MDPI

Short Note

2,6-*exo*-8,10-*exo*-4-Butyl-9-oxa-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}] undecane-3,5-dione

R. Alan Aitken *, Fiona M. Fotherby and Alexandra M. Z. Slawin

EaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife KY16 9ST, UK; fmf1@st-and.ac.uk (F.M.F.); amzs@st-and.ac.uk (A.M.Z.S.)
* Correspondence: raa@st-and.ac.uk; Tel.: +44-1334-463865

Abstract: The title epoxide was obtained by spontaneous epoxidation of the corresponding unsaturated imide in air or by peracid oxidation. Unambiguous assignment of the ^{1}H- and ^{13}C-NMR spectra is achieved by comparison between analogous compounds and its X-ray structure confirms the *exo,exo*-configuration.

Keywords: epoxide; cyclic imide; X-ray structure; NMR assignment

1. Introduction

Cyclic carboximides have a wide range of applications, as described in a recent monograph [1]. In particular, those fused to a norbornene skeleton have been of interest for ring-opening metathesis polymerisation (ROMP) to produce a variety of functional polymers [2–5], while norbornane-fused examples have been patented for the medical treatment of depression [6]. In a continuation of our work on heterocyclic synthesis based on addition of the crystalline adduct of tributylphosphine and carbon disulfide to norbornene systems [7,8], we recently prepared the *N*-butyl imide **2** and were surprised to observe that this underwent spontaneous oxidation upon storage in air over a period of months to afford the epoxide **3** (Scheme 1). In this paper, we describe the full characterisation of this previously unknown compound, including its X-ray structure, as well as spectroscopic characterisation of the precursor **2** and the related epoxy anhydride **4**, which allowed unambiguous assignment of the NMR spectra for all three compounds (Supplementary Materials).

Scheme 1. Structures, numbering, and interconversion of compounds **1–4**.

2. Results

Our synthesis started from *exo*-anhydride **1**, readily available [9] from thermal isomerisation of the *endo*-isomer formed by Diels–Alder cycloaddition of maleic anhydride with cyclopentadiene. As an improvement to the literature procedure, we used acetone [2] rather than the more toxic benzene to separate the isomers by recrystallisation. This was converted into *N*-butyl imide **2** in moderate yield using a literature method [3] involving reaction with butylamine in the presence of hexamethyldisilazane. Although product **2** initially gave the expected NMR spectroscopic data, rerunning the spectra after storage under normal laboratory conditions for a few months showed partial conversion into a new compound, which rather surprisingly proved to be epoxide **3**. Specifically, a spectrum run after 11 months showed a composition of 30% **2** to 70% **3,** while after 20 months, this had changed further to 15% **2** and 85% **3**. Such facile epoxidation of a bicyclic alkene in air is unusual but has been observed before in similar compounds such as **5** [10], for which the X-ray structure was found to be disordered by the presence of 6% of the cocrystallised monoepoxide **6** (Scheme 2). In an earlier quantitative study [11], anhydride **7** with the double bond *anti* to the anhydride function was found to epoxidise 19 times more rapidly than isomer **8** with the double bond *syn* to the anhydride and for diene **9,** epoxidation of the double bond *anti* to the anhydride to give **10** was favoured over epoxidation of the *syn* double bond by a rate factor of over 8:1. It therefore seems clear that the spatial arrangement of the imide function in compound **2** makes its double bond particularly susceptible to oxidation.
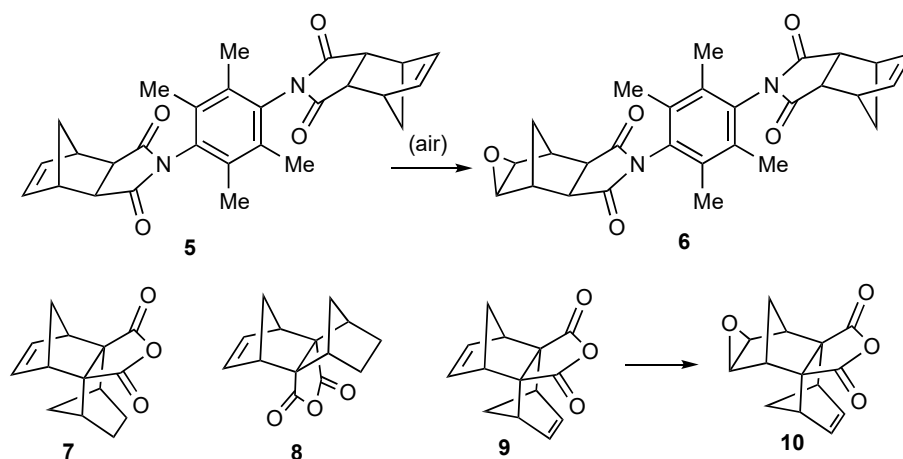
Scheme 2. Other readily epoxidised bicyclic alkenes.

