The Chemistry of Heterocycles

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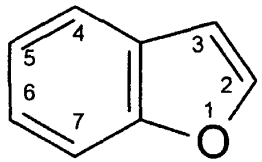
The Chemistry of Heterocycles, (Second Edition).

By Theophil Eicher and Siegfried Hauptmann, Wiley-VCH Veriag GmbH, 2003

5.2 Benzo[*b*]furan

[A] Benzo[*b*]furan, often called benzofuran, shows the following UV absorption bands and NMR signals:



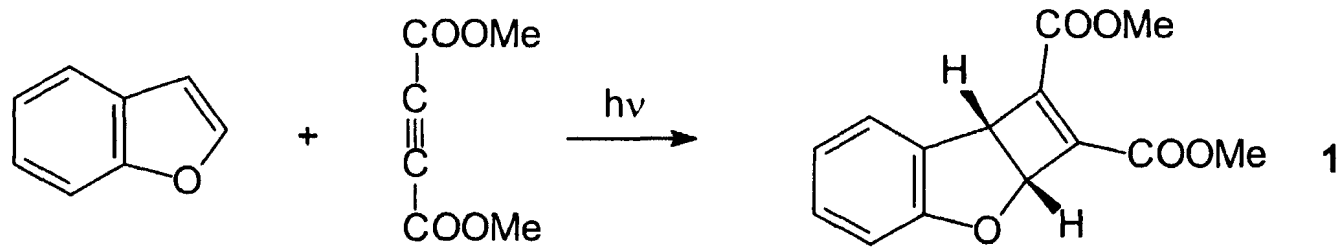
UV (ethanol)	^{1}H-NMR (acetone-d_6)		^{13}C-NMR (CS_2)	
λ (nm) (ε)	δ (ppm)		δ (ppm)	
244 (4.03)	H-2: 7.79	H-6: 7.30	C-2: 141.5	C-6: 124.6
274 (3.39)	H-3: 6.77	H-7: 7.52	C-3: 106.9	C-7: 111.8
281 (3.42)	H-4: 7.64		C-4: 121.6	C-3a: 127.9
	H-5: 7.23		C-5: 123.2	C-7a: 155.5

The signals for the furan protons again are found in the region of benzenoid protons. The C-2/C-3 bond, in contrast, behaves chemically rather like a localized olefinic double bond, i.e. it undergoes addition reactions.

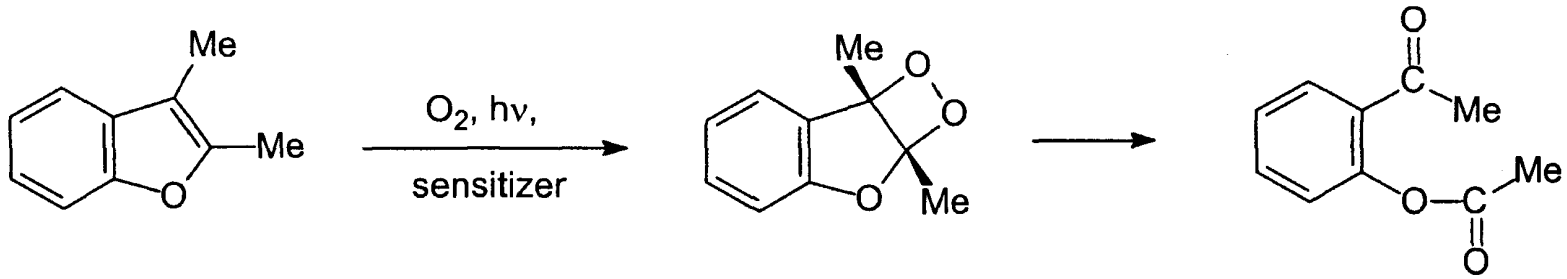
[B] Benzo[*b*]furan, when treated with nitric and acetic acids, yields 2-nitrobenzo[*b*]furan. When the VILSMEIER formylation is used, 2-benzo[*b*]furaldehyde is obtained, and 2-lithiobenzo[*b*]furans are formed with butyllithium.

With addition of bromine, benzo[*b*]furan reacts to give *trans*-2,3-dibromo-2,3-dihydrobenzo[*b*]furan. On dehydrobromination, this compound yields a mixture of 2-bromo- and 3-bromobenzo[*b*]furan.

