Isomerism of 9-Arylaminomethylene-6,7,8,9-tetrahydro-4-oxo-4H-pyrido-[1,2-a]pyrimidines [1]

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Several 9-arylaminomethylene-6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]pyrimidines have been synthesized and studied by ^{1}H and [13]C n.m.r. spectroscopy. The dominant tautomeric form has been established. Fast Z–E isomerisation has been found around the enamino C=C double bond. The effect of the solvent, temperature, and various structural modifications on the equilibrium Z:E isomeric ratios has been measured.
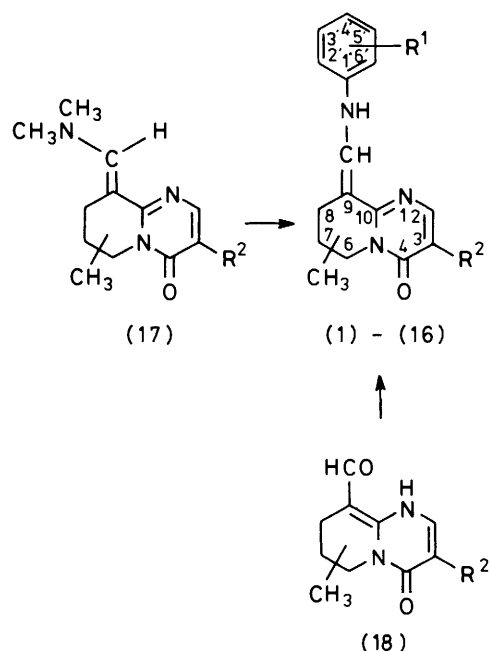
We have shown in our earlier work that the active methylene group in the 9-position of 6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-ones easily undergoes a reaction with electrophilic reagents.[2] The transformation of the functional groups obtained this way renders feasible the further transformation [3] of the parent compound, giving derivatives with advantageous pharmacological activity.[4] In this paper we report the synthesis of 9-arylaminomethylene-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones (1)—(16) (Table 1) and their detailed ^{1}H and [13]C n.m.r. investigations.

Results and Discussion

9-Arylaminomethylene-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones possessing antiallergic activity [5] can be obtained by the reaction of 9-formyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones (18) or 9-dimethylamino-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones (17) with aromatic primary amines (Scheme 1).

Investigation of Tautomerism.—The 9-arylaminomethylene-pyridopyrimidine derivatives (1)—(16) are potential tautomeric systems which can exist in forms (A)—(D) (Scheme 2). In the cases of tautomers (A), (B), and (D) the possibility of Z–E geometrical isomerism should be also considered. Due to the more extended conjugation a lower energy can be anticipated for tautomers (B) and (D). In fact forms (A) and (C) can be ruled out by the careful integration of their [1]H n.m.r. spectrum because there is a total of five alicyclic protons, whereas form (A) it would be expected to have six and form (C) three. The coupling constant of the vinyl proton, $J_{=CH;NH}$ 12—14 Hz and $^4J_{=CH;C(8)H_2}$ ca. 1 Hz [Supplementary Publication No. SUP 23484 (3 pp.)†] support the assumption of the predominance of tautomer (D). The large value of $J_{=CH;NH}$ shows that the two protons are *trans*-antiperiplanar. A further, independent proof for form (D) is that 2-H appears as a singlet, because in 9-formyl derivatives, which are analogous to (B), there is a $J_{2-H;NH}$ coupling.[2d] The ^{13}C chemical shifts (Table 2) give support for structure (D).

