CHROMENES AND CHROMANONES. PART II.[1]
THE BIRCH REDUCTION OF PRECOCENE I AND PRECOCENE II

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Abstract -*The reduction of precocene I* (**1a**), *precocene II* (**1c**) *and* 6-methoxy-2,2-dimethyl-2*H*-chromene (**1b**) with sodium or lithium in liquid ammonia was examined. The phenolic compounds and the bicyclic one with partially reduced benzene ring were obtained as the major products from precocene I and **1b**, respectively. The demethoxylation during the reduction of precocene II was observed.

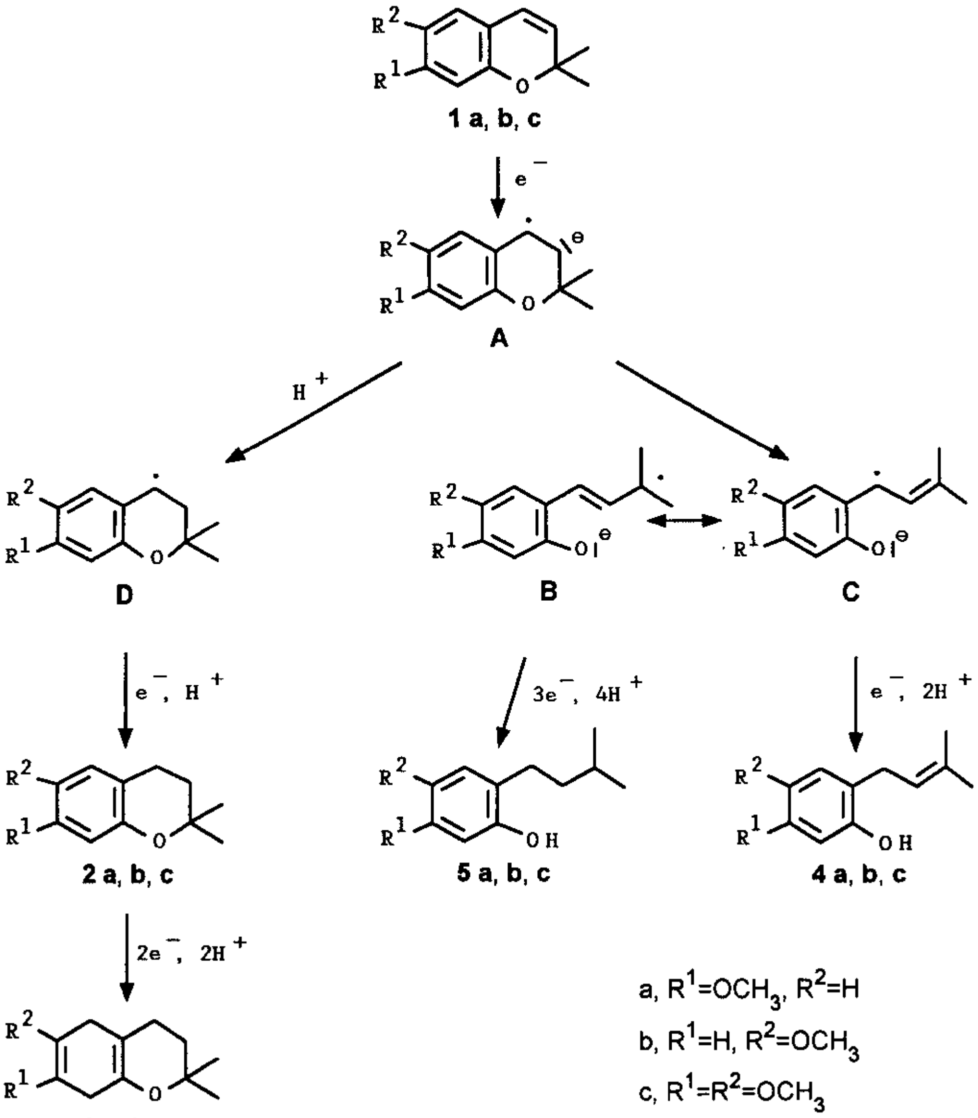
INTRODUCTION

Continuing our attempts to synthesize structural analogues of precocenes without the C_3-C_4 double bond and with partially reduced benzene ring, the Birch reduction of precocene I (**1a**) and precocene II (**1c**) was carried out.

