Reaction of Dichlorocarbene with 2,3-Dihydro-5,6-dimethyl-1,4-oxathiin and 2,3-Dihydro-5,6-dimethyl-1,4-dithiin

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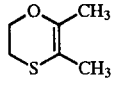
Received May 11, 1995

Dichlorocarbene, generated from ethyl trichloroacetate and sodium ethoxide, reacts with 2,3-dimethyl-5,6-dihydro-1,4-oxathiin to give 7,7-dichloro-1,6-dimethyl-2-oxa-5-thiabicyclo[4,1,0]heptane, and with 2,3-dimethyl-5,6-dihydro-1,4-dithiin to give 6-chloro-2,3-dihydro-7-methyl 5-methylene-5(*H*)-1,4-dithiepin. Both products were oxidised to the corresponding sulfone.

J. Heterocyclic Chem., **33**, 217 (1996).

In the course of some work aimed at elaborating the 2,3-dihydro-1,4-oxathiin and 2,3-dihydro-1,4-dithiin heterocyclic nuclei, areas which have shown wide and varied biological activities [1-3], we had occasion to examine the reaction of dichlorocarbene with alkyl-substituted examples of both ring systems. It was shown that, in the one case, the previously undescribed 2,5-oxathiabicyclo[4.1.0]heptane ring system was made, and in the other, a novel ring-expansion to a 2,3-dihydro-5-methylene-5(*H*)-1,4-dithiepin occurred.



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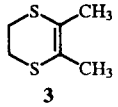

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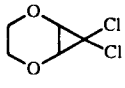

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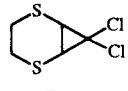

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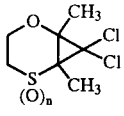
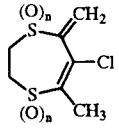
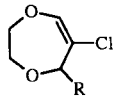


2a, n = 0
2b, n = 2



4a, n = 0
4b, n = 2

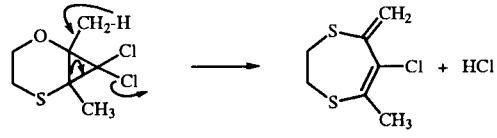


6a, R = Cl
6b, R = Xalkyl (X = O,S)

When a solution of 2,3-dihydro-5,6-dimethyl-1,4-oxathiin (**1**) [4] in toluene was treated, at 0°, with ethyl trichloroacetate and sodium ethoxide, a poor yield of 7,7-dichloro-1,6-dimethyl-2-oxa-5-thiabicyclo[4.1.0]heptane (**2a**) was obtained as a distillable, somewhat unstable, oil. By contrast, under the same conditions the corresponding 2,3-dihydro-5,6-dimethyl-1,4-dithiin (**3**) [5] gave, as the only identifiable product, 6-chloro-2,3-dihydro-7-methyl-5-methylene-5(*H*)-1,4-dithiepin (**4a**).

It does not appear that the reaction of dichlorocarbenes with 2,3-dihydro-1,4-oxathiins has previously been described. The corresponding reaction with 2,3-dihydro-1,4-dioxin gives 7,7-dichloro-2,5-dioxabicyclo[4.1.0]heptane (**5**) [6-8]. This compound appears to be somewhat unstable: in refluxing xylene it ring-expands to 5,6-dichloro-2,3-dihydro-5(*H*)-1,4-doxepin (**6a**) [6] and in the presence of alcohols or thiols, to the corresponding 5-alkoxy-or 5-alkylthio-6-chloro-2,3-dihydro-5(*H*)-1,4-dioxepin (**6b**) [8].

Scheme 1



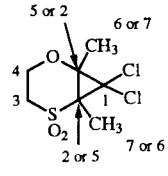
In the corresponding dithiin cases, it is reported that 2,3-dihydro-1,4-dithiin gives 7,7-dichloro-2,5-dithiabicyclo[4.1.0]heptane (**7**) [9].

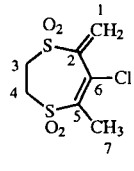
None of the above examples involves compounds with alkyl groups situated on the double-bond, or in the bridgehead position of the presumed or actual bicyclic intermediate. Hence ring-expansion, at least *via* a mechanism of the type hypothesised in Scheme 1, is not a possibility.

Previous syntheses of 2,3-dihydro-5(*H*)-1,4-dithiepins have all involved the reaction of three-carbon fragments with ethane-1,2-dithiol [10-13]. The formation of this ring system from a 5,6-dihydro-1,4-dithiin has not before been described.

Since both the 2-oxa-5-thiabicyclo[4.1.0]heptane and the 5(*H*)-1,4-dithiepin were relatively unstable, and decomposed slowly at room temperature, each was oxidised to the corresponding dioxide **2b** and tetraoxide **4b**. These were white crystalline solids which appeared to be completely stable.

