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NEW SYNTHESIS OF THE DIHYDROINDOLIZINO-QUINOLINE SYSTEM BY INTRAMOLECULAR CYCLIZATION OF SULFUR YLIDE

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An efficient method is proposed for obtaining the dihydroindolizinoquinoline system by intramolecular cyclization of keto-stabilized sulfonium ylide obtained from β-alanine and quinoline-2,3-dicarboxylic acid anhydride.

Keywords: keto-stabilized sulfur ylide, 6-methylthio-8,9-dihydroindolizino[1,2-*b*]quinoline-7,11-dione, intramolecular cyclization.

The indolizinoquinoline system is a structural fragment of certain natural compounds, such as alkaloid camptothecin and its closest analogs, which possess anticancer activity [1-3]. Previously we discovered a new intramolecular cyclization of sulfur ylides [4-6], synthesized from substituted α- and β-amino acids [7], which opened a convenient route for constructing nitrogen-containing condensed heterocyclic systems. In the present work a method is proposed for the synthesis of 6-methylthio-8,9-dihydroindolizino[1,2-*b*]quinoline-7,11-dione (**1**) by the cyclization of sulfur ylide **2** containing quinoline-2,3-dicarboximide fragment.

Sulfonium ylide **2** was obtained by the procedure of [7] from quinoline-2,3-dicarboxylic acid anhydride (**3**) [8] and β-alanine. N-Substituted β-alanine **4** was converted into diazo ketone **5**. The yield of diazo ketone **5** synthesized by interacting CH_2N_2 with acid **4** chloride [7] was 50%. On using the mixed anhydride formed by interacting acid **4** with methyl chloroformate the yield of diazo ketone **5** became practically quantitative and the obtained diazo ketone did not require additional purification. On sequential treatment of diazo ketone with 48% HBr solution and Me_2S sulfonium salt **6** is formed, the deprotonation of which with a mixture of saturated K_2CO_3 solution and 12.5 N NaOH gives ylide **2** in 91% yield. Heating ylide **2** in the presence of equimolar quantity of benzoic acid in toluene solution leads to 6-methylthio-8,9-dihydroindolizino[1,2-*b*]quinoline-7,11-dione (**1**) in 90% yield (Scheme 1).

We investigated the possibility of obtaining compound **1** by the one-pot method directly from diazo ketone **5**. Ylide **2** is formed on catalytic decomposition of diazo ketone **5** with rhodium acetate in the presence of Me_2S at 40°C. The ylide, without isolation from the reaction mixture, becomes involved in an intramolecular cyclization giving product **1** in 60% yield.

The intramolecular cyclization of sulfonium ylide **2** proceeds regioselectively with the formation of one isomer of **1**. The nucleophilic character of sulfur ylide enables the suggestion that the cyclization comprises interaction of the carbanionic center with the electron-deficient carboximide carbon atom located in the position β to the nitrogen atom of the pyridine ring. In the ^{13}C NMR spectrum of compound **1** taken in modulation mode at the CH constant the signals from the $C_{(8)}$ and $C_{(9)}$ atoms are defined unequivocally, being displayed as two triplets at 36.90 and 35.95 ppm respectively, and the singlets of the carbonyl carbon atoms were at 190.78 and

