Recl. Trav. Chim. Pays-Bas **111**, 183–187 (1992) 0165–0513/92/04183–05$1.75

Sulfonation of anisole, phenol, toluene and related alkyl and alkoxy derivatives with SO_3. The influence of the solvent system on the reactivity and the sulfonic acid product distribution§,†

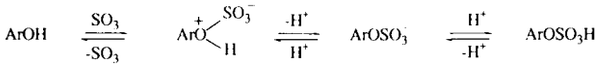
Harold R. W. Ansink and Hans Cerfontain*

Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands
(Received October 30th, 1991)

Abstract. The reactions of anisole (**1**), phenol (**2**), the alkoxy- and alkylphenyl ethers **3–11**, toluene (**12**) and the *o*-dialkylbenzenes **13–15** with sulfur trioxide in dichloromethane or trichlorofluoromethane have been studied. Our results have been compared with those obtained with the same substrates upon reaction with SO_3 in nitromethane and dioxane. We show that *ortho* substitution is enhanced for sterically unhindered phenyl ethers and phenols due to complex formation between SO_3 and the C(sp^2)-bonded oxygen when dichloromethane is used as solvent instead of nitromethane or dioxane. This is mainly as a result of intramolecular SO_3 transfer from the oxygen to the *ortho* carbon and subsequent conversion of the resulting σ-complex into the *ortho* sulfonic acid.

Introduction

The sulfonation of phenols with sulfur trioxide proceeds by initial sulfation to yield the corresponding phenyl hydrogen sulfate and subsequent formation of the phenolsulfonic acid[1]. The formation of the phenyl hydrogen sulfate occurs via complexation of the hydroxy oxygen by SO_3 and subsequent proton transfer, as depicted in Scheme 1[2]. Whether



Scheme 1. Mechanism for conversion of phenols into phenyl hydrogen sulfates.

the phenomenon of complexation between oxygen and sulfur trioxide also occurs in other systems, and if so, to what extent, is the issue of interest in our research studies regarding the sulfonation of aromatic ethers[3-7].

Electrophilic attack on an aromatic hydroxy or alkoxy oxygen has been observed[8-11]. Complexation by SO_3 and protonation on a methoxy oxygen leading to demethylation has been reported for the sulfonation of chloroanisoles and dichloroanisoles with fuming sulfuric acid[8]. Protonation of substituted methyl and ethyl ethers in superacids has been observed. In the case of ethyl ethers, this may lead to *O*-dealkylation which, in some cases, leads to subsequent *C*-alkylation *meta* to the oxy substituent[9]. Bromination of ring-methylated phenols and anisoles in superacidic media leads mainly to bromination *meta* to the oxygen substituent due to the "complete" primary protonation at oxygen: *e.g.*, bromination of 4-methylphenol gives the 3-bromo isomer in a yield of 51%[10]. Reaction of 4-methylanisole (**11**) in superacidic medium with Br_2 leads to bromination *meta* to the OCH_3 group[11], whereas with the 2-methyl isomer **7** it does not, the only product being the 4-bromo derivative of **7**[12]. Metal-catalyzed acylation of phenols leads to an enhanced degree of *ortho* substitution[13]. Strongly coordinating species, such as Al(III) and MgBr, yield in fact selective *ortho* substitution.

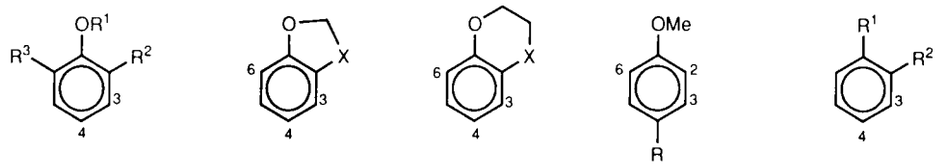
In this work, the reactions of anisole (**1**), phenol (**2**) and the related alkylphenyl and alkoxyphenyl ethers **3–11** with SO_3 in the non-complexing solvents dichloromethane or trichlorofluoromethane have been studied in comparison with toluene (**12**) and the *o*-dialkylbenzenes **13–15** in order to obtain information on the effect of the solvent on the amount of *ortho* substitution in the initial sulfonation step. Using dioxane[14] or nitromethane[15] as complexing solvent, anisole (**1**), phenol (**2**) and the *ortho*-disubstituted ethers **3–5** and **7–10** yield, as the primary sulfonation product, exclusively the 4-sulfonic acid (≥99%)[1,2,4,16], whereas the *para*-substituted substrates **6** and **11** yield the 2-sulfonic acid for ≥99%[2,3]; the carbon analogues **12–15** under these conditions yield a mixture of the *ortho*- and *para*-substitution products[17].

