Chemistry of Pyrones Related to Dehydroacetic Acid. Functionalization at C-5 and at the Methyl Group at C-6. An Attempted Synthesis of a Thromboxane B_2 Analogue

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Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday.

New derivatives of dehydroacetic acid and triacetic acid lactone functionalized at both C-5 and at the methyl group at C-6 have been synthesized as intermediates for the preparation of thromboxane B_2 analogues. 6-Mercaptomethyl-4-methoxy-2-pyrone and some derived thioethers have been also prepared. New thioether derivatives of *O*-alkyloximes of dehydroacetic acid have been synthesized and tested for herbicidal activity.

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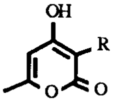
Introduction.

3-Acetyl-4-hydroxy-6-methyl-2-pyrone (dehydroacetic acid), **1**, is an industrially available dimer of diketene. Its deacetylation to afford 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone), **2**, is known since the end of the 19th century thanks to the pioneering work by Collie on the chemistry and biogenesis of polyketides [1]. Pyrone **2** is itself a natural product [2] and many related natural pyrones containing biogenetically acceptable radicals at C-3, C-5 and C-6 have been isolated and identified.



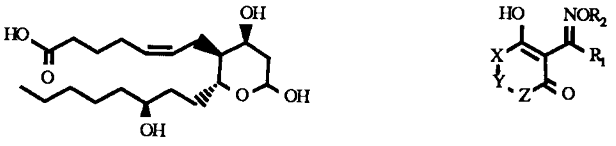
1 $R = COCH_3$
2 $R = H$

Formulae

Since both **1** and **2** are easily available they are good candidates as starting materials for the synthesis of related pyrones. We have already studied the alkylations at C-3 and C-5. Alkylations at C-3 can be performed by a thioalkylation-desulfuration sequence on **2** [3], by copper mediated regioselective alkylation of methyl 3,5-dioxohexanoate followed by cyclization [4] and by thermodynamically controlled palladium catalyzed allylation of **2** followed by hydrogenation of the allylic substituent [5]. Position C-5 is unreactive and alkylations have been achieved only by indirect methods such as transfer of functionalization from C-6 through [3,3]sigmatropic rearrangements, *e.g.* transformation **3** → **4** of Scheme II [6], and by means of [2,3]sigmatropic rearrangements of sulfonium ylides [7,8]. Also, cobalt mediated regioselective alkylation of methyl 3,5-dioxohexanoate followed by cyclization affords C-5 alkyl derivatives of triacetic acid lactone [9]. Since transfer of functionality from C-6 to C-5 through sigmatropic rarrangements results in the loss of the functional group at C-6 we have developed a modification in which a [2,3]sigmatropic rearrangement of a sulfonium ylide is followed by [1,3] allylic migration of bromine from C-5 back to the carbon atom attached at C-6 (see transformation **15** → **16**) [8].

On the other hand thromboxane B_2 (Scheme I) is a metabolite biogenetically related to arachidonic acid for which interesting biological properties have been recognized [10]. Several syntheses of thromboxane analogues have been described. In general the analogues retain the typical side chains of the arachidonic acid derivatives, the variations being introduced in the ring system [11-17]. We thought that the synthesis of new analogues of thromboxane B_2 exemplified by structure **27** containing the 4-methoxy-2-pyrone skeleton and the side chains at C-5 and C-6 could be of interest.

Scheme I



TBX B_2 Pesticides

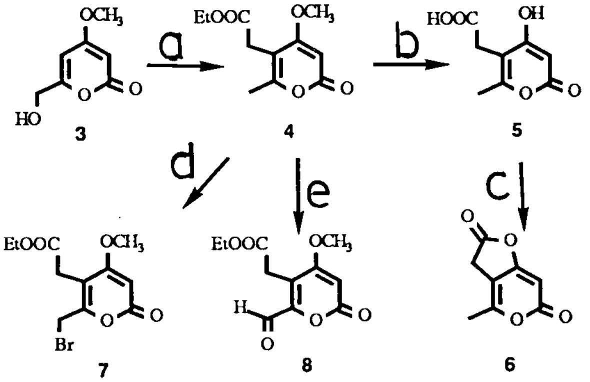
Moreover, products of the general structure indicated in Scheme I containing a thioether moiety at Y are known to posses herbicidal activity [18]. The best activities are shown when R_2 is ethyl or allyl. We also considered of interest the synthesis and evaluation of some selected examples containing an oxygen atom in Z.

All the above introduction justifies our goals: a) synthesis of triacetic acid lactone derivatives containing a chain at C-5 and a functional group at the carbon atom attached at C-6; b) approach to the synthesis of analogues of thromboxane B_2 such as **27**; c) development of triacetic acid lactone derivatives containing a thioether moiety at C-6 and d) synthesis of products with potential herbicide activity such as **40-43**.

Results.

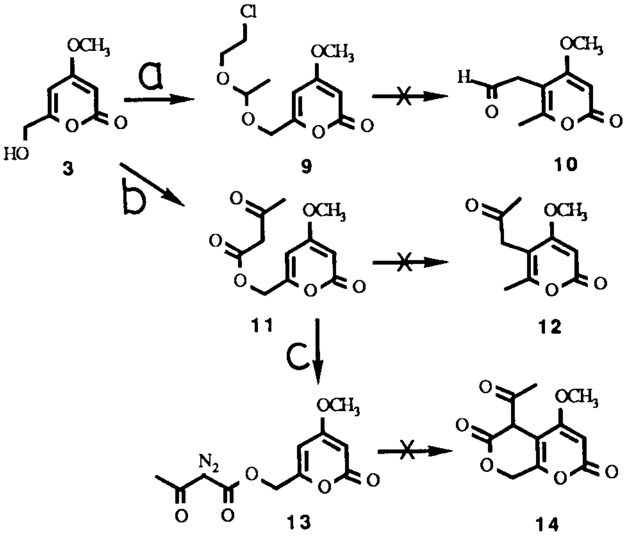
In connection with our first goal we wanted to prepare lactone **8** (Scheme II). 6-Hydroxymethyl-4-methoxy-2-pyrone (opuntiol), **3**, is a natural product available from the methyl ether of triacetic acid lactone by oxidation with selenium dioxide [6]. Its treatment with methyl orthoacetate results in a Claisen rearrangement to afford 5-ethoxycarbonylmethyl-4-methoxy-6-methyl-2-pyrone, **4**, [6]. However, product **4** had lost the function at CH_3-C-6 (Scheme II).

Scheme II a: Ref [6]. b: Aqueous HBr. c: Oxalyl chloride. d: NBS, benzoyl peroxide, tetrachloromethane. e: Selenium dioxide, dioxane.



