Tetrahedron Vol. 45, No. 12, pp. 3683 to 3694, 1989
Printed in Great Britain.

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

FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS III. SYNTHESIS AND ASSIGNMENT OF CONFIGURATION OF TWO ISOMERIC MORPHOLINOBICYCLO[3.1.0]HEXANE DERIVATIVES

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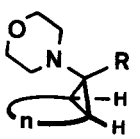
(*Received in Germany* 23 *December* 1988)

Abstract - Reaction of the acylated chloroenamine 7 with cyanide gave the endo-morpholino compound 11. The endo-morpholino configuration of 11 was established by subsequent ring closure reactions generating tricyclic derivatives 14, 16 and 17. $LiAlH_4$ reduction of 11 afforded aminoalcohol 12. The corresponding exo-morpholino isomer 20 could be obtained by $LiAlH_4$ reduction of exo-morpholino compound 19 which was accessible from N-tosylcarbamoylated chloroenamine 10 and cyanide. $\Delta G^{\ddagger}$ values of 75.4-77.6 kJ/mol and 52.1 kJ/mol were determined for the morpholine dynamics in the two isomeric compounds 12 and 20, respectively. This demonstrates that ^1H NMR spectroscopic determination of the dynamics of morpholine allows an assignment of the configuration even in the case of twofold substituted morpholinobicyclo[n.1.0]alkane derivatives.

We have found a very simple method for the assignment of the configuration of aminobicyclo[n.1.0]alkanes of type 1 and 2 by observation of the dynamics of the morpholino group.[1-5] ^1H NMR spectra indicate that the dynamics of the morpholine or of other similar heterocyclic systems are more strongly hindered in 1 than in 2. In the simplest case this is detectable from the type of signal pattern of the heterocycle in the ^1H NMR spectrum. Thus, at room temperature, morpholine displays in the bicyclo[n.1.0]hexane -heptane , or octane system an AA'XX' pattern in the exo-position [2, n = $(CH_2)_{3-5}$] and an ABXY pattern in the endo-postion [1, n = $(CH_2)_{3-5}$]. In compounds 1 (R = H) the $\Delta G^{\ddagger}$ values for the dynamics of the endo-morpholine amount to 70-80 kJ/mol.[1-5] The dynamic behaviour of the exo-morpholine in 2 is comparable[1,2,4,5] to that of N-methylmorpholine ($\Delta G^{\ddagger}$ = 48 kJ/mol[6]). The three membered ring in 1 and 2 possesses a $-(CH_2)_n-$ bridge on one side and two



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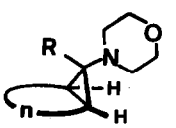
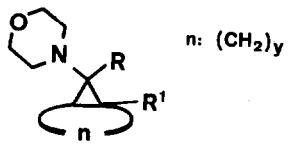


2

n: $(CH_2)_y$

hydrogen atoms on the other side. The strong difference of the steric interactions between these substituents and the morpholine represents the basis for the assignment of the configuration by ^{1}H NMR spectroscopy.

Thus far it is not known whether the presence of an additional substituent as in the bridge head position of an aminobicycloalkane 1 or 2 allows the determination of the configuration by the ^{1}H NMR spectrum, too. Twofold substituted aminobicycloalkanes 3, representing this type of compounds, recently could be obtained from functionalized chloroenamines and nucleophiles.[7,8]



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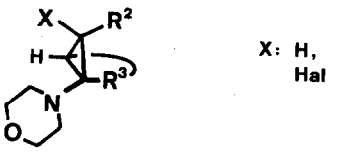


4

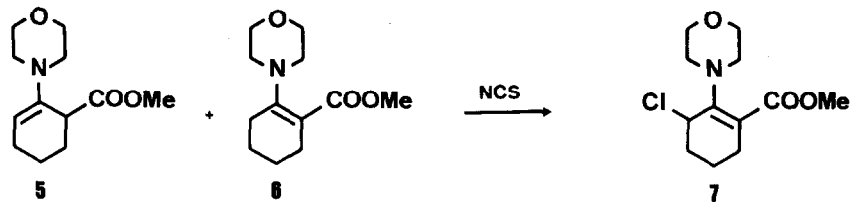
Compounds 4 also correspond to twofold substituted aminobicycloalkanes. In contrast to 3, however, the morpholino moiety in 4 is connected to the bridge head C-atom. Different line shapes (strongly split or broad and unsplit) were observed for the morpholino ^{1}H NMR signals depending on the nature of the substituent X (X = R^2 = H; X = R^2 = Cl or Br).[9] On the basis of this observation the configuration of a chloro-fluoro compound 4 (X = Cl, R^2 = F) was established.[9] This kind of assignemt, without any knowledge of the temperature dependency of the ^{1}H NMR spectra, is rather unreliable since the important information about the chemical shifts of the coalescing protons is missing.

