64. Stable Quinone Methides: Regioselective *para*-Oxidation of a 2,4-Bis[(alkylthio)methyl]phenol and Addition Reactions to Quinonemethides

by **Hansrudolf Meier*** and **Hanspeter Kuenzi**

Research Laboratories, Additives Division, *Ciba Corporation*, CH-1723 Marly 1

and **Hermann Fuhrer** and **Günther Rist**

Physics Department, *Ciba Corporation*, CH-4002 Basel

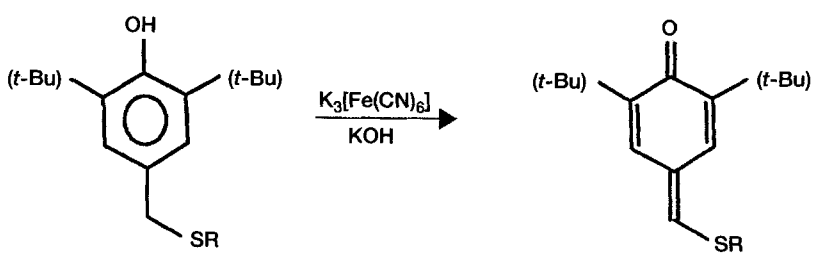
(17.II.94)

The 2,4-bis-functionalized phenol **1** is dehydrogenated regioselectivity with potassium ferricyanide, affording the corresponding *p*-quinonemethide **2**. Hydrolysis of **2** affords a mixture of dithioacetal **5a** and benzaldehyde **6**; 1,6-addition of thiols to **2** gives the dithioacetals **5** of benzaldehyde **6**; reaction of **2** with 2,2′-azobis(isobutyronitrile) (= 2,2′-dimethyl-2,2′-azobis(propanenitrile)) leads to **9a**, **9b**, and **10**, addition products of the 1-cyano-1-methylethyl radical. The structures of all products are confirmed mainly by ^{1}H- and ^{13}C-NMR spectroscopy, and the mode of their formation is discussed.

Knowledge on mechanism of antioxidant activity in polymers is of considerable practical relevance for application and development of new stabilizers [1]. The following results are a small part of an investigation on the 2,4-bis-functionalized phenol **1** [2], a commercial antioxidant for elastomers [3]. Compound **1** is known to react with hydrogen peroxide which oxidizes the thioether moieties, affording the corresponding sulfoxides [2] [4].

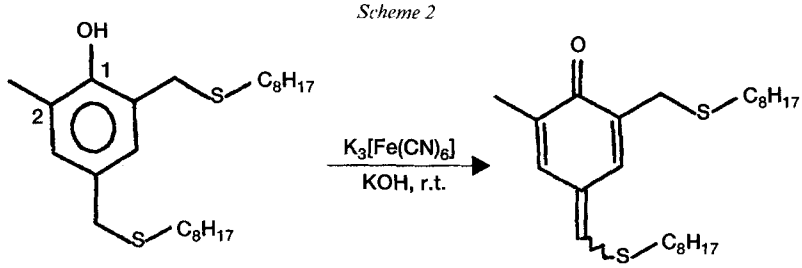
We report now a chemoselective and regioselective oxidation of **1** to *p*-quinonemethide **2** (without affecting the thioether groups; see below *Scheme 2*) and first results of reactions of **2** with nucleophiles and free radicals. *Pastor* [5] described the first example of a chemoselective oxidation of a *p*-thiomethylated phenol **3** leading to a stable *p*-quinonemethide **4** with one S-substituent at position 6; this was obtained by oxidation of **3** (R = $CH_2COOCH_2CH(Et)(CH_2)_3Me$) with ferricyanide (*Scheme 1*). *Koutek* and coworkers