In contrast to furan, the benzene ring in benzo[*b*]furan (because of its large resonance energy) is dominant to such an extent that [4+2] cycloadditions are not possible. On the other hand, photochemical [2+2] cycloaddition occurs readily on the C-2/C-3 double bond leading, e.g. with an acetylene dicarboxylic ester, to the cyclobutene derivative **1**:

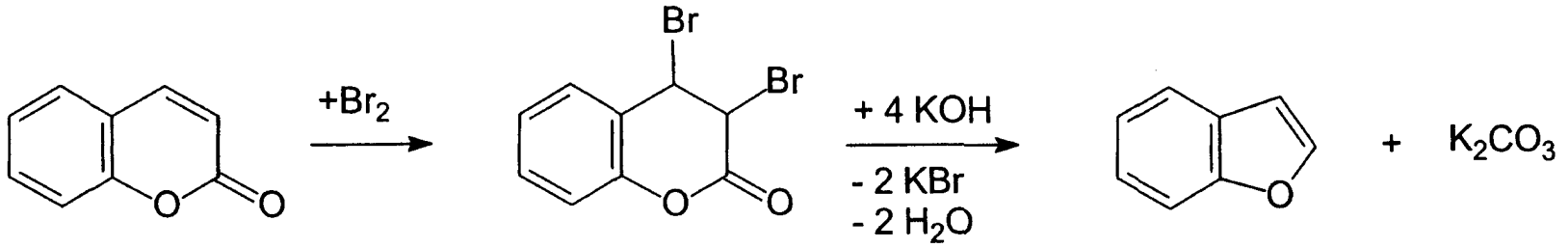


Photooxygenation of 2,3-dimethylbenzo[*b*]furan at -78 °C produces a dioxetane which isomerizes at room temperature to give 2-acetoxyacetophenone:



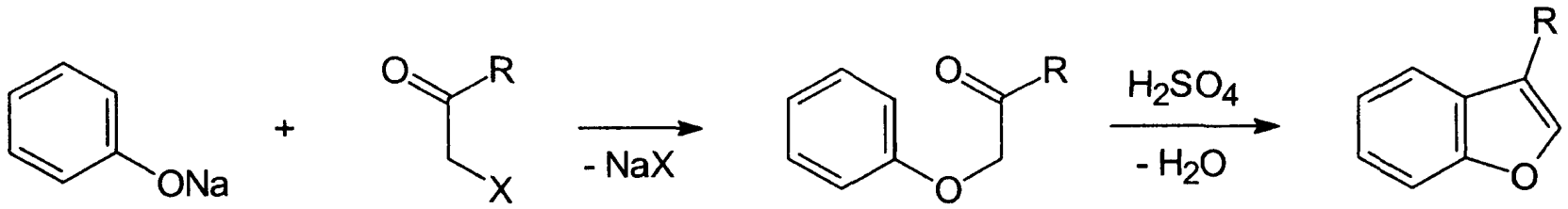
The reactivity of the C-2/C-3 double bond in benzo[*b*]furan corresponds approximately to that of a vinyl ether.

[C] Benzo[*b*]furan was first prepared from coumarin as follows:

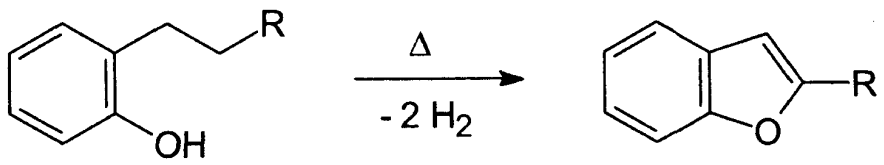


The name coumarone, which was previously used for benzo[*b*]furan, originates from this synthesis. The reaction of the intermediate 3,4-dibromo-3,4-dihydrocoumarin with KOH leading to benzofuran is known as PERKIN rearrangement.

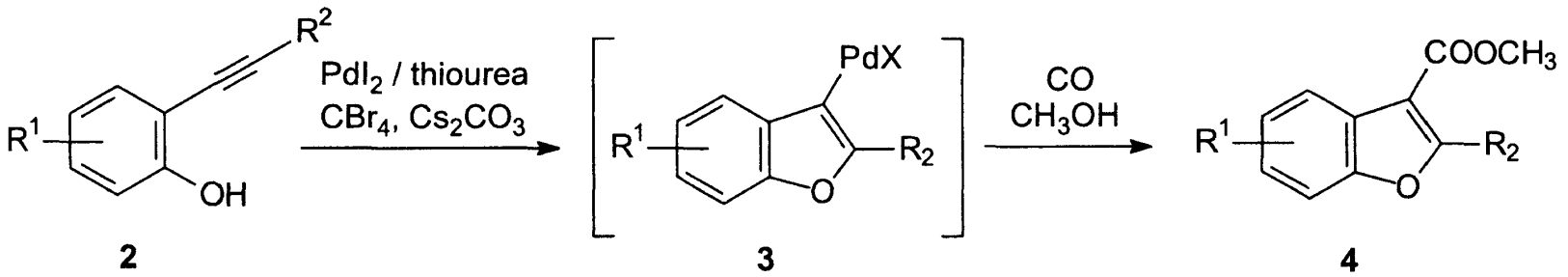
Benzo[*b*]furans are also accessible by reaction of phenolates with halo ketones followed by cyclodehydration with H_2SO_4, polyphosphoric acid or zeolites:



In contrast, the thermal cyclodehydration of 2-alkylphenols leads to 2-alkylbenzo[*b*]furans:



(*o*-Hydroxyaryl)acetylenes **2** can be subjected to transition-metal mediated cyclization by means of a PdI_2 / thiourea / CBr_4 cocatalysis system followed by carbonylation of the Pd-intermediate (simplified as **3**) in methanol to give methyl benzo[*b*]furan-3-carboxylates **4**:

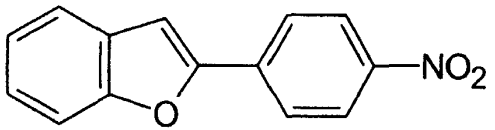


2 **3** **4**

[D] Benzo[*b*]furan, a colorless, oily, water-insoluble liquid, bp 173 °C, occurs in coal tar. It is probably formed during coal carbonization by cyclodehydration of 2-ethylphenol.

