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Dealkylation of *N*(3)-methyl-6-amino-3-aza-bicyclo[3.1.0]hexane derivatives

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Abstract

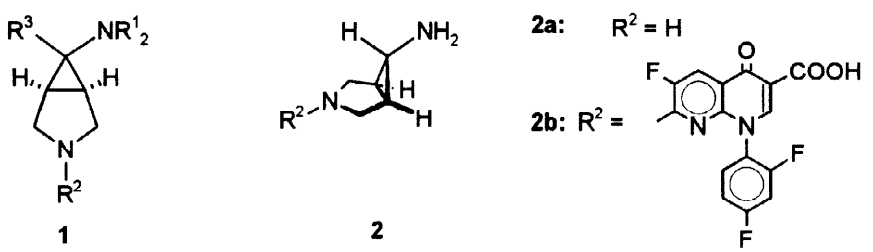
N-Methyl-6-amino-3-azabicyclohexane derivatives **8**, **9** and **25** can be demethylated by reacting the corresponding *N*-oxides with acetic anhydride in a Polonovsky reaction and subsequent cleavage of the resulting acetamides by hydrochloric acid. Other demethylating reagents such as cyanogen bromide, vinyl chloroformate or trichloroethyl chloroformate caused an opening of the pyrrolidine unit of the investigated model compounds **8** - **10**.

Keywords: Aza compounds; Bicyclic heterocyclic compounds; Cleavage reactions; Dealkylation;

1. Introduction

A 6-aminosubstituted 3-azabicyclo[3.1.0]hexane building block **1** is found as subunit in some biological active compounds: Bicyclic derivative **2a** represents the diamine of the highly potent Gyrase inhibitor trovafloxacin **2b** [1-6] (Figure 1).

Figure 1



Diastereomeric piperidinocarboxamides **3b/4b** and **3c/4c** were applied as constrained models for mimicking defined conformations of the 4-aminopiperidine moiety in the neuroleptic agent pipamperone **5b** [7] and the analgetic agent piritramide **5c** [8], respectively (Figure 2).

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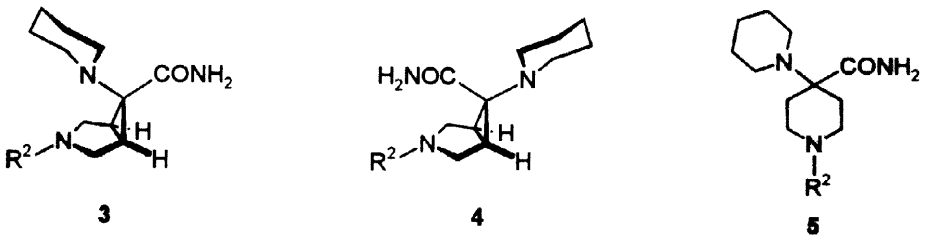
Figure 2



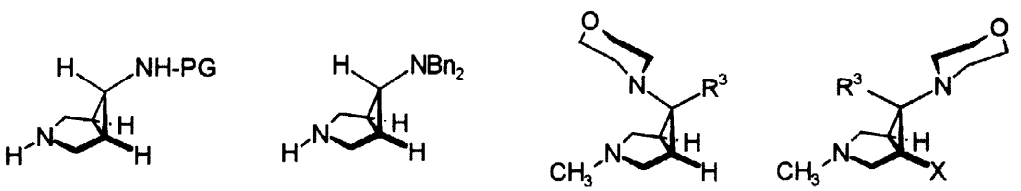
3 **4** **5**

3a, 4a: R^2 = H **3b - 5b:** R^2 = (p)F-C_6H_4-CH_2-CH_2-CH_2-CO

3c - 5c: R^2 = $(C_6H_5)_2C(CN)$-CH_2-CH_2

All syntheses of these compounds are based on N(3)-protected species which were deblocked to give N(3)-H derivatives **3a** [7], **4a** [7,8] and **6** [1-6,9,10] or **7** [11] and its 6β-diastereomer [11,12] (Figure 2 and 3) as building blocks for the construction of the target molecules **2b**, **3b,c** and **4b,c.** Protecting groups such as a benzyl-[1-9], a trityl-[3] or an alkyloxycarbonyl group (Cbz [1,2,8,9], EtO_2C [7]) were used thus far for the N(3)-atom. The general applicability of a C_1-C_6-alkyl or C_3-C_6-cycloalkyl moiety as protecting group for N(3) in compound **6** was proposed in this context in a patent [3,4]; it was stated that these groups "may be removed by reaction with α-chloroethyl chloroformate" according to references [13] and [14].

Figure 3



6 **7** **8** **9:** X = H

10: X = Cl, R^3 = CN

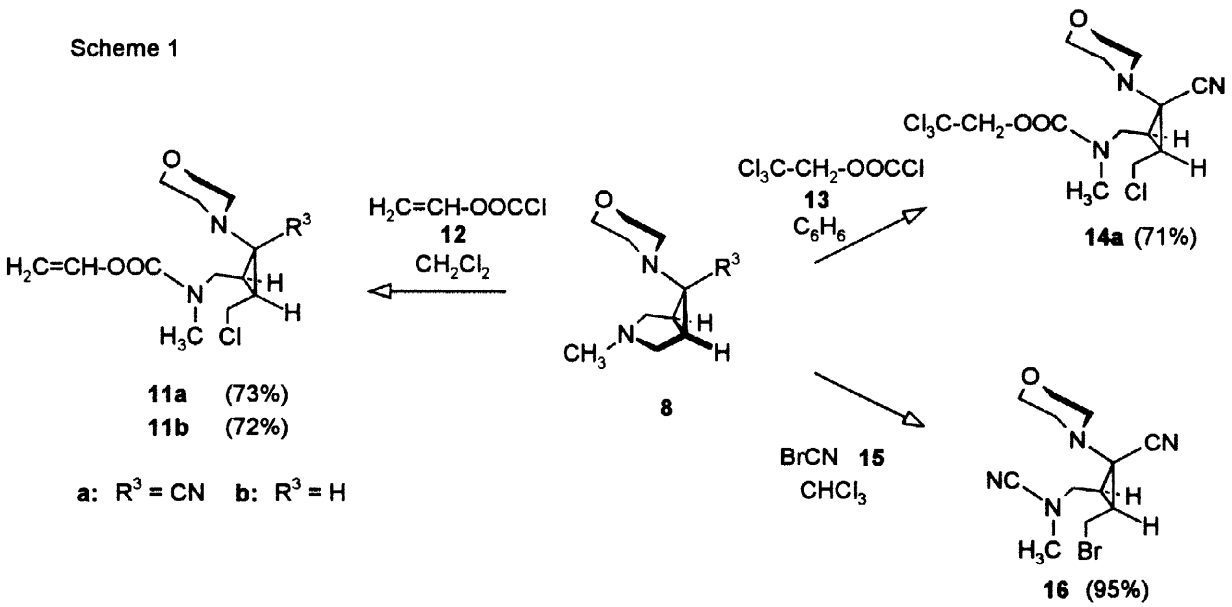
An N(3)-demethylation would be especially of interest for providing 6-alkyl- or 6-aryl substituted species of type **1** (R^2 = H, R^3 = alkyl, aryl)[1] for a further coupling with a pharmacophoric group. We examined, therefore, the behavior of *N*(3)-methyl-6-aminoazabicyclohexane derivatives **1** (R^2 = CH_3) against usually applied N-demethylating reagents. Morpholino compounds **8**, **9** and **10** were used first as model compounds in these investigations (Figure 3).

