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USE OF SELECTIVE HETERONUCLEAR $^{13}C\{^{1}H\}$ NOE MEASUREMENTS. A SECOND NOTE OF WARNING ON THE ASSIGNMENT OF STRUCTURE TO THE PRODUCTS FORMED IN THE REACTIONS BETWEEN 4-HYDROXY-2H-PYRAN-2-ONES AND CARBONYL COMPOUNDS.

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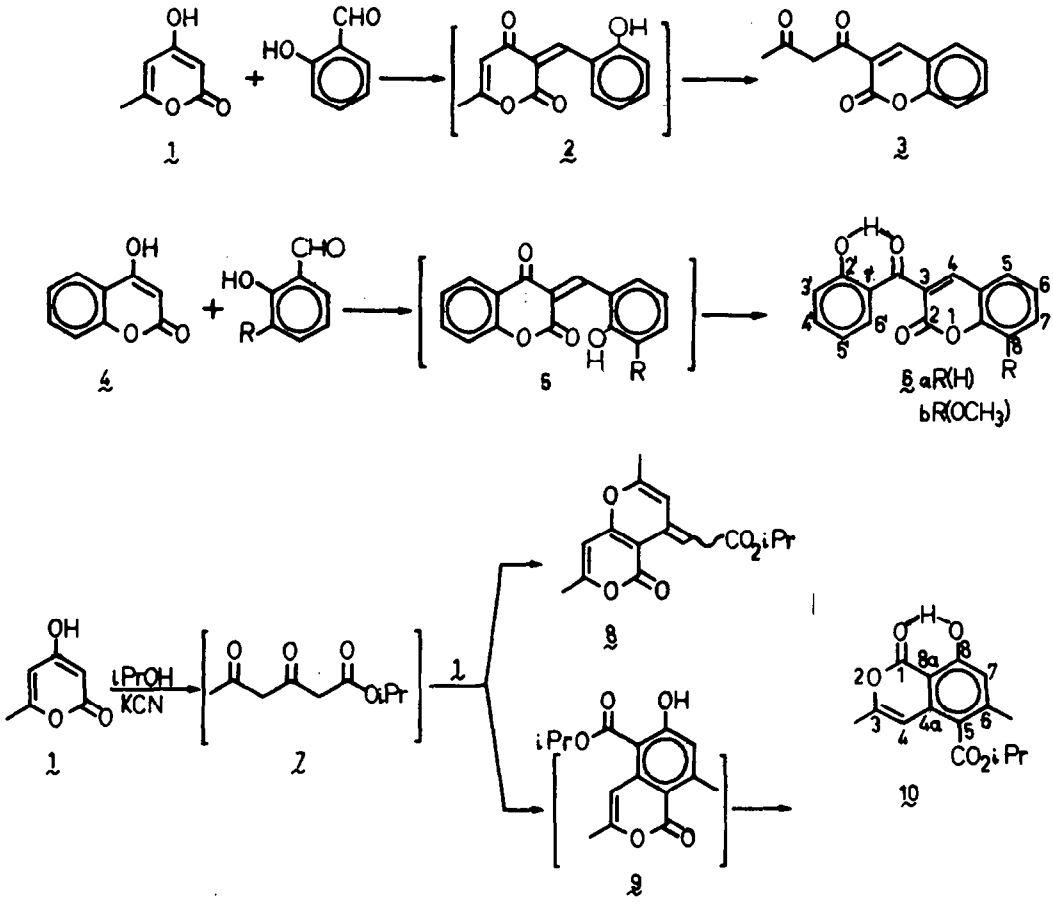
Abstract.- Further examples of the occurrence of intramolecular translactonization during condensation of 4-hydroxy-6-methyl-2H-pyran-2-one, 1, or 4-hydroxycoumarin, 4, with carbonyl compounds are described. The structure of previously misassigned products **6a,b** is proven by NMR techniques. Application of the HETNOE method to the distinction between structures **9** and **10** is demonstrated.

