Dimethyldioxirane Epoxidation of 3-Phenyl-Substituted Benzofurans: A Reversible Valence Isomerization between Benzofuran Epoxides and Quinone Methides

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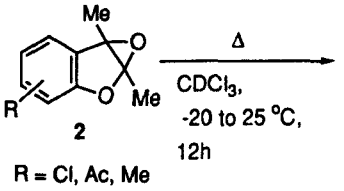
Received 3 September 1993

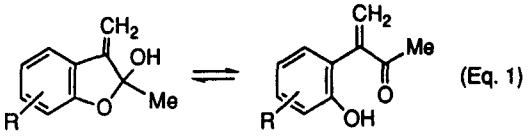
Low-temperature oxidation of the phenyl-substituted benzofurans **1** by dimethyldioxirane afforded the rather labile benzofuran epoxides **2**, which are in equilibrium with their equally labile quinone methides **3** through valence isomerization. This reversible valence isomerization was established on the basis of the chemical transformations displayed by the benzofuran epoxides **2** and quinone methides **3**. These include tetraethylammonium bromide catalyzed rearrangement of epoxide **2a** to benzofuran-2-one **4a**, dimerization of quinone methide **3c** to dibenzofurodioxane **4c**, nucleophilic trapping by methanol in the form of the adducts **5**, the 1,3-dipolar cycloaddition with tetracyanoethylene (TCNE) to afford **6**, and the inverse Diels–Alder reaction to the [4+2] cycloadducts **7** with ethyl vinyl ether. Also styrene gave with epoxide **2a** the benzodihydropyran **8a** through cycloaddition to its quinone methide valence isomer **3a**, while with acetic anhydride the diacetylated adduct **9a** was obtained. The driving force for these latter transformations derives from strain relief and aromatization. The labile benzofuran epoxides function as effective alkylating agents, which add nucleophiles at subambient temperatures without acid and base activation.

Benzofurans are known to be cytotoxic to animals and man, yet they have been widely employed as food additives.[1] For example, it has been shown that furans oxidized by cytochrome P450[2] exhibit enhanced biological activity, which implies that labile epoxides are responsible for the observed toxicity. Thus, to establish this implication on a firm experimental basis, especially their genotoxicity, it was our intention to investigate the oxidation of benzofurans and to explore the chemistry of these novel epoxides.[3] Prior to our work,[4] benzofuran epoxides were unknown and to date no sufficiently persistent furan epoxides have been documented for their spectral detection even at subambient temperatures above $-100\,^{\circ}C$.

The epoxidation agent of choice as a chemical mimic for cytochrome P450 and the mixed-function oxidase enzyme systems in general, is dimethyldioxirane,[5] especially as an acetone solution.[6] This efficient but selective oxidant operates under mild and strictly neutral conditions and was, therefore, applied in many epoxidations of electron-rich alkenes such as enol ethers,[7] enol silyl ethers,[8] and enol esters and lactones,[9] whose epoxides are usually too labile for isolation and even spectral detection.

The epoxidation of 2,3-dimethylbenzofurans by dimethyldioxirane has been reported earlier.[4a-c] These reactive and thus elusive epoxides were prepared for our genotoxicity studies with benzofuran dioxetanes, since the former were held responsible for the high mutagenicity observed for the latter in the Ames test.[10] Presumably, the benzofuran epoxides, which are produced *in situ* by efficient deoxygenation of the corresponding benzofuran dioxetanes with sulfides, e.g. the biologically relevant methionine, operate as DNA-alkylating agent in *Salmonella typhimurium TA100*.[4a,b]

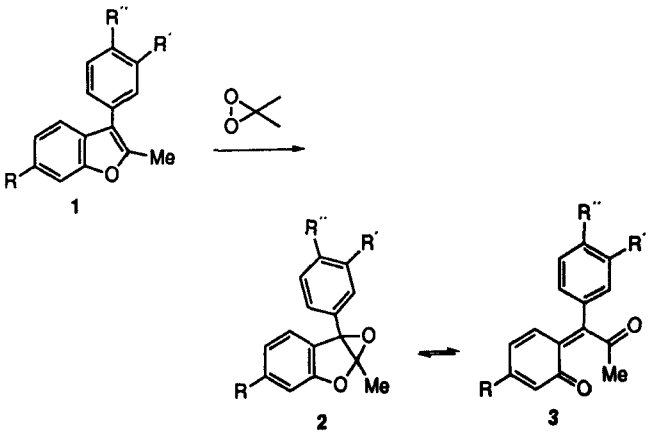




(Eq. 1)

A thorough investigation of the chemistry[4] of the labile 2,3-dimethylbenzofuran epoxides revealed facile 1,3 hydrogen migration from the 3-methyl group to the epoxide oxygen already at $-10\,^{\circ}C$ to form mixtures of hemiacetals and their ring-opened phenols (Eq. 1). Since this rearrangement severely reduces the lifetime of 3-methyl-substituted epoxides and, thus, limits their utility for biological studies, it was of interest to prepare the hitherto

Table 1. Product Studies of the Dimethyldioxirane (DMD) Oxidation[a] of Benzofurans **1a–e**



1	Substituents R	R′	R″	Ratio 1 : DMD	Temp. (°C)	Time (h)	Observed[b] Product
a	H	H	H	1 : 1.17	−78 → −10	7	**2**
b	Ac	H	H	1 : 2.16	−78 → 0	14	**2**
c	MeO	H	H	1 : 1.29	−78 → −20	1	**3**
d	MeO	NO_2	H	1 : 1.39	−78 → −20	3	**3**
e	MeO	H	MeO	1 : 1.07	−78 → −20	1	**3**

[a] In acetone under nitrogen gas atmosphere.
[b] Conversions, mass balances, and yields > 95%, determined by ^1H NMR spectroscopy directly on the mixture, the minor product could not be detected.

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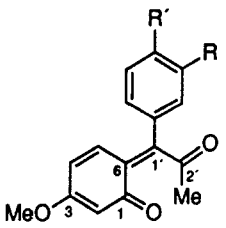
unknown epoxides of the 3-phenylbenzofurans **1**. In these derivatives, the undesirable 1,3 hydrogen shift to the corresponding allylic alcohols is circumvented, which allows the exploration of some interesting chemistry of these highly reactive benzofuran epoxides. Here we report the full details of our preliminary results.[4e]

Dimethyldioxirane Oxidation of the Benzofurans 1a–e

The epoxidation of the 3-phenyl-substituted benzofurans **1** (Table 1) was performed with isolated dimethyldioxirane (ca. 0.1 M) in acetone[11] by starting at −70 °C and warming to −20 °C over a period of 1–14 h (Table 1). The oxidation of the known[12] benzofuran **1a** with dimethyldioxirane at −70 to −20 °C afforded, as revealed by the NMR spectral data, quantitatively the remarkably persistent benzofuran epoxide **2a** as a red oil. Since epoxide **2a** itself should not absorb in the visible region, it was concluded that the corresponding quinone methide **3a** was present in low concentration in the product mixture by valence isomerization of the epoxide. The isomerization of epoxide **2a** to quinone methide **3a** is analogous to that of furans to the *cis*-enediones, when the former are treated with *m*-CPBA[13] or dioxirane.[14] Indeed, the oxidation mixture exhibited strong absorption at $\lambda_{max} = 411$ nm (acetone) with extensive tailing up to 575 nm (hence the red color), which is consistent with the quinone methide **3a** structure.[15] However, the amount of quinone methide **3a** present in the solution of benzofuran epoxide **2a** was under the IR and NMR detection limit (< ca. 1 %).