[1] Both diastereomers of 6-alkyl- or 6-aryl substituted species of type **1** (NR^1_2 = morpholine, R^3 = alkyl, aryl) were only obtained with high selectivity if R^2 corresponds to a methyl moiety; a benzyl moiety (R^2 = Bn) gave only one single diastereomer [15]; an alkoxycarbonyl protecting group (R^2 = COOEt) could not be applied in this approach (reaction of an organometallic compound with an N(1)-protected chloroenamine or an N(3)-protected bicyclic N,O-acetal [16]).

2. Dealkylation by opening of the pyrrolidine ring

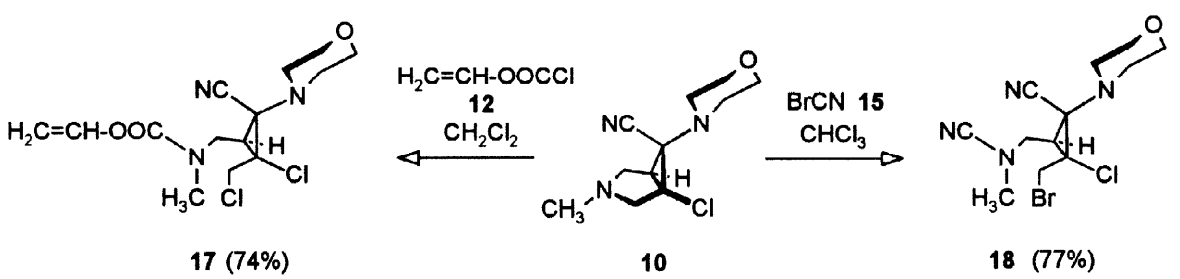
Reaction of bicyclic nitriles **8a** and **8b** with vinyl chloroformate (**12**) under usual conditions [13,14,17,18] caused an opening of the pyrrolidine unit to give compounds **11a** and **11b** in good yields. Ring opened derivatives **14** and **16** were obtained instead of expected demethylation products also exclusively from **8a** and trichloroethyl chloroformate (**13**) or in a von Braun reaction [19] with cyanogen bromide (**15**) (Scheme 1).

Scheme 1



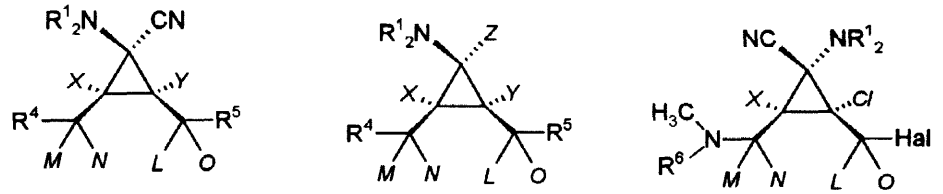
An analogous behavior was found for endo-nitrile **10** upon the interaction with chloroformate **12** or cyanogen bromide (**15**) leading to pentasubstituted cyclopropane compounds **17** and **18**, respectively (Scheme 2).

Scheme 2



The cleavage of the pyrrolidine unit in these reactions can be deduced from the ^1H and ^{13}C NMR data indicating still the presence of an *N*-methyl moiety in the reaction products. The ^1H NMR spectra of urethane derivatives **11a**, **14** and **17** were run at higher temperatures (95°-103°C) in order to exclude the interfering influence of carbaminate dynamics; **11b** decomposed already at this temperature. The ^1H NMR signals of the R^4CH_2-cyclopropane-CH_2 R^5 unit were designated as LMNOXY-, LMNOXYZ- or MNX-/LO systems as depicted in figure 4. The determination of MNX- and LOY- subunits is based on decoupling experiments. The nature of R^4 and R^5 in the methylene subunits R^4-CMN and R^5-CLO can be assigned without any doubts for compounds **17** and **18**. An unequivocal assignment of the CH_2-^1H NMR signals to either the amino or the halogeno group in the cases of **11a,b**, **14** and **16** would require further investigations. The spectra were simulated by the Calm program [20]. Relatively strong coupling of both hydrogen atoms of each methylene unit with the adjacent cyclopropane H-atom (J_{MX}/J_{NX} and J_{LY}/J_{OY}) are in accordance only with products from an opening of the pyrrolidine ring (J_{MX}/J_{NX} [Hz]: **11a**: 7.3/7.3; **11b**: 7.1/7.1; **14**: 7.0/7.2; **16**: 7.9/7.2; **17**: 10.2/5.8; **18**: 11.1/5.6; J_{LY}/J_{OY} [Hz]: **11a**: 6.6/6.6; **11b**: 5.2/8.4; **14**: 5.7/7.8; **16**: 6.1/5.1).