Undertaking this work, we expected also that reduction of these compounds and additionally of 6-methoxy-2,2-dimethyl-2*H*-chromene (**1b**) will deliver some new information concerning influence of the electron donating groups on the course of the Birch reduction process of chromene systems.

RESULTS AND DISCUSSION

The results obtained from the Birch reduction of chromenes[1,2] showed that when the reaction was carried out without or with a small amount of *tert*-butanol or ethanol as an additional proton donor, the phenolic compounds were isolated as products. The compounds with partially reduced benzene ring and with the bicyclic system retained were formed when the excess of methanol was used.



a, R^1=OCH_3, R^2=H
b, R^1=H, R^2=OCH_3
c, R^1=R^2=OCH_3

Scheme 1

Due to our interest in the synthesis of bicyclic chromane derivatives, all the reductions described here were carried out in the presence of an excess of methanol or ethanol. The conditions of the experiments and the results are given in the Table.

Compositions of the product mixtures obtained from reduction of precocene I (**1a**), precocene II (**1c**) and 6-methoxy-2,2-dimethyl-2*H*-chromene (**1b**) when the only 7 eq. of ethanol were applied

Table: Compositions (in % according to gc) of the product mixtures

Entry	Metal (eq.)	Alcohol (eq.)	Time min	R^1	R^2	**2 a-c**	**3 a**	**3b**	**3c**	**4 a-c**	**5 a-c**
1	Na (5)	EtOH (7)	60	OMe	H	-	1	-	-	92	7
2	Na (7)	EtOH (70)	20	OMe	H	-	12	-	-	78	10
3	Na (14)	MeOH (140)	15	OMe	H	-	40	-	-	53	7
4	Li (7)	MeOH (70)	15	OMe	H	-	12	-	-	75	13
5	Li (14)	MeOH (70)	15	OMe	H	-	16	-	-	70	14
6	Na (5)	EtOH (7)	60	H	OMe	-	-	23	-	74	3
7	Na (14)	MeOH (140)	10	H	OMe	-	-	97	-	3	0
8	Li (7)	MeOH (70)	10	H	OMe	-	-	93	-	6	1
9	Na (5)	EtOH (7)	60	OMe	OMe	5	1	2	13	73	6
10.	Na (7)	EtOH (70)	20	OMe	OMe	35	1	2	20	37	5
11	Na (14)	MeOH (70)	15	OMe	OMe	-	6	9	69	14	2
12	Na (14)	MeOH (140)	15	OMe	OMe	-	7	11	73	8	1
13	Li (7)	MeOH (70)	10	OMe	OMe	22	3	4	41	25	5
14.	Li (14)	MeOH (70)	30	OMe	OMe	-	4	5	61	26	4

a, R^1= OMe, R^2= H; b, R^1= H, R^2= OMe; c, R^1=R^2= OMe.

(Entries 1, 6, 9) are consistent with those observed for reduction of unsubstituted chromenes.[1] The phenolic compounds (**4a**, **5a**, **4b**, **5b** and **4c**, **5c**) were obtained as the major products.

Compounds with the C-O bond cleaved were also isolated as the major products (above 85 %) from the reduction of precocene I (**1a**) (Entries 2, 4, 5) despite the presence of excess (70 eq.) of methanol or ethanol in the reaction medium. Only the application of 140 eq. of methanol (Entry 3) led to formation of the desired bicyclic compound (**3a**) in 40 % yield.

Quite different results were obtained from the reduction of 6-methoxy-2,2-dimethyl-2*H*-chromene (**1b**). In this case only when 7 eq. of ethanol were used (Entry 6), the compounds with the cleaved C-O bond predominated in the product mixture. In two experiments (Entries 7, 8) which were carried out with excess of methanol, the bicyclic compound (**3b**) was identified as almost only product (above 93 %).

