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BIOLOGICAL ACTIVITY OF 5- AND 6-MEMBERED AZAHETEROCYCLES AND THEIR SYNTHESIS FROM 5-ARYL-2,3-DIHYDROFURAN-2,3-DIONES. (REVIEW)

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The biological activity of nitrogen-containing heterocycles obtained by the decyclization or recyclization of 5-aryl-2,3-dihydrofuran-2,3-diones under the action of functionalized amines and diamines has been considered.

Keywords: 5-Aryl-2,3-dihydrofuran-2,3-diones, azaheterocycles, biological activity.

5-Aryl-2,3-dihydrofuran-2,3-diones were synthesized and described in 1975 simultaneously by the Russian school of chemists under the guidance of Yu. S. Andreichikov [1,2] and Japanese chemists under the leadership of S. Murai [3]. These compounds proved to be interesting in a chemical context [4] and extremely convenient synthons enabling the synthesis of various azoles and azines with a wide spectrum of pharmacological action [5-7]. Published data on the biological activity of the conversion products of furandiones are extremely scattered and have not previously been correlated. The accent in the review is on the assessment of anti-inflammatory activity. The sequence of arranging the material in the study is traditionally linked with ring size and the number of heteroatoms in them.

BIOLOGICAL ACTIVITY OF FIVE-MEMBERED AZAHETEROCYCLES

Compounds **2-11** represented in Scheme 1 were obtained by reacting furandiones **1** with functionalized amines. The pyrrolones **2**, synthesized from furandiones **1** and the ethyl ester of 3-benzylamino-2-butenoic acid [8,9] had low toxicity (LD_{50} >1000 mg/kg) and a weak bacteriostatic action (MIC in relation to *Escherichia coli* was 1000 μg/ml, to *Staphylococcus aureus* 125-500 μg/ml). In the maximal electroshock test the anticonvulsive activity of compounds **2** subjected to screening was less than that of phenobarbital, however the analgesic action, investigated by the hot plate test, was comparable to dipyrone (defensive reflex time for **2**, R = H was 29.6 sec) [10].

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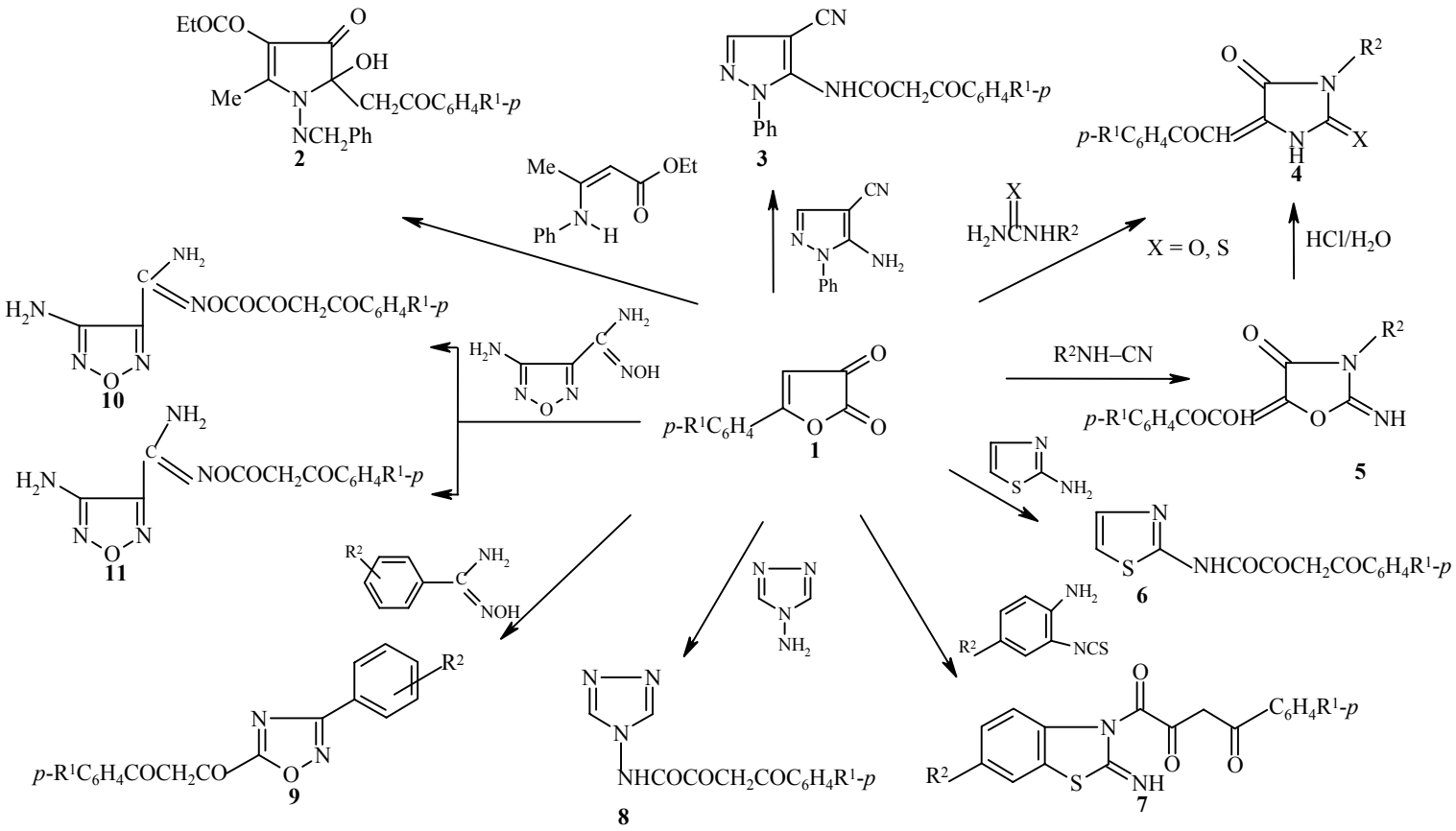
Scheme 1


