SYNTHESIS AND BIOLOGICAL ACTIVITY OF SUBSTITUTED 3-ACYLMETHYLENE AND 3-HYDROXY-2-INDOLONES

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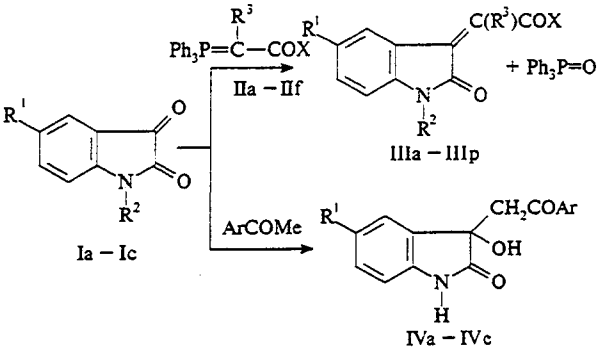
As is known, 3-acylmethylene-2-indolones may serve as initial compounds for obtaining various 3-spiro derivatives of hydroxyindole by the Diels – Alder reaction with alkadienes [1, 2]. Analogous compounds with close structures – 3-spiroindolones – are formed by the Michael reaction of 3-acylmethylene-2-indolones with various CH-activated carbonyl compounds [3, 4] and enamines [5], and by condensation with binucleophiles such as thiourea, phenylthiourea [6], and hydrazine hydrate [4, 7]. 3-Benzoylmethylene hydroxyindoles are used as dipolarophiles in reactions with 1,3-dipoles – azomethinilides [8, 9]. Also described were the reactions of heterocyclization of 3-acylmethylene-2-indolones under the action of hydrazine and phenylhydrazine [4, 7, 10] and recyclization of 3-aroylmethylene-2-indolones in an acid medium into derivatives of 2-arylcinchoninic acids [11, 12] possessing antiviral activity [11]. However, the lack of convenient preparative methods for the synthesis of some 3-acylmethylene-2-indolones (e.g., those having 3-alkioxycarbonyl fragments) renders this class of compounds difficultty accessible [2, 5, 13 – 15].

Fragmentary evidence of the antibacterial [3, 16], insecticide [16], antiviral [11], and anticonvulsive [17 – 21] activity of 3-methylene-2-indolones and their precursors – 3-hydroxy-2-indolones [12], and the data on the use of these compounds in the synthesis of tryptamine, serotonin [22, 23] and biologically active polymethine dyes [24] stimulated further search for the biologically active compounds among the 3-substituted hydroxyindoles [16, 25].

It was reported that some 3-methylene-2-indolones can be obtained by the Wittig reaction between isatins and methylenetriphenylphosphoranes [5, 13, 15, 22, 26, 27]. Judging from the published data, the olefination has a regiospecific character, leading to the formation of (E)-isomers of 3-methylene hydroxyindoles [5, 13], rather than regioisomeric 2- methyleneindoxyls. In the previous paper we suggested a short quantum-chemical justification for the formation of hydroxyindoles substituted in position 3 by the Wittig reaction [28].



I	R^1	R^2
a	H	H
b	Br	H
c	H	COMe

II	R^3	X
a	H	OMe
b	H	Ph
c	H	4-BrC_6H_4
d	Me	4-BrC_6H_4
e	H	4-ClC_6H_4
f	H	4-$O_2NC_6H_4$

III	R^1	R^2	R^3	X
a	H	H	H	OMe
b	Br	H	H	OMe
c	H	COMe	H	OMe
d	H	H	H	Ph
e	H	COMe	H	Ph
f	Br	H	H	Ph
g	H	H	H	4-MeC_6H_4
h	Br	H	H	4-BrC_6H_4
i	H	COMe	H	4-BrC_6H_4
j	H	H	Me	4-BrC_6H_4
k	H	H	H	4-ClC_6H_4
l	Br	H	H	4-ClC_6H_4
m	H	COMe	H	4-ClC_6H_4
n	H	H	H	4-$O_2NC_6H_4$
o	Br	H	H	4-$O_2NC_6H_4$
p	H	COMe	H	4-$O_2NC_6H_4$

IV	R^1	Ar
a	H	Ph
b	Br	Ph
c	H	4-MeC_6H_4
d	H	4-ClC_6H_4
e	Br	4-ClC_6H_4

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In contrast to the published data, our results showed evidence of the predominant formation of isomer mixtures in the Wittig reaction between isatins with acylmethylenetriphenylphosphoranes, and of a change in the process direction and the regiocontrol in oxalyl ilides [16, 28, 29]. For example, the reaction of isatin, 5-bromoisatin, or 1-acetylisatin (Ia – Ic) with methoxy carbonyl- or aroylmethylenetriphenylphosphorans (IIa – IIf) on boiling the reagent mixtures in dioxane or acetic acid allowed us to obtain (usually, with a satisfactory yield) brightly colored (yellow to light-brown) 3-acylmethylene-2-indolones (IIIa – IIIp) [28] (Table 1).