Scheme 1



3 **4** R = $CH_2COOCH_2CH(Et)(CH_2)_3Me$

Scheme 2



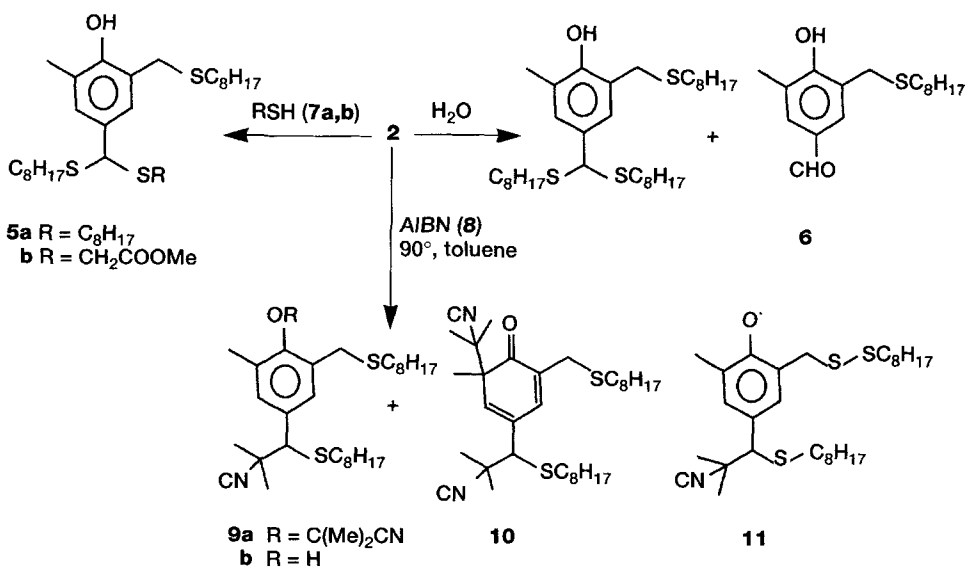
1 **2**

[6] who attempted to synthesize **4** (R = Ph) could only isolate a mixture of the substituted benzaldehyde and benzoic acid, arising most probably from **4** (R = Ph) by hydrolysis and partial oxidation.

When using the same oxidation conditions ($K_3[Fe(CN)_6]$/aqueous KOH solution/hexane, room temperature) starting from **1**, analytically pure *p*-quinonemethide **2** is obtained without further purification as an orange oil in an almost quantitative yield (98%; *Scheme 2*). Structure **2** is confirmed by its spectral data (^{1}H- and ^{13}C-NMR, IR, UV, and MS, see *Exper. Part*); both (*E*)- and (*Z*)-isomers are present in the reaction mixture. No indication for formation of an *o*-quinonemethide is found.

Flash chromatography of **2** on silica gel is not possible, since an (acid-catalyzed) addition of H_2O occurs (*Scheme 3*), affording a mixture of dithioacetal **5a** and aldehyde **6** (HPLC, using an aprotic eluent mixture, is the most appropriate method to monitor the

Scheme 3



conversion of **2**). A product ratio **6**/**5a** of *ca.* 1.2:1 is observed in a preparative hydrolysis with acetone/H_2O (17 h at 58°, separation by flash chromatography (silica gel); yields 91 (**6**) and 71% (**5a**)) or in hydrolysis attempts using catalyses such as AcOH (2.5 h, 67°) and 2N HCl (1 min, room temperature) in THF (HPLC evidence). The structures of **5a** and **6** are confirmed by their spectral data and NOE experiments.

