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DIELS-ALDER CYCLOADDITION OF HIGHLY SUBSTITUTED PYRAN-2-ONES WITH MALEIC ANHYDRIDE[#]

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Abstract – The Diels-Alder cycloaddition reaction of substituted 3-benzoylamino-pyran-2-ones (**1**) with maleic anhydride (**2**) in 1,2,3,4-tetrahydronaphthalene yielding representatives of bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid 2,3;5,6-dianhydride (**5**) has been investigated. The emphasis was given both on the study of the influence of substituents on the reaction and development of the synthesis of derivatives with unprecedented substituent patterns. Structures of products were determined by the X-Ray study and by the spectroscopic analyses.

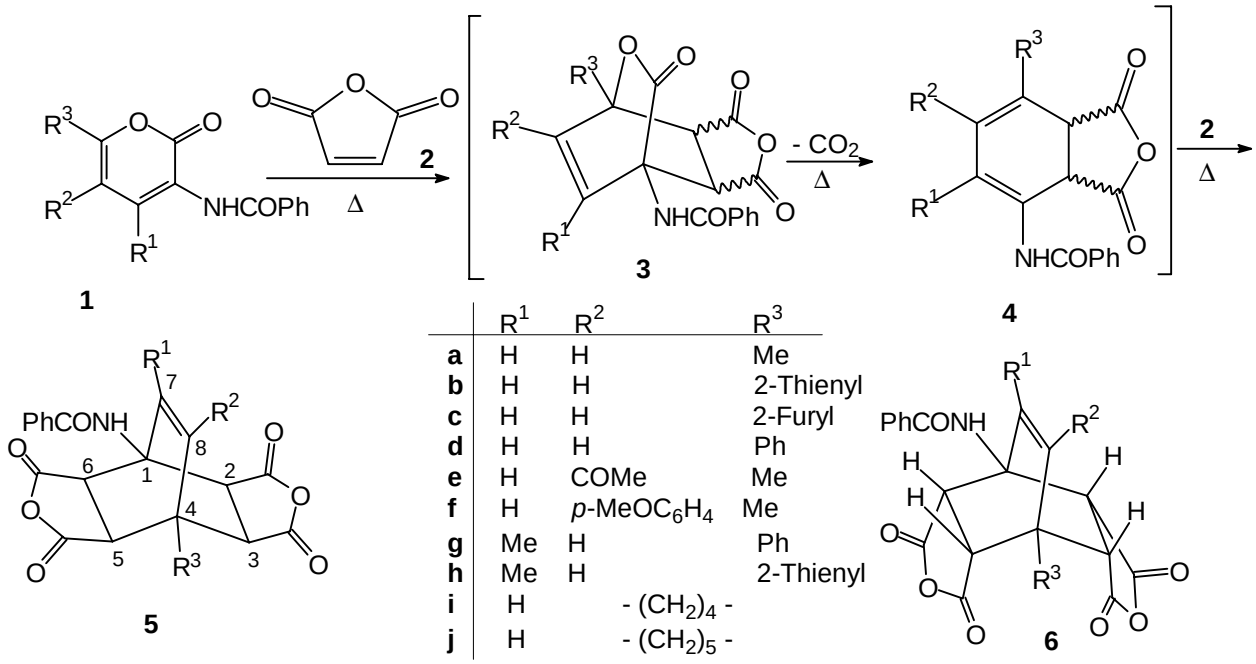
Pyran-2-ones and fused pyran-2-ones are important synthons and building blocks in organic synthesis.[1] They have been often used as dienes in the Diels-Alder reaction yielding structural units of natural products.[2] Their transformation with maleic acid anhydride has also been investigated.[3] Most of these investigations were dealing with simple derivatives containing different pattern of substitutents. To our knowledge, compounds containing an amino or substituted amino group as well as a heterocyclic ring at the bridgehead carbon atom have not yet been synthesised. For these reasons we have decided to carry out investigation of the Diels-Alder reaction with pyran-2-ones containing 3-benzoylamino moiety as well as a variety of substituents at other positions; besides other groups at the position 6 they also contain 2-thienyl or 2-furyl moieties. The expected polycyclic compounds would contain benzoylamino and heterocyclic moieties bound at the bridgehead carbon atoms, thus opening up new possibilities for a further design.

