Tetrahedron Vol. 45, No 21, pp 6683 to 6696, 1989
Printed in Great Britain

0040-4020/89 $3.00+.00
Pergamon Press plc

FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS IV A SYNTHESIS FOR BICYCLIC LACTAMS FROM CARBAMOYLATED CHLOROENAMINES - THE RESULT OF A TANDEM RING CONTRACTION - CYCLIZATION PROCESS

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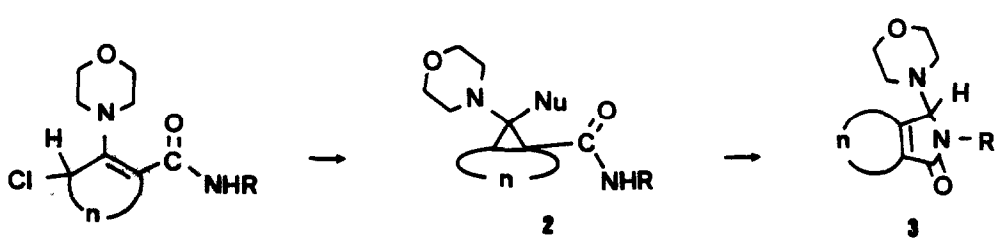
(*Received in Germany* 17 *July* 1989)

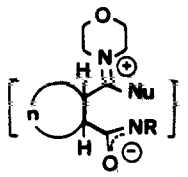
Abstract: Reaction of N-tosylcarbamoylated chloroenamines 6b-d with sodium cyanide in acetonitrile gave [n.3.0]bicyclic lactams 8b-d instead of the expected [n.1.0]bicyclic compounds of type 7. X-ray structure analyses of 8b-d established an uniform cis-anellation of the pyrrolidone system and an uniform exo-position of the morpholino moiety. A similar formation of a lactam was observed upon the reaction of the carbamoylated chloroenamines 6b and 11 with sodium borohydride. In the case of 11 an endo-morpholino product 12 could be isolated which rearranged to the more stable exo-morpholino bicyclic system 13 upon heating. 6b directly provided the thermodynamically controlled exo-morpholino isomer 10. Using $LiAlH_4$ as hydride reagent converted 6a-c into aminocyclopropanes 20a-c; the carbamoyl moiety, thereby, simultaneously was reduced to an aminomethyl group. A bicyclo[2.1.0]pentyl morpholine 20a, accessible by this method, isomerized into a cyclopentenyl morpholine 22 upon heating in the presence of acid. 8, 10, 12 and 13 could be regarded as subsequent product of primarily formed aminocyclopropane derivatives 2. A tandem ring contraction - cyclization process better seems to explain at least the formation of the [n.3.0]bicyclic lactams 8 from chloroenamines 6 and cyanide.

Reaction of chloroenamines 1 with succinimide yielding aminobicycloalkane carboxamides 2 and thermolysis of the latter in a homoenamine type reaction provides an easy route to bicyclic lactams 3.[1] Ring opening of 2 generating zwitterion 4, subsequent ringclosure of 4 producing a lactam, elimination of succinimide and isomerization of the CC-double bond are discussed as intermed-



Nu = Succinimide n = $(CH_2)_{3,4,9}$ R = Aryl

iate steps on the way from 2 to 3. Alternatively the formation of 3 from 2 could be interpreted as a hetero-vinyl cyclopropane rearrangement[2] via the tautomeric imidic acid 5 (Scheme I).



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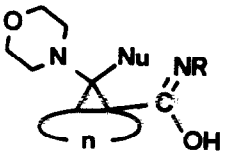

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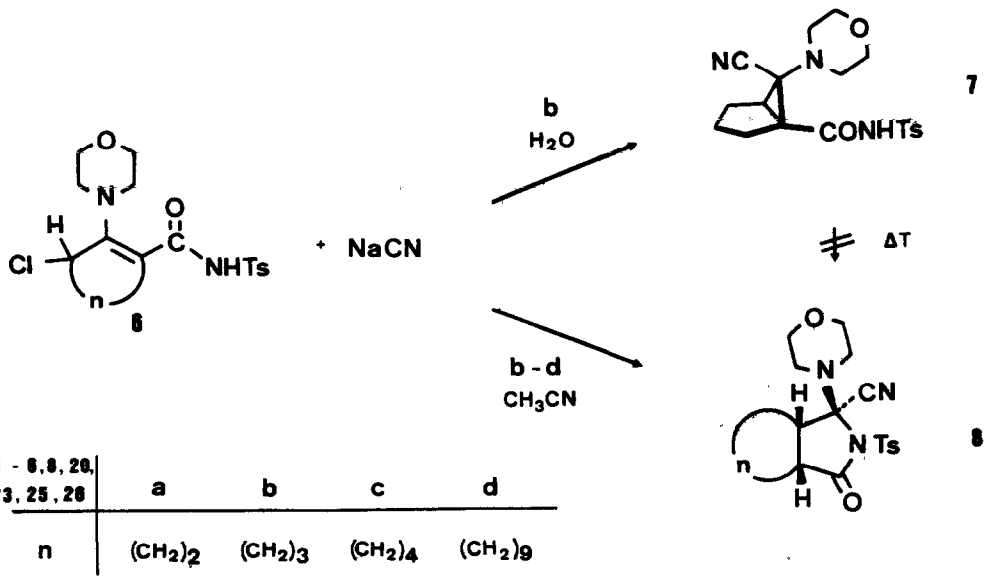
[n.1.0]BICYCLIC NITRILES 8 FROM 6 AND CYANIDE

Continuing these investigations we found a direct access to [n.3.0]bicyclic lactams by the reaction of carbamoylated chloroenamines of type 1 with cyanide using special conditions. A [3.1.0]bicyclic nitrile 7 was accessible from the N-tosylcarbamoylated chloroenamine 6b and cyanide in water.[3] Interaction of 6b with sodium cyanide in acetonitrile, however, gave the anellated lactam 8b in 75% yield instead of 7. Analogously, lactams 8c (42% yield) and 8d (43% yield) resulted from 6c and 6d by the same procedure. Again [n.1.0]bicyclic nitriles, the originally expected products, could not be obtained from the reaction mixture.



1 - 6, 8, 20, 23, 25, 26	a	b	c	d
n	$(CH_2)_2$	$(CH_2)_3$	$(CH_2)_4$	$(CH_2)_9$

The compounds isolated from the interaction of 6 and NaCN proved to be sterically pure. The lactam moiety of 8b-d shows a strong absorption at 1735-1760 cm^{-1} in the IR-spectrum. In the ^{13}C NMR spectra the pyrrolidinone ring system is represented by two doublets between 39.3 ppm and 47.0 ppm, one singlet at about 84 ppm and the carbonyl singlet at about 174 ppm.

