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Hydroperoxide and Endoperoxide Lactones from Photooxygenation of 3-Alkylidenedihydrofuran-2,4-diones

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Received August 21, 2003

Abstract: 3-Alkylidenedihydrofuran-2,4-diones **1** can be photooxygenated with O_2/TBHP to hydroperoxides **3** which slowly decompose to diols **5**. Stable endoperoxides **4** are best prepared by photooxygenation of **1** with 2 equiv of O_2 in the presence of $CuSO_4$ and *p*-TosOH following a nonradical mechanism. They are rapidly reduced by anhydrous $FeBr_2$ to give butenolide **9** indicating a potential antimalarial activity.

We had previously reported that 3-alkylidenedihydrofuran-2,4-diones **1**, which can be easily obtained from a thermal domino pericyclic reaction of the respective allyl tetronates,[1] are slowly autoxidized with air to the corresponding hemiketal endoperoxide lactones **4**.[2] However, products **4** were in each case found to be contaminated with the corresponding diols **5**, which did not originate from decay of **4**. Given the current interest in natural[3] and synthetic[4] endoperoxides with antimalarial and other pharmacological properties, we have optimized the selective conversions of **1** into either pure endoperoxides **4** or hydroperoxides **3**.

The autoxidation of **1** with air can be entirely suppressed by addition of radical chain-breakers such as 2,6-di-*tert*-butylphenol (DTBP), whereas the treatment of solutions of **1a** in CH_2Cl_2 at room temperature or slightly above with catalytic amounts of initiators such as azobisisobutyronitrile (AIBN) or dibenzoylperoxide (DBPO) enhanced the rate and the yields of products **4a** and **5a** considerably. Hence, a mechanism commencing with formation of a tertiary allylic carbon radical and progressing through the corresponding hydroperoxides **2a** or **3a** or both seemed most likely. However, the proposed hydroperoxides could not be isolated under these conditions (Scheme 1). André-Barrès' synthesis of natural endoperoxide G-factors, first extracted from *Eucalyptus grandis*, from 2-alkylidenecyclohexan-1,3-diones showed very similar characteristics. It proceeded via a radical mechanism, slowly in the dark and more rapidly under UV-irradiation in the presence of a sensitizer, suppressable by DTBP and insensitive to the singlet oxygen quencher DABCO.[5]

We now report that pure hydroperoxides **3** are obtained in good yields by photooxidation (low-pressure mercury vapor lamp, 150 W) of **1** in the presence of a 10-fold excess of *tert*-butyl hydroperoxide (TBHP). Dussault[6] and Courtneidge[7] had successfully employed TBHP as a reservoir of radicals and a protective against decomposition of hydroperoxides in similar autoxidations of alkenes. Sensitizers were not needed, and no endoperoxides **4**, or diols **5**, or regioisomeric hydroperoxides were formed (Scheme 2). The absence of **4** in particular suggests the formation of a tertiary radical quickly adopting the favorable π-electronic structure of tetronic acid **3** prior to the uptake of oxygen, thus bypassing hydroperoxide **2**.

The molecular structure of **3a** as obtained from an X-ray single crystal structure analysis reveals the hydroperoxy group pointing away from the hydroxy group of the tetronic acid moiety and forming a hydrogen bridge with the carbonyl oxygen in a puckered eight-membered ring. This might be merely a crystal packing effect. It would, however, if it persisted in solution, explain the reluctance of **3** to cyclize to endoperoxides **4** when treated with *p*-TosOH in methanol[8] (no reaction), or with NaOMe in methanol (→ decomposition via ring opening), or when irradiated in dry CH_2Cl_2 in the presence of *p*-TosOH (→ formation of **5**).

A convenient access to pure hemiketal endoperoxide lactones **4** was eventually found in the photooxygenation of **1** with 1.5−2 equiv of oxygen in the presence of catalytic amounts of *p*-TosOH and $CuSO_4$ (Scheme 3). The latter had been used by Snider[9] both as a photosensitizer and as a means to isomerize enones to the corresponding 1-hydroxy-1,3-dienes, which in turn could react with singlet oxygen yielding six-ring endoperoxides.

