

Indoloquinolines, Indolobenzoxazines and Quinazolophthalazines Prepared from Norbornane/eneamino Acids and Hydrazides

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Dedicated to Professor András Lipták on the occasion of his 70th birthday

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The reactions of di-*endo*- and di-*exo*-aminonorbornane/enecarboxylic acids **1–4** with ethyl 2-(2-oxocyclohexyl)acetate afforded methanoindoloquinolines **5**, **6**, **8**, and **9**, the oxo ester participating as a two-membered sp² building block. In the cases of di-*exo*- and di-*endo*-aminonorbornenecarboxylic acids **2** and **4**, methanoindolobenzoxazinediones **7** and **10** were also formed; compound **7** was also isolated from the mother liquor of **10**. The reactions of ethyl 2-(2-oxocyclohexyl)acetate with aminonorbornane/enecarbohydrazides

11–14 result in the methanoquinazolophthalazines **15–18**. The structures of the compounds were elucidated by NMR spectroscopy, and for **6**, **7**, **8**, and **10** also by X-ray crystallography.

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Introduction

Di-*endo*- and di-*exo*-norbornane/eneamino acids **1–4** and their derivatives with bidentate nucleophiles have often been used in the preparation of condensed heterocycles.^[1,2] Cyclocondensation followed by a retro-Diels–Alder reaction has proved very effective in the syntheses of condensed hetero compounds, with cyclopentadiene or furan being cleaved off in the final thermal process.^[3,4] As hydrazides are a highly reactive, versatile class of nitrogen-substituted molecules that are used in the preparation of many important organic molecules,^[5] we recently prepared norbornene-condensed 1,5-diazatricyclododecanediones, which were formed together with pentacyclic bis(acyl hydrazides) and cyclopenta-fused pyridazinone.^[3] These reactions have now been extended to the preparation of cyclohexane derivatives: amino acids **1–4**^[6,7] and carbohydrazides **11–14**^[8] were cyclized with ethyl 2-(2-oxocyclohexyl)acetate, with the amino acids giving an interesting new type of end-product through an elimination process.

Results

On refluxing di-*endo*-3-aminobicyclo[2.2.1]heptane- and -hept-5-ene-2-carboxylic acids (**1** and **2**) with ethyl 2-(2-oxocyclohexyl)acetate in chlorobenzene, in the presence of *p*-toluenesulfonic acid (PTSA) as catalyst, the methanoindolo[4,5-*ab*]quinolinediones **5** and **6**, respectively, were produced in low yields of 25–28% (Scheme 1, and **6** in Figure 1). The reason for the low yields may be the high (ca. 30%) recovery of the amino acids.

Similarly, the reactions of the stereoisomeric di-*exo*-amino acids **3** and **4** resulted in condensed pentacyclic derivatives **8** (Figure 1) and **9**, respectively. Besides the formation of **5**, **6**, **8**, and **9** by this route, the methylene-bridged indolobenzoxazines **7** and **10** (Figure 2), differing in the annelation of the norbornene ring and in the stereostructures of the saturated indole moiety, were isolated from the reactions of **2** and **4** with the oxo ester by column chromatography and crystallization.

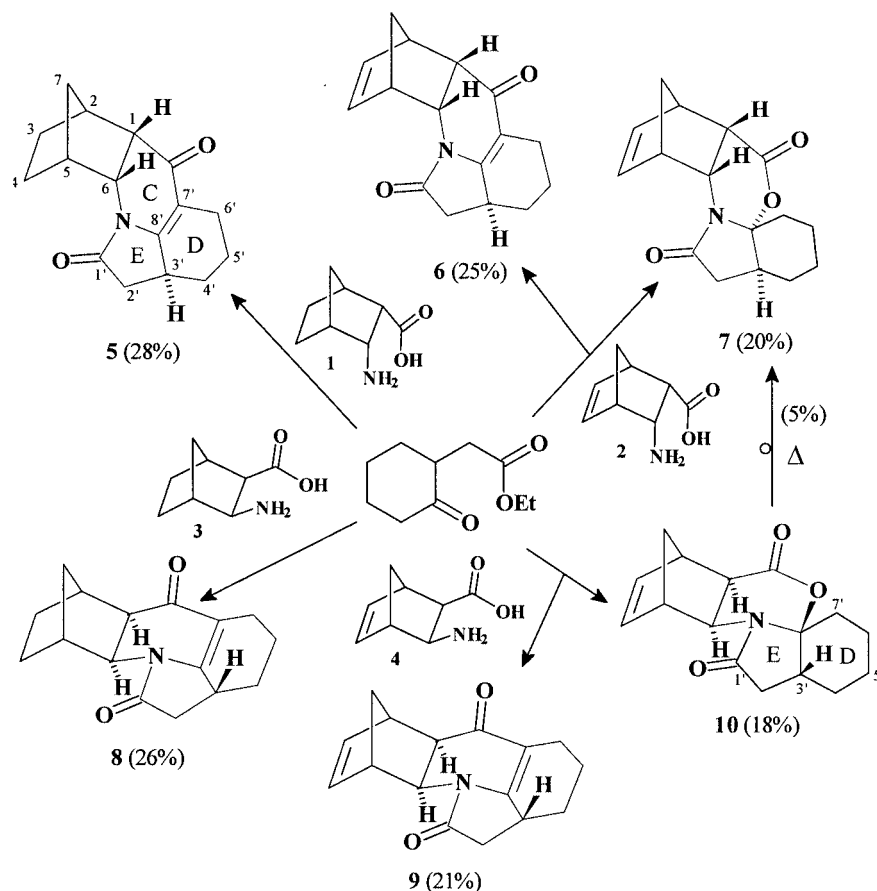
Schiff-base formation followed by tautomerization to an enamine and then acylation at the carbon and nitrogen atoms (**A**) can be postulated as a mechanism for the formation of **5**, **6**, **8**, and **9**, while trapping of the intermediate imine would lead to products **7** and **10** (**B**) (Scheme 2). Compound **7** was also isolated from the mother liquor of **10**; the conversion (8 %) of **10** through a retro-Diels–Alder reaction and *endo*-selective recombination would also result in the formation of **7**.