Here we report a transformation of pyran-2-ones (**1a**–**h**)[4] and fused pyran-2-ones (**1i**–**j**)[4d] with an excess of maleic anhydride in boiling 1,2,3,4-tetrahydronaphthalene (tetralin). The corresponding bicyclo[2.2.2]-oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3;5,6-dianhydrides (4,8-etheno-3a,4,4a,5,7,7a,8,8a-

[#]Dedicated to Dr. A. I. Meyers, Professor of Colorado State University, on the occasion of his 70th birthday.

octahydro-1,3,5,7-tetraoxo-1*H*,3*H*-benzo[1,2-*c*:4,5-*c*']difurans) (**5a**–**h**) as well as fused cycloalkane derivatives (**5i**) and (**5j**) [*N*-(1,3a,4,6,7,8,9,9b,10,11,13,14-dodecahydro-1,3,11,13-tetraoxo-3*H*-4,9a-[3',4']-furanonaphtho[1,2-*c*]furan-4-yl)benzamide and *N*-(1,3a,4,6,7,8,9,10b,11,12,14,15-dodecahydro-1,3,12,14-tetraoxo-3*H*,10*H*-4,10a[3',4']furano-10a*H*-cyclohept[*e*]isobenzofuran-4-yl)benzamide derivatives] were isolated in moderate to high yields (Scheme, Table). No other isomers were detected by ^{1}H NMR spectroscopy in the crude products.

Scheme



	R^1	R^2	R^3
a	H	H	Me
b	H	H	2-Thienyl
c	H	H	2-Furyl
d	H	H	Ph
e	H	COMe	Me
f	H	*p*-$MeOC_6H_4$	Me
g	Me	H	Ph
h	Me	H	2-Thienyl
i	H	- $(CH_2)_4$ -	
j	H	- $(CH_2)_5$ -	

Table. Synthesis of bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid 2,3;5,6-dianhydrides (**5**):

Run	Starting **1**	R^1	R^2	R^3	t (min)	Yield (%)	Product
1	**1a**[4a]	H	H	Me	15	64	**5a**
2	**1b**[4a]	H	H	2-Thienyl	60	76	**5b**
3	**1c**[4a]	H	H	2-Furyl	60	72	**5c**
4	**1d**[4a]	H	H	Ph	120	76	**5d**
5	**1e**[4b]	H	COMe	Me	90	39	**5e**
6	**1f**[4d]	H	*p*-$MeOC_6H_4$	Me	10	94	**5f**
7	**1g**[4c]	Me	H	Ph	90	80	**5g**
8	**1h**[4c]	Me	H	2-Thienyl	90	80	**5h**
9	**1i**[4d]	H	-$(CH_2)_4$-		30	63	**5i**
10	**1j**[4d]	H	-$(CH_2)_5$-		60	69	**5j**

Previously such reactions have been carried out in various solvents (toluene, *m*-xylene, mesitylene, etc.) under different conditions (heating at normal pressure, heating in a sealed tube) and usually required long heating periods.[3] For these reasons we decided to use tetralin as a solvent with relatively high boiling point (207 °C). All the reactions were finished within 2 h of heating as monitored by TLC. It is also evident (Table) that electron-donating group on the pyran-2-one ring facilitates the reaction, while the acceptor makes the reaction more difficult. This corresponds to the previously observed Diels-Alder reactions with normal electron demand.[3f,5] One has to take into account also steric effects of groups at the position 6, which decrease reactivity of pyran-2-ones having the benzoylamino moiety at the position 3. Phenyl group at the position 6 of the pyran-2-one (**1d**) seems to have the most pronounced effect on the reactivity if compared with the heterocyclic moieties (Runs 2–4) as a result of electronic and steric effects; this is not so evident with compounds (**1g**) and (**1h**) (Runs 7 and 8). Strong withdrawing effect of the acetyl group seems to be responsible for the low yield in the synthesis of product (**5e**) (Run 5). It is also worth mentioning that higher reactivity of pyran-2-one ring in comparison with furan or thiophene rings is shown for derivatives (**1b**), (**1c**) and (**1h**) (Runs 2, 3 and 8), where the reaction takes place exclusively with the pyran-2-one ring.

