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New diols with imidazoquinazoline ring

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ABSTRACT

The objective of these studies was to synthesize and characterize new diols with an imidazoquinazoline ring. New diols were obtained in reactions of 2,6-bis-(ethoxycarbonylmethyl)-1-phenylimidazo[1,5-*c*]quinazoline-3,5-dione with excess of ethylene glycol or in reaction of 1-phenyl-2H,6H-imidazo[1,5-*c*]quinazoline-3,5-dione with 2-M excess of ethylene oxide. The products were isolated at high yield and characterized by instrumental methods (IR, ^{1}H- and ^{13}C-NMR, MS-ESI, UV, TGA). The structure of 2,6-bis(2-hydroxyethyl)-1-phenylimidazo[1,5-*c*]quinazoline-3,5-dione (BEFIQ) was also investigated by single-crystal X-ray diffraction. BEFIQ crystallizes in the monoclinic $P2_1/n$ space group with two molecules in the asymmetric unit of the crystal lattice. The nature of the packing of molecules in the crystal lattice of BEFIQ was investigated by Hirshfeld surface analysis. The described methods enable the synthesis of new diols with an imidazoquinazoline ring. The new diols are quite soluble in typical organic solvents. Therefore, they can be used as raw materials for the synthesis of thermally stable polymers, and they can also have biological activity.

1. Introduction

In order to modify the polymer properties, e.g. enhanced thermostability or reduced combustibility, aromatic rings [1–10] or heteroaromatic rings [11–20] are incorporated into the polymer structure.

Thermal stability is closely related to the macromolecule structure. The improvement of thermostability is promoted by high molecular rigidity. It can be enhanced by the presence of aromatic or heteroaromatic rings or the presence of hydrogen bonds. A structural symmetry, a substituent presence and a cross-linking degree have also meaning for the polymer thermostability.

According Szczerba, a thermally stable polymer is a polymer which does not undergo degradation during long term exploitation (30,000 h) at a temperature of 170 °C, and neither changes shape nor undergoes melting during brief heating to a temperature of 400 °C [21].

In turn, according to the Marvel classification, a thermally stable polymer does not undergo the degradation process subsequent to long exploitation time (up to 25,000 h) at a temperature of 300 °C. Moreover, the polymer does not change shape and does not melt during a brief annealing (up to 300 h) at temperatures reaching 500 °C [22].

Heterocyclic compounds also used the polymer structure and properties modification, usually have low solubility, e.g. melamine [13–15], cyanuric acid [19], uric acid [16], or barbituric acid [17,18]. Therefore, in order to incorporate these above-mentioned rings into the polymer structure, soluble derivatives of these compounds must be obtained. This is possible by the introduction of substituents to heterocyclic rings. Unfortunately, their presence decreases the polymer thermostability somewhat.

These soluble derivatives are usually obtained in the hydroxyalkylation process with the use of formaldehyde [23–25], oxiranes [26,27], or alkylene carbonates [24,28]. Both formaldehyde and oxiranes are toxic and carcinogenic [29–32]. Furthermore, oxiranes form explosive mixtures with the air and require the use of the pressure reactors [33]. In contrast, alkylene carbonates are nontoxic, non-flammable, and they are simultaneously either the reagents or the reaction environment. This makes that an additional solvent application is unnecessary. However, the main method of alkylene carbonate synthesis is based on the oxiranes as

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raw materials [34,35].

Imidazoquinazoline is also a heterocyclic compound whose ring can enhance the thermal stability of polymers. Up to now, compounds with an imidazoquinazoline ring have been widely used in the field of pharmacy and medicine because of their versatile biological properties. These compounds have antitumour, antiviral, antibacterial and anticonvulsant effects. In addition, some derivatives belonging to this class of compounds can be used to neutralize free radicals, and consequently to prevent lipid peroxidation and cell damage [36,37].

This work refers to the synthesis of new diols with an imidazoquinazoline ring with the use of 1-phenyl-2H,6H-imidazo[1,5-*c*] quinazoline-3,5-dione. This compound is almost insoluble in organic solvents. Therefore, in order to enable the introduction of the imidazoquinazoline ring into the polymer structure, new diols were obtained using two methods. In the first, ethylene oxide reacted with 1-phenyl-2H,6H-imidazo[1,5-*c*]quinazoline-3,5-dione (FIQ). An alternative method of synthesizing diols did not use oxiranes. For this purpose a nucleophile substitution reaction was applied. At first, diester – 2,6-bis(ethoxycarbonylmethyl)-1-phenylimidazo[1,5-*c*]quinazoline-3,5-dione was obtained, and the next transesterification was performed using ethylene glycol. In this study, the synthesis route, and spectral and instrumental characterization within the thermal properties of the two new diols is shown.

