Condensation of 2-Naphthol and Naphthalenediols with *o*-Dichlorobenzene in the Presence of Aluminum Halides

Konstantin Yuryevich Koltunov,[a,b,c] Aleksey Nikolaevich Chernov,[a,b] Gubbi Krishnamurthy Surya Prakash,*,[c] and George Andrew Olah[c]

[a] *Boreskov Institute of Catalysis; Pr. Akademika Lavrentieva, 5, Novosibirsk 630090, Russia:* [b] *Novosibirsk State University; Pirogova, 2, Novosibirsk 630090, Russia: and* [c] *Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California; University Park, Los Angeles, California 90089–1661, U.S.A.*

It is known that 1-naphthol, as a result of superelectrophilic (dicationic) activation in superacid media, is able to react with such deactivated aromatic compound as *o*-dichlorobenzene to give 4-(3,4-dichlorophenyl)-1-tetralone (2), which is a highly valuable intermediate in the synthesis of the antidepressant, sertraline (1) and other useful derivatives. However, the analogous reactivity of 2-naphthol and a variety of naphthalenediols towards *o*-dichlorobenzene has not been investigated thus far, although the corresponding tetralones, bearing dichlorophenyl moiety, could be of great pharmacochemical interest. In present work, we disclose that 1,5-, 1,6-, and 1,7- naphthalenediols (6a–c) react smoothly with *o*-dichlorobenzene in the presence of an excess of aluminum chloride or aluminum bromide to give the pairs of isomeric 4-(3,4-dichlorophenyl)- and 4-(2,3-dichlorophenyl)- 5-, 6-, and 7-hydroxy-1-tetralones (10a–c and 11a–c) in high overall yields. 2-Naphthol and 2,7-naphthalenediol (6d) exhibited comparatively lower reactivity, which however was sufficient to obtain the corresponding dichlorophenyl-2-tetralones in moderate yields. The mechanism of these reactions involving superelectrophilic dicationic or even tricationic intermediates, is discussed.

Key words   superacid; superelectrophilic activation; 2-naphthol; naphthalenediol; tetralone

Tetralones are useful molecules as starting material for the synthesis of biologically active compounds and pharmaceutical substances.[1–8] For example, one of the major commercial pharmaceutical agents, sertraline ((+)-*cis*-(1*S*,4*S*)-1-methylamino-4-(3,4-dichlorophenyl)tetralin, **1**), an antidepressant known under the trade name Zoloft, is a competitive inhibitor of synaptosomal serotonin uptake.[9,10] The current commercial process for the production of sertraline involves the synthesis of (±)-**1** followed by resolution.[1,3,11–14]

A key intermediate in the synthesis of **1** is 4-(3,4-dichlorophenyl)-1-tetralone (**2**), which has been prepared by a few synthetic routes.[15–17] The most efficient route to tetralone **2** is based on one-stage condensation reaction of 1-naphthol with *o*-dichlorobenzene under the influence of aluminum halides.[3,16,17]

Originally, a similar method for the synthesis of 4-aryl-1-tetralones had been demonstrated for reactions of 1-naphthol with benzene, chlorobenzene, fluorobenzene and toluene under the influence of aluminum halides or in the HF–SbF$_5$ superacid medium[18–22] (Chart 1). Analogously, 2-naphthol reacts with benzene in the presence of aluminum halides to give 4-phenyl-2-tetralone[19,23] (Chart 1). Furthermore, selective ionic reduction of naphthols by alkanes leads to tetralones under similar reaction conditions[24,25] (Chart 1).

The mechanism of these reactions was recognized to involve superelectrophilic[26] dications (structures **3** and **4**, Chart 1) as the key intermediates formed by *C,C*-diprotonation and a number of analogous dications have indeed been generated as long-lived species by dissolving naphthols and/or their derivatives in liquid superacids.[27,28] Moreover, a set of isomeric naphthalenediols was reacted similarly with benzene and cyclohexane in the presence of AlBr$_3$ and AlCl$_3$ to afford the corresponding hydroxytetralones[29–31] (Chart 2).
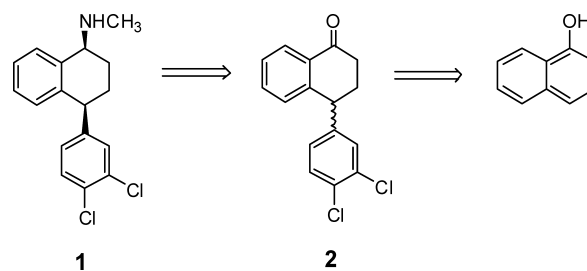
In addition, it has been found that, in contrast to 1-naphthol and naphthalenediols, 5-amino-1-naphthol is activated by *N,C*-diprotonation in superacids and reacted with benzene and cyclohexane under the influence of aluminum halides through dications **5** to give 5-amino-3-phenyl-1-tetralone and 5-amino-1-tetralone, respectively[32] (Chart 3).

