4.16 g potassium iodide, heated to 80°, and treated dropwise with a solution of 3.3 g 2-methylbenzimidazole in 40 ml cyclohexanone. The reaction mixture is boiled for 16 h, the residue filtered off, and the filtrate washed with water and extracted with a 15% solution of tartaric acid. The acidic aqueous phase is neutralized with aqueous sodium hydroxide solution and extracted with dichloroethane. The dichloroethane is evaporated off, and the resulting dark-brown oil is dissolved in ethanol. The solution is treated dropwise with an ether solution of picric acid. The precipitate is filtered off and crystallized from 80% ethanol, to give 3.9 g (40%) of a yellow crystalline powder, mp 223-225° (decomp.). Found, %: C 58.98; H 4.42; N 13.57; S 5.03. $C_{24}H_{33}N_3S \cdot C_6H_3N_3O_7$. Calculated, %: C 59.10; H 4.27; N 13.60; S 5.18.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-ARYL-SUBSTITUTED 4,7-DIHYDRO- AND 4,5,6,7-TETRAHYDROISOINDOLES

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Information about the antimicrobial activity of compounds containing an isoindole fragment is restricted to just a few patents [1-3]. This is evidently due to the fact that, until recently, isoindoles have been little studied because of the considerable difficulties involved in their synthesis.

In [4, 5], we developed a convenient method for preparing 2-aryl-substituted 4,7-dihydro- and 4,5,6,7-tetrahydroisoindoles from adducts formed by Diels—Adler condensation of 2,5-dimethoxy-2,5-dihydrofuran with various dienes.

In order to search for new antibacterial agents and to study the relation between their structure and biological activity, we have synthesized a number of isoindoles according to the scheme

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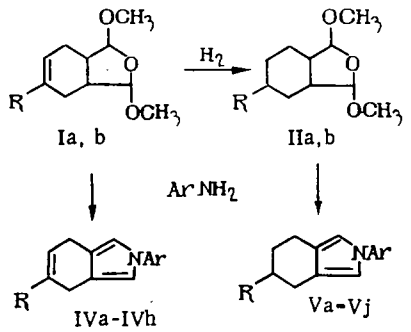
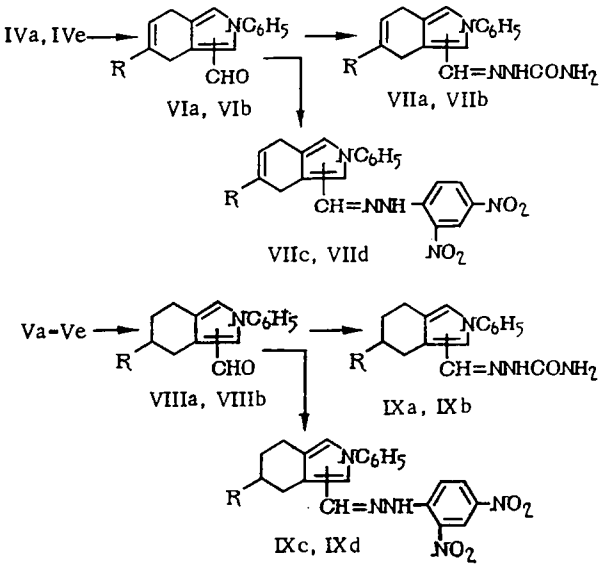


Ia, b IIa, b IVa-IVh Va-Vj

Ia, IIa: R = H; Ib, IIb: R = CH_3; IIIa: Ar = C_6H_5; IIIb: Ar = o–$CH_3C_6H_4$; IIIc: Ar = m–$CH_3C_6H_4$; IIId: Ar = p–$CH_3C_6H_4$; IIIe: Ar = m–$NO_2C_6H_4$; IIIf: Ar = p–$NO_2C_6H_4$; IVa, Va: R = H, Ar = C_6H_5; IVb, Vb: R = H, Ar = o–$CH_3C_6H_4$; IVc, Vc: R = H, Ar = m–$CH_3C_6H_4$; IVd, Vd: R = H, Ar = p–$CH_3C_6H_4$; IVe, Ve: R = CH_3, Ar = C_6H_5; IVf, Vf: R = CH_3, Ar = o–$CH_3C_6H_4$; IVg, Vg: R = CH_3, Ar = m–$CH_3C_6H_4$; IVh, Vh: R = CH_3, Ar = p–$CH_3C_6H_4$; Vi: R = CH_3, Ar = m–$NO_2C_6H_4$; Vj: R = CH_3, Ar = p–$NO_2C_6H_4$.