In order to fully characterise epoxide **3**, a sample was prepared by oxidation of alkene **2** using performic acid [12], leading to a high yield of the product after kugelrohr distillation. Although this gave satisfactory spectroscopic data, there was some ambiguity in the assignment of the NMR spectra, particularly the three CH signals relating to the norbornane ring system. This prompted an assessment of the literature NMR data for precursors **1** and **2**, which showed that both ^{1}H- and ^{13}C-NMR spectra for **1** had been satisfactorily assigned [2], but for compound **2**, only images of the H and C spectra appeared in a single paper [4] with no numerical data and no attempt at assignment. In order to make the task of assignment easier, we also prepared the *exo,exo*-epoxy anhydride **4** by oxidation of **1** using mCPBA in boiling ethyl acetate [13], which gave the product in low but adequate yield. This compound is well known, having been first prepared in 1958 [14], but owing to the early date of the work, no NMR spectra have been reported. It might be noted that ^{1}H-NMR data have been documented for the *exo*-epoxy-*endo*-anhydride isomeric with **4** [15] and for the *endo*-*N*-butyl imide isomeric with **2** [16].

Good quality ^{1}H- and [3]C-NMR spectra, as well as a 2D HSQC C–H correlation, were obtained for compounds **2**, **3**, and **4** (see Supplementary Materials) and, by carefully

considering these in comparison with the assigned spectra [2] for **1**, a comprehensive and self-consistent assignment for all four compounds was produced (Figure 1). The presence of an HMBC correlation for compound **3** between δ_C 177.0 and δ_H 2.74 and 3.30 but not 2.96 further supports the assignment.
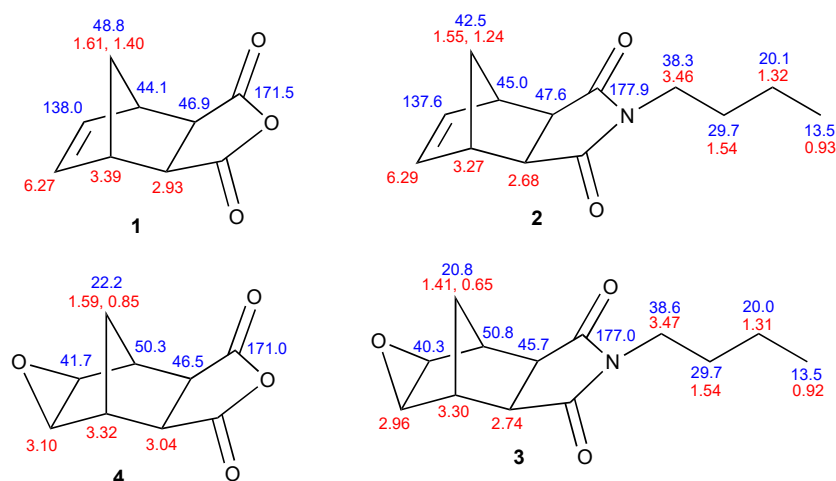

Figure 1. ^{1}H (in red) and ^{13}C (in blue) NMR chemical shift assignments for **1** [2], **2**, **3**, and **4** (δ in ppm).

