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Novel Reduction of 2,6-Di-*t*-butyl-*p*-quinols with Sodium Borohydride

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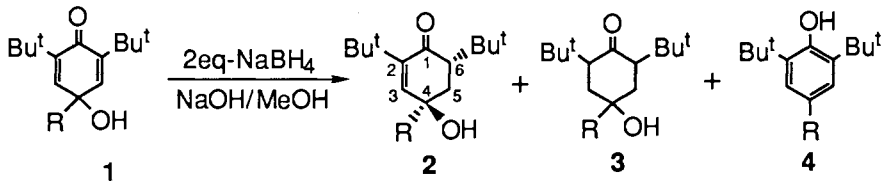
Reduction of 2,6-di-*t*-butyl-*p*-quinols with $NaBH_4$ results unexpectedly in the regio- and stereoselective formation of the corresponding dihydro-*p*-quinols. The novel reduction occurs via a quinoxyborohydride anion intermediate, which regulates the stereochemistry of the 4- and 6-positions in the products. Aromatization of the products is blocked by the *t*-butyl groups.

The reduction of *p*-quinols normally gives the corresponding phenols: e.g. with Zn/HCl,[1] $LiAlH_4$,[2] Al-Hg.[3] As a part of the series of studies on the quinonoid chemistry,[4 - 8] the reduction of 2,6-di-*t*-butyl-4-hydroxy-2,5-cyclohexadienonones (*p*-quinols) (**1**) with $NaBH_4$ has been investigated. We have found that the reduction proceeds stereospecifically to give unexpected products, 2,6-di-*t*-butyl-4-hydroxy-2-cyclohexenones (**2**), in which the 6-Bu^t group is trans to the 4-OH group. It is also found that this type of reduction occurs via anionic borohydride species formed by complexation with the 4-hydroxyl group.

To a solution of 2,6-di-*t*-butyl-4-hydroxy-4-methyl-2,5-cyclohexadienone (**1a**) (1 mmol) in methanol (2.5 ml) was added a solution of $NaBH_4$ (2 mmol) in 1M-NaOH methanol solution (2.5 ml). The resulting mixture was stirred at room temperature for 48 h. The usual work-up gave an oily residue (0. 25 g). Tlc (silica gel) separation gave 2,6-di-*t*-butyl-4-hydroxy-4-methyl-2-cyclohexenone (**2a**) (0.17 g, 86%), 2,6-di-*t*-butyl-4-hydroxy-4-methylcyclohexanone (**3a**) (0.014 g, 6%), and 2,6-di-*t*-butyl-4-methylphenol (**4a**) (0.005 g, 2%). Similar results are obtained with other *p*-quinols (**1**) (Table 1). In the case of **1a** - **1d** (R = alkyl), the reaction rate depended on the size of the R group: the larger size resulted in the slower reaction. The reaction rate was independent of the substituent at the *para* position of the phenyl ring in **1e** - **1h**.

The structure of **2e** was determined by X-ray crystallography (Fig. 1),[9] which shows that the 6-Bu^t group is oriented trans to the 4-OH group. The analytical and ^1H NMR data of **2a** - **2i** are in good agreement with those of **2e** (Table 2), indicating the same stereochemistry as that of **2** in all cases, except for **2a**, which was obtained as a mixture of the trans and cis isomers: trans/cis ratio = 96/4 as judged by ^1H NMR. The assignment of signals for 5-H_a, 5-H_e and 6-H were determined by means of usual 2D-NMR techniques.



	a	b	c	d	e	f	g	h	i	j
R	Me	Et	i-Pr	t-Bu	Ph	4-ClC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$	CCl_3	mesityl

Table 1. Reduction of quinols (**1**) with $NaBH_4$ in MeOH[a)]

1	Reaction temp/°C	Reaction time/h	Conversion /%	Product yield/%[b)] 2	3	4
a	30	48	83	90[c)]	7	3
b	30	48	68	90	6	4
c	30	48	49	90	6	4
d	30	48	29	90	0	7
e	30	48	69	90	4	6
f	30	48	75	83	11	6
g	30	48	64	92	5	3
h	30	48	66	89	11	0
i	30	48	58	100	0	0
j	30	48	31	42	0	0

a) Conditions: **1** (1 mmol), $NaBH_4$ (2 mmol) in 0.5 M NaOH MeOH solution (5 ml). b) Isolated yield based on the conversion. c) A mixture of stereoisomers with respect to the 6-Bu^t and 4-OH groups:*trans*/*cis* = 96/4.

