Intramolecular hydrogen bonding and tautomerism of acylpyran-2,4-diones, -2,4,6-triones and acylpyridinediones and benzannelated derivatives. Deuterium isotope effects on ^{13}C NMR chemical shifts

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The structures of acylpyran-diones, -triones and acylpyridinediones have been studied primarily by deuterium isotope effects on ^{13}C chemical shifts. The 3,5-diacetyltetrahydropyran-2,4,6-trione forms a double tautomeric system involving one of the carbonyl carbons of the anhydride moiety. This compound also exists as a minor symmetrical isomer with two intramolecular hydrogen bonds to the same acceptor. This isomer shows isotopic perturbation of the OH proton resonance upon deuteriation. A similar situation is found for 1,5-diphenylpentane-1,3,5-trione.

The 3-acetyl-6-methyl-2*H*-pyran-2,4(3*H*)-dione is found to be tautomeric and mainly in the 4-hydroxy form. The corresponding 5-acetyl derivative forms a very weak hydrogen bond as is also found in the 5-ethoxycarbonyl-6-methylpyridine-2,4(3*H*)-dione. The same pattern is found for 3- and 5-acetyl-6-methylpyridine-2,4(3*H*)-dione. This difference in the two-bond deuterium isotope effect is related to the bond orders of the bonds linking the hydrogen bond donors and acceptors and reflects the strength of the intramolecular hydrogen bonds. The 3-acetyl-4-hydroxy-2(1*H*)-quinolones are tautomeric in a similar fashion.

The formal hydroxypyridines are shown by isotope effects to be of the 2-pyridone form.

The formal imines of most of the above compounds have also been studied and are shown to exist in their keto-enamine forms. In the case of 3-(1-amino)ethylidenequinoline-2,4(1*H*,3*H*)-diones and 2-(1-amino)ethylidene-6,7-dihydro-5*H*-benzo[*ij*]quinolizine-1,3(2*H*)-diones two different forms with hydrogen bonds to either the carbonyl at C-4 or the amide carbonyl group at C-2 are observed. Deuterium isotope effects on chemical shifts again turned out to be crucial in the structure elucidation.

Acetylpyran-2,4-diones (Fig. 1) and -2,4,6-triones (Fig. 2) have attracted some interest.[1–6] One major interest in the latter is the inherent possibility of involving the anhydride moiety in tautomeric equilibria. 2-Hydroxypyridines have likewise been studied in order to establish the preferred tautomeric form,[2,7–9] 2-pyridone or pyridin-2-ol (Fig. 1). Hydroxypyridines are very interesting model compounds for nucleic acids and show a high tendency to dimerize.[10] The structures of some of these compounds (**1**, **2**, **5**, **6**) have been discussed previously based on ^{13}C chemical shifts.[3] It is possible with a sufficiently large base of very similar model compounds to make some progress. However, it is evident that the ^{13}C chemical shifts of the present compounds cannot satisfactorily be predicted based on chemical shifts of the parent compounds and substituent effects. This also means that ^{13}C chemical shifts are less useful in predicting the tautomeric forms.

Another interesting tautomeric equilibrium is the hydroxy-imine–ketone-amine one (Fig. 1). The compounds **16–18** serve as very useful models for the amine form.[11,12]

Deuterium isotope effects on ^{13}C chemical shifts have proven useful in investigation of intramolecular hydrogen-bonded systems[13,14] and also in establishing the preferred acceptor group in intramolecularly hydrogen-bonded systems.[15] Deuterium isotope effects may also be of help in establishing the presence and the preferred tautomer of tautomeric systems.[16] The strength of intramolecular hydrogen bonds has been related to the double bond order of the double bond linking the donor and the acceptor group.[16,17] The series of pyran-2,4-dione, -2,4,6-trione and formally pyridinedione-like molecules provides a useful set with which to investigate tautomeric systems, intramolecular hydrogen bonds and hydrogen-bonded systems with two hydrogen bonds to one acceptor (Scheme 1).

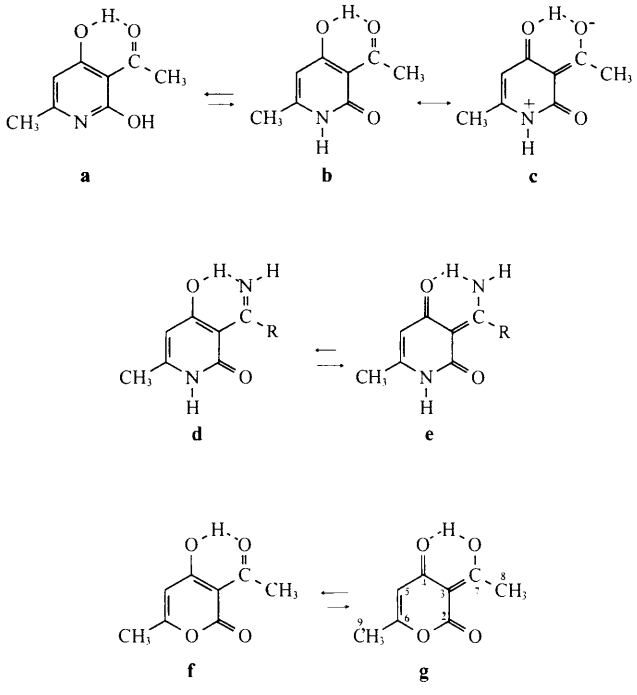


Fig. 1 Pyridin-2-ol (**a**) and mesomeric 2-pyridone (**b**) and (**c**) forms of **7**. The enol-imine for (**d**) and the keto-enamine form (**e**) of **12**.

