SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 1H,10H-BENZO[E]PYRROLO[3,2-G]INDOLE DERIVATIVES

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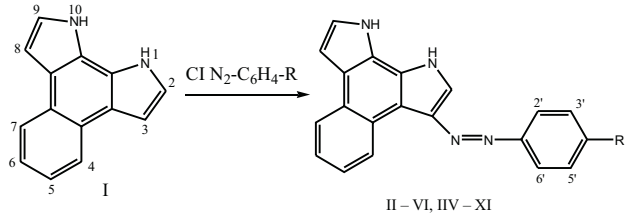
We have synthesized a series of new phenylazo derivatives of 1*H*,10*H*-benzo[*e*]pyrrolo[3, 2-*g*]indole containing 3-(*p*-bromophenylazo) (**II**), 3-(*p*-iodophenylazo) (**III**), 3-(*p*-sulfamidophenylazo) (**IV**), 3-formyl (**V**), 3,8-diformyl (**VI**), 3-phenylazo (**VII**), 3-(*p*-chlorophenylazo) (**VIII**), 3-(*p*-nitrophenylazo) (**IX**), 2,9-di(adamantylaminocarbonyl) (**X**), 2,9-di(*p*-benzenesulfamidoaminocarbonyl) (**XI**), 2,9-di(isonicotinoylhydrazidecarbonyl) (**XII**), and 2,9-di(carbohydrazide) (**XIII**) substituents. The antimicrobial, antifungal, and antituberculosis activity was investigated *in vitro* with respect to various microorganisms including conditionally pathogenic mycobacteria and pathogenic fungi. It is established that the tested compounds possess high antimicrobial activity. The synthesized compounds are of great interest for further, more thorough investigations and experiments on animals with the corresponding infectious diseases.

Key words: benzopyrroloindole, phenylazoderivatives, azocoupling, antimicrobial, antifungal, antituberculosis activity.

Herein we present results from an investigation of the biological activity of several new and previously synthesized derivatives of 1*H*,10*H*-benzo[*e*]pyrrolo[3,2-*g*]indole (**I**). New phenylazo derivatives were synthesized by azocoupling of benzopyrroloindole **I** with *p*-bromo-, *p*-iodo-, and *p*-sulfamidophenyldiazonium chlorides in order to study the antimicrobial activity. Electrophilic substitution produced mono-substituted products 3-(*p*-bromophenylazo)- (**II**), 3-(*p*-iodophenylazo)- (**III**), and 3-(*p*-sulfamidophenylazo)-1*H*,10*H*-benzo[*e*]pyrrolo[3, 2-*g*]indoles (**IV**).



II: R = Br; III: R = I; IV: R = SO_2NH_2; VII: R = H; VIII: R = CI; IX: R = NO_2.

Because **I** was poorly soluble in water, the azocoupling was carried out in aqueous dioxane mixtures at a substrate:diazonium salt mole ratio of 1:3. Like for azocoupling of benzopyrroloindole **I** with phenyl-, *p*-chlorophenyl-, and *p*-nitropheyldiazonium chlorides [1], disubstituted products could not be prepared.

IR spectra of **II** – **IV** exhibited absorption bands for NH at 3250 – 3450 cm^{-1}. A narrow strong band at 1600 – 1400 corresponded to vibrations of the azo group. The spectrum of **IV** also showed absorption bands at 1580 cm^{-1} (amide-II band) and at 1170 (S=O band). Azocompounds **II** – **IV** were colored due to the presence of the –N=N– chromophore. Their UV spectra had absorption bands in the visible region at 500 – 514 nm.

PMR spectra of **II** – **IV** contained two sets of resonances because of the asymmetry of the molecules. There were two resonances for NH protons of substituted and unsubstituted pyrrole rings. The presence of an azo group in the 3-position of the benzopyrroloindole in these compounds was confirmed by the lack of a resonance for the 3-H proton and the weak-field shift of the resonance for the 2-H proton compared to the analogous resonance for the unsubstituted ring of **I**. This resonance appeared as a broad singlet due to rapid NH → ND exchange in contrast with the resonance for the 9-H proton of the unsubstituted pyrrole ring [1].

