SYNTHESIS AND BIOLOGICAL ACTIVITY OF AROYLPYRUVOYLAMINOBENZONITRILES AND 3-PHENACYLIDENE-6(7)-CYANO-3,4-DIHYDRO-2-QUINOXALONES

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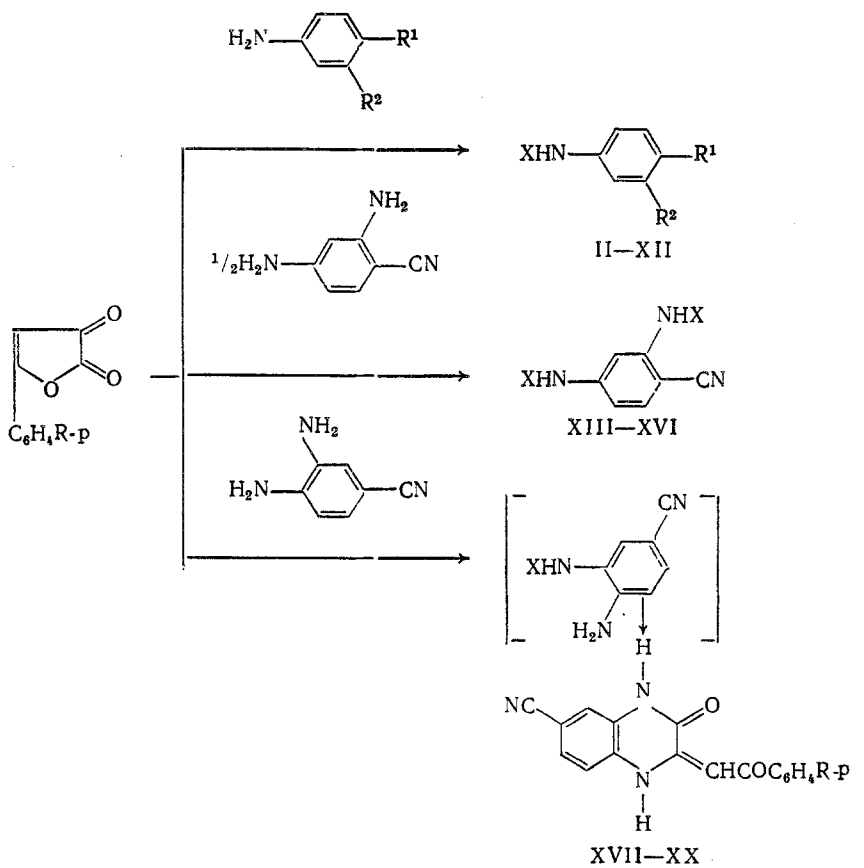
It was found earlier that the reaction of 5-aryl-2,3-dihydrofuran-2,3-diones (I) with aminobenzonitriles may proceed by two different paths, depending on the structure of the latter compounds: either with the liberation of carbon monoxide and formation of aroylketenes, which undergo a [4π + 2π]-cycloaddition reaction with the participation of the cyano group of the reagent, or with the opening of the furandione ring by the amino group of the reagent. In the first case, cyclic products — 6-aryl-2-amino-1,3-oxazin-4-ones are formed, and in the second acyclic products — 2-cyanophenylamides of aroylpyruvic acids are obtained [6]. Among the two types of compounds, compounds were discovered with a broad spectrum of biological activity [1, 2, 8]. In continuation of these investigations, it was of interest to study the reaction of compounds I with aminobenzonitriles containing one or two amino or cyano groups, variously positioned in the benzene ring relative to one another, and to examine the biological activity of the reaction products.



