82. Transamidation Reactions

Part 11[1])

N-Substituted 3-Aminopropanenitriles and 2-Aminoacetonitriles as *Schiff*-Base Equivalents

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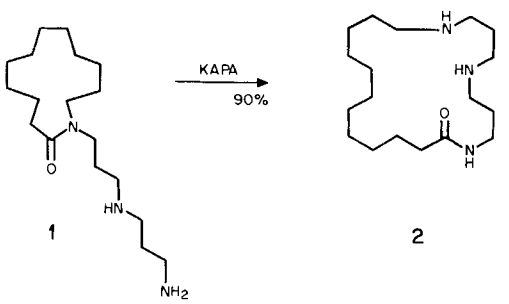
In presence of a strong base, the 13-membered cyclic compound **3** yielded, by loss of acetonitrile or its equivalent, the bicyclic product **5** instead of the 17-membered compound **4** as expected *(Scheme 2)*. Investigation of model compounds *(Scheme 4)* and of model reactions (*Schemes 5* and *6*) led to the conclusion that the reaction proceeds *via* an intermediate formaldehyde imine; a *Schiff* base, *e.g.* **3b** *(Scheme 5)*, which reacts intra- and intermolecularly with a nucleophile to form a *Mannich*-type product. It seems to be a general principle that *N*-substituted 3-aminopropanenitrile and 2-aminoacetonitrile derivatives behave in the presence of a strong base as *Schiff*-base equivalents (*Schemes 5* and *6*).

1. Introduction. – In presence of a base the transamidation reaction of *N*-(*γ*-aminopropyl)-lactams yields the corresponding ring-enlarged azalactams in nearly quantitative yield (*Zip*-reaction) [2]; *e.g.* treatment of 1-(7-amino-4-azaheptyl)azacyclotridecan-2-one (**1**) with KAPA ($KNH-(CH_2)_3-NH_2/NH_2-(CH_2)_3-NH_2$) [3] led to 1,5,9-triazacyclohenicosan-10-one (**2**) in 90% yield [4] *(Scheme 1)*. By use of bases other than KAPA the same transamidation products resulted, however, their yields were sometimes significantly lower; in most cases *t*-BuOK gave reasonable yields.

Scheme 1



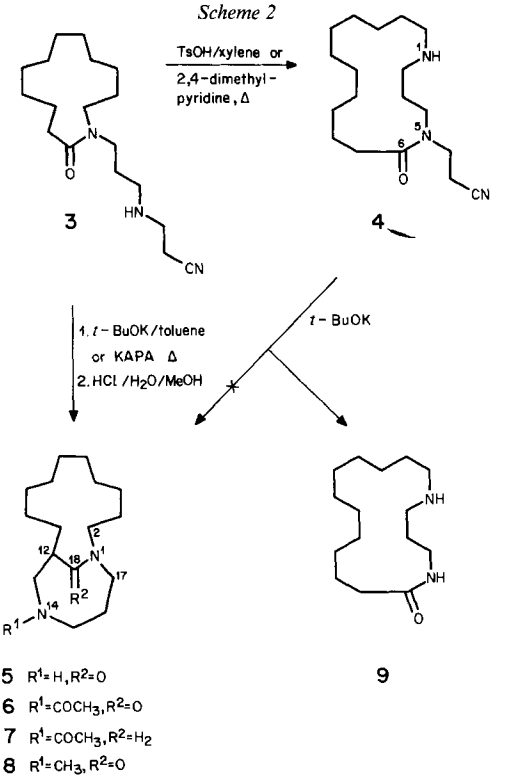
[1]) Part 10: [1]. In earlier papers of this series the lactam nomenclature was used. Beginning with this paper the 'replacement nomenclature' is preferred. Both systems are in agreement with IUPAC nomenclature of organic chemistry.

[2]) Part of the Ph. D. thesis of *E. A.*, University of Zürich 1984.

On the basis of these investigations it was expected that 7-(2-oxo-1-azacyclotridecyl)-4-azaheptanenitrile (**3**) [4] should be transformed with KAPA to 3-(6-oxo-1,5-diazacycloheptadecyl)propanenitrile (**4**) *(Scheme 2)*. However, in the presence of 2 mol-equiv. of KAPA (6 h, reflux), a new product, 1,14-diazabicyclo[10.5.1]octadecan-18-one (**5**, 46%), was formed besides the starting material. A better yield of **5** (79%) was achieved using 1 mol-equiv. of *t*-BuOK in dry toluene (1 h, reflux). Compound **4** can be prepared from **3** by acid-catalysis (reflux, TsOH) [5] or by reflux of **3** in 2,4-dimethylpyridine *(Scheme 2)*.

In this paper, we report on the structure elucidation of **5** and the mechanism of its formation.

Scheme 2



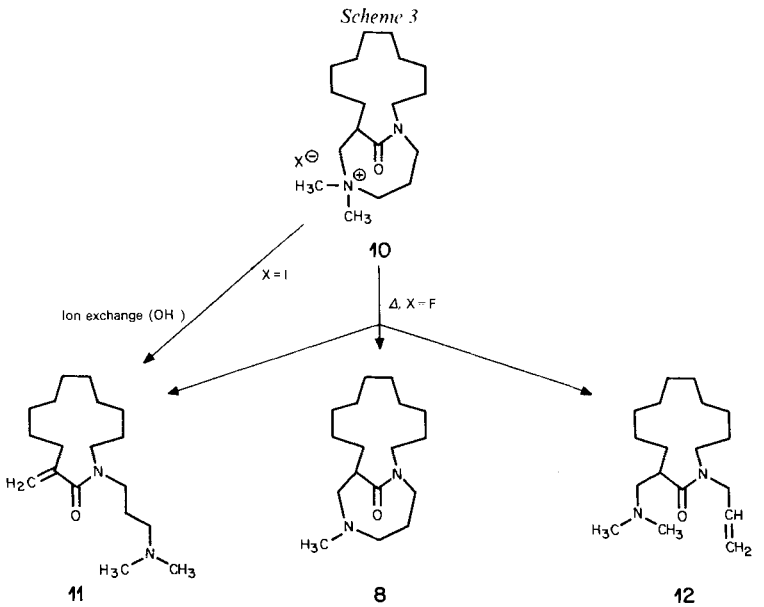
2. Structure Elucidation of 5. – The oily compound **5** ($C_{16}H_{30}N_2O$, M = 266) differs from the starting material **3** by C_2H_3N (*e.g.* MeCN). The spectral analysis of the crystalline hydrochloride (m.p. 248.5–250.0°) indicated the presence of the following structure elements: *N,N*-disubstituted amide (IR[3]): 1633 cm^{-1}); H–N< (^{1}H-NMR[3]): 1,92 ppm, *s*, exchangeable with D_2O); $-H_2C(2)-N(CO)-H_2C(17)-$ [4.42 ppm, *dddd* for 1H–C(2); 2.61, *ddd* for 1H–C(2); 3.97, *dddd* for 1H–C(17), and 3.25 ppm, *dt* for 1H–C(17)], and two CH_2 groups in the neighbourhood to the amino N-atom (in this case, a coupling with H–C(12) was observed). These structural features were also recognized in the ^{13}C-NMR spectra (see *Exper. Part*).