Z–E Isomerism.—We have found the existence of Z–E isomerism in tautomer (D). The significant difference between

Scheme 1

† For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, 1981, Index Issue.

the two isomers is that a strong internal hydrogen bond is present in the Z-isomer. This is well shown in the [1]H n.m.r. spectra: the NH signal of the Z-isomer appears in the range δ 11.75—12.40 whereas in the E-isomer it occurs at δ 6.50—8.75. Comparing the chemical shifts of the NH protons in compounds (1), δ 12.13 and 8.26, and (4)—(8), δ 11.75—12.24 and 6.57—7.50, it is clear that if the substituent R[2] is strongly electron-withdrawing, then the chemical shift of NH is shifted upfield, *i.e.* its positive polarization is increased. The chemical shift of the vinyl proton in the E-isomer appears *ca.* 1.3 p.p.m. higher than in the Z-isomer, due to the deshielding effect resulting from the diamagnetic anisotropic effect of the C(10)=N(1) double bond. Nearly the same $^4J_{=CH;C(8)H_2}$ coupling constants of 1—2 Hz have been found in the isomeric pairs.

In the [13]C n.m.r. spectra of the equilibrium mixture of the E- and Z-isomers C(8) and C(9) have relatively large differences in chemical shift. The 5—6 p.p.m. difference can be

Table 1

Compound	R¹	Me	R²	Method of preparation	Yield (%)	M.p. (°C)
(1)	H	6-Me	CO₂Et	A	92	174—175
(2)	H	7-Me	CO₂Et	A	85	180—182
(3)	H	8-Me	CO₂Et	A	66	100—102
(4)	H	6-Me	CO₂H	C	92	262
(5)	H	6-Me	CH₂CO₂Et	D	53	Oil
(6)	H	6-Me	H	D	62	139—141
(7)	H	6-Me	Ph	D	84	82—84
(8)	H	6-Me	Me	D	72	128—129
(9)	p-Me	6-Me	CO₂Et	A	80	116—118
(10)	p-OEt	6-Me	CO₂Et	B	79	118—120
(11)	p-Cl	6-Me	CO₂Et	B	78	170—172
(12)	p-NO₂	6-Me	CO₂Et	A	77	217—219
(13)	o-Me	6-Me	CO₂Et	C	91	182—184
(14)	o-OMe	6-Me	CO₂Et	B	52	Oil
(15)	o-OH	6-Me	CO₂Et	C	73	216
(16)	o-CO₂Me	6-Me	CO₂Et	A	86	162—164
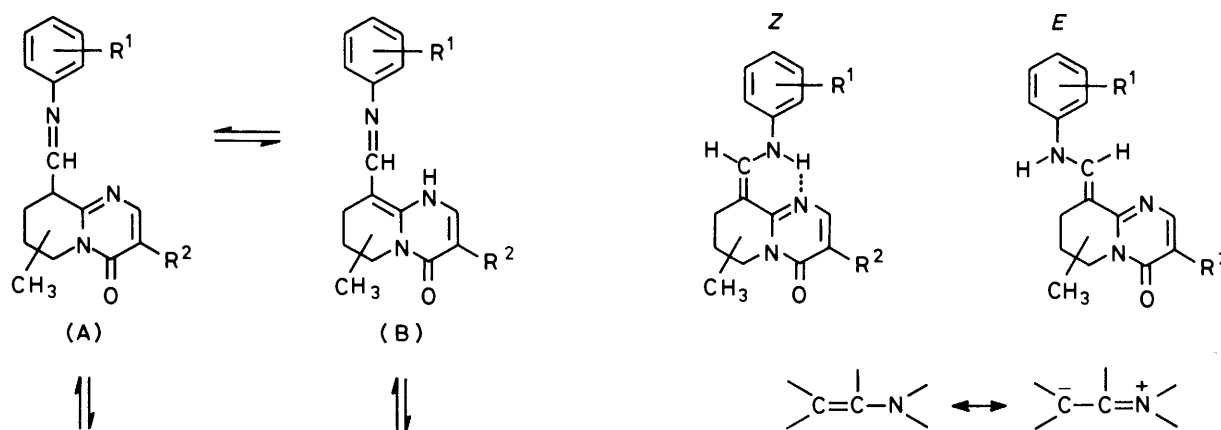
Scheme 2
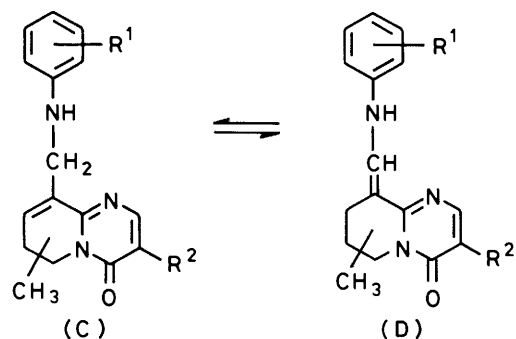
Scheme 3