Now we wish to report that treatment of **4** with aqueous hydrobromic acid afforded 5-carboxymethyl-4-hydroxy-6-methyl-2-pyrone, **5**, which without further purification reacted with oxalyl chloride to give the dilactone **6**. Attempts to oxidize the methyl group of **6** to aldehyde, both with selenium dioxide and through dibromination with *N*-bromosuccinimide, failed. However, the monolactone **4** could be converted into 6-bromomethyl-5-ethoxycarbonylmethyl-4-methoxy-2-pyrone, **7**, by treatment with *N*-bromosuccinimide and into 5-ethoxycarbonylmethyl-6-formyl-4-methoxy-2-pyrone, **8**, by oxidation with selenium dioxide (Scheme II).

Scheme III a: Chloroethyl vinyl ether, mercury(II) acetate. b: Diketene, dioxane. c: Tosyl azide, piperidine, dichloromethane.

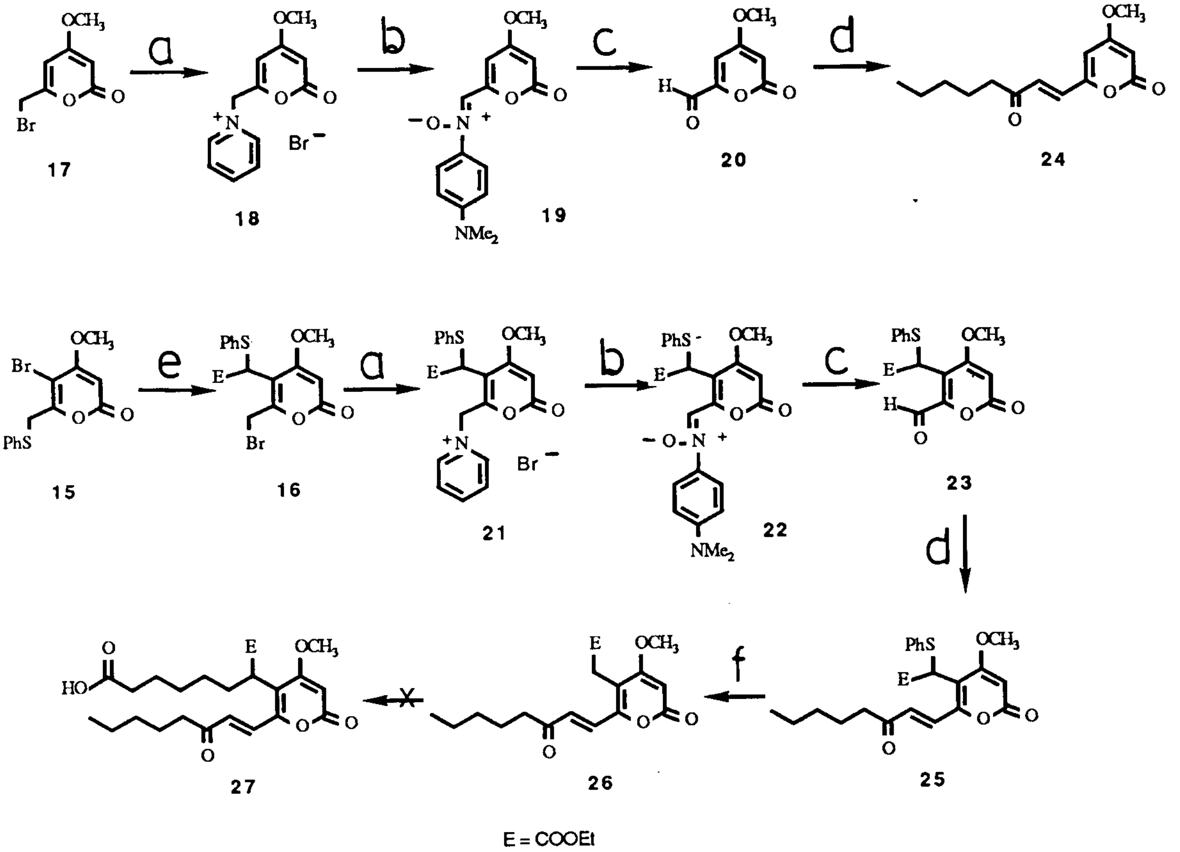


Some of our additional attempts to perform the rearrangements required for the functionalization at C-5 are shown in scheme III. A recently described synthesis of allyl vinyl ethers consists in the reaction of an allylic alcohol with chloroethyl vinyl ether under mercury(II) acetate catalysis [19]. The acetal **9** was prepared by this technique. However, it could not be transformed into **10** by pyrolysis, only **3** and the starting material **9** being recovered. The reaction of **3** with diketene in the presence of triethylamine afforded opuntiol acetoacetate, **11**. Attempts to perform a Carroll rearrangement to **12** by treatment with sodium methoxide were unsuccessful as it was the modification of Tsuji based on palladium catalysis [20]. The diazo compound **13** was prepared from **11** by reaction with tosyl azide. Attempted insertion of the corresponding carbene in order to obtain **14** was also unsuccessful (copper powder in chlorobenzene at 130°; rhodium acetate in benzene at 65°; and copper(I) triflate in chlorobenzene at 65°). Only opuntiol, **3**, could be identified as the major product.

[2,3]Sigmatropic rearrangements of sulfur ylides have proved useful for the transfer of functionality and a modification accomplishes the simultaneous transfer of a bromine atom from C-5 to the carbon atom attached to C-6 as exemplified in the transformation **15** → **16** [8] (Scheme IV). Therefore, we studied the best conditions to oxidize the bromomethyl group of **16** to the aldehyde **23**. We used compound **17** [21] for our initial experiments which included treatments with silver nitrate in dioxane-water [22], with the sodium salt of 2-nitropropane in dimethyl sulfoxide [23,24] and with sodium bicarbonate or silver nitrate-triethylamine in dimethyl sulfoxide [25]. All these methods failed. Finally, Kröhnke oxidation [26] proved to be useful for the conversion of **17** into **20** and of **16** into **23**. Thus, the pyridinium salt **18** was quantitatively formed by reaction of **17** with pyridine. The reaction of the pyridinium salt with 4-nitroso-*N*,*N*-dimethylaniline afforded the nitrone **19** that upon hydrolysis gave the aldehyde **20** in a 55% overall yield from **17**. A similar sequence permitted isolation of the pyrone **23** from **16** in 82% yield.

We have prepared 4-methoxy-6-(3-oxo-1-octenyl)-2-pyrone, **24**, in 76% yield by condensation of aldehyde **20** with dimethyl 2-oxoheptylphosphonate in tetrahydrofuran in the presence of sodium hydride (Scheme IV). Similarly, condensation of **23** with the same phosphonate afforded the conveniently functionalized pyrone **25** in 88% yield. Desulfuration of **25** to **26** with Raney-Nickel was difficult to reproduce, overreduction being frequently a problem. Pyrone **26** was finally prepared using deactivated Raney-Nickel. However, several attempts (sodium hydride in tetrahydrofuran, lithium diisopropylamide in THF) to con-

Scheme IV a: Pyridine. b: 4-Nitroso-*N*,*N*-dimethylaniline, potassium carbonate, water. c: 6*N* HCl. d: Dimethyl (2-oxoheptyl)phosphonate, sodium hydride, THF. e: Ref 8. f: Raney-Nickel W2, acetone.



densate **26** with ethyl 6-bromohexanoate did not lead to the expected *27*.

