[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE STATE UNIVERSITY OF IOWA AND GUSTAVUS ADOLPHUS COLLEGE]

The 1,2,4-Thiadiazine Ring System. III. The Dissociation of 1,2,4,2H-Thiadiazine-3,5(4H,6H)-dione 1,1-Dioxide[1]

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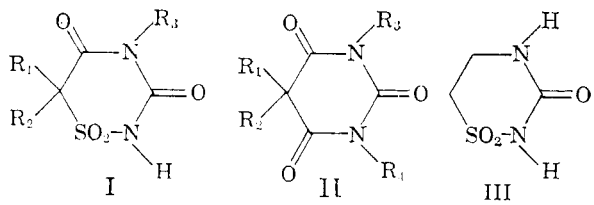
It has been determined by means of pK'_a and NMR measurements that the site of the most acidic hydrogen in 1,2,4,2H-thiadiazine-3,5(4H,6H)-dione 1,1-dioxide (Ia) and a number of its *N*- and C-methyl derivatives (Ib–d) is the 2-position. The hydrogen on the sulfonamide nitrogen is also the most acidic in a number of α-carbamylmethanesulfonamide and methanesulfonylurea precursors of the thiadiazines. Above *p*H 11 solutions of the thiadiazines (Ia–d) show a maximum near 240 mμ, which is ascribed to the removal of a second proton from either the 4- or 6-position. Although formally analogous to barbituric acid, Ia resembles barbital in its first dissociation. The hydrogens at the 6-position (the "active" methylene) of Ia do not enolize below *p*H 10. The pK'_a, ultraviolet, and infrared spectra of a variety of sulfonamides and sulfonylureas are reported.

The pronounced acidity of 1,2,4,2H-thiadiazine-3,5(4H,6H)-dione-1,1-dioxide (Ia), reported in the previous papers of this series,[4] prompted us to determine the sites of the dissociable protons. We were particularly interested in comparing the dissociation of Ia with that of the formally analogous but less-acidic barbituric acid (IIa). It was anticipated that the hydrogen at position-2 of Ia or that at position-6 would be the most acidic, the former by analogy with the well-known acidity of the sulfonylureas,[5] and the latter by analogy with barbituric acid.[6] The imide hydrogen at position-4 might also be highly acidic, and the picture is further complicated by the various possibilities for enolization. The problem was attacked by studying the acidities, and the ultraviolet, infrared and proton magnetic resonance spectra of Ia and certain of its C- and *N*- methyl derivatives.



I II III

Ia. $R_1 = R_2 = R_3 = H$
b. $R_1 = CH_3$; $R_2 = R_3 = H$
c. $R_1 = R_2 = H$; $R_3 = CH_3$
d. $R_1 = R_2 = CH_3$; $R_3 = H$
IIa. $R_1 = R_2 = R_3 = R_4 = H$
b. $R_1 = R_2 = C_2H_5$; $R_3 = R_4 = H$
c. $R_1 = R_2 = C_2H_5$; $R_3 = R_4 = CH_3$
d. $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$

In dilute aqueous solutions the thiadiazines (Ia-d) are essentially completely dissociated. NMR measurements of aqueous solutions of Ib showed that the 6-hydrogen was retained in the anion formed in the first dissociation.[7,8] The 60 mc. spectrum of a 17% solution of Ib in water contained only two lines; these were of equal area, separated by ~7.5 cps., at a mean distance of 193 cps. (3.22 ppm.) from the solvent line. Hydrogens on amide or imide nitrogens generally appear at low fields (~ −3.0 ppm.) relative to water.[9] The observed lines can therefore be due only to the split resonance of the 6-methyl. The coupling constant is of the size expected for the group >CHCH$_3$. The resonance lines of the other hydrogens are not observed. Hydrogens on nitrogen are frequently difficult to detect,[10] and in the present case might well have been obscured by the broad solvent line. A similar spectrum was obtained from a 13.5% solution of the sulfonylurea VIa in water. Only two lines separated by ~7 cps. were found at a mean distance of 191 cps. (3.12 ppm.) from the water line.

From these results it is clear that the proton of the first dissociation of Ib must come from the 2- or 4-position. As the pK_a' values (Table I) of the parent thiadiazine (Ia) and its 4-methyl (Ic), 6-methyl (Ib), and 6,6-dimethyl (Id) derivatives are

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(4)(a) R. L. Hinman and L. Locatell, Jr., *J. Am. Chem. Soc.*, **81**, 5655 (1959). (b) B. E. Hoogenboom, R. Abbott, L. Locatell, Jr., and R. L. Hinman, *J. Org. Chem.*, **24**, 1983 (1959).

(5) F. Kurzer, *Chem. Rev.*, **50**, 1 (1953).

(6) J. J. Fox and D. Shugar, *Bull soc. chim. belg.*, **61**, 44 (1952).

(7) The authors are indebted to Dr. Earl Whipple of the Union Carbide Research Institute for determining the NMR spectra.

(8) The spectrum of the parent thiadiazine (Ia) in water showed a single line of little interest, since there was nothing to which its area could be compared.

(9) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High-resolution Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959, pp. 272–273.

