Naphthalenes as Water-Soluble Singlet Oxygen Carriers and Detectors: Hydrophobic and Kinetic Properties

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The syntheses of endoperoxides of naphthalene derivatives with propionic acid and ethanesulfonic acid side chains are described. The partition coefficients and half-lives for the thermal decomposition in phosphate buffer of all compounds have been determined. Because of their high stability in phosphate buffer at 37°C, 3,3'-(4-Methyl-1,3-naphthylene)dipropionic acid and its corresponding methyl ester may be used as chemical traps for the detection of $^1O_2$ in biological systems.

Naphthaline als wasserlösliche Träger- und Nachweissubstanzen von Singulett-Sauerstoff: Hydrophobe und kinetische Eigenschaften

Die Herstellung von Naphthalin-Derivaten mit Propionsäuren- und Ethansulfonsäuren-Seitenketten wird beschrieben. Die Verteilungskoeffizienten und Halbwertszeiten für den thermischen Zerfall in Phosphatpuffer sämtlicher Verbindungen wurden ermittelt. Wegen der hohen Stabilität in Phosphatpuffer bei 37°C können 3,3'-(4-Methyl-1,3-naphthylen)dipropionsäure und ihr entspr. Methylester auch zum Nachweis von $^1O_2$ in biologischen Systemen verwendet werden.

The present study is concerned with two aspects of alkyl-substituted naphthalenes. Firstly, the preparation and characterization of naphthalene derivatives as sources of electronically excited molecular oxygen (singlet oxygen, $^1O_2$) for experiments with intact cell systems and *in vivo* assays. Secondly, their possible use as trapping agents for $^1O_2$ in biological systems.

For mechanistic studies of $^1O_2$ reactions in aqueous systems 1,4-endoperoxides derived from naphthalenes turned out to be quite useful, because they are known to release $^1O_2$ in a reverse *Diels-Alder* reaction under mild conditions[1,2]. Contrary, in photochemical systems the sensitizer may also interact directly with the substrate resulting in hydrogen atom or electron transfer to produce radicals[3] which react with triplet oxygen to give oxygenated products. On the other hand, preparation of $^1O_2$ from naphthalene endoperoxides[1] seems to be a clean source, since no side reactions have yet been reported. Although these sources of $^1O_2$ are readily soluble in water, however, the lipophilicity of a compound is important for the biological effectiveness, too. The lipophilic-hydrophilic balance, which is expressed by the partition coefficient between the membrane and the ambient medium of a bioactive compound, is critical for absorption and transport. For studying the effects of $^1O_2$ in intact cell systems, where permeation and distribution processes play a major role, the hydrophobic properties of a $^1O_2$ carrier are important for the ability to reach its biological target.

In this report we describe the syntheses of endoperoxides of naphthalene derivatives with different partition coefficients and half-lives for the thermal decomposition in phosphate buffer. Compounds with the substitution pattern **a** and **c** were prepared by bromomethylation of 1-methylnaphthalene (Scheme 1). Compounds with the substitution pattern **b** were prepared from **1b**, which was obtained by bromination of **1a** according to *Marvel* and *Wilson*[4]. Naphthalene propionic acids were synthesized from the products of bromomethylation of 1-methyl-naphthalene through malonic ester synthesis by the method of *Saito* et al.[1] (Scheme 1, route **A**). The naphthalene sulphonamides were obtained from the products of bromomethylation of 1-methylnaphthalene, followed by cyanation, esterification, reduction, and conversion to the sulphonamides according to common methods (Scheme 1, route **B**).

The endoperoxides (Scheme 2) were prepared either photochemically with methylene blue as a sensitizer at low temp. or, if the substrates were only poorly reactive, $^1O_2$ was provided by the molybdate catalyzed disproportionation of H_2O_2 according to *Aubry*[2]. From among the naphthalene sulphonamides only the endoperoxide of compound **11a** could be isolated. Introduction of an additional side chain with a sulphonamide functional group into the naphthalene system leads to significant decrease in reactivity with $^1O_2$. Even after prolonged photooxidation of **11b** or **11c** no endoperoxide could be detected.

The values of the rate constants and the corresponding half-lives as well as the partition coefficients of the endoperoxides are given in Table 1.

