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DEVELOPMENT OF SYNTHESIS METHOD OF β-AMINO ACID OF THIOPHENONAPHTHOQUINONE

Розроблено зручний метод синтезу 2-аміно-4,9-діоксо-4,9-дигідронафто[2,3-*b*] тіофен-3-карбонової кислоти на основі взаємодії 2,3-дихлоро-1,4-нафтохінону з етилціаноацетатом та сульфідом натрію в етанолі. Досліджено вплив різних чинників та запропоновано ймовірний механізм реакції.

Ключові слова: 1,4-нафтохінон, гетероциклізація, етиловий естер ціаноцтової кислоти, тіофеннафтохінон.

A convenient method of synthesis of 2-amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b] thiophene-3-carboxylic acid by interaction of 2,3-dichloro-1,4-naphthoquinone with ethylcyanacetate and sulfide sodium in ethanol was developed.The influence of different factors was investigated and probable mechanism of reaction proposed.

Key words: 1,4-naphtoquinone, heterocyclization, ethylcyanacetate, thiophenonaphthoquinone.

Statement of the problem. The continuous growth of scientific interest to derivatives of 1,4-naphthoquinone due to their high reactivity and the possibility of synthesis based on these various new compounds with a wide range of biological activity. Preparations based on heterocyclic compounds of 1,4-naphthoquinone efficiently used in treating of disorders of the functions of the brain (cerebral infarction, stroke, atherosclerosis) and have high antioxidant, cytolytic and cytostatic activities. Recently, as increased the number of studies on various aspects of chemistry of thiophene and its derivatives. One of the important niches among them are occupying derivatives of amino acid of thiophene and condensed systems based on them. They have found use as pharmaceuticals, pesticides, intermediates of synthesis of dyes and in various fields of fine chemicals.

Among the thiophene derivatives were found effective therapeutic drugs with anticholinergic, antispasmodic, anthelmintic, hepatoprotective, anti-allergic, anti-inflammatory, analgesic and diuretic properties.

Analysis of recent research and publications. First study the reactions of 2,3-dichloronaphthoquinone with CH-acids with the active methylene group, in particular ethylcyanacetate, were begun in 1899 by Lieberman [3].

Despite the relatively long period that have elapsed since then, and numerous publications on the subject what have appeared over the last century, information about the course of the reaction is mixed. As it turned out, in practice, the result of the reaction is highly dependent on many factors such as the structure of methylene components, nature of the solvent and the base used as catalyst, reaction conditions (for example, temperature, reaction time, the amount of solvent). So, it is very difficult to find the optimal reaction conditions for a methylene component (in our case - for ethylcyanacetate), namely the conditions under which possible of obtaining a pure reaction product with maximum yield.

Considering above, is actual to development of convenient preparative methods for the synthesis of new condensed systems of 1,4-naphthoquinone with mono- and polyheterocycles is very attractive and interesting area of chemistry of 1,4-naphthoquinone. The combination of quinonic and heterocyclic fragments, including thiophene, in one molecule will lead to new heterocyclic compounds - potential biologically active substances.

Aim. Development of preparative method of the synthesis of heterocyclic system of ethyl 2-amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b]thiophene-3-carboxylic acid on it basis.

Experimental part. NMR spectra were obtained on a spectrometer "Varian XL-400" (400 MHz), ^1H chemical shifts expressed in δ-scale relative to DMCO-d_6, integrated intensities is correspond to allocation made by protons.

IR spectra were recorded on a spectrophotometer "Specord IR-80" in tablets with KBr.

Monitoring the progress of reaction and the identity of substances was carried out by TLC on plates "Sorbfil PTSH-AF-A".

In determining the melting point of compounds amendment to the protruding column of mercury was undertaken.

Cleaning and drying of solvents was carried out by the methods described in the literature [1].

Methods of preparation. *Ethyl (3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate **(3)***.