The mechanistic picture for this process is, however, far from clear. In their respective syntheses of sponge endoperoxides chondrillin and plakorin from enones, Snider[9] and Dussault[6] both assumed the initial formation of a 4-hydroperoxy-2-enone. Dussault found evidence for

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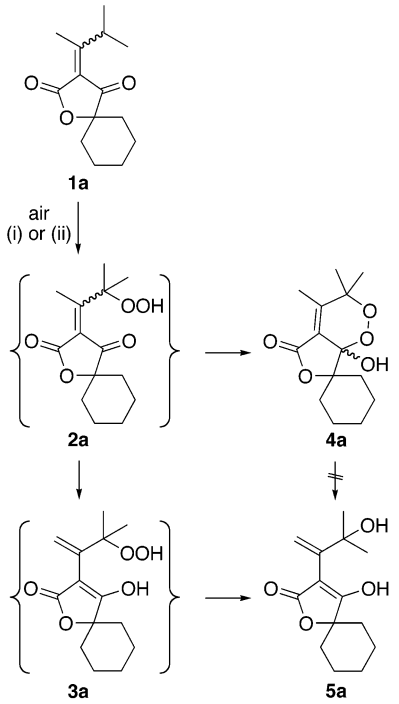
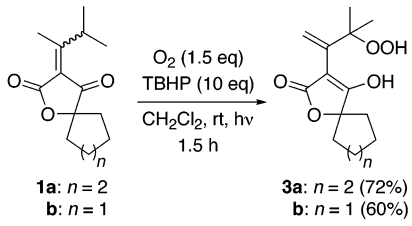
10.1021/jo030270a CCC: $25.00
Published on Web 11/11/2003

SCHEME 1. Radical Autoxidation of 3-Alkylidenedihydrofuran-2,4-diones 1a with Air[a]

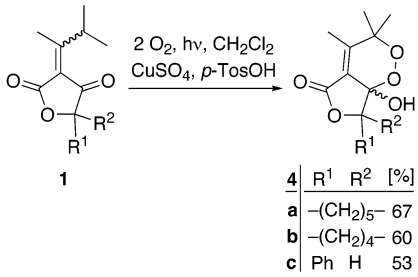


[a] Reagents and conditions: (i) CH_2Cl_2, 0 °C, 72 h, 6% (**4a**), 14% (**5a**); (ii) CH_2Cl_2, cat. $(PhCO_2)_2$, 34 °C, 48 h, 24% (**4a**), 35% (**5a**).

SCHEME 2. Radical Photooxygenation of 1 To Give Hydroperoxides 3

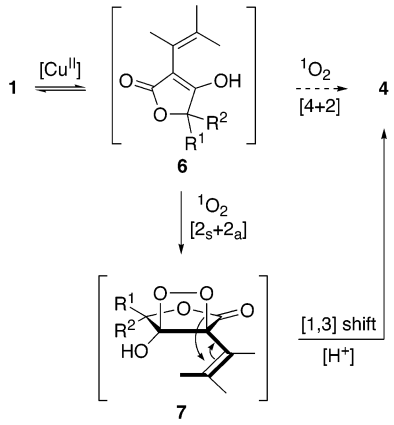


SCHEME 3. Photooxygenation of 1 To Give Endoperoxides 4



this step to be a sequential singlet oxygenation of the enol double bond of the 1,3-diene tautomer to give a 2-hydroperoxy-3-enone followed by a peroxyl radical rearrangement,[10] proceeding also in the dark and amenable to acceleration by radical sources such as AIBN or TBHP. Frimer et al. reported a similar domino two-step process for the conversion of 2-exo-alkylidenecycloalkanones to mixtures of hemiketal endoperoxides and allylic hydroperoxides which can be inhibited with DABCO and with radical scavengers such as DTBP.[11] More recent ab initio calculations generally favor a stepwise photoaddition of $^1O_2$ to conjugated dienes through a biradicaloid allyl-peroxide intermediate without involvement of perepoxides or vinyl dioxetanes.[12]

