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FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS I. - BICYCLIC AND PENTACYCLIC LACTAMS FROM CARBAMOYLATED CHLOROENAMINES

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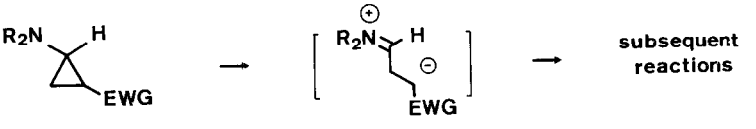
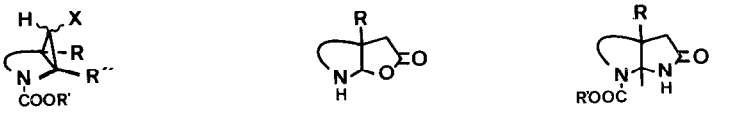
Abstract - Carbamoylated chloroenamines 15 were synthesized by acylation of cyclic enamines 11 with an arylisocyanate and subsequent chlorination using NCS. In the case of the seven membered enamine 11c a bicyclic ß-lactam 16c was isolated as primary product, which rearranged to the conjugated chloroenamine 15c via its non-conjugated isomer 14c. In acetonitrile as a solvent this isomerization additionally produced a methylene pyrroline derivative 19c as byproduct. Interaction of 15a-d with succinimide (20) gave succinimido cis-bicycloalkane carboxamides 21a-d. A trans bicyclic carboxamide 22e resulted from the analogous reaction of 15e as established by X-ray structural analysis. Upon heating 21 or 22 produced bicyclic lactams 25 in a homoenamine type reaction. Reduction of 25a by lithium aluminum hydride led to diamine 26. The corresponding reaction of 25c,e generated pyrrole derivatives 27c,e. Pentacyclic lactams 28b,d were formed by heating 15b,d in acetonitrile without addition of a nucleophile. Reduction of 28d yielded the pentacyclic diamine 29d.

An electron withdrawing group (EWG) in the ß-position of aminocyclopropanes 1 facilitates a ring opening generating zwitterion 2. A compound of type 1 can therefore be regarded as a homoenamine species.[1] However such a reaction thus far was used for organic synthesis in only a few cases. The most outstanding examples



1 2



3 X = COOR; R'' = H
4 X = CN; R'' = H,Me
5 6

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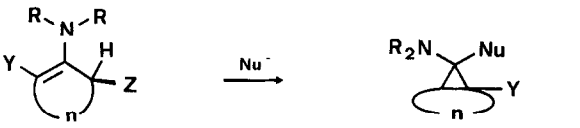
* Dedicated to Prof. Dr. Dr. h.c. Adolf Steinhofer on the occasion of his 80th birthday

are represented by the conversion of aminocyclopropanes 3 and 4 into lactones 5[2-4] or lactams 6[3], which were performed for the preparation of some natural products. The carboxylate or the carboxamide function, necessary for the ring closure, is formed under the corresponding reaction conditions from the ester and the cyano moiety in 3 and 4, respectively. The aminocyclopropanes 3 and 4 as starting materials for these syntheses were obtained either by a [2+1] cycloaddition reaction (3)[2,3] or by a photochemical process (4)[4,5].

One of the most simple and convenient methods for the preparation of aminocyclopropanes 9 is represented by the reaction of chloroenamines 7 (Z = Cl) or enaminosulfonium salts 7 (Z = $^{+}SMe_2$ FSO_3^- or $^{+}SMe_2$ TsO^-) with nucleophiles Nu^-.[1,6]



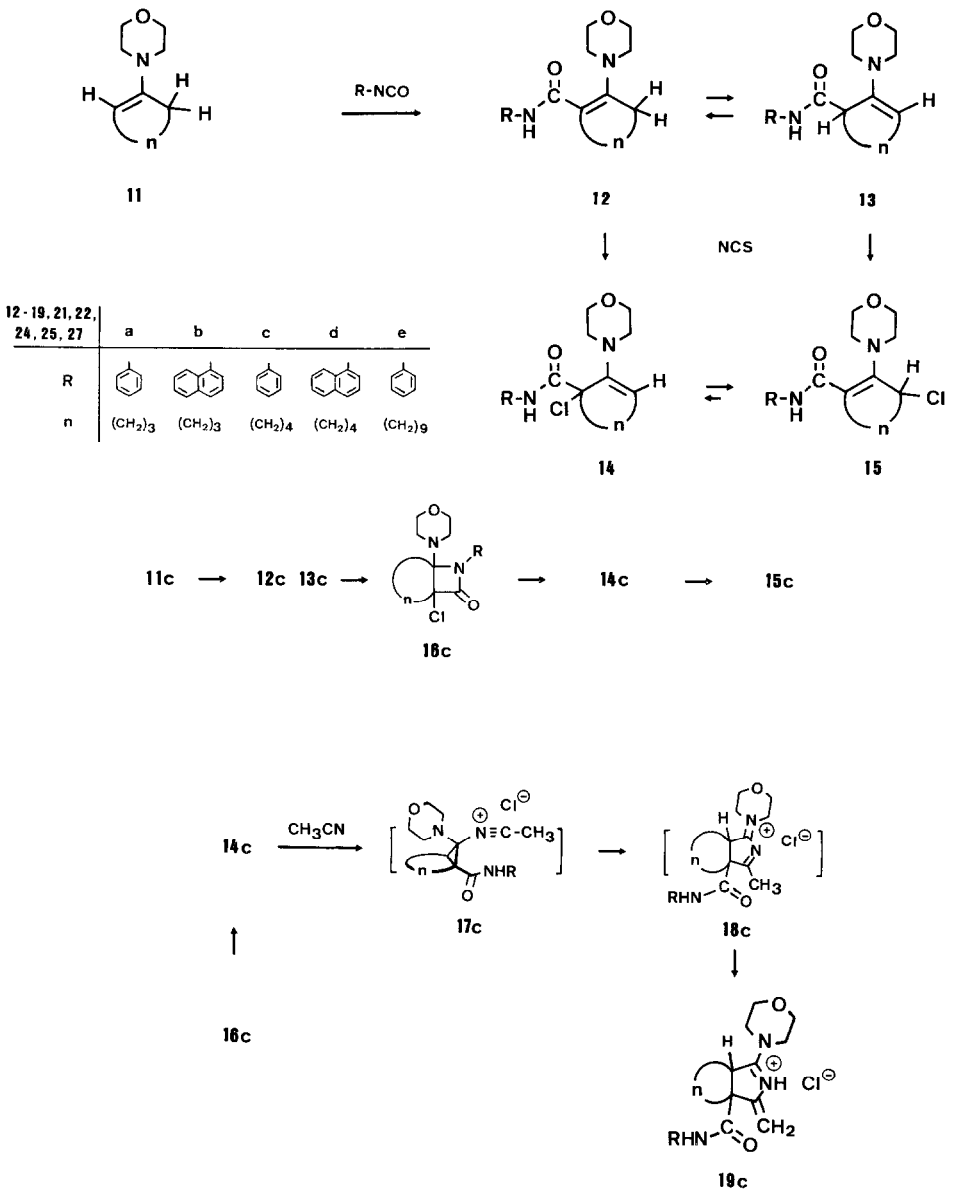
7 Z: Cl or $\overset{\oplus}{S}Me_2$, Y: H
8 Z: Cl, Y: C(=O)-NHR'

9 Y: H
10 Y: C(=O)-NHR'

Analogously, carbamoylated chloroenamines 8 should lead to aminocyclopropanes 10, which should possess the structural requirement for a lactam formation via a homoenamine process as well. Therefore, we have investigated the preparation of lactam compounds on the basis of 8 via aminocyclopropanes 10. Succinimide was chosen as a nucleophile for cyclopropane formation.

