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FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS - II. TRICYCLIC AMIDINES FROM CARBAMOYLATED CHLOROENAMINES

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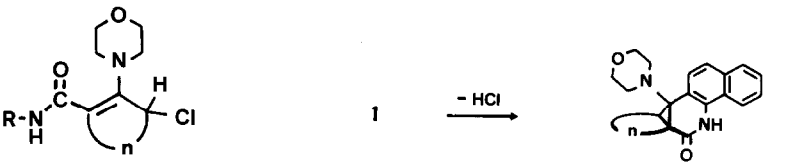
Abstract - Tricyclic amidines **9a-d** were obtained from the reaction of cyanide with carbamoylated chloroenamines **2a-d** at room temperature. At elevated temperatures the rearranged amidine **10a** was the reaction product from **2a** and cyanide. Rearranged amidines **10a-c** also were accessible by heating **9a-c** in the presence of cyanide. Chlorocyclododecene carboxamide **2e** gave a cyanobicycloalkane carboxamide **18e** in which a trans position of the carboxamide and the cyano moiety prevented a ring closure. Amidine **19** and triamino derivative **20** were generated by lithium aluminum hydride reduction of **9a**; analogously **10a** gave amidine **21**.

A tandem cyclization of carbamoylated chloroenamine **1** proved to be a very convenient access to a twofold anellated aminocyclopropane **3**.[1] This new type of an aminocyclopropane was formed by two cyclization steps which were induced by the naphthyl moiety acting as a nucleophile.

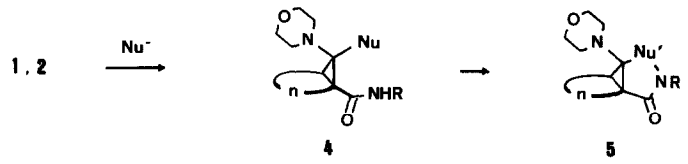


1 R = 1-$C_{10}H_7$
2 R = C_6H_4-R^1

3 n = $(CH_2)_{3,4}$

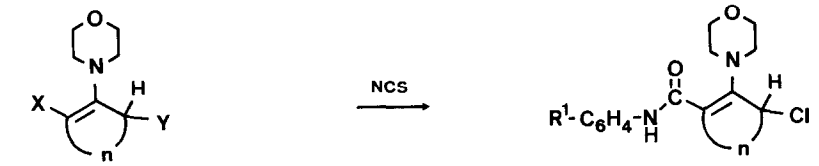
Since aminocyclopropanes generally are of interest as potential active substances[2] we have looked for further ways to twofold anellated aminocyclopropanes from functionalized chloroenamines. The overall result of a tandem cyclization also should be performed by the reaction sequence **1/2** → **4** → **5**. In this case a nucleophile possessing the structural requirement for a cyclization with a carboxamide moiety has to be used for cyclopropane formation from **1/2**. In the literature[3,4] a very easy ring closure reaction was reported to take place between a carboxamide moiety and a ß-standing cyano function generating amidines. Compounds **4** (Nu = CN) with these two structural units in a suitable distance are

expected from the reaction of 1 or 2 with cyanide. Therefore we have investigated the reaction of carbamoylated chloroenamines 2 with cyanide as a potential basis for the formation of twofold anellated aminocyclopropane derivatives.



4 5

Carbamoylated chloroenamines 2 as starting materials were obtained by chlorination of carbamoylated enamines 6/7 by N-chlorosuccinimide, as already published for 2d,e.[1] Analogously the derivatives 2a, 2b and 2c could be synthesized from NCS and a mixture of 6a/7a, 6b/7b or 6c/7c in 89%, 63% and 88% yield, respectively. ^1H NMR and especially ^{13}C NMR data clearly demonstrate the chloroallyl structure of compounds 2a-c (see exp. part and ref.[1]). As shown for 2d[1], 2a-c are to be regarded as the endproducts of a thermodynamically controlled chlorination reaction. Therefore pure substances 2 were obtained though mixtures of isomers 6 and 7 were used as starting materials (see ref.[1]).



6 X = H; Y = $CONHC_6H_4$-R^1
7 X = $CONHC_6H_4$-R^1; Y = H

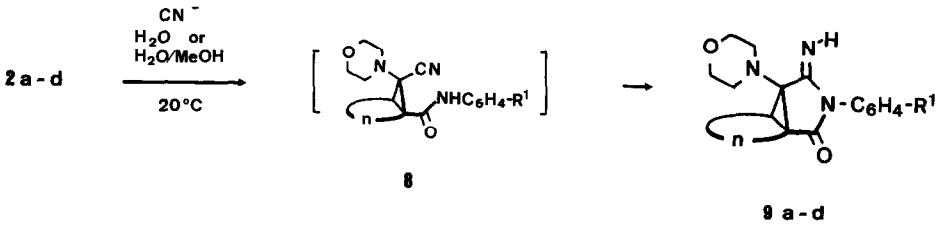
2

2, 6-13, 18	a	b	c	d	e
R^1	H	3-Cl	3-CF_3	H	H
n	$(CH_2)_3$	$(CH_2)_3$	$(CH_2)_3$	$(CH_2)_4$	$(CH_2)_9$