The reaction between 4-hydroxy-6-methyl-2H-pyran-2-one, 1, with 2-hydroxybenzaldehyde was shown to afford 3-acetoacetyl-2H-chromen-2-one, 3, instead of 3-(2-hydroxybenzylidene)-6-methyl-3,4-dihydro-2H-pyran-2,4-dione, 2. Clearly 3 is formed from 2 by intramolecular translactonization. We attributed[1] structure 3 to the formed product by comparison with a sample of 3 independently synthesized and kindly provided by Prof. F.M. Dean (University of Liverpool).[2,3] Moreover, we performed an X-ray structure determination[4] which fully confirmed structure 3. In addition, structure 3 has been also mentioned in the patent literature.[5]

Furthermore, reactions of 2-hydroxybenzaldehydes with different 4-hydroxycoumarins (i.e., 4) have been reported,[6-9] and in all cases the 3-(2-hydroxybenzylidene)chroman-2,4-dione structures of type 5 have been attributed to the reaction products. On the basis of only mass spectral evidence we suggested that the products from the reactions of 4-hydroxycoumarin, 4, and 2-hydroxybenzaldehydes were not **5a,b**, but 3-(2-hydroxybenzoyl)-2H-chromen-2-ones **6a,b**.[1]

All the above emphasizes the problems inherent to the structural assignments in pyrone chemistry when intramolecular translactonizations are possible. This paper presents conclusive NMR evidence for structure **6a** , based on complete analysis of its 400 MHz ^{1}H NMR spectrum, confirmed by a long-range 2-D COSY experiment.[10] It also shows the use of the recently reported HETNOE technique[11,12] to elucidate the structure of a product, **10**, formed by condensation of 4-hydroxy-6-methyl-2H-pyran-2-one, 1, with isopropyl 3,5-dioxohexanoate, 7 (generated in situ), a reaction in which there is also a fair chance for translactonization.

In the course of our research we needed isopropyl 3,5-dioxohexanoate 7. Since cyanide ion appears to be an effective transesterification catalyst,[13] we treated 1 with potassium cyanide and isopropanol. However, instead of 7, two products formed by condensation of 7 with 1 were isolated in low yields. The structure isopropyl 2,7-dimethyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-4-ylideneacetate, 8, was attributed to the product of mp 179-180 °C, on the basis of its spectroscopic behaviour. A second product, mp 80-84 °C, could be isopropyl 6-hydroxy-3,8-dimethyl-1-oxo-1H-benzo[c]pyrano-5-carboxylate, 9. However, since translactonization to isopropyl 8-hydroxy-3,6-dimethyl-1-oxo-1H-benzo[c]pyrano-5-carboxylate, 10, was possible, we performed an NMR analysis that fully confirmed constitution 10.



NMR STRUCTURAL ANALYSIS

The 400 MHz ^{1}H NMR spectrum of **6a** in $CDCl_3$ was completely assigned by iterative computer simulation (Fig. 1). The resulting chemical shifts and coupling constants, given in Table 1, agree reasonably well with those reported earlier for unsubstituted coumarin.[14] The key features of this spectrum, which rule out the alternative structure **5a**, are the intramolecularly bonded OH proton at δ 11.72 ppm and the long range coupled double doublet at δ 7.95 ppm, assigned to H(4). The latter chemical shift is reasonably close to the reported[15] signal of H(4) in 3-acetylcoumarin (δ 8.5 ppm), while the rather deshielded position of the former is best accomodated by structure **6a** (hydrogen bonding results in a six-membered ring) than **5a** (hydrogen bonding requires an eight-membered ring). In addition, the long range couplings exhibited by H(4) connect this proton with other hydrogens of the coumarin moiety ($J_{4,5}$ = 0.37 Hz; $J_{4,8}$ = 0.61 Hz), a fact very hard to explain in structure **5a**, for which the δ 7.95 ppm signal should be assigned to the very distant olefinic proton. Further confirmation for structure **6a** was obtained by means of a 250 MHz two-dimensional long range[10] COSY spectrum (Fig. 2), which revealed all the long range couplings listed in Table 1, and a two-dimensional NOESY spectrum (Fig. 3), which showed cross peaks relating all next-neighbour proton pairs as required by structure **6a**.

