Effects of 5-Acyl Substituents on Some Properties of Pyran-2,4-diones

Sau-Fun Tan, Kok-Peng Ang, and Harilakshmi Jayachandran
Department of Chemistry, National University of Singapore, Kent Ridge, Singapore 0511
Michael P. Sammes
Department of Chemistry, University of Hong Kong, Pokfulam Road, Hong Kong

The effects of 5-acyl substituents on the tautomerism of pyran-2,4-diones are revealed by comparison of the u.v., i.r., ^{1}H, and ^{13}C n.m.r. spectral properties of 5-acetyl-6-methyl-, 5-acetyl-6-phenyl-, 5-benzoyl-6-methyl-, and 3,5-diacetyl-6-methyl-pyran-2,4-diones (**3**)—(**6**), with those of 6-methyl- (**1**) and 3-acetyl-6-methyl-pyran-2,4-dione (**2**). The differences in the behaviour of the 5-acyl and 3-acyl derivatives towards primary amines are also discussed. Compound (**6**) reacts with aniline to form 5-acetyl-2,6-dimethyl-1-phenyl-4-oxopyridine-3-carboxylic acid (**7**).

Pyran-2,4-diones may exist in the tautomeric 4-hydroxy-2-pyrone or 2-hydroxy-4-pyrone forms, the dioxo form being unimportant. The tautomeric equilibrium of 2- and 4-pyrone could be affected by the nature and orientation of substituent groups as well as by the physical state. Thus, the 2-pyrone form appears to be the predominant tautomer for 3,5-dimethylpyran-2,4-dione.[1] On the other hand, 6-methylpyran-2,4-dione (**1**) appears to be associated in the solid state, through strong intermolecular hydrogen-bonds with cyclic electron delocalization which facilitates interconversion between the 4-hydroxy-2-pyrone and 2-hydroxy-4-pyrone forms. However, in dilute solutions, the 2-pyrone form is favoured.[2] This is consistent with the observation that 4-methoxy-2-pyrone is more stable than 2-methoxy-4-pyrone by at least 12.5 kJ mol^{-1} at 140 °C.[3]

A 3-acyl substituent could further enhance the preference for the 2-pyrone structure by forming a conjugate chelate ring through strong intramolecular hydrogen-bond with the 4-hydroxy-group. This has been confirmed for 3-acetyl-6-methyl-pyran-2,4-dione (**2**) by various studies.[4,5] Changing the acyl substituent from C-3 to C-5, however, produces some interesting and significant effects. 5-Acetyl-6-methyl-, 5-acetyl-6-phenyl-, and 5-benzoyl-6-methyl-pyran-2,4-diones (**3**)—(**5**) have been synthesized but there is no complete agreement among previous workers regarding their detailed structures. Butt and Elvidge[6] first prepared compound (**3**) and assigned to it the 2-hydroxy-4-pyrone structure, while Omori *et al.*[7] suggested the 4-pyrone structure in the solid state but the 2-pyrone structure in solution. Butt and Elvidge also assigned the 4-hydroxy-2-pyrone structure to compound (**4**) and postulated a tautomeric change to the 2-hydroxy-4-pyrone structure when heated above its m.p. (168 °C). However, Ziegler and Hradetzky[8] showed that the thermal reaction was not a tautomeric change but a rearrangement from compound (**4**) to (**5**). They also prepared 3,5-diacetyl-6-methylpyran-2,4-dione (**6**)[9] and assigned 4-hydroxy-2-pyrone structures to all three compounds (**4**)—(**6**).

In the course of our studies on the acidities of hydroxypyrones, we have re-examined u.v., i.r., and ^{1}H n.m.r. spectra of compounds (**3**)—(**5**)[10] and have now recorded the same for compound (**6**) as well as ^{13}C n.m.r. spectra of all four compounds. Comparison of these spectral data (Tables 1 and 2) with those of compounds (**1**) and (**2**) affords an insight into the influence of the C-5 acyl group on the tautomerism and some other properties such as m.p. and reactivity towards primary amines.

