# Nitrogen Bridgehead Compounds. Part 29.[1,2] Tautomerism and *Z–E* Isomerism of Ethyl 9-Aminomethylene-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and their Homologues

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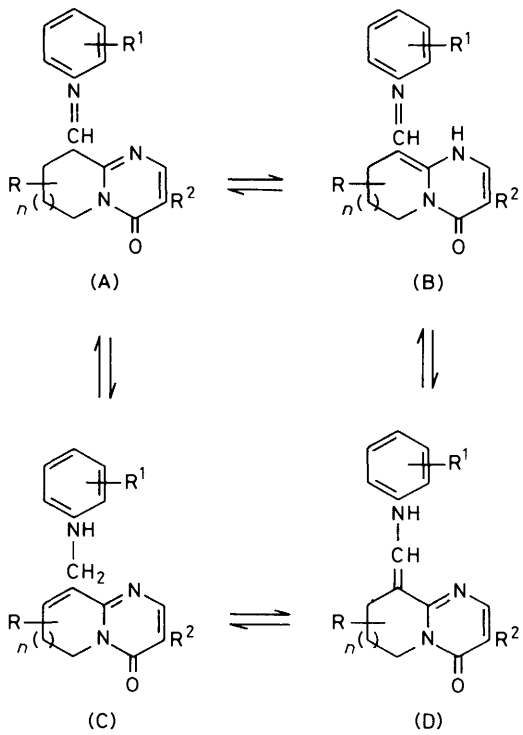
$^1$H and $^{13}$C n.m.r. studies have proved that ethyl 9-dimethylaminomethylene-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates (2)—(5) and the corresponding pyrrolo homologue (6) exist in the form of *E*-isomers whereas the azepino[1,2-*a*]pyrimidine derivative (7) appears as an equilibrium mixture of *Z*- and *E*-isomers. On the basis of $^{15}$N chemical shifts an analogous tautomeric structure has been established for the 9-dimethylaminomethylene derivatives (2)—(7) and the ethyl 9-arylaminomethylene-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates (8)—(12) as well. $^{15}$N Shifts were sensitively affected by the *Z–E* isomerism and structural changes in remote parts of the molecule, too. Protonation of compounds (2)—(12) takes place on the N(1) atom, forming a 1,6,7,8-tetrahydro structure.

Recently we reported the tautomerism and isomerism of some arylaminomethylene-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones [1] which are of interest because of their antiallergic–antiasthmatic activity.[3] On the basis of their $^1$H and $^{13}$C n.m.r. spectra we have established that the possible tautomeric equilibrium (A) ⇌ (B) ⇌ (C) ⇌ (D) (Scheme 1) in solution of these compounds and their differently substituted derivatives is essentially shifted towards form (D).[1] However, at the same time *Z–E* isomers could be observed and it has been found that the isomeric ratio is controlled by steric factors and solvation. The interconversion of *Z*- and *E*-isomers requires low activation energy.

Ethyl 9-dimethylaminoethylene-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines (2)—(5) are useful intermediates for the arylaminomethylene derivatives (Scheme 2).[1] As these compounds as well as their homologues (6) and (7) have a fixed (D) type structure the existence of *Z*- and *E*-isomers can also be considered. In this paper we give an account of the $^1$H and $^{13}$C n.m.r. spectra of compounds (2)—(7) and our study is made complete by the $^{15}$N n.m.r. investigation of compounds (2)—(5) compared with some arylaminomethylene derivatives (8)—(12).




**Scheme 1.**

## Results and Discussion

$^1$H *and* $^{13}$C *N.m.r. Investigations.*—Characteristic $^1$H n.m.r. data for compounds (2)—(7) are summarized in Table 1 and $^{13}$C n.m.r. data are shown in Table 2. In the spectra of (2)—(6) only one set of signals can be observed whilst (7) shows a doubling of several resonance lines in its spectra with an intensity ratio of 88 : 12. The doubled signals may be assigned to *E*- and *Z*-isomers, respectively, so the coexistence of this isomer serves as a proof that the rate of *Z–E* interconversion must be slow on the n.m.r. timescale. This slow rate of isomerism must be characteristic of compounds (2)—(6) as well; however, the observed single set of signals cannot be regarded as a result of a time-averaged equilibrium. It means (2)—(6) are present as only one isomer.

