agrochemicals

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Cyclic Organic Peroxides as New Fungicides against Phytopathogenic Fungi

Ivan A. Yaremenko [1], Peter S. Radulov [1], Yulia Yu. Belyakova [1], Dmitrii I. Fomenkov [1], Vera A. Vil' [1], Maria A. Kuznetsova [2], Valentina N. Demidova [2], Alexei P. Glinushkin [2] and Alexander O. Terent'ev [1,*]

[1] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Prospekt, 119991 Moscow, Russia; yaremenko@ioc.ac.ru (I.A.Y.); vil@ioc.ac.ru (V.A.V.)
[2] All-Russian Research Institute for Phytopathology, B. Vyazyomy, 143050 Moscow, Russia
* Correspondence: terentev@ioc.ac.ru

Abstract: The search for new classes of fungicides has long been important in plant protection due to the development of fungal resistance to currently used agrochemicals. Organic peroxides have long been regarded as exotic and unstable compounds. The discovery of the antimalarial activity of the peroxide natural product Artemisinin, an achievement that was recently recognized with the Nobel Prize, has brought organic peroxides into the medicinal and agrochemistry. In this paper, fungicidal activity of synthesized organic peroxides—geminal bishydroperoxide, bridged 1,2,4,5-tetraoxanes, and tricyclic monoperoxides—were tested in vitro against an important species of phytopathogenic fungi (*F. culmorum*, *R. solani*, *A. solani*, *P. infestans*, *C. coccodes*). We discovered that substituted bridged 1,2,4,5-tetraoxanes exhibit fungicidal activity comparable or superior to azoxystrobin and superior to geminal bishydroperoxide and tricyclic monoperoxides. The contact mode of action was demonstrated for the bridged 1,2,4,5-tetraoxane.

Keywords: crop protection; fungicides; organic peroxides

Citation: Yaremenko, I.A.; Radulov, P.S.; Belyakova, Y.Y.; Fomenkov, D.I.; Vil', V.A.; Kuznetsova, M.A.; Demidova, V.N.; Glinushkin, A.P.; Terent'ev, A.O. Cyclic Organic Peroxides as New Fungicides against Phytopathogenic Fungi. *Agrochemicals* **2023**, *2*, 355–366. https://doi.org/10.3390/agrochemicals2030021

Academic Editor: Christos G. Athanassiou

Received: 15 March 2023
Revised: 30 May 2023
Accepted: 19 June 2023
Published: 28 June 2023

1. Introduction

Plant diseases account for up to 15% of global agricultural production losses each year, with 70–80% of these diseases caused by phytopathogenic fungi [1]. Phytopathogenic fungi cause the most destructive diseases from seed germination to harvest and storage. This threatens food security and results in significant financial losses for producers. Fungi also cause food spoilage [2]. In addition, fungi produce dangerous mycotoxins that endanger the health and lives of humans and animals [3]. Thus, modern crop production would be unthinkable without the use of chemical crop protection products, in particular, fungicides. Approximately 80% of all fungicides used in agriculture represent only six modes of acting—30% demethylation-inhibitor fungicides (triazole fungicides), 21% multisite/chemical reactives (dithiocarbamates), 19% Q_o-site inhibitors of complex III (strobilurin derivatives) and 6% succinate dehydrogenase inhibitors of complex II [4]. The limited variety of fungicides in terms of their mechanism of action has led to the emergence of aggressive resistant strains of fungi, which is a major concern for food safety [5,6]. The challenge is therefore to develop fungicides with a new mode of action.

In the past few decades, organic peroxides have been the objects of research in the development of bioactive compounds, since cyclic synthetic peroxides exhibit antiparasitic [7–11], anticancer [12–22], antitubercular [23–25] and antiviral [26–29] activities (Figure 1). The key role of the natural peroxide artemisinin and its derivatives in the treatment of malaria was acknowledged with the 2015 Nobel Prize in Medicine [30,31]. It is now clear that organic peroxides, which were once considered to be exotic and dangerous compounds of little importance, can lead to breakthroughs not only in medicinal chemistry, but also in agricultural chemistry.

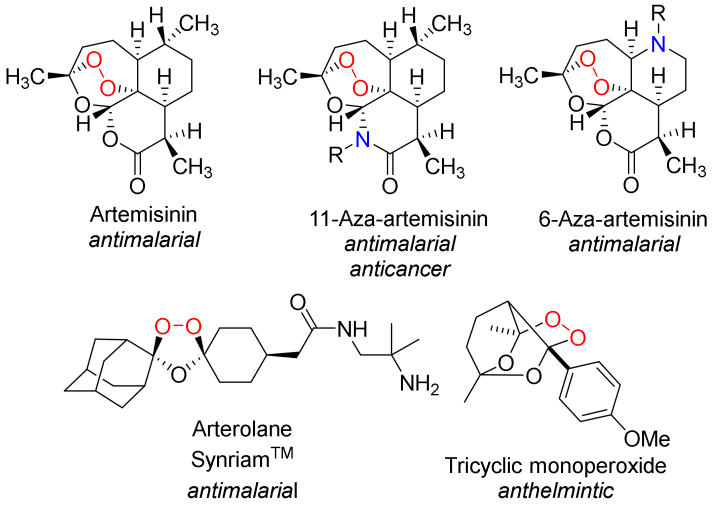


Figure 1. Bioactive organic peroxides.

