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A REGIOSELECTIVE REDUCTION OF *GEM*-DISUBSTITUTED SUCCINIMIDES

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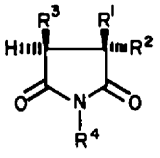
Abstract—The $NaBH_4$ reduction of mono- and disubstituted succinimides in the presence of hydrochloric acid leading to ω-carbinol-lactams shows a remarkable regio- and/or stereo-selectivity. The reduction takes place at the most substituted CO in the succinimides. Possible explanations are reviewed. The preparative value of the method is amply illustrated.

$NaBH_4/H^+$ reduction of cyclic imides has been shown to afford ω-carbinol-lactams in high yields via a simple experimental procedure.[2] The latter compounds are of interest as valuable synthetic intermediates in the synthesis of a great number of heterocyclic compounds including alkaloids[3] and may be regarded as cyclic α-amido-alkylation reagents.

In order to examine more closely the regio- and/or stereo-selectivity of the $NaBH_4/H^+$ reduction a number of substituted succinimides were subjected to the general reduction procedure, the results of which are reported herein.[4]

A series of representative succinimides **1a–1z** were selected and prepared for the greater part according to standard procedures (Experimental).

The ring substituents were chosen on the basis of an anticipated steric influence on the reaction course. A standard reduction technique was applied to all cases investigated which effected conversion of a single CO group into a hydroxy- or alkoxy function. Both the ratio



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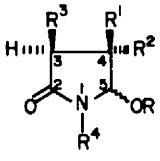

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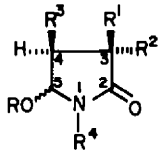
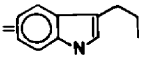


3

	2	3	
a: $R^1 = CH_3$	$R^2 = H$	$R^3 = H$	$R^4 = CH_3$
b: $R^1 = Ph$	$R^2 = H$	$R^3 = H$	$R^4 = CH_3$
c: $R^1 = p\text{-MeOPh}$	$R^2 = H$	$R^3 = H$	$R^4 = CH_3$
d: $R^1 = p\text{-}NO_2Ph$	$R^2 = H$	$R^3 = H$	$R^4 = CH_3$
e: $R^1 = o\text{-}NO_2Ph$	$R^2 = H$	$R^3 = H$	$R^4 = CH_3$
f: $R^1 = CH_3$	$R^2 = CH_3$	$R^3 = H$	$R^4 = CH_3$
g: $R^1 = Ph$	$R^2 = CH_3$	$R^3 = H$	$R^4 = CH_3$
h: $R^1 = o\text{-}NO_2Ph$	$R^2 = CH_3$	$R^3 = H$	$R^4 = CH_3$
i: $R^1 = o\text{-}NO_2Ph$	$R^2 = CH_2Ph$	$R^3 = H$	$R^4 = CH_3$
j: $R^1 = Ph$	$R^2 = CH_2Ph$	$R^3 = H$	$R^4 = CH_3$
k: $R^1 = Ph$	$R^2 = CH_2Ph\text{-}3,4diMeO$	$R^3 = H$	$R^4 = CH_3$
l: $R^1 = Ph$	$R^2 = CH_2CH{=}C(Cl)CH_3$	$R^3 = H$	$R^4 = CH_3$
m: $R^1 = Ph$	$R^2 = Ph$	$R^3 = H$	$R^4 = CH_3$
n: $R^1 = Ph$	$R^2 = CH_2N(CH_2)_4$	$R^3 = H$	$R^4 = CH_3$
o: $R^1 = Ph$	$R^2 = CH_2N(CH_2)_5$	$R^3 = H$	$R^4 = CH_3$
p: $R^1 = Ph$	$R^2 = CH_2N$⟨O⟩	$R^3 = H$	$R^4 = CH_3$
q: $R^1 = H$	$R^2 = CH_3$	$R^3 = CH_3$	$R^4 = CH_3$
r: $R^1R^3 = -(CH_2)_4-$	$R^2 = H$		$R^4 = CH_3$
s: $R^1R^3 = -CH_2CH{=}CHCH_2-$	$R^2 = H$		$R^4 = CH_3$
t: $R^1 = Ph$	$R^2 = H$	$R^3 = Ph$	$R^4 = CH_3$
u: $R^1 = H$	$R^2 = Ph$	$R^3 = Ph$	$R^4 = CH_3$
v: $R^1 = Ph$	$R^2 = H$	$R^3 = H$	$R^4 = H$
w: $R^1 = Ph$	$R^2 = Ph$	$R^3 = H$	$R^4 = H$
x: $R^1 = CH_3$	$R^2 = CH_3$	$R^3 = H$	$R^4 = H$
y: $R^1 = CH_3$	$R^2 = CH_3$	$R^3 = H$	$R^4 = Ph$
z: $R^1 = CH_3$	$R^2 = CH_3$	$R^3 = H$	$R^4 =$ 

of stereoisomers and the regioselectivity were determined preparatively (in part) and by ^{1}H NMR. In some monosubstituted succinimides the values so obtained were independently controlled by conversion into the corresponding 3-pyrrolin-2-ones via elimination of H_2O (or EtOH) under influence of acid. The results are collected in Table 1.

Table 1. $NABH_4/H^+$ reduction of succinimides **1a–1p** and **1v–1z**

Compound	% 2 (R = H or Et)†	% 3 (R = H or Et)†
1a	59	41
1b	40	60
1c	45	55
1d	62	38
1e	17	83
1f	79	21
1g	63	37
1h	87	13
1i	100‡	—
1j	100‡	—
1k	100‡	—
1l	100‡	—
1m	100‡	—
1n	85	15
1o	100‡	—
1p	100‡	—
1v	40	60
1w	100‡	—
1x	83	17
1y	83	17
1z	73	27

†Product ratio were determined on the crude reaction products.

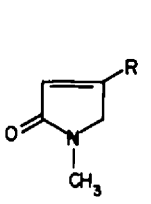
‡Small amounts (<5%) of the isomeric hydroxy (alkoxy) lactams **3** may be present.

RESULTS AND DISCUSSION

Regioselectivity. To obtain information on the role of substituents on the selectivity of the reduction two categories of succinimides were selected: the 3-mono (**1a–1e** and **1v**) and 3,3-disubstituted succinimides (**1f–1p** and **1w–1z**). Reduction and work-up (method A or B, see experimental) of **1a** gave a mixture of the ω-carbinol-lactams **2a** (59%) and **3a** (41%) which was not separated but directly converted into the corresponding 3-pyrrolin-2-ones **4** and **5**. ^{1}H NMR ($CDCl_3$) integration of the latter mixture confirmed its composition. H_3 in **4** was found at δ 5.81 and H_4 in **5** at δ 6.65. This product ratio is in closed correspondence with the results of Ohki.[5]

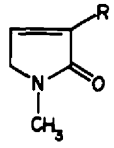
On the contrary substitution of the Me-group by a phenyl favored the reduction to occur at the less substituted side. A mixture of **2b** (40%) and **3b** (60%) was obtained the composition of which was also independently determined by acid-catalyzed conversion to a mixture of **6** and **7**. In the ^{1}H NMR of the latter compound the characteristic downfield shift of both *o*-aryl protons as a result of the magnetic anisotropy of the neighbouring lactam-CO also confirmed the structural assignment. Introduction of a substituent in the aromatic ring considerably affected the product ratio of **2**:**3** depending on the nature and place of the substituent. In case of **1c** (R^1 = *p*-MeOPh) the product ratio was **2c**:**3c** = 45:55. On the other hand introduction of a *p*-NO_2 group (**1d**) showed a product ratio of **2d**:**3d** = 62:38. Elimination of H_2O (EtOH) from the reduction products of **1c** progressed smoothly in refluxing EtOH in presence of HCl giving **8** and **9**. The same procedure failed in case of **1d** only decomposition being observed. However, when the reduction products of **1d** were stirred in formic acid at room temperature a mixture of three compounds was formed.

According to ^{1}H NMR ($CDCl_3$) the mixture was com-

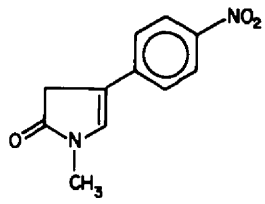


4,6,8,10

4,5: R = CH_3
6,7: R = Ph
8,9: R = p-CH_3OPh
10,11: R = p-NO_2Ph



5,7,9,11



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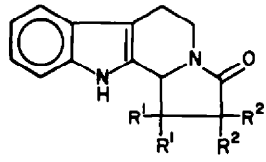
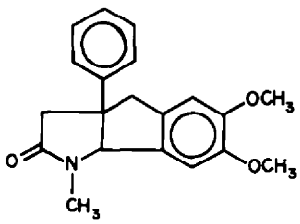


13: R^1 = CH_3, R^2 = H
14: R^1 = H , R^2 = CH_3



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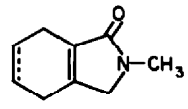
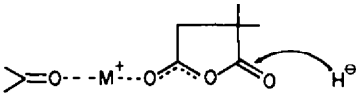


16
17: 5,6 dehydro

posed of **10** (47%), **11** (38%) and **12** (15%). Column chromatography and recrystallization afforded moderately stable **10** and **11**. It was not possible, however, to isolate **12** in pure form because of contamination with decomposition products of **10**. Introduction of the *o*-NO_2 group dramatically changed the product ratio. Reduction of **1e** (R^1 = *o*-NO_2Ph) gave **2e** (R = H) and **3e** (R = H) in a ratio of 17:83. In the latter case the observed a difference in the reduction pattern is probably due to some form of dipole interaction beween the NO_2 group and the neighbouring CO.