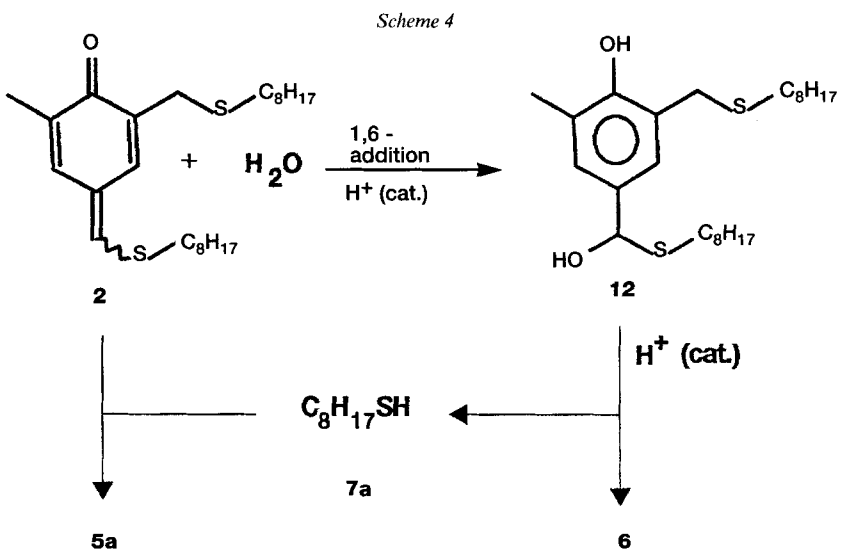
Another 1,6-addition of nucleophiles occurs, when **2** is heated for 9 h with 1 equiv. of thiol **7a** or **7b** in hexane, affording **5a** and **5b** in yields of 98 and 76%, respectively (*Scheme 3*), after purification by flash chromatography (silica gel). The product **5a** formed with octanethiol (**7a**) is identical to the product arising from **2** in the hydrolysis experiment.

Heating of a toluene solution of **2** and an excess of 2,2′-azobis(isobutyronitrile) (AIBN = 2,2′-dimethyl-2,2′-azobis(propanenitrile); **8**) for 3 h to 90° and repeated flash chromatography of the residue after distillation *in vacuo* affords the three nitriles **9a**, **9b**, and **10** in 41, 5.5, and 14% yield, respectively (*Scheme 3*). The structures of **9a**, **9b**, and **10** were confirmed by their spectral data and by NOE experiments.

Discussion. – The preparation of **2** is the first example of a regioselective dehydrogenation of a 2,4-bis[(alkylthio)methyl]phenol to a *p*-quinonemethide. The latter appears to have a large preference for 1,6-addition of nucleophiles such as thiols and H_2O. This 1,6-selectivity appears to be due to the resonance-energy gain by rearomatization. This synthesis opens a new access top asymmetric *p*-hydroxybenzaldehyde dithioacetals such as **5b**. Related transformations of such interesting synthetic equivalents of functionalized benzaldehydes (*e.g.* **2**) and benzoic acids (*e.g.* dehydrogenated **5**) will be reported in a subsequent paper [7].

Addition of C-centered free radicals, such as the 1-cyano-1-methylethyl radical, probably occurs with preference at the C-end of the dienone system of **2** since all products isolated can be accounted for by a mechanism starting with formation of **11** (see *Scheme 3*). The fact that the quinonemethide **2** and related compounds are efficient C-radical

Scheme 4



traps will be discussed more in detail in a publication concerning the antioxidant activity of **1** and especially the mechanism of incorporation of **1** into the polymer[1]). Hydrolysis of **2** probably passes through the hemithioacetal **12** which can form the benzaldehyde **6** by elimination of the thiol or thiolate anion which in turn is trapped by **2**, affording the dithioacetal **5a** (*Scheme 4*). Further work is planned to evaluate the use of **2** and related compounds as intermediates for new functionalized phenols [7].

We thank *Ciba-Geigy AG* for kindly supporting this work.