To a solution of 10 g (44 mmol) of 2,3-dichloronaphthoquinone and 6 ml (6.38 g, 55.2 mmol) of ethylcyanacetate in 2 liters of 96 % ethanol with vigorous stirring, for 30 minutes at room temperature add 300 ml of 25 % solution of NH_4OH. The reaction mixture becomes a blue color. Stir for another 30 min and acidified with 10 % HCl until the color will change to red-brown and leave overnight. The filtrate was several times extracted with methylene chloride, the combined organic phases were washed with water and dried over $CaC1_2$. Solvent was distilled at atmospheric pressure to a residual volume of about 50 ml. Remaining of solvent was distilled off under vacuum by water jetting pump. The dry residue was dissolved in boiling methanol (~ 150 ml), after added activated carbon, and boil for 10 minutes, then filtered and the filtrate cooled to room temperature first, then in the freezer. Dropping out dark green crystals that was filtered and dried. Mp. 120-121 °C [2]. Yield 8.6 g (64%).

IR (KBr, cm^{-1}): 1680 (C = 0), 2240 (C = N).

PMR ($CDCI_3$, δ): 1,4 (t, 3H,-$COOCH_2\underline{CH_3}$), 4.4 (q, 2H,-$COO\underline{CH_2}CH_3$) 5.5 (s, 1 H, C3-CH), 7.8 -7.9 (m, 2H, CH, C5, C6), 8,2-8,3 (m, 2H, CH, C4, C7).

Calculated ($C_{15}H_{10}NO_4C1$),%: C 59.32; H 3,32; N 4,61.

Found ($C_{15}H_{10}NO_4C1$),%: C 59.26; H 3,03; N 4,65.

Ethyl 2-amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b] thiophene-3-carboxylate **(4).**

To a cooled to 5-10 ° C solution 2.4 g (0.01 mol) of $Na_2S·9H_2O$ in 300 ml of water with vigorous stirring and cooling by ice water was slowly added a solution 3.03 g (0.01 mol) of ethyl (3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate **(3)** in 15 mL of acetone, so that the temperature of the reaction mixture did not rise above 20-25 ° C. Obtained suspension was kept under stirring for 2 h and left overnight. Precipitate of ethyl 2-amino-4,9-dioxo-4,9-dihydronaphto[2,3-b]thiophene-3-carboxylate was filtered, washed with water and recrystallized from DMF. A dark red crystals with mp. 180-182 °C were obtained. Yield 2.26 g (75%).

IR (KBr, cm^{-1}): 3300 (NH_2), 3466 (NH_2), 1691 (C = O).

PMR (CDCI3, δ): 1,33 (t, CN, -$COOCH_2\underline{CH_3}$), 4.26 (q, 2H, -$COO\underline{CH_2}CH_3$) 6.5 (s, 2H, NH_2); 7,80 - 7.84 (m, 2H, CH, C5, C6), 8,09-8,21 (m, 2H, CH, C4, C7).

Calculated ($C_{15}H_{11}NO_4S$),%: C 59.80; H 3,65; N 4,65; S 10,63.

Found ($C_{15}H_{11}NO_4S$),%: C 59.72; H 3,57; N 4,72; S 11,12.

2-Amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b] thiophene-3-carboxylic acid **(5).**

To a fresly prepared 2.8 g (0.05 mol) of potassium hydroxide in 300 ml aqueous ethanol was added 3.01 g (0.01 mol) of ethyl 2-amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b] thiophene-3-carboxylate **(4)**. The reaction mixture was kept under stirring at room temperature for 12 hours and then heated to boiling and kept boiling for another 2 hours. After cooling, was added 1000 ml of water, stirred until complete dissolution of the solid phase, filtered and the filtrate neutralized with dilute hydrochloric acid. The precipitate that was obtained, filtered off and dried. Brown crystals with mp. > 300 °C. Yield 2.53 g (92,5 %).

IR (KBr, cm^{-1}): 3340 (NH_2), 3490 (NH_2), 1685 (C = O), 3520 (O-H), 1603 (C = O).