Upon introduction of a second C_3-substituent the regioselectivity is markedly improving. While the 3,3-dimethyl- and 3-methyl-3-phenyl-derivatives **1f** and **1g** already show a clear effect the reduction of derivatives **1h–1p** proceeds almost completely at the most substituted CO (Table 1). In addition a high degree of stereoselectivity is observed only one stereoisomer being isolated. Thus the introduction of two relatively large substituents at a single carbon atom in succinimides effectively governs the course of the reduction, almost independent of the chemical nature of the substituent. Some reductions were carried out also with KBH_4. The results of this latter reduction process showed exactly the same product ratios as found in the $NaBH_4$ reduction.

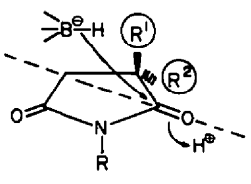
In order to explain the foregoing result a hydride transfer according to a linear mechanism[6] is most likely the course of which is determined by steric hindrance of the ring substituents. Furthermore the rate of the reduction is highly dependent on the addition of acid. A mechanism in which the less hindered carbonyl of a nonsymmetrical cyclic anhydride complexes with the reagent cation and a CO from a second mole of substrate followed by hydride transfer to the more hindered CO[7] seems unlikely.



Although the latter mechanism eventually might account for the observed regioselectivity of the imide reduction it fails to give an answer for the activation by acid. Furthermore it does not account for the similarity of the results of the KBH_4 reduction.

Also our first hypothesis[4] in which the regioselectivity was rationalized on the basis of a different electronic character of the two CO groups as a result of steric interactions has recently been shown to be incorrect.

X-ray measurements carried out with **1j** show the complete coplanarity of the imide CO groups.[8] Therefore a mechanism based on a general proposal for nucleophilic addition to CO groups[9] offers a satisfactory explanation. The hydride ion approaches via the less hindered CO and adds to the C atom of the more hindered one virtually along a straight line through the C–O bond. In the latter explanation the steric demands of the R^1 and R^2 substituents will effectively govern the stereochemistry of the reduction process.



Although the mechanism does not cover all our results it gives a reasonable explanation for the observed regio- and stereo-selectivity.

As was mentioned earlier[2b] the reduction of unsubstituted succinimides in absence of H^+ proceeds sluggishly and incomplete while the majority of the products consists of ring opened material. In case of unsymmetrically ringsubstituted imides, such as **1m**, however, the reduction without acid gave in nearly quantitative yield **2m** (R = H) after stirring at 0° for 40 hr. These results establish that H^+ activates the imide C=O and inhibits ring opening the latter process being also disfavored by the presence of ring substituents.[10] Furthermore the regioselectivity is not affected by omitting the use of acid.

The nature of the N-substituent has only a minor effect on the determination of the regioselectivity of the $NaBH_4/H^+$ reduction. This is demonstrated by the reduction of **1v** and **1w** which compared to **1b** and **1m** gave almost similar product ratios. Also the reduction of **1x–1z** compared to **1f** showed an analogous pattern (Table 1).[11]

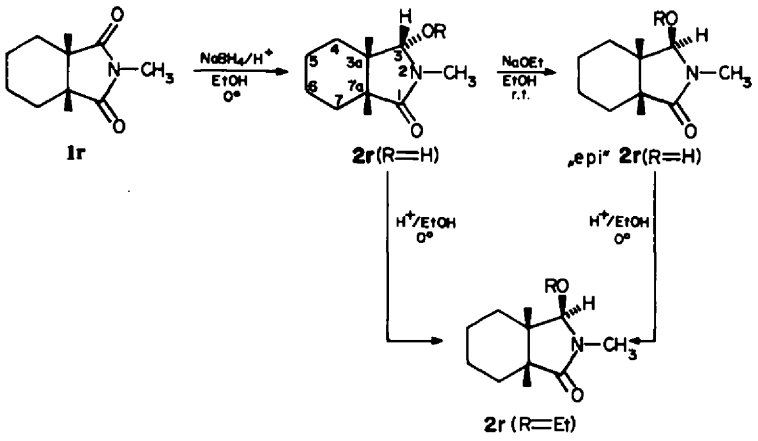
Since other borohydride systems ($NaBH_3CN$,[12] $NaBH_4$/HOAc[13]) failed to reduce imides the $NaBH_4/H^+$ procedure is the preferred method for the synthesis of substituted ω-carbinol-lactams. A different way of synthesizing alkoxylactams was reported recently.[14]

O-alkylated imides prepared by the corresponding imide-Ag salts and ethyl iodide were reduced at room temperature with $NaBH_4$/EtOH to ethoxylactams in good yield. However, this method is restricted to N–H imides solely. Application of this technique to unsymmetrical imides gave in case of **1w** a mixture of **2w** (R = Et) (64%) and **3w** (R = Et) (36%) and in case of **1x** a mixture of **2x** (R = Et) (54%) and **3x** (R = Et) (46%). From the results it appears that a similar pattern is observed as for the $NaBH_4/H^+$ reduction, albeit with much lower regioselectivity.

The observed regioselectivity effect is of vital importance for practical applications of the method, e.g. in the synthesis of unsymmetrically substituted and N-condensed indoloalkaloids. Thus reduction and subsequent cyclization of **1z** provides a mixture of **13** (73%) and **14** (27%) easily separable via column chromatography. A second category of polyheterocyclics which can be synthesized is represented by the HCl/MeOH cyclization of **2k** affording **15** in good yield. Furthermore new syntheses of mesembrine,[15] dihydromaritidine[16] and physostigmine[17] have been realized which will be communicated separately.

Stereochemical course. Although no definite proof exists for the position of H_5 in the reduced compounds **2j–2p** (R = H) it is most likely to assume preferential hydride attack from the least hindered side. Pertinent information with regard to this question, however, could be obtained from reduction of selected 3,4-disubstituted succinimides **1q–1u**. The bicyclic derivatives **1r** and **1s** gave single stereoisomers **2r** (R = H), m.p. 107–108°C (EtOH), ^{1}H NMR δ ($CDCl_3 + D_2O$) 5.07 (d, J = 5.5 Hz, 1H, –N–CH–OD) and **2s** (R = H), m.p. 111–114°C (EtOH), ^{1}H NMR δ ($CDCl_3 + D_2O$) 5.07 (d, J = 5.5 Hz, 1H, –N–CH–OD) respectively in the reduction process. Both products show a coupling constant $J_{H_3H_{3a}} = 5.5$ Hz being indicative for a *cis* relation between H_3 and H_{3a}.[18]

Further support for this assignment was obtained from epimerization studies on **2r** (R = H). Stirring of **2r** (R =



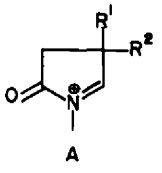
Scheme 1.

H) in NaOEt/EtOH for 47 hr at room temperature gave a complete conversion to "epi" **2r** (R = H) ^{1}H NMR δ ($CDCl_3 + D_2O$) 4.63 (d, J = 1.5 Hz, 1H, -N-CH-OD). The coupling constant $J_{H_3H_{3a}} = 1.5$ Hz indicates a *trans* relationship between H_3 and H_{3a}. Also the upfield shift (*ca.* 0.4 ppm) strongly suggests the location of H_3 in "epi" **2r** (R = H) to be on the same side of the 5-membered ring as the C_{3a}–C_4 bond.[19]

The imides **1r** and **1s** afforded in nearly quantitative yields the oily ethoxylactams **2r** (R = Et) and **2s** (R = Et) after $NaBH_4/H^+$ reduction and acidic work-up (method B). In the ^{1}H NMR spectra of these lactams the C_3 proton signal possesses, in both cases, a sharp structure (δ 4.27(s) for **2r** (R = Et) and δ 4.38(s) for **2s** (R = Et)) a fact which suggests a *trans* stereochemistry between the C_3 and C_{3a} protons, which would be the expected result of the reduction process in *cis*-fused hydroisoindole-1,3 diones. In view of the steric hindrance, EtOH will approach from the least hindered side in the conversion of the hydroxylactam to the ethoxylactam. As expected treatment of "epi" **2r** (R = H) with H^+/EtOH afforded the same stereoisomer **2r** (R = Et) as did the initially formed hydroxylactam **2r** (R = H).