(10) Ref. 9, p. 102.

of comparable magnitude,[11] the site of the most acidic hydrogen in every case is assumed to be the same as that of Ib, and cannot be the 4-position. The hydrogen at the 2-position (the sulfonimide hydrogen) is therefore the one involved in the first dissociation of Ia–d.[12]

Whether the hydrogens written formally at the 2- and 4-positions are involved in enolization has not been conclusively established. In the solid state, however, a high percentage of the molecules of the thiadiazines have the hydrogens bonded to nitrogen, as the infrared spectrum of each shows two bands in the carbonyl region (Table II),[13] and cogent evidence has been accumulated against "enolization" of the sulfonyl group (Holst and Fernelius, ref. 12). The presence of the group $>CHCH_3$ in the anion of Ib shows that enolization of the 6-hydrogen does not occur.

Ultraviolet spectra; the second dissociation. From *p*H 1–13 methanesulfonamide, methanesulfonylurea, and III at 10^{-3} *M* are transparent from 220–300 mμ (Table II). The introduction of a carbamyl group α to the sulfonyl function, as in V, VII, VI, and X, while producing no change in the acidity of the parent molecules (Table I), does bring about measurable though featureless absorption in the 220–240 mμ region (Fig. 1, curve 3). This absorption must arise from interaction of the carbonyl and sulfonyl functions through the saturated carbon atom, and resembles the absorption of simple β-

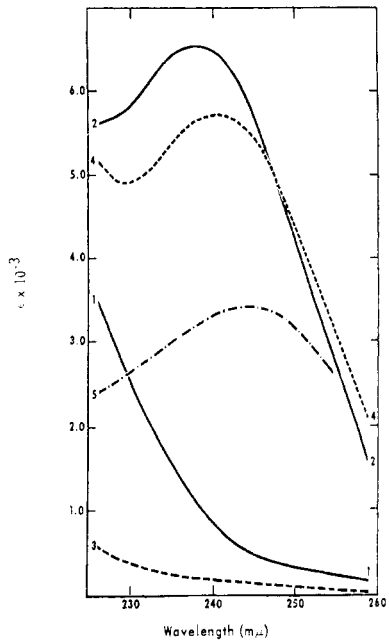


Fig. 1. Ultraviolet absorption spectra: 1, parent thiadiazine (Ia) at *p*H 8; 2, Ia in 0.1*N* sodium hydroxide; 3, $NH_2COC(CH_3)_2SO_2NHCONH_2$ (VIb) at *p*H 10; 4, VIb after 20 min. in 0.36*N* sodium hydroxide; 5, Ic in 0.1*N* sodium hydroxide

TABLE I

ACIDITIES OF THIADIAZINES AND PRECURSORS

Compound		*p*Ka′	Neut. equiv. Calcd.	Found
$CH_3SO_2NHCONH_2$		5.10[a]	138	141
$NH_2COCH_2SO_2NHCONH_2$		5.05[a]	181	181
$NH_2COCH(CH_3)SO_2NHCONH_2$ (VIa)		5.21[a]	195	195
$NH_2COC(CH_3)_2SO_2NHCONH_2$ (VIb)		5.15[a]	209	212
$CH_3NHCOCH_2SO_2NHCONH_2$ (X)		4.89[a]	195	194
III		4.51[a]	150	149
p-$NH_2C_6H_4SO_2NHCONH_2$		5.42[b]		
$CH_3SO_2NH_2$		10.80		
$NH_2COCH_2SO_2NH_2$(VII)		9.70		
$NH_2COCH(CH_3)SO_2NH_2$(Va)		9.86		
$NH_2COC(CH_3)_2SO_2NH_2$(Vb)		9.92		
$C_6H_5SO_2NH_2$		10.11		
p-$NH_2C_6H_4SO_2NH_2$		10.69[c]		
Ia	pKa_1	2.88[d]	164	165
	pKa_2	11.00[e]		
Ib		2.89[d]	178	181
Ic		2.63[d]	178	178
IIa		4.52[a,f]	128	129

[a] Determined by titration, as described in the Experimental. [b] P. H. Bell and R. O. Roblin, Jr., *J. Org. Chem.*, **64**, 2905 (1942). [c] Reported value: 10.43 (footnote b). [d] Calculated from the *p*H of a 0.01*N* solution of known concentration. [e] Determined spectrophotometrically. [f] Thermodynamic pK_a from extrapolation to infinite dilution was 4.05, in good agreement with the reported value of 3.98 (25°) [J. K. Wood, *J. Chem. Soc.*, **89**, 1831 (1906); see also ref. 6]

(11) The 6,6-dimethylthiadiazine (Id) could only be obtained about 50% pure. The mixture showed the typical titration curve of a strong acid, but with considerable buffering above *p*H 8, as would be expected if the contaminants were the sulfonylurea and sulfonamide hydrolysis products. By assuming that the thiadiazine was the only strong acid present, the pK_a' of Id was found to be 2.2 ± 0.5. With a mixture containing 28% of Id a value of 2.5 ± 0.5 was found.

