Ring Contraction of 1,2,6-Thiadiazines to 1,2,5-Thiadiazoles: Synthesis of 2-Substituted 4-Amino-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-Dioxides

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

Nitrosation of 2-substituted 2,3,5,6-tetrahydro-3,5-dioxo-1,2,6-thiadiazine 1,1-dioxides (**2a—d**) yielded the corresponding 4-hydroxyimino derivatives (**3a—d**), which by mild acid treatment were converted into 2-substituted 4-amino-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxides (**4a—d**). A tentative mechanism is proposed. 2,6-Disubstituted 2,3,5,6-tetrahydro-3,5-dioxo-1,2,6-thiadiazine 1,1-dioxide (**2e**) also yielded the corresponding 4-hydroxyimino derivative (**3e**), but this compound does not react following the same pattern and under acid treatment, only the corresponding *N,N'*-disubstituted sulphamide (**1e**) was obtained.

In continuation of our research into the chemistry of 1,2,6-thiadiazine 1,1-dioxides and other sulphamide-derived heterocycles, we report a ring contraction of tetrahydro-3,5-dioxo-1,2,6-thiadiazine 1,1-dioxides to 2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxides. The chemistry of 1,2,5-thiadiazole 1-oxides and 1,1-dioxides has been elucidated [1] in recent years but only lately has this heterocyclic system been shown to be of interest in the field of histamine H_2-receptor antagonists.[2]

Results and Discussion

The reaction of *N*-mono- and *N,N'*-disubstituted sulphamides (**1a—c, e**) with malonyl chloride, following reported procedures,[3] yielded 2-mono- and 2,6-di-substituted tetrahydro-3,5-dioxo-1,2,6-thiadiazine 1,1-dioxides (**2a—c, e**). Nitrosation of these compounds afforded the corresponding 4-hydroxyimino derivatives (**3a—c, e**) (Scheme 1). Their formation in almost quantitative yield can be observed by t.l.c.; the spots develop a deep blue colour with ferrous salts, as do isosteric violuric acids (5-hydroxyiminobarbituric acids).[4] Compounds (**3b**) and (**3c**) were isolated as the sodium salt monohydrates, and (**3e**) as free acid. Compound (**3a**) was obtained as a syrup which could not be crystallized and was not characterized.

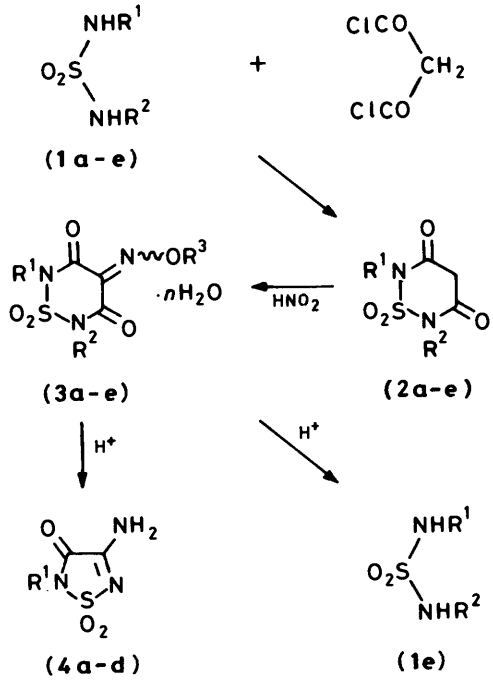
Treatment of aqueous solutions of (**3a—c**) with dilute hydrochloric acid furnished the 2-substituted 4-amino-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxides (**4a—c**).†

Reaction conditions depend on the nature of the substituents at position 2; when R^1 is a cyclohexyl or a phenethyl group, the reaction is complete after a short period under reflux. Under these conditions, when R^1 is a benzyl group, hydrolytic cleavage of the ring takes place, and a considerable amount of the corresponding sulphamide (**1a**) is obtained. In this case, the reaction was allowed to stand for several days at room temperature and pure compound (**4a**) crystallized in good yield.

The reaction of phenylsulphamide (**1d**) with malonyl chloride yielded a very complex mixture of products, from which the corresponding thiadiazine 1,1-dioxide (**2d**) could not be isolated. Nevertheless, nitrosation of the mixture and acid treatment afforded the thiadiazole 1,1-dioxide (**4d**) in poor yield.

