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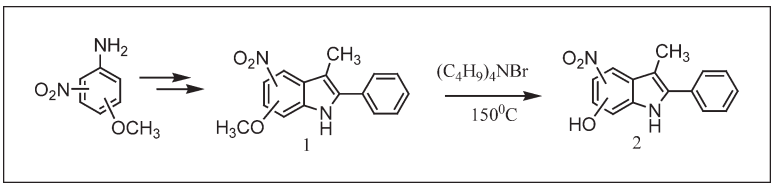

A new procedure for the cleavage of aryl methyl ethers was developed. On this basis representatives of new types of 2-arylhydroxynitroindoles were synthesized.

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INTRODUCTION

The synthesis of indoles and investigation of their reactivity are essential scientific issues, because an indole ring stands among the most common structural moieties of many natural alkaloids and biologically active substances. In particular, an indole ring incorporates an indispensable amino acid tryptofan that is involved in protein building in all living organisms. 3-Indolylacetic acid and some of its derivatives generated in plants in the course of oxidative deamination of tryptofan are growth hormones [1]. Among the indole derivatives applied in medicine most popular are indometacin, an antiinflammatory agent and analgesic [2], indomecin, an antibiotic, and pindolol, a noncardioselective β-adrenoreceptor blocking agent with antianginal, antiarrhythmic, and hypotensive action [3]. Vincristine, alkaloid of pink periwinkle (*Vinca rosea*), is a natural antitumoral agent that also includes an indole moiety [4].

RESULTS AND DISCUSSION

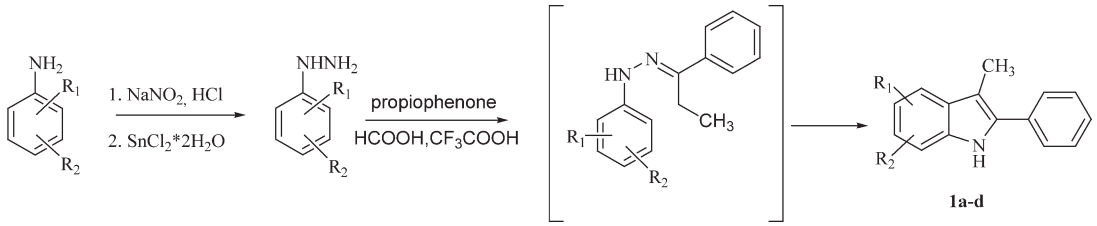
In our previous articles, we communicated a synthetic procedure for the preparation of new 2-arylindole representatives with hydroxyl and nitro groups in 4- and 6-positions, accordingly [5]. Our interest in the representatives of this indole type was caused by the results of biological tests that demonstrated high fungicidal activity of 2-aryl-4-hydroxy-6-nitroindole and its intermediates when compared with the conventional benchmark, triadimethon. In this article, we propose a method for the synthesis of 2-aryl-X-hydroxy-Y-nitroindoles.

The most popular and well-known method for the preparation of indoles is Fischer synthesis based on the acid-catalyzed rearrangement of phenylhydrazones accompanied by ammonia emission. Methoxynitroindoles **1a–d** (Table 1) were synthesized from commercial methoxynitroanilines by this method (Scheme 1).

As a next step, we supposed to transform methoxynitroindoles to the end product, that is, hydroxynitroindoles. The ether bond cleavage techniques with the use of $AlCl_3$ [6], BBr_3 [7], and PhSH in the presence of K_2CO_3 [8], HBr [9], and $(CH_3)_3SiI$ [10] described in literature failed. Either resinification occurred or the reaction did not run at all. Two researches formally not related to our case prompted us the solution of this problem. The authors of the first article [11] emphasize the impact of ionic liquids as high polar media on the cleavage of ethers under the action of benzoyl chloride. The second [12] examines transesterification of methyl esters of carbonic acids as affected by tetraalkylammonium halides to produce corresponding alkyl esters and points out that the tertiary ammonium salt melt used without any solvent is optimal for the reaction. Originating from these results, we decided to look at the behavior of indoles **1** in the melt of tetrabutylammonium bromide, being both a high polar medium and, moreover, a source of less solvated, and hence more nucleophilic, bromide ions. Furthermore, tetrabutylammonium bromide is neither hygroscopic nor high-melting, and at the same time is rather readily available. It appeared that in its melt, once the temperature reached 150°C, the reaction ran *via* the below scheme **2** to yield products **2c** and **3c** (reaction time—0.5h), which we managed to separate.

Of note is that in the reaction of tetrabutylammonium bromide with preisolated ether, **3c** the latter is spent completely and dealkylation product **2c** is generated. We

Scheme 1. Synthesis of methoxynitroindoles **1a–d**.



found that the increasing of the reaction time led to product **2c** only. Products **2a**, **2b**, and **2d** were obtained in the same manner for 1.5 h (Table 2). As known from literature, the tetrabutylammonium bromide decomposition occurs during the thermolysis to yield tributyl amine and butyl bromide, which, in our instance, alkylates hydroxyindole-2 resulted from demethylation. HPLC fully proves the fact of the initial generation of hydroxyindole-2 rather than of ether **3** in the reaction mixture.