Results and discussion

The reactions of anisole (**1**), phenol (**2**), the alkoxyphenyl and alkylphenyl ethers **3–11**, toluene (**12**) and the *o*-dialkylbenzenes **13–15** with SO_3 in dichloromethane and trichloro-

§Aromatic sulfonation 114. For part 113, see ref. 6.

†For reasons of convenience, the aromatic ring positions of both the substrates and their sulfonic acids have been numbered as for the corresponding 1,2-dimethoxybenzene (**3**) and 2-methylanisole (**7**).



1 R^1 = Me; R^2 = R^3 = H
2 R^1 = R^2 = R^3 = H
3 R^1 = Me; R^2 = OMe; R^3 = H
7 R^1 = R^2 = Me; R^3 = H
8 R^1 = R^2 = R^3 = Me

4 X = O
9 X = CH_2

5 X = O
10 X = CH_2

6 R = OMe
11 R = Me

12 R^1 = Me; R^2 = H
13 R^1 = R^2 = Me
14 R^1 + R^2 = -$(CH_2)_3$-
15 R^1 + R^2 = -$(CH_2)_4$-

Table I Sulfonation of anisole (**1**), *phenol* (**2**), *the alkyl- and alkoxyphenyl ethers* **3–11**, *and of the non-oxygen-containing analogues toluene* (**12**) *and o-dialkylbenzenes* **13–15** *in dichloromethane or trichlorofluoromethane and in nitromethane for 30 min.*

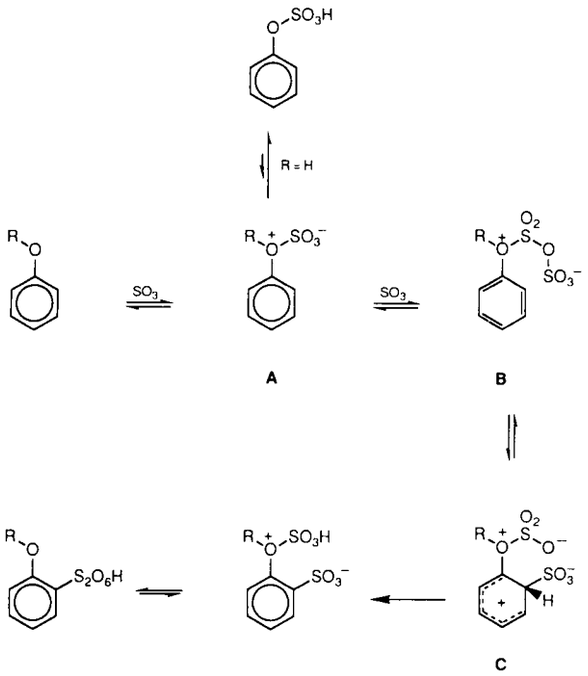
Substrate	Method[a]	SO_3 mol-equiv (±0.1)	Product mixture composition (%, ±2)[b,c]				
			in CH_2Cl_2 or CCl_3F (at −20°C)[d]			in CH_3NO_2 (at 0°C)	
1	A	0.03 ± 0.01	2 (16)	4 (84)		4 (≥99)[e]	
	A	0.10 ± 0.01	2 (21)	4 (79)			
2	D	0.5[f]	2 + 4 (5)		O (95)		
		0.5[g]	2 (17)	4 (11)	O (72)		
		0.5[h]	2 (37)	4 (25)	O (38)	4 (≥99)[i]	
3	A	0.6		4 (≥99)		4 (≥99)[j]	
	A	2.0		4 (≥99)		4 (≥99)[j]	
4	A	0.6	3 (13)	4 (87)		4 (≥99)[j]	
5	C	0.6	3 (15)	4 (78)	3,5 (7)	4 (≥99)[j]	
6	B	4.0	2 (4)	2,5 (94)	2,6 (2)	2 (4)	2,5 (96)[k]
7	A	0.7		4 (≥99)		4 (≥99)[l]	
	B	4.0		4 (30)	4,6 (70)	4 (94)	4,6 (6)[l]
8	A	0.7	3 (13)	4 (87)		3 (3)	4 (97)[l]
	B	4.0	3 (0.5)	4 (68)[m]			
9	C	0.6	4 (79)	6 (3)	4,6 (18)	4 (≥99)[j]	
10	C	0.6	4 (76)	6 (11)	4,6 (13)	4 (≥99)[j]	
11	A	0.7	2 (≥99)			2 (98)[i]	
	B	4.0	2 (57)		2,6 (43)	2 (95)	2,6 (5)[i]
12	C	0.6	2 (14)	4 (86)		2 (11)	4 (89)[n]
13	C	0.6	3 (6)	4 (94)		3 (6)	4 (94)[n]
14	C	0.6	3 (12)	4 (88)		3 (15)	4 (85)[n]
15	C	0.6	3 (15)	4 (85)		3 (12)	4 (88)[n]

