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[4+2]-Cycloaddition of maleic anhydride to substituted cycloheptatrienes for the synthesis of novel 4-oxatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-diones

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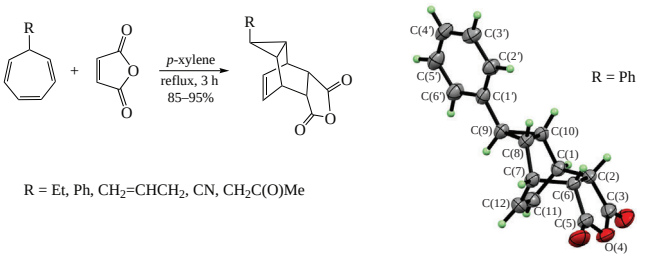
The [4+2]-cycloaddition of maleic anhydride to 7-substituted 1,3,5-cycloheptatrienes involves their 7-R-bicyclo[4.1.0]-hepta-2,4-diene tautomers and affords new 4-oxatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-diones in 85–95% yields. The structure of the resulting adducts is proved using advanced 1D and 2D NMR techniques and X-ray diffraction analysis. The cycloaddition proceeds stereospecifically providing *meso*-(1*S,2*S**,6*R**,7*R**,8*R**,9-*anti*,10*S**)-configuration in the products.**



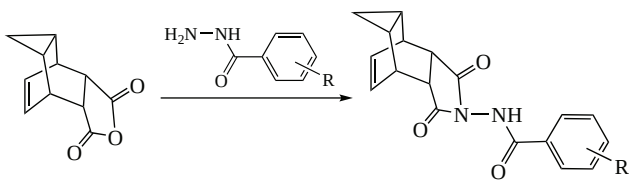
Keywords: cycloaddition, 7-substituted 1,3,5-cycloheptatrienes, maleic anhydride, 4-oxatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-diones, biologically active compounds.

The development of effective methods for the synthesis of new bridged carbo- and heterocyclic compounds based on cycloaddition reactions is a highly promising trend in the modern organic synthesis. Cycloaddition reactions involving cyclic polyenes, which open up the way to previously inaccessible bridged bi- and polycyclic systems, deserve special attention.[1–4] In this respect, mention should be made of cyclocodimerization of 1,3,5-cycloheptatrienes with structurally diverse unsaturated compounds,[1(*a*),5] which enables the synthesis of valuable bridged polycycles in one preparative step. The cycloadducts obtained from 1,3,5-cycloheptatrienes are used as key structural blocks in the synthesis of important biologically active and medicinal compounds.[6]

Currently, studies of the targeted transformations of 4-oxatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-dione, the cycloheptatriene cycloadduct with maleic anhydride, are especially relevant. This compound served for the preparation of a series of promising *N*-carboxamides, which exhibited a high antiviral activity against the orthopoxvirus [the antiviral agent tecovirimat (ST-246) for the treatment of smallpox][7] and a high anti-HIV-1 activity[8] (Scheme 1).

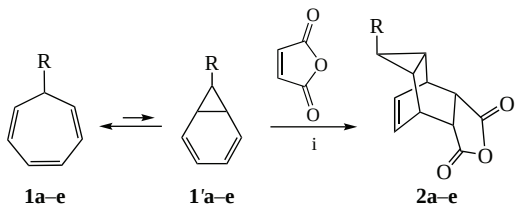
The [4+2]-cycloaddition of maleic anhydride to parent 1,3,5-cycloheptatriene was investigated in detail;[9–11] the real substrate which underwent the cycloaddition was its bicyclo[4.1.0]hepta-2,4-diene tautomer. However, the examples of reactions of substituted 1,3,5-cycloheptatrienes with maleic anhydride are scarce.[12] For example, Reichardt[12(*a*)] reported on the cyclocodimerization of (2,4,6-cycloheptatrien-1-yl)-malonaldehyde with maleic anhydride (chloroform, room temperature, 48 h), leading to the target tricyclic cycloadduct in a 23% yield. Other authors[12(*b*),(*c*)] studied [4+2]-cycloaddition of maleic anhydride to substituted 3,8a-dihydroazulen-1(2*H*)-ones (CH_2Cl_2, reflux, 6 h; ethyl acetate, reflux, 16 h) with the formation of cycloadducts in 25–90% yields. In 2021, Ito[12(*d*)] reported on the cyclocodimerization of maleic anhydride with cycloheptatriene containing a pyrrole substituent with a *p*-bromophenylsulfonyl group (chlorobenzene, 100 °C, 24 h); the reaction proceeded to form 4-oxatetracyclo[5.3.2.0^{2,6}.0^{8,10}]-dodec-11-ene-3,5-dione in a 79% yield.

