Marylène Chollet-Krugler*[1],E. Finner[2], Marie-Odile Christen[3] and Jean-Louis Burgot[1]

[1] Laboratoire de chimie analytique – UPRES 2231 – Université de Rennes I – France
[2] Kali-Chemie AG – Hannover - Allemagne
[3] Laboratoire Solvay-Pharma – 42 rue Rouget de Lisle – 92151 Suresnes Cedex – France

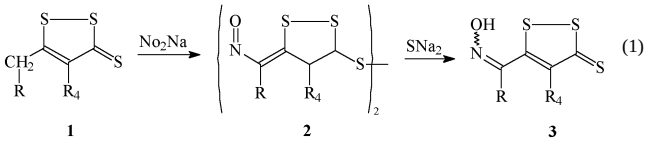
Received March 14, 2002
Received Revised December 16, 2002

Alkylation of 5-[1-hydroxyiminoalkyl]-1,2-dithiole-3-thiones using methyl iodide in the presence of sodium hydroxide gives derivatives which may be considered as being 5-methylthio-1-oxa-6,6a λ^{IV}-dithia-2-azapentalenes with quantitative yields. The structure of oxadithiazapentalene attributed to the alkylation products is founded on X-ray analysis and NMR and IR data.

J. Heterocyclic Chem., **40**, 155 (2003).

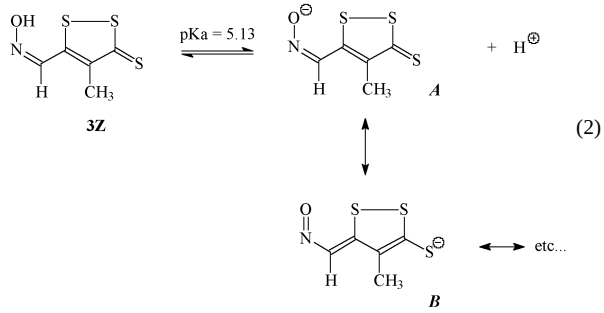
Introduction.

5-[1-Hydroxyiminoalkyl]-1,2-dithiole-3-thiones (dithiolethiones oxime) **3** are patented for pharmacological reasons [1]. They are prepared the most efficiently starting from 5-alkyldithiolethiones **1** (eq 1) by action of sodium nitrite in anhydrous acetic acid. The disulphides **2**, which form in a first step, are reduced by sodium sulphide to afford dithiolethiones oxime **3** [2].



1 2 3 (1)

According to the structure of the starting dithiolethione **1**, oximes **3** *Z* or *E* (or a mixture of both) are obtained. It is likely that experimental conditions play a part in defining the configuration since studies show that the interconversion of these isomers may be easy but, so far, experimental conditions are not well defined [3]. The determination of pKa of oxime **3n*E*** and **3n*Z*** ($R_4 = CH_3$, R = H) have been performed in water at 25 °C after separation by column chromatography on silica gel (eluent heptane – diethylether) of the mixture of *E* and *Z* isomers. Only **3n*E*** was obtained in a "geometrically" pure state while **3n*Z*** was obtained in a mixture. However, this did not preclude the determination of pKa of the *Z* isomer because the calculation took into account this problem [4]. Thus, we obtained a pKa value of 8.28 for oxime **3n*E*** which, although very low for an oxime, may be explained still simply by the very strong withdrawing effect of the 5-[1,2-dithiole-3-thione]-yl moiety [5]. Conversely the value obtained with oxime **3n*Z*** (pKa = 5.13) is strongly anomalous and looks like that obtained with a thiophenol substituted by a withdrawing group. It is well within accordance with a resonant conjugated base involving the oximate form ***A*** and the thiolate form ***B*** which owing to the pKa value would be by far the most important (eq 2).



