 0.01 mol) was added. The reaction

Table 1. Yield of compounds (**4a—f**) and (**5a—f**)

Compounds	Mol fraction of (**4**)	Mol fraction of (**5**)	Overall yield (%)
a	0.00	1.00	95
b	0.26	0.74	68
c	0.46	0.54	82
d	0.57	0.43	93
e	0.62	0.38	65
f	0.58	0.42	69

Table 2. M.p. and analytical data of compounds (**4b—f**)

Name	Molecular formula	M.p. (°C) (solvent)	Found (%) (Required) C	H	N	S
(**4b**) 2-Amino-*N*-benzyl-2-[(*N*-benzylsulphamoyl)-imino]acetamide	$C_{16}H_{18}N_4O_3S$	129—131 (propan-1-ol)	55.6 (55.5)	5.5 (5.2)	16.5 (16.2)	9.2 (9.3)
(**4c**) 2-Amino-2-[(*N*-benzylsulphamoyl)imino]-*N*-phenethylacetamide	$C_{17}H_{20}N_4O_3S$	123—125 (propan-1-ol)	56.6 (56.7)	5.6 (5.6)	15.6 (15.5)	8.9 (8.9)
(**4d**) 2-Amino-2-[(*N*-benzylsulphamoyl)imino]-*N*-butylacetamide	$C_{13}H_{20}N_4O_3S$	115—117 (propan-1-ol)	49.9 (50.0)	6.2 (6.45)	17.9 (17.9)	10.0 (10.3)
(**4e**) 2-Amino-2-[(*N*-benzylsulphamoyl)imino]-*N*-{2-[5-(dimethylaminomethyl)furfurylthio]-ethyl}acetamide	$C_{19}H_{27}N_5O_4S_2$	glass[a]	50.1 (50.3)	6.1 (6.0)	15.1 (15.4)	14.0 (14.1)
(**4f**) 2-Amino-2-[(*N*-benzylsulphamoyl)imino]-*N*-{2-[(5-methylimidazol-4-yl)methylthio]-ethyl}acetamide	$C_{16}H_{22}N_6O_3S_2$	glass[a]	46.6 (46.8)	5.7 (5.4)	20.7 (20.5)	15.6 (15.6)

[a] These compounds were purified by p.l.c., with chloroform–ethanol mixtures as the developing solvent.

Table 3. M.p. and analytical data of compound (**5a—g**)

Name	Molecular formula	M.p. (°C) (solvent)	Found (%) (Required) C	H	N	S
(**5a**) 4-Anilino-2-benzyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide	$C_{15}H_{13}N_3O_3S$	210—212 (propan-1-ol)	57.4 (57.1)	4.4 (4.2)	13.6 (13.3)	10.2 (10.2)
(**5b**) 2-Benzyl-4-benzylamino 2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide	$C_{16}H_{15}N_3O_3S$	174—176 (propan-1-ol)	58.2 (58.35)	4.85 (4.6)	12.8 (12.8)	9.9 (9.7)
(**5c**) 2-Benzyl-2,3-dihydro-3-oxo-4-phenethylamino-1,2,5-thiadiazole 1,1-dioxide	$C_{17}H_{17}N_3O_3S$	195—197 (propan-1-ol)	59.6 (59.5)	4.9 (5.0)	12.1 (12.2)	9.2 (9.3)
(**5d**) 2-Benzyl-4-butylamino-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide	$C_{13}H_{17}N_3O_3S$	145—147 (propan-1-ol)	52.8 (52.9)	5.75 (5.8)	14.2 (14.2)	11.1 (10.85)
(**5e**) 2-Benzyl-4-{2-[5-(dimethylaminomethyl)furfurylthio]-ethylamino}-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide	$C_{19}H_{24}N_4O_4S_2$	106—108[a]	52.4 (52.3)	5.7 (5.5)	12.7 (12.8)	14.4 (14.7)
(**5f**) 2-Benzyl-4-{2-[(5-methylimidazol-4-yl)methylthio]ethylamino}-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide	$C_{16}H_{19}N_5O_3S_2$	136—138[a]	48.7 (48.8)	4.6 (4.9)	17.6 (17.8)	16.5 (16.3)
(**5g**) 2-Benzyl-2,3-dihydro-3-oxo-4-piperidino-1,2,5-thiadiazole 1,1-dioxide	$C_{14}H_{17}N_3O_3S$	129—131 (propan-1-ol)	54.5 (54.7)	5.6 (5.6)	13.6 (13.7)	10.4 (10.4)

[a] These compounds were purified by p.l.c., with chloroform–ethanol mixtures as the developing solvent.