2. Materials and methods

2.1. Materials

2,6-bis(ethoxycarbonylmethyl)-1-phenylimidazo[1,5-*c*]quinazoline-3,5-dione was obtained from 1-phenyl-2H,6H-imidazo[1,5-*c*]quinazoline-3,5-dione according to procedure [38].

The rest reagents were purchased and used as obtained.

Ethylene glycol, pure for analysis, zinc acetate, pure for analysis, acetone, pure for analysis, ethanol, pure for analysis, were purchased from POCH Poland. Dimethyl sulfoxide (DMSO) pure for analysis, and triethylamine (TEA), pure for analysis, were supplied by Avocado, Germany. Ethylene oxide (EO), pure for analysis, was provided by Merck, Germany.

2.2. Syntheses

2.2.1. Synthesis of 2,6-bis(2-hydroxyethyl)-1-phenylimidazo[1,5-c] quinazoline-3,5-dione

2.77 g (1 mmol) of FIQ [38] was inserted into a high pressure reactor with a volume of 100 cm^3 and dissolved in 20 cm^3 of DMSO. Then 0.01 g (0.1 mmol) TEA and 0.88 g (2 mmol) EO were added. The reaction mixture was stirred with a magnetic stirrer and heated to a temperature of 70–80 °C. The reaction course was determined on the basis of the epoxy number of the reaction mixture. When the epoxy number was zero, DMSO was distilled under vacuum (p = 7 mm Hg, liquid distillation temperature: 65–110 °C, vapour distillation temperature: 68–72 °C). The product was precipitated with acetone and crystallized from ethanol. Product purity was monitored by TLC (elution systems chloroform - ethanol, 9:1) on Alugram SIL G/UV254 foil (Macherey-Nagel).

Product characterization: yield 85%, white crystals, melting point 217–218 °C (from ethanol); EA: % calcd (found) for $C_{20}H_{19}N_3O_4$: C 65.75 (65.60), N 11.57 (11.41), H 5.24 (5.08); IR (KBr): ν = 3435 (s, O–H valence), 3030 (w, CH, deformation of phenyl ring), 2955 (w, $^{-}CH_2^{-}$, asymmetric, valence), 2883 (w, $^{-}CH_2^{-}$, symmetric valence), 1742 (s, C=O, valence), 1053 (m, C–O–H, valence), 1660, 1612, 1509, 1445 (s, skeletal of phenyl ring), 1156 (w, C–H, planar deformation), 752, 699 (s, C–H, nonplanar deformation), 1631, 1587, 1485 (s, skeletal of quinazoline ring) [cm^{-1}]; ^{1}H-NMR (500 MHz, DMSO-d_6, δ = 3.35 (2 H, t, $-N^{-}CH_2^{-}$, $J_{20,21}$ = 5.51 Hz), 3.47 (2H, t, $^{-}CH_2$–OH, $J_{20,21}$ = 6.24 Hz), 3.64 (2 H, t, $-N^{-}CH_2^{-}$, $J_{22,23}$ = 5.51 Hz), 4.10 (2H, t, $^{-}CH_2$–OH, $J_{22,23}$ = 6.24 Hz), 4.81 (1 H, t, $^{-}$OH, $J_{0,21}$ = 5.42 Hz), 4.90 (1 H, t, $^{-}$OH, $J_{0,23}$ = 5.42 Hz), 6.72 (1 H, d, $J_{8,9}$ = 8.07 Hz), 6.80 (1 H, t, $J_{10,11}$ = 7.45 Hz), 7.21 (1 H, t, $J_{9,8}$ = 7.25 Hz), 7.29 (1 H, d, $J_{11,10}$ = 8.09 Hz) 7.54 (2 H, m), 7.62 (3 H, m); ^{13}C-NMR (DMSO-d_6), δ = 147.90 (C_3), 145.10 (C_5), 134.79 (C_7), 131.05 (C_{17}), 129.94 ($C_{16,}$ C_{18}), 129.44 (C_{15} and C_{19}), 128.26 (C_{14}), 127.88 (C_9), 125.29 (C_{11}), 122.48 (C_{10}), 121.13 (C_8), 117.75 (C_1), 114.01 (C_{13}), 111.84 (C_{12}), 57.75 (C_{21}), 57.49 (C_{23}), 44.12 (C_{22}), 43.15 (C_{20}), [ppm]; UV, 224, 264, 335 [nm], MS-ESI: *m/z* 366 $[M+H]^+$ (100%); EI-MS of precursor ion *m/z* 366: *m/z* 322 $[M + H-C_2H_4O]^+$, 276 $[M-2C_2H_4O]^+$, 261 $[M-C_2H_4O-CO-CH_3OH]$+(100%), 257, 235.