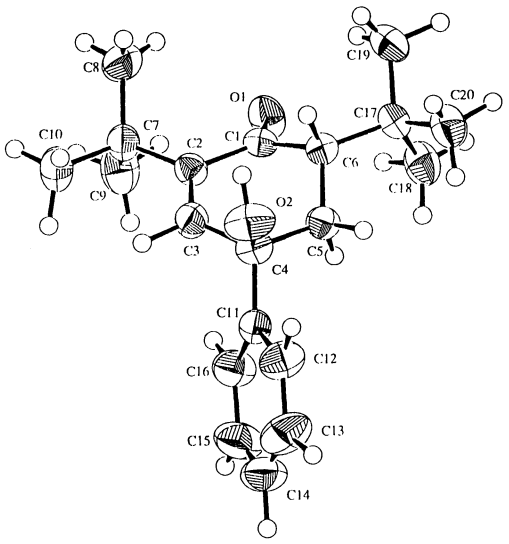


Fig. 1. An ORTEP drawing of **2e** showing the atomic numbering and the trans stereochemistry between the OH and 6-Bu^t groups.

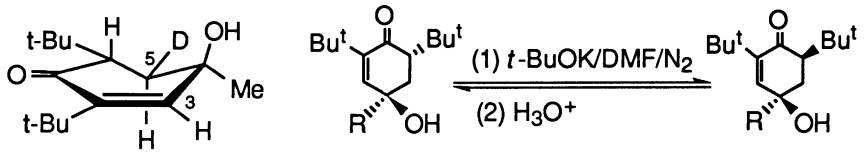
Table 2. Analytical and spectral data for **2** and **3**

2	mp	IR (KBr)/cm^{-1}		^{1}H NMR ($CDCl_3$), δ/ppm					
		ν_{OH}	ν_{CO}	6-Bu^t	2-Bu^t	5-H$_a$[a)]	5-H$_e$[b)]	6-H[c)]	3-H[d)]
2a	-[h)]	3380	1695	1.03	1.16	1.82	2.14	2.51	6.20
2a (*c*)	-[h)]	-	-	1.03	1.16	1.87	2.17[e)]	2.08[f)]	6.37[g)]
2b	71.0-72.1[i)]	3526	1699	1.03	1.15	1.75	2.03	2.53	6.15
2c	92.2-93.0[i)]	3518	1676	1.04	1.16	1.77	1.95	2.52	6.12
2d	-[l]	3532	1681	1.04	1.17	1.88	2.03	2.52	6.34
2e	97.6-99.0[i)]	3546	1679	1.04	1.22	2.02	2.32	2.72	6.34
2f	119.0-120.9[i)]	3430	1655	1.04	1.21	2.00	2.31	2.71	6.32
2g	116.0-117.2[i)]	3540	1676	1.04	1.22	2.01	2.31	2.72	6.33
2h	125.0-126.1[i)]	3542	1673	1.03	1.21	1.98	2.29	2.69	6.282[i)]
2i	119.5-120.0[i)]	3354	1665	1.03	1.20	2.31	2.48	2.62	6.56
3a(*t*)[j)]	-[l)]	3498	1694	0.98[k)]	0.97[k)]	1.80[k)]	2.07[k)]	2.22, 2.34[k)]	-
3a(*c*)[j)]	-[l)]	3434	1711	0.98[k)]	0.98[k)]	1.91[k)]	1.92[k)]	2.34[k)]	-

a) d; J = 13.5 Hz. b) d, d, d; J = 13.5 Hz, 4.2 Hz, 2.2 Hz. c) d, d; J = 13.5 Hz, 4.2 Hz. d) d; 2.2 Hz. e) d, d; J = 4.5 Hz, 2.1 Hz. f) d; J = 4.5 Hz. g) d; J = 2.1 Hz. h) An oily mixture of stereoisomers. i) C, H analytical data: C, < ± 0.4%; H, < ± 0.3%. j) A mixture of (*c*) and (*t*). k) Tentatively assigned. l) Not determined.