Hydrogen peroxide and peracids are the active ingredients in antiseptic and disinfectant products used in many areas, including agriculture [32–34]. The mechanism of the antiseptic action of hydrogen peroxide and of the most commonly used peracids (performic acid, peracetic acid, etc.) has been elucidated in a number of studies [35–37]. H_2O_2 released from the oxidative burst has been shown to play an important role in the expression of plant disease resistance [38–40]. There are known examples of natural peroxides exhibited antifungal activity [11,41,42].

Recently, we developed the first examples of synthetic antifungal peroxides [43,44]. Therein, the range of fungi tested was broadened, and translaminar activity was investigated. The key feature of these compounds is that, due to the presence of the O-O bond, their mechanism of action can potentially be different from that of commercial fungicides. This feature will facilitate the control of resistant phytopathogens due to their lack of resistance to peroxides. In addition, cyclic peroxides are not only safe for pollinators but also beneficial to them, as they show activity against the entomopathogenic fungus *Ascosphaera apis*, which causes bee mortality [43]. However, their potential as effective fungicides is underexplored. In the present work, cyclic peroxides were found to have high fungicidal activity in vitro against phytopathogenic fungi of different taxonomic classes that cause economic damage to agriculture and crop production.

2. Materials and Methods

2.1. General Information and Materials

NMR spectra were recorded on a commercial instrument (300.13 MHz for ^{1}H, 75.48 MHz for ^{13}C) in $CDCl_3$. The TLC analysis was carried out on silica gel chromatography plates Macherey-Nagel Alugram UV254; Sorbent: Silica 60, specific surface (BET) ~500 m^2/g, mean pore size 60 Å, specific pore volume 0.75 mL/g, particle size 5–17 μm; Binder: highly polymeric product stable in almost all organic solvents and resistant towards aggressive visualization reagents. The melting points were determined on a Kofler hot-stage apparatus. Chromatography of 1,3-diketones, β,δ′-triketones and peroxides was performed on silica gel (0.060–0.200 mm, 60 A, CAS 7631-86-9).

Ethyl acetoacetate, benzyl and alkyl halides, methyl vinyl ketone, 4-*tert*-butylcyclohexanone, H_2O_2 (35% aqueous solution), petroleum ether (PE) $MgSO_4$, $NaHCO_3$, NaI, $CeCl_3 \cdot 7H_2O$, $Na_2S_2O_3$, TWEEN 80 were purchased from commercial sources and were used as is. A solution of H_2O_2 in Et_2O (5.12 M) was prepared by the extraction with Et_2O (5 × 100 mL) from a 35% aqueous solution (100 mL) followed by drying over $MgSO_4$. Then, part of Et_2O was removed in the vacuum of a membrane vacuum pump at 20–25 °C and titrated iodometrically [44,45]. All solvents were distilled before use using standard procedures.

2.2. Synthesis of Starting Compounds

1,3-Diketones **2**–**10** [21,44] and β,δ′-triketones **11**–**13** [46,47] were synthesized according to known procedures.

*2.3. Procedure for the Synthesis Peroxide **P1***

Geminal bishydroperoxide **P1** [48] was synthesized according to a known procedure.
Procedure for the synthesis peroxide **P1**.

Concentrated H_2SO_4 (0.3 mol per mol of ketone **1**) was dissolved in a mixture of a 34% aq. H_2O_2 (10 mol of H_2O_2 per mol of ketone **1**) and THF (20–25 mL). Then, ketone **1** (308.5 mg, 2.0 mmol) was added with vigorous stirring at 15–20 °C over 15 min. The reaction mixture was stirred for 3 h. Then, CH_2Cl_2 (80 mL) and a saturated aqueous $NaHCO_3$ solution were added to pH 7–8. The organic layer was separated, washed with water (4 × 10 mL), and dried over $MgSO_4$. The precipitate was filtered off, and the solvent was removed in a water jet vacuum. Product **P1** was isolated by chromatography on SiO_2 using a PE/Et_2O (4:1). Compound **P1**: 375.8 mg, 1.84 mmol, yield 92%.

4-*Tert*-butyl-1,1-dihydroperoxycyclohexane **P1** [48]

White crystals. Yield 92%, 375.8 mg. M.p. = 80–82 °C (cf. lit data [48]: m.p. 81–82.5 °C). R_f = 0.34 (TLC, PE/EA, 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 0.87 (s, 9H), 1.02–1.12 (m, 1H), 1.16–1.33 (m, 2H), 1.45 (dt, *J* = 3.2, 13.0, 2H), 1.73 (d, *J* = 12.0 Hz, 2H), 2.31 (d, *J* = 12.0 Hz, 2H), 8.35 (br.s, 2H). ^{13}C NMR (75.48 MHz, $CDCl_3$) δ: 23.5, 27.7, 29.9, 32.4, 47.5, 111.2. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 59.08; H, 10.02.

*2.4. Synthesis of Bridged 1,2,4,5-Tetraoxanes **P2**–**P10***

Bridged 1,2,4,5-tetraoxanes **P2**–**P8** [44] and **P9**–**P10** [21] were synthesized according to known procedures. NMR spectra of the synthesized peroxides are presented in Supplementary Materials.

General procedure for the synthesis of tetraoxanes **P2**–**P8** from diketones **2**–**8**.

