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BIOMIMETIC α-ACYLIMMONIUM CYCLISATIONS OF UNACTIVATED OLEFINS†

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Abstract—Cyclisation of olefinic ω-ethoxylactams **9–16** leads to ringclosed products in excellent yields. The reaction is weakly acid-catalyzed, in several cases also stereospecific and proceeds at ambient temperature. The structure and configuration of the products are discussed. Possible relationships with other immonium cyclisations and with cationic carbocyclic olefincyclisations are reviewed. The cyclisation of one example—**13b**—deserves special attention because of the concomitant operation of synchronous and stepwise cyclisation mechanisms.

In the last decade the acid-catalyzed condensation of polyolefines to form cyclic compounds in a stereochemically controlled manner has been developed into a method of high synthetic potential.[2] The impetus for this work was derived in greater part from the increasing knowledge on analogous enzymatic processes. Yet a number of other factors among which the experimental verification of the Stork–Eschenmoser hypothesis[3] and the development of possible routes of practical interest for the total synthesis of steroids[4a,b] and terpenes,[4c] have also contributed to the success of the method.

The principle of cationic cyclisation, however, is by no means restricted to the carbocyclic field. Although a biosynthetic example of cyclisation over more than one C–C bond is clearly absent in polyolefinic heterocyclisation the role of the immonium ion in ring closures of monolefins to form a variety of alkaloid families has been well established.[5] Apart form the synthetic usefulness of the latter principle a few studies have also appeared on a more detailed investigation of the rules involved in such a process.[6]

With the discovery of the cyclic α-acylimmonium intermediate[7] as a highly reactive initiating centre for olefin type cyclisations both practical applications and mechanistically oriented work became feasible. The facile preparation of imide starting materials coupled with the eventual conversion possibilities of the lactam formed renders direct synthetic uses most obvious, as was already exemplified in the total synthesis of different alkaloids.[8] On the other hand, with a view on the great number of studies concerning the rules which govern the olefin cyclisations[9] an investigation on the stereochemical outcome of the process as well as the scope and limitations of the method particularly aiming at an evaluation of the α-acylimmonium ion as one of the few currently known workable cation-initiating centres seemed highly demanded.

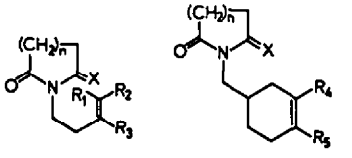
In addition the eventual inverse relationship with the stereoelectronically governed heterolytic fragmentation[10] is of theoretical interest.

Starting materials. Imides **1–8** were selected on the basis of the anticipated reactivity of the cyclic acylimmonium intermediate towards unsaturated C–C bonds. In this respect both the eventual synthetic utility as well as the stereochemical outcome are important with regard to further application. The unsubstituted alkenes **1a** and **1b** were chosen to test the general reactivity while **2a**, **2b**, **3a** and **3b** were expected to provide data on the steric behaviour. Additional modification of the double bond then such as in compounds **4** and **5–8** would give rise to information on a more precise evaluation of the properties of the cyclic α-acylimmonium species as a novel cyclisation inducing cationic centre, especially with regard to the influence of rigidity.

All of the imides were synthesized according to the oxidation-reduction technique in which the N–H imide is condensed at room temperature with the appropriate alcohol in presence of triphenylphosphine and dimethyl azodicarboxylate.[11] Apart form the satisfying yields and simple experimental techniques the method allows considerable flexibility with respect to easily available starting materials especially the unsaturated alcohol components. The latter were either commercially available or could be synthesized according to known procedures.

All of the so obtained imides were converted into the ω-ethoxylactams **9–16** via $NaBH_4/H^+$ reduction.[12] Cyclisation experiments on the latter derivatives were carried out with chromatographically homogeneous samples.

Cyclisation. Although the actual starting material in this type of reaction is the ω-ethoxylactam, the real intermediate is most probably the cyclic α-acylimmonium species. Evidence for this assumption is presented in the sequel; from earlier experiences[13] the



n = 1	n = 2	R_1	R_2	R_3	R_4	R_5	n = 1	n = 2
X=O							X=OEt, H	
1a	1b	H	H	H	-	-	9a	9b
2a	2b	H	Me	H	-	-	10a	10b
3a	3b	Et	H	H	-	-	11a	11b
4a	4b	H	H	Me	-	-	12a	12b
	5b	H	$-(CH_2)_4-$		-	-		13b
6a	6b	-	-	-	H	H	14a	14b
	7b	-	-	-	H	Me		15b
	8b	-	-	-	Me	Me		16b

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acid-catalyzed dimerisation of pyrrolinones can be best explained by assuming rapid H^+-catalyzed equilibria between enamide and α,β-unsaturated amide form.

Cyclisation of the ω-OEt-lactams **9a** and **9b** occurred smoothly at room temperature by stirring in formic acid for 18 hr to yield single reaction products **17a** and **17b** in nearly quantitative yield. Aliquots of the reaction mixture of **9a** taken at two intervals showed the reaction to be incomplete after 3 and 6 hr. The structure of the products was evident from the ^{1}H NMR analysis (*vide infra*). Furthermore hydrolysis of **17a** gave the corresponding alcohol **18a**. In order to obtain information on the mechanism of the ring closure the reaction was also carried out in DCOOD. Mass spectral analysis of **19a** showed the incorporation of a single deuterium atom located in the OOCD moiety. In the ^{1}H NMR spectrum of **19a** the OOCH absorption at δ 8.05 was absent while the CHO signal at δ 5.05 sharpened. Cyclisation of **9b** with 2 equivalents of HCOONa in HCOOH was also investigated. At room temperature (44 hr) little reaction was observed after 53 hr at 45° the starting material had disappeared and **17b** was isolated albeit in lower (79%) yield. In AcOH at room temperature no cyclic material was formed upon reaction of **9a**.

The (E)Me isomers **10a** and **10b** underwent complete ring closure to single *trans*-stereoisomers **20a** and **20b** upon HCOOH treatment for 18 hr. Structure determination was based upon ^{1}H NMR analysis (*vide infra*) which proved also maintenance of the starting olefin geometry.

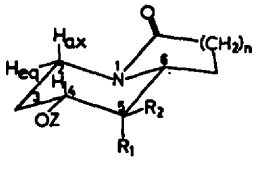
†In the cyclisation of a N-butynyl OEt-lactam complete identification of a dimer proved possible.[14]

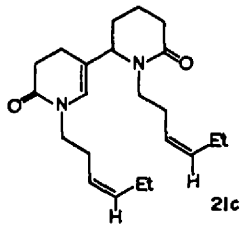
In the HCOOH-cyclisation of (Z)-Et isomers **11a** and **11b** (room temp. 18 hr) variable amounts of secondary products were formed although the yields of **21a** and **21b** were still over 85%. Tentative identification of one of the byproducts as the dimer† **21c** of a dihydropyridone proved possible in the reaction of **11b**; formation of it could be simply suppressed by working under higher dilution conditions and employing longer reaction times. Hydrolysis of **21a** and **21b** in HCl/MeOH yielded the crystalline alcohols **22a** and **22b**.

Analysis of a sample of the reaction mixture of **11b** and HCOOH which was taken after 2 hr showed the complete disappearance of the ω-OEt-lactam and partial formation of the corresponding enamide. Elimination of EtOH therefore most probably precedes cyclisation at least in the glutarimide series which indicates the cyclic α-acylimmonium ion most likely to be the initiating centre. Again single *cis*-isomers were formed exclusively, no traces of other stereoisomers being detectable. Thus all of the cyclisation reactions of lactams **9**, **10** and **11** appear to proceed stereoselectively.

In contrast the HCOOH reaction of **12a** and **12b** gave mixtures of two Me-epimers of **23** and **24a**. The rate of cyclisation proved to be considerably faster, the reaction being complete within 15 min at 8°. Furthermore it was noted that the size of the acid anion had some influence on the epimer ratio, as indicated by the following data (Table 1).

