Nitrogen Bridgehead Compounds. Part 50 [1]. Vilsmeier-Haack Acylation of 6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, Part 5

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6-Methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **1-5** were subjected to Vilsmeier-Haack acylation with complexes of phosphoryl chloride and different amides. Acylation at position 9 of the pyridopyrimidines was successful with the iminium salt formed *in situ* from *N*-formylpiperidine, *N*-methylformanilide or *N,N*-diethylbenzamide, but unsuccessful with the iminium salt formed from *N,N*-diethylacetamide or *N,N*-diethylisobutyramide, respectively. The iminium salt formed from formanilide, *N*-methylpyrrolidinone or formamide reacted only with those tetrahydropyridopyrimidinones which contain a strongly electronegative substituent (*e.g.* CN or CO_2Et) in position 3. With the latter derivatives, the 9-phenylaminomethylene group could be introduced using *N,N'*-diphenylformamide or in a "one-pot" procedure with aniline and triethyl orthoformate. Ethanolysis of 9-*N*-methyl-*N*-phenylaminomethylene derivatives **15** and **19** afforded 9-ethoxymethylene compounds **26** and **27** in the presence of hydrogen chloride. The structures of the 9-substituted 6-methyltetrahydropyridopyrimidin-4-ones **14-25** were elucidated by means of uv, ^1H and ^{13}C nmr spectroscopy. 9-Piperidinomethylene **14**, 9-(*N*-methyl-*N*-phenylaminomethylene **15-19** and 9-(*N*-methyl-2-pyrrolidinylidene) **21** derivatives exist as *E* geometric isomers. 9-Phenylaminomethylene-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile **20** displays a solvent-dependent *E-Z* isomerism. The bis-compound **25** contains both *E* and *Z* geometric exo C=CH double bonds. 9-Benzoyl derivatives **23** and **24** exist predominantly as the 1,6,7,8-tetrahydropyridopyrimidin-4-one tautomer.

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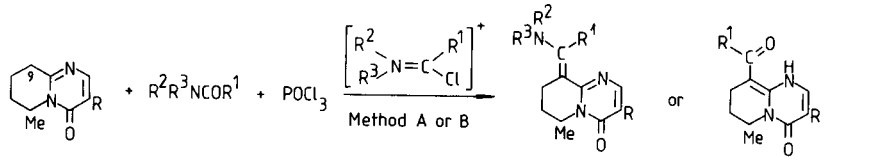
We recently reported that nitrogen bridgehead compounds having valuable pharmacological properties [2] can be reacted at their active methylene group [3] with phosphoryl chloride-dimethylformamide reagent [4] to yield dimethylamino or formyl derivatives [5,6]. The formyl group further activates the methylene group [6a,7], and thus compounds with antiallergic-antiasthmatic effects can be synthesized [8]; a facile total synthesis of indolo-[2',3':3,4][2,1-*b*]quinazolines too can be achieved [9].

We now describe studies on the applicability of amides other than dimethylformamide in the Vilsmeier-Haack acylation of 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. The structures of the products were elucidated by uv, ^1H and ^{13}C nmr spectroscopy. Iminium chlorides formed with amides other than dimethylformamides are known to be generally less reactive [10] and may be subject to self-condensation [11].

In the reaction of 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones and dimethylformamide-phosphoryl chloride, 9-dimethylaminomethylene derivatives are formed when the substrate contains strongly electronegative substituents (*e.g.* CHO, CN or CO_2Et) at C-3, while the primary dimethylaminomethylene products hydrolyse to the 9-formyl derivatives when C-3 is either unsubstituted or substituted by other groups (*e.g.* Me, Ph or CH_2CO_2Et) [5b].



	R	R1	R2	R3
1	CO_2Et			
2	Me			
3	CN			
4	CH_2CO_2Et			
5	Ph			
6		H	$-(CH_2)_5-$	
7		H	Me	Ph
8		H	Ph	H
9		Me	Et	Et
10		iPr	Et	Et
11		$-(CH_2)_3-$		Me
12		Ph	Et	Et

	R	R1	R2	R3
14	CO_2Et	H	$-(CH_2)_5-$	
15	CO_2Et	H	Me	Ph
16	Me	H	Me	Ph
17	CN	H	Me	Ph
18	CH_2CO_2Et	H	Me	Ph
19	Ph	H	Me	Ph
20	CN	H	Ph	H
21	CN	$-(CH_2)_3-$		Me

	R	R1
22	Me	H
23	CO_2Et	Ph
24	Ph	Ph

Scheme 1

Table 1

Products from Vilsmeier-Haack Acylation of 6-Methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **1-5** and Subsequent Reactions

