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Synthesis of Methylene-bridged Partially Saturated Quinazolones

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With imidates, esters (**5**–**8**) of di-*endo* (**1** and **2**) and di-*exo* (**3** and **4**) norbornane- and norbornene-β-amino acids yield methylene-bridged tetrahydro- (**18** and **20**) and hexahydro-4-quinazolinones (**17** and **19**); the reaction of the corresponding carboxamides (**9**–**12**) with 4-chlorobenzaldehyde furnish hexahydro- (**14** and **16**) and octahydro-4-quinazolinones (**13** and **15**). The tetrahydro derivatives **18a,b** can be selectively reduced to the hexahydro (**17a,b**) or octahydro (**13b**) compounds. The reaction with aldehyde is stereospecific; only the isomers containing the 2-H and 8a-H atoms in identical steric positions are formed. When boiled in a solvent or heated to melting, the 4-quinazolines having a double bond in the carbobicycle split off cyclopentadiene with formation of the 2-substituted 4(3*H*)-pyrimidinones (**21**).

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Aus den Estern (**5**–**8**) der di-*endo* (**1** und **2**) und di-*exo* (**3** und **4**) Norbornan- und Norbornen-β-aminosäuren wurden mit Imidaten die Methylen-überbrückten Tetrahydro- (**18** und **20**) und Hexahydro-4-chinazolinone (**17** und **19**) sowie aus den entsprechenden Aminosäureamiden (**9**–**12**) mit 4-Chlorbenzaldehyd die Hexahydro- (**14** und **16**) und Octahydro-4-chinazolinone (**13** und **15**) gewonnen. Die Tetrahydro-Verbindungen **18a,b** konnten zu Hexahydro- (**17a,b**) oder Octahydro-Derivaten (**13b**) reduziert werden. Die Reaktion mit Aldehyd ist stereospezifisch, wobei sich nur die 2- und 8a-Wasserstoffatome in identischen Stereopositionen enthaltenden Isomere bilden. Die im carbocyclischen Ring eine Doppelbindung enthaltenden 4-Chinazolone zersetzen sich beim Kochen in Lösung oder beim Schmelzen, wobei sich Cyclopentadien abspaltet und substituierte 4(3*H*)-Pyrimidinon-Derivate bilden.

Di-*endo*[2] (**1**) and di-*exo*[3] (**3**) 3-aminobicyclo[2.2.1]-heptane-2-carboxylic acids and their 5-unsaturated analogues[3,4] (**2** and **4**) have previously been used as starting compounds in our syntheses of 1,3-heterocycles condensed with norbornane and norbornene skeletons[4–6]. In the class of fused tricyclic, partly saturated heterocyclic compounds, we have prepared 1,3-oxazines, the isomeric methano-3,1-benzoxazines[7], and 1,3-oxazin-2-ones and -thiones, and the NMR spectroscopic properties of these compounds have been systematically studied[1,8,9]. Through cycloreversion of the tricyclic 1,3-oxazin-4-ones and 2-thioxo-4-pyrimidinones obtained from the amino acids **2** and **4**, a method has been developed for the synthesis of heteromonocycles such as 6*H*-1,3-oxazin-6-ones[4,5] and thiouracils[6], which are accessible only with difficulty by other means.

In the present work the synthesis of methylene-bridged tetrahydro- and octahydroquinazolones is described. These compounds have been prepared for pharmacological testing, since some of them are cyclopentane ring ethylene- or ethylidene-bridged derivatives of *cis*-5,6-trimethylene-2-(3-chlorophenyl)pyrimidin-4(3*H*)-one[10], a compound we prepared earlier which has outstanding anti-inflammatory and analgesic effects.

Synthesis

The starting compound *endo*-3-aminobicylo[2.2.1]hept-5-ene-*endo*-2-carboxylic acid (**2**) was synthesized by ammonolysis of the Diels-Alder adduct of cyclopentadiene and maleic anhydride, followed by Hofmann degradation with sodium hypochlorite[3]. After esterification, the double bond was hydrogenated and the ester was hydrolysed to obtain the corresponding bicyclo[2.2.1]heptanecarboxylic acid[2] **1**. The *cis-exo* isomers were prepared from norbornene and norbornadiene by means of chlorosulfonyl isocyanate addition[11]. After sulfite reduction of the adduct[12], opening of the azetidinone ring with hydrochloric acid gave the amino acids **3** and **4**[3,5].

The di-*endo* (**1** and **2**) and di-*exo* (**3** and **4**) amino acids were esterified with ethanol and the ester bases **5**–**8**, liberated from the hydrochlorides, were treated with ammonia to furnish the amides **9**–**12**. With 4-chlorobenzaldehyde, these compounds were cyclized to 2-(4-chlorophenyl)-2,3,4a*r*,5*t*,6,7,8*t*,8a*c*-octahydro-5,8-methano-4(1*H*)-quinazolinone (**13b**), the corresponding 2,3,4a*r*,5*t*,8*t*,8a*c*-hexahydro derivative (**14b**), and the 5*c*,8*c* isomers (**15b** and **16b**) (Scheme 1).