SCHEME 4. Conceivable Nonradical Mechanisms for the Photooxygenation of 1 to Give 4



In our case, no adverse effect on the formation of **4** from **1** was observed, when DTBP was added prior to irradiation, whereas DABCO completely prevented the formation of endoperoxides **4** and eventually initiated decomposition of the starting material. Neither were allylhydroperoxides such as **2** or **3** detected as intermediates enroute to **1** → **4** nor could **3** be cyclized to **4** under these conditions when prepared independently as described above.

These experimental results are hardly compatible with a Snider-Dussault mechanism. As a working hypothesis we rather assume a two-step process comprised of a $[2_s + 2_a]$ photoaddition of $^1O_2$ across the electron-rich enol double bond of **6** leading to a vinyl dioxetane **7** and of a subsequent pericyclic or zwitterionic [1,3] O-shift furnishing **4** (Scheme 4). The calculations cited above did not entirely rule out vinyl dioxetanes as conceivable precursors to endoperoxides but deemed them unlikely due to their usually observed thermal decomposition to carbonyl compounds.[13] A $[2_s + 2_a]$ cycloaddition mechanism had also been proposed for the photooxygenation of alkoxy-substituted *E*,*E*-1,3-dienes to give isolable vinyl dioxetanes.[14] Although rearrangements of the latter to the corresponding endoperoxides are hitherto unknown, examples of the reverse process, the acid-catalyzed rearrangement of ketal endoperoxides to aryl dioxetanes are well documented.[15] An alternative direct [4 + 2] cycloaddition of singlet oxygen[16] to **6** cannot be ruled out, but

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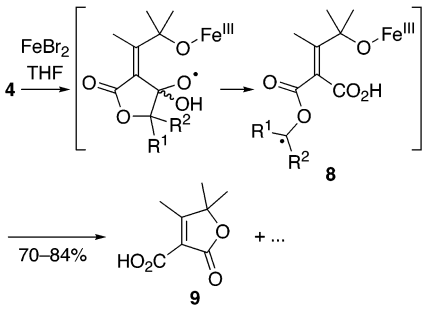
SCHEME 5. Biomimetic Reduction of 4 with $FeBr_2$



would not account for the requirement for an acid catalyst like *p*-TosOH.

With respect to potential antimalarial activity we have finally treated the endoperoxides **4** with pure anhydrous ferrous bromide, the simplest possible non-heme Fe(II) system.[17] As the chief product of a rapid redox reaction, complete after ca. 10 min at room temperature, we obtained butenolide **9**,[18] irrespective of the starting endoperoxide, as a surrogate marker for the involvement of tertiary carbon radical **8** (Scheme 5). This is consistent with the complex radical rearrangements proposed for the mechanism of action of artemisinin and related antiplasmodial compounds.[19] In-vitro screening of a series of derivatives of **4** against plasmodium-infested blood is currently underway. Hydroperoxides **3**, on the other hand, are reduced by $FeBr_2$ more quickly than **4** to give diols **5** as chelate complexes of Fe(III) in 50−60% yield.