Several features of this are of interest, including the dramatic shielding of the carbon bridge and only one of its protons on moving from alkenes **1** and **2** to epoxides **4** and **3**, significant deshielding of the bridgehead (1/7) carbons but not protons in moving from alkenes to epoxides, and the cross-over in order between H and C signals for 1/7, 2/6, and epoxide positions in all four compounds. By way of comparison, the bridge signals of δ_H 1.34 and 1.12 and δ_C 48.8 for norbornene move, upon epoxidation, to δ_H 1.28 and 0.64 and δ_C 25.0 [17].

Since the polycyclic epoxy imide framework of **3** is fairly unusual and the compound formed good quality crystals, we confirmed its structure by X-ray diffraction. The resulting molecular structure (Figure 2) confirms the *exo, exo*-configuration and has the epoxide and imide rings at angles of 69.4° and 61.5° to the norbornane core, respectively.
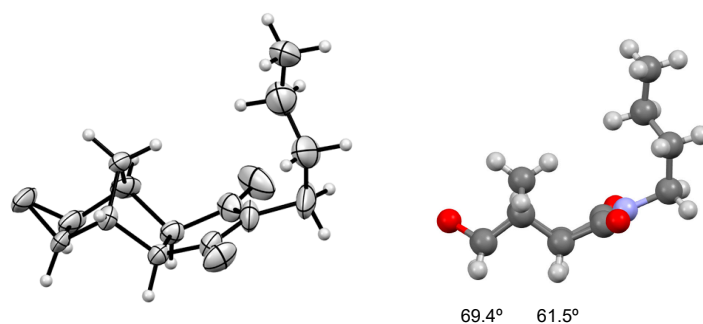

Figure 2. Molecular structure of **3** (thermal ellipsoids at 50% level) and side view showing angles of 3- and 5-membered rings to norbornane core.

A selection of similar norbornane compounds with fused 3- and 5-membered rings that have been crystallographically characterised is shown in Figure 3 with CCDC reference codes, literature references, and angles [18–20].
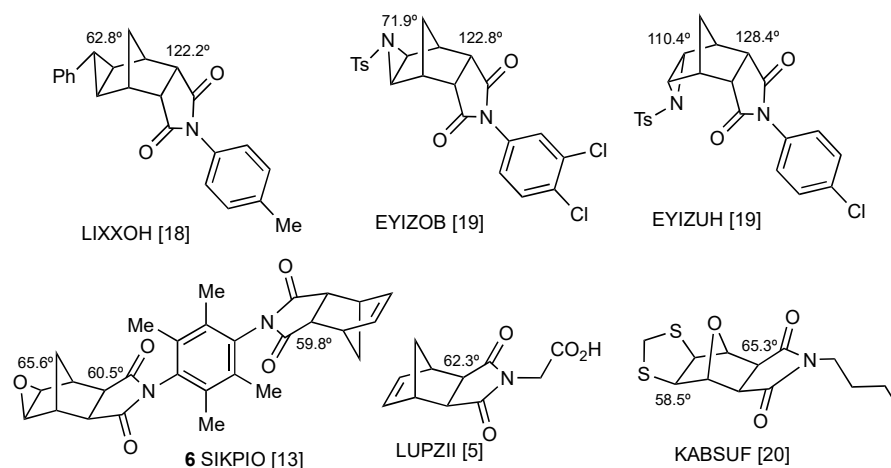
Figure 3. Similar crystallographically characterised compounds with inter-ring angles.

