**Vol. 2, No. 3, 2008** **Chemistry**

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# SYNTHESIS OF CONDENSED S-, N-CONTAINING HETEROCYCLIC SYSTEMS ON THE BASE OF 2-AMINO-4,9-DIOXO-4,9-DIHYDRONAPHTHO[2,3-b]THIOPHENE-3-ETHYLCARBOXILATE

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*Received: April 07, 2008*

**Abstract.** Synthesis of a new 2-aryl-4H-naphtho[2',3',4,5]thieno[2,3-*d*][1,3]oxazine-4,5,10-triones, 2-arylnaphtho[2',3',4,5]thieno[2,3-*d*][1,3] pyrimidine-4,5,10(*3H*)-triones, 3-phenyl naphtho[2',3', 4,5]thieno[2,3-*d*][1,3]pyrimidine-2,4,5,10(1*H*, *3H*)-tetraone and 2-thioxo-2,3-dyhydronaphth [2',3',4,5]thieno[2,3-*d*]pyrimidine-4,5,10(1H)-trione was carried out. The mechanism of 2-aryl-4H-naphtho [2',3',4,5]thieno[2,3-*d*][1,3]oxazine-4,5,10-triones formation was suggested.

**Key words:** oxazynetriones, pyrimidinetriones, pyrimidinetetraone, 2-amino-4,9-dioxo-4,9-dihydro-naphtho[2,3-b]thiophene-3-ethylcarboxilate

## 1. Introduction

Oxazine and pyrimidine derivatives show a wide spectrum of pharmacological properties. High physiological action and biological activity with a wide spectrum of action such as antimicrobial, fungicide, analgesic, tranquilizer, antitumor and others like that are relevant for them. Permanent growth of scientific interest to the derivatives of 1,4-naphthoquinone is caused by it high reactionary ability and possibility of synthesis on their basis of new various compounds with the wide spectrum of biological activity, as, for example, bacteriostatic, bactericidic [1-4] and fungicidic [5] activity, antiviral [10], antiphthisic [11, 12], antibiotic [13, 14], antimalarial effect [15], and also can be used as fungicides and insecticides [6-9], pharmacological preparations for treatment of respirator diseases [16] and others like that. Taking into account the properties of quinonic and thiophen cycles in combination with oxazine and pirymidine, it is possible to predict the widening of biological action spectrum or synergism of properties. [17-25].

This work is a continuation of scientific researches in the series of derivatives of 1,4-naphthoquinone, which have been carried out at the Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology for many years. Heterocycles on the basis of 2-amino-4,9-dioxo-4,9-dihydronaphtho[2,3-b] thiophene-3-ethylcarboxilate were unknown and un-described in literature up to the present.

The purpose of this work was synthesis of new geterocycles on the basis of 2-amino-4,9-dioxo-4,9-dihydronaphtho[2,3-b]thiophene-3-ethylcarboxilate [26], namely – oxazynetriones, pyrimidinetriones and pyrimidinetetraone.

## 2. Experimental

Melting points were measured on a Nagema melting-point apparatus and were uncorrect. $^1$H NMR spectra were recorded on Varian VXR (300 MHz) spectrometer as solutions in DMSO-$d_6$ with TMS as the internal standard. IR spectra were recorded on Specord M80 in KBr tablets.

### 2.1. Materials

*2-Amino-4,9-dioxo-4,9-dihydronaphtho[2,3-b] thiophene-3-ethylcarboxilate* was used as described [26].

*2-Arylamino-3-carbetoxynaphtho[2,3-b] thiophene-4,9-diones 2a-d.* An equimolar amount of triethylamine and 32.7 mmol of aroylchloride was added to 6.54 mmol of 2-amino-4,9-dioxo-4,9-dihydro-naphtho[2,3-b]thiophene-3-ethylcarboxilate (**1**) in dioxane at constant stirring. Reaction mixture was heated to 343–353 K during 5 h. Then the reaction mixture was evaporated, washed by water and dried.

*2-Aryl-4H-naphtho[2',3',4,5]thieno[2,3-d] [1,3]oxazine-4,5,10-triones 3a-d.* Mixture of **2a-d** (3.48 mmol), $Ph_3P$ (3.83 mmol) and $Et_3N$ (10.5 mmol) was suspended in 20 ml of absolute toluene and heated to 353 K. Tetrachloroethane was added by drops (3.83 mmol) in an absolute toluene. Reaction mixture was stirred for 30 min and then filtered. The product was evaporated in a vacuum. The residue was recrystallized from EtOH:MeCN (1:4).