(12) The pK_a' of III is comparable to that of the linear sulfonylureas, indicating the importance of the 5-carbonyl to the marked acidity of thiadiazines Ia–d. At first sight it might appear that the introduction of the 5-carbonyl is accompanied by the formation of a new acidic site: the 6-methylene group. However, the acid-strengthening effect of the 5-carbonyl could also be exerted by means of electron-withdrawal from the 4-nitrogen and thence from the 2-nitrogen. It should also be noted that despite the presence of the carbamyl group on the methylene group of the linear precursors, the acidic hydrogen is on the sulfonimide nitrogen, as shown by the comparable acidities of methanesulfonylurea, carbamylmethanesulfonylurea, 2-carbamyl-2-propanesulfonylurea (VIb), and compound III. The acidities of the diamides Va, Vb, and VII are also of comparable magnitude. These results are in accord with the general principle that the acidity of a proton attached to carbon is decreased slightly by replacement of an adjacent carbonyl by a sulfonyl group (as reported for β-ketosulfones by E. H. Holst and W. C. Fernelius, *J. Org. Chem.*, **23**, 1881 (1958)), whereas the acidity of hydrogen on nitrogen (or oxygen) is greatly increased by the same change.

(13) The carbonyl of the sulfonimide group of saccharin may be involved in enolization to the extent of about 20% in nonpolar solvents, but the value obtained depends on the method of carrying out the experiment (F. Arndt and H. Scholz, *Ann.*, **510**, 62 (1934)).

ketosulfones such as *n*-butylsulfonylacetone in neutral solution.[14] However, unlike the latter compound, which undergoes a 650-fold increase in ϵ in basic solution, the α-carbamylalkanesulfonamides undergo only slight intensification of absorption in basic media. This fact, together with the comparable spectra of Vb and VII over the entire *p*H range, supports the conclusion drawn from the acidities of Vb and VII, that the site of the acidic hydrogen is the sulfonamide nitrogen. The same argument applies to the sulfonylureas.

From *p*H 1–10 the spectra of the thiadiazines (Ia–c) also exhibit rising end absorption which changes little with *p*H but which is much more intense than that of the linear precursors (Fig. 1, curve 1). In this *p*H range it is the spectrum of the monoanion which is observed. Above *p*H 10 the intensity of absorption increases with *p*H until a well-defined maximum is observed near 240 mμ (Fig 1, curve 2). In the case of Ia ϵ_{238} increased from 1400 at *p*H 9.9 to 6800 in 1*N* sodium hydroxide. This maximum is ascribed to the absorption of the dianion, formed by removal of a second proton.[15] The pK_a' of the second dissociation of Ia is 11.0. As only the hydrogen at the 6-position of Ic is available for this dissociation, it appeared at first as if Ia and Ib also lose the 6-hydrogen in the second dissociation. An accidental observation led to a different conclusion.

When 2-carbamyl-2-propanesulfonylurea (VIb) was allowed to stand for fifteen minutes in 0.1*N* sodium hydroxide, or for two minutes in 1*N* sodium hydroxide, the intensity of absorption increased rapidly, from ϵ_{241} 200 to a maximum at 241 mμ, ϵ_{max} >5800 (Fig. 1, curve 4). The same behavior was observed with carbamylmethanesulfonylurea and a spectrum with λ_{max} 238 mμ, identical with that of the dianion of Ia, was recorded after a few minutes. From these results it is clear that ring closure to the thiadiazines takes place in the alkaline solutions and that the spectrum of the first example cited is due to the dianion of 6,6-dimethyl-1,2,4,2H-thiadiazine-3,5(4H)-dione-1,1-dioxide (Id). In both cases the absorbancy rose to a maximum and then decreased; the rate of decrease was much faster in the case of the 6,6-dimethylthiadiazine. The decrease was undoubtedly due to hydrolysis which would also account for our failure to obtain Id in pure form, when we used this method on a preparative scale (see below). At *p*H 13 a solution of the impure Id immediately showed the same maximum at 241 mμ as that observed after the sulfonylurea precursor (VIb) had been standing for a few minutes at the same *p*H.[16]

It is interesting to compare the dissociations of the thiadiazines to those of the analogous barbiturates. Compounds Ia, b, and d resemble barbital (IIb) rather than barbituric acid (IIa) in the sites of the acidic hydrogens and in the fact that the 6-carbon remains saturated throughout so that resonance around the entire ring is not possible. However, the anion from the first dissociation of barbital has λ_{max} 239 mμ (ϵ_{max} 10600),[6] whereas the monoanions of the thiadiazines show intense but featureless end absorption in the ultraviolet.[17] The removal of the second proton from the thiadiazines produces an absorption maximum, but the dianion of barbital absorbs more intensely and at longer wavelengths (λ_{max} 255 mμ, ϵ_{max} 7950). The less-developed absorption spectra of the thiadiazines may be a consequence of the inability of the sulfonyl group to participate as well in resonance as the carbonyl group[12] or it may be due to the lack of symmetry in the ring system which would reduce the importance of resonance contributions, compared to those of the completely symmetrical barbital system. The 4-methyl derivative (Ic), like barbital, loses a proton from nitrogen in the first dissociation, but the dianion resembles that of 1-methylbarbituric acid (IId). There is again little similarity in the spectra.

Infrared spectra. As shown in Table II, α-carbamylalkanesulfonylureas show two bands in the carbonyl region. Since methanesulfonylurea and III have strong bands at 1710 and 1700 cm.$^{-1}$ respectively, the band at higher frequencies in the α-carbamylalkanesulfonylureas is assigned to the urea carbonyl.[18] The band at lower frequencies is then due to the amide carbonyl, displaced to slightly higher frequencies than in the diamide precursors of the sulfonylureas.

