# SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3-(5-ARYL-3-OXO-2,3-DIHYDRO-2-FURANYL)-1,2,3,4-TETRAHYDRO-2-QUINOXALONES AND 2-AROYLMETHYLENEQUINOXALINES*

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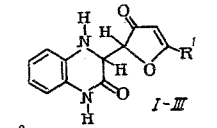
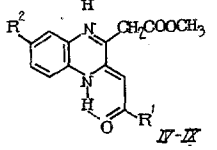
It is known that the 3-substituted 2-quinoxalones, including derivatives of 3-aroylmethylene-1,2,3,4-tetrahydro-2-quinoxalones [1, 19], possess anti-tuberculoses [6, 14], anti-inflammatory [17, 19], analgesic [13, 19, 31], hypothermal [16, 19], spasmolytic [13, 31], antidepressant [24], and tranquilizing [15, 19] action and are also widely utilized in the synthesis of physiologically active compounds [3, 19, 31]. Biological activity is also found in the structurally close 2-(1'adamantyl)amino-3-aroylmethylene-3,4-dihydroquinoxalines [2]. Interest is presented by the search for biologically active substances among both derivatives of heterylquinoxalones, including those having the active synthone 3-furanone [9], and in the series of 3-substituted 2-aroylmethylenequinoxalines. In this connection, we obtained the 3-(5-aryl-3-oxo-2,3-dihydro-2-furanyl)-1,2,3,4-tetrahydro-2-quinoxalones (I)-(III) by the reaction of 5-aryl-2-methoxycarbonylmethylene-2,3-dihydro-3-furanones with o-phenylenediamine in benzene [8, 21].

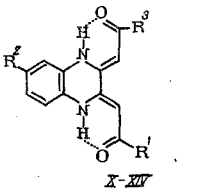
The performing of the reaction in the presence of hydrochloric acid in methanol (method A) leads to the recyclization of the methylenefuranones with the formation of other products –



I-III



IV-IX



X-XIV

$R^1$=$C_6H_4X$-4, where X=H (I, IV, IX—XIV), $CH_3$ (II, V), $CH_3O$ (VI), Br (VII), Cl (III, VIII);
$R^2$=H (IV—VIII, X—XIII), $NO_2$ (IX, XIV); $R^3$=$C_6H_4Y$-4, where Y=H (X, XIV), Br (XI), Cl (XII), $NO_2$ (XIII)

the 2-aroylmethylene-3-methoxycarbonylmethyl-1,2-dihydroquinoxalines (IV)-(VIII) [4, 8]. These compounds and the quinoxaline (IX) were also isolated as a result of the recyclization of the 5-aryl-2-hydroxy-2-methoxycarbonylmethyl-2,3-dihydro-3-furanones by the action of o-phenylenediamine or 4-nitro-1,2-phenylenediamine (method B) with yields of 65-87%.

The two aroylmethylene fragments were successfully introduced into the quinoxaline molecule by the interaction of o-phenylenediamine with the structurally close 5-aryl-2-aroylmethylene-2,3-dihydro-3-furanones (method C). The reslting 2,3-bis(aroylmethylene)-1,2,3,4-tetrahydroquinoxalines (X)-(XIV) were also obtained by the heterocyclization of 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-diones by the action of o-phenylenediamine or 4-nitro-1,2-

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TABLE 1. Physicochemical and Spectral Characteristics of 3-Substituted 2-Aroylmethylenequinoxalines (IX)-(XIV) and 2-p-Bromophenylquinoxaline (XV)