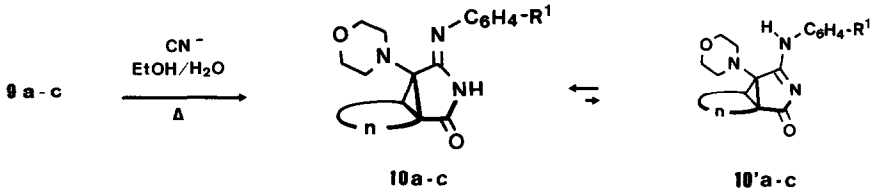
REACTION OF CARBAMOYLATED CHLOROENAMINES 2 WITH CYANIDE

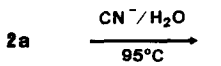
Stirring carbamoylated chloroenamines 2a-d at room temperature in a solution of sodium cyanide in water or ethanol - water gave tricyclic compounds 9a-d as colorless precipitates. Formation of 9d (68% yield) required a longer reaction time (6d) than that of 9a (20 h, 91% yield), 9b (15 h, 84% yield) or 9c (15 h, 76% yield). Cyanobicycloalkane carboxamides 8a-d representing the intermediate

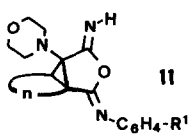
reaction products on the way to 9, could not be isolated. Thus the bicyclic derivatives 8a-d - analogously to ß-cyanopropionamides[3,4] - very rapidly cyclized in the basic reaction medium generating twofold anellated aminocyclopropane derivatives 9a-d.



Interaction of 2a with cyanide in water at 95°C gave an isomeric amidine 10a in 78 % yield. A tautomeric structure 10'a can be written additionally to 10a, the latter, however, should best describe the obtained product due to the observed spectroscopic data. 10a is generated by a thermodynamically induced isomerization of 9a, this easily could be demonstrated by heating 9a in a water - ethanol mixture in the presence of cyanide to give 10a in 61% yield. Analogously 10b (65% yield) and 10c (66% yield) were available from 9b and 9c. The transformation 9 → 10 may be understood by a ring opening - ring closure sequence induced by an attack of a nucleophile at the carbonylgroup in 9. An isomerization of this type starting from a substituted iminopyrrolidinone was reported to take place in the presence of alkoxide.[5,6] This interconversion represents an example of a Dimroth rearrangement, a well known and widespread principle in heterocyclic chemistry.[7]







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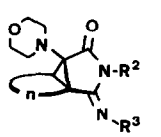


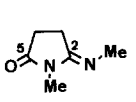
12 $R^2 = C_6H_4\text{-}R^1$, $R^3 = H$

13 $R^2 = H$, $R^3 = C_6H_4\text{-}R^1$

The structures of 9a-d and of 10a-c mainly were established on the basis of the ^{13}C NMR data (see Table I). One doublet with a characteristic coupling constant of 166 - 172 Hz and two singlets in the expected region represent the cyclopropane system. The amidino heterocyclus in 9a-d is indicated by one singlet at 173 - 176 ppm for the carbonyl moiety and one singlet at 162 - 164 ppm for the amidino group. The analogous signals for 10a-c are observed at about 175 ppm and at 153 - 154 ppm. 9a-d and 10a-c differ strongly in the phenyl-C(1)-signals giving resonance at 131.7 - 135.4 ppm for 9a-d and at 148.2 - 149.6 ppm for 10a-c. The latter values are characteristic of a phenylimino structure or an anilino moiety. The former values, however, are very similar to the corresponding signal of N-phenyl-phthalimide (132.0 ppm). Thus a 1-phenyl-2-imino-pyrrolidin-5-one constitution 9 can be deduced especially from this signal. Additionally it allows the exclusion of isomeric structures 10 or 11 for the products obtained from 2a-d and cyanide at 20°C.

A difference of about 21 ppm for the two low field signals of the thermodynamically more stable tricyclic products is consistent with structure 10 (a carbonyl group and an amidine group) but it is not in accordance with a compound 11 possessing two imino moieties. A further scrambling of the oxygen atom leading to compounds of type 12 or 13 could be excluded by using a ^{13}C labelled cyanide for the formation of the tricylic systems. In both substances which were obtained from 2a and potassium cyanide, containing 25% of isotope ^{13}C, the ^{13}C label was found in the signals at 161.9 ppm (9a) and 153.3 ppm (10a), respectively. According to these values the labelled signals do not correspond to the carbonyl group. The linkage of the labelled carbon atom to the C(6)-atom of the bicyclohexane derivative is indicated by an additional coupling of the signal of C(6) ($^{1}J_{CC}$: 9a: 62 Hz; 10a: 66 Hz).

The ^{13}C NMR data clearly establish an imino structure 10 for the rearranged products and exclude an amino structure 10'. The ^{13}C NMR spectra of the two isomeric compounds 14[8] and 15[8] can be used for this structural assignment. Thereby a very strong low field shifting of the carbonyl group and of the amidino moiety is observed for 15 with respect to 14. The values which are obtained for the carbonyl group [174.6 - 175.0 ppm (173.3 - 173.7 ppm for the carbonyl group of 9a-c)] and for the amidino moiety [153.3 - 154.2 ppm (161.9 - 163.3 ppm for the amidino moiety in 9a-c)] unequivocally indicate the imino tautomer 10 to be existing most predominantly.