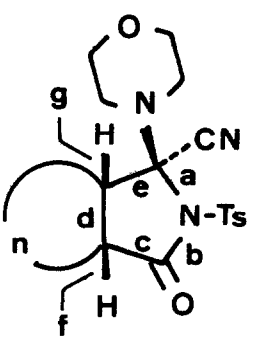
In the ^{1}H NMR spectra the morpholino system gave complex signals due to the asymmetry of the bicyclic compounds. The bridge head hydrogen-atom in α-position of the carbonyl group is the most downfield shifted proton of the carbocyclic signals appearing as a multisplit system [8b (C_6D_6) δ = 2.24 ppm, d of d of d, $^{3}J_{HH} = {}^{3}J_{HH} = 8.7$ Hz, $^{3}J_{HH} = 3.5$ Hz; 8c (CD_2Cl_2) δ = 3.09 ppm, d of d, $^{3}J_{HH} = {}^{3}J_{HH} = 5.6$ Hz; 8d (C_6D_6, 50°C) δ = 2.53 ppm, d of d of d, $^{3}J_{HH} = 8.8$ Hz, $^{3}J_{HH} = 7.2$ Hz, $^{3}J_{HH} = 4.5$ Hz].

X-ray structural analyses of 8b, 8c and 8d established the configuration of the [n.3.0]bicyclic lactams. It turned out that the two cycles uniformly are cis-linked and that the cyano-group uniformly is in the endo-position of the bicyclic system. A comparison of the torsional angles (see Table 1) shows almost the same values for 8c and 8d; in 8b, however, the anellated five membered ring strongly influences the puckering of the lactam cycle. A similar behaviour is found for the torsional angle involving the two bridgehead C-H-bonds (Table 1, f-d-g). No great differences are observed for the bond lengths of the lactam ring being almost the same in 8b, 8c and 8d (see Table 1).

Table 1. Bond Lengths and Torsional Angles of the Pyrrolidinone Ring in 8b, 8c and 8d

bond length [Å]	8b	8c	8d
a	1.474(4)	1.478(4)	1.481(4)
b	1.394(4)	1.412(4)	1.404(4)
c	1.482(4)	1.506(5)	1.508(4)
d	1.537(5)	1.526(5)	1.535(5)
e	1.546(4)	1.561(4)	1.560(4)

torsional angle [°]	8b	8c	8d
a-b-c	-12.0	-0.8	-1.9
b-c-d	-4.5	25.4	-24.4
c-d-e	18.1	-38.7	39.3
d-e-a	-24.0	37.7	-39.9
e-a-b	22.7	-23.5	26.7
f-d-g	8.1	-46.2	44.4



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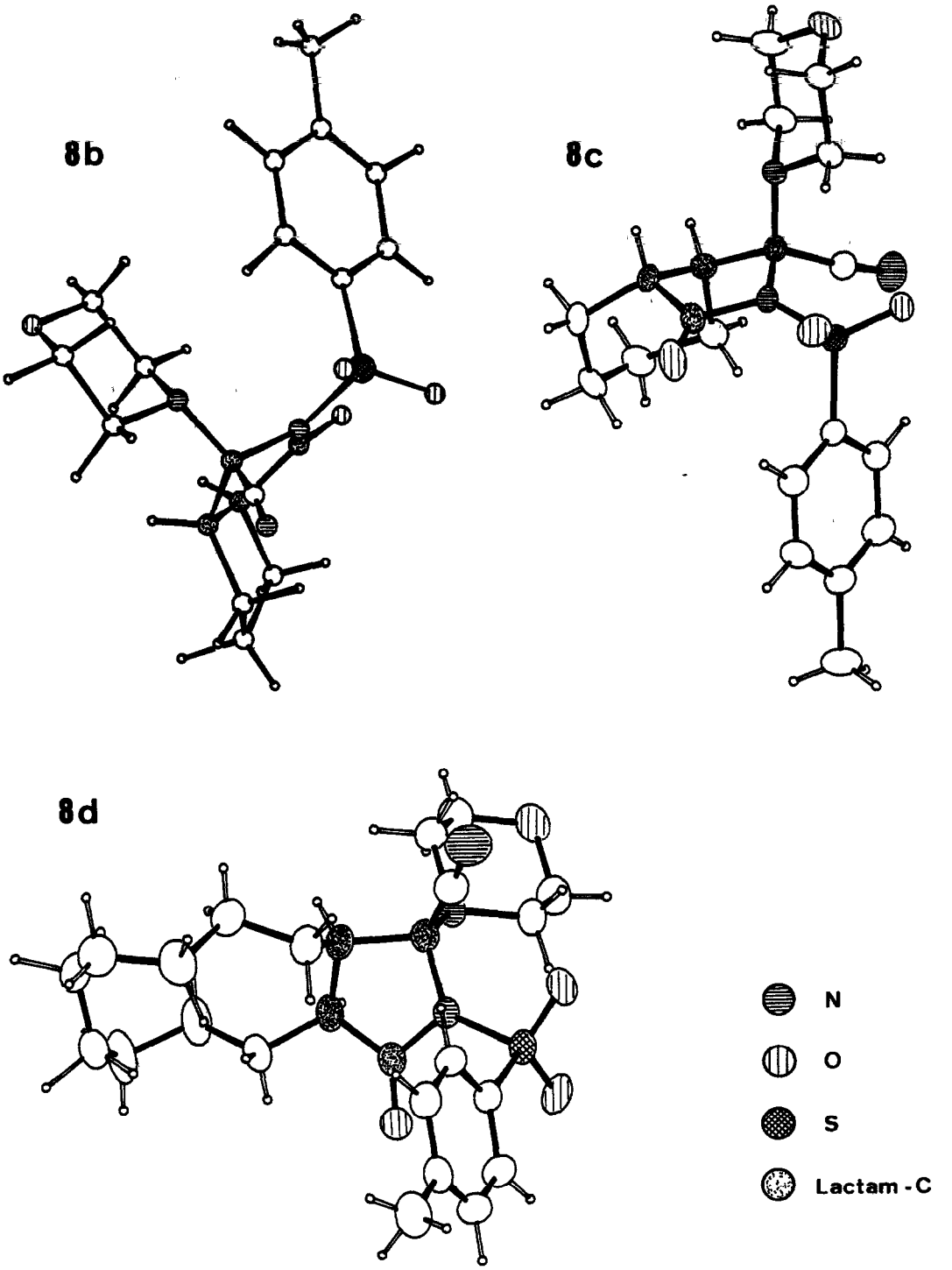
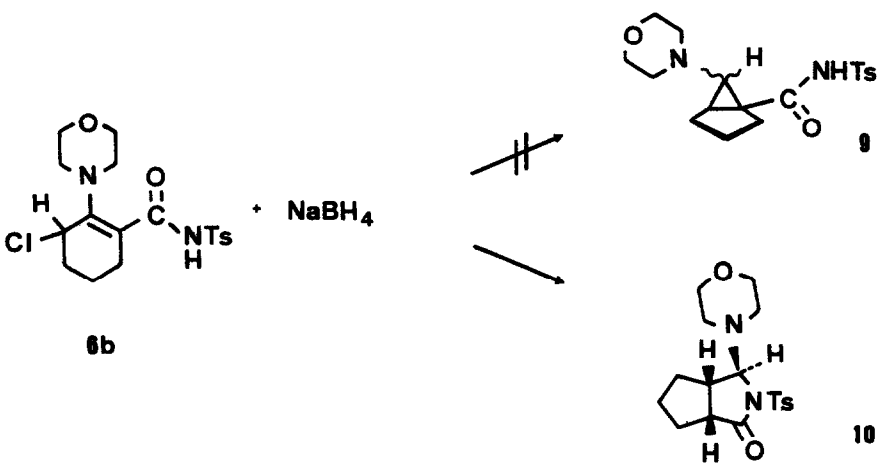


Figure 1. Molecule plots of the [n.3.0]bicyclic lactams 8b, 8c and 8d.