explained by a γ-*gauche* steric effect [6] in the Z-isomer. The C(9) atom is in the β-position of the enamine unit; for such carbon atoms chemical shift differences of 5—7 p.p.m. have been measured by Giasuddin and Hickmott [7] as well as by Stradi *et al.*[8] It was suggested that this difference is due to the different conjugation in the isomers.[8] In our case, in the Z-isomer, because of the internal hydrogen bond a planar structure is realized in which the lone pair of the enamine nitrogen atom is more thoroughly conjugated with the highly delocalized electron structure of the molecule which gives rise to the probability of the ionic canonical formula in Scheme 3. In our opinion this is responsible for the 5—6 p.p.m. shielding at C(9) in the Z-isomer.

There is other evidence for the extended delocalization, *e.g.* even at C(3), which is five bonds away from the carbon atom of different configuration a *ca.* 1 p.p.m. difference has been observed.

Another characteristic feature is that the chemical shift of C(7) is always lower in the E-isomer which is in good agreement with those found in oximes.[6]

Equilibrium Z : E *Isomeric Ratios and Conformation.*—We have determined the isomeric ratio of compound (1) immediately after dissolving it in various solvents; the results obtained are summarized in Table 3. These values, depending on the solvent, did not change with time. This indicates that a rapid isomerization takes place on dissolution and the equilibrium isomeric ratio is established instantaneously. The solvent dependence of Z : E isomeric ratio is interesting. In dimethyl sulphoxide and methanol in which strong hydrogen bonds can be built up between the solvent molecules and the E-isomer, the preference for the Z-isomer found in chloroform no longer exists, and the E-isomer predominates. In tetrachloroethylene the ratio is nearly 1 : 1. On elevating the temperature, the internal hydrogen bonds, even in this solvent, are broken and the proportion of sterically preferred E-isomer is increased, and at 120 °C only the signals of this isomer could be observed. After cooling the original equilibrium is re-established and thus the isomerization along the *exo*-9-C=C double bond requires little activation energy. The preference for the Z-

Table 2. ^{13}C N.m.r. spectra [δ (p.p.m.); CDCl₃]

Carbon	(1Z)	(1E)	(2Z)	(2E)	(3Z)	(3E)	(5Z)	(5E)	(6Z)	(6E)	(7Z)	(7E)	(8Z)	(8E)
CH=	143.1	140.5	142.2	140.0	142.0	140.1	138.9	135.8	139.6	136.1	139.2	136.1	137.8	135.0
2	156.8	158.5	156.8	158.6	156.8	158.5	150.0	151.9	151.1	153.2	149.0	150.9	148.4	150.0
3	108.1	107.0	108.5	107.3	108.0	106.9	114.0	113.5	108.3	108.0	119.9	119.4	116.9	116.3
4	158.2	158.7	158.9	159.4	158.6	159.6	156.6	156.6	157.8	a	156.6	156.3	155.6	155.2
6	46.2	45.3	48.6	47.0	38.8	37.1	46.5	45.7	46.2	45.2	46.7	45.7	46.4	45.5
7	26.4	25.3	26.6	26.2	27.8	26.6	26.8	25.5	26.8	25.7	27.0	25.7	26.9	25.7
8	21.9	16.9	35.1	29.4	30.2	24.2	22.0	17.2	22.3	16.8	22.2	17.2	22.2	17.1
9	94.0	100.0	94.9	100.8	100.7	106.0	94.5	100.4	94.6	100.5	94.8	100.6	94.7	100.4
10	159.8	160.6	160.2	161.1	160.1	161.0	161.4	161.7	161.7	162.3	160.6	160.6	162.5	162.5
CO₂	164.6	165.0	164.6	165.2	164.5	164.5								
CH₂	60.4	60.1	60.5	60.2	60.4	60.1								
CH₃	14.4	14.4	14.4	14.4	14.4	14.4								
1'	140.1	141.0	140.2	140.9	140.2	141.0	141.2	141.8	141.2	141.6	141.3	141.5	141.3	141.9
2'6'	116.1	116.4	116.0	116.3	116.0	116.3	115.6	115.6	115.8	115.8	115.8	115.8	115.4	115.6
3'5'	129.6	129.4	129.7	129.5	129.6	129.6	129.7	129.7	129.7	129.7	129.7	129.7	129.6	129.6
4'	123.3	123.0	123.2	123.2	123.2	123.2	122.2	122.2	122.5	122.5	122.4	122.4	121.9	121.9
6-Me	18.2	17.2					18.2	18.2	18.3	17.2	18.3		18.2	17.4

