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METHOD FOR THE SYNTHESIS OF INITIAL PRODUCTS OF DERIVATIVES 8-FORMYL-1,4-BENZODIOXANES

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ABSTRACT

The article investigates an efficient method for the synthesis of new initial derivatives of 8-formyl-1,4-benzodioxanes. Ways of obtaining aromatic aldehydes with 1,4-benzodioxane fragments, their chloromethylation, transformations into the corresponding formyl derivatives, and electrophilic substitution reactions for benzodioxane under Sommle reaction conditions were studied. The physicochemical properties have been studied. Using the program for predicting the spectrum of biological activity of substances (Online), the biological activity of synthesized compounds of 8-formyl-1,4-benzodioxanes was predicted.

Keywords: synthesis, chloromethylation, Sommle reaction, 8-chloromethyl-, 8-formyl-1,4-benzodioxanes, screening.

Introduction

All flavonoids belong to the substances of "secondary synthesis", but this does not mean that they play a secondary role in plant life. Many "secondary compounds" are important in the survival and adaptation of plants, in the relationship of plants with the environment, i.e. the synthesis of a huge variety of polyphenols, along with photosynthesis, is one of the characteristic features of plants [1].

Oxygen-containing heterocyclic systems of pyran, dioxol, dioxane and their benzoanalogues are widespread in the plant world. Especially 1,4-benzodioxane rings are included in many phenolic compounds: chalcones, flavones, flavanones, isoflavones, coumarins, and others [2].

Some derivatives of (2-aminoalkyl) benzodioxane have various types of biological activity, in particular, they inhibit or stimulate the activity of the central nervous system. Domestic industry produces preparations "Benzodioxin", "Pyrroxan", "Butiroxan" [3]. The first of them belongs to the group of ß-blockers, the other two are used for hypertensive and diencephalic crises.

6-Formyl-1,4-benzodioxane is used in the perfume industry [4]. As for derivatives and analogs of dioxane, most of the literature data on their practical use relates to the study of biological

activity and, above all, in the field of medicine. The derivatives of 1,4-benzodioxane are studied most intensively in this regard.

Many messages give a wide range of action. Thus, in particular, for the condensation products of 6-formyl-1,4-benzodioxane with acetylresorcinol derivatives, vasodilating, antiulcer, sedative, diuretic, bronchodilatory, antichomenergic, antispasmodic, antihistamine, hypotensive and hypertensive activities are noted [5]. Hypotensive, antihistamine, and α-adrenolytic activities have been found in 1,4-benzodioxane derivatives with various substituents in the heterocycle [6].

Methods for obtaining derivatives of 1,4-benzodioxane with an imidazoline fragment, which have hypotensive activity and are antagonists of presynaptic α2 receptors, are patented [5]. This also applies to pyrrolidine derivatives, for piperazine and piperidine derivatives of 1,4-benzodioxane with amino groups or an imidazole fragment in the side chain of the heterocycle. The ability to suppress anxiety is also possessed by 8-hydroxy-1,4-benzodioxane derivatives substituted in the aromatic nucleus. Anti-inflammatory activity has been reported for ethylenedioxyindole derivatives [7, 8].

Many already known derivatives of 1,4-benzodioxane analogues of flavonoids, previously obtained by us [9-12], have significant hepatoprotective, anticytolytic, cytoprotective, hypoglycemic, and other properties.

Previously, the authors of [13] synthesized substituted 1,3-benzodioxanes, which were subsequently used as starting products. Also, taking into account the valuable biological properties of natural and synthetic derivatives of heterocycles, it can be assumed that the combination of a chromone and benzodioxane ring in one molecule will make it possible to obtain heterocyclic systems with new biological properties. Therefore, our goal was an improved way to carry out the synthesis of some substituted 8-formyl-1,4-benzodioxanes for use as the main starting products, which would allow us to obtain new compounds with useful biological properties and for their further use in chemical modification.

