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Catalytic Activities of Salicylaldehyde Derivatives. IV. A Synthesis of 2-Formyl-3-hydroxyphenyltrimethylammonium Chloride

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Synopsis. 4-Ethoxy-1,3-benzodioxan-5-yltrimethylammonium salt, prepared from 4-ethoxy-5-nitro-1,3-benzodioxane *via* 5-dimethylamino-4-ethoxy-1,3-benzodioxane, was hydrolyzed to obtain 2-formyl-3-hydroxyphenyltrimethylammonium chloride in a good yield.

In a previous paper,[1] among the salicylaldehyde derivatives tested 4-formyl-3-hydroxyphenyltrimethylammonium bromide was found to be the most powerful catalyst in the racemization of L-glutamic acid in the presence of cupric ions at pH 10 and at 80 °C. Yoshikawa *et al.*[2] pointed out that the catalytic effects of nitrosalicylaldehydes on the racemization under the conditions described above were decreased in the order of 4-, 6-, 5-, and 3-nitrosalicylaldehydes at an early stage of the reaction. Accordingly, it was expected that 2-formyl-3-hydroxyphenyltrimethylammonium chloride (**1**) might also be an effective catalyst in the racemization.

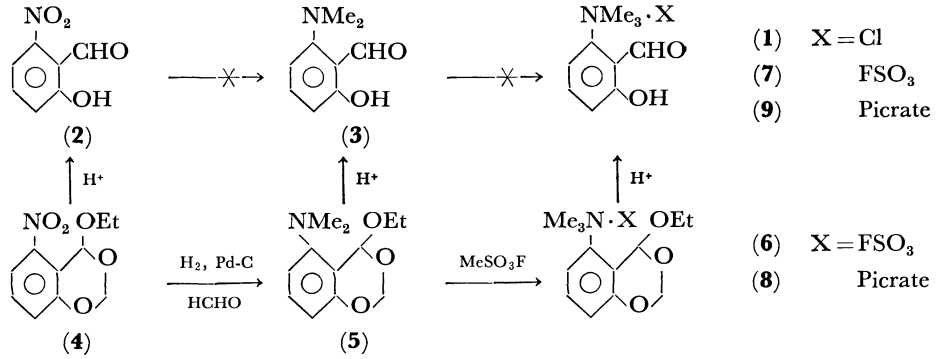
The reductive methylation of 6-nitrosalicylaldehyde (**2**)[3] over palladium on carbon (Pd-C) in the presence of formaldehyde did not give 6-dimethylaminosalicylaldehyde (**3**), although a similar treatment of *m*-nitrobenzaldehyde afforded *m*-dimethylaminobenzaldehyde.[4] On the other hand, 4-ethoxy-5-nitro-1,3-benzodioxane (**4**)[3] gave 5-dimethylamino-4-ethoxy-1,3-benzodioxane (**5**), which was then hydrolyzed to **3** with acid. With the usual methylating reagents, the *N*-methylation of **3** and **5** was unsuccessful. However, when methyl fluorosulfate (MFS)[5] was used, the *N*-methylation of **5** took place easily to give syrupy 4-ethoxy-1,3-benzodioxan-5-yltrimethylammonium fluorosulfate, (**6**), together with crystalline 2-formyl-3-hydroxyphenyltrimethylammonium fluorosulfate (**7**), a hydrolysis product of **6**. On the other hand, no separable product was obtained from **3**. Both fluorosulfates, **6** and **7**, were converted, separately or not separately, into **1** via the corresponding picrates, (**8**) and (**9**), the former being then easily hydrolyzed to **1**.

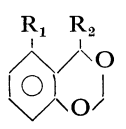
Some other methods of preparing **1** from 5-amino-1,3-benzodioxane derivatives were also attempted. The catalytic reduction of 5-nitro-1,3-benzodioxane (**10**)[3] and **4** over Pd-C gave the corresponding 5-amino derivatives, (**11**) and (**12**). 5-Dimethylamino-1,3-benzodioxane (**13**) was prepared from **10** by reductive methylation. The *N*-methylation of **13** with MFS gave 1,3-benzodioxan-5-yltrimethylammonium fluorosulfate (**14**) alone. The corresponding picrate (**15**) and then chloride (**16**) were obtained in the usual way. The attempted bromination of benzodioxane rings of **11**, **13**, and **16** to **1** proceeded with unsatisfactory results. The catalytic activity of **1** will be discussed together with that of other salicyalaldehydes in the near future.

