Nitrogen Bridgehead Compounds. Part 64.[1] Protonation of 9-Formyltetrahydropyrido[1,2-*a*]pyrimidin-4-ones and their Analogues

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As shown by ^{1}H, ^{13}C, and ^{15}N n.m.r. spectroscopy, protonation of 9-formyltetrahydropyrido[1,2-*a*]pyrimidin-4-ones takes place at the formyl oxygen atom. As a result, the enamine tautomer, predominant in the base form, is transformed into a protonated enolimine tautomer having an exocyclic double bond. ^{15}N N.m.r. shifts reflect not only the state of the tautomeric equilibria but also the state of *Z*/*E* isomerism and the effect of remote substituents.

9-Formyltetrahydropyrido[1,2-*a*]pyrimidin-4-ones are important intermediates in the synthesis of other 9-substituted pyridopyrimidines having valuable pharmacological properties.[2] Earlier we have reported the preparation and tautomeric behaviour of 9-formylpyridopyrimidines and their analogues.[3–7] We have demonstrated that in the equilibrium of imine, enamine, and enolimine tautomers, in solution the enamine form, stabilized by an internal hydrogen bridge, is predominant. By ^{15}N n.m.r. studies we have established that in the mobile tautomeric equilibrium about 10% of the enolimine form is present; the percentage of the imine form containing a non-conjugated formyl group is negligible.[6,7] An investigation of ring homologues has shown that the tautomeric composition is highly dependent on the size of the ring containing a single nitrogen atom.[5,7] The relative stability of the individual tautomeric forms was explained in terms of conjugative and steric interactions, as well as the strength of stabilizing hydrogen bridges.[5,7]

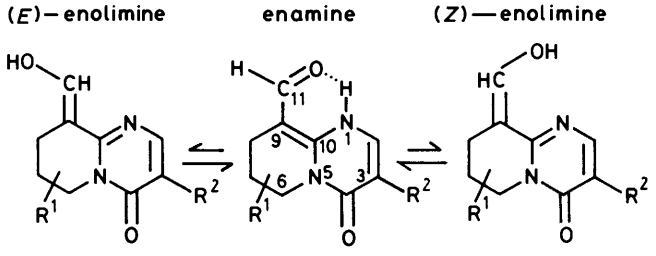
The 9-formylpyridopyrimidine system is characterized by extended delocalization and several basic centres; therefore it seemed of interest to examine both the site of protonation and the effect of salt formation on the tautomeric equilibrium.

Results and Discussion

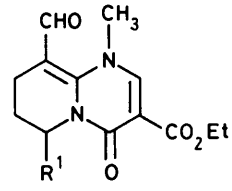
Studies of protonation and tautomerism of the formyl derivatives and analogous model compounds (**1**)—(**17**) were carried out in a 1:1 mixture of $CDCl_3$ and trifluoroacetic acid (TFA) at concentrations such that the acid was not in large excess.

In a previous study of the protonation of various 9-aminomethylenetetrahydropyrido[1,2-*a*]pyrimidines we found that protonation takes place at N(1).[8] With the formyl derivatives (**1**)—(**9**) we observed that the H-2 n.m.r. signal was significantly shifted downfield on protonation (N–C*H*= ⟶ N$^+$–C*H*=), while that of H-11 was shifted upfield (C*H*=O ⟶ O–C*H*=). This is attributed to initial protonation in this case at the formyl oxygen atom, followed by rearrangement of the double bonds to give a 'protonated enolimine' structure in which the positive charge is mainly centred at N(1) (Scheme 2).

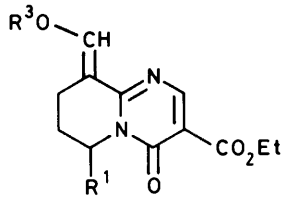
The spectra show two series of signals, which indicate the presence of both *Z*- and *E*-isomers. The *Z*/*E* ratio observed immediately after dissolution did not change in time. Owing to anisotropic shielding by the adjacent C=N bond, H-11 shows a larger shift in the *E*- than in the *Z*-isomers.[9] Despite being more crowded the *Z*-isomers predominate in the equilibrium mixture; this can be rationalized in terms of the presence of an internal hydrogen bridge in these isomers.[8,9] In $CDCl_3$–TFA proton exchange is fast and therefore *J*(NH,H-2) could not be observed. As with the 9-aminomethylene[9] and 9-hydrazono derivatives,[10] in the protonated ester (**4**) a further shift of the isomeric ratio in favour of the *Z*-isomer was observed, since the *E*-form is destabilized by steric interaction of the OH and 8-Me groups. As with the non-protonated compounds, of the two half-chair