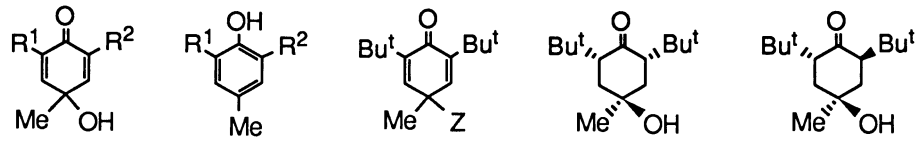
The reduction of **1a** with $NaBD_4$ has revealed that the hydride anion is incorporated into the 3 or 5 position stereospecifically from the same side of the 4-OH group, that is, the coupling between H_3 and H_5 protons in the resulting deuterated product was disappeared, which is indicative of the formation of **5**. The stereochemistry of **2** is rather unusual, since normal conjugate addition of a hydride anion to such cyclic α,β-enone system would be expected to give trans configuration between the hydride incorporated into the 5-position and the hydrogen generated at the 6-position. When **2a** and **2e** were treated with *t*-BuOK in DMF under N_2 at 0 °C, an equilibrium mixture of the trans and cis isomers was obtained: **2a**(t)/**2a**(c) = 35/65; **2e**(t)/**2e**(c) = 50/50 as judged by comparison of the chemical shifts of H_3: δ; trans: 6.20 (**2a**), 6.34 (**2e**) and cis, 6.37 (**2a**), 6.57 (**2e**),

respectively. The results indicate that the thermodynamic stablility of cis and trans isomers is almost same. Therefore, it is concluded that exclusive formation of **2** results from a kinetic controlled process.



5 **2(*t*)** **2(*c*)**

In order to find out the origine of the novel reduction of **2**, the reduction of **1a** has been examined under different conditions (Table 3). The product distribution depends on the reaction conditions and the nature of the reducing agent as well. The presence of the 2,6-di-*t*-Bu and 4-OH groups in the substrate seems to be essential



6 **7** **8** **3a(*t*)** **3a(*c*)**

a; R^1 = *t*-Bu, R^2 = Me
b; R^1 = R^2 = Me

a; Z = OMe
b; Z = $OOBu^t$

Table 3. Reduction of **1a**, **6** and **8** with different reducing agents under various conditions[a)]

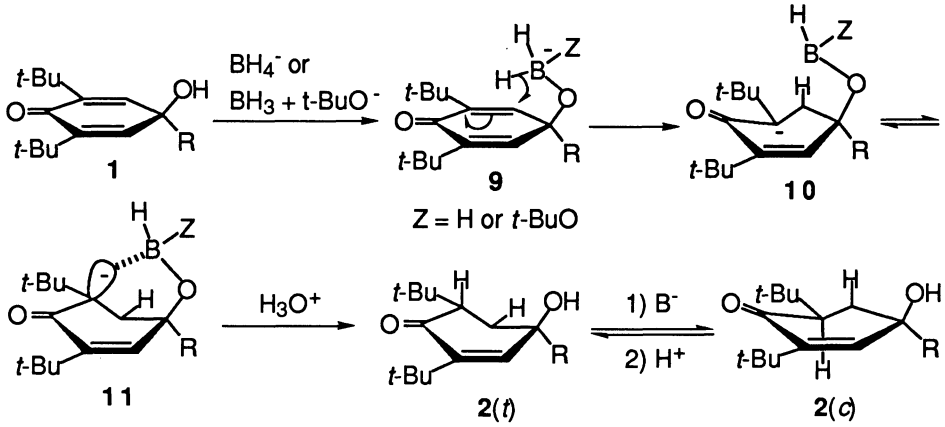
Entry No.	Substrate	Reagent[b)]	Solvent	Reaction temp/°C	Reaction time/h	Conversion /%	Product yield/%[c)] 2a(*t*)	2a(*c*)	3a(*t*)	3a(*c*)	4a
1	**1a**	$NaBH_4$[d)]	MeOH	30	24	75	80	7	10(*t* + *c*)		3
2	**6a**	$NaBH_4$[d)]	MeOH	30	24	100	0	0	0	0	100(**7a**)
3	**6b**	$NaBH_4$[d)]	MeOH	30	24	100	0	0	0	0	100(**7b**)
4	**8a**	$NaBH_4$[d)]	MeOH	30	24	0	-	-	-	-	-
5	**8b**	$NaBH_4$[d)]	MeOH	30	24	0	-	-	-	-	-
6	**1a**	$LiBH_4$	THF	25	24	100	18	5	25	22	16
7	**8a**	$LiBH_4$	THF	25	24	12	0	0	0	0	100
8	**1a**	$LiAlH_4$	THF	25	2	98	34	3	0	0	63
9	**8a**	$LiAlH_4$	THF	25	24	100	0	0	0	0	100
10	**1a**	BH_3	THF	25	30	34	0	0	0	0	100
11	**8a**	BH_3	THF	25	30	96	0	0	0	0	100
12	**1a**	BH_3[d)]	THF	25	30	86	22	38	0	0	40
13	**8a**	BH_3[d)]	THF	25	30	9	0	0	0	0	100
14	**1a**	9-BBN	THF	25	24	0	-	-	-	-	-
15	**8a**	9-BBN	THF	25	24	0	-	-	-	-	-
16	**1a**	9-BBN[d)]	THF	25	24	86	22	50	22	(*t* + *c*)	6