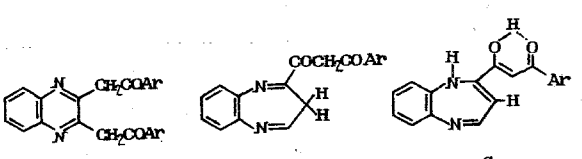
| Compound | Method of synthesis | Yield, % | mp, °C | Empirical formula | IR spectrum, ν, $cm^{-1}$, crystals | PMR spectrum, δ, ppm, $CDCl_3$ |
|---|---|---|---|---|---|---|
| IX | B | 75 | 188—189 | $C_{19}H_{15}N_3O_5$ | 1725 ($COOCH_3$), 1590—1615 (CO chelate, Ar) | 3,81s (3H, $OCH_3$), 4,63s (2H, $CH_2$), 6,42s (1H, CH), 7,33s (1H, NH), 750—8,05m (8H, $C_6H_5$, $C_6H_3$) |
| X | D | 94 | 212—213[a] | $C_{24}H_{18}N_2O_2$ | 1582—1597 (CO chelate, Ar)[b] | 6,44s (2H, 2CH), 7,15sh(2H, 2NH), 7,40—7,95m (14H, $2C_6H_5$, $C_6H_4$) |
| XI | C<br>D | 59<br>78 | 201—202 | $C_{24}H_{17}BrN_2O_2$ | 1580—1595 (CO chelate, Ar) | 6,47s (1H, CH), 6,52s(1H, CH), 7,20sh(2H, 2NH), 7,55—8,00m (13H, $C_6H_5$, $2C_6H_4$) |
| XII | D | 86 | 205—206 | $C_{24}H_{17}ClN_2O_2$ | 1585—1595 (CO chelate, Ar) | 6,96s (1H, CH), 7,12s(1H, CH), 7,35sh(2H, 2NH), 7,55—8,30m (13H, $C_6H_5$, $2C_6H_4$)[c] |
| XIII | C<br>D | 63<br>67 | 220—221 | $C_{24}H_{17}N_3O_4$ | 1580—1593 (CO chelate, Ar) | 7,02s (1H, CH), 7,12s(1H, CH), 7,70—8,05m (13H, $C_6H_5$, $2C_6H_4$), 8,43sh(2H, 2NH)[c] |
| XIV | D | 82 | 214—215 | $C_{24}H_{17}N_3O_4$ | 1575—1590 (CO chelate., Ar) | 6,95s (1H, CH), 7,05s (1H, CH), 7,43sh(2H, 2NH), 7,50—8,18m(13H, $C_6H_5$, $2C_6H_4$)[c] |
| XV | C | 30 | 138—139[d] | $C_{14}H_9BrN_2$ | 1585, 1605 (Ar, C=N) | 7,76—8,32m (8H, $2C_6H_4$), 9,48s (1H, $C^3H$) |

[a]mp 206-207°C [29]. [b]In the solution of $CHCl_3$: 2353 $cm^{-1}$ (NH), 1543 $cm^{-1}$ (CO chelate) [29]. [c]The spectra were taken in DMSO-$D_6$. [d]mp 136-137°C [22].

phenylenediamine (method D). AS a result of the reaction of 2-p-bromobenzoylmethylene-5-phenyl-2,3-dihydro-3-furanone with o-phenylenediamine, an insignificant yield of 2-p-bromophenylquinoxaline (XV) was obtained besides the compound (XI). The formation of (XV) is not unexpected since, judging from the literature data, analogous compounds were obtained by the action of o-phenylenediamine on 1,2-diaroylethylenes [11, 12].

The physicochemical and spectral characteristics of the 2-quinoxalones (I)-(III) are presented in the work [8]; those of the 2-aroylmethylenequinoxalines (IV)-(VIII), obtained by the method A, are presented in the works [4, 8], and those of the compounds (IX)-(XIV) are presented in the Table 1. The structure of the substances obtained was confirmed by the data of the UV, IR, and PMR spectroscopy, and of the mass spectrometry and the elemental analysis.