Although cyclic NH imides show a wide variety of intermolecular hydrogen bonding patterns in the crystalline state [21], this relies on having a free NH present and, as might be expected, there are no strong intermolecular interactions between molecules of **3** in the crystal. A view of the unit cell does however show the molecules arranged with hydrophobic butyl groups in a layer between the more polar epoxy imide moieties (Figure 4).
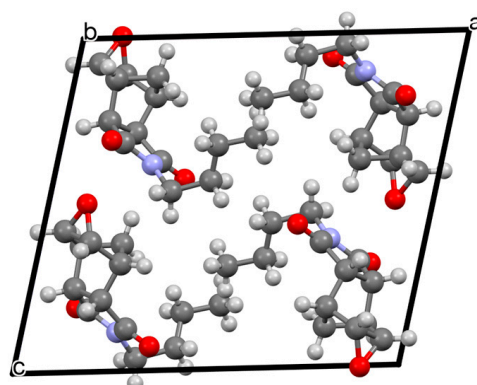

Figure 4. Unit cell of **3** viewed along the b axis showing alignment of the four molecules.

In summary, the epoxy imide **3** is readily formed by spontaneous air oxidation of the corresponding unsaturated imide **2** and preparation of the related epoxy anhydride **4** allowed unambiguous assignment of ^{1}H- and ^{13}C-NMR spectra for all three compounds. The X-ray structure for **3** confirms the configuration and shows similar inter-ring angles to related tetracyclic compounds.

3. Experimental

Melting points were recorded on a Reichert hot-stage microscope (Reichert, Vienna, Austria) and are uncorrected. IR spectra were recorded using the ATR technique on a Shimadzu IRAffinity 1S instrument. NMR spectra were obtained for ^{1}H at 300 or 400 MHz and for carbon at 75 or 100 MHz using, respectively, Bruker AV and AV-II instruments (Bruker, Billerica, MA, USA). Spectra run at 25 °C on solutions in CDCl$_3$ with internal Me$_4$Si as the reference. Chemical shifts are reported in ppm to high frequency of the reference and coupling constants *J* are in Hz. The starting *exo*-anhydride **1** was prepared by thermal isomerisation of the *endo*-isomer as described in the literature [9], with the distinction that acetone [2] rather than benzene was used for the recrystallisation.

3.1. 2,6-exo-4-Butyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (**2**)

Following a literature procedure [3], a solution of *exo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride **1** (2.00 g, 12.2 mmol) was dissolved in MeOH/THF (1:1) (40 cm^3). A solution of *n*-butylamine (0.89 g, 1.21 cm^3, 12.2 mmol) in MeOH/THF (1:1) (7 cm^3) was added dropwise to the stirring solution cooled at 0 °C over 15 min. The mixture was stirred at 0 °C for 30 min, then heated to 65 °C, with the addition of hexamethyldisilazane (2.42 g, 3.14 cm^3, 15 mmol), and the heating was continued for 72 h. After cooling, the solvent was removed under reduced pressure and the residue dissolved in CH$_2$Cl$_2$, which was washed successively with aq. NaHCO$_3$, 2.0 M HCl, and water. The organic layer was dried over MgSO$_4$ and the solvent removed under reduced pressure to yield a light brown oil. This was subjected to column chromatography using EtOAc/hexane (1:1) to yield a yellow oil (1.37 g, 48%). The ^{1}H- and ^{13}C-NMR spectra were in good agreement with the literature images [4] although these are given here in numerical form for the first time. ^{1}H-NMR (300 MHz, CDCl$_3$): δ 6.29 (2H, t, *J* 2, =CH–), 3.46 (2H, t, *J* 7.5, NCH$_2$), 3.27 (2H, t, *J* 1.5, 1,7-H), 2.68 (2H, d, *J* 1.2, 2,6-H), 1.59–1.49 (3H, m, Bu C-2 and 10-Ha), 1.32 (2H, sextet, *J* 7.2, Bu C-3), 1.24 (1H, d, $J_{10a-10b}$ 10, 10-Hb), 0.93 (3H, t, *J* 7.2, Bu C-4); ^{13}C-NMR (75 MHz, CDCl$_3$): δ 177.9 (C=O), 137.6 (2CH, =CH–), 47.6 (2CH, C-2,6), 45.0 (2CH, C-1,7), 42.5 (CH$_2$, C-10), 38.3 (CH$_2$, Bu C-1), 29.7 (CH$_2$, Bu C-2), 20.1 (CH$_2$, Bu-C-3), 13.5 (CH$_3$, Bu C-4).

