(10), 111 (44), 109 (30), 97 (40), 95 (24), 85 (46), 83 (44), 71 (64), 69 (48), 57 (100); ^{1}H NMR (360 MHz, $CDCl_3$) 5.15 (d, J = 9.4 Hz, 2 H, exactly superimposed ester methines), 5.00 (s, 1 H), 4.83 (s, 1 H), 3.35 (d, J = 13.3 Hz, 1 H), 3.15 (d, J = 12.6 Hz, 1 H), 2.84 (s, 1 H), 2.69 (s, 1 H), 2.50–2.64 (m, 6 H), 2.10–2.48 (m, 7 H), 2.07 (s, 3 H), 2.02 (s, 3 H), 1.77 (m, 2 H), 1.55 (m, 1 H), 1.24 (d, J = 7 Hz, 3 H), 1.19 (s, 3 H), 0.97 ppm (t, 3 H).

Dihydrogeyerine. Geyerine (35 mg, 0.082 mmol) was added to a flask containing 20 mg of $NaBH_4$ (large excess) dissolved in 5 mL of 95% EtOH and 0.5 ml of H_2O. The solution was stirred at 25 °C for 25 min, at which time no starting material remained by TLC but with the appearance of one major, less polar spot. The excess $NaBH_4$ was decomposed with dilute H_2SO_4 and the solution made basic with 1 M NaOH and extracted twice with $CHCl_3$. The combined $CHCl_3$ washes were concentrated under reduced pressure. A ^{1}H NMR spectrum of the residue showed essentially one compound. Purification of the residue was achieved on a silica gel PLC plate (12:3:1 EtOAc/EtOH/NH_4OH) to yield 26 mg (0.06 mmol, 73% purified yield) of dihydrogeyerine as a viscous oil: UV λ_{max} (EtOH) 254 sh, 282 sh; ^{1}H NMR (250 MHz, $CDCl_3$) 5.17 (d, J = 9.9 Hz, 1 H), 4.95 (s, 1 H), 4.76 (s, 1 H), 4.32 (d, J = 9.0 Hz, 1 H), 4.18 (m, $W_{1/2}$ = 12 Hz, 1 H), 3.73 (s, 1 H), 3.15 (d, J = 11.9 Hz, 1 H), 3.03 (d, J = 11.9 Hz, 1 H), 2.93 (br d, J = 15.3 Hz, 1 H), 2.53–2.40 (m, 3 H), 2.37–2.25 (m, 4 H), 2.09 (s, 1 H), 2.08–2.00 (m, 3 H), 1.99 (s, 1 H), 1.87–1.60 (m, 6 H), 1.59 (s, 1 H), 1.58–1.38 (m, 3 H), 1.35 (s, 3 H), 1.19 (d, J = 7 Hz, 3 H), 0.91 ppm (t, 3 H).

Bioassays. Migratory grasshoppers, *Melanoplus sanguinipes* (Fabricius), were either obtained from a nondiapausing population kept by the Capinera research group or collected from local populations, sorted, and reared under the conditions described by Melman.[4]

Young male and female adult grasshoppers were offered a choice of filter paper strips impregnated with wheat extract only or wheat extract and diterpene alkaloid components from *D. geyeri*. After having been starved for 24 h, two grasshoppers were placed in a 500-mL plastic cup containing the filter paper strips inserted into a piece of florist's block. The cup was vented and water provided. For every experiment, 12 grasshoppers were used to evaluate each alkaloidal sample. Grasshopper consumption of filter paper strips was rated on scale of 0–4 as follows: 0, no consumption; 1, occasional nibbling around perimeter of strip; 2, nibbling around most of strip; 3, nibbling around most of perimeter with occasional areas of heavy consumption; 4, more than $^2/_3$ of the strip consumed. Deterrence was indicated by a significant difference in consumption level by Sign test ($P < 0.05$).

Wheat extract was prepared by macerating wheat sprouts (25 g) with methanol (150 mL). After 3 days the solution was filtered and the volume reduced to 50 mL. Of this solution 50 μL was delivered to each filter paper strip (1 × 4 cm). Alkaloid-containing strips were prepared by delivering 30 μL of a 5 mg/mL alkaloidal–methanolic solution to a filter paper already impregnated with wheat extract. In the case of the total plant extract, a 50 mg/mL solution was used due to the large amount of nonalkaloidal material present.

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Nitrogen Bridgehead Compounds. 62.[1] Conformational Analysis of 6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and Their Methyl Derivatives by NMR Spectroscopy

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Proton and carbon-13 chemical shift data have been acquired for 2 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and 20 methylated derivatives. Least-squares regression analysis has been undertaken on the aliphatic ring carbons of compounds with unequivocal conformations to determine the methyl substituent parameters for the four distinct aliphatic positions, and the results have been used to estimate the position of equilibrium of conformationally mobile compounds. It is concluded that at room temperature the 6-methyl derivatives predominantly adopt the conformation with a pseudoaxial methyl group and the 7- and 8-methyl derivatives that with an equatorial methyl group, but the 9-methyl derivatives exist in essentially equally populated conformers. Substituent parameters are compared with those previously determined for methylated tetralins.