Experimental Part

General. Reactions were carried out under either N_2 or Ar. Flash chromatography (FC): see [8]. HPLC: *SP-8100* (*Spectra Physics*); *Nucleosil-RP-C18* column (5 μ, 126 × 4.6 mm), elution with H_2O/MeCN/i-PrOH 20:60:20 für 2 min, then within 6 min change to MeCN/i-PrOH 80:20 followed by 18 min isocratic with the last solvent (*Method A*) or isocratic elution with MeCN/AcOEt 98:2 (*Method B*). TLC: silica gel; R_f values for hexane/AcOEt 9:1 (*A*). M.p.: *Tottoli* (*Büchi*); corrected. UV Spectra: *Shimadzu UV-240 Graphicord* spectrometer; λ_{max} (ε) in nm. IR Spectra: *Nicolet 20 SX*; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra (*Tables 1* and *2*): *Bruker AC300* (300 MHz), *AM360* (^1H 360 MHz; ^{13}C 90.552 MHz), or *Varian Unity 500* (500 MHz) δ in ppm rel. to $SiMe_4$ (= 0 ppm), *J* in Hz. MS: *SSQ 710 Finnigan MAT*; EI or DCI; *m/z* (% rel. intensity). Elemental analyses were performed by the Analytical Research Services, *Ciba Corporation*.

2-Methyl-6-[(octylthio)methyl]-4-[(octylthio)methylidene]cyclohexa-2,5-dien-1-one (**2**). To a N_2-purged soln. of $K_3[Fe(CN)_6]$ (97.2 g, 0.295 mol) and KOH (5.55 g, 0.099 mol) in H_2O (370 ml) was added a N_2-purged soln. of **1** (*Irganox 1520* [3]; 9.28 g, 0,0218 mol) in hexane (100 ml). The mixture was stirred at r.t. for 2 h and the org. phase separated, dried (Na_2SO_4), and evaporated at 60°/0.05 Torr: 9.05 g (98%) of a viscous orange oil ((*E*)/(*Z*)-mixture). Attempts to purify **2** by FC (silica gel) always led to hydrolytic decomposition (HPLC evidence (*Method B*)). UV (MeCN): 387 (30560), 263 (5760). IR (KBr): 1632 (C=O), 1606 (C=C). EI-MS: 422 (3, M^+), 309 (32, $[M - C_8H_{17}]^+$), 278 (100). Anal. calc. for $C_{25}H_{42}OS_2$ (422.73): C 71.03, H 10.01, S 15.17; found: C 71.06, H 9.89, S 15.08.

Hydrolysis of **2** *in Acetone/Water.* A soln. of **2** (15 g, 35.4 mmol) in acetone (200 ml) and H_2O (20 ml) was heated for 17 h at 58° and then evaporated. FC (hexane/AcOEt 98:2, 95:5, and 90:10) afforded **5a** and **6**.

4-[Bis(octylthio)methyl]-2-methyl-6-[(octylthio)methyl]phenol (**5a**): 9.21 g (91.4%) of yellow liquid. R_f (*A*) 0.53. Further purification by recrystallisation from hexane at −45° afforded a slightly yellowish liquid. M.p. −30° (DSC). IR (KBr): 3320 (OH). MS: 423 (23, M^+), 278 (32, $[M - C_8H_{17}S]^+$), 277 (34), 165 (36), 135 (24), 41 (100). Anal. calc. for $C_{33}H_{60}OS_3$ (569.02): C 69.66, H 10.63, S 16.90; found: C 69.89, H 10.79, S 16.38.

4-Hydroxy-3-methyl-5-[(octylthio)methyl]benzaldehyde (**6**). Recrystallisation from hexane (at −20°): 3.65 (71.3%). M.p. 46°. R_f (*A*) 0.18. IR ($CHCl_3$): 3265 (OH), 1685 (C=O), 1597 (C=C). EI-MS: 294 (7, M^+), 149 (100, $[M - C_8H_{17}S]^+$), 145 (34, $C_8H_{17}S^+$). Anal. calc. for $C_{17}H_{26}O_2S$ (294.45): C 69.34, H 8.90, S 10.89; found: C 69.20, H 8.83, S 11.02.