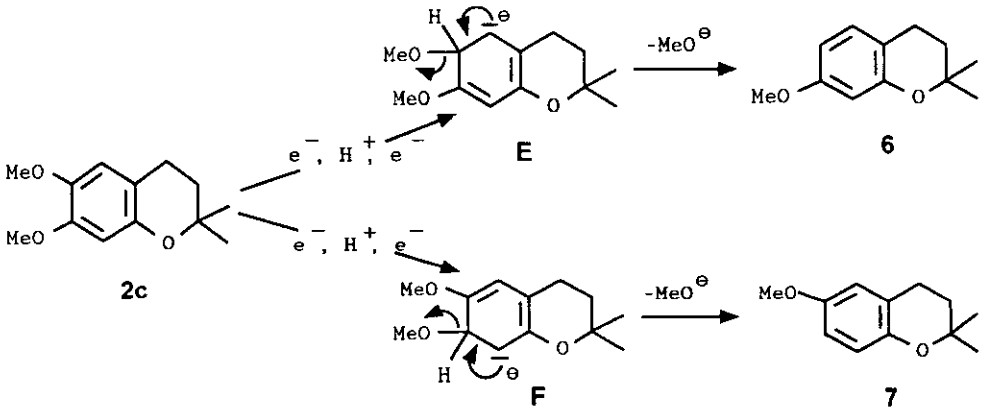
Such different course of the reduction of 6-methoxy-2,2-dimethyl-2*H*-chromene (**1b**) and 7-methoxy-2,2-dimethyl-2*H*-chromene (**1a**) is probably caused by different electron density distribution in the radical anions (**A**) (Scheme 1). The increased electron density at the C-4a position in the radical anion (**A**) derived from **1a** pushes the electrons to C-2 that leads to formation of radical anion (**C**). In contradistinction to it, the increased electron density at the C-8a position in the radical anion (**A**) formed from **1b** prevents the addition of the electron pair by the neighboring oxygen atom, that causes the increased stability of this radical anion.

The antagonistic influence of methoxy groups on the stability of radical anion (**A**) formed from precocene II (**1c**) causes that in the product mixtures of the reduction of this compound (Entries 9-14) the phenolic (**4c**, **5c**) as well as bicyclic products (**3a**, **b**, **c**) are present. Analysis of the results obtained from the reduction of **1c** confirmed our earlier observations[1] that contribution of bicyclic compounds with the partially reduced benzene ring in the product mixture depends on the kind of alcohol used (Entries 10, 13) as well as on its concentration (Entries 11, 12) in the reaction medium. Unlike to earlier observations, the composition of product mixture depends also on the kind (Entries 11, 14) and amounts (Entries 13, 14) of metal applied. The influence of the amount of metal used is especially visible. When 7 eq. of lithium (Entry 13) or sodium (Entry 10) were used, the bicyclic compound with the reduced C_3-C_4 double bond, **2c**, possesed substantial contribution in the product mixture (22 and 35% respectively). The increase in the amount of metal used to 14 eq. caused more effective reduction of **2c** to the products with partially reduced benzene ring

(**3a**, **3b**, **3c**) (Entries 11, 12 and 14).

The presence of the compounds with only one methoxy group (**3a**, **3b**) among the products of reduction of precocene II is the result of leaving of one methoxy group during the reduction process. Such reductive removal of the methoxy group was observed earlier in the reduction of 3,4,5-trimethoxytoluene,[3] 2,3-dimethoxynaphthalene,[4] 2-(3,4,5-trimethoxyphenyl)ethylamine[5] and 2,3-dimethoxy-1-naphthylalkylketones.[6] Mechanisms of demethoxylation proposed by authors[4, 6] do not seem to be adequate for the description of this process in the case of reduction of precocene II.

We suggest that this process takes place during the reduction of **2c** and that the rearomatisation of the anions **E** or **F** to the corresponding monomethoxy compounds (**6** and **7**) is its motive force. We did not identify **6** or **7** in the product mixture, because they probably had been immediately reduced to **3a** or **3b,** respectively.



Scheme 2

EXPERIMENTAL SECTION

^{1}H Nmr spectra were recorded for solutions (CCl_4-C_6D_6, 7:1) with TMS as an internal standard, on a 80 MHz Tesla BS 587A spectrometer. Infrared spectra were determined with a SPECORD M80 infrared spectrophotometer. Mass spectra were determined on a GC/MS HP 5890/ HP 5971A spectrometer at an ionisation potential of 1800 eV. Gas chromatographic analyses were performed on a Hewlett Packard 5890 instrument using HP-5 (30 m × 0.31 mm) column or CP-Cyclodextrin (25 ×0.31 mm) for analyses of **3a** and **3b**. The compositions of product mixtures presented in Table were determined by gas chromatographic analyses. Precocene I and precocene II were purchased from Aldrich. 6-Methoxy-2,2-dimethyl-2*H*-chromene (**1b**) was obtained by intramolecular oxidative cyclisation of 4-methoxy-2-(3-methyl-2-butenyl)phenol catalysed by palladium chloride.[7] All reductions were carried out under an inert atmosphere of dry, oxygen free nitrogen.