6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and their methyl-substituted derivatives have recently acquired much interest as intermediates in the synthesis of various pharmacologically active agents.[2]

So far, however, only the 6-methyl derivatives have been subjected to stereochemical investigation.[3-5] As concerns the conformation of the tetrahydropyridine ring in these derivatives, the half-chair conformer with a pseudoaxial methyl group has been shown to be energetically most

Scheme I

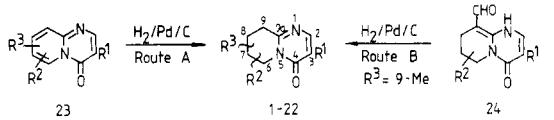

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Table I. 6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and Their Methyl Derivatives[a]

cmpd	R^1	R^2	R^3	relative position of R^2 and R^3	route	yield, %	mp, °C	lit. mp, °C	isomeric ratio %
1	COOEt	H	H		A	90	134	132[b]	
2	COOEt	6-Me	H		A	92	55–56	55–56[b]	
3	COOEt	7-Me	H		A	78	89–90	88–89[b]	
4	COOEt	8-Me	H		A	70	70–72	68–72[b]	
5	COOEt	9-Me	H		A	85	38	38[b]	
6	COOEt	6-Me	8-Me	cis	A	86	oil	oil[b]	66
7	COOEt	6-Me	8-Me	trans					34
8	COOEt	6-Me	9-Me	cis	B	92	oil		60
9	COOEt	6-Me	9-Me	trans					40
10	COOEt	7-Me	9-Me	cis	B	20	oil		53
11	COOEt	7-Me	9-Me	trans					47
12	COOEt	8-Me	9-Me	cis	B	35	oil		30
13	COOEt	8-Me	9-Me	trans					70
14	CH_2COOEt	H	H		A	85	63–65		
15	CH_2COOEt	6-Me	H		A	86	64–66		
16	CH_2COOEt	7-Me	H		A	87	oil		
17	CH_2COOEt	8-Me	H		A	82	44–45		
18	CH_2COOEt	9-Me	H		A	80	oil		
19	CH_2COOEt	6-Me	8-Me	cis	A	64	oil		66
20	CH_2COOEt	6-Me	8-Me	trans					34
21	CH_2COOEt	6-Me	9-Me	cis	B	70	oil[c]		60[d]
22	CH_2COOEt	6-Me	9-Me	trans			oil[c]		40[d]

[a] Satisfactory analytical data (±0.4% for C, H, N) were obtained for all compounds. [b] Reference 9. [c] Separated by preparative liquid chromatography. [d] Determined from the crude reaction mixture.

Table II. Characteristic ^1H NMR Data (δ) on 6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones[a]

cmpd	6-H_a	6-H_e	9-H_a	9-H_e	couplings, Hz[b]
1	3.99 (t)		2.98 (t)		$J_{6,7}$ = 6.5, $J_{8,9}$ = 6.5
2		5.04 (m)	2.92 (ddd)	3.07 (ddd)	$J_{6e,7a} \sim J_{6e,7e} \sim 3.0$,[c] $J_{9a,8a}$ = 9.8, $J_{9a,8e}$ = 7.2
3	3.22 (dd)	4.36 (ddd)	2.95 (ddd)	3.07 (ddd)	$J_{6a,7a}$ = 10.0, $J_{6e,7a}$ = 4.8, $^2J_{6a,6e}$ = 14.5
4	3.69 (ddd)	4.31 (ddd)	2.55 (dd)	3.07 (ddd)	$J_{7a,8a}$ = 10.0, $J_{8a,9a}$ = 10.0, $J_{8a,9e}$ = 5.0
5	3.88 (dt)	4.13 (dt)	3.00 (sx)		$J_{6,9}$ = 6.7, $J_{9,Me}$ = 6.7, $J_{6,7}$ = 6.5
6		4.97 (m)	2.45 (m)	2.95 (ddd)	$J_{8a,9e}$ = 4.2, $^2J_{9a,9e}$ = 16.4; $^4J_{7e,9e}$ = 2.7
7				3.15[d]	
8–9		5.00 (m)		3.00 (m)	
10–11	2.90 (m)[d]	4.5 (m)[d]		2.75–3.50 (m)[d]	
12				3.02 (qd)	$J_{8a,9e} \sim 4.5$,[c] $J_{8,Me}$ = 6.6, $J_{9,Me}$ = 7.0
13	3.50–4.50 (m)[d]			2.57 (qi)	$J_{8,9} \sim 7.5$,[c] $J_{9,Me}$ = 6.9, $J_{8,Me}$ = 6.6
14	3.98 (t)			2.92 (t)	$J_{6,7}$ = 6.5, $J_{8,9}$ = 6.5
15		4.98 (m)	2.88 (ddd)	3.01 (ddd)	$J_{6e,7a} \sim J_{6e,7e} \sim 3.0$,[c]; $J_{9a,8a}$ = 10.2, $J_{9a,8e}$ = 6.2
16	3.24 (dd)	4.38 (ddd)	2.90 (ddd)	3.00 (ddd)	$J_{6a,7a}$ = 10.5, $J_{6e,7a}$ = 5.0; $^2J_{6a,6e}$ = 14.5
17	3.67 (ddd)	4.24 (ddd)	2.50 (dd)	2.98 (ddd)	$J_{7a,8a}$ = 10.5, $J_{8a,9a}$ = 10.0; $J_{8a,9e}$ = 5.0
18	3.90 (dt)	4.11 (dt)	3.00 (sx)		$J_{8,9}$ = 6.7, $J_{9,Me}$ = 6.7, $J_{6,7}$ = 6.5
19		4.92 (m)	2.45 (m)[d]	2.89 (ddd)	$J_{6a,9e}$ = 4.0, $^2J_{9a,9e}$ = 16.0, $^4J_{7e,9e}$ = 2.8
20				3.09 (ddd)	$J_{6a,9e}$ = 5.2, $J_{7a,8a}$ = 13.0, $J_{6e,7a}$ = 5.0
21		4.92 (m)	2.85 (m)		$J_{6a,9a} \sim 9.1$,[c] $J_{8e,9a} \sim 6.6$,[c] $J_{9a,Me}$ = 6.9
22		4.98 (m)		3.05 (m)	$J_{8a,9e} \sim 5.8$,[c] $J_{8e,9e} \sim 2.9$,[c] $J_{9e,Me}$ = 7.1