Starting Compound	Amide	R	R_1	R_2	R_3	Product	Method	Yield %	Mp °C	Recrystallization solvent	Molecular formula	Analyses Calcd. C	H	N	Found C	H	N
1	**6**	CO_2Et	H	$-(CH_2)_5-$	—	**14**	A-1	95	136-137	EtOH	$C_{18}H_{25}N_3O_3$	65.24	7.63	12.68	65.15	7.74	12.50
2	**6**	Me	H	$-(CH_2)_5-$	.	**22**	A-1	53	130 [a]	EtOH							
1	**7**	CO_2Et	H	Me	Ph	**15**	A-1	88	156	EtOH	$C_{20}H_{23}N_3O_3$	67.98	6.56	11.90	67.80	6.41	11.69
2	**7**	Me	H	Me	Ph	**16**	A-1	61	140-142	EtOH-Et_2O	$C_{16}H_{21}N_3O$	73.19	7.17	14.23	73.16	7.10	14.05
3	**7**	CN	H	Me	Ph	**17**	A-1	82	161-163	EtOAc	$C_{16}H_{18}N_4O$	70.57	5.92	18.29	70.53	6.03	18.03
4	**7**	CH_2CO_2Et	H	Me	Ph	**18**	A-1	51	109	EtOH-Et_2O	$C_{21}H_{25}N_3O_3$	68.64	6.86	11.43	68.49	6.75	11.35
5	**7**	Ph	H	Me	Ph	**19**	A-1	75	146-147	EtOH-Et_2O	$C_{23}H_{23}N_3O$	77.08	6.49	11.76	76.89	6.44	11.62
3	**8**	CN	H	Ph	H	**20**	A-2	58	207	EtOH-Et_2O	$C_{17}H_{16}N_4O$	69.85	5.50	19.17	69.86	5.74	19.02
5	**8**	Ph	H	Ph	H		A-2		no reaction								
1	**9**	CO_2Et	Me	Et	Et		B-1		no reaction								
1	**10**	CO_2Et	iPr	Et	Et		B-1		no reaction								
3	**11**	CN	$-(CH_2)_3-$	.	Me	**21**	B-2	44	151-152	EtOAc	$C_{15}H_{18}N_4O$	66.65	6.70	20.77	66.41	6.76	20.79
5	**11**	Ph	$-(CH_2)_3-$	.	Me		B-2		no reaction								
1	**12**	CO_2Et	Ph	Et	Et	**23**	B-1	38	166-167	EtOH	$C_{19}H_{20}N_2O_4$	67.05	5.92	8.23	67.24	5.92	8.18
5	**12**	Ph	Ph	Et	Et	**24**	B-1	35	214-215	EtOH	$C_{22}H_{20}N_2O_2$	76.72	5.85	8.13	76.41	5.83	8.25
1	**13**	CO_2Et	H	H	H	**25**	C	15	218-220	EtOH	$C_{26}H_{31}N_3O_6$	61.29	6.13	13.74	61.54	6.13	13.70
5	**13**	Ph	H	H	H		C		no reaction								
15		CO_2Et	H	Me	Ph	**26**	D	62	114-115 [b]	EtOH							
19		Ph	H	Me	Ph	**27**	D	68	117-118 [c]	EtOH							
27		Ph	H	Ph	H	**28**	E	95	280 [d]	EtOH	$C_{22}H_{22}ClN_3O$	69.56	5.57	11.06	69.76	5.63	10.89
1		CO_2Et	H	Ph	H	**29**	F	65	174-175 [e]	EtOH							
1		CO_2Et	H	Ph	H	**29**	G-1	24	172-173 [e]	EtOH							
1		CO_2Et	H	Ph	H	**29**	G-2	65	172-173 [e]	EtOH-Et_2O							
3		CN	H	Ph	H	**20**	G-1	38	206-207	EtOH							
3		CN	H	Ph	H	**20**	G-2	68	206-207	EtOH							

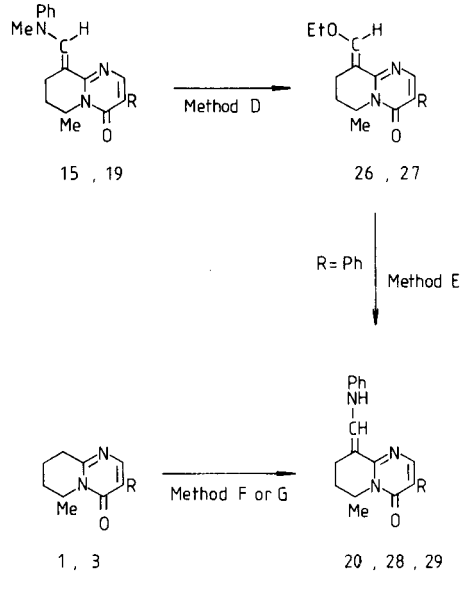
[a] Lit [5b], mp 130-131°. [b] Lit [5b], mp 114-116°. [c] Lit [5b], mp 118°. [d] Hydrochloride. [e] Lit [6b], mp 174-175°.