As the norbornane skeleton has a high rigidity, the configurations of the starting compounds are generally retained

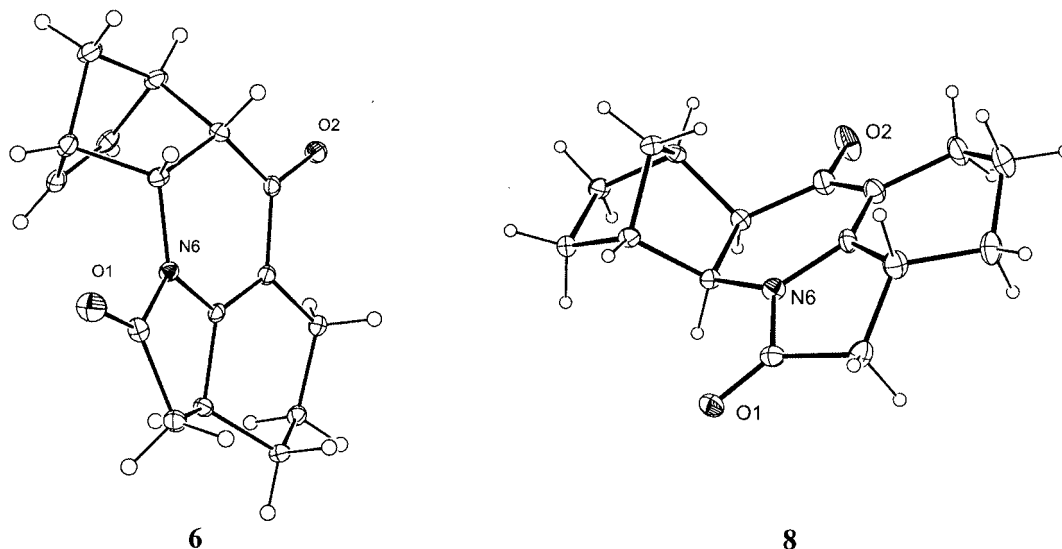
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Scheme 1.

Figure 1. Perspective views of **6** and **8**; thermal ellipsoids are drawn at a probability level of 30% for **6** and 20% for **8**.

in the products. Only a few examples of epimerization of the norbornane annelation carbon atoms, C-2 and C-3, have been reported. Thus, Craig has described a reversible di-*endo*-to-di-*exo* isomerization;^[9] on heating, the di-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride was

transformed into the di-*exo* analog. This change was attributed to the formation of a tautomeric intermediate (not isolated). Moreover, a similar, but single isomerization was observed in the cyclization of phenyl-substituted di-*endo*-3-aryl-2-norbornanecarboxylic acid with ethylenediamines,

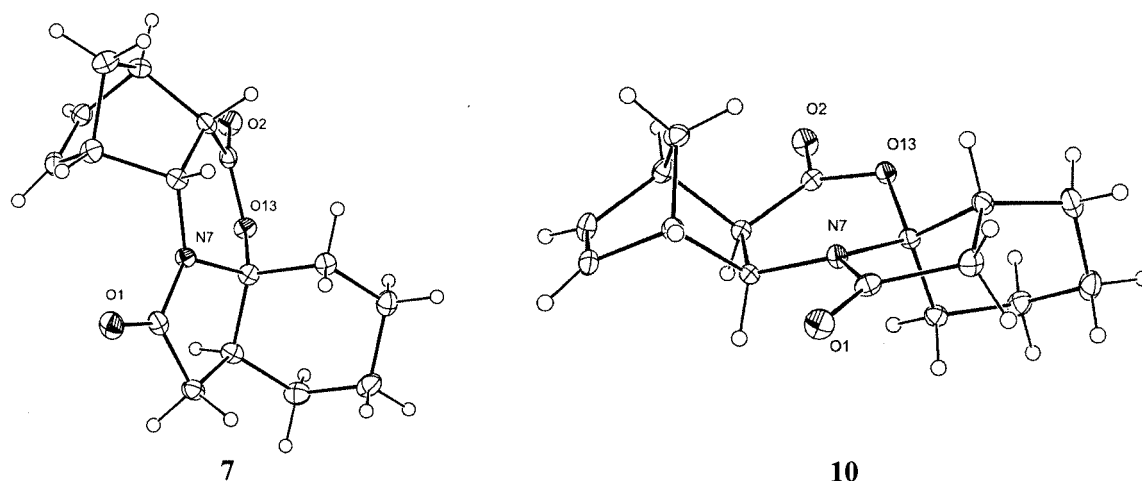
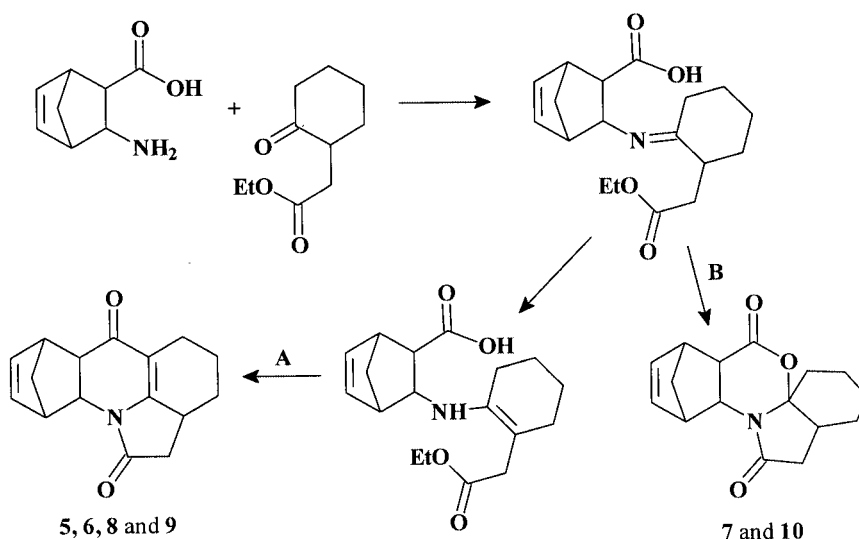


