Structural Studies on 9-Hydrazono-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines by ^{1}H, ^{13}C and ^{15}N NMR Spectroscopy†

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^{1}H, ^{13}C and ^{15}N NMR studies demonstrated that 9-hydrazono-6,7,8,9-tetrahydro-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidines exist as an equilibrium mixture of *Z*–*E* isomers in the hydrazono–imino tautomeric form having an exocyclic double bond. Proton-catalysed *Z*–*E* interconversion is fast. Substituent and solvent effects revealed that the decisive factors controlling the *Z*:*E* ratio are internal hydrogen bonding in the *Z*-isomer, stabilization by solvation and steric interaction.

INTRODUCTION

In recent papers we reported on tautomerism and isomerism in 9-carbamoyl-,[2,3] 9-aminomethylene-[4,5] and 9-formyl-tetrahydro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines.[6,7] In this paper we describe ^{1}H, ^{13}C and ^{15}N NMR studies of the 9-hydrazono derivatives **1–20**. Several members of this group exhibited considerable antiasthmatic–antiallergic effects.[8]

EXPERIMENTAL

Synthesis

The preparation of the compounds is shown in Scheme 1. The ester **1** was prepared by esterification of the acid **21**[9] in ethanolic hydrogen chloride and was then transformed into the 9-benzoylhydrazono derivative **3** with benzoyl chloride–triethylamine. The hydrazones **2** and **4–14** were prepared from compounds **22–25** by diazo coupling in water in the presence of sodium acetate. With the hydrazones **15–18**, diazo coupling of the 9-formyltetrahydropyrido[1,2-*a*]pyrimidines **26–29** (Japp–Klingemann reaction) gave better yields. In order to prepare the hydrazone **19**, compound **30** was brominated in acetic acid in the presence of sodium acetate and the tribromo product **31** was then reacted with phenylhydrazine in ethanol. Finally, **20** was obtained by condensing the hydrazide **32** with acetone.

The new compounds gave satisfactory elemental analyses.

Ethyl 9-hydrazono-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (1). A suspension of **21** (34.0 g, 0.14 mol) in ethanol (700 ml) was saturated at 10–15 °C with dry hydrogen chloride gas. After standing overnight in a refrigerator, the solvent was evaporated and the residue taken up in water (50 ml) and neutralized with 5% sodium carbonate. The product was extracted with chloroform (4× 100 ml), the extract dried over sodium sulphate, evaporated and the residue crystallized from methanol to give **1** (26.9 g, 73%), m.p. 206–208 °C.

Ethyl 9-benzoylhydrazono-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (3). **1** (2.0 g, 7.57 mmol), triethylamine (1.6 ml, 11.36 mmol) and benzoyl chloride (3.0 ml, 11.36 mmol) in dry chloroform (20 ml) were refluxed for 2 h. The cooled solution was shaken with water (20 ml), the aqueous phase separated and extracted with chloroform (10 ml) and the combined organic phases were dried over sodium sulphate and evaporated. The residue was crystallized from methanol to give **3** (1.5 g, 54%), m.p. 209–210 °C.

Hydrazones 2 and 4–14. To a mixture of the primary aromatic amine (10 mmol) and 1 : 1 hydrochloric acid–water (5 ml) a solution of sodium nitrite (0.7 g, 10 mmol) in water (5 ml) was added in portions with stirring below −10 °C. Thereafter sodium acetate (6 g) and, dropwise, a solution of the pyrido[1,2-*a*]pyrimidine components **22–25**[10,11] in water (5 ml) were added. Stirring at 0–5 °C was continued for 3 h, and the reaction mixture was left to stand overnight in a refrigerator. The product was filtered off and recrystallized to give **2** (64%), m.p. 137–138 °C; **4** (60%), m.p. 165–167 °C; **5** (62%), m.p. 108–110 °C; **6** (83%), m.p. 186–187 °C; **7** (56%), m.p. 147–149 °C; **8** (48%), m.p. 91–93 °C; **9** (56%), m.p. 174–175 °C; **10** (36%), m.p. 210–211 °C; **11** (59%), m.p. 185 °C; **12** (54%), m.p.

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† Nitrogen Bridgehead Compounds, Part 37. For Part 36, see Ref. 1.

