Nitrogen Bridgehead Compounds. 48.[1] Synthesis and Stereochemistry of 4-Oxo-1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides

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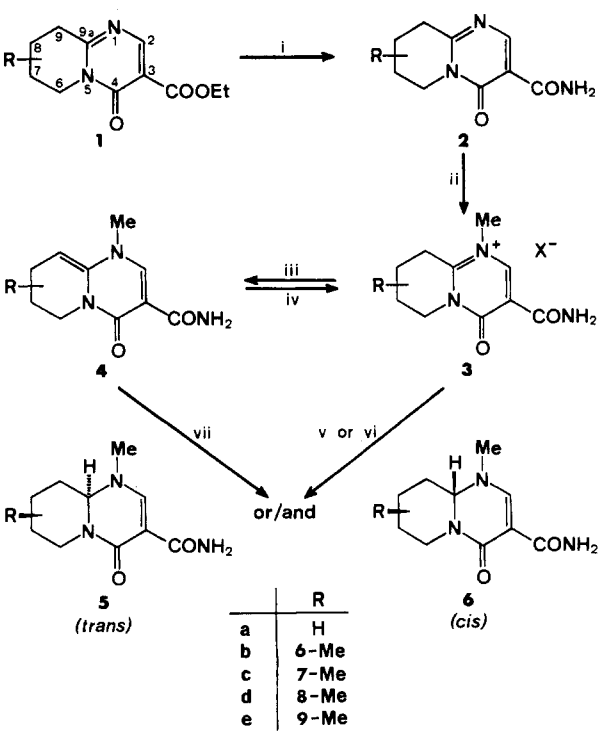
The synthesis, the UV, CD, and ^1H, ^{13}C, and ^{15}N NMR characterization, and the X-ray diffraction analysis of a series of methyl-substituted 4-oxo-1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides **5** and **6** are described. Catalytic (H_2/Pd–C) and $NaBH_4$ reductions of quaternary salts **3** and enamines **4** led to the formation of the 9a-epimeric cis–trans pairs **5** and **6**. $NaBH_4$ reduction of the quaternary salts of type **3** proceeded with high diastereoselectivity to give the thermodynamically more stable epimers. The largest influence of the methyl substituent on the diastereomer ratio was observed in the different reductions of the 6-methyl derivatives **3b** and **4b**. X-ray diffraction analysis of **5a**, **5b**, **6b**, and **9** revealed that while the N(1) atom is nearly planar, the nitrogen atom of the cyclic amide moiety, N(5), is significantly pyramidal. Due to the nonplanarity of the bridgehead nitrogen, the annelation of the two rings can be of either cis or trans type; this is determined by the substituent at N(1). Hexahydropyridopyrimidinone **9** unsubstituted at N(1) has the two rings trans annelated, whereas in the N(1)-methyl derivatives **5a**, **5b**, and **6b** the ring junction is cis. The CD spectra indicate that the chiroptical properties are determined by the inherent chirality of the chromophoric NC=CCON chain in the pyrimidinone ring.

The biologically active 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones[5] include some 1,6,7,8,9,9a-hexahydro derivatives[6] that are a new type of nonacidic, nonsteroidal antiinflammatory agents. The interesting pharmacological features encouraged us to make a systematic study of the synthesis and stereochemistry of the title compounds. Of the hexa- and perhydropyrido[1,2-*a*]pyrimidines,[7,8] only the perhydro compound, 1,5-diazabicyclo[4.4.0]decane, has been the subject of stereochemical study;[8b] IR Bohlmann bands revealed its trans annelation.

In the present paper we report on (i) the preparation of the hexahydro derivatives **5** and **6** by reduction (H_2/Pd–C and/or $NaBH_4$) of the quaternary salts **3** or of the enamines **4**, (ii) the determination of the relative configurations and solution conformations of the synthesized compounds using ^1H, ^{13}C, and ^{15}N NMR spectroscopy, (iii) X-ray diffraction studies on the molecular structures in the solid state, and (iv) experimental and theoretical investigations on the chiroptical properties of the optically active 6-methylhexahydropyridopyrimidinone derivatives.

Results obtained with our bicyclic molecules can be applied to various polycyclic systems containing the pyrido[1,2-*a*]pyrimidine skeleton, e.g., pyrimido[2,1-*b*]-quinazolines and indolo[3′,2′:3,4]pyrido[2,1-*b*]quinazolines,

Scheme I[a]



[a] (i) cc NH_4OH; (ii) Me_2SO_4-$MeNO_2$; (iii) $NaHCO_3$; (iv) 5% HCl; (v) $NaBH_4$-MeOH; (vi) H_2/Pd–C, 5% HCl; (vii) H_2/Pd–C, EtOH.

which constitute the basic framework of a number of alkaloids.[9]

Results

Syntheses. The quaternary salts **3** and enamines **4** used as starting substances in the reductions were prepared

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Table I. Ratio of Diastereomers 5 and 6 in the Crude Reduction Products

	starting compd											
	3b		3c		3d		4b		4c		4d	
	5b	6b	5c	6c	5d	6d	5b	6b	5c	6c	5d	6d
rel config of Me and 9a-H	trans	cis	trans	cis	trans	cis	trans	cis	trans	cis	trans	cis
orientation of Me	eq	ax	ax	eq	eq	ax	eq	ax	ax	eq	eq	ax
red. method												
H_2/Pd-C,[a] %	35	65	35	65	100	0	80	20	29	71	100	0
$NaBH_4$,[b] %	0	100	0	100	100	0						

[a] Starting compound: **3**, X^- = Cl^-. [b] Starting compound: **3**, X^- = $MeSO_4^-$.

Table II. ^1H NMR ($CDCl_3$) Data on 5, 6, and 9

compd	2-H	6-H_{eq}	6-H_{ax}	7-H_{eq}	7-H_{ax}	8-H_{eq}	8-H_{ax}	9-H_{eq}	9-H_{ax}	9a-H	N-Me	Me	$CONH_2$
5a = 6a	7.77 s	4.58 dm	2.44 ddd	———	———	1.40-2.10 m		———	———	4.67 dd	3.06 s		5.52 br, 7.87 br
5b	7.85 s		3.42 ddd	———	———	1.60-2.10 m		———	———	4.56 dd	3.13 s	1.59 d	5.51 br, 8.68 br
								—1.97[a]—					
5c[b]											3.11 s	1.05 d	
5d	7.83 s	4.60 ddd	2.40 td	-1.20-2.00 m-			—1.20-2.00 m—			4.65 dd	3.07 s	0.98 d	5.20 br, 8.80 br
						1.75[a]							
6b	7.83 s	5.00 m		———	———	1.40-2.05 m		———	———	4.90 dd	3.12 s	1.24 d	6.20 br, 8.70 br
								—1.82[a]—					
6c	7.87 s	4.55 ddd	2.13 dd		———	1.50-2.20 m		———		4.70 dd	3.12 s	0.90 d	5.65 br, 8.77 br
					1.75[a]								
9[c]	7.75 d	4.67 m		———	———	1.20-1.95 m		———	———	5.00 dd	8.15 d[d]	1.12 d	6.73 br, 8.50 br

