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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW DERIVATIVES OF 2-PHENYLINDONE

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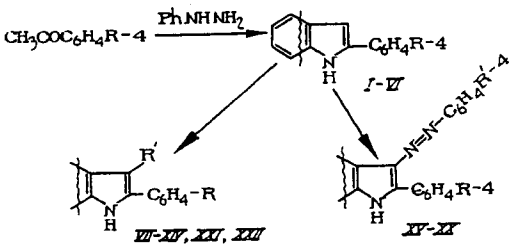
Some derivatives of 2-phenylindole display neuroleptic [4], antimicrobial [2], antiinflammatory [2, 9], antitumor [11], herbicidal [3], and other types of activity [10]. In this regard, they are nontoxic [4, 9].

In the present work we describe the synthesis of some new derivatives of 2-phenylindole (I-XX) and the testing of their antimicrobial activity:



I:R=NO_2 [1, 5]; II:R=Br [1]; III:R=OMe [8]; IV:R=NHAc; V:R=NH_2 [5];

VI:R=$NH_2 \cdot HCl$; VII:R=Br, R^1=CHO; VIII:R=OMe, R^1=CHO [6]; IX:R=NHAc, R^1=CHO; X:R=N=CH-NMe_2, R^1=H; XI:R=N=CH-$N(ME_2)$; R^1=CHO; XII:R=Br, $R^1=CH_2N(ME_2)$; XIII:R=OMe, $R^1=CH_2N(Me_2)$;

XIV:R=NHAc, $R^1=CHN(Me_2)$; XV:R=Br, R^1=H; XVI:R=Br, $R^1=NO_2$;

XVII:R=OMe, R^2=H; XVIII:R=OMe, $R^1=NO_2$, XIX:R=NHAc, R^1=H; XX:R=NHAc,

$R^1=NO_2$; XXI:R=Br, $R^1=CH=N-NH-\underset{\underset{S}{\|}}{C}-NH_2$; XXII:R=OMe,

$R^1=CH=N-NH-\underset{\underset{S}{\|}}{C}-NH_2$.

Compounds I-V were synthesized from phenylhydrazine and p-substituted acetophenones in polyphosphoric acid [5] in one step, without intermediate isolation of the corresponding phenylhydrazones. The synthesis of 2-(p-aminophenyl)indole V, previously described by us [1], was more laborious. Hydrochloride VI was synthesized from amine V in absolute ethanol.

The chemical properties of compounds I-V were studied in the Vilsmeier–Haack, Mannich, and nitrogen-combining reactions.

Substituents in the phenol ring affect the course of these reactions little: substitution occurs at the β position of the pyrrole ring, under conditions analogous to those for the synthesis of indole and 2-phenylindole [6], with high yield of the corresponding derivatives VII-XX. An exception is 2-(p-nitrophenyl)indole.

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TABLE 1. Physicochemical Characteristics of Compounds I-XXII

Compound	mp, °C	Yield, %	R_f*	Empirical formula
I	241-3	82	0.69[a] [1]	$C_{14}H_{10}N_2O_2$
II	209-10	80	0.9[b] [6]	$C_{14}H_{10}NBr$
III	226-7	84	0.67[b] [8]	$C_{15}H_{13}NO$
IV	282-4	55	0.7[b]	$C_{16}H_{14}N_2O$
V	207-8	80	0.45[b] [1]	$C_{14}H_{12}N_2$
VI	300, (dec.)	90	-	$C_{14}H_{13}N_2Cl$
VII	258-9	84	0.73[a]	$C_{15}H_{10}NBrO$
VIII	212-3	51	0.55[a] [7]	$C_{16}H_{13}NO_2$
IX	305-7	54	0.47[b]	$C_{17}H_{14}N_2O_2$
X	224-6	39	0.9[b]	$C_{17}H_{17}N_3$
XI	252-3	63	0.82[c]	$C_{18}H_{17}N_3O$
XII	141-3	97	0.91[c]	$C_{17}H_{17}N_2Br$
XIII	310-1	98	0.72[c]	$C_{18}H_{20}N_2O$
XIV	83-4	95	0.89[c]	$C_{19}H_{21}N_3O$
XV	180-1	73	0.66[d]	$C_{20}H_{14}N_3Br$
XVI	226-7	65	0.43[d]	$C_{20}H_{13}N_4O_2Br$
XVII	149-50	60	0.33[d]	$C_{21}H_{17}N_3O$
XVIII	223-5	99	0.87[a]	$C_{21}H_{16}N_4O_3$
XIX	273-5	70	0.55[b]	$C_{22}H_{18}N_4O$
XX	280, (dec.)	98	0.52[b]	$C_{22}H_{17}N_5O_3$
XXI	255-7	81	0.71[b]	$C_{16}H_{13}N_4SBr$
XXII	224-6	93	0.68[a]	$C_{17}H_{16}N_4SO$