Figure 2. Perspective views of **7** and **10**; thermal ellipsoids are drawn at a probability level of 30%.



Scheme 2.

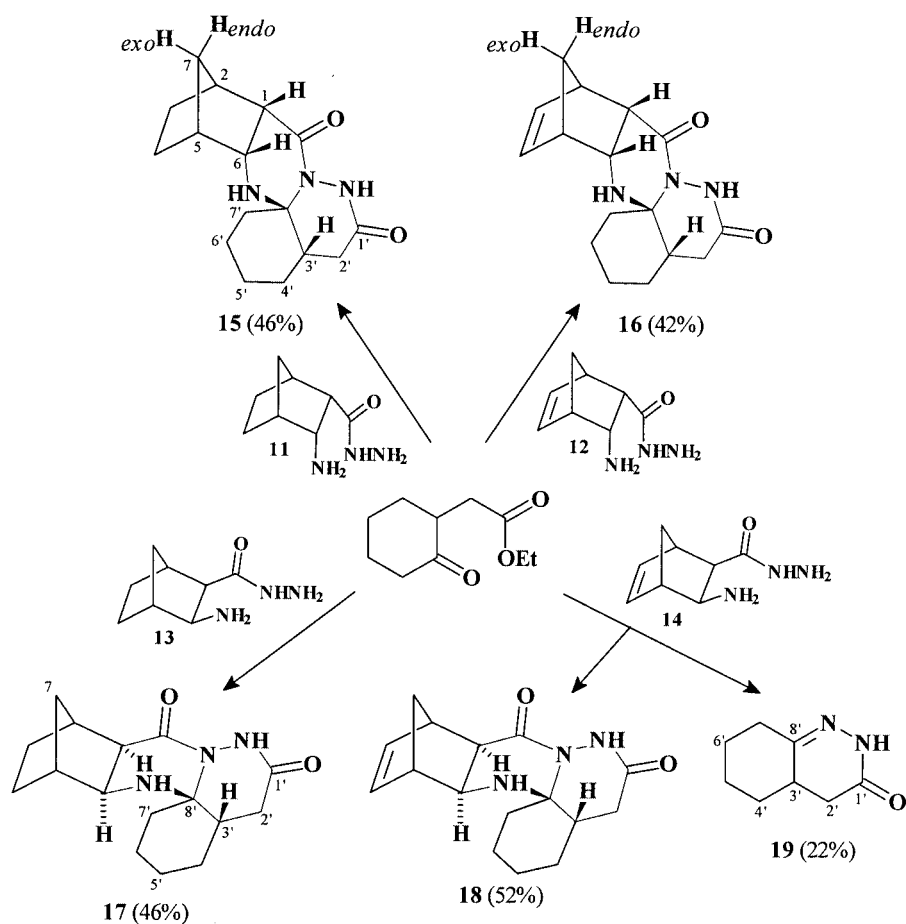
which resulted in mixtures of methylene-bridged di-*exo*- and di-*endo*-imidazoloisindolones.^[10] No derivatives analogous to **7** and **10** were isolated from the reactions of the oxo ester with **1** or **3**.

Note that, in contrast, the reactions of 4-oxopentanoic acid with the di-*endo*-amino acids **1** and **2** gave pyrrolidone-condensed methanobenzoxazine products similar to **7** and **10**, whereas the di-*exo* compounds **3** and **4** resulted in partly or fully analogous dioxypyrroloquinolines through the elimination of water in a Claisen condensation reaction.^[11] These products suggest some differences in the reactions of di-*endo*- and di-*exo*-norbornaneamino acids, resulting in elimination products such as **5**, **6**, **8**, and **9**, or in aza keto acetals similar to **7** and **10**.

