

Catalytic Activities of Salicylaldehyde Derivatives. VI.¹⁾ Syntheses of Some Dimethylsulfonio Derivatives of Salicylaldehyde

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Synopsis. 3-, 4-, and 5-dimethylsulfonio derivatives of salicylaldehyde have been prepared from the corresponding 6-, 5-, and 4-bromo-2-methylanisoles *via* the bromo-2-methoxybenzylidene dibromides, bromo-*o*-anisaldehyde diethyl acetals, methylthio-*o*-anisaldehydes, and (methylthio)salicylaldehydes. 4-Methylthio-*o*-anisaldehyde has also been prepared from 2-bromo-5-(methylthio)anisole.

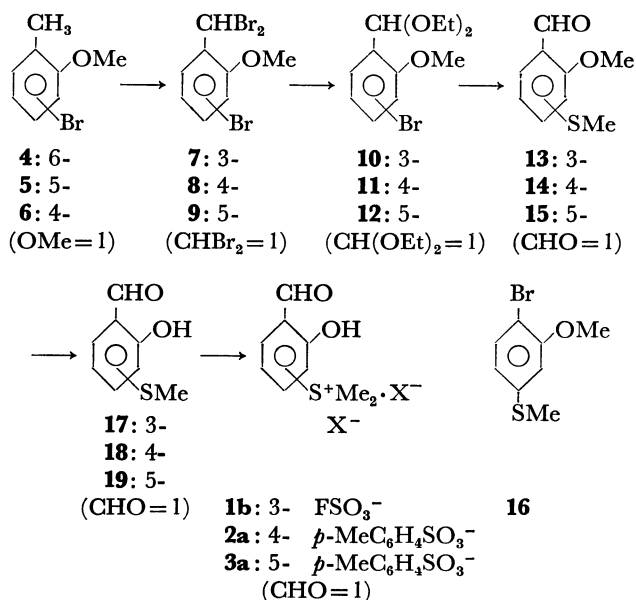
The racemization of L-glutamic acid catalyzed by various salicylaldehyde derivatives at pH 10 and at 80 °C in the presence of copper(II) ion has been examined. The Hammett's plots for the racemization catalyzed by 4- and 5-substituted salicylaldehydes *versus* the Hammett's constant, σ , were on a straight line.²⁾ Since the σ -values of the dimethylsulfonio groups are the largest among the σ -values obtained,³⁾ the dimethylsulfonio derivatives of salicylaldehyde appear to be more active catalysts than the known salicylaldehyde derivatives. Syntheses of 3- (1), 4- (2), and 5-dimethylsulfonio derivatives of salicylaldehyde (3) are described.

Treatment of 6- (4),⁴⁾ 5- (5),⁵⁾ and 4-bromo-2-methylanisoles (6)⁶⁾ with bromine gave the corresponding 3- (7), 4- (8), and 5-bromo-2-methoxybenzylidene dibromides (9), which were converted into the corresponding 3- (10), 4- (11), and 5-bromo-*o*-anisaldehyde diethyl acetals (12) with sodium ethoxide. The corresponding 3- (13), 4- (14), and 5-methylthio-*o*-anisaldehydes (15) were synthesized from 10, 11, and 12 by the Grignard reaction with dimethyl disulfide and subsequent hydrolysis. In the synthesis of 14⁷⁾ the overall yield was remarkably improved by the Grignard reaction of 2-bromo-5-(methylthio)anisole (16)⁸⁾ with diethyl phenyl orthoformate.⁹⁾

Demethylation of the methoxyl group in 13 and 15 with hydrogen bromide in acetic acid gave the corresponding 3- (17) and 5-(methylthio)salicylaldehydes (19). The reaction of 14 with the same reagents gave only a resinous product. Compound 14 was consequently treated with boron tribromide in dichloromethane in the usual way but no demethylation took place. The desired 4-(methylthio)salicylaldehyde (18) was obtained when the reaction was carried out in benzene under reflux. Compounds 18 and 19 were *S*-methylated with methyl *p*-toluenesulfonate to give the corresponding dimethylsulfonium *p*-toluenesulfonates, 2a and 3a. No *S*-methylation of 17 took place with the same reagent. The desired dimethylsulfonium fluorosulfate (1b) was obtained by treatment of 17 with methyl fluorosulfate.

