Studies on the Monoalkylation of Hydroquinone[1]

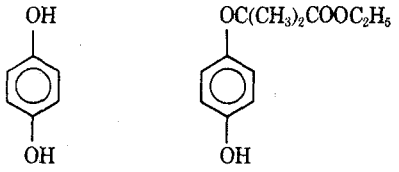
Melvin S. Newman* and James A. Cella[2]

Evans Chemistry Laboratory, The Ohio State University, Columbus, Ohio 43210

Received September 11, 1973

Conditions have been worked out for monoalkylation of hydroquinone to give the following compounds in the yields indicated: ethyl α-(*p*-hydroxyphenoxy)isobutyrate (56%), *tert*-butyl α-(*p*-hydroxyphenoxy)acetate (80%), hydroquinone monobenzyl ether (72%), and hydroquinone monomethyl ether (62%). Generalizations have been made which may help in the monoalkylation of other polyhydric phenols.

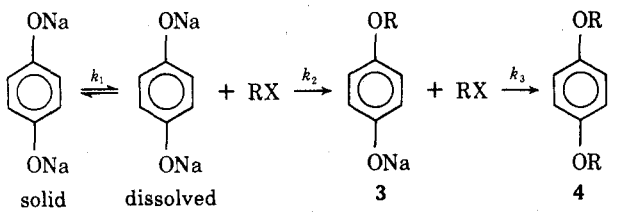
The monoalkylation of hydroquinone (2) represents a problem for which no generally satisfactory procedure has as yet been developed. Monoalkylation has been accomplished by using a large excess of hydroquinone[3-5] but this method is not efficient if the yield is calculated on 2. In general, alkylation of 2 *via* the monosodium salt and 1 equiv of alkylating agent gives poor yields of monoalkylated product.[6,7] Alternately, one can make a monoprotected hydroquinone, itself a difficult process, alkylate, and remove the protecting group.[8] With the above in mind we report our efforts to prepare ethyl α-(*p*-hydroxyphenoxy)-isobutyrate (1), a compound desired for other research. We report also on some general features which may make monoalkylation in other cases more readily accomplished than by existing methods.



2 1

The principle which guided our efforts was the use of a dianion as originally conceived by the late Hauser[9] and developed by him and others.[10,11] Thus we prepared the disodium salt of hydroquinone (2s) and studied its alkylation with a few alkylating agents under differing conditions. The results are summarized in Table I and are discussed in terms of the reactions illustrated in Scheme I.

Scheme I



The experiments in Table I all began with the solid disodium salt of hydroquinone (2s). This salt was only partly soluble at room temperature in dimethyl sulfoxide (DMSO) and dimethylformamide (DMF), but was soluble in the partly aqueous solvents. Examination of the results listed in Table I reveals that good yields of monoalkylation product are obtainable, although no one set of conditions is ideal for all alkylating agents. For example, monoalkylation with ethyl α-bromoisobutyrate (5) to give ethyl α-(*p*-hydroxyphenoxy)isobutyrate (1) proceeded well in dimethyl sulfoxide (DMSO, expt 1) and in dimethylformamide (DMF, expt 3). However, similar attempts at alkylation in partly aqueous media (expt 4 and 5) failed, as did attempts with *tert*-butyl α-bromopropionate (6) (expt 14 and 15). On the other hand, alkylation with *tert*-butyl bromoacetate (7) (expt 10 and 11), benzyl chloride (8) (expt 8), and methyl iodide (9) (expt 12) gave reasonably good yields of the respective monoalkylation products in partly aqueous media. However, when alkylation with benzyl chloride was attempted in DMF and DMSO, low yields of monoalkylation products, accompanied by larger amounts of dialkylation products, were obtained (expt 6 and 7).

