(ester CO), 1647 (C=N$^+$); NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.28 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$), 3.98 and 4.04 (3H each, s, two MeO's), 4.17 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$), 6.92 (1H, s, $H_{(8)}$), 7.24 (1H, s, $H_{(11)}$).

***trans*-2-Ethoxycarbonylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxybenzo[*a*]quinolizinium Perchlorate (15)**——$AgClO_4$ (250 mg, 1.21 mmol) was added to a hot solution of **14** (560 mg, 1.15 mmol) in EtOH (5 ml). The resulting precipitate of AgI was filtered off while hot and washed with hot EtOH (2×10 ml). The filtrate and the washings were combined and kept in a refrigerator. The colorless needles that resulted were filtered off and dried to give **15** (470 mg, 89%), mp 115—117°. Recrystallization from EtOH produced an analytical sample,[19] mp 116—117° (lit.[13] mp 113—114°); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 246 (16800), 304 (9350), 354 (9200).

Ethyl *trans*-3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetate (16)——The foregoing quaternary perchlorate **15** was reduced as reported previously,[13] and the free base **16** (91% yield) was isolated as colorless needles, mp 71—72°[19] (lit.[13] mp 66—66.5°); IR ν_{max}^{Nujol} cm^{-1}: 2800, 2760 (*trans*-quinolizidine), 1720 (ester CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2820, 2764 (*trans*-quinolizidine), 1726 (ester CO); NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.28 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$), 3.88 (6H, s, two MeO's), 4.20 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$), 6.61 and 6.72 (1H each, s, aromatic protons).

The Perchlorate of **16**: Colorless needles (from EtOH), mp 149—150°[19] (lit.[13] mp 145—146.5°); IR ν_{max}^{Nujol} 1720 cm^{-1} (ester CO).

The Picrate of **16**: Minute yellow prisms (from EtOH), mp 166—167° (lit.[13] mp 165—166°).

Acknowledgment We wish to thank Emeritus Professor Dr. Shigehiko Sugasawa (Tokyo) and Professor Yoshio Ban (Sapporo) for their interest and encouragement. Financial support from the Ministry of Education, Culture and Science, Japan, in the form of a Grant-in-Aid for Cancer Research (to Professor D. Mizuno), is also gratefully acknowledged.

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Reduction of *o*-Acylphenols through Ethyl *o*-Acylphenylcarbonates to *o*-Alkylphenols with Sodium Borohydride[1]

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(Received December 4, 1979)

It was found that the ethoxycarbonyl derivatives of *o*-acylphenols were reduced to the corresponding *o*-alkylphenols by sodium borohydride under mild conditions; the use of 3 molar equivalents of sodium borohydride was sufficient for this reduction. Various kinds of *o*-acylphenols (**1**, **3**, **5**, **7**, **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23**, **25** and **27**) were reduced to the corresponding *o*-alkylphenols (**2**, **4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, **20**, **24**, **26** and **28**, respectively) in high yield by this method. *o*-Acetylphenyl acetate (**29**) afforded *o*-ethylphenol (**8**) in better yield with sodium borohydride than ethyl *o*-acetylphenylcarbonate, but *o*-acetylphenyl *p*-toluenesulfonate (**30**) did not give **8**.

