Reactions of Levulinic Acid with Norbornane/ene Amino Acids and Diamines

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Whereas the cyclizations of di-*endo*-3-aminobicyclo-[2.2.1]heptane-2-carboxylic acid (**2**) and di-*endo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**3**) with 4-oxopentanoic acid (**1**) yield methanodioxopyrrolo[1,2-*a*][3,1]benzoxazines **6** and **7**, the di-*exo* analogues give either the pyrrolo[1,2-*a*]pyridine **8** as sole product (in the case of **4**), or **10** together with the methyl-substituted derivative **9** (in the case of **5**). Compound **1** reacts with di-*exo*-3-aminobicyclo[2.2.1]heptane-2-methanamine (**11**) and di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-methanamine (**12**) to give the methylene-bridged pyrrolo[2,1-*b*]quinazolinones **13** and **14** respectively; a pentacyclic product containing a dipyrrolodiazepine moiety **15** was also isolated. The structures and stereochemistry were elucidated by means of IR and NMR spectroscopy, including COSY, DIFFNOE, DEPT, HMQC and HMBC techniques.

Introduction

4-Oxopentanoic (levulinic) acid **1** has often been used for the preparation of fused heterocycles.[1] For example, reaction with phenylenediamine yields pyrrolo[1,2-*a*]benzimidazoles,[2–7] reaction with anthranilic hydrazides provides pyridazo[3,2-*b*]quinazolines,[8] and reaction with anthranilamides results in pyrrolo[2,1-*a*]quinazolinones.[9,10] Syntheses of chiral oxopyrrolooxazoles and compounds containing quaternary carbon centres have also been described.[11–14]

The preparation of methanooxopyrrolo[1,2-*a*][3,1]benzoxazines from **1** by reaction with cyclic amino alcohols was recently reported;[15] this work fits into the frame of our studies on oxocarboxylic acids,[16,17] in which the versatility of the starting materials was confirmed by the synthesis of new types of fused heterocyclic systems. In the continuation of this work, interesting results were obtained by condensation of **1** with the di-*endo*- and di-*exo*-amino acids **2**–**5**. In the di-*exo* cases (**4** and **5**), the methyl group of **1** participates in the reaction to yield the partly fused pyrrolopyridinediones **8** and **10**, which contain a double bond in the nitrogen-containing part of the ring. On treatment of **1** with the di-*exo*-norbornene-derived diamine **12**, a pyrrole-condensed pentacyclic benzodiazepine derivative **15** was formed due to ring enlargement.

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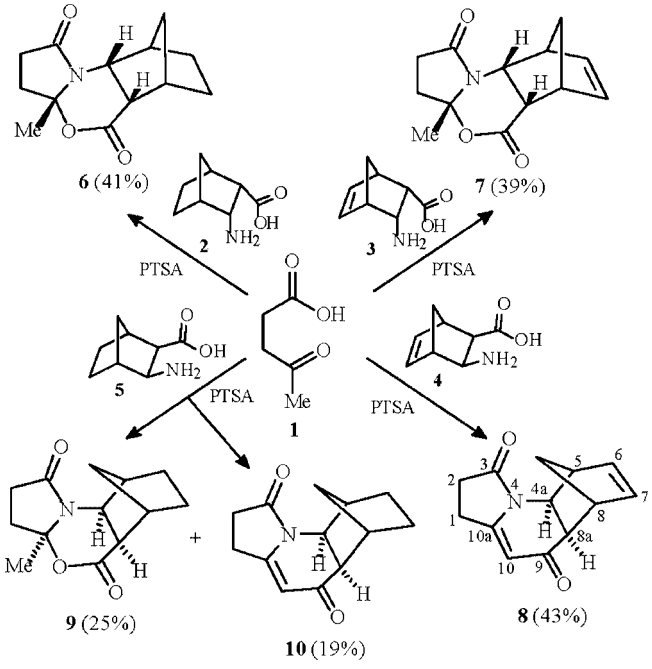
Results and Discussion

The reaction of **1** with the di-*endo*-norbornane-derived amino acid **2** yields **6**, in which the methyl group and the norbornane bridgehead hydrogens lie on the same side of the molecular skeleton (Scheme 1).