7-Me: (2Z) 18.2, (2E) 18.4

8-Me: (3Z) 21.2, (3E) 18.2

CH₂CO₂CH₂CH₃ (5Z, 5E): 33.3; 171.3; 60.7 — 14.2

3-Ph (7Z, 7E): 135.0; 128.4; 128.5 — 127.4

3-Me (8Z, 8E): 13.5; 13.5

Carbon	(9Z)	(9E)	(10Z)	(10E)	(11Z)	(11E)	(12Z)	(12E)	(13Z)	(14Z)	(14E)	(15Z)	(15E)	(16Z)	(16E)
CH=	143.6	140.8	144.6	142.2	142.8	140.2	138.8	137.1	142.9	142.2	138.5	143.5	139.9	140.5	137.0
2	157.0	158.7	157.1	159.0	156.8	158.8	156.2	158.4	156.7	157.1	158.7	157.8	158.9	157.2	158.6
3	107.7	106.7	107.7	106.4	108.9	107.7	110.3	109.2	108.2	108.1	107.7	107.5	107.5	108.9	108.3
4	158.4	158.9	158.5	159.1	158.4	160.0	157.9	158.5	158.4	158.5	158.7	159.3	159.7	158.6	160.0
6	46.1	45.2	46.1	45.3	46.5	45.5	46.8	45.7	46.2	46.2	45.4	46.4	45.7	46.5	45.6
7	26.4	25.2	26.5	25.5	26.6	25.5	26.6	25.5	26.4	26.5	25.2	26.6	25.3	26.7	25.3
8	21.9	16.9	21.9	17.0	22.0	17.0	22.2	17.1	21.9	22.0	16.7	22.1	16.9	22.2	17.3
9	93.4	99.4	93.0	99.1	95.1	101.0	98.7	104.7	94.3	94.6	100.7	93.9	99.8	97.5	103.2
10	159.8	160.5	160.0	160.9	160.2	160.8	159.8	159.9	159.8	159.8	160.1	159.7	160.5	159.2	160.0
CO	164.8	165.4	164.8	165.6	164.7	165.4	164.2	164.8	164.8	164.9	165.2	165.3	165.3	165.0	165.0
CH₂	60.5	60.2	60.6	60.3	60.6	60.3	60.8	60.5	60.5	60.4	60.4	60.7	60.7	60.4	60.4
CH₃	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.5	14.5
1'	137.7	138.3	133.9	134.8	139.2	140.2	145.8	146.9	138.7	130.0	129.7	129.0	128.8	142.3	143.0
2'	116.1	116.3	115.8	115.6	117.5	117.8	115.1	115.4	125.8	148.6	148.0	146.4	135.8	115.8	113.5
3'	130.2	130.0	117.9	118.2	129.9	129.5	126.0	125.8	131.0	111.5	111.1	116.5	116.2	108.9	108.3
4'	133.1	132.8	155.8	155.6	128.4	128.1	142.5	142.5	122.9	123.3	123.3	120.7	120.7	121.2	121.2
5'			117.9	118.2	129.9	129.5			127.2	121.4	121.4	123.8	123.8	135.0	135.0
6'			115.8	115.6	117.5	117.8			112.9	112.9	113.5	114.0	114.0	113.9	113.5
6-Me	18.2	17.2	18.3	17.3	18.3	17.4	18.3	17.4	18.3	18.2	17.2	18.4	17.3	18.3	17.3

