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The Synthesis of 6,7-Dehydroquebrachamine

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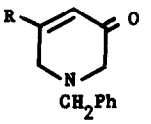
Numerous Aspidosperma alkaloids exist with unsaturation at the C_6-C_7 position[2] adjacent to the quaternary carbon center at C_5. In light of our previous approach to quebrachamine[3] it was apparent that the Claisen rearrangement would be well suited for simultaneously establishing the position of the double bond, the requisite quaternary center and the carbonyl functionality necessary for the elaboration of the quebrachamine skeleton. This Letter details this approach with a synthesis of 6,7-dehydroquebrachamine (6), a degradation product of tabersonine[4].

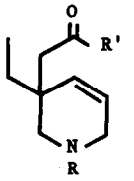
Alkylation of ethyl N-benzylglycinate with chloroacetone in aqueous tetrahydrofuran in the presence of sodium bicarbonate afforded the known ethyl N-acetonyl-N-benzylglycinate[5a] in 80% yield. Cyclization of this keto ester with potassium t-butoxide in t-butanol-ether gave rise to the crude diketone 1a[5b], which was directly treated with ethereal diazomethane to produce the enol ether 1b[6] in 38% yield. Treatment of the enol ether with ethereal ethyl magnesium bromide and subsequent aqueous acid hydrolysis produced the unsaturated ketone 1c, mp 89-89.5°, in 80% yield. Reduction of the unsaturated ketone with sodium borohydride in ethanol gave the corresponding allylic alcohol, which was subsequently converted to the olefinic amide 2a (45% yield from 1c) by refluxing in diglyme with dimethylacetamide dimethylacetal[7].

Having successfully achieved the desired substitution pattern, the benzyl group was removed with phenylchloroformate[8] to produce the urethan 2b, mp 66.5-67°, in 71% yield. Refluxing a mixture of the urethan and potassium hydroxide in methyl cellosolve followed by esterification with methanolic hydrogen chloride led to an oil whose nmr spectrum was consistent with structure 2c. Attempts to distill this material resulted in decomposition.

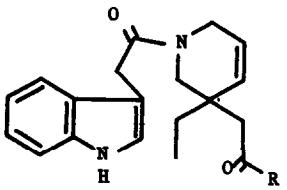
Acylation of the 2° amine 2c with β-indolylacetyl chloride[9] produced the neutral lactam ester 3a [ir($CHCl_3$) 1730 cm^{-1} and 1630] as an oil which was directly saponified to the corre-



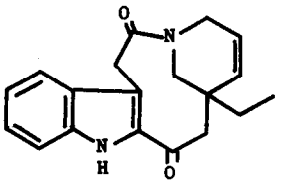
1 a, R=OH
b, R=OMe
c, R=Et



2 a, R=CH_2Ph , R'=NMe_2
b, R=CO_2Ph, R'=NMe_2
c, R=H , R'=OMe



3 a, R=OMe
b, R=OH



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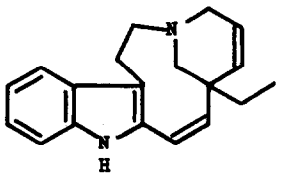

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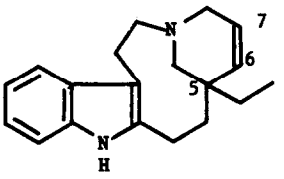

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sponding lactam acid 3b [ir($CHCl_3$) 1715 cm^{-1} and 1630]. The acid, obtained as an amorphous solid, was cyclized with polyphosphoric acid at 85°C affording the ketolactam 4, mp 225-6°, [ir($CHCl_3$) 1640 cm^{-1}; uv λ_{max}^{MeOH} 319 mμ(20,400) and 243(18,100)] in 28% yield from the urethan 2b. Hydrogenation of ketolactam 4 over 10% palladium on charcoal gave rise to the known dihydroketolactam[3].

Reduction of ketolactam 4 with lithium aluminum hydride in refluxing dioxane produced 3,4,6,7-dehydroquebrachamine (5), mp 151-152°, [ir($CHCl_3$) 3480 cm^{-1} (NH) and 3020 (cis C = C); uv λ_{max}^{MeOH} 291 mμ(6,820), 282(8,900), and 226(37,200); mass spec. m/e 278 (parent) and 249 (base)] and 6,7-dehydroquebrachamine (6) as an amorphous solid, (homogeneous on tlc) [ir

($CHCl_3$) 3480 cm^{-1} (NH), 3020 (cis C = C), 2830, 2760, and 2710 (trans bands); uv λ_{max}^{MeOH} 295 mμ (5,700), 287(6,200), and 231(30,750); mass spec., m/e 280 (parent) and 143 (base)]. Confirmation of the skeletal structure of 6 was achieved by catalytic hydrogenation to racemic quebrachamine, identical in all respects with a synthetic sample[3].

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