(14) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 231 (1949).

(15) Acidification of a solution of Ia in 1*N* sodium hydroxide regenerated the monoanion, as shown by the changes in the ultraviolet spectra.

(16) The dianion of Id lacks the 2- and 4-hydrogens, while the dianion of Ic lacks the 2- and 6-hydrogens. The spectra are so similar (Table II and Figure 1) that no certain conclusion can be drawn from them about the site of the proton involved in the second dissociation of Ia and Ib. Two observations lead us to suggest tentatively that the last two compounds resemble Id rather than Ic and lose the 4-hydrogen in the second dissociation. Ia, b, and d all have ϵ_{max} >5800, whereas ϵ_{max} for Ic is 3400. (The spectra of Ib and Id are nearly identical.) Compound Ic is less acidic than Ia, b, and d, as shown by the fact that the last three compounds show well-defined maxima at *p*H 11.5, whereas the spectrum of Ic is still unchanged at this *p*H. Whether or not these inferences are valid, from the examples of Ic and Id it is clear that the ultraviolet spectra of the dianions of the thiadiazines are similar, whether the two protons are removed from the 2- and 4- or from the 2- and 6-positions.

(17) Even 1,3-dimethylbarbital (IIc), in which dissociation of any kind is prohibited, shows a well-defined absorption maximum at 228 mμ (ϵ_{max} 6300).[6]

(18) The urea carbonyl absorbs at much higher frequencies in the sulfonylureas than in simple alkylureas (*e.g.*, methanesulfonylurea and β-ureidoethanesulfonamide; *cf.* J. L. Boivin and P. A. Boivin, *Can. J. Chem.*, **32**, 561 (1954)). The displacement to higher frequencies is undoubtedly due to the electron-withdrawing effect of the sulfonyl group. This effect also accounts for the absorption at 1725 cm.$^{-1}$ in nitrourea (E. Lieber, D. R. Levering, and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951)).

TABLE II

ABSORPTION SPECTRA

Compound	Ultraviolet[a]			Infrared[b]			
						sulfonyl region[d]	
	pH or [NaOH]	λ[c]	ε	carbonyl region		antisym	sym.
$CH_3SO_2NH_2$	—	[e]	—			1332 s.[g]	1162 s.[f]
$NH_2COCH_2SO_2NH_2$ (VII)	—	—	—		1654 v.s.	1334 v.s.	1170 v.s.
$NH_2COCH(CH_3)SO_2NH_2$ (Va)	5	(230)	50		1658 v.s.	1310 v.s.	1168 w.
	10	(230)	200				
	0.1*N*	(230)	280				
	1*N*	(230)	290				
$NH_2COC(CH_3)_2SO_2NH_2$ (Vb)	10	(230)	228		1676 v.s.	1317 v.s.	1168 v.s.
	0.1*N*	(230)	370				
$CH_3NHCOCH_2SO_2NH_2$ (IX)	—	—	—		1667 v.s.	1327 s.[g]	1162[g]
$NH_2CONHCH_2CH_2SO_2NH_2$	—	—	—		1648 s.	1337 s.	1146 m.
$CH_3SO_2NHCONH_2$	—	[e]	—	1710 v.s.[g,h]		1331	1150 v.s.[g,h]
						1318 s.[g,h]	
III	—	[e]	—	1700 v.s.		1320 v.s.	1172 v.s.
$CH_3NHCOCH_2SO_2NHCONH_2$ (X)	2	(230)	140	1706 s.	1646 v.s.	1315 s.	1168 v.s.
	5	(230)	140				
	10	(230)	240				
	0.1*N*	(230)	240				
$NH_2COCH_2SO_2NHCONH_2$	10[i]	(230)	150	1706 m.	1686 s.	1337 m.	1170 m.
$NH_2COCH(CH_3)SO_2NHCONH_2$ (VIa)	—	—	—	1698 s.	1670 v.s.	1317 s.	1156 v.s.
$NH_2COC(CH_3)_2SO_2NHCONH_2$ (VIb)	10[i]	(230)	400	1722 w.	1688 s.	1313 m.-s.	1168 m.
Ia	1	(238)	950	1714 (sh)	1698 s.	1360 s.	1172 s.
	5	(238)	1150				
	10	(238)	1600				
	11.5	237	5440				
	1*N*	238	6800				
Ib	10	(240)	1350	1710 v.s.	1690 v.s.	1331 s.	1154 v.s.
	0.1*N*	240	5860[j]				
Ic	10	(244)	1050	1738 v.s.	1678 v.s.	1355 v.s.	1170 v.s.
	0.1*N*	244	3420[j]				
Id[k]	11.1	(241)	1350	1740 s.	1705 s.	1325 s.	1170 s.
	0.1*N*	241	5850[j]				

[a] All spectra taken in aqueous buffers (details in Experimental). [b] Values corrected and taken from Nujol mulls except where noted otherwise. [c] Figures in parentheses are arbitrary wave lengths where only rising end absorption was observed. [d] Assignment made on basis of Ref. 20. [e] Transparent at $10^{-3}M$. [f] Reported values: 1336, 1169 cm.$^{-1}$ (Ref. 20). [g] Potassium bromide pellet. [h] Uncorrected. [i] At other *p*H values the spectra are similar to those given for α-*N*-methylcarbamylmethanesulfonylurea. [j] Undergoes rapid decrease in ε in strongly basic solutions, probably due to hydrolysis. [k] Measurements made on sample 50% pure, as determined by titration.