Figure 4



11a, 14, 16

11b

17 R^6 = $COOCH=CH_2$

18 R^6 = CN

11a,b, 14, 16: R^4 / R^5 H_3C-N-$COOCH=CH_2$; H_3C-N-$COOCH_2CCl_3$; H_3C-N-CN; Cl or Br

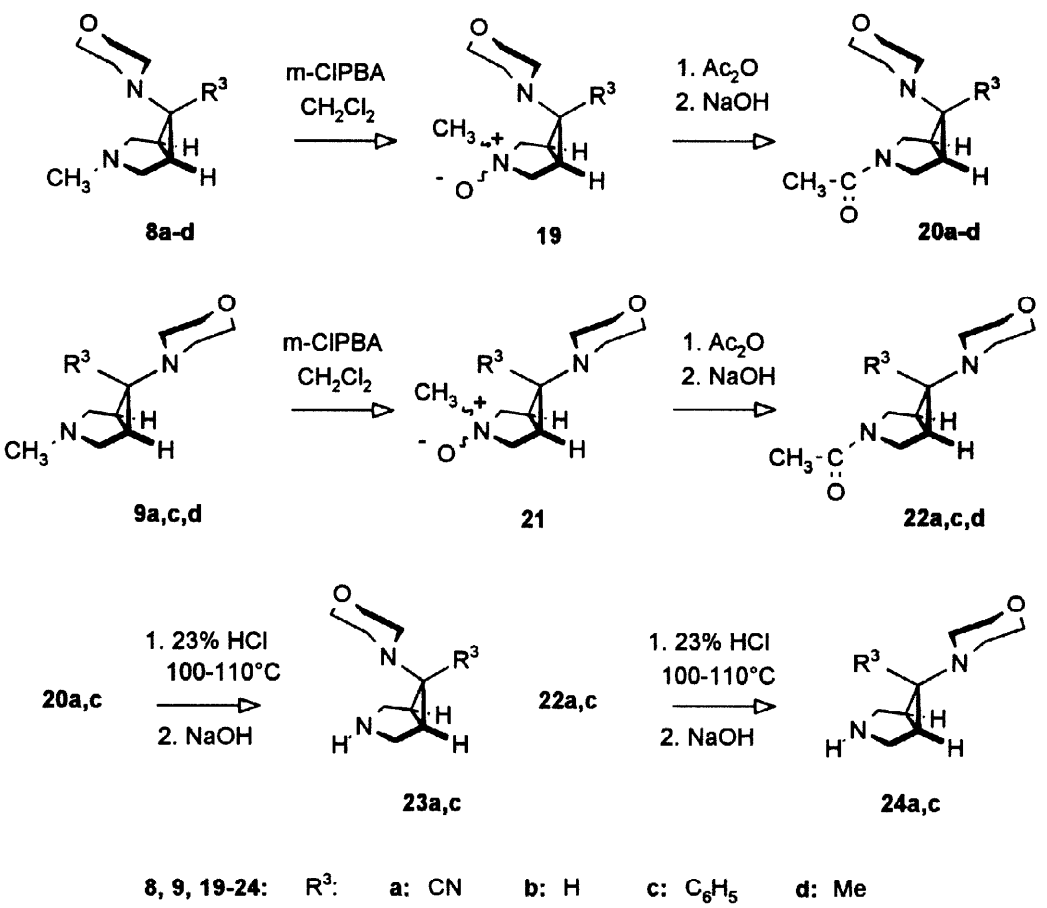
NR^1_2 = morpholine

3. Dealkylation by removal of the *N*(3)-methyl group

A demethylation of 3-methyl-3-azabicyclo[3.1.0]hexane derivatives could be realized by applying a Polonovsky [21] reaction. Oxidation of diamines **8a-d** and **9a,c,d** with 3-chloroperbenzoic acid and treatment of the resulting *N*-oxides with acetic anhydride caused a clear cut demethylation leading to *N*(3)-acetylated diamines **20a-d** and **22a,c,d** in good yields (Scheme 3). Water was excluded in the acetylation step of the Polonovsky reaction by using

vacuo-dried 3-chloroperbenzoic acid [22]. *N*-Oxide formation at N(3)-atom of the 6-morpholino-3-azabicyclo[3.1.0]hexane derivatives was proved with diamines **8a** and **9a** as starting materials. The *N*-oxides **19a** and **21a** were obtained as adducts with 3-chlorobenzoic acid. Strong low field shifting of the ^{13}C NMR signals of the N(3)-CH_3 (**19a**: $\Delta\delta$ = 13.0 ppm, **21a**: $\Delta\delta$ = 15.7 ppm) and the N(3)-CH_2-signal (**19a**: $\Delta\delta$ = 14.4 ppm, **21a**: $\Delta\delta$ = 16.6 ppm) and almost no influencing of the morpholine signals ($\Delta\delta$ < 0.6 ppm) indicate the location of the *N*-oxide oxygen at N(3)-atom[2,3]. The configuration at N(3) can not be assigned unequivocally by these data; an outside attack of the oxygen, however, seems to be most likely. ^1H and ^{13}C NMR spectra indicate the presence of only one single diastereomer. The acetyl group in the resulting morpholino-3-azabicyclo[3.1.0]hexane derivatives **20** and **22** can be cleaved by treatment with aqueous hydrochloric acid as shown exemplarily by the transformation of **20a,c** to **23a,c** and of **22a,c** to **24a,c**. A cyano moiety as in **20a** or **22a** remained unchanged, thereby (Scheme 3).

Scheme 3



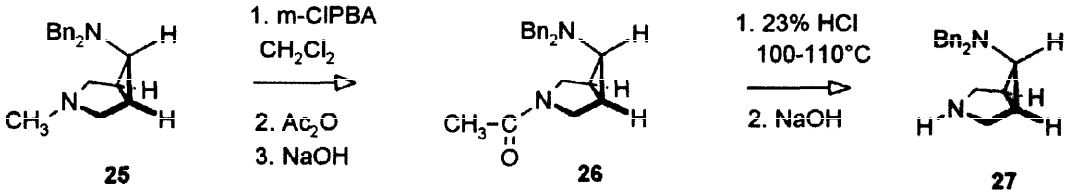
[2] For ^{13}C NMR signals of starting materials **8a** and **9a** see ref. [23] and [24], respectively.

[3] A strong downfield shifting was reported for two ^{13}C NMR signals of *N*-methylpyrrolidine upon oxidation to N-oxide: N-CH_3 : $\Delta\delta$ = 13.9 ppm; NCH_2: $\Delta\delta$ = 13.1 ppm [25].

The presented demethylation of easily available 3-methyl-6-phenyl-3-azabicyclo[3.1.0]hexyl-morpholine diastereomers **8c** and **9c** indeed leads to building blocks **23c** and **24c** which may be of interest for construction of active compounds.

This simple way for demethylation of morpholino derivatives **8** and **9** prompted us to test its applicability to dibenzylamino derivative **25**, too. This would provide compound **27** which was used [12] for the synthesis of the 6β-diastereomer of trovafloxacin **2b**.

Scheme 4

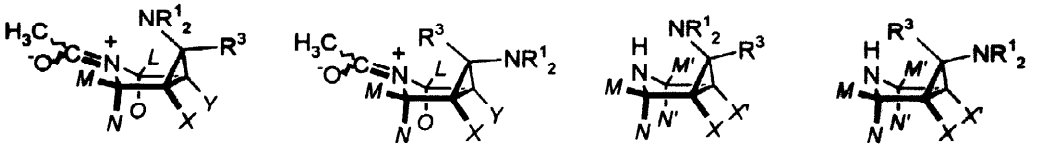


Oxidation of **25** with 3-chloroperbenzoic acid and treatment of the resulting *N*-oxide with acetic anhydride indeed caused a highly selective reaction at N(3) leading to acetylated compound **26** which was deacetylated without further purification by acidic hydrolysis to give demethylated compound **27** (66% yield) (Scheme 4). Since starting material **25** is easily accessible in a three step procedure from 4-dibenzylamino-1-methyl-1,2,5,6-tetrahydropyridine in 74% overall yield [26], this Polonovsky type demethylation reaction complements an easy way to compound **27**.

The structures of the demethylated compounds **20**, **22-24**, **26** and **27** were deduced from the ^{13}C and ^{1}H NMR data. Hindrance of rotation of the amide function in **20a-d**, **22a,c,d** and **26** led generally to the observation of six different ^{1}H NMR signals for the pyrrolidine unit which were simulated with the Calm program [20] and designated as LMNOXY system as depicted in Figure 5 (**26**: LMNOXYZ system; R^3 corresponds to Z). A plane of symmetry is present in the demethylated compounds **23a,c**, **24a,c** and **27**; the corresponding ^{1}H NMR signals are to be described by an MM'NN'XX' system and simulated by the Calm program [21], too (Figure 5).

Figure 5

NR^1_2 = morpholine, dibenzylamine



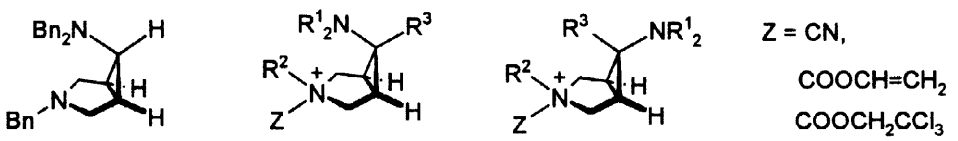
20/26 22 23/27 24

The chemical shifts and the coupling constants of the pyrrolidine subunit of the acetylated and the demethylated compounds **20a-d**, **22c,d**, **23c**, **24a,c** and **26** are given in the Experimental Part. ^1H and ^{13}C NMR spectra of compounds **23a** and **27** are identical with respect to the published data [12, 27].