	R^1	R^2
(**1**)	H	CO_2Et
(**2**)	6—Me	CO_2Et
(**3**)	7—Me	CO_2Et
(**4**)	8—Me	CO_2Et
(**5**)	6—Me	Me
(**6**)	6—Me	CH_2CO_2Et
(**7**)	6—Me	H
(**8**)	6—Me	Ph
(**9**)	6—Me	CN



(**12**) R^1 = H
(**13**) R^1 = Me



(**10**) R^1 = H, R^3 = Me
(**11**) R^1 = Me, R^3 = Et

Scheme 1.

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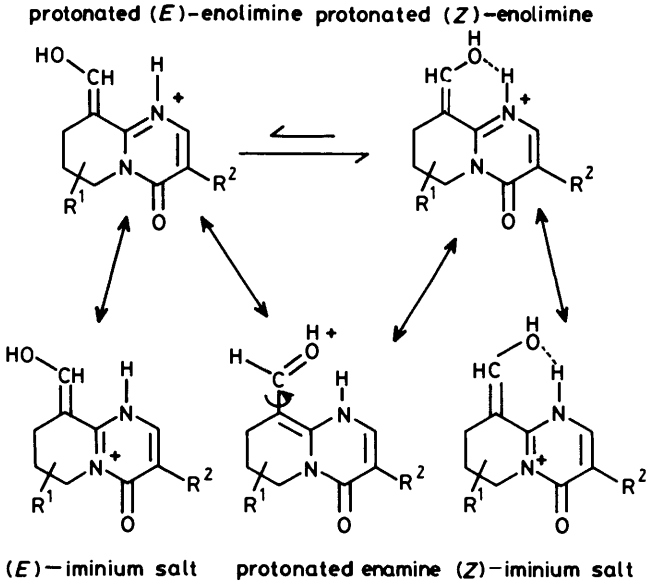
Table 1. Selected ^{1}H n.m.r. chemical and $\Delta\delta$[a] protonation shifts for compounds (**14**) and (**15**) and salts of (**1**)—(**9**)

	(1)		(2)		(3)		(4)	(5)		(6)		(7)		(8)			(14)	(15)
	Z	*E*	*Z*	*E*	*Z*	*E*	*Z*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	(9)	*E*	*E*
11-H	8.38	8.63	8.25	8.53	8.32	8.70	8.44	7.79	8.26	7.96	8.45	7.92	8.40	7.83	8.35	8.67	8.40	8.72
Δδ(11-H)	−0.40	−0.15	−0.67	−0.39	−0.39	−0.01	−0.36	−0.82	−0.35	−0.69	−0.20	−0.75	−0.27	−0.79	−0.27	0.05	1.09	−0.79
2-H	8.58	8.47	8.66	8.63	8.54	8.42	8.57	7.79	7.59	7.85	7.72	7.85	7.69	*c*	*c*	8.20	8.62	8.50
Δδ(2-H)	0.33	0.22	0.43	0.40	0.33	0.21	0.35	0.55	0.35	0.50	0.37	0.62	0.46			0.37	0.14	0.32
6-H_{eq}[b]	4.01		5.20		3.27		3.81	5.20		5.15		5.11		5.19		5.02	4.27	4.35
Δδ(6-H_{eq})	0.12		0.20		0.19		0.30	0.26		0.18		0.18		0.18		0.10	0.09	0.15
Z/*E* (%)	85	15	82	18	90	10	>95	85	15	80	20	80	20	95	5	100	>90	>90

