111. N^4-Benzoylspermidine from *Oncinotis tenuiloba*: Analytical Differentiation of the Three Isomeric *N*-Benzoylspermidines

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During the examination of extracts from *Oncinotis tenuiloba* STAPF a new polyamine, N^4-benzoylspermidine (**8**), was isolated. For unambiguous structure elucidation, it was transformed into the diacetyl derivative **13**, and the three possible *N*-benzoyl-substituted isomers of spermidine **5**, **8**, and **11** together with their peracetylated derivatives **12–14**, respectively, were synthesized and identified.

Introduction. – The polyamines putrescine (= butane-1,4-diamine), spermidine (= *N*-(3-aminopropyl)butane-1,4-diamine), spermine (= *N*,*N*′-bis(3-aminopropyl)-butane-1,4-diamine), and further biogenic amines are the basic part of a group of naturally occurring compounds, the polyamine alkaloids. Broad interest in such compounds developed, since they were found to play important roles in many medicinal aspects. The increased level of polyamines found in human carcinoma cells [1] or the presumed regulatory role in synaptic transmission by interaction between the negatively charged groups of the synaptic membrane with the polycationic form of the polyamines [2] are only two examples indicating the broad pharmacological significance of the polyamines. Furthermore, it should be noted that the neurotoxic spider and wasp toxins also contain an acyl-polyamine part in their structures [3]. During the investigation of some species of the genus *Oncinotis* (Apocynaceae), several spermidine alkaloids have been isolated. The first one was oncinotine found in *O. nitida* BENTH, a macrocyclic lactam alkaloid containing additionally a piperidine ring [4]. In *O. inandensis* WOOD *et* EVANS several inandeninones were detected, and some of them have been isolated. In these inandeninones, spermidine is cyclized with 9-oxo- and 10-oxopalmitic acid to give two isomeric compounds, which have not been separated so far [5]. Other naturally occurring polyamines of a linear structure, partially acylated or alkylated have already been found in the tissues of numerous plants and animals [3] [6] [7]. We now investigated the extracts obtained from the leaves of *O. tenuiloba* STAPF, and succeeded in isolating a novel polyamine alkaloid, N^4-benzoylspermidine[2]) (**8**), which was accompanied by other alkaloids. Its structure was established by spectroscopic means and comparison with the synthetic isomeric benzoylspermidines **5**, **8**, and **11**, and corresponding diacetyl derivatives **12–14**.

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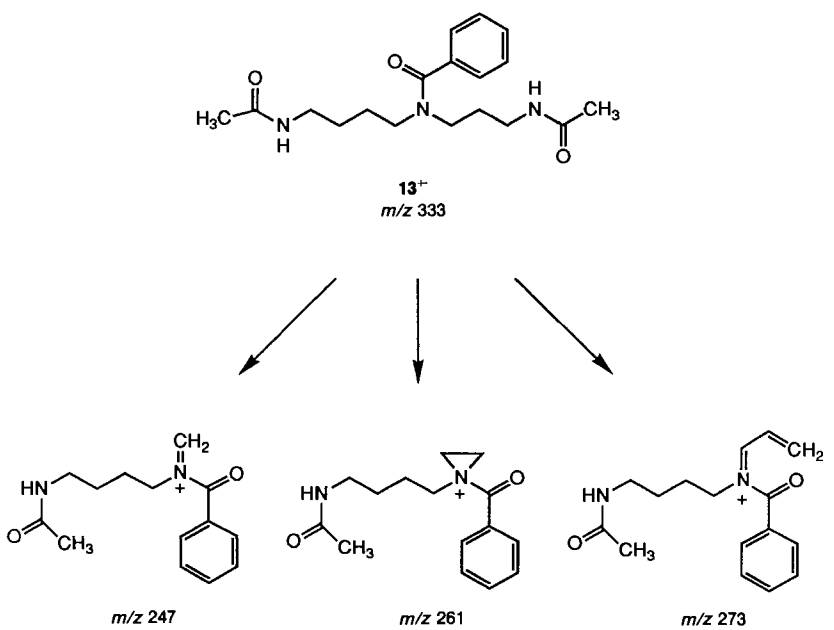
[1]) Part of the planned Ph. D. Thesis of *M.K.-H.D.*, Universität Zürich.