Table 2. Characteristic ^{13}C NMR Data[a] for the Quinone Methides **3c–e**



3

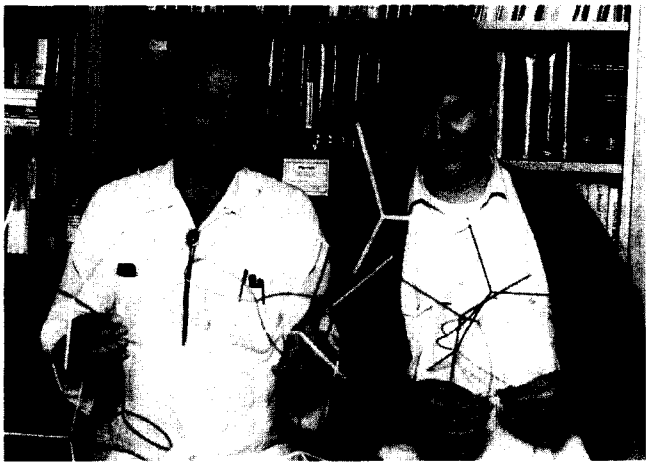
	R	R'
c	H	H
d	NO_2	H
e	H	MeO

3	C-1	C-3	C-6	C-1'	C-2'	2'-Me
c[b]	185.1	170.5	130.1	160.0	203.9	28.0
d[c]	185.2	170.8	133.6	156.4	203.9	28.4
e[d]	185.4	170.7	126.6	161.3	204.9	28.4

[a] Measured at −20 °C
[b] 100 MHz, CD_2Cl_2.
[c] 50 MHz, CD_2Cl_2.
[d] 50 MHz, $CDCl_3$.

Biographical Sketches

Karl Peters was born in Münster, Germany in 1940. He received his doctorate degree in inorganic chemistry for work on single-crystal structure determinations, under the direction of Professor H.G. von Schnering. Since 1975 he has been a senior research associate at the Max-Planck-Institut für Festkörperforschung at Stuttgart and his research interests concentrate on the application of X-ray crystallography.



Waldemar Adam was born in 1937 in the Ukraine. He obtained his B.Sc. from the University of Illinois and his Ph.D. from Massachusetts Institute of Technology under the supervision of F.D. Greene. He was a Professor at the University of Puerto Rico from 1970 to 1980, when he moved to his present position at the University of Würzburg. His research interests include high energy molecules, photochemistry and diradicals.

Markus Sauter received his Dipl. Chem. degree from the University of Würzburg in 1991 and is currently a doctoral student in the Adam's group.

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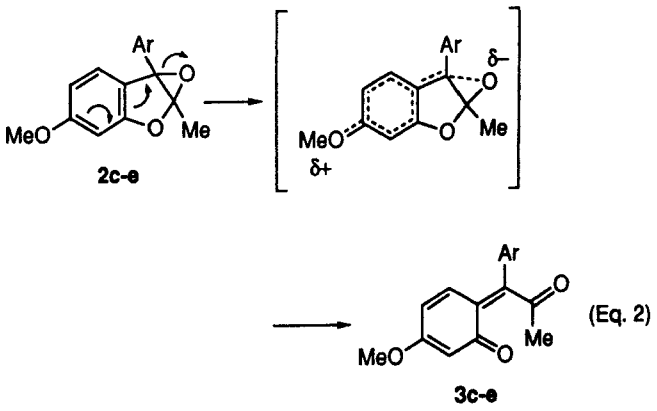
Also benzofuran **1b**, with an acetyl group in position 6 of the benzo ring, gave on dimethyldioxirane epoxidation exclusively the benzofuran epoxide **2b** (Table 1).

The structure of epoxides **2a,b** was assigned on the basis of their ^1H and ^{13}C NMR spectral data. Particularly characteristic are the signals of the epoxide carbon atoms C-2/C-3 at $\delta = 96.4/96.5$ and 70.6/69.5 in the ^{13}C NMR spectrum *versus* $\delta = 151.2/153.6$ and 132.8/133.1 for the corresponding olefinic carbon atoms of the benzofurans **1a,b**.

An astonishing result was obtained in the dimethyldioxirane oxidation of the benzofurans **1c**,[16] **d,e**[17] with a 6-methoxy substituent in the benzo ring. Whereas for the benzofurans **1a,b** only their epoxides **2a,b** were detected by NMR spectroscopy, the 6-methoxy-substituted benzofurans **1c–e** gave on epoxidation quantitatively the quinone methides **3c–e** as dark red solids (Table 1). These were isolated and spectrally characterized at − 20 °C (Table 2). The spectral data agree with those reported for known quinone methides.[18]

In this context it is important to call attention to the fact that epoxide **2e** was claimed in the *m*-CPBA epoxidation of the benzofuran **1e**.[17] However, our spectral data (Table 2) unequivocally establish that quinone methide **3e** is the only oxygen transfer product in the dimethyldioxirane oxidation of **1e**.



Presumably, electronic reasons seem to be responsible in controlling the prevalence of the quinone methides **3c–e** and the epoxides **2a,b**. We argue that the 6-methoxy substituent *para* to the benzylic center in the epoxides **2c–e** facilitates heterolysis of the epoxide ring (Eq. 2) through its (+ M) effect by stabilization of the benzylic cation center and thereby promotes valence isomerization to the quinone methides **3c–e**. Benzofurans **1a,b** do not possess

