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The unexpected product of Diels-Alder reaction between "indanocyclon" and maleimide

Michał A. Dobrowolski [a, *], Piotr Roszkowski [a], Marta Struga [b], Daniel Szulczyk [b]

[a] Faculty of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland
[b] Department of Pharmacogenomics, Faculty of Pharmacy, Medical University, 02-097 Warsaw, Poland

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ABSTRACT

A heterocyclic compound commonly known as "indanocyclon" undergoes an unexpected Diels-Alder addition with maleimide. The resulting product has been isolated and characterized in order to get an information about its structure and possible mechanism of the reaction. Extensive comparison of single crystal properties of 3-(2,8-dioxo-1,3-diphenyl-2,8-dihydrocyclopenta[*a*]inden-8a(1*H*)-yl)pyrrolidine-2,5-dione and favorable product of the reaction has been also performed.

1. Introduction

The Diels-Alder reaction has become one of the most efficient and practical methods for the synthesis of six-membered carbocyclic and heterocyclic rings since its discovery in 1928 [1]. The cycloaddition is a very important process and has been extensively studied over last few decades [2]. Importantly, heteroatoms, such as *e.g.* oxygen and/or nitrogen, can be included either in the diene or the dienophile, what increases the value of this synthetic approach [3]. The reaction may be executed under relatively mild conditions by heating together two components, diene and dienophile, in non-polar solvents, followed by evaporation which usually leads to high yields of the products. The reaction is disciplined by the Woodward-Hoffmann rules as a $[_{\pi}4_{s} + _{\pi}2_{s}]$ cycloaddition occurring in a concerted but probably not symmetrically synchronous fashion, thus leading to highly predictable product structures in which two new carbon-carbon sigma bonds are formed in a stereospecific manner with the creation of up to four new stereogenic centres [4]. It should be pointed out that [2 + 2], [4 + 4] and [6 + 6] cycloadditions are thermally disallowed, but there are some recognized modifications such as radical cation Diels-Alder reactions or photochemical cycloadditions [5].

The Diels-Alder reaction is very often conducted under specific conditions, in which all the participating reagents are neither ionic, nor highly polar. Therefore, the role of the solvent might be significant. It is not a decisive factor in designing Diels-Alder reaction synthetic pathways, although combined with selected specific dien-dienophile pair reactants may be the reason of possible side reactions and arising of unexpected products. Here we present such a case, where an interesting product in typical Diels-Alder reaction was obtained.

There have been investigations on large molecules in order to corroborate affinity to serotonin receptors (5-HT_{1A}, 5-HT_{2A}, 5-HT_{7}) [6]. Unexpected product aroused our interest for further work on synthesizing analogues of buspirone. Maleimide moiety in this structure may fulfill the three-point pharmacophore model for 5-HT_{1A} receptor ligands [7] to a larger extent, due to the unusual single bond. Adding a piperazine fragment might result in a series of new compounds showing strong affinity to serotonin receptors.

Here we propose a mechanism of obtaining a product (unexpected), that take place during well-known Diels-Alder reaction. Optimization of reaction conditions to enhance its yield was of key importance at this stage. Further research is planned on a series of compounds based on the resulting imide.

2. Results and discussion

The 1,3-phenylcyclopenta[*a*]indene-2,8-dione, also well known

* Corresponding author.
E-mail address: miked@chem.uw.edu.pl (M.A. Dobrowolski).

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as “indanocyclon”, is a widely used heterocyclic compound for many organic transformations [8]. Our synthetic strategy was to use this skeleton and combine its properties with common motif in many biologically active compounds, maleimide, in order to receive a series of new complex butylarylpiperazin-1-yl derivatives [6]. The synthesis started from obtaining “indanocyclon” with the application of widely used procedure [9], where the starting material is ninhydrin (Scheme 1). The reaction was conducted in suitable medium, which in this case was absolute ethanol.

Received dien is characterized by quite complex structure in case of cycloaddition reactions. However, there are no literature reports of any limitations from the regard on possible steric hindrance, because the reactivity of unsaturated fragment and its relation to dienophile is decisive. Both conditions were theoretically met. Dien-dienophile pair (“indanocyclon”- maleimide) was subjected to standard conditions of the Diels-Alder reaction for the purpose of obtaining desirable product (Scheme 2). Synthesized with good yield 4,10-diphenylindeno[1,2-*f*]isoindole-1,3,9(2*H*)-trione (**2**) reveals characteristic arrangement of coupled benzene rings, what was documented by X-ray structural analysis. The product is described by recognized mechanism, typical for the majority of pericyclic reactions, so it will not be the object for further deliberation.

