THE CHEMISTRY OF THIADIAZOLE AND THIADIAZINE S-OXIDES

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Contents

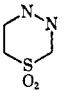
I. Introduction

Whereas the various thiadiazoles and thiadiazines have in recent years been the subject matter of a number of reviews, little mention[1-3] has been made of the corresponding S-oxide and S-dioxide derivatives. In this review therefore, an attempt has been made to bring together the known chemistry of the various thiadiazole and thiadiazine S-oxides. Except for the 1,2,4-benzothiadiazine 1,1-dioxides which merit a separate review, the benzo analogs of these heterocyclic systems, where known, are reported. Other fused addends have not been included.

The various possible isomeric thiadiazole and thiadiazine S-dioxides have been schematically tabulated (Table I) according to their common structural aspects; this arrangement provides a framework for the review, with the separate sections as indicated.

Table I

Arrangement of Contents

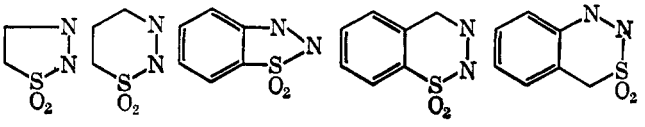
Cyclic sulfonylhydrazides	 
Cyclic α- and β-aminosulfonamides	  
Cyclic sulfamide derivatives	 
Cyclic hydrazino sulfones	  

The literature has been searched to December 1968, and every effort has been made to collect more recent data where available. For the most part the main source of information was the subject indexes of *Chemical Abstracts* which list the S-dioxide compounds among the reduced parent analogs.

II. Cyclic Sulfonyl Hydrazides

A. INTRODUCTION

Representative derivatives of the 1,2,3-thiadiazole and 1,2,3-thiadiazine 1,1-dioxides (A–D) have been prepared, the only remaining type as yet not synthesized being system E. The



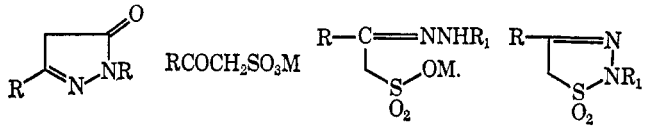
A B C D E

most interesting 1,2,3-benzothiadiazoles (C) have been considered only as heterocyclic members of the series. Benzyne derivatives have not been dealt with as their chemistry has been fully dealt with elsewhere. It is perhaps worthy of note that until recently[2] the only known 1,2,3-benzothiadiazine heterocycles were in fact the S-dioxides.

B. SYNTHESIS FROM SULFONIC ACID DERIVATIVES

These compounds have been prepared by ring closure of β-ketoalkylsulfonic acid derivatives. The first synthesis, de-

(1) L. L. Bambas in "The Chemistry of Heterocyclic Compounds," Vol. 4, Interscience, New York, N. Y., 1962, p 3.
(2) R. C. Elderfield, "Heterocyclic Compounds," Vol. 7, Wiley, New York, N. Y., 1961.
(3) A. Dolars, "Houben-Weyl, Methoden der Organischen Chemie," Vol. 11, 2nd ed, Georg Thieme, Stuttgart, 1958, p 725.



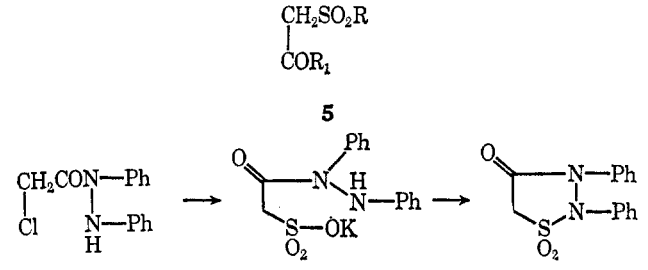
1 2 3 4

scribed by Mazak and Suszko[4] in 1929, was only developed much later on by other workers[5] seeking analogs of Δ^5-pyrazol-3-ones (**1**). The β-ketoalkylsulfonic acid (**2**), readily available[6,7] from the ketone on treatment with the sulfur trioxide–dioxane complex, was converted to the corresponding hydrazone (**3**), which was ring-closed in phosphorus oxychloride to give the Δ^3-1,2,3-thiadiazoline 1,1-dioxide (**4**). The ring closure of analogous carbonyl derivatives (*i.e.*, oxime and semicarbazone) appears not to have been attempted.

C. SYNTHESIS FROM ACYL HYDRAZONES

1. Ring Closure of α-Sulfoacetylhydrazides

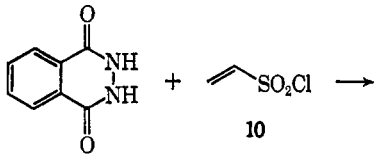
The utility of the monosulfo analogs of malonic acid, *i.e.*, the α-carboxyalkylsulfonic acid derivatives (**5**), as precursors in heterocyclic S-oxide synthesis is more fully exemplified under cyclic α- and β-aminosulfonamides (section III). It is, however, interesting to note their use in synthesizing another ring system. Treatment of the chloroacetylhydrazide (**6**) with potassium sulfite gave in excellent yield in the usual way the sulfonic acid derivative (**7**) which was then ring-closed[8] in phosphorus oxychloride (as in section B above) to give the 2,3-diphenyl-1,2,3-thiadiazolidin-4-one 1,1-dioxide (**8**). A patent literature claim[9] described the synthesis of this derivative (**8**) by action of the diacid chloride (**5**, R = R_1 = Cl) upon N,N′-diphenylhydrazine directly.



5

6 7 8

Considering this and the previous reaction (section B above), the method of ring closure, presumably *via* the interim formation of a sulfonyl halide followed by an intramolecular acylation, would appear to merit further study, as it seems the choice of suitable starting materials might by this route provide general access to the 1,2,3-thiadiaza-S-dioxo system.



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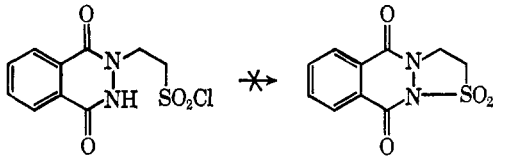
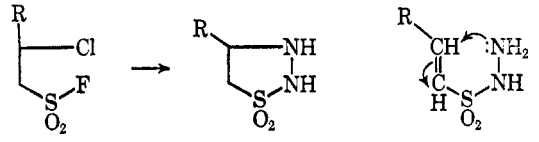


11 12

A recent attempt[10] to prepare the fused ring system **12** from the sulfonyl chloride **11**, which in turn came from the action of ethylenesulfonyl chloride (**10**) upon the cyclic hydrazide **9**, failed, even though the analogous system with a carbonyl group replacing the sulfonyl group gave the required fused ring system.[11] Presumably, both the rigidity of the cyclic hydrazide and the large sulfonyl group conspire to prohibit this reaction.

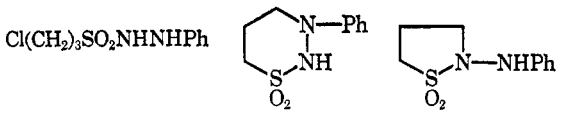
2. Ring Closure of β- or γ-Haloalkylsulfonylhydrazides

The only reported route[12] for the synthesis of the fully saturated parent five-membered ring (**13**) is by the action of hydrazine upon the β-halogenoalkylsulfonyl fluoride (**14**). This reaction is not so surprising in spite of the ready dehydrohalogenation to α,β-unsaturated derivatives that β-halogenoalkylsulfonyl halides undergo.[13] The product might have been **15**, or possibly its formation involved the ring closure of **15**, a not unlikely process,[14] or that of the β-hydrazinosulfonyl fluoride formed by hydrazine addition after dehydrohalogenation.



14 13 15

The analogous six-membered ring compound (**17**) was prepared by Helferich, *et al.*,[15] in the course of an extended study of sultam chemistry, *via* the classical but very inefficient ring closure of the γ-chloropropylsulfonylhydrazide (**16**) with base. The possibility that the product was the alternative isomer (**18**) was discounted by its solubility in alkali, thereby demonstrating the presence of the sulfonamide N–H group.

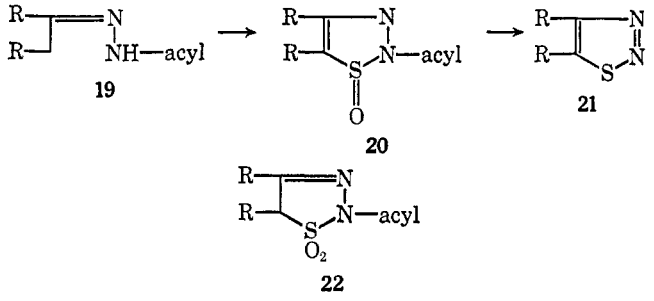


16 17 18

(4) P. Mazak and J. Suszko, *Rocz. Chem.*, **9**, 431 (1929); *Chem. Abstr.*, **23**, 3468 (1929).
(5) A. P. Terent'ev and M. N. Preobrazhenskaya, *Zh. Obshch. Khim.*, **26**, 3468 (1956).
(6) E. E. Gilbert, "Sulphonation and Related Reactions," Interscience, New York, N. Y., 1965.
(7) L. C. Schroeter, "Sulphur Dioxide," Pergamon Press, London, 1966.
(8) A. Mustafa, M. Kira, and H. Hanna, *Angew. Chem.*, **76**, 919 (1964).
(9) R. Doson and V. Papesch, U. S. Patent 3,037,027 (1962); *Chem. Abstr.*, **57**, 12502 (1962).
(10) A. le Berre and B. Dumaitre, *C. R. Acad. Sci.*, **265**, 642 (1967).
(11) A. le Berre, M. Dormoy, and J. Godin, *ibid.*, **261**, 1872 (1965).
(12) W. S. Friedlander, U. S. Patent 2,895,958 (1959); *Chem. Abstr.*, **54**, 4622 (1960).
(13) C. S. Rondestvedt, Jr., *J. Amer. Chem. Soc.*, **76**, 1926 (1954).
(14) A. Goldberg, *J. Chem. Soc.*, 464 (1945).
(15) B. Helferich, R. Hoffmann, and H. Mylenbusch, *J. Prakt. Chem.*, **19**, 56 (1962).

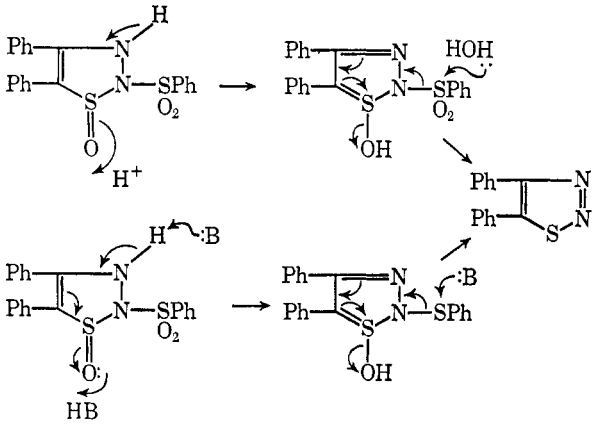
3. From Acyl Hydrazones

The action of thionyl chloride upon acyl hydrazones of the type **19** has been shown[16] to give Δ^4-1,2,3-thiadiazoline 1-oxides (**20**). This reaction was, however, complicated by the fact that the S-oxide (**20**) was converted by either acid or base catalysis to the 1,2,3-thiadiazole (**21**), to the extent that this



method with suitably chosen conditions provided a simple and direct synthesis of **21** from **19**. The acid and base catalysis mechanisms shown in Scheme I have been proposed.[16]

Scheme I

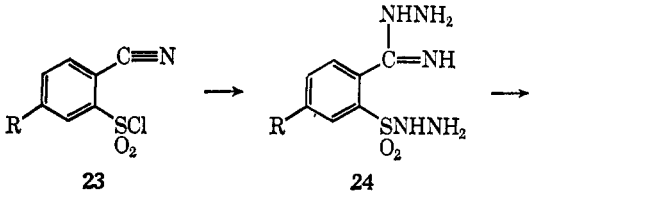


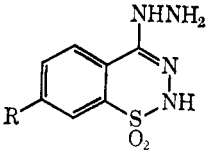
A conversion to the probably more stable dioxide (**22**) was unfortunately not attempted, neither by the use of sulfuryl chloride nor by the oxidation of **20**.

D. SYNTHESIS FROM *ortho*-SUBSTITUTED BENZENESULFONIC ACID DERIVATIVES

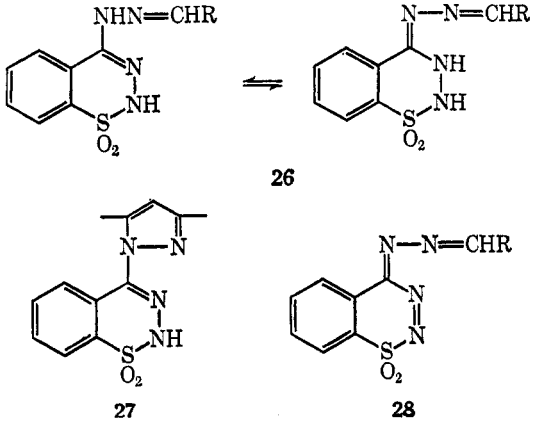
1. From o-Cyanobenzenesulfonyl Chloride (23)

The first recorded members of this class were prepared by the method of Schrader,[17] from the action of anhydrous hydrazine upon *o*-cyanobenzenesulfonyl chloride, to give the 4-hydrazino-2H-1,2,3-benzothiadiazine 1,1-dioxide (**25**, R = H). Although two further sources[18,19] confirmed this reaction,





indicating that hydrazine hydrate could be used[18] and that **23** (R = H) was available from saccharin by the action of phosphorus pentachloride,[19] the only serious study was that of a group[20] seeking analogs of the pharmacologically active 1,2,4-benzothiadiazine 1,1-dioxides. Thus it was shown[20] that the intermediate (**24**, R = OEt) could be isolated as its hydrochloride and ring-closed in dilute aqueous–ethanolic hydrochloric acid to give the same ring compound (**25**, R = OEt) as obtained by direct synthesis, so confirming its intermediary presence. Whereas the side-chain hydrazino group was established by the ready formation of hydrazones (**26**) as well as ring formation to **27** with acetylacetone, the ring hydrazino group was confirmed by oxidation of the isopropylidene derivative (**26**, R = *i*-Pr) to the novel azine (**28**). The detailed structure of **26** was not commented upon despite the plausibility of such tautomerism (see the case for amidines[21]). A claim[22] for the synthesis of compound **25** (R = H) reports a compound of melting point different from both the product and its hydrochloride obtained by the method already noted above.[4,19]

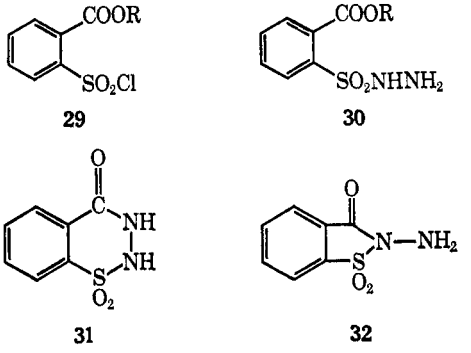


2. From o-Chlorosulfonylbenzoic Acid Esters

In the course of studying the chemistry of *o*-sulfobenzoic acid esters it was shown[23] that the ester (**29**) did not give the anticipated sulfonyl hydrazine (**30**) but the ring-closed derivative (**31**). Once again the alkali solubility of the compound was regarded as a sufficient criterion to specify the structure

(16) C. D. Hurd and R. I. Mori, *J. Amer. Chem. Soc.*, 77, 5359 (1955).
(17) E. Schrader, *J. Prakt. Chem.*, 96, 180 (1917).
(18) Ciba Ltd., Belgian Patent 615,374 (1962); *Chem. Abstr.*, 60, 1779*h* (1964).
(19) M. Goudal, A. Goudal, P. Vernadeau, and J. Vernadeau, French Patent M 2166 (1963); *Chem. Abstr.*, 60, 8048*f* (1964).
(20) P. Schmidt, K. Eichenberger, and M. Wilhelm, *Helv. Chim. Acta*, 45, 996 (1962).
(21) D. C. Prevorsek, *J. Phys. Chem.*, 66, 769 (1962).
(22) J. E. Robertson, U. S. Patent 3,153,614 (1964); *Chem. Abstr.*, 62, 1675*b* (1965).
(23) B. Loev and M. Kormendy, *J. Org. Chem.*, 27, 1703 (1962).

as **31** rather than **32**. A compound of the same melting point was previously reported[24] as sulfobenzoic acid hydrazide.

