Nitrogen Bridgehead Compounds. Part 46.[1] Synthesis and Stereochemistry of 9-Formyl-6,7,8,9-tetrahydro-2-oxo-2*H*- and 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and their Homologues

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The structures of the title compounds, bearing five-, six-, seven-, or eight-membered rings, have been investigated by u.v. and ^{1}H n.m.r. spectroscopy. In the 4-oxo derivatives the enol–enamine–imine tautomerism depends greatly on the ring size, whereas in the 2-oxo series the enamine tautomer always predominates, independently of the ring size. In the 4-oxo series the five-membered homologues are mainly in the enol form, and the six-membered ones in the enamine form. The seven-membered derivative (**21**) exists as a mixture of the enamine and imine tautomers. In the eight-membered homologue (**22**) the imine form is preferred. The enol tautomer of the five-membered 4-oxo derivatives has the *Z*-configuration in chloroform, and the *E*-configuration in dioxane, whereas in ethanol and dimethyl sulphoxide *E–Z* isomeric mixtures are present, with concentration-dependent isomer ratios.

Recently a structural study[2] on tricyclic formyl derivatives (**1**; n = 0—2) has revealed a dependence of tautomerism on ring size. Since the correlation of the ring size (n) and the tautomeric equilibrium shown in Scheme 1 had not been known earlier, it was of interest to study in more detail the effect of the ring size on the tautomeric equilibrium, using as models the isomeric 4-oxo (**17**)—(**22**) and 2-oxo (**24**)—(**27**) nitrogen bridgehead derivatives, where the ring size of rings A varies from five to eight (n = 0—3).

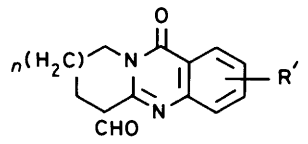
Investigations[3,4] on the six-membered 4-oxo homologues (**19**) and (**20**) have shown that, of the three possible tautomeric forms (see Scheme 1), the enamine form predominates.

Syntheses.—The formyl group was introduced into the nitrogen bridgehead compounds (**2**)—(**11**)[5] by Vilsmeier–Haack formylation using $POCl_3$–DMF [Method A(1)], in some cases in 1,2-dichloroethane [Method A(2)]. With the 4-oxo- (**4**) and (**5**) and 2-oxo-pyridopyrimidines (**9**) formylation took place at room temperature, while with the further homologues (**2**), (**3**), (**6**)—(**8**), (**10**), and (**11**) containing a less reactive methylene group, the reaction required the higher temperatures specified in Table 1.

In some cases the *NN*-dimethylaminomethylene intermediates (**12**)—(**16**) and (**23**) could be isolated. For the remaining compounds hydrolysis took place during work-up and the formyl derivatives (**22**) and (**25**)—(**27**) were obtained directly (Scheme 2). Acidic hydrolysis of the dimethylaminomethylene derivatives (**12**)—(**16**) and (**23**) led also the formyl compounds (**17**)—(**21**) and (**24**) (Method B).

Certain fixed tautomers were also prepared (*cf.* Scheme 3). The alkoxymethylene derivatives (**28**)—(**30**) were obtained by treating the dimethylaminomethylene derivatives (**12**) and (**15**) with alcoholic hydrogen chloride (Method C).

The methoxymethylene compounds (**31**) and (**32**) were prepared by reacting the formyl compounds (**20**) and (**21**) with diazomethane (Method D). The *O*-methyl derivative (**31**) was accompanied by the *N*(1)-methyl derivative (**34**). The latter could be obtained in good yield by formylating the quaternary salt[6] (**33**) using Method A(1).



(**1**)

U.v. Studies.—U.v. spectral data on compounds (**12**)—(**16**), (**23**), and (**28**)—(**32**) in ethanol are compiled in Supplementary Publication No. SUP 56353 (7 pp.),† and those for the formyl derivatives in Table 2.

Whereas the shapes of the u.v. curves of the homologues (**12**)—(**16**) and (**28**)—(**32**), respectively, and also those of the 2-oxo-formyl derivatives (**24**)—(**27**) were independent of the ring size, the spectra of the homologous 4-oxo compounds (**17**)—(**22**) were highly dependent on it.

In the 2-oxo compound containing a five-membered ring, (**23**), the presence of the dimethylaminomethylene group resulted in a bathochromic shift of 74 nm of the longest wavelength u.v. maximum compared with the parent compound (**8**).[5] From the bathochromic shift of 75 ± 6 nm of the highest wavelength band of the 2-oxo-formyl derivatives (**24**)—(**27**) compared with the respective maximum at 290 ± 6 nm for the parent compounds (**8**)—(**11**),[5] a preponderance of the imine tautomer containing a non-conjugated formyl group can be excluded. As evidenced by ^{1}H n.m.r. (see below), the enamine tautomer featuring a conjugated formyl group can be suggested as the predominant form of compounds (**24**)—(**27**).