[3]) IR spectra were recorded in $CHCl_3$, ^{1}H-NMR spectra in $CDCl_3$.

Compound **5** was transformed into its *N*-acetyl derivative **6** (M = 308, m.p. 119–120°, IR: 1635 cm^{-1}) by treatment with Ac_2O/pyridine. Reduction of **5** with $LiAlH_4$, followed by acetylation yielded the desoxo-acetyl compound **7** (M = 294, IR: 1628 cm^{-1}). By methylation ($CH_2O/NaBH_4$), **5** was converted to the *N*-methyl derivative **8** (M = 280, IR: 1631 cm^{-1}). The structural elements established in the spectra of **5** correspond to those established in the ^{1}H-NMR spectrum of **8**; $CH_3(N)$ at 2.35 ppm.

Permethylation of **5** with MeI gave the methoiodide **10** (X = I), which, in the presence of an anion exchange resin (*Amberlite IRA-400*, $OH^\ominus$, H_2O/MeOH 1:1), was converted exclusively to the *Hofmann* base **11** (M = 294) [6] *(Scheme 3)*. In favour of structure **11** are IR absorptions at 1607 and 915 cm^{-1} for an α,β-unsaturated amide, two vinylic proton signals (5.64–5.00 ppm, *m*) in the ^{1}H-NMR, and the base peak at m/z 58 in MS corresponding to the ion $[(CH_3)_2NCH_2]^+$.

Scheme 3

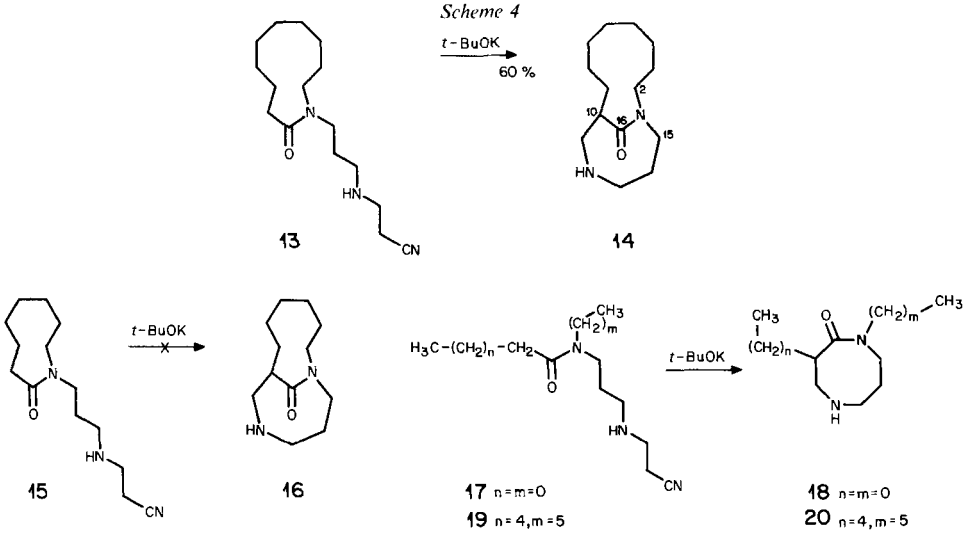


By high-vacuum distillation of the methofluoride **10** (X = F) prepared by ion exchange (*Dowex 2*, $F^\ominus$, H_2O/MeOH 1:1) from **10** (X = I), three pyrolysis products were formed: the *Hofmann* bases **11** and **12** as well as the demethylation product **8**. The isomeric base **12** gives similar spectral data as **11**. Besides different R_f values on TLC, the intensities of the peaks at m/z 58 in MS are of significant difference; **11**: 40% Σ_{35} and **12**: 80% Σ_{35}. Furthermore, the UV curves of both components have the same λ_{max} values, but they are different in shape. They both correspond to those of the model compounds (see *Exper. Part*).

It was not possible to cleave **5** under acidic ($HCl–H_2O/CH_3COOH$, 150°, 24 h), or under basic (KCH_2SOCH_3/DMSO, 60°, 24 h, or KAPA [7]) conditions; in all cases **5** was recovered unchanged.

3. Syntheses of Model Compounds Corresponding to 5. – In order to verify the general validity of the transformation **3**→**5**, the following experiments were carried out. In the