p-Me (9Z, 9E): 20.7; 20.7

p-OCH₂CH₃ (10Z, 10E): 63.8 / 14.8; 63.8 / 14.8

o-Me (13Z): 17.8

o-Me (14Z, 14E): 56.0; 56.0

o-CO₂Me (16Z, 16E): 160.8 / 52.1; 160.8 / 52.4

a Could not be assigned because of low intensity.

Table 3. $Z : E$ isomeric ratios of (1) in different solvents at 25 °C

CDCl$_3$	C$_2$Cl$_4$	CD$_3$OD	[^{2}H$_6$]DMSO
72 : 28	50 : 50	27 : 73	12 : 88

isomer can be explained by the gain in energy owing to the formation of internal hydrogen bond. We have determined the values of equilibrium isomeric ratios of compounds (1)—(16) in CDCl$_3$ and [^{2}H$_6$]DMSO (Table 4).

Evidence in support of the hypothesis that the isomeric ratios are determined mainly by solvation and steric conditions was obtained by determining the isomer ratios for compounds (1)—(3). When the methyl group is in the 6- or 7-position, we have found, in agreement with the hypothesis, that the Z-isomer was predominant, whilst in dimethyl sulphoxide the E-isomer was predominant. If the methyl group is in position 8 [compound (3)] then the previously preferred E-isomer becomes sterically crowded, and a significantly higher proportion of Z-isomer is expected in [^{2}H$_6$]-DMSO. The measurements gave evidence for this, in that the proportion of Z-isomer in [^{2}H$_6$]DMSO had increased up to 50%.

We established earlier in the investigation of 6-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidines, that the 6-methyl group in the predominant conformer is in the quasiaxial position.[9] This equilibrium is unaltered if an additional sp^2 carbon atom is inserted into the 9-position in compounds (1) and (4)—(16). Compound (2), however, can be characterized by a half-chair conformation in which the methyl group is in the equatorial position confirmed by the $^3J_{H6a;H7}$ 10.0 Hz coupling constant found in the ^{1}H n.m.r. spectrum. In compound (3) on irradiation of the methyl group the signal for 8-H appears as a triplet of 4.6 Hz splitting, giving evidence for the quasiaxial position of the methyl group. By comparison with the ^{13}C n.m.r. spectrum of the corresponding demethyl compound the γ-*gauche* substituent chemical shift value of 8-Me measured at C(6) is -3.9 p.p.m. for both Z- and E-isomers; this is also in agreement with the data found in the literature confirming the quasiaxial position of the methyl group.[10]

By comparison of the isomeric ratios of compounds (1) and (4)—(9) the effect of R^2 on the equilibrium can be studied. On increasing the electron-donating strength of R^2 the proportion of Z-isomer is higher in both solvents, which can be explained by the greater basicity of N(1) and consequently the greater strength of the internal hydrogen bond.

The *para*-substitution of the phenyl ring has only a moderate effect on the $Z : E$ isomer ratio for (1) and (9)—(12) which is manifested by the slight increase in the proportion of Z-isomer by the effect of the electron-withdrawing nitro-group in (12). This can be explained by the positive polarization of NH and its greater tendency to establish a hydrogen bond.