[a] The solvent used in methods A, C and D is dichloromethane; with method B, it is trichlorofluoromethane. [b] The first datum gives the positions of the potassium sulfonate group(s) or (in the case of method D) the sulfonic acid group and that between brackets the relative yield. [c] The amount of unconverted substrate has not been determined for methods A–C. [d] This work. [e] Taken from Ref. 2; the amount SO_3 used was 0.9 mol-equiv. [f] Reaction performed at −50°C; 49% of substrate was also present. [g] Reaction mixture composition after standing at −20°C for 60 min. [h] Reaction mixture composition after standing at −20°C for 60 min and at room temperature for 30 min. [i] Taken from Ref. 1. [j] Taken from Ref. 4. [k] Taken from Ref. 3. [l] Taken from Ref. 2. [m] In addition, 18% of 2,6-dimethylphenol-4-sulfonate is formed. [n] Taken from Ref. 17.

fluoromethane at −20°C for 30 min have been studied. The results are compiled in Table I.

On reaction of anisole (**1**) with SO_3 in dichloromethane as solvent, the amount of 2-sulfonic acid formed (between 16 and 21%) is substantially greater than on reaction with SO_3 in nitromethane or dioxane (<0.5%[2,16]). Two factors may play a role in this difference. Firstly, the nature and size of the sulfonating entity in the three systems is different; steric hindrance in the sulfonation σ-complex or in any preceding encounter complex may reduce the rate of *ortho* sulfonation relative to *para* sulfonation. The moderating agent (*e.g.*, 1,4-dioxane) is a very strong Lewis base, and SO_3 will be present very predominantly as a complex with the moderator[14,15]. SO_3 is transferred directly from the (bulky) complex to the substrate molecule, which leads to an enhanced degree of steric hindrance compared with the sulfonation with "free" SO_3 in the halogenomethanes as solvent. Secondly, the free electrons on the ether oxygen may enhance *ortho* substitution due to bonding of SO_3 to the ether oxygen forming the oxonium sulfonate and oxonium pyrosulfonate species **A** and **B**, respectively. Subsequent "intramolecular" transfer of the external SO_3 of **B** to the *ortho* position in a six-membered ring transition state (see Scheme 2) yields the *ortho* σ-complex **C** which, upon intramolecular proton transfer of the C(sp^2)-bonded hydrogen in a six-membered ring transition state, eventually yields the 2-(pyro)sulfonic acid. In dioxane and nitromethane as solvent, this route will be improbable, as both solvents, present in a very large excess, are stronger Lewis bases than anisole.

The formation of 60% phenol-2-sulfonic acid (**2**-2-S) upon



*Scheme 2. Mechanism for complexation and subsequent sulfonation of anisole (***1***, R = CH_3) and phenol (***2***, R = H) by SO_3.*

reaction of phenol (**2**) with SO_3 in dichloromethane is indicative of an intramolecular transfer of SO_3 to the *ortho* position after complexation on the hydroxy oxygen, as shown in Scheme 2.

For *ortho* sulfonation, two SO_3 molecules are involved. It has been shown that sulfonation of *p*-dichlorobenzene in trichlorofluoromethane is first order in SO_3 although two molecules are involved in the formation *p*-dichlorobenzene-2-(pyro)sulfonic acid[18], which infers that the addition of the second SO_3 is not rate-determining. The rate-limiting step for sulfonation of anisole and phenol on C(2) is probably SO_3 transfer in a six-membered ring, which implies that this process will be second order in SO_3. For sulfonation on C(4), as for dichlorobenzene, the initial step of attack of the electrophile SO_3 is rate-limiting, and thus, sulfonation at C(4) is first order in SO_3.