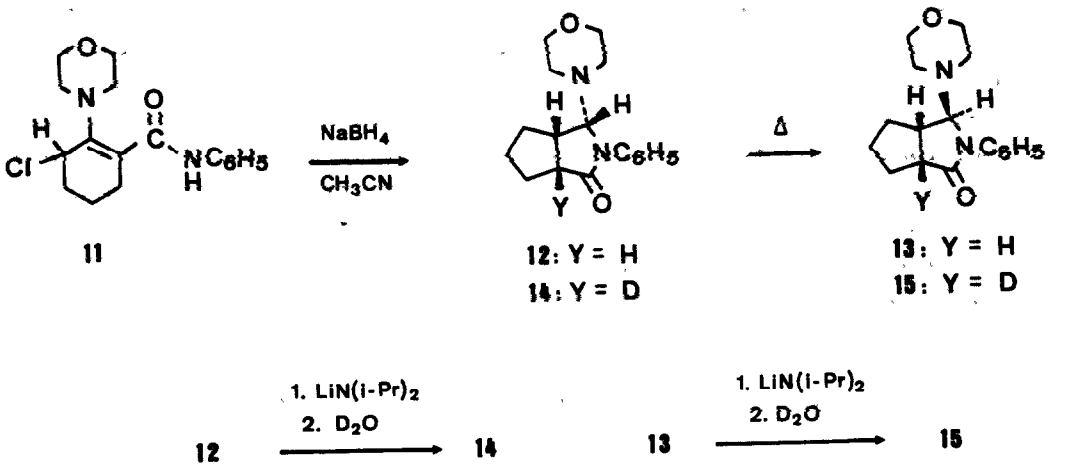
Information about the cis-connection of the bicyclic systems is of interest for the assignment of the coupling constant of the two bridgehead C-H units. The coupling of the two bridgehead H-atoms can be determined unequivocally only for 8b and 8c. The relatively large AB-coupling constant of 8.7 Hz (8b) is in accordance with the small torsional angle from the X-ray structural analysis (8.1°) and should be characteristic of a cis-connected bicyclo-[3.3.0]octane derivative. The smaller coupling constant J_{AB} = 5.6 Hz agrees with the larger torsional angle of the bridge head C-H - bonds in 8c (46.2°) effected by the sixmembered ring strongly preferring a chair conformation.

[3.3.0]BICYCLIC LACTAMS FROM 6 OR 11 AND SODIUM BOROHYDRIDE

Sodium borohydride reacted with the acylated chloroenamines 6b and 11 in a similar manner forming [3.3.0]bicyclic systems. Thus 6b and $NaBH_4$ in methanol produced the lactam 10 which could be isolated in 34% yield. Again, a [3.1.0]bicyclic 9 compound was not accessible by this method.

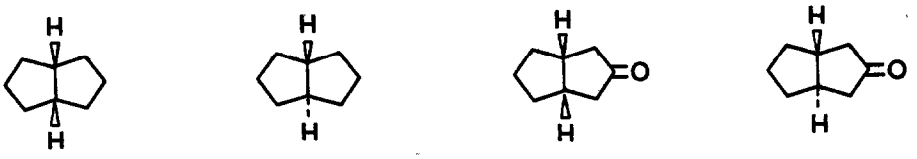


Analogously a lactam 12 could be obtained in 39% yield from chloroenamine 11 and $NaBH_4$. Unexpectedly, 12 isomerized to lactam 13 upon distillation in a Kugelrohr apparatus. The ^{13}C NMR data clearly indicate a lactam unit for 10, 12 and 13 (1 singlet, 10: 176.1 ppm; 12: 176.6 ppm; 13 176.3 ppm; 3 doublets, 10: 85.0, 48.1, 37.7 ppm; 12: 80.1, 48.1, 42.0 ppm; 13: 86.1, 47.2, 36.8 ppm). The bridgehead H-atom in α-position of the C=O group appears as a characteristic multiline signal in the ^1H NMR spectrum (d of d of d, 10: 2.29 ppm, $^3J_{HH}$ = $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 3.1 Hz; 12: 2.66 ppm, $^3J_{HH}$ = $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 4.1 Hz; 13: 2.65 ppm, $^3J_{HH}$ = $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 2.6 Hz). The aminal



C-H group shows different coupling for the two isomeric lactams. Whilst no coupling is observed for 13 (4.15 ppm), the same signal of 12 (4.57 ppm) is split into a doublet ($^3J_{HH}$ = 7.3 Hz). The X-ray structural analysis of 8b gave torsional angles of -19.5° for the exo-group and 103.7° for the endo group with respect to the adjacent bridgehead C-H bond. Comparing the coupling behaviour with these torsional angles allows the establishment of an endo-morpholino structure 12 for the primarily formed lactam and an exo-morpholino unit for the thermodynamically controled product 13. Analogously, 10 is to be described by an exo-morpholino structure due to the missing coupling of the aminal H-signal (4.78 ppm).

H-D-exchange experiments showed that the origin of the isomerism of the compounds obtained from 11 and $NaBH_4$ is not a cis-trans problem. Both compounds subsequently were treated with lithium diisopropylamide and D_2O to give 14 and 15, respectively. This caused a complete H-D-exchange of the O=C-C-H moiety as shown by ^1H NMR spectroscopy. Apart from this H-signal, not being present, each of the resulting compounds 14 and 15 was identical with the corresponding starting material. A cis-bicyclo[3.3.0]octane 16 was shown to be more stable than the corresponding trans isomer 17.[4] A difference of 6.0

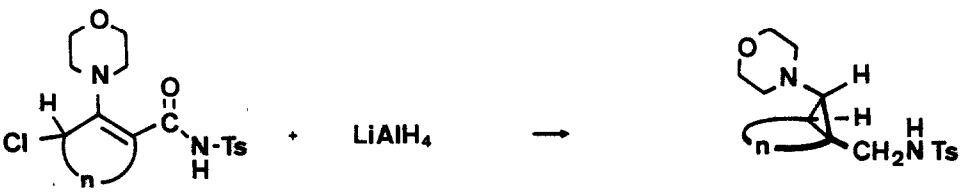


kcal/mol was reported[4] for the heat of combustion of 16 and 17 which were synthesized[4] from the ketones 18 and 19. H-D-exchange in 12 and 13 without changing the ring linkage, therefore, indicates a cis configuration in both cases.

