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Synthesis and Characterization of New Polynuclear Bis-5-oxy-1*H*-tetrazoles*

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Abstract—Different bis-phenols reacted with cyanogen bromide in the presence of triethylamine as base to give the corresponding bis-cyanates which were treated with sodium azide in acetone as solvent to produce new bis(5-oxy-1*H*-tetrazole) derivatives. One more bis-tetrazole derivative was synthesized by reaction of 5-(4-aminophenoxy)-1*H*-tetrazole with adipoyl chloride. The prepared compounds were characterized by usual spectroscopic techniques.

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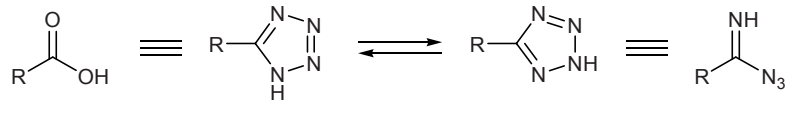
Tetrazoles constitute a very important class of compounds for medicinal chemistry. Substituted tetrazoles were found to exhibit a wide spectrum of neurological activity which, depending on the substitution pattern, ranges from strong stimulation of the nervous system to depressant action. 5-Substituted-1*H*-tetrazoles may serve as nonclassical isosters for the carboxylic acid moiety (RCOOH) in the design of anticancer, antimicrobial, antihypertensive, and antiallergic agents. The term *nonclassical isosterism* (used interchangeably with the term *bioisosterism*) refers to the concept implying that functional groups having similar physicochemical properties may be interchangeable, resulting in similar biological properties [1].

The main difficulty in studies on tetrazole compounds is related to possible equilibrium between 1*H*-tetrazole, 2*H*-tetrazole, and imidoyl azide (open-chain isomer of 1*H*-tetrazole) tautomers in solution (Scheme 1). The composition of the tautomer mixture depends on the 5-substituent, solvent polarity, and other factors. Generally, each isomer is characterized by its own specific chemical and pharmaceutical behavior. For example, some 1,5-disubstituted tetrazoles show strong stimulating effect on the central nervous system, while 2,5-disubstituted tetrazoles do not [2]. On the other hand, most azides (important precursors of many classes of compounds such as amines, aziridines, ureas, oxadiazoles, and others) are carcinogenic [3–5].

Dabbagh and co-workers used tetrazoles in many chemical reactions. They reported on the equilibrium between 5-substituted 1- and 2-acyltetrazoles, their thermal decomposition, and conversion into imidoyl azides, isoureas, and oxadiazoles [6–8]. Also, the synthesis of new azo dyes containing an aryloxytetrazole fragment was described [9], While studying the reactivity of polynuclear tetrazoles toward different electrophiles, Filichev et al. [10] synthesized new mono- and bis-3-substituted thymidine derivatives containing a 1,5-bis(tetrazol-5-yl)-3-oxapentane fragment as linker. Such compounds attract interest as inhibitors of DNA chain extension and antisense agents. Syntheses of nonfused methylene-bridged polynuclear triazole- and tetrazole-containing systems were also reported by Verkhozina et al. [11]. Bronisz [12] described the first coordination polymer based on 1,2-bis(2*H*-tetrazol-2-

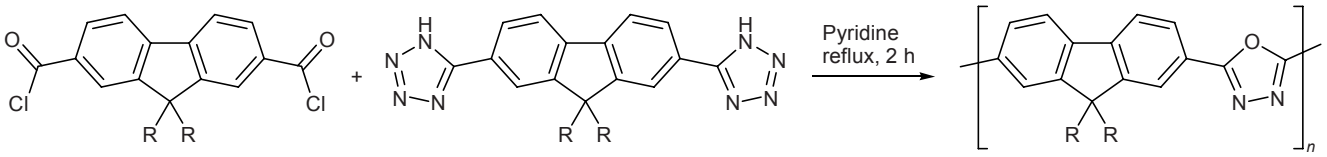
Scheme 1.



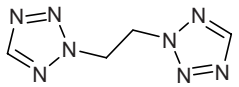
Carboxylic acid 1*H*-Tetrazole 2*H*-Tetrazole Imidoyl azide

* The text was submitted by the authors in English.

Scheme 2.



yl)ethane (ebtz, **A**). The ligand was synthesized by alkylation of 1*H*-tetrazole. The author showed that the coordination geometry of Zn(II) in $[Zn(ebtz)_3](ClO_4)_2$ is not simply propagated in the network because of the presence of elastic linkage in ebtz enabling the coordinated ligand molecule to adopt a *syn* conformation in contrast to *anti* conformation of the free ligand molecule in the solid state [12].