In this paper we describe a selective synthesis of some endo- and exo-morpholino bicyclohexane derivatives of type 3. This access was found in the reaction of cyanide with the chloroenamines 7 and 10. Studying the ^{1}H NMR spectra of the bicyclohexane derivatives, thus prepared, gave the information about the applicability of morpholine as a stereoindicator also in the case of multiply substituted morpholinobicycloalkane derivatives.

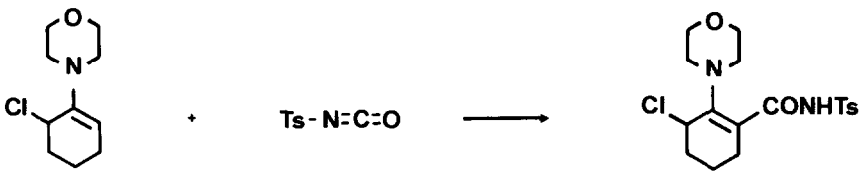
CHLORO-MORPHOLINOCYCLOHEXENE DERIVATIVES 7 AND 10

Methyl chloro-morpholinocyclohexenecarboxylate could be obtained by chlorination of a mixture of the isomeric enamines 5/6 by NCS. The formation of a pure substance 7 in 91% yield from a mixture of 5/6 (35:65) should be the consequence of a thermodynamically controlled chlorination reaction (see ref.[7,8]).

Chloromorpholino-N-tosyl-cyclohexenecarboxamide 10 was accessible in 78% yield by acylation of chloroenamine 8 with tosylisocyanate 9. ^1H and ^{13}C NMR data clearly establish the chloroenamine structures 7 and 10. The CHCl-moiety of the chloroallyl unit is indicated by a characteristic signal in the ^1H NMR (m_c; 7: 4.75 ppm; 10: 4.88 ppm) and in the ^{13}C NMR (d; 7: 58.3 ppm; 10: 53.6 ppm) in the expected regions.



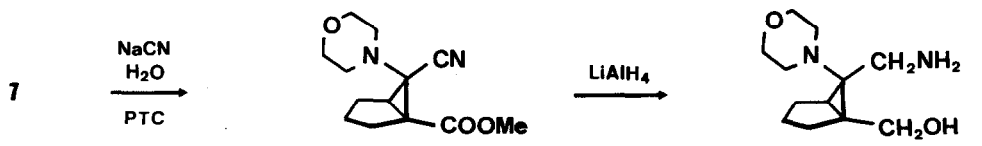
5 6 7



8 9 10

endo-MORPHOLINO-BICYCLOHEXANE DERIVATIVES 11 - 17

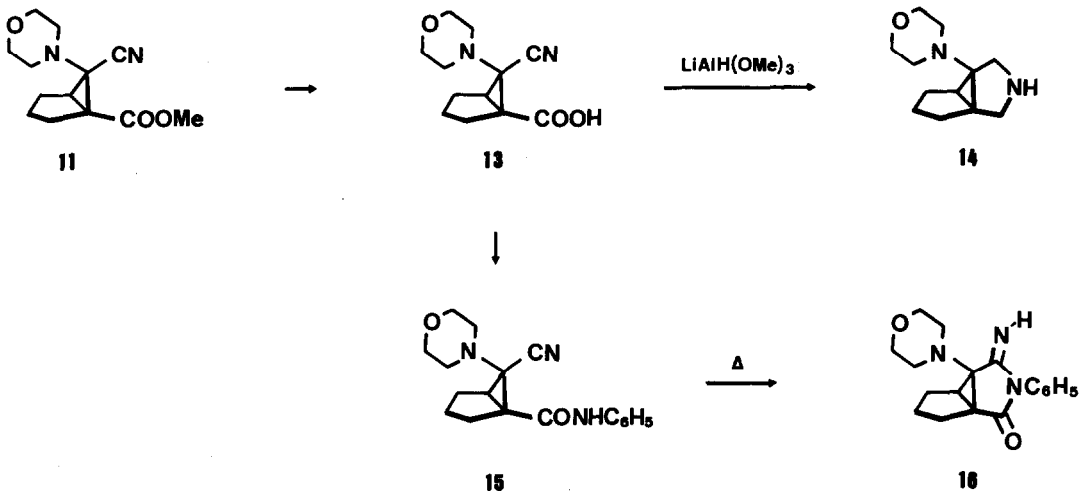
Reaction of chloroenamine 7 with cyanide in water gave bicyclic nitrile 11 in 42% yield. The yield of 11 was increased to 65% by using an equimolar amount of tetrabutylammonium chloride as a phase transfer catalyst. A sterically pure substance was isolated in both cases from the reaction mixture. $LiAlH_4$ reduction converted 11 into aminoalcohol 12.