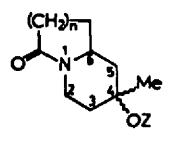
In the final epimer mixture the epimer ratio was not altered upon additional treatment with acid, while also no exchange with the added acid anion was observed. Thus additional stirring of **24a** in dichloroacetic acid did not affect its epimer ratio, while the corresponding reaction



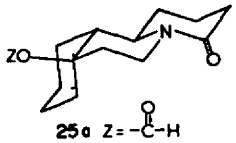


21c

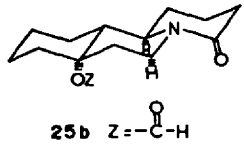
17a $R_1=R_2=H$ Z = -C(=O)-H , n = 1
17b $R_1=R_2=H$ Z = -C(=O)-H , n = 2
18a $R_1=R_2=H$ Z = -H , n = 1
19a $R_1=R_2=H$ Z = -C(=O)-D , n = 1
20a $R_1=H$; $R_2=Me$ Z = -C(=O)-H , n = 1
20b $R_1=H$; $R_2=Me$ Z = -C(=O)-H , n = 2
21a $R_1=Et$; $R_2=H$ Z = -C(=O)-H , n = 1
21b $R_1=Et$; $R_2=H$ Z = -C(=O)-H , n = 2
22a $R_1=Et$; $R_2=H$ Z = -H , n = 1
22b $R_1=Et$; $R_2=H$ Z = -H , n = 2



23 n = 1 ; Z = -C(=O)-H
24a n = 2 ; Z = -C(=O)-H
24b n = 2 ; Z = -C(=O)-CH_3
24c n = 2 ; Z = -H
24d n = 2 ; Z = -C(=O)-$CHCl_2$



25a Z = -C(=O)-H
25c Z = -H



25b Z = -C(=O)-H
25d Z = -H

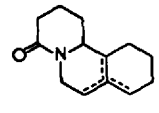


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Table 1. Cyclisation of OEt-lactam **12b**

Acid	Temp.	Time[a]	Compound formed	Isomer / Ratio[b]
HCOOH	r.t	1 hr	24a	57 / 43
CH_3COOH	r.t.	23 hr	24b	60[f] / 40[f]
CH_3COOH-H_2O[c]	r.t.	2 hr	24c	60 / 40
$CHCl_2COOH$	r.t.	2 hr	24d	70 / 30
HCOOH/Et_2O[d]	r.t.	19 hr	24a	57 / 43
HCOOH/HCOONa[e]	r.t.	18 hr	24a	56 / 44

a Time after which reaction is completed.
b Determined via ^{1}H-NMR.
c CH_3COOH/H_2O 1:19 by vol.
d HCOOH/Et_2O 1:10 by vol.
e 3 ml HCOOH, 0·55 mmole 12b, 1·49 mmole HCOONa
f Accuracy ±5%.

of alkene **12b** afforded a 7:3 mixture of C_4-epimeric dichloroacetates **24d**. The different ratios were established via ^{1}H NMR integration of the OOCH or CH_3 signals (**24a–24c**) or the $CHCl_2$ absorptions (**24d**). Reactions of **12b** in AcOH or AcOH/H_2O (1:19) afforded acetate **24b** and alcohol **24c** respectively as C_4-epimer mixtures. In the latter case the epimer which was formed in 60% yield could be obtained in crystalline state. Tentatively in this isomer the hydroxylgroup is assigned an equatorial position. The other C_4-epimer of **24c**, formed in 40% yield, possessed an axial OH group because of the observed downfield shifts of the axial C_2 and C_6 protons in the ^{1}H NMR spectrum.[15] The aforementioned data most probably represent the state of affairs when the cyclisation is complete.

Most significant results with regard to the actual cyclisation mechanism were obtained in the HCOOH reaction of **13b**. After a reaction time of 2 hr a 61:39 mixture of **25a** and **25b** was obtained, combined yield 80%, in addition to a mixture of olefines **26** (20%). When the reaction was allowed to continue for 16 hr the ratio between **25a** and **25b** changed to 34:66 the amount of olefin almost remaining constant. Thus in essence an epimerization at the carbon bearing the formate residue has taken place *after the cyclisation had been completed.* The latter ratio was not significantly altered upon prolonging the reaction time for 120 hr although the decomposition of **25a** + **25b** into the olefin mixture **26** gradually continued.

A possible explanation for this result rests on the assumption that the *cis*-isomer **25a** is the kinetically formed product which is slowly converted into an equilibrium mixture of *cis*-**25a** and *trans*-**25b**. The latter isomer then is formed via isomerisation of **25a** through the corresponding tertiary carbenium ion which alternatively may give rise to olefin **26**. Support for this contention is found in the result of the AcOH-H_2O (1:19) cyclisation of **13b** (24 hr; r.t.) affording a mixture of the *cis* and *trans* hydroxy derivatives **25c** and **25d** in 85% yield. Crystallization of the mixture afforded pure **25c** in 69% yield. Formylation of **25c** with formic-acetic anhydride gave the formate **25a**.

Since the amount of **26** increased upon standing in HCOOH of the formate mixture **25a** + **25b** it can be considered unlikely that the isomerisation **25a** → **25b** proceeds via intermediacy of the alkenes **26**. The alternative explanation of the occurrence of tertiary carbenium ion pathway in the transformation of **25a** into **25b** has important bearings on the cyclisation mechanism.

Interesting behaviour was also found upon acid treatment of cyclohexenyl lactams **14a** and **14b**. From previous results in the solvolysis of cyclo-octenyl hydroxymethyl tosylates[6] the existence of an equilibrium between classical and nonclassical carbenium ions **A** and **B** was postulated in order to explain the formation of expected *endo*-bicyclo[3,3,1]nonanol-2 and anomalous *exo*-bicyclo[3,3,1]nonanol-3.

Similar results were found in the HCOOH-reaction of **14a** and **14b**, the products being *exo*-6- and *exo*-7 formates **27a** and **27b** and **28a** and **28b** in a ratio of 56:44. Separation of the isomers in the glutarimide series via crystallization allowed unambiguous structure determination of isomers **27b** and **28b** possessing most likely *cis*-C_4H–C_5H stereochemistry. It proved possible to alter this ratio considerably upon varying the acidic character of the cyclisation medium as is shown in Table 2 for the reaction of **14b**.

As can be deduced from these data major factors determining the ratio of **27** and **28** are acid strength and solvent nucleophilicity. Thus it appears that in stronger acidic less nucleophilic medium the proportion of the carbenium form **C** is enhanced. While **C**, however, is a necessary intermediate for the generation of the 7-*exo*-isomer it should be emphasized that a non-classical ion **D** is not a prerequisite for the formation of the 6-*exo*-isomer. The latter isomer could be also formed via a synchronous process as indicated in **E**. Furthermore, in contrast to the results reported in the carbocyclic series only the less stable 6-*exo*-isomer can be formed via this route which is in agreement with the experimental result. Concurrent formation of the more stable 6-*endo*-isomer could be expected if the classical form **C** is the real precursor for the generation of 6-substituted bicyclo[3,3,1]nonanes. Since none of the 6-*endo*-isomer could be detected in all of the cyclisation experiments performed it appears that the intermediacy of **C** exclusively

gives rise to hydride transfer from C_7. The driving force for the latter process is supposedly found in a relief of non-bonded N–C_7 interactions, which is expected to be more prominent when additional rigidity is added in the form of an extra ring.

Upon use of AcOH as medium a mixture of OH-lactam **29** and enamide **30** is formed, no tricyclic material being found. In a mixture of Ac_2O-AcOH (97.5:2.5) exclusive formation of the enamide **30** is observed. Of importance are the facts that under these circumstances no enamide dimerization occurs while the enamide itself is completely converted into the 54:46 mixture of **27b** and **28b** upon HCOOH reaction. When the cyclisation is carried out in HCOOH/Et_2O (3:10) for 168 hr a number of products is formed among which **27b** is present. No trace of the C_7-isomer **28b** is detected.

For further evaluation of the influence of double bond substitution in more rigid systems lactams **15b** and **16b** were also cyclized. In view of the aforementioned results the presence of a C_6-Me should enhance the cyclisation rate while the additional C_5-Me was expected to induce additional rigidity presumably slightly favoring an eventual boatlike transition state. Upon HCOOH reaction of **15b** (room temp. 20 hr) a quantitative conversion into a mixture of the aza-bicyclo[3,3,1] derivatives **31** and **32** occurred. Although **31** was produced in better than 90% yield, both compounds presumably were—at least in part—secondary products since exposure of lactam **15b** to HCOOH for 15 min resulted in its complete disappearance and formation of four cyclisation products: alkenes **31** and **32** and the corresponding C_6-formate **33** and its epimer. Similar results are found in the HCOOH-reaction of **16b** (room temp. 18 hr) *endo*-olefin **34** being the major product while in addition a minor amount of **35** is formed.