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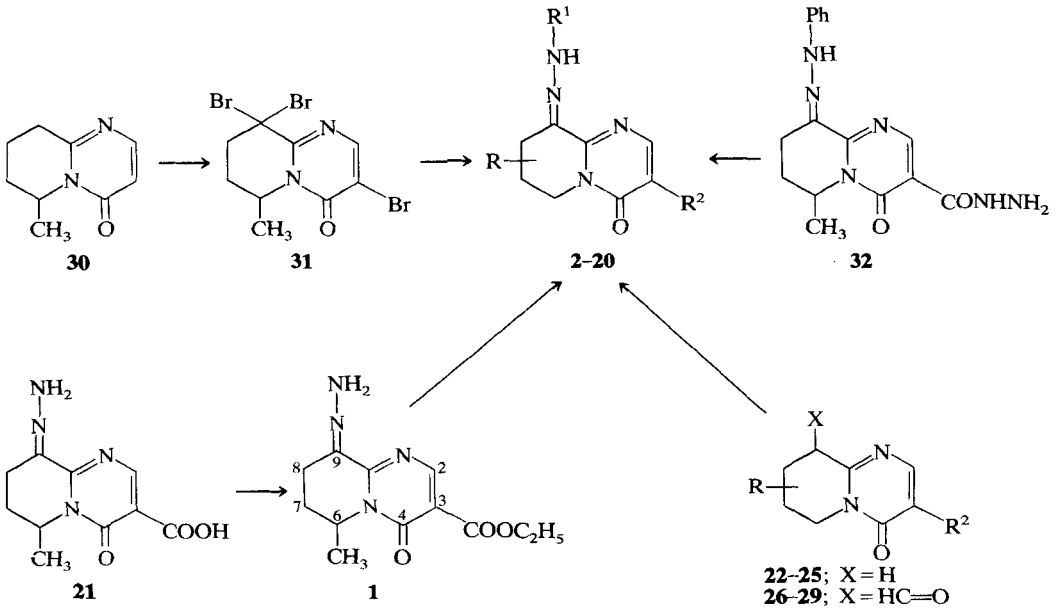


Scheme 1

147–148 °C; **13** (81%), m.p. 206–208 °C; and **14** (70%), m.p. 156–157 °C.

Hydrazones 15–18. The above procedure was used except that the formyl compounds **26–29**[11] were used as substrates. The products were **15** (90%), m.p. 165 °C; **16** (60%), m.p. 102 °C; **17** (84%), m.p. 146–148 °C; and **18** (96%), m.p. 163–165 °C.

6-Methyl-3,9,9-tribromo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (31). To a solution of **30**[6] (0.8 g, 5 mmol) and sodium acetate (2.2 g) in acetic acid (10 ml), bromine (1.0 ml, 18 mmol) was added dropwise with stirring at room temperature. Stirring was continued at 50–60 °C for 30 min, and the acetic acid was evaporated *in vacuo*. The residue was triturated with chloroform (10 ml). The crystals were filtered off, washed with chloroform, the filtrate evaporated and the residue crystallized from methanol to give **31** (1.5 g, 75%), m.p. 157–159 °C.

3-Bromo-9-phenylhydrazono-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (19). To a solution of **31** (4.0 g, 10 mmol) in dimethyl sulphoxide (10 ml), phenylhydrazine (2.8 ml, 30 mmol) was added and the solution was left to stand for 3 days. Addition of water (20 ml) precipitated the product, which was filtered off and triturated with methanol to give **19** (2.7 g, 72%), m.p. 190–192 °C (from methanol).

6-Methyl-9-phenylhydrazono-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-(*N'*-isopropylidene carbohydrazide) (20). **32** (0.5 g, 1.53 mmol) was refluxed with stirring for 3 h in acetone (20 ml). The product which separated on cooling was filtered off, washed with acetone and recrystallized from acetic acid to give **20** (0.5 g, 89%), m.p. 293–295 °C.

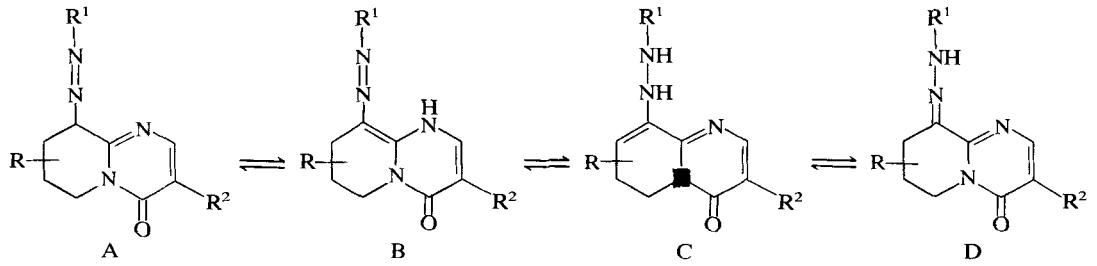
Spectroscopy

The ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded in the PFT mode (16K data points for the FID) at 99.6, 25.0 and 10.04 MHz, respectively, with internal deuterium lock at ambient temperature using a Jeol FX-100 multinuclear spectrometer. The ^{1}H and ^{13}C chemical shifts were determined on the δ scale using tetramethylsilane ($\delta_{TMS} = 0$ ppm) as internal standard. For the ^{13}C measurements a spectral width of 5000 Hz, a flip angle of 30° and a pulse delay of 1.6 s were used. The concentrations of the ^{1}H NMR samples were approximately 0.1 mol dm^{-3}, and of the ^{13}C and ^{15}N NMR samples 0.5–1.0 mol dm^{-3}.