Based on this background, in continuation of our interest in superelectrophilic activation of naphthols and their derivatives, a study on the reactivity of 2-naphthol and isomeric 1,5-, 1,6-, 1,7-, and 2,7-naphthalenediols (**6a–d**)[33] towards *o*-dichlorobenzene is reported with the aim of synthesizing the corresponding dichlorophenyl-1- and 2-tetralones, which are considered as promising intermediates for medicinal chemistry.[8,34] The main aim of the work was also to determine the regioselectivity of these reactions.

Results and Discussion

Reactions of 2-Naphthol   Until now, attempts to involve 2-naphthol in reaction with *o*-dichlorobenzene were not successful.[23] Thus, 2-naphthol did not give any product at conditions, essential for the reaction of 1-naphthol, which reacted with *o*-dichlorobenzene in the presence of an excess of AlCl$_3$ (or AlBr$_3$) at elevated temperature, normally at 100–120°C (65°C), to give tetralone **2** in 65–80% yield over 1–2h.[3,16,17] Therefore, at the time it was concluded that dicationic intermediate **4** is not electrophilic enough to react with such

key intermediates

Chart 1. Reactions of Naphthols with Arenes (ArH) and Alkanes (AlkH).

$X = H$ or $Al_nCl_{3n}^-$ or $Al_nBr_{3n}^-$

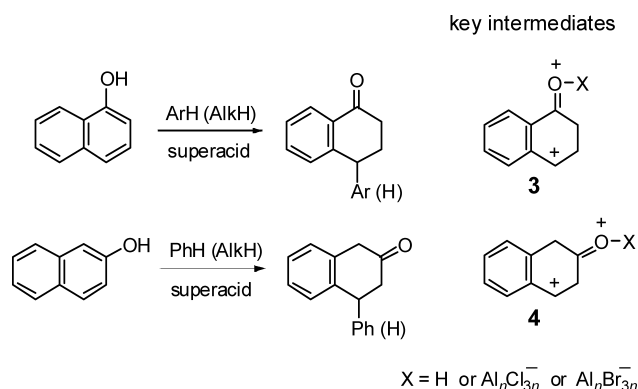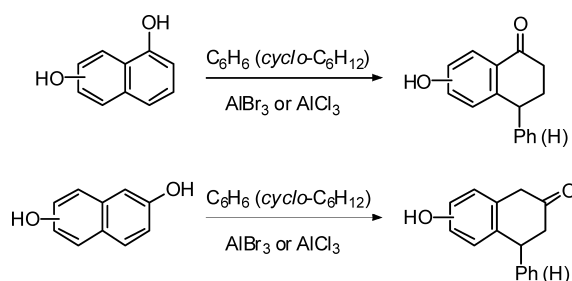Chart 2. Reactions of Naphthalenediols with Benzene and Cyclohexane

Chart 3. Reactions of 5-Amino-1-naphthol with Benzene and Cyclohexane

deactivated aromatic compound as *o*-dichlorobenzene. Indeed, according to density functional theory (DFT) calculations, dication **4** is less electrophilic compared to the diprotonated form of 1-naphthol[35] (structure **3**).

Nevertheless, 2-naphthol was observed to react with *o*-dichlorobenzene to give isomeric 4-(3,4-dichlorophenyl)- and 4-(2,3-dichlorophenyl)-2-tetralones **7** and **8** in *ca.* 9:1 ratio, respectively, in a moderate overall yield. A condition, favorable to ensure the successful result, appeared to be a long term reaction performed at room temperature (Table 1).

The plausible mechanism of the reaction includes generation of dications **4**, similar to that described in Chart 1. Dications **4** (X=H) have been previously detected by ^{1}H- and ^{13}C-NMR spectroscopy as long-lived species in HF-SbF_5-SO_2ClF superacid system at $-40°C$.[28] However, in the presence of aluminum halides, participation of dicationic species **4** (X=Al_nHal_{3n}^-, Hal=Cl, Br) seems more probable, as 2-naphthol is converted quantitatively into complexes **9** upon action of AlCl_3 and AlBr_3.[36] The subsequent *C*-protonation of **9** results in formation of **4** (X=Al_nHal_{3n}^-) in equilibrium with **9**. A catalytic amount of protic superacid (HHal–Al_nHal_{3n} or H_2O–Al_nHal_{3n}), which is required for *C*-protonation of intermediate species **9**, is normally present in such reaction media due to presence of traces of water in the starting materials. The acid strength of HHal–Al_nHal_{3n} (Hal=Br, Cl) is estimated to be -15 to -18 in the *Ho* scale.[37–39] So, additional saturation of the reaction mixture with gaseous HHal, which usually accelerates similar reactions,[40] is not generally needed.