For the 4-oxo isomers the introduction of a dimethylaminomethylene group caused a bathochromic shift of almost 100 nm in the corresponding band of the parent 4-oxo compounds (**2**)—(**7**) (298 ± 6 nm) being taken as reference.[5]

The dependence of the u.v. spectra of the homologous 4-oxo-formyl compounds (**17**)—(**22**) on the ring size indicated that the positions of the tautomeric equilibria shown in Scheme 1 are strongly influenced by the ring size (n).

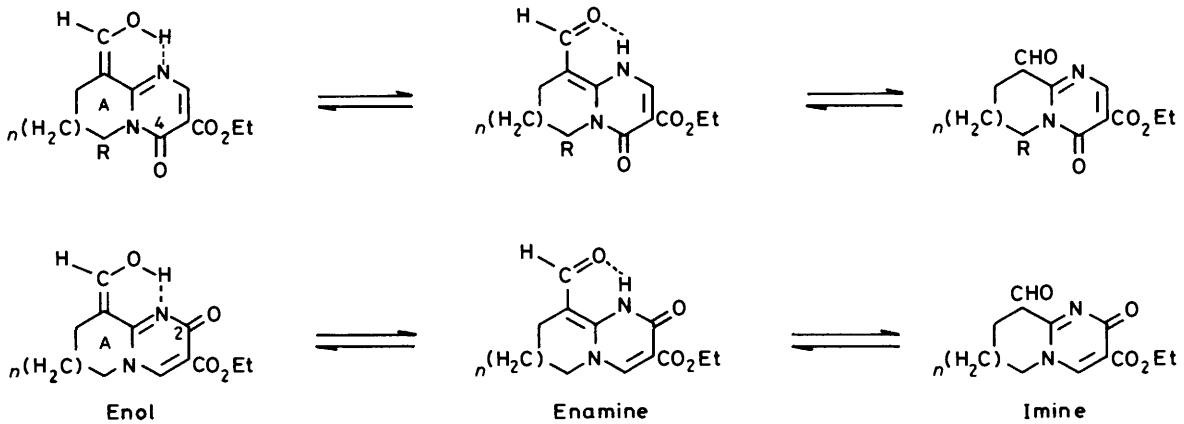
The solvent dependence of the u.v. spectra was most pronounced for the five-membered 4-oxo compounds (**17**) and (**18**) (SUP 56353). Compared with the highest wavelength maximum for (**2**) and (**3**), a bathochromic shift of 85 and 82 nm, respectively, resulted in ethanol. At the same time, in contrast to other 4-oxo-formyl derivatives, a maximum could be observed at

† For details of Supplementary Publications see Instructions for Authors in *J. Chem. Soc., Perkin Trans. 2*, 1985, Issue 1.

Table 1. Products from Vilsmeier–Haack formylation of 4-oxo-4*H*- and 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and their homologues and subsequent reactions

Starting compound	Product	R	R^1	*n*	Method	Reaction temp. (°C)	Reaction (h)	Yield %	Recryst. solvent	M.p. (°C)	Ref.
(2)	(12)	H		0	A2	60	3	75	EtOAc	183	
(3)	(13)	Me		0	A2	60	3	88	EtOAc	145	
(4)	(14)	H		1	A1	25	2	65	EtOH	151—152	3
(5)	(15)	Me		1	A1	25	2	76	EtOH	136—137	3
(6)	(16)	H		2	A2	85	2	42	EtOAc	138	
(7)	(22)	H		3	A1	100	2	68	EtOAc	144	
(12)	(17)	H		0	B	25	1	83	EtOH	223	
						60	1				
(13)	(18)	Me		0	B	25	2	88	EtOH	200	
(14)	(19)	H		1	B	25	2	83	EtOH	160—161	3
						50	1				
(15)	(20)	Me		1	B	25	2	83	EtOH	135—136	3
						50	1				
(16)	(21)	H		2	B	25	2	82.5	EtOAc	82	
(12)	(28)[a]	H	Et	0	C	80	0.5	64	EtOH	170—171	
(15)	(29)[b]	Me	Me	1	C	65	1	53	EtOAc	155	
(15)	(30)[a]	Me	Et	1	C	80	0.5	62	EtOH	114—116	3
(20)	(31)[a]	Me	Me	1				54	EtOH	126—127	
	and				D	−10	1				
	(34)	Me	Me	1				4[c]	EtOH	132—133	
(21)	(32)[a]	H	Me	2	D	0	2	39		106—108	
(33)	(34)				A1	60	2	62	EtOH	134—135	
(8)	(23)	H		0	A1	25	2	76	H_2O	249—250	
(23)	(24)	H		0	B	25	1	76	MeCN[d]	262	
						60	1				
(9)	(25)	H		1	A1	25	2	56	EtOAc	206—207	
(10)	(26)	H		2	A2	85	1.5	49	EtOH	185	
(11)	(27)	H		3	A2	85	2	35[c]	EtOAc	158	

[a] R^2 = Et. [b] R^2 = Me. [c] Isolated with the application of preparative t.l.c. (DC Kieselgel 60F-254; eluant benzene–methanol 4:1). [d] Refluxed in the solvent given.