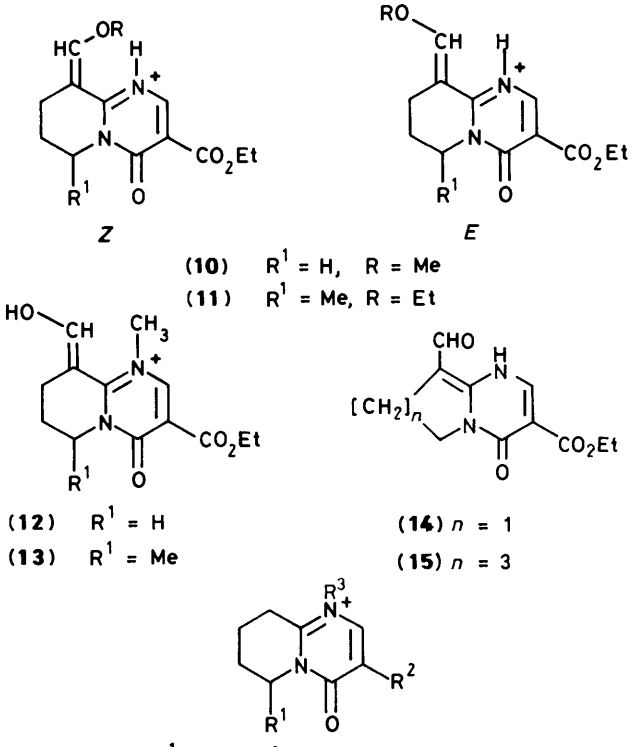
[a] $\Delta\delta = \delta_{salt} - \delta_{base}$. [b] 6-H signals exhibit the same chemical shifts for *E*- and *Z*-isomers. [c] Overlapped.



Scheme 2.

conformers interconverting by ring inversion of the flexible tetrahydropyridine ring, the predominant form is that which contains the 6-Me and 8-Me groups in a quasiaxial and the 7-Me group in a quasiequatorial disposition.

For a more detailed characterization of the electron distribution in the protonated compounds (**1**)—(**9**), the protonated enamine structure has to be considered as well as the protonated enolimine tautomer. Participation of the former increases when the R^2 group exerts an electron-attracting [in particular a $-I$ (inductive)] effect. This is reflected by the shifts for H-11 in protonated (*Z*)-(**7**) (R^2 = H) and (*Z*)-(**2**) (R^2 = CO_2Et) (7.92 and 8.25, respectively); in conformity with the formyl structure the signal for (**2**) shows a paramagnetic shift. However, the possibility that under the effect of an electron-attracting group R^2 the basicity of the compound drops to a level where protonation is incomplete and a salt–base equilibrium is established cannot be excluded *a priori*. In $CDCl_3$–TFA, fast proton exchange and therefore an averaging of the signals for the stereoisomeric salts and the base would be expected. However, except for one case (R = CN), the signals for the *Z*- and *E*-isomers appeared side by side; thus the foregoing possibility could be ruled out. The protonation shift, Δδ(H-2), was highest with the compounds (*Z*)-(**7**) and (*Z*)-(**5**) (R^2 = H or Me) (0.55 and 0.6 p.p.m., respectively), in accord with the high contribution of the enolimine canonical formula with a positive charge on N(1). A small but characteristic difference was observed between the Δδ(H-2) values for the *Z*- and *E*-isomers, the latter being smaller.



Scheme 3.

Unlike the case of the 9-aminomethylenepyridopyrimidines,[8] in the present case Δδ(H-6) protonation shifts were well defined. In view of the measured values, for the characterization of the protonated formyl derivatives the iminium-type canonical formulas were also considered (see Scheme 2).

Among the Δδ(H-11) protonation shifts of compounds (**1**)—(**4**) that for the 6-Me compound (**2**) was the highest. Δδ(H-11) was similarly high for the other 6-Me derivatives (**5**)—(**9**). It seems that this kind of substitution modifies selectively the effect of protonation. A ^{15}N study on the non-protonated formyl derivatives revealed that 6-Me substitution enhances the percentage of the enamine tautomer.[7] The fact that δ(H-11) is highest with (**2**) points in the same direction. All this indicates that differences in the protonation behaviour of the 6-Me derivatives can be traced back to differences in the tautomeric equilibria of the corresponding bases.

Table 2. ^{13}C N.m.r. chemical shifts and Δδ protonation shifts for compounds (**14**) and (**15**) and salts of (**1**)—(**9**)

