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Structure Determination of Substituted Naphthalenes by Nuclear Overhauser Enhancement Measurements

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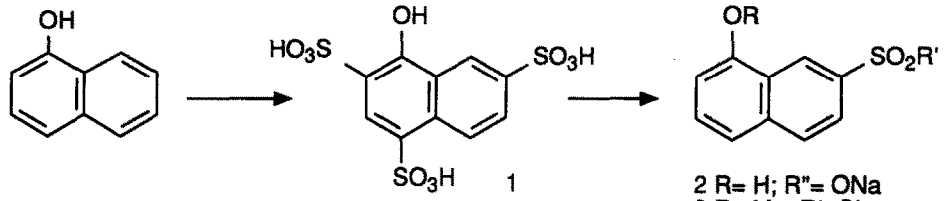
Abstract: Methods are described by means of case studies for ascertaining the orientation of substituents in naphthalene, in particular in products derived from naphthalenesulphonic acid derivatives, by means of a combination of modern ^{1}H NMR methods.

Substituted naphthalenes, in particular those derived from sulfonation and nitration reactions, have been studied intensively during the period from 1880 to 1950, mainly in view of their importance as dyestuff intermediates. During this pre-NMR period structure determination of such products was long, tedious and equivocal in the majority of cases. Since then, in aromatic systems such as benzene, the use of NMR methods has quickly become a matter of routine and has involved merely the measurement of coupling constants, of chemical shifts, and analysis of patterns; but with naphthalenes such data are often not adequate for the unequivocal determination of substituent orientation. Up to the middle 1980's chemical shifts and coupling constants were indeed used with substituted naphthalenes; and these applications were summarised by Freeman[1] and his co-workers in 1988. Since then there have been a few reports on the use of more advanced methodology involving ^{13}C NMR spectroscopy[2,3]; however, these are by nature laborious and require relatively large amounts of material. In recent work on the metal-ammonia reduction of N-alkyl naphthalenesulfonamides and on the possibility this has opened up of a nucleophilic route to substituted naphthalenes[4] the need arose for a rapid and relatively simple method for structure determination and corroboration using modern methods of ^{1}H NMR spectroscopy. We have found that an approach based on deductive and eliminative reasoning in conjunction with the use of N.O.E. and COSY measurements shows promise, and easily can be applied to any polyaromtic system. The essence and advantages of this approach are demonstrated by means of the following case studies.

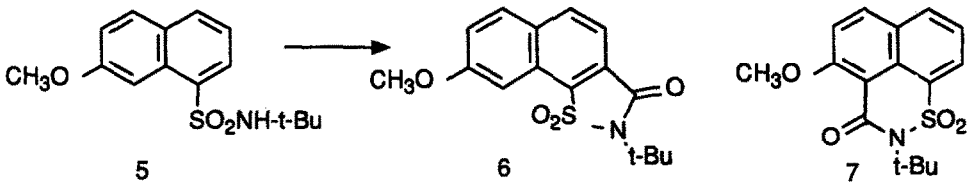
A. **The Position of the third Sulfonic Acid Group in the Trisulfonation of 1-Naphthol.** The sulfonation of 1-naphthol, a reaction studied thoroughly many years ago, was shown to occur first (not unexpectedly) at C_2 and C_4; and thereafter, not quite so convincingly, was said to occur at C_7 (**Scheme I**). We were interested in obtaining larger quantities of 8-hydroxynaphthalene-2-sulfonic acid (1-naphthol-7-sulfonic