A 7.0 M ethereal solution of H_2O_2 (0.857 mL, 6.0 mmol, 3.0 mol H_2O_2/1.0 mol of **2**–**8**) and PMA/SiO_2 (1.216 g, 30 wt.% $H_3PMo_{12}O_{40}$, 0.2 mmol of $H_3PMo_{12}O_{40}$, 0.10 mol $H_3PMo_{12}O_{40}$/1.0 mol 1,3-diketone **2**–**8**) were successively added to a stirred solution of 1,3-diketone **2**–**8** (0.300–468 mg; 2.0 mmol) in toluene (10 mL) at 20–25 °C. The reaction mixture was stirred at 20–25 °C for 1 h. After that time, the catalyst was filtered off and washed with CH_2Cl_2 (3 × 10 mL). The solvent was removed in vacuum of a water jet pump. Tetraoxanes **P2**–**P8** were isolated by chromatography on SiO_2 using PE:EA (10:1). Compounds: **P2**: 233.4 mg, 1.24 mmol, yield 62%; **P3**: 258.8 mg, 1.28 mmol, yield 64%; **P4**: 263.8 mg, 1.22 mmol, yield 61%; **P5**: 342.0 mg, 1.40 mmol, yield 70%; **P6**: 301.9 mg, 1.30 mmol, yield 65%; **P7**: 442.1 mg, 1.66 mmol, yield 83%; **P8**: 351.1 mg, 1.58 mmol, yield 79%.

General procedure for the synthesis of bridged 1,2,4,5-tetraoxanes **P9**–**P10** from diketones **9**–**10**.

A 34% aq H_2O_2 solution (0.892 g, 10.0 mmol, 5 mol of H_2O_2/1 mol of β-diketone **9**–**10**) was added to a solution of β-diketone **9**–**10** (0.468–0.496 mg, 2.0 mmol) in PhMe (10 mL). Then, ion exchange resin Lewatit MonoPlus SP112H (4.0 g, 2.0 g of ion exchange resin/1.0 mmol of β-diketone **9**–**10**) was added to the mixture. The reaction mixture was stirred at 20–25 °C for 24 h. The solid was filtered off, washed with $CHCl_3$ (3 × 5 mL). The filtrate was washed with 5% aq $NaHCO_3$ (10 mL), and H_2O (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure using a rotary evaporator (bath temperature ca. 20–25 °C). Products **P9**–**P10** were isolated by column chromatography on SiO_2, eluent PE—EtOAc, gradient from 30:1 to 5:1. Compounds: **P9**: 454.1 mg, 1.80 mmol, yield 90%; **P10**: 468.7 mg, 1.76 mmol, yield 88%.

2.4.1. 7-Butyl-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, **P2** [44]

Slightly yellow oil. Yield 62%, 233.4 mg R_f = 0.68 (TLC, PE:EA, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$) *δ*: 0.93 (t, *J* = 7.0 Hz, 3H), 1.32–1.48 (m, 4H), 1.53 (s, 6H), 1.55–1.59 (m,

2H), 2.60 (t, *J* = 5.9 Hz, 1H). ^{13}C NMR (75.48 MHz, $CDCl_3$) *δ*: 9.9, 13.9, 22.9, 23.7, 29.9, 59.2, 110.9. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 59.58; H, 8.70.

2.4.2. 7-Isopentyl-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, **P3** [44]

Slightly yellow oil. Yield 64%, 258.8 mg R_f = 0.60 (TLC, PE:EA, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$) *δ*: 0.93 (d, *J* = 6.6 Hz, 6H), 1.32–1.40 (m, 2H), 1.54 (s, 6H), 1.52–1.64 (m, 3H), 2.59 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (75.48 MHz, $CDCl_3$) *δ*: 10.0, 21.9, 22.5, 28.4, 36.9, 59.5, 111.0. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.48; H, 9.12.

2.4.3. 7-Hexyl-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, **P4** [44]

Slightly yellow oil. Yield 61%, 263.8 mg R_f = 0.66 (TLC, PE:EA, 10:1). ^{1}H NMR (300.13 MHz, $CDCl_3$) *δ*: 0.89 (t, *J* = 7.0 Hz, 3H), 1.27–1.38 (m, 6H), 1.43–1.56 (m, 4H), 1.54 (s, 6H), 2.61 (t, *J* = 5.9 Hz, 1H). ^{13}C NMR (75.48 MHz, $CDCl_3$) *δ*: 10.0, 14.1, 22.7, 24.0, 27.8, 29.6, 31.6, 59.3, 111.0. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.20; H, 9.47.

2.4.4. 1,4-Dimethyl-7-octyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, **P5** [44]

Slightly yellow oil. Yield 70%, 342.0 mg R_f = 0.52 (TLC, PE:EA, 20:1). ^{1}H NMR (300.13 MHz, $CDCl_3$) *δ*: 0.88 (t, *J* = 7.0 Hz, 3H), 1.22–1.40 (m, 10H), 1.46–1.59 (m, 4H), 1.54 (s, 6H), 2.61 (t, *J* = 5.8 Hz, 1H). ^{13}C NMR (75.48 MHz, $CDCl_3$) *δ*: 10.0, 14.2, 22.7, 24.0, 27.8, 29.3, 29.4, 29.9, 31.9, 59.3, 111.0. Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 64.05; H, 10.08.