However, under the same reaction conditions an unusual additional product was formed (Scheme 3). That proves the presence of competitive mechanism, different from well-known [4 + 2] addition reactions.

At that point we decided to study the influence of reaction solvent, since this was the only factor that could be responsible for the formation of alternative product (Table 1).

Changing the solvent gives poorer yields of 3-(2,8-dioxo-1,3-diphenyl-2,8-dihydrocyclopenta[*a*]inden-8a(1*H*)-yl)pyrrolidine-2,5-dione (**3**). Reaction was conducted in boiling temperatures of chosen solvents and in the same time period. It was found that benzene and chlorobenzene provides the largest amount of side product. At this stage no further tests were conducted, since the reaction was performed using only solvent and reactants.

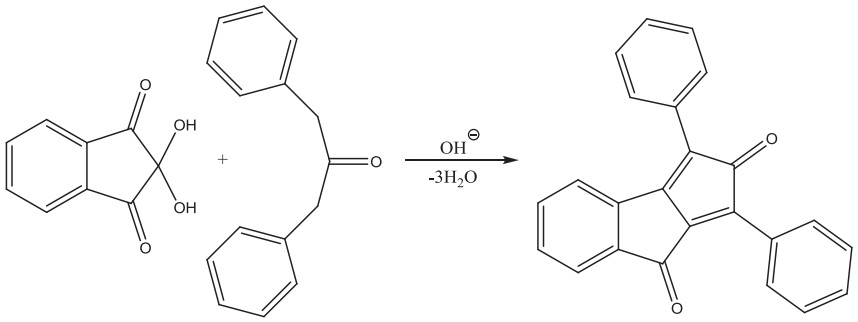
It is supposed that in the same reaction conditions alternative reaction is achievable. Less possible, although commonly seen mechanism comes into mind at first glance. The [2 + 2] cycloaddition, but this one is reserved for photochemical reactions. There are some exceptions from this rule, for example some cycloadditions of ethylene derivatives. It should be mentioned that the transition state of [2 + 2] addition products depend on radical mechanism. However, this one has not been recognized in this case. Product that should be isolated (Scheme 4) according to that mechanism doesn't agree with the one we have obtain.

We take into consideration that the mechanism of this reaction (Scheme 5) is completely different from already recognized Diels-Alder reactions, however we can draw out several presumptions. Firstly, at least two transition states arise, so we are able to receive two different products. Favored transition state in which 10 and 12 carbon atoms of “indanocyclon” are engaged will lead to the product of [4 + 2] cycloaddition. The alternative mechanism would probably lead to the transition state in which 8 and 9 carbon atoms will be engaged. Regrouping of electrons shall occur in the next stage. The structure of the product shows that it is more favorable to form the bond with 8 carbon atom of dien. We assumed that this is linked with the smaller steric hindrance of the product and the presence of the carbonyl group in the closest area. The carbonyl group can additionally have the influence on creation of the product, because of the possible hydrogen bond formation with maleimide. It is hard to explain why the bond between maleimide and 9 carbon atom of “indanocyclon” is not formed. We presume that it is related to the tension generated by bond between 8 carbon atom of “indanocyclon” and maleimide. Probably this strain is the main reason why double bond between 9 and 12 carbon atoms is reproduced. We suggest more privileged position of bond formation near carbonyl group because of maleimide and carbonyl group interactions. Furthermore, two hydrogen ions are generated in reaction environment due to formation of the favored product, which eliminates two ions during the aromatization of the newly formed six-membered ring. This explains why unfavored product has two more H atoms compared with the starting materials “indanocyclon” and maleimide.

To understand the reasons of 3-(2,8-dioxo-1,3-diphenyl-2,8-dihydrocyclopenta[*a*]inden-8a(1*H*)-yl)pyrrolidine-2,5-dione formation we have isolated single crystals of both reaction products and transfer them to intensive structural studies.