Coupling Constants, Hz

compd	$^3J_{9_{eq},9a_{ax}}$	$^3J_{9_{ax},9a_{ax}}$	$^2J_{6_{eq},6_{ax}}$	$^3J_{6_{ax},7_{ax}}$	$^3J_{6_{ax},7_{eq}}$	$^3J_{6_{eq},7_{ax}}$	$^3J_{6_{eq},7_{eq}}$	$^4J_{6_{eq},8_{ax}}$
5a	2.5	9.5	13.5	11.0	3.2	4.0	2.5	2.0
5b	3.5	9.5		7.0	2.5			
5d	2.5	10.5	13.0	11.0	2.5	2.0	4.5	
6b	3.5	9.5				4.0	3.0	
6c	3.6	8.5	13.2	11.0		3.6		2.5
9	2.0	11.0				3.0	3.0	

[a] Proved by double-resonance experiments. [b] Determined in a mixture containing 35% 5c and 65% 6c. [c] In Me_2SO-d_6. [d] NH signal.

from the tetrahydro compounds **1**[7b,10] as shown in Scheme I.

Quaternization of the 9-methyl derivative **2e** failed, due to steric hindrance by the methyl group.[11] In the compounds **1c,d–4c,d** the methyl group is equatorially situated, whereas in the 6-methyl derivatives **1b–4b** it is forced into the axial position[12] because an equatorial 6-methyl group would cause severe steric strain of the A[(1,3)] allylic type[13] with the carbonyl oxygen atom.

In the hexahydro derivatives **5b–d** the relative configuration of 9a-H and the C-Me group is trans, whereas in the series **6b–d** it is cis. The ratios of the two diastereomers **5** and **6**, determined from the relative intensities of the C-Me signals in the ^1H NMR spectra of the crude reduction products, are shown in Table I.

The highest diastereoselectivity was observed in the reduction of the quaternary salts **3** with $NaBH_4$. Hydride anion attack on the face of the molecule, which leads to **6b**, **6c**, or **5d**, passes through a chair-like transition state of the ring being reduced, whereas in attack on the other face, which would lead to **5b**, **5c**, or **6d**, the ring would be forced to assume a twist-boat-like conformation of higher energy in the transition state. For these steric reasons, formation of the former compounds in the $NaBH_4$ reduction is strongly preferred over that of their diastereomers.

From the 8-methyl derivatives **3d** and **4d** only the trans derivative **5d** containing an equatorial C-Me group was formed.

In the catalytic hydrogenation the 6-methyl enamine **4b** underwent addition mainly at the face opposite the C-Me group, and (in contrast to the reduction of **3b**, X = Cl^- or $MeSO_4^-$) the less stable trans diastereomer **5b** containing an equatorial C-Me group was formed in excess (80%). The 6-methyl group in the quasi-axial position bends better over the piperidine ring in the enamine **4b** than in the quaternary salt **3b**; the shielding effect of the methyl group is therefore more effective in the hydrogenation of the C(9)=C(9a) double bond of the former structure than in that of the C(9a)=N(1) double bond of the latter. This reasoning is supported by X-ray data: the torsional angle Me(6)–C(6)–N(5)–C(9a) is 104° and 101° in the tetrahydro compound **1b**[14] and the quaternary salt **7**,[15] respectively, while it is only 87° in the enamine-type molecule 1,6-dimethyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid.[16]

The only compound that could not be obtained in a pure state was **5c**, with an axial 7-methyl group.

^1H and ^{13}C NMR Spectra. ^1H and ^{13}C NMR data recorded in $CDCl_3$ are given in Tables II and III (for Table III, see supplementary material).

Although the 9a-CH and 9-CH_2 protons form an ABX-type spin system and the line separations are therefore not exactly equal to the coupling constants, the significant differences between the larger ($^3J_{9_{ax},9a}$ = 8.5–11.0 Hz) and

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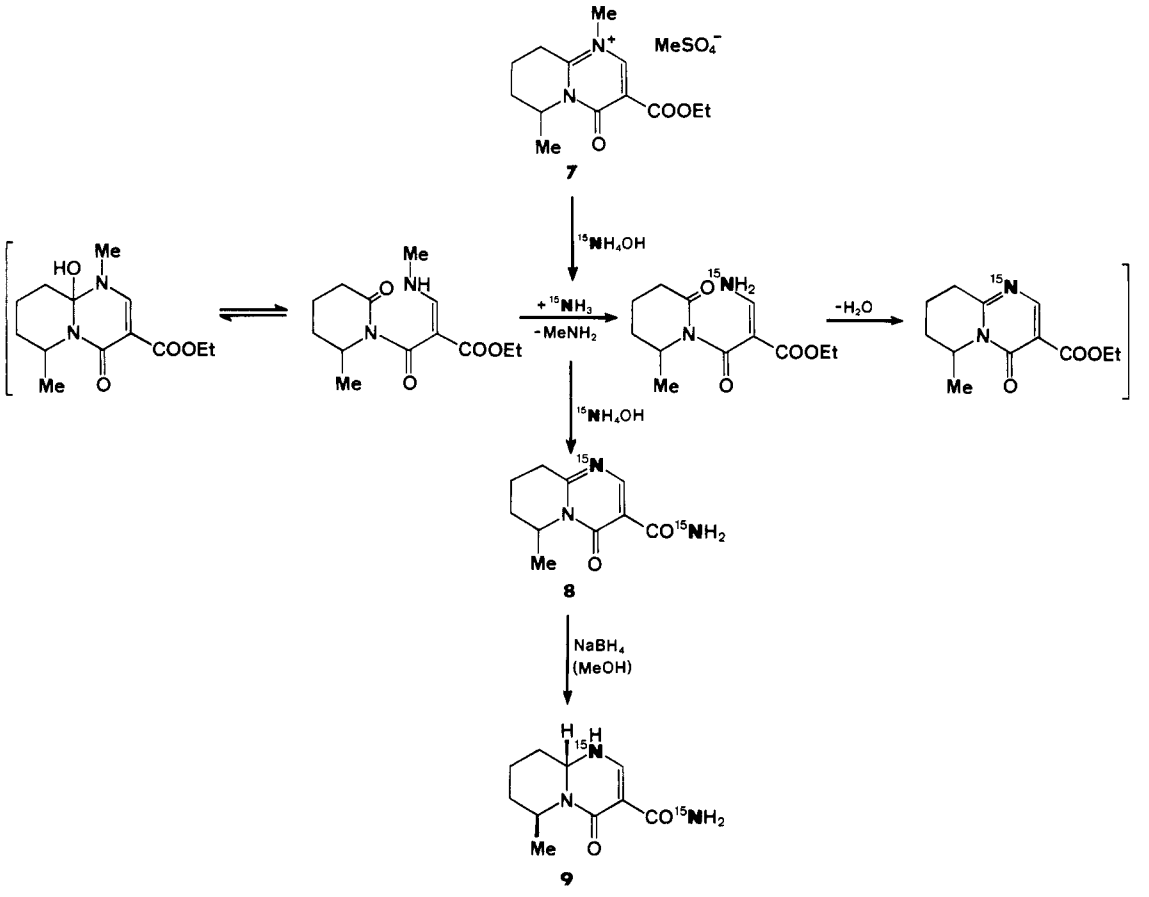
Scheme II



