Synthesis and Structure of Methanobenzocyclooctene Derivatives†

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10-Oxo-5,9-methanobenzocyclooctene-8-carboxylic acid 4a was prepared by the intramolecular cyclization of 4-phenylcyclohexane-1r,2c-dicarboxylic acid 1a in concentrated H2SO4 or in the reaction of 4-phenylcyclohexane-1r,2c-dicarboxylic anhydride 2 in 80% H2SO4. To improve the yield, the esters 3a,b were cyclized to the methanocyclooctene isomers 5a,b, in a 1:5 ratio from 3a, and in a 5:4 mixture (54%) from 3b at elevated temperature. After separation, 5a was hydrolysed, the keto group of 4a was reduced by the Wolff-Kishner method and the resulting cis and trans methylene-bridged benzocyclooctenes 6a,b (1:2) were separated. From 4a with hydrazine, the tetracyclic pyridazine derivative 7 was obtained. The structures were determined by 1H and 13C NMR methods and for 4a also by X-ray crystallography.

In our earlier studies on fused-skeleton saturated and partially saturated 1,3-heterocycles, we studied the reactions of cyclic β-oxo carboxylic acids with alicyclic 1,3-amino alcohols in which one of the functional groups was attached directly, and the other through a methylene group to carbocycles such as cyclohexene, cyclohexene, norbornane or norborneone.1-4 In these cyclizations, tetracyclic and pentacyclic hetero compounds were formed, and isomerization of the starting stereohomogeneous cis and trans amino alcohols also often occurred. Consequently, structure elucidation of the fairly complex tetracyclic or pentacyclic systems, and determination of the configuration and conformation, was always a challenging task; a comparative study of closely related ring systems and the cis- and trans-fused isomers added to the importance. The new compounds were synthesized with pharmacological aims.

For the synthesis of fused-skeleton isoindolones, cis- or trans-2-aryoyl-1-cyclohexene-carboxylic acids were used as starting materials in our earlier studies. In the present paper, cis-4-cyclohexene-1,2-dicarboxylic anhydride was applied; through the addition of benzene to the double bond,5 this furnished 4r-phenylcyclohexane-1r,2c-dicarboxylic acid 1a with a phenyl equatorial5 to the neighbouring carboxy group. The 4-phenyl substituent on cyclohexane-1,2-dicarboxylic acid was thought might provide a good opportunity to construct highly condensed systems by intramolecular acylation of the phenyl substituent with the 2-carboxy group. These systems containing two functional groups are suitable for the preparation of heterocycles and they provide good starting molecules for the production of new pharmacologically active derivatives as target compounds.

Results

When heated in concentrated H2SO4, trans-4-phenylcyclohexane-cis-1,2-dicarboxylic acid (1a) or in 80% H2SO4, the anhydride 2 yielded 10-oxo-5,6,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (4a; yield 13% and 15%, respectively) by intramolecular cyclization.

Similar cyclization via AlCl3-catalysed intramolecular Friedel–Crafts acylation provides only a moderate yield (14–21%),6 in spite of the absence of strain in the bicyclononanone ring system.7 Other preparations,8-9 e.g., from benzylcyclohexanone with MeLi,10 from unsaturated enol silyl esters with ceric ammonium nitrates,11,12 from alkenes by MeSO3H cyclization13 and by carbo-
catic cyclization of unsaturated bromo imines are also known.

To improve the yield of 4a, we started from dimethyl 4-trans-phenylcyclohexane-cis-1,2-dicarboxylate (3a); cyclization with PPA at elevated temperature yielded a mixture of the isomeric esters 5a and 5b in a ratio of 1:5. In contrast, cyclization of dimethyl 4-trans-phenylcyclohexane-1r,2r-dicarboxylate (3b) gave the esters 5a and 5b in a 2:3 ratio (the yield of 5a,b was 54%). Consequently, as a result of the transformation 3b → 5a,b with PPA, the 30% yield of 5a (Table 3) isolated from the mixture 5a,b by column chromatography proved to be enough to permit further reactions. We presume that in the cyclization the 2-carboxy groups which are axial in the ground state come close to the phenyl group by ring inversion and 3a and 3b partly isomerize to form the products 5a,b. After separation of the isomers, the structures were established by NMR spectroscopy. The esters 5a,b were hydrolysed and the acids 4a,b were characterized by NMR and for 4a also by X-ray analysis (Fig. 1). The oxide group was reduced by the Wolff–Kishner method to afford a mixture of cis- and trans-5,6,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acids (6a,b). With hydrazine, the oxo