2.4.5. Ethyl 3-(1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptan-7-yl)propanoate, **P6** [44]

Slightly yellow oil. Yield 65%, 301.9 mg R_f = 0.52 (TLC, PE:EA, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$) *δ*: 1.21 (t, *J* = 7.1 Hz, 3H), 1.50 (s, 6H), 1.84 (q, *J* = 7.3 Hz, 2H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.63 (t, *J* = 5.9 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H). ^{13}C NMR (75.48 MHz, $CDCl_3$) *δ*: 9.7, 14.2, 19.0, 31.7, 58.1, 60.7, 110.7, 172.3. Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.86; H, 7.11.

2.4.6. 7-(Adamantan-1-yl)-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, **P7** [44]

White crystals. Yield 83%, 442.1 mg M.p. = 131–132 °C (Lit. [44] M.p. = 130–131 °C). R_f = 0.67 (TLC, PE:EA, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$) *δ*: 1.64–1.67 (m, 6H), 1.68–1.74 (m, 6H), 1.82–1.88 (m, 6H), 1.98–2.04 (m, 3H), 2.40 (s, 1H). ^{13}C NMR (75.48 MHz, $CDCl_3$) *δ*: 12.8, 28.5, 33.1, 36.9, 40.7, 67.0, 110.7. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.78; H, 8.45.

2.4.7. 7-Benzyl-1,4-dimethyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, **P8** [49]

White crystals. Yield 79%, 351.1 mg M.p. = 58–60 °C (Lit. [49] M.p. = 58–60 °C). R_f = 0.45 (TLC, PE:EA, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 1.42 (s, 6H), 2.96 (d, *J* = 7.3 Hz, 2H), 3.10–3.17 (m, 1H), 7.25–7.39 (m, 5H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 9.9, 30.4, 59.3, 110.8, 127.0, 128.9, 137.3. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.99; 6.48.

2.4.8. 4-(1-Adamantyl)-1-methyl-2,3,5,6-tetraoxabicyclo[2.2.1]heptane, **P9** [21]

White crystals. Yield 90%, 454.1 mg R_f = 0.65 (TLC, PE:EA, 5:1). M.p. 111–113 °C (Lit. [21] M.p. = 111–113 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 1.64 (s, 3H), 1.66–1.73 (m, 6H), 1.79–1.85 (m, 6H), 1.96–2.07 (m, 3H), 2.66 (s, 2H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 10.9, 28.1, 35.6, 36.6, 38.0, 46.5, 109.4, 116.0. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.81; 8.12.

2.4.9. 4-(1-Adamantyl)-1-ethyl-2,3,5,6-tetraoxabicyclo[2.2.1]-heptane, **P10** [21]

White crystals. Yield 88%, 468.7 mg R_f = 0.68 (TLC, PE:EA, 5:1). M.p. 93–95 °C (Lit. [21] M.p. = 93–95 °C). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 1.09 (t, *J* = 7.6, 3H), 1.65–1.75 (m, 6H), 1.79–1.87 (m, 6H), 1.92–2.07 (m, 5H), 2.62 (s, 2H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 9.1, 19.2,

28.1, 35.7, 36.6, 38.0, 44.7, 112.3, 115.8. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.76; 8.45.

*2.5. Synthesis of Tricyclic Peroxides **P11–P13***

Tricyclic peroxides **P11–P13** [50] were synthesized according to known procedures.

General procedure for the synthesis of tricyclic peroxides **P11–P13**.

A 34% aqueous H_2O_2 solution (0.154−0.190 g, 1.72−2.13 mmol) and a solution of H_2SO_4 (1.0 g, 0.01 mol) in EtOH (1 mL) were added with stirring to a solution of triketone **11–13** (0.3 g, 1.15–1.42 mmol) in EtOH (4 mL) at 10−15 °C. The reaction mixture was stirred at 20−25 °C for 1 h, and a mixture of CH_2Cl_2/PE = 1:1 (10 mL) was added. Then, $NaHCO_3$ was added to the reaction mixture with stirring until the pH reached 7.0. The precipitate was filtered off. The filtrate was dried over Na_2SO_4, the precipitate was filtered off, and the solvent was removed in a water jet vacuum. Products **P11–P13** were isolated by chromatography on SiO_2 using a PE/EA mixture as the eluent with a gradient of ethyl acetate from 5 to 50 vol %. Compounds: **P11**: 256.9 mg, 1.06 mmol, yield 80%; **P12**: 196.9 mg, 0.87 mmol, yield 61%; **P13**: 216.5 mg, 0.78 mmol, yield 68%.

2.5.1. 3a-Butyl-3,6,7a-trimethyltetrahydro-3H,4H-3,6-epoxy[1,2]-dioxolo[3,4-b]pyran, **P11** [50]

White crystals. Yield 80%, 256.9 mg M.p. 60–62 °C (Lit. [50] M.p. = 60–61 °C). R_f = 0.40 (TLC, PE:EA, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.91 (t, 3H, *J* = 7.0 Hz), 1.21−1.78 (m, 10H), 1,40 (s, 3H), 1.47 (s, 6H). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 14.0, 16.2, 19.1, 23.8, 24.9, 26.5, 31.0, 31.1, 50.7, 94.1, 107.4. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.54; H, 9.28.