In AcOH slightly different behaviour of lactams **15b** and **16b** was noted. After 25 hr at room temperature **15b** cyclized for a major part into a mixture of olefines **31** and **32**. Under these circumstances **16b** gave mainly the enamide **36** which deteriorated partly upon prolonged reaction time. However, it proved possible to cyclize **16b** in Ac_2O/AcOH at room temperature to the 9:1 alkene mixture of **34** and **35** upon stirring for 168 hr. The slightly lessened reactivity of **16b** may well be explained in steric terms by the presence of the extra methyl substituent.

Spectral data. As can be derived from the data in

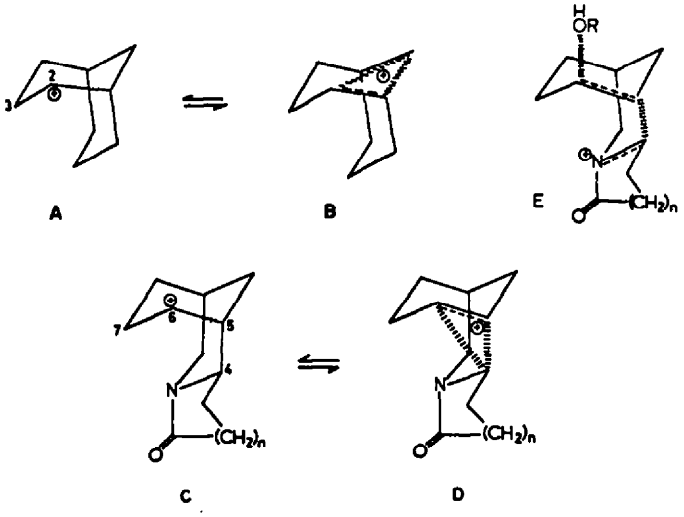
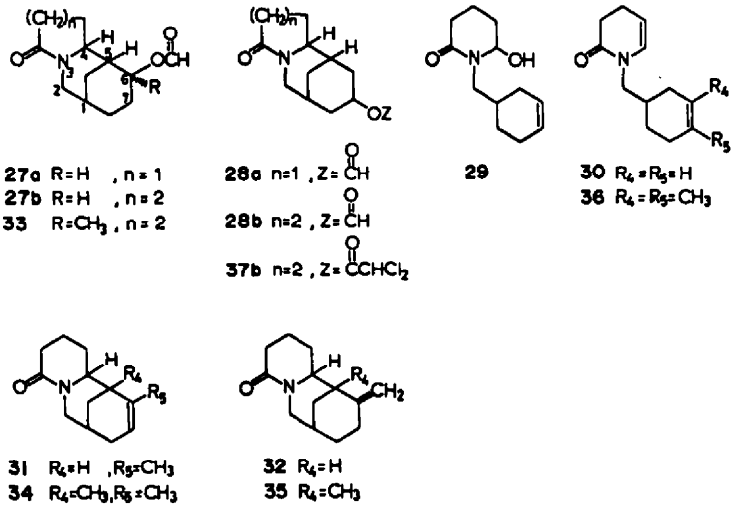


Table 2. Cyclisations of **14b**

Acid	Time	Temp.	%-6-isomer[a]	%-7-isomer[a]
HCOOH	18 hr	r.t.	54	46
HCOOH/HCOONa[b]	50 hr	45°	60	40
HCOOH	30 min	reflux	51	49
HCOOH/H_2O[c]	18 hr	r.t.	70	30
HCOOH/Et_2O[d]	6 days	r.t.	e	e
$CHCl_2COOH$	18 hr	r.t.	30	70
CH_3COOH	6 days	r.t.	f	f

a Determined via ^{1}H-NMR.
b 45 ml HCOOH, 1·11 mmole 14b, 1·84 mmole NaOCH (O)
c 15% H_2O by vol.
d HCOOH/Et_2O 1:10 by vol.
e Enamide formation.
f Enamide + hydroxylactam formation.



most spectra first-order analysis suffices to accurately determine the J-values. In some cases decoupling techniques have been applied to derive and confirm the magnitude of the parameters.

Important characteristics of all compounds are (1) the position of CHO around $\delta = 5$; (ii) the $H_{2,eq}$ absorption at δ 4.0–4.5 arising from its equatorial position in the N–CH_2 group; (iii) the H_6 signal at δ 3.0–4.0 providing vital information on the ring junction and the stereochemistry of the adjacent substituent and (iv) the position of $H_{2,ax}$ at δ 2.5 as the axial N–CH_2 proton.

As an illustration partial spectra of the *crude* cyclisation products **17a**, **20a** and **21a** are given in Fig. 1.

In all compounds the equatorial position of the formate residue is at once clear; furthermore from the multiplicity of H_4 in **20a** and **21a** an equatorial Me viz axial Et substituent are also prominent. The latter conclusions are confirmed from analysis of the H_6 signal in **20a** and **21a**; both from the difference in $W_{1/2}$ in the piperidone compounds as well as from the actual J-values in the pyrrolidones the presence of diaxial and ax–eq couplings are established. While the axial H_6 positions in the piperidone and pyrrolidone rings also follow from the observed $W_{1/2}$ values the observed coupling constants of $J_{6,7} = 6.0$ Hz and $J_{6,7'} = 6.0$ Hz in the latter series again emphasize the unreliable character of J-values for stereochemical assignments in 5-membered rings.

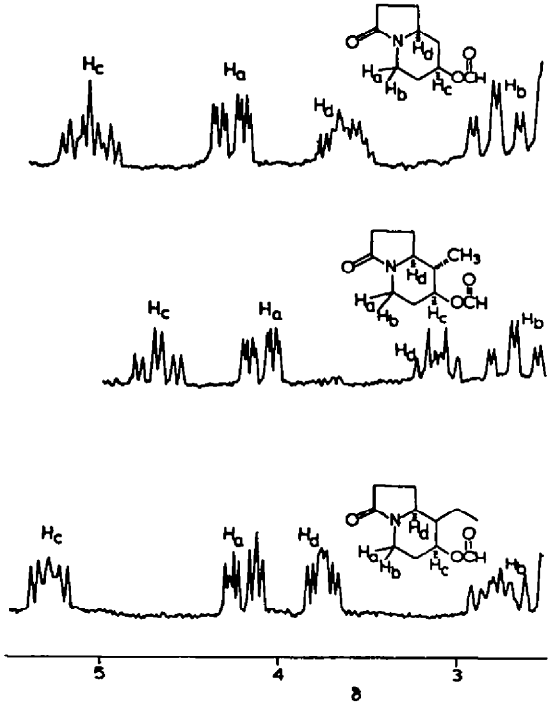


Fig. 1.

On the other hand, the observed $J_{4,5}$ in **20a** of 10.0 Hz is also in accord with an axial position of H_5. The $J_{4,5} = 3.0$ Hz finally in **21a** is indicative for the axial position of the Et group. The latter assignments were also verified by means of decoupling techniques. Similar conclusions can be derived from the analysis of the spectra of **17b**, **20b** and **21b**. Since the shape of the CHO signal was not informative, the spectra were also run in C_6D_6 which allowed accurate determination of J-values.

The spectra of the bicyclo[3,3,1] derivatives prove unequivocally the *exo* position of the formate residue. The magnitude of J-values in **28a** and **28b** indicate an axial C_7–H while the observed $W_{1/2} = 7.0$ Hz for C_6–H in **27a** and **27b** is in accordance with its equatorial position. Unfortunately, no definite proof is available for the C_4–C_5 *cis* stereochemistry, although several observations favor the latter assignment.

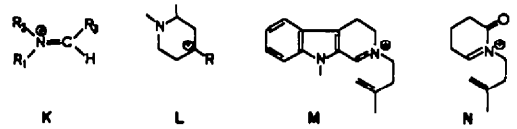
If a chairlike transition state is followed for the cyclisation process the C_4–C_5 relationship has to be *cis*. Since the corresponding *trans* stereochemistry, however, is found in the naturally occurring alkaloid sparteine,[17] which possesses therefore a boat-like cyclohexane structure a definite proof of the geometry of the present bicyclo[3,3,1]nonane derivatives has to await the results of an X-ray analysis.

