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METALATION REACTIONS

V. PRODUCT DISTRIBUTION IN THE METALATION OF ALKOXY(ALKYLTHIO)BENZENES *

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Summary

The product distributions have been determined for metalations of *o*-, *m*- and *p*-alkoxy(alkylthio)benzenes with n-butyllithium. The results show that the alkoxy group has a stronger orientating effect than the thioalkyl group. The presence of products of metalation *ortho* to the thioalkyl group or in the thiomethylic chain, however, indicates that the thioalkyl group also has a significant influence on the preferred position of attack.

Introduction

In a previous investigation [1] of the metalation of *o*-, *m*- and *p*-alkoxy(alkylthio)benzenes with n-butyllithium, only the main products were isolated and identified. Since these compounds contain, along with the alkoxy group, a thioalkyl group, which normally gives rise to *ortho* orientation because its electron withdrawing effect [2,3], additional products would be expected. We describe below a re-examination of the metalation aimed at a complete account of the product distribution and assessment of the selectivity of the metalating agent.

Results and discussion

The metalation of Ia, Ib, IIa, IIb, IIIa, IIIb, IIIc was carried out by treatment of ether solutions with n-butyllithium in hexane. The reaction mixtures were carbonated and the products examined by GLC before the main products were

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* For Part IV see ref. 7.

TABLE 1

REACTIONS OF n-BUTYLLITHIUM WITH ALKOXYALKYLTHIOBENZENES (I, II AND III)

Starting material	Products after carbonation	Fraction ^{a} (%)	Products after desulfuration
1-Methoxy-2-(methylthio)-benzene (Ia)	((2-Methoxyphenyl)thio)acetic acid (IVa)	63	Methoxybenzene (XII)
	2-Methoxy-3-(methylthio)benzoic acid (IVb)	31	2-Methoxybenzoic acid (XIa)
	3-Methoxy-2-(methylthio)benzoic acid (IVc)	6	3-Methoxybenzoic acid (XIb)
1-Methoxy-2-(isopropylthio)-benzene (Ib)	2-Methoxy-3-(isopropylthio)benzoic acid (Va)	68	2-Methoxybenzoic acid (XIa)
	3-Methoxy-2-(isopropylthio)benzoic acid (Vb)	32	3-Methoxybenzoic acid (XIb)
1-Methoxy-3-(methylthio)-benzene (IIa)	2-Methoxy-6-(methylthio)benzoic acid (VIa)	73	2-Methoxybenzoic acid (XIa)
	2-Methoxy-4-(methylthio)benzoic acid (VIb)	8	2-Methoxybenzoic acid (XIa)
	4-Methoxy-2-(methylthio)benzoic acid (VIc)	6	4-Methoxybenzoic acid (XIc)
	((3-Methoxyphenyl)thio)acetic acid (VId)	13	Methoxybenzene (XII)
1-Methoxy-3-(isopropylthio)-benzene (IIb)	2-Methoxy-6-(isopropylthio)benzoic acid (VIIa)	65	2-Methoxybenzoic acid (XIa)
	2-Methoxy-4-(isopropylthio)benzoic acid (VIIb)	21	2-Methoxybenzoic acid (XIa)
	4-Methoxy-2-(isopropylthio)benzoic acid (VIIc)	14	4-Methoxybenzoic acid (XIc)
1-Methoxy-4-(methylthio)-benzene (IIIa)	2-Methoxy-5-(methylthio)benzoic acid (VIIIa)	92	2-Methoxybenzoic acid (XIa)
	3-Methoxy-6-(methylthio)benzoic acid (VIIIb)	2	3-Methoxybenzoic acid (XIb)
	((4-Methoxyphenyl)thio)acetic acid (VIIIc)	6	Methoxybenzene (XII)
1-Methoxy-4-(isopropylthio)-benzene (IIIb)	2-Methoxy-5-(isopropylthio)benzoic acid (IXa)	96	2-Methoxybenzoic acid (XIa)
	3-Methoxy-6-(isopropylthio)benzoic acid (IXb)	4	3-Methoxybenzoic acid (XIb)
1-Isopropoxy-4-(methylthio)-benzene (IIIc)	2-Isopropoxy-5-(methylthio)benzoic acid (Xa)	94	2-Isopropoxybenzoic acid (XIIIa)
	3-Isopropoxy-6-(methylthio)benzoic acid (Xb)	2	3-Isopropoxybenzoic acid (XIIIb)
	((4-Isopropoxyphenyl)thio)acetic acid (Xc)	4	Isopropoxybenzene (XIV)

^{a} All percentages were obtained by GLC analysis.