[2]) From 1 kg of the dry leaves, *ca.* 10 mg of this compound could be obtained; more details of the isolation and purification will be reported later [8]. Five years ago, *Alemayehu et al.* reported the isolation of a N^1,N^8-dibenzoylspermidine from the leaves of *Cassia floribunda* CAV. (Leguminosae) [9] as the first naturally occurring benzoylated polyamine.

Results and Discussion. – In the mass spectrum (CI mode), the natural compound **8** showed the $[M + 1]^+$ ion at m/z 250. Exhaustive acetylation by treatment with Ac_2O and NaOAc resulted in the diacetyl derivative **13** with a molecular weight of 333. Mass spectra (EI) of the non-acetylated **8** showed the most abundant fragment ion at m/z 105, indicating benzoyl substitution, and the ^{1}H-NMR spectrum of the dihydrochloride **8**·2 HCl exhibited signals corresponding to five aromatic protons.

Since polyamine alkaloids are known to occur also in other *Oncinotis* species and, in our case, acetylation proceeded in two positions, we considered the presence of a polyamine moiety (*e.g.* putrescine, an isomer or an homologue, or spermidine), supported by the low molecular weight determined. Most important is the fact that polyacetyl derivatives of polyamines show a characteristic fragmentation in their MS (EI mode), giving rise to the so-called *peak triade* [10]. Accordingly, if the diacetyl derivatives of N^4- or N^8-benzoylspermidine are taken into consideration the peak triade m/z 247, 261, and 273 should be observed (different from that of the N^1-benzoylated isomer[3]), because the fragmentation takes place at the C_3 chain and, thus, the benzoyl group would be removed to give a peak triade with lower m/z values). Since this fragmentation pattern was observed in the EI-MS of the *N,N'*-diacetyl derivative **13** of **8** (*Scheme 1*), the latter could be a N^4- or N^8-monobenzoylspermidine. Unfortunately, it was not possible to determine the benzoylation site of **8** only by interpretation of its spectroscopic data. Thus, for direct

Scheme 1. *Peak Triade of* **13** *Observed in EI-MS*

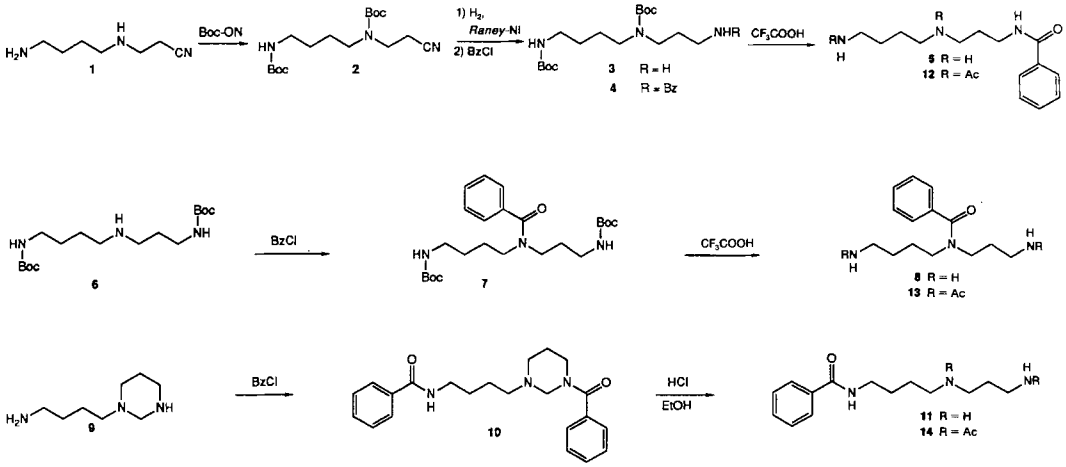


[3]) For convenience, the following numbering of spermidine is used: $H_2NCH_2(1)CH_2CH_2(3)NH(4)CH_2(5)CH_2CH_2CH_2(8)NH_2$.
For systematic names, *cf.* the *Exper. Part.*

comparison and for the unambiguous structure elucidation, we synthesized the three isomers, **5**, **8**, and **11**, and their corresponding *N,N'*-diacetyl derivatives **12–14**.

