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REDUCTIVE N-CYCLIZATION OF LACTAMOESTERS

W. J. Rodewald and J. W. Morzycki
Institute of Fundamental Problems of Chemistry
University of Warsaw, 02093 Warszawa, Poland

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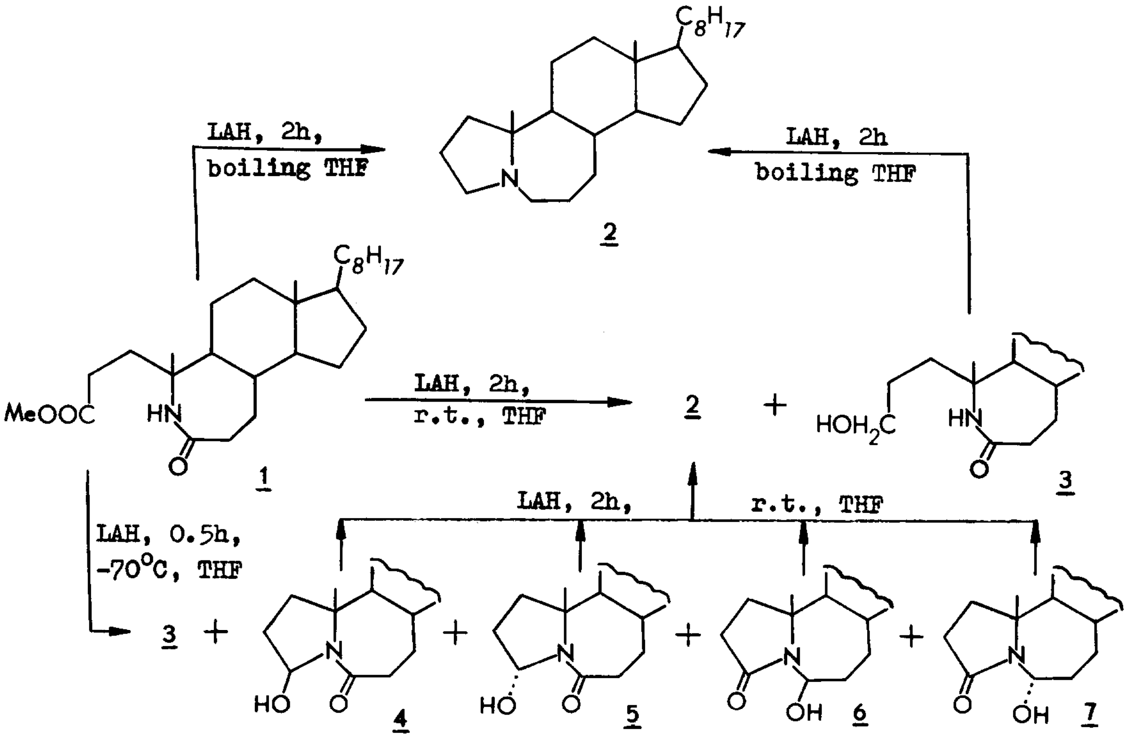
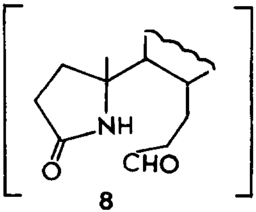
During our investigations on 5-azasteroid 1,2) synthesis the problem of lactam carbonyl reduction arose. Our previous experiments indicated that the carbonyl groups of A-seco-lactams are usually resistant towards lithium-aluminium hydride (LAH), whereas imides with the closed ring A are easily reduced to the corresponding amines. On the other hand, it has been established 3) that in a number of cases lactamoesters of type 1 undergo a reductive N-cyclization to give respective 5-azasteroids 4).

In the present communication we report the results of our studies on the course of reductive N-cyclization of lactamoester 1 during the LAH reduction.

