CONVERSION OF CAPROLACTAM TO EIGHT-MEMBERED ENE-LACTAM[1]

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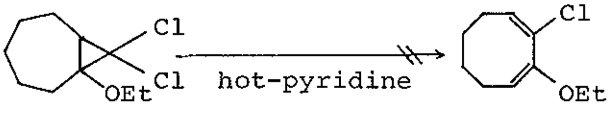
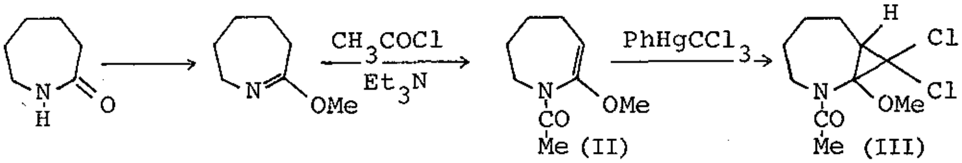
Dichlorocarbene adduct of N-acetyl ketene-O,N-acetal(II) derived from caprolactam afforded the homologous ene-lactam on $LiAlH_4$ reduction followed by base treatment.

On the assumption that addition of dichlorocarbene or its congeners to the carbon-nitrogen double bond of the cyclic imino ether followed by cleavage of the resulting aziridines would afford the ring enlargement products of the original lactams, reaction of the imino ether from piperidone with $PhHgCCl_3$[2] was undertaken but the products resulted from the introduction of 2 or 3 molar equi of the CCl_2 unit to the former were only obtained . Since this difficulty is obviously associated with a basic charactor of the starting imino ether, the N-masked ketene-O,N-acetal(II)[3] derived from the corresponding imino ether was chosen as a substrate. Since the bicyclo[5.1.0]octane(I) is reported to be resistant to hot pyridine treatment[4], the expected adduct(III) having comparable structure with I is also considered to be stable enough to its formation condition. However, when once N-protecting group is removed, the resulting dichlorocyclopropane derivatives substituted with two hetero atoms would have enough potential to cleave to the otherwise difficultly accessible unsaturated eight-membered lactam.

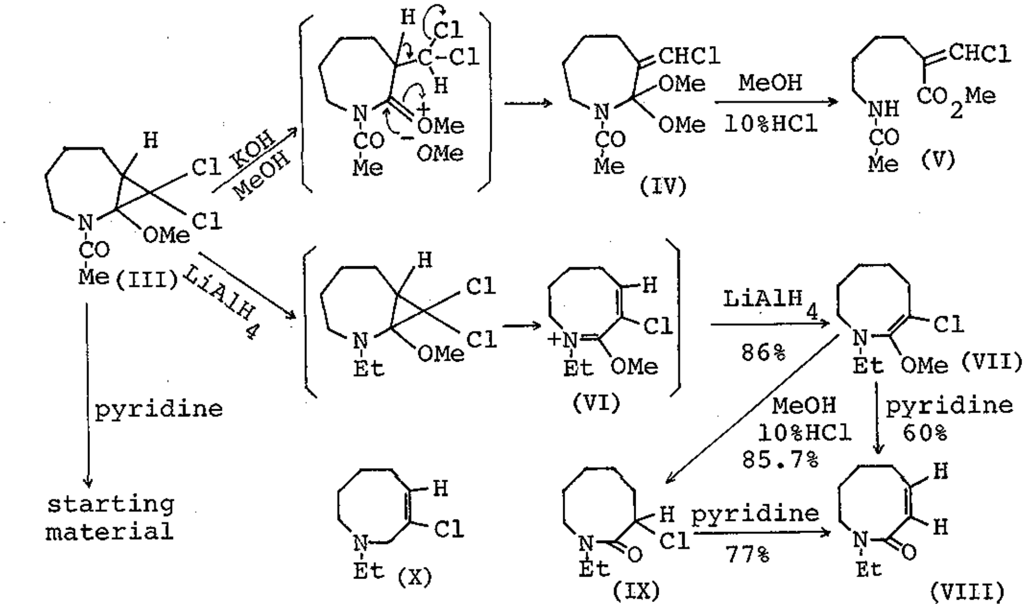


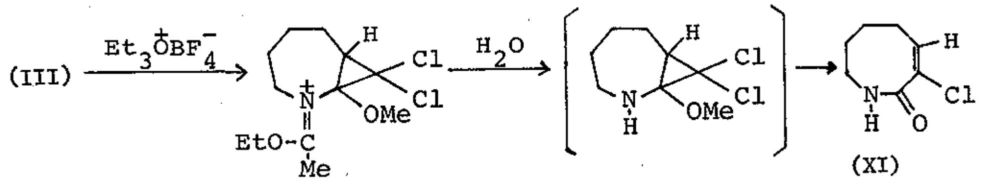
(I)



When II was refluxed with a molar equiv of $PhHgCCl_3$ in benzene for 60 hr, the desired adduct(III) was obtained as a viscous oil(bp_{3-4}140-3°)(23%) along with the recovered starting material(46%). The mass spectrum of III revealed a series of peaks characteristic of the chlorine containing compound[m/e 216, 218 (intensity ratio, 3:1); m/e 208,210, 212(10:6.5:1)], which are consistent with the assigned structure.