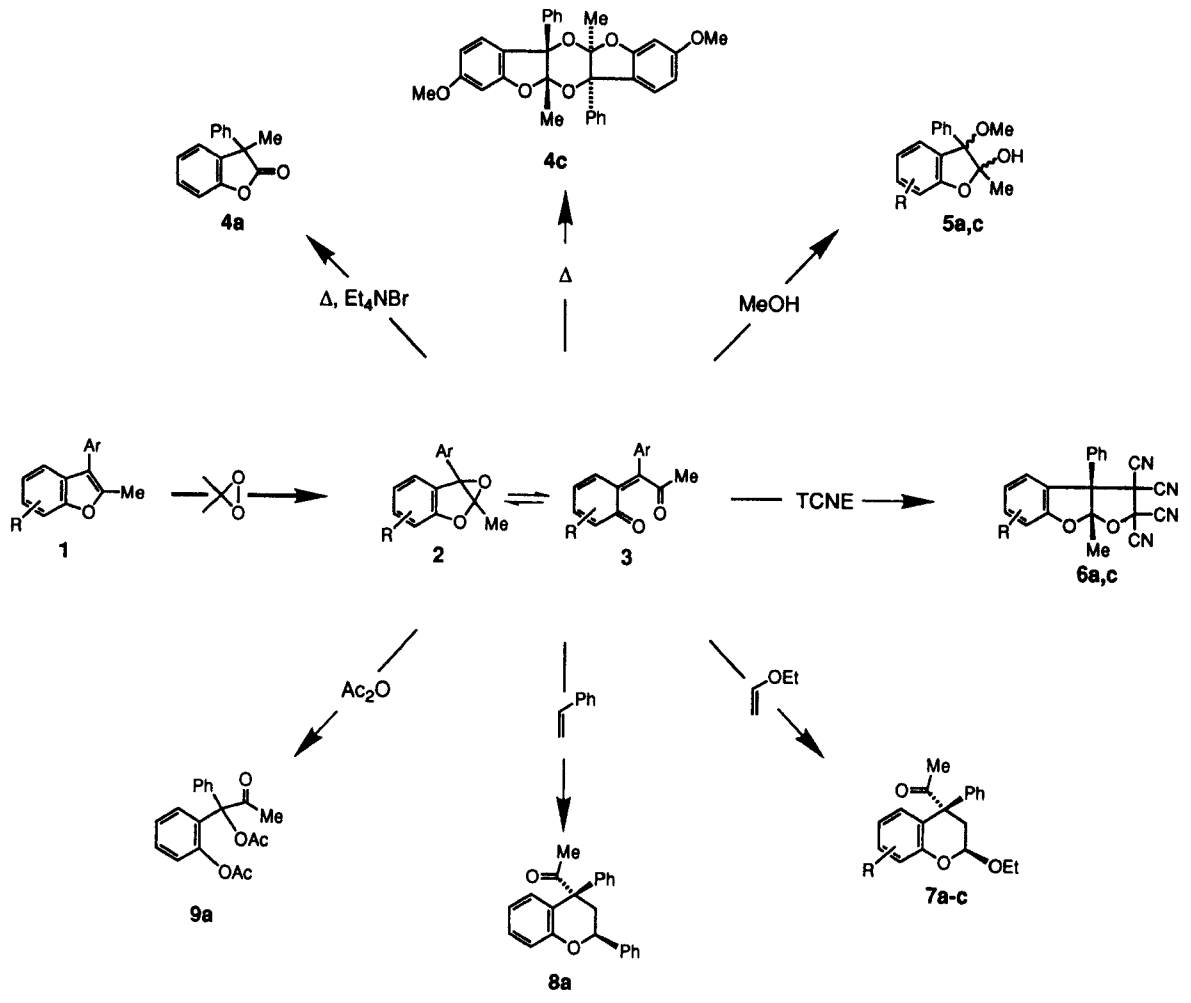


Figure 1. Chemical transformations of the epoxides **2** and their quinone methides **3**

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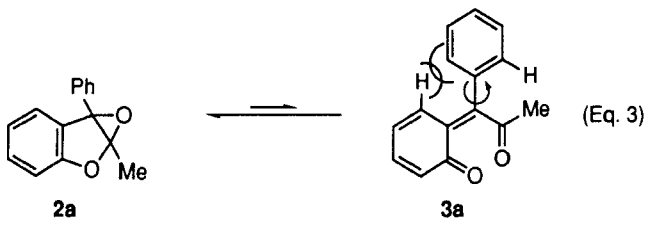
such electronic driving force and, therefore, the epoxides **2a,b** persist (Table 1).

For all the benzofuran epoxides **2** investigated so far, we can generalize that electron-withdrawing substituents (acetyl group) in the benzo ring stabilize the epoxide **2** as a persistent valence isomer, while electron-donating substituents (methoxy) facilitate the isomerization to the quinone methides **3**. Nevertheless, substituents in the 3-phenyl group do not affect the valence isomer distribution since the benzofurans **1c–e** gave on epoxidation with dimethyldioxirane exclusively (by NMR analysis) the quinone methides **3c–e** (Table 1). Irrespective of whether the 3-phenyl group bears no substituent as in **3c** or a *p*′-NO_2 and *m*′-OCH_3 substituent as in **3d** and **e**, the quinone methide valence isomers prevail. Apparently, for the aryl group to conjugate with the planarized benzylic center in the quinone methide structure, severe steric repulsions between its *ortho* hydrogen atoms and the *peri* hydrogen atom at the position 4 of the benzo ring must be overcome. Such steric interaction presumably also operates in the unsubstituted epoxide **2a** (Eq. 3) and



2a **3a** (Eq. 3)

prevents its valence isomerization of the quinone methide **3a** in the first place. However, the electronic driving force of the 6-methoxy group overrides the steric repulsion and promotes the transformation **2** → **3** so that the quinone methides **3c–e** predominate.

Transformations of the Epoxides 2 and Quinone Methides 3

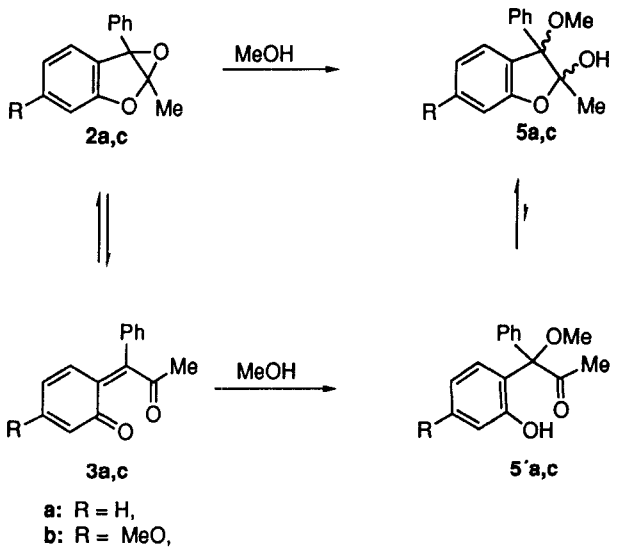
At ambient temperature the epoxides **2a,b** persist in solution as well as in solid form. Prolonged exposure of **2a,b** to elevated temperatures (e.g. during attempted distillation), however, led to total decomposition into an intractable mixture of higher-molecular-weight material. Also the quinone methides **3d–e** behaved similarly on warming, as testified by the complex ^{1}H NMR spectra.

In the presence of catalytic amounts (ca. 0.1 mol%) of tetraethylammonium bromide, an acetone solution of epoxide **2a** gave on heating at 40 °C the known[19] benzofuran-2-one **4a** (Figure 1). Presumably, the ammonium salt associates at the nucleophilic epoxide oxygen through electrostatic coordination, reduces the propensity towards oligomerization, and thereby facilitates the 2,3 methyl shift to the benzofuran-2-one **4a**. Although the condensation of ethylene oxide with carbonyl compounds into 1,3-dioxolanes is promoted by catalytic amounts of tetraethylammonium bromide,[20] even with acetone as solvent only the rearrangement of epoxide **2a** to **4a** was observed in the presence of tetraethylammonium bromide.

In contrast, the quinone methide **3c** dimerized to the dioxane **4c** on warming to room temperature. Dioxane **4c** exhibits in the mass spectrum the molecular peak at *m/z* 508 and due to its S_2 symmetry, a single set of signals in the ^{1}H and ^{13}C NMR spectra. Related dimerizations of epoxides to dioxanes are reported.[21] Since not even traces of the epoxide **2c** could be detected by NMR spectroscopy for the quinone methide **3c**, the observed dimerization of **3c** implies the reversible valence isomerization **2** ⇌ **3** and a ring-opened 1,3-dipolar structure of epoxide **2c** as precursor of the dimer **4c**.

