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SYNTHESIS AND ALKYLATION OF 3-CYANO-4-ISOBUTYL-5-OXO-1,4,5,6,7,8-HEXAHYDROQUINOLINE-2-THIOL

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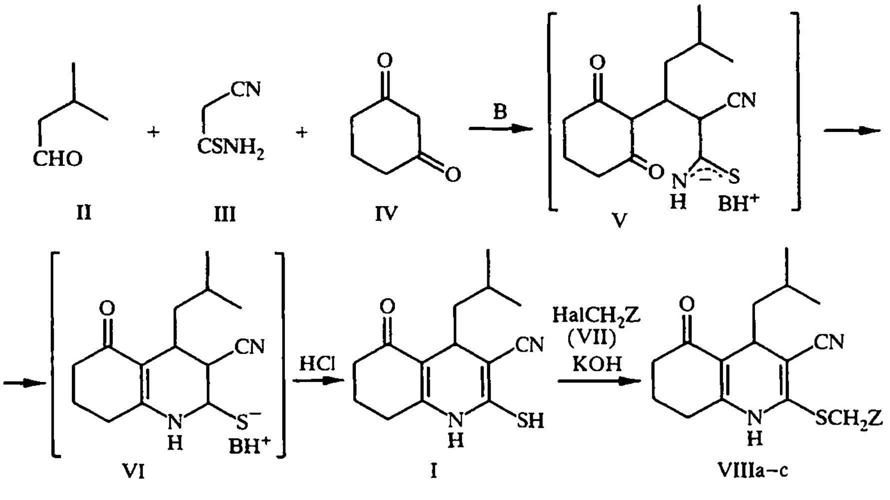
By reaction of isovaleric aldehyde with cyanothioacetamide and cyclohexane-1,3-dione, 3-cyano-4-isobutyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-1-thiol has been obtained, and subsequently used in synthesis of the corresponding substituted 2-alkylthiohexahydroquinolines.

1,3-Cyclohexanedione has been successfully used in synthesis of substituted 3-cyanothiazolo[4,5-*f*]-quinoline-2(1H)-ones, which exhibit cardiotonic activity [1]. No data are available in the literature on use of this reagent for obtaining derivatives of hydrogenated quinolinethiones. Recently we demonstrated that it is possible to synthesize 3-cyano-4-isopropyl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydroquinoline-2(1H)-thione by condensation of isobutyric aldehyde with cyanothioacetamide and dimedone [2], which made it possible to develop convenient methods for obtaining 3-cyano-4-isobutyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-2-thiol (I) and its derivatives. In this work, we have investigated the reaction of isovaleric aldehyde (II) with cyanothioacetamide (III) and 1,3-cyclohexanedione (IV) in the presence of an organic base in ethanol at 20°C. This reaction probably proceeds through a stage of formation of intermediate V, which then undergoes cyclocondensation with formation of salt VI. Subsequent treatment of the reaction mixture with 10% hydrochloric acid leads to compound I, and sulfides VIII are obtained upon alkylation of I by halides VII in alkaline medium.



B = N-methylmorpholine; VII a,b Hal = I; c Hal = Cl; VII, VIII a Z = H;
b Z = CH_3; c Z = 4-BrC_6H_4NHCO

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Substituted and partially hydrogenated quinoline I exists in DMSO solution and in vaseline oil suspension exclusively in the thiol form, evidence for which comes from the IR and PMR spectra (see Experimental). Thus in the IR spectrum of this compound absorption band for vibrations of the conjugated cyano group in the 2200 cm^{-1} region was recorded, and its PMR spectrum contains a signal from the $C_{(4)}H$ proton in the form of triplet at 3.48 ppm.

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).

