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NEW METHODS FOR THE SYNTHESIS OF ALKYL-SUBSTITUTED 6-OXO-3-CYANO-1,4,5,6-TETRAHYDROPYRIDINE-2-THIOLATES AND THEIR DERIVATIVES

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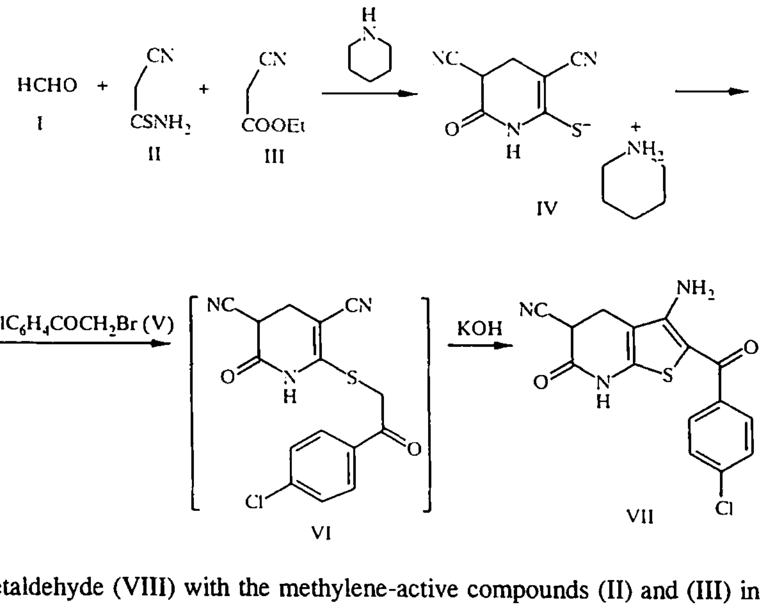
Condensation of formaldehyde or acetaldehyde with cyanothioacetamide and cyanoacetic ester in the presence of organic bases afforded 6-oxo-3,5-dicyano-4-R-1,4,5,6-tetrahydropyridine-2-thiolates (R = H, CH_3), which were utilized in the synthesis of substituted 2-alkylthiopyridones and thieno[2,3-b]pyridone.

We have proposed convenient methods for the synthesis of alkyl-substituted 6-oxo-3-cyano-1,4,5,6-tetrahydropyridine-2-thiolates consisting of the condensation of aliphatic aldehydes with cyanothioacetamide and Meldrum's acid [1] and the reaction of ethyl crotonates with cyanothioacetamide [2] in the presence of N-methylmorpholine. Taking into account the biological significance of cyanopyridones [3], new methods for synthesizing them were developed, and it was shown that the reaction of formaldehyde (I) with cyanothioacetamide (II) and cyanoacetic ester (III) in the presence of piperidine proceeds with the formation of the substituted tetrahydropyridinethiolate (IV). The last is converted by equimolar amounts of the bromide (V) and the 10% aqueous solution of KOH to compound (VI), which undergoes ready cyclization under the reaction conditions to give the substituted thienopyridone (VII).



Condensation of acetaldehyde (VIII) with the methylene-active compounds (II) and (III) in the presence of N-methylmorpholine gives the thiolate (IX) which, according to PMR spectral data, occurs as the 1:1 mixture of the cis and trans isomers A and B; this agrees with published data for its isostructural analogs [4].

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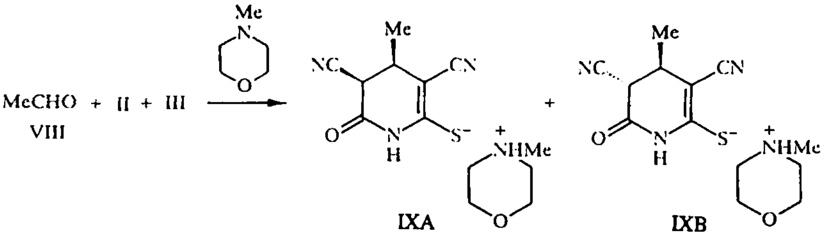
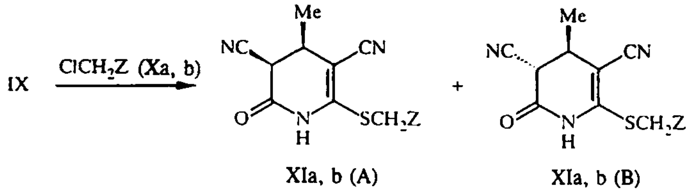


Thus, the signals of the protons of the methyl group connected with the $C_{(4)}$ atom of the tetrahydropyridine nucleus in the salt (IX) appear as two doublets of equal intensity at 1.05 and 1.17 ppm, and the signal of the $C_{(5)}H$ proton is registered as two doublets at 4.28 ppm (^3J = 1.5 Hz) and 3.90 ppm (^3J = 3 Hz). The higher spin–spin coupling constant probably thereby pertains to the cis isomer (IXA), and the lower spin–spin coupling constant pertains to the trans isomer (IXB) [5].