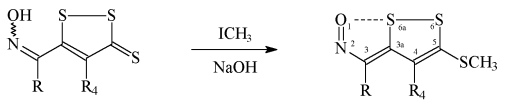
3Z A B (2)

This result induces the question of the site of alkylation of oximes **3** in basic medium. This question is not only interesting from the purely mechanistic standpoint but also, of course, for synthetic reasons. We report here results obtained by action of methyl iodide on dithiolethiones oxime **3** in aqueous sodium hydroxide solution.

Results and Discussion.

Worked out dithiolethiones oxime **3** are given in table 1. Initial ratios *E*/*Z* were determined by NMR. Particularly noticeable for the identification of *E* and *Z* isomers was the $^3J_{C,H}$ coupling constant of 10 Hz between the aldehydic carbon and the hydroxyl proton in the *E* isomer only [2].

Methylation of oximes **3** by methyl iodide in aqueous sodium hydroxide solution affords exclusively and with quantitative yields nitrosoderivatives **4** (eq 3) in which a weak interaction between the oxygen atom and the adjacent sulfur atom 6a occurs. These compounds are named “heteropentalenes” by some authors (see below). It is interesting to note that whatever the initial *E* or *Z* configuration the result is exclusively the obtainment of heteropentalene **4**. This means that once in these conditions the sulphur atom is alkylated, the oxygen atom becomes quasi-linear with the two sulphur atoms of the dithiole.



3 4 (3)

Table 1

Structures of Starting Dithiolethiones Oxime **3**

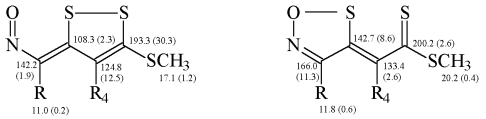
Compound	R_4	R	*E* / *Z* [a]
3a	H	H	2 / 1
3b	OCH_3	H	4 / 1
3c	CH_2Ph	H	1 / 2
3d	H	CH_3	*Z*
3e	H	C_2H_5	*Z*
3f	$–CH_2–CH_2–CH_2–$		*Z*
3g	CH_3	CH_3	1 / 2
3h	C_2H_5	CH_3	*Z*
3i	CH_2Ph	CH_3	*Z*
3j	Ph	CH_3	*E*
3k	Ph	Ph	*E*
3l	CH_3	i / r	*Z*
3m	Ph	H	*E*
3n	CH_3	H	*E* and 7 / 3 [b]

[a] Initial ratio determined by NMR; [b] Two distinct experiments have been performed.

From the thermodynamic standpoint this may be accounted for by the occurrence of a partial bond between the oxygen atom and the vicinal sulphur atom. This result means that during the alkylation reaction there is a change of configuration of the *E* isomers. This is somewhat surprising because the coherent results obtained in the determination of pKa of oxime **3*E*** took into account the fact that no isomerization of this isomer occurs [4]. Hence the change in configuration may be attributed to the action of methyl iodide.

Some characteristics of the obtained derivatives **4** are given in Tables 2 and 3. The assessment of the structure of 5-methylthio-1-oxa-6,6a λ^{IV}-dithia-2-azapentalenes to compound **4** is based on the following arguments. At first glance, a structure of a nitrosoderivative of the type **5** or of an oxathiazole **6** would be attributed to the obtained products of alkylation if there is no-bond resonance in the structure of the compound involved.

Scheme 1

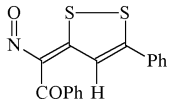


5 **6**

^{13}C Chemical shift estimation (+/-).

^{13}C chemical shift predictions [6] (Scheme 1) for **5** and **6** (R_4 = H, R = CH_3) deviate so much from those observed experimentally (Table 3) that neither structure **5** nor **6** describes the system correctly. IR spectra confirm these results. Neither the characteristic group frequency of an N=O moiety nor that of a C=N group is attributable to the absorptions observed. Incidentally it is interesting to note that heteropentalenes **4** exhibit IR spectra very similar to these of disulphides **2** with the same substituents R and R_4 (Figure 1).