Synthesis and Discussion.

Iminium salts formed *in situ* from amides and phosphoryl chloride were each reacted with two tetrahydropyridopyrimidin-4-ones, one with a more reactive methylene group, **1** (R = CO_2Et) or **3** (R = CN), and one with a less reactive one, **2** (R = Me), **4** (R = CH_2CO_2Et) or **5** (R = Ph) (Scheme 1). As reagents, first the phosphoryl chloride complexes of *N*-formyl-piperidine and *N*-methylformanilide were used in boiling 1,2-dichloromethane [Method A (1)].

With *N*-formylpiperidine the ester **1** afforded the 9-piperidinomethylene derivative **14**, while the 3-methyl compound **2** gave the 9-formyl derivative **22** [5b]. The ester **14** was also obtained by heating 9-formyl-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate [5a,b] with piperidine in ethanol. When *N*-methylformanilide was used, the primary products, *viz.* the 9-(*N*-phenyl-*N*-methylamino)methylene derivatives **15-19**, could always be isolated. Owing to the presence of the phenyl group, the basicity of the amino group is reduced and therefore hydrolysis of the aminomethylene group during work-up does not take place at all or is much slower than for the 9-piperidinomethylene and 9-(*N,N*-dimethylaminomethylene) derivatives [5b].

The 9-(*N*-phenyl-*N*-methylamino)methylene derivatives **15** and **19** are transformed by heating with ethanolic hydrogen chloride to the known [5b] 9-ethoxymethylene compounds **26** and **27** (Method D), while ethanol itself is ineffective (Scheme 2).

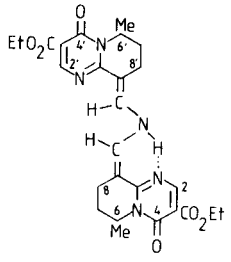


Scheme 2

In order to avoid self-condensation of the iminium salt [11a] formed from formanilide, the reaction was carried out at room temperature in 1,2-dichloromethane [Method A(2)]. Of the 3-cyano **3** and 3-phenyl **5** derivatives, only the former reacted, giving rise to the 9-phenylamino-methylene derivatives **20** (In both cases *N,N'*-diphenylformamidine formed by self-condensation and subsequent hydrolysis of the dimer could be detected by tlc.). The phenylaminomethylene group could be introduced by reacting 9-ethoxymethylenetetrahydropyridopyrimidin-4-one with

aniline (Method E, Scheme 2). With the more active tetrahydropyridopyrimidin-4-ones [*i.e.* **1** and **3**], the 9-phenylaminomethylene group could also be formed using *N,N'*-diphenylformamidine (Method F) or in a "one-pot" procedure with aniline and triethyl orthoformate [Method G(1)]. In the latter case, yields were higher when a Lewis acid ($AlCl_3$) was added [Method G(2)].

When the amide component was formamide **13** and the reaction was carried out in an excess of the reagent at 80-85 °C (Method C), only the 3-ester **1** reacted, but the 3-phenyl derivative **5** not. From the tarry product obtained from the latter, only a bis-compound **25** could be isolated.



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N,N'-Diethylacetamide **9** and *N,N*-diethylisobutyramide **10** failed to react, even with the 3-ester derivative **1**, when the substrate was heated in an excess of the reagent [Method B(1)]. When the reaction in the case of *N,N*-diethylacetamide was followed by tlc, we observed that the amide spot gradually dissappeared, but the characteristic yellow spot of the 9-aminomethylenepyridopyrimidin-4-one did not appear. The amide **9** presumably underwent self-condensation, which is known to occur under the given conditions [11b,c]. With *N*-methylpyrrolidinone **11** [Method B(2)], acylation was successful with the 3-cyano compound **3**, whereas it failed with the 3-phenyl derivative **5**.

With *N,N*-diethylbenzamide, both the 3-ester **1** and the 3-phenyl compound **5** yielded the expected 9-benzoyltetrahydropyridopyrimidin-4-ones **23** and **24**, respectively [Method B(1)]. With the ester **1**, hydrolysis of the intermediate aminomethylene derivative during work-up was only partial, but was completed by heating in 1 *N* hydrochloric acid.

We earlier demonstrated for 9-formyl-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [5b] that the formyl group can be removed by either acidic or alkaline hydrolysis. In a similar way, the 9-benzoyl-3-ester **23** can be hydrolysed in 5% sodium hydroxide solution at room temperature to 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carboxylic acid and benzoic acid.