Procedure for Metal-Ammonia Reduction

The metal was added in pieces for 5 min to a solution of methoxy-2,2-dimethyl-2*H*-chromenes (228 mg **1a** or **1b**, 264 mg **1c**, 1.20 mmol) in ammonia (50 ml), containing THF (10 ml) and anhydrous proton donor (7-140 eq., see Table) at -78 °C. After 1 h or when blue color had disappeared, the reaction was quenched by adding aqueous saturated ammonium chloride solution. The ammonia was evaporated from the reaction mixture and saturated aqueous sodium chloride (10 ml) was added. Products were extracted with ether (3x10 ml). The combined ethereal solutions were washed with saturated aqueous sodium chloride (3x10 ml), and dried over anhydrous magnesium sulfate. Pure products were separated by column chromatography on 230-400 mesh silica gel 60 (Merck) with hexane-acetone 6:1

3,4-Dihydro-6,7-dimethoxy-2,2-dimethyl-2*H*-1-benzopyran (**2c**): solid; mp 55-57 (lit.,[8] 60 °C). **3,4,5,8-Tetrahydro-7-methoxy-2,2-dimethyl-2*H*-1-benzopyran** (**3a**): oil; n_D^{20}=1.4905; ^{1}H nmr (CCl_4:C_6D_6) δ: 1.19 (s, 6H, $C(CH_3)_2$), 1.40-2.00 (m, 4H, CH_2CH_2), 2.63 (s, 4H, $CH_2C=CCH_2$), 3.45 (s, 3H, OCH_3), 4.48 (s, 1H, C=CH); ir (cm^{-1}): 1720(s), 1684(m), 1152(s), 1120(s); mass spectrum m/z 194 (M^+). Anal. Calcd for $C_{12}H_{18}O_2$: C,74.19; H,9.34. Found: C,74.05; H,9.45. **3,4,5,8-Tetrahydro-6-methoxy-2,2-dimethyl-2*H*-1-benzopyran** (**3b**): oil; n_D^{20}=1.4970; ^{1}H nmr (CCl_4:C_6D_6) δ: 1.18 (s, 6H, $C(CH_3)_2$), 1.40-2.00 (m, 4H, CH_2CH_2), 2.62 (s, 4H, $CH_2C=CCH_2$), 3.43 (s, 3H, OCH_3), 4.43 (s, 1H, C=CH); ir (cm^{-1}): 1720(w), 1684(s), 1164(s), 1116(s); mass spectrum m/z 194 (M^+). Anal. Calcd for $C_{12}H_{18}O_2$: C,74.19; H,9.34. Found: C,73.97; H,9.33. **3,4,5,8-Tetrahydro-6,7-dimethoxy-2,2-dimethyl-2*H*-1-benzopyran** (**3c**): oil; n_D^{20}=1.4920;^{1}Hnmr (CCl_4:C_6D_6) δ: 1.17 (s, 6H, $C(CH_3)_2$), 1.40-2.00 (m, 4H, CH_2CH_2), 2.67 (s, 4H, $CH_2C=CCH_2$), 3.53, 3.56 (2s, 6H, $(OCH_3)_2$); ir (cm^{-1}): 1728(m), 1700(s), 1148(s), 1128(s); mass spectrum m/z 224 (M^+). Anal. Calcd for $C_{13}H_{20}O_3$: C,69.61; H,8.99. Found: C,70.13; H,8.84. **5-Methoxy-2-(3-methyl-2-butenyl)phenol** (**4a**): oil; n_D^{20}=1.5350; ^{1}H nmr (CCl_4:C_6H_6) δ: 1.71 (s, 6H, $C=C(CH_3)_2$), 3.18 (d, J=7 Hz, 2H, CH_2), 3.62 (s, 3H, OCH_3), 5.06 (s, 1H, OH), 5.25 (m, 1H, C=C**H**), 6.10-7.00 (m, 3H, $C_6\mathbf{H}_3$); ir (cm^{-1})· 3440(s,b), 1628(s), 1604(m), 1208(s), 1164(s); mass spectrum m/z 192 (M^+). Anal. Calcd for $C_{12}H_{16}O_2$: C,74.97; H,8.39. Found: C,74.78; H,8.32.

