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SYNTHESIS AND PROPERTIES OF 5-ACETYL-3-CYANO-4-ISOBUTYL-6-METHYL-3,4-DIHYDROPYRIDINE-2(1H)-THIONE

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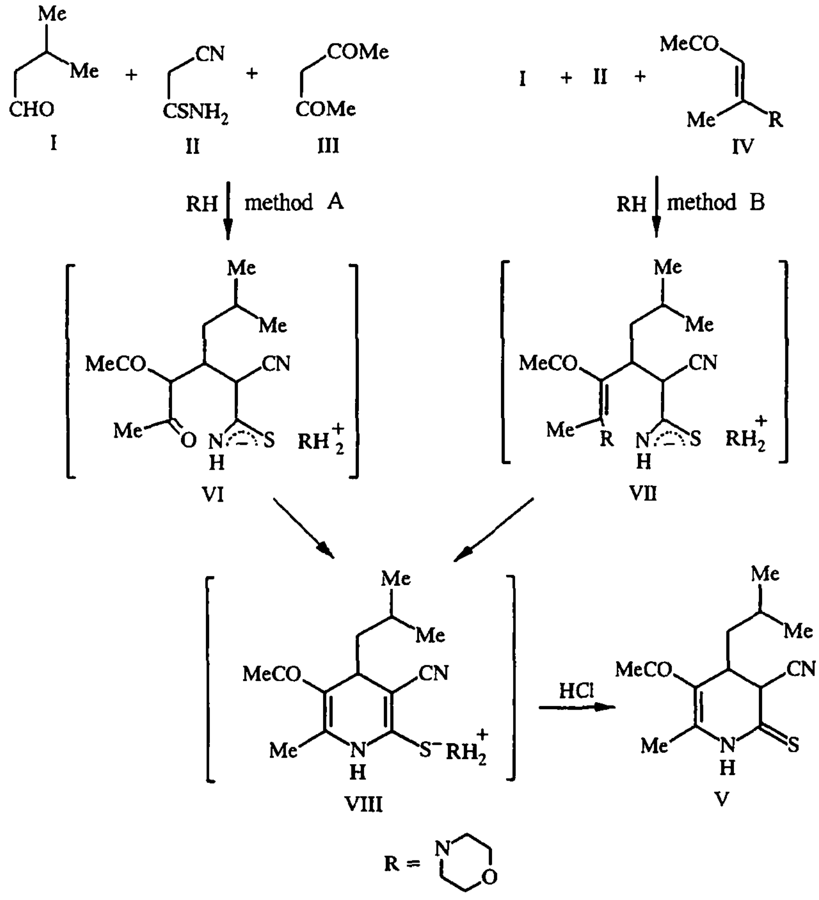
Condensation of isovaleric aldehyde with cyanothioacetamide and acetylacetone or its enamine produces 5-acetyl-3-cyano-4-isobutyl-6-methyl-3,4-dihydropyridine-2(1H)-thione, from which 5-acetyl-3-cyano-4-isobutyl-6-methylpyridine-2(1H)-thione and the corresponding substituted 2-alkylthio-1,4-dihydropyridines are prepared.

The synthesis and properties of 5-acetyl-4-aryl(hetaryl)-3-cyano-6-methyl-3,4-dihydropyridine-2(1H)-thiones have been reviewed [1-3]. However, until now the 4-alkylsubstituted analogs have not been reported. In



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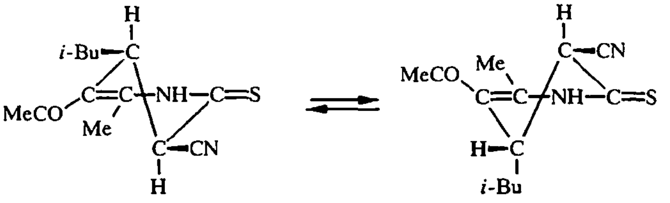
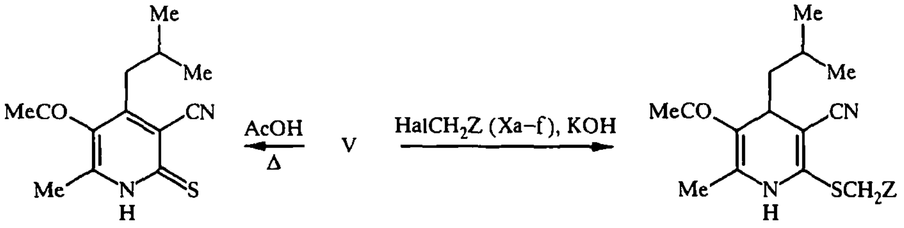
continuation of our studies on the possible practical use of aliphatic aldehydes to synthesize partially hydrogenated 3-cyanopyridinethiones [4, 5], we now demonstrate that condensation of isovaleric aldehyde (I) with cyanothioacetamide (II) and acetylacetone (III) (method A) or its enamine (IV) (method B) in ethanol at 20°C in the presence of morpholine with subsequent acidification of the reaction mixture by 10% HCl produces the substituted 3,4-dihydropyridine-2(1H)-thione (V). These reactions probably involve the formation of the corresponding adducts VI and VII, which transform into the salt VIII. These hypotheses agree with recently published results [4].

