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Some Aspects of the Chemistry of Arylindoles

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ABSTRACT. Some derivatives of 2-phenylindole are synthesized according to the E. Fischer's Indolization. A one-step synthesis are conducted in polyphosphoric acid without isolation of intermediate hydrazones. It is noted that electronacceptor substituents of the carbonyl fragment markedly facilitate the process of indolization. *© 2019 Bull. Georg. Natl. Acad. Sci.*

Key words: indole, arylindole, fisher reaction, mannich reaction

Arylindoles are one of the most studied groups among indole derivatives. This primarily refers to 2-phenylindole, of which derivatives have many interesting beneficial properties, including pharmacological activity [1]. Existing researches are mainly focused on alkyl, alkoxy and halogen containing derivatives of 2-phenylindole and consequently, many significant substances are synthesized. The most interesting synthesis are the derivatives of 4'.5-diacetoxy-2-phenylindole anti-cancer drugs D-16726 and D-15413 [1-4]. As well as 4',6-diamidino-2-phenylindol (DAPI), which is successfully used in microscopy as a fluorescent dye for DNA labeling [1,5, 6]. Over the past 15 years, this drug is mentioned in more than thousands of publications.

In our opinion Arylindoles have much more interesting, yet not reported properties, and decided to further research them. We have already reported the synthesis of nitro, amino and some other group containing 2-phenylindole derivatives [1, 7–11].

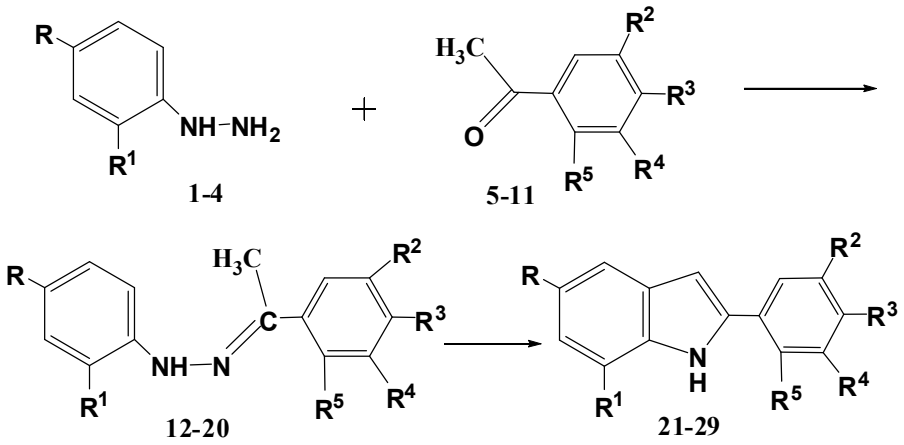
In order to obtain new fluorescent DNA markers, we carried out some transformations of previously synthesized compounds. In particular, nitration, aminomethylation, Wilsmeier-Haak acylation and other reactions were carried out [1,12,13]. Some newly synthesized amino derivatives of 2-phenylindole possess antimicrobial activity [1,12], as well as high sensitivity in materials for holographic recording of information. The use of compound 22 leads to an increase in the sensitivity and diffraction efficiency of polymer layers based on amine-containing charge transfer complexes [1]. Some derivatives of this series have similar 4'6-diamidino-2-phenylindole (DAPI) properties, and 4'5-dibromo-2-phenylindole (29) have more contrasting image when colored [14].

Some patterns of the indolization reaction in polyphosphoric acid are also noted. Specifically,

electronacceptor substituents of the carbonyl moiety facilitate the process of indolization. The reaction takes place at a markedly low temperature compared to the phenylhydrazone of unsubstituted acetophenone (12) [1,15].

We obtained some derivatives (22-29) by the method of E. Fisher. Polyphosphoric acid is used as a condensing agent. The optimum temperatures and yields of the target products are given in the Table. It is more convenient to carry out the synthesis in one stage, without isolating intermediate hydrazones 12–20 (Scheme, Table):

The values of the optimal temperatures of these reactions once again confirm our considerations regarding the influence of the carbonyl substituents. The greatest influence was exerted by p-dimethylamino, m-amino and p-nitro groups of hydrazones (13.14 and 17). Apparently, dimethylamino and amino groups, after protonation in polyphosphoric acid, become potent acceptors. Probably, the protonation of the amino group of hydrazone 15 is hampered by neighboring bromine atoms. It is noteworthy that a similar temperature (90°C) is observed during the cyclization of



Scheme. General scheme of synthesis of Arylindoles.