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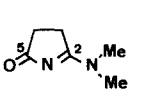

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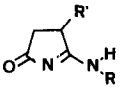

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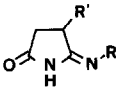


17

		14	15
^{13}C NMR [δ][8]:	C(2)	161.91	185.17
	C(5)	176.47	192.03
IR [cm^{-1}][8]:	C=O	1739	1705
	C=N	1673	1592

Table 1 ^{13}C NMR Data of Tricyclic Amidines 9, 10, 19 and 21 and Bicyclic Compounds 18 and 20

	C=O (s)	C=N (s)	Phenyl-C-atoms[a]	Morpholine OCH_2 (t)	Morpholine NCH_2 (t)	Cyclopropane (s)	Cyclopropane (s)	Cyclopropane (d)[b]	CH_2N (t)	$-(CH_2)_n-$
9a	173.7	161.9[c]	131.7 (s) 130.1, 129.2 128.2	68.1 67.5	51.1 49.3	57.9	44.4	46.0 (168)	-	26.5, 26.3 23.1
9b	173.3	162.9[c]	135.4 (s) 133.4 (s) 130.7, 129.1 128.4, 126.2	68.1 67.5	51.3 49.3	57.9	44.5	45.9 (172)	-	26.5, 26.3 23.1
9c[d]	173.5	163.3[c]	133.1 (s) 132.4 (q)[e] 131.5, 130.4 125.6, 125.1	68.2 67.6	51.4 49.4	58.0	44.7	46.0 (170)	-	26.7, 26.4 23.2
9d	175.8	163.8	131.9 (s) 129.7, 128.7 127.8	67.9 67.6	50.8 49.3	54.2	47.0	34.8 (166)	-	21.4, 20.7 20.0, 17.3
10a	174.8	153.3	148.2 (s) 129.9, 124.4 121.6	68.1 67.6	51.0 49.4	59.1	44.8	46.4 (172)	-	26.4, 26.4 22.9
10b	175.0	154.2	149.6 (s) 135.5 (s) 130.9, 124.5 121.4, 119.4	68.2 67.6	51.1 49.4	59.2	45.0	46.6 (168)	-	26.5[f], 22.9
10c[g]	174.6	154.0	148.3 (s) 131.3 (q)[e] 130.1, 124.0 120.8, 117.7	67.9 67.3	50.8 49.2	58.9	44.7	46.5 (168)	-	26.3[f], 22.7
18e	166.0	-[h]	137.1 (s) 129.2, 124.4 119.9	66.5	51.3	49.3	38.7	37.0 (162)	-	33.5, 26.3 25.7, 24.9[f] 24.3[f], 23.1 22.1
19	-	166.6	140.8 (s) 129.1, 123.6 121.2	68.3 67.6	50.4 50.0	58.0	39.2	35.6 (169)	53.3	27.0, 26.7 26.4
20	-	-	149.3 (s) 129.4, 117.6 113.6	68.1 67.7	50.5 49.3	56.9	43.1	36.6 (161)	52.9 42.7	32.4, 28.8 26.5
21	-	161.2	151.3 (s) 129.5, 122.5 122.3	68.4 67.9	50.5 47.2	56.9	42.0	35.7 (167)	50.3	27.4, 26.4 25.1

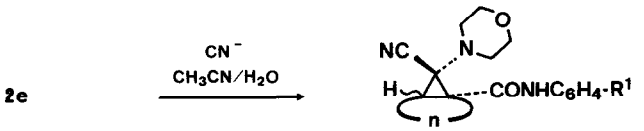
[a] Doublets unless otherwise noted. [b] ($^1J_{CH}$ [Hz]). [c] Broad signal which gives further broadening upon cooling. [d] CF_3: 123.8 (q), $^1J_{CF}$ = 268 Hz. [e] $^2J_{CF}$ = 32 Hz. [f] Signal for 2 C-atoms (double intensity). [g] CF_3: 123.9 (q), $^1J_{CF}$ = 270 Hz. [h] C N: 115.9 ppm (s).

It was shown that the equilibrium 16 ⇕ 17 is strongly influenced by a substituent R which is linked to the nitrogen atom: While an N-aryl moiety favours the imino structure 17[9,10], an alkyl group or a hydrogen atom as substituent R leads to an amino structure 16 as the preferential compound[8-11]. Thus the presence of an N-phenyl group obviously is the reason for the occurence of an iminopyrrolidinone structure 10.

The formation of the imino tautomer 10 instead of an amino derivative 10' also is shown by the IR data. Strong absorption bands are observed in the IR spectra of 9a-d and 10a-c for the carbonyl group (9a,b: 1750 cm^{-1}; 9c,d: 1745 cm^{-1}; 10a: 1755 cm^{-1}; 10b: 1740 cm^{-1}; 10c: 1750 cm^{-1}) and for the amidino moiety (9a: 1660 cm^{-1}; 9b,d: 1670 cm^{-1}; 9c: 1665 cm^{-1}; 10a: 1690 cm^{-1}; 10b,c: 1680 cm^{-1}). These absorption frequencies well correspond with those reported for 14; they strongly differ from the IR data of 15 (see also ref.[5,6,9,10]).

The twofold anellation of the cyclopropane in 9a-d and 10a-c necessarily leads to an endo-position of the morpholino group. According to this endo position ABXY-type signals[12] are expected for the morpholino moiety of 9a-d and 10a-c in the ^1H NMR spectra. Thereby the asymmetry of 9 and 10 requires two ABXY-systems for each morpholino moiety. A sufficient resolution of the two ABXY-systems was observed for 9a-d only. The morpholino signals of 10a-c mainly appeared as unsplit signals. A low field shifting to about δ = 2.5 ppm is observed for one H-atom of the $-(CH_2)_n-$ bridge of 9a-d and 10a-c. This most likely should be the consequence of the anisotropy of the carbonyl function.

