THE QUESTION OF THE CYCLIZATION OF 3-{(2-CARBOXYETHYL)-3-[BIS(2-CARBOXYETHYL)AMINO]ANILINO}PROPANOIC ACID

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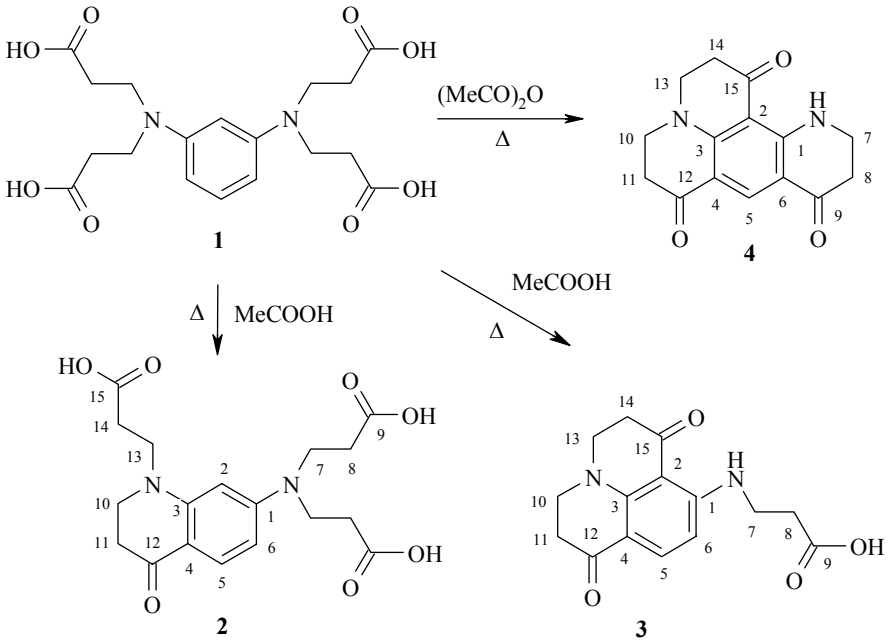
The benzo[*i*,*j*]quinolizine (julolidine) system occurs in the composition of a series of alkaloids [1]. Quinolizine derivatives are used as medicinal compounds [2], several of which have antimicrobial activity [3]. Cyclization of N-aryl-N-carboxyethyl-β-alanines to 1-(2-carboxy-ethyl)tetrahydroquinolinone has been reported in a series of studies while the cyclization leading to the formation of quinolizine derivatives is a greater problem. One of the first syntheses of diketo julolidine derivatives was brought about by cyclization of N,N-bis(2-cyanoethyl)aniline in the presence of aluminium chloride [4]. The action of PPA on N-carboxyethyl-N-



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methylenedioxy- and N-ethylenedioxyphenyl-β-alanines gave the corresponding benzo[*i,j*]quinolizinediones [5]. Heating 3-{(2-carboxyethyl)-3-[bis(2-carboxy-ethyl)amino]anilino}propanoic acid (**1**) (prepared by treatment of *m*-phenylenediamine with acrylic acid) in acetic acid gives the products of partial cyclization 3-{7-[bis(2-carboxyethyl)amino]-4-oxo-3,4-dihydro-1(2H)-quinolinyl}propanoic acid (**2**) and 3-[9-(3-hydroxy-3-oxopropyl)-4,6-dioxo-3,4,6,7,8,9-hexahydropyrido[3,2-*g*]quinoline-1(2H)-propanoic acid. A more detailed study of this process shows that, after heating the tetraacid **1** in glacial acetic acid, along with compound **2** were able to separate from the reaction mixture the tricyclic N-(1,7-dioxo-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-*ij*]quinolin-8-yl)-β-alanine (**3**). Refluxing compound **1** in acetic anhydride causes dealkylation of the carboxyethyl group and cyclization to form the 2,3,11,12-tetrahydro-1H,5H-pyrido[3,2,1-*gh*]phenanthroline-1,7,9(6H,10H)-trione (4).

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Inova instrument (300 and 75 MHz respectively) with TMS as internal standard. Mass spectra were taken on a Waters ZQ 2000 instrument.

3-{(2-Carboxyethyl)-3-[bis(2-carboxyethyl)amino]anilino}propanoic acid (1) was prepared in 70% yield by method [6]. Mp 157.0-157.7°C (mp 159-160°C [6]).