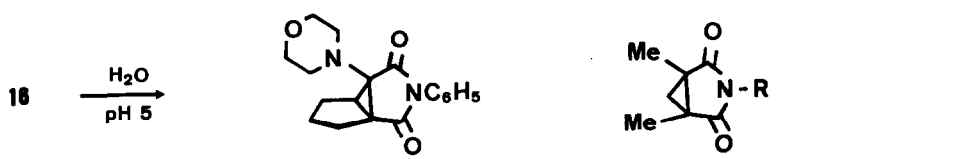
11 12

The endo-morpholino configuration of 11 and 12 could be established by subsequent reactions indicating the syn connection of the cyano- and the ester group in 11. This was achieved by a ring closure reaction involving the

two latter functional groups to give tricyclic compounds 14 and 16. In the first step of these reaction sequences methyl carboxylate 11 was saponified to the bicyclic carboxylic acid 13 (91% yield) by alcoholic potassium hydroxide. Reduction of 13 by lithium aluminum trimethoxyhydride directly led to a tricyclic diamine 14 in 55% yield. A second tricyclic derivative 16 was accessible from 13 via the amide 15 which cyclized upon heating. As described previously,[8] the tricyclic amidine 16 was obtained by the reaction of chloromorpholino-N-phenyl-cyclohexenecarboxamide with cyanide. The bicyclic carboxamide 15 as the primary product of the reaction, thereby, could not be isolated due to a too fast cyclization in the basic medium.

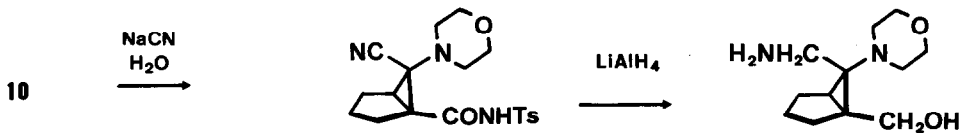


Amidine 16 could be hydrolyzed to the tricyclic imide 17 upon heating in a buffer solution (pH = 5). 17 possesses an N-phenyl cyclopropanosuccinimide moiety which is the central structural unit of the fungicidal compounds 18a or 18b (Procymidone, Trade Names: Sumilex®, Sumisclex®)[10-12].



exo-MORPHOLINOBICYCLOHEXANE DERIVATIVES 19 AND 20

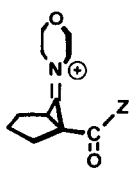
Reaction of N-tosylcarbamoylated chloroenamine 10 with cyanide in water provided bicyclic nitrile 19 in 53% yield. The latter could be transferred into a bicyclic aminoalcohol 20 (48% yield) by $LiAlH_4$. Surprisingly the N-tosylcarboxamide moiety in 19 was reduced to an alcohol group instead of an amino function.



19 20

The bicyclohexane structure of the compounds 11 - 15, 17 19 and 20 was established by three triplets (δ = 32.7-22.7 ppm), two singlets and one doublet ($^2J_{CH}$ = 160-176 Hz) in the ^{13}C NMR spectrum. 12 and 20 represent diastereomeric compounds with different spectroscopic properties. In the ^{13}C NMR spectrum the CH_2NH_2 moiety appears at lower field for 12 (42.8 ppm) than for 20 (37.0 ppm). This clearly indicates the endo-position of the amino-methyl group in 20 and the uniform exo-morpholino configuration of 19 and 20.

POTENTIAL INTERMEDIATE



21

A: Z = OMe

B: Z = N-Ts ⊖

The varying stereochemical results best can be understood by assuming a bicyclic iminium ion 21 as an intermediate in the formation of 11 and 19. Thus 21A is attacked from the less hindered exo-side leading to the endo-morpholino derivative 11. Since a tosylcarbamoyl moiety is deprotonated already in a weak basic medium, the iminium ion 21B - in contrast to 21A - has an anionic center in the exo-position. Repulsion effects between this anion and the cyanide would explain the endo-attack in this special case generating exo-morpholino compound 19 from chloroenamine 10.

1H NMR SPECTRA OF THE DISUBSTITUTED MORPHOLINOBICYCLOHEXANE DERIVATIVES 11, 12 AND 19, 20 - A BASIS FOR ASSIGNMENT OF CONFIGURATION

The morpholine ^1H NMR signals of compounds 11 - 13 and 15 strongly differ from those of the derivatives 19 and 20. At room temperature signals of the ABXY-type are observed for 11 - 13 and 15; 19 and 20 give relatively narrow unsplit signals. 14 shows morpholine ^1H NMR signals being in coalescence (one broad unsplit signal for OCH_2 and two broad unsplit signals for NCH_2). In the case of 17 beginning coalescence of the morpholine peaks is indicated (four unsplit signals for OCH_2 and NCH_2). We have investigated the temperature dependency of the morpholine ^1H NMR spectra of compounds of type 3 using derivatives 11, 12, 14, 17, 19 and 20.

