Pergamon

*Tetrahedron Letters*, Vol. 36, No. 33, pp. 5983-5986, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01159-5

# Quinoline Analogues of *Ortho*-Quinodimethane

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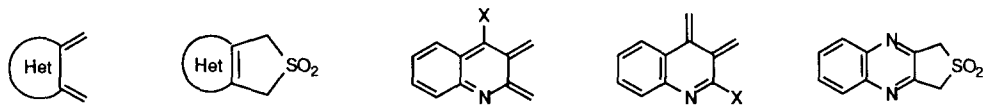
***Abstract:*** *2-Methoxyquinoline 3,4-quinodimethane **4**, X=OMe, can be generated from the quinoline 3,4-fused dihydrothiophene S,S-dioxide **23** and trapped with dienophiles but 4-methoxyquinoline 2,3-quinodimethane **3**, X=OMe, cannot be obtained from the corresponding sulfone. Quinolone 2,3- and 3,4-quinodimethanes are readily available from the sulfones **9** and **19** respectively*

Heterocyclic *o*-quinodimethanes **1** are now established as valuable intermediates in organic synthesis.[1] Such species can be conveniently generated by thermal extrusion of sulfur dioxide from heterocyclic fused sulfones **2** which in turn are readily available by annelation and oxidation of suitable dihydrothiophenes. The quinoline nucleus occurs widely in compounds with biological and pharmaceutical activity and therefore the hitherto unknown quinoline *o*-quinodimethanes are of particular interest. We now report our attempts to produce both the 2,3- and 3,4-quinolinequinodimethanes **3** and **4** from the corresponding quinoline fused sulfones.