Table 2

UV Data on 9-Substituted 6-Methyltetrahydropyrido[1,2-*a*]pyrimidin-4-ones **14-21** and **23-25** in Ethanol

Compound No.	λ max (log ε)			
14	400 (4.70)	288i (3.44)	277 (3.47)	233 (3.96)
15	402 (4.68)	306i (3.47)	281 (3.65)	232 (4.20)
16	372 (4.42)	290i (3.51)	234 (3.94)	
17	407 (4.68)	281 (3.53)	227 (4.14)	
18	377 (4.48)	235 (3.96)		
19	395 (4.55)	286i (3.65)	239 (4.07)	
20	416 (4.66)	305i (3.66)	296i (3.67)	243 (4.22)
21	415 (4.60)	304i (3.29)	280 (3.34)	231 (4.29)
25	459 (4.75)	350 (4.13)	317 (3.93)	230 (4.30)
23	370 (4.45)	240i (3.90)	224 (4.11)	
24	371 (4.57)	238 (4.15)		

Table 3

^{1}H NMR Data on 9-Substituted 6-Methyltetrahydropyrido[1,2-*a*]pyrimidin-4-ones **14-21** and **23-25** in deuteriochloroform

Compound No.	Isomer	H-2	H-6	H_2-7	H_2-8	6-Me	C(9)=CH	Substituent in position 3	Substituent in position 9
14	*E*	8.47 s	5.00-5.40 m	1.55-2.10 m [a]	2.50-2.75 m	1.27 d	8.29 s	4.32 q, 1.28 t	3.40-3.80 m (-CH_2NCH_2-) 1.55-2.10 m [a] (-$(CH_2)_3$-)
15	*E*	8.50 s	5.00-5.32 m	1.60-1.85 m	2.05-2.30 m	1.28 d	8.35 t	4.35 q, 1.41 t	3.60 s (NMe), 7.05-7.45 m (NPh)
16	*E*	7.76 s	4.98-5.40 m	- 1.60-2.56 m -		1.29 d	8.01 s	2.08 s (Me)	3.48 s (NMe), 6.95-7.61 m (NPh)
17	*E*	8.04 s	4.80-5.25 m	- 1.45-2.25 m -		1.23 d	8.43 s		3.60 s (NMe), 7.02-7.58 m (NPh)
18	*E*	7.83 s	4.91-5.39 m	1.65-2.00 m	2.18-2.48 m	1.20 d	8.08 s	3.50 s (-CH_2-), 4.25 q, 1.39 t	3.50 s (NMe), 6.95-7.58 m (NPh)
19	*E*	8.10 s	5.04-5.49 m	1.60-2.00 m	2.08-2.47 m	1.30 d	8.18 s	6.90-7.95 m [a] (Ph)	3.48 s (NMe), 6.90-7.95 m [a] (NPh)
20[b]	*E*	8.10 s	4.98-5.40 m	1.71-2.20 m	2.46-3.20 m	1.28 d	8.72 dt		6.95-7.45 m (Ph) 6.78 d (NH)
	Z	8.20 s				1.32 d	7.50 dt		11.92 d (NH)
21	*E*	8.13 s	5.02-5.41 m	1.51-2.37 m [a]	2.44-2.80 m	1.25 d			3.08 s (NMe), 3.73 t (NCH_2-), 3.08 t (3'-CH_2), 1.51-2.37 m [a] (4'-CH_2)
25	*E*	8.58 s	4.88-5.53 m	1.65-2.28 m	2.30-2.98 m	1.34 d	8.16 d	4.40 q [c], 1.40 t [d]	12.55 dd (NH)
	Z	8.68 s					7.15 d	4.35 q [c], 1.38 t [d]	
23		8.29 d	4.85-5.20 m	1.50-2.05 m	2.15-2.98 m	1.31 d		4.34 q, 1.38 t	7.43 s (Ph), 16.42 d, br (NH)
24		[a]	4.85-5.25 m	1.50-2.05 m	2.18-3.00 m	1.36 d		(Ph) [a]	7.25-7.75 (Ph) [a], 16.75 d, br (NH)

Coupling constants (Hz): for **15** $J_{H_2\text{-}8,=CH}$ = 1.0; for *E*-**20** $J_{CH,NH}$ = 14.1; $J_{H_2\text{-}8,=CH}$ = 1.6; for *Z*-**20** $J_{CH,NH}$ = 12.0; for *E*-**25** $J_{CH,NH}$ = 12.9; for *Z*-**25** $J_{CH,NH}$ = 10.8; for **23** $J_{NH,H\text{-}2}$ = 4.9. [a] Overlapping. [b] *E:Z* ratio 20:80. [c] Interchangeable. [d] Interchangeable.

Structures of the products.

The uv data on the new compounds in ethanol are compiled in Table 2 and ^{1}H nmr data on their solutions in deuteriochloroform in Table 3.