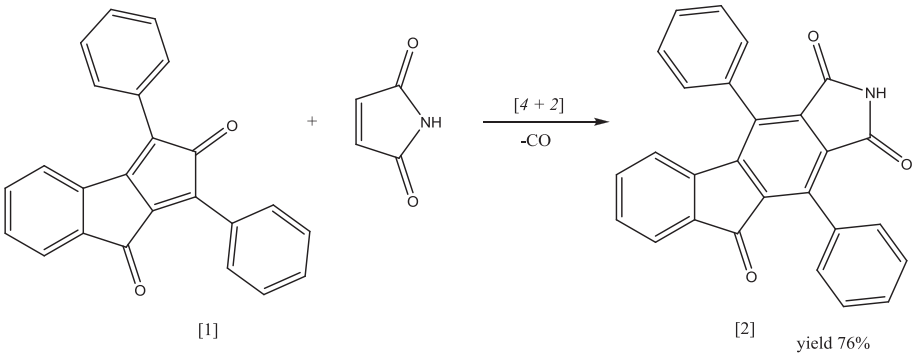
2.1. Crystal structures of 4,10-diphenylindeno[1,2-f]isoindole-1,3,9(2H)-trione and 3-(2,8-dioxo-1,3-diphenyl-2,8-dihydrocyclopenta[a]inden-8a(1H)-yl)pyrrolidine-2,5-dione

4,10-diphenylindeno[1,2-*f*]isoindole-1,3,9(2*H*)-trione (**2**) crystallizes in the $P2_1/c$ space group (Fig. 1, Table 3), the asymmetric unit contains one molecule of (**2**) and acetonitrile, which was used as a solvent. The main part of the molecule (4 rings) is almost planar with deviation of 5.5°. Two substituted phenyl rings are tilted with respect to benzene ring by 48.5° and 70.8°, respectively. The structure is governed by strong N–H···O hydrogen bonding between adjacent molecules forming dimers (N–H···O distance 2.877 Å, see Table 2). Consequently, the layers built of dimeric chains are formed (Fig. 2). Additionally, there are C–H···O interactions of 3.328 Å stabilizing the structure. The crystal is somehow “bound” together by two acetonitrile molecules lying in

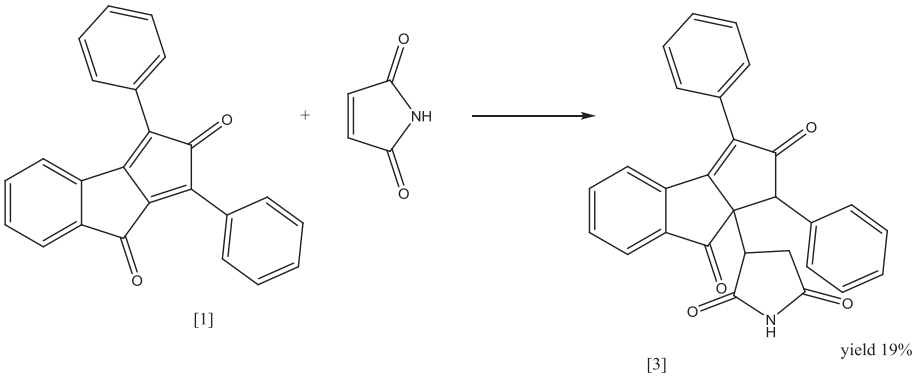


[1]

Scheme 1. Synthesis of 1,3-phenylcyclopenta[*a*]indene-2,8-dione (**1**) from ninhydrin as a starting material.



Scheme 2. Designed reaction of 1,3-phenylcyclopenta[*a*]indene-2,8-dione (**1**) and maleimide.



Scheme 3. Synthesis of 3-(2,8-dioxo-1,3-diphenyl-2,8-dihydrocyclopenta[*a*]inden-8a(1*H*)-yl)pyrrolidine-2,5-dione.

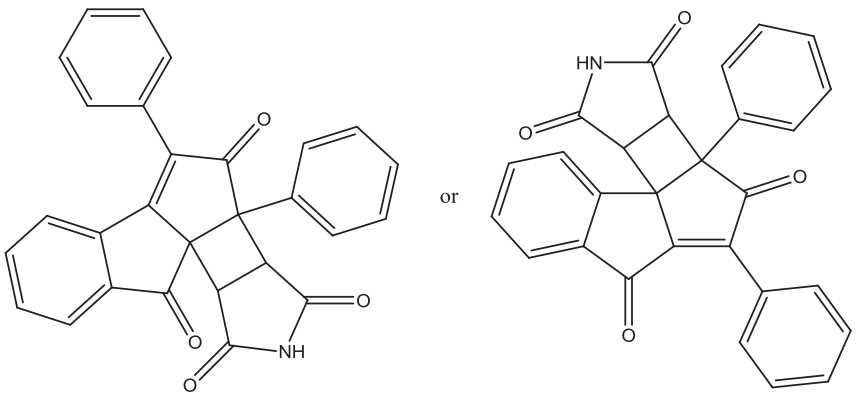
Table 1
Solvent - formation of additional product dependency study results.

