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

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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

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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.

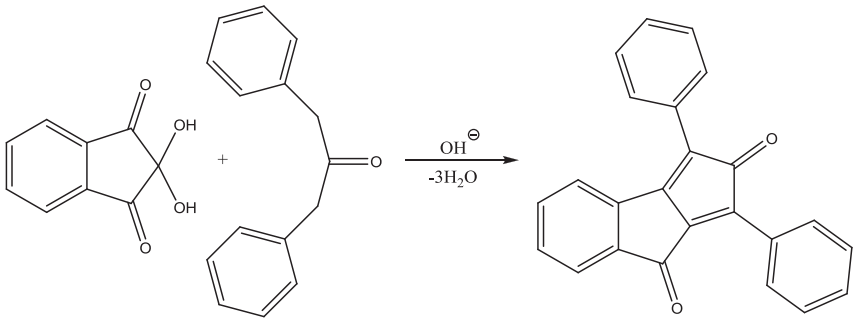
It is supposed that in the same reaction conditions alternative reaction is achievable. Less possible, although commonly seen mechanism comes into mind at first glance. The [2 + 2] cycloaddition, but this one is reserved for photochemical reactions. There are some exceptions from this rule, for example 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.