Synthesis (*Scheme 2*). The synthesis of N^1-benzoylspermidine (**5**) was best accomplished by monocyanoethylation of putrescine with acrylonitrile according to *Israel et al.* [11] affording 3-[(4-aminobutyl)amino]propanenitrile (**1**), which was then bis-protected by treatment with 2-{[(*tert*-butoxy)carbonyl]oxyimine}-2-phenylacetonitrile (Boc-ON) [12] to yield **2**. After catalytic reduction [13] (→ **3**), acylation by benzoyl chloride [13] [14] (→ **4**), removal of the protecting groups by treatment with CF_3COOH [13], and chromatographic purification, the desired N^1-benzoylated compound **5** was obtained. The isomeric N^4-benzoylspermidine (**8**) was obtained similarly by benzoylation of N^1,N^8-bis[-(*tert*-butoxy)carbonyl]spermidine (**6**; prepared according to [15]), deprotection of **7** and purification.

Scheme 2



For the preparation of N^8-benzoylspermidine (**11**), we followed the procedure of *Tice* and *Ganem* to prepare N^1-acetylspermidine [16]. Thus, *N*-(4-aminobutyl)hexahydropyrimidine (**9**; prepared according to [16]) was treated with benzoyl chloride to yield the corresponding bis-benzoylated compound **10** from which the benzoyl group at the heterocycle, was selectively removed during hydrolysis of the aminal in HCl/EtOH to form **11**. The monobenzoylspermidines **5**, **8**, and **11** were acetylated to the corresponding diacetyl derivatives **12**, **13**, and **14**, respectively.

Analytical Differentiation of Isomers. Comparison of the MS (EI mode) of the peracetylated natural product with those of the three synthetic isomers **12–14** showed, that synthetic **13** leads to the same spectrum as the natural product including the peak triade *m/z* 247, 261, and 273 (see *Scheme 1*), and a clear difference in peaks and intensities compared to the MS of the two other isomers **12** and **14**. In all three MS, the signal at *m/z* 105 was most abundant (base peak). Comparison of the ^{1}H- and ^{13}C-NMR spectra of the acetylated and non-acetylated compounds confirmed the identity of **8** with the natural product.

The spectrum of **8** was clearly distinct from those of the two other isomers **5** and **11**. It displayed extensive broadening and shoulder formation, and most surprisingly a different resonance for the aromatic protons: while

the terminally substituted compounds **5** and **11** exhibited two clearly separated *multipletts* with the *ortho* H-atoms shifted *ca.* 0.3 ppm downfield, the five aromatic protons of **8** gave rise to one single *multiplett*. This could be explained by considering **8** as a *N,N*-disubstituted benzamide where the more bulky *N*-substitution causes a reduced coplanarity of the amide linkage and, therefore, a reduced delocalization of the electrons over the Ar–CO–NR_2 system, in contrast to **5** and **11** which can be regarded as *N*-monosubstituted benzamides. As a consequence the two *ortho* H-atoms of **8** are less deshielded than those of **5** and **11**. The same effect was observed in the ^{1}H-NMR of the corresponding *N,N'*-diacetylated compounds **12–14**; furthermore, the spectrum of **13** was identical to that of the diacetylated natural product. The reduced coplanarity of the amide linkage in **8** is also supported by the ^{13}C-NMR spectra. It results in a lower electron density at the carbonyl C-atom, because the $+M$ effect of the N-atom is reduced. Consequently, the resonance of the CO group of **8** is shifted downfield (174.8 ppm) than in **5** (171.0 ppm) and **11** (173.5 ppm; see *Exper. Part*).

Although no striking difference in polarity would be expected, the three polyamines **5**, **8**, and **11** can be distinguished from each other even by TLC due to their slightly different R_f values and color reaction when detected with the *Schlittler* reagent. Compound **8** is a little less polar than its isomer **5** and **11** and showed the same TLC properties as the natural substance (see *Exper. Part*). Also for the *N,N'*-diacetyl derivatives **12–14** slightly different R_f values were observed, the N^4-substituted compound **13** being, in this case, more polar than **12** and **14**. A clear differentiation could be done by HPLC too, with compound **13** showing the same retention time as the diacetylated alkaloid (see *Fig.*).