Results and Discussion

The 2-pyrone ring, though pseudoaromatic, shows considerable localization of π bonds[11] with much higher electron density between C-3 and -4 than between C-4 and -5 so that the 5-acetyl and 4-hydroxy-groups of compound (**3**) cannot be expected to form an intramolecular hydrogen-bond of similar strength to that in the isomeric compounds (**2**). Moreover, the absence of a substituent at C-3 allows the possibility of association through intermolecular hydrogen-bonds similar to the type present in compound (**1**). Hence compared to compound (**2**), isomer (**3**) shows a much less overwhelming preference for the 2-pyrone structure and a greater inclination towards the 4-pyrone tautomer. The much shorter wavelength of the u.v. absorption of (**3**) than (**2**) and the absence of ν(C=O) > 1 700 cm^{-1} in the i.r. spectrum were cited by Butt and Elvidge as evidence for the 4-pyrone structure. In addition, the u.v. absorption of (**2**) is practically the same in different solvents. However, the u.v. spectra of (**3**) in different solvents (Figure) suggest varying equilibria between tautomeric forms. Moreover, the i.r. spectrum of (**3**) in the solid state (KBr) shows clearly the very strong and broad OH stretching bands at 3 100—2 400 cm^{-1} typical of association *via* intermolecular hydrogen-bond as in compound (**1**) and strong C=O absorption at 1 670 cm^{-1}, but in its i.r.

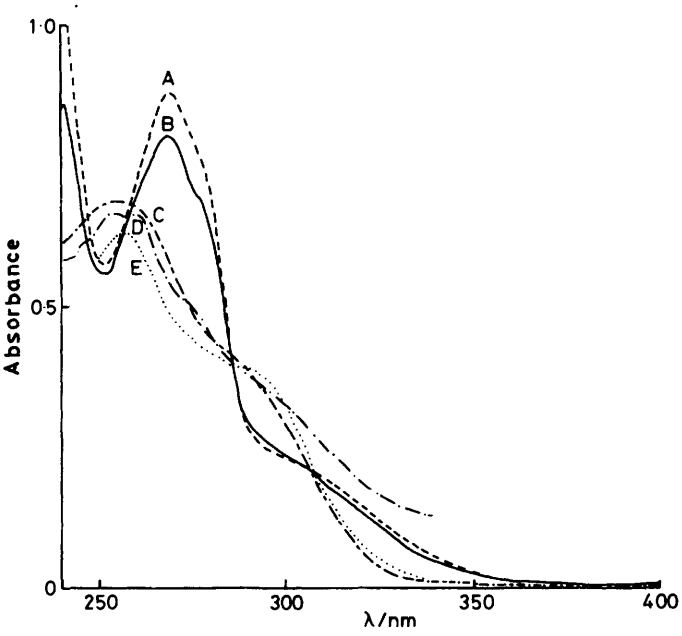
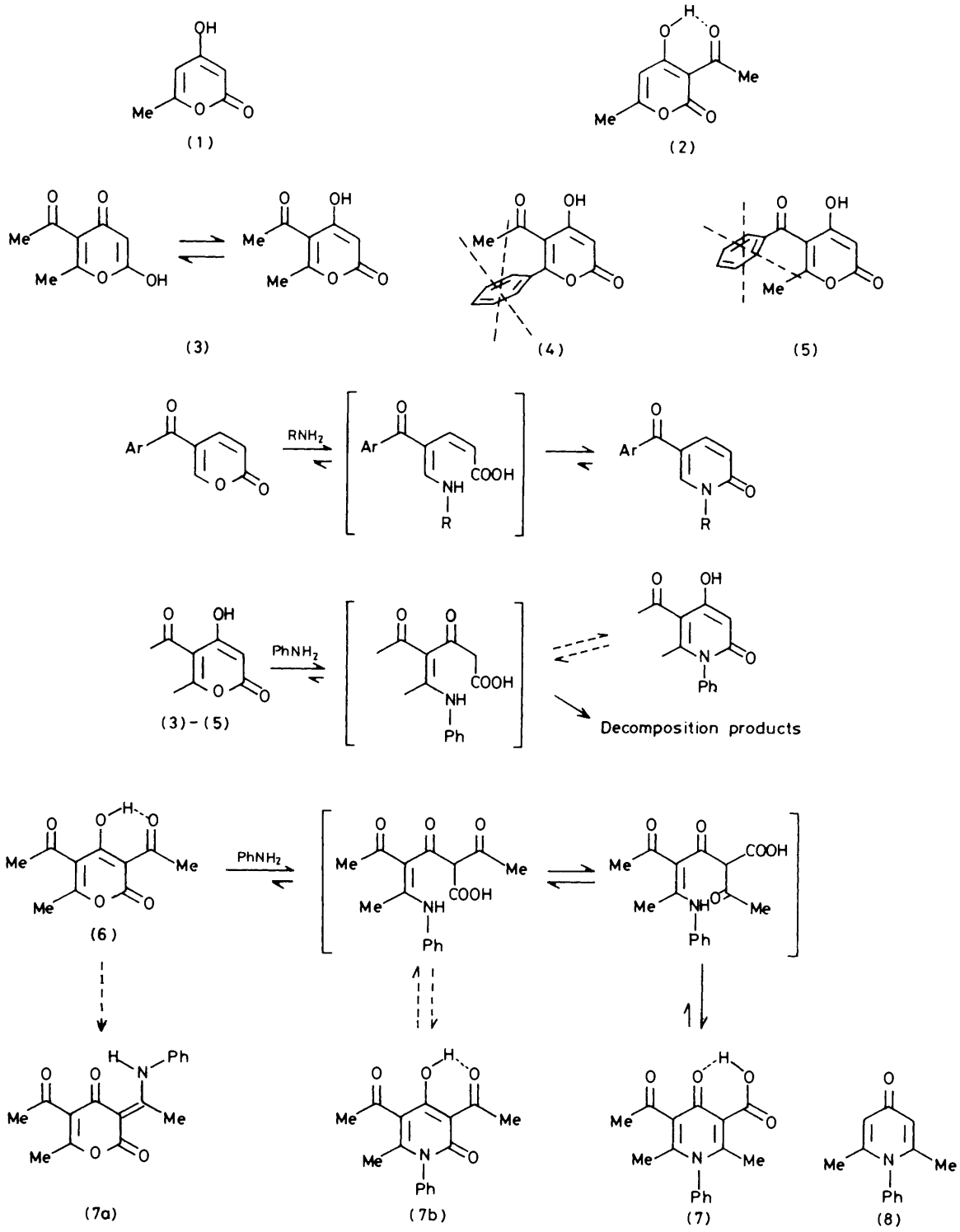