Scheme 4

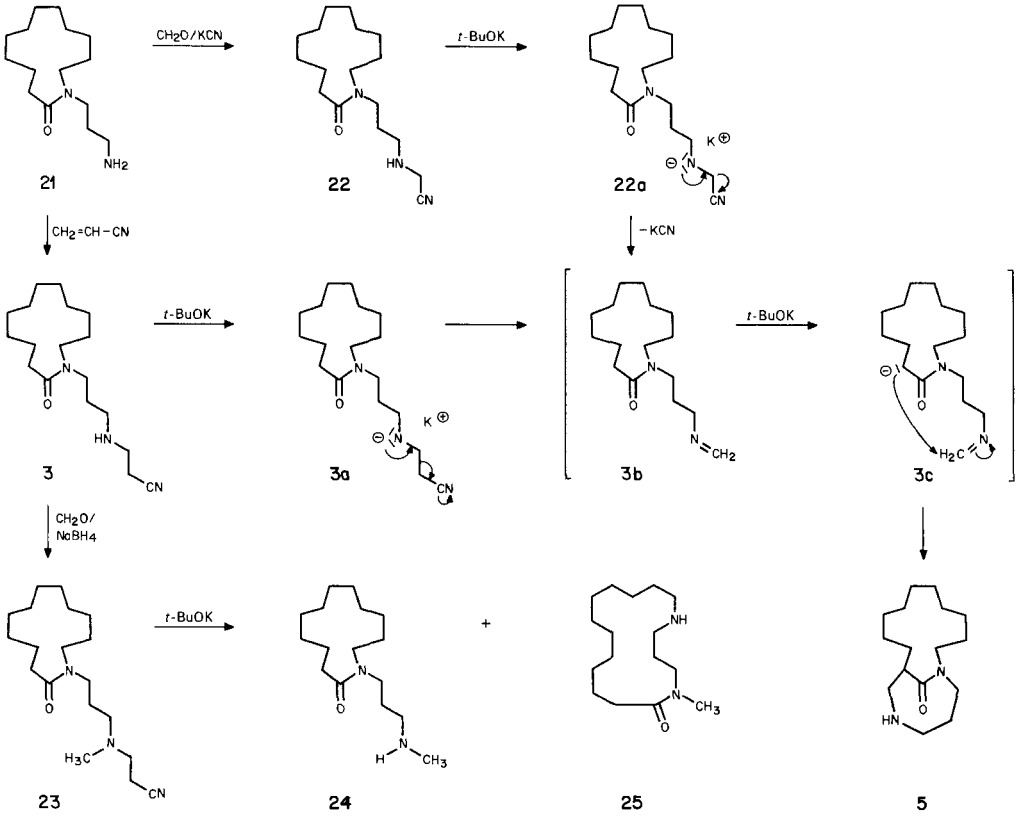


presence of 2 mol-equiv. of *t*-BuOK 1,12-diazabicyclo[8.5.1]hexadecan-16-one (**14**, $C_{14}H_{26}N_2O$, $M = 238$, IR: 1634 cm^{-1}; the ^{1}H-NMR data are comparable with those of **5**) was prepared from the 11-membered lactam **13** *(Scheme 4)*. Compound **14** was not obtained when only 1 mol-equiv. of the catalyst was used. In this case starting material was recovered. Under the same reaction conditions necessary for the transformation **13**→**14**, the 9-membered lactam **15** could not be converted to 1,10-diazabicyclo[6.5.1]tetradecan-14-one (**16**). Besides a wide range of compounds, traces of **15** were recovered. We assume that steric factors are responsible for the failure of the attempted transformation **15**→**16**. In absence of such steric factors, following transformations of the open chained systems could be achieved: *N*-(6-cyano-4-azahexyl)-*N*-methylpropionamide (**17**) was converted into 1,3-dimethyl-1,5-diazacyclooctan-2-one (**18**), and *N*-(6-cyano-4-azahexyl)-*N*-hexylheptanamide (**19**) into 1-hexyl-3-pentyl-1,5-diazacyclooctan-2-one (**20**) *(Scheme 4)*. In both cases, formally MeCN was eliminated. The yields – 41% and 56%, respectively – are rather low because of formation of polar side products. The ^{1}H-NMR and mass spectra of the compounds **18** and **20** are comparable with those of **5** and **14**. They indicate clearly the 8-membered cyclic nature of the reaction products (see *Exper. Part*).

These model transformations clearly indicate that the formation of **5** from **3** reflects a general reaction principle.

4. Mechanism of the Formation of 5 from 3. – It can be assumed that treatment of **3** with base leads to the anion **3a** *(Scheme 5)*. There are two alternatives for further reactions of the anion **3a**: in presence of 2,4-dimethylpyridine, the N-anion **3a** attacks in a *Zip*-reaction step the lactam carbonyl group yielding the ring-enlarged product **4** [5] *(Scheme 2)*. In case of KAPA or *t*-BuOK as bases, **3a** undergoes a *retro-Mannich*-type reaction leading to the intermediate formaldehyde imine **3b**. The latter can be transformed by base to **3c**, which, by cyclisation, gives the 8-membered-ring-containing compound **5**. Compound **4** is not formed under these reaction conditions. Treatment of **4** with *t*-BuOK leads to **9** as the main component *(Scheme 2)*.

Scheme 5



When no secondary amino group is present as in the case of the *N*-methyl derivative **23**, treatment with *t*-BuOK leads to a *retro-Michael* reaction generating **24**, which, in turn, is transformed to the ring-enlarged product **25** *(Scheme 5)*.

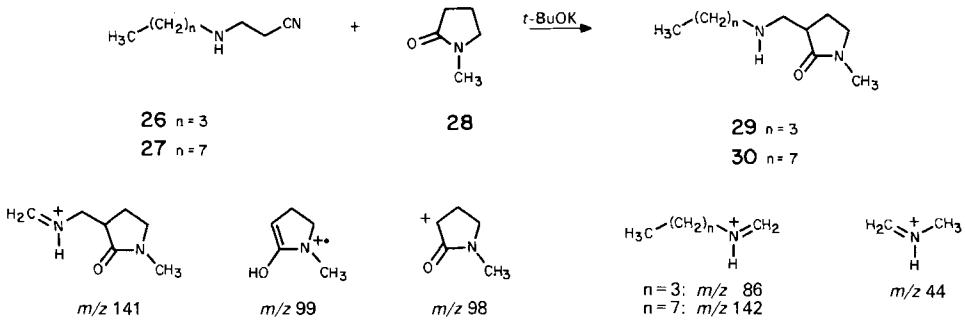
To exclude formaldehyde, present in MeOH which was used as solvent for chromatography *etc.* [8], as the source for the additional CH_2 group between C(12) and N(14) in **5**, compound **21** was treated with formaldehyde/*t*-BuOK. In this case **5** was not formed. MeCN or – during workup – AcOH and ammonium salt which could have accompanied the conversion of **3**→**5**, were not detected.