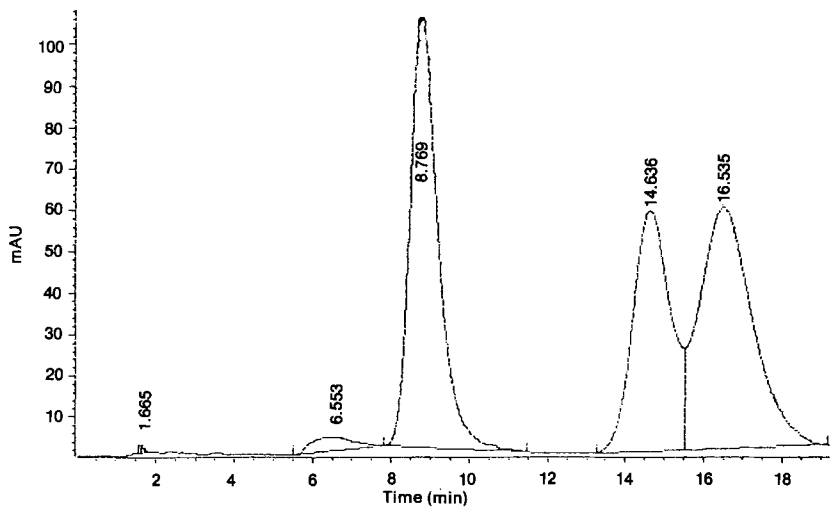


Figure. *HPLC Separation of the three isomers* **12–14**. System: *MN Nucleosil 7* C_{18}, MeOH/H_2O 1:3, 1.5 ml/min. Retention times: **13**: 8.769, **14**: 14.636, and **12**: 16.535 min

Undoubtedly, the natural alkaloid is N^4-benzoylspermidine (**8**).

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Experimental Part

General. The leaves of *O. tenuiloba* STAPF were collected in Kenya in 1989 by Mr. *G. M. Mungai* (E.A. Herbarium, P.O. Box 45166, Nairobi). All commercially available chemical reagents were used without further purification. TLC: silica gel *60* F_{254} precoated plates (*Merck*); for *Schlittler* reagent, see [17]. Column chromatography (CC): silica gel *60* (0.063–0.200 mesh; *Merck*). IR [cm^{-1}]: *Perkin-Elmer 781*. NMR: *Bruker AC-300*, *Bruker AM-400*, and *Bruker XL-200*; δ in ppm and J in Hz using the appropriate solvent as internal standard. MS: *Finnigan MAT SSQ 700*, *Finnigan MAT 90*; chemical ionisation (CI) with NH_3.

3-[(4-Aminobutyl)amino]propanenitrile (**1**). According to [11] acrylonitrile (15.9 g, 0.3 mol) was added within 30 min dropwise to butane-1,4-diamine (26.4 g, 0.3 mol) while stirring and cooling (ice-bath). After 15 min, the mixture was heated to 50° for 3 h and stirred at 23° overnight. Fractional distillation gave 15.9 g (38%) of **1**. B.p. $94°/5 \cdot 10^{-2}$ Torr.

tert-*Butyl* N-{4-{[(tert-*Butyloxy)carbonyl]amino}butyl}-N-(2-cyanoethyl)carbamate* (**2**). To a soln. of **1** (10.0 g, 0.07 mmol) and Et_3N (22.0 g) in dioxane/H_2O 9:1 (250 ml) was added in small portions Boc-ON (35.0 g, 0.14 mol). The flask was protected against light and the mixture stirred at 23° for 3 d. After evaporation, the crude material was dissolved in Et_2O (200 ml) and the extract washed with 1N aq. NaOH (3 × 50 ml) and brine (2×), dried (Na_2SO_4), and evaporated: 23.9 g of crude product. CC (hexane/Et_2O 1:1→Et_2O) yielded 19.8 g (84%) of colorless, oily **2**. ^{1}H-NMR: identical with that in [12] (yield: 70%). CI-MS: 359 (81, $[M + NH_4]^+$), 342 (63, $[M + 1]^+$), 303 (100), 286 (7), 247 (61), 242 (6).

tert-*Butyl* N-*(3-Aminopropyl)*-N-{4-{[(tert-*butyloxy)carbonyl]amino}butyl}carbamate* (**3**). In a soln. of NaOH (1.8 g) in 94% EtOH (40 ml) was dissolved **2** (6.0 g, 17.6 mmol), followed by addition of *Raney*-Ni (1.2 g). The mixture was continuously shaken overnight under H_2 (3.5 bar). After filtration through *Celite*®, the soln. was concentrated *in vacuo* to *ca.* 10 ml and diluted with H_2O (60 ml). Extraction with CH_2Cl_2 followed by drying (Na_2SO_4) and evaporation gave 4.94 g (82%) of **3**. Slightly yellow oil. ^{1}H-NMR ($CDCl_3$): 4.60 (*s*, NH); 3.40–3.30 (*m*, 2 H–C(1'), 2 H–C(1), 2 H–C(4)); 2.69 (*t*, J = 6.7, 2 H–C(3')); 1.82–0.98 (*m*, 2 H–C(2'), 2 H–C(2), 2 H–C(3), 2 *t*-Bu). CI-MS: 346 (100, $[M + 1]^+$), 290 (25), 246 (44).

