Synthesis of New Cantharimide Analogues Derived from 3-Sulfolene

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Abstract: New types of norcantharimide analogues were prepared by three methods: epoxidation, photooxidation, and bromination. Epoxidation of deoxynorcantharimide with *m*-chloroperoxybenzoic acid gave an isomeric mixture. The selective formation of the *syn*-isomers was attributed to dipole–dipole interactions between the peracid and imide moiety. Photooxidation of deoxynorcanthamide gave *syn*- and *anti*- hydroperoxide analogues through ene addition of singlet oxygen; the *anti*-hydroperoxide was the major product in this case, as a result of the steric effect of the imide ring. Bromination of deoxynorcantharimide and subsequent transformations gave a pyrrolidine and the phthalimide core structure.

Key words: ene reactions, epoxidation, photooxidations, halogenation, stereoselective synthesis, heterocycles

Cantharidin (**1**; Figure 1) is a naturally occurring cyclic anhydride found in many species of blister beetles, most notably *Lytta vesicatoria*, widely known as Spanish fly.[2] Spanish fly induces the formation of blisters upon contact with skin, and its ingestion produces dose-dependent physiological symptoms, including abdominal pain and gastrointestinal hemorrhage. Although it is highly toxic, dried Spanish fly has been used as an aphrodisiac since the time of the ancient Greeks and Romans. Spanish fly has also been used as a natural remedy in China for the past 2000 years, and it has been used worldwide as an anticancer agent since 1264, particularly in the treatment of hepatoma and oesophageal carcinoma.[3] Cantharide and its analogues are of considerable interest as potential inhibitors of the serine/threonine protein phosphates 1 and 2A (PP1 and PP2A).[4]

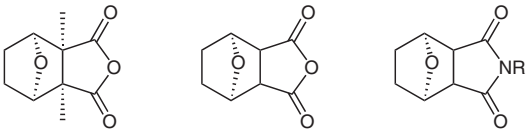

Figure 1

Norcantharidin, the demethylated analogue of cantharidin, also shows anticancer activity and stimulates bone marrow, while showing no nephrotoxicity. Derivatives of modified synthetic norcantharidin (**2**) and N-substituted norcantharimides (**3**) are potentially useful as anticancer agents. Cantharimides have been tested for various effects and have been shown to inhibit xanthenes oxidase[5] and to have antiplatelet effects on thrombin, arachidonic acid, collagen, and platelet-activating factor-induced aggregation. *N*-Methylcantharimide (**3**, R = Me), for example, shows tumor-inhibitory action in animals. McCluskey et al.[6] synthesized various norcantharimides through simple synthetic modifications of norcantharidin. This facilitated the development of a novel series of norcantharimides displaying modest-to-good broad-spectrum cytotoxicity against various carcinomas. Lin et al.[7] reported that cantharimide derivatives containing aliphatic, aryl, or pyridyl groups showed some effects in vitro against HepG2 and HL-60 cells, suggesting that they may have anticancer activity. Chan and Tang[8] studied the synthesis and cytotoxicity of some cantharimide derivatives, and they concluded that cantharimide has shown relatively less toxicity in treatment of nonmalignant hematological disorders of bone marrow cells.

Here, we report a synthesis of a series of new norcantharimide analogues, including **4**–**6** (Figure 2), from 3-sulfolene (**7**; 2,5-dihydrothiophene 1,1-dioxide) and the characterization of the products.

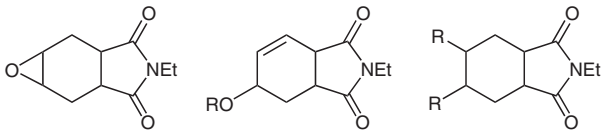

Figure 2

Our approach involved assembling the cyclic scaffold by Diels–Alder cycloaddition of maleic anhydride (**8**) to 3-sulfolene (**7**) to give the dione **9**, as reported in the literature.[9] Condensation of ethylamine with dione **9** in the presence of a 3:1 mixture of toluene and triethylamine gave the imide **10** in 80% yield (Scheme 1).[6]