No.	Solvent [reflux]	Reaction time [h]	Yield [%]
1	Benzene	8	19
2	Toluene	8	11
3	Acetonitrile	8	*
4	1,2-Dichloroethane	8	*
5	Cyclohexanone	8	*
6	Chlorobenzene	8	15
7	*o*-Xylene	8	7
8	Chloroform	8	*

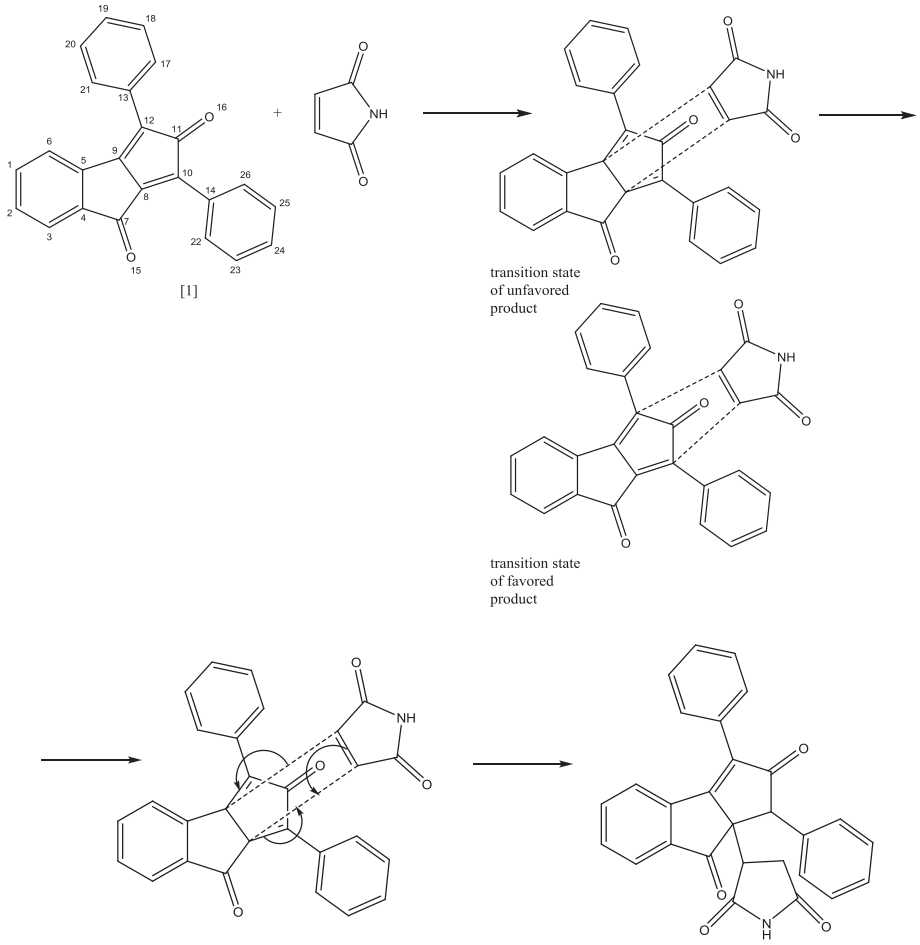
*Additional product (**3**) not found (TLC).

3-(2,8-dioxo-1,3-diphenyl-2,8-dihydrocyclopenta[*a*]inden-8a(1*H*)-yl)pyrrolidine-2,5-dione (**3**) crystallizes without solvent in the $Pca2_1$ space group (Fig. 3), and the asymmetric unit contains a single molecule. The main part of the molecule resembles a butterfly with the angle between two five-membered rings of 29.5°. Two substituted phenyl rings are tilted with respect to 5-membered ring by 47.8° and 88.9°, respectively. The structure is stabilized by strong N–H···O hydrogen bonding between nitrogen from maleimidyl ring and 5-membered ring oxygen (N–H···O distance 2.843 Å, see Table 2). Additionally, there are C–H···O interactions of 3.090, 3.261, 3.3 Å (Fig. 4).

the middle of the unit cell related by an inversion center.



Scheme 4. Expected products of [2 + 2] cycloaddition for 1,3-phenylcyclopenta[*a*]indene-2,8-dione **[1]**.



Scheme 5. Proposed mechanism of 3-(2,8-dioxo-1,3-diphenyl-2,8-dihydrocyclopenta[*a*]inden-8a(1*H*)-yl)pyrrolidine-2,5-dione formation.