Scheme 1.

335 and 336 nm, respectively. In ethanol and dimethyl sulphoxide the u.v. spectra of the 4-oxo compounds (**17**) and (**18**) were significantly dependently on concentration (Table 3 and SUP 56353). At higher dilution (concentrations $< 5 \times 10^{-5}$M) the maximum at 377 nm is the more intense, while at higher concentrations ($< 10^{-4}$M) that at 336 nm is the stronger. The position of the latter peak coincides with the highest wavelength maximum (336 nm) for the ethoxymethylene derivative (**28**), which the ^{1}H n.m.r. results (see later) show to have the *E*-configuration. Thus, we may conclude that in dioxane, and at higher concentration in ethanol, the homologues (**17**) and (**18**) are both present as the *E*-isomer of the enol tautomer. The maximum at 377 nm in chloroform, dimethyl sulphoxide, or dilute ethanolic solution cannot be assigned to the enamine tautomer containing a conjugated formyl group, for in the presence of this functionality only a bathochromic shift by 60 nm of the highest wavelength maximum, compared with parent compounds (**2**) and (**3**) (293 and 295 nm, respectively), should have occurred [*cf.* the u.v. spectra of the homologous 4-oxo-formyl compounds (**19**)—

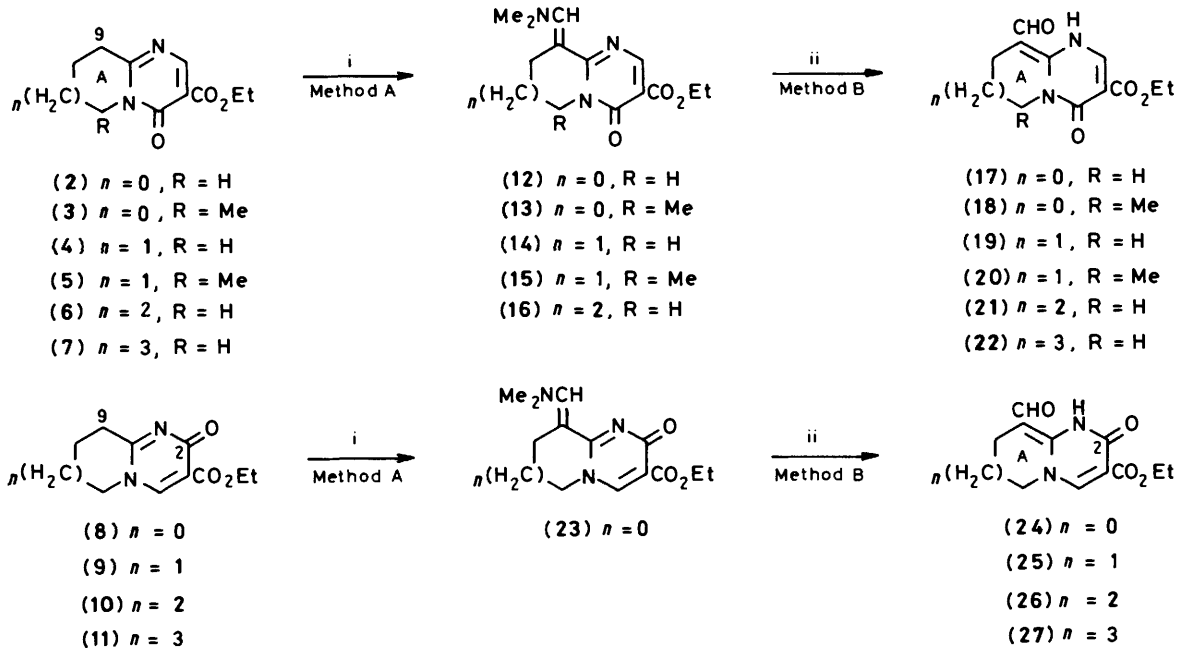
Table 2. U.v. data of formyl derivatives (**17**)—(**22**), (**24**)—(**27**), and (**34**) in EtOH