In literature some heteropentalenes (without a methylthio in position 5) are described [7]. An X-ray analysis of the derivative:



has even been performed [8]. It gives a distance between the adjacent oxygen and sulfur atoms of 2.034 Å, which is the shortest intramolecular S—-O contact other than normal S—-O covalent bonds. It indicates that there is a weak bond between both atoms. This justifies the name of oxadithiazapentalene for these kinds of derivatives. The struc-

Table 2

Some Characteristics of Heteropentalenes **4**

	R_4	R	Formula	mp °C [a]	^1H Chemical Shifts ($CDCl_3$))
4a	H	H	$C_5H_5NO\,S_3$	105	H(3):8.70; H(4):7.79; SCH_3(5):2.74
4b	OCH_3	H	$C_6H_7NO_2S_3$	108	H(3):8.67; OCH_3(4):3.96; SCH_3(5):2.70
4c	CH_2-Ph	H	$C_{12}H_{11}NOS_3$	109	H(3):8.69; CH_2:4.39; Ph:7.12(o), 7.27(m), 7.21(p); SCH_3:2.72
4d	H	CH_3	$C_6H_7NO\,S_3$	108	CH_3(3):2.59; H(4):7.67; SCH_3:2.75
4e	H	C_2H_5	$C_7H_9NO\,S_3$	79	C_2H_5(3):2.97 and 1.41; H(4):7.67; SCH_3:2.73
4f	-CH_2-CH_2-CH_2-		$C_8H_9NO\,S_3$	113	CH_2(3):2.87; CH_2(4):3.05; CH_2:2.12; SCH_3:2.75
4g	CH_3	CH_3	$C_7H_9NOS_3$	107	CH_3(3):2.78; CH_3(4):2.72; SCH_3:2.70
4h	C_2H_5	CH_3	$C_8H_{11}NOS_3$	100	CH_3(3):2.79; C_2H_5(4):3.25 and 1.26; SCH_3:2.68
4i	CH_2-Ph	CH_3	$C_{13}H_{13}NOS_3$	118	CH_3(3):2.85;CH_2:4.71;Ph:7.02(*o*),7.30(*m*),7.23(*p*); SCH_3:2.67
4j	Ph	CH_3	$C_{12}H_{11}NOS_3$	159	CH_3(3):1.83; Ph(4):7.32(*o*), 7.53(*m*), 7.51(*p*); SCH_3:2.61
4k	Ph	Ph	$C_7H_{13}NOS_3$	201	Ph(3):6.95(*o*), 6.95(*m*), 7.05(*p*), Ph(4):6.89(*o*), 7.02(*m*), 7.08(*p*) ; SCH_3: 2.60
4l	CH_3	i-pr	$C_9H_{13}NOS_3$	98	i pr(3):3.79 and 1.45; CH_3(4):2.78; SCH_3:2.72
4m	Ph	H	$C_{11}H_9NOS_3$	117	H(3):8.27; Ph(4):7.37(*o*) and 7.55 (*m* and *p*); SCH_3:2.69
4n	CH_3	H	$C_6H_7NOS_3$	114	H(3):8.38; CH_3(4):2.56; SCH_3:2.79

[a] The solvent of crystallization was systematically toluene, yellow derivatives.