The ^{15}N chemical shifts were determined relative to the signal of external $K^{15}NO_3$ ($\delta = -3.55$ ppm) and then converted to external neat nitromethane ($\delta_{CH_3NO_2} = 0$ ppm). Chemical shifts upfield from the reference are negative. The reproducibility of the ^{13}C and ^{15}N chemical shift data is better than 0.1 ppm. Typical acquisition parameters for the determination of the ^{15}N spectra included a spectral width of 5000 Hz, a flip angle of 30° and pulse delays of up to 5 s. Samples were run in 10 mm o.d. tubes in $CDCl_3$. $^{1}J(^{15}NH)$ coupling constants were determined using an adaptation of the INEPT method for the FX-100 instrument.[12,13] The $Z:E$ ratios were obtained by integration of the ^{1}H NMR spectrum, and from the peak heights of the corresponding signal in the ^{13}C NMR spectrum, by averaging the values of 5–8 signals. The maximum deviation was ±2%.

RESULTS AND DISCUSSION

9-Hydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines are potentially tautomeric systems which can



Scheme 2

be characterized as shown in Scheme 2. Tautomers A, B and D may also give rise to *Z*–*E* stereoisomerism. Isomerism and tautomerism of the hydrazones **1–20** could be elucidated by information provided by the ^{1}H, ^{13}C and ^{15}N NMR spectra of these compounds.

^{1}H and ^{13}C NMR

Tautomerism. Characteristic ^{1}H and ^{13}C NMR data are compiled in Tables 1 and 2. The decision between alternative structures was allowed from the following arguments. The total intensity in the alicyclic region indicated six protons in **6** and five in compounds **1–5** and **7–20**. This excluded structures A and C. Tautomer B could also be excluded since (a) in the ^{1}H NMR spectrum of compounds **2** and **4–20** the characteristic shielding of the diazo group affecting the *ortho*- and *para*-protons of the attached aryl group[14] was absent and (b) in **1–20** H-2 gave a singlet, (except for **18**), whereas in the 1,6,7,8-tetrahydropyrimidine B it would have shown coupling with the adjacent NH and

Table 1. Characteristic ^{1}H NMR data and equilibrium *Z*:*E* isomeric ratios of compounds 1–20 at 25 °C[a]