Experimental Section

3-(3′-Hydroperoxy-3′-methylbut-1′-en-2′-yl)-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (3a). Under an atmosphere of nitrogen, a flame-dried Schlenk tube was charged with **1a** (80 mg, 0.34 mmol), absolute CH_2Cl_2 (40 mL), and *tert*-butyl hydroperoxide (320 μL, 10 equiv). It was sealed with a rubber stopper, pressurized with dry oxygen (20 mL) through the lateral gas inlet, and then placed ca. 8 cm from a glass-jacketed Heraeus low-pressure mercury lamp within a shared cooling bath kept at room temperature and entirely wrapped in aluminum foil. The solution was irradiated until the yellow color had faded (ca. 90 min) and all volatiles were removed in vacuo. The yellowish oil thus obtained was dropwise layered with pentane until a white suspension persisted and the mixture was then left in a refrigerator for crystallization. The supernatant was withdrawn, and the crystals were washed with pentane (2 mL) and dried in vacuo to leave 66 mg (72%) of colorless **3a**: mp 112 °C; R_f 0.26 (cyclohexane/diethyl ether 1:4); ν_{max} (KBr)/cm^{-1} 3446, 3322, 3175, 2942, 1711, 1654, 1615, 1229; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50−2.05 (m, 10 H), 1.44 (s, 6 H, Me), 5.60 (d, ^2J = 0.38 Hz, 1 H, =CH), 5.82 (d, ^2J = 0.38 Hz, 1 H, =CH′), 8.7 (s, br., 1 H, OH), 10.0 (s, br., 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 23.9, 25.5, 34.0, 83.8, 85.8, 100.1 (C-3), 121.0, 141.1, 175.8 (C-2), 181.5 (C-4); *m*/*z* (EI) 250 (4), 234 (28), 219 (17), 194 (17), 176 (13), 136 (43), 109 (46), 99 (53), 81 (61), 43 (100). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.76; H, 7.46. Crystal data deposited with CCDC (No. 220052).[20]

3-(3′-Hydroperoxy-3′-methylbut-1′-en-2′-yl)-4-hydroxy-1-oxaspiro[4.4]non-3-en-2-one (3b). Using the setup and the conditions described above, 105 mg of **3b** (60%) was obtained from **1b** (145 mg, 0.65 mmol) and TBHP (405 μL): mp 108 °C; R_f 0.15 (cyclohexane/diethyl ether 1:4); ν_{max} (KBr)/cm^{-1} 3410, 3055, 2981, 1709, 1655, 1615; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 6 H, Me), 1.70−2.20 (m, 8 H), 5.54 (s, 1 H, =CH), 5.66 (s, 1 H, =CH′), 10.2 (s, br., 2 H, OH, OOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 25.2, 36.2, 85.9, 90.6, 99.1 (C-3), 120.5, 138.1, 173.9 (C-2), 176.5 (C-4); *m*/*z* (EI) 254 (3) [M$^+$], 220 (88), 205 (29), 177 (37), 161 (22), 136 (44), 43 (100). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.44; H, 7.14. Found: C, 61.53; H, 7.12.

8-Hydroxy-4,5,5-trimethyl-1,6,7-trioxaspirotricyclo[2.4.0.5]-tetradecan-2-one (4a).[2] Under an atmosphere of nitrogen, a dry Schlenk tube was charged with **1a** (70 mg, 0.30 mmol), absolute CH_2Cl_2 (40 mL), anhydrous $CuSO_4$ (4.6 mg, 0.03 mmol), and *p*-toluenesulfonic acid (13 mg, 0.08 mmol), stoppered, and then pressurized with dry oxygen (10 mL) through the lateral gas inlet. It was irradiated for 1 h in the setup described above while vigorously stirring. The resulting mixture was filtered over a fritted Schlenk-type funnel, and the filtrate was concentrated in vacuo to give a yellow crude oil. This was purified by column chromatography (1.5 × 20 cm, silica gel 60; cyclohexane/diethyl ether 1:1): yield 53 mg (67%); colorless crystalline solid; mp 140 °C; R_f 0.47 (cyclohexane/diethyl ether 1:4); ν_{max} (KBr)/cm^{-1} 3683, 3155, 2989, 2249, 1789, 1472, 1378, 1096; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40−1.80 (m, 10 H), 1.33, 1.43 (s, 6 H, Me), 2.17 (s, 3 H, Me), 5.00 (s, br., 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 21.4, 24.8, 28.9, 31.8, 80.4, 87.0, 99.3, 122.3, 153.7, 166.7; *m*/*z* (EI) 251 (1), 236 (50) [M$^+$ − O_2], 218 (32), 203 (20), 181 (11), 155 (20), 153 (22), 137 (98), 43 (100).

