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# Dianhydrides of 1(4)-substituted 7,8-diphenylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acids

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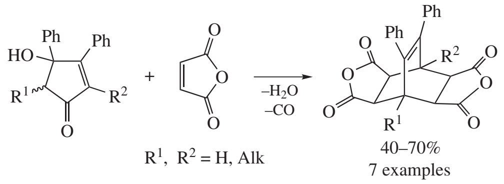
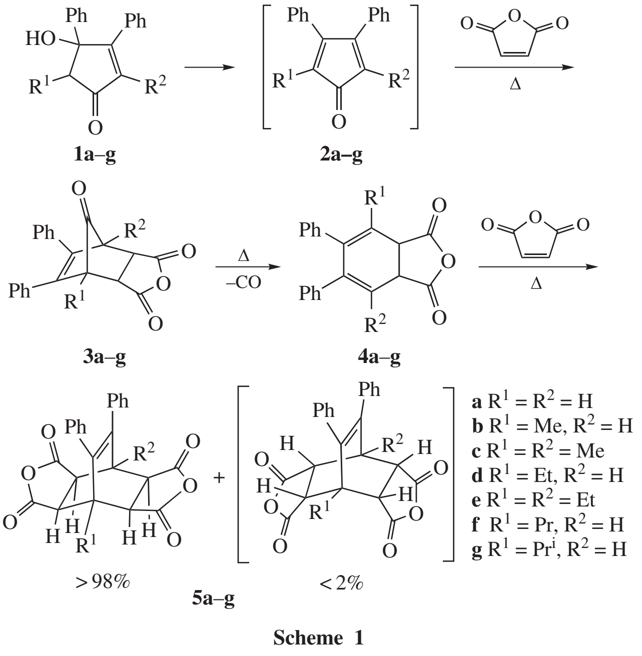
**2(5)-Substituted 4-hydroxy-3,4-diphenylcyclopent-2-en-1-ones easily react with 2.5 molar excess of maleic anhydride to give 1(4)-substituted 7,8-diphenylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydrides containing alkyl groups at bridgehead of the bicycle. The stereochemistry of the obtained bicyclic bis-anhydrides was determined to be *syn-syn*.**



The classical Diels–Alder reaction widely used for stereo- and regioselective synthesis of six-membered cycles containing up to four stereogenic centers involves cycloaddition of conjugated diene to a dienophile containing a $\pi$-bond ([4+2] cycloaddition). Cyclopentadiene reacts with maleic anhydride vigorously to give an adduct with *anti*-configuration which on heating would isomerise to *syn*-adduct. The latter dissociates by further heating (above 200 °C) into the starting components (retro-diene degradation).[1] The stereoselectivity of the Diels–Alder reaction is nowadays widely investigated. Attempts to model the enantioselectivity of such a reaction by molecular and quantum mechanics with further experimental study including the assistance of a chiral solvents and chiral promotion were described.[2]

Cyclopentadienones are also very active towards maleic anhydride. The refluxing of 2,3,4,5-tetraphenylcyclopentadienone with maleic anhydride in benzene almost quantitatively gives the adduct which on further heating in a higher boiling solvent is decarbonylized yielding a cyclohexadiene derivative. Bis-adduct is formed if the elimination of carbon monoxide occurs in the presence of maleic anhydride[1] (Scheme 1).



**Scheme 1**

Bicyclic dianhydrides of tetracarboxylic acids **5** easily react with aliphatic amines to afford the corresponding imides. In the case of bis-amines, flame-retardant and thermally stable polymers are formed.[3] Such compounds exhibit anticancer[4] and anxiolytic[5] activites.

Earlier we described the synthesis and the structure determination of all possible isomers of 2(5)-substituted 4-hydroxy-3,4-diphenylcyclopent-2-en-1-ones **1** formed by the interaction of benzil with ketones.[6]

Classical method for obtaining 2(5)-substituted dianhydrides of bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acids comprises the condensation of 2-pyrone with maleic anhydride at a temperature above 140 °C followed by pyrolytic decarbonylation of monoadduct to cyclohexadiene derivative, which takes up an additional maleic anhydride molecule to give the target compound.[7] The disadvantages of this method are the instability of 2-pyrones, as well as the unavailability of 4,5-diphenyl-3(6)-(di)alkyl-2-pyrones. Compounds **5a**[8] and **5c**[9] were previously described, however, without experimental preparation details.

We have developed a simple method for the preparation of dianhydrides of bicyclic tetracarboxylic acids of type **5** (see Scheme 1) containing alkyl substituents in the bridgehead 1- and/or 4-positions of the bicyclic system. Two sequentially occurring reactions comprise a single treatment of 2(5)-substituted 3,4-diphenylcyclopentenones with 2.5 molar excess of maleic anhydride on heating the reaction mixture to 200–225 °C without solvent.[†]

The reaction between 2(5)-substituted 4-hydroxy-3,4-diphenylcyclopent-2-en-1-one **1** and one equivalent of maleic anhydride gives unstable 1(4)-substituted 7-oxo-2,3-diphenylbicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic acid anhydride **3**. The latter decomposes *in situ* on heating releasing CO molecule to yield the second diene, 2(5)-substituted 3,4-diphenylbicyclohexadiene-

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[†] $^1$H NMR spectra were recorded on a Bruker AMW-700 spectrometer (700 MHz) in DMSO-$d_6$. Chemical shifts were measured relative to the residual solvent protons.