3.2. 2,6-exo-8,10-exo-4-Butyl-9-oxa-4-azatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3,5-dione (**3**)

Following a literature procedure [12], the imide **2** (1.37 g, 6.25 mmol) was dissolved in formic acid (10 cm^3) and hydrogen peroxide (30% *w/w* in H$_2$O, 1.5 g, 13.23 mmol) was added dropwise. The mixture was stirred at rt for 24 h, and then evaporated *in vacuo* to yield a yellow crystalline solid. The crude material was purified by kugelrohr distillation at 250 °C and 15 Torr. Upon cooling, the product (1.32 g, 90%) formed waxy, colourless crystals, mp 75–76 °C. IR (ATR): 1767, 1686, 1437, 1395, 1373, 1294, 1194, 1138,934, 910, 851, 766, 610, 552, 457 cm^{-1}; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 3.47 (2H, t, *J* 7.6, N-CH$_2$), 3.30 (2H, s, 1,7-H), 2.96 (2H, s, 8,10-H), 2.74 (2H, d, $J_{11a-2,6}$ 1.2, 2,6-H), 1.54 (2H, m, Bu C-2), 1.41 (1H, d of t, $J_{11a-11b}$ 11.6, $J_{11a-2,6}$ 1.2, 11a-H), 1.31 (2H, sextet, *J* 7.6, Bu C-3), 0.92 (3H, t, *J* 7.2, Bu C-4), 0.65 (1H, d, $J_{11a-11b}$ 11.6, 11b-H); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 177.0 (C=O), 50.8 (2CH, C-1,7), 45.7 (2CH, C-2,6), 40.3 (2CH, C-8,10), 38.6 (CH$_2$, Bu C-1), 29.7 (CH$_2$, Bu C-2), 20.8 (CH$_2$, C-11), 20.0 (CH$_2$, Bu C-3), 13.5 (CH$_3$, Bu C-4); HRMS (ESI): Calcd. for C$_{13}$H$_{18}$NO$_3$ (M + H): 236.1287. Found: 236.1281.

Crystal data for C$_{13}$H$_{17}$NO$_3$, *M* = 235.28 g mol^{-1}, colourless plate, crystal dimensions 0.10 × 0.10 × 0.01 mm, monoclinic, space group *P*2$_1$/c, *a* = 14.0208(9), *b* = 6.8847(3), *c* = 12.3947(7) Å, β = 103.388(6)°, *V* = 1163.93(12) Å^3, *Z* = 4, *D*$_{calc}$ = 1.343 g cm^{-3}, *T* = 93 K, *R*1 = 0.0790, *Rw*2 = 0.2127 for 1389 reflections with *I* > 2σ(*I*), and 155 variables. Data were collected using graphite monochromated Mo Kα radiation λ = 0.71073 Å and deposited at the Cambridge Crystallographic Data Centre as CCDC 2128556. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/getstructures. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXL, Version 2018/3 [22]).

3.3. 2,6-exo-8,10-exo-4,9-dioxatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3,5-dione (**4**)

Following a literature procedure [13], a solution of *exo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride **1** (0.30 g, 1.83 mmol) in ethyl acetate (7 cm^3) was stirred at rt while mCPBA (50%, 1.26 g, 3.63 mmol) was added, and the reaction was heated under reflux for 18 h. After cooling to 0 °C, the mixture was filtered to yield a crude product (0.18 g) still containing some chlorobenzoic acid. This was purified by recrystallisation first from petroleum/acetone (1:1) and then from chloroform, producing the pure product (0.10 g, 30%) as colourless crystals, mp 205–207 °C (lit. [14] 204–206 °C). IR (ATR) 1857, 1771, 1196, 1082, 928, 903, 849, 754, 694, 592, 534, 480 cm^{-1}; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 3.32 (2H, s, 1,7-H), 3.10 (2H, s, 8,10-H), 3.04 (2H, d, $J_{11a-2,6}$ 2, 2,6-H), 1.59 (1H, d of t, $J_{11a-11b}$ 12, $J_{11a-2,6}$

1.6, 11a-H), 0.85 (1H, d, $J_{11a-11b}$ 12, 11b-H); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 171.0 (C=O), 50.3 (2CH, C-1,7), 46.5 (2CH, C-2,6), 41.7 (2CH, C-8,10), 22.2 (CH$_2$, C-11).