the smaller coupling constants ($^3J_{9_{eq},9a}$ = 2.0–3.6 Hz) clearly point to the axial orientation of 9a-H with respect to the piperidine ring. In the hexahydro derivatives **5b–d** and **6b,c**, the orientation of the C-Me group was determined via the γ_{gauche} effects[17] in the ^{13}C NMR spectra, and in **5b** and **6b,c** via the ^1H coupling constants. Table IV (supplementary material) contains the ^{13}C shifts caused by the C–Me group in the α, β, γ, and δ positions in the piperidine ring, the unsubstituted compound **5a** being taken as the reference. For comparison, the corresponding data for an axial and an equatorial methyl group in cyclohexane[18] are also given. As with cyclohexane, the α and β effects of an equatorial methyl group (5.7–12.5 and 4.8–8.5 ppm, respectively) always have higher positive values than those caused by an axial methyl group (1.0–3.9 and 3.9–5.4 ppm, respectively). The unusually high effect (12.5 ppm) in the 6-methyl derivative **5b** is probably due to steric interaction of the $A^{(1,3)}$ type between the equatorial methyl and the carbonyl group in the peri position. The ^{13}C shift of C(4) in **5b** is also characteristically different from the corresponding data for the other hexahydro compounds (see Table III). Through their γ_{gauche} steric effect, axial methyl groups cause an upfield shift of 3.9–5.5 ppm at the γ-carbon atoms, while the corresponding effect of equatorial methyl groups is only 0.1–2.1 ppm. As expected, the δ effect of the methyl groups is small (–0.3 to +1.0 ppm).

^{15}N NMR Spectra. ^{15}N NMR spectra of **5a,b**, and **6b** were recorded at natural abundance in $CDCl_3$ (Table V, supplementary material). In order to facilitate signal assignment, the desmethyl derivative **9** labeled with ^{15}N to 50% enrichment at N(1) and the carboxamide group was prepared. The synthesis of labeled **9** was based on the reversible ring-opening reaction[19] of quaternary salts of type **3** shown in Scheme II. The ^1H and ^{13}C NMR data indicated that the end product obtained by reduction with $NaBH_4$ contained an axial 6-methyl group. Methylation of an unlabeled specimen of **9** gave **6b**.

The ^{15}N NMR data reveal significant nagative NOEs for all three types of nitrogen, the largest being that of the 3-carboxamide moiety. This group also exhibits the lowest variation in chemical shift in the four hexahydro compounds examined. Introduction of a methyl group at C(6) in either the equatorial or the axial position (**5b** and **6b**) results in a downfield shift of the N(5) signal by 7 ppm as compared with the unsubstituted analogue **5a**.

In the labeled compounds **8** and **9** some ^{15}N–^{13}C and ^{15}N–^1H coupling constants could be measured (see Table V, supplementary material). The coupling constants $^1J_{N(1),C(9a)}$ = 9.8 Hz and $^1J_{N(1),C(2)}$ = 13.4 Hz indicate[20] that, as a consequence of the delocalization of the lone pair of N(1) with the π electrons of the neighboring C=C double bond, N(1) has sp^2 character in **9**. In **8**, which contains a lone pair on the sp^2-hybridized N(1), the values of the coupling constants $^1J_{N(1),C}$ are close to zero.[20b] The value of the coupling constant $^2J_{N(1),C(9)}$ = 9.1 Hz is relatively high, as the lone pair of N(1) is located close to C(9).[21]

The coupling constants $^1J_{N,H}$ in the carboxamide moiety are of interest. In amides the coupling constant for the

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Table IX. Puckering Parameters in 5a, 5b, 6b, and 9[a]

		piperidine ring N(5)C(6)C(7)C(8)C(9)C(9a)			pyrimidine ring N(1)C(2)C(3)C(4)N(5)C(9a)		
compd	absolute config of C(9a)	Q, Å	Θ,[b] deg	Φ,[c] deg	Q, Å	Θ,[b] deg	Φ,[c] deg
5a	*R*	0.582 (3)	176.3 (3)	128 (5)	0.310 (2)	61.2 (4)	283.1 (5)
5b	*R*	0.596 (4)	171.2 (4)	181 (3)	0.344 (3)	60.4 (5)	279.2 (6)
6b	*R*	0.570 (7)	174.4 (7)	117 (7)	0.278 (4)	63.8 (8)	289.6 (9)
9	*R*	0.550 (4)	175.7 (4)	32 (5)	0.189 (3)	120.6 (9)	105.8 (10)

[a] Esds are given in parentheses. [b] $\Theta_{mirror} = 180° \pm \Theta$. [c] $\Phi_{mirror} = \Phi \pm 180°$.

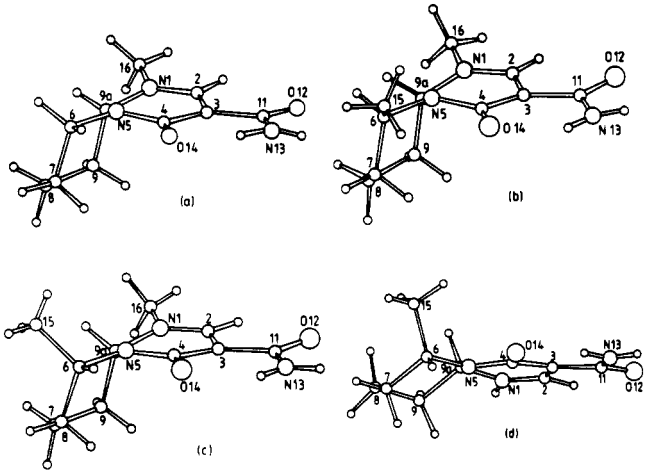


Figure 1. Molecular diagrams for the 9a*R* enantiomers of compounds **5a** (a) **5b** (b), **6b** (c), and **9** (d) with crystallographic atomic numbering. The plane of the C(3), N(5), and C(9a) atoms is perpendicular to the plane of the drawing. The N(5)–C(9a) bond is at an angle of 10° to the normal to the plane of the drawing.