4. The regioselection in the dealkylation of 3-methyl-3-azabicyclo[3.1.0]hexane derivatives

The missing demethylation for **8** - **10** contratsts strongly with the selective N(3)-debenzylation of tribenzyl derivative **28** by vinyl chloroformate (**12**) [12].[4] The cyanation or acylation of N(3)-nitrogen atom in **1** should take place from the exo-side to lead to azonia intermediates **29** or **30** (Figure 6). An inside located benzyl group (R^2 = Bn) may be split off easily as cation leading to a debenzylated compound. Analogous removal of a methyl moiety from N(3) in **29** or **30** (R^2 = Me), however, would require an S_N2-reaction. The strongly hindered attack of the halide anion to the C-atom of the methyl group in the inside hemisphere of **29** and **30** is circumvented in this case by the observed ring opening reaction.

Figure 6



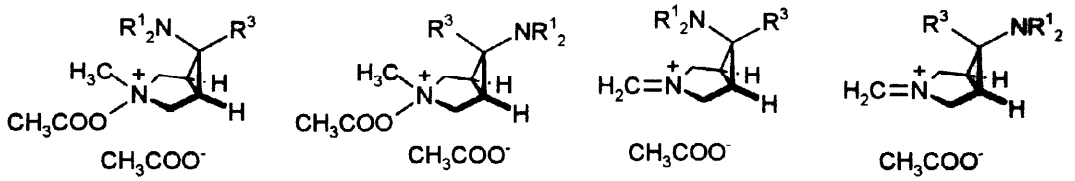
28 29 30

Z = CN, $COOCH{=}CH_2$, $COOCH_2CCl_3$

[4] Similar differences of regioselectivity of dealkylation were found for the reaction of cyanogen bromide with *N*-butylpyrrolidine [28] and an *N*-benzylpyrrolidine derivative [29].

Eliminations generally are less influenced by steric restrictions than S_N2-reactions. Thus, the stronger C-H-acidity of the methyl group with respect to the methylene moiety in acetoxy compounds **31** and **32** becomes product determining in the elimination of acetic acid leading to intermediates **33** and **34** (Figure 7). The way from the latter to acetamides **20** and **22** should pass the steps by which the mechanism of the Polonovsky reaction is usually described [21].

Figure 7



31 **32** **33** **34**

R^1_2N = morpholine, dibenzylamine

5. Experimental

^1H NMR and ^{13}C NMR spectra were obtained with a Bruker AMX 400 spectrometer (TMS as internal standard). Microanalyses were performed using a Perkin-Elmer 2400 Elemental Analyzer. Dealkylation reactions were run with exclusion of moisture (nitrogen atmosphere) in water free solvents.

Reaction of 3-methyl-6-morpholino-3-azabicyclo[3.1.0]hexane derivatives **8a,b** *and* **10** *with vinyl chloroformate (***12***) - general procedure*: Vinyl chloroformate (**12**) was added to a solution of the bicyclic *N*-methyl compound (4.0 mmol; **8a** [23]: 0.83 g; **8b** [30]: 0.73 g; **10** [23]: 0.975 g) in 25 mL of dichloromethane (**8a** and **10**) or ether (**8b**). The mixture was refluxed for 24 h and then cooled to 0°C and poured into ice-cooled water (50 mL). Separation of the organic phase and extraction of the aqueous layer with dichloromethane (3 x 25 mL) gave crude urethane which was crystallized from ether (**11a**, **17**) or pentane (**11b**).

Vinyl N-[(1α,2α,3α-3-chloromethyl-2-cyano-2-morpholino-cyclopropyl)-methyl]-N-methyl-carbamate (**11a**). Addition of 0.54 mL (5.4 mmol) of vinyl chloroformate (**12**); yield 0.92 g (73%), mp 86°C; ^1H NMR ($CD_3C_6D_5$, 90°C): δ 1.26 (H_Y, 1H), 1.38 (H_X, 1H), 3.13 (H_L, 2H), 3.24 (H_{M1}, 1H), 3.30 (H_N, 1H) (L_2MNXY system, J_{LY} = 6.6 Hz, J_{M1N} = 11.6 Hz, J_{M1X} = J_{NX} = 7.3 Hz, J_{XY} = 9.9 Hz), 2.50 (s, 3H), 2.37 (m_c, 4H), 3.39 (m_c, 4H), 4.22 (H_{M2}, 1H), 4.65 (H_B, 1H), 7.22 (H_A, 1H) (ABM system, J_{AB} = 14.3 Hz, J_{AM2} = 6.4 Hz, J_{BM2} = 1.0 Hz); ^{13}C NMR ($CDCl_3$): δ 153.5 (s), 142.8 (d), 117.4 (s), 96.1 (t), 66.5 (t), 51.9 (t), 42.1 (t), 42.0 (s), 38.4 (t, $^1J_{CH}$ = 153 Hz), 34.0 (q), 30.9 (d, $^1J_{CH}$ = 169 Hz), 27.8 (d, $^1J_{CH}$ = 165 Hz). Anal. Calcd. for $C_{14}H_{20}ClN_3O_3$: C, 53.59; H, 6.42; N, 13.39. Found: C, 53.5; H, 6.3; N, 13.4.

Vinyl N-[(1α,2α,3α-2-chloromethyl-3-morpholino-cyclopropyl)-methyl]-N-methylcarbamate (**11b**). Addition of 1.2 mL (12 mmol) of vinyl chloroformate (**12**); yield 0.84 g (72%), mp 73°C; ^{1}H NMR (CD_3CN, 25°C): δ 1.30 (H_Y, 1H), 1.36 (H_X, 1H), 1.97 (H_Z, 1H), 3.50 (H_L, 1H), 3.68 (H_O, 1H), 3.75 (H_{M1}, 1H), 3.91 (H_N, broadened, 1H) (LMNOXYZ system, J_{LO} = 14.4 Hz, J_{LY} = 5.2 Hz, J_{M1N} = 11.1 Hz, J_{M1X} = 7.1 Hz, J_{NX} = 7.1 Hz, J_{OY} = 8.4 Hz, J_{XY} = 9.6 Hz, J_{XZ} = J_{XZ} = 7.1), 2.92 and 2.96 (s, 3H), 2.42 (m_c, 2H), 2.51 (m_c, 2H), 3.59 (m_c, 4H), 4.43 (H_{M2}, 1H), 4.76 (H_B, 1H), 7.15 (H_A, 1H) (ABM system, J_{AB} = 13.8 Hz, J_{AM2} = 5.6 Hz, J_{BM2} = 1.0 Hz); ^{13}C NMR ($CDCl_3$): δ 153.4 (s), 142.4 (d), 95.0 (t), 66.8 (t), 54.4 (t), 45.7 (d, $^1J_{CH}$ = 173 Hz), 42.9 (t), 41.2 (t, $^1J_{CH}$ = 142 Hz), 33.7 (q), 22.6 (d, $^1J_{CH}$ = 167 Hz), 19.5 (d, $^1J_{CH}$ = 159 Hz). Anal. Calcd. for $C_{13}H_{21}ClN_2O_3$: C, 54.07; H, 7.33; N, 9.70. Found: C, 54.2; H, 7.4; N, 9.4.