*2-Arylnaphtho[2',3',4,5]thieno[2,3-d][1,3]pyrimidine-4,5,10(3H)-triones 4a-d.* Mixture of **3a-d** (5 mmol) in 20 ml of ethanol with 10 ml of concentrated ammonium hydroxide was suspended, heated for 2 h and evaporated in vacuum. The residue was heated to boiling for 30 min in 5 % water solution of KOH. Then the reaction mixture was acidified and filtered. The residue was recrystallized from ethanol.

*3-Phenyl naphtho[2',3',4,5]thieno[2,3-d][1,3] pyrimidine-2,4,5,10(1H, 3H)-tetraone5.*

The equimolar amount of phenylisocyanate was added to 6.54 mmol of 2-amino-4,9-dioxo-4,9-dihydronaphtho[2,3-b]thiophene-3-ethylcarboxilate (**1**) in pyridine at constant stirring. The reaction mixture was heated to 343–353 K during 5 h, then filtered, washed by water and dried.

*2-Thioxo-2,3-dyhydronaphth[2',3':4,5]thieno [2,3-d]pyrimidine-4,5,10(1H)-trione 6.*

The equimolar amount of benzoylisothiocyanate was added to 6.54 mmol of 2-amino-4,9-dioxo-4,9-dihydronaphtho[2,3-b]thiophene-3-ethylcarboxilate (**1**) in acetone at constant stirring. The reaction mixture was heated during 2 h. The solvent was evaporated, the residue was hydrolyzed by 5 % water solution of KOH. The reaction mixture was filtered and washed by water. The residue was dried.

The constants of obtained compounds are presented in Tables 1 and 2.

*Table 1*

**Yields and data of elemental analysis of synthesized compounds**

| № | Yield, % | Calculated<br>Found, % | | | | |
|---|---|---|---|---|---|---|
| | | C | H | N | S | Cl |
| 2a | 61 | 60.07<br>59.95 | 3.21<br>2.99 | 3.18<br>3.25 | 7.29<br>7.38 | 8.06<br>8.00 |
| 2b | 64 | 65.86<br>65.97 | 4.09<br>4.15 | 3,34<br>3.20 | 7.64<br>7.75 | |
| 2c | 72 | 58.66<br>58.78 | 3.13<br>3.02 | 6.22<br>6.34 | 7.12<br>7.01 | |
| 2d | 70 | 65.18<br>65.23 | 3.73<br>3.81 | 3,45<br>3.60 | 7.91<br>8.00 | |
| 3a | 74 | 61.00<br>59.94 | 2.05<br>2.10 | 3,56<br>3.61 | 8.14<br>8.21 | 9.00<br>8.90 |
| 3b | 75 | 67.55<br>67.71 | 2.97<br>3.02 | 3,75<br>7.02 | 8.59<br>8.40 | |
| 3c | 78 | 59.41<br>59.50 | 1.99<br>1.79 | 6.93<br>7.01 | 7.93<br>7.99 | |
| 3d | 76 | 66.85<br>66.92 | 2.52<br>2.69 | 6.90<br>7.05 | 8.92<br>8.78 | |
| 4a | 78 | 61.15<br>61.20 | 2.31<br>2.42 | 7.13<br>7.29 | 8.16<br>8.28 | 9.03<br>9.10 |
| 4b | 72 | 67.73<br>67.83 | 3.25<br>3.31 | 7.52<br>7.39 | 8.61<br>8.69 | |
| 4c | 73 | 59.55<br>65.59 | 2.25<br>4.45 | 10.42<br>5.69 | 7.95<br>12.25 | |
| 4d | 76 | 67.03<br>67.12 | 2.81<br>2.84 | 7.82<br>7.96 | 8.95<br>9.01 | |
| 5 | 72 | 64.16<br>64.22 | 2.69<br>2.76 | 7.48<br>7.41 | 8.57<br>8.53 | |
| 6 | 71 | 53.49<br>53.52 | 1.92<br>2.00 | 8.91<br>8.85 | 20.40<br>20.46 | |