If **3b** is an intermediate in the formation of **5**, the 2-aminoacetonitrile derivative **22**, a lower homologue of **3**, should also give **5** under similar reaction conditions. Compound **22** was prepared according to [9] from the primary amine **21** with CH_2O/KCN[4]). Treatment of **22** with *t*-BuOK in boiling toluene led, by a β-elimination of KCN, to the same bicyclic *Mannich* product **5** in good yield. If an internal nucleophile is present, as in the case of **3c** *(Scheme 5)*, ring closure occurs even if a medium-sized ring is formed. It should be possible to trap the proposed intermediate of type **3b**. Treatment of **3** and 1-methyl-2-

[4]) It is known that in the presence of RLi or RMgX, 2-amino-nitriles react to form $-NH-CH_2-R$ derivatives [10].

pyrrolidone (**28**) (molar ratio 1:1) with *t*-BuOK gave only **5** and unreacted **28**, *i.e.* the intramolecular reaction, namely the formation of the 8-membered ring, is preferred over the intermolecular reaction. However, the trapping can be achieved if **28** reacts with 3-azaoctanenitrile (**26**) or with 3-azadodecanenitrile (**27**) in the presence of 2 mol-equiv. of *t*-BuOK. With **26**, 3-(2′-azahexyl)-1-methyl-2-pyrrolidone (**29**, M = 184), and with **27** 3-(2′-azadecyl)-1-methyl-2-pyrrolidone (**30**, M = 240) were formed[5]). The physical data of both products, especially the fragment ions at m/z 141, 99, 98, 86 or 142, and 44, were in agreement with the proposed structures *(Scheme 6)*.

Scheme 6



The transformation **3**→**5** can be considered as the combination of a *retro-Mannich* and *Mannich* reaction. The formaldehyde equivalent is formed from the 3-amino-propanenitrile or 2-aminoacetonitrile unit under the influence of base. The amino group must be secondary.

We thank Dr. *R. Charubala* for preliminary experiments and the analytical departments of our institute for spectra (Dr. *A. Lorenzi-Riatsch, N. Bild, H. Frohofer,* Dipl.-chem. *A. Hafner,* Dr. *R. Kyburz*). The support of this work by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* is thankfully acknowledged.

Experimental Part

General. All org. solvents were dried over Na_2SO_4. Column chromatography was carried out by using silica gel 60 (0.063–0.200 mm, *Merck*). Melting points (m.p.): *Mettler FP-5* apparatus, IR spectra: in $CHCl_3$, NMR spectra: *Varian XL 200,* in $CDCl_3$, coupling constants J in Hz, internal TMS = 0 ppm. MS: *Varian MAT 711* and *Varian MAT 112S* [m/z (rel. intensities) of signals < 5%].

1. *1,14-Diazabicyclo[10.5.1]octadecan-18-one* (**5**). – 1.1. *From 7-(2-Oxo-azacyclotridec-1-yl)-4-azaheptanenitrile* (**3**) [4]. Under Ar, a soln. of dry toluene (500 ml), fresh distilled **3** (1.27 g), and *t*-BuOK (473 mg, 1 mol-equiv.) was boiled under reflux for 1 h. The soln. was neutralized dropwise by addition of MeOH/HCl soln., the solvent evaporated, the residue solved in H_2O, basified with K_2CO_3, and extracted several times with CH_2Cl_2. Chromatography (silica gel, $CHCl_3$/MeOH 4:1) followed by distillation (130–140°/10^{-3} Torr) gave the oily **5** (863 mg, 79%). M.p. (**5**·HCl, prepared by neutralizing with 2N HCl): 248.5–250° (EtOH/Et_2O). IR (KBr): 1633 (*N,N*-disubst. amide). **5**: ^{1}H-NMR: 4.42 (*dddd*, J = 13.7, 10.1, 3.4, 1.5, 1H–C(2)); 3.97 (*dddd*, J = 15.2, 12.2, 3.0, 1.5, H–C(17)); 3.25 (*dt*, J = 15.2, 3.6, H–C(17)); 3.13–2.93 (*m*, H–C(12)); 2.91–2.72 (*m*, 2H–C(13), 2H–C(15)); 2.61 (*ddd*,

[5]) The reaction conditions were not optimized.

J = 13.7, 5.0, 3.3, H–C(2)); 2.10–1.89 (*m*, H–C(11)); 1.92 (*s*, HN, exchangeable with D_2O); 1.89–1.49 (*m*, 2H–C(3), 2H–C(16)); 1.49–1.04 (*m*, 15H). Decoupling experiments: irradiation: 4.42→3.97 (*ddd*, J = 15.2, 12.2, 3.0), 2.61 (*dd*, J = 5.0, 3.3), 1.89–1.49 (*m*, change), 3.97→4.42 (*ddd*, J = 13.7, 10.1, 3.4), 3.25 (*t*, J = 3.6), 1.89–1.49 (*m*, change); 3.25→3.97 (*ddd*, J = 12.2, 3.0, 1.5), 1.89–1.49 (*m*, change); 3.13–2.93→2.10–1.89 (*m*, change); 2.61→4.42 (*ddd*, J = 10.1, 3.4, 1.5), 1.89–1.49 (*m*, change). ^{13}C-NMR: 176.1 (*s*, CO); 55.9 (*t*, C(15)); 46.4 (*t*, C(13)); 45.0 (*t*, C(2)); 42.9 (*t*, C(17)); 42.3 (*d*, C(12)); 31.9, 29.2, 27.1, 26.9, 26.3, 26.2, 26.1, 26.1, 25.4, 24.7 (10*t*, 10 C). MS: 267 (6), 266 (34, $C_{16}H_{30}N_2O$, M^+), 238 (8), 237 (7), 224 (6), 223 (15), 210 (6), 209 (7), 198 (8), 169 (6), 168 (6), 167 (6), 155 (7), 154 (6), 140 (6), 127 (6), 126 (9), 125 (7), 124 (6), 114 (6), 113 (9), 112 (12), 111 (6), 110 (8), 100 (8), 99 (18), 98 (16), 97 (10), 96 (13), 85 (14), 84 (17), 83 (16), 82 (9), 72 (8), 71 (15), 70 (49), 69 (66), 68 (11), 67 (6), 58 (25), 57 (22), 56 (51), 55 (29), 54 (5), 44 (100).

