

Catalytic Activities of Salicylaldehyde Derivatives. V. Syntheses and Catalytic Activities of Some Trimethylammonio Derivatives of Salicylaldehyde in the Racemization of L-Glutamic Acid

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Synopsis. (3-Formyl-2-hydroxyphenyl)trimethylammonium (**2**) and (3-formyl-4-hydroxyphenyl)trimethylammonium salts (**3**) have been prepared from the corresponding 3- and 5-nitrosalicylaldehydes *via* the 3- and 5-(dimethylamino)salicylaldehydes. The catalytic activities of **2**, **3**, and the (2-formyl-3-hydroxyphenyl)trimethylammonium salt have been studied at pH 10 and at 80 °C in the presence of copper(II) ion.

The rate constants, k_{obsd} , for the racemization of L-glutamic acid catalyzed by various 3-, 4-, and 5-substituted salicylaldehydes at pH 10 and at 80 °C in the presence of copper(II) ion have been examined. The plots of $\log k_{\text{obsd}}$ versus Hammett's constant, σ , for the corresponding substituent were on two straight lines: one corresponding to the 4- and 5-substituted salicylaldehydes and the other to the 3-isomers.¹⁾ (4-Formyl-3-hydroxyphenyl)trimethylammonium bromide (**1**) was found to be the most active catalytically salicylaldehyde derivative.¹⁾ Since the σ -value of the *m*-trimethylammonio group is larger than that of the *p*-group,²⁾ (3-formyl-2-hydroxyphenyl)trimethylammonium halide (**2**) and (3-formyl-4-hydroxyphenyl)trimethylammonium halide (**3**) may catalyze the racemization to a greater extent than **1**.

The syntheses of **2** and **3** and the catalytic activities of **2**, **3**, and (2-formyl-3-hydroxyphenyl)trimethylammonium salt (**4**)³⁾ in the racemization of L-glutamic acid under the conditions described above will be described.

Syntheses of 3- (**5**) and 5-(dimethylamino)salicylaldehydes (**6**) were carried out by the catalytic hydrogenation of the corresponding 3- (**7**)⁴⁾ and 5-nitrosalicylaldehydes (**8**)⁵⁾ over palladium on carbon in the presence of formaldehyde.⁶⁾

For the *N*-methylation of 4-(dimethylamino)salicylaldehyde with methyl iodide to give **1**, it was necessary to add sodium hydroxide in methanol and to reflux the reaction mixture, the resulting products being a mixture of *N*-methylated and *N,O*-dimethylated compounds.⁷⁾ In the cases of **5** and **6**, however the corresponding iodides of **2** (**2a**) and **3** (**3a**) were synthesized in good yield at room temperature with neither solvent nor sodium hydroxide. Compounds **2a** and **3a** were converted into the corresponding bromides, **2b** and **3b**, in the usual way. Syntheses of the chloride of **4** (**4c**) and the fluorosulfate of **4** (**4d**) have been reported.³⁾

The catalytic racemization of L-glutamic acid was carried out at pH 10 and at 80 °C in the presence of copper(II) ion.^{1,7)} Since the catalytic racemization follows first-order kinetics, the catalytic activity, $(\log \alpha_0 - \log \alpha_t)/t$, should be a constant, where t is the time and α_0 and α_t are the observed optical rotations at the reaction time 0 and t min, respectively. The observed

rate constant, k_{obsd} , was calculated by the following equation.

$$k_{\text{obsd}} = \frac{2.30 \times (\log \alpha_0 - \log \alpha_t)}{t}$$

TABLE 1. CATALYTIC ACTIVITY

Time min	$(\log \alpha_0 - \log \alpha_t) \times 10^3/t, (\text{min}^{-1})$		
	2a	3a	4c
20	3.58	5.54	2.48
40	3.61	5.70	2.40
60	3.66	5.72	2.30
80	3.67	5.69	2.19
100	3.61	5.47	2.08
120	3.84	5.60	2.04
150	3.70	5.38	1.95
180	3.73	5.35	1.89
210	3.64	5.25	1.69
240	3.65	5.32	1.67
300	3.77	5.28	1.57
360	3.83	5.68	1.44

The catalytic activities of **2a** and **3a** were found to be almost constant, the catalytic activity of **4c** decreasing during the course of reaction, as shown in Table 1. The absorption peak of the reaction mixture at *ca.* 380 nm has been attributed to the chelation of the Schiff base of the catalyst and glutamic acid with copper(II) ion.⁸⁾ In the cases of **2a** and **3a**, the absorption peaks were nearly constant throughout the reaction, the absorption peak of **4c** decreasing gradually. Catalytic activity of **4c** also decreased, suggesting the decomposition of **4c**. Thus, the rate constant for the reaction catalyzed by **4c** could not be determined.