Copolymerization of indene in the presence of BRÖNSTED or LEWIS acids yields the so-called coumarone resins, which find use in industry (adhesives, paints, binders).

Several natural products and pharmaceuticals are derived from benzo[*b*]furan, e.g. the bacteriocidal 2-(4-nitrophenyl)benzo[*b*]furan **5**. Amiodarone **6**, a substituted 3-benzoyl-2-butylbenzo[*b*]furan, is used in the treatment of cardiac arrhythmia:



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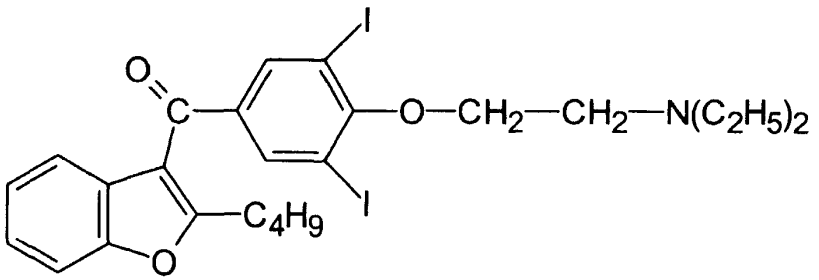

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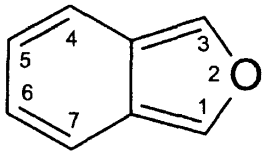
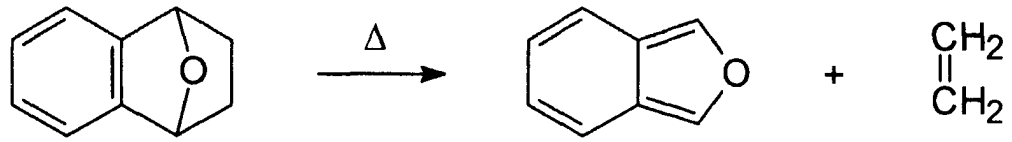
5.3 Isobenzofuran



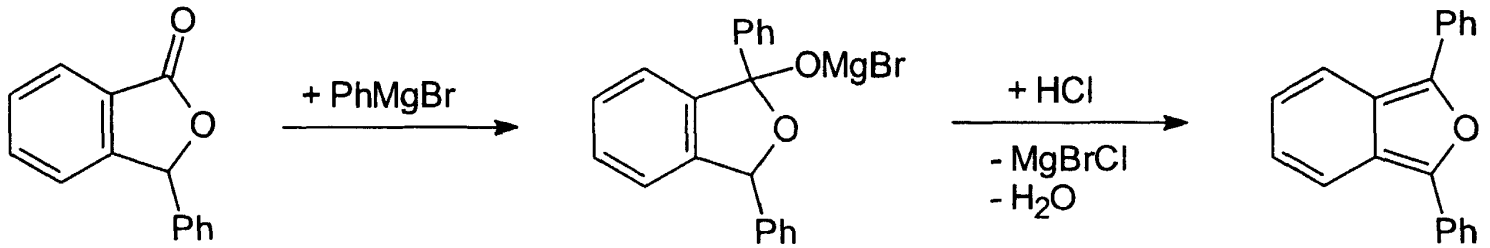
[A-D] The name isobenzofuran is retained for benzo[c]furan. It is apparent from its structure that the six-membered ring does not possess a π-electron sextet, but that the compound is of an orthoquinonoid type.

The resonance energy of isobenzofuran is thus much less than that of benzo[*b*]furan. As a consequence, isobenzofuran has so far not been isolated as a pure substance. It is formed by flash vacuum pyrolysis of benzo[*b*]-7-oxabicyclo[2.2.1]hept-2-ene **1**, and it polymerizes rapidly even at low temperature.