DISCUSSION

From the data described above several conclusions can be drawn. First of all the heterocyclisations may be regarded as reactions of the biomimetic type of olefin cyclisations insofar yields, stereoselectivity and mildness of the procedure satisfy as criteria for this reaction type. Above all, however, the α-acylimmonium heterocyclisation method is highly versatile and practical. Secondly, the reactions have to be examined from the viewpoints of general immonium reactivity as well as the mechanis-

tically closely related carbocyclic cationic olefin cyclisations.

In the heterocyclic series no systematic investigations on the latter reaction type are known although from incidental reports some information can be derived. Thus one might consider different reactivities for immonium intermediates K depending on their structural characteristics.



K L M N

This however would not fully explain the observed behaviour as is shown by the following analysis. Chosing mono- and 2,2-disubstituted olefins as reference materials the necessary reaction conditions for cyclisation indicate the reactivity of the individual immonium ion. From the results reported so far it may seem that only the cyclic acylimmonium ion (K: R_1 = acyl) is reactive enough to induce cyclisations of mono- and 1,2-disubstituted olefins via HCOOH treatment at room temperature.† This conclusion, however, may be regarded as premature insofar cyclisation alone is considered.

When the general type of reaction is advanced from a classical viewpoint the secondary carbenium ion L (R = H) is involved as an intermediate which in general would have also a high fragmentation tendency since the nitrogen lone part is not blocked. On the contrary, if the terminating centre is tertiary carbenium ion L (R = Me) smooth cyclisation occurs for K: R_1, R_2 and R_3 = alkyl[18] as well as K: R_1, R_2 = alkyl, R_3 = aryl.[19] In the latter case even high stereoselectivity is reported. Since reaction of the methylbutenyl derivative M proceeds rapidly in solvents of relatively low acidity, e.g. AcOH/H_2O and AcOH/MeOH the initiating immonium centre must possess high reactivity. As compared to the α-acyl-immonium analogue N it might be probably even more reactive since only the AcOH/H_2O medium promotes cyclisation via N while AcOH/MeOH induces acetal exchange of the starting α-ethoxylactam.

These results can be rationalized in terms of a competition between fragmentation and ionisation. From extensive studies[20] it is known that a direct relationship exists between the rates of synchronous fragmentation and ionisation of molecules of the general type N–C–C–C–X. If the ionisation of the C–X bond is favored, e.g. because of generation of a relatively stable tertiary carbeniumion, fragmentation might well be comparatively slow resulting in the formation of cyclic products.

Thus in regard to the reactivity of the different immonium species it can be postulated that the high potential of the α-acyl derivative is due to a combination of two factors: sufficient reactivity to undergo nucleophilic olefin attack combined with a low tendency to fragmentation in the product. Coupled with a ready accessibility of a variety of starting materials it appears that the imide-oxylactam procedure is the method of choice for the construction of heterocyclics via olefin cyclisations.

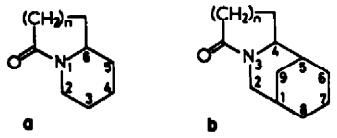
The second aspect is connected with the comparison of the α-acylimmonium process and the related reactions in the carbocyclic series. Although mechanistic investigations were not carried out several observations allow such a procedure to be justified. The extensive results out of the Stanford school indicate the allylic cation as the best model to compare with, the carbenium ion now being stabilized via the adjacent amide nitrogen instead of the C=C bond. From the experimental data on compounds **17**, **20** and **21** a stereoelectronically controlled cyclisation process is the only observed mode of reaction. Particularly for **21a** and **21b** this result is striking since models of the chairlike transition state indicate severe steric interactions between Et-group and lactam ring. A boatlike transition state, leading to the epimeric formate would therefore offer an alternative cyclisation route, especially because one of the destabilizing factors for such a form—the 1,4 interaction between nitrogen and C–H—is clearly absent. Yet, only the formate resulting from the chairform is obtained. Therefore the Stork–Eschenmoser hypothesis fully predicts also the outcome of the heterocyclic ring closure. The question whether this type of reaction proceeds via a synchronous or stepwise mechanism cannot be answered in a general way. The result of the DCOOD experiment leading to **19a** and the complete retention of stereochemistry in the Z-Et derivatives **21a** and **21b** both favor a nearly concerted bond formation. The large rate enhancement, however, observed in the cyclisation of the methylbutenyl derivatives **12a** and **12b** coupled with the formation of stereoisomers the proportion of which varies with the size of the acid anion strongly suggest the intermediacy of a terminating carbenium centre. Similar findings have already been discussed for the 3-aza-bicyclo[3,3,1] series, the difference between the classical carbenium intermediate (step-wise process) and a synchronous process being influenced by the nature of the acid used. Convincing evidence, however, for the operation of the two possible mechanisms in one cyclisation process is obtained from the results of the HCOOH reaction of **13b**. In the latter case both the kinetic (**25a**) and thermodynamic (**25b**) products are formed via consecutive steps. Since the rates of formation of the *cis*-isomer **25a** and the *trans*-isomer **25b** differ markedly it is clearly evident that the compounds have to be formed via different mechanistic routes. Following the rules of stereoelectronic control a synchronous pathway can only lead to the *cis*-product, while the stepwise process may result in the formation of both *cis* and *trans* isomers. The latter reaction presumably proceeds via heterolysis of the C–O bond in **25a** after which the tertiary carbenium ion via conformational isomerisation is converted in part to the more stable *trans*-isomer **25b**. As far as we are aware the aforementioned example is the first clear-cut case in which both cyclisation mechanisms indeed do operate in a concomitant fashion. At the same time, however, the observed process may be also considered rather unique. It might well be therefore that the two possibilities in the majority of cyclisation reactions are extremes on the scale of reaction and that depending on type of substrate and reaction conditions a path in between both extremes is followed.

Note added in proof: X ray analysis of compound **28b** was in complete accordance with the proposed stereochemistry.[26]

EXPERIMENTAL

IR spectra were recorded on Unicam SP 200 and Perkin–Elmer 257 instruments. ^1H NMR spectra were taken on Varian A-60, HA-100 and XL-100 instruments. All cyclised products showed correct mass spectral data and were recorded on an AEI-902 or Varian Mat 711 mass spectrometer. M.ps are uncorrected. Microanalyses were carried out by Messr. H. Pieters of the microanalytical department of our laboratory. The IUPAC-nomencla-

†For an example of a closely related reaction, see Ref. 5c.



a b

ture is followed in naming the compounds. However, in the description of the ^{1}H NMR spectra an uniform numbering system is used according to the formula's **a** and **b** (Scheme 6).

Preparation of alkenols. The alkenols 3-butene-1-ol, (z)-3-hexene-1-ol, 3 - methyl - 3 - butene - 1 - ol and 3 - cyclohexene - 1 - methanol were commercially available. (E) - 3 - pentene - 1 - ol was prepared from cyclopropyl - methyl - carbinol according to a known procedure.[21] 4 - Methyl - 3 - cyclohexene - 1 - methanol was prepared by a Diels–Alder reaction of isoprene and methylacrylate. Hydrolysis of the ester mixture to the corresponding carboxylic acid mixture, separation of the two isomers by repeated crystallization and reduction of the acid with LAH afforded the alkenol.[22a,b] 3,4 - Dimethyl - 3 - cyclohexene - 1 - methanol was prepared from 2,3-dimethylbutadiene and methylacrylate.[22a] 1'-Cyclohexene-2-ethanol was prepared from cyclohexanone and ethyl bromoacetate.[23]

Preparation of the imides. The imides were generally prepared according to the procedure of Mitsunobu *et al.*[24] 1 eq of alkenol, 1 eq of ϕ_3P and 1.2–1.4 eq of succinimide resp. glutarimide were dissolved in freshly distilled THF. To the cooled and stirred soln 1 eq dimethylazodicarboxylate in THF was added slowly. Stirring was continued overnight at r.t.

