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Chen Chang-bai, R. P. Evstigneeva, and N. A. Preobrazhenskii

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Abstract

Full Text

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Synthesis of the Alkaloid Cinchonamine

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The alkaloid cinchonamine, from the bark of the cinchona tree, is a connecting link between the cinchona alkaloids of the quinoline series and the alkaloids of the indole series. This was shown by the direct synthetic conversion of dihydroquinine into 5-methoxydihydrocinchonamine (^{1}) and of dihydrocinchonine into dihydrocinchonamine (^{2}).

In the present communication, the synthesis of optically active cinchonamine is described.

The synthesis was carried out according to a scheme that we had previously developed for obtaining the pyridine analogue of cinchonamine (^{3}).

$$\begin{gathered}\text{(I)} \longrightarrow \text{(III)} \longrightarrow \\ \text{[intermediate]} \longrightarrow \text{(IV)} \longrightarrow \\ \text{(V)} \longrightarrow \text{(VI)}\end{gathered}$$

Ethyl ester of 3-vinylquinuclidinecarboxylic acid-6 (b.p. 80–82°/0.5 mm; n_D^{20} 1.4850; d_4^{20} 1.028; MR_D found 58.35, calculated 58.34, $[\alpha]_D^{21.5}$ + 69.58° in C 1.006, 95% C_2H_5OH) (I) is condensed with γ-butyrolactone (b.p. 70.5–72°/5 mm; n_D^{20} 1.4336) (II) in dry benzene in the presence of sodium ethylate at 40–85°. After the appropriate treatment, α-(3-vinylquinuclidoyl-6)-γ-butyrolactone (III) is obtained in the form of a colorless, viscous, oily substance, readily soluble in ether, alcohol, benzene, and water. B.p. 152–153°/0.5 mm. Yield 35.7%.

Found, %: C 67.21; 67.32; H 7.96; 7.98; N 5.61
$C_{14}H_{19}O_3N$. Calculated, %: C 67.45; H 7.68; N 5.62

Reineckate, m.p. 152.5–154° (with decomposition).

$$C_{14}H_{19}O_3N \cdot C_4H_7N_6S_4Cr.$$

Found, %: C 38.21; 38.35; H 4.43; 4.74; N 17.20; 17.14
Calculated, %: C 38.03; H 4.61; N 17.25

On heating compound (III) with 2 N sulfuric acid at 120°, opening of the lactone ring and decarboxylation take place, with formation of ω-hydroxypropyl-α-(3-vinylquinuclidyl-6)-ketone (IV). Yield 70.3%.

The light-yellow liquid obtained is heated with a 10% alcoholic solution of phenylhydrazine for 8 hours. The phenylhydrazone of ω-hydroxypropyl-α-(3-vinylquinuclidyl-6)-ketone (V) formed is a viscous yellow oil. Yield 76.5%.

Reineckate, after recrystallization from aqueous alcohol, m.p. 136.5–138° (with decomposition)

$$C_{19}H_{27}ON_3 \cdot C_4H_7N_6S_4Cr.$$

Found, %: C 43.36; H 5.28
Calculated, %: C 43.65; H 5.42

To the base of phenylhydrazone (V) in anhydrous ethyl alcohol, a twofold amount of concentrated sulfuric acid is added, and the mixture is heated for one hour at 60° (^{4}). It is then neutralized with an alcoholic solution of ammonia, ammonium sulfate is separated, the alcohol is distilled off, the base is liberated with potassium hydroxide, and it is extracted with ether. After removal of the solvent, the light-yellow oil is treated with alcohol, and cinchonamine is obtained in the form of colorless crystals, readily soluble in hot alcohol, ether, chloroform, and benzene, less soluble in cold alcohol, and poorly soluble in petroleum ether and water.

$$\text{m.p. } 196^{\circ}, \quad [\alpha]_D^{21} + 120^{\circ}\ (C\ 0.208,\ 96\%C_2H_5OH).$$

$$\lambda_{\text{max}}(C_2H_5OH)\ 280\ \text{m}\mu \quad (\log\varepsilon\ 3.98)$$

$$\lambda_{\text{min}}(C_2H_5OH)\ 247\ \text{m}\mu \quad (\log\varepsilon\ 3.71)$$

The constants given for the optically active cinchonamine synthesized by us fully coincide with those described in the literature for the natural alkaloid (^{5}).

The reaction developed by us, which has led to the synthesis of cinchonamine, opens a route to the preparation of other alkaloids of this series.

Moscow Institute of Fine
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Note: Figure translations are in progress. See original paper for figures.

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