CARBAMOYLATED CHLOROENAMINES 15

Carbamoylated chloroenamines 15 were obtained by successive interaction of enamines 11 with an arylisocyanate and N-chlorosuccinimide. Carbamoylation of enamines 11 as the first step of this sequence led to a mixture of isomeric carbamoylated enamines 12 and 13, as already published for 12a/13a[7-10] and 12c/13c[11]. The mixture 12/13 could be used directly for the chlorination by NCS, which was best performed in acetonitrile or an acetonitrile/ether mixture. Thereby 15a[12], 15b,d and 15e were isolated in 50-89% yield as crystalline compounds (for halogenation of electronically desactivated enamines by N-halosuccinimides see ref.[13-15]). In the case of 12c/13c, compound 12c strongly predominates in the mixture. Here the analogous chlorination procedure gave a ß-lactam[16] 16c as the primary product in 73% yield. 16c proved to be stable at room temperature in the solid state, but it isomerized in solution (chloroform) at 10°C within 22 h to give 15c in 46% yield. Following the isomerization by ^{13}C NMR spectroscopy, it was shown that 16c first was converted into 14c, which afforded 15c upon further standing. In acetonitrile as a solvent this isomerization (5°C, 68 h) additionally produced a methylenepyrroline derivative 19c (19% yield) besides 15c (15% yield). Most probably a bicyclic intermediate 17c initially is generated from 14c by acetonitrile acting as a nucleophile. Subsequent ring enlargement of 17c to 18c and transfer of a proton are further steps on the way to 19c. The latter could not be obtained under similar conditions from chloroenamine 15c and acetonitrile, as shown by control experiments.



Formation of 15 generally should therefore be described by the following picture: Chlorination of 13 directly produces 15, whereas 12 is chlorinated to 16/14. Since the latter isomerizes to 15, the thermodynamically more stable 15 is the isolable end product of the chlorination reaction. Acetonitrile proved to be a suitable solvent for the synthesis of 15. Only in those cases, in which chloroenamine 14 is involved to a greater extend in the chlorination reaction, acetonitrile can lead to a byproduct of type 19.

The ^{13}C NMR spectra clearly demonstrate the constitution of the carbamoylated chloroenamines 15a-d; additionally they indicate the absence of isomeric compounds 14. A characteristical doublet at 55 - 58 ppm corresponds to the CHCl -

moiety of 15. The singlet for C(1) of the enamine CC-double bond appears between 148.5 and 151.5 ppm. The signal of the C(2) atom can be established only for 15c,e, it differs from a singlet of the phenyl system by the absence of a fine coupling. In the case of the naphthyl derivatives 15b,d a similar differentiation was not possible. Two singlets at 151.6 ppm and 81.7 ppm and a doublet at 131.1 ppm correspond to the chloroallyl unit of 14c. The unexpected low field shifting of this doublet (the corresponding doublet for 3-chloro-2-morpholino-cycloheptene[17] is observed at 113.3 ppm) should be the consequence of an interaction of the morpholino moiety and the carboxamide group in 14c resulting in a decrease of the donor effect of the morpholino system. This interaction also is indicated in the ^{1}H NMR spectrum of 14c by an absorption of the vinylic proton at 5.9 ppm, a value not very typical for an enamine function. The -CHCl- moiety of 15b-e appears in the ^{1}H NMR spectrum as a characteristical signal at about 5 ppm.

The ß-lactam structure of 16c unequivocally was established by the ^{13}C NMR spectrum by two singlets at 88.4 and 84.0 ppm for the bridgehead carbon atoms, one singlet at 165.3 ppm for the carbonyl group and four signals for the phenyl moiety without any further low field signals. The observation of the phenyl-C(1)-signal at 138.1 ppm excludes the presence of an isomeric imidate unit. In this case, absorption is expected at about 150 ppm.[18] An IR absorption at 1770 cm^{-1} for the carbonyl group (e.g. see papers cited in ref.[16]) and the absence of any -NH-, -CHCl- or =CH- signal in the ^{1}H NMR spectrum are in accordance with structure 16c.

Table 1 ^{13}C NMR Data of the isomeric Chloroderivatives 14c, 15c and 16c

	C=O	Allyl moiety or bridgehead C-atoms	-$(CH_2)_n$-	Morpholine		Phenyl ring	
				OCH_2	NCH_2		
	[s]		[t]	[t]	[t]	[s][a]	[d]
14c[b]	168.6	151.6 [s], 131.1 [d][c], 81.7 [s]	35.8, 25.2 24.7, 23.5	67.7	56.2 53.2	137.0	129.2 124.8 120.1
15c[d]	165.9	151.5 [s], 135.2 [s], 56.3 [d]	33.8, 25.9, 25.2, 25.1	66.8	50.2	138.6	129.4 123.9 119.7
16c[e]	165.3	88.4 [s], 84.0 [s]	38.1, 33.5 30.5, 26.7 24.2	68.0	47.2	138.1	130.0 125.4 118.3

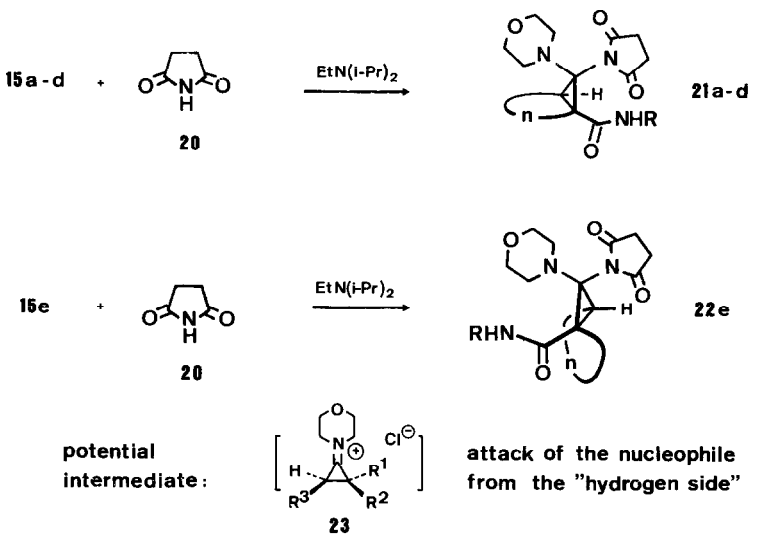
[a] Split off by a fine coupling ([t], $^2J_{CH}$: 7 Hz [15c, 16c], 8 Hz [14c]).- [b] $CDCl_3$, -35°C. The solution of 14c was prepared by a complete isomerization of 16c in $CDCl_3$ at 15°C within 10 min, then the solution was cooled to -35°C to record the ^{13}C NMR spectrum. Exclusively the ^{13}C NMR signals of 15c could be detected, when this solution afterwards was stored for 5 h at 20°C. Strictly anhydrous $CDCl_3$ and exclusion of moisture were necessary for these experiments.- [c] Selective H-decoupling at 5.9 ppm transfers this signal into a singlet.- [d] $CDCl_3$, 20°C.- [e] CD_2Cl_2, -30°C.-

An AB-system (H_A = 5.30 ppm, H_B = 5.06 ppm, J_{AB} = 2.5 Hz) in the ^{1}H NMR and a triplet at 96.0 ppm (J_{CH} = 163 Hz) in the ^{13}C NMR represent the methylene moiety in 19c. High field shifting of these signals is caused by the conjugated morpholi-

no moiety acting as a donor substituent. Consequently the NCH_2-signals of the morpholino group characteristically are shifted downfield giving resonance at about 3.9 ppm in the ^1H NMR spectrum.