A soln. of **3** (100 mg), dry toluene (70 ml) and KAPA (2 mol-equiv.) was boiled 6 h under reflux and worked up. The separation of the crude product (97 mg) was achieved by TLC: **3** (31 mg) and **5** (41 mg).

1.2. *From 6-(2-Oxo-1-azacyclotridec-1-yl)-3-azahexanenitrile* (**22**). Compound **22** (180 mg) in dry toluene (75 ml) was treated under Ar with *t*-BuOK (138 mg, 2 mol-equiv.) and refluxed for 1 h. It was acidified with MeOH/HCl (strong smell of HCN!), evaporated, the residue solved in aq. K_2CO_3 and extracted with CH_2Cl_2, dried and evaporated. The hydrochloride, prepared in usual manner, was crystallized from EtOH/Et_2O: **5**·HCl (127.4 mg, 68%). The mother liquor consisted of **5**·HCl and traces of **21**·HCl.

2. *14-Acetyl-1,14-diazabicyclo[10.5.1]octadecan-18-one* (**6**). A sample of **5** was acetylated as usual (Ac_2O/pyridine) to give **6**. M.p. 119–120°, b.p. 120°/10^{-3} Torr. IR: 1635. ^{1}H-NMR: 4.35 (*dddd*, 1H–C(2)); 3.93–3.61 (*m*, 2H; therein at 3.78 *dddd*, 1H–C(17)); 3.51 (*dd*, J = 11.8, 13.6, 1H); 3.39–3.02 (*m*, 4H); 2.60 (*ddd*, J = 13.7, 5.1, 3.3, H–C(2)); 2.07 (*s*, CH_3); 2.27–1.95 (*m*, H–C(11)); 1.82–1.00 (*m*, 19H). MS: 308 (40, M^+), 280 (9), 266 (9), 265 (40), 237 (22), 222 (8), 194 (10), 180 (8), 168 (13), 167 (11), 155 (9), 154 (8), 153 (8), 141 (19), 140 (11), 129 (19), 128 (12), 127 (8), 126 (9), 124 (8), 114 (8), 113 (14), 112 (14), 111 (9), 110 (9), 100 (24), 99 (19), 98 (21), 97 (12), 96 (16), 95 (8), 86 (10), 85 (10), 84 (20), 83 (21), 82 (12), 81 (11), 72 (10), 71 (12), 70 (49), 69 (34), 68 (13), 67 (13), 58 (19), 57 (22), 56 (43), 55 (37), 54 (5), 44 (100).

3. *14-Acetyl-1,14-diazabicyclo[10.5.1]octadecane* (**7**). In an evacuated sealed tube, **5** (10 mg) in THF (2 ml) was treated 15 h at 100° with an excess of $LiAlH_4$. After workup, the residue (9 mg) was acetylated and separated by prep. TLC (silica gel, $CHCl_3$/MeOH 9:1) to yield **7** (3 mg). IR: 1628. MS: 294 (100, M^+), 279 (22), 265 (20), 251 (80), 237 (15), 222 (22), 208 (45), 194 (50), 180 (30), 168 (23), 154 (18), 141 (40), 124 (25), 110 (38), 96 (38), 82 (60), 70 (45).

4. *14-Methyl-1,14-diazabicyclo[10.5.1]octadecan-18-one* (**8**). A mixture of **5** (30 mg) in MeOH (10 ml) and a 37% H_2O/CH_2O soln. (1 ml) was allowed to stand for 45 min at 20° and afterwards reduced with an excess of $NaBH_4$. Workup under usual conditions gave **8** (29 mg). M.p. of **8**·HCl (prepared with 2N HCl): 214.2–215.5° (MeOH/Et_2O). **8**: IR: 1631. ^{1}H-NMR: 4.40 (*dddd*, J = 13.6, 10.5, 3.3, 1.3, H–C(2)); 3.87 (br. *t*, $J \approx 14$, H–C(17)); 3.20 (*dt*, J = 15, 3.7, H–C(17)); 3.01 (*tdd*, $J \approx 11$, ≈ 4, ≈ 3, H–C(12)); 2.70–2.35 (*m*, 2H–C(13), 2H–C(15), H–C(2)); 2.35 (*s*, CH_3N); 2.10–1.05 (*m*, 20H). MS: 280 (32, M^+), 265 (5), 251 (5), 237 (9), 223 (4), 181 (5), 140 (7), 126 (10), 112 (13), 98 (17), 84 (40), 70 (67), 58 (100).

5. *Methylation of* **5** *and* Hofmann *degradation.* Compound **5** (300 mg) in MeOH (3 ml) was treated with MeI (30 ml) in the presence of K_2CO_3 (150 mg) at 20° for 15 h. The soln. was evaporated, the residue solved in H_2O/MeOH 1:1 and passed through an ion-exchange resin column (*Amberlite IRA-400* (OH^-)) and washed with the same solvent. The eluate was brought to dryness and the residue purified by prep. TLC: *1-(3'-dimethylaminopropyl)-3-methylene-1-azacyclotridecan-2-one* (**11**, 167 mg) as an oil. UV: λ_{max} 203 (3.90), points on the curve: 220 (3.63), 230 (3.41); 240 (3.16)[6]). IR: 1607, 915. ^{1}H-NMR: 5.64–5.00 (*m*, $H_2C{=}C<$); 4.46–4.18 (*m*, H–C(13)); 3.80–3.35 (*m*, 1H–C(13), 2H–C(1')); 3.24–2.96 (*m*, H–C(4)); 2.86–2.64 (*m*, H–C(4)); 2.52–2.14 (*m*, 8H); 1.96–1.16 (*m*, 18H). MS: 294 (6, M^+), 85 (7), 72 (23), 58 (100).

In another experiment the methofluoride of **10** (X = F, 78 mg) was distributed into 7 *Kugelrohrs* and distilled (100–240°, 10^{-3} Torr). The combined distillates (56 mg) were separated by prep. TLC (silica gel, $CHCl_3$/MeOH 9:1) to give **12** (44 mg, fast running), **8**, and **11** (10 mg). The base **12** was purified by prep. TLC (Alox, Et_2O/hexane 4:1). UV: λ_{max} 204 (3.94), points on the curve: 220 (3.54), 230 (3.00), 240 (2.50). IR: 1625, 920. MS: 294 (1, M^+), 250 (1), 98 (1), 84 (1), 70 (2), 58 (100).

