

DIELS-ALDER REACTION OF FURAN WITH SOME DIENOPHILES

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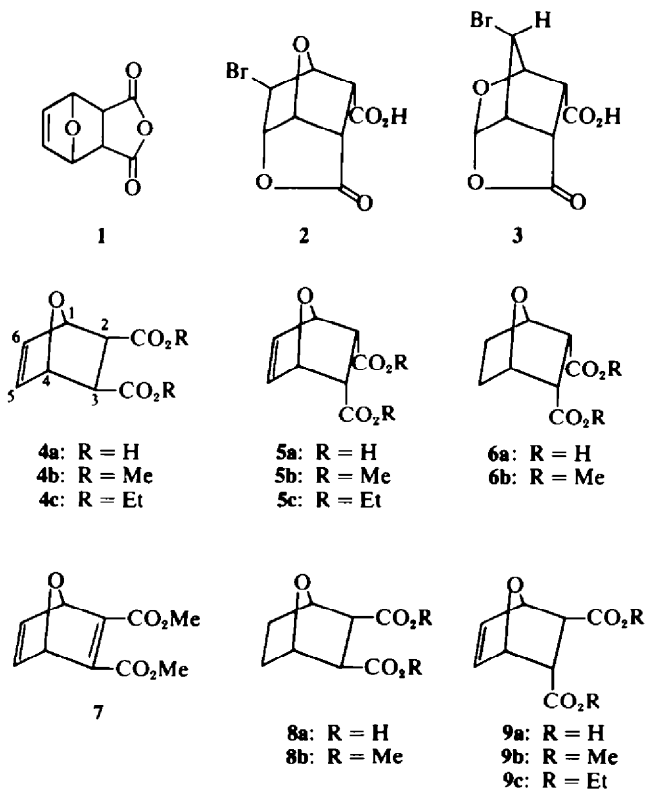
Abstract—The reaction of furan and maleic acid was carried out in several solvents. The *endo*-adduct was isolated and the structure established by its spectral properties and conversion into known compounds. The adducts of furan with fumaric acid, diethyl fumarate and diethyl maleate are reported.

The reaction between furan and maleic anhydride was first investigated by Diels and Alder.¹ They assigned structure 1 to the crystalline adduct obtained from reaction in ether. Diels and Alder² observed that furan dissolved slowly in an aqueous solution of maleic acid with formation of an adduct, which was not isolated, but could be converted

into bromolactone 2 by treatment of the reaction mixture with bromine. The authors assumed that the acid obtained on hydrolysis of 1, was identical with the adduct obtained from the reaction carried out in water; so adduct 1 should have the *endo*-configuration, analogous to the adduct of cyclopentadiene and maleic anhydride.³ Woodward and Baer⁴ showed that assignment of *endo*-configuration to adduct 1 was incorrect and that treatment of 1 with dilute base and bromine afforded bromolactone 3, which was formed *via* a Wagner–Meerwein

^aTaken in part from the forthcoming doctorate dissertation of T. A. Eggelte.

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rearrangement from *exo*-acid **4a**. They did not succeed in isolating *endo* acid **5a**, the adduct formed when the reaction was carried out in water. All attempts resulted only in isolation of maleic acid, indicating that the reaction is readily reversible. Bearson and Swidler⁵ studied the kinetics of the reaction carried out in water, which was found to proceed in a non-stereospecific way. Both *exo*- and *endo*-adduct **4a** and **5a** were formed, their ratio depending on the time of reaction. These results were confirmed by Stockmann⁶—using a titrimetric determination method—and by Anet, who carried out the reaction in D₂O, analysing the reaction mixture with NMR.⁷

The impossibility to isolate until now the *endo*-acid **5a** from the reaction between furan and maleic acid, is due to the reversibility of the reaction. Attempted isolation by evaporation of the solvent or by extraction after acidification of the reaction mixture yielded maleic acid only.⁴

In our opinion, it should be possible to induce crystallisation of **5a** from the reaction mixture. However, no product separated from the mixture upon cooling, even when high concentrations of reactants were used. Finally, some crystals of **5a** were obtained from a reaction mixture by leaving it at room temperature for a week. Seeding a cooled reaction mixture with these crystals caused rapid crystallisation of *endo*-adduct **5a**, which could be obtained in fair yield (43%). The compound* is stable in crystalline form and shows a m.p. of 148–149° (dec). The structure of **5a** was evidenced by NMR spectroscopy and by chemical conversions into known compounds.

NMR. In Table 1 the chemical shifts of the protons in compounds **4a** and **5a** are given, and com-

*Satisfactory analytical (C, H) data were obtained for this compound.

†Values of $\delta = 2.66$ for the *exo*- and $\delta = 3.30$ for the *endo*-compound were found.

pared with those listed in the literature. The NMR spectra of **4a** and **5a** show a significant difference in chemical shift and multiplicity of protons at C₂ and C₃ in *exo*- and *endo*-positions. The *endo*-protons of **4a** appear in the spectrum as a singlet, while the *exo*-protons in **5a** appear as a four-line pattern down-field compared to the *endo*-protons in **4a**. From molecular models of **4a** it can be seen that the torsion angle between the protons at C₁ and C₂ and also at C₃ and C₄ is about 90°, which would account for a singlet for the *endo*-protons. The difference in chemical shift (~0.6 ppm) between the protons at C₂ and C₃ in *endo*- and *exo*-positions in **4a** and **5a** is due to a shielding effect of the olefine double bond. A deshielding effect of the oxygen bridge—as suggested by Nelson⁸ for similar compounds—is unlikely, because about the same difference† in chemical shift between *endo*- and *exo*-protons is found when in compounds **4b** and **5b** the oxygen bridge is replaced by a methylene group.