The results in the solvents studied may be explained by assuming that (1) all alkylations occur only with soluble anions and alkylating agent, RX; (2) the rates of reaction, k_2, are greater with benzyl chloride, methyl iodide, and *tert*-butyl bromoacetate (7) than with ethyl α-bromoisobutyrate (5); and (3) the rate of reaction of dianion from **2d** (k_2) is greater than the rate of reaction of monoanion (k_3) in all cases.[12] The yield of **1** is good (expt 1 and 3) because k_3 is smaller than k_1. With the more reactive alkylating agents, **7**, **8**, and **9**, the yield of monoalkylated product, **3**, in nonaqueous media, DMF and DMSO, is poor because k_3 is greater than k_1. Hence the monoalkylated product reacts with reagent before more **2s** dissolves.

The results in the partly aqueous media are different with the various alkylating agents because the disalt is completely soluble. With the reactive alkylating agents **7**, **8**, and **9** (only 1 equiv of alkylating agent is used), the bis anion from **2d** is more reactive than the phenoxide **3**, so that good yields of monoethers of hydroquinone can be obtained. However, the less reactive alkylating agents, ethyl α-bromoisobutyrate (5) and *tert*-butyl α-bromopropionate, either are unreactive to **2d** in this medium or react with the medium. In either event, no monoalkylated product is obtained.

In conclusion, it appears that good yields of monoalkylation product of hydroquinone may be obtained under two sets of conditions: (1) when the disodium salt is not highly soluble in a nonaqueous solvent but the rate of reaction of the alkylating agent is slower than the rate of solution of the disodium salt in the solvent medium; and (2) when the disodium salt is soluble in a partly aqueous medium and the alkylating agent is sufficiently reactive to alkylate the dianion. How well this finding will relate to other polyhydric phenols remains to be seen.

Experimental Section[13]

***tert*-Butyl Bromoacetate.** To an ice-cold mixture of 38 g (0.51 mol) of *tert*-butyl alcohol and 40 g (0.51 mol) of pyridine was added 100 g (0.50 mol) of bromoacetyl bromide (Aldrich). After stirring overnight at room temperature, the mixture was poured into water and extracted thrice with ether. Combined ether extracts were worked up in the usual way except that Na_2SO_4 and K_2CO_3 were used to dry the extracts. This process yielded 61 g (63%) of *tert*-butyl bromoacetate, bp 78–79° (25 mm) [lit.[14] bp 78–79° (25 mm)].

2-Bromopropionyl Chloride. To a slurry of 52.1 g (0.25 mol) of phosphorus pentachloride in 200 ml of dry methylene chloride was

Table I
Alkylation of the Disodium Salt of Hydroquinone

Expt	Alkylating agent	Solvent	Temp, °C	Time, hr	Yield, %[a] Mono	Yield, %[a] Bis
1	$BrC(CH_3)_2CO_2C_2H_5$	DMSO	25	4	56	
2	$BrC(CH_3)_2CO_2C_2H_5$	DMSO	80	2	37	
3	$BrC(CH_3)_2CO_2C_2H_5$	DMF	25	4	50	20
4	$BrC(CH_3)_2CO_2C_2H_5$	50% Dioxane–H_2O	25	4		
5	$BrC(CH_3)_2CO_2C_2H_5$	75% NMP–H_2O	25	4		
6	$C_6H_5CH_2Cl$	DMF	25	4	13.2	77.5
7	$C_6H_5CH_2Cl$	DMSO	25	4	42	52.4
8	$C_6H_5CH_2Cl$	50% Dioxane–H_2O	25	1	72	
9	$BrCH_2CO_2C_4H_9$-*t*	DMF	80	2	6.4	54.1
10	$BrCH_2CO_2C_4H_9$-*t*	50% Dioxane–H_2O	25	1	80	
11	$BrCH_2CO_2C_4H_9$-*t*	75% NMP–H_2O	25	1	65	
12	CH_3I	50% Dioxane–H_2O	25	1	62	36
13	$BrCH(CH_3)CO_2C_4H_9$-*t*	DMF	80	2		81.5
14	$BrCH(CH_3)CO_2C_4H_9$-*t*	50% Dioxane–H_2O	25	4		
15	$BrCH(CH_3)CO_2C_4H_9$-*t*	75% NMP–H_2O	25	4		

[a] All yields represent isolated material and are based on alkylating agent. The yield based on hydroquinone is the sum of (mono + bis)/2.

added 38.3 g (0.25 mol) of 2-bromopropionic acid. After becoming homogeneous the mixture was refluxed for 30 min and solvent was removed by distillation at atmospheric pressure. The residue was distilled and the distillate, bp 60–70° (15 mm), was redistilled through a 10-cm Vigreux column to yield 42 g of 2-bromopropionyl chloride, bp 64–66° (100 mm) (contaminated with *ca.* 5% $POCl_3$). This material was of suitable purity to be used in the next step.

