Pergamon

Tetrahedron, Vol. 52, No. 5, pp. 1735-1746, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)01009-2

Pyrimidine *ortho*-Quinodimethanes

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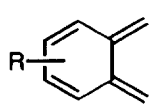
Abstract: The pyrimidine sulfones **10**, R = Me; Nu = OMe, NEt_2, SPh, H and **11**, R = Ph; Nu = OMe were synthesised from the dihydrothienopyrimidones **7**, R = Me, Ph by conversion to the chloro derivatives **8** followed by oxidation with mCPBA and reaction with the appropriate nucleophile or hydrogen and Pd. Heating of the sulfones in 1,2,4-trichlorobenzene gave the pyrimidine *o*-quinodimethanes which were intercepted in Diels-Alder reactions to give tetrahydroquinazolines.

1. INTRODUCTION

o-Quinodimethanes **1** and **2** are extremely reactive dienes which have been used as versatile intermediates in the synthesis of polycyclic compounds. From the synthetic point of view, the heterocyclic *o*-quinodimethanes **2** are potentially more interesting than their carbocyclic analogs **1** because of the wide range of heterocyclic systems which can be incorporated. Inter or intramolecular cycloaddition reactions involving heterocyclic *o*-quinodimethanes provides an attractive route to heteropolycyclic compounds of type **4** and **5**, respectively, and an increasing number of examples of such processes are to be found in recent reviews of the generation and chemistry of *o*-quinodimethanes.[1,2]



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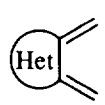

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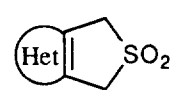

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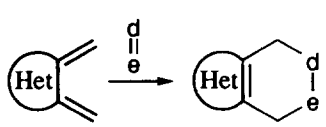

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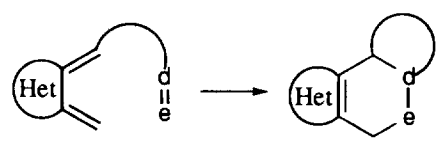

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One of the most versatile methods for the generation of *o*-quinodimethanes is the thermal extrusion of

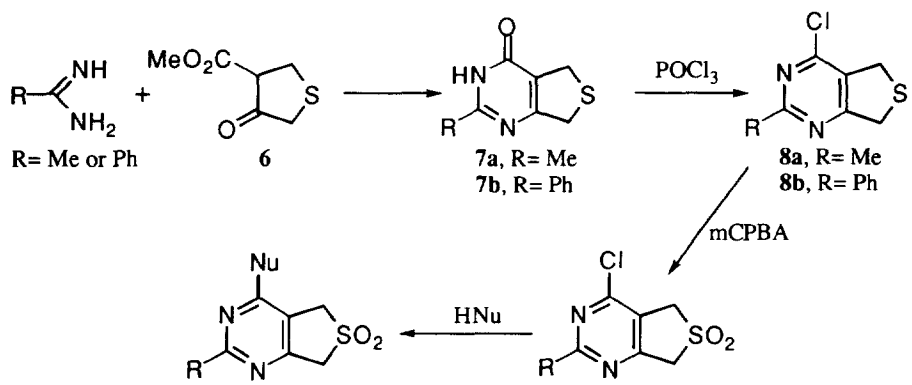
sulfur dioxide from aromatic fused 3-sulfolenes **3**. Access to these sulfones is reasonably easy, they can be functionalised on the positions α to the sulfonyl group and the extrusion of SO_2 can be carried out thermally in solution in the presence of dienophiles.

We have recently described the synthesis of some pyrimidone[3,4] and pyrimidine[5] fused 3-sulfolenes and their use as precursors to the corresponding *o*-quinodimethanes which were used as intermediates in the synthesis of 5,6,7,8-tetrahydroquinazolones and 5,6,7,8-tetrahydroquinazolines. Such tetrahydroquinazoline systems are known to possess important biological activities and some compounds of this type have been patented for their pharmacological,[6] fungicidal,[7] and herbicidal[8] activities. New routes to this class of compounds are, therefore, very important and we present here full details of this new and versatile approach.

2. RESULTS AND DISCUSSION

2.1 Synthesis of pyrimidine fused 3-sulfolenes

Our approach to the pyrimidine fused 3-sulfolenes is based on the transformation of the readily available dihydrothienopyrimidones **7**.[3,4] Conversion of pyrimidones **7** into 4-chloropyrimidines **8**, followed by oxidation at sulfur and subsequent displacement of the chlorine atom by nucleophiles would give a variety of 4-substituted pyrimidine derivatives (Scheme 1).

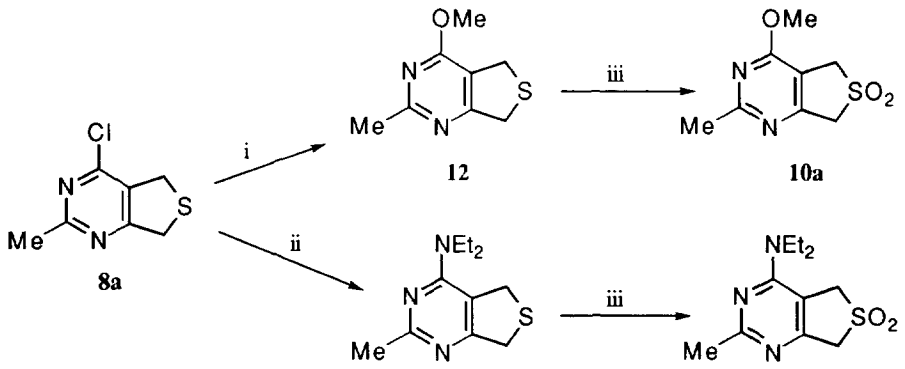


Scheme 1

Our strategy was evaluated with pyrimidones **7a** and **7b** which were obtained in high yields from reaction of keto-ester **6** with acetamidine or benzamidine, respectively.[4] The transformation of these 4-pyrimidones into 4-chloropyrimidines followed by nucleophilic substitution of the chlorine atom by a range of nucleophiles proved to be a highly versatile route to 4-substituted pyrimidines. The 4-chloropyrimidine **8a**[9] was obtained in 55% yield, after purification by column chromatography (alumina), by refluxing the pyrimidone **7a** with $POCl_3$, in the presence of triethylamine. The same procedure was used for the transformation of pyrimidone **7b** into the corresponding 4-chloropyrimidine **8b** (96% yield). Oxidation of 4-

chloropyrimidines **8a,b** with mCPBA (2 equiv.) gave the corresponding sulfones **9a,b** in good yields.