Imide **10** is a deoxy derivative of *N*-ethylnorcantharimide (**3**, R = Et). We used three methods to prepare synthetic analogues of **3**: epoxidation, an ene reaction involving singlet oxygen, and bromination. Epoxidation of imide **10** with *m*-chloroperoxybenzoic acid at room temperature gave an isomeric mixture of epoxides *syn*-**4a** and *anti*-**4b** in a ratio of 4:1 (determined from the ^{1}H NMR spectrum of the crude reaction product mixture) (Scheme 2). The isomeric mixture of epoxides **4a** and **4b** was separated by column chromatography, and the structures of **4a** and **4b**

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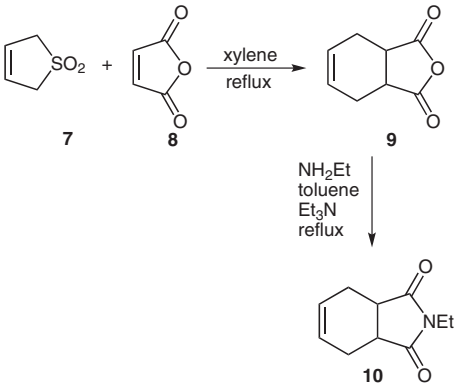
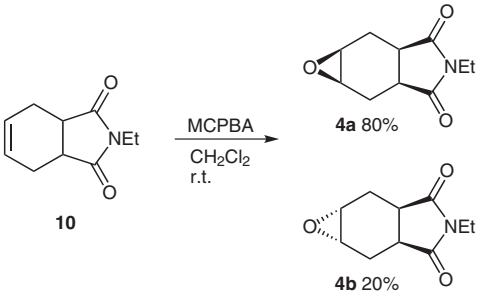


Scheme 1



Scheme 2

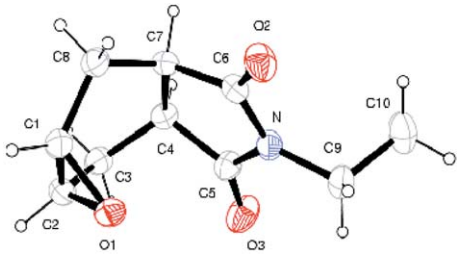
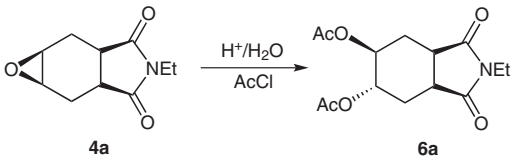


Figure 3 Molecular structure of compound **4a**

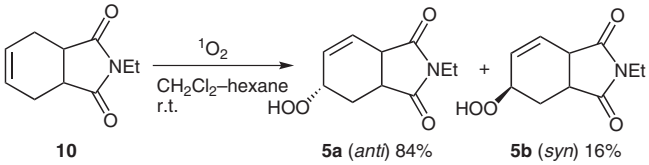
were assigned by ^{1}H and ^{13}C NMR spectrocopy and confirmed by single-crystal X-ray analysis (Figure 3).

The two faces of the double bond in **10** are not symmetric, and *syn*- or *anti*- product may form with respect to the imide ring. Attack on the double bond was expected to occur predominantly from the more-open face opposite the imide ring. However, contrary to expectations, the *syn*-isomer was obtained as the major product of the reaction, showing that electronic effects dominate steric effects. Similar results, in which electronic effects overshadow steric effects, have been observed in the stereoselective oxidation of 5,6-dimethyl-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-diones by *m*-chloroperoxybenzoic acid.[10] The predominance of the *syn*-isomer over the *anti*-isomer can be explained in terms of the dipole–dipole interaction between the peracid and imide moieties of **10**. In the epoxy derivative **4**, the epoxy oxygen atom is attached to the carbon atoms in the 2- and 3-positions unlike norcantharimide (**3**, R = H), where it is attached at the 1- and 4-positions. Acid-catalyzed ring cleavage of *syn*-epoxide **4a**, followed by acetylation, gave imide **6a** in 70% yield (Scheme 3). The structure of **6a** was assigned by ^{1}H and ^{13}C NMR spectroscopy. There are two distinct AB-systems in the ^{1}H NMR spectrum, corresponding to six methylene protons. The methyl protons resonate at $\delta = 2.0$ and 1.9 ppm. The structure was confirmed by double resonance experiments and by the presence of 14 lines in the ^{13}C NMR.