*Table 2*

**Spectral data of synthesized compounds**

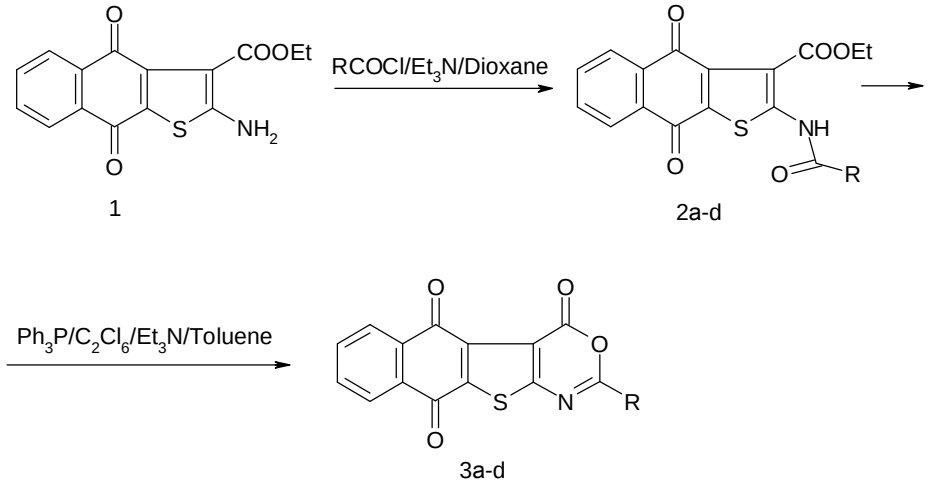
| № | Formula, mp K | $^1$H NMR (δ, ppm) | IR, cm$^{-1}$ |
|---|---|---|---|
| 2a | $C_{22}H_{14}NSO_5Cl$ 457-459 | 7,82; 7,77 (2H, td, $CH_{Ar}$), 8,23;8,09 (2H, dd, $CH_{Ar}$); 3.30(1H, s, -NH); 7.37-7.82(4H, dd, $CH_{Ar}$); 4,24-4,30(2H, q, $CH_2$); 1,35(3H, t, $CH_3$) | 1655 (C=O) |
| 2b | $C_{23}H_{17}NSO_5$ 453-454 | 7,81; 7,75 (2H, m, $CH_{Ar}$), 8,21;8,08 (2H, dd, $CH_{Ar}$); 3.30(1H, s, -NH); 7.30 (2H, m, $CH_{Ar}$); 7.03(2H, m, $CH_{Ar}$); 4,24-4,30(2H, q, $CH_2$); 2,35 (3H, s, $CH_3$); 1,35(3H, t, $CH_3$) | 3431 (NH); 1671 (C=O) |
| 2c | $C_{22}H_{14}N_2SO7$ 460 | 7,83; 7,73 (2H, m, $CH_{Ar}$), 8,23;8,08 (2H, m, $CH_{Ar}$); 3.30(1H, s, -NH); 8,0-8,11 (2H, m, $CH_{Ar}$); 8,27-8,30(2H, m, $CH_{Ar}$); 4,24-4,30(2H, q, $CH_2$); 2,35 (3H, s, $CH_3$); 1,35(3H, t, $CH_3$) | 3453 (NH); 1669 (C=O) |
| 2d | $C_{22}H_{15}NSO_5$ 452 | 7,81; 7,77 (2H, m, $CH_{Ar}$), 8,21;8,08 (2H, m, $CH_{Ar}$); 3.30(1H, s, -NH); 7,60-7,79 (5H, m, $CH_{Ar}$); 4,24-4,30(2H, q, $CH_2$); 2,35 (3H, s, $CH_3$); 1,35(3H, t, $CH_3$) | 3447 (NH); 1682 (C=O) |
| 3a | $C_{20}H_8NSO_4Cl$ 565-566 | 8,14-7,75 (4H, m, $CH_{Ar}$), 8,47;8,41 (2H, m, $CH_{Ar}$); 7,45-7,47 (2H, m, $CH_{Ar}$); | 1653 (C=O) |
| 3b | $C_{21}H_{11}NSO_4$ 563 | 8,16; 7,74 (4H, m, $CH_{Ar}$), 8,47;8,41 (2H, m, $CH_{Ar}$); 7,20-7,21 (2H, m, $CH_{Ar}$); 2,39 (3H, s, $CH_3$) | 1668 (C=O) |
| 3c | $C_{20}H8N_2SO_6$ 539-541 | 8,47;8,29 (4H, мм, $CH_{Ar}$); 8,16;7,74(4H, мм, $CH_{Ar}$); | 1669 (C=O) |
| 3d | $C_{20}H_9NSO_4$ 561 | 8,16;7,74(2H, m, $CH_{Ar}$); 8,47;8,41 (2H, m, $CH_{Ar}$); 7,33-7,52 (5H, m, $CH_{Ar}$) | 1672 (C=O) |
| 4a | $C_{20}H_9N_2SO_3Cl$ > 573 | 10,40 (1H, s, NH); 8,27-7,99 (2H, m, $CH_{Ar}$), 7.77-7.66 (2H, m, $CH_{Ar}$); 7,51-7,53 (2H, m, $CH_{Ar}$); 7,37-7,39 (2H, m, $CH_{Ar}$) | 3128(NH); 1687 (C=O) |
| 4b | $C_{21}H_{12}N_2SO_3$ > 573 | 10,40 (1H, s, NH); 8,25-7,99 (2H, m, $CH_{Ar}$), 7.90-7.68 (4H, m, $CH_{Ar}$); 7,21-7,24 (2H, m, $CH_{Ar}$); 2,05 (3H, s, $CH_3$) | 3129 (NH); 1688 (C=O) |
| 4c | $C_{20}H_9N_3SO_5$ > 300 | 10,40 (1H, s, NH); 8,25-7,99 (6H, m, $CH_{Ar}$), 7.78-7.68 (2H, m, $CH_{Ar}$); | 3124 (NH); 1663 (C=O) |
| 4d | $C_{20}H_{10}N_2SO_3$ > 573 | 10,40 (1H,s, NH); 8,27;7,99(2H, m, $CH_{Ar}$); 7.77;7.66 (2H, m, $CH_{Ar}$); 7,42-7,50 (5H, m, $CH_{Ar}$) | 3131 (NH); 1688 (C=O) |
| 5 | $C_{20}H_{10}N_2SO_4$ > 573 | 8.43 (1H, s, NH); 8,25-7,98 (2H, m, $CH_{Ar}$), 7.77-7.66 (2H, m, $CH_{Ar}$); 7,19-7,55 (5H, m, $CH_{Ar}$) | 3123 (NH); 1690 (C=O) |
| 6 | $C_{14}H_6N_2SO_3$ > 573 | 11.09 (1H, c, NH); 8,08;7,81(2H, мм, $CH_{Ar}$); 7.76;7.67 (2H, m, $CH_{Ar}$); 4.94(1H, s, NH); | 3130 (NH); 1678 (C=O) |