Compound	R	*n*	Concentration (10^{-4}M)	$\lambda_{max.}$/nm (ε)			
(**17**)	H	0	1.6	378 (3 760)	336 (15 100)	292i[b] (6 520)	225 (8 800)
(**18**)	Me	0	1.6	377 (3 300)	335 (16 700)	282 (5 860)	220 (9 900)
(**19**)	H	1	1.6	361 (21 800)	320i (8 200)	271 (3 600)	232 (12 200)
(**20**)	Me	1	1.6	358 (21 900)	315i (7 250)	265 (3 090)	223 (15 900)
(**21**)	H	2	2.1	355 (8 300)	324i (6 600)	220 (8 300)	
(**22**)	H	3	1.4	364 (630)	305 (8 200)	227 (6 960)	
(**24**)	H	0	*a*	368	308	235i	221
(**25**)	H	1	1.3	361 (19 550)	312 (9 380)	268i (1 880)	223 (11 700)
(**26**)	H	2	1.5	365 (15 320)	311 (6 100)	244i (5 290)	226 (11 900)
(**27**)	H	3	1.0	362 (15 000)	315i (5 770)	246i (2 090)	225 (10 500)
(**34**)				353 (17 600)	327i (14 600)	269i (8 700)	228 (15 700)

[a] Saturated solution. [b] Inflection.

Table 3. U.v. data of concentration dependence of 8-formyl-6-methyl-4-oxopyrrolo[1,2-*a*]pyrimidine (**18**) in EtOH

Concentration (M)	$\varepsilon_1/\varepsilon_2$	$\lambda_{max.}$/nm ε_1	ε_2	ε_3	ε_4
4×10^{-5}	2.58	377 (19 800)	339i (7 650)	286i (7 500)	226 (10 300)
4.5×10^{-5}	1.36	377 (15 500)	339i (11 400)	286i (4 800)	222 (11 300)
5×10^{-5}	0.88	377 (10 600)	338 (12 000)		222 (9 200)
6×10^{-5}	0.57	377 (8 300)	338 (14 700)	285i (5 700)	223 (8 700)
8×10^{-5}	0.43	377 (7 500)	337 (17 300)	282i (6 250)	221 (11 800)
1.2×10^{-4}	0.28	378i (4 800)	336 (17 350)	282i (6 200)	221 (10 500)
1.6×10^{-4}	0.198	379i (3 300)	336 (16 700)	282i (5 900)	220 (9 900)
3.2×10^{-4}	0.13	380i (2 350)	336 (17 500)	283i (7 000)	219 (10 200)
4×10^{-4}	0.095	380i (1 750)	336 (18 400)	283i (7 400)	220 (10 500)