Reaction of the cyclododecene derivative 2e with cyanide gave a bicyclic morpholino cyano carboxamide 18e. The missing of an amidine formation in this case indicates an anti-position of the carboxamide moiety and the cyano function. Analogously to the generation of a trans-bicyclododecane compound[1] from 1c and succinimide a trans-bicyclic system should be present in 18e, as well.

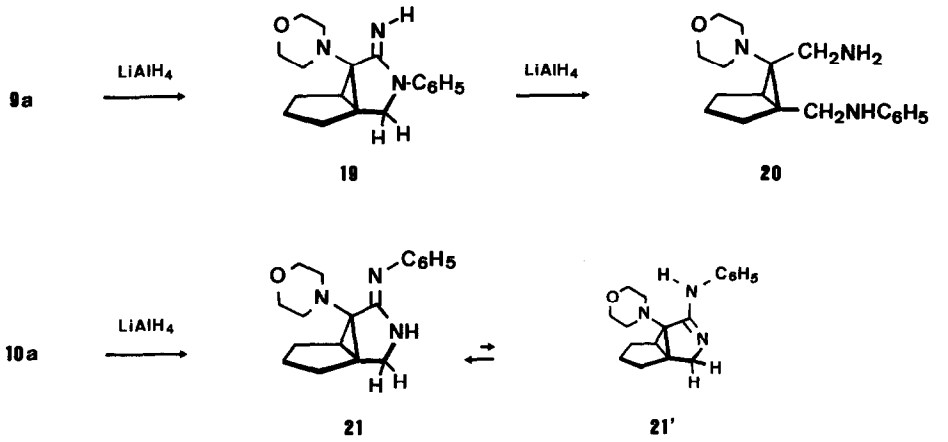


18e

REDUCTION OF THE TRICYCLIC AMIDINES 9 AND 10

The carbonyl group of the compounds 9a and 10a specifically could be reduced by lithium aluminum hydride. Thus cyclic amidine 19 (77% yield) was obtained from 9a. Analogously the isomeric amidine 21 (72% yield) was produced from 10a. Formation of the isomeric compounds 19 and 21 by these reduction reactions confirms the structures 9a and 10a of the starting materials. Upon prolonged reaction time 9a could be transferred to the bicyclic triamine 20 (62% yield).

Structures 19, 20 and 21 were established by the ^{13}C NMR data (see Table I). The phenyl-^{13}C NMR signals of 21 well correspond with those which were reported for 2-(phenylimino)pyrrolidine (δ = 149.0, 129.0, 122.0, 121.2 ppm)[13]. These values are characteristic of an imino structure, they allow the exclusion of a tautomeric structure 21'.



19 20

21 21'

Signals of the ABXY type[12] are observable for the morpholino group in the ^1H NMR spectra of 19 and 20. The morpholino signals of 21 appear as unresolved multiplets. AB systems are found for the methylene moieties generated by the reduction. Removal of the carbonyl group causes a remarkable high field shift of the cyclopropane H-atom (9a: 2.35 ppm, 19: 1.57 ppm, 20: 1.19 ppm; 10a: 2.34 ppm, 21: 1.52 ppm). Additionally the low field shifting of one hydrogen atom of the tricyclic oxo compounds 9 and 10 disappears with 19 - 21 due to the lacking carbonyl group.

These investigations show that the reaction of carbamoylated chloroenamines 2a-d with cyanide easily leads to tricyclic amidines 9, 10, 19 and 21 representing twofold anellated aminocyclopropane derivatives. Further research being in progress, however, demonstrated that the reaction conditions, reported here, are essential for a clean formation of 9 and 10.

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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 Infrared Spectrophotometer. Melting points were determined with a Mettler FP 61 apparatus. Microanalyses were performed with a Perkin-Elmer 240 Elemental Analyzer.

Carbamoylated Enamines 6/7: The carbamoylated enamines 6/7 b,c were prepared according to a general procedure (6a[14], 6a/7a[15-18], 6d/7d[19], 6e/7e[1]) by the reaction of 10 mmol (1.67 g) of N-(1-cyclohexen-1-yl)-morpholine with 10 mmol of isocyanate (3-chlorophenylisocyanate: 1.54 g; 3-[trifluoromethyl]phenylisocyanate: 1.87 g) in acetone (3 mL). Since mixtures of isomers 6/7 were formed, only yields and elemental analyses are mentioned. The ratios 6/7 were determined by ^1H NMR spectroscopy [$CDCl_3$, 6: NH- (s) and olefinic CH-signal; 7: NH-signal (s)].

N-(3-Chlorophenyl)-2-morpholino-cyclohexene-1-carboxamide **6b/7b**: Yield: 2.75 g (86%); ^{1}H NMR δ **6b**: 5.15 (CH, t), 10.0 (NH), **7b**: 12.4 (NH); ratio **6b/7b**: 55/45. Anal. Calcd for $C_{17}H_{21}ClN_2O_2$: C, 63.65; H, 6.60; N, 8.75. Found: C, 63.5; H, 6.54; N, 8.9.

2-Morpholino-N-[3-(trifluoromethyl)-phenyl]-cyclohexene-1-carboxamide **6c/7c**: Yield: 2.40 g (68%); ^{1}H NMR δ **6c**: 5.18 (CH, t), 10.3 (NH), **7c**: 12.6 (NH); ratio **6c/7c**: 50/50. Anal. Calcd for $C_{18}H_{21}F_3N_2O_2$: C, 61.01; H, 5.97; N, 7.91. Found: C, 60.8; H, 5.97; N, 7.9.