hydrogen situated trans to the carbonyl is reported[22] to be higher than that for the *cis* one. (The relationship is essentially maintained as a function of the solvent.[22b,d]) This was found to be the case with the tetrahydro derivative **8**, but the opposite was true for the hexahydro compound **9**. It is to be noted that, because of the poor solubility of **9**, the spectrum was taken in Me_2SO-d_6. For 2-pyrrolidone the $^1J_{N,H}$ was found to be almost solvent independent.[23]

X-ray Diffraction Studies. To obtain support for our interpretation of the unusual chiroptical behavior of some 6-methyl derivatives (see later), X-ray analysis of **5a,b 6b**, and **9** was carried out on single crystals prepared from the racemic compounds. **5a** and **5b** form conglomerates. Figure 1 depicts the solid-state structures for the 9a*R* enantiomers.

The sign of the torsion angles of junction (i.e., the torsional angle in each ring that has the common N(5)–C(9a) bond as its central bond[24]) is opposite for the *N*-desmethyl derivative **9** to those for **5a,b** and **6b** (see Table VII, supplementary material). This corresponds to a transoid ring junction in **9** and to a cisoid one in **5a,b** and **6b**.

The puckering parameters[25] show that in all four compounds the piperidine ring assumes an almost ideal chair conformation (Table IX). The pyrimidine ring is flatter when involved in a transoid ring junction (such as in **9**, Q = 0.189 Å) than in the case of a cisoid ring (as in the 1-methyl derivatives **5a,b** and **6b**). The pyrimidine rings

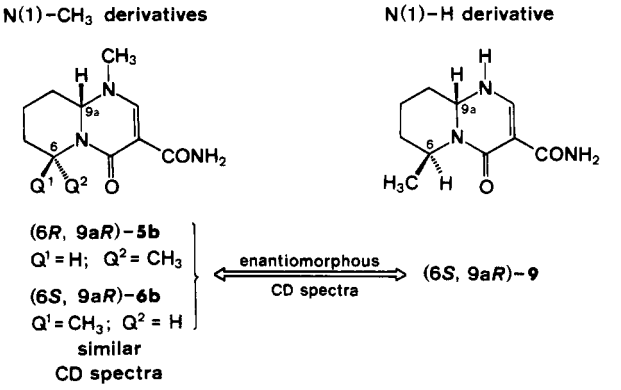
Table X. Conformational Parameters for the Amide and Enamine Groups[a,26,27]

$\chi_N = \omega_2 - \omega_3 + 180° = \omega_4 - \omega_1 + 180°$
$\chi_C = \omega_1 - \omega_3 + 180° = \omega_4 - \omega_2 + 180°$
$\tau'_{CN} = \omega_1 + \omega_2 = \omega_3 + \omega_4$

	5a	5b	6b	9
Amide group A				
$\chi_{N(5)}$	−33.6	−38.3	−28.0	21.4
$\tau'_{N(5)C(4)}$	11.8	15.1	6.1	−6.6
$\chi_{C(4)}$	4.8	4.8	4.1	−3.0
enamine group (E)				
$\chi_{C(2)}$		1.3	−0.5	−3.8
$\tau'_{C(2)N(1)}$		−13.3	−13.2	13.0
$\chi_{N(1)}$	−5.6	−3.3	−6.3	−1.8

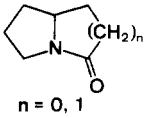
[a] Torsion angles (ω values) are given in Table VII.

Scheme III



in compounds with cisoid and transoid ring junctions are related as mirror images.

As the pyramidality parameters (χ)[26,27] reveal, the tertiary N(1) atom is nearly sp^2 in character (Table X), indicating the extensive conjugation of its nonbonding electron pair with the π electrons of the neighboring enone system. This is also reflected in the length of the N(1)–C(2) bond (1.315–1.327 Å), which practically corresponds to a double bond. In contrast, the N(5) atom of the cyclic amide moiety is distinctly pyramidal. For a bridgehead nitrogen, pyramidality of such magnitude has been found only in compounds of type **10**.[28]



10

Chiroptical Studies. Optically active **5b**, **6b**, and **9** were prepared from the enantiomers of carboxamide **2b**

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Table XI. Experimental UV and CD Data for 5, 6, and 9 in EtOH

compd	UV, λ, nm (ε)	absolute config	CD, λ, nm (Δε)	$[\alpha]^{20}_D$, deg
5a	319 (7450), 233 (40000)	9a*R*	320 (+1.77), 255 (+1.42), 230 (−2.47)	
5b	316 (6940), 234 (19500)	6*R*, 9a*R*	321 (+4.65), 259 (+9.01), 223 (−11.87)	+227
5d	318 (7420), 233 (22000)			
6b	318 (7980), 233 (24200)	6*S*, 9a*R*	317 (+4.76), 253 (+4.30), 230 (−6.50)	+261
6c	318 (6770), 233 (20500)			
9	310 (5440), 232 (20000)	6*S*, 9a*R*	307 (−4.79), 251 (−5.21), 215 (+6.91)	−150

with known absolute configuration[29] according to Schemes I and II.

The specific rotations of the trans and cis 6-methyl derivatives **5b** and **6b**, which are homochiral at C(6) [e.g., (6*R*,9a*R*)-**5b** and (6*R*,9a*S*)-**6b**], are opposite in sign (+227° and −261°, respectively), and even the CD spectra of the two 9a epimers are almost mirror images. These findings suggest that the chiroptical properties of **5b** and **6b** depend primarily on the configuration of C(9a), whereas that of C(6) has almost no influence on the optical activity. It was rather unexpected, therefore, that the CD spectrum of the N(1)-desmethyl cis derivative (6*R*,9a*S*)-**9** was enantiomorphic with that of its homochiral analogue (6*R*,9a*S*)-**6b** and resembled the spectrum of the trans derivative (6*R*,9a*R*)-**5b** epimeric at C(9a). Thus, depending on the sign patterns of their CD spectra, the enantiomers of **5b**, **6b**, and **9** homochiral at C(9a) can be divided into two groups (Scheme III; cf. Table XI).

Since it is the absolute *conformation* of the molecule that is reflected in its chiroptical properties, the above results lead to the conclusion that the conformations of the hexahydropyridopyrimidinones are determined not only by the configurations of the chiral centers (or, at least, by that of one of them) but even by the presence or absence of a methyl group at N(1). Our further research was therefore aimed at finding a correlation between the CD spectra and the absolute conformations and also between the latter and the other structural characteristics (constitution and configuration) of the compounds studied.