[a] In $CDCl_3$, δ_{Me_4Si} 0.00. [b] a = axial and e = equatorial. [c] Gained from double-resonance experiment. [d] Overlapping signal. d, doublet; t, triplet; q, quartet; qi, quintet; sx, sextet; m, multiplet.

favorable both in the solid phase, by X-ray investigations,[3] and in solution, by NMR spectroscopy.[4] The other possible half-chair form, with a pseudoequatorial methyl group, is highly unfavorable due to the 1–3 allylic strain[6] arising between the pseudoequatorial methyl group and the adjacent carbonyl group.

In the present paper we report a ^1H and ^{13}C NMR investigation of 20 mono- and dimethyl-substituted 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. To organize and systematize the conformation-dependent shifts in these systems, linear least-squares regression analysis has been undertaken for the ^{13}C chemical shifts, utilizing methyl substituent parameters similar to those used earlier to analyze the ^{13}C chemical shifts in the methyl-substituted cyclohexanes.[7]

Results

Synthesis. The synthesis routes for the compounds are depicted in Scheme I, and the characteristics of the compounds are compiled in Table I.

The investigated tetrahydropyridopyrimidinones were obtained from 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones[8] (**23**) (route A) or 9-formyl-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones[9] (**24**) (route B) by catalytic hydrogenation over a 10% palladium-on-carbon catalyst. With tetrahydropyridopyrimidines **1**, **3–5**, and **10–13**, saturation of the C(9a)–N(1) double bond, which is polarized due to

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Table III. Characteristic ^{13}C NMR Chemical Shifts (δ) of 6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones[a]

cmpd	R^1	R^2, R^3	preferred conformation in half-chair form	C-6	C-7	C-8	C-9	R^2	R^3
1	*b*	H	*d*	43.0 (42.8)	21.7 (21.5)	18.8 (18.9)	32.2 (32.3)		
2	*b*	6-Me	6_a	48.1 (48.7)	27.9 (27.9)	14.9 (15.0)	31.6 (31.6)	18.9	
3	*b*	7-Me	7_e	49.2 (49.4)	26.9 (27.5)	27.8 (27.6)	32.0 (31.9)	18.8	
4	*b*	8-Me	8_e	42.8 (42.8)	29.6 (29.7)	25.5 (25.3)	40.2 (40.5)	20.8	
5	*b*	9-Me	*e*	42.9	20.0	27.2	36.1	19.0	
6	*b*	*cis*-6,8-Me_2	*f*	49.2	38.4	26.1	40.6	21.5	22.2
7	*b*	*trans*-6,8-Me_2	6_a–8_e	49.0 (48.7)	36.5 (36.1)	21.4 (21.4)	40.2 (39.9)	19.6	21.4
8	*b*	*cis*-6,9-Me_2	6_a–9_e	48.7 (48.7)	27.6 (27.9)	23.9 (24.0)	36.7 (36.8)	19.3	20.1
9	*b*	*trans*-6,9-Me_2	6_a–9_a	48.4 (48.2)	24.6 (24.6)	22.8 (22.5)	35.0 (35.1)	19.3	20.8
10	*b*	*cis*-7,9-Me_2	7_e–9_e	49.7 (49.4)	27.8 (27.5)	36.9 (36.7)	37.0 (37.0)	19.0[g]	19.2[g]
11	*b*	*trans*-7,9-Me_2	7_e–9_a	48.8 (48.9)	24.6 (24.2)	34.8 (35.2)	35.9 (35.4)	18.9[g]	20.0
12	*b*	*cis*-8,9-Me_2	8_e–9_a	42.0 (42.3)	26.1 (26.5)	28.9 (29.2)	40.6 (40.3)	16.4	14.1
13	*b*	*trans*-8,9-Me_2	*e*	41.7	28.6	32.7	43.6	20.2	17.6
14	*c*	H	*d*	42.7 (42.6)	21.9 (21.6)	19.1 (19.3)	31.6 (31.6)		
15	*c*	6-Me	6_a	47.8 (48.5)	28.1 (28.0)	15.3 (15.4)	31.1 (31.0)	19.0	
16	*c*	7-Me	7_e	49.2 (49.2)	27.4 (27.6)	28.0 (28.0)	31.3 (31.2)	18.9	
17	*c*	8-Me	8_e	42.5 (42.6)	29.9 (29.9)	25.9 (25.6)	39.8 (39.8)	21.0	
18	*c*	9-Me	*e*	42.7	20.1	27.5	35.4	19.3	
19	*c*	*cis*-6,8-Me_2	*f*	49.3	38.4	26.0	39.3	21.2	22.2
20	*c*	*trans*-6,8-Me_2	6_a–8_e	49.3 (48.6)	36.4 (36.3)	21.5 (21.8)	38.8 (39.2)	19.5	21.5
21	*c*	*cis*-6,9-Me_2	6_a–9_e	48.6 (48.6)	27.8 (28.0)	24.3 (24.4)	36.2 (36.1)	19.5	20.3
22	*c*	*trans*-6,9-Me_2	6_a–9_a	48.1 (48.0)	24.7 (24.8)	23.2 (22.9)	34.4 (34.4)	19.5	21.1