The solvent is then evaporated under reduced pressure and the residual oil is taken up in $CHCl_3$ and 5% KOH soln. The aqueous layer is extracted 3 times with $CHCl_3$. The combined organic layers are then washed with 2N HCl (3 times), $NaHCO_3$ aq and sat NaCl aq dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil is taken up in EtOAc, upon which the $\phi_3P \rightarrow 0$ crystallizes. The imides were obtained by vacuum-destillation (I), column chromatography (II) or crystallization from EtOH (III) (Table 3).

†Dipe = diisopropylether.

General procedure for the synthesis of ethoxylactams.[25] The $NaBH_4/H^+$ reductions were carrried out with a stirred soln of imide in EtOH at temps of −15° to −10° (for glutarimides) or 0°–5° (for succinimides) with an excess of $NaBH_4$. At regular intervals (mostly 15 min) 2–3 drops of 2N HCl in EtOH were added. The reaction time was 4–5 hr. The excess $NaBH_4$ was destroyed in 15–30 min at the temp. of the reaction by adding acid till pH = 3. The mixture was stirred for an additional 45–60 min at +5° and poured into dil $NaHCO_3$ aq. Extraction with $CHCl_3$ and work-up of the extract yielded the crude reaction product. The products were purified by column chromatography on silicagel.

General procedure for the cyclisation reaction. The ethoxylactam is dissolved in HCOOH and the soln is stirred for 18 hr (unless otherwise indicated) at r.t. Two work-up methods were used.

Method A: The solvent is evaporated under reduced pressure at r.t. The residual oil is taken up in $CHCl_3$ and washed with dil $NaHCO_3$ aq and with sat NaCl aq.

Method B: The soln is poured into dil $NaHCO_3$ aq and extracted with $CHCl_3$ (5 times).

Work-up of the organic layer afforded the reaction products.

1 - *Aza* - 4 - *formyloxy-bicyclo*[4.3.0]*nonane* - 9 - *one* (**17a**)

(a) 1-(3-*Butenyl*)-5-*ethoxy-pyrrolidinone*-2 (**9a**). Compound **1a** (4.0 g; 26.0 mmole) was reduced in EtOH (200 ml) with 7 g of $NaBH_4$ at 0° during 4 hr. Work-up afforded **9a** as an oil. Vacuum destillation yielded 3.4 g (18.5 mmole) of **9a** (85–92°/0.05 mm), yield: 71%. IR($CHCl_3$): 1680 cm^{-1} (lactam-CO). ^{1}H NMR: δ($CDCl_3$): 5.78 (m, 1H, CH=CH_2), 4.80–5.30 (m, 3H, C=CH_2 and N–CHOEt), 3.0–3.86 (m, 4H, OCH_2–CH_3, N–CH_2–), 1.20 (t, 3H, –OCH_2–CH_3), 1.9–2.6 (m, 6H).

(b) *Cyclisation of* **9a**. Compound **9a** (200 mg; 1.09 mmole) was dissolved in 3 ml of HCOOH and stirred for 18 hr at r.t. Work-up (method A) afforded 199 mg (1.09 mmole, quant. yield) of **17a** as an oil, which crystallized upon treatment with dipe;† m.p.: 82–87°. IR($CHCl_3$): 1720 cm^{-1} (ester-CO), 1675 cm^{-1} (lactam-CO). ^{1}H NMR: δ($CDCl_3$): 8.05 (s, 1H, OOCH), 5.05 (t of t, $J_1 = J_2 = 11$ Hz, $J_3 = J_4 = 4$ Hz, 1H, H_6-ax), 4.25 (m, $J_1 = 14$ Hz, $J_2 = 5.5$ Hz, J_3 =

Table 3. Preparation of imides

imide	yield[a]	method[d]	physical constants
1a	65	I,II[c]	
1b	57	I,II[b]	
2a	64	I	85–95°/0·05 mm
2b	44	I	90–98°/0·03 mm
3a	60	I	94–102°/0·02 mm
3b	59	I,II[b]	
4a	72	I	73–79°/0·01 mm
4b	48	I	78–88°/0·05 mm
5b	53	II,III[b]	59–60° (m.p.)
6a	34	I,II,III[c]	74–76° (m.p.)
6b	69	III	100–102° (m.p.)
7b	60	III	98–100° (m.p.)
8b	56	III	104–106° (m.p.)

a Not optimized.

b Columnchromatography on silicagel (act.II) with chloroform/acetone 19/1 as an eluent.

c Columnchromatography on silicagel (act.I) with chloroform/acetone 4/1 as an eluent.

d Methods of preparation I, II and III indicated in the experimental.

2 Hz, 1H, H_2-eq) 3.62 (m, $W_{1/2}$ = 28 Hz, 1H, H_6) 2.76 (t of d, $J_1 = J_2 = 14$ Hz, $J_3 = 3$ Hz, 1H, H_2-ax) 1.20–2.70 (m, 8H). (Found: C, 59.1; H, 7.2; N, 7.7. $C_9H_{13}NO_3$ M = 183.20. Calc.: C, 59.00; H, 7.15; N, 7.65%).

(c) 1- *-Aza - 4 - hydroxy-bicyclo*[4.3.0]*nonane - 9 - one* (**18a**). Compound **17a** (40 mg; 0.22 mmole) was dissolved in 15 ml of MeOH and 3 drops of conc HCl were added. The soln was refluxed for 1 hr. Work-up (method A) afforded 32 mg (0.21 mmole) of **18a** as an oil, which crystallized upon treatment with dipe; m.p. 99–101°. IR($CHCl_3$): 1650 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 4.04–4.31 (m, J_1 = 13 Hz, J_2 = 5 Hz, J_3 = 2 Hz, 1H, H_2-eq), 3.35–4.00 (m, 2H, H_6 and H_4-ax), 1.00–2.80 (m, 10H). (Found: C, 62.0; H, 8.5; N, 8.9. $C_8H_{13}NO_2$ M = 155.19. Calc.: C, 61.91; H, 8.44; N, 9.03%).

1-*Aza-8-formyloxy-bicyclo*[4,4,0]*decane-2-one* (**17b**)

(a) 1-(3-*Butenyl*)-6-*ethoxy-piperidone*-2 (**9b**). Compound **1b** (1.86 g; 11.1 mmole) was reduced in EtOH (100 ml) with 3.6 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography on silicagel (act. II) with EtOAc as an eluent afforded 1.55 g (7.9 mmole) of **9b** as an oil, yield 71%. IR($CHCl_3$) 1635 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 5.50–6.05 (m, 1H, $CH{=}CH_2$), 4.90–5.20 (m, 2H, $CH{=}CH_2$), 4.56 (m, 1H, NCHOEt), 2.90–3.95 (m, 4H, OCH_2–CH_3 and N–CH_2), 1.20 (t, J = 7 Hz, 3H, OCH_2–CH_3), 1.38–2.60 (m, 8H).

(b) *Cyclisation of* **9b**. Compound **9b** (1.08 g; 5.5 mmole) was dissolved in 13 ml of HCOOH and stirred for 18 hr at r.t. Work-up (method A) afforded 1.06 g (5.5 mmole, quant. yield) of **17b** as an oil, which crystallized upon treatment with dipe; m.p.: 103–104° (dipe). IR($CHCl_3$): 1725 cm^{-1} (ester-CO), 1635 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 8.02 (s, 1H, OOCH), 4.70–5.20 (m, 2H, H_2-eq and H_4-ax), 3.38 (m, $W_{1/2}$ = 20 Hz, 1H, H_6), 1.20–2.70 (m, 11H). δ: (C_6D_6): 8.09 (s, 1H, HCOO), 4.86 (m, J_1 = 14 Hz, J_2 = 5 Hz, J_3 = 3 Hz, 1H, H_2-eq), 4.65 (septet, $J_1 = J_2 = 11$ Hz, $J_3 = J_4 = = 4$ Hz, 1H, H_4-ax), 2.53 (m, $W_{1/2}$ = 23 Hz, 1H, H_6), 0.60–2.30 (m, 11H). (Found: C, 61.0; H, 7.7; N, 7.1. $C_{10}H_{15}NO_3$ M = 197.23. Calc.: C, 60.89; H, 7.67; N, 7.10%).