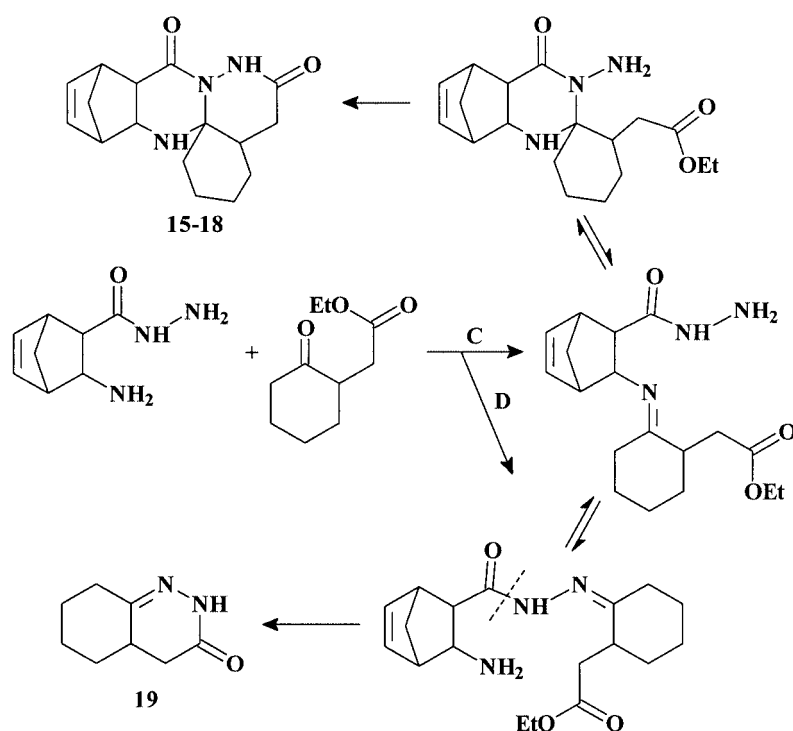
The above ring-formation reactions that give **5**, **6**, **8**, and **9**, in which the oxo ester serves as a two-membered building block in the cyclization step by providing two sp^2 carbon

atoms for the process, seem to be a feature of 2-(2-oxocyclohexyl)acetate. The literature contains examples of the formation of condensed quinolones from ketones and ester imides^[12–14] by cyclodehydration, and the reaction of acetophenone with phthalic anhydride to give pyrroloquinoline has been described.^[15] However, neither of these processes nor other syntheses involving the use of anthranilamides and 3- or 4-oxoalkanoic acids,^[16] nor the cyclization of aromatic amines with β -oxo esters,^[17] lead to heterocycles similar to the above elimination products.

No elimination occurs in the cyclodehydration reactions of 3-aminobicyclo[2.2.1]heptane- or -hept-5-ene-2-carbohydrazides **11–14**, which result in the pentacyclic bis(acyl hydrazides) **15–18** (Scheme 3), analogously to the reactions of **12** and **14** with ethyl 2-(2-oxocyclopentyl)acetate.^[3] In contrast with the latter, no product containing an amino group could be isolated from the mixture.



Scheme 3.



Scheme 4.

The mechanism proposed for these reactions involves the formation of a Schiff base with the amino group followed by cyclization with the carboxamide nitrogen atom to give its tautomeric ring^[18] and acylation leads to compounds **15–18** (**C**) (Scheme 4), while a Schiff base formed with the hydrazide amino group and intramolecular transacylation of the ester results in the pyridazinone **19** (**D**). This mechanism operates readily only in the di-*exo* case; the di-*endo* compound **12** does not give the pyridazinone **19** for steric reasons (owing to the crowded structure).^[3]

Structure Elucidation

Selected IR, ¹H, and ¹³C NMR spectroscopic data for the new compounds **5–10** and **15–19** are given in Tables 1 and 2. The spectra unambiguously confirm the proposed constitutions; only the following additional remarks are necessary. (For easier comparison of the spectroscopic data in this section and in the Tables, the numbering shown in Schemes 1 and 2 is used; to illustrate the stereostructure, the orientations of 1-, 6-, and 3'-H are indicated in the schemes.)

The presence of the enone moiety in **5**, **6**, **8**, and **9** is evident from the very large difference in the ¹³C NMR chemical shifts of the signals of the olefinic carbon atoms^[19a] and the downfield-shifted signal of the carbonyl carbon atom that is characteristic of ketones.^[19b] The long-range coupling between 1-H and C-7' (demonstrated by HMBC measurements) proves the position of the former group in the molecules.

Instead of the ketone carbon signal in **5**, **6**, **8**, and **9** (δ = 192.9–195.0 ppm), the ester carbonyl moieties in **7** and **10** exhibit chemical shifts of δ = 170.8 and 171.1 ppm, respectively, the olefinic carbon signals are absent, and signals due to the quaternary sp³ carbon atoms (at δ = 94.6 and 94.8 ppm) as well as ¹H and ¹³C NMR signals from an additional CH₂ group relative to **5**, **6**, **8**, and **9** are observed.

For **15–18**, the amide-I IR bands of the six-membered lactams have frequencies in the region expected^[20a] (1624–1677 cm⁻¹), while the corresponding bands of the γ -lactam rings in **5–10** and also the lactone carbonyl bands of **7** and **10**, which are characteristic of these functional groups, appear at higher frequencies (1706–1731 and 1742 and 1733 cm⁻¹, respectively).^[20b] The amide-I frequencies of **5**,

Table 1. Characteristic IR frequencies^[a] and ¹H NMR chemical shifts^[b] for compounds **5–10** and **15–19**.^[c]

