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SYNTHESIS OF 3-CYANO-5-ETHOXYCARBONYL-4-METHYL-6-PHENYLPYRIDINE-2(1H)-THIONE AND ITS ALKYLATION

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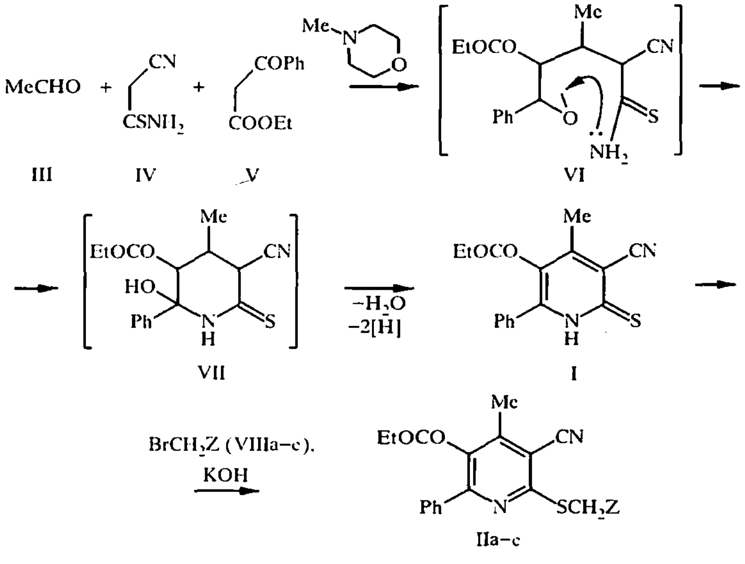
The condensation of acetaldehyde with cyanothioacetamide and ethyl benzoylacetate in the presence of N-methylmorpholine leads to the formation of 3-cyano-5-ethoxycarbonyl-4-methyl-6-phenylpyridine-2(1H)-thione. Alkylation of the last afforded the corresponding substituted 2-alkylthiopyridines.

Three-component condensations of aliphatic aldehydes with cyanothioacetamide and some active methylene compounds (acetoacetanilide, acetoacetamide, Meldrum's acid, cyanothioacetamide, dimedone, malononitrile, cyclohexane-1,3-dione, acetylacetone, cyanoacetic ester, and acetoacetic ester) may serve as convenient methods for the synthesis of substituted 4-alkyl-3-cyanopyridine-2(1H)-thiones and their partially hydrogenated analogs [1-13]. In the continuation of the work indicated, and taking into account the practical significance of alkylpyridines [14], we accomplished the synthesis of 3-cyano-5-ethoxycarbonyl-4-methyl-6-phenylpyridine-2(1H)-thione (I) and its derivatives (II). The reaction of acetaldehyde (III) with cyanothioacetamide (IV) and ethyl benzoylacetate (V) in the presence of N-methylmorpholine at 20°C in ethanol leads to thione I with the yield of 76%. The formation of thione I is probably the result of the conversion of the hypothetical intermediates VI and VII under the given reaction conditions. The subsequent alkylation of the compound I with bromides VIII in a basic medium led to the isolation of the corresponding substituted 2-alkylthiopyridines II.



II, VIII a PhCO, b 4-ClC$_6$H$_4$CO, c 4-MeOC$_6$H$_4$CO

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EXPERIMENTAL

The IR spectra were taken on the IKS-29 spectrophotometer in mineral oil. The PMR spectra were recorded on the Bruker WP 100 SY instrument (100 MHz) in DMSO-d_6, with TMS as the internal standard. The monitoring of the course of the reaction and the discreteness of the substances was accomplished using TLC on Silufol UV-254plates, acetone–heptane mixture (3:5) was used as the eluent.

3-Cyano-5-ethoxycarbonyl-4-methyl-6-phenylpyridine-2(1H)-thione (I). Mixture of acetaldehyde (III) (1.12 ml, 20 mmol), cyanothioacetamide (IV) (2.00 g, 20 mmol), ethyl benzoylacetate (V) (3.44 ml, 20 mmol), and N-methylmorpholine (2.75 ml, 25 mmol) in ethanol (35 ml) was stirred at 20°C for 30 min. The mixture was then left for 12 h. The resulting residue was filtered off and washed with ethanol and heptane. Compound I was obtained with the yield of 4.54 g (76%); mp 147-149°C. IR spectrum: 3450 (NH), 2228 (CN), and 1726 cm^{-1} (CO). PMR spectrum: 0.80 (3H, t, $\underline{CH_3}CH_2O$); 2.43 (3H, s, CH_3); 3.94 (2H, q, CH_2O); 7.50 (5H, m, Ph); 14.36 ppm (1H, br. s, NH). Found, %: C 64.28; H 4.59; N 9.47; S 10.61. $C_{16}H_{14}N_2O_2S$. Calculated, %: C 64.41; H 4.73; N 9.39; S 10.75.

2-Alkylthio-3-cyano-5-ethoxycarbonyl-4-methyl-6-phenylpyridines (IIa-c). To suspension of thione I (1.49 g, 5 mmol) in ethanol (25 ml) 10% aqueous solution of KOH (2.8 ml, 5 mmol) was added with stirring, and, after 1 min, the corresponding bromide VIII (5 mmol) was added. After 30 min, the resulting residue was filtered off and washed with ethanol and heptane.

Compound IIa. Yield 1.71 g (82%); mp 111-113°C (ethanol). IR spectrum: 2215 (CN), 1710, 1740 cm^{-1} (2CO). PMR spectrum: 0.95 (3H, t, $\underline{CH_3}CH_2O$); 2.50 (3H, s, CH_3); 4.09 (2H, q, CH_2O); 4.97 (2H, s, CH_2S); 7.23-8.03 ppm (10H, m, 2Ph). Found, %: C 69.00; H 4.71; N 6.81; S 7.61. $C_{24}H_{20}N_2O_3S$. Calculated, %: C 69.21; H 4.84; N 6.73; S 7.70.

Compound IIb. Yield 1.67 g (74%); mp 116-118°C (ethanol). IR spectrum: 2210 (CN), 1715, 1740 cm^{-1} (2CO). PMR spectrum: 0.95 (3H, t, $\underline{CH_3}CH_2O$); 2.50 (3H, s, CH_3); 4.10 (2H, q, CH_2O); 4.94 (2H, s, CH_2S); 7.24-7.35 (5H, m, Ph); 7.56 and 8.03 ppm (4H, two d, Ar). Found, %: C 63.79; H 4.13; N 6.14; S 7.01. $C_{24}H_{19}ClN_2O_3S$. Calculated, %: C 63.92; H 4.25; N 6.21; S 7.11.

Compound IIc. Yield 1.54 g (69%); mp 135-137°C (ethanol). IR spectrum: 2217 (CN); 1680, 1720 cm^{-1} (2CO). PMR spectrum: 0.95 (3H, t, $\underline{CH_3}CH_2O$); 2.49 (3H, s, CH_3); 3.86 (3H, s, CH_3O); 4.11 (2H, q, CH_2O); 4.90 (2H, s, CH_2S); 7.01 and 8.03 (4H, two d, Ar); 7.26 ppm (5H, m, Ph). Found, %: C 67.10; H 4.81; N 6.12; S 7.11. $C_{25}H_{22}N_2O_4S$. Calculated, %: C 67.25; H 4.97; N 6.27; S 7.18.

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