Supplementary Materials: The following are available online. Figure S1: ^{1}H-NMR spectrum of **2**; Figure S2: ^{13}C-NMR spectrum of **2**; Figure S3: HSQC 2D C–H correlation NMR spectrum of **2**; Figure S4: ^{1}H-NMR spectrum of **3**; Figure S5: ^{13}C-NMR spectrum of **3**; Figure S6: HSQC 2D C–H correlation NMR spectrum of **3**; Figure S7: IR spectrum of **3**; Figure S8: ^{1}H-NMR spectrum of **4**; Figure S9: ^{13}C-NMR spectrum of **4**; Figure S10: HSQC 2D C–H correlation NMR spectrum of **4**; Figure S11: IR spectrum of **4**. Cif and check-cif files for compound **3**.

Author Contributions: F.M.F. prepared the compounds; A.M.Z.S. collected the X-ray data and solved the structure; R.A.A. designed the experiments, analysed the data, and wrote the paper. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement: X-ray data are deposited at CCDC and all other data are shown in the Supplementary Materials.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Luzzio, F.A. (Ed.) *Imides: Medicinal, Agricultural, Synthetic Applications and Natural Products Chemistry*; Elsevier: Oxford, UK, 2019; 456p.
2. Khosravi, E.; Iqbal, F.; Musa, O.M. Thermosetting ROMP materials with thermally degradable linkages. *Polymer* **2011**, *52*, 243–249. [CrossRef]
3. Liu, M.; van Hensbergen, J.; Burford, R.P.; Lowe, A.B. Thiol-Michael coupling chemistry: Facile access to a library of functional exo-7-oxanorbornenes and their ring-opening metathesis (co)polymerization. *Polym. Chem.* **2012**, *3*, 1647–1658. [CrossRef]
4. Chang, A.B.; Lin, T.-P.; Thompson, N.B.; Luo, S.-X.; Liberman-Martin, A.L.; Chen, H.-Y.; Lee, B.; Grubbs, R.H. Design, synthesis and self-assembly of polymers with tailored graft distributions. *J. Am. Chem. Soc.* **2017**, *139*, 17683–17693. [CrossRef] [PubMed]
5. Birchall, L.T.; Shehata, S.; McCarthy, S.; Shepherd, H.J.; Clark, E.R.; Serpell, C.J.; Baigini, S.C.G. Supramolecular behaviour and fluorescence of rhodamine-functionalised ROMP polymers. *Polym. Chem.* **2020**, *11*, 5279–5285. [CrossRef]
6. Scappaticci, K.A. Treatment of Depression. US Patent 5011841, 30 April 1991.
7. Aitken, R.A.; Carcas, K.; Hill, L.; Massil, T.; Raut, S.V. Cycloaddition of Bu$^n_3$P•CS$_2$: Direct One-pot Conversion of Strained Double Bonds to 2-Alkylidene-1,3-dithiolanes. *Tetrahedron* **1997**, *53*, 2261–2270. [CrossRef]
8. Aitken, R.A.; Hill, L.; Lightfoot, P. Direct One Pot Construction of Norbornane-fused Dihydrotetrathiafulvalenes. *Tetrahedron Lett.* **1997**, *38*, 7927–7930. [CrossRef]
9. Craig, D. The rearrangement of endo-3,6-methylene-1,2,3,6-tetrahydro-cis-phthalic anhydride. *J. Am. Chem. Soc.* **1951**, *73*, 4889–4892. [CrossRef]
10. Murphy, R.B.; Pham, D.-T.; White, J.M.; Lincoln, S.F.; Johnston, M.R. Molecular tweezers with a rotationally restricted linker and freely rotating porphyrin moieties. *Org. Biomol. Chem.* **2018**, *16*, 6206–6223. [CrossRef] [PubMed]
11. Bartlett, P.D.; Combs, G., Jr.; Le, A.-X.T.; Watson, W.H.; Galloy, J.; Kimura, M. Reactivities of norbornene-type double bonds in propellane derivatives and their precursors; furan as a diene. *J. Am. Chem. Soc.* **1982**, *104*, 3131–3138. [CrossRef]
12. Petrova, T.; Tarabara, I.; Palchikov, V.; Kasyan, L.; Kosenkov, D.; Okovytyy, S.; Gorb, L.; Shishkina, S.; Shishkin, O.; Leszczynski, J. Ethanolysis of N-substituted norbornane epoxyimides: Discovery of diverse pathways depending on substitu-ent's character. *Org. Biomol. Chem.* **2010**, *8*, 2142–2157. [CrossRef]
13. Aitken, R.A.; Gosney, I.; Farries, H.; Palmer, M.H.; Simpson, I.; Cadogan, J.I.G.; Tinley, E.J. Chemical repercussions of orbital interactions through bond and through space. The reactivity of the double bond in unsaturated cyclic sulphones towards aziridine formation and epoxidation. *Tetrahedron* **1984**, *40*, 2487–2503. [CrossRef]
14. Berson, J.A.; Suzuki, S. The hydration of exo-cis-3,5-endomethylene Δ^4-tetrahydrophthalic anhydride. *J. Am. Chem. Soc.* **1958**, *80*, 4341–4345. [CrossRef]
15. Kas'yan, L.I.; Krishchik, O.V.; Tarabara, I.N.; Kas'yan, A.O.; Pal'chikov, V.A. Lactonization of epoxyendic anhydride in re-actions with amines. *Russ. J. Org. Chem.* **2006**, *42*, 501–508. [CrossRef]
16. Meijer, A.; Otoo, S.; Engberts, J.B.F.N. Effects of the hydrophobicity of the reactants on Diels-Alder reactions in water. *J. Org. Chem.* **1998**, *63*, 8989–8994. [CrossRef]
17. Kang, B.; Kim, M.; Lee, J.; Do, Y.; Chang, S. Trimanganese complexes bearing bidentate nitrogen ligands as a highly efficient catalyst precursor in the epoxidation of alkenes. *J. Org. Chem.* **2006**, *71*, 6721–6727. [CrossRef] [PubMed]
18. Mao, J.; Zhang, S.-Q.; Shi, B.-F.; Bao, W. Palladium(0)-catalyzed cyclopropanation of benzyl bromides via C(sp^3)H bond acti-vation. *Chem. Commun.* **2014**, *50*, 3692–3694. [CrossRef] [PubMed]

