The Synthesis of 5,6-Dihydro-1,4-oxathiin-2,3-dicarboxylic Acid and Some Derivatives

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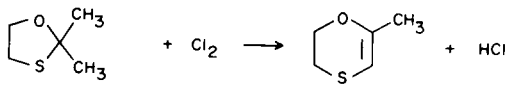
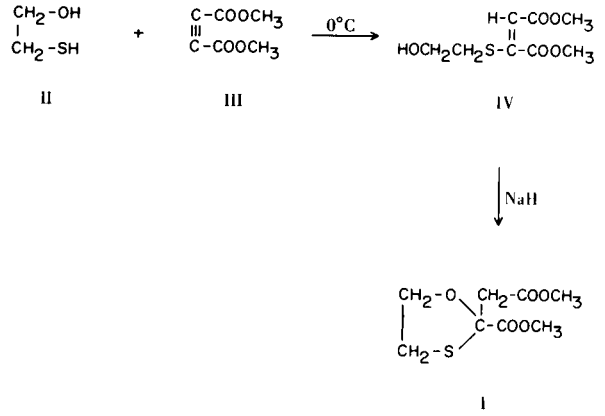
In 1965 Wilson (1) published a method for the conversion of 1,3-oxathiolanes, containing no functional groups, into 5,6-dihydro-1,4-oxathiins by chlorination of the parent oxathiolane at low temperatures.



The present note shows that this reaction is also applicable to oxathiolanes containing functional groups, *e.g.* to compound I (see Table I). Compound I was prepared by a two-step synthesis starting from dimethyl acetylenedicarboxylate and 2-mercaptoethanol.

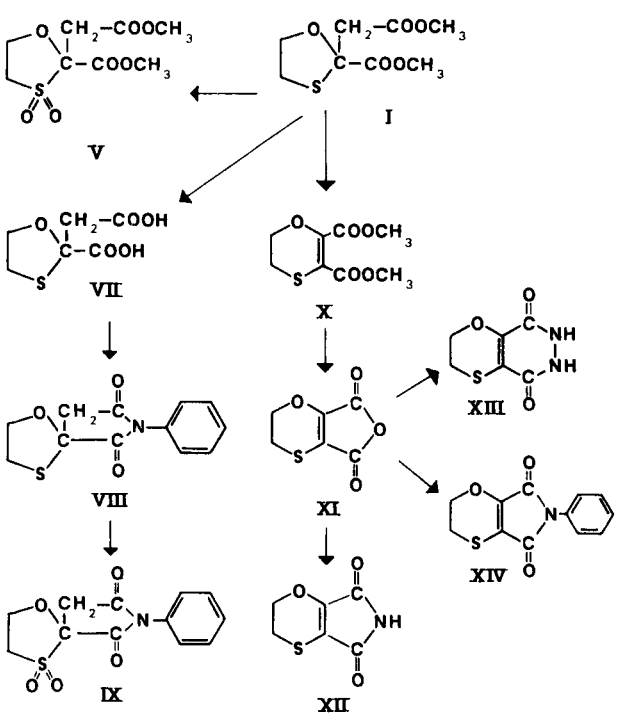


The structure of I is supported by NMR and IR data: 2 OCH_3 singlets at 3.7 δ and 3.8 δ (6 protons), 1 exogenous methylene multiplet at 4.4 δ (2 protons) and 2 endogenous overlapping methylene multiplets at 3.2 δ (4 protons) in deuteriochloroform. IR indicates absence of a double bond (no adsorption in the 1500-1730 cm^{-1} region).

Attempts to carry out the preparation of I by a one-step synthesis, *i.e.* by sodium hydride (or other base) catalysed addition of mercaptoethanol to the acetylenic ester led to a different product.

A number of derivatives of I were made, including the sulphone (VI), the free acid (VII), the *N*-phenylimide (VIII) and the sulphone of the *N*-phenylimide (IX) (see Experimental).