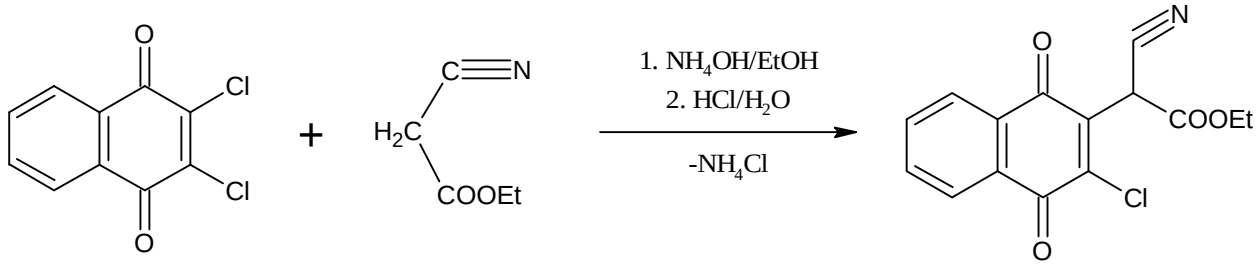
PMR ($CDC1_3$, δ): 5,9 (s., 2H, NH,); 7,80-8,15 (m, 2H, CH, C5, C6) 8,36-8.39 (m, 2H, CH, C4, C7), 12.39 (s, 1H,-COOH).

Calculated ($C_{13}H_7NO_4S$),%: C 57.14; H 2,58; N 5,13; S 11,73.

Found ($C_{13}H_7NO_4S$),%: C 57.02; H 2.52; N 5,03; S 11,70.

Discussion of results.

A convenient method for the synthesis of new heterocyclic system of ethyl 2-amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b]thiophene-3-carboxylate **(4)** was suggested. As a starting material in the synthesis of ethyl (3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate **(3)** was used technical 2,3-dichloronaphthoquinone **(1)**.



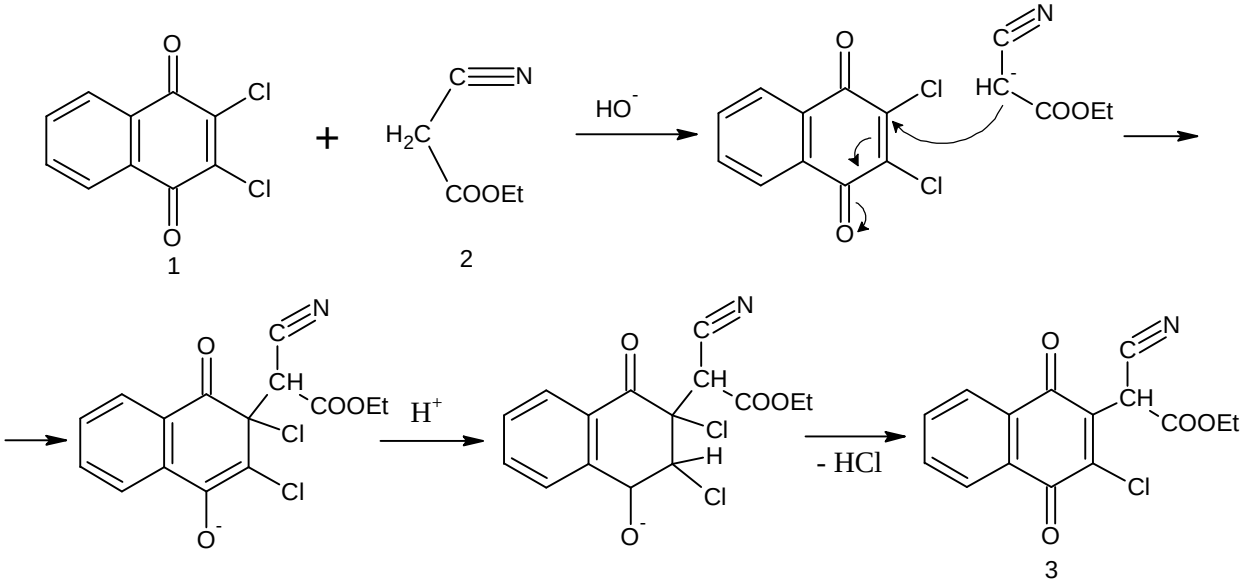
1 **2** **3**

The synthesis was carried out by interaction of 2,3-dichloronaphthoquinone (1) with a slight excess of ethylcyanacetate **(2)** at room temperature in ethanol. As a basis was used 25% aqueous solution of NH_4OH. The reaction was carried out with stirring for 30 minutes, followed by acidification of the reaction mixture with dilute HC1. After separation of the precipitate of NH_4Cl, the target compound was extracted from filtrate with methylene chloride. With the help of recrystallization from methanol was obtained pale yellow crystals of ethyl(3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate **(3)** with melting temperature 120-121 °C, that consistent with literature data [2]. The reaction was monitored by TLC.