sodium salt, **2**) which, to our knowledge, is not available commercially. Sulfonic acid groups ortho- or para-, to either phenolic or amino groups are known to be removable by desulphonation, caused by hydrolysis with dilute aqueous acid. This should make desired acid salt **2** accessible from **1**. Indeed, this route had been reported previously, in an allegedly "unsuccessful" patent application dated 1887[5] and many years later in a Japanese[6] and Czech[7] patent. There still remained the question of clear proof of the structure of **2**, i.e. attachment of the sulfonic group attached to C_7 relative to the phenolic group and not to C_6. Trisulfonation of 1-naphthol was carried out according to[8] using 98% sulfuric acid at 135-145°C, followed by addition of water, reflux, and eventual isolation of **2** (see **Experimental Part**), which was converted into the methoxysulfonyl chloride **3** as described recently[4]. Essentially one regioisomer was formed after these operations, and this was converted into the N-t-butylamide **4**. Confirmation of the latter's structure was arrived at as follows. The six aromatic protons in the ^1H NMR spectrum were arbitrarily termed *A*, *B*, *C*, *D*, *E*, and *F*, which were a singlet, doublet, , triplet, doublet and doublet respectively, where B^d and C^d form one AB system and D^t and E^d another. From these multiplicities and interactions it could be concluded that the sulfonamide group could not be attached to ring A (i.e. the one containing the methoxyl group); and had to be either at C_6 or C_7. Further, since *D* is a triplet it must be H_3, the only feasible position with such multiplicity. On irradiation of the signal of proton *D* N.O. effects of 9.4% and 1.6% were observed on protons *E* and *F* respectively. Irradiation of the methoxyl proton signal led to N.O effects of 4.2% and 4.7% on protons *F* and *A* respectively. From these irradiation results we can conclude that *F* is H_2 and *E* is H_4. Irradiation of *E* led to a 6.3%. N.O. effect on *C* which is thus assigned as H_5. Since the latter proton is a doublet and *A* is a singlet we come to the conclusion expressed in **4a**, i.e. that the sulfonamide group is indeed at C_7.

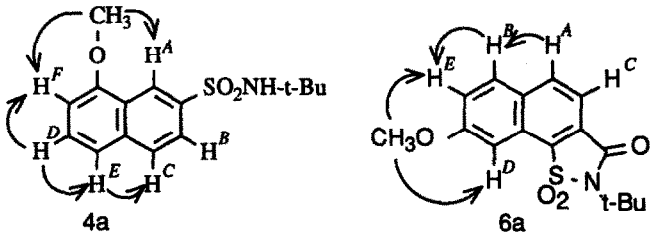


Scheme I

B. N-t-Butyl-7-methoxynaphthalene-1-sulfonamide (5), Direction of Ring Metallation. N-Alkyl and N,N-dialkylsulfonamide groups are among the most powerful ortho-directors known in aromatic metallation[9]. In the case of sulfonamide groups in the naphthalene 1-position there appears to be some controversy as to whether metallation is directed predominantly to the naphthalene 2- or to the peri 8-position[10]. In the case of compound **5** the peri - position is doubly activated by both the sulfonamide and methoxyl groups but at the same time would appear to be sterically hindered. Compound **5** was di-metallated in the usual way (2.1 equivs. of n-butyl lithium in THF/cyclohexane) and then carboxylated. The acidic part of the product was heated at 150-160°C in diethylene glycol dimethyl ether (diglyme) and a single neutral product was formed. From its ^1H NMR spectrum it was possible to conclude directly that the original carboxylation, and hence metallation, had occurred at C_2, since among the aromatic protons four, *A*, *B*, *C*, and *E*, are doublets, and one, *D* is a singlet. Had these reactions occurred at C_8, one proton (the one at C_3) would have to appear as a triplet. On irradiation of the methoxyl protons a N.O. effect of 6.3% was observed on the signal of proton D^s, which can thus be assigned to H_8, further confirming that reaction had taken place at C_2. Complete assignments were made possible by the fact that methoxyl proton irradiation also led to a N.O. effect (0.5%) on E^d, that irradiation of B^d gave one of 3.1% on E^d, and that irradiation of A^d gave one of 3.1% on proton B^d, see **6a**. Hence *E*, *B*, *A*, and *C* are to be assigned to H_6, H_5, H_4 and H_3 respectively, and the product is **6** and not **7**.