Scheme 3

To synthesize other derivative of **3**, imide **10** was subjected to a singlet oxygen ene reaction.[11] Tetraphenylporphyrin-sensitized photooxygenation of **10** in dichloromethane at room temperature gave two isomeric products *anti*-**5a** and *syn*-**5b** in a ratio of 5.25:1 (determined by ^{1}H NMR spectroscopy of the crude product) (Scheme 4).



Scheme 4

Compound *anti*-**5a** was isolated by fractional crystallization from the mixture and its structure was assigned by ^{1}H and ^{13}C NMR spectroscopy. The configuration of the hydroperoxide was confirmed by single-crystal analysis (Figure 4).

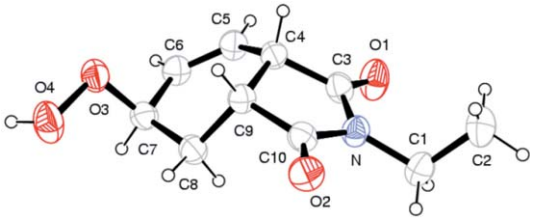
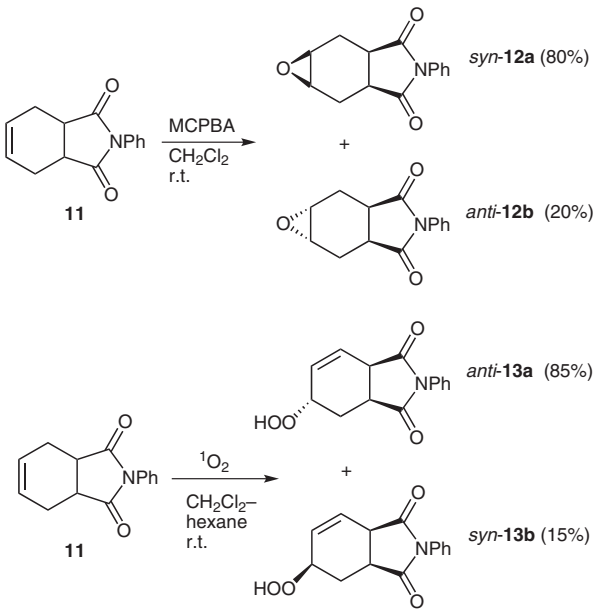


Figure 4 Molecular structure of hydroperoxide **5a**

The *syn*-**5b** isomer could not be purified by crystallization or by the usual chromatographic techniques, so its structure was elucidated by comparison of the ^{1}H NMR spectrum of the isomeric *anti*-**5a** with that of the isomeric mixture. The predominant formation of *anti*-hydroperoxide **5a** cannot be explained solely in terms of steric effects of the imide group. The oxygen molecule is nonpolar and cannot therefore interact with the amide or carbonyl group, whereas oxidation by *m*-chloroperoxybenzoic acid

proceeds predominantly in favor of the *syn*-product **4a** as a result of a dipole–dipole interaction.

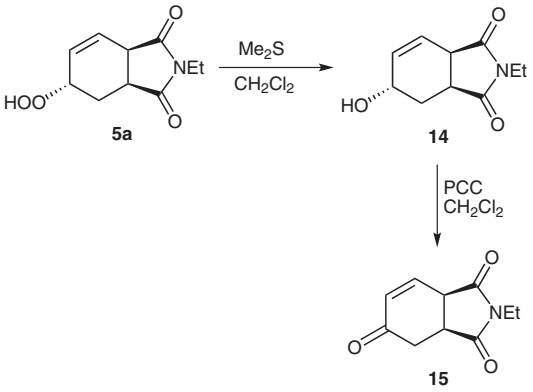
When the ethyl group in **10** was replaced by a phenyl group, the epoxidation and ene reactions of compound **11** proceeded in a similar manner to those of compound **10** (Scheme 5).