tert-*Butyl* N-*[3-(Benzamido)propyl]*-N-{4-{[(tert-*butyloxy)carbonyl]amino}butyl}carbamate* (**4**). A soln. of **3** (4.0 g, 11.6 mmol) and Et_3N (1.54 g, 15.2 mmol) in CH_2Cl_2 (160 ml) was stirred under N_2 and cooled to 0°. Within 45 min, a soln. of benzoyl chloride (1.85 g, 13.1 mmol) in CH_2Cl_2 (17 ml) was added, the resulting mixture allowed to warm to 23°, and stirring continued for 18 h. After addition of CH_2Cl_2 (50 ml), the org. phase was washed with 3% aq. HCl soln. (3×, overall 100 ml), H_2O (3 × 30 ml), 5% aq. $NaHCO_3$ soln., and again H_2O, dried (Na_2SO_4), and evaporated: 4.63 g of crude product. CC (AcOEt/hexane 3:2) gave 3.33 g (64%) of **4**. Highly viscous, colorless oil. IR ($CHCl_3$): 3450*w*, 3350*w*, 3070*m*, 2930*m*, 1710*s*, 1660*s*, 1510*m*, 1480*m*, 1450*m*, 1420*m*, 1365*m*, 1305*m*, 1250*m*, 1165*s*. ^{1}H-NMR ($CDCl_3$): 7.89–7.72 (*m*, 2 H_o); 7.52–7.41 (*m*, 2 H_m, H_p); 3.48–3.36 (*m*, 2 H–C(3), 2 H–C(4')); 3.20–3.13 (*m*, 2 H–C(1), 2 H–C(1')); 1.75–1.44 (*m*, 2 H–C(2), 2 H–C(2'), 2 H–C(3'), 2 *t*-Bu). ^{13}C-NMR ($CDCl_3$): 167.1 (*s*, PhCO); 156.0 (*s*, 2 CO (Boc)); 136.4 (*s*, C_{ipso}); 131.1 (*d*, C_p); 128.4 (*d*, C_o); 127.0 (*d*, C_m); 79.9, 79.2 (2*s*, Me_3C); 46.6 (2*t*, C(1), C(1')); 43.4, 40.0, 35.8 (3*t*, C(3), C(2), C(4')); 28.4 (*q*, 2 Me_3C); 27.4, 25.7 (2*t*, C(2'), C(3')). CI-MS: 450 (76, $[M + 1]^+$), 350 (100), 294 (12). EI-MS: 449 (< 5, $M^{+\cdot}$), 349 (13), 276 (27), 191 (70), 179 (27), 171 (30), 162 (50), 105 (97, $[C_6H_5CO]^+$), 57 (100, $[t\text{-Bu}]^+$).

N-*(8-Amino-4-azaoctyl)benzamide* (= N-{3-[(4-*Aminobutyl)amino]propyl*}*benzamide*; **5**). To **4** (0.85 g, 1.89 mmol) CF_3COOH (25 ml) was added, the resulting mixture stirred for 2 h, then evaporated, and several times co-evaporated with MeOH, and the residue dried at 10^{-2} Torr. CC ($CHCl_3$/MeOH/conc. NH_4OH soln. 7:3:1) gave **5** (0.40 g, 85%). TLC ($CHCl_3$/MeOH/conc. NH_4OH soln. 7:3:1): R_f 0.070. Colorless viscous oil. The colorless amorphous **5**·2 HCl was prepared by evaporating **5** in HCl/MeOH. IR (KBr; **5**·2 HCl): 3320*m*, 2950*m*, 2780*m*, 2520*m*, 2440*m*, 1675*s*, 1640*s*, 1575*m*, 1530*s*, 1460*m*, 1430*m*, 1315*s*, 1200*s*, 1130*m*, 1085*w*, 1010*w*, 895*w*, 830*w*, 795*m*, 720*s*, 690*s*. ^{1}H-NMR (CD_3OD; **5**·2 HCl): 7.75–7.72 (*m*, 2 H_o); 7.45–7.33 (*m*, 2 H_m); 3.43–3.39 (*t*-like *m*, 2 H–C(1)); 2.96 (*t*, J = 7.2, 2 H–C(3), 2 H–C(5)); 2.91–2.86 (*t*-like *m*, 2 H–C(8)); 1.89 (*q*, J = 6.7, 2 H–C(2)); 1.70–1.67 (*m*, 2 H–C(6), 2 H–C(7)). ^{13}C-NMR (CD_3OD; **5**·2 HCl): 171.0 (*s*, PhCO); 135.0 (*s*, C_{ipso}); 132.9 (*d*, C_p); 129.6 (*d*, C_o); 128.4 (*d*, C_m); 48.2 (*t*, C(1)); 46.6 (*t*, C(8)); 40.1, 37.5 (2*t*, C(3), C(5)); 27.7 (*t*, C(2)); 25.6, 24.3 (2*t*, C(6), C(7)). CI-MS: 250 ($[M + 1]^+$). EI-MS: 250 (< 5, $M^{+\cdot}$), 191 (54), 162 (46), 105 (100, $[C_6H_5CO]^+$), 84 (33), 77 (43), 70 (35), 69 (27), 51 (20), 45 (23), 44 (20).