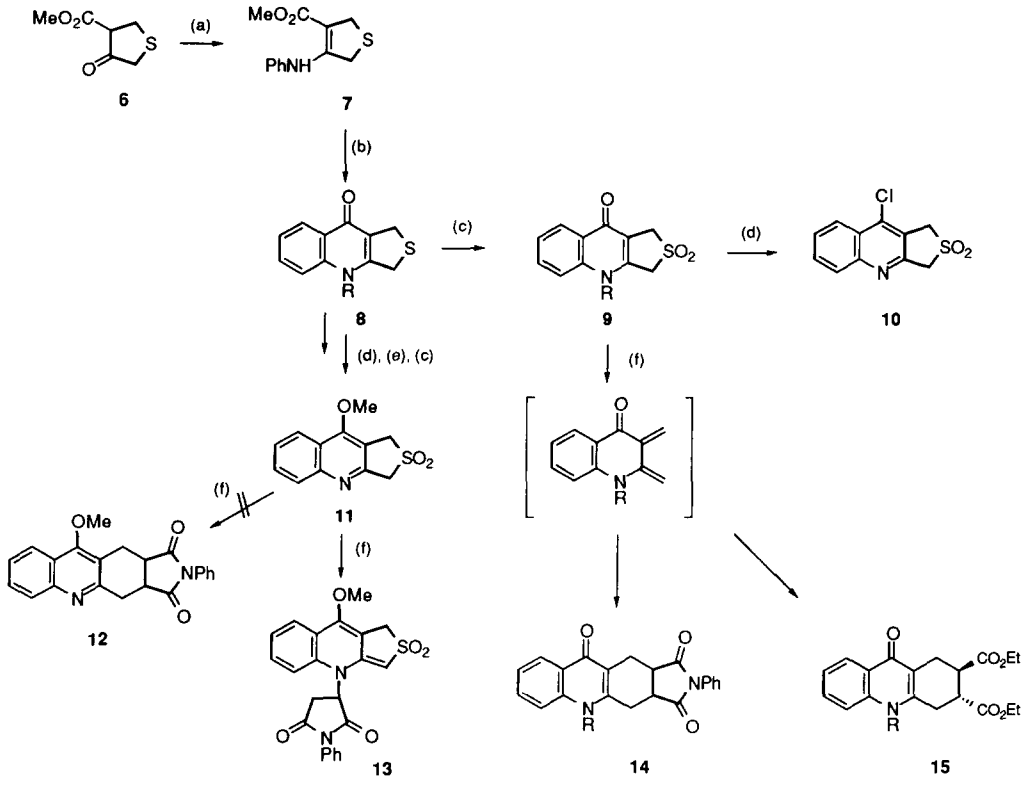



**1** **2** **3** **4** **5**

Our approach to the quinoline-2,3-quinodimethanes started with the readily available keto ester **6** [2] (Scheme 1) Reaction with aniline gave the enamine **7** which was cyclised to the quinolone **8** (R=H) by heating in biphenyl.[3] This was oxidised with *m*-chloroperbenzoic acid (m-CPBA) to the sulfone **9** (R=H)[4] and converted to the chloro derivative **10** by reaction with $POCl_3$. Conversion of **8** (R=H) to the methoxy quinoline **11** [5] was effected by chlorination with $POCl_3$, reaction with NaOMe in methanol and oxidation with m-CPBA.

The ease of cheletropic extrusion of $SO_2$ from 3-sulfolenes depends on the bond order of the sulfolene 3,4-bond; simple 3-sulfolenes (bond order 2) lose $SO_2$ rapidly at 110°C whereas benzosulfolenes (bond order 1.5) require temperatures approaching 200°C. Bond fixation in the quinoline derivatives **10** and **11** further reduces the bond order and extrusion of $SO_2$ might well be difficult. Indeed, extrusion of $SO_2$ from the related quinoxaline-sulfone **5** proved to be impractical.[6] In the event extrusion of $SO_2$ was not achieved from either **10** or **11**. Heating of **10** in solution in the presence of N-phenylmaleimide at temperatures up to 250°C led to decomposition and none of the expected *o*-quinodimethane Diels-Alder adduct. The methoxy derivative **11**

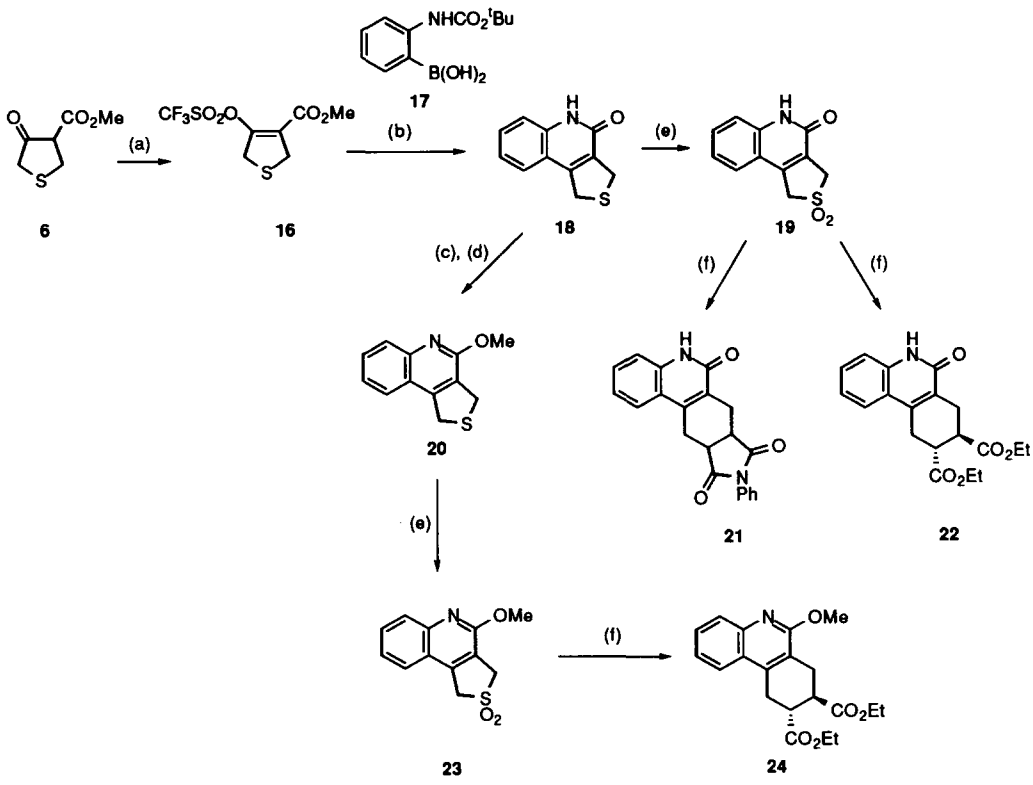
also gave no such adduct **12** but instead gave **13** [7] in which $SO_2$ is retained. This product presumably arises by nucleophilic attack of the quinoline N on the electrophilic dienophile followed by loss of a proton.