Indeed, for a different set of benzofuran derivatives we have recently rigorously established[4f] that the valence isomerization **2** ⇌ **3** is not only thermally reversible, but that a *bona fide* equilibrium occurs. Thus, photochemical cyclization of mixtures of 5-methoxy- or 7-methoxy-2,3-dimethylbenzofuran epoxides **2** and their quinone methides **3** afforded quantitatively the corresponding benzoxetenes, which slowly reverted to the same mixture of the epoxides **2** and quinone methides **3** as were obtained in the dioxirane epoxidation of the corresponding benzofurans **1**.[4f] A related but thermally irreversible valence isomerization was reported[22] in the photochemical rearrangement of 2*H*-chromenes into oxabenzobicyclohexenes through the intermediacy of *ortho*-quinone allides.

Of interest is the methanolysis reaction of the oxyfunctionalized benzofuran valence isomers. In the presence of methanol at − 20 °C, epoxide **2a** and quinone methide **3c** gave the hemiacetals **5a** (d.r. 50:50) and **5c** (d.r. 43:57), as shown in Fig. 1. This confirms once again the high alkylation propensity of these reactive epoxides: while arene oxides[23] require base or acid catalysis for nucleophilic reactions, benzofuran epoxides **2** do not, even at low temperatures. The driving force for the latter could be derived from aromatization during the Michael-type addition of the nucleophile to the intermediary quinone methides **3** in the valence-isomeric equilibrium **2** ⇌ **3**. The resulting adducts **5**′ cyclize in turn to their hemiacetals **5** (Scheme 1).



2a,c **5a,c**

3a,c **5′a,c**

a: R = H,
b: R = MeO,

Scheme 1

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Since the stereochemical label is erased in this sequence of transformations, it is difficult to differentiate this mechanism from direct attack of methanol on the epoxide **2**. However, unlike the corresponding hemiacetals derived from the 3-methyl-substituted benzofuran epoxides,[4a,c] the corresponding ring-opened tautomers **5'a,c** could not be detected by spectral means. If the tautomerism **5a,c** ⇌ **5'a,c** is irreversible, the fact that a ca. 50:50 mixture of diastereomers **5a,c** was formed, lends credence to the suggested Michael-type methanolysis by way of the quinone methide valence tautomer. In this respect, the reaction of benzofuran epoxide **2a** with freshly distilled acetic anhydride is relevant. At room temperature after three days the diester **9a** was obtained as a crystalline product (Figure 1). The ring-opened structure suggests that the addition of acetic anhydride proceeded through the quinone methide **3a** valence isomer rather than the epoxide **2a**. Again, aromatization may serve as driving force, but the mechanistic details are obscure at this stage.

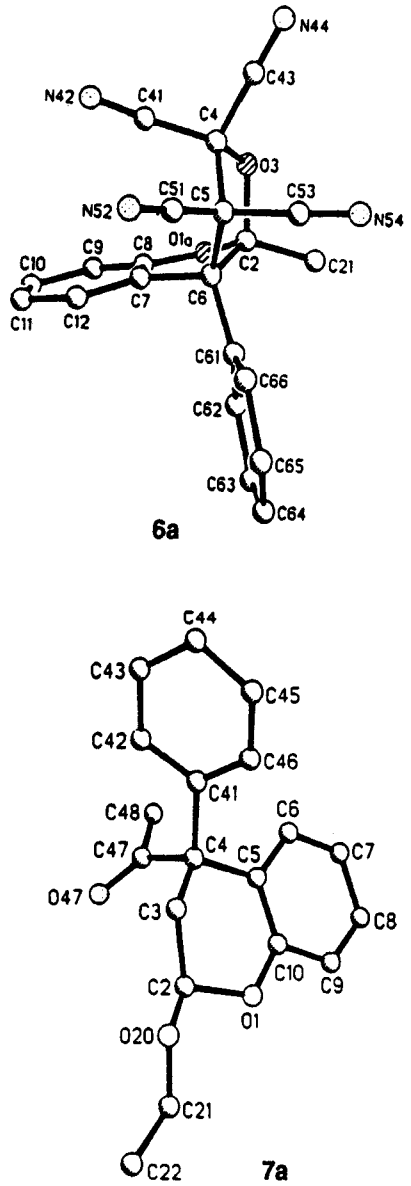

Figure 2. Crystal structures of the benzofurofuran **6a** and benzopyran **7a** (for further details, see ref. 4e, and Experimental section).

The formation of the 1,3-dipolar type cycloadducts of benzofuran epoxide **2a** with tetracyanoethylene (TCNE) to afford the benzofurofuran **6a** is, indeed, an unexpected result (Figure 1). Usually epoxides are inert towards TCNE,[24] although in the reaction of phenanthrene-9,10-oxide with TCNE an adduct was reported.[25] The authors suggested that TCNE induced the isomerization of the epoxide to 9-phenanthrol and the latter led to the observed adduct.

The structure of cycloadduct **6a** was unequivocally assigned on the basis of its crystal structure determination[4e] (Figure 2). Equally surprising is the formation of furofuran **6c** on TCNE treatment of quinone methide **3c** at −40 °C (Figure 1).Trapping of the 1,3-dipole derived from ring-opening of the epoxide in the **2c** ⇌ **3c** equilibrium is unlikely in view of the expected short lifetime of such an intermediate.

When the epoxides **2a,b** were treated with an excess of ethyl vinyl ether at room temperature for two days, the Diels–Alder products **7a,b** (Figure 1) were isolated after distillation of the solvent and chromatography. Again, an X-ray structure analysis[4e] of the [4+2] cycloadduct **7a** certifies the proposed structure (Figure 2). The initial *Z* stereochemistry of the quinone methides **3** is strictly conserved in the benzopyran cycloadducts **7**, as confirmed by the X-ray structure.[4e]

The quinone methide **3c** led with ethyl vinyl ether to benzopyran **7c**, which is exceedingly sensitive towards moisture and, therefore, no satisfactory elemental analysis could be obtained; however, the spectral data of the [4+2] cycloadduct **7c** are in agreement with those of **7a** and **b**. Analogous to ethyl vinyl ether, styrene afforded benzopyran **8a** as [4+2] cycloadduct with epoxide **2a** (Figure 1), whose stereochemistry is identical to benzopyran **7a**.

In summary, the various transformations presented in Figure 1, especially the cycloadditions, convincingly demonstrate that a reversible valence isomerization operates between epoxide **2** and quinone methide **3**. How otherwise could epoxide **2a** produce the [4+2] cycloadduct **7a** and quinone methide **3c** afford the dioxane dimer **4c**, were it not for the respective sequences **2a** → **3a** → **7a** and **3c** → **2c** → **4c**? In fact, the present set of mutual reactions signify that the two valence isomers exist in the thermal equilibrium **2** ⇌ **3** with one another. Most relevant for biological implications is their high alkylation propensity since the oxidized benzofurans count among the most reactive epoxide-type alkylating agents to date, capable of reacting with nucleophiles at subambient temperatures without acid or base catalysis.