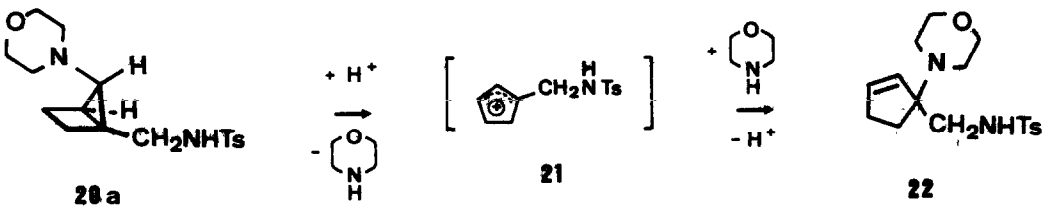
Isomerization of 12 to 13 is described best by a proton catalyzed ring opening - ring closure sequence of the aminal moiety. In the case of 10 the use of methanol as solvent and the presence of the tosyl group should facilitate the isomerization process; thus the exo-morpholino compound 10 was isolated directly.

BICYCLO[n.1.0]ALKYL DERIVATIVES 20 FROM 6 AND LITHIUM ALUMINUM HYDRIDE

Six-membered monochloroenamines of type 25b gave bicyclo[3.1.0]hexylamines upon treatment with $LiAlH_4$ leading mainly to the endo-amino derivatives besides some exo-isomer.[5,6] We investigated, therefore, the reaction of the carbamoylated chloroenamines 6 additionally with $LiAlH_4$ instead of $NaBH_4$. Analogous interaction of excess $LiAlH_4$ with carbamoylated chloroenamines 6 indeed provided bicyclic diamines 20. A reduction of the carboxamide function, thereby, took place besides the cyclopropane ring closure. A seven-, six-, and even a five-membered carbamoylated chloroenamine 6 led to the corresponding bicyclic systems 20c (38% yield), 20b (52% yield) and 20a (45% yield). To our knowledge[7] this is the first example for the preparation of the strained bicyclo[2.1.0]pentane skeleton from a chloroenamine.



6a-c 20a-c



20a 21 22

The ^{13}C NMR data clearly indicate the bicyclic constitution of 20; one singlet and two doublets in the expected regions represent the cyclopropane moiety. The $^{1}J_{CH}$ coupling constants of the doublets show characteristically high values (e.g. 20a: 176 Hz and 162 Hz; corresponding values for bicyclo[2.1.0]-pentane: 176 Hz and 160 Hz[8]).

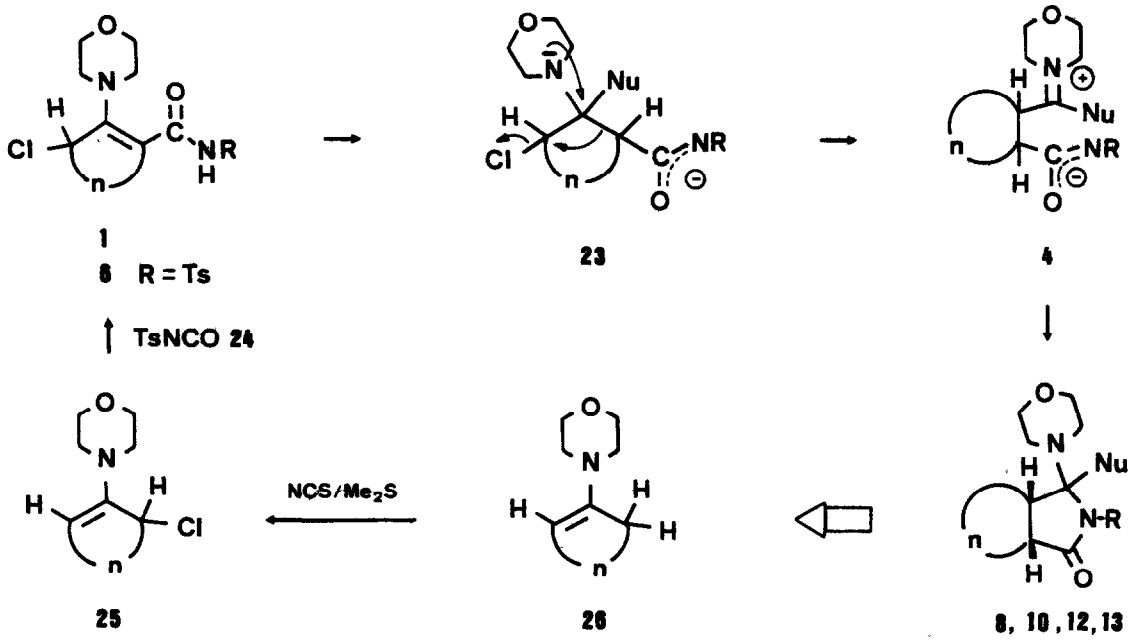
20a-c were isolated as pure endo-morpholino derivatives; the endo-morpholino configuration could be assigned by the $^{3}J_{HH}$ coupling constant of the two cyclopropane hydrogen atoms. The observed values (20a: 5.5 Hz; 20b: 7.4 Hz; 20c: 7.7 Hz) well correspond to those which are described for similar endo--substituted bicyclic systems; they strongly differ from the coupling constants of exo-substituted bicyclic compounds (bicyclopentane[9], bicyclohexane[6] and bicycloheptane[6,12] derivatives). The coupling constant unequivocally could be determined at the signal of the hydrogen atom of the C_1-bridge appearing as a doublet or A-part of an AB-system without any further coupling. In the case of 20a a clear identification of this signal required C_6D_6 instead of $CDCl_3$ as a solvent[13] even using a 400 MHz spectrometer.

The bicyclo[2.1.0]pentyl derivative 20a rearranged upon heating in the presence of acid to give a cyclopentenyl morpholine 22 (74% yield). The isomerization starts with an elimination of the endo-morpholino moiety in 20a generating cation 21 which yields 22 upon addition of morpholine. Such a type of rearrangement of a bicyclo[2.1.0]pentylamine was described to proceed very easily.[10]

FORMATION OF THE [n.3.0]BICYCLIC LACTAMS 8, 10, 12 AND 13

The reaction of 6a with sodium cyanide in water as a solvent yielded bicyclic nitrile 7[3], as already mentioned. Heating 7 in acetonitrile in a sealed tube to 130°C, however, gave no 8a as a product of a cyclopropane ring opening reaction. The same negative result was observed upon repeating the experiment in the presence of sodium cyanide. Attempted distillation of 7 in vacuo caused a total decomposition forming a black tar. Consequently 7 is no intermediate on the way from 6 to 8, at least in the case of 8a. Formation of 8 from 6, therefore, best is described by the sequence 6 → 23 → 4 → 8, a tandem ring contraction - cyclization process. The first step is represented by an addition of cyanide to the activated CC-double bond of 6, followed by a proton transfer from the tosylamide to the carbanionic center. Subsequent removal of the chloride by a ring contraction leads to zwitterion 4. A cyclization of 7 finally generates the [n.3.0]bicyclic lactam 8. The alternative formation of an [n.1.0]bicyclic nitrile 7 from 6a and sodium cyanide in water could be explained in terms of an S_N1-mechanism involving a bicyclic iminium ion. Thus

far it is not clear why a cis connection of the two ring systems and an exo-morpholino configuration is found uniformly, even for the bicyclo[9.3.0]tetradecane compound. Furthermore a participation of a cyclopropane intermediate 9 in the formation of the lactams 10, 12 and 13 remains an open question. 9, in contrast to 7, has no acceptor substituent at the C_2-bridge; this could strongly facilitate a ring opening to 4. An attempted preparation of 9 from 6 and $LiAlH_4$ in fact gave a cyclopropane system, but the acceptor group, necessary for a ring opening reaction, was removed by the strong hydride reagent.