	Amide-I band ^[d]	ν C=O ^[e]	(NC=O)CH ₂ 2 × dd (2 × 1 H) [f]	Cyclohexane/ene ring			Norbornane/ene moiety				
				3'-H ^[g]	4'-H ^[h]	6'/7'-H ^[i]	CH ₂ (7) ^[k]	1-H ^[l]	2-H ^[m]	5-H ^[m]	6-H ^[n]
5	1728	1659	2.28, 2.72	2.92	1.32, 2.15	ca. 2.03, ^[o] 2.40	1.43, 1.50	2.83 ^[p]	2.82 ^[p]	2.75	4.22
6	1731	1662	ca. 2.22, ^[o] ca. 2.68 ^[p]	2.75 ^[p]	1.27, ca. 2.1 ^[r]	ca. 2.1, ^[r] 2.28 ^[o]	1.36, 1.47	3.11	3.46	3.59	4.44
7	1710	1742	2.18, ^[s] ca. 2.38 ^[o]	ca. 2.38 ^[o]	ca. 1.6, ^[p] 1.82	ca. 1.6, ^[p] 1.99	1.36, ca. 1.6 ^[p]	3.05	3.44	4.01	4.05
8	1729	1660	2.15, 2.63	2.80	1.22, ca. 2.05 ^[o]	ca. 2.05, ^[o] 2.27	1.15, 1.43	2.54	2.48 ^[p]	2.48 ^[p]	3.90
9	1731	1660	2.30, 2.75	2.88	1.34, 2.15 ^[o]	ca. 2.20, ^[o] 2.42	1.42, 1.51	2.52	3.20	3.24	3.88
10	1706	1733	ca. 2.18, ca. 2.47 ^[o]	ca. 2.45 ^[o]	ca. 1.6, ^[p] 1.85	ca. 1.6, ^[p] 1.95	1.35, 1.48	2.45 ^[o]	ca. 3.45 ^[p]	4.12	ca. 3.45 ^[p]
15	1653	1627	2.37, 2.73	ca. 2.05 ^[o]	ca. 1.4, ^[p] ca. 2.05 ^[o]	1.70, 1.77	1.40 ^[p]	2.43	2.70	2.45	3.48
16	1670	1655	2.22, 2.56	2.07	1.28, ca. 1.85 ^[o]	1.76, ca. 1.85 ^[o]	1.42, ^[p] 1.44 ^[p]	2.77	3.20	3.02	3.80
17	1677	1624	2.35, 2.70	ca. 2.0	ca. 1.36, ^[o] 2.05	ca. 1.68, ^[p] 1.80	1.14, 1.43	2.18	2.84	2.17	3.17
18	1650	1630	2.35, 2.50	2.22	ca. 1.32, ^[p] ca. 1.86 ^[o]	1.78 ^[o]	1.29, 1.68	2.09	3.24	2.73	3.08 ^[s]
19	1673	—	2.16, 2.62	ca. 2.50	1.28, 2.05	2.12, 2.55	—	—	—	—	—

[a] In KBr discs [cm⁻¹]. Further bands: ν NH band: ca. 3345 (**15**), 3268 and 3212 (**16**), 3215 (**17**), 3327 and 3312 (**18**), 3216 and 3095 (**19**); ν C=O: 1161 and 1139 (**7**), 1161, 1131, and 1059 (**10**); 1160, 1069, and 1036 (**7**); ν C=C band (enone), very strong: 1612 (**5**), 1606 (**6**), 1621 (**8**), 1615 (**9**). [b] In CDCl₃ solution (in [D₆]DMSO for **16** and **18**) at 500 MHz. Chemical shifts are given in ppm (δ_{TMS} = 0 ppm), coupling constants in Hz, see footnote. Further signals: $\delta_{3,4\text{-H}}$ = 1.25–1.60 (4 or 2 m, 4 × 1 H or 2 × 2 H for **5**, **8**, **15**, and **17**), 6.0–6.4 (2 × dd, 2 × 1H for **6**, **7**, **9**, **10**, **16**, and **18**); $\delta_{5'\text{-H}}$ = 1.30–2.05 (2 × m, 2 × 1 H for **5**, **6**, **8**, and **9**) or $\delta_{5',6'\text{-H}}$ = 1.30–2.05 (4 × m, 4 × 1 H for **7**, **8**, **10**, and **15–19**). [c] Assignments were supported by HMQC, HMBC (except for **19**), and DIFNOE (except for **6–8** and **19**), and for **6**, **8**, **15**, and **17–19** also by 2D-COSY measurements. [d] Lactam group, five- (**5–10**) or second six-membered (**15–19**). [e] Conjugated ketone (**5**, **6**, **8**, and **9**), lactone (**7** and **10**), and *tert*- δ -lactam (**15–18**). [f] J = 17.0, 8.8, and 9.0 (**5**, **8**, and **9**), 15.5, 9.1, and 8.6 (**10**), 18.2, 5.8, and 12.3 (**15** and **17**), 17.3, 5.5, and 11.2 (**16**), 17.0, 5.4, and 10.2 (**18**), 17.1, 12.3, and 8.7 Hz (**19**). [g] m, 1 H. [h] 2 × m, 2 × 1 H, upfield signal: dqa/qad (**6**, **8**, **9**, and **19/16**). [i] 6'-H (**5**, **6**, **8**, and **9**) or 7'-H (**7**, **10**, and **15–19**): 2 × m, 2 × 1 H; downfield signal: dd (**5**, **6**, **8**, and **9**), J $\approx$ 17.0 and 6.5 (**8** and **9**); "d" (**7**, **10**, **15**, and **17**). [k] AB-type spectrum, 2 × d, 2 × 1 H, J = 10.6 (**5**, **8**, and **17**), 9.1 (**6** and **9**), 9.4 (**7**), 9.8 Hz (**10** and **18**). [l] dd, J = 10.0 and 3.9 (**6**); 8.5 and 4.0 Hz (**7** and **16**); d, J = 9.1 (**8**), 8.8 (**9**), 7.2 (**17**), 6.8 Hz (**18**). [m] "s", 1 H. [n] dd, J = 12.1 and 4.2 (**5**), 10.0 and 3.8 (**6**), 8.5 and 3.5 Hz (**7**); d, J = 9.0 (**8** and **9**), 6.7 (**15**), 7.0 Hz (**17**); ddd, J = 10.6, 8.8, and 3.7 Hz (**16**). [o,p,r] Overlapped signals with the 5'-H (**5**^[o]), 5'-H/6-H' (**17**^[o,p]) signal. [s] Multiplet with unresolved lines.

