Nitrogen Bridgehead Compounds. Part 76 [1]. Synthesis and Stereochemistry of Ethyl 9-Benzylidene-6,7,8,9-tetrahydro-2-oxo-2*H*- and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and their Homologues

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Ethyl 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **1-4**, their piperidine ring homologues **5-6** and their 2-oxo isomers **7-9** were reacted with benzaldehyde. At low temperature, kinetically stable addition products were formed. Thermodynamically stable condensation products were obtained at higher temperature, which were also formed when the addition products were refluxed in benzene. The 9-benzyl derivatives were prepared by the hydrogenation of the condensation products over Pd/C. The stereochemical features of the new compounds were determined *via* ^{1}H and ^{13}C nmr chemical shift and coupling constant analysis and NOE measurements.

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Introduction.

Reactions of the active 9-methylene group [2,3] of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with electrophilic reagents [4-10] earlier led to the synthesis of biologically active derivatives [11-15].

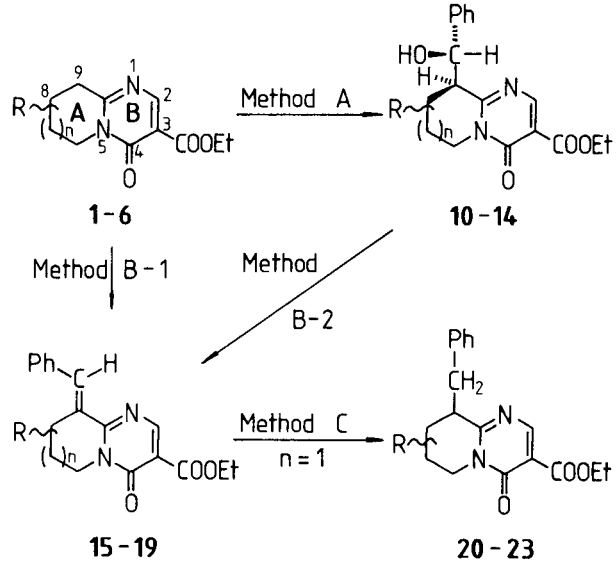
The reactions of aromatic aldehydes with 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones resulted in condensation products. The benzylidene group of these derivatives could be eliminated by treatment with hydrazine hydrate, to give the parent compounds; thus the procedure served as a protection against the reaction of the active 9-methylene group [16]. However, the reactions between aldehydes and the active methylene group can also be used to prepare new derivatives for pharmacological screening [11].

This paper deals with an investigation of the reactions between benzaldehyde and ethyl 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates **1-4**, their piperidine ring (ring "A") homologues **5-6**, and their 2-oxo isomers **7-9**. Catalytic reduction of the condensation products **15-18** has also been investigated. The stereostructures of the compounds have been studied by uv, ^{1}H and ^{13}C nmr spectroscopy.

Results.

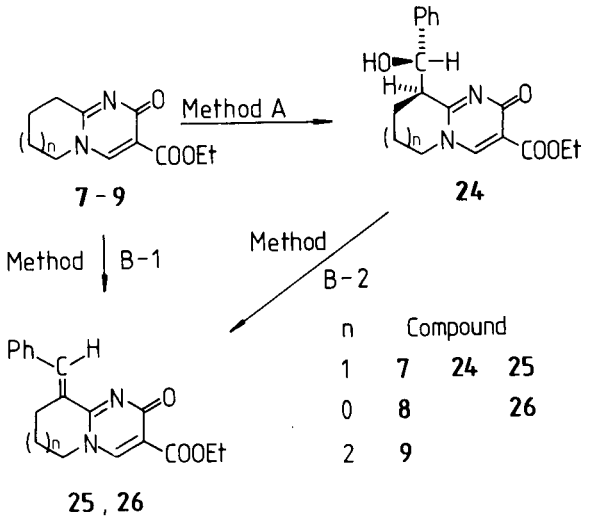
The reactions of benzaldehyde with compounds **1-5** and **7** without solvent, below 40° resulted in addition products **10-14** and **24** (Method A, Schemes 1 and 2). When these products were refluxed in benzene, condensation products **15-19** and **25** were obtained (Method B-2). The condensation products were also prepared from the reactions of the parent compounds and benzaldehyde in refluxing benzene

