SYNTHESIS OF 4-SUBSTITUTED 1-METHYL-5-ARYL- AND 1,5-DIARYLTETRAHYDROPYRROLE-2,3-DIONES AND THEIR ANTIVIRAL ACTION

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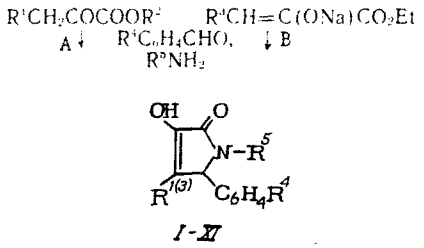
The esters of arylsulfonylpyruvic acids are known to have a pronounced anti-inflammatory activity [1], aroylmethylquinaxol-2-ones to have an analgetic action [2], while β-substituted esters of aroylpyruvic acids are known to exhibit antimicrobial activity [3]. Most of the compounds of this series are characterized by low toxicity [1, 2]. It was of interest to carry out the synthesis of 1,4,5-trisubstituted tetrahydropyrrole-2,3-diones, which can be regarded as cyclic amides of β-substituted acylpyruvic acids, in order to look for compounds among them with antiviral activity.

The reaction of esters of pyruvic acids containing acetyl, cyano, and ethoxycarbonyl groups as a substituent at the tertiary carbon atoms or their sodium salts with a mixture of an aromatic aldehyde and an aryl- or alkylamine, gave 4-substituted 1-methyl-5-aryl- and 1,5-diaryltetrahydropyrrole-2,3-diones (I-XI).

The compounds obtained are colorless or cream-tinged compounds, which are soluble in ethanol. The spectral characteristics of the synthesized compounds correspond to the ascribed structure.



I-XI

R^1=EtOCO (I—V), Ac (VI—IX); R^3=CN (X, XI);
R^4=p-Br (I, IV, VI, XI), H (II, V, X), *o*-F (III), p-MeO (VII), p-Cl (VIII), p-NO_2 (IX);
R^5=p-$CH_3C_6H_4$ (I, V), p-$Br_2C_6H_4$ (II, IV), Ph (III, VI, X, XI), p-$MeOC_6H_4$ (V), Me (VII—IX); I—V, X, XI obtained from $R^1CH_2COCOOR^2$ (R^2=Et), a VI—IX —from $R^1CH_2COCOOR^2$ (R^2=Me).

In the IR spectra of all the compounds there are absorption bands of the enolic hydroxyl (3050-3320 cm^{-1}) and a lactam carbonyl (1663-1695 cm^{-1}). Moreover, for compounds I-V, absorption bands of the ester carbonyl are observed (1690-1730 cm^{-1}).

The shift of the absorption bands of the ester carbonyl and the enolic hydroxyl for compound I to the high-field region may be explained by the less pronounced intra- and intermolecular hydrogen bonds due to decrease in the acidity of the enolic hydroxyl group, as a result of the electron—donor influence of the p-tolyl substituent in the I-position of the heterocyclic ring.

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For compounds VI-IX, absorption bands are observed of the ketonic carbonyl of the acetyl group (1630-1655 cm^{-1}), the shift of which to the low-frequency region can be attributed to the conjugation of the ketonic carbonyl group with the ring double bond.

For compounds X, XI absorption bands of the cyano group are observed (2201-2228 cm^{-1}). In the PMR spectra signals were noted corresponding to the resonance of the H(5) proton (5.05-6.32 ppm), of aromatic protons (6.95-7.77 ppm), a proton of enolic hydroxyl (8.31-11.27 ppm). In the spectra of compounds I-V there are signals of the resonance of the ethoxycarbonyl group protons [1.04-1.12 (t) and 4.03-4.11 (q) ppm]. In the spectra of compounds VI-IX, signals of the acetyl group protons (2.25-2.28 ppm), and of compounds VII-IX – proton signals of the methyl group attached to the pyrrole ring nitrogen atom (2.65 ppm).