EtOCO
O
OH
Me
N
CH2COC6H4R1-p
NCH2Ph
2
CN
N
N
Ph
NHCOCH2COC6H4R1-p
3
O
R2
N
p-R1C6H4COCH
N
H
X
4
Me
OEt
Ph
N
H
O
CN
N
N
Ph
NH2
X
H2NCNHR2
X = O, S
HCl/H2O
NH2
C
NOCOCOCH2COC6H4R1-p
H2N
N
O
N
10
NH2
C
NOCOCH2COC6H4R1-p
H2N
N
O
N
11
H2N
C
NOH
N
O
N
O
O
p-R1C6H4
O
1
R2NH–CN
O
R2
N
p-R1C6H4COCOH
O
NH
5
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S
NH2
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S
NHCOCOCH2COC6H4R1-p
6
R2
C
NOH
NH2
N
N
N
NH2
NH2
R2
NCS
R2
N
N
O
p-R1C6H4COCH2CO
9
N
N
N
NHCOCOCH2COC6H4R1-p
8
O
C6H4R1-p
N
O
O
R2
S
NH
7

Pyrazoles **3**, unlike pyrrolones **2**, were more toxic (LD_{50} when R^1 = Cl was 532 mg/kg, when $R^1 = OC_2H_5$, 790 mg/kg), they displayed analgesic activity (defensive reflex time 28.8 and 29.6 sec respectively) and possessed anti-inflammatory activity (edema inhibition 45.8 and 31.0% respectively). Screening did not reveal any advantage compared with amidopyrine and orthofen, which are used in medicinal practice [11].

Imidazolidinediones **4** were obtained by the reaction of furandiones with ureas and thioureas [12,13]. We also developed a method for the synthesis of these compounds (X = O) by the rearrangement of 2-iminooxazolidones **5** in hydrochloric acid medium [13]. Compounds **4** (R^1 = H, Cl, Br, R^2 = H, X = O) proved to have a suppressing action on the central nervous system, their secondary action was expressed less than for diphenylhydantoin [14]. The introduction of an aryl substituent into position 3 of the heterocycle leads to a reduction in the anti-convulsive action [15]. An analogous effect was displayed on substituting the oxygen atom at position 2 in compounds **4** by a sulfur atom [16].

Iminooxazolidones **5** were synthesized by the reaction of furandiones with unsubstituted and monosubstituted cyanamides [17,18]. These compounds possess a wide spectrum of action and were investigated for antimicrobial, antiviral, anti-inflammatory, analgesic, anticonvulsive [15,19], and pesticidal activity [20]. Their pharmacological activity has been considered in a review [21]. Later investigations of compounds of this type (such as with $R^1 = CH_3$, R^2 = H) revealed the presence of an antihypoxic effect in addition to anti-inflammatory and analgesic activity [22]. It was shown by experiments *in vivo* that iminooxazolidones **5** when applied *per os* were rearranged in the acidic medium of the stomach into imidazolidinediones **4** (X = O), which leads to loss of the anti-inflammatory action [15,19]. The need to use acid-stable protective capsules and films restricts the further study of these highly active compounds.

