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REACTIONS OF 1-(4-HYDROXYPHENYL)-3-(4-NITROPHENYL)-5-ETHYL-1,2,4-TRIAZOLE WITH ELECTROPHILIC AGENTS

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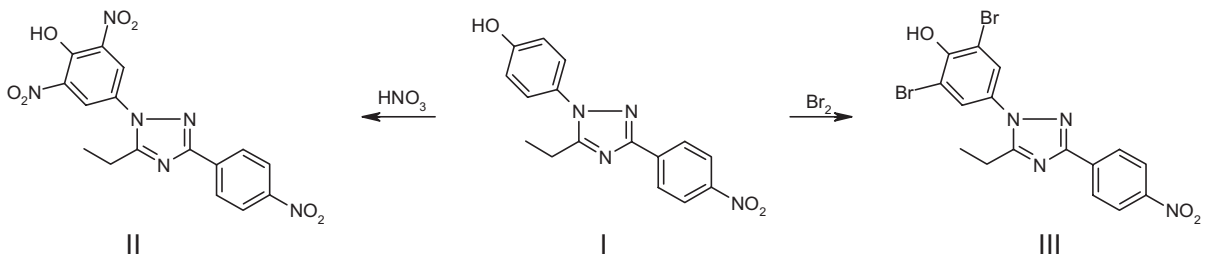
To synthesize new biologically active compounds, the reactions of electrophilic substitution of 1-(4-hydroxyphenyl)-3-(4-nitrophenyl)-5-ethyl-1,2,4-triazole (I) have been studied. In the reaction of nitration and bromination of 1,2,4-triazole (I), even if the equimolar ratio of the reagents, dibromo- and dinitrosubstituted products (II, III) were obtained. In the reaction of alkylation and acylation reactions, only O-esters (IV, V a-e) were formed. The structure of the new compounds was confirmed by ^{1}H NMR spectra. Spectra of potential biological activity of the initial 1,2,4-triazole (I) and compounds (II, III, IV, V a-e) were studied by using PASS.

The derivatives of 1,2,4-triazoles have a wide application in various branches of economy. They have been used as a base for the production of medications having anti-inflammatory, anti-tuberculosis, anti-viral, anti-histamine, antineoplastic and psychotropic activity [1–4], chemicals for agricultural purposes, including effective fungicides, herbicides and plant growth regulators [5].

We have previously developed a convenient method for the synthesis of 1-(4-hydroxyphenyl)-3-(4-nitrophenyl)-5-ethyl-1,2,4-triazole by reaction of 4-nitrophenilalazines 1,4-benzoquinone with n-propylamine. [6]. The purpose of this research is the synthesis of new potential bioactive compounds viz. derivatives of 1-(4-hydroxyphenyl)-3-(4-nitrophenyl)-5-ethyl-1,2,4-triazole (I).

It is known that nitration of s-triazoles is possible only if the molecule contains a strong electron-donating or aryl substituents [2]. We have established that the nitration and bromination occurs into the benzene ring. In both cases, we observed the formation of products (II) and (III) with substituents in ortho-position to the hydroxyl group (schema 1).



II I III

Schema 1

Moreover, even under the conditions of equimolar ratio of the reagents, only dibromo-and dinitrosubstituted products (II, III) were obtained.

The 1,2,4-triazoles are characterized by alkylation and acylation reaction, which can occur either at the nitrogens of triazole cycle (more often at N-1 atom), or involve the substituents [7]. It has been established that the reaction of triazole (I) with dimethyl sulfate and series of carboxylic acid chloro anhydrides produces only O-esters (IV, V a-e) (schema 2).

Products of the methylation reactions at the nitrogen atom in the triazole ring were not observed even when the solution was boiled and there was a large excess of dimethylsulfate (pH more than 10).

The structures of the synthesized compounds are confirmed by 1H NMR spectroscopy. The spectra revealed almost constant characteristic signals of AB-systems of the two substituted phenyls, a multiplet of the ethyl group. Characteristics of 1H NMR spectra are shown in Table 1.

Spectra of potential biological activity of the initial 1,2,4-triazole (I) and compounds (II, III, IV, V a-e) were obtained by using PASS. The data indicate that the triazole (I) is very likely to be an inhibitor of the ubiquinol-cytochrome c-reductase (index Pa=0.78). Nitration of the triazole does not practically affect the probability of this type of activity (for compound (II) ratio Ra=0.79), however, the product of nitration (II) is also a chloride channel blocker (Pa=0.75). Brominated triazole (III) acquires the properties of dimethylallyltransferase inhibitor (Pa=0.72). Compounds (V a-e) are cytochromes CYP2H (Pa=0.68−0.72). Ethers (IV) are inhibitors of quinosine and saccharopepsin (Ra=0.74−0.76).