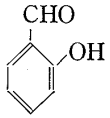
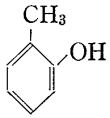
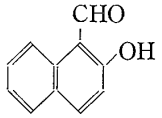
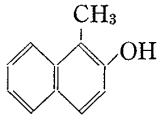
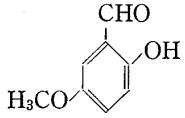
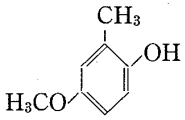
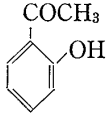
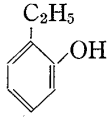
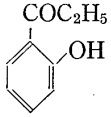
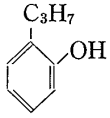
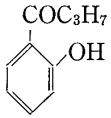
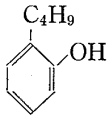
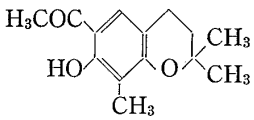
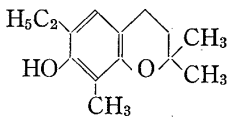
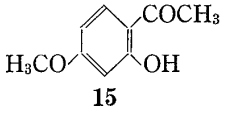
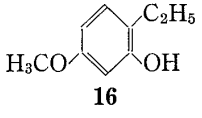
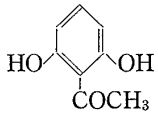
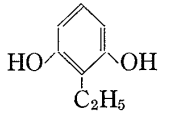
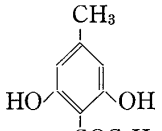
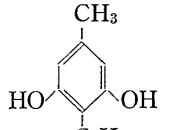
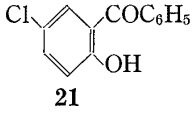
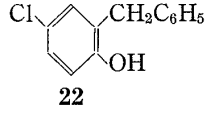
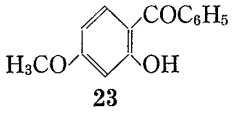
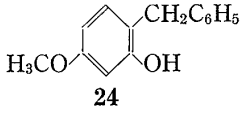
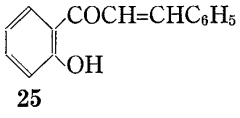
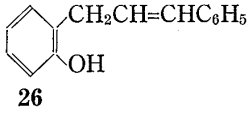
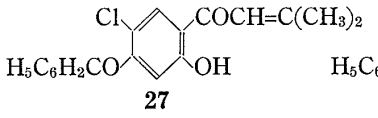
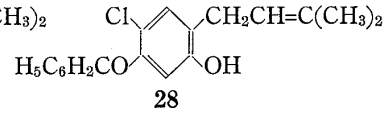
Keywords——sodium borohydride reduction; *o*-acylphenols; ethyl *o*-acylphenylcarbonates; synthesis of *o*-alkylphenols; synthesis of *o*-aralkylphenols; reduction of *o*-acetylphenyl acetate

In the preceding paper[3] we reported that ethoxycarbonyl derivatives of *o*-hydroxyphenyl carboxylic acids could be reduced to the corresponding *o*-methylphenols with sodium borohydride under mild conditions.

In this paper, we wish to report the sodium borohydride reduction of *o*-acylphenols through ethyl *o*-acylphenylcarbonates, as shown in Chart 1. As described in our previous

1) This work was presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April 1978.
2) Location: *Koishikawa 4-6-10, Bunkyo-ku, Tokyo 112, Japan.*
3) N. Minami and S. Kijima, *Chem. Pharm. Bull.* (Tokyo), **27**, 816 (1979).

TABLE I. Reduction of *o*-Acylphenols through Ethyl *o*-Acylphenylcarbonates to *o*-Alkylphenols with Sodium Borohydride

Run	*o*-Acylphenol	Product	Yield (%)
1	 **1**	 **2**	77.8
2	 **3**	 **4**	82.9
3	 **5**	 **6**	87.0
4	 **7**	 **8**	78.7
5	 **9**	 **10**	89.7
6	 **11**	 **12**	96.0
7	 **13**	 **14**	88.6
8	 **15**	 **16**	85.0
9	 **17**	 **18**	75.4
10	 **19**	 **20**	85.0
11	 **21**	 **22**	97.3
12	 **23**	 **24**	88.9
13	 **25**	 **26**	88.6
14	 **27**	 **28**	72.2

work, ethyl *o*-acylphenylcarbonate was prepared from *o*-acylphenol and ethyl chloroformate in the presence of triethylamine in tetrahydrofuran, and a filtered solution of the ethyl *o*-acylphenylcarbonate was added to an aqueous solution of sodium borohydride (4 equivalents) at 5—15°. As shown in Table I, various kinds of *o*-acylphenols were examined.