Some of them were also subjected to the following formylation reaction:



VIa, VIb VIIa, VIIb VIIc, VIId VIIIa, VIIIb IXa, IXb IXc, IXd

VIa-IXa, VIIc, IXc : R = H; VIb-IXb, VIId, IXd : R = CH_3

The starting materials used for the synthesis of the isoindoles were 1,3-dimethoxy-1,3,4,7,8,9-hexahydrobenzofuran (Ia), its 5-methyl homolog (Ib), 1,3-dimethoxyoctahydrobenzofuran (IIa), and its 5-methyl homolog (IIb) [6]. The amine reactants used were aniline (IIIa), o-, m- and p-toluidine (IIIb-IIId, respectively), and m- and p-nitroaniline (IIIe and IIIf, respectively). The reaction was effected by heating in glacial acetic acid.

An analysis of the results obtained showed that the yield of the reaction products under optimun conditions depends to a considerable extent on the position and nature of the substituent in the ring of the aromatic amine (Table 1 and [5]). High isoindole yields (80-97%) are obtained with aniline, p-toluidine and p-nitroaniline. In the case of substituents in the meta and ortho position, an appreciable decrease in yield is observed (to 55-68%) and repeated recrystallization is required to purify the reaction products, while o-nitroaniline does not react at all. In this case, the starting materials (amine and adduct) are recovered when the reaction mixture is worked up. This is clearly connected with the steric hindrance exerted by the substituents in the ortho and meta positions and with the electron-density distribution in the isoindole molecule.

Compounds IVa, IVe, Va and Ve were subjected to Vilsmeier formylation while cooling [7], giving good yields of 1-formyl-2-phenyl- and 5-methyl-(1- or 3-)formyl-2-phenyl-4,7-dihydroisoindole (VIa and VIb, respectively) and of 1-formyl-2-phenyl- and 5-methyl-(1- or 3-)formyl-2-phenyl-4,5,6,7-tetrahydroisoindole (VIIIa and VIIIb, respectively). Semicarbazones (VIIa, VIIb, IXa, and IXb) and 2,4-dinitrophenylhydrazones (VIIc, VIId, IXc, and IXd) were prepared

TABLE 1. 4,7-Dihydro- and 4,5,6,7-Tetrahydroisoindoles

Compound	Adduct	Amine	Yield, %	Melting point, deg*	R_f†	Found, %			Empirical formula	Calculated, %			IR spectrum (cm^{-1})		
						C	H	N		C	H	N	$\nu_{pyrrole}$	ν_{C-N}	$\nu_{=CH}$
IVb	Ia	IIIb	60	—‡	0,51	85,69	7,49	6,94	$C_{15}H_{15}N$	86,08	7,22	6,69	1535	1065	762
IVc	Ia	IIIc	55	68—9	0,52	86,22	6,98	6,95	$C_{15}H_{15}N$	86,08	7,22	6,69	1535	1063	800
IVf	Ib	IIIb	68	69—70	0,50	86,37	7,62	6,30	$C_{16}H_{17}N$	86,06	7,67	6,27	1530	1067	740
IVg	Ib	IIIc	63	57—8	0,51	85,97	7,85	6,21	$C_{16}H_{17}N$	86,06	7,67	6,27	1535	1060	795
Va	IIa	IIIa	86	103—4	0,57	85,49	7,85	6,91	$C_{14}H_{15}N$	85,35	7,68	7,11	1528	1040	695, 758
Vb	IIa	IIIb	63	64—5	0,60	85,43	7,98	6,62	$C_{15}H_{17}N$	85,26	8,11	6,63	1530	1060	760
Vc	IIa	IIIc	61	42—3	0,62	85,50	8,30	6,71	$C_{15}H_{17}N$	85,26	8,11	6,63	1528	1055	790
Vf	IIb	IIIb	59	49—51	0,65	85,54	8,80	5,89	$C_{16}H_{19}N$	85,28	8,50	6,22	1535	1060	759
Vg	IIb	IIIc	60	37—8	0,67	85,52	8,73	6,12	$C_{16}H_{19}N$	85,28	8,50	6,22	1530	1058	800
Vi	IIb	IIIe	55	63—4	0,13	69,88	6,46	10,83	$C_{15}H_{16}N_2O_2$	70,30	6,29	10,93	1535	1021	810
Vj	IIb	IIIf	97	114—6	0,08	70,16	6,46	11,05	$C_{15}H_{16}N_2O_2$	70,30	6,29	10,93	1535	1048	833