1-*Aza-4-formyloxy-5-methyl-bicyclo*[4.3.0]*nonane-9-one* (**20a**)

(a) 1 - [(*E*) - 3 - *Pentenyl*] - 5 - *ethoxy - pyrrolidinone* - 2 (**10a**). Compound **2a** (3.0 g; 18.0 mmole) was reduced in EtOH (100 ml) with 5 g of $NaBH_4$ at 0° during 4 hr. Work-up and column chromatography on silicagel (act I) with $CHCl_3$/acetone 4/1 as an eluent afforded 3.0 g (15.2 mmole) of **10a** as an oil, yield 85%. IR($CHCl_3$): 1680 cm^{-1} (lactam-CO). ^1H NMR: δ(CCl_4): 5.39 (m, 2H, HC=CH), 4.87 (m, 1H, NCHOEt), 2.84–3.60 (m, 4H, O–CH_2–CH_3 and N–CH_2), 1.63 (broad d, 3H, C=C–CH_3), 1.17 (t, 3H, O–CH_2–CH_3), 1.8–2.5 (m, 6H).

(b) *Cyclisation of* **10a**. Compound **10a** (200 mg; 1.01 mmole) was dissolved in 3 ml of HCOOH and stirred for 18 hr at r.t. Work-up (method A) afforded 200 mg (1.01 mmole, quant. yield) of **20a** as an oil, which crystallized upon treatment with dipe; m.p.: 83–85°. IR($CHCl_3$): 1720 cm^{-1} (ester-CO), 1680 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 8.00 (s, 1H, OOCH), 4.68 (t of d, $J_1 = J_2 = 11$ Hz, $J_3 = 4$ Hz, 1H, H_4-ax), 4.11 (m, $J_1 = 14$ Hz, J_2 = 5.5 Hz, $J_3 = 2$ Hz, 1H, H_2-eq), 3.11 (d of t, $J_1 = 10$ Hz, $J_2 = J_3$ = 6 Hz, 1H, H_6), 2.68 (t of d, $J_1 = J_2 = 14$ Hz, $J_3 = 3$ Hz, 1H, H_2-ax), 0.85 (d, 3H, C–CH_3), 1.10–2.90 (m, 7H). (Found: C, 60.8; H, 7.6; N, 7.0. $C_{10}H_{15}NO_3$ M = 197.23. Calc.: C, 60.89; H, 7.67; N, 7.10%).

1-*Aza-7-methyl-8-formyloxy-bicyclo*[4.4.0]*decane-2-one* (**20b**)

(a) 1-[(*E*)-3-*Pentenyl*]-6-*ethoxy-piperidone*-2 (**10b**). Compound **2b** (1.46 g; 8.1 mmole) was reduced in EtOH (100 ml) with 2.70 g of $NaBH_4$ at − 12° during 5 hr. Work-up and column chromatography on silicagel (act II) with EtOAc as an eluent afforded 1.47 g (7.0 mmole) of **10b** as an oil, yield 86%. IR($CHCl_3$): 1645 cm^{-1} (lactam-CO). ^1H NMR: δ(CCl_4): 5.20–5.60 (m, 2H, CH=CH), 4.52 (m, 1H, NCHOEt), 1.18 (t, J = 7 Hz, 3H, O–C–CH_3), 1.42–3.89 (m, 15H).

(b) *Cyclisation of* **10b**. Compound **10b** (499 mg; 2.36 mmole) was dissolved in 4.5 ml of HCOOH and stirred for 18 hr at r.t. Work-up (method A) afforded 500 mg (2.36 mmole, quant. yield) of **20b** as an oil, which crystallized upon treatment with dipe; m.p.: 85–87° (dipe). IR($CHCl_3$): 1635 cm^{-1} (lactam-CO), 1720 cm^{-1} (ester-CO). ^1H NMR: δ($CDCl_3$): 8.08 (s, 1H, OOCH), 4.87 (m, $J_1 = 14$ Hz, $J_2 = 5$ Hz, $J_3 = 3$ Hz, 1H, H_2-eq), 4.72 (t of d, $J_1 = J_2 = 11$ Hz, $J_3 = 5$ Hz, 1H, H_4-ax), 3.04 (m, $W_{1/2}$ = 25 Hz, H_6), 2.52 (t of d, $J_1 = J_2 = 14$ Hz, $J_3 = 3$ Hz, 1H, H_2-ax), 0.94 (d, 3H, C–CH_3), 1.20–2.47 (m, 9H). δ: (C_6D_6): 8.16 (s, 1H, OOCH), 4.47 (m, $J_1 = J_2 = 11$ Hz, $J_3 = 5$ Hz, 1H, H_4-ax), 4.90 (m, $J_1 = 14$ Hz, $J_2 = 5$ Hz, $J_3 = 3$ Hz, 1H, H_2-eq), 0.56 (d, 3H, C–CH_3), 0.80–2.50 (m, 11H). (Found: C, 62.6; H, 8.2; N, 6.7. $C_{11}H_{17}NO_3$ M = 211.25. Calc.: C, 62.54; H, 8.11; N, 6.63%).

1-*Aza-4-formyloxy-5-ethyl-bicyclo*[4.3.0]*nonane-9-one* (**21a**)

(a) 1-[(*Z*)-3-*Hexenyl*]-5-*ethoxy-pyrrolidone*-2 (**11a**). Compound **3a** (2.0 g; 11.0 mmole) was reduced in EtOH (100 ml) with 3.5 g of $NaBH_4$ at 0° during 4 hr. Work-up and column chromatography on silicagel (act I) with $CHCl_3$/acetone 4/1 as an eluent afforded 1.7 g (8.1 mmole) of **11a** as an oil, yield 73%. IR($CHCl_3$): 1680 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 5.47 (m, 2H, CH–CH) 4.88 (m, 1H, NCHOEt), 2.9–3.7 (m, 4H, OCH_2–CH_3 and N–CH_2), 1.22 (t, 3H, OCH_2–CH_3), 0.95 (t, 3H, C=C–CH_2–CH_3), 1.9–2.6 (m, 8H).

(b) *Cyclisation of* **11a**. Compound **11a** (200 mg; 0.89 mmole) was dissolved in 3 ml of HCOOH and stirred for 18 hr at r.t. Work-up (method B) afforded 200 mg (4.89 mmole, quant. yield) of **21a** as an oil. IR($CHCl_3$): 1710 cm^{-1} (ester-CO) 1670 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 8.08 (3, 1H, OOCH), 5.10 (m, $W_{1/2}$ = 25 Hz, 1H, H_4-ax), 4.19 (m, $J_1 = 14$ Hz, $J_2 = 5.5$ Hz, J_3 = 2 Hz, 1H, H_2-eq), 3.74 (m, $J_1 = J_2 = 6$ Hz, $J_3 = 3$ Hz, 1H, H_6), 2.76 (m, $W_{1/2}$ = 25 Hz, 1H, H_2-ax), 0.8–2.60 (m, 12H).

(c) 1-*Aza-4-hydroxy-5-ethyl-bicyclo*[4.3.0]*nonane-9-one* (**22a**). Compound **21a** (108 mg; 0.48 mmole) was dissolved in 40 mol of MeOH with 3 drops of HCl (conc) and refluxed for 1 hr. Work-up (method A) afforded 90 mg of **22a** (0.46 mmole, 96%) recrystallization from ether/dipe afforded pure **22a**; m.p.: 104–106°. IR($CHCl_3$): 1650 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 4.9 (m, 1H, H_4-ax), 4.12 (m, $J_1 = 13$ Hz, $J_2 = 5$ Hz, $J_3 = 2$ Hz, 1H, H_2-eq), 3.66 (m, $J_1 = J_2 = 7$ Hz, $J_3 = 3$ Hz, 1H, H_6), 1.1 (m, 3H, CH_2–CH_3), 1.2–2.9 (m, 10H with at 2.67 m, $J_1 = J_2 = 14$ Hz, $J_3 = 4$ Hz, 1H, H_2-ax). (Found: C, 65.5; H, 9.5; N, 7.6. $C_{10}H_{17}NO_2$ M = 183.24. Calc.: C, 65.54; H, 9.35; N, 7.64%).

