REACTIVITY OF 5-METHYL-2*H*-1,2,6-THIADIAZIN-3(6*H*)-ONE 1,1-DIOXIDE TOWARDS ALKYLATING AGENTS AND CARBENES

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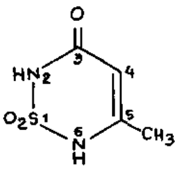
Abstract : The reaction between 5-methyl-2H-1,2,6-thiadiazin-3(6H)-one 1,1-dioxide **1** *and a variety of alkylating agents (diazomethane, trimethyl phosphite, dimethyl sulfate, and methyl iodide) in different conditions has been studied. Five methyl derivatives have been isolated and characterized. The reaction between* **1** *and carbenes proceeds with difficulty and only in the case of the carbene obtained from ethyl diazoacetate has the addition product been isolated.*

Compound **1**, 5-methyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-dioxide, is an isosteric analog of 6-methyluracil in which a carbonyl group is replaced by a sulfone group.[1] This molecule has four different nucleophilic positions, namely N_2, O_3, C_4, and N_6, thus, four monosubstituted, six disubstituted, and three trisubstituted derivatives may be expected from alkylation reactions. However, only five isomers (**2**, **3**, **4**, **5**, and **6**) could be isolated.[2]



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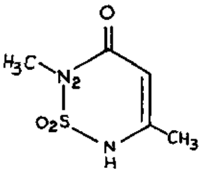

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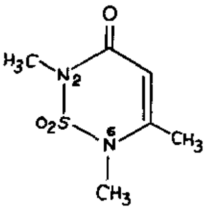

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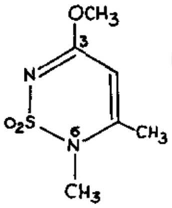

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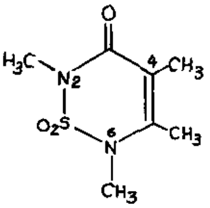

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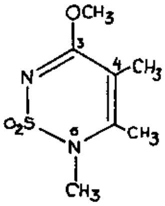

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The relative amounts of the methylated isomers are strongly dependent on the experimental conditions (Table 1). Treatment of compound **1** with an excess of diazomethane in an ethereal solution gave three isomers which were separated by TLC (toluene as eluent). These same isomers were also obtained with trimethyl phosphite but in a slightly different ratio. Reaction of **1** with dimethyl sulfate at room temperature afforded different isomers depending on the reaction medium used. Thus, when working in 1N NaOH only compound **2** (white needles from water) precipitated after acidification. When $NaHCO_3$ was used a complex mixture of four isomers was obtained. These were separated by TLC (chloroform as eluent). Finally, when compound **1** was dissolved in acetone, and methyl iodide and potassium carbonate (1:1) were added, a mixture of four isomers containing the 3,4,6-trisubstituted **6** was obtained. The relative amounts of the isomers (Table 1) have been determined by ^1H NMR on the crude reaction mixtures.

Table 1. Methylation of compound **1**

Experimental conditions	Total yield	**2**	**3**	**4**	**5**	**6**
Diazomethane	95%	--	55	30	15	--
Trimethyl phosphite	75%	--	50	45	5	--
Dimethyl sulfate (NaOH)	60%	100	--	--	--	--
Dimethyl sulfate ($NaHCO_3$)	70%	5	65	25	5	--
Methyl iodide (K_2CO_3)	95%	--	45	15	30	10

All the compounds have been obtained in an analytical grade of purity except **6** which was contaminated by **4**. Their physical properties are gathered in Table 2.

Table 2. Physical data of methylated derivatives of compound **1**

Compound	R_f^a	mp^b	UV^c	IR^d	^1H NMR^e				
					2	3	4	5	6
2	0.11	184°C	262	3100, 1675	3.11	----	5.48	2.05	8.7 (broad)
3	0.45	oil	264	1675	3.28^g	----	5.64	2.19	3.34^g
4	0.63	114°C^f	294	1610	----	3.90	5.46	2.25	3.42
5	0.67	oil	259	1670	3.27^g	----	1.96	2.15	3.17^g
6	0.78	oil	---	----	----	3.98	1.93	2.06	3.42

^{a}Silica gel, eluent : chloroform ; ^{b}uncorrected ; $^c\lambda_{max}$ (nm) in 95% ethanol ; ^{d}cm^{-1}, pure compounds (oils) or nujol mull (solids) ; ^{e}solvent : $CDCl_3$ except for **2** (DMSO-d_6) ; ^{f}crystallized from ethanol-water ; ^{g}see note 3.