Figure. U.v. spectra of compound (**3**) in dichloromethane (A), chloroform (B), ethanol (C), dioxane (D), and 80% (w/w) DMSO–H_2O (E)



spectrum in solution ($CHCl_3$) the OH band is now broad and weak and the C=O absorption shifts to 1 760 cm^{-1}, suggesting intramolecular hydrogen-bonding and 2-pyrone structures respectively.

Compounds (**4**) and (**5**) also show major u.v. absorptions in the region 260—280 nm and these also change with solvents although no definite trend could be detected for these changes. Their i.r. spectra in KBr also show the strong and broad bands of strongly intermolecularly hydrogen-bonded OH groups. Compound (**4**) resembles (**3**) in showing similar changes in the pyrone carbonyl absorptions in its i.r. spectra in the solid state and in solution but compound (**5**) shows carbonyl stretching > 1 700 cm^{-1} in both states.

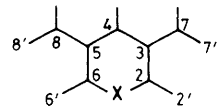
Compound (**6**), on the other hand, resembles (**2**) in its u.v. absorptions and its i.r. spectra show a weak and broad intramolecularly hydrogen-bonded OH band and carbonyl stretching of the 2-pyrone both in solid state and in solution, thus indicating that when both 3- and 5-acetyl groups are present, 4-hydroxy preferentially chelates with the 3-acetyl group.

Table 1. U.v., i.r., and ^{1}H n.m.r. spectral data for compounds (**1**)—(**7**)