1-*Aza-7-ethyl-8-formyloxy-bicyclo*[4.4.0]*decane-2-one* (**21b**)

(a) 1-[(*Z*)-3-*Hexenyl*]-6-*ethoxy-piperidone*-2 (**11b**). Compound **3b** (1.44 g; 7.4 mmole) was dissolved in EtOH (100 ml) with 2.62 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography on silicagel (act II) with EtOAc on an eluent afforded 1.35 g (6.0 mmole) of **11b** as an oil, yield 81%. IR($CHCl_3$): 1640 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 5.13–5.59 (m, 2H, CH–CH), 4.59 (m, 1H, NCHOEt), 2.90–3.88 (m, 4H, NCH_2 and O–CH_2–CH_3), 1.21 (t, 3H, O–CH_2–CH_3), 0.93 (t, 3H, C=C–C–CH_3) 1.35–2.55 (m, 10H).

(b) *Cyclisation of* **11b**. Compound **11b** (160 mg; 0.71 mmole) was dissolved in 80 ml of HCOOH and stirred for 95 hr at r.t. Work-up (method A) afforded 160 mg (0.71 mmole, quant. yield) of **21b** as an oil. IR($CHCl_3$): 1625 cm^{-1} (lactam-CO) 1710 cm^{-1} (ester-CO). ^1H NMR: δ($CDCl_3$): 8.05 (s, 1H, OOCH), 4.58–5.25 (m, 2H, H_4-ax and H_2-eq), 3.42 (m, 1H, H_6), 0.75–2.83 (m, 15H).

(c) 1-*Aza-7-ethyl-8-hydroxy-bicyclo*[4.4.0]*decane-2-one* (**22b**) Compound **21b** (160 mg; 0.71 mmole) was dissolved in 40 ml of the MeOH, 4 drops of HCl (conc) were added and the soln was refluxed for 1 hr. Work-up (method A) afforded 138 mg of **22b** (0.6 mmole, 97%) as an oil, which solidified; m.p. 96–99° (dipe). IR($CHCl_3$): 1620 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 4.58–4.88 (m, 1H, H_2-eq), 3.62–3.98 (m, 1H, H_4-ax. After addition of D_2O the signal became a d of t, $J_1 = 11$ Hz, $J_2 = J_3 = 4$ Hz) 3.20–3.50 (m, 1H, H_6) 0.85–2.65 (m, 16H). (Found: C, 66.9; H, 9.6; N, 7.1. $C_{11}H_{19}NO_2$ M = 197.27. Calc.: C, 66.97; H, 9.71; N, 7.10%).

1 - *Aza* - 8 - *methyl* - 8 - *dichloroacetoxy* - *bicyclo*[4.4.0]*decane* - 2 - *one* (**24d**)

(a) 1(3 - *Methyl* - 3 - *butenyl*) - 6 - *ethoxy-piperidone* - 2 (**12b**). Compound **4b** (2.12 g; 11.7 mmole) was reduced in EtOH (100 ml) with 4 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography on silicagel (act II) with EtOAc as an eluent afforded 1.44 g (6.8 mmole) of **12b** as an oil, yield 58%. IR($CHCl_3$): 1650 cm^{-1} (lactam-CO). ^1H NMR: δ(CCl_4): 4.51 (m, 1H, NCHOEt), 4.57–4.78 (m, 2H, $C{=}CH_2$), 2.90–3.82 (m, 4H,

O–CH$_2$–CH$_3$ and NCH$_2$) 1.38–2.45 (m, 11H), 1.19 (t, 3H, O–CH$_2$–CH$_3$).

(b) *Cyclisation of* **12b** *in* $CHCl_2COOH$. Compound **12b** (70 mg; 0.33 mmole) was dissolved in 3 ml of $CHCl_2COOH$ and stirred for 2 hr at r.t. Work-up (method B, removal of $CHCl_2COOEt$ by coevaporation with $CHCl_3$, 10 times) afforded 97 mg (0.33 mmole, quant. yield) of a 7:3 mixture of the two epimers **24d** as an oil. The two isomers could not be separated by column chromatography. IR($CHCl_3$): 1750 cm^{-1} (ester-CO), 1620 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 5.91 (70%) and 5.84 (30%) (2s, 1H, CHCl$_2$), 4.78 (m, 1H, H$_2$-eq), 3.48 (m, $W_{1/2}$ = 25 Hz, 1H, H$_4$), 1.58 and 1.69 (two s, 3H, C–CH$_3$), 1.10–2.92 (m, 11H). (Found: C, 49.2; H, 5.8; N, 4.8; Cl, 24.0. $C_{12}H_{17}NO_3Cl_2$ M = 294.18. Calc.: C, 48.99; H, 5.83; N, 4.76; Cl, 24.11%).

1-*Aza*-8-*methyl*-8-*hydroxy*-*bicyclo*[4.4.0]*decane*-2-*one* (**24c**)

Via cyclisation of **12b** *in* H_2O/HOAc (19:1). Compound **12b** (200 mg; 0.95 mmole) was dissolved in 95 ml H_2O and 5 ml HOAc. The soln was stirred for 2 hr at r.t. Work-up (method B) afforded 172 mg (0.95 mmole, quant. yield) of a 60:40 mixture of the two epimers **24c** as an oil. IR($CHCl_3$): 1620 cm^{-1} (lactam-CO). ^1H NMR ($CDCl_3$): 4.49–4.85 (m, 1H, H$_2$-eq), 3.45–3.83 (m, 0.4H, H$_6$-ax), 3.10–3.43 (m, 0.6H, H$_6$-ax), 1.28 (s, 1.8H, CH$_3$), 1.21 (s, 1.2H, CH$_3$), 1.35–3.05 (m, 11H). The isomer with the equatorial OH crystallizes upon standing at 0° (44 mg; 0.24 mmole, 25% yield); m.p. 107–109° (dipe). IR($CHCl_3$): 1620 cm^{-1} (lactam-CO). ^1H NMR ($CDCl_3$): 4.65–4.85 (m, 1H, H$_2$-eq), 3.10–3.43 (m, 1H, H$_6$-ax), 1.35–2.66 (m, 11H), 1.28 (s, 3H, CH$_3$). (Found: C, 65.5; H, 9.4; N, 7.7. $C_{10}H_{17}NO_2$ MW = 183.24. Calc.: C, 65.54; H, 9.35; N, 7.64%).

1-*Aza*-4-*hydroxy*-*tricyclo*[8.4.0^{1,10}.0^{4,9}]*tetradecane*-14-*one* (**25a**)

(a) 1 - [2 - (*Cyclohexenyl* - 1)*ethyl*] - 6 - *ethoxy*-*piperidone* - 2 (**13b**). Compound **5b** (0.34 g; 1.54 mmole) was reduced in EtOH (100 ml) with 1.54 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography on silicagel (act II) with EtOAc as an eluent afforded 0.32 g (1.27 mmole) of **13b** as an oil, yield 83%. IR($CHCl_3$): 1640 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 5.42 (m, 1H, C=CH), 4.56 (m, 1H, NCHOEt), 2.93–4.00 (m, 4H, NCH$_2$ and O–CH$_2$–CH$_3$), 1.23 (t, 3H, OCH$_2$–CH$_3$), 1.43–2.53 (m, 16H).

(b) *Cyclisation of* **13b** *in* AcOH/H_2O (1:19). Compound **13b** (72 mg; 0.29 mmole) was dissolved in 100 ml of H_2O and 5 ml of HOAc and the soln was stirred for 2 hr at r.t. (Work-up (method B) afforded 65 mg (quant. yield) of an oily mixture of **25c** and **25d**. Crystallization with dipe afforded 44 mg (0.20 mmole, 68%) of **25c** (GLC pure), m.p. 183–185°. IR($CHCl_3$): 1620 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 4.66–4.91 (m, 1H, H$_2$-eq), 3.30–3.59 (m, 1H, H$_4$), 1.0–2.73 (m, 19H). (Found: C, 70.0; H, 9.4; N, 6.4. $C_{13}H_{21}NO_2$ M = 223.31. Calc.: C, 69.92; H, 9.48; N, 6.27%).

