

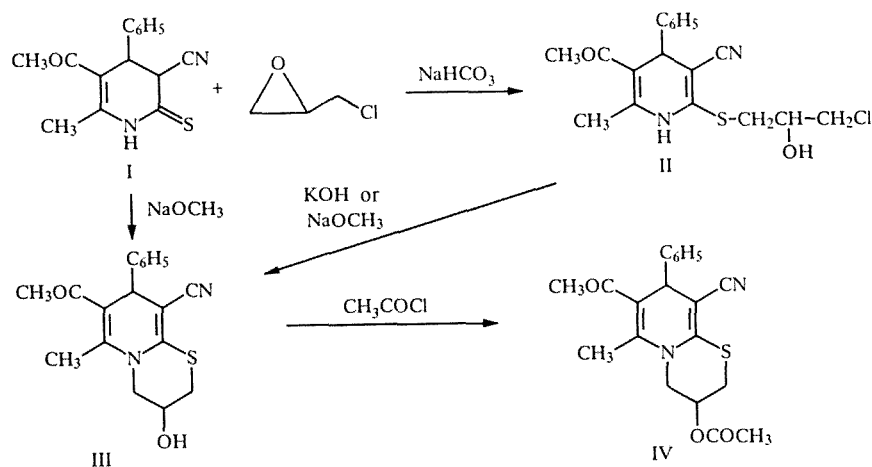
THE REACTION OF 1,4-DIHYDROPYRIDIN-2(3H)-THIONE WITH EPICHLORHYDRIN

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The reaction of 1,4-dihydropyridin-2(3H)-thione, which has several nucleophilic centers, with epichlorohydrin, which contains a labile sp^3 carbon-oxygen bond, has been carried out for the first time with the object of preparing derivatives of 2-dioxypropylthio-1,4-dihydropyridine for the synthesis of mimetic glyceride derivatives of 1,4-dihydropyridine.

We have established that the initial reaction of 6-methyl-4-phenyl-5-acetyl-3-cyano-1,4-dihydropyridin-2(3H)-thione (I) [1] with epichlorohydrin occurs exclusively at the sulfur atom.

2-(1-Chloro-2-hydroxy-3-propyl)thio-1,4-dihydropyridine (II) was obtained in 41.3% yield when the reaction was carried out with equimolar amounts of the reagents in methanol at room temperature in the presence of sodium hydrogen carbonate. The precipitate was separated, washed with water and purified on a silica gel (40/100 range) column by elution with 1-5% methanol in dichloromethane. When stronger bases than sodium hydrogen carbonate were used — potassium hydroxide and sodium methoxide — 3-hydroxy-(2H)3,4,5,8-tetrahydrothiazino[3,2-*a*]pyridine (III) was obtained (in yields of 50 and 59% respectively). In the presence of sodium methoxide compound II readily cyclized at room temperature by intramolecular alkylation to give the thiazinopyridine III in 68.9% yield. It differs in this respect from the intermolecular alkylation of 2-ethylthio-1,4-dihydropyridine. Compound III was characterized by acylation with acetyl chloride to give the 3-acetyloxythiazinopyridine IV in 63.8% yield. Formation of thietanes was not observed on cyclization of the 2-(1-chloro-2-hydroxy-3-propyl)thio derivatives of 1,4-dihydropyridin-2(3H)-thiones, in contrast to the behavior of 6-mercaptapurines [2] and 2-mercaptopyridines [3].



2-(1-Chloro-2-hydroxy-3-propyl)thio-6-methyl-4-phenyl-5-acetyl-3-cyano-1,4-dihydropyridine (II, $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2\text{SCl}$), m.p. 202-203°C (ethanol). IR spectrum: 3247 sh, 3240, 3128 (OH, NH), 2194 (CN), 1652 cm^{-1} (CO). ^1H NMR spectrum ($\text{DMSO}-d_6$): 2.06 (3H, s, CH_3CO), 2.33 (3H, s, 6- CH_3), 3.14 (2H, m, SCH_2), 3.66 (2H, m, CH_2Cl), 3.90 (1H, m, CH-OH), 4.64 (1H, s, 4-H), 6.14 (1H, d, $J = 4.2$ Hz, OH, exchanges with D_2O), 7.18-7.36 (5H, m, 4- C_6H_5), 9.58 (1H, s, NH, exchanges with D_2O).

3-Hydroxy-6-methyl-8-phenyl-7-acetyl-9-cyano-(2H)-3,4,5,8-tetrahydrothiazino[3,2-*a*]pyridine (III, $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$), m.p. 245-247°C (ethanol). IR spectrum: 3424 (OH), 2202 (CN), 1680 cm^{-1} (CO). ^1H NMR spectrum ($\text{DMSO}-d_6$): 1.94 (3H, s, CH_3CO), 2.36 (3H, s, 6- CH_3), 3.44 and 3.54 (4H, m and m, CH_2S and CH_2N), 4.64 (1H, m, 3-H), 4.80 (1H, s, 8-H), 5.32 (1H, dd, $J = 5.0$ Hz, OH, exchanges with D_2O), 7.2-7.4 (5H, m, 8- C_6H_5).

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3-Acetoxy-6-methyl-8-phenyl-7-acetyl-9-cyano-(2H)-3,4,5,8-tetrahydrothiazino[3,2-*a*]pyridine (IV, C₂₀H₂₀N₂·O₃S). M.p. 182-184°C (ethanol). IR spectrum: 2200 (CN), 1742, 1735, 1665 cm⁻¹ (CO). ¹H NMR spectrum (CDCl₃): 1.92 (3H, s, CH₃CO), 2.08 (3H, s, CH₃COO), 2.38 (3H, s, 6-CH₃), 3.09-3.53 and 4.09-4.42 (4H, m and m, SCH₂ and NCH₂), 4.62 (1H, m, 3-H), 4.68 (1H, s, 8-H), 7.23 (5H, m, 8-C₆H₅).

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