Also, were made attempts to obtain ethyl(3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate **(3)** in other conditions, but none of them gave the desired result. Thus, by the interaction of 2,3-dichloronaphthoquinone with sodium salt of ethylcyanacetate in ethanol, when heated in the presence of NaOH as a base compound was obtained indefinite composition with a m.p. > 300 ° C.

Synthesis of ethyl(3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate is an example of long-known reaction of nucleophiles 1,4-addition by Michael [4]. This reaction is widely used in organic synthesis and is an effective way of extending the carbon chain electrophile into three (or more) carbon atoms. In the classic version of this reaction as nucleophiles was used stabilized carbanions - derivatives of active methylene compounds, which generated under the influence of weak bases directly into the reaction medium in the presence of acceptors of Michael including quinones [5].

Probable the mechanism of this reaction:



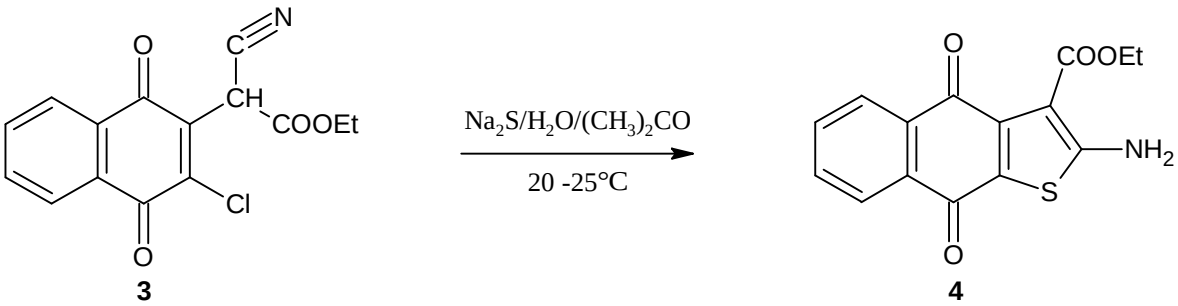
1 2 3

Initially from ethylcyanacetate under the action of the base, was eliminated proton and formed carbanion that attacked on one of equivalent electrophilic center of the molecule 2,3-dichloronaphthoquinone. Herewith during addition occurs the migration of the double bond to the atom C_1. After the next acidification of the reaction mixture the formed intermediate captures a proton from the reaction medium, and simultaneously elimination of HCl.

The structure of the obtained ethyl(3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate was confirmed by IR and ^{1}H NMR spectroscopies.

Currently synthesized many quinolic condensed systems, to the structure of which included oxygen- or nitrogen-containing heterocycles. Meanwhile, the literature contains much less information about this class of compounds with sulfur-containing heterocycles, in particular thiophene.

Synthesis of ethyl 2-amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b]thiophene-3-carboxylate **(4)** was carried out by reaction of acetone solution of ethyl(3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate **(3)** with an aqueous solution of sodium sulfide at a temperature not above 20 °C. With vigorous stirring to a cooled aqueous solution of Na_2S was added a solution of ethyl (3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate **(3)** in acetone. Precipitate of ethyl-2-amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b]thiophene-3-carboxylate **(4)** was filtered. After recrystallization from DMF was obtained dark red crystals with a melting point of 180-182 °C.