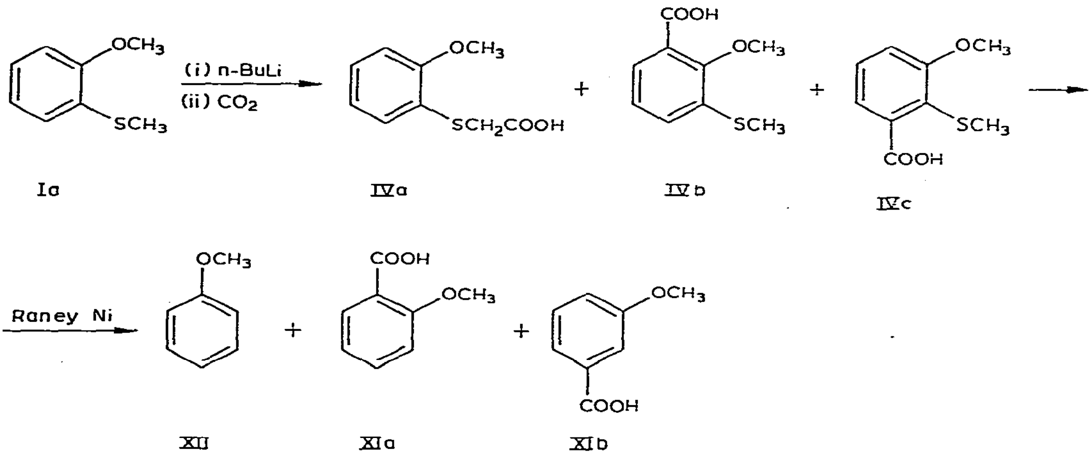
isolated. The chromatograms exhibited peaks in addition to those of the main products previously reported [1]. The new products were identified as carboxylic acids and the yields, when added to those of the main products, accounted for all of the reacted starting material.

The results (see Table 1) can be summarized as follows.

Ortho-disubstituted benzenes (Ia, Ib)

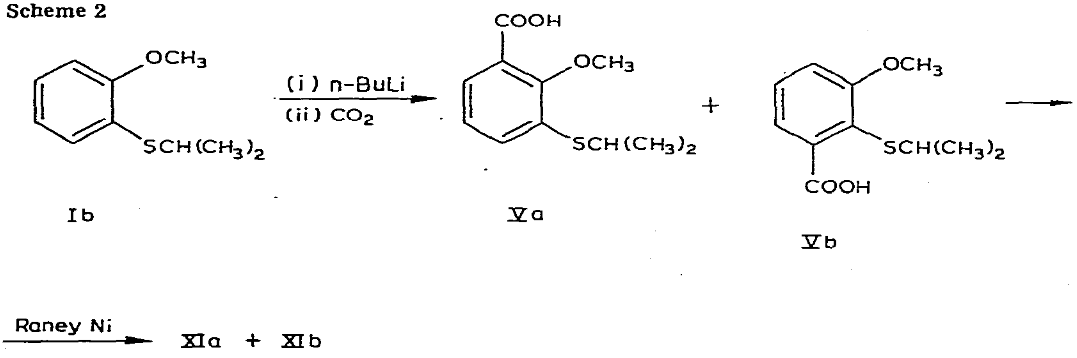
Metalation of 1-methoxy-2-(methylthio)benzene (Ia) (Scheme 1) occurs mainly in the thiomethylic group, but with significant ring metalation *ortho* to the methoxy group; ring metalation *ortho* to the thiomethylic group occurs only to a very small extent.

