Nitrogen Bridgehead Compounds. Part 34.[1] A Study of Tautomerism in 9-Formyltetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones by ^{1}H, ^{13}C, and ^{15}N Nuclear Magnetic Resonance Spectroscopy

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It has been established (^{1}H and ^{13}C n.m.r.) that for 9-formyltetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones the tautomeric system imine ⇌ enamine ⇌ enol-imine [(A) ⇌ (B) ⇌ (C)] is dominated by form (B) which is stabilized by internal hydrogen bonds. The presence of *ca.* 15% of (C) in the equilibrium was shown by ^{15}N n.m.r. while no (A) could be detected.

We have reported the preparation of 9-formyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [2,3] as intermediates of the antiallergic–antiasthmatic 9-hydrazonotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.[4] A ^{1}H, ^{13}C, and ^{15}N n.m.r. study of the title compounds is now presented.

Results and Discussion

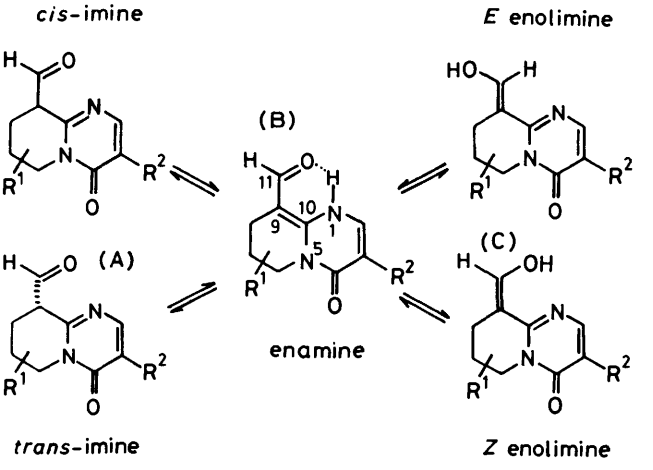
9-Formyltetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones are potentially tautomeric systems which may be represented as shown in Scheme 1.

An earlier study of the 9-carbamoyl derivatives showed that with a secondary nitrogen atom in the carbamoyl group the enamine form was predominant,[5] while with a tertiary nitrogen it was the *cis*-imine tautomer.[6] A comparison of the 9-formyl tautomers, however, reveals that conjugation of the substituent at C-9 with the ring system is possible both in forms (B) and (C), but this is excluded in form (A). In the *s*-*Z* rotamer of form (B) and in the *Z*-enol-imine form of tautomer (C) additional stabilization by internal hydrogen bonding may be possible too.

Characteristic ^{13}C chemical shifts of the compounds investigated are listed in Table 1. A choice among possible tautomeric structures was based on the following arguments. Integration showed the presence of six alicyclic protons in (1) and five in (2)—(9). The multiplicity of the 2-H signal indicated coupling with the adjacent 1-H. The latter is involved in a strong internal hydrogen bond as demonstrated by its high chemical shift (δ *ca.* 14). All these features support the predominance of the enamine tautomer (B). The appearance of the formyl proton signals at relatively high field (δ 8.62—8.92) may be indicative of the presence of enol–imine tautomers (C) besides (B) in the mobile tautomeric equilibrium.[2] This is also evidenced by the chemical shift value of 11-H (δ 9.60) in compound (10) being fixed in the enamine form. It has to be noted, however, that the downfield shift of 11-H in (10) must be partly ascribed to the fact that, due to *N*-methylation, the conformation of the C=O group changed from *s*-*Z* to *s*-*E* thus the formyl proton became deshielded by the double bond.[7]

Signals for C-9 appear in the range of δ 90.8—98.8 p.p.m., that for C-11 between δ 180.5 and 186.4 p.p.m. while in (10) it is δ 184.6 p.p.m. This also indicates the predominance of tautomer (B), but since C-11 is strongly deshielded (δ 160.3 p.p.m.) in (11) which is fixed in the enol-imine structure, the presence of a few percent of tautomer (C) cannot be excluded.

The usefulness of ^{15}N n.m.r. spectroscopy in the study of tautomeric equilibria is well documented.[8–10] ^{15}N Chemical shifts of compounds (2) and (10)—(17) are shown in Scheme 2.