In this communication, we report the first study of the [4+2]-cycloaddition of maleic anhydride to 7-substituted 1,3,5-cycloheptatrienes **1a**–**e** (Scheme 2). The reaction was performed by refluxing in *p*-xylene for 3 h, which truly afforded the anticipated adducts **2a**–**e** in 85–95% yields (for details, see Online Supplementary Materials). Apparently, the transformation would undergo the diene tautomers **1′a**–**e** (see Scheme 2).



– antiviral activity against orthopoxviruses
– anti-HIV-1 activity

Scheme 1



1a–e **1′a–e** **2a–e**

a R = Et, 93%
b R = Ph, 95%
c R = CH_2=$CHCH_2$, 89%
d R = CN, 90%
e R = CH_2Ac, 85%

Scheme 2 *Reagents and conditions*: i, *p*-xylene, reflux, 3 h.

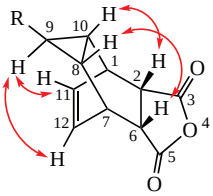


Figure 1 Key NOESY (↔) correlations for compounds **2a**–**e**.

The structure of cycloadducts **2a**–**e** was confirmed by 1D (^{1}H, ^{13}C) and 2D (COSY, NOESY, HSQC, and HMBC) NMR experiments. The *syn*-orientation of the cyclopropane ring relative to the double bond was proved by the presence of cross-peaks between the signals of the HC(9) proton and the HC(11) and HC(12) protons at the double bond in the ^{1}H–^{1}H NOESY experiment. The *endo*-configuration of the anhydride moiety was proved by the presence of cross-correlations between the HC(8), HC(10) and HC(2), HC(6) proton signals in the ^{1}H–^{1}H NOESY spectrum (Figure 1).

9-Phenyl-4-oxatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-dione **2b** was studied by X-ray diffraction, which unambiguously confirmed its structure and configuration (Figure 2).† It crystallizes in the monoclinic space group $P2_1/n$ with one molecule in the asymmetric unit. The stereogenic centers at C(1), C(2), C(6), C(7), C(8) and C(10) atoms in **2b** have the *S**, *S**, *R**, *R**, *R** and *S** configuration, respectively, which provides a *meso*-configuration of the whole molecule. The bond lengths in the anhydride moiety are consistent with literature data[13] and are 1.1934(19), 1.1869(18), 1.3827(19), and 1.388(2) Å for C(3)=O(1), C(5)=O(2), C(3)–O(4), and C(5)–O(4), respectively. The root-mean-square deviation of atoms from the plane of a five-membered ring containing an anhydride group is 0.001 Å, which indicates its planar structure. It should be noted that in the ring system of bicyclo[2.2.2]-octene, both C(9) and atoms of the anhydride functional group occupy the *endo* position relative to the atoms of the C(11)=C(12) alkene bridge. The planes of the phenyl and cyclopropyl rings are almost perpendicular to each other, and the C(1′)C(2′)C(3′)C(4′)C(5′)C(6′)/C(8)C(9)C(10) dihedral angle is 112.52(11)°. The C(11)=C(12) double bond length is 1.315(2) Å, and the bond angles of the cyclopropyl ring take values in a narrow range from 59.86 to 60.13°.

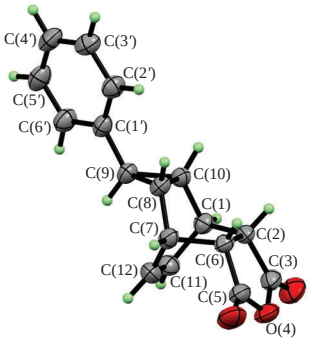


Figure 2 Molecular structure of compound **2b**. Displacement ellipsoids are drawn at a 50% probability level.

In summary, [4+2]-cycloaddition reactions of maleic anhydride with 7-ethyl-, phenyl-, allyl-, nitrile-, and acyl-substituted 1,3,5-cycloheptatrienes resulted in previously unknown 9-substituted 4-oxatetracyclo[5.3.2.0^{2,6}.0^{8,10}]dodec-11-ene-3,5-diones in high yields (85–95%). The obtained functionally substituted bridged structures have a high potential for the application in experimental pharmacology as key precursors for the targeted synthesis of new biologically active compounds and valuable medicinal agents.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.036.

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† *Crystal data for* **2b**. $C_{17}H_{14}O_3$ (M = 266.28), monoclinic, space group $P2_1/n$, a = 13.7039(15), b = 6.2945(5) and c = 16.394(2) Å, α = 90°, β = 114.320(14)°, γ = 90°, V = 1288.7(3) Å^3, Z = 4, d_{calc} = 1.372 g cm^{-3}, μ(MoKα) = 0.094 mm^{-1}, F(000) = 560.0. Total of 17148 were collected (6440 independent reflections, R_{int} = 0.0803) and used in the refinement, which converged to wR_2 = 0.1678, GOOF 0.959 for all independent reflections [R_1 = 0.0660 was calculated for 6440 reflections with $I > 2\sigma(I)$].

CCDC 2265539 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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