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CYCLOPROPANONE EQUIVALENTS FORMATION OF 1-PYRROLIZIDINONE BY A DICYCLOPROPYL IMINE REARRANGEMENT

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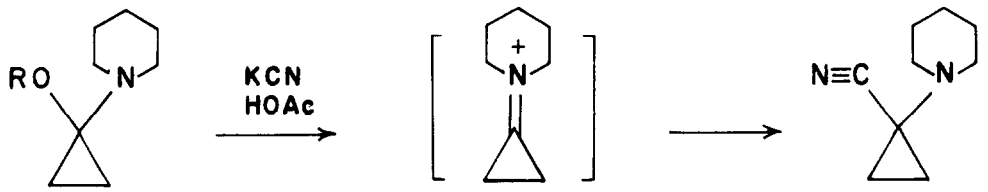
Summary A dicyclopropyl ketimine may be formed by the addition of cyclopropyllithium to 1-cyano-1-piperidinocyclopropane Rearrangement of the ketimine takes place under acid catalysis to form 1-pyrrolizidinone

In an earlier communication[1] we have shown that 1-hydroxy-1-piperidinocyclopropane (1a) or the corresponding trimethylsilyl ether (1b), both readily available from β-chloropropionyl chloride, may serve as convenient reagents for forming cyclopropane derivatives In this report we describe the use of these cyclopropanone equivalents for the attachment of two cyclopropyl residues to an imine function Ring expansions of this species through successive cyclopropyl imine rearrangements[2,3] permit a direct synthesis of the pyrrolizidine system

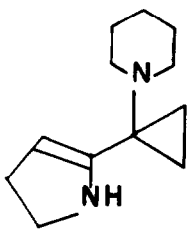


1 a, R = H
b, R = $SiMe_3$ 2 3

Treatment of 1 with KCN in the presence of aqueous acetic acid gave the nitrile (3), most probably by addition of cyanide to the iminium salt (2) [4] The yield of addition product (3) was somewhat better with the carbinol amine (1a) (73%) than with the silyloxy derivative (1b) (62%) The nitrile was then allowed to react with cyclopropyllithium in ether at -78°C followed by warming to 0° for 1h, after which $Na_2SO_4 \cdot 10H_2O$ was added The reaction mixture containing the dicyclopropyl ketimine was filtered, the ether removed, and the resulting oil identified as 4 by spectroscopic evidence IR (neat) 3190, 1618 cm^{-1}, 90 MHz ^1H NMR ($CDCl_3$) δ 2 40 (br t, 4H), 1 48 (br m, 7H), 1 04-0 60 (m, 9H), high resolution mass spectrum, Calcd for $C_{12}H_{20}N_2$ 192 163 Found 192 161.

The imine (4) was taken up directly into xylene and heated for 4h, whereupon it underwent transformation exclusively to the pyrroline (6) (78%). The conversion of 4 to 6 involves a cyclopropyl imine rearrangement to the enamine (5) followed by isomerization to the cyclic imine tautomer (6) While the rearrangement appeared to take place without addition of acid catalyst, the Kugelrohr-distilled ketimine (4) was completely unreactive when the xylene solution was heated to reflux in a reaction vessel which had previously been carefully washed with base Thes-

results and the work reported below confirm Stevens' earlier conclusions regarding the requirement for acid catalysis in the thermal rearrangement of cyclopropyl ketimines



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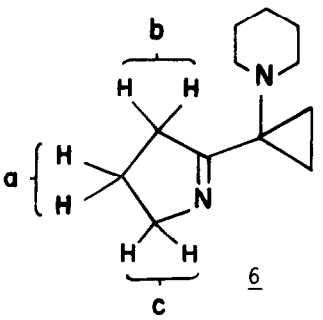

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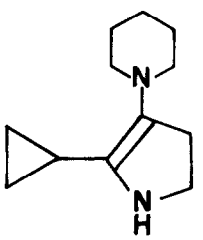

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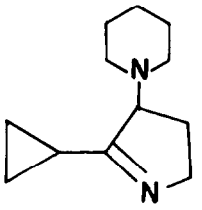

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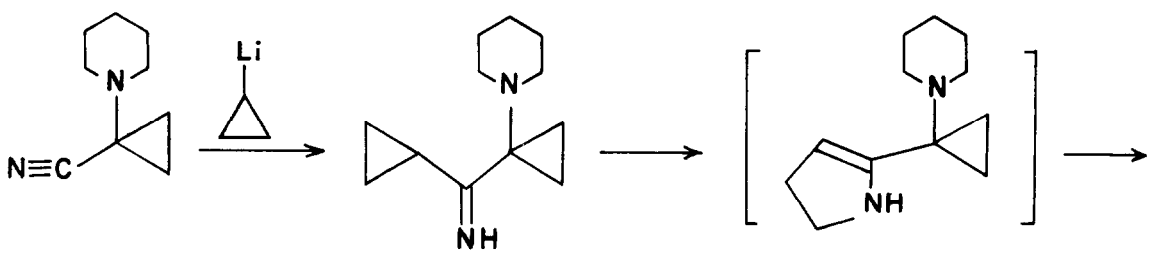
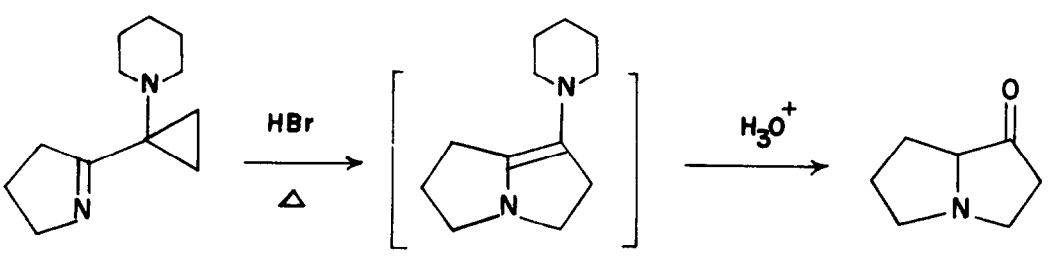
Proof of structure of 6 and unambiguous exclusion of the isomeric possibilities (5), (9) and (10), was provided by IR, and NMR spectroscopy.[5] In particular, the 500 MHz ^1H spectrum displays complex but discrete groups of resonances for methylene protons at positions b and c centered at δ 2 40 and 3.80, and a quintuplet at 1.82 corresponding to the protons at a Irradiation of the 1 82 signal (a) yields singlets at 2.40 and 3 80, irradiation of the 2.40 signal (b) yields triplets at 3 80 and 1.83, while irradiation of the 3 80 resonance (c) yields triplets at 1 82 and 2.40 All of the above evidence clearly establishes 6 as the structure of the rearrangement product