We have synthesized different thioethers in order to study possible cyclizations (Scheme V). Thus, thioether **28** was formed by conventional Williamson reaction of the bromomethyl derivative **17** [21] with the dianion of thioglycolic acid. However, several treatments of **28** with polyphosphoric acid or with trifluoroacetic anhydride did not lead to the bicyclic compound **29**. The bromopyrone **17** was converted into the thiol **30** by reaction with sodium trithiocarbonate under controlled conditions which included the absence of oxygen. Lack of control in these reactions leads to the formation of variable amounts of the thioether **33** and the disulfide **34**. Conventional Williamson reaction of **30** with chloroacetone afforded the new thioether **31** which could not be transformed into **32** by reaction with polyphosphoric acid. Reactions of **30** with dimethyl acetylenedicarboxylate produced a mixture of the isomers **35-E** and **35-Z** in 35-40% yields. Thermal treatments of **35** (in 1,2-dimethoxyethane, *N,N*dimethylformamide, diethylenglycol dimethyl ether, or by simple distillation) did not lead to **36**.

Finally, we prepared the new thioethers **38** and **39** by Williamson reactions of the bromo compound **37** [21] with thiophenol and with propanethiol (Scheme VI). Each thioether reacted with *O*-ethylhydroxylamine and with *O*-allylhydroxylamine to afford in good yields the oximes **40-43** of undetermined stereochemistry. Only compound **42** showed significant herbicidal activity.

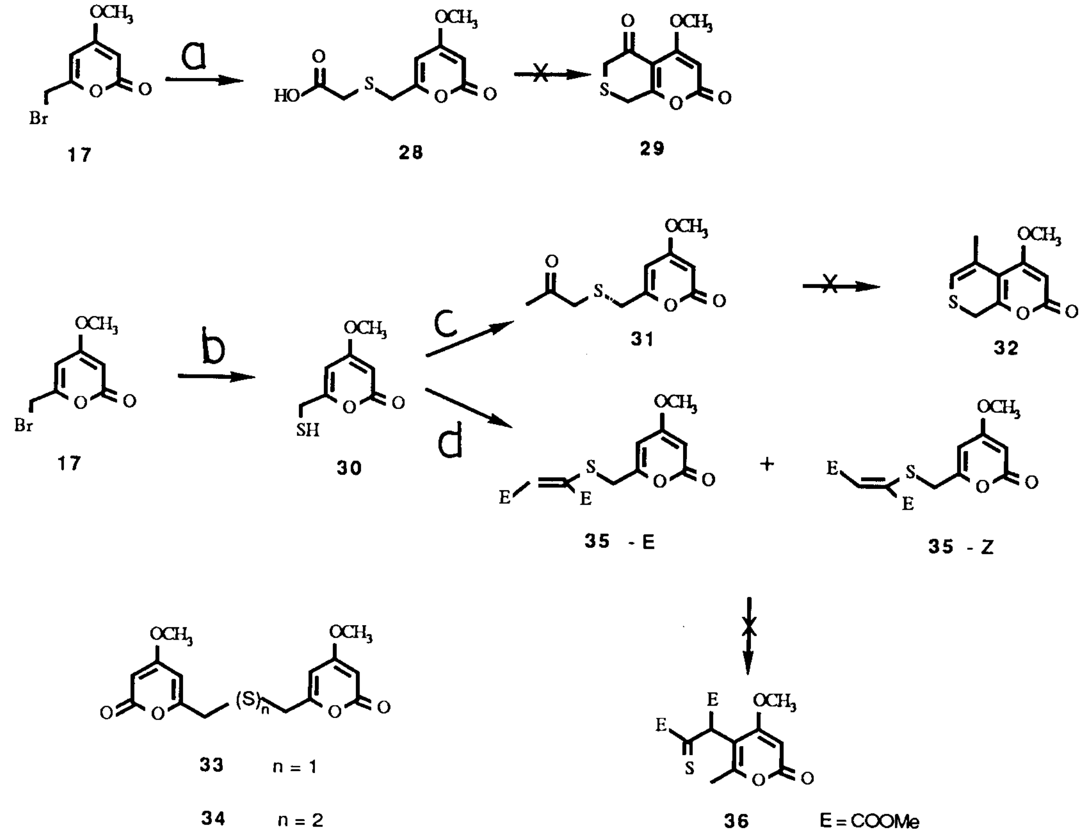
EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The nmr spectra were recorded on a Bruker WP80SY spectrometer. The ms were run on a Hewlett-Packard 5985-B spectrometer; only peaks with intensity higher than 20% are reported unless they belong to molecular ions or to significant fragments.

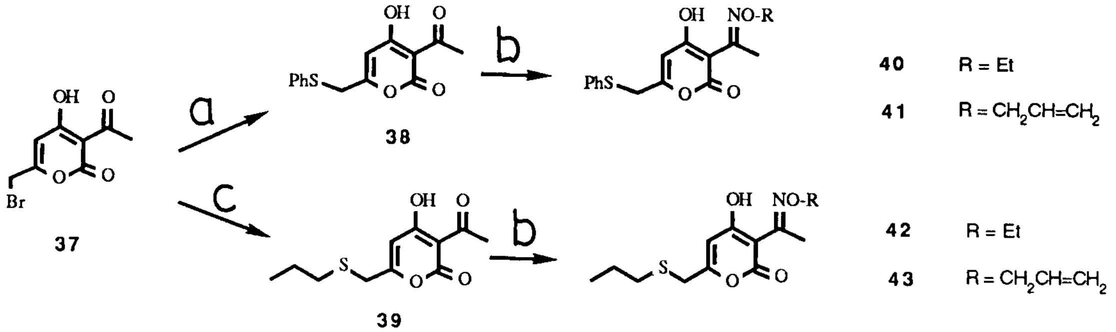
4-Methyl-3*H*-furo[3,2-*c*]pyran-2,6-dione (**6**).

A mixture of pyrone **4** [6] (660 mg, 2.92 mmoles) and 45% aqueous hydrobromic acid (20 ml) was heated at 80° for 75 minutes and then evaporated to dryness to afford 5-carboxymethyl-4-hydroxy-6-methyl-2-pyrone, **5**, (448 mg, 83%) mp 213-217° dec; ir (potassium bromide): 3500-2300, 1710, 1670, 1630, 1250, 1200 cm^{-1}; pmr (dimethyl sulfoxide-d$_6$): δ 2.1 (s, 3H), 3.3 (s, 2H), 5.4 (s, 1H), 6.7-8.2 (broad s, 2H, interexchanges with deuterium oxide); ms: 184 (M, 1), 110 (26), 69 (47), 55 (37), 53 (24), 43 (100).