When the salt (IX) is alkylated by methyl monochloracetate (Xa) or 4-bromo-α-chloracetanilide (Xb), the ratio of the cis (XIA) and trans (XIB) stereoisomers in the reaction products is preserved. Thus, the PMR spectra of the sulfides (XIa,b) obtained contain equally intense signals of the protons of the $C_{(4)}CH_3$ group in the form of doublets at 1.30-1.32 and 1.15-1.16 ppm and the $C_{(5)}H$ proton in the form of doublets at 4.30-4.33 and 4.60-4.63 ppm with the SSCCs of 3 and 1.5 Hz correspondingly.

Therefore, the condensation of acetaldehyde with cyanothioacetamide and cyanoacetic ester in the presence of a base proceeds nonstereoselectively and leads to the formation of 4-methyl-6-oxo-3,5-dicyano-1,4,5,6-tetrahydropyridine-2-thiolate, which does not undergo cyclization under the reaction conditions to the corresponding thienopyridone.



X, XI a Z = COOMe, b Z = 4-BrC_6H_4NHCO

EXPERIMENTAL

The PMR spectra were taken on the Bruker WP-100 SY instrument (100 MHz) in DMSO-D_6 using TMS as the internal standard. The IR spectra were taken on the IKS-29 spectrophotometer in mineral oil. The monitoring of the course of reaction and the discreteness of the substances was accomplished by TLC on plates of Silufol UV-254 utilizing the 3:5 mixture of acetone–hexane as the eluent.

Piperidinium 6-Oxo-3,5-dicyano-1,4,5,6-tetrahydropyridine-2-thiolate (IV). To the stirred mixture of 1.38 ml (20 mmole) of the 40% solution of formaldehyde (I) in water, 2.00 g (20 mmole) of cyanothioacetamide (II), and 3 drops of piperidine in 25 ml of ethanol at 20°C are added 2.13 ml (20 mmole) of cyanacetic ester (III) and 2.47 ml (25 mmole) piperidine. After 1 h, the resulting white residue is filtered off and washed with acetone. The yield of 3.80 g (72%) of the salt (IV) is obtained; it has the mp 212-214°C. The IR spectrum is as follows: 3210 cm^{-1} (NH), 2200 cm^{-1}, 2264 cm^{-1} (CN), and 1700 cm^{-1} (C=O). The PMR spectrum is as follows: 1.58 ppm (6H, m, $3CH_2$), 2.52 ppm s and 2.60 ppm d (2H, $C_{(4)}H_2$), 3.00 ppm (4H, m, CH_2NCH_2), 4.10 ppm (1H, t, $C_{(5)}H$), and 9.23 ppm (1H, broad s, NH). Found, %: C 54.39, H 5.92, N 21.07, and S 12.03. $C_{12}H_{16}N_4OS$. Calculated, %: C 54.52, H 6.10, N 21.19, and S 12.13.

3-Amino-2-(4-chlorobenzoyl)-5-cyano-4,5,6,7-tetrahydrothieno[2,3-b]pyridin-6-one (VII). To the solution of 2.64 g (10 mmole) of the salt (IV) in 15 ml of DMF are added, with stirring, 2.34 g (10 mmole) of 4-chlorophenacyl bromide (V) and, after 5 min, 5.6 ml (10 mmole) of the 10% aqueous solution of KOH. The resulting residue is filtered off after 3 h and is washed with water, ethanol, and hexane. After recrystallization from glacial acetic acid, the yield of 1.89 g (57%) of compound (VII) is obtained; it has the mp 200°C (start of decomp.). The IR spectrum is as follows: 3300-3410 cm^{-1} (NH, NH_2), 2262 cm^{-1} (CN), and 1740 cm^{-1} (C=O). The PMR spectrum is as follows: 2.75-3.30 ppm (2H, m, $C_{(4)}CH_2$), 4.59 ppm (1H, q, $C_{(5)}H$), 7.61 ppm (6H, m, NH_2 and Ar), and 11.30 ppm (1H, broad s, NH). Found, %: C 54.16, H 2.91, Cl 10.59, N 12.54, and S 9.55. $C_{15}H_{10}ClN_3O_2S$. Calculated, %: C 54.30, H 3.04, Cl 10.69, N 12.66, and S 9.66.