XVII—XX

X = $COCOCH_2COC_6H_4R$-p; R = H (II, VI, X, XIII, XVII), CH_3 (III, IV, VII, VIII, XI, XII, XIV, XV, XIII), Cl (V, IX, XVI, XIX), Br (XX); R^1 = H (II—V), CN (VI—XII); R^2 = H (VI—IX), CN (II—V, X—XII)

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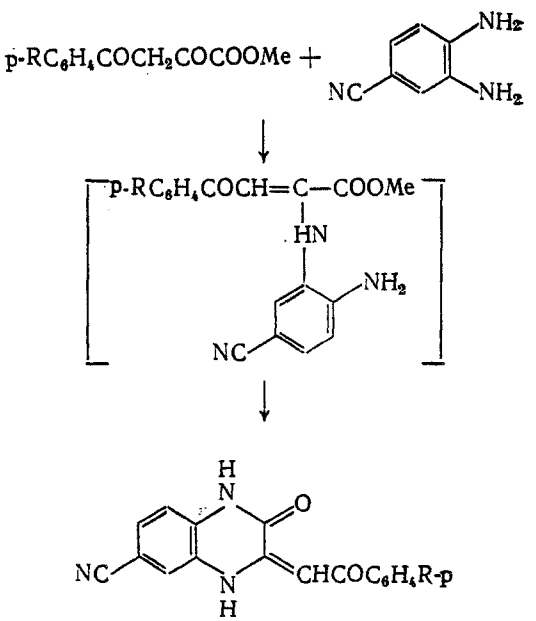
We have found that 3- and 4-aminobenzonitriles react with compounds I at room temperature in equimolar amounts similarly to 2-aminobenzonitrile [6], and the reaction products are 3- and 4-cyanophenylamides of aroylpyruvic acids (II-IX). 4-Aminophthalonitrile, because of some reduction in the nucleophilic properties of the amino group, undergoes reaction with compounds I at a higher temperature (30-50°C), forming 3,4-dicyanophenylamides of aroylpyruvic acids (X-XII). In the case of 2,4-diaminobenzonitrile two amino groups of the reagent participate in the reaction with furandiones. The reaction products are 2,4-bis(aroylpyruvoylamino) benzonitriles (XIII-XVI). The mechanism of the nucleophilic opening of the dihydrofuran ring has been investigated in detail in [9, 10].

The IR and PMR spectra of compounds II-XVI are similar to the spectra of 2-cyanophenylamides of aroylpyruvic acids previously obtained [6]. In compounds XIII-XVI an additional peak of the NH bond appears in the 3230-3270 cm^{-1} region. The PMR spectra of compounds XIII-XVI could not be recorded because of their low solubility.

In the reaction of 3,4-diaminobenzonitrile with the compound I, the furandione ring is opened in the first stage of the reaction by the action of the most nucleophilic amino group at the 3-position. The substituted phenylamide of the aroylpyruvic acid thus formed undergoes cyclization with the participation of the α-carbonyl and the amino group at the 4-position of the phenyl ring. As a result of the reaction, 3-phenacylidene-7-cyano-3,4-dihydro-2-quinoxalones XVII-XX are formed.

To verify the presence of the nitrile group in the 7-position of the quinoxalone ring of compounds XVII-XX, we carried out a reaction between 3,4-diaminobenzonitrile and methyl esters of aroylpyruvic acids, which proceeded in accordance with [3] with the participation of α-ketonic group and resulted in isomers XVII-XX — 3-phenacylidene-6-cyano-3,4-dihydro-2-quinoxalones (XXI-XXIV). Judging from the TLC data on Silufol plates (CSSR), compounds XVII-XXIV do not contain impurities of structural isomers.

The IR and UV spectra of compounds XVII-XX and XXI-XXIV are very similar to one another. Their IR spectra contain absorption bands at 3175-3170 cm^{-1} (NH of the quinoxalone ring), 2235-2225 cm^{-1} (C≡N), 1695-1685 cm^{-1} (amide carbonyl) and 1620-1600 cm^{-1} (ketonic carbonyl). The vibrations in the 3095-3070 cm^{-1} region are characteristic of the vibrations of =C—H bond of the phenacylidene substituent. In the UV spectra, the λ_{max} is present at 417-425 nm (log ε 4.32-4.46). The IR and UV spectra of these compounds are similar to the IR and UV spectra of 3-phenacylidene 3,4-dihydro-2-quinoxalones, described previously in [4, 5].