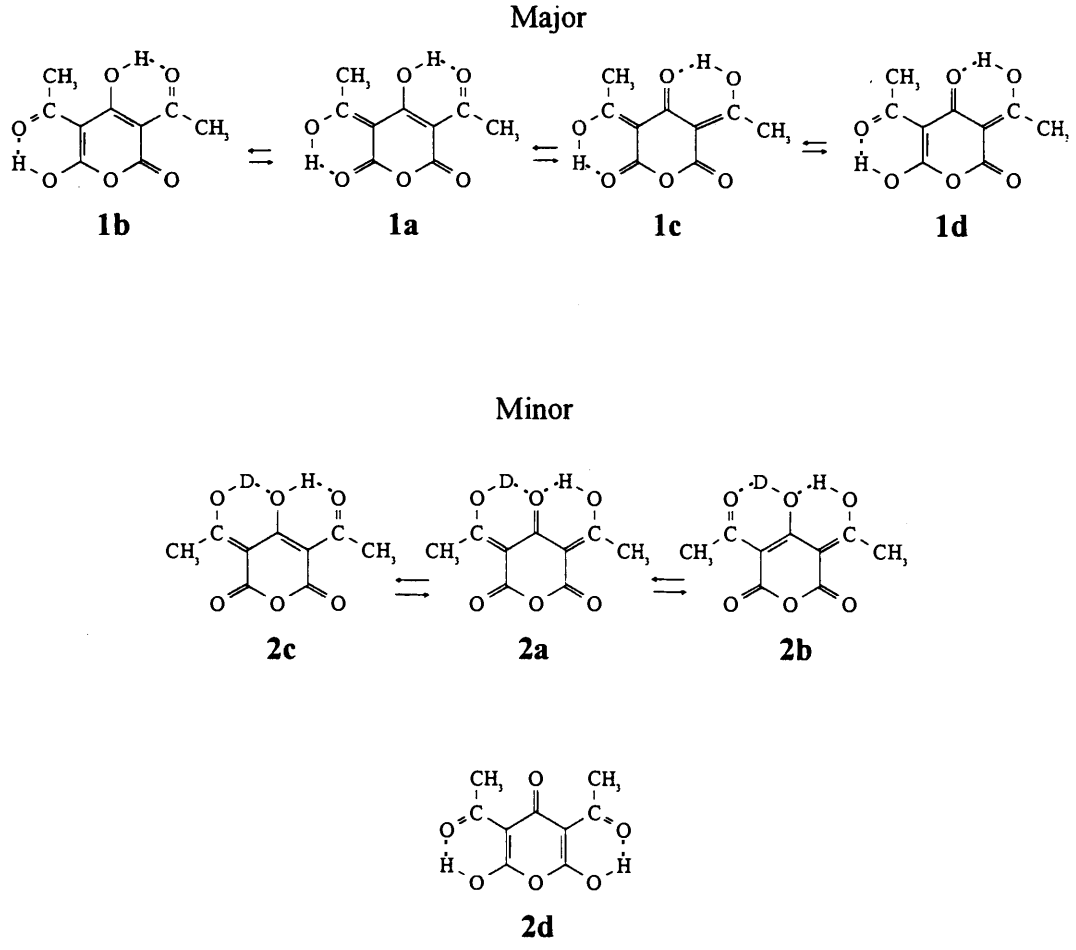


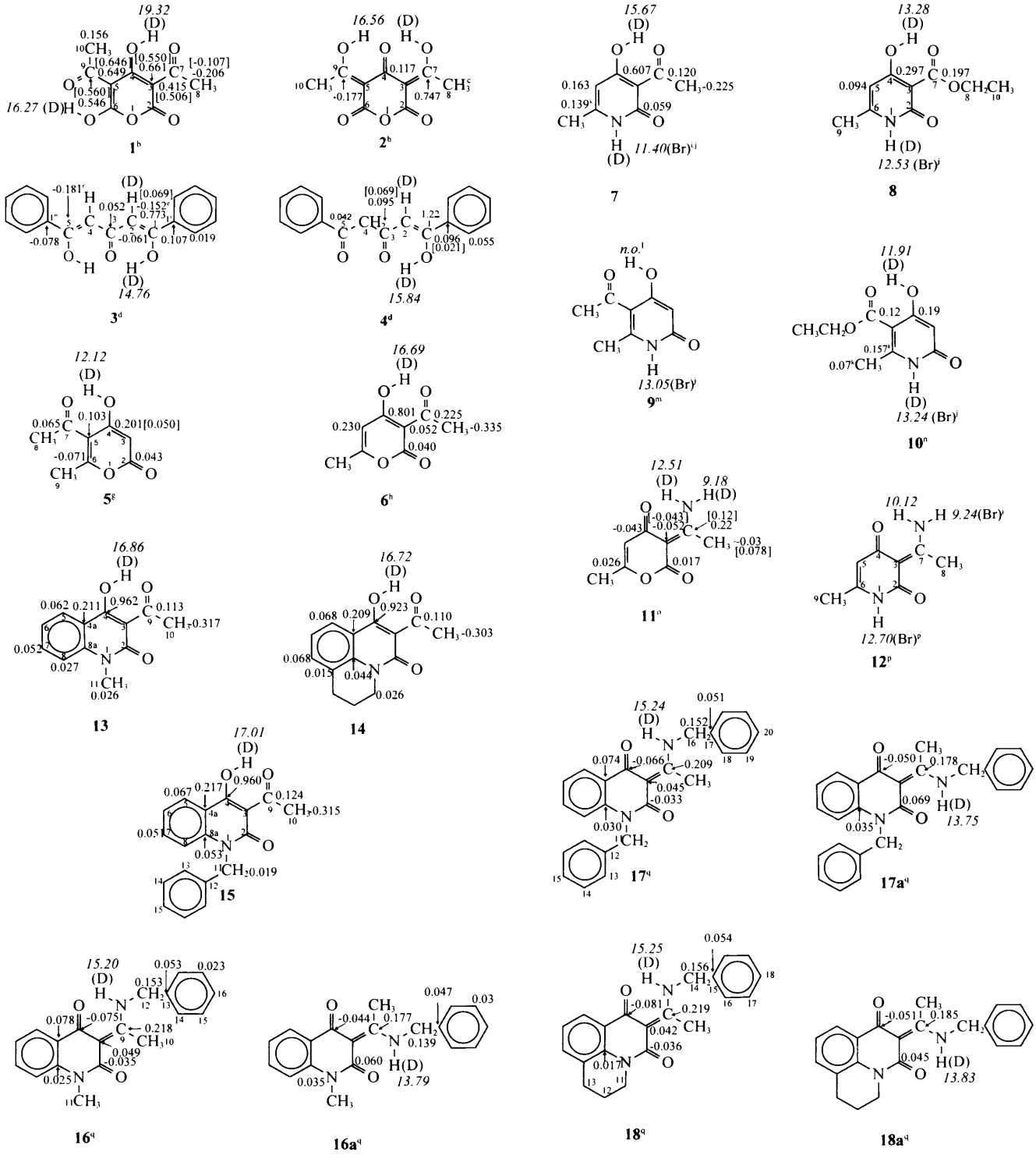
Fig. 2 Tautomeric forms of **1** and **2**

Results and discussion

Deuteriation of OH and NH groups is usually done very conveniently by dissolving the compounds in mixtures of methanol and methan[^{2}H]ol. The level of deuterium incorporation was varied to ensure assignment of the ^{13}C resonances of the deuteriated species. The isotope effects are measured from samples containing both species. The isotope effects are defined as $\Delta = \delta C(H) - \delta C(D)$. However, for **5** this mild procedure leads to incorporation of deuterium at the unsubstituted ring carbon, C-3. Ring deuteriation is a help in the assignment of the neighbouring carbons. The chemical shifts of **1–6** have been assigned previously.[3,18]

The ^{13}C NMR spectrum of 3,5-diacetyltetrahydropyran-2,4,6-trione shows two species a major, **1**, and a minor, **2** (Fig. 2).[3] **1** and **2** have two OH groups, both being deuteriated during treatment with methan[^{2}H]ol. The magnitudes of the intrinsic isotope effects depend on the distance to the site of deuteriation,[17] whereas if a chemical equilibrium is at hand, the observed isotope effects will most likely be dominated by equilibrium isotope effects.[14,16,17] This is clearly the case for β-diketones, which show isotope effects of the order of 0.6 ppm.[14,17] As two deuteriation sites are present, each carbon resonance can in principle show two isotope effects, leading to a maximum of four lines for each. The isotope effects of **1** show four large values for C-4, C-7, C-6 and C-9. All are of the order of 0.5 ppm at 300 K (Scheme 1). This is clearly indicative of a double tautomeric system as shown in Fig. 2 (**1a**–**1d**). The magnitudes of the isotope effects show that C-4 and C-7 are enolized to almost the same extent at room temperature, whereas for the pair C-6 and C-9, the latter is more enolized. The large isotope effects are paired as shown in Scheme 1. The isotope effects of C-6 and C-9 do not vary with temperature, whereas the other pair, C-4 and C-7, does. These findings are in agreement with the suggestions of Tan *et al.*[3] based on ^{13}C chemical shifts. The isotope effect of C-4 increases with a lowering of the temperature showing that the tautomers **1a** or **1b** become more stable at lower temperature.

