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SYNTHESIS OF DERIVATIVES OF 1-(2-CARBOXYETHYL)-(1H,3H)-QUINAZOLINE-2,4-DIONE

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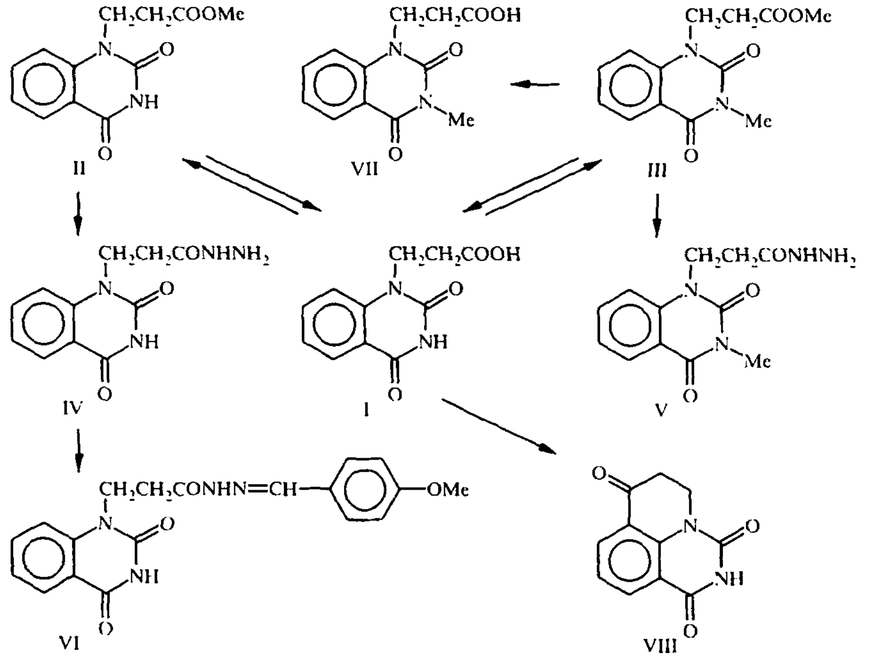
The action of alkylating agents on 1-(2-carboxyethyl)-(1H,3H)-quinazoline-2,4-dione was utilized to synthesize corresponding esters. The hydrolysis and hydrazinolysis of the last were accomplished. Polyphosphoric acid effected the conversion of 1-(2-carboxyethyl)quinazolinedione to 1,3,7-trioxopyrido[1,2,3-k,j]quinazoline.

We previously found that the condensation of 1-(2-carboxyphenyl)-β-alanine with urea in an acidic medium results in the formation of 1-carboxyethyl-2,4-(1H,3H)-quinazolinedione with a good yield [1]. In the given work, some chemical conversions of the given compound were accomplished with the purpose of seeking biologically active substances, since the quinazoline series is known to include substances possessing anticonvulsive [2, 3], fungicidal [4], and growth-regulating [5] activity.

In the alkylation of 1-(2-carboxyethyl)-2,4-(1H,3H)-quinazolinedione (I) by the equimolar amount of dimethyl sulfate in an alkaline medium, the main reaction product is the methyl ester — 1-(2-methoxycarbonylethyl)-(1H,3H)-quinazoline-2,4-dione (II), whereas the alkylation by iodomethane in DMF is also directed at the nitrogen atom of the heterocycle. The esters (II) and (III) yielded the corresponding hydrazides (IV) and (V), readily undergoing condensation reaction with aldehydes. Therefore, the hydrazide of 3-[2,4-dioxo-(1H,3H)-quinazolin-1-yl]propanoic acid (IV) reacted with anisaldehyde to give the corresponding hydrazone (VI). The PMR spectrum of (VI) contains signals of protons of the methoxy group in the form of a singlet at 3.78 ppm and signals of aromatic protons in the range 7.0-8.1 ppm in the form of a multiplet, together with signals of protons of the quinazolinedione (I). Alkaline hydrolysis of the methyl ester (III) led to the synthesis of 1-(2-carboxyethyl)-3-methyl-(1H,3H)-quinazoline-2,4-dione (VII), which could not be obtained by acid hydrolysis.