Table. The optimum temperatures and yields of the target products

Compound	R	R^1	R^2	R^3	R^4	R^5	T, °C	Yield, %
12,21	H	H	H	H	H	H	130-140*	90
13,22	H	H	H	$N(CH_3)_2$	H	H	80	77
14,23	H	H	NH_2	H	H	H	75-80	44
15,24	H	H	Br	NH_2	Br	H	90	47
16,25	H	H	H	Br	H	Br	110	30
17,26	H	CH_3	H	NO_2	H	H	75-80	32
18,27	Cl	H	H	Br	H	H	90-95	21
19,28	Cl	H	H	C_6H_5	H	H	100	51
20,29	Br	H	H	Br	H	H	90	25

* according to [16] 180°C, 76%.

5-halophenyl hydrazones 4-bromoacetophenone (18.20). The temperature of cyclization of hydrazones 16 and 19 is increased to 110–100°C respectively.

4'-Dimethylamino-2-phenindole (22). A mixture of 30 g of polyphosphoric acid, 1.63 g (10 mmol) of p-dimethylaminoacetophenone and 1.2 g (11 mmol) of phenylhydrazine is stirred at 30°C, cooled and slowly heated to 80°C with stirring at 30 min. Then cooled, poured into 300 ml of water. The precipitate is filtered, washed with water to pH 7 and dried. Yield 2.2 g purified by column chromatography. Benzene was used as an eluent. Yield 1.81g, m.p. 194-196^{0}C. Rf 0.62 (ether). IR spectrum: 3340 cm^{-1} (NH). UV spectrum, λmax (lg ε): 215 (4,5); 250 (4.1); 260 (3.3); 320 nm (3.8). ^{1}H NMR spectrum (DMSO-D6,), δ ppm, (J, Hz): 11.27 (1H, s, NH); 7.68 (2H, d, Jab = 9.9, Hb); 7.44 (1H, d, J = 7.92, H-4); 7.32 (1H, d, J = 7.92, H-7); 7.01 (1H, t.d, J = 7.92, J = 1.2 H-6); 6.94 (1H, t.d, J = 7.92, J = 1.2, H-5); 6.64 (1H, d, J = 1.24, H-3); 2.96 (6H, s, CH3). Found,%: C 81.63; H 7.0; N 12.0. $C_{16}H_{16}N_2$. Calculated,%: C 81.4; H 6.8; N 11.9. M 236.

3'-amino-2-phenylindole (23). It is prepared similarly to compound 22 from 20 g of polyphosphoric acid, 1.35 g (10 mmol) of m-aminoacetophenone and 1.2 g (11 mmol) of phenylhydrazine. Benzene-CCI_4 1: 1 was used as an eluent. Yield 0.91g. M.p. 201-203^{0}C. Rf 0.45 (benzene-ether, 5: 4). IR spectrum: 3200 (NH2), 3430 cm^{-1} (NH). UV spectrum, λmax (lg ε): 230 (4.4); 311 nm (4.2). Found,%: C 81.22; H 6.80; N 13.65. $C_{12}H_{12}N_2$. Calculated,%: C 80.74; H 5.81; N 13.45. M 208.

4'-Amino-3',5'-dibromo-2-phenylindole (24). It is prepared similarly to compound 22 from 40 g of polyphosphoric acid, 2.93 g (10 mmol) of 4-amino-3,5-dibromoacetophenone and 1.2 g (11 mmol) of phenylhydrazine. Benzene was used as an eluent.. Yield 1.71, m.p. 203-204^{0}C. Rf 0.76 (benzene). IR spectrum: 3370 (NH_2), 3450 cm^{-1} (NH). UV spectrum, λmax (lg ε): 212 (4.7); 226 (4.7); 250 (4.1) 267 (4.2); 324 nm (4.5). ^{1}H NMR (DMSO-D6,), δ ppm, (J, Hz): 11.40 (1H, s, NH); 7.96 (2H, s, H-Ph); 7.47 (1H, d, J = 7.41, H-4); 7.34 (1H, d, J = 7.41, H-7); 7.06 (1H, t, J = 7.41, H-6); 6.96 (1H, t, J = 7.41, H-5); 6.78 (1H, s, H-3); 5.49 (2H, s, NH_2). Found,%: C 45.6; H 3.0; N 7.2; M + 368; 366; 364. $C_{14}H_{10}N_2Br_2$. Calculated,%: C 45.94; H 2.758; N 7.65: Br 43.66. M 366.