2.5.2. 3a-Allyl-3,6,7a-trimethyltetrahydro-3H,4H-3,6-epoxy[1,2]-dioxolo[3,4-b]pyran, **P12** [50]

White crystals. Yield 61%, 196.9 mg M.p. 42–44 °C (Lit. [50] M.p. = 43–44 °C). R_f = 0.46 (TLC, PE:EA, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.48 (s, 6H), 1.70−1.72 (m, 4H), 2.27 (d, 2H, *J* = 7.3 Hz), 5.04−5.18 (m, 2H), 5−79−5.96 (m, 1H). ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 16.2, 19.2, 24.9, 31.0, 35.9, 50.8, 94.2, 107.3, 118.7, 133.4. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.86; H, 8.18.

2.5.3. 3a-Benzyl-3,6,7a-trimethyltetrahydro-3H,4H-3,6-epoxy[1,2]dioxolo[3,4-b]pyran, **P13** [50]

White crystals. Yield 68%, 216.5 mg M.p. = 94–96 °C (Lit. [50] M.p. = 94–95 °C). R_f = 0.38 (TLC, PE:EA, 5:1). NMR (300.13 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.46 (s, 6H), 1.69–1.77 (m, 2H), 1.84–1.91 (m, 2H), 2.90 (s, 2H), 7.22–7.32 (m, 5H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 16.7, 19.0, 24.8, 31.0, 36.9, 51.9, 93.8, 107.6, 127.0, 128.2, 131.3, 136.5. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.70; 7.48.

2.6. Investigation of Fungicidal Activity In Vitro

The antifungal activities were tested according to the conventional procedure [51–53] with six phytopathogenic fungi from different taxonomic classes: *Fusarium culmorum* (*F.c.*) (causes seedling blight, root rot, ear blight, stalk rot, and other diseases of cereals) [54–56], *Rhizoctonia solani* (*R.s.*) (causes black scurf of potatoes) [57], *Alternaria solani* (*A.s.*) (causes seedling blight of tomatoes and potatoes) [58,59], *Phytophthora infestans* (*P.i.*) (the causal agent of potato blight) [60], and *Colletotrichum coccodes* (*C.c.*) (causes anthracnose on tomatoes and black dot disease of potatoes) [61,62]. Phytopathogenic fungi sensitivity to azoxystrobin was tested before the study. The effect of the chemicals on mycelial radial growth was determined by dissolving concentration 3 mg·mL^{-1} in acetone and suspending aliquots in potato-saccharose agar at 50 °C to give the concentration 30 μg·mL^{-1}. The same medium without a sample was used as the blank control (the same volume of pure acetone without the substance was added). The final acetone concentration of both fungicide-containing and control samples was 10 mL·L^{-1}. Petri dishes containing 15 mL of the agar medium were inoculated by placing 2 mm micelial agar discs on the agar surface. Plates were incubated at 25 °C, and radial growth was measured after 5 days. Three replicates of

each test were carried out. The mycelium elongation diameter (mm) of fungi settlements was measured after 5 days of culture. The growth inhibition rates were calculated with the following equation: I = [(DC − DT)/DC] × 100%. Here, I is the growth inhibition rates (%), DC is the control settlement diameter (mm), and DT is the treatment group fungi settlement diameter (mm). The results are summarized in Table 1.

Data from the experiments were analyzed using the STATISTICA 6.1 software (StatSoft Inc., Tulsa, OK, USA). Mean values, standard deviations and standard errors were calculated. The least significant difference ($LSD_{0.95}$) was used to compare the levels of a pathogen growth inhibition and disease severity between the tested compounds and to determine the significance of differences between results for different compounds at a 95% confidence level.

2.7. Investigation of Fungicidal Activity to Control Leaf Blight on Detached Potato Leaves

The fungicidal activities to control leaf blight were tested according to the conventional procedure [63–66].

2.7.1. Chemicals and Formulations

The leader compound **P4** was compared with fluazinam (Shirlan, Syngenta, 0.4 L/ga) as a well-known contact fungicide. The final fluazinam concentration was 2.0 g/L. Compound **P4** was formulated as 0.17 g/L solution in distilled water with 0.1% TWEEN 80 and with the addition of 1 mL/L commercial adjuvant (Atomic™, the adjuvant contains siloxanes modified with polyester) (application rate 30 g/ga).

2.7.2. Plants

Potato leaves (*Solanum tuberosum*, Arizona) were separated from plants grown in the field and brought to the laboratory for testing. One fully expanded leaf per plant was treated, and in total, 10 plants were used per one treatment.

2.7.3. Pathogens and Inoculation

An isolate of *P. infestans* M.(161), maintained on plants in our laboratory (VNIIF, Russia), was used in this study. The pathogens were 10 days old. Concentration of isolate *P. infestans* suspension was 20,000 conidium/mL.

