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THE ALKYLATION OF CYCLIC ENAMINES: A SYNTHESIS OF THE QUEBRACHAMINE SKELETON

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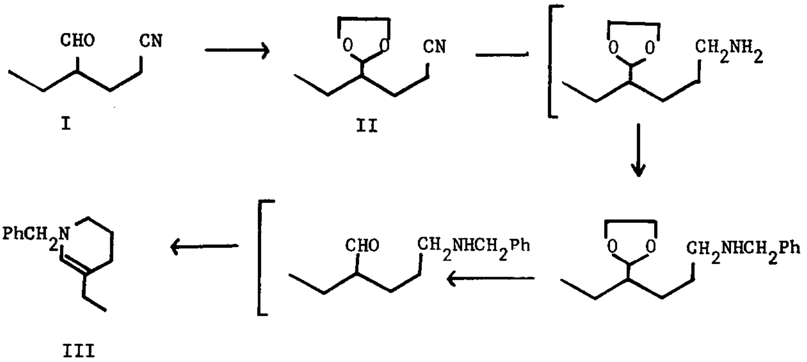
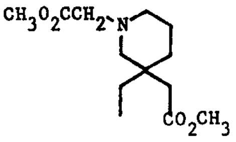
The cyclic enamine 1-benzyl-3-ethyl-1,4,5,6-tetrahydropyridine (III)[1] is of potential use as an intermediate in the synthesis of aspidosperma alkaloids. We have prepared this enamine and have transformed one of its alkylation products into a compound having the skeleton of quebrachamine (VIIIb)[2].

Cyanoethylation of 1-piperidino-1-butene[3] afforded α-(2-cyanoethyl)-n-butyraldehyde (I)[4] in 77% yield: bp 109-111° (10 mm); ir (film) 2725, 2250, 1725 cm^{-1}. Subsequent conversion to the ethylene glycol acetal II was achieved in 88% yield: bp 147-149° (20 mm); ir (film) 2250 cm^{-1}. Reduction of the nitrile function was accomplished with ethereal lithium aluminum hydride. Benzylation of the crude primary amine was realized by reductive alkylation with benzaldehyde in ethanol solution over 10% palladium on charcoal. Exposure of the crude benzylation product to normal aqueous hydrochloric acid for 18 hr followed by drying an ethereal solution of the hydrolysis products over anhydrous magnesium sulfate for 48 hr afforded the cyclic enamine III[6] in 56% yield (based on cyanoacetal): bp 91-94° (0.25 mm); ir (film) 1675 cm^{-1}; nmr (CCl_4) δ.95 (3H, t, J = 7 cps), 1.80 (6H,m), 2.60 (2H,m), 3.75 (2H,s), 5.60 (1H,s) and 7.20 (5H,s).

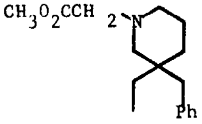


Alkylation of the cyclic enamine with methyl bromoacetate in methanol followed by reduction with sodium borohydride gave rise to a mixture of three tertiary amines upon distillation, bp 100-145° (0.6 mm). The amines were separated by vpc affording diester IV (2% yield): ir (CCl$_4$) 1735 cm^{-1}; nmr (CDCl$_3$) δ0.85 (3H,t,J = 7 cps), 1.20-1.80 (6H,m), 2.10-2.80 (6H,m), 3.25 (2H,s), 3.70 (3H,s) and 3.75 (3H,s), monester V (< 1% yield): ir (CCl$_4$) 1750 cm^{-1}; nmr (CDCl$_3$) δ0.90 (3H,t,J = 7 cps), 1.05-1.90 (6H,m), 2.20 (2H,s), 2.30-2.90 (4H,m), 3.10 (2H,s) 3.60 (3H,s) and 7.15 (5H,m) and the N-benzylamine VIa (22% yield): ir (CCl$_4$) 1735 cm^{-1}; nmr (CDCl$_3$) δ0.75 (3H,t,J = 7 cps), 1.20-1.70 (6H,m) 1.80-2.50 (6H,m), 3.35 (2H,s), 3.50 (3H,s) and 7.20 (5H,m).

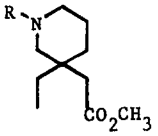
The mixture of tertiary amines was hydrogenated over 10% palladium on charcoal in ethanol containing hydrochloric acid to effect selective conversion of the N-benzylamine VIa to the secondary amine VIb.



IV

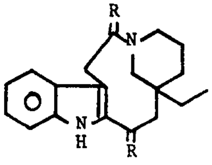


V



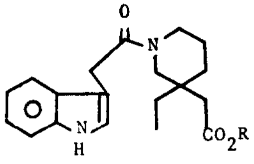
VI a, R = C$_7$H$_7$

b, R = H



VIII a, R = O

b, R = H$_2$



VII a, R = CH$_3$

b, R = H

Treatment of the hydrogenolysis mixture with 3-indolyl acetyl chloride[7] in a suspension of aqueous sodium carbonate-methylene chloride yielded a neutral, non-crystalline lactam ester VIIa: ir (film) 1735, 1640 cm^{-1}. Saponification with dilute sodium hydroxide (water-methanol) gave rise to the corresponding amorphous acid VIIb (44% yield based on the mixture of tertiary amines): ir 3500-2500, 1710, 1630 cm^{-1}. Exposure of the lactam acid to polyphosphoric acid[8] for 20 minutes at 90° afforded the ketolactam VIIIa in 85% yield: mp 231-233° (acetone), ir 1640 cm^{-1}, uv. $\lambda_{max}^{CH_3OH}$ 312 (17,700) and 245 (12,450) mμ[9].

Further investigations are in progress to explore the utility of the ketolactam in the synthesis of aspidosperma alkaloids.

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4. All liquids and crystalline solids gave satisfactory elemental analyses.
5. The hydrolysis products appear to be a complex mixture of amino-aldehyde, cyclic carbinolamine and cyclic enamine.
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