EXPERIMENTAL CHEMICAL PART

The course of reactions, the purity of products, and the R_f values were determined using TLC on Silufol UV-254 plates.

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TABLE 1. Antimicrobial Activity of Benzopyrroloindole Derivatives *in vitro* MIC (μg/mL)

Compound	*Staphylococcus aureus* 209-p	*Bacillus subtilis* 6633 ATCC	*Escherichia coli* 25922 ATCC	*Proteus vulgaris* 6896 ATCC	*Pseudomonas aeruginosa* 165	*Mycobacterium tuberculosis* H37 Rv	*Mycobacterium tuberculosis Academia*	*Mycobacterium tuberculosis bovis* 8	*Mycobacterium cansasii*	*Mycobacterium intracellulaze*	*Mycobacteruim fortuitum*	*Mycrospo rum canis* No 3/84	*Frichophy tongypseu m* No 5/85	*Candida albicans* 1755
II	2.0	15.6	> 250.0	> 250.0	> 250.0	23.0	–	< 0.08	< 0.08	< 0.08	1000.0	> 250.0	> 250.0	> 250.0
III	125.0	> 250.0	> 250.0	> 250.0	> 250.0	153.0	–	23.0	23.0	3.5	> 1000.0	> 250.0	> 250.0	> 250.0
IV	3.9	7.8	> 250.0	> 250.0	> 250.0	0.55	–	< 0.08	< 0.08	< 0.08	153.0	> 250.0	> 250.0	> 250.0
V	62.5	125.0	> 250.0	> 250.0	> 250.0	23.0	–	< 0.08	23.0	> 1000.0	> 1000.0	15.6	31.2,0	> 250.0
VI	> 250.0	> 250.0	> 250.0	> 250.0	> 250.0	3.5	–	0.55	23.0	23.0	> 1000.0	> 250.0	250.0	> 250.0
VII	2.0	2.0	> 250.0	> 250.0	> 250.0	< 0.08	< 0.08	< 0.08	0.55	< 0.08	0.55	7.8	31.5	125.0
VIII	3.9	15.6	> 250.0	> 250.0	> 250.0	< 0.08	< 0.08	< 0.08	< 0.08	< 0.08	1000.0	> 250.0	> 250.0	> 250.0
IX	31.2	62.5	> 250.0	> 250.0	> 250.0	23.0	–	–	23.0	153.0	–	> 250.0	> 250.0	> 250.0
X	> 250.0	> 250.0	> 250.0	> 250.0	> 250.0	23.0	153.0	23.0	> 1000.0	> 1000.0	–	–	–	–
XI	–	–	–	–	–	> 1000.0	–	> 1000.0	–	153.0	> 1000.0	–	–	–
XII	> 250.0	> 250.0	> 250.0	> 250.0	> 250.0	< 0.08	–	< 0.08	> 1000.0	23.0	3.5	> 250.0	> 250.0	> 250.0
XIII	> 250.0	> 250.0	> 250.0	> 250.0	> 250.0	> 1000.0	–	–	–	–	–	> 250.0	> 250.0	> 250.0

IR spectra in mineral oil were recorded on a UR-20 instrument (Germany); UV spectra in ethanol, on a Specord spectrophotometer (Germany); PMR spectra, on a Bruker WP-200 SY (USA) spectrometer at operating frequency 200 MHz with TMS internal standard. The accuracy of chemical shifts was ± 0.01 ppm; of the spin-spin coupling constants, ± 0.1 Hz. Yields are given for chromatographically pure compounds. Elemental analyses agreed with those calculated.