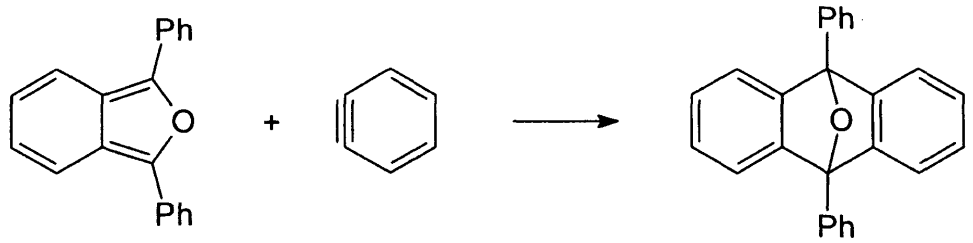
1

In contrast, 1,3-diphenylisobenzofuran **3** can be prepared from 3-phenyl-1,3-dihydroisobenzofuran-1-one **2** as follows:



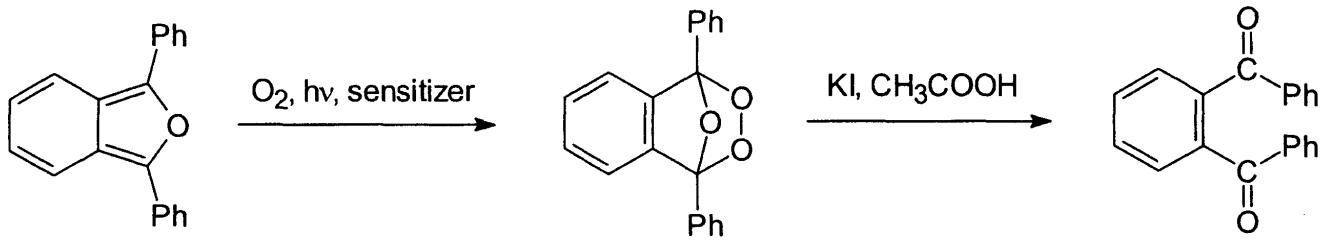
2 **3**

The intensely yellow compound melts at 127 °C. Its solution exhibits a blue-green fluorescence. 1,3-Diphenylisobenzofuran proves to be an extremely reactive diene in [4+2] cycloadditions. It is used to trap unstable alkenes or acetylenes, e.g. 1,2-dehydrobenzene (benzyne) with formation of the adduct **4**:



4

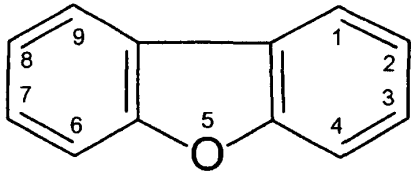
The photooxygenation occurs at -50 °C as a [4+2] cycloaddition in an analogous way, but differently to that of benzo[*b*]furan. The product **5** is reduced by potassium iodide in acetic acid to 1,2-dibenzoylbenzene:



5

The reactions of 1,3-diphenylisobenzofuran are characterized by the fact that the orthoquinonoid structure can transform into a benzenoid structure with a π-electron sextet, thereby liberating resonance energy.

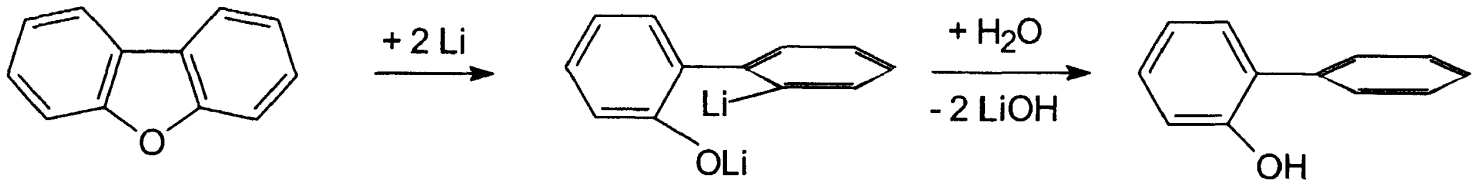
5.4 Dibenzofuran



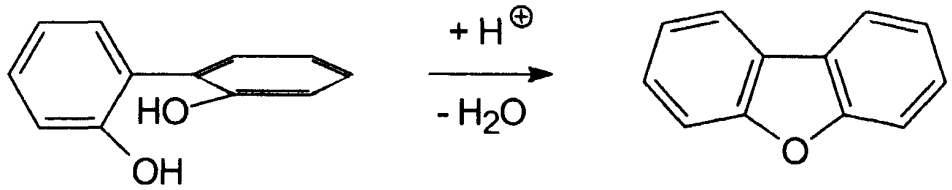
[A-D] The designation [*b,d*] can be omitted, as no other ring fusion can exist. Dibenzofuran was previously known as diphenylene oxide.

Dibenzofurans behave like *o,o'*-disubstituted diphenyl ethers, i.e. they undergo substitution reactions typical for benzenoid compounds. Halogenation, sulfonation and acylation occur in the 2-position, and subsequently 2,8-disubstituted compounds are formed. Nitration yields 3-nitro- and then 3,8-dinitro compounds.