The O-methylene and the N-methylene moieties of an achiral morpholine appear as two AB-systems in the ^1H NMR spectrum upon less frequent interconversions (e.g. 1 at room temperature, 2 or N-methylmorpholine at low temperatures). Thereby one part of each AB-system additionally is split off due to a large coupling between the two axial protons. Since this vicinal coupling constant mostly is of the same value as one of the geminal coupling constants, generally signals are resulting as depicted for the OCH_2-group in Fig. 1a. In many cases a further fine coupling ($^3J_{BB}$ = 2-3 Hz) is observable for the triplet type signal. The ΔG^+-value of the interconversion process can be estimated on the basis of the chemical shifts of H_A and H_B and the coalescence temperature by using a well known approximation formula.[13]

Asymmetric compounds 3 should give rise to four AB-systems for the morpholine methylene moieties upon less frequent interconversions. In most cases the two AB-systems especially of the O-methylene groups are relatively close together allowing a less complicated study of the dynamics of the interconversion (Fig. 1b). This "hydrogen-equilibrating process" is induced by a combination of the rotation about the cyclopropane morpholine bond, of the morpholine ring inversion and of the N-inversion (see ref.[14]). For an asymmetric morpholine coalescence takes place between H_{A1} and H_{B2} on the one hand and H_{A2} and H_{B1} on the other hand leading to one AB-system. We have used the aproximation formula[15] for the uncoupled case due to the absence of a coupling between the coalescing H-atoms in this case. Though the two sets of H_A and H_B signals mostly can be distinguished (exception: 11 H_{A1}/H_{A2}; 14 and 20 H_{A1}/H_{A2}; H_{B1}/H_{B2}), the signals can not be assigned to pairs H_{A1}/H_{B2} and H_{A2}/H_{B1}.

Consequently we have calculated a maximum and a minimum ΔG^+-value resulting from the coalescence between H_{A1} and the farest H_B (maximum) and the coalescence between H_{A2} and the nearest H_B (minimum) (Fig. 1b).

Dynamics of the morpholine system were studied for 11, 12, 14, 17 19 and 20 using the OCH_2 signals according to this procedure. ΔG^+-values additionally

could be determined on the basis of the NCH_2 groups in the case of 11, 12 and 17 (Table 1). Thereby the NCH_2 group of 12 and 17 gave two sets of H_X and H_Y signals which were separated far enough to allow the observation at least of one definite interchange process. The values found for 11 (78.5-79.4 kJ/mol) and 12 (75.4-77.6 kJ/mol) are characteristic of a morpholine in the endo-position of a bicyclo[3.1.0]hexane system. 19 and 20 on the other hand gave ΔG^{+}-values of 55.1-56.0 kJ/mol and 52.1 kJ/mol, respectively. These latter results demonstrate that the bridge head substituent has almost no influence on the dynamics of the morpholine in the exo-position (N-methylmorpholine: ΔG^{+}: 48 kJ/mol[6]). Furthermore the influence of the asymmetry in 3 leading to two sets of morpholine signals is not as great as to give severe problems for the determination of ΔG^{+}. Maximum and minimum values of ΔG^{+} are differing only within the limit of error caused generally by the application of the approximation formula[13,15].

Fig. 1a ^1H NMR Signals of the OCH_2-moiety of an achiral morpholine (R = achiral) in the case of less frequent interconversions

Fig. 1b ^1H NMR Signals of the OCH_2-moiety of an asymmetric morpholine (R = asymmetric) in the case of less frequent interconversions

A fine coupling is depicted for H_B, H_{B1} and H_{B2} as usually observable.

Table 1 ΔG^{+}-Values of the Dynamics of Morpholine on the Basis of ^{1}H NMR Data and Coalescence Temperatures (T_c) of the Compounds 11, 12, 14, 17, 19 and 20

OCH_2 Moiety:

	T [°C]	H_{A1}	H_{A2}	$^{2}J_{HH}$ [Hz]	H_{B1} / H_{B2}	$^{2}J_{HH}$ / $^{3}J_{HH}$ [Hz]	T_c [°C]	Solvent	ΔG^{+} [a] Maximum [kJ/mol]	Minimum
11	20	3.87[b]		10.5	3.59 / 3.58	10.5	108	$C_6D_5NO_2$	78.7	78.6
12	25	3.75	3.70	9.0	3.50 / 3.42	9.0	95	$C_6D_5NO_2$	77.0	75.4
14	-55	3.58[b]		10.0	3.32[b]	10.0	33	$C_6D_5CD_3$	62.9 (62.6)[c]	
17	-10	3.61	3.55	11.5	3.18 / 3.14	11.5	60	$C_6D_5CD_3$	67.7	67.0
19	-80	3.89	3.85	11.4	3.63 / 3.57	11.4	-1	CD_2Cl_2	55.1	56.0
20	-70	3.79[b]		10.0	3.42[b]	10.0	-14	CD_2Cl_2	52.1 (52.0)[c]	

NCH_2-Moiety:

	T [°C]	H_{X1}	H_{X2}	$^{2}J_{HH}$ / $^{3}J_{HH}$ [Hz]	H_{Y1}	H_{Y2}	$^{2}J_{HH}$ [Hz]	T_c [°C]	Solvent	ΔG^{+} [a] Maximum	Minimum
11	20	2.78	2.76	11.2	2.61	2.58	11.2	102	$C_6D_5NO_2$	79.4	78.5
12	25	2.86	2.80	10.8	2.91[d]	2.34[e]	10.8	70[f] 110[g]	$C_6D_5NO_2$	76.6[f] 77.6[g]	
17	-10	3.79	2.90	11.5	2.29[e]	-[h]	11.5	66[g]	$C_6D_5CD_3$	67.5[g]	

[a] Calculated by the approximation formula for uncoupled interchanging protons.[15] [b] Signals of the two hydrogen atoms are not separated. [c] Calculated by the approximation formula for coupled interchanging protons.[13] [d] H_{Y2}. [e] H_{Y1}. [f] Coalescence H_{X1}/H_{Y2}, T_c difficult to be determined exactly. [g] Coalescence H_{X2}/H_{Y1}. [h] H_{Y2} appears together with the trimethylene moiety; exact chemical shift is not determinable.

The relatively low ΔG^{+}-values of the dynamics of the endo-morpholine of 14 and 17 should be the consequence of the tricyclic ring system: Incorporation of the exo substituent of the C_1-bridge into a five membered ring decreases

its steric interaction with morpholine. The resulting facilitation of the dynamics of the morpholine system is more effective with 14 (neighboring CH_2-moiety) than with 17 (neighboring CO-moiety).

Thus, using morpholine as a "stereoindicator" in compounds of type 3 requires a more differentiating procedure: The appearance of signals of an ABXY-type at room temperature allows the assignment of the endo-position of morpholine without further investigation. A similar simple indication, however, is not existing for an exo morpholino moiety as demonstrated by the comparison of the ^1H NMR spectra of the compounds 14, 17, 19 and 20. 14 and 17 show unsplit ^1H NMR signals for morpholine, though this heterocycle is in the endo-position. The determination of the $\Delta G^{\ddagger}$-value of the morpholine dynamics obviously is necessary to establish an exo-morpholino configuration in compounds of type 3 representing twofold substituted aminobicyclohexane derivatives.

EXPERIMENTAL

^1H NMR and ^{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, a Beckman Acculab 3 or a Beckman IR 20 A Infrared Spectrophotometer. Melting points are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 Elemental Analyzer. N_2 as inert gas and strictly anhydrous solvents were used for the $LiAlH_4$ reductions.

Methyl 3-chloro-2-morpholino-1-cyclohexene-1-carboxylate (7): A solution of N-chlorosuccinimide (2.67 g, 20 mmol) in 50 mL of dichloromethane was dropped within 15 min to a stirred solution of methyl morpholinocyclohexenecarboxylate 5/6[16] (4.51 g, 20 mmol, 5/6 = 35/65) in dichloromethane (10 mL) at 0°C. Then the ice bath was removed and stirring was continued for 1 h. Removal of the solvent in vacuo, extraction of the residue with ether (3 x 30 mL) and evaporation of the ethereal solution gave 7 as pale yellow oil, which could not be purified further (attempted distillation in vacuo caused decomposition). Yield: 4.27 g (91%); IR (film, cm^{-1}) 1695, 1585 (C=O, C=C); ^1H NMR ($CDCl_3$) δ 1.56-2.50 (m, 6H), 2.51 (m_c, 1H), 2.75-3.09 (m, 4H), 3.45-3.74 (m) and 3.61 (s) (7H), 4.75 (m_c, 1H); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 152.5 (s), 110.8 (s), 67.3 (t), 58.3 (d), 51.8 (q), 50.9 (t), 32.7 (t), 27.1 (t), 16.7 (t). Anal. Calcd for $C_{12}H_{18}ClNO_3$: C, 55.49; H, 6.99; N, 5.39. Found: C, 54.4; H, 6.72; N, 4.8.

3-Chloro-2-morpholino-N-(4-toluenesulfonyl)-1-cyclohexene-1-carboxamide (10): A solution of chlorocyclohexenyl morpholine 8[17] (4.03 g, 20 mmol) and of 4-toluenesulfonylisocyanate 9 (3.94 g, 20 mmol) in 50 mL of dichloromethane was refluxed for 20 h under stirring. Unreacted starting materials were removed by evaporation of the solvent and extraction with ether (3 x 50 mL). The residue was dried in vacuo, crystallized from acetonitrile (20 mL, -18°C), isolated by suction and washed consecutively with ice-cold acetonitrile (20 mL), ether (20 mL) and pentane (20 mL) to give pure 10. Yield: 6.24 g (78%); mp 131-132°C; IR (KBr, cm^{-1}) 1675, 1595 (C=O, C=C); ^1H NMR ($CDCl_3$) δ 1.70-2.18 (m, 6H), 2.43 (s, 3H), 2.70 (m_c, 1H), 3.04-3.20 (m, 4H), 3.80-4.06 (m, 4H), 4.88 (m_c, 1H), 7.31, 7.35 (2H) and 7.96, 8.00 (2H) (AA'BB'-type-signals), 13.3 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 163.6 (s), 153.2 (s), 144.8 (s), 136.5 (s), 129.6 (d), 128.3 (d), 124.9 (s), 66.6 (t), 53.6 (d), 52.2 (t), 32.4 (t), 25.0 (t), 21.6 (q), 15.9 (t). Anal. Calcd for $C_{18}H_{23}ClN_2O_4S$: C, 54.20; H, 5.81; N, 7.02. Found: C, 53.8; H, 5.94; N, 7.0.