The position of the methyl group was established according to the data of Table 2. Compound **2** is an N-monosubstituted derivative (N-Me at 3.11 ppm) ; the fact that the nitrogen atom is N_2 was deduced from the UV data since the corresponding 2-*n*-butyl and 6-*n*-butyl derivatives (prepared from *n*-butylsulfamide[4]) show their maxima, respectively, at 258 and 295 nm. Compound **3** is an N_2,N_6-disubstituted derivative (N-Me at 3.28 and 3.34 ppm). Compound **4** is an N_2,O-disubstituted derivative (N-Me at 3.42 and O-Me at 3.90 ppm) with an electronic spectrum of a fully conjugated structure. Compound **5** is similar to **3** with a supplementary methyl group bonded to carbon C_4 (C-Me at 1.96 ppm). Finally, compound **6** closely ressembles compound **4** ; its third methyl group is bonded to C_4 (C-Me at 1.93 ppm).

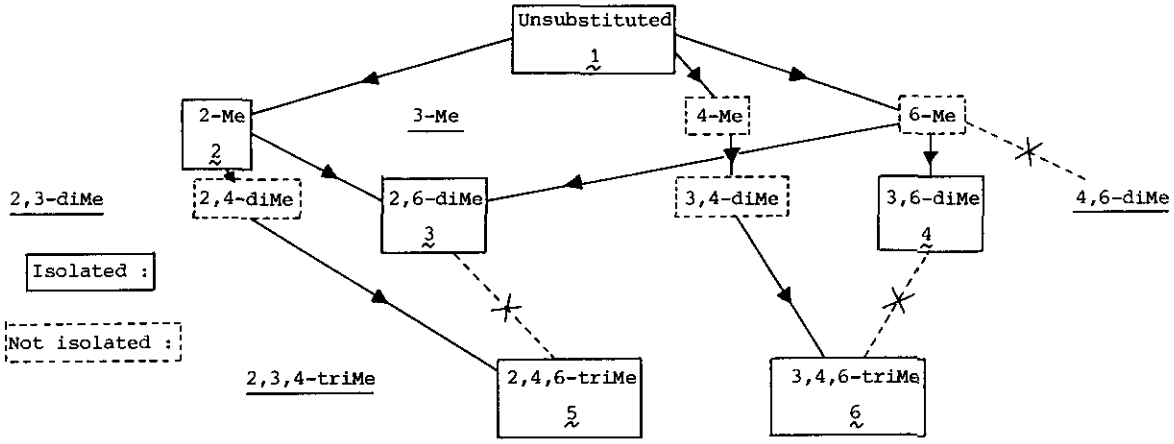
Some of these compounds have been studied by ^{13}C NMR spectroscopy (Table 3).

Table 3. Carbon-13 NMR spectra of 2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-dioxides (ppm from TMS)

Compound	Solvent	C_3	C_4	C_5	Me_5	N_2-Me	O-Me	N_6-Me
1	DMSO-d_6	162.3	89.6	156.4	19.5	----	----	----
2	DMSO-d_6	162.4	98.7	151.0	19.8	25.6	----	----
3	$CDCl_3$	161.8	104.6	150.9	20.1	27.5	----	32.7
4	$CDCl_3$	167.0	92.1	157.4	20.7	----	54.7	30.8

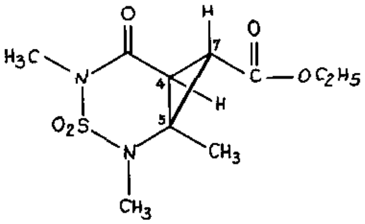
The differences observed in the ^{13}C chemical shifts of C_4 and C_5 when 1 and 2 are compared may arise from tautomeric modifications (presence of 3-hydroxy or 4*H*-tautomers). Otherwise, the spectra are consistent with the structures proposed.