Although these dimethylsulfonium salts are unstable at pH 10 and at 80 °C, the catalytic activities of the dimethylsulfonium salts in the racemization of L-glutamic acid are apparently larger than the salicylaldehyde derivatives examined in the initial stage of

reaction.



Experimental

Melting points and boiling points are uncorrected. IR spectra were recorded on a Shimadzu IR-27G instrument. Typical examples of syntheses of the intermediates are described. Reaction conditions, physical properties, and analytical data are given in Table I.

3-Bromo-2-methoxybenzylidene Dibromide (7). Under illumination with a tungsten lamp, a solution of bromine (167 g) in carbon tetrachloride (100 ml) was added dropwise to a solution of 6-bromo-2-methylanisole (4) (99.3 g) in carbon tetrachloride (400 ml) with stirring over a period of 2 h under reflux. After a further 3 h reflux, the mixture was fractionally distilled.

3-Bromo-*o*-anisaldehyde Diethyl Acetal (10). To a solution of sodium (12.0 g) in absolute ethanol (350 ml) was added dropwise 7 (94.0 g) over a period of 30 min at room temperature with stirring. The mixture was refluxed and the solvent removed. The residue was extracted with water and ether and the ethereal extract dried (MgSO₄) and distilled.

3-Methylthio-*o*-anisaldehyde (13). Under a nitrogen atmosphere, a solution of dimethyl disulfide (20.8 g) in dry THF (100 ml) was added with stirring to a Grignard reagent prepared from a solution of 10 (63.8 g) in dry THF (500 ml) and magnesium (5.4 g), over a period of 20 min at room temperature and then refluxed for 2 h. The mixture was treated with a 20% NH₄Cl solution (1 l) below 20 °C and extracted with ether. The extract was dried (MgSO₄) and concentrated. To the residue was added 2 M sulfuric acid (500 ml) and the resulting mixture steam-distilled. The ethereal extract of the distillate was washed with aqueous NaOH and water successively and dried (MgSO₄). Re-

TABLE I. PREPN AND CHARACTERISTICS OF THE INTERMEDIATES

Compd	Reaction time (h)	Yield (%)	Bp (°C/mmHg) (mp (°C))	IR (cm ⁻¹)	Found (%)			Calcd (%)
					C	H	Br or S	
7	3	93	138—140/3		27.03	1.87	66.32	C, 26.77
8	2	74	144—148/4 (38—39)		27.04	1.98	66.37	H, 1.97
9	2	85 ^{a)}	(83—84)		26.94	1.98	66.74	Br, 66.80
10	48	71	119—122/2		49.56	5.56	27.95	C, 49.83
11	1	92	131—136/2		49.81	5.71	27.71	H, 5.93
12	4	95	131—133/3		49.75	6.02	27.85	Br, 27.63
13	2	68	(73—74)	1690 ^{b)}	59.36	5.37	17.50	C, 59.33
14	5	48 ^{c,d)}	(65) ^{e)}	1670 ^{b)}	59.19	5.63	17.77	H, 5.53
15	2	70	136—138/3	1690 ^{f)}	58.71	5.34	16.99	S, 17.60
17	1	86	119—120/3	1670 ^{f)}	57.18	4.80	19.04	C, 57.12
18	— ^{g)}	59 ^{d)}	(51)	1650 ^{b)}	57.35	4.68	19.04	H, 4.79
19	2	41	114—118/4	1660 ^{f)}	56.95	4.94	18.90	S, 19.06

a) Recrystd from *n*-BuOH. b) KBr disc. c) Prepd from **11**. d) Purified by a column of silica gel. e) Lit.⁷⁾ mp 63 °C; prepd by an alternative method. f) Neat. g) See Exptl.

removal of the solvent gave crude **13**, which was recrystallized from methanol.

