Nitrogen Bridgehead Compounds. Part 75.[1] Study of Tautomerism of 9-Oxalyl Derivatives of Condensed Pyrimidinones by ^1H and ^{13}C Nuclear Magnetic Resonance and Ultraviolet Spectroscopy

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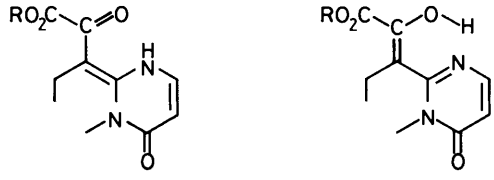
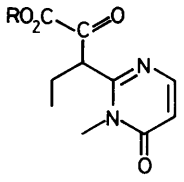
The tautomerism of the title compounds has been investigated by ^1H and ^{13}C n.m.r. and u.v. spectroscopy. The effect of ring size, substituents, and various annellations of the tautomerism have also been studied. The ring size has been found to be decisive from the point of view of tautomerism.

Oxalyl ester derivatives of condensed heterocycles have been synthesized by condensation of the parent compounds with ethyl oxalate.[2] In these compounds the oxalyl moiety may exist in three tautomeric forms, namely, the oxo-enamine (**A**), enol-imine (**B**), and oxo-imine (**C**) forms.



(**A**)

(**B**)



(**C**)

As the tautomerism may be important for regioselective transformations of the compounds we have carried out a systematic study using ^1H and ^{13}C n.m.r., and u.v. spectroscopic methods. All of the methods provided valuable information about the structure of the compounds. Some heteroaryl pyruvic acid analogues and heterocyclic acylmethyl derivatives have previously been studied by several authors and in the majority of compounds the enamine form was found to be predominant.[3–10] A more recent ^1H, ^{14}N, and ^{17}O n.m.r. study of 2-acylmethylquinazolines has shown that the oxo-enamine form predominates in the equilibrium.[11]

Recently the tautomerism of 9-formyl derivatives of related compounds, which can be regarded as the closest analogues of the oxalyl ester derivatives shown below, has been extensively studied[12–16] mainly by n.m.r. and u.v. spectroscopy. The tautomerism of the 9-formyl derivatives depends upon the size of the ring bearing the formyl group. The five-membered rings assume an enol-imine structure, whereas the six-membered rings are oxo-enamines. Recently an *X*-ray structural analysis[17] of (*Z*)-3-(α-hydroxybenzylidene)-1,2,3,9-tetrahydropyrrolo-[2,1-*b*]quinazolin-4-one, a benzoyl analogue of (**12**) gave evidence for the existence of an enol-imine structure.

Compounds (**1**)–(**12**) were studied.†

^1H *N.M.R. Investigations.*—The ^1H n.m.r. spectra were recorded in $CDCl_3$. We have found that the δ_{NH}, or δ_{OH} signals were the most sensitive probes of the tautomeric forms. On the basis of this signal the compounds studied can be classified into two groups (Table 1). In the first, the signal of the mobile proton appears in the region 15–16 ppm as a broadened peak indicating a hydrogen bond of considerable strength. In compounds (**1**)–(**4**) the spin–spin coupling between the NH, and 2-H, and in some cases 3-H as well, provides unequivocal proof for the predominance of the oxo-enamine structure. This finding served as a reliable reference to the other tautomeric species.

In the enol-imine group of compounds this signal is far broader, in some cases could not even be localized, thus, indicating an entirely different species. Compound (**19**) represents a special case owing to another potential tautomeric system, though the range of the δ_{OH} signal is very much like those of the compounds (**17**) and (**18**). In those compounds where a hydrogen atom is attached to C-2 [compounds (**1**)–(**4**) and (**17**) and (**18**)], the chemical shift of 2-H is also characteristic of the tautomeric species. In the oxo-enamine form (**21**) this signal appears upfield[13] of that of the parent compound of imine structure (**20**)[18] (R = CO_2Et $\delta_{2\text{-H}} = 8.55 \pm 0.14$; R = H $\delta_{2\text{-H}} = 7.80 \pm 0.10$), or to that of derivatives containing an *exo*-double bond in position 9 (**22**)[13] ($\delta_{2\text{-H}} = 8.50 \pm 0.10$).