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1,6-dicarboxylic acid anhydride **4**. The latter reacts with the second equivalent of maleic anhydride to afford 2(5)-substituted-7,8-diphenylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydrides **5** in preparative yields. The reaction proceeds in the absence of solvents. The products are isolated by boiling in acetic acid followed by recrystallization from the same solvent. The structure and purity of compounds **5a–g** were proved by elemental analysis, $^1$H NMR spectroscopy and X-ray data.

The stereochemistry of the obtained bicyclic dianhydrides is of special interest. The existence of three isomers, *syn-syn*, *syn-anti* and *anti-anti*, relative to bicycle is theoretically possible. The attachment of the first molecule of maleic anhydride leads to compound **3** in *anti*-configuration. The release of CO molecule results in nearly flat cyclohexadiene **4**, which, under kinetic control, attaches a second maleic anhydride molecule (retro-Diels–Alder reaction) and *syn-anti* isomer **5** is formed. The resulting product is the *syn-syn* isomer **5**, that is, a spontaneous stereoselective synthesis occurs. The singlet nature of the bridgehead proton and CH–C=O proton signals in the region of 3.6–3.8 ppm confirms the formation of this isomer. In a *syn-syn* isomer, these protons form a dihedral angle of almost 90° and, consequently, they cannot interact with each other. Alternative configurations of the anhydride rings should provide interaction of these protons and thus splitting of their $^1$H NMR signals. The structure of representative **5b** was confirmed by X-ray data (Figure 1).[‡]

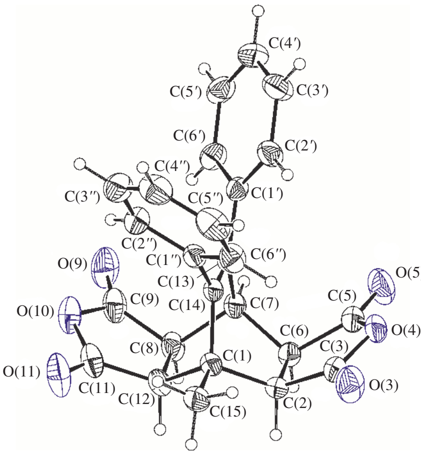

**Figure 1** Crystal structure of compound **5b**.

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*General procedure.* 2(5)-Substituted 4-hydroxy-3,4-diphenylcyclopent-2-en-1-one **1a**–**g** (18 mmol) and thoroughly powdered maleic anhydride (46 mmol) were heated for 4 h in a flask equipped with an air condenser at 200–225 °C in metallic bath. After cooling, glacial acetic acid (100–150 ml) was added, the mixture was brought to boiling and then cooled. The precipitate was separated and washed with cold acetic acid (3×50 ml) and diethyl ether (3×100 ml). Pure compounds **5a**–**g** were obtained after three recrystallizations from acetic acid.

*7,8-Diphenylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride* **5a**, yield 60%, mp 330 °C. $^1$H NMR $\delta$: 3.84 (4s, 4H, CH–C=O), 3.87 (4s, 4H, CH–C=C), 6.88 (m, 4H, Ph), 7.20 (m, 6H, Ph). MS, *m/z*: 400 [M]$^+$. Found (%): C, 72.16; H, 4.13. Calc. for $C_{24}H_{16}O_6$ (%): C, 72.00; H, 4.03.

*1-Methyl-7,8-diphenylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride* **5b**, yield 40%, mp 272–275 °C. $^1$H NMR $\delta$: 1.56 (s, 3H, Me), 3.58 (2s, 2H, CH–C=O), 3.88 (m, 3H, 2CH–C=O + CH–C=C), 6.70 (m, 2H, Ph), 6.82 (m, 2H, Ph), 7.10 (m, 3H, Ph), 7.20 (m, H, Ph), 7.22 (m, 2H, Ph). $^{13}$C NMR, $\delta$: 18.03 (Me), 39.52, 42.81, 44.67, 48.88, 127.34, 127.41, 127.84, 128.07, 128.28, 128.72, 135.79, 137.09, 138.34, 141.82, 171.39 (C=O), 172.27 (C=O). MS, *m/z*: 414 [M]$^+$. Found (%): C, 72.66; H, 4.53. Calc. for $C_{25}H_{18}O_6$ (%): C, 72.46; H, 4.38.