*Chromatographic system: a) benzene—ether, 1:1; b) ether; c) isopropanol—ammonia, 40:1; d) benzene; e) benzene—ether, 2:1.

The result of formylation of 2-(p-aminophenyl)indole V depends on the ratio of reagents: at a 1:1 ratio, compound X is formed, and with a 10-fold excess of formylating complex—compound XI.

Aldehydes VII and VIII are converted to the corresponding thiosemicarbazones XXI and XXII by boiling with thiosemicarbazide in alcoholic solution.

Data confirming the properties and structures of compounds synthesized are presented in Tables 1 and 2.

EXPERIMENTAL (CHEMICAL)

The course of reactions and purity of compounds were monitored by TLC on Silufol UV-254 and UV-360 plates. IR spectra were taken on a UR-20 instrument (Germany) in vaseline mull, UV spectra on a Specord spectrophotometer (Germany) in ethanol, and PMR spectra on a Varian CFT-20 spectrometer (USA), with TMS as internal standard. Accuracy for measurement of chemical shifts was ±2 ppm, and for spin–spin coupling constant was ±1 Hz. Molecular weight was determined by mass spectrometry on an MX-1303 instrument, with a modified sample injection system (direct injection into the ion source), at an electron ionization energy of 50 eV. Values found in elemental analyses agree with those calculated.

2-(p-Nitrophenyl)indole (I). A mixture of 1.65 g (10 mmoles) of p-nitrophenol, 1.08 g (10 mmoles) phenylhydrazine, and 20 g of polyphosphoric acid (PPA) was heated to 70°C, and mixed at 70-80°C for 30 min. This was cooled and poured into 200 ml of cold water. The residue was filtered, washed to water to pH 7, dried under vacuum, and crystallized from benzine. Yield: 1.19 g. From the mother liquor on a chromatographic column, another 0.76 g was isolated. Compounds II-V were obtained analogously.

2-(p-Aminophenyl)indole Hydrochloride (VI). A solution of 2.1 g (10 mmoles) of amine V in 150 ml absolute ethanol was refluxed in a stream of dry HCl for 3 h. The residue was filtered and washed with absolute ethanol, absolute ether, and dried. Yield: 2.4 g.

2-(p-Bromophenyl)-3-formylindole (VII). To 6 ml of DMFA at —5°C was added 1.9 g (12 mmoles) $POCl_3$. This was mixed at room temperature for 1 h, cooled, and a solution of 0.54 g (2 mmoles) of compound II in 3 ml DMFA added. This was mixed at 30-35°C for 2 h, poured onto 100 g of ice, and alkalinized to pH 10. The residue was filtered, washed with