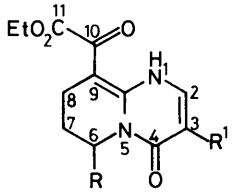
The difference is obvious between the groups of compounds (**1**)–(**11**) and (**12**)–(**19**). The first group of compounds consists of pyrido[1,2-*a*]pyrimidin-4-ones or quinazolones, whereas the latter compounds are pyrrolo[2,1-*b*]pyrimidin-4-ones. Signals of other tautomeric forms were not detected in the spectra, either because the equilibrium is very much shifted to one side, or because of a fast exchange.

^{13}C *N.M.R. Investigations.*—The ^{13}C n.m.r. spectra were recorded in $CDCl_3$, 1:1 $(CD_3)_2SO$–$CDCl_3$, or $(CD_3)_2SO$ when poor solubility in $CDCl_3$ rendered it impossible to obtain a useful spectrum. On the basis of the carbon-13 spectra the compounds can be classified into two groups (Table 2).‡

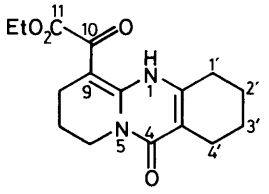
In the first group a signal attributable to a carbonyl group

† For making the comparison easier the numbering of the heterocycles in this paper is not regular, but follows the pattern of the parent compound (*cf.* Scheme 1).

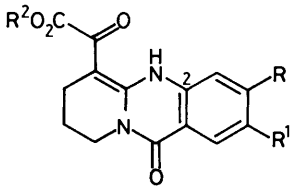
‡ The complete list of ^1H and ^{13}C n.m.r. resonance data (Tables 5–7) have been deposited as a supplementary publication SUP. No. 56763 (6 pp.). For details of the Supplementary Deposition Scheme see 'Instructions for Authors (1989),' *J. Chem. Soc., Perkin Trans. 2*, 1989, Issue 1.



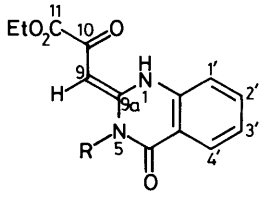
(1) R = R¹ = H
(2) R = H, R¹ = CO_2Et
(3) R = Me, R¹ = H
(4) R = Me, R¹ = CO_2Et



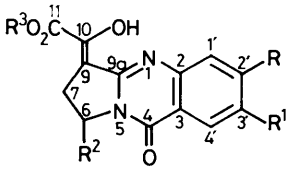
(5)



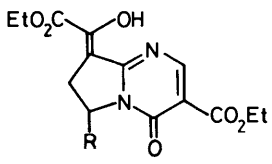
(6) R = R¹ = R² = H
(7) R = H, R¹ = CO_2Et, R² = Me
(8) R, R¹ = $-OCH_2O-$, R² = Et



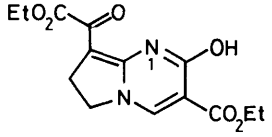
(9) R = Me
(10) R = CH_2CH_2OH
(11) R = CH_2CO_2Et



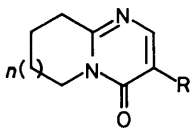
(12) R = R¹ = R² = R³ = H
(13) R = R¹ = H, R² = Me, R³ = Et
(14) R = H, R¹ = CO_2Me, R² = H, R³ = Me
(15) R = H, R¹ = NO_2, R² = H, R³ = Et
(16) R = CO_2Et, R¹ = R² = H, R³ = Et



(17) R = H
(18) R = Me



(19)



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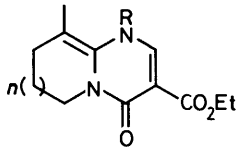
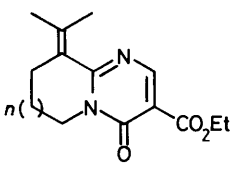


(21) n = 0,1



(22)

(C-10) resonates above 170 ppm [compounds (1)–(11) and (19)] whereas in the second there is no signal above 170 ppm [compounds (12)–(18)]. This clearly shows that, in the first group, a ketonic carbonyl moiety is present, whereas in the other compounds there are no carbonyls other than those of the ester moieties; the C-10 atom being enolized gives rise to signals in the region of 155–160 ppm.

