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A REMARKABLY REGIOSELECTIVE REDUCTION OF gem-DISUBSTITUTED SUCCINIMIDES

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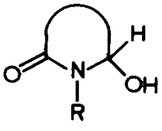
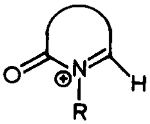
$NaBH_4/H^{\oplus}$ reduction of cyclic imides afforded quantitatively the α-carbinollactams 1.[1)] The latter class of compounds may be considered as precursors of the reactive cyclic acylimmoniumions 2 in a novel extension of the well-known α-amido alkylation.[2)] In particular the synthesis of a great number of condensed heterocyclics can be achieved in quantitative yields by a proper choice of the nitrogen substituent R.[3)] In addition the introduction of ring substituents coupled with a preferential reduction pattern would allow direct synthesis of different types of alkaloidal compounds. When a series of selected mono- and disubstituted succinimides was reduced a dramatic increase in regioselectivity has been uncovered thus expanding the scope of this method considerably. Upon introducing two relatively bulky substituents at C-3, a completely regioselective reduction occurs at C-2 as is shown in the table:



1



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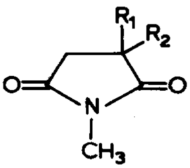

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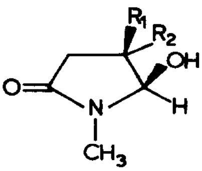
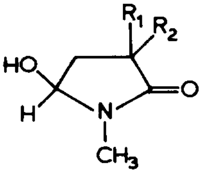


4A



4B

3^{a}	R_1	R_2	%4A^{b,c,d}	%4B^{b,d}	M.p.°C	$\delta_{H,OH}$ in 4A^{e}
a	CH_3	H	60	40	-	-
b	C_6H_5	H	40	60	-	-
c	CH_3	CH_3	75	25	-	4.55
d	C_6H_5	CH_3	60	40	-	4.99
e	C_6H_5	C_6H_5	100	-	173 - 175°	5.65
f	C_6H_5	$CH_2C_6H_5$	100	-	185 - 188°	5.10 (DMSO)
g	C_6H_5	$CH_2\text{-}NC_4H_8$	100	-	-	5.69
h	C_6H_5	$CH_2NC_5H_{10}$	100	-	-	5.69
i	C_6H_5	$CH_2\text{-}\underset{H}{N}C_4H_8O$	100	-	168 - 170°	5.53
j	C_6H_5	$CH_2\text{-}C{=}\underset{Cl}{C}\text{-}CH_3$	100	-	134 - 136°	5.15

a) Prepared according standard procedures

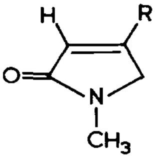
b) Yields of 4A and 4B determined by PMR analysis

c) The pure compounds listed gave correct analytical data

d) Combined yield quantitative

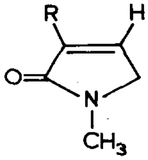
e) Measured in $CDCl_3$ except when otherwise stated

The product ratio of the reduced compounds starting from imides 3a and 3b was separately confirmed by quantitative conversion (HOAc/reflux) into mixtures of pyrrolidinones 5A and 5B, respectively 6A and 6B and PMR-integration of the olefinic proton signals which were found in 5A at δ5.81 p.p.m.[4], in 5B at δ6.65 p.p.m., in 6A at δ6.45 p.p.m. in 6B at δ7.17 p.p.m.



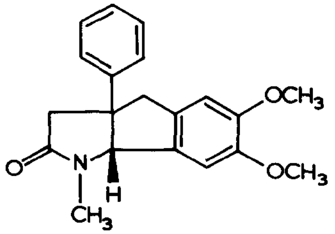
5A R=CH_3

6A R=C_6H_5



5B R=CH_3

6B R=C_6H_5



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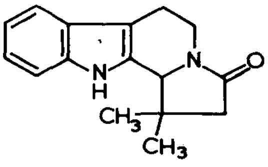

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This finding can be most conveniently applied in the synthesis of substituted heterocyclics. For instance $NaBH_4/H^{\oplus}$ reduction of 3 ($R_1=C_6H_5$, $R_2=CH_2$-di-OMe-C_6H_5) and subsequent ring closure led to 7 in 83% yield. 3-[β-(3',3'-dimethyl-succinimidyl)-ethyl]-indole afforded in the same manner 8 in 73% yield. Furthermore new syntheses of mesembrine and physostigmine have been realized which will be communicated separately.

Apart from the complete regioselectivity the reduction appears to be also stereospecific as was demonstrated by the formation of single stereoisomers in the reductions of 3f-3j. This unique stereospecifity could also be proven by chemical conversion. For instance the reduction product of 3f upon HCl-EtOH treatment underwent OH → OEt conversion into a 2:1 mixture of two stereoisomeric ethoxyderivatives which upon treatment with a silica-alumina catalyst5) in dioxane-water were converted back into 3f + its OH-stereoisomer (ratio 2:1).

Although definite proof is lacking, the observed pattern in the reduction of unsymmetrically substituted imides may be rationalized in terms of a different electronic character of the two carbonyl groups. Presumably as a result of steric interactions one carbonyl group is tilted out of the plane of the remaining amide bond and overlaps less effectively with the nitrogen lone pair. The decrease in amide character naturally governs the course of the reduction while the function of the added $H^{\oplus}$ may be rate accelerating6,7) at the same time suppressing the undesired ring opening of the intermediate oxyanion by lowering of the PH.

Further studies on the actual reduction mechanism will be presented in our full papers.

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