[Chem. Pharm. Bull. 27(3) 816—820 (1979)]

UDC 547.587.1.04 : 546.271.04

Reduction of *o*-Hydroxyaromatic Carboxylic Acids through Ethoxycarbonyl Derivatives with Sodium Borohydride[1)]

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(Received October 26, 1978)

It was found that the ethoxycarbonyl derivative (**2**) of salicylic acid (**1**) was reduced to *o*-cresol (**3**) with sodium borohydride in good yield and the best reaction conditions were the use of 4 molar equivalents of sodium borohydride in tetrahydrofuran–H_2O at 5—15.° *p*-Hydroxybenzoic acid (**4**) and *m*-hydroxybenzoic acid (**6**) did not give the corresponding cresols in this procedure, and *o*-hydroxyphenylacetic acid (**8**) did not give *o*-ethylphenol. These results show that the existence of *o*-hydroxy group is necessary to reduce the carboxyl groups to the methyl groups and only the carboxyl groups which are directly attached to aromatic nuclei are reduced to the methyl groups. Several *o*-hydroxybenzoic or -naphthoic acids (**1**, **10**, **12**, **15**, **17**, **19** and **24**) were reduced to the corresponding *o*-methylphenols in good yields. It was found that all hydrogen atoms of the methyl group were introduced from sodium borohydride.

Keywords——sodium borohydride reduction; *o*-hydroxyaromatic carboxylic acids; mixed carbonic-carboxylic acid anhydrides; new synthesis of *o*-methylphenols; phase-transfer catalyst; sodium borodeutride; synthesis of *o*-trideuteromethylphenol

Although carboxylic acids are not generally reduced by sodium borohydride, it was found by Perron *et al.*[3)] that the mixed anhydride of benzyl penicillinic acid was reduced to the corresponding alcohol by sodium borohydride. Later, Yamada *et al.*[4)] modified Perron's procedure and added a solution of a mixed anhydride in tetrahydrofuran to an aqueous solution of sodium borohydride and obtained the desired alcohol in good yield.

We found that the application of Yamada's procedure to salicyclic acid (**1**) afforded *o*-cresol as shown in Chart 1. Thus, the ethoxycarbonyl derivative (**2**) was prepared from salicylic acid (**1**) and 2 equivalents of ethyl chloroformate in the presence of 2 equivalents of triethylamine in tetrahydrofuran and was added to an aqueous solution of sodium borohydride. To our best knowledge, there is no report that mixed carbonic-carboxylic acid anhydrides are reduced to the corresponding methyl compounds with sodium borohydride. This communication describes that *o*-hydroxyaromatic carboxylic acids are reduced to the corresponding methyl compounds through ethoxycarbonyl derivatives with sodium borohydride under mild conditions.

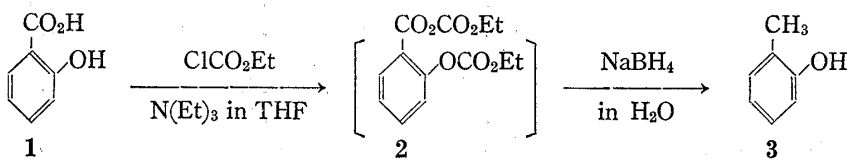


Chart 1

1) This work was presented at the 98th Annual Meeting of Pharmaceutical Society of Japan, Okayama, April 1978.
2) Location: *4 Koishikawa, Bunkyo-ku, Tokyo, 112, Japan.*
3) Y.G. Perron, L.B. Crast, J.M. Essery, R.R. Fraser, J.G. Godfrey, C.T. Hodrege, W.F. Minor, M.E. Neubert, R.A. Partyka and L.C. Chency, *J. Med. Chem.*, **7**, 483 (1964).
4) K. Ishizumi, K. Koga and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 492 (1968).

Salicylic acid was reduced by this method with various molar ratios of sodium borohydride in order to examine the amount of the reagent required for this reduction. It was found that the use of 4 molar equivalents of sodium borohydride was sufficient as shown in Table I.