In the mild acid treatment of (**3e**) there was no reaction and only the starting material was recovered; under forcing conditions, the corresponding *N,N'*-disubstituted sulphamide was obtained.

Since during the transformation of (**3**) into (**4**), carbon dioxide is evolved, we assume the reaction takes place as shown in Scheme 2. Hydration of the carbonyl group at position 5 occurs first followed by contraction of the ring to yield an intermediate acid, which spontaneously decarboxylates to the imino tautomer of (**4**). This mechanism can be related to that proposed[6] for the transformation of alloxan hydrate into alloxanic acid, under basic conditions. Nevertheless, the latter is stable and does not decarboxylate spontaneously to parabanic acid.



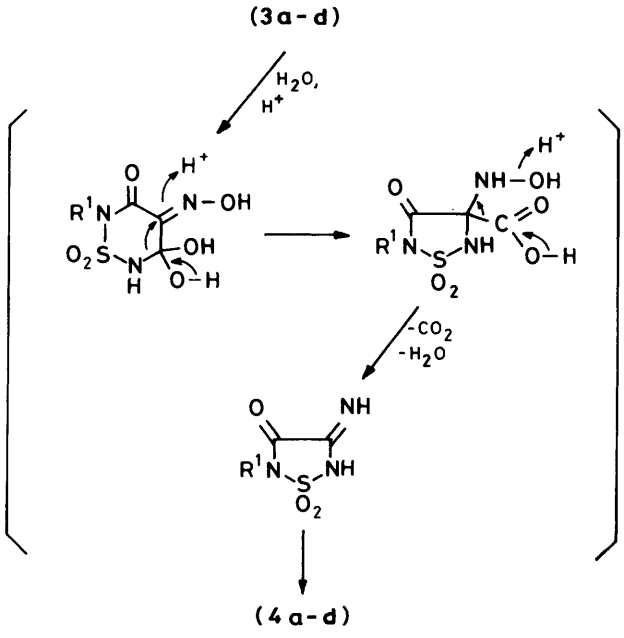
	R^1	R^2	R^3	n
a	$PhCH_2$	H		
b	$PhCH_2CH_2$	H	Na	1
c	c-C_6H_{11}	H	Na	1
d	Ph	H		
e	$PhCH_2$	$PhCH_2$	H	0

Scheme 1.

The structure of all new compounds has been established on the basis of chemical, analytical, and spectral ‡ evidence.

† Acid treatment of violuric acids only yields the corresponding alloxans and hydroxylamine (ref. 5).

‡ The most striking spectral feature of compounds (**4**) is the carbonyl stretching absorption at *ca.* 1 750 cm^{-1}, also found in some closely related compounds (ref. 7).



Scheme 2.

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 20.1 MHz on a Bruker WP-80 spectrometer, using tetramethylsilane as internal standard; mass spectra were obtained at 70 eV on a Varian MAT-711 spectrometer.

Preparation[8] *of Substituted Sulphamides* (**1a—e**).—Compounds (**1a—c,e**) were obtained from sulphamide and the corresponding amines, following the method of Paquin.[3] Compound (**1d**) was obtained from sulphamoyl chloride and aniline, following the procedure of Graf.[9]