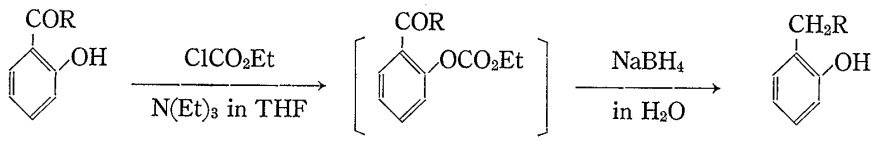


Chart 1

o-Formylphenols (**1**, **3**, and **5**) were reduced to the corresponding *o*-methylphenols (**2**, **4**, and **6**, respectively) as well as *o*-hydroxyphenyl carboxylic acids.

o-Acylphenols (**7**, **9**, **11**, **13**, and **15**) were reduced to the corresponding *o*-alkylphenols (**8**, **10**, **12**, **14**, and **16**, respectively) in high yield, irrespective of the length of the acyl group.

In 2-acylresorcinols (**17** and **19**), the ethyl carbonate derivatives were prepared from 2-acylresorcinols and 2 equivalents of ethyl chloroformate in the presence of 2 equivalents of triethylamine, and the reduction products were hydrolyzed with 5% sodium hydroxide in water–methanol, affording 2-alkylresorcinols (**18** and **20**, respectively). Diphenyl ketones (**21** and **23**) afforded the corresponding diphenylmethanes (**22** and **24**, respectively) in high yield.

It is well known that the sodium borohydride reduction of an α,β-unsaturated ketone to an allylic alcohol is often accompanied by double bond reduction,[4] but this method is very attractive in that the carbonyl groups of α,β-unsaturated acylphenols (**25** and **27**) are reduced to give 2-allylphenols (**26** and **28**, respectively). Giuliana *et al.*[5] reported that the sodium borohydride reduction of **25** and 4-methyl-2-(3-methylcrotonyl)-phenol gave allylic alcohols, which were converted to **26** and 4-methyl-2-(3-methylcrotyl)phenol by a hydride transfer mechanism in a weak acid solution. As stated above, the ethyl carbonate derivative of **25** afforded **26** directly in high yield.

o-Acylphenol 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. As shown in Table II, it was found that the use of 3 molar equivalents of sodium borohydride was sufficient. Four molar equivalents of sodium borohydride was required in the reduction of *o*-hydroxyphenyl carboxylic acids.[3]

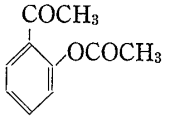
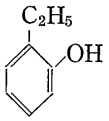
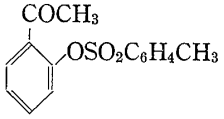
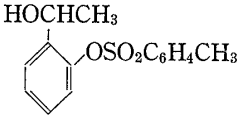
Sodium borohydride reduction was examined with other derivatives of *o*-acetylphenol. As shown in Table III, *o*-acetylphenyl acetate (**29**) afforded **8** in a better yield (91.8%) than ethyl *o*-acetylphenylcarbonate, and *o*-acetylphenyl *p*-toluenesulfonate (**30**) gave not **8**, but 2-(1-hydroxyethyl)-phenyl *p*-toluenesulfonate (**31**) in quantitative yield. This reduction method provides a good procedure for obtaining *o*-alkyl-, -allyl-, or -aralkyl-phenols from *o*-acetylphenols under mild conditions.

Table II. Reduction of *o*-Acetylphenol (**7**) through Ethyl *o*-Acetylphenylcarbonate with Various Molar Ratios of Sodium Borohydride

Molar ratio ($NaBH_4$/**7**)	1	2	3	4
Yield of **8** (%)	36.1	72.1	80.3	78.7

4) W.R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965).
5) C. Giuliana, C. Renato, M. Lucio, and N. Gianluca, *Gazz. Chim. Ital.*, **99**, 612 (1969).

Table III. Sodium Borohydride Reduction of Other Derivatives of *o*-Acetylphenol (**7**)

Deriv. of **7**	Product	Yield (%)
 **29**	 **8**	91.8
 **30**	 **31**	99.0

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a Hitachi 215 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured with a JEOL PS-100 spectrometer using TMS as an internal standard. Mass spectra were measured with a JEOL TMS-OISG spectrometer. Thin-layer chromatography (TLC) was carried out on Merck Kieselgel GF_{254} plates with ultraviolet (UV) detection.

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

Reductions——Unless otherwise stated, all reduction were carried out in a manner similar to that described below.