The results obtained with the n-butyl derivatives[3] *and the fact that it was not possible to* C-methylate compounds 3 and 4 (to obtain 5 and 6 respectively)[5] shows that the simplest tree which connects all the compounds is the following one (3-methyl derivatives are methoxy compounds) :

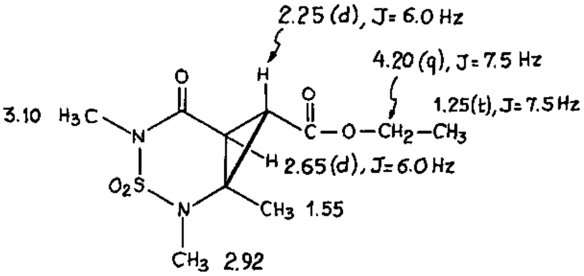


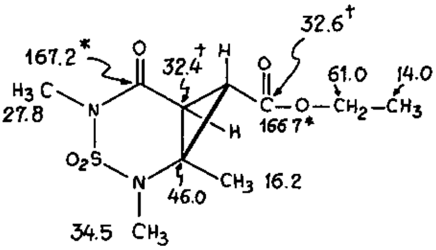
Pandit *et al.*[6] have studied the reaction of carbenes with uracil and uridine derivatives and isolated the adducts both with dihalogenocarbenes and with ethoxycarbonylcarbene. In a similar way and following the analogy between uracil and our thiadiazine 1,1-dioxides we have studied the addition of carbenes to the C_4-C_5 double bond of compound 3.

When the thiadiazinone 1,1-dioxide 3 was allowed to react with ethoxycarbonylcarbene (generated by copper catalyzed decomposition of ethyl diazoacetate[7]) in dimethoxyethane, in addition to the starting material the following adduct was isolated in 30% yield (TLC, hexane-ethyl acetate 4:1).



It is an analytically pure oily product, with no UV absorption in EtOH (showing the saturation of the C_4-C_5 double bond) and with IR bands (pure sample) at 3040 (cyclopropane ring) and 1725 and 1720 cm^{-1} (C=O). In mass spectrometry the highest m/e peak appears at 231 (M-EtO). In ^{1}H NMR (solvent : $CDCl_3$) the value of the coupling constant between H_4 and H_7 (6.0 Hz) proves the *trans* configuration of both protons.[6] No *endo* isomer was observed. The ^{13}C NMR spectrum (same solvent) is also in agreement with the proposed structure (signals marked with * or † may be reversed).





Other experiments were carried out to prepare cyclopropane adducts from thiadiazinone 1,1-dioxide derivatives. The reactions between 5 and ethoxycarbonylcarbene, 3 and 5 and diazomethane (catalyzed with palladium acetate[8]), and 3 and dimethylsulfoxonium methylide[9] were unsuccessful : in all the cases, the starting materials were recovered unchanged.

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REFERENCES AND NOTES

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2. In a preceding paper (P. Goya, P. Martínez, C. Ochoa, and M. Stud, *J. Heterocyclic Chem.*, 1981, 18, 459) methylation (dimethyl sulfate, diazomethane) of 4-nitro, 4-cyano, and 4-ethoxycarbonyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-dioxide has been described. Depending on the thiadiazine and the alkylating agent, 2-methyl, 6-methyl, and 3-methoxy-6-methyl derivatives could be isolated.
3. Methylation (ICH_3/K_2CO_3/acetone) of 5-methyl-2-*n*-butyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-dioxide[4] gave a mixture of the 5,6-dimethyl (Me_6 : 3.36 ppm) and 4,5,6-trimethyl (Me_6 : 3.19 ppm) derivatives. Methylation in the same conditions of 5-methyl-6-*n*-butyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-dioxide[4] gave a mixture of the 2,5-dimethyl (Me_2 : 3.31 ppm) and 3-methoxy-5-methyl (the 6-butyl analog of 4) isomers. These chemical shifts have been used to assign the N-methyl signals of compounds 3 and 5 (Table 2).
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5. The following experiments have been carried out : reaction of 3 and 4 with diazomethane and with ethyl bromoacetate (K_2CO_3/acetone) ; in both cases, the starting materials were recovered unchanged.
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