All the compounds synthesized give intense red-pink coloration with an alcoholic solution of $FeCl_3$. The data obtained indicate that compounds I-XI exist in the form of 4-substituted 3-hydroxy-1-methyl-5-aryl- and 1,5-diaryl-2,5-dihydropyrrol-2-ones.

EXPERIMENTAL (CHEMICAL)

The IR spectra were obtained in mineral oil on a UR-20 spectrophotometer, the PMR of solutions in DMSO-d_6 or $CDCl_3$ were recorded on a RYa-2310 spectrometer (60 MHz, HMDS internal standard). The elemental analysis data correspond the calculated values.

1,5-Diaryl-4-ethoxycarbonyltetrahydropyrrol-2,3-diones (I-V). A. A mixture of 0.02 mole of the aromatic aldehyde and 0.02 mole of arylamine in 15 ml of ethanol was added to a solution of 0.02 mole of the diethyl oxaloacetate in 5 ml of ethanol. The reaction mixture was allowed to stand for 24 h at 20°C. The precipitate that separated out was filtered off and recrystallized from toluene. B. A 0.02 mole portion of the aromatic aldehyde and 0.02 mole of arylamine was added to a solution of 0.02 mole of a sodium salt of diethyl oxaloacetate in 50 ml of AcOH. The reaction mixture was allowed to stand at 20°C for 24 h. The precipitate that separated out was filtered off and recrystallized from toluene.

1-Phenyl-5-p-bromophenyl-4-acetyltetrahydropyrrole-2,3-dione (VI). A solution of 3.70 g (0.02 mole) of p-bromobenzaldehyde and 1.86 g (0.02 mole) of aniline in 15 ml of ethanol was added to a solution of 2.28 g (0.02 mole) of methyl acetylpyruvate in 15 ml of ethanol. After 30 min, the precipitate that separated out was filtered off and recrystallized from toluene.

1-Methyl-5-aryl-4-acetyltetrahydropyrrole-2,3-diones (VII-IX). A 0.032 mole portion of a 25% aqueous solution of methylamine was added to a solution of 0.008 mole of methyl acetylpyruvate and 0.008 mole of an aromatic aldehyde in 10 ml of ethanol. After 30 min, the precipitate that separated out was filtered off and recrystallized from ethanol.

1,5-Diaryl-4-cyanotetrahydropyrrole-2,3-diones (X, XI). A solution of 0.04 mole of the aromatic aldehyde and 0.04 mole of aniline in 20 ml of ethanol was added to a solution of 0.04 mole of a sodium salt of ethyl β-cyanopyruvate in 20 ml of AcOH. The reaction mixture was allowed to stand for 24-28 h. The precipitate that separated out was filtered off and recrystallized from ethanol (X) or toluene (XI).

The main characteristics of compounds I-XI are given in Table 1.

EXPERIMENTAL (BIOLOGICAL)

All the compounds obtained were studied for their antiviral activity with respect to viruses: herpex simplex type I (VHS), smallpox vaccine (SPV), classical fowl plaque (VCFP), vesicularstomatitis (VVS), respiratory syncytial (RS), Venuzuela equine encephalomyelitis (VEE), the ECHO-6 in experiments on tissue cultures by the methods of "screening test" and plaque reduction under an agar coating. With the ECHO virus, the investigations were carried out on passivated cultures of skin-muscle cells of human embryo, with respiratory-syncytial virus (RS) – on implanted cells of a rabbit lung and with the remaining viruses – on primarily trypsinized fibroblasts of chicken embryos.

The criterion for the antiviral action was the presence of a plaque formation suppression zone in the investigation by the "screening test" and decrease in the titer of the virus by the action of compounds studied in comparison with untreated control in the investigation by the plaque reduction method [4].

TABLE 1. Characteristics of 4-Substituted 1-Methyl- and 1-Aryl-5-aryltetrahydropyrrole-2,3-dione

Compound	Yield, % A	Yield, % B	mp., °C	Empirical formula	IR spectra, ν_{max}, cm^{-1} C=C	C=O ketone	C=O lactam	C=O ester	OH	PMR spectra, δ, ppm C_2H_5OCO	CH_3CO	5-H	Ar-H	1-CH_3	OH	remaining protons
I	18	35	194—6	$C_{20}H_{18}BrNO_4$	1665	—	1695	1730	3320	1,12 t 4,05 q	—	5,53 s	7,00 m	—	8,70 br.s	2,12 (3H,s.CH_3)
II	30	—	170—2	$C_{19}H_{16}BrNO_4$	1635	—	1670	1690	3237	1,09 t 4,11 q	—	5,68 s	7,35 s	—	9,09 br.s	
III	—	30	183—5 (p)	$C_{19}H_{16}FNO_4$	1645	—	1663	1700	3220—3290	1,04 t 4,04 q	—	6,32 s	7,27 m	—	—	—
IV		52	192—4 (p)	$C_{19}H_{15}Br_2NO_4$	1645	—	1670	1710	3300	1,09 t 4,03 q	—	6,09 s	7,37 m	—	—	—
V	28		157—60	$C_{20}H_{19}NO_5$	1635	—	1665	1690	3200	1,11 t 4,11 q	—	5,51 s	7,04 m	—	8,62 br.s	3,62 (3H,s,CH_3O)
VI	54		199—200	$C_{18}H_{14}BrNO_3$	—	1633	1663	—	3220	—	2,27 s	5,82 s	7,31 m	—	—	—
VII	62		227—9 (p)	$C_{11}H_{15}NO_4$	1627	1655	1673	—	3157	—	2,28 s	5,05 s	6,97 m	2,65 s	—	3,73 (3H,s. CH_3O)
VIII	75		232—4 (p)	$C_{13}H_{12}ClNO_3$	1630	1650	1680	—	3138	—	2,25 s	5,05 s	7,18 m	2,65 s	8,31 br.s	—
IX	50		218—20 (p)	$C_{13}H_{12}N_2O_5$	1630		1680	—	3155	—	2,25 s	5,21 s	7,77 m	2,65 s	10,85 br.s	—
X*	56		193—5 (p)	$C_{17}H_{12}N_2O_2$	—	—	1680	—	3050	—	—	5,98 s	6,95 m	—	—	—
XI*	50		214—6 (p)	$C_{17}H_{11}BrN_2O_2$	—	—	1668	—	3100	—	—	6,07 s	7,28 m	—	11,27 br.s	—

Notes. For compounds X, XI, the absorption band of the cyano group is observed at 2201-2228 cm^{-1}.

TABLE 2. Characteristics of Antiviral Action of 4-Substituted 1-Methyl-5-aryl- and 1,5-Diaryltetrahydropyrrole-2,3-diones

Compound	Antiviral activity with respect to viruses						
	VHS	SPV	VCFP	VVS	RS	VEE	ECHO-6
I	++	–	–	–	++	–	–
II	+++	++	–	–	–	++	++
III	–	++	–	+	+++	++	–
IV	+++	+	–	+	–	++	–
V	+	+	–	–	–	+	–
VI	+	++	+	++	++	+	–
VII	+	+	–	–	++	+	–
VIII	+	++	–	–	+	–	++
IX	–	–	–	–	–	+	–
X	–	–	+	–	–	–	–
XI	–	–	–	–	–	–	–

Notes. –) Absence of activity; +, ++) weak activity; +++) medium activity.

Analysis of the results presented in Table 2 shows that the character of the substituent at the 4-position influences the degree of antiviral activity. Thus, a pronounced activity with respect to all the examined groups of viruses is observed preferentially in compounds having aryl substituents in the 1- and 5-positions and an ethoxycarbonyl group in the 4-position (compounds I-IV). Introduction of an acetyl group into the 4-position (compounds VI-VIII) causes some decrease in the antiviral action, while in compounds containing a cyano group in the 4-position (compounds X, XI), no antiviral activity is observed. The absence of antiviral activity in compounds V and IX may be due to their limited solubility in ethanol.

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