Melting points were determined on a Reichert Thermovar hot stage apparatus. IR spectra were recorded on a Perkin-Elmer 1420 instrument. ^1H and ^{13}C NMR spectra were run on a Bruker AC 200 (200 MHz), AC 250 (250 MHz) or WM 400 (400 MHz) spectrometers. Carbon multiplicities were established by DEPT experiments. Chemical shifts refer to chloroform-*d*, methylene chloride-d_2, or acetone-d_6. Mass spectra were obtained on a Varian 8200 Finnigan Mat. Elemental analyses were performed by the Analytical Division of the Institute of Inorganic Chemistry (University of Würzburg). Compounds **1b,d**, **4c**, **5,c**, **6a,c**, **7a,b**, **8a** and **9a** gave

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C,H,N ± 0.4%, except **1b**, C-0.45, and **4c**, C-0.49%. All solvents were purified by following standard literature methods. Dimethyldioxirane (as acetone solution) was prepared according to the published procedure;[11] its peroxide content was determined by oxidation of methyl phenyl sulfide to its sulfoxide, the latter quantified by ^{1}H NMR. The dimethyldioxirane solutions were stored over molecular sieves at −20°C.

2-Methylbenzofurans 1a,c,e:
These compounds were prepared in moderate overall yields according to literature procedures[16,17] by H_2SO_4 cyclization of 2-aroyloxy-1-alkyl-1-propanone, which in turn were obtained by the reaction of substituted phenols with 3-chloro-2-butanone in boiling butanone in presence of K_2CO_3.

6-Acetyl-2-methyl-3-phenylbenzofuran (1b):
This compound was prepared according to the procedure reported by Royer,[26] in which 3-methyl-3-phenylbenzofuran **(1a)** (1.00 g, 4.80 mmol) was acetylated in dichloroethane through Friedel–Crafts acylation to yield **1b** as a colorless powder (1.20 g, 95%), mp 97–98°C.

IR (CCl_4): ν = 2980, 2940, 1730, 1695, 1430, 1370, 1300, 1285, 1230, 710 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3H), 2.65 (s, 3H), 7.32–7.51 (m, 5H), 7.60 (d, J = 8.2 Hz, 1H), 7.86 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H), 8.05 (d, J = 1.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.1 (q), 26.7 (q), 111.0 (d), 117.3 (s), 119.0 (d), 123.2 (d), 127.3 (d), 128.8 (2x d), 131.9 (s), 133.0 (s), 133.1 (s), 153.6 (s), 155.2 (2), 197.5 (s).

6-Methoxy-2-methyl-3-(3-nitrophenyl)benzofuran (1d):
This compound was prepared analogous to ref. 14, in which 2-bromo-1-(3-nitrophenyl)propanone (3.30 g, 12.8 mmol) was etherified with 3-methoxyphenol (1.40 g, 12.8 mmol) in boiling butanone for 5 d, base-catalyzed by K_2CO_3. Without further purification, the ether was cyclized with conc. H_2SO_4 at −10°C to r.t. within 1 h to yield **1d** as a pale yellow powder (2.56 g, 70%), mp 124–126°C.

IR (CCl_4): ν = 2940, 2810, 1535, 1500, 1350, 1290, 1200, 1150, 1110 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.55 (s, 3H), 3.88 (s, 3H), 6.89 (dd, J_1 = 8.6 Hz, J_2 = 2.2 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.65–7.70 (m, 1H), 7.82–7.87 (m, 1H), 8.19–8.23 (m, 1H), 8.34–8.39 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.0 (q), 55.6 (q), 95.4 (d), 111.4 (d), 114.6 (s), 118.9 (d), 120.7 (s), 121.7 (d), 123.2 (d), 129.8 (d), 134.6 (s), 134.7 (d), 148.1 (s), 151.1 (s), 154.6 (s), 157.3 (s).

Epoxidation of Benzofurans 1 by Dimethyldioxirane; General Procedure:
A cooled (−78°C) solution of dimethyldioxirane (40–100% molar excess) in acetone (0.050–0.084 M), dried over molecular sieves at −20°C, was rapidly added to a cooled (−78°C), stirred solution of the 2,3-dimethylbenzofuran **1** (0.84–1.00 mmol) in dry CH_2Cl_2 (2 mL) under a N_2 atmosphere. The stirring was continued until complete consumption of the benzo[*b*]furan **1** (monitored by TLC), while the reaction temperature was allowed to increase to −20°C. The solvent was evaporated (−20°C at 0.01 Torr, 1–2 h) to yield quantitatively the hitherto unknown epoxides **2** or quinone methides **3** in high purity (by ^{1}H NMR).

2,3-Dihydro-4-methoxy-2-methyl-3-phenyl-2,3-epoxybenzofuran (2a):
This compound was obtained quantitatively from benzofuran **1a** (164 mg, 0.788 mmol) and dimethyldioxirane (11 mL, 0.084 M, 0.924 mmol) by following the above procedure at −78 to −10°C for 7 h.

^{1}H NMR (200 MHz, $CDCl_3$, −20°C): δ = 1.73 (s, 3H), 7.01–7.09 (m, 2H), 7.34–7.55 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$, −20°C): δ = 13.7 (q), 70.6 (s), 96.4 (s), 112.0 (d), 121.9 (d), 125.8 (d), 127.5 (d), 129.2 (d), 129.3 (d), 129.9 (s), 130.7 (d), 131.8 (s), 161.3 (s).

6-Acetyl-2,3-dihydro-2-methyl-3-phenyl-2,3-epoxybenzofuran (2b):
This compound was obtained quantitatively from benzofuran **1b** (125 mg, 0.500 mmol) and dimethyldioxirane (15 mL, 0.072 M, 1.08 mmol) by following the above procedure at −78 to 0°C for 14 h.

^{1}H NMR (200 MHz, $CDCl_3$, −20°C): δ = 1.78 (s, 3H), 2.59 (s, 3H), 7.45 (s, 5H), 7.50–7.66 (m, 3H).

^{13}C NMR (50 MHz, $CDCl_3$, −20°C): δ = 13.5 (q), 26.7 (q), 69.5 (s), 96.5 (s), 110.9 (d), 121.7 (d), 125.7 (d), 126.7 (2x d), 128.5 (3x d), 130.2 (s), 134.0 (s), 138.7 (s), 160.5 (s), 197.0 (s).

3-Methoxy-(2-oxo-1-phenylpropylidene)-2,4-cyclohexadienone (3c):
This compound was obtained quantitatively from benzofuran **1c** (130 mg, 0.550 mmol) and dimethyldioxirane (9 mL, 0.079 M, 0.711 mmol) by following the above procedure at −78 to −20°C for 1 h.

^{1}H NMR (400 MHz, CD_2Cl_2, −20°C): δ = 2.20 (s, 3H), 3.75 (s, 3H), 5.70 (d, J = 1.6 Hz, 1H), 6.19 (dd, J_1 = 10.1 Hz, J_2 = 1.6 Hz, 1H), 6.78 (d, J = 10.1 Hz, 1H), 7.35–7.50 (m, 5H).

^{13}C NMR (100 MHz, CD_2Cl_2, −20°C): δ = 28.0 (q), 56.1 (q), 101.2 (d), 122.6 (d), 127.3 (s), 128.6 (d), 129.2 (d), 130.1 (s), 131.4 (d), 131.8 (d), 160.0 (s), 170.5 (s), 185.1 (s), 203.9 (s).

3-Methoxy-6-[1-(3-nitrophenyl)-2-oxopropylidene]-2,4-cyclohexadienone (3d):
This compound was obtained quantitatively from benzofuran **1d** (142 mg, 0.500 mmol) and dimethyldioxirane (11 mL, 0.063 M, 0.693 mmol) by following the above procedure at −78 to −20°C for 3 h.