**Table 1.** IR carbonyl frequencies in KBr and **1H** NMR data on compounds 4–7 in **CDCl₃** solution at 250 MHz.

<table>
<thead>
<tr>
<th>Compound</th>
<th>V_C=O Posn. 8</th>
<th>V_C=O Posn. 10</th>
<th>H-1 dd (1 H)</th>
<th>H-4 dd (1 H)</th>
<th>H-5,9 distinguishably</th>
<th>H-ax Poisson. 7</th>
<th>H-8 (1 H)</th>
<th>H-eq’ Poisson. 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>1713</td>
<td>1678</td>
<td>8.03</td>
<td>7.24</td>
<td>3.2</td>
<td>1.50</td>
<td>2.79</td>
<td>2.50</td>
</tr>
<tr>
<td>4b</td>
<td>1696</td>
<td>1681</td>
<td>8.04</td>
<td>7.24</td>
<td>3.25</td>
<td>1.48</td>
<td>2.94</td>
<td>2.30</td>
</tr>
<tr>
<td>5a</td>
<td>1728</td>
<td>1685</td>
<td>8.06</td>
<td>7.23</td>
<td>3.2</td>
<td>1.52</td>
<td>2.73</td>
<td>2.45</td>
</tr>
<tr>
<td>5b</td>
<td>1729</td>
<td>1679</td>
<td>8.05</td>
<td>7.25</td>
<td>3.18</td>
<td>1.40</td>
<td>2.85</td>
<td>2.25</td>
</tr>
<tr>
<td>6a</td>
<td>1712</td>
<td>—</td>
<td>7.1</td>
<td>7.00</td>
<td>2.98</td>
<td>1.35</td>
<td>2.7</td>
<td>2.00</td>
</tr>
<tr>
<td>6b</td>
<td>1701</td>
<td>—</td>
<td>7.1</td>
<td>7.00</td>
<td>2.98</td>
<td>1.45</td>
<td>2.68</td>
<td>2.00</td>
</tr>
<tr>
<td>7</td>
<td>1671</td>
<td>—</td>
<td>7.80</td>
<td>7.20</td>
<td>3.1</td>
<td>1.35</td>
<td>2.55</td>
<td>2.00</td>
</tr>
</tbody>
</table>

in cm⁻¹. bChemical shifts in δ, δ_{TMS} = 0 ppm, coupling constants in Hz. c4a was also measured in DMSO-d₆ solution. dAssignments were proved by DR (4a) and DNOE (6a,b) measurements. Further signals, ¹H NMR: CH₂ (s, 3 H): 3.72 (5a), 3.77 (5b); CH₂ (posn. 6, 7eq, 11ax), 4 × m (4 × 1 H) in the interval 1.7–2.2 ppm, partly overlapped. Separated signals: H-6ax: 1.90 (4a, 5a), 2.18 (4b, H-6eq: 1.85 (4a), 1.65 (4b), 1.80 (5a), 1.60 (5b), 1.55 (6b); H-7eq: 1.75 (4a, 5a), 2.05 (4b), 1.93 (5b). H-11ax: 2.05 (4a, 5a), 2.22 (4b), 1.85 (6a); CH₂ (posn. 10): 2.78 d (split by 18.4) and 2.98 (6a), 2.68 and 3.27 dd (split by 18.0 and 7.5) for 6b; H-2, 3, 2 x 2, t (2 x 1 H): 7.30 and 7.50 (4a, 5a,b), 7.38 and 7.54 (4b), coalesced at 7.1 (6a,b) and 7.3 (7); NH, (br s, 1 H); 8.67 (7); H-9 (t, 1 H); 3.00 (for 4a in DMSO-d₆); IR, Y_MOH: 3300–2200 (4a,b, 6a,b); ν_MOH: 3185 (7). eOverlapping signals, except for 6a,b, where the H-9 signal at about 2.7 ppm is coalesced with the H-8 (m) and the upfield m of CH₂ (posn. 10) group (6b). fTo ring C (s-cis to the condensed aromatic ring). g Quartet split by ca. 13.5 with further doublet split by ca. 4.5. hDoublet split by 13.2 ± 0.2 with further triplet split by ca. 4 (for H-8) or 2.5 (H-11ax). iQuartet split by ca. 13 with further quartet split by 2.5, jTriplet split by ca. 13.5 (H-6ax) or 14.5 (H-7ax) and 4. kSinglet-like signal with coalesced fine structure. lDoublet-like signal with coalesced further fine structure, split by 14 ± 0.5. mIn overlap with the H-2,3 signal. nν_{TMS} = 0 ppm. oAssignments were confirmed by 2D-HSC (except for 4b and 7) and DEPT measurements. For easier comparison of spectroscopically analogous data, the numbering of 4 and 5 is used also for 6 and 7 here and in the text. The IUPAC naming is given in the Experimental part. pInterchangeable assignments. qOCH₃: 51.8 (5a), 51.5 (5b). rTwo overlapping lines.