Attempted displacement of the chlorine atom in pyrimidine **8a** by nucleophiles proved to be more difficult than expected. For instance, the reaction of 4-chloropyrimidine **8a** with sodium methoxide, at room temperature, yielded the 4-methoxypyrimidine **12**[10] in only 54% yield together with recovered starting material. Reaction of the same 4-chloropyrimidine with diethylamine, in refluxing dichloromethane, did not occur and the 4-(N,N-diethylamino)pyrimidine **13** was obtained only when the diethylamine was used as solvent. In this case, after refluxing for two hours and purification by column chromatography, compound **13** was obtained in 83% yield but again 11% of the starting 4-chloropyrimidine was recovered unchanged. Oxidation of sulfides **12** and **13** with mCPBA yielded the corresponding sulfones.



i) NaOMe; ii) Et_2NH; iii) mCPBA

Scheme 2

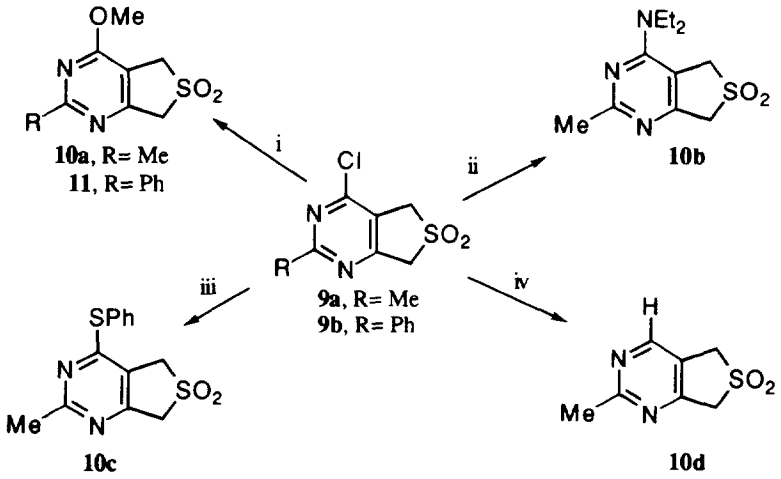
A more efficient way of obtaining the required 4-substituted pyrimidine fused 3-sulfolenes **10** and **11** involved prior oxidation of the 4-chloropyrimidines **8a,b** to their corresponding sulfones **9a,b** and subsequent nucleophilic substitution of the chlorine atom. This alternative approach has several advantages over the preceding route. The first one is the transformation of the smelly compounds **8** into more stable and easily handled products. The second advantage is the higher reactivity of the sulfones **9** compared with the sulfides. Thus, the sulfone **9a** reacts with diethylamine, in dichloromethane solution and at room temperature, yielding the compound **10b** while, even in refluxing conditions, the sulfide **8a** do not react. This higher reactivity of the sulfones is attributed to electron withdrawal by the sulfonyl group which makes the pyrimidine ring more electrophilic, and thus facilitates substitution of the chlorine atom by nucleophiles.

The sulfones **10a** and **11** were obtained in high yields by treatment of the corresponding 4-chloropyrimidines **9a,b** with sodium methoxide. Similarly, the sulfone **10c** was obtained by reaction of **9a** with sodium thiophenoxide. The sulfone **10d** was obtained in 92% yield by catalytic dehalogenation of the pyrimidine **9a** over palladium on charcoal.

2.2 Characterization of the pyrimidines

The synthesised pyrimidines were characterized mainly by ^1H and ^{13}C-NMR and mass spectrometry (MS). As expected, the differences found in the NMR and MS spectra of these compounds in the sulfide or

sulfone oxidation state are significant. For instance, in the ^1H NMR spectra of the sulfides, the signals of the SCH_2 groups typically show as triplets (J ~ 2.5 Hz) in the region of 4.0 to 4.3 ppm. This long distance coupling disappears when the sulfides are oxidized to the corresponding sulfones. In these compounds the signals of the SO_2CH_2 groups are singlets in the region of 4.3 to 4.5 ppm. The ^{13}C-NMR technique allows the assignment of the four pyrimidine ring carbons. The easiest carbon to identify is C-4a which appears typically between 110 and 120 ppm.[11] The chemical shift of C-4a can appear outside this range if there is a substituent at C-4 with strong electron donating or withdrawing character. For instance, the C-4a signals of the 4-N,N-diethylaminopyrimidine **10b** and the 4-chloropyrimidine **8a** appear, respectively, at 103.0 and 127.5 ppm. However, the signals corresponding to C-4 do not change significantly with the different substituents at C-4 and usually appear at 160-170 ppm.



i) NaOMe; ii) Et_2NH;iii) NaSPh; iv) H_2/Pd(C)