(1) R^1 = H, R^2 = $CO_2C_2H_5$
(2) R^1 = 6-CH_3, R^2 = $CO_2C_2H_5$
(3) R^1 = 7-CH_3, R^2 = $CO_2C_2H_5$
(4) R^1 = 8-CH_3, R^2 = $CO_2C_2H_5$
(5) R^1 = 6-CH_3, R^2 = CH_3
(6) R^1 = 6-CH_3, R^2 = Ph
(7) R^1 = 6-CH_3, R^2 = H
(8) R^1 = 6-CH_3, R^2 = CHO
(9) R^1 = 6-CH_3, R^2 = CN

Scheme 1.

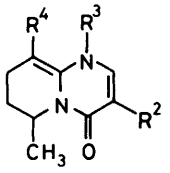
Assignments were based on the spectra of compounds that had been investigated earlier by us, *viz.* (12) of the imine type (A) and (13) of the enamine type (B). In the enamines both N-1 and N-5 are much more shielded than in (12), especially N-1 where the difference exceeds 100 p.p.m.

A comparison of the spectra of (10) and (13) revealed that the introduction of the electron-attracting 9-formyl group entails, mainly by the strong conjugative interaction, a downfield shift by 23.5 p.p.m. at N-5, whereas the γ-effect at N-1 is rather small (0.5 p.p.m. upfield).

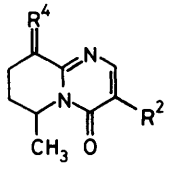
Earlier we published a detailed analysis of the ^{15}N n.m.r. spectra of 9-methyleneaminotetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones [11] which demonstrated that the chemical shift of N-5 is rather susceptible to the electronic character of the C-11 substituent. This is in accord with the shift of the

Table 1. ^{13}C Chemical shifts [δ(p.p.m.); $CDCl_3$] for compounds (1)—(11)

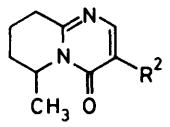
	C-2	C-3	C-4	C-6	C-7	C-8	C-9	C-10	C-11
(1)	147.5	105.4	157.0	41.4	20.0	22.1	92.8	151.3	184.6
(2)	147.3	105.0	156.4	45.7	25.2	17.7	91.4	149.8	186.4
(3)	147.4	105.8	157.0	47.2	25.5	30.0	92.5	151.2	184.5
(4)	147.5	105.4	157.1	37.4	26.9	26.4	98.8	151.1	185.1
(5)	137.1	113.1	160.8	45.9	25.7	17.8	90.0	151.8	180.5
(6)	137.9	117.2	159.2	46.7	25.8	17.6	90.9	151.7	181.3
(7)	140.1	103.8	159.9	45.8	25.4	18.0	90.2	151.7	183.8
(8)	144.1	111.3	158.9	45.6	25.0	17.7	92.8	149.0	186.3
(9)	149.5	93.9	156.7	46.8	25.1	17.7	91.5	151.7	182.9
(10)	153.2	103.1	155.6	47.5	25.1	18.5	99.7	152.2	184.6
(11)	158.5	109.7	160.3	46.3	25.3	16.0	107.1	158.2	160.3



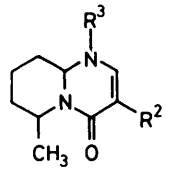
(2), (10), (13)



(11), (14), (15)



(12)



(16) (17)

		δ_{N-1} (p.p.m.)	δ_{N-5} (p.p.m.)
(10)	$R^2=CO_2C_2H_5$, $R^3=CH_3$, $R^4=H-C(=O)-$	-268·3	-222·5
(11)	$R^2=CO_2CH_3$, $R^4=CH_3O-C(=O)-H$	-161·2	-193·5
(12)	$R^2=CO_2C_2H_5$,	-144·9	-183·5
(13)	$R^2=CO_2C_2H_5$, $R^3=CH_3$,	-267·8	-245·0
(14)	$R^2=CO_2C_2H_5$, $R^4=(CH_3)_2N-C(=O)-H$	-164·2	-204·0
(15)	$R^2=CO_2C_2H_5$, $R^4=PhHN-C(=O)-H$	-162·1	-199·1
(16)	$R^2=CONH_2$, $R^3=H$,	-281·9	
(17)	$R^2=CONH_2$, $R^3=CH_3$,	-287·1	
(2)	$R^2=CO_2C_2H_5$, $R^3=H$, $R^4=H-C(=O)-$	-247·0	-231·6

Scheme 2.