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The heating of the quinazolinedione (I) in the 2.5:1 mixture of P_2O_5 and H_3PO_4 results in heterocyclization with the formation of 1,3,7-trioxopyrido[1,2,3-k,j]quinazoline (VIII), the structure of which was confirmed by PMR and mass spectra.

EXPERIMENTAL

The PMR spectra were recorded on the Tesla BS 487C instrument (80 MHz) with HMDS as the internal standard. The mass spectra were recorded on the MCLKB 2091 spectrometer (70 eV).

1-(2-Methoxycarbonylethyl)-(1H,3H)-quinazoline-2,4-dione (II). The quinazolinedione (I) (11.7 g, 0.005 mole) is dissolved in a solution of sodium hydroxide (2.2 g of NaOH in 50 ml of H_2O), and the mixture is heated up to 80°C prior to the addition of 6 ml (0.055 mole) of dimethyl sulfate with stirring for 10 min. The stirring is continued at the same temperature for 30 min. The residue of the ester (II), which separated out, is filtered off and washed with water. Compound (II) is obtained with the yield of 11.0 g (88%). The mp is 184-185°C (ethanol). The PMR spectrum (CF_3COOH) is as follows: 2.62 ppm (2H, t, CH_2CO), 3.5 ppm (3H, s, CH_3), 4.31 ppm (2H, t, $N-CH_2$), and 6.9-8.1 ppm (4H, m, H arom.). Found, %: C 58.33, H 4.80, and N 11.41. $C_{12}H_{12}N_2O_4$. Calculated, %: C 58.07, H 4.87, and N 11.29.

1-(2-Methoxycarbonylethyl)-3-methyl-(1H,3H)-quinazoline-2,4-dione (III). The quinazolinedione (I) (4.68 g, 0.02 mole) is dissolved in 25 ml of DMF prior to the addition of 8.6 g of potassium hydroxide powder, and the mixture is stirred for 10 min. To the resulting mixture are added, with stirring for 0.5 h, 3.6 ml (0.06 mole) of MeI, and the stirring is continued for 0.5 h more. The mixture is left for 24 h at 18-20°C. To the reaction mixture are added 50 ml of water, and the liquid fractions are distilled off *in vacuo*. The residue is primed with 50 ml of water, and the mixture is left for 12 h at 4°C. The methyl ester (III), which separated out into crystals, is filtered off and washed with water. The yield is 2.92 g (56%). The mp is 105-106°C (toluene). The PMR spectrum (acetone-D_6) is as follows: 2.70 ppm (2H, t, CH_2CO), 3.32 ppm (3H, s, $N-CH_3$), 3.61 ppm (3H, s, $COCH_3$), 4.42 ppm (2H, t, $N-CH_2$), and 7.0-8.4 ppm (4H, m, H arom.). Found, %: C 59.85, H 5.21, and N 10.53. $C_{13}H_{14}N_2O_4$. Calculated, %: C 59.54, H 5.39, and N 10.66.

Hydrazide of 3-[2,4-Dioxo-(1H,3H)-quinazolin-1-yl]propanoic Acid (IV). To the boiling solution of 2.48 g (0.01 mole) of the methyl ester (II) in 50 ml of 2-propanol are added 3 ml of 99% hydrazine hydrate, and the mixture is boiled for 3 min more and left for 1 h at 20°C. The crystals of the hydrazide (IV), which separated out, are filtered off and washed with 2-propanol. The yield is 2.15 g (87%). The mp is 252°C (with decomp., 80% ethanol). The PMR spectrum (CF_3COOH) is as follows: 2.74 ppm (2H, t, CH_2CO), 4.35 ppm (2H, t, $N-CH_2$), and 6.9-8.1 ppm (4H, m, H arom.). Found, %: C 53.04, H 4.93, and N 22.68. $C_{11}H_{12}N_4O_3$. Calculated, %: C 53.23, H 4.87, and N 22.57.