EXPERIMENTAL

All reagents and solvents were used without further purification or drying. All reagents were purchased from Acros Organics. The ^{1}H-NMR spectra were recorded by Bruker AM-300. The chemical shifts were given relative to Me_4Si in DMSO-d_6, δ, p.p.m., J, Hz. Melting points of the synthesized compounds were measured on a Boetius hot stage according to Koffler (heating rate 4°C min^{-1}).

Compounds **a–c** were prepared by the known procedures [13]. Compound **d** was prepared according to procedure given in Ref. 13c.

3-Methoxy-6-nitrophenylhydrazine (d). This compound was obtained as red solid, 68%, m.p. = 160–161°C. ^{1}H-NMR: 3.91 (s, 3H, OCH_3), 6.59–6.63 (m, 1H, Ar), 6.98 (d, 1H, J = 8.7), 8.12 (d, 1H, J = 8.8), 9.35 (s, 1H, N—H), 10.51(s, 2H, N—H). Anal. Calc. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.76; H, 4.67; N, 22.74.

General procedure for the preparation of compounds 1(a–d). Propiophenone (1.34 g, 0.01 mol) and trifluoroacetic acid (0.5 g, 0.004 mol) are added to methoxynitrophenylhydrazine solution (1.83 g, 0.01 mol) in formic acid (15 mL) and refluxed for 2 h. The reaction mass is cooled, and the precipitate is filtered off, dried, and purified using column chromatography (silica gel, eluent—chloroform).

3-Methyl-7-methoxy-5-nitro-2-phenylindole (1a) This compound was obtained as yellow solid, 36%, m.p. = 175–176°C. ^{1}H-NMR: 2.42 (s, 3H, CH_3), 4.05 (s, 3H, OCH_3), 7.38–7.43 (m, 1H, Ar), 7.48–7.53 (m, 3H, Ar), 7.68–7.71 (m, 2H, Ar), 8.21 (s, 1H, Ar), 11.98 (s, 1H, NH). Anal. Calc. for. $C_{16}H_{14}N_2O_3$: C 68.07; H 5.00; N 9.92. Found: C 68.41; H 5.14; N 9.67.

3-Methyl-5-methoxy-7-nitro-2-phenylindole (1b) This compound was obtained as yellow solid, 55%, m.p. = 127–128°C.^{1}H-NMR: 2.37 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.40–7.45 (m, 1H, Ar), 7.50–7.55 (m, 2H, Ar), 7.63–7.70 (m, 4H, Ar), 11.27 (s, 1H, NH). Anal. Calc. for $C_{16}H_{14}N_2O_3$: C 68.07; H 5.00; N 9.92. Found: C 68.38; H 4.89; N 9.69.

3-Methyl-7-methoxy-4-nitro-2-phenylindole (1c) This compound was obtained as orange solid, 63%, m.p. = 130–131°C. ^{1}H-NMR: 2.31 (s, 3H, CH_3), 4,05 (s, 3H, OCH_3), 6,83(d, 1H, J = 8,6), 7.41–7.46 (m, 1H, Ar), 7.49–7.54 (m, 2H, Ar), 7.60–7.63 (m, 2H, Ar), 7.86 (d, 1H, J = 8.7), 12.00 (s, 1H, N—H). Anal. Calc. for $C_{16}H_{14}N_2O_3$: C 68.07; H 5.00; N 9.92. Found: C 68.18; H 5.21; N 9.61.

3-Methyl-4-methoxy-7-nitro-2-phenylindole (1d) This compound was obtained as yellow solid, 43%, m.p. = 139–140°C. ^{1}H-NMR: 4.03 (s, 3H, OCH_3), 6.76 (d, 1H, J = 9), 7.39–7.44 (m, 1H, Ar), 7.48–7.53 (m, 2H, Ar), 7.60–7.62 (m, 2H, Ar), 8.10–8.13 (d, 1H, J = 9), 11.36 (s, 1H, N—H). Anal. Calc. for $C_{16}H_{14}N_2O_3$: C 68.07; H 5.00; N 9.92. Found: C 68.23; H 5.11; N 9.81.

General procedure for the preparation of compounds 2(a–d). A mixture of methoxynitroindole (1g, 0.004 mol) and tetrabutylammonium bromide (7 g) is heated up to 150°C and stirred for 90 min (as the preparation of the mixture of compounds **2c** and **3c** and time of reaction is 30 min). The reaction mass is poured into 5% HCl and extracted with chloroform. The extract is dried over Na_2SO_4, and the solvent is distilled. The dry residue is purified using column chromatography (silica gel, eluent—the mixture CCl_4/EtOAc = 10/4).