*1,2-Dimethyl-7,8-diphenylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride* **5c**, yield 61%, mp 322 °C. $^1$H NMR $\delta$: 1.50 (s, 6H, Me), 3.61 (s, 4H, CH–C=O), 6.60 (dd, 4H, *o*-$H_{Ph}$), 7.06 (t, 2H, *p*-$H_{Ph}$), 7.12 (t, 4H, *m*-$H_{Ph}$). MS, *m/z*: 428 [M]$^+$. Found (%): C, 73.01; H, 4.86. Calc. for $C_{26}H_{20}O_6$ (%): C, 72.89; H, 4.70.

*1-Ethyl-7,8-diphenylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride* **5d**, yield 43%, mp 306 °C. $^1$H NMR: 1.15 (s, 3H, Me), 1.85 (m, 2H, $CH_2$), 3,70 (2s, 2H, CH–C=O), 3.86 (m, 3H, 2CH–C=O + CH–C=C), 6.64 (d, 2H, Ph), 6.82 (d, 2H, Ph), 7.07 (m, 3H, Ph), 7.23 (m, 3H, Ph). MS, *m/z*: 428 [M]$^+$. Found (%): C, 73.06; H, 4.89. Calc. for $C_{26}H_{20}O_6$ (%): C, 72.89; H, 4.70.

*1,2-Diethyl-7,8-diphenylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride* **5e**, yield 58%, mp 301–302 °C. $^1$H NMR $\delta$: 1.07 (t, 6H, Me, *J* 7.31 Hz), 1.83 (q, 4H, $CH_2$, *J* 7.31 Hz), 3.75 (s, 4H, CH–C=O), 6.56 (m, 4H, *o*-$H_{Ph}$), 7.04 (m, 2H, *p*-$H_{Ph}$), 7.10 (m, 4H, *m*-$H_{Ph}$). MS, *m/z*: 456 [M]$^+$. Found (%): C, 73.82; H, 5.43. Calc. for $C_{28}H_{24}O_6$ (%): C, 73.67; H, 5.30.

*7,8-Diphenyl-1-propylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride* **5f**, yield 43 %, mp 299–300 °C. $^1$H NMR $\delta$: 0.89 (t, 3H, Me, *J* 7.22 Hz,), 1.57 (m, 2H, $CH_2$), 1.81 (m, 2H, $CH_2$), 3.70 (d, 2H, CH–C=O, *J* 8.55 Hz), 3.86 (s, 1H, CH–C=O), 3.88 (s, 1H, CH–C=O), 3.89 (d, 1H, CH–C=C), 6.65 (m, 2H, *o*-$H_{Ph}$), 6.79 (m, 2H, *o*-$H_{Ph}$), 7.08 (m, 3H, Ph), 7.19 (m, 1H, Ph), 7.24 (m, 2H, Ph). MS, *m/z*: 456 [M]$^+$. Found (%): C, 93.25; H, 6.75. Calc. for $C_{27}H_{22}O_6$ (%): C, 93.60; H, 6.40.

*1-(1-Methylethyl)-7,8-diphenylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride* **5g**, yield 38%, mp 292 °C. $^1$H NMR $\delta$: 0.85 (m, 6H, Me), 3.17 (m, 1H, C*H*Me), 3.80 (s, 2H, CH–C=O), 3.83 (s, 1H, CH–C=C), 3.89 (m, 2H, CH–C=O), 6.72 (m, 2H, Ph), 6.78 (m, 2H, Ph), 7.07 (m, 3H, Ph), 7.20 (m, 3H, Ph). MS, *m/z*: 442 [M]$^+$. Found (%): C, 73.44; H, 5.13. Calc. for $C_{27}H_{22}O_6$ (%): C, 73.30; H, 5.01.

[‡] *Crystallographic data.* The crystals of **5b** ($C_{25}H_{18}O_6$, $M$ = 414.39) were grown on cooling from the solution in acetic acid, monoclinic, space group $P2_1/n$, at 295(2) K, $a$ = 7.9467(4), $b$ = 24.2817(10) and $c$ = = 10.7249(6) Å, $\beta$ = 96.596(4)°, $V$ = 2055.77(18) Å$^3$, $Z$ = 4, $d_{\text{calc}}$ = = 1.339 g cm$^{-3}$, $\mu$(CuK$\alpha$) = 0.795 cm$^{-1}$, $F$(000) = 864. Intensities of 14387 reflections were measured with a Stoe STADI VARI Pilatus100K diffractometer [$\lambda$(CuK$\alpha$) = 1.54186 Å, $\omega$- and $\varphi$-scans, $\theta$ < 72.88°] and 4010 independent reflections ($R_{\text{int}}$ = 0.0517) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against $F^2$ in the anisotropic approximation. The refinement converged to $wR_2$ = 0.1139 and GOF = = 0.942 for all independent reflections [$R_1$ = 0.0483 was calculated for 3065 observed reflections with $I > 2\sigma(I)$] using SHELXL2013 program.

CCDC 1550365 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.