The method of synthesis of amides of aroylpyruvic acids obtained from the reaction of furandiones with arylamines [23] was extended to the preparation of heterylamides of aroylpyruvic acids [24]. The heterylamide **6** (R^1 = Br) containing a thiazole ring showed inhibition of inflammation by 39.1% [24,25]. The toxicity of this compound was less than 600 mg/kg. In difference to alkylamides [26,27], the heterylamides of aroylpyruvic acids did not show anticonvulsive action [24].

Pharmacological screening of iminothiazolines **7** for anti-inflammatory and analgesic activity in the carrageenin model of inflammation and in the hot plate test respectively, showed inhibition of inflammation at R^1 = H, $R^2 = CO_2C_2H_5$ of 39%, at R^1 = H, $R^2 = SO_2NH_2$ of 40%, and at $R^1 = CH_3$, $R^2 = SO_2NH_2$ of 48%, and also suppression of defensive reflexes in the range 19.6-24.5 sec. The toxicity of these compounds was 1000-1500 mg/kg. The analogous properties for the drug voltaren were 64.1%; 20.2 sec, 380 mg/kg. This suggests the need to search for anti-inflammatory activity in this series [28,29].

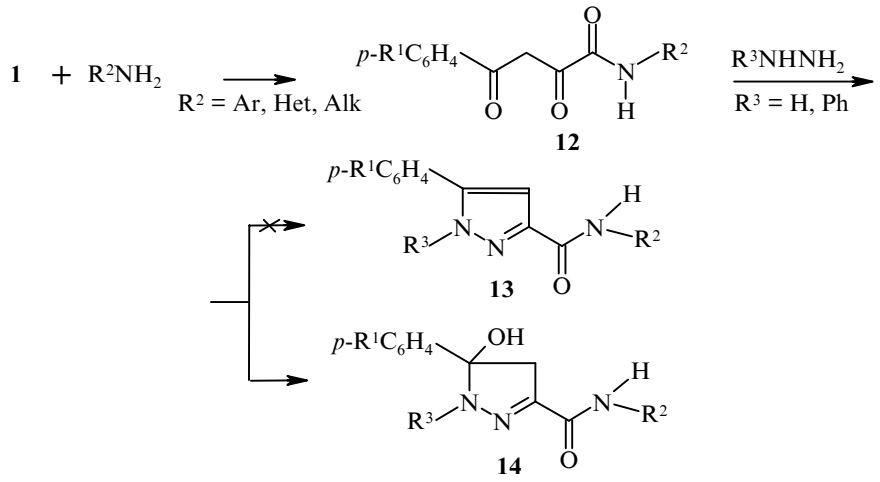
The triazolamides **8** showed antimicrobial activity comparable to the activity of ethacridine lactate [30]. The amide with $R^1 = CH_3$ causes inhibition of exudation by 30.3% which is two thirds of the activity of orthophen [30].

Derivatives of 1,2,4-oxadiazoles **9** were synthesized by the reaction of furandiones with arylamidoximes [31,32]. Investigation of the activity showed that compounds with $R^1 = CH_3$, R^2 = H suppress the activity of *Escherichia coli* and *Staphylococcus aureus* at dilutions of 1 : 2000 and 1 : 16000 respectively. Compounds with $R^1 = CH_3$, $R^2 = N(CH_3)_2$ increase the defensive reflex time twofold and suppress the development of acetate spasms by 46%, which indicates the expression of an analgesic effect. The closely related compounds with R^1 = H, $R^2 = N(CH_3)_2$ express the analgesic effect weakly and the anti-inflammatory action predominates (edema inhibition was 50%) which indicates the selective action of these compounds on the organism [33].

Depending on the reaction conditions O-aroylpyruvoyl derivatives **10** and O-aroylacetyl derivatives **11** are obtained on acylation of 4-amino-1,2,5-oxadiazole-3-carboxamidoxime with furandiones. Both types of compound proved to have low toxicity (LD_{50} >1000 mg/kg). The analgesic effect was expressed more for compounds **11** (defensive reflex time at R^1 = H was 20.3 sec, $R^1 = CH_3$, 14.8 sec, R^1 = Cl, 19.5 sec) and was comparable to voltaren (20.2 sec). In spite of the structural similarity of compounds **10** and **11** the first displayed no analgesic, only anti-inflammatory action, however it was expressed somewhat more weakly than for voltaren (when R^1 = H, 42%, when $R^1 = CH_3$, 50.2%, voltaren 64.1%) [34].