NMR Assignments





Assignments of ^1H NMR Signals From Compounds **2b** and **4b**

	Compound **2b** Chemical Shift (ppm)		Compound **4b** Chemical Shift (ppm)	
C/H	^1H	^{13}C	^1H	^{13}C
1	none	70.1 (quaternary)	6.8 (2)	137.1 (methylene)
2	none	68.7 (quaternary)	none	145.8 (quaternary)
3	3.7 (1), 3.1 (1)	53.4 (methylene)	4.0 (2)	51.5 (methylene)
4	4.2 (1), 4.3 (1)	65.2 (methylene)	3.8 (2)	51.4 (methylene)
5	none	49.2 (quaternary)	none	143.7 (quaternary)
6	1.6 (3)	15.2 (methyl)	none	134.7 (quaternary)
7	1.7 (3)	12.1 (methyl)	2.2 (3)	16.9 (methyl)

EXPERIMENTAL

All melting-points and boiling-points are uncorrected.

7,7-Dichloro-1,6-dimethyl-2-oxa-5-thiabicyclo[4.1.0]heptane (**2a**).

To a solution of 2,3-dihydro-5,6-dimethyl-1,4-oxathiin (**1**) [4] (43.5 g) in toluene (300 ml), stirred in an ice-bath, was added sodium ethoxide (26.8 g). Under a nitrogen atmosphere ethyl trichloroacetate (76.8 g) was added over 20 minutes from a dropping-funnel. The solution was allowed to warm to room temperature after two hours, then saturated aqueous sodium bicarbonate (200 ml) was added with strong agitation.

The organic layer was separated, dried with magnesium sulphate and the toluene removed under reduced pressure. The residual oil was distilled; after a major fore-run at 30-64°/3 mm (consisting mostly of unreacted starting-material) a fraction at 90-94°/0.7 mm was collected; the pot had major quantities of tars. Acceptable analyses could not be obtained for this oil; however, the mass spectrum had a molecular ion of 212 (214, 216), corresponding to $C_7H_{10}Cl_2OS$.

7,7-Dichloro-1,6-dimethyl-2-oxa-5-thiabicyclo[4.1.0]heptane, 5,5-Dioxide (**2b**).

The bicycloheptane (**2a**) (6.3 g) in acetic acid (10 ml) was cautiously added in a dropwise fashion to 40% peracetic acid in acetic acid (25 ml), while maintaining the temperature at around 5° by an ice-salt bath. When addition was complete, the reaction mixture was stirred in an ice-bath for an additional two hours then allowed to come to room temperature. Some solids had appeared; precipitation was completed by adding water (25 ml), then the solids were collected, washed carefully with water, and dried after testing for residual peroxides. The white solid was recrystallised from ethanol to give 2.1 g of white crystalline plates, mp 133-147°; molecular ion 244 (246, 248); calcd. 244, (246, 248).

Anal. Calcd. for $C_7H_{10}Cl_2O_3S$: C, 34.30; H, 4.11. Found: C, 34.01; H, 4.00.

6-Chloro-2,3-dihydro-7-methyl-5-methylene-5(*H*)-1,4-dithiepin (**4a**).

To a solution of 2,3-dihydro-5,6-dimethyl-1,4-dithiin [5] (28.5 g) in toluene (200 ml) stirred in an ice-salt bath, was added sodium ethoxide (42 g), followed by ethyl trichloroacetate (72.6 g) over a period of 60 minutes. The reaction was carried out under a nitrogen atmosphere. The reaction mixture was allowed to come to room temperature slowly and left overnight. The solution was then extracted with aqueous saturated sodium bicarbonate solution (200 ml) and water (200 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* and the residual oil distilled at reduced pressure. The fraction boiling at 95-97°/0.4 mm was collected, yield 11 g. There were substantial quantities of tars in the pot residue.

Anal. Calcd. for $C_7H_9ClS_2$: C, 43.62; H, 4.70; Found: C, 43.77; H, 4.95.

6-Chloro-2,3-dihydro-7-methyl-5-methylene-5(*H*)-1,4-dithiepin, 1,1,4,4-Tetraoxide (**4b**).

The dithiepin (**4a**) (12.7 g) dissolved in acetic acid (10 ml) was cautiously added dropwise to 40% peracetic acid in acetic acid, with stirring in an ice-salt bath. The temperature was not allowed to exceed 0°. As addition proceeded white crystals began to appear. It was stirred for another two hours in an ice-bath, then allowed to come to room temperature. The solids were filtered, washed thoroughly with water, dried after testing for residual peroxides, and recrystallised from ethyl acetate to give chunky white needles, mp 166-174°; molecular ion 256 (258); calcd. 256 (258).

Anal. Calcd. for $C_9H_9ClO_4S_2$: C, 32.76; H, 3.53; Found: C, 32.92; H, 3.45.

The ^1H nmr spectra were run on a Varian Unity 400 MHz spectrometer, in deuteriochloroform solution with TMS as the internal standard. Chemical shifts are quoted in ppm downfield from TMS. Mass spectra were run using a Hewlett-Packard 5989A MS engine with a direct injection probe.

Acknowledgements.

The assistance of Dr. D. S. Mitchell with the nmr spectra, and the technical assistance of Ms. J. Wiebe and Ms. J. Zalba, is gratefully acknowledged.

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* Author to whom enquiries should be addressed.

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