Partition coefficients (log P) of this series are of the order of -0.13 to 2.17, the half-lives range from 25 to 412 min. An unexpected observation is the much higher stability of the endoperoxides **18** and **19** in phosphate buffered saline at physiological temp. Therefore, these compounds may be suitable sources of $^1O_2$ in biological assays with long incubation periods. Moreover, their parent naphthalenes **3c** and **4c** provide useful chemical traps of $^1O_2$ for mechanistic studies in biological systems. A number of techniques have been developed for this purpose. However, many of the chemical traps employed are reactive with other oxidizing species in the system and therefore not specific for $^1O_2$, or these traps are photosensitizers by themselves[5]. Experiments with **4c** did not result in production of $^1O_2$ when irradiated in the presence of the acceptor tetramethylethylene. Therefore, no conversion to the allylic hydroperox-

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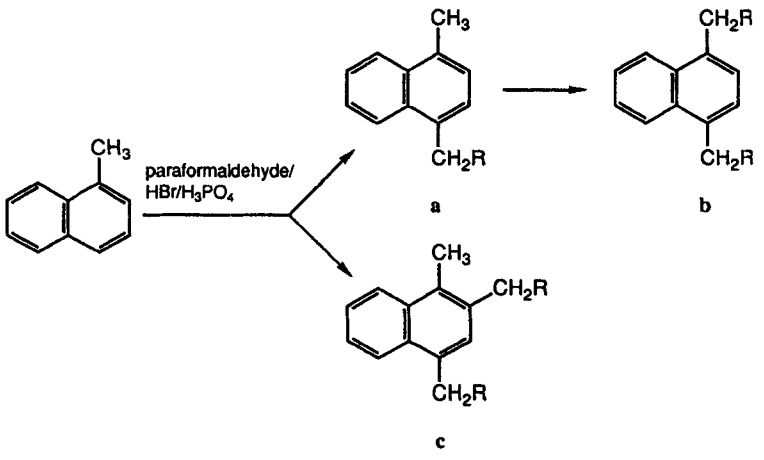
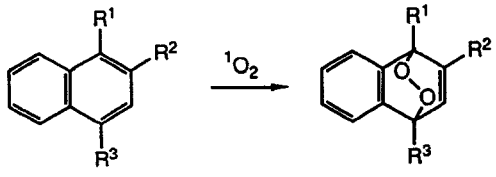


R	A: Route to naphthalene propionic acids	R	B: Route to naphthalene sulphonamides
Br	1a, 1b, 1c	CN	5a, 5b, 5c
$CH(COOC_2H_5)_2$	2a, 2b, 2c	COOH	6a, 6b, 6c
CH_2COOH	3a, 3b, 3c	$COOC_2H_5$	7a, 7b, 7c
CH_2COOCH_3	4a, 4b, 4c	CH_2OH	8a, 8b, 8c
		CH_2Br	9a, 9b, 9c
		$CH_2SO_3^-Na^+$	10a, 10b, 10c
		$CH_2SO_2NH_2$	11a, 11b, 11c



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ide (*Schenck*-reaction[6]) by the ene-reaction could be detected. Additionally, no endoperoxides were formed in a self-sensitized process.

Another drawback of many specific traps is their low reactivity with $^1O_2$, whereas **4c** reacts rapidly ($k_R + k_Q = 9.8 \cdot 10^7\ M^{-1}\ s^{-1}$) with $^1O_2$ to the corresponding endoperoxide **19**, which has been established in a separate piece of work[7].

Experimental Section

Melting points: apparatus according to Dr. Tottoli (Büchi), uncorrected.- IR spectra (KBr): Beckman Acculab III.- UV spectra: Shimadzu 210.- ^{1}H-NMR spectra: Varian EM 390 (90 MHz) or Bruker WM 250 (250 MHz), TMS as internal standard.- MS: Varian MAT CH5, 70 eV.- NI-FAB-MS: Varian MAT 311A.- AAS: Beckman 1227.- HPLC: Kontron 420, Kontron Uvikon 735 LC UV detector, Nucleosil 7 C 18 (250 x 4 mm) column.