Preparation of 2-*Mono- and* 2,6-*Di-substituted* 2,3,5,6-*tetrahydro*-3,5-*dioxo*-1,2,6-*thiadiazine* 1,1-*Dioxides* (**2a—c, e**).—These compounds were obtained, following the method of Paquin,[3] from substituted sulphamides and malonyl chloride, using toluene as solvent. 2,3,5,6-*Tetrahydro*-3,5-*dioxo*-2-*phenethyl*-1,2,6-*thiadiazine* 1,1-*dioxide* (**2b**) (88%), m.p. 158—159 °C (decomp.) (from toluene) (Found: C, 49.4; H, 4.65; N, 10.4; S, 12.1. $C_{11}H_{12}N_2O_4S$ requires C, 49.25; H, 4.5; N, 10.4; S, 11.95%); $\nu_{max.}$(Nujol) 3 060 br (NH) and 1 730 and 1 690 cm^{-1} (CO); $\delta_H[(CD_3)_2CO]$ 2.97 (2 H, t, CH_2Ph), 3.87 (2 H, s, $COCH_2CO$, exch.), 4.02 (2 H, t, CH_2N), 7.27 (5 H, s, Ph), and 9.80 (1 H, br s, NH, exch.). 2,6-*Dibenzyl*-2,3,5,6-*tetrahydro*-3,5-*dioxo*-1,2,6-*thiadiazine* 1,1-*dioxide* (**2e**) (75%), m.p. 145—147 °C (from toluene) (Found: C, 59.1; H, 4.9; N, 8.4; S, 9.0. $C_{17}H_{16}N_2O_4S$ requires C, 59.3; H, 4.7; N, 8.1; S, 9.3%); $\nu_{max.}$(Nujol) 1 735 and 1 720 cm^{-1} (CO); $\delta_H[(CD_3)_2CO]$ 4.10 (2 H, s, $COCH_2CO$, exch.), 5.02 (4 H, s, CH_2Ph), and 7.33 (10 H, s, Ph).

Preparation of 2-*Mono- and* 2,6-*Di-substituted* 4-*Hydroxyimino*-2,3,5,6-*tetrahydro*-3,5-*dioxo*-1,2,6-*thiadiazine* 1,1-*Dioxides* (**3a—c, e**).—To an ice-cooled solution of the corresponding compound (**2**) (10 mmol) in a mixture of dioxane (30 ml) and acetic acid (3 ml), a solution of sodium nitrite (0.76 g, 11 mmol) in water (5 ml) was slowly added. The reaction was set aside for 1 h at 0 °C and then overnight at room temperature. For (**3a—c**) the solvent was evaporated to dryness to yield a syrupy residue which for compounds (**3b, c**) solidified overnight; this solid was then recrystallized. Compound (**3a**) did not crystallize and was used in the next step without purification. In the case of (**3e**), the reaction mixture was poured with stirring into 1M hydrochloric acid (250 ml) and then set aside overnight; the solid so obtained was filtered off and recrystallized. 2,3,5,6-*Tetrahydro*-4-*hydroxyimino*-3,5-*dioxo*-2-*phenethyl*-1,2,6-*thiadiazine* 1,1-*dioxide*, *sodium salt monohydrate* (**3b**) (78%), m.p. 194—195 °C (decomp.) (from water) (Found: C, 39.3; H, 3.3; N, 12.4; S, 9.5. $C_{11}H_{10}N_3O_5SNa{\cdot}H_2O$ requires C, 39.2; H, 3.6; N, 12.5; S, 9.5%); $\nu_{max.}$(Nujol) 3 640, 3 520 (H_2O, NH), 1 680, 1 620 (CO), and 1 550 cm^{-1} (C=N); $\delta_H[(CD_3)_2SO]$ 2.93 (2 H, t, CH_2Ph), 3.87 (2 H, t, CH_2N), and 7.27 (5 H, s, Ph). 2-*Cyclohexyl*-2,3,5,6-*tetrahydro*-4-*hydroxyimino*-3,5-*dioxo*-1,2,6-*thiadiazine* 1,1-*dioxide*, *sodium salt monohydrate* (**3c**) (79%), m.p. 214—215 °C (decomp.) (from water) (Found: C, 34.2; H, 4.5; N, 13.4; S, 10.1. $C_9H_{12}N_3O_5SNa{\cdot}H_2O$ requires C, 34.3; H, 4.5; N, 13.3; S, 10.2%); $\nu_{max.}$(Nujol) 3 520, 3 340 (H_2O, NH), 1 670, 1 625 (CO), and 1 540 cm^{-1} (C=N); $\delta_H[(CD_3)_2SO]$ 1.0—2.3 [10 H, m, $(CH_2)_5$] and 4.10 [1 H, m, C(H)N]. 2,6-*Dibenzyl*-2,3,5,6-*tetrahydro*-4-*hydroxyimino*-3,5-*dioxo*-1,2,6-*thiadiazine* 1,1-*dioxide* (**3e**) (72%), m.p. 143—145 °C (decomp.) (from toluene) (Found: C, 54.8; H, 4.0; N, 11.1; S, 8.6. $C_{17}H_{15}N_3O_5S$ requires C, 54.7; H, 4.05; N, 11.25; S, 8.6%); $\nu_{max.}$(Nujol) 3 230 (OH), 1 730 (CO), and 1 695 cm^{-1} (C=N); $\delta_H(Cl_3CD)$ 5.03, 5.10 (both 2 H, both s, CH_2Ph), and 7.36 (10 H, s, Ph).