The starting lactamoester 1 (m.p. 155.5-156.5°C,$[\alpha]_D^{25}$ +53.6°) 5), treated with LAH 6) in boiling THF, afforded a single product, A-nor-B-homo-5-azacholestane 2 (m.p. 60-61°C,$[\alpha]_D^{25}$ -23.0°, lit.7)m.p. 60-61°C,$[\alpha]_D^{15}$ -23.0°) in 91% yield. However, the same reaction carried out at -70°C (dry ice - acetone) yielded a mixture of five compounds (TLC), which were separated by silica-gel column chromatography. The most polar product was a known compound, A-seco-lactamo-alcohol 3 (18%, m.p. 153-155°C,$[\alpha]_D^{25}$ +47.6°, lit.8)m.p. 151°C,$[\alpha]_D^{21}$ +45.2°). Four others were identified as isomeric hydroxylactams 4, 5, 6 and 7. Their structure was established by IR, ^{1}H-NMR and MS spectra. The position of the lactam carbonyl group in 5- or 7-membered ring followed from its IR-bands. The assignement was corroborated by the electron impact fragmentation of compounds 4, 5, 6 and 7. The configuration of hydroxyl group was deduced from the ^{1}H-NMR spectra. The relevant spectral data and physical constants have been collected in Table 1.

The anomeric relation of 6 and 7 was confirmed by their equilibration. While heated separately in boiling heptane for 10 minutes, compounds 6 and 7 gave the same mixture of these two epimers in the ratio 45:55. The reaction probably proceeds *via* an intermediate lactamoaldehyde 8. It has to be noticed that hydroxylactams 4 and 5 did not equilibrate under the foregoing conditions.





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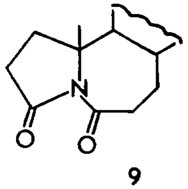

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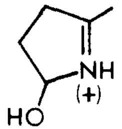
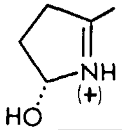
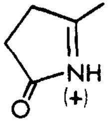
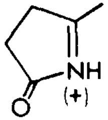
Each hydroxylactam (4, 5, 6 and 7), oxidized with RuO_4, gave the same known compound, imide 9 (m.p. 179°C, $[\alpha]_D^{25}$ +75.8°, lit.[7] m.p. 179-180°C, $[\alpha]_D^{21}$ +90.5°) in 80-90% yield. It can be assumed that imide 9 is formed as an intermediate during the reduction of lactamoester 1. This is suggested by the appearance of compounds with a carbonyl group in ring A and a hydroxyl group in ring B (6 and 7) among the reaction products.

T A B L E I

Compd No	Yield	m.p.	$[\alpha]_D^{25}$ (CCl_4)	IR ν_{max}^{KBr} (cm^{-1})		PMR (δ) (CCl_4)				MS
				O-H	C=O	18-$\underline{H}$	19-$\underline{H}$	-O$\underline{H}$	-C$\underline{H}$-OH	
<u>4</u>	7%	113°C (heptane)	+80.1° (c 0.44)	3403	1613	0.72	1.42	4.90	5.40 (m, $\frac{W}{2}$=12Hz)	m/e 403 M^+ (11%)  m/e 100 (100%)
<u>5</u>	30%	121-122°C (acetone)	+26.6° (c 0.47)	3414	1628	0.73	1.31	4.17	5.56 (m, $\frac{W}{2}$= 7Hz)	m/e 403 M^+ (14%)  m/e 100 (100%)
<u>6</u>	27%	159-160°C (ether-hexane)	+41.8° (c 0.47)	3319	1683	0.74	1.48	4.56	5.48 (m, $\frac{W}{2}$=21Hz)	m/e 403 M^+ (1%)  m/e 98 (100%)
<u>7</u>	3%	148.5-150°C (ether-hexane)	+30.4° (c 0.52)	3308	1695	0.71	1.28	4.28	5.25 (m, $\frac{W}{2}$= 8Hz)	m/e 403 M^+ (1%)  m/e 98 (100%)

All hydroxylactams 4, 5, 6 and 7 which were formed during the reduction of lactamoester 1 at the temperature -70°C underwent at room temperature a further reduction with LAH to A-nor-B-homo-5-azacholestane (2) as the final product in a very good yield. On the other hand, compound 3 was proved to be almost completely resistant towards LAH at room temperature. This explained the result of lactamoester 1 reduction at room temperature, when A-seco-lactamoalcohol 3 was formed in 14% yield in addition to the main product 2 (78%). At the boiling point of THF the reduction of compound 3 to 5-azasteroid 2 took place in high yield. The results of investigations on reduction of compounds obtained during the reaction of 1 with LAH at the temperature -70°C offer a unequivocal explanation of lactamoester 1 reduction at the boiling point of THF.

The process carried out at low temperature makes possible to obtain derivatives functionalized in α-position relative to nitrogen, this being, *inter alia*, the subject of our further investigations.

References and Notes

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