The band of the stretching vibrations of the carbonyl groups of the aroylmethylene fragments at 1575-1597 $cm^{-1}$ in the IR spectra of the 2,3-bis-(aroylmethylene)-1,2,3,4-tetrahydroquinoxalines (X)-(XIV) (Table 1) occurs in the low-frequency region; this is caused by the formation of the H-chelate ring with the intramolecular hydrogen bond between the carbonyl oxygen atoms and the hydrogen atoms of the amino group of the quinoxaline. That fact, as well as the presence of signals of the methine protons of the aroylmethylene fragments at 6.44-7.12 ppm in the PMR spectra of the compounds (X)-(XIV), and the absence of the signals of the $CH_2$ groups permits a rejection of the tautomeric form of the 2,3-bis-(aroylmethyl)quinoxalines (A), which was previously given to the products of the reaction of 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-diones, having the same substituents in the benzene rings or 2-(p-halogenobenzoylmethylene)-5-n-halogenophenyl)-2,3-dihydro-3-furanones with o-phenylenediamine [25, 26, 28]. For the same reasons, the compounds obtained cannot have the isomeric structure of 4-aryl-2-aroylacetyl-3H-1,5-benzodiazepines (B) [23]. The mass spectrum of the compound (XI) lacks the peaks of benzonitrile (103), p-bromobenzonitrile (183), and the benzoylacetyl (147) and p-bromobenzoylacetyl (227) ions, but has intense peaks of the benzoyl (105) and p-bromobenzoyl (185) ions, which cannot be described starting from the alternative structure of 1H-1,5-benzodiazepines (C)




A B C

TABLE 2. Antimicrobial Activity of the Compounds (I)-(XVIII)

| Compound | Minimum inhibitory concentration, MIC, μg/ml | |
|---|---|---|
| | E. coli M17 | S. aureus P-209 |
| I | 1000 | 500 |
| II | Inactive | 1000 |
| III | 500 | 500 |
| IV | 1000* | 500* |
| V | 500 | 250 |
| VI | 1000 | 1000 |
| VII | Inactive | 1000 |
| VIII | 1000 | 500 |
| IX | Inactive | Inactive |
| X | 1000 | 1000 |
| XI | 1000 | 1000 |
| XII | 1000 | 500 |
| XIII | Inactive | 1000 |
| XIV | 1000 | 1000 |
| XV | Inactive | Inactive |
| XVI | 1000 | 500 |
| XVII | Inactive | 500 |
| XVIII | 1000 | 500 |
| Mercury dichloride | 1000 | 1000 |
| Ethacridine lactate | 2000 | 500 |

*The data are presented in the work [4].

## EXPERIMENTAL (CHEMICAL)

The IR spectra of the compounds synthesized were taken on the UR-20 spectrometer using a paste in mineral oil. The UV spectra were obtained on the SF-26 spectrophotometer for the $1 \cdot 10^{-5}$ M solutions of the compounds in ethanol. The PMR spectra were recorded on the RYa-2310 instrument (60 MHz) in DMSO-$D_6$ and $CDCl_3$; the internal standard was HMDS. The mass spectra were obtained on a Varian MAT-311 instrument using the regime of direct input, the emission current of 1000 mA, the energy of the ionizing electrons of 70 eV, and the vaporizer temperature of 95 and 120°C. The monitoring of the course of the reaction, as well as the determination of the purity of the compounds, was performed on plates of Silufol UV-254 in the 3:2 system of benzene–ether and the 10:9:1 system of benzene–ether–acetone; plates were developed with iodine or examined in UV light.

The characteristics of the compounds obtained for the first time are presented in Table 1. The data of the elemental analysis correspond with the calculated data.

2-Benzoylmethylene-3-methoxycarbonylmethyl-6-nitro-1,2-dihydroquinoxaline (IX). To the solution of 1.24 g (5 mmole) of 2-hydroxy-2-methoxycarbonylmethyl-5-phenyl-2,3-dihydro-3-furanone [5, 9] in 100 ml of methanol is added, with stirring, 0.76 g (5 mmole) of 4-nitro-1,2-phenylenediamine; the mixture is boiled for 20 min (method B). The residue is filtered off and recrystallized from acetonitrile.

2,3-Bis-(aroylmethylene)1,2,3,4-tetrahydroquinoxalines (X)-(XIV). The mixture of 5 mmole portions of the 5-aryl-2-aroylmethylene-2,3-dihydro-3-furanones [9] and o-phenylenediamine (method C) or the 1,6-diaryl-3,4-dihydroxy-2,4-hexadiene-1,6-diones [9, 25] and o-phenylenediamine or 4-nitro-1,2-phenylenediamine (method D) is boiled in 100-150 ml of ethanol for 10-40 min with monitoring by TLC. The residue is filtered off and recrystallized from ethanol, acetonitrile, or ethyl acetate. The residue after the evaporation of the solvent is treated analogously.