N-Methylmorpholinium 4-Methyl-6-oxo-3,5-dicyano-1,4,5,6-tetrahydropyridine-2-thiolate (IX). Synthesis is performed by analogy with the salt (IV) utilizing correspondingly 1.12 ml (20 mmole) of acetaldehyde (VIII), 2.00 g (20 mmole) of cyanothioacetamide (II), 2.13 ml (20 mmole) of cyanacetic ester (III), and 2.75 g (25 mmole) of N-methylmorpholine. The yield of 4.71 g (80%) of the thiolate (IX) is obtained; it has the mp 147-148°C. The IR spectrum is as follows: 3150 cm^{-1} (NH), 2260 cm^{-1}, 2180 cm^{-1} (CN), and 1675 cm^{-1} (C=O). The PMR spectrum is as follows: 1.05 ppm d and 1.17 ppm d (3H, CH_3), 2.30 ppm (1H, m, $C_{(4)}H$), 2.75 ppm (3H, s, NCH_3), 3.11 ppm (4H, t, CH_2NCH_2), 3.77 ppm (4H, t, CH_2OCH_2), 3.90 ppm d (^{3}J = 3 Hz) and 4.28 ppm d (^{3}J = 1.5 Hz, 1H, $C_{(5)}H$), and 9.30 ppm (1H, broad s, NH). Found, %: C 52.92, H 6.07, N 18.80, and S 10.74. $C_{13}H_{18}N_4O_2S$. Calculated, %: C 53.04, H 6.16, N 19.03, and S 10.89.

4-Methyl-2-Z-methylthio-6-oxo-3,5-dicyano-1,4,5,6-tetrahydropyridines (XIa,b). The mixture of 2.94 g (10 mmole) of the salt (IX) and 0.88 ml (10 mmole) of methyl monochloracetate (Xa) or 2.49 g (10 mmole) of 4-bromo-α-chloracetanilide (Xb) in 30 ml of 80% ethanol is heated until the solution of the initial reagents is effected, and the mixture is filtered through a folded filter. The resulting residue is separated after 12 h, washed with ethanol and hexane, and recrystallized from the corresponding solvent.

Compound (XIa). The yield is 1.75 g (66%). The mp is 134-136°C (ethanol). The IR spectrum is as follows: 3330 cm^{-1} (NH), 2194 cm^{-1}, 2250 cm^{-1} (CN), 1695 cm^{-1}, and 1730 cm^{-1} (C=O). The PMR spectrum is as follows: 1.15 ppm d and 1.30 ppm d (3H, CH_3), 3.20 ppm (1H, m, $C_{(4)}H$), 3.67 ppm (3H, s, OCH_3), 3.97 ppm (2H, s, SCH_2), 4.30 ppm d (^{3}J = 3 Hz) and 4.60 ppm d (^{3}J = 1.5 Hz, 1H, $C_{(5)}H$), and 7.87 ppm (1H, broad s, NH). Found, %: C 49.64, H 4.11, N 15.71, and S 11.97. $C_{11}H_{11}N_3O_3S$. Calculated, %: C 49.80, H 4.18, N 15.84, and S 12.09.

Compound (XIb). The yield is 2.96 g (73%). The mp is 245-247°C (1-butanol). The IR spectrum is as follows: 3338 cm^{-1} (NH), 2202 cm^{-1}, 2253 cm^{-1} (CN), 1690 cm^{-1}, and 1755 cm^{-1} (C=O). The PMR spectrum is as follows: 1.16 ppm d and 1.32 ppm d (3H, CH_3), 3.22 ppm (1H, m, $C_{(4)}H$), 3.96 ppm (2H, s, SCH_2), 4.33 ppm d (^{3}J = 3 Hz) and 4.63 ppm d (^{3}J = 1.5 Hz, 1H, $C_{(5)}H$), 7.59 ppm (4H, s, Ar), 10.48 ppm (1H, broad s, NH), and 11.18 ppm (1H, broad s, CONH). Found, %: C 47.30, H 3.12, Br 19.59, N 13.68, and S 7.80. $C_{16}H_{13}BrN_4O_2S$. Calculated, %: C 47.42, H 3.23, Br 19.72, N 13.82, and S 7.91.

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