2.7.4. Study of Fungicidal Activity to Control Leaf Blight

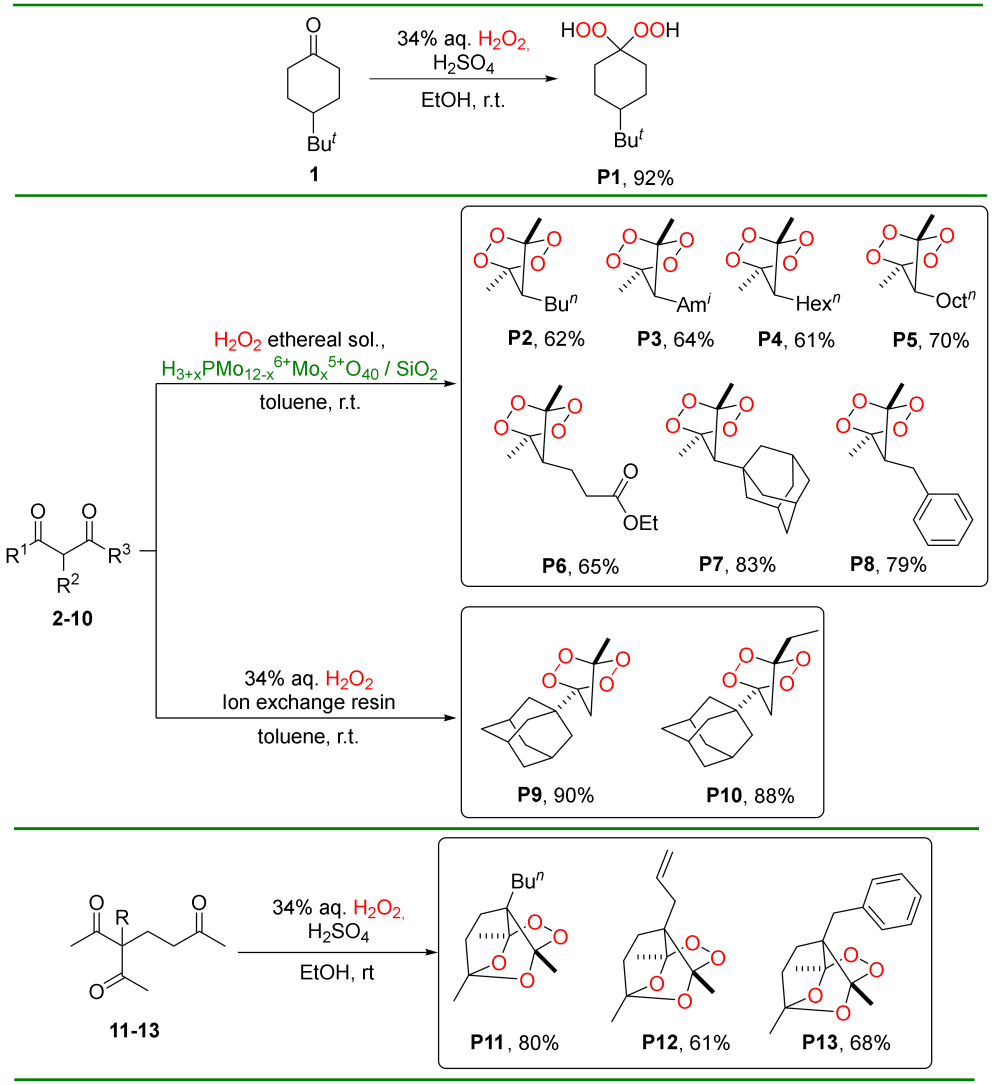
To study fungicide activity, compositions of compound **P4** and fluazinam were sprayed 24 h before the inoculation of the plants, on the adaxial (upper) leaf surface. Fungicide solutions were applied to "run-off" with a hand sprayer. Control seedling plants were sprayed with sterile tap water 24 h before the inoculation. After 24 h, fungicide treated leaves were inoculated on the abaxial (lower) surface. A similar set of plants and leaves was treated with the same fungicides on the abaxial (lower) leaf surface and inoculated 24 h later on the same leaf surface. Inoculum on the leaves in the form of a suspension of conidia was applied locally (1–2 drops per leaf). We used a microdispenser that allows you to apply drops of 10 µL. The inoculated leaves were kept for 18 h in a humid chamber in the dark. Then, the remains of the suspension are removed from the leaves with filter paper and again placed in a humid chamber at a temperature of 20 °C. On the fourth day, the diameter of necrosis is measured, in mm. The productivity of sporulation on *P. infestans*-affected spots was assessed in points on the fifth day. Measurements were based on the 12-scale disease index of Horsfall and Barrat [67].

3. Results and Discussion

3.1. The Synthesis of Acyclic and Cyclic Organic Peroxides

We have synthesized and tested a series of organic peroxides—geminal bishydroperoxide **P1** [48], bridged 1,2,4,5-tetraoxanes **P2**–**P10** [21,49] and tricyclic monoperoxides **P11**–**P13** [50] (Scheme 1). Although we have encountered no difficulties in working with

the peroxides described below, the proper precautions, such as the use of shields, fume hoods, and the avoidance of transition metal salts, heating and shaking, should be taken whenever possible.



Scheme 1. Synthetic approaches to organic peroxides **P1**–**P13** used in the present study.

Geminal bishydroperoxide **P1** was prepared from cyclohexanone **1** using 34% aq. H_2O_2 and H_2SO_4 in a 92% yield. A previously developed synthetic procedure using phosphomolybdic acid supported on SiO_2 as the catalyst was applied for the synthesis of bridged 1,2,4,5-tetraoxanes **P2**–**P8** in 62–83% yields. Adamantane-containing peroxides **P9** and **P10** were synthesized by peroxidation of corresponding 1,3-diketones **9** and **10** using ion exchange resin as the catalyst. The advantages of these methods are high selectivity, reusability of the catalyst and no acidic waste. The peroxidation of β,δ′-triketones **11**–**12** with 35% aq. H_2O_2 in the presence of sulfuric acid led to tricyclic monoperoxides **P11**–**P13** in 61–80% yields.