Vinyl N-[(1α,2β,3β-2-chloro-2-chloromethyl-3-cyano-3-morpholino-cyclopropyl)-methyl]-N-methylcarbamate (**17**). Addition of 0.98 mL (9.8 mmol) of vinyl chloroformate (**12**); yield 1.03 g (74%), mp 142°C; ^{1}H NMR ($CD_3C_6D_5$, 102°C): δ 1.65 (H_X, 1H), 3.11 (H_{M1}, 1H), 3.31 (H_N, 1H, broad signal, in coalescence) (MNX system, J_{M1N} = 11.1 Hz, J_{M1X} = 10.2 Hz, J_{NX} = 5.8 Hz), 2.76 (s, 3H), 2.49 (m_c, 4H), 3.41 (m_c, 4H), 3.06 (H_L, 1H), 3.77 (H_O, 1H) (AB system, J_{LO} = 15.3 Hz), 4.25 (H_{M2}, 1H), 4.73 (H_B, 1H), 7.22 (H_A, 1H) (ABM system, J_{AB} = 14.0 Hz, J_{AM2} = 6.4 Hz, J_{BM2} = 1.6 Hz); ^{13}C NMR ($C_6D_5NO_2$, 100°C): δ 154.3 (s), 143.4 (d), 113.5 (s), 96.4 (t), 67.0 (t), 56.0 (s), 51.4 (t), 51.2 (t), 51.0 (s), 41.5 (d), 40.5 (t), 36.0 (q). Anal. Calcd. for $C_{14}H_{19}Cl_2N_3O_3$: C, 48.29; H, 5.50; N, 12.07. Found: C, 48.1; H, 5.6; N, 11.7.

2,2,2-Trichloroethyl N-[(1α,2α,3α-3-chloromethyl-2-cyano-2-morpholino-cyclopropyl)-methyl]-N-methylcarbamate (**14**) *from the reaction of 3-methyl-6-morpholino-3-azabicyclo[3.1.0]hexane derivative* **8a** *with 2,2,2-trichloroethyl chloroformate* (**13**): Trichloroethyl chloroformate **13** (1.5 mL, 10.9 mmol) was added to a solution of the bicyclic N-methyl compound **8a** [23] (1.00 g, 4.8 mmol) in benzene (25 mL). The mixture was refluxed for 48 h. Then ether (25 mL) was added and the solution was extracted with aqueous hydrochloric acid (3 M, 3 x 20 mL). Addition of aqueous sodium hydroxide solution (5 M) to the combined acidic solutions until pH 12 is reached and subsequent extraction with dichloromethane (3 x 25 mL) gave crude carbamate **14** which was recrystallized from ether. Yield 1.43 g (71%), mp 80°C; ^{1}H NMR ($CD_3C_6D_5$, 102°C): δ 1.36 (H_Y, 1H), 1.42 (H_X, 1H), 3.16 (H_L, 1H), 3.27 (H_O, 1H), 3.30 (H_M, 1H), 3.36 (H_N, 1H) (LMNOXY system, J_{LO} = 14.9 Hz, J_{LY} = 5.7 Hz, J_{MN} = 11.9 Hz, J_{MX} = 7.0 Hz, J_{NX} = 7.2 Hz, J_{OY} = 7.8 Hz, J_{XY} = 10.0 Hz), 2.61 (s, 3H), 2.36 (m_c, 2H), 2.42 (m_c, 2H), 3.40 (m_c, 4H), 4.51 (H_B, 1H), 4.55 (H_A, 1H), (AB system, J_{AB} = 12.2 Hz); ^{13}C NMR ($C_6D_5NO_2$, 100°C): δ 158.8 (s), 116.9 (s), 95.7 (s), 75.0 (t), 65.9 (t), 51.7 (t), 42.0 (s), 42.0 (t), 38.5 (t, $^1J_{CH}$ = 154 Hz), 33.5 (q), 31.0 (d, $^1J_{CH}$ = 167 Hz), 27.9 (d, $^1J_{CH}$ = 165 Hz). Anal. Calcd. for $C_{14}H_{19}Cl_4N_3O_3$: C, 40.12; H, 4.57; N, 10.03. Found: C, 40.0; H, 4.4; N, 9.9.

Reaction of 3-methyl-6-morpholino-3-azabicyclo[3.1.0]hexane derivatives **8a** *and* **10** *with cyanogen bromide* (**15**) *- general procedure*: Cyanogen bromide (**15**) was added to a solution of the bicyclic *N*-methyl compound (4.0 mmol; **8a** [23]: 0.83 g; **10** [23]: 0.975 g) in chloroform (30 mL) (caution, hood!). The mixture was refluxed for 3 h. Removal of the solvent led to a brown residue which was recrystallized from ether to give colorless crystals.

N-[(1α,2α,3α-3-Bromomethyl-2-cyano-2-morpholino-cyclopropyl)-methyl]-N-methylcyanamide (**16**). Addition of 0.62 g (5.8 mmol) of cyanogen bromide (**15**); yield 1.19 g (95%), mp 92°C; ^{1}H NMR (CD_3CN): δ 1.98 (H_Y, 1H), 2.18 (H_X, 1H), 3.26 (H_L, 1H), 3.31 (H_O, 1H), 3.55 (H_M, 1H), 3.75 (H_N, 1H) (LMNOXY system, J_{LO} = 13.3 Hz, J_{LY} = 6.1 Hz, J_{MN} = 10.8 Hz, J_{MX} = 7.9 Hz, J_{NX} = 7.2 Hz, J_{OY} = 5.1 Hz, J_{XY} = 10.5 Hz), 2.12 (s, 3H), 2.60 (2H), 2.67 (2H), 3.56 (2H), 3.75 (2H) (broad, unsplit signals, morpholine); ^{13}C NMR ($CDCl_3$): δ 117.3 (s), 116.6 (s), 66.3 (t), 51.8 (t), 46.2 (t), 42.9 (s), 39.1 (q), 30.9 (d, $^1J_{CH}$ = 168 Hz), 27.7 (d, $^1J_{CH}$ = 162 Hz), 24.2 (t, $^1J_{CH}$ = 154 Hz). Anal. Calcd. for $C_{12}H_{17}BrN_4O$: C, 46.02; H, 5.47; N, 17.89. Found: C, 46.0; H, 5.5; N, 17.9.

N-[(1α,2β,3β-3-Bromomethyl-3-chloro-2-cyano-2-morpholino-cyclopropyl)-methyl]-N-methylcyanamide (**18**). Addition of 0.98 g (9.3 mmol) of cyanogen bromide (**15**); yield 1.07 g (77%), mp 105°C; ^{1}H NMR ($CDCl_3$): δ 2.27 (H_X, 1H), 3.23 (H_M, 1H), 3.81 (H_N, 1H) (MNX system, J_{MN} = 11.3 Hz, J_{MX} = 11.1 Hz, J_{NX} = 5.6 Hz), 3.44 (H_L, 1H), 3.66 (H_O, 1H) (AB system, J_{LO} = 15.2 Hz), 3.07 (s, 3H), 2.80 (m_c, 4H), 3.74 (m_c, 4H); ^{13}C NMR ($CDCl_3$): δ 117.0 (s), 112.4 (s), 66.3 (t), 55.3 (s), 55.1 (t), 50.2 (t), 50.0 (s) 40.7 (d, $^1J_{CH}$ = 169 Hz), 40.6 (q), 25.4 (d, $^1J_{CH}$ = 154 Hz). Anal. Calcd. for $C_{12}H_{16}BrClN_4O$: C, 41.46; H, 4.64; N, 16.12. Found: C, 41.4; H, 4.7; N, 16.1.

