Synthesis of Medium- and Macrocyclic Ketothiolactones. Photosensitized Oxygenation of Bicyclic Thioenol Ethers[1]

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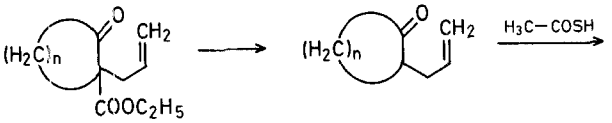
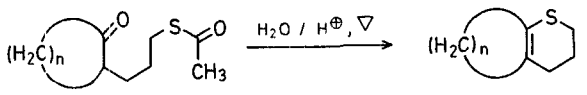
The macrolide antibiotics constitute an important group of natural products and have been engaging ever-increasing attention in the last few years. Recently, various interesting procedures for the preparation of medium and large ring lactones, including several natural products, have been reported and their importance has been well recognized[2].

We have described the synthesis of medium- and macrocyclic ketolactones by the oxidative cleavage of bicyclic enol ethers[3,4,5] as well as by the intramolecular reverse Dieckmann reaction[6]. Herein, we describe the synthesis of the title compounds **5** through the photosensitized oxygenation of the bicyclic thioenol ethers **4**. Although there has been no mention of the natural or synthetic thiomacrolides so far[2], we hope that the series described herein could give an impetus to the study of this new class of compounds.

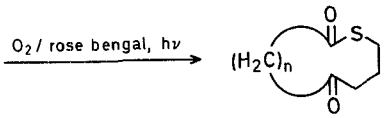


1 **2**

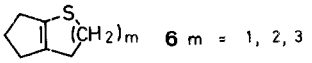
n = 4, 5, 6, 10



3 **4**



5



6 m = 1, 2, 3

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Mayer and Liebster have prepared some bicyclic thioenol ethers **6**, derived from cyclopentanone, through the corresponding 2-(ω-bromoalkyl)-cyclopentanones by displacement reaction with sodium hydrogen sulphide and subsequent dehydration of the ketothiol[7]. We have developed an alternative route to the desired thioenol ethers **4** by the free-radical addition of thiolacetic acid[8] to 2-allylcycloalkanones **2**, which produces the intermediate 2-(3-acetylthiopropyl)-cycloalkanones (**3**) in almost quantitative yield. Subsequent acid hydrolysis of the ketothiolacetates **3** in refluxing 1 normal hydrochloric acid/ethanol (1 : 1), directly furnished the thioenol ethers **4**, in 75–90% yield (Table 3). Bateman and Glazebrook have already prepared some monocyclic thioenol ethers (thiacycloalk-2-enes) through an identical route[9].

Attempted hydrolytic nitrosation[3] of thioenol ether (**4**, n = 4) was very slow and furnished a complex mixture of, as yet, unidentified products. Oxidation of **4** (n = 6) with *m*-chloroperbenzoic acid[5], sodium periodate[10], and hydrogen peroxide in acetone[11] also gave a mixture of products, containing probably the corresponding sulphoxide and sulphone (I.R.) but no trace of the desired ketothiolactone (T.L.C.)[12]. On the other hand, ozonolysis[4] at −20° gave 10–30% yield of the desired ketothiolactones **5**, the rest of the material again being a mixture of sulphoxide and sulphone (I.R., T.L.C.[12]). However, we found that photosensitized oxygenation of these substrates **4** constituted the best procedure in terms of reagents involved, easy work-up, and purification of the products. Our typical procedures are outlined below and the results are summarized in Tables 1–4.

Preparation of 2-Allylcycloalkanones (2); General Procedure:
Allyl bromide (0.11 mol) is added dropwise to a stirred solution of 2-ethoxycarbonylcycloalkanone[13] (0.10 mol) in 1 normal potassium *t*-butoxide in *t*-butanol (110 ml, 0.11 mol). There is a slight exothermic reaction and the mixture is stirred until it reaches room temperature (~ 1 h). It is then gently refluxed on a water bath for 4–6 h, until a test portion gives a negative color reaction with 1% ethanolic iron(III) chloride. The cooled reaction mixture is diluted with water, extracted with ether, and the *2-allyl-2-ethoxycarbonylcycloalkanone* (**1**) purified by distillation (n = 4: 84% yield; b.p. 94–96°/1.5 torr; n = 5: 80% yield; b.p. 110–118°/3 torr; n = 6: 88% yield; b.p. 100–102°/0.5 torr) or recrystallization (n = 10, 83% yield, m.p. 53–55°, from 40–60° petroleum ether).

The 2-allyl-2-ethoxycarbonylcycloalkanones (**1**) are decarboxylated by refluxing (10–18 h) in 5% aqueous ethanolic (1 : 1) potassium hydroxide (3 equivalents). The completion of the reaction is detected by the disappearence of the ethoxycarbonyl protons by N.M.R. spectrometry. Then the cooled reaction mixture is extracted with ether, the product is distilled under reduced pressure and characterized by I.R. and N.M.R. spectra (Table 1).

Preparation of Thiolacetates 3 from 2-Allylcycloalkanones 2 by the Free Radical Addition of Thiolacetic Acid; General Procedure:
Freshly distilled thiolacetic acid (3 ml, 39 mmol, excess) is added to 2-allylcycloalkanone (10 mmol). After a short period of induction, there is a moderate exothermic reaction and the whole is kept under laboratory fluorescent light, until it reaches room temperature (1–2 h). After removal of excess of thiolacetic acid at normal pressure, the residue is diluted with ether and successively washed with water, saturated solutions of sodium hydrogen carbonate and brine. Usual work-up gives the crude product which is purified by vacuum distillation affording the desired thiolacetate **3** in almost quantitative yield (Table 2).