Carbamoylated Chloroenamines 2a-c - General procedure[1]: A solution of N-chlorosuccinimide (1.34 g, 10 mmol) in 20 mL of acetonitrile was added dropwise with stirring to a suspension of the carbamoylated enamine **6/7** (10 mmol; **6a/7a**[15-18]: 2.86 g, **6b/7b**: 3.21 g, **6c/7c**: 3.54 g) in 6 mL of acetonitrile at 20°C. When the addition of the NCS was finished the reaction mixture was stirred for 2 h at 0°C to give a colorless precipitate of **2a-c**. Crystallization was completed by standing at -18°C for 24 h. The precipitate was isolated by suction, washed successively with water (20 mL), ice-cold acetonitrile (20 mL), ether (30 mL) and pentane (30 mL) and dried in vacuo.

3-Chloro-2-morpholino-N-phenyl-1-cyclohexene-1-carboxamide (**2a**) : Yield: 2.85 g (89%); mp 131-132°C; IR (KBr, cm^{-1}) 1655, 1595 (C=O, C=C); ^{1}H NMR ($CDCl_3$) δ 1.77-2.25 (m, 5H), 2.97 (X-part of an ABX-system, 1H), 3,15 (4H), 3.78 (4H) (AA'XX'-type signals), 4.94 (unsplit signal, 1H), 7.05-7.67 (m, 5H), 10.98 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 165.4 (s), 148.7 (s), 138.6 (s), 129.2 (d), 125.3 (s), 123.8 (d), 119.4 (d), 67.2 (t), 54.9 (d), 51.8 (t), 32.7 (t), 26.0 (t), 16.4 (t). Anal. Calcd for $C_{17}H_{21}ClN_2O_2$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.5; H, 6.63; N, 8.7.

3-Chloro-N-(3-chlorophenyl)-2-morpholino-1-cyclohexene-1-carboxamide (**2b**): Yield: 2.24 g (63%); mp 114°C; IR (KBr, cm^{-1}) 1670, 1600 (C=O, C=C); ^{1}H NMR ($CDCl_3$) δ 1.83-2.20 (m, 5H), 2.92 (X-part of an ABX-system, 1H), 3.15 (4H), 3.79 (4H) (AA'XX'-type signals), 4.94 (unsplit signal, 1H), 7.00-7.31 (m, 3H), 7.78 (s, 1H), 11.07 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 165.3 (s), 149.3 (s), 139.6 (s), 134.8 (s), 130.0 (d), 125.0 (s), 123.7 (d), 119.4 (d), 117.1 (d), 67.2 (t), 54.7 (d), 51.9 (t), 32.9 (t), 25.8 (t), 16.3 (t). Anal. Calcd for $C_{17}H_{20}Cl_2N_2O_2$: C, 57.48; H, 5.67; N, 7.89. Found: C, 57.3; H, 5.63; N, 8.1.

3-Chloro-2-morpholino-N-[3-(trifluoromethyl)-phenyl]-1-cyclohexene-1-carboxamide (**2c**): Yield: 3.42 g (88%); mp 145°C (decomp.); IR (KBr, cm^{-1}) 1665, 1610 (C=O, C=C); ^{1}H NMR ($CDCl_3$) δ 1.78-2.26 (m, 5H), 2.97 (X-part of an ABX-system), 3.18 (4H), 3.80 (4H) (AA'XX'type signals), 4.93 (unsplit signal, 1H), 7.33-7.80 (m, 3H), 8.10 (s, 1H), 11.10 (s, NH, 1H); ^{13}C NMR ($CDCl_3$) δ 165.5 (s), 149.5 (s), 139.0 (s), 131.7 (q, $^2J_{CF}$ = 32 Hz), 129.6 (d), 126.7 (s), 124.2 (q, $^1J_{CF}$ = 272 Hz), 122.2 (d), 120.2 (d), 116.1 (d), 67.2 (t), 54.5 (d), 52.0 (t), 32.5 (t), 25.8 (t), 16.3 (t). Anal. Calcd for $C_{18}H_{20}ClF_3N_2O_2$: C, 55.60; H, 5.19; N, 7.21. Found: C, 55.4; H, 5.16; N, 7.2.

Tricyclic Amidines 9a-9d: General procedure: 5.0 mmol of carbamoylated chloroenamine **2** (**2a**: 1.60g; **2b**: 1.78 g; **2c**: 1.94 g; **2d**[1]: 1.67 g) were added to a solution of sodium cyanide (0.25 g, 5.0 mmol) in 50 mL of water (**2a,d**) or in 40 mL of a water-methanol mixture (1:1) (**2b,c**). The suspension was stirred at 20°C (**2a**: 20 h; **2b,c**: 15 h; **2d**: 6 d). Then in the case of **2b,c** the solvent was concentrated to a volume of 20 mL. The colorless precipitate was isolated by suction, washed successively with water (50 mL), ether (50 mL) and pentane (50 mL) and recrystallized from acetonitrile. For the preparation of ^{13}C labelled **9a** an 1:3 mixture of K^{13}CN (0.17 g) and KCN (0.39 g) (together 5.0 mmol) was used instead of sodium cyanide.

