Orientation in nitration and sulfonation of 2,5-dimethylbenzoic acid[1]

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Nitration of 2,5-dimethylbenzoic acid was only 29% at the *meta*[2] position vs. 41% at the *ortho*, in contrast to sulfonation which was 85% *meta* vs. 15% *para*. Identity of the products (and of their derived amino esters and phenolic esters) was determined from the nuclear magnetic resonance spectra and confirmed by chemical means.

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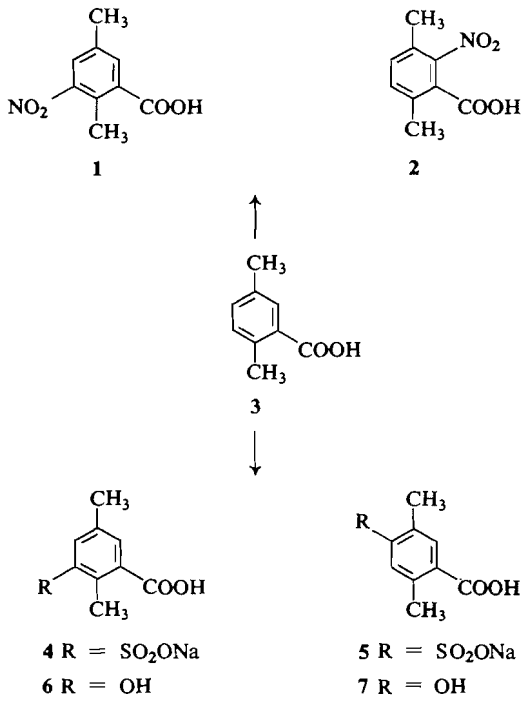
In some synthetic studies related to alkaloids, we required the *meta*-substitution[2] products from the nitration and sulfonation of 2,5-dimethylbenzoic acid (**3**). When carried out, these reactions showed striking differences in orientation effects, illustrative of the complex interplay of electronic and steric influences in reactions of a poly-substituted benzene. Nitration of **3** with fuming nitric acid occurred mainly in the *ortho*[2] position, despite the considerable steric hindrance, to form a mixture of *meta*- and *ortho*-nitro acids, **1** and **2** (in 29 and 41% yields, respectively). In contrast, sulfonation of **3** with oleum afforded mostly the *meta* sulfonate (about 85%, isolated as the sodium salt **4**) accompanied by about 15% of the *para* isomer **5**. This sulfonation was previously reported (1) to form only the *meta* product **4**, but inspection of the n.m.r. spectrum readily disclosed the presence of the *para* isomer.[3] In the nitration of **3**, the ratio of isomers closely resembled that reported (2*a*) for nitration of 2,5-dimethylacetophenone. Other, similarly substituted benzenes have also given predominantly *o*-nitration (2*b*).

The *m*-nitro acid **1** was separated from the mixture of **1** and **2** by crystallization. The *o*-nitro acid **2** was then purified after treatment with methanolic hydrogen chloride, which selectively esterified **1** and left the hindered *ortho* isomer unchanged. This *o*-nitro acid **2** could be esterified successfully only with diazomethane or with methanol – sulfuric acid (3). The sulfonation product (mixture of **4** and **5**) was subjected to alkali fusion (1), and the nuclear magnetic resonance (n.m.r.) spectra showed that the *meta* to *para* ratio of phenolic acids **6** and **7** was essentially the same as the ratio of sodium sulfonates **4** and **5**. Separation of isomers was possible only after esterification of **6** and **7**, when the predominant *meta* methyl ester **11** could be purified by fractional crystallization; a small sample of the *para* ester **12** was obtained from the mother liquors.



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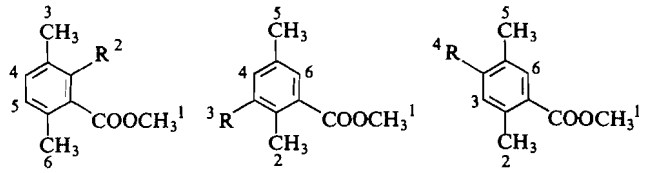
[2]The terms *ortho*, *meta*, and *para* refer to the carboxyl as point of reference.

[3]Though no *ortho* sulfonation was detected, a referee has pointed out the likelihood that the *ortho* position may be the site of kinetically governed reaction, but that, since sulfonation is a reversible reaction, the more thermodynamically stable *meta* and *para* products were obtained under conditions used.