Methyl 1α,5α,6ß-6-cyano-6-morpholino-bicyclo[3.1.0]hexane-1-carboxylate (11): Chloroenamine 7 (5.20 g, 20 mmol) was added to a solution of sodium cyanide (1.01 g, 20 mmol) and tetrabutylammonium chloride (5.56 g, 20 mmol) in 20 mL of water and stirred vigorously 12 h at 55°C. Cooling to 20°C, addition of 30 mL of water, isolation of the precipitate by suction and consecutive washing with water (4 x 20 mL) and ether (5 mL) gave crude 11 which was recrystallized from a mixture of dichloromethane (15 mL) - ether (40 mL). Yield: 3.26 g (65%); mp 133.5°C; IR (KBr, cm^{-1}) 2220 (C≡N), 1740 (C=O); ^1H NMR ($CDCl_3$)δ 1.66-2.44 (m, 6H), 2.47 (d, 1H), 2.58 (H_{Y1}, H_{Y2}, $^2J_{HH}$ = 10.9 Hz, 2H), 2.79 (H_{X1}, $^2J_{HH}$ = $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 3.1 Hz, 1H), 2.82 (H_{X2}, $^2J_{HH}$ = $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 3.1 Hz, 1H), 3.57 (H_{B1}, $^2J_{HH}$ = $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 1.6 Hz, 1H), 3.59 (H_{B2}, $^2J_{HH}$ = $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 1.6 Hz, 1H), 3.78 (s, 3H), 3.87 (H_{A1}, H_{A2}, $^2J_{HH}$ = 10.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 170.7 (s), 114.7 (s), 66.9 (t), 52.6 (q), 51.0 (t), 50.6 (t), 48.8 (s), 46.2 (s), 40.3 (d, $^1J_{CH}$ = 172 Hz), 27.5 (t), 26.7 (t), 26.0 (t). Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.0; H, 7.20; N, 11.2.

Identical 11 (0.52 g, yield: 42%, mp 133-134°C) was obtained from chloroenamine 7 (1.30 g, 5.0 mmol) and sodium cyanide (0.25 g, 5.0 mmol) in water (50 mL). The mixture was heated to 95°C for 20 h and then worked up as described above.

1α,5α,6ß-6-Cyano-6-morpholino-bicyclo[3.1.0]hexane-1-carboxylic acid (13): A mixture of bicyclic nitrile 11 (2.5 g, 10 mmol), 1.81 g potassium hydroxide (1.81 g, 28.7 mmol), ethanol (60 mL) and water (3 mL) was refluxed for 2 h. Then the solvent was removed in vacuo, the residue was dissolved in water (50 mL) and concentrated hydrochloric acid was added till pH = 1. The precipitate was isolated by suction, washed with water (20 mL) and ether (4 mL) and dried in vacuo. Yield: 2.15 g (91%); mp 156°C (decomp.); IR (KBr, cm^{-1}) 2240 (C≡N), 1700 (C=O); ^1H NMR ($CDCl_3$) δ 1.73-2.45 (m, 6H), 2.50 (d, 1H), 2.55 (H_{Y1}, H_{Y2}, $^2J_{HH}$ = 11.6 Hz, 2H), 2.81, 2.83 (H_{X1}, H_{X2}, $^2J_{HH}$ = $^3J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 3.6 Hz, 2H), 3.57, 3.58 (H_{B1}, H_{B2}, $^2J_{HH}$ = $^3J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 1.9 Hz, 2H), 3.90 (H_{A1}, H_{A2}, $^2J_{HH}$ = 11.2 Hz, 2H) (2 ABXY-systems), 8.82 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 175.8 (s), 114.3 (s), 66.9 (t), 51.0 (t), 50.0 (t), 49.6 (s), 46.0 (s), 41.4 (d, $^1J_{CH}$ = 172 Hz), 27.7 (t), 27.3 (t), 27.0 (t). Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.0; H, 6.78; N, 11.9.