3. Conclusions

New unexpected compound was synthesized. Unique product was characterized by structural and spectrochemical analysis. 3-(2,8-dioxo-1,3-diphenyl-2,8-dihydrocyclopenta[*a*]inden-8a(1*H*)-yl)pyrrolidine-2,5-dione (**3**) was intensively studied and mechanism of the reaction, in which it was obtained, was proposed. Two types of mechanisms were excluded, because of small influence of polar solvents (ion mechanism) and the absence of inhibitors (radical mechanism). Presumptions considering possible mechanism of reaction were made. There is definitely a significant influence of unfavorable transition state during formation of unexpected product. The single bond formation may be attributed to a strong N–H···O hydrogen bond between nitrogen from maleimidyl ring and 5-membered ring oxygen.

Investigations on series of arylpiperazine derivatives of (**3**) and their affinity to serotonin receptors are in progress.

4. Experimental

4.1. Synthesis

Melting points were determined in a Kofler's apparatus and are uncorrected. All reactions were run under atmosphere of argon. Solvents used in reactions were freshly dried by passing through an activated alumina column. The NMR spectra were recorded on a Bruker AVANCE DMX400 spectrometer, operating at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR). The chemical shift values are expressed in ppm relative to TMS as an internal standard. Mass spectral ESI (Electrospray Ionization) measurements were carried out on a Mariner Perspective – Biosystem instrument with TOF detector. The spectra were obtained in the positive ion mod with a declustering potential 140–300 V. Flash chromatography was performed on Merck silica gel 60 (200–400 mesh) using chloroform/methanol (19:1 vol) mixture as eluent. Analytical TLC was carried out on silica gel F254 (Merck) plates (0.25 mm thickness).

4.1.1. 1,3-phenylcyclopenta[a]indene-2,8-dione (*1*)

1,3-diphenylpropan-2-one (4.62 g, 0.022 mol) was added to a suspension of ninhydrin (4.02 g, 0.023 mol) in absolute ethanol (50 ml). Subsequently, the MeOH/KOH solution (5 ml) was instilled in portions (5–6 drops) every 15 min of reaction. The stirred reaction mixture turned red after adding first portion, and finally after last portion it turned violet. The reaction ended after 1 h heating in 80 °C. Obtained violet crystals (5.87 g) was washed with cold methanol (120 ml) and then recrystallized from acetonitrile (yield 72%). The structure of final product is already known [9], therefore full spectrochemical analysis was not performed. Mp. 205–206 °C. $C_{24}H_{14}O_2$, M = 334.37 gmol^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.42–7.56 (m, 6H, CH_{arom}); 7.70–7.77 (m, 4H, CH_{arom}); 8.04–8.10 (m, 1H, CH_{arom}); 8.18–8.24 (m, 1H, CH_{arom}); 8.59–8.64 (m, 2H, CH_{arom}). ESI MS: m/z = 357.1 $[M + Na]^+$ (100%).

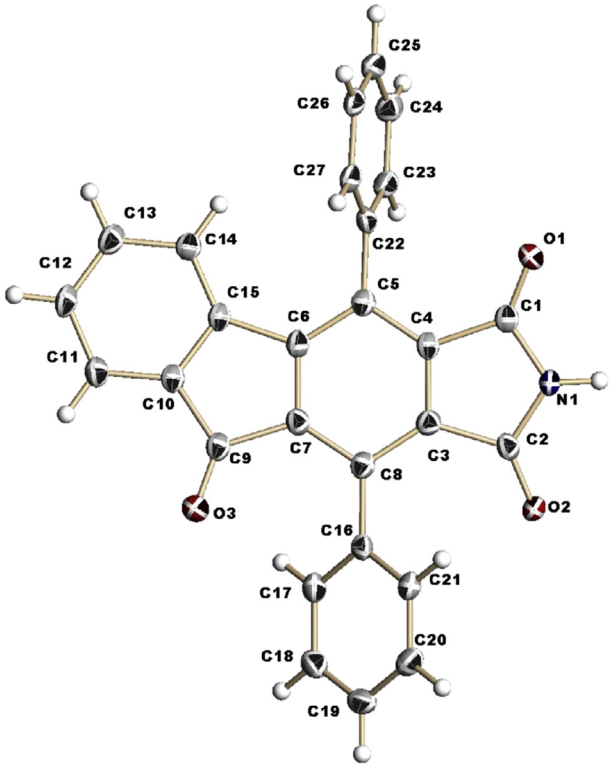


Fig. 1. The molecular structure of (**2**) showing displacement ellipsoids at the 50% probability level, acetonitrile molecule omitted for clarity.

