Tetrahedron, Vol. 37, pp. 2021 to 2025, 1981
Printed in Great Britain.

0040-4020/81/102021-05$02.00/0

ORIENTATION EFFECTS IN THE PECHMANN REACTION

SYNTHESIS OF 5,6-DIMETHYLCOUMARIN AND AN EXAMINATION OF *ORTHO*-PROXIMITY EFFECTS IN ^{13}C NMR SPECTROSCOPY

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(*Received in UK 20 October 1980*)

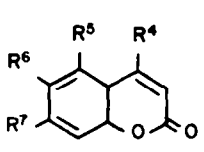
Abstract—In the Pechmann reaction with malic acid, *m*-cresol and 3,4-xylenol give mixtures of alkylcoumarins containing about 10% of the 5- and 5,6-isomers respectively. 7-Alkylcoumarins only are obtained from the reaction with ethylacetoacetate. A study of *ortho*-proximity effects on the ^{13}C NMR of dimethylcoumarins is reported, and the results have been correlated with similar effects in other aromatic and heteroaromatic systems.

In connection with studies of proximity effects in ^{13}C NMR spectroscopy we had need of a sample of 5,6-dimethylcoumarin **1c**, a hitherto unreported compound. Application of the two well known routes to coumarin derivatives, viz. the Perkin synthesis[1] and the Pechmann reaction[2,3] was first considered.

The required starting material for the Perkin synthesis, 6-hydroxy-2,3-dimethylbenzaldehyde **2a** is only difficultly accessible, since application of the Riemer–Tiemann reaction to 3,4-xylenol is reported[4] to give the cyclohexadienone **3** as the main product and only a small amount of the mixed aldehydes **2a** and **2b** which then require a tedious mechanical separation through sorting of crystals.[5] The two aldehydes have virtually the same m.p., but different IR spectra.[6]

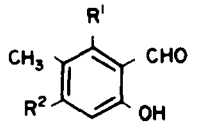
As an alternative route the Pechmann reaction[2,3] was next considered. Although the condensations of asymmetric alkylphenols with malic acid in the presence of sulphuric acid have been described previously[7,8] the products were regarded solely as 7-methylcoumarin **1b** and as 6,7-dimethylcoumarin **1d**. The alternative less favoured mode of cyclisation to produce 5-methylcoumarin **1a** or 5,6-dimethylcoumarin **1c** was not considered by the earlier workers.

The reaction with *m*-cresol was performed by Fries and Klosterman[7] in 1906 in order to confirm the identity of the products obtained from the Riemer–Tiemann reaction . This latter reaction was first studied by Tiemann and Schotten,[9] two products were obtained from *m*-cresol, the *para*-formylated compound **4a** and an *ortho*-formylated derivative identified as **4b**. Chuit and Bolsing[10] later repeated this reaction and separated three products. That both *ortho*-formylated derivatives **4b** and **4c** had been obtained was established by their subsequent conversion via the Perkin reaction to **1b** (m.p. 126°) and **1a** (m.p. 65°) respectively, a procedure previously attempted by Schmidt.[11] The identity of the formylated derivatives has recently been confirmed by Bruce *et al.*[12] Fries and Klostermann[7] then performed an independent synthesis of **1b** through the Pechmann reaction of *m*-cresol with malic acid. The product (m.p. 128°) was considered as **1b**. Soon afterwards, Clayton[8] carried out a similar reaction with 3,4-xylenol and, based on the earlier work of Fries and Klostermann,[7] regarded the product as **1d**, the alternative mode of cyclisation to produce the alternative isomer **1c** was not considered.



