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Allantoin: synthesis and chemical properties

The availability and multifunctionality of allantoin makes it extremely attractive to unlock the synthetic potential on the basis thereof, especially for the needs of the pharmaceutical industry. Numerous publications on the allantoin chemistry are scarce, nonsystematic in nature and do not allow a deep understanding of the methods for its preparation and its chemical properties. In order to close this gap, the present review integrates the systematic data on the methods for the allantoin synthesis and the study of its chemical properties as well as the areas of allantoin practical application. In the present work, the methods most widely used in preparative practice to produce allantoin from the carbonyl compounds and urea are considered, and the ways of transformation of a number of nitrogen-containing heterocycles under the influence of various reagents leading to the target product are presented. The main chemical properties of allantoin are shown in hydrolysis reactions, complexation with organic and inorganic substrates, interactions with nucleophilic reagents, in chemoluminescence processes. In some cases, when the unconventional methods for the allantoin synthesis are given and allantoin transformations are considered, the mechanisms of the formation of final compounds are shown. A systematic material on the preparation methods and the chemical properties of allantoin can serve as a reliable navigator for those specialists who aim at manufacturing of allantoin-based practically important substances. Based on the integrated data it is pointed out that allantoin can be successfully used as a basic azaheterocycle to manufacture a wide range of new compounds, including bioactive ones.

Keywords: allantoin, urea, carbonyl compounds, azaheterocycles, complexes, luminescence, hydrolysis.

Introduction

Allantoin belongs to the widely known azaheterocycles of the imidazolidinone series (in particular, hydantoins). Its useful biological properties have been the subject of several generalizing communications [1, 2]. However, at the same time, to date, there are no works in the literature that reflect the generalized chemistry of allantoin. Based on the aforesaid, this review aims to draw the attention of chemists and specialists in related fields to the methods for allantoin preparation as well as its chemical properties to expand the potential for application of allantoin-based compounds in organic synthesis and daily life.

1. General information and application of allantoin

Allantoin (Fig. 1), also known as (2,5-dioxo-4-imidazolidinyl)urea, is a heterocyclic compound comprising a five-membered ring containing a urea substituent in the 4th position. Table 1 represents the main physical-chemical properties of allantoin.

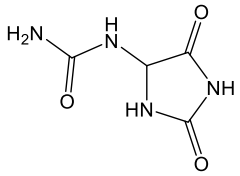

Figure 1. Allantoin structure

Table 1

Physical-chemical properties of allantoin

Parameter	Value
Appearance	White crystalline powder, odorless and tasteless
Melting point, °C	225 (with decomposition)
Solubility in water at 25 °C, g/l	5.7
Density, kg/m^3	800
pH of 5 g/l solution at 25 °C	4.5–6
IR-spectrum, ν, cm^{-1}	3436 (NH_2), 3068 (NH_2), 3192 (NH), 2947 (CH), 1780 (C=O), 1719 (C=O), 1667 (C=O)
IR-spectrum, δ, cm^{-1}	1602 (NH_2), 1430 (NH)
NMR ^{1}H (DMSO-d_6), δ, ppm	8.05 (1H, s), 6.94 (1H, d), 5.83 (2H, s), 5.24(1H, d)
NMR ^{13}C (DMSO-d_6), δ, ppm	173.79 (C=O), 157.70 (C=O), 157.06 (C=O), 62.61 (C-tert.)

Allantoin attracts the attention of researchers due to the fact that it is widely used as one of the active ingredients in skin care products, promotes the healing of scar tissue and scars that makes it the in-demand material for cosmetology and pharmaceutical practice. Currently, allantoin is included in more than 1300 various cosmetic products [1]. Thus, for instance, having a regenerating effect, allantoin helps to remove cicatricle tissues and scars [3]. As a part of creams, allantoin protects the skin from sunburns, chapping and cracking [4]. Allantoin also has a genotoxic effect [5] and restores normal skin moisture and elasticity [6]. The compound is able to reduce the genotoxic effect of ultraviolet radiation [7] and inhibit the development of a number of destructive processes caused by reactive oxygen species, i.e. exhibits antioxidant properties.

The main allantoin consumers are the cosmetics manufacturers as well as the pharmaceutical companies that use it as a feedstock to manufacture drugs intended for the treatment of various diseases [8]. Moreover, allantoin is used in agriculture as a plant growth regulator and is a component of fertilizers and veterinary disinfectants [9].

2. Methods for allantoin preparation

2.1. Isolation from the cell structure of plants

Allantoin was found in the callus of the Coffea Arabica plant [10]. To date, several methods are known for isolation of allantoin from the natural raw materials from the Coffea Arabica cell culture [10] and from the explants of leaves and apical shoots of the Mertensia maritima plant [11].

2.2. Synthetic methods for allantoin preparation

2.2.1. Synthesis of allantoin from carbonyl compounds and urea

The reactions of low molecular weight carbonyl compounds with urea are probably the most important in the allantoin synthesis since they represent the best conditions in terms of the availability of the reagents and the manufacturability of the process in general. Figure 2 illustrates the generalized methods for the allantoin preparation using carbonyl compounds with urea.

The principle of allantoin formation is exemplified by the use of mesoxalic acid or its monohydrate as the initial substrate in the reaction with urea at 110–115 °C.

One of the approaches to synthesize allantoin is the reaction in the presence of hydrogen peroxide as an oxidant, where glyoxal interaction with urea gives allantoin with a 58 % yield [12]. During the implementation of this process, the in situ transformation of glyoxal into glyoxalic acid under the action of the oxidant is postulated, and the acid is responsible for the final heterocyclization stage. Allantoin can be synthesized from various derivatives of acetic acid and urea, namely, from diethoxyacetic acid in the presence of HCl with a yield of 45 % [13], from dichloroacetate or dichloroacetic acid with a yield of 62 % [14].