Taking into account a quantitative recovery of unreacted 2-naphthol, it is very likely that the moderate yield of tetralones **7** and **8** (no more than 36%, Table 1) is close to the equilibrium concentration of the product. The sensitivity of the reaction to the reverse process is in agreement with the known reactivity of 2-naphthol towards benzene. Thus, in spite of a 90% yield of 4-phenyl-2-tetralone in reaction of 2-naphthol with benzene in the presence of a 2.5-fold molar excess of AlCl_3 (20°C, 16h),[19] the equilibrium of a similar reaction is shifted completely to 2-naphthol, when HF-SbF_5 superacid at $-20°C$ or HUSY-zeolites at 130°C used.[23,41] The observed poor reactivity of 2-quinolinol (heterocyclic analog of 2-naphthol) towards benzene is also relevant to this case.[42]

Reactions of Naphthalenediols 6a–c For isomeric naphthalenediols, the possibility of superelectrophilic activation has been demonstrated earlier only for their reactions with cyclohexane and benzene[29–31] (Chart 2). Reactions of diols **6a–c** with the electrondeficient *o*-dichlorobenzene gave products similar to 1-naphthol. Reactions took place under the influence of a 3-fold molar excess of AlCl_3 at 110°C or AlBr_3 at 25°C to give pairs of 5-, 6-, and 7-hydroxy-substituted 4-(3,4-dichlorophenyl)-1-tetralones (**10a–c**) and 4-(2,3-dichlorophenyl)-1-tetralones (**11a–c**), respectively, in *ca.* 95% overall yields (Table 2).

The ratio of isomers **10a–c** and **11a–c** in the obtained mixtures is about 4:1, in each case. The same ratio of product **2** and isomeric 4-(2,3-dichlorophenyl)-1-tetralone was found,
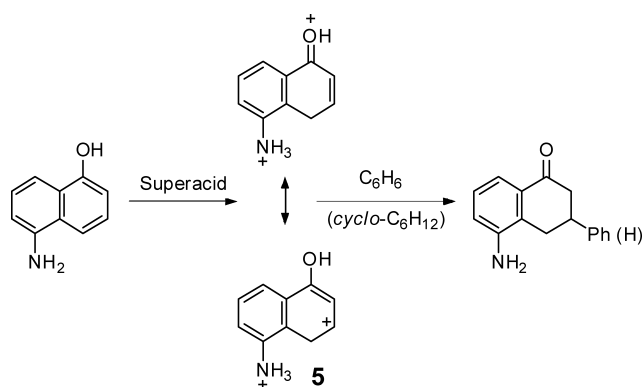
Table 1. Electrophilic Reactions of 2-Naphthol

| Reaction conditions			7 and 8 overall yield[a] (%)
Acid (eq)	Time (d)	*T* (°C)	
AlCl_3 (3.0)	7	25	11
AlCl_3 (3.0)	14	25	19
AlCl_3 (5.0)	14	25	35
AlCl_3 (5.0)	14	60	24
AlCl_3 (5.0)	1	110	1
HCl–AlCl_3 (3.0)	7	25	29
HCl–AlCl_3 (3.0)	14	25	36
AlBr_3 (3.5)	7	25	24
AlBr_3 (3.5)	1	60	1

a) Based on ^{1}H-NMR spectroscopic data. The balance is mainly unreacted 2-naphthol. The ratio of **7/8** is about 9:1 in each case.

previously, for the reaction of 1-naphthol with *o*-dichlorobenzene.[17] This is to be expected based on these reactions having a common mechanism. Dicationic electrophiles **12** (Y=OH), which are the key intermediates of the reactions studied, may also be additionally protonated (or coordinated with aluminum halide) to give tricationic **12** (Y=OHX[+]) in the limiting cases. Differences in the activation of naphthalenediols **6a–c** compared to 5-amino-1-naphthol (Chart 3) can be explained by the weaker basicity of hydroxy group in relation to the aminogroup. As a consequence, higher equilibrium concentration of *C,C*-diprotonated forms can be found in the first case. On the other hand, *O,C*-diprotonated dications **13** (X=H) and similar complexes **13** (X=Al$_n$Hal$_{3n}^-$), which are comparatively more easily formed,[43,44] than *C,C*-diprotonated forms **12**, do not react with *o*-dichlorobenzene, probably, because of the diminished electrophilicity. Therefore, intermediates **12** are stronger electrophiles and could react predominantly despite their relatively low equilibrium concentrations. Calculational estimations of electrophilicity of a number of dications showed, for example, that *C,C*-diprotonated naphthols are more electrophilic than *N,C*-diprotonated 5-amino-1-naphthol (structure **5**) and isomeric hydroxyquinolines.[32,35]