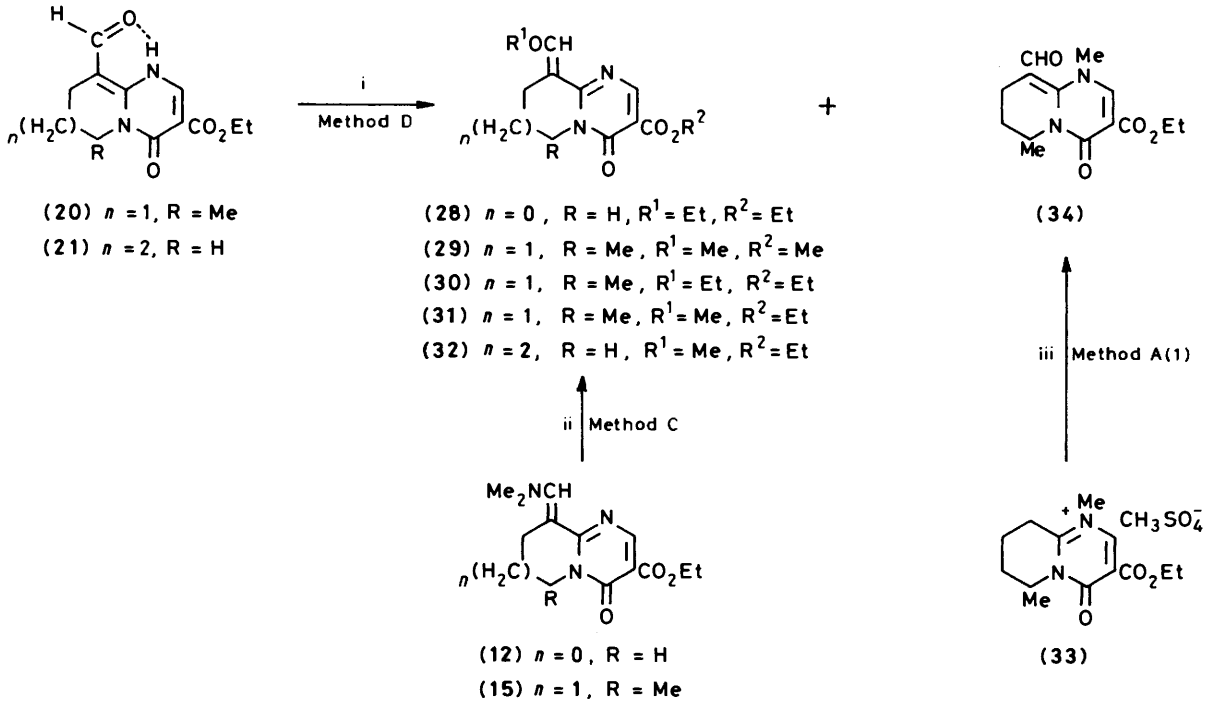


Scheme 2. *Reagents:* i, $POCl_3$–DMF, then H_2O; ii, H_3O^+

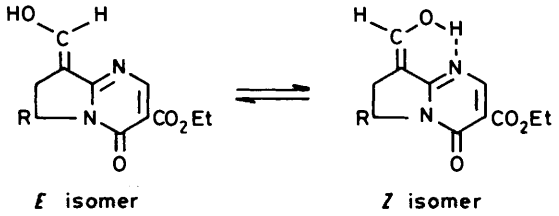
(**22**)]. The difference between the maxima in the spectra recorded in ethanol, 41 and 43 nm, respectively, suggests that the band at 377 nm can be attributed to the *Z*-stereoisomer of the enol tautomer.

Differences of similar magnitude were observed earlier between the longest wavelength maxima in the u.v. spectra of the *E*- and *Z*-isomers of 9-phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines.[7]

The longest wavelength maximum of the u.v. spectrum in ethanol of the homologue (**21**) with a seven-membered ring exhibited a bathochromic shift of 51 nm compared with the corresponding maximum of the parent compound (**6**).[5] This



Scheme 3. *Reagents:* i, CH_2N_2; ii, R^1OH–HCl; iii, $POCl_3$–DMF, then H_2O



suggests that the predominant tautomer of (**21**) is the enamine containing a conjugated formyl group.

In the u.v. spectrum of the homologue (**22**) with an eight-membered ring the maximum at 364 nm associated with the enamine form was of quite low intensity (ε *ca.* 360). Its bathochromic shift in relation to the corresponding maximum of the parent compound (**7**)[5] was 60 nm. On the other hand, a very strong absorption could be observed at 305 nm, coinciding with the highest wavelength maximum (304 nm) for the parent compound (**7**). This implies that in compound (**22**) the main tautomeric form is the imine containing a non-conjugated formyl group. In dimethyl sulphoxide, however, the percentage of the enamine tautomer is comparable with that of the imine since the maxima at 366 and 310 nm are of similar intensities (SUP 56353).

^1H *N.m.r. Studies.*—Data on ^1H n.m.r. spectra recorded in chloroform are compiled in SUP 56353 and Table 4, except those for the dimethylaminomethylene-4-oxo derivatives which were published previously.[8]

In (**13**) and (**23**) signals for the exocyclic methylene group appear at δ 7.53 and 7.52, respectively, due to the anisotropic effect of the C=N double bond, thereby proving the presence of the sterically more favoured *E*-stereoisomer.[8]

The alkoxymethylene derivatives (**28**)—(**31**) are also all present as the *E*-isomers. The maximum deviation in the shift of the C(9)=CH proton as compared with the corresponding signal for the (*E*)-dimethylaminomethylene analogue[8] was 0.3 p.p.m.

As a consequence of the protonation at N(1), a 3:1 mixture of *E*- and *Z*-isomers was observed when the spectrum of the 9-ethoxymethylenepyridopyrimidine (**30**) was recorded in $CDCl_3$–CF_3CO_2H (1:1). This ratio we established by means of the C(9)=CH proton signal, which appeared at relatively low field (δ 8.29) for the *E*-isomer, and at δ 7.63 for the *Z*-isomer. In the homologue with a five-membered ring (**28**), protonation affected only the signal shifts, but not the appearance of two stereoisomers.

In the spectrum of compound (**34**), in which there is no possibility of tautomerism, the formyl proton signal appears at δ 9.60. Similarly as in the 1-methyl-1,6,7,8-tetrahydropyridopyrimidin-4-ones[6,9] H-2 absorbs at relatively high field (δ 8.04), compared with the shifts of H-2 in compound (**33**) and also in 9-alkoxymethylene- and 9-aminomethylene-6,7,8,9-tetrahydropyridopyrimidines (δ 8.55 ± 0.14).[3,5,8–11] On protonation at the formyl group (vinylogues amide), the *E*-stereoisomer of the enol tautomer is formed, as indicated by an upfield shift (to δ 8.08) of C(9)=CH and the downfield shift of H-2 to δ 8.51.