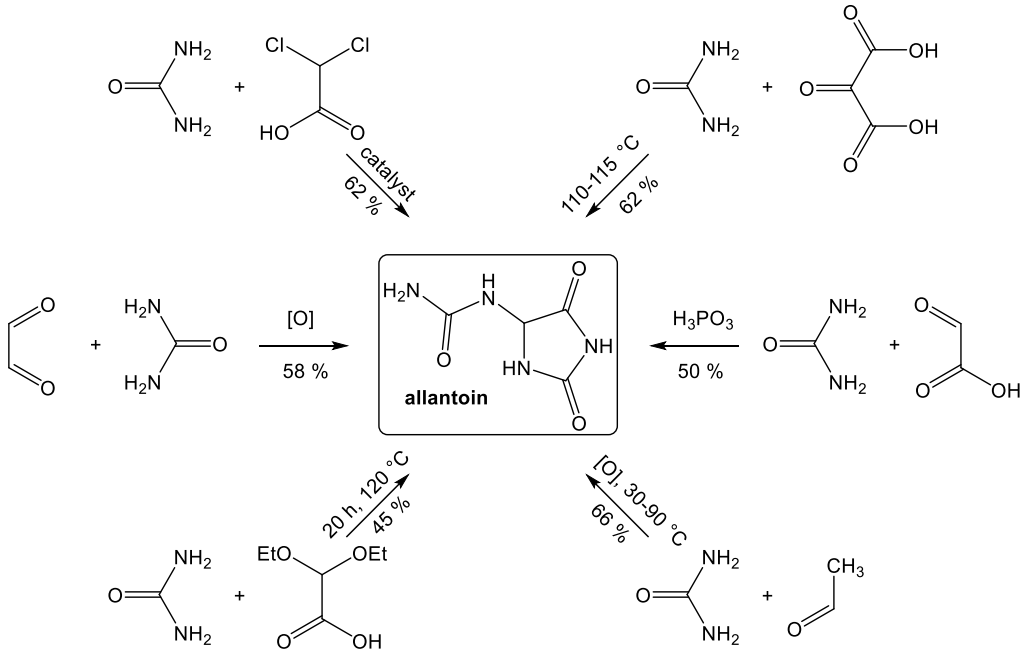

Figure 2. Synthesis of allantoin from carbonyl compounds and urea

The acetaldehyde-based allantoin synthesis involves the one-pot aldehyde oxidation with nitric acid followed by cyclization of the intermediate glyoxalic acid with urea, while the yield of the target product reaches 66 % [15].

Currently, the industrial allantoin production is based on the condensation of glyoxalic acid and urea in the presence of various catalysts: mineral acids [16], cation exchange resins [17], solid acids [18], ionic liquids [19], supported catalysts and zeolites [20, 21].

2.2.2. Synthesis from azaheterocycles

Figure 3 represents the most successful methods for allantoin production that utilize the chemical methods of transformation of various nitrogen-containing heterocycles.

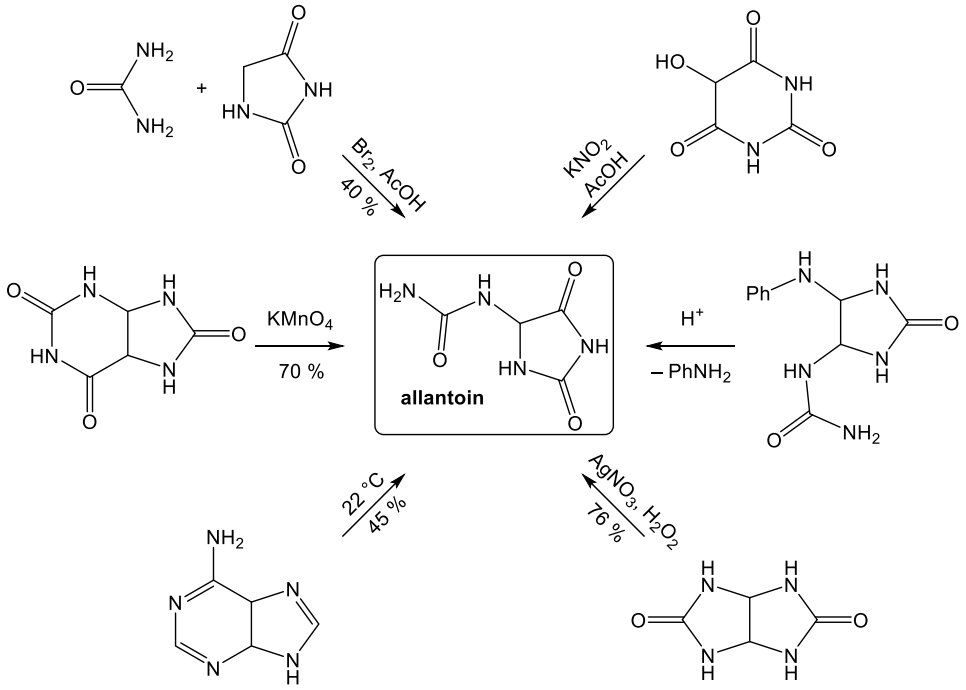

Figure 3. Allantoin synthesis from azaheterocycles

The oxidation of uric acid with potassium permanganate in an aqueous solution was found to lead to the allantoin formation with a yield of 70 %. The use of other oxidants results in a non-selective reaction performance since along with the target allantoin, various by-products are formed: acyclic amides, hydantoin, oxonic acid, 4-imidazolidine carboxamide, oxalic acid, etc.