Scheme 1



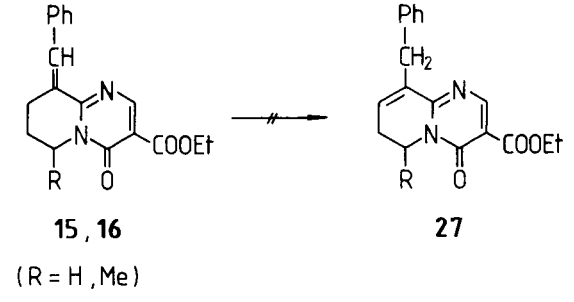
R	n	Compound			
H	1	**1**	**10**	**15**	**20**
6-Me	1	**2**	**11**	**16**	**21**
7-Me	1	**3**	**12**	**17**	**22**
8-Me	1	**4**	**13**	**18**	**23**
H	0	**5**	**14**	**19**	
H	2	**6**			

Scheme 2



in the presence of a few drops of concentrated hydrochloric acid (Method B-1). The reaction of pyrrolo[1,2-*a*]pyrimidin-2-one **8** at room temperature gave a 2:3 mixture of addition and condensation products, from which the condensation product **26** was isolated. The formation of addition and condensation products in the reactions of azepino-[1,2-*a*]pyrimidines **6** and **9** could be detected only by tlc chromatography, even after a reaction period of 50 hours.

Scheme 3



The *exo* double bond of condensation products **15** and **16** could not be arranged into the *endo* position either under basic conditions (heating in ethanol in the presence of potassium hydroxide) or thermally (heating in Dowtherm A at 250° for 2 hours), due to the greater thermodynamic stability of benzylidene derivatives than that of benzyl derivatives (**27**, Scheme 3).

Benzylidene derivatives **15-18** were hydrogenated in ethanol over palladium-carbon catalyst, resulting in 9-benzyltetrahydropyridopyrimidines **20-23** (Method C).

The uv, ^{1}H and ^{13}C nmr spectra of compounds **10-26** were recorded. The data are listed in Tables 1-3.

Table 1

UV Data on Compounds **10-26** in Ethanol [a]

Compound	max [nm] [ε]			
10		304	(11750)	228 (8910)
11		305	(12590)	229 (7760)
12		303	(10000)	226 (7760)
13		304	(10000)	228 (8320)
14		297	(8260)	226 (7340)
15	352 (25120)	304 sh	(11480)	226 sh (12590)
16	354 (24550)	304 sh	(11480)	224 sh (11750)
17	352 (19950)	304 sh	(10230)	225 sh (12780)
18	348 (22390)	300 sh	(10970)	224 sh (13180)
19	343 (25270)			228 (13000)
20		303	(8910)	226 (6610)
21		306	(10720)	230 (6310)
22		303	(9120)	226 (6760)
23		303	(6920)	226 (5250)
24		286	(7760)	238 (18200)
25	310 (18620)	250	(13490)	238 sh (12300)
26	322 (29510)	250	(11750)	236 (11220)

[a] sh: shoulder

The characteristic vicinal coupling constants of the ^{1}H nmr spectra are given in Table 4. Assignment of the signals in the ^{1}H and ^{13}C nmr spectra was facilitated by ^{1}H nmr spin decoupling experiments and by gated spin-echo ^{13}C nmr spectra. The assignments were confirmed in a 2D homonuclear shift correlation experiment (COSY-45) for compound **12** and in 2D ^{1}H-^{13}C heteronuclear shift correlation experiments for compound **17**. The ^{1}H nmr NOE measurements were performed on the condensation compounds **15-19** and **25-26**. The irradiation of 8-H resulted in an intensity enhancement of about 10% for the *ortho*-aromatic protons, whereas no intensity enhancement was detected at the exo CH= signal.

