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Short Communication

Anthraquinones by Cyclisation of Benzoylbenzoic Acids Produced by the $AlCl_3$-Mediated Friedel–Crafts Reaction of Phthalic Anhydrides with Aromatic Compounds

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Anthraquinones are widely distributed in Nature. Their major role is often in pigmentation, although they may have a role as anti-feedants in some cases.[1] Medicinally, they have found uses both in traditional and in modern medicine.[1,2] In Nature they arise by at least two different biosynthetic routes. The type substituted in both A and C rings is usually derived by the acetate–malonate pathway, whereas the type substituted only in the A ring is normally of shikimate–mevalonate origin.[3]

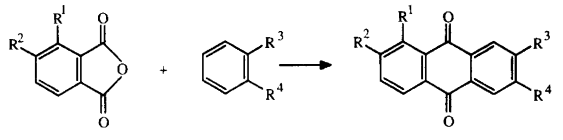
Anthraquinones are also prepared synthetically by various methods, giving both naturally occurring anthraquinones and purely synthetic derivatives. Among the most common synthetic approaches is the $AlCl_3$-mediated Friedel–Crafts reaction in which phthalic anhydrides are condensed with various aromatic compounds and subsequently cyclised with hot sulfuric acid to yield the anthraquinone.[4–6] Other methods employed are the Diels–Alder reaction with various benzo- or naphthoquinones as dienophiles and the reaction with aromatic Grignard reagents and phthalic anhydrides and subsequent cyclisation.[7–11]

In the present study Friedel–Crafts condensation has been used. Phthalic anhydride, 3-hydroxyphthalic anhydride and 4-methylphthalic anhydride have been condensed with benzene, 1,2-dimethoxybenzene and toluene in the case of 3-hydroxyphthalic anhydride. Cyclisation of the adducts obtained resulted in a number of anthraquinones (Fig.1), some of which have not been previously prepared this way, and in one of the cases an anthraquinone which so far has never been reported.

To differentiate between different isomers in cases where more than one isomer was possible, various ^1H and ^{13}C NMR techniques were employed and the strength of NMR spectroscopy in determining substitution patterns of anthraquinones was demonstrated. While ^1H NMR data for 9,10-anthraquinones are normally provided in the literature, ^{13}C NMR data are surprisingly lacking. Due to the antitumour/antiviral activity of anthraquinones and anthraquinone-derived anthracyclinones, the importance of a complete analysis of the ^{13}C NMR spectra of these compounds is obvious.[12]

Results and discussion

Examining the products obtained by using benzene as the aromatic component, reveals that one compound is unsubstituted (**1**) and two compounds are substituted in the A-ring and unsubstituted in the C-ring (**3** and **6**). This substitution pattern creates a situation where the protons H-5 and H-8 experience an almost identical environment, which is also the case for protons H-6 and H-7. This results in a very small difference in chemical shift for H-5/H-8 and H-6/H-7, making the assignments of the ^1H and ^{13}C chemical shifts of all the protons and carbons of the C-ring difficult. This difficulty is reflected



Compound	R^1	R^2	R^3	R^4
1	H	H	H	H
2	H	H	OMe	OMe
3	OH	H	H	H
4	OH	H	H	Me
5	OH	H	OMe	OMe
6	H	Me	H	H
7	H	Me	OMe	OMe

Fig. 1. Structures of anthraquinones discussed in this paper.

by the fact that in the only ^{13}C chemical shift assignment of compound **6** found in the literature, eleven of fifteen shifts are tentatively assigned.[13] We recently reported the assignments for some anthraquinones with this kind of substitution pattern, including compound **3**.[12,14] In these papers, both total assignment due to significant resolution of the shifts of H-5/H-8 and H-6/H-7 and assignment by means of additive substitution effects, were achieved. Due to the fact that these assignments were achieved using a 400 MHz spectrometer, it was hoped that the 600 MHz NMR spectrometer now available would totally separate all the resonances of the different protons of compound **6** and thereby permit assignment of all the ^{1}H and ^{13}C chemical shifts. Unfortunately, this was not quite the case, but the enhanced resolution at least made the assignment of most of the resonances possible. The assignment of the ^{1}H and ^{13}C chemical shifts of compounds **3** and **6** are given in Tables 1 and 2, respectively. Compared to Berger *et al.*,[12] assignments of some of the shifts of compound **6** are corrected.