**Table 2.** ¹³C NMR chemical shifts on compounds 4–7 in **CDCl₃** solution at 63 MHz.

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
<th>C-7</th>
<th>C-8</th>
<th>C-9</th>
<th>C-10</th>
<th>C-11</th>
<th>C-10α</th>
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<tbody>
<tr>
<td>4a</td>
<td>125.4</td>
<td>126.8</td>
<td>134.2</td>
<td>128.5</td>
<td>147.1</td>
<td>33.6</td>
<td>29.8</td>
<td>19.6</td>
<td>44.4</td>
<td>174.1</td>
<td>198.1</td>
<td>45.0</td>
</tr>
<tr>
<td>4b</td>
<td>126.7</td>
<td>127.0</td>
<td>134.4</td>
<td>128.2</td>
<td>147.2</td>
<td>34.5</td>
<td>27.6</td>
<td>19.1</td>
<td>41.9</td>
<td>179.6</td>
<td>200.3</td>
<td>43.8</td>
</tr>
<tr>
<td>5a</td>
<td>126.9</td>
<td>126.5</td>
<td>134.1</td>
<td>129.0</td>
<td>146.8</td>
<td>34.3</td>
<td>30.3</td>
<td>19.7</td>
<td>45.3</td>
<td>173.4</td>
<td>198.5</td>
<td>45.4</td>
</tr>
<tr>
<td>5b</td>
<td>126.0</td>
<td>126.4</td>
<td>133.7</td>
<td>127.7</td>
<td>146.7</td>
<td>34.0</td>
<td>27.1</td>
<td>18.7</td>
<td>41.3</td>
<td>173.1</td>
<td>199.4</td>
<td>43.6</td>
</tr>
<tr>
<td>6a</td>
<td>128.0</td>
<td>125.7</td>
<td>125.4</td>
<td>128.0</td>
<td>140.5</td>
<td>33.6</td>
<td>33.2</td>
<td>19.2</td>
<td>47.8</td>
<td>181.2</td>
<td>30.7</td>
<td>29.5</td>
</tr>
<tr>
<td>6b</td>
<td>127.9</td>
<td>125.7</td>
<td>125.5</td>
<td>128.2</td>
<td>140.6</td>
<td>33.7</td>
<td>30.2</td>
<td>18.8</td>
<td>46.5</td>
<td>181.3</td>
<td>35.3</td>
<td>28.8</td>
</tr>
<tr>
<td>7</td>
<td>123.5</td>
<td>127.4</td>
<td>129.5</td>
<td>127.9</td>
<td>143.4</td>
<td>32.2</td>
<td>28.9</td>
<td>18.3</td>
<td>35.0</td>
<td>174.9</td>
<td>156.7</td>
<td>39.0</td>
</tr>
</tbody>
</table>

α_{TMS} = 0 ppm. bAssignments were confirmed by 2D-HSC (except for 4b and 7) and DEPT measurements. For easier comparison of spectroscopically analogous data, the numbering of 4 and 5 is used also for 6 and 7 here and in the text. The IUPAC naming is given in the Experimental part. cInterchangeable assignments. OCH₃: 51.8 (5a), 51.5 (5b). dTwo overlapping lines.
carboxylic acid 4a was cyclized to the tetracyclic methanobenzocycloocta[9,8-c,d]pyridazine 7.