The bicyclic lactams 8, 10, 12 and 13 as formal homoenamine products retrosynthetically are deduced from the enamines 26. The anellation of the heterocycle, thereby, is accompanied by a contraction of the carbocycle. The carbamoylated chloroenamines 1 are important intermediate products of the three-step synthesis. The N-phenylcarbamoylated chloroenamine 11 (= 1, R = C_6H_5) is synthesized by carbamoylation of 26 followed by a chlorination of the carbamoylated enamine.[15] In the case of 6 (= 1, R = Ts), the sequence of the two steps has to be reversed as already described for the preparation of 6b from 25b.[3] Analogously, 6a, 6c and 6d were accessible in 83%, 53% and 64% yield from the reaction of 24 with 25a, 25c and 25d, respectively.

Acknowledgement: We have to thank the Fonds der Chemischen Industrie for financial support of this work.

EXPERIMENTAL

^{1}H NMR spectra were obtained with a Bruker AM 400 or, if not otherwise noted, a Bruker WP 200 spectrometer; ^{13}C NMR spectra were recorded with a Bruker WP 200 spectrometer (TMS as internal standard). IR spectra were measured on a Perkin-Elmer 397 Infrared Spectrophotometer. Melting points are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 Elemental Analyzer.

Bicyclic Lactams 8b-d - General procedure: Finely powdered sodium cyanide (0.25 g, 5.0 mmol) was added to a suspension of 5.0 mmol of chloroenamine (6b[3]: 1.99 g; 6c: 2.06 g; 6d: 2.42 g) in 50 mL of acetonitrile and stirred (6b,c: 2 h, reflux; 6d: 7 h, 20°C). The solvent was removed in vacuo, dichloromethane (50 mL) and water (30 mL) were added to the remaining residue. The dichloromethane was separated and washed with water (2 x 30 mL). Removal of the solvent gave crude 8b-d which were recrystallized from acetonitrile.

1,2,3,3a,4,5,6,6a-Octahydro-1-morpholino-3-oxo-2-(4-toluenesulfonyl)-cyclopenta[c]pyrrole-1-carbonitrile (8b): Yield: 1.46 g (75%); mp 144-145°C; IR (KBr, cm^{-1}) 1735 (C=O); ^{1}H NMR (C_6D_6, 400 MHz) δ 0.80-1.00 (m, 2H), 1.22-1.65 (m, 4H), 1.72 (s, 3H), 1.97 (d of t, 1H), 2.24 (d of d of d, $^3J_{HH}$ = $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 3.5 Hz, 1H), 2.52-2.61 (m, 4H), 3.39-3.50 (m, 4H), 6.67, 6.70, 8.30, 8.33 (AA'XX'-system, 4H); ^{13}C NMR ($CDCl_3$) δ 175.1 (s), 145.9 (s), 143.8 (s), 129.6 (d), 129.2 (d), 114.2 (s), 83.4 (s), 66.6 (t), 47.7 (t), 46.2 (d), 45.2 (d), 32.5 (t), 29.7 (t), 25.1 (t), 21.8 (q). Anal. Calcd for $C_{19}H_{23}N_3O_4S$: C, 58.59; H, 5.95; N, 10.79. Found: C, 58.5; H, 5.94; N, 10.8.

1,3,3a,4,5,6,7,7a-Octahydro-1-morpholino-3-oxo-2-(4-toluenesulfonyl)-isoindole-1-carbonitrile (8c): Yield: 0.85 g (42%); mp 192-193°C; IR (KBr, cm^{-1}) 1760; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 0.25-0.50 (m, 2H), 1.01-1.05 (m, 1H), 1.32-1.53 (m, 3H), 1.90-2.01 (m, 2H), 2.44 (s, 3H), 2.59 (d of d of d, 1H), 2.73-2.86 (m, 4H), 3.09 (d of d, $^3J_{HH}$ = $^3J_{HH}$ = 5.6 Hz, 1H), 3.67-3.78 (m, 4H), 7.36, 7.38, 7.99, 8.01 (AA'XX'-system, 4H); ^{13}C NMR δ 173.8 (s), 146.3 (s), 134.7 (s), 129.9 (d), 129.3 (d), 111.9 (s), 83.3 (s), 66.9 (t), 49.2 (t), 42.3 (d), 39.3 (d), 26.0 (t), 23.1 (t), 22.3 (t), 22.0 (t), 21.9 (q). Anal. Calcd for $C_{20}H_{25}N_3O_4S$: C, 59.53; H, 6.25; N, 10.41. Found: C, 59.1; H, 6.19; N, 10.4.

1,2,3,3a,4,5,6,7,8,9,10,11,12,12a-Tetradecahydro-1-morpholino-3-oxo-2-(4-toluenesulfonyl)-cycloundeca[c]pyrrole-1-carbonitrile (8d): Yield: 1.03 g (43%); mp 170-172°C; IR (KBr, cm^{-1}) 1760 (C=O); ^{1}H NMR (C_6D_6, 400 Mz, 50°C)δ 0.98- 1.59 (m, 18H), 1.79 (s, 3H), 2.15 (d of d of d, 1H), 2.53 (d of d of d, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 4.5 Hz), 2.83-2.98 (m, 4H), 3.39-3.47 (m, 4H), 6.76, 6.78, 8.32, 8.34 (AA'XX'-system, 4H); ^{13}C NMR ($CDCl_3$) δ 174.1 (s), 145.9 (s), 134.6 (s), 129.6 (d), 129.2 (d), 113.6 (s), 84.5 (s), 67.1 (t), 48.7 (t), 47.0 (d), 44.8 (d), 26.3 (t, 2C), 25.6 (t), 24.8 (t), 24.7 (t), 24.3 (t), 23.9 (t), 23.5 (t), 23.1 (t), 21.9 (q). Anal. Calcd for $C_{25}H_{35}N_3O_4S$: C, 63.40; H, 7.45; N, 8.87. Found: C, 63.1; H, 7.33; N, 9.0.