Scheme 5

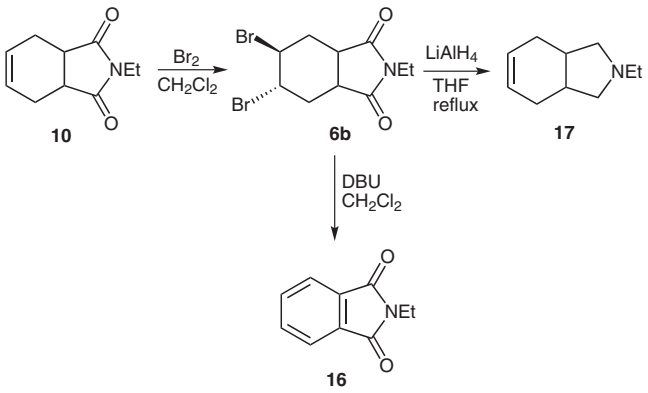
The peroxide group in *anti*-**5a** was selectively reduced by using dimethyl sulfide as a reducing agent,[12] to give the desired hydroxy derivative **14** (Scheme 6). The structure of **14** was assigned by ^1H and ^{13}C NMR spectroscopy. In the ^1H NMR spectrum of compound **14**, there are two distinct AB-systems corresponding to two olefinic protons and two methylene protons. Although the hydroperoxide proton of *anti*-**5a** appeared at δ = 8.59 ppm, the hydroxy proton of **14** moved to δ = 4.12 ppm and appeared as a broad singlet after cleavage of the hydroperoxide bond.

Treatment of compound **14** with pyridinium dichromate gave ketone **15** as the sole product. The structure of **15** was assigned by ^1H and ^{13}C NMR spectroscopy. In the ^1H NMR spectrum of compound **15**, there are three distinct AB-systems corresponding to two olefinic protons, two methine (CH) protons, and two methylene protons. These protons resonated at δ = 6.88–6.19, 3.75–3.54, and 3.05–2.69 ppm respectively. The CH_2 protons of ethyl groups appears as quartet at 3.56 ppm and methyl protons resonates at 1.15 ppm. The ^{13}C NMR spectrum was also consistent with structure **15**.



Scheme 6

Imide **10** was smoothly brominated in dichloromethane to give the expected *trans*-dibromo compound **6b** in high yield (Scheme 7). Attempts to synthesize the corresponding diene by elimination of hydrogen bromide from dibromide **6b** were unsuccessful; treatment of **6b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in conversion of the dibromide into the aromatic phthalimide derivative **16**,[13] instead of the expected diene (Scheme 7). The structure of **16** was assigned by ^1H and ^{13}C NMR spectroscopy.



Scheme 7

We decided to carry out a reduction reaction to prepare derivatives from **6b**. Surprisingly, reduction of dibromide **6b** with lithium aluminum hydride gave the hexahydroindole **17** exclusively.[14] The formation of compound **17** can be explained by reductive elimination of bromine atoms. The hydride reacts in a similar manner to zinc metal atoms in the dibromide elimination reaction. To the best of our knowledge, this is a unique example of a reaction that gives a pyrrolidine by lithium aluminum hydride induced elimination and reduction. The inversion of the ethyl group in **17** was deduced from the duplication of six overlapping lines in the ^{13}C NMR spectrum. Product **17** was also obtained directly by reduction of imide **10** with lithium aluminum hydride.

To summarize, we have developed novel and efficient routes for the synthesis of new classes of norcantharimide analogues **4**, **5**, **6**, **12**, and **13**, starting from readily available 3-sulfolene. The methods should be applicable to the synthesis of a large number of new norcantharimide analogues. Furthermore, the difference in the distributions of the products obtained from **10** and **11** by oxidation with *m*-chloroperoxybenzoic acid and by photooxygenation was rationalized in terms of dipole–dipole interactions and steric effects that direct the stereochemical outcome

of the reaction. Note that the synthesis the cantharimide derivatives is versatile and has further applications. We obtained a key compound for the preparation of pyrrolidines that may be useful in preparing biologically active compounds. We are currently working on extending this method to permit studies on biological properties of cantharimide analogues.

Column chromatography: silica gel 60 (70–230 mesh) and neutral Al_2O_3 (III activated) were used. Solvents were purified and dried by standard procedures before use. Melting points were determined on a Büchi-539 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer. Elemental analyses were carried out with a Leco CHNS-932 instrument.