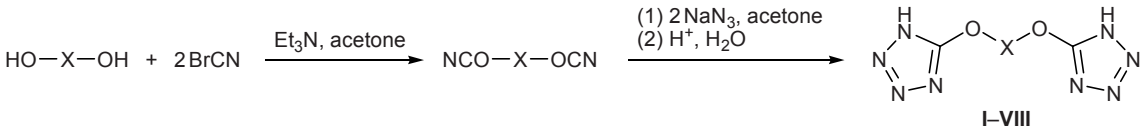
A

Zubarev et al. [13] have recently reported on the synthesis of a series of podand (polydentate ligand) systems containing two to four 2-(tetrazol-5-yl)ethyl fragments in one molecule. The molecular structure and physicochemical properties of these tetrazole podands enabled their high complexing ability toward metal ions. Efficient filtering materials based on these complexones have been developed recently for thorough purification of biological fluids from heavy metals and radionuclides [13].

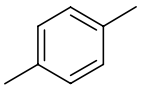
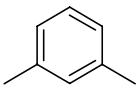
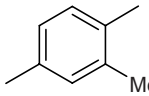
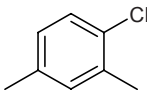
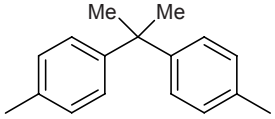
Furthermore, bis-tetrazole compounds can react with dicarboxylic acid chlorides (Huisgen reaction) or bis-isocyanates to give polymers containing 1,3,4-oxadiazole units. These polymeric compounds, displaying tough mechanical properties and excellent heat resistance, are advanced materials for high-performance applications, e.g., in electronic devices [14] (Scheme 2).

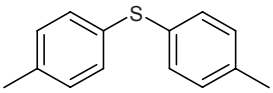
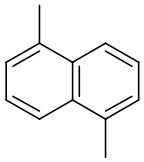
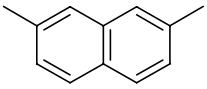
In the present work, we synthesized new bis(5-oxy-1*H*-tetrazole) derivatives **I**–**VIII** (Scheme 3). Different bis-phenols reacted with cyanogen bromide in the presence of triethylamine as base in acetone at 0–5°C to give the corresponding bis-cyanates. Treatment of the latter with sodium azide afforded (after acidification) the desired bis-tetrazoles **I**–**VIII** in 20–75% yield

Scheme 3.

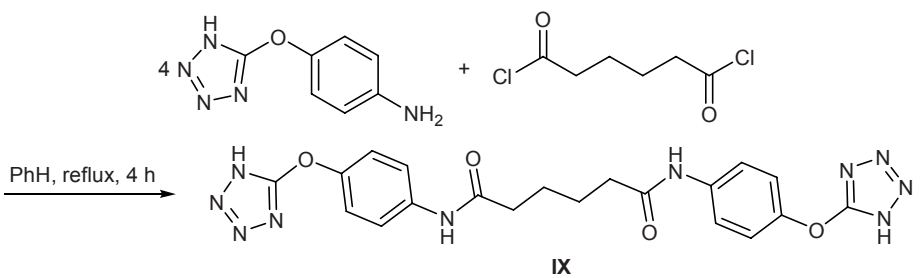


I–**VIII**

I, X =  ; **II**, X =  ; **III**, X =  ; **IV**, X =  ; **V**, X =  ;

VI, X =  ; **VII**, X =  ; **VIII**, X =  .

Scheme 4.



IX

Yields, melting points, and IR, ^{1}H NMR, and mass spectra of bis-tetrazoles **I**–**IX**[a]