Discussion.

The thermodynamically stable reaction products of benzaldehyde with **1-9** heterocycles are the condensation products **15-19** and **25-26**, while at low temperature the kinetically stable addition products **10-14** and **24** can be isolated. The observed reactivity of the ring homologues decreases in the sequence of six- > five- ≫ seven-membered ring "A". This is in agreement with the sequence of kinetic acidity of the active methylene group of the parent

Table 2

^{1}H NMR Chemical Shifts and Multiplicities for Compounds **10-26** [a]

Compound	2-H	6-H_a	6-H_e	7-H_a	7-H_e	8-H_a	8-H_e	9-H	9-CH	OH	CH_3	OCH_2---CH_3		Phenyl
10	8.60 s	----------4.0 m----------		----------1.50-2.15 m----------				3.22 m	5.60 dd	4.00 d	---	4.33 q	1.38 t	7.33 s
11	8.65 s	---	4.88 m	----------1.70-2.10 m----------				3.38 m	5.46 dd	4.67 d	1.03 d	4.38 q	1.38 t	7.33 s
cis	8.75 s	2.98 dd	4.31 ddd	1.48 m	---	1.65 ddd	1.23 dddd	3.27 ddd	5.95 dd	5.71 d	0.73 d			
12 [b]												4.24 q	1.22 d	7.15-7.60 m
trans	8.70 s								5.85 dd	5.77 d				
13 [b]	8.88 s	3.42 dd	4.29 ddd	0.64	1.45	2.07 m	---	2.95	5.70 dd	5.85 d	0.28 d	4.35 q	1.22 t	7.0-7.6 m
14	8.71 s	---------3.8-4.2 m---------		---	---	-------1.8-2.55 m-------		3.62 ddd	5.52 dd	2.80 d	---	4.36 q	1.36 t	7.40 s
15	8.70 s	----------4.10 m----------		---1.75-2.18 m---		------2.80-3.00 m------		---	8.38 t	---	---	4.36 q	1.38 t	7.45 s
16	8.70 s	---	5.19 m	---1.60-2.10 m---		------2.80-3.10 m------		---	8.38 t	---	1.36 d	4.37 t	1.37 t	7.30-7.60 m
17	8.71 s	3.35 dd	4.58 dddd	2.00 m	---	2.35 ddt	3.0 ddt	---	8.41 t	---	1.13 d	4.27 q	1.38 t	
18	8.78 s	-------3.60-4.35 m-------		------1.98 m------		--------3.47 m---------		---	8.29 t	---	1.25 d	4.43 q	1.37 t	7.50 s
19	8.80 s	4.13	4.50 m	---	---	--------3.1-3.5 m--------		---	7.87 t	---	---	4.38 q	1.37 t	7.75 m
20	8.68 s	----------3.98 t----------		----------1.5-2.1 m----------				3.10 m	2.80 dd 3.52 dd	---	---	4.38 q	1.40 t	7.28 s
cis	8.80 s													
21		---	4.68 m	----------1.5-2.1 m----------				------2.7-3.6 m------		---	1.08 d	4.38 q	1.38 t	7.25 s
trans	8.76 s													
cis	8.73 s													
22		2.6-3.8 m	4.3 o	----------1.5-2.3 m----------				------2.6-3.8 m------		---	1.05 d	4.40 q	1.35 t	7.28 s
trans	8.71 s													
cis	8.68 s										0.92 d			
23		2.8-3.9 m	4.1 m	----------1.5-2.25 m----------				------2.75-3.9 m------		---		4.38 q	1.38 t	7.28 s
trans	8.75 s										1.05 d			
24	7.95 s	------3.75-4.50 m-------		---	---	----------3.85-3.25 m----------			5.98 d	4.95 b	---		1.37 t	7.35 m
25	8.05 s	---------4.10 m---------		---1.90-2.25 m---		---------3.00 m---------		---	8.42 t	---	---	4.38 q	1.38 t	7.44 s
26	8.25 s	---------4.25 m---------		---	---	--------3.35 td--------		---	7.95 t	---	---	4.35 q	1.38 t	7.48 s

[a] In deuteriochloroform unless otherwise stated; δ TMS = 0.00 ppm; s, singulet; d, doublet; t, triplet; q, quartet; m, multiplet; o, overlapping signal.