Structural elucidation of some related types of compounds was based on different techniques, such as comparison of 1DNMR spectral data with previously known compounds,[3e–h] use of 2DNMR techniques,[3g] prediction on the assumption of the strong preference for the "*endo*-kinetic control" of the Diels-Alder reaction,[3e] etc. In the case of our compounds there are no hydrogen atoms at the bridgehead carbon atoms 1-C and 4-C and consequently no coupling constants with these hydrogen atoms can be taken into consideration. Chemical shifts of hydrogen atoms 2-H, 3-H, 5-H and 6-H are all in the narrow δ ranges (4.52–4.88 ppm) for hydrogen atoms at positions 2 and 6 (as determined on the basis of the NOESY spectra for the products **5e**, **5g** and **5j**), which have nearly the same environment in all the products (the benzoylamino moiety at the position 1 and two anhydride rings). The differences are larger for 3-H and 5-H (δ range 3.61–4.28 ppm) because of the group at position 4 (R^3). The signals for these hydrogen atoms are doublets with the coupling constants 8.6–8.8 Hz. A comparison with the previous data[3] for related compounds shows that our compounds, due to the presence of different groups, exhibit higher chemical shifts for these hydrogen atoms. The ^{1}H and ^{13}C NMR spectral patterns indicate the magnetic equivalence of hydrogen atoms (2-H and 6-H; 3-H and 5-H) as well as of carbon atoms (2-C and 6-C; 3-C and 5-C). On this basis only symmetric structures (**5**) and (**6**) have to be taken into account for double-cycloadducts. Since chemical shifts of protons are not completely conclusive, we decided to perform the X-Ray study of the compound (**5e**) (Figure).[6] Structure of the thienyl derivative (**5b**) was also unequivocally determined by the transformation with hydrazine hydrate to the corresponding hydrazide derivative for which an X-Ray analysis was performed. Similarly, structure of the product (**5i**) was elucidated by comparing NMR

spectral data with the spectrum of related *bis*cycloadduct obtained from the pyran-2-one (**1i**) and *N*-phenylmaleimide (this structure was also determined by an X-Ray analysis). Having these data in hand, we also tried to confirm structure of some compounds by the NOESY spectra. In all the analysed spectra (for **5e**, **5g** and **5j**) only very weak NOEs' between hydrogen atoms 2-H, 3-H, 5-H or 6-H and hydrogen(s) on the bridge (R^1 = H and/or R^2 = H) were observed. Since distances between these hydrogens should be much shorter in the compounds of type (**6**), the cross-peaks had to be more intensive for these derivatives. On the basis of these facts and after a detailed analysis of ^{1}H NMR and ^{13}C NMR spectra (including HMQC spectra of products **5a, 5b, 5g** and **5h**) we ascribed to all our products the structure type (**5**).

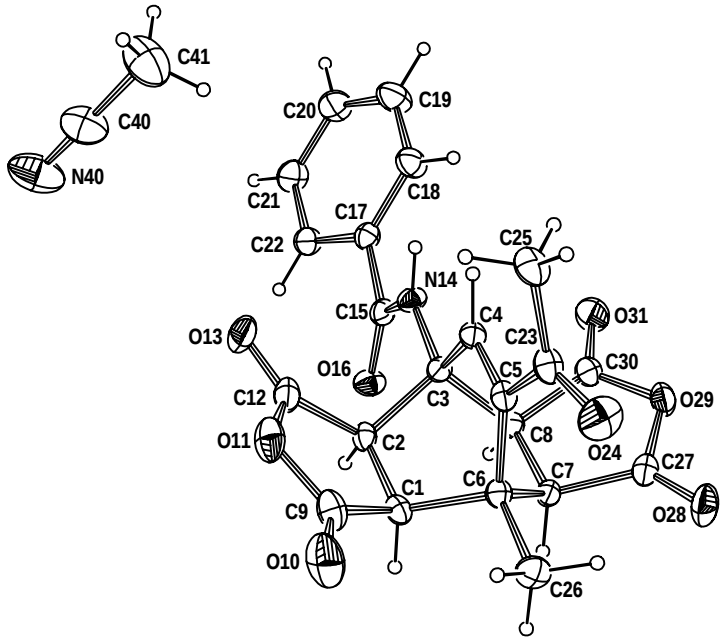


Figure. ORTEP view of the molecular adduct of **5e**

In conclusion, we presented an efficient method for the synthesis of bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid 2,3;5,6-dianhydrides containing a new structural pattern, that might enable synthesis of novel types of products.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage, and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 29 °C (except where stated otherwise) with the Bruker Avance DPX 300 spectrometer, using TMS as an internal standard. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Bio-Rad FTS 3000MX. MS spectra were recorded with a VG-Analytical AutoSpec Q instrument. X-Ray data were collected on Nonius KappaCCD. Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. TLC was carried out on Fluka silica gel TLC-

cards.

General procedure for the preparation of dianhydrides (5).