SUCCINIMIDOBICYCLOALKANE CARBOXAMIDES 21 AND 22

Heating the carbamoylated chloroenamines 15a,b,d in acetonitrile or in an acetonitrile-water mixture in the presence of excess succinimide (20) and ethyldiisopropylamine gave bicyclic succinimido compounds 21a,b,d in 84%, 70% and 32% yield, respectively. A one pot procedure for chlorination and cyclopropane formation was used for the preparation of 21c (44% yield calcd for 12c/13c) due to the accessibility of 15c in lower yields. Interaction of cyclododecene derivative 15e with 20 led to pure trans-bicyclic compound 22e in 73% yield. This formation of a trans-bicyclic system agrees with the results of analogous reactions of 20 with unsubstituted chloroenamines 7 (Z = Cl, n = $[CH_2]_{7-9}$).[6,19]



The three membered ring of the bicyclic system in 21a-d and 22e clearly is indicated in the ^{13}C NMR spectrum by two singlets and one doublet; for the latter a ^1J coupling constant of 152-171 Hz is found, which is typical of a three membered ring. The configuration of the cis-bicyclic compounds 21a-d can be deduced from the type of the morpholino signals in the ^1H NMR spectrum.[19,20] The observed signal patterns of the ABXY-type at room temperature establish the endo-morpholino configuration in 21a-d. Due to the asymmetry of 21, two ABXY-systems are expected for the morpholino moiety. Resolution of the two different ABXY-systems generally is easier to observe for the N-methylene moieties than for the O-methylene groups. Compound 22e gives a characteristic high field resonance for one hydrogen atom at 0.57 ppm. This signal corresponds to one hydrogen atom of a methylene moiety giving resonance in the ^{13}C NMR at 33.5 ppm (t) as shown by

selective decoupling. Since high field shifting in this molecule is induced by the anisotropy effect of a carbonyl group, a trans-connection of the bicyclic system is most likely. An X-ray structural analysis of 22e confirms the trans-linkage of the two ring systems. Additionally it gives the information about the syn arrangement of the morpholino group and the carboxamide moiety. A molecule plot of 22e is depicted in Figure 1. Selected bond lengths and bond angles are listed in Table 2.

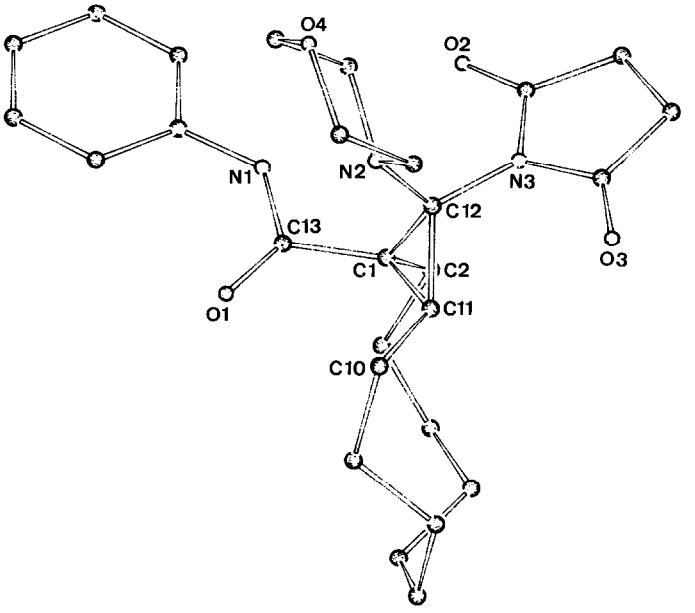


Figure 1

Molecular structure of 22e

Table 2 Selected Bond Lengths and Bond Angles for 22e

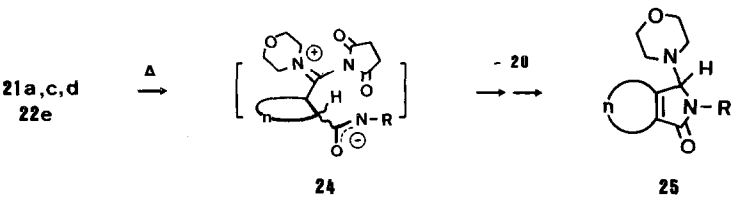
bond length [Å]					
C(11)-C(1)	1.507(4)	C(2)-C(1)	1.531(4)	N(2)-C(12)	1.430(4)
C(12)-C(1)	1.529(4)	C(11)-C(10)	1.526(4)	N(3)-C(12)	1.463(4)
C(12)-C(11)	1.496(4)	C(13)-C(1)	1.523(4)		

bond angle [°]			
C(12)-C(1)-C(11)	59.0(2)	C(12)-C(1)-C(2)	122.7(3)
C(12)-C(11)-C(1)	61.2(2)	C(12)-C(11)-C(10)	124.0(3)
C(11)-C(12)-C(1)	59.8(2)	N(3)-C(12)-N(2)	115.9(3)
C(13)-C(1)-C(2)	113.3(3)	N(3)-C(12)-C(1)	116.5(3)
C(13)-C(1)-C(12)	113.8(3)	N(2)-C(12)-C(1)	118.6(3)

The position of the succinimido moiety in the compounds 21 and 22 easily can be understood by the intermediate generation of a cyclopropane iminium ion 23 from 15. The iminium ion 23 is attacked from the sterically less hindered direction.

HOMOENAMINE REACTION OF 21 AND 22 - FORMATION AND CHARACTERIZATION OF BICYCLIC LACTAMS 25

Compounds 21a,c,d and 22e decomposed upon distillation in vacuo, thereby forming a mixture of lactams 25 and succinimide (20). Pure lactams 25 were obtained in 39-88% yield after separation from 20 by aqueous Na_2CO_3 solution and recrystallization or distillation of the crude products.

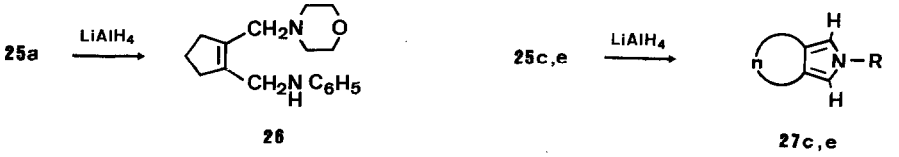


Compounds 25 gave the expected signals in the ^1H NMR and the ^{13}C NMR spectrum. In the ^1H NMR spectrum of 25a,c-e a characteristic singlet appears between 5.26 and 5.44 ppm. The corresponding C-signal shows resonance in the ^{13}C NMR between 78.6 and 81.5 ppm as a doublet, representing the CH-aminal moiety. As already mentioned, a N-phenyl amide structure easily can be distinguished from an isomeric N-phenyl imidate unit by the chemical shift of the phenyl-C(1)-^{13}C NMR signal.[14] This signal is found for 25a (138.6 ppm), 25c (138.6 ppm) and 25e (139.1 ppm) within the area, which is typical for amides. A fine coupling observed for this signal ($^2J_{CH} \approx 7$-8 Hz, t) allowed its differentiation from the signals of the CC-double bond (25a: 162.5, 144.6 ppm; 25c: 151.2, 133.8; 25e: 152.3, 135.4) by selective C-H-decoupling. Irradiation at 7.3 ppm (phenyl area) caused the disappearance of the fine coupling at the phenyl signal, while the CC-double bond signals remained unchanged. The naphthyl derivative 25d corresponds with the phenyl derivatives 25a,c,e in the position of the aminal CH-structural unit in the ^1H- and ^{13}C NMR spectrum (5.36 ppm and 84.2 ppm, respectively); therefore an isomeric imidate structure can be excluded for 25d, too.

Formation of 25 starts with a homoenamine ring opening of 21 or 22 leading to a zwitterion of type 2. Transfer of a proton from the carboxamide to the carbanionic center generates zwitterion 24. The latter closes the ring to give a lactam. Elimination of succinimide (20) and tautomerization of the initially formed Δ^2 pyrrolinone to a Δ^3 pyrrolinone via a hydroxypyrrole intermediate represent the final steps on the way to 25.

It was expected that the reduction of 25 with lithium aluminum hydride would give a further confirmation of the lactam structure. Unexpectedly, treatment of 25c,e with lithium aluminum hydride afforded pyrroles 27c,e in 44% and 49% yield, respectively. In contrast to this, 25a was transferred to a bis(aminomethyl)cyclopentene derivative 26 (72% yield) by the same reagent and upon the same reaction conditions. Differences in the ring strain between 25a and 25c,e most likely should be the reason for the varying reaction behaviour. ^1H- and ^{13}C NMR data clearly indicate the constitution of 26 and 27 (see Experimental part). In the ^1H NMR spectrum two singlets at 3.03 and 3.80 ppm (each 2 H) represent typical

signals for 26; 27, on the other hand, shows a characteristic singlet at 6.78 ppm (27c) or 6.83 ppm (27e) for the pyrrole system.