The electrolysis of an adenine aqueous solution in a phosphate buffer at room temperature is accompanied by the oxidative degradation [22] to a number of nitrogen-containing heterocycles, where allantoin is the main product (45 %).

The interaction of hydantoin and urea in the presence of bromine and acetic acid [23] allows synthesizing allantoin with a relatively low yield (40 %). The allantoin formation implies an intermediate C-bromination process followed by N-alkylation of urea with brominated hydantoin.

The practical result affected the alloxan by KNO_2 and acetic acid is that in this case it is preferable to narrow the pyrimidine trion cycle to the allantoin one, and the urea molecule, a product of the complete destruction of alloxan, is involved in the allantoin formation.

Ref. [24] shows that under the action of H_2O_2 in the presence of $AgNO_3$ at 65 ºC, glycoluril transforms with the opening of one of the imidazolinone rings leading to allantoin with a high yield (76 %).

An example is given for the selective hydrolysis of the phenylamino derivative of allantoin in the presence of mineral acids [25] yielding allantoin.

3. Chemical properties of allantoin

Already at the beginning of the last century, a communication appeared [26] postulating the phenomenon of reversible isomerism (keto-enol tautomerism) for the allantoin molecule, and Figure 4 represents the tautomeric equilibrium established.

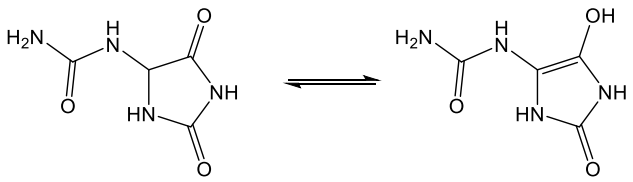

Figure 4. Allantoin tautomeric equilibrium

Allantoin is known to exist as a racemic mixture of (R) and (S) stereoisomers. A number of studies [27, 28] considers the accumulation of (R)-allantoin and (S)-allantoin during the non-enzymatic and enzymatic oxidative urate decomposition into allantoin during the purine catabolism in many organisms. The non-enzymatic racemization of allantoin was found to result in the accumulation of (R)-allantoin, since the enzymes that convert allantoin to allantoate are specific for the (S)-isomer. The allantoin racemase enzyme catalyzes the reversible conversion between the two allantoin enantiomers, thereby ensuring the overall efficiency of the catabolic pathway and preventing the allantoin accumulation. Figure 5 shows the racemic mixture of allantoin.

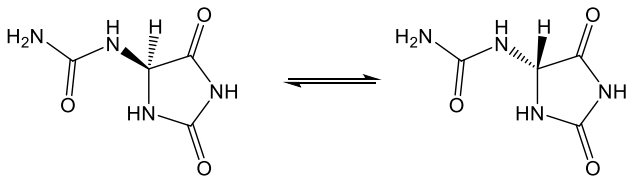

Figure 5. Allantoin racemization

To explain the spatial orientation paths in the allantoin stereochemistry, a mechanism was proposed [29] for the mutual transition of allantoin stereoisomers into a racemic mixture under the action of urate oxidase (Fig. 6).

Further studies [30] of allantoin diastereomers showed that the allantoin molecule had two optical centers and two stereoisomers that are not the mirror images of each other and confirmed the transition of one stereoisomer into another one (Fig. 7).