In accordance with u.v. studies, the 2-oxo-formyl derivatives (**25**)—(**27**) gave very similar ^1H n.m.r. spectra, whereas characteristic differences could be observed between the spectra in the 4-oxo-formyl series (**17**)—(**22**) (see Table 4). The chemical shift of H-2 reflects very sensitively[9] whether one of the double bonds is between C(9a) and N(1) ($\delta_{H\text{-}2}$ 8.40—8.70) or C(9) and C(9a) ($\delta_{H\text{-}2}$ 7.90—8.20) [*cf.* also SUP 56353 and the discussion on compound (**34**)].

A comparison was made of the five-membered 4-oxo compounds (**17**) and (**18**) with the homologues with a six-membered ring (**19**) and (**20**). The latter exist[4] as a 1:10 mixture of enol and enamine tautomers with H-2 absorbing at δ 8.25 and 8.23. The relative downfield shift of H-2 (δ 8.48 and 8.46) in the lower homologues is indicative of a considerable shift in favour of the enol form in the tautomeric equilibrium. On protonation the six-membered homologues (**19**) and (**20**) gave *E*–*Z* isomeric mixtures (15:85 and 20:80, respectively) of the enol tautomer.

Table 4. ^{1}H N.m.r. data of formyl derivatives (**17**)—(**22**), (**25**)—(**27**), and (**34**) in $CDCl_3$

Compound	Tautomer	R	*n*	NH	H-2 or H-4	H-6 or H_2-6	H_2-7	H_2-7a	H_2-7b	H_2-8, H-9	Me	CHO or –CH=	OCH_2CH_3
(**17**)[a]	*Z*-A	H	0		8.48s	4.18td				2.92td		7.31t	4.32q; 1.35t
(**18**)	*Z*-A	Me	0		8.46s	4.70m				e2.48ddd a3.12ddd	1.50d	7.34t	4.35q; 1.37t
(**19**)	B	H	1	14.39br	8.35d	3.89t	1.93m			2.51t		8.78d	4.29q; 1.33t
(**19p**)[b]	*E*-A *Z*-A	H	1		8.47s 8.58s	4.01t	2.00m			2.59t		8.63br,s 8.38br,s	4.35q 1.36t
(**20**)	B	Me	1	14.50br	8.23d	5.00m	1.93m			2.54m	1.25d	8.92d	4.23q; 1.42t
(**20p**)[c]	*E*-A *Z*-A	Me	1		8.63s 8.67s	5.20m	2.02m			2.77m	1.40d	8.53br,s 8.25br,s	4.45q; 1.44t
(**21**)[d]	B C	H	2	15.15br	8.18br,s 8.49br,s	4.20t 5.20m	——1.8—2.2m——			2.63t		8.72br,s 9.90br,s	4.32q; 1.32t
(**21p**)	*Z*-A	H	2		8.50s	4.35m	——1.7—2.1m——			2.60m		7.92s	4.41q; 1.38t
(**22**)[e]	B	H	3	16.34br	8.26d		1.5—2.1m					8.7br,s	4.38q; 1.37t
	C				8.59s	e4.92ddd a4.35m				e3.6—4.0m a2.40m		9.88d	
(**25**)	B	H	1	12.90br	7.92s	3.82t	2.02q			2.52t		9.00s	4.25q; 1.32t
(**26**)	B	H	2	13.86br	8.02s	4.13t	——1.8—2.3m——			2.67t		9.03s	4.31q; 1.32t
(**27**)	B	H	3	14.82br	7.90s	4.28m	1.5—2.2m			2.85m		8.90s	4.32q; 1.37t
(**34**)	B			3.79s[f]	8.04s	5.12m	1.80m			2.50m	1.16d	9.60s	4.29q; 1.35t
(**34p**)	*E*-A			4.05s[f]	8.51s	5.40m	2.00m			2.80m	1.25d	8.08br,s	4.42q; 1.38t

(**19p**), (**20p**), (**21p**), and (**34p**): in $CDCl_3$–CF_3COOH (1:1). Coupling constants (Hz): for (**18**): $J_{8,8}$ 16.0, $J_{6a,8a}$ 10.0, $^4J_{8e,-CH=} \approx {}^4J_{8a,-CH=}$ = 2.0; for (**19**) $J_{2,NH}$ 3.00; for (**20**) $J_{2,NH}$ 5.0, $^5J_{NH,CHO}$ 1.0; for (**22C**) $J_{6,6}$ 15.0, $J_{6e,7a} \approx J_{6e,7e}$ = 3.0, $J_{9,CHO}$ 0.7; a = axial and e = equatorial.

