A New Route for the Synthesis of Quinolizidine Derivatives

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Abstract

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Quinolizidine (norlupinane) derivatives constitute an important group of heterocyclic compounds, to which the alkaloids lupinine, lupanine, sparteine, anagyrine, cytisine, and others belong ([1]). Some of them possess clearly pronounced physiological activity and are used in medicine, for example as respiratory stimulants ([2,3]).

For constructing the quinolizidine system, reactions of intramolecular alkylation and acylation of piperidine derivatives are used; these derivatives are usually obtained from the corresponding pyridine compounds ([4]).

In the present work we have developed a new, simple route for the synthesis of quinolizidine derivatives from dihydroresorcinol according to the following scheme:

[reaction scheme]

In the hydrogenation of 2-methyl-2-(β-cyanoethyl)-dihydroresorcinol (I) over skeletal nickel in the presence of alkali, followed by treatment of the reaction product with acetic acid, apparently through the intermediate stages of hydrolytic cleavage (I $\rightarrow$ II), reductive cyclization (II $\rightarrow$ III), and intramolecular acylation (III $\rightarrow$ IV), 1-methyl-6-ketoquinolizidine (IV) is formed in high yield; its structure is confirmed by the IR spectrum* (presence of the lactam carbonyl band at 1643 cm^{-1}) ([5]). Reduction of 1-methyl-6-ketoquinolizidine (IV) with $LiAlH_4$ leads to the α-form of d,l-lupinine (V), characterized by a sparingly soluble picrate in methanol with m.p. 183–184° and an iodomethylate with m.p. 263–264°. The d,l-lupinine obtained by us has in the IR spectrum frequencies (2802 and 2759 cm^{-1}) characteristic of trans-quinolizidine compounds ([6]).

* The IR spectra ($CHCl_3$) were recorded by G. A. Kogan, to whom we express our gratitude.

Experimental Section

2-Methyl-2-(β-cyanoethyl)dihydroresorcinol (I) (b.p. 134-137° at 0.5 mm and n_D^{20} 1.4886) was obtained by the method developed by I. N. Nazarov and co-workers ([7]).

1-Methyl-6-ketoquinolizidine (IV). 16.9 g (0.094 mole) of 2-methyl-2-(β-cyanoethyl)dihydroresorcinol (I) in 100 ml of methanol was hydrogenated in the presence of 5.26 g (0.094 mole) of caustic potash and $\sim$ 1 g of skeletal nickel until three equivalents of hydrogen had been absorbed (80–85°, 85–70 atm., 12 hr). After removal of the catalyst and distillation of the methanol, the reaction product was boiled for 1.5 hr with 50 ml of acetic acid. The resulting solution was evaporated to dryness ($\sim$ 15 mm, 30–40°), the residue was treated with water and extracted with ether, giving 12.2 g (78%) of 1-methyl-6-ketoquinolizidine (IV), b.p. 99–103° at 0.8 mm and n_D^{20} 1.5095. Chromatography on alumina, activity II (elution with petroleum ether–benzene, 4 : 1, benzene, and benzene–methanol, 7 : 1) gave 8.8 g (55%) of 1-methyl-6-ketoquinolizidine, b.p. 88° at 0.5 mm and n_D^{20} 1.5085. R_f = 0.49 (chromatographic plate with Al_2O_3, activity II, benzene–acetone mixture, 1 : 1).

Found, %:	*C* 71.27; 71.45;	*H* 10.20; 10.10;	*N* 8.51; 8.34
$C_{10}H_{17}ON$. Calculated, %:	*C* 71.80;	*H* 10.10;	*N* 8.38

***d, l*-Lupinine (V).** To 1.7 g (0.04 mole) of $LiAlH_4$ in 250 ml of absolute ether was added 4.2 g (0.025 mole) of 1-methyl-6-ketoquinolizidine (IV) in 250 ml of absolute ether. The solution was boiled for 5 hr with stirring, then treated at 0–3° with 10 ml of ethyl acetate and, after 15 min of stirring at 20°, shaken with 7 g of $NaOH$ in 170 ml of water. From the ethereal layer there was isolated 3.2 g (84%) of *d, l*-lupinine (V), b.p. 64–65° at 7 mm and n_D^{20} 1.4815. R_f = 0.7 (chromatographic plate with Al_2O_3, activity II, benzene–acetone mixture 1 : 1).

Found, %:	*C* 78.52; 78.73;	*H* 12.40; 12.41;	*N* 9.13; 9.01
$C_{10}H_{19}N$. Calculated, %:	*C* 78.36;	*H* 12.50;	*N* 9.14

Picrate (yield 57%), m.p. 183–184° (from methanol).

Found, %:	*C* 50.46; 50.44;	*H* 5.73; 5.66;	*N* 15.11; 14.91
$C_{10}H_{19}N \cdot (NO_2)_3C_6H_2OH$. Calculated, %:	*C* 50.26;	*H* 5.80;	*N* 14.65

Iodomethylate, m.p. 263–264°.

Found, %:	*N* 4.59; 4.69
$C_{10}H_{19}N \cdot CH_3J$. Calculated, %:	*N* 4.75

The following constants are given in the literature for *d, l*-lupinine: b.p. 75–77°/11 mm, picrate of the α-form, m.p. 187° [8], 185° [9], 192–193° [10,11], picrate of the β-form, m.p. 163° [8,12].

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Note: Figure translations are in progress. See original paper for figures.