As in the starting materials **1-5** [13], in all the new compounds the C(6)-Me group is oriented axially. This is indicated by the relatively large shift of the equatorial H-6 signal (δ = 4.80-5.20 ppm) due to the anisotropic effect of the adjacent C(4)=O group. The quasi-equatorial position for the C(6)-Me group is disfavoured by ^{1,3}A allylic strain [14] and a peri-effect caused by the C(4)=O group.

Our earlier studies on 9-(*N,N*-dimethylaminomethylene)-tetrahydropyrido[1,2-*a*]pyrimidin-4-ones demonstrated that the configuration around the exocyclic double bond is exclusively the sterically less hindered *E*-configuration [5a,b,6c]. With monosubstituted amines, the configuration is *E* in the solid state [6a], and solvent-dependent in solution [6a,8e] (*e.g.* the predominant form is *Z* in chloroform and *E* in dimethylsulphoxide [8a]). The *E-Z* interconversion has a low free energy of activation. The *Z*-isomer is stabilized by internal hydrogen bonding between NH and N(1).

Geometrical isomers can readily be identified *via* the C(9)=CH- proton signal or the C-8 signal. As a consequence of the anisotropy effect of the C(9a)=N(1) double bond, the former signal is at lower field (δ = 8.10-8.40 ppm) [5a,b,6,8e] in the *E*-isomer than in the *Z*-isomer (δ = 7.30-7.60 ppm) [6]. In 9-aminomethylene-6-methyltetrahydropyrido[1,2-*a*]pyrimidin-4-ones, the C-8 signal is at 21.9-22.3 ppm in the *Z*-isomer, and at 16.7-19.5 ppm in the *E*-isomer [6b,8e], as a consequence of the γ-gauche steric effect [16] of the amino moiety.

In the 9-piperidinomethylene derivative **14**, a ^{1}H signal at 8.27 ppm and a ^{13}C signal at 19.8 ppm for C-8 indicate that the compound is an *E*-isomer.

The 9-(*N*-methyl-*N*-phenylaminomethylene) derivatives **15-19** are all in the *E*-form (δ_{CH} = 8.01-8.43 ppm). The =CH- proton shifts are slightly affected by the substituent at C(3). Table 4 includes data on some known 9-dimethylaminomethylene [5b] and 9-phenylaminomethylene [8e] compounds.

Table 4.

Chemical Shifts (δ, ppm) of 9-Methylene Protons in *E* Isomers of 9-Aminomethyl-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones in Deuteriochloroform

Substituent in position 3	9-(*N,N*-dimethylamino) methylene derivatives	9-(*N*-methyl-*N*-phenylamino) methylene derivatives	*E* geometric isomer of 9-(*N*-phenylamino)-methylene derivatives
CHO	8.50 [a]	8.67 [a]	
CN	8.39 [a]	8.43	8.72
CO_2Et	8.31 [a]	8.35	8.75 [b]
Ph		8.18	8.48 [b]
H		8.12 [a]	8.47 [b]
CH_2CO_2Et		8.08	8.43 [b]
Me		8.01	8.38 [b]

[a] Ref [5b]. [b] Ref [8e].

When recorded immediately after dissolution in either deuteriochloroform or DMSO-d_6, the spectrum of 9-phenylaminomethylenetetrahydropyrido[1,2-*a*]pyrimidin-4-one **20**, shows only signals of the *E*-isomer, indicating that the compound is present in this form in the solid state. The