Comp. no.	Yield, %	Decomposition point, °C	^{1}H NMR spectrum (DMSO-d_6), δ, ppm	IR spectrum (KBr), ν, cm^{-1}
I	50	241–242	7.50 s	3100 w, 2920 m, 2600 s, 2450 m, 1613 s, 1497 s, 1179 s
II	20	179–180	7.30–6.80 m	3025 m, 2893 m, 2745 m, 2648 m, 2480 w, 1595 s, 1484 s, 1418 s, 1242 s, 1137 s, 1074 s
III	40	212–214	7.80–7.00 m (3H), 2.20 s (3H)	3028 m, 2889 m, 2745 m, 2630 m, 1593 s, 1490 s, 1412 s, 1171 s, 1062 s
IV	35	110–111[b]	9.70–8.50 br.s, 7.45–7.10 m (2H), 7.80 d (1H, J = 7.8 Hz)	3053 m, 2727 m, 2630 m, 2498 m, 1611 s, 1569 s, 1509 m, 1430 s, 1286 m, 1045 m, 857 w
V	75	197–199	7.20 s (8H), 1.50 s (6H)	3034 w, 2969 m, 2867 m, 2741 m, 2628 m, 1585 s, 1497 s, 1407 s, 1168 s, 1043 s
VI	46	174–175	11.40 s (2H), 7.60 s (4H)	3022 m, 2890 m, 2733 m, 2624 m, 2452 w, 1617 s, 1569 s, 1484 s, 1192 s, 1052 s, 839 s
VII	30	226–228	8.20–7.30 m	3047 m, 2896 m, 2739 m, 2624 m, 2450 w, 1589 s, 1502 s, 1388 s, 1249 s, 1171 m, 1050 s
VIII	60	176–178	15.00–11.00 br (2H), 9.5–7.8 m (6H)	3239 m, 3044 m, 2889 m, 2738 m, 2638 m, 1569 s, 1508 s, 1448 s, 1206 s, 1056 s, 954 s
IX	16	205–207	10.10 s (2H), 9.00 br.s, 7.20 d (4H, J = 8.2 Hz), 7.70 d (4H, J = 8.2 Hz), 2.65–2.0 m (4H), 1.95–1.20 m (4H)	3264 s, 3059 s, 2914 s, 2727 s, 2613 s, 2468 m, 1648 s, 1623 s, 1539 s, 1503 s, 1406 s, 1183 m, 1044 m

[a] Mass spectrum, *m*/*z*: **II**, 246; **III**, 260; **V**, 264; **VII**, 296.
[b] mp 94–95°C.

(see table). In addition, bis-tetrazole **IX** was synthesized by the reaction of 5-(4-aminophenoxy)-1*H*-tetrazole with adipoyl dichloride (Scheme 4). In this case, two equivalents of the amine was used, one of which acted as base to bind liberated hydrogen chloride. The yields, melting points, and spectral parameters of compounds **I**–**IX** are given in table.

Unlike the initial bis-phenols, the IR spectra of bis-tetrazoles **I**–**IX** lacked absorption bands assignable to stretching vibrations of hydroxy groups (3600 cm^{-1}), while a complex absorption pattern was observed in the region 3000–2480 cm^{-1}, and C=N absorption bands were present at 1610–1590 cm^{-1}. No OH signal was observed in the ^{1}H NMR spectra of **I**–**IX**, and the NH signal usually appeared in the region δ 10–20 ppm, though it was strongly broadened in most cases. The mass spectra of compounds **II**, **III**, **V**, and **VII** contained the corresponding molecular ion peaks.

The synthesized compounds can be used for the preparation of new thermally stable polymers containing 1,3,4-oxadiazole units via Huisgen reaction. This part of the study is now under implementation.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Joel JNM-EX 90A spectrometer. The IR spectra were measured in KBr on a Buck Infrared Spectrophotometer Model 500. The mass spectra (electron impact, 70 eV) were obtained on a Shimadzu QP-5050 mass spectrometer coupled with a Shimadzu GC-17A gas chromatograph.

Typical procedure for the preparation of bis-tetrazole compounds I–VIII. A 100-ml two-necked round-bottom flask equipped with a magnetic stirrer was charged with a solution of 4.3 mmol of the corresponding bis-phenol and 9 mmol of cyanogen bromide in 10 ml of anhydrous acetone. The solution was cooled to 0–5°C, and a solution of 0.91 g (9 mmol) of triethylamine in 5 ml of anhydrous acetone was added dropwise. Triethylamine hydrobromide gradually separated as a white solid. The mixture was stirred for an additional 30 min and filtered, and the filtrate was added to a suspension of 0.96 g (14.7 mmol) of sodium azide in 5 ml of anhydrous acetone at room temperature. The mixture was stirred for 90 min on heating under reflux, 10 ml of water was

added, and the mixture was concentrated under reduced pressure, cooled in an ice bath, and acidified by dropwise addition of concentrated hydrochloric acid. The precipitate of bis-tetrazole **I–VIII** was filtered off, washed with cold water, and recrystallized from ethyl acetate–hexane (see table).

***N*,*N*′-Bis[4-(1*H*-tetrazol-5-yloxy)phenyl]adipamide (IX).** Adipoyl chloride, 0.99 g (5.47 mmol) was added dropwise under stirring to a suspension of 3.87 g (21.85 mmol) of 5-(4-aminophenoxy)-1*H*-tetrazole in anhydrous benzene (preliminarily dried with metallic sodium). The mixture was stirred for 4 h on heating under reflux, the solvent was removed under reduced pressure, the residue was poured into water, and the mixture was acidified to pH 1 with concentrated hydrochloric acid and stirred for 2 h at room temperature. The brown precipitate was filtered and washed with cold water. Yield 1.58 g (16%).

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