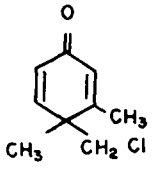
1

a: $R^5 = CH_3$, $R^4 = R^6 = R^7 = H$
b: $R^7 = CH_3$, $R^4 = R^5 = R^6 = H$
c: $R^5 = R^6 = CH_3$, $R^4 = R^7 = H$
d: $R^6 = R^7 = CH_3$, $R^4 = R^5 = H$
e: $R^4 = R^7 = CH_3$, $R^5 = R^6 = H$
f: $R^4 = R^6 = R^7 = CH_3$, $R^5 = H$



2

a: $R^1 = CH_3$, $R^2 = H$
b: $R^2 = CH_3$, $R^1 = H$



3

4

a: $R^1 = CHO$, $R^2 = R^3 = H$
b: $R^2 = CHO$, $R^1 = R^3 = H$
c: $R^3 = CHO$, $R^1 = R^2 = H$

At this stage our experience of orientation effects in the synthesis of quinoline derivatives was recalled. In the Skraup synthesis, the reaction with *m*-toluidine was similarly reported[13] at the outset in 1884 to give one product only, regarded as 7-methylquinoline, which was later confirmed by other workers.[14,15] It was not until the advent of modern analytical tools such as gas chromatography and IR that Palmer[16] detected the presence of the second isomer. The parallel reaction with *m*-ethylaniline was similarly clarified in these laboratories recently through the use of NMR spectroscopy.[17]

It therefore appeared that there was reasonable

Table 1. ^{13}C NMR spectra of coumarin derivatives (a, b)

Compound	Chemical shift (δ, p.p.m.)												
	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-4'	C-5'	C-6'	C-7'
1a (c)	160.9	116.2	140.7	136.5	125.9	131.9	115.1	154.8	117.9		18.3		
1b	161.3	115.7	143.6	127.8	125.9	143.4	117.3	154.5	116.7				21.8
1c (d)	161.1	116.0	140.9	134.2	132.8	133.7	114.3	153.4	(e)		14.5	20.0	
1d	161.6	115.7	143.6	128.2	133.4	142.2	117.6	152.8	116.9			19.2	20.3
1e	161.4	114.2	152.7	124.5	125.6	143.2	117.4	153.9	117.8	18.6			21.6
1f	161.6	114.2	152.6	125.0	133.1	141.9	117.8	152.2	117.9	18.6		19.4	20.1

NOTES (a) - 10% solution in $CDCl_3$, reference TMS.

(b) - carbons numbered with (') are associated with the CH_3 group.

(c) - in admixture with 1b.

(d) - in admixture with 1d.

(e) - peak obscured by major isomer.

justification to suggest that the Pechmann synthesis with asymmetric alkylphenols could produce a mixture of products, and accordingly this reaction has been re-investigated.

Analysis of the crude product from condensation of *m*-cresol with malic acid with sulphuric acid indicated that a mixture of **1a** and **1b** was indeed obtained. The major product was **1b** in accordance with the work of Fries and Klostermann.[7] That **1a** was also present was evident from the ^1H NMR spectrum through the presence of a second Me singlet and also from an additional pair of low intensity doublets (J 9.2 Hz) for the pyran ring protons. Furthermore the H-4 signal of **1a** was shifted downfield due to a characteristic *peri*-deshielding effect.[18] From a comparison of the integrals of the respective Me and H-4 peaks the ratio of isomers was established as 88:12. The remaining aromatic protons for **1b** appeared as an ABC system, further broadened by long range benzylic coupling,[19] but the aromatic peaks of **1a** were obscured. The presence of both isomers was additionally confirmed by ^{13}C NMR spectroscopy through comparison with the spectra of the individual methylcoumarins as reported by Ernst.[20]

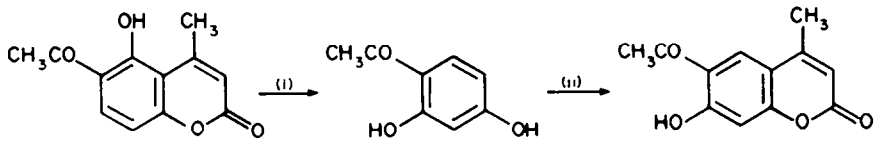
Careful recrystallisation of the crude product from an ethanol–water solvent pair afforded a pure sample of **1b** as shown by ^1H and ^{13}C NMR spectroscopy (Table 1).