Table 2. ^{13}C NMR chemical shifts^[a] for compounds **5–10** and **15–19**.^[b,c]

	Indolone (5–10)/cinnolone ring (15–19)								Norbornane/ene moiety							
	C=O(1')	C-2'	C-3'	C-4'	C-5'	C-6'	C-7'	C-8'	C=O ^[d]	C-1	C-2	C-3	C-4	C-5	C-6	CH ₂ (7)
5	174.7	36.5	35.3	27.4	21.9	19.8	109.9	159.0	195.0	47.5	42.7	25.4	22.1	43.0	53.9	37.5
6	174.6	36.4	35.3	27.4	21.8	19.6	108.7	159.7	194.0	48.7	49.9	138.2	133.9	48.4	53.8	46.9
7	172.2	34.6	38.7	24.1	20.1 ^[e]	20.5 ^[e]	35.3	94.6	170.8	42.5	46.7 ^[d]	137.2	135.6	46.4 ^[d]	52.4	46.1
8	174.3	36.0	35.1	27.3	21.8	20.0	108.1	160.1	192.9	53.0	44.0	29.9	26.1	45.5	57.5	34.9
9	174.6	36.3	35.4	27.4	21.9	20.1	109.0	159.7	193.4	47.8	49.7	140.4	135.5	51.6	53.8	44.4
10	173.3	35.0	38.3	24.7	21.0 ^[e]	20.5 ^[e]	34.3	94.8	171.1	42.5	47.6	137.8	136.7	46.4	53.0	44.9
15	164.4	32.1	38.1	26.1	22.4	19.2	27.9	74.6	162.5	44.6	40.5	24.1	22.0	41.3	50.9	37.9
16	165.0	32.0	36.6	25.4	21.1	18.7	28.4	74.3	161.9	42.8	45.6	138.1	134.0	138.1	45.6	46.7
17	164.4	32.0	38.1	25.9	22.3	19.2	27.8	73.3	161.9	49.0	41.1	29.0	27.0	42.9	55.8	34.3
18	166.2	32.4	36.8	25.4	22.2	19.2	27.9	73.8	162.6	42.8	44.7	138.0	135.7	47.2	51.5	43.9
19	167.0	34.0	34.7	34.2	24.8	25.9	33.3	155.8	–	–	–	–	–	–	–	–

[a] In ppm ($\delta_{\text{TMS}} = 0$ ppm) at 125.7 MHz. Solvent: CDCl_3 (for **16** and **18**, $[\text{D}_6]\text{DMSO}$). [b] Assignments supported by DEPT, HMQC, and also HMBC (except for **19**) measurements. [c] For numbering, see Schemes 1 and 2. [d,e] Interchangeable assignments.

6, **8**, and **9** ($1728\text{--}1731\text{ cm}^{-1}$) are higher by ca. 20 cm^{-1} than those of **7** and **10** (1710 and 1706 cm^{-1}) as a result of the imide-like ($-\text{CO}-\text{N}=\text{C}-$) structure.^[20a]

The di-*endo* or di-*exo* annelation of the norbornane/ene moiety is unaltered in all the main products (an exception is the by-product **7**, isomerized by enolization), as indicated by our “splitting rule”:^[21,22] as a consequence of the dihedral angles of ca. 90° , the 1,2- and 5,6-vicinal H,H couplings do not cause a double split of the 1-H and 6-H signals of the di-*exo* compounds, while these couplings lead to an easily detectable 2–4 Hz split for the di-*endo*-annelated molecules, in which the dihedral angles are ca. 30° . As a result of the 1-H,6-H interaction, the 1- and 6-H atoms give a doublet for the di-*exo* derivatives and a double doublet for the di-*endo* analogs. Owing to signal overlap in **10**, the di-*exo* annelation cannot be demonstrated either by the splitting pattern of the 1-H and 6-H signals or by the NOE between these hydrogen atoms and 7(*endo*)-H. However, the X-ray measurements confirmed the stereostructure given in Scheme 1 and Figure 2.

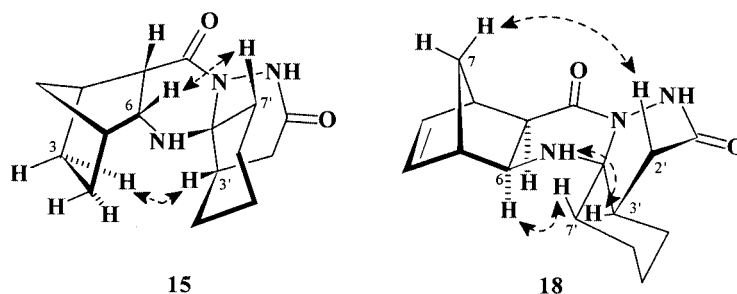
To determine the stereostructures, DIFFNOE measurements were carried out. On saturation of the 6-H multiplet of **5**, the 3'-H signal did not respond. This negative result cannot be accepted as definite proof of the distant arrangement of these hydrogen atoms (6 and 3'). The X-ray results for **6**, however, demonstrate that the 1,6-H and 3'-H atoms are positioned on opposite sides of the molecular skeleton. Because of the very similar ^1H and ^{13}C NMR chemical shifts of the atoms in rings C–E of **5** and **6**, an analogous

stereostructure is very plausible for **5**. For the same reason as in the cases of **5** and **6**, **7** and **8** must also have analogous stereostructures, and this was confirmed in fact by X-ray measurements on **8**. The *cis*-D/E annelation in both **7** and **10** is straightforward on the basis of the similar 2'-H and 3'-H coupling constants (9.1 and 8.6 Hz for **10**) and the C-3' carbon signal shifts ($\delta = 38.7$ and 38.3 ppm). The DIFFNOE results suggest a close-lying arrangement of 1,6-H atoms and the 7'-CH₂ group, in agreement with the X-ray findings. Similarly, the downfield shifts of the 1,6-H signals of **7**, relative to those of **10**, may originate from the anisotropic effect of the C–O bond;^[19c] such an observation is to be expected from the stereostructure given in Scheme 1.