A mixture of 2*H*-pyran-2-one (**1**) (1 mmol) and maleic anhydride (**2**) (392 mg, 4 mmol) was refluxed in 3 mL of tetralin. Thereafter the reaction mixture was cooled to the rt, MeOH (2–3 mL) was added, precipitated solid was filtered off and washed with MeOH (0.5–1 mL). Reaction conditions and yields are given in Table.

Analytical and spectroscopic data of products (5a–j):

1-Benzoylamino-4-methylbicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3;5,6-dianhydride (5a): mp 323–325 °C (petroleum ether/AcOEt); ^{1}H NMR δ 1.72 (s, 3H, Me), 3.62 (d, 2H, *J* 8.8, 3-H, 5-H), 4.59 (d, 2H, *J* 8.8, 2-H, 6-H), 6.23 (d, 1H, *J* 8.8), 6.63 (d, 1H, *J* 8.8) (7-H, 8-H), 7.57 (m, 3H, Ph), 7.90 (m, 2H, Ph), 9.02 (s, 1H, NH); ^{13}C NMR δ 17.8, 38.5, 44.7 (2-C, 6-C), 48.8 (3-C, 5-C), 56.6, 127.6, 128.3, 131.5, 132.5, 134.8, 136.0, 168.2, 169.3, 170.6; IR (KBr) 1856, 1784, 1651, 1533; MS (m/z, %) 381 (M^+, 9), 105 (100). Anal. Calcd for $C_{20}H_{15}NO_7$: C, 62.99; H, 3.96; N, 3.67. Found: C, 63.20; H, 3.70; N, 3.58.

1-Benzoylamino-4-(2-thienyl)bicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3;5,6-dianhydride (5b): mp 303–304 °C (MeOH); ^{1}H NMR (80 °C) δ 4.12 (d, 2H, *J* 8.7, 3-H, 5-H), 4.78 (d, 2H, *J* 8.7, 2-H, 6-H), 6.88 (AB, 2H, J_{AB} 9, 7-H, 8-H), 7.08 (dd, 1H, J_1 5.1, J_2 3.6, 4-H of 2-thienyl), 7.35 (dd, 1H, J_1 3.6, J_2 1.1, 3-H of 2-thienyl), 7.56 (m, 4H, Ph and 5-H of 2-thienyl), 7.92 (m, 2H, Ph), 8.93 (s, 1H, NH); ^{13}C NMR (60 °C) δ 43.4, 44.7 (2-C, 6-C), 51.4 (3-C, 5-C), 56.9, 125.3, 126.2, 126.8, 127.3, 128.0, 131.2, 132.5, 133.2, 134.7, 141.1, 168.1, 168.3, 168.5; IR (KBr) 1852, 1784, 1665, 1528; MS (m/z, %) 449 (M^+, 2), 105 (100). Anal. Calcd for $C_{23}H_{15}NO_7S$: C, 61.47; H, 3.36; N, 3.12. Found: C, 61.50; H, 3.18; N, 3.00.

1-Benzoylamino-4-(2-furyl)bicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3;5,6-dianhydride (5c): mp 300–301 °C (AcOEt); ^{1}H NMR δ 4.10 (d, 2H, *J* 8.8, 3-H, 5-H), 4.74 (d, 2H, *J* 8.8, 2-H, 6-H), 6.50 (dd, 1H, J_1 1.8, J_2 3.4, 4-H of 2-furyl), 6.66 (dd, 1H, J_1 3.4, J_2 0.8, 3-H of 2-furyl), 6.85 (AB, 2H, J_{AB} 9, 7-H, 8-H), 7.58 (m, 3H, Ph), 7.76 (dd, 1H, J_1 1.8, J_2 0.8, 5-H of 2-furyl), 7.92 (m, 2H, Ph), 9.10 (s, 1H, NH); ^{13}C NMR δ 42.1, 44.5, 48.7, 57.0, 109.2, 110.7, 127.6, 128.3, 131.2, 131.6, 133.5, 134.7, 143.1, 149.5, 168.2, 168.7, 169.0; IR (KBr) 1857, 1786, 1665, 1532; MS (m/z, %) 433 (M^+, 2), 105 (100). Anal. Calcd for $C_{23}H_{15}NO_8$: C, 63.74; H, 3.49; N, 3.23. Found: C, 63.71; H, 3.48; N, 2.90.