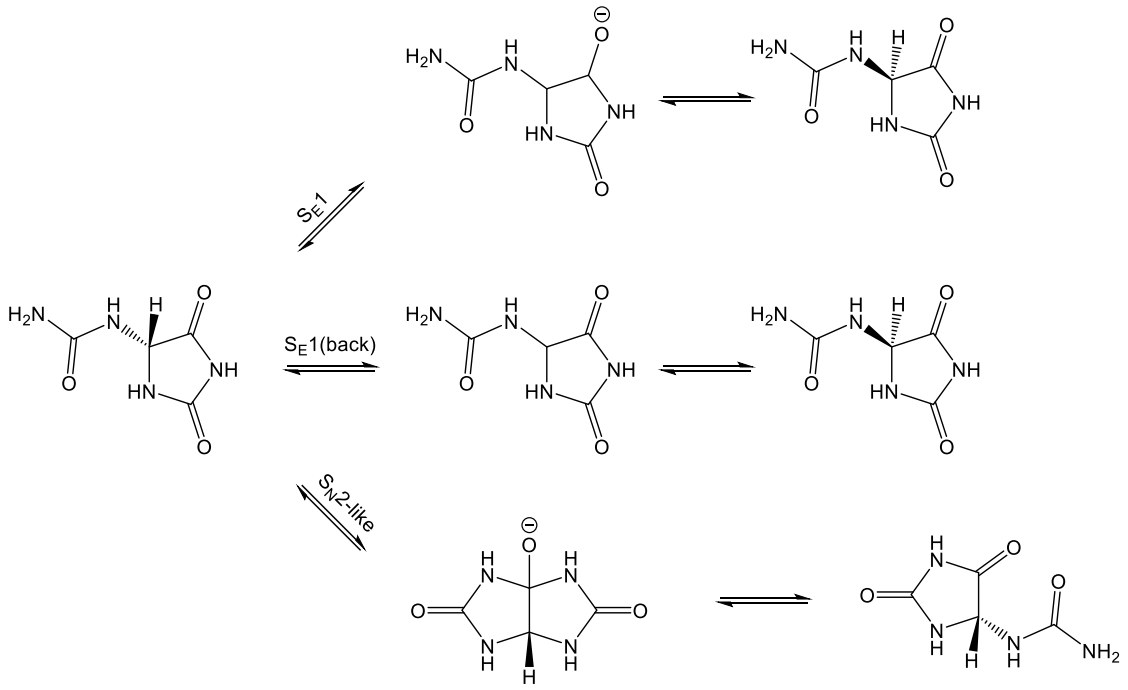

Figure 6. The mechanism of formation of allantoin stereoisomers

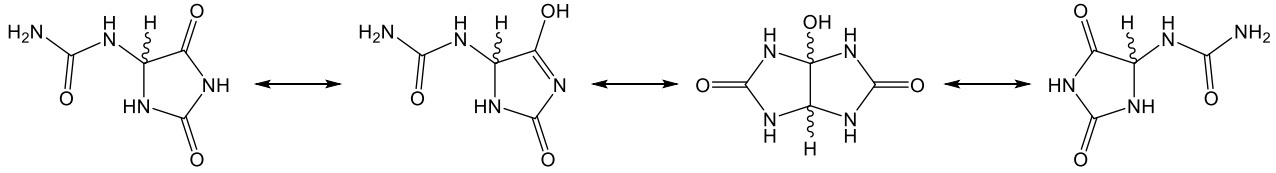

Figure 7. Transition of allantoin stereoisomers

3.1. Complexation reactions

Currently, numerous studies are devoted to the methods to prepare various organic and organometallic complexes of allantoin by changing the nature of the ligand, including the use of the mechanochemical synthesis. Thus, the synthesis of the allantoin organic complexes with pantotheonic [31], polygalacturonic [32], ascorbic [33], and urocanic [34] acids as well as glycine [35], was carried out. Figure 8 shows several examples.

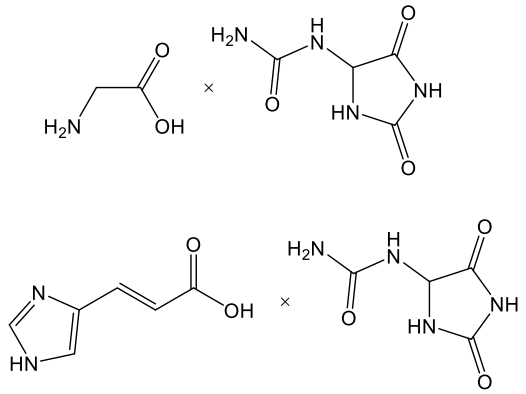

Figure 8. Allantoin complexes with organic acids

The synthesized allantoin-aluminum and allantoin-chlorohydroxyaluminium complexes with various organic acids [36] have found application in cosmetology as a part of deodorants, astringent lotions, aftershave, and other personal hygiene products (Fig. 9) [37, 38].

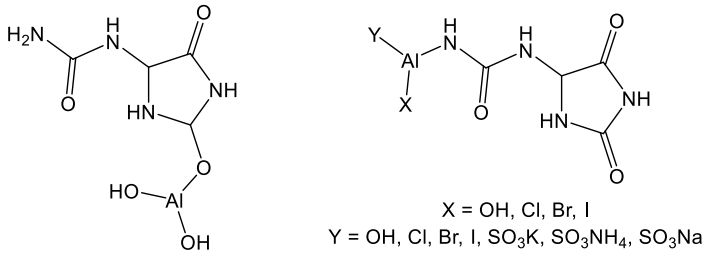

Figure 9. Allantoin-aluminum complexes

There is no doubt that the abovementioned examples of the preparation of allantoin complexes with organic ligands do not exhaust all the opportunities to create such compounds.

Figure 10 represents certain successes achieved in the synthesis of allantoin complexes and the composition of the allantoin-chlorohydroxyaluminium complex with ascorbic acid with the participation of the imide atom of the allantoin heterocyclic fragment [33].

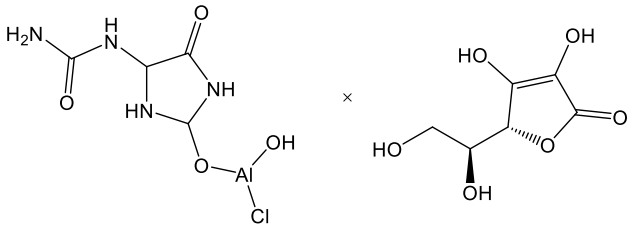

Figure 10. Allantoin-aluminum complexes

Figure 11 shows the same type of complex, where the total composition of the allantoin-aluminum complexes with various organic acids is presented [37, 38], however, the terminal amino group of the urea substituent is involved.

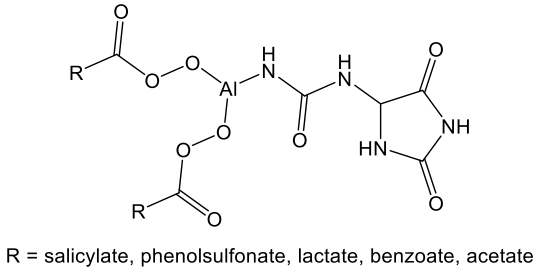

Figure 11. Allantoin-aluminum complexes

The intensive development was the study of allantoin complexes with silver, zinc and organic acids due to their manifestation of the wound healing, bactericidal [39, 40] and antithrombotic properties [41]. Figure 12 illustrates the overall composition of allantoin-zinc-silver complexes.

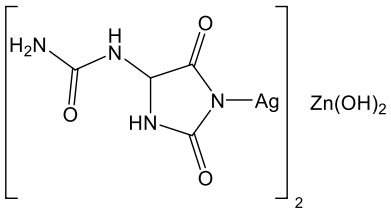

Figure 12. Complexes of allantoin with silver and zinc

3.2. Hydrolysis reactions

Allantoin is prone to chemical and enzymatic hydrolysis reactions, including those in living organisms [42] leading to allantoic acid (Fig. 13).