Table 4. I.r. and ^{1}H n.m.r. spectral data of compounds (**4b—f**)

	$\nu_{max.}$(Nujol)/cm^{-1}	δ_H[a]
(**4b**)	3 420, 3 330, 3 280, 1 710, and 1 625	[$(CD_3)_2CO$] 4.23 (2 H, s, CH_2NHSO_2), 4.45 (2 H, s, CH_2NHCO), and 7.30 (10 H, m, Ph)
(**4c**)	3 450, 3 320, 3 300, 1 705, and 1 630	[$(CD_3)_2CO$] 2.85 (2 H, t, CH_2CH_2Ph), 3.47 (2 H, t, CH_2CH_2Ph), 4.20 (2 H, s, $NHCH_2Ph$), and 7.30 (10 H, m. Ph)
(**4d**)	3 440, 3 320, 3 270, 1 700, and 1 615	[$(CD_3)_2CO$] 0.92 (3 H, t, Me), 1.1—1.8 (4 H, m, $[CH_2]_2Me$), 3.25 (2 H, t, CH_2NHCO), 4.23 (2 H, s, CH_2Ph), and 7.33 (5 H, m, Ph)
(**4e**)	3 420, 3 290, 1 705, and 1 630	[$(CD_3)_2CO$] 2.20 (6 H, s, NMe_2), 2.67 (2 H, t, CH_2CH_2S), 3.42 (2 H, s, NCH_2Fu), 3.52 (2 H, t, CH_2CH_2N), 3.80 (2 H, s, SCH_2Fu), 4.25 (2 H, s, CH_2Ph), 6.22 (2 H, q, Fu), and 7.33 (5 H, m, Ph)
(**4f**)	3 400, 3 290, 1 700, and 1 635	[$(CD_3)_2SO$] 2.10 (3 H, s, Im*Me*), 2.52 (2 H, t, CH_2CH_2N), 3.42 (2 H, t, CH_2CH_2N), 3.67 (2 H, s, CH_2Im), 4.10 (2 H, s, CH_2Ph), 7.16 (5 H, s, Ph), and 7.39 (1 H, s, Im)

[a] These spectra have been simplified by addition of deuterium oxide to the solvent, to eliminate N*H*–C*H* coupling; NH protons signals are not indicated.

Table 5. I.r. and ^{1}H n.m.r. spectral data of compounds (**5a—g**)

	$\nu_{max.}$(Nujol)/cm^{-1}	δ_H[a]
(**5a**)	3 280, 1 740, and 1 645	[$(CD_3)_2CO$] 4.88 (2 H, s, CH_2Ph) and 7.63 (10 H, m, Ph)
(**5b**)	3 325, 1 750, and 1 660	[$(CD_3)_2CO$] 4.68 (2 H, s, $NHCH_2Ph$), 4.82 (2 H, s, NCH_2Ph), and 7.40 (10 H, m, Ph)
(**5c**)	3 340, 1 760, and 1 675	[$(CD_3)_2CO$] 3.03 (2 H, t, CH_2CH_2Ph), 3.75 (2 H, t, CH_2CH_2Ph), 4.80 (2 H, s, NCH_2Ph), and 7.30 (10 H, m, Ph)
(**5d**)	3 310, 1 755, and 1 670	[$(CD_3)_2CO$] 0.95 (3 H, t, Me), 1.2—1.9 (4 H, m, $[CH_2]_2Me$), 3.50 (2 H, t, $NHCH_2CH_2$), 4.83 (2 H, s, CH_2Ph), and 7.38 (5 H, m, Ph)
(**5e**)	3 320, 1 750, and 1 675	[$(CD_3)_2CO$] 2.18 (6 H, s, NMe_2), 2.85 (2 H, t, CH_2CH_2S), 3.38 (2 H, s, NCH_2Fu), 3.62 (2 H, t, CH_2CH_2N), 3.80 (2 H, s, SCH_2Fu), 4.82 (2 H, s, CH_2Ph), 6.20 (2 H, q, Fu), and 7.37 (5 H, m, Ph)
(**5f**)	3 320, 1 750, and 1 670	[$(CD_3)_2SO$] 2.12 (3 H, s, Im*Me*), 2.70 (2 H, t, CH_2CH_2S), 3.52 (2 H, t, CH_2CH_2N), 3.67 (2 H, s, CH_2Im), 4.80 (2 H, s, CH_2Ph), 7.33 (5 H, s, Ph), and 7.55 (1 H, s, Im)
(**5g**)	1 735 and 1 630	[$(CD_3)_2CO$] 1.72 (6 H, br s, $C[CH_2]_3C$), 3.77 and 4.40 (both 2 H, and br s, CH_2NCH_2], 4.73 (2 H, s, CH_2Ph), and 7.35 (5 H, m, Ph)