8-Hydroxy-4,5,5-trimethyl-1,6,7-trioxaspirotricyclo[2.4.0.4]-tridecan-2-one (4b). A 52 mg portion of **4b** (60%) was obtained as described above from **1b** (75 mg, 0.34 mmol), $CuSO_4$ (8 mg), *p*-toluenesulfonic acid (12 mg), and oxygen (10 mL): mp 140 °C; R_f 0.62 (cyclohexane/diethyl ether 1:4); ν_{max} (KBr)/cm^{-1} 3448, 3377, 2919, 1736, 1678, 1243; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60−2.20 (m, 8 H), 1.35, 1.46 (s, 6 H, Me), 2.15 (s, 3 H, Me), 3.70 (s, br., 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 21.6, 23.2, 23.8, 31.5, 34.0, 80.5, 96.1, 98.5, 122.6, 152.9, 166.5; *m*/*z* (EI) 222 (27) [M$^+$ - O_2], 204 (46), 181 (100), 165 (32), 153 (40), 137 (43). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.44; H, 7.14. Found: C, 61.34; H, 7.11. Crystal data deposited with CCDC (No. 220053).[20]

7a-Hydroxy-3,3,4-trimethyl-5-oxo-7-phenyl-(5*H*)-furo-[3,4-*c*]-3,7*a*-dihydro[1,2]dioxin (4c). A 43 mg portion of **4c** (53%; 1.7:1 mixture of diastereomers) was obtained as described above from **1c**[1] (70 mg, 0.29 mmol), $CuSO_4$ (7 mg), *p*-toluenesulfonic acid (10 mg), and oxygen (13 mL): mp 28 °C; R_f 0.43 (cyclohexane/diethyl ether 1:4); mixture of diastereoisomers ν_{max} (film)/cm^{-1} 3295, 3154, 2978, 1725, 1642, 1384; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99/1.38, 1.28/1.52 (s, 6 H, Me), 2.18/2.20 (s, 3 H, Me), 3.20/4.15 (s, br., 1 H, OH), 5.20/5.56 (s, 1 H), 7.00−7.10 (m, 2 H), 7.30−7.40 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8/12.9, 21.3/21.9, 22.7/23.5, 80.6/80.7, 98.1/98.4, 119.5/121.3, 125.3/126.5, 128.4/128.7, 129.0/129.3, 131.4/133.1, 155.0/156.0, 166.4/167.1; *m*/*z* (EI) 276 (18) [M$^+$], 243 (5), 205 (4), 165 (6), 105 (10), 41 (100). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.24; H, 5.84. Found: C, 65.33; H, 5.87.

3-Hydroxycarbonyl-4,5,5-trimethyl-2,5-dihydrofuran-2-one (9). $FeBr_2$ (14 mg, 0.065 mmol) was suspended in dry THF (20 mL) and treated with a solution of **4a** (18 mg, 0.067 mmol) in THF (1 mL). After being stirred for 90 min, the mixture was diluted with water (20 mL) and extracted repeatedly first with

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(20) Crystallographic data for the structures of **3a** and **4b** have been deposited with the Cambridge Crystallographic Data Centre [CCDC Nos. 220052 (**3a**); 220053 (**4b**)]. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code+(1223) 336-033, e-mail: teched@chemcrys.cam.ac.uk).

CH_2Cl_2 and then with diethyl ether. The combined organic phases were dried over $MgSO_4$ and concentrated on a rotary evaporator. Recrystallization of the brownish crude solid from CH_2Cl_2/pentane left off-white crystals of **9**: yield 9.5 mg (84%); mp 107 °C (lit.[18] mp 107−107.8 °C); ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.4, 24.0, 89.2, 115.1, 160.5, 172.8, 184.9.

Acknowledgment. We acknowledge the generous support from the British EPSRC (Grant No. GR/M97961) and the Deutsche Forschungsgemeinschaft (Grant No. Scho 402/7-2).

Supporting Information Available: X-ray crystallographic data for **3a** and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030270A