The anthraquinones obtained when *ortho*-dimethoxybenzene is the chosen aromatic component are of a different character. The symmetrical compound **2** is well documented.[15,16] A more interesting product is compound **5**. To the best of our knowledge this compound has never before been reported in the literature. Physical and spectroscopic data are given in the experimental section and in Tables 1 and 2.

The third product obtained by using *ortho*-dimethoxybenzene, is compound **7**. This is an naturally occurring anthraquinone, isolated only from *Hedyotis diffusa*, a common medicinal plant growing throughout India and China.[9] To verify the structure of the isolated compound, the authors prepared the compound in a four-step Diels–Alder reaction. By comparing the time and effort spent on this reaction (86 h) to the Friedel–Crafts reaction performed in the present study (3 h), it is obvious that the latter method is both time- and cost-saving. The assignments of the ^{1}H and ^{13}C NMR chemical shifts of compound **7** are found in Tables 1 and 2, respectively.

In contrast with the other reaction, where only one product is expected, the cyclisation of the condensation product of 3-hydroxyphthalic anhydride and toluene could theoretically result in two products. This is due to the Hayashi rearrangement.[17] Hayashi reported in 1927 that certain asymmetrical benzoylbenzoic acids under-

Table 1. ^{1}H NMR chemical shifts (δ) for 9,10-anthraquinone (**1**), 2,3-dimethoxy-9,10-anthraquinone (**2**), 1-hydroxy-9,10-anthraquinone (**3**), 1-hydroxy-6-methyl-9,10-anthraquinone (**4**), 1-hydroxy-6,7-dimethoxy-9,10-anthraquinone (**5**), 2-methyl-9,10-anthraquinone (**6**) and 2,3-dimethoxy-6-methyl-9,10-anthraquinone (**7**).

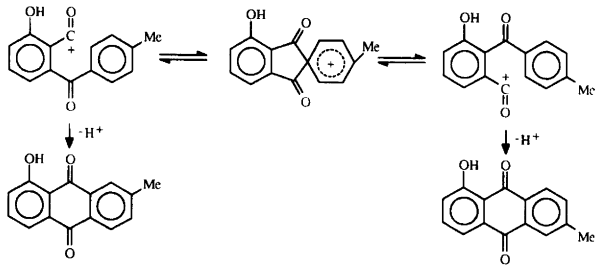
	Compound						
H-atom	**1**	**2**	**3**	**4**	**5**	**6**	**7**
H-1	8.31	7.72	—	—	—	8.02	7.68
H-2	7.80	—	7.38	7.27	7.24	—	—
H-3	7.80	—	7.81	7.63	7.61	7.53	—
H-4	8.31	7.72	7.71	7.79	7.76	8.13	7.68
H-5	8.31	8.27	8.17	8.05	7.65	8.24[a]	8.03
H-6	7.80	7.75	7.96	—	—	7.73[b]	—
H-7	7.80	7.75	7.93	7.57	—	7.74[b]	7.53
H-8	8.31	8.27	8.22	8.16	7.65	8.25[a]	8.13
CH_3	—	—	—	2.52	—	2.50	2.51
OCH_3	—	4.06	—	—	4.04	—	4.05
OH	—	—	12.41	12.63	12.58	—	—

[a] Shifts may be reversed. [b] Shifts may be reversed.

Table 2. ^{13}C NMR chemical shifts (δ) for 9,10-anthraquinone (**1**), 2,3-dimethoxy-9,10-anthraquinone (**2**), 1-hydroxy-9,10-anthraquinone (**3**), 1-hydroxy-6-methyl-9,10-anthraquinone (**4**), 1-hydroxy-6,7-dimethoxy-9,10-anthraquinone (**5**), 2-methyl-9,10-anthraquinone (**6**) and 2,3-dimethoxy-6-methyl-9,10-anthraquinone (**7**).