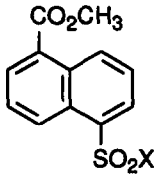


Scheme II

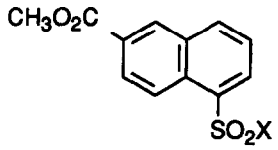


C. **Products from Chlorosulfonation of Methyl Naphthalene-1-and 2-Carboxylates.** The sulfonation, under regular conditions, of naphthalene-1- and 2-carboxylic acids gives in both cases a complex mixture of the 5-, 6-, and 7-sulfonic acids. These are difficult to separate, and hence these products have not received practical attention. Chlorosulfonation[11], using an excess of chlorosulfonic acid, either alone or in an indifferent solvent such as chloroform, can lead directly to sulfonyl chlorides and hence offers several advantages: the mildness of the reaction conditions, greater ease of purification of products and the fact that these can lead directly either to the sulfonic acids themselves or to sulfonic esters or amides. The chlorosulfonation of methyl naphthalene-2-carboxylate has been reported[12] to give a crystalline product to which no structure was assigned. We have repeated this work, and have found that the 1-carboxylate under the same reaction conditions likewise gives a crystalline sulfonyl chloride. Both products were each converted into the corresponding N-t-butylsulfonamides **11** and **9** respectively. The conclusion that in either case chlorosulfonation had occurred at the C_5-position was arrived at in the following way. Analysis of the aromatic proton region of **9** and application of the COSY technique revealed two proton systems: A^d, F^t, C^d, and D^d, E^t, B^d; but this grouping and multiplicity pattern alone did not differentiate between chlorosulfonation at either C_5 or C_8. However, on irradiation of the ester methoxyl group protons N.O. effects of 1.6% and 2.3% were observed on the signals of protons A^d and D^d respectively, showing that C_8 was unsubstituted. Full assignment was made possible by the observation that irradiation of proton B^d showed a strong N.O. effect (12.5%) on the NH proton *G* leading to the placing of B^d, E^t and D^d at C_6, C_7 and C_8; of A^d, F^t and C^d at C_2, C_3 and C_4 (see **9a**). In the case of compound **11** the observed multiplicity of aromatic protons was A^d, B^s, C^d, D^d, E^d and F^t. This pattern both excluded chlorosulfonation in ring A and restricted it to either C_5 or C_8. By application of the COSY technique it could be shown that C^d and E^d are both ortho to F^t and thus on ring B and hence that D^d, A^d and B^s are on ring A. Irradiation of *B* gave an N.O.E on the *E* signal (8.3%), indicating that the latter is H_8, thus completing the picture as shown in **11a**.

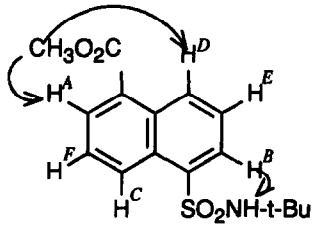
D. **Products arising from Metal-Ammonia Reduction of N-t-Butyl-6-methoxynaphthalene--2-Sulfonamide.** In our new route to substituted naphthalenes based on metal-ammonia reduction or reductive alkylation of naphthalenesulfonamides[4] we had occasion to study the latter reaction on the title compound **12**. When the lithium-ammonia reduction of the N-lithio derivative of the latter was quenched with iodomethane, C-methylation took place; but unlike as in the corresponding 1-sulfonamide the methyl group was introduced at a position other than at the sulfonamide carbon, as evidenced by the appearance of a methyl doublet in the ^1H NMR spectrum. One possibility was that of γ-alkylation leading to compound **13**. However,