*All compounds were crystallized from 96% ethanol.
†Solvent heptane/benzene (19:1).
‡Boiling point 144-146°/1 mm.

TABLE 2. Formylated 2-Phenyl-4,7-dihydro- and -4,5,6,7-tetrahydroisoindoles

Compound	Starting isoindole	Yield, %	Boiling point, deg/mm	Found, %			Empirical formula	Calculated, %			IR spectrum, cm^{-1}	
				C	H	N		C	H	N	$\nu_{C=O}$	$\nu_{pyrrole}$
VIa	IVa	52	192—5/1	80,68	5,95	5,86	$C_{15}H_{13}NO$	80,78	5,88	6,28	1655	1535
VIb	IVд	56	190—3/1	80,53	6,48	6,06	$C_{16}H_{15}NO$	80,98	6,38	5,90	1650	1535
VIIIa	Va	75	75—6*	80,23	6,76	6,46	$C_{15}H_{15}NO$	79,97	6,71	6,22	1665	1530
VIIIb	Vд	58	165—6/1	79,98	7,10	5,86	$C_{16}H_{17}NO$	80,30	7,16	5,85	1665	1532

*Melting point 75-76° (from n-heptane).

TABLE 3. Semicarbazones and 2,4-Dinitrophenylhydrazones of Formylated 2-Phenyl-4,7-dihydro- and -4,5,6,7-tetrahydroisoindoles

Compound	Starting aldehyde	Yield, %	Melting point, deg	Found, %	Empirical formula	Calculated, %
				N		N
VIIa	VIa	78	177—9	20,29	$C_{16}H_{16}N_4O$	19,95
VIIb	VIb	80	166—7	18,84	$C_{17}H_{18}N_4O$	19,04
IXa	VIIIa	76	172—4	19,93	$C_{16}H_{18}N_4O$	19,84
IXb	VIIIb	79	160,5—1,5	19,01	$C_{17}H_{20}N_4O$	18,91
VIIb	VIa	97	163—4*	17,84	$C_{21}H_{17}N_5O_4$	17,37
VIId	VIb	95	166—9*	16,74	$C_{22}H_{19}N_5O_4$	16,87
IXc	VIIIa	93	193—8*	17,69	$C_{21}H_{19}N_5O_4$	17,31
IXd	VIIIb	95	197—200*	16,70	$C_{22}H_{21}N_5O_4$	16,79

*With decomposition.

for all the formyl derivatives.

Compounds VIb, IXb, VIId, and IXd may be pure substances or they may be mixtures of isomers differing in the position of the CH_3 group relative to the CHO, $CHNNHCONH_2$ or $CHNNH-(C_6H_3)(NO_2)_2$ group. According to the results of thin-layer chromatography, all these substances are isomer mixtures.

The structure of the isoindoles and their derivatives is in good agreement with their elementary analysis data and their IR and UV spectra (Tables 1-3, Fig. 1). The UV spectra of compounds IVa-IVh and Va-Vj contain one characteristic maximum in the 245-275-nm region. The absorption curves for Vi and Vj have an additional maximum in the 345-355-nm region due to the presence of a nitro group in the isoindole molecule. The UV spectra of VIa-IXa and VIb-IXb have two characteristic maxima at 225-228 and 300-303 nm. Comparison of the UV spectra of the formyl derivatives with those of the starting isoindoles shows that the introduction of the aldehyde group leads to a considerable shift in the long-wavelength maximum (by ∿30 nm). The bathochromic shift is even greater in the case of the semicarbazones due to the increased length of conjugation in the molecule [8].

