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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-AMINO-2-ARYLAZOINDOLE HYDROCHLORIDES

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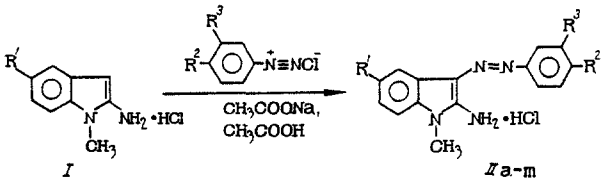
Indole series compounds that have an aryl group in the β-position are known to exhibit tuberculostatic activity [1]. As a continuation of our research on derivatives of 2-aminoindole, we synthesized the previously unknown compounds 2-amino-3-arylazoindoles (IIa-m) and investigated their antimicrobial activity.

We synthesized the 2-amino-3-arylazoindoles by reacting 2-amino-1-methylindoles (I) with aryldiazonium salts. Electrophilic substitution reactions among the 2-aminoindoles (bromination, nitration, and sulfonation) yield substitution products in position 3 [3]. Substitution occurs at position 5 of the benzene ring only in strongly acid media where 2-aminoindole exists in the iminoindole tautomer form [3]. Under the reaction conditions we selected (acetate buffer solution pH 5.0), the reaction between the diazonium salts and the 2-amino-1-methylindoles I takes place more readily at position 3, which is more susceptible to electrophilic attack that results in the formation of the 2-amino-3-arylazoindoles IIIa-m.



I IIa-m

All of the synthesized compounds IIa-m have been described by IR-spectral and element analysis data. The IR spectra of compounds IIa-m have broad absorption bands at 3600-2500 cm^{-1} that correspond to the absorption of the saline amino group, and the absorption bands at 1670-1710 cm^{-1} correspond to the absorption band of the C=N bond. The azo group band apparently falls into the absorption region of the aromatic rings. The structure of the 2-amino-3-arylazoindoles II was also confirmed by PMR spectral data. Thus, for example, the PMR spectrum of compound IIa exhibits proton signals of the NCH_3 groups at 2.80 ppm, the OCH_3 groups at 3.09 ppm, and in the aromatic protons (in the region 6.13-6.50 and 6.80-7.15 ppm) there is a broadened proton signal of the NH_2 group at 7.40 ppm.

The synthesized 2-amino-3-arylazoindole hydrochlorides IIa-m appear as yellow or orange dyed crystalline substances with a mp over 200°C. Their characteristics are given in Table 1.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a Perkin–Elmer 577 spectrophotometer in petroleum jelly. PMR spectra were recorded on a Tesla BS-467 (60 MHz) instrument in DMSO-D_6.

General Method for Obtaining 2-Amino-3-arylazo-1-methylindole Hydrochlorides (IIa-m). A solution of 0.69 g (0.01 mole) of $NaNO_2$ in 5 ml of water was added to 0.01 mole of substituted aniline in 7 ml of diluted HCl (1:1) upon cooling to 0°C. The resultant solution of

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TABLE 1. Characteristics of 2-Amino-3-arylazo-1-methylindole Hydrochlorides IIa-m

Compound	R'	R''	R'''	mp, °C	Yield, %	Empirical formula	IR spectrum, cm^{-1}
IIa	H	O Me	H	264 (decomposition)	84	$C_{16}H_{17}ClN_4O$	3200—2550, 1675
IIb	H	OEt	H	240 (decomposition)	78	$C_{17}H_{19}ClN_4O$	3500—2550, 1670
IIc	H	OCH_2Ph	H	>250	75	$C_{22}H_{21}ClN_4O$	3500—2800, 1690
IId	H	—O—CH_2—O—		231 (decomposition)	60	$C_{16}H_{15}ClN_4O_2$	3300—2750, 1675
IIe	H	H	Cl	208	82	$C_{15}H_{14}Cl_2N_4$	3450—2600, 1690
IIg	Br	Cl	H	>280	80	$C_{15}H_{13}BrCl_2N_4$	3450—2700, 1715
IIh	Br	Br	H	>270	64	$C_{15}H_{13}Br_2ClN_4$	3500—2700, 1690
IIi	H	Cl	Cl	>250	75	$C_{15}H_{13}Cl_3N_4$	3600—2700, 1700
IIj	H	H	CF_3	254 (decomposition)	77	$C_{16}H_{14}ClFN_4$	3600—3100, 1705
IIk	H	$NHCOCH_3$	H	>250	68	$C_{17}H_{18}ClN_5O$	3400—2800, 1705, 1675
IIℓ	H	COOH	H	>250	62	$C_{16}H_{15}ClN_4O_2$	3600—2600, 1710
IIm	H	H	COOH	>250	64	$C_{16}H_{15}ClN_4O_2$	3550—2550, 1700

TABLE 2. Antimicrobial Activity of 2-Amino-3-arylazo-1-methylindole Hydrochlorides (minimum suppressive concentration, μg/liter)