a) Reaction conditions: [**1a**], [**8a**]; 1 mmol in an appropriate solvent (5 ml) under nitrogen. b) Reducing agent (2 eq.). c) Yield based on the conversion and structures of the products were determined by ^1H NMR.
d) *t*-BuOK (3 eq.) was added.

for the formation of **2**. The keto form of 2,6-di-*t*-butylphenols is known to be stabilized sometimes by the *t*-Bu groups due to their steric hindrance.[4, 10)] In the $NaBH_4$ reduction, quinols **6a** and **6b** gave phenols **7a** and **7b**, respectively, and **8a**[11)] and **8b**[12)] were not reactive (Entries 2 - 5). The reduction of **1a** with $LiBH_4$ or $LiAlH_4$ also gave **2a**, but other products predominated (Entries 6 and 8). It is noted that the reduction of **1a** with BH_3 gave only **4a**, whereas **2a** was formed predominantly upon addition of *t*-BuOK to this system (Entries 10 and 12). These results are rationalized by assuming a quinoxyborohydride anion intermediate (**9**) (Scheme 1), but

not direct attack by the reducing agent to the unsaturated system in the substrate. The stereochemistry of the 6-position in **2** may result from the coordination of the carbanion generated on the boron atom (**11**).

On the other hand, the reduction with $LiBH_4$, $LiAlH_4$, and BH_3 giving rise to **4a** should involve the direct attack of these reducing agents to the unsaturated system, because even compound **8a** was reduced to **4a** with these agents. Such a direct attack by 9-BBN is inhibited by its steric hindrance (Entries 14 and 15), but



Scheme 1.

upon addition of *t*-BuOK to this system, **1a** mainly gave a mixture of **2a**(*t* + *c*) (Entry 16). The predominant formation of **2a** (*c*) may be due to the equilibrium mentioned above under the basic conditions, since the coordinative interaction of type **11** is hindered by the BBN group.

Since further reduction of **2** with $LiAlH_4$ gave cyclohexanone derivatives **3** quantitatively, the reduction of **1** with $NaBH_4$ followed by $LiAlH_4$ provides a good method for the preparation of 2,6-di-*t*-butylcyclohexanones.

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9) All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Cu-Kα radiation and a 12kW rotating anode generator. A colorless prismatic crystal, monoclinic cell with dimensions: a = 11.262(3) Å, b = 10.798(3) Å, c = 14.872(2) Å, β = 99.11(1)°, V = 1785.7(6) Å^3; space group, $P2_1/a$ (#14).
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11) Compound **8a** was conveniently prepared by the oxidation of **1a** with NaClO in methanol or the treatment of **1a** with *p*-toluene sulfonic acid in methanol.
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