TABLE 2. Spectral Characteristics of Compounds Synthesized

Compound	IR spectrum, ν_{max}, cm^{-1}	UV spectrum, λ_{max}, nm	PMR spectrum	
			δ, ppm	SSCC, J, Hz
I	1313,1510(NO_2) 3430(NH)	217(4,4), 235(4,2), 250(4,0), 268(4,1), 394(4,3)	11,6(1H,s), 7,1(3H,m),6,9-7,6(4H,7H,m), 8,2(AH,d). 8,3(BH,d)	J_m = 2,5; $J_0 = J_{AB}$ = 9,3
II	3400(NH)	215(4,5), 251(4,3), 320(4,5)	11,4(1H,s), 6,89(3H,d), 7,53(4H,dd); 6,99(5H,m), 7,1(6H,m), 7,4(7H,dd); 7,62(AH,d), 7,79(BH,d)	$J_{1,3}$ = 2,1; J_m = 1,22; J_0 = 7,9; J_{AB} =8,55
IV	1660,1680(C=O) 3260,3320,3420(NH)	213(4,5), 222(4,3), 246(4,1)	11,2(1H,s), 6,76(3H,dd); 7,49(4H,dd); 7,96(5H,m), 7,06(6H,m), 7,37(7H,dd); 7,64(AH,d), 7,75(BH,d), 9,81(NHCO,s), 2,06(CH_3CO,s)	J_m = 1,2; J_0 = 7,95; J_{AB} = 8,7
V	3200,3400(NH)	2179(4,4), 242(4,0), 259(4,1), 322(4,0)	11,1(1H,s), 6,56(3H,d), 7,43(4H,d), 6,9-7,0(5H,6H,m), 7,33(7H,d), 7,5(AH,d), 6,61(BH,d), 5,52(NH_2,s)	J_0 = 8,2; J_{AB} = 8,4
VI	2600,3420(NH)	-	-	-
VII	1610,1620(C=O) 3100,3180(NH)	213(4,6), 236(4,30, 263(4,3), 320(4,3)	12,47(1H,s), 8,22(4H,dd); 7,22-7,34(5H,6H,m), 7,53(7H,dd); 7,74(AH,d), 7,81(BH,d), 9,97(CHO,s)	J_m = 1,83; J_0 = 6,6; J_{AB} = 8,8
VIII	1610,1630(C=O),3100, 3150(NH)	213(4,6), 226(4,3), 262(4,6), 321(4,3)	12,28(1H,s), 8,21(4H,d), 7,21-7,31(5H,6H,m), 7,49(7H,d), 7,73(AH,d), 7,16(BH,d), 9,96(CHO,s), 3,86(OCH_3,s)	J_m = 2; J_0 = 7; J_{AB}=8,8
IX	1630,1680(C=O),3100, 3170(NH)	213(4,5), 250(4,3), 263(4,5), 338(4,1)	12,28(1H,s); 8,21(4H,d); 7,2-7,3(5H,6H,m); 7,51(7H,d); 7,72(AH,d); 7,81(BH,d); 9,98(CHO,s); 10,21(NH-CO,s); 2,11(CH_3-CO,s)	J_m =1,85; J_0 = 7,0; J_{AB} = 7,7
X	1645(N=C),2865, 2980(NH)	273(4,3), 331(4,4)	11,33(1H,s), 6,72(3H,m);7,0-7,5(4H-7H,m); 7,62(AH,d); 7,12(BH,d); 7,90(CH=11,s); 3,01(CH_3-11s)	
XI	1610(C=N);1710, 1745(C=O),3150(NH)	213(4,3), 274(4,4) 339(4,1)	12,22(1H,s); 8,18(4H,dd); 7,2(5H,m); 7,26(6H,m); 7,48(7H,dd); 7,62(AH,d); 7,16(BH,d); 9,98(CHO,s); 7,88(CH=11,s); 3,08(CH_3-11,s)	J_m = 2,2; J_0 = 7,0; J_{AB} = 8,4
XII	3120,3190(NH)	213(4,5), 250(4,4), 263(4,1), 310(4,3)	11,48(1H,s); 7,64(4H,dd); 7,02(5H,m); 7,12(6H,m); 7,39(7H,d); 7,87(AH,d); 7,69(BH,d); 3,49(CH_2-11,s); 2,21(CH_3N,s)	J = 8,0; J_{AB} = 8,6