Experimental

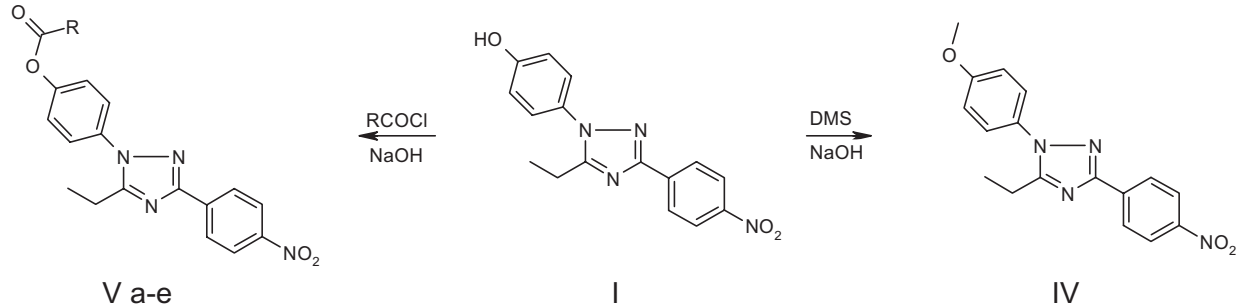
^{1}H NMR spectra were recorded on a Varian Gemini 2000 spectrometer (400 MHz) in DMSO-d_6. Plates Kieselgel 60 F254 (Merck) and Sorbfil PTLC-AF-A-UV (Russia) were used for thin layer chromatography. Methods of synthesis and physical and chemical properties of 1-(4-hydroxyphenyl)-3-(4-nitrophenyl)-5-ethyl-1,2,4-triazole are reported in [6].

Procedure 1: Synthesis of 1-(3,5-dinitro-4-hydroxyphenyl)-3-(4-nitrophenyl)-5-ethyl-1,2,4-triazole (II): 1.0 ml of 56% solution of nitric acid and a few crystals of sodium nitrite is added to a solution of 0.3 g of the triazole (I) in 60 ml of acetic acid. The reaction mixture is stirred and heated to reflux to 80^{0}C, held at this temperature for 1h and then cooled to room temperature and left for 24 hours. Then, 100 ml of 1,2-dichloroethane, 100 ml of water are added to the reaction mixture, stirred, the dichloroethane layer is separated, dried over anhydrous calcium chloride and the solvent is distilled off under vacuum to a small volume. The residue is poured into the Petri dish and evaporated to dryness at room temperature. The precipitate is washed several times with warm hexane and dried.

Procedure 2: Synthesis of 1-(3,5-dibromo-4-hydroxyphenyl)-3-(4-nitrophenyl)-5-ethyl-1,2,4-triazole (III): weighed portion of 0.2 g of the triazole (I) is dissolved in 50 ml acetic acid, 2 ml of bromine is added and maintained for 10 hours at a temperature of 80^{0}C. Crystallization of the product occurs in cooling. The precipitate is filtered off, washed on the filter with a small amount of acetic acid and dried.

Procedure 3: Synthesis of (4-Methoxyphenyl)-3-(4-nitrophenyl)-5-ethyl-1,2,4-triazole (IV): a round bottom flask is charged with 20 ml of 15% sodium hydroxide solution, 1.0 g of triazole (I) is added, stirred until dissolved and 3.0 ml of dimethylsulfate is added. The mixture is heated for 12 hours under reflux, with pH more than 10 controls. Then, 100 ml of water and 100 ml of diethyl ether is added to the reaction mixture, stirred and the ether layer is separated, dried with anhydrous sodium sulfate, the solvent is evaporated to a small volume and the residue is evaporated in a Petri dish. The precipitate is washed several times with warm hexane and dried.