A. Experimental UV and CD Spectra. The UV spectra of hexahydropyridopyrimidinones of types **5**, **6**, and **9** are very similar (Table XI, cf. ref 30). With regard to their relatively high intensities and their bathochromic shifts with increasing polarity of the solvent, the two UV bands were assigned to $\pi \rightarrow \pi^*$ transitions of the conjugated NC=CCON, chromophore in the pyrimidine ring.

In the CD spectra of the enantiomers of **5b**, **6b**, and **9**, three bands appear. The first and the third one can be correlated with the two UV bands, while the second band, at 250–260 nm, has no counterpart in the UV spectra, which display a minimum at this wavelength. This band is therefore assigned to an electric dipole forbidden $n \rightarrow \pi^*$ transition. The sign pattern of the three CD bands in the sequence of decreasing wavelengths is + + − for the 9a*R* enantiomers of **5b** and **6b** and − − + for (9a*R*)-**9**.

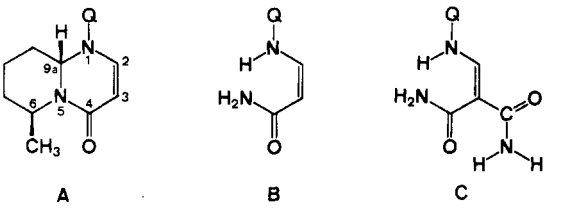
If the origin of the optical activity is ascribed to the inherent chirality of the chromophoric system, the sign inversion caused in the CD spectrum either by a change of configuration at C(9a) or by replacing a hydrogen atom for a methyl group at N(1) can be explained by inversion of the chiral conformation (helicity) or the NC=CCON chromophoric moiety of the pyrimidine ring. This assumption was completely supported by the X-ray analysis (vide infra), indicating that the conformation of the pyrimidinone ring in **5b** and **6b** is nearly the mirror image of that in **9** (Figure 1b–d); all these compounds are homochiral at C(9a).

Table XII. Comparison of Calculated and Experimental Chiroptical Data

calcd for model (*P*)-C (Q = H)			exptl for (6*S*,9a*R*)-**9**			
transition type	λ, nm	$[R]^a$	transition type	λ, nm	Δε	$[R]^b$
$\pi \rightarrow \pi^{*c}$	234	−28.5	$\pi \rightarrow \pi^*$	307	−4.79	−14.9
$n \rightarrow \pi^{*c}$	305	−32.3	$n \rightarrow \pi^*$	251	−5.21	−15.4
$n \rightarrow \pi^{*c}$	304	+0.5				
calcd for model (*M*)-C (Q = CH_3)			exptl for (6*S*,9a*R*)-**6b**			
transition type	λ, nm	$[R]^a$	transition type	λ, nm	Δε	$[R]^b$
$\pi \rightarrow \pi^{*c}$	243	+35.0	$\pi \rightarrow \pi^*$	317	+4.76	+15.5
$n \rightarrow \pi^{*c}$	303	+22.6	$n \rightarrow \pi^*$	253	+4.30	+15.3
$n \rightarrow \pi^{*c}$	301	−8.4				

[a] Reduced rotational strength. [b] $[R]_{exptl} = 26.5\Delta\epsilon_{max}\,\Delta_{1/2}/\lambda_{max}$. Both $\Delta_{1/2}$ and λ in nm. [c] The sequence of the calculated $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions is interchanged.

B. Theoretical Calculations. In the knowledge of the absolute geometries, we also sought a theoretical interpretation of the CD spectra. In looking for the simplest system that would, at least qualitatively, reproduce the characteristic chiroptical properties of the hexahydropyridopyrimidinone derivatives, we performed quantum-chemical calculations in the CNDO/S-CI approximation[31,32] on some simplified models (A–C) having the geometries of the molecules studied.



(Q = H or CH_3)

Two sets of geometrical parameters were applied, one being taken from the X-ray data on (6*S*,9a*R*)-**6b** and the other from those on (6*S*,9a*R*)-**9** (cf. Figure 1 and Tables VI and VII, supplementary material). The helicity of models derived from the former and the latter molecule will be specified as *M* (minus) and *P* (plus), respectively. Each model was taken in two constitutional variants, with either a hydrogen atom or a methyl group at N(1) (Q = H or CH_3). In the construction of the simplified models, the fragments eliminated by the truncation of the original molecules **6b** or **9** were substituted by hydrogen atoms generated at distances of 0.1 nm from the neighboring atoms (C or N) in the direction of the original bonds.

The results of our calculations can be summarized as follows: (i) The experimental energy sequence for the first $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions can be correctly obtained

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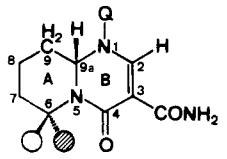
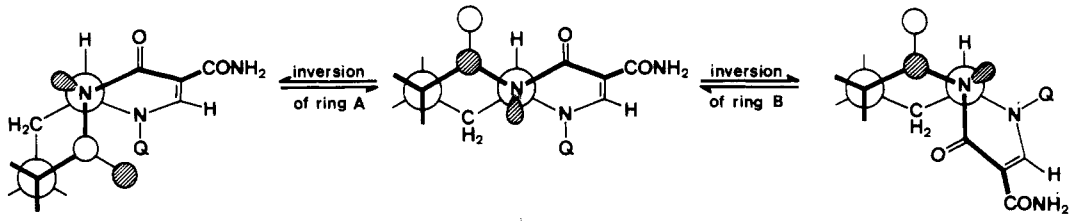
Scheme IV



Q = H or CH_3



	C_A	T	C_B
anellation of rings A and B	cis	trans	cis
helicity of ring A[a]	*P*	*M*	*M*
helicity of ring B[b]	*P*	*P*	*M*
CIP config of N(5)	*R*	*S*	*R*
orientation of (6*R*)-CH_3	ax	eq	eq
orientation of (6*S*)-CH_3	eq	ax	ax

[a] Sign of torsion angle C(9)-C(9a)-N(5)-C(6). [b] Sign of torsion angle N(1)-C(9a)-N(5)-C(4).

with the single-transition approximation (STA), but it is reversed by the configuration interaction (CI) calculation.

(ii) Model B, i.e., the simple chromophoric chain, proved to be sufficient to reproduce the sign and order of magnitude of the rotational strength due to the first $\pi \rightarrow \pi^*$ transition. For the $n \rightarrow \pi^*$ transition, however, the correct sign of the rotational strength can only be obtained by using model C, i.e., by also taking the carboxamide substituent into account. In Table XII the chiroptical data calculated for the first transitions by using model C are compared with those obtained from the experimental CD spectra of (6*S*,9a*R*)-**6b** and (6*S*,9a*R*)-**9**.