With imidates, the esters **5**–**8** furnished the tricyclic 2-substituted 4a*r*,5*t*,6,7,8*t*,8a*c*-hexahydro-5,8-methano-4(3*H*)-quinazolinones (**17**), the 4a*r*,5*t*,8*t*,8a*c*-tetrahydro analogues (**18**), and the 5*c*,8*c* isomers (**19** and **20**).

When the norbornene-β-amino acids **2** and **4** were boiled with benzimidates in ethanol, the products were not the expected di-*endo* (**18**) and di-*exo* (**20**) norbornene-fused pyrimidinones; the tricyclic compounds formed split off cyclo-

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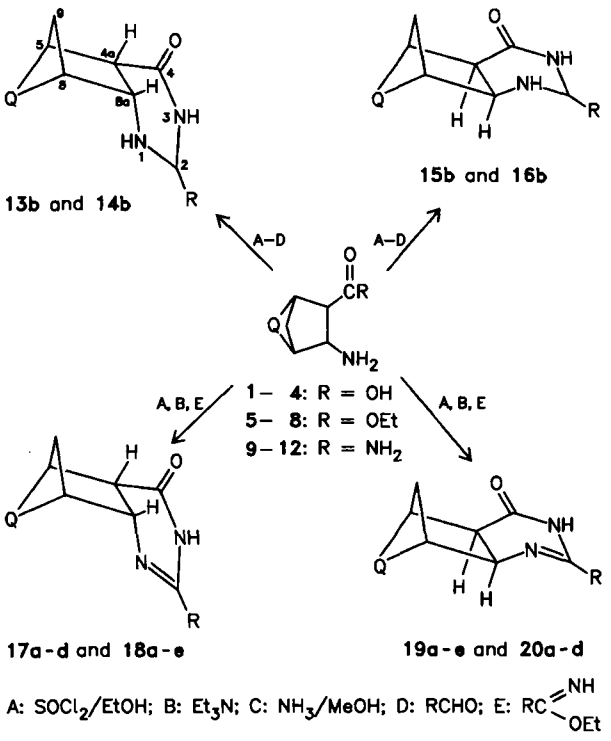
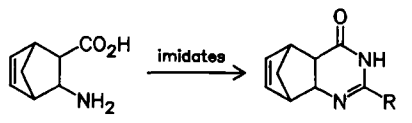
pentadiene to yield the corresponding 2-aryl-4(3*H*)-pyrimidinones (**21**) (Scheme 2). At their melting point, the pyrimidinones fused with norbornene underwent a retro Diels-Alder reaction to give the known compounds[13-17] **21a, b** and **d**; **21a–d** were previously prepared in this laboratory from the di-*exo* norbornene-fused azetidinone via ring transformation with imidates, followed by cycloreversion[18].

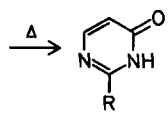
Scheme 1



		Q		R
1, 5, 9, 13, 17	di-*endo*	CH_2-CH_2	a	C_6H_5
2, 6, 10, 14, 18	di-*endo*	CH=CH	b	C_6H_4Cl-(4)
3, 7, 11, 15, 19	di-*exo*	CH_2-CH_2	c	C_6H_4Cl-(3)
4, 8, 12, 16, 20	di-*exo*	CH=CH	d	$C_6H_4CH_3$-(4)
			e	cyclohexyl

Scheme 2





	R
21a	C_6H_5
b	C_6H_4Cl-(4)
c	C_6H_4Cl-(3)
d	$C_6H_4CH_3$-(4)

Compounds **18a, b** were hydrogenated in the presence of Pd/C at room temperature to yield **17a, b**. When a platinum oxide catalyst was used, the C=N double bond was also reduced; in this way, **18b** gave the octahydro derivative **13b**.

Structure Determination by Spectroscopy

The IR, ^1H- and ^{13}C-NMR spectral data of the new compounds, supporting the proposed structures, are shown in Tables 1 and 2. A systematic spectroscopic investigation of the 1,3-oxazine analogues has been reported earlier[1,8,9].

The suggested structures of compounds **17–20** are corroborated not only by all the expected spectral characteristics, but also by the significant downfield shift of the carbonyl (C-4) signal and the "amidine" (C-2) line. Due to the greater –I effect of the hetero ring, the 4a,5,8,8a-H atoms and similarly the 4a,8a carbons are deshielded compared to those for the oxazine derivatives[1]; the largest downfield shift is found for the 5-H signal of series **19** and **20**, where the anisotropic effect[19a] of the coplanar carbonyl group contributes to this shift. The downfield shifts of the C-4a signal are in accordance with the values expected from the substituent constants[19b] only for the norbornenes. For the norbornanes, the substituent effect is partly compensated by the steric compression shift[20] with opposite sign, resulting from the increased steric hindrance.