## 3. Results and Discussion

Synthetic potential of 2-amino-4,9-dioxo-4,9-dihydronaphtho[2,3-b]thiophene-3-ethylcarboxilate (**1**) has not been studied much. It is known that nucleophilic property of amino-group in the third position at heteroatomic enaminoesthers is very weak and needs the reagent with a high-elecrophylic center for obtaining the target products with high yields. We carried out the interaction of 2-amino-4,9-dioxo-4,9-dihydronaphtho [2,3-b]thiophene-3-ethylcarboxilate (**1**) with various arylchloranhydrides under different conditions. In the first case the reaction was carried out in the medium of pyridine at 343 K during 5–7 h. The mixture of 2-monoarylamino- and 2,2-diarylaminosubstituted-3-carbetoxynaphtho [2,3-b]thiophen-4,9-diones was got as the result of this reaction in correlation 70–78 %:22–30 %. During the reaction in dioxane with equimolar amount of triethylamine

(343–353 K, 5 h) we got 2-monoarylamino-3-carbetoxynaphtho[2,3-b]thiophen-4,9-diones with the yields of 87–98 %. The formation of 2,2-diarylaminosubstituted derivatives in this case was not observed.

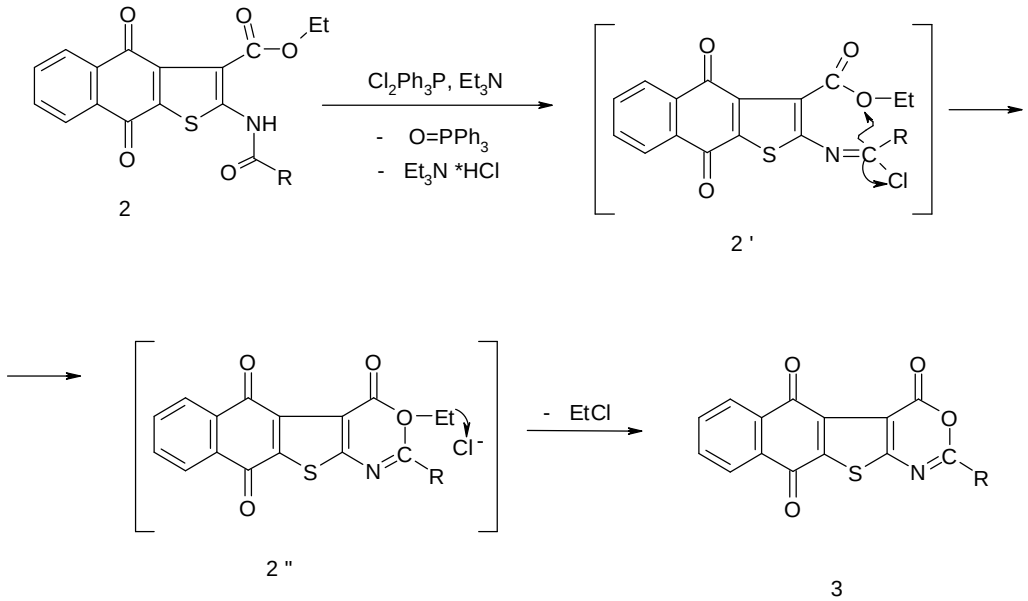
During the reaction of 2-monoarylamino-3-carbetoxynaphtho[2,3-b]thiophen-4,9-diones **(2a-d)** with dichlorotriphenylphosphorane, which appears at the interaction of triphenylphosphine with hexachloroethane, in toluene at 343 K during 2–7 h have been obtained early unknown 2-aryl-4H-naphtho[2',3':4,5]thieno[2,3-d][1,3]oxazine-4,5,10-triones **(3a-d)** (Scheme 1).




R= *p*-$ClC_6H_4$-(a); *p*-$CH_3C_6H_4$-(b); *p*-$NO_2C_6H_4$-(c); Ph-(d)

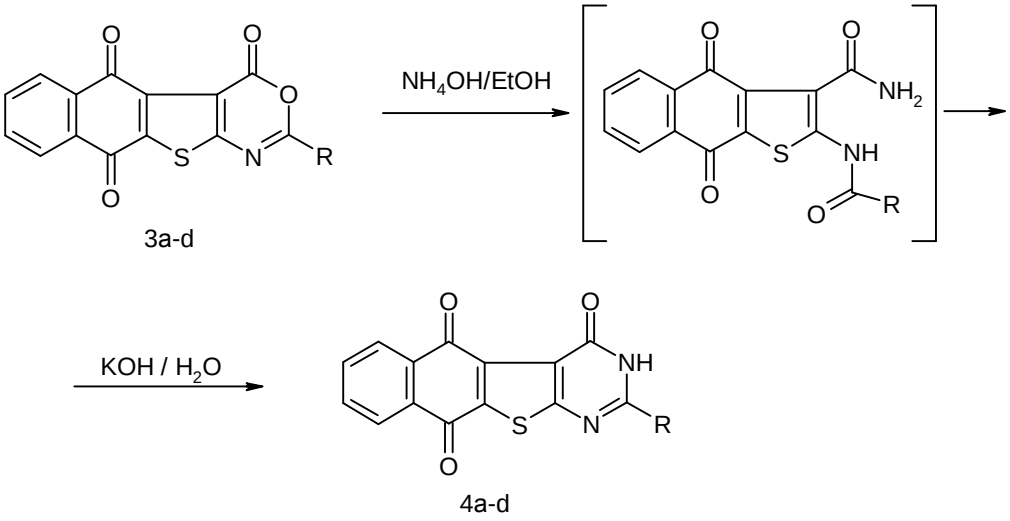
**Scheme 1**

The mechanism of compounds **(3a-d)** formation, to our opinion, is the following:

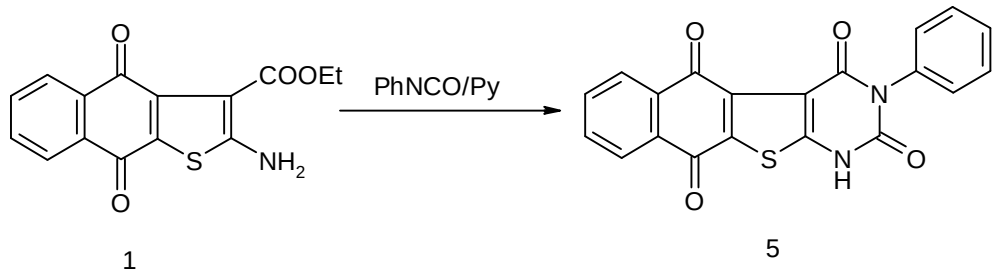



2-Arylamino-3-carbetoxynaphtho[2,3-b]thiophen-4,9-dione (**2**) at the interaction with dichlorotriphenylphosphorane in the presence of triethylamine forms imidoilchloride **(2')**. A newly obtained electrophylic carbon center is attacked by estheric etxo-group, forming thermodynamic six-membered cyclic intermediate **(2")**. The elimination of ethylchloride gives the stable oxazintrione (**3**).