^{1}H NMR (200 MHz, CD_2Cl_2, −20°C): δ = 2.34 (s, 3H), 3.82 (s, 3H), 5.75 (d, J = 2.2 Hz, 1H), 6.28 (dd, J_1 = 10.1 Hz, J_2 = 2.2 Hz, 1H), 6.68 (d, J = 10.1 Hz, 1H), 7.65–7.83 (m, 2H), 8.23–8.37 (m, 2H).

^{13}C NMR (50 MHz, CD_2Cl_2, −20°C): δ = 28.4 (q), 56.4 (q), 101.5 (d), 124.2 (d), 124.8 (2x d), 128.7 (s), 129.9 (d), 130.2 (d), 133.6 (s), 135.0 (d), 147.8 (s), 156.4 (s), 170.8 (s), 185.2 (s), 203.9 (s).

3-Methoxy-6-[1-(3-methoxyphenyl)-2-oxopropylidene]-2,4-cyclohexadienone (3e):
This compound was obtained quantitatively from benzofuran **1e** (134 mg, 0.500 mmol) and dimethyldioxirane (8 mL of 0.067 M, 0.536 mmol) by following the above procedure at −78 to −20°C for 1 h.

^{1}H NMR (200 MHz, $CDCl_3$, −20°C): δ = 2.29 (s, 3H), 3.77 (s, 3H), 3.84 (s, 3H), 5.71 (d, J = 2.3 Hz, 1H), 6.21 (dd, J_1 = 10.1 Hz, J_2 = 2.2 Hz, 1H), 6.87–6.97 (m, 3H), 7.33–7.47 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$, −20°C): δ = 28.4 (q), 55.4 (q), 56.0 (q), 101.5 (d), 114.2 (2 × d), 122.2 (s), 123.6 (d), 126.6 (s), 131.7 (2 × d), 131.8 (d), 160.8 (s), 161.3 (s), 170.7 (s), 185.4 (s), 204.9 (s).

3-Methyl-3-phenylbenzofuran-2-one (4a):[19]
A solution of the epoxide **2a** (91.0 mg, 0.500 mmol) in $CDCl_3$ (0.6 mL) was allowed to warm up from −30 to 20°C for 12 h. After evaporation of the solvent (20°C at 15 Torr), the residue was purified by column chromatography (silica gel, Et_2O/pentane) to yield **4a** (57.0 mg, 63%) as a colorless oil.

^{1}H NMR: δ = 1.81 (s, 3H), 7.07–7.31 (m, 9H).

^{13}C NMR: δ = 23.8 (q), 49.8 (s), 110.0 (d), 123.50 (d), 123.53 (d), 125.4 (d), 126.1 (d), 126.8 (d), 127.8 (2 × d), 128.0 (d), 131.6 (s), 138.4 (s), 151.7 (s), 177.7 (s).

Dimer 4c:
A solution of the quinone methide **3c** (150 mg, 0.590 mmol) in $CDCl_3$ (0.6 mL) was kept at 0°C for 4 h. After evaporation of the solvent, the residue was purified by column chromatography (silica gel, Et_2O/pentane) to yield **4c** (98 mg, 65%) as colorless needles, mp 276–277°C (Et_2O).

IR (CCl_4): ν = 3000, 2940, 2900, 2880, 1595, 1565, 1465, 1420, 1275, 1140 cm^{-1}.

^{1}H NMR: δ = 1.02 (s, 6H), 3.78 (s, 6H), 6.42 (d, J = 2.3 Hz, 2H), 6.53 (dd, J_1 = 9.0 Hz, J_2 = 2.3 Hz, 2H), 7.06 (d, J = 9.0 Hz, 2H), 7.14–7.27 (m, 10H).

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^{13}C NMR: δ = 24.2 (q), 56.0 (q), 86.0 (s), 96.8 (d), 109.0 (d), 110.1 (s), 124.0 (s), 127.0 (d), 127.6 (d), 128.2 (d), 128.3 (d), 141.0 (s), 159.1 (s), 162.5 (s).

MS (70 eV): *m/z* (%) = 509 (1, $M^+ + 1$), 508 (1, M^+), 465 (13), 238 (32), 223 (23), 84 (100), 47 (20).

Methanol Trapping of Epoxides 2 and Quinone Methides 3; General Procedure:

A solution of the epoxide **2** (ca. 0.500 mmol) or quinone methide **3** (ca. 0.500 mmol) in 2 mL of dry CH_2Cl_2 was treated at −78 °C with 5 mL of abs. MeOH. The reaction mixture was stirred for 0.5 h at this temperature, the solution was allowed to warm to r.t., and the solvent was evaporated (20 °C at 15 Torr). The residue was purified by column chromatography (silica gel, Et_2O).

2,3-Dihydro-3-methoxy-2-methyl-3-phenyl-2-benzofuranol (5a):

This compound (211 mg, 82%, d.r. = 50:50) was obtained as a colorless powder, mp 102–102.5 °C, according to the above procedure by treatment of the epoxide **2a** (240 mg, 1.00 mmol) with MeOH (1 mL).

IR (CCl_4): *v* = 3545, 3080, 3040, 3005, 2950, 1620, 1600, 1490, 1470, 1410, 1375, 1300, 1260, 995, 720 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.91 (s, 3 H), 1.69 (s, 3 H), 2.96 (s, 3 H), 3.04 (s, 3 H), 5.44 (s, 1 H), 5.89 (s, 1 H), 6.86–7.50 (n, 18 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 20.2 (q), 23.9 (q), 51.2 (q), 51.3 (q), 87.3 (s), 90.7 (s), 111.3 (d), 111.7 (d), 112.6 (d), 113.9 (d), 120.1 (d), 125.9 (d), 128.3 (d), 128.6 (d), 128.9 (d), 129.1 (d), 129.5 (d), 131.1 (d), 131.7 (d), 136.7 (s), 137.0 (s), 159.8 (s), 161.2 (s).

MS (70 eV): *m/z* (%) = 257 (1, $M^+ + 1$), 256 (9, M^+), 213 (74), 221 (100), 105 (42), 77 (50), 51 (13), 43 (8).

2,3-Dihydro-3,6-dimethoxy-2-methyl-3-phenyl-2-benzofuranol (5c):

This compound (160 mg, 56%, d.r. = 57:43) was obtained according to the above procedure as a colorless oil by treatment of the quinone methide **3c** (254 mg, 1.00 mmol) with MeOH (0.5 mL).

IR (CCl_4): *v* = 3510, 2940, 2830, 1640, 1600, 1400, 1305, 1205, 1170, 1090, 1075 cm^{-1}.

^{1}H NMR: δ = 0.85 (s, 3 H), 1.63 (s, 3 H), 2.90 (s, 3 H), 2.94 (s, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 6.04 (s, 1 H), 6.40 (s, 1 H), 6.48–5.59 (m, 4 H), 7.12 (d, *J* = 8.0 Hz, 1 H), 7.23 (d, *J* = 8.2 Hz, 1 H), 7.36–7.45 (m, 10 H).