Lithiation and mercuration lead to 4-substituted and finally to 4,6-disubstituted products. The action of lithium in boiling dioxan causes 'ether fission' of dibenzofuran. On hydrolysis, the product yields 2-hydroxybiphenyl:



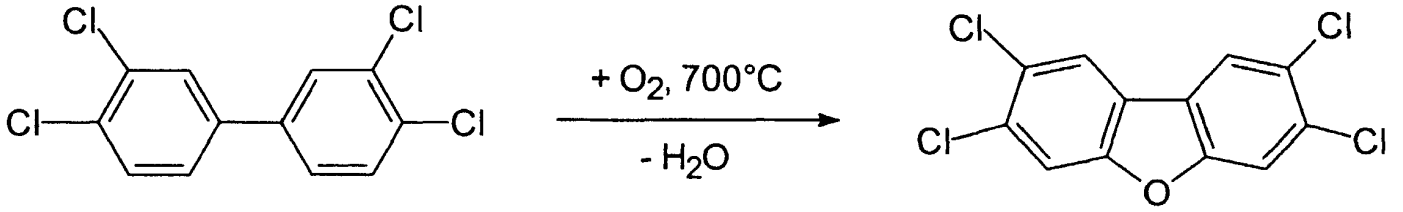
Dibenzofuran is conveniently prepared by the acid-catalyzed dehydration of 2,2'-dihydroxybiphenyl:



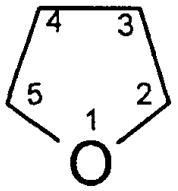
Dibenzofuran, colorless, fluorescent crystals, mp 86 °C, bp 287 °C, occurs in coal tar.

2,3,7,8-Tetrachlorodibenzofuran and other polychlorodibenzofurans (abbreviated PCDFs) are extremely toxic and, like 2,3,7,8-tetrachlorodibenzo[1,4]dioxin, belong to a group of compounds known as supertoxins. The lethal dose for monkeys lies in the region of 0.07 mg/kg body weight.

PCDFs are formed in traces during the industrial production of polychlorobenzenes, polychlorophenols and polychlorobiphenyls, as well as during the combustion or thermal decomposition of products which contain such compounds. Among these are pesticides, wood preserved with polychlorophenols, as well as transformer oils, e.g.:

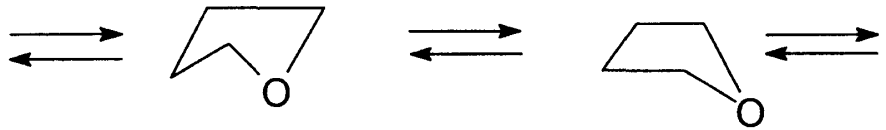


5.5 Tetrahydrofuran



[A] The C-O and C-C bond lengths in tetrahydrofuran (oxolan) are 142.8 and 153.5 pm, respectively. These values are close to the corresponding bond lengths in dialkyl ethers.

The ring is virtually strain-free, but not planar. There are 10 twist and 10 envelope conformations which interconvert rapidly through pseudorotation (activation energy 0.7 kJ mol^{-1}). This results in a molecule which has almost free conformational mobility.



twist
(half-chair)

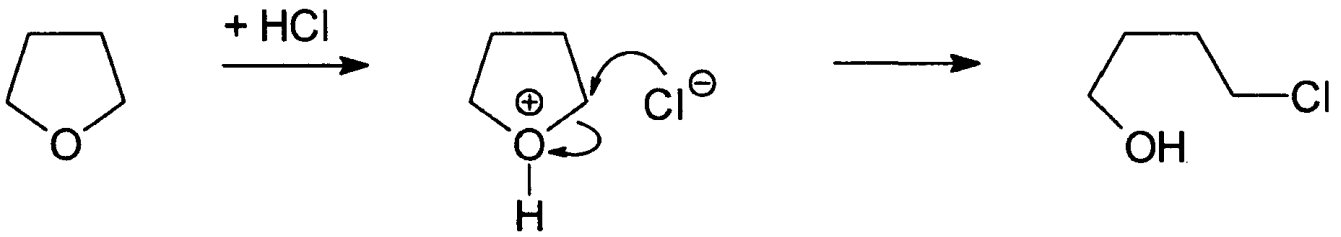
envelope

Three ring atoms are coplanar in the twist conformation and four in the envelope conformation. The chemical shifts of the H- and C-atoms of tetrahydrofuran in the NMR spectra are as follows:

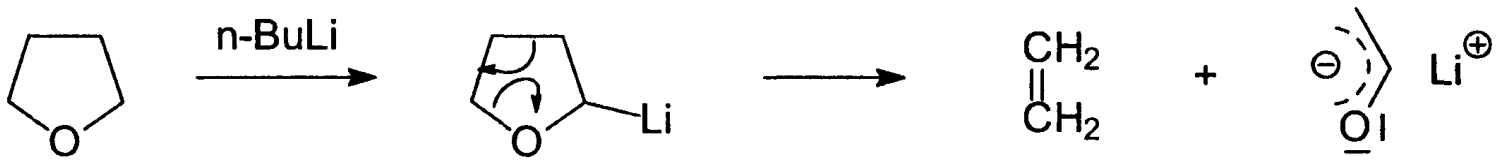
^{1}H-NMR (CCl_4) δ (ppm)		^{13}C-NMR (D_2O) δ (ppm)	
H-2/H-5:	3.61	C-2/C-5:	68.60
H-3/H-4:	1.79	C-3/C-4:	26.20

These values are typical for dialkyl ethers and are significantly different from those of furan.