3α,3aα,6aα-1,2,3,3a,4,5,6,6a-Octahydro-3-morpholino-2-(4-toluenesulfonyl)--cyclopenta[c]pyrrol-1-one (10): A mixture of sodium borohydride (2.27 g, 60 mmol) and N-tosylcarbamoylated chloroenamine 6b[3] (1.20 g, 3.0 mmol) in 60 mL of methanol was stirred for 20 h at room temperature. The solvent was removed, then 200 mL of a saturated aqueous KH_2PO_4/K_2HPO_4-buffer solution were added to the residue. Extraction with ether (3 x 100 mL) and evaporation of the ether gave crystalline 10 which was washed with 30 mL of pentane. Yield: 0.37 g (34%); mp 150-151°C; IR (KBr, cm^{-1}) 1720 (C=O); ^{1}H NMR (C_6D_6, 400 MHz)δ 1.10-1.13 (m, 2H), 1.13-1.23 (m, 1H), 1.36-1.49 (m, 2H), 1.76-1.87 (m) and 1.83 (s) (5H), 1.98-2.16 (m, 4H), 2.29 (d of d of d, $^3J_{HH}$ = $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 3.1 Hz, 1H), 4.78 (s, 1H), 6.74, 6.76, 8.23, 8.25 (AA'XX'-system, 4H); ^{13}C NMR ($CDCl_3$) δ 176.1 (s), 144.9 (s), 135.8 (s), 129.2 (d), 128.8 (d), 85.0 (d, $^1J_{CH}$ = 159 Hz), 66.5 (t), 48.1 (d), 47.0 (t), 37.7 (d), 33.4 (t), 30.9 (t), 25.5 (t), 21.7 (q). Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 59.0; H, 6.61; N, 7.6.

3β,3aα,6aα-1,2,3,3a,4,5,6,6a-Octahydro-3-morpholino-2-phenyl-cyclopenta[c]-pyrrol-1-one (12) Sodium borohydride (0.45 g, 12 mmol) was added to a solution of N-phenylcarbamoylated chloroenamine 11[15] (3.20 g, 10 mmol) in 60 mL of acetonitrile. The mixture was stirred at 40°C for 5 d. Then the solvent was evaporated and the residue was triturated with 20 mL of 0.2 n aqueous sodium hydroxide solution. The remaining solid was extracted with 70 mL of dichloromethane. Removal of the solvent gave a colorless precipitate which was recrystallized from acetone (10 mL) and washed with ice-cold ether (3 x 20 mL). Yield: 1.13 g (39%); mp 164°C; IR (KBr, cm^{-1}) 1670 (C=O); ^1H NMR (C_6D_6) δ 1.18-1.81 (m, 5H), 2.15-2.42 (m, 5H), 2.66 (d of d of d, $^3J_{HH}$ = $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 4.1 Hz, 1H), 3.18-3.35 (m, 4H), 4.57 (d, $^3J_{HH}$ = 7.3 Hz, 1H), 6.95-7.03 (m, 1H), 7.15-7.25 (m, 2H), 7.49 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 176.6 (s), 138.4 (s), 128.8 (d), 126.2 (d), 124.9 (d), 80.1 (d, $^1J_{CH}$ = 148 Hz), 67.4 (t), 49.3 (t), 48.1 (d), 42.0 (d), 29.7 (t), 28.1 (t), 27.2 (t). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.2; H, 7.80; N, 9.7.

3α,3aα,6aα-1,2,3,3a,4,5,6,6a-Octahydro-3-morpholino-2-phenyl-cyclopenta[c]-pyrrol-1-one (13): endo-Morpholino-lactam 12 (0.71 g, 2.5 mmol) was distilled in a Kugelrohr-apparatus at 170°C/0.001 Torr. The resulting oil was triturated with ether (30 mL) to give colorless crystals of 13. Yield: 0.60 g (84%); mp 112°C; IR (KBr, cm^{-1}) 1665 (C=O); ^1H NMR (C_6D_6) δ 1.03-1.16 (m, 1H), 1.19-1.35 (m, 2H), 1.41-1.72 (m,2H), 1.88-2.27 (m, 6H), 2.65 (d of d of d, $^3J_{HH}$ = $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 2.6 Hz, 1H), 3.31-3.43 (m, 4H), 4.15 (s, 1H), 6.95-7.03 (m, 1H), 7.15-7.28 (m, 2H), 7.85 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 176.3 (s), 138.3 (d), 128.4 (d), 125.4 (d), 123.6 (d), 86.1 (d, $^1J_{CH}$ = 152 Hz), 66.5 (t), 47.2 (d), 46.7 (t), 36.8 (d), 33.8 (t), 30.2 (t), 25.1 (t). Anal. Cald for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.1; H, 7.96; N, 9.8.

Deuterated Cyclopenta[c]pyrrol-1-one Derivatives 14 and 15 - General procedure: 0.43 g (1.5 mmol) Cyclopenta[c]pyrrol-1-one 12 or 13 were dissolved in 5 mL of THF and added to a solution of 15 mmol of lithium diisopropylamide [obtained from 9.4 mL butyllithium solution (1.6 M in hexane) (15 mmol butyllithium) and 2.55 mL (18.2 mmol) diisopropylamine] in pentane (12.3 mL). The mixture was stirred at room temperature for 3 h, then quenched with 0.25 mL (15 mmol) of D_2O and additionally stirred for 30 min. Removal of the solvent mixture gave a residue which was triturated with 5 mL of dichloromethane. The solution was filtered and the solvent evaporated in the vacuo.

3β,3aα,6aα-6a-Deutero-1,2,3,3a,4,5,6-heptahydro-3-morpholino-2-phenyl-cyclopenta[c]pyrrol-1-one (14): Addition of 5 mL of ether to the residue, trituration and isolation of the resulting crystals gave 0.19 g (44 %) monodeuterated 14; mp 161°C; the ^1H NMR spectrum (C_6D_6) was identical with that of 12 except for the missing signal at 2.66 ppm. Anal. Calcd for $C_{17}H_{21}DN_2O_2$: C, 71.05; H (for H_{22}) 7.71; N, 9.75. Found: C, 70.3; H, 7.71; N, 9.4.

3α,3aα,6aα-6a-Deutero-1,2,3,3a,4,5,6-heptahydro-3-morpholino-2-phenyl-cyclopenta[c]pyrrol-1-one (15): The residue was distilled in a Kugelrohr apparatus at 170°C/0.001 Torr. 0.24 g (56 %) of monodeuterated 15; mp 110°C; the ^1H NMR spectrum (C_6D_6) was identical with that of 13 except for the missing signal at 2.65 ppm. Anal. Calcd for $C_{17}H_{21}DN_2O_2$: C, 71.05; H (for H_{22}) 7.71; N, 9.75. Found: C, 71.1; H, 7.70; N, 9.6.

N-[(Morpholinobicycloalkyl)methyl]-4-toluenesulfonamides 20a-c - General procedure: N-Tosylcarbamoylated chloroenamine 6 (6a: 3.85 g, 10 mmol; 6b:[3] 1.99 g, 5.0 mmol; 6c: 2.06 g, 5.0 mmol) was added to a suspension of $LiAlH_4$ (1.90 g, 50 mmol) in ether (70 mL) and refluxed (6a,b: 20 h; 6c: 5 d). In the case of 20a the reaction mixture was poured into 300 mL of ether, then ice-water was added until the $LiAlH_4$ was destroyed. Filtration, washing the residue with water (50 mL), separation of the ether, extraction of the aqueous layer with ether (2 x 30 mL) and evaporation of the solvent from the combined ether layers gave crude 20a. It was crystallized twice from ether (30 mL) at -18°C. In the case of 20b,c 40% aqueous sodium hydroxide solution (50 mL) slowly was added to the reaction mixture. The precipitate was separated by

suction and washed with ether (2 x 50 mL). Then the aqueous layer of the filtrate was continuously extracted[18] by the ether solution in a Kutscher-Steudel apparatus. Separation of the ethereal phase and evaporation of the solvent gave crude 20b,c which was recrystallized from 30 mL of ether - pentane (1:1).