Oxidation of methylazabicyclohexanecarbonitriles **8a** *and* **9a** *with m-chloroperbenzoic acid (m-ClPBA):* m-Chloroperbenzoic acid (m-ClPBA; 70%, 0.296 g, corresponds to 1.2 mmol of pure m-ClPBA) was dried in vacuo at room temperature (1 h) and then dissolved in dichloromethane (20 mL). This solution was added to a solution of methylazabicyclo[3.1.0]hexanecarbonitrile **8a** [23] or **9a** [24] (0.207 g, 1.0 mmol) in dichloromethane (7 mL) at 0°C. The mixture was stirred for 0.5 h at 0°C and for 2.5 h at 20°C. Removal of the solvent in vacuo, washing with ether (3 x 20 mL) and recrystallization of the residue from toluene gave an equimolar adduct of N-oxide **19a** or **21a** with m-chlorobenzoic acid.

1α,5α,6β-6-Cyano-3-methyl-6-morpholino-3-azabicyclo[3.1.0]hexane-3-oxide (**19a**) • *3-chlorobenzoic acid:* Yield 0.36 g (95%), mp 100°C; ^{1}H NMR ($C_6D_5CD_3$): δ 1.29 (2H), 2.33 (2H), 2.82 (2H), 3.39 (2H) (ABXY system, morpholine), 1.82 (H_X, $H_{X'}$, 2H), 2.18 (H_M, $H_{M'}$, 2H), 3.82 (H_N, $H_{N'}$, 2H) (MM'NN'XX' system, J_{MN} = $J_{M'N'}$ = 12.6 Hz, J_{MX} = $J_{M'X'}$ = 3.2 Hz, J_{NX} = $J_{N'X'}$ = 7.2 Hz, $J_{NN'}$ = -1.5 Hz, $J_{XX'}$ = 8.6 Hz), 2.79 (s, 3H), 6.93 (t, 1H), 7.15 (d, 1H), 8.27 (d, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 169.8 (s), 135.9 (s), 133.8 (s), 131.3 (d), 129.4 (d), 129.2 (d), 127.5 (d), 115.4 (t, $^3J_{CH}$ = 3.8 Hz), 68.0 (t, $^1J_{CH}$ = 148 Hz), 66.2 (t), 53.5 (q), 49.8 (t), 46.2 (s), 32.4 (d, $^1J_{CH}$ = 184 Hz). Anal. Calcd. for $C_{18}H_{22}ClN_3O_4$: C, 56.92; H, 5.84; N, 11.06. Found: C, 56.8; H, 6.0; N, 10.9.

1α,5α,6α-6-Cyano-3-methyl-6-morpholino-3-azabicyclo[3.1.0]hexane-3-oxide (**21a**) • *3-chlorobenzoic acid:* Yield 0.33 g (87%), mp 135°C (decomp.); ^{1}H NMR ($CDCl_3$): δ 2.76 (H_X, $H_{X'}$, 2H), 3.38 (H_M, $H_{M'}$, 2H), 4.57 (H_N, $H_{N'}$, 2H) (MM'NN'XX' system, J_{MN} = $J_{M'N'}$ = 13.2 Hz, J_{MX} = $J_{M'X'}$ = 3.8 Hz, J_{NX} = $J_{N'X'}$ = 7.0 Hz, $J_{NN'}$ = -1.5 Hz, $J_{XX'}$ = 8.5 Hz), 2.71 (m_c, 4H), 3.68 (m_c, 4H) (morpholine), 3.45 (s, 3H), 7.33 (t, 1H), 7.46 (d, 1H), 7.93 (d, 1H), 8.04 (t, 1H);

^{13}C NMR ($CDCl_3$): δ 169.5 (s), 135.4 (s), 133.9 (s), 131.5 (d), 129.6 (d), 129.3 (d), 127.6 (d), 113.0 (s), 70.9 (t, $^1J_{CH}$ = 141 Hz), 66.2 (t), 55.8 (q), 53.8 (s), 50.6 (t, $^1J_{CH}$ = 135 Hz), 33.6 (d, $^1J_{CH}$ = 184 Hz). Anal. Calcd. for $C_{18}H_{22}ClN_3O_4$: C, 56.92; H, 5.84; N, 11.06. Found: C, 56.5; H, 5.8; N, 10.7.

3-Acetyl-3-azabicyclo[3.1.0]hexane derivatives **20a-d**,*and* **22a,c,d** - *general procedure*: m-Chloroperbenzoic acid (m-ClPBA; 70%, 0.296 g, corresponds to 1.2 mmol of pure m-ClPBA) was dried in vacuo at room temperature (1h) and then dissolved in dichloromethane (20 mL). This solution was added to a solution of 3-methyl-azabicyclo[3.1.0]hexane derivative **8** or **9** (1.0 mmol; **8a** [23]/**9a** [24]: 0.207 g; **8b** [30]: 0.182 g; **8c/9c** [15]: 0.258 g; **8d/9d** [15]: 0.196 g) in dichloromethane (7 mL) at 0°C. The mixture was stirred for 0.5 h at 0°C and for 2.5 h at 20°C. Then acetic anhydride (1.42 ml, 15.0 mmol) was added and stirring was continued (**9c**: 2h; **8a/9a**: 4h; **8b-d**, **9d**: 16h). Removal of the solvent in vacuo, addition of aqueous sodium hydroxide solution (20%, 5 mL) to the residue and subsequent extraction with ether (3 x 50 mL) and dichloromethane (3 x 50 mL) gave crude acetyl derivatives **20** and **22** which were purified by distillation in a Kugelrohr apparatus and recrystallization.

1α,5α,6β-3-Acetyl-6-morpholino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**20a**): Distillation at 120°C/0.001 Torr and recrystallization from ether; yield 0.166 g (71%), mp 139°C; ^{1}H NMR ($CDCl_3$): δ 2.32 (H_X, 1H), 2.36 (H_Y, 1H), 3.46 (H_L, 1H), 3.63 (H_N, 1H), 3.70 (H_M, 1H), 3.78 (H_O, 1H) (LMNOXY system, J_{LO} = 11.2 Hz, J_{MN} = 13.1 Hz, J_{NX} = 5.6 Hz, J_{OY} = 5.1 Hz, J_{XY} = 8.4 Hz), 1.97 (s, 3H), 2.52 (2H), 2.77 (2H), 3.46 (2H), 3.81 (2H) (broad, unsplit signals, morpholine); ^{13}C NMR ($CDCl_3$): δ 167.8 (s), 116.4 (s), 66.5 (t), 51.0 (t), 46.6 (t), 44.9 (t), 40.9 (s), 30.6 (d, $^1J_{CH}$ = 177 Hz), 29.8 (d, $^1J_{CH}$ = 176 Hz), 22.5 (q). Anal. Calcd. for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28; N, 17.86. Found: C, 61.2; H, 7.4; N, 17.8.