Phenol **5a** *from* **2** *and Thiol* **7a**. A mixture of **2** (10.0 g, 23.65 mmol) octanethiol (**7a**; 4.0 g, 27.20 mmol), and hexane (20 ml) was heated for 9 h under reflux and then evaporated at 80°/0.03 mbar: 13.22 g (98%) of a yellow liquid, purity 96.5% (HPLC, *Method B*). It was further purified by FC (hexane/AcOEt 95:5): 10.10 g (75%), purity 98.6% (HPLC). R_f (*A*) 0.53. ^1H-NMR and IR: identical with those of **5a** obtained by hydrolysis of **2**. Anal. calc. for $C_{33}H_{60}OS_3$ (569.02): C 69.66, H 10.63, S 16.90; found: C 69.69, H 10.72, S 16.89.

4-{[(Methoxycarbonyl)methylthio](octylthio)methyl}-2-methyl-6-[(octylthio)methyl]phenol (= *Methyl {{4-Hydroxy-3-methyl-5-[(octylthio)methyl]phenyl}(octylthio)methylthio}acetate*; **5b**). As described for **5a**, **5b** was prepared from **2** (10 g, 23.7 mmol) and methyl thioglycolate (= methyl (thio)acetate; 3.39 g, 31.9 mmol) in hexane (20 ml). The solvent was evaporated and the residue purified by FC (hexane/AcOEt 95:5): 9.15 g (76%) of

[1]) This work is part of an investigation on the stabilization mechanism of the commercial phenolic antioxidant **1** (*Irganox 1520*) in elastomers [2].

Table 1. *^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of Compounds* **1**–**10**[a])

	1	*trans*-**2**	*cis*-**2**	**5a**	**5b**	**6**	**9a**[b])	**9b**[b])	**10**[b])
CH_2–C(6)	3.77 (*s*)	3.55 (*s*)	3.57 (*s*)	3.76 (*s*)	3.78 (*s*)	3.85 (*s*)	3.78 (*s*)	3.81 (*s*)	3.53, 3.50 (*AB*, *J* = 15), 3.32, 3.28 (*AB*, *J* = 15)
H–C(5)	6.85 (*d*, *J* = 2)	7.01 (*d*, *J* = 2)	7.45 (*d*, *J* = 2)	7.03 (*d*, *J* = 2)	7.03 (*d*, *J* = 2)	7.48 (*d*, *J* = 2)	7.22 (*d*, *J* = 2)	6.86 (*d*, *J* = 2)	7.35 (*d*, *J* = 2), 7.32 (*d*, *J* = 2)
CH_2–C(4) or CH–C(4)	3.60 (*s*)	7.2 (*s*)	7.17 (*s*)	4.77 (*s*)	5.0 (*s*)	9.81 (*s*)	3.63 (*s*)	3.60 (*s*)	3.30, 3.28 (*s*)
H–C(3)	7.05 (*d*, *J* = 2)	7.32 (*d*, *J* = 2)	6.87 (*d*, *J* = 2)	7.12 (*d*, *J* = 2)	7.15 (*d*, *J* = 2)	7.63 (*d*, *J* = 2)	7.28 (*d*, *J* = 2)	7.05 (*d*, *J* = 2)	6.28 (*d*, *J* = 2), 6.23 (*d*, *J* = 2)
Me–C(2)	2.25 (*s*)	2.07 (*s*)	2.03 (*s*)	2.23 (*s*)	2.25 (*s*)	2.31 (*s*)	2.37 (*s*)	2.25 (*s*)	not resolved
OH	6.70 (*s*)			6.83 (*s*)	6.88 (*s*)	7.77 (*s*)		6.67 (*s*)	

[a]) Assignments verified by double-resonance and nuclear *Overhauser* experiments; $CDCl_3$ soln. at 25°.
[b]) For convenience, the numbering of **1** is used.