Chemical methods. The structure of *endo*-adduct **5a** was evidenced by conversion into known compounds and comparison with corresponding compounds in the *exo*-series.

Catalytic hydrogenation of **5a** in methanol over 10% Pd/C catalyst gave *endo*-acid **6a**, which could be esterified with diazomethane to give **6b**. Ester **6b** was also obtained by catalytic hydrogenation of **7**, the Diels–Alder adduct of furan and dimethyl acetylenedicarboxylate.² Hydrogenation of **4a** gave **8a** and subsequent esterification with diazomethane afforded ester **8b**. Esterification of **4a** and **5a** yielded **4b** and **5b**, respectively. Both **4b** and **5b** could be isomerized with NaOMe/MeOH to the *trans*-ester **9b** (m.p. 90–91°). The structures of compounds **4–9** were evidenced by their NMR spectra (Table 1): their m.ps were in agreement with those listed in the literature, as far as known. Treatment of **5a** with base and bromine⁵ afforded bromolactone **2**.

The Diels–Alder reaction of furan and maleic acid has always been carried out in water. We have

Table 1. Chemical shifts of some 2,3-substituted 7-oxabicyclo[2.2.1]heptane derivatives

	C ₂ —H, C ₃ —H	C ₁ , C ₄	C ₅ , C ₆	—OCH ₃
4a	2.61, ^a 2.95, ^b (2.9) ^c	5.03, ^a 5.26, ^b (5.2) ^c	6.42, ^a 6.60, ^b (6.50) ^c	3.68
b	2.82 ^d	5.23 ^d	6.45 ^d	
5a	3.25, ^a 3.55, ^b (3.5) ^c	5.01, ^a 5.21, ^b (5.2) ^c	6.42, ^a 6.52, ^b (6.5) ^c	
b	3.41 ^d	5.10 ^d	6.52 ^d	3.62
6a	3.06 ^a	4.59 ^a	{ 1.3–1.75 and 1.75–2.15 ^a	
b	3.23 ^d	4.71 ^d	1.5–2.2 ^d	3.66
8a	2.91 ^a	4.68 ^a	1.52 ^a	
b	3.11, ^a 3.0 ^d	4.76, ^a 4.88 ^d	1.55, ^a 1.4–2.0 ^d	3.51 ^a and 3.65 ^d
9a	2.60 (<i>endo</i>), 3.35 (<i>exo</i>) ^a	5.1 ^a	6.25–6.7 ^a	
b	2.89 (<i>endo</i>), 3.67 (<i>exo</i>) ^d	5.3 ^d	6.3–6.75 ^d	3.69 and 3.77

^aDMSO-d₆

^bD₂O

^cSee ref. 7

^dCDCl₃

also used CD₃OD and DMSO-d₆ as solvents, analysing the reaction mixtures with NMR. It turned out that the reaction in D₂O was faster than the reaction in other solvents. After reaction for 5 days at room temperature, we observed the following conversions:

D₂O ≈ 55%, CD₃OD ≈ 33%, DMSO-d₆ ≈ 10%. There was hardly an effect on the ratio of *endo* to *exo*-adducts formed during the reactions (about 2.2:1). If we take into account that—in contrast to the other solvents—the reaction in water is heterogeneous, the reaction in D₂O is much faster than the reaction in CD₃OD and DMSO-d₆. This finding is rather surprising because there is only found a slight influence of the solvent on the Diels–Alder reaction.⁹

Reaction of furan and fumaric acid in DMSO-d₆ at room temperature for one month gave rise to the formation of adduct **9a**, which is formed slower than the adduct of furan and maleic acid. The *trans*-acid **9a** could be obtained in low yield from a reaction in DMSO by addition of water—which caused precipitation of unreacted fumaric acid—and leaving the filtrate after acidification for several days at 5°, during which time the *trans*-acid **9a** slowly crystallized from the solution. The compound* is stable in crystalline form and sublimes at *c* 175°.

According to the literature¹⁰ dimethyl maleate does not give a Diels–Alder reaction with furan under a wide variety of conditions. We carried out the reaction of diethyl maleate and an excess of furan without solvent and observed the formation of adduct **5c**. Reaction at room temperature for one month gave 18% and for two months 33% conversion. While in the reaction of furan with maleic acid a considerable amount of *exo*-adduct is also

formed, only a very small amount of *exo*-adduct **4c** is formed in the reaction with diethyl maleate (about 2% after two months). The *endo*-adduct **5c** can be isolated by column chromatography. Considering our observation that even attempted short path distillation of **5b** *in vacuo* already causes considerable fragmentation into furan and dimethyl maleate, failure to detect a Diels–Alder adduct by attempted isolation in the literature¹⁰ is not surprising.

Similar reaction of furan and diethyl fumarate led to the formation of adduct **9c**, which is formed faster than the adduct of furan and diethyl maleate. After reaction for two months at room temperature the NMR spectrum of the reaction mixture showed the same conversion (~40%) as after one month. Apparently, the formation of adduct **9c** reaches an equilibrium which might also be concluded from the observation that, when the reaction mixture was separated over a silica gel column, the NMR spectrum of the obtained product (oil) showed the presence of considerable amounts of diethyl fumarate and furan.

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*See footnote on p. 2.