Table 2
Intermolecular hydrogen bond lengths (Å) and bond angles (°) for (**2**) and (**3**).

D–H···A	d (D–H)	d (H···A)	d (D···A)	∠DHA
Compound (**2**)				
N1–H1···O1	0.92	1.985	2.877	169.77
Compound (**3**)				
N1–H51···O1	0.895	1.959	2.843	169.07

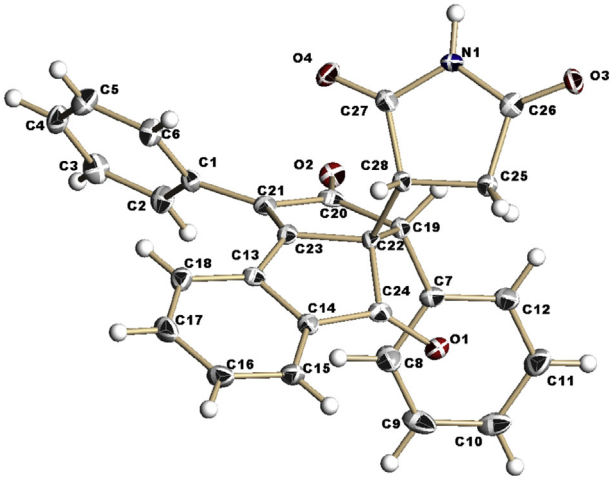


Fig. 3. The molecular structure of (**3**) showing displacement ellipsoids at the 50% probability level.

*4.1.2. (a) 4,10-diphenylindeno[1,2-f]isoindole-1,3,9(2H)-trione (**2**) and (b) 3-(2,8-dioxo-1,3-diphenyl-2,8-dihydrocyclopenta[a]inden-8a(1H)-yl)pyrrolidine-2,5-dione (**3**)*

(a) 0.55 g of maleimide was added to a solution of 1,3-phenylcyclopenta[*a*]indene-2,8-dione (2.06 g, 0.0061 mol) in dry benzene (50 ml) and then refluxed for 8 h. Subsequently, the reaction mixture was cooled to a room temperature and then evaporated. Purification by column chromatography with chloroform/methanol 19:1 as eluent resulted in 1.71 g (0.0043 mol) of yellow precipitate (yield 76%). Recrystallization from hot toluene/methanol 1:1 solution gave colorless crystals [R_f = 0.68 (chloroform/methanol 9.8:0.2)]. $C_{27}H_{15}NO_3$, M = 401.41 gmol^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.40–7.44 (m, 4H, CH_{arom}); 7.45–7.46 (d, 2H, CH_{arom}, J = 2.1 Hz); 7.49–7.51 (m, 2H, CH_{arom}); 7.52–7.53 (d, 2H, CH_{arom}, J = 2.1 Hz); 7.58–7.59 (m, 2H, CH_{arom}); 7.60–7.61 (d, 2H, CH_{arom}, J = 2.7 Hz); 11.29 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 124.54, 124.59, 127.91 (2C), 128.59 (2C), 129.09 (3C), 129.28 (2C), 129.34, 129.87, 130.54, 130.57, 131.95, 134.24, 134.81, 135.14, 135.52, 135.58, 139.37, 141.97, 149.69, 165.73, 165.89, 190.91. ESI MS: m/z = 424.1 $[M + Na]^+$ (100%).