Similarly, the C-5 atom in the norbornenes is more shielded by about 4 ppm as compared with the oxazinones[1], just as expected (the β-effect of the methylene substituent[21] gives rise to a downfield shift which is about 6 ppm larger than that due to the carbonyl group[19b]); at the same time, in series **17** there is no change relative to the oxazine derivatives, while for compounds **19** an ≈2 ppm downfield shift of the C-5 line is observed. In the quinazolones, the field effect of the 4-methylene group, acting in the oxazines, is absent, and this fact compensates the difference between the β-effects. (As compared with the 4-methylene group, the 4-carbonyl increases the strain on the C-4a atom; on the other hand, the hindrance between 4-H and 5-H, observed in the oxazine derivatives, is absent in the 4-oxo series.)

As compared with the 4-methylene analogues, the C-9 signal is shifted upfield in the di-*endo* compounds **17** and **18**, and in the opposite direction in the di-*exo* series. Thus, the substituent effect clearly stands out in the di-*endo* series, whereas in the di-*exo* compounds it is "concealed" again, because of the absence of the field effect (no hindrance between 4-H and 9-H).

A new problem emerges as concerns the configuration at C-2 in compounds **13b–16b**. In these derivatives the proposed structures are obviously supported by the presence and position of the 2-H and the corresponding C-2 signals. The latter are found not in the shift range 146.2–148.1 ppm characteristic of compounds **17–20**, but between 68.7 and 69.3 ppm, in accordance with the difference $sp^2 \rightarrow sp^3$.

Elucidation of the configuration at C-2 is difficult, because the flexibility of the hetero ring allows two relatively stable conformations. In one of them, for the di-*endo* compounds **13b** and **14b**, very great steric hindrance would occur between the *endo*- (**13b**) or olefinic (**14b**) 6,7-H and 2-H atoms, the interatomic distance being ≈1.4 Å; therefore, this ar-

Table 1. IR [cm^{-1}] and ^1H-NMR data[a]

	Amide-I band	vNH band (broad)	vC=N band	4a-H d/dd (1H)[b]	5-H s (1H)	8-H s (1H)	8a-H d/dd (1H)[b]	6,7-H 2 × dd or s/m (2/4H)[c]	9-H 2 × d/s (2H)[d]	NH ≈s (1H)[e]	ArH[f]
13b[g]	1643	≈3215	–	2.55	2.75	2.50	3.65	1.4–1.8[h]		6.30	7.40
14b[g]	1640	≈3190	–	2.69	3.47	3.16	4.02	6.50 6.12	1.52 1.64	6.30	7.27, 7.37
15b[g]	1645	3275, 3190	–	≈2.2[h]	2.87	≈2.2[h]	3.34	1.1–1.7[h]		7.00	7.34
16b[g]	1646	3200, 3150	–	2.12	3.44	2.82	3.32	6.31 6.12	1.51 1.72	6.53	7.37
17a	1680	3250–3000	1655	2.73	2.80		4.28	1.3–1.5[g]	1.4[h] 1.56	≈9.2	≈7.43, 7.77
17b	1690	3250–2700	1645	2.75	2.81		4.30	1.3–1.5[g]	1.45[h] 1.59	9.07	7.41, 7.73
17c	1680	3300–3000	1650	2.65–2.85[h]			4.28	1.3–1.6[h]		≈10.15	7.30, 7.38 7.69, 7.83
17d[i]	1680	3300–3000	1650	2.6–2.8[h]			4.25	1.3–1.6[h]		≈9.75	7.16, 7.68
18a	1680	3300–2800	1660	2.96	3.52[j]	3.48[j]	4.53	6.12	1.40 1.48	≈8.8	≈7.43, 7.67
18b	1680	3300–2800	1655	2.96	3.50		4.51	6.12	1.41 1.48	9.39	7.36, 7.67
18c	1695	3300–2700	1650	2.97	3.52		4.53	6.13	1.40 1.49	9.51	7.32, 7.41 7.60, 7.74
18d[i]	1690	3300–2800	1670	2.94	≈3.48		4.40	6.10	1.35 1.42	9.08	7.19, 7.58
18e	1705	3300–2750	1670	2.86	3.42		4.32	6.09	1.2–1.45[j]	9.12	–
19a	1680	≈3235	1650	2.53	2.73	2.60	3.98	≈1.43[h] ≈1.67	≈1.43[h] 1.22	≈9.0	≈7.45, 7.76
19b	1680	≈3220	1650	2.56	2.76	2.61	4.00	1.4–1.7[h]	≈1.5[h] 1.25	8.00	7.42, 7.66
19c	1680	≈3230	1655	2.52	2.74	2.60	3.97	≈1.39[h] ≈1.64	≈1.39[h] 1.22	≈9.8	7.33, 7.41 7.67, 7.83
19d[i]	1680	≈3235	1650	2.54	2.74	2.60	3.98	≈1.43[h] ≈1.64	≈1.43[h] 1.22	≈8.7	7.23, 7.64
19e	1705	3250–3000	1660	2.42	2.65	2.44	3.77	1.1–1.9[k]		≈9.3	–
20a	1684	≈3250	1650	2.41	3.36	3.28	3.94	6.35 6.26	1.45	8.9	≈7.48, 7.79
20b	1684	≈3230	1653	2.42	3.38	3.27	3.94	6.37 6.27	1.41 1.47	8.05	7.44, 7.68
20c	1682	≈3200	1653	2.41	3.38	3.28	3.94	6.36 6.27	1.44	≈9.6	7.38, 7.44 7.70, 7.87
20d[i]	1690	≈3400	1653	≈2.42[h]	3.37	3.28	3.93	6.36 6.25	1.44	≈8.4	7.25, 7.67