Like the arylsubstituted 3,4-dihydropyridine-2(1H)-thiones V [6-8], exists in DMSO solution as a mixture of the *cis* and *trans* isomers in a 1:1 ratio. This is consistent with the PMR spectra (see Experimental). Two idealized interchargeable conformations can be proposed for V:


V (*trans*) V (*cis*)

Thione–thiol tautomerism of V was not observed. This is additionally confirmed by the presence in the IR spectrum of only one weak absorption band near 2250 cm^{-1} for the stretching vibration of the unconjugated cyano group.

3,4-Dihydropyridine-2-thione V is stable in the crystalline state. However, dissolution in glacial acetic acid and heating in air readily transform it into IX. Interaction of V with various halides X in the presence of base gives the substituted 2-alkylthio-1,4-dihydropyridines XI. The characteristics of these are listed in Tables 1 and 2.


IX XIa-f

Xa Hal = I, b,c Hal = Cl, d-f Hal = Br;
X, XIa Z = H, b Z = $CONH_2$, c Z = 4-BrC_6H_4NHCO,
d Z = PhCO, e Z = 4-FC_6H_4CO, f Z = 4-ClC_6H_4CO

TABLE 1. Characteristics of Compounds XIa-f

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	S		
XIa	$C_{14}H_{20}N_2OS$	63,49 63,60	7,52 7,62	10,71 10,60	12,07 12,13	152...154	76
XIb	$C_{15}H_{21}N_3O_2S$	58,50 58,61	6,76 6,89	13,59 13,67	10,33 10,43	136...138	84
XIc	$C_{21}H_{24}BrN_3O_2S$	54,47 54,55	5,11 5,23	9,18 9,09	6,81 6,93	208...210	66
XId	$C_{21}H_{24}N_2O_2S$	68,31 68,45	6,47 6,56	7,47 7,60	8,62 8,70	151...153	76
XIe	$C_{21}H_{23}FN_2O_2S$	65,12 65,26	5,88 6,00	7,14 7,25	8,24 8,30	135...137	81
XIf	$C_{21}H_{23}ClN_2O_2S$	62,51 62,60	5,61 5,75	6,86 6,95	7,84 7,96	123...125	89

TABLE 2. Spectral Characteristics of Compounds XIa-f

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm
XIa	3270 (NH) 2192 (CN) 1620 (C=O)	0,87 (6H, q, 2CH$_3$); 1,20 (2H, m, CH$_2$); 1,70 (1H, m, CH) 2,25 (6H, s, 6-CH$_3$ and OCCH$_3$); 2,50 (3H, s, SCH$_3$) 3,46 (1H, dd, C(4)H); 9,47 (1H, br. s, NH)
XIb	3390, 3150 (NH, NH$_2$) 2203 (CN) 1690, 1630 (C=O)	0,89 (6H, q, 2CH$_3$); 1,18 (2H, m, CH$_2$); 1,68 (1H, m, CH) 2,24 (6H, s, 6-CH$_3$ and OCCH$_3$); 3,50 (1H, m, C(4)H) 3,67 (2H, s, SCH$_2$); 7,56 br. s and 7,89 br. s (2H, CONH$_2$) 10,35 (1H, br. s, NH)
XIc	3330...3180 (NH, CONH) 2197 (CN) 1690, 1620 (C=O)	0,83 (6H, q, 2CH$_3$); 1,25 (2H, m, CH$_2$); 1,68 (1H, m, CH) 2,23 (6H, s, 6-CH$_3$ and OCCH$_3$); 3,55 (1H, m, C(4)H) 3,91 (2H, s, SCH$_2$); 7,52 (4H, s, Ar); 9,77 (1H, br. s, NH) 10,44 (1H, br. s, CONH)
XId	3300 (NH) 2195 (CN) 1710, 1620 (C=O)	0,84 (6H, q, 2CH$_3$); 1,25 (2H, m, CH$_2$); 1,60 (1H, m, CH) 2,21 (6H, s, 6-CH$_3$ and OCCH$_3$); 3,39 (1H, m, C(4)H) 4,70 (2H, s, SCH$_2$); 7,61...7,98 (5H, m, Ph) 9,53 (1H, br. s, NH)
XIe	3300 (NH) 2197 (CN) 1690, 1605 (C=O)	0,86 (6H, q, 2CH$_3$); 1,25 (2H, m, CH$_2$); 1,60 (1H, m, CH) 2,23 (6H, s, 6-CH$_3$ and OCCH$_3$); 3,42 (1H, m, C(4)H) 4,67 (2H, s, SCH$_2$); 7,40 t and 8,06 q (4H, Ar) 9,54 (1H, br. s, NH)
XIf	3290 (NH) 2194 (CN) 1680, 1630 (C=O)	0,85 (6H, t, 2CH$_3$); 1,23 (2H, m, CH$_2$); 1,57 (1H, m, CH) 2,21 (6H, s, 6-CH$_3$ and OCCH$_3$); 3,41 (1H, m, C(4)H) 4,65 (2H, s, SCH$_2$); 7,62 d and 7,99 d (4H, Ar) 9,52 (1H, br. s, NH)