The minor form, **2**, is symmetric judging from the number of ^{13}C and ^{1}H resonances. Several symmetric structures can be suggested, **2a** and **2d** and the average of **2b** + **2c** (Fig. 2). **2d** in equilibrium with **1d** + **1b** was suggested by Tan *et al.*[3] Upon deuteriation, the OH resonance splits into two resonances with a splitting of 0.21 ppm at 250 K in $CDCl_3$. Furthermore, the C-7, C-9 resonance splits into four resonances with the outer pair of resonances of equal intensity. The extra OH resonance can be explained by the finding that deuteriation at the other OH group leads to a weakening of that hydrogen bond[19] and consequently to a strengthening of the hydrogen bond in question. This strengthening leads to a low field shift of the OH resonance. 1,8-Dihydroxyanthraquinone behaves similarly.[20] A change in the hydrogen bond strength will lead to a change in the chemical shifts of C-7, C-9 and the long-range effect at C-7, C-9 can be explained. An alternative explanation is a shift in the equilibrium towards **2b** and **2c** leading to isotopic perturbation of equilibrium.[21] This possibility will be discussed later in relation to **3** and **4**. Observation of an isotopic perturbation shows that the structure has to be **2a**-like rather than **2d**-like (Fig. 2). *Ab initio* calculations (6–31** basis set)[22] show that **2a** is more stable than **2b** and **2c** by 22.6 kJ mol^{-1}. However, it is calculated that the symmetric compound **2** is more stable than the non-symmetric compound **1** by 14.0 kJ mol^{-1}. This is contrary to the NMR results. The calculations are carried out



Scheme 1 Deuterium isotope effects on ^{13}C chemical shifts (in ppm) and XH chemical shift (X = N or O) (shown in italics and given in ppm) of compounds **1**–**18**.[a] [a] The predominant form is shown for each compound. The solvent is $CDCl_3$ if nothing else is given. [b] The tautomers are shown in Fig. 2. The isotope effects are observed at 250 K. Values in square brackets were measured at 300 K. [c] Cannot be determined because of overlap. [d] Values in square brackets are due to deuteriation at C-2. [e] Owing to deuteriation at 5-O^{2}H. [f] Owing to deuteriation at 1-O^{2}H. [g] Solvent CD_2Cl_2–[$^2H_8$]THF, 170 K. Isotope effects are also seen at 200 K, $^2\Delta$C-4(OD) = 0.19 ppm and at 220 K in $CDCl_3$, $^2\Delta$C-4(OD) = 0.22 ppm. The number in square brackets is due to deuteriation at C-3. [h] The possible tautomers are shown in Fig. 4. [i] Value varies slightly. [j] br; broad. [k] Value owing to deuteriation at NH. [l] N.O.; not observed. [m] In $CDCl_3$–[$^2H_6$]DMSO the OH and NH proton chemical shifts are 11.82 and 11.57 ppm. [n] Observed at 240 K. [o] Solvent [$^2H_8$]THF, 200 K. Similar isotope effects are seen in [$^2H_6$]DMSO at 300 K. The values in square brackets are due to deuteriation at the imine NH position. [p] In $CDCl_3$–[$^2H_6$]DMSO. [q] Measured at 220 K.

for single molecules *in vacuo* and are therefore lacking solvent interactions.

1,5-Diphenylpentane-1,3,5-trione exists in two enolic forms; a symmetric, **3**, and a non-symmetric, **4**, form. The latter has only one enolic carbon (Scheme 1). The ratio of the two forms can be varied according to treatment. In CD_2Cl_2 only the

symmetric form is present. After being dissolved in methanol, the solvent subsequently evaporated and the compound was redissolved in CD_2Cl_2 without any visible traces of methanol being present, the ratio is 1 : 3 in favour of **3**. Upon deuteriation, the OH resonance belonging to **3** splits into four resonances with a large splitting of 0.141 ppm (200 K in $CDCl_3$). This is similar to **2**. The smaller splitting, 0.013 ppm, is due to deuteriation at C-2 and C-4. This is rather significant as it supports a structure like **3** with the OH groups at C-1 and C-5, whilst an OH group at C-3 would have resulted in two similar, small isotope effects. C-1 and C-5 splits into eight resonances in the ^{13}C NMR spectrum, caused by deuteriation at C-2 and C-4, in addition to the OH sites. The assignment of the eight resonances is accomplished by varying the degree of deuteriation. Again a long-range effect at C-5 is seen as a consequence of deuteriation at 1-OH.

For **4** a large $^2\Delta$C-1 (OD1) is found. The non-symmetrical structure leads to a larger shift in the equilibrium of the two enol forms for **4** than has been seen for similar β-diketones like hexane-2,4-dione.[23,24]

The assignment of the ^{13}C NMR spectrum of **5** in $CDCl_3$ at 300 K is in agreement with that of Tan *et al.*[3] The resonances of C-4 and C-6 change position and shift to high field when the solvent is changed to CD_2Cl_2–[$^2H_8$]THF. The assignment of the low temperature spectrum is aided by the observation of $^2\Delta$C-4(D) (Scheme 1).