		λ_{max}/nm ($\log_{10}\varepsilon$)					ν/cm^{-1}		Chemical shift *, δ		
Compound	M.p. (°C)	$CHCl_3$	Dioxane	Cyclohexane†	Ethanol	80% DMSO–water	Nujol—KBr	$CHCl_3$	OH	CH_3	Others
(**1**)	188—189	284 (3.77)	284 (3.72)		276 (3.86)	284 (3.78)	1720 (s) 1661 (w) 1630, 1594 1543 (w)	1720 (sh) 1705 (s) 1645 (v, w) 1580 (s)	11.20 (br)	2.19 (6-Me)	5.25 (3-H) 5.95 (5-H)
(**2**)	108—111	310 (4.03)	310 (4.02)	310	230 (3.90) 295 (4.23)	310 (4.08)	3400—2600 (b, w) 1725 (s) 1645 (s) 1555 (s)	3500 (b) 1750 1730 (s) 1650 (s) 1580 (s)	16.68 (35 °C) 16.72 (−50 °C)	2.28 (6-Me) 2.62 (Ac-Me)	6.0 (5-H)
(**3**)	158—159	268 (4.00) 295 (sh)	265 (3.95) 295 (sh)		260 (3.97) 295 (sh)	258 (3.87) 290 (sh)	3300—2400 (b, s) 1670 (s) 1600 (s) 1560 (m)	3400—2400 (b, w) 1750 (s) 1675 (s) 1540	12.31 (25 °C) 12.80 (−50 °C)	2.63 (6-Me) 2.69 (Ac-Me)	5.52 (3-H)
(**4**)	165—166	266 (4.13) 320 (w, b)	260 (4.03) 315	260 320 (w)	255 (3.96) 308	255 (4.05) 310	3100—2400 (b, w) 1685 (s) 1620 1560	3400—2400 (b, w) 1740 (s) 1660 (s) 1550	11.65 (25 °C) 11.99 (−50 °C)	1.95 (Ac-Me)	5.63 (3-H) 7.56 (Ph)
(**5**)	220	260 (4.49) 275 (sh)	250 (4.50) 280 (w)		248 (4.49) 270 (sh)	258 (4.49) 280 (sh)	3200—2400 (b, s) 1730 (s) 1675 1620	3400—2400 (b, w) 1730 (s) 1660 1570	10.35 (25 °C) 11.33 (−50 °C)	2.04 (6-Me)	5.6 (3-H) 7.54—7.74 (Ph)
(**6**)	95—96	312	310	224 312	228 305	268 310 (sh)	1745 (s) 1705 (s) 1610 (s) 1560 (w)	1745 (s) 1705 (m) 1610 (s) 1560 (w)	17.9	2.40 (6-Me) 2.52 (Ac-Me at C-5) 2.68 (Ac-Me at C-3)	
(**7**)	188	262 (4.22) 300 (w)	262 (4.22) 300 (w)		262 (4.17) 300 (w)	260 (4.17) 295 (sh)	1710 (s) 1690 (sh) 1630 (w) 1590 (m)	1710 (s) 1620 (m) 1590 (m)	17.15 (−40 °C)	2.00 2.60 2.68	7.50 (Ph)

† Saturated solutions were used due to poor solubility. * ^{1}H n.m.r spectra of compounds (**2**), (**3**), (**6**), and (**7**) were obtained in $CDCl_3$ and those of compounds (**1**), (**4**), and (**5**) in [$^2H_6$]DMSO.

Table 2. Carbon-13 chemical shifts of compounds (**1**)—(**7**) in $CDCl_3$ at 35 C [a] [δ (p.p.m.) from Me_4Si]



numbering of carbon skeleton

Compound / Assignment	(1)	(2)	(3)	(4)	(5)	(6)	(7)
C-2	167.74 (s)	161.18 (s)	161.52 (d, 3.1)	161.16	162.04	159.87	159.3
C-3	89.26 (dd, 168, 3.6)	99.92	90.42 (d, 151.0)	90.81	90.8	99.39	130.3/115.0
C-4	172.13 (t, 1.7)	181.17 (5.3, 1.8)	170.35 (d, 3.3)	169.2	168.6	179.95	177.1
C-5	101.6 (dq, 170, 3.5)	101.46 (173, 3.7)	111.39 (br, s)	110.62	110.61	115.92	115/130.3
C-6	163.61 (q, 6.4)	169.18 (6.3)	172.86 (q, 6.3)	170.02	170.83	172.17	148.8
C-7		205.23 (6.5)				205.61	166.7
C-8			202.27 (q, 5.4)	204.2	197.84	196.71	201.8
C-2[1]							19.2
C-6[1]	19.79 (dq, 129.5, 2.8)	20.69 (120, 2.7)	22.99 (q, 131)		22.15	20.07	20.6
C-7[1]		29.97 (129.6)				29.63	
C-8[1]			32.8 (q, 129)	31.28		32.29	31.8
ortho-H				129.55	128.87		130.9
meta-H				129.23	129.24		127.5
para-H				132.8	134.13		130.7
ipso-H				132.55	138.7		138.95