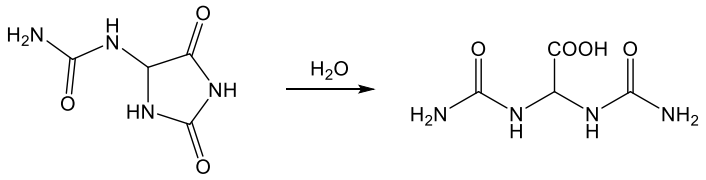

Figure 13. Hydrolysis of allantoin

By changing the depth of the allantoin hydrolysis it was found [43] that 5-aminohydantoin and fulminic or carbamic acid are the products of this reaction (Fig. 14).

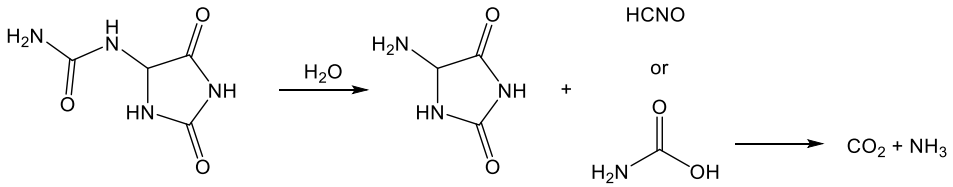

Figure 14. Hydrolysis of allantoin

3.3. Chemo- and electrochemoluminescence

Saqib et al. [44] found the allantoin ability for intensive chemoluminescence with lucigenin. To explain the results, a reaction mechanism was proposed (Fig. 15) suggesting that allantoin can decompose and release a cyanide radical in an alkaline medium to react with lucigenin.

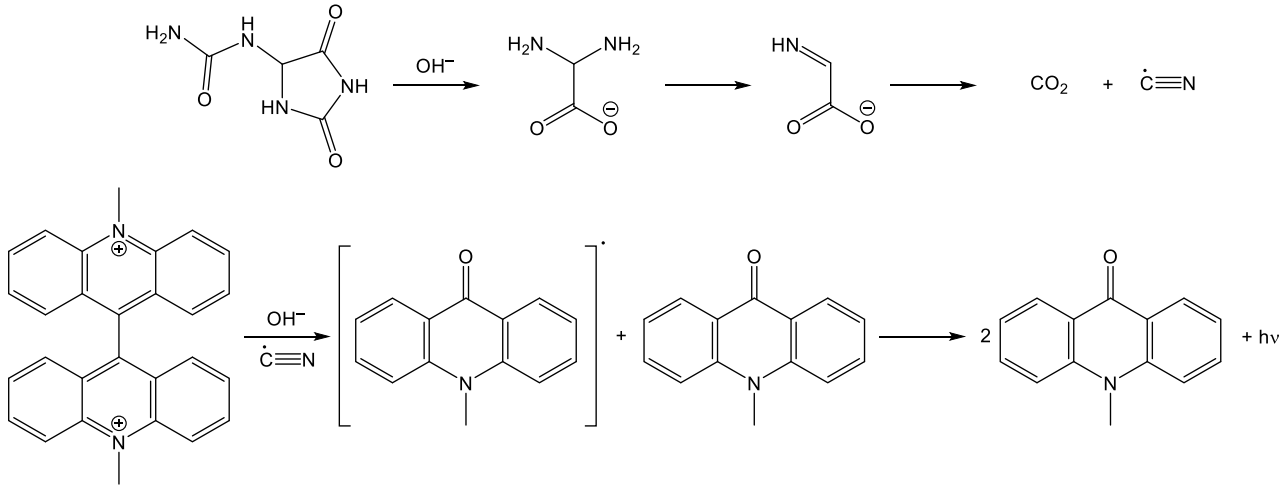

Figure 15. The mechanism of allantoin chemoluminescence

In the experiment described in Ref. [45], the electrochemiluminescence based on allantoin and tris(2,2'-bipyridine) ruthenium $[Ru(bPy)_3]^{2+}$ in an alkaline buffer solution at pH = 11.0 was studied. Given the specific nature of the established effect, the reaction mechanism (Fig. 16) suggests that allantoin in an alkaline medium turns into a radical anion involved in further stages of electrochemiluminescence.

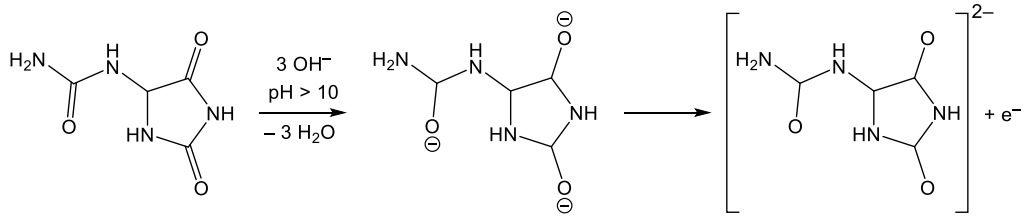

Figure 16. Allantoin-based electrochemiluminescence

3.4. Interaction with phenol

A method based on the reaction of allantoin and phenol [20] in the presence of heterogeneous catalysts comprising mineral acids supported on solid zeolite supports allows producing the ortho/para-hydroxyphenyl-hydantoins (Fig. 17).