Scheme 1



The metalation position was determined by GLC analysis of the product mixture. There were three peaks. A peak which accounted for 63% of the total area arises from the main product IVa, previously isolated [1]. Desulfuration of the mixture with Raney nickel catalyst was carried out to identify the remaining two peaks. Evidence for metalation *ortho* to the methoxy group is provided by the presence of XIa (31%), while the presence of XIb (6%) may be reasonably attributed to a metalation product *ortho* to the thiomethyl group. Metalation *meta* to the methoxy and *para* to the thiomethyl group, which would also

Scheme 2



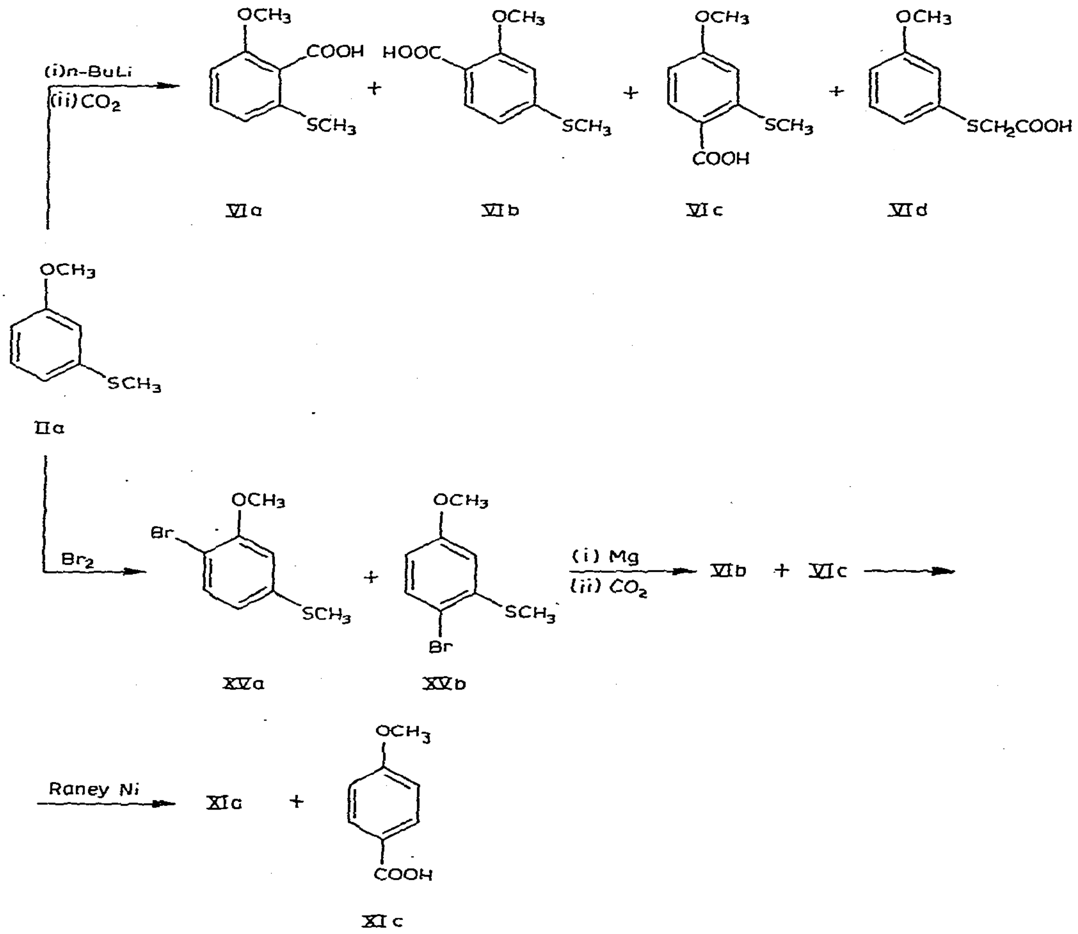
account for the formation of XIb, must be discarded since these reactions preferentially occur *ortho* to electron-withdrawing groups [1,4–6]. Further, the product of metalation *para* to the methoxy and *meta* to the thiomethyl group, which would also be expected with the possibility, was not detected.