Structure. The characteristic IR, $^1$H and $^{13}$C NMR data are listed in Tables 1 and 2. For the isomeric pairs 4a,b and 5a,b, establishment of the stereo structure is complicated by the flexibility of ring C resulting in two relatively stable (chair and boat) conformations. Hence, both the C-8 configuration and the conformation have to be determined.

Owing to the strong steric hindrance between the two axial COOR and the skeleton (no sign of which appears in the spectra), the presumption of a cis H-8,9-H-9 configuration ($5R^*,8S^*,9R^*$) allows no boat conformation of ring C (Scheme 1, 4a). For a chair conformation and a cis configuration (Scheme 1, 4a), the axial H-8 is in a trans-diaxial position with one of the neighbouring H-7 atoms, and the correspondingly large coupling appears in the $^1$H NMR spectra of one of each of the acid and ester isomers; for 4a and 5a, the H-8 signal is a triplet of doublets split by 13.3, 4.1 and 4.1 Hz. (For a boat conformation of ring C, the equatorial H-8 would not display as large coupling as 13.3 Hz.)

As the H-8 multiplet of 4b and 5b does not exhibit a large splitting, the chair conformation of ring C is also preferred for the trans isomers ($5R^*,8R^*,9R^*$ configuration); hence, the COOR group is axial and the equatorial H-8 has no diaxial (i.e., large vicinal) coupling (Scheme 1). Accordingly, for trans 4b and 5b, the $^{13}$C NMR spectra indicate a sterically more unfavourable structure: the sum of the chemical shifts of the carbons in ring C is less (by 8.8 and 14.8 ppm) than that for the isomers 4a and 5a. If the simultaneous alteration of the C-8 configuration and C-ring conformation for the trans isomers is assumed, no essential difference in steric hindrance would be observable in comparison with the cis compounds, because the COOR group is equatorial in both isomers.

Further proof of the tentative structures is the field effect (i.e., the upfield shift of the $^{13}$C lines), which indicates sterically unfavourable structures and which is higher for the C-6 and C-11 (and of course C-8) lines than for the other three carbons (C-5,7,9), because the first two carbons are positioned 1,3-diaxially to the 8-COOR group. For the cis-trans pairs of acids and esters, the sum of the shift differences for the C-6,8,11 lines amounts to 8.0 and 11.7 ppm, while the corresponding values for C-5,7,9 are only 0.8 and 3.1 ppm.

For 4a, the X-ray determination (Fig. 1) revealed that the compound forms hydrogen-bonded monomers in the solid state. In the H-bond $\{O(2) \cdots H(14) \cdots O(3)\}$, $L = -x, 2-y, -z$, the $O \cdots O$ distance is 2.661(2) Å and the $OH \cdots O$ angle is linear 177(2)$^\circ$. These are typical values for carboxylic acid dimers.

The spectral data on the reduced products 6a,b confirm the above structures. For C-7 and C-11, the chemical shifts hardly differ from those measured for 4a,b and 5a,b. In the event of a boat conformation, the hindrance between the axial H-7 and H-11 would cause a strong steric effect, i.e., significant upfield shifts of the C-7 and C-11 lines. On the basis of the summed carbon shifts for ring C (the difference is 9.2 ppm), the assignments of the cis ($5R^*,8S^*,9R^*$) and trans ($5R^*,8R^*,9R^*$) H-8,9-H-9 configurations to the two isomers are unambiguous.

As stated above, for the isomeric pairs 4a,b and 5a,b, the shifts of C-6, C-8 and C-11 differ significantly due to the strong steric hindrance between the axial 8-COOR group and H-6a and H-11a in the trans isomers. For 6a,b, only the shift difference for C-6 and C-11 is significant; that for C-8 is significantly smaller ($\Delta \delta C-8 = 1.3$ ppm). The explanation lies in the strong steric hindrance between the endo 10-methylene hydrogen and the equatorial 8-COOH group of the cis isomer, and therefore the C-8 line is also shifted upfield for the cis isomer.

