93. High-Pressure [2+4]-Cycloaddition of Dimethylmaleic Anhydride to 3,4-Dimethoxyfuran; Synthesis of Dimethoxycantharidin[1])

Preliminary Communication

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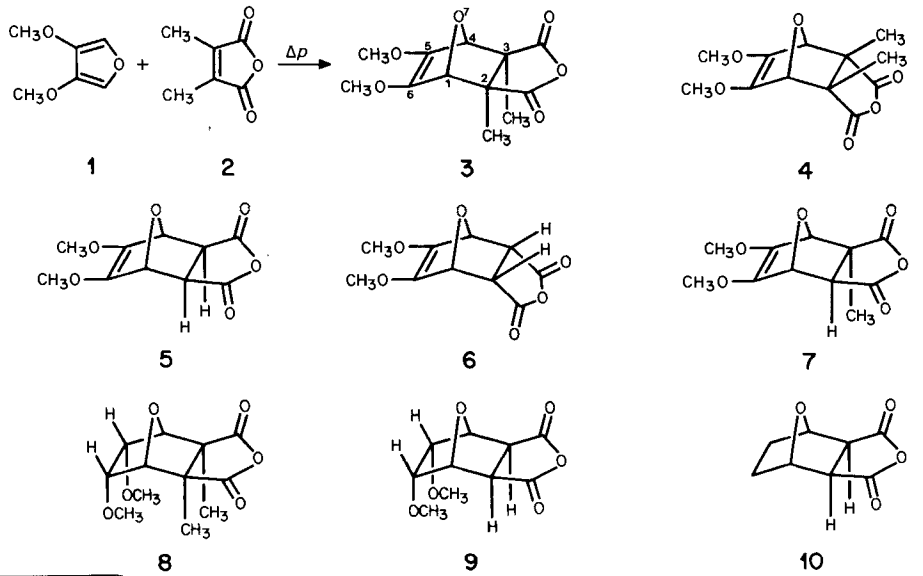
As an active diene (more active than furan itself), 3,4-dimethoxyfuran (**1**) affords with many dienophiles the respective cycloadducts in a high yield [2]. It has recently been found that under thermal conditions **1** easily reacts with maleic anhydride and its monomethyl derivative, but not with dimethylmaleic anhydride (**2**) [3]. This is probably due to steric hindrance resulting from the location of two methyl groups on the double bond of the dienophile. Since all *Diels-Alder* reactions – in particular those with steric hindrance – are pressure-sensitive [4], we resolved to perform the title reaction under conditions of static high pressure.

Scheme



[1]) Organic Syntheses under High Pressure. Part IV. For Part III see [1].

All experiments were carried out in a piston-cylinder high-pressure apparatus for pressures up to 32 kbar. The main features of this apparatus are outlined in [5]. The high-pressure vessel consisted of two external steel rings in which an internal conical steel vessel was placed. The internal high-pressure vessel (cylindrical volume about 70 ml) was closed from below with a steel stopper. All electrical connections (manganin manometer, thermocouple) were led through a conical electrode placed in the stopper. The internal vessel was closed from above by a mobile piston. Sealing of the piston and the stopper was attained using resin-O-rings and brass sealing rings. For the reactions performed at temperatures exceeding room temperature, an external heating jacket was used.

The high-pressure reaction between **1** and **2** was carried out for 6 h in toluene as solvent, at room temperature, under 22 kbar. The reaction mixture was placed in a *Teflon* ampoule *(Figure)* which was inserted into the high-pressure vessel filled with hexane as transmission medium.

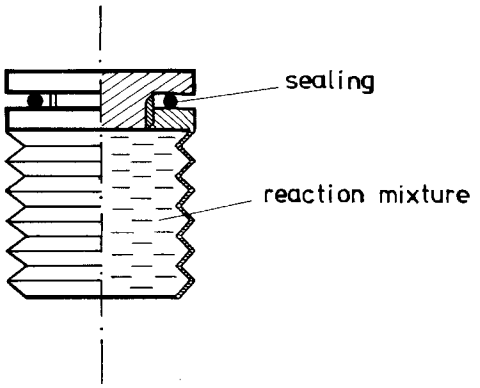


Figure. Teflon *ampoule*

After completion of the reaction the crystalline cycloadduct **3** precipitated from the solvent and was isolated by filtration, yield 50%. The filtrate was evaporated and the ^{1}H-NMR. spectrum of the residue showed that it still contained about 10% of **3**. Reactions performed at lower pressures, *e.g.* 10 kbar, neither at room temperature nor at 60° afforded (even after 16 h) the cycloadduct.