tert-*Butyl* N-{4-{N-*Benzoyl*-N-{3-[(tert-*butyloxycarbonyl)amino]propyl*}*amino*}*butyl*}*carbamate* (**7**). As described for **4**, from tert-*butyl* N-{4-{N-{3-[(tert-*butyloxycarbonyl)amino]propyl*}*amino*}*butyl*}*carbamate* (**6**; 2.00 g, 5.80 mmol): **7** (2.1 g, 81%). Colorless resin. IR ($CHCl_3$): 3450*w*, 2980*w*, 2930*w*, 1705*s*, 1620*s*, 1510*s*, 1365*m*, 1250*m*, 1165*s*. ^{1}H-NMR ($CDCl_3$): 7.41–7.32 (*m*, Ph); 3.58–3.47 (*m*, 2 H–C(3')); 3.21–3.19 (*m*, 2 H–C(1'), 2 H–C(4)); 2.97–2.90 (*m*, 2 H–C(1)); 1.80–1.24 (*m*, 2 H–C(2'), 2 H–C(3), 2 H–C(2), 2 *t*-Bu). ^{13}C-NMR ($CDCl_3$):

172.3 (*s*, PhCO); 156.0, 155.9 (2*s*, CO(Boc)); 136.7 (*s*, C_{ipso}); 129.3 (*d*, C_p); 128.5 (*d*, C_o); 126.2 (*d*, C_m); 79.2, 79.1 (2*s*, Me_3C); 48.7, 41.7, 39.9, 37.5 (4*t*, C(3'), C(1'), C(4), C(1)); 27.9, 27.2, 25.8 (3*t*, C(2'), C(3), C(2)). CI-MS: 467 (< 5, $[M + NH_4]^+$), 450 (100, $[M + 1]^+$), 350 (59), 250 (< 5). EI-MS: 349 (7, $[M - Boc + 1]^+$), 292 (36), 276 (40), 214 (22), 106 (20), 106 (100, $[C_6H_5CO]^+$), 77 (45), 70 (26), 57 (54), 41 (32).

N-*(4-Aminobutyl)*-N-*(3-aminopropyl)benzamide* (**8**). As described for **5** and **5**·2 HCl, from **7** (0.65 g, 1.45 mmol): **8** (0.31 g, 86%). Colorless viscous oil (**8**) and amorphous colorless solid (**8**·2 HCl). IR ($CHCl_3$; **8**): 3660*w*, 3360*m*, 2920*s*, 2860*s*, 2480*w*, 1700*m*, 1670*s*, 1620*s*, 1495*m*, 1425*s*, 1375*s*, 1300*m*, 1090*m*, 1050*w*, 880*w*, 695*s*, 655*s*. ^{13}C-NMR (CD_3OD; **8**·2 HCl): 174.8 (*s*, PhCO); 137.4 (*s*, C_{ipso}); 130.9 (*d*, C_p); 129.9 (*d*, C_o); 127.5 (*d*, C_m); 50.2 (*t*, C(2")); 43.1 (*t*, C(1')); 40.3, 38.5 (2*t*, C(3"), C(4')); 26.9, 26.7, 25.6 (3*t*, C(2"), C(2'), C(3')). Additonal data: see below.