The antimicrobial activity of the 4,7-dihydro- and 4,5,6,7-tetrahydroisoindoles and their derivatives was studied by twofold serial dilution in a semisynthetic nutrient medium with a pH of 7.2 (Soviet-produced TU 10P 332-69 yeast hydrolyzate) against the test microorganisms *Staphyloccus aureus* 209 r., *Escherichia coli* M-17, *Proteus vulgaris* No. 30, *Pseudomonas pyocyanea* No. 7, and *Candida albicans* No. 35. The experimental data, which are given in Table 4, indicate that the compounds synthesized are highly active against the test microorganisms.

We could discern no clear difference in the effect of the various substituents in the isoindole ring on the antimicrobial activity, since the latter was always of the same order of magnitude (37-75 μg/ml) against the above group of microorganisms. It is noteworthy, however, that the isoindoles have an inhibiting effect on Gram-negative bacteria, especially *Proteus vulgaris* and *Pseudomonas pyocyanea*, which, as is known, are extremely resistant to the action of various chemotherapeutic agents.

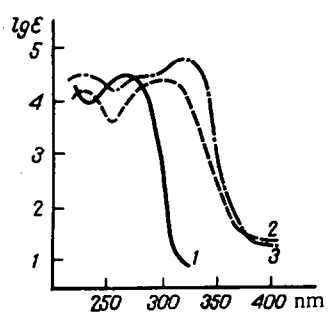


Fig. 1. UV spectra in ethanol: 1) Va; 2) VIIIa; 3) IXa.

TABLE 4. Antimicrobial Activity of Test Compounds (minimum inhibitory concentration in μg/ml)

Compound	Microorganisms				
	St. aureus	E. coli	Pr. vulgaris	Ps. pyocyaneum	Candida albicans
IVa	25	37	75	37	25
IVc	37	37	75	75	37
IVd	50	50	75	75	37
IVe	4,5	37	75	37	17
IVh	50	37	75	37	37
Va	75	37	75	75	75
Vb	37	37	37	37	37
Vd	37	37	75	37	37
Vg	17	37	37	37	37
Vh	37	37	75	37	37
Vi	17	25	25	37	25
Vj	17	37	37	37	25
VIIIa	17	37	75	75	37
VIIIb	4,5	37	75	37	17
VIIa	25	37	75	37	37
VIIb	25	37	75	37	25
IXa	37	37	75	75	37
IXb	37	37	75	37	37
VIIc	17	37	75	75	25
VIId	17	37	75	37	17
IXc	37	37	75	75	25
IXd	37	37	75	37	37

The isoindoles and their derivatives are considerably more active against *Staphylococcus aureus*. Isoindole IVe and aldehyde VIIIb, which contain a methyl radical in the 5 position of the isoindole ring, prove to have the highest activity against *St. aureus* and the fungus *Candida* (the minimum inhibitory concentration of these compounds against *St. aureus* is 4.5 μg/ml, and that against *Candida* is 17 μg/ml). Replacement of the aldehyde group by a semicarbazone or dinitrophenylhydrazone group somewhat weakens the antimicrobial effect: Compounds VIIa, IXa, VIIb and IXb are active at a concentration of 17-25 μg/ml, and compounds VIIc, IXc, VIId and IXd are active at a concentration of 37 μg/ml. A similar decrease in activity is observed when there is no methyl group in the 5 position of the isoindole ring.

The introduction of substituents into the benzene ring in the ortho, meta or para position with respect to the nitrogen atom has no effect on the antimicrobial activity of the test isoindoles.