Diethyl(4-methyl-1-naphthyl)methylmalonate (**2a**)

was prepared from 1-chloromethyl-4-methylnaphthalene[8] analogously to *Fieser* and *Gates*[9]. Yield: 56% (colorless oil), b.p. 161-163°C / 0.1 Torr.- $C_{19}H_{22}O_4$ (314.2) Calc. C 72.6 H 7.00 Found C 72.6 H 7.01.- UV (Methanol): λ max (log ε) = 287 (3.9), 226 nm (4.7).- IR (film): 1750 cm^{-1} (CO).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.15-7.80 (m; 2H, Ar), 7.59-7.06 (m; 4H, Ar),

Table 1: Rate constants (k), half-lives ($\tau_{1/2}$) for the decomposition in phosphate buffered saline at 37°C and partition coefficients (logP) of the endoperoxides.

compound	(Scheme 2)	k [$s^{-1} \cdot 10^4$]	$\tau_{1/2}$ [min]	logP
12	$R^1 = R^3 = CH_3$; $R^2 = H$	2.67	43	2.17
13	$R^1 = CH_3$; $R^2 = H$, $R^3 = CH_2CH_2COOH$	4.62	25	1.19
14	$R^1 = CH_3$; $R^2 = H$, $R^3 = CH_2CH_2CO_2CH_3$	3.73	31	2.13
15	$R^1 = CH_3$; $R^2 = H$, $R^3 = CH_2CH_2SO_2NH_2$	2.22	52	1.66
16	$R^1 = R^3 = CH_2CH_2COOH$; $R^2 = H$	4.18	28	-0.13
17	$R^1 = R^3 = CH_2CH_2CO_2CH_3$; $R^2 = H$	3.31	35	2.08
18	$R^1 = CH_3$; $R^2 = R^3 = CH_2CH_2COOH$	0.29	398	0.24
19	$R^1 = CH_3$; $R^2 = R^3 = CH_2CH_2CO_2CH_3$	0.28	412	2.06

4.10 (q; J = 7.5 Hz, 4H, -CH_2-CH_3), 3.91-3.58 (m; 3H, CH_2-CH), 2.55 (s, 3H, CH_3), 1.10 (t; J = 7.5 Hz, 6H, -CH_2-CH_3).- MS (70 eV): m/z = 314 (23%, M^+).

Methyl 3-(4-methyl-1-naphthyl)propionate (**4a**)

was prepared by esterification (methanol/H^+) of 3-(4-methyl-1-naphthyl)propionic acid (**3a**)[10]. Yield: 87% as a colorless oil, b.p. 70-80°C / 0.05 Torr).- $C_{15}H_{16}O_2$ (228.3) Calc. C 78.9 H 7.06 Found C 79.2 H 6.77.- UV (MeOH): λ max (log ε) = 287 (4.0), 223 nm (4.5).- IR: 1740 cm^{-1} (CO).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.17-7.90 (m; 2H, Ar), 7.70-7.40 (m; 2H, Ar), 7.20 (s; 2H, Ar), 3.63 (s; 3H, OCH_3), 3.50-3.25 (m; 2H, CH_2), 2.85-2.60 (m; 5H, CH_2 and CH_3).- MS (70 eV): m/z = 228 (37%, M^+).

Dimethyl 3,3'-(1,4-naphthylene)dipropionate (**4b**)

was prepared by esterification (methanol/H^+) of 3,3'-(1,4-naphthylene)dipropionic acid (**3b**)[4]. Yield: 71% (white powder), m.p. 59-60°C.- $C_{18}H_{20}O_4$ (300.4) Calc. C 72.0 H 6.71 Found C 72.2 H 6.29.- UV (MeOH): λ max (log ε) = 287 (3.9), 224 nm (4.6).- IR: 1735 cm^{-1} (CO).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.25-7.95 (m; 2H, Ar), 7.72-7.43 (m; 2H, Ar), 7.33 (s; 2H, Ar), 3.75 (s; 3H, OCH_3), 3.67 (s; 3H, OCH_3), 3.58-3.28 (m; 4H, 2 CH_2), 2.90-2.62 (m; 4H, 2 CH_2).- MS (70 eV): m/z = 300 (85%, M^+).