4-(4-Aza-tricyclo[4.3.0.$0^{2,6}$]non-2-yl)-morpholine (14): A mixture of methanol (0.50 g, 15.8 mmol) and THF (6.0 mL) was added at 0°C to a suspension of lithium aluminum hydride (0.30 g, 7.9 mmol) in THF (7 mL). When hydrogen evolution had finished an insoluble residue was removed by suction. This solution was dropped slowly under stirring to a solution of bicyclic carboxylic acid 13 (0.41 g ,1.75 mmol) in THF (5 mL) at 0°C. The reaction mixture was stirred for 2 h at 0°C and for 19 h at 20°C. Then 10 mL of aqueous sodium hydroxide solution (10%) and 10 ml of THF were added. After removing the residue by suction the solvent was evaporated in vacuo. The remaining crude 14 was purified by distillation in a Kugelrohr apparatus (85-90°C/0.001Torr). Yield: 0.20 g (55%); mp 81°C; ^1H NMR ($CDCl_3$) δ 1.20 (d, 1H), 1.60-2.10 (m, 6H and NH), 2.78 (H_{N1}), 2.88 (H_{N2}), 3.03 (H_{M2}), 3.26 (H_{M1}) (2 AB-systems, J_{M1N1} = 10.95 Hz, J_{M2N2} = 11.0 Hz, 4 H), 2.50 (2H), 2.80 (2H), 3.67 (4H) (broad, unsplit signals); ^{13}C NMR ($CDCl_3$) δ 67.9 (t), 56.7 (s), 51.4 (t), 51.3 (t), 46.1 (t), 46.0 (t), 45.2 (s), 30.7 (d, $^1J_{CH}$ = 160 Hz), 26.8 (t), 25.7 (t), 25.5 (t). Anal. Calcd for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 68.9; H, 9.59; N, 13.4.

1α,5α,6ß-6-Cyano-6-morpholino-N-phenyl-bicyclo[3.1.0]hexane-1-carboxamide (15): A solution of dicyclohexylcarbodiimide (0.68 g, 3.3 mmol) in dichloromethane (5 mL) was added to a solution of bicyclic carboxylic acid 13 (0.71 g, 3.0 mmol) and aniline (0.32 g, 3.3 mmol) in 25 mL of dichloromethane. The mixture was stirred at 20°C for 13 h. Then the precipitate was removed by suction; the solution was washed with 10 mL of water and the solvent was evaporated in vacuo. The residue gave pure 15 after washing with ether and recrystallization from acetonitrile. Yield: 0.52 g (56%); mp 161°C; IR (KBr, cm^{-1}) 2020 (C≡N), 1640 (C=O); ^1H NMR ($CDCl_3$) δ 1.73-2.40 (m, 6H),

2.56 (d, 1H), 2.59 (H_{Y1}, H_{Y2}, $^2J_{HH}$ = 11.5 Hz, 2H), 2.83 (H_{X1}, H_{X2}, $^2J_{HH}$ = $^3J_{HH}$ = 11.5 Hz, 2H), 3.58 (H_{B1}, H_{B2}, $^2J_{HH}$ = $^3J_{HH}$ = 11.3 Hz, 2H), 3.89 (H_{A1}, H_{A2}, $^2J_{HH}$ = 11.3 Hz, 2H) (ABXY-system), 7.13 (t, 1H), 7.33 (t, 2H), 7.54 (d, 2H), 7.68 (s, 1H, NH); ^{13}C NMR (CD_3COCD_3) δ 167.5 (s), 139.7 (s), 129.3 (d), 124.5 (d), 120.8 (d), 115.3 (s), 67.1 (t), 51.7 (t), 51.3 (t), 49.6 (s), 48.4 (s), 38.9 (d, $^1J_{CH}$ = 170 Hz), 29.0 (t), 27.3 (t), 26.2 (t). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.1; H, 7.02; N, 13.5.

4-Imino-5-morpholino-3-phenyl-3-aza-tricyclo[4.3.0.0^{1,5}]nonan-2-one (16): Sublimation of bicyclic carboxamide 15 (0.62 g, 2.0 mmol) at 150–170°C/0.001 Torr and recrystallization of the sublimate from acetonitrile gave pure 16. Yield: 0.41 g (66%); mp 175–176°C (lit.[8] 176–177°C); IR- and ^{1}H NMR spectra were identical with those of an authentic sample.[8]

5-Morpholino-3-phenyl-3-aza-tricyclo[4.3.0.0^{1,5}]nonan-2,4-dione (17): A suspension of 1.56 g (5.0 mmol) of tricyclic iminoderivative 16 in 50 mL of a sodium hydroxide – citric acid buffer solution (pH = 5) was heated to 90°C for 10 h. The mixture was cooled to 20°C, the precipitate was filtered by suction and successively washed with water (25 mL) and pentane (10 mL). Recrystallization from acetonitrile – water (4:1) gave pure 17. Yield: 0.83 g (53%); mp 164°C; IR (KBr, cm^{-1}) 1710 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.89–2.20 (m, 5H), 2.44–2.68 (m), 2.53 (d) (3H), 2.74–2.90 (m, 1H), 3.05–3.27 (m, 1H), 3.37–3.95 (m, 5H), 7.19–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 174.0 (s), 173.8 (s), 131.8 (s), 129.3 (d), 128.4 (d), 126.7 (d), 67.9 (t), 67.5 (t), 58.0 (s), 50.8 (t), 49.8 (t), 47.7 (d, $^1J_{CH}$ = 176 Hz), 44.3 (s), 26.4 (t), 25.9 (t), 22.7 (t). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.1; H, 6.52; N, 9.1.