[a] IR in KBr pellet; ^1H NMR: in $CDCl_3$ solution at 250 MHz; $\delta_{TMS} = 0$ ppm, coupling constants in Hz. – [b] dd for di-*endo* compounds (**13b**, **14b**, **17a–d** and **18a–e**), J(4a,8a) = 10.6 (**13b**), 9.0 (**14b**), 11.5 (**17a, b**), 11.6 (**17c, d**), 9.6 (**18a, d**), 9.7 (**18b, e**), and 9.8 (**18c**); J(8,8a) = 4.3 (**13b**, **17d**), 3.8 (**14b**, **18a, b**), 4.2 (**17a, c**), 4.4 (**17b**), 3.6 (**18c, e**), and 3.7 (**18d**); d for di-*exo* compounds (**15b**, **16b**, **19a–e** and **20a–d**), J(4a,8a) = 7.6 (**15b**, **16b**), 8.9 (**19a, c–e**), 8.8 (**19b**), 8.7 (**20a, b**), and 8.6 (**20c, d**). – [c] 2 × dd (2 × 1H) (**14b**, **16b** and **20a–d**, respectively), or s (2H) for norbornenes (**18a–e**), one or two signals of overlapping m's (4H or 2 × 2H) for norbornanes (**13b**, **15b**, **17a–d** and **19a–e**), partly or fully overlapping also with one or both of the 9-H d's. J(6,7) = 5.5 ± 0.2, J(5,6) = J(7,8); 2.8–3.1 for compounds **14b**, **16b** and **20a–d**. – [d] 2 × d (AB spin system, 2H) coalesced to an s for **20a, c, d**, due to isochrony of the two 9-H atoms (A_2 limiting case), ^2J(A,B) = 8.9 (**14b**), 9.2 (**16b**, **20b**), ≈10 (**17a**, **19d**), 9.9 (**17b**), ≈9 (**18a, c**), 8.8 (**18b**), 8.7 (**18d**), 10.4 (**19a, b**) and 10.3 (**19c**). – [e] Broad signal of NH-3. The signal of NH-1 of compounds **13b–16b** appears at 1.73 (**14b**), 1.54 (**16b**), and about 1.3–1.6 ppm, overlapping with the 6,7,9-H m's (**13b**, **15b**). – [f] s (4H) for **13b**, **15b**, and **16b**; AA'BB' type spectrum, 2 × ≈d (2 × 2H) for **14b**, **17b, d**, **18b, d**, **19b, d**, and **20b, d**, J(A,B) = 8.5 (**14b**, **18b**), 8.6 (**17b**, **19b**, **20b**), 8.1 (**17d**, **19d**), and 8.0 (**18d**, **20d**). (The upfield d's correspond to 2',6'-H of the phenyl ring). For phenyl-substituted compounds **a** m (3H, 3',4',5'-H) + dd (2H, 2',6'-H) (m is the upfield signal). Four signals (4 × 1H) in order of increasing downfield shifts ≈t (5'-H), ≈d (4'-H), ≈d (6'-H), and ≈s (2'-H) for *meta*-chlorophenyl derivatives **c**. – [g] 2-H, s (1H): 5.24 (**13b**), 5.20 (**14b**), 5.10 (**15b**), and 5.19 (**16b**). – [h] Overlapping signals. – [i] CH_3(Ar) s (3H): 2.33 (**17d**), 2.36 (**18d**), 2.39 (**19d**), and 2.40 (**20d**). – [j] Due to overlap of the near lines in the 5-H and 8-H m's, these signals appear as approximate singlets in most cases, except for **18a**, where doublets are observed (split by 1.6 and 1.4 Hz, respectively). – [k] These signals overlap with the methylene signals of the cyclohexyl ring in Pos. 3,4 (**18e**) and Pos. 2,3,4 (**19e**), respectively; thus, the total intensities are 8H and 16H (**19e**); CH_2 (cyclohexyl, Pos. 2, **18e**): 1.65–1.84 m (4H); CH (cyclohexyl, Pos. 1), t (1H); 2.03 (**18e**), 2.08 (**19e**).

rangement need not be considered. In the other (N-1 *endo*, C-2 *exo*) conformer, if the isomer contains the 2-H and 8a-H atoms in the *trans* position, high steric hindrance must occur between the quasiaxial phenyl ring and the 4a,8a-H atoms. However, as the C-4a signal in **13b** is shifted downfield as compared with that for the analogue **17b**, while the upfield shift of the C-8a signal is due to the substituent effect, it is much more probable that the phenyl ring is quasiequatorial, as was likely from the outset (thus, the 2-H and 8a-H atoms are *cis*-arranged and the C-2 configuration is 2*R**). The anisotropy (increased shielding) of a quasiaxial phenyl ring cannot be observed for the 4a-H and 8a-H signals, either.