(a) $PhNH_2$, 50°C
(b) biphenyl, heat, 280°C
(c) m-CPBA, $CH_2Cl_2$
(d) $POCl_3$, heat
(e) NaOMe, MeOH, heat
(f) dienophile, 1,2,4-trichlorobenzene or sulfolane, reflux

**Scheme 1**

The, not unexpected, failure to achieve extrusion of $SO_2$ from the quinoline sulfones **10** and **11** led us to consider quinolone sulfones as precursors to the quinolone quinodimethanes which could serve as quinoline *o*-quinodimethane equivalents. The quinolone **8** (R=H) is extremely insoluble and was, therefore, converted to the N-methylquinolone **8** (R=Me) by methylation with $MeI/K_2CO_3$.[8] Oxidation with m-CPBA gave the quinolone **9** (R=Me).[9] As expected, extrusion of $SO_2$ from this quinolone occurred readily on heating in 1,2,4-trichlorobenzene at 200°C and in the presence of N-phenylmaleimide the Diels-Alder adduct **14** [10] was obtained in 67% yield. Heating of the less soluble, unsubstituted quinolone **9** (R=H) in sulfolene in the presence of diethyl fumarate also gave an adduct **15**.[11] These experiments establish that although quinoline-2,3-quinodimethanes cannot be produced directly by extrusion of $SO_2$ from the quinoline sulfones, the quinolone analogues are easily generated and the products can, in principle, be manipulated so that they serve as synthetic equivalents.




(a) $(^{i}Pr)_2NEt$, $(CF_3SO_2)_2O$, $CH_2Cl_2$, -78°C
(b) $Pd(PPh_3)_4$, 2M $Na_2CO_3$, DME, heat
(c) $POCl_3$, heat
(d) NaOMe, MeOH, heat
(e) m-CPBA, $K_2CO_3$, $CH_2Cl_2$
(f) dienophile, 1,2,4-trichlorobenzene, reflux

**Scheme 2**

Extrusion of $SO_2$ from the quinoline 3,4-sulfolenes **3** should not present the problems encountered with the 2,3-isomers in view of the higher 3,4-bond order. The 3,4-quinoline sulfones were again obtained from the keto ester **6** as shown in scheme 2. The keto ester was first converted to the enol triflate **16** with triflic anhydride. Suzuki coupling with the boronic acid **17** [12] gave the cyclised quinolone **18** directly since deprotection of the t-butoxycarbonylamino group occurs under the reaction conditions. This quinolone was converted to the methoxy quinoline **20** via the chloroquinoline using $POCl_3$ followed by reaction with NaOMe in methanol. Subsequent oxidation with m-CPBA gave the sulfone **23** [13] which on heating in trichlorobenzene in the presence of diethyl fumarate gave the methoxyquinoline quinodimethane adduct **24** (64%).[14] The quinolone 3,4-quinodimethane was also readily obtained.[15] Thus oxidation of **18** with m-CPBA gave the sulfone **19** which on heating in trichlorobenzene in the presence of N-phenylmaleimide or diethyl fumarate gave the quinolone quinodimethane adducts **21** (70%)and **22** (79%) respectively.[16]

