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Pyrimidine *o*-Quinodimethanes: Formation of 1:1 and 2:1 Adducts with Dienophiles

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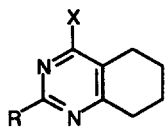
Abstract: Pyrimidine fused dihydrothiophene S,S-dioxides 7 undergo thermal elimination of sulfur dioxide to give the pyrimidine o-quinodimethanes 8 which can be intercepted in Diels-Alder reactions to give substituted 5,6,7,8-tetrahydroquinazolines; these form cyclooctapyrimidines on heating with more dienophile.

The 5,6,7,8-tetrahydroquinazoline system **1** is known to possess important biological activity and several compounds of this type have been patented for their pharmacological,[1] fungicidal[2] and herbicidal[3] properties. The cyclooctapyrimidines **2** are also of interest as pharmaceuticals[4] and we now present a new route to both types of systems via the hitherto unknown pyrimidine *o*-quinodimethanes.



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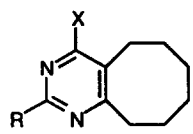

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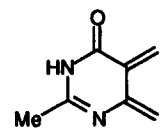

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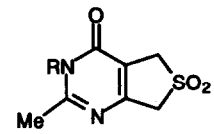

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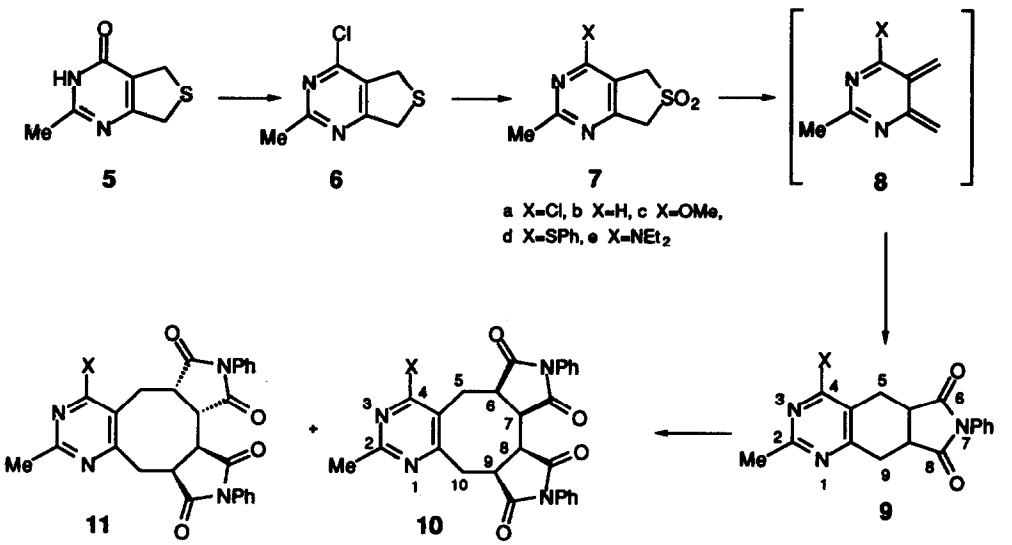
Recently we described the generation of the novel diene **3** by thermal extrusion of sulfur dioxide from the pyrimidone sulfone **4** (R=H).[5] The route to **4** (R=H) can be modified to provide access to a range of pyrimidine fused sulfones **7** (Scheme 1) which are the desired precursors to the highly reactive pyrimidine *o*-quinodimethanes. Thus compound **5** is easily converted into **6** with phosphorus oxychloride in the presence of triethylamine. Oxidation of this pyrimidine fused dihydrothiophene with 3-chloroperbenzoic acid leads to the sulfone **7a**[6] which is a key precursor to a number of other 4-substituted derivatives. Catalytic dehalogenation of **7a** over Pd-C gave pyrimidine **7b** and nucleophilic displacement of the chlorine in **7a** with sodium methoxide, sodium thiophenoxide or diethylamine gave **7c-e** respectively.[7]

When heated in refluxing 1,2,4-trichlorobenzene (214°C) in the presence of an excess of N-phenylmaleimide the sulfones **7a-e** all underwent extrusion of SO_2[8] and the resulting pyrimidine *o*-quinodimethanes **8** were intercepted as the 1:1 adducts **9** (65-75%).[9] Under these conditions[10] the 1:1 adducts **9** were always accompanied by a pair of 2:1 adducts (20-30%). These 2:1 adducts could be separated by preparative TLC and showed similar spectral characteristics which were consistent with the *cis* and *trans* structures **10** and **11**.[11] Thus the ^{13}C NMR spectra of both adducts indicate that the pyrimidine ring is intact, ruling out Diels-Alder