4-Methoxy-2-(3-methyl-2-butenyl)phenol (4b): oil; n_D^{20}=1.5280; ^{1}H nmr (CCl_4:C_6D_6) δ: 1.71 (s, 6H, C=C($C\mathbf{H}_3$)$_2$), 3.24 (d, J=7Hz, 2H, $C\mathbf{H}_2$), 3.63 (s, 3H, $OC\mathbf{H}_3$), 5.17 (s, 1H, O**H**), 5.25 (m, 1H, C=C**H**), 6.50-6.60 (m, 3H, $C_6\mathbf{H}_3$); ir (cm^{-1}): 3440(s, b), 1628(m), 1204(s), 1168(s); mass spectrum m/z 192 (M^+). Anal. Calcd for $C_{12}H_{16}O_2$: C,74.97; H,8.39. Found C,74.53; H,8.28.

4,5-Dimethoxy-2-(3-methyl-2-butenyl)phenol (4c): oil; n_D^{20}=1.5310; ^{1}H nmr (CCl_4:C_6D_6) δ: 1.72 (s, 6H, C=C($C\mathbf{H}_3$)$_2$), 3.17 (d, J=7 Hz, 2H, $C\mathbf{H}_2$), 3.61, 3.67 (2s, 6H, ($OC\mathbf{H}_3$)$_2$), 4.53 (s, 1H, O**H**), 5.30 (m, 1H, C=C**H**), 6.22, 6.49 (2s, 2H, $C_6\mathbf{H}_2$); ir (cm^{-1}): 3480(s,b), 1624(m), 1208(s), mass spectrum m/z 222 (M^+). Anal. Calcd for $C_{13}H_{18}O_3$: C,70.24; H,8.16. Found: C,70.12; H,8.22.

5-Methoxy-2-(3-methylbuthyl)phenol (5a): oil; n_D^{20}=1.5135; ^{1}H nmr (CCl_4:C_6D_6) δ: 0.92 (d, J=5.5 Hz, 6H, CH($C\mathbf{H}_3$)$_2$), 1.20-1.80 (m, 3H, $C\mathbf{H}_2$CH(CH_3)$_2$), 2.30-2.60 (m, 2H, $C_6H_3C\mathbf{H}_2$), 3.62 (s, 3H, $OC\mathbf{H}_3$), 4.59 (s, 1H, O**H**), 6.00-7.00 (m, 3H, $C_6\mathbf{H}_3$); ir (cm^{-1}): 3440(s,b), 1628(s), 1604(m), 1388(m), 1208(s), 1168(s); mass spectrum m/z 194 (M^+). Anal. Calcd for $C_{12}H_{18}O_2$· C,74.19; H,9.34. Found: C,74.41; H,9.31.

4-Methoxy-2-(3-methylbutyl)phenol (5b): oil; n_D^{20}= 1.5130; ^{1}H nmr (CCl_4:C_6D_6) δ: 0.91 (d, J=5.5 Hz, 6H, CH($C\mathbf{H}_3$)$_2$), 1.20-1.80 (m, 3H, $C\mathbf{H}_2$CH(CH_3)$_2$), 2 30-2.60 (m, 2H, $C_6H_3C\mathbf{H}_2$), 3 63 (s, 3H, $OC\mathbf{H}_3$), 4 52 (s, 1H, O**H**), 6.50-6.60 (m, 3H, $C_6\mathbf{H}_3$); ir (cm^{-1}): 3480(s, b), 1628(m), 1388(m), 1208(s), 1168(s); mass spectrum m/z 194 (M^+). Anal. Calcd for $C_{12}H_{18}O_2$·C,74.19; H,9.34. Found: C,74.25; H,9.33.

4,5-Dimethoxy-2-(3-methylbutyl)phenol (5c): oil; n_D^{20}=1.5150; ^{1}H nmr (CCl_4:C_6D_6) δ: 0.94 (d, J=5.5 Hz, 6H, CH($C\mathbf{H}_3$)$_2$), 1.20-1.80 (m, 3H, $C\mathbf{H}_2$CH(CH_3)$_2$), 2.30-2.60 (m, 2H, $C_6H_2C\mathbf{H}_2$), 3.64, 3.67 (2s, 6H, C_6H_2($OC\mathbf{H}_3$)$_2$), 4.75 (s, 1H, O**H**), 6.11, 6.49 (2s, 2H, $C_6\mathbf{H}_2$); ir (cm^{-1}): 3480(s,b), 1628(m), 1388(m), 1384(m), 1208(s); mass spectrum m/z 224 (M^+). Anal. Calcd for $C_{13}H_{20}O_3$· C,69.61; H,8.99 Found· C,68.98; H,9.01.

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