Typical Procedure——Ethyl chloroformate (6.5 g, 0.06 mol) was added at 0—5° over a period of 30 min to a solution of *o*-hydroxybenzaldehyde (6.1 g, 0.05 mol) and triethylamine (6.0 g, 0.06 mol) in tetrahydrofuran (50 ml), and the whole was stirred for 30 min at the same temperature. The white precipitate ($Et_3\overset{+}{N}H\overset{-}{Cl}$) was collected by filtration and washed with tetrahydrofuran (25 ml), and the combined filtrate was added to a solution of $NaBH_4$ (7.6 g, 0.2 mol) in H_2O (75 ml) with stirring at 5—15° over a period of 45 min. When the addition was completed, the reaction mixture was stirred at room temperature for 1.5 hr, then diluted with H_2O, made acidic with dil. HCl and extracted with ether (250 ml). The ether layer was extracted with aqueous 10% NaOH (50 ml), and the aqueous layer was neutralized with dil. HCl then extracted with ether (150 ml). The ether layer was washed with H_2O, aqueous 5% $NaHCO_3$, and dried over $MgSO_4$. Removal of ether by evaporation gave *o*-cresol (4.2 g, 77.8%). It was found to be identical with an authentic sample (IR spectra and TLC).

1-Methyl-2-naphthol (4)——**4** was obtained from 2-hydroxy-1-naphthaldehyde (**3**). The residue obtained from ether extracts after acidification of the reaction mixture was chromatographed on silica gel using hexane–ether as an eluent to yield **4** as a solid of mp 115—116° (reported,[6] mp 111°) in 82.9% yield. It was identical with an authentic sample[3] on the basis of IR spectra and TLC behavior.

4-Methoxy-2-methylphenol (6)——**6** was obtained from 2-hydroxy-5-methoxybenzaldehyde (**5**) as a solid of mp 72—73° (reported,[7] mp 70°) in 87.0% yield, and was identical with an authentic sample[3] (IR spectra and TLC).

***o*-Ethylphenol (8)**——**8** was obtained from *o*-acetylphenol (**7**) as a liquid in 78.7% yield, in a manner similar to that described for **4**. It was identical with an authentic sample (IR spectra and TLC).

***o*-Propylphenol (10)**——**10** was obtained from *o*-propionylphenol (**9**) as a liquid in 89.7% yield in a manner similar to that described for **4**. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3350 (–OH). NMR (in $CDCl_3$) δ: 0.70 (3H, t, $-CH_3$), 1.00—1.80 (2H, m, $>CH_2$), 2.40 (2H, t, $>CH_2$), 4.70 (1H, broad, –OH), 6.40—7.00 (4H, m, aromatic H).

***o*-Butylphenol (12)**——**12** was obtained from *o*-butyrylphenol (**11**) as a liquid in 96.0% yield in a manner similar to that described for **4**. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3400 (–OH). NMR (in $CDCl_3$) δ: 0.94 (3H, t, $-CH_3$), 1.10—1.80 (4H, m, $-CH_2CH_2-$), 2.62 (2H, t, $>CH_2$), 4.70 (1H, s, –OH), 6.68—7.22 (4H, m, aromatic H). MS *m/e*: 150 (M^+).

6-Ethyl-7-hydroxy-2,2,8-trimethylchroman (14)——**14** was obtained from 6-acetyl-7-hydroxy-2,2,8-trimethylchroman (**13**) as crystals of mp 82—83° (from hexane) in 88.6% yield. IR ν_{max}^{Nujol} cm^{-1}: 3350 (–OH), 1110. NMR (in $CDCl_3$) δ: 1.20 (3H, t, $-CH_3$), 1.60 (6H, s, $2\times-CH_3$), 1.75 (2H, t, $>CH_2$), 2.10 (3H, s, $-CH_3$), 2.55 (2H, q, $>CH_2$), 2.70 (2H, t, $>CH_2$), 4.50 (1H, s, –OH), 6.10 (1H, s, aromatic H). MS *m/e*: 220 (M^+), 165 (base peak). *Anal.* Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.37; H, 9.21.