EXPERIMENTAL PART

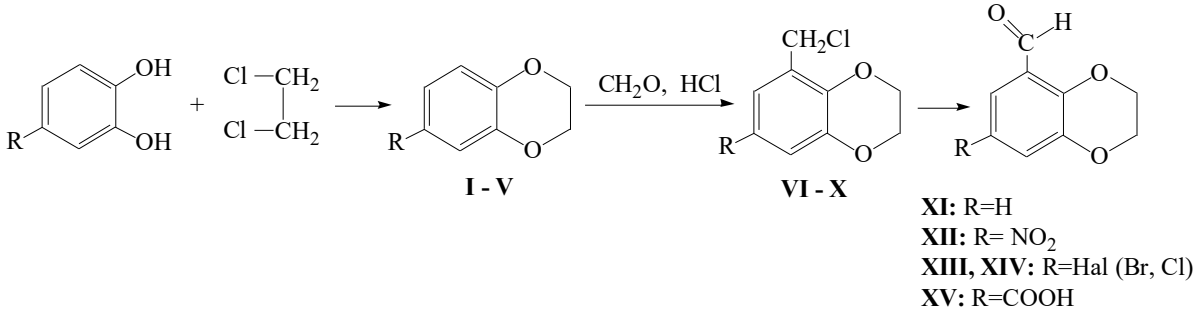
The course of the reaction and the purity of the obtained compounds were monitored by thin-layer chromatography on standard Silufol UV-254 plates (Czechoslovakia) in benzene : ethanol (9 : 1) systems; spots were detected under ultraviolet light. 1H-NMR spectra were recorded on a Unity-400+ instrument (Varian, USA, 400 MHz) in acetone - d6 (δ, ppm; J, Hz); tetramethylsilane was used as an internal standard. Elemental analysis was carried out on an instrument for microdetermination of carbon, hydrogen, and halogen (Russia). The elemental analysis data for the compounds corresponded to those calculated. Compounds **(VI) – (XV)** were synthesized and characterized as described in [10, 11].

Method for the synthesis of 1,4-benzodioxanes (I) – (V). 370 g (3.4 mol) of pyrocatechol, 500 g (4.7 mol) of soda, 500 g (5.1 mol) of dry dichloroethane and 330 ml of ethylene glycol are loaded into a two-liter flask equipped with a mechanical stirrer and a reflux condenser, and the mixture is boiled for 25 hours. this time practically stops the release of CO_2. The reaction mixture is distilled with steam and the reflux condenser is replaced with a descending condenser. The lower distillate layer is separated and dried over sodium sulfate. Dichloroethane

is distilled off, the residue is distilled in vacuum at 98°/15 mm or at 81-82°/8 mm, nD20 1.5492, n2020 1.1707. Yield 412 g (90%).

RESULTS AND DISCUSSION

In the vast majority of methods for obtaining natural and synthetic flavonoids and isoflavonoids, various aromatic aldehydes are used as the main starting products. One of the many ways to obtain aromatic aldehydes with 1,4-benzodioxane fragments **(XI) – (XV)** is chloromethylation of aromatic compounds and their further transformation into the corresponding formyl derivatives (Scheme 1).



Scheme 1. Synthesis of substituted 1,4-benzodioxanes **(I) – (XV)**

The classical method for the synthesis of these compounds is the cyclization of catechol or its derivatives under the influence of vicinal dihalogen derivatives. The interaction of pyrocatechol with 1,2-dibromoethane in an alkaline medium leads to the formation of benzodioxane **(I) - (V)** with a yield of 30-50% when the reaction is carried out in an aqueous solution of alkali or in alcoholic solutions of alcoholates, and 60-75% when carried out in glycol or glycerol in the presence of sodium and potassium carbonates, sometimes using a copper catalyst. Benzodioxane is characterized by an electrophilic substitution reaction. Thus, 8-chloromethyl derivatives are formed during chloromethylation [14].

In order to improve and simplify the method for obtaining 1,4-benzodioxane and some of its derivatives, we carried out the reaction of the corresponding pyrocatechol with dichloroethane in the presence of soda in ethylene glycol in an inert gas atmosphere. In this case, the yield of 1,4-benzodioxanes **(I) - (V)** reaches 85-90%. Chloromethylation of the resulting 1,4-benzodioxanes **(I) – (V)** was carried out according to the Blank reaction [14] in an acidic medium with a $ZnCl_2$ catalyst by the action of the chloromethylating agent paraform in a medium of concentrated hydrochloric acid at room temperature. These conditions protonate the formaldehyde carbonyl group, increasing the electrophilic properties of the carbon. The aldehyde is then attacked by aromatic pi electrons, followed by rearomatization of the aromatic ring. The resulting benzyl alcohol is rapidly converted to chloride under these conditions.

As a result of the reaction, substituted 8-chloromethyl-1,4-benzodioxanes **(VI) - (X)** were obtained with a yield of 58-60% (Scheme 1).

It should be noted that in order to obtain the highest yields of chloromethyl derivatives based on p-nitrophenol 7 and p-hydroxybenzoic acid (X), it is necessary to raise the temperature of the reaction mixture to 100°C.

The interaction of the corresponding 8-chloromethyl-1,4-benzodioxanes **(VI) – (X)** with an excess of hexamethylenetetramine (urotropine) under Sommle reaction conditions [15] leads to

substituted 8-formyl-1,4-benzodioxanes **(XI) – (XV)** with a yield of 60-63.8% (Scheme 1). In the reaction, the resulting salt is directly hydrolyzed to the aldehyde. The advantage of this method is that practically no side products are formed during the reaction.