Table 2. *^{13}C-NMR Chemical Shifts* [ppm] *of Compounds* **1**–**10**[a])

	1	*trans*-**2**[b])	**5a**	**5b**	**6**	**9a**[c])	**9b**[c])	**10**[c])
C(6)	125.6 (*s*)	133.0 (*s*)	126.2 (*s*)	126.2 (*s*)	126.8 (*s*)	133.8 (*s*)	126.2 (*s*)	132.3 (*s*), 132.4 (*s*)
C(5)	128.0 (*d*)	135.9 (*d*)	127.5 (*d*)	127.4 (*d*)	130.1 (*d*)	129.9 (*d*)	129.1 (*d*)	136.6 (*d*), 136.8 (*d*)
C(4)	129.3 (*s*)	128.5 (*s*)	132.0 (*s*)	130.5 (*s*)	129.0 (*s*)	135.3 (*s*)	129.6 (*s*)	135.1 (*s*), 135.3 (*s*)
C(3)	130.4 (*d*)	129.1 (*d*)	129.9 (*d*)	129.9 (*d*)	132.6 (*d*)	130.9 (*d*)	131.7 (*d*)	140.1 (*d*), 140.2 (*d*)
C(2)	121.2 (*s*)	136.4 (*s*)	121.9 (*s*)	121.8 (*s*)	122.2 (*s*)	133.4 (*s*)	122.1 (*s*)	51.8 (*s*), 52.0 (*s*)
C(1)	152.2 (*s*)	185.7 (*s*)	153.5 (*s*)	153.6 (*s*)	159.8 (*s*)	151.1 (*s*)	153.9 (*s*)	200.1 (*s*)
CH_2–C(6)	32.7 (*t*)	31.8 (*t*)	33.3 (*t*)	33.2 (*t*)	32.9 (*t*)	not resolved	32.5 (*t*)	not resolved
CH_2–C(4) or *C*H–C(4)	35.3 (*d*)	149.4 (*d*)	52.9 (*d*)	52.8 (*d*)	191.0 (*d*)	57.6 (*d*)	57.8 (*d*)	57.9 (*d*), 58.0 (*d*)
Me–C(2)	15.4 (*q*)	16.7 (*q*)	16.1 (*q*)	15.9 (*q*)	15.9 (*q*)	18.9 (*q*)	16.3 (*q*)	22.1 (*q*), 23.3 (*q*)

[a]) Multiplicity (in parentheses) deduced from DEPT spectra; $CDCl_3$ soln. at 25°.
[b]) Minor *cis*-**2**: resonances only weak or not detected.
[c]) For convenience, the numbering of **1** is used.

a waxy product. R_f (*A*) 0.24. IR ($CHCl_3$): 3330 (OH), 1734 (C=O). DCI-MS: 528 (< 1, $M^{+\cdot}$), 527 (2), 425 (11), 424 (22), 423 (100, $[M - AcOCH_2S]^+$), 384 (12), 383 (57, $[M - C_8H_{17}S]^+$), 279 (13), 278 (23), 277 (20). Anal. calc. for $C_{28}H_{48}O_3S_3$ (528.87): C 63.59, H 9.15, S 18.19; found: C 63.66, H 9.18, S 18.42.

Reaction of **2** *with AIBN* (**8**). A mixture of **2** (15.13 g, 35.8 mmol) and **8** (23.51 g, 143.13 mmol) in toluene (150 ml) was heated for 3 h to 90° and then evaporated. Repeated FC (hexane/AcOEt 98:2, 96:4, and 80:20) afforded **9a**, **9b**, and **10** as three pure fractions.

3-{4-(1-Cyano-1-methylethoxy)-3-methyl-5-[(octylthio)methyl]phenyl}-2,2-dimethyl-3-[(octylthio)methyl]-propanenitrile (**9a**): 8.29 g (41%) of a yellowish oil. R_f (*A*) 0.18. IR (KBr): 2234 (C≡N). EI-MS: 558 (6, $M^{+\cdot}$), 490 (59, $[M - C(Me)_2CN]^+$), 423 (7), 346 (29), 277 (19), 202 (35), 68 (100, $C(Me)_2 - CN^+$). Anal. calc. for $C_{33}H_{54}N_2OS_2$ (558.93): C 70.91, H 9.74, N 5.01, S 11.47; found: C 70.98, H 9.75, N 5.07, S 11.42.