Table 1. $\delta_{2\text{-H}}$, δ_{NH} and δ_{OH} chemical shifts, and relevant coupling constants of compounds (1)–(19) ($CDCl_3$; $SiMe_4$; 80 MHz).

Compound	$\delta_{2\text{-H}}$	δ_{NH}	δ_{OH}	*J*/Hz
(1)	7.40 dd	15.3 br	—	$^3J_{NH,2H}$ 4; $^4J_{NH,3H}$ *ca.* 1 $^3J_{2H,3H}$ *ca.* 2
(2)	8.30 d	15.1 br	—	$^3J_{NH,2H}$ *ca.* 6
(3)	7.38 dd	15.3 br	—	$^3J_{NH,2H}$ *ca.* 5; $^3J_{NH,3H}$ *ca.* 1.5; $^3J_{2H,3H}$ 7.4
(4)	8.30 q	15.1 br	—	$^3J_{NH,2H}$ 5.7
(5)	—	15.7 br	—	—
(6)	—	15.7 br	—	—
(7)	—	15.0 br	—	$^3J_{1H,2H}$ 8
(8)	—	16–17 br	—	—
(9)	—	15.1 br	—	—
(10)	—	15.1 br	—	—
(11)	—	15.2 br	—	—
(12)	—	—	9–14 br	—
(13)	—	—	9–14 br	—
(14)	—	—	not detectable	—
(15)[a]	—	—	not detectable	—
(16)	—	—	7.4–8.0 br	—
(17)	8.65 s	—	8–11 br	—
(18)	8.62 s	—	not detectable	—
(19)	8.25 s[b]	—	9–12 br	—

[a] In $(CD_3)_2SO$. [b] $\delta_{4\text{-H}}$.

U.V. Spectroscopic Investigations.—The u.v. spectra of the compounds also provided a useful tool for distinguishing the tautomeric species, though some consideration and care is necessary especially when other chromophores are present, *e.g.* in (19) where a further extension of conjugation is possible (*cf.* Table 3). The u.v. spectra of the 9-oxalylpyrido[1,2-*a*]pyrimidin-4-ones (1) and (4) are very similar to those of the corresponding 9-formylpyrido[1,2-*a*]pyrimidin-4-ones which suggests the predominance of the exo-enamine tautomers (A) in these derivatives.[13] The pattern of the u.v. spectra of 9-oxalyl derivatives (1) and (3) is analogous to that of the tricyclic compound (5), furthermore, compounds (6) and (9) have analogous u.v. spectra. However, the u.v. spectra of the five-membered analogues (12), (17), and (18) are substantially different from those of six-membered homologues (2), (4), and (6), respectively, indicating that these derivatives exist in different tautomeric forms in ethanol.

It is worth noting that in the 9-dimethylaminomethylene analogue of (19) it is the 2-oxo form that predominates as indicated by a u.v. spectrum similar to those of the 4-oxo isomers.[13] The oxo-enamine tautomers in general, owing to the lower extent of conjugation, reveal absorptions at lower wavelengths than the enol-imine tautomers with the exception of (19) (*vide supra*). The u.v. spectra of the enol-imine tautomers usually reveal several distinct maxima, whereas those of oxo-enamine forms show no such structured curves.

Results and Discussion

The spectroscopic data showed that the annellation usually produces no remarkable effect on the tautomerism of these compounds. The size of the ring bearing the oxalyl moiety, however, plays a decisive role. This is in full agreement with earlier observations in the study of 9-formylpyrido[1,2-*a*]-

Table 2. Selected carbon-13 chemical shifts of compounds (**1**)–(**19**) in deuteriochloroform.