The NOEs for the pairs 6-H and 7'(eq)-H, and 3(*endo*)-H and 3'-H (Figure 3) are decisive as concerns the constitution and stereostructure of **15**. The former [6-H,7'(eq)-H] interaction and the very similar ^{13}C NMR shifts of ring E suggest an analogous stereostructure for **16**. This is also valid for **17** and **18**, and the further NOEs prove the sterically close arrangement of 2'(ax)-H and 7(*endo*)-H and 3'-H and the amine-NH, respectively, which confirms the 3D structures of **17** and **18**, as illustrated for **18** in Figure 3.

Conclusion

The reaction of aminonorbornane/enecarboxylic acids **1–4** with ethyl 2-(2-oxocyclohexyl)acetate gives methanoindol-

Figure 3. NOE interactions in **15** and **18**.

oquinolines **5**, **6**, **8** and **9** where the ester group participates as a two-membered sp^2 building block. With carbohydrazides **11–14** the oxoester forms the pentacyclic bis(acyl hydrazides) **15–18** by cyclodehydration.

Experimental Section

General: IR spectra were recorded in KBr disks with 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 temp. with a Bruker DRX-500 spectrometer at 500.13 (^1H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as the internal standard. The variable-temperature NMR measurements were carried out in $[\text{D}_6]\text{DMSO}$ in the range of 298–353 K with a Bruker AM 300 spectrometer. The standard Bruker microprogram NOEMULT with a selective pre-irradiation time was used to generate NOE^[23] and DIFFNOE spectra^[19d,24]. DEPT spectra^[25] were recorded in a standard manner^[26] using only a $\theta = 135^\circ$ pulse to separate the CH/CH_3 and CH_2 lines phased “up” and “down”, respectively. The 2D-COSY,^[27a,28a] HMQC,^[27b,28b] and HMBC^[29,30] spectra were obtained by using the standard Bruker pulse programs COSY-45, INV4GSSW, and INV4GSLRNDWS, respectively.

7,10-Methano-1,2,3,3a,6ar,7t,8,9,10t,10ac- and **-1,2,3,3a,6ar,7c,8,9,10c,10ac-decahydroindolo[4,5-ab]quinoline-5,11-diones (5 and 8)**, **7,10-Methano-1,2,3,3a,6ar,7t,10t,10ac-** and **-1,2,3,3a,6ar,7c,10c,10ac-octahydroindolo[4,5-ab]quinoline-5,11-diones (6 and 9)**, **8,11-Methano-1,2,3,4,4a,7ac,8t,11t,11ac,13a-** and **-1,2,3,4,4a,7ac,8c,11c,11ac,13a-decahydroindolo[1,7a-ab][3,1]benzoxazine-6,12-diones (7 and 10):** A mixture of amino acid **1–4** (1.5 g, 0.01 mol), ethyl 2-(2-oxocyclohexyl)acetate (1.8 g, 0.01 mol), and PTSA (0.05 g) in dry chlorobenzene (100 mL) was refluxed for 5 h. After cooling, the mixture was filtered, the filtrate was concentrated, and the residue was transferred onto a chromatographic column (Acros, Al_2O_3 basic, 50–200 μ) and eluted with EtOAc. The first eluates resulted

in **5**, **6**, **8**, or **9** [monitoring by TLC, silica gel, TLC aluminium sheets, solvent: benzene/EtOH/petroleum ether (b.p. 40–60 $^\circ\text{C}$), 4:1:3, development in iodine vapour] and the later ones contained **7** or **10**. The latter eluates were combined, concentrated and purified by chromatography again with EtOAc on SiO_2 (Kieselgel 60, Merck, 0.040–0.063 mm, EtOAc) (monitoring on TLC as above). The eluates were concentrated and crystallized. Compound **7** was also obtained from the mother liquor of **10**. Data on the colourless compounds **5–10** are listed in Table 3.

9,12-Methano-3,3a,4,5,6,7,8ar,9t,10,11,12t,12ac- and **-3,3a,4,5,6,7,8ar,9c,10,11,12c,12ac-dodecahydro-** (**15 and 17**) and **9,12-Methano-3,3a,4,5,6,7,8ar,9t,12t,12ac-** and **-3,3a,4,5,6,7,8ar,9c,12c,12ac-decahydroquinazolo[3,2-b]phthalazine-2,13-diones (16 and 18):** A mixture of aminonorbornane- or -norbornenecarbohydrazide **11–14** (1.7 g, 0.01 mol), ethyl 2-(2-oxocyclohexyl)acetate (1.8 g, 0.01 mol), and PTSA (0.05 g) in dry toluene (50 mL) was refluxed for 5 h. After filtration, the solution was concentrated to dryness, and the residue was transferred onto a SiO_2 column (Kieselgel 60, Merck, 0.040–0.063 mm) and eluted with an *n*-hexane/EtOAc (2:1) mixture. The residue was crystallized to obtain colourless crystals.

Isolation of the Cyclohexane-Fused Pyridazinone 19: After the isolation of **18**, the above SiO_2 column was further eluted with EtOH. Pyridazinone **19** was obtained from the residue by crystallization from Et_2O . Yield: 0.33 g (22%), m.p. 113–114 $^\circ\text{C}$.