Compound	S. aureus 209P	E. coli ATCC 25922	Mycobacterium									Microsporum canis 3/84	Trichophyton gypseum 5/33	Candida albicans 1755
			H37RV	academia	bovis 8	kansasii	avium	intracellulare	fortuitum	aquae	ATCC 607			
IIa	62,5	>250	3,5	—	—	—	—	—	—	—	—	62,5	62,5	125
IIb	31,2	>250	0,55	1,0	2,0	—	—	—	—	8,0	23	125	125	125
IIc	>250	>250	3,5	—	3,5	153	1000	—	>1000	—	>1000	31,2	31,2	31,2
IId	62,5	>250	<0,08	2,5	0,55	<0,08	3,5	—	0,55	—	23	31,2	31,2	31,2
IIe	7,8	>250	<0,08	<0,08	<0,08	3,5	3,5	—	3,5	—	3,5	3,9	31,2	2,0
IIg	0,5	>250	—	—	—	—	—	—	—	—	—	3,9	7,8	62,5
IIh	0,5	>250	—	—	—	—	—	—	—	—	—	3,9	3,9	31,2
IIi	2,0	>250	<0,08	<0,08	<0,08	<0,08	3,5	—	0,55	—	3,5	16,0	8,0	16,0
IIj	3,9	>250	<0,08	—	<0,08	0,55	0,55	—	—	3,5	3,5	62,5	62,5	62,5
IIk	125	>250	23	23	23	—	23	23	23	—	23	>250	>250	>250
IIℓ	>250	>250	>1000	>1000	>1000	—	1000	—	>1000	—	—	>250	>250	>250
IIm	>250	>250	>1000	>1000	>1000	—	>1000	—	>1000	—	>1000	>250	>250	>250

the diazonium salt was added dropwise with stirring to a mixture of 1.82 g (0.01 mole) of 2-amino-1-methylindole hydrochloride and 2.5 g (0.03 mole) of AcONa in 16 ml of AcOH at a temperature of ~5°C. The reaction mixture was stirred for 2 h, and the resultant precipitate was filtered off, then washed with water, dried, and recrystallized from aqueous ethanol (Table 1).

EXPERIMENTAL (BIOLOGICAL)

The activity of the 2-amino-3-arylazo-1-methylindole hydrochlorides was tested in vitro against true bacteria (12 compounds), mycobacteria (10 compounds), and fungi. The series dilution method was employed on fluid nutrient media: Hottinger's broth (120 mg % of amine nitrogen) for the bacteria; Soton's agent for the mycobacteria, and Hottinger's broth with 4% glucose for the fungi [7]. The experiments were conducted with the following strains: S. aureus 209P, E. coli ATCC 25922, Mycobacterium tuberculosis H37Rv, Academia and bovis 8, and with the conventional pathogenic mycobacteria M. cansasii, M. avium, M. Intracellulare, and M. fortium, and with the saprophytic mycobacteria M. aquae and M. ATCC 607, and with the fungi Microsporum canis 3/84, Trichophyton gypseum 5/35, and Candida albicans 1755.

The two compounds that exhibited pronounced activity against M. canis and Tr. gypseum (IIg) and against C. albicans (IIi) were tested in vivo. Compound IIg was tested on a guinea pig microspore model [7] upon the local application of a 3% ointment on an aqueous emulsion base, whereby the treatment was begun 7 days after infection (inoculation on scarified surface of dorsal skin) and continued for 3 weeks. Compound IIi, which was active against C. albicans 1755 at a minimum suppressive concentration of 16 μg/ml, was tested on a mouse canidiasis meningoencephalitis [2] elicited by intracerebral inoculation and oral administration of the compound for 5 days at doses of 31.2 and 62.5 mg/(kg·day).

Our investigations (Table 2) show that the dihalide substituted derivatives IIg-i were the most active in the experiments with S. aureus. Compounds IIe, j exhibited significant activity. All of the tested compounds were practically inactive against E. coli.

The haloid-containing derivatives IIe, i, j were also considerably active against mycobacteria in the experiments with most strains. Compounds IIa-c, k also exhibited activity. The introduction of a carboxylic radical into position 4 or 3 of the benzene ring completely eliminated any activity against bacteria.

The compounds with the highest level of activity in the experiments with S. aureus and the mycobacteria exhibited significant activity in the experiments with pathogenic fungi and were active against C. albicans.

Compound IIg did not exhibit any chemotherapeutic effect when applied locally in the guinea pig microspore model tests. The substance did cause local irritation.

The results of the mouse candidiasis model tests tabulated 10 days after inoculation indicated a certain therapeutic effect (the survival rate in the experimental groups was 30-40% of the treated animals and 10% of the nontreated animals). However, there was no reliable difference between the survival rate data for the experimental and control groups on the 30th day following inoculation.

The observed in vitro activity of the 2-amino-3-arylazo-1-methylindoles against the above-mentioned microorganisms that are quite apart from each other in the lower-plants classification [5, 6, 8] is apparently of a nonspecific character. The high level of activity that arylazoindoles exhibit against mycobacteria, as described in a number of studies [1, 4, 9], makes the continued testing of the above-mentioned compounds mandatory.

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