The reaction with 3,4-xylenol also gave a mixture of isomers. The ^1H NMR spectrum confirmed that the major product was **1d** as reported by Clayton,[8] the presence of **1c** was evident from the additional Me signals and a second set of pyran ring doublets, that for H-4 again being *peri*-deshielded. From the spectral integration the ratio of isomers was assessed as 91:9. In the aromatic region despite the simplification of the **1d** spectrum (two broadened singlets) the expected two doublets for **1c** were still not visible. The ^{13}C NMR spectrum of the mixture was particularly informative and is shown in Fig. 1. In the alkyl region, two high intensity and two low intensity signals are evident corresponding to the Me absorptions of the isomers, one low intensity signal is significantly removed which will be discussed later. A total of 17 signals appear in the aromatic region, including the two CO peaks. Initial differentiation between quaternary carbons of **1d** and non-quaternary carbons of **1c** was difficult due to their similar intensities, this was later resolved after separation. The spectrum of **1c** exhibited certain interesting features which facilitated identification, the C-4 signal exhibited a *peri*-shielding effect[20] whilst C-8 was *para*-shielded.[20] Of particular interest was the upfield shift of Me(5) due to the *ortho*-proximity effect which is discussed later.

Separation of pure **1d** was more difficult than in the case of **1b**, but fractional crystallisation from ethanol eventually afforded the pure product. Since the pruification was difficult it is perhaps surprising that Clayton[8] should have made no mention of the significant variation in m.p. between the crude and purified products The ^{13}C NMR spectra of **1b** and of **1d** were almost identical (largest deviation 0.2 ppm) when pure or in the presence of the second isomer.

Reaction of *m*-cresol and of 3,4-xylenol with ethylacetoacetate gave **1e** and **1f** respectively as the sole products, with no detectable quantity (^1H and ^{13}C NMR) of the alternative isomers. The lack of formation of the 5- or 5,6-isomer may be attributed to steric hindrance by the 4-Me substituent, as previously experienced in the quinoline series.[17]

As far as we are aware the present work represents the first example of the simultaneous formation of isomeric products in the Pechmann reaction with malic acid. Extension of these studies to other substituted phenols is in progress. Although the proportion of the isomer formed through the sterically hindered pathway is much lower than that obtained in the Skraup synthesis of quinoline derivatives[16] the Pechmann reaction nevertheless still provides a plausible method for the synthesis of small quantities of otherwise inaccessible 5- and 5,6-substituted coumarin derivatives for use as authentic spectroscopic or chromatographic reference materials. The present work is a further form of orientation effect and is different to that already known for dihydric phenols,[3,21] which involves a preferential single cyclisation under the influence of a specific catalyst as exemplified below:[21]



(i): EAA/$AlCl_3$ (ii): EAA/H_2SO_4

The synthesis of **1c** was performed in connection with studies of *ortho*-proximity effects in ^{13}C NMR spectroscopy. These effects are to be reported at a later stage but some preliminary results are presented here. The *ortho*-proximity effects cause deviations from the normal additivity of Substituent Chemical Shifts (SCS), which are most prominent closest to the site of substitution.[22-4] In the case of the aromatic carbons of **1d** both C-6 and C-7 appear upfield of their predicted positions, the shifts (−1.9, −1.8 ppm) being similar to those experienced with 2,3-dimethylnaphthalene (−2.3 ppm).[22] Upfield shifts also occur with **1c** with C-6 (−2.6 ppm) being shifted to a greater extent than C-5 (−1.9 ppm), parallel effects have also been reported for 1,2-dimethylnaphthalene (C-2: -3.2 ppm, C-1: -2.1 ppm).[22]

The deviations which occur at off-ring carbons such as Me groups are particularly characteristic. With **1d** both Me carbons are shielded with respect to the appropriate monoMe derivatives, the effect seen with **1c** is again different, since Me(5) is significantly shielded whilst Me(6) is shifted only slightly. Differentiation between the two Me signals of **1c** was accomplished by an examination of the proton coupled spectrum in which only Me(6) displayed additional long range coupling to H-7.[25]

The *ortho*-proximity effects observed at the Me carbons in the coumarin series have been correlated with those experienced in other similar *ortho*-dimethyl substituted aromatic and heteroaromatic compounds, and the results presented in Table 2. The shift deviations appear to be both characteristic and comparatively reproducible and therefore should prove to be of value in the identification of similar dimethyl substituted compounds. Differentiation between possible isomers may therefore be achieved from a consideration of the less numerous Me signals rather than from the more complex aromatic region.