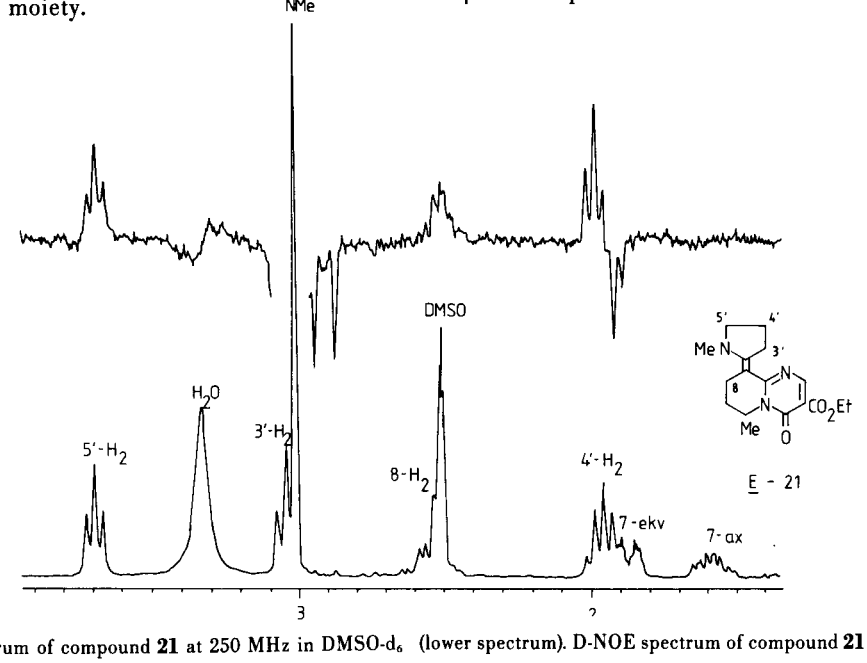


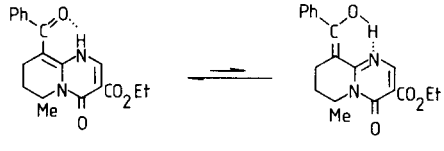
Figure 1. ^{1}H nmr spectrum of compound **21** at 250 MHz in DMSO-d_6 (lower spectrum). D-NOE spectrum of compound **21** with low-energy irradiation of the *N*-CH_3 signal (upper spectrum).

equilibrium *E/Z* ratio is 20:80 in deuteriochloroform and 95:5 in DMSO-d_6.

In the bis-compound **25**, the configuration is *E* relative to one of the ring systems ($\delta_{=CH}$ = 8.16, $\delta_{H\text{-}2}$ = 8.58 and $\delta_{C(8)}$ = 17.8 ppm) and *Z* relative to the other ($\delta_{=CH}$ = 7.15, $\delta_{H\text{-}2}$ = 8.68 and $\delta_{C(8)}$ = 21.8 ppm). Assignments were based on an earlier detailed analysis of the spectra of 9-arylaminomethylenetetrahydropyridopyrimidin-4-ones [6b,8e]. The disposition of the NH proton is antiperiplanar relative to both =CH- protons ($J_{NH,=CH}$ = 10.8 and 12.9 Hz, respectively).

The 9-(2-pyrrolidine) derivative **21** was a single stereoisomer, but its configuration could evidently not be assigned by the above approach. In this case application of the differential nuclear Overhauser effect (D-NOE) [17] was the method of choice. The H_2-8 protons are in the proximity of the *N*-CH_3 group in the *E*-isomer, and near CH_2-3′ of the pyrrolidine ring in the *Z*-isomer. In the ^{1}H nmr spectrum of **21** (at 250 MHz in DMSO-d_6), the *N*-CH_3 signal overlaps only with the high-field peak of the H_2-3′ triplet (Figure 1, lower spectrum), and thus low-energy irradiation of the *N*-CH_3 signal (γB_2 ~ 1 Hz) permitted verification of an *E*-configuration (Figure 1, upper spectrum). Besides the H_2-5′ signal, positive signals were also obtained for the H_2-8 signal. It should be noted that, on irradiation of the high-field peak of the H_2-3′ triplet, those lines of the H_2-4′ quintet which are regressively coupled with this transition give negative signals, while the ones that are progressively coupled give positive signals.

For the 9-benzoyl compounds **23** and **24**, the 9-benzoyl-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-one tautomer could be excluded on the basis of uv data (maximum at 370 and 371 nm, respectively). Doublets at 16.42 and 16.75 ppm, respectively ($J_{NH,H\text{-}2}$ = 4.9 and 4.9 Hz, respectively) for the N(1)H protons in the ^{1}H nmr spectra recorded in deuteriochloroform are indicative of the 9-benzoyl-1,6,7,8-tetrahydropyrido[1,2-*a*]pyrimidin-4-one tautomer in which there is a strong internal hydrogen bridge between N(1)-H and the carbonyl oxygen of the benzoyl group.



23 30

The position of the 9-CO signal (190.7 ppm) for the 9-benzoyl derivative **23** reveals that, as in 9-formylpyridopyrimidines [15], in the present case too a contribution is made to the tautomeric equilibrium by enolized form **30**. The carbonyl signal is at 196.4 ppm in benzophenone and at 197.4 ppm in acetophenone in deuteriochloroform [18].

EXPERIMENTAL

The melting points are uncorrected. Yields were not optimized. The uv spectra were recorded in ethanol with a UNICAM SP-800 spectrometer, ^{1}H (TMS as internal standard) and ^{13}C nmr spectra in deuteriochloroform solutions with a Bruker WP-80 DS spectrometer. D-NOE ^{1}H nmr spectra of **21** were recorded in DMSO-d_6 at 250 Hz with a Bruker WM-250 spectrometer. Solvents for recrystallization, yields and melting points of the products are given in Table 1.

Acylation. Method A(1).