GLC analysis of the product mixture from 1-methoxy-2-(isopropylthio)benzene (Ib) after desulfuration showed that metalation occurs *ortho* to the methoxy group to give Va (68%) and *ortho* to the isoporpylthio group to give Vb (32%) (Scheme 2).

Meta-disubstituted benzenes (IIa, IIb)

GLC analysis of the product mixture from metalation of 1-methoxy-3-(methylthio)benzene (IIa) (Scheme 3) shows four peaks. The acid responsible for the main peak (73%) is VIa, which was previously isolated [1]. The remaining three peaks were assigned as follows. That from VId (13%) was identified by comparison with an authentic sample synthesized by a different route. To identify VIb and VIc (8% and 6% respectively), IIa was brominated and the

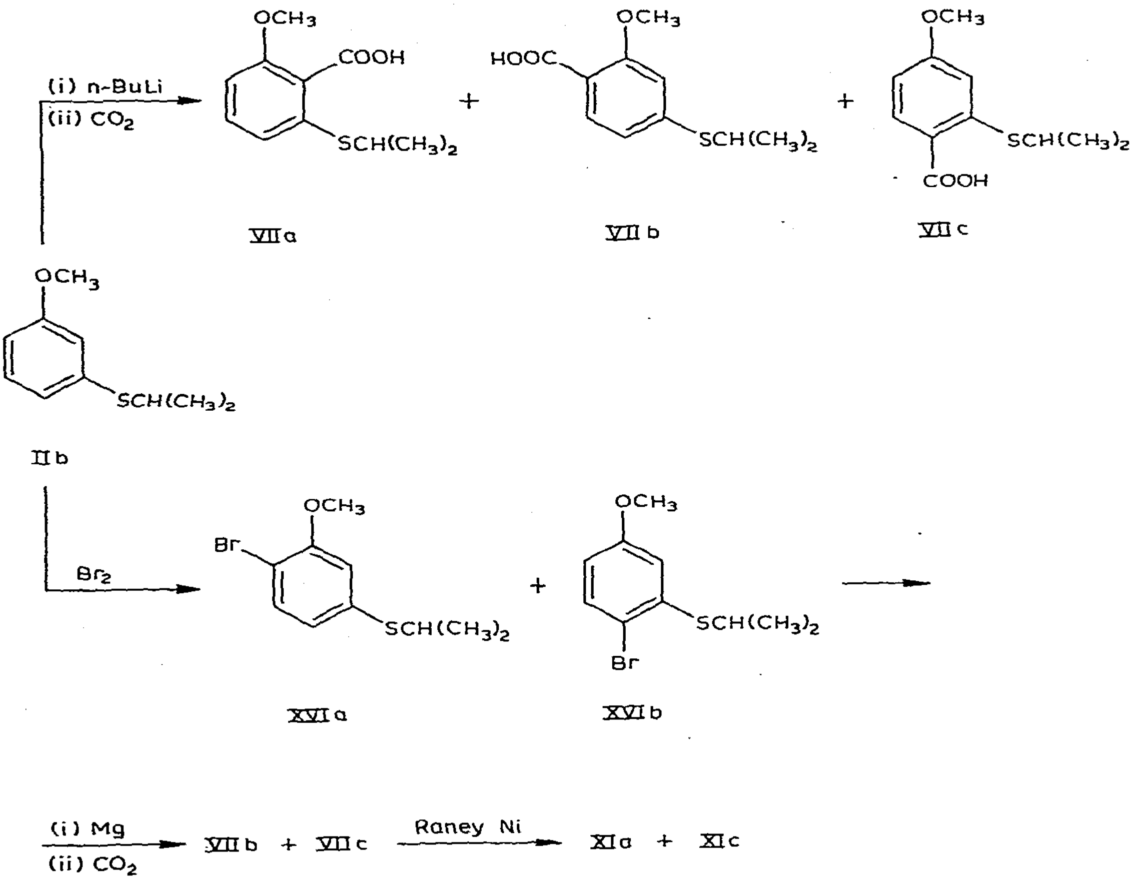
Scheme 3



corresponding bromo derivatives XVa and XVb were converted into the acids VIb and VIc, which were found in a ratio of 35/65. The identity of VIb and VIc was also demonstrated by desulfuration with Raney nickel catalyst.