4-(1α,5α,6β-3-Acetyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (**20b**): Distillation at 80°C/0.001 Torr and recrystallization from pentane; yield 0.13 g (62%), mp 70.5°C; ^{1}H NMR ($CDCl_3$): δ 1.69 (H_X, 1H), 1.73 (H_Y, 1H), 1.83 (H_Z, 1H), 3.39 (H_L, 1H), 3.56 (H_N, 1H), 3.61 (H_M, 1H), 3.65 (H_O, 1H) (LMNOXYZ system, J_{LO} = 10.4 Hz, J_{MN} = 12.4 Hz, J_{NX} = 5.8 Hz, J_{OY} = 5.6 Hz, J_{XY} = 8.0 Hz, J_{XZ} = J_{YZ} = 6.65 Hz), 1.98 (s, 3H), 2.50 (m_c, 4H), 3.62 (m_c, 4H); ^{13}C NMR ($CDCl_3$): δ 168.1 (s), 66.9 (t), 53.6 (t), 46.8 (t), 45.0 (t), 44.4 (d, $^1J_{CH}$ = 170 Hz), 22.6 (q), 21.9 (d, $^1J_{CH}$ = 172 Hz), 21.2 (d, $^1J_{CH}$ = 172 Hz). Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.4; H, 8.4; N, 13.5.

4-(1α,5α,6β-3-Acetyl-6-phenyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (**20c**): Distillation at 120-130°C/0.001 Torr and recrystallization from pentane - ether (4:2); yield 0.187 g (65%), mp 140°C; ^{1}H NMR ($CDCl_3$): δ 2.05 (H_X, 1H), 2.09 (H_Y, 1H), 3.59 (H_L, 1H), 3.70 (H_N, 1H), 3.79 (H_M, 1H), 3.81 (H_O, 1H) (LMNOXY system, J_{LO} = 10.7 Hz, J_{MN} = 12.6 Hz, J_{NX} = 5.7 Hz, J_{OY} = 5.7 Hz, J_{XY} = 8.4 Hz), 2.06 (s, 3H), 2.34 (2H), 2.56 (2H), 3.48 (2H), 3.73 (2H) (broad, unsplit signals, morpholine), 7.22 (m_c, 2H), 7.32 (m_c, 3H); ^{13}C NMR ($CDCl_3$): δ 167.9 (s), 135.8 (s), 130.5 (d), 128.0 (d), 127.7 (d), 67.2 (t), 54.4 (s), 50.5 (t), 50.4 (t), 47.4 (t), 45.7 (t), 29.9 (d, $^1J_{CH}$ = 170 Hz), 29.2 (d, $^1J_{CH}$ = 170 Hz), 22.7 (q). Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 70.9; H, 7.4; N, 9.8.

4-(1α,5α,6β-3-Acetyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (**20d**): Distillation at 80°C/0.001 Torr and recrystallization from ether; yield 0.142 g (63%), mp 91°C; ^{1}H NMR ($CDCl_3$): δ 1.54 (H_X, 1H), 1.57 (H_Y, 1H), 3.35 (H_L, 1H), 3.53 (H_N, 1H), 3.55 (H_M, 1H), 3.63 (H_O, 1H) (LMNOXY system, J_{LO} = 10.5 Hz, J_{MN} = 11.3 Hz, J_{NX} = 4.4 Hz, J_{OY} = 5.8 Hz, J_{XY} = 7.8 Hz), 1.05 (s, 3H), 1.98 (s, 3H), 2.42 (2H), 2.70 (2H), 3.48 (2H), 3.76 (2H) (broad, unsplit signals, morpholine); ^{13}C NMR ($CDCl_3$): δ 167.7 (s), 67.3 (t), 49.6 (t), 47.4 (t), 45.6 (t), 45.4 (s), 30.8 (d, $^1J_{CH}$ = 170 Hz), 30.1 (d, $^1J_{CH}$ = 170 Hz), 22.5 (q), 14.2 (q). Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.2; H, 9.0; N, 12.7.

1α,5α,6α-3-Acetyl-6-morpholino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**22a**): Distillation at 200°C/0.001 Torr and recrystallization from toluene; yield 0.12 g (51%), mp 195°C; ^{1}H NMR ($CDCl_3$): δ 2.12 (H_X, 1H), 2.15 (H_Y, 1H), 3.65 (H_N, 1H), 3.71 (H_L, 1H), 3.79 (H_O, 1H), 3.89 (H_M, 1H) (LMNOXY system, J_{LO} = 11.2 Hz, J_{MN} = 12.9 Hz, J_{NX} = 4.7 Hz, J_{OY} = 4.8 Hz, J_{XY} = 7.9 Hz), 2.02 (s, 3H), 2.70 (m_c, 4H), 3.67 (m_c, 4H); ^{13}C NMR ($CDCl_3$): δ 169.1 (s), 112.9 (s), 66.5 (t), 50.6 (t), 47.5 (t), 46.4 (s), 46.0 (t), 31.8 (d, $^1J_{CH}$ = 177 Hz), 31.0 (d, $^1J_{CH}$ = 177 Hz), 22.5 (q). Anal. Calcd. for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28; N, 17.86. Found: C, 61.2; H, 7.3; N, 17.5.

4-(1α,5α,6α-3-Acetyl-6-phenyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (**22c**): Distillation at 150°C/0.001 Torr and recrystallization from ether; yield 0.212 g (74%), mp 147°C; ^{1}H NMR ($CDCl_3$): δ 1.98 (H_X, 1H), 2.00 (H_Y, 1H), 3.35 (H_N, 1H), 3.42 (H_L, 1H), 3.55 (H_O, 1H), 3.75 (H_M, 1H) (LMNOXY system, J_{LO} = 10.8 Hz, J_{MN} = 12.6 Hz, J_{NX} = 4.7 Hz, J_{OY} = 4.7 Hz, J_{XY} = 8.3 Hz), 1.45 (s, 3H), 2.46 (m_c, 4H), 3.60 (m_c, 4H), 7.09 (d, 2H), 7.29 (t, 1H), 7.37 (t, 2H); ^{13}C NMR ($CDCl_3$): δ 167.9 (s), 130.0 (d), 128.0 (d), 127.9 (d), 127.1 (s), 67.2 (t), 53.7 (s), 49.6 (t), 50.4 (t), 47.7 (t), 45.5 (t), 30.2 (d, $^1J_{CH}$ = 172 Hz), 29.7 (d, $^1J_{CH}$ = 172 Hz), 21.8 (q). Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.2; H, 7.8; N, 9.5.

4-(1α,5α,6α-3-Acetyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (**22d**): Distillation at 100-105°C/0.001 Torr and recrystallization from ether; yield 0.141 g (63%), mp 123°C; ^{1}H NMR ($CDCl_3$): δ 1.60 (H_X, 1H), 1.63 (H_Y, 1H), 3.31 (H_L, 1H), 3.41 (H_M, 1H), 3.52 (H_N, 1H), 3.62 (H_O, 1H) (LMNOXY system, J_{LO} = 10.6 Hz, J_{MN} = 12.7 Hz, J_{NX} = 5.2 Hz, J_{OY} = 5.0 Hz, J_{XY} = 8.4 Hz), 0.89 (s, 3H), 1.95 (s, 3H), 2.54 (m_c, 4H), 3.58 (m_c, 4H); ^{13}C NMR ($CDCl_3$): δ 168.7 (s), 67.2 (t), 48.7 (t), 47.2 (t), 46.3 (s), 45.6 (t), 29.6 (d, $^1J_{CH}$ = 171 Hz), 28.6 (d, $^1J_{CH}$ = 171 Hz), 22.5 (q), 2.2 (q). Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.3; H, 9.0; N, 12.6.