The results of reactions of the aromatic ethers **3–11** with SO_3 in dichloromethane and trichlorofluoromethane support the hypothesis of initial ether complexation and subsequent intramolecular SO_3 transfer as an (additional) route of sulfonation *ortho* to the hydroxy and methoxy groups. Contrary to the reactions performed in nitromethane, the cyclic ethers 1,2-(methylenedioxy)benzene (**4**), 1,2-(ethylenedioxy)benzene (**5**), 2,3-dihydrobenzofuran (**9**) and 2,3-dihydrobenzopyran (chromane, **10**) yield *ortho* substitution products in the initial sulfonation in dichloromethane and trichlorofluoromethane. However, no *ortho* substitution is observed in the primary sulfonation when there is a substituent adjacent to the methoxy group, as in 1,2-dimethoxybenzene (**3**) and 2-methylanisole (**7**). These results indicate that severe steric restrictions are involved with the latter two substrates. Both the hydroxy and the methoxy groups have a strong preference to be co-planar with the phenyl group to enable optimal conjugative stabilization; the methoxy methyl(s) of **3** and **7** will, therefore, be directed toward the unsubstituted position(s) [*viz.*, 6-C (and 3-C)] for steric reasons[19]. For the rigid cyclic substrates, this cannot occur, allowing substitution at the *ortho* position.

The formation of 13% of 2,6-dimethylanisole-3-sulfonic acid (**8**-3-S) in addition to 87% of **8**-4-S upon reaction of **8** with SO_3 in dichloromethane, as opposed to only 3% when nitromethane is the solvent[2], indicates that SO_3 complexation occurs on the ether oxygen of **8**. Complex formation will reduce the activating *para*-directing effect of the methoxy group, and will lead to an increase in the 3-S/4-S ratio, as is in fact observed. Complexation of SO_3 on the ether oxygen is also apparent from the observed demethylation on reaction of **8** with a large excess of SO_3.

On reaction of 1,4-dimethoxybenzene (**6**) with 4.0 mol-equiv of SO_3, **6**-2,5-S_2 is the main product (94%). This indicates steric hindrance encountered for substitution of **6**-2-S at the 6-position, where the adjacent 1-methoxy group is neighbouring the large sulfo substituent. For when only considering the electronic directing effects of the substituents of **6**-2-S, the expected disulfonation product would be **6**-2,6-S_2.

An important factor that must be taken into consideration is the much higher sulfonating reactivity of the present two sulfonating systems compared with that of SO_3 in nitromethane and dioxane. In principle, this could lead to a lower degree of selectivity in the substitution pattern, which may also account for the enhanced formation of the *ortho* substitution products. The fact that phenol in the halogenomethane solvents is already *C*-sulfonated (5%) at −50 °C in addition to 95% *O*-sulfonation indicates that these sulfonating systems are, in fact, less selective, as in nitromethane at −35 °C only phenyl hydrogen sulfate is formed[1]. However, the sulfo-product compositions obtained with (di)alkylated benzenes **12–15** seem to contradict this argument. Toluene (**12**) yields a mixture of **12**-2-S and **12**-4-S in a ratio of 0.16, whereas *o*-xylene (**13**), indane (**14**) and tetralin (**15**) yield a mixture of their respective 3-S and 4-S in a ratio of 0.064, 0.14 and 0.18. All these substitution ratios are similar to those observed for nitromethane as solvent[17], *viz.*, 0.13, 0.067, 0.18 and 0.13, respectively. These results indicate the occurrence, in the sulfonation of phenyl ethers with SO_3 in dichloromethane, of complex formation between the ether oxygen and SO_3, as the *ortho*/*para* ratio in the absence of an ether oxygen is independent of the solvent system. The higher reactivity of the present sulfonating system is, on the other hand, confirmed by the formation of 70% of **7**-4,6-S_2 with 4.0 mol-equiv of SO_3 as opposed to only 6% in nitromethane as solvent[2].

When the reactions of the various substrates with SO_3 in dichloromethane are compared with those in SO_3-complexing solvents, it can be concluded that the presence of an alkoxy or hydroxy group leads to an enhanced degree of *ortho* substitution in the primary sulfonation due to initial complexation between the C(sp^2)-bonded oxygen and a sulfur trioxide molecule, provided that steric hindrance is not a prohibitive factor.

Experimental

Most compounds were obtained commercially and used as such. 2,6-Dimethylanisole (**8**) was synthesized from 2,6-dimethylphenol using dimethyl sulfate[20]. Chromane (**10**) was prepared following a described method starting from phenol[21]. The ^{1}H NMR spectra were recorded on Bruker AC-200 and WM-250 spectrometers.