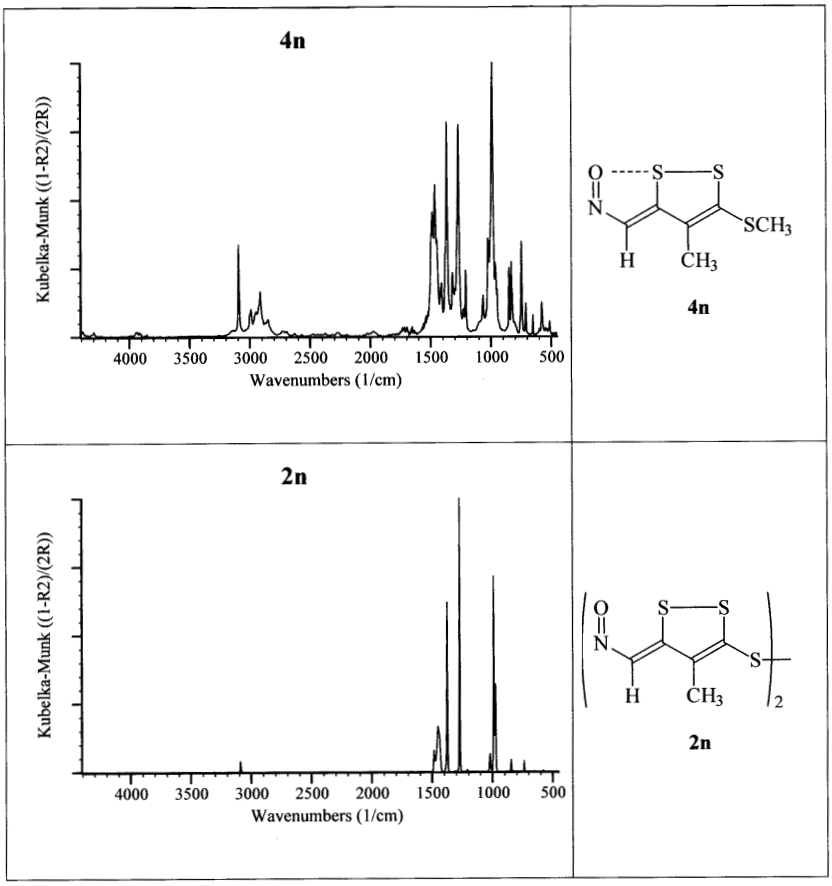


Figure 1. Comparison of the IR spectra of compound **4n** and **2n**.

Table 3

^{13}C Chemical Shifts of Heteropentalenes **4** ($CDCl_3$)

	C(3)	C(3a)	C(4)	C(5)	5-SCH_3	miscellaneous
4a	143.4	164.6	121.4	189.2	18.9	
4b	141.9	154.3	149.1	179.6	17.9	OCH_3: 61.6
4c	143.3	162.6	133.1	185.4	19.2	CH_2: 35.4; Ph: 136.9(*i*), 127.9 (*o*), 128.8 (*m*), 127.0 (*p*)
4d	151.3	164.8	119.8	190.3	18.9	CH_3: 14.3
4e	156.1	164.6	119.7	190.3	18.9	CH_2: 22.5; CH_3: 11.8
4f	153.5	159.0	133.7	184.6	18.9	CH_2(3): 26.2; CH_2(4): 25.1; CH_2: 21.7
4g	151.4	162.3	130.8	185.4	19.4	CH_3(3):18.1; CH_3(4):16.2
4h	150.8	162.2	137.5	185.3	19.2	CH_3:17.1; CH_2CH_3: 22.6 and 14.6
4i	151.4	163.7	132.3	187.5	19.4	CH_3:17.0; CH_2: 34.6; Ph: 137.9(i), 127.9(*o*), 128.9(*m*) 126.7(*p*)
4j	152.2	161.6	136.1	189.5	19.7	CH_3: 16.4; Ph: 134.9(*i*), 131.3(*o*), 128.8(*m*), 129.5(*p*)
4k	156.5	160.4	137.0	188.7	19.6	Ph(3):129.9(*i*), 129.9(*o*), 127.4(*m*), 127.9(*p*); Ph(4):133.5(*i*), 131.0(*o*), 128.2(*m*), 128.5 (*p*)
4l	160.0	162.4	129.8	185.9	19.4	i-pr : 29.2 and 22.7; CH_3: 16.5
4m	144.4	162.7	136.4	187.2	19.4	Ph:134.1(*i*), 130.1(*o*), 129.5(*m*), 129.6(*p*)

ture of Heteropentalenes are considered as no-bond resonance compounds [9,10].