N-[(1α,4α,5β-Morpholino-bicyclo[2.1.0]pent-1-yl)-methyl]-4-toluenesulfonamide (20a): *Yield:* 1.51 g (45%); mp 143°C; ^{1}H NMR (C_6D_6, 400 MHz) δ 1.22 (H_A of an AB-system $^2J_{AB}$ = 5.5 Hz, 1H), 1.29-1.37 (m, 2H), 1.49-1.55 (m, 1H), 1.68-1.77 (m, 1H), 1.78-1.85 (m, 1H), 1.90 (s, 3H), 2.19-2.30 (m, 4H), 2.85 (H_C), 2.97 (H_D) (AB-system, $^2J_{AB}$ = 12 Hz, 2H), 3.44-3.66 (m, 4H), 5.12 (m_c, 1H, NH), 6.80, 6.85, 7.95, 8.00 (AA'XX'-system, 4H); ^{13}C NMR ($CDCl_3$) δ 143.5 (s), 137.3 (s), 128.8 (d), 127.2 (d), 67.1 (t), 52.8 (t), 52.5 (d, $^1J_{CH}$ = 162 Hz), 47.1 (t), 31.0 (s), 23.1 (d, $^1J_{CH}$ = 176 Hz), 21.6 (q), 20.1 (t), 16.3 (t). Anal. Calcd for $C_{17}H_{24}N_2O_3S$: C, 60.69; H, 7.19; N, 8.33. Found: C, 60.5; H, 7.20; N, 8.2.

N-[(1α,5α,6β-Morpholino-bicyclo[3.1.0]hex-1-yl)-methyl]-4-toluenesulfonamide (20b): Yield: 0.92 g (52%); mp 110-111°C; ^{1}H NMR ($CDCl_3$) δ 1.06-1.16 (m, 1H), 1.54 (d, $^3J_{HH}$ = 7.4 Hz), 1.59-1.95 (m, 6H), 2.26-2.45 (m) and 2.42 (s) (7H), 2.91 (br. s, 2H), 3.51-3.66 (m, 4H), 4.7 (s, 1H, NH), 7.31, 7.35, 7.69, 7.73 (AA'XX'-system, 4H); ^{13}C NMR ($CDCl_3$) δ 143.3 (s), 137.3 (s), 129.7 (d), 127.1 (d), 67.1 (t), 53.8 (t), 52.5 (d, $^1J_{CH}$ = 152 Hz), 49.5 (t), 35.3 (s), 28.8 (d, $^1J_{CH}$ = 164 Hz), 28.8 (t), 26.8 (t), 26.0 (t), 21.4 (q). Anal. Cacld for $C_{18}H_{26}N_2O_3S$: C, 61.69; H, 7.48; N, 7.99. Found: C, 61.5; H, 7.35; N, 7.8.

N-[(1α,6α,7β-Morpholino-bicyclo[4.1.0]hept-1-yl)-methyl]-4-toluenesulfonamide (20c): Yield: 0.69 g (38%); mp 148-149°C; ^{1}H NMR ($CDCl_3$) δ 0.65 (d of d of d, $^2J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = $^3J_{HH}$ = 7.7 Hz), 1.06-1.78 (m) and 1.24 (d, $^2J_{HH}$ = 7.7 Hz) (9H), 2.25-2.44 (m) and 2.42 (s) (7H), 2.57 (H_A), 2.71 (H_B) (AB-system, $^2J_{AB}$ = 11.7 Hz, additional coupling by NH $^3J_{HH}$ = 5.9 Hz, 2H), 3.47-3.64 (m, 4H), 4.45 (t, $^3J_{HH}$ = 5 Hz, 1H, NH), 7.31, 7.35, 7.68, 7.72 (AA'XX'-system, 4H); ^{13}C NMR ($CDCl_3$) δ 143.7 (s), 137.3 (s), 130.0 (d), 127.4 (d), 67.2 (t), 53.8 (t, 2C), 49.7 (d, $^1J_{CH}$ = 164 Hz), 22.5 (t), 21.9, 21.8, 21.7 (3t and 1s), 21.6 (q), 19.2 (d, $^1J_{CH}$ = 156 Hz), 19.2 (t). Anal. Calcd for $C_{19}H_{28}N_2O_3S$: C, 62.61; H, 7.74; N, 7.69. Found: C, 62.6; H, 7.85; N, 7.6.

N-[(1-Morpholino-2-cyclopenten-1-yl)-methyl]-4-toluenesulfonamide (22): A solution of 20a (0.336 g, 1.0 mmol) and benzoic acid (0.112 g, 1.0 mmol) in 5 mL of chloroform was heated for 16 h to 60°C. Extraction of the solution with 2 mL of saturated aqueous Na_2CO_3 gave crude 22. Pure 22 was obtained by crystallization from ether - pentane (1 : 1) (20 mL). Yield: 0.250 g (74%); mp 108°C; ^{1}H NMR ($CDCl_3$) δ 1.21-1.45 (m, 1H), 1.96-2.50 (m) and 2.45 (s) (10 H), 2.96 (s, 2H), 3.51-3.60 (m, 4H), 5.48-5.57 (m, 1H), 5.81-5.90 (m, 1H), 7.29, 7.33, 7.73, 7.77 (AA'XX'-system, 4H); ^{13}C NMR ($CDCl_3$) δ 143.1 (s), 136.6 (s), 133.6 (d), 132.0 (d), 129.4 (d), 126.9 (d), 73.9 (s), 67.2 (t), 48.1 (t), 46.3 (t), 31.7 (t), 26.1 (t), 21.5 (q). Anal. Calcd for $C_{17}H_{24}N_2O_3S$: C, 60.69; H, 7.19; N, 8.33. Found: C, 60.6; H, 7.05; N, 8.2.

3-Chloro-2-morpholino-N-(4-toluenesulfonyl)-1-cyclopentene-1-carboxamide (6a): A solution of chloroenamine 25a[17] (3.0 g, 16 mmol) in 30 mL of acetonitrile was cooled to -10°C. 4-Toluenesulfonylisocyanate (24) (3.16 g, 16 mmol) was added within 10 min under stirring. Continuous stirring at -10°C for 30 min gave a colorless precipitate which was isolated by suction, washed with ice-cold acetonitrile (20 mL) and dried in vacuo. Yield: 5.1 g (83%); mp 131°C; IR (KBr, cm^{-1}) 1645, 1590 (C=O, C=C); ^{1}H NMR ($CDCl_3$) δ 2.06-2.35 (m, 2H), 2.42 (s, 3H), 2.42-2.61 (m, 1H), 2.74-2.93 (m, 1H), 3.10-3.35 (m, 4H), 3.82-4.00 (m, 4H), 5.02 (m_c, 1H), 7.32, 7.36, 7.96, 8.00 (AA'XX'-system, 4H), 10.1 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 161.5 (s), 158.4 (s), 145.0 (s), 136.6 (s), 129.7 (d), 128.4 (d), 116.8 (s), 66.7 (t), 62.7 (d, $^1J_{CH}$ = 158 Hz), 51.8 (t), 31.7 (t), 28.4 (t), 21.6 (q). Anal. Calcd for $C_{17}H_{21}ClN_2O_4S$: C, 53.05; H, 5.50; N, 7.28. Found: C, 52.8; H, 5.50; N, 7.3.