The case is similar in the di-*exo* compounds **15b**, **16b**, where, owing to the close vicinity (≈1.4 Å) of the *exo*-2-H and the inner 9-H atom, one of the relatively stable conformations of the hetero ring can obviously be excluded. In the other conformer with *trans* 2-H,8a-H configuration involving the quasiequatorial position of the aryl substituent, upfield shifts of the C-4a,8a lines and the 4a,8a-H signals would be expected, due to the field effect and the anisotropic effect. However, for the pair **16b**, **15b** the C-4a line is shifted downfield. Though an upfield shift (0.5 ppm) can be observed for compound **16b** compared with **20b**, it is too small to be responsible for the mentioned field effect. The C-8a atom is more shielded in isomers **15b** and **16b** than in their counterparts **19b** and **20b**, but this can be explained by the α-effect of the sp^2 nitrogen, which gives rise to a larger downfield shift than the NH group does. (Evidence against a field effect is provided by the larger shift for the norbornene pair **20b**, **16b**, since this would be greater in the norbornanes.)

The increases in shielding of the 4a-H and 8a-H atoms for the pairs **15b**, **19b** and **16b**, **20b** are almost equal to those found for the analogues **13b**, **17b** and **14b**, **18b**; they

Table 2. ^{13}C-NMR data[a-c]

	C-2	C = O (4)	C-4a[d]	C-5[d]	C-6[e]	C-7[e]	C-8[d]	C-8a	C-9	C-1′	C-2′,6′	C-3′,5′	C-4′	CH_3
13b[h]	62.9	173.1	45.5	39.8	24.1	22.1	41.6	56.4	37.5	138.2	128.1	129.4	135.4	–
14b[h]	69.3	173.0	46.7	44.3	133.1	140.2	46.2	59.0	47.6	137.9	127.5	129.4	135.3	–
15b	68.9	172.9	50.3	40.8	30.3	27.6	44.1	62.5	35.0	140.8	129.7	130.6	134.7	–
16b[h]	68.7	173.2	48.4	44.1	135.1	139.0	45.1	57.3	44.5	137.9	129.4	128.1	135.4	–
17a	147.9	172.0	44.2	42.1	25.1	21.5	42.4	61.6	37.3	134.2	126.4	128.8	130.9	–
17b[h]	146.8	172.1	44.2	42.0	25.0	21.5	42.4	61.7	37.3	137.2	127.8	129.1	132.5	–
17c	146.9	172.4	44.3	42.1	25.1	21.6	42.4	61.7	37.3	135.1[f]	127.1 124.5	135.9[f] 129.9[g]	130.9[g]	–
17d	148.1	172.7	44.2	41.7	25.0	21.4	42.3	61.2	37.1	131.2	126.6	129.1	140.8	21.3
18a[h]	147.5	171.6	50.3	42.6	135.4	136.5	49.0	62.3	46.4	134.2	126.3	128.7	130.8	–
18b	146.8	171.8	50.4	42.7	135.4	136.4	49.1	62.4	46.4	137.0	127.9	128.4	132.7	–
18c	146.7	172.1	50.5	42.7	135.5	136.5	49.1	62.4	46.4	135.0[f]	127.1 124.6	136.1[f] 129.8[g]	130.8[g]	–
18d	147.6	171.8	50.4	42.7	135.3	136.5	49.0	62.2	46.3	131.5	126.4	129.2	140.9	21.2
18e	153.6	171.6	50.1	42.9	135.1	136.4	49.0	61.7	46.2	44.4	30.0 30.2	25.9		–
19a[h]	147.3	171.5	47.5	43.2	29.9	26.6	46.3	65.2	34.7	134.2	126.2	128.8	130.9	–
19b	146.2	171.0	47.6	43.3	29.9	26.7	46.3	65.4	34.8	137.4	127.5	129.2	132.6	–
19c	146.9	172.0	47.5	43.3	30.0	26.7	46.3	65.2	34.8	135.0[f]	127.1 124.4	136.0[f] 129.9[g]	130.9[g]	–
19d	147.1	171.4	47.7	43.3	30.0	26.7	46.4	65.2	34.8	131.5	126.2	129.5	141.2	21.3
20a	147.8	171.5	48.9	41.8	136.5	139.0	52.7	61.6	44.5	134.0	126.3	128.9	131.0	–
20b[h]	146.6	171.0	48.9	41.9	136.6	139.0	52.7	61.8	44.5	137.4	127.5	129.2	132.5	–
20c	146.8	172.0	49.0	41.7	136.5	139.0	52.7	61.6	44.5	135.1[f]	127.1 124.4	135.7[f] 130.0[g]	131.0[g]	–
20d	147.8	171.6	48.9	41.8	136.6	139.0	52.8	61.5	44.5	131.2	126.2	129.6	141.4	21.4

[a] In $CDCl_3$ solution, at 62.89 MHz, $\delta_{TMS} = 0$ ppm. – [b] In [D_6]DMSO solution for **15b**. – [c] At 20.14 MHz for **20a,c,d**. – [d-g] Reversed assignments may also be possible. – [h] Assignments were proved by DEPT measurements.

are not greater than expected[22] (corresponding to the saturation of the C=N double bond). Accordingly, in the di-*exo* compounds **15b** and **16b**, too, the *cis* position of the 2-H and 8a-H atoms, and hence the 2*S** configuration at the C-2 atom, seem probable.