[a] NH Protons appeared as very broad signals at δ_H 8.5—9.5, and are not included in the Table.

mixture was kept for 4 days at room temperature, and then compound (**6**), which had precipitated, was filtered off and recrystallized as above (yield 62%). The filtrate was chromatographed on a silica-gel column, with chloroform as eluant. The first eluted product was *2-benzyl-2,3-dihydro*-3-oxo-4-*piperidino*-1,2,5-*thiadiazole* 1,1-*dioxide* (**5g**), as white plates (9%). M.p. and analytical data are in Table 3. ^{1}H N.m.r. and i.r. spectral data are in Table 5.

δ_C[$(CD_3)_2SO$] 22.97 (t, C-4′), 24.96 and 25.64 [both t, C-3′ and -5′ (or *vice versa*)], 44.09 (t, CH_2Ph), 46.93 and 48.78 [both t, C-2′ and -6′ (or *vice versa*)], 127.76 (d), 128.13 (d), 128.32 (d), and 134.48 (s) (Ph), and 153.37 and 155.00 [both s, C-3 and -4 (or *vice versa*)]; *m/z* 307 (M^+, 22%), 243 ($M^+ - SO_2$, 7), 216 (9), 152 (100), 111 (21), 109 (14), 97 (13), 91 (61), 85 (15), 84 (26), 83 (71), and 69 (29). If anhydrous ethanol was used as solvent, only compound (**5g**) could be isolated (22%).

4-Anilino-2-benzyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-Dioxide (**5a**).—A solution of compound (**1**) (2.4 g, 0.01 mol) and aniline (1.0 g, 0.011 mol) in ethanol (20 ml) was refluxed for 5 h, and then cooled. The crystallized solid was filtered off, and was shown to be pure (**5a**). See Tables 1, 3, and 5 for yield, m.p., and analytical and spectral data. *m/z* 315 (M^+, 88%), 251 ($M^+ - SO_2$, 43), 132 (22), 120 (24), 119 (61), 118 (61), 104 (22), 93 (31), 92 (39), 91 (100), 77 (59), and 65 (57).

Hydrogenolysis of Compound (**5g**) *to* 2,3-*Dihydro*-3-*oxo*-4-*piperidino*-1,2,5-*thiadiazole* 1,1-*Dioxide* (**7**).—A solution of compound (**5a**) (0.31 g, 0.001 mol) in ethanol (50 ml) was treated with hydrogen (35 p.s.i.), in the presence of 10% palladium–carbon catalyst, at room temperature. After 4 h, the catalyst was removed and the resulting solution was evaporated to dryness under reduced pressure. The residue was purified by p.l.c. on silica-gel, with a 7:3 mixture of chloroform and ethanol, to yield *compound* (**7**) as a thick oil (85%) (Found: C, 38.5; H, 5.2; N, 19.6; S, 15.0. $C_7H_{11}N_3O_3S$ requires C, 38.7; H, 5.1; N, 19.3; S, 14.8%); $\nu_{max.}$(Nujol) 3 500, 3 150, 1 740, and 1 625 cm^{-1};

$\delta_H[(CD_3)_2CO]$ 1.73 (6 H, br s, $C[CH_2]_3C$), 3.73 and 4.37 (both 2 H, and br s, CH_2NCH_2), and 6.88 (1 H, br s, NH, exchangeable); $\delta_C[(CD_3)_2SO]$ 23.01 (t, C-4′), 24.98 and 25.80 [both t, C-3′ and -5′ (or *vice versa*)], 46.54 and 48.79 [both t, C-2′ and -6′ (or *vice versa*)], and 154.00 and 157.51 [both s, C-3 and -4 (or *vice versa*)]; *m/z* 217 (M^+, 30%) 153 ($M^+ - SO_2$, 36), 124 (15), 109 (16), 98 (9), 83 (100), and 55 (27).