Next, the solvent system was examined. As shown in Table I, tetrahydrofuran–H_2O system was the best. The reduction of **2** did not proceed in the two-phase system of benzene–H_2O. However, when phase-transfer catalyst such as tetra-*n*-butylammonium bromide or dodecyltrimethylammonium bromide was added to benzene–H_2O system, the reduction of **2** proceeded to give *o*-cresol in 51.5% or 66.7% yield, respectively. C.M. Starks *et al.*[5] reported the sodium borohydride reduction of 2-octanone using quaternaryammonium bromide.

Table I. Reduction of the Ethoxycarbonyl Derivative (**2**) of Salicylic Acid (**1**) with Sodium Borohydride

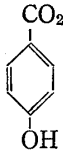
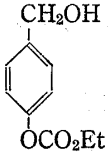
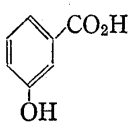
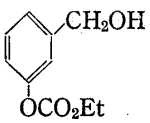
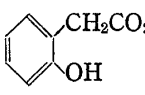
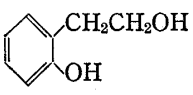
Run	Molar ratio ($NaBH_4$/ salicylic acid)	Solvent system	Reaction temp. (°C)	Yield (%)
1	2	THF–H_2O	5—15	38.9
2	3	THF–H_2O	5—15	63.0
3	4	THF–H_2O	5—15	77.8
4	5	THF–H_2O	5—15	77.8
5	4	IPA–H_2O	5—15	66.7
6	4	C_6H_6–H_2O	5—15	no reaction
7	4	$(C_4H_9)_4\overset{+}{N}Br^-$ [a] (C_6H_6–H_2O)	5—15	51.5
8	4	$C_{12}H_{25}\overset{+}{N}(CH_3)_3Br^-$ [a] (C_6H_6–H_2O)	5—15	66.7
9	4	THF–H_2O	33—36	50.0

a) 10% of phase-transfer catalyst was added to the reaction mixture.

As to reaction temperature, lower temperature gave better yield as shown in Table I.

Based on these results, all experiments in this paper were carried out under the fixed reaction conditions, namely, the use of 4 molar equivalents of sodium borohydride in tetrahydrofuran–H_2O at 5—15°.

Table II. Reduction of Position Isomers of Salicylic Acid and *o*-Hydroxyphenylacetic Acid

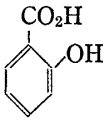
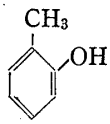
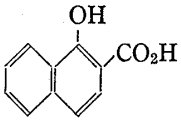
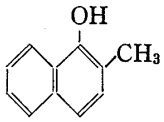
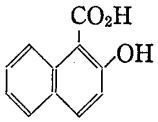
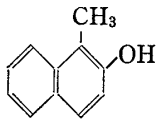
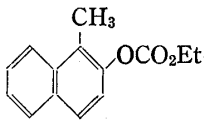
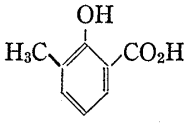
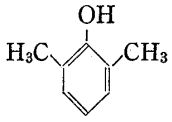
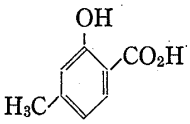
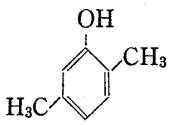
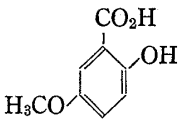
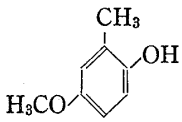
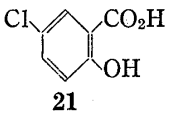
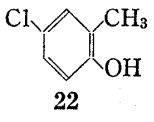
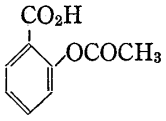
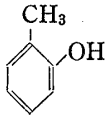
			Yield (%)
 **4**	1. $ClCO_2Et/N(Et)_3$ in THF 2. $NaBH_4$ in H_2O	 **5**	66.3
 **6**	1. $ClCO_2Et/N(Et)_3$ in THF 2. $NaBH_4$ in H_2O	 **7**	65.3
 **8**	1. $ClCO_2Et/N(Et)_3$ in THF 2. $NaBH_4$ in H_2O	 **9**	72.1

5) C.M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971).

p-Hydroxybenzoic acid (**4**) and *m*-hydroxybenzoic acid (**6**), position isomers of salicylic acid, gave ethyl *p*- and *m*-hydroxymethylphenyl carbonate, respectively. *o*-Hydroxyphenylacetic acid (**8**) gave ethyl *o*-(2-hydroxyethyl)-phenol. The results are summarized in Table II.