*3.2. Study of the Fungicidal Activity of Synthesized Peroxides **P1**–**P13** In Vitro*

The synthesized peroxides **P1**–**P13** were tested against plant pathogenic fungi of various taxonomic classes, which cause great damage to agriculture and crop production. The effect of the tested compounds on the mycelium radial growth in potato-saccharose agar was measured at a concentration of 30 mg L^{-1}. The fungicide Quadris®, whose active

compound is Azoxystrobin, was used as the reference standard (Table 1). The concentration of Azoxystrobin was 30 mg·L^{-1}.

Among tested classes of peroxides, the most active were bridged 1,2,4,5-tetraoxanes. Acyclic peroxide **P1** demonstrates low antifungal activity. Peroxides **P2**–**P5** completely inhibit the growth of *P. infestans* mycelium (100%). Tetraoxane **P8** with the benzyl radical exhibits high antifungal activity (100% inhibition of mycelium growth) against both *R. solani* and *P. infestans*. This peroxide is also very active against *F. culmorum* and *A. solani* (78% and 89%, respectively). In all these cases, tetraoxane **P8** is more active than Quadris®. Tetraoxane **P5** with the *n*-octyl radical is more active than Quadris® against *F. culmorum*, *R. solani* and *P. infestans* (86%, 88% and 100%, respectively). With a decrease in the length of the alkyl radical, as well as with the introduction of a polar functional group, the fungicidal activity of peroxides decreases. Thus, tetraoxanes **P2**, **P3** and **P6** are more active than Quadris® only against *F. culmorum*.

Table 1. Growth inhibition of the mycelium of the pathogenic fungi by peroxides **P1**–**P13** [1].

No	Cmpd.	Mycelium Growth Inhibition ± SD, % C = 30 mg·L^{-1}				
		F.c.	*R.s.*	*A.s.*	*P.i.*	*C.c.*
1	**P1**	0 ± 0.0	1 ± 7.5	11 ± 2.1	37 ± 5.0	4 ± 8.5
2	**P2**	**87 ± 1.0**	**84 ± 2.3**	**62 ± 3.6**	**100 ± 0.0**	44 ± 4.5
3	**P3**	**56 ± 2.2**	50 ± 2.5	50 ± 2.5	**100 ± 0.0**	38 ± 2.5
4	**P4**	22 ± 2.2	45 ± 2.2	50 ± 2.5	**100 ± 0.0**	57 ± 2.5
5	**P5**	**86 ± 1.1**	**88 ± 6.2**	55 ± 4.2	**100 ± 0.0**	33 ± 4.5
6	**P6**	**54 ± 1.1**	58 ± 2.2	35 ± 1.8	79 ± 4.8	18 ± 4.4
7	**P7**	**45 ±2.2**	67 ± 1.1	**63 ± 2.5**	48 ± 3.7	25 ± 2.5
8	**P8**	**78 ± 1.1**	**100 ± 0.0**	**89 ± 1.1**	**100 ± 0.0**	47 ± 4.4
9	**P9**	25 ± 5.0	56 ± 3.8	**66 ± 2.1**	67 ± 2.5	27 ± 6.4
10	**P10**	12 ± 7.5	17 ± 6.3	**66 ± 2.1**	62 ± 2.5	30 ± 6.3
11	**P11**	1 ± 7.5	0 ± 0.0	6 ± 2.1	5 ± 7.5	0 ± 0.0
12	**P12**	0 ± 0.0	2 ± 7.5	15 ± 2.1	20 ± 7.5	0 ± 0.0
13	**P13**	2 ± 7.5	1 ± 7.5	6 ± 2.1	0 ± 0.0	0 ± 0.0
14	Azoxystrobin in Quadris®	46 ± 2.7	85 ± 4.4	63 ± 3.6	95 ± 2.5	87 ± 2.5
$LSD_{0.95}$		12.8	12.3	12.9	16.1	12.6

[1] Values given in bold indicate an activity superior or equal to that of Quadris®. SD—standard deviation.

3.3. Study of Fungicidal Activity to Control Leaf Blight on Detached Potato Leaves

The fungicidal activity of the synthesized compound **P4** against leaf blight was investigated on detached potato leaves in comparison with the commercial contact fungicide Shirlan®, whose active compound is fluazinam (Table 2 and Figure 2). The treatment of the abaxial leaf surface with peroxide **P4** resulted in a significant reduction in leaf infestation and spore production of the pathogen *P. infestans* in comparison with the control. However, compound **P4** was inferior to the contact fungicide Shirlan in protecting leaves from *P. infestans*. When the adaxial leaf surface was treated with compound **P4** and then inoculated on the abaxial leaf surface with a suspension of *P. infestans*, a significant reduction in protection efficiency was observed compared to the contact fungicide Shirlan. Compound **P4** was found to have no translaminar activity and no good redistribution across the leaf surface of potatoes. Thus, when translaminar redistribution was required, both **P4** and the commercial fungicide provided less protection. The superior activity of the commercial fungicide can be attributed to the presence of auxiliary compounds in its composition, which may improve such parameters as wetting and sorption to the leaf surface. Also, the absence of high fungicidal activity on detached potato leaves in the case of a particular substance does not indicate the absence of such activity in the remaining bridged 1,2,4,5-tetraoxanes. This class of organic peroxides should continue to be explored as fungicides.