The main products **10** can be isolated from the reaction mixture by simple recrystallization. Moreover, undesired tetralones **11** can also be transformed into the useful isomers **10**. For example, the mixture of isomers **10b** and **11b** with the ratio 45:55 (obtained from the mother liquor after recrystallization of the initial mixture) gave the equilibrium ratio 78:22 after 15h reaction in *o*-dichlorobenzene with AlCl$_3$ at 120°C. Such isomerisation of aryltetralones have earlier been
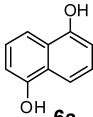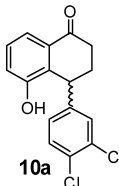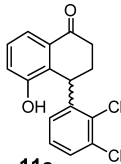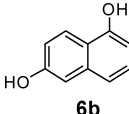

9

(X = Al$_n$Cl$_{3n}^-$, Al$_n$Br$_{3n}^-$)
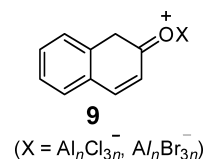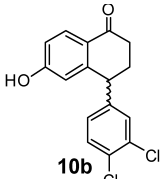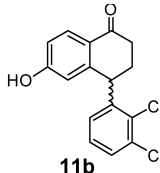
reported.[20]

Based on the structure–activity relationship of **1** and its derivatives, it is well known that the presence of 3,4-dichlorophenyl group is actually necessary to induce the biological activities and the attempts to improve the activities by variation of 4-aryl-group were unsuccessful.[45] Nevertheless, the properties of **1** should likely 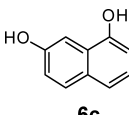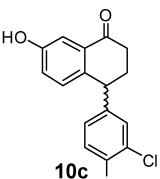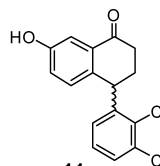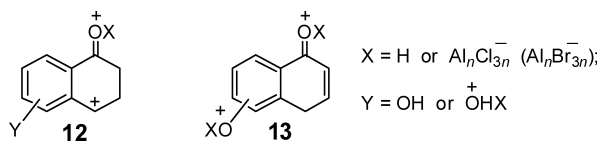be improved by structural changes in the tetraline aromatic ring. Literature precedence exists for this contention as 4-(4-chlorophenyl)-1-methylaminotetralin (the close analog of **1**) has been reported to exhibit close or even enhanced therapeutic properties due to introduction of 7-methoxy group.[45] This provides an incentive that similar functionalized derivatives of **1** can be pharmaceutically important. From this point of view, the presently obtained products **10a–c** or their close derivatives, as alkyl or aryl ethers and others may serve as useful synthons for the synthesis of analogs of **1**.

Reactions of Naphthalenediol 6d Since **6d** represents exclusively derivatives of 2-naphthol, its poor reactivity toward *o*-dichlorobenzene could be anticipated. However, **6d** reacted more readily, than the parent 2-napthol to give isomeric 4-(3,4-dichlorophenyl)- and 4-(2,3-dichlorophenyl)-7-hydroxy-2-tetralones **14** and **15** (9:1) in 56% overall yield (Chart 4).

Table 2.　Condensation of Naphthalenediols **6a–c** with *o*-Dichlorobenzene

Naphthalenediol	Products		Reaction conditions			**10** and **11** overall yield and (ratio)[a]
			Acid (eq)	Time (h)	*T* (°C)	
6a	**10a**	**11a**	AlBr$_3$ (3)	100	25	95% (77:23)
6b	**10b**	**11b** isolated yield 61%	AlCl$_3$ (3) AlBr$_3$ (3)	20 72	110 25	98% (79:21) 95% (78:22)
6c	**10c**	**11c** isolated yield 60%	AlCl$_3$ (3) AlBr$_3$ (3)	20 72	110 25	93% (78:22) 94% (85:15)

a) Based on ^{1}H-NMR spectroscopic data.

Chart 4. Condensation of Naphthalenediol **6d** with *o*-Dichlorobenzene

Chart 5. Superelectrophilic Activation of Naphthalenediol **6d** Proposed

Notably, the reaction proceeded slowly, for 7 d, in the presence of a 4-fold molar excess of AlBr$_3$ at room temperature, whereas attempts to replace AlBr$_3$ by AlCl$_3$ were not successful. This is probably due to the lack of solubility of complexes of **6d** with AlCl$_3$ in *o*-dichlorobenzene at room temperature. Increasing the reaction time from one to two weeks did not change either the yield or the ratio of **14** and **15**, which indicates the achievement of equilibrium values influencing both of these parameters.