(iii) The high-energy bands in the UV and CD spectra correspond to complex mixtures of one-electron transitions. They cannot be assigned correctly without a more detailed analysis of the experimental and theoretical results.

Discussion

In the subsequent stereochemical analysis, only the 9a*R* enantiomers will be considered. All these molecules can assume one or perhaps more of the three structures represented in Scheme IV by Newman projections in the direction of the N(5)–C(9a) bond, including the nonbonding pair of electrons at N(5). (These simplified stereoformulas can easily be compared with the corresponding stereoscopic pictures of Figure 1.) The two possible positions of the methyl substituent at C(6), *R* or *S* in configuration, are represented by a hatched or an unshaded circle, respectively. Some characteristics of the individual conformations are listed under the formulas.

A trans-annelated hexahydropyridopyrimidinone can transform, into a cis-annelated form, by inversion of N(5) with a low energy barrier.[33] This inversion is coupled with the inversion of either ring A or ring B, thereby generating two diastereomeric *cis*-annelated conformations, C_A or C_B, respectively. The configurations of the two bridgehead chiral centers C(9a) and N(5) are the same in C_A and C_B, but the helicities of the two rings are opposite in sense (cf. Scheme IV).

It may be assumed that in solution there is an equilibrium of the above three structures. However, the close correlation between the X-ray structures and the spectroscopic properties of the compounds examined indicates that one of the possible conformations, viz., that found in the crystalline state, must occur in appreciable excess in the equilibrium in solution. It is therefore worth examining the stereochemical factors that control the preferred conformation of the individual molecules.

The simplest member of this family of compounds, unsubstituted hexahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, is unknown. However, on analogy with the decalin system, it seems reasonable to suppose that this molecule would assume the T conformation lacking any 1,3-syn-diaxial contacts. In the two cis conformations, either N(1) or C(4) takes up an axial position relative to ring A, involving an increase of energy for these structures. However, since the pyramidality of N(5) is lower than that of the normal tetracovalent carbon atom C(9a), the quasi-axial position of the C(4)=O group in conformation C_B does not cause such close 1,3 contacts as that of the N(1)-H group in conformation C_A.

In the T conformation of (6*S*,9a*R*)-**9**, the 6-methyl group is in the axial position, involving two 1,3-syn-diaxial interactions with the axial hydrogen atoms at C(8) and C(9a). This strain is absent in conformation C_A, in which N(1) is axially oriented. In *cis*-decahydroquinoline it is the nitrogen atom that adopts the axial position,[34] indicating that an axial nitrogen is less unfavored than an axial carbon. In conformation C_A of **9**, however, there is a short contact between the equatorial methyl group and the carbonyl oxygen atom, which is more unfavorable (3–5 kcal/mol[13]) than the presence of an axial methyl in conformation T (1.7 kcal/mol[35]). Besides the steric effects, conformation T is stabilized over C_A by a nonnegligible stereoelectronic effect, too. In the former structure the 2p orbitals on the individual atoms of the amide moiety

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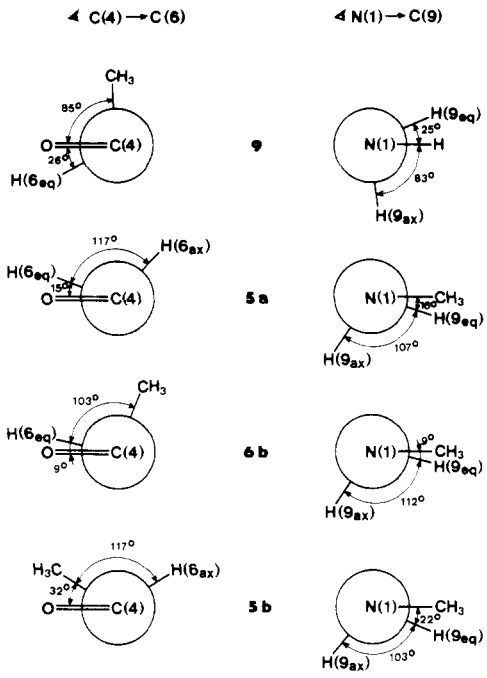

Figure 2. Newman-like projections of compounds **5a**, **5b**, **6b**, and **9**.

N(5)C(4)=O are oriented nearly parallel, giving rise to conjugation, whereas in the C_A form the orientation of the nonbonding pair of electrons at N(5) is almost perpendicular to that of the C=O π-type orbitals. X-ray and NMR results show that the molecules of **9** indeed adopt conformation T both in the crystalline state and in solution. (The CD spectra cannot distinguish between conformations T and C_A, in which the chromophoric moiety has the same helicity).

For N(1)-methyl-substituted derivatives, the simplest of which is **5a**, in conformation T an unfavorable steric interference arises between the N(1)-methyl group and the hydrogen atoms (mostly the equatorial one) at C(9). This strain is released in conformation C_B, in which the two groups are farther apart. In conformation C_A, even closer contacts would be present between the N(1)-CH_3 group and several atoms of ring A. In fact, compound **5a** and also its 6-methyl derivatives **5b** and **6b** assume conformation C_B both in the crystalline state and in solution.

In order to assess the magnitude of the interactions controlling the conformation of N(1)-methyl-substituted derivatives, calculations by the EENYC method[36] were carried out. Figure 2 shows Newman-like projections, based on X-ray data, along atoms C(4) and C(6) and along N(1) and C(9) for the 9a*R* enantiomers of molecules **9**, **5a**, **6b**, and **5b**.

When the calculations were started from the geometry of **9** and a methyl group with appropriate bond length was generated instead of the hydrogen atom at N(1), the results indicated a strain of 4.8 kcal/mol between N(1)-Me and 9-CH_2. This strain is eliminated in conformation C_B.

Conformation C_B is slightly influenced by the substituent at C(6). While the angle of the equatorial C(6)-H and the C(4)=O bonds is +15° in **5a**, it is only +9° in **6b** with the methyl group in the axial position but as high as +32° between the C(6)-CH_3 bond of the equatorial methyl group and C(4)=O in **5b**. In the first case 1,3-syn-diaxial interactions are operative between C(6)-Me, C(8)-H, and C(9a)-H, whereas in **5b** an $A^{(1,3)}$-type allylic strain[13] results in displacement of the methyl group but now in the opposite derection. (These effects involve a slight displacement of N(1)-Me and 9-CH_2 too).