The =CH signal in isomer (7*E*) reveals a *ca.* 1.0 p.p.m. downfield shift compared with that of isomer (7*Z*) owing to the anisotropic effect of the C(10)=N(1) double bond.[1] The vinyl protons in (2)—(6) are similar or more deshielded than that in the isomer (7*E*) giving evidence for the *E*-configuration in these compounds. The above proposed structure of isomers is also supported by the $^{13}$C n.m.r. spectra. A significant difference could be observed for the C(8) signals of (7*Z*) and (7*E*) isomers (7.0 p.p.m.). This is caused by the γ-*gauche* steric effect [4] of the $NMe_2$ moiety in the *E*-isomer. The assignments of the =CH and C(2) carbon signals were made by utilizing the influence of different substituents on $^1J_{C,H}$ couplings.[5] The imino-group has a stronger electron-withdrawing character

**Table 1.** $^1$H N.m.r. data [δ (p.p.m.); *J*/Hz] of compounds (2)—(7) in $CDCl_3$

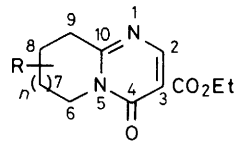
| Compd. | *n* | R | $NMe_2$ | =CH | 2-H | 6-H | 7-H | 8-H | OEt | CMe | Couplings |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (2) | 1 | H | 3.18s | 8.14t | 8.42s | 3.94m | 1.84m | 2.72t | 4.28q, 1.35t | | $J_{7\text{-}H_2,\ 8\text{-}H_2}$ 6.4 |
| | | | | | | | | | | | $^4J_{8\text{-}H_2,\ CH=}$ 1.0 |
| (3) | 1 | 6-Me | 3.25s | 8.19t | 8.41s | 5.16m | 1.85m | 2.80m | 4.31q, 1.39t | 1.28d | |
| (3p) | | | 3.47s | 8.13t | 8.39s | 5.10m | 1.85m | 2.86m | 4.28q, 1.33t | 1.28d | |
| (4) | 1 | 7-Me | 3.21s | 8.22t | 8.48s | a, 3.20 e, 4.46 | 1.88m | a, 2.28 e, 2.88 | 4.31q, 1.36t | 1.09d | $^2J_{8\text{-}H}$ 14.0 |
| | | | | | | | | | | | $J_{8\text{-}H_{ax},\ 7\text{-}H_{ax}}$ 10.7 |
| (5) | 1 | 8-Me | 3.22s | 8.17d | 8.41s | a, 3.50 e, 4.46 | 1.84m | 3.20 | 4.28q, 1.35t | 1.14d | |
| (6) | 0 | H | 3.13s | 7.47t | 8.53s | 4.08m | | 3.10m | 4.30q, | | $^4J_{8\text{-}H_2,\ CH=}$ 1.7 |
| (7*E*) | 2 | H | 3.13s | 7.47t | 8.51s | 4.18t | 1.75m | 2.77m | 4.34q, | 1.37t | $^4J_{8\text{-}H_2,\ CH=}$ 1.5 |
| (7*Z*) | | | 2.82s | 6.47t | 8.64s | | | | 4.36q, | | |
| (8p) | 1 | 6-Me | | 8.94d | 8.37s | 5.05m | a, 1.25m e, 1.95m | a, 2.42m e, 3.15m | 4.39q, 1.45t | 1.15d | $J_{NH,\ CH}$ 13.0 |

a, Axial; e, equatorial. (3p) and (8p): in $CDCl_3$–$CF_3CO_2H$ (1 : 1).