[B] By analogy with oxetanes, tetrahydrofurans are ring-opened by nucleophiles. For example, 4-chlorobutan-1-ol is obtained on heating tetrahydrofuran with hydrochloric acid:

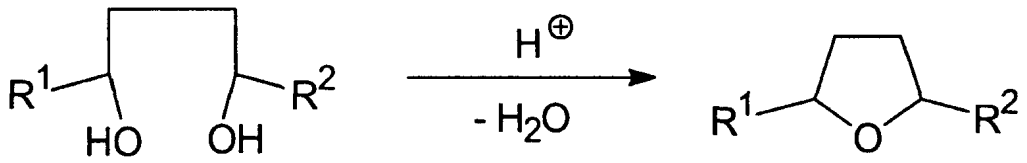


Lithium alkyls, e.g. *n*-butyllithium, also effect ring-opening. First, 2-lithiotetrahydrofuran is formed, which at room temperature slowly decomposes through a [3+2] cycloreversion into ethene and the lithium enolate of acetaldehyde:



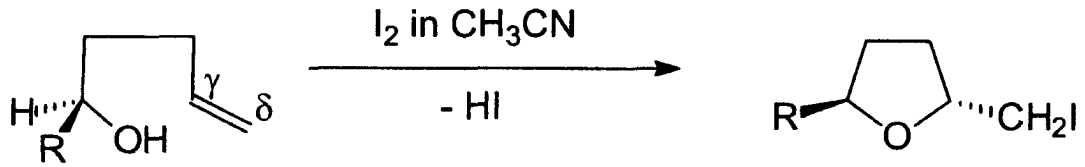
Tetrahydrofurans thus behave essentially like dialkyl ethers.

[C] The simplest method for obtaining tetrahydrofurans is by cyclodehydration of 1,4-diols:



Tetrahydrofuran is produced industrially by catalytic cyclodehydration of butane-1,4-diol.

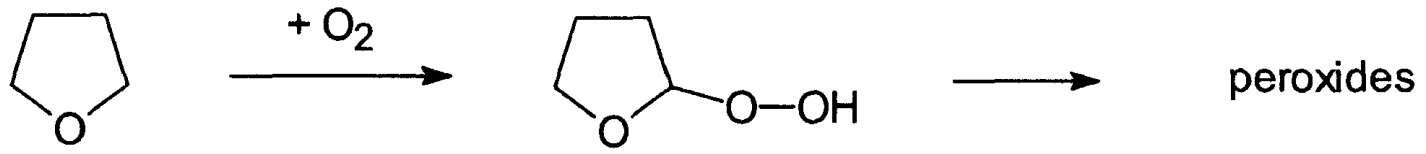
A further method for the synthesis of tetrahydrofurans is the cyclization of appropriately substituted γ,δ-unsaturated alcohols **1**:



1 **2**

This reaction differs from a simple cyclization because of the introduction of the iodomethyl group in addition to ring formation. The reaction proceeds diastereoselectively producing a *trans*-2,5-disubstituted tetrahydrofuran **2**.

[D] Tetrahydrofuran, often abbreviated as THF, is a colorless, water-soluble liquid of pleasant odor, bp 64.5 °C. Inhalation of its vapors leads to severe poisoning. When stored in air, tetrahydrofuran is converted to a hydroperoxide by autoxidation:



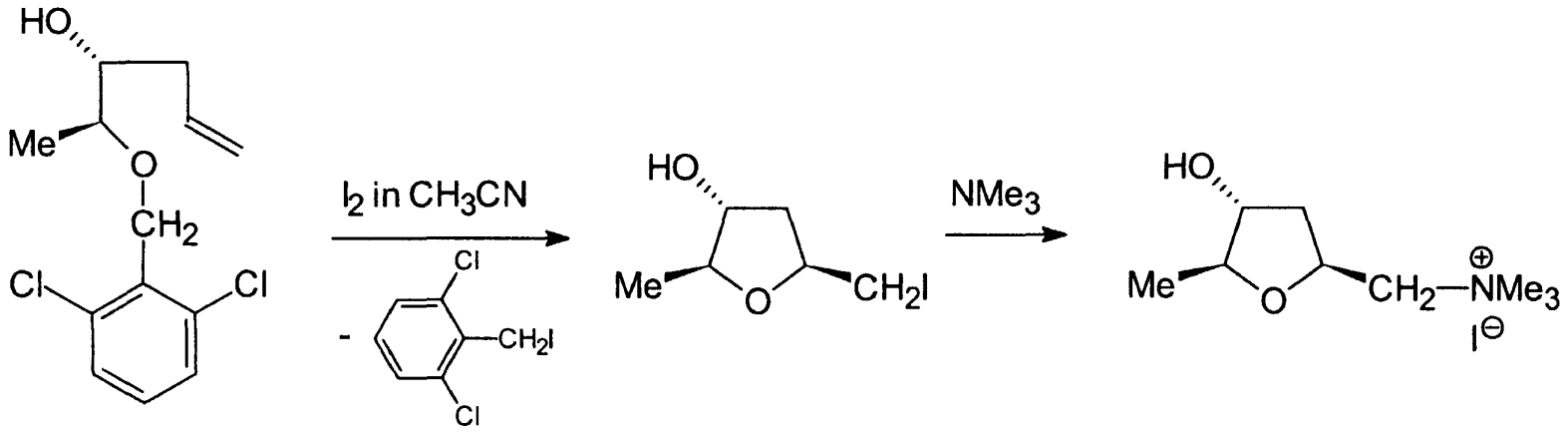
This can easily be demonstrated by the liberation of iodine upon the addition of potassium iodide. The hydroperoxide transforms to highly explosive peroxides.

