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ALIPHATIC ALDEHYDES IN SYNTHESIS OF 4-ALKYL-5-CARBAMOYL-3-CYANO-6-METHYLPYRIDINE-2(1H)-THIONES

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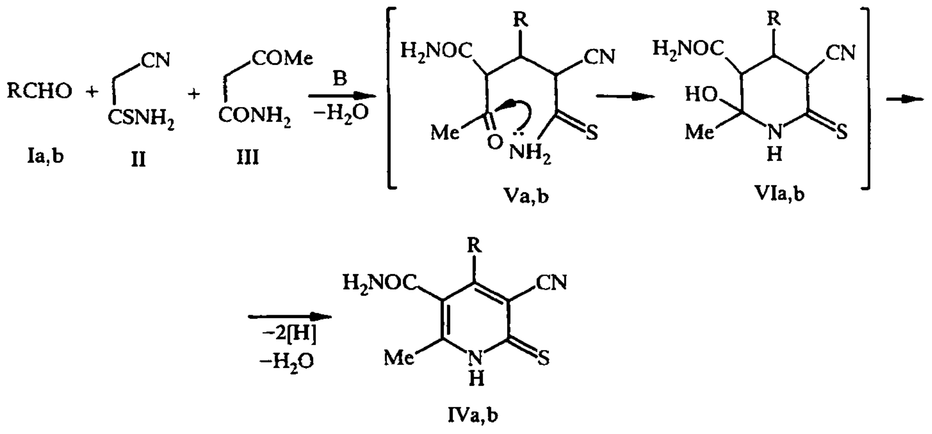
Condensation of isovaleric or acetic aldehydes with cyanothioacetamide and acetoacetamide leads to formation of 4-isobutyl(methyl)-5-carbamoyl-3-cyano-6-methylpyridine-2(1H)-thiones. By alkylation of 5-carbamoyl-3-cyano-4,6-dimethylpyridine-2(1H)-thione with 4-methoxyphenacyl bromide, 5-carbamoyl-3-cyano-4,6-dimethyl-2-(4-methoxybenzoyl)methylthiopyridine has been obtained.

Continuing our study of the synthetic potential of aliphatic aldehydes for obtaining alkyl-substituted pyridinethiones [1-5], we have established that condensation of isovaleric or acetic aldehydes (Ia,b) with cyanothioacetamide (II) and acetoacetamide (III) at 20°C in ethanol in the presence of N-methylmorpholine proceeds with formation of 4-alkyl-5-carbamoyl-3-cyano-6-methylpyridine-2(1H)-thiones (IVa,b). In this case, formation of Michael adducts Va,b probably occurs, with subsequent cyclocondensation leading to piperidines VIa,b (which are unstable under the reaction conditions). The latter are easily converted to compounds IVa,b.

The structure of pyridinethiones IVa,b has been confirmed by spectroscopic methods. In their IR spectra, in addition to the absorption bands of the $CONH_2$ and NH groups appearing in the characteristic regions, an intense absorption band from the CN group in the 2222-2223 cm^{-1} region is observed. In the PMR spectra of compound IV, a doublet from protons of the $CONH_2$ group in the 7.86-7.88 ppm region and a broadened singlet from the NH group in the 13.98 ppm region (for thione IVa) are recorded.



B = N-methylmorpholine

I, IV — VI a R = CH_2CHMe_2, b R = Me

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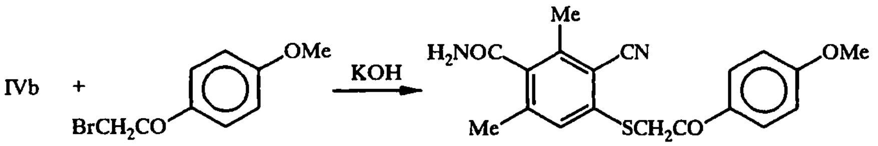
Compound IVb in ethanol in the presence of equimolar amount of an aqueous KOH solution is alkylated by bromide VII at the sulfur atom, with formation of organic sulfide VIII in 83% yield:



VII VIII

EXPERIMENTAL

The IR spectra were taken on an IKS-29 spectrophotometer in vaseline oil. The PMR spectra were recorded on a Bruker WP-100 SY (100 MHz) in DMSO-d$_6$ (internal standard TMS). The course of the reaction and the purity of the compounds were monitored using TLC on Silufol UV-254 plates (eluent acetone—heptane, 3:5).

5-Carbamoyl-3-cyano-4-isobutyl(methyl)-6-methylpyridine-2(1H)thiones (IVa,b). Mixture of 10 mmol of aldehyde Ia,b, 1 g (10 mmol) of cyanothioacetamide II, 1.01 g (10 mmol) of acetoacetamide III, and 1.5 ml (15 mmol) of N-methylmorpholine in 20 ml of ethanol at 20°C was stirred for 15 min, and then allowed to stand for 12 h. The precipitate of product IV was filtered off and then washed with ethanol and heptane.

Compound IVa. Yield 1.82 g (73%); mp 258-260°C. IR spectrum: 3195, 3320, 3460 (NH_2, NH), 2223 (CN), 1670 cm^{-1} (C=O). PMR spectrum: 13.98 (1H, br. s, NH); 7.88 (2H, d, $CONH_2$); 2.59 (2H, d, CH_2); 2.37 (3H, s, 6-CH_3); 2.05 (1H, m, CH); 0.91 ppm (6H, d, 2CH_3). Found, %: C 57.90; H 6.13; N 16.77; S 12.83. $C_{12}H_{15}N_3OS$. Calculated, %: C 57.81; H 6.06; N 16.85; S 12.86.

Compound IVb. Yield 1.22 g (59%); mp 295°C (decomp.). IR spectrum: 3180, 3270, 3395 (NH_2, NH), 2220 (CN), 1693 cm^{-1} (C=O). PMR spectrum: 7.86 (2H, d, $CONH_2$); 2.35 ppm (6H, s, 2CH_3) (a signal does not appear from the NH proton, probably as a result of deuterium exchange). Found, %: C 52.24; H 4.48; N 20.21; S 15.42. $C_9H_9N_3OS$. Calculated, %: C 52.16; H 4.38; N 20.27; S 15.47.

5-Carbamoyl-3-cyano-4,6-dimethyl-2-(4-methoxybenzoyl)methylthiopyridine (VIII). 10% Aqueous KOH solution (5.6 ml, 10 mmol) was added to suspension of 2.07 g (10 mmol) of thione IVb in 25 ml of ethanol with stirring at 20°C; after 1 min, 2.29 g (10 mmol) of bromide VII was added. After 30 min, the precipitate was filtered off, washed with ethanol and heptane. Compound VIII (2.95 g, 83%) was obtained; mp 236-238°C (from AcOH). IR spectrum: 3195, 3370 (NH_2), 2204 (CN), 1670 cm^{-1} (C=O). PMR spectrum: 8.08 d and 7.08 d (4H, Ar); 7.96 br. s and 7.82 br. s (2H, $CONH_2$); 4.83 (2H, s, SCH_2); 3.87 (3H, s, OCH_3); 2.40 (3H, s, 4-CH_3); 2.23 ppm (3H, s, 6-CH_3). Found, %: C 60.89; H 4.95; N 11.74; S 8.87. $C_{18}H_{17}N_3O_3S$. Calculated, %: C 60.83; H 4.82; N 11.82; S 9.02.

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