8 R = NH_2 **9** R = NH_2 **10** R = NH_2
11 R = OH **12** R = OH

The compounds could be readily identified from the n.m.r. spectra by observing splitting patterns of the 2 aryl protons in each isomer. Characteristic coupling constants (4) were $J_{para} < 1$ Hz, $J_{meta} = 2$–3 Hz, and $J_{ortho} = 7.5$ Hz, determined respectively from sharp singlets, broad singlets partially resolved, and an AB quartet. Spectra of the nitration products were best studied after esterification and reduction of **1** and **2** to form the amino esters **8** and **9**, because (*a*) the distinctly different *para* isomer **10**, methyl 4-amino-2,5-dimethylbenzoate, was then available (5) for comparison, and (*b*) in the *o*-nitro compounds (**2** and its methyl ester) the aryl protons had identical resonances so that the resultant 2-proton singlets gave no information as to the orientation. The *p*-hydroxy ester **12** exhibited proton chemical shifts nearly identical to those for the corresponding protons in the *p*-amino ester **10**. Chemical shifts of the aryl protons were generally as predicted from summation of known shielding effects (6) of the various substituents. Although no attempt was made in the present work to study spectra at high dilutions or with rigorously calibrated instrumentation, the additive shielding parameters developed by several workers (6) could usually be applied to the assigned structures.

For instance, the large differences in shielding of the aryl protons for the *p*-amino ester **10** ($\delta_{H-3} - \delta_{H-6} = 1.27$ p.p.m.) and the *p*-hydroxy ester **12** ($\delta_{H-3} - \delta_{H-6} = 1.14$ p.p.m.) were predictable. Relative to benzene (δ 7.32) as standard (or to *p*-xylene, δ 7.05), the C_3-protons in **10** and **12** (δ 6.43 and 6.58) were shifted upfield by the adjacent 4-NH_2 and 4-OH (shielding) but were little affected by the *meta*-oriented $COOCH_3$ (deshielding); the $COOCH_3$ shifted the adjacent 6-H's downfield (δ 7.70 and 7.72), with little effect on the 6-H's from the *meta*-oriented OH or NH_2. In contrast, the *m*-amino and *m*-hydroxy esters **9** and **11** showed little difference in the aryl protons ($\delta_{H-4} - \delta_{H-6} = 0.45$ and 0.38 p.p.m., respectively). Upfield shift of the 4-H's (δ 6.55 and 6.85) by the adjacent NH_2 and OH was still observed, though somewhat lessened perhaps by the $COOCH_3$ now *para* to these 4-H's. Surprisingly, the 6-H's (δ 7.00 and 7.23) in **9** and **11** were little affected by the 1-$COOCH_3$ (deshielding expected) or were perhaps at the same time shielded by a strong *para* effect of the 3-NH_2 or 3-OH. A strong shielding effect by *p*-NH_2 seemed to be evident in the *o*-amino ester **8**, where 1 proton (apparently H-5, *para* to the 2-NH_2) was as far upfield (δ 6.47) as the proton in **10** (δ 6.43) that was *ortho* to the NH_2. The other proton in **8** (H-4, δ 6.98) seemed to be as much affected by the *m*-NH_2 (shielding) as by the *p*-$COOCH_3$.

Similar substituent effects were seen on resonances of the aryl methyl groups, i.e., the shielding tendency of an adjacent amino group, the deshielding tendency of an adjacent methoxycarbonyl. This was clearly observed with the *p*-amino ester **10**. The 5-CH_3 (δ 2.12) was shielded relative to the CH_3's in *p*-xylene (δ 2.30) by the adjacent 4-NH_2, and the 2-CH_3 (δ 2.52) was deshielded by the 1-$COOCH_3$. In the *ortho* isomer **8**, the 3-CH_3 (δ 2.12) was shielded by the adjacent 2-NH_2, but the 6-CH_3 was only slightly deshielded by the adjacent $COOCH_3$, perhaps a reflection of steric restriction on the $COOCH_3$ at this crowded position, interfering with its free rotation or its planarity with the ring.[4] In the *m*-amino isomer **9**, the NH_2 and $COOCH_3$ groups are *ortho* to the 2-CH_3 and are *meta* to the 5-CH_3; the opposing effects were nearly cancelled out, and the methyl resonances were nearly coincident (δ 2.26 and 2.20).

[4]Some further chemical evidence of steric crowding in the *ortho* series was the difficulty of *N*-acetylating the anthranilic acid obtained on reduction of **2**. Only a low yield of *N*-acetyl product was obtained with refluxing acetic anhydride overnight, though yields in the analogous *meta* and *para* series were quantitative after a few hours. We are indebted to Mr. Nasser Sadri for this observation.

Experimental

Melting points were determined on a Fisher–Johns micro hot stage and are uncorrected. The n.m.r. spectra were determined with a Varian A-60A spectrometer on 25–30% (w/v) solutions in chloroform-*d* (4% internal tetramethylsilane as standard, $\delta = 0$), and, with external tetramethylsilane, in dimethylsulfoxide-d_6 (DMSO) and in D_2O. Signals were observed as singlets (s) or doublets (d). Accuracy was ± 0.07 p.p.m. for chemical shifts, ± 0.2 Hz for coupling constants. Signals exchangeable with D_2O are not recorded.