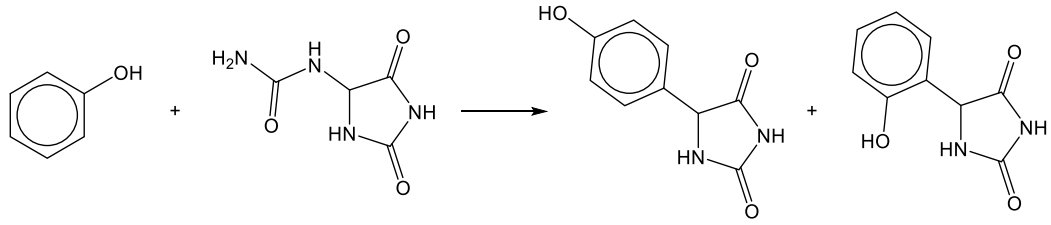

Figure 17. Reaction of allantoin and phenol

3.5. Nitrogen Substitution Reactions

For the first time, the N-alkylation of allantoin was carried out at the beginning of the 20th century [46]. In the proposed method, the silver-substituted allantoin was initially prepared followed by the Ag replacement by methyl group under the influence of methyl iodide. Figure 18 shows the process for producing of 1-(1-methyl-2,5-dioxoimidazolidin-4-yl)urea and 1-(3-methyl-2,5-dioxoimidazolidin-4-yl)urea using these reactions.

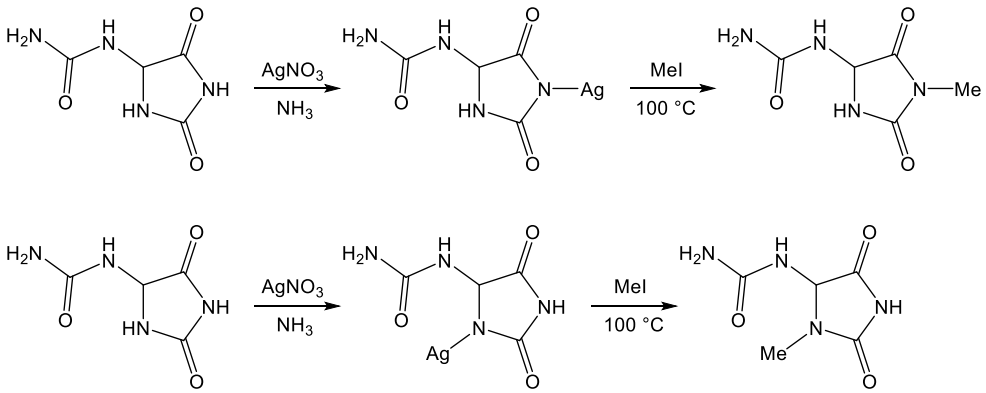

Figure 18. N-methylation of allantoin

In Ref. [47], a comprehensive silylation of allantoin was carried out by heating the latter with bistrimethylsilylacetamide (BSA) in pyridine (Fig. 19).

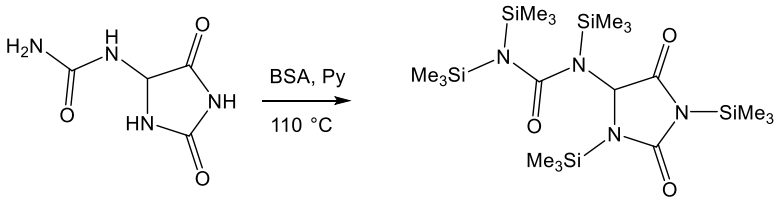

Figure 19. N-silylation of allantoin

3.6. Reactions with aldehydes

There is a noticeable amount of bactericidal substances that are synthesized by the interaction of allantoin with glutaraldehyde [48] and formaldehyde [49]. Figure 20 shows an example of the allantoin condensation reaction with glutaraldehyde.

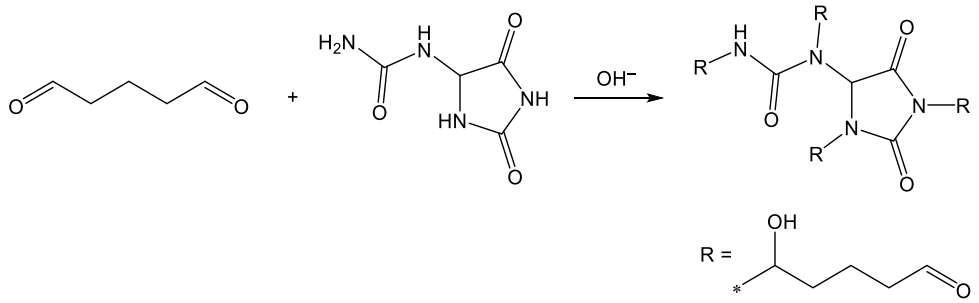

Figure 20. Allantoin condensation with glutaraldehyde

The most studied are the allantoin condensation reactions with formaldehyde (Fig. 21).