These results show that the existence of *o*-hydroxy group is necessary to reduce the carboxyl groups to the methyl groups and only the carboxyl groups which are directly attached to aromatic nuclei are reduced to the methyl groups.

Table III. Reduction of *o*-Hydroxyaromatic Carboxylic Acids through Ethoxycarbonyl Derivatives with Sodium Borohydride

Run	Carboxylic acid	Product	Yield (%)
1	 **1**	 **3**	77.8
2	 **10**	 **11**	62.2
3	 **12**	 **13**	44.3
		 **14**	8.7
4	 **15**	 **16**	65.6
5	 **17**	 **18**	72.1
6	 **19**	 **20**	77.3
7	 **21**	 **22**	23.9
8	 **24**	 **3**	61.1

In order to ascertain the generality of these reactions, we have performed experiments on several *o*-hydroxybenzoic or -naphthoic acids. As shown in Table III, *o*-hydroxyaromatic acids were converted by this method to the corresponding methyl compounds in good yields except 2-hydroxy-1-naphthoic acid (**12**) and 5-chloro-2-hydroxybenzoic acid (**21**). Compound **12** gave ethyl 1-methyl-2-naphthyl carbonate (**14**) in 8.7% yield in addition to 1-methyl-2-naphthol.

Because compound **14** was obtained, we assumed that ethyl 2-methylaryl carbonates were reduction intermediates from ethoxycarbonyl derivatives to 2-methylphenols. But, when ethyl 2-methylphenyl carbonate (**23**) was allowed to react with sodium borohydride under the same conditions, **23** was recovered. This means that ethyl 2-methylaryl carbonates are not reduction intermediates.

Sodium borohydride reduction was examined about other derivatives of salicylic acid. In these derivatives, the mixed anhydride (**25**) of acetylsalicylic acid (**24**) afforded *o*-cresol in 61.1% yield.

When salicylic acid was reduced by this method with sodium borodeuteride ($NaBD_4$) instead of sodium borohydride, it gave *o*-trideuteromethylphenol in 55.5% yield. This result shows that all hydrogen atoms of the methyl group were introduced from sodium borohydride.

We consider that this reduction method is very effective to reduce *o*-hydroxyaromatic acids to the corresponding methyl compounds under mild conditions. Further studies on these reactions are undergoing.

Experimental

All melting points are not corrected. Infrared (IR) spectra were measured with a Hitachi-215 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured with a JEOL PS-100 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were measured with a JEOL TMS-OISG spectrometer. Thin-layer chromatography (TLC) was carried out on Merck kiesel gel GF_{254} plates and detected under ultra violet light.

Materials——Authentic samples of reduction products were obtained commercially, unless otherwise stated.

Reductions——Unless otherwise stated, all reductions were carried out in a manner similar to that described in a typical procedure.

A Typical Procedure——Ethyl chloroformate (12 g, 0.11 mol) was added at 0—5° over a period of 1 hr to the solution of salicyclic acid (7.9 g, 0.05 mol) and triethylamine (11.1 g, 0.11 mol) in tetrahydrofuran (75 ml), and the whole was stirred for 45 min at the same temperature. The white precipitate (triethylammonium chloride) was filtered off, washed with tetrahydrofuran (25 ml), and the combined filtrate was added to a solution of sodium borohydride (7.9 g, 0.2 mol) in water (75 ml) with stirring at 5—15° over a period of 1 hr. After the addition was complete, the reaction mixture was stirred at room temperature for 2 hr, then made acidic with dil.HCl, diluted with water and extracted with ether (250 ml). Ether layer was extracted with 10% aqueous NaOH (50 ml), and the aqueous layer was neutralized with dil.HCl, and extracted with ether (150 ml). Ether layer was washed with water, 5% aqueous $NaHCO_3$, and dried over $MgSO_4$. Evaporation of ether gave *o*-cresol (4.2 g, 77.8%). It was identified with the authentic sample by IR spectra and TLC.