To a stirred solution of the pyridopyrimidin-4-one (10 mmoles) in 1,2-dichloroethane (15 ml) was added a mixture of the amide (20 mmoles) and phosphoryl chloride (20 mmoles) at ambient temperature and the mixture was then refluxed for 1 hour. After the mixture was cooled to 5° it was poured onto crushed ice (20 g) and the *p*H of the aqueous phase was adjusted to 7 with 20% aqueous sodium carbonate solution at 0-5°. The aqueous phase was then extracted with 1,2-dichloroethane (2 × 10 ml). The combined extracts were dried (sodium sulfate) and evaporated to dryness to obtain the 9-substituted pyridopyrimidin-4-one.

Compound **15** had ^{13}C nmr: δ 14.4 (q, CH_2CH_3), 17.6 (q, 6-Me), 19.7 (t, C-8), 26.2 (t, C-7), 44.0 (q, N-CH_3), 45.5 (d, C-6), 60.2 (t, OCH_2), 101.0 (s, C-9), 107.6 (s, C-3), 122.9 (d, C-2 and 6 of Ph), 125.6 (d, C-4 of Ph), 129.4 (d, C-3 and 5 of Ph), 146.0 (s, C-1 of Ph), 148.0 (d, =CH-), 158.3 (d, C-2), 159.0 (s, C-4), 161.6 (s, C-9a), 165.5 ppm (s, 3-CO).

Method A(2).

Acylation was carried out as for Method A(1), but 20 ml of 1,2-dichloroethane was used and the reaction mixture was stirred at ambient temperature for 48 hours. The cooled reaction mixture was poured onto 30 g of crushed ice.

Method B(1).

To a stirred mixture of the pyridopyrimidin-4-one (10 mmoles) and the amide (20 mmoles) was added phosphoryl chloride (20 mmoles) at ambient temperature and the mixture was heated at 50° for 0.5 hour and then at 95° for 3 hours on a water-bath. After the mixture was cooled to 10° it was poured onto water (30 ml).

Starting from 3-phenylpyridopyrimidinone **5** and *N,N*-diethylbenzamide, the precipitated oil was treated with aqueous ethanol to obtain crystalline 9-benzoylpyridopyrimidine **24** while starting from ester **1** and *N,N*-diethylbenzamide, the acidic aqueous solution was extracted with diethyl ether (2 × 10 ml) to eliminate the unreacted *N,N*-diethylbenzamide. The *p*H of the aqueous phase was adjusted to 7 with 20% aqueous sodium carbonate solution and it was then extracted with benzene (3 × 30 ml). The combined extracts were dried (sodium sulfate) and evaporated to dryness. The oily product was stirred in 1*N* hydrochloric acid at ambient temperature for 1 hour, and then heated at 50° for 1 hour. After the reaction mixture had cooled, the precipitated 9-benzoylpyridopyrimidine-3-carboxylate **23** was filtered off.

Compound **23** had ^{13}C nmr: δ 14.4 (q, CH_2CH_3), 17.6 (q, 6-Me), 20.6 (t, C-8), 25.7 (t, C-7), 46.1 (d, C-6), 60.8 (t, OCH_2), 91.0 (s, C-9), 106.0 (s, C-3), 127.3 (d, C-3 and 5 of Ph), 128.2 (d, C-2 and 6 of Ph), 129.8 (d, C-4 of Ph), 140.4 (s, C-1 of Ph), 147.9 (d, C-2), 153.2 (s, C-9a), 156.9 (s, C-4), 163.2 (s, 3-CO), 190.7 ppm (s, 9-CO).

Method B(2).

To a mixture of the pyridopyrimidin-4-one (5 mmoles) and *N*-methylpyrrolidinone (15 mmoles) was added phosphoryl chloride (20 mmoles) at the ambient temperature and the mixture was stirred at 50° for 0.5 hour and then at 95° for 2 hours. The cooled reaction mixture was poured onto crushed ice (15 g), and the acidic aqueous solution was extracted with chloroform (2 × 10 ml) to eliminate the unreacted *N*-methylpyrrolidinone. The *p*H of the aqueous phase was adjusted to 7 with 20% aqueous sodium carbonate solution. After cooling the precipitated 9-substituted product **21** was filtered off and washed with water.

Method C.