To obtain final proof of the steric structures, DNOE measurements were made on compounds **13b**, **14b**, and **16b**.

When the 2-H signal is saturated, an increased intensity of the 8a-H signal (and also of the singlet of the 2-aryl ring) is observed in the spectra of all three compounds; this is unequivocal evidence of the close vicinity of the 2-H and 8a-H atoms, i.e. of their *cis* position relative to the hetero ring, thereby confirming the suggested steric structures.

The reverse experiment, i.e. saturation of the 8a-H signal, also gave the expected result; the intensity of the 2-H signal increased significantly, while that of the aromatic signal remained unchanged. The intensity of the 4a-H signal, too, increased, of course, for all three compounds.

The DNOE measurements further allowed the corroboration of some uncertain assignments.

As concerns the 5,8-H singlets, when the 4a-H signal of **14b** was saturated, the intensity of the downfield singlet increased, while that of its counterpart decreased. On saturation of the 8a-H signal, this pair of singlets reacted in the opposite sense, affording evidence that the former relates to the 5-H, and the latter to the 8-H atom.

In the spectrum of **16b**, saturation of the 5-H signal (and simultaneously also of the 8-H signal) affected the downfield olefin signal, showing that this dd is assignable to the 6-H atom.

Experimental

^{1}H-NMR spectra: $CDCl_3$ solutions in 5-mm tubes at room temperature, Bruker WM-250 FT spectrometer, Aspect 2000 computer, 250.13 MHz, deuterium signal of the solvent as lock, TMS internal standard, Lorentzian exponential multiplication for signal-to-noise enhancement (LB: 0.7 Hz). – ^{13}C-NMR spectra: in $CDCl_3$ or [D_6]DMSO, 5 or 10-mm tubes, room temperature, Bruker WP-80-SY or WM-250 FT spectrometer, Aspect 2000 computer, 20.14 or 62.89 MHz, deuterium signal of the solvent as lock, TMS internal standard, Lorentzian exponential multiplication for signal-to-noise enhancement (2.0 or 1.0 Hz). – DEPT[24] spectra: standard method[25] with only the $\Theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization. – DNOE experiments: Bruker microprogram 12.5, Aspect 2000 pulse programmer.

Ethyl endo-3-Aminobicyclo[2.2.1]heptane-endo-2-carboxylate (**5**), *Ethyl endo-3-Aminobicyclo[2.2.1]hept-5-ene-endo-2-carboxylate* (**6**), *Ethyl exo-3-Aminobicyclo[2.2.1]heptane-exo-2-carboxylate* (**7**), *and Ethyl exo-3-Aminobicyclo[2.2.1]hept-5-ene-exo-2-carboxylate* (**8**): 90 ml of absol. ethanol was cooled to −10°C and 8 ml (0.11 mol) of thionyl chloride was added by drops, with stirring. To this mixture, 15.5 g (0.10 mol) of amino acid **3**, or 15.3 g (0.10 mol) of **2** or **4**, was added and stirring was continued at 0°C for 30 min. After the mixture had stood for 3 h at room temp., it was refluxed for 1 h, and evaporated to dryness. Crystallization of the residue from

ethanol gave the ester hydrochloride as colourless crystals: 13.4 g (62%) of **7** · HCl, m.p. 153–155°C, or 16.2 g (75%) of **6** · HCl, m.p. 178–180°C, or 15.7 g (72%) of **8** · HCl, m.p. 142–144°C.

7 · HCl: $C_{10}H_{18}ClNO_2$ (219.7)	Calcd.	C 54.67	H 8.26	N 6.38
	Found	C 54.85	H 8.42	N 6.22
6/8 · HCl: $C_{10}H_{16}ClNO_2$ (217.7)	Calcd.	C 55.17	H 7.41	N 6.43
6:	Found	C 54.86	H 7.54	N 6.68
8:	Found	C 55.02	H 7.51	N 6.54

The ester hydrochloride of **6** (15.24 g; 70 mmol) in 250 ml of ethanol was reduced with hydrogen at ambient temperature and pressure, with stirring, in the presence of 0.3 g of 5% platinum on activated carbon under nitrogen. After absorption of the calculated amount of hydrogen (4 to 6 h), the catalyst was removed by filtration and the filtrate was evaporated to dryness. The solid residue was crystallized from ethanol to give the hydrochloride of ester **5** as colourless crystals, m.p. 177–180°C, yield 14.6 g (95%).