In addition the reduction of *cis* and *trans* 3,4-diphenyl derivatives **1t** and **1u** afforded single stereoisomers although concurrent epimerization **1t** → **1u** and/or **2t** → **2u** occurred in the reduction of **1t** under the alkaline conditions of the reduction. Quantitative epimerization **2t** (R = H) → **2u** (R = H) was noted upon additional stirring of the mixture of **2t** (R = H) and **2u** (R = H) for 24 hr in NaOEt/EtOH at room temperature. The observed $J_{H_4H_5} = 5$ Hz corresponds closely with the assignment of a *cis* 5 OH, 4 Ph relation in both products **2t** (R = H) and **2u** (R = H). A similar result was obtained in the reduction of **1g** affording **2q** (R = H) ($J_{H_4H_5} = 5$ Hz). Upon treatment of the hydroxylactams **2q** (R = H), **2t** (R = H) and **2u** (R = H) with HCl/EtOH (or acidic work-up (method B) of the $NaBH_4/H^+$ reduction products which gives the same results) the corresponding ethoxylactams were obtained in quantitative yield albeit not in every instance as single stereoisomers. **2t** (R = Et) was obtained as a single stereoisomer, ^{1}H NMR δ ($CDCl_3$) 4.96 (broad s, J < 1 Hz) while **2q** (R = Et) and **2u** (R = Et) were obtained as mixtures of two stereoisomers in a product ratio of approximately 2:1 (Experimental). The major stereoisomer has, in both cases, probably a *trans* relation between the C_4 and C_5 protons ($J_{H_4H_5} = 3.5$ Hz).

Further information about the stereochemical course of the $NaBH_4/H^+$ reduction cam from the reduction of **1j**.[20] Basic work-up (method A) afforded **2j** (R = H) as a single stereoisomer although the presence of small amounts (<3%) of the isomeric hydroxylactams could not be excluded. This stereospecificity could also be proven by chemical conversion. HCl/EtOH treatment of **2j** (R = H) afforded a mixture of two stereoisomeric ethoxyderivatives **2j** (R = Et) in a ratio 2:1. The return reaction OEt → OH (refluxing dioxane/H_2O/silica-alumina catalyst[21]) gave two stereoisomers **2j** (R = H) again in a ratio 2:1. It is likely, therefore, that the latter transformation occurs via a cyclic acylimmonium ion A.



A

As in the actual $NaBH_4/H^+$ reduction of **1j** almost exclusively one stereoisomer is formed which result is also found in the reduction of both **1k** and **1l** it becomes highly probable that steric factors determine the outcome of the reduction. The OH → OEt conversion in **2k** and **2l** via HCl/EtOH treatment afforded a mixture of two stereoisomeric ethoxyderivatives in a ratio of approximately 2:1 as was found for **2j**. The analogous conversion of **2m** (R = H) gave **2m** (R = Et). In the series **1n–1p** a slightly different result was found in the reduction of **1n**. In this case **2n** (R = H) was formed as a mixture of two stereoisomers in a ratio of 3:1 in 85% yield together with **3n** (R = H) in 15% yield. Probably because of the rather flat structure of the pyrrolidine ring the steric hindrance is less effective (comparable to for example **1g**). The reduction of the imides **1o** and **1p** occurred regioselective and stereospecific.

The influence of an eventual interaction between an imide carbonyl and a neighbouring heteroatom or polar moiety is illustrated in the reduction of the *o*-NO_2-phenyl imide **1h**. Whereas **1g** shows a "normal" regioselectivity pattern the $NaBH_4/H^+$ reduction of **1h** proceeds highly regio- and stereoselective. Formation of **2h** (R = H) occurs in 83% yield together with **3h** (R = H) in 17%. Thus compared with **1g** there is an increase of the regioselectivity (probably due to an increase of the steric hindrance) and a complete stereoselectivity.

A final point of interest is found in the relatively facile

elimination of EtOH from ethoxyderivatives **2r** and **2s** giving access to the isoindolin-1-one derivatives **16** and **17**. Because of the convenient preparation of the corresponding imides via (4+2) cyclo-additions[22] the method may serve to prepare a variety of 1,4-dihydrobenzene derivatives.

In summary the foregoing results demonstrate the potential usefulness of functionally substituted ω-carbinol-lactams in certain types of heterocyclic synthesis. Further applications will be reported in due time.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were determined on Unicam SP-200 or Perkin-Elmer 257 instruments. The absorptions are located by their wave numbers (in cm^{-1}). ^1H NMR spectra were measured with a Varian A-60, A-60D, HA-100 or XL-100 spectrometer using TMS as internal reference. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were recorded on an AEI MS-902 or Varian Mat-711 mass spectrometer. Analyses were performed by Mr. H. Pieters of the Micro-analytical Department of our laboratory. Column chromatography was carried out on silicagel (activity grade II, Woelm).

Preparation of imides

(a) *Direct method.* The imides **1a–1c, 1f, 1m, 1q–1s** and **1u–1y** were prepared by heating an appropriate primary amine with a dicarboxylic acid or its anhydride during 1 hr at 200–250°. In the preparation of the N-H and N-Me imides an excess of a 25% ammonia soln or 35% methylamine soln in water was used; heating at 200–250° was continued till no more amine was liberated. The products were purified by recrystallization or distillation.

Imide†	Yield (%)	b.p. (°C/mm)	m.p. (°C)‡	
1a	85	114–116/20		
1b	74		69–71	(EtOH)
1c	76		125–126	(EtOH)
1f	80	96–99/13		
1m	70		90–92	(EtOH)
1q	80	100–104/14		
1r	82		50–51	(ether)
1s	86		73–74	(EtOH)
1u	77		106–108	(EtOH)
1v	60		88–90	(EtOH)
1w	66		139–141	(EtOH)
1x	64		104–107	(EtOH)
1y	76		85–87	(EtOH)

†The compounds listed gave correct analytical data.
‡Uncorrected.

(b) *Alkylation reaction.* To a stirred mixture of the imide **1b** or **1e** and K_2CO_3 (5 weight eq.) in dry DMF was added an excess of the appropriate halogen compound. The mixture was stirred at r.t. under N_2 for 24–48 hr and finally poured into H_2O and extracted with ether. The crude product was purified by crystallization or distillation.

Imide†	Yield (%)	b.p. (°C/mm)	m.p. (°C)‡	
1g	69	128–129/0.3		
1h	72		133–135	(EtOH)
1i	81		184–186	(EtOH)
1j	66		82–86	(EtOH)
1k	88		125–127	(EtOH)
1l	95		77–79	(EtOH)

†The compounds listed gave correct analytical data.
‡Uncorrected.

(c) *Mannich reaction.* The imides **1n–1p** were prepared by the method of Magarian[23] from **1b**.

Imide†	Yield (%)	m.p. (°C)‡	
1n	74	221–223§	(EtOH)
1o	69	185–187§	(isopropanol)
1p	57	131–133	(EtOH)

†The compounds listed gave correct analytical data.
‡Uncorrected.
§M.p. of imide-HCl.

(d) *Synthesis of* **1d**. A soln of **1b** (2.13 g, 11.27 mmole) in HOAc (25 ml) was treated with fuming HNO_3 (12.5 ml). The mixture was stirred for 3 hr at 60–70° and 12 hr at r.t. The slightly coloured mixture was poured into ice-water and extracted with $CHCl_3$. The organic soln was washed with sat $NaHCO_3$ aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a pale yellow oil in nearly quantitative yield. ^1H NMR analysis of the oil showed a mixture of **1d** (61%) and **1e** (39%). After crystallization from EtOH pure **1d** was obtained (0.91 g), yield: 34%, m.p. 126–128° (EtOH). IR ($CHCl_3$): 1785 (w) (imide-CO) 1705 (vs) (imide-CO) 1520, 1350 (s) (NO_2); ^1H NMR: δ ($CDCl_3$) 2.70–3.46 (m, 2H, CH_2-CO) 3.10 (s, 3H, -N-CH_3) 4.10–4.30 (double d, 1H, CO-CH-Ar) 7.46 (d, 2H, aromatic H) 8.24 (d, 2H, aromatic H). (Found: C, 56.5; H, 4.2; N, 11.9. $C_{11}H_{10}N_2O_4$ M = 234.21. Calc.: C, 56.41; H, 4.30; N, 11.96%).

(e) Imide **1e** was prepared by the method of Speckamp[17] from *o*-nitro-benzaldehyde.