1,3-Dibromomethyl-4-methylnaphthalene (**1c**)

The mixture of 96 g (0.675 mol) freshly distilled 1-methylnaphthalene, 45 g paraformaldehyde, 300 ml of 47% HBr, 105 ml glacial acetic acid, and 70 g of 85% phosphoric acid was vigorously stirred for 5 h at 80-85°C. After cooling and addition of 800 ml of water and 300 ml of saturated NaCl the mixture was extracted with CH_2Cl_2, neutralized with saturated $NaHCO_3$, washed with water, dried with Na_2SO_4 and evaporated. The product immediately solidified and was digested in methanol, filtered by suction and dried at 80°C. 119.1 g (54%) white powder, m.p. 138-139°C.- $C_{13}H_{12}Br_2$ (328.0) Calc. C 47.6 H 3.66 Found C 47.6 H 3.79.- UV (MeOH): λ max (log ε) = 299 (3.9), 240 nm (4.6).- IR: 1510; 755 (C-Br) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.30-8.00 (m; 2H, Ar), 7.80-7.47 (m; 3H, Ar), 4.87 (s; 2H, CH_2), 4.63 (s; 2H, CH_2), 2.70 (s; 3H, CH_3).- MS (70 eV): m/z = 326/328/330 (6/13/6%, M^+).

Tetraethyl(4-methyl-1,3-naphthylenedimethylene)dimalonate (**2c**)

was prepared from **1c** by malonic synthesis analogously to *Marvel* and *Wilson*[4]. Yield: 64% white powder.- m.p. 56°C.- $C_{27}H_{34}O_8$ (486.5) Calc. C 66.7 H 7.00 Found C 66.7 H 7.05.- UV (MeOH): λ max (log ε) = 289 (3.9), 231 nm (4.8).- IR: 1755 cm^{-1} (CO).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.20-7.90 (m; 2H, Ar), 7.63-7.40 (m; 2H, Ar), 7.20 (s; 1H, Ar), 4.20 (q; J = 7.5 Hz, 8H, 4 CH_2-CH_3), 3.83-3.43 (m; 6H, 2 CH_2-CH), 2.63 (s; 3H, CH_3), 1.20 (t; J = 7.5 Hz, 12 H, 4 -CH_2-CH_3).- MS (70 eV): m/z = 486 (100%, M^+).

3,3'-(4-Methyl-1,3-naphthylene)dipropionic acid (**3c**)

was prepared from **2c** by analogy to *Lock* and *Walter*[11]. Yield: 35% of a white powder.- m.p. 163-165°C.- $C_{17}H_{18}O_4$ (286.3) Calc. C 71.3 H 6.29 Found C 71.3 H 6.33.- UV (MeOH): λ max (log ε) = 279 (3.9), 231 nm (4.6).- IR: 1720 cm^{-1} (CO).- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 8.20-7.93 (m; 2H, Ar), 7.63-7.43 (m; 2H, Ar), 7.23 (s; 1H, Ar), 6.35 (br s; 2H, 2 OH), 3.30-3.17 (m; 2H, CH_2), 3.06-2.94 (m; 2H, CH_2), 2.70-2.38 (m; 4H, 2 CH_2), 2.55 (s, 3H, CH_3).- MS (70 eV): m/z = 286 (39%, M^+).

Dimethyl 3,3'-(4-methyl-1,3-naphthylene)dipropionate (**4c**)

was prepared by esterification of **3c**. Yield: 52% white powder, b.p. 150°C (0.05 Torr), m.p. 58-59°C.- $C_{19}H_{22}O_4$ (314.4) Calc. C 72.6 H 7.05 Found C 72.4 H 6.80.- UV (MeOH): λ max (log ε) = 288 (3.8), 226 nm (4.7).- IR: 1740 cm^{-1} (CO).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.12-7.95 (m; 2H, Ar), 7.65-7.45 (m; 2H, Ar), 7.18 (s; 1H, Ar), 3.70 (s; 6H, 2 OCH_3), 3.42-3.32 (m; 2H, CH_2), 3.19-3.09 (m; 2H, CH_2), 2.79-2.59 (m; 4H, 2 CH_2), 2.62 (s; 3H, CH_3).- MS (70 eV): m/z = 314 (62%, M^+).

(4-Methyl-1-naphthyl)acetonitrile (**5a**)

47.75 g (0.25 mol) of 1-chloromethyl-4-methylnaphthalene[8], 18.4 g (0.375 mol) NaCN and 1.9 g NaI were refluxed for 20 h. After cooling the resulting precipitate was collected by filtration, rinsed with acetone and the combined filtrates were evaporated. The brown residue was digested in ether and filtered by suction. 23 g (51%) as a yellow powder.- m.p. 61-62°C.- $C_{13}H_{11}N$ (181.2) Calc. C 86.2 H 6.08 Found C 85.8 H 6.28.- UV (MeOH): λ max (log ε) = 284 (4.0), 274 (3.9), 224 nm (4.7).- IR: 2260 cm^{-1} (CN).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.15-7.15 (m; 6H, Ar), 3.92 (s; 2H, CH_2), 2.60 (s; 3H, CH_3).- MS (70 eV): m/z = 181 (100%, M^+).