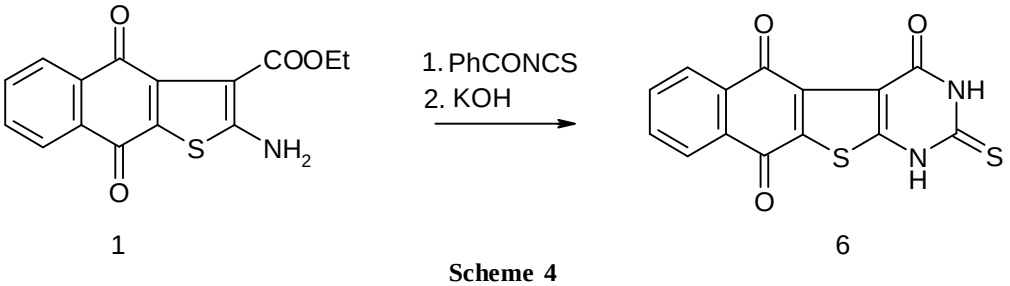
2-Aryl-4H-naphtho[2',3':4,5]thieno[2,3-d][1,3]oxazine-4,5,10-triones **(3a-d)** allow to get 2-arylnaphtho[2',3',4,5]thieno[2,3-*d*][1,3]pyrimidine-4,5,10(*3H*)-triones **(4a-d)** easily (Scheme




**Scheme 2**




**Scheme 3**




**Scheme 4**

2).Pirymidinetriones are obtained at the interaction of oxazinetriones with ammonium hydrate in ethanol at 351–353 K without the selection of intermediate compounds with the next action by 5 % solution KOH during 1 h.

The interaction of 2-amino-4,9-dioxo-4,9-dihydronaphtho[2,3-b]thiophene-3-ethylcarboxilate (**1**) with phenylisocyanate in the presence of pyridine was carried out with the formation of 3-phenylnaphtho [2',3':4,5]thieno[2,3-d][1,3]pyrimidine-2,4,5,10(1*H*,*3H*)-tetraone (**5**) (Scheme 3).

The interaction of the compound (**1**) with benzoylisothiocyanate in acetone at heating and the subsequent alkaline hydrolysis forms 2-thioxo-2,3-dyhydronaphth[2',3',4,5]thieno[2,3-*d*]pyrimidine-4,5,10(1H)-trione (**6**) (Scheme 4).

## 4. Conclusions

Thus, for the first time new heterocyclic compounds were synthesized on the basis of 2-amino-4,9-dioxo-4,9-dihydronaphtho[2,3-b]thiophene-3-ethylcarboxilate – oxazynetriones, pyrimidinetriones and pyrimidinetetraone. The mechanism of their formation is offered for 2-aryl-4H-naphtho[2',3',4,5]thieno[2,3-d] [1,3]oxazine-4,5,10-triones **(3a-d)**.

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## СИНТЕЗ КОНДЕНСОВАНИХ S-, N-ВМІСНИХ ГЕТЕРОЦИКЛІЧНИХ СИСТЕМ НА ОСНОВІ 2-АМІНО-4,9-ДІОКСО-4,9-ДИГІДРОНАФТО [2,3-b]ТІОФЕН-3-ЕТИЛКАРБОКСИЛАТУ

***Анотація.*** *Проведено синтез нових, раніше неописаних 2-арил-4Н-нафто[2',3',4,5]тієно[2,3-d][1,3] оксазин-4,5,10-трионів,2-арилнафто[2',3',4,5]тієно[2,3-d][1,3]піримідин-4,5,10(3Н)-трионів,3-фенілнафто[2',3',4,5]тієно[2,3-d][1,3]піримідин-2,4,5,10(1Н,3Н)-тетраону та 2-тіоксо-2,3-дигідронафто[2',3',4,5]тієно[2,3-d]піримідин-4,5,10(1Н)-триону. Для 2-арил-4Н-нафто [2',3',4,5]тієно[2,3-d][1,3]оксазин-4,5,10-трионів запропонований механізм їх утворення.*

***Ключові слова:*** *оксазинтріони, піримідинтріони, піримідинтетраон, 2-аміно-4,9-діоксо-4,9-дигідронафто [2,3-b]тіофен-3-етилкарбоксилат.*