2-Ethyl-5-methoxyphenol (16)——**16** was obtained from 2-acetyl-5-methoxyphenol (**15**) as a brown liquid in 85.0% yield in a manner similar to that described for **4**. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3430 (–OH). NMR (in

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$CDCl_3$) δ: 1.10 (3H, t, $-CH_3$), 2.50 (2H, q, $>CH_2$), 3.70 (3H, s, $-OCH_3$), 5.64 (1H, s, –OH), 6.36 (1H, d, aromatic H), 6.44 (1H, d×d, aromatic H), 7.04 (1H, d, aromatic H). MS *m/e*: 152 (M^+).

2-Ethylresorcinol (18)——**18** was obtained from 2-acetylresorcinol (**17**). The residue obtained from ether extracts after acidification of the reaction mixture was refluxed with 5% NaOH in H_2O–MeOH. The reaction mixture was acidified with dil. HCl and extracted with ether. The ether layer was washed with H_2O and dried over $MgSO_4$. After removal of ether by evaporation, the residue was chromatographed on silica gel using hexane–ether as an eluent to provide **18** as a solid of mp 104—105° (reported,[8] mp 97—99°) in 75.4% yield. IR ν_{max}^{Nujol} cm^{-1}: 3300 (–OH). NMR (in $CDCl_3$) δ: 1.20 (3H, t, $-CH_3$), 2.65 (2H, q, $>CH_2$), 6.45 (2H, d, aromatic H), 6.90 (1H, t, aromatic H). *Anal.* Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.40; H, 7.20. MS *m/e*: 138 (M^+), 125.

5-Methyl-2-propylresorcinol (20)——**20** was obtained from 5-methyl-2-propionylresorcinol (**19**) as a solid of mp 108—110° in 71.4% yield in a manner similar to that described for **18**. IR ν_{max}^{Nujol} cm^{-1}: 3350 (–OH). NMR (in $CDCl_3$) δ: 0.95 (3H, t, $-CH_3$), 1.40—1.80 (2H, m, $>CH_2$), 2.25 (3H, s, $-CH_3$), 2.70 (2H, t, $>CH_2$), 4.80 (2H, s, 2×–OH), 6.20 (2H, s, aromatic H). MS *m/e*: 166 (M^+), 137. *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.20; H, 8.63.

5-Chloro-2-hydroxydiphenylmethane (22)——**22** was obtained from 5-chloro-2-hydroxybenzophenone (**21**) as a solid of mp 48.5° (reported,[9] mp 48.5°) in 97.3% yield. IR ν_{max}^{Nujol} cm^{-1}: 3430 (–OH). NMR (in $CDCl_3$) δ: 3.80 (2H, s, $>CH_2$), 4.65 (1H, broad, –OH), 6.45 (1H, d, aromatic H), 6.80—7.20 (7H, m, aromatic H). MS *m/e*: 218 (M^+), 220 (M^+). *Anal.* Calcd. for $C_{13}H_{11}ClO$: C, 71.40; H, 5.07. Found: C, 71.52; H, 4.94.

2-Hydroxy-4-methoxydiphenylmethane (24)——**24** was obtained from 2-hydroxy-4-methoxybenzophenone (**23**) as a solid of mp 53—54° in 88.9% yield in a manner similar to that described for **4**. IR ν_{max}^{Nujol} cm^{-1}: 3400 (–OH). NMR (in $CDCl_3$) δ: 3.65 (3H, s, $-OCH_3$), 3.85 (2H, s, $>CH_2$), 5.40 (1H, broad, –OH), 6.30 (1H, d, aromatic H), 6.40 (1H, d×d, aromatic H), 7.00 (1H, d, aromatic H), 7.20 (5H, s, aromatic H). MS *m/e*: 214 (M^+). *Anal.* Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.57; H, 6.70.

2-Cinnamylphenol (26)——**26** was obtained from *o*-cinnamoylphenol (**25**) as a wax in 88.6% yield in a manner similar to that described for **4**. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3500 (–OH), 1650 (>C=C<). NMR (in $CDCl_3$) δ: 3.48 (2H, d, $>CH_2$), 5.80 (1H, s, –OH), 6.28—6.40 (2H, m, –CH=CH–), 6.60—7.40 (9H, m, aromatic H). MS *m/e*: 210 (M^+).