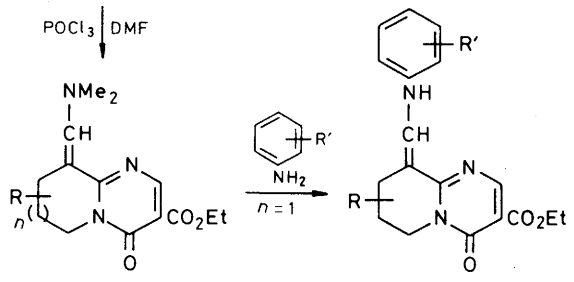
**Table 2.** $^{13}$C N.m.r. data [δ (p.p.m.); *J*/Hz] of compounds (2)—(8) in $CDCl_3$

| C | (2) | (3) | (3p) | (4) | (5) | (6) | (7*E*) | (7*Z*) | (8p) |
|---|---|---|---|---|---|---|---|---|---|
| $NMe_2$ | 43.8 | 43.8 | 44.6 | 43.8 | 43.3 | 42.3 | 43.6 | 45.7 | |
| =CH | 152.2 | 152.2 | 157.2 | 152.4 | 150.6 | 145.8 | 150.6 | 146.4 | 148.7 [d] |
| C(2) | 158.2 | 158.2 | 147.1 | 157.9 | 157.5 | 161.7 | 158.4 | 157.3 | 148.0 [d] |
| C(3) | 104.4 | 105.6 | 104.8 | 104.3 | 103.9 | 107.8 | 108.4 | 110.7 | 106.5 |
| C(4) | 159.6 | 159.0 | 155.8 | 159.4 | 159.5 | 158.8 | 160.1 | *a* | 157.7 |
| C(6) | 41.0 | 44.9 | 46.3 | 46.7 | 36.6 | 44.5 | 43.1 | 43.8 | 48.6 |
| C(7) | 21.2 | 26.5 | 24.8 | 26.6 | 25.4 | | 24.2 [b] | 28.3 [c] | 24.2 |
| C(7a) | | | | | | | 22.5 [b] | 25.5 [c] | |
| C(8) | 23.5 | 19.1 | 18.4 | 31.6 | 23.8 | 23.2 | 26.2 | 33.2 | 16.5 |
| C(9) | 95.0 | 94.7 | 89.1 | 94.5 | 100.2 | 95.9 | 100.3 | 98.0 | 94.1 |
| C(10) | 162.5 | 161.9 | 154.6 | 162.2 | 161.5 | 166.8 | 168.5 | *a* | 154.7 |
| Me | | 17.3 | 16.3 | 18.4 | 20.8 | | | | 16.2 |
| COO | 165.5 | 165.5 | 161.9 | 165.1 | 164.9 | 165.1 | 165.2 | *a* | 163.8 |
| $CH_2$ | 59.8 | 59.8 | 60.8 | 59.5 | 59.3 | 60.1 | 60.4 | 60.7 | 63.5 |
| $CH_3$ | 14.5 | 14.5 | 13.7 | 14.4 | 13.9 | 14.4 | 14.4 | 14.4 | 13.8 |

[a] Could not be assigned because of low intensity or overlap. [b–d] Tentative assignment is possible. (3p) and (8p) in 1 : 1 $CDCl_3$–$CF_3CO_2H$. Characteristic coupling constants for (2): $^1J_{C(2),\ H}$ 178.2 $^1J_{=CH,H}$ 167.2, $^3J_{C(4),\ 2\text{-}H}$ 7.0.