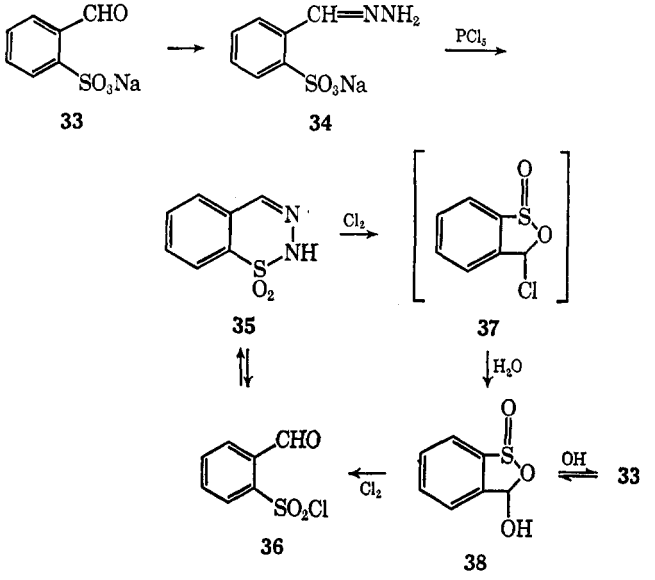


29 **30**

31 **32**

3. *From o-Aldehydo- and Keto-Substituted Benzenesulfonyl Chlorides*

Two recent independent applications[25,26] of the same route to 1,2,3-benzothiadiazine 1,1-dioxides have led to the parent and 4-substituted systems **35** and **41**. Thus by treating the hydrazone **34** from the sodium salt of *o*-sulfobenzaldehyde with phosphorus pentachloride, the thiadiazine (**35**) could be obtained in good yield. The structure,[25] arising in a study of sulfene chemistry, was confirmed by the action of hydrazine upon the corresponding sulfonyl chloride (**36**). The action of an equimolar quantity of chlorine gave, after vigorous loss of nitrogen, a compound tentatively assigned the structure **37**, which on hydrolysis produced the novel pseudo acid **38** and could be converted with alkali to **33** or with chlorine to **36**.

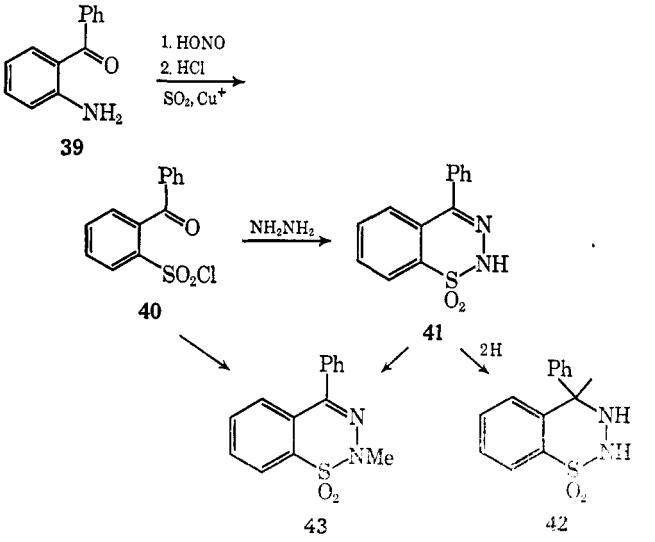


33 **34**

35 **37**

36 **38**

The ready access to *o*-benzoylbenzenesulfonyl chloride (**40**) by the diazotization of the amine (**39**) followed by treatment with sulfur dioxide in the presence of cuprous ions has led to the synthesis of a number of novel heterocyclic systems,[26,27] and particularly, using hydrazine,[26] to the 1,2,3-benzothiadiazine system (**41**). Replacing the hydrazine by



39

40 **41**

43 **42**

methylhydrazine gave the same product (**43**) as resulted from the alkylation of **41** with methyl iodide and sodium hydroxide, while catalytic reduction on platinum gave the fully saturated molecule (**42**).

4. *From o-Aminobenzenesulfonic Acid Derivatives*

Since the first synthesis in 1961 by Wittig and Hoffmann[28] of the 1,2,3-benzothiadiazole 1,1-dioxide (**45**), this compound has now become accepted[29] as a standard interim step in the generation, under mild conditions, of the reactive intermediate benzyne (**48**). The diazotization of sodium *o*-aminobenzenesulfinate[30-32] (**44**) at low temperatures (∽−20°) followed by repeated extraction with ether gave a compound which decomposed at 60° and has been shown[32] to have the structure **45**. The kinetic[32] behavior of **45** together with the fact[31] that reduction with zinc–acetic acid gave compound **46**, which with lead tetraacetate gave back **45**, ruled out the alternative structure **47**.

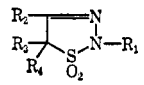
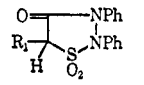
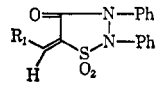
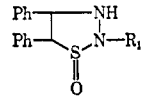
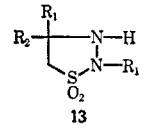
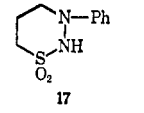
The preparation of substituted precursors **49** and their conversion to 1,2,3-benzothiadiazole 1,1-dioxides together with the reaction of the consequently available benzynes with nucleophiles has been examined[33,34] in some detail. It is of interest to note that the reduction products (**46**, and its 5- and 6-substituted derivatives), the 1,2,3-benzothiadiazoline 1,1-dioxides, appear to be thermally stable compounds.

A more recent extension[35] of the above method, devised so as to provide dehydronaphthalene intermediates, has resulted in the preparation of the fused ring system **51**. Again this compound is directly prepared by diazotizing the corresponding *peri*-aminosulfinate **50**. The compound is, however, considerably more thermally stable than the presumably ring-strained five-membered analog (**45**) and does

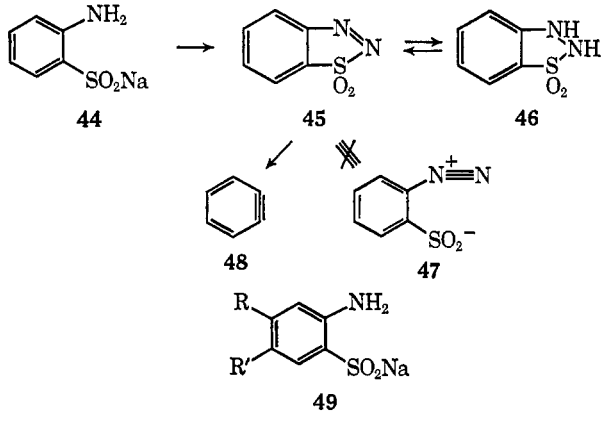
(24) H. A. Offe, W. Siefken, and G. Domagk, *Z. Naturforsch.*, **76**, 446 (1952).
(25) J. F. King, A. Hanson, D. Deaken, and J. Komery, *J. Chem. Soc. D*, 33 (1969).
(26) J. B. Wright, *J. Heterocycl. Chem.*, **5**, 453 (1968).
(27) J. B. Wright, *ibid.*, **5**, 719 (1968).
(28) G. Wittig and R. W. Hoffmann, *Angew. Chem.*, **73**, 435 (1961).
(29) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y. (Verlag Chemie, Weinheim), 1967.
(30) G. Wittig and R. W. Hoffmann, *Angew. Chem.*, **73**, 435 (1961).
(31) G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2718 (1962).
(32) R. W. Hoffmann, W. Sieber, and G. Guhn, *ibid.*, **98**, 3470 (1965).
(33) R. W. Hoffmann, W. Sieber, G. Guhn, and G. E. Vargas-Nunez, *ibid.*, **98**, 2074 (1965).
(34) G. Vargas-Nunez, *Bol. Soc. Quim. Peru*, **31**, 6 (1965); *Chem. Abstr.*, **64**, 9713*b* (1966).
(35) R. W. Hoffmann and W. Sieber, *Justus Liebigs Ann. Chem.*, **703**, 96 (1967).

Table II

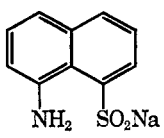
Monocyclic Derivatives of the 1,2,3-Thiadiaza-S-dioxo System

Compound		R_1	R_2	R_3	R_4	Yield, %	Mp, °C	Solvent[a]	Ref
 4	a	Ph	Me	H	H	62	85–86	Aq EtOH	5
	b	Ph	Me	Me	H	62	83–84	Aq EtOH	5
	c	Ph	Me	*i*-Pr	H	37	59–60	Aq EtOH	5
	d	Ph	*p*-Tol	H	H	37	155–156 d[b]	EtOH	5
 8	a	H					150 (150–152)[6]		8
	b	Et					109		8
	c	$PhCH_2$					181		8
	d	*p*-$MeOC_6H_4CH_2$					290 d		8
	e	2-Furylmethyl					116		8
 8	a	Ph					176		8
	b	*p*-$MeOC_6H_4$					290 d		8
	c	2-Furyl					183		8
	d	$OHOC_6H_4$					230		8
	e	$C_6N_5CH{=}CH$					197		8
 20	a	CH_3CO					169–170	EtOH	16
	b	$C_6H_5SO_2$					164–165	EtOH	16
 13	a	Et	H			45	138–140		12
	b	Me	Me			6	179–190 d		12
	c	Hexyl	H				123 d		12
 17						9	162		15

[a] Solvent of crystallization. d = decomposition.



not show any indication in terms of anticipated products, such as perylene (**52**), of decomposing *via* the desired dehydro entity. Reduction gave once more the corresponding dihydro product (**53**) which could be oxidized back to **51** with lead tetraacetate.



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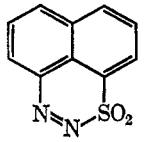

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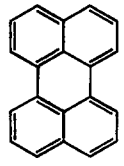

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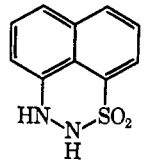

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E. PHYSICAL AND CHEMICAL PROPERTIES

Tables II and III record the rather limited list of physical properties of the compounds so far discussed. Only the more recent reports[25,26] provide any spectroscopic data by way of structural confirmation.

The reported[19] ir spectra of **25** (R = H) do little to explain the different melting points reported for supposely identical products (Table III). The uv spectra of 1,2,3-benzothiadiazine 1,1-dioxides are as follows: for **41b** (Table III), λ (ε) 211 (35,800), 243 sh (15,500), 313.5 (5350), 354 sh (527); **41c**, λ (ε) 213 (37,000), 245 sh (13,800), 321 (6250); **41e**, λ (ε) 230 sh (14,300), 251 sh (2650), 264 sh (1800), 272 sh (1600), 281 (1350), 305 (846), 358 (687) (sh = shoulder).

Scattered reports have provided knowledge of the susceptibility of the 1,2,3-thiadiaza-S-dioxo system to hydrolysis. Thus the compounds **4** and **8**, while stable to acid, were hydrolyzed by alkali to the open-chain precursor[5] **3** and N,N′-diphenylhydrazine,[8] respectively. The benzo system (**25**, R = H), on the other hand, gave on heating the disulfide

Table III

1,2,3-Benzothiadiaza-S-dioxo Compounds

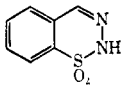
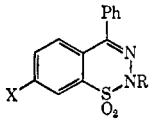
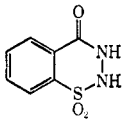
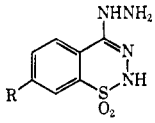
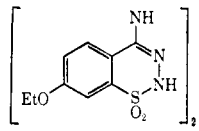
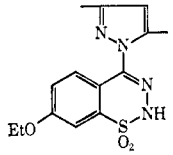
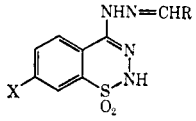
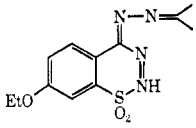
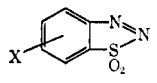
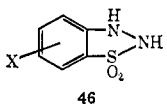
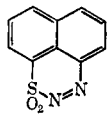
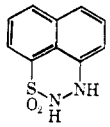
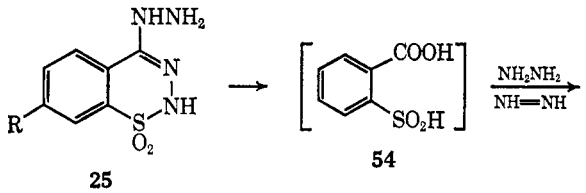
Compound		Yield, %	Mp, °C	Solvent[a]	Ref
 35		80		EtOH	25[e]
 41	**a**, X = H; R = H	39	192 d[b]	EtOH	26
	b, X = Cl; R = H	70	187 d	EtOAc	
	c, X = Cl; R = Me	62	124–125	EtOH	
	d, X = Cl; R = CH_3CO	87	140–145	Et_2O	
	e, X = Cl; R = H (3,4-dihydro)	61	142 d	*i*-PrOH	
 31		36	212–215	EtOAc–hexane	23
			210		24
 25	**a**, R = H		154	H_2O–EtOH	17, 18
			146	H_2O–EtOH	22[f]
			196	H_2O–EtOH	19
			176–177	(HCl salt)	22
	b, R = OEt	75	191–192 d	EtOH	20
	c, R = Cl		159 e[c]	EtOH	20
			195 d		20
 23			163–164	EtOH	20
 26	**a**, X = H; R = Ph		179		17
	b, X = H; RH = diPh		181 e		22
	c, X = H; R = −COOEt		120–125		22
	d, X = OEt; RH = diMe		150–152	EtOH	20
 28[d]			161 d	EtOH	20
 45	**a**, X = H	65	60 d		31
	b, X = 5-Me	82	30 d		33, 34
	c, X = 6-Me	79			33
	d, X = 5-Cl	45			33
	e, X = 6-Cl	54			33
	f, X = 5-Br	38			33
	g, X = 6-Br	44			33
	h, X = 5-OMe	17			33
	i, X = 6-NO_2	40			33
 46	**a**, X = H		116–117.5		31
	b, X = 5-Me	76	124		32
	c, X = 6-Me	40	143		32
	d, X = 5-Cl	20	160–162		32
	e, X = 5-Cl	17	156–158		32
	f, X = 5-Br	16	156–157		32
	g, X = 5-Br	9	159–161		32
	h, X = 5-OMe	12	158		32

Table III (Continued)

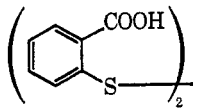
Compound	Yield, %	Mp, °C	Solvent[a]	Ref
 51	10–30	193	EtOH and $CHCl_3$	35
 53	88	218	MeOH	35

[a] Solvent of crystallization. [b] d = decomposition. [c] e, with explosive decomposition. [d] A yellow compound. [e] ν_{max} (NH) 3280, (CN) 1657, (SO_2) 1345, 1165 cm^{-1}; τ 6.9 (1 H, NH), 2.8 (1 H, CN=N), 2.1 (4 H, ArH). [f] ν_{max} 3500, 3300, 1630, 1600, 1370, 1170 cm^{-1}.

(55), no doubt by combined hydrolysis and reduction, the latter possibly involving diimide formed as an intermediate in the reaction



25 54



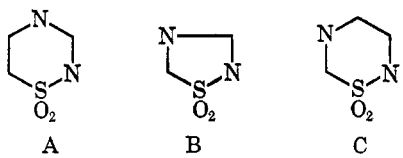
55

That the type 1 possessed an active methylene group was confirmed by the ease with which this compound formed alkylidene derivatives,[8,12] which on reduction gave the correspondingly substituted alkyl compounds. The ability of the analogous type (4) to couple with *p*-nitrophenyldiazonium chloride in the 5 position, though not with other diazonium compounds, reflects a limited activity at this position.

III. Cyclic α- and β-Aminosulfonamides

A. INTRODUCTION

This section describes the chemistry of the systems A, B, and C, *i.e.*, formally the 1,2,4-thiadiazine and thiadiazole 1,1-dioxides and the 1,2,5-thiadiazine 1,1-dioxides. It is convenient to discuss types B and C together, so placing type A in a separate section, thereby drawing a distinction between the cyclic α- and β-aminosulfonamides.

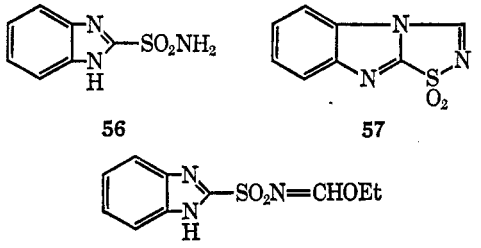


A B C

B. CYCLIC α-AMINOSULFONAMIDES

The two systems B and C are among the most poorly represented of all the derivatives considered in this review. As yet the system C has not been recorded, though two derivatives of the corresponding monooxide system have been reported (178 and 179).