		C(2)	δΔ[C(2)]	C(3)	C(4)	C(6)	C(7)	C(8)	C(9)	δΔ[C(9)]	C(10)	C(11)	δΔ[C(11)]
(1)	*Z*	147.0	−0.5	107.7	158.0	43.8	19.8	22.4	95.0	2.2	154.1	178.6	−6.0
	E	147.0	−0.5	109.2	161.7	43.8	19.8	19.6	101.9	9.1	156.7	166.7	−17.9
(2)	*Z*	147.3	0.0	106.7	157.5	47.8	25.2	17.8	92.8	1.4	152.5	183.8	−2.6
	E	147.3	0.0	109.2	158.4	49.0	24.5	16.6	100.6	9.2	156.1	168.7	−17.7
(3)	*Z*	147.1	−0.3	109.0	159.6	49.9	25.9	30.3	96.1	3.6	155.4	174.9	−9.6
	E	147.1	−0.3	109.4	*b*	49.9	25.9	27.0	102.3	9.8	157.3	166.7	−17.8
(4)	*Z*	147.2	−0.3	107.4	158.0	39.6	26.9	26.9	100.0	1.2	153.8	180.7	−4.4
	E	147.2	−0.3	109.1	*b*	39.7	29.0	24.7	106.7	7.9	*b*	167.8	−17.3
(5)	*Z*	137.3	0.2	122.0	161.8	50.9	25.9	18.0	96.9	6.9	155.0	163.1	−17.4
	E	137.6	0.5	130.8	161.8	50.5	24.9	17.5	101.9	11.9	157.4	160.5	−19.9
(6)	*Z*	138.6	−0.5	116.8	161.4	49.9	25.2	17.5	95.7	5.5	155.1	165.4	−15.0
	E	139.0	−0.1	116.0	161.4	49.8	24.3	15.1	101.2	11.0	*b*	*b*	
(7)	*Z*	140.7	0.6	109.0	160.2	49.0	25.4	18.0	94.0	3.8	155.1	172.1	−11.7
	E	140.7	0.6	109.2	160.2	49.0	24.9	16.4	100.9	10.7	158.2	159.3	−24.5
(8)	*Z*	137.4	0.5	124.6	160.7	50.8	25.9	18.3	96.6	5.7	154.7	164.6	−16.7
	E	137.4	0.5	*b*	*b*	50.6	24.9	15.6	101.9	11.0	*b*	*b*	
(9)		148.9	−0.6	94.4	157.7	49.1	24.8	17.8	91.6	0.1	151.7	185.5	+2.6
(14)	*E*	147.4	−10.0	111.6	161.7	47.0		20.8	104.6	*b*	155.8	164.4	6.7
(15)	*E*	146.9	−0.2	112.2	159.6	45.8	20.3 22.0[a]	23.3	106.6	7.8	156.9	164.4	−22.6

[a] Value of C(7) and C(7a). [b] Could not be assigned owing to low intensity or overlap.

This rationalization is supported by *X*-ray studies on 6-methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-ones, which showed that the 1,3-allylic strain between 6-Me and C(4)=O is much larger than in the 1-methyl analogue, which has a fixed enamine structure.[11]

Protonation of compounds (**10**) and (**11**), which have a fixed enolimine structure, takes place, as expected, at N(1). Since in this case a change in the tautomeric equilibrium need not be considered, changes in the ^1H shifts reflect directly the development of positive charge. Interestingly, in $CDCl_3$–TFA an equilibrium of *Z*- and *E*-isomers is again established; the intensity ratio of the two series of signals is about 4:1.

Formation of a sterically crowded protonated *Z*-enolimine-type isomer is again made possible by internal hydrogen bonding. The isomers can be readily distinguished by the paramagnetic shift of the H-11 signals in the *E*-isomers. Since the base is of *E*-configuration,[5,6] quoted Δδ protonation shifts refer to this isomer.

With compounds (*E*)-(**10**) and (*E*)-(**11**) the paramagnetic shift Δδ(H-11) is about 0.3 p.p.m. This is understandable if we consider that an increase of the positive polarization at C(11) is experienced when the C=N group is transformed into the $C{=}N^+$ ion. Due to the extended delocalization of the positive charge, however, the shift change for the methine proton adjacent to N(1) is slight.

Examination of the protonation of the models (**12**) and (**13**) having a fixed enamine structure was useful: in this case the combined effects of protonation and a complete tautomeric transformation could be observed. The spectral changes associated with the enolimine ⟶ enamine transformation have already been reported in connection with a study of the non-protonated compounds (**10**)—(**13**).[5–7] In compounds (**12**) and (**13**) protonation resulted in a substantial diamagnetic or paramagnetic shift, respectively, for the H-11 and H-2 signals. The latter originated from superposition of a slight paramagnetic shift due to the positive charge and the effect of enolimine ⟶ enamine tautomerization acting in the same direction. At the same time the protonation shift Δδ(NMe) values were only 0.21 and 0.26 p.p.m., respectively, in good accord with extended delocalization of the positive charge in these models too. Positive polarization at N(5) was supported by deshielding by 0.26 and 0.28 p.p.m., respectively, observed for the signal of H-6.