19. Bortoluzzi, A.J.; Andrade, E.S.; Nunes, R.J. 4-(3,4-Dichlorophenyl)-9-(4-methylphenylsulfonyl)-4,9-diazatetracyclo[5.3.1.0^{2,6}.0^{8,10}] undecane-3,5-dione and 4-(4-chlorophenyl)-9-(4-methylphenylsulfonyl)-4,9-diazatetracyclo[5.3.1.0^{2,6}.0^{8,10}]undecane-3,5-dione. *Acta Crystallogr. Sect. C* **2004**, *60*, o614–o616. [CrossRef] [PubMed]

20. Aitken, R.A.; Fotherby, F.M.; Slawin, A.M.Z. 2,6-exo-8,12-exo-10-Butyl-13-oxa-3,5-dithia-10-azatetracyclo[5.5.1.0^{2,6}.0^{8,12}]tridecane-9,11-dione. *Molbank* **2020**, *2020*, M1123. [CrossRef]

21. Aitken, R.A.; Sonecha, D.K. The solid-state structures of cyclic NH carboximides. *Crystals* **2020**, *10*, 606. [CrossRef]

22. Sheldrick, G.M. A short history of SHELXL. *Acta Crystallogr. Sect. A* **2008**, *64*, 112–122. [CrossRef] [PubMed]