The infrared spectrum of each thiadiazine has two bands in the carbonyl region. Taking III as the closest model of a simple sulfonylurea, the band of lower frequency in Ia-d is assigned to the 3-carbonyl, while that at higher frequencies is ascribed to the 5-carbonyl. These assignments are analogous to those of dihydrouracil, which has bands at 1696 (2-carbonyl) and 1760 cm.$^{-1}$ (4-carbonyl).[19]

In the sulfonyl region there is little variation in the positions of the bands for symmetrical and antisymmetrical stretching frequencies[20] whether a carbamyl group is introduced α to the sulfonyl group, or the sulfonamide group is converted to the sulfonylurea group. Substitution of the methylene carbon is accompanied in all cases by a decrease in frequency of the 1340 cm.$^{-1}$ band.

The cyclic compounds, like typical secondary amides, show no absorption peaks above 3280 cm.$^{-1}$ whereas the sulfonylureas and α-carbamylalkanesulfonamides all absorb strongly in the region of 3330–3380 cm.$^{-1}$, and some absorb also above 3400 cm.$^{-1}$ (The absorption at these frequencies must be due to the carboxamide group in the α-carbamylalkanesulfonamides, as methanesulfonamide does not absorb above 3300 cm.$^{-1}$). The purity of the thiadiazines Ia–d and III can be determined by the extent of absorption above 3280 cm.$^{-1}$ This provides a convenient check on samples which may have undergone hydrolysis on standing.

Synthesis of Model Compounds. Compounds Ia and III were prepared by the method described previously,[4b] and Ib and Ic by modifications of that method as outlined in equations 1 and 2.

The alkylation of diphenylsulfoacetate (Equation 1) was complicated by cleavage to phenyl methanesulfonate when carried out in the presence of aqueous sodium hydroxide or sodium ethoxide in

(19) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. van Nostrand Co., New York, 1949, p. 179.

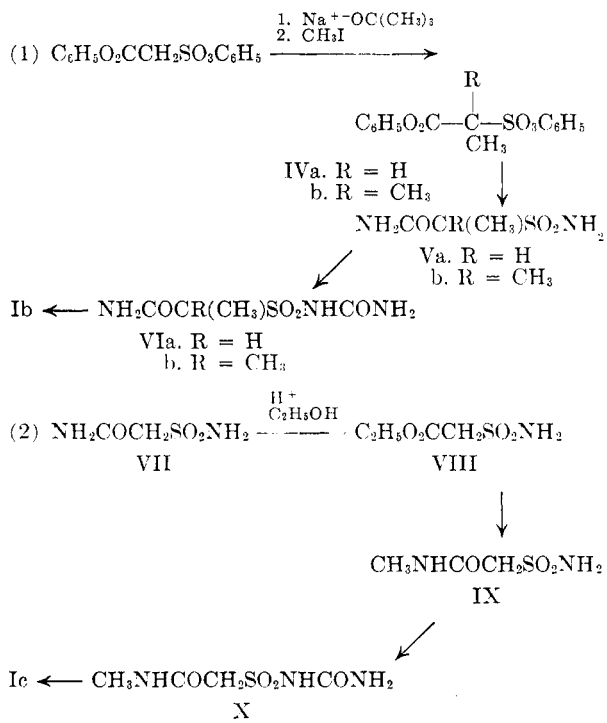
(20) J. N. Baxter, J. Cymerman-Craig, and J. B. Willis, *J. Chem. Soc.*, 669 (1955).

TABLE III

ANALYTICAL DATA

Compound	No.	R_1	R_2	R_3	M.P. or B.P. (Mm)	Yield, %	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
Diphenyl sulfo esters	IVa	H	CH_3	—	183–184 (0.3)	61	58.82	58.88	4.58	4.68	—	—
$C_6H_5O_2CCR_1R_2SO_3C_6H_5$	IVb	CH_3	CH_3	—	179–80 (0.3)	35	60.00	60.07	5.00	5.04	—	—
Sulfonamides	Va	CH_3	H	H	184–185[a]	68	23.69	23.56	5.27	5.19	18.43	18.14
$R_3NHCOCR_1R_2SO_2NH_2$	Vb	CH_3	CH_3	H	213–214d[b]	21[e]	28.68	28.42	6.02	6.02	16.87	16.60
	IX	H	H	CH_3	129.5–130[b]	68	23.69	23.69	5.27	5.00	18.35	18.12
Sulfonylureas	VIa	CH_3	H	H	165–165.5d[c]	59[e]	24.61	24.86	4.62	4.79	21.55	21.30
$R_3NHCOCR_1R_2SO_2$-NHCONH$_2$	VIb	CH_3	CH_3	H	178–179d[c]	73	28.70	28.84	5.26	5.64	—	—
	X	H	H	CH_3	168–169d[b]	48	24.61	24.88	4.62	4.62	21.55	21.50
Pyridinium	Ib	CH_3	H	H	148–149.5[c]	53[e]	42.05	42.08	4.28	4.49	16.35	16.03
salts of	Ic	H	H	CH_3	149–150d[b]	37[e]	42.05	42.30	4.28	4.24	16.35	16.24
Thiadiazines	Ib	CH_3	H	H	200–201d[d]	77[e]	26.95	26.84	3.37	3.40	15.73	15.41
	Ic	H	H	CH_3	129.5–130d[d]	[f]	26.95	26.94	3.37	3.23	—	—