[b] In deuteriobenzene;dimethyl d_6-sulphoxide 5:1.

Table 3

^{13}C NMR Chemical Shifts for Compounds **10-13** and **15-25** in deuteriochloroform [a]

Compound	C(2)	C(3)	C(4)	C(6)	C(7)	C(8)	C(9)	C(9a)	9-CH	CH_3	COO--CH_2--CH_3			C(1')	C(2')	C(3')	C(4')
10	157.0	114.3	158.7	42.7	20.8	19.2	48.0	166.4	74.0	-	164.2	61.7	14.3	141.6	126.2	128.6	127.7
11	156.2	113.9	158.0	48.1	27.1	15.8	47.9	165.7	74.9	18.1	163.7	61.2	14.3	141.3	126.2	128.4	127.7
12 *cis*	157.1	114.2	158.7	49.2	27.7	28.0	48.9	165.9	74.1	19.1	164.2	61.3	14.3	141.5	126.2	128.5	127.6
12 *trans*	157.8	114.4	158.5	47.8	26.1	26.9	45.9	166.3	74.6	18.4					126.0	128.5	127.4
13	157.1	114.2	158.5	41.6	29.8	27.0	55.0	166.6	75.9	21.3	164.1	61.2	14.3	141.7	126.3	128.6	127.9
15	157.2	112.1	159.5 [c]	42.3	21.0	24.9	128.5	158.5 [c]	139.0	-	164.0	60.7	14.1	135.2	129.0	128.3	128.8
16	157.7	112.6	159.5 [c]	46.6	26.5	21.1	127.6	158.2 [c]	140.0	17.5	164.4	61.0	14.3	135.5	130.5	128.6	129.2
17	157.3	112.3	159.3 [c]	48.3	27.1	33.0	128.1	158.7 [c]	139.3	18.3	164.1	60.7	14.1	135.3	130.1	128.3	128.9
18	157.5	112.6	159.6 [c]	39.0	27.1	26.5	134.2	158.9 [c]	138.5	17.7	164.2	60.9	14.2	135.3	129.4	128.6	128.9
19	160.6	114.0	163.6 [c]	45.1	-	25.2	130.9	157.9 [c]		-	164.0	61.0	14.2	134.6	130.0	128.9	129.8
20	157.5	113.7	158.8	43.0	19.7	23.4	42.7	167.2	39.1	-	164.1	61.0	14.3	139.0	129.3	128.7	126.7
21 *cis*	157.5	113.7	158.5	48.5	27.4	20.0	42.9	167.0	40.0	18.7	164.3	61.0	14.3	138.7	128.7	129.5	126.8
21 *trans*	157.6	114.0		48.4	24.4	19.5	41.8	167.3	40.4	18.1				139.0	128.8	129.3	
22 *cis*	156.7	113.1	158.2	49.0	26.9	32.7	42.8	166.1	38.6	18.4	163.4	60.3	13.7	138.5	128.8	128.7	126.0
22 *trans*	157.0		158.0	48.3	23.7	29.8	41.3	166.7	39.1	18.0				138.4	128.1	128.6	126.2
23 *cis*	157.1	114.2	158.4	39.7	28.0	26.6	46.8	166.6	33.8	15.4	164.0	60.8	14.3	139.7	129.0	128.6	126.4
23 *trans*	157.6	113.4	158.6	41.1	27.2	28.1	50.2	167.2	38.5	19.9				138.7	129.3		126.7
24	[b]	[b]	149.1	52.6	21.0	18.5	47.5	[b]	73.7	-	164.2	61.3	14.3	142.4	126.1	128.3	127.1
25	163.7	112.3	148.6	51.2	21.1	24.5	128.4		135.8	-	164.1	60.0	14.0	135.3	128.4	129.7	128.4

[a] TMS = 0.00 ppm. [b] Low-intensity signal. [c] Tentative assignment.