Tetrahydrofuran is used as a solvent, especially for GRIGNARD reactions, and at low temperature also for the preparation of organolithium compounds.

Many natural products are derived from tetrahydrofuran. Of great biological importance are those carbohydrates (pentoses, and to a lesser extent hexoses and glycosides derived therefrom), which contain a tetrahydrofuran ring and which are therefore known as 'furanoses'.

Muscarine **5**, one of the active ingredients in the toadstool fly agaric (*Amanita muscarid*), contains a 2,3,5-trisubstituted tetrahydrofuran structure. A number of stereocontrolled syntheses have been worked out for muscarine.

One of these starts with methyl vinyl ketone and cyclizes stereoselectively the appropriately substituted γ,δ-unsaturated 2,6-dichlorobenzyl ether **3** with iodine:

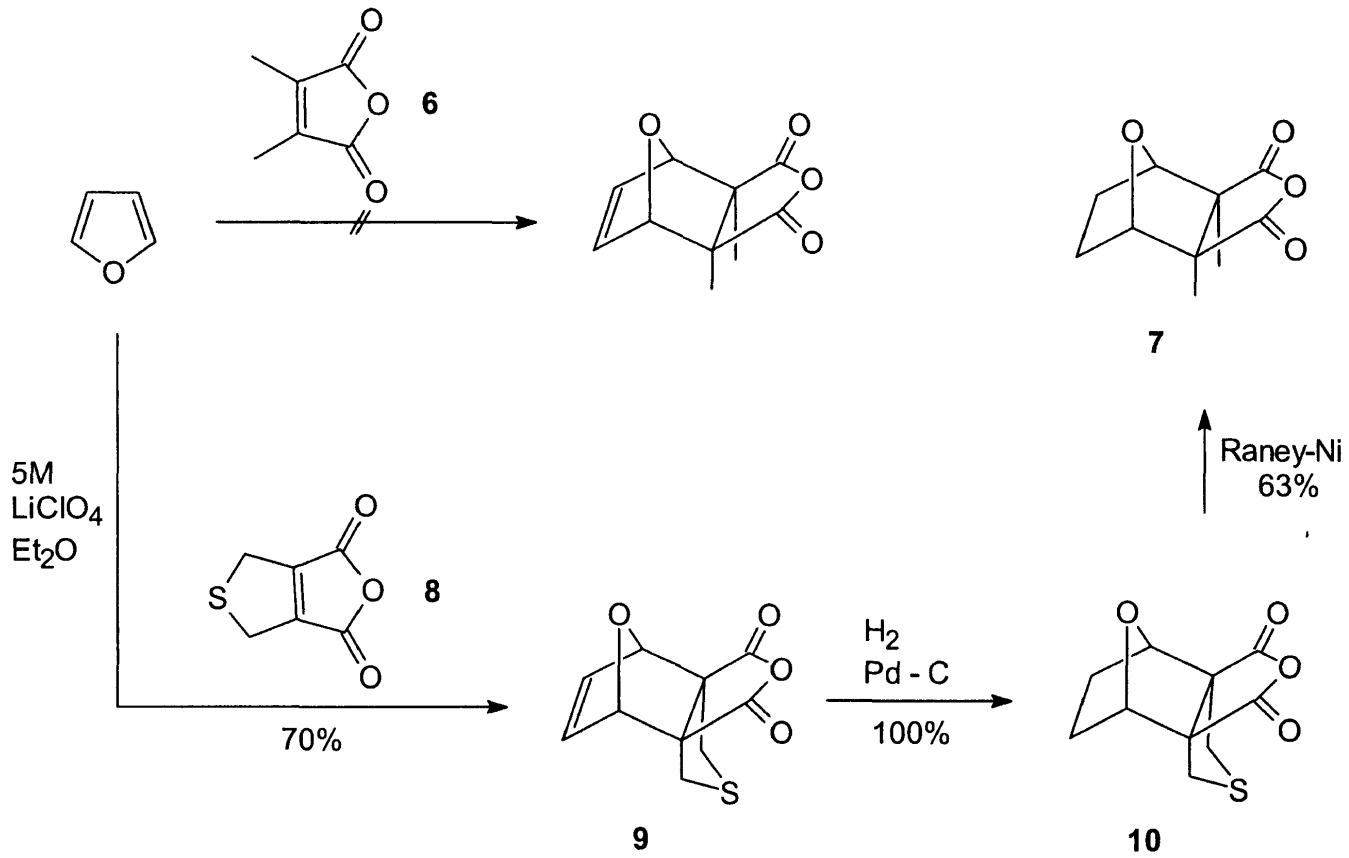


3 **4** **5**

Differently to the alcohol **1**, the diastereomer **4** is formed, whose 2,5-substitutents are in the *cis* configuration; on reaction with triethylamine **4** is transformed to (+)-muscarine **5**.

Cantharidin **7** is the poison of the cantharis beetles, among them the Spanish fly, native to Southern Europe. Cantharidin is a skin irritant and vesicant.