The two-bond isotope effect of **5**, $^2\Delta$C-4(OD), is rather small (Scheme 1) indicating a weak hydrogen bond. It is therefore of interest to establish under which conditions this hydrogen bond is formed. The OH resonance is broad at temperatures above 220 K and shows some variation in the position: 12.26 and 12.64 ppm ($CDCl_3$, 300 and 220 K); 12.68 ppm (CD_2Cl_2, 200 K); 11.96 and 12.12 ppm (CD_2Cl_2–[$^2H_8$]THF, 200 and 170 K). The ^{13}C chemical shifts show a pronounced change in a mixture of CD_2Cl_2 and [$^2H_8$]THF compared with $CDCl_3$. This change (Table 1) is most clearly seen for C-4, C-5, C-6, C-7 and C-9. The largest changes are concentrated around C-4, C-5 and C-6 and are probably caused by a conformational change of the acetyl group. The ^{13}C chemical shifts in $CDCl_3$ are not very temperature sensitive, whereas those samples with [$^2H_8$]THF added approach the ^{13}C chemical shifts of samples in $CDCl_3$ at a high temperature (Table 1). The high field shift of C-9 and OH upon addition of [$^2H_8$]THF can be explained by comparison with 4,6-dimethyl-2-hydroxyacetophenone.[20] The high field shift is caused by a stronger twist of the acetyl group by addition of the more polar solvent.

The isotope effects observed for **6** are rather large. The temperature variations of the ^{13}C chemical shifts are moderate, less than 1 ppm for a change of 85 °C. The variations in the chemical shifts are towards larger isotope effects at lower temperatures except for C-7 and C-8. The OH chemical shift is found at 16.69 ppm at 300 K. This value and the magnitude of the isotope effects suggest a rather strong hydrogen bond as seen in (Fig. 1**f**). The temperature changes of both the isotope effects and the chemical shifts[21] are rather small. Both findings support that the tautomeric equilibrium is shifted far towards tautomer **f** of Fig. 1.[24]

The ^{13}C chemical shifts of **7** are for C-3, C-4, C-5, C-7 and C-8 quite similar to those of **6**. The δ_{OH} and the isotope effects are generally numerically smaller. One exception is at C-6. This effect could be due to deuteriation at the nitrogen.

The deuterium isotope effects of **8** are straightforward and suggest a medium strong intramolecular hydrogen bond between 4-OH and the ester group. This is best accomplished in a pyridone-type structure (Scheme 1). The OH chemical shift is assigned by means of a two-bond correlation to C-4 in a COLOC spectrum.[25] This resonance is the sharper.

Compound **9** is too insoluble at low temperatures to allow measurement of deuterium isotope effects. A tentative assignment of the ^{13}C NMR spectrum in [$^2H_6$]DMSO–$CDCl_3$ is given in Table 1. The chemical shifts of C-2 and C-6 are similar to those of **10**.

The ^1H NMR spectrum of **10** shows two low field resonances varying somewhat in position with temperature and the polarity of the solvent. The low field resonance is the broader and shows the largest positional variation (11.66–13.64 ppm compared with 11.42–12.26 ppm). The ^{13}C NMR spectrum has been assigned (Table 1). The isotope effects could only be observed at a low temperature (250 K). The $^2\Delta$C-4(OD) is lower than observed for **8**.

Treatment of **6** with concentrated ammonia leads to **11**. The position of the high frequency NH resonance is relatively solvent independent: 12.81 ppm in $CDCl_3$ *vs.* 12.15 ppm in [$^2H_6$]DMSO, whereas the position of the low frequency NH proton varies from 6.81 ppm in $CDCl_3$ to 9.72 in [$^2H_6$]DMSO. From these values we may assume that one NH proton is involved in hydrogen bonding and the other NH proton is not. The $^2\Delta$C-7(ND) values are small. Two isotope effects are also seen at the CH_3 carbon. The observation of two isotope effects at both C-3, C-7 and at C-8 shows that this has to be an amine form (Scheme 1) despite the claim that a compound made in a similar fashion is an imine.[26] The two-bond isotope effects are small and of similar magnitude to values observed in enaminones,[15] but are clearly smaller than those observed in 1,4-diamino-2,3-dihydro-9,10-anthraquinone.[27] The imine form is excluded as no three-bond isotope effect is observed at C-5. Such an isotope effect is observed in all phenols.[13,14]

12 was claimed in a recent paper to be of the imine form.[28] The ^{13}C chemical shifts for **12** are for C-3 to C-5 and C-7 to C-9 similar to those of **11** (Table 1).

Compounds **13**, **14** and **15** are seen to give slightly larger isotope effects than those of **7**, but are clearly of an equilibrium type (Scheme 1). For **15** the CH_2 resonance at 5.46 ppm is broad at room temperature. This splits upon cooling into two resonances with chemical shifts of 4.74 and 6.27 ppm (220 K). A similar feature is seen for **17**.