[a] Parentheses indicate shifts calculated with parameters of Table IV. [b] COOEt. [c] CH_2COOEt. [d] Two equally populated half-chair forms. [e] Two differently populated half-chair forms. [f] Highly strained form. [g] Ambiguous assignments.

the presence of an ethoxycarbonyl group at position 3, also occurred, with a lower rate. In these cases, if the reaction mixtures were worked up after the absorption of 2 mol equiv of hydrogen, the tetrahydro derivatives could be separated on the basis of their water solubilities. Of the dimethyl compounds (**6–13** and **19–22**), only the *cis*-**21** and *trans*-**22** diastereomers were separated, by means of preparative HPLC; the other compounds were investigated as mixtures of cis and trans isomers.

Conformational Analysis of Compounds 1–22 by NMR Spectroscopy. The characteristic ^1H NMR data are tabulated in Table II. The detailed data are given in the supplementary material.

The proton–proton coupling constants of the tetrahydropyridine ring, obtained from ^1H NMR spectra at 250 MHz, show that the unsubstituted compounds (**1** and **14**) have two equally populated but rapidly interconverting half-chair forms, while the 6-methyl derivatives (**2** and **15**) exist in a highly favored conformation with a pseudoaxial methyl group. At the same time, similarly as for the corresponding methyltetralins,[10–12] the 7- and 8-methyl derivatives (**3**, **4**, **16**, and **17**) exist almost exclusively in a single conformation with an equatorial methyl group, while the 9-methyl derivatives (**5** and **18**) have almost equal populations of conformers with a pseudoequatorial or a pseudoaxial methyl group.

As the cis and trans isomers of the dimethyl derivatives (**6–13** and **19–22**) were mainly investigated as diastereomeric mixtures, only some characteristics proton–proton coupling constants could be determined. The conformational analysis of these derivatives was therefore based on their ^{13}C NMR data, collected in Table III. (All the ^{13}C NMR data are given in the supplementary material.)

Assignments were made by using the gated spin–echo decoupling technique. Regression analysis of the ^{13}C NMR shifts was carried out on those molecules that exist primarily in a single conformation, because of unfavorable steric interactions in the alternative half-chair conformation (**2–4**, **7–12**, **15–17**, **20–22**), and also included the unsubstituted compounds **1** and **14**, which undergo rapid interconversion between identical conformers of equal energy. Thus, other compounds were excluded from the fit: **5**, **13**, and **18** may exist in more than one form with differing energies, while **6** and **19** are so highly strained due to the *cis*-6,8-dimethyl substitution that the fitting procedure cannot be expected to predict the chemical shifts adequately. A preliminary determination of the best-fit values was made first, using all possible parameters in the calculation; substituent effects that were neglible in size were then removed, and the calculation was redone. These results are given in Table IV. The calculated shifts using these parameters are indicated in parentheses in

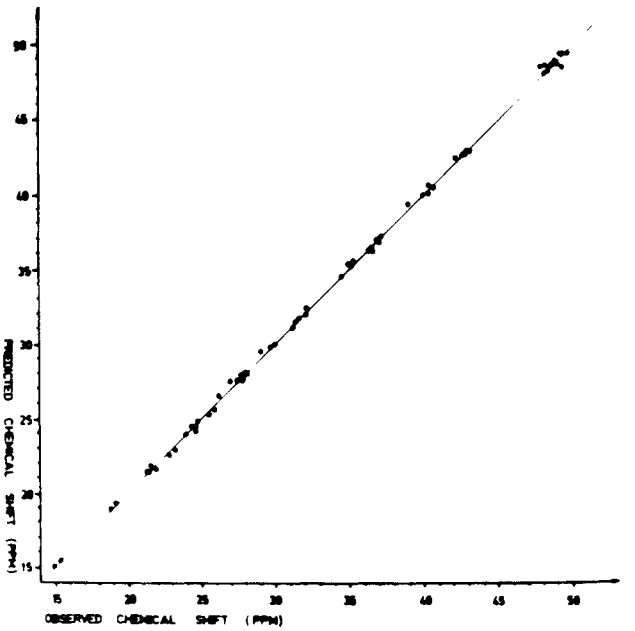

Figure 1. Comparison of predicted and observed carbon-13 chemical shifts for the ring carbons of the 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones of this study.