3-(*p*-Bromophenylazo)-1*H*,10*H*-benzo[*e*]pyrrolo[3, 2-*g*]indole (II). A solution of **I** (0.2 g, 1 mmol) in dioxane (10 mL) and water (10 mL) at –5°C was treated dropwise with a solution of *p*-bromophenyldiazonium chloride (3 mmol) keeping the pH at 6 – 7 by adding NaOAc, stirred for 30 min, extracted with ether, and dried over ahydrous Na_2SO_4. The extract was evaporated. The compound was dried and purified over a column of silica gel with elution by benzene:ether (10:1). Yield of **II**, 0.22 g (59%), wine-red crystals, mp 265°C (dec.), R_f 0.6 (benzene:ether, 3:1). IR spectrum (ν, cm^{-1}): 3420, 3370 (NH), 1425 (–N=N–). UV spectrum (λ_{max}, nm, log ε): 231 (4.52), 261 (4.38), 269 (4.41), 313 (4.01), 500 (4.57).

PMR spectrum (acetone-d_6, δ, ppm, *J*/Hz): 11.7 (br.s, 1-H), 7.9 (d, 2-H), 8.33 (dd, 4-H), 7.4 – 7.5 (5-H, 6-H), 8.21 (dd, 7-H), 7.09 (d, 8-H), 7.39 (d, 9-H), 10.7 (br.s, 10-H), 7.77 (d, 2′-H, 6′-H), 7.65 (d, 3′-H, 5′-H), $J_{12} = 2.6$; $J_{45} = J_{67} = 9.5$; $J_{46} = J_{57} = 5.8$; $J_{89} = 2.9$; $J_{810} = 1.8$; $J_{2'3'} = J_{5'6'} = 9.1$. $C_{20}H_{13}N_4Br$.

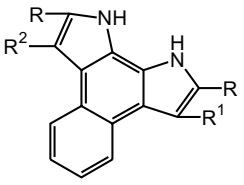
3-(*p*-Iodophenylazo)-1*H*,10*H*-benzo[*e*]pyrrolo[3, 2-*g*]indole (III) was prepared analogously to **II** from **I** (0.2 g, 1 mmol) and a solution of *p*-iodophenyldiazonium chloride (3 mmol). Yield of **III**, 0.34 g (80%), violet crystals, mp 350°C (dec.). R_f 0.6 (benzene:ether, 3:1). IR spectrum (ν, cm^{-1}): 3450, 3370 (NH), 1420 (–N=N–). UV spectrum (λ_{max}, nm): 231, 263, 269, 312, 504.

PMR spectrum (acetone-d_6, δ, ppm, *J*/Hz): 11.4 (br.s, 1-H), 8.05 (d, 2-H), 8.36 (d, 4-H), 7.5 – 7.6 (5-H, 6-H), 8.25 (dd, 7-H), 7.18 (dd, 8-H), 7.5 (9-H), 11.0 (br.s, 10-H), 7.90 (d, 2′-H, 6′-H), 7.62 (d, 3′-H, 5′-H), $J_{12} = 1.5$; $J_{45} = J_{67} = 8.6$; $J_{89} = 2.6$; $J_{810} = 1.5$; $J_{2'3'} = J_{5'6'} = 8.8$. $C_{20}H_{13}N_4I$.

3-(*p*-Sulfamidophenylazo)-1*H*,10*H*-benzo[*e*]pyrrolo[3,2-*g*]indole (IV) was prepared analogously to **II** from **I** (0.2 g, 1 mmol) and a solution of *p*-sulfamidophenyldiazonium chloride (3 mmol). Yield of **IV**, 0.3 g (78%), wine-red crystals, mp 355°C (dec.), R_f 0.59 (benzene:acetone, 2:1). IR spectrum (ν, cm^{-1}): 3340, 3250 (NH), 1580 (NH_2), 1425 (-N=N-), 1175 (SO_2). UV spectrum (λ_{max}, nm): 231, 263, 270, 313, 514.