XXI—XXIV R = H (XXI), CH_3 (XXII, XXIII), Cl (XXIV)

TABLE 1. Characteristics of Compounds II-XXIV

Compound	mp, °C	Yield, %	Empirical formula
II	149—50	92	$C_{17}H_{12}N_2O_3$
III	184—5	91	$C_{18}H_{14}N_2O_3$
IV	171—2	88	$C_{18}H_{14}N_2O_4$
V	205—6	94	$C_{17}H_{11}ClN_2O_3$
VI	201—3	93	$C_{17}H_{12}N_2O_3$
VII	215—6	94	$C_{18}H_{14}N_2O_3$
VIII	213—4	91	$C_{18}H_{14}N_2O_4$
IX	254—5	95	$C_{17}H_{11}ClN_2O_3$
X	211—2	85	$C_{18}H_{11}N_3O_3$
XI	248—9	90	$C_{19}H_{13}N_3O_3$
XII	252—3	93	$C_{19}H_{13}N_3O_4$
XIII	195—6	96	$C_{27}H_{19}N_3O_6$
XIV	275—6	95	$C_{29}H_{23}N_3O_6$
XV	277—8	93	$C_{29}H_{23}N_3O_8$
XVI	280—2	98	$C_{27}H_{17}Cl_2N_3O_6$
XVII	289—90	98	$C_{17}H_{11}N_3O_2$
XVIII	296—7	96	$C_{18}H_{13}N_3O_2$
XIX	311—2	99	$C_{17}H_{10}ClN_3O_2$
XX	312—3	97	$C_{17}H_{10}BrN_3O_2$
XXI	304—5	98	$C_{17}H_{11}N_3O_2$
XXII	305—6	99	$C_{18}H_{13}N_3O_2$
XXIII	288—9	94	$C_{18}H_{13}N_3O_3$
XXIV	295—6	82	$C_{17}H_{10}ClN_3O_2$

Note. The yields given are based on the recrystallized product.

EXPERIMENTAL (CHEMICAL)

The IR spectra were recorded in mineral oil on a UR-20 spectrophotometer (GDR), the PMR spectra on an RS-60 spectrometer (USSR) (60 MHz), using HMDS as internal standard. The UV spectra were run in ethanol solution on a "Specord UV-Vis" spectrophotometer (GDR) at a 10^{-3}-10^{-5} M concentration of the samples. The characteristics of the synthesized compounds are given in Table 1. The results of the elemental analysis correspond to the calculated values.

3(4)-Cyano(3,4-dicyano)phenylamides of Aroylpyruvic Acids (II-XII). A 0.01 mole portion of an aromatic aminonitrile is added at 20-50°C to a solution of 0.01 mole of compound I in 15-20 ml of anhydrous dioxane. The reaction mixture is stirred, the precipitate that separates out is filtered off, and recrystallized from dioxane.

2,4-Diaroylpyruvoylaminobenzonitriles (XIII-XVI). A 0.005 mole portion of 2,4-diaminobenzonitrile is added at room temperature to a solution of 0.01 mole of compound I in 15 ml of anhydrous dioxane. The reaction mixture is stirred, the precipitate that separates out is filtered off, and washed with a small portion of dioxane.

2-Phenacylidene-6(7)-cyano-3,4-dihydro-2-quinoxalones (XVII-XXIV). A solution of 0.01 mole of 3,4-diaminobenzonitrile in anhydrous dioxane is added to a solution of 0.01 mole of compound I or methyl aroylpyruvate in the same solvent. After the evaporation of the solvent, the product is recrystallized from ethanol.

EXPERIMENTAL (PHARMACOLOGICAL)

The acute toxicity was studied on white mice by intraperitoneal administration, using the method of G. N. Pershin [11].