In conclusion, routes to the quinoline and quinolone 3,4-quinodimethane and to the quinolone 2,3-quinodimethane systems from the corresponding sulfones have been established. Although the quinoline 2,3-quinodimethanes cannot be produced directly the 2,3-quinolone analogues serve as synthetic equivalents. The

possibilities for functionalisation of the dihydrothiophene **6** or the sulfones **9**, **10**, **19** and **23**, the use of substituted anilines or boronic acids and the range of dienophiles offer considerable versatility for the synthesis of target quinoline derivatives.

**Acknowledgements.** We thank the Wellcome Trust and EPSRC for support.

**References and Notes**


1. For leading references see: Chou T.-S. *Reviews on Heteroatom Chem.*, 1993, **8**, 65; Chaloner, L.M.; Crew, A.P.A.; O'Neill, P.M.; Storr, R.C.; Yelland, M. *Tetrahedron*, 1992, **48**, 8101, and Chou, T-S.; Chang, R-C. *J. Org. Chem.*, 1993, **58**, 493.
2. Woodward, R.B.; Eastman, R.H. *J. Amer. Chem. Soc.*, 1946, **68**, 2229.
3. MacDowell, D.N.H.; Jeffries, A.T.; Meyers, M.B. *J. Org. Chem.*, 1971, **36**, 1416; this procedure was modified by the use of biphenyl as solvent.
4. Yield 85%, m.p. 136-138°C. $\nu_{max}$ 3092 (NH), 1629 (C=O), 1377 and 1133 (S=O) $cm^{-1}$; $\delta_H$ (DMSO 55°C) 4.20 (s, 2H), 4.66 (s, 2H), 7.48 (t, 1H, J 6.6Hz), 7.69 (d, 1H, J 6.6Hz), 7.82 (t, 1H, J 6.6Hz) and 8.06 (d, 1H, J 6.6Hz).
5. Yield 50%, m.p. 202-204°C; $\delta_H$ ($CDCl_3$) 4.15 (s, 3H, OMe), 4.60 (s, 2H), 4.69 (s, 2H), 7.58 (t, 1H, J 8.25Hz), 7.77 (t, 1H, J 8.25Hz), 8.02 (d, 1H, J 8.25Hz) and 8.16 (d, 1H, J 8.25Hz).
6. Chou, T.S.; Ko, C.W. *Tetrahedron*, 1994, **50**, 10721.
7. Yield 25%, m.p. 160-162°C. $\delta_H$ ($CDCl_3$) 2.74 (dd, 1H, J 5.5 and 18.7Hz), 3.14 (dd, 1H, J 9.4 and 18.7Hz), 3.96 (ddd, 1H, J 2.75, 5.5 and 9.4Hz), 4.20 (s, 3H, OMe), 4.67 (d, 1H, J 15.0Hz), 4.74 (d, 1H, J 15.0Hz) 5.25 (d, 1H, J 2.75Hz), 7.45-7.55 (m, 6H), 7.60 (t, 1H, J 8.25Hz), 7.83 (d, 1H, J 8.25Hz) and 8.12 (d, 1H, J 8.25Hz).
8. Hromatka, O.; Binder, D.; Eichinger, K. *Monatshefte*, 1974, **105**, 1164.