Scheme V a: Thioglycolic acid, sodium methoxide. b: Sodium trithiocarbonate, methanol-water. c: Sodium methoxide, methanol, chloroacetone. d: Dimethyl acetylenedicarboxylate, benzene.



Scheme VI a: Sodium thiophenoxide, ethanol. b: *O*-alkylhydroxylamine, sodium acetate, 2-propanol. c: Sodium thiopropoxide, methanol.



A mixture of crude **5** and oxalyl chloride (10 g) was refluxed under magnetic stirring for 1 hour. The solution was evaporated and the resdiue was chromatographed through silica gel to afford 265 mg (55% from **4**) of dipyrone **6**, mp 120-122° (from chloroform); ir (potassium bromide): 1830, 1720, 1680 cm^{-1}; pmr (deuteriochloroform): δ 2.23 (d, J = 1.5 Hz, 3H), 3.52 (broad s, 2H), 5.67 (s, 1H); ms: 166 (M, 22), 69 (56), 53 (25), 51 (23), 50 (30), 43 (100), 42 (42), 41 (60).

Anal. Calcd. for $C_6H_6O_4$: C, 57.84; H, 3.64. Found: C, 57.56; H, 3.79.

6-Bromomethyl-5-ethoxycarbonylmethyl-4-methoxy-2-pyrone (**7**).

A stirred mixture of pyrone **4** (75 mg, 0.24 mmole), *N*-bromosuccinimide (63 mg, 0.35 mmole), a catalytic amount of benzoyl peroxide and anhydrous tetrachloromethane (35 ml) was refluxed upon irradiation with a 500W bulb. After 2 hours the solvent was evaporated and the residue partitioned between chloroform and an aqueous solution of potassium carbonate. The organic layer was dried and evaporated and the residue recrystallized from dichloromethane-pentane to afford 56 mg (55%) of **7**, mp 135-137°; ir (potassium bromide): 1735, 1720 cm^{-1}; pmr (deuteriochloroform): δ 1.3 (t, J = 7 Hz, 3H), 3.5 (s, 2H), 3.9 (s, 3H), 4.25 (q, J = 7 Hz, 2H), 4.3 (s, 2H), 5.65 (s, 1H).

5-Ethoxycarbonylmethyl-6-formyl-4-methoxy-2-pyrone (**8**).

A magnetically stirred mixture of pyrone **4** (600 mg, 2.6 mmoles), selenium dioxide (1.5 g, 13.5 mmoles) and anhydrous dioxane (20 ml) was heated for 3 hours at 185-190° in a closed reactor. After cooling the mixture was filtered and the filtrate was evaporated. The residue was chromatographed through silica gel. Elution with dichloromethane-ether (4:1) afforded 378 mg (59%) of pyrone **8**, mp 97-98° (from dichloromethane-pentane); ir (potassium bromide): 1740, 1730, 1710 cm^{-1}; pmr (deuteriochloroform): δ 1.3 (t, J = 7 Hz, 3H), 3.98 (s, 3H), 3.98 (s, 2H), 4.25 (q, J = 7 Hz, 2H), 5.93 (s, 1H), 9.95 (s, 1H); ms: 241 (M+1, 1), 240 (M, 6), 184 (29), 183 (36), 167 (21), 155 (100), 86 (28), 84 (41), 83 (25), 69 (56), 55 (22), 51 (32), 49 (40).

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.84; H, 4.99.

6-(6-Chloro-3-methyl-2,4-dioxahexyl)-3-methoxy-2-pyrone (**9**).

A mixture of pyrone **3** [6] (312 mg, 2.0 mmoles), chloroethyl vinyl ether (419 mg, 3.9 mmoles), a catalytic amount of mercury(II) acetate and anhydrous dioxane (20 ml) was refluxed under argon atmosphere. The starting pyrone had disappeared after 48 hours (tlc monitoring). The mixture was evaporated and the residue was partitioned between chloroform and aqueous sodium chloride. The organic layer was dried and evaporated to afford 830 mg of an orange oil which was chromatographed through a silica gel column. The acetal **9** (358 mg, 68%) was eluted with hexane-ethyl acetate (4:1). This product is not very stable and exhibits propensity to hydrolize; ir (chloroform): 1695 cm^{-1}; pmr (deuteriochloroform): δ 1.35 (d, J = 6 Hz, 3H), 3.55-3.80 (m, 4H), 3.80 (s, 3H), 4.35 (s, 2H), 4.95 (q, J = 6 Hz, 1H), 5.45 (d, J = 2 Hz, 1H), 6.05 (d, J = 2 Hz, 1H); cmr (deuteriochloroform): δ 19.0, 42.9, 55.6, 62.3, 65.2, 88.1, 99.5, 99.7, 161.2, 163.5, 170.7; ms: 264 (2), 262 (M, 7), 183 (45), 125 (100), 111 (56), 107 (27), 69 (37), 63 (37), 43 (28).

4-Methoxy-6-(3-oxobutanoyl)oxymethyl-2-pyrone (**11**).

To a magnetically stirred solution of **3** (1.78 g, 11.4 mmoles) in anhydrous dioxane (100 ml) under argon and at 90°, diketene (1.12 g, 13.3 mmoles) and 5 drops of anhydrous triethylamine were added. The mixture was kept for 2 hours (tlc monitoring) under these conditions. The solvent was evaporated and the residue was partitioned between chloroform and a saturated aqueous solution of sodium chloride. The organic layer was dried and evaporated to afford 2.75 g of a brown solid which was chromatographed through a silica gel column. With hexane-ethyl acetate (1:1) 2.19 g (80% yield) of compound **11** were eluted, mp 107-109° (from hexane-ethyl acetate); ir (potassium bromide): 1740, 1720 cm^{-1}; pmr (deuteriochloroform): δ keto form: 2.3 (s, 3H), 3.55 (s, 2H), 3.85 (s, 3H), 4.9 (s, 2H), 5.45 (d, J = 2 Hz, 1H), 6.1 (d, J = 2 Hz, 1H), δ enol form (15%): 2.0 (s, 3H), 6.0 (s, 1H), 11.8 (s, 1H); cmr (deuteriochloroform): δ keto form: 29.7, 49.1, 55.8, 61.4, 88.7, 100.8, 157.6, 162.9, 165.8, 170.3, 199.6, δ enol form: 20.8, 60.3, 88.5, 100.6, 158.2; ms: 240 (M, 4), 156 (21), 125 (100), 85 (21), 83 (23), 69 (41), 43 (24).

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.72; H, 5.25.

6-(2-Diazo-3-oxobutanoyl)oxymethyl-4-methoxy-2-pyrone (**13**).