5-Benzyloxy-4-chloro-2-(3-methylcrotyl)phenol (28)——**28** was obtained from 5-benzyloxy-4-chloro-2-(3-methylcrotonyl)phenol (**27**) as crystals of mp 69—70° (from hexane–ether) in 72.2% yield in a manner similar to that described for **4**. IR ν_{max}^{Nujol} cm^{-1}: 3450 (–OH), 1625 (>C=C<). NMR (in $CDCl_3$) δ: 1.72 (6H, s, 2×$-CH_3$), 3.20 (2H, d, $>CH_2$), 5.00 (2H, s, $>CH_2$), 5.24 (1H, t, >CH), 6.44 (1H, s, aromatic H), 7.10 (1H, s, aromatic H), 7.30—7.60 (5H, m, aromatic H). MS *m/e*: 302 (M^+), 304 (M^+). *Anal.* Calcd. for $C_{18}H_{19}ClO_2$: C, 71.40; H, 6.33. Found: C, 71.37; H, 6.42.

Reduction of *o*-Acetylphenyl Acetate (29) with Sodium Borohydride——A solution of **29** (4.45 g, 0.025 mol) in tetrahydrofuran (50 ml) was added to a solution of $NaBH_4$ (3.78 g, 0.1 mol) in H_2O (50 ml) with stirring at 5—15° over a period of 30 min. When the addition was completed, the reaction mixture was stirred at room temperature for 1 hr, then diluted with water, made acidic with dil. HCl, and extracted with ether (150 ml). The ether layer was washed with aqueous 5% $NaHCO_3$ and dried over $MgSO_4$. Removal of ether by evaporation gave *o*-ethylphenols (2.8 g, 91.8%), which was identical with the authentic sample in terms of the IR spectra and TLC behavior.

Synthesis of 2-Acetylphenyl *p*-Toluenesulfonate (30)——A solution of *o*-hydroxyacetophenone (6.8 g, 0.05 mol) and *p*-toluenesulfonyl chloride (14.3 g, 0.075 mol) in pyridine (70 ml) was refluxed for 5 hr, diluted with H_2O, and extracted with AcOEt (200 ml). The AcOEt layer was washed with dil. HCl and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from AcOEt–hexane to give **30** as crystals of mp 97—98° in 53.1% yield. IR ν_{max}^{Nujol} cm^{-1}: 1695 (>C=O), 1370, 1170 ($-SO_2O-$). NMR (in $CDCl_3$) δ: 2.35 (3H, s, $-CH_3$), 2.40 (3H, s, $-CH_3$), 6.90—7.80 (8H, m, aromatic H). MS *m/e*: 290 (M^+), 275. *Anal.* Calcd. for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86. Found: C, 62.17; H, 4.67.

Reduction of 30 with $NaBH_4$——A solution of **30** (2.9 g, 0.01 mol) in tetrahydrofuran (30 ml) was added to a solution of $NaBH_4$ (1.51 g, 0.04 mol) in H_2O (30 ml) with stirring at 5—15° over a period of 30 min. When the addition was completed, the reaction mixture was stirred at room temperature for 45 min, diluted with H_2O, and extracted with ether (100 ml). The ether layer was washed with H_2O and dried over $MgSO_4$. Removal of ether gave 2-(1-hydroxyethyl)phenyl *p*-toluenesulfonate (**31**) quantitatively (2.9 g) as a slightly yellow liquid. IR $\nu_{max}^{Liq.}$ cm^{-1}: 3450 (–OH), 1380, 1180 ($-SO_2O-$). NMR (in $CDCl_3$) δ: 1.25 (3H, d, $-CH_3$), 2.35 (3H, s, $-CH_3$), 3.05 (1H, s, –OH), 5.05 (1H, q, >CH), 6.70—7.80 (8H, m, aromatic H). MS *m/e*: 292 (M^+), 277. *Anal.* Calcd. for $C_{15}H_{16}O_4S$: C, 61.62; H, 5.52. Found: C, 61.60; H, 5.60.

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