Scheme 3

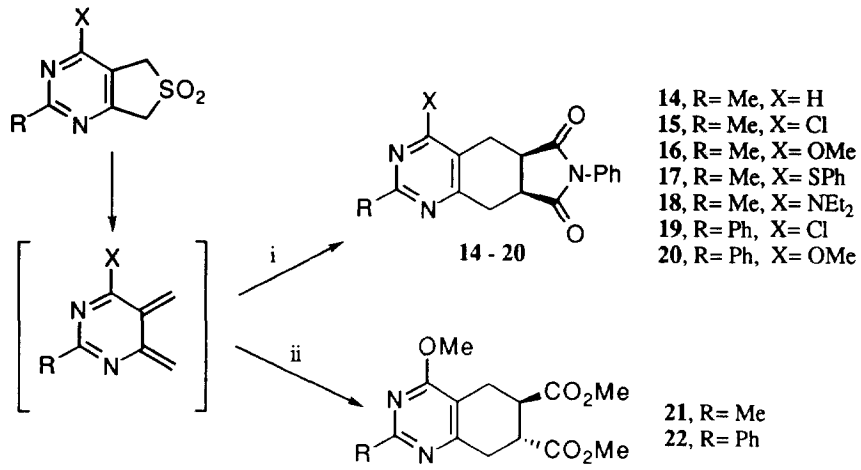
The MS of the pyrimidines in the sulfide oxidation state show a base peak corresponding to the molecular ion $M^{+\cdot}$. On contrary, in the 3-sulfolenes the peak corresponding to $M^{+\cdot}$ has a low relative intensity, usually less than 25% (except for compounds **9b** (41%) and **10b** (76%)). In these compounds the base peak corresponds to the ion $(M\text{-}SO_2)^{+\cdot}$, consistent with their great tendency to extrude sulfur dioxide to generate the corresponding *o*-quinodimethanes.

2.3 Thermal extrusion of sulfur dioxide from pyrimidine fused 3-sulfolenes

The pyrimidine fused 3-sulfolenes extrude sulfur dioxide to generate the corresponding pyrimidine *o*-quinodimethanes when heated in 1,2,4-trichlorobenzene at reflux (ca. 214°C). The temperature required for the extrusion of sulfur dioxide from the pyrimidine fused 3-sulfolenes is higher than that required for the extrusion of sulfur dioxide from the 4-pyrimidones (ca. 150°C);[3,4] this reflects the lower aromatic character and

the higher 4a-7a bond order of the pyrimidone ring.

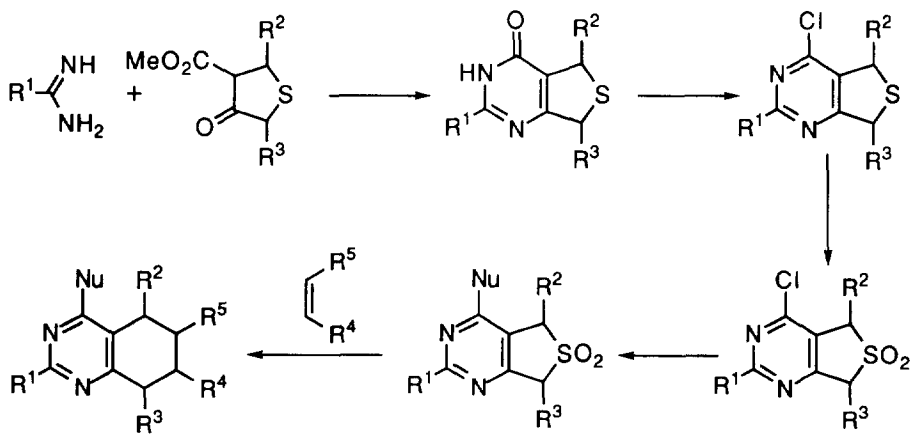
When the extrusion of sulfur dioxide was carried out in the presence of N-phenylmaleimide or dimethyl fumarate, the tetrahydroquinazolines **14-20** and **21-22**, respectively, were obtained (scheme 4).



i) N-phenylmaleimide; ii) dimethyl fumarate

Scheme 4

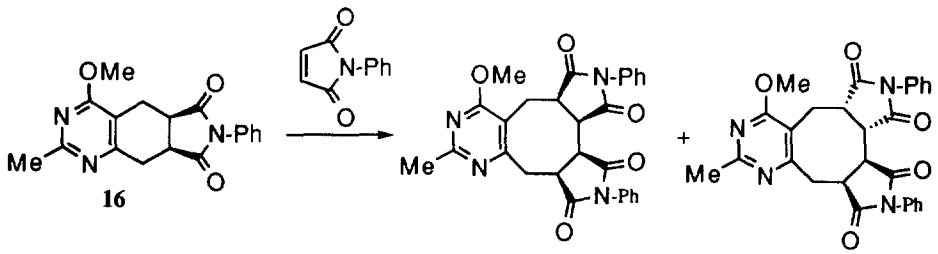
This reaction constitutes a new and versatile method for the synthesis of 5,6,7,8-tetrahydroquinazolines and, in principle, by using the appropriate starting reagents allows the synthesis of 5,6,7,8-tetrahydroquinazolines specifically substituted at any position (scheme 5).



Scheme 5

During our studies we found that when the 2-methylpyrimidine fused 3-sulfolenes are heated in trichlorobenzene in the presence of an excess of N-phenylmaleimide, the expected tetrahydroquinazolines are

always accompanied by a pair of diastereoisomeric cyclooctapyrimidines (scheme 6).[5] The complete scope of this new ring expansion reaction, which constitutes a novel approach to the synthesis of cyclooctapyrimidines, is still under study. Our results in this area will be published separately elsewhere.



Scheme 6

3. EXPERIMENTAL

The IR spectra were recorded on a Perkin Elmer 1600 Series FTIR spectrometer. The NMR spectra were recorded on a Bruker AMX 300 and on a Bruker ACE 200 spectrometers. Deuteriochloroform was used as solvent (except when indicated) and TMS as internal reference. Coupling constants are in Hz. Mass spectra were recorded under electron impact (EI) at 70 eV on a VG Micromass 7070E and on a VG AutoSpec-Q instruments. Microanalyses were performed in the microanalytical laboratory at Liverpool University.