6. *Synthesis of* **22**. – *1-(3-Aminopropyl)-1-azacyclotridecan-2-one-hydrochloride* (**21**·HCl, 290 mg, [4]), KCN (65 mg), H_2O (1 ml), 35% aq. HCHO soln. (0.1 ml), and Et_2O (5 ml) were vigorously stirred for 19 h at 20°. The

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[6]) N,N-*Diethyl-2-methylacrylamide* (as model compound for **11**): UV: λ_{max} 202 (3.86), points on the curve: 220 (3.52), 230 (3.23), 240 (2.77).

Et_2O soln. was separated and acidified with aq. HCl (pH ≈ 3). After 1 h, it was evaporated and the residue was purified by chromatography (15 g silica gel, $CHCl_3$ saturated with 25% aq. NH_4OH): **22** (181 mg, 62%) and **21**. Oil. IR: 3450, 3340, 2240 (very weak [2]), 1626. ^{1}H-NMR: 3.60–3.07 (*m*, 2 CH_2NCO) therein at 3.51 (*s*, NCH_2CN); 2.83–1.0 (*m*). MS: 293 (3, M^+), 253 (9), 224 (6), 210 (9), 198 (25), 69 (76), 56 (44), 44 (100).

7. *3-(6-Oxo-1,5-diazacycloheptadec-5-yl)propionitrile* (**4**). A soln. of *7-(2-oxo-1-azacyclotridec-1-yl)-4-aza-heptanenitrile-hydrochloride* (**3**·HCl, 100 mg), and 2,4-dimethylpyridine (10 ml) under Ar was refluxed for 5 h. After evaporation the residue was crystallized: **4**·HCl (75 mg, 75%). The mother liquor contained besides **4** only starting material **3**. M.p. 168–169° ($EtOH/Et_2O$). The identification (TLC, IR, mixed m.p.) was achieved by comparison with a known compound [4] [5].

Reaction of **4** *with* t-*BuOK*. A soln. of **4** (54 mg, [5]) and *t*-BuOK (20 mg) in toluene (50 ml) was boiled under reflux for 5 min and worked up as usual *(Exper. 1.1)*: *1,5-diazacycloheptadecan-6-one* (**9**, 41 mg, 92%) which was identified by comparison (TLC, MS) with an authentic sample [4]. The same result was achieved when only catalytic amounts of *t*-BuOK were used.

8. *Synthesis of 1,12-diazabicyclo[8.5.1]hexadecan-16-one* (**14**). – 8.1. *7-(2-Oxo-1-azacycloundec-1-yl)-4-aza-heptanenitrile* (**13**). In acrylonitrile (195 ml) 1-(3-aminopropyl)-1-azacycloundecan-2-one [7] (9 g) was solved at 20° according to [4]. After evaporation, the residue was treated with $CHCl_3$/MeOH 46:1 and filtered through silica gel to give **13** (9.4 g, 85%). B.p. 190°/0.01 Torr, m.p. 141–143° (Et_2O/pentane). IR: 2248 (CN), 1618 (*N,N*-disubst. amide). ^{1}H-NMR: 3.99–3.11 (*m*, 2 CH_2NCO); 2.92 (*t*, *J* = 6.7, CH_2CN); 2.76–2.34 (*m*, CH_2N, CH_2CON), therein at 2.62 (*t*, *J* = 6.7, CH_2N); 2.26–1.0 (*m*, 17H). MS: 279 (16, M^+), 240 (7), 239 (36), 210 (12), 197 (7), 196 (28), 183 (14), 182 (27), 170 (31), 168 (14), 166 (7), 155 (9), 154 (18), 152 (6), 142 (5), 141 (8), 140 (54), 138 (6), 127 (13), 126 (42), 114 (6), 113 (11), 112 (16), 111 (6), 110 (20), 109 (8), 101 (12), 100 (9), 99 (8), 98 (18), 97 (25), 96 (6), 87 (13), 86 (8), 84 (17), 83 (36), 82 (6), 81 (6), 73 (5), 72 (10), 71 (8), 70 (50), 69 (16), 68 (8), 67 (7), 58 (32), 57 (17), 56 (39), 55 (38), 54 (16), 53 (7), 45 (5), 44 (100).

8.2. **14**: According to *Exper. 1.1*, the reaction of **13** (1.03 g) in the presence of *t*-BuOK (829 mg) in toluene (400 ml) gave **14** (528 mg, 60%). B.p. 150°/0.01 Torr. IR: 3370, 1634. ^{1}H-NMR: 4.53 (*ddd*, *J* = 13.8, 9.6, 5.6, H–C(2)); 4.01 (*ddd*, *J* = 15.0, 11.9, 3.0, H–C(15)); 3.19 (*dt*, *J* = 19.8, 3.2, H–C(15)); 3.11–9.97 (*m*, H–C(10)); 2.90–2.72 (*m*, 2H–C(11), 2H–C(13)); 2.65 (*dt*, *J* = 13.8, 4.3, H–C(2)); 2.0–1.48 (*m*, 8H, therein at 1.75 (*s*, HN)); 1.48–0.94 (*m*, 9H). MS: 238 (23, M^+), 210 (6), 209 (5), 196 (7), 195 (12), 182 (11), 181 (14), 170 (5), 168 (6), 167 (9), 166 (6), 155 (6), 154 (7), 153 (6), 152 (9), 141 (5), 140 (7), 138 (6), 127 (7), 126 (8), 125 (7), 124 (6), 113 (11), 112 (10), 111 (6), 110 (7), 100 (9), 99 (39), 98 (14), 96 (11), 85 (13), 84 (18), 83 (13), 82 (9), 81 (6), 72 (8), 71 (14), 70 (52), 69 (45), 68 (13), 67 (7), 58 (22), 57 (26), 56 (46), 55 (41), 54 (7), 53 (6), 45 (4), 44 (100).