3-(Methylthio)salicylaldehyde (17). A mixture of **13** (10.0 g), anhydrous hydrogen bromide (26.5 g) in acetic acid (100 ml), and a 48% hydrobromic acid (20 ml) was refluxed for 1 h, concentrated, and extracted with water and ether. The ethereal layer was extracted with NaOH solution and the aqueous layer acidified with hydrochloric acid. The resulting oily product was extracted with ether, dried (MgSO₄), and fractionally distilled.

(3-Formyl-2-hydroxyphenyl)dimethylsulfonium Fluorosulfate (1b). A solution of methyl fluorosulfate (6.7 g) in dry benzene (10 ml) was added with stirring to a solution of **17** (10.0 g) in dry benzene (50 ml) at room temperature over a period of 10 min. Stirring was continued for another 1 h and the mixture allowed to stand overnight. The resulting precipitates were recrystallized from methanol giving 6.1 g (36%) of **1b**: mp 137—139 °C; IR (KBr) 3440 and 1650 cm⁻¹. Found: C, 38.22; H, 3.82; S, 22.37%. Calcd for C₉H₁₁FO₅S₂: C, 38.29; H, 3.93; S, 22.71%.

4-Methylthio-o-anisaldehyde (14) from 2-Bromo-5-(methylthio)-anisole (16). Under a nitrogen atmosphere, diethyl phenyl orthoformate (5.9 g) was added to a Grignard reagent prepared from a solution of **16** (7.0 g) in dry THF (100 ml) and magnesium (730 mg), over a period of 10 min at room temperature with stirring. The mixture was refluxed for 3 h and worked up in the usual way giving 4.2 g (77%) of **14**: mp 65 °C.

4-(Methylthio)salicylaldehyde (18). A solution of boron tribromide (15.1 g) in dry benzene (50 ml) was added to a stirred solution of **14** (11.0 g) in dry benzene (200 ml) over a period of 20 min in an ice bath. The mixture was stirred for 30 min at room temperature and then refluxed for 5 h. After removal of the solvent, ethanol (200 ml) and sodium acetate trihydrate (10.0 g) in water (30 ml) were added successively to the residue, refluxed for 2 h, and worked up in the usual way.

(4-Formyl-3-hydroxyphenyl)dimethylsulfonium p-Toluenesulfonate (2a). A mixture of methyl *p*-toluenesulfonate (2.0 ml) and **18** (1.0 g) was heated at 100 °C for 8 h and cooled. Ethyl

acetate (5 ml) was added to the cold mixture. The resulting precipitates were recrystallized from methanol–acetone affording 0.7 g (33%) of **2a**: mp 146—147 °C; IR (KBr) 3450, 1660, 1210, and 1170 cm⁻¹. Found: C, 54.45; H, 5.04; S, 18.02%. Calcd for C₁₆H₁₈O₅S₂: C, 54.22; H, 5.12; S, 18.10%.

(3-Formyl-4-hydroxyphenyl)dimethylsulfonium p-Toluenesulfonate (3a). A mixture of **19** (5.0 g) and methyl *p*-toluenesulfonate (10 ml) was heated at 100 °C for 3 h and then cooled. Acetone (10 ml) was added to the mixture. The resulting precipitates were 9.6 g (91%) of **3a**: mp 178—179 °C; IR (KBr) 1670, 1200, and 1170 cm⁻¹. Found: C, 54.28; H, 5.20; S, 18.00%. Calcd for C₁₆O₁₈O₅S₂: C, 54.22; H, 5.12; S, 18.10%.

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