Preparation of 2-*Substituted* 4-*Amino*-2,3-*dihydro*-3-*oxo*-1,2,5-*thiadiazole* 1,1-*Dioxides* (**4a—d**).—A mixture of the corresponding hydroxyimino derivative sodium salt (**3b, c**), water (50 ml), and concentrated hydrochloric acid (2 ml) was refluxed for 1 h. The solution was then cooled in an ice-bath and the separated solid filtered off and recrystallized. To prepare (**4a**), the syrupy residue obtained from (**2a**) (10 mmol) was dissolved in water (50 ml) and concentrated hydrochloric acid (2 ml) added; after 5 days at room temperature the solution was filtered and the precipitate so obtained recrystallized. The 2-phenyl derivative (**4d**) was prepared as follows, without isolation of the intermediates. To a suspension of *N*-phenylsulphamide (**1d**) (8.60 g, 50 mmol) in dry toluene (200 ml) heated at 50 °C, a solution of malonyl chloride (7.33 g, 52 mmol) in dry toluene (50 ml) was slowly added. The mixture was then heated at 70 °C for 2 h, after which it was cooled and the precipitated solid filtered off and dissolved in a mixture of dioxane (150 ml) and acetic acid (10 ml); this solution was then cooled in an ice-bath and sodium nitrite (3.45 g, 50 mmol) in water (20 ml) slowly added. After 1 h at 0 °C and 10 h at room temperature, the solvent was removed and the residue treated with 0.5M hydrochloric acid (100 ml). The brown oil which separated after 5 days at room temperature was extracted with ethyl acetate and purified by column chromatography over silica gel, using chloroform–ethanol (95:5) as eluant. The fractions containing the main product were evaporated to dryness, and the residue recrystallized.

4-*Amino*-2-*benzyl*-2,3-*dihydro*-3-*oxo*-1,2,5-*thiadiazole* 1,1-*dioxide* (**4a**) [75% from (**2a**)], m.p. 182—184 °C (from isopropyl alcohol) (Found: C, 45.4; H, 3.8; N, 17.8; S, 13.6. $C_9H_9N_3O_3S$ requires C, 45.2; H, 3.8; N, 17.6; S, 13.4%); $\nu_{max.}$(Nujol) 3 450, 3 420, 3 320, 3 300, 3 240 (NH), 1 750 (CO), and 1 675 cm^{-1} (C=N); $\delta_H[(CD_3)_2CO]$ 4.80 (2 H, s, CH_2Ph), 7.38 (5 H, m, Ph), and 8.48 (2 H, br s, NH_2, exch.); $\delta_C[(CD_3)_2SO]$ 44.11 (t, CH_2Ph), 127.84 (d), 127.95 (d), 128.41 (d), and 134.36 (s) (Ph), and 154.96 and 157.24 (both s, C-3 and -4); *m/z* 239 (M^+, 23%), 175 (87, $M - SO_2$), 132 (63), 105 (33), 104 (43), and 91 (100). 4-*Amino*-2,3-*dihydro*-3-*oxo*-2-*phenethyl*-1,2,5-*thiadiazole* 1,1-*dioxide* (**4b**) [76% from (**3b**)], m.p. 229—231 °C (decomp.) (from