9. *7-(2-Oxo-1-azacyclonon-1-yl)-4-azaheptanenitrile* (**15**). A soln. of 1-(3-aminopropyl)-1-azacyclononan-2-one [7] (1.347 g) in acrylonitrile was allowed to stand for 4 h at 20°. After evaporation the residue was filtrated through a short column (silica gel, $CHCl_3$/MeOH 95:5): **15** (1.41 g, 83%) as a colorless oil. IR: 2250, 1618. ^{1}H-NMR: 3.60–3.20 (*m*, 2 CH_2NCO); 2.91 (*t*, *J* = 6.8, CH_2CN); 2.62 (*t*, *J* = 6.8, CH_2N); 2.56–2.34 (*m*, CH_2N, CH_2CON); 1.89–1.00 (*m*, 13H). MS: 251 (14, M^+), 211 (25), 182 (21), 169 (6), 168 (30), 155 (13), 154 (18), 142 (30), 140 (18), 138 (11), 137 (7), 127 (19), 126 (53), 114 (10), 113 (21), 112 (44), 110 (15), 109 (7), 99 (9), 98 (14), 97 (17), 87 (12), 86 (7), 84 (14), 83 (28), 72 (9), 71 (8), 70 (45), 69 (10), 68 (12), 58 (37).

From the treatment of **15** (50 mg) in toluene (50 ml) with *t*-BuOK (22 mg) for 1 h under reflux, no product was formed. After addition of more *t*-BuOK (22 mg) and boiling for 0.5 h, besides traces of **15**, no products could be detected (TLC).

10. *Synthesis of 1,3-Dimethyl-1,5-diazacyclooctan-2-one* (**18**). – 10.1. *N-(6-Cyano-4-azahexyl)-N-methyl-propionamide* (**17**). According to [4], *N*-(3-aminopropyl)-*N*-methylpropionamide [11] (209 mg) was treated with acrylonitrile (7 ml) and worked up. By chromatography, pure **17** (184 mg, 64%[7])) was isolated. B.p. 140°/0.01 Torr. IR: 2255, 1630. ^{1}H-NMR: 3.64–3.22 (*m*, 2H); 2.96 (*s*, CH_3); 2.90 (*t*, *J* = 6.8, 2H); 2.74–2.43 (*m*, 4H); 2.43–2.12 (*m*, 2H); 1.92–1.51 (*m*, 3H); 1.15 (*t*, *J* = 7.3, CH_3). MS: 197 (7, M^+), 157 (12), 128 (11), 115 (8), 114 (9), 110 (11), 101 (23), 100 (12), 98 (5), 97 (16), 88 (9), 87 (5), 86 (6), 83 (16), 73 (7), 72 (8), 71 (8), 70 (32), 69 (5), 68 (6), 59 (5), 58 (44), 57 (35), 56 (22), 55 (7), 54 (13), 45 (35), 44 (100).

10.2. **18**: Compound **17** (724 mg), *t*-BuOK (824 mg), and toluene (500 ml) were treated and worked up as in *Exper. 1.1* to yield after chromatography (silica gel, $CHCl_3$/MeOH 19:1) pure **18** (237 mg, 41%). IR: 3410, 1623. ^{1}H-NMR: 4.12 (*ddd*, *J* = 15.1, 12.8, 3.4, H–C(8)); 3.11 (*ddd*, *J* = 15.1, 4.2, 2.5, H–C(8)); 3.03–2.83 (*m*, H–C(3), H–C(4), H–C(6), therein at 2.92 *s*, CH_3N); 2.67 (*dd*, *J* = 13, 11, H–C(4)); 2.46 (*ddd*, *J* = 14.2, 9.9, 3.7, H–C(6));

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[7]) Under the reaction conditions, *N*-(3-aminopropyl)-*N*-methylpropionamide rearranged in part to *N*-(3-methylaminopropyl)propionamide which explains the low yield of **17** [11].

1.96 (*s*, HN); 1.80 (*ddddd*, J = 13.7, 9.9, 4.4, ≈4, ≈4, H–C(7)); 1.67–1.44 (*m*, H–C(7)); 1.05 (*d*, J = 6.3, CH_3–C(3)). Decoupling experiments: irradiation: 1.80→4.12 (*d*, J = 15.1), 3.11 (*d*, J = 15.1), 2.46 (*dd*, J = 14.2, 3.7), 1.67–1.44 (change); 1.67–1.44→4.12 (*dd*, J = 15.1, 12.8), 3.11 (*dd*, J = 15.1, 4.2), 2.46 (*d*, J = 14.2). MS: 156 (66, M^+), 128 (25), 113 (16), 100 (9), 99 (49), 98 (15), 88 (10), 83 (16), 72 (12), 71 (27), 70 (57), 69 (32), 68 (17), 58 (94), 57 (50), 56 (32), 55 (10), 45 (9), 44 (100).

11. *Synthesis of 1-Hexyl-3-pentyl-1,5-diazacyclooctan-2-one* (**20**). – 11.1. *N-(6-Cyano-4-azahexyl)-N-hexylheptaneamide* (**19**). *N*-(3-Aminopropyl)-*N*-hexylheptaneamide (4 g) [11] was treated with acrylonitrile (65 ml) at 20° according to [4]. After workup and chromatography, **19** (3.65 g, 79%) was isolated. B.p. 190°/0.01 Torr. IR: 2248, 1625. ^{1}H-NMR: 3.46–3.04 (*m*, 2 CH_2NCO); 2.96–2.79 (*m*, CH_2CN); 2.70–2.37 (*m*, 2 CH_2N); 2.37–2.12 (*m*, CH_2CON); 1.90–1.40 (*m*, 7H); 1.40–1.08 (*m*, 12H); 1.03–0.60 (*m*, 2 CH_3). MS: 323 (6, M^+), 283 (11), 254 (6), 214 (19), 210 (13), 184 (11), 170 (20), 156 (8), 142 (31), 140 (6), 128 (36), 115 (6), 114 (50), 110 (9), 109 (5), 101 (8), 100 (9), 97 (10), 87 (13), 85 (7), 84 (5), 83 (16), 72 (6), 70 (24), 69 (5), 58 (18), 57 (15), 56 (18), 55 (17), 54 (6), 44 (5), 43 (100).