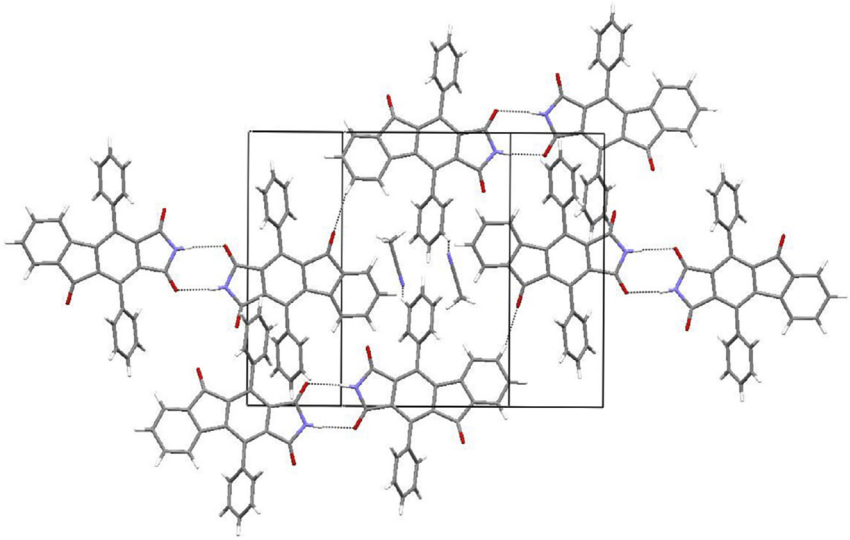


Fig. 2. Crystal packing showing the dimeric chains of (**2**) and two acetonitrile molecules. Hydrogen bonds and short contacts showed with dashed lines.

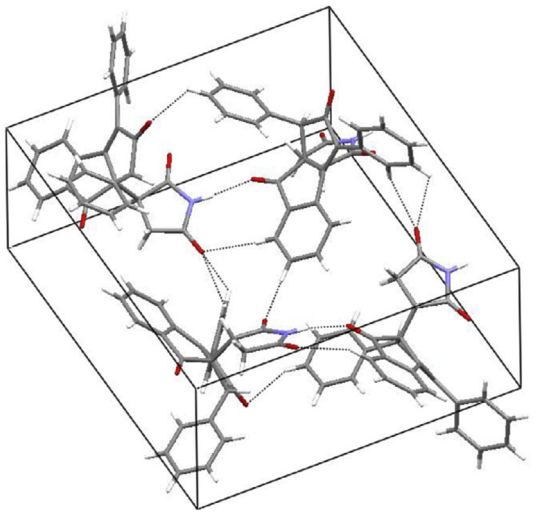


Fig. 4. Crystal packing of (**3**). Hydrogen bonds and short contacts showed with dashed lines.

(b) 0.55 g of maleimide was added to a solution of 1,3-phenylcyclopenta[*a*]indene-2,8-dione (2.06 g, 0.0061 mol) in dry benzene (50 ml) and then refluxed for 8 h. Subsequently, the reaction mixture was cooled to a room temperature and then evaporated. Purification by column chromatography with chloroform/methanol 19:1 as eluent resulted in 0.41 g (0.0043 mol) of yellow precipitate (yield 19%). Recrystallization from hot ethanol gave colorless crystals [R_f = 0.59 (chloroform/methanol 9.8:0.2)]. $C_{28}H_{19}NO_4$, M = 433.45 gmol^{-1}. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.50–2.61 (q, 1H, CH, J = 5.4 Hz); 2.70–2.79 (q, 1H, CH, J = 9.0 Hz); 3.38–3.43 (dd, 1H, CH, J_1 = 5.7 Hz, J_2 = 5.4 Hz); 4.24 (s, 1H, CH); 6.92–6.94 (d, 2H, CH_{arom} J = 7.8 Hz); 7.15–7.23 (m, 3H, CH_{arom}); 7.52–7.60 (m, 5H, CH_{arom}); 7.75–7.77 (d, 2H, CH_{arom} J = 3.9 Hz); 7.80–7.85 (m, 1H, CH_{arom}); 7.91–7.93 (d, 1H, CH_{arom} J = 7.2 Hz); 11.39 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 33.04, 47.58, 58.23, 62.89, 124.28, 124.62, 127.22 (3C), 128.59 (2C), 128.96 (2C), 129.41, 129.70 (2C), 129.92, 133.66, 136.16, 136.24, 136.89, 137.23, 141.39, 166.06, 176.44, 176.60, 197.61, 203.85. ESI MS: m/z = 456.2 $[M + Na]^+$ (100%).

4.2. Crystallography

The X-ray measurement of (**2**) and (**3**) were performed at 100 (2) K on a KUMA CCD k-axis diffractometer with graphite-monochromated Mo Kα radiation (0.71073 Å). The crystals were positioned 62.25 mm from the KM4CCD camera; 588 frames were measured at 1.0° intervals with a counting time of 50 s, 1200 frames were measured at 1.0° intervals with a counting time of 40 s, respectively for (**2**) and (**3**). Data collection, cell refinement and data reduction were carried out with the KUMA Diffraction programs: CrysAlis CCD and CrysAlis RED [10]. The data were corrected for Lorentz and polarization effects, numerical absorption correction was applied. The structures were solved by direct methods [11] and refined using SHELXL [12]. The refinement was based on F^2 for all reflections except for those with very negative F^2. The weighted R factor, wR and all goodness-of-fit S values are based on F^2. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from a difference map and were refined isotropically. The atomic scattering factors were taken from the International Tables [13]. Selected crystal data are given in Table 3. CCDC 1503579-1503580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

Table 3
Crystal data and structure refinement for (**2**) and (**3**).