(4-Methyl-1-naphthyl)acetic acid (**6a**)

11.05 g (0.061 mol) of nitrile **5a** in 40 ml of 25% NaOH were refluxed for 20 h. The mixture was acidified with dil. H_2SO_4 and the resulting precipitate was rinsed with water. Recrystallization from benzene afforded 7 g (57%) white needles.- m.p. 162-164°C.- $C_{13}H_{12}O_2$ (200.2) Calc. C 78.0 H 6.00 Found C 77.7 H 6.31.- UV (MeOH): λ max (log ε) = 286 (3.9), 225 nm (4.7).- IR: 1700 cm^{-1} (CO).- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 12.37 (br s; 1H, OH), 8.15-7.82 (m; 2H, Ar), 7.65-7.40 (m; 2H, Ar), 7.27 (s; 2H, Ar), 3.97 (s; 2H, CH_2), 2.60 (s; 3H, CH_3).- MS (70 eV): m/z = 200 (40%, M^+).

2-(4-Methyl-1-naphthyl)ethan-1-ol (**8a**)

Esterification (EtOH/H^+) of **6a** afforded 96% of a yellow oil **7a** (7 g, 0.031 mol) which was reduced without purification in a suspension of 0.71 g $LiAlH_4$ and 50 ml dry THF. The mixture was worked up by addition of ice and dil. H_2SO_4, followed by extraction with CH_2Cl_2. The org. layer was washed with saturated NaCl and water, dried with Na_2SO_4 and concentrated to give 5.04 g of a pale yellow oil (88%), b.p. 115°C / 0.1 Torr; Lit.[12]: m.p. 60°C.

1-Bromo-2-(4-methyl-1-naphthyl)ethane (**9a**)

A mixture of **8a** (3.72 g, 20 mmol), 0.54 ml of conc. H_2SO_4 and 1.84 g of 62% HBr was refluxed for 30 min. The cooled solution was diluted with water and extracted with CH_2Cl_2. The org. phase was washed with $NaHCO_3$ and water, dried, and concentrated. Kugelrohr distillation of the residue at 140°C / 0.01 Torr gave 1.74 g (35%) of a white solid, m.p. 43-44°C; Lit.[12]: 45-46°C.

Sodium 2-(4-methyl-1-naphthyl)ethane-1-sulphonate (**10a**)

1.25 g (5 mmol) of **9a**, 1.9 g Na_2SO_3 and 0.23 g NaI in 50 ml dioxane/H_2O (1:1) were refuxed for 24 h. The mixture was filtered, the filtrate was concentrated and saturated with NaCl, evaporated, and the residue was washed with cooled methanol and then with ethanol. When dried white crystals were obtained (0.88 g, 70%) as the monohydrate.- $C_{13}H_{13}O_3SNa \cdot H_2O$ (290.3) Calc. C 53.8 H 5.17 Na 7.93 Found C 53.2 H 5.28 Na 7.98 (AAS).- UV (MeOH): λ max (log ε) = 288 (3.9), 226 nm (4.5).- IR: 3710-3180 (H_2O), 1185 (SO_3^-), 1060 (SO_3Na) cm^{-1}.- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 8.17-7.82 (m; 2H, Ar), 7.72-7.37 (m; 2H, Ar), 7.23 (s; 2H, Ar), 3.53-3.10 (m; 4H, CH_2 and H_2O), 2.70-2.38 (m; 2H, CH_2), 2.58 (s; 3H, CH_3).- NI-FAB-MS (MNBA/toluene): m/z = 249 (95%, $(M-Na)^-$).