	R	R^1	R^2	H-2	H-6	Me(R)	NH	$CDCl_3$ *Z*(%)	$CDCl_3$ *E*(%)	DMSO-d_6 *Z*(%)	DMSO-d_6 *E*(%)
1*Z*	6-Me	H	CO_2Et	8.60s	5.10m	1.36d	6.83	19	81	8	92
1*E*	6-Me	H	CO_2Et	8.65s	5.36m	1.35d	6.83				
2*Z*	6-Me	Ph	CO_2Et	8.62s	5.10m	1.39d	14.16	80	20	17	83
2*E*	6-Me	Ph	CO_2Et	8.74s	5.34m	1.34d	9.07				
3*Z*	6-Me	COPh	CO_2Et	8.72s	5.15m	1.46d	15.32	100	0	100	0
4*Z*	7-Me	Ph	CO_2Et	8.70s	ax.3.28 eq.4.38	1.17d	14.09	95	5	17	83
4*E*	7-Me	Ph	CO_2Et	8.80s	[b]	[b]	[b]				
5*Z*	8-Me	Ph	CO_2Et	8.68s	ax.3.80 eq.4.22	1.35d	14.12	100	0	75	25
6*Z*	H	Ph	CO_2Et	8.62s	3.99t	—	13.96	93	7	18	82
6*E*	H	Ph	CO_2Et	8.70s	[b]	[b]	8.38				
7*Z*	6-Me	*p*-Me-Ph	CO_2Et	8.69s	5.10m	1.38d	14.24	87	13	11	89
7*E*	6-Me	*p*-Me-Ph	CO_2Et	8.77s	5.30m	[b]	8.30				
8*Z*	6-Me	*p*-OEt-Ph	CO_2Et	8.66s	5.12m	1.40d	14.28	84	16	11	89
8*E*	6-Me	*p*-OEt-Ph	CO_2Et	8.72s	5.35m	[b]	8.65				
9*Z*	6-Me	*p*-Cl-Ph	CO_2Et	8.64s	5.13m	1.41d	14.18	88	12	12	88
9*E*	6-Me	*p*-Cl-Ph	CO_2Et	8.72s	5.35m	[b]	8.67				
10*Z*	6-Me	*p*-NO_2Ph	CO_2Et	8.68d	5.16m	1.46d	14.42	100	0	16	90
11*Z*	6-Me	*o*-Me-Ph	CO_2Et	8.69s	5.15m	1.43d	14.36	100	0	76	24
12*Z*	6-Me	*o*-OMe-Ph	CO_2Et	8.71s	5.12m	1.39d	14.28	87	13	69	31
12*E*	6-Me	*o*-OMe-Ph	CO_2Et	8.78s	5.39m	[b]	8.57				
13*Z*	6-Me	*o*-OH-Ph	CO_2Et	8.65s	5.10m	1.38d	14.34	80	20	46	54
13*E*	6-Me	*o*-OH-Ph	CO_2Et	8.68s	5.30m	[b]	8.75				
14*Z*	6-Me	*o*-MeO_2C-Ph	CO_2Et	8.91s	5.15m	1.44d	15.36	42	58	44	56
14*E*	6-Me	*o*-MeO_2C-Ph	CO_2Et	8.80s	5.40m	1.35d	11.74				
15*Z*	6-Me	Ph	Me	7.81s	5.03m	1.35d	14.08	85	15	40	60
15*E*	6-Me	Ph	Me	7.86s	5.10m	1.25d	8.50				
16*Z*	6-Me	Ph	$(CH_2)_2CO_2Et$	7.89s	5.02m	1.36d	14.10	90	10	30	70
16*E*	6-Me	Ph	$(CH_2)_2CO_2Et$	7.95s	[b]	[b]	7.75				
17*Z*	6-Me	Ph	Ph	8.10s	5.10m	1.40d	14.18	94	6	20	80
17*E*	6-Me	Ph	Ph	8.18s	[b]	1.26d	[b]				
18*Z*	6-Me	Ph	H	7.81d	5.02m	1.37d	14.15	95	5	25	75
18*E*	6-Me	Ph	H	7.91d	5.28m	1.27d	8.33				
19*Z*	6-Me	Ph	Br	8.24s	5.07m	1.36d	13.80	87	13	18	82
19*E*	6-Me	Ph	Br	8.30s	5.25m	1.31d	[b]				
20*Z*	6-Me	Ph	$CONHNCMe_2$	9.11s	5.11m	1.40d	14.30	92	8	25	75
20*E*	6-Me	Ph	$CONHNCMe_2$	8.95s	[b]	1.29d	[b]				

[a] Couplings (Hz): **4***Z*, *J*(6a7a) = 9.6, *J*(7a8a) = 10.5; **5***Z*, *J*(7a8a) = 8.5, *J*(7e8a) = 4.2.
[b] Could not be assigned because of low intensity or overlap.

Table 2. ^{13}C chemical shifts of compounds 1–6, 11–15 and 18 (solvent: $CDCl_3$; for 5, DMSO-d_6)