Table 4

Characteristic ^{1}H NMR Vicinal Coupling Constants for Compounds **10-13** and **17-18** [b]

	10	**11**	**12** [c] *cis*	**12** [d] *trans*	**13**	**14**	**17**	**18**
$J_{6e,7e}$		4	-	-	4.5	-	-	
$J_{6e,7a}$		6	4.2		4.0	-	3.9	
$J_{6a,7e}$		-	-	-	3.5	-	-	
$J_{6a,7a}$		-	11.0	10.0	11.0	-	10.0	
$J_{7e,8e}$					-		-	3.7
$J_{7e,8a}$					6.0		-	
$J_{7a,8e}$			6.0				3.8	3.7
$J_{7a,8a}$			12.6		11.0		10.8	
$J_{8e,9a}$		7.8	7.7	-	-	7.3	-	
$J_{8a,9e}$		-	-		6.1	-	-	
$J_{8a,9a}$		10.6	10.3	-	-	9.5	-	
$J_{9,9\text{-}CH}$	3.1	3.5	2.4	2.5	3.5	2.9	-	2.3
$J_{9\text{-}CH,OH}$	4.5	6.6	5.7	5.5		4.4	-	

[b] In Hz, measured in deuteriochloroform unless otherwise stated, a: axial, e: equatorial. [c] In deuteriobenzene:dimethyl d_6-sulphoxide 5:1. [d] In deuteriobenzene.

Table 5

^{13}C SCS for Methyl Groups in Compounds **16-18** [b]

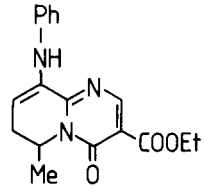
16			**17**			**18**		
α	6a	4.3 (6.0)	α	7e	6.1 (6.0)	α	8a	5.2
β	6a	5.5 (6.4)	β	7e,6	6.0 (6.6)	β	8a	6.1
γ	6a	-3.8 (-3.9)	γ	7e,8	8.1 (8.8)	γ	8a	-3.3
δ	6a	-0.9 (-0.6)	δ	7e	-0.4 (-0.4)			

[b] Values from ref [18] in parentheses; a, axial methyl group; e, equatorial methyl group.

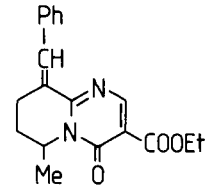
compounds, measured in deuteration experiments [3], where the same trend was observed.

The bathochromic shift of 50 ± 3 nm for the longest wave-length uv maximum of condensation products **15-19** compared that of the starting 4-oxo compounds **1-5** [3] indicates a conjugation interaction between the electrons of the phenyl ring and the pyrimidinone moiety, which is in agreement with the 9-benzylidine structure. A comparison of the uv spectra of ethyl 9-phenylamino-6-methyl-6,7-dihydropyrido[1,2-*a*]pyrimidine-3-carboxylate (**28**) [17] and compound **16** (Scheme 4) also indicates that the latter compound exists in the 9-benzylidine-6,7,8,9-tetrahydro form rather than in the 9-benzyl-6,7-dihydro form **27**.

Scheme 4



28



16

UV data [nm] (ε) in EtOH

259 (17410)	224 sh (11750)
322 (11960)	304 sh (11480)
380 sh (2290)	354 (24550)

Condensation products **15-19** and **25-26** can be described as *Z* or *E* isomers as concerns the exocyclic double bond. There is only one set of signals in their ^{1}H and ^{13}C nmr spectra, proving that only one isomer exists in solution. The results of the ^{1}H nmr NOE studies showed that this is the *E* isomer (as shown in Schemes 1 and 2). The two half-chair conformations of the tetrahydropyridine ring have equal energies, and the two equally populated forms rapidly interconvert in compounds **15** and **25**. The two conformers have unequal energies in compounds **16-18**. The ^{1}H and ^{13}C data were used to study their con-