2',4'-Dibrom-2-phenylindole (25). It is prepared similarly to compound 22 from 40 g of polyphosphoric acid, 2.76 g (10 mmol) of 2,4-dibromoacetophenone and 1.2 g (11 mmol) of phenylhydrazine. Benzene was used as an eluent. Yield 1.1g. M.p. 209-211°C. Rf 0.78 (benzene). IR spectrum: 3480 cm^{-1} (NH). Found,%: C 45.46; H 2.9; N 4.6; M + 353; 351; 349. $C_{14}H_9Br_2N$. Calculated,%: C 47.90; H 2.58; N 3.98: Br 45.52. M 351.

4'-Nitro-7-methyl-2-phenylindole (26). It is prepared similarly to compound 22 from 20 g of polyphosphoric acid, 1.65 g (10 mmol) of p-nitroacetophenone and 1.74 g (11 mmol) of o-tolylhydrazine hydrochloride. Benzene was used as an eluent. Yield 0.91g. M.p. 205-207 ^{0}C. Rf 0.5 (benzene). IR spectrum: 1330.1520 (NO_2), 3430 cm^{-1}(NH). UV spectrum, λmax (lgε): 208 (4.4); 238 (4.1); 269 (4.0); 365 nm (4.2). Found,%: C 72.42; H 4.80. $C_{15}H_{12}N_2O_2$. Calculated%: C 71.42; H 4.79; N 11.0. M 252.

5-Chloro-4'-bromo-2-phenyllindole (27). It is prepared similarly to compound 22 from 20 g of polyphosphoric acid, 1.65 g (10 mmol) of p-nitroacetophenone and 1.96 g (11 mmol) of p-chlorophenylhydrazine hydrochloride. Hexane-ether, 5:3 was used as an eluent. Yield 0.64 g. M.p. 208-209 ^{0}C. Rf 0.58 (hexane-ether, 5:3). IR spectrum: 3440 cm^{-1} (NH). UV spectrum, λmax (lg ε): 208 (4.5); 233 (4.3); 248 (4.3); 320 nm (4.4). Found,%: C 55.02; H 3.8; N 4.60. $C_{14}H_9BrClN$. Calculated,%: C 54.85; H 2.96; N 4.57. M 306.5.

5-Chloro-2-p-diphenylindole (28). It is prepared similarly to compound 22 from 20 g of polyphosphoric acid, 2 g (10 mmol) of p-acetyldiphenyle and 1.96 g (11 mmol) of p-chlorophenylhydrazine hydrochloride. Benzene-hexane 1: 1 was used as an eluent. Yield 1.54 g. M.p. 240-242^{0}C. Rf 0.36 (benzene-hexane, 1: 1). IR spectrum: 3445 cm^{-1} (NH). UV spectrum, λmax (lg ε): 227 (4.4); 261 (4.3); 334 nm (4.6). Found, %: C 79.4; H 4.9; N 4.9. $C_{20}H_{14}ClN$. Calculated,%: C 79.07; H 4.65; N 4.61. M 303.5.

4',5-dibrom-2-phenylindol (29). It is prepared similarly to compound 22 from 40 g of polyphosphoric acid, 2.27 g (10 mmol) of 4-bromoacetophenone and 2.46 g (11 mmol) of p-bromophenylhydrazine hydrochloride. Purified by column chromatography. Benzene was used as an eluent. Yield 0.88 g. M.p.200-201°C. Rf 0.86 (benzene). IR spectrum: 3450 cm^{-1} (NH). Found,%: C 45.6; H 3.0; N 4.8; M^+ 353; 351; 349. $C_{14}H_9Br_2N$. Calculated,%: C 47.90; H 2.58; N 3.98; M 351.

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