XIII	3140,3400(NH)	213(4,5), 248(4,4), 261(4,2), 286(4,0), 303(4,1)	11,03(1H,s);7,36(4H,d); 6,93-7,1(5H,6H,m); 7,61(7H,d); 7,05(AH,d); 7,78(BH,d); 3,82(CH_3O,s); 3,52(CH_2N,s); 2,2(CH_3N,s)	J_m = 1,8; J_0 = 7,3; J_{AB} = 8,8
XIV	1630,1640(C=O);3180, 3240(NH)	213(4,5), 223(4,4), 251(4,2), 262(4,2), 316(4,3)	11,27(1H,s); 7,62(4H,d); 7,0-7,1(5H,6H,m); 7,37(7H,d); 7,82(AH,d); 7,7(BH,d); 3,5(CH_2N,s); 2,21(CH_3N,s); 10,05(NH/CO,s); 2,08(CH_3CO,s)	J_0 = 7,6; J_{AB} = 8,4
XV	1450(N=N),3380(NH)	215(4,5), 242(4,2), 248(4,3), 258(4,3), 322(4,4), 396(4,3)	12,45(1H,s); 8,49(4H,dd); 7,25-7,5(5H-7H,m); 7,83(AH,d); 8,11(BH,d); 7,54(AH,dd); 7,84(BH,m); 7,5(BH,d)	J_m = 1,5; J_0 = 7,31; J_{AB} = 8,8
XVI	1320,1500(NO_2), 1450(N=N),3350(NH)	214(4,5), 243(4,4), 249(4,1), 261(4,5), 282(4,5), 452(4,5)	12,78(1H,s); 8,51(4H,dd); 7,32-7,38(5H,6H,m); 7,55(7H,dd); 7,85(AH,d); 8,1(BH,d); 7,99(A'H,d); 8,38(BH,d)	J_m = 2,0; J_{AB}= 8,4; J_{AB} =9,15
XVIII	1450(N=N), 3420(NH)	213(4,5), 224(4,8), 252(4,3), 300(4,4), 401(4,3)	12,03(1H,s); 8,48(4H,dd); 7,22-7,25(5H,6H,m); 7,38(7H,dd); 7,79(AH,d); 7,16(BH,d); 8,15(A'H,d); 8,38(BH,d)	J_m = 1,8; J_0 = 7,2; J_{AB} = 8,9
XVIII	1320,1510(NO_2), 1450(N=N), 3340(NH)	214(4,4), 242(4,1), 248(4,2), 261(4,2), 294(4,2), 476(4,6)	12,59(1H,s); 8,5(4H,s); 7,28-7,4(5H,6H,m); 7,51(7H,dd); 7,97(AH,d); 7,21BH,d); 8,16(A'H,d); 8,37(B'H,d); 3,89(CH_3O,s)	J_m = 2,2; J_0 = 7,4; J_{AB} = 8,8
XIX	1450(N=N), 1660(C=O), 3300, 3380(NH)	212(4,5), 238(4,1), 256(4,2), 270(4,2), 309(4,4), 403(4,2)	12,29(1H,s); 8,5(4H,d); 7,3-7,5(5H-7H,m); 7,82(AH,d); 8,13(BH,d); 7,4-7,8(A'H-B'H,m); 10,26(11H-CO,s); 2,12(CH_3-CO,s)	J_0 = 6,2; J_{AB} = 7,7
XX	1350,1550(NO_2), 1450(N=N),1680(C=O), 3190-3260,3310(NH)	214(4,4), 244(4,2), 255(4,3), 292(4,5), 465(4,2)	12,6(1H,s); 8,15(4H,d); 7,25-7,52(5H-7H,m); 7,84(AH,d); 8,13(BH,d); 7,97(A'H,d); 8,38(B'H,d)	J_0 = 7,0; J_{AB} = 8,4
XXI	1285,1295(C=S) 1610(C=N),3130,3250, 3410(NH)	213(4,6), 245(4,4), 262(4,2), 297(4,5), 356(4,4)	11,93(1H7s); 8,33(4H,d); 7,16-7,44(5H-7H,m); 7,57(AH,d); 7,77(BH,d); 8,46(CH=N,s); 11,11(NHN,s); 8,03(NH_2,b,s,)	J_0 = 8,4
XXII	1285(C=S),1620(C=N), 3120,3250,3410(NH)	212(4,4), 234(4,2), 245(4,2), 270(4,6)	11,78(1H,s); 8,3(4H,dd); 7,16-7,43(5H-7H,m); 7,58(AH,d); 7,14(BH,d); 8,48(CH=N,s); 11,08(NH/N,s); 8,0(NH_2,b s,)	J_0 = 1,47; J_0 = 8,0; J_{AB} = 8,6