The first preparation of a 1,2,4-thiadiazole 1,1-dioxide derivative was that of Stanovnik and Tisler[36] who treated benzimidazole-2-sulfonamide (56) with triethyl orthoformate to give the fused-ring derivative (57). The intermediate N-ethoxymethylenebenzimidazole-2-sulfonamide (58) could be isolated and, on heating, melted and then solidified again to give the higher melting (332–335°) derivative (57). The structure was supported by spectroscopic data. The likely generality of this reaction has as yet not been examined, owing no



56 57 58

doubt to the relative inaccessibility of the sulfonamide starting materials.

The recent preparation[37a] of the parent system 59 arose from a study of the chemistry of α-iodomethylsulfonylamidines of the type 59a, as compounds of this type underwent a facile cyclization upon treatment with base. It appeared that the ability to ring-close depended upon the stereochemistry of the precursor (59a), since the derivatives (59a, R = H, Ph; R_1 = *t*-Bu) did not undergo significant ring closure. These results were ascribed to the fact that these derivatives adopted the "opposite" geometrical isomeric forms (59b and 59c). Definite evidence was provided for structure 59c by infrared spectra studies.[37b]

The versatility of this route has been demonstrated by the synthesis of compounds with R_1 = alkyl, aryl, arylamino, alkylamino, as well as hydrogen or acyl (aroyl and sulfonyl). An unambiguous synthesis of 59 (R_1 = $MeSO_2$, R = Ph) from methylsulfonylbenzimidoyl chloride and iodomethylsulfonamide showed that the acylative ring closure of 59a (R = Ph, R_1 = H) as well as direct acylation of 59 (R = Ph, R_1 = H) gave only the one product (59, R = Ph; R_1 =

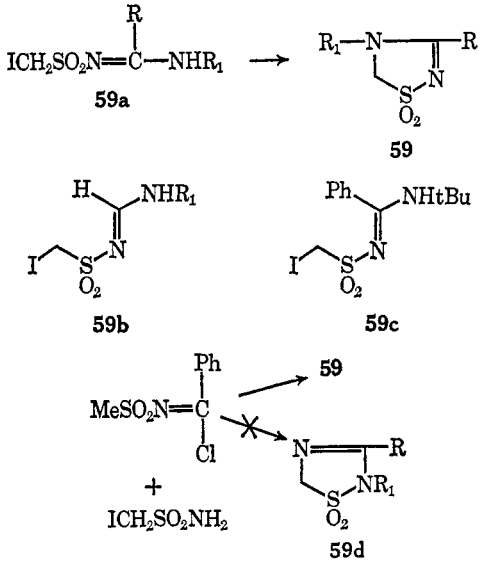
(36) B. Stanovnik and M. Tisler, *Arch. Pharm.* (Weinheim), **300**, 322 (1967).

(37) (a) A. Lawson and R. B. Tinkler, *J. Chem. Soc. C*, 652 (1969); in press; (b) R. B. Tinkler, *ibid., B*, in press.

Table IV

Derivatives of 1,2,4-Thiadiazoline 1,1-Dioxides (59)[87]

R_1	R	%	Mp, °C	Ir bands ν_{SO_2}, cm^{-1}	Uv bands: λ, nm	Uv bands: Log ε
Ph	Ph	70	198–199	1312, 1302	232	4.14
				1148, 1142	248	4.12
p-$C_6H_4NO_2$	Ph	82	151–153	1309, 1302		
				1161		
p-$C_6H_4NO_2$	Ph	62	226–228	1318	231	4.21
				1150	250	4.07
					308	4.08
$PhCH_2$	Ph	47	161–162	1327	236	4.09
				1144	268 sh	3.63
Et	Ph	13	96–97	1307	235	4.08
				1146	265 sh	3.59
$(Ph)_2CH$	Ph	78	216–218 d			
C_6H_{11}	Ph	82	134–136			
(Et)(Me)CH	Ph	58	112–114			
H	Ph	90	142 d	1348, 1320	240	4.22
				1157, 1138	269	3.64
o-Tol	*o*-TolNH	92	241–242	1296, 1138		
p-Tol	*p*-TolNH	95	194–195 d	1294, 1140		
Ph	PhNH	61	205–206 d	1295, 1138		
ICH_2SO_2	Ph	2	185–186	1344, 1330	241	4.23
				1170, 1160	267	3.68
PhCO	Ph	66	196–197	1332	225	3.08
				1166	251	4.24
$PhSO_2$	Ph	55	184–185	1381, 1354	222	4.08
				1173, 1160	252	4.08
EtOCO	Ph	80	178–179	1335	253	4.11
				1160, 1170		
MeOCO	Ph	79	187–189	1336	253	4.10
				1162		
$MeSO_2$	Ph	50	190–191	1328	241	4.18
				1161	268	3.70



acyl), there being no evidence for the alternative form (**59d**). This ring system (**59**) was unstable to the action of acid and base, giving unidentified products. Infrared and nmr spectral data confirming these structures have been summarized (Table IV).

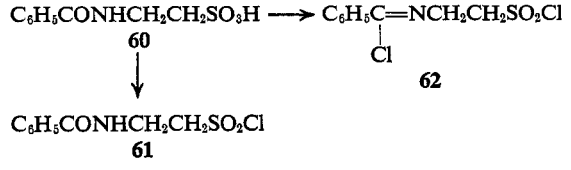
C. CYCLIC β-AMINOSULFONAMIDES

The discussion in this section has been restricted to 1,2,4-thiadiazine 1,1-dioxides that do not have any fused-ring addends, so that the pharmacologically interesting 1,2,4-benzothiadiazine 1,1-dioxides and hetero analogs will not be mentioned herein. A preliminary survey of the literature indicated that a full record of the chemistry of this benzothiadiazine system would stem from upwards of 400 references and could be the subject matter for a separate review.

The three main routes to this ring system (A) are more conveniently discussed in terms of the method used rather than the product formed. However, the tabulation of known compounds in the physical properties section (III.G) provides a cross reference to the methods of synthesis used for each compound.

D. SYNTHESIS FROM TAURINE PRECURSORS

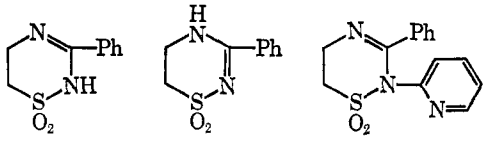
In the course of preparing 2-benzamidoethylsulfonyl chloride (**61**) from the corresponding sulfonic acid (**60**), it was found[38]



that N-(2-chlorosulfonylethyl)benzimidoyl chloride (**62**), a by-product, could be obtained in good yield if excess thionyl chloride was used. The treatment then of this intermediate

(38) R. Winterbottom, J. W. Clapp, W. H. Miller, J. P. English, and R. O. Roblin, Jr., *J. Amer. Chem. Soc.*, **69**, 1393 (1947).

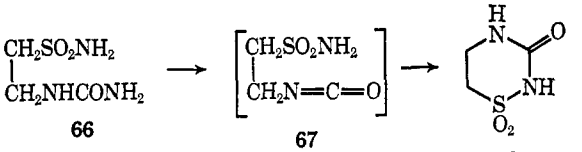
with ammonia provided a good yield of the cyclic derivative 3-phenyl-5,6-dihydro-2H-1,2,4-thiadiazine (**64**), while with 2-aminopyridine the derivative **65** resulted. Though the structure of **65** is likely to be unambiguous, the possible isomerism of **63** to **64** was not mentioned. It might be reasonable to favor structure **64** since this would extend the con-



63 **64** **65**

jugation from the sulfonyl group through to the phenyl group.[37a]

The β-ureidoethanesulfonamide (**66**), readily accessible from taurinamide hydrochloride and potassium cyanate, was readily ring-closed[39] in refluxing anhydrous pyridine to give the 5,6-dihydro-1,2,4-thiadiazin-3-one (**68**) in good yield. As suggested by the authors for another instance (see section E below), it would appear very likely that this ring closure involves the intermediate isocyanate (**67**).

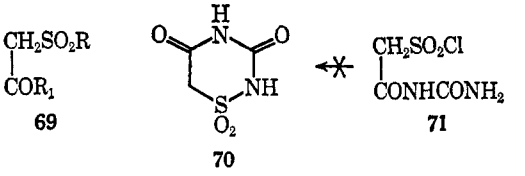


66 **67** **68**

It is surprising that taurinamide has not been subjected to the many other ring-closure reactions that have been applied to other diamino-, and amino-amide systems such as, for example, the action of ortho esters, formate derivatives, and so on.

E. SYNTHESIS FROM SULFOACETIC ACID PRECURSORS

The use of sulfoacetic acid derivatives (**69**) as precursors in the synthesis of 1,2,4-thiadiazine 3,5-diones[39-45] (**70**), a system

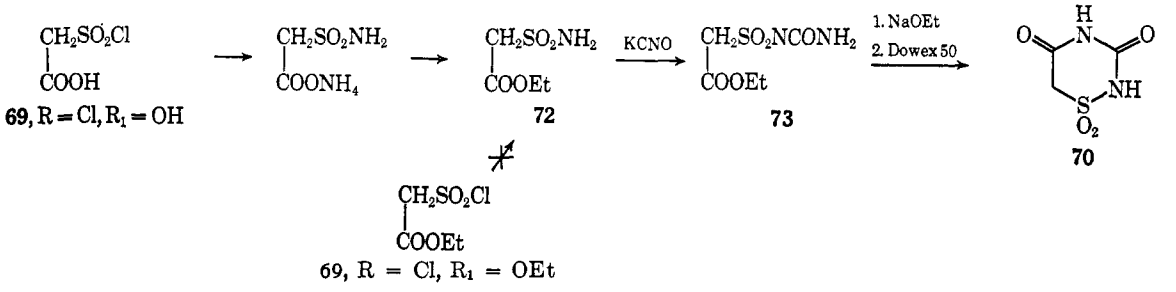


69 **70** **71**

Early attempts[45] to find a synthesis of **70** failed because it was not known at the time that sulfonylureas cannot be prepared directly from the urea and sulfonyl halide.[49] Thus the derivative **71** prepared by the action of urea upon the diacid chloride (**69**, R = R_1 = Cl) could not be induced to ring close to **70**.

The first successful route[40,41] involved the reaction sequence **69** (R = Cl, R_1 = OH) to **70**. The starting material (**69**, R = Cl; R_1 = OH) was obtained in poor yield from the diacid chloride by controlled hydrolysis and converted, possibly through intermediate formation of the reactive sulfene, >C=SO_2, in a manner analogous to the suggested isocyanate formation in the ring closure of **66** to **68**, to the amide with ammonia (sealed tube at 75°). The product refluxed in alcohol with gaseous hydrogen chloride (Fischer-Speier) gave α-carbethoxymethylsulfonamide (**72**). As sulfonic acids cannot be esterified by this procedure, the structure of **72** was established by this preparation. Treatment of the sulfonamide group with potassium cyanate then gave in the usual way[49,50] the sulfonylurea potassium salt which was in turn finally ring-closed in refluxing ethanolic sodium ethoxide solution.

It is interesting to note an unsuccessful alternative route to **70** related to the above method. The α-carbethoxymethylsulfonyl chloride (**69**, R = Cl; R_1 = OEt) could not be converted with ammonia under a variety of conditions to the α-carbethoxyamide (**72**), which is reminiscent of the failure of ammonia to react with α-nitromethylsulfonyl chloride,[51] both effects being no doubt attributable to the presence of a strongly electron-withdrawing α substituent, facilitating the



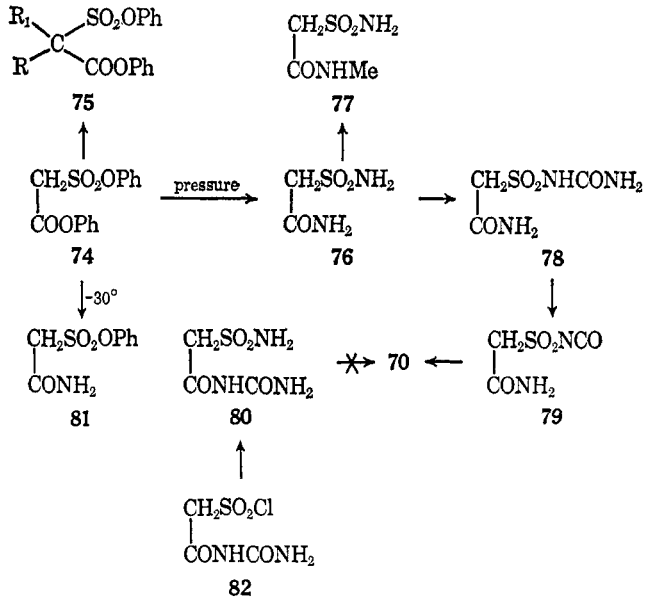
69, R = Cl, R_1 = OH **72** **73** **70**

69, R = Cl, R_1 = OEt

of interest because of its relation to barbituric acid as well as other heterocyclic compounds,[46,47] has offered a great stimulus formation of a reactive sulfene which could give secondary reactions.

A considerably more efficient route[39] from related precursors, involved the reaction sequence **74** to **78**. The diester **74** was readily available in good yield from the corresponding acid chloride, and in turn could be converted to the diamide **76**, though without the forcing conditions (liquid ammonia

(39) B. E. Hoogenboom, R. Abbott, L. Locatell, and R. L. Hinman, *J. Org. Chem.*, **24**, 1983 (1959).
(40) R. L. Hinman and L. Locatell, Jr., *J. Amer. Chem. Soc.*, **81**, 5655 (1959).
(41) L. Locatell, Jr., *Diss. Abstr.*, **17**, 2819 (1957).
(42) B. E. Hoogenboom, *ibid.*, **19**, 442 (1958).
(43) R. L. Abbott, *ibid.*, **23**, 65 (1962).
(44) R. L. Hinman and B. E. Hoogenboom, *J. Org. Chem.*, **26**, 3461 (1961).
(45) K. Bodendorf and N. Senger, *Chem. Ber.*, **72B**, 571 (1939).
(46) B. E. Loev, M. F. Kormendy, and K. M. Snader, *J. Org. Chem.*, **31**, 3531 (1966).
(47) B. J. Nicolaus, E. Bellasio, and E. Testa, *Helv. Chim. Acta*, **45**, 717 (1962).
(48) B. E. Hoogenboom, E. D. Hogansen, and M. El-Faghi, *J. Org. Chem.*, **33**, 2113 (1968).
(49) F. Kurzer, *Chem. Rev.*, **50**, 1 (1952).
(50) O. Henke, U. S. Patent 2,390,253 (1946); *Chem. Abstr.*, **40**, 1876 (1946).
(51) B. E. Loev, F. Dowalo, I. M. Fried, and M. M. Goodman, *Tetrahedron Lett.*, 817 (1968).

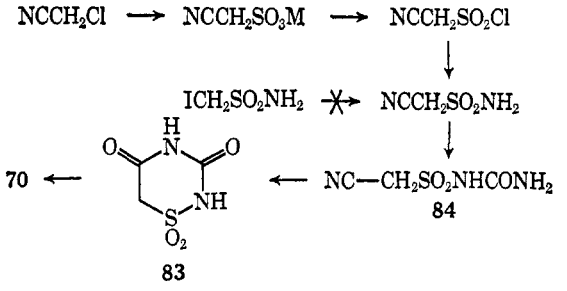


at 75° in a sealed tube) only the monoamide **81** resulted. The α-carboxamidomethylsulfonylurea (**78**) was then readily prepared as before[49,50] and cyclized to the pyridinium salt of the required **70** on refluxing in anhydrous pyridine. Other basic reagents such as N,N-dimethylaniline, sodamide in liquid ammonia, or alcoholic ethoxide were ineffective as was damp pyridine. The authors[39] suggested a plausible mechanism of cyclization involving the sulfonyl isocyanate (**79**), a view supported by the fact that damp pyridine led to the diamide (**76**) as a by-product, while the alternative isomer (**80**) (from the diacid chloride with urea to **82** and thence with ammonia under pressure) could not be ring-closed under a variety of conditions.

These methods were extended in two ways. The diester (**74**) could under suitable conditions (ethyl sulfate added to **74** previously treated with powdered sodium in toluene,[52] or with sodium *t*-butoxide in *t*-butyl alcohol followed by methyl iodide[44]), as might be expected of such a malonate analog, be mono- or dialkylated to give **75** (R = R_1 = H or alkyl), which in turn was converted to the corresponding thiadiazine as before. Attempts to prepare the 6,6-dialkyl-substituted thiadiazine system appeared to introduce added complications at the ring-closure stage, and pure derivatives could not be obtained. The other extension involved carbethoxymethylsulfonamide (**72**) which on treatment with methylamine was converted[44] to the derivative **77**, and this was in turn ring-closed as before to give the 4-methyl derivative of **70**.