[a] At 50 °C. [b] *E*:*Z* ratio 15:85. [c] *E*:*Z* ratio 20:80. [d] **B**:C ratio 90:10. [e] **B**:C ratio 15:85. [f] NMe signal. A = enol tautomer. **B** = enamine tautomer. C = imine tautomer.

For compounds containing a seven- or an eight-membered ring, (**21**) and (**22**), signals revealing the presence of the imine form can be recognized in the spectra. On the basis of the integrals for the non-conjugated formyl proton signals at δ 9.90 and 9.88, the share of the imine tautomer was assessed to be 10% in (**21**) and 85% in (**22**). Signals of a conjugated formyl proton at δ 8.72 and 8.76 permit the conclusion that, besides the enamine form, the enol tautomer also participates in the equilibrium. The proportion of the latter may be similar to that in (**19**) and (**20**) containing a six-membered ring. Protonation of the seven-membered homologue (**21**) yielded only the (*Z*)-enol tautomer in $CDCl_3$–CF_3COOH (1:1).

The close similarity of the ^1H n.m.r. spectra of the 2-oxo isomers (**25**)—(**27**) suggests that, regardless of the ring size, all of them represent the corresponding tautomer or a similar mixture of tautomers. The poor solubility precluded the recording of a useful spectrum of the 2-oxo-formyl compound containing a five-membered ring (**24**). The chemical shift of the formyl proton indicates a mixture of enamine and enol tautomers with more enamine than in the case of the 4-oxo isomers.

Discussion

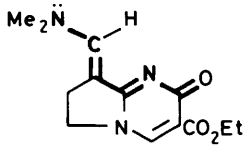
Conjugation in the enol tautomer is more extended in the 4-oxo isomers than in the 2-oxo isomers. For instance, a comparison of the u.v. spectra of the 2-oxo- and 4-oxo-dimethylaminomethylene isomers (**23**) and (**12**) demonstrates that in the latter the highest wavelength π–π^* transition is shifted by 22 nm to longer wavelengths compared with that for the 2-oxo isomer (**23**). On the other hand, the chromophore systems of the enamine forms in the 2-oxo and 4-oxo isomers are rather similar. Accordingly, the shapes of the u.v. spectra position and intensity of maxima and minima in ethanol of the 2-oxo and 4-oxo isomers (**25**) and (**19**), which both exist predominantly in the enamine form, are almost identical. In the 4-oxo derivatives the most extended conjugated system involves N(1), while in the 2-oxo isomers it involves N(5). The only difference between the two chromophores is that in the 2-oxo isomer the arrangement of the formyl group and N(5) is *trans*, while in the 4-oxo derivative that of the formyl group and N(1) is *cis* around the C(9a)=C(9) double bond.

The phenomenon that in the 2-oxo series (**24**)—(**27**) the dominant conformer is independent of the ring size, whereas in the 4-oxo isomers (**17**)—(**22**) it is dependent, can be explained by a stronger internal hydrogen bond in the 2-oxo compounds between the N(1)–H and formyl groups due to polarization caused by the adjacent C(2)=O group. Therefore, while both internal and external factors (such as ring size and solvent effects, respectively) play only a secondary role in the 2-oxo compounds, these effects cannot be neglected in the 4-oxo isomers. At the same time, due to its more extended conjugation the enamine form of the 2-oxo isomers is more stable than the enol tautomer formed by enolization of the formyl group.

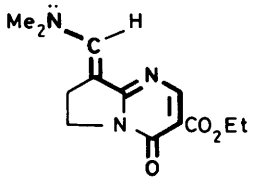
Of the 4-oxo compounds (**17**)—(**22**), those with two six-membered rings (**19**) and (**20**) contain a relatively strong chelate ring and exist predominantly as the enamine tautomer independently of the solvent.[3]

In the pyrrolopyrimidin-4-ones, because of the five-membered ring, oxygen and nitrogen which should form hydrogen bonds become more distant and such bonding can no longer come about. In the enol tautomer, however, in which the extent of conjugation is similar, the more acidic O–H bond is longer than the N(1)–H bond in the enamine form, and therefore in certain solvents such as chloroform there is the possibility of a weak internal hydrogen bond. At higher concentrations in ethanol and dimethyl sulphoxide or in the poorly solvating dioxane, presumably due to the intermolecular association of the pyrrolopyrimidin-4-one molecules, the internal hydrogen bond is ruptured and the *E*-stereoisomer of the enol tautomer becomes predominant.