[a] Recrystallized from methanol. [b] Absolute ethanol. [c] Absolute ethanol-ether. [d] Sublimed. [e] Crude. [f] Low.



anhydrous ethanol.[21] Although some alkylated product was usually obtained, the yields were low and variable. When diphenyl sulfoacetate itself was heated with alkaline aqueous ethanol for two hours, phenyl methanesulfonate was isolated in 46% yield.[22,23]

$$C_6H_5O_2CCH_2SO_3C_6H_5 \longrightarrow CH_3SO_3C_6H_5 + C_6H_5O^- + CO_2$$

Alkylation of diphenyl sulfoacetate without cleavage was achieved by using sodium in *t*-butyl alcohol at room temperature. Diphenyl α-sulfopropionate (IVa) was then obtained in 65% yield and diphenyl α-sulfoisobutyrate (IVb) in 35% yield. The esters were converted to the corresponding diamides (Va-b) by reaction with liquid ammonia in a sealed tube.[24]

(21) In one instance, when the reaction was carried out at room temperature under the conditions for the synthesis of diphenyl α-sulfoisobutyrate, phenyl ethanesulfonate was the major product, indicating that alkylation had taken place before cleavage.

(22) Diphenyl sulfoacetate was recovered unchanged after prolonged heating in ethanolic hydrochloric acid.

(23) The cleavage of sulfo esters, such as dipheny sulfoacetate, has not been reported. It is closely related, however, to the well-known base-catalyzed cleavage of β-sulfo ketones, acids, and esters [A. W. Weston and C. M. Suter, *J. Am. Chem. Soc.*, **61**, 389 (1939); E. Barr, W. M. Ziegler, and R. Conner, *J. Am. Chem. Soc.*, **63**, 105 (1941)].

(24) The synthesis of α-sulfamylisobutyramide (Vb) by ammonolysis of methyl α-chlorosulfonylisobutyrate was reported by M. J. Moll van Charante [*Rec. trav. chim.*, **32**, 91 (1913)]. However, the reported m.p. was >340°, whereas the diamide obtained in the present work melted at 214–215° dec., more in accord with the melting points of the other diamides prepared in this series. The structure of our diamide is established by its analysis and by conversion to the sulfonylurea. From its melting point and solubility characteristics the product reported by Moll van Charante was probably a salt.

The cyclization of the sulfonylureas VIa and X to the pyridinium salts of the thiadiazines Ib-c occurred smoothly in refluxing pyridine. Compound Ib was obtained from the salt by treatment with a cation exchange resin, as described previously,[4b] but when this method was applied to the salt of Ic, sulfamyl *N*-methylacetamide (IX) was the principal product. Heating the salt of Ic under reduced pressure proved to be a superior method for obtaining the thiadiazine.

When 2-carbamyl-2-propanesulfonylurea (VIb) was heated in pyridine, a crystalline material was obtained which had the properties of a pyridine salt, but an analysis in agreement with the composition of the salt of Id could not be obtained. Attempts to convert the salt to Id were unsuccessful. It seems likely that cyclization occurred but that hydrolysis took place during the reaction and in the subsequent workup. Cyclization of VIb was finally achieved by scaling up the conditions used for following spectrophotometrically the conversion of VIb to Id.

Physical properties are summarized in Table III.

EXPERIMENTAL[25]

Diphenyl α-sulfopropionate. A solution of 1.97 g. (0.086 mole) of clean cut sodium metal in 200 ml. of warm, freshly distilled *t*-butyl alcohol was added dropwise to a rapidly stirred slurry of 25.0 g. (0.086 mole) of diphenyl sulfoacetate[4b] and 24.3 g. (10.7 ml., 0.17 mole) of methyl iodide in 100 ml. of dry *t*-butyl alcohol. The addition was carried out at such a rate that a phenolphthalein indicator in the mixture remained colorless or only slightly pink in color. The addition required a total of 29 hr. at room temperature. After the final addition, stirring was continued until the mixture became neutral to moist litmus. It was then washed with several portions of saturated sodium chloride solution to remove sodium iodide and then dried over anhydrous magnesium sulfate. After volatile materials had been removed under aspirator pressure, the residual oil was distilled. The light yellow distillate [b.p. 187–188° (0.40 mm.)] weighed 15.9 g. (61%). A portion of the product was redistilled for analysis at 183–184° (0.30 mm.).

Diphenyl α-sulfoisobutyrate. The above procedure was used with 1.58 g. (0.067 mole) of sodium (in 100 ml. of *t*-butyl alcohol), and 10.0 g. (0.034 mole) of diphenyl sulfoacetate and 20.0 g. (8.5 ml., 0.14 mole) of methyl iodide in 100 ml. of *t*-butyl alcohol. Addition of the sodium *t*-butoxide solution required 4 days. Distillation of the crude product yielded 3.9 g. (35%) of a yellow oil, b.p. 178–180° (0.40 mm.). A portion of this material was redistilled for analysis at 179–180° (0.40 mm.).