Table I



Chlorination of I gave dimethyl 5,6-dihydro-1,4-oxathiindicarboxylate (X). It showed IR adsorption for conjugated C=C at 1600 cm^{-1} and C=O adsorption at 1710 cm^{-1} (film between sodium chloride discs). NMR (in deuteriochloroform) showed 2 CH_2 triplets at 3.02 δ and 4.35 δ (4 protons and 2 OCH_3 singlets at 3.70 δ and 3.72 δ (6 protons). The UV adsorption λ max at 298 mμ (in ethanol) is consistent with structure X.

Derivatives prepared include the anhydride (XI), the imide (XII), the cyclic hydrazide (XIII) and the *N*-phenylimide (XIV).

Details of preparation, physical constants not mentioned in the text and analytical data are given with the experimental details.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 257, UV spectra on a Perkin-Elmer 137 instrument. The NMR spectra were taken

on a Varian H.A. 100 spectrometer using tetramethylsilane as an internal standard. Melting points and boiling points are uncorrected.

Dimethyl-2-(2-hydroxyethylthio)fumarate (IV).

Ice cooled dimethyl acetylenedicarboxylate (0.4 mole) was treated dropwise over a period of 1½ hours with 2-mercaptoethanol (0.4 mole). The mixture was left at room temperature for 2 days and fractionated to give a colourless oil, b.p. 124°/0.013 mm., yield 75%.

Anal. Calcd. for $C_8H_{12}SO_5$: C, 43.6; H, 5.5; S, 14.5. Found: C, 44.0; H, 5.5; S, 14.6.

Methyl 2-Carbomethoxymethyl-1,3-oxathiolan-2-carboxylate (I).

To 0.18 mole of IV in 70 ml. of dry xylene at 20° was added 0.009 mole of sodium hydride. The ensuing exothermic reaction raised the temperature to 46°. Stirring was continued for 0.75 hour after the mixture had reached ambient temperature. Base was removed by washing with dilute acetic acid and water. The oil remaining after removal of solvent gave on fractionation I in 66% yield, b.p. 72°/0.007 mm; UV maxima λ 253 mμ and 322 mμ.

Anal. Calcd. for $C_8H_{12}SO_5$: C, 43.6; H, 5.5; S, 14.5. Found: C, 43.7; H, 5.5; S, 14.4.

Sulphone of the Methyl Ester of 2-Methylcarboxymethyl-1,3-oxathiolan-2-carboxylic Acid (VI).

A solution of 0.05 mole of I in 75 ml. of glacial acetic acid was treated with 0.11 mole of hydrogen peroxide (50% aqueous) at such a rate that the temperature remained below 35°. After the exothermic reaction had subsided, the mixture was heated on the boiling water bath until all the excessive peroxide had been destroyed. The viscous oil that remained after removal of solvent in vacuum was taken up in chloroform, washed with sodium bicarbonate solution, filtered and again freed from solvent.

The residue on recrystallisation from hot water gave VI in 42.5% yield, colourless crystals, m.p. 87-88°; IR: C=O: 1720 and 1750 cm^{-1}, oxathiolan ring: 1080 cm^{-1} (as in I), SO_2: 1170 (split) and 1320 cm^{-1} (mull in liquid paraffin).

Anal. Calcd. for $C_8H_{12}SO_7$: C, 38.1; H, 4.8; S, 12.7. Found: C, 38.3; H, 4.6; S, 12.7.

2-Carboxymethyl-1,3-oxathiolan-2-carboxylic Acid (VII).

A solution of 0.4 mole of sodium hydroxide in 200 ml. of water and 0.09 mole of I were heated on the boiling water bath for one half hour. The cooled mixture was extracted with chloroform and the aqueous phase acidified with hydrochloric acid 1:1. The solids obtained after filtration of the ice cold solution were recrystallised from water to give VII in 70% yield, colourless crystals, m.p. 134-136°.

Anal. Calcd. for $C_6H_8SO_5$: C, 37.6; H, 4.2; S, 16.7. Found: C, 37.6; H, 4.1; S, 16.6.