For steric reasons, the cis H-8,9-H-9 ($5R^*,8S^*,9R^*$) configuration is retained in the tetracyclic 7, while for the starting 4a, a change in the configuration on ring closure is not expected. The splittings of H-8 (13, 4 and 4 Hz) suggest the chair form of ring C, i.e., the conformation remains; the $\approx 13$ Hz split confirms diaxial coupling (Scheme 1), and such an interaction is impossible in the boat form (H-8 would not be equatorial).

Conclusions

To summarize, the intramolecular cyclization of 3a with PPA yielded the isomers 5a and 5b, which differ in the configuration of C-8; for 5a, H-5, H-8 and H-9 lie on the same side of ring C, while in 5b, H-5 and H-9 are on the same side and opposite to the hydrogen geminal to the carboxy group. On reduction of the acid 4a, the isomers 6a (all-cis) and 6b (5R,8H,9cH) are formed in a 1:2 ratio; the epimerization probably takes place via enolization of the 8-CO (carboxy) group.

5a can be prepared from the trans ester 3b more advantageously than from the cis ester 3a, and its 90% yield allows its use as a starting molecule for the synthesis of highly condensed systems. Hence, intermolecular acylation with PPA at an elevated temperature is an appropriate method of obtaining the methano-benzocyclooctene system.

Experimental

IR spectra were run for samples in KBr discs on a vacuum optic Bruker IFS-113v FT spectrometer equipped with an Aspect 2000 computer. $^1$H and $^{13}$C NMR spectra were recorded for CDCl$_3$ solutions in 5 mm tubes at room temperature, on a Bruker WM-250 FT-spectrometer controlled by an Aspect 2000 computer at 250 (T$^1$H) and 63 ($^{13}$C) MHz, respectively, using the deuterium signal of the solvent as the lock and Me$_3$Si as an internal standard. For DNOE measurements, the standard Bruker microprogram DNOEMLT.AU to generate NOE was used. 2D-HSC spectra$^{19}$ were obtained by using the standard Bruker pulse program.
XHCCORRD.AU. DEPT spectra\(^{20}\) were run in a standard way,\(^{21}\) using only the \(\theta = 135^\circ\) pulse to separate the \(\text{CH}/\text{CH}_3\) and \(\text{CH}_2\) lines phased up and down, respectively.

**Crystal data for 4a.** Triclinic, space group \(\text{P} \bar{1}\) (No. 2), \(a = 8.526(2), b = 10.784(2), c = 7.368(2) \AA, \alpha = 93.97(2), \beta = 112.68(2), \gamma = 67.53(1), V = 575.2(3) \AA^3, Z = 2, D_c = 1.329 g cm\(^{-3}\), \(\mu(\text{Mo K} \alpha) = 0.87 \text{ cm}^{-1}, F(000) = 244, T = 294(1) \text{ K}\) colourless prisms, crystal dimensions 0.26 \(\times\) 0.34 \(\times\) 0.40 mm.

**Data collection and refinement.** A Rigaku AFC5S diffractometer was used with graphite monochromated Mo K\(\alpha\) radiation (\(\lambda = 0.71069\)) in the \(\omega\)-scan mode with an \(\omega\) scan rate of 8.0 \(\text{min}^{-1}\) and a scan width of 1.63 \(\pm\) 0.30 \(\tan \theta\). The weak reflections \([F < 10\sigma(F)]\) were rescanned up to two times. The data obtained were corrected for Lorentz and polarization effects. A total of 2165 unique reflections were measured \((2\theta_{\text{max}} = 50^\circ\) and \(R_{\text{int}} = 0.011\)). The structure was solved by direct methods\(^{22}\) and difference Fourier syntheses.\(^{23}\) Structural parameters were refined by a full-matrix least-squares refinement, non-hydrogen atoms with anisotropic, and non-aromatic hydrogen atoms with fixed isotropic temperature parameters (1.2 times \(B_{eq}\) of carrying atom). The aromatic hydrogens were kept in the calculated positions. In the final cycles, the 1531 data with \(I > 2\sigma(I)\) yielded an \(R\) value of 0.043 \((R_w = 0.037\), sigma weights\) for 184 parameters. The residual electron density was from 0.15 to 0.17 e \(\text{Å}^{-3}\).