Table 6

^{13}C SCS for 9-Benzyl Group in Compounds **20-22** [a]

Compound	α	β	γ	δ
20	10.4	4.5	-1.8	0.2
21-*cis*	11.3	5.0	-0.5	-0.2
21-*trans*	10.2	4.5	-3.5	-0.3
22-*cis*	10.9	5.1	-0.6	-0.4
22-*trans*	9.4	2.2	-3.8	-1.1

[a] Calculated by subtracting the appropriate chemical shift for compounds **1-3** (ref [18]) from the chemical shift for compounds **20-22**.

formation equilibria. The ^{13}C substituent chemical shifts of the methyl groups were calculated for these compounds; they are listed in Table 5, together with similar data obtained from, a rigorous statistical treatment of the chemical shifts of several methyl derivatives of 6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-ones [18]. The close agreement between the two sets of SCS values indicates that the exocyclic double bond at C(9) has little effect on the geometry of the tetrahydropyridine ring. The chemical shift of 6-H is 5.19 ppm in **16**, suggesting a predominance of the conformer in which 6-H is equatorial; the large chemical shift is due to the deshielding effect of the C(4)=O double

Table 7

Physical and Analytical Data on Compounds **10-26**

Compound	Mp [a] °C	Formula	Mw [b]	Anaylsis Calcd./Found C%	H%	N%	Method	Yield %
10	154-156	$C_{18}H_{20}N_2O_4$	328.371	65.84 65.95	6.14 6.16	8.53 8.72	A	17
11	174-175	$C_{19}H_{22}N_2O_4$	342.398	66.65 66.58	6.48 6.56	8.18 8.20	A	20
12	171-172	$C_{19}H_{22}N_2O_4$	342.398	66.65 66.51	6.48 6.36	8.18 8.08	A	38
13	145-147	$C_{19}H_{22}N_2O_4$	342.398	66.65 66.56	6.48 6.38	8.18 8.04	A	37
14	178-180	$C_{17}H_{18}N_2O_4$	314.343	64.96 64.49	5.77 5.45	8.91 9.00	A	38
15	143-144	$C_{18}H_{18}N_2O_3$	310.355	69.66 69.35	5.84 5.66	9.03 8.98	B (1)	68
16	135-136	$C_{19}H_{20}N_2O_3$	324.382	70.35 69.91	6.21 6.21	8.64 8.39	B (1) B (2)	82 49
17	123-125	$C_{19}H_{20}N_2O_3$	324.382	70.35 70.02	6.21 6.08	8.64 8.71	B (1)	68
18	180	$C_{19}H_{20}N_2O_3$	324.382	70.35 69.97	6.21 6.19	8.64 8.61	B (1)	76
19	208-210	$C_{17}H_{16}N_2O_3$	296.327	68.91 68.75	5.44 5.49	9.45 9.46	B (1)	24
20	oil	$C_{18}H_{20}N_2O_3$	312.371	69.21 69.10	6.45 6.40	8.97 8.95	C	96
21	oil	$C_{19}H_{22}N_2O_3$	326.398	69.92 69.80	6.79 6.73	8.56 8.48	C	98
22	oil	$C_{19}H_{22}N_2O_3$	326.398	69.92 69.95	6.79 6.98	8.56 8.76	C	98
23	oil	$C_{19}H_{22}N_2O_3$	326.398	69.92 69.89	6.79 6.40	8.56 8.45	C	70
24	144-146	$C_{18}H_{20}N_2O_4$	328.371	65.84 65.76	6.14 6.16	8.53 8.72	A	42
25	223-225	$C_{18}H_{18}N_2O_3$	310.355	69.66 69.80	5.85 5.82	9.03 9.06	B (1)	71
26	275-276	$C_{17}H_{16}N_2O_3$	296.327	68.91 68.64	5.44 5.09	9.45 9.48	B (1)	79