***tert*-Butyl α-Bromopropionate.** To a mixture of 15 g (0.22 mol) of *tert*-butyl alcohol and 20 g (0.25 mol) of pyridine was added 26.1 g (0.15 mol) of α-bromopropionyl chloride. After stirring for 2 hr at reflux, the cooled mixture was added to an equal volume of water and extracted (3 × 150 ml) with ether. The combined ether extracts were worked up as usual to yield 10.0 g (32%) of *tert*-butyl α-bromopropionate, bp 88–90° (60 mm).

General Alkylation Procedure. To a solution of 5.5 g (50 mmol) of hydroquinone in 50 ml of DMSO was added 4.4 g (100 mmol) of sodium hydride (57% NaH in mineral oil suspension, washed with pentane). The resulting mixture was stirred at 80° for 2 hr and then cooled to room temperature. To the rapidly stirred slurry was added rapidly with caution 7.3 ml (5 mmol) of α-bromoisobutyrate in 3 ml of DMSO. After 4 hr the mixture was acidified (excess avoided when *tert*-butyl esters were involved) with 3 *N* HCl. The reaction products were extracted with ether and washed to remove DMSO. The washings were reextracted with ether and the combined ether extracts were washed with saturated $MgSO_4$. The ether was distilled and the residue was distilled to yield 6.3 g (56%) of **1**, bp 200° (3 mm), mp 85–86° (lit.[15] mp 84–86°).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.7; H, 7.1. Found (vacuum-sublimed sample): C, 64.7; H, 7.1.

Aqueous Alkylations. The following procedure is representative of alkylations carried out in aqueous media. A solution of 1.7 g (40 mmol) of sodium hydroxide and 2.2 g (20 mmol) of hydroquinone in 75 ml of degassed 1:1 dioxane–water was stirred in a nitrogen atmosphere. To this solution was added a solution of 3.9 g (20 mmol) of *tert*-butyl bromoacetate in 5 ml of dioxane. The mixture was stirred for 1 hr, at which time no odor of *tert*-butyl bromoacetate could be detected. After acidification of the mixture with 15 ml of 3 *N* HCl and extraction of 2:1 ether–benzene, the organic extracts were worked up in the usual way to yield 3.6 g (80%) of *tert*-butyl 2-(*p*-hydroxyphenoxy)acetate: mp 93°; ir (KBr) 2.94 (3401) (OH) and 5.78 μ (1730 cm^{-1}) (C=O); nmr ($CDCl_3$) δ 6.74 (s, 4, ArH), 4.45 (s, 2, $ArOCH_2CO_2R$), and 1.48 [s, 9, $COOC(CH_3)_3$]; mass spectrum *m/e* 224.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.2; H, 7.2.

Other compounds prepared by one or both of these methods include hydroquinone bisbenzyl ether, mp 127–128° (lit.[15] mp 128–130°); hydroquinone monobenzyl ether, mp 119–121° (lit.[15] mp 123–125°); hydroquinone dimethyl ether, mp 54–55.5° (lit.[16] mp 55–56°); hydroquinone monomethyl ether, mp 51–53° (lit.[16] mp 53°); hydroquinone bis[1-(carbo-*tert*-butoxy)]ethyl ether, mp 111–113°, ir (KBr) 5.73 μ (1745 cm^{-1}) (C=O), nmr ($CDCl_3$) δ 6.80 (s, 4, ArH), 4.55 [q, 2, $ArOCH(CH_3)$–], 1.55 [d, 6, $ArOCH(CH_3)$–], and 1.41 ppm [s, 18, $CO_2C(CH_3)_3$], mass spectrum *m/e* 366.

Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.6; H, 8.3. Found: C, 65.7; H, 8.1.

Hydroquinone bis(carbo-*tert*-butoxymethyl) ether had mp 71–72°; ir (KBr) 5.74 μ (1742 cm^{-1}) (C=O); nmr (CCl_4) δ 6.72 (s, 4, ArH), 4.35 (s, 4, $ArOCH_2CO_2R$), and 1.44 [s, 18, $CO_2C(CH_3)_3$]; mass spectrum *m/e* 338.

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.9; H, 7.7 Found: C, 63.7; H, 7.6.

Registry No. **1**, 42806-90-6; **2**, 123-31-9; **2s**, 7664-46-2; *tert*-butyl bromoacetate, 5292-43-3; *tert*-butyl alcohol, 75-65-0; bromoacetyl bromide, 598-21-0; 2-bromopropionyl chloride, 7148-74-5; methylene chloride, 75-09-2; 2-bromopropionic acid, 598-72-1; *tert*-butyl α-bromopropionate, 39149-80-9; *tert*-butyl 2-(*p*-hydroxyphenoxy)acetate, 42806-92-8; hydroquinone bis[1-(carbo-*tert*-butoxy)]ethyl ether, 42806-93-9; hydroquinone bis(carbo-*tert*-butoxymethyl) ether, 42806-94-0.

References and Notes

(1) This work was supported by Grant 12445 of the National Science Foundation.
(2) This work was taken from the Ph.D. dissertation presented by James A. Cella to The Ohio State University, 1973.
(3) E. Gottlesman, *Chem. Ber.*, **66**, 1168 (1933).
(4) A. Luttringhaus, *Justus Liebigs Ann. Chem.*, **528**, 181 (1937).
(5) M. Kohn and L. Benczen, *Justus Liebigs Ann. Chem.*, **433**, 305 (1923).
(6) R. R. Renshaw and C. V. Hopkins, *J. Amer. Chem. Soc.*, **55**, 1524 (1933).
(7) C. M. Moser, *J. Amer. Chem. Soc.*, **72**, 1413 (1950).
(8) H. Sobotka and J. Austin, *J. Amer. Chem. Soc.*, **74**, 3813 (1952).
(9) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958).
(10) P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **35**, 262 (1970), and references cited therein.
(11) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 190, 2nd ed, 1972, p 533 ff, and references cited therein.
(12) The two ionization constants of hydroquinone differ by almost 100: S. E. Sheppard, *Trans. Amer. Electrochem. Soc.*, **39**, 429 (1921).
(13) All melting points and boiling points are uncorrected. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich. Ir spectra were recorded on a Perkin-Elmer Infracord using sodium chloride disks or potassium chloride pellets. Nmr spectra were recorded on an A-60 instrument, Varian Associates, Palo Alto, Calif., and are reported as δ units relative to tetramethylsilane as an internal standard. The terms "usual work-up" and "worked up as usual" mean that after the organic solution was washed with 3 *N* HCl or 3 *N* K_2CO_3, water, and saturated salt solution, it was dried by passage through a cone of $MgSO_4$ and the solvents were removed on a rotary evaporator. All reactions were conducted under nitrogen. All solvents were deaerated in a nitrogen stream prior to use. Dimethylformamide (DMF), dimethyl sulfoxide (DMSO), *N*-methyl-2-pyrrolidone (NMP), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride and stored over Linde Molecular Sieves (4A) prior to degassing. Hydroquinone, ethyl α-bromoisobutyrate, benzyl chloride, and methyl iodide were obtained commercially and were used without further purification.
(14) A. L. McCloskey, G. S. Fonken, R. K. Kluiber, and W. S. Johnson, "Organic Syntheses," Collect. Vol. 4, Wiley, New York, N. Y., 1963, p 261.
(15) Ph.D. thesis of F. W. Hetzel, The Ohio State University, 1968.
(16) H. Hlasiwetz and J. Habermann, *Justus Liebigs Ann. Chem.*, **177**, 334 (1875).