Experimental

All the mps and bps are uncorrected. The hydrogenation was carried out at room temperature under atmospheric pressure with 10% Pd-C.

*5-Dimethylamino-4-ethoxy-1,3-benzodioxane (**5**).* A solution of 4-ethoxy-5-nitro-1,3-benzodioxane (**4**) (15 g) and aqueous 37% formaldehyde (40 ml) in ethanol (300 ml) was hydrogenated with Pd-C (6 g). After 5 mol of hydrogen had been absorbed, the filtrate from the catalyst was concentrated under reduced pressure to a syrup, which was then extracted with ether. The extracts, washed with a dil sodium hydroxide solution and then with water, were fractionally distilled in a vacuum to afford 12.3 g (83%) of **5**; bp 123—124 °C/4 mmHg.





	R_1	R_2
(**10**)	NO_2	H
(**11**)	NH_2	H
(**12**)	NH_2	OEt
(**13**)	NMe_2	H

	R_1	R_2
(**14**)	$NMe_3 \cdot FSO_3$	H
(**15**)	$NMe_3 \cdot$ Picrate	H
(**16**)	$NMe_3 \cdot Cl$	H

Scheme.

Found: C, 64.66; H, 7.69; N, 6.15%. Calcd for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27%.

*6-Dimethylaminosalicylaldehyde (**3**).* A mixture of **5** (13.6 g), sulfuric acid (55 ml), ethanol(150 ml), and water (150 ml) was refluxed for 1 hr while being stirred. To the cold mixture, 4 M sodium hydroxide aqueous solution (550 ml) was added, and it was all shaken with ether. The aqueous solution, treated with charcoal, was neutralized with dil hydrochloric acid. Benzene extracts of an oily product were concentrated under diminished pressure; the residue was passed through a silica gel column (250 g). At first **3** was eluted with benzene; fractional distillation then gave 4.8 g (48%) of **3**; bp 114—117 °C/2 mmHg.

Found: C, 65.35; H, 6.78; N, 8.28%. Calcd for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48%.

Hydrochloride: Mp>280 °C.

Found: C, 53.61; H, 6.01; N, 7.02; Cl, 17.78%. Calcd for $C_9H_{12}O_2NCl$: C, 53.60; H, 6.00; N, 6.95; Cl, 17.58%.

*2-Formyl-3-hydroxyphenyltrimethylammonium Fluorosulfate (**7**) and 4-Ethoxy-1,3-benzodioxan-5-yltrimethylammonium Picrate (**8**).* Into ice-cooled MFS (5 g), ice-cooled **5** (10 g) was stirred all at once. Within 30 min it became viscous and difficult to stir. After 2 hrs' stirring, the reaction mixture was allowed to stand overnight at room temperature. The resultant glassy mixture was dissolved in a mixture of water and ethyl acetate. The aqueous layer, treated with charcoal, was concentrated under diminished pressure to a syrup, which was then treated with acetone to precipitate 2.2 g (17%) of **7**; mp 192—193 °C (decomp). The filtrate, concentrated to a syrup, was treated with picric acid (5 g) in methanol. Recrystallization from methanol gave 8.3 g (40%) of **8**; mp 163—164 °C. Although the total yield of **7** and **8** was nearly constant, each yield was considerably variable.

Compound **7**: Found: C, 42.90; H, 5.24; N, 4.90; S, 11.38%. Calcd for $C_{10}H_{14}O_5NFS$: C, 43.01; H, 5.05; N, 5.02; S, 11.48%.

Compound **8**: Found: C, 49.00; H, 4.73; N, 12.20%. Calcd for $C_{19}H_{22}O_{10}N$: C, 48.93; H, 4.75; N, 12.01%.

*2-Formyl-3-hydroxyphenyltrimethylammonium Picrate (**9**).* By the usual treatment, **7** was converted into **9**, which was then recrystallized from methanol; mp 209—210 °C; yield 94%.

Found: C, 46.94; H, 3.95; N, 13.83%. Calcd for $C_{16}H_{16}O_9N_4$: C, 47.06; H, 3.95; H, 13.72%.

*2-Formyl-3-hydroxyphenyltrimethylammonium Chloride (**1**).*

a) From 9: By the usual process, **1** was obtained; it was then recrystallized from methanol; mp 217 °C (decomp); yield 92%.