Scheme 1

The di-*endo*-norbornene-derived amino acid **3** reacts similarly, resulting in the analogous product **7**. In contrast, the di-*exo*-norbornene-derived amino acid **4** condenses with

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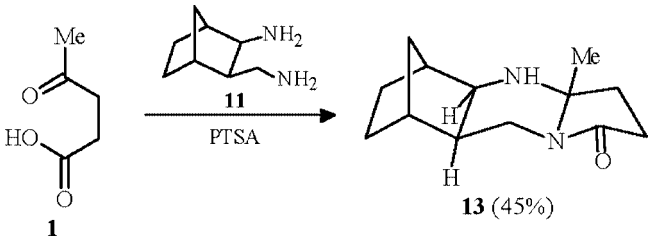
1 to give the methanopyrrolo[1,2-*a*]pyridinone **8** (43 % yield). Similarly, the di-*exo*-norbornane-derived amino acid **5** condenses with **1** to give **10** (19 % yield), as well as **9** (25 % yield). This Claisen-type condensation of only the di-*exo* compounds **4** and **5** to form **8** and **10** seems unusual — in the past, the di-*exo*- and di-*endo*-norbornane/ene difunctional compounds have been observed to react similarly.[18,19] Kinetic measurements have revealed that di-*endo* compounds are more hindered — the retro-Diels−Alder reaction of di-*endo* derivatives is known to be twice as fast as for di-*exo* compounds.[20] The present case focusses attention on the difference between the reactivities of these stereoisomeric norbornane/ene derivatives. No condensation of **1** in which the methyl group participates (as above) has been reported in the literature.

Levulinic acid **1** reacts with di-*exo*-norbornane-derived diamine **11** at reflux in chlorobenzene through acylation of the aminomethyl group and cyclization with the ketone functionality to provide the methylene-bridged pyrrolo[2,1-*b*]quinazolinone **13** (Scheme 2).



Scheme 2

The analogous reaction of the di-*exo*-norbornene-derived diamine **12** under the same conditions affords a mixture of the methanopyrrolo[2,1-*b*]quinazoline **14** and the 1,4-diazepine **15**, which contains two fused pyrrole rings, and is the first representative of a novel heterocyclic system (Scheme 3).

The ring transformation leading to **15** could proceed by the formation of the methylene-bridged pyrrolo[1,2-*a*]quinazoline **i**, which, with a further molecule of levulinic acid, gives the zwitterionic intermediate **ii**. The reversible cleavage of the pyrimidine ring leads, via irreversible closure of **iii**, to the 1,4-diazepine **15**. It seems reasonable that similar transformation of **14** would be unfavourable because the NH group in the analogue of the intermediate **i** would be in a more sterically crowded position.