In the literature[21], antibacterial properties were reported for 27c, which was synthesized by the interaction of aniline with the hydrogenated Diels-Alder adduct of 2,5-dimethoxy-2,5-dihydrofuran and butadiene.

PENTACYCLIC LACTAMS 28 FROM CARBAMOYLATED CHLOROENAMINES 15b,d

Heating the N-naphthylamino compounds 15b,d in acetonitrile in the presence of ethyldiisopropylamine without adding a nucleophile gave pentacyclic lactams 28b and 28d in 15% and 51% yield, respectively. The N-naphthyl moiety thereby acts as an intramolecular nucleophile. Formation of a twofold annellated aminocyclopropane by such a type of a tandem cyclization is new. An intramolecular trapping of a cyclopropylidenamine during a Favorskii rearrangement was reported recently for the first time by De Kimpe et al..[22] They obtained bicyclic N,O-acetals as side products in 3-30% yield. Interaction of 28d with lithium aluminum hydride caused the reduction of the amido function leading to the pentacyclic diamine 29d in 55% yield.

28, 29 :	b $(CH_2)_3$	d $(CH_2)_4$

The ^{13}C NMR data clearly prove the pentacyclic constitution; two singlets and one doublet in the typical region indicate the three membered ring. The substitution of the naphthyl system in 1,2-position can be deduced from the ^{1}H NMR spectrum. A fine coupling is observed for the triplet type signals (d of d) of the aromatic protons of 28b and 28d in the 400 MHz ^{1}H NMR spectra. Additionally two doublets are found without further fine coupling or broadening; they correspond to H(3) and H(4). These unsplitted doublets would not be expected for a 1,8-disubstituted naphthalene derivative[23], in which a fine coupling should be missing in the triplet type signals (d of d). Two ABXY-systems, mostly separated from each other, appear for the morpholino moiety in 28b, 28d and 29d.

Contrary to the succinimido compounds 21 and 22, the pentacyclic lactams 28 thus far could not be decomposed to products of a homoenamine type ring enlargement.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker WP 200 spectrometer (TMS as internal standard). For the ^{1}H NMR spectra of 28a, 28d and 29d a Bruker AM 400 spectrometer was used. IR spectra were measured on a Perkin-Elmer 397 Infrared Spectrophotometer. Melting points were determined with a Mettler FP 61 apparatus. Microanalyses were performed with a Perkin-Elmer 240 Elemental Analyzer.

Carbamoylated Enamines 12/13: The carbamoylated enamines 12/13 b-e were prepared according to a general procedure (13a[8], 12a/13a[7,9,10], 12c/13c[11]) by the reaction of 50 mmol of enamine 11 (n=3: 8.36 g; n=4: 9.06 g; n=9: 12.56 g) with 50 mmol of phenylisocyanate (5.96 g) or 1-naphthylisocyanate (8.46 g). Since mixtures of isomers 12/13 were formed, only yields and elemental analyses are mentioned. The ratios 12/13 were determined by ^{1}H NMR spectroscopy [$CDCl_3$, 12: NH-signal (s); 13: NH- (s) and olefinic CH-signal].

2-Morpholino-N-naphthyl-cyclohexene-1-carboxamide 12b/13b: Prepared in 30 mL of acetone; yield: 14.23 g (85%); ^{1}H NMR δ 12b: 12.4 (NH), 13b: 5.2 (CH, t), 9.8 (NH); ratio 12b/13b: 24/76. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.1; H, 7.26; N, 8.2.

2-Morpholino-N-phenyl-cycloheptene-1-carboxamide 12c/13c: Prepared in 30 mL of acetone; yield: 12.59 g (84%); ^{1}H NMR δ 12c: 12.6 (NH), 13c: 5.2 (CH, t), 8.5 (NH); ratio 12c/13c: 77/23. Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.0; H, 8.06; N, 9.3.

2-Morpholino-N-naphthyl-cycloheptene-1-carboxamide 12d/13d: Prepared in 40 mL of acetonitrile; yield: 14.55 g (83%); ^{1}H NMR δ 12d: 12.5 (NH), 13d: 5.3 (CH, t), 8.9 (NH); ratio 12d/13d: 53/47. Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.6; H, 7.47; N, 8.1.

2-Morpholino-N-phenyl-cyclododecene-1-carboxamide 12e/13e: Prepared in 350 mL of dichloromethane; yield: 15.75 g (85%); ^{1}H NMR δ 12e: 10.8 (NH), 13e: 4.8 (CH, d of d), 8.9 (NH); ratio 12e/13e: 23/77. Anal. Calcd for $C_{23}H_{34}N_2O_2$: C, 74.56; H, 9.25; N, 7.56. Found: C, 74.2; H, 9.15; N, 7.4.

3-Chloro-2-morpholino-1-cycloalkene-1-carboxamides 15b-e and 7-Chloro-1-morpholino-9-phenyl-9-aza-bicyclo[5.2.0]nonan-8-one (16c): 15b,d,e and 16c were synthesized according to a procedure for the preparation of 15a[12]: A solution of N-chlorosuccinimide (2.67 g; 20 mmol) in 20 mL of acetonitrile was added dropwise to a suspension of 20 mmol of 6/7 b,c,e in 10 mL of acetonitrile or 20 mmol of 6d/7d in 50 mL of ether, respectively. A colorless precipitate was obtained; in the case of 15b,d,e the crystallization was completed by storing the reaction mixture at -18°C for 18 h. The precipitate was isolated by suction and washed consecutively with 10 mL of ice-cold water, 10 mL of ice-cold acetonitrile and 10 mL of ice-cold ether and dried in vacuo. 15b was recrystallized from acetonitrile. In the case of 12c/13c the reaction mixture directly was used for the preparation of 21c without isolation of 15c.

3-Chloro-2-morpholino-N-naphthyl-1-cylohexene-1-carboxamide (15b): Prepared from 6.72 g (20 mmol) of 12b/13b at 20°C (reaction time: 30 min). Yield: 5.51 g (74%); mp 150°C; IR (KBr, cm^{-1}) 1645, 1605, 1530 (C=O, C=C); ^{1}H NMR ($CDCl_3$) δ 1.79-2.30 (m, 5H), 2.98-3.29 (m, 5H), 3.53-3.72 (m, 4H), 4.99 (m_c, 1H), 7.44-8.24 (m, 7H), 11.27 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 166.1 (s), 149.4 (s), 134.5 (s), 133.2 (s), 129.2 (d), 126.5 (s), 126.3 (d, 3C), 125.5 (s), 125.0 (d), 121.1 (d), 119.3 (d), 67.0 (t), 55.1 (d), 52.2 (t), 32.8 (t), 26.1 (t), 16.5 (t). Anal. Calcd for $C_{21}H_{23}ClN_2O_2$: C, 68.01; H, 6.25; N, 7.56. Found: C, 68.0; H, 6.27; N, 7.6.

3-Chloro-2-morpholino-N-naphthyl-1-cycloheptene-1-carboxamide (15d): Prepared from 7.01 g (20 mmol) of 12d/13d at 0°C (reaction time: 10 min). Yield: 6.03 g (78%); mp 124°C; IR (KBr, cm^{-1}) 1640, 1605, 1510 (C=O, C=C); ^{1}H NMR ($CDCl_3$) δ 1.29-2.31 (m, 7H), 2.62-3.10 (m, 5H), 3.68-3.74 (m, 4H), 5.04 (m_c, 1H), 7.43-8.01 (m, 7H), 9.60 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 167.6 (s), 151.5 (s), 135.5 (s), 134.5 (s), 133.2 (s), 129.0 (d), 127.6 (s), 126.2 (d, 2C), 126.1 (d), 125.6 (d), 121.6 (d), 120.9 (d), 66.8 (t), 56.5 (d), 50.6 (t), 33.8 (t), 26.1 (t), 26.0 (t), 25.0 (t). Anal. Calcd for $C_{22}H_{25}ClN_2O_2$: C, 68.65; H, 6.55; N, 7.28. Found: C, 68.9; H, 6.56; N, 7.2.