3.1 Synthesis of pyrimidones

The experimental procedure for the synthesis of pyrimidones **7a** and **7b** is described in the preceding paper.[4]

3.2 Synthesis of 4-chloropyrimidines

4-Chloro-2-methyl-5,7-dihydrothieno[3,4-d]pyrimidine, **8a**

The pyrimidone **7a** (1.0 g; 5.9 mmol) was dissolved in previously distilled phosphoryl chloride ($POCl_3$) (10 ml). Freshly distilled triethylamine (1.5 ml) was added and the mixture was refluxed for 90 minutes in an oil bath at 140°C. The excess of $POCl_3$ was removed by distillation under reduced pressure and the residue was dissolved in dichloromethane. This solution was washed with aqueous ammonia, water, dried ($MgSO_4$) and the chloro compound (0.62 g; 55%) was isolated by column chromatography (alumina) using dichloromethane as eluent and recrystallized from dichloromethane/petroleum ether. Note: This compound has a strong unpleasant smell. M.p. 71-72°C; **^{1}H NMR**: 2.71 (s, 3H, 2-CH_3), 4.22 -4.23 (m, 2H, CH_2), 4.31-4.32 (m, 2H, CH_2); **^{13}C NMR**: 25.3 (2-CH_3), 33.5 (C-5), 39.0 (C-7), 127.5 (C-4a), 157.5 (C-4), 168.1 (C-7a), 171.8 (C-2); **MS** m/z (rel. int.): 186 ($M^{+\cdot}$, 100), 185 (98), 151 (45), 124 (34), 110 (35), 84 (17), 64 (19).
Anal.: Calcd for $C_7H_7ClN_2S$: C, 45.04; H, 3.78; N, 15.01. Found: C, 45.07; H, 3.79; N, 14.90%.

4-Chloro-2-phenyl-5,7-dihydrothieno[3,4-d]pyrimidine, **8b**

This compound was prepared in 96% yield by the same method as 4-chloropyrimidine **8a**. It showed only one spot on TLC and was used directly in the preparation of sulfone **9b**. For its characterization, a small portion of the compound was purified by column chromatography (alumina) using dichloromethane as eluent. The compound was crystallized from dichloromethane/hexane.
M.p. 139-140°C; **IR** ν_{max} (KBr) 1570, 1530, 1401, 742, 690 cm^{-1}; **^{1}H NMR**: 4.20-4.22 (m, 2H, CH_2), 4.33-4.35 (m, 2H, CH_2), 7.40-7.50 (m, 3H, Ar-H), 8.36-8.41 (m, 2H, Ar-H); **^{13}C NMR**: 33.5 (C-5), 39.0 (C-7), 127.9 (C-4a), 128.4 (C-2'+C-6'), 128.6 (C-3'+C-5'), 131.3 (C-4'), 135.7 (C-1'), 157.8 (C-4), 164.6 (C-7a), 172.0 (C-2); **MS** m/z (rel. int.): 248 ($M^{+\cdot}$, 100), 247 (82), 213 (28), 186 (17), 110 (8), 104 (17), 93 (12), 84 (7), 77 (14).
Anal.: Calcd for $C_{12}H_9ClN_2S$: C, 57.95; H, 3.65; N, 11.26. Found: C, 57.90; H, 3.63; N, 11.24%.

3.3 Oxidation of 4-chloropyrimidines

4-Chloro-2-methyl-5,7-dihydrothieno[3,4-d]pyrimidine 6,6-dioxide, **9a**

This compound was obtained by oxidation of the sulfide **8a** (0.80 g; 4.3 mmol) with mCPBA (1.92 g; 9.5 mmol; 2.2 equiv.) in dichloromethane (30 ml). The reaction mixture was stirred at room temperature for 18h, the excess of mCPBA was reduced with sodium thiosulfate and the *m*-chlorobenzoic acid was extracted with a saturated solution of $NaHCO_3$ (2 x 20 ml). The organic solution was concentrated and the product purified by column chromatography (silica) using chloroform: acetone (95:5) as eluent. The sulfone (0.87 g; 93%) was crystallized from dichloromethane/petroleum ether. M.p. 150-152°C; **IR** ν_{max} (KBr) 1577, 1528, 1328, 1244, 1131, 902 cm^{-1}; **^{1}H NMR**: 2.75 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 4.49 (s, 2H, CH_2); **^{13}C NMR**: 25.8 (CH_3), 55.2 (C-5), 58.5 (C-7), 121.8 (C-4a), 158.0 (C-4), 161.6 (C-7a), 169.6 (C-2); **MS** m/z (rel. int.): 218 ($M^{+\cdot}$, 19), 154 (93), 119 (100), 78 (31), 73 (14).
Anal.: Calcd for $C_7H_7ClN_2O_2S$: C, 38.45; H, 3.23; N, 12.81. Found: C, 38.36; H, 3.21; N, 12.72%.

4-Chloro-2-phenyl-5,7-dihydrothieno[3,4-d]pyrimidine 6,6-dioxide, **9b**

This compound was obtained by oxidation of the sulfide **8b** with mCPBA according to the procedure used for the synthesis of sulfone **9a**. The sulfone **9b** was obtained in 93% yield and was crystallized from acetone/cyclohexane. M.p. 230-231°C; **IR** ν_{max} (KBr) 1578, 1522, 1337, 1236, 1132, 941, 858, 746 cm^{-1}; **^{1}H NMR** (DMSO-d_6): 4.71 (s, 2H, CH_2), 4.85 (s, 2H, CH_2), 7.45-7.60 (m, 3H, Ar-H), 8.26-8.30 (m, 2H, Ar-H); **^{13}C NMR** (DMSO-d_6): 54.6 (C-5), 58.1 (C-7), 124.1 (C-4a), 128.4 (C-2'+C-6'), 129.3 (C-3'+C-5'), 132.4 (C-4'), 135.2 (C-1'), 157.4 (C-4), 163.9 (C-7a), 164.0 (C-2); **MS** m/z (rel. int.): 280 ($M^{+\cdot}$, 41), 216 (88), 181 (100), 104 (74), 83 (11), 77 (16).
Anal.: Calcd for $C_{12}H_9ClN_2O_2S$: C, 51.34; H, 3.23; N, 9.98. Found: C, 51.15; H, 3.09; N, 9.85%.