Hydrazide of 3-[3-Methyl-2,4-dioxo-(1H,3H)-quinazolin-1-yl]propanoic Acid (V). This compound was obtained from 2.62 g (0.01 mole) of the methyl ester (III) and 3 ml of 99% hydrazine hydrate by analogy with (IV). The yield is 2.2 g (80%). The mp is 204-206°C (water). The PMR spectrum (DMSO-D_6) is as follows: 2.37 ppm (2H, t, CH_2CO), 3.27 ppm (3H, s, CH_3), 4.26 ppm (2H, t, $N-CH_2$), 7.0-8.2 ppm (4H, m, H arom.), and 8.7-9.3 ppm (1H, broad s, NH). Found, %: C 54.55, H 5.16, and N 21.48. $C_{12}H_{14}N_4O_3$. Calculated, %: C 54.86, H 5.38, and N 21.36.

4-Methoxybenzylidenehydrazide of 3-[2,4-Dioxo-(1H,3H)-quinazolin-1-yl]propanoic Acid (VI). The mixture of 1.24 g (0.005 mole) of the hydrazide (IV), 1.36 g (0.01 mole) of 4-methoxybenzaldehyde, and 50 ml of dioxane is boiled for 3 h. Crystals of (VI), which separated out on cooling, are filtered off and washed with dioxane and ether. The yield is 1.28 g (70%). The mp is 231-233°C (dioxane). The PMR spectrum (CF_3COOH) is as follows: 2.85 ppm (2H, t, CH_2CO), 3.78 ppm (3H, s, CH_3), 4.50 ppm (2H, t, $N-CH_2$), 7.0-8.1 ppm (8H, m, H arom.), and 8.32 ppm (1H, s, CH). Found, %: C 62.57, H 4.53, and N 15.03. $C_{19}H_{18}N_4O_4$. Calculated, %: C 62.29, H 4.95, and N 15.29.

1-(2-Carboxyethyl)-3-methyl-(1H,3H)-quinazoline-2,4-dione (VII). The methyl ester (III) (1.31 g, 0.05 mole), 1 g of sodium hydroxide, and 10 ml of water are boiled for 1 h. The mixture is cooled and filtered off, and the filtrate is neutralized with acetic acid. The mixture is left to stand at 4°C. The crystals of (VII), which separated out, are filtered off and washed with water and ethanol. The yield is 0.35 g (28%). The mp is 159-160°C (toluene). The PMR spectrum (CF_3COOH) is as follows: 2.6-3.0 ppm (2H, t, CH_2CO), 2.77 ppm (3H, s, CH_3), 3.55 ppm (2H, t, $N-CH_2$), and 7.1-8.0 ppm (4H, m, H arom.). Found, %: C 57.88, H 4.59, and N 11.43. $C_{12}H_{12}N_2O_4$. Calculated, %: C 58.07, H 4.87, and N 11.29.

1,3,7-Trioxopyrido[1,2,3-k,j]quinazoline (VIII). The mixture of 50 g of P_2O_5 and 20 g of H_3PO_4 is heated for 30 min at 140°C prior to the addition of 4.68 g (0.02 mole) of the quinazolinedione (I). The mixture is heated for 4 h more at the same temperature. The mixture is cooled to 100°C, and 200 ml of water are added carefully. The crystals of (VIII), which separated out, are filtered off and washed with water. The yield is 3.55 g (82%). The mp is 348-350°C (DMSO). The PMR spectrum (CF_3COOH) is as follows: 2.59 ppm (2H, t, CH_2CO), 4.11 ppm (2H, t, $N-CH_2$), and 7.2 and 8.08 ppm (3H, dd, H arom.). The mass spectrum is characterized by the m/z 216 [M^+]. Found, %: C 61.50, H 3.58, and N 12.89. $C_{11}H_8N_2O_3$. Calculated, %: C 61.12, H 3.73, and N 12.96.

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