TABLE 3. Antimicrobial Activity of Compounds (MIC, μ/ml)

Compound	Staphylococcus aureus ATCC 25913	Bacillus subtilis ATCC 6633	M.tuberculosis H-37 RV	M. bovis	M. kansasii	M. avium
VI	125	125	1,0	4,0	-	-
X	>250	>250	>1000	-	-	>1000
XV	3,9	7,8	153	-	23	>1000
XVI	>250	>250	153	-	-	>1000
XVII	2	15,6	>1000	-	153	153
XVIII	>250	>250	23	-	-	>1000
XIX	>250	>250	>1000	-	>1000	>1000
XX	125	250	153	-	-	153
XXI	62,5	> 2,5	>1000	>1000	>1000	>1000
XXII	>250	>250	>1000	>1000	>1000	>1000

Note. Test compounds were inactive against the bacteria *Escherichia coli* ATCC 29522, *Proteus vulgaris* ATCC 6896, *Pseudomonas aeruginosa* ATCC 27853, and the fungi *Candida albicans* 1755, *Microsporum canis* 3/84, and *Trichophyton mentagraphytes* 5/85.

water to pH 7, and dried. Yield: 0.49 g. Crystallization from ethanol gave 0.36 g. Compounds VIII-XI were obtained analogously.

2-(p-Bromophenyl)-3-dimethylaminomethylindole (XII). To 5.6 ml (0.041 mole) of 33% aqueous dimethylamine at 0°C was 6 ml glacial acetic acid, 3 ml of 40% formalin, and a solution of 0.54 g 2-(p-bromophenyl)indole II in 20 ml of glacial acetic acid. This was mixed at 25-30°C for 2 h. Yield: 0.63 g. Compounds XIII and XIV were prepared analogously.

2-(p-Bromophenyl)-3-phenylazoindole (XV). To a solution of 0.27 g (1 mmole) of 2-(p-bromophenyl)indole II in 30 ml of dioxane was added 10 ml of water. This was cooled to 0°C and a solution obtained by diazotizing 0.26 g (3 mmoles) of aniline was added dropwise, maintaining the pH at 5-6 by the addition of sodium acetate. This was mixed for 3 h at 0-5°C, diluted with water, and the precipitate was filtered, washed with water to neutrality, and dried over $CaCl_2$. Yield: 0.27 g. Compounds XVI-XX were prepared analogously.

2-(p-Bromophenyl)-3-formylindole Semicarbazone (XXI). 0.3 g (1 mmole) of 2-(p-bromophenyl)-3-formylindole VII was dissolved with refluxing in 40 ml ethanol and a solution of 0.18 g thiosemicarbazide in 30 ml ethanol added. The alcoholic solution was brought to pH 4-5 with dry HCl, refluxed for 1 h, and cooled. The precipitate was filtered, washed with ethanol, and dried. Yield: 0.30 g. Compound XXII was prepared analogously.

EXPERIMENTAL (BIOLOGICAL)

Antimicrobial activity was determined in the Laboratory for Chemotherapy of Infectious Diseases of with *in vitro* experiments on liquid media (Hottinger and Saburo broth), and antituberculous activity – on Soton medium. The inoculate for bacteria was $1\text{-}3\cdot10^5$ CFU/ml, and for fungi $-2\text{-}4\cdot10^6$ CFU/ml. Culturing time for yeast was 20-24 h, for fungi – 5 days at 25°C, and for bacteria – 18-20 h at 37°C. Activity of compounds was expressed as minimal inhibitory concentrations (MIC, μg/ml). Experimental results are presented in Table 2. 2-(p-Bromophenyl)-3-phenylazoindole possessed high activity against gram-positive bacteria. Compound VI possessed high, and compounds XV-XVIII and XX weak antituberculous activity (Table 3).

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