N-5 signal in (11) to −193.5 p.p.m. relative to (14) and (15) due to the effect of the methoxy-group.

In a comparison of compound (12), unsubstituted at C-9, with compounds (11), (14), and (15), all containing an exocyclic double bond attached to C-9 and showing very similar chemical shifts for N-1, it becomes apparent that the observed upfield shifts (*ca.* 15 p.p.m.) are characteristic for the enol-imines (C) shown in Scheme 1. The shifts observed with (11), (14), and (15) indicate increased electron density around N-1.

In order to get more insight into the tautomerism of the 9-formyl derivatives, compound (2) was selected as a model in which both chemical shifts and $^1J_{N,H}$ couplings provided direct evidence for the presence of 11—16% of tautomer (C).

$^1J_{N,H}$ Values in enamines are known to be *ca.* 92 Hz.[12,13] With the enol-imine tautomers (C) this value must be zero. Since in (2) $^1J_{N,H}$ was found to be 81.2 Hz, this gave a (B) : (C) ratio of 89 : 11.

An independent assessment of this ratio is possible using chemical shifts. As shown, chemical shifts for N-1 in the enamines (B) and enol-imines (C) have a very substantial difference (*ca.* 100 p.p.m.) and therefore the error of estimating the (B) : (C) ratio by taking as reference the corresponding values in the enamine (10) and enol-imine (11), both having fixed structures, is small.

It is known that with ^{15}N n.m.r. spectra the α-substituent chemical shift (α-SCS) effect of a single methyl group is relatively small.[8] For the estimation of this value, compounds (16) and (17) were taken[14] where α-SCS was −5.2 p.p.m. Since (11) and (2) only differ in one methyl group situated in the ε-position relative to N-1, no significant change in the shielding of N-1 by the additional methyl group could be anticipated. Accordingly for the enamine structure δ −263.1 p.p.m. and for the imine structure δ −161.2 p.p.m. were taken as the standard shifts of N-1. Thus the percentage of enol-imine is given by equation (1).

$$\%\,(C) = \frac{\delta_{N-1}(10) + 5.2 - \delta_{N-1}(2)}{\delta_{N-1}(10) + 5.2 - \delta_{N-1}(11)} \cdot 100 = 15.8 \quad (1)$$

Considering that both calculations have limited accuracy the agreement of the results is satisfactory and the presence of *ca.* 11—16% of the enol-imine (C) along with form (B) in (2) is highly probable.

It was also found that ^1H shifts are rather similar in $CDCl_3$, C_2Cl_4, and [$^2H_6$]DMSO proving that in all three solvents tautomer (B) is the major component. No significant change of the equilibrium was observed in tetrachloroethene in the range 20—120 °C. Broadening of certain signals at room temperature in [$^2H_6$]DMSO was experienced and these sharpened at 80 °C (*e.g.* signals for 2-H, 11-H, NH, and also C-2, C-8, C-9, and C-11). This phenomenon can be explained by a partial cleavage of the intramolecular hydrogen bonds under the influence of DMSO involving the concurrent appearance of *s-Z* and *s-E* rotamers of the enamine tautomer (B). Interconversion of these rotamers becomes fast on elevating the temperature.

In another paper we report[15] that with 9-substituted tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones variation of the substituent at C-3 substantially influences the tautomeric equilibria. We could not observe this with the 9-formyl compounds (2) and with (5)—(9).