Until recently the pyrazolecarboxamides obtained by the reaction of aroylpyruvic acid amides **12** (products of the fission of the furandione ring with amines) with hydrazines were allotted the structure **13** [25]. It was since established that they have the structure **14** [35].

Scheme 2



The anti-inflammatory activity of both the initial amides **12** [25] and the pyrazolecarboxamides **14** [25] was discovered by testing on carrageenin inflammation. The analgesic activity of the latter was less than that of amidopyrine. Screening for anticonvulsive activity by the maximal electroshock test at a dose of 300 mg/kg did not reveal this activity for these compounds [25]. Antimicrobial tests on compound **14** showed higher activity towards *St. aureus* than towards *E. coli* depending on the character of the substituents in the benzene ring [36].

BIOLOGICAL ACTIVITY OF SIX-MEMBERED HETEROCYCLES WITH ONE OR TWO NITROGEN ATOMS

Pyridine amides **15** and **16** were obtained by the decyclization of the furan ring of compound **1** with 2- and 3-aminopyridines. Like the heterylamides **6** and **8** compounds **15** and **16** proved to have low toxicity (LD_{50} = 600-1600 mg/kg). Both the indicated types of compound were exceeded in analgesic activity by amidopyrine but the substituents in the benzene and pyridine rings did not influence the character of their action. The anti-inflammatory effect of compounds **15** and **16** depended significantly on their substituents, electron-donating groups afforded an increase in activity but electron-withdrawing groups reduced it.

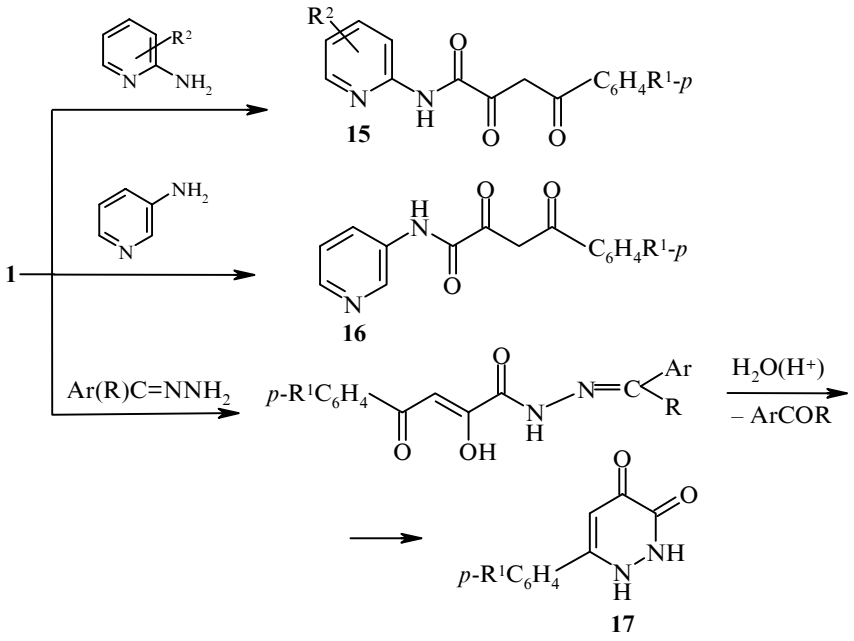
The pyridine amides **15** and **16** possess moderate bacteriostatic action, the latter were more active against *St. aureus* than *E. coli.* [37].

The synthesis of pyridazinediones **17**, possessing anticonvulsive properties, proceeds in two stages. The first is fission of the furan ring of compound **1** by arylidenehydrazines, and the second is the cyclization of the resulting hydrazides of aroylpyruvic acids to the final products [38].

The methods of obtaining piperazine and quinoxaline derivatives by the recyclization of furandiones by aliphatic, aromatic, and heterocyclic diamines are shown in Scheme 4.