1α,5α,6α-6-Cyano-6-morpholino-N-(4-toluenesulfonyl)-bicyclo[3.1.0]hexane-1-carboxamide (19): N-Tosylcarbamoylated chloroenamine 10 (1.99 g, 5.0 mmol) was added to a solution of sodium cyanide (0.25 g, 5.0 mmol) in 50 mL of water and refluxed under stirring for 3 h. After cooling to 20°C the precipitate was isolated by suction, washed consecutively with water (50 mL), ether (50 mL) and pentane (50 mL) and recrystallized from acetonitrile. Yield: 1.03 g (53%); mp 201–203°C; IR (KBr, cm^{-1}) 1715 (C=O), 1355, 1190 (SO_2); ^{1}H NMR (C_5D_5N) δ 1.47–2.55 (m) and 2.19 (s) (9H), 2.58 (d, 1H), 2.66–2.76 (m, 4H), 3.47–3.65 (unsplit signal, 4H), 7.26, 7.30 (2H) and 8.26, 8.30 (2H) (AA'BB'-type signals), 11.8 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 167.4 (s), 145.6 (s), 136.0 (s), 130.2 (d), 129.9 (d), 112.6 (s), 66.2 (t), 52.7 (s), 51.1 (t), 47.1 (s), 42.9 (d, $^1J_{CH}$ = 170 Hz), 27.7 (t), 27.1 (t), 24.1 (t), 21.7 (q). Anal. Calcd for $C_{19}H_{23}N_3O_4S$: C, 58.59; H, 5.95; N, 10.79. Found: C, 58.3; H, 5.87; N, 10.7.

$LiAlH_4$-Reduction of 11 and 19: Bicyclic nitrile 11 (1.25 g, 5.0 mmol) or 19 (1.95 g, 5.0 mmol) was added to a suspension of lithium aluminum hydride (1.52 g, 40 mmol) in 50 mL of ether and refluxed for 20 h. Then excess $LiAlH_4$ was destroyed at 0°C by addition of 50 mL of aqueous sodium hydroxide solution (30%) and subsequent stirring for 1 h. The precipitate was removed by suction, the ethereal solution was separated and the aqueous solution was extracted with ether (5 x 100 mL). The crude products obtained by evaporation of the solvent from the combined ether extracts were purified by recrystallization from ether (12) or distillation in a Kugelrohr apparatus (20).

1α,5α,6β-6-(Aminomethyl)-6-morpholino-bicyclo[3.1.0]hex-1-yl-methanol (12): Yield: 0.87 g (77%); mp 97–98°C; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 1H), 1.54–2.19 (m, 6H), 2.13 (H_M), 3.58 (H_M), 3.85 (H_O), 3.86 (H_P) (2 AB-systems, $^2J_{MP}$ = 14.1 Hz, $^2J_{MO}$ = 12.2 Hz, 4H), 2.49 (H_Y, $^2J_{HH}$ = 10.5 Hz, 1H), 2.82 (H_X, $^2J_{HH}$ = $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 3 Hz, 1H), 2.86 (H_X, $^2J_{HH}$ = $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 3 Hz, 1H), 2.99 (H_Y, $^2J_{HH}$ = 10.5 Hz), 3.47, 3.58 (H_{B1}, H_{B2}, $^2J_{HH}$ = $^3J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 2.5 Hz, 2H), 3.78, 3.80 (H_{A1}, H_{A2}, $^2J_{HH}$ = 11.0 Hz, 2H) (2 ABXY-systems); ^{13}C NMR ($CDCl_3$) δ 68.3 (t), 67.8 (t), 57.0 (s), 53.4 (t), 50.5 (t), 46.5 (s), 42.8 (t), 38.9 (d, $^1J_{CH}$ = 161 Hz), 32.7 (t), 29.1 (t), 26.7 (t). Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.7; H, 9.67; N, 12.4.

1α,5α,6α-6-(Aminomethyl)-6-morpholino-bicyclo[3.1.0]hex-1-yl-methanol (20): Yield: 0.54 g (48%); colorless oil, bp 145-150°C/0.06 torr; ^{1}H NMR ($CDCl_3$) δ 1.46-2.18 (m, 7H), 2.76-2.90 (unsplit signal, 4H), 3.00 (s, 2H), 3.58-3.74 (unsplit signal, 4H), 3.85 (H_M), 4.10 (H_N) (AB-system, J_{MN} = 11.1 Hz); ^{13}C NMR ($CDCl_3$) δ 67.6 (t), 64.0 (t), 57.0 (s), 50.5 (t), 44.6 (s), 37.0 (t), 34.3 (d, $^1J_{CH}$ = 163 Hz), 30.5 (t), 27.0 (t), 26.3 (t). Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80; N, 12.38. Found: C, 64.0; H, 9.64; N, 11.9.

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

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