^{13}C NMR: δ = 20.1 (q), 23.9 (q), 50.5 (q), 50.7 (q), 55.4 (q), 86.6 (s), 90.0 (s), 96.7 (d), 97.5 (d), 105.6 (d), 106.0 (d), 113.1 (s), 114.4 (s), 117.4 (s), 119.8 (s), 128.2 (d), 128.3 (d), 128.6 (d), 128.8 (d), 129.1 (d), 129.3 (d), 136.6 (s), 136.8 (s), 160.7 (s), 162.2 (s), 162.5 (s), 162.8 (s).

MS (70 eV): *m/z* (%) = 287 (5, $M^+ + 1$), 286 (28, M^+), 254 (53), 243 (100), 239 (88), 227 (78), 225 (65), 211 (66), 105 (38), 43 (15).

Reaction of Epoxides 2 and Quinone Methides 3 with Tetracyanoethylene (TCNE); General Procedure:

An NMR tube was charged with a solution of the epoxide **2a** or quinone methide **3c** (ca. 0.500 mmol) in 0.5 mL $CDCl_3$ and a solution of TCNE (0.500 mmol) in 0.1 mL $CDCl_3$ and 0.1 mL acetone-d_6 at −50 °C was added. After ca. 0.5 h, the sample was transferred to the NMR spectrometer and the benzofurofurans **6a,c** were determined to be the only products. After evaporation of the solvent and purification by column chromatography (Et_2O/pentane as eluent), the pure benzofurofurans were isolated in high yields.

2,2,3,3-Tetracyano-2,3,3a,8a-tetrahydro-8a-methyl-3a-phenylfuro-[2,3-*b*]benzofuran (6a):

This compound (271 mg, 96%) was obtained according to the above procedure as colorless needles, mp 183–184 °C (Et_2O), by treatment of the epoxide **2a** (180 mg, 0.802 mmol) with TCNE (103 mg, 0.802 mmol).

IR (CCl_4): *v* = 3080, 2260, 1620, 1600, 1505, 1480, 1470, 1450, 1395, 1115, 1080, 1045, 950, 870, 700 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.83 (s, 3 H), 7.05–7.52 (m, 9 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 22.7 (q), 52.1 (s), 68.0 (s), 72.2 (s), 107.6 (s), 107.7 (s), 109.1 (s), 109.3 (s), 112.0 (d), 124.2 (s), 124.9 (s), 125.3 (d), 125.9 (d), 126.2 (d), 129.5 (d), 129.6 (d), 133.2 (s), 133.8 (d), 157.2 (s).

MS (70 eV): *m/z* (%) = 353 (8, $M^+ + 1$), 352 (33, M^+), 272 (14), 209 (75), 224 (46), 209 (100), 181 (69), 152 (20), 147 (11), 43 (54).

Crystal structure of benzofurofuran **6a** (see Figure 2); hydrogen atoms have been omitted for clarity: **6a** is monoclinic and possesses the structural parameters $P2_1/c$, *a* = 1732.9 (5), *b* = 1311.3 (4), *c* = 702.3 (2) pm, β = 97.60 (2)°, d_{calc} (g/cm^{-3}) = 1.244, *Z* = 4; 2792 observed unique reflections, *R* = 0.057, R_w = 0.050; selected bond distances (pm) and angles (°): O1a-C2 141.0(4), C2-O3 146.1(4), O3-C4 140.6(4), C4-C5 156.9(4), C5-C6 156.0(4), C2-C6 157.8(5), C6-C7 151.0(4), O1a-C8 139.5(4); C2-O1a-C8 107.2(2), O1a-C2-O3 107.2(2), O1a-C2-C6 107.3(2), C2-O3-C4 112.2(2), O3-C2-C6 105.7(3), C2-C6-C7 98.9(2), C2-C6-C5 100.8(2), C5-C6-C7 113.3(3), C6-C7-C8 109.7(3), O3-C4-C5 103.7(2), C4-C5-C6 101.8(2).

2,2,3,3-Tetracyano-2,3,3a,8a-tetrahydro-6-methoxy-8a-methyl-3a-phenylfuro[2,3-*b*]benzofuran (6c):

This compound (176 mg, 78%) was obtained according to the above procedure as colorless needles, mp 125–127 °C (Et_2O), by treatment of the quinone methide **3c** (150 mg, 0.590 mmol) with TCNE (76 mg, 0.590 mmol).

IR (CCl_4): *v* = 2960, 2915, 2250, 1625, 1590, 1500, 1295, 1110, 1080, 700 cm^{-1}.

^{1}H NMR: δ = 1.94 (s, 3 H), 3.68 (s, 3 H), 6.77 (dd, J_1 = 8.7 Hz, J_2 = 2.3 Hz, 1 H), 6.87 (d, H = 2.3 Hz, 1 H), 7.23 (d, *J* = 8.7 Hz, 1 H), 7.42–7.62 (m, 5 H).

^{13}C NMR: δ = 23.5 (q), 53.3 (s), 56.4 (q), 69.0 (s), 72.5 (s), 98.3 (d), 109.2 (s), 109.4 (s), 110.8 (s), 111.0 (s), 112.6 (d), 117.5 (s), 125.8 (s), 127.0 (d), 127.5 (d), 130.4 (2 × d), 135.3 (s), 159.9 (s), 165.3 (s).

Reaction of Epoxides 2 or Quinone Methides 3 with Ethyl Vinyl Ether; General Procedure:

A solution of the epoxide **2** or of the quinone methide **3** (0.68–1.37 mmol) in 2 mL of dry CH_2Cl_2 was charged with a large excess of ethyl vinyl ether (5 mL) at −30 °C. The reaction mixture was stirred at this temperature for up to 4 d, the solution was allowed to warm to r.t. and the solvent was evaporated (20 °C at 15 Torr). The residue was purified by column chromatography (silica gel, Et_2O/pentane).

4-Acetyl-2-ethoxy-3,4-dihydro-4-phenyl-2*H*-1-benzopyran (7a):

This compound (273 mg, 86%) was obtained as colorless needles, mp 72–73 °C (pentane), from the epoxide **2a** (240 mg, 1.07 mmol) and excess ethyl vinyl ether (1.00 g), by following the above procedure at 20 °C for 2 d.

IR (CCl_4): *v* = 3065, 3040, 2985, 2940, 1715, 1490, 1355, 1150, 1045, 910, 710 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 1.94 (dd, J_1 = 8.9 Hz, J_2 = 13.6 Hz, 1 H), 2.18 (s, 3 H), 2.91 (dd, J_1 = 3.2 Hz, J_2 = 13.6 Hz), 1 H), 3.58–4.12 (m, 2 H), 5.25 (dd, J_1 = 3.2 Hz, J_2 = 8.9 Hz, 1 H), 6.78–7.45 (m, 9 H).

^{13}C NMR: δ = 15.1 (q), 27.9 (q), 40.4 (t), 59.4 (s), 64.3 (t), 98.0 (d), 117.9 (d), 120.5 (d), 120.0 (s), 127.1 (d), 127.3 (d), 128.6 (d), 129.1 (s), 130.4 (d), 142.8 (s), 154.2 (s), 208.0 (s).

MS (70 eV): *m/z* (%) = 297 (2, $M^+ + 1$), 296 (8, M^+), 253 (100), 209 (75), 197 (11), 178 (26), 152 (20), 119 (34), 91 (42), 43 (23).