Calculations for the 1,6-dimethyl derivatives were also carried out by retaining the geometry of **5b** but interchanging hydrogen and methyl at C(6). This resulted in a strain of 7.5 kcal/mol between the methyl group and the two axial hydrogens at C(8) and C(9a). The same procedure for **6b** gave a strain increase of 32.8 kcal/mol due to the interaction of C=O and the equatorial methyl group.

Though the numerical values for the energies of the steric interactions seem to be overestimated in the simple calculation, their relative magnitudes may be considered realistic and indicate the main effects that control the conformations of the individual molecules.

The conformations of the 7-methyl compounds **5c** and **6c** and of the 8-methyl analogue **8d**, are similar to those of **5a**, since the structural features controlling the conformations are the same.

Experimental Section

General. Melting points were determined in capillary tubes and are uncorrected. Yields were not maximized. The ^1H, ^{13}C, and ^{15}N NMR spectra were recorded in the PFT mode (16K data points for the FID) at 99.6, 25.0, and 10.04 MHz, respectively, with an internal deuterium lock, using a JEOL FX-100 multinuclear spectrometer. The ^1H and ^{13}C chemical shifts were determined on the δ scale, with tetramethylsilane (δ_{Me_4Si} 0) as internal standard. The ^{15}N chemical shifts were determined relative to the signal of external $K^{15}NO_3$ (δ -3.55) and then converted to external neat nitromethane ($\delta_{CH_3NO_2}$ 0). Chemical shifts upfield from the reference are negative.

UV and CD spectra were recorded on a Unicam SP-800 spectrophotometer and a Rousell–Jouan Dichrograph III. Optical rotations were determined by use of a Zeiss polarimeter.

Crystallography. The main X-ray analysis data are given in Table XIII (supplementary material). The unit cell parameters were obtained for each structure through a least-squares analysis of at least 15 reflections with experimental diffractometer settings. Intensities were measured on an Enraf-Nonius CAD 4 diffractometer for **5a** and **5b** and on a Siemens diffractometer for **6b** and **9**. The structures were solved by means of direct methods, with a MULTAN 78[37] (**5a** and **5b**) or a SHEL-X[38] (**6b** and **9**) program. Refinement was carried out with the Enraf-Nonius structure determination package (**5a** and **5b**) or with a SHEL-X program (**6b** and **9**). Hydrogen atom positions were determined from a difference Fourier map, and the parameters were refined for **5a** and **5b**. The weighting scheme was $w = I(\mathrm{Lp})/[\sigma^2(I) + (pI)^2]$, where p was 0.01 in all cases and Lp is the Lorentz and polarization factor. Reflections with $I > 3\delta(I)$ were included in the refinement.

4-Oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (2a) and 6-Methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide [2b, (6*S*)-2b, (6*R*)-2b]. These compounds were prepared as earlier[7b,c,29] and exhibited spectral properties and melting points corresponding with those reported.[7b,c,29]

General Procedure for Preparation of 6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides (2). A solution of ethyl tetrahydropyrido[1,2-*a*]pyrimidine-3-carboxylate 1[10] (25 mmol) in concentrated ammonium hydroxide solution (30 mL) was left to stand at ambient temperature for 3 h. The precipitated carboxamide was filtered off, washed with water, dried, and recrystallized.

7-Methyl derivative **2c**: 91%; mp 222–224 °C (MeOH).

8-Methyl derivative **2d**: 93%; mp 262–263 °C (DMF).

9-Methyl derivative **2e** did not precipitate from aqueous solution. It was extracted with chloroform (3 × 30 mL). The organic

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(38) Scheldrick, G. M. The SHEL-X Crystal Structure Calculation Program, University of Cambridge, Cambridge, England, 1976.

phase was dried (Na_2SO_4) and evaporated in vacuo to dryness, and the carboxamide **2e** (1.97 g, 38%) was crystallized from ethanol: mp 160–161 °C.

General Procedure for Preparation of 3-Carbamoyl-1-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidinium Methyl Sulfates (3). A solution of tetrahydropyrido-[1,2-*a*]pyrimidine-3-carboxamide **2** (10 mmol) and dimethyl sulfate (20 mmol) in nitromethane (25 mL) was refluxed for 5 h. After evaporation of the solution, the residue was recrystallized from methanol.

1-Methyl derivative **3a**: 86%; mp 191–192 °C.

1,6-Dimethyl derivative **3b**: 45%; mp 199–200 °C (lit.[7c] mp 175–176 °C).[39]

Enantiomer with 6*S* absolute configuration [(6*S*)-**3b**]: 48%; mp 225–226 °C; $[\alpha]^{20}_D$ +37.5° (*c* 2, MeOH).

Enantiomer with 6*R* absolute configuration [(6*R*)-**3b**]: 50%; mp 225–226 °C; $[\alpha]^{20}_D$ −37.5° (*c* 2, MeOH).

1,7-Dimethyl derivative **3c**: 67%; mp 189–190 °C.

1,8-Dimethyl derivative **3d**: 60%; mp 228–229 °C.

General Procedure for Preparation of 1-Methyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides (4). The pH of a solution of 3-carbamoyl-1-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidinium methyl sulfate **3** (6 mmol) in water (6 mL) was adjusted to 7.5 with aqueous sodium bicarbonate solution. The precipitated yellow amide **4** was filtered off and recrystallized.

1-Methyl derivative **4a**: 94%; mp 241–242 °C (EtOH).

1,6-Dimethylderivative **4b**: 86%; mp 170–172 °C (EtOH).

Enantiomer with 6*S* absolute configuration [(6*S*)-**4b**]: 85%; mp 171 °C (EtOH); $[\alpha]^{20}_D$ −70° (*c* 2, MeOH).

Enantiomer with 6*R* absolute configuration [(6*R*)-**4b**]: 89%; mp 172 °C (EtOH); $[\alpha]^{20}_D$ +70° (*c* 2, MeOH).[40]

1,7-Dimethyl derivative **4c**: 89%; mp 232–234 °C (MeOH).

1,8-Dimethyl derivative **4d**: 72%; mp 190–192 °C (MeOH).

Reduction of Methosulfate 3 with $NaBH_4$. General Procedure. To a solution of methosulfate **3** (5 mmol) in methanol (20 mL) was gradually added $NaBH_4$ at ambient temperature. After stirring for 1 h, the solution was adjusted to pH 4 with 10% hydrochloric acid, and methanol was removed by distillation in vacuo. Water (15 mL) was added, and the solution was adjusted to pH 7 with 5% sodium carbonate solution. The hexahydro derivative **5** or **6** was extracted with chloroform (4 × 10 mL). The dried (Na_2SO_4) organic extract was evaporated to dryness in vacuo. The crude product was investigated by ^1H NMR spectroscopy.

1-Methyl derivative **5a** = **6a**: 64%; mp 199 °C (MeOH).