The cycloadduct **3**, $C_{12}H_{14}O_6$, m.p. 116°, is a single diastereomer, as shown by NMR. data *(Table 1)*. No **4** could be detected. Solutions in chloroform at room temperature and ordinary pressure slowly revert to the starting compounds. Mass spectra revealed the presence of the molecular ion (*m/z* 254) and of ions resulting from *retro*-diene cleavage (*m/z* 128 and 126). The IR. spectrum shows characteristic strong bands at 1845, 1763, 1688, 1380 and 1340 cm^{-1}.

Hydrogenation of the adduct **3** in the presence of 10% Pd/C at 5 atm in a methanolic solution gave a single stereoisomer **8**, $C_{12}H_{16}O_6$, m.p. 130–131°, in 95% yield. Comparison of the NMR. spectra of **3** and **8** with those of the model compounds **5–7** [3], and of **9** [3] and **10** [6], respectively (s. *Table*), clearly shows that the former has the proposed structure **3** and that hydrogenation has occurred from the *exo*-face to yield exclusively **8**.

Therefore, **3** is 5,6-dimethoxy-2*endo*, 3*endo*-dimethyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride, and its hydrogenation product **8** is 5*endo*, 6*endo*-

Table. *NMR. spectra of* **3**, **8** *and related compounds*

^{1}H-NMR.	**3**, m.p. 116°[a])	**5**, m.p. 94.5–95.5°[b])	**6**[c])	**7**[d])	**8**, m.p. 130–131°[a])	**9**, m.p. 118°[b])	**10**, m.p. 116–117°[g])
H–C(2) and H–C(3)	–	3.48 *s*	3.95 *m*	3.10 *s*	–	3.72 *s*	3.04 *s*
H_3C–C(2) and H_3C–C(3)	1.29 *s*	–	–	1.43 *s*	1.53 *s*	–	–
H–C(1) and H–C(4)	4.38 *s*	5.11 *s*	5.20 *m*	4.82 and 5.02 each br.*s*	4.73 *d*×*d*[e])	5.03 *m*	4.90 *d*×*d*[h])
H–C(5) and H–C(6)	–	–	–	–	3.91 *d*×*d*[f])	3.77 *m*	1.80/1.60 *m*[i])
CH_3O–C(5) and CH_3O–C(6)	3.78 *s*	3.76 *s*	3.70 *s*	3.77 *s*	3.46 *s*	3.47 *s*	
^{13}C-NMR.	[a])	[a])			[a])		[a])
CH_3–C(2) and CH_3–C(3)	13.1	–			11.4		–
C(2) and C(3)	57.1	50.7			55.9		52.6
CH_3O–C(5) and CH_3O–C(6)	58.9	59.3			59.4		–
C(1) and C(4)	85.2	81.7			83.5		78.7
C(5) and C(6)	139.0	139.2			78.4		29.1
C(O)OC(O)	174.5	170.0			175.8		174.1

[a]) This paper; $CDCl_3$, 80 (20) MHz.
[b]) $CDCl_3$, 100 MHz [3].
[c]) Compound **3** in [3], supplementary data.
[d]) Compound **2** in [3], *Table 1*, supplementary data.
[e]) $^3J = 3.22$ and $^4J = 2.21$ Hz.
[f]) $^3J = 3.22$ and $^4J = 2.13$ Hz.
[g]) Ref. [6], supplementary data, $CDCl_3$, 200 MHz, $CDCl_3/D_6$-acetone *ca.* 5:1.
[h]) $^3J = 3.20$ and $^4J = 2.22$ Hz.
[i]) High field signal corresponds to H_{endo}

dimethoxy-2*endo*, 3*endo*-dimethyl-7-oxabicyclo[2.2.1]heptane-2, 3-dicarboxylic anhydride. Remarkably, **8** has the same configuration as cantharidin [7–9].

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