The antimicrobial activity of the compounds was studied by the method of double serial dilutions in a meat peptone bullion with reference to E. coli and Staphylococcus aureus. The lowest concentration (LC) of the compound inhibiting the growth of the bacteria was accepted as the active dose. Samples of the compounds were dissolved, depending on solubility, in 95% ethanol or dimethyl sulfoxide, which in the control did not have a suppressing action on the microorganisms.

The anti-inflammatory activity was established by means of an inflammation model, produced by a subplantary administration of 0.1 ml of a 1% solution of Carragheen into a posterior paw of rats [7]. The increment in the volume of the inflamed paws with subsequent calculation of the inflammation inhibition index was taken into account oncometrically according to the formula:

$$\frac{(K-O)\cdot 100}{K},$$

where K is the result in control, O is the experimental result. The anti-inflammatory activity was evaluated 5 h after the administration of the compound.

The anticonvulsant activity was evaluated according to the maximal electrical shock test [12] during intraperitoneal administration of the compounds in a dose of 300 mg/kg.

Investigation of the antimicrobial activity showed that compound II has the highest activity: the LC is equal to 125 mg/ml for Staphylococcus aureus and 500 mg/ml for E. coli. The remaining compounds (both cyanophenylamides of aroylpyruvic acids and cyanoquinoxalones) have weak action. Variation of substituents in the aromatic ring of cyanoarylamides II-VIII and in the phenacylidene substituent of cyanoquinoxazolones XVIII-XXII inappreciably affects the antimicrobial action.

Compounds XVII, XVIII, and XXII exhibit anti-inflammatory activity in a dose of 100 mg/kg. Compounds XVII and XVIII are somewhat inferior to amidopyrine, while compound XXII surpasses it by a factor of two. All these compounds are less toxic than amidopyrine and are effective in a dose of 0.3 LD_{50}. Cyanophenylamides II and VI did not restrict exudation.

Compounds II-IX, XIX were tested for anticonvulsant activity. None of the compounds tested displayed this type of activity.

LITERATURE CITED

1. Inventor's Certificate No. 623,356 (USSR); Otkrytiya, No. 33 (1978).
2. Inventor's Certificate No. 750,971 (USSR); Otkrytiya, No. 27 (1980).
3. Yu. S. Andreichikov, A. P. Kozlov, S. P. Tendryakova, and Yu. A. Nalimova, Zh. Org. Khim., 13, 2559-2564 (1977).
4. Yu. S. Andreichikov, S. G. Pitirimova, R. F. Saraeva, et al., Khim. Geterotsikl. Soedin., No. 3, 407-410 (1978).
5. Yu. S. Andreichikov, S. G. Pitirimova, S. P. Tendryakova, et al., Zh. Org. Khim., 14, 169-172 (1978).
6. Yu. S. Andreichikov, D. D. Nekrasov, M. A. Rudenko, and A. Yu. Konovalov, Khim. Geterotsikl. Soedin., No. 6, 740-743 (1987).
7. A. S. Zaks and M. L. Suslina, Farmakol. Toksikol., No. 3, 308-312 (1975).
8. V. É. Zaks, I. P. Yakovlev, and B. A. Ivin, Khim. Geterotsikl. Soedin., No. 11, 1443-1462 (1987).
9. A. P. Kozlov, D. I. Sychev, and Yu. S. Andreichikov, Zh. Org. Khim., 21, 2147-2154 (1985).
10. A. P. Kozlov, D. I. Sychev, and Yu. S. Andreichikov, Zh. Org. Khim., 22, 188-196 (1986).
11. G. N. Pershin and M. L. Belen'kii, Elements of Quantitative Evaluation of Pharmacological Effect [in Russian], Leningrad, (1963), p. 51.
12. K. S. Raevskii, Farmakol. Toksikol., No. 4, 495-497 (1961).