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A NEW REGIOSELECTIVE SYNTHESIS OF 2-METHOXYMETHYL-3-OXO-2,3-DIHYDRO-7H-THIAZOLO[3,2-*a*]PYRIDINE-8-CARBOXYLIC ACID METHYLAMIDE

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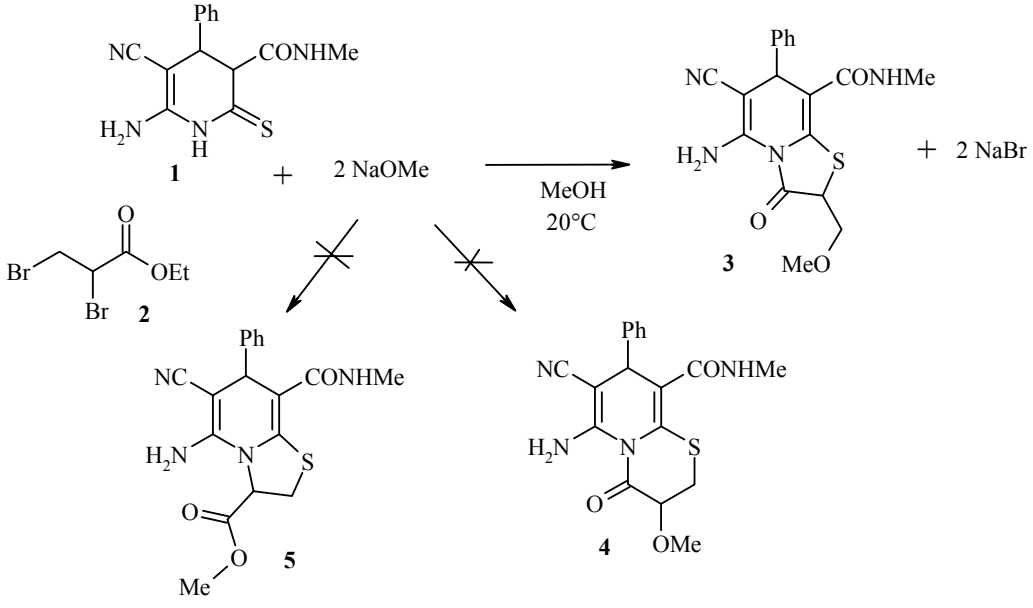
Keywords: 2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine, methylamide of 2-thioxo-1,2,3,4-tetrahydro-3-pyridinecarboxylic acid, ethyl ester of 2,3-dibromopropionic acid.

3-Oxo-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridines have been obtained by the dehydration of 6-carbamoylmethylsulfanyl-1,4-dihydropyridines [1] or the multicomponent reaction of benzylidenemalononitrile, 2-thiocarbamoylacetamide, pyridine, and a halomethyl ketone [2]. In a continuation of our study of the reaction of 1,4-dihydro-2-pyridinethiolates with electrophilic reagents [3], we carried out the reaction of the methylamide of 2-thioxo-1,2,3,4-tetrahydro-3-pyridinecarboxylic acid **1** [4], which has several nucleophilic sites (1-N, S, 3-C, 6-NH_2, and NHMe), with the ethyl ester of 2,3-dibromopropionic acid **2**, which, in turn, has three electrophilic sites (C=O, 2-C, and 3-C).



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The alkylation of thione **1** by the ethyl 2,3-dibromopropionate **2** in the presence of an equimolar amount of sodium methylate or piperidine at room temperature gives a complex mixture of products but the action of two equivalents of sodium methylate on a mixture of **1** and **2** gives the methylamide of 5-amino-6-cyano-2-methoxymethyl-3-oxo-7-phenyl-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-8-carboxylic acid (**3**) in 73% yield. The alkylation of thione **1** by ester **2** apparently initially gives the ethyl ester of 3-bromo-2-(3,4-dihydropyridyl-2-sulfanyl)propionic acid (the alkylation of thione **1** with the ethyl bromoacetate gives the ethyl ester of 2-(3,4-dihydropyridyl-2-sulfanyl)acetic acid [2]), which cyclizes losing ethanol and then reacts with a second molecule of sodium methylate to give 2-methoxymethyl-3-oxo-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine **3**.