3-Chloro-2-morpholino-N-phenyl-1-cyclododecene-1-carboxamide (15e): Prepared from 7.42 g (20 mmol) of 12e/13e at -20°C (reaction time: 20 min). Yield: 4.08 g (50%); mp 108°C; IR (KBr, cm^{-1}) 1655, 1610, 1510 (C=O, C=C); ^{1}H NMR ($CDCl_3$) 1.16-1.97 (m, 14H), 2.09-2.24 (m, 2H), 2.39-2.59 (m, 2H), 3.14-3.39 (m, 4H),

3.57-3.73 (m, 4H), 5.11 (m_c, 1H), 7.12 (t, 1H), 7.33 (t, 2H), 7.59 (d, 2H), 8.32 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 168.9 (s), 148.5 (s), 138.5 (t, $^2J_{CH}$ = 8 Hz), 131.5 (s), 129.4 (d), 124.4 (d), 119.9 (d), 67.6 (t), 57.6 (d), 52.6 (t), 33.6 (t), 27.9 (t), 27.2 (t), 26.5 (t), 24.0 (t), 23.4 (t, 2C), 22.2 (t), 20.8 (t). Anal. Calcd for $C_{23}H_{33}ClN_2O_2$: C, 68.21; H, 8.21; N, 6.92. Found: C, 68.4; H, 8.15; N, 6.9.

7-Chloro-1-morpholino-9-phenyl-9-aza-bicyclo[5.2.0]nonan-8-one (16c): Prepared from 6.01 g (20 mmol) of 12c/13c at -20°C (reaction time: 5 min). Yield: 4.90 g (73%); mp 93°C; IR (KBr, cm^{-1}) 1770 (C=O); ^1H NMR (CD_2Cl_2, 0°C) δ 1.10-1.70 (m, 9H), 1.70-2.26 (m, 1H), 2.31-3.30 (m, 4H), 3.38-3.73 (m, 4H), 7.18 (t, 1H), 7.42 (t, 2H), 7.71 (d, 2H). Anal. Calcd for $C_{18}H_{23}ClN_2O_2$: C, 64.57; H, 6.92; N, 8.37. Found: C, 64.5; H, 6.91; N, 8.2.

3-Chloro-2-morpholino-N-phenyl-1-cycloheptene-1-carboxamide (15c): A solution of 16c (1.67 g, 5.0 mmol) in chloroform (10 mL) was stirred at 10°C for 22 h. The solvent was removed in vacuo and the residue was dissolved in acetonitrile (5 mL) and cooled to -18°C for 18 h. The precipitated crystals were isolated by suction, washed with ice-cold acetonitrile (10 mL) and ether (10 mL) and dried in vacuo. Yield: 0.77 g (46%); mp 122°C decomp.; IR (KBr, cm^{-1}) 1650, 1600, 1540 (C=O, C=C); ^1H NMR ($CDCl_3$) δ 1.34-1.46 (m, 1H), 1.73-2.22 (m, 5H), 2.56-2.70 (m, 1H), 2.91-2.96 (m, 4H), 3.03-3.14 (m, 1H), 3.81-3.86 (m, 4H), 4.99 (m_c, 1H), 7.09 (t, 1H), 7.34 (t, 2H), 7.64 (d, 2H), 11.39 (s, NH, 1H). Anal. Calcd for $C_{18}H_{23}ClN_2O_2$: C, 64.57; H, 6.92; N, 8.37. Found: C, 64.6; H, 6.95; N, 8.41.

Isomerization of 16c in Acetonitrile: A suspension of 16c (2.01 g, 6.0 mmol) in 15 mL of acetonitrile was stirred for 68 h at 5°C under exclusion of moisture. The resulting precipitate was isolated by suction and washed subsequently with 5 mL of ice-cold acetonitrile and 5 mL of ice-cold ether. The crystalline residue (0.94 g) was triturated with boiling acetonitrile (10 mL). Thereby pure 19c remained. 15c [0.30 g (15%), mp 122°C decomp., IR and ^1H NMR identical with 15c obtained from 16c in chloroform] crystallized from the hot filtrate upon cooling to -18°C.

3a,4,5,6,7,7a-Hexahydro-3-methylene-1-morpholino-3a-(phenylcarbamoyl)-isoindolium chloride (19c): 0.43 g (19%); mp 199°C; IR (KBr, cm^{-1}) 1660 (C=N); ^1H NMR ($CDCl_3/CD_3OD$ 1:5) δ 1.12-1.59 (m, 3H), 1.70-1.96 (m, 3H), 2.01-2.25 (m, 1H), 2.65-2.80 (m, 1H), 3.67-4.07 (m, 9H), 5.06 (H_B), 5.30 (H_A) (AB-system, J_{AB} = 2.5 Hz), 7.15 (t, 1H), 7.34 (t, 2H), 7.49 (d, 2H), 9.17 (s, amide-NH, 1H); ^{13}C NMR ($CDCl_3/CD_3OD$ 1:5) δ 172.5 (s), 171.6 (s), 146.2 (s), 138.9 (s), 129.8 (d), 126.1 (d), 122.6 (d), 96.0 (t), 67.2 (t), 66.4 (t), 56.1 (s), 44.8 (d), 27.5 (t), 27.2 (t), 22.7 (t), 22.3 (t), (NCH_2-resonances hidden by the CD_3OD-signal). Anal. Calcd for $C_{20}H_{26}ClN_3O_2$: C, 63.90; H, 6.97; N, 11.18. Found: C, 63.3; H, 6.83; N, 11.0.

Morpholino-succinimido-bicyclo[n.1.0]alkane carboxamides 21a-d and 22e - General procedure: A mixture of chloroenamine 15 (10 mmol; 15a: 3.21 g; 15b: 3.71 g; 15d: 3.85 g; 15e: 4.05 g), succinimide (20) (50 mmol; 4.95 g) and ethyldiisopropylamine (30 mmol; 5.22 mL) in acetonitrile or acetonitrile/water was heated under stirring. In the case of 15c succinimide (20) (40 mmol, 3.96 g) and ethyldiisopropylamine (30 mmol; 5.22 mL) were added directly to the mixture obtained from 12c/13c and NCS. After the reaction had been finished, the solvent was removed in vacuo, the residue was dissolved in 100 mL of dichloromethane and consecutively washed with 3 x 30 mL of saturated aqueous Na_2CO_3-solution, 30 mL of water, 3 x 30 mL of saturated aqueous KH_2PO_4- solution and again 30 mL of water. Pure 21a-d and 22e were obtained by evaporation of the dried ($MgSO_4$) solution, by washing the residue and if necessary by recrystallization.

1α,5α,6α-6-Morpholino-N-phenyl-6-succinimido-bicyclo[3.1.0]hexane-1-carboxamide (21a): Reaction performed in 15 mL of acetonitrile and 0.2 mL of water 5 h at 60°C; product washed with 10 mL of ice-cold methanol and 10 mL of ice-cold pentane. Yield: 3.2 g (84%); mp 186°C; IR (KBr, cm^{-1}) 1705, 1645 (C=O); ^1H NMR ($CDCl_3$) δ 1.94-2.74 (m, H_{A1}, H_{A2}, 13H), 2.84 (H_{B1}), 2.94 (H_{B2}) (J_{B1A1} = J_{B2A2} = 12.1 Hz, 2H), 3.51 (H_{X1}) 3.53 (H_{X2}) (J_{X1Y} = J_{X2Y} = 11.4 Hz; J_{X1A1} = J_{X2A2} = 11.1 Hz, 2H), 3.77 ($H_{Y1,2}$, J_{XY} = 11.4 Hz, 2H), 7.05-7.40 (m, 5H), 7.46 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 183.5 (s), 182.5 (s), 173.7 (s), 141.5 (s), 132.3 (d), 127.8 (d), 124.1 (d), 68.8 (t), 63.5 (s), 52.6 (t), 51.6 (t), 48.1 (s), 39.9 (d, J = 170 Hz), 29.7 (t), 29.1 (t), 28.5 (t, 2 C), 27.0 (t). Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.8; H, 6.62; N, 10.9.