C	1Z	1E	2Z	2E	3Z	4Z	4E	5Z	5E	6Z	6E	11Z	12Z	12E	13Z	13E	14Z	14E	15Z	15E	18Z	18E
2	155.8	158.4	155.4	158.5	154.2	155.3	157.0	155.0	155.9	155.3	158.3[b]	155.3	155.6	158.6	155.4	157.3	155.7	158.3	146.8	149.4	149.8	152.9
3	[a]	113.0	113.4	[a]	116.6	113.6	[a]	112.9	[a]	113.4	112.4	113.7	113.5	[a]	113.8	112.3	113.1	111.7	122.5[b]	[a]	112.9	112.1
4	[a]	155.8	157.3	[a]	156.6	157.8	[a]	156.9	[a]	157.9	158.4[b]	157.3	157.4	157.7	158.6	157.9	157.4	157.0	161.3	160.7	160.5	[a]
6	47.2	45.6	47.1	45.4	48.2	49.0	46.2	41.1	40.2	43.1	40.4	47.3	47.2	45.5	47.2	45.6	47.2	45.6	46.9	45.9	46.8	45.0
7	26.4	24.5	26.2	24.7	26.3[b]	26.8	26.2	27.8	25.7[b]	20.8	19.8	26.3	26.3	24.7	26.1	24.6	26.3	24.6	26.6	24.2	26.4	24.7
8	25.2	17.5	24.7	17.6	26.0[b2]	38.2	30.7	33.2	25.0[b]	30.3	22.8	25.2[b]	25.3	18.4	25.0	17.4[b]	25.5	17.1	25.5	18.9	25.5	19.1
9	[a]	133.7	121.8	131.2	132.7	122.7	130.5	127.4	134.7	122.7	132.1	122.6	122.6	132.4[b]	120.3	128.9	125.0	134.6	122.9[b]	130.4	122.4	131.7
10	[a]	155.8	153.3	[a]	153.1	153.6	[a]	152.4	[a]	153.8	156.7	153.5	153.3	155.9	153.4	155.4	152.3	155.7	149.5	151.3	151.4	[a]
1′	—	—	143.0	[a]	132.8	143.1	142.8	143.3	[a]	143.0	[a]	141.5	132.9	132.2[b]	128.3	128.3	145.4	145.6	143.7	143.1	143.5	[a]
2′	—	—	114.3	114.8	128.8	114.1	114.8	113.7	114.4	114.1	114.7	122.5	147.2	146.5	146.9	146.3	114.0	113.1	113.7	114.6	113.9	114.4
3′	—	—	129.2	129.2	127.7	129.3	129.3	129.2	128.9	129.3	129.3	130.6	110.9	110.7	117.6	119.9	114.2	114.8	129.2	128.1	129.2	129.2
4′	—	—	122.8	122.8	132.5	122.7	123.9	121.9	121.9	122.7	123.0	123.0	122.6	122.6	123.9	123.7	130.8	131.0	121.6	121.1	122.0	122.0
5′	—	—	—	—	—	—	—	—	—	—	—	126.7	121.6	121.6	120.1	117.6	134.0	134.9	—	—	—	—
6′	—	—	—	—	—	—	—	—	—	—	—	112.8	113.1	114.5	115.9	115.5	114.2	113.1	—	—	—	—
Me	18.1	17.2	18.1	17.0	18.0	18.1	18.1	18.5	18.5	—	—	18.1	18.1	17.1	18.1	17.5[b]	19.4	18.0	18.1	17.0	18.1	17.1
CO_2	[a]	164.2	163.6	[a]	164.1	163.5	[a]	162.9	163.7	163.5	164.2	163.9	164.0	164.3	163.,7	164.3	163.8	164.0	—	—	—	—
CH_2	61.1	61.1	61.1	60.9	61.1	61.1	61.1	60.3	60.1	61.1	60.9	61.2	61.0	61.0	61.4	61.1	61.1	60.9	—	—	—	—
CH_3	14.3	14.3	14.3	14.3	14.3	14.3	14.3	14.0	14.0	14.3	14.3	14.3	14.4	14.4	14.3	14.3	14.3	14.3	—	—	—	—
					CO							o-Me	o-OMe				o-CO_2Me		3-Me			
					162.9							17.2	56.0	56.0			166.8	168.8	13.3	13.3		
																	51.9	52.3				

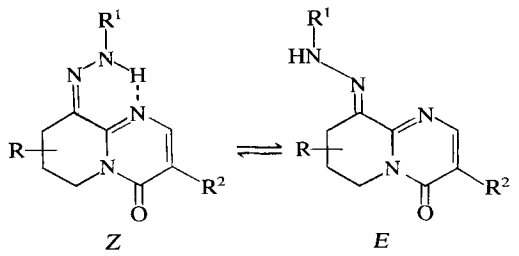
[a] Could not be assigned because of low intensity or overlap.
[b] Tentative assignment.

also would have appeared at higher field (cf. the 9-formyl[6,7] and 9-carbamoyl[3] derivatives). All these facts suggested that, as with the 9-arylaminomethylene derivatives,[4,5] the tautomeric equilibrium was shifted very much in favour of form D.

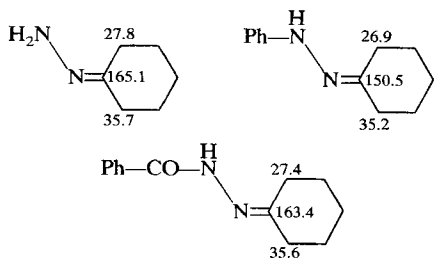
^{13}C NMR data allowed the same conclusion. C-6, C-7 and C-8 were found to be sp^3-bonded, while C-9 and C-10 were sp^2-bonded. This also excluded tautomers A and C, while tautomer B could be discarded because the characteristic deshielding effect of the diazo group[15] could not be observed at the *ortho*- and *para*-carbons. Comparing the chemical shifts of C-2,3,4,9 and 10 in 1,6,7,8-[2,6,7,16] and 6,7,8,9-tetrahydropyridopyrimidines,[2–5,16] a significant increase in the chemical shifts in the latter group could be observed. The ^{13}C shifts in the 9-hydrazonopyridopyrimidines showed good correlation with the shifts observed for the 6,7,8,9-tetrahydropyridopyrimidines, which was also indicative of the predominance of tautomer D.