Hydrolysis of diphenyl sulfoacetate. A. *Alkaline hydrolysis.* Diphenyl sulfoacetate (4.0 g., 0.014 mole) was heated with a solution of 0.75 g. of sodium hydroxide in 75 ml. of 50% aqueous ethanol at reflux temperature for a period of 2 hr. After the reflux period, the pink mixture was cooled and extracted with several portions of ether, which were combined and dried over anhydrous magnesium sulfate. When the ether was removed the residual oil readily solidified on cooling. By rinsing several times with a mixture of ether and petroleum ether (b.p. 60–80°), 1.1 g. (46%) of powdery white solid, m.p. 59–60.5°, was obtained. It was identified by its analysis and melting point[26] as phenyl methanesulfonate.

Anal. Calcd. for $C_6H_8O_3S$: C, 48.80, H, 4.65; Found: C, 49.00, H, 4.68.

Cleavage also occurred in the presence of refluxing ethanolic potassium cyanate.

B. *Attempted acidic hydrolysis.* A mixture of 4.0 g. (0.014 mole) of diphenyl sulfoacetate, 3.0 ml. of concd. hydrochloric acid and 100 ml. of a 50% aqueous ethanol solution was refluxed for 1.5 hr. The hot mixture was then filtered and cooled thoroughly in an ice bath. The white solid which separated was removed by filtration. This material was identified as unchanged diphenyl sulfoacetate, m.p. 80–81°.

Ethyl sulfamylacetate. A mixture of 9.53 g. (0.069 mole) of sulfamylacetamide,[4b] 6.5 ml. of concd. sulfuric acid, and 150 ml. of absolute ethanol was refluxed on a steam bath for a period of 17 hr. At the conclusion of the heating period the excess ethanol was removed by distillation; the last traces were removed azeotropically with benzene. The residual oil was then extracted continuously with benzene until it became crystalline. The benzene solution was thoroughly chilled, filtered and the solid material thus obtained was washed with pet. ether, yielding 5.7 g. of shiny white platelets. By evaporation and chilling of the filtrate an additional 2.5 g. was obtained. The total yield of product, m.p. 66–67°, was 8.2 g. (71%) (reported[4a] m.p. 67–68°).[27]

An attempt to apply this procedure to the synthesis of ethyl α-sulfamylpropionate from α-sulfamylpropionamide was unsuccessful. The attempted methanolysis of α-sulfamylacetamide also failed.

α-Sulfamyl-N-methylacetamide. A mixture of 3.63 g. (0.022 mole) of ethyl sulfamylacetate and 15–20 ml. of liquid methylamine contained in a tube immersed in a Dry Ice-isopropyl alcohol bath was allowed to stand with frequent stirring for a period of 16 hr. After 10 hr. a heavy white precipitate had formed. At the conclusion of the reaction time, the mixture was dissolved in methanol and the resulting solution warmed slightly to remove excess methylamine. The warm solution was then filtered, chilled, and filtered again. In this way 3 g. (68%) of a white, crystalline solid, m.p. 129–130°, was obtained. A sample of analytical purity, m.p. 129.5–130°, was obtained by recrystallization from absolute ethanol.

N-Methylcarbamylmethanesulfonylurea. A mixture of 3.73 g. (0.021 mole) of the potassium salt of carbethoxymethanesulfonylurea and 20–25 ml. of liquid methylamine, to which was added 2 ml. of water to increase the solubility of the salt in the amine, was allowed to stand with frequent stirring in a Dry Ice-isopropyl alcohol bath for a period of 24 hr. The mixture was then transferred to a flask by rinsing with small portions of absolute ethanol. The ethanolic solution was warmed slighty to remove excess methylamine and then reduced in volume by boiling for several minutes. An equal volume (approximately 40 ml.) of water was added and the resulting solution passed through a column of Dowex-50 cationic exchange resin. The strongly acidic eluant was evaporated under a jet of air. The concentrated solution after cooling yielded 1.4 g. (48%) of a white crystalline material, m.p. 168–170° dec. After two recrystallizations from an absolute ethanol-ether mixture, this material melted at 168–170° dec. and was found to be identical to the *N*-methylcarbamylmethanesulfonylurea prepared from sul-

(25) Melting points and boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 21 recording spectrophotometer equipped with sodium chloride optics. Ultraviolet spectra were obtained with a Beckman DK-2 recording spectrophotometer, using quartz cuvettes of 1 cm. light path.

(26) C. Schall, *J. prakt. Chem.*, (2), **48**, 244 (1893).

(27) This method of preparation of ethyl sulfamylacetate is much superior to that reported earlier,[4b] because it avoids the half-hydrolysis of sulfoacetic diacid chloride, a reaction which could not be carried out in better than 15–20% yield.

famyl-*N*-methylacetamide by reaction with potassium cyanate.[4b,28]

4-Methyl-1,2,4,2H-thiadiazine-3,5(4H,6H)-dione-1,1-dioxide by thermal decomposition of the pyridinium salt. Approximately 0.5 g. of the pyridinium salt obtained by the cyclization procedure described previously,[4b] was heated in a sublimation block at 120–125° and 0.2 mm. After several minutes the salt decomposed without charring, releasing a gas. At the end of the decomposition the fused mass solidified and sublimed, leaving no residue. The white sublimate, m.p. 124–134° dec. was sublimed again, yielding analytically pure product, m.p. 130–131.5° dec., which was identical to material obtained in low yield by treatment of a methanolic solution of the pyridinium salt with a cation exchange resin. (In aqueous solution complete hydrolysis of the pyridinium salt to *N*-methylsulfamylacetamide took place during treatment by the ion exchange resin.)