Paper chromatography was done by the descending technique on Whatman No. 1 paper, in 1-butanol – ethanol – 15 *M* ammonium hydroxide – water (4:1:1:4), spots detected under ultraviolet (u.v.) light.

2,5-Dimethyl-3-nitrobenzoic Acid (1)

To 150 ml of red fuming nitric acid (*d* 1.50) at 5° were added, with stirring, 25.0 g (0.167 mole) of 2,5-dimethylbenzoic acid (Eastman) in portions, over 35 min, while the temperature was maintained at 5–10°. The solution was allowed to stand another 60 min at 10° and was poured onto 1.5 kg of ice with stirring. The white precipitate was collected on a filter and washed with water (in a typical experiment, the dried weight amounted to a 75% yield). Paper chromatography showed 2 isomers were present, R_f 0.51 (**2**) and R_f 0.59 (**1**). The damp solid was recrystallized from 225 ml of hot ethanol by adding 375 ml of water; after 15 h at room temperature, 7.5 g of the *meta* isomer **1** was collected, m.p. 130–160°. Recrystallization from 150 ml of benzene then afforded 6.4 g (20%), m.p. 178–181° with a crystal transition at 165–175° (lit. (*2a*) m.p. 168–170°), chromatographically homogeneous with R_f 0.59; n.m.r. (DMSO-d_6) δ 7.86 broad s (H-4, estimated $J_{4,6}$ ca. 2 Hz), 7.62 broad s (H-6, estimated $J_{4,6}$ ca. 2 Hz), 2.57 s and 2.39 (aryl CH_3's). The yield was consistently 20%, even on 10 times the scale. An analytical sample melted at 180–181.5° with crystal transition at 163–175°.

Anal. Calcd. for $C_9H_9NO_4$: C, 55.4; H, 4.65; N, 7.18. Found: C, 55.8; H, 4.64; N, 7.00.

3,6-Dimethyl-2-nitrobenzoic Acid (2)

The combined mother liquors from **1** were evaporated to yield a mixture of the isomers (ca. 50% based on **3**; estimated 41% **2** and 9% **1**, from n.m.r.). A 15 g sample of the solid mixture was refluxed with 175 ml of saturated anhydrous methanolic hydrogen chloride overnight. The solution was concentrated to a residual solid, which was suspended in 150 ml of dichloromethane and extracted with 2 100-ml portions of 5% aqueous sodium hydroxide. Acidification of the combined extracts to p*H* 2 with 12 *M* hydrochloric acid afforded 10.1 g (34% based on **3**) of precipitated 2-nitro acid **2**, m.p. 143–145°. An analytical sample, previously obtained (16% yield) by recrystallization of the crude mixture of acids from benzene–methanol, then methanol–water, melted at 141–143°; n.m.r. (DMSO-d_6) δ 7.23 s (H-4 and H-5), 2.27 s and 2.18 s (aryl CH_3's).

Anal. Calcd. for $C_9H_9NO_4$: C, 55.4; H, 4.65; N, 7.18. Found: C, 55.6; H, 4.72; N, 7.27.

The extracted dichloromethane solution contained 3.8 g of a syrupy mixture of the *m*-nitro and *o*-nitro esters, in a ratio of 2:1 as estimated from the n.m.r. spectrum.

Methyl 3,6-Dimethyl-2-nitrobenzoate

This compound was obtained (*a*) in quantitative yield by esterification of the acid **2** in tetrahydrofuran with diazomethane in ether (7), and (*b*) in 47% yield with 100% sulfuric acid and methanol (3). The syrup crystallized on standing, m.p. 36–40°; n.m.r. ($CDCl_3$) δ 7.24 s (H-4 and H-5), 3.82 s ($COOCH_3$), 2.39 s and 2.35 s (aryl CH_3's).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.30; N, 6.70. Found: C, 57.6; H, 5.19; N, 6.71.

Methyl 3,6-Dimethyl-2-aminobenzoate (8)

This compound was obtained by hydrogenation with platinum oxide in methanol, as a syrup in quantitative yield; n.m.r. ($CDCl_3$) δ 6.98 d (H-4, $J_{4,5} = 7.5$ Hz), 6.47 d (H-5, $J_{4,5} = 7.5$ Hz), 3.88 s ($COOCH_3$), 2.40 s and 2.10 s (aryl CH_3's).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.31; N, 7.82. Fonud: C, 66.7; H, 7.20; N, 7.97.