The reaction between **4** and 3-methoxy-2-hydroxybenzaldehyde (o-vanillin) furnished a product, mp 194-196°C, which was assigned constitution **6b** by analogy with **6a**.[1] Indeed, the 80 MHz ^{1}H NMR spectra of both compounds were very similar. Thus, **6b** displayed an intramolecularly bonded OH proton at δ 11.71 ppm (d, J = 0.35 Hz) and a well resolved singlet at δ 7.94 ppm, assigned to H(4). In addition, the very similarly shaped aromatic absorptions of both compounds covered almost the same frequency ranges (δ 7.61-6.87 ppm for **6b**; δ 7.78-6.77 ppm for **6a**), and other spectra (IR and MS) were also very similar.

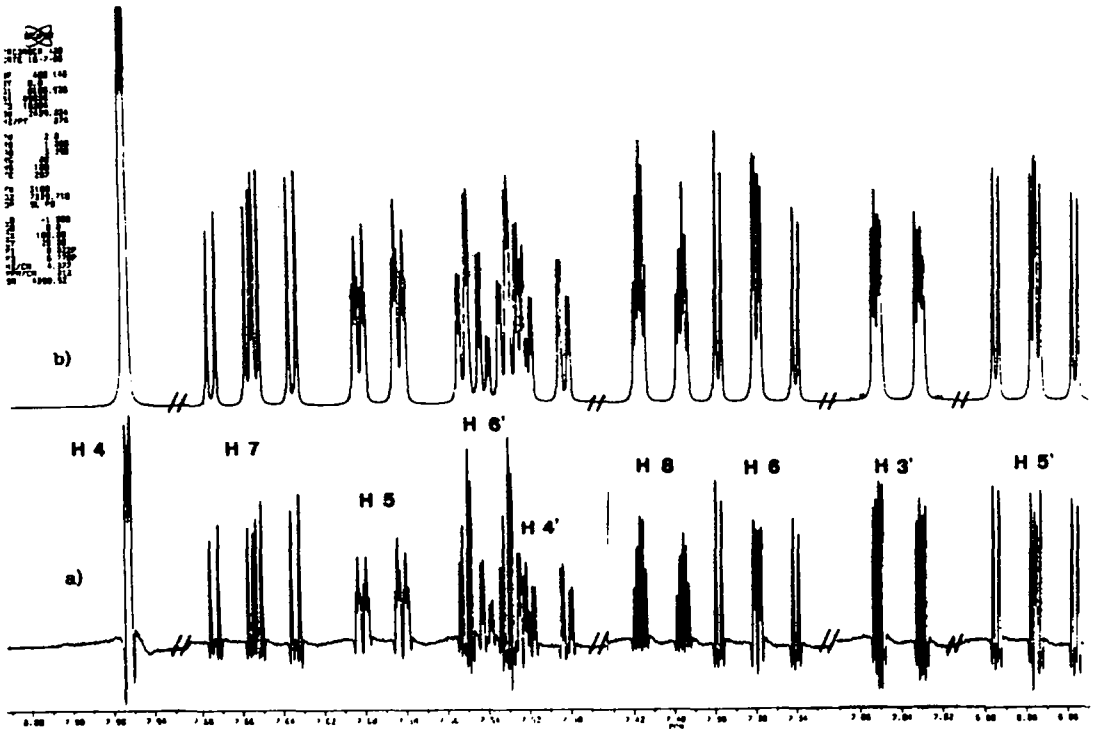


Fig. 1.- a) Resolution enhanced 400MHz ^1H NMR spectrum of 6a in $CDCl_3$ (OH not shown); b) simulated spectrum with the shifts and couplings listed in Table 1.