N-Phenyl-3-(1,3-oxathiolan-2-yl)pyrrolidin-2,5-dione (VIII).

A solution of 0.0308 mole of VII in 25 ml. of dry dioxan was mixed with 0.0308 mole of aniline and left for 1 hour. The solvent was then removed under vacuum and the residue refluxed in 100 ml. of xylene under a Dean and Stark trap until no more water was collected. After removal of solvent in vacuum there remained a multi-component mixture (T.L.C.).

Chromatography (silica gel/methylene chloride) gave 4.3 g. of VIII as first product to come off the column. This was homogeneous on T.L.C.; white needles, m.p. 114-115°, yield 56%.

Anal. Calcd. for $C_{12}H_{11}NSO_3$: C, 57.8; H, 4.4; N, 5.6; S, 12.8. Found: C, 58.0; H, 4.6; N, 5.4; S, 12.9.

N-Phenyl-1-(3,3-dioxo-1,3-oxathiolan-2-yl)succinimide (IX).

When VIII is oxidised and worked up under the same conditions as I to VI, IX is obtained in about 3% yield of material recrystallised from ethanol. The low yield could be due to decomposition during the prolonged (5 hours) period of heating since the compound decomposes rapidly at its melting point; colourless crystals, m.p. 125° dec.; IR: C=O: 1720 cm^{-1}, SO_2: 1170 (split) and 1320 cm^{-1} (mull in liquid paraffin).

Anal. Calcd. for $C_{12}H_{11}NSO_5$: C, 51.2; H, 3.9; N, 4.0; S, 11.4. Found: C, 51.4; H, 4.0; N, 4.9; S, 11.2.

Dimethyl 5,6-Dihydro-1,4-oxathiin-2,3-dicarboxylate (X).

A solution of 0.1 mole of I in 100 ml. of dry methylene chloride was cooled to -20° and treated dropwise with a solution of 0.11 mole of chlorine in 170 ml. of dry carbon tetrachloride. During the hour addition period the temperature was kept at -20°. When the addition was completed the cooling bath was removed and the mixture allowed to reach ambient temperature (19°). The mixture was then swept with dry nitrogen and simultaneously heated slowly. At 25° hydrogen chloride evolution started. The mixture was then heated to boiling point and refluxed for one half hour, by which time the evolution of hydrogen chloride had ceased. The mixture was left overnight at room temperature. After removal of solvent, there remained 28.1 g. of an oil, which was subsequently heated at 120° for 2 hours, during which the weight was reduced to 23.3 g. This material showed C=C absorption at 1620, 1600 and 1560 cm^{-1} and T.L.C. indicated the presence of at lease three components.

Chromatography (silica gel/methylene chloride) was followed by IR spectroscopy. The fractions containing product that absorbed at 1600 cm^{-1} only were collected and freed from solvent. The product was homogeneous on T.L.C. and solidified on standing, yield 21%, m.p. 42.5-43.5° (from cyclohexane).

Anal. Calcd. for $C_8H_{10}SO_5$: C, 44.1; H, 4.5; S, 14.6. Found: C, 44.0; H, 4.5; S, 14.5.

Anhydride of 5,6-Dihydro-1,4-oxathiin-2,3-dicarboxylic Acid (XI).

Since the dicarboxylic acid cyclises very rapidly, it was difficult to obtain pure samples and therefore it was isolated as the anhydride.

On boiling 0.05 mole of X with 120 ml. of *N* sodium hydroxide for 5 minutes, hydrolysis took place. The cooled mixture was neutralised with 120 ml. of *N* hydrochloric acid and the water removed on a rotary evaporator. The residue was suspended in 200 ml. of benzene and refluxed under a Dean and Stark trap to remove last traces of water. Acetic anhydride (0.1 mole) was then added and reflux continued until all the organic material had gone into solution (~one half hour). The filtered solution on removal of benzene, acetic acid and acetic anhydride gave XI in almost quantitative yield.