To a solution of the pyridopyrimidin-4-one (5 mmoles) in formamide (50 mmoles) was added, dropwise, phosphoryl chloride (10 mmoles). The reaction mixture was stirred at 50° for 1 hour and then at 80-85° for 4 hours. After the mixture was cooled to 10° it was poured onto crushed ice (20 g). The *p*H of the aqueous solution was adjusted to 7 with aqueous 20% sodium carbonate solution. The precipitated product **25** was filtered off and washed with water (see Table 1); ^{13}C nmr: δ 14.4 (q, 2 × CH_2CH_3), 17.4 (q, 6'-Me), 17.8 (t, C-8'), 18.4 (q, 6-Me), 21.8 (t, C-8), 25.6 (t, C-7'), 26.6 (t, C-7), 45.9 (s, C-6'), 47.0 (s, C-6), 60.8 (t, OCH_2 at *E* isomer), 61.1 (t, OCH_2 at *Z* isomer), 100.6 (s, C-9), 106.4 (s, C-9'), 110.3 (s, C-3'), 111.1 (s, C-3), 140.0 (d, =CH-, at *E* isomer), 143.7 (d, =CH-, at *Z* isomer), 156.3 (d, C-2), 157.9 (s, C-4), 158.5 (s and d, C-4' and C-2'), 159.5 (s, C-9a), 159.8 (s, C-9'a), 164.6 (s, 3-CO), 165.1 ppm (s, 3'-CO).

Method D.

The 9-[(*N*-Phenyl-*N*-methylamino)methylene] derivative **15** or **19** (5 mmoles) was heated under reflux for 0.5 hour in ethanol (15 ml) containing 10% of dry hydrogen chloride. After being cooled to 5° the reaction mixture was poured onto crushed ice (30 g) and the *p*H of the aqueous phase was adjusted to 7 by the addition of 20% aqueous sodium carbonate solution. The precipitated 9-ethoxymethylene derivative **26** or **27** was filtered off and washed with water.

Method E.

A mixture of the 9-ethoxymethylenepyridopyrimidin-4-one **27** (10 mmoles) and aniline (10 mmoles) was heated at 100-110° for 1 hour. The cooled reaction mixture was dissolved in diethyl ether (15 ml) and ethanol containing 15% of dry hydrogen chloride (1 ml) was added. The precipitated hydrochloride, **28**·HCl, was filtered off and recrystallizated.

Method F.

A mixture of the tetrahydropyridopyrimidin-4-one **1** (5 mmoles) and *N,N'*-diphenylformamidine (6 mmoles) was heated at 120° for 1 hour, and then at 140-150° for 1 hour. The cooled reaction mixture was dissolved in a mixture of ethanol (1 ml) and diethyl ether (15 ml). The precipitated crystals of **29** were filtered off and washed with diethyl ether.

Method G(1).

A solution of the tetrahydropyridopyrimidin-4-one (10 mmoles), aniline (10 mmoles) and triethyl orthoformate (12 mmoles) in ethanol (20 ml) was refluxed for 16 hours. The reaction mixture was poured onto water (30 ml). After the aqueous solution was cooled to 0°, the precipitated product was filtered off and recrystallized.

Method G(2).

A mixture of the tetrahydropyridopyrimidin-4-one (10 mmoles), aniline (10 mmoles) and triethyl orthoformate (12 mmoles) was stirred at 100-110° for 1 hour then aluminum trichloride (0.1 g) was added to the mixture which was stirred for an additional 20 minutes at this temperature. The cooled reaction mixture was crystallized from ethanol (18 ml) for **20** or a mixture of ethanol (2 ml) and diethyl ether (8 ml) for **29**. The crystals were filtered off, and recrystallized.

Ethyl 9-(Piperidinomethylene)-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**14**).

An ethanolic solution (15 ml) of ethyl 9-formyl-6-methyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate [5b] (1.45 g, 5 mmoles) and piperidine (0.43 g, 5 mmoles) was refluxed for 3 hours. After being cooled to 5° the reaction mixture was poured onto water (50 ml) the precipitated product **14** (1.16 g, 70%) was filtered off and crystallized from ethanol, mp 136-137°; ^{13}C nmr, δ 14.5 (q, CH_2CH_3), 17.2 (q, 6-Me), 19.8 (t, C-8), 23.9 (t, C-4', piperidino), 26.2 (t, C-7), 26.8 (2xt, C-3' and 5'), 44.8 (d, C-6), 53.2 (2xt, C-2' and 6'), 59.9 (t, OCH_2), 93.4 (s, C-9), 104.9 (s, C-3), 151.1 (d, =CH-), 158.5 (d, C-2), 159.4 (s, C-4), 162.1 (s, C-9a), 165.9 ppm (s, 3-CO).

Hydrolysis of the Ethyl 9-Benzoyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,-2-*a*]pyrimidine-3-carboxylate (**23**).

The 9-benzoyl compound **23** (0.68 g, 2 mmoles) was stirred in 5% aqueous sodium hydroxide solution (7 ml) at ambient temperature for 24 hours. The *p*H of the reaction mixture was then adjusted to 1.5 with 1:1 hydrochloric acid. The precipitated crystals (0.43 g) were filtered off.

Part of the product was sublimated to give benzoic acid, mp 121° (Lit 122° [19]), the other part was crystallized from benzene to give 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid, mp 141° (Lit 141-142° [12]). The ir spectra of both product were superimposable upon those of the authentic samples.

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