Thioenol Ethers 4 obtained from the Acid Hydrolysis of Thiolacetates 3; General Procedure:
To the thiolacetate (**3**; 10 mmol) is added 1 normal hydrochloric acid (10 ml) and 95% ethanol (10–15 ml) to render a clear solution. The solution is refluxed on a water bath for 6–8 h, during which time the thioenol ether separates from the solution. The product is extracted with ether, purified by distillation and characterized by I.R. and N.M.R. spectra (Table 3).

Photosensitized Oxygenation of Bicyclic Thioenol Ethers 4 to Ketothiolactones 5; General Procedure:
A solution of thioenol ether (**4**; 10 mmol) in methanol (200 ml) containing rose bengal (20 mg) and 2,6-di-*t*-butylphenol (4 mg) is stirred under an oxygen atmosphere and irradiated with a 250 watt mercury vapor pressure lamp at 25° for 4–30 h, until there is no more of the starting material present (T.L.C.[12]). The solvent is removed on a rotary evaporator, the residue extracted with petroleum ether (40–60°) to obtain the crude product, which is purified by chromatography on a silica gel column, using benzene as eluent. Subsequent sublimation or recrystallization from an appropriate solvent gives the pure products which are characterized by I.R., N.M.R., and microanalysis (Table 4).

Although there is no example of photosensitized oxygenation of a thioenol ether in the review by Denny and Nickon[14], Ando et al.[15] have recently described the photo-oxygenation of 1-ethylthiocyclohexene.

Table 1. 2-Allylcycloalkanones **2** prepared from 2-Allyl-2-ethoxycarbonylcycloalkanones **1**

n	b.p./torr	Yield[a] [%]	I.R. (neat) $\nu_{C=O}$; $-CH=CH_2$ [cm^{-1}]	References[d]
4	60–62°/5[b]	60	1709, 1639, 944, 911	16, 17, 18
5	70–72°/5[c]	80	1703, 1642, 1000, 913	17, 18
6	102–104°/3	90	1704, 1642, 994, 912	—
10	100–106°/0.2	70	1706, 1645, 944, 912	—

[a] Yields of purified products based on **1**.
[b] Lit.[16] b.p. 86–88°/15 torr.
[c] Lit.[17] b.p. 105°/20 torr.
[d] References for previous methods of preparation.

Table 2. Thiolacetates **3**[a] obtained from 2-Allylcycloalkanones **2** by the Addition of Thiolacetic Acid

n	b.p./torr	Yield[b] [%]	I.R. (neat or KBr) $\nu_{C=O}$ [cm^{-1}]
4	114–116°/0.4	95	1706, 1695
5	124–128°/0.4	95	1695[c]
6	128–130°/0.3	~ 100	1692[c]
10	42–44°[d]	96	1695[c]

[a] All the reported compounds gave the expected I.R. (solids in KBr, liquids neat) and N.M.R. spectra.
[b] Yields of purified products based on **2**.
[c] Broad band due to the superposition of the thiolacetate and cycloalkanone carbonyls.
[d] m.p., recrystallized from 40–60° petroleum ether.

Table 3. Thioenol Ethers **4** obtained from the acid hydrolysis of Thiolacetates **3**.

n	b.p./torr or m.p. (solvent)	Yield[a] [%]	I.R. (neat or KBr) $\nu_{C=C}$ [cm^{-1}]
4	90–94°/3	82	1656
5	92–98°/3	90	1642
6	80–82°/0.4	77	1647
10	39–41° (C_2H_5OH)	88	1629

[a] Yields of purified products based on **3**.

Table 4. Ketothiolactones **5** obtained by the Photosensitized Oxygenation of Thioenol Ethers **4**.

n	Reaction time	Yield[a] [%]	m.p. (solvent)	I.R. (neat or KBr) $\nu_{C=O}$ [cm^{-1}]	Molecular formula[b]
4	4 h	60	72–73° (40–60° PE)	1695, 1664	$C_9H_{14}O_2S$ (186.2)
5	14 h	34	liquid[c]	1706, 1684	$C_{10}H_{16}O_2S$[c] (200.2)
6	30 h	36	50–52° (40–60° PE)	1706, 1678	$C_{11}H_{18}O_2S$ (214.3)
10	30 h	47	39–41° (C_2H_5OH)	1704, 1689	$C_{15}H_{26}O_2S$ (270.4)

[a] The reported yields are of the pure products, based on thioenol ethers **4**.

[b] All the reported compounds gave satisfactory microanalysis (Alfred Bernhardt) (C ±0.29%, H ±0.13%, S ±0.13%) and expected I.R. and N.M.R. spectra.

[c] Semicarbazone, m.p. 200–202°;
$C_{11}H_{19}N_3O_2S$ (257.3) calc. C 51.35 H 7.44
found 51.38 7.50
2,4-Dinitrophenylhydrazone, m.p. 137–140°;
$C_{16}H_{20}N_4O_5S$ (380.4) calc. C 50.53 H 5.30 S 8.41
found 50.34 5.42 8.28

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