(f) Imide **1t** was prepared by the following method: A soln of *trans*-3,4-diphenylsuccinic anhydride (0.98 g, 3.88 mmole) in C_6H_6 (100 ml) was stirred at r.t. while methylamine was bubbled through the soln. The mixture was extracted with H_2O. The H_2O layer was acidified and the formed solid was filtered, washed and dried (0.97 g). A soln of this solid (0.97 g) in $SOCl_2$ (50 ml) was refluxed for 46 hr. Evaporation to dryness afforded a green solid (0.89 g). Column chromatography on silicagel with benzene/toluene 1/1 as an eluent afforded 1 - methyl - 3,4 - diphenylmaleimide as pale green crystals (0.67 g) (65%): m.p. 161–162° (EtOH) (lit.[24]: 158°). IR (KBr): 1760 (w) (imide-CO) 1690 (vs) (imide-CO); ^1H NMR: δ ($CDCl_3$) 3.13 (s, 3H, -N-CH_3) 7.20–7.70 (10H, aromatic H). MS: *m/e* = 178 (66%), 205 (61), 263 (100). M^+ (Found: C, 77.6; H, 5.0; N, 5.3. $C_{17}H_{13}NO_2$ M = 263.28. Calc.: C, 77.55; H, 4.98; N, 5.32%).

1 - Methyl - 3,4 - diphenylmaleimide (0.65 g, 2.47 mmole) was hydrogenated in EtOAc (350 ml) over PtO_2 (0.20 g) under at atmosphere of H_2 till no uptake of H_2 was observed (1.5 hr). The catalyst was removed by filtration and the filtrate evaporated. The residual solid was crystallized from $CHCl_3$/EtOH giving 0.45 g of **1t**; yield: 68%; m.p. 184–186° ($CHCl_3$/EtOH). IR (KBr): 1765 (w) (imide-CO) 1670 (vs) (imide-CO). ^1H NMR: δ (DMSO-d_6) 2.98 (s, 3H, -N-CH_3) 4.29 (s, 2H, -CH-CH-) 7.28 (s, 10H, aromatic H). (Found: 76.8; H, 5.7; N, 5.4. $C_{17}H_{15}NO_2$. M = 265.30. Calc.: C, 76.96; H, 5.70; N, 5.28%).

(g) Imide **1z** was prepared by refluxing tryptamine (2.00 g, 12.5 mmole) and 2,2-dimethylsuccinic anhydride (1.60 g, 12.5 mmole) in Na-dried toluene for 17 hr with use of a Dean and Stark apparatus filled with molecular sieves 4A. After evaporation of the solvent and crystallization from EtOH 2.43 g pure **1z** (72%) was obtained: m.p. 128–130° (EtOH). IR ($CHCl_3$): 3470 (s) (NH) 1770 (w) (imide-CO) 1695 (vs) (imide-CO); ^1H NMR: δ ($CDCl_3$) 1.19 (s, 6H, 2×-CH_3) 2.45 (s, 2H, -C-CH_2-CO) 3.10 (broad t, 2H, Ar-CH_2-CH_2-N-) 3.86 (broad t, 2H, Ar-CH_2-CH_2-N-) 6.98–7.43 (4H, indole H) 7.60–7.77 (1H, indole H) 8.28 (1H, indole NH). (Found: C, 71.1; H, 6.7; N, 10.3. $C_{16}H_{18}N_2O_2$ M = 270.32. Calc.: C, 71.09; H, 6.71; N, 10.36%).

General procedure for the $NaBH_4/H^+$ *reduction*

The $NaBH_4/H^+$ reductions were carried out with a stirred soln of the imide in EtOH or a mixture of EtOH and THF or EtOAc

at 0° with an excess of $NaBH_4$. At regular intervals (mostly 15 min) 3–4 drops of 2N HCl in EtOH were added. The reaction time was 4–6 hr. Two work-up methods were followed.

Method A (basic): After reduction the soln was poured into ice-water. Extraction with $CHCl_3$ and work-up of the extract afforded the reaction product.

Method B (acidic): The excess of $NaBH_4$ was destroyed in 15–30 min at the temp of reaction by adding acid till pH = 3. The mixture was stirred for an additional 45–60 min at 0° and poured into H_2O. Extraction with $CHCl_3$ and work-up of the extract afforded the reaction product.

$NaBH_4/H^+$ *Reduction of monosubstituted succinimides* **1a–1d**

The general procedure for the $NaBH_4/H^+$ reduction and work-up (method A or B) was employed. The crude product was mostly a mixture of at least three isomers. It was often difficult to determine the product ratio exactly. Therefore subsequent H_2O or EtOH elimination under the influence of acid was carried out giving a more simplified mixture of pyrrolin-2-ones which product ratio was determined by ^1H NMR analysis without further separation.

Imide	Elimination† conditions	Products (%)‡§	^1H NMR data $\delta_{\text{olefinic H}}$
1a	A, 22.5 hr	**4** (59)	5.81 (m, –C=CH–CO)
		5 (41)	6.65 (m, –CH=C–CO)
1b¶	B, 17 hr	**6** (40)	6.45 (broad s, –C=CH–CO)
		7 (60)‖	7.17 (m, –CH=C–CO)
1c	B, 22.5 hr	**8** (45)	6.42 (broad s, 7–C=CH–CO)DMSO-d_6
		9 (55)	7.40 (m, –CH=C–CO)DMSO-d_6)
1d	C, 44 hr	**10** (47)	6.61 (broad s, –C=CH–CO)
		11 (38)	7.39 (m, –CH=C–CO)
		12 (15)	7.03 (m, –C=CH–N)

†A, refluxing HOAc; B, refluxing 2N HCl/EtOH; C, HCOOH, r.t.

‡Product ratio determined by ^1H NMR analysis.

§Measured in $CDCl_3$ except when otherwise stated.

¶A similar product ratio was found for **1v**.

‖The downfield shift of both ortho-aryl protons as a result of the magnetic anisotropy of the neighbouring lactam-CO to δ 7.93 is highly characteristic.

1 - *Methyl* - 3 - o - *nitrophenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **3e** (R = H)

Compound **1e** (0.486 g, 2.0 mmole) was reduced in EtOH (100 ml) with 0.80 g $NaBH_4$ at 0° for 5 hr. Work-up (method A) afforded a pale yellow solid (0.47 g) which according to ^1H NMR was a mixture of **2e** (R = H) (17%) and **3e** (R = H) (83%). After crystallization from EtOH pure **3e** (R = H) (0.125 g) was obtained, yield: 45%, m.p. 160–164° (EtOH). IR (KBr): 3320 (s) (OH) 1650 (vs) (lactam-CO); ^1H NMR: δ (DMSO-d_6) 1.67–1.97 (m, 1H, –C–CH–C–) 2.70–3.08 (m, 1H, –C–CH–C) 2.75 (s, 3H, –N–CH_3) 4.00–4.23 (broad t, 1H, CO–CH–C–) 5.04–5.26 (m, J = 6.5 Hz, 1H, –N–CH–OH; becomes a q with D_2O added) 6.40 (d, J = 6.5 Hz, 1H, –OH; disappears with D_2O added) 7.40–8.00 (4H, aromatic H). (Found: C, 55.9; H, 5.1; N, 11.8. $C_{11}H_{12}N_2O_4$ M = 236.22. Calc.: C, 55.93; H, 5.12; N, 11.86%).

$NaBH_4/H^+$ *Reduction of disubstituted succinimides* **1f, 1g, 1n** *and* **1y**

The general procedure for the $NaBH_4/H^+$ reduction and basic work-up (method A) was employed. The product ratio was determined by ^1H NMR analysis without separation.

Imide	% 2 (R = H)†,‡	% 3 (R = H)†,‡	δ H_5 in 2 (R = H)§	δ H_5 in 3 (R = H)§
1f	79	21	4.56 (s)	5.09 (m)
1g¶	63	37	4.97 (s)	5.07 (m)
			4.99 (s)	
1n¶	85	15	5.69 (s)	4.95 (m)
			5.30 (s)	
1y‖	83	17	4.90 (s)	5.50 (m)

†Product ratio determined by ^1H NMR analysis.

‡Combined yield quantitative.

§Measured in $CDCl_3 + D_2O$.

¶**2g** (R = H) and **2n** (R = H) were formed as mixtures of two stereo-isomers in product ratio 3:2 and 3:1 respectively.

‖Combined yield **2y** (R = H) and **3y** (R = H) 80%; 20% ring opening was observed.[2b]

1,4 - *Dimethyl* - 4 - o - *nitrophenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **2h** (R = H)

Compound **1h** (2.00 g, 8.06 mmole) was reduced in a mixture of EtOH (190 ml) and THF (35 ml) with 3.00 g $NaBH_4$ at 0° for 6 hr. Work-up (method A) afforded a solid (1.97 g) which according to ^1H NMR (DMSO-d_6) was a mixture of **2h** (R = H) (87%) and **3h** (R = H) (13%). After crystallization from acetone pure **2h** (R = H) (1.637 g) was obtained; yield: 81%, m.p. 188–191° (acetone). IR (KBr): 3200 (s) (OH) 1670 (vs) (lactam-CO); ^1H NMR: δ (DMSO-d_6) 1.34 (s, 3H, C–CH_3) 2.25 (A part AB system, J = 16 Hz, 1H, CO–CH–C–) 2.54 (B part AB system, J = 16 Hz, 1H, CO–CH–C–) 2.64 (s, 3H, –N–CH_3) 5.21 (d, J = 7 Hz, 1H, –N–CH–OH; becomes a s with D_2O added) 6.80 (d, J = 7 Hz, 1H, –OH; disappears with D_2O added) 7.36–7.88 (4H, aromatic H). (Found: C, 57.7; H, 5.7; N, 11.1. $C_{12}H_{14}N_2O_4$ M = 250.25. Calc.: 57.59; H, 5.64; N, 11.2%).