Piperidine (0.806 g, 9.5 mmoles) in dichloromethane (8 ml) and tosyl azide (1.786 g, 9.1 mmoles) were added under argon atmosphere over a stirred and ice-cooled solution of **11** (2.17 g, 9.0 mmols) in dichloromethane (47 ml). The mixture was kept at 0° for 40 minutes (tlc monitoring). The solution was washed with 1% aqueous sodium hydroxide and with aqueous sodium chloride, dried and evaporated. The residue was washed with 2-propanol (20 ml) to afford 1.56 g (65%) of **13**, mp 122-123° (from ethanol); ir (potassium bromide): 2135, 1725 cm^{-1}; pmr (deuteriochloroform): δ 2.45 (s, 3H), 3.8 (s, 3H), 4.95 (s, 2H), 5.45 (d, J = 2 Hz, 1H), 6.0 (d, J = 2 Hz, 1H); cmr (deuteriochloroform): δ 27.6, 55.8, 61.5, 75.5, 89.0, 101.5, 157.1, 160.1, 162.7, 170.0, 188.7; ms: 266 (M, 11), 155 (100), 125 (100), 111 (26), 69 (33).

Anal. Calcd. for $C_{11}H_{10}O_6N_2$: C, 49.63; H, 3.79; N, 10.52. Found: C, 49.82; H, 4.08; N, 10.12.

N-[(4-Methoxy-2-oxo-6-pyranyl)methyl]pyridinium Bromide (**18**).

A stirred solution of the bromolactone **17** [21] (600 mg, 2.74 mmoles) in anhydrous pyridine (13.5 ml) was kept under argon at room temperature for 23 hours. The formed precipitate was filtered and washed with anhydrous pyridine (3 ml) to afford 810 mg (99% yield) of **18**, mp 202-204° (from ethanol); ir (potassium bromide): 1720 cm^{-1}; pmr (deuterium oxide): δ 3.9 (s, 3H), 5.65 (s, 2H), 5.7 (broad s, 1H), 6.5 (broad s, 1H), 8.05 (deceptive t, apparent J = 7 Hz, 2H), 8.55 (deceptive t, apparent J = 7 Hz, 1H), 8.85 (d, J = 6 Hz, 2H).

Anal. Calcd. for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70; Br, 26.80. Found: C, 48.32; H, 4.10; N, 4.77; Br, 26.82.

N-(4-Methoxy-2-oxo-6-pyranyl)methylene-4-dimethylaminoaniline *N*-Oxide (**19**).

A solution of potassium carbonate (1.45 g, 10.5 mmoles) in water (6 ml) was added over a stirred solution of the pyridinium salt **18** (550 mg, 1.85 mmoles) and 4-nitroso-*N*-*N*-dimethylaniline (288 mg, 1.92 mmoles) in ethanol (9 ml). The mixture was kept under stirring at room temperature for 30 minutes, then cooled at 0° and filtered. The orange precipitate was washed with water, ethanol and ether (3 ml each) previously cooled at 0° to afford 531 mg (100% yield) of the nitrone **19**, mp 195-196° (from ethanol); ir (potassium bromide): 1720 cm^{-1}; pmr (dimethyl sulfoxide-d_6): δ 3.0 (s, 6H), 3.85 (s, 3H), 5.75 (d, J = 2 Hz, 1H), 6.65, 6.80, 7.70 and 7.85 (AA'BB' system), 8.0 (d, J = 2 Hz, 1H), 8.3 (s, 1H); ms: 288 (M, 24), 272 (15), 164 (27), 147 (100), 136 (24), 134 (29), 133 (27), 125 (28), 77 (21), 69 (41), 57 (25), 55 (22), 43 (30), 42 (20).

6-Formyl-4-methoxy-2-pyrone (**20**).

A mixture of the nitrone **19** (200 mg, 0.69 mmole), ethyl acetate (25 ml) and 6*N* hydrochloric acid (10 ml) was shook for 10 minutes in a separatory funnel. Aqueous sodium chloride (10 ml) was added and the mixture was extracted with ethyl acetate. The organic layer was washed, dried and evaporated to afford 60 mg (56% yield) of the aldehyde **20**, mp 176-178° (Lit [27] mp 177-178°).

5-[(Ethoxycarbonyl)(phenylthio)methyl]-6-formyl-4-methoxy-2-pyrone (**23**).

This product was prepared by a previously reported procedure [8]. The spectroscopic data for the pyridinium bromide **21** are: ir (chloroform): 1720 cm^{-1}; pmr (deuteriochloroform): δ 1.2 (t, J = 7 Hz, 3H), 3.8 (s, 3H), 4.25 (q, J = 7 Hz, 2H), 5.25 (d, J = 14.5 Hz, 1H), 5.5 (s, 1H), 6.0 (s, 1H), 6.5 (d, J = 14.5 Hz, 1H), 7.35 (m, 3H), 7.60 (m, 2H), 8.10 (deceptive t, apparent J = 7 Hz, 2H), 8.55 (deceptive t, apparent J = 7 Hz, 1H), 9.20 (d, J = 6 Hz, 2H); cmr (deuteriochloroform): δ 13.9, 47.4 , 56.7, 58.0, 62.5, 90.8, 113.8, 128.3, 129.1, 129.2, 131.7, 134.9, 145.2, 146.8, 151.5, 160.6, 167.8, 168.3; ms: 413. (0.1), 218 (27), 109 (69), 83 (23), 82 (26), 81 (57), 79 (58), 78 (23), 77 (22), 69 (22), 65 (27), 52 (27), 51 (55), 50 (40), 45 (100).

4-Methoxy-6-(2-oxo-1-octenyl)-2-pyrone (**24**).

Dimethyl (2-oxoheptyl)phosphonate (184 mg, 0.82 mmole) in anhydrous tetrahydrofuran (2 ml) was added over sodium hydride (36 mg, 0.82 mmole in the form of a 55% suspension in mineral oil) in anhydrous tetrahydrofuran (5 ml). The mixture was stirred at room temperature for 30 minutes. Then, a solution of the aldehyde **20** (125 mg, 0.82 mmole) in anhydrous tetrahydrofuran (8 ml) was added. The reaction was kept under stirring at room temperature for 1 hour (tlc monitoring). Acetic acid was added to *p*H 6 and the mixture was evaporated. The residue was chromatographed through a silica gel column. Elution with hexane-ethyl acetate (65-35) afforded 155 mg (76% yield) of **24**, mp 109-111° (from dichloromethane-pentane); ir (potassium bromide): 1725, 955 cm^{-1}; pmr (deuteriochloroform): δ 0.95 (t, J = 5.5 Hz, 3H), 1.1-1.85 (m, 6H), 2.6 (t, J = 6 Hz, 2H), 3.85 (s, 3H), 5.65 (d, J = 2.5 Hz, 1H), 6.15 (d, J = 2.5 Hz, 1H), 6.9 (d, J = 16 Hz, 1H), 7.1 (d, J = 16 Hz, 1H); cmr (deuteriochloroform): δ 13.6, 22.2, 23.5, 31.2, 42.5, 56.0, 91.2, 106.4, 130.2, 130.6, 156.1, 162.6, 169.9, 199.1; ms: 250 (M, 17), 194 (68), 179 (100), 166 (41), 125 (38), 95 (41), 69 (31).