3-{7-[Bis(2-carboxyethyl)amino]-4-oxo-3,4-dihydro-1(2H)-quinolinyl}propanoic acid (2) and N-(1,7-Dioxo-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-*ij*]quinolin-8-yl)-β-alanine (3). The tetracarboxylic acid **1** (5 g, 13 mmol) was refluxed in acetic acid (30 ml) for 8 h. The liquid fractions were distilled off and the remaining mass was dissolved in alcohol and left at 4°C. The crystals of **3** formed were filtered off, washed with ethanol and crystallized from acetic acid. Yield of **3** 0.95 g (26%). Mp 192-193°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.51-2.57 (4H, m, H-11,14); 2.65 (2H, t, *J* = 6.7, H-8); 3.39-3.45 (4H, m, H-10,13); 3.50 (2H, dt, *J* = 6.1, 5.8, H-7); 6.22 (1H, d, *J* = 9.2, H-6); 7.71 (1H, d, *J* = 9.2, H-5); 10.21 (1H, t, *J* = 5.8, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 33.55 ($C_{(8)}$); 36.02 ($C_{(11)}$); 37.12 ($C_{(14)}$); 37.84 ($C_{(7)}$); 49.08 ($C_{(10)}$); 50.01 ($C_{(13)}$); 100.95 ($C_{(6)}$); 101.53 ($C_{(2)}$); 108.01 ($C_{(4)}$); 134.71 ($C_{(5)}$); 155.61 ($C_{(3)}$); 156.91 ($C_{(1)}$); 172.66 ($C_{(9)}$); 188.96 ($C_{(12)}$; 194.36 ($C_{(15)}$). Mass spectrum (20 eV), *m/z* (I_{rel}, %): 289 $[M+H]^+$ (100). Found, %: C 62.33; H 5.49; N 9.41. $C_{15}H_{15}N_2O_4$. Calculated, %: C 62.56; H 5.62; N 9.73.

After removal of the acid **3** and distillation of the liquid fractions, the remaining product was dissolved in methanol and passed through a silica gel column (eluent methanol). Yield of **2** 1.95 g (41%). Mp 197-198°C (mp 194-195°C [6]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.42 (2H, t, *J* = 6.8, H-11); 2.48-2.54 (6H, m, H-8,14); 3.43 (2H, t, *J* = 6.8, H-10); 3.61-3.65 (6H, m, H-7,13); 5.82 (1H, d, *J* = 1.8, H-2); 6.14 (1H, dd, *J* = 9.0, *J* = 1.8, H-6); 7.53 (1H, d, *J* = 9.0, H-5); 12.33 (3H, br. s, COOH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 31.10 ($C_{(14)}$); 32.21 ($C_{(8)}$); 37.32 ($C_{(11)}$); 46.29 ($C_{(7)}$); 46.54 ($C_{(13)}$); 48.89 ($C_{(10)}$); 92.76 ($C_{(2)}$); 102.54 ($C_{(6)}$); 110.56 ($C_{(4)}$); 129.56 ($C_{(5)}$); 152.15 ($C_{(1)}$ or $C_{(3)}$); 152.20 ($C_{(1)}$ or $C_{(3)}$); 173.06 ($C_{(9)}$); 173.28 ($C_{(15)}$); 190.03 ($C_{(12)}$). Mass spectrum (20 eV), m/z (I_{rel}, %): 379 $[M+H]^+$ (100). Found, %: C 57.01; H 6.11; N 6.99. $C_{18}H_{22}N_2O_7$. Calculated, %: C 57.19; H 5.87; N 7.41.

2,3,11,12-Tetrahydro-1H,5H-pyrido[3,2,1-*gh*][1,7]phenanthroline-1,7,9(6H,10H)-trione (4). The tetracarboxylic acid **2** (8.77 g, 22 mmol) was dissolved in acetic anhydride (50 ml) and refluxed for 3 h. The liquid fraction was distilled off and the remaining mass was purified by rapid passage through a chromatography column (eluent methanol). Yield 1.19 g (20%). Mp 287-288°C. IR spectrum (KBr), ν, cm^{-1}: 3218 (NH), 2852-2962 (aliph. C–H); 1577, 1626, 1661 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.63-2.67 (2H, m, H-8); 2.72-2.82 (4H, m, H-11,14); 3.55-3.60 (4H, m, H-10,13); 3.66-3.72 (2H, m, H-7); 8.60 (1H, s, H-5); 10.34 (1H, br. s NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.49-2.71 (6H, m, H-8,11,14); 3.55-3.67 (6H, m, CH_2N, H-7,10,13); 8.20 (1H, s, H-5); 10.21 (1H, br. s, NH). ^{13}C NMR Spectrum (DMSO-d_6), δ, ppm: 35.63 ($C_{(11)}$); 35.89 ($C_{(14)}$); 36.41 ($C_{(8)}$); 48.7 ($C_{(7)}$); 49.21 ($C_{(13)}$); 49.21 ($C_{(10)}$); 100.68 ($C_{(2)}$); 108.68 ($C_{(4)}$); 109.42 ($C_{(6)}$); 133.39 ($C_{(5)}$); 156.24 ($C_{(1)}$); 158.12 ($C_{(3)}$); 189.72 ($C_{(12)}$); 190.46 ($C_{(9)}$); 193.77 ($C_{(15)}$). Mass spectrum, (20 eV), *m/z* (I_{rel}, %): 271 $[M+H]^+$ (100). Found, %: C 66.22; H 5.09; N 9.99. $C_{15}H_{14}N_2O_3$. Calculated, %: C 66.66; H 5.22; N 10.36.

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