3a,4,7,7a-tetrahydro-2-benzofuran-1,3-dione (9)
Maleic anhydride (6.23 g, 63.3 mmol) was added over 5 h to a magnetically stirred soln of 3-sulfolene (**7**; 10.0 g, 84.6 mmol) in xylene (10 mL) at 150 °C. The mixture was then cooled to r.t. The solvents were removed by rotary evaporation the product was crystallized (CH_2Cl_2–hexane) as white crystals; yield: 6.85 g (93–97%); mp 99–102 °C.

2-Ethyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (10)
$EtNH_2$ (18 mmol, 1 equiv) was added to a magnetically stirred soln of dione **9** (18 mmol, 1 equiv) and Et_3N (1.5 mL) in toluene (15 mL), and the mixture was refluxed for 36 h. The soln was cooled, diluted with EtOAc (45 mL), washed with sat. aq $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude product was recrystallized (EtOAc–hexanes) to give colorless crystals; yield: 73%; mp 43–45 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.87 (m, 2 H), 3.50 (q, *J* = 7 Hz, 2 H), 3.05 (m, 2 H), 2.60 (dm, *J* = 16 Hz, A part of AB system, 2 H), 2.20 (dm, *J* = 16 Hz, B part of AB system, 2 H), 1.00 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CHCl_3$): δ = 180.0, 127.9, 39.3, 34.1, 23.7, 13.2.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.02; H, 7.31; N, 7.73.

2-Phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (11)
Prepared from **9** (18 mmol, 1 equiv) and $PhNH_2$ (18 mmol, 1 equiv) by using the above procedure for **10**. Colorless crystals; yield: 78%; mp 114–115 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 5.98 (m, 2 H), 3.26 (m, 2 H), 2.72 (dm, *J* = 15.5 Hz, A part of AB system; 2 H), 2.31 (dm, *J* = 15.5 Hz, B part of AB system, 2 H).

^{13}C NMR (100 MHz, $CHCl_3$): δ = 179.4, 132.3, 129.0, 128.8, 128.1, 126.7, 39.5, 24.0.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 73.99, H, 5.77; N, 6.16. Found: C, 73.99; H, 5.77; N, 6.16.

(*syn*)-4-Ethyltetrahydro-1a*H*-oxireno[*f*]isoindole-3,5(2*H*,4*H*)-dione (4a) and (*anti*)-4-Ethyltetrahydro-1a*H*-oxireno[*f*]isoindole-3,5(2*H*,4*H*)-dione (4b)
The imide **10** (13.3 mmol, 1 equiv), 70–80% MCPBA (20 mmol, 1.5 equiv), and excess $NaHCO_3$ were magnetically stirred in CH_2Cl_2 (120 mL) for 6 h. The resulting slurry was transferred to a separatory funnel and treated with 15% aq $Na_2S_2O_3$ (50 mL) to eliminate unreacted peracid. The soln was then washed successively with 10% aq $NaHCO_3$ (50 mL) and brine, dried ($MgSO_4$), and concentrated to give a crude product; yield: 91%. The isomeric products were separated by column chromatography [EtOAc–hexane (first isomer, 15:85; second isomer, 40:60)] then crystallized (CH_2Cl_2–hexanes).

4a
Colorless crystals; mp 75–76 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.45 (qd, *J* = 7.1, 1.0 Hz, 2 H), 3.19 (m, 2 H), 2.85 (m, 2 H), 2.54 (m, 2 H), 1.83 (m, 2 H), 1.07 (td, *J* = 7.1, 1.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CHCl_3$): δ = 179.6, 49.3, 35.4, 33.7, 23.2, 13.1.

4b
Colorless crystals; mp 79–80 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.53 (q, *J* = 7.3 Hz, 2 H), 3.13 (m, 2 H), 2.71 (m, 3 H), 2.68 (m, 1 H), 2.13 (dd, *J* = 15, 2 Hz, 2 H), 1.15 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CHCl_3$): δ = 180.5, 50.9, 35.6, 34.3, 22.6, 12.5.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.91; H, 7.16; N, 6.81.

(*syn*)-4-Phenyltetrahydro-1a*H*-oxireno[*f*]isoindole-3,5(2*H*,4*H*)-dione (12a) and (*anti*)-4-Phenyltetrahydro-1a*H*-oxireno[*f*]isoindole-3,5(2*H*,4*H*)-dione (12b)
These were prepared in a similar manner to **4a** and **4b** described above.