All calculations were performed with TEXSAN-89 software,\(^{24}\) using a VAXSTATION 3520 computer. The neutral atomic scattering and dispersion factors were those included in the program. Figures were drawn with ORTEP.\(^{25}\) The final atomic positional coordinates, bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre, Lensfield Rd., Cambridge, CB2 1EW, UK.

HPLC: ISCO system with two pumps, suitable for gradient elution. The Chem. Research control system and data processing program were used. For the semi-preparative separation, a 5 \(\mu\)m BST Si-100-S 10-RP-18 column (250 \(\times\) 16 mm) was used; eluent: \(n\)-hexane–isopropyl alcohol (98:2 v/v\%); flow rate: 8 \(\text{ml}^{-1}\); injected sample: 250 \(\mu\)l; 0.5 g dichloromethane–eluent (1:3) detection at 220 nm.

10-Oxo-5r,6,7,8c,9c,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (4a): method A. 4t-Phenylcyclohexane-1r,2c-dicarboxylic acid\(^{2} (1a)\) (5.0 g, 0.02 mol) in concentrated \(\text{H}_2\text{SO}_4\) (20 ml) was heated to 150 °C and kept at this temperature for 1 h. After being cooled, the mixture was poured onto ice and extracted
with CH₂Cl₂ (3 × 20 ml). The extract was washed with water and dried (Na₂SO₄). On evaporation, the residue crystallized from EtOAc, m.p. 210–215 °C, yield 0.60 g (13%). Analytical data: found C 73.2; H 6.1. Calc. for C₁₄H₁₄O₃: C 73.0; H 6.1%.

Method B. To H₂SO₄ (80%, 30 ml), 4t-phenylcyclohexane-1r,2c-dicarboxylic anhydride (2) (5.0 g, 0.02 mol) was added in portions, with stirring. The mixture was kept at 80 °C for 16 h and, after being cooled, poured onto ice and then extracted with CHCl₃ (3 × 300 ml). The extract was washed with water (2 × 50 ml), dried (Na₂SO₄) and evaporated to dryness. The product (4a) was purified on a silica gel column (Acros 0.035–0.07 mm) eluting with n-hexane–EtOAc (2:1). On evaporation, the residue crystallized from EtOAc, yield 0.70 g (15%).

**Dimethyl 4t-phenylcyclohexane-1r,2c-dicarboxylate (3a) and 4t-phenyl-1r,2t-dicarboxylate (3b).** A mixture of anhydride 2⁰ (4.6 g, 0.02 mol) or dimethyl 4t-phenylcyclohexane-1r,2c-dicarboxylate 1b (5.0 g, 0.02 mol) and benzene (25 ml) in MeOH (45 ml) was refluxed with concentrated H₂SO₄ (0.23 ml) for 4 h, a Dean–Stark water separator being applied. After evaporation of the solvent, the residue was neutralized with Na₂CO₃ solution (5%) and extracted with Et₂O (3 × 25 ml). The Et₂O extract was washed with water (2 × 20 ml), dried (Na₂SO₄) and evaporated to dryness. The residue was loaded onto a silica gel column (Acros 0.035–0.07 mm) and eluted with n-hexane–EtOH (5:1). On evaporation, the yield was 4.30 g (78%) 3a, n°D: 1.5176, or 4.73 g (86%) 3b, n°D: 1.5162. The products were used for the further preparations without purification.