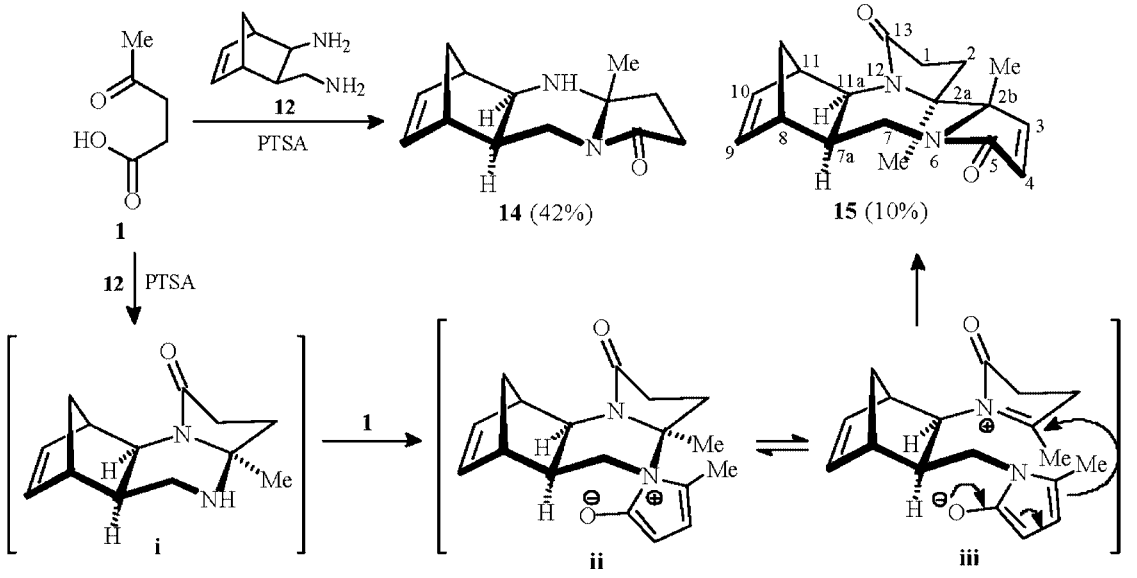
Structure Elucidation

Some remarks on the spectroscopic data follow. To clarify the stereostructures, DIFFNOE measurements (Table 1) were applied.

In **6**, **7** and **9**, the ketoazaacetal-type quaternary carbons (C-10a) give very characteristic downfield-shifted lines[21a] at δ = 95.5, 95.4 and 94.9 ppm. The enone system in **8** and **10** results in split bands in the IR; one of the $\nu_{C=O}$ bands appears at an extremely low frequency (1636 and 1640 cm^{-1}). Characteristically,[21b] the ^{13}C NMR chemical shifts for the conjugated C=C double bond are very different (101.7 and 162.0 ppm for **8**, and 100.9 and 162.4 ppm for **10**).

The $-I$ effect of the ester functionality in **6**, **7** and **9**, and the effect of the C=C double bond in **8** and **10**, give rise to lactam $\nu_{C=O}$ frequencies that are respectively 29 cm^{-1} and 63 cm^{-1} higher than the "normal" value[22] of 1671 cm^{-1} for **13**−**15**.

The assignment of di-*endo* and di-*exo* ring systems follows from the previously observed "splitting rule".[23,24] The oxazine−norbornane/ene bridgehead hydrogens are split into double doublets for the di-*endo* compounds (**6** and **7**), but doublets for the di-*exo* compounds (**8**−**10** and **13**−**15**). The further splitting in the di-*endo* compounds is



Scheme 3

Table 1. Results of DIFFNOE experiments with compounds **6**, **7**, **9** and **13**−**15**; interacting pairs showing only trivial effects (NOEs between geminal or vicinal H atoms) are not included; only responses relevant for determination of the stereostructures are given.

Saturated signal	Responding signals			
	CH(C=O)	NCH	$CH_{endo}H_{exo}$ (bridging)	NCH_2
$CH_{endo}H_{exo}$ (bridging)	**6**, **7**	**6**,[a] **7**	–	**13**, **14**
CH_3	**6**, **7**, **9**[b]	**6**, **7**, **9**,[b] **15**[c]	**13**, **14**	**13**, **14**, **15**[d]

[a] Indirect proof because of signal overlap. [b] Reversed measurements were applied because of the signal overlap of the responding signal. [c] Response to saturation of the methyl group on the pyrrolidinone ring. [d] Response to saturation of the methyl group on the pyrrolinone ring.

due to the coupling with the 5-H/8-H protons, which is absent in the di-*exo* compounds because of the dihedral angles of about 90°.

The relative position of the 4a-H and 8a-H protons (see the numbering scheme on **8**, Scheme 1) in the bicycloalkane ring (in **6**, **7**, **9**, **13** and **14**) and the methyl group was determined by means of DIFFNOE measurements (Table 1).[21c,25] The intensity enhancement of the CHC=O (or NCH) protons observed by saturating the methyl group in **6**, **7** and **9** unequivocally confirmed the closeness of these units, and therefore, the *cis* orientation of the methyl group and the 4a-H and 8a-H protons. In **6** and **7**, the NOEs between the *endo*-H of the norbornane CH_2 bridge and the CHC=O and NCH protons proved that di-*endo* annelation had taken place. The NOE observed for the *endo*-H in the CH_2 bridge of **13** and **14** on irradiation of the methyl signal likewise proved their structures (Schemes 2 and 3).