12a
Colorless crystals; mp 217–218 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5 H), 3.25 (m, 2 H), 2.95 (dm, *J* = 4.3 Hz, 2 H), 2.82 (dm, *J* = 15.4 Hz, A part of AB system, 2 H), 2.25 (ddd, *J* = 15.4, 5.1, 2.4 Hz, B part of AB system, 2 H).

^{13}C NMR (100 MHz, $CHCl_3$): δ = 179.9, 132.9, 129.4, 128.8, 127.0, 51.0, 35.9, 23.0.

12b
Colorless crystals; mp 209–210 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5 H), 3.24 (m, 2 H), 2.95 (m, 2 H), 2.82 (dm, *J* = 15.3 Hz, A part of AB system, 2 H), 2.25 (dm, *J* = 15.3 Hz, A part of AB system, 2 H).

^{13}C NMR (100 MHz, $CHCl_3$): δ = 179.9, 132.8, 129.4, 128.8, 126.9, 51.0, 35.9, 23.0.

Singlet Oxygen Ene Reactions of 10 and 11
Tetraphenylporphyrin (20 mg) was added to a stirred soln of dione **10** or **11** (5.5 mmol, 1 equiv) in CH_2Cl_2 (150 mL). The mixture was irradiated with a tungsten–halogen projection lamp (500 W) while oxygen was passed through the soln and the mixture was stirred at r.t. The solvent was then evaporated at 30 °C under reduced pressure. The major products (**5a** or **13a**) were separated by fractional crystallization in CH_2Cl_2–hexanes.

(*anti*)-2-Ethyl-5-hydroperoxy-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (5a)
Mp 101–102 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.3 (s, 1 H, OOH), 6.1 (m, 2 H), 4.46 (m, 1 H), 3.53 (q, *J* = 7 Hz, 2 H), 3.46 (dm, *J* = 8 Hz, A part of AB system, 1 H), 3.23 (q, *J* = 8 Hz, B part of AB system, 1 H), 2.18 (t, *J* = 6 Hz, 2 H), 1.14 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7, 176.2, 129.1, 126.2, 75.5, 41.3, 36.3, 34.0, 25.5, 13.1.

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.92; H, 6.38; N, 6.61.

(*anti*)-2-Phenyl-5-hydroperoxy-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (13a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1 H, OOH), 7.47 (m, 5 H), 6.17 (m, 2 H), 6.29 (m, 1 H), 3.66 (dm, *J* = 8 Hz, A part of AB system, 1 H), 3.23 (q, *J* = 8 Hz, B part of AB system, 1 H), 2.29 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 175.3, 131.8, 129.4, 129.3, 128.9, 126.5, 126.1, 75.4, 41.5, 36.5, 25.6.

(3a*S,5*S**,7a*R**)-2-Ethyl-5-hydroxy-3a,4,5,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (14)**

A soln of peroxide **5a** (300 mg, 1.42 mmol) in CH_2Cl_2 (25 mL) was added to magnetically stirred slurry of Me_2S (176 mg, 2.84 mmol) in CH_2Cl_2 (25 mL) at r.t. After the addition was complete (~10 min), the mixture was stirred for 6 h. The solvent was then removed by rotary evaporation, and the residue was extracted with CH_2Cl_2 (3 × 30 mL). The extracts were dried (Na_2SO_4) and the soln was concentrated to give a residue that was crystallized (CH_2Cl_2–hexanes) to give colorless crystals; yield: 200 mg (72%); mp 93–94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (dtd, *J* = 10.1, 2.2, 0.7 Hz, A part of AB system, 1 H), 5.85 (ddd, *J* = 10.1, 4.2, 1.8 Hz, B part of AB system, 1 H), 4.11 (m, 1 H, OH), 3.49 (q, *J* = 7.3 Hz, 2 H), 3.44 (tt, *J* = 6.4, 1.8 Hz, 1 H), 3.18 (dt, *J* = 5.5, 1.1 Hz, 1 H), 2.43 (dtd, A part of AB system *J* = 13, 4.9, 0.7 Hz, 1 H), 1.73 (ddd, B part of AB system *J* = 13, 9.2, 6.2 Hz, 1 H), 1.09 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8, 176.8, 135.2, 122.9, 62.6, 41.1, 37.0, 34.0, 30.2, 13.1.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.53; H, 6.78; N, 7.15.