Preparation of Ethyl 2-Methylphenyl Carbonate (23)——Ethyl chloroformate (12.0 g) was added at 0—10° over a period of 1 hr to the solution of *o*-cresol (10.8 g) and triethylamine (11.1 g) in ether (100 ml), and the reaction mixture was stirred for 1 hr at the same temperature. After addition of ice-water, ether layer was separated and washed with 2% aqueous NaOH, water, and dried over $MgSO_4$. Evaporation of ether gave **23** (18 g, slightly brown liquid) quantitatively. IR $\nu_{max}^{Liq.}$ cm^{-1}: 1760 (>C=O). NMR (in $CDCl_3$) δ: 1.40 (3H, t, $-CH_3$), 2.25 (3H, s, $-CH_3$), 4.30 (2H, q, $>CH_2$), 7.10—7.30 (4H, m, aromatic H).

Reduction of 2-Acetylsalicylic Acid (24)——Mixed anhydride was prepared from **24** (4.5 g, 0.025 mol) and ethyl chloroformate (2.7 g, 0.025 mol) in the presence of triethylamine (2.5 g, 0.025 mol) in tetrahydrofuran (40 ml). *o*-Cresol was obtained in 61.1% yield (2.7 g), and identified with the authentic sample by IR spectra and TLC.

Reduction of the Mixed Anhydride of Salicylic Acid with Sodium Borodeuteride——Mixed anhydride (2) was prepared from salicylic acid (0.59 g) and ethyl chloroformate (1.3 g) in the presence of triethylamine (1.2 g) in tetrahydrofuran (10 ml). The filtered solution of **2** was added to an aqueous (10 ml) solution of sodium borodeuteride (0.7 g) with stirring at 5—15° over a period of 30 min. Work up was carried out in

Table IV. Physical Data of Reduction Compounds

Compd. No.	mp (°C) (Reported)	NMR ($CDCl_3$) δ	IR ν_{max} cm^{-1}	MS m/e
5[a]	Liq.	1.40 (3H, t, $-CH_3$) 3.60 (1H, broad, –OH) 4.20 (2H, q, $>CH_2$) 4.40 (2H, s, $>CH_2$)	3350 (–OH) 1755 (>C=O)	
7[a]	Liq.	1.30 (3H, t, $-CH_3$) 3.60 (3H, t, –OH) 4.24 (2H, q, $>CH_2$) 4.32 (2H, d, $>CH_2$)	3350 (–OH) 1760 (>C=O)	190 (M^+)
9[a]	Liq.	2.75 (2H, t, $>CH_2$) 3.80 (2H, t, $>CH_2$) 5.20—6.20 (2H, broad, –OH)	3300 (–OH)	
11[b]	64—66 (61)[6]			
13[a]	115—116 (111)[7]	2.58 (3H, s, $-CH_3$) 5.00 (1H, broad, –OH)	3300 (–OH)	
14[a]	Liq.	1.32 (3H, t, $-CH_3$) 2.50 (3H, s, $-CH_3$) 4.28 (2H, q, $>CH_2$)	1765 (>C=O)	230 (M^+)
16[b]	47—48 (48.5—49.5)[8]			
18[b]	68—71 (71—73)[9]			
20	72—73 (70)[10]	2.26 (3H, s, $-CH_3$) 3.76 (3H, s, $-OCH_3$) 5.10 (1H, s, –OH)	3250 (–OH)	138 (M^+)
22[b]	46—47 (48—49)[11]			

a) Purification was carried out by column chromatography on silica gel using *n*-hexane–ether as an eluent.
b) It was identified with the authentic sample by IR spectra and TLC.

a manner similar to that described in typical procedure. *o*-Trideuteromethylphenol was obtained in 55.5% yield (0.31 g). IR $\nu_{max}^{Liq.}$ cm^{-1}: 3400 (–OH). NMR (in $CDCl_3$) δ: 5.60 (1H, broad, –OH), 6.50—7.10 (4H, m, aromatic H). MS m/e: 111 (M^+).

Acknowledgement We are grateful to Drs. Y. Machida, I. Saito, Y. Ishino, S. Toyoshima and M. Tomoeda for encouragement.

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