EXPERIMENTAL

M.ps were determined on a Kofler hot stage apparatus. ^1H NMR spectra were recorded at 100 MHz using a Jeol JNM-MH-100 instrument, chemical shifts are reported as ppm (δ) downfield from TMS. ^{13}C NMR spectra (Table 1) were obtained with a Jeol

Table 2. *Ortho*-proximity effects at methyl carbons for dimethylcoumarins and related compounds

Compound	Chemical shift (δ) Monosubst. derivatives		Disubst. derivatives		Proximity effects (p.p.m.)[a]	
	CH_3 (A)	CH_3 (B)	CH_3 (A)	CH_3 (B)	CH_3 (A)	CH_3 (B)
1,2,4,5-tetramethylbenzene[23]	20.9	20.9	19.2	19.2	-1.7	-1.7
2,3-dimethylnaphthalene[22]	21.6	21.6	20.1	20.1	-1.5	-1.5
6,7-dimethylquinoline[b]	21.5	21.9	19.9	20.3	-1.6	-1.6
2,4,5-trimethylaniline[24,b]	20.4	21.0	18.6	19.4	-1.8	-1.4
6,7-dimethylcoumarin	20.7	21.8	19.2	20.3	-1.5	-1.5
1,2,3,4-tetramethylbenzene[23]	20.4	20.9	15.5	20.6	-4.9	-0.3
1,2-dimethylnaphthalene[22]	19.2	21.6	14.4	20.6	-4.8	-1.0
5,6-dimethylquinoline[b]	18.5	21.5	14.0	(c)	-4.5	(c)
5,6-dimethylcoumarin	18.3	20.7	14.5	20.0	-3.8	-0.7
2,3,4-trimethylphenol[24]	19.8	20.3	15.6	20.0	-4.2	-0.3

NOTES (a) - δ (disubst.) - δ (monosubst.), negative values denote upfield shifts.

(b) - present work.

(c) - peak obscured by 6,7-dimethylquinoline present in admixture.