3-Chloro-2-morpholino-N-(4-toluenesulfonyl)-1-cycloheptene-1-carboxamide (6c): 4-Toluenesulfonylisocyanate (24) (3.94 g, 20 mmol) was added to a solution of chloroenamine 25c[17] (4.31 g, 20 mmol) in 50 mL of dichloromethane. The solution was stirred at 20°C for 1 h. The solvent was evaporated and the residue was triturated with 30 mL of ethanol. Standing at -18°C for 24 h gave a cristalline precipitate which was isolated by suction and washed successively with ice-cold ethanol, ether and pentane (each 30 mL). Yield: 4.40 g (53%); mp 135-136°C; IR (KBr, cm^{-1}) 1665, 1600 (C=O, C=C); ^1H NMR ($CDCl_3$)δ 1.12-2.47 (m, 8H), 2.44 (s, 3H), 2.98 (m_c, 4H), 3.97 (m_c, 4H), 4.92 (m_c, 1H), 7.31, 7.35, 7.74, 7.78 (AA'XX'-system, 4H); ^{13}C NMR ($CDCl_3$) δ 164.0 (s), 155.7 (s), 144.9 (s), 137.0 (s), 135.3 (s), 129.8 (d), 128.6 (d), 66.2 (t), 49.8 (t), 55.2 (d, $^1J_{CH}$ = 150 Hz), 33.7 (t), 25.5 (t), 25.1 (t), 23.4 (t), 21.7 (q). Anal. Calcd for $C_{19}H_{25}ClN_2O_4S$: C, 55.27; H, 6.10; N, 6.78. Found: C, 55.1; H, 6.14; N, 6.6.

3-Chloro-2-morpholino-N-(4-toluenesulfonyl)-1-cyclododecene-1-carboxamide (6d): A solution of 4-toluenesulfonylisocyanate (24) (1.97 g, 10 mmol) in ether (20 mL) was dropped under stirring to a solution of chloroenamine 25d[18] (2.86 g, 10 mmol) in 40 mL of ether at -20°C. Stirring was continued for 45 min. Crystallization was completed by standing at -20°C for 2 h. The crystalline solid was isolated by suction, washed with 20 mL of ether and dried in vacuo. Yield: 3.09 g (64%); mp 103°C; IR (KBr, cm^{-1}) 1695, 1615 (C=O, C=C); ^1H NMR ($CDCl_3$, -30°C) δ 0.86-1.55 (unstruct. signal, 13H), 1.65-2.28 (m, 4H), 2.30-2.55 (m) and 2.39 (s) (4H), 3.20 (m_c, 4H), 3.74 (m_c, 4H), 5.00 (m_c, 1H), 7.29, 7.33, 7.91, 7.95 (AA'XX'-system, 4H), 13.2 (s, NH, 1H); ^{13}C NMR ($CDCl_3$, -30°C) δ 166.4 (s), 153.2 (s), 145.4 (s), 135.5 (s), 129.9 (d), 129.9 (s), 128.5 (d), 66.6 (t), 57.1 (d, $^1J_{CH}$ = 146 Hz), 52.2 (t), 32.2 (t), 26.9 (t), 26.3 (t, 2C), 23.1, 22.9, 22.7, 21.9, 21.0, 19.3 (5t and 1q). Anal. Calcd for $C_{24}H_{35}ClN_2O_4S$: C, 59.67; H, 7.30; N, 5.80. Found: C, 59.6; H, 7.18; N, 5.8.

X-Ray Crystal Structure Analyses[19,20]

8b: $C_{19}H_{23}N_3O_4S$, F.W. = 389.5; triclinic, space group $P\bar{1}$; a = 11.175(5), b = 11.736(3), c = 7.923(6) Å, α = 103.27(3), ß = 109.77(4), γ = 92.37(3)°, V = 944(2) Å^3; 2 molecules per unit cell, D_x = 1.37 g cm^{-3}; μ(Mo-K_α) = 1.921 cm^{-1}; crystal size 0.50 x 0.40 x 0.30 mm. Data collection: Diffractometer Enraf-Nonius CAD 4, monochromatized Mo-K_α radiation; 3583 independent reflections with 2.00 < θ < 25.00° [ω/2θ scan, scan width (0.85 + 0.35 tan θ)°, scan speed 0.9 - 5.0°min^{-1}], no absorption correction. Structure solution and refinement: Full-matrix least-squares method, H atoms refined isotropically, 2700 reflections with I > 3σ(I); 244 variables, unit weights, maximum shift/error ratio < 0.72, R = 0.050, $R_w = (\Sigma\Delta^2F / \Sigma F_o^2)^{1/2}$ = 0.051.

8c: $C_{20}H_{25}N_3O_4S$, F.W. = 403.5; monoclinic, space group $P2_1/c$; a = 12.424(1), b = 9.023(3), c = 18.114(3) Å, ß = 101.35(1)°, V = 1991(1) Å^3; 4 molecules per unit cell, D_x = 1.346 g cm^{-3}; μ(Mo-K_α) = 1.845 cm^{-1}; crystal size 0.40 x 0.25 x 0.10 mm. Data collection: Diffractometer Enraf-Nonius CAD 4, monochromatized Mo-K_α radiation; 2752 independent reflections with 2.00 < θ < 23.00° [ω/2θ scan, scan width (0.90 + 0.35 tan θ)°, scan speed 0.9 - 5.0°min^{-1}], no absorption correction. Structure solution and refinement: Full-matrix least-squares method, H atoms refined isotropically, 2170 reflections with I > 2σ(I); 353 variables, unit weights, maximum shift/error ratio < 0.50, R = 0.043, $R_w = (\Sigma\Delta^2F / \Sigma F_o^2)^{1/2}$ = 0.041.

8d: $C_{25}H_{35}N_3O_4S$, F.W. = 473.6; monoclinic, space group $P2_1/c$; a = 12.016(6), b = 15.916(9), c = 13.797(17) Å, ß = 107.37(6)°, V = 2518(3) Å^3; 4 molecules per unit cell, D_x = 1.249 g cm^{-3}; μ (Cu-K_α) = 13.86 cm^{-1}; crystal size 0.30 x 0.45 x 0.70 mm. Data collection: Diffractometer Enraf-Nonius CAD 4, monochromatized Cu-K_α radiation; 4271 independent reflections with 4.00 < θ < 65.00° [ω/2θ scan, scan width (0.90 + 0.14 tan θ)°, scan speed 0.9 - 5.0°min^{-1}], linear correction for intensity loss (< 3.4%), empirical absorption correction[21]. Structure solution and refinement: Full-matrix least-squares method, H atoms refined isotropically, 3731 reflections with I > 2.2σ(I); 483 variables, unit weights, maximum shift/error ratio 1.23, R = 0.053, $R_w = (\Sigma\Delta^2F / \Sigma F_o^2)^{1/2}$ = 0.053.

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