(3a*S,7a*R**)-2-Ethyl-3a,7a-dihydro-1*H*-isoindole-1,3,5(2*H*,4*H*)-trione (15)**

Hydroxy derivative **14** (103 mmol, 1 equiv) at 0 °C was added to a mixture of PCC (228 mmol, 2 equiv) and powdered MS (3 Å, half the weight of PCC) in anhyd CH_2Cl_2 (25 mL). The mixture was stirred 4 h at r.t., then CH_2Cl_2 was evaporated and to the residue was slurried in Et_2O (50 mL). The slurry was stirred and filtered through a pad of Celite. The residue was washed with Et_2O (3 or 4 × 25 mL) and filtered. The filtrate was concentrated to give virtually pure ketone; yield: 73 mg (72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (dd, A part of AB system, *J* = 10.3, 4.4 Hz, 1 H), 6.18 (dd, B part of AB system, *J* = 10.3, 2.6 Hz, 1 H), 3.75 (m, A part of AB system, 1 H), 3.56 (q, *J* = 7.3 Hz, 2 H), 3.44 (m, B part of AB system, 1 H), 3.05 (dd, A part of AB system, *J* = 17.6, 3.3 Hz, 1 H), 2.69 (dd, B part of AB system, *J* = 17.6, 9.2 Hz, 1 H), 1.15 (t, *J* = 7.3 Hz, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.6, 177.0 (2C), 141.9, 131.6, 41.8, 37.7, 34.5, 33.5, 13.0.

2-Ethyl-1,3-dioxooctahydro-1*H*-isoindole-5,6-diyl Diacetate (6a)

A catalytic amount of concd H_2SO_4 was added to stirred soln of epoxide **4a** (200 mg, 0.77 mmol) in Ac_2O (2 mL), and the mixture was stirred for 3 h at r.t. The mixture was cooled to 0 °C, H_2O (20 mL) was added, and the mixture stirred for 1 h. The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were washed with sat. aq $NaHCO_3$ (15 mL) and H_2O (15 mL), then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a colorless liquid; yield: 118 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.91 (m, 2 H), 3.53 (q, *J* = 7.1 Hz, 2 H), 2.99 (m, A part of AB system, 1 H), 2.91 (m, B part of AB system, 1 H), 2.15–2.06 (m, 4 H), 2.05 (s, 3 H), 1.96 (s, 3 H), 1.14 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6, 178.1, 169.7 (2C), 69.4, 69.0, 36.9, 36.3, 33.8, 25.8, 24.4, 21.1, 21.0, 13.1.

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.65; H, 6.52; N, 4.82.

5,6-Dibromo-2-ethylhexahydro-1*H*-isoindole-1,3(2*H*)-dione (6b)

A soln of Br_2 (0.89 g, 5.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 10 min to a magnetically stirred soln of epoxide **10** (1.0 g, 5.6 mmol) in anhyd CH_2Cl_2 (30 mL) at 0 °C. The mixture was stirred for an additional 30 min at r.t. Evaporation of the solvent and crystallization of the residue from CH_2Cl_2–hexanes at 0 °C gave white crystals; yield: 1.86 g (98%); mp 133–134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.49 (m, 2 H), 3.53 (q, *J* = 7.1 Hz, 2 H), 3.13 (q, *J* = 10.3 Hz, 1 H), 2.86 (dt, *J* = 8.1, 2.6 Hz, 1 H), 2.78 (ddd, A part of AB system, *J* = 15.8, 8.1, 4.0 Hz, 1 H), 2.65 (dt, B part of AB system, *J* = 15.8, 2.6 Hz, 1 H), 2.48 (ddd, A part of AB system, *J* = 15.4, 10.3, 2.9 Hz, 1 H) 2.40 (dddd, B part of AB system, *J* = 15.4, 7.6, 4.0, 1.1 Hz, 1 H), 1.12 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5, 177.4, 49.3, 48.6, 36.3, 35.9, 33.9, 29.0, 26.5, 12.9.