1-Methoxy-3-(isopropylthio)benzene (IIb) (Scheme 4) gives three acids, and

Scheme 4



these were identified as VIIa (comparison with an authentic sample) VIIb and VIIc, the last two being identified by the route described above for VIb and VIc.

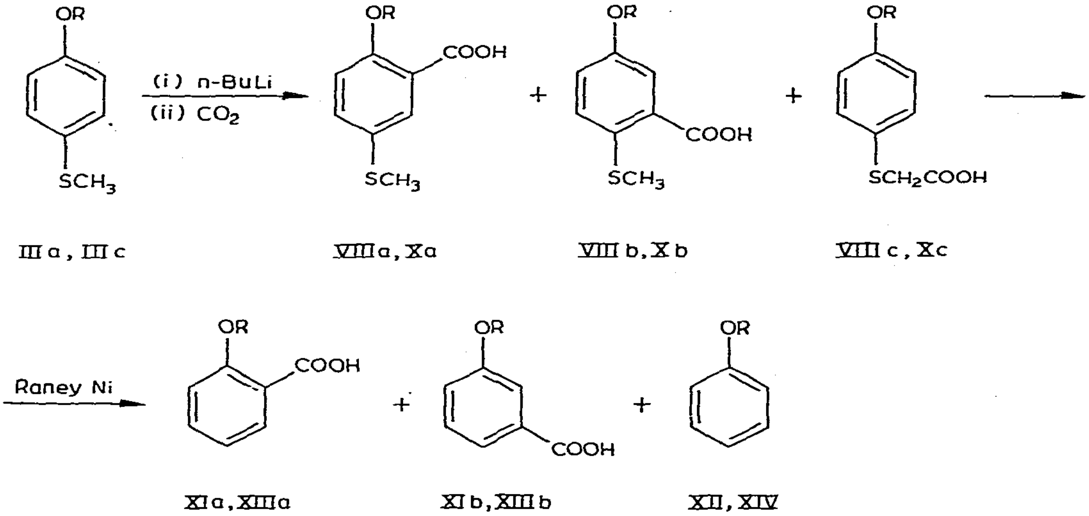
Para-disubstituted benzenes (IIIa, IIIb, IIIc)

Metalation of 1-alkoxy-4-(methylthio)benzenes (IIIa, IIIc) (Scheme 5) also shows that reaction occurs mainly *ortho* to the alkoxy group (92—94%). The products of the reaction *ortho* to the thioalkyl group and at the thiomethylic chain are obtained in low yield (2—6%), as shown by GLC analysis of the product mixture after desulfuration with Raney nickel catalyst.

Analogous results were obtained in the metalation of 1-methoxy-4-(isopropylthio)benzene (IIIb).

The results show that the *ortho* orientating power of the alkoxy group is stronger than that of the thioalkyl group. This can be attributed to a larger

Scheme 5



IIIa, IIIc — VIIIa, Xa — VIIIb, Xb — VIIIc, Xc

XIa, XIIIa — XIb, XIIIb — XII, XIV

IIIa, VIIIa, VIIIb, VIIIc, XIa, XIb, XII : R = CH_3

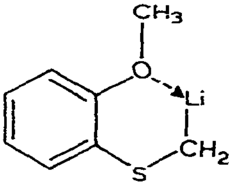
IIIc, Xa, Xb, Xc, XIIIa, XIIIb, XIV: R = $CH(CH_3)_2$

overall electron-withdrawing effect by the oxygen compared with the sulphur atom [3]. However, the thioalkyl group does have some effect, giving rise to products from metalation *ortho* to the sulphur atom.

The low steric requirement of this reaction is demonstrated by the observation that metal replacement occurs at the position *ortho* to both substituents in IIa and IIb. Presumably the *ortho* orientating effects of the two substituents reinforce each other, making the latter position especially reactive.