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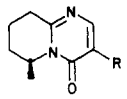
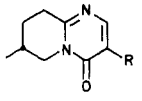
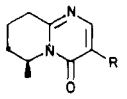
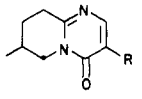
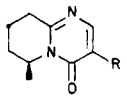
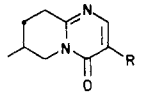
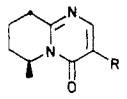
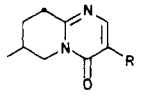
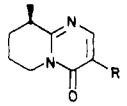
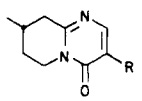
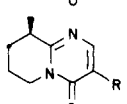
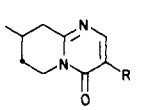
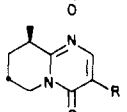
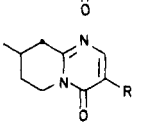
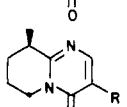
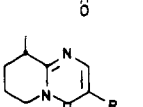
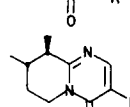
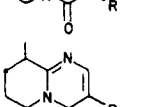
Table IV. Carbon-13 Chemical Shift Parameters Indicating the Effects of Methyl Substitution in 6,7,8,9-Tetrahydropyridopyrimidinones[a,b]

	$\alpha_{6_a} = 5.9 \pm 0.2$		$\alpha_{7_e} = 6.0 \pm 0.3$
	$\beta_{6_a} = 6.4 \pm 0.2$		$\beta_{7_e,6} = 6.6 \pm 0.3$
	$\gamma_{6_a} = -3.9 \pm 0.2$		$\beta_{7_e,8} = 8.8 \pm 0.2$
	$\delta_{6_a} = -0.6 \pm 0.2$		$\gamma_{7_e} = -0.4 \pm 0.2$
	$\alpha_{9_a} = 3.5 \pm 0.2$		$\alpha_{8_e} = 6.4 \pm 0.2$
	$\beta_{9_a} = 7.5 \pm 0.2$		$\beta_{8_e,7} = 8.3 \pm 0.2$
	$\gamma_{9_a} = -3.3 \pm 0.2$		$\beta_{8_e,9} = 8.2 \pm 0.2$
	$\delta_{9_a} = -0.5 \pm 0.2$		$\alpha_{9_e} = 5.1 \pm 0.2$
	$V_{ea} = -3.6 \pm 0.3$		$\beta_{9_e} = 9.0 \pm 0.2$

[a] Determined by least-squares analysis of 68 chemical shifts. In ppm ± standard error, γ_{8_e}, γ_{9_e}, and δ_{9_e} were found to be negligible. Calculated base values (ppm) for compounds with 3-COOEt: C-6 = 42.8, C-7 = 21.5, C-8 = 18.9, C-9 = 32.3. Calculated base values (ppm) for compounds with 3-CH_2COOEt: C-6 = 42.6, C-7 = 21.6, C-8 = 19.3, C-9 = 31.6. [b] The lower index of α_{6_a}, β_{6_a}, etc. refers to the positions of the methyl group; a = axial; e = equatorial. V_{ea} indicates the vicinal correction term[12] between two vicinal equatorial and axial methyl groups.

Table III. A graphical comparison of the predicted and observed shifts is shown in Figure 1. The line plotted is a least-squares line with slope = 0.999 and intercept = 0.05 ppm. The standard error of the estimation is 0.3 ppm, and the correlation coefficient is 0.996. The agreement between predicted and observed shifts indicates that each compound used in the calculation exists almost exclusively in a single conformation, and the set of parameters used in the fitting procedure describes the chemical shifts quite well.

The chemical shifts obtained for aliphatic carbons earlier[4] and in the present study show that these are not strongly affected by the nature of the substituent at position 3.

Discussion

It is worthwile to compare the calculated carbon-13 chemical shift parameters (Table IV) with one another to clarify how they depend upon the location and steric position and also to compare them with the similar parameters for methyltetralins[12] to investigate how they are influenced by the presence of an amide group in positions C(4)–N(5) and/or an amidine moiety in positions N(5)–C(9a)–N(1).

The values of the α and β effects of an equatorial 7- or 8-methyl group are similar to those for methylcyclohexane[7] (5.96 and 9.03 ppm, respectively) and methyltetralins[12] (5.91 and 8.67 ppm, respectively), except for the β effect of the 7-methyl group on C(6). The lower value here (6.6 ppm) indicates the influence of the neighboring amide group.