3.4 Reaction of 4-chloropyrimidines with nucleophiles

4-Methoxy-2-methyl-5,7-dihydrothieno[3,4-d]pyrimidine, **12**

The 4-chloropyrimidine **8a** (1.49 g; 8 mmol) was added to a solution of sodium methoxide (22 mmol) in methanol (20 ml). The mixture was stirred at room temperature for one hour and then at 50°C for 15 minutes. After evaporation of the methanol, the residue was purified by column chromatography (silica) using

dichloromethane as eluent. The first fraction corresponds to the unchanged chloropyrimidine (0.48 g; 32%) and the second fraction corresponds to the 4-methoxypyrimidine **12** (0.79 g; 54%). The melting point and the NMR spectra of this compound match those of the product with higher R_f obtained from the methylation of pyrimidone **7a** with diazomethane.[4]

4-(N,N-Diethylamino)-2-methyl-5,7-dihydrothieno[3,4-d]pyrimidine, **13**

A solution of 4-chloropyrimidine **8a** (0.314 g, 1.68 mmol) in diethylamine (3 ml) was refluxed for 2h. The diethylamine in excess was evaporated and the residue purified by column chromatography (silica) using chloroform as eluent. The first fraction corresponds to the starting pyrimidine (35 mg; 11%) and the second one corresponds to the desired product (0.31 g; 83%). **^{1}H NMR**: 1.19 (t, 6H, 2 x $CH_2\underline{CH}_3$, J = 7.1), 2.46 (s, 3H, 2-CH_3), 3.56 (q, 4H, 2 x $\underline{CH}_2CH_3$, J = 7.1), 4.07-4.10 (m, 2H, CH_2), 4.28-4.31 (m, 2H, CH_2); **^{13}C NMR**: 14.1 ($CH_2\underline{C}H_3$), 25.4 (2-CH_3), 35.6 (C-5), 38.1 (C-7), 43.3 ($\underline{C}H_2CH_3$), 108.2 (C-4a), 159.4 (C-7a), 165.6 (C-4), 169.3 (C-2).

4-Methoxy-2-methyl-5,7-dihydrothieno[3,4-d]pyrimidine 6,6-dioxide, **10a**

The sulfide **12** (0.46 g; 2.5 mmol) in dichloromethane (20 ml) was oxidized with a solution of the mCPBA (1.12 g; 5.5mmol; 2.2 equiv.) in dichloromethane (30 ml) in the same way as sulfide **12**. The product was purified by column chromatography (silica) using a mixture of chloroform: acetone (90:10) as eluent. The sulfone (0.52 g; 96%) was crystallized from dichloromethane/petroleum ether. The same compound was obtained by reaction of 4-chloropyrimidine **9a** with sodium methoxide. Yellow crystals, m.p. 119-121°C; **IR** ν_{max} (KBr) 2968, 1570, 1475, 1311, 1253, 1133, 1079, 758 cm^{-1}; **^{1}H NMR**: 2.63 (s, 3H, 2-CH_3), 4.03 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2), 4.35 (s, 2H, CH_2); **^{13}C NMR**: 25.9 (2-CH_3), 53.5 (OCH_3), 54.4 (C-5), 57.9 (C-7), 108.6 (C-4a), 159.7 (C-7a), 165.3 (C-2), 169.0 (C-4); **MS** m/z (rel. int.): 214 ($M^{+\cdot}$, 5), 150 (100), 120 (9), 94 (8), 79 (13), 66 (15).
Anal.: Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08. Found: C, 44.87; H, 4.70; N, 13.04%.

4-(N,N-Diethylamino)-2-methyl-5,7-dihydrothieno[3,4-d]pyrimidine 6,6-dioxide, **10b**

To a solution of 4-chloropyrimidine **9a** (0.44g, 2.0 mmol) in dichloromethane (15 ml) was added diethylamine (2 ml). The mixture was stirred at room temperature for 3 h and then refluxed for 30 minutes. The excess of amine was removed by evaporation and the residue was purified by column chromatography (silica) using chloroform: acetone (90:10) as eluent. The sulfone (0.38g, 75%) was crystallized from dichloromethane/petroleum ether. M.p. 160-162°C; **IR** ν_{max} (KBr) 2982, 1569, 1420, 1320, 1261, 1145, 1106, 757 cm^{-1}; **^{1}H NMR**: 1.22 (t, 6H, 2 x $CH_2\underline{CH}_3$, J = 7.0), 2.47 (s, 3H, 2-CH_3), 3.51 (q, 4H, 2 x $\underline{CH}_2CH_3$, J = 7.0), 4.22 (s, 2H, CH_2), 4.41 (s, 2H, CH_2); **^{13}C NMR**: 13.9 ($CH_2\underline{C}H_3$), 25.9 (2-CH_3), 43.4 ($\underline{C}H_2CH_3$), 56.4 (C-5), 56.7 (C-7), 103.0 (C-4a), 158.2 (C-7a), 159.1 (C-4), 166.9 (C-2); **MS** m/z (rel. int.): 255 ($M^{+\cdot}$, 76), 240 (8), 226 (47), 191 (88), 176 (76), 162 (100), 148 (27), 135 (26), 119 (19), 78 (16).
Anal.: Calcd for $C_{11}H_{17}N_3O_2S$: C, 51.74; H, 6.71; N, 16.46. Found: C, 51.55; H, 6.70; N, 16.37%.