A higher reactivity of **6d** compared to that of 2-naphthol can be explained by invoking the intermediacy of tricationic species **16** (Chart 5), which is more electrophilic than dications **4**. The intermediate *O,C*-diprotonated forms **17** (X=H) and similar complexes **17** (X=Al$_n$Br$_{3n}^-$) have been generated earlier as long-lived species in HF-SbF$_5$-SO$_2$ClF and AlBr$_3$-CH$_2$Br$_2$ superacid systems.[43,44] Alternatively, dicationic species **18**, which is effectively stabilized by positive charge delocalization over an intact hydroxyl group, may also contribute to the reaction. Owing to a higher concentration of **18** (compared to **16**), the equilibrium of reaction with *o*-dichlorobenzene could be shifted to tetralones **14** and **15** in spite of the diminished electrophilicity of **18**.

From a synthetic point of view, the studied reactions of **6d** and 2-naphthol may represent a convenient way to access dichlorophenyl-2-tetralones. The close derivative of product **14**, 4-(3,4-dichlorophenyl)-7-methoxy-2-tetralone, as well as the parent product **7** are regarded as important intermediates in medicinal chemistry.[8,34] These materials were produced previously by using inefficient multistep procedures. Therefore, the results obtained on the reactivity of 2-naphthols may be of practical interest. We suggest also that analogous reactions can be followed to obtain 2-tetralones with other deactivated (halogenated) aromatic compounds.

Conclusions

In summary, we have found that 2-naphthol and naphthalenediol **6d** are able to react with *o*-dichlorobenzene under the influence of aluminum halides, which provide a new one-step procedure for the preparation of dichlorophenyl-2-tetralones. Naphthalenediols **6a**–**c** condense with *o*-dichlorobenzene to give as the main products hydroxy substituted 4-(3,4-dichlorophenyl)-1-tetralones **10a**–**c**. Since the starting materials are commercially readily available the reactions offer a convenient one step synthetic approach for preparation of novel derivatives of **2**.

Experimental

General Remarks The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian 300 (300, 75 MHz) or Bruker Avance III 500 (500, 125 MHz) NMR spectrometers. GC-MS spectra recorded on Agilent 5973N electron ionization/positive chemical ionization instrument. High-resolution mass spectra were measured at the Southern California Mass Spectrometry Facility 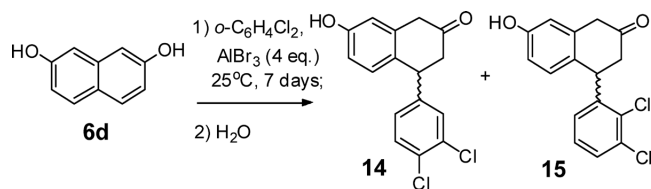at the University of California at Riverside. Aluminum bromide, aluminum chloride, *o*-dichlorobenzene, 2-naphthol and naphthalendiols **6a**–**d** were purchased from suppliers and used as received.
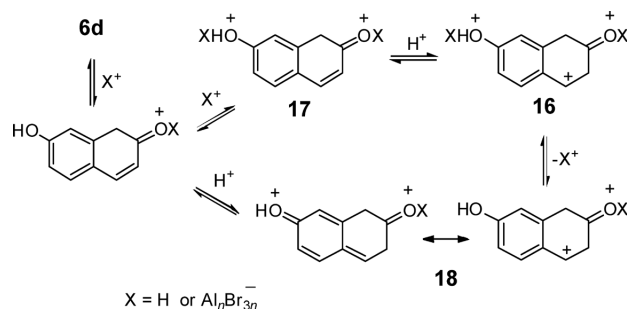
4-(3,4-Dichlorophenyl)-2-tetralone (7) and 4-(2,3-Dichlorophenyl)-2-tetralone (8) To a stirred suspension of AlCl$_3$ (freshly sublimed, 8.0 g, 60 mmol) in *o*-dichlorobenzene (15 mL) was added 2-naphthol (2.9 g, 20 mmol). The mixture was saturated with gaseous HCl at 25°C for 20 min. The resulting suspension was stirred at 25°C for 2 weeks, and then poured onto ice. The resulting mixture was extracted with ether. The organic phase was washed with dilute HCl and then several times with water. The organic solution was subjected to steam distillation to remove solvents and the rest of 2-naphthol. The residue was dissolved in ether, dried over anhydrous MgSO$_4$ and concentrated *in vacuo* to give a brown, viscous oil [2.11 g (36%), mixture of **7/8** (89 : 11), according to ^{1}H-NMR spectroscopic data]. Compound **7**: ^{1}H-NMR (500 MHz, CD$_3$OD) δ: 2.78 (1H, dd, *J*=16.5, 7 Hz), 2.85 (1H, dd, *J*=16, 5.5 Hz), 3.5 (1H, d, *J*=20.5 Hz), 3.68 (1H, d, *J*=20.5 Hz), 4.46 (1H, dd, *J*=6.5, 6 Hz), 6.92 (1H, d, *J*=7.5 Hz), 6.99 (ddd, *J*=8, 2, 0.5 Hz, 1H), 7.16–7.24 (4H, m), 7.4 (1H, d, *J*=8 Hz). ^{13}C-NMR (125 MHz, CD$_3$OD) δ: 45.1, 45.3, 46.6, 127.1, 127.2, 128.2, 128.7, 129.9, 130.4, 131.2, 131.9, 133.6, 136.4, 139.3, 144.3, 211.5. GC-MS [M]$^+$: 290. The tetralone **7** is a known compound; spectroscopic data are listed here as an update.[8] Compound **8** (fragmentary data were taken from the spectrum of the mixture of products **7** and **8**): ^{1}H-NMR (500 MHz, CD$_3$OD) δ: 2.81 (1H, dd, *J*=16.5, 7 Hz), 2.87 (1H, dd, *J*=16, 5.5 Hz), 3.62 (1H, d, *J*=20.5 Hz), 3.79 (1H, d, *J*=20.5 Hz), 5.0 (1H, t, *J*=6.5 Hz). GC-MS [M]$^+$: 290.