2-(4-Methyl-1-naphthyl)ethane-1-sulphonamide (**11a**)

0.73 g (2.7 mmol) of **10a** was well triturated with 0.62 g (3 mmol) of PCl_5, then the trituration was heated for 30 min at 120°C and allowed to

cool. After addition of 15 ml benzene the reaction mixture was refluxed for 5 min, cooled and NaCl was filtered off. After evaporation the solid residue was dissolved in 5 ml conc. NH_3 and stirred under reflux for 15 min. After dilution with water the residue was collected and recrystallized from EtOH/water (1:1) to afford white crystals (0.22 g, 33%), m.p. 185-187°C.- $C_{13}H_{15}NO_2S$ (249.3) Calc. C 62.6 H 6.06 Found C 62.9 H 5.98.- UV (MeOH): λ max (log ε) = 286 (3.9), 223 nm (4.6).- IR: 3340 (NH_2); 3250 (NH_2) cm^{-1}.- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 8.25-7.95 (m; 2H, Ar), 7.75-7.52 (m; 2H, Ar), 7.35 (s; 2H, Ar), 7.03 (s; br., 2H, NH_2), 3.53-3.27 (m; 4H, 2 CH_2), 2.65 (s; 3H, CH_3).- MS (70 eV): m/z = 249 (13%, M^+).

Disodium 2,2'-(1,4-naphthylene)diethane-1,1'-sulphonic acid (**10b**)

was prepared from 1,4-bis-(2-bromoethyl)naphthalene (**9b**)[13] as described for **10a**. Yield: 78% white powder.- UV (MeOH): λ max (log ε) = 287 (3.9), 226 (4.7).- IR: 1175 (SO_3^-); 1060 (SO_3^-) cm^{-1}.- ^{1}H-NMR (D_2O): δ (ppm) = 8.03-7.83 (m; 2H, Ar), 7.60-7.40 (m; 2H, Ar), 7.17 (s; 2H, Ar), 3.40-3.00 (m; 8H, 4 CH_2).- NI-FAB-MS (glycerol/methanol): m/z = 365 (100%, $(M-Na)^-$).

2,2'-(1,4-naphthylene)diethane-1,1'-sulphonamide (**11b**)

was prepared from **10b** as described for **11a**. Yield: 11% white powder, m.p. 177-179°C.- $C_{14}H_{18}N_2O_4S_2$ (342.4) Calc. C 49.1 H 5.30 Found C 49.4 H 5.63.- UV (MeOH): λ max (log ε) = 287 (4.0), 226 nm (4.8).- IR: 3340 (NH_2); 3250 (NH_2) cm^{-1}.- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 8.25-8.03 (m; 2H, Ar), 7.78-7.60 (m; 2H, Ar), 7.47 (s; 2H, Ar), 7.07 (s; 4H, 2 NH_2), 3.38 (s; 8H, 4 CH_2).- MS (70 eV): m/z = 342 (1%, M^+).

(4-Methyl-1,3-naphthylene)diacetonitrile (**5c**)

was prepared from **1c** as described for **5a**. Yield: 83% as a sandy powder, m.p. 137-138°C.- $C_{15}H_{12}N_2$ (220.3) Calc. C 81.8 H 5.45 Found C 81.4 H 5.80.- UV (MeOH): λ max (log ε) = 286 (3.9), 276 (3.9), 226 nm (4.5).- IR: 2250 cm^{-1} (CN).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.30-8.05 (m; 1H, Ar), 8.00-7.78 (m; 1H, Ar), 7.75-7.43 (m; 3H, Ar), 4.13 (s; 2H, CH_2), 3.90 (s; 2H, CH_2), 2.67 (s; 3H, CH_3).- MS (70 eV): m/z = 220 (100%, M^+).

(4-Methyl-1,3-naphthylene)diacetic acid (**6c**)

was prepared from **5c** as described for **6a**. Yield: 79% white powder, m.p. 223-225°C.- $C_{15}H_{14}O_4$ (258.3) Calc. C 69.8 H 5.43 Found C 69.4 H 5.36.- UV (MeOH): λ max (log ε) = 277 (4.0), 229 nm (4.7).- IR: 1705 cm^{-1} (CO).- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 11.23 (s; 2H, OH), 8.23-7.83 (m; 2H, Ar), 7.67-7.43 (m; 2H, Ar), 7.30 (s; 1H, Ar), 3.97 (s; 2H, CH_2), 3.80 (s; 2H, CH_2), 2.57 (s; 3H, CH_3).- MS (70 eV): m/z = 258 (85%, M^+).