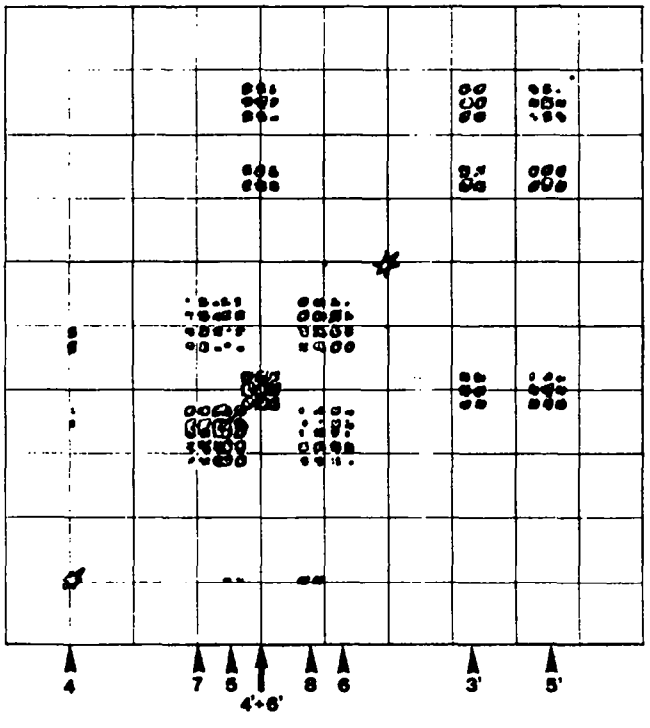


Fig. 2.- The 250 MHz long range COSY spectrum of 6a in $CDCl_3$ after D_2O exchange. Assignments shown under the arrows.

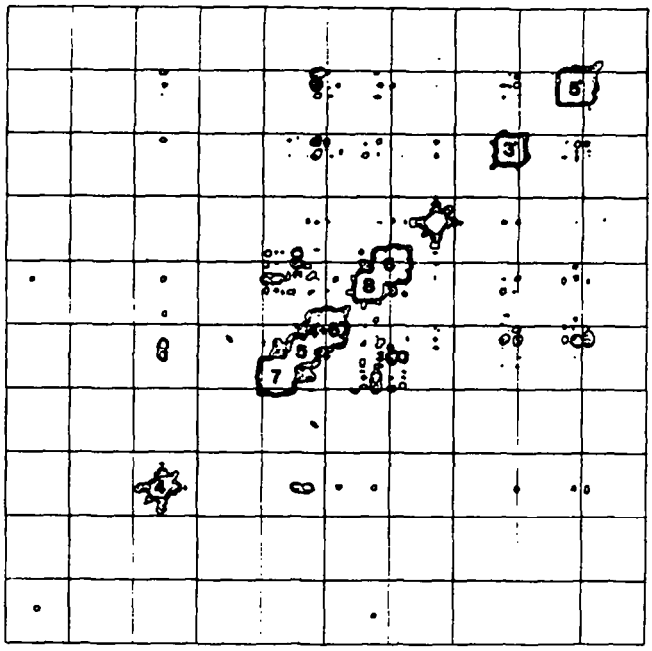


Fig. 3.- The 250 MHz NOESY spectrum of 6a in $CDCl_3$ after D_2O exchange. Assignments shown inside diagonal peaks.

TABLE 1. The assigned 400 MHz ^1H NMR spectrum of 6a in $CDCl_3$ [a]

Proton	Apparent Multiplicity	δ/ppm	J/Hz
H(4)	dd	7.952	$J_{4,5}$ = 0.37; $J_{4,8}$ = 0.61.
H(5)	ddt	7.590	$J_{5,6}$ = 7.77; $J_{5,7}$ = 1.60; $J_{5,8}$ = 0.49.
H(6)	ddd	7.360	$J_{6,7}$ = 7.40; $J_{6,8}$ = 1.10.
H(7)	ddd	7.652	$J_{7,8}$ = 8.40.
H(8)	d quintuplet	7.407	
OH [b]	br. doublet	11.720	$J_{3',OH}$ = -0.56; $J_{4',OH}$ = 0.49; $J_{6',OH}$ = 0.53
H(3') [c]	ddd	7.040	$J_{3',4'}$ = 8.48; $J_{3',5'}$ = 1.12.
H(4') [c]	dddd	7.520	$J_{4',5'}$ = 7.22; $J_{4',6'}$ = 1.70.
H(5') [c]	ddd	6.875	$J_{5',6'}$ = 8.06.
H(6') [c]	ddd	7.540	

a) Chemical shifts and coupling constants from iterative computer analysis (see Fig. 1).
b) Signal disappeared after D_2O exchange.
c) Multiplicity decreased after D_2O exchange.