Sulfonation procedures

Method A. The desired amount of SO_3 in 1.0 ml of CH_2Cl_2 at −20 °C was added to a solution of 0.25 mmol of substrate in 1.0 ml of CH_2Cl_2 under an argon atmosphere. After 30 min, 1 ml of H_2O or ^2H_2O was added and the mixture was heated to 35 °C to hydrolyze the anhydrides and hydrogen sulfates possibly formed. The aqueous layer was subsequently separated and bubbled through with nitrogen to remove any dichloromethane present. In case of quenching with H_2O, the solution was neutralized with

Table II ^1H *NMR data of the sulfo products of* **1–15** *in* ^2H_2O.

Species[a]	δ (ppm, ±0.05)[b,c]						
	1-H	2-H	3-H	4-H	5-H	6-H	H_{aliph}
1-2-S	3.92		7.78	7.08	7.56	7.17	
1-4-S	3.87	7.05	7.75				
1-2,4-S_2	3.99		8.18		7.95	7.26	
2-O-SO_3H[d]	----------	----------	----------	7.36	----------	----------	
2-2-S			7.75	7.05	7.50	7.05	
2-2-SO_3H[d]			7.75		7.55		
2-4-S		6.90	7.68				
2-4-SO_3H[d]		7.08	7.80				
3-4-S	3.79	3.85	7.35		7.42	6.95	
4-3-S	-------	6.21 -------				6.87	
4-4-S		6.05 -------	7.25		7.35	6.94	
5-3-S	-------	4.40 -------		7.37	6.97	7.17	
5-4-S	-------	4.36 -------	7.35		7.33	7.04	
5-3,5-S_2	-------	4.46 -------		7.76		7.51	
6-2-S	3.96		7.47	3.85	-------	7.23 -------	
6-2,5-S_2	4.02		7.64				
6-2,6-S_2			7.85				
7-4-S	3.90	2.27	7.61		7.64	7.06	
7-4,6-S_2	3.97	2.44	7.90		8.08		
8-3-S	3.77	2.53		7.60	7.30	2.32	
8-4-S	3.73	2.30	7.55				
9-4-S			7.68		7.60	6.88	3.26 (t, 2H); 4.66 (t, 2H)
9-6-S			7.46	6.96			3.26; 4.66
9-4,6-S_2			7.81		7.92		3.22
10-4-S			7.57		7.55	6.91	2.02; 2.84; 4.26
10-6-S			7.32	6.96	7.60		2.02; 2.84; 4.32
10-4,6-S_2			7.73		8.00		2.02; 2.84; 4.38
11-2-S	3.93		7.65	2.35	7.42	7.11	
11-2,6-S_2	4.10		7.89	2.41			
12-2-S	2.62	7.88	7.45				
12-4-S	2.41	7.39	7.71				
13-3-S	2.34	2.55					
13-4-S	2.34	2.34	7.61		7.55	7.34	
14-3-S					7.29	7.46	2.08; 2.93; 3.15
14-4-S			7.67		7.58	7.38	2.07; 2.93
15-3-S				7.71	7.30		1.77; 2.78; 3.09
15-4-S			7.52		7.50	7.24	1.77; 2.78

[a] S stands for SO_3^-. [b] All *ortho* and *meta* $J_{H,H's}$ were found to be 7.5–9 and 1.5–2.5 Hz, respectively. [c] δ relative to virtual internal TMS as standard. [d] Values for $C^2H_2Cl_2$ as solvent.

aqueous KOH and freeze-dried. A ^1H NMR spectrum was recorded of the resulting potassium sulfonates in ^2H_2O; in case of quenching with ^2H_2O, a spectrum was recorded of the acidic solution.

Method B. This method is a modified version of method A, in which trichlorofluoromethane is the solvent. This method was used for higher sulfur trioxide concentrations to avoid possible phosgene formation, as may occur with CH_2Cl_2[22].

Method C. This method is also a modified version of method A. To reduce the amount of disulfonation due to the high reactivity of the system, the reaction mixtures are more diluted. A solution of the desired amount of SO_3 in 7.5 ml of CH_2Cl_2 at −20°C was added to a solution of 0.6 mmol of substrate in 7.5 ml of CH_2Cl_2 under argon. Further manipulations are as described in method A.