Thiomethylic metalation may, as previously suggested, be attributed to a proton abstraction process by direct attack on the thioalkyl group or to a two-step *trans*-metalation [7,8].

The higher percentage of thiomethylic metalation found with the compound Ia, compared to that obtained from IIa or IIIa, can be accounted for in terms of formation of a six-membered coordinate ring [6], as shown below.



Such an intermediate, which could not be formed in the case of IIa and IIIa, would stabilize the carbanion Ar—S—CH_2^-.

Experimental

General procedures were described in Part IV [7].

Starting materials

The preparations of 2-(methylthio)- (Ia), 2-(isopropylthio)- (Ib), 3-(methylthio)- (IIa), 3-(isopropylthio)- (IIb), 4-(methylthio)- (IIIa) and 4-(isopropylthio)-1-methoxybenzene (IIIb) and 1-isopropoxy-4-(methylthio)benzene (IIIc) were previously described [1].

Authentic samples

Methoxybenzene (XII), 2-methoxy- (XIa), 3-methoxy- (XIb) and 4-methoxy-benzoic acid (XIc) were commercial products (Aldrich Chemical Company).

(2-Methoxyphenyl)- (IVa) and (3-methoxyphenyl)thio acetic acid (VId), 3-(isopropylthio)- (Va), 6-methylthio)- (VIa), 6-(isopropylthio)- (VIIa), 5-(methylthio)- (VIIIa) and 5-(isopropylthio)-2-methoxybenzoic acid (IXa), 2-isopropoxy-5-(methylthio)benzoic acid (Xa), 2-isopropoxy- (XIIIa) and 3-isopropoxybenzoic acid (XIIIb) and isopropoxybenzene (XIV) were prepared by published procedures [1,9—12].

2-Methoxy-4-(methylthio)- (VIb) and 4-methoxy-2-(methylthio)benzoic acid (VIc).

A mixture of IIa (0.065 mol), *N*-bromosuccinimide (0.065 mol) and carbon tetrachloride (40 cm^3) was refluxed for 30 minutes. After cooling, the mixture was poured into water and extracted several times with carbon tetrachloride. The carbon tetrachloride extracts were washed with 10% aqueous sodium hydroxide, water and dried ($CaCl_2$). After evaporation of solvent the residue was distilled to give an isomeric mixture of 2-methoxy-4-(methylthio)- (XVa) and 4-methoxy-2-(methylthio)-1-bromobenzene (XVb) in a ratio of 35/65. Yield 81% [13].

A solution of this isomeric mixture (0.1 mol) in anhydrous diethyl ether (80 cm^3) was treated with activated magnesium (0.11 mol). After initiation of the reaction, the mixture was stirred for one hour and then warmed for thirty minutes. After cooling, it was poured onto ca. 300 g of crushed solid carbon dioxide and allowed to stand for 24 h. The residue was treated successively with 10% aqueous sodium bicarbonate and diethyl ether and then acidified with cold concentrated hydrochloric acid. The acidified layer was extracted with chloroform. The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was distilled to give an isomeric mixture of 2-methoxy-4-(methylthio)- (VIb) and 4-methoxy-2-(methylthio)benzoic acid (VIc) in a ratio of 40/60 (determined from GLC analysis). Yield 53%. (Found: C, 54.39; H, 5.02; S, 16.08. $C_9H_{10}O_3S$ calcd.: C, 54.53; H, 5.08; S, 16.17%). IR: 3100 (OH), 1700 (C=O), 820 cm^{-1} (1,2,4-trisubstituted benzene).

The structures of VIb and VIc were determined by desulfuration. After treatment with Raney nickel catalyst [1], the mixture gave 2-methoxy- (XIa) and 4-methoxybenzoic acid (XIc), which were identified by comparison of their GLC retention times with those of authentic samples.

2-Methoxy-4-(isopropylthio)- (VIIb) and 4-methoxy-2-(isopropylthio)benzoic acid (VIIc).