2-Methyl-4-phenylthio-5,7-dihydrothieno[3,4-d]pyrimidine 6,6-dioxide, **10c**

To a solution of the 4-chloropyrimidine **9a** (0.437 g; 2 mmol) in toluene (20 ml) was added thiophenol (0.41 ml; 4 mmol) and sodium hydride (in excess). The suspension was stirred for one hour at room

temperature and then at 50°C for 20 minutes. The suspension was transferred to the top of a small column of alumina and the thiophenol was eluted with toluene. The pyrimidine **10c** was then eluted with dichloromethane: acetone (80:20) and recrystallized from dichloromethane: hexane to yield colourless crystals (0.52 g; 88%). M.p. 142-144°C; **IR** ν_{max} (KBr) 1529, 1406, 1324, 1238, 1130, 898, 750 cm^{-1}; **^{1}H NMR**: 2.51 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 7.44-7.57 (m, 5H, Ar-H); **^{13}C NMR**: 25.9 (CH_3), 54.5 (C-5), 57.6 (C-7), 118.7 (C-4a), 126.5 (C-1´), 129.4 (C-2´ and C-6´), 130.0 (C-4´), 135.2 (C-3´ and C-5´), 158.1 (C-7a), 166.8 (C-2), 168.3 (C-4); **MS** m/z (rel. int.): 292 ($M^{+\cdot}$, 24), 228 (57), 227 (35), 186 (12), 135 (12), 125 (37), 119 (58), 109 (19), 78 (70), 65 (17), 51 (54), 42 (100).

2-Methyl-5,7-dihydrothieno[3,4-d]pyrimidine 6,6-dioxide, **10d**

To a solution of the 4-chloropyrimidine **9a** (0.437 g; 2 mmol) in toluene (25 ml) was added a solution of potassium acetate (0.2 g; 2 mmol) in ethanol (5 ml) and 50 mg of palladium on charcoal (10%). The mixture was stirred overnight under hydrogen at atmospheric pressure and at room temperature. The solution was filtered through celite, the solvent was evaporated and the residue was purified by column chromatography (silica) using dichloromethane: ethyl acetate (80:20) as eluent. The first fraction corresponds to the starting material (c.a. 15 mg) and the second fraction is the pyrimidine **18**. This pyrimidine was recrystallized from dichloromethane: hexane yielding colourless crystals (0.338 g; 92%). M.p. 134-136°C; **IR** ν_{max} (KBr) 2924, 1585, 1545, 1427, 1316, 1233, 1131, 830, 782, 630 cm^{-1}; **^{1}H NMR**: 2.65 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 8.53 (s, 1H, Ar-H); **^{13}C NMR**: 25.7 (CH_3), 54.4 (C-5), 57.2 (C-7), 122.1 (C-4a), 153.8 (C-4), 160.2 (C-7a), 168.6 (C-2); **MS** m/z (rel. int.): 184 ($M^{+\cdot}$, 9), 120 (93), 93 (18), 79 (15), 52 (100), 51 (31).

Anal.: Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38; N, 15.21. Found: C, 45.63; H, 4.40; N, 15.11%.

4-Methoxy-2-phenyl-5,7-dihydrothieno[3,4-d]pyrimidine 6,6-dioxide, **11**

This compound was obtained by reaction of the 4-chloropyrimidine **9b** with sodium methoxide by a procedure similar to that of the synthesis of pyrimidine **10a**. The compound was obtained with an almost quantitative yield (98%). It was crystallized from acetone/cyclohexane. M.p. 218-220°C; **IR** ν_{max} (KBr) 1590, 1560, 1474, 1384, 1324, 1132, 1068, 756 cm^{-1}; **^{1}H NMR** (DMSO-d_6): 4.11 (s, 3H, OCH_3), 4.49 (s, 2H, CH_2), 4.70 (s, 2H, CH_2), 7.52-7.55 (m, 3H, Ar-H), 8.35-8.40 (m, 2H, Ar-H); **^{13}C NMR** (DMSO-d_6): 52.5 (OCH_3), 54.2 (C-5), 57.2 (C-7), 110.3 (C-4a), 127.9 (C-2´ and C-6´), 128.7 (C-3´ and C-5´), 131.4 (C-4´), 136.2 (C-1´), 161.7 (C-7a), 163.0 (C-2), 164.9 (C-4); **MS** m/z (rel. int.): 276 ($M^{+\cdot}$, 19), 212 (100), 181 (10), 141 (10), 104 (27), 77 (7).

Anal.: Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14. Found: C, 56.53; H, 4.35; N, 10.12%.

3.5 Generation and trapping of pyrimidine *o*-quinodimethanes

General procedure:

The sulfone (1 mmol) and the dienophile (2 mmol) were heated in 1,2,4-trichlorobenzene (5 ml) at reflux, under nitrogen atmosphere, for 3h. After cooling, the mixture was applied to the top of a column of silica and the trichlorobenzene was eluted with petroleum ether: dichloromethane (2:1). The adducts were then eluted with more polar eluents (chloroform/acetone or dichloromethane/ethyl acetate). For all the reactions of this series, the products were always eluted in the same order: first the dienophile not consumed, then the fraction

corresponding to the 2:1 adducts and finally the 1:1 adduct.

2-Methyl-7-phenyl-5,5a,8a,9-tetrahydropyrrolo[3,4-g]quinazolin-6,8-dione, **14**

Obtained in 75% yield by reaction of sulfone **10d** with N-phenylmaleimide. The adduct was purified by column chromatography (silica) using acetone: ethyl acetate (2:1) as eluent and crystallized from dichloromethane/hexane. M.p. 149-151°C; **IR** ν_{max} (KBr) 1717, 1558, 1507, 1436, 1388, 1182, 693 cm^{-1}; **^{1}H NMR**: 2.70 (s, 3H, CH_3), 3.00-3.53 (m, 6H, CH_2 and CH), 7.00-7.05 (m, 2H, Ar-H), 7.30-7.39 (m, 3H, Ar-H), 8.39 (s, 1H, H-4); **^{13}C NMR**: 25.5 (C-5), 25.6 (CH_3), 31.5 (C-9), 38.9, 39.2 (C-5a/C-8a), 124.4 (C-4a), 126.0 (C-2' and C-6'), 128.6 (C-4'), 129.0 (C-3' and C-5'), 131.3 (C-1'), 154.7 (C-4), 164.3 (C-9a), 167.2 (C-2), 177.0, 177.3 (C-6/C-8); **MS** m/z (rel. int.): 293 ($M^{+\cdot}$, 100), 264 (6), 173 (8), 146 (78), 145 (72), 119 (18), 118 (19), 105 (11), 104 (11), 91 (11), 85 (27), 83 (41), 77 (21).