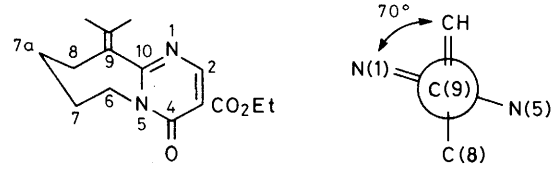
(1) R = H, Me; *n* = 0,1,2



(2) R = H, *n* = 1
(3) R = 6-Me, *n* = 1
(4) R = 7-Me, *n* = 1
(5) R = 8-Me, *n* = 1
(6) R = H, *n* = 0
(7) R = H, *n* = 2

(8) R = 6-Me, R′ = H
(9) R = 7-Me, R′ = H
(10) R = 8-Me, R′ = H
(11) R = 6-Me, R′ = *p*-Me
(12) R = 6-Me, R′ = *o*-Me

**Scheme 2.**



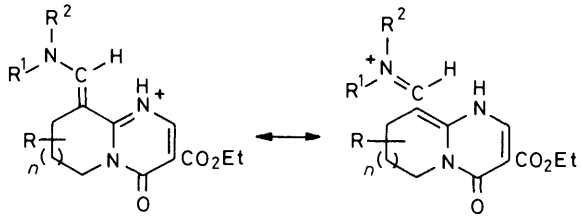
**Scheme 3.**

than the amino-group so this results in a higher value of the $^1J_{C(2),H}$ coupling than that of $^1J_{=C,H}$. In the spectra of compound (2) values of 178.2 and 162.2 Hz were observed for the $^1J_{C,H}$ couplings of signals at δ 158.2 and 152.2 p.p.m., respectively, suggesting that the former belongs to C(2) and the latter to =CH. The C(10) and C(4) signals were assigned on the basis of their different multiplicity in the proton-coupled spectrum.[b]

Inspection of Dreiding models of compounds indicates that for the pyridopyrimidine derivatives (2)—(5) the C(10)=N(1) and C(9)=CH double bonds are coplanar in the stable half-chair conformations of the tetrahydropyridine ring. This results in a sterically unfavourable position of the $NMe_2$ group in the *Z*-isomer. The same situation is also valid for the pyrrolo-derivative (6), whereas in the azepino-compound (7), assuming a chair conformation for the seven-membered ring, the N(1)=C(10)–C(9)=CH dihedral angle is *ca.* 70° (Scheme 3). Thus, in this case the steric interaction is reduced even in the *Z*-configuration, leading to the appearance of this isomer in a

**Table 3.** $^{13}C$ SCS values (p.p.m.) for the methyl group in (3)—(5)

| Compound | α | β | γ |
|---|---|---|---|
| (3) | +3.9 | +5.3 | −4.4 |
| (4) | +5.4 | +5.7 at C(6)<br>+8.1 at C(8) | |
| (5) | +0.3 | +4.2 | −4.4 |



(F) (G)

(2) - (7) $R^1 = R^2 =$ Me

(8) - (12) $R^1 = H$, $R^2 =$ Ar

**Scheme 4.**

proportion of 12%. It is a characteristic feature of compound (7) that the C(9) and C(10) signals are deshielded as a consequence of the decreased conjugation of the double bonds owing to their non-coplanar arrangement. In the methyl-substituted compounds (3)—(5) there are two possible half-chair conformations for the tetrahydropyridine ring which can be characterized by the quasiaxial or quasiequatorial position of the methyl group. In the conformational equilibrium for compounds (3) and (5) the quasiaxial, and for compound (4) the quasiequatorial, methyl group is predominant. In the latter compound $J_{8\text{-}H_{ax},7\text{-}H_{ax}}$ 10.7 Hz is found in the $^1H$ n.m.r. spectrum, and in the $^{13}C$ spectra of compounds (3) and (5) the −4.4 p.p.m. γ-SCS (substituent chemical shift) value (Table 3), in agreement with the literature data,[1,7] gave evidence for the proposed position of the methyl group. It is noteworthy that the α-SCS virtual value of 8-Me is only 0.3 p.p.m. which may be due to the interaction of 8-Me and $NMe_2$ groups. In this case the $NMe_2$ group, which probably occupies a coplanar position in the unsubstituted molecule, is forced out of the plane of the *exo*-double bond and therefore its downfield δ-effect [8] on C(8) is diminished.