Elucidation of the structure of **15** was a more complicated task. The presence of one pyrrolinone and one pyrrolidinone moiety followed from the ^1H and ^{13}C NMR spectra. In particular, the signals from two methyl groups, two carbonyl carbons, two additional methylene signals, two olefinic CH groups, and two sp^3-type quaternary carbon atoms were apparent. The next step was to elucidate the carbon skeleton of **15**, in particular, the position of the two methyl groups, relative both to each other and to the bridging CH_2 group (or the bridgehead protons 7a-H and 11a-H).

Firstly, we determined the identity of the carbonyl resonances of the pyrrolidinone and pyrrolinone rings by long-range C,H couplings (HMBC).[26,27] Cross-peaks between methylene signals at δ = 2.35 and 2.46 ppm and the carbonyl resonance at δ = 176.2 ppm confirmed that this C=O group was part of the saturated heterocycle. Likewise, cross-peaks between the signals for the olefinic H atoms at δ = 6.09 and 6.87 ppm and the carbonyl resonance at δ = 169.7 ppm proved that this C=O group belonged to the pyrrolinone ring. The HMBC spectrum also indicated a long-range coupling between the carbonyl with a resonance at δ = 176.2 ppm and the NCH (11a-H) proton (Scheme 3), whereas the other carbonyl resonance at δ = 169.7 ppm correlated with the *N*-methylene (7-H) protons. Therefore, it was clear that the nitrogen atom bound to the CH group was a part of the pyrrolidinone ring, and that the nitrogen atom vicinal to the CH_2 group was a part of the pyrrolinone ring.

Furthermore, the protons of each methyl group show long-range coupling to the quaternary carbon that bears the other methyl group, and in the HMBC spectrum, these quaternary centres show cross-peaks to the NCH and NCH_2 carbons. From these results, the connectivity of **15** followed, and thus the HMBC spectrum furnished unequivocal proof of the ring-enlargement process.

Finally, NOE measurements on **15** confirmed the *trans* orientation of the two methyl groups, and the *cis* relationships of the C-2a methyl group with the NCH proton, and the C-2b methyl group with the *axial*-H atom of the NCH_2 group.

Experimental Section

The IR spectra were determined in KBr discs on a Bruker IFS-55 FT-spectrometer controlled by Opus 3.0 software. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature on a Bruker DRX-500 spectrometer at 500.13 MHz (for ^1H) and 125.76 MHz (for ^{13}C) , with the deuterium signal of the solvent as the lock and tetramethylsilane as the internal standard. To generate NOE[28] spectra and to acquire DIFFNOE spectra,[21c,25] the standard Bruker microprogram NOEMULT was used, with a selective pre-irradiation time. DEPT spectra[29] were run in a standard manner,[30] using only a Θ = 135° pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The COSY,[31a,32a] HMQC[31b,32b] and HMBC[26,27] spectra were obtained by using the standard Bruker pulse programs COSY-45, INV4GSSW and INV4GSLRNDSW, respectively.

Di-*endo*-2,3,5a,6,7,8,9,9a-octahydro-1a-methyl-6,9-methanopyrrolo[1,2-*a*][3,1]benzoxazine-4,10-dione (6): A mixture of di-*endo*-3-aminobicyclo[2.2.1]heptane-2-carboxylic acid (**2**) (1.5 g, 0.01 mol), 4-oxopentanoic acid (**1**) (1.2 g, 0.01 mol) and *p*-toluenesulphonic acid (PTSA) (0.05 g), in dry chlorobenzene (50 mL) was refluxed for 10 h. After filtration, the solvent was evaporated off and the residue was transferred to an Al_2O_3 column (Merck aluminium oxide 90, active, neutral) and eluted with EtOAc (50 mL). On evaporation of the solvent, the residue crystallized to give **6** (1.06 mg, 41 %) as a white solid. M.p. 151−153 °C (from EtOAc). IR (KBr): $\tilde{\nu}$ = 1732 (ester C=O), 1703 (amide-I), 1235, 1079 (ester C−O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = ca. 1.35 (m, 2 H, 6,7-CH_2), ca. 1.5 (m, 2 H, 6,7-CH_2), 1.44 (d, 1 H, with further t splitting due to long range coupling, 11-CH_2), 1.48 (d, 1 H, with further t splitting due to long range coupling, 11-CH_2), 1.58 (s, 3 H, CH_3), ca. 2.35 (m, 3 H, 1,2-CH_2), ca. 2.55 (m, 1H, 2-CH_2), 2.76 (br. s, 1 H, 8-H), 2.88 (dd, 1 H, ^3J = 10.3 and 4.5 Hz, 8a-H), 3.78 (dd, 1 H,