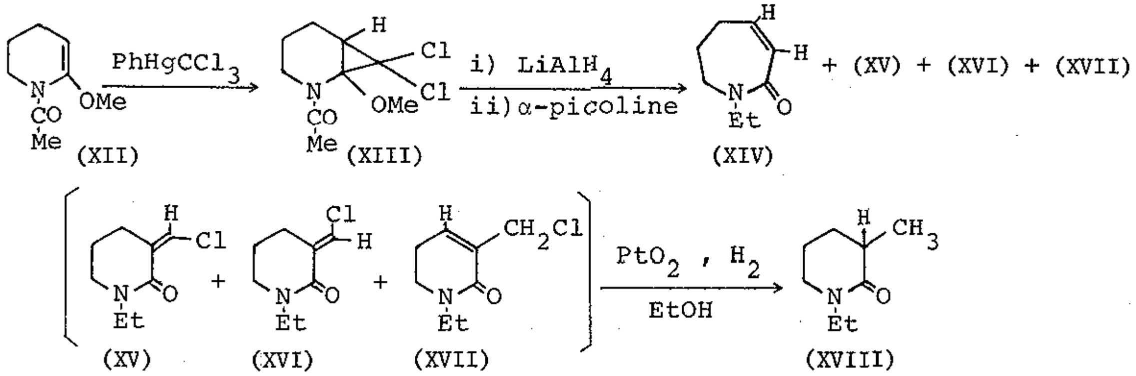
Then, rearrangement of the adduct(III) was investigated. The adduct(III) did not react with hot pyridine as expected. However, when it was treated with 10% KOH-MeOH at room temperature, cleavage did take place but only the seven-membered imide acetal(IV) [nmr(CCl_4) δ 6.5(1H, s, $\rangle\!\!=\underset{H}{C}-Cl$)] was obtained in high yield. Hydrolysis of IV with 10% HCl-MeOH afforded the amide ester(V)[nmr(CCl_4) δ 7.2 (1H, s, $-\underset{O}{\overset{\|}{C}}-\overset{|}{C}=\underset{H}{C}-Cl$)]. On the other hand, reduction of III with $LiAlH_4$ in THF at room temperature afforded the homologous ketene-O,N-acetal(VII)(86%), which without purification was gently refluxed in pyridine to yield the desired eight-membered unsaturated lactam(VIII), a viscous oil[$bp_6$140°(bath), nmr(CCl_4) δ 5.56 (1H, d, J=12 Hz, $-\underset{O}{\overset{\|}{C}}-\underset{\underline{\underline{H}}}{C}=\underset{H}{C}-$) ; 5.90(1H, dt, J=12, 5 Hz, $-\underset{O}{\overset{\|}{C}}-\underset{H}{C}=\underset{\underline{\underline{H}}}{C}-$)],in 60% yield. The structure VIII was confirmed by the double-resonance technique. Hydrolysis of VII with 10% HCl-MeOH followed by base treatment produced also VIII via IX. Formation of VII clearly shows that the unmasking of the N-protective group facilitated the cleavage of the cyclopropane ring and 1,4-hydride addition took place on the resulting VI. The fact that compound X could not be detected was unexpected. Ethylation of III with $Et_3O^+BF_4^-$ followed by hydrolysis under ice cooling gave the N-unsubstituted olefinic lactam(XI)[mp.98-102°, nmr (CCl_4) δ 6.28(1H, t, J=7 Hz, $-CH_2-\underset{H}{C}=\underset{Cl}{C}-\underset{O}{\overset{}{C}}-$)] although the yield was poor.





The above method was then applied to the ring enlargement of piperidone. Although dichlocarbene adducts of cyclohexanone morpholine or piperidine enamine was reported to rearrange thermally without expansion of the ring[5], it seemed worthwhile to apply this method for the homologation of piperidone since additional effect by methoxy group is expected in the present system. However although dichlorocarbene addition to XII proceeded in high yield(73%) affording

XIII, the desired seven-membered unsaturated lactam(XIV), an oil[nmr($CDCl_3$) δ 5.95(1H, dt, J=12, 1 Hz); 6.21(1H, dt, J=12, 5 Hz)], was obtained only in 9 % yield by the same $LiAlH_4$ reduction and the subsequent base treatment. The chlorine containing products, XV, XVI, and XVII, still holding six-membered ring, were obtained in a ratio of ca 1:1:1 as a mixture. The presence of these compounds was suggested by the appearance of three splitted peaks in the olefinic reagion(total, 1H) and their structures were deduced from the finding that catalytic hydrogenation over PtO_2 in ethanol at 3 atm. pressure afforded XVIII as a sole product. The structure XVIII was confirmed by the comparison of ir spectrum with that of the authentic sample prepared by the unequivocal method.



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