[a] Melting point. [b] Molecular weight.

bond on the equatorial 6-H. The same conclusion can be drawn from the γ-effect of −3.8 ppm for the methyl group in compound **16**. The large vicinal coupling constants of 7-H with 6-H_a and 8-H_a (Table 4) indicate a predominance of the half-chair conformation with an equatorial methyl group in **17**. A predominance of the conformation with an axial 8-methyl in **18** is indicated by the ^1H vicinal coupling constants of 8-H (Table 4) and by the ^{13}C SCS values of the methyl group (Table 5). The conformation with an equatorial 8-methyl is unfavourable, due to the 1,3-allylic strain between the methyl and 9-benzylidine groups in this compound.

The stereochemistry of 9-benzyl derivatives **20-23** was studied *via* ^1H and ^{13}C nmr spectroscopy. There was only one set of signals in the spectra of **20**, whereas two sets of signals were obtained in the spectra of **21-23**. These could be assigned to *cis* and *trans* isomers by calculating the ^{13}C SCS effect of the 9-benzyl group; the data are given in Table 6. The *cis* and *trans* isomers can interconvert slowly, due to the mobility of 9-H [3]. The intensity ratio of the two sets of signals for compounds **21-23** did not change in time, even in the presence of a trace of acid catalyst, indicating that the reduction results in a mixture of isomers, with a ratio close to the equilibrium value. The chemical shift of 6-H (5.1 ppm) in both isomers of **21** showed that the conformer in which the 6-methyl group is axial is predominant in both isomers. The ^{13}C SCS values of the 9-benzyl group are therefore characteristic of its axial position in the *trans* isomer and for its equatorial position in the *cis* isomer. Similar ^{13}C SCS values were calculated for the two isomers of **22**, indicating that the *cis* isomer can be described by a predominance of the conformer in which both the 7-methyl and 9-benzyl groups are in equatorial positions, while in the dominant conformer of the *trans* isomer the 7-methyl group is equatorial and the 9-benzyl group is axial. The ^{13}C SCS values of the benzyl group in compound **20** are between the values characteristic of the axial and equatorial positions (Table 6). This indicates that there is a conformation equilibrium of the two half-chair forms with roughly equal energies and populations in a solution of this compound. In other words, the axial and equatorial positions of the benzyl group have about equal energies. This is in agreement with the fact that the equilibrium ratio of the *cis* and *trans* isomers of **21** and **22** is about 1:1, and the conformations of the two isomers of both compounds are each determined by the energetically favoured positions of the methyl groups. The effects of the substituents on the conformational energy in compounds **21** and **22** can be considered independently, since there is no steric interaction between them. In compound **23**, however, such an interaction between the vicinal substituents also affects the conformational energy of the molecule. This is reflected by the measured *cis:trans* isomer ratio for 4:1 in **23**. The assignments of the isomers were based on chemical shift analogies with 8,9-dimethyl-substituted derivatives [18]. Both isomers probably exists as mixtures of the two half-chair conformers with about equal populations.

C(9) and 9-C are adjacent asymmetric centres connected by an open-chain bond in addition products **10-14** and **24**. This gives rise to an *erythro-threo* isomer pair, where the configurations of the two centres are either equal (*RR* or *SS*) or different (*RS* or *SR*). Further, methyl-substituted derivatives **11-13** can be described as *cis* and *trans* isomers, so four diastereomers are possible in these derivatives. However, only one set of signals is observed in the nmr spectra of compounds **10-11**, **13-14** and **24**, and two sets of signals in the nmr spectra of the 7-methyl derivative **12**. The small value of $J_{9,9\text{-CH}}$ for all addition products (Table 4) indicates a perferred rotamer along the C(9)-9-CH bond. We earlier observed similar spectroscopic data for the 9-(1-hydroxy-2,2,2,-trichloroethyl)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [19].