4-(3,4-Dichlorophenyl)-6-hydroxy-1-tetralone (10b) and 4-(2,3-Dichlorophenyl)-6-hydroxy-1-tetralone (11b). Method a To a stirred suspension of AlCl$_3$ (4.2 g, 37.5 mmol) in *o*-dichlorobenzene (6 mL) was added naphthalendiol **6b** (2 g, 12.5 mmol). The resulting mixture was stirred at 110°C for 20 h, then cooled and poured over several grams of ice. After stirring the quenched mixture for 10 min, hexane (20 mL) was added and stirring continued for 1 h. The crude reaction product was filtered off, washed with water and hexane and

dried to give 3.75 g (98%) of **10b** and **11b** mixture (the ratio 79 : 21, respectively, according to ¹H-NMR spectroscopic data). Recrystallization of the mixture from aqueous ethanol (twice) and toluene (twice) gave tetralone **10b** (2.33 g, 61%) as white crystals. Compound **10b**: mp 240–241°C. IR (CHCl₃): v=1655 cm⁻¹. ¹H-NMR (300 MHz, acetone-d_6) δ: 2.22–2.46 (2H, m), 2.51–2.59 (2H, m), 4.36 (1H, dd, J=8.54, 4.63 Hz), 6.34 (1H, d, J=2.44 Hz), 6.86 (1H, dd, J=8.55, 2.44 Hz), 7.2 (1H, dd, J=8.3, 2.2 Hz), 7.45 (1H, d, J=2.2 Hz), 7.57 (1H, d, J=8.3 Hz), 7.94 (1H, d, J=8.55 Hz), 9.13 (s, 1H). ¹³C-NMR (75 MHz, acetone-d_6) δ: 32.1, 37.0, 45.2, 115.5, 115.6, 126.4, 129.5, 130.3, 130.7, 131.4, 131.5, 132.6, 146.1, 148.8, 162.7, 195.4. High resolution (HR)-MS Calcd for $C_{16}H_{12}Cl_2O_2$ [M]⁺: 306.0214; Found 306.0225. Compound **11b** (data were taken from the spectrum of the mixture of products **10b** and **11b**): ¹H-NMR (300 MHz, acetone-d_6) δ: 2.2–2.65 (4H, m), 4.85 (1H, t, J=8 Hz), 6.34 (1H, d, J=2.2 Hz), 6.88 (1H, dd, J=8.2, 2.2 Hz), 7.05 (1H, dd, J=8, 1.6 Hz), 7.32 (1H, t, J=8 Hz), 7.54 (1H, dd, J=8, 1.6 Hz), 7.95 (1H, d, J=8.2 Hz), 9.16 (1H, s).

Method b To a solution of AlBr₃ (10 g, 37.5 mmol) in o-dichlorobenzene (7 mL) was added **6b** (2 g, 12.5 mmol). The resulting mixture was stirred at 25°C for 72 h, followed by the workup, as described above, to give 3.63 g (95%) of **10b** and **11b** (78 : 22) mixture.