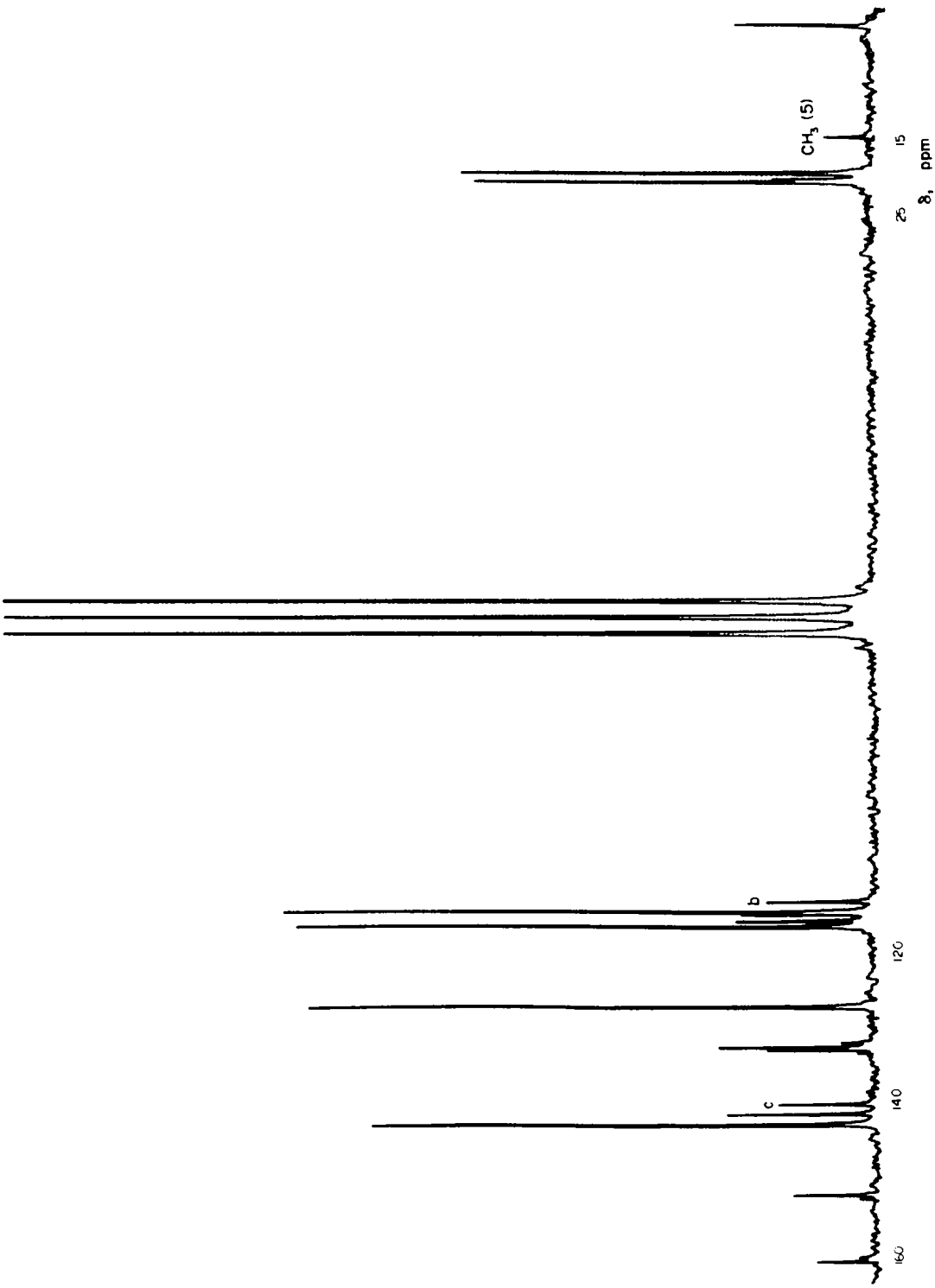


Fig. 1. ^{13}C NMR spectrum of 5,6-/6,7-dimethylcoumarin mixture (15 MHz, $CDCl_3$). Characteristic peaks for 5,6-isomer shown Me(5); b – C–8; c – C–4.

JNM-FX-60 spectrometer operating in the pulsed Fourier transform mode at 15 MHz, with broad band noise decoupling; pulse width 7μs(45° pulse angle), pulse repetition rate 4 sec, spectral width 2500 Hz with 8 K data points.

Pechmann reaction with malic acid

The freshly redistilled phenol (0.1 mole) was dissolved in conc H_2SO_4 (10 ml) and heated to 120–30°. Malic acid (13.4 g, 0.1 mole) was then added portionwise over a period of 1 hr. The final dark viscous liquid was poured on to ice, and the brown ppt obtained was collected and then steam distilled.

(i) *With* m-*cresol* The crude product crystallised in the receiver as colourless needles (5.8 g, 36%), m.p. 125–6° (lit.[10] m.p. 126°, lit.[7] m.p. 128°). ^{1}H NMR analysis showed this product to be a mixture of **1b** (88%) and **1a** (12%).

^{1}H NMR ($CDCl_3$) (peaks characteristic of 5-methylcoumarin only, for ^{1}H NMR of pure **1b** see below): 2.58 (3H, s, Me); 6.55 (1H, d, J_{34} 9.5 Hz, H-3); 8.09 (1H, d, J_{34} 9.5 Hz, H-4).