Compounds **16**–**18** are in the amine form in [$^2H_6$]DMSO.[12] These compounds show at room temperature in $CDCl_3$ and in CD_2Cl_2 two NH resonances with the resonance at high frequency the dominant. The ^{13}C NMR spectra at room temperature show broad resonances for a large number of carbons. At low temperatures, a second set of low intensity resonances are seen in both the ^1H and ^{13}C NMR spectra and the NH resonances for both the major and minor forms are sharpening up, both showing a typical triplet (J = 5.10 and 5.45 Hz, respectively). This supports an amine structure for both. Isotope effects are seen for both the major and the minor species (Scheme 1). The high frequency CH_2 resonance (δ = 5.43 ppm) is broad at room temperature. This resonance splits into two doublets (δ = 6.12 and 4.60 ppm, J = 16.6 Hz) at 190 K for **17**. For **17a**, a similar trend is also seen although the high field resonance is obscured by overlapping resonances. **15** showed after prolonged treatment with CH_3OD at 65 °C extensive deuterium incorporation at the C-8 methyl group.

Pyridone–pyridinol tautomerism

The dimerization of simple 2-pyridones is well known[10] and leads to low field shifts of the NH protons.[7,29,30] A similar feature is seen for compounds **7**–**10**. The NH resonances are broad probably owing to intermolecular exchange. This is likely also to be the reason for the absence of deuterium isotope effects in **8** caused by deuteriation at the NH position.

Simple pyridinols are known to exist almost exclusively in the pyridone form.[30] Solvents with low relative permittivity promote the pyridinol form and so do electronegative

Table 1 ^{13}C chemical shifts of **5–12** in ppm

Compound	Solvent	*T*/K	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
5	$CDCl_3$[a]	220	162.85	90.30	170.50	112.03	172.07	202.19	33.27	22.75
	$CDCl_3$[a]	300	162.06	90.35	170.34	111.99	172.09	201.86	32.75	22.53
	CD_2Cl_2–[$^2H_8$]THF[c]	300	162.19	89.54	168.82	114.56	167.83	199.41	32.13	19.91
	CD_2Cl_2–[$^2H_8$]THF[c]	170	162.59	88.25	167.81	114.86	165.47	198.87	31.76	18.62
	b	—	167.2	101.4	170.0	103.2	163.0	—	—	—
	d	—	169.9	104.1	177.1	98.2	164.0	—	—	—
6	$CDCl_3$	300	161.16	99.89	181.14	101.46	169.23	205.19	29.96	20.69
	b	—	163.2	110.5	170.0	94.1	167.0	—	—	—
	d	—	164.2	105.0	177.1	96.8	169.7	—	—	—
7	$CDCl_3$[e]	240	164.97	105.36	177.69	100.33	152.77	205.03	31.18	19.48
	b	—	166.6	114.3	169.1	94.7	151.0	—	—	—
	d	—	167.7	109.3	176.2	97.4	153.7	—	—	—
8[f]	$CDCl_3$[a]	300	163.53	96.59	176.06	99.73	151.86	171.98	61.57	19.14
	b	—	167.4	107.0	169.9	112.4	150.6	—	—	—
9	[$^2H_8$]DMSO[g]	300	163.07[h]	112.02	166.05[h]	95.85	149.05	199.07	31.97	17.73
	b	—	170.6	105.2	169.1	103.8	147.0	—	—	—
	d	—	173.3	107.9	176.2	98.8	148.0	—	—	—
10[i]	$CDCl_3$[a]	300	169.93[h]	97.70	165.96[h]	99.30	155.22	170.10[h]	62.19	21.51
	b	—	171.6	106.0	169.9	96.5	148.0	—	—	—
11	[$^2H_8$]THF[a]	200	163.21	96.38	184.85	107.81	163.35	177.64	25.31	19.64
12	$CDCl_3$–[$^2H_6$]DMSO	300	165.68	100.88	183.37	105.64	147.18	175.38	24.15	18.51

Compound	Solvent	*T*/K	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9	C-10	C-11
13	$CDCl_3$[a]	300	161.40	105.95	173.89	115.33	126.05	121.99	134.83	114.11	141.59	206.70	31.45	29.04
14[k]	$CDCl_3$[a]	300	161.16	105.73	173.74	115.06	123.90	121.55	134.00	124.76	138.48	206.66	31.48	41.89
15[l]	$CDCl_3$[a]	300	161.46	105.42	174.03	115.10	125.93	122.32	135.13	114.97	140.62	207.08	32.28	45.32
16[m]	$CDCl_3$[a]	220	163.64	102.04	176.74	121.00	126.22	121.38	133.14	114.01	140.56	180.14	19.62	28.71
16a[n]	$CDCl_3$[a]	220	166.49	100.75	175.87	121.89[h]	126.81	123.07[h]	132.83	n.o.[j]	139.78	179.11	19.79	28.86
17[o]	$CDCl_3$[a]	220	163.71	101.72	176.93	121.20	126.34	121.52	133.17	114.66	140.00	180.34	19.60	45.15
17a[p]	$CDCl_3$[a]	220	166.60	100.48	176.08	122.01[h]	n.o.[j]	123.23[h]	132.89	n.o.[j]	139.22	179.20	19.85	45.06
18[q]	$CDCl_3$[a]	220	163.38	101.74	176.53	120.75	124.18	120.69	132.54	124.40	137.24	180.14	19.47	47.75
18a[r]	$CDCl_3$[a]	220	166.09	100.45	175.75	122.89[h]	124.53	121.23[h]	132.31	124.80	n.o.[j]	179.07	n.o.[j]	n.o.[j]