X-ray Crystallographic Study: Crystallographic data were collected at 173 K with a Nonius-Kappa CCD area detector diffractometer using graphite-monochromatized Mo-K_α radiation ($\lambda = 0.71073 \text{ \AA}$). The data were collected by φ and ω rotation scans and processed with the DENZO-SMN v0.93.0 software package.^[31]

Crystal Data for 6: $\text{C}_{16}\text{H}_{17}\text{NO}_2$, $M_r = 255.31$, monoclinic, $a = 11.1876(6)$, $b = 6.4193(2)$, $c = 17.4923(11) \text{ \AA}$, $\beta = 102.975(2)^\circ$, $V = 1224.16(11) \text{ \AA}^3$, $T = 173 \text{ K}$, space group $P2_1/n$ (no. 14), $Z = 4$, $\mu(\text{Mo-K}_\alpha) = 0.091 \text{ mm}^{-1}$, 2007 unique reflections ($R_{\text{int}} = 0.0213$), which were used in the calculations. The final $wR(F^2)$ value was 0.088 (all data).

Table 3. Physical and analytical data for compounds **5–10** and **15–19**.

Compound	M.p. [$^\circ\text{C}$]	Yield [%]	Empirical formula (formula mass)	Analysis					
				C	Found H	N	C	Calcd. H	N
5	182–184 ^[a]	28	$\text{C}_{16}\text{H}_{19}\text{NO}_2$ (257.33)	74.54	7.17	5.17	74.68	7.44	5.44
6	191–193 ^[b]	25	$\text{C}_{16}\text{H}_{17}\text{NO}_2$ (255.31)	75.43	6.85	5.67	75.27	6.71	5.49
7	135–137 ^[b]	20	$\text{C}_{16}\text{H}_{19}\text{NO}_3$ (273.33)	70.46	6.92	5.25	70.31	7.01	5.12
8	148–150 ^[b]	26	$\text{C}_{16}\text{H}_{19}\text{NO}_2$ (257.33)	74.47	7.23	5.27	74.68	7.44	5.44
9	154–156 ^[b]	21	$\text{C}_{16}\text{H}_{17}\text{NO}_2$ (255.31)	75.48	6.42	5.25	75.27	6.71	5.49
10	157–159 ^[b]	18	$\text{C}_{16}\text{H}_{19}\text{NO}_3$ (273.33)	70.49	7.19	4.90	70.31	7.01	5.12
15	208–210 ^[c]	46	$\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}_2$ (289.37)	66.70	8.25	14.31	66.41	8.01	14.52
16	235–237 ^[c]	42	$\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_2$ (287.36)	66.58	7.11	14.85	66.88	7.37	14.62
17	212–214 ^[c]	46	$\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}_2$ (289.37)	66.75	7.74	14.27	66.41	8.01	14.52
18	220–222 ^[c]	52	$\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_2$ (287.36)	66.70	7.63	14.48	66.88	7.37	14.62
19	113–114 ^[d]	22	$\text{C}_8\text{H}_{12}\text{N}_2\text{O}$ (152.19)	62.85	7.67	18.20	63.13	7.95	18.41

[a] Crystallization solvent: EtOAc. [b] Crystallization solvent: benzene. [c] Crystallization solvent: EtOH. [d] Crystallization solvent: Et_2O .

Crystal Data for 7: $C_{16}H_{19}NO_3$, $M_r = 273.32$, monoclinic, $a = 12.9300(8)$, $b = 6.4605(2)$, $c = 16.6447(10)$ Å, $\beta = 103.886(2)^\circ$, $V = 1349.77(12)$ Å³, $T = 173$ K, space group $P2_1/n$ (no. 14), $Z = 4$, $\mu(Mo-K_\alpha) = 0.093$ mm⁻¹, 2223 unique reflections ($R_{int} = 0.0337$), which were used in the calculations. The final $wR(F^2)$ value was 0.0964 (all data).

Crystal Data for 8: $C_{16}H_{19}NO_2$, $M_r = 257.32$, orthorhombic, $a = 8.7872(4)$, $b = 16.9539(10)$, $c = 17.3647(10)$ Å, $\alpha = \beta = \gamma = 90^\circ$, $V = 2586.9(2)$ Å³, $T = 173$ K, space group $Pcab$ (no. 61), $Z = 8$, $\mu(Mo-K_\alpha) = 0.087$ mm⁻¹, 2537 unique reflections ($R_{int} = 0.0351$), which were used in the calculations. The final $wR(F^2)$ value was 0.1639 (all data).

Crystal Data for 10: $C_{16}H_{19}NO_3$, $M_r = 273.32$, monoclinic, $a = 8.3478(6)$, $b = 6.4362(2)$, $c = 24.4770(14)$ Å, $\beta = 94.637(3)^\circ$, $V = 1310.80(13)$ Å³, $T = 173$ K, space group $P2_1/n$ (no. 14), $Z = 4$, $\mu(Mo-K_\alpha) = 0.096$ mm⁻¹, 2398 unique reflections ($R_{int} = 0.0459$), which were used in the calculations. The final $wR(F^2)$ value was 0.1096 (all data).

The structures were solved by direct methods by use of the SIR92 program^[32] and full-matrix, least-squares refinements on F^2 were performed by use of the SHELXL-97 program.^[33] In all cases the heavy atoms were refined anisotropically. The hydrogen atoms were included at fixed distances with fixed displacement parameters from their host atoms. Figures were drawn with ORTEP-3 for Windows.^[34] CCDC-262063 to -262066 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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