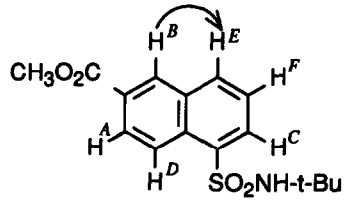
8 X= Cl
9 X= NH-t-Bu



10 X= Cl
11 X= NH-t-Bu



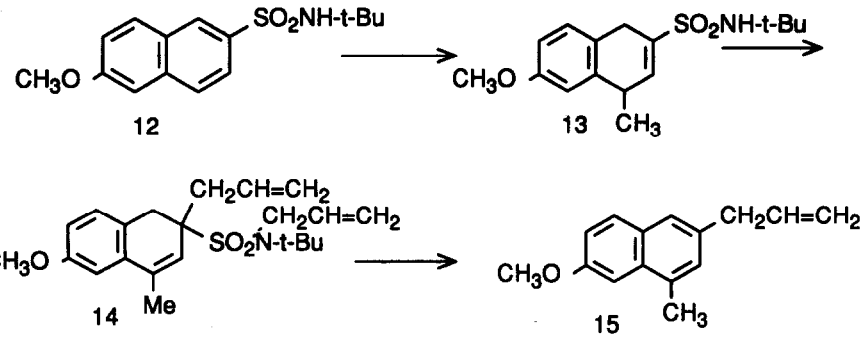
9a



11a

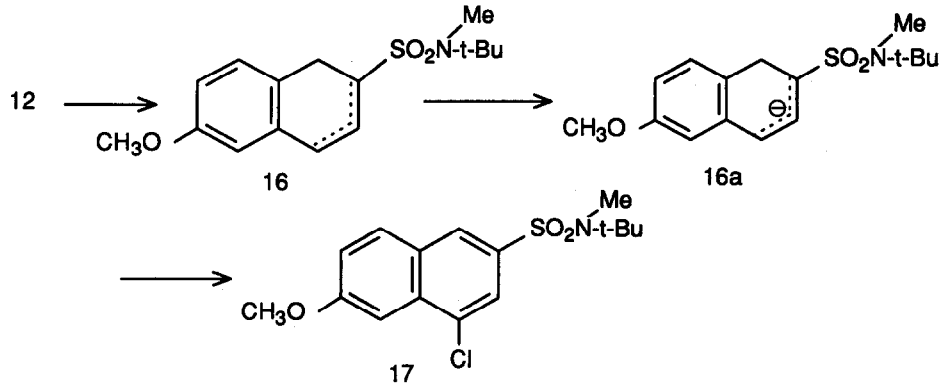
a structure assignment was complicated by the fact that all three non-vinyl protons in the non-aromatic ring coincidentally appeared as a non-resolvable singlet. Collapse of the methyl doublet following double irradiation of that singlet indicated that one of these three was indeed adjacent to the methyl group, but this could not rule out positioning of the methyl group at C_1 or C_3 (with appropriate positioning of the double bond), rather than at C_4 as in structure **13**. A solution to this problem was offered by the results of a further alkylation reaction on **13**. N,C-Diallylation of this, with an excess of sodium hydride and 3-bromo-1-propene in dimethylformamide, should lead to **14** (C-allylation being mechanistically feasible now only on the sulfonamide carbon). The latter was not isolated but, like other products alkylated at sulfonamide carbons in this series, it fragmented thermally with ease to give an allyl methyl methoxy naphthalene (with formal loss of SO_2 and the appropriate secondary amine). This naphthalene should now be **15**, having a 1,3-relationship between the two alkyl groups (**Scheme III**). The following arguments support this view. At the outset the only assumption was that of the methoxyl group being at C_2, with the position of both alkyl groups in doubt. The aromatic portion of the ^1H NMR spectrum showed the following picture: A^d, B^s, $C^{(s)}$, $D^{(s)}$, F, with the last three overlapping. Irradiation on the OCH_3 protons gave a 6.3% N.O. enhancement on proton C^s which is thus at either C_1 or C_3. Irradiation of proton C gave a 0.8% N.O. effect on the methyl group; hence the latter is at C_8 if proton C is at C_1, or at C_4 if it is at C_3. Irradiation of the methyl group led to a 3.1% effect on proton D, which is therefore at either C_7 or C_5. Thus there remain two alternatives throughout. A decision between these two could be made after irradiation of the protons of the allyl group. This led to an N.O.E. of 2.3% on both B^s and D^s. In view of the multiplicity of the last two the possibility that the methyl group is at C_4 can be ruled out. Hence the final structure and the proton assignments are as shown in **15a**. An additional feature of interest arising from inspection of the latter structure (including additional interactions not detailed here) is the preferred conformation of the methoxyl group towards H_1. This phenomenon has been observed by ^1H NMR studies in other similar systems[13, 14, 15] and its existence in the solid state has now been confirmed by perusal of the X-ray crystallographically determined structures of a number of compounds incorporating a 2-methoxynaphthalene moiety[16].

Another problem in this series arose from a reaction with the dihydro-N,t-butyl-N-methylsulfonamide **16** which was derived from **12** by two steps. By deprotonation with n-butyl lithium a hybrid monocarbanion **16a** was formed, with the aim of introducing a chlorine atom by nucleophilic halogenation, using carbon