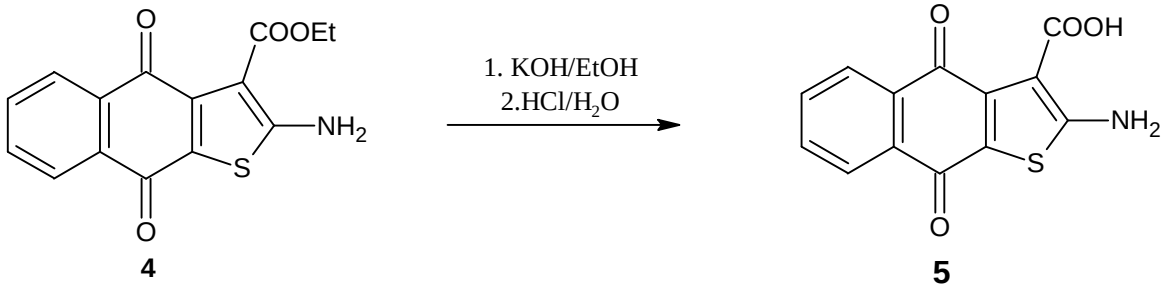


3 **4**

In general, this reaction belongs to reactions of intramolecular cyclization with forming new σ-bond. Although the reaction of ring closure includes the formation of one communication, intermediate, that directly was subjected to cyclization, obtained *in situ* from two simple reagents - ethyl(3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate **(3)** and sodium sulfide.

It is known that esters hydrolyze in the presence of bases, and in the presence of acids, but in practice hydrolysis is usually carried out by using the base [6].

In our case, the synthesis of 2-amino-4,9-dioxonaphto[2,3-b]thiophene-3-carboxylic acid **(5)** was carried out by interaction of source ester - ethyl 2-amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b]thiophene-3-carboxylate **(4)** with an excess of potassium hydroxide in ethanol.



4 **5**

The reaction was carried out with stirring at room temperature for 12 h and then the reaction mixture boiled for 2 h. Then cooled suspension of potassium salt of 2-amino-4,9-dioxonaphto[2,3-b]thiophene-3-carboxylic acid was diluted with water until complete dissolution of solids, filtered and the filtrate acidified with dilute hydrochloric acid. The precipitate was filtered and dried. The light brown crystals of 2-amino-4,9-dioxonaphto[2,3-b]thiophene-3-carboxylic acid with a m.p. > 300 °C were obtained.

Conclusions. Preparative of method of synthesis of ethyl(3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)(cyano)acetate **(3)** was developed. The influence of various factors on the reaction was investigated.

Also, was suggested a convenient method for the synthesis of new heterocyclic system of ethyl 2-amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b]thiophene-3-carboxylate **(4)**. Probable mechanism of the reaction was proposed.

A hydrolysis of ethyl-2-amino-4,9-dioxo-4,9-dyhidronaphto[2,3-b]thiophene-3-carboxylate (4) and 2-amino-4,9-dioxonaphto[2,3-b]thiophene-3-carboxylic acid was carried out.

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ВДОСКОНАЛЕННЯ ПРОЦЕСУ ОБРОБКИ СИВУШНОЇ ОЛІЇ

Наведені результати експериментальних досліджень різних способів обробки сивушної олії з метою концентрування вищих спиртів. Встановлено, що найкращі результати надає обробка хлоридом натрію стандартизованої сивушної олії з високим вмістом ізоамілового спирту та низьким вмістом н-пропанолу та етанолу. Процес висолювання води з сивушної олії необхідно здійснювати після її промивання водою і екстрагування з неї нижчих спиртів. Вивчено вплив хлориду натрію, температури і тривалості процесу висолювання води з сивушної олії на фазоутворення та склад органічної та водної фаз.

Ключові слова: сивушна олія, висолювання, спирти.

This article is devoted to the experimental results of the different methods of processing of fusel oil to the concentration of higher alcohols. It is found that the best results are obtained by processing with sodium chloride of standardized fusel oil with a high content of isoamyl alcohol and low content n-propanol and ethanol. The process of salting out of water from fusel oil should be implemented after flushing with water and extracting from it the lower alcohols. The influence of sodium chloride, temperature and duration of the salting out of water from fusel oil by phase formation and composition of the organic and aqueous phases has been studied.

Key words: fusel oil, salting, alcohols.

Постановка проблеми. Сивушну олію (СО) спиртового виробництва можна використовувати як сировину для одержання індивідуальних вищих спиртів (ізоамілового (іАС), ізобутилового (іБС) і н-пропілового (ПС)), які застосовують в органічному синтезі, під час виготовлення медичних препаратів і пахучих речовин, розчинників у лакофарбовій