Found: C, 55.88; H, 6.51; N, 6.50; Cl, 16.41%. Calcd for $C_{10}H_{14}O_2NCl$: C, 55.69; H, 6.54; N, 6.49; Cl, 16.44%.

b) From 8: In the usual way, upon treatment with dil hydrochloric acid, hydrolysis occurred to give **1** in a 58% yield.

c) From 5: MFS (5 g) and **5** (10 g) were treated as has been described in the preparation of **7** and **8**. A resultant syrupy mixture of **6** and **7** was treated with picric acid (10 g) in methanol. Diluting the solution with water gave, upon the removal of a clear supernatant, a non-crystalline residue, which was then treated with nitrobenzene and dil hydrochloric acid. The aqueous layer, washed with ether, was concentrated to give **1**. Recrystallization from methanol afforded 4.2 g (43%) of **1**.

*5-Amino-1,3-benzodioxane (**11**).* A solution of 5-nitro-1,3-benzodioxane (**10**) (10 g) in ethanol (250 ml) was hydrogenated with Pd-C (2.5 g). After 3 mol of hydrogen had been absorbed, the treatment of the reaction mixture as has been described in the preparation of **5** gave 7.8 g (94%) of **11**; mp 71—72 °C.

Found: C, 63.41; H, 5.96; N, 9.21%. Calcd for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27%.

Hydrochloride: Mp>280 °C.

Found: C, 51.35; H, 5.36; N, 7.42; Cl, 18.76%. Calcd for $C_8H_{10}O_2NCl$: C, 51.21; H, 5.37; N, 7.47; Cl, 18.90%.

N-*Acetyl Derivative*: Mp 154—155 °C.

Found: C, 62.28; H, 5.75; N, 7.15%. Calcd for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25%.

*5-Amino-4-ethoxy-1,3-benzodioxane (**12**).* A solution of **4** (5 g) in ethanol (150 ml) was hydrogenated with Pd-C (1 g) to give 3.7 g (85%) of **12**; bp 120—123 °C/3 mmHg.

Found: C, 61.61; H, 6.50; N, 7.17%. Calcd for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18%.

N-*Acetyl Derivative*: Mp 146 °C.

Found: C, 60.66; H, 6.37; N, 5.78%. Calcd for $D_{12}H_{15}O_4N$: C, 60.75; H, 6.37; N, 5.90%.

*5-Dimethylamino-1,3-benzodioxane (**13**).* In a way similar to that used in the synthesis of **5**, **13** was given from **10** in a 77% yield; bp 104—105 °C/4 mmHg.

Found: C, 67.12; H, 7.05; N, 7.86%. Calcd for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82%.

Hydrochloride: Mp 182 °C (decomp).

Found: C, 55.88; H, 6.49; N, 6.51; Cl, 16.48%. Calcd for $C_{10}H_{14}O_2NCl$: C, 55.69; H, 6.54; N, 6.49; Cl, 16.44%.

*1,3-Benzodioxan-5-yltrimethylammonium Fluorosulfate (**14**).* MFS (3.3 g) and **13** (5 g) were treated as has been described for the *N*-methylation of **5**. The addition of ethyl acetate to the final residue precipitated 6.5 g (84%) of **14**; mp 142 °C. It was soluble in acetone.

Found: C, 45.12; H, 5.45; N, 4.84; S, 10.97%. Calcd for $C_{11}H_{16}O_5NFS$: C, 45.03; H, 5.50; N, 4.78; S, 10.93%.

*1,3-Benzodioxan-5-yltrimethylammonium Picrate (**15**).* In the usual way, **15** was obtained from **14** in a 98% yield; mp 162 °C.

Found: C, 48.32; H, 4.21; N, 13.27%. Calcd for $C_{17}H_{18}O_9N_4$: C, 48.34; H, 4.30; N, 13.27%.

*1,3-Benzodioxan-5-yltrimethylammonium Chloride (**16**).* In the usual way, **16** was obtained from **15** in a 73% yield; mp 202—203 °C (decomp).

Found: C, 57.48; H, 6.97; N, 6.29; Cl, 15.51%. Calcd for $C_{11}H_{16}O_2NCl$: C, 57.52; H, 7.02; N, 6.10; Cl, 15.43%.

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