Anal. Calcd. for $C_{14}H_{18}O$: C, 67.18; H, 7.25. Found: C, 67.20; H, 7.53.

5-(Ethoxycarbonyl)(phenylthio)methyl-4-methoxy-6-(2-oxo-1-octenyl)-2-pyrone (**25**).

It was prepared in 88% yield from **23** by the same procedure as for **24**. Pyrone **25** had mp 93-95°; ir (potassium bromide): 1720, 1700, 950 cm^{-1}; pmr (deuteriochloroform): δ 0.9 (t, J = 5 Hz, 3H), 1.1-1.7 (m, 9H), 2.5 (t, J = 7 Hz, 2H), 3.85 (s, 3H), 4.3 (q, J = 7 Hz, 2H), 5.00 (s, 1H), 5.65 (s, 1H), 6.8 (deceptive s, 2H), 7.1-7.6 (m, 5H); cmr (deuteriochloroform): δ 13.7, 13.9, 22.2, 23.5, 31.2, 42.2, 48.3, 56.3, 62.3, 91.7, 114.2, 126.8, 128.9, 129.1, 130.7, 132.4, 135.3, 153.8, 161.3, 167.9, 168.1, 198.8; ms: 444 (M, 9), 335 (31), 237 (100), 191 (25), 109 (66), 99 (26), 71 (49), 69 (37), 59 (23), 55 (63), 43 (46), 41 (23).

Anal. Calcd. for $C_{24}H_{28}O_6S$: C, 64.84; H, 6.35; S, 7.21. Found: C, 64.88; H, 6.62; S, 7.27.

5-(Ethoxycarbonylmethyl)-4-methoxy-6-(2-oxo-1-octenyl)-2-pyrone (**26**).

Raney-Nickel W2 (1.5 ml in ethanol) was washed at room temperature with acetone (3 x 6 ml) and boiled in acetone for 2 hours. The solvent was replaced by a solution of the pyrone **25** (100 mg, 0.22 mmole) in acetone (6 ml). The mixture was refluxed for 30 minutes (tlc monitoring) and filtered through silica gel which was washed with hot ethyl acetate (100 ml). The combined filtrates were evaporated and the residue was chromatographed through a column of silica gel. Elution with hexane-ethyl acetate (3:1) afforded 60 mg (79% yield) of pyrone **26**, mp 96-98° (from dichloromethane-pentane); ir (potassium bromide): 1715, 1695, 950 cm^{-1}; pmr (deuteriochloroform): δ 0.9 (t, J = 6 Hz, 3H), 1.1-1.9 (m, 9H), 2.65 (t, J = 6.5 Hz, 2H), 3.5 (s, 2H), 3.9 (s, 3H), 4.15 (q, J = 7 Hz, 2H), 5.7 (s, 1H), 7.05 (d, J = 16 Hz, 1H), 7.3 (d, J = 16 Hz, 1H); cmr (deuteriochloroform): δ 13.6, 13.9, 22.2, 23.4, 29.3, 31.1, 42.9, 56.4, 61.2, 91.4, 111.5, 127.1, 130.8, 153.5, 161.8, 168.8, 169.1, 199.1; ms: 336 (M, 10), 249 (29), 239 (22), 193 (32), 191 (21), 190 (23), 167 (33), 165 (78), 149 (100), 109 (20), 71 (36), 69 (52), 57 (52), 55 (45), 43 (62), 41 (60).

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.32.

6-Carboxymethylthiomethyl-4-methoxy-2-pyrone (**28**).

A solution of thioglycolic acid (1.553 g, 16.2 mmoles) in methanol (18 ml) was added over a methanolic solution of sodium methoxide prepared from sodium (0.811 g, 35.2 mmoles) and methanol (60 ml). This mixture was dropwise added during 1 hour under argon atmosphere over a stirred solution of 6-bromomethyl-4-methoxy-2-pyrone, **17**, [21] (3.043 g, 13.9 mmoles) in methanol (80 ml). The mixture was then neutralized with hydrochloric acid, concentrated and partitioned with chloroform. The aqueous layer was acidified and percolated with chloroform during 13 hours. The combined organic extracts were dried and evaporated to afford 2.23 g (70% yield) of crude **28**, mp 126-128° (from chloroform); ir (potassium bromide): 3200-2800 (broad), 1705 cm^{-1}; pmr (acetone-d_6): δ 3.3 (s, 2H), 3.65 (s, 2H), 3.9 (s, 3H), 5.5 (d, J = 2 Hz, 1H), 6.1 (d, J = 2 Hz, 1H); cmr (methanol-d_4): δ 34.0, 34.4, 57.0, 89.2, 102.6, 162.4, 166.8, 172.1, 173.2; ms: 230 (M, 33), 171 (45), 125 (100).

Anal. Calcd. for $C_9H_{10}O_5S$; C, 46.95; H, 4.38. Found: C, 47.05; H, 4.35.

6-Mercaptomethyl-4-methoxy-2-pyrone (**30**).

A solution of **17** (1.81 g, 8.3 mmoles) in deoxygenated methanol (80 ml) was added during 1 hour and under argon atmosphere over a stirred and ice-cooled mixture of 8 ml of a 2.2*M* solution of sodium trithiocarbonate [28]. The mixture was then acidified to *p*H 2 and kept under ice-cooling for 1 hour and partitioned with ether. The organic layer was dried and evaporated to afford 1.340 g (94% yield) of crude **30** (this is the best experiment; depending upon the deoxygenation degree variable amounts of disulfide **34** were formed which could be eliminated by filtration before extraction with ether was performed). Crude **30** was used for the next steps, since attempts to purify it by column chromatography on silica gel resulted in partial oxidation to **34**.

Product **30** was an oily white solid; pmr (deuteriochloroform): δ 2.0 (t, J = 8 Hz, 1H), 3.4 (d, J = 8 Hz, 2H), 3.75 (s, 3H), 5.3 (d, J = 2 Hz, 1H), 5.9 (d, J = 2H, 1H); cmr (deuteriochloroform): δ 25.8, 55.8, 88.2, 99.9, 162.7, 163.8, 170.9; ms: 172 (M, 48), 125 (100), 69 (52).

Bis[(4-methoxy-2-oxo-6-pyranyl)methyl] Disulfide (**34**).