In contrast to the case of 6a, low-field 1D NMR methods were enough for distinguishing between structures 9 and 10. We resorted to the HETNOE technique, developed in our laboratories[11,12] and recently applied to the constitutional assignment of fused heterocycles[16] and to the conformational analysis of fluorinated compounds.[17] The HETNOE technique allows the generation of selective heteronuclear $^{13}C\{^1H\}$ NOE on quaternary carbons by low-power continuous wave selective irradiation of a *given proton signal; measurement of Overhauser enhancement factors* is achieved by peak height comparison between the perturbed, NOE-containing ^{13}C NMR spectrum and a control. Both spectra having been obtained under broadband proton decoupling, a key feature of this method is the familiar appearance of all ^{13}C NMR peaks as singlets, a fact which greatly facilitates the interpretation of results. Enhancements over 10-15% usually indicate close proximity between the irradiated protons and the NOE-undergoing carbons.[12]

The ^1H NMR spectrum of 10 was assigned in a straightforward manner as listed in the experimental section. Thus, as in the case of 6, the signal at δ 11.25 ppm was assigned to an intramolecularly hydrogen bonded hydroxyl proton. The assignment of the two olefinic protons and the two neighbouring methyls was more involved. The methyl at δ 2.26 ppm showed a 1.0 Hz coupling with the proton at δ 6.52, while the other two signals (at δ 6.69 and 2.41 ppm) appeared as broad singlets. In addition, the C(3) carbon signal at δ 154.5 ppm showed long range couplings to the protons appearing at δ 2.26 and 6.52 ppm, but not to the other pair of signals, as shown by the corresponding low power heteronuclear decoupling experiments. Furthermore, HETNOE enhancements over 50% were observed for C(3) upon presaturation at δ 2.26 and 6.52 ppm (see below). Therefore, this pair of proton signals was attributed to the pyrone moiety of 10. Thus, the ^1H NMR spectrum of 10 was completely assigned. However, a distinction between 9 and 10 could not yet be reached on that basis.

The ^{13}C NMR spectrum of 10 is given in Table 2. The signals of all protonated carbons were unambiguously assigned by intermediate power selective decoupling of the corresponding protons (SFORD technique[18]). Most quaternary carbons were also assigned by low power selective decoupling of the neighbouring protons, which resulted in removal of the corresponding long range heteronuclear splittings. Thus, two carbonyl peaks appeared at δ 166.5 and 165.9 ppm. The former, in the fully coupled spectrum, appeared as a doublet with a splitting of 2.8 Hz, while the latter was a broad singlet. Low power selective irradiation of the isopropyl methine proton at δ 5.31 ppm collapsed the δ 166.5 signal into a narrow singlet, and therefore this high frequency peak was assigned to the ester carbonyl carbon, while the 165.9 ppm signal was attributed to the pyrone carbonyl carbon. However, again these data were insufficient to distinguish between structures 9 and 10.