Procedure 4: Synthesis of 1-(R-carboxyphenyl)-3-(4-nitrophenyl)-5-ethyl-1,2,4-triazole (V a-e): 2.0 mmol of the appropriate carboxylic acid chloride is added to a solution of 1.0 mmol of the triazole (I) in 50 ml of sodium hydroxide 5% solution. The



Schema 2

V: a) R=4-NO_2-C_6H_4-; b) R=C_6H_5-; c) R=4-OCH_3-C_6H_4-; d) R=2-Br-C_6H_4-; e) R=CH_3-

Table 1

Compound	1H NMR spectrum (Varian Gemini 2000 spectrometer, 400 MHz), δ, ppm. (J, Hz)
I	1.27 (3H, t, J=7.6, CH_3); 2.76 (2H, q, J=7.6, CH_2); 6.93 (2H, d, J=8.8, Ar); 7.42 (2H, d, J=8.8, Ar); 8.22–8.36 (4H, dd, J=8.9, $C_6H_4NO_2$)
II	0.95 (3H, t, J=7.2, CH_3); 2.84 (2H, q, J=7.3, CH_2); 8.28–8.36 (4H, dd, J=8.8, $C_6H_4NO_2$); 8.5 (2H, s, Ar)
III	1.25 (3H, t, J=7.6, CH_3); 2.83 (2H, q, J=8.8, CH_2); 7.9 (2H, s, Ar); 8.25–8.32 (4H, dd, J=9.0, $C_6H_4NO_2$)
IV	1.26 (3H, t, J=7.6, CH_3); 2.81 (2H, q, J=7.5, CH_2); 3.84 (3H, s, CH_3); 7.35 (2H, d, J=8.8, Ar); 7.65 (2H, d, J=8.8, Ar); 8.25–8.4 (4H, dd, J=8.6, $C_6H_4NO_2$)
Va	1.34 (3H, t, J=8.0, CH_3); 2.91 (2H, q, J=8.0, CH_2); 7.61 (2H, d, J=8.3, Ar); 7.79 (2H, d, J=8.3, Ar); 8.3–8.45 (8H, м, Ar)
Vb	1.32 (3H, t, J=7.6, CH_3); 2.91 (2H, q, J=7.9, CH_2); 7.54-7.67 (5H, м, C_6H_5); 7.79 (2H, d, J=7.9, Ar); 8.19 (2H, d, J=7.9, Ar); 8.29–8.39 (4H, dd, J=8.9, $C_6H_4NO_2$)
Vc	1.32 (3H, t, J=7.6, CH_3); 2.90 (2H, q, J=7.6, CH_2); 3.90 (3H, s, CH_3O); 7.16 (2H, d, J=8.8, Ar); 7.54 (2H, d, J=8.8, Ar); 7.67 (2H, d, J=8.8, Ar); 8.13 (2H, d, J=8.8, Ar); 8.3–8.39 (4H, dd, J=8.8, $C_6H_4NO_2$)
Vd	1.29 (3H, t, J=7.6, CH_3); 2.9 (2H, q, J=7.6, CH_2); 7.57-7.6 (2H, m, O–BrC_6H_4); 7.62 (2H, d, J=8.8, Ar); 7.81 (2H, d, J=8.8, Ar); 7.87 (1H, m, O–BrC_6H_4); 8.13 (1H, m, O–BrC_6H_4); 8.3–8.39 (4H, dd, J=8.8, $C_6H_4NO_2$)
Ve	1.29 (3H, t, J=7.6, CH_3); 2.52 (3H, s, CH_3); 2.85 (2H, q, J=7.6, CH_2); 7.38 (2H, d, J=8.8, Ar); 7.75 (2H, d, J=8.8, Ar); 8.28–8.4 (4H, dd, J=8.8, $C_6H_4NO_2$)

Table 2

The yields and physical and chemical (II, III, IV, V a-e)

Compound	Yield, %	Appearance	The melting point, ^{0}C	Elemental analysis					
				Found, %			Calculated, %		
				C	H	N	C	H	N
II	60	yellow	169–172	48.10	3.08	21.01	48.01	3.02	20.99
III	40	light yellow	253–255	41.55	2.61	11.83	41.05	2.58	11.97
IV	15	light gray	138–140	62.90	4.99	17.23	62.95	4.97	17.27
Va	48	brick red	205–208	60.13	4.91	15.24	60.25	4.86	15.35
Vb	54	light-brown	180–183	67.28	4.42	13.08	67.10	4.38	13.02
Vc	32	beige	176–179	64.86	4.58	12.61	65.02	4.54	12.63
Vd	42	yellow	127–130	61.36	4.35	17.23	61.96	4.45	15.85
Ve	63	brown	150–153	48.28	4.45	9.79	48.35	4.85	9.95

reaction mixture is stirred for 3 hours. The product thus precipitates as a precipitate which is filtered under vacuum, washed several times with water and dried first in air and then in the desiccator over sulfuric acid. The yields and physical and chemical data of the compounds are shown in Table 2.

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