The formylpyrrolopyrimidine (**14**), a ring homologue, was shown to exist in $CDCl_3$ predominantly in the enolimine form; the participation of the enamine tautomer was only about 10%.[5,7] Salt formation again resulted in the concurrent appearance of enolimine-type *Z*- and *E*-isomers, but in this case the contribution of the *Z*-isomer was less than 10%. The value of Δδ(H-11) (1.31 p.p.m.) arises from addition of paramagnetic shifts caused by the *Z* ⟶ *E* transformation and the positive charge development at the C=N groups in the β-position.

The formylazepinopyrimidine (**15**) was found to exist mainly in the enamine form.[5,7] Protonation leads again to an enolimine-type structure with the *E*-isomer dominating. The low intensity of accompanying signals did not permit an unambiguous identification of the *Z*-isomer.

The foregoing observations permit the conclusion that despite a modification of the size of the ring containing the single nitrogen atom, the characteristic tautomer remains the protonated enolimine structure. In derivatives with a six-membered ring, predominance of the *Z*-isomer is supported by the formation of an internal hydrogen bridge; in the pyrrolo and azepine compounds the geometrical situation does not allow the formation of such a bridge and the *E*-isomer prevails.

^{13}C N.m.r. studies lent further support to the enolimine structure for the product of protonation of the 9-formylpyridopyrimidines. Characteristic chemical shifts are compiled in Tables 2 and 3. Assignments were based on earlier results obtained with 9-formylpyridopyrimidine bases[6,7] and the corresponding 9-aminomethylene derivatives,[8,9] as well as on known substituent effects.[12]

When 9-aminomethylenepyridopyrimidines, analogous to enolimines, were protonated, rearrangement of the double bonds gave a 1,6,7,8-tetrahydropyridopyrimidine, *i.e.* a structure corresponding to a protonated enamine. This transformation was associated with diamagnetic shifts of the signals for C(2), C(4), C(9), and C(10).[8] Since on protonation of the 9-formyl compounds structural changes occur in the opposite direction for these signals a paramagnetic shift would be

Table 3. Characteristic ^1H and ^{13}C n.m.r. data for model compounds (**10**)—(**13**) and (**16**)—(**18**)

	(10)		(11)		(12)	(13)	(16)	(17)	(18)
	Z	*E*	*Z*	*E*	*E*	*E*			
11-H	7.42	8.26	7.63	8.29	8.00	8.08			
Δδ(11-H)	−0.53	0.31	−0.36	0.30	−1.74	−1.52			
2-H	8.63	8.53	8.56	8.63	8.62	8.51	8.58	8.65	7.90
Δδ(2-H)	+0.07	−0.03	+0.11	+0.18	0.45	0.47	0.0	+0.07	+0.13
$6\text{-}H_{eq}$	4.10		5.25		4.15	5.40	4.02	5.09	5.00
$\Delta\delta(6\text{-}H_{eq})$	0.06		−0.02		0.26	0.28	+0.02	+0.07	+0.03
Isomer ratio	15%	85%	25%	75%	100%	100%			
C(2)	145.5	145.5	146.6	147.5	151.4	154.7	148.5	146.2	138.1
Δδ[C(2)]	−12.7	−11.7	−11.4	−10.5	−1.5	+1.5	−9.1	−10.4	−11.9
C(3)	*a*	110.0	112.3	110.7	113.3	111.2	112.4	113.4	120.2
C(4)	159.0	159.0	*a*	159.2	160.7	161.1	160.8	160.8	162.9
C(6)	43.2	43.2	51.5	50.7	43.5	48.0	43.6	50.9	50.6
C(7)	19.4	19.4†	26.5	24.7	20.8	25.5	19.8	26.1	26.8*
C(8)	21.9	18.9†	18.9	16.5	20.8	18.2	16.3	13.2	13.4
C(9)	93.6	103.0	98.2	102.9	101.3	100.8	28.3	27.6	26.4*
Δδ[C(9)]	−14.4	−5.0	−8.3	−4.0	−0.1	+1.1	−3.9	−3.0	−3.2
C(10)	*a*	155.6	*a*	156.9	154.6	152.2	156.0	155.1	158.3
C(11)	*a*	167.0	168.7	167.8	164.1	166.8			
Δδ[C(11)]		7.4	10.3	9.4	−20.4	−17.8			