Crystal structure of benzopyran **7a** (see Figure 2); hydrogen atoms have been omitted for clarity: **7a** is triclinic and possesses the structural parameters $P\bar{1}$, *a* = 1174.1 (3), *b* = 1477.4 (5), *c* = 1042.2 (3) pm, α = 90.85 (3)°, β = 91.82 (2)°, γ = 76.05 (2)°, *Z* = 4, d_{calc} = 1.330 g cm^{-3}, 4593 unique reflections were observed, *R* = 0.055, R_w = 0.043. Selected bond distances (pm) and angles (°): O1-C2 143.7(3), C2-C3 (150.8(3), C3-C4 153.9(3), C4-C41 153.4(3), O1-C10 137.1(3), C2-O20 138.7(3), C4-C5 153.4(3), C4-C47 155.5(3); C2-O1-C10 116.7(1), O1-C2-C3 110.5(2), O1-C2-O20 107.5(2), C3-C2-O20 108.3(2), C2-C3-C4 111.8(2), C3-C4-C5 109.2(1), C3-C4-C41 107.6(2), C5-C4-C41 113.4(2), O1-C10-C9 115.7(2), O1-C10-C5 123.7(2), C2-O20-C21 113.8(2).

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4,6-Diacetyl-2-ethoxy-3,4-dihydro-4-phenyl-2*H*-1-benzopyran (7b):
This compound (137 mg, 90%) was obtained as colorless oil from the epoxide **2b** (120 mg, 0.451 mmol) and excess ethyl vinyl ether (1.00 g), by following the above procedure at 20 °C for 2 d.

IR (CCl_4): ν = 3000, 2950, 1740, 1720, 1440, 1380, 1305, 1175, 1060, 725 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3H), 1.99 (dd, J_1 = 13.7 Hz, J_2 = 8.8 Hz, 1H), 2.20 (s, 3H), 2.59 (s, 3H), 2.93 (dd, J_1 = 13.7 Hz, J_2 = 3.4 Hz, 1H), 3.68 (dq, J_1 = 7.1 Hz, J_2 = 2.4 Hz, 1H), 4.05 (dq, J_1 = 7.1 Hz, J_2 = 2.4 Hz, 1H), 5.30 (dd, J_1 = 8.8 Hz, J_2 = 3.4 Hz, 1H), 7.05–7.53 (m, 8H).

^{13}C NMR: (50 MHz, $CDCl_3$): δ = 15.1 (q), 26.6 (q), 27.9 (q), 39.9 (t), 59.7 (s), 64.6 (t), 98.3 (d), 118.0 (d), 120.1 (d), 127.2 (d), 127.4 (d), 128.5 (s), 128.9 (d), 130.7 (d), 137.9 (s), 141.9 (s), 154.1 (s), 197.3 (s), 207.0 (s).

4-Acetyl-2-ethoxy-3,4-dihydro-6-methoxy-4-phenyl-2*H*-1-benzopyran (7c):
This compound (43 mg, 26%) was obtained as colorless oil from the quinone methide **3c** (127 mg, 0.500 mmol) and excess ethyl vinyl ether (1.00 g) by following the above procedure at −40 °C for 10 d.

IR (CCl_4): ν = 2970, 2940, 1710, 1625, 1495, 1085, 700 cm^{-1}.

^1H NMR (250 MHz, acetone-d_6): δ = 1.15 (t, J = 7.1 Hz, 3H), 1.90 (dd, J_1 = 13.5 Hz, J_2 = 8.2 Hz, 1H), 2.14 (s, 3H), 2.83 (dd, J_1 = 13.5 Hz, J_2 = 3.4 Hz, 1H), 3.62 (dq, J_1 = 7.1 Hz, J_2 = 2.4 Hz, 1H), 3.84 (s, 3H), 4.08 (dq, J_1 = 7.1 Hz, J_2 = 2.4 Hz, 1H), 5.27 (dd, J_1 = 8.2 Hz, J_2 = 3.4 Hz, 1H), 6.55–6.67 (m, 2H), 7.10–7.54 (m, 6H).

^{13}C NMR (63 MHz, acetone-d_6): δ = 14.5 (q), 27.2 (q), 40.6 (t), 55.5 (q), 58.9 (s), 63.7 (t), 98.3 (d), 117.5 (s), 119.5 (d), 126.9 (d), 127.3 (d), 127.6 (d), 128.0 (d), 135.5 (s), 143.2 (s), 147.5 (s), 207.3 (s).

Due to its sensitivity towards hydrolysis, no satisfactory elemental analysis could be obtained.

4-Acetyl-3,4-dihydro-2,4-diphenyl-2*H*-1-benzopyran (8a):
A solution of the benzofuran epoxide **2a** (150 mg, 0.669 mmol) in $CDCl_3$ (2 mL) was charged with styrene (1.0 g, 9.59 mmol) at r.t. for 2 d. Workup followed by column chromatography (silica gel, Et_2O/pentane) gave **8a** (197 mg, 82%) as a colorless oil, which slowly crystallized from pentane at −20 °C as colorless needles, mp 115–117 °C.

IR (CCl_4): ν = 3000, 2950, 2880, 1715, 1490, 1455, 1390, 1235, 1135, 710 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 (dd, J_1 = 13.8 Hz, J_2 = 1.8 Hz, 1H), 1.92 (dd, J_1 = 13.8 Hz, J_2 = 11.8 Hz, 1H), 2.43 (s, 3H), 5.16 (dd, J_1 = 11.8 Hz, J_2 = 1.8 Hz, 1H), 6.91–7.53 (m, 14H).

^{13}C NMR: δ = 28.4 (q), 43.4 (t), 59.7 (s), 75.7 (d), 118.0 (d), 120.2 (d), 121.6 (s), 126.0 (d), 127.1 (d), 127.2 (d), 127.9 (d), 128.5 (d), 128.8 (d), 129.1 (d), 131.9 (d), 141.1 (s), 143.9 (s), 156.1 (s), 208.5 (s).

3-Acetoxy-3-(2-acetoxy)phenyl-3-phenylpropan-2-one (9a):
Treatment of a solution of the benzofuran epoxide **2a** (200 mg, 0.893 mmol) in CH_2Cl_2 with Ac_2O (122 mg, 1.20 mmol) at 20 °C for 2 d gave after solvent evaporation and crystallization from Et_2O/pentane at −20 °C analytically pure **9a** (176 mg, 59%) as a colorless powder, mp 120–122 °C.

IR (CCl_4): ν = 3060, 1765, 1755, 1725, 1445, 1370, 1235, 1195, 1020, 700 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.86 (s, 3H), 2.12 (s, 3H), 2.14 (s, 3H), 6.91–6.74 (m, 1H), 7.23–7.46 (m, 7H), 8.01–8.12 (m, 1H).

^{13}C NMR: (50 MHz, $CDCl_3$): δ = 20.6 (q), 21.3 (q), 24.5 (q), 88.2 (s), 124.2 (d), 125.0 (d), 127.0 (d), 128.1 (d), 129.8 (d), 130.7 (s), 131.7 (d), 137.2 (s), 148.5 (s), 168.9 (s), 169.3 (s), 201.0 (s).

We thank the Deutsche Forschungsgemeinschaft (SFB 172 "Molekulare Mechanismen kanzerogener Primärveränderungen") and the Fonds der Chemischen Industrie for generous funding.

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