7-Hydroxy-3-methyl-5-nitro-2-phenylindole (2a) This compound was obtained as red solid, 64%, m.p. = 196–197°C.^{1}H-NMR: 2.41 (s, 3H, CH_3), 7.37–7.42 (m, 2H, Ar), 7.48–7.53 (m, 2H, Ar), 7.68–7.71 (m, 2H, Ar), 8.05 (d, 1H, J = 8,6), 10.57 (s, 1H, O—H), 11.80 (s, 1H, N—H). Anal. Calc. for $C_{15}H_{12}N_2O_3$: C 67.16; H 4.51; N 10.44. Found: C 67.31; H 4.26; N 10.32.

5-Hydroxy-3-methyl-7-nitro-2-phenylindole (2b) This compound was obtained as red solid, 53%, m.p. = 172–173°C.^{1}H-

Table 1

Methoxynitroindoles.

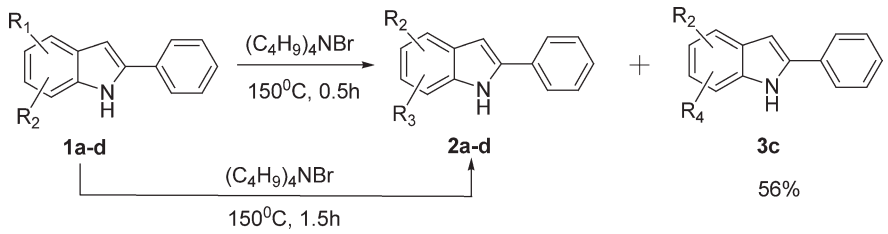
Product	R_1	R_2	Yield (%)
1a	7-OCH_3	5-NO_2	36
1b	5-OCH_3	7-NO_2	55
1c	7-OCH_3	4-NO_2	63
1d	4-OCH_3	7-NO_2	43

Table 2

Hydroxynitroindoles.

Entry	R_1	R_2	R_3	R_4	Yield (%)
a	7-OCH_3	5-NO_2	7-OH	–	64
b	5-OCH_3	7-NO_2	5-OH	–	53
c	7-OCH_3	4-NO_2	7-OH	7-OC_4H_9	61
d	4-OCH_3	7-NO_2	4-OH	–	86

Scheme 2. Cleavage of aryl methyl ethers.



NMR: 2.33 (s, 3H, CH_3), 7.40–7.44 (m, 2H, Ar), 7.49–7.56 (m, 2H, Ar), 7.66–7.68 (m, 2H, Ar), 9.62 (s, 1H, O—H), 11.14 (s, 1H, N—H). Anal. Calc. for $C_{15}H_{12}N_2O_3$: C 67.16; H 4.51; N 10.44. Found: C 67.42; H 4.17; N 10.53.

7-Hydroxy-3-methyl-4-nitro-2-phenylindole (2c) This compound was obtained as red solid, 61%, m.p. = 219–220°C.^{1}H-NMR: 2.33 (s, 3H, CH_3), 6.63 (d, 1H, J = 8,5), 7.42–7.46 (m, 1H, Ar), 7.50–7.55 (m, 2H, Ar), 7.61–7.64 (m, 2H, Ar), 7.77–7.80 (d, 1H, J = 8,5), 11.10 (s, 1H, O—H), 11.83 (s, 1H, N—H). Anal. Found %: C 67.21; H 4.30; N 10.57. Calcd. for. $C_{15}H_{12}N_2O_3$ %: C 67.16; H 4.51; N 10.44.

4-Hydroxy-3-methyl-7-nitro-2-phenylindole (2d) This compound was obtained as red solid, 86%, m.p. = 201–202°C.^{1}H-NMR: 6.57 (d, 1H, J = 8,9), 7.38–7.43 (m, 1H, Ar), 7.48–7.53 (m, 2H, Ar), 7.61–7.64 (m, 2H, Ar), 7.98–8.01 (d, 1H, J = 8.9), 11.19 (s, 1H, O—H), 11.32 (s, 1H, N—H). Anal. Calc. for $C_{15}H_{12}N_2O_3$: C 67.16; H 4.51; N 10.44. Found: C 67.03; H 4.68; N 10.37.

7-Butoxy-3-methyl-4-nitro-2-phenylindole (3c) This compound was obtained as yellow solid, 56%, m.p. = 139–140°C.^{1}H-NMR: 0.93–0.98 (m, 3H), 1.49–1.61 (m, 2H), 1.77–1.86 (m,2H), 2.31 (s,3H), 4.24–4.28 (m, 2H), 6.80 (d,1H, J = 8,7), 7.43–7.48 (m,1H), 7.51–7.56 (m, 2H), 7.59–7.62 (m, 2H), 7.83(d, 1H, J = 8,7), 11.92 (s, 1H). Anal. Calc. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.13; H, 6.37; N, 8.36.

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