Z–E Isomerism. Duplication of certain signals in both the ^1H and ^{13}C spectra of compounds **1–20** suggested the coexistence of *Z*- and *E*-isomers (Scheme 3). Although sterically hindered, the *Z*-isomer is capable of forming a strong internal hydrogen bond which may offset steric interaction. It was observed that in hydrazones the proton in the *Z* disposition to the tricoordinated nitrogen absorbed at lower field than that in the *E* orientation.[17] In cyclohexanone hydrazones the signal of the equatorial proton of the methylene group in the *Z* orientation to the sp^3 nitrogen was shifted upfield, whereas that of its axial partner was shifted downfield, resulting in a shift difference of 0.7–0.9 ppm.[18] No such spreading of the signals was observed in our compounds, and the 8-methylene protons gave strongly coupled signals, not more than 0.5 ppm apart, in both stereoisomers. Configurational assignment was therefore based on the assumption that, owing to the coplanarity of the N=C-10—C-9=N—NH grouping, a strong internal hydrogen bridge was formed in the *Z*-form which may shift the NH signal to values exceeding 14 ppm. On the other hand, this phenomenon could not be expected for the *E*-isomer, resulting in NH shifts in the range 7.75–9.05 ppm. In most of the compounds H-2 and H-6 were more shielded in the *Z*- than in the *E*-isomers, whereas 6-Me was more shielded in the *E*-isomers.

With compound **1**, which gave only a single two-proton NH signal at 6.83 ppm, ^{13}C shifts had to be invoked for configurational assignment. Differences in the shifts of the γ-carbons in stereoisomeric hydrazones provides a convenient means for the assignment of isomers.[19,20] Owing to steric interaction, the α-carbon signals in the (Z)-*N*,*N*-dimethylhydrazones of cyclohexanones are shifted upfield by 7–8 ppm.[21] Since in our compounds a hydrogen atom was attached to the tricoordinated nitrogen, the ^{13}C shifts of the hydrazone, the *N*-phenylhydrazone and the *N*-benzoylhydrazone of cyclohexanone were recorded as references (Scheme 4). It seems that mono- and disubstitution of the amino group (δ-effect) does not



Scheme 3



Scheme 4

impair appreciably the validity of the above method of assignment. The upfield shift of the C-8 signal of (*E*)-9-hydrazonotetrahydropyridopyrimidines permitted the distinction of *Z*- and *E*-isomers. The shift difference for the C-9 signal was also characteristic: the signal for the *Z*-isomer appeared at higher field. A similar phenomenon was observed with the analogous 9-phenylaminomethylenepyridopyrimidines.[4] This upfield shift of approximately 10 ppm in the *Z*-isomer is a consequence of the fixation of the molecule in a quasi-planar arrangement by the internal hydrogen bridge. In this conformation the non-bonding pair of the amino nitrogen becomes strongly conjugated with the N=C-9 double bond and, thereby, with the highly delocalized electrons of the pyrimidinone ring. Accordingly, replacement of phenyl by benzoyl, as in **2** and **3**, as well as with cyclohexanone *N*-phenyl- and *N*-benzoyl-hydrazone, resulted in a downfield shift of 10.9 and 12.9 ppm, respectively. The non-bonding pair in this case becomes involved in delocalization within the amide group itself, thereby cancelling conjugation with the N=C-9 group.

Differences in the shielding of C-2 can be traced to differences in conjugation in the *Z*- and *E*-isomers. Similarly to the 9-arylaminomethylene derivatives,[4] the shifts of C-6 and C-7 were smaller in the *E*-isomers.

Conformation and factors influencing the *Z*:*E* ratio. The equilibrium *Z*:*E* ratios for compounds **1–20** were determined in $CDCl_3$ and DMSO-d_6 and are shown in Table 1. In chloroform the *Z*-isomer, stabilized by internal hydrogen bonding, predominated whereas in DMSO-d_6, which can itself form strong hydrogen bonds with solutes, the equilibrium was shifted in favour of the sterically unhindered *E*-isomer. *Z*:*E* ratios measured immediately after dissolution did not change (except for **15** and **18**) after several days, i.e. they represented equilibrium values. Thus, *Z*–*E* interconversion was very fast under the given conditions. Several mechanisms can be envisaged for the *Z*–*E* isomerization of hydrazones, e.g. rotation around the C=N bond, a so-called lateral shift, an =N— type nitrogen inversion via an sp-hybridized nitrogen, a combination of the two and, finally, that involving tautomerization.[22–25] In our opinion the latter mechanism may be operative, since with compounds **15** and **18**, lacking an electron-attracting substituent at C-3, as well as with the analogous pyrrolopyrimidine phenylhydrazones,[1] isomerization was catalysed even by water. Only under very rigorous experimental conditions, excluding the presence of even catalytic amounts of H^+ ions, is it possible to suppress isomerization by tautomerization.

In order to verify that the *Z*:*E* ratio was primarily determined by steric factors and solvent effects, the position of the methyl group was varied. With methyl groups attached to C-6 or C-7 the *Z*:*E* ratio was as described above. In the case of a methyl group at C-8, however, the *E*-isomer also became sterically hindered and, therefore, a predominance of the *Z*-isomer could be expected, even in dimethyl sulphoxide. In fact, the proportion of the latter increased to 75% in **5**.