The effects of a 9-methyl group, either pseudoequatorial or pseudoaxial, differ both from those of a methyl group at other positions, and from those of a methyl group at the identical position in methyl tetralin.[12] However, the differences between the carbon chemical shift parameters for a pseudoequatorial and a pseudoaxial methyl group show a similar tendency to that observed for 1-methyltetralin.[12]

The effects (primarily the α and β effects) of a pseudoaxial 6-methyl group differ substantially from those of pseudoaxial 9-methyl group. The absolute value of the γ effect is somewhat higher than that of a pseudoaxial 9-methyl group because the distance between C(6) and C(7) is shorter than that between C(8) and C(9).[13] Further, the piperidine ring is puckered when a 6-methyl group is present in the pseudoaxial position, so as to decrease the strain between the methyl group and the 4-carbonyl group.[14]

At the same time, the value of the vicinal correction term for the neighboring equatorial 8-methyl group and pseu-

(13) Sasvári, K.; Simon, K. *Acta Crystallogr., Sect. B* **1973**, *B29*, 1245.
(14) Breining, T.; Hermecz, I.; Podányi, B.; Mészáros, Z.; Tóth, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1015.

doaxial 9-methyl group is very similar to that in tetralins (V_{ea} -3.19 ppm).[12]

The substituent effects may now be used to predict the chemical shifts of different conformations of the compounds not included in the regression analysis, e.g., compound **5**. For C(7) we may predict a shift of 18.2 ± 0.3 ppm for a pseudoaxial methyl and 21.5 ± 0.2 ppm for a pseudoequatorial methyl. From the observed 20.0 ppm we estimate that this molecule exists as 55 ± 9% pseudoequatorial methyl derivative. The uncertainties are obtained from the error limits of the best-fit parameters.

The same result was obtained for the analogous 9-methyl derivative **18**. It is interesting to note that a similar conformational ratio was found for 1-methyltetralin.[12] In both cases the half-chair form with a pseudoaxial methyl group contains a quache-butane-type interaction between the methyl group and the axial proton on the γ-carbon, while the conformation with a pseudoequatorial methyl group suffers from a peri interaction[15] between the methyl group and H(8) (in 1-methyltetralin[12]) or the lone pair of N(1) (in 9-methyltetrahydropyridopyrimidinones). It was earlier demonstrated[16] that the repulsive interaction between a methyl group and the nitrogen lone pair is less than that between the methyl group and a CH group. However, the bond between C(9a) and N(1) in the tetrahydropyridopyrimidinones[13] is shorter than that between C(8) and C(8a) in the tetralins.[17]

Similar calculations on C(6) and C(7) in compound **13** (*trans*-8,9-dimethylpyridopyrimidinone) give 72 ± 12% and 71 ± 12% diequatorial conformation, respectively (assuming β_{8a} to be 7.5 ± 0.4 ppm and γ_{8a} to be -3.5 ± 0.4 ppm, on the basis of the literature results for tetralins[12] and our own data). A similar conformer ratio (65 ± 10%) is found from the coupling constant, $J_{8,9} \sim 7.5$ Hz assuming $J_{8a,9a}$ to be 10 Hz and $J_{8e,9e}$ to be 3.0 Hz. The conformer ratio in this case indicates that two gauche-butane interactions (between 8-Me_a and 6-H_a, and between 9-Me_a and 7-H_a) in the diaxial conformation are only slightly higher in energy than the peri (between 9-Me_e and N(1)) and gauche interactions (between 8-Me_e and 9-Me_e) in the diequatorial conformation.

Thus, for a substantial proportion of the time (about 29 ± 12%) this molecule exists with diaxial methyl groups.

In the *cis*-6,8-dimethyl derivatives (**6** and **19**) both half-chair conformations are very destabilized by the steric crowding. In the diaxial conformation an unfavorable 1,3-diaxial interaction[18] of the *cis*-6,8-dimethyl groups is present, while the diequatorial conformation contains a severe 1,3-allyl strain[6] between the pseudoequatorial 6-methyl group and the neighboring carbonyl group. These derivatives therefore adopt an evelope or a *skew-boat* conformation. This is indicated by the substantial differences between the experimental and calculated shifts for both half-chair conformations. The very downfield absorption of 6-H indicates that it lies in the plane of the amido grouping.[19] Thus, the 6-methyl group is at right angle to the plane of C(4)–N(5)–C(6).

(15) Due to the shorter C(4a)–C(8a) bond than the C(4a)–C(5) or C(8a)–C(8) bond in 1-methyltetralin a similar unfavorable interaction in the conformer with a pseudoequatorial substituent has been ascribed to a ^{1,2}A allylic strain.[11] In contrast to tetralins,[17] in tetrahydropyridopyrimidinones[3,13] the C(9a)–N(1) bond is shorter than the C(9a)–N(5) bond. In the latter cases the unfavorable interaction in the conformer with a pseudoequatorial 9-substituent should therefore be regarded as a peri effect or a ^{1,3}A allylic strain, rather than a ^{1,2}A allylic strain.