The mycostatic properties of isoindoles with different structures are approximately the same. The fact that the isoindoles have antimicrobial activity indicates the need for a deeper study of this group of chemicals as agents for the etiotropic therapy of infectious diseases.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 instrument. The liquid substances were investigated as thin films, and the crystals were mulled in mineral oil. The UV spectra were recorded with an SF-4A instrument. Thin-layer chromatography was carried out on alumina (activity II) using hexane/ethyl acetate, cyclohexane/ethyl acetate, cyclohexane/benzene and cyclohexane/ethanol as solvent systems. The spots were visualized with iodine vapor.

The synthesis of compounds IVa, IVd, IVe, IVh, Vd, Ve, and Vh is described in [5].

2-(m-Tolyl)-4,7-dihydroisoindole (IVc). A mixture of 2.1 g Ia, 1.1 g IIIc and 3 ml glacial acetic acid was refluxed on a boiling-water bath for 1 h. The crystals precipitated after cooling were separated, washed with water, and recrystallized from ethanol. Compounds IVg, Va, Vg, Vi, and Vj were prepared analogously.

2-(o-Tolyl)-4,5,6,7-tetrahydroisoindole (Vc). A mixture of 2.1 g IIa, 1.1 g IIIc and 3 ml glacial acetic acid was heated on a boiling-water bath for 1.5 h. The cooled mixture was poured onto crushed ice (10 g) and the resulting oil extracted with ether. The extract

was washed several times with saturated sodium bicarbonate solution and water, and dried with calcined magnesium sulfate. After removing the solvent, the residue was distilled under vacuum. The resulting liquid product crystallized on standing. Compounds IVb, IVf, Vb, and Vf were prepared analogously.

1-Formyl-2-phenyl-4,7-dihydroisoindole (VIa). A solution of 5 g IVa in 150 ml of freshly distilled dimethylformamide was cooled with a mixture of ice and salt for 30 min. The stirred mixture was then treated dropwise with 3.8 g of freshly distilled phosphorus oxychloride, the reaction temperature being kept at 0-5°. The solution darkened. The mixture was gradually warmed to room temperature, boiled on a water bath for 2 h, cooled to 0°, treated with crushed ice (50 g), and stirred while adding saturated sodium bicarbonate solution to neutralize the hydrochloric acid formed by decomposition of the $POCl_3$. An oil separated on standing in the cold. The oil was extracted with ether, the extract washed with water and dried with calcined magnesium sulfate, the solvent removed, and the residue distilled under vacuum. Compounds VIb and VIIb were prepared analogously.

1-Formyl-2-phenyl-4,5,6,7-tetrahydroisoindole (VIIa). A solution of 3 g Va in 50 ml dimethylformamide was cooled with a mixture of ice and salt for 30 min. The stirred solution was treated dropwise with 2.3 g of freshly distilled phosphorus oxychloride while keeping at a temperature no higher than −10°. The mixture was stirred vigorously while warming to room temperature, boiled for 3 h on a water bath, cooled to 0°, treated with 30 g of crushed ice, and stirred while adding saturated sodium bicarbonate solution to neutralize the hydrochloric acid formed by decomposition of the phosphorus oxychloride in such a way that the temperature of the mixture did not exceed 2°. An oil separated on standing in the cold. The oil was extracted with ether, the extract washed with water and dried with calcined magnesium sulfate, and the solvent removed to give yellow acicular crystals.

1-Formyl-2-phenyl-4,7-dihydroisoindole Semicarbazone (VIIa). A solution of 1 g semicarbazide hydrochloride in 5 ml water was mixed with a solution of 1 g potassium acetate in 5 ml ethyl alcohol. The mixture was treated with 0.5 g VIa. The yellowish precipitate was washed several times with water and benzene. Compounds VIIb, IXa, and IXb were prepared analogously.

1-Formyl-2-phenyl-4,7-dihydroisoindole 2,4-Dinitrophenylhydrazone (VIIc). A solution of 1.5 g 2,4-dinitrophenylhydrazine in 3 ml concentrated sulfuric acid was diluted with 15 ml ethyl alcohol. A solution of 0.5 g VIa in 5 ml ethyl alcohol was added at once. A dark-red precipitate formed immediately. Compounds VIId, IXc, and IXd were prepared analogously.

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