11.2. **20**: Compound **19** (905 mg), *t*-BuOK (629 mg), and toluene (600 ml) were treated and worked up as described in *Exper. 1.1* to yield, after chromatography ($CHCl_3$/MeOH 19:1), **20** (443 mg, 56%[8]). IR: 3350, 1625. ^{1}H-NMR: 4.11–3.67 (*m*, 2H); 3.21 (*dt*, J = 15.5, 3.1, 1H); 3.02–2.36 (*m*, 6H); 1.94–1.42 (*m*, 5H); 1.42–1.04 (*m*, 14H); 1.04–0.65 (*m*, 2 CH_3). MS: 282 (14, M^+), 254 (7), 239 (9), 226 (6), 225 (32), 214 (16), 211 (9), 197 (6), 196 (12), 184 (5), 183 (6), 182 (7), 170 (17), 169 (29), 168 (6), 155 (5), 142 (7), 141 (6), 140 (17), 130 (5), 129 (5), 128 (33), 127 (7), 126 (34), 114 (30), 113 (14), 112 (33), 101 (5), 100 (9), 99 (30), 98 (16), 97 (5), 96 (6), 85 (16), 84 (16), 83 (8), 82 (7), 72 (7), 71 (12), 70 (52), 69 (59), 68 (13), 59 (8), 58 (29), 57 (20), 56 (39), 55 (25), 44 (100).

12. *Reaction of 7-(2-Oxo-1-azacyclotridec-1-yl)-4-methyl-4-azaheptanenitrile* (**23**) *with* t-*BuOK. – Synthesis of* **23**. Compound **3**, prepared from 482 mg of its hydrochloride, was methylated with CH_2O/$NaBH_4$ as described in *Exper. 4*. After workup, the crude product was purified by chromatography (silica gel, hexane/acetone 3:2) and distilled (190°/0.01 Torr) to give **23** (193 mg, 43%). IR: 2230, 1625. ^{1}H-NMR: 3.46–3.06 (*m*, 4H); 2.85–2.60 (*m*, 2H); 2.60–2.00 (*m*, 6H); 2.27 (*s*, CH_3N); 2.00–1.15 (*m*, 20H). MS: 321 (26, M^+). 281 (7), 268 (6), 167 (10), 254 (5), 238 (20), 224 (9), 211 (7), 210 (6), 198 (5), 126 (6), 124 (16), 112 (12), 111 (32), 98 (12), 97 (69), 84 (21), 70 (28), 69 (9), 58 (41), 57 (20), 56 (25), 55 (29), 54 (12), 45 (8), 44 (62).

Reaction of **23**. A soln. of **23** (94 mg), toluene (100 ml), and *t*-BuOK (33 mg) was refluxed for 3 h. Since no reaction had taken place, another batch of t-BuOK (40 mg) was added and boiled further for 3 h. After workup the crude product was separated by prep. TLC (silica gel, lower phase of $CHCl_3$/MeOH/25proz. NH_3 soln. 98:2:10) to give three products which were identified by comparison (TLC, MS) with authentic materials: **23** (3 mg), *1-(3-methylaminopropyl)-1-azacyclotridecan-2-one* (**24**) [7], and *5-methyl-1,5-diazacycloheptadecan-6-one* (**25**) [7].

13. *3-(2'-Azahexyl)-1-methyl-2-pyrrolidone* (**29**). A soln. of *1-methyl-2-pyrrolidone* (**28**, 0.07 ml), *3-azaoctanenitrile* (**26**, 100 mg, prepared from $BuNH_2$ and acrylonitrile), *t*-BuOK (177.5 mg), and dry toluene (70 ml) was boiled under reflux for 3 h, and worked up (see *Exper. 1.1*). The crude product was separated by TLC (silica gel, $CHCl_3$/MeOH 9:1) to give **29** (55.2 mg, 38%) as the main component. B.p. 110°/0.1 Torr. IR: 3360 (NH), 1672 (*N,N*-disubst. amide). ^{1}H-NMR: 3.37 (*dd*, J = 8.5, 1.1, H–C(5)); 3.33 (*d*, J = 8.5, H–C(5)); 3.04–2.76 (*m*, 2H–C(1') with *s* at 2.85, CH_3(N)); 2.76–2.56 (*t*-like *m*, 2H–C(3'), H–C(3)); 2.50 (br. *s*, HN); 2.32–2.09 (*m*, H–C(4)); 1.96–1.70 (*m*, H–C(4)); 1.60–1.22 (*m*, 2H–C(4'), 2H–C(5')); 0.91 (*t*, J = 7.1, H_3C(6')). MS: 184 (5, M^+), 141 (46), 112 (9), 99 (37), 98 (47), 86 (23), 72 (21), 71 (7), 70 (11), 57 (10), 56 (7), 55 (28), 44 (100).

14. *3-(2'-Azadecyl)-1-methyl-2-pyrrolidone* (**30**). According to *Exper. 13*, from **28** (0.05 ml), 3-azadodecanenitrile (**27**, 100 mg, prepared from octylamine and acrylonitrile), *t*-BuOK (123.4 mg), and dry toluene (70 ml), **30** (63.4 mg, 48%, distilled at 130–140°/0.1 Torr) was prepared. IR: 3310, 1672. ^{1}H-NMR: 3.37 (*dd*, J = 8.6, 1.1, H–C(5)); 3.33 (*d*, J = 8.7, H–C(5)); 3.00–2.76 (*m*, 2H–C(1') with *s* at 2.85, CH_3N); 2.76–2.54 (*t*-like *m*, 2H–C(3'), H–C(3)); 2.35 (br. *s*, HN); 2.30–2.08 (*m*, H–C(4)); 1.96–1.69 (*m*, H–C(4)); 1.69–1.11 (*m*, 12 H); 0.88 (*t*, J = 6.4, H_3C(10')). MS: 240 (4, M^+), 142 (26), 141 (100), 128 (30), 127 (10), 113 (8), 112 (13), 100 (9), 99 (49), 98 (41), 85 (7), 84 (7), 70 (6), 55 (14), 44 (67).

[8]) The formation of polar products during the reaction is responsible for the low yield of **20**.

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