2.2.2. Synthesis of 2,6-bis((2-hydroxyethoxy)carbonylmethyl)-1-phenylimidazo[1,5-c]quinazoline-3,5-dione

2.225 g (5 mmol) of 2,6-bis(ethoxycarbonylmethyl)-1-phenylimidazo[1,5-*c*]quinazo-line-3,5-dione [39], 0.70 g (11 mmol) ethylene glycol, 0.004 g (0.02 mmol) zinc acetate were placed in a three-necked flask equipped with a mechanical stirrer thermometer, a Dean Stark trap, and a reflux condenser. The reaction mixture was heated to a temperature of 190–195 °C in a nitrogen atmosphere. Methanol, which was released from the reaction mixture upon the transesterification process, was condensed and collected in the trap. When the reaction temperature rose to 197–198 °C, the excess ethylene glycol was distilled off. Next, the reaction mixture was cooled in an inert atmosphere. The crude, solidified product was purified by crystallization from acetone. Its purity was monitored by TLC (elution systems chloroform - ethanol, 9:1) on Alugram SIL G/UV254 foils (Macherey-Nagel).

Product characterization: yield 70%. yellowish crystals, melting point 99 °C (from acetone); EA: % calcd (found) for $C_{24}H_{23}N_3O_8$: C 59.88 (59.68); H 4.82 (4.90); N 8.72 (8.68); IR: 3700–3200 (s, O–H valence), 3059 (w, CH, deformation of phenyl ring), 2953 (w, $^{-}CH_2^{-}$, asymmetric, valence), 2940(w, $^{-}CH_2^{-}$, symmetric valence), 1749 (s, C=O, valence), 1604, 1584, 1505, 1486 (s, skeletal of phenyl ring), 1296 (s, C–O(O), symmetric, valence), 1201 (m, C–O(O), asymmetric, valence), 1072 (m, C–O–H, valence), 753, 665 (s, C–H nonplanar, deformation), 1631, 1583, 1485 (s, skeletal of quinazoline ring), [cm^{-1}]; ^{1}H-NMR (500 MHz, DMSO-d_6), δ = 3.49 (2H, t, CH_2–OH, $J_{22,23}$ = 5.82 Hz), 3.63 (2H, t, CH_2–OH, $J_{26,27}$ = 5.94 Hz), 4.02 (2 H, q, CH_2–O, $J_{22,23}$ = 5.82 Hz), 4.17 (2H, q, $^{-}CH_2$–O, $J_{26,27}$ = 5.94 Hz), 4.26 (2 H, s, CH_2), 4.81 (2 H, s, CH_2), 4.81 (1 H, s, C_{23}^{-}OH), 4.91 (1 H, s, C_{27}^{-}OH), 6.82 (1 H, d, $J_{10,11}$ = 7.57 Hz), 6.88 (1 H, t, $J_{10,9}$ = 7.54 Hz), 7.12 (1 H, d, $J_{9,8}$ = 8.28 Hz), 7.24 (1 H, t, $J_{11,10}$ = 7.56 Hz), 7.48 (2 H, m), 7.61 (3 H, m); ^{13}C-NMR (DMSO-d_6),δ = 168.33 (C_{25}), 167.82, (C_{21}), 147.80 (C_3), 145.00 (C_5), 134.52 (C_{13}), 130.68 (C_{19}), 130.37 (C_{15}), 130.08 (C_{17}), 129.65 (C_{18}), 129.15 (C_{14}), 128.52 (C_{10}), 127.16 (C_{16}), 123.17 (C_9), 121.44 (C_{11}), 117.68 (C_1), 114.94 (C_8), 113.46 (C_7), 112.08 (C_{12}), 66.96 (C_{26}), 66.82 (C_{22}), 58.75 (C_{27}), 58.55 (C_{23}), 43.91 (C_{24}), 42.23 (C_{20}), [ppm]; MS-ESI: *m/z* 482 $[M+H]^+$ (100%); EI-MS of precursor ion *m/z* 482: *m/z* 320 [M + H-2 C_2H_4O $-CO_2$, $-CH_2O$ $]^+$, 275 $[M+2H^+$-2 C_2H_4O – 2 CO_2, -2 $CH_4]^+$, 259 [M + – 2 C_2H_4O – 2 CO_2, - 2 CH_2 $-H_2O]^+$ (100%), 247, 232, 219, 204.

2.2.3. Analytical methods

The epoxy number of the reaction mixtures was determined by standard [40].

Melting points were measured in capillary apparatus.

Infrared spectra of the obtained diols were measured in the range of 4000–400 cm^{-1}, from KBr disks. Spectra were recorded on a Bruker ALPHA FT-IR instrument with resolution of 0.01 cm^{-1}.