PMR spectrum (acetone-d_6, δ, ppm, *J*/Hz): 11.9 (br.s, 1-H), 8.05 (br.s, 2-H), 8.37 (dd, 4-H), 7.5 (5-H, 6-H), 8.25 (dd, 7-H), 6.67 (d, 8-H), 7.17 (d, 9-H), 10.9 (br.s, 10-H), 8.02 (d, 2′-H, 6′-H), 7.92 (d, 3′-H, 5′-H), $J_{89} = 2.56$; $J_{2'3'} = J_{5'6'} = 9.14$. $C_{20}H_{15}N_5SO_2$.

Syntheses of 3-formyl- (**V**); 3,8-diformyl- (**VI**); 3-phenylazo- (**VII**); 3-(*p*-chlorophenylazo)- (**VIII**); and 3-(*p*-nitrophenylazo)-1*H*,10*H*-benzo[*e*]pyrrolo[3,2-*g*]-indoles (**IX**) [1]; of 2,9-di(adamantylaminocarbonyl)- (**X**), 2,9-di(*p*-benzenesulfamidoaminocarbonyl)- (**XI**), and 2,9-di(isonicotinoylhydrazidocarbonyl)-1*H*,10*H*-benzo[*e*]pyrrolo[3,2-*g*]indoles (**XII**) [2]; and of 2,9-di(carbohydrazide)-1*H*,10*H*-benzo-[*e*]pyrrolo[3,2-*g*]indole (**XIII**) [3] have been published.



V: R=R²=H, R¹=–CHO;
VI: R¹=R²=–CHO, R=H;
X: R =–CONH–Ad, R¹=R²=H;
XI: R=–CONH–C₆H₄–SO₂NH₂, R¹=R²=H;
XII: R=–CONH–NHCO–  , R¹=R²=H;
XIII: R=–CONHNH₂, R¹=R²=H

EXPERIMENTAL BIOLOGICAL PART

Antimicrobial activity was studied in the Laboratory of Chemotherapy of Infectious Diseases of the Center of Drug Chemistry (VNIKhFI) in *in vivo* experiments by double serial dilutions in liquid nutrient media (antimicrobial activity, in Hottinger broth; antituberculosis, in Soton medium; antifungal, in Sabureau medium) against the microorganisms *Staphylococcus aureus* 209-p, *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 25922, *Proteus vulgrais* ATCC 6896, *Pseudomonas aeruginosa* ATCC 27853, *Mycobacterium tuberculosis* H37, *M. tuberculosis* acedemia, *M. tuberculosis bovis* 8; conditionally pathogenic mycobacteria *M. cansasii*, *M. intracellulaze*, *M. fortuitum*; and pathogenic fungi *Microsporum canis* No. 3/84, *Frichophyton gypseum* No. 5/85, and *Candida albicans* No. 1755.

The activity of the compounds was expressed as the minimal inhibiting concentration (MIC, μg/mL). The microbial loading in experiments with bacteria was 1×10^5 CFU; with mycobacteria, 0.02 mg; with fungi, 1×10^6 CFU/mL. Bacteria were incubated at 37°C for 18 h; tuberculosis mycobacteria, 14 d; conditionally pathogenic mycobacteria, 9, 7, and 5 d, respectively; fungi, at 25°C for 24 h in experiments with *C. albicans*; 5 d in those with dermatophytes. Table 1 gives the experimental results.

The investigations established that compounds **II**, **IV**, **VII**, and **VIII** are highly active against *S. aureus* 209-p and *B. subtilis*; compounds **II**, **IV**, **VII**, **VIII**, and **XII**, against mycobacteria; compounds **V** and **VII**, against fungi.

The results showed that introducing a phenylazo group into the 3-position of the pyrrole ring of benzopyrroloindole imparts to the key heterocycle, 1*H*,10*H*-benzo[*e*]pyrrolo-[3,2-*g*]indole, antimicrobial activity against various pathogenic bacteria and conditionally pathogenic mycobacteria. It was shown that introducing electron-accepting groups into the *p*-position of the phenylazo group does not affect the activity.

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