Table 3. SCS values (ppm) of the Me substituent[a]

Compound	α	β	γ
2*Z* (6-Me)	4.0	5.4	−5.6
4*Z* (7-Me)	6.0	5.9 (at C-6); 7.9 (at C-8)	
5*Z* (8-Me)	3.7	7.0	−1.8

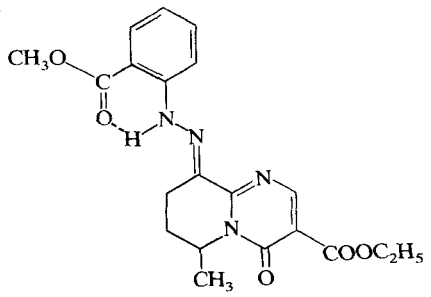
[a] Positive values correspond to downfield SCS (substituent chemical shifts) and negative to upfield SCS; solvent: $CDCl_3$. For comparison, the chemical shift values measured for **6** were used as a reference.

In our studies on 6-methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-ones[16] and some of its 9-halogeno derivatives,[26] we have demonstrated that of the two possible half-chair conformations of the tetrahydropyrido ring the favoured one was that in which the 6-Me group was in a quasi-axial orientation. This situation was unchanged when the C-9 atom became sp^2-hybridized.[4,7] The quasi-axial disposition of the 6-Me group was apparent from the multiplicity of H-6 observed after decoupling the 6-Me signal. Since in compound **4** *J*(6a7a) was found to be 9.0 Hz, the 7-Me group was quasi-equatorial. As indicated by the coupling constants of H-8 (8.5 and 4.2 Hz) in the case of the 8-Me compound **5**, the equilibrium was also shifted in favour of the conformer with a quasi-equatorial methyl group. Interestingly, in the 9-arylaminomethylene derivative the quasi-axial disposition was favoured for the 8-Me group.[4] As compared with and *exo*-=CH— group, steric interaction of =N— and a quasi-equatorial methyl group is smaller. The orientation of the 6-, 7- and 8-Me groups in the dominant conformer was also reflected by the SCS values summarized in Table 3. Since the usual γ-SCS value for a quasi-axial 6-Me group is −5.6 ppm, and only −1.8 ppm was observed for the 8-Me group, the predominance of the conformer with a quasi-equatorial 8-Me group found further support.

The influence of R^2 on the *Z*:*E* ratio was relatively slight. A higher electronegativity of R^2 slightly decreased the percentage of the *Z*-isomer by reducing the basicity of N-1 and, thereby, the stability of the hydrogen bridge.

The nature of R^1 exerted a characteristic effect on the internal hydrogen bridge and, thus, also on the *Z*:*E* ratio. In compound **1** (R^1 = H) the amino nitrogen is pyramidal and its tendency for hydrogen bonding is weak. As a consequence, the *E*-isomer was preponderant both in dimethyl sulphoxide and chloroform. In the *N*-arylhydrazono derivatives studied the non-bonding electron pair of the amino-nitrogen was highly conjugated, involving a quasi-planar disposition of bonds which favoured the formation of strong internal hydrogen bridges. In the *N*-benzoylhydrazono compound **3**, owing to electron attraction by the benzoyl group and amide mesomerism, the positive polarization and hydrogen bond-forming ability of the NH group was further increased. This resulted in the exclusive presence of the *Z*-isomer in both chloroform and dimethyl sulphoxide.

The role of *para*-substitution at the *N*-phenyl group on the *Z*:*E* ratio was unimportant. A nitro group,



14*E*

Scheme 5

such as in **10**, further enhancing the positive polarization of NH, resulted in the exclusive presence of the *Z*-isomer in chloroform. *ortho*-Substitution was more effective. On *ortho*-carbomethoxy substitution, e.g. **14**, an internal hydrogen bridge was established between NH and the ester carbonyl in both solvents. This was indicated by the shift of the NH signal of the *E*-isomer in $CDCl_3$ (11.74 ppm), being approximately 2.5 ppm higher than in other models. The high percentage of the *E*-isomer in chloroform can be explained when the stabilization of this isomer by an internal hydrogen bridge is also considered (Scheme 5). The very high percentage, in dimethyl sulphoxide, of the *Z*-isomer in the *ortho*-substituted derivatives **11–14** is remarkable. This can be rationalized by a steric shielding effect of the *ortho*-substituent, which interferes with solvation of the NH group, leading to the cleavage of the NH · · · N-1 hydrogen bond.