1 - *Methyl* - 4 - *benzyl* - 4 - o - *nitrophenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **2i** (R = H)

Compound **1i** (0.187 g, 0.58 mmole) was reduced in a mixture of EtOH (190 ml) and THF (10 ml) with 0.42 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded **2i** (R = H) as a white solid in quantitative yield; m.p. 186–192° (acetone). IR (KBr): 3150 (s) (OH) 1660 (vs) (lactam-CO); ^1H NMR: δ (DMSO-d_6) 2.37 (A part AB system, J = 16 Hz, 1H, –CH–C–) 2.55 (s, 3H, –N–CH_3) 2.80 (B part AB system, J = 16 Hz, 1H, –CH–C–) 3.15 (broad s, 2H, –C–CH_2–) 5.36 (d, J = 6 Hz, 1H, –N–CH–OH; becomes a s with D_2O added) 6.90–7.30 (6H, aromatic H and –OH; one proton disappears with D_2O added) 7.30–7.80 (4H, aromatic H). (Found: C, 66.2; H, 5.5; N, 8.5. $C_{18}H_{18}N_2O_4$ M = 326.34. Calc: C, 66.24; H, 5.56; N, 8.58%).

1 - *Methyl* - 4 - *benzyl* - 4 - *phenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **2j** (R = H)

Compound **1j** (1.50 g, 5.38 mmole) was reduced in EtOH (150 ml) with 2.00 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded **2j** (R = H) as a white solid in quantitative yield; m.p. 192–198° (EtOAc). IR (KBr): 3150 (s) (OH) 1650 (vs) (lactam-CO); ^1H NMR: δ (DMSO-d_6) 2.42 (A part AB system, J = 16 Hz, 1H, –C–CH–) 2.64 (s, 3H, –N–CH_3) 2.68 (B part AB System, J = 16 Hz, 1H, –C–CH–) 3.00 (A part AB system, J = 14 Hz, 1H, –CH–C–) 3.21 (B part AB system, J = 14 Hz, 1H, –CH–C–) 5.10 (d, J = 7 Hz, 1H, –N–CH–OH; becomes a s with D_2O added) 6.66 (d, J = 7 Hz, 1H, –OH; disappears with D_2O added) 6.70 (2H, aromatic H) 6.95–7.13 (3H, aromatic H) 7.14–7.30 (5H, aromatic H). MS: *m/e* = 180 (60%) 189 (100) 194 (48) 281 (7) M^+. (Found: C, 76.8; H, 6.9; N, 5.0. $C_{18}H_{19}NO_2$ M = 281.34. Calc.: C, 76.84; H, 6.81; N, 4.98%).

1 - *Methyl* - 4 - (3,4 - *dimethoxybenzyl*) - 4 - *phenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **2k** (R = H)

Compound **1k** (0.61 g, 1.80 mmole) was reduced in EtOH (100 ml) with 1.04 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded a white solid in quantitative yield which according to ^1H NMR was pure **2k** (R = H): m.p. 171–174° (EtOH). IR ($CHCl_3$):

3340 (w) (OH) 1675 (vs) (lactam-CO); ^{1}H NMR: δ (DMSO-d_6) 2.40 (A part AB system, J = 16 Hz, 1H, –C–CH–C–) 2.63 (s, 3H, –N–CH$_3$) 2.64 (B part AB system, J = 16 Hz, 1H, –C–CH–C–) 2.88 (A part AB system, J = 13.5 Hz, 1H, –CH–C–) 3.11 (B part AB system, J = 13.5 Hz, 1H, –CH–C–) 3.34 (s, 3H, –O–CH$_3$) 3.61 (s, 3H, –O–CH$_3$) 5.09 (d, J = 6 Hz, 1H, –N–CH–OH; becomes a s with D_2O added) 5.98 (1H, aromatic H) 6.35 (1H, aromatic H) 6.61 (d, J = 6 Hz, 1H, OH; disappears with D_2O added) 6.65 (1H, aromatic H) 7.14–7.40 (5H, aromatic H). MS: *m/e* = 151 (100%) 341 (6) M$^+$. (Found: C, 70.4; H, 6.7; N, 4.1. $C_{20}H_{23}NO_4$ M = 341.39. Calc.: C, 70.36; H, 6.79; N, 4.10%).

1 - *Methyl* - 4 - (3 - *chloro* - 2 - *butenyl*) - 4 - *phenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **2l** (R = H)

Compound **1l** (4.48 g, 16.14 mmole) was reduced in EtOH (300 ml) with 8.28 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded a white solid in nearly quantitative yield which according to ^{1}H NMR was pure **2l** (R = H): m.p. 134–136° (EtOH). IR ($CHCl_3$): 3400 (m) (OH) 1695 (vs) (lactam-CO); ^{1}H NMR: δ ($CDCl_3$) 1.90–2.20 (3H, –C=C–CH$_3$) 2.57–3.20 (4H, CO–CH$_2$– and –C=C–CH$_2$–C–) 2.90 (s, 3H, –N–CH$_3$) 5.03–5.33 (2H, –C=CH– and –N–CH–OH; sharpens with D_2O added) 7.20–7.60 (5H, aromatic H). MS: *m/e* = 103 (100%) 105 (67) 131 (45) 133 (87) 157 (95) 186 (43) 190 (74) 279 (68) M$^+$. (Found: C, 64.4; H, 6.4; N, 5.0; Cl, 12.7. $C_{15}H_{18}NO_2Cl$ M = 279.76. Calc.: C, 64.39; H, 6.49; N, 5.01; Cl, 12.67%).

1 - *Methyl* - 4,4 - *diphenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **2m** (R = H)

Compound **1m** (1.02 g, 3.85 mmole) was reduced in EtOH (100 ml) with 2.01 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded a white solid in nearly quantitative yield which according to ^{1}H NMR was pure **2m** (R = H): m.p. 173–175° (EtOH). IR ($CHCl_3$): 3600, 3400 (m) (OH) 1695 (vs) (lactam-CO); ^{1}H NMR: δ ($CDCl_3$) 2.88 (A part AB system, J = 16 Hz, 1H, –CH–CO) 2.94 (s, 3H, –N–CH$_3$) 3.07 (d, J = 9.5 Hz, 1H, –OH; disappears with D_2O added) 3.43 (B part AB system, J = 16 Hz, 1H, –CH–CO) 5.66 (d, J = 9.5 Hz, 1H, –N–CH–OH; becomes a s with D_2O added) 7.10–7.50 (10H, aromatic H). MS: *m/e* = 165 (57%) 180 (100) 208 (56) 267 (17) M$^+$. (Found: C, 76.3; H, 6.4; N, 5.2. $C_{17}H_{17}NO_2$ M = 267.31. Calc.: C, 76.38; H, 6.41; N, 5.24%).

1 - *Methyl* - 4 - *phenyl* - 4 - (1 - *piperidinomethyl*) - 5 - *hydroxy* - 2 - *pyrrolidinone* **2o** (R = H)

Compound **1o** (0.52 g, 1.82 mmole) was reduced in EtOH (100 ml) with 1.12 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded **2o** (R = H) as a solid in quantitative yield: m.p. 134–137° (isopropylether). IR ($CHCl_3$): 3400 (w) (OH) 1685 (vs) (lactam-CO); ^{1}H NMR: δ ($CDCl_3$) 1.18–1.62 (6H, –(CH$_2$)$_3$–) 2.00–2.28 (4H, –CH$_2$–N–CH$_2$–) 2.48 (AB system, J = 16.5 Hz, 2H, –CH$_2$–C–) 2.74 (A part AB system, J = 12.5 Hz, 1H, –CH–C–) 2.93 (s, 3H, –N–CH$_3$) 3.02 (B part AB system, J = 12.5 Hz, 1H, –CH–C–) 5.56 (s, 1H, –N–CH–OH) 7.23–7.55 (5H, aromatic H). (Found: C, 70.9; H, 8.4. $C_{17}H_{24}N_2O_2$ M = 288.38. Calc.: C, 70.80; H, 8.39%).