Attempts to ring-close the diamide (**76**) with a variety of reagents (refluxing ethyl carbonate, ethyl chloroformate, or urea (fusion)) were without success, presumably because of the poor reactivity of the carboxamide function. The formation of the sulfonylurea (**78**) suggested that the sulfonamide group behaved normally.

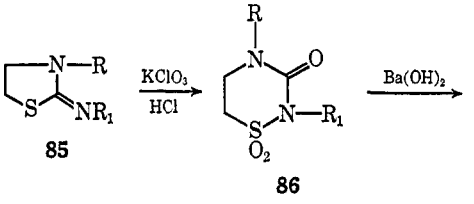
An alternative route[43] to the 1,3-dione (**70**) involved hydrolysis of the monoimine derivative (**83**) which was in turn obtained by the base cyclization of α-cyanomethylsulfonylurea (**84**). This latter starting material was available from α-chloroacetonitrile (but not iodomethylsulfonamide; see section II) in four steps *via* the sulfonic acid and the acid chloride, and thence from the action of potassium cyanate upon the amide as before.



A synthesis reported by Dickey in the patent literature[53,54] has been a source of some concern, since the method described involved the ring closure of **82**, a route which failed in other workers' hands.[40,45] Unfortunately, because of the absence of physical data[53,54] (melting point, etc.), the Dickey product could not be compared with the known compound.

F. SYNTHESIS BY OXIDATIVE METHODS

It is of interest to note the surprising lack of syntheses of S-oxo compounds from the reduced parent compounds by oxidative methods. Such a synthesis accompanied, however, by ring expansion was initiated by Andreasch[55,56] and used by others.[57,58] This, aimed at clarifying the structures of thiazolidine derivatives (**85**), involved their oxidation and subsequent hydrolysis. Thus the action of hydrochloric acid and potassium chlorate upon **85** gave a product assigned the structure **86**, *i.e.*, a 2,4-disubstituted 3,6-dihydro-1,2,4-thiadiazin-3-one 1,1-dioxide. The hydrolysis of this compound served to assign unambiguously the orientation of the R and R_1 groups (the original purpose of the experiment[56]), since both the substituted taurine (**87**) and more particularly the amine (**88**) were readily identified. No subsequent investigation of the formation of **86** has been reported so that proof of this structure still rests only upon analytical data and the results of hydrolysis.



A report[59] of an oxidative method closely related to the above, the authors of which make no mention of the above earlier work,[55,56] described the chlorination at 0° in aqueous media of the Δ^2-2-aminothiazolin-4-one (**89**) and assigned to the product the structure **90**, claiming that the oxidation

(52) S. Wawzonek and R. L. Abbott, *J. Med. Chem.*, 6, 603 (1963).

(53) J. B. Dickey, U. S. Patent 2,466,396 (1949); *Chem. Abstr.*, 43, 4868*d* (1949).

(54) J. B. Dickey, U. S. Patent 2,466,397 (1949); *Chem. Abstr.*, 43, 4868*f* (1949).

(55) Reference 2, p 816.

(56) R. Andreasch, *Monatsh. Chem.*, 4, 131 (1893).

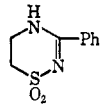
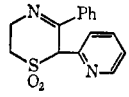
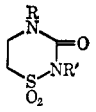
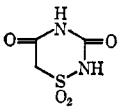
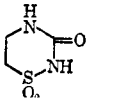
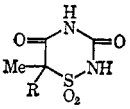
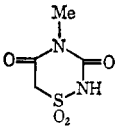
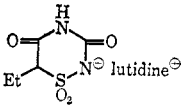
(57) H. Wolfbauer, *ibid.*, 25, 682 (1904).

(58) F. Kucera, *ibid.*, 35, 137, 151 (1914).

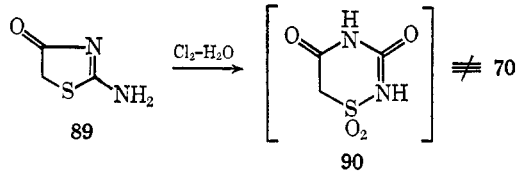
(59) P. N. Rylander and E. Campaigne, *J. Org. Chem.*, 15, 249 (1950).

Table V

Derivatives of 1,2,4-Thiadiazine 1,1-Dioxides

Compound	R	R_1	Yield, %	Mp, °C	Solvent[a] and properties	Ref
 64			92	214–215	EtOH	38
 65				176–177	EtOH	38
 86	**a** Ph	$PhCH_2$		139–140	EtOH	58
	b *p*-Tol	Ph		181	EtOH	58
	c	*p*-Tol		204		57
	d Ph	Ph		186–187	EtOH	56
 70	(pK_a' = 2.7 ± 0.10)		74	226–227 d[b]	Sublm 190°, (1 mm) Soluble in H_2O $\nu_{C=O}$ 1725, 1698 cm^{-1} ν_{SO_2} 1368, 1162 cm^{-1}	40, 41 39
	(pK_{a_1} = 2.88) (pK_{a_2} = 11.00)					
	(pK_a = 4.51)		67	272–273 d	EtOH $\nu_{C=O}$ 1700 cm^{-1}	39
	H (pK_a = 2.89) Me		77	200–201	ν_{CO} 1710, 1690 cm^{-1} ν_{SO_2} 1331, 1154 cm^{-1} ν_{CO} 1740, 1705 cm^{-1} imp[c]	44 44
	(pK_a = 2.63)		Low	130–132	Sublimed ν_{CO} 1738, 1678 cm^{-1} ν_{SO_2} 1355, 1170 cm^{-1}	44
 93				204–206	EtOH ν_{CO} 1695, 1616 cm^{-1} ν_{SO_2} 1381, 1136 cm^{-1}	52

[a] Solvent of crystallization. d = decomposition. [c] Impure sample.



89 90

was accompanied by ring expansion as well as rearrangement. However, as the structure of this compound has already been established[39-41] and the melting point of the above product (110–120°) is considerably below that of the authentic material (226–227°), as well as there being major differences with regard to their stability, it must be concluded that the structural assignment made above is incorrect. As only sulfur analysis data were reported, no further speculation regarding these structures can be entertained. Whether or not this failure casts some doubt upon the oxidation (**85** → **86**) must await further experimental work.

G. PHYSICAL AND CHEMICAL PROPERTIES

The relatively few examples of 1,2,4-thiadiazine 1,1-dioxides so far prepared are recorded in Table V, together with the few spectroscopic data available.

Following the synthetic work done,[39-41,44] Hinman and Hoogenboom made a detailed study[44] of the system **70**, and the 4- and 6-substituted derivatives, in order to establish the site of the most acidic hydrogen. They were able to show by pK_a measurements (Table V) and from the nmr data that the hydrogen in the 2 position was, as might have been expected, the most acidic.

This paper[44] is of value in that it also reports ir and pK_a values for some of the derivatives intermediate in the synthesis of the thiadiazines. As elsewhere in this review the ir bands assigned to the sulfonyl group occur in the regions expected.[60]

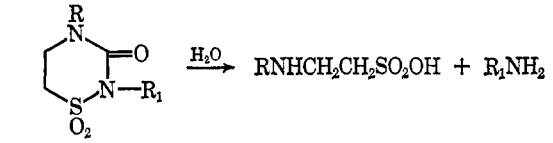
It is of interest to note that, apart from an intense but featureless end absorption, neither the thiadiazines nor the

(60) E. A. Robinson, *Can. J. Chem.*, **39**, 247 (1961).

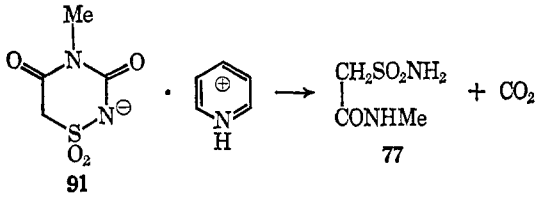
first monoanion have a uv spectrum, whereas the dianion shows a maximum near 240 nm which resembles that of the first ionization of 5,5-diethylbarbituric acid.

Very little information is available regarding the chemistry of this ring system. It would appear that these compounds are fairly readily hydrolyzed; thus compound **64** gives[38] the taurinamide hydrochloric and benzoide acid in good yield on being refluxed with 20% hydrochloric acid, while the ease of hydrolysis of **86** has already been mentioned in the text above.

64

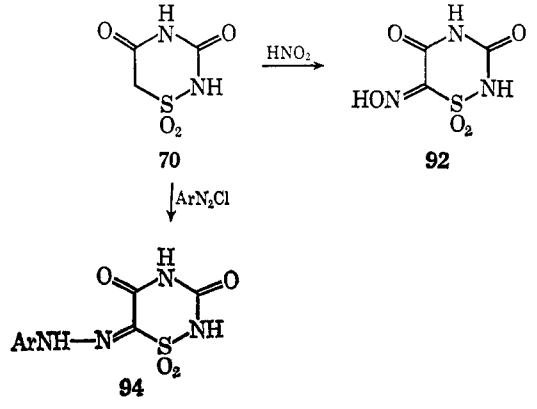


86



91 **77**

In the experimental work-up[44] required to isolate the free 4-methyl-1,2,4-thiadiazine 1,1-dioxide from its pyridinium salt (**91**), it was reported that the product was readily hydrolyzed if an aqueous rather than alcoholic solvent system was used for the ion-exchange process.

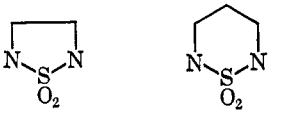


70 **92** **94**

Nitrosation of the 1,2,4-thiadiazine-1,3-dione (**70**) gave[43] the 6-oximino derivative (**92**), though the inconsistent nature of the reaction indicated that some alternative unknown reaction might also be taking place. Coupling with diazonium compounds was also reported, giving the 6-hydrazono compounds (**94**). Unfortunately no further studies (reduction, etc.) were carried out to characterize these derivatives.

IV. Cyclic Sulfamide Derivatives

In two previous[3,61] reviews aspects of the chemistry of 1,2,5-thiadiazole 1,1-dioxide (A) and 1,2,5-thiadiazine 1,1-dioxide (B) have been mentioned. However, as neither review was specifically aimed at these classes of compound in the present context the whole literature has been reviewed in greater detail.



A B

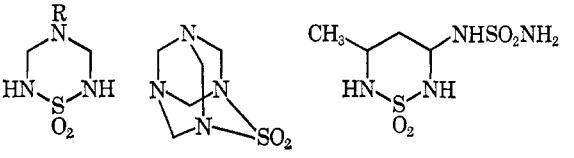
As the introduction of the unit –N–SO_2–N– into heterocyclic systems has its origin almost entirely in sulfamic acid derivatives, and as many different ring compounds are formed, the synthetic methods have been arranged according to the starting material used rather than the product formed.

A. SYNTHESES FROM SULFAMIDE

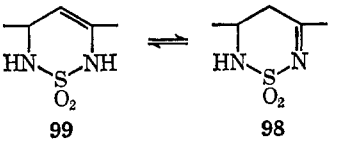
The advent of commercially available sulfamide has resulted in a revival of interest in its chemistry and particularly its use as a starting material in heterocyclic synthesis. Although there is an analogy with urea (amino groups flanking an electron-withdrawing group), logical application of the standard routes to the barbiturate and hydantoin analogs have been found to be inoperable.[62] Nevertheless, a variety of reactions has been evolved providing considerable numbers of derivatives.

1. Sulfamide with Carbonyl Compounds

The reaction of sulfamide with formaldehyde has been historically linked[63] with the analogous use of the urea in resin formation. Other reactions with aldehydes have been documented,[3] providing with amines compounds such as the 1,2,4,6-thiatriazine 1,1-dioxide (**95**) and thiazaadamantane S-dioxides, *e.g.*, **96**. Crotonaldehyde gave with 2 mol of sulfamide in ethanolic hydrochloric acid a product[64] assigned, without evidence, the 1,2,6-tetrahydrothiadiazine 1,1-dioxide



95 **96** **97**



99 **98**

(61) L. M. Weinstock and P. Pollock, *Advan. Heterocycl. Chem.*, **9**, 107 (1968).

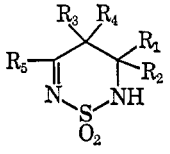
(62) C. C. Chappelow, Jr., *Diss. Abstr.*, **29**, 129 (1968).

(63) (a) L. F. Audrieth, M. Sveda, H. H. Sisler, and M. J. Butler, *Chem. Rev.*, **26**, 49 (1940); (b) R. C. Wood and A. E. Battye, *J. Soc. Chem. Ind.*, **52**, 3461 (1933).

(64) A. M. Paquin, *Kunststoffe*, **37**, 171 (1947); *Chem. Abstr.*, **43**, 59955 (1949).

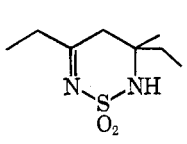
structure (**97**). It would seem possible, comparing this reaction with that of sulfamide with unsaturated ketones[65] (below), that the intermediate (**98** ⇌ **99**) was first formed followed by the addition of a second molecule of sulfamide.

Recently monoketones were shown to react[66] much more effectively with sulfamide than aldehydes, presumably because resin formation was less likely. Two molecules of ketone with one molecule of sulfamide give in ethanolic hydrochloric acid moderate yields of compounds such as **100**, the structure being confirmed by ir and nmr data (*vide infra*). The product from sulfamide with 2-butanone was separated into two

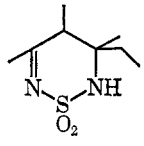


100

isomers (**101** and **102**) corresponding to the two possible orientations during reaction. The failure of the method for some ketones (3-methyl-2-butanone and 4-methyl-2-pentanone) due to self-condensation was noted.

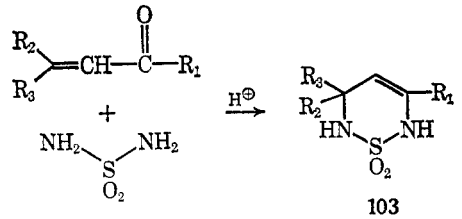


101



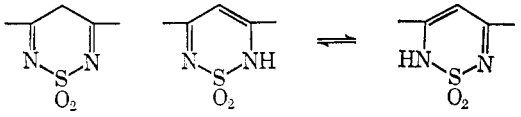
102

A brief report[65] describes the condensation of sulfamide with α,β-unsaturated ketones, again in ethanolic hydrochloric acid (saturated in this example) to give the dihydro-1,2,6-thiadiazine 1,1-dioxides (**103**), without supporting evidence for this likely structure. The reaction proceeds particularly smoothly with *p*-halogenobenzylidene acetophenones. With maleic acid and its esters under these conditions only isomerism to the corresponding fumaric derivatives took place. The ready reaction of sulfamide with ketones was fully explored by Wright[67-76] who greatly extended the reaction with β-diones discovered by Glenn[77] and Degering and Wilson.[78] Sulfamide with pentane-2,4-dione gave in ethanol at 60° with a trace of dry HCl the 4H-1,2,6-thiadiazine 1,1-dioxide with the originally favored structure **106**.[78] Subsequent studies[67,79] showed that spectroscopic evidence (ir

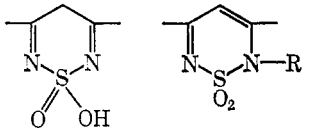


103

and nmr; *vide infra*) indicated that the structure **105** prevailed, except in 4,4-disubstituted compounds when the bond arrangement was as in **104**.



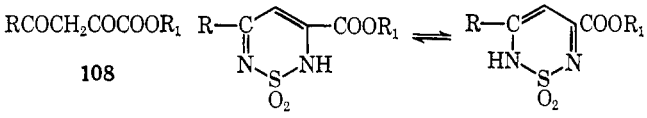
104 **105a** **105b**



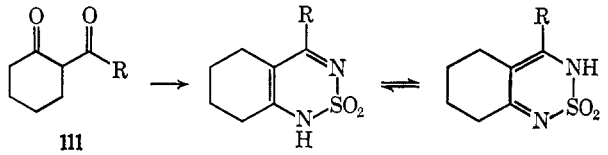
106 **107**

The use of monosubstituted sulfamides provided[67,79] the N-substituted compounds (**107**), also available by direct alkylation of the parent ring compound (**105**), while a more recent method[80] using sulfuric rather than hydrochloric acid catalysis gave extremely good yields.