2,3-Bis-(benzoylmethylene)-1,2,3,4-tetrahydroquinoxaline (X). The UV spectrum [λ, nm (log ε)] is as follows: 212 (3.26), 313 (2.95), 427 (3.01), 451 (2.97), and 484 (2.94). The mass spectrum at 120°C, given as the m/z (I, %), is presented for the 10 most intense peaks: 366 (31) $M^{1+}$, 338 (7) $M - CO^{1+}$, 264 (9) $M - C_6H_4CN^{1+}$, 262 (24), 261 (100), $M - C_6H_5CO^{1+}$, 247 (7) $M - C_6H_5COCH_2^{1+}$, 105 (91) $C_6H_5CO^{1+}$, 97 (7) $C_6H_5N_2^{1+}$, 77 (18) $C_6H_5^{1+}$, and 69 (16) $O{\equiv}C{-}CH{=}C{=}O^{1+}$.

2-p-Bromobenzoylmethylene-3-benzoylmethylene-1,2,3,4-tetrahydroquinoxaline (XI). The UV spectrum [λ, nm (log ε)] is as follows: 216 (3.40), 315 (3.26), 429 (3.36), 463 (3.25), and 488 (3.24). The mass spectrum at 95°C, given as the m/z, is as follows ($^{81}Br$ peaks are presented for the bromine-containing ions): 446 $M^{1+}$, 418 $M - CO^{1+}$, 341 $M - C_6H_5CO^{1+}$, 262 M –

TABLE 3. Antiinflammatory and Analgesic Activity of Some Synthesized Compounds

| Compound | Dose, mg/kg | Antiinflammaotry activity | | Analgesic activity. Reflex time at different times after application of the component | | | |
|---|---|---|---|---|---|---|---|
| | | mean increment in the size of the rat paw, % referred to the initial | inhibition of the exudation, % referred to the control | 0.5 h | 1.0 h | 2.0 h | 3.0 h |
| II | 50 | 75,6 | +28,0 | 9,8 | 11,6 | 11,7 | 9,6 |
| | 150 | 60,8 | +42,1 | 17,7 | 16,1 | 16,2 | 14,4 |
| IV | 50 | — | — | 17,8 | 16,8 | 18,2 | 15,5 |
| IX | 50 | 46,5 | +49,9 | 14,1 | 11,1 | 12,4 | 11,8 |
| X | 50 | 82,6 | +11,0 | 15,6 | 14,3 | 13,9 | 12,4 |
| XVI | 50 | 125,4 | —35,1 | 18,2 | 13,6 | 14,2 | 13,0 |
| XVIII | 50 | 77,1 | +17,0 | 11,8 | 10,5 | 11,1 | 7,7 |
| Control – 2% starch mucilage | — | 92,8 | — | 10,2 | 12,0 | 11,6 | 11,6 |
| Amidopyrine | 50 | —* | —* | 13,6 | 11,5 | 16,8 | 14,2 |
| | 100 | 42,0 | +60,0 | 27,6 | 18,6 | 17,7 | 14,1 |
| Ortofen | 10 | 38,8 | +58,2 | 17,2 | 17,4 | 13,8 | 12,5 |

*The preparation is inactive at the dose of 50 mg/kg.

4-$BrC_6H_4CO^+$, 185 4-$BrC_6H_4CO^+$, 157 4-$BrC_6H_4^+$ or M – 4-$BrC_6H_4CO$ – $C_6H_5CO^+$, 130 quinoxaline$^+$, 105 $C_6H_5CO^+$, and 77 $C_6H_5^+$.

2-p-Bromophenylquionoxaline (XV). The mixture of 1.78 g (5 mmole) of 2-p-bromobenzoylmethylene-5-phenyl-2,3-dihydro-3-furanone and 0.53 g (5 mmole) of o-phenylenediamine (method C) is boiled in 100 ml of ethanol for 20 min. The residue is filtered off and recrystallized from acetonitrile; the compound (XI) is obtained. The residue after the evaporation of the solvent is recrystallized from hexane; the compound (XV) is obtained. The mass spectrum of (XV) at 120°C, given as the m/z (I, %), where the peaks of $^{81}Br$ are presented, is as follows: 286 (100) $M^+$, 259 (19) M – $HCN^+$, 205 (28) M – $Br^+$, 183 (4) 4-$BrC_6H_4CN^+$, 178 (24) M – HCN – $Br^+$, 177 (11) M – HCN – Br – $H^+$, and 76 (44) $C_6H_4^+$.