[a] Could not be observed owing to low intensity or overlap. *,† Tentative assignment.

expected. However, the C(2) signal was almost unaffected by protonation. In view of the foregoing arguments, in this case the opposite effect should operate; indeed under the effect of a positive charge at N(1) the C(2) signal is normally shifted by about 10 p.p.m. upfield. This is clearly shown with compounds (**10**) and (**11**) {Δδ[C(2)] = −11.7 and −10.5 p.p.m., respectively} and also with the model compounds (**16**)—(**18**) (−9.1, −10.4, and −11.9 p.p.m.). In compounds (**1**)—(**9**) the protonation shift at C(4) is about 1 p.p.m. Much more significant is the paramagnetic protonation shift of the signals for C(9) and C(10). With the stereoisomeric *Z*- and *E*-salts we found that Δδ[(*E*)-C(9)] > Δδ[(*Z*)-C(9)], which can be ascribed to differences in charge distribution and conjugation. Earlier we have demonstrated that in the *Z*-isomers, constrained to a planar geometry by an internal hydrogen bridge, delocalization of the non-bonding electron pair at the heteroatom adjacent to C(11) is more extended;[6,7] consequently δ[(*Z*)-C(9)] < δ[(*E*)-C(9)]. This observation could be exploited for differentiation of the stereoisomers in the present case too. The shift of C(8) is also of diagnostic value in this respect, since as a result of a γ-gauche effect between C(8) and the oxygen atom in the *E*-isomer, δ[(*Z*)-C(8)] > δ[(*E*)-C(8)]. In accordance with the transformation HC=O ⟶ O–CH=, protonation of compounds (**1**)—(**8**) involved a significant diamagnetic shift of the signals of C(11). Increasing electron attraction by R^2 was associated with an increase of δ[C(11)], which can be explained, as with the ^1H n.m.r. data, by an increasing contribution of the protonated enamine canonical formula. At C(11), separated by six bonds from the site of protonation, owing to a highly conjugated planar π-system, protonation shifts are much greater in the *Z*-isomers than in the *E*-isomers.

With compound (**9**) ^1H n.m.r. studies indicated the predominance of a protonated enamine canonical formula, explained by the −*I* effect of R^2 (R^2 = CN). This seems to be further supported by the small paramagnetic shift of the C(11) signal on salt formation.

Of the changes occurring on protonation of the fixed enolimine tautomers (**10**) and (**11**) Δδ[C(2)] has been discussed already. In conformity with the transformation C=N ⟶ $C{=}N^+$ the positive polarization of the β-carbon atom of the C(9)=C(11) bond increased further, which was reflected by the enhancement of δ[C(11)] in the salt. Distinction between *Z*- and *E*-isomers was again made possible by the diagnostic signals for C(8) and C(9). A considerable diamagnetic shift of the C(11) signal on protonation of the fixed enamine tautomers (**12**) and (**13**) was also observed. If we take into account the substituent chemical shift values for an NMe group, there is good agreement with the ^{13}C shifts of the *E*-salts of (**1**) and (**3**).

Table 4. ^{13}C Substituent chemical shift values (p.p.m.) of the methyl substituent for salts of (**2**)—(**4**)[a]

Compound	α	β	γ
(*Z*)-(**2**)	4.0	5.4	−4.6
(*Z*)-(**3**)	6.1	6.1 [at C(6)] 7.9 [at C(8)]	1.1
(*Z*)-(**4**)	4.5	7.1	−4.2
(*E*)-(**2**)	5.2	4.7	−3.0
(*E*)-(**3**)	6.1	6.1 [at C(6)] 7.4 [at C(8)]	0.4
(*E*)-(**4**)	5.1	9.2	−4.1

[a] Positive values correspond to downfield substituent chemical shifts). For comparison, the chemical shift values measured for (*Z*)-(**1**) and (*E*)-(**1**) were used as reference.

With the pyrrolopyrimidine analogue (**14**), since the base is also in the enolimine form, no significant shift of the C(11) signal was observed on protonation, and Δδ[C(2)] = −10.0 p.p.m. This is in good agreement with data for (**10**) and (**11**).

With the azepinopyrimidine (**15**) protonation shifts are similar to those recorded for the pyridopyrimidine analogue (**1**).