(16) Brignell, P. J.; Katritzky, A. R.; Russell, P. L. *J. Chem. Soc. B* **1968**, 1459.

(17) (a) Aversa, M. C.; Bombieri, G.; Bruno, G.; Cum, G.; Giannetto, P.; Romeo, G. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1213. (b) Barnett, J. W.; Bedford, K. R.; Burton, G. W.; de la Mare, P. O. B.; Nicolson, S.; Suzuki, H. *Ibid.* **1974**, 1908 and references cited therein.

Conclusions

The agreement between the predicted and observed shifts indicates that the structural features of unstrained compounds with unequivocal conformations are described quite well by the set of parameters used in the fitting procedure.

The least-squares regression analysis of the carbon-13 chemical shifts of the ring carbons resulted in 7- and 8-methyl substituent parameters similar to those found in 2-methyltetralins,[12] but 6- and 9-methyl substituent parameters are quite different from those found in 1-methyltetralins.

The calculated carbon-13 chemical shift parameters can be used to predict the shifts of the aliphatic carbons not only in the present bicycle but also in other polycyclic nitrogen bridgehead compounds containing a tetrahydropyridopyrimidinone moiety, e.g., 6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones.[20]

Experimental Section

^{1}H NMR spectra were obtained on a Bruker WM-250 or a Bruker WP-80 spectrometer, operating at 250 and 80 MHz, respectively. Samples were run in $CDCl_3$ solutions with tetramethylsilane as internal standard.

^{13}C NMR spectra were obtained at 20.1 MHz on a Bruker WP-80 spectrometer. Samples were run as saturated solutions in $CDCl_3$ with tetramethylsilane as internal standard.

Hydrogenation. 4*H*-Pyrido[1,2-*a*]pyrimidin-4-one[8] (**23**) (10 mmol) (route A) or 9-formyl-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[9] (**24**) (10 mmol) (route B) in ethanol (50 mL) was hydrogenated over a 10% palladium-on-carbon catalyst (0.5 g) at ambient temperature at atmospheric pressure. After the absorption of 2 mol equiv of hydrogen, the catalyst was filtered off and the filtrate was evaporated to dryness in vacuo. The hydrogenated product of a 3-ester derivative was dissolved in water (50 mL), and the undissolved hexahydropyrimidinone was filtered off. The aqueous phase was extracted with chloroform (3 × 30 mL). The combined and dried organic phase was evaporated to dryness, in vacuo to give the tetrahydropyridopyrimidinone. Tetrahydropyridopyrimidinones **1**–**4**, **14**, **15**, and **17** were recrystallized from ethyl acetate. The diastereomeric pair **21** and **22** were separated on a Prep-500 silica (Waters) column with a Waters preparative liquid chromatograph with a 2-propanol–dichloromethane–ligroin (2:2:1) eluent.

Computation. The least-squares regression analyses were done on a Commodore personal computer by the COMPAC 801 program written in BASIC.

Acknowledgment. We thank Tibor Pokorny (Focus Co., Budapest) for providing the COMPAC 801 computer program. We are grateful to Prof. Pál Sohár and Drs. Péter Dvortsák and István Pelczer for recording the 250-MHz ^{1}H NMR spectra.

Registry No. **1**, 38326-36-2; **2**, 32092-14-1; **3**, 64405-35-2; **4**, 70999-47-2; **5**, 85808-41-9; **6**, 99655-92-2; **7**, 99655-93-3; **8**, 99655-94-4; **9**, 99655-95-5; **10**, 99655-96-6; **11**, 99655-97-7; **12**, 99655-98-8; **13**, 99655-99-9; **14**, 54504-53-9; **15**, 54804-24-9; **16**, 54504-54-0; **17**, 54504-56-2; **18**, 99656-00-5; **19**, 99656-01-6; **20**, 99656-02-7; **21**, 99656-03-8; **22**, 99656-04-9; **23** (R^1 = CO_2Et, R^2 = R^3 = H), 32092-18-5; **23** (R^1 = CO_2Et, R^2 = 6-Me, R^3 = H), 16867-53-1; **23** (R^1 = CO_2Et, R^2 = 7-Me, R^3 = H), 5435-82-5; **23** (R^1 = CO_2Et, R^2 = 8-Me, R^3 = H), 34667-64-6; **23** (R^1 = CO_2Et, R^2 = 9-Me, R^3 = H), 16878-14-1; **23** (R^1 = CO_2Et, R^2 = 6-Me, R^3 = 8-Me), 16867-54-2; **23** (R^1 = CH_2CO_2Et, R^2 = R^3 = H), 50609-59-1; **23** (R^1 = CH_2CO_2Et, R^2 = 6-Me, R^3 = H), 50609-57-9; **23** (R^1 = CH_2CO_2Et, R^2 = 7-Me, R^3 = H), 64399-34-4; **23** (R^1 = CH_2CO_2Et, R^2 = 8-Me, R^3 = H), 50609-56-8; **23** (R^1 = CH_2CO_2Et,

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R^2 = 9-Me, R^3 = H), 50834-58-7; **23** (R^1 = CH_2CO_2Et, R^2 = 6-Me, R^3 = 8-Me), 50609-65-9; **24** (R^1 = CO_2Et, R^2 = 6-Me), 70999-37-0; **24** (R^1 = CO_2Et, R^2 = 7-Me), 71165-64-5; **24** (R^1 = CO_2Et, R^2 = 8-Me), 71165-59-8; **24** (R^1 = CH_2CO_2Et, R^2 = 6-Me), 71165-44-1.