TABLE 2.- The assigned 20 MHz ^{13}C NMR spectrum of 10 in $CDCl_3$

Carbon	δ/ppm	Assignment Method	HETNOE enhancements Irradiated proton	NOE/%
C(1)	165.9	b) c)	OH	51
C(3)	154.6	b) c)	H(4)	53
			C(3)-Me	57
C(4)	101.8	a)	---	--
C(4a)	136.1	b) c)	H(4)	39
C(5)	119.5	c)	C(6)-Me	31
C(6)	147.1	b) c)	C(6)-Me	42
			H(7)	52
C(7)	116.2	a)	---	--
C(8)	162.1	b) c)	OH	86
			H(7)	33
C(8a)	103.3	c)	OH	39
C(3)-Me	19.4	a)	---	--
C(6)-Me	21.3	a)	---	--
iPr-O_2C	166.5	b) c)	Me_2CH	24
Me_2CH	68.9	a)	---	--
CHMe_2	21.6	a)	---	--

a) Intermediate power selective decoupling of directly attached protons.
b) Low power selective decoupling of long range coupled protons.
c) Assignment confirmed by HETNOE enhancement.

A series of HETNOE experiments provided conclusive evidence in favor of constitution 10 (Table 2). The HETNOE method was modified in order to ensure adequate saturation to all lines of the isopropyl methine multiplet[19]. Thus, the individual frequencies of the septet at δ 5.31 ppm were saturated for 0.5 s consecutively and the process repeated six times, yielding a total presaturation time of 21 s. This HETNOE experiment confirmed the assignment of the ester carbonyl at δ 166.5 ppm, as this signal showed an Overhauser enhancement of 24%.

The crucial HETNOE experiment (Fig. 4) was carried out by low power presaturation of the OH signal at δ 11.25 ppm. This resulted in enhancements of 86% at C(8), 39% at C(8a) and 51% at C(1), thus showing that the intramolecular hydrogen bond was to the C(1) carbonyl. The HETNOE method, as shown previously[11,17], is therefore very useful in hydrogen bonded systems, since it can single out the carbon atom of the acceptor group.

As demonstrated in this paper and elsewhere[1,4], extreme care is necessary in the structural assignment of the products of condensation between pyrones and carbonyl compounds. The possibility of intramolecular translactonization has to be accounted for explicitly. Intramolecular hydrogen bond formation, as in the cases of 6 and 10, could drive the reaction to the product with the strongest hydrogen bond.

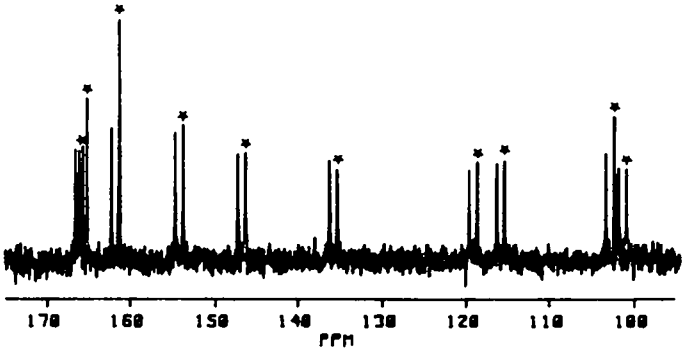


Fig. 4.- Partial 20 MHz ^{13}C NMR HETNOE spectra of 10. Two plots shown with an horizontal offset of 4 mm. Starred peaks correspond to the HETNOE spectrum after presaturation of the OH proton, while unstarred peaks correspond to the NOE-devoid control spectrum.

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EXPERIMENTAL

NMR methods

Proton NMR spectra were determinad at 400, 250 and 80 MHz using Bruker instruments, models WH-400, WM-250 and WP-80. The 20 MHz ^{13}C NMR spectra were determined in the latter instrument. Fourier transform mode and quadrature detection were used throughout.

The spectrum shown in Fig. 1a was obtained at 400 MHz by accumulation of 100 scans on 16 K data points with a spectral width of 2439 Hz (digital resolution 0.3 Hz per point). The FID was resolution enhanced by Gaussian multiplication (LB = -1.0; GB = 0.3) and zero filling up to 64 K before Fourier transformation. The simulation shown in Fig. 1b was carried out in two parts, one for the coumarin proton subsystem and the other for the hydroxybenzoyl proton subsystem, using the PANIC program (standard Bruker software). After convergence of the two iterations, the resulting simulated spectra were coadded by software.