Natural Product **8**. TLC ($CHCl_3$/MeOH/conc. NH_4OH soln. 7:3:1, R_f 0.109): ^{1}H-NMR ($CDCl_3$; **8**·2 HCl): 7.37–7.29 (*m*, Ph); 3.58–3.53 (*m*, 2 H–C(1")); 3.26–3.24 (*m*, 2 H–C(1')); 2.95–2.90 (*m*, 2 H–C(3")); 2.70–2.62 (*m*, 2 H–C(4')); 1.98–1.94 (*q*-like *m*, 2 H–C(2")); 1.67–1.34 (*m*, 2 H–C(2'), 2 H–C(3')); all signals unusually broad, no improvement on temperature variation. CI-MS: 250 ($[M + 1]^+$). EI-MS: 248 (< 5, $[M - 1]^+$), 191 (13), 179 (19), 162 (22), 105 (100, $[C_6H_5CO]^+$), 84 (17), 77 (51), 70 (39). Other data: identical to those of synthetic **8**.

N-*[4-(3-Benzoylhexahydropyrimidin-1-yl)butyl]benzamide* (**10**). A soln. of 1-(4-aminobutyl)-hexahydropyrimidine (**9**; 1.00 g, 6.37 mmol) and Et_3N (1.69 g, 16.70 mmol) in dry CH_2Cl_2 (40 ml) was stirred under N_2 at 0°. Under stirring and cooling, a soln. of benzoyl chloride (2.02 g, 14.39 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise. Stirring was continued overnight at 23°. After evaporation, the residue was dissolved in CH_2Cl_2 (50 ml) and washed with 5% aq. $NaHCO_3$ soln. (1×) and H_2O (2×; the pooled washing waters were re-extracted once with CH_2Cl_2). Drying of the org. layer, evaporation, and CC (AcOEt/CH_2Cl_2/MeOH 5:5:2) gave **10** (1.07 g, 46%). Colorless oil. IR ($CHCl_3$): 3450*w*, 2990*m*, 2940*m*, 1625*s*, 1580*m*, 1520*s*, 1430*s*, 1280*s*, 1105*m*, 1020*m*, 700*s*. CI-MS: 366 ($[M + 1]^+$). EI-MS: 365 (6, $M^{+\cdot}$), 260 (2, $[M - PhCO]^+$), 231 (3), 203 (5), 189 (9), 174 (5), 105 (100, $[C_6H_5CO^+]$), 77 (48), 70 (9).

N-*(8-Amino-5-azaoctyl)benzamide* (= N-{*4-[(3-Aminopropyl)amino]butyl*}*benzamide*; **11**). A soln. of **10** (0.37 g, 1.01 mmol), in 2N HCl/EtOH (5 ml) was refluxed for 3 h. Evaporation and CC as described for **5** and **5**·2 HCl gave **11** (0.12 g, 48%) and **11**·2 HCl. Colorless viscous oil (**11**) and colorless amorphous solid (**11**·2 HCl). TLC ($CHCl_3$/MeOH/conc. NH_4OH soln. 7:3:1): R_f 0.085. IR (KBr; **11**·2 HCl): 3320*m*, 2940*m*, 2770*m*, 2480*w*, 2420*w*, 1635*s*, 1600*w*, 1575*w*, 1530*s*, 1485*m*, 1460*m*, 1400*w*, 1340*w*, 1265*w*, 1150*w*, 1070*w*, 1010*w*, 710*w*, 690*w*. ^{1}H-NMR (CD_3OD; **11**·2 HCl): 7.74–7.71 (*m*, 2 H_o); 7.47–7.33 (*m*, 2 H_m, H_p); 3.36–3.32 (*t*, J = 6.3, 2 H–C(1)); 3.05–2.93 (*m*, 2 H–C(8), 2 H–C(6), 2 H–C(4)); 1.98 (*q*, J = 7.8, 2 H–C(7)); 1.71–1.60 (*m*, 2 H–C(3), 2 H–C(2)). ^{13}C-NMR (D_2O; **11**·2 HCl): 173.5 (*s*, PhCO); 136.2 (*s*, C_{ipso}); 134.7 (*d*, C_p); 131.4 (*d*, C_o); 129.6 (*d*, C_m); 50.0 (*t*, C(1)); 47.0 (*t*, C(8)); 41.6, 39.2 (2*t*, C(6), C(4)); 28.2, 26.3, 25.6 (3*t*, C(7), C(3), C(1)). CI-MS: 250 ($[M + 1]^+$). EI-MS: 250 (1, $[M + 1]^+$), 249 (< 5, $M^{+\cdot}$), 205 (22), 193 (10), 175 (10), 105 (100, $[C_6H_5CO]^+$), 87 (19), 84 (15), 77 (38), 70 (15), 57 (12), 44 (59).