*Protonation.*—Since the 9-aminomethylene derivatives (2)—(12) possess more basic centres, we have investigated the site of protonation and the mesomeric structure of trifluoroacetate salts. The comparison of the $^1H$ n.m.r. spectra of (2)—(12) and the corresponding salts has proved that the site of protonation is always the N(1) atom. The fast exchange of N(1)H caused a broadening of its signal and the coupling with 2-H could not be observed either. However, the canonical forms (F) and (G) should be taken into consideration to characterize the salts of compounds (2)—(12) (Scheme 4). Since the chemical shifts of the 2-H signals remain essentially unchanged by protonation, it is very likely that the contribution of the canonical structure (F), bearing a positive charge at the N(1) atom, is much lower than that of (G). An increase of chemical shift of the =CH signal (*ca.* 0.2 p.p.m.) has been observed after protonation of compounds (8)—(12). The doublet splitting of this signal (12—14 Hz) gave evidence for the *trans*-arrangement of the =CH and NH protons. All these observations suggest a structure close to (G). This is supported by the fact that at room temperature the *Z*- and *E*-isomers of the salts could not be distinguished. Furthermore, it is probable that the proton-catalysed *Z*–*E* isomerization of the bases described earlier [1] proceeds *via* a structure of type (G).

**Table 4.** $^{15}N$ Chemical shifts [δ (p.p.m.)] of compounds (2)—(5) and (8)—(12) in $CDCl_3$

| Compd. | R | $R^1$ | N(1) | N(5) | N |
|---|---|---|---|---|---|
| (2) | H | | −164.4 | −214.8 | −291.8 |
| (3) | 6-Me | | −164.2 | −204.0 | −291.9 |
| (4) | 7-Me | | −165.3 | −215.9 | −290.3 |
| (5) | 8-Me | | −163.7 | −214.8 | −292.9 |
| (8*E*) | 6-Me | H | −162.1 | −199.1 | −264.5 |
| (8*Z*) | | | −160.8 | −199.1 | −253.2 |
| (9*E*) | 7-Me | H | *a* | *a* | −265.5 |
| (9*Z*) | | | −161.2 | −211.6 | −255.4 |
| (10*Z*) | 8-Me | H | −161.0 | −211.6 | −254.9 |
| (11*E*) | 6-Me | *p*-Me | *a* | *a* | −265.0 |
| (11*Z*) | | | −160.6 | −200.7 | −253.5 |
| (12*Z*) | 6-Me | *o*-Me | −161.6 | −200.3 | −254.8 |

[a] Could not be assigned because of low intensity or overlap. $\delta_{MeNO_2}$ 0.0 p.p.m.; negative values denote upfield shifts.

The formation of the salts of the dimethylaminomethylene derivatives (2)—(7) do not produce the considerable downfield shift mentioned above for the =CH signal, but a 0.3 p.p.m. deshielding of the $NMe_2$ signal can be found. This shows the participation of (F) in a greater extent than (G). The upfield shifts of C(2), C(4), C(9), and C(10) can be explained by the rearrangement of double bonds in the salts resulting in a structure of the 1,6,7,8-tetrahydropyrido-pyrimidine type.[1,6] Consequently, coalescence of the $NMe_2$ signal has been observed [*e.g.* for (3p) at 20 °C] owing to the partial double bond character of the $Me_2N$–C= bond in the salts. The activation free energy [9] of the rotation for (3p) is $\Delta G^{\ddagger}$ 58.0 ± 1.2 kJ $mol^{-1}$.