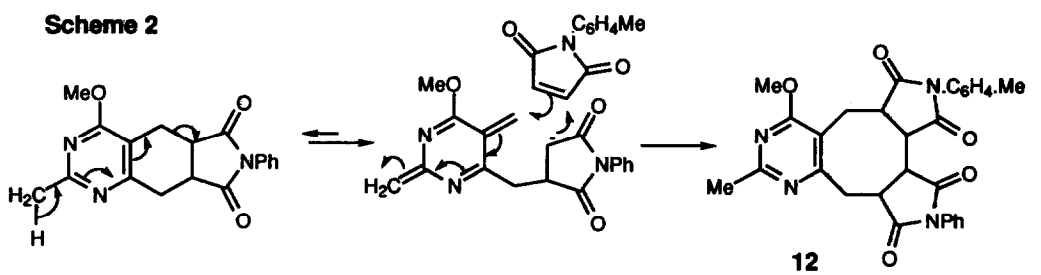
addition of the second molecule of N-phenylmaleimide to the pyrimidine ring. Both adducts also show the requisite number of saturated and aromatic carbon atoms.

Scheme 1

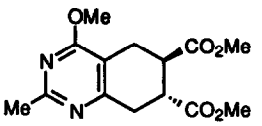


The methoxy derivative **7c** was studied in more detail. With one equivalent of N-phenylmaleimide the yield of 1:1 adduct **9c** was optimised (93%) and 2:1 adduct formation was almost eliminated. On the other hand, heating of the 1:1 adduct **9c** with an excess of N-p-tolylmaleimide gave, in high yield, a single *cis* and *trans* pair of 2:1 mixed adducts believed to have the regiochemistry **12**[12] (*vide infra*). Also the 1:1 adduct **13**, from interception of **8** with dimethyl fumarate, gives a single pair of diastereoisomeric 2:1 adducts with N-phenylmaleimide. These experiments clearly demonstrate that the 2:1 adducts are formed by regiospecific insertion of the second molecule of maleimide into one of the σ–bonds of **9**. Unfortunately, ^{1}H and ^{13}C NMR spectra do not allow unambiguous assignment of the regio and stereochemistry of these compounds and the crystalline form of all 2:1 adducts has so far proved unsuitable for X-ray analysis.

Scheme 2



At this stage we can only speculate as to the mechanism of formation of these novel 2:1 adducts. Preliminary indications are that the reaction is not completely general since the related 1:1 adducts **14** and **15** do not form similar 2:1 adducts in the same reaction conditions. With the pyrimidine system the reaction occurs irrespective of the nature of the 4-substituent and we tentatively suggest that the key to the reaction lies in the 2-methyl group because the corresponding 2-phenyl compound (**9**, Ph for Me) does not give such 2:1 adducts. The 2-methyl hydrogen atoms are acidic and may labilise the C-C bond shown in Scheme 2 allowing insertion of the second molecule of maleimide. Such a mechanism would account for the fact that the reaction is regioselective and imply that it is in the sense indicated.



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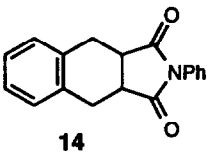

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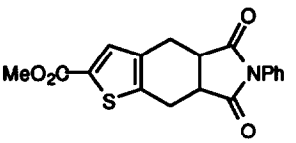

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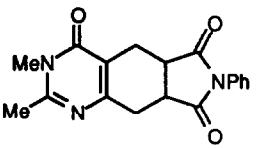

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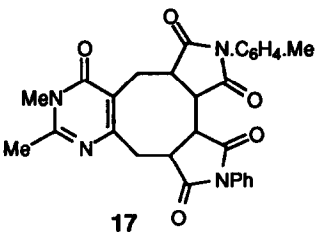

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The N-methyl pyrimidone **4** (R=Me), obtained in 3:1 ratio with **7c** by methylation of the sulfone **4** (R=H) with diazomethane in ether, also gives an analogous 1:1 adduct **16** with N-phenylmaleimide. On heating with N-p-tolylmaleimide this 1:1 adduct also gives a 2:1 adduct regiospecifically. Again, **4** (R=Me) similarly has a reactive 2-methyl group capable of labilising the corresponding C-C bond, suggesting that the regioselectivity is as shown in **17**. As expected, the temperature required for extrusion of SO_2 from the pyrimidine sulfones **7** (ca. 214°C) is higher than that required for extrusion from **4** (R=H, Me) (ca. 160°C) presumably reflecting the lower aromatic character of the pyrimidone ring.