Supplementary Material Available: Detailed ^1H and ^{13}C NMR data for 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones **1–22** are presented (3 pages). Ordering information is given on any current masthead page.

A Stereocontrolled Synthesis of Thienamycin from 6-Aminopenicillanic Acid[1]

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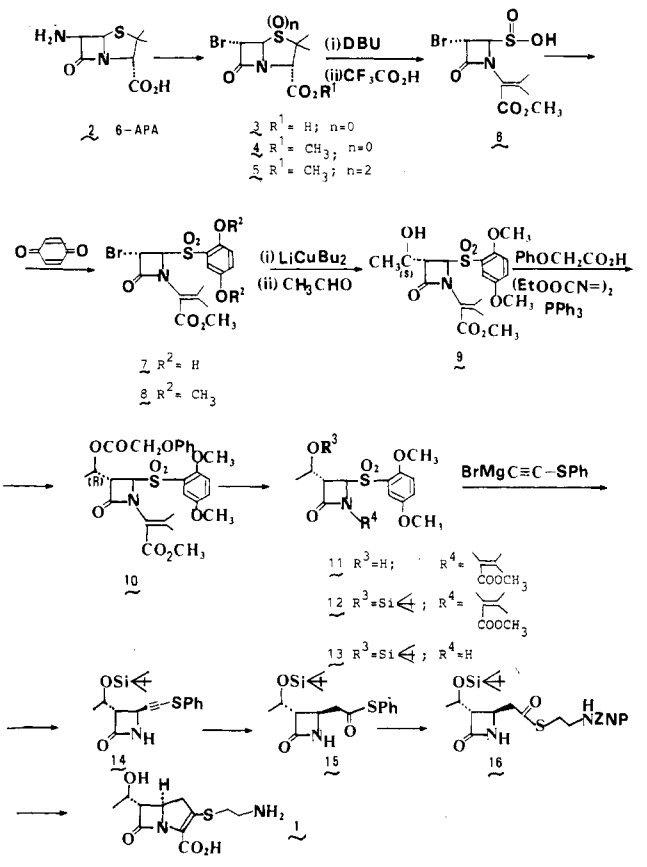
Received September 26, 1985

A stereocontrolled efficient synthesis of thienamycin (**1**) from 6-aminopenicillanic acid (6-APA) (**2**) was achieved. The thiazolidine ring of bromosulfone **3** was cleaved with DBU and the resulting sulfenic acid **4** was trapped with *p*-benzoquinone to give the sulfone **5**, which, after methylation, was transformed to the (hydroxyethyl)-azetidinone **6** in a stereocontrolled way. Carbon–carbon extension reaction of **6** at the 4-position with an acetylenic Grignard reagent, the following hydration, thiol ester exchange, and cyclization afforded natural thienamycin (**1**) in good yield.

Recently, much attention has been focused on thienamycin[2] since it has very high and broad activity against a variety of bacteria.[3] Syntheses of thienamycin and its analogues have been disclosed by a Merck group[4] and others.[5] Also conversion of penicillin to thienamycin[6] has been carried out since fermentation yields of thienamycin have been relatively low.[2] The purpose of our research was the synthesis of thienamycin utilizing inexpensive 6-aminopenicillanic acid (6-APA) whose thiazolidine ring can be cleaved off and reconstructed to the carbapenem nucleus. In this synthesis two major tasks need to be undertaken: (i) a carbon–carbon extension reaction at the 5- and 6-positions of 6-APA and (ii) stereocontrol of the three asymmetric centers in thienamycin. These problems were solved by careful analysis of the environments of the starting material and the target molecule and the formal total synthesis of thienamycin was achieved.

6-APA (**2**) was converted to the known methyl 6α-bromopenicillanate (**4**)[7] in 74% yield which was oxidized to the sulfone **5** with *m*-chloroperbenzoic acid. The thiazoline dioxide ring of compound **5** was cleaved with DBU according to Stoodley's method[8] to give the sulfenic acid salt which was transformed into the free acid **6** by neutralization with trifluoroacetic acid (Scheme I). Sulfenic acid **6** could be isolated and was characterized by its NMR spectrum. The intermediate sulfenic acid **6** was treated, without isolation, with *p*-benzoquinone to afford the sulfone **7**.[9] When this sulfenic acid salt (6-DBU salt) was trapped with methyl iodide, a mixture of the sulfone **17** and methyl sulfinate **18** was obtained, the ratio depending upon the reaction conditions. During this ring-opening reaction the stereochemistry of compound **7** was retained 3,4-trans, this being apparent from the coupling constant

Scheme I



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