Compound	(2)	(3)
Empirical formula	$C_{27}H_{15}NO_3$, CH_3CN	$C_{28}H_{19}NO_4$
Formula weight	442.45	433.44
Space group	$P2_1/c$	$Pca2_1$
Unit cell dimensions		
a [Å]	7.1918 (3)	17.8729 (9)
b [Å]	15.3921 (8)	7.4691 (4)
c [Å]	19.6560 (11)	15.7345 (8)
β [°]	95.723 (4)	90.00
Volume V [Å^3]	2165.01 (19)	2100.47 (19)
Z [molecules/cell]	4	4
$D_{calculated}$ [Mg m^{-3}]	1.357	1.371
Absorption coefficient μ/mm^{-1}	0.089	0.092
θ range for data collection [°]	2.08–25.00	2.96–25.00
Limiting indices	$-8 <= h => 8$	$-21 <= h => 21$
	$-18 <= k => 16$	$-8 <= k => 8$
	$-21 <= l => 23$	$-18 <= l => 18$
Reflections collected/unique	7391/3827	15425/1922
Data/parameters	3827/312	1922/302
Goodness of Fit	1.071	0.857
Final R index ($I > 2\sigma$)	0.0583	0.0263
wR^2	0.1415	0.0432
Largest diff. Peak and hole [Å^{-3}]	0.304 and −0.387	0.156 and −0.154

References

[1] O. Diels, K. Alder, Eur. J. Org. Chem. Justus Liebig's Ann. Chem. 460 (1928) 98–122.
[2] (a) R.B. Woodward, T.J. Katz, Tetrahedron 5 (1959) 70–89;
(b) K.C. Nicolaou, S.A. Snyder, T. Montagnon, G. Vassilikogiannakis, Angew. Chem. Int. Ed. Engl. 41 (2002) 1668–1698.
[3] X. Ding, S.T. Nguyen, J.D. Williams, N.P. Peet, Tetrahedron Lett. 55 (2014) 7002–7006.
[4] (a) J. Sauer, Angew. Chem. Int. Ed. Engl. 6 (1967) 16–33;
(b) T.J. Brocksom, J. Nakamura, M.L. Ferreira, U. Brocksom, J. Braz. Chem. Soc. 12 (2001) 597–622.
[5] (a) R.A. Pabon, D.J. Bellville, N.L. Bauld, J. Am. Chem. Soc. 105 (1983) 5158–5159;
(b) D. Sun, S.M. Hubig, J.K. Koch, J. Photochem. Photobiol. A Chem. 122 (1999) 87–94.
[6] D. Szulczyk, A. Bielenica, M.A. Dobrowolski, Ł. Dobrzycki, M. Krawiecka, B. Kuran, M. Struga, Med. Chem. Res. 23 (2014) 1519–1536.
[7] Z. Chilmończyk, A. Szelejewska-Woźniakowska, J. Cybulski, M. Cybulski, A.E. Kozioł, M. Gdaniec, Arch. Pharm. Pharm. Med. Chem. 330 (1997) 146–160.
[8] (a) B. Eister, M.A. El-Chahawi, Eur. J. Inorg. Chem. 103 (1970) 173–182;
(b) W. Ried, H. Kohl, Eur. J. Org. Chem. Justus Liebigs Ann. Chem. 734 (1970) 203–206;
(c) P. Balasubramanian, S. Jayaraman, K. Narasimhan, Org. Prep. Proced. Int. 11 (1979) 264–265;
(d) S.E. Mallakpour, R.G. Gharehdaghi, Indian J. Chem. Sect. B 40 (2001) 465–469.
[9] W. Ried, D. Freitag, Chem. Ber. 99 (1966) 2675–2677.
[10] Oxford Diffraction, CrysAlis CCD and CrysAlis RED. Version 171.33.66, Oxford Diffraction Ltd., Wrocław, Poland, 2001.
[11] G.M. Sheldrick, Acta Crystallogr. Sect. A Found. Crystallogr. 46 (1990) 467–473.
[12] G. M. Sheldrick, SHELXL93. Program for the Refinement of Crystal Structures, University of Göttingen, Germany.
[13] A.J.C. Wilson (Ed.), International Tables for Crystallography vol. C, Kluwer, Dordrecht, 1992.