The structure of pyridine **3** was solved spectroscopically and supported by elemental analysis. The carbonyl group stretching bands at 1667 and 1718 cm^{-1} and cyano group stretching band at 2178 cm^{-1} are the most characteristic IR bands. The ^1H NMR spectra show signals for H-7 at 4.59 and 4.62 ppm and for the OCH_3 group at 3.28 and 3.32 ppm as two singlets, indicating the formation of methylamide **3** as two diastereomers. The signals for the $CHCH_2O$ system protons form two ABX multiplets at 4.33-4.39 (CH protons) and 3.63-3.88 ppm (OCH_2 protons). The ^{13}C NMR chemical shifts at 72.1 and 72.0 ppm, characteristic for the OCH_2 fragment but not for the SCH_2 fragment support the structure of 2-methoxymethyl-3-oxo-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-8-carboxylic acid **3** and exclude alternative structures, namely, 3-methoxy-4-oxo-3,4-dihydro-2H,8H-pyrido[2,1-*b*][1,3]thiazine-9-carboxylic acid **4**, whose formation is possible in the case of alternative alkylation, and the methyl ester of 2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-3-carboxylic acid **5**, whose formation is possible in the case of cyclocondensation with the loss of hydrogen bromide and transformation of the ethyl ester into a methyl ester. The skeleton of the structure of methylamide **3** and the assignment of the ^1H and ^{13}C NMR signals were also indicated by the NOESY, TOCSY, HSQC, and HMBC 2D spectra. The mass spectrum of compound **3** shows a molecular ion peak at *m/z* 370.

The ^1H and ^{13}C NMR spectra were obtained on a Varian Inova were taken at 600 and 150 MHz, respectively, in DMSO-d_6 with TMS as the internal standard. The two-dimensional ^1H-^1H TOCSY, ^1H-^1H NOESY spectra as well as the ^{13}C-^1H HMBC and ^{13}C-^1H HSQC spectra were taken at 25°C using the pulse gradient technique. The mixing time was 1 sec in the 2D-NOESY spectrum but 70 msec in the TOCSY spectrum. The ^{13}C-HMBC spectra were taken with 62.5 msec evolution period for generation of long-range correlations. A 4098×1024 data matrix was used to record all the 2D spectra, which provides for τ_{2max} = 250 msec for ^1H in recording along the F2 axis and τ_{1max} = 100 msec for ^1H or τ_{1max} = 50 msec for ^{13}C in recording along the F1 axis. Prior to the Fourier transformation, the data matrix was supplemented twice with zeros and multiplied by the cosine function in order to improve the signal-to-noise ratio. The chemical shifts of the hydrogen and carbon atoms are given relative to the residual signals of the solvent: 2.5 and 39.5 ppm, respectively, in DMSO. The IR spectra were taken on a Specord IR-75 spectrometer for vaseline mulls, while the mass spectra were taken on an AEI MS-905 spectrometer at 70 eV.

Methylamide of 5-Amino-6-cyano-2-methoxymethyl-3-oxo-7-phenyl-2,3-dihydro-7H-thiazolo-[3,2-*a*]pyridine-8-carboxylic Acid (3) was obtained in 73% yield; mp 220-222°C (ethanol). IR spectrum, ν, cm^{-1}: 1667, 1718 (C=O), 2178 (C≡N), 3316, 3390, 3425 (NH, NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.47 and 2.50 (3H, two d, *J* = 4.4, $NHC\underline{H}_3$); 3.28 and 3.32 (3H, two s, OCH_3); 3.63-3.88 (2H, m, OCH_2); 4.33-4.39 (1H, m, 2-CH); 4.59 and 4.62 (1H, two s, H-7); 7.19-7.51 (7H, m, 7-C_6H_5 and NH_2); 7.51 and 7.50 (1H, two q, *J* = 4.4, $N\underline{H}CH_3$). ^{13}C NMR spectrum, δ, ppm: 26.0 and 26.1 (NMe); 38.7 and 38.8 (C-7); 46.7 and 47.0 (C-2); 58.7 and 58.9 (OMe); 65.8 and 65.9 (C-6); 72.0 and 72.2 (OCH_2); 105.0 and 105.2 (C-8); 119.4 and 119.5 (C≡N); 126.9 and 127.0 (C_o-Ph); 127.1 and 127.2 (C_p-Ph); 128.5 and 128.6 (C_m-Ph); 141.2 and 141.8 (C_i-Ph); 144.0 and 144.1 (C-5); 147.9 and 148.1 (C-8a); 165.3 and 165.4 (8-C=O); 174.2 and 174.4 (3-C=O). Mass spectrum, *m/z* (I_{rel}, %): 370 (24), 338 (63), 310 (26), 309 (31), 284 (62), 261 (78), 253 (64), 207 (49), 69 (20), 43 (20). Found, %: C 58.16; H 4.97; N 14.93; S 8.60. $C_{18}H_{18}N_4O_3S$. Calculated, %: C 58.36; H 4.90; N 15.12; S 8.65.

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