	Compound						
C-atom	**1**	**2**	**3**	**4**	**5**	**6**	**7**
C-1	127.23	108.38	161.46	162.49	162.24	127.41	108.30
C-2	134.12	153.87	124.02	124.28	124.11	145.20	153.74[a]
C-3	134.12	153.87	137.17	136.49	136.25	134.85	153.64[a]
C-4	127.23	108.38	119.01	119.43	119.37	127.35	108.30
C-5	127.23	127.01	126.83	127.72	108.54[a]	127.05[a]	127.31
C-6	134.12	133.73	135.08	146.03	154.25[b]	133.96[b]	144.81
C-7	134.12	133.73	134.61	134.96	153.81[b]	133.84[b]	134.46
C-8	127.23	127.01	126.53	127.10	107.83[a]	127.08[a]	127.20
C-9	183.16	182.53	188.17	188.57	187.95	183.30	182.78
C-10	183.16	182.53	181.81	182.68	181.73	182.86	182.38
C-11	133.53	133.60	133.03	133.49	128.69[c]	133.48[c]	133.44
C-12	133.53	133.60	132.73	130.90	127.86[c]	133.51[c]	131.30
C-13	133.53	128.49	115.92	116.12	116.01	133.30	128.53[b]
C-14	133.53	128.49	133.16	133.53	133.50	131.20	128.45[b]
CH_3	—	—	—	21.96	—	21.75	21.84
OCH_3	—	56.55	—	—	56.57	—	56.50
OCH_3	—	56.55	—	—	56.52	—	56.50

[a] Shifts may be reversed. [b] Shifts may be reversed. [c] Shifts may be reversed.



Scheme 1

went some kind of rearrangement on treatment with H_2SO_4, see Scheme 1. The key intermediate is the spiro-cation which can open in two ways. When examining the ^1H and ^{13}C NMR spectra of the product obtained, we found that only one of the isomers is produced. To decide which isomer is produced is not an easy task employing chemical tests, but the problem can be solved by the information gained from heteronuclear NMR decoupling techniques. Studying the two possible isomers reveals that both A-rings contain one proton with only a four-bond coupling to a neighbouring proton, giving rise to a doublet with a small *meta*-coupling. This doublet is easily found in the ^1H spectrum. By irradiating this resonance with a low power decoupling pulse while collecting ^{13}C data, different coupling patterns will appear for the two isomers. In the case of 1-hydroxy-7-methyl-9,10-anthraquinone, C-9 will appear as a singlet and C-10 as a multiplet, due to the fact that the latter couples to both H-4 and H-5. On the other hand, carrying out the same procedure with 1-hydroxy-6-methyl-9,10-anthraquinone makes both C-9 and C-10 appear as doublets due to the coupling to H-8 and H-4, respectively. The appearance of two doublets proves the product obtained to be 1-hydroxy-6-methyl-9,10-anthraquinone. Naturally occurring, this compound is only reported twice in the literature,[18,19] in contrast with 1-hydroxy-7-methyl-9,10-anthraquinone (barleriaquinone), which is widely distributed.[1]

The complete assignments of the ^1H and ^{13}C NMR chemical shifts of compound **4** are given in Tables 1 and 2, respectively. Compared to the so far preferred Diels–Alder reaction employed by other authors,[7–9,20,21] the Friedel–Crafts condensation and subsequent cyclisation is both time- and cost-saving. Also, the fact that only one isomer is produced, in contrast with the Diels–Alder reaction where both isomers are found, favours the present method if 1-hydroxy-6-methyl-9,10-anthraquinone is the required product.

Experimental

Phthalic anhydride, $AlCl_3$ and 1,2-dimethoxybenzene were purchased from Lancaster Synthesis, England. 3-Hydroxyphthalic anhydride, 4-methylphthalic anhydride, benzene and toluene were obtained from Aldrich, Germany.

Melting points were taken on a Gallenkamp melting point apparatus. Mass spectra were obtained using a Fisons VG 7070F mass spectrometer operating at an electron impact energy of 70 eV, at the minimum temperature required for volatilisation. Infrared spectra were recorded as Nujol mulls on a Nicolet Impact 400 infrared spectrophotometer. Ultraviolet spectra were recorded for samples in $CHCl_3$ on a Varian Cary UV–VIS spectrophotometer.

