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

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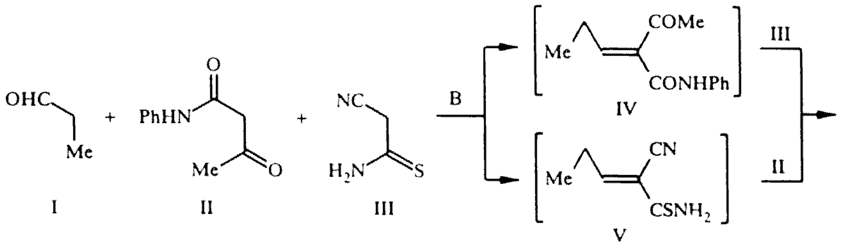
By condensation of the anilide of acetoacetic acid, propionaldehyde, and cyanothioacetamide, 6-methyl-5-phenylcarbamoyl-3-cyano-4-ethylpyridine-2(1H)thione has been obtained. In an alkaline medium, this compound is alkylated, forming the corresponding substituted 2-pyridyl sulfides. From these pyridines, 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)thiones. 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 SCH_2 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 SCH_2 group protons are observed, thus confirming the direction of the reaction.



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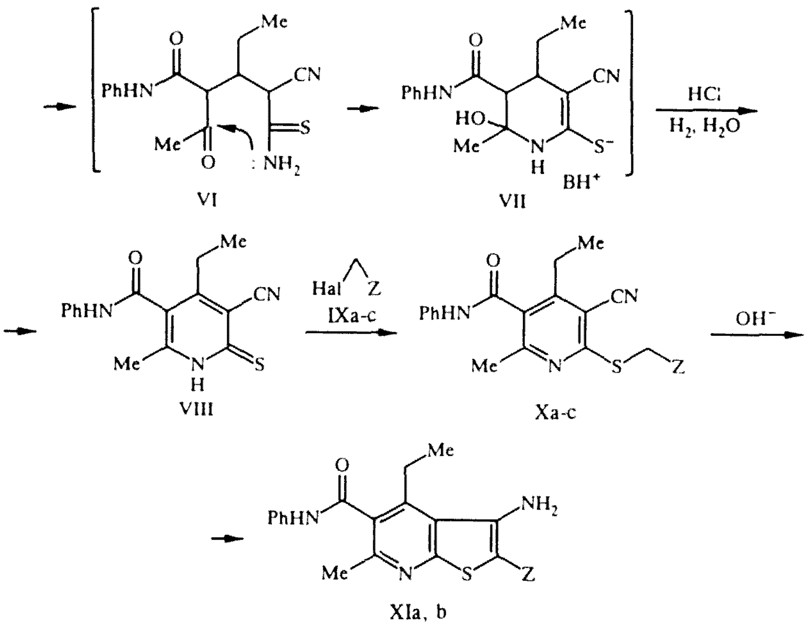

B = N-methylmorpholine. In compounds IX-XI: *a*) Hal = Br; Z = C_4H_3SCO; *b*) Hal = Br; Z = 4-ClC_6H_4CO; *c*) Hal = I, Z = H.

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 (eluent 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. $C_{16}H_{15}N_3OS$. 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), 1700 (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. $C_{22}H_{19}N_3O_2S_2$. 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, SCH_2), 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. $C_{24}H_{20}ClN_3O_2S$. 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

(3H, s, SCH_3), 2.55 (3H, s, CH_3), 1.22 (3H, s, CH_3). Found, %: C 65.51, H 5.44, N 13.42, S 10.26. $C_{17}H_{17}N_3OS$. Calculated, %: C 65.57, H 5.50, N 13.49, S 10.30.

3-Amino-6-methyl-2-(2-thenoyl)-5-phenylcarbamoyl-4-ethylthieno[2,3-b]pyridine (XIa). To a solution of 2.1 g (5 mmoles) of compound Xa in 8 ml of DMF, 2.8 ml (5 mmoles) of a 10% aqueous solution of KOH was added while stirring; the stirring was continued for 6 h, the mixture was then diluted with 10 ml of water, and the resulting precipitate was filtered off and washed with water and ethanol, obtaining 1.55 g (69%) of compound XIa, mp 212-215°C (AcOH). IR spectrum, cm^{-1}: 3255-3320 (NH, NH_2), 1690 (C=O). PMR spectrum (DMSO-d_6): 10.66 (1H, s, NH), 8.29 (2H, s, b, NH_2), 7.10-7.99 (8H, m, Ph and Ar), 3.09 (2H, q, CH_2), 2.59 (3H, s, CH_3), 1.31 (3H, t, CH_3). Found, %: C 62.59, H 4.48, N 9.99, S 15.13. $C_{22}H_{19}N_3O_2S_2$. Calculated, %: C 62.68, H 4.54, N 9.97, S 15.21.

3-Amino-6-methyl-5-phenylcarbamoyl-2-(4-chlorobenzoyl)-4-ethylthieno[2,3-b]pyridine (XIb) was obtained by a procedure analogous to that described above for XIa, in this case using 1.13 g (5 mmoles) of compound Xb. Yield 1.64 g (73%), mp 207-210°C (AcOH). IR spectrum, cm^{-1}: 3240, 3460 (NH, NH_2), 1670 (δNH_2). PMR spectrum (DMSO-d_6), ppm: 10.64 (1H, s, NH), 8.25 (2H, s, b, NH_2), 7.12-7.80 (9H, m, Ph and Ar), 3.07 (2H, q, CH_2), 2.54 (3H, s, CH_3), 1.30 (3H, t, CH_3). Found, %: C 63.90, H 4.34, N 9.21, S 7.00. $C_{24}H_{20}ClN_3O_2S$. Calculated, %: C 64.06, H 4.48, N 9.34. S 7.13.

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REFERENCES

1. FRG Pat. Appl. 4,122,866.
2. U.S. Pat. 4,999,452.
3. A. A. Krauze, A. G. Odynets, A. A. Verreva, S. K. Germane, A. N. Kozhukhov, and G. Ya. Dubur, Khim.-Farm. Zh., **25**, No. 7, 40 (1991).
4. E. Ger. Pat. 269,849.
5. E. Ger. Pat. 250,122.