4-Chloro-2-methyl-7-phenyl-5,5a,8a,9-tetrahydropyrrolo[3,4-g]quinazolin-6,8-dione, **15**

Obtained in 72% yield by reaction of sulfone **9a** with N-phenylmaleimide. The adduct was purified by column chromatography (silica) using chloroform: acetone (85:15) as eluent. It was crystallized from dichloromethane/hexane. M.p. 167-170°C (dec.); **IR** ν_{max} (KBr) 1707, 1570, 1534, 1400, 1186, 696 cm^{-1}; **^{1}H NMR**: 2.67 (s, 3H, CH_3), 3.03-3.58 (m, 6H, CH_2 and CH), 7.08-7.12 (m, 2H, Ar-H), 7.33-7.45 (m, 3H, Ar-H); **^{13}C NMR**: 24.6 (C-5), 25.5 (CH_3), 31.9 (C-9), 38.88, 38.94 (C-5a/C-8a), 123.3 (C-4a), 126.0 (C-2' and C-6'), 128.8 (C-4'), 129.1 (C-3' and C-5'), 131.3 (C-1'), 159.0 (C-4), 166.0 (C-9a), 167.2 (C-2), 176.8, 176.9 (C-6/C-8); **MS** m/z (rel. int.): 327 ($M^{+\cdot}$, 100), 293 (10), 207 (7), 180 (75), 145 (29), 119 (49), 104 (32), 91 (34), 77 (49), 64 (14).

Anal.: Calcd for $C_{17}H_{14}ClN_3O_2$: C, 62.30; H, 4.31; N, 12.82. Found: C, 62.33; H, 4.33; N, 12.65%.

4-Methoxy-2-methyl-7-phenyl-5,5a,8a,9-tetrahydropyrrolo[3,4-g]quinazolin-6,8-dione, **16**

Obtained from reaction of sulfone **10a** with N-phenylmaleimide, in refluxing trichlorobenzene for 4 h. When an excess of NPM (2 equiv.) was used, the adduct **16** was obtained in 84%, toghether with a fraction corresponding to the 2:1 adducts (11%). When the reaction was carried out in the presence of only one equivalent of N-phenylmaleimide, the 1:1 adduct was obtained in 93% yield. In this case, only trace quantities of the 2:1 adducts are formed. The 1:1 adduct was purified by column chromatography (silica) using chloroform: acetone (85:15) as eluent and it was crystallized from dichloromethane/hexane. M.p. 158-160°C; **IR** ν_{max} (KBr) 3052, 2954, 2898, 2361, 1716, 1570, 1392, 1187, 765, 706 cm^{-1}; **^{1}H NMR**: 2.57 (s, 3H, 2-CH_3), 2.80-3.54 (m, 6H, CH_2 and CH), 3.96 (s, 3H, OCH_3), 7.10-7.13 (m, 2H, Ar-H), 7.34-7.41 (m, 3H, Ar-H); **^{13}C NMR**: 20.6 (C-5), 25.8 (2-CH_3), 31.1 (C-9), 39.1, 39.3 (C-5a/C-8a), 53.9 (OCH_3), 110.7 (C-4a), 126.2 (C-2' and C-6'), 128.6 (C-4'), 129.1 (C-3' and C-5'), 131.6 (C-1'), 163.4 (C-9a), 166.0, 166.1 (C-2/C-4), 177.5, 177.8 (C-6/C-8); **MS** m/z (rel. int.): 323 ($M^{+\cdot}$,100), 294 (9), 203 (5), 175 (73), 161 (31), 143 (5), 118 (30), 104 (7), 91 (7), 83 (13), 77 (17), 65 (7), 55 (13).

Anal.: Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.80; H, 5.30; N, 12.97%.

2-Methyl-7-phenyl-4-phenylthio-5,5a,8a,9-tetrahydropyrrolo[3,4-g]quinazolin-6,8-dione, **17**

Obtained in 72% yield by reaction of sulfone **10c** with N-phenylmaleimide. The adduct was purified by column chromatography (silica), using dichloromethane: ethyl acetate (3:2) as eluent, and it was crystallized from dichloromethane/hexane. M.p. 126-128°C; **IR** ν_{max} (KBr) 1716, 1540, 1388, 1187, 745, 688 cm^{-1};

^{1}H NMR: 2.44 (s, 3H, CH_3), 2.95-3.51 (m, 6H, CH_2 and CH), 7.11-7.16 (m, 2H, Ar-H), 7.36-7.55 (m, 8H, Ar-H); **MS** m/z (rel. int.): 401 ($M^{+\cdot}$,65), 253 (99), 227 (24), 143 (46), 104 (37), 77 (100), 51 (22).
Anal.: Calcd for $C_{23}H_{19}N_3O_2S$: C, 68.81; H, 4.77; N, 10.47. Found: C, 68.73; H, 4.74; N, 10.45%.

4-(N,N-Diethylamino)-2-methyl-7-phenyl-5,5a,8a,9-tetrahydropyrrolo[3,4-g]quinazolin-6,8-dione, **18**

Obtained in 56% yield by reaction of sulfone **16** with N-phenylmaleimide. The adduct was purified by column chromatography (silica) using dichloromethane: ethyl acetate (3:2) as eluent and it was crystallized from dichloromethane/hexane. M.p. 200-203°C.; **IR** ν_{max} (KBr) 2930, 2360, 1716, 1560, 1386, 1196, 754, 699 cm^{-1}; **^{1}H NMR**: 1.21 (t, 6H, $CH_2\underline{CH_3}$), 2.46 (s, 3H, CH_3), 2.85-3.47 (m, 10H, $\underline{CH_2}CH_3$, CH_2 and CH), 7.02-7.07 (m, 2H, Ar-H), 7.35-7.45 (m, 3H, Ar-H).