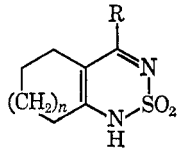
Wright[67] showed that suitable β-dicarbonyl compounds could provide a number of new systems. Thus the interaction of sulfamide with acyl pyruvates (**108**) gave the carbethoxy-substituted compounds (**109** and **110**), while 2-acylcyclohexanones (**111**) gave the tetrahydrobenzothiadiazine 1,1-dioxides (**112**). The extension of this latter reaction to the general type (**114**) has been claimed.[72] Although mentioned, the possible tautomeric equilibria (**105a** ⇌ **105b**, **109** ⇌ **110**, and **112** ⇌ **113**) recieved no formal attention.



108 **109** **110**



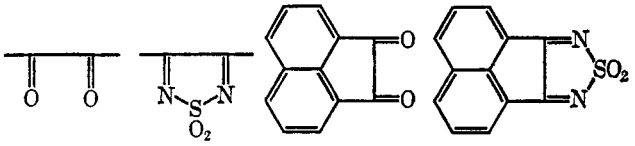
111 **112** **113**



114

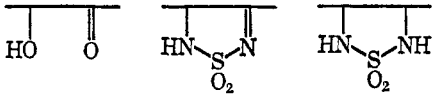
The first examples of 1,2,5-thiadiazole 1,1-dioxides (**115**) were prepared[67] by applying the β-dione methods to α-diones, the method even providing a good yield with the less flexible

(65) R. Zimmerman and H. Hotze, *Angew. Chem., Int. Ed. Engl.*, **2**, 757 (1963).
(66) A. Ouchi and T. Moeller, *J. Org. Chem.*, **29**, 1865 (1964).
(67) J. B. Wright, *ibid.*, **29**, 1905 (1964).
(68) J. B. Wright, U. S. Patent 3,115,493 (1963); *Chem. Abstr.*, **60**, 5513*b* (1964).
(69) J. B. Wright, U. S. Patent 3,115,496 (1963); *Chem. Abstr.*, **60**, 5512*c* (1964).
(70) J. B. Wright, U. S. Patent 3,186,998 (1965); *Chem. Abstr.*, **63**, 13275*h* (1965).
(71) J. B. Wright, U. S. Patent 3,203,954 (1965); *Chem. Abstr.*, **63**, 14888*h* (1965).
(72) J. B. Wright, U. S. Patent 3,201,396 (1965); *Chem. Abstr.*, **63**, 14887*c* (1965).
(73) J. B. Wright, U. S. Patent 3,223,704 (1965); *Chem. Abstr.*, **64**, 8217*h* (1966).
(74) J. B. Wright, *J. Org. Chem.*, **30**, 3960 (1965).
(75) Upjohn Co., Netherlands Patent Application 6,604,034 (1967); *Chem. Abstr.*, **66**, 46441*k* (1967).
(76) Upjohn Co., Netherlands Patent Application 6,603,940 (1967); *Chem. Abstr.*, **66**, 55527*v* (1967).
(77) A. Glenn, Ph.D. Thesis, Purdue University, 1949.
(78) E. F. Degering and J. E. Wilson, *J. Org. Chem.*, **17**, 339 (1952).
(79) A. M. Roe and J. B. Harbridge, *Chem. Ind. (London)*, **96**, 216 (1965).
(80) H. K. Vorreither and E. Ziegler, *Monatsh. Chem.*, **96**, 216 (1965).



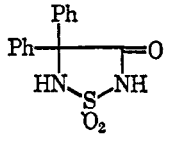
115 116

dione acenapthoquinone (**116**). Use of an α-hydroxy ketone gave instead, as might be expected, the corresponding thiadiazoline (**117**), from which, by reduction, the thiadiazolidine analog (**118**) became available.



117 118

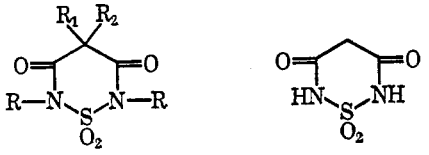
In a briefly mentioned modification of the α-dione–sulfamide reaction it was claimed[80] that sulfamide and benzil refluxed in ethanol with 50% potassium hydroxide gave the thiadiazolinone (**119**), this structure being supported by ir and nmr data.



119

2. *Sulfamide with Malonyl Derivatives*

The first synthesis of the 1,2,6-thiadiazin-3,5-dione system (**120**) was due to Paquin[81] who showed that malonyl dichloride (or malonic acid with phosphorus oxychloride) gave with sulfamide or symmetrically disubstituted sulfamides the parent dione (**121**) or the dialkyl derivative (**120**, $R_1 = R_2 = H$; R = alkyl), respectively. The extension of this method

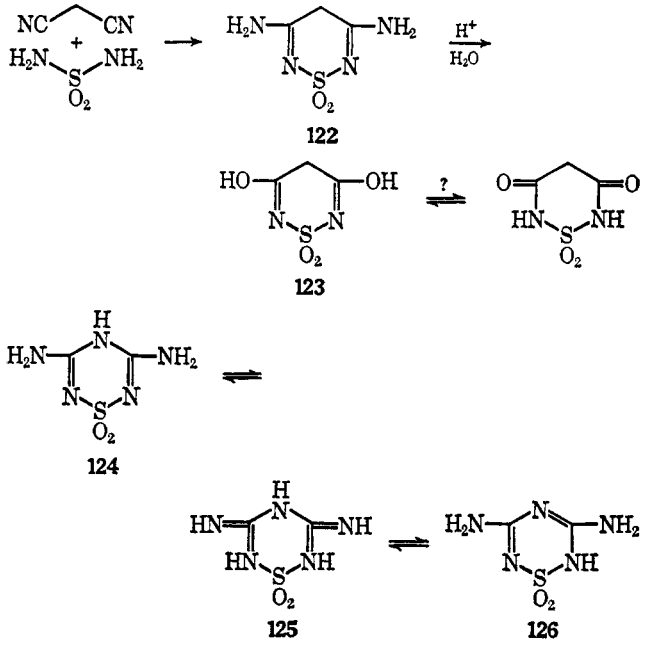


120 121

to provide many more examples, as well as the 4- and 4,4-substituted derivatives (**120**) from the corresponding substituted malonic acid derivatives has been reported in a massive patent claim.[82] The use of the malonic acid sodium salt with acetyl chloride also provided a suitable source of *in situ* malonyl dichloride.

In another patent[83,84] it was claimed that the reaction of sulfamide with malonyldinitrile in ethanol at room temperature gave a product assigned the structure **122** which was hydrolyzed[84,85] in dilute acid to the "dihydroxy derivative" (**123**), presumably the same compound as the known 3,5-diketo compound noted above. As no physical constants were given a comparison cannot be made.

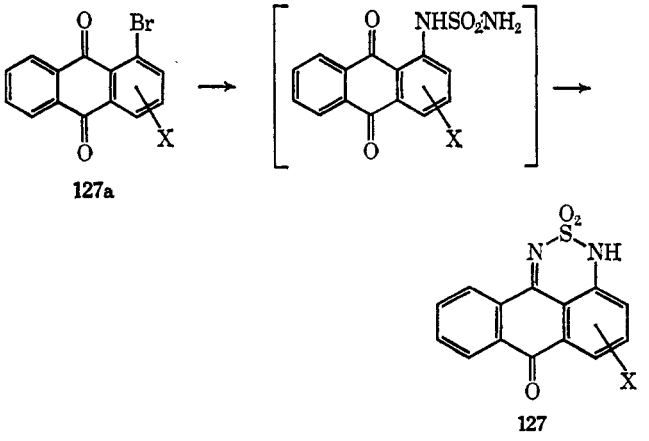
A related reaction[86,87] is that between sulfamic acid and dicyandiamide at 120°, claimed to give the thiatriazine (**124**). Again the solubility in alkali and insolubility in acid or water suggests that this structure might be better presented as **125** or **126**.



122 123 124 125 126

3. *Sulfamide with Other Difunctional Compounds*

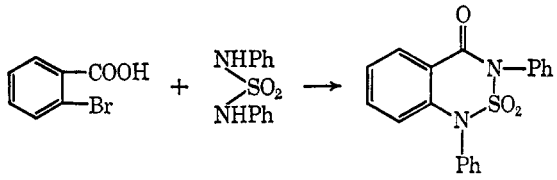
One of the earliest thiadiazine S-dioxide derivatives prepared[3,88] was the anthrone derivative (**127**), obtained from sulfamide and the 1-halogenoanthraquinone (**127a**) in refluxing amyl alcohol with potassium or copper acetate. Further applications of this method appear not to have been examined; α-halogeno ketones might be expected to give corresponding ring compounds.



127a 127

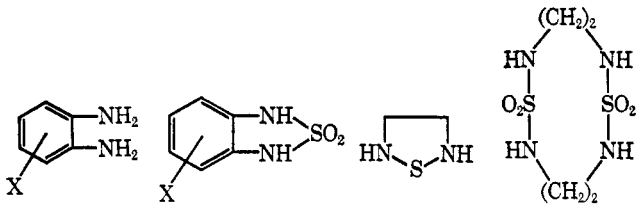
(81) A. M. Paquin, *Angew. Chem.*, **A60**, 316 (1958).
(82) H. Teufel, U. S. Patent 2,956,997 (1960); *Chem. Abstr.*, **55**, 8446*f* (1961).
(83) H. A. Walter, U. S. Patent 2,454,262 (1948); *Chem. Abstr.*, **43**, 2648*e* (1949).
(84) H. A. Walter, U. S. Patent 2,473,042 (1949); *Chem. Abstr.*, **43**, 6674*a* (1949).
(85) H. A. Walter, U. S. Patent, 2,479,441, 1949; *Chem. Abstr.*, **43**, 9528*a* (1949).
(86) H. A. Walter, U. S. Patent 2,449,520, 1947; *Chem. Abstr.*, **43**, 903*d* (1949)..
(87) H. A. Walter, U. S. Patent 2,454,261, 1948; *Chem. Abstr.*, **43**, 2648*c* (1949).
(88) G. Kranzlein and K. Penn, German Patent 673,389 (1936); *Chem. Abstr.*, **33**, 4436 (1939).

A number of *ortho*-disubstituted benzene derivatives have been condensed with sulfamide to give benzo derivatives of the heterocyclic compounds under consideration. Thus *o*-bromobenzoic acid gave with *sym*-diphenylsulfamide in boiling xylene a poor yield of the 2,1,3-benzothiadiazin-4-one[89] (**128**), and *o*-phenylenediamines gave with sulfamide in refluxing diglyme materials claimed to be 2,1,3-benzothiadiazoline 2,2-dioxides (**129**). Similarly ethylenediamine heated with



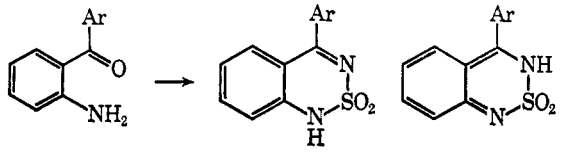
128

sulfamide gave the parent saturated thiadiazolidine[90] (**130**), as well as large ring compounds such as **131**.



129 **130** **131**

The reaction of *o*-aminobenzophenones with sulfamide gave in refluxing pyridine poor yields of the corresponding 4-phenyl-1H-2,1,3-benzothiadiazines (**132**); however, direct fusion[74] of the starting material with excess sulfamide at 140° and then at 180–190° produced improved yields of the same product. Such reactions of sulfamide probably proceed

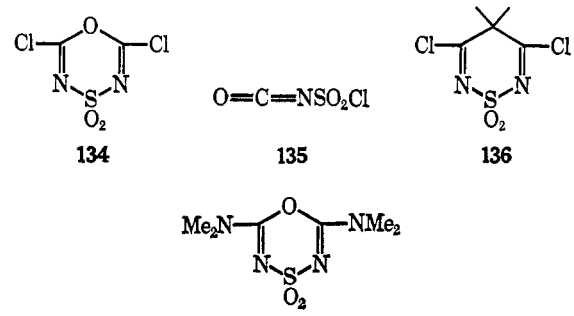


132 **133**

through the intermediate formation of the reactive sulfimide R—N=SO_2. Structure **132** was preferred to **133** since methylation produced the same product as did the action of sulfamide with N-methylaminobenzophenone. The corresponding reaction with a substituted sulfamide appears not to have been explored.

B. SYNTHESIS FROM SULFAMOYL HALIDES

The development by Graf of the reaction between cyanogen halides and sulfur trioxide[92] made the intermediate **134** and particularly the reagent **135** readily available.[93]

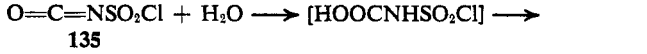


134 **135** **136**

137

The 1,4,3,5-oxathiadiazine 2,2-dioxide (**134**) is of interest in the resemblance it bears to the thiadiazines, particularly as this compound behaves as a conventional imidoyl chloride with dimethylamine to give the diamino derivatives[3,94] (**137**), whereas the corresponding derivative (**136**) has not yet been prepared.

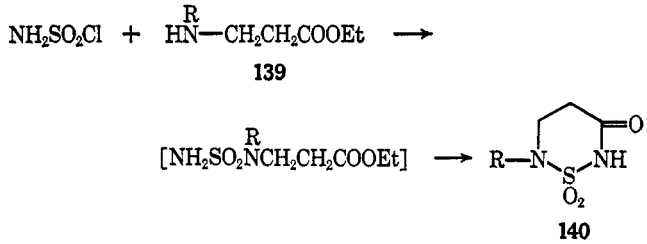
The N-carbonylsulfamoyl chloride (**135**) has been of particular value in that controlled hydrolysis of this material made the parent unsubstituted sulfamoyl chloride (**138**)



135 **138**

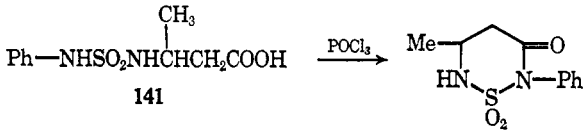
available[93] for the first time. As might have been expected this then led to the development of 1,2,5-thiadiazine 1,1-dioxide syntheses[89,95,96] using sulfamoyl and substituted sulfamoyl halides.

In a patent claim[89] the action of sulfamoyl chloride upon β-N-substituted aminocarboxylic acid esters (**139**) is reported to give on treatment (extraction) of the intermediate sulfamido ester with alkali, the 3-oxo-6-substituted 1,2,6-thiadiazine 1,1-dioxide (**140**). A 3-oxo-2-phenyl-substituted product (**142**) could be obtained by heating the β-(N-phenylsulfamido)-butyric acid (**141**) with phosphorus oxychloride in refluxing



139 **140**

ethylene chloride. (For the synthesis of the corresponding

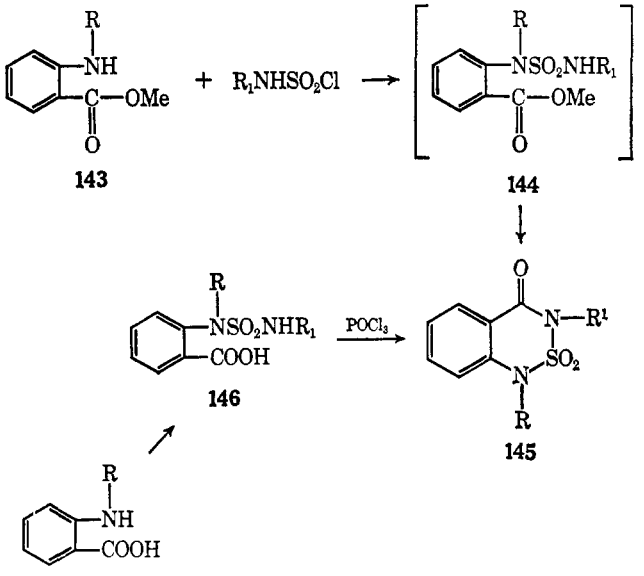


141 **142**

2,6-diphenyl compound see Miscellaneous Methods, section IV.D.) Application of this reaction to α-aminocarboxylic acid

(89) H. Teufel, German Patent 1,120,456 (1959); *Chem. Abstr.*, **57**, 844*b* (1962).
(90) H. Beecken, *Chem. Ber.*, **100**, 2151 (1967).
(91) W. J. Houlihan, U. S. Patent 3,278,532 (1964); *Chem. Abstr.*, **53**, 1601*f* (1959).
(92) Reference 1, p 700.
(93) Reference 1, p 698.
(94) R. Graf, German Patent 965,401 (1957); *Chem. Abstr.*, **53**, 1606*f* (1959).
(95) H. Teufel, German Patent 1,120,457 (1961); *Chem. Abstr.*, **57**, 843*h* (1962).
(96) E. Cohen and B. Klarberg, *J. Amer. Chem. Soc.*, **84**, 1994 (1962).