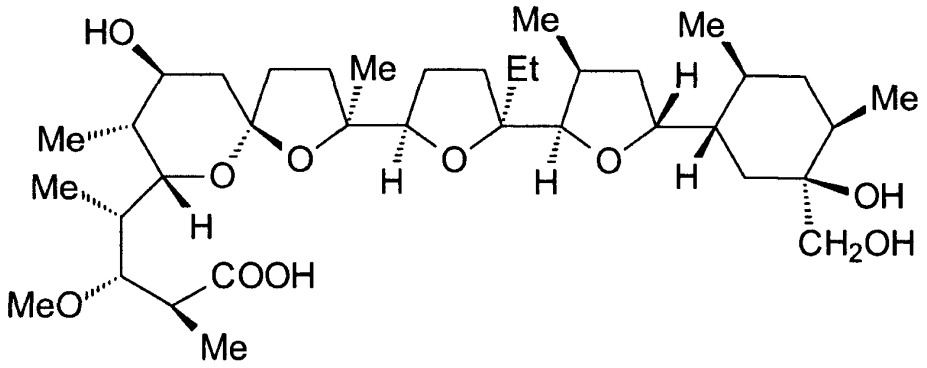
The direct synthesis of Cantharidin by a DIELS-ALDER reaction of furan with dimethyl maleic anhydride **6** is not possible. However, cycloaddition can be carried out with 2,5-dihydrothiophene-3,4- dicarboxylic acid anhydride **8** as dienophile. The cycloadduct **9** (*exo*/*endo* mixture 85:15) is subsequently hydrogenated and the tetrahydrothiophene ring in **10** is cleaved by a reductive desulfurization:



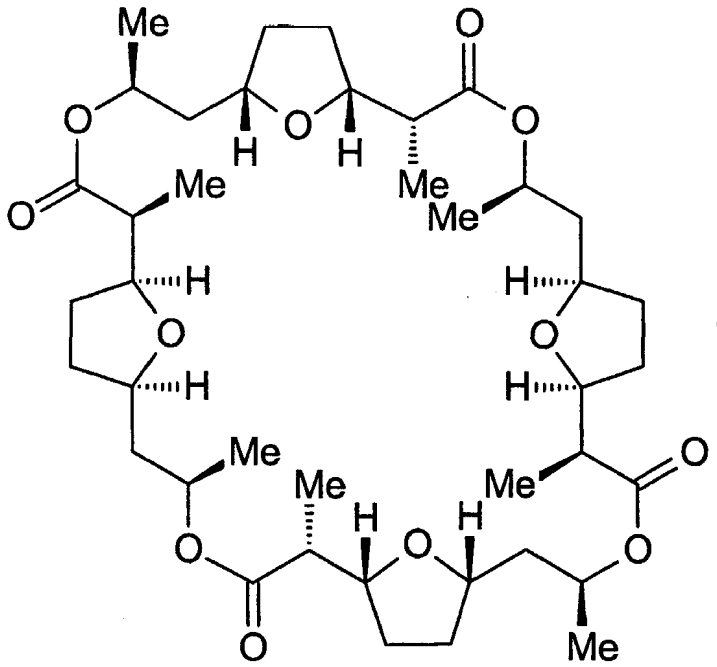
Polyether antibiotics contain tetrahydrofuran rings, in monensin **11**, three tetrahydrofuran rings are linearly connected. The molecule contains **17** asymmetric centres.

In nonactin **12**, the rings are interconnected in an $\alpha.\alpha$'-orientation via ester groupings. Nonactin is therefore classed as a macrolide antibiotic.

Polyethers of the type **11**/**12** are capable of facilitating ion transport across biological membranes; they are, therefore, also known as ionophores.



11



12

Organic compounds have essential information about their reactivity encoded in their structural formulae from which their reactivity can be deduced. Furan, benzo[*b*]furan, isobenzofuran, dibenzofuran and tetrahydrofuran are good examples of this.