This compound had mp 171-173° (from chloroform); ir (potassium bromide): 1710 cm^{-1}; pmr (deuteriochloroform + methanol-d_4): δ 3.7 (s, 4H), 3.9 (s, 6H), 5.6 (d, J = 2 Hz, 2H), 6.1 (d, J = 2 Hz, 2H); ms: 342 (M, 6), 172 (27), 129 (30), 125 (100), 111 (83), 69 (95), 59 (37), 45 (25).

Anal. Calcd. for $C_{14}H_{14}O_6S_2$: C, 49.11; H, 4.12; S, 18.73. Found: C, 49.12; H, 4.15; S, 18.72.

Bis[(4-methoxy-2-oxo-6-pyranyl)methyl] Sulfide (**33**).

A 0.6*M* solution of sodium trithiocarbonate [28] was added during 1 hour over a stirred suspension of the bromopyrone **17** (327 mg, 1.5 mmoles) and deoxygenated water (6 ml) cooled at −5°. The mixture was kept 10 minutes under these conditions. The solid was filtered to afford 60 mg of the thioether **33** (26% yield), mp 137-139° (from dichloromethane-hexane). The filtrate was acidified with 2*N* hydrochloric acid to *p*H 3 and left overnight in the refrigerator to afford 168 mg of the disulfide **34**. The sulfide **33** had: ir (potassium bromide): 3600-3400 (water, see elemental analysis), 1700 cm^{-1}; pmr (deuteriochloroform + methanol-d_4): δ

3.55 (s, 4H), 3.8 (s, 6H), 5.45 (d, J = 2 Hz, 2H), 6.05 (d, J = 2 Hz, 2H); cmr (deuteriochloroform + methanol-d_4): δ 32.6, 55.5, 87.7, 100.8, 160.4, 164.2, 170.8; ms: 310 (M, 5), 140 (40), 125 (100), 69 (36).

Anal. Calcd. for $C_{14}H_{14}O_6S + H_2O$: C, 51.21; H, 4.91. Found: C, 51.11; H, 4.63.

4-Methoxy-6-(2-oxopropyl)thiomethyl-2-pyrone (**31**).

A mixture of thiol **30** (290 mg, 1.7 mmoles) and deoxygenated methanol (7 ml) was cooled at −78° under stirring. A solution of 0.18*M* sodium methoxide in methanol (1.63 mmoles) was added in 15 minutes. Next, chloroacetone (190 mg, 2.05 mmoles) in methanol (8 ml) was added dropwise. The mixture was left for 30 minutes under the described conditions (*p*H monitoring) and two hours at room temperature. The mixture was concentrated and partitioned between dichloromethane and water. The organic layer was dried and evaporated to afford 323 mg of a black oil which was chromatographed through a column of silica gel. Upon elution with hexane-ethyl acetate (3:1) product **31** (260 mg, 67% yield) was isolated, mp 52-54° (from dichloromethane-pentane): ir (potassium bromide): 1700 cm^{-1}; pmr (deuteriochloroform): δ 2.3 (s, 3H), 3.3 (s, 2H), 3.4 (s, 2H), 3.85 (s, 3H), 5.4 (d, J = 2 Hz, 1H), 6.0 (d, J = 2 Hz, 1H); cmr (deuteriochloroform + acetone-d_6): δ 27, 32, 40, 55, 88, 100, 160, 163, 170, 202; ms: 228 (M, 27), 171 (48), 140 (65), 125 (100), 69 (51), 59 (36), 43 (51).

Anal. Calcd. for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30; S, 14.04. Found: C, 52.38; H, 5.61; S, 14.29.

Dimethyl 4-(Methoxy-2-oxo-6-pyranyl)methylthiomaleate (**35**-*E*) and Dimethyl 4-(Methoxy-2-oxo-6-pyranyl)methylthiofumarate (**35**-*Z*).

A mixture of the thiol **30** (604 mg, 3.5 mmoles) and dimethyl acetylenedicarboxylate (547 mg, 3.9 mmoles) in anhydrous benzene (16 ml) was refluxed for two hours and evaporated and the residue was chromatographed through a column of silica gel. Upon elution with hexane-ethyl acetate (7:3) the following compounds were isolated:

Isomer **35**-*E* had mp 89-90° (340 mg, 31% yield) (from dichloromethane-pentane); ir (potassium bromide): 1720, 1695 cm^{-1}; pmr (deuteriochloroform): δ 3.70 (s, 3H), 3.75 (s, 2H), 3.85 (s, 3H), 3.90 (s, 3H), 5.45 (d, J = 2.5 Hz, 1H), 5.95 (s, 1H), 6.05 (d, J = 2.5 Hz, 1H); cmr (deuteriochloroform + methanol-d_6): δ 32.7, 51.5, 52.7, 55.8, 88.3, 101.8, 117.2, 145.7, 158.3, 163.6, 164.1, 165.0, 170.9; ms: 314 (M, 11), 125 (100), 69 (31), 59 (28).

Anal. Calcd. for $C_{13}H_{14}O_7S$: C, 49.68; H, 4.49; S, 10.18. Found: C, 49.67; H, 4.48; S, 10.20.

Isomer **35**-*Z* had mp 138-140° (110 mg, 10% yield) (from dichloromethane-pentane); ir (potassium bromide): 1720, 1700 cm^{-1} pmr (deuteriochloroform): δ 3.75 (s, 3H), 3.77 (s, 3H), 3.90 (s, 3H), 3.95 (s, 2H), 5.40 (d, J = 2 Hz, 1H), 5.90 (d, J = 2 Hz, 1H), 6.60 (s, 1H); cmr (deuteriochloroform): δ 33.2, 51.4, 52.9, 55.6, 88.1, 101.0, 122.8, 144.3, 159.8, 162.9, 163.6, 164.7, 170.2; ms: 314 (M, 8), 125 (100), 69 (28), 59 (22).

Anal. Calcd. for $C_{13}H_{14}O_7S$: C, 49.68; H, 4.49; S, 10.18. Found: C, 49.44; H, 4.44; S, 10.02.

The disulfide **34** was obtained in 27% yield (160 mg).

3-Acetyl-4-hydroxy-6-phenylthiomethyl-2-pyrone (**38**).

A solution of sodium thiophenoxide was prepared from thiophenol (3.113 g, 28.3 mmoles) and sodium ethoxide [from sodium (0.651 g, 28.3 mmoles) and ethanol (13 ml)]. The solution of sodium thiophenoxide was dropwise added at room temperature over the bromolactone **37** [21] (3.5 g, 14.0 mmoles) in ethanol (25 ml). The mixture was stirred for two hours, the solvent was evaporated and the residue was chromatographed through a silica gel column to afford on elution with dichloromethane 2.23 g (57% yield) of **38**, mp 61-63°; pmr (tetrachloromethane): δ 2.5 (s, 3H), 3.7 (s, 2H), 5.8 (s, 1H), 7.25 (m, 5H); ms: 276 (M, 2), 218 (20), 109 (100), 65 (27).