[a] $^1J_{C-H}$ and $^2J_{C-H}$ values in brackets

Although ^1H n.m.r. spectra of compounds (**3**) and (**5**) were previously recorded, the enolic proton was detected only for compound (**3**). These spectra as well as that of compound (**6**) have now been studied at low temperatures. Not only are signals of enolic protons detected for all four compounds but the structural effects on the chemical shifts of methyl and phenyl signals reveal significant information. The enolic protons of compounds (**3**)—(**5**) (in $CDCl_3$) at 25 °C give broad signals at δ 12.31, 11.65, and 10.35 p.p.m., respectively. These sharpen and move downfields to 12.80, 11.99, and 11.33 p.p.m. at −60 °C. When compared with the enolic proton signal given by compound (**2**), these considerably higher field signals of compounds (**3**)—(**5**), their relative breadth at ambient temperature, and their much more marked movements downfield on lowering of temperature are all consistent with weaker hydrogen-bonds, faster exchange, and possible intermolecular association[12] (in chloroform) as deduced from other observations. Compound (**6**), on the other hand, shows a sharp signal even at 35 °C at δ 17.9 p.p.m., *ca.* 1.2 p.p.m. lower field than that of compound (**2**), confirming the presence of very strong intramolecular hydrogen-bond which may have been enhanced by the steric crowding due to the 5-acetyl group.

The presence of the 5-acetyl group also produces deshielding effect on the 6-methyl protons in compounds (**3**) and (**6**), when compared with compounds (**1**) and (**2**). However, the 6-methyl protons of compound (**5**) give a significantly higher field signal, most probably as a result of being in the shielding region of the phenyl group which therefore must be orthogonal to the pyrone ring. Similarly, the 6-phenyl group in compound (**4**) exerts shielding influence on the methyl protons of the 5-acetyl group which resonate at much higher field than the similar protons of compounds (**2**) and (**3**).

The ^{13}C n.m.r. spectrum of unsubstituted 2-pyrone clearly shows alternation of π-electron densities around the ring.[10] Assignments of the ^{13}C signals of compounds (**3**)—(**6**) have been made taking into account the effects of substituent groups. A hydroxy group deshields the α-carbon by inductive effect but shields a β-carbon by resonance effect. Both methyl and acetyl groups deshield an α-carbon. The methyl carbons attached to C-6 resonate in the range 19—22 p.p.m., while those of the acetyl group are in the range 26—31 p.p.m. The lowest field signals are assigned to the side-chain carbonyl carbons. Using acetophenone as model compound, hydrogen-bonding in *o*-hydroxyacetophenone produces a pronounced downfield shift of 6—7 p.p.m. This effect is clearly seen in the low field resonance of the acetyl carbon in compound (**2**). In view of the much weaker hydrogen-bond of compounds (**3**) and (**4**), it is surprising that their acetyl resonances occur at comparably low field. A possible explanation could be the steric interaction with the 6-substituent twisting the acetyl group out of plane, thus minimising the conjugation of the acetyl group with the π system of the pyrone ring: an analogous effect has been observed with some sterically hindered acetophenones.[13] The benzoyl carbon of compound (**5**) resonates at higher field, with a chemical shift comparable to that of the acetophenone carbonyl because of its conjugation with the phenyl group although it might be out of plane with the pyrone ring. In line with the above, the signals of compound (**6**) at δ 205.6 and 196.7 p.p.m. have been assigned to the 3- and 5-acetyl carbonyl carbons respectively.