An X-ray analysis (Table 4) has been performed on the derivative **4n** in which the S—-O length is of 1.927 Å, which is still shorter than that previously reported. As a result, derivatives **4** must be considered as 5-methylthio-1-oxa-6,6a λ^{IV}-dithia-2-azapentalenes.

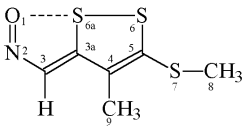
EXPERIMENTAL

Instrumentation.

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The nmr spectra were taken on a 300 MHz Bruker AM 300 instrument. Observation frequency was at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts were

Table 4

Determination by X-ray of Bond Lengths (Å) for Compound **4n**



Bond Lengths (Å)

S(6a) – C(3a)	1.715
S(6a) – O(1)	1.927
S(6a) – S(6)	2.276
S(6) – C(5)	1.691
S(7) – C(5)	1.738
S(7) – C(8)	1.793
C(3a) – C(4)	1.397
C(3) – C(3a)	1.429
C(4) – C(5)	1.398
C(4) – C(9)	1.501
O(1) – N(2)	1.336
N(2) – C(3)	1.299

referred to tetramethylsilane (δ=0 ppm). FTIR spectra were obtained with a Perkin-Elmer FTIR 16PC instrument. Single crystal X-ray diffraction data collection has been performed at room temperature with a Nonius KappaCCD diffratometer (Centre de Diffractométrie, Université de Rennes 1, France), with Mo Kα radiation (λ = 0.71073 Å).

Synthesis.

Dithiolethiones oxime **3** were dissolved in a 10% (w/w) sodium hydroxide in water solution. A net excess (= 2 eq) of methyl iodide was added at 0 °C during half a hour and the mixture was left about 12 h at room temperature. It was then extracted by toluene. The organic phase was successively washed with water, dried on sodium sulphate, filtrated, concentrated and chromotographied on silica gel. Heteropentalenes were eluted with a mixture ligroin-toluene (30 – 70).

Anal. Calcd. for compound **4a** $C_5H_5NOS_3$: C, 31.39; H, 2.63; N, 7.32; O, 8.36. Found: C, 31.80; H, 2.65; N, 7.07; O, 8.71.

Anal. Calcd. for compound **4n** $C_6H_7NOS_3$: C, 35.10; H, 3.44; N, 6.82; O, 7.79. Found: C, 35.24; H, 3.42; N, 6.59; O, 8.21.

REFERENCES AND NOTES

[1] M.-O. Christen and J.-L. Burgot, French Patent, Appl., Fr2676057 (1992); *Chem. Abstr*., 124522w (1993).

[2] M. Abazid, H.-O. Bertrand, M.-O. Christen and J.-L. Burgot, *Phosphor, Sulfur and Silicon*, **88**, 195 (1994).

[3] J.-L. Burgot, unpublished results

[4] H.-O. Bertrand, M-O. Christen and J-L. Burgot, *The Analyst*, **120**, 2639 (1995).

[5] M. Chollet, B. Legouin and J-L Burgot, *J. Chem. Soc., Perkin Trans. 2*, 2227 (1998).

[6] Shift estimation using the INKA on-line ^{13}C NMR Data Bank.

[7] R. M. Christie, A. S. Ingram, D. H. Reid and R. G. Webster, *J. Chem. Soc., Perkin Trans. 1*, 722 (1974).

[8] P. L. Johnson, K. I. Reid, I. C. Paul and W. A. Noyes, *J. Chem. Soc*. (B), 946 (1971).

[9] R. Gleiter, R. Gygax, *Inst. Org. Chem*., Tech. Hochsch. Darmstadt, Darmstadt, Ger., *Top. Curr. Chem.*, **63** (Bonding and Struct.), 49 (1976).

[10] M. G. Marei and M. M. Mishrikey, *Phosphor, Sulfur and Silicon*, **73**, 229 (1992).