1α,5α,6α-6-Morpholino-N-(1-naphthyl)-6-succinimido-bicyclo[3.1.0]hexane-1-carboxamide (21b): Reaction performed in 30 mL of acetonitrile 2.5 h at 70°C; product washed with 10 mL of ice-cold methanol, recrystallized from 45 mL of chloroform. Yield: 3.02 g (70%); mp 198-201°C; IR (KBr, cm^{-1}) 1705, 1635 (C=O); ^1H NMR ($CDCl_3$) δ 2.05-2.73 (m, H_{A1}, H_{A2}, 13H), 2.95 (H_{B1}), 3.10 (H_{B2}) (J_{B1A1} = J_{B2A2} =

11.7 Hz, 2H), 3.59 (H_{X1}), 3.60 (H_{X2}) ($J_{X1Y} = J_{X2Y} = 11.4$ Hz; $J_{X1A1} = J_{X2A2} = 11.4$ Hz, 2H), 3.81 ($H_{Y1,2}$, $J_{XY} = 11.4$ Hz, 2H), 7.41-7.96 (m and NH, 8H); ^{13}C NMR ($CDCl_3/CD_3OD$ 1:1) 179.9 (s), 179.2 (s), 171.2 (s), 134.6 (s), 133.4 (s), 129.8 (s), 128.6 (d), 127.2 (d), 126.6 (d), 126.4 (d), 125.9 (d), 123.9 (d), 122.9 (d), 67.6 (t), 67.5 (t), 62.5 (s), 51.5 (t), 50.5 (t), 47.2 (s), 39.6 (d, J = 171 Hz), 29.5 (t), 28.6 (t), 28.14 (t), 28.08 (t), 26.5 (t). Anal. Calcd for $C_{29}H_{27}N_3O_4$: C, 69.27; H, 6.28; N, 9.69. Found: C, 68.6; H, 6.33; N, 9.4.

1α,6α,7α-7-Morpholino-N-phenyl-7-succinimido-bicyclo[4.1.0]heptane-1-carboxamide (21c): Reaction performed in 30 mL of acetonitrile 3 h at 80°C; product stirred 30 min in 20 mL of ether, stored at -18°C for 2 h, filtered by suction and washed with 10 mL of ether. Yield: 1.74 g (44%, calcd for 12c/13c); mp 171°C; IR (KBr, cm^{-1}) 1705, 1660 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.30-1.90 (m, 6H), 2.03-2.73 (m, H_{A1}, H_{A2}, 9H), 2.86 (H_{B1}), 2.94 (H_{B2}) ($J_{B1A1} = J_{B2A2} = 12.6$ Hz, 2H), 3.57 (H_{X1}), 3.59 (H_{X2}) ($J_{X1Y} = J_{X2Y} = 12.0$ Hz; $J_{X1A1} = J_{X2A2} = 11.6$ Hz, 2H), 3.77 ($H_{Y1,2}$, $J_{XY} = 12.0$ Hz, 2H), 7.06-7.40 (m, 5H), 7.56 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 179.4 (s), 178.3 (s), 170.3 (s), 138.4 (s), 129.2 (d), 124.8 (d), 121.2 (d), 67.1 (t), 60.7 (s), 51.4 (t), 50.3 (t), 34.4 (s), 28.3 (t), 27.7 (t), 27.3 (d, J = 170 Hz), 22.5 (t), 21.6 (t), 20.5 (t), 18.4 (t). Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.3, H, 6.81; N, 10.4.

1α,6α,7α-7-Morpholino-N-(1-naphthyl)-7-succinimido-bicyclo[4.1.0]heptane-1-carboxamide (21d): Reaction performed in 50 mL of acetonitrile 1.5 h at 80°C; product recrystallized from chloroform methanol (1:1; 10 mL). Yield: 1.42 g (32%); mp 130°C; IR (KBr, cm^{-1}) 1700, 1650 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.29-1.52 (m, 1H), 1.53-2.03 (m, 4H), 2.04-2.28 (m, 1H), 2.29-2.81 (m, H_{A1}, H_{A2}, 9H), 2.89 (H_{B1}), 3.01 (H_{B2}) ($J_{B1A1} = J_{B2A2} = 15.0$ Hz, 2H), 3.62 ($H_{X1,2}$, $J_{XY} = 13.2$ Hz, $J_{A1X1} = J_{A2X2} = 14.6$ Hz, 2H), 3.79 ($H_{Y1,2}$, $J_{XY} = 13.2$ Hz, 2H), 7.34-7.97 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 179.6 (s), 178.4 (s), 171.2 (s), 134.5 (s), 133.4 (s), 128.8 (s), 128.8 (d), 126.6 (d, 2C), 126.3 (d), 126.0 (d), 122.1 (d), 122.0 (d), 67.1 (t), 64.3 (s), 51.3 (t), 50.2 (t), 34.2 (s), 28.3 (t), 27.9 (d, J = 166 Hz), 27.6 (t), 22.5 (t), 21.6 (t), 20.6 (t), 18.2 (t). Anal. Calcd for $C_{26}H_{29}N_3O_4$: C, 69.77; H, 6.53; N, 9.39. Found: C, 70.1; H, 6.58; N, 8.9.

1α,11ß,12ß-12-Morpholino-N-phenyl-12-succinimido-bicyclo[9.1.0]dodecane-1-carboxamide (22e): Reaction performed in 50 mL of acetonitrile and 3 mL of water 15 h at 60°C; product washed with ether (10 mL) and ice-cold ethanol (30 mL). Yield: 3.40 g (73%); mp 178°C; IR (KBr, cm^{-1}) 1745, 1730, 1625 (C=O); ^{1}H NMR ($CDCl_3$) δ 0.49-0.65 (m, 1H), 1.23-1.87 (m, 18H), 2.32-2.93 (m, 8H), 3.41-3.81 (m, 4H), 7.07 (t, 1H), 7.36 (t, 2H), 7.52 (d, 2H), 8.45 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 179.6 (s), 177.8 (s), 167.5 (s), 138.3 (s), 129.4 (d), 124.2 (d), 119.8 (d), 67.0 (t), 61.0 (s), 51.5 (t), 40.2 (s), 35.7 (d, J = 152 Hz), 33.5 (t), 28.6 (t), 27.8 (t), 26.2 (t), 25.4 (t), 24.6 (t, 2C), 24.0 (t), 23.7 (t), 23.4 (t), 22.2 (t). Anal. Calcd for $C_{27}H_{37}N_3O_4$: C, 69.35; H, 7.98; N, 8.99. Found: C, 69.1; H, 7.93; N, 8.9.

Bicyclic Lactams 25: General Procedure: Bicyclic succinimido compounds 21 or 22 (5.0 mmol; 21a: 1.92 g; 21c: 1.99 g; 21d: 2.24 g; 22e: 2.34 g) were decomposed by distillation in a Kugelrohr apparatus. The reaction products were dissolved in 30 mL of dichloromethane, succinimide was removed by extraction (2x) with saturated aqueous Na_2CO_3-solution; the organic layer was washed with 15 mL of water, dried ($MgSO_4$) and evaporated in vacuo. 25a,c,e were recrystallized from methanol (10 mL); 25d was purified by distillation (Kugelrohr apparatus).