Using the procedure for XVa and XVb, starting from IIb and *N*-bromosuccinimide an, isomeric mixture of 2-methoxy-4-(isopropylthio)- (XVIa) and 4-methoxy-2-(isopropylthio)-1-bromobenzene (XVIb) was obtained in a ratio of 20/80 (determined by GLC analysis). Yield 68%. (Found: C, 45.91; H, 5.03. $C_{10}H_{13}BrOS$ calcd.: C, 45.98; H, 5.08%). IR: 810 cm^{-1} (1,2,4-trisubstituted benzene). Treatment of this mixture with Raney nickel gave a mixture of 2-bromo- and 4-bromoanisole, which were identified by GLC analysis.

By essentially the same procedure the mixture of XVIa and XVIb was converted to an isomeric mixture of 2-methoxy-4-(isopropylthio)- (VIIb) and 4-methoxy-2-(isopropylthio)benzoic acid (VIIc) in a ratio of 25/75 (determined by GLC). Yield 49%. (Found; C, 58.27; H, 6.18; S, 13.99. $C_{11}H_{14}O_3S$ calcd.: C, 58.38; H, 6.24; S, 14.17%). IR: 3200 (OH), 1720 (C=O), 810 cm^{-1} (1,2,4-trisubstituted benzene).

The structures of VIIb and VIIc were determined by desulfuration with Raney nickel. The products, 2-methoxy- (XIa) and 4-methoxybenzoic acid (XIc) were identified by comparison of their GLC retention times with those of authentic samples.

General metalation procedure

The starting material (0.05 mol) was dissolved in dry diethyl ether (70 cm^3) at room temperature under nitrogen and 1.6 *M* n-butyllithium in hexane (0.05 mol, 36.5 cm^3) was slowly added. When the addition was complete, the mixture was stirred under reflux for 4 h. After cooling, the mixture was poured onto ca. 100 g of crushed solid carbon dioxide and allowed to stand for 24 h. The residue was treated successively with 10% aqueous sodium bicarbonate and diethyl ether. The aqueous layer was separated, washed with diethyl ether, and then acidified with cold concentrated hydrochloric acid. The acidified layer was then extracted with diethyl ether and the extract dried (Na_2SO_4). A portion of this ethereal solution of the carboxylic acids was treated with a 30% molar excess of diazomethane in ether. The diethyl ether and excess diazomethane were allowed to evaporate in a hood. No unchanged carboxylic acid could be detected in the products. The resulting methyl esters were analyzed by GLC.

The remaining ethereal solution of the carboxylic acids was concentrated in vacuo, and the products were desulfurized with Raney nickel catalyst [1], and analyzed by GLC after treatment with diazomethane.

The results are listed in Table 1.

Acknowledgement

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References

1 S. Cabiddu, S. Melis, P.P. Piras and M. Secci, J. Organometal. Chem., 132 (1977) 321.

2 E.S. Gould, Mechanism and Structure in Organic Chemistry, Holt, Rinehart and Winston, Inc., New York, 1959, p. 200.

3 C.K. Ingold, Structure and Mechanism in Organic Chemistry, Cornell University Press, Ithaca-New York, 1969, p. 78.

4 R.A. Finnegan and J.W. Alschuld, J. Organometal. Chem., 9 (1967) 193.

5 D.A. Shirley, J.R. Johnson and J.P. Hendrix, J. Organometal. Chem., 11 (1968) 217.
6 D.W. Slocum and C.A. Jennings, J. Org. Chem., 41 (1976) 3653.
7 S. Cabiddu, S. Melis, P.P. Piras and F. Sotgiu, J. Organometal. Chem., 178 (1979) 291.
8 D.A. Shirley and B.J. Reeves, J. Organometal. Chem., 16 (1969) 1.
9 K. Fries, H. Heering, E. Hemmecke and G. Siebert, Justus Liebigs Ann. Chem., 527 (1936) 83.
10 B. Jones and J.C. Speakman, J. Chem. Soc., (1944) 19.
11 B. Jones, J. Chem. Soc., (1943) 430.
12 A.I. Vogel, J. Chem. Soc., (1948) 616.
13 A. Arcoria and G. Scarlatta, Ann. Chim. (Rome), 54 (1964) 139.