Finally, we examined the effect of *ortho*-substitution on the equilibrium for (1) and (13)—(16). In a chloroform solution of (16) the proportion of Z-isomer is much lower (see Table 4). This can be understood from structure (E), in which a strong six-membered internal hydrogen bonded structure is formed between the NH and the ester carbonyl. This is indicated by the δ 10.70 signal for NH found in (16), which is 2 p.p.m. higher than those of all the other E-isomers. In dimethyl sulphoxide the ratio of Z-isomer is increased in compounds (13)—(16). This can be explained by the fact that the solvent molecules can solvate NH less thoroughly owing to the *ortho* substituent, and consequently the destruction of the internal hydrogen-bonded structure is less feasible. In the hydroxy-

Table 4. $Z : E$ isomeric ratios at 25 °C

Compound	CDCl$_3$	DMSO
(1)	72 : 28	12 : 88
(2)	86 : 14	16 : 84
(3)	92 : 8	50 : 50
(4)	76 : 24	11 : 89
(5)	83 : 17	31 : 69
(6)	86 : 14	27 : 73
(7)	86 : 14	25 : 75
(8)	88 : 12	33 : 67
(9)	78 : 22	16 : 84
(10)	76 : 24	15 : 85
(11)	81 : 19	13 : 87
(12)	85 : 15	19 : 81
(13)	100 : 0	50 : 50
(14)	79 : 21	73 : 27
(15)	60 : 40	75 : 25
(16)	15 : 85	50 : 50

(E)
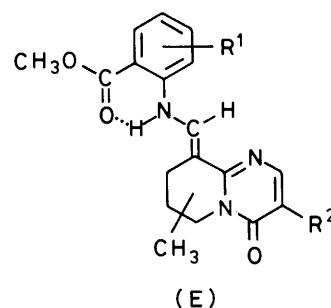
derivative (15) the hydroxy-group may be strongly solvated, maintaining the NH $\cdots$ N(1) bond.

Experimental

M.p.s are uncorrected. Elemental analyses are SUP 23484. N.m.r. spectra were recorded in the Fourier transform mode on JEOL FX-100 and Bruker WP-80 spectrometers using SiMe$_4$ as internal standard. ^{1}H N.m.r. spectra were taken in 5 mm tubes using 5—10% solutions at 100 and 80 MHz. The ^{13}C n.m.r. spectra were obtained in 5 or 10 mm tubes using saturated solutions at 25.0 or 20.1 MHz with complete proton noise decoupling, sweep width 5 000 Hz, and 30° pulses. When it was necessary for an unequivocal assignation ^{1}H single frequency off resonance decoupling spectra were recorded.

The $Z : E$ ratios were obtained by integration of the ^{1}H n.m.r. spectrum and from the peak heights of the corresponding signal of the ^{13}C spectrum, by averaging the values of 5—8 signals. The maximum deviation was $\pm 2\%$.

Preparation of 9-Arylaminomethylene-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]*pyrimidin-4-ones.—Method* A. A 9-dimethyl-aminomethylenepyridopyrimidinone derivative [2d] (10.0 mmol) and an amine (10.0 mmol) were heated to reflux for 3 h in ethanol (25 ml) and the reaction mixture was poured into water (10 ml). The crystals which precipitated were filtered off after cooling and then recrystallized.

Method B. A 9-dimethylaminomethylenepyridopyrimidinone derivative (10.0 mmol) and an amine (10.0 mmol) were stirred continuously in acetic acid (99.5%; 20 ml) for 24 h at room temperature, then diluted with chloroform (50 ml). The solution was neutralized with 20% Na$_2$CO$_3$, separated, and

the chloroform fraction dried (Na_2SO_4), evaporated to dryness, and the residue recrystallized.

Method C. A 9-dimethylaminomethylenepyridopyrimidinone derivative (10 mmol) and an amine (10 mmol) were stirred continuously in acetic acid (99.5%; 20 ml) for 24 h, then poured into water (80 ml). After filtering off the precipitated product, it was recrystallized.

Method D. A 9-formylpyridopyrimidinone derivative (10.0 mmol) and aniline (10.0 mmol) were stirred continuously in acetic acid (99.5%; 20 ml) for 24 h at room temperature. Work-up was the same as in method B.

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