The long range 2D COSY spectrum shown in Fig. 2 was obtained at 250 MHz, using the COSYLR.AU sequence (standard Bruker software) 90°-t_1-Δ-90°-Δ-Acq, for a spectral width of 360 Hz in both dimensions, with Δ fixed at 80 ms. The digital resolution was 0.7 Hz in both dimensions. Processing by an unshifted sinebell window, double Fourier transformation and symmetrization yielded the final 2D spectrum.

The 2D NOESY spectrum shown in Fig. 3 was obtained at 250 MHz using the NOESY.AU sequence (standard Bruker software) Relax-90°-t_1-90°-Δ-90°-Acq. Scalar correlations were suppressed by random variation of the mixing period Δ, viz. 1.0±0.2 s. A spectral width of 1000 Hz and a digital resolution of 2.0 Hz were used in both dimensions and the matrix was symmetrized after double Fourier transformation.

Heteronuclear decoupling experiments for correlation of protons with directly attached carbons (SFORD method) were carried out by collecting 20 MHz ^{13}C NMR FIDs under CW decoupling with a decoupler power setting of 18H, i.e., a decoupler output attenuation of 18 dB below a nominal 10 W full power. Similarly, long range coupled quaternary carbons were selectively decoupled from the corresponding protons by CW decoupling of the latter with a decoupler power setting of 30-50L, i.e., an attenuation of 30-50 dB below a nominal 0.2 W full power. The same 30-50L value was used for selective generation of heteronuclear $^{13}C\{^1H\}$ NOE.

Compounds

Coumarins **6a** and **6b** were obtained as reported in ref. 7.

Isopropyl 2,7-dimethyl-5-oxo-4H,5H-pyrano[4,3-b]pyran-4-ylideneacetate, **8**, and isopropyl 8-hydroxy-3,6-dimethyl-1-oxo-1H-benzo[c]pyran-5-carboxylate, **10**.

A mixture of 10.0 g (0.079 mole) of 4-hydroxy-6-methyl-2H-pyran-2-one, **1**, 0.10 g of potassium cyanide and 80 ml of isopropanol was refluxed for 48 h and then kept at -30° for 48 additional hours. The precipitate formed was filtered, washed with isopropanol and recrystallized from methanol, yielding 1.113 g of a mixture of two products (tlc analysis). Column chromatography on silica gel eluting with hexane/dichloromethane (2:1) afforded pure samples of both compounds.

The first compound eluted was **10** (0.40 g), m.p. 80-84 °C; IR ($CHCl_3$): 1680 (br), 1640 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$): δ 1.40 (d, J = 6.3 Hz, 6H [$CHMe_2$]), 2.26 (d, J = 1.0 Hz, 3H [C_3-Me]), 2.41 (s, 3H [C_6-Me]), 5.31 (septet, J = 6.3 Hz, 1H, [Me_2CH]), 6.52 (q, J = 1.0 Hz, 1H [H-4]), 6.69 (s, 1H [H-7]), 11.25 (s, 1H [OH]); 20 MHz ^{13}C NMR: see Table 2; MS: m/e = 276(M^+, 34), 234 (54), 217 (44), 189 (14), 164 (26), 147 (9), 135 (100), 89 (12), 77 (17), 65 (9), 43 (100). Calculated for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.43; H, 5.78.

The second compound eluted was **8** (0.26 g), m.p. 179-180 °C; IR ($CHCl_3$): 1720, 1680, 1660, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.2 (d, J = 7.5 Hz, 6H), 2.1 (s, 3H), 2.3 (s, 3H), 5.1 (septet, J = 7.5 Hz, 1H), 5.9 (s, 1H , 6.8 (s, 1H), 7.8 (s, 1H); ^{13}C NMR ($CDCl_3$): 18.8, 19.7, 21.8, 66.0, 98.9, 100.5, 103.0, 106.3, 136.3, 152.4, 159.8, 163.5, 164.1, 167.6; MS: m/e = 276 (M^+, 12), 234 (4), 219 (23), 217 (33), 190 (84), 119 (8), 43 (100). Calculated for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.35; H, 5.84.

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