2,3,5,6-Tetrahydro-3-morpholino-2-phenyl-(4H)cyclopenta[c]pyrrol-1-one (25a): Distillation conditions: 190-210°C, 0.001 Torr. Yield: 0.55 g (39%); mp 163°C; IR (KBr, cm^{-1}) 1640, 1600 (C=O, C=C); ^{1}H NMR ($CDCl_3$) δ 2.36-2.70 (m, 10H), 3.54-3.58 (m, 4H), 5.29 (s, 1H), 7.13-7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 166.7 (s), 162.5 (s), 144.6 (s), 138.6 (t, $^2J_{CH}$ = 8Hz), 128.7 (d), 125.0 (d), 123.6 (d), 78.6 (d), 67.1 (t), 47.8 (t), 30.2 (t), 27.5 (t), 25.7 (t). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.6; H, 7.12; N, 9.8.

2,3,4,5,6,7-Hexahydro-3-morpholino-2-phenyl-isoindol-1-one (25c): Distillation conditions: 170-180°C, 0.005 Torr. Yield: 0.83 g (56%); mp 152°C; IR (KBr, cm^{-1}) 1680, 1610 (C=O, C=C); ^{1}H NMR ($CDCl_3$) δ 1.74-1.81 (m, 4H), 2.11-2.35 (m, 4H), 2.38-2.67 (m, 4H), 3.47-3.56 (m, 4H), 5.26 (s, 1H), 7.15-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 169.7 (s), 151.2 (s), 138.6 (t, $^2J_{CH}$ = 7Hz), 133.8 (s), 128.8 (d), 125.3 (d), 124.3 (d), 81.5 (d), 67.3 (t), 47.9 (t), 23.9 (t), 22.2 (t), 21.9 (t), 20.2 (t). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 71.9; H, 7.30; N, 9.3.

2,3,4,5,6,7-Hexahydro-3-morpholino-2-(1-naphthyl)-isoindol-1-one (25d): Distillation conditions: 180-190°C, 0.005 Torr. Yield: 1.55 g (89%); mp 85°C; IR (KBr, cm^{-1}) 1690, 1660 (sh.) (C=O, C=C); ^{1}H NMR ($CDCl_3$, 50°C) δ 1.37-1.93 (m, 4H),

2.00-2.40 (m, 6H), 2.43-2.64 (m, 2H), 3.25-3.59 (m, 4H), 5.37 (s, 1H), 7.12-8.08 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 171.2 (s), 152.6 (s), 136.6 (s), 135.0 (s), 134.1 (s), 130.6 (s), 128.7 (d, 2C), 128.1 (d), 126.7 (d), 126.5 (d), 125.7 (d), 122.7 (d), 84.2 (d), 67.3 (t), 48.4 (t), 48.3 (t), 23.7 (t), 22.2 (t), 22.0 (t), 20.4 (t). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.4; H, 6.87; N, 7.8

2,3,5,6,7,8,9,10,11,12-Decahydro-3-morpholino-2-phenyl-4H-cycloundeca[c]pyrrol--1-one (25e): Distillation conditions: 250-270°C, 0.02 Torr. Yield: 1.01 g (55%); mp 148°C; IR (KBr, cm^{-1}) 1700, 1605 (C=O, C=C); ^{1}H NMR ($CDCl_3$) δ 1.05-2.05 (m, 14H), 2.28-2.55 (m, 8H), 3.33-3.74 (m, 4H), 5.44 (s, 1H), 7.15-7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 170.3 (s), 152.3 (s), 139.1 (t, $^2J_{CH}$ = 8 Hz), 135.4 (s), 129.2 (d), 125.8 (d), 124.8 (d), 80.0 (d), 67.6 (t), 48.4 (t), 27.2 (t), 26.8 (t), 26.5 (t), 26.1 (t), 25.2 (t), 25.0 (t, 2C), 24.2 (t), 24.0 (t). Anal. Cacld for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 74.9; H, 8.68; N, 7.5.

Lithium aluminum hydride reductions of 25 - General Procedure: 25 (2.0 mmol; 25a: 0.57 g, 25c: 0.60 g, 25e: 0.74 g) was added to a suspension of $LiAlH_4$ (0.38 g, 10 mmol) in 15 mL of ether and refluxed for 24 h. Excess $LiAlH_4$ was destroyed at 0°C by addition of water (10 mL), the reaction mixture was filtered and washed with 30 mL of ether; the organic layer was washed with water (3 x 20 mL), in the case of pyrroles 27 triturated with saturated aqueous KH_2PO_4 solution (2 x 20 mL), dried and removed in vacuo. 26 was purified by distillation; 27c,e were recrystallized from ether (3 mL).

N-{[2-(Phenylaminomethyl)-cyclopent-1-en-1-yl]methyl}-morpholine (26): Kugelrohr distillation at 180-190°C/0.01 Torr gave pure 26 as a pale yellow oil. Yield: 0.39 g (72%); IR (film, cm^{-1}) 1620 (C=C); ^{1}H NMR ($CDCl_3$) δ 1.71-1.88 (m, 2H), 2.13-2.48 (m, 8H), 3.03 (s, 2H), 3.68-3.75 (m, 4H), 3.80 (s, 2H), 3.94 (s, NH, 1H), 6.63 (d, 2H), 6.73 (t, 1H), 7.18 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 148.6 (s), 137.9 (s), 135.4 (s), 129.1 (d), 117.2 (d), 112.7 (d), 67.0 (t), 56.4 (t), 53.7 (t), 42.2 (t), 36.8 (t), 35.8 (t), 21.7 (t). Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 74.5; H, 8.84; N, 10.3.

4,5,6,7-Tetrahydro-2-phenyl-isoindole (27c): Yield: 0.17 g (43%); mp 101°C (lit.[21] 103-104°C); ^{1}H NMR ($CDCl_3$) δ 1.76 (m_c, 4H), 2.63 (m_c, 4H), 6.78 (s, 2H), 7.14-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 141.3 (s), 129.7 (d), 125.0 (d), 122.4 (s), 120.1 (d), 114.8 (d, J = 183 Hz), 24.3 (t), 22.4 (t). Anal. Calcd for $C_{14}H_{15}N$: C, 85.23; H, 7.66; N, 7.10. Found: C, 85.3; H, 7.75; N, 7.0.

5,6,7,8,9,10,11,12-Octahydro-2-phenyl-4H-cycloundeca[c]pyrrole (27e) Yield: 0.26 g (49%); mp 69°C; ^{1}H NMR ($CDCl_3$) δ 1.19-1.49 (m, 10H), 1.62-1.74 (m, 4H), 2.56-2.62 (XX'-part of an AA'XX'-system, 4H), 6.83 (s, 2H), 7.11-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 141.1 (s), 129.6 (d), 126.7 (s), 124.7 (d), 119.6 (d), 116.2 (d, J = 181 Hz), 30.2 (t, 2C), 27.3 (t), 26.2 (t), 24.6 (t), 23.6 (t). Anal. Calcd for $C_{19}H_{25}N$: C, 85.34; H, 9.42; N, 5.24. Found: C, 85.5; H, 9.38; N, 5.2.

Pentacyclic Lactams 28: General Procedure: A mixture of N-naphthyl chloro compounds 15 (5.0 mmol; 15b: 1.85 g; 15d: 1.93 g), ethyldiisopropylamine (1.94 g, 15.0 mmol) and acetonitrile (20 mL) was heated to 80°C. The resulting precipitate was filtered, successively washed with a saturated aqueous KH_2PO_4 solution (10 mL), water (10 mL), acetonitrile (10 mL) and ether (10mL) and dried in vacuo.