4-(3,4-Dichlorophenyl)-7-hydroxy-1-tetralone (10c) and 4-(2,3-Dichlorophenyl)-7-hydroxy-1-tetralone (11c) Using the **a** and **b** methods, the mixtures of title compounds, **10c** and **11c** (the ratios 78 : 22 and 85 : 15, respectively) were prepared in 93–94% yields. Recrystallization of the mixtures from toluene (twice) and ethanol (twice) gave **10c** (60%) as a white crystalline product. Compound **10c**: mp 192–193°C. IR (CHCl₃): v=1664 cm⁻¹. ¹H-NMR (300 MHz, acetone-d_6) δ: 2.2–2.5 (2H, m), 2.55–2.65 (2H, m), 4.37 (1H, dd, J=8.06, 3.42 Hz), 6.85 (1H, d, J=8.54 Hz), 7.02 (1H, dd, J=8.54, 2.93 Hz), 7.16 (1H, dd, J=8.3, 2.2 Hz), 7.41 (1H, d, J=2.2 Hz), 7.47 (1H, d, J=2.93 Hz), 7.54 (1H, d, J=8.3 Hz), 8.68 (s, 1H). ¹³C-NMR (75 MHz, acetone-d_6) δ: 32.3, 36.9, 44.2, 112.6, 122.0, 129.4, 130.6, 131.3, 131.4, 131.5, 132.5, 134.6, 137.2, 146.6, 157.2, 196.9. HR-MS Calcd for $C_{16}H_{12}Cl_2O_2$ [M]⁺: 306.0214; Found 306.0214. Compound **11c** (data were taken from the spectrum of the mixture of products **10c** and **11c**): ¹H-NMR (300 MHz, acetone-d_6) δ: 2.2–2.65 (4H, m), 4.85 (1H, dd, J=6.84, 1.95 Hz), 6.85 (1H, d, J=8.3 Hz), 6.92 (1H, dd, J=7.82, 1.47 Hz), 7.04 (1H, dd, J=8.3, 2.9 Hz), 7.28 (1H, t, J=7.82 Hz), 7.49 (1H, d, J=2.9 Hz), 7.55 (1H, dd, J=7.82, 1.47 Hz), 8.77 (1H, s).

4-(3,4-Dichlorophenyl)-5-hydroxy-1-tetralone (10a) and 4-(2,3-Dichlorophenyl)-5-hydroxy-1-tetralone (11a) Using the **b** method (completion of the reaction required 100 h), the mixture of title compounds, **10a** and **11a** (77 : 23) was prepared in 95% yield. HR-MS Calcd for $C_{16}H_{12}Cl_2O_2$ [M]⁺: 306.0214; Found 306.0213. Compound **10a**: ¹H-NMR (300 MHz, acetone-d_6) δ: 2.2–2.6 (4H, m), 4.71 (1H, dd, J=4.8, 2 Hz), 7.06 (1H, dd, J=8.3, 2.2 Hz), 7.14 (1H, dd, J=7.81, 1.2 Hz), 7.3 (1H, d, J=2.2 Hz), 7.32 (1H, t, J=7.81 Hz), 7.48 (1H, d, J=8.3 Hz), 7.59 (1H, dd, J=7.81, 1 Hz), 8.77 (1H, s). ¹³C-NMR (75 MHz, acetone-d_6) δ: 30.7, 33.9, 37.5, 118.5, 120.6, 128.8, 128.8, 130.1, 130.7, 130.9, 131.7, 132.3, 134.9, 145.1, 155.4, 197.1. Compound **11a**: ¹H-NMR (300 MHz, acetone-d_6) δ: 2.2–2.6 (4H, m), 5.09 (1H, t, J=8 Hz), 6.69 (1H, dd, J=7.8, 1.4 Hz), 7.13 (1H, dd, J=7.8, 1.2 Hz), 7.17 (1H, t, J=7.8 Hz), 7.33 (1H, t, J=7.8 Hz),

7.47 (1H, dd, J=7.8, 1.4 Hz), 7.61 (1H, dd, J=7.8, 1.2 Hz), 8.77 (1H, s).

4-(3,4-Dichlorophenyl)-7-hydroxy-2-tetralone (14) and 4-(2,3-Dichlorophenyl)-7-hydroxy-2-tetralone (15) To a solution of AlBr₃ (28.4 g, 0.105 mol) in o-dichlorobenzene (30 mL) was added **6d** (4.2 g, 0.026 mol). The resulting solution was stirred at 25°C for 1 week, and then poured onto ice. The resulting mixture was extracted with ether. The organic phase was washed with dilute HCl and then several times with water. The organic solution was subjected to steam distillation to remove solvents and the rest of **6d** (which is soluble in a hot water). After removing of a hot water solution and cooling the residue, a brown solid was isolated to give a mixture of title compounds, **14** and **15** (89 : 11) in 56% overall yield. Recrystallization of the mixture from hexane gave 2.99 g (37%) of **14** as a pale-yellow crystalline product. Compound **14**: mp 93–95°C. ¹H-NMR (500 MHz, CD₃OD) δ: 2.8 (1H, dd, J=16.5, 7 Hz), 2.89 (1H, dd, J=16, 5.5 Hz), 3.45 (1H, d, J=20.5 Hz), 3.64 (1H, d, J=20.5 Hz), 4.43 (1H, t, J=6 Hz), 6.63–6.68 (2H, m), 6.79 (1H, d, J=8 Hz), 7.02 (1H, dd, J=8.5, 2.5 Hz), 7.24 (1H, d, J=2 Hz), 7.42 (1H, d, J=8.5 Hz). ¹³C-NMR (125 MHz, CD₃OD) δ: 43.6, 44.6, 45.2, 115.2, 116.2, 128.9, 130.0, 130.2, 131.1, 131.6, 131.8, 133.5, 136.1, 145.2, 157.9, 211.7. HR-MS Calcd for $C_{16}H_{12}Cl_2O_2$ [M]⁺: 306.0214; Found 306.0210. Compound **15** (fragmentary data were taken from the spectrum of the mixture of products **14** and **15**): ¹H-NMR (500 MHz, CD₃OD): δ: 2.76 (1H, dd, J=16.5, 7 Hz), 2.87 (1H, dd, J=16, 5.5 Hz), 3.54 (1H, d, J=20.5 Hz), 3.7 (1H, d, J=20.5 Hz), 4.92 (1H, dd, J=6.5, 6 Hz). GC-MS [M]⁺: 306.