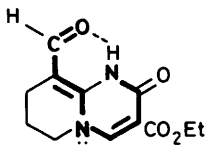
In the 4-oxo-formyl homologues with a seven- or an eight-membered ring (**21**) and (**22**), due to the deviation of the ring conformation from that in the six-membered homologue, formation of the internal hydrogen bond is also disfavoured, less so in (**21**) and more so in (**22**). In the azocinopyrimidin-4-one (**22**), therefore, the imine tautomer containing a non-conjugated formyl group becomes dominant. The appearance of a considerable proportion of the enamine tautomer in dimethyl sulphoxide may be explained by the formation of hydrogen bonds between N(1)–H and the solvent.[12]



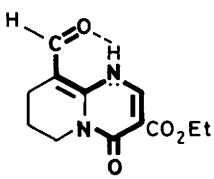
(**23**)



(**12**)



(**25**)



(**19**)

Experimental

M.p.s are uncorrected. Yields were not optimized. U.v. spectra were recorded with a UNICAM SP-800 spectrophotometer and ^1H n.m.r. spectra with a JEOL FX-100 spectrometer ($SiMe_4$ as internal standard). Analytical results on the new compounds agreed with calculated data, details are given in the Supplementary Publication No. SUP 56353 (6 pp.). Solvents for recrystallization, yields, and m.p.s are given in Table 1.

Vilsmeier–Haack Formylation.—Method A(1). To a cooled solution of the nitrogen bridgehead compound[5] (10 mmol) in DMF (100 ml) was added, dropwise, $POCl_3$ (20 mmol) at 15—20 °C and the mixture was then stirred for the time and at the temperature indicated in Table 1. After the mixture had cooled it was poured onto crushed ice (40 g) and the aqueous phase was adjusted to pH 7.5 with 20% aqueous Na_2CO_3 at 0—5 °C. The product was filtered off and recrystallized. For the preparation of (**34**) the neutral, aqueous mixture was extracted with benzene (2 × 20 ml), the aqueous phase was then adjusted to pH 8.5 and NaCl (6 g) was added to it. The aqueous phase was shaken with a mixture of chloroform and ethanol (60 ml and 12 ml, respectively) three times. The combined organic layers were dried (Na_2SO_4) and evaporated to obtain (**34**). For the preparation of (**25**) the neutral, aqueous mixture was extracted with chloroform (3 × 10 ml), then the combined organic phase was shaken with water (2 × 10 ml), and dried (Na_2SO_4) and evaporated to obtain (**25**).

Method A(2). To a stirred solution of the nitrogen bridgehead compound (10 mmol) in 1,2-dichloroethane (30 ml), DMF (20 mmol) and then $POCl_3$) (20 mmol) were added at ambient temperature and the mixture was stirred for the time and the temperature indicated in Table 1. After the mixture had cooled it was poured onto crushed ice (15 g) and the aqueous phase was adjusted to pH 7 with 20% aqueous Na_2CO_3 solution at 0—5 °C. The aqueous phase was then extracted with chloroform

(2 × 10 ml). The combined extracts (1,2-dichloroethane and chloroform) were dried (Na_2SO_4) and evaporated to obtain (**12**) and (**26**). For the preparation of (**13**) the residue was treated with diethyl ether; for the preparation of (**16**) the residue was treated with ethyl acetate. The (**27**) was isolated from the residue by preparative t.l.c. on DC Kieselgel 60F-254 plates (benzene–methanol 4:1).

Method B. A solution of the dimethylaminomethylene compound (10 mmol) in 0.5N aqueous hydrochloric acid was stirred during the time and at the temperature indicated in Table 1. After the mixture had cooled the precipitated formyl derivative was filtered off and washed with water.

Method C. The dimethylaminomethylene compound (5 mmol) was heated under reflux in ethanol (15 ml) containing 15% HCl. After being cooled to 5 °C the mixture was poured onto crushed ice (15 g) and the aqueous mixture was adjusted to pH 7 with 20% aqueous Na_2CO_3 solution. The precipitated ethoxymethylene compound was filtered off and recrystallized. For the preparation of (**29**) methanol (10 ml) containing 15% HCl was applied and during the reaction the ester group in position 3 was re-esterified.

Method D. To a cooled, stirred solution of the formyl compound (10 mmol) in chloroform (40 ml) was added dropwise a solution of diazomethane prepared from *N*-nitrosomethylurea[13] (20 mmol) in diethyl ether (30 ml) at − 10 °C, then the mixture was stirred for 2 h at − 10 °C. After glacial acetic acid (0.15 ml) had been added, the mixture was evaporated and the oily residue was treated with diethyl ether–ethyl acetate. The crystalline product was filtered off and washed with diethyl ether. From the mother liquor of (**31**), (**34**) was isolated by t.l.c. on DC Kieselgel 60F-254 plates (benzene–methanol 4:1).

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