9. Yield 48%, m.p. 236-238°C. $\nu_{max}$ 1623 (C=O), 1377 and 1111 ($SO_2$) $cm^{-1}$; $\delta_H$ (DMSO) 3.74 (s, 3H, NMe), 4.36 (s, 2H), 5.03 (s, 2H), 7.42 (t, 1H, J 8.25Hz), 7.75-7.79 (m, 2H) and 8.17 (d, 1H, J 8.8Hz).
10. M.p. 256-258°C. $\nu_{max}$($CH_2Cl_2$) 1711 $cm^{-1}$; $\delta_H$ ($CDCl_3$) 2.70 (dd, 1H, J 7.15 and 14.9Hz), 2.95 (dd, 1H, J 5.5 and 14.9Hz), 3.38-3.87 (m, 4H), 3.74 (s, 3H, NMe), 7.02 (d, 2H, J 7.7Hz), 7.23-7.49 (m, 5H), 7.63 (t, 1H, J 8.8Hz) and 8.46 (d, 1H, J 8.8Hz).
11. Yield 46%, m.p. 204-206°C. $\nu_{max}$ 1730 (C=O) $cm^{-1}$, $\delta_H$ ($CDCl_3$) 1.21 (t, 6H, J 7.15Hz), 2.14-3.11 (m, 6H), 4.14 (2xq, 4H, J 7.15Hz), 7.27-7.51 (m, 3H), 8.29 (d, 1H, J 8.25Hz), 10.32 (s, br, 1H, NH).
12. Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Quéguiner, G.; Siddiqui, M.A.; Snieckus, V. *J. Org. Chem.*, 1995, **60**, 292.
13. Yield 73%, m.p. 198-200°C. $\nu_{max}$ 1619 (C=N), 1316 and 1133 ($SO_2$) $cm^{-1}$; $\delta_H$ ($CDCl_3$) 4.12 (s, 3H, OMe), 4.46 (s, 2H), 4.67 (s, 2H), 7.48-7.56 (m, 2H), 7.70 (t, 1H, J 8.25Hz) and 7.92 (d, 1H, J 8.25Hz).
14. $\nu_{max}$ 1734 (C=O) and 1612 (C=N) $cm^{-1}$; $\delta_H$ ($CDCl_3$) 1.23 (2xt, 6H, 7.15Hz), 2.60 (dd, 1H, J 4.4 and 16.5Hz), 2.82-2.98 (m, 3H), 3.12 (dd, 1H, J 8.8 and 16.5Hz), 3.37 (d, 1H, J 13.0Hz), 3.97 (s, 3H, OMe), 4.07-4.20 (m, 4H), 7.26 (t, 1H, J 8.25Hz), 7.45 (t, 1H, J 8.25Hz), 7.61 (d, 1H, J 8.25Hz) and 7.71 (d, 1H, J 8.25Hz).
15. A 3,4-dimethylenequinolin-2-one derivative has been reported previously by ring opening of a quinolone fused cyclobutene: Kaneko, C.; Naito, T.; Ito, M. *Tetrahedron Lett.*,1980, **20**, 1645.
16. **21**: m.p. > 250°C. $\nu_{max}$ 1705 (C=O) and 1645 (C=O) $cm^{-1}$; $\delta_H$(DMSO) 2.72 (dd, 1H J 8.25, 15.1Hz), 2.97 (dd, 1H, J 6.6, 15.1 Hz), 3.48-3.65 (m, 4H), 6.96 (d, 2H, J 8.25Hz), 7.20-7.48 (m, 6H), 7.86 (d, 1H, J 8.25Hz) and 9.58 (s, br, 1H, NH); **22**: m.p. 196-198°C. $\nu_{max}$ 1739 and 1646 (C=O) $cm^{-1}$; $\delta_H$(DMSO) 1.16 (t, 3H, J 7.0Hz), 1.18 (t, 3H, J 7.0Hz), 2.85-3.19 (m, 6H), 7.14 (t, 1H, J 7.7Hz), 7.25 (d, 1H, J 7.7Hz), 7.42 (t, 1H, J 7.7Hz), 7.64 (d, 1H, J 7.7Hz) and 9.56 (s, br, 1H, NH).


(*Received in UK* 17 *May* 1995; *accepted* 23 *June* 1995)