Erythro-threo isomer pairs were identified in those derivatives, and characteristic differences in the chemical shift of 9-CH in the ^1H nmr spectra and of C(8) in the ^{13}C nmr spectra of the isomers were observed. A comparison of the measured chemical shifts of these nuclei in compounds **10-14** and **24** with the known shift ranges of the two isomers resulted in the assignment of these compounds as *erythro* isomers (this structure is shown in Scheme 1; the configuration of C(9) is arbitrarily chosen as *R*, but racemates were obtained). The ^1H nmr coupling constants of the ring "A" protons were used to establish the *cis-trans* isomer status of compounds **11-14**. The coupling constants were different from the averaged values indicating the existence of single dominant conformers of the tetrahydropyridine ring in these compounds (Table 4). On the basis of the coupling constants, the only set of signals of **11** was assigned to the *cis* isomer, where the 6-methyl group is axial and 9-C is equatorial in the dominant conformer. There are two sets of signals for compound **12**, with an intensity ratio of 4:1. The more intense set can be assigned to the *cis* isomer, where both substituents are equatorial in the dominant conformation. The minor form is the *trans* isomer, where the 7-methyl group is equatorial and 9-C is axial in the dominant conformation. The only set of signals was assigned to the *cis* isomer for compound **13**, where the coupling constant data indicate that the 8-methyl group is equatorial and 9-C is axial in the dominant conformer.

EXPERIMENTAL

Melting points were uncorrected. Yields were not optimized. The uv spectra were recorded in ethanol on a Unicam SP-800 spectrophotometer. The ^1H nmr spectra of compounds **11-13**

were measured at 200 MHz on a Bruker WP-200 NMR spectrometer. The ^1H nmr spectra of all other compounds were measured at 80 MHz on a Bruker WP-80 spectrometer. The ^{13}C nmr spectra and gated spin-echo ^{13}C nmr spectra of the compounds were measured at 20.1 MHz on a Bruker WP-80 NMR spectrometer; a 7 ms delay time was used in the gated spin-echo spectra. TMS was used as internal standard in all ^1H and ^{13}C nmr experiments. The ^1H nmr NOE measurements on compounds **15-19** and **26** were carried out in the difference mode on a JEOL FX-100 NMR spectrometer. Homonuclear shift correlation measurement (COSY-45) on **12** was performed at 200 MHz on a Bruker WP-200 spectrometer with the DISNMR software. Heteronuclear shift correlation measurements on compounds **17** was performed on a JEOL FX-100 NMR spectrometer.

Melting points, yields and analytical data are given in Table 7.

Method A.

A mixture of one of compounds **1-9** (10 mmoles) and benzaldehyde (1.06 g, 10 mmoles) was thoroughly mixed at ambient temperature. The temperature of the melted reaction mixture decreased by some degrees, but it then slowly began to rise on dilution. During this process the reaction temperature did not rise above 40°. After about 30 minutes, the reaction mixture became solid, and it was diluted with ethanol (5 ml). The reaction mixtue was allowed to react in a refrigerator at 0-5° for a month. The presipitated addition product, one of **10-14** and **24** was then filtered off and recrystallized from ethanol.

Method B-1.

A solution of one of compounds **1-9** (10 mmoles) was refluxed with benzaldehyde (1.06 g, 10 mmoles) in benzene (15 ml) in the presence of a few drops of concentrated hydrochloric acid. The reaction mixture was next cooled to room temperature and the precipitated condensation product, one of **15-19** and **25-26**, was filtered off and recrystallized from ethanol.

Method B-2.

One of the addition products **10-13** (2.5 mmoles) was refluxed in benzene (30 ml) for 3 hours. The reaction mixture was then cooled to room temperature and the precipitated condensation product, one of **15-18**, was filtered off, and recrystallized from ethanol.

Method C.

A solution of one of the condensation products **15-18** (10 mmoles) in ethanol (350 ml) was hydrogenated at atmospheric pressure over a 10% Pd/C catalyst (1.5 g) at ambient temperature. After the absorption of 1 molar equivalent of hydrogen, the catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*; this gave the 9-benzylpyridopyrimidinone **20-23** as a light-yellow oil.

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