In the previous paper [28] we have also proved in detail the proposed structure of hydroxyindoles III, which was confirmed by the results of IR and ^{1}H NMR measurements and the calculation of the position of ^{1}H NMR signal from a methine proton in the spectra of geometric isomers. Compounds IIIg and IIIk were also obtained by the direct synthesis based on the dehydration of 3-(4-methylbenzoyl)- and 3-(4-chlorobenzoylmethyl)-3-hydroxy-2-indolones (IVc and IVd) in the presence of hydrochloric acid by the known method [11, 12, 19]. The latter compound, together with some other 3-hydroxy-2-indolones (IVa – IVc, IVe) (Table 1), necessary for the biological tests, were obtained through the condensation of isatins (Ia and Ib) with arylmethylketones by the Knoevenagel process in the presence of basic catalysts (diethylamine, triethylamine, or potassium carbonate [25]) using the general method described in [11, 19, 23, 24, 30].

EXPERIMENTAL CHEMICAL PART

The IR spectra of synthesized compounds were recorded on an UR-20 and Specord M-80 spectrophotometers using samples prepared as nujol mulls. The ^{1}H NMR spectra were obtained on a RYa-2310 spectrometer operated at 60 MHz, using DMSO-d_6 as the solvent and HMDS as the internal standard. The mass spectra were measured with a Varian MAT-311 spectrometer with direct injection of the samples, operated at the emission current 1000 mA and the ionizing electron energy 70 eV. The course of reactions was followed and the purity of synthesized compounds was checked by TLC on Silufol UV-254 plates eluted in the benzene – ether – acetone (10 : 9 : 1) system and developed by iodine vapors. Some of the characteristics of hydroxyindoles III and IV not reported in the previous paper [28] are given in Tables 1 and 2 and described in the text below. The results of elemental analyses and some spectral characteristics were presented in [28]. The IR data for compound IIIn were given in [11], and the spectral characteristics of 3-acylmethylene-2-indolones with close structures were considered in [5, 8, 13, 15, 30]. Characteristics of the model regioisomeric 2-methoxycarbonylmethylene-3-indolone were given in [31]. Some spec-

TABLE 1. Yields and Characteristics of 3-Substituted 2-Indolones IIIa – IIIp and IVa – IVe

Compound	R^1	R^2	R^3	X /Ar	Yield, %	M.p., °C	Empirical formula
IIIa	H	H	H	OMe	64	181 – 182	$C_{11}H_9NO_3$
IIIb	Br	H	H	OMe	98	214 – 215	$C_{11}H_8BrNO_3$
IIIc	H	COMe	H	OMe	59	138 – 139[1)]	$C_{13}H_{11}NO_4$
IIId	H	H	H	Ph	69	201 – 202[2)]	$C_{16}H_{11}NO_2$
IIIe	H	COMe	H	Ph	18	109 – 110[3)]	$C_{18}H_{13}NO_3$
IIIf	Br	H	H	Ph	67	210 – 211[4)]	$C_{16}H_{10}BrNO_2$
IIIg	H	H	H	4-MeC_6H_4	52[5)]	170 – 171	$C_{17}H_{13}NO_2$
IIIh	Br	H	H	4-BrC_6H_4	80	249 – 250	$C_{16}H_9Br_2NO_2$
IIIi	H	COMe	H	4-BrC_6H_4	50	177 – 178	$C_{18}H_{12}BrNO_3$
IIIj	H	H	Me	4-BrC_6H_4	37	169 – 170	$C_{17}H_{12}BrNO_2$
IIIk	H	H	H	4-ClC_6H_4	74[5)], 58[6)]	211 – 212	$C_{16}H_{10}ClNO_2$
IIIl	Br	H	H	4-ClC_6H_4	71	214 – 215	$C_{16}H_9BrClNO_2$
IIIm	H	COMe	H	4-ClC_6H_4	45	155 – 156	$C_{18}H_{12}ClNO_3$
IIIn	H	H	H	4-$O_2NC_6H_4$	74	252 – 253[7)]	$C_{16}H_{10}N_2O_4$
IIIo	Br	H	H	4-$O_2NC_6H_4$	60	239 – 240	$C_{16}H_9BrN_2O_4$
IIIp	H	COMe	H	4-$O_2NC_6H_4$	44	159 – 160	$C_{18}H_{12}N_2O_5$
IVa	H	–	–	Ph	76[8)]	177 – 178[9)]	$C_{16}H_{13}NO_3$
IVb	Br	–	–	Ph	53[10)]	207 – 208[11)]	$C_{16}H_{12}BrNO_3$
IVc	H	–	–	4-MeC_6H_4	60[8)]	195 – 196[12), 13)] 186 – 187[13)]	$C_{17}H_{15}NO_3$
IVd	H	–	–	4-ClC_6H_4	73[10)]	211 – 212[14)]	$C_{16}H_{12}ClNO_3$
IVc	Br	–	–	4-ClC_6H_4	56[10)]	206 – 207	$C_{16}H_{11}BrClNO$