The crude product was recrystallised twice from an EtOH-water solvent pair which afforded pure (^{1}H and ^{13}C NMR) 7-methylcoumarin as colourless needles, m.p. 128–9° (lit.[10] m.p. 126°, lit.[7] m.p. 128°). ^{1}H NMR ($CDCl_3$): 2.50 (3H, s, Me; 6.34 (1H, d, J_{34} 9.5 Hz, H-3); 7.08 (1H, d of d, J_{56} 7.8 Hz, H-6); 7.12 (1H, br, H-8); 7.36 (1H, d, J_{56} 7.8 Hz, H-5); 7.66 (1H, d, J_{34} 9.5 Hz, H-4).

(ii) *With* 3,4-*xylenol* The crude product crystallised in the receiver as colourless needles (5.6 g, 32%), m.p. 138–9° (lit.[8] m.p. 148–9°). ^{1}H NMR analysis showed this product to be a mixture of **1d** (91%) and **1c** (9%).

^{1}H NMR ($CDCl_3$) (peaks characteristic of 5,6-dimethylcoumarin only, for ^{1}H NMR of pure **1d** see below); 2.51 (3H, s, Me); 6.54 (1H, d, J_{34} 9.5 Hz, H-3); 8.14 (1H, d, J_{34} 9.5 Hz, H-4). The peak for the other Me group was obscured.

The crude product was recrystallised thrice from an EtOH-water solvent pair which did not affect the separation of **1c**. Fractional crystallisation from EtOH eventually afforded pure (^{1}H and ^{13}C NMR) 6,7-dimethylcoumarin as colourless needles, m.p. 148–9° (lit.[8] m.p. 148–9°). ^{1}H NMR ($CDCl_3$): 2.33 (3H, s, Me); 2.38 (3H, s, Me); 6.36 (1H, d, J_{34} 9.5 Hz, H-3); 7.16 (1H, br, H-8); 7.26 (1H, br, H-5), 7.67 (1H, d, J_{34} 9.5 Hz, H-4).

Pechmann reaction with ethylacetoacetate

The freshly distilled phenol (0.1 mole) was dissolved in 75% H_2SO_4 (15 ml) and heated to 70–80°. Ethylacetoacetate (13.0 g, 0.1 mole) was then added portionwise over a period of 15 min. The final orange liquid was poured on to ice, and the resultant off-white ppt collected and then steam distilled. ^{1}H NMR analysis indicated that one product only was formed.

(i) *With* m-*cresol* The product crystallised in the receiver as colourless needles (10.1 g, 58%), m.p. 130–1°. Recrystallisation from an EtOH-water solvent pair gave pure 4,7-dimethylcoumarin as colourless needles, m.p. 131–2° (lit.[7,26] m.p. 132°). ^{1}H NMR ($CDCl_3$): 2.41 (3H, s, Me); 2.44 (3H, s, Me); 6.18 (1H, br, $J_{3,Me}$ 1.2 Hz, H-3); 7.04 (1H, d, J_{56} 8.0 Hz, H-6); 7.08 (1H, br, H-8); 7.42 (1H, d, J_{56} 8.0 Hz, H-5).

(ii) *With* 3,4-*xylenol* The product cyrstallised in the receiver as colourless needles (12.03 g, 66%), m.p. 169–70°. Recrystallisation from an EtOH-water solvent pair gave pure 4,6,7-trimethylcoumarin as colourless needles, m.p. 171–2° (lit.[8] m.p. 169–70°, lit.[26] m.p. 170–1°). ^{1}H NMR ($CDCl_3$); 2.34 (6H, s, CH_3); 2.40 (3H, s, Me); 6.16 (1H, br, $J_{3,Me}$ 1.2 Hz, H-3); 7.05 (1H, br, H-8); 7.27 (1H, br, H-5).

In all of the above experiments ^{1}H NMR analysis of the initial ppts indicated that the proportions of isomers formed was not affected by the steam distillation process.

Acknowledgements—Thanks are due to the S.R.C. for funds to purchase the NMR instrumentation, and to Miss A. I. Kasilingam for assistance is the experimental work.

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