**Cyclization of dimethyl 4t-phenylcyclohexane-1r,2c-dicarboxylate (3a) to the isomeric methyl esters (5a and 5b).** To PPA (28.0 g), 3a (2.76 g, 0.01 mol) was added dropwise at 110 °C with stirring. The mixture was heated at this temperature for 3 h, then cooled and poured onto crushed ice. The mixture was extracted with Et₂O (3 × 150 ml), and the combined extract was washed with water (2 × 200 ml), dried (Na₂SO₄) and evaporated to dryness. The residue was transferred onto a silica gel column (Acros 0.035–0.07 mm) and eluted initially with an n-hexane–EtOAc mixture (5:1). First 5b was eluted [higher Rₚ on monitoring by TLC, Alufolien Kieselgel 60 F₂₅₄ Merck, 0.2 mm, solvent: benzene–EtOH–petroleum ether (b.p. 40–60 °C)] 4:1:3, development in iodine vapour] and 5a (lower Rₚ) was then eluted with an n-hexane–EtOAc mixture 4:1. On evaporation of the solvents and crystallization, from EtOAc–Et₂O, m.p. 122–123 °C, yield 0.77 g (31.5%) (5b) and from EtOAc, m.p. 105–107 °C, yield 0.15 g (6%) (5a) were obtained. Analytical data: found C 73.6; H 6.55 (5b) and C 73.85; H 6.8 (5a). Calc. for C₁₃H₁₄O₂: C 73.75; H 6.6%.

Cyclization of dimethyl 4t-phenylcyclohexane-1r,2c-dicarboxylate (3b) to the isomeric 5,6,7,8,9,10-hexahydro-5,9-methanocyclooctene derivatives (5a,b). The reaction was performed with 3b (2.76 g, 0.01 mol) according to the cyclization of 3a to 5a,b in PPA, but at 120 °C. After chromatographic purification (silica gel column, Acros 0.035–0.07 mm; n-hexane–EtOAc 5:1), yields of 0.59 g (24%) for 5b and 0.73 g (30%) for 5a were obtained.

10-Oxo-5r,6,7,8t,9c,10-10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (4b). 5b (2.44 g, 0.01 mol) in NaOH solution (10%, 20 ml) was stirred for 3 h at 50 °C. After being cooled, the solution was acidified with concentrated HCl to pH 3, then extracted with CHCl₃ (3 × 30 ml); the extract was washed with water (2 × 50 ml) and dried (Na₂SO₄). On evaporation, the residue was crystallized from Et₂O–n-hexane, m.p. 135–137 °C, yield 2.02 g (88%). Analytical data: found C 72.9; H 5.9. Calc. for C₁₄H₁₄O₃: C 73.0; H 6.1%.

5r,6,7,8c,9c,10- (6a) and 5r,6,7,8t,9c,10-10-hexahydro-5,9-methanobenzocyclooctene-8t-carboxylic acid (6b). The oxo acid 4a (2.30 g, 0.01 mol) and hydrazine hydrate (98%, 1.53 g, 0.03 mol) were added to a solution of KOH (1.68 g, 0.03 mol) in diethylene glycol (15 ml) at such a rate as to keep the temperature below 100 °C. The mixture was then heated for 1 h at 110 °C. The temperature was then raised slowly to 200 °C and maintained there for 4 h, during which time some hydrazine–water mixture distilled off. After being cooled, the mixture was added to water and the pH was adjusted to 2. Following extraction with CHCl₃ (3 × 50 ml), the extract was washed with water (2 × 50 ml) and dried (Na₂SO₄), and the CHCl₃ was evaporated off. Crystallization from n-hexane yielded a mixture of isomers 6a and 6b (1:2). Separation of a 60 mg sample by HPLC and crystallization from CH₂Cl₂–n-hexane, yielded 6a: m.p. 110–112 °C, yield 34 mg (56%) and, from n-hexane 6b: m.p. 145–148 °C, yield 20 mg (33%). Analytical data: found C 77.6; H 7.4 (6a) and C 77.6; H 7.4 (6b). Calc. for C₁₄H₁₄O₂: C 77.75; H 7.5%.

5r,6,7,7ae,10a,10bc - Hexahydro-5,10b - methanobenzocycloocta/[9,8-cd]/pyridazin-8-one (7). A mixture of 4a (0.46 g, 2 mmol) and hydrazine hydrate (98%, 0.1 g, 2 mmol) in EtOH (20 ml) was refluxed for 2 h and then evaporated. The residue was dissolved in 1,2-dichlorobenzene (10 ml) and refluxed for an additional 2 h. The crystals that separated out on cooling were filtered off by suction and recrystallized from EtOH, m.p. 238–239 °C, yield 0.29 g (65%). Analytical data: found C 74.15; H 6.15; N 12.95. Calc. for C₁₄H₁₄N₂O: C 74.3; H 6.2; N 13.2%.

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