2,2'-(4-Methyl-1,3-naphthylene)diethan-1,1'-ol (**8c**)

was obtained by esterification of **6c** and reduction as described for **8a**. Yield: 91% white solid, m.p. 71-72°C.- $C_{15}H_{18}O_2$ (230.3) Calc. C 78.3 H 7.83 Found C 78.4 H 8.08.- UV (MeOH): λ max (log ε) = 289 (3.9), 227 nm (4.6).- IR: 3540-3100 cm^{-1} (OH).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.17-7.85 (m; 2H, Ar), 7.63-7.37 (m; 2H, Ar), 7.17 (s; 1H, Ar), 4.02-3.63 (m; 4H, 2 CH_2), 3.20 (t; J = 7.5 Hz, 2H, CH_2), 3.00 (t; J = 7.5 Hz, 2H, CH_2), 2.53 (s; 2H, 2 OH), 2.53 (s; 3H, CH_3).- MS (70 eV): m/z = 230 (56%, M^+).

1,3-Di-(2,2'-bromoethyl)-4-methylnaphthalene (**9c**)

was prepared from **8c** as described for **9a**. Yield: 37% white powder, m.p. 53-54°C.- $C_{15}H_{16}Br_2$ (356.1) Calc. C 50.6 H 4.49 Found C 50.6 H 4.48.- UV (MeOH): λ max (log ε) = 290 (3.9), 232 nm (4.8).- IR: 775 cm^{-1} (C-Br).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.20-7.90 (m; 2H, Ar), 7.67-7.43 (m; 2H, Ar), 7.20 (s; 1H, Ar), 3.73-3.37 (m; 8H, 4 CH_2), 2.63 (s; 3H, CH_3).- MS (70 eV): m/z = 354/356/358 (49/99/48%, M^+).

Disodium 2,2'-(4-Methyl-1,3-naphthylene)diethane-1,1'-sulphonic acid (**10c**)

was prepared from **9c** as described for **10a**. Yield: 53% white solid.- $C_{15}H_{16}O_6S_2Na_2 \cdot H_2O$ (420.4) Calc. C 42.8 H 4.29 Na 10.95 Found C 42.4 H 4.04 Na 10.88 (AAS).- UV (MeOH): λ max (log ε) = 289 (3.7), 229 nm (4.6).- IR: 1190 (SO_3^-); 1060 cm^{-1} (SO_3^-).- ^{1}H-NMR (D_2O): δ (ppm) = 7.78-7.47 (m; 2H, Ar), 7.37-7.12 (m; 2H, Ar), 6.90 (s; 1H, Ar), 3.10-2.70 (m; 8H, 4 CH_2), 2.09 (s; 3H, CH_3).- NI-FAB-MS (glycerol/methanol): m/z = 379 (70%, $(M-Na)^-$).

2,2'-(4-Methyl-1,3-naphthylene)diethane-1,1'sulphonamide (**11c**)

was prepared from **10c** as described for **11a**. Yield: 16% white powder, m.p. 210-212°C.- $C_{15}H_{20}N_2O_4S_2$ (356.5) Calc. C 50.5 H 5.66 Found C 50.1 H 5.65.- UV (MeOH): λ max (log ε) = 288 (4.0), 229 nm (4.9).- IR: 3310 (NH_2); 3250 (NH_2) cm^{-1}.- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 8.27-7.93 (m; 2H, Ar), 7.70-7.50 (m; 2H, Ar), 7.37 (s; 1H, Ar), 7.13-6.85 (m; 4H, 2 NH_2), 3.50-3.15 (m; 8H, 4 CH_2), 2.63 (s; 3H, CH_3).- MS (70 eV): m/z = 356 (8%, M^+).

General procedure for the preparation of the endoperoxides

Method **A**: Photooxidations were carried out in an apparatus as described[14]. A solution composed of 3 mmol of the naphthalene derivative and methylene blue (10^{-4} M) in 30 ml CH_2Cl_2 was irradiated for 10 h at -5°C with halogen lamps (Osram Halostar, 2 x 100 W) under continuous bubbling of O_2. The solvent was removed at 0°C and the residue was purified by column chromatography at 15°C (SiO_2/CH_2Cl_2). The column was provided with a cool jacket and the eluent was precooled. Purity was checked by HPLC.

Method **B**: H_2O_2/Na_2MO_4 method as described by *Aubry*[15].

1,4-Epidioxy-1,4-dimethylnaphthalene (**12**)[16]

Method **A**, obtained as white solid. Data correspond to Lit.[16].

3-(1,4-Epidioxy-4-methyl-1-naphthyl)propionic acid (**13**)[1]

Method **A**, obtained as white solid. Data correspond to Lit.[1].