1-Benzoylamino-4-phenylbicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3;5,6-dianhydride (5d): mp 305 °C (decomp, MeOH); ^{1}H NMR δ 4.28 (d, 2H, *J* 8.7, 3-H, 5-H), 4.73 (d, 2H, *J* 8.72-H, 6-H), 6.85 (d, 1H, *J* 9.2), 7.21 (d, 1H, *J* 9.2) (7-H, 8-H), 7.35 (m, 2H, Ph), 7.48 (m, 1H, Ph), 7.56

(m, 4H, Ph), 7.92 (m, 3H, Ph), 9.10 (s, 1H, NH); ^{13}C NMR δ 44.8, 45.3, 50.0, 57.2, 127.2, 127.4, 127.5, 127.6, 127.7, 128.3, 128.5, 131.5, 131.6, 133.1, 134.8, 136.6, 168.3, 169.2, 169.4; IR (KBr) 1856 br, 1784 br, 1667, 1531; MS (m/z, %) 443 (M^+, 2), 105 (100). HRMS Calcd for $C_{25}H_{17}NO_7$: 443.1005. Found: 443.1019. Anal. Calcd for $C_{25}H_{17}NO_7$: C, 67.72; H, 3.86; N, 3.16. Found: C, 68.09; H, 3.90; N, 3.15.

8-Acetyl-1-benzoylamino-4-methylbicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3;5,6-dianhydride (5e): mp 310 °C (decomp, MeOH/DMF); ^{1}H NMR δ 1.87 (s, 3H, Me), 2.19 (s, 3H, COMe), 3.70 (d, 2H, *J* 8.8, 3-H, 5-H), 4.64 (d, 2H, *J* 8.8, 2-H, 6-H), 7.50 (s, 1H, 7-H), 7.59 (m, 3H, Ph), 7.91 (m, 2H, Ph), 9.09 (s, 1H, NH); ^{13}C NMR δ 16.7, 27.5, 40.3, 40.5, 49.4, 56.5, 127.2, 128.1, 131.4, 134.2, 138.6, 143.3, 167.7, 168.5, 169.8, 195.6; IR (KBr) 1861, 1784, 1699, 1652, 1534; MS (m/z, %) 423 (M^+, 5), 105 (100). Anal. Calcd for $C_{22}H_{17}NO_8$: C, 62.41; H, 4.05; N, 3.31. Found: C, 62.60; H, 3.89; N, 3.41.

1-Benzoylamino-4-methyl-8-(4-methoxyphenyl)bicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3;5,6-dianhydride (5f): mp 318–319 °C (petroleum ether/AcOEt); ^{1}H NMR δ 1.67 (s, 3H, Me), 3.77 (m, 5H, MeO, 3-H, 5-H), 4.64 (d, 2H, *J* 8.7, 2-H, 6-H), 6.48 (s, 1H, 7-H), 6.84 and 6.97 (AA'BB', 2H each, *J* 8.7, C_6H_4OMe), 7.58 (m, 3H, Ph), 7.92 (m, 2H, Ph), 9.00 (s, 1H, NH); ^{13}C NMR δ 17.4, 41.7, 44.8, 49.7, 55.1, 57.0, 114.0, 127.6, 128.0, 128.3, 128.5, 128.7, 131.5, 134.8, 146.9, 159.3, 168.2, 169.2, 171.1; IR (KBr) 1859, 1838, 1783, 1651, 1513; MS (m/z, %) 487 (M^+, 21), 105 (100). Anal. Calcd for $C_{27}H_{21}NO_8$: C, 66.53; H, 4.34; N, 2.87. Found: C, 66.68; H, 4.16; N, 2.60.

1-Benzoylamino-7-methyl-4-phenylbicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3;5,6-dianhydride (5g): mp 300–302 °C (AcOEt); ^{1}H NMR δ 2.07 (d, 3H, *J* 1.8, Me), 4.25 (d, 2H, *J* 8.7, 3-H, 5-H), 4.83 (d, 2H, *J* 8.7, 2-H, 6-H), 6.89 (q, 1H, *J* 1.8, 8-H), 7.33 (m, 2H, Ph), 7.56 (m, 5H, Ph), 7.89 (m, 3H, Ph), 8.00 (s, 1H, NH); ^{13}C NMR δ 18.4, 44.7 (2-C, 6-C), 45.2, 50.0 (3-C, 5-C), 59.0, 124.7, 127.1, 127.4, 127.6, 128.0, 128.2, 128.4, 131.6, 135.0, 136.7, 140.5, 168.8, 169.3, 169.4; IR (KBr) 1858, 1790, 1661, 1516; MS (m/z, %) 457 (M^+, 1), 105 (100). Anal. Calcd for $C_{26}H_{19}NO_7$: C, 68.27; H, 4.19; N, 3.06. Found: C, 68.35; H, 4.09; N, 2.90.