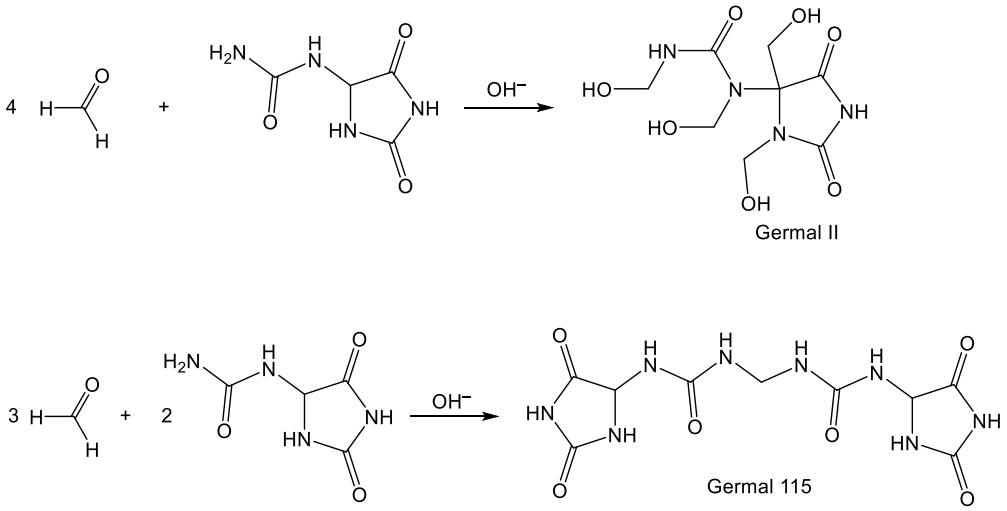

Figure 21. Allantoin condensation with formaldehyde

Diazolidinyl urea (Germal II) and imidazolidinyl urea (Germal 115) are the well-known methylol derivatives of allantoin widely used in various fields of human activity. Diazolidinyl urea (Germal II) is a heterocyclic compound comprising methyl-substituted allantoin derivative. Currently, the location of substituted methylol groups in this compound is a matter of discussion, and two main configurations are assumed. According to the published data [49], diazolidinyl urea is a tetra-N-methylol derivative of allantoin, however, recent studies [50] have shown that the product of the allantoin condensation with formaldehyde is a compound where one of the four methylol groups is bonded to the tertiary carbon atom of the hydantoin cycle. Table 2 represents the physical-chemical properties of Germal II and Germal 115.

Table 2

Physical-chemical properties of diazolidinyl urea and imidazolidinyl urea

Parameter	Value	
	Diazolidinyl urea [51]	Imidazolidinyl urea [52]
Appearance	White crystalline powder with a slight characteristic odor	White crystalline powder with a slight characteristic odor
Solubility	Easily soluble in water, propylene glycol	Soluble in water, ethylene glycol, propylene glycol, glycerin, slightly soluble in methanol, insoluble in ethanol

Diazolidinyl urea is one of the most commonly used preservatives in cosmetics [53–55] releasing formaldehyde as a result of decomposition. The concentrations of the released formaldehyde in the cosmetic products and the factors affecting the release of formaldehyde during the decomposition of diazolidinyl urea have been previously studied [56, 57]. However, to date, there is not much data on its decomposition, and analytical methods to determine the diazolidinyl urea have been developed during the last 15 years [53, 58]. It was previously reported that (4-hydroxymethyl-2,5-dioxo-imidazolidin-4-yl)urea (HU compound in Figure 22) is the only decomposition product of diazolidinyl urea [53]. The scheme 21 shows a possible decomposition path for diazolidinyl urea. Doi et al. [59] proved that diazolidinyl urea (compound 1) releases formaldehyde to form the HU (compound 8) and six other decomposition intermediates (compounds 2–7).