4-Imino-5-morpholino-3-phenyl-3-aza-tricyclo[4.3.0.0^{1,5}]nonan-2-one (**9a**): Yield: 1.42 g (91%); mp 176-177°C; IR (KBr, cm^{-1}) 1750 (C=O), 1660 (C=N); ^{1}H NMR ($CDCl_3$) δ 1.93-2.21 (m, 5H), 2.35 (d, $^3J_{HH}$ = 5.0 Hz, 1H), 2.45-2.70 (H_B and $H_{carbocycl.}$, m, 2H), 2.91 (H_G, $^3J_{HH}$ = $^2J_{HH}$ = 11.5 Hz, 1H), 3.27 (H_F, $^3J_{HH}$ = $^2J_{HH}$ = 11.5 Hz, 1H), 3.52 (H_E, $^3J_{HH}$ = $^2J_{HH}$ = 11.5 Hz, 1H), 3.60 (H_D, $^3J_{HH}$ = $^2J_{HH}$ = 11.5 Hz, 1H), 3.88 (H_A, H_B, H_C, $^2J_{HH}$ = 11.5 Hz, 3H) (2 ABXY-systems), 7.13 (d, 2H), 7.27-7.53 (m, 3H and NH). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.5; H, 6.83; N, 13.4.

3-(3-Chlorophenyl)-4-imino-5-morpholino-3-aza-tricyclo[4.3.0.0^{1,5}]nonan-2-one (**9b**): Yield: 1.45 g (84%); mp 190°C; IR (KBr, cm^{-1}) 1750 (C=O), 1670 (C=N); ^{1}H NMR ($CDCl_3$) δ 1.90-2.25 (m, 5H), 2.35 (d, $^3J_{HH}$ = 5.0 Hz, 1H), 2.45-2.67 (H_B and $H_{carbocycl.}$, m, 2H), 2.94 (H_G, $^2J_{HH}$ = 12 Hz, 1H), 3.26 (H_F, $^3J_{HH}$ = $^2J_{HH}$ = 12 Hz, 1H), 3.46-3.94 (H_A, H_B, H_C, H_D, H_E, m, 5H) (2 ABXY-systems), 7.03-7.46 (m, 4H). Anal. Calcd for $C_{18}H_{20}ClN_3O_2$: C, 62.52; H, 5.83; N, 12.15. Found: C, 62.3; H, 5.83; N, 12.2.

4-Imino-5-morpholino-3-[3-(trifluoromethyl)-phenyl]-3-aza-tricyclo[4.3.0.0^{1,5}]-nonan-2-one (9c): Yield: 1.44 g (76%); mp 169°C; IR (KBr, cm^{-1}) 1745 (C=O), 1665 (C=N); ^{1}H NMR ($CDCl_3$) δ 1.95-2.28 (m, 5H), 2.39 (d, $^3J_{HH}$ = 5.0 Hz, 1H), 2.50-2.68 (H_B and $H_{carbocycl}$, m, 2H), 2.96 (H_C, $^2J_{HH}$ = 11 Hz, 1H), 3.25 (H_F, $^3J_{HH}$ = $^2J_{HH}$ = 11 Hz, 1H), 3.47-3.94 (H_A, H_B, H_C, H_D, H_E, m, 5H) (2 ABXY-systems), 7.38-7.68 (m, 4H). Anal. Calcd for $C_{19}H_{20}F_3N_3O_2$: C, 60.15; H, 5.31; N, 11.08. Found: C, 60.0; H, 5.32; N, 11.1.

4-Imino-5-morpholino-3-phenyl-3-aza-tricyclo[4.4.0.0^{1,5}]decan-2-one (9d): Yield: 1.10 g (68%); mp 185°C; IR (KBr, cm^{-1}) 1745 (C=O), 1670 (C=N); ^{1}H NMR ($CDCl_3$) δ 1.37-2.01 (m) and 1.87 (d, $^3J_{HH}$ = 2.6 Hz) (8H), 2.40-2.71 (H_B and $H_{carbocycl.}$, m, 2H), 2.93 (H_C, $^2J_{HH}$ = 11.1 Hz, 1H), 3.22 (H_F, $^3J_{HH}$ = $^2J_{HH}$ = 11.1 Hz, 1H), 3.56 (H_E, $^3J_{HH}$ = $^2J_{HH}$ = 11.1 Hz, 1H), 3.62 (H_D, $^3J_{HH}$ = $^2J_{HH}$ = 11.1 Hz, 1H), 3.85 (H_A, H_B, H_C, $^2J_{HH}$ = 11.1 Hz, 3H) (2 ABXY-systems), 7.12 (d, 2H), 7.34-7.51 (m, 3H and NH). Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.0; H, 7.12; N, 13.1.

Tricyclic Amidine 10a from 2a and Cyanide: Carbamoylated chloroenamine 2a (1.60 g, 5.0 mmol) was added to a solution of sodium cyanide (0.25 g, 5.0 mmol) in 50 mL of water. The mixture was stirred and heated to 95°C for 24 h. Working up as described for 9a gave 10a which was recrystallized from acetonitrile.

5-Morpholino-4-phenylimino-3-aza-tricyclo[4.3.0.0^{1,5}]nonan-2-one (10a): Yield: 1.22 g (78%); mp 200-202°C; IR (KBr, cm^{-1}) 1755 (C=O), 1690 (C=N); ^{1}H NMR ($CDCl_3$) δ 1.81-2.25 (m, 5H), 2.34 (d, $^3J_{HH}$ = 5.1 Hz, 1H), 2.40-2.55 (m, 2H), 2.84 (d, 1H), 3.35-3.65 (m, 3H), 3.72-4.05 (m, 3H), 6.83 (d, 2H), 7.00 (s, NH), 7.07 (t, 1H), 7.32 (t, 2H). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.5; H, 6.83; N, 13.4.