Scheme III

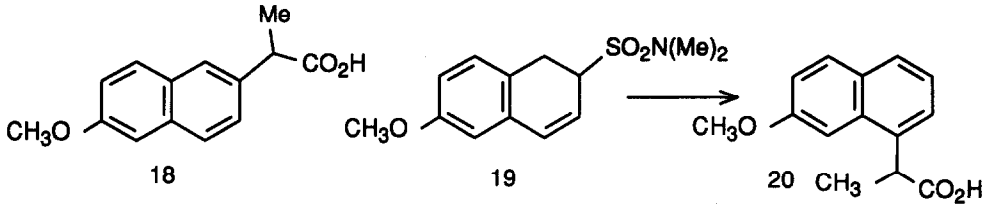
tetrachloride as electrophile[17]. The main product from this reaction was a fully aromatic N-t-butyl-N-methylsulfonamide (from the ^{1}H NMR spectrum) containing one chlorine atom (from its mass spectrum), and the question was where this was located. In this product the multiplicity of the aromatic protons was as follows: A^s, B^s, C^d, D^s and E^d. Barring a quite unlikely rearrangement the compound still has a methoxyl group at C_2 and the sulfonamide group at C_6; hence, since there is only one pair of doublets, the chlorine cannot be at either C_1 or C_5. Irradiation, this time on the protons of the t-butyl group led to a N.O. effect on protons A^s, B^s and the N-CH_3 proton (1, 0.8 and 0.5% respectively). Taking into account all the remaining possibilities this latter result means that the chlorine cannot be at C_5 or at C_7, leaving C_8 as the only location fitting all the results. The structure is therefore as in **17**, probably arising from both nucleophilic substitution (γ-directed) and proton transfer.



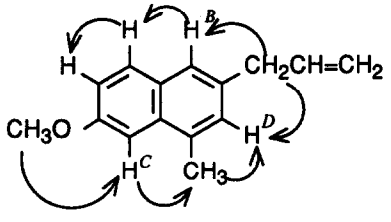
Scheme IV

E. **Formation of "Iso-Naproxen"**. Naproxen, an important anti-inflammatory drug active as its S-enantiomer, has structure **18**. The hybrid mono-carbanion **19** (likewise derived from **12**) had been found to undergo predominantly alkylation at C_2 when using simple alkyl halides; and such products had been formed to be easily separable from the C_4-alkylated by-products formed in small amounts, by the former being aromatised by thermal means alone. However, when using methyl 2-bromopropanoate as alkylating agent a product was obtained from which no substituted naphthalene (i.e. the desired (±) naproxen methyl ester) resulted from heating. Instead, vigorous alkaline hydrolysis (which had been found to lead to aromatisation of all substituted dihydronaphthalenesulfonamides) gave an acidic product different from (±) naproxen[4]. That

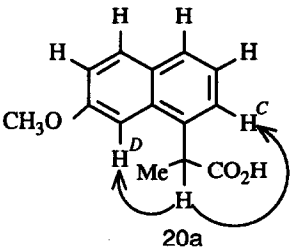
this was the regio-isomer **20** was confirmed in the following manner. From the multiplicity of the aromatic protons: A^d, B^d, C^d, D^s, E^t and F^d, it can be concluded that with the methoxyl group at C_2 the propionic acid side chain must be at either C_5 or C_8. Irradiation of the C-H proton on that side chain led to N.O. enhancements of 1.2 and 1.6% on protons C^d and D^s respectively. Since the latter proton is the only singlet among the six, the side chain cannot be at any other position but at C_8, leading to structure and assignment as in **20a**.



Scheme V



15a



20a

In summary it seems to us that structure determination of polysubstituted aromatic systems can easily be solved by applying NOE technique. It was demonstrated that even remote protons like those of a methoxy ester can be used for the analyses in some cases.

EXPERIMENTAL

n-Butyl lithium in cyclohexane was obtained from Metallgesellschaft AG; its concentration was determined by titration aginst pure substrate (e.g. **5**). TBME= t-Butyl methyl ether. Anhydrous THF was added to the previously flamed-out reaction vessel through active alumina against an argon stream. TLC was done on Merck 60 F-254 silica plates using ethyl acetate-cyclohexane mixtures. Mass spectra were determined on a Finnegan MATA 711 instrument (Data system SS 300). NMR spectra were measured on Bruker 400 MHz, and all were determined in $CDCl_3$. NOE spectra were measured using the NOEMULT program[18] on Aspect 3000.