$C_{10}H_{18}ClNO_2$ (219.7)	Calcd.	C 54.67	H 8.26	N 6.38
	Found	C 54.77	H 8.49	N 6.20

The hydrochloride of ester **5** or 7 (2.20 g; 10 mmol), or of **6** or **8** (2.17 g; 10 mmol), was mixed with 1.0 g (10 mmol) of triethylamine in 20 ml of acetone. After 10 min the solid was filtered off by means of suction, and the filtrate was concentrated. Fractional distillation of the oily residue gave the product as a colourless oil. **5**: b.p. 88–90°C/530 Pa, yield 1.15 g (63%); **6**: b.p. 118–120°C/400 Pa, yield 1.1 g (61%); 7: b.p. 90–92°C/400 Pa, yield 1.2 g (66%); **8**: b.p. 99–101°C/530 Pa, yield 1.0 g (55%).

endo-3-Aminobicyclo[2.2.1]heptane-endo-2-carboxamide (**9**), *endo-3-Aminobicyclo[2.2.1]hept-5-ene-endo-2-carboxamide* (**10**), *exo-3-Aminobicyclo[2.2.1]heptane-exo-2-carboxamide* (**11**), *and exo-3-Aminobicyclo[2.2.1]hept-5-ene-exo-2-carboxamide* (**12**): The amino acid ester **5** or 7 (3.66 g; 20 mmol) or **6** or **8** (3.60 g; 20 mmol) was allowed to stand for 14 days in 100 ml of methanol saturated with ammonia. The mixture was evaporated under reduced pressure and the residue was crystallized from ethanol. **9**: yield 1.6 g (52%), m.p. 183–185°C; **10**: yield 1.26 g (42%), m.p. 198–200°C; **11**: yield 2.1 g (68%), m.p. 224–225°C; **12**: yield 1.75 g (58%), m.p. 223–225°C.

10, **12**: $C_8H_{12}N_2O$ (152.2)	Calcd.	C 63.13	H 7.95	N 18.41
10:	Found	C 63.44	H 7.71	N 18.05
12:	Found	C 63.30	H 7.85	N 18.12
9, **11**: $C_8H_{14}N_2O$ (154.2)	Calcd.	C 62.31	H 9.15	N 18.17
9:	Found	C 62.58	H 9.31	N 17.95
11:	Found	C 62.20	H 9.03	N 18.23

2-(4-Chlorophenyl)-2,3,4ar,5t,6,7,8t,8ac-octahydro-5,8-methano-4(1H)-quinazolinone (**13b**), *2-(4-Chlorophenyl)-2,3,4ar,5t,8t,8ac-hexahydro-5,8-methano-4(1H)-quinazolinone* (**14b**), *2-(4-Chlorophenyl)-2,3,4ar,5c,6,7,8c,8ac-octahydro-5,8-methano-4(1H)-quinazolinone* (**15b**), *and 2-(4-Chlorophenyl)-2,3,4ar,5c,8c,8ac-hexahydro-5,8-methano-4(1H)-quinazolinone* (**16b**): 20 mmol of carboxamide (3.04 g of **10** or **12**; 3.1 g of **9** or **11**) was refluxed in 20 ml of absol. ethanol with 2.8 g (20 mmol) of 4-chlorobenzaldehyde, after the addition of one drop of ethanol saturated with hydrogen chloride. The residue obtained on evaporation was crystallized from ethanol. The data of the colourless crystalline compounds **13b**–**16b** are listed in Table 3.

4ar,5t,6,7,8t,8ac-Hexahydro-5,8-methano-4(3H)-quinazolinones (**17a**–**d**), *4ar,5t,8t,8ac-Tetrahydro-5,8-methano-4(3H)-quinazolinones* (**18a**–**e**), *4ar,5c,6,7,8c,8ac-Hexahydro-5,8-methano-4(3H)-quinazolinones* (**19a**–**e**), *and 4ar,5c,8c,8ac-Tetrahydro-5,8-methano-4(3H)-quinazolinones* (**20a**–**d**): 20 mmol of the amino acid ester (3.66 g of **5** or 7; 3.3 g of **6** or **8**) and 20 mmol of imidate (**a**: 3.0 g of ethyl benzimidate; **b**: 3.67 g of ethyl 4-chlorobenzimidate; **c**: 3.67 g of ethyl 3-chlorobenzimidate; **d**: 3.3 g of ethyl 4-methylbenzimidate; **e**: 3.1 g of ethyl cyclohexanecarboximidate) was refluxed for 10 h in 20 ml of absol. ethanol to which one drop of ethanol saturated with hydrogen chloride had been added. The reaction