Derivatives of piperazinone **18** were obtained by boiling furandiones with diaminoglyoxime in dioxan [32,39]. Anti-inflammatory activity was revealed for compounds with $R^1 = CH_3O$ which grew in proportion to the test dose. The absence of analgesic, anticonvulsive, and antitremor action enabled the possible specificity of anti-inflammatory action to be proposed for this substance [40]. Carrying out the reaction of furandiones with

Scheme 3



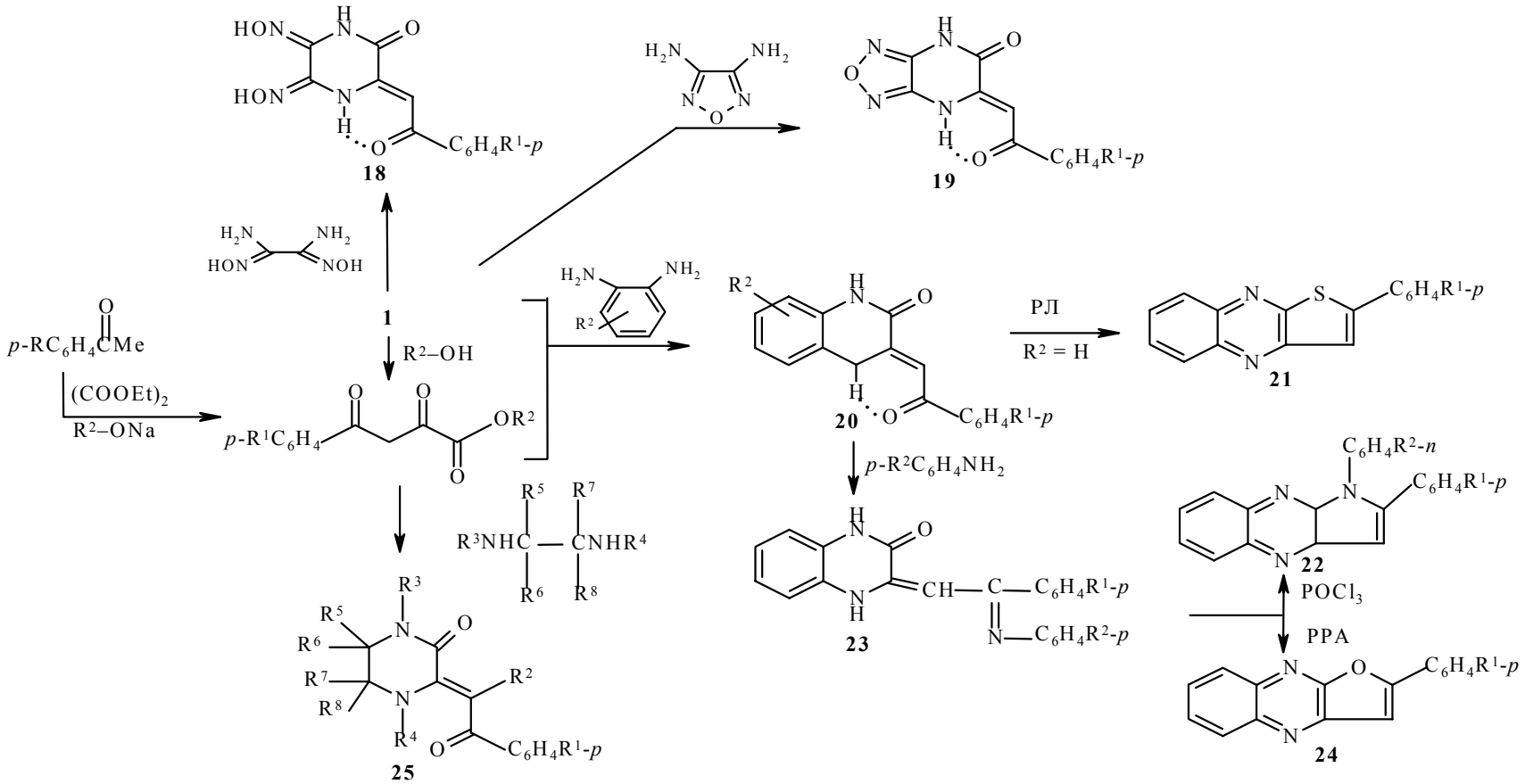
diaminoglyoxime at room temperature leads to the formation of bis(O-aroylpyruvyl) derivatives of diaminoglyoxime, which also possesses an anti-inflammatory effect [41]. The presence in compound **19** (R^1 = H) of a furan ring condensed with piperazine leads to a change of the anti-inflammatory to a tranquillizing effect which surpasses the activity of elenium [42].