1-Benzoylamino-7-methyl-4-(2-thienyl)bicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3;5,6-dianhydride (5h): mp 300–301 °C (AcOEt); ^{1}H NMR (70 °C) δ 2.05 (d, 3H, *J* 1.7, Me), 4.11 (d, 2H, *J* 8.7, 3-H, 5-H), 4.88 (d, 2H, *J* 8.7, 2-H, 6-H), 6.59 (deg q, 1H, 8-H), 7.08 (dd, 1H, J_1 5.3, J_2 3.6, 4-H of 2-thienyl), 7.35 (dd, 1H, J_1 3.6, J_2 1.1, 3-H of 2-thienyl), 7.58 (m, 4H, Ph and 5-H of 2-thienyl), 7.75 (s, 1H, NH), 7.88 (m, 2H, Ph); ^{13}C NMR (80 °C) δ 17.5, 43.4, 44.6 (2-C, 6-C), 51.3 (3-C, 5-C), 58.5, 125.0, 125.7, 126.0, 126.6, 127.3, 127.9, 131.2, 134.6, 140.6, 140.9, 167.9, 168.2, 168.5; IR (KBr) 1857, 1791, 1660, 1516; MS (m/z, %) 463 (M^+, 2), 105 (100). Anal. Calcd for $C_{24}H_{17}NO_7S \times 0.33\ H_2O$: C, 61.40; H, 3.79; N, 2.98. Found: C, 61.58; H, 3.82; N, 2.84.

Fused 1-benzoylaminobicyclo[2.2.2]oct-7-ene-2*exo*,3*exo*,5*exo*,6*exo*-tetracarboxylic acid 2,3;5,6-di-anhydrides:

5i: mp 295 °C (decomp, acetone/H_2O); ^{1}H NMR δ 1.36 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.21 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 3.64 (d, 2H, *J* 8.6, 3-H, 5-H), 4.52 (d, 2H, *J* 8.6, 2-H, 6-H), 6.29 (s, 1H, 7-H), 7.55 (m, 3H, Ph), 7.89 (m, 2H, Ph), 8.89 (s, 1H, NH); ^{13}C NMR δ 20.6, 22.3, 26.3, 28.8, 39.9, 44.8, 49.9, 56.4, 124.5, 127.6, 128.2, 131.4, 134.8, 142.9, 168.1, 169.2, 171.4; IR (KBr) 1852 br, 1790 br, 1652, 1533; MS (m/z, %) 421 (M^+, 2), 105 (100). HRMS Calcd for $C_{23}H_{19}NO_7$: 421.1161. Found: 421.1176.

5j: mp 284–286 °C (acetone/H_2O); ^{1}H NMR δ 1.39 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 1.89 (m, 2H, CH_2), 2.22 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 3.61 (d, 2H, *J* 8.6, 3-H, 5-H), 4.58 (d, 2H, *J* 8.6, 2-H, 6-H), 6.34 (s, 1H, 7-H), 7.55 (m, 3H, Ph), 7.89 (m, 2H, Ph), 8.91 (s, 1H, NH); ^{13}C NMR δ 23.4, 26.6, 30.4, 32.2, 35.5, 45.2, 46.1, 50.8, 56.0, 125.9, 127.6, 128.2, 131.4, 134.8, 147.6, 168.0, 169.1, 171.0; IR (KBr) 1853 br, 1789 br, 1655, 1536; MS (m/z, %) 435 (M^+, 2), 105 (100). HRMS Calcd for $C_{24}H_{21}NO_7$: 435.1318. Found: 435.1329.

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6. Crystallographic data of **5e**: $C_{22}H_{17}NO_8 \times CH_3CN$, F.W. = 464.42, triclinic, space group P-1 (No. 2), a = 7.5461(1), b = 12.5041(2), c = 12.7185(3) Å, α = 73.5240(10), β = 78.1110(10), γ = 86.3850(10)°, V = 1126.10(4) Å^3, Z = 2, D_{calc} = 1.370 g.cm^{-3}, μ(MoKα) = 0.104 mm^{-1}, F(000) = 484, MoKα radiation, KappaCCD diffractometer, colourless crystals, plate, size 0.3 × 0.2 × 0.1 mm.