8-Methoxynaphthalene-2-sulfonic acid sodium salt 2: 1-Naphthol (72 g, 0.5 mol) was added to sulphuric acid (97%, 108 mL), and with stirring the whole was heated to 130° upon which the internal temperature rose spontaneously to 145°. The solution was then allowed to cool slowly to 90° during 1 hr. at which point sodium sulphate (anh., 75 g) and then dropwise water (150 mL) were added, and the mixture heated under reflux for 45 min. While still hot it was neutralised by cautious addition of calcium carbonate (total of ca. 150 g); towards the end the use of silicone anti-foam was essential. The suspension was filtered while hot and the filter cake washed with hot water, to a total filtrate volume of 1 L. Sodium carbonate (anh., 30 g) was added, and after renewed filtration the solution was saturated with NaCl (250 g) and stirred overnight. The salt which crystallised out was filtered off, washed with sat. NaCl, pressed as dry as possible, redissolved in water (350 mL) and sodium hydroxide (63 g) was added. To the warm (40-45°) solution dimethyl sulphate (150 mL) was added dropwise with stirring during 1 hr. keeping the temperature below 50°.

On cooling to 25° a sandy-yellow product crystallised out. After adding NaCl (40 g) this was filtered off, washed with sat. NaCl and then with CCl_4 and dried overnight at 80° to give 51.6 g of the crude **product 2**. From the filtrate upon further saturation with NaCl and stirring, another 5.7 g were obtained.

Conversion of this salt (51.4 g) into the **chloride 3** as described elsewhere[4] gave the latter upon crystallisation from TBME, finally at 0°, in two crops, yield 24.8 g, m.p. 73-74°. Conversion of this into the **sulphonamide 4**, m.p. 168-169° by the general method described[4] proceeded in 92.2% yield. The mother liquors of **3** (8.8 g) afforded another 5.07 g of **4**, indicating an overall yield of 25.6% of chloride **3** from 1-naphthol.

Metallation - Carboxylation of Sulphonamide 5: To the latter (1.51 g, 5.15 mol) in dry THF (15 mL) was added n-butyl lithium in cyclohexane (2.2M, 4.92 mL, 2.1 equiv.) at -40°, and the orange solution obtained was transferred by argon pressure onto an excess of solid CO_2. After reaching room temperature the THF was removed in vacuo, the solid was dissolved in water, a small amount of neutral material removed by extraction with CH_2Cl_2 and the solution acidified. Isolation by extraction with ethyl acetate gave the acidic product (1.62 g) which was heated in diglyme (6 mL) to 160-165° for 30 min. Addition of water, extraction with $CHCl_3$, washing with 5% Na_2CO_3 to remove acidic material (0.19 g), removal of solvent after drying and recrystallisation of the neutral product from $CHCl_3$- cyclohexane gave **product 6**, m.p. 177.5-178.5°, yield 0.86 g (52.3% overall), IR ($CHCl_3$) 2900, 1725, 1635, 1605, 1328, 1300, 1158 cm^{-1}; ^1H NMR (400 MHz) δ 1.82 (s, 9H), 3.98 (s, 3H), 7.33-8.10 (total 5H); nominal MS, m/z 319 (M^+), 304, 264, 263, 200, 113; exact mass, m/z calcd. for $C_{16}H_{17}NO_4S^+$: 319.0878, found 319.0852.

Chlorosulphonation of Methyl Naphthalene 2- and 1-Carboxylates: (a) The 2-ester (24.56 g) was added in small portions with stirring to chlorosulphonic acid (redistilled and completely miscible with CH_2Cl_2, 44 mL, ca. 5 equivs.) in a three-necked flask with magnetic stirrer, connected via a drying tube to an argon trap, while keeping the temperature below 20°. After stirring at room temperature overnight the mixture was diluted with CH_2Cl_2 and the solution added cautiously to ice. The organic layer, after washing with cold water and drying, was concentrated and the residue recrystallised from CH_2Cl_2- TBME, to give the **sulphonyl chloride 10**, m.p. 121-121.5° (11.54 g), IR ($CHCl_3$) 1722, 1372, 1290 cm^{-1}; ^1H NMR (400 MHz) δ 4.00 (s, 3H), 7.62-8.85 (total 6H); nominal MS, m/z 286 (m^+), 285, 284 (M^+), 255, 253, 249, 189, 185, 154, 126; exact mass, m/z calcd. for $C_{12}H_9{}^{35}ClO_4{}^+$: 283.9910, found 283.9912. From the mother liquors a second crop (3.35 g) of m.p. 110-115° was obtained which was ca. 80% pure (by NMR).