Scheme I

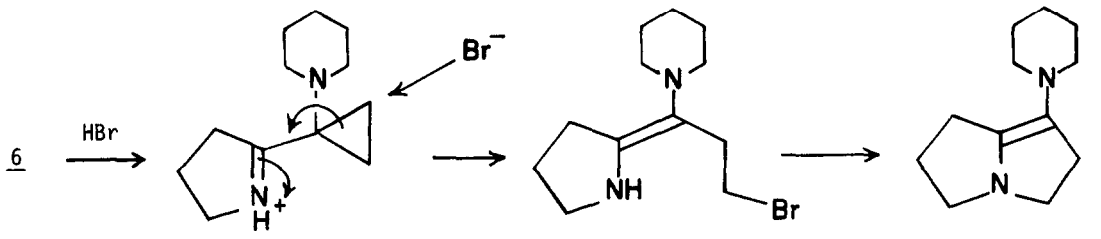


3 4 5



6 7 8

Prolonged heating of the pyrroline (6) in xylene did not lead to further ring expansion, but when it was converted to the hydrobromide salt with anhydrous HBr and then heated, neat, at 140° for 10 min, under nitrogen, a second cyclopropyl imine rearrangement took place (Scheme I) The product was the pyrrolizidinone (8)[6] (51%) We assume that the intermediate (7) underwent hydrolysis to 8 during dilute acid workup. It was possible to convert the nitrile (3) directly to the pyrrolizidinone (8) as follows After addition of 3 to cyclopropyllithium, and workup with Na_2SO_4 $10H_2O$, the resulting imine was treated *in situ* with anhydrous HBr, the solvent removed, and the salt heated under N_2 at 150° for 5 min Hydrolysis of the reaction mixture yielded 8 (30% from 3)



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The direct conversion of the imine (4) to the pyrrolizidinone (8) as well as the rearrangement of the pyrroline (6) to 8 may involve ring-opening of the cyclopropane ring by HBr, forming the intermediate (11) as shown [2] While the individual steps in the formation of 8 have precedent in the work of Stevens[2] and Pinnick,[3] the bis-ring expansion process is novel

A noteworthy feature of the formation of 6 from 4 is the exclusive participation of the *less substituted* cyclopropane ring in the formation of the pyrroline. This result is unexpected in the light of earlier findings of other investigators[7,8,9,10,11] on substituent effects in the *thermal* conversion of vinylcyclopropanes to cyclopentenes While it seems reasonable that cleavage of the more substituted ring in 4 would be favored by the enhanced stabilization of a carbonium ion intermediate, steric effects may play a dominant role in a process analogous to the cyclopropane ring opening in the conversion of 6→11, pictured above [12]

In our further work on the rearrangement of dicyclopropyl ketimines we plan to investigate substituent effects in promoting ring-opening at each stage of the double ring-expansion process We will also study the use of this sequence as a route to pyrrolizidines of interest in natural product synthesis

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5 IR (neat) 1625 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$) δ 3 80 (t of t, 2H), 2 82 (br t, 4H), 2 40 (t of t, 2H), 1 82 (m, 2H), 1 40 (br m, 6H), 0 96 (m, 2H), 0 87 (m, 2H), ^{13}C NMR (22 5 MHz, $CDCl_3$) δ 179 (s), 60 2 (t), 50 4 (t), 41 6 (s), 36.9 (t), 26 6 (t), 24 4 (t), 22 3 (t), 15 6 (m), MS m/e (%) 193 (12), 192 (92.7), 141 (100) Calcd for $C_{12}H_{20}N_2$ 192 163 Found 192.162

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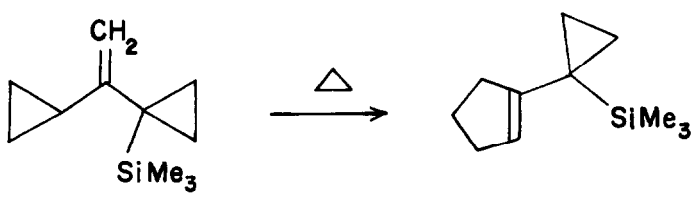
11 Paquette has recently observed that pyrolysis (570°C) of the dicyclopropylethylene (12) appears to take place exclusively through intermediate (13), presumably by a first-step cleavage of the less-substituted cyclopropane ring He notes that since α-silyl radicals are known to lack stabilization, the $SiMe_3$ group may exert a rate-retarding effect on the rupture of the cyclopropyl ring L A Paquette. G J Wells, K A Horn and T -H Yan, *Tetrahedron Lett*, in press



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