With regard to the substituent chemical shift values of the methyl group in compounds (**2**)—(**4**) (Table 4) the characteristic γ-gauche values found with (**2**) and (**4**) prove the axial orientation of the methyl group in the dominant conformation.

Assignment of the closely spaced C(4) and C(10) signals in the model compounds (**16**)—(**18**) was achieved by n.m.r. titration, which revealed that the correlation δ[C(10)] < δ[C(4)], found

Table 5. ^{15}N N.m.r. chemical shifts and Δδ protonation shifts for salts (**1**), (**2**), (**4**), (**6**), (**7**), (**10**), (**12**), and (**16**)—(**19**)

	(16)	(17)	(18)	(19)[a]	(10) *E*	(12)	(1) *Z*	(2) *Z*	(4) *Z*	(6) *Z*	(7) *Z*	(7) *E*
δ(N-1)	−229.7	−222.8	−226.3	−231.0	−248.8	−242.0	−246.9	−244.7	−245.4	−243.8	−243.6	−248.7
Δδ	−84.2	−77.9	−82.8	−86.1	−87.0	25.3	0.2	6.9	3.1	3.7	9.5	4.4
δ(N-5)	−187.8	−177.9	−168.8	−178.0	−224.6	−196.6	−216.4	−201.9	−214.9	−201.9	−202.4	−197.7
Δδ	7.0	5.6	5.4	5.5	20.0	35.6	15.1	20.0	16.9	18.7	18.4	23.1

[a] Value of Δδ corresponds to Me quaternization shift.

earlier for the bases, is also true for the salts.[13] The validity of the same correlation for the 9-formyl compounds and model compounds containing an exocyclic double bond at C(9) was supported by a series of selective $^{13}C\{^1H\}$ decoupling experiments. In the dominant *Z*-isomers of the 9-formyl salts, C(10) is coupled by about 9 Hz with 2-H and 11-H, while the C(4) signal exhibited only a large vicinal coupling {^3J[2-H,C(4)] *ca.* 9 Hz}. Other significant features are the increase in ^1J[2-H,C(2)] on salt formation [*e.g.* with (**17**) 182 ⟶ 193 Hz; with (**7**) 181 ⟶ 190 Hz], and an increase by about 11 Hz of ^1J[11-H,C(11)]. The latter has already been observed in connection with the transformation H–CO ⟶ H–C= associated with the 9-formyl and 9-alkoxymethylene derivatives.[7]

^{15}N *N.m.r. Studies.*—Analysis of the ^{15}N n.m.r. spectra of 9-substituted tetrahydropyrido[1,2-*a*]pyrimidines demonstrated the utility of this method for the qualitative, and occasionally quantitative, characterization of the tautomeric equilibria of these compounds. Stereoisomers (*Z*- and *E*- as well as *cis*- and *trans*-) showed significant changes in ^{15}N shift differences.[6–8,10,11,14]

^{15}N Shifts for protonated 9-formyltetrahydropyridopyrimidines and for corresponding model compounds, and chemical shift changes induced by salt formation (Δδ), are shown in Table 5. These data further support conclusions drawn on the basis of ^1H and ^{13}C n.m.r. data concerning the structure, tautomerism, and electron distribution of these compounds.

It is known that protonation of sp^2-hybridized nitrogen atoms results in a large shielding,[15] whereas that of sp^2 nitrogens results in a small deshielding.[16] On protonation of lactams and amides a paramagnetic shift of about 10 p.p.m. has been measured.[17] The effect of salt formation on the ^{15}N chemical shifts of tetrahydropyridopyrimidines was first studied on the model compounds (**16**)—(**18**). The N(1) signal suffered a large diamagnetic shift, whereas the N(5) signal was shifted by 5—7 p.p.m. towards lower field. Signal assignments were again supported by a comparison of the spectra of the 6-methyl and 6-demethyl derivatives (**17**) and (**16**); the N(5) signal showed under the effect of the β-methyl group a paramagnetic shift of more than 10 p.p.m.[7,8] Assignment of the signals for N(1) and N(5) was assisted by n.m.r. titration. On gradually increasing the concentration of trifluoroacetic acid the nitrogen signals moved in opposite directions and to a different degree.