Addition of **10** to 1.4 equivs. of t-butylamine in $CHCl_3$ in the presence of 1.4 equivs. of aqueous 1.5N NaOH with stirring as described elsewhere[4] gave the **sulphonamide 11**, m.p. 184-184.5° (from $CHCl_3$ - cyclohexane), IR ($CHCl_3$) 3375, 2945, 1723, 1325, 1290, 1158, 1135 cm^{-1}; ^1H NMR (400 MHz) δ 1.13 (s, 9H), 3.97 (s, 3H), 5.12 (s, lH), 7.55-8.69 (total 6H); ^{13}C NMR (100 MHz) δ 166.5, 138.35, 135.0, 133.4, 131.85, 131.05, 130.3, 128.15, 127.3, 125.15, 55.1, 52.45, 30.0, 27.75; nominal MS, m/z 321 (M^+), 307, 306, 299, 231, 186, 185; exact mass, m/z calcd. for $C_{16}H_{19}O_4S^+$: 321.1035, found 321.1010.

(b) Addition of the 1-ester (12.6 g) in the same manner to chlorosulphonic acid (23 mL) followed by proceeding as described under (a) and recrystallisation of the product from CH_2Cl_2 - TBME gave the **sulphonyl chloride 8**, m.p. 114-115°, yield 4.53 g, IR ($CHCl_3$) 1720, 1372, 1275, 1143 cm^{-1}; ^1H NMR (200 MHz) δ 4.02 (s, 3H), 7.67-9.38 (total 6H); nominal MS, m/z 286 (M^+), 285, 284 (M^+), 255, 253, 249, 220, 189, 186, 185, 170, 154, 153, 126, 125, 114; exact mass, m/z calcd. for $C_{12}H_9{}^{35}ClO_4S^+$: 283.9910, found 283.9914. Reaction with t-butylamine as described under (a) gave the **sulphonamide 9**, m.p. 177.5-178.5°, IR ($CHCl_3$) 3370, 2950, 1718, 1323, 1272, 1133 cm^{-1}; ^1H NMR (200 MHz) δ 1.13 (s, 9H), 4.00 (s, 3H), 5.06 (s, 1H), 7.59-9.15 (total 6H), nominal MS, m/z 321 (M^+), 307, 306, 249, 185, 170, 126; exact mass, m/z calcd. for $C_{16}H_{19}NO_4S^+$: 321.1035, found 321.0988.

4-Chloro-N-1,1-dimethylethyl-N-methyl-6-methoxynaphthalene-2-sulphonamide (17): The dihydrosulphonamide **16**[(4)] (0.618 g, 2 mmol) was added to a suspension of NaH (from 0.14 g 49% suspension

washed with pentane, 1.4 equivs.) in dry DMF (1.5 mL), while cooling to -50°, followed by addition of CCl_4 (0.4 mL). The stirred suspension was allowed to reach room temperature overnight. Water was added and the product isolated with CH_2Cl_2. TLC showed the presence of one major and one very minor product.Two recrystallisations from MeOH gave **product 17**, m.p. 121-121.5°,yield 0.86 g, IR ($CHCl_3$) 2940, 1622, 1500, 1468, 1330, 1150 cm^{-1}; ^1H NMR (400 MHz) δ 1.35 (s, 9H), 2.97 (s, 3H), 3.96 (s, 3H), 7.24-8.19 (total 5H); ^{13}C NMR δ 160.75, 137.7, 133.65, 131.45, 131.15, 128.55, 128.35, 123.35, 121.05, 102.95, 59.0, 55.6, 32.55, 29.3; nominal MS m/z 343 (M^+), 341 (M^+), 328, 327, 326, 292, 287, 285, 257, 255, 231, 207, 193, 192, 191, 180, 176, 169, 131; exact mass, m/z calcd. for $C_{16}H_{20}{}^{35}ClNO_3S^+$: 341.0852, found 341.0836.

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16. Perusal of 20 such X-ray crystallographically determined structures from databases in Zurich and Cambridge (U.K.) revealed the presence of this preferred methoxyl conformation (towards the 1-position) in each case. We are grateful to J. Dunitz (E.T.H. Zurich) and O. Kennard (University of Cambridge, U.K.) for this information. The same phenomenon has also been observed by N.O.E. in a 2-isopropoxynaphthalene (L. Gottlieb, H. J. E. Loewenthal, unpublished observation).
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