[a] Relative to TMS. [b] Calculated from substituent effects on benzene using pyran-2-one as the backbone structure for **5**, **6** and 2-pyridone for **7–10**. [c] Relative to CD_2Cl_2 (53.6 ppm). [d] Calculated from substituent effects, using pyran-2-one as the backbone structure for **5**, **6** and 2-pyridone for **7** and **9**, the hydroxy and acetyl substituent effects are derived from 2-hydroxyacetophenone and the methyl group values are derived from toluene. [e] Chemical shift very similar in $CDCl_3$–[$^2H_6$]DMSO. [f] $\delta_{C\text{-}10}$ = 14.13 ppm. [g] Relative to [$^2H_6$]DMSO (39.6 ppm). [h] May be interchanged. [i] $\delta_{C\text{-}10}$ = 14.21 ppm. [j] n.o.; not observed. [k] C-12 = 20.64, C-13 = 27.64. [l] C-12 = 135.67, C-13 = 128.82, C-14 = 125.85, C-15 = 127.23. [m] C-12 = 47.83, C-13 = 135.14, C-14 = 129.09, C-15 = 127.14, C-16 = 128.06. [n] C-12 = 47.57, C-13 = 135.26, C-14 = n.o., C-15 = 127.04, C-16 = n.o. [o] C-12 = 136.64, C-13 = 128.70, C-14 = 125.73, C-15 = 126.86, C-16 = 47.79, C-17 = 135.11, C-18 = 129.07, C-19 = 127.11, C-20 = 128.04. [p] C-12 = 136.24, C-13 = 128.79, C-14 = 125.50, C-15 = n.o., C-16 = 47.58, C-17–C-20 = n.o. [q] C-12 = 20.49, C-13 = 27.66, C-14 = 41.36, C-15 = 135.19, C-16 = 129.04, C-17 = 127.11, C-18 = 127.99. [r] C-12–C-18 = n.o.

substituents at the C-6 position.[30] The compounds **7**–**10** and **12** can thus be either 2-pyridones, pyridin-2-ols or a tautomeric mixture of both. They could in principle also be 4-pyridones. The pyridinols are aromatic and deuterium isotope effects on ^{13}C chemical shifts, $^{n}\Delta C(OD)$, are thus expected to behave like those obtained in benzene derivatives.[13] Consequently, as compounds **7** and **8** show large OH chemical shifts and a large $^{2}\Delta C$-4(OD) isotope effect, these parameters do not indicate that very much pyridinol exists.

Having established the tautomeric form, the ^{13}C chemical shifts can be examined as a possible way of assigning the tautomeric forms. The ^{13}C chemical shifts as predicted either from simple additivity of substituent effects[31] or obtained by using data for 2-hydroxyacetophenone[32] do not fit well as seen in Table 1. The most promising parameter for distinguishing the two tautomers (pyridinols *vs.* pyridones) is the chemical shift of C-6. The ^{13}C chemical shift for C-6 is generally 13 ppm to higher frequency for the pyridinol form. For **7**, **8** and **9** in [$^{2}H_6$]DMSO–$CDCl_3$ the agreement with predicted chemical shifts is rather good (Table 1). However, for **10**, the C-6 chemical shift is predicted poorly and the value is actually midway between that of a pyridin-2-ol and a 2-pyridone.

A comparison of $^{2}\Delta C$-4(OD) for 3- and 5-substituted esters shows that $^{2}\Delta C$-4(OD) for the 3-substituted esters are the larger. This most likely can be ascribed to the differences in double bond lengths of the C-3–C-4 and C-4–C-5 bonds or analogously as a difference in double bond order. For 2-pyridone, the bond lengths were calculated by AM1 calculations[33] to be 1.358 and 1.428 Å, respectively. Similar values are obtained from *ab initio* calculations.[34] A comparison of OH chemical shifts and magnitudes of two- and four-bond isotope effects of **6**, **7**, **13**, **14** and **15** gives the following order **13** ~ **14** ~ **15** ~ **6** > **7**. These compounds reveal β-diketone tautomerism involving carbons C-3, C-4 and C-7. The sum of the two-bond and four-bond isotope effects are assumed to be a measure of the hydrogen bond strength[17,24] and show the same order as above.