$^{15}N$ *N.m.r. Studies.*—Since the $^{15}N$ chemical shifts are remarkably affected by the extent of conjugation of the lone pair of electron at the nitrogen atom and the structural changes even in relatively remote parts of the molecule as well, we have determined the $^{15}N$ chemical shifts for compounds (2)—(5) and (8)—(12). The data measured at natural isotope abundance are collected in Table 4. From the assignment of the N(1) and N(5) signals, as in the case of the analogous 9-carbamoyl-derivatives,[10] we could measure the chemical shift changes caused by a methyl substitution at the tetrahydropyridine ring. The comparison of the N(5) chemical shifts in compounds (2)—(5) shows that in agreement with literature data [11] the β-, γ-*anti*-, and δ-SCS values are 10.8, −1.1, and 0.0 p.p.m., respectively. In the case of arylamino-methylene derivatives (9)—(11), assuming that the δ-SCS effect of the methyl group is also zero, then β- and γ-*anti*-SCS values are 11.5 and 0.0 p.p.m., respectively.

The data in Table 4 show that the chemical shifts of N(5) are not influenced by *Z*–*E*-isomerism. However, exchange of $NMe_2$ for NHPh causes a 3—5 p.p.m. downfield shift in the fairly remote ε-position. This is a consequence of the diminished electron density on N(5) because the electron-donating ability of the NHPh group is less than that of the $NMe_2$ group. The 2.1 p.p.m. deshielding on the N(1) signal of (8*E*) compared to (3) is also caused by the latter phenomenon.

The $^{15}N$ n.m.r. chemical shifts of the $NMe_2$ groups of compounds (2)—(5) appear within a close range. In the spectrum of (5) a small upfield shift has been observed due to the steric interaction of the $NMe_2$ and 8-$Me_{ax}$ groups mentioned above. This phenomenon results in reduced $p,\pi$ inter-

action of the lone electron pair and the *exo*-double bond, in accord with Roberts' investigations.[12] The good correlation between the $^{15}N$ chemical shift values measured for compounds (8)—(12) and (2)—(5) [the latter series has a fixed (D) type structure] also supports the predominance of form (D) in the arylaminomethylene derivatives. Namely, in tautomer (A) two signals have appeared in the range of imino-nitrogens; however, for form (B) a large shielding of N(1) would have been expected. Furthermore, the NH group in tautomer (C) has aniline-like character and it would be expected to appear upfield of the measured signal.[11]

The simultaneous coexistence of *Z*- and *E*-isomers can be unambiguously observed for the NH signal in the $^{15}N$ n.m.r. spectra. A 10.1—11.5 p.p.m. deshielding has been found for this signal in the *Z*-isomer owing to internal hydrogen bonding, which makes this isomer particularly favourable. A similar effect was reported by Kozerski and von Philipsborn for analogous enaminone derivatives as well.[13] A characteristic, though much smaller difference, could be observed for the N(1) signals of isomers (8*Z*) and (8*E*). It is striking, however, that the higher shielding occurs in the *E*-isomer, though it is known that *e.g.* in arylimines the formation of hydrogen bonds gives rise to a 5—12 p.p.m. upfield shift.[14] Thus, we have to conclude that in the *Z*-isomer such an effect operates, which reduces the shielding of N(1) and slightly overcompensates for the opposing effect of the hydrogen bonding. This phenomenon can be ascribed to the different conjugation of the *Z*- and *E*-isomers.

## Experimental

The n.m.r. spectra were recorded on a JEOL FX-100 instrument. $^{1}H$ and $^{13}C$ n.m.r. spectral conditions were the same as described previously.[1] $^{15}N$ N.m.r. spectra were recorded at 10.04 MHz under proton broadband decoupling. Samples were measured for $CDCl_3$ solutions at 0.5—1.0 mol $dm^{-3}$ in 10 mm o.d. sample tubes. The chemical shifts were determined relative to the signal of external aqueous $K^{15}NO_3$ ($\delta_{K^{15}NO_3}$ −3.55 p.p.m.) and then converted to external nitromethane. Shifts upfield from the reference are negative. Typical acquisition parameters are: spectral width 5 000 Hz, flip angle 30°, and pulse delay 5 s.

The syntheses are shown in Scheme 2. The preparation of compounds (2)—(5) [15] and (8)—(12) [1] has been described elsewhere, while compounds (6), m.p. 185 °C, and (7), m.p. 138 °C, will be reported in ref. 16.

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