Thus, the spectral studies discussed above have revealed pronounced effects of the different positions of the acyl substituent at C-3 and -5 on the properties of these pyran-2,4-diones. The 3-acyl group, by virtue of formation of a conjugate chelate ring, favours overwhelmingly the 4-hydroxy-2-pyrone tautomer for compounds (**2**) and (**6**). The 5-acyl group, on the other hand, cannot form similar chelate rings and hence compounds (**3**)—(**5**) show varying degrees of tautomeric equilibria between 2- and 4-pyrone forms with intermolecular association, at least in the solid state and possibly in non-polar solvents. The latter deduction is also consistent with observed large differences in m.p.s between the two groups of compounds. Compounds (**1**), (**3**), (**4**), and (**5**), existing as associated molecules, have higher m.p.s than compounds (**2**) and (**6**) which exist as discrete intramolecularly hydrogen-bonded molecules. Moreover, it is noted that compound (**2**) sublimes readily

under reduced pressure, its isomer (**3**), does so much less readily and at higher temperatures.

Differences in reactivity of compounds (**2**)—(**5**) towards primary amines may also be correlated with structural differences. An acyl-substituted pyrone could, at least theoretically, react with a primary amine at either the side chain carbonyl to yield a Schiff's base or at the pyrone ring to form a pyridone. The position of the acyl substituent apparently has pronounced effect on the competition between these two possible reactions. The 3-acetyl group in compound (**2**) reacts with a number of aliphatic and aromatic amines readily, giving Schiff's bases[14,15] often with high yields. This is reminiscent of the observed ease of reaction of *o*-hydroxyacetophenone but lack of reactivity of the *m*- or *p*-isomers and the unsubstituted acetophenone towards primary amines. These Schiff's bases of (2) have been prepared without added catalysts under milder conditions than those generally required for Schiff's bases of aromatic aldehydes and ketones. As Schiff's base formation is accelerated by general acid catalysis,[16] the intramolecularly hydrogen-bonded 4-hydroxy-group could provide an internal catalytic effect.[17] Moreover, similar chelation could also stabilise the products and thus contribute to their ease of formation.

An acyl group at C-5 would withdraw electrons from C-6, facilitating attack by the amine at this site. Wiley and Slaymaker[18] found that 5-aroyl-2-pyrones were converted to pyridones by reaction with amines. The reactions of compounds (**3**)—(**5**) with amines are probably more complex as the intermediates formed by cleavage of the pyrone ring are 3,5-dioxocarboxylic acids and their decomposition could compete effectively against recyclization to pyridones. No crystalline products have been isolated from reactions of compounds (**3**)—(**5**) with aniline.

Compound (**6**), on the other hand, with acetyl substituents at both C-3 and -5, reacts readily with aniline to give a crystalline 1:1 molar condensation product. This could conceivably be a mono-Schiff's base [structure (**7a**)] formed at the more reactive 3-acetyl group or either of the pyridones (**7**) or (**7b**) formed by attack of aniline at C-6 followed by recyclization in two different ways. The ^{1}H n.m.r. spectrum (at −40 °C) shows a sharp, lowfield signal at δ 17.2, suggestive of a strongly hydrogen-bonded OH proton and therefore inconsistent with structure (**7a**). The NH protons in analogous Schiff's bases recently studied[13] generally resonate at δ 13—16 p.p.m. Moreover, one of the three methyl signals in the parent compound (**6**) has now shifted considerably upfield to δ 1.98 whereas such a change is not expected on formation of a Schiff's base.[13] The coupled ^{13}C n.m.r. spectrum shows only one acetyl C=O at δ 201.8 p.p.m. thus eliminating the possibility of structure (**7b**) but favouring structure (**7**). The other two quartets at higher fields δ 159.3 and 148.8 p.p.m. are identified as ring carbons attached to methyl groups, namely C-2 and -6. For confirmation, 2,6-dimethyl-1-phenyl-4-oxopyridine (**8**)[19] has been prepared as a model compound. The aryl protons in the ^{1}H n.m.r. spectra of (**7**) and (**8**) are strikingly similar and the methyl signal of (**8**) at δ 1.92 is very close to the high field methyl signal also noted in the spectrum of (**7**) which may now be assigned to the 2-methyl group. In the ^{13}C spectra, the phenyl carbons of compound (**7**) match very well those of compound (**8**) and are 1—3 p.p.m. lower field than those of Schiff's base of compound (**2**), probably due to the electron-withdrawing effect of the involvement of the nitrogen in a pyridone ring. The ^{13}C chemical shifts of the ring methyl and the C-4 carbonyl carbons of compounds (**7**) and (**8**) are also in agreement. There remains some uncertainty in the assignment of the singlets at δ 115.0 and 130.3 p.p.m. to C-3 or -5.