In compound (1) fast inversion of the flexible tetrahydropyridine ring effected the averaging of the chemical shifts for the quasi-axial and quasi-equatorial methylene protons. We have already demonstrated that in the predominant conformer the 6-Me group is quasi-axially oriented.[3] In compound (3) the quasi-equatorial disposition of the 7-CH_3 group is proved by the value of $J_{6a,7a}$ (9.5 Hz). In (4) the 8-CH_3 group is quasi-axial ($J_{8e,7e} = J_{8e,7a} = 4$ Hz). The predominance of this conformer is caused by a 1,3-allylic strain in the conformer with a quasi-equatorial 8-CH_3.

Table 2. SCS values of the CH_3 group at various carbon atoms for compounds (2)—(4)

	C-6	C-7	C-8	C-9	C-10
(2) 6-CH_3	4.3	5.2	−4.4	−1.4	−1.5
(3) 7-CH_3	6.6	6.3	8.7	0.5	0.7
(4) 8-CH_3	−4.0	6.9	4.3	6.0	−0.1

These conformational assignments were further supported by the substituent effects of $R^2 = CH_3$ in the ^{13}C n.m.r. spectra. SCS values are compiled in Table 2, from which a significant γ_{gauche} effect due to steric interaction in (3) and (4) becomes apparent. It is also characteristic that the α-SCS effect of a quasi-equatorial 7-CH_3 group is higher by 2 p.p.m. than that of a quasi-axial one.

Experimental

N.m.r. spectra were recorded on a JEOL FX-100 instrument. The ^1H and ^{13}C n.m.r. spectral conditions were the same as described previously.[11] ^{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°, and pulse delay 5 s.

References

1 Part 33, I. Hermecz, T. Breining, Z. Mészáros, J. Kökösi, L. Mészáros, F. Dessy, and C. DeVos, *J. Med. Chem.*, in the press.

2 Á. Horváth, I. Hermecz, L. Vasvári-Debreczy, K. Simon, M. Pongor-Csákvári, Z. Mészáros, and G. Tóth, *J. Chem. Soc., Perkin Trans. 1*, 1983, 369.

3 I. Hermecz, I. Bitter, Á. Horváth, G. Tóth, and Z. Mészáros, *Tetrahedron Lett.*, 1979, 2557.

4 (*a*) G. Tóth, I. Hermecz, Á. Szöllősy, Z. Mészáros, T. Breining, Á. Horváth, F. Dessy, and C. DeVos, VII. International Symposium on Medicinal Chemistry, Malaga, 1980, Abstract p. 139; (*b*) Chinoin Pharm. Works Ltd., Belg. P. 873,194 (*Chem. Abstr.*, 1979, **91**, 91,658).

5 I. Bitter, I. Hermecz, G. Tóth, P. Dvortsák, Z. Bende, and Z. Mészáros, *Tetrahedron Lett.*, 1979, 5039.

6 G. Tóth, C. de la Cruz, I. Bitter, I. Hermecz, B. Pete, and Z. Mészáros, *Org. Magn. Reson.*, 1982, **20**, 229.

7 J. W. Apsimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1967, **23**, 2357.

8 G. C. Levy and R. L. Lichter, ' Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy,' Wiley, New York, 1979.

9 ' Nitrogen NMR,' eds. M. Witanowski and G. A. Webb, Plenum Press, London, 1973.

10 G. Tóth and A. Almásy, *Org. Magn. Reson.*, 1982, **19**, 219.

11 G. Tóth, Á. Szöllősy, B. Podányi, I. Hermecz, Á. Horváth, Z. Mészáros, and I. Bitter, *J. Chem. Soc., Perkin Trans. 2*, 1983, 165.

12 G. O. Dudek and E. P. Dudek, *J. Am. Chem. Soc.*, 1964, **86**, 4283.

13 A. J. H. Mercer and S. Selvakumar, 2nd European Symposium on Organic Chemistry, Stresa, Lago Magiore, 1981, Abstract, p. 48B.

14 G. Tóth, Á. Szöllősy, T. Meisel, I. Hermecz, Z. Mészáros, and F. Ungvári, International Symposium on NMR Spectroscopy, Smolenice, 1980, Abstract, p. 38.

15 G. Tóth, Á. Szöllősy, B. Podányi, I. Hermecz, Á. Horváth, Z. Mészáros, and I. Bitter, *J. Chem. Soc., Perkin Trans. 2*, in the press.

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