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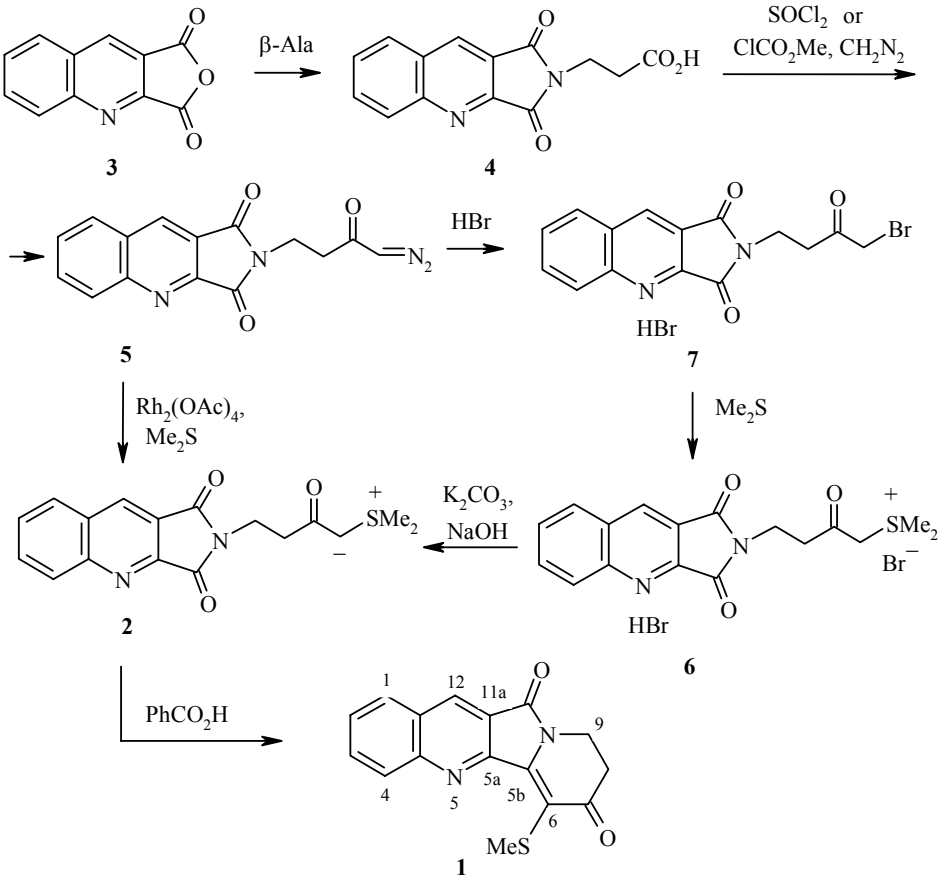
Scheme 1



162.92 ppm. The signals of the $C_{(5a)}$ and $C_{(6)}$ atoms were displayed as singlets at 146.18 and 116.02 ppm. Comparison of the chemical shifts obtained for compound **1** with calculated values and with the chemical shifts of the carbon atoms of dihydrodiazafluorenedione derivative studied by us previously [9], the structure of which is identical to the main fragment of the compound **1** molecule, confirmed the above hypothesis on the structure of the cyclization product obtained.

The structures of all the obtained compounds were confirmed by IR and NMR spectroscopic methods, and by data of elemental analysis.

We have therefore proposed a simple and efficient method of obtaining the dihydroindolizinoquinoline structure, which opens a new route to the synthesis of biologically active compounds.

EXPERIMENTAL

The IR spectra were obtained on UR 20 and Specord M 80 instruments (in thin films or in nujol). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer (300 and 75 MHz respectively), internal standard was TMS. The progress of reactions was followed by TLC on Silufol UV 254 plates with detection of substances in UV light or after spraying plates with a solution of ninhydrin developer and then heating at 100-120°C. Reaction products were isolated by column chromatography on silica gel. Solvents were purified by distillation. Toluene and dioxane were boiled and distilled over sodium.

3-(1,3-Dioxo-1,3-dihydro-2H-pyrrolo[3,4-*b*]quinolin-2-yl)propionic Acid (4). Mixture of anhydride **3** [8] (1 g, 5 mmol) and β-alanine (0.44 g, 5 mmol) in dry dioxane (20 ml) was boiled with stirring in the presence of molecular sieves 4A, checking the progress of the reaction by TLC. At the end of the reaction the solution was filtered hot and cooled to room temperature. The precipitated crystals were filtered off. Yield 0.81 g (65%); mp 208-210°C, R_f 0.5 (EtOH–H_2O, 7:3). IR spectrum (nujol), ν, cm^{-1}: 1685 CON), 1740 (CO), 3300 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.7 (2H, t, *J* = 7.4, CH_2N); 3.9 (2H, t, *J* = 7.3, CH_2CO); 7.6-8.9 (5H, m, C_9H_5N). ^{13}C NMR spectrum, δ, ppm: 31.11, 34.82, 123.0, 127.29, 128.36, 129.0, 130.34, 132.49, 132.71, 149.53, 150.80, 165.57, 165.9, 172.02. Found, %: C 61.95; H 3.45; N 10.25. $C_{14}H_{10}N_2O_4$. Calculated, %: C 62.22; H 3.73; N 10.37.