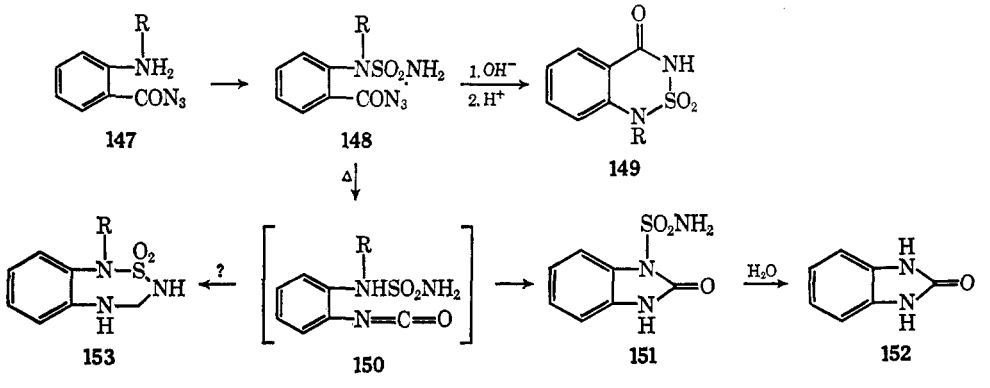
esters has not been described. The extension of this method to produce the benzo analogs (**145**) was first described in a patent[89] and then later examined by other workers.[96] In a typical example, a sulfamoyl chloride, probably converted to the intermediate sulfimide, $R_1N{=}SO_2$, gave with methyl N-substituted anthranilate (**143**) the 2,1,3-benzothiadiazin-4-one (**145**) on extracting the reaction mixture with alkali and acidifying. It has been shown[96] that the intermediate (**144**, R = R_1 = H) had a real existence but was difficult to purify. Suitable choice of the substituents R and R_1 permitted the preparation of a variety of compounds, while the use of a substituted sulfamoyl chloride could be avoided as the product (**145**, R_1 = H) was readily alkylated.



143 **144** **146** **145**

Preparation of the sulfamoylanthranilic acid derivative (**146**) followed by an alternative ring closure using phosphorus oxychloride[89] also gave **145**.

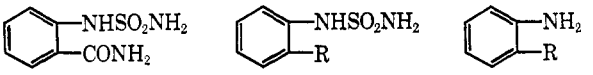
Two further methods of preparation were devised[96] so as to leave little doubt as to the structure of **145**. The anthranilazide (**147**, R = H) readily gave the sulfamoyl derivative (**148**, R = H) (not isolated) which with alkali and then acid as



147 **148** **149** **153** **150** **151** **152**

before gave the parent compound (**149**) identical with that previously prepared. The identity of **148** (R = H) was established by refluxing in toluene to give, *via* **150** (R = H), the sulfonamidobenzimidazolone (**151**) which hydrolyzed readily to the known benzimidazolone (**152**). It is perhaps of interest to speculate as to whether or not **150** (R = alkyl) could be made to produce the novel system **153**.

Finally the anthranilamide derivative (**154**) was converted in aqueous alkali to the anticipated ring compound (**149**, R = H) with concomitant loss of ammonia.



154 **155** **156**

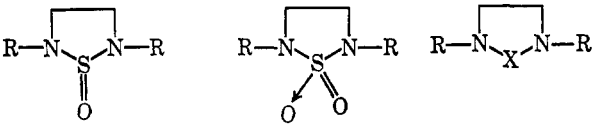
It is of interest to note[96] that the stability to boiling water of the phenylsulfamide derivatives (**155**) was greatly dependent upon the substituent R; thus for R = electron-withdrawing group, such as COOH or NO_2, the compounds were readily hydrolyzed to the amino derivatives (**156**). This observation subsequently led to a study of the intermediary existence of sulfimide ($HNSO_2$) in this reaction.

C. SYNTHESES FROM THIONYL AND SULFURYL HALIDES

The action of thionyl and sulfuryl halides on N,N′-dialkylethylenediamines, the classical type of route to thiadiazolidine S-oxide and S-dioxides (**157** and **158**, respectively), has received little attention. A patent claim[97] gave reaction conditions, *viz.* sulfur halide and diamine in an inert solvent, while a more formal study[98] indicated that suitable conditions involved these reactants in ether at −78°.

An organometallic study[99] of the synthesis of the heterocyclic systems (**159**, X = P—Ph, B—Ph, As—Cl, or S=O) disclosed that the substance **159** (X = $SiMe_2$) when treated with the appropriate covalent halide provided a suitable route to each of these compounds (**159**).

It is of interest to note that compounds of the type **157** and **158** (R = alkyl) are physically different from most other

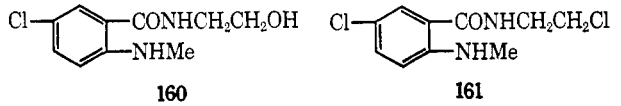


157 **158** **159**

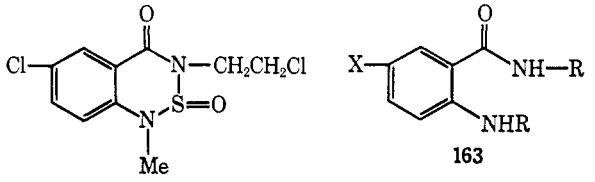
heterocycles in this section in that they are high-boiling oils rather than solids. In an attempt to convert the benzamide (**160**) to the corresponding chloro compound (**161**) with

(97) S. Melamed and W. L. Croxall, U. S. Patent 2,624,929 (1953); *Chem. Abstr.*, **47**, 1125c (1953).
(98) E. W. Abel, R. D. Bush, and E. H. Hopton, *Trans. Faraday Soc.*, **62**, 3277 (1966).
(99) E. W. Abel and R. D. Bush, *J. Organometal. Chem.*, **3**, 245 (1965).

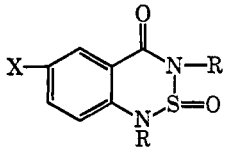
thionyl chloride, it was found[100] that the 2,1,3-benzothiadiazin-4-one 2-oxide (**162**) resulted in good yield. A study of the requirements for the nature of the general starting material (**163**) in this reaction showed that both nitrogen atoms had to



160 **161**



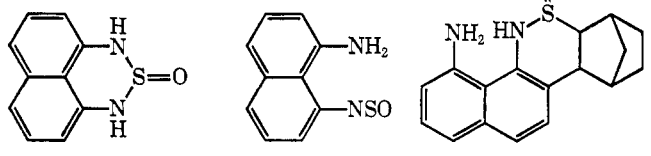
162 **163**



164

be substituted and an electron-withdrawing group was obligatory in the 4 position. Attempts to replace the thionyl chloride with sulfuryl chloride led only to chlorination products.

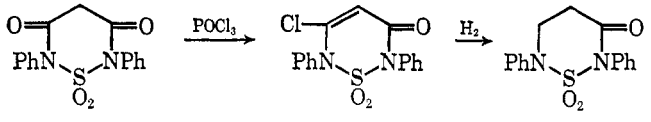
The treatment of 1,8-diaminonaphthalene with thionyl chloride,[101] or sulfur dioxide and triethylamine[102,103] or N-sulfinylaniline,[103] led to, among other products, the labile S-oxide (**165**) which at temperatures above 50° gave the amino-N-sulfinyl isomer (**166**), this having been proven by its interaction with bicyclo[2.2.1]heptene-2 to give **167** (*vide infra*).



165 **166** **167**

D. MISCELLANEOUS METHODS

The conversion[94] of the 3,5-dione (**168**) *via* the chloro compound (**169**) and reduction to the 3-one (**170**) served to provide both proof of structure for **168** (*vide infra*) as well as an extension of the chemistry of these compounds, there being few reports describing functional group modifications.

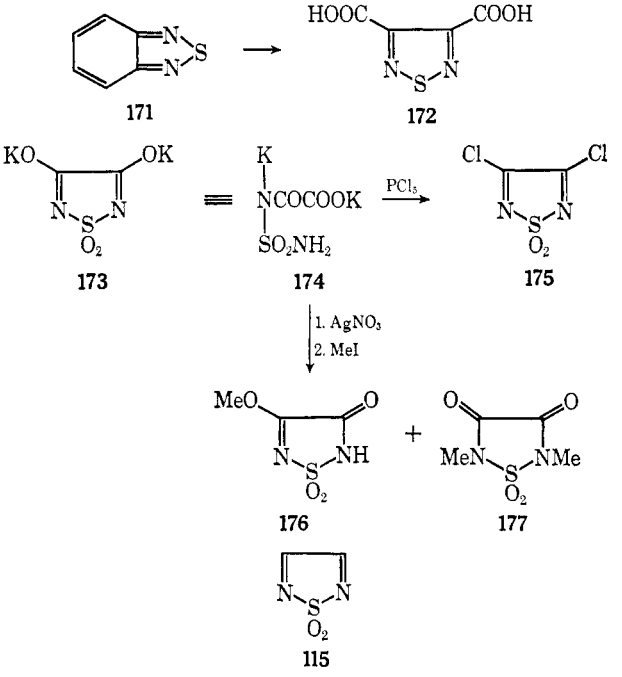


168 **169** **170**

An alternative reduction with zinc–ammonium chloride in benzene, rather than catalytic hydrogenation, was reported[104] to give a compound with a different melting point.

(100) A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **29**, 2717 (1964).
(101) H. Beecken, *Chem. Ber.*, **100**, 2170 (1967).
(102) H. Beecken, *ibid.*, **100**, 2164 (1967).
(103) H. Behringer and K. Leiritz, *ibid.*, **98**, 3196 (1965).
(104) H. Teufel, U. S. Patent 3.041,366 (1962); *Chem. Abstr.*, **62**, 14705*g* (1965).

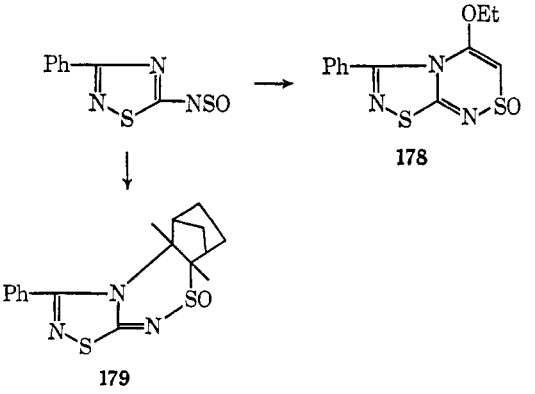
Few examples of the preparation of thiadiaza-S-dioxo systems by the oxidation of the reduced parent heterocycle have been reported. The oxidation[61] of 2,1,3-benzothiadiazole (**171**), shown to give among other products the dicarboxylic acid (**172**) and the dipotassium salt (**173**), which was later shown[105] to be the open-chain compound (**174**), suggests that certainly in this instance the sulfur atom in the ring was resistant to oxidation, though the existence of analogs of **174** such as **115** (*vide supra*) suggests that this oxidation should not necessarily have opened the ring.



171 **172** **173** **174** **175** **176** **177** **115**

The product **173**, also prepared from sulfamide and methyl oxalate, was used as a starting material for the synthesis of the functionalized derivatives **175**, **176**, and **177**, by the action of phosphorus pentachloride and methylation of the disilver salt of **174**, respectively.

The current interest in cycloaddition reactions lends importance both to the conversion (above) **166** → **167** and to the following synthetic method which constitutes the only mention of the 1,2,5-thiadiazo S-oxide system (see page 600). It has been shown[90] that heterocyclic N-sulfinyl derivatives, which have an *ortho* nitrogen, will react with ethoxyacetylene or more readily with bicyclo[2.2.1.]heptane-2 to give ring compounds such as **178** and **179**. These structures though not rigorously proven are supported by ir spectra and analysis.

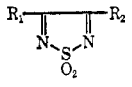
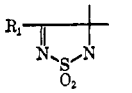
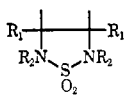
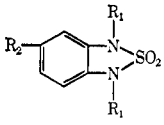
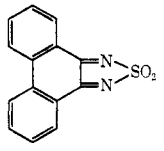
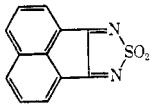


178 **179**

(105) R. Y. Wen, *Diss. Abstr.*, **23**, 4121 (1963).

Table VI

Derivatives of 1,2,5-Thiadiazole 1,1-Dioxides

Compound		R_1	R_2	Mp or bp (mm), °C	Yield, %	Solvent[a]	Ref
 180	a	Ph	Ph	248–250	58	Acetone	67
	b	Me	Me	154	74	Benzene	67
	c	Me	Ph	135 d[b]	29	Benzene	67
	d	*p*-$MeOC_6H_4$	$=R_2$	185–186	45	EtOAc	80
 181	a	Ph	H	135–136	63	EtOH–cyclohexane (1:1)	67
	b	Ph	Me	158–160	42	EtOH	67
	c	Ph	CH_3CO—	170–171	92	EtOH	67
	d	*p*-$CH_3C_6H_4$	H	72–75 d	45	Benzene–cyclohexane (3:1)	67
 182	a	H	H	171–172 d			90
	b	Ph	H	203	75	EtOH	90
	c	Ph	Me	164–165	88	EtOH	90
	d	H[c]	Et	93 (4)	48[87a]	$n^{23}D$ 1.4843[24]	97–99
	e	H	Et	95 (0.05)	51	$n^{20}D$ 1.4716	98
	f	H[c]	Me	55 (0.3)	55	$n^{19}D$ 1.4941	98
	g	H[c]	C_6H_4	94–96	40		97
 183	a	H	H	181–183		Benzene–ether	*d*
	b	H	Cl	199 d			*d*
	c	$PhCH_2$	H	128–131		Methylcyclohexane	*d*
				315	82	Acetic acid	80
				233–234	71	Pyridine	67

[a] Solvent of crystallization. [b] d = decomposition. [c] The S-monooxide. [d] J. Carson, U. S. Patent 3,177,221 (1965); *Chem. Abstr.*, **63**, 611*b* (1965).

E. PHYSICAL AND CHEMICAL PROPERTIES

Whereas the synthetic methods above were arranged according to the method and starting materials used, it would seem more appropriate to discuss the physical properties of each class of compound separately. Therefore, the physical properties (mainly melting point and crystallization solvent) of representative[106] compounds in each group have been tabulated and are accompanied by a discussion of spectroscopic data where pertinent.

1. 1,2,5-Thiadiazole 1,1-Dioxide Derivatives (Table VI)

What few spectroscopic data have been reported relate to the fully reduced compounds (**182**). The >S=O vibration was tentatively assigned[99] to the band at 1110 cm^{-1}, while the remainder of the spectrum was reported without further comment. The nmr spectra provide some interesting results[98,99] associated with the asymmetry introduced by the >S=O group, this effect disappearing with the dioxo compounds. A detailed study[98] involving comparisons with computed spectra provided all the relevant coupling constants.

(106) In those instances where many derivatives of a system have been prepared, only a few selected examples will be given; whereas as elsewhere in this review, all known compounds in the less well-developed sections are recorded.

2. 2H-1,2,6-Thiadiazine 1,1-Dioxides (Table VIIa)

The spectroscopic data collected for these compounds have been used to clarify[67] and finalize[79] the structure. Degering and Wilson[77,78] considered the three possible structures **184a**, **186**, and **187** as likely and favored **186** because of the pronounced acidity exhibited. The ir spectra[67] showed a distinct N–H (though possibly –OH) band at 3140 cm^{-1}, while the nmr spectra indicated the presence of *one* vinylic proton (δ 6.74 ppm), so that structure **187** was eliminated and structure **186** made less likely, particularly as such "enol" forms[107] are not favored. Final proof that **184** was the preferred type of structure came from the work of Roe and Harbridge[79] who demonstrated the identity of 2-alkyl compounds prepared either by alkylation of **184a** or directly from N-alkylsulfamide, thereby clarifying the site of the acidity. Uv spectra (Table VIIB) also demonstrated that compounds **184** were markedly different from **185**.

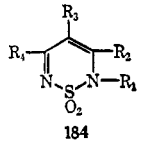
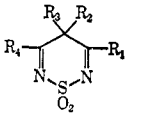
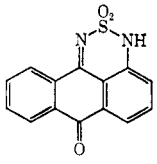
3. 2H-1,2,6-[(3,4) and (3,6)]-Dihydrothiadiazine 1,1-Dioxides (Table VIIIA)

A comparison of the melting points of compounds **188a** and **189** immediately poses a query as to whether their similar-

(107) F. Arndt and B. Eistert, *Chem. Ber.*, **74**, 423 (1941).