## EXPERIMENTAL (BIOLOGICAL)

The antimicrobial, anti-inflammatory, analgesic, and anticonvulsant activity of the synthesized compounds was studied.

The acute toxicity $LD_{50}$ of the compounds obtained was determined by the method of G. N. Pershin [18] using the ip injection of the suspension in 2% starch mucilage into white mice of 16-24 g mass.

The antimicrobial activity of the compounds toward the standard strains of Escherichia coli $M_{17}$ and Staphylococcus, S. aureus P-209 was determined by the standard method of double serial dilutions in beef–peptone broth [18] with the bacterial loading of 250,000 microbe units in 1 ml of the solution. The acting dose was taken to be the minimal inhibitory concentration (MIC) of the compound – the maximal dilution leading to the complete supression of the growth of the test microbes. The antimicrobial activity of the compounds obtained (Table 2) was compared with the activity of mercury dichloride (mercuric chloride) [10] and ethacridine lactate – an antimicrobial preparation employed in medicine [10].

The antiinflammatory action was studied using the model of acute inflammatory edema induced by the subplantar introduction of 0.1 ml of a 1% aqueous solution of carragenin into the rear foot of white rats of mass 160-200 g. The antiinflammatory action was judged from the degree of inhibition of the exudation (in % relative to the control) after the ip injection of the compounds as a suspension in 2% starch mucilage at the doses of 50 and 150 mg/kg. The effect was compared with those of amidopyrine [7] and ortofen (Table 3).

The analgesic activity was investigated by the "hot plate" method [30] using white mice of mass 16-24 g receiving the compounds ip at the doses of 50 and 150 mg/kg. The reflex time was determined, and the effect was compared with that of amidopyrine (Table 3).

The anticonvulsant activity was determined from the test of maximal electroshock [20] using white mice of the mass 18-22 g after the ip injection of the compounds in 2% starch mucilage.

For the comparative evaluation of the activity of the quinoxaline derivatives (I)-(XV), 3-furanones, and hexadiene-diones, biological testing was also performed on some starting reagents – 2-hydroxy-2-methoxycarbonylmethyl-5-phenyl-2,3-dihydro-3-furanone (XVI) [5,9], 2-p-nitrobenzoylmethylene-5-phenyl-2,3-dihydro-3-furanone (XVII), and 1-p-bromophenyl-6-phenyl-3,4-dihydroxy-2,4-hexadiene-1,6-dione (XVIII) [9].

The acute toxicity of the compounds tested occurred in the range from 540 mg/kg [compound (II)] to 2240 mg/kg [compound (IX)]. Therefore, these compounds are much less toxic than the comparison preparations – mercury dichloride [$LD_{50}$ 3.9 mg/kg), ethacridine lactate ($LD_{50}$ 70.0 mg/kg), amidopyrine ($LD_{50}$ 249 mg/kg) [7], and ortofen ($LD_{50}$ 74.1 mg/kg).

As a result of the study of the antimicrobial activity of the compounds (I)-(XVIII) (Table 2), it was established that the majority of them possess weak bacteriostatic action with the MICs from 250 to 1000 μg/ml; six compounds [(II), (VII), (XI), (XIII), (XV), and (XVII)] were inactive toward one or both strains of the test microbes. The greatest anti-inflammatory activity is possessed by the compound (IX) which, at the dose of 50 mg/kg comprising 0.022 $LD_{50}$, is hardly inferior in its effect to ortofen, which acts at the sixfold greater equitoxic dose of 0.13 $LD_{50}$. The analgesic action is shown by all the investigated substances; the most active compound is (IV).

The anticonvulsant effect is absent from all the investigated compounds at doses up to 600 mg/kg.

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