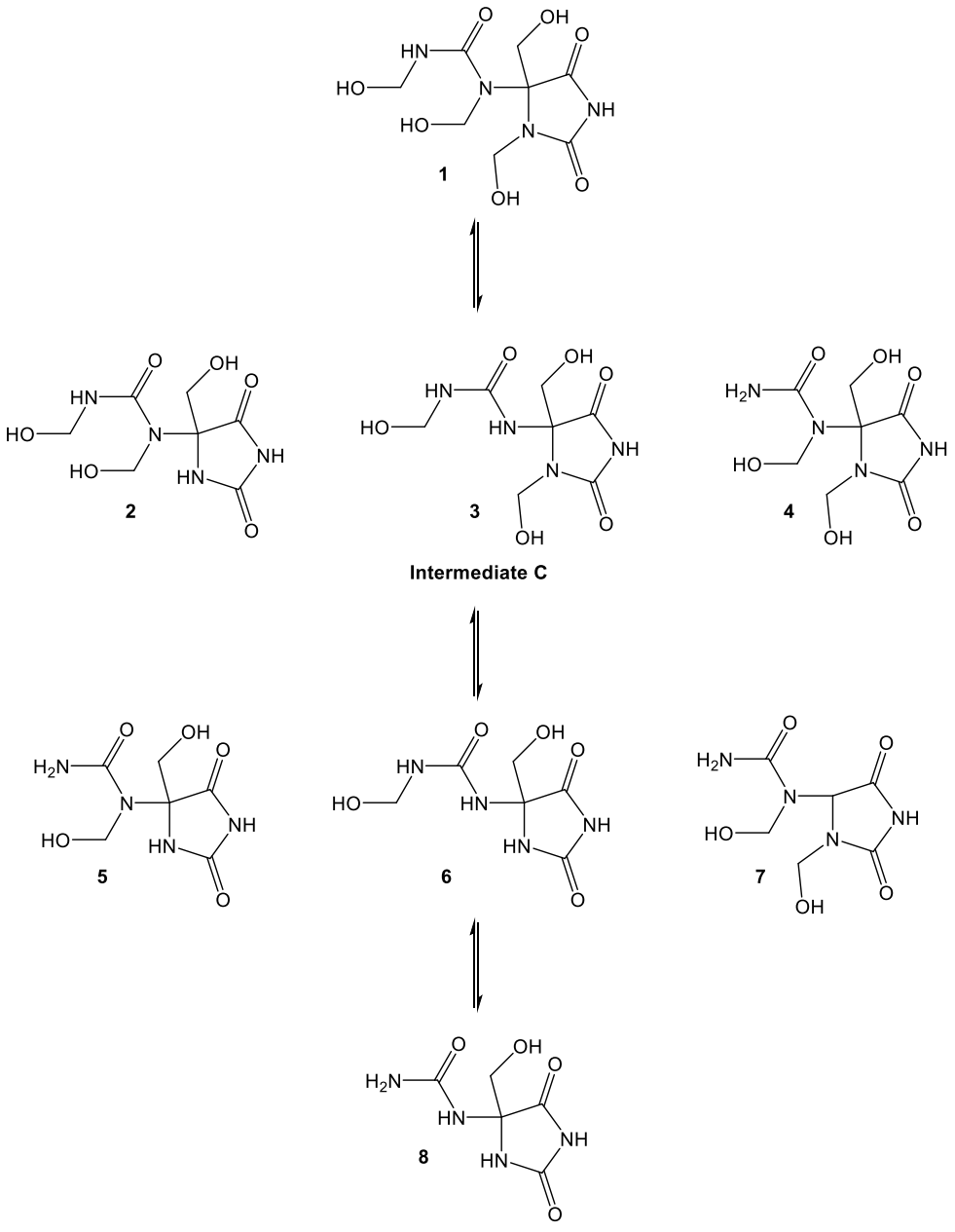

Figure 22. Decomposition products of diazolidinyl urea

The Germal II and Germal 115 are bactericidal components that are mainly used as preservatives in cosmetic products, protect them from bacteria, yeast, and mold. These substances are a part of various shampoos, hair conditioners, shaving gels. Being active against both gram-negative and gram-positive bacteria, these compounds have antimicrobial activity, can be used individually [50] and in a combination with para-

hydroxybenzoic acid esters (parabens), are also synergistic with a number of other preservatives. Imidazolidinyl urea has the same positive effects as diazolidinyl urea, but it has no antifungal effect [60].

Both compounds can cause irritation to the eyes and skin, and are also capable of causing the contact dermatitis, since they release free formaldehyde, however, the amount of this formaldehyde is much lower than the recommended limits [61]. The use of diazolidinyl urea as a part of the personal care products is allowed in concentrations of up to 0.5 wt.% [51].

Conclusions

Thus, this work summarizes the information on the methods for producing allantoin from various substrates and considers its inherent chemical properties. An analysis of the literature on the chemical properties of allantoin shows that it is most characteristic for the complexation reactions that allow obtaining new biologically active compounds. In some cases, the work is focused on the methods to prepare and use allantoin under industrial conditions.

Acknowledgement

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Аллантоин: синтезі және химиялық қасиеттері

Аллантоиннің қол жетімділігі мен көп функционалдылығы оның негізінде синтетикалық заттар алуда, соның ішінде фармацевтикалық өндіріс қажеттіліктері үшін үлкен қызығушылық туғызуда. Аллантоин химиясы туралы көптеген әдеби көздер толық емес, жүйесіз және бұл мәліметтер оның алыну әдістері мен химиялық қасиеттерін толық түсінуге мүмкіндік бермейді. Осы мақалада аллантоинді синтездеу және химиялық қасиеттерін зерттеу әдістері, оның практикалық қолданылуы туралы жүйеленген мәліметтер келтірілген. Бұл жұмыста аллантоиннің карбонилді қосылыстар мен мочевинадан алудың препаративтік тәжірибеде кеңінен қолданылатын әдістері қарастырылған және азоткұрамды гетероциклдердің әртүрлі реагенттер әсерінен негізгі өнімге әкелетін трансформациялық айналулар жолдары көрсетілген. Аллантоиннің негізгі химиялық қасиеттері гидролиз реакцияларында, органикалық және бейорганикалық субстраттармен комплекстүзуде, нуклеофильді реактивтермен әрекеттесуде, хемолюминесценция процестерінде көрсетілген. Аллантоин синтезінің стандартты емес әдістері мен оның химиялық өзгерістерге ұшырауы берілген жерлерінде соңғы өнімдердің түзілу механизмдері көрсетілген. Аллантоиннің синтезі мен химиялық қасиеттері туралы жүйелі материал аллантоин негізінде маңызды заттарды синтездеп алуға бағытталған мамандар үшін қажетті құрал бола алады. Жалпыланған мәліметтер негізінде аллантоинді азаэтероцикл ретінде жаңа биологиялық белсенді және басқа да қосылыстардың кең спектрін алу үшін қолдануға болатындығы айтылған.

Кілт сөздер: аллантоин, мочевина, карбонилді қосылыстар, азагетероциклдер, комплекстер, люминесценция, гидролиз.

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Аллантоин: синтез и химические свойства

Доступность и полифункциональность аллантоина делают его крайне привлекательным для реализации синтетического потенциала на его основе, особенно для нужд фармацевтической промышленности. Многочисленные литературные сведения по химии аллантоина носят отрывочный, несистемный характер, и они не позволяют иметь полноценное представление о методах его получения и его химических свойствах. С целью устранения данного пробела в представленной обзорной статье приведены систематизированные данные по методам синтеза аллантоина и изучению его химических свойств, а также затронуты области практического применения аллантоина. Рассмотрены наиболее распространенные в препаративной практике методы получения аллантоина из карбонильных соединений и мочевины, а также приведены пути трансформации ряда азотсодержащих гетероциклов под действием различных реагентов, приводящие к целевому продукту. Основные химические свойства аллантоина представлены в реакциях гидролиза, комплексообразования с органическими и неорганическими субстратами, взаимодействия с нуклеофильными реагентами, в процессах хемолюминесценции. В отдельных случаях, когда приводятся нетиповые методы синтеза аллантоина и рассматриваются его превращения, показаны механизмы образования конечных соединений. Систематизированный материал по методам синтеза и химическим свойствам аллантоина может служить надежным навигатором для тех специалистов,

которые нацелены получать практически важные вещества на основе аллантоина. На основании обобщенных данных отмечено, что аллантоин может быть успешно использован в качестве базового азагетероцикла для получения широкого круга новых биологически активных и других соединений.

Ключевые слова: аллантоин, мочевина, карбонильные соединения, азагетероциклы, комплексы, люминесценция, гидролиз.

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