The quinoxalone **20** (R^1 = CH_3, R^2 = 7-CN) obtained by the reaction of the appropriate furandione and phenylenediamine showed anti-inflammatory action somewhat lower than that of amidopyrine. Its regioisomer, synthesized from aroylpyruvic acid methyl ester and having a cyano group in position 6, surpassed amidopyrine twofold [43].

Cyclization of compound **20** (R^1 = R^2 = H) into compound **21** under the action of the Lavesson reagent (LR) leads to disappearance of anti-inflammatory activity from compound **21** and the development of antimicrobial action with maximal MIC 120 mg/kg [44]. The pyrroloquinoxalines **22** obtained by the cyclization of aryliminoquinoxalones **23** [45] showed analgesic action which was approximately 50% of that of amidopyrine [46]. The furoquinoxalines **24** obtained by the cyclization of compound **23** by the action of polyphosphoric acid [46], unlike the pyrroloquinoxalines **22**, displayed anti-inflammatory action in the agar and carrageenin tests. Suppression of the inflammatory reaction took place both in the early and later stages and enabled the authors to recommend these compounds for the treatment of arthritis [49]. It should be noted that the furoquinoxalines **24** may also be obtained directly by the cyclization of quinoxalines **20** under the action of $POCl_3$ or PCl_5 [47,48].

When synthesizing piperazinones **25** by the interaction of furandiones with ethylenediamine a mixture is often formed of products difficult to identify. Because of this esters of aroylpyruvic acids, obtained by opening the furan ring with alcohols, and not the actual furandiones themselves are used in the reaction [50]. The esters were also obtained by Claisen condensation of acetophenones with diethyl oxalate [51]. About 50 compounds **25** were synthesized [52-60]. Study of their acute toxicity showed that this was low. The anti-inflammatory effect depends on the character of the substituent at position 3 of the heterocycle. Compounds with aryl substituents display a higher effect than compounds with alkyl substituents. The same dependence is observed in the case of 1 and 6 substituted piperazinones. All the compounds **25** studied show a moderate analgesic effect, which also depends on the character of the substituents in positions 1, 3, and 6. Modification of the

Scheme 4

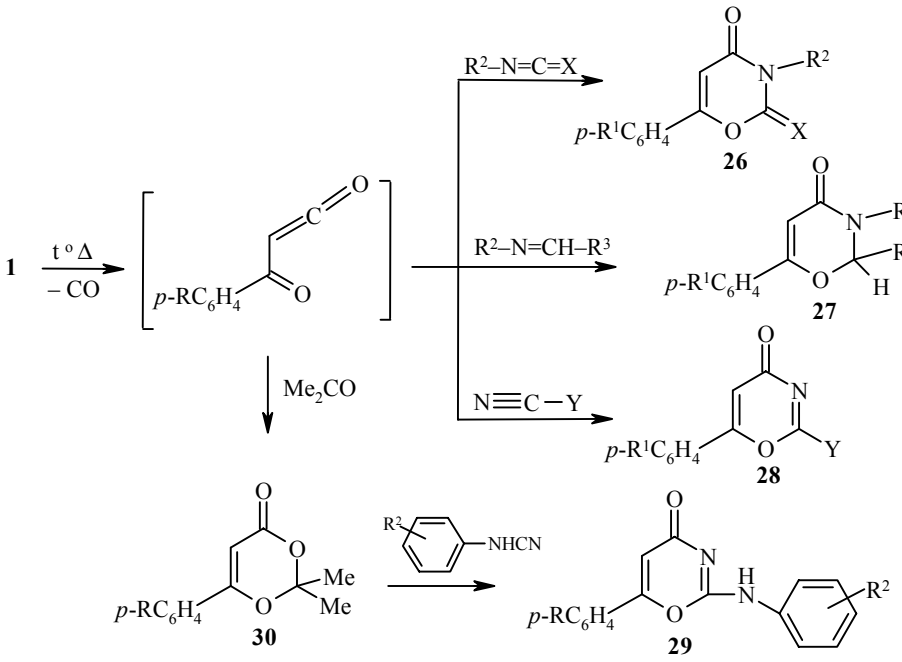


structure of the **25** molecule revealed the most active anti-inflammatory compound ($R^1 = CH_3$, $R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = R^8 = H$), which passed extended pharmacological and clinical testing under the name mefepyron [61]. The low toxicity and absence of negative action on the gastrointestinal tract are essential advantages for this compound compared with preparations in use [62].