Temperature-dependent ^1H NMR spectra recorded in tetrachloroethylene provided an interesting possibility for the comparison of hydrogen bonding in the *Z*-isomer in 9-arylhydrazono- and 9-arylaminomethylenepyridopyrimidines.[4] Whereas in the latter type hydrogen bridges were disrupted at 120 °C, shifting the equilibrium totally towards the *E*-isomer, with the 9-hydrazono compound the *Z*-isomer still dominated at the same temperature. These factors show that NH · · · N-1 bonds are stronger in the hydrazones, which was not unexpected on considering the differences in electronegativity of =N— and =C— attached to the amino nitrogen.

^{15}N NMR

^{15}N NMR spectroscopy is a valuable tool in the qualitative and, occasionally, also in the quantitative study of tautomerism in nitrogen-containing compounds.[27–29] The data in Table 4 provide additional proof for the dominant nature of the hydrazono–imino tautomer D.

It has been shown that for azo-hydrazo tautomeric equilibria, owing to fast interconversion ^{15}N chemical shifts and ^1J (^{15}NH) values are weighted averages and are, therefore, informative for the state of tautomeric equilibria.[30–32] This method is sensitive, since chemical shift differences for hydrazono[33,34] and azo nitrogens[32,35] are over 300 ppm. ^{15}N shifts in the studied compounds were between −212.8 and −227.1 ppm, which suggested that participation of the azo-type tautomers A and B, even to a small extent, was improbable. Tautomer C could also be excluded, since this would have involved the presence of two NH signals in the high-field region of the spectrum.[36]

For compounds **14** and **18** $^1J(^{15}NH)$ values were also determined (**14**, 97.0 and 96.4 Hz; **18**, 94.0 Hz). The high values, and their close agreement with those measured for other hydrazones,[37–40] also supported the almost exclusive presence of the hydrazono–imino tautomer D in chloroform. In a study of the imino–enamino tautomerism of pyrido[1,2-*a*]pyrimidines, we have shown that in the enamine form both N-1 and N-5 are much more deshielded than in the imine form; the chemical shift differences for N-1 may even exceed 100 ppm.[3,5,7] Hence these signals are also sensitive monitors for tautomeric equilibria.

^{15}N NMR is also suitable for the detection and identification of *Z*–*E* isomers. In accordance with the presence of an internal hydrogen bridge in the *Z*-isomer, the NH signals are shifted significantly downfield relative to those for the *E*-isomer (by 12.9 and 14.2 ppm for **2** and **4**, respectively). An effect of similar magnitude was also experienced with the corresponding arylaminomethylenepyridopyrimidines.[5] The small downfield shift found for the N-1 signal in the *Z*-isomer was also paralleled in this class of compounds. Differences in conjugation in the *Z*- and *E*-isomers may be the reason for approximately 4 ppm upfield and 7.9 ppm downfield shifts for the N-5 and =N— signals, respectively, in the *Z*-isomers.

With $R^2 = CO_2Et$, owing to electron attraction, a significant downfield shift of the signals of the remote nitrogen atoms of the hydrazono group could be observed, reflecting extensive delocalization in these molecules. The effect of *ortho*-CO_2Me substitution at the phenyl ring on hydrogen bonding was demonstrated by the upfield shift of the =N— signals and the downfield shift of the N-1 signal. Taking the N-1 and

Table 4. ^{15}N chemical shifts, $\delta_{CH_3NO_2} = 0$ ppm (solvent $CDCl_3$)

	2Z	2E	4Z	5Z	14Z	14E	18Z
NH	−212.8	−225.7	−214.6	−215.0	−212.9	−227.1[c]	−218.3[d]
N=	−28.0	[a]	−30.5	−29.6	−33.3	−41.2	−35.2[e]
N-1	−154.9	[a]	−155.7	−155.3	−149.0	−151.6	−150.1
N-5	−194.7	−190.4	−206.8	−206.0	−193.3	−189.0	−196.0

[a] Could not be measured because of low intensity or overlap.
[b] $^1J(NH) = 97.0$
[c] $^1J(NH) = 96.4$.
[d] $^1J(NH) = 94.0$.
[e] Measured after adding 70 mg of $Cr(AcAc)_3$. Chemical shift deviations: at NH, 0.0; at N-1, 1.0; at N-5, 0.2 ppm.

N-5 shifts of ethyl 4-oxo-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (−144.9 and −183.5 ppm)[3] as a reference, it can be seen that increased conjugation caused by introducing an *exo*-C-9=N—NH— group resulted in an approximately 10 ppm upfield shift of the N-1 and N-5 signals. A comparison of 9-arylaminomethylene-[5] and 9-hydrazono-pyridopyrimidines revealed that, in accordance with the higher electronegativity of nitrogen, the replacement of =CH— by =N— was also associated with a downfield shift of 4–6 ppm of the N-1 and N-5 signals.

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Received 25 February 1983; accepted (revised) 30 April 1983