3-*Aza*-11-*dichloroacetoxy*-*tricyclo*[7.3.1.0^{3,8}]*tridecane*-4-*one* **37b**; 3-*Aza*-11-*formyloxy*-*tricyclo*[7.3.1.0^{3,8}]*tridecane*-4-*one* **28b**; 3-*Aza*-10-*formyloxy*-*tricyclo*[7.3.1.0^{3,8}]*tridecane*-4-*one* (**27b**)

(a) 1-[(3-*Cyclohexenyl*)-*methyl*]-6-*ethoxy*-*piperidone*-2 (**14b**). Compound **6b** (3.0 g; 14.5 mmole) was reduced in EtOH (200 ml) with 4.6 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography on silicagel (act II) with EtOAc as an eluent afforded 2.87 g (11.7 mmole) of **14b** as an oil, yield 81%. IR($CHCl_3$): 1635 cm^{-1} (lactam-CO). ^1H NMR: δ(CCl_4): 5.57 (broad s, 2H, HC=CH), 4.51 (m, 1H, NCHOEt), 3.28–3.84 (m, 2H, OCH$_2$ and 1H, NCH–C–C–C=C), 1.18 (t, 3H, O–C–CH$_3$), 1.30–2.90 (m, 14H).

(b) *Cyclisation of* **24b** *in* HCOOH. Compound **14b** (1.51 g; 6.4 mmole) was dissolved in 7 ml of HCOOH and stirred for 18 hr at r.t. Work-up (method A) afforded 1.52 g (6.4 mmole, quant. yield) of a 56:44 mixture of **27b** and **28b** (according to NMR). Fractionated crystallization with ether/EtOH afforded 220 mg (0.94 mmole, 14%) of pure **28b**, m.p. 153–155° (dipe), 45 mg 3%) of pure **27b**, m.p. 112–114° (EtOH) and a crystalline rest fraction, consisting of a mixture of the two isomers.

Compound **27b**, m.p. 112–114° (EtOH). IR($CHCl_3$): 1636 cm^{-1} (lactam-CO), 1720 cm^{-1} (ester-CO). ^1H NMR: δ($CDCl_3$): 8.05 (s, 1H, OOCH), 5.36 (broad s, $W_{1/2}$ = 7 Hz, 1H, H$_6$-eq), 4.62 (d of m, J_d = 13 Hz, 1H, H$_2$-eq), 3.52 (m, $W_{1/2}$ = 20 Hz, 1H, H$_4$), 1.10–2.95 (m, 15H). (Found: C, 66.0; H, 8.1; N, 5.9. $C_{13}H_{19}NO_3$ MW = 237.29. Calc.: C, 65.80; H, 8.07; N, 5.90%).

Compound **28b**, m.p. 153–155° (dipe). IR($CHCl_3$): 1630 cm^{-1} (lactam-CO), 1720 cm^{-1} (ester-CO). ^1H NMR: δ($CDCl_3$): 7.97 (s, 1H, OOCH), 5.30 (septet, $W_{1/2}$ = 25 Hz, $J_1 = J_2$ = 11.5 Hz. $J_3 = J_4$ = 5 Hz, 1H, H$_7$-ax), 4.62 (d of m, J_d = 13 Hz, 1H, H$_2$-eq), 3.44 (m, $W_{1/2}$ = 15 Hz, 1H, H$_4$), 1.25–2.93 (m, 15H). (Found: C, 65.9; H, 8.1; N, 5.8. $C_{13}H_{29}NO_3$ M = 237.29. Calc.: C, 65.80; H, 8.07; N, 5.90%).

(c) *Cyclisation of* **14b** *in* $CHCl_2COOH$. Compound **14b** (162 mg; 0.68 mmole) was dissolved in 4.5 ml of $CHCl_2COOH$ and stirred for 18 hr at r.t. Work-up (method B) afforded a 70:30 mixture of the C_7 resp. C_6 isomers. The C_7 isomer **37b** crystallized upon treatment with either, m.p. 132–133° (ether). IR(KBr): 1640 cm^{-1} (lactam-CO), 1745 cm^{-1} (ester-CO). ^1H NMR: δ($CDCl_3$): 5.85 (s, 1H, OOCCHCl$_2$), 5.39 (septet, $W_{1/2}$ = 25 Hz, 1H, H$_7$-ax), 4.63 (d of m, J = 14 Hz, 1H, H$_2$-eq), 3.40 (m, 1H, H$_4$). 1.20–2.90 (m, 15H). (Found: C, 52.6; H, 6.0; N, 4.4; Cl, 22.1. $C_{14}H_{19}NO_3Cl_2$ M = 320.21. Calc.: C, 52.51; H, 5.98; N, 4.38; Cl, 22.15%).

3-*Aza*-10-*methyl*-*tricyclo*[7.3.1.0^{3,8}]*tridec*-10-*ene*-4-*one* (**31**)

(a) 1-[(4-*Methyl*-3-*cyclohexenyl*)*methyl*]-6-*ethoxy*-*piperidone*-2 (**15b**). Compound **7b** (1.5 g; 7.2 mmole) was reduced in EtOH (100 ml) with 2.6 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography on silicagel (act II) with EtOAc as an eluent afforded 1.54 g (6.1 mmole) of **15b** as an oil, yield 85%. IR($CHCl_3$): 1640 cm^{-1} (lactam-CO). ^1H NMR: δ(CCl_4): 5.27 (m, 1H, C–C–H), 4.50 (m, 1H, NCH$_2$OEt), 3.25–3.85 (m, 2H, OCH$_2$CH$_3$ and 1H, NCH–C–C–C=C), 1.14 (t, 3H, OCH$_2$–CH$_3$) 1.05–2.90 (m, 17H).

(b) *Cyclisation of* **15b**. Compound **15b** (1.43 g; 5.70 mmole) was dissolved in 7 ml of HCOOH and stirred for 20 hr at r.t. Work-up (method B) afforded 1.19 g of an oily mixture (9/1) of **31** and **32** which solidified. Recrystallization from dipe afforded 820 mg (4 mmole) of pure crystallyne **31** (yield 70%), m.p. 62–64° (dipe). IR($CHCl_3$): 1625 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 5.54 (m, 1H, C=C–H), 4.69 (d of m, J_d = 13 Hz, 1H, H$_2$-eq), 3.41 (m, $W_{1/2}$ = 17 Hz, 1H, H$_4$), 1.40–2.75 (m, 16H). (Found: C, 76.2; H, 9.3; N, 6.7. $C_{13}H_{19}NO$ M = 205.29. Calc.: C, 76.05; H, 9.33; N, 6.82%).

3-*Aza*-9,10-*dimethyl*-*tricyclo*[7.3.1.0^{3,8}]*tridec*-10-*ene*-4-*one* (**34**)

(a) 1 - [(3,4 - *Dimethyl* - 3 - *cyclohexenyl*)*methyl*] - 6 - *ethoxy* - *piperdone*-2 (**16b**). Compound **8b** (1.08 g; 4.6 mmole) was reduced in EtOH (100 ml) with 1.8 g of $NaBH_4$ at −12° during 5 hr. Work-up and column chromatography on silicagel (act II) with EtOAc as an eluent afforded 1.02 g (3.85 mmole) of **16b** as an oil, yield 84%. IR($CHCl_3$): 1640 cm^{-1} (lactam-CO). ^1H NMR: δ(CCl_4): 4.51 (m, 1H, NCH–OEt), 3.30–3.90 (m, 2H, OCH$_2$ and 1H, NCH–C–C–C=C), 1.50–2.90 (m, 14H), 1.57 (5, 6H, CH$_3$–C=C–CH$_3$), 1.19 (t, 3H, –O–CH$_2$–CH$_3$).

(b) *Cyclisation of* **16b**. Compound **16b** (1.0 g; 3.7 mmole) was dissolved in 6 ml of HCOOH and stirred for 5 hr at r.t. Work-up (method B) afforded an oily mixture (9/1) of **34** and **35** in quant. yield, which solidified. Recrystallization from dipe afforded 620 mg (2.8 mmole) of **34** (76%), m.p. 104–105° (dipe). IR($CHCl_3$): 1620 cm^{-1} (lactam-CO). ^1H NMR: δ($CDCl_3$): 5.57 (m, 1H, C=CH), 4.79 (d of m, J_d = 13 Hz, 1H, H$_2$-eq), 3.08 (m, $W_{1/2}$ = 16 Hz, 1H, H$_4$), 1.12 (s, 3H, –C–CH$_3$), 1.30–2.69 (m, 15 H). (Found: C, 76.6; H, 9.6; N, 6.4. $C_{14}H_{21}NO$ M = 219.32. Calc.: C, 76.66; H, 9.65; N, 6.39%).

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