Recrystallisation from benzene gave brick-red crystals, m.p. 123-124°; IR: C=C at 1530 cm^{-1}, C=O at 1740 cm^{-1} and 1830 cm^{-1} (split) (mull in liquid paraffin); NMR: CH_2 triplets at 3.2 δ and 4.65 δ in deuteriochloroform.

Anal. Calcd. for $C_6H_4SO_4$: C, 41.8; H, 2.3; S, 18.6. Found: C, 42.1; H, 2.4; S, 18.8.

Imide of 5,6-Dihydro-1,4-oxathiin-2,3-dicarboxylic Acid (XII).

Compound XI (0.03 mole) was heated in an oil bath until the pot temperature reached 155°, when a slow stream of dry ammonia was passed in for one half hour. The gas stream was then discontinued and the pot temperature raised to 190° in 15 minutes.

The cooled reaction mixture was then leached with seven 50 ml. portions of water on the boiling water bath. A deep yellow solid crystallised out of the leachings, which on recrystallisation from boiling water gave XII in 21.4% yield, m.p. 219-220°; IR: C=C at 1620 cm^{-1}, C=O at 1720 cm^{-1} and 1760 cm^{-1}, NH at 3220 cm^{-1} (mull in liquid paraffin); UV: λ max 224 mμ (in ethanol); NMR: CH_2 triplets at 3.2 δ and 4.5 δ (2 sets of 2 protons), NH at 10.6 δ (1 proton), solvent DMSO d_6.

Anal. Calcd. for $C_6H_5NSO_3$: C, 43.1; H, 2.9; N, 8.2; S, 18.7. Found: C, 42.2; H, 3.0; N, 8.2; S, 18.4.

Hydrazide of 5,6-Dihydro-1,4-oxathiin-2,3-dicarboxylic Acid (XIII).

An aqueous solution of 0.03 mole of hydrazine hydrate in 10 ml. of water and 0.03 mole of XI were heated on the boiling water bath for 6 hours. The solids formed were filtered off and recrystallised from boiling water to give XIII as white needles in 25.6% yield, m.p. $>300°$; IR: maxima at 1540, 1560, 1580, 1610 and 1615, 3100 and 3200 cm^{-1} (mull in liquid paraffin); NMR: CH_2 triplets at 3.16 δ and 4.4 δ; (2 sets of 2 protons) NH broad peak at about 11.1 δ (2 protons), solvent DMSO d_6.

Anal. Calcd. for $C_6H_6N_2SO_3$: C, 38.7; H, 3.2; S, 17.2. Found: C, 38.6; H, 2.9; S, 17.3.

The fact that XIII is soluble in 3 *N* sodium hydroxide and can be precipitated from this solution unchanged by excess hydrochloric acid and the (admittedly broad) single peak at 11.1 δ in NMR favours the cyclic hydrazide structure rather than the *N*-aminoimide form.

N-Phenylimide of 5,6-Dihydro-1,4-oxathiin-2,3-dicarboxylic Acid (XIV).

On refluxing a solution of 0.035 mole of XI and 0.035 mole of aniline in 250 ml. of toluene for 2 minutes, a solid was formed. The solid was filtered off from the cooled solution. On heating the solid for one half hour at 200° XIV was formed in 90% yield. Recrystallisation from cyclohexane gave yellow needles, m.p. 135-138°; IR: C=C at 1630 cm^{-1}, C=O at 1720 and 1770 cm^{-1} (mull in liquid paraffin); NMR: CH_2 triplets at 3.14 δ and 4.57 δ (2 sets of 2 protons) 5 phenyl protons at 7.36 δ in deuteriochloroform.

Anal. Calcd. for $C_{12}H_9NSO_3$: C, 58.3; H, 3.7; S, 13.0. Found: C, 58.3; H, 3.7; S, 12.8.

REFERENCES

(1) G. E. Wilson, *J. Am. Chem. Soc.*, 87, 3785 (1965).

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