ethanol) (Found: C, 47.7; H, 4.4; N, 16.5; S, 12.9. $C_{10}H_{11}N_3O_3S$ requires C, 47.4; H, 4.4; N, 16.6; S, 12.7%); $\nu_{max.}$(Nujol) 3 420, 3 390, 3 260, 3 190 (NH), 1 755 (CO), and 1 680 cm^{-1} (C=N); δ_H[$(CD_3)_2CO$] 3.07 (2 H, t, CH_2Ph), 3.90 (2 H, t, CH_2N), 7.30 (5 H, s, Ph), and 8.45 (2 H, br s, NH_2, exch.). 4-*Amino*-2-*cyclohexyl*-2,3-*dihydro*-3-*oxo*-1,2,5-*thiadiazole* 1,1-*dioxide* (**4c**) [71% from (**3c**)], m.p. 164—166 °C (from diluted ethanol) (Found: C, 41.7; H, 5.7; N, 18.2; S, 14.1. $C_8H_{13}N_3O_3S$ requires C, 41.55; H, 5.7; N, 18.2; S, 13.9%); $\nu_{max.}$(Nujol) 3 370, 3 280, 3 200, 3 160 (NH), 1 750 (CO), and 1 690 cm^{-1} (C=N); δ_H[$(CD_3)_2CO$] 1.0—2.2 [10 H, m, $(CH_2)_5$], 3.95 [1 H, m, C(H)N], and 8.37 (2 H, br s, NH_2, exch.). 4-*Amino*-2,3-*dihydro*-3-*oxo*-2-*phenyl*-1,2,5-*thiadiazole* 1,1-*dioxide* (**4d**) [25% from (**1d**)], m.p. 199—201 °C (decomp.) (from isopropyl alcohol) (Found: C, 42.9; H, 3.4; N, 18.8; S, 14.4. $C_8H_7N_3O_3S$ requires C, 42.7; H, 3.1; N, 18.7; S, 14.2%); $\nu_{max.}$(Nujol) 3 420, 3 340, 3 290, 3 210 (NH), 1 750 (CO), and 1 670 cm^{-1} (C=N); δ_H[$(CD_3)_2CO$] 7.60 (5 H, s, Ph) and 8.67 (2 H, br s, NH_2, exch.).

Acid Treatment of 2,6-*Dibenzyl*-4-*hydroxyimino*-3,5-*dioxo*-1,2,6-*thiadiazine* 1,1-*Dioxide* (**3e**).—A mixture of (**3e**) (0.75 g, 2 mmol), ethanol (30 ml), and 2M hydrochloric acid (50 ml) was refluxed for 1 h; only starting material was present as observed by t.l.c. When the mixture was refluxed for 10 h and then cooled, a crystalline precipitate formed and was filtered off and identified as *N,N'*-dibenzylsulphamide (**1e**) (69%), m.p. 180—181 °C (lit.,[10] 181—182 °C).

Acknowledgements

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

References

1 L. M. Weinstock and I. Shinkai, in 'Comprehensive Heterocyclic Chemistry,' ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 6, p. 529, and references therein.
2 W. C. Lumma, Jr., P. S. Anderson, J. J. Baldwin, W. A. Bolhofer, Ch. 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. Phillips, and K. B. Streeter, *J. Med. Chem.*, 1982, **25**, 207; A. A. Algieri, G. M. Luke, R. T. Standridge, M. Brown, R. A. Partyka, and R. R. Crenshaw, *J. Med. Chem.*, 1982, **25**, 210.
3 A. M. Paquin, *Angew. Chem.*, 1948, **60**, 316.
4 M. A. Whiteley, *J. Chem. Soc.*, 1907, **91**, 1330; P. A. Leermakers and W. A. Hoffman, *J. Am. Chem. Soc.*, 1958, **80**, 5663.
5 M. Ceresole, *Chem. Ber.*, 1883, **16**, 1133; W. Techow, *Chem. Ber.*, 1894, **27**, 3082.
6 G. M. Badger and J. W. Clark-Lewis, in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York and London, 1963, vol. 1, p. 632, and references therein; H. C. van der Plaas, 'Ring Transformations of Heterocycles,' Academic Press, London and New York, 1973, vol. 2, p. 128, and references therein.
7 R. Y. Wen, A. P. Komin, R. W. Street, and M. Carmack, *J. Org. Chem.*, 1975, **40**, 2743.
8 For a review see: S. D. McDermott and W. J. Spillane, *Org. Prep. Proced. Int.*, 1984, **16**, 49. Nomenclature used by these authors for sulphamides and related compounds has been followed in this paper.
9 R. Graf, *Chem. Ber.*, 1959, **92**, 509.
10 B. Helferich and D. Wiehle, *J. Prakt. Chem.*, 1961, **14**, 177.

Received 26*th July* 1985; *Paper* 5/1281