SYNTHESIS AND ALKYLATION OF 6-METHYL-5-PHENYLCARBAMOYL-3-CYANO-4-ETHYL-PYRIDINE-2(1H)THIONE

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By condensation of the anilide of acetoacetic acid, propionaldehyde, and cyanothioacetamide, 6-methyl-5-phenylcarbamoyl-3-cyano-4-ethylpyridine-2(1H)thione has been obtained. In an alkaline medium, this compound is alkylated, forming the corresponding substituted 2-pyridyl sulfides. From these pyridines, substituted thieno[2,3-b]pyridines have been synthesized through the Thorpe–Ziegler reaction.

Substituted cyanopyridine-2(1H)chalcogenones and their derivatives containing an amide grouping are known as active mono- and diazo dyes [1], pharmaceutical preparations used in the treatment of cardiac insufficiency [2], substances with hepatoprotector activity [3], and intermediates in the synthesis of other biologically active compounds [4, 5].

With the aim of searching for substances with properties that will be useful in practice, we have developed a method for synthesizing previously unknown 6-methyl-5-phenylcarbamoyl-3-cyano-4-ethylpyridine-2(1H)thione. Upon mixing equimolar quantities of propionaldehyde I with CH acids II and III in ethanol at 20°C in the presence of excess base, they undergo Knoevenagel condensation, forming only the intermediate IV as the result of reaction of compounds I and II, or forming the intermediate V as a result of reaction of I and III. Subsequent interaction of IV with III, or V with II, affords exactly the same adduct VI, which undergoes cyclocondensation to form a salt VII that is unstable under the conditions of reaction; upon dilution of the reaction mixture with 10% hydrochloric acid, this salt readily splits out water to form a stable thione VIII.

The structure of compound VIII was confirmed by spectroscopic studies and by chemical conversions. Thus, upon interaction of the substituted pyridine-2(1H)thione (VIII) with halides IX in an alkaline medium, sulfides X are formed, which are cyclized through the Thorpe–Ziegler reaction to thieno[2,3-b]pyridines XI. The IR spectra of compounds VIII and X contain characteristic absorption bands of stretching vibrations of the conjugated cyano group at 2220 cm⁻¹, which disappear upon changing to the structures XI; also, absorption bands of C=O groups are observed at 1680-1710 cm⁻¹. In the PMR spectra of the synthesized compounds VIII, X, and XI, characteristic signals are observed from ethyl-group protons in the form of a triplet in the 1.20-1.31 ppm region and a quadruplet at 2.71-3.09 ppm, a singlet of 6-Me at 2.19-2.64 ppm, a singlet of the NH proton of the amide group at 10.59-10.68 ppm, protons of the phenyl substituent in the 7.13-7.64 ppm region, and also a signal of SCH₂ group protons for compounds X. In the PMR spectra of the thienopyridines XI, signals appear from protons of the amino group in the form of a broadened singlet in the 8.25-8.29 ppm region, but no signals of SCH₂ group protons are observed, thus confirming the direction of the reaction.
EXPERIMENTAL

IR spectra were taken in an IKS-29 spectrophotometer in white mineral oil. PMR spectra were recorded in a Bruker WP-100 SY instrument (100 MHz) in DMSO-d$_6$ (internal standard TMS). The course of the reaction and the individuality of the substances were monitored by means of TLC on Silufol UV-254 plates (eluents acetone–heptane, 3:5).

6-Methyl-5-phenylcarbamoyl-3-cyano-4-ethylpyridine-2(1H)thione (VIII). A mixture of 0.72 ml (10 mmoles) of the aldehyde I, 1.17 g (10 mmoles) of the anilide II, 1 g (10 mmoles) of cyanothioacetamide III, and 1.5 ml (15 mmoles) of N-methylmorpholine in 15 ml of absolute ethanol at 20°C was stirred for 4 h, after which it was allowed to stand for 24 h. The resulting precipitate was filtered off and washed with 10 ml of ethanol, obtaining 2.17 g (73%) of the thione VIII, mp 242-244°C (AcOH). IR spectrum, cm$^{-1}$: 3150-3225 (NH), 2220 (CN), 1710 (C=O). PMR spectrum (DMSO-d$_6$), ppm: 10.59 (1H, s, NH), 7.13-7.64 (5H, m, Ph), 2.67 (2H, q, CH$_2$), 2.39 (3H, s, CH$_3$), 1.20 (3H, t, CH$_3$). Found, %: C 64.55, H 5.03, N 14.21, S 10.69. C$_{16}$H$_{15}$N$_3$OS. Calculated, %: C 64.62, H 5.08, N 14.13, S 10.78.

6-Methyl-2-(2-thenoylmethylthio)-5-phenylcarbamoyl-3-cyano-4-ethylpyridine (Xa). To a suspension of 3 g (10 mmoles) of the thione VIII in 10 ml of DMF, 5.6 ml (10 mmoles) of a 10% aqueous KOH solution was added while stirring; then, after 1 min, 2.05 g (10 mmoles) of compound IXa was added. The mixture was stirred for 4 h and then diluted with 10 ml of water. The precipitate was filtered off and then washed with water and ethanol, obtaining 2.95 g (70%) of compound Xa, mp 186-188°C (AcOH). IR spectrum, cm$^{-1}$: 3270 (NH), 2220 (CN), 1710 (C=O). PMR spectrum (DMSO-d$_6$), ppm: 10.60 (1H, s, NH), 7.10-8.23 (8H, m, Ph and Het), 4.84 (2H, s, SCH$_2$), 2.71 (2H, q, CH$_2$), 2.19 (3H, s, CH$_3$), 1.20 (3H, t, CH$_3$). Found, %: C 62.61, H 4.45, N 9.91, S 15.15. C$_{22}$H$_{19}$N$_3$O$_2$S$_2$. Calculated, %: C 62.68, H 4.54, N 9.97, S 15.21.

6-Methyl-5-phenylcarbamoyl-2-(4-chlorobenzoylmethylthio)-3-cyano-4-ethylpyridine (Xb) was obtained by a procedure analogous to that used for Xa, in this case with 2.34 g (10 mmoles) of compound IXb. Yield 3.78 g (84%), mp 183-185°C (AcOH). IR spectrum, cm$^{-1}$: 3250 (NH), 2220 (CN), 1680 (C=O). PMR spectrum (DMSO-d$_6$), ppm: 10.59 (1H, s, NH), 7.11-8.12 (9H, m, Ph and Ar), 4.87 (2H, s, SCHR), 2.71 (2H, q, CH$_2$), 2.14 (3H, s, CH$_3$), 1.21 (3H, t, CH$_3$). Found, %: C 63.98, H 4.42, N 9.29, S 7.08. C$_{24}$H$_{20}$ClN$_3$O$_2$S. Calculated, %: C 64.04, H 4.48, N 9.34, S 7.13.

6-Methyl-2-methylthio-5-phenylcarbamoyl-3-cyano-4-ethylpyridine (Xc) was obtained analogously, using 0.62 ml (10 mmoles) of methyl iodide IXc. Yield 2.7 g (87%), mp 152-154°C (AcOH). IR spectrum, cm$^{-1}$: 3180-3285 (NH), 2220 (CN), 1648 (C=O). PMR spectrum (DMSO-d$_6$), ppm: 10.64 (1H, s, NH), 7.15-6.80 (5H, m, Ph), 2.70 (2H, q, CH$_2$), 2.64...