Tricyclic Amidines 10a-c from 9a-c by Isomerization: 5.0 mmol amidine 9 (9a: 1.56 g; 9b: 1.73 g; 9c: 1.90 g) and 0.5 mmol (0.025 g) sodium cyanide were added to 40 mL of a mixture of ethanol and water (1:1). The suspension was refluxed under stirring for 3 d. The solvent was concentrated to 20 mL in vacuo, the remaining residue was isolated by suction, washed consecutively with water (2 x 10 mL) and pentane (10 mL) and recrystallized from acetonitrile.

5-Morpholino-4-phenylimino-3-aza-tricyclo[4.3.0.0^{1,5}]nonan-2-one (10a): Yield: 0.95 g (61%); mp 200°C; in the IR- and ^{1}H NMR spectra identical with 10a obtained from 2a and cyanide at 95°C.

4-(3-Chlorophenyl)imino-5-morpholino-3-aza-tricyclo[4.3.0.0^{1,5}]nonan-2-one (10b): Yield: 1.12 g (65%); mp 200°C; IR (KBr, cm^{-1}) 1740 (C=O), 1680 (C=N); ^{1}H NMR ($CDCl_3$) δ 1.85-2.18 (m, 5H), 2.34 (d, $^3J_{HH}$ = 5.0 Hz, 1H), 2.35-2.56 (m, 2H), 2.82 (d, 1H), 3.34-3.98 (m, 6H), 6.73 (d, 1H), 6.85 (s, 1H), 7.06 (d, 1H), 7.25 (t, 1H and s, NH). Anal. Calcd for $C_{18}H_{20}ClN_3O_2$: C, 62.52; H, 5.83; N, 12.15. Found: C, 62.5; H, 5.85; N, 12.3.

5-Morpholino-4-[3-(trifluoromethyl)-phenyl]-imino-3-aza-tricyclo[4.3.0.0^{1,5}]nonan-2-one (10c): Yield: 1.26 g (66%); mp 229°C; IR (KBr, cm^{-1}) 1750 (C=O), 1680 (C=N); ^{1}H NMR ($CDCl_3$) δ 1.85-2.20 (m, 5H), 2.34 (d, $^3J_{HH}$ = 5.2 Hz, 1H), 2.38-2.56 (m, 2H), 2.82 (d, 1H), 3.36-3.98 (m, 6H), 7.01 (d, 1H), 7.09 (s, 1H), 7.33 (s, NH), 7.38 (d, 1H), 7.44 (t, 1H). Anal. Calcd for $C_{19}H_{20}F_3N_3O_2$: C, 60.15; H, 5.31; N, 11.08. Found: C, 60.0; H, 5.32; N, 11.1.

12-Cyano-12-morpholino-N-phenyl-bicyclo[9.1.0]dodecane-1-carboxamide 18e: A solution of sodium cyanide (0.49 g; 10 mmol) in water (20 mL) was added to a suspension of 10 mmol of chloroenamine 2e[1] (4.05 g) in 30 mL of acetonitrile. The mixture was stirred at 50°C for 24 h. Then the mixture was stored for 2 h at 0°C. Pure 14e was isolated by suction, washed consecutively with water (20 mL) and ether (20 mL) and dried in vacuo. Yield: 2.65 g (67%); mp 190-192°C; IR (KBr, cm^{-1}) 2230 (C-N), 1710 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.20-2.15 (m, 18H), 2.62-2.86 (m, 5H), 3.60-3.84 (m, 4H), 7.12 (t, 1H), 7.34 (t, 2H), 7.52 (d, 2H), 9.34 (s, 1H, NH). Anal. Calcd for $C_{24}H_{33}N_3O_2$: C, 72.90; H, 8.41; N, 10.62. Found: C, 72.7; H, 8.47; N, 10.8.

Reaction of Amidines 9a and 10a with Lithium Aluminum Hydride - General procedure: 10 mmol (1.56 g) of bicyclic amidine 9a or 10a were added to a suspension of lithium aluminum hydride (1.52 g, 40 mmol) in ether (50 mL) at 5°C. After refluxing for 20 h (19 and 21) or 7 d (20) the mixture was cooled to 0°C; excess $LiAlH_4$ was destroyed by addition of aqueous sodium hydroxide solution (30%, 50 mL). The precipitate was removed by suction and washed consecutively with water (100 mL) and ether (100 mL). Extraction of the aqueous phase with ether (3 x 100 mL) and removal of the solvent from the combined ethereal solutions gave crude products which were purified by recrystallization from ether (19 and 21) or by distillation in a Kugelrohr apparatus (20).

2-Morpholino-4-phenyl-4-aza-tricyclo[4.3.0.0^{2,6}]nonan-3-imine (19): Colorless crystals; yield: 1.14 g (77%); IR (KBr, cm^{-1}) 1660 (C=N); ^{1}H NMR ($CDCl_3$) δ 1.57 (d, $^3J_{HH}$ = 4.5 Hz, 1H), 1.71-2.16 (m, 6H), 2.46 (H_B, $^2J_{HH}$ = 11 Hz, 1H), 2.93 (H_G, $^2J_{HH}$ = 11 Hz, 1H), 3.27 (H_F, $^3J_{HH}$ = $^2J_{HH}$ = 11 Hz, 1H), 3.48 (H_E, $^3J_{HH}$ = $^2J_{HH}$ = 11 Hz), 3.56 (H_D, $^3J_{HH}$ = $^2J_{HH}$ = 11 Hz, 1H), 3.73-3.86 (H_A, H_B, H_C, m, 3H) (2 ABXY-systems), 3.56 (H_M), 3.99 (H_N) (AB-system, $^2J_{HH}$ = 9.6 Hz, 2H), 7.06 (t, 1H), 7.33 (t, 2H), 7.42 (d, 2H). Anal. Calcd for $C_{18}H_{23}N_3O$: C, 72.70; H, 7.80; N, 14.13. Found: C, 72.6; H, 7.80; N, 14.1.