3-Cyano-4-isobutyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-2-thiol (I). Mixture of 5.38 ml (50 mmol) of isovaleric aldehyde (II), 5 g (50 mmol) of cyanothioacetamide (III), 5.61 g (50 mmol) of 1,3-cyclohexanedione (IV) and 5.5 ml (50 mmol) of N-methylmorpholine in 75 ml of ethanol was stirred at 25°C for 3 h; then 10% hydrochloric acid solution was added until pH 5 was reached. The precipitate formed after 12 h was filtered off and washed with ethanol. Compound I (7.08 g, 54%) was obtained; mp 218-220°C. IR spectrum: 3230 (NH), 2200 (CN), 1620 cm^{-1} (C=O). PMR spectrum: 0.84-1.25 (8H, m, $2CH_3$ and CH_2); 1.65 (1H, m, CH); 1.90 m and 2.24 m (4H, $2CH_2$); 2.50 (2H, m, CH_2CO); 3.48 (1H, t, $C_{(4)}H$); 10.16 ppm (1H, br. s, NH). Found, %: C 63.96; H 6.81; N 10.59; S 12.15. $C_{14}H_{18}N_2OS$. Calculated, %: C 64.09; H 6.92; N 10.68; S 12.22.

3-Cyano-4-isobutyl-5-oxo-2-*Z*-methylthio-1,4,5,6,7,8-hexahydroquinolines (VIIIa-c). 10% Aqueous KOH solution (5.6 ml) and 10 mmol of halide VII were added to suspension of 2.62 g (10 mmol) of thiol I in 15 ml of ethanol with stirring. After 3 h, the precipitate formed was separated, then washed successively with ethanol and hexane. Substituted hexahydroquinolines VIIIa-c were obtained, which were recrystallized from 1-butanol.

Compound VIIIa: Yield 72%; mp 225-227°C. IR spectrum: 3090-3255 (NH), 2180 (CN), 1620 cm^{-1} (C=O). PMR spectrum: 0.85 (6H, t, $2CH_3$); 1.10 (2H, m, CH_2); 1.70 (1H, m, CH); 1.89 m and 2.26 m (4H, $2CH_2$); 2.50 (5H, m, CH_2CO and SCH_3); 3.44 (1H, q, $C_{(4)}H$); 9.65 ppm (1H, br. s, NH). Found, %: C 65.33; H 7.19; N 10.32; S 11.34. $C_{15}H_{20}N_2OS$. Calculated, %: C 65.18; H 7.29; N 10.13; S 11.60.

Compound VIIIb: Yield 66%; mp 178-180°C. IR spectrum: 3075-3300 (NH), 2193 (CN), 1615 cm^{-1} (C=O). PMR spectrum: 0.86 (6H, t, $2CH_3$); 1.19 (5H, m, CH_2 and $SCH_2\underline{CH_3}$); 1.73 (1H, m, CH): 1.87 m and 2.22 m (4H, $2CH_2$); 2.50 (2H, m, CH_2CO); 3.00 (2H, m, $\underline{SCH_2}CH_3$); 3.46 (1H, q, $C_{(4)}H$); 9.72 ppm (1H, br. s, NH). Found, %: C 66.31; H 7.52; N 9.51; S 10.91. $C_{16}H_{22}N_2OS$. Calculated, %: C 66.17; H 7.64; N 9.65; S 11.04.

Compound VIIIc: Yield 87%; mp 256-258°C. IR spectrum: 3180-3330 (NH), 2182 (CN), 1650-1710 cm^{-1} (C=O). PMR spectrum: 0.81 (6H, t, $2CH_3$); 1.10 (2H, m, CH_2); 1.63 (1H, m, CH); 1.85 m and 2.23 m (4H, $2CH_2$); 2.50 (2H, m, CH_2CO); 3.45 (1H, m, $C_{(4)}H$); 3.91 (2H, s, SCH_2); 7.52 (4H, s, Ar); 9.95 (1H, br. s, NH); 10.42 ppm (1H, br. s, NHCO). Found, %: C 55.59; H 5.02; Br 16.73; N 8.60; S 6.61. $C_{22}H_{24}BrN_3O_2S$. Calculated, %: C 55.70; H 5.10; Br 16.84; N 8.86; S 6.76.

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