N,N'-*Diacetyl Derivatives* **12–14**. A mixture of **5**·2 HCl, **8**·2 HCl, or **11**·2 HCl (10 mg) and anh. AcONa (*ca.* 0.20 g) in Ac_2O (5 ml) was stirred overnight at 23°. The excess of Ac_2O was evaporated and the residue dried at 10^{-2} Torr. The solid was dissolved in H_2O (2 ml) and basified with Na_2CO_3. Extraction with $CHCl_3$, drying (Na_2SO_4), and evaporation gave the corresponding diacetyl-benzoyl-spermidines.

N-*(8-Acetamido-4-acetyl-4-azaoctyl)benzamide* (= N-{*3-*{N-*Acetyl*-N-*[4-(acetylamino)butyl]amino*}*propyl*}*benzamide*; **12**). TLC ($CHCl_3$/MeOH 9:2): R_f 0.469. ^{1}H-NMR (CD_3OD): 7.74–7.69 (*m*, 2 H_o); 7.46–7.33 (*m*, 2 H_m, H_o); 3.36–3.19 (*m*, 2 H–C(1), 2 H–C(3), 2 H–C(5), 2 H–C(8)); 3.11–3.30 (*m*, 2 H–C(2)); 2.01, 1.98 (2*s*, Ac); 1.81, 1.80 (2*s*, Ac); 1.56–1.36 (*m*, 2 H–C(6), 2 H–C(7)). CI-MS: 351 (43, $[M + NH_4]^+$), 334 (100, $[M + 1]^+$), 292 (10). EI-MS: 334 (< 5, $[M + 1]^+$), 333 (< 5, $M^{+\cdot}$), 290 (15), 169 (5), 112 (22), 105 (69, $C_6H_5CO]^+$), 98 (30), 91 (7), 84 (30), 77 (70), 72 (34), 70 (100, $[C_4H_8N]^+$), 58 (20), 56 (60), 55 (27), 51 (33).

N-*(4-Acetamidobutyl)*-N-*(3-acetamidopropyl)benzamide* (**13**). TLC ($CHCl_3$/MeOH 9:2): R_f 0.422. ^{1}H-NMR (CD_3OD): 7.36–7.25 (*m*, Ph); 3.44–3.41 (*m*, 2 H–C(3")); 3.21–3.13 (*m*, 2 H–C(1"), 2 H–C(1')); 2.93–2.88 (*m*, 2 H–C(4')); 1.85–1.78 (*m*, 2 Ac); 1.65–1.44 (*m*, 2 H–C(2'), 2 H–C(3')); 1.24–1.18 (*m*, 2 H–C(2")). CI-MS: 351 (55, $[M + NH_4]^+$), 334 (100, $[M + 1]^+$), 292 (6). EI-MS: 334 (< 5, $[M + 1]^+$), 333 (< 5, $M^{+\cdot}$), 332 (< 5, $[M - 1]^+$), 228 (16), 112 (21), 105 (100, $[C_6H_5CO]^+$), 98 (6), 84 (11), 77 (60), 70 (38), 56 (20), 51 (14).

N-*(8-Acetamido-5-acetyl-5-azaoctyl)benzamide* (= N-{*4-*{N-*Acetyl*-N-*[3-(acetylamino)propyl]amino*}*butyl*}*benzamide*; **14**). TLC ($CHCl_3$/MeOH 9:2): R_f 0.453. ^{1}H-NMR (CD_3OD): 7.72–7.69 (*m*, 2 H_o); 7.45–7.32 (*m*, 2 H_m, H_p); 3.35–3.19 (*m*, 2 H–C(8'), 2 H–C(6'), 2 H–C(4'), 2 H–C(1')); 3.11–3.01 (*q*-like *m*, 2 H–C(7')); 2.00, 1.98 (2*s*, Ac); 1.83, 1.82 (2*s*, Ac); 1.62–1.50 (*m*, 2 H–C(3'), 2 H–C(2')). CI-MS: 351 (34, $[M + NH_4]^+$), 334 (100, $[M + 1]^+$), 292 (10). EI-MS: 334 (< 5, $[M + 1]^+$), 290 (23), 231 (18), 105 (100, $[C_6H_5CO]^+$), 100 (28), 98 (21), 84 (21), 77 (48), 72 (14), 70 (26), 58 (19), 56 (38), 51 (20).

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