2-(4-Diazo-3-oxobutyl)pyrrolo[3,4-*b*]quinoline-1,3(2H)-dione (5). Methyl chloroformate (0.085 ml, 1.1 mmol) was added dropwise with stirring to suspension of acid **4** (0.27 g, 1 mmol) in CH_2Cl_2 (60 ml), and the mixture stirred for 2 h. Then NEt_3 (0.14 ml, 1.1 mmol) was added in two portions with an interval of 1 h. After adding the second portion the resulting mixture was stirred for 1 h further. An ether solution of diazomethane, obtained from nitrosomethylurea (0.2 g, 2 mmol), was then added dropwise to the stirred solution at 0°C, and the mixture kept at this temperature for a further 12 h. The solvent was evaporated. The residue was chromatographed through a thin layer of SiO_2 (chloroform–acetone, 15:1). Yield 0.29 g (99%); mp 148°C (decomp.), R_f 0.47 (chloroform–acetone, 15:1). IR spectrum (nujol), ν, cm^{-1}: 1700 (CON), 1750 (CO), 2130 (C=N_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.8 (2H, t, *J* = 7.7, CH_2N); 3.4 (1H, s, CH=N_2); 3.9 (2H, t, *J* = 7.4, CH_2CO); 7.5-8.9 (5H, m, C_9H_5N). ^{13}C NMR spectrum, δ, ppm: 32.24, 34.08, 62.79. 123.04, 128.46, 129.42, 129.77, 130.42, 132.64, 132.88, 149.67, 150.74, 165.68, 165.79, 182.11. Found, %: C 60.85; H 3.35; N 18.25. $C_{15}H_{10}N_4O_3$. Calculated, %: C 61.22; H 3.43; N 19.04.

2-(4-Bromo-3-oxobutyl)pyrrolo[3,4-*b*]quinoline-1,3(2H)-dione Hydrobromide (7). 48% HBr solution (0.51 ml) was added dropwise to stirred solution of diazo ketone **5** (0.45 g, 1.53 mmol) in CH_2Cl_2 (100 ml). The solution was stirred for 1 h, dried over $MgSO_4$, and the solvent evaporated. Yield 0.46 g (71%); mp 181-182°C. IR spectrum (nujol), ν, cm^{-1}: 1710 (CON), 1730 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.6 (2H, m, CH_2N); 3.9 (2H, m, CH_2CO); 4.1 (2H, s, CH_2Br); 7.7-9.0 (5H, m, C_9H_5N). ^{13}C NMR spectrum, δ, ppm: 32.11, 33.74, 60.13, 122.87, 128.3, 129.25, 130.3, 132.46, 132.52, 132.95, 149.53, 150.57, 165.5, 165.71, 197.9. Found, %: C 41.83; H 2.45; Br 36.85; N 6.18. $C_{15}H_{12}Br_2N_2O_3$. Calculated, %: C 42.09; H 2.83; Br 37.33; N 6.54.

{4-(1,3-Dioxo-1,3-dihydro-2H-pyrrolo[3,4-*b*]quinolin-2-yl)-2-oxobutyl}dimethylsulfonium Bromide Hydrobromide (6). Dimethyl sulfide (0.186 g, 3 mmol) was added with stirring to solution of bromo ketone **7** (0.42 g, 0.9 mmol) in CH_2Cl_2 (40 ml). The solution was kept for 12 h. The precipitated crystals were filtered off. Yield 0.29 g (66%); mp 146-148°C. IR spectrum (nujol), ν, cm^{-1}: 1700, 1720 (CON), 1790 (CO). ^{1}H NMR spectrum (CF_3COOH), δ, ppm: 2.8 [6H, s, $S(CH_3)_2$]; 3.2 (2H, s, CH_2N); 4.1 (2H, s, CH_2CO); 4.6 (2H, s, CH_2S); 7.9-9.4 (5H, m, C_9H_5N). ^{13}C NMR spectrum, δ, ppm: 25.28, 34.02, 39.21, 54.61, 122.85, 123.88, 131.85, 132.29, 133.27, 139.64, 140.03, 144.47, 144.81, 160.79, 163.81, 198.75.