NMR. The ^1H and ^{13}C NMR spectra were recorded at 600.13 and 400.13, 150.90 and 100.62 MHz, respectively, on a Bruker 600 DRX and a Bruker 400 DMX instrument equipped with 5 mm $^1H/^{13}C$ dual probes. Ca. 15–50 mg of the sample were dissolved in 500 µl of deuteriochloroform (**1**, **2** and **4–7**) or 500 µl of dimethyl sulfoxide-d_6 (**3**). The measurements were carried out at room temperature applying internal lock, and are referenced to the central peak of the solvent ($\delta = 2.50$ and 39.50 DMSO-d_6, $\delta = 7.25$ and 77.00 $CDCl_3$) corresponding to $\delta = 0.00$ for TMS.

Assignment techniques: the spin-echo Fourier transform (SEFT) experiment was performed using the gated decoupler mode, the decoupler was gated 'off' during the first delay and 'on' during the second delay and acquisition. The 2D heteronuclear one-bond correlation experiment was performed in the normal mode. Both experiments were optimised for a 165 Hz one-bond proton–carbon coupling constant, corresponding to an evolution period of 6.1 ms.

Selective decoupling was performed by irradiation of a specific proton at its exact frequency at a low power level, while recording carbon. The directly bonded ^{13}C signal loses its one-bond coupling, while the remaining ^{13}C absorptions show residual coupling.

Synthetic procedure. Phthalic anhydrides (150 mg), aromatic substrates (0.75 ml) and $AlCl_3$ (300 mg) in a 5 ml reaction tube were carefully heated in a hot sand bath, 60–70 °C, until evolution of HCl gas practically ceased. After being cooled in ice the product was mixed with 1 g of ice and 0.1 ml conc. HCl.

(A) (**1–3** and **7**). The crude product was filtered at the pump, washed with water, collected and dissolved in 10% Na_2CO_3 solution and carefully precipitated with conc. HCl with cooling and stirring.

(B) (**4–6**). Diethyl ether was added (2 ml) and the solution extracted. The organic layer was collected, dried (Na_2SO_4) and concentrated to ca. 0.5 ml under nitrogen. Petroleum ether, b.p. 60–80 °C was added until the solution was slightly turbid, then the products were allowed to precipitate.

Both methods resulted in 50–200 mg of the various benzoylbenzoic acids. The ring closure of the benzoylbenzoic acid was performed with conc. H_2SO_4 (1–2 ml) at 100 °C for 30 min. After cooling, the mixture was poured onto ice and stirred. The precipitate was filtered at the pump, washed with water, twice with diluted ammonia solution and dried until constant weight. The products yielded from 30–150 mg of the various anthra-

quinones. If necessary the products were crystallised in absolute alcohol.

Products. **1**, *9,10-Anthraquinone*; m.p. 286 °C (lit.[1] m.p. 286 °C); MS, 208 (M). **2**, *2,3-Dimethoxy-9,10-anthraquinone*; m.p. 237–238 °C (lit.[5] m.p. 237–238 °C); MS, 268 (M). **3**, *1-Hydroxy-9,10-anthraquinone*; m.p. 192–194 °C (lit.[1] m.p. 194–195 °C); MS; 224 (M). **4**, *1-Hydroxy-6-methyl-9,10-anthraquinone*; m.p. 143–145 °C (lit.[7] m.p. 145.6–146.5 °C); MS, 238 (M). **5**, *1-Hydroxy-6,7-dimethoxy-9,10-anthraquinone*; yellow crystals, m.p. 251.5–252.5 °C; IR (Nujol) 1514.0, 1581.4, 1629.9, 1656.9 and 3350.0 cm^{-1}; UV λ_{max} ($CHCl_3$) 271 (s), 279 and 399 nm ($\log \varepsilon$ 4.77, 4.82 and 4.03); MS, 284 (M), 269 (M − Me), 254 (269 − Me), 241 (269 − CO) and 213 (241 − CO). **6**, *2-Methyl-9,10-anthraquinone*; m.p. 178–179 °C (lit.[1] m.p. 178–179 °C); MS, 222 (M). **7**, *2,3-Dimethoxy-6-methyl-9,10-anthraquinone*; m.p. 236–238 °C (lit.[9] m.p. 237–238 °C); MS, 282 (M).

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