EXPERIMENTAL

PMR spectra were obtained on a Bruker WP-100 SY (100 MHz) instrument in DMSO-d$_6$ with TMS as internal standard. IR spectra were recorded on an IKS-29 spectrometer in vaseline oil. TLC was performed on Silufol UV-254 plates using acetone–heptane (3:5) as a mobile phase; spots were visualized by iodine vapor.

5-Acetyl-3-cyano-4-isobutyl-6-methyl-3,4-dihydropyridine-2(1H)-thione (V). A. Mixture of isovaleric aldehyde I (5.38 ml, 50 mmol), cyanothioacetamide II (5 g, 50 mmol), acetylacetone III (5.15 ml, 50 mmol), and morpholine (6.54 ml, 75 mmol) in ethanol (75 ml) was stirred for 3 h at 20°C, after which the mixture was acidified with 10%HCl until pH = 5. After 24 h the solid formed was filtered off and washed with ethanol and hexane. Yield 11.14 g (89%) of thione V; mp 129-132°C. IR spectrum: 3300 (NH), 2250 (CN), 1680 cm^{-1} (C=O). PMR spectrum: 0.85 (6H, q, 2CH$_3$), 1.15 (2H, m, CH$_2$), 1.56 (1H, m, CH), 2.21 s and 2.28 s (3H, 6-CH$_3$), 2.30 s and 2.33 s (3H, OCCH$_3$), 3.21 (1H, m, C(4)H), 4.27 (1H, d, C(3)H, $^3J = 2.5$ Hz (*cis* isomer)), 4.59 (1H, d, C(3)H, $^3J = 5$ Hz (*trans* isomer)), 11.88 br. s and 12.15 ppm (1H, br. s, NH). Found, %: C 62.23; H 7.17; N 11.13; S 12.70. $C_{13}H_{18}N_2OS$. Calculated, %: C 62.37; H 7.25; N 11.19; S 12.81.

B. 3 Drops of morpholine and the enamine of acetylacetone IV (8.46 g, 50 mmol) were added to stirred mixture of isovaleric aldehyde I (5.38 ml, 50 mmol) and cyanothioacetamide II (5 g, 50 mmol) in ethanol (75 ml) at 20°C. After 3 h the reaction mixture was acidified with 10% HCl until pH = 5 and left for 24 h. The solid formed was filtered off and washed with ethanol and hexane. Yield 9.14 g (73%) of V with spectral properties identical to those of the product obtained *via* method A.

5-Acetyl-3-cyano-4-isobutyl-6-methylpyridine-2(1H)-thione (IX). Compound V (2.5 g, 10 mmol) was recrystallized from glacial acetic acid (15 ml). The solid formed after 24 h was filtered off and washed with ethanol and hexane. Yield 1.71 g (69%) of pyridinethione IX; mp 178-180°C. IR spectrum: 3295 (NH), 2218 (CN), 1680 cm^{-1} (C=O). PMR spectrum: 0.87 (6H, d, 2CH$_3$), 1.83 (1H, m, CH), 2.34 (3H, s, 6-CH$_3$), 2.50 (5H, m, CH$_2$ and OCCH$_3$), 14.06 ppm (1H, br. s, NH). Found, %: C 62.73; H 6.39; N 11.22; S 12.83. $C_{13}H_{16}N_2OS$. Calculated, %: C 62.87; H 6.49; N 11.28; S 12.91.

5-Acetyl-3-cyano-4-isobutyl-6-methyl-2-Z-methylthio-1,4-dihydropyridines (XIa-f). Suspension of thione V (2.5 g, 10 mmol) in ethanol (20 ml) is treated with aqueous KOH (10%, 5.6 ml, 10 mmol) with stirring. After 1 min the corresponding halide (X, 10 mmol) was added. The solid formed after 4 h is filtered off, washed with ethanol and hexane, and recrystallized from butan-1-ol. Characteristics of the resulting products XIa-f are listed in Tables 1 and 2.

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