BIOLOGICAL ACTIVITY OF SIX-MEMBERED HETEROCYCLES CONTAINING NITROGEN AND OXYGEN ATOMS

The synthesis is shown in Scheme 5 of 1,3-oxazin-4-one derivatives **26-29** from furandiones and reactants containing multiple carbon–nitrogen bonds, *viz*. carbodiimides [63], ketenimines [64], Schiffs' bases [65,66], and N-cyanoamino compounds [67-69].

Scheme 5



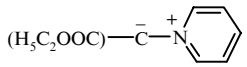
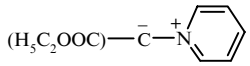
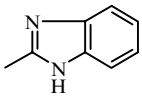
With furandiones the latter form oxazolidones **5**, consequently their reaction with dioxinones **30** is used to obtain compounds **29** [70].

The data of anti-inflammatory and analgesic activity of compounds **28** (see Table 1) indicate that oxazinones **28** containing aminoformamidine substituents display the greatest anti-inflammatory activity. They exceed significantly the activity of 2-alkylamino and arylamino oxazinone derivatives. The greatest analgesic effect, surpassing that of amidopyrine, was shown by oxazinones containing $N(CH_2CH{=}CH_2)_2$ and $N{=}CHNHC_6H_4CH_3$-*p* groups as substituents.

All the oxazinones subjected to screening had low or moderate toxicity, their LD_{50} values were from 450 to 1500 mg/kg.

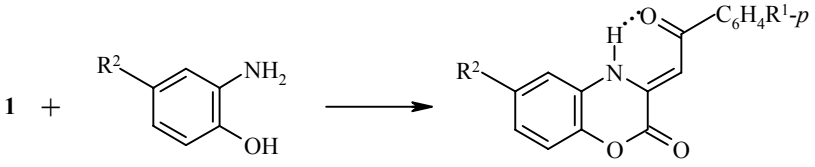
Compounds with tranquillizing activity in addition to the anti-inflammatory and analgesic activity were discovered among this series. For example, oxazinone **28** [R^1 = H, Y = $N(CH_3)C_6H_5$] depresses spontaneous motor activity in rats, potentiates the hypnotic effect of hexenal and the analgesic effect of amidopyrine, and depresses the orientating–investigating reflex in mice [80].

TABLE 1. Results of Initial Investigations of Anti-inflammatory and Analgesic Properties of 2-Substituted 6-Aryl-1,3-oxazin-4-ones **28**

R^1	Y	Anti-inflammatory activity, % edema reduction	Analgesic activity, defensive reflex time, sec	Literature
CH_3O	$N(C_2H_5)_2$	—	18.4	[70, 72, 73]
CH_3	$NHC(CH_3)_3$	—	Inactive	[15]
H	$N(CH_2CH_2CN)_2$	—	22.1	[70, 73]
H	$N(CH_2–CH=CH_2)_2$	—	46.7	[71]
H	$N(CH_2CH_2CH_2CH_3)_2$	—	13.8	[72]
H	NHC_6H_5	5.5	25.9	[73]
CH_3	NHC_6H_5	48.1	19.2	[73]
Cl	NHC_6H_5	31.6	29.1	[73]
C_2H_5O	NHC_6H_5	23.3	41.0	[73]
H	$NHC_6H_4CH_3$-*o*	39.0	21.3	[73]
CH_3	$NHC_6H_4CH_3$-*o*	38.0	19.0	[73]
H	$N=CHNHC_6H_4CH_3$-*p*	—	44.5	[74, 75]
H	$N=CHNHC_6H_5$	54.1	—	[74, 76]
CH_3	$N=CHNHC_6H_4CH_3$-*p*	58.6	—	[74, 77]
C_2H_5O	$N=CHNHC_6H_4CH_3$-*p*	55.0	—	[74]
CH_3	$N=CHNHC_6H_5$	55.0	—	[74]
Cl	$NHC(=NH)NHC_6H_5$	—	16,0	[70, 73]
H		39.0	21.3	[7, 73, 78]
CH_3		43.0	23.0	[7, 78]
CH_3		25.0	20.8	[9, 69, 73]
H		—	17.0	[73, 79]

Somewhat weaker tranquillizing activity was expressed by compound **27** ($R^1 = CH_3O$, $R^2 = R^3 = C_6H_5$) [81]. The oxazinones **27** (R^1 = H or Cl, $R^2 = CH_2COOK$, R^3 = H) displayed marked antiaggregating activity towards thrombocytes, close to the activity of papaverine, and the indicated compounds were 8.1 to 10.4 times less toxic than the comparative standard [82-84].