1,6_{ax}-Dimethyl derivative **6b**: 81%; mp 186–187 °C (EtOH) (lit.[7c] mp 186 °C).

Enantiomer with 6*S*,9a*R* absolute configuration: 83%; mp 209–210 °C (EtOH), $[\alpha]^{20}_D$ +268° (*c* 1, EtOH).

Enantiomer with 6*R*,9a*S* absolute configuration: 85%; mp 209–210 °C (EtOH), $[\alpha]^{20}_D$ −261° (*c* 1, EtOH).

1,7_{eq}-Dimethyl derivative derivative **6c**: 89%; mp 242–244 °C (MeOH).

1,8_{eq}-Dimethyl derivative **5d**: 89%; mp 215–217 °C (MeOH).

Catalytic Reduction of Enamine 4 in Hydrochloric Acid. General Procedure. Enamine **4** (5 mmol) was dissolved in 5% hydrochloric acid (20 mL). The aqueous solution was hydrogenated over 10% Pd–C catalyst (0.3 g) at ambient temperature and atmospheric pressure. After absorption of the theoretical amount of hydrogen (1 mol equiv), the catalyst was filtered off and washed with water. The aqueous filtrate was adjusted to pH 7.5 with 5% sodium carbonate solution. The neutralized reaction mixture was extracted with chloroform (4 × 10 mL). The dried (Na_2SO_4) organic phase was evaporated to dryness in vacuo to give hexahydropyridopyrimidinecarboxamide **5** and/or **6** in 85–90% yield. The diastereomer ratio of the crude product was analyzed by ^1H NMR spectroscopy (see Table I).

Catalytic Reduction of Enamine 4 in Ethanol. General Procedure. Enamine **4** (5 mmol) in ethanol (100 mL) was hydrogenated over 10% Pd–C catalyst (0.3 g) at ambient temperature and atmospheric pressure. After absorption of the theoretical amount of hydrogen (1 mol equiv), the catalyst was filtered off and washed with ethanol. The filtrate was evaporated to dryness in vacuo to give hexahydropyridopyrimidinecarboxamide **5** and/or **6** in 90–95% yield. The diastereomer ratio of the crude product was analyzed by ^1H NMR spectroscopy (see Table I).

1,6_{eq}-Dimethyl derivative **5b**: 39%; mp 205–206 °C (EtOH).

Enantiomer with 6*S*,9a*S* absolute configuration: 40%; mp 220–222 °C (EtOH), $[\alpha]^{20}_D$ −228° (*c* 1, EtOH).

Enantiomer with 6*R*,9a*R* absolute configuration: 41%; mp 220–222 °C (EtOH), $[\alpha]^{20}_D$ +227° (*c* 1, EtOH).

6_{ax}-Methyl-4-oxo-1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (9). To a solution of $NaBH_4$ (0.57 g, 15 mmol) in cooled (10 °C) water (20 mL) was added carboxamide **2b** (2.07 g 10 mmol). The reaction mixture was stirred for 24 h at 10 °C. The precipitated hexahydrocarboxamide **9** was filtered off, washed with water, and dried: 79%, mp 229–230 °C (EtOH).

Enantiomer with 6*S*,9a*R* absolute configuration: 67%; mp 223–225 °C (EtOH), $[\alpha]^{20}_D$ −150° (*c* 2, MeOH).

Enantiomer with 6*R*,9a*S* absolute configuration: 67%, mp 227–229 °C (EtOH), $[\alpha]^{20}_D$ +150° (*c* 2, MeOH).

1,6_{ax}-Dimethyl-4-oxo-1,6,7,8,9,9a-hexahydro-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carboxamide (6b) from 9. To a stirred suspension of hexahydrocarboxamide **9** (2.04 g, 10 mmol) in 2.5% sodium hydroxide solution (4 mmol, 6 mL), were added dimethyl sulfate (1.9 g, 15 mmol) and 15% sodium hydroxide solution (20 mmol, 5 mL) dropwise in parallel at ambient temperature. After stirring for 1 h, the solution was adjusted to pH 7 with 10% hydrochloric acid solution. The aqueous reaction mixture was extracted with chloroform (4 × 10 mL). The dried (Na_2SO_4) organic phase was evaporated to dryness in vacuo to give 1,6_{ax}-dimethyl derivative **6b** in 98% yield: mp 187 °C (EtOH), no melting point depression with an authentic sample.

Starting from (6*S*,9a*R*)-**9**, we obtained (6*S*,9a*R*)-**6b**: 95%; mp 207–208 °C (EtOH); $[\alpha]^{20}_D$ +259° (*c* 1, EtOH).

^{15}N-Labeled Compounds. A solution of 3-(ethoxycarbonyl)-1,6-dimethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidinium methyl sulfate (1 g) in 20% ammonium hydroxide solution (5 mL) labeled with ^{15}N to 51.5% (Isocommerz) was left to stand for 3 days at ambient temperature. The precipitated carboxamide **8** labeled with ^{15}N in position 1 and the carboxamide group to 51.5% was filtered off and washed with water: 0.35 g; 42%; mp 190–192 °C.

To a stirred methanolic (10 mL) solution of carboxamide **8** (0.35 g) was gradually added $NaBH_4$ (0.1 g) in MeOH (2 mL), and the reaction mixture was stirred at ambient temperature for 1 h. The solution was adjusted to pH 4 with 5% hydrochloric acid (ca. 3.4 mL), the methanol was removed in vacuo, and the aqueous residue was adjusted to pH 7.5 with 10% sodium carbonate solution. The aqueous reaction mixture was extracted with chloroform (3 × 10 mL). The dried (Na_2SO_4) organic extract was evaporated to dryness in vacuo to give hexahydrocarboxamide **9** (18.7 mg, 53%) labeled with ^{15}N in position 1 and the carboxamide group to 51.5%.

Supplementary Material Available: ^{13}C NMR data for compounds **5**, **6**, and **9** (Table III); substituent chemical shift of the methyl group in **5** and **6** (Table IV); ^{15}N NMR data for compounds **5a,b**, **6b**, 8, and **9** (Table V); bond lengths and selected bond angles (Table VI), selected torsional angles (Table VII), fractional atomic coordinates (Table VIII), and crystallographic data (Table XIII) for compounds **5a,b**, **6b**, and **9**; UV and ^1H NMR data for compound **3c,d** and **4c,d** (Table XIV); analytical data for all new compounds (Table XV); furthermore, a detailed description of the theoretical calculations for CD spectra of optically active compounds **6b** and **9** (22 pages). Ordering information is given on any current masthead page.

(39) Earlier the quaternerization reaction was carried out in suspension in benzene.[7c]

(40) The specific rotation data give in the previous paper[29] were obtained in ethanol (*c* 1).