Methyl 2,5-Dimethyl-3-nitrobenzoate

This compound was obtained from **1** by esterification with refluxing anhydrous methanolic hydrogen chloride and was recrystallized from methanol (5 ml/g), m.p. 57–58° (81%); n.m.r. ($CDCl_3$), 7.78 broad s (H-4, estimated $J_{4,6}$ ca. 2 Hz), 7.63 broad s (H-6, estimated $J_{4,6}$ ca. 2 Hz), 3.91 s ($COOCH_3$), 2.54 s and 2.39 s (aryl CH_3's).

Anal. Calcd. for $C_{10}H_{14}NO_4$: C, 57.4; H, 5.30; N, 6.70. Found: C, 57.4; H, 5.30; N, 6.58.

Methyl 2,5-Dimethyl-3-aminobenzoate (9)

This compound was obtained by hydrogenation of the nitro ester with platinum oxide in methanol, as a syrup in quantitative yield; n.m.r. ($CDCl_3$) δ 7.00 broad s (H-6, estimated $J_{4,6}$ ca. 2 Hz), 6.55 broad s (H-4, estimated $J_{4,6}$ ca. 2 Hz), 3.81 s ($COOCH_3$), 2.26 s and 2.20 s (aryl CH_3's).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.31; N, 7.82. Found: C, 66.7; H, 7.36; N, 7.75.

Sulfonation of 2,5-Dimethylbenzoic Acid (3)

This acid, when prepared as described by Charlesworth and Levene (1), yielded quantitatively the mixture of sodium sulfonates **4** and **5**; n.m.r. (D_2O) δ 7.85 broad s (H-4 of **4**, estimated $J_{4,6}$ ca. 2 Hz), 7.53 broad s (H-6 of **4**, estimated $J_{4,6}$ ca. 2 Hz), 2.63 s and 2.31 s (aryl CH_3's of **4**); contamination with ca. 17% of the *para*-substituted isomer **5** was indicated by singlets at δ 7.72 and 7.76 (H-3 and H-6) and at 2.52 and 2.43 (aryl CH_3's).

Potassium Hydroxide Fusion (1)

Fusion of the mixture of **4** and **5** at 210° for 1.5 h afforded the mixture of hydroxy acids **6** and **7**, isolated by acidification with concentrated hydrochloric acid and reprecipitated from a bicarbonate solution. The yield was 61%, m.p. 162–164° (lit. (1) 163–165°); n.m.r. (DMSO) δ 6.95 broad s (H-6 of **6**, estimated $J_{4,6}$ ca. 2 c.p.s.), 6.71 broad s (H-4 of **6**, estimated $J_{4,6}$ ca. 2 c.p.s.), 2.22 s and 2.08 s (aryl CH_3's of **6**); singlets at 7.59 (H-6) and 6.57 (H-3), and at 2.37 and 2.01 (aryl CH_3's) indicated the presence of 12% of the 4-hydroxy isomer **7**.

*Methyl 2,5-Dimethyl-3-hydroxybenzoate (**11**)*

This benzoate was obtained from the mixture of **6** and **7** with refluxing anhydrous methanolic hydrogen chloride after 2 h; the residual oil crystallized on standing and was washed with water (97% yield), m.p. 61–74°. Most of the 4-hydroxy isomer **12** (ca. 15% estimated by n.m.r.) was removed by recrystallization from benzene – petroleum ether (1:1, 15 ml/g), then from carbon tetrachloride (4 ml/g), to yield 58% of **11** (96% purity), m.p. 77.5–79.5°. Further fractional recrystallization from benzene afforded an analytical sample (free of **12**), m.p. 79–79.5°; n.m.r. ($CDCl_3$) δ 7.22 broad s (H-6, $J_{4,6}$ estimated 2 Hz), 6.78 broad s (H-4, $J_{4,6}$ estimated 2 Hz), 3.91 s ($COOCH_3$), 2.41 s and 2.23 s (aryl CH_3's).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.6; H, 6.71. Found: C, 66.6; H, 6.66.

*Methyl 2,5-Dimethyl-4-hydroxybenzoate (**12**)*

This compound was obtained from the mother liquors of **11** as light white needles, along with the dense prisms of **11**, and was separated and recrystallized from benzene – petroleum ether (1:1), m.p. 116–117°; n.m.r. ($CDCl_3$) δ 7.72 s (H-6), 6.58 s (H-3), 3.80 s ($COOCH_3$), 2.49 s and 2.19 s (aryl CH_3's). The sample was identical to an authentic sample, m.p. 116–117°, obtained by diazotization of 2,5-dimethyl-4-aminobenzoic acid (5), hydrolysis of the diazonium salt, and esterification of the resultant **7**.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.6; H, 6.71. Found: C, 66.6; H, 6.69.

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