	(1)	(2)	(3)	(4)	(5)	(6)[a,b]	(7)[c]	(8)	(9)	(10)[c]	(11)	(12)	(13)	(14)[a]	(15)[a,b]	(16)	(17)	(18)	(19)
C-2	140.3	146.7	140.1	146.7	147.9	138.3 (138.5)[d]	141.6	137.3	138.3	138.2	138.6	145.7	145.5	148.8	144.5	146.3	130.0	154.2	156.5
C-3	105.1	106.9	105.3	106.7	113.4	117.2 (116.1)	125.5	111.8	116.6	116.6	116.4	120.3	120.7	119.9	119.7	123.2	109.3	113.3	105.7
C-4	160.1	156.8	159.6	156.3	160.6	159.25 (159.34)	158.8	159.4	159.8	159.4	159.5	160.0	159.8	159.5[e]	159.1	159.5	162.5	159.2	147.6
C-9	88.9	89.7	87.6	88.4	89.3	88.3 (88.4)	88.3	91.9	81.7	82.4	81.5	109.5	107.9	109.7	107.6	110.4	114.1	105.3	95.6
C-9a	155.0	153.8	154.2	152.8	153.8	152.5 (152.1)	152.5	154.4	155.7	155.6	155.4	153.1	154.1	153.2	156.7	151.9	154.0	156.7	155.9
C-10	177.9	180.7	178.8	181.6	174.6	177.4	179.0	172.0	173.5	175.5	175.4	157.7	157.3	158.9[e]	158.3	158.5	155.8	161.5	174.5
C-11	165.3	164.9	165.4	165.0	165.2	166.7	165.1	165.0	163.8	163.7	163.6	163.4	163.0	165.7	162.4	165.3	163.6	163.2	163.0
C=O (3-ester)	—	162.8	—	162.8	—	165.0 (165.05)	165.6	—	—	—	166.8	—	—	163.0	—	162.6	163.3	162.6	162.3

[a] Recorded at 101 MHz. [b] In $CDCl_3$–$(CD_3)_2SO$. [c] $(CD_3)_2SO$. [d] Shifts of minor component in parentheses. [e] Interchangeable assignment.

Table 3. Ultraviolet spectroscopic data of compounds (**1**)–(**19**) in 96% ethanol.

Compound	λ nm (ε/dm³ mol⁻¹ cm⁻¹)
(**1**)	348 (20 890)
(**2**)	364 (26 920), 270 (3 160)
(**3**)	345 (22 390)
(**4**)	362 (12 590), 270 (1 290)
(**5**)	349 (22 910)
(**6**)	358 (19 950), 276 (7 080)
(**7**)	368 (27 540), 287 (9 120), 265 (8 130), 230 (22 390)
(**8**)	367 (5 500), 329 (5 890), 317 (4 100), 287 (5 250), 238 (28 130)
(**9**)	361 (30 200), 279 (9 550)
(**10**)	363 (22 910), 278 (20 890)
(**11**)	362 (22 910), 276 (7 080)
(**12**)	383 (7 760), 360 (10 230), 340 (14 790), 326 (16 600), 312 (15 140), 290 (15 140)
(**13**)	380infl. (7 240), 361 (9 330), 342 (12 300), 326 (13 180), 312 (11 480), 290 (11 220), 280infl. (9 770)
(**14**)	369 (8 510), 349 (10 470), 334 (10 230), 316 (9 120), 290 (11 480)
(**15**)	412infl (5 370), 375 (14 450), 359 (18 200), 343 (14 850), 326infl. (12 300), 301 (10 470)
(**16**)	382infl. (5 130), 357 (10 960), 340 (18 200), 325 (20 420), 311 (17 000), 298 (16 220), 271infl. (13 490), 233 (34 670)
(**17**)	387 (9 120), 365 (10 470), 348 (11 750), 337 (11 480)
(**18**)	388 (8 510), 366 (9 550), 350 (10 960), 338 (10 230)
(**19**)	397 (14 130), 338 (6 170), 234 (9 120)

Table 4. 9-Oxalyl derivatives of condensed pyrimidinones (**1**)–(**19**).