^3J = 10.3 and 3.5 Hz, 4a-H), 3.34 (br. s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.2 (C-6), 25.5 (C-7), 25.8 (CH_3), 29.4 (C-2), 33.2 (C-1), 36.8 (C-11), 40.3 (C-5), 41.1 (C-8), 42.8 (C-8a), 52.1 (C-4a), 95.4 (C-10a), 170.9 (ester CO), 172.3 (amide CO). $C_{13}H_{17}NO_3$ (235.28): calcd. C 66.36, H 7.28, N 5.95, found C 66.19, H 7.15, N 6.17.

Di-*endo*-2,3,5a,6,9,9a-hexahydro-1a-methyl-6,9-methanopyrrolo-[1,2-*a*][3,1]benzoxazine-4,10-dione (7): Di-*endo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**3**) (1.5 g, 0.01 mol) and 4-oxopentanoic acid (**1**) (1.2 g, 0.01 mol) were reacted as described for compound **6**, to afford **7** (0.91 mg, 39 %) as a white solid. M.p. 138−140 °C (from EtOH). IR (KBr): $\tilde{\nu}$ = 1738 (ester C=O), 1697 (amide-I), 1172, 1080 (ester C−O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.33 (d, ^2J = 9.3 Hz, 1 H, 11-H_{endo}), 1.57 (dt, ^2J = 9.3 and ^4J = 1.7 Hz, 1 H, 11-H_{exo}), 1.58 (s, 3 H, CH_3), ca. 2.2 (m, 2 H, 2-CH_2), ca. 2.3 (m, 1 H, 1-CH_2), ca. 2.4 (m, 1 H, 1-CH_2), 3.05 (dd, ^3J = 8.3 and 4.1 Hz, 1 H, 8a-H), 3.38 (br. s, 1 H, 8-H), 4.05 (m, 2 H, 4a,5-H), 6.00 (dd, 1 H, 6-CH), 6.16 (dd, 1 H, 7-CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.8 (CH_3), 29.2 (C-2), 32.7 (C-1), 43.2 (C-8a), 46.0 (C-11), 46.1 (C-5), 46.5 (C-8), 52.7 (C-4a), 95.5 (C-10a), 135.7 (C-6), 137.4 (C-7), 170.8 (ester CO), 172.1 (amide CO) ppm. $C_{13}H_{15}NO_3$ (233.26): calcd. C 66.94, H 6.48, N 6.00, found C 66.74, H 6.60, N 6.12.

Di-*exo*-1,2,4a,5,8,8a-hexahydro-5,8-methanopyrrolo[1,2-*a*]quinoline-3,9-dione (8): A mixture of di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**4**) (1.5 g, 0.01 mol), 4-oxopentanoic acid (**1**) (1.2 g, 0.01 mol) and PTSA (0.05 g) in dry chlorobenzene (50 mL) was refluxed for 10 h. After filtration, the solvent was evaporated off and the residue was purified by column chromatography (neutral Al_2O_3, eluent: EtOAc) and crystallized, to afford **8** (0.92 g, 43 %) as a white solid. M.p. 176−178 °C (from EtOAc). IR (KBr): $\tilde{\nu}$ = 1735 (γ-lactam C=O), 1636, 1623 (enone C=O), 1612 (enone C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.40 (d, ^2J = 9.3 Hz, 1 H, 11-CH_2), 1.44 (d, ^2J = 9.3 Hz, 1 H, 11-CH_2), ca. 2.0 (m, 2 H, 1,2-CH_2), 2.48 (d, ^3J = 9.2 Hz, 1 H, 8a-H), ca. 2.9 (m, 2 H, 1,2-CH_2), 3.29 (br. s, 1 H, 8-H), 3.38 (br. s, 1 H, 5-H), 3.87 (d, ^3J = 9.2 Hz, 1 H, 4a-H), 5.27 (s, 1 H, 10-H), 6.20 (dd, ^3J = 5.2 and 3.0 Hz, 1 H, 6-CH), 6.37 (dd, ^3J = 5.2 and 2.8 Hz, 1 H, 7-CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.3 (C-1), 28.1 (C-2), 44.4 (C-11), 46.4 (C-8a), 49.7 (C-8), 50.6 (C-5), 55.0 (C-4a), 101.7 (C-10), 135.7 (C-6), 140.2 (C-7), 162.0 (C-10a), 176.0 (γ-lactam CO), 193.6 (ketone CO) ppm. $C_{13}H_{13}NO_2$ (215.25): calcd. C 72.54, H 6.09, N 6.51, found C 72.73, H 6.25, N 6.65.