4-{1,5,6β-6-Aminomethyl-1-(phenylamino)methyl-bicyclo[3.1.0]hex-6-yl}-morpholine (20): Colorless oil; yield: 0.93 g (62%); bp 150-155°C/0.005 Torr; ^{1}H NMR ($CDCl_3$) δ 1.19 (d, $^3J_{HH}$ = 4.7 Hz, 1H), 1.55-2.09 (m, 6H), 2.48 (H_O), 3.41 (H_P) (AB-system, $^2J_{HH}$ = 14.2 Hz, 2H), 3.07 (H_N), 3.44 (H_M) (AB-system, $^2J_{HH}$ = 12.1 Hz, 2H), 2.54 (H_B, $^2J_{HH}$ = 11 Hz, 1H), 2.81 (H_G, $^2J_{HH}$ = 11 Hz, 1H), 2.94 (H_F, $^3J_{HH}$ = $^2J_{HH}$ = 11 Hz, 1H), 3.12 (H_E, $^3J_{HH}$ = $^2J_{HH}$ = 11 Hz, 1H), 3.49 (H_D, $^3J_{HH}$ = $^2J_{HH}$ = 11 Hz, 1H), 3.56 (H_C, $^3J_{HH}$ = $^2J_{HH}$ = 11 Hz, 1H), 3.76-3.85 (H_A, H_B, m, 2H) (2 ABXY-systems), 6.64 (d, 2H), 6.70 (t, 1H), 7.17 (t, 2H). Anal. Calcd for $C_{18}H_{27}N_3O$: C, 71.72; H, 9.03; N, 13.94. Found: C, 72.1; H, 9.25; H, 13.7.

2-Morpholino-4-aza-tricyclo[4.3.0.0^{2,6}]nonan-3-(N-phenyl)-imine (21): Colorless crystals; yield: 1.07 g (72%); IR (KBr, cm^{-1}) 1635 (C=N); ^{1}H NMR ($CDCl_3$) δ 1.52 (m_C, 1H), 1.70-2.18 (m, 6H), 2.47 (m_C, 1H), 2.83 (m_C, 1H), 3.45-4.14 (m, 6H), 3.31 (H_N), 3.51 (H_M) (AB-system, $^2J_{HH}$ = 10.4 Hz, 2H), 6.89 (d, 2H), 6.97 (t, 1H), 7.26 (t, 2H). Anal. Calcd for $C_{18}H_{23}N_3O$: C, 72.70; H, 7.80; N, 14.13. Found: C, 72.5; H, 7.80; N, 14.2.

REFERENCES

1. P. Altmeier, E. Vilsmaier and G. Wolmershäuser, Tetrahedron, in press.
2. E. Vilsmaier in The Chemistry of the Cyclopropyl Group; Z. Rappoport, Ed.; Wiley, Chichester 1987, p. 1341.
3. A. Foucaud, Bull. Soc. Chim. Fr., 1964, 123.
4. A. Foucaud and H. Person, Bull. Soc. Chim. Fr., 1965, 995.
5. A. Foucaud and G. Barret, Tetrahedron Lett., 1968, 1075.
6. G. Barret and A. Foucaud, Bull. Soc. Chim. Fr., 1968, 4594.
7. G. L'abbe, J. Heterocycl. Chem., 21, 627 (1984).
8. L. I. Spiessens and M. J. O. Anteunis, Bull. Soc. Chim. Belg., 93, 191 (1984).
9. A. Foucaud and P. Plusquellec, Bull. Soc. Chim. Fr., 1968, 3813.
10. P. Plusquellec and A. Foucaud, C. R. Acad. Sci., Ser. C., 262, 1276 (1966).
11. P. Gluzinski, J. Rajewski, J. Lange, G. D. Andreetti and G. Bocelli, Acta Chrystallogr. Sect. C, C40, 108 (1984).
12. E. Vilsmaier and W. Tröger, Angew. Chem., 91, 860 (1979), Angew. Chem. Int. Ed. Engl., 18, 798 (1979); E. Vilsmaier, W. Tröger and G. Haag, Chem. Ber., 114, 67 (1981); E. Vilsmaier, Bull. Soc. Chim. Belg., 94, 521 (1985) and references cited therein.
13. L. M. Jackman and T. Jen, J. Am. Chem. Soc., 97, 2811 (1975).
14. G. A. Berchthold, J. Org. Chem., 26, 3043 (1961).
15. R. Fusco, G. Bianchetti and S. Rossi, Gazz. Chim. Ital., 91, 825 (1961).
16. S. Hünig; K. Hübner and E. Benzing, Chem. Ber., 95, 926 (1962).
17. W. Ried and W. Käppeler, Liebigs Ann. Chem., 673, 132 (1964).
18. F. P. Colonna, G. Pitacco and E. Valentin, Tetrahedron, 27, 5481 (1971).
19. S. D. Sharma, P. K. Gupta and A. L. Gauba, Indian J. Chem., Sect. B, 16, 424 (1978); Chem. Abstr., 90, 38767 (1979).

Dedicated to Prof. Dr. R. Carrié on the occasion of his 60th birthday.