Compound	Solvent	t/h	T/°C	Yield (%)	M.p./°C	Recryst. solvent
(**1**)	Et_2O	4	20	64.8	126–127	EtOH
(**2**)	Et_2O	12	0	72.6	130–132	EtOH
(**3**)	Et_2O	4	20	66.0	154–157	EtOAc
(**4**)	Et_2O	12	0	74.0	100–102	EtOH
(**5**)	Et_2O	12	20	87.0	171–173	EtCOMe
(**6**)	EtOH	12	20	86.0	147–149	DMF
(**7**)	MeOH	12	20	71.0	165–167	DMF
(**8**)	EtOH	3	80	75.6	230–231	DMF
(**9**)	1:1 EtOH–Et_2O	12	0	97.0	173–174	EtOH
(**10**)	EtOH	3	80	95.0	193–196	MeCN
(**11**)	EtOH	5	80	47.0	152–153	EtOH
(**12**)	EtOH	12	20	78.0	213–214	EtOH
(**13**)	1:1 EtOH–Et_2O	12	20	79.4	169–171	MeCN
(**14**)	MeOH	3	20	72.0	270–272	MeOH
(**15**)	EtOH	6	20	91.0	223–225	DMF
(**16**)	EtOH	6	20	86.6	199–200	DMF
(**17**)	EtOH	12	20	93.0	213–214	EtOH
(**18**)	Et_2O	12	0	73.4	149–152	EtCOMe
(**19**)	EtOH	12	0	70.0	140–142	Pr^iOH

pyrimidin-4-ones[12–16] and their homologues. In the compounds where the oxalyl moiety is attached to a six-membered ring, only the oxo-enamine structure can be detected, whereas in the compounds containing five-membered ring the enol-imine form can be exclusively observed. However, no signs of *Z*/*E* geometric isomerism have been detected, in contrast with the 9-formyl derivatives[12–16] of (**17**) and (**18**) in which both isomers could be observed. In compound (**6**) a significant doubling of signals has been found in the ^{13}C n.m.r. spectrum. This can be well explained by the assumption of restricted rotation around the C(9)–C(10) bond. Special care is required when another potential tautomeric system is present as in the case of (**19**) where, in spite of the presence of the five-membered ring, a special oxo-enamine form exists which may be explained by the higher degree of conjugation, hence the lower energy content of the 2-hydroxy form. No solvent effect was found, though it was not our aim to investigate it in detail. All of the structures are stabilized by intramolecular H-bonds.

Experimental

The ^1H and ^{13}C n.m.r. spectra were recorded on Bruker WP-80 DS and Varian XL-400 FT-spectrometers, at 80 MHz (^1H), and 20.115 or 101 MHz (^{13}C), respectively, in $CDCl_3$ and in $(CD_3)_3SO$ solutions at ambient temperature using $SiMe_4$ as an internal reference. The 80 MHz ^1H n.m.r. spectra were run applying 2 μs pulses (*ca.* 45°) and a spectral width of 1 700 Hz. In the recording of ^{13}C n.m.r. spectra, 10 μs (*ca.* 30°) and 5 μs (*ca.* 35°) pulse lengths were applied at 5 000 and 24 000 Hz spectral width, at 20.115 and 101 MHz, respectively. A delay of 1 or 2 s was used between the pulses during the recording of the 20.115 MHz ^{13}C n.m.r. spectra. The u.v. spectra were recorded in 96% ethanol on a Pye–Unicam SP-8-200 spectrophotometer.

General Procedure for the Preparation of the Heterocyclic Oxalyl Derivatives.—A nitrogen bridgehead compound[18b,19] or quinazoline[20] (0.01 mol) and ethyl oxalate (2.72 cm³, 0.02 mol) were allowed to react in the presence of sodium ethoxide (1.32 g, 0.02 mol) in a solvent (20 cm³) for a period of time and at a temperature as given in Table 4. The reaction mixture was

then diluted with diethyl ether (100 cm^3). If the sodium salt of the product precipitated as crystals they were filtered off, and if the product separated as an oil, the solvent was decanted off. The sodium salt of the product was then treated with 5% hydrochloric acid (15 cm^3) for 1 h at ambient temperature. The crystals were filtered off, dried, and recrystallized. Satisfactory elemental analyses were obtained for all new compounds (Table 7, Supplementary Publication).

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