2-*Piperidino*-2-(*sulphamoylimino*)*acetic Acid, Piperidinium Salt* (**9**).—This product was obtained in 53% yield from 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (**8**) and piperidine, as reported[4] by Carmack and co-workers for the preparation of compound (**7**). Compound (**9**) could also be prepared by reaction of compound (**7**) (100 mg, 0.5 mmol) with an excess of piperidine (100 mg, 1.2 mmol) in water (10 ml). The mixture was kept at room temperature for 2 h, the solvent and the remaining piperidine were evaporated off, and the residue was purified by p.l.c., with a mixture of propan-2-ol–ammonia–water (7:1:2) as developing solvent, to give compound (**9**) (72%). Compound (**9**) was also formed when an aqueous solution of the acid (**10**) was neutralized with piperidine (yield 89%). The piperidinium salt (**9**) was a very hygroscopic yellow glass for which a satisfactory analysis could not be obtained. I.r. and mass spectra were identical with those reported;[4] $\delta_H[(CD_3)_2CO]$ 1.3—2.0 (12 H, br s, $C[CH_2]_3C$ of both piperidine rings), 3.82 (4 H, br s, CH_2NCH_2 of piperidinium ring), and 3.63 and 4.38 [both 2 H and br s, CH_2NCH_2 of piperidine ring]; $\delta_C[(CD_3)_2SO]$ 21.60 (t, C-4″), 22.16 (t, C-3″ and -5″), 23.58 (t, C-4′), 25.23 and 26.45 [both t, C-3′ and -5′ (or *vice versa*)], 43.81 (t, C-2″ and -6″), 45.62 and 48.45 [both t, C-2′ and -6′ (or *vice versa*)], and 159.44 and 164.01 [both s, C-2 and -1 (or *vice versa*)].

2-*Piperidino*-2-(*sulphamoylimino*)*acetic Acid* (**10**).—A solution of the salt (**9**) (1.60 g, 0.005 mol) in water (50 ml) was passed through a strongly acidic ion-exchange resin (H^+ form) column, with water as eluant. The solvent was evaporated off, and the residue was recrystallized from propan-1-ol, to give the *acid* (**10**) as white crystals (95%), m.p. 307—309 °C (decomp.) (Found: C, 35.7; H, 5.2; N, 17.8; S, 13.7. $C_7H_{13}N_3O_4S$ requires C, 35.7; H, 5.6; N, 17.9; S, 13.6%); $\nu_{max.}$(KBr) 3 520, 3 400, 2 945, 2 930, 2 850, 1 660, and 1 600 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.60 (6 H, br s, $C[CH_2]_3C$), and 3.50 and 4.33 (both 2 H, and br s, CH_2NCH_2).

Acknowledgements

Support of this work by the Comisión Asesora de Investigación Científica y Técnica is gratefully acknowledged.

References

1 V. J. Arán, A. G. Bielsa, J. R. Ruiz, and M. Stud, *J. Chem. Soc., Perkin Trans. 1*, 1986, 643.
2 W. C. Lumma, Jr., P. S. Anderson, J. J. Baldwin, W. A. Bolhofer, C. N. Habecker, J. M. Hirschfield, A. M. Pietruszkiewicz, W. C. Randall, M. L. Torchiana, S. F. Britcher, B. V. Clineschmidt, G. H. Denny, R. Hirschmann, J. M. Hoffman, B. T. Philips, and K. B. Streeter, *J. Med. Chem.*, 1982, **25**, 207.
3 A. A. Algieri, G. M. Luke, R. T. Standridge, M. Brown, R. A. Partyka, and R. R. Crenshaw, *J. Med. Chem.*, 1982, **25**, 210.
4 R. Y. Wen, A. P. Komin, R. W. Street, and M. Carmack, *J. Org. Chem.*, 1975, **40**, 2743.
5 V. J. Arán, J. R. Ruiz, E. Davila, I. Alkorta, and M. Stud, Proceedings of 'IV Jornadas Hispano-Francesas de Quimica Organica,' Jaca (Spain), 1986, p. 92.
6 G. J. Durant, J. C. Emmet, C. P. Ganellin, P. D. Miles, M. E. Parsons, H. D. Prain, and G. R. White, *J. Med. Chem.*, 1977, **20**, 901.

Received 18*th September* 1985; *Paper* 5/1614