1 - *Methyl* - 4 - *phenyl* - 4 - (1 - *morpholinomethyl*) - 5 - *hydroxy* - 2 - *pyrrolidinone* **2p** (R = H)

Compound **1p** (0.95 g, 3.30 mmole) was reduced in EtOH (100 ml) with 1.75 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded **2p** (R = H) as a white solid in quantitative yield: m.p. 168–170° (EtOH). IR ($CHCl_3$): 3400 (w) (OH) 1680 (vs) (lactam-CO); ^{1}H NMR: δ ($CDCl_3$) 2.00–2.30 (4H, –CH$_2$–N–CH$_2$–) 2.51 (AB system, J = 17 Hz, 2H, –C–CH$_2$–) 2.78 (A part AB system, J = 13.5 Hz, 1H, –CH–C–) 2.93 (s, 3H, –N–CH$_3$) 3.05 (B part AB system, J = 13.5 Hz, 1H, –CH(C–) 3.39–3.64 (4H, –CH$_2$–O–CH$_2$–) 5.58 (s, 1H, –N–CH–OH) 7.15–7.54 (5H, aromatic H). (Found: C, 66.2; H, 7.7C. $C_{16}H_{22}N_2O_3$ M = 290.35. Calc.: C, 66.18; H, 7.64%).

2 - *Methyl* - 3 - *hydroxy* - cis - 3a,4,5,6,7,7a - *hexahydroisoindolin* - 1 - *one* **2r** (R = H)

Compound **1r** (0.93 g, 5.5 mmole) was reduced in EtOH (100 ml) with 1.80 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded **2r** (R = H) as a white solid in quantitative yield: m.p. 107–108° (EtOH). IR (KBr): 3180 (s) (OH) 1650 (vs) (lactam-CO); ^{1}H NMR: δ ($CDCl_3$) 1.15–2.20 (8H, –(CH$_2$)$_4$–) 2.20–2.52 (2H, –CH–CH–) 2.82 (s, 3H, –N–CH$_3$) 4.02 (d, J = 7.5 Hz, 1H, –OH; disappears with D_2O added) 4.98–5.16 (double d, J = 7.5 and J = 5.5 Hz, 1H, –N–CH–OH; becomes a d (J = 5.5 Hz) with D_2O added). MS: *m/e* = 60 (100%) 169 (51) M$^+$. (Found: C, 63.9; H, 8.9; N, 8.4. $C_9H_{15}NO_2$ M = 169.22. Calc.: C, 63.88; H, 8.94; N. 8.28%).

Epimerization of **2r** (R = H)

A soln of **2r** (R = H) (0.05 g, 0.30 mmole) in EtOH (10 ml) containing an excess of NaOEt, was stirred at r.t. for 47 hr. The mixture was poured into H_2O and extracted with $CHCl_3$. Work-up of the filtrate afforded a pale yellow oil in 46% yield which according to ^{1}H NMR ($CDCl_3$) was nearly pure "epi" **2r** (R = H). The H_5 signal was found at δ 4.63 (d, J = 1.5 Hz) and the N–Me signal at δ 2.85. Column chromatography on silicagel with $CHCl_3$/acetone 4/1 as an eluent gave pure "epi" **2r** (R = H) with analytical data identical to **2r** (R = H). Treatment of "epi" **2r** (R = H) with 2N HCl in EtOH at 0° yielded quantitatively **2r** (R = Et) which was the same product as obtained after reduction and acidic work-up (method B) of **1r**.

2 - *Methyl* - 3 - *hydroxy* - cis - 3a,4,4,7a - *tetrahydroisoindolin* - 1 - *one* **2s** (R = H)

Compound **1s** (0.56 g, 3.4 mmole) was reduced in EtOH (100 ml) with 0.96 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded **2s** (R = H) as a white solid in quantitative yield: m.p. 111–114° (EtOH). IR (KBr): 3160 (s) (OH) 1640 (vs) (lactam-CO); ^{1}H NMR: δ ($CDCl_3$) 2.06–2.43 (4H, 2×–CH$_2$–) 2.43–2.76 (2H, –CH–CH–) 2.84 (s, 3H, –N–CH$_3$) 4.18 (d, J = 7.5 Hz, 1H, –OH; disappears with D_2O added) 4.97–5.17 (double d, J = 7.5 and J = 5.5 Hz, 1H, –N–CH–OH; becomes a d (J = 5.5 Hz) with D_2O added) 5.82 (m, 2H, –CH=CH–). MS: *m/e* = 79 (43%) 149 (41) 167 (100) M$^+$. (Found: C, 64.8; H, 7.9; N, 8.4. $C_9H_{13}NO_2$ M = 167.20. Calc.: C, 64.65; H, 7.84; N, 8.38%).

$NaBH_4/H^+$ *Reduction of* **1t**

Compound **1t** (0.39 g, 1.46 mmole) was reduced in a mixture of EtOH (150 ml) and EtOAc (25 ml) with 0.60 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded a white solid in quantitative yield which according to ^{1}H NMR ($CDCl_3$) was a mixture of **2t** (R = H) (52%) and **2u** (R = H) (48%). The H_5 signals were found at δ 5.08 (d, J = 5 Hz) for **2t** (R = H) and δ 4.82 (d, J = 5 Hz) for **2u** (R = H) with D_2O added. The N–Me signals were found at δ 2.88 (s) for **2t** (R = H) and δ 2.73 (s) for **2u** (R = H). A soln of this mixture (0.28 g) in EtOH (50 ml), containing an excess of NaOEt, was stirred for 24 hr at r.t. The mixture was poured into H_2O and extracted with CH_2Cl_2. Work-up of the extract afforded pure **2u** (R = H) (0.21 g). A soln of a mixture of **2t** (R = H) (52%) and **2u** (R = H) (48%) (see above) (0.10 g) in EtOH (50 ml) was cooled to 0°, acidified with 7.63 N HCl in EtOH (0.8 ml) and stirred for 19 hr at 0°. The soln was poured into dil $NaHCO_3$ soln and extracted with $CHCl_3$. Work-up of the extract afforded a pale yellow oil in quantitative yield which according to ^{1}H NMR ($CDCl_3$) was a mixture of **2t** (R = Et) (52%) and **2u** (R = Et) (48%). The H_5 signal for **2t** (R = Et) was found at δ 4.96 (broad s, J < 1 Hz).

1 - *Methyl* - trans - 3,4 - *diphenyl* - 5 - *hydroxy* - 2 - *pyrrolidinone* **2u** (R = H)

Compound **1u** (0.33 g, .1.25 mmole) was reduced in EtOH (100 ml) with 0.68 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method A) afforded **2u** (R = H) as a white solid in quantitative yield: m.p. 145–147° (EtOH). IR (KBr): 3320 (s) (OH) 1660 (vs) (lactam-CO); ^{1}H NMR: δ ($CDCl_3$) 2.73 (s, 3H, –N–CH$_3$) 3.11–3.28 (double d, J = 5 and J = 8.5 Hz, 1H, –C–CH–ϕ) 3.52–3.66 (d, J = 8.5 Hz, 1H, CO–CH–ϕ) 4.75–4.90 (double d, J = 5 and J = 6.5 Hz, 1H, –N–CH–OH; becomes a d (J = 5 Hz) with D_2O added) 5.06 (d, J = 6.5 Hz, 1H, –OH; disappears with D_2O added) 6.80–7.34 (10H, aromatic H) MS: *m/e* = 220 (42%) 249 (10) 267 (10) M$^+$. (Found: C, 76.3; H, 6.4; N, 5.2. $C_{17}H_{17}NO_2$ M = 267.31. Calc.: C, 76.38; H, 6.41; N, 5.24%).

$NaBH_4/H^+$ *Reduction of disubstituted succinimides* **1k, 1l, 1g** *and* **1u**

The general procedure for the $NaBH_4/H^+$ reduction and acidic work-up (method B) was employed. The crude reaction product was according to ^1H NMR a mixture of two stereoisomers **2** (R = Et) and "epi" **2** (R = Et) which could not be separated by preparative chromatography.

Imide	% **2** (R = Et)†‡¶	% "epi" **2** (R = Et)†‡¶	δ H_5 in **2** (R = Et)§	δ H_5 in "epi" **2** (R = Et)§
1k	62	38	5.02 (s)	4.80 (s)
1l	67	33	4.85 (s)	4.62 (s)
1g	62	38	4.37 (d, J = 3.5 Hz)	4.57 (d, J = 5 Hz)
1u	67	33	4.82 (d, J = 3.5 Hz)	4.79 (d, J = 5 Hz)

†Product ratio determined by ^1H NMR analysis.
‡Combined yield quantitative.
§Measured in $CDCl_3$.
¶Similar results were obtained after $NaBY_4/H^+$ reduction and basic work-up (method A) followed by treatment of the crude reaction product with 2 N HCl/EtOH at 0° for 2 hr.