Table 2. Severity of potato blight developed on potato leaves treated with fungicides on the adaxial (upper) or the abaxial (lower) leaf surface and inoculated on the abaxial (lower) leaf surface.

No.	Fungicide Treatment	Application Dose (mg/mL)	Abaxial Leaf Surface Treatment [1]		Adaxial Leaf Surface Treatment [2]	
			Average Spot Growth Diameter, mm	Points	Average Spot Growth Diameter, mm	Points
1	**P4**	0.17	9.0	4.2	20.4	9.6
2	fluazinam in Shirlan®	2.0	0.5	0	8.6	4.8
3	Control (H_2O)		22.8	11.4	23.8	11.4
	$LSD_{0.95}$		2.8	1.3	2.5	1.2

[1] Fungicides were applied on the abaxial leaf surface 24 h before inoculation of the plants on the same leaf surface. [2] Fungicides were applied on the adaxial leaf surface 24 h before inoculation of the plants on the opposite leaf surface.

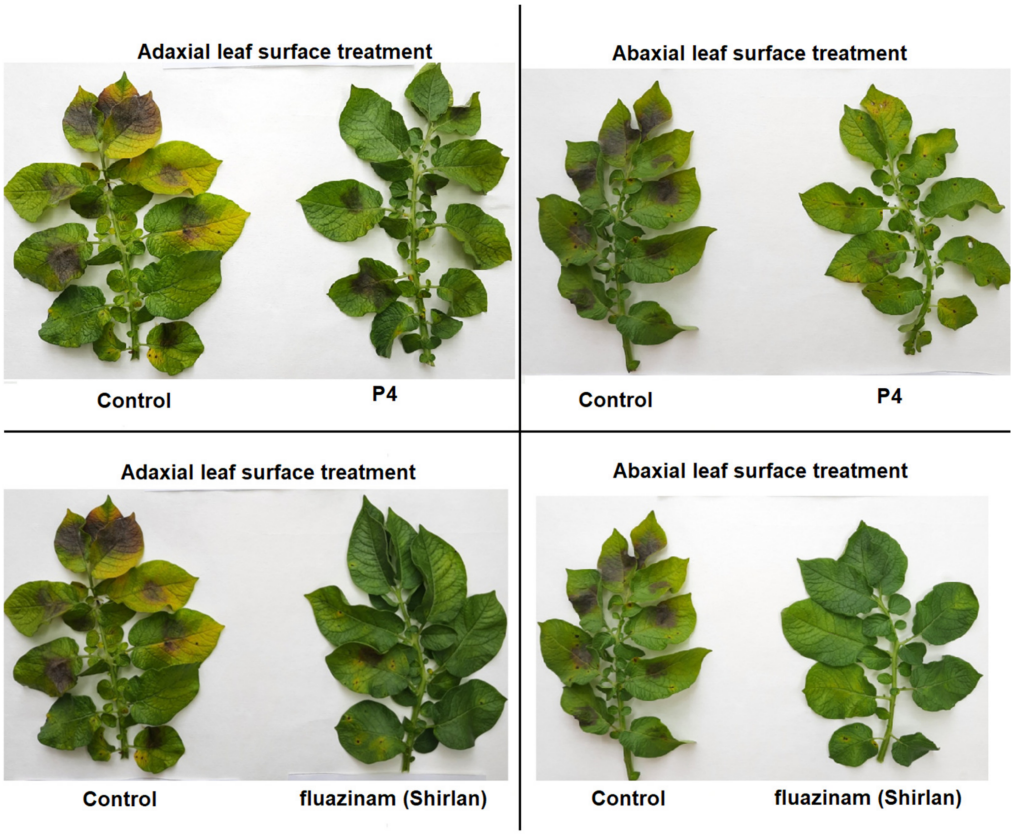


Figure 2. Late blight on the leaves on the 4th day after infection.

4. Conclusions

A wide range of cyclic organic peroxides were found to have a promising broad-spectrum fungicidal activity. The highest fungicidal activity was observed for the substituted bridged 1,2,4,5-tetraoxanes **P2**–**P8** with the inhibition of colony growth: *F. culmorum* from 22 to 87%; *R. solani* from 45 to 88%; *A. solani* from 35 to 89%; *P. infestans* from 79 to 100%; *C. coccodes* from 18 to 57%. Geminal bishydroperoxide **P1**, adamantyl-containing 1,2,4,5-tetraoxanes **P9**–**P10** and tricyclic monoperoxides **P11**–**P13** showed lower activity. For the most active structures, efficient synthesis methods with the possibility of catalyst recycling have been applied. The contact mode of activity against *P. infestans* for peroxide **P4** was demonstrated on detached potato leaves.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/agrochemicals2030021/s1, ^{1}H and ^{13}C NMR spectra of the synthesized compounds.

Author Contributions: Conceptualization, V.A.V. and A.O.T.; investigation, I.A.Y., P.S.R., Y.Y.B., D.I.F., V.N.D. and M.A.K.; writing—original draft preparation, V.A.V., I.A.Y. and M.A.K.; writing—review and editing, V.A.V., I.A.Y. and A.O.T.; supervision, A.P.G. and A.O.T.; project administration, V.A.V. and A.O.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Russian Science Foundation, grant number 21-73-10016.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors are grateful to the Center for Collective Use at the Institute of Phytopathology for providing equipment for phytopathological studies.

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

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