Methods of synthesis of the known 3,4-dihydro-2H-benzo[*b*]-1,4-oxazin-2-ones **31** were improved in [85], and it was reported that these compounds possess marked bacteriostatic and antitumor activity.



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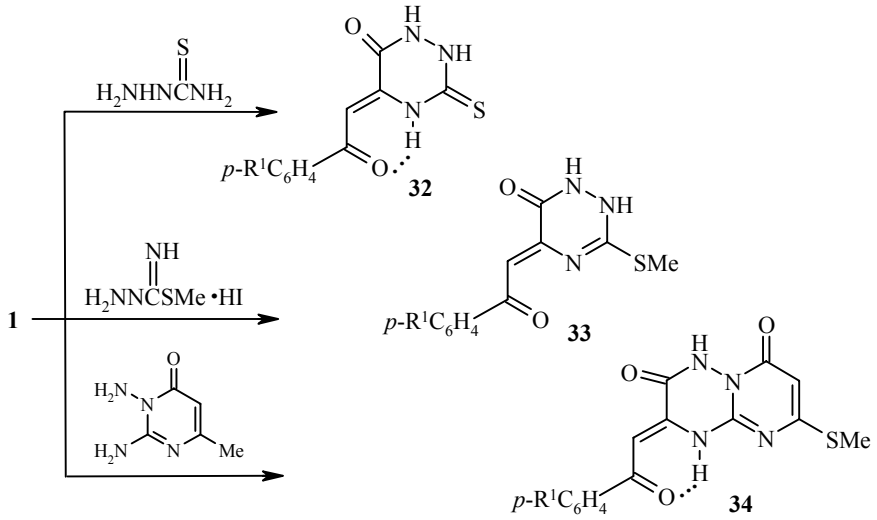
The anti-inflammatory activity of these compounds was shown previously [86].

BIOLOGICAL ACTIVITY OF SIX-MEMBERED HETEROCYCLES CONTAINING THREE HETEROATOMS

Routes for the synthesis of triazinones **32-34** described in [87-89] are shown in Scheme 6.

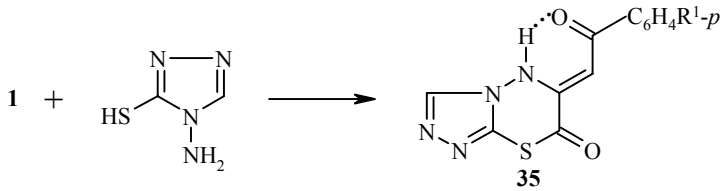
Compound **32**, shown in Scheme 6, displays weak antibacterial and anti-inflammatory action [87-90]. Results of testing triazinones **33** (R^1 = Cl, Br, NO_2) for these forms of activity showed an antistaphylococcal effect comparable to the activity of ethacridine lactate [88].

Scheme 6



Triazinones **34** did not show anticonvulsive action but had a marked anti-inflammatory effect with inhibition of exudation 30-41%. The defensive reflex time was
15-25 sec. These results are 1.5 to 2 times less than the corresponding activity of orthofen and amidopyrine [90,91].

The interaction of furandiones with 4-amino-3-mercapto-1,2,4-(4H)-triazole leads to the formation of derivatives of 1,2,4-triazolo[3,4-*b*]-1,3,4-triazin-3-ones **35** [30].



Compound **35** (R^1 = Br) displayed anti-inflammatory activity (inhibition of inflammation by 41%), somewhat exceeded by orthofen (47%). The antimicrobial activity of these compounds is comparable to the activity of ethacridine lactate [30].

The data considered show that continuing the study of the biological properties of the conversion products of 5-aryl-2,3-dihydrofuran-2,3-diones may lead to the creation of effective medicinal agents. Especially promising in this respect is the search for new analogs of the anti-inflammatory preparation mefepyrone. The recently accomplished synthesis of 4- [93,94] and 5-heteryl-2,3-dihydrofuran-2,3-diones [95,96] enables the preparation from them of previously inaccessible azaheterocycles, which will undoubtedly give new impetus to the investigation of the biological activity of these products.

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