References and Notes

1) Williams M., Quallich G., *Chem. Ind.*, **10**, 315–319 (1990).
2) Meyer M. D., Hancock A. A., Tietje K., Sippy K. B., Prasad R., Stout D. M., Arendsen D. L., Donner B. G., Carroll W. A., *J. Med. Chem.*, **40**, 1049–1062 (1997).
3) Vukics K., Fodor T., Fischer J., Fellegvary I., Levai S., *Org. Process Res. Dev.*, **6**, 82–85 (2002).
4) Descamps-François C., Yous S., Chavatte P., Audinot V., Bonnaud A., Boutin J. A., Delagrange P., Bennejean C., Renard P., Lesieur D., *J. Med. Chem.*, **46**, 1127–1129 (2003).
5) Kim H., Kim K., Chung Y. K., *J. Org. Chem.*, **71**, 8264–8267 (2006).
6) Souvie J.-C., Blanco I. G., Thominot G., Chapuis G., Horvath S., Damien G., U.S. Patent 7250531 (2007).
7) Lucarini S., Bedini A., Spadoni G., Piersanti G., *Org. Biomol. Chem.*, **6**, 147–150 (2008).
8) Shao L., Wang F., Malcolm S. C., Ma J., Hewitt M. C., Campbell U. C., Bush L. R., Spicer N. A., Engel S. R., Saraswat L. D., Hardy L. W., Koch P., Schreiber R., Spear K. L., Varney M. A., *Bioorg. Med. Chem.*, **19**, 663–676 (2011).
9) Welch W. M., Kraska A. R., Sarges R., Koe B. K., *J. Med. Chem.*, **27**, 1508–1515 (1984).
10) Koe B. K., Weissman A., Welch W. M., Browne R. G., *J. Pharmacol. Exp. Ther.*, **226**, 686–700 (1983).
11) Corey E. J., Gant T. G., *Tetrahedron Lett.*, **35**, 5373–5376 (1994).
12) Quallich G. J., Woodall T. M., *Tetrahedron*, **48**, 10239–10248 (1992).
13) Lautens M., Rovis T., *J. Org. Chem.*, **62**, 5246–5247 (1997).
14) Chen C.-Y., Reamer R. A., *Org. Lett.*, **1**, 293–294 (1999).

15) Quallich G. J., Williams M. T., Friedmann R. C., *J. Org. Chem.*, **55**, 4971–4973 (1990).

16) Guy A., Eur. Patent 346226 (1989).

17) Repinskaya I. B., Koltunov K. Yu., *Sib. Khim. Zh.*, **3**, 73–76 (1993).

18) "Methoden der Organischen Chemie," Vol. 7, 2b, ed. by Thomas H. G., Thieme, Stuttgart, 1976, p. 1710.

19) Koptyug V. A., Andreeva T. P., *J. Org. Chem. USSR*, **7**, 2490–2495 (1971).

20) Repinskaya I. B., Koryabkina N. A., Makarova Z. S., Koptyug V. A., *J. Org. Chem. USSR*, **18**, 754–760 (1982).

21) Repinskaya I. B., Barkhutova D. D., Makarova Z. S., Alekseeva A. V., Koptyug V. A., *J. Org. Chem. USSR*, **21**, 759–767 (1985).

22) Repinskaya I. B., Koltunov K. Yu., Shakirov M. M., Shchegoleva L. N., Koptyug V. A., *Russ. J. Org. Chem.*, **29**, 803–810 (1993).

23) Koltunov K. Yu., Repinskaya I. B., Shakirov M. M., Shchegoleva L. N., Koptyug V. A., *Russ. J. Org. Chem.*, **30**, 88–96 (1994).

24) Koltunov K. Yu., Subbotina E. N., Repinskaya I. B., *Russ. J. Org. Chem.*, **33**, 689–693 (1997).

25) Koltunov K. Yu., Ostashevskaya L. A., Repinskaya I. B., *Russ. J. Org. Chem.*, **34**, 1796–1797 (1998).

26) Olah G. A., Klumpp D. A., "Superelectrophiles and Their Chemistry," Wiley, New York, 2008.