Table 3. Physical and analytical data of the compounds obtained

Compd.	M.p. °C	Yield %	Mol. formula	Mol. weight	Analysis Calcd. C	H	N	Found C	H	N
13b	200–201	52	$C_{15}H_{17}ClN_2O$	276.8	65.10	6.19	10.12	64.93	6.05	10.07
14b	234–236	43	$C_{15}H_{15}ClN_2O$	274.75	65.75	5.50	10.20	65.49	5.44	10.23
15b	196–198	47	$C_{15}H_{17}ClN_2O$	276.8	65.10	6.19	10.12	65.37	6.33	9.87
16b	199–201	53	$C_{15}H_{15}ClN_2O$	274.75	65.57	5.50	10.20	65.65	5.29	10.35
17a	188–189	62	$C_{15}H_{16}N_2O$	240.3	74.97	6.71	11.66	74.71	6.92	11.45
17b	283–284	53	$C_{15}H_{15}ClN_2O$	274.75	65.58	5.50	10.20	65.75	5.75	10.14
17c	144–146	62	$C_{15}H_{15}ClN_2O$	274.75	65.58	5.50	10.20	65.27	5.78	10.02
17d	230–231	81	$C_{16}H_{18}N_2O$	254.3	75.56	7.13	11.01	75.82	6.91	10.82
18a	174–176[a]	68	$C_{15}H_{14}N_2O$	238.3	75.61	5.92	11.76	75.55	6.20	11.90
18b	256–258[a]	54	$C_{15}H_{13}ClN_2O$	272.7	66.06	4.80	10.27	66.36	5.03	10.36
18c	170–172[a]	64	$C_{15}H_{13}ClN_2O$	272.7	66.06	4.80	10.27	66.35	5.00	9.96
18d	160–162[a]	68	$C_{16}H_{16}N_2O$	252.3	76.17	6.39	11.10	76.45	6.72	11.03
18e	151–152	59	$C_{15}H_{20}N_2O$	244.3	73.74	8.25	11.46	74.01	8.36	11.25
19a	195–197	65	$C_{15}H_{16}N_2O$	240.3	74.97	6.71	11.66	75.21	6.50	11.67
19b	223–224	58	$C_{15}H_{15}ClN_2O$	274.75	65.58	5.50	10.20	65.47	5.20	10.43
19c	143–145	56	$C_{15}H_{15}ClN_2O$	274.75	65.58	5.50	10.20	65.56	5.64	10.05
19d	186–188	69	$C_{16}H_{18}N_2O$	254.3	75.56	7.13	11.01	75.32	7.48	10.90
19e	129–131	52	$C_{15}H_{22}N_2O$	246.35	73.13	9.00	11.37	72.96	8.90	11.26
20a	162–163	74	$C_{15}H_{14}N_2O$	238.3	75.61	5.92	11.76	75.44	5.79	11.91
20b	250–252[a,b]	56	$C_{15}H_{13}ClN_2O$	272.7	66.06	4.80	10.27	66.25	4.92	10.49
20c	167–169	62	$C_{15}H_{13}ClN_2O$	272.7	66.06	4.80	10.27	66.20	4.92	10.22
20d	210–211	68	$C_{16}H_{16}N_2O$	252.3	76.17	6.39	11.10	76.41	6.24	11.03

[a] By decomposition. – [b] Crystallized from AcOH (poor solubility).

mixture was then evaporated and the residue was crystallized from ethanol/benzene (1:1) to yield colourless crystals. The data of **17**–**20** are listed in Table 3.

Reduction of Compounds **18a, b**

Method A: 0.50 g of **18a** or **18b** was dissolved in 30 ml of ethanol and reduced with hydrogen in the presence of 0.10 g of 5% palladium on activated carbon at ambient temperature and pressure. After the calculated amount of hydrogen had been absorbed (≈1.5 h), the catalyst was removed by filtration, the solvent was evaporated and the residue was crystallized from ethanol. **17a**: m.p. 187–189°C (57%); **17b**: m.p. 281–283°C (61%).

Method B: 0.050 g of platinum oxide catalyst was prehydrogenated in 30 ml of ethanol (30 min) and 0.50 g of **18b** was added. Reduction (2 h) and work-up as described under Method A gave **13b**, m.p. 199–201°C (49%).

CAS Registry Numbers

2: 88330-29-4 / **3**: 88330-32-9 / **4**: 92511-32-5 / **5**: 95630-77-6 / **5** · HCl: 95630-76-5 / **6**: 105786-34-3 / **6** · HCl: 95630-74-3 / **7**: 105786-35-4 / **7** · HCl: 95630-75-4 / **8**: 105786-36-5 / **8** · HCl: 104770-18-5 / **9**: 105786-37-6 / **10**: 105786-38-7 / **11**: 105786-39-8 / **12**: 105786-40-1 / **13b**: 105786-41-2 / **14b**: 105786-42-3 / **15b**: 105879-68-3 / **16b**: 105879-69-4 / **17a**: 105786-43-4 / **17b**: 105786-44-5 / **17c**: 105786-45-6 / **17d**: 105786-46-7 / **18a**: 105786-47-8 / **18b**: 105786-48-9 / **18c**: 105786-49-0 / **18d**: 105786-50-3 / **18e**: 105817-83-2 / **19a**: 105881-17-2 / **19b**: 105879-70-7 / **19c**: 105879-71-8 / **19d**: 105879-72-9 / **19e**: 105786-51-4 / **20a**: 105879-73-0 / **20b**: 105879-74-1 / **20c**: 105881-18-3 / **20d**: 105879-75-2 / 4-Cl-C_6H_4CHO: 104-88-1 / ethyl benzimidate: 825-60-5 / ethyl 4-chlorobenzimidate: 827-72-5 / ethyl 3-chlorobenzimidate: 827-64-5 / ethyl 4-methylbenzimidate: 827-71-4 / ethyl cyclohexanecarboximidate: 52186-77-3

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