4,5-Dihydro-5b-morpholino-3H-2a,5b-cyclo-cyclopenta[e]naphth[1,2-b]azepin-2-(1-H)-one (28b): Reaction time: 20 h. Yield: 0.25 g (15%); mp 270°C beginning decomp.; IR (KBr, cm^{-1}) 1640 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69-1.71 (m, 1H), 1.95-2.06 (m, 3H), 2.22-2.28 (m, 2H), 3.06-3.12 (m, 1H), 2.40 (H_C, $^2J_{HH}$ = 11.7 Hz, 1H), 3.03 (H_D, $^2J_{HH}$ = $^3J_{HH}$ = 11.7 Hz, 1H), 3.26 (H_E, $^2J_{HH}$ = 11.7 Hz, 1H), 3.58 (H_F, $^2J_{HH}$ = $^3J_{HH}$ = 11.7 Hz, 1H), 3.61 (H_G, $^2J_{HH}$ = $^3J_{HH}$ = 11.7 Hz, 1H), 3.76 (H_H, $^2J_{HH}$ = 11.7 Hz, 1H), 3.87 (H_I, $^2J_{HH}$ = $^3J_{HH}$ = 11.7 Hz, 1H), 3.88 (H_J, $^2J_{HH}$ = 11.7 Hz, 1H) (H_C - H_J 2 ABXY-systems), 7.50 (d of d of d, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 6.8 Hz, $^5J_{HH}$ = 1.5 Hz, 1H), 7.53 (t, 1H), 7.55 (d of d of d, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 6.8 Hz, $^5J_{HH}$ = 1.5 Hz, 1H), 7.81 (d, 1H), 7.84 (d of d, J_{HH} = 8.8 Hz, $^5J_{HH}$ = 1.3 Hz, 1H), 7.87 (d, br. 1H), 8.45 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 171.2 (s), 132.8 (s), 129.0 (s), 128.7 (d), 126.6 (d), 126.3 (d), 124.4 (d), 122.4 (s), 122.1 (d), 121.1 (s), 120.0 (d), 68.4 (t), 67.9 (t), 58.2 (s), 52.4 (t), 50.2 (t), 45.7 (s), 41.3 (d, J = 166 Hz), 28.4 (t), 26.6 (t), 26.4 (t). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.36. Found: C, 75.4; H, 6.69; N, 8.3.

3,4,5,6-Tetrahydro-6b-morpholino-2a,6b-cyclobenzo[e]naphth[1,2-b]azepin-2(1H)-one (28d)[24]: Reaction time: 3 h. Yield: 0.89 g (51%); mp 286°C decomp.; IR (KBr, cm^{-1}) 1630 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35-1.53 (m, 1H), 1.50-1.61 (m, 4H), 1.81-1.95 (m, 2H), 2.08-2.12 (m, 1H), 2.86-2.97 (m, 1H), 2.28 (H_C, $^2J_{HH}$ = 12.2 Hz, 1H), 3.18 (H_D, $^2J_{HH}$ = $^3J_{HH}$ = 12.2 Hz, 1H), 3.28 (H_E, $^2J_{HH}$ = 11.1 Hz, 1H), 3.65 (H_F, $^2J_{HH}$ = $^3J_{HH}$ = 11.1 Hz, 1H), 3.67 (H_G, $^2J_{HH}$ = $^3J_{HH}$ = 11.1 Hz, 1H), 3.78 (H_H, $^2J_{HH}$ = 11.1 Hz, 1H), 3.91 (H_I, $^2J_{HH}$ = 12.2 Hz, 1H), 3.94 (H_J, $^2J_{HH}$ = $^3J_{HH}$ =

12.2 Hz, 1H) (H_C - H_J 2 ABXY-systems), 7.48 (d of d of d, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 7.3 Hz, $^5J_{HH}$ = 1.2 Hz, 1H), 7.52 (d, 1H), 7.53 (d of d of d, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 7.3 Hz, $^5J_{HH}$ = 1.2 Hz, 1H), 7.82 (d of d, $^3J_{HH}$ = 8.5 Hz, $^5J_{HH}$ = 1.2 Hz, 1H), 7.86 (d, 1H), 8.06 (d, br., 1H), 9.21 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 173.1 (s), 132.5 (s), 128,5 (s), 128.5 (d), 126.2 (d), 125.9 (d), 124.2 (d), 122.3 (s), 121.8 (s), 121.4 (d), 120.2 (d), 68.1 (t), 67.8 (t), 55.3 (s), 51.7 (t), 49.4 (t), 34.4 (s), 31.3 (d, J = 160 Hz), 21.7 (t), 20.6 (t, 2C), 18.3 (t). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 74.9; H, 6.90; N, 8.0.

1,2,3,4,5,6-Hexahydro-6b-morpholino-2a,6b-cyclobenzo[e]naphth[1,2-b]azepine: (29d) 28d (5.0 mmol, 1.74 g) was added to a suspension of $LiAlH_4$ (0.95 g, 25 mmol) in 30 mL of ether and refluxed for 24 h. Excess $LiAlH_4$ was destroyed at 0°C by addition of water (10 mL), the reaction mixture was filtered and washed with 30 mL of ether; the organic layer was washed with water (3 x 20 mL). The ether was removed in vacuo, the residue was triturated with ice-cold ether (30 mL), filtered and dried in vacuo. Yield: 0.92 g (55%); mp 153°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26-1.38 (m, 1H), 1.46-1.60 (m, 2H), 1.66-1.94 (m, 6H), 3.17 (H_A), 3.41 (H_B) (AB-system, J_{AB} = 10.4 Hz, 2H), 2.44 (H_C, $^2J_{HH}$ = 12.4 Hz, 1H), 3.11 (H_D, $^2J_{HH}$ = 11.4 Hz, 1H), 3.26 (H_E, $^2J_{HH}$ = $^3J_{HH}$ = 11.4 Hz, 1H), 3.66 (H_F, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 11.4 Hz, H_G, $^2J_{HH}$ = $^3J_{HH}$ = 11.4 Hz, 2H), 3.78 (H_H, $^2J_{HH}$ = 11.4 Hz, 1H), 3.85 (H_I, $^2J_{HH}$ = 11.4 Hz, 1H), 3.86 (H_J, $^2J_{HH}$ = $^3J_{HH}$ = 11.4 Hz, 1H), 4.41 (s, NH, 1H), 7.22 (d, 1H), 7.34-7.39 (m, 2H), 7.61-7.63 (m, 1H), 7.72-7.76 (m, 1H), 7.76 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 138.6 (s), 132.0 (s), 128.4 (d), 126.0 (d), 124.7 (d, 2C), 123.4 (s), 122.8 (s), 119.3 (d), 116.6 (d), 68.2 (t), 67.9 (t), 51.3 (t), 49.3 (t), 47.2 (s), 33.0 (s), 25.8 (d, 163 Hz), 23.4 (t), 22.2 (t), 21.8 (t), 20.6 (t). Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.01; H, 7.84; N, 8.38. Found: C, 79.2; H, 7.83; N, 8.2.

X-Ray Crystal Structure Analysis of 22e Single crystals were obtained by crystallization from acetonitrile.

Crystal data: $C_{27}H_{37}N_3O_4$, M_r = 467.61; triclinic space group $P\bar{1}$; a = 12.376(2), b = 12.821(2), c = 8.621(2) Å, α = 95.42(2), ß = 109.71(1), γ = 84.77(2)°; V = 1279.3(3) Å^3; Z = 2; D_{calc} = 1.214 g cm^{-3}; μ = 5.8 cm^{-1}.

Data collection: Crystal size: 0.5 x 0.2 x 0.08 mm^3; Enraf-Nonius-CAD4 diffractometer; monochromatised Cu-K_α radiation; 2690 out of 3777 unique reflections were observed; $F_o^2 > 2\sigma(F_o^2)$, 4° < 2 Θ < 120°; scan width (0.85 + 0.14tanΘ)°; ω scan.

Solution and refinement: The phase problem was solved with SHELXS-86; the structure was refined with a Full-matrix-Least-squares programm. H-atoms were placed on geometrically calculated positions; the phenyl ring as well as CH_2-, CH- and NH- groups were treated as rigid bodies (d_{C-H} = 1.08 Å). A common temperature factor for groups of H-atoms (depending on the size of the temperature factors for the corresponding C-atoms) was refined. R = 0.058; R_w = 0.069; largest shift/error ratio: 0.003; residual electron density: 0.28 e Å^{-3}.

F_o-tables, fractional coordinates and temperature factors with standard deviations and bond distances and angles are deposited at the Cambridge Crystallographic Data Center.[25]

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