Characteristic is the proton signal of the 8-H 1,4-benzodioxane nucleus. It is located at 6.9-7.0 ppm. and does not coincide with the multiplet of other aromatic protons. Consideration of the issues of structural analysis of compounds **(XI) - (XV)** indicates that when solving the structure of those substances whose molecules contain a 1,4-dioxane ring, not only spectral methods are required, but also chemical transformations, including experiments on synthesis and cleavage of starting compounds and model samples.

Therefore, we have developed an improved version of effective and simple methods for obtaining 6-nitro-, 6-carboxy-, 6-halo-8-chloromethyl-1,4-benzodioxanes **(VI) - (X)** and ways of their transformation into 6-nitro- , 6-carboxy-, 6-halogen-8-formyl-1,4-benzodioxanes **(XI) – (XV)**, for which some physicochemical constants were studied (Table 1).

Table 1 Some physicochemical constants of 8-formyl-1,4-benzodioxanes (XI) - (XV)

Compound	Gross formula	Mol. weight	Melting point, °C	Element	Found, %	Calculated, %	Solvent for crystallization
(XI)	$C_9H_8O_3$	164	280	C H O	65.85 4.91 29.24	65.8 4.9 29.2	EtOH
(XII)	$C_9H_7NO_5$	209	119	C H N O	51.68 3.37 6.70 38.25	51.6 3.37 6.7 38.2	EtoAc
(XIII)	$C_9H_7BrO_3$	243	314	C H Br O	44.47 2.90 32.87 19.75	44.47 2.90 32.8 19.7	EtoAc
(XIV)	$C_9H_7ClO_3$	198,5	230	C H Cl O	54.43 3.55 17.85 24.17	54.4 3.5 17.8 24.2	EtoAc
(XV)	$C_{10}H_8O_5$	208	369	C H O	57.70 3.87 38.43	57.7 3.8 38.4	EtOH

The prediction of the biological activity of synthetic compounds **(VI) - (XV)** was carried out using the PASS computer program developed at the State Research Institute of Biomedical Chemistry named after. V.N. Orekhovich RAMS [16, 17]. The forecast, in accordance with the requirements of the program, was carried out on the basis of an analysis of the database on the relationship between the chemical structure of the compound and the biological activity of substances. The performed calculations showed that a number of synthesized compounds **(VI) – (XV)** can exhibit different activity (Tables 2 and 3).

Table 2
The result of predicting the biological activity of the synthesized 8-chloromethyl-1,4-benzodioxanes (VI) - (X)

Compound	Type of biological activity	The value of the probability of having (lack of) activity	Possible side effects and toxic effects*	The value of the probability of having (lack of) activity
(VI)	Aspulvinone dimethylallyl transferase inhibitor	0.821 (0.028)	Weakness	0.885 (0.009)
(VII)	Chymosin, saccharopepsin, acrocylindropepsin inhibitor	0.841 (0.013)	Eye irritation	0.937 (0.003)
(VIII)	Aspulvinone dimethyl allyl transferase inhibitor	0.834 (0.024)	Muscle weakness	0.853 (0.009)
(IX)	Treatment of phobic disorders	0.828 (0.024)	Eye irritation	0.925 (0.003)
(X)	Arginine-2-monooxygenase inhibitor	0.874 (0.004)	Muscle weakness	0.939 (0.004)

Table 3
The result of predicting the biological activity of the synthesized 8-formyl-1,4-benzodioxanes (XI) - (XV)

Compound	Type of biological activity	The value of the probability of having (lack of) activity	Possible side effects and toxic effects*	The value of the probability of having (lack of) activity
(XI)	Membrane integrity agonist	0.911 (0.008)	Shiver	0.779 (0.046)
(XII)	Chymosin, saccharopepsin, acrocylindropepsin inhibitor	0.869 (0.009)	Urine color change	0.765 (0.013)
(XIII)	Aspulvinone dimethylallyl transferase inhibitor	0.854 (0.019)	Spermicide	0.600 (0.015)
(XIV)	Membrane integrity agonist	0.877 (0.017)	Hypomagnesemia	0.762 (0.009)
(XV)	Inhibitor of arginine-2-monooxygenase, sugar phosphatase	0.872 (0.004)	Toxic, breath	0.804 (0.025)

*Note: * The prognosis is based on clinical manifestations, which are sometimes observed in several or even one patient.*

Tables 2 and 3 show the highest results of predicting biological activity and possible side and toxic effects of the obtained compounds **(VI) - (XV)**.
Based on the results of the prediction of biological activity, it is possible to observe an increase in the presence of activities in new compounds **(XI) - (XV)** compared to compounds **(VI) - (X)**, and in terms of possible side and toxic effects, a decrease in the activities of compounds **(XI) -**

(XV) compared to compounds **(VI) – (X)**. Compound **(XI)** showed the highest biological activity of the membrane integrity agonist (91%).

CONCLUSION

The synthesized initial compounds **(I) - (V)** will allow using them for the synthesis by modified methods of a number of new analogues of flavonoid compounds with useful biological properties, which we can provide their use in subsequent articles.

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