Methyl 3-(1,4-epidioxy-4-methyl-1-naphthyl)propionate (**14**)

was prepared from **4a** by *method* **A**, obtained as colourless oil.- UV (MeOH): λ max (log ε) = 286 (3.8), 225 (4.6), 210 nm (4.6).- IR: 1740 cm^{-1} (CO).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.45-7.23 (m; 4H, Ar), 6.78 (s; 2H, CH=CH), 3.75 (s; 3H, OCH_3), 2.70 (s; 4H, 2 CH_2), 1.87 (s; 3H, CH_3).

2-(1,4-Epidioxy-4-methyl-1-naphthyl)ethane-1-sulphonamide (**15**)

was prepared from **11a** by *method* **A**, obtained as white solid.- UV (MeOH): λ max (log ε) = 287 (3.2), 226 (4.1), 207 nm (4.3).- IR: 3380 (NH_2); 3270 (NH_2) cm^{-1}.- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 7.47-7.28 (m; 4H, Ar), 7.00 (s; br., 2H, NH_2), 6.95-6.80 (m; 2H, CH=CH), 4.53-4.30 (m; 4H, 2 CH_2), 1.83 (s; 3H, CH_3).

3,3'-(1,4-Epidioxy-1,4-naphthylene)dipropionic acid (**16**)[2,15]

Method **B**, obtained as white solid. Data correspond to Lit.[2,15].

Dimethyl 3,3'-(1,4-epidioxy-1,4-naphthylene)dipropionate (**17**)

was prepared from **4b** by *method* **A**, obtained as white solid.- UV (MeOH): λ max (log ε) = 276 (3.3), 226 (4.1), 205 nm (4.3).- IR: 1725 cm^{-1} (CO).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.43-7.20 (m; 4H, Ar), 6.80 (s; 2H, CH=CH), 3.73 (s; 6H, 2 OCH_3), 2.67 (s; 8H, 4 CH_2).

3,3'-(1,4-Epidioxy-4-methyl-1,3-naphthylene)dipropionic acid (**18**)

was prepared from **3c** by *method* **B**, obtained as white solid.- UV (MeOH): λ max (log ε) = 260 nm (2.8), 227 nm (3.3), 206 nm (4.3).- IR: 1710 cm^{-1} (CO).- ^{1}H-NMR (D_6-DMSO): δ (ppm) = 7.57 (s; br., 2H, 2 OH), 7.47-7.20 (m; 4H, Ar), 6.46 (s; 1H, =CH), 2.73-2.20 (m; 8H, 4 CH_2), 1.77 (s; 3H, CH_3).

Dimethyl3,3'-(1,4-epidioxy-4-methyl-1,3-naphthylene)dipropionate (**19**)

was prepared from **4c** by *method* **A**, obtained as colourless oil.- UV (MeOH): λ max (log ε) = 260 nm (2.7), 226 (3.5), 205 nm (4.4).- IR: 1735 cm^{-1} (CO).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.32 (s; 4H, Ar), 6.35 (s; 1H, =CH), 3.75 (s; 3H, OCH_3), 3.63 (s; 3H, OCH_3), 2.67-2.47 (m; 8H, 4 CH_2), 1.87 (s; 3H, CH_3).

Kinetic studies on the thermal decomposition of the endoperoxides

The decomposition was examined in phosphate buffered saline (composed of 8.00 g NaCl, 0.20 g KCl, 1.00 g $Na_2HPO_4 \cdot 2H_2O$, 0.15 g $NaH_2PO_4 \cdot H_2O$, 0.20 g KH_2PO_4, adjusted to pH 7.4 with 3 N-NH_3 in a final volume of 1000 ml bidist. H_2O) at 37°C in a shaking water bath. Decomposition of **12** was followed in methanol. The disappearance of the endoperoxides (10 μM in 5 ml buffer solution) was monitored by HPLC using methanol/water/acetic acid (77:23:0.1) as eluent and UV detection at 232 nm. Methanol/water/acetic acid (60:40:0.1) was used for **15**.

Determination of octanol-water partition coefficients

A standard reversed-phase HPLC procedure was used[17] to provide log k' values: $k' = (t-t_0)/t_0$; log P_{oct} was obtained from regression lines according to log $P_{oct} = a + b \log k'$. Eluents were composed as described above. Standards: anthracene, benzoic acid, benzophenone, naphthalene, 4-nitrophenol.

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