6,6-Dimethyl-1,2,4,2H-thiadiazine-3,5-(4H)-dione-1,1-dioxide. Compound VIb (0.09 g.) was dissolved in 0.2*N* sodium hydroxide solution and allowed to stand for 45 min. The alkaline solution was passed down a column of Dowex-50-X4 resin and the strongly acidic eluant was evaporated under a current of air. The crude material (0.08 g.) melted at 157–165° dec. and showed strong bands at 1695, 3240, 3350, and 3470 cm.$^{-1}$ A weak band at 1740 cm.$^{-1}$ showed the presence of thiadiazine. The ultraviolet spectrum of the crude material in 0.1*N* sodium hydroxide contained a peak at 241 mμ. Vacuum sublimation (120–138° at 0.35 mm.) gave three fractions. The first melted at 152–153° and showed greatly increased absorption at 1740 cm.$^{-1}$ By titration it was shown to contain 28% of Id. The second fraction melted at 153–154° and contained 50% Id. The third fraction melted at 188–190° dec. and showed no peak at 1740 cm.$^{-1}$ Absorption at 1680, 3340, and 3440 cm.$^{-1}$ had increased greatly. This fraction contained no strongly acidic material and its basic solution showed no maximum in the ultraviolet. This fraction apparently consisted of a mixture of the hydrolysis products, Vb and VIb.

pK_a' Measurements. The apparent pK_a values of the sulfonamides and sulfonylureas were determined at 25° by titration, with the aid of a Model G Beckman *p*H meter equipped with calomel and glass electrodes and standardized before use with standard buffer at *p*H 7.00. Two-milliliter aliquots of aqueous stock solutions (ca. $1.6 \times 10^{-2}M$) of the compounds were titrated with 0.1020*N* sodium hydroxide solution. The *p*Ka′ was calculated from the *p*H at approximately 20%, 40%, and 60% neutralization by means of the Henderson equation.[29] The *p*Ka values of the more acidic thiadiazines (Ia–d) were calculated from the *p*H values of solutions of known concentration (about 0.01*M*). The values reported for the thiadiazines and their precursors are the means of at least two determinations. The average deviation $\leq$ 0.06 *p*K unit, with the exception of Id, for which the a.d. $\sim \pm$ 0.5.

For the spectrophotometric determination of pK_a' of Ia and for determination of all other ultraviolet spectra, the following buffers were used: *p*H 1, 0.1*N* hydrochloric acid–potassium chloride; *p*H 5, 0.14*N* acetate; *pH* 8–10, 0.05*M* borate; *p*H 10–11.75 *ca.* 0.05*M* glycine (and sodium hydroxide).

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(28) This synthesis, together with the preparation of both isomeric amide ureides of sulfoacetic acid,[4b] establishes clearly that potassium cyanate attacks the sulfonamide group rather than the carboxamide group under these conditions.

(29) S. Glasstone, *The Electrochemistry of Solutions*, Methuen and Co., Ltd., London, 1930, p. 207.

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The Preparation and Desulfurization of Some Unsymmetrically Substituted Thiiranes

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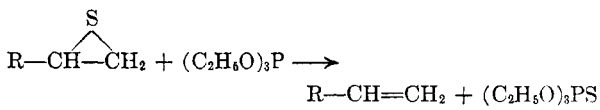
A number of unsymmetrically substituted thiiranes, 2-alkoxymethylthiiranes, 2-thioalkylmethylthiiranes, and 2-diethylaminoethylthiirane, have been prepared. The reaction of triethyl phosphite with the 2-alkoxymethylthiiranes as well as with several known thiiranes has been investigated and found to result, in all cases, in the desulfurization of the thiirane with the formation of triethyl thionophosphate and an olefinic compound corresponding to the thiirane. Desulfurization of the 2-alkoxymethylthiiranes was also noted in their reactions with phenyllithium, butyllithium and with methyl iodide, yielding again an olefinic compound corresponding to the thiirane.

Recently[2] it was reported, from these laboratories, that heating an equimolar mixture of triethyl phosphite and a thiirane at its reflux temperature, for a short period, results in the formation of triethyl thionophosphate with the simultaneous conversion of the thiirane to its corresponding unsaturated compound.



Davis,[3] at the same time, described the formation of cyclohexene and triethyl thionophosphate from the reaction of 2,3-tetramethylenethiirane and triethyl phosphite in ether.

This paper reports on further investigations of this desulfurization reaction with the thiiranes,

(1) Abstracted in part from the doctoral thesis of R. L. Jacobs.

(2) R. D. Schuetz and R. L. Jacobs, *J. Org. Chem.*, **23**, 1799 (1958).

(3) R. E. Davis, *J. Org. Chem.*, **23**, 1767 (1958).