1 - *Methyl* - 4 - *benzyl* - 4 - *phenyl* - 5 - *ethoxy* - 2 - *pyrrolidinone* **2j** (R = Et)

Compound **1j** (1.00 g; 3.58 mmole) was reduced in EtOH (100 ml) with 1.68 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method B) afforded a colourless oil in nearly quantitative yield which according to ^1H NMR ($CDCl_3$) was a mixture of two stereoisomers **2j** (R = Et) in a product ratio 2:1. The H_5 signals were found at δ 4.81 (s) (33%) and δ 5.05 (s) (67%). After several months in the refrigerator the minor stereoisomer crystallized out in part; m.p. 118–120°. IR ($CHCl_3$): 1680 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 1.38 (t, J = 7 Hz, 3H, –O–CH_2–CH_3) 2.65 (AB system, J = 16 Hz, 2H, –C–CH_2–) 2.79 (s, 3H, –N–CH_3) 3.22 (AB system, J = 14 Hz, 2H, –CH_2–C–) 3.88 (q, J = 7 Hz, 2H, –O–CH_2–CH_3) 4.81 (s, 1H, –N–CH–OEt) 6.55–6.78 (2H, aromatic H) 6.90–7.40 (8H, aromatic H). MS: *m/e* = 88 (100%) 91 (42) 309 (40) M^+. (Found: C, 77.6; H, 7.4; N, 4.6. $C_{20}H_{23}NO_2$ M = 309.39. Calc.: C, 77.64; H, 7.49; N, 4.53%).

Conversion of **2j** (R = Et) → **2j** (R = H)

A soln of **2j** (R = Et) (0.25 g, 0.81 mmole) in dioxane/H_2O 5/2 (14 ml) containing a few mg of "Ketjencat"[20] was refluxed for 3 days. The catalyst was removed by filtration and the filtrate was evaporated to yield a yellow solid in quantitative yield which according to ^1H NMR (DMSO-d_6) was a mixture of two stereoisomers **2j** (R = H) in a product ratio 2:1. The H_5 signals were found at δ 5.10 (s, with D_2O added) (67%) and δ 5.20 (s, with D_2O added) (33%).

Cyclisation of **2k** (R = Et) *to* **15**

A soln of **2k** (R = Et) (0.58 g, 1.57 mmole) in MeOH (100 ml) was acidified with conc. HCl (15 ml) and refluxed for 2 days. The reaction mixture was poured into dil. $NaHCO_3$ soln (250 ml) and extracted with $CHCl_3$. Work-up of the extract afforded a white solid in 46% yield which according to ^1H NMR was pure **15**: m.p. 150–152° (EtOH). IR ($CHCl_3$): 1670 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 2.95 (s, 5H, –N–CH_3 and –C–CH_2–Ar) 3.30 (broad s, 2H, –CH_2–CO) 3.85 (s, 3H, –O–CH_3) 3.92 (s, 3H, –O–CH_3) 4.87 (s, 1H, –N–CH–Ar) 6.76 (s, 1H, aromatic H) 6.95 (s, 1H, aromatic H) 7.10–7.40 (5H, aromatic H). MS: *m/e* = 265 (100%) 323 (76) M^+. (Found: C, 74.2; H, 6.6; N, 4.4. $C_{20}H_{21}NO_3$ M = 323.38. Calc.: C, 74.28; H, 6.55; N, 4.33%).

1 - *Methyl* - 4,4 - *diphenyl* - 5 - *ethoxy* - 2 - *pyrrolidinone* **2m** (R = Et)

Compound **1m** (1.04 g, 3.92 mmole) was reduced in EtOH (100 ml) with 1.98 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method B) afforded pure **2m** (R = Et): m.p. 103–104° (EtOH). IR ($CHCl_3$): 1695 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 0.87 (t, J = 7 Hz, 3H, –O–CH_2–CH_3) 2.75 (A part AB system, J = 16 Hz, 1H, –CH–CO) 2.99 (s, 3H, –N–CH_3) 3.25 (m, J = 7 Hz, 2H, –O–CH_2–CH_3) 3.47 (B part AB system, J = 16 Hz, 1H, –CH–CO) 5.29 (s, 1H, –N–CH–OEt) 7.00–7.43 (10H, aromatic H). MS: *m/e* = 88 (74%) 180 (100) 295 (44) M^+ (Found: C, 77.3; H, 7.2; N, 4.7. $C_{19}H_{21}NO_2$ M = 295.37. Calc.: C, 77.26; H, 7.17; N, 4.74%).

2 - *Methyl* - 3 - *ethoxy* - cis - 3a,4,5,6,7,7a - *hexahydroisoindolin* - 1 - *one* **2r** (R = Et)

Compound **2r** (R = Et) was prepared from **2r** (R = H) in quantitative yield as described by J. C. Hubert.[25]

2 - *Methyl* - 3 - *ethoxy* - cis - 3a,4,7,7a - *tetrahydroisoindolin* - 1 - *one* **2s** (R = Et)

Compound **2s** (R = Et) was prepared from **2s** (R = H) in quantitative yield as described by J. C. Hubert.[25]

2 - *Methyl* - 4,5,6,7 - *tetrahydroisoindolin* - 1 - *one* **16**

A soln of **2r** (R = Et) (1.50 g, 7.10 mmole) in HOAc (20 ml) was refluxed for 16 hr. The soln was poured into H_2O and extracted with $CHCl_3$. Work-up of the extract (washing with sat $NaHCO_3$ aq and sat NaCl aq drying over Na_2SO_4 and evaporation) afforded **16** after distillation under reduced pressure (b.p. 90–92°/0.4 mm) in 92% yield. IR ($CHCl_3$): 1660 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 1.50–1.85 (4H, –C–CH_2–CH_2–C–) 2.00–2.40 (4H, –CH_2–C–C–CH_2–) 2.99 (s, 3H, –N–CH_3) 3.76 (broad s, 2H, –C=C–CH_2–N–). MS: *m/e* = 122 (38%) 151 (100) M^+. (Found: C, 71.3; H, 8.6. $C_9H_{13}NO$ M = 151.20. Calc.: C, 71.49; H, 8.67%).

2 - *Methyl* - 4,7 - *dihydroisoindolin* - 1 - *one* **17**

As described above for **16**: **2s** (R = Et) (2.00 g, 10.30 mmole) afforded **17** in 88% yield as white crystals: m.p. 118–120° (EtOAc). IR ($CHCl_3$): 1660 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 2.90 (broad s, 4H, –CH_2–C=C–CH_2–) 3.00 (s, 3H, –N–CH_3) 3.80 (s, 2H, –N–CH_2–C=C–) 5.78 (broad s, 2H, –CH=CH–). MS: *m/e* = 91 (48%) 148 (43) 149 (100) M^+. (Found: C, 72.3; H, 7.4; N, 9.4. $C_9H_{11}NO$ M = 149.19. Calc.: C, 72.45; H, 7.43; N, 9.39%).

4,4 - *Diphenyl* - 5 - *ethoxy* - 2 - *pyrrolidinone* **2w** (R = Et)

Compound **1w** (0.78 g, 3.11 mmole) was reduced in EtOH (100 ml) with 1.57 g $NaBH_4$ at −15° for 4.5 hr. Work-up (method B) afforded **2w** (R = Et) as a white solid in quantitative yield: m.p. 100–102° (EtOH). IR ($CHCl_3$): 3420 (w) (NH) 1700 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 1.00 (t, J = 7 Hz, 3H, –O–CH_2–CH_3) 2.82 (A part AB system, J = 16 Hz, 1H, –CH–CO) 3.17–3.75 (m, 2H, –O–CH_2–CH_3) 3.45 (B part AB system, J = 16 Hz, 1H, –CH–CO) 5.41 (broad s, J = 1.5 Hz, 1H, –NH–CH–OEt; becomes a s with D_2O added) 7.20 (broad s, 10H, aromatic H) 8.37 (1H, –NH; disappears with D_2O added). MS: *m/e* = 180 (100%) 281 (8) M^+. (Found: C, 76.6; H. 6.7; N, 5.1. $C_{18}H_{19}NO_2$ M = 281.34. Calc.: C, 76.84; H, 6.81; N, 4.98%).

$NaBH_4$ *reduction of* O-*alkylated imide* **1w**[14]

To a soln of **1w** (1.25 g, 4.98 mmole) in dil KOH aq (1.1 eq) (50 ml) $AgNO_3$ (0.85 g, 5.0 mmole) was added. The ppt was filtered, washed with H_2O and dried. The white solid (1.78 g) was dispersed in C_6H_6 (100 ml) and EtI (2.34 g, 15 mmole) was added, followed by refluxing for 3 hr. After removal of AgI by filtration the solvent was evaporated. The resultant residue (0.42 g) was a mixture of two compounds. To a soln of the latter mixture (0.32 g, 1.15 mmole) in EtOH (50 ml) $NaBH_4$ (0.14 g) was added, followed by stirring at r.t. for 3 hr. The mixture was poured into H_2O and extracted with $CHCl_3$. Work-up afforded an oil (0.27 g) which according to ^1H NMR ($CDCl_3$) was a mixture of **2w** (R = Et) (64%) and **3w** (R = Et) (36%). The H_5 signals were found at δ 5.04 (m) for **3w** (R = Et) and δ 5.41 (broad s, J = 1.5 Hz) for **2w** (R = Et).