Dimethylsulfonio{4-(1,3-dioxo-1,3-dihydro-2H-pyrrolo[3,4-*b*]quinolin-2-yl)-2-oxobutyl}ylide (2). Mixture of 12.5 N NaOH (0.125 ml) and saturated K_2CO_3 solution (0.71 ml) was added in one portion to stirred suspension of sulfonium salt **6** (0.243 g, 0.5 mmol) in $CHCl_3$ (10 ml) at 10°C. The reaction mixture was then stirred at this temperature for a further 20 min. The organic layer was separated, dried over K_2CO_3, and the solvent evaporated. Yield 0.15 g (91%). IR spectrum (nujol), ν, cm^{-1}: 1710, 1720 (CON), 1555 (CO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.5 (2H, t, *J* = 6.93, CH_2N); 2.8 [6H, s, $S(CH_3)_2$]; 3.6-3.8 (1H, br s, CH); 4.1 (2H, t, *J* = 6.87, CH_2CO); 7.7-8.6 (5H, m, C_9H_5N). ^{13}C NMR spectrum, δ, ppm: 28.28, 36.79, 39.07, 51.91, 123.11, 128.78, 129.4, 129.94, 131.38, 132.44, 132.61, 150.7, 150.76, 165.86, 166.17, 186.86. Found, %: C 61.91; H 4.55; N 8.78; S 9.85. $C_{17}H_{16}N_2O_3S$. Calculated, %: C 62.18; H 4.91; N 8.53; S 9.76.

6-(Methylthio)-8,9-dihydroindolizino[1,2-*b*]quinoline-7,11-dione (1). Ylide **2** (0.1 g, 0.304 mmol) was dissolved in hot toluene (30 ml). Benzoic acid (0.037 g, 0.304 mmol) was then added to the hot solution and the mixture was boiled under reflux for 1 h. The progress of the reaction was checked by TLC (chloroform–acetone, 9:1). At the end of the reaction the solvent was evaporated. The product was isolated by column chromatography (chloroform–acetone, 9:1). Yield 0.08 g (90%); mp 175-177°C. IR spectrum (nujol), ν, cm^{-1}: 1710 (CON), 1725 (CO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.6 (3H, s, SCH_3); 2.9 (2H, t, *J* = 7.35, CH_2N); 4.3 (2H, t, *J* = 8.07, CH_2CO); 7.7-8.7 (5H, m, C_9H_5N). ^{13}C NMR spectrum, δ, ppm: 18.42, 35.95, 36.9, 116.02, 121.5, 127.12, 128.72, 129.55, 131.0, 132.08, 132.66, 146.18, 150.4, 152.45, 162.92, 190.78. Found, %: C 64.61; H 3.85; N 9.18; S 10.55. $C_{16}H_{12}N_2O_2S$. Calculated, %: C 64.85; H 4.08; N 9.45; S 10.82.

Preparation of Compound 1 from Diazo Ketone 5 without Isolating Ylide 2. Solution of diazo ketone **5** (0.05 g, 0.165 mmol) in CH_2Cl_2 (6 ml) was added dropwise to solution of $Rh_2(OAc)_4$ (0.07 g, 0.016 mmol) and Me_2S (0.5 g, 15.6 mmol) in toluene (20 ml) with stirring at 40°C. The mixture was stirred at 40°C for 1 h. The progress of the reaction was checked by TLC (chloroform–acetone, 9:1) for the disappearance of the diazo ketone spot. After this, benzoic acid (0.02 g, 0.165 mmol) was added, and the mixture was boiled under reflux for 1 h. The solvent was evaporated. The residue was chromatographed through a thin layer of SiO_2 (chloroform–acetone, 9:1). Yield 0.029 g, (60%).

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