Anal. Calcd. for $C_{14}H_{12}O_4S$: C, 60.35; H, 4.37. Found: C, 60.63; H, 4.60.

3-Acetyl-4-hydroxy-6-propylthiomethyl-2-pyrone (**39**).

Propanothiol (0.319 g, 42 mmoles) was added to a solution of sodium methoxide (0.445 g, 82.4 mmoles) in methanol (20 ml). The bromolactone **37** (1.00 g, 40.4 mmoles) was then added in a portion and the mixture was stirred at room temperature for 2 hours after which dry acid resin IR-120 (2 g) was added and the stirring continued for 10 minutes. The mixture was filtered and the filtrate was concentrated to a volume of 10 ml. Upon standing in the refrigerator 0.70 g (84% yield) of **39** precipitated, mp 61-63° (from methanol); ir (potassium bromide): 1710 cm^{-1}; pmr (deuteriochloroform): δ 1.0 (t, J = 7.2 Hz, 3H), 1.75 (qt, J = 7.2 and 7.2 Hz, 2H), 2.7 (t, J = 7.2 Hz, 2H), 2.8 (s, 3H), 3.45 (s, 2H), 6.1 (s, 1H), 16.8 (s, 1H); cmr (deuteriochloroform): δ 13.1, 22.4, 29.7, 33.8, 34.8, 100.2, 101.1, 160.6, 168.9, 181.0, 205.0; ms: 242 (M, 30), 168 (47), 153 (100), 111 (29), 69 (20), 43 (52).

Anal. Calcd. for $C_{11}H_{14}O_4S$: C, 54.55; H, 5.79. Found: C, 54.60; H, 5.74.

3-[1-(Ethyloximino)ethyl]-4-hydroxy-6-phenylthiomethyl-2-pyrone (**40**).

A solution of the pyrone **38** (5.0 g, 18.1 mmoles) in 2-propanol (75 ml) was mixed with another solution of *O*-ethylhydroxylamine hydrochloride (1.77 g, 18.1 mmoles) and sodium acetate trihydrate (2.47 g, 18.1 mmoles) in the minimal amount of water. The combined solution was refluxed under stirring for 20 hours, cooled and filtered and the filtrate was evaporated. The residue was chromatographed through a silica gel column with dichloromethane-hexane (4:1) to afford 4.80 g (83% yield) of **40**, mp 46-48°; ir (potassium bromide): 1710 cm^{-1}; pmr: δ 1.3 (t, J = 7.4 Hz, 3H), 2.45 (s, 3H), 3.85 (s, 2H), 4.15 (q, J = 7.4 Hz, 2H), 5.95 (s, 1H), 7.3 (m, 5H); cmr (deuteriochloroform): δ 13.9, 14.0, 36.5, 70.2 96.4, 101.9, 127.4, 129.1, 130.9, 134.1, 159.9, 161.6, 172.0; ms: 319 (M, 76), 274 (23), 196 (100), 182 (24), 154 (31), 152 (30), 126 (77), 123 (36), 109 (24), 82 (28), 69 (27).

Anal. Calcd. for $C_{16}H_{17}NO_4S$: C, 60.19; H, 5.33; N, 4.39. Found: C, 60.14; H, 5.35; N, 4.43.

3-[1-(Allyloximino)ethyl]-4-hydroxy-6-phenylthiomethyl-2-pyrone (**41**).

This product was prepared from **38** and *O*-allylhydroxylamine hydrochloride by the same procedure as for **40**. Compound **41** was an oil; ir (film): 1715 cm^{-1}; pmr (deuteriochloroform): δ 2.5 (s, 3H), 3.85 (s, 2H), 4.6 (d, J = 6 Hz, 2H), 5.2-5.5 (m, 2H), 5.8-6.2 (m, 1H), 6.0 (s, 1H), 7.25 (m, 5H), 14.0 (broad s, 1H); cmr (deuteriochloroform): δ 14.0, 36.5, 75.3, 96.4, 101.8, 119.1, 127.4, 129.1, 131.0, 133.1, 134.1, 160.1, 161.5, 161.7, 171.8; ms: 331 (M, 77), 208 (65), 166 (100), 152 (70), 126 (95), 109 (37), 69 (31), 67 (22), 41 (29).

Anal. Calcd. for $C_{17}H_{17}NO_4S$: C, 61.63; H, 5.14; N, 4.23. Found: C, 61.40; H, 5.20; N, 4.37.

3-[1-(Ethyloximino)ethyl]-4-hydroxy-6-propylthiomethyl-2-pyrone (**42**).

This product was prepared from **39** by the same procedure as for **40**. Compound **42** was an oil; ir (film): 1720 cm^{-1}; pmr (deuteriochloroform): δ 1.0 (t, J = 7 Hz, 3H), 1.3 (t, J = 7 Hz, 3H), 1.7 (m, 2H), 2.5 (s, 3H), 2.55 (t, J = 7 Hz, 2H), 3.5 (s, 2H), 4.2 (q, J = 7 Hz, 2H), 6.1 (s, 1H), 14.0 (broad s, 1H); cmr (deuteriochloroform): δ 13.1, 13.9, 14.0, 22.4, 33.4, 34.6, 70.2, 96.3, 101.4, 160.0, 161.7, 163.0, 172.2; ms: 285 (M, 45), 196 (100), 168 (22), 154 (28), 126 (84), 82 (22), 69 (33), 43 (26).

Anal. Calcd. for $C_{13}H_{19}NO_4S$: C, 54.74; H, 6.67; N, 4.91. Found: C, 54.59; H, 6.67, N, 5.10.

3-[1-(Allyloximino)ethyl]-4-hydroxy-6-propylthiomethyl-2-pyrone (**43**).

This product was prepared from **39** by the same procedure as for **41**. Compound **43** was an oil; ir (film): 1720 cm^{-1}; pmr (deuteriochloroform): δ 1.0 (t, J = 7 Hz, 3H), 1.7 (m, 2H), 2.5 (s, 3H), 2.5 (t, J = 7 Hz, 2H), 3.5 (s, 2H), 4.6 (d, J = 6 Hz, 2H), 5.2-5.5 (m, 2H), 5.8-6.2 (m, 1H), 6.05 (s, 1H), 14.0 (broad s, 1H); cmr (deuteriochloroform): δ 13.1, 13.9, 22.4, 33.3, 34.5, 75.3, 96.3, 101.2, 119.0, 133.1, 160.1, 161.6, 163.1, 171.9; ms: 297 (M, 34), 208 (47), 166 (63), 152 (25), 126 (100), 69 (35), 67 (32), 55 (23), 43 (25), 41 (43).

Anal. Calcd. for $C_{14}H_{19}NO_4S$: C, 56.57; H, 6.40; N, 4.71. Found: C, 56.41; H, 6.43; N, 4.73.

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