Further studies of the scope and mechanism of this unexpected 8-membered ring forming reaction are in progress.

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6 All new compounds show satisfactory analytical and mass spectral data. Compound **7a**: 93%, m.p. 150-152 °C, ^{1}H-NMR ($CDCl_3$) 2.75 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 4.49 (s, 2H, CH_2) ;^{13}C-NMR ($CDCl_3$) 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)

7 Compound, yield %, m.p. °C: **7b**, 92, 134-136; **7c**, 97, 119-121; **7d**, 88, 142-144; **7e**, 75, 160-162.

8 A few 6-membered heterocyclic fused sulfones have been reported but this is the first report of the generation of the corresponding *o*-quinodimethanes by extrusion of SO_2. T.-S. Chou, *Reviews on Heteroatom Chem.* 1993, **8**, 65.

9 Compound, yield %, m.p. °C: **9a**, 72, 167-170; **9b**, 75, 149-151; **9c**, 93, 158-160; **9d**, 72, 126-128; **9e**, 56, 200-203. NMR data for **9c**: δ^1H ($CDCl_3$) 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); δ^{13}C ($CDCl_3$) 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, 128.6, 129.1, 131.6 (NPh), 163.4 (C-9a), 166.0/166.1 (C-2/C-4), 177.5/177.8 (2 x C=O). Other adducts show analogous NMR spectra.

10 Typical conditions: the sulfone (1 mmole) and the N-phenylmaleimide (2 mmole) were heated in refluxing 1,2,4-trichlorobenzene (3 ml), under nitrogen atmosphere, for 3h. The work-up was by column chromatography on silica; the trichlorobenzene was removed with cyclohexane and the adducts were then eluted with a more polar eluent (dichloromethane/ ethyl acetate).

11 Compounds **10** and **11** could not be assigned unambiguously. Isomer with higher Rf (SiO_2): m.p. 148-151 °C, ^{13}C NMR ($CDCl_3$) 20.8 (C-5), 25.9 (2-CH_3), 34.9 (C-10), 38.4/39.8/41.1/42.0 (C-6 to C-9), 54.0 (OCH_3), 112.1 (C-4a), 126.3, 126.4, 128.3, 128.8, 129.0, 129.2, 131.4, 132.3 (2 x NPh), 163.7 (C-10a), 165.3 (C-2), 165.8 (C-4), 176.0, 176.7, 177.8, 179.1 (4 x C=O). Isomer with lower Rf (SiO_2): m.p. 142-145 °C, ^{13}C NMR ($CDCl_3$) 20.3 (C-5), 26.0 (2-CH_3), 31.3 (C-10), 39.5/39.6/39.8/42.0 (C-6 to C-9), 54.0 (OCH_3), 112.2 (C-4a), 126.3, 126.4, 128.3, 128.9, 129.1, 129.3, 131.3, 132.5 (2 x NPh), 163.1 (C-10a), 165.5 (C-2), 166.0 (C-4), 175.9, 176.3, 176.6, 178.5 (4 x C=O).

12 The regiochemistry shown for **12** has not been confirmed and the *cis* and *trans* stereochemistry could not be assigned unambiguously. Isomer with higher Rf (SiO_2): m.p. 159-162 °C, ^{13}C NMR ($CDCl_3$) 21.0 (C-5), 21.2 (Ar-CH_3), 26.0 (2-CH_3), 35.0 (C-10), 38.5/39.9/41.2/42.1 (C-6 to C-9), 54.0 (OCH_3), 112.1 (C-4a), 126.2, 126.5, 128.9, 129.3, 129.7, 129.8, 131.5, 138.4 (NC_6H_5 and $NC_6H_4CH_3$), 163.8 (C-10a), 165.5 (C-2), 166.0 (C-4), 176.2, 176.8, 177.8, 179.3 (4 x C=O). Isomer with lower Rf (SiO_2): m.p. 155-158 °C ^{13}C NMR ($CDCl_3$) 20.1 (C-5), 21.1 (Ar-CH_3), 25.9 (2-CH_3), 31.2 (C-10), 39.4/39.6/39.7/41.9 (C-6 to C-9), 53.9 (OCH_3), 112.1 (C-4a), 126.0, 126.4, 128.7, 129.1, 129.7, 129.8, 131.4, 138.3 (NC_6H_5 and $NC_6H_4CH_3$), 163.1 (C-10a), 165.3 (C-2), 165.9 (C-4), 176.0, 176.4, 176.5, 178.6 (4 x C=O).

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