The observed rate constants for the racemization catalyzed by **2a** and **3a** were 8.5×10^{-3} and $12.7 \times 10^{-3} \text{ min}^{-1}$, respectively, compared with $11.0 \times 10^{-3} \text{ min}^{-1}$ for **1**.⁷⁾ As expected from Hammett's constant, σ , the catalytic activity of **3a** was the largest among the salicylaldehyde derivatives examined. The catalytic activity of **2a**, having a bulky 3-substituent was considerably lower than that of **3a**, though both compounds had *m*-trimethylammonio groups with the same σ -value. Similar phenomena were also observed in various salicylaldehyde derivatives having a non-charged substituent at positions 3 and 5.¹⁾ The catalytic activities of the 3-substituted salicylaldehydes were lowered since the phenol group's activity in the catalytic racemization was sterically hindered by the adjacent substituent at position 3.¹⁾

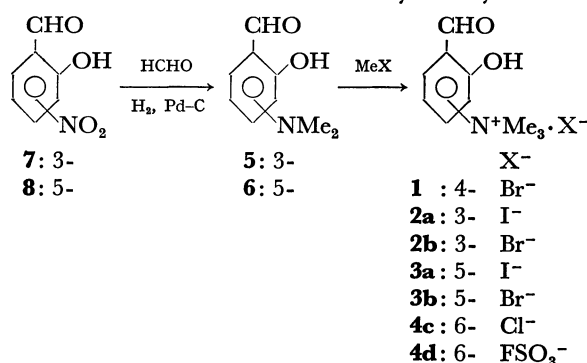
No conspicuous effect of the anion of the trimethylammonium salt was observed on the racemization yield

TABLE 2. COMPARISON OF ANIONS IN THE RACEMIZATION YIELD OF L-GLUTAMIC ACID

	$100 \times (\alpha_0 - \alpha_t) / \alpha_0, (\%)$	
	40 min	2 h
2a	40.8	78.7
2b	41.3	79.0
4c	18.3	42.9
4d	18.9	43.3

of L-glutamic acid (Table 2).

The plot of Hammett's constant, σ , versus $\log k_{\text{obsd}}$ for the racemization catalyzed by **3a** was on a straight line, on which the Hammett's plots for the racemization catalyzed by other 4- and 5-substituted salicylaldehydes were.¹⁾ The Hammett's plot for **2a**, however deviates a great deal from the straight line of the Hammett's plots for the other 3-substituted salicylaldehydes.¹⁾



Experimental

Boiling points and melting points are uncorrected. Silica gel 60 (Merck No. 7734) was used for the column chromatography. IR spectra were measured with a Shimadzu IR-27G spectrometer.

3-(Dimethylamino)salicylaldehyde (5). A solution of 3-nitrosalicylaldehyde (**7**) (10.0 g) and a 37% formaldehyde solution (40 ml) in ethanol (250 ml) was catalytically hydrogenated over 10% Pd-C (5.0 g) at room temperature at atmospheric pressure. After 5 mol of hydrogen had been absorbed, the reaction mixture was filtered and the filtrate acidified with dilute hydrochloric acid and concentrated. The residue was dissolved in water, treated with charcoal, and neutralized with sodium hydroxide solution. The resulting mixture was extracted with ether, the extract dried (MgSO₄) and concentrated to give an oily residue. The residue was chromatographed on a silica-gel column (350 g). Elution with ethyl acetate-cyclohexane (1:1 v/v) gave 6.8 g (69%) of **5**: bp 96–100 °C/3 mmHg; IR (neat) 1650 cm⁻¹. Found: C, 65.52; H, 6.54; N, 8.53%. Calcd for C₉H₁₁NO₂: C, 65.44; H, 6.71; N, 8.48%.

5-(Dimethylamino)salicylaldehyde (6). The compound was prepared from 5-nitrosalicylaldehyde (**8**) (10.0 g) in 71% yield following the method for the preparation of **5** except that 3.0 g of the catalyst was used: mp 33 °C; bp 123–126 °C/4 mmHg; IR (KBr) 3200 and 1660 cm⁻¹. Found: C, 65.70; H, 6.81; N, 8.60%. Calcd for C₉H₁₁NO₂: C, 65.44; H, 6.71; N, 8.48%.

(3-Formyl-2-hydroxyphenyl)trimethylammonium Iodide (2a). Methyl iodide (10 ml) was added immediately to **5** (2.5 g) at room temperature and the reaction mixture allowed to stand overnight at room temperature. Upon treatment with acetone, a crystalline product separated. This was recrystallized from water giving 4.1 g (90%) of **2a**: mp 198–199 °C dec; IR (KBr) 1650 cm⁻¹. Found: C, 39.07; H, 4.65; I, 41.16; N, 4.78%. Calcd for C₁₀H₁₄INO₂: C, 39.11; H, 4.60; I, 41.33; N, 4.56%.

(3-Formyl-4-hydroxyphenyl)trimethylammonium Iodide (3a). The compound was prepared from **6** in 88% yield following the method for the preparation of **2a**: mp 228–229 °C dec; IR (KBr) 1700 cm⁻¹. Found: C, 39.10; H, 4.63; I, 41.22; N, 4.33%. Calcd for C₁₀H₁₄INO₂: C, 39.11; H, 4.60; I, 41.33; N, 4.56%.

(3-Formyl-2-hydroxyphenyl)trimethylammonium Bromide (2b) and **(3-Formyl-4-hydroxyphenyl)trimethylammonium Bromide (3b).** Compounds **2a** and **3a** were converted in the usual way with silver bromide at room temperature into the corresponding **2b** and **3b** in 90% yields. **2b**: mp 199–200 °C dec. Found: C, 46.23; H, 5.47; Br, 30.58; N, 5.35%. Calcd for C₁₀H₁₄BrNO₂: C, 46.17; H, 5.43; Br, 30.72; N, 5.39%. **3b**: mp >300 °C. Found: C, 46.11; H, 5.47; Br, 30.73; N, 5.46%. Calcd for C₁₀H₁₄BrNO₂: C, 46.17; H, 5.43; Br, 30.72; N, 5.39%.

Procedure of Racemization. Racemization was carried out as described previously.⁷⁾

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