Deacetylation of 3-Acetyl-6-morpholino-3-azabicyclo[3.1.0]hexane derivatives **20a,c** and **22a,c** - *general procedure*: Acetyl derivative **20** or **22** (0.5 mmol, **20a/22a**: 0.118 g; **20c/22c**: 0.143 g) was stirred in an aqueous solution of hydrochloric acid (22%, 8.5 mL) at 100-110°C (**20a/22a**: 6h; **20c/22c**: 14h). Then solid sodium hydroxide was added to the ice-cooled solution until pH = 14 was reached. Extraction with ether (5 x 20 mL), distillation of the ether extract in a Kugelrohr apparatus and recrystallization from ether gave pure deacetylated products.

1α,5α,6β-6-Morpholino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**23a**): Distillation at 60°C/0.001 Torr; yield 0.058 g (60%), mp 81°C (lit [27]: 81°C); identical in the ^{1}H NMR and ^{13}C NMR spectra with respect to published data [27]).

4-(1α,5α,6β-6-Phenyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (**23c**): Distillation at 80°C/0.001 Torr; yield 0.091 g (75%), mp 149°C; ^{1}H NMR ($CDCl_3$): δ 1.87 (H_X, $H_{X'}$, 2H), 3.11 (H_N, $H_{N'}$, 2H), 3.22 (H_M, $H_{M'}$, 2H) (MM'NN'XX' system, $J_{MN} = J_{M'N'} = 12.3$ Hz, $J_{NX} = J_{N'X'} = 3.7$ Hz, $J_{XX'} = 7.5$ Hz), 2.34 (2H), 2.61 (2H), 3.50 (2H), 3.75 (2H) (ABXY system, morpholine), 2.45 (broad, 1H, NH), 7.20-7.34 (m_c, 5H); ^{13}C NMR ($CDCl_3$): δ 136.4 (s), 130.7 (d), 127.8 (d), 127.3 (d), 67.5 (t), 55.6 (s), 50.7 (t), 48.9 (t), 31.8 (d, $^1J_{CH} = 168$ Hz). Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.46. Found: C, 73.5; H, 8.1; N, 11.5.

1α,5α,6α-6-Morpholino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**24a**): Distillation at 120°C/0.007 Torr; yield 0.080 g (83%), mp 120°C; ^{1}H NMR ($CDCl_3$): δ 1.99 (H_X, $H_{X'}$, 2H), 3.13 (H_N, $H_{N'}$, 2H), 3.23 (H_M, $H_{M'}$, 2H) (MM'NN'XX' system, $J_{MN} = J_{M'N'} = 12.3$ Hz, $J_{NX} = J_{N'X'} = 4.0$ Hz, $J_{XX'} = 7.5$ Hz), 1.81 (s, broad, NH), 2.66 (m_c, 4H), 3.66 (m_c, 4H); ^{13}C NMR ($CDCl_3$): δ 115.1 (s), 66.6 (t), 50.4 (t), 47.5 (t), 44.0 (s), 34.6 (d, $^1J_{CH} = 174$ Hz). Anal. Calcd. for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.74. Found: C, 62.49; H, 8.24; N, 21.18.

4-(1α,5α,6α-6-Phenyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (**24c**): Distillation at 70°C/0.001 Torr; yield 0.093 g (76%), mp 131°C; ^{1}H NMR ($CDCl_3$): δ 1.87 (H_X, $H_{X'}$, 2H), 2.87 (H_M, $H_{M'}$, 2H), 2.90 (H_N, $H_{N'}$, 2H) (MM'NN'XX' system, $J_{MN} = J_{M'N'} = 12.6$ Hz, $J_{NX} = J_{N'X'} = 3.9$ Hz, $J_{XX'} = 7.9$ Hz), 2.42 (m_c, 4H), 3.60 (m_c, 4H), 7.12 (d, 2H), 7.31 (t, 1H), 7.37 (t, 2H); ^{13}C NMR ($CDCl_3$): δ 129.6 (d), 129.1 (s), 128.3 (d), 127.6 (d), 67.2 (t), 53.1 (s), 49.4 (t), 47.5 (t), 33.1 (d, $^1J_{CH} = 169$ Hz). Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.46. Found: C, 73.6; H, 8.3; N, 11.5.

1α,5α,6β-6-Dibenzylamino-3-azabicyclo[3.1.0]hexane (**27**): m-Chloroperbenzoic acid (m-ClPBA; 70%, 0.168 g, corresponds to 0.68 mmol of pure m-ClPBA) was dried in vacuo at room temperature (1 h) and then dissolved in dichloromethane (20 mL). This solution was added to a solution of 3-methyl-6-dibenzylamino-3-azabicyclo[3.1.0]hexane **25** (0.200 g, 0.68 mmol) in dichloromethane (7 mL) at 0°C. The mixture was stirred for 0.5 h at 0°C and for 2 h at 20°C. Then acetic anhydride (0.128 mL, 1.36 mmol) was added and stirring was continued for 5 h. Addition of saturated aqueous solution of sodium carbonate (10 mL) and water (10 mL) to the solution at 0°C, separation of the organic layer, subsequent extraction with dichloromethane (4 x 20 mL) and removal of the dichloromethane in vacuo at 15°C gave crude acetyl derivative **26** (spectroscopic data: ^{1}H NMR ($CDCl_3$): δ 1.64 (H_X, 1H), 1.70 (H_Y, 1H), 2.05 (H_Z, 1H), 2.95 (H_L, 1H), 3.43 (H_O, 1H), 3.52 (H_N, 1H), 3.60 (H_M, 1H) (LMNOXYZ system, $J_{LO} = 10.6$ Hz, $J_{MN} = 12.5$ Hz, $J_{NX} = J_{OY} = 5.7$ Hz, $J_{XY} = 8.0$ Hz, $J_{XZ} = J_{YZ} = 6.8$ Hz), 1.87 (s, 3H), 3.47 (H_A, 2H), 3.63 (H_B, 2H) (AB system $J_{AB} = 14.0$ Hz), 7.14-7.28 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 168.0 (s), 137.5 (s), 129.4 (d), 128.2 (d), 127.1 (d), 57.8 (t), 46.9 (t), 45.3 (t), 43.7 (d, $^1J_{CH} = 162$ Hz), 23.9 (d, $^1J_{CH} = 171$ Hz), 22.4 (q), 22.2 (d, $^1J_{CH} = 171$ Hz). An aqueous solution of hydrochloric acid (22%, 8.5 mL) was added to the crude product and the mixture was stirred at 100-110°C for 3 h. Then the cooled solution was extracted with ether (3 x 20 mL). Addition of solid sodium hydroxide to the ice-cooled solution until pH = 14 was reached, extraction with ether (4 x 30

mL) and distillation of the ether extract in a Kugelrohr apparatus at 110-120°C/0.001 Torr gave pure dibenzylaminoazabicyclohexane **27**. Yield 0.125 g (66%), mp 87°C (lit [12]: 86°C); identical in the ^{1}H NMR and ^{13}C NMR spectra with respect to published data [12]).

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7. References

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