Observation of a large isotope effect at C-8 due to isotopic perturbation of equilibrium showed that the structure had to be symmetrical and similar to **2**. The structure can be either localized as in **2a** or a tautomeric mixture of **2a**, **2b** and **2c** time averaged fast enough on the NMR timescale that leads to a symmetrical NMR spectral appearance. The magnitude of the perturbation points towards an equilibrium.[17,19,20]

Intramolecular hydrogen bonding is a common and important structure determining factor for the investigated compounds. Breaking of this bond leads to conformational changes as seen for **5**. The strength of the hydrogen bond can for tautomeric systems be determined by the sum of $^{2}\Delta C(OD)$ and $^{4}\Delta C(OD)$.[17,24] A comparison of sums for **1**, **4**, **6** and **7** with δ_{OH} reveals a difference in order. In particular, the δ_{OH} values for **1**, **6** and **7** seem too high, probably due to the high acidity of these protons.[4] This is also the case for the non-tautomeric compounds **5**, **8**–**10** explaining why cooling for **5**, **9** and **10** is necessary to observe sharp OH resonances.

For the non-tautomeric compounds **2** and **3**, both with two hydrogen bonds to the same acceptor, we observed weaker individual hydrogen bonds than is seen for compounds with a full double bond.[24] This is clearly caused by the acceptor being unable to form strong hydrogen bonds of RAHB type.[14,17,35]

Keto-enamine–enol-imine tautomerism

The structure of **11** has been claimed to be the enol-imine form.[26] However, the observation of two isotope effects at both C-7 and C-8 shows that this has to be the keto-enamine form.

The observation of two forms for **16**–**18** in non-polar solvents, the close resemblance in chemical shift of the major and the minor forms and the similar $^{2}\Delta C(ND)$ isotope effects

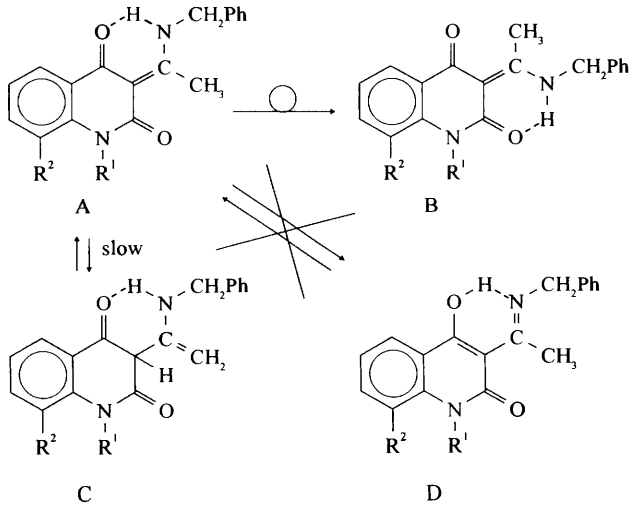


Fig. 3 Tautomeric forms of **16** (R^1 = CH_3, R^2 = H), **17** (R^1 = CH_2Ph, R^2 = H) and **18** [R^1, R^2 = $-(CH_2)_3-$]

with the one of the minor form the smaller suggest that these are the structures shown in Fig. 3 (A, B). The observation that both NH resonances show triplets rules out the keto-imine form (D). The finding that the major (A) and the minor (B) forms are at equilibrium at room temperature has been explained in similar compounds based on aldehydes to be due to rotation around the double bond.[12] The finding that the protons of C-10 exchange with methan[^{2}H]ol with prolonged treatment suggests also that C exists, but in slow exchange on the NMR timescale.

A survey of Scheme 1 reveals that the preferred form of several compounds, **2**, **11**, **12** and **16**–**18**, contains multiple exocyclic double bonds. This phenomenon is especially common for compounds in which an enamine is formed.

Experimental

Compounds

1 and **6** were purchased from Aldrich Chemicals, Weinheim, Germany. Compounds **3**,[36] **5**,[26] **7**,[37,38] **8**,[39] **10**,[39] **12**,[37,38] **13**–**18**[12] were prepared as described. Compounds **9**[26] and **11**[40] were prepared by dissolving the corresponding pyrans in conc. ammonia overnight. An attempt to prepare **7** from acetoacetamide in pyrophosphoric acid was also made.[28] This procedure led to a mixture of **7** and **9**. Deuteriation was usually achieved by dissolving the compounds in a mixture of CH_3O^2H and CH_3OH for an hour or more and subsequent evaporation. In the case of **11** the compound was deuteriated partially by means of the traces of D_2O in [$^{2}H_6$]DMSO.

NMR spectroscopy

The ^{13}C NMR spectra of deuteriated species were recorded on a Bruker AC 250 NMR spectrometer at 62.896 MHz with a digital resolution of 0.55 Hz per point. Chemical shifts are measured relative to internal TMS. Spectra were recorded at 300 K and in $CDCl_3$ unless otherwise given. Spectra of both non-deuteriated species and of mixtures of protonated and deuteriated species in different ratios were recorded for all compounds.

Low temperature spectra were recorded in CD_2Cl_2.

Acknowledgements

Thanks are due to Annelise Gudmundsson for assistance with recording of NMR spectra, Associate Professor J. Spanget

Larsen for the AM1 calculations on pyridones and Morten Langgård for the GAUSSIAN 92 calculations.

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Paper 5/01272D
Received 2nd *March* 1995
Accepted 25th *April* 1995