Di-*exo*-2,3,5a,6,7,8,9,9a-octahydro-1a-methyl-6,9-methanopyrrolo-[1,2-*a*][3,1]benzoxazine-4,10-dione (9) and di-*exo*-1,2,4a,5,6,7,8,8a-octahydro-5,8-methanopyrrolo[1,2-*a*]quinoline-3,9-dione (10): A mixture of di-*exo*-3-aminobicyclo[2.2.1]heptane-2-carboxylic acid (**5**) (1.5 g, 0.01 mol), 4-oxopentanoic acid (**1**) (1.2 g, 0.01 mol) and PTSA (0.05 g) in dry chlorobenzene (50 mL) was refluxed for 10 h. After filtration, the residue was transferred to an Al_2O_3 column (Aluminium oxide 90, active, neutral) and eluted with EtOAc. The early fractions [higher R_f on Polygram SILG, eluant: benzene/ethanol/petroleum ether (b.p. 40−70 °C), 3:1:4, development in iodine vapour] contained **9** (0.59 g, 25 %), isolated as a white solid. M.p. 143−145 °C (from EtOAc). IR (KBr): $\tilde{\nu}$ = 1725 (ester C=O), 1700 (amide-I), 1152, 1081 (ester C−O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.18 (d, ^2J = 10.8 Hz, 1 H, 11-CH_2), ca. 1.25 (m, 2 H, 6,7-CH_2), 1.30 (d, ^2J = 10.8 Hz, 1 H, 11-CH_2), ca. 1.6 (m, 2 H, 6,7-CH_2), 1.57 (s, 3 H, CH_3), ca. 2.16 (m, 1 H, 1-CH_2), 2.18 (m, 1 H, 1-CH_2), 2.28 (m, 1 H, 2-CH_2), 2.48 (m, 1 H, 2-CH_2), 2.55 (d, ^3J = 7.8 Hz, 1 H, 8a-H), 2.88 (br. s, 1 H, 8-H), 3.60 (d, ^3J = 7.8 Hz, 1 H, 4a-H), 3.71 (br. s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.5 (CH_3), 27.2 (C-6), 28.1 (C-7), 29.6 (C-2), 32.9 (C-1), 34.9 (C-11), 38.1 (C-5), 42.2 (C-8), 48.0 (C-8a), 57.3 (C-4a), 94.9 (C-10a), 170.5 (ester CO), 172.8 (amide CO). $C_{13}H_{17}NO_3$ (235.28): calcd. C 66.36, H 7.28, N 5.95, found C 66.53, H 7.15, N 6.13. The later fractions [lower R_f, development as above] contained **10** (0.41 g, 19 %), isolated as a white solid. M.p. 134−135 °C (from EtOH). IR (KBr): $\tilde{\nu}$ = 1733 (γ-lactam C=O), 1640 (enone C=O), 1612 (enone C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.20 (dt, ^2J = 10.5 and ^4J = 1.5 Hz, 1 H, 11-CH_2), ca. 1.4 (m, 2 H, 6,7-CH_2), 1.43 (d, ^2J = 10.5 Hz, 1 H, 11-CH_2), ca. 1.55 (m, 1 H, 7-CH_2), ca.1.6 (m, 1 H, 7-CH_2), ca. 2.6 (m, 3 H, 8a-H and 2-CH_2), 2.67 (br. s, 1 H, 5-H), 2.70 (br. s, 1 H, 8-H), ca. 2.85 (m, 2 H, 1-CH_2), 3.99 (d, ^3J = 8.4 Hz, 1 H, 4a-H), 5.14 (s, 1 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.4 (C-1), 26.5 (C-6), 27.9 (C-2), 29.3 (C-7), 35.0 (C-11), 44.0 (C-5), 44.7 (C-8), 52.0 (C-8a), 58.6 (C-4a), 100.9 (C-10), 162.4 (C-10a), 175.8 (γ-lactam CO), 193.6 (ketone CO) ppm. $C_{13}H_{15}NO_2$ (217.26): calcd. C 71.87, H 6.96, N 6.45, found C 71.71, H 6.84, N 6.32.