Table VIIA

Derivatives of 2H- and 4H-1,2,6-Thiadiazine 1,1-Dioxides

Compound		R_1	R_2	R_3	R_4	Mp, °C	Yield, %	Solvent[a]	Ref
 184	a	H	H	Me	Me	146		H_2O	77–79
	b	H	Me	Me	Me	193		H_2O[c]	77–79
		H	Me	Me	Me	189–190	97	H_2O	80
	c	Me	Me	H	Me	79		H_2O	79
	d	Me	Me	Me	Me	135		H_2O	79
	e	CH_3CO	Me	H	Me	54		Et_2O	79
	f	CH_2OH	Me	H	Me	233		H_2O	79
	g	$PhCH_2$	H	H	H	91		EtOH	79
	h	H	Ph	H	Ph	278–279	95	EtOH	67
	i	H	CH_3	H	$PhCH_2$	67–69	68	Benzene–cyclohexane (4:1)	
	j	H	COOEt	H	Me	101–103	69	Benzene	67
	k	H	$CONH_2$	H	Me	243 d[b]	61	H_2O	67
	l	H	COOEt	H	Ph	188–189	92	EtOH	67
	m	H	$CONH_2$	H	Ph	265 d	94	EtOH	67
	n	H	Me	Ph	Me	195	73	Benzene–cyclohexane (9:1)	67
	o	H	Me	H	Ph	183–184	98	EtOH–H_2O (1:1)	80
	a	Me	Me	Me	Me	165		H_2O	79
 185						338–340			88

[a] Solvent of crystallization. [b] d = decomposition. [c] ν_{max} (N–H) 3140 cm^{-1}, ν_{max} (NH) 3165 cm^{-1}.

Table VIIB

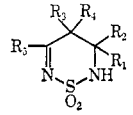
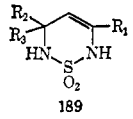
Uv Spectra of Compound 184

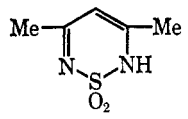
R_1	R_2	R_3	R_4	λ_{max}, nm	Log ε	λ_{max}, nm	Log ε
H	Me	H	Me	250	2.9	318	3.8
H	Me	Me	Me	251	2.9	329	3.8
Me	Me	H	Me	248	2.9	323	4.2
$PhCH_2$	Me	H	Me	253	3.1	323	3.9
Compound	**184a**			256	2.0		

ity is coincidental or not. Compounds **188** were the first examples prepared. Unfortunately in the evidence (ir and nmr) provided for the structure assigned, the isomeric structure **189** was not considered. Nevertheless from ir data[66] alone (Table VIIIB), particularly the single N–H vibration (~3260 cm^{-1}) and the >C=N vibration (~1620 cm^{-1}), which in compound **188b** moves to 1605 cm^{-1} (an effect attributable to conjugation with the adjacent phenyl ring), structure **188** must be considered as correctly established.

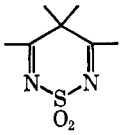
Table VIIIA

Derivatives of 2H-1,2,6-[(3,4) and (5,6)]-Dihydrothiadiazine 1,1-Dioxides

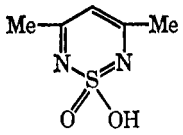
		R_1	R_2	R_3	R_4	R_5	Mp, °C	Yield, %	Solvent of crystn	Ref
 188	a	Me	Me	H	H	Me	142	66.5		66
	b	Me	Ph	H	H	Ph	137	20.8		66
	c	Me	Et	H	H	Et	130	40.7	Acetone–pet. ether (80–100°) (1:1)	66
	d	Me	Et	H	Me	Me	158	1.6		
	e	Et	Et	H	Me	Et	117	24.8		66
	f	*n*-Pr	Me	H	H	*n*-Pr	78	33.1		66
	g	*i*-Pr	H	Me	Me	H	193	42.8		66
 189	a	Me	Me	Me			141	81		65
	b	Ph	H	Ph			164–165	49		65
	c	*p*-ClC_6H_4	H	Ph			201	82		65
	d	Ph	H	*p*-ClC_6H_4			212–213	80		65
	e	Ph	H	*p*-$MeOC_6H_4$			199–200	80		65
	f	*p*-ClC_6H_4	H	*p*-$MeOC_6H_4$			210	42		65
	g	3,4,5-Trimethoxyphenyl	H	*p*-ClC_6H_4			213–214	41		65



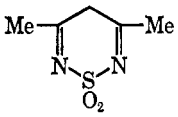
184a



185



186



187

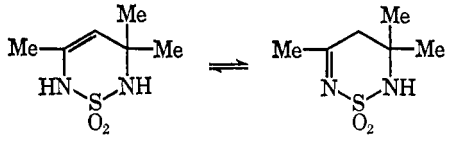
Nmr data[66] (the traces only being reported) while supporting this view had features which could be considered consistent with structure **189**.

As the structures of compounds **189** were unsupported by spectroscopic data, the assignment being presumably made upon the basis of the synthetic method used without considering the likelihood of subsequent isomerism, it would seem reasonable to suggest that until further supporting evidence is produced some doubt must rest upon this structural assignment (*cf.* **103**). Certainly it would appear likely that conforma-

Table VIIIB

Ir Data Describing Compounds 188

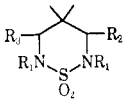
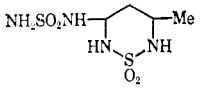
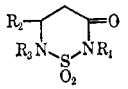
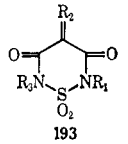
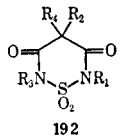
	ν_{max}, cm^{-1}					
Compd	*N—H*	*C—H*	*C=N*	*SO_2*		
188a	3200	2950	1628	1333	1175	1163
b	3250	3080, 3000	1605	1330	1170	1155
c	3260	2960	1620	1320	1170	
d	3260	2960	1620	1320	1170	
e	3280	2990	1620	1325	1150	
f	3210	2960, 2880	1623	1322	1165	
g	3280	2980	1615	1350	1180	



189a 188a

Table IX

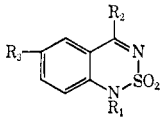
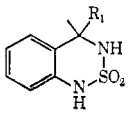
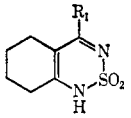
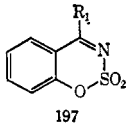
Derivatives of 1,2,6-Tetrahydrothiadiazine 1,1-Dioxides

		R_1	R_2	R_3	R_4	*Mp*, °C	*Yield*, %	*Solvent*[a]	*Ref*
 190	**a**	H	Me	Me		144–145	49	ν_{N-H}[d] 3210, ν_{SO_2} 1340	67
	b	R[b]	H	H			73	1175 and no C=C or C=N	97
						154			
 191	**a**	H	H	Ph		122–124	23	EtOH–H_2O	95
	b	H	H	*i*-Pr		140–142			95
	c	H	H	Bu		110–112			95
	d	H	H	C_6H_{11}		142–144			95
	e	H	H	$PhCH_2$		190–192			95
	f	Me	H	C_6H_{11}		138–140			95
	g	Me	H	Ph		169–170	80		95
	h	Ph	H	Me	4-Ph	230–232			95
	i	Ph	H	Ph		133–135	85	EtOH	95
	j	Ph	H	Ph		189–190		CCl_4	104
 193	**a**	Ph	PhCH<	Ph		223–224		EtOAc	82
	b	Ph	$(Me)_2C$=	Ph		204–205		EtOAc	82
	c	Ph		Ph		251–253		EtOAc	82
 192	**a**	H	H	H		174–175 d[c]			81
	b	*i*-Bu	H	*i*-Bu		63		EtOH	81
	c	C_6H_{11}	H	C_6H_{11}		152			81
	d	H	Me	H		226–228		MeOH	82
	e	H	Et	H		151–152			82
	f	H	Pr	H		154–155			82
	g	H	*i*-Pr	H		243–244			82
	h	H	Bu	H		177–178			82
	i	Ph	Ph	Ph		229–230			82
	j	Ph	H	Ph		240–241 d			82
	k	Ph	$PhCH_2$	Ph		215			82
	l	Ph	$PhCH_2$	Ph	$PhCH_2$	168–169			82
	m	Ph	$MeNCH_2$	Ph		202–204			82

[a] Solvent of crystallization, when data available. [b] R = $C_4H_9C(CH_2-)CHC_2H_5$. [c] d = decomposition. [d] In cm^{-1}.

Table XA

Derivatives of 1H-2,1,3-Benzothiadiazine 2,2-Dioxides

Compound		R_1	R_2	R_3	Mp, °C	Yield, %	Solvent[a]	Ref
 194	a	H	Ph	H	102–104		MeOH	91
		H	Ph	H	216–217	97	*i*-PrOH	74
	b	H	Me	H	207–209		MeOH–H_2O	91
		H	Me	H	209–211	68	*i*-PrOH	74
	c	H	Ph	Cl	206–208	53	EtOAc	74
	d	Me	Ph	H	207–208	96	EtOAc	74
	e	$PhCH_2$	Ph	H	153–154	57	EtOH	74
 195	a	Me					Nmr (DMF) 4-H	91
	b	Ph			134–135	36	(db → s in acid), 5.77 ppm	74
 196	a	Me			180–181	86	EtOH	67
	b	Ph			141–142	84.5	*i*-PrOH	67
	c	*p*-$MeOC_6H_4$			149–151	83	*i*-PrOH	67
	d	3,4,5-$(MeO)_3C_6H_2$			214–216	100	EtOH	67
 197	a	Me			119–121	42	EtOH	74
	b	Ph			149–150	30	*i*-PrOH	74

[a] Solvent of crystallization.

Table XB

Uv[a] Data for Compounds 194, 195, and 197

Compound				
194	a	223 (20,400)	269 (12,000)	359 (3200)
	b	223 (24,000)	264 (6800)	347 (25,400)
	c	231 (27,400)	268 (10,300)	295 sh (5300), 372 (3100)
	d	228 (21,700)	276 (12,650)	365 (3950)
	e	226 (21,750)	274 (13,650)	293 sh (10,450), 360 (4650)
195	b	228 sh (9100)	278 (3200)	355 (710)
197	a R_1 = Ph	241 sh (7800)	246 (7850), 302 (15,100)	320 (14,700)
	b R_1 = Me		264 (9950), 308 (1700)	

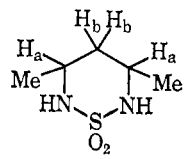
[a] In ethanol. Data from ref 74

tion effects might make an important contribution to the equilibrium position of such an isomeric system.

4. *1,2,6-Tetrahydrothiadiazine 1,1-Dioxides (Table IX)*

This section collects the properties of all the fully reduced systems, including the mono and diketo derivatives, together.

An immediate query arises regarding compounds **191i** and **191j** which, though they are claimed[95,104] as identical, have been accredited different melting points. Ir and nmr spectra of one of the fully reduced derivatives (**190a**) have been examined and support the assigned structure admirably. The N–H band in the ir, together with the absence of the >C=N– or >C=C< bands, clearly supports the ring structure, which is also unambiguously supported by the nmr data[67] (solvent not mentioned) given below:



190a

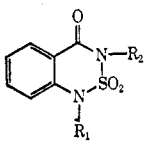
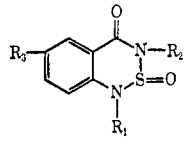
Me's (6H) 1.2 doublet, $J = 7$ cps
H_a's (2H) 3.6
H_b's (2H) 1.78, 1.08 AB triplets

5. *1H-2,1,3-Benzothiadiazine 2,2-Dioxides (Table X)*

Apart from the discrepancy in the two melting points assigned compound **194a**, the first being clearly suspect, these compounds require little comment. It is perhaps interesting to note the immense change that occurs in the uv spectrum (Table XB) when the nitrogen atom at position 1 (**194**) is changed to oxygen (**197a**).

Table XIA

Derivatives of 2,1,3-(1,2-Dihydro)benzothiadiazine 2,2-Dioxides

Compound		R_1	R_2	R_3	Mp, °C	Yield, %	Solvent[a] or λ_{max}, nm (ε)	Ref
 198	a	H	H		228–230	66	312 (2400),[b] 345 (3560)[c]	96
	b	Me	Me		85–89	62	305 (1810),[b] 305 (1810)[c]	96
	c	Me	H		204–205	55	MeOH–H_2O	89
		Me	H		204–207		320 (2200),[b] 315 (2960)[c]	96
	d	H	Me		199–201			89
		H	Me		201–203		315 (2040),[b] 340 (3220)[c]	96
	e	H	Ph		203–205	60	Ethylene chloride	89
	f	H	Et		177–179			89
	g	H	C_6H_{11}		158–159			89
	h	H	$PhCH_2$		191–193			89
	i	Bu	H		124–125	27	MeOH, cyclohexene	89
	j	Ph	Ph		163–164			89
	k	Me	Ph		189–190			104
	l	Bu	Ph		105–106			104
	m	$HOCH_2CH_2$	Ph		187–189			104
	n	$PhCH_2$	$PhCH_2$		127–128			104
 199	a	Me	Et	SO_2NHEt	150–152	83	MeOH	100
	b	Me	CH_2CH_2Cl	NO_2	161–162	67	2-Ethoxyethanol	100
	c	Me	Et	Cl	95–96	94	EtOH	100
	d	Me	CH_2CH_2Cl	Cl	153–154	80	EtOH	100
	e	Me	CH_2CH_2OEt	Cl	73–74	62	Cyclohexane	100
	f	Me	CH_2CH_2Ph	Cl	127–128	60	EtOH	100

[a] Solvent of crystallization. [b] In ethanol. [c] In base.

6. *Derivatives of 2,1,3-(1,2-Dihydro)benzothiadiazine 2,2-Dioxides (Table XIA)*

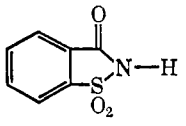
The study[96] of the N-methyl derivatives of **198** provided some interesting ir and uv data (Table XIB). In the ir, the N–H

Table XIB

Ir Data for Compounds 198 and 199 (ν, cm^{-1})

Compound	N—H	C=O	SO_2	SO
198a	3448, 2778	1695	1333, 1163	
c	2778			
d	3333			
199		1669–1645		1136–1122

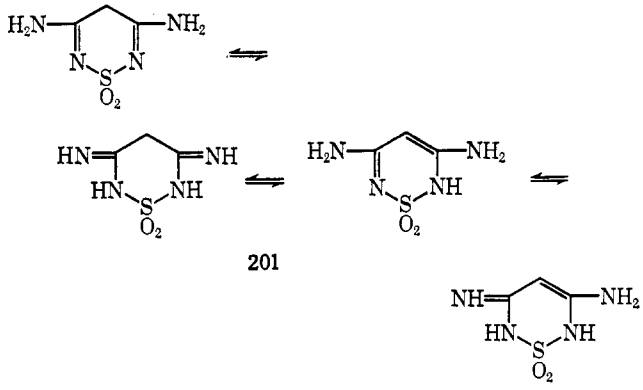
lying between the two electron-withdrawing groups was quoted as appearing at 3.6 mμ (2778 cm^{-1}), a very surprising result indeed, particularly as the corresponding N–H in saccharin[108] (**200**) appears at 3400 cm^{-1} though, of course, the smaller ring size may have some effect.



200

7. *Miscellaneous Compounds*

A number of compounds that have been prepared and do not fit the above categories are listed in Table XII. It is quite clear that there are many compounds here that could bear further investigation, for example, the diamino compound (**201**), the structure of which might be one of a number of possibilities (*cf.* the structure of the compound **184**).



201

Apart from a few miscellaneous reactions the most thoroughly examined feature of these compounds was their susceptibility to alkylation. Although Degering and Wilson[77,78] were unable to alkylate **184** (R_1 = H) by the action of alkyl halide on the sodium salt with heat (a method used for saccharin[109]), Roe and Harbridge[79] were successful in using the alkyl halide in refluxing acetone with anhydrous potassium carbonate. These workers also found that this system was stable in and alkylated by refluxing triethyl phosphite, as were saccharin and phthalimide.

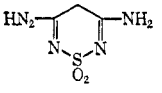
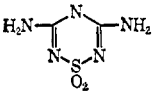
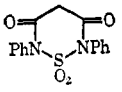
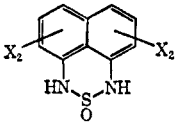
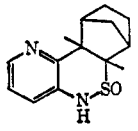
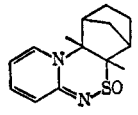
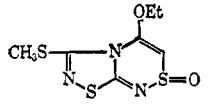
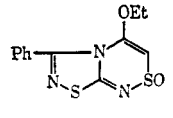
Most of the other systems were readily alkylated by standard procedures such as alkyl halide upon the sodium salt,[67,74,104] dimethyl sulfate with alkali,[96] and diazomethane.[67]

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

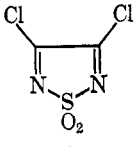
(109) L. Merritt, S. Levey, and H. Cutter, *J. Amer. Chem. Soc.*, **61**, 15 (1939).