3-{4-Hydroxy-3-methyl-5-[(octylthio)methyl]phenyl}-2,2-dimethyl-3-[(octylthio)methyl]propanenitrile (**9b**): 0.97 g (5.5%) of a yellowish oil. R_f (*A*) 0.29. IR (KBr): 3400 (br., OH), 2235 (C≡N). EI-MS: 491 (11, $M^{+\cdot}$), 423 (100, $[M - C(Me)_2CN]^+$), 346 (44, $[M - C_8H_{17}S]^+$), 277 (36, $[M - C(Me)_2CN - C_8H_{17}SH]^+$), 202 (21). Anal. calc. for $C_{29}H_{49}NOS_2$ (491.84): C 70.80, H 10.04, N 2.85, S 13.04; found: C 70.82, H 10.10, N 2.54, S 12.82.

3-{3-(1-Cyano-1-methylethyl)-3-methyl-5-[(octylthio)methyl]-4-oxocyclohexa-1,5-dienyl}-2,2-dimethyl-3-[(octylthio)methyl]propanenitrile (**10**): 2.88 g (16%) of a yellow oil. R_f (*A*) 0.11; mixture of diastereoisomers containing *ca.* 10% of an isomer of unknown structure. IK (KBr): 2234 (C≡N), 1664 (C=O), 1648 (C=C). EI-MS: 558 (2, $M^{+\cdot}$), 490 (72, $[M - C(Me)_2CN]^+$), 423 (8), 413 (11), 344 (15, $[M - C(Me)_2CN - C_8H_{17}SH]^+$), 277 (14), 202 (100). Anal. calc. for $C_{33}H_{54}N_2OS_2$ (558.93): C 70.91, H 9.74, N 5.01, S 11.47; found: C 70.88, H 9.72, N 4.78, S 11.45.

REFERENCES

[1] P. P. Klemchuk, 'Polymer Stabilization and Degradation', ACS Symposium Ser. 280, American Chemical Society, Washington, D.C., 1985.

[2] H. Berttermann, P. Dubs, G. Knobloch, U. Kolczak, H. Künzi, R. Martin, H. Meier, G. Rist, in preparation.

[3] P. Dubs, G. Knobloch, H. Meier, Eur. Pat. EP428973 to *Ciba-Geigy AG*, priority date 29.5.1991 (*CA*: **1991,** *115,* 185157r); W. Stegmann, H. Meier, S. Evans, R. Martin, R. Luisoli, Eur. Pat. EP275832 to *Ciba-Geigy AG*, priority date 24.12.1986 (*CA*: **1989,** *110,* 25732t).

[4] H. Meier, R. Pitteloud, Eur. Pat. EP441742 to *Ciba-Geigy AG*, priority date 5.2.1990 (*CA*: **1991,** *115,* 255805b).

[5] St. D. Pastor, *Sulfur Lett.* **1991,** *12,* 273; for a review on quinonemethides, see A. A. Volod'kin, V. V. Ershov, *Russ. Chem. Rev.* **1988,** *57,* 336.

[6] J. Velek, B. Koutek, O. Schmidt, L. Pavlickova', M. Soucek, *Collect. Czech. Chem. Commun.* **1976,** *41,* 1419; B. Koutek, L. Pavlickova', J. Velek, V. Beranek, M. Soucek, *ibid.* **1976,** *41,* 2607; *ibid.* **1976,** *41,* 2614.

[7] H. Fuhrer, H. Künzi, H. Meier, G. Rist, in preparation.

[8] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978,** *43,* 2923.