1a-Methyl-2,3,6a,7,8,9,10,10a-octahydro-7,10-methanopyrrolo[2,1-*b*]-quinazolin-4-one (13): A mixture of diamine **11** (1.4 g, 0.01 mol) (obtained from di-*exo*-3-aminobicyclo[2.2.1]heptane-2-carboxamide by reduction with LAH in THF), 4-oxopentanoic acid (**1**) (1.2 g, 0.01 mol) and PTSA (0.05 g) in dry chlorobenzene (50 mL) was refluxed for 5 h. After evaporation, the residue was purified by column chromatography (Merck 60 silica gel, 230-400 mesh ASTM). Elution with benzene yielded **13** (0.99 g, 45 %) as a white solid. M.p. 97−99 °C (from Et_2O). IR (KBr): $\tilde{\nu}$ = 3297 (N−H), 1670 (broad, amide-I) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = ca. 0.9 (m, 2 H, 6,7-CH_2), 0.96 (d, ^2J = 10.7 Hz, 1 H, 11-H_{exo}), 1.06 (s, 3 H, CH_3), 1.25 (m, 1 H, 6,7-CH_2), ca. 1.35 (m, 1 H, 6-CH_2), 1.47 (d, ^2J = 10.7 Hz, 1 H, 11-H_{endo}), 1.55 (ddd, ^3J = 12.0, 6.8 and 6.4 Hz, 1 H, 8a-H), ca. 1.65 (m, 1 H, 1,2-CH_2), 1.73 (d, ^3J = 3.1 Hz, 1 H, 8-H), 1.87 (d, ^3J = 3.9 Hz, 1 H, 5-H), ca. 1.9 (m, 1 H, 1-CH_2), ca. 2.05 (m, 1 H, 2-CH_2), ca. 2.2 (m, 1 H, 2-CH_2), 2.57 (d, ^3J = 6.9 Hz, 1 H, 4a-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.9 (CH_3), 26.9 (C-6), 29.3 (C-7), 31.1 (C-2), 32.9 (C-1), 33.5 (C-11), 36.4 (C-9), 39.1 (C-8), 42.1 (C-5), 45.8 (C-8a), 55.2 (C-4a), 74.2 (C-10a), 173.4 (amide CO). $C_{13}H_{20}N_2O$ (220.31): calcd. C 70.87, H 9.15, N 12.72, found C 70.70, H 9.00, N 12.58.