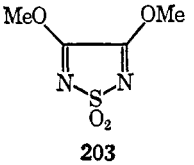
Table XII

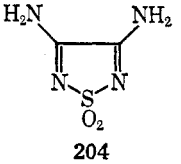
Miscellaneous Thiadiaza S-Dioxides

Compound	Mp, °C	Yield, %	Solvent	λ (log ε) or ν, cm^{-1}	Ref
 201					83–85
					86, 87
	169–170				95
	X = H, 160 d X = Cl, 245		Toluene Dioxane		103
	261–262	76	EtOH	ν_{N-H} 3105, ν_{SO} 1068	90
	224–226	35	MeOH	339 (3.61), 263 (3.83), 200 (4.29) ν_{SO} 1082	90
	145–146	58	Benzene	237 (4.24), 200 (4.12) ν_{SO} 1056	90
	151–152	73	Benzene	270 sh, 226 (4.35), 200 (4.40) ν_{SO} 1075	90

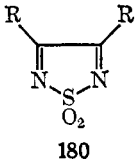
The dichloro compound **202** behaved[105] as might be expected, as an active imidoyl chloride giving derivatives **203** and **204** with refluxing methanol or ammonia (or amine), respectively, while compound **203** in the manner of an imino ether reacted readily with ammonia to give **204**.

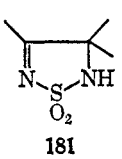

202

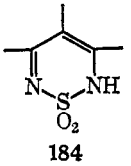

203

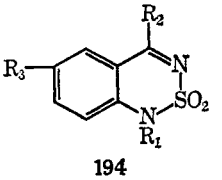

204

The stability of the sulfonyl group to reduction permitted the catalytic reduction[67,74,107] with hydrogen at 3 atm of the ring systems **180, 181, 184,** and **194,** to give the corresponding saturated compounds.


180


181


184


194

The instability of **180** (R = Ph) at its melting point gave among other products benzonitrile and sulfur dioxide.[110] Whereas the oxidation of sulfoxides to sulfones proceeds quite readily, an attempt[100] to oxidize **199d** to the corresponding dioxide with hydrogen peroxide in acetone failed. Since other conditions were not explored and little is known of such monoxide systems, clarification must wait upon further experiment.

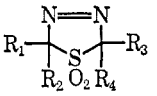
This same system (**199**) underwent an interesting elimination of the SO entity upon treatment with morpholine. Thus the action of morpholine upon **199d,** with a view to producing the β-morpholinoethyl-substituted heterocycle **206,** gave the sulfur-free compound **205,** other derivatives behaving similarly.

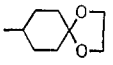
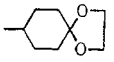
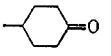
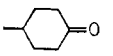
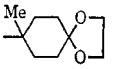
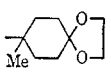
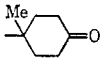
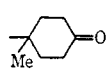
The reduction of **201a,**[95,104] used as an intermediate in the conversion of the dione to the mono-one (**191**), gives different compounds depending on whether catalytic hydrogenation or zinc–ammonium chloride is used. The 1,2,6-thiadiazine-3,5-diones (**192**), originating from malonyl derivatives and still possessing the active methylene group, underwent the expected typical reactions of such systems, 4-alkyl, 4-dialkyl, and 4-aminomethyl derivatives being readily accessible[82]

(110) J. Schaeffer, unpublished results; see ref 61.

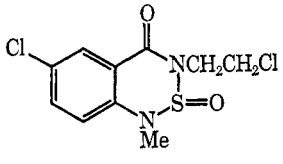
Table XIII

Characteristics of Δ^3-1,3,4-Thiadiazoline 1,1-Dioxides

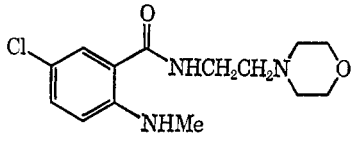


Compound	R_1	R_2	R_3	R_4	*Mp, °C*	*Yield, %*	*Solvent*[a]	*Ref*
207a	Et	C_6H_{11}	Et	C_6H_{11}	111–112 89–90	36 36	MeOH	112
207b	Et		Et		177–178 144–145		MeOH–C_6H_6 ν_{SO_2} 1295–1300, 1136–1156 λ_{max} 369 nm (ϵ 165)	113
207c	Et		Et		185–186	19.5	$(CH_3)_2CO$ at −20° ν_{SO_2} 1295–1300, 1136–1156, and 1100	113
207d	Et		Et		217–219		Et_2O ν_{SO_2} 1295–1300, 1136–1156	113
207e	Me		Me		215–235	63	$CHCl_2$–Et_2O ν_{SO_2} 1285–1130	113
207f	Me		Me		195–197	80	Acetone ν_{SO_2} 1287–1140 γ_{max} 370 (ϵ 170), 285 (ϵ 48)	113
207g	Me		Me		128–130 103–105		MeOH ν_{SO_2} 1150–1300 λ_{max} 364 (ϵ 163)	113

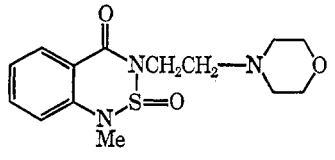
[a] Solvent for crystallization and other data.



199d



205



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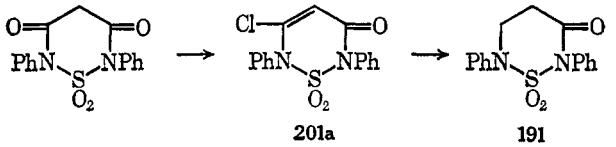
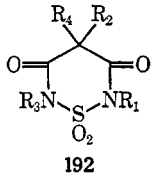


201a 191



192

when the 2 and 6 positions were suitably substituted. It is still quite apparent, however, that many other functional extensions of this system such as imidoyl chloride formation and so forth have yet to be investigated.

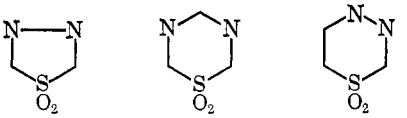
F. INDUSTRIAL USES

Apart from applications as pharmacologically active compounds, derivatives in this class have found application in resin formation,[3,64,85-87] and the hydrophylicity of the sulfamide entity has been used[88] to introduce water solubilizing properties.

V. Cyclic Hydrazino Sulfones

A. INTRODUCTION

Following the scheme laid down in the introduction to this review, this section describes the known chemistry of the possible systems A, B, and C. Of these, however, examples of systems B and C have yet to be synthesized. The discussion



A B C

in this part will therefore relate to derivatives of the 1,3,4-thiadiazole 1,1-dioxide system (A).

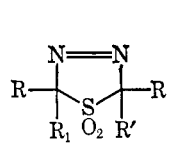
B. SYNTHESIS

The limited chemistry of this system is based entirely upon the Staudinger–Pfenninger reaction,[111] which involves the action

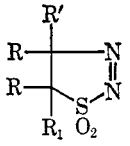
(111) H. Staudinger and F. Pfenninger, *Ber.*, **49**, 1941 (1916).

of sulfur dioxide upon diazo compounds to give the thermally labile Δ^3-1,3,4-thiadiazoline 1,1-dioxides (**207**).

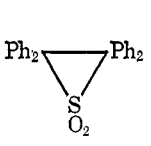
The original report,[111] while describing the interaction of sulfur dioxide with diphenyldiazomethane, suggested that the intermediate (not isolated) was the Δ^2-1,2,3-thiadiazoline 1,1-dioxide system (**208**) since a major product from this reaction was the tetraphenylethylene sulfone (**209**). However, the recent reappraisal of the reaction by Hesse and Reichold[112] and examination of this heterocyclic derivative have provided convincing evidence if not absolute proof that structure **207** is to be preferred. This conclusion is further favored by the known instability of the benzo analog of the system **208** (compound **45**).



207



208



209

The general synthetic procedure[111-113] involved generation of the diazo compound from the appropriate hydrazone by the action of mercuric oxide and potassium hydroxide in a nonpolar solvent, followed by treatment of a cold solution of diazo compound (**211**) with a stream of sulfur dioxide, until the intense red color was removed. Concentration of the solution and suitable work-up (avoiding chromatography) provided usually poor yields of the desired heterocycle, though in a few instances[113] good yields were obtained (Table XIII).

The mechanism proposed by Hesse[114] and Inhoffen[113] provided an elegant rationale for the preference of the 1,3,4-thiadiazoline structure by invoking the participation of a sulfene (**212**), generated by loss of nitrogen from the sulfur dioxide–diazo complex (**213**), in a 1,3-dipolar addition with further diazo compound (see Scheme II). This proposal was tested out[115] using a sulfene generated from another source and did in fact lead to thiadiazoline formation.

The extension of this synthesis, so far limited to purely aliphatic and alicyclic side chains (Table XIII), to other side-chain derivatives and to a further study of the influence of the side chain upon the products of decomposition (see below), as well as to a more detailed assessment of the mechanism of formation, might provide the basis for a useful investigation.

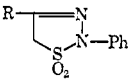
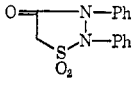
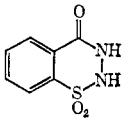
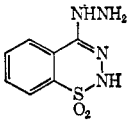
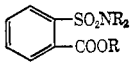
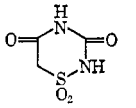
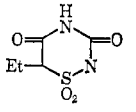
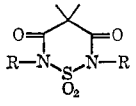
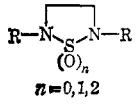
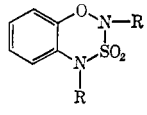
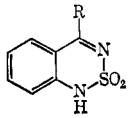
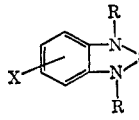
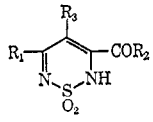
C. DECOMPOSITION

The primary interest in the Staudinger–Pfenninger reaction has not, however, been in the synthesis of 1,3,4-thiadiazoline 1,1-dioxides but in the decomposition products thereof. This reaction provides, depending upon the conditions (and possibly, without contrary evidence, the side-chain substituents), such products or by-products (upon induced decomposition) as the ketazine (**214**), the cyclic sulfone (**215**), and the highly substituted ethylene (**216**).

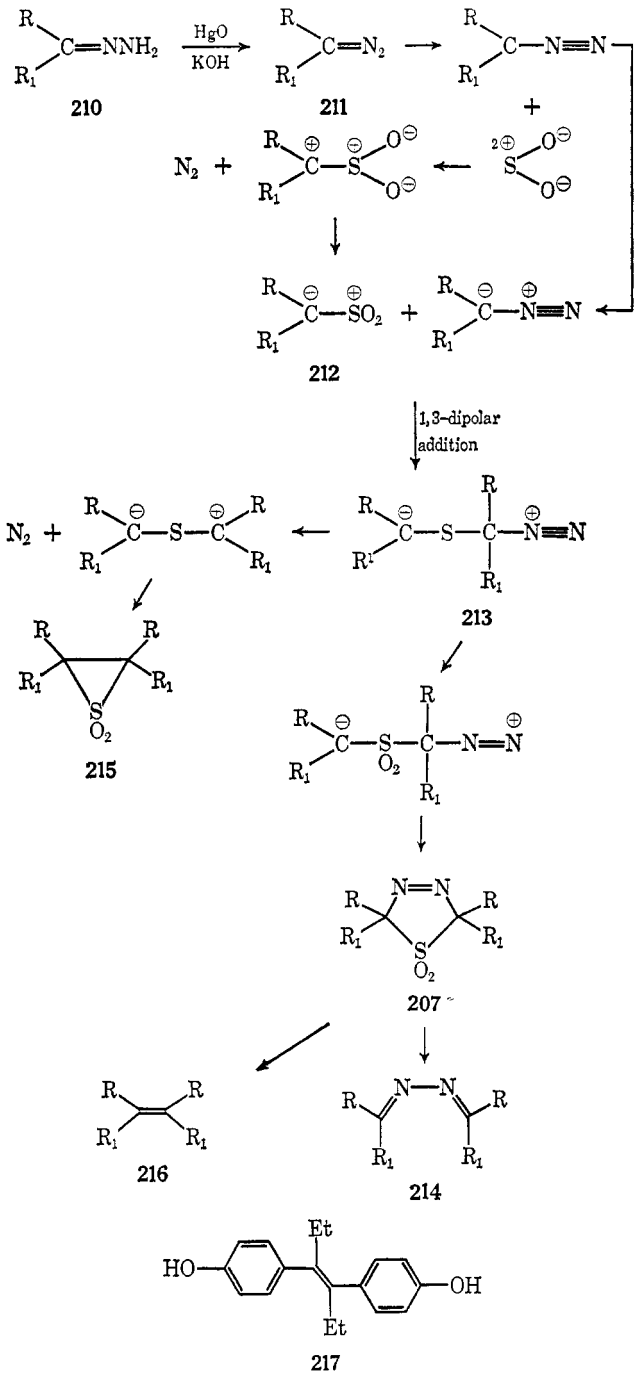
The controlled thermal, as well as photolytic, and catalytic (chromatography upon alumina) decomposition of **207** (R = C_2H_5, R_1 = C_6H_{11}) produces[112] significant amounts of the

(112) G. Hesse and E. Reichold, *Ber.*, **90**, 2101 (1957).
(113) H. H. Inhoffen, R. Jonas, H. Krosche, and U. Eder, *Justus Liebigs Ann. Chem.*, **694**, 19 (1966).
(114) G. Hesse, E. Reichold, and S. Majunder, *Chem. Ber.*, **90**, 2106 (1957).
(115) S. Rossi and S. Maiorana, *Tetrahedron Lett.*, 263 (1966).

Table XIV

Compound	Purpose claimed	Ref
	Claimed to have greater bacteriostatic activity than the open-chain compound (3)	5
	Claimed to exhibit antiinflammatory activity	9
	Found not active against mycobacterium tuberculosis	17
	Put into an antihypertensive composition	18
	Used as hypotensor	19
	Hypotensive as well as diuretic properties	20
	A potent depressor and useful for treating hypertension.	22
	Potential anticonvulsants	23
	Study carried out relating these to barbiturates	40, 41
	Did *not* induce sleep	52
	Antipyretic and analgesic activity	81, 82
	Blood pressure control	84
	Used as sprays against aphids and red spiders	97
	Antiinflammatory agents	104
	Sedatives and tranquilizers	91
	Nervous system depressants, muscle relaxants, and tranquilizers	106
	Antiviral or sedative activity	67

Scheme II



ketazine (**214**, R = C_2H_5; R_1 = C_6H_{11}), a consideration central to the arguments favoring the 1,3,4-thiadiazoline structure rather than the 1,2,3-thiadiazoline structure.

Carefully controlled reaction conditions have enabled this route to be used for the preparation of dodecahydrostilbene-type derivatives[112,113] and analogs of diethylstilbestrol[116] (**217**), the interesting biologically active analog of the oestradiol.

Synthesis of sulfones was mentioned by Staudinger[111] and this route adapted by Hesse[114] to prepare the then little known ethylene sulfone (**215**, R = R_1 = H). As both the diphenyl- or dihydrogen-substituted intermediates (**207**, R = R_1 = Ph, or (**207**, R = R_1 = H) represent special types of substituent, either too sterically crowded for stability or insufficiently substituted possibly for purposes of promoting ring closure, the generality or viability of this method as a route to such cyclic sulfones begs further experimentation.

D. PHYSICAL AND CHEMICAL PROPERTIES

The few data available characterizing the few known derivatives are collected in Table XIII.

These compounds appear in general to be high melting and difficult to crystallize, though whether this latter problem contributes to the poor yields usually obtained is not known.

Where available the ir data support the structure having the isolated sulfonyl group, though again a further study in this regard is required.

The presence of the two theoretically possible isomeric forms was demonstrated in some instances (Table XIII) by mechanical separation of the fractionally crystallized products. This stereoisomerism prompts a closer investigation into the stereochemical consequences of the proposed cycloaddition mechanism and raises the problem of whether the reaction proceeds by a concerted mechanism or otherwise.

The decomposition (above) of these compounds constitutes the main aspect of the chemical behavior of this class described. It is, however, appropriate to note here that no attempt to reduce the N,N double bond or to perform any other chemical modifications has been reported.

VI. Physiological Properties of Some Thiadiazole and Thiadiazine S-Oxides

Because of the many varied and sometimes conflicting claims made regarding the compounds so far discussed, the physiological properties of these compounds have been tabulated (Table XIV) for the sake of brevity, together with the source references.

(116) L. V. Vargha and E. Kovaco, *Chem. Ber.*, **75**, 794 (1942).