Anal. Calcd for $C_{10}H_{13}Br_2NO_2$: C, 35.43; H, 3.86; N, 4.13. Found: C, 35.40; H, 3.77; N, 4.11.

2-Ethyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole (17)

A soln of dibromide **6b** (1 g, 2.9 mmol) in THF (20 mL) was added over 0.5 h to a magnetically stirred slurry of $LiAlH_4$ (0.67 g, 17.7 mmol) in anhyd THF (50 mL) under N_2 at 0 °C, and the mixture was then stirred at 60 °C for 4 h. The mixture was cooled to r.t., EtOAc (5 mL) was added, and the mixture was washed with sat. aq NH_4Cl (10 mL). The solid was filtered off and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with sat. aq NH_4Cl (20 mL) then dried (Na_2SO_4) and concentrated to give the crude amine that was purified by column chromatography [Al_2O_3 (20 g), EtOAc–hexanes (20:80)] to give a pale-yellow liquid; yield: 0.3 g (68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.42 (m, 2 H), 2.56 (m, 2 H), 2.10 (m, 2 H), 2.02 (m, 2 H), 1.79 (m, 4 H), 1.52 (m, 2 H), 0.72 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.46 (127.37), 60.49 (60.42), 50.54 (50.46), 35.51 (35.46), 26.35 (26.31), 13.89 (13.83).

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.21; H, 5.21; N, 7.95.

2-Ethyl-1*H*-isoindole-1,3(2*H*)-dione (16)

A solution of DBU (0.24 g, 1.62 mmol) in CH_2Cl_2 (10 mL) was added to a soln of dibromide **6b** (0.25 g, 0.73 mmol) in CH_2Cl_2 (10 mL) at r.t., and the mixture was stirred for 12 h at r.t. The solid was filtered off and the organic phase was poured into H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with sat. aq NH_4Cl (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give a colorless liquid;[14] yield: 0.09 g (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (m, 4 H), 3.72 (q, *J* = 7.1 Hz, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 134.0, 132.5, 123.3, 33.1, 14.1.

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.0. Found: C, 68.21; H, 5.21; N, 7.95.

Crystallography

Crystals of **4a** and **4b** were obtained from CH_2Cl_2–hexane.

Crystal data for **4a**: $C_{10}H_{13}NO_3$, crystal system, space group: triclinic, $P\bar{1}$ (no. 2); unit cell dimensions: *a* = 5.0310(2), *b* = 7.7379(3),

c = 12.9939(4) Å, α = 83.90(2), β = 82.63(3), γ = 77.65(2)°; volume: 488.46(9) Å^3; Z = 2; calculated density: 1.33 g/cm^3; absorption coefficient: 1.33 mm^{-1}; F(000): 208; θ-range for data collection 2.7 –26.4°; refinement method: full-matrix least-square on F^2; data/parameters: 1992/128; goodness-of-fit on F^2: 1.053; final R indices [$I > 2\sigma(I)$]: R_1 = 0.051, wR_2 = 0.130; R indices (all data): R_1 = 0.073, wR_2 = 0.144.

Crystal data for **5a**: $C_{10}H_{13}NO$, crystal system, space group: monoclinic, $P2_1/n$; unit cell dimensions: a = 7.5245(2), b = 8.8253(3), c = 15.8110(6) Å, α = 90, β = 103.16(3), γ = 90°; volume: 1022.35(5) Å^3; Z = 4; calculated density: 1.37 g/cm^3; absorption coefficient: 0.107 mm^{-1}; F(000): 448; θ-range for data collection 2.7–26.5°; refinement method: full-matrix least-square on F^2; data/parameters: 2097/138; goodness-of-fit on F^2: 1.046; final R indices [$I > 2\sigma(I)$]: R_1 = 0.063, wR_2 = 0.144; R indices (all data): R_1 = 0.104, wR_2 = 0.167; largest diff. peak and hole: 0.180 and -0.192 e Å^{-3}; largest diff. peak and hole: 0.136 and –0.142 e Å^{-3}

Crystallographic data, excluding structure factors, for compounds **4a** and **5a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 789887 and 789999, respectively. Copies can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK or e-mail: deposit@ccdc. cam.ac.uk.

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