$NaBH_4/H^+$ *Reduction of* **1x**

Compound **1x** (0.57 g, 4.51 mmole) was reduced in EtOH (100 ml) with 0.90 g $NaBH_4$ at 0° for 4.5 hr. Work-up (method B) afforded an oil in 46% yield which according to ^1H NMR ($CDCl_3$) was a mixture of **2x** (R = Et) (83%) and **3x** (R = Et) (17%). The H_5

signals were found at δ 4.33 (s with D_2O added) for **2x** (R = Et) and δ 4.85 (m with D_2O added) for **3x** (R = Et).

$NaBH_4$ *Reduction of* O-*alkylated imide* **1x**[14]

3,3 - Dimethyl-succinimide - Ag salt (3.24 g, 13.92 mmole) (prepared from 3,3-dimethyl-succinimide (3.81 g, 30.00 mmole) and Ag_2O (3.81 g, 16.42 mmole) according to Djerrassi[26]) was dispersed in C_6H_6 (200 ml) and EtI (6.8 g, 54.4 mmole) was added to the mixture, followed by refluxing for 4 hr. After removal of AgI by filtration the solvent was evaporated. The resultant residue (2.05 g) was a mixture of two compounds. To a soln of the latter mixture (0.81 g, 5.22 mmole) in EtOH (50 ml) $NaBH_4$ (0.61 g) was added, followed by stirring at r.t. for 3 hr. The mixture was poured into dil HOAc aq and extracted with $CHCl_3$. Work-up afforded a colourless oil (0.71 g) which according to ^1H NMR ($CDCl_3$) was a mixture of **2x** (R = Et) (54%) and **3x** (R = Et) (46%). After several weeks in the refrigerator the minor compound **3x** (R = Et) crystallized out in part: m.p. 84–86°. ^1H NMR: δ ($CDCl_3$) 1.14 (s, 3H, –C–CH$_3$) 1.19 (t, J = 7 Hz, 3H, –O–CH$_2$–CH$_3$) 1.27 (s, 3H, –C–CH$_3$) 1.91 (m, 1H, –CH–C–OEt) 2.14 (m, 1H, –CH–C–OEt) 3.23–3.75 (m, 2H, –O–CH$_2$–CH$_3$) 4.85 (m, 1H, –NH–CH–OEt) 8.22 (1H, –NH; disappears with D_2O added). MS: *m/e* = 99 (55%) 112 (100) 157 (29) M^+. (Found: C, 61.0; H, 9.5; N, 8.9. $C_8H_{15}NO_2$ M = 157.12. Calc.: C, 61.12; H, 9.62; N, 8.91%).

$NaBH_4/H^+$ *Reduction and cyclization of* **1z**

Compound **1z** (0.80 g, 2.96 mmole) was reduced in EtOH (100 ml) with 1.20 g $NaBH_4$ at 0° for 5 hr. The excess of $NaBH_4$ was destroyed in 15–30 min by adding 2 N HCl in EtOH to the cooled soln till pH = 3. The mixture was stirred for an additional 20 hr at r.t. The mixture was neutralized with a 1% KOH soln in EtOH the evaporated to dryness. Extraction of the residue with $CHCl_3$ and evaporation of the extract afforded a mixture of **13** (73%) and **14** (27%) (0.748 g). Treatment of the mixture with ether gave pure **13** (0.408 g) (54%): m.p. 267–269° (EtOH). IR ($CHCl_3$): 3460 (m) (NH) 1670 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 0.84 (s, 3H, –C–CH$_3$) 1.53 (s, 3H, –C–CH$_3$) 1.74–3.28 (5H, –CH$_2$–CH–N– and –CH$_2$–CO) 4.59 (m, 1H, –C–CH–N–) 4.70 (s, 1H, –C–CH–N–) 7.10–7.63 (4H, indole H) 8.09 (1H, indole NH). (Found: C, 75.5; H, 7.2; N, 11.1. $C_{16}H_{18}N_2O$ M = 254.31. Calc.: C, 75.56; H, 7.13; N, 11.02%). The mother liquor was chromatographed on silicagel with EtOAc as an eluent and afforded pure **14** (0.181 g) (24%) as a pale brown solid: m.p. 200–203° (EtOAc). IR (KBr): 3250 (s) (NH) 1660 (vs) (lactam-CO); ^1H NMR: δ ($CDCl_3$) 1.20 (s, 3H, –C–CH$_3$) 1.26 (s, 3H, –C–CH$_3$) 1.68–1.96 (m, 1H, –C–CH–C–) 2.30–2.56 (m, 1H, –C–CH–C–) 2.73–3.25 (3H, –CH$_2$–CH–N–) 4.39–4.65 (m, 1H, –C–CH–N–) 4.75–5.00 (broad t, 1H, –C–CH–N–) 7.05–7.58 (4H, indole H) 8.71 (1H, indole NH). (Found: C, 75.4; H, 7.2; N, 11.1. $C_{16}H_{18}N_2O$ M = 254.31. Calc.: C, 75.56; H, 7.13; N, 11.02%). From the following fractions 0.114 g pure **13** (15%) was obtained.

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REFERENCES

[1]Part of the forthcoming Ph.D. Thesis, of J. B. P. A. Wijnberg, University of Amsterdam.
[2a]J. C. Hubert, W. Steege, W. N. Speckamp and H. O. Huisman, *Synth. Comm.* **1**, 103 (1971); [b]J. C. Hubert, J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron* **31**, 1437 (1975).
[3a]E. Winterfeldt and J. M. Nelke, *Chem. Ber.* **103**, 1174 (1970); [b]E. Winterfeldt, *Synthesis* 617 (1975).
[4]For a preliminary communication see: J. B. P. A. Wijnberg, W. N. Speckamp and H. E. Schoemaker, *Tetrahedron Letters* 4073 (1974).
[5a]S. Ohki, T. Watanabe, M. Uchiyama, N. Ozawa and F. Hamaguchi, *Yakugaku Zasshi* **91**, 841 (1973); [b]T. Watanabe, F. Hamaguchi and S. Ohki, *Ibid.* **93**, 845 (1973).
[6]D. C. Wigfield and F. W. Gowland, *Tetrahedron Letters* 3373 (1976).
[7a]J. J. Bloomfield and S. L. Lee, *J. Org. Chem.* **32**, 3919 (1967); [b]M. E. Birckelbaw, P. W. Le Quesne and C. K. Wocholski, *Ibid.* **35**, 558 (1970); [c]D. M. Bailey and R. E. Johnson, *Ibid* **35**, 3574 (1970).
[8]We are highly indebted to Prof. J. D. Dunitz for the X-ray measurements and his helpful comments.
[9]H. B. Bürgi, J. D. Dunitz, J. M. Lehn and G. Wipff, *Tetrahedron* **30**, 1563 (1974).
[10]T. Fuji and S. Yoshifuji, *Ibid.* **26**, 5953 (1970).
[11]Similar results were found by A. R. C. Oostveen, unpublished observation.
[12]R. Tschesche, J. Moch and Ch. Spilles, *Chem. Ber.* **108**, 2247 (1975).
[13]G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton and J. L. Johnson, *J. Am. Chem. Soc.* **96**, 7812 (1974).
[14]K. Matoba and T. Yamazaki, *Chem. Pharm. Bull.* **22**, 2999 (1974).
[15]J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron Letters* 3963 (1975).
[16]J. B. P. A. Wijnberg and W. N. Speckamp, results to be published.
[17]J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron Letters* 4035 (1975).
[18]A. J. McAlees and R. McCrindle, *J. Chem. Soc.* (C), 2425 (1969).
[19]L. M. Jackman and S. Sternhell, *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, p. 236. Pergamon Press, Oxford (1969).
[20]Definite proof about the stereochemical course will be obtained from X-ray measurements of **2j** (R = H).
[21]D. P. Roelofsen and H. van Bekkum, *Rec. Trav. Chim.* **91**, 605 (1972).
[22]A. C. Cope and E. C. Herrick, *Org. Synth.* Coll. Vol. **4**, 890 (1963).
[23]H. Clemson, E. O. Magarian, G. C. Fuller and R. O. Langler, *J. Pharm. Sci.* **57**, 384 (1968).
[24]R. Lukes and V. Sperling, *Coll. Czech. Chem. Comm.* **8**, 461 (1936).
[25]Ph.D. thesis of J. C. Hubert, University of Amsterdam (1974).
[26]C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.* **75**, 3494 (1953).