The rather striking difference in behaviour of compound (**6**) from (**2**) and (**3**) towards aniline may now be related to the previously noted difficulty in measuring the pK of compound (**6**).[10] Its instability in 80% DMSO–water solution, as shown by changes in u.v. spectrum, is probably the result of nucleophilic cleavage of the pyrone ring at C-6. The combined electron-withdrawing influence of two acetyl groups predisposes the ring to reaction with nucleophiles.

Experimental

Compounds (**3**)—(**6**) and (**8**) were prepared according to literature procedures.[6,8,9,19]

U.v. spectra were recorded with a Shimadzu spectrometer model UV240 using matched 1.0 cm silica cells. Solutions of concentrations ranging from 4.0×10^{-5} to 9×10^{-5} M were prepared using redistilled solvents. I.r. spectra were recorded on a Unicam SP 1000 spectrophotometer for KBr discs or Nujol mulls. Spectra for the solutions (in spectroscopic grade chloroform) were obtained using NaCl cells of 1.0 mm path length.

^{1}H N.m.r. spectra were recorded with a Perkin-Elmer R32 spectrometer at 90 MHz and ^{13}C n.m.r. spectra with Bruker HFX-270 and JEOL JMN FX-100 spectrometers.

5-Acetyl-2,6-dimethyl-1-phenyl-4-oxopyridine-3-carboxylic Acid (**7**)—Compound (**6**) (160 mg) was refluxed with aniline (90 mg) in ethanol (8 ml) for 10 min. *5-Acetyl-2,6-dimethyl-1-phenyl-4-oxopyridine-3-carboxylic acid* was recrystallised from ethanol, m.p. 188° (Found: C, 67.15; H, 5.45; N, 4.6. $C_{16}H_{15}NO_4$ requires C, 67.4; H, 5.3; N, 4.9%).

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References

1 E. Niccoli, U. Vaglini, and C. Cassarelli, *Ann. Chim. (Rome)*, 1968, **58**, 664.
2 J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 1960, 502.
3 P. Beak, *Tetrahedron Lett.*, 1963, 863.
4 S. Forsen and M. Nillson, *Ark. Kemi*, 1961, **17**, 523.
5 E. E. Royals and J. C. Leffingwell, *J. Org. Chem.*, 1965, **30**, 1255.
6 M. A. Butt and J. A. Elvidge, *J. Chem. Soc.*, 1963, 4483.
7 A. Omori, N. Sonada, S. O. Kano, and S. Tsutsumi, *Tetrahedron Lett.*, 1968, 3647.
8 E. Ziegler and F. Hradetzky, *Monatsh. Chem.*, 1966, **97**, 710.
9 F. Hradetzky and E. Ziegler, *Monatsh. Chem.*, 1966, **97**, 398.
10 Sau-Fun Tan, Kok-Peng Ang, and H. L. Jayachandran, *J. Chem. Soc., Perkin Trans. 2*, 1983, 471.
11 W. V. Turner and W. H. Pirkle, *J. Org. Chem.*, 1974, **39**, 1935.
12 G. O. Dudek and E. P. Dudek, *J. Am. Chem. Soc.*, 1964, **86**, 4283.
13 J. B. Stothers and P. C. Lauterbur, *Can. J. Chem.*, 1964, **42**, 1563.
14 Sau-Fun Tan, Kok-Peng Ang, H. L. Jayachandran, A. J. Jones, and W. R. Begg, *J. Chem. Soc., Perkin Trans. 2*, 1982, 513.
15 J. D. Edwards, J. E. Page, and M. Pianka, *J. Chem. Soc.*, 1964, 5200.
16 W. P. Jencks, in 'Progress in Physical Organic Chemistry', eds. S. G. Cohan, A. Streitweiser Jr., and R. W. Taft, Interscience, New York, 1964, vol. 2, pp. 85—95.
17 W. P. Jencks, 'Catalysis in Chemistry and Enzymology', McGraw-Hill, New York, 1969, pp. 323—325.
18 R. H. Wiley and S. C. Slaymaker, *J. Am. Chem. Soc.*, 1956, **78**, 2393.
19 S. Hünig and G. Kobrich, *Liebig's Ann. Chem.*, 1958, **617**, 181.

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