4-Chloro-2,7-diphenyl-5,5a,8a,9-tetrahydropyrrolo[3,4-g]quinazolin-6,8-dione, **19**

This adduct was obtained in 86% yield by reaction of the sulfone **9b** with N-phenylmaleimide. M.p. 215-217°C; **IR** ν_{max} (KBr) 1706, 1570, 1522, 1395, 1156, 752, 700 cm^{-1}; **^{1}H NMR**: 3.10-3.20 (m, 1H), 3.23-3.31 (dd, 1H, J = 15.6 and J = 7.3), 3.42-3.49 (dd, 1H, J= 15.6 and J = 4.1), 3.47-3.62 (m, 3H), 7.08-7.12 (m, 2H, Ar-H), 7.32-7.52 (m, 6H, Ar-H), 8.42-8.45 (m, 2H, Ar-H); **^{13}C NMR**: 24.9 (C-5), 32.3 (C-9), 39.0, 39.1 (C-5a/C-8a), 124.1 (C-4a), 126.1, 128.5, 128.6, 128.8, 129.2, 131.3, 131.4, 135.9 (2 x C_6H_5), 159.6 (C-4), 163.5 (C-9a), 166.2 (C-2) 176.9, 177.0 (2 x C=O); **MS** m/z (rel. int.): 389 ($M^{+\cdot}$, 100), 354 (6), 241 (56), 205 (13), 194 (8), 180 (14), 104 (20), 83 (19), 77 (19).

2,7-Diphenyl-4-methoxy-5,5a,8a,9-tetrahydropyrrolo[3,4-g]quinazolin-6,8-dione, **20**

This compound was obtained in 94% yield by reaction of the sulfone **11a** with N-phenylmaleimide. M.p. 207-210°C; **IR** ν_{max} (KBr) 1709, 1560, 1400, 1185, 746, 699 cm^{-1}; **^{1}H NMR**: 2.89-2.97 (dd, 1H, J = 15.5 and J = 7.0), 3.14-3.22 (dd, 1H, J = 15.5 and J = 7.8), 3.37-3.58 (m, 4H), 4.09 (s, 3H, OCH_3), 7.11(d, 2H, Ar-H), 7.30-7.47 (m, 6H, Ar-H), 8.43-8.46 (m, 2H, Ar-H); **^{13}C NMR**: 20.9 (C-5), 31.4 (C-9), 39.2, 39.3 (C-5a/C-8a), 53.8 (OCH_3), 111.7 (C-4a), 126.2, 128.1, 128.4, 128.6, 129.1, 130.6, 131.5, 137.4 (2 x C_6H_5), 162.3 (C-9a), 164.0 (C-2), 166.1 (C-4) 177.6, 177.8 (2 x C=O); **MS** m/z (rel. int.): 385 ($M^{+\cdot}$, 100), 370 (6), 356 (6), 237 (56), 223 (19), 180 (26), 118 (8), 104 (7), 77 (12).

trans-6,7-Bis(methoxycarbonyl)-4-methoxy-2-methyl-5,6,7,8-tetrahydroquinazoline, **21**

Obtained in 99% yield by reaction of sulfone **10a** with dimethyl fumarate. The adduct was purified by column chromatography (silica) using dichloromethane: ethyl acetate (15:85) as eluent and it was crystallized from hexane. M.p. 93-96°C; **IR** ν_{max} (KBr) 2956, 1734, 1576, 1376, 1300, 1180, 1095, 767 cm^{-1}; **^{1}H NMR**: 2.54 (s, 3H, 2-CH_3), 2.60-3.20 (m, 6H, CH_2 and CH), 3.74 (s, 6H, 2x CO_2CH_3), 3.97 (s, 3H, OCH_3); **^{13}C NMR**: 23.3 (C-5), 25.0 (2-CH_3), 32.7 (C-8), 40.3, 40.6 (C-6/ C-7), 51.7 ($CO_2\underline{C}H_3$), 53.2 (OCH_3), 110.0 (C-4a), 161.0 (C-8a), 164.6 (C-2), 166.5 (C-4), 173.5, 173.6 (2 x C=O); **MS** m/z (rel. int.): 294 ($M^{+\cdot}$, 12), 263 (17), 235 (100), 175 (66), 118 (50), 77 (20), 56 (25).
Anal.: Calcd for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 57.24; H, 6.18; N, 9.50%.

trans-6,7-Bis(methoxycarbonyl)-4-methoxy-2-phenyl-5,6,7,8-tetrahydroquinazoline, **22**

Obtained in 88% yield by reaction of sulfone **11** with dimethyl fumarate. The adduct was purified by column chromatography (silica) using dichloromethane: ethyl acetate (15:85) as eluent. M.p. 99-102°C; **IR**

ν_{max} (KBr) 2954, 1740, 1564, 1408, 1178, 761, 701 cm^{-1}; **^{1}H NMR**: 2.60-3.25 (m, 6H, CH_2 and CH), 3.74 (s, 6H, 2x CO_2CH_3), 4.05 (s, 3H, OCH_3), 7.06-7.45 (m, 3H, Ar-H), 8.36-8.39 (m, 2H, Ar-H); **^{13}C NMR**: 24.0 (C-5), 33.4 (C-8), 40.7, 41.0 (C-6/ C-7), 52.1 ($CO_2\underline{C}H_3$), 53.6 (OCH_3), 111.5 (C-4a), 127.8 (C-2´ and C-6´), 128.2 (C-3´ and C-5´), 130.2 (C-4´), 137.4 (C-1´), 161.3 (C-8a), 161.8 (C-2), 167.0 (C-4), 174.0, 174.1 (2 x C=O); **MS** m/z (rel. int.): 356 ($M^{+\cdot}$, 50), 325 (15), 297 (100), 237 (35), 180 (19), 118 (7), 85 (11), 83 (17), 77 (6).

Acknowledgement: We thank INIC (Lisbon) for support.

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(*Received in UK* 12 *September* 1995; *revised* 14 *November* 1995; *accepted* 16 *November* 1995)