1a-Methyl-2,3,6a,7,10,10a-hexahydro-7,10-methanopyrrolo[2,1-*b*]-quinazolin-4-one (14) and 2a,2b-dimethyl-3,4,7a,8,11,11a-hexahydro-8,11-methanodipyrrolo[1,2-*a*;1,2-*c*][1,4]benzodiazepine-5,13-dione (15): A mixture of diamine **12** (1.4 g, 0.01 mol) [obtained from di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxamide (Acros 27.780.38) by reduction with LAH in THF], 4-oxopentanoic acid (**1**) (1.2 g, 0.01 mol) and PTSA (0.05 g) in dry chlorobenzene (50 mL) was refluxed for 5 h. After evaporation, the residue was purified by column chromatography (Merck 60 silica gel, 230-400 mesh ASTM). Elution with EtOAc yielded **14** (0.91 g, 42 %) as a white solid. M.p. 85−87 °C (from Et_2O). IR (KBr): $\tilde{\nu}$ = 3311 (N−H), 1671 (amide-I) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.24 (s, 3 H, CH_3), 1.42 (d, ^2J = 9.5 Hz, 1 H, 11-H_{exo}), 1.61 (m, 1 H, 8a-H), 1.69 (d, ^2J = 9.5 Hz, 1 H, 11-H_{endo}), ca. 1.8 (m, 1 H, 1-CH_2), ca. 2.0 (m, 1 H, 1-CH_2), ca. 2.15 (m, 1 H, 2-CH_2), ca. 2.35 (m, 1 H, 2-CH_2), 2.44 (br. s, 1 H, 8-H), 2.57 (br. s, 1 H, 5-H), 2.64 (d, ^3J = 6.8 Hz, 1 H, 4a-H), 5.90 (dd, ^3J = 5.7 and 3.1 Hz, 1 H, 6-CH), 6.05 (dd, ^3J = 5.7 and 3.0 Hz, 1 H, 7-CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.2 (CH_3), 31.3 (C-2), 33.0 (C-1), 38.5 (C-9), 40.5 (C-8a), 42.9 (C-11), 44.0 (C-8), 47.4 (C-5), 51.1 (C-4a), 74.7 (C-10a), 134.4 (C-6), 139.3 (C-7), 173.7 (amide CO) ppm. $C_{13}H_{18}N_2O$ (218.30): calcd. C 71.53, H 8.31, N 12.83, found C 71.74, H 8.47, N 12.95. Subsequent elution with EtOH yielded **15** (0.30 g, 10 %) as a white solid. M.p. 258-260 °C (from EtOAc). IR (KBr): $\tilde{\nu}$ = 1673 (amide-

I) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.98 (s, 3 H, pyrrolidinone CH_3), 1.28 (s, 3 H, pyrrolinone CH_3), 1.62 (d, ^2J = 9.3 Hz, 1 H, 11-H_{exo}), 1.75 (m, 2 H, 8a-H and $COCH_{ax}$), 1.97 (d, ^2J = 9.3 Hz, 1 H, 11-H_{endo}), 2.04 (ddd, ^2J = 13.5, ^3J = 9.3 and 1.3 Hz, 1 H, $COCH_{eq}$), 2.35 (dd, ^2J = 17.7, ^3J = 11.1 Hz, 1 H, $C_{quat}CH_{eq}$), 2.46 (m, 1 H, $C_{quat}CH_{ax}$), 2.60 (br. s and t, ^3J = 13.3 Hz, 2 H, 8-H and NCH_{ax}), 3.13 (d, ^3J = 7.4 Hz, 1 H, 4a-H), 4.01 (dd, ^2J = 13.3, ^3J = 4.9 Hz, 1 H, NCH_{eq}), 4.19 (br. s, 1 H, 5-H), 5.95 (dd, ^3J = 5.5 and 3.2 Hz, 1 H, 6-CH), 6.09 (d, ^3J = 6.0 Hz, 1 H, COCH), 6.20 (dd, ^3J = 5.5 and 3.0 Hz, 1 H, 7-CH), 6.87 (d, ^3J = 6.0 Hz, 1 H, $C_{quat}CH$) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.4 (pyrrolinone CH_3), 23.3 (pyrrolidinone CH_3), 30.9 ($COCH_2$), 33.1 ($C_{quat}CH_2$), 40.9 (NCH_2), 43.9 (C-8a), 45.1 (C-8), 45.3 (C-5), 46.2 (C-11), 59.6 (C-4a), 68.3 (pyrrolidinone C_{quat}), 73.8 (pyrrolinone C_{quat}), 127.6 ($COCH{=}CH$), 136.3 (C-6), 141.2 (C-7), 150.2 ($C_{quat}CH{=}CH$), 169.7 (pyrrolinone C=O), 176.2 (pyrrolidinone C=O) ppm. $C_{18}H_{22}N_2O_2$ (298.38): calcd. C 72.46, H 7.43, N 9.39, found C 72.65, H 7.57, N 9.55.

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