Method D. The desired amount of SO_3 at the desired temperature was added to a solution of 0.125 mmol of substrate in 1.0 ml of $C^2H_2Cl_2$ under argon. Part of the sample thus obtained was transferred into an NMR tube and ^1H NMR spectra were recorded at appropriate time intervals and temperatures.

The structural assignments of the sulfo products of the SO_3 sulfonations were made on the basis of the observed chemical shifts, absorption area ratios and coupling constants in combination with the shielding parameters of the Me, OH, OMe, OSO_3H, SO_3^- and SO_3H substituents[1,23,24]. The assignments are compiled in Table II.

References

[1] *H. Cerfontain, A. Koeberg-Telder, H. J. A. Lambrechts* and *P. de Wit*, J. Org. Chem. **49**, 4917 (1984).

[2] *H. D. Goossens, H. J. A. Lambrechts, H. Cerfontain* and *P. de Wit*, Recl. Trav. Chim. Pays-Bas **107**, 426 (1988).

[3] *H. Cerfontain, N. J. Coenjaarts* and *A. Koeberg-Telder*, Recl. Trav. Chim. Pays-Bas **108**, 7 (1989).

[4] *H. R. W. Ansink* and *H. Cerfontain*, Recl. Trav. Chim. Pays-Bas **108**, 395 (1989).

[5] *H. Cerfontain, H. R. W. Ansink, N. J. Coenjaarts, E. J. de Graaf* and *A. Koeberg-Telder*, Recl. Trav. Chim. Pays-Bas **108**, 445 (1989); *H.R.W. Ansink* and *H. Cerfontain*, Phosphorus, Sulfur, and Silicon **63**, 335 (1991).

[6] *H. R. W. Ansink* and *H. Cerfontain*, Recl. Trav. Chim. Pays-Bas, accepted for publication.

[7] *H. Cerfontain, H. J. A. Lambrechts, Z. R. H. Schaasberg-Nienhuis, R. G. Coombes, P. Hadjigeorgiou* and *G. P. Tucker*, J. Chem. Soc. Perkin Trans. 2, 659 (1985).

[8] *P. de Wit* and *H. Cerfontain*, Recl. Trav. Chim. Pays-Bas **107**, 418 (1988).

[9] *J.-P. Gesson, L. di Giusto* and *J. C. Jacquesy*, Tetrahedron **34**, 1715 (1978).

[10] *J. C. Jacquesy, M. P. Jovonnetard* and *S. Makani*, J. Chem. Soc., Chem. Comm. 110 (1980).

[11] *G. Cherry, J.-C. Culmann* and *J. Sommer*, Tetrahedron Lett. **31**, 2007 (1990).

[12] *J. M. Britain, P. B. D. de la Mare* and *P. A. Newman*, Tetrahedron Lett. 4111 (1980).
[13] *F. Bigi, G. Casiraghi, G. Casnati* and *G. Sartori*, J. Chem. Soc. Perkin Trans. 1, 2655 (1984); *G. Sartori, G. Casnati, F. Bigi* and *G. Bonini*, Synthesis 763 (1988); *G. Sartori, G. Casnati* and *F. Bigi*, J. Org. Chem. **55**, 4371 (1990).
[14] *E. E. Gilbert*, Sulfonation and Related Reactions. Wiley Interscience, New York, 1965, Chapter 1.
[15] *H. Cerfontain* and *A. Koeberg-Telder*, Recl. Trav. Chim. Pays-Bas **89**, 569 (1970).
[16] *H. R. W. Ansink*, unpublished results.
[17] *H. Cerfontain, A. Koeberg-Telder* and *E. van Kuipers*, J. Chem. Soc. Perkin Trans. 2, 2091 (1972).
[18] *J. K. Bosscher* and *H. Cerfontain*, Tetrahedron **24**, 6543 (1968).
[19] *W. Hummel, K. Huml* and *H.-B. Bürgi*, Helv. Chim. Acta **71**, 1291 (1988).
[20] *A. Vogel*, "Practical Organic Chemistry", 3rd ed., Longmans, Green and Co. Ltd., London, 1970, p. 669.
[21] *P. Maitte*, Ann. Chim. **9**, 431, 448 (1954).
[22] Ref. 14, p. 83.
[23] *H. Cerfontain, A. Koeberg-Telder, C. Kruk* and *C. Ris*, Anal. Chem. **46**, 72 (1974).
[24] *M. Hesse, H. Meier* and *B. Zeeh*, "Spectroscopische Methoden in der Organischen Chemie", George Thieme Verlag, Stuttgart, 2nd ed., 1984, p. 176.