In a study of 9-carbamoyltetrahydropyridopyrimidines we discussed the effect of the electronic character of the C(3) substituent on the shift of N(5).[14] By comparing the N(5) values in the salts (**18**) and (**17**) we concluded that on exchanging the CH_2CO_2Et group for the electron-attracting function CO_2Et, a paramagnetic shift (8.9 p.p.m.) occurred similar to that found with the bases.[14] For the transmission of the substituent effect the two mechanisms suggested for the carbamoyl compounds may be considered.[14]

In the case of ethyl 1,6-dimethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyridinium-3-carboxylate chemical shifts and Δδ values were similar to those with (**17**). The methyl α-substituent effect associated with the change $=N^+Me$ is small (−8.2 p.p.m.) and the γ-substituent chemical shift is practically zero. In the model salt (**10**) the effect of substitution by an (*E*)-RO–CH=C(9) group can be studied. Owing to extended conjugation and charge delocalization the signals for N(1) and N(5) were diamagnetically shifted by −19.1 and −36.8 p.p.m. respectively. These shifts are much higher than those observed for the corresponding base (−16.3 and −9.8 p.p.m. respectively).[6,7] All this indicates that conjugation is more intensive in the salt than in the base.

As to the protonation shifts in (**10**), that for N(1) was in good agreement with those for the 9-unsubstituted analogues (**16**) and (**19**), whereas for the N(5) signal a diamagnetic shift of −20.0 p.p.m. was observed. This indicates intensive participation of the non-bonding electron pair of N(5) in internal electron delocalization and an increased contribution by the 'iminium salt' canonical formula.

The model compound (**12**) differs from (**10**) in that *H*O–CH=C(9) replaces *Me*O–CH=C(9) and *Me*–N^+ replaces *H*–N^+=. Since in (**19**) α-methyl substitution at N(1) involves a diamagnetic shift of −8.2 p.p.m. and the same in (**12**) gives a deshielding of +6.8 p.p.m., the paramagnetic effect of MeO ⟶ HO substitution should be rather high. Indeed the paramagnetic shift at N(5) (ε-position) was also quite high (28.0 p.p.m.). Still significant, but smaller changes are observed in the chemical shift of N(5) {δ[N(5)] −204.0, −199.1, and −193.5 p.p.m., respectively}, when the C(9) substituent of the analogous non-protonated 6-methyl-4-oxotetrahydropyridopyrimidine was varied as follows: $Me_2NCH=$, PhNHCH=, MeCCH=.[6,8] The extremely high paramagnetic shift of the N(5) signal in (**12**) is probably due to an increased contribution from the 'iminium salt' canonical formula under the effect of methyl substitution at N(5). The same is apparent in comparing the N(5) shifts for (**12**) and (**1**).

Poor signal-to-noise ratio did not permit the determination of the ^{15}N chemical shifts for the *E*-isomers of the protonated 9-formyl derivatives (**1**), (**2**), (**4**), and (**6**). The effect of the *Z* ⟶ *E* transformation on the chemical shifts could be directly studied only with the salt of (**7**), in which the N(1) signal was shifted by −5.1 and the N(5) signal by +4.7 p.p.m. In the analogous non-protonated 9-hydrazino-4-oxotetrahydropyridopyrimidines it was the *E*-isomer which showed a diamagnetic shift of a few p.p.m. for the N(1) signal; in the *Z*-isomer, as a result of its coplanar arrangement fixed by an internal hydrogen bridge, conjugation and thus shielding of N(5) is higher than in the *E*-isomer.[10] ^{15}N N.m.r. is thus suitable also for the detection and identification of *Z*- and *E*-isomers of these compounds. In addition, concerning the tautomeric equilibria, it can be established that with the various 9-formyl salts the similarity in the chemical shifts for N(1) and N(5) as well as the good agreement of the Δδ protonation shifts is evidence for the transformation of the dominant enamine tautomer into a protonated enamine. The paramagnetic shift of the N(5) signal in (**2**), (**6**), and (**7**) is the consequence of the already discussed β-substituent chemical shift effect of the methyl group.

Experimental

N.m.r. spectra were recorded with a JEOL FX-100 instrument. The ^{1}H and ^{13}C n.m.r. spectral conditions were the same as described previously.[9] ^{15}N N.m.r. spectra were recorded at 10.04 MHz with proton broadband decoupling. The chemical shifts were determined relative to the signal of external aqueous $K^{15}NO_3$ and then converted to external nitromethane [$\delta(CH_3NO_2) = 0.0$ p.p.m.]. Shifts upfield from the reference have negative values. Typical acquisition parameters are: spectral width 5 000 Hz; flip angle 30°; pulse delay 5 s.

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