[1)] M.p. 138 – 140°C (yield, 80%) [5]: [2)] m.p. 189°C [27], 192 – 194°C [19], 193 – 194 [30]; [3)] m.p. 121°c [1]; [4)] m.p. 204 – 205°C [19]; [5)] yields indicated for the reaction of dehydration of hydroxyindoles IVc and IVd; [6)] yield for the Wittig reaction; [7)] m.p. 247 – 248°C [11]; [8)] catalyst, K_2CO_3; [9)] m.p. 160 – 161°C [11]; 165°C [23], 173 – 175°C [19], 169 – 171°C [30]; [10)] catalyst Et_3N; [11)] m.p. 220 – 221 [19]; [12)] m.p. 189 – 192°C [19]; [13)] two crystalline forms with differing m.p. (see notes in the text); [14)] m.p. 197 – 199°C [19].

tral characteristics of 3-aroylmethyl-3-hydroxy-2-indolones IV were reported in [11, 19, 30]. The initial methoxycarbonyl IIa and aroylmethylenetriphenylphosphoranes IIb – IIf were obtained by the known methods [32, 33].

3-Acylmethylene-2-indolones (IIIa – IIIf, IIIh – IIIp). To a solution of 0.005 mole of the corresponding methylenetriphenylphosphorane IIa – IIf [32, 33] in 100 – 150 ml of dioxane or 100 – 120 ml of acetic acid was added 0.005 mole of isatin Ia, 5-bromoisatin Ib, or 1-acetylisatin Ic, the mixture was heated with stirring until complete dissolution of the solid component, and then boiled for a time period of 30 min to 3 h (TLC control). Then the solvent was distilled off, the residue recrystallized from ethanol, isopropanol, acetonitrile, or ethyl acetate. Compounds IIIg and IIIk were also obtained by dehydration of 3-(4-methylbenzoylmethyl)- (IVc) or 3-(4-chlorobenzoylmethyl)-3-hydroxy-2-indolone (IVd) in the presence of hydrochloric acid as described in detail elsewhere [11, 19].

(*E*)-1-Acetyl-benzoylmethylene-2-indolone (IIIe). ^{1}H NMR spectrum (δ, ppm): 2.62 (s, 3H, CH_3), 7.03 (s, 1H, CH), 7.15 – 8.15 (m, 9H, C_6H_5, C_6H_4). The spectrum was assigned to (*E*)-isomer on the basis of comparison of the observed position of the signal of methine proton with the results of calculation [28] and the published data available [34].

(*Z*)-3-(4-Methylbemzoylmethylene)-2-indolone (IIIg). ^{1}H NMR spectrum (δ, ppm): 2.38 (s, 3H, CH_3), 6.81 (s, 1H, CH), 7.05 – 8.10 (m, 8H, $2C_6H_4$), 10.72 (bs, 1H, NH).

A general method for obtaining **3-aroylmethyl-3-hydroxy-2-indolones IV** was described in [19, 23].

3-(4-Methylbanzoylmethyl)-3-hydroxy-2-indolone (IVc). To a solution of 1.47 g (0.01 mole) of isatin Ia in 80 ml of ethanol was added 1.34 g (0.01 mole) of *p*-methylacetophenone and 0.2 g potassium carbonate, and the mixture was boiled for 1 h (TLC control). Then the solvent was distilled off and the two crystalline forms were isolated by fractional distillation. Product A: yield, 1.46 g (52%), colorless cotton-like crystals; m.p., 195 – 196°C. Product B: yield, 0.28 g (10%); yellowish needle crystals; m.p., 186 – 187°C. Judging from the spectral data, form A corresponds to the structure with a hydroxy group free of hydrogen bonds, and form B, to the structure with an intramolecular hydrogen bond of the type >C=...H–O–C≤.

Form A. IR spectrum (ν_{max}, cm^{-1}): 3376 (OH), 3340 (NHCO), 1726 ($COC_6H_4CH_3$-4), 1672 (CONH). 1624, 1608 (C=...C in Ar); ^{1}H NMR spectrum (δ, ppm): 2.31 (s, 3H, CH_3), 3.75 (dd, 2H, CH_2, J 17.6 Hz), 6.75 – 7.80 (m, 8H, $2C_6H_4$), 10.20 (bs, 1H, NH); mass spectrum (see Fig. 1) *m/z* (intensity I, % of he maximum peak, I > 3%): 281 (9) $[M]^+$, 263 (3) $[M-H_2O]$, 237 (20) $[M-CO_2]^+$, 236 (31) $[M-COOH]^+$ (decarboxylation of the product of intramolecular recyclization, 2-*p*-tolylcinchoninic acid [12]), 235 (3), 162 (17) $[M-4\text{-}MeC_6H_4CO]^+$, 148 (13) $[M-4\text{-}MeC_6H_4COCH_2]^+$, 147 (9) $[M-4\text{-}MeC_6H_4COCH_2-H]^+$, 146 (6) $[M-4\text{-}MeC_6H_4COCH_2-2H]^+$, 135 (4), 134 (25) $[4\text{-}MeC_6H_4COCH_3]^+$, 133 (3) $[4\text{-}MeC_6H_4COCH_2]^+$,

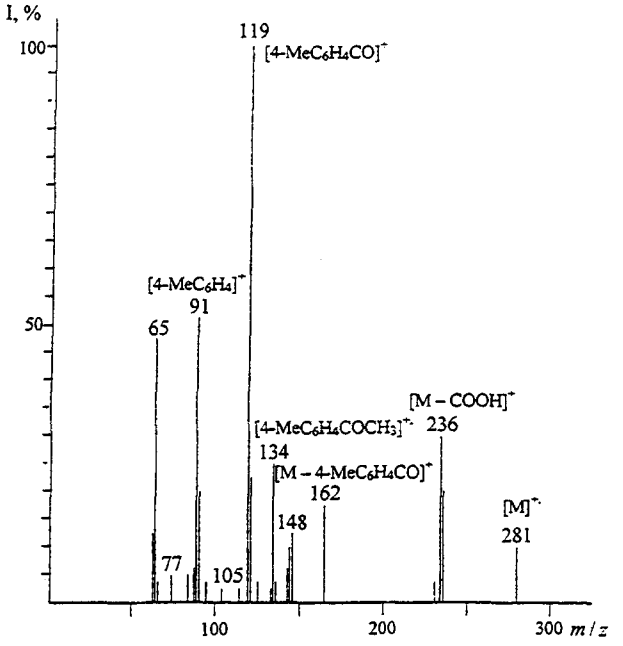


Fig. 1. Mass spectrum of 3-(4-methylbenzoyl)-3-hydroxy-2-indolone (IVc).

121 (4), 120 (23), 119 (100) $[4\text{-}MeC_6H_4CO]^+$, 117 (3), 105 (3) $[PhCO]^+$, 92 (21) $[4\text{-}CH_3C_6H_5]^{+\cdot}$, 91 (52) $[4\text{-}CH_3C_6H_4]^+$, 90 (7), 89 (5), 77 (5) $[C_6H_5]^+$, 65 (42). The mass spectrum is characterized by a high selectivity of fragmentation (N = 2, I > 50%), the main nine peaks with I_{rel} > 15% occurring within five homologous groups [35]: 7, 9, 12, 8, 13 (in the order of decreasing intensity).

Form B. IR spectrum (ν_{max}, cm^{-1}): 3368 (OH chel.), 3200 (NHCO), 1704 ($COC_6H_4CH_3$-4 chel.), 1680 (CONH).

TABLE 2. Parameters of the IR Spectra of 3-Acylmethylene-2-Indolones III

Compound	ν_{max}, cm^{-1}
IIIa	3192 (NHCO), 1712 (COOMe), 1652 (C=C, CO lactam)
IIIc	1752 (MeCON<), 1718 (COOMe), 1676 (C=C, CO lactam)[1)]
IIId	3230 (NHCO), 1710 (COPh), 1658 (C=C, CO lactam)[2)]
IIIe	1756 (MeCON<), 1722 (COPh), 1676 (C=C, CO lactam)
IIIf	3035 (NHCO), 1715 (COPh), 1656 (C=C, CO lactam)
IIIg	3164 (NHCO), 1712 (COAr), 1656 (C=C, CO lactam)
IIIh	3190 (NHCO), 1712 (COAr), 1668 (C=C, CO lactam)
IIIi	1744 (MeCON<), 1704 (COAr), 1668 (C=C, CO lactam)
IIIk	3152 (NHCO), 1718 (COAr), 1668 (C=C, CO lactam)
IIIl	3200 (NHCO), 1720 (COAr), 1665 (C=C, CO lactam)
IIIm	1744 (MeCON<), 1704 (COAr), 1664 (C=C, CO lactam)
IIIo	3132 (NHCO), 1711 (COAr), 1625 (C=C, CO lactam)

[1)] For comparison: the IR spectrum of 1-acetylisatin Ic has bands at 1784 (MeCON<), 1758 (C^3=O), 1720 (CO lactam), 1608 (C=C in Ph); [2)] in our opinion, the different set of peaks (3460, 3240, 1739, 1677) reported in [30] does not correspond to the structure of 3-benzoylmethylene-2-indolone. The data agree with the structure of 3-benzoylmethyl-3-hydroxy-2-indolone (IVa). Data reported in [19] (1710, 1660 cm^{-1}) agree with our frequencies.

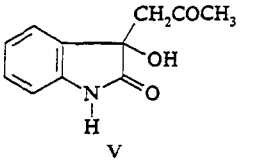
1622, 1606 (C⋯C in Ar); ^{1}H NMR spectrum (δ, ppm): 2.26 (s, 3H, CH_3), 3.78 (dd, 2H, CH_2, J 15.0 Hz), 6.02 (s, 1H, OH) [the signal vanishes on adding a drop of CF_3COOH], 6.82 – 7.80 (m, 8H, $2C_6H_4$), 10.22 (bs, 1H, NH); mass spectrum (see Fig. 1) *m/z* (intensity I, % of he maximum peak, I > 3%): 281 (9) $[M]^+$, 263 (3) $[M - H_2O]^+$, 236 (31) $[M - COOH]^+$, 235 (3), 162 (18) $[M - 4\text{-}MeC_6H_4CO]^+$, 148 (13) $[M - 4\text{-}MeC_6H_4COCH_2]^+$, 147 (10) $[M - 4\text{-}MeC_6H_4COCH_2 - H]^+$, 146 (6) $[M - 4\text{-}MeC_6H_4COCH_2 - 2H]^+$, 135 (4), 134 (25) $[4\text{-}MeC_6H_4COCH_3]^+$, 133 (3) $[4\text{-}MeC_6H_4COCH_2]^+$, 121 (4), 120 (24), 119 (100) $[4\text{-}MeC_6H_4CO]^+$, 117 (3), 105 (3) $[PhCO]^+$, 92 (20) $[4\text{-}CH_3C_6H_5]^+$, 91 (49) $[4\text{-}CH_3C_6H_4]^+$, 90 (6), 89 (4), 77 (5) $[C_6H_5]^+$, 65 (39).

EXPERIMENTAL BIOLOGICAL PART

We have studied the antimicrobial and anticonvulsive activity of the synthesized hydroxyindole derivatives.

The antimicrobial activity of the synthesized compounds with respect to standard strains *Escherichia coli* M_{17} and *Staphylococcus aureus* P-209 was determined by a conventional method of sequential double serial dilutions in a beef-infusion broth for a bacterial load of 250×10^3 microbial cells per 1 ml solution [28]. The active dose was determined as the minimum inhibiting concentration (MIC) of the compound, that is, the maximum dilution ensuring complete inhibition of the growth of test microbes. The antimicrobial activity of the synthesized compounds was compared to that of several modern antibacterial preparations belonging to the 4-oxoquinoline-3-carboxylic acid group, including oxolinic and nalydixic acids, flumequine and norfloxacin [37, 38].

The anticonvulsive activity was studied using the maximum electroshock test [39] on white mice weighing 18 – 24 g. The compounds were intraperitoneally injected to test animals in the form of a 2% starch suspension. The effect was compared to that of a model compound 3-acetonyl-3-hydroxy-2-indolone (V) [19, 21] and a reference drug haxamidine [40].



V

It was established that 3-acylmethylene-2-indolones III exhibited bacteriostatic action upon both bacterial strains studied (Table 3). The maximum bacteriostatic activity with respect to *St. aureus* was observed for compound IIIb (MIC = 3.9 μg/ml). Hydroxyindole IIIa showed equally high activity (MIC = 7.8 μg/ml) with respect to both the *E. coli* and *St. aureus* strains. The action of compounds IIIa and IIIb on *St. aureus* exceeded that of oxolinic and nalydixic acids and flumequine, but was lower than the effect of norfloxacin. The latter fact is by no means unexpected, since molecules of 3-acylmethylene-2-indolones contain no fluorine atoms that usually favor the antimicrobial activity in the series of active compounds. Compound IIIa produced a maximum effect on *E. coli* that was still less pronounced as compared as to the action of reference drugs.

Note that 3-aroylmethylene-2-indolones IIId, IIIk, and IIIn (having no substituents in the benzene nucleus) are, for the most part, of low active and are characterized by a less pronounced antistaphylococcal action as compared to that of the corresponding 5-bromo derivatives IIIf, IIIh, IIIl, and IIIo. At the same time, a comparison of the activity of these analogs with respect to *E. coli* showed a more or less clearly

TABLE 3. Antibacterial Activity (MIC, μg/ml) of 3-Substituted 2-Indolones III – V

Compound	*St. aureus* P-209	*E. coli* M_{17}
IIIa	7.8	7.8
IIIb	3.9	31.2
IIIc	250	250
IIId	1000	1000
IIIf	250	500
IIIg	62.5	1000
IIIh	31.2	1000
IIIi	250	500
IIIj	125	125
IIIk	250	250
IIIl	15.6	1000
IIIm	62.5	62.5
IIIn	Inactive	500
IIIo	15.6	1000
IIIp	62.5	31.2
IVb	250	1000
IVc	125	1000
IVd	500	250
IVe	500	500
V	1000	500
Oxolinic acid*	12.5 – > 256	0.5 – 16
Nalydixic acid*	12.5 – > 256	0.5 – 8
Flumequin*	12.5 – > 256	0.5 – 16
Norfloxacin*	0.25 – 1.0	0.06 – 1.0

* MIC range [37, 38].

TABLE 4. Anticonvulsive Activity of Some 3-Substituted 2-Indolones III (Maximum Electroshock Test)

Compound	Maximum dose, mg/kg	ED_{50}, mg/kg
IIId	600	359.2 (269.9 – 448.5)
IVa	600	245.2 (184.3 – 306.2)[1]
IVc	600	375.8 (296.9 – 454.7)
V	–	40[2]
Hexamidine	–	90 (79 – 103)[3]

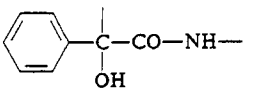
[1] reported ED_{50} = 102 mg/kg, LD_{50} = 414 mg/kg (protection index $LD_{50}/ED/50 = 4.06$) [21]; [2] LD_{50} = 490 mg/kg (protection index 12.25); [3] protection index 3.77.

manifested inverse correlation, whereby the 5-bromo derivatives have proved to be less active. Replacing the hydrogen atom of the lactam NH group in compounds IIIa, IIIk, and IIIn by the acetyl group (compounds IIIc, IIIm, and IIIp) increases the bacteriostatic on both cultures, but this trend is clearly manifested only in 3-aroylmethylene-2-indolones unsubstituted in position 5. Indoles having no substituents in the benzene nucleus and compounds III unsubstituted in position 5 showed an increase in the antistaphylococcal action in the following order: X = 4-$O_2NC_6H_4$ (IIIn) < Ph (IIId) < 4-ClC_6H_4 (IIIk) < 4-MeC_6H_4 (IIIg) < OMe (IIIa). Thus, the effect increases with the electron donor properties of substituent X in the acylmethylene fragment. A different order of the growth in activity with respect to *St. aureus* was observed for the 5-bromo derivatives: X = Ph (IIIf) < 4-BrC_6H_4 (IIIh) < 4-ClC_6H_4 (IIIl) = 4-$O_2NC_6H_4$ (IIIo) < OMe (IIIb). No such correlations in the degree of the activity manifestations were revealed with respect to the *E. coli* culture.

A much lower bacteriostatic activity was observed in 3-aroylmethyl-3-hydroxy-3-indolones (IV) and 3-acetonyl-3-hydroxy- 3-indolone (V) showing only a weak effect (MIC = 125 – 1000 μg/ml) on both the test cultures studied. Thus the transition from compounds with acylmethylene fragments to their hydrolysis products (3-hydroxy-3-acylmethyl derivatives) markedly reduces the antibacterial activity. This fact agrees with our earlier data showing a higher bacteriostatic activity of 2- acylmethylene 2,3-dihydro-3-furanones [41 – 43] as compared to that of the products, obtained by adding water [41], arylamines, or hydrazines [44] in the methylene fragment, or the corresponding 2-hydroxy-2-acylmethyl derivatives of the five- membered 3-oxoheterocycles [42, 43, 45]. Thus we have once again confirmed the assumption that the double bond, activated by acceptor substituents, is a pharmacophore unit responsible for the antimicrobial manifestations.

As for the results of the maximum electroshock tests, a weak anticonvulsive effect (lower as compared to the action of hexamidine) was observed for three of the hydroxyindole derivatives studied: 3-phenacylidene derivative (IIId) and 3-aroylmethyl-3-hydroxy-2-indolones (IVa and IVc) (Table 4). Our results agree with the other published data showing the absence of anticonvulsive properties in 3-aroylmethylene-2-indolones having substituents in the benzene rings [19, 21] at doses up to 600 mg/kg.

On the basis of the structural data, obtained by the x-ray diffraction analysis, it was earlier suggested that the comparative anticonvulsive properties of 3-benzoylmethyl-3-hydroxy-2-indolone (IVa), diphenin, and carbamazepine are due to their close electronic configurations [17]. Later we have established that the anticonvulsive effect can be attributed to the simultaneous presence of a hydroxy group at the tertiary asymmetric carbon atom (connected to at least one unsubstituted or only *ortho*-substituted benzene ring) and a secondary or primary amide group (fragment VI) [46, 47]. These data do not contradict the commonly accepted notions that the anticonvulsive activity is determined by certain structural fragments having either cyclic or linear structures [48].



VI

Apparently, the hydroxyindole ring by itself is not a pharmacophore and the anticonvulsive properties are determined by the presence of an active structural fragment (VI) in the initial compounds or their active metabolites. The anticonvulsive activity of other hydroxyindoles, such as 3-hydrazone isatin [49], is explained by the presence of a hydrazone pharmacophore fragment [49, 50].

Finally, it should be noted that, according to the published data, the 3-substituted 2-indolones III and IV are medium-toxicity compounds with LD_{50} above 400 mg/kg [11, 12].

REFERENCES

1. T. Kato, H. Yamanaka, and H. Ichikawa, *Chem. Pharm. Bull.*, **17**(3), 481 – 489 (1969).
2. K. Okada, M. Kondo, H. Tanino, et al., *Heterocycles*, **34**(3), 589 – 598 (1992).
3. K. C. Joshi, A. Dandia, and S. Khanna, *Indian J. Chem.*, **29B**(12), 1125 – 1128 (1990).
4. A. A. S. El-Ahl, H. Hussein, and M. A. Metwally, *J. Chem. Res. Synop.*, No. 1, 14 – 15 (1994).
5. G. Tacconi, A. G. Invernizzi, and G. Desimoni, *J. Chem. Soc. Perkin Trans. 1*, No. 17, 1872 – 1879 (1976).
6. K. C. Joshi, R. Jain, and S. Arora, *Indian J. Chem.*, **29B**(4), 369 – 371 (1990).
7. K. C. Joshi, A. Dandia, and S. Bhagat, *Indian J. Chem.*, **31A**(2), 98 – 104 (1992).
8. A. Casaschi, G. Desimoni, G. Faita, et al., *Gazz. Chim. Ital.*, **123**(3), 137 – 143 (1993).
9. A. Casaschi, G. Desimoni, G. Faita, et al., *Heterocycles*, **37**(3), 1673 – 1686 (1994).
10. K. C. Joshi, A. Dandia, C. S. Sharma, et al., *J. Indian Chem. Soc.*, **71**(6 – 8), 459 – 462 (1994).
11. R. S. Belen'kaya, E. I. Borenko, M. N. Zemtsova, et al., *Khim.-Farm. Zh.*, **15**(3), 29 – 35 (1981).
12. R. Élderfield (ed.), *Heterocyclic Compounds* [Russian translation], Vol. 3, Moscow (1954), pp. 96, 118, 166, 174.
13. J. Bergman, *Acta Chem. Scand.*, **25**(8), 2865 – 2870 (1971).
14. P. L. Julian and H. C. Printy, *J. Am. Chem. Soc.*, **75**(18), 5305 – 5309 (1953).
15. H. A. Brandman, *J. Heterocycl. Chem.*, **10**(3), 383 – 384 (1973).
16. E. N. Koz'minykh, E. S. Berezina, V. O. Koz'minykh, et al., *Abstracts of Papers. Conf. Synthesis of New Drugs* [in Russian], Penza (1993), pp. 29 – 30.
17. P. W. Codding, T. A. Lee, and J. F. Richardson, *J. Med. Chem.*, **27**(5), 649 – 654 (1984).
18. N. Hirose, S. Sohda, and S. Toyoshima, *J. Pharm. Soc. Jpn.*, **91**(12), 1323 – 1334 (1971).
19. F. D. Popp and B. E. Donigan, *J. Pharm. Sci.*, **68**(4), 519 – 520 (1979).
20. F. D. Popp, R. Parson, and B. E. Donigan, *J. Heterocycl. Chem.*, **17**(6), 1329 – 1330 (1980).

21. F. D. Popp, R. Parson, and B. E. Donigan, *J. Pharm. Sci.*, **69**(10), 1235 – 1237 (1980).
22. US Patent No. 3428649 (1968), *Ref. Zh. Khim.*, No. 11, 11N 588P (1970).
23. C. S. Franklin and A. C. White, *J. Chem. Soc.*, No. 2, 1335 – 1337 (1963).
24. Z. H. Khalil, *Z. Naturforsch.*, **33**(2), 209 – 211 (1978).
25. V. O. Koz'minykh, E. E. Kal'nitskaya, V. G. Armaginova, et al., *Problems of Pharmaceutics, Teaching and Employment of Pharmacists. Proc. Rep. Sci. Conf. on Pharmaceutics and Pharmacology* [in Russian], Pyatigorsk (1993), pp. 200 – 201.
26. J. Parrick, *Canad. J. Chem.*, **42**(1), 190 – 191 (1964).
27. H. Strzelecka, *Acad. Sci. C.*, **273**(18), 1194 – 1197 (1971).
28. E. N. Koz'minykh, E. S. Berezina and V. O. Koz'minykh, *Zh. Obshch. Khim.*, **66**(6), 1790 – 1796 (1966).
29. E. S. Berezina, E. N. Koz'minykh, N. D. Kalmykova, et al., in: *Current Problems of Pharmaceutics: Interinst. Collection of Sci. Papers* [in Russian], Perm Pharmaceutical Institute, Perm (1995), p. 2 – 3.
30. D. Zacharova-Kalavska and A. Kosturiak, *Coll. Czech. Chem. Commun.*, **40**(9), 2626 – 2631 (1975).
31. S. Khetan and M. V. George, *Canad. J. Chem.*, **47**(19), 3545 – 3551 (1969).
32. A. V. Dombrovskii and M. I. Shevchuk, *Zh. Obshch. Khim.*, **33**(4), 1263 – 1269 (1963).
33. O. Isler, H. Gutmann, M. Montavon, et al., *Helv. Chim. Acta*, **40**(5), 1242 – 1249 (1957).
34. G. Faita, M. Mella, P. P. Righetti, et al., *Tetrahedron*, **50**(37), 10955 – 10962 (1994).
35. I. G. Zenkevich and B. F. Ioffe, *Interpretation of the Mass spectra of Organic compounds* [in Russian], Leningrad (1986).
36. *Methods of Experimental Chemotherapy* [in Russian], G. N. Pershin (ed.), Moscow (1971), pp. 100 – 117.
37. R. G. Glushkov, I. B. Levshin, N. B. Marchenko, et al., *Khim.-Farm. Zh.*, **18**(9), 1048 – 1064 (1984).
38. G. A. Mokrushina, V. N. Charushin, and O. N. Chupakhin, *Khim.-Farm. Zh.*, **29**(9), 5 – 19 (1995).
39. K. S. Raevskii, *Farm. Toksikol.*, No. 4, 495 – 497 (1961).
40. M. A. Klyuev (ed.), *Drugs Used in Medical Practice in the USSR. A Handbook* [in Russian], Moscow (1990).
41. V. O. Koz'minykh, N. M. Igidov, E. N. Koz'minykh, et al., *Khim.-Farm. Zh.*, **25**(12), 43 – 47 (1991).
42. V. O. Koz'minykh, N. M. Igidov, E. N. Koz'minykh, et al., *Pharmazie*, **47**(4), 261 – 263 (1992).
43. V. O. Koz'minykh, N. M. Igidov, E. N. Koz'minykh, et al., *Pharmazie*, **48**(2), 99 – 106 (1993).
44. V. O. Koz'minykh, N. M. Igidov, E. N. Koz'minykh, et al., *Khim.-Farm. Zh.*, **26**(2), 35 – 38 (1992).
45. V. O. Koz'minykh, G. A. Shavkunova, E. S. Berezina,et al., *Khim.-Farm. Zh.*, **28**(12), 31 – 35 (1994).
46. S. A. Shelenkova, V. O. Koz'minykh, and V. É. Kolla, *Biologically Active Compounds: Synthesis and Application* [in Russian], Penza (1992), pp. 113 – 115.
47. S. A. Shelenkova, V. É. Kolla, and V. O. Koz'minykh, *Abstract of Papers. Neuropharmacology at the Millenium Threshold: Int. Conf. on the 100 Anniversary of Acad. S. V. Anichkov* [in Russian], St. Petersburg, Part. II (1992).
48. R. Barlow, *Introduction to Chemical Pharmacology* [Russian translation], Moscow (1959), pp. 99 – 107.
49. V. O. Koz'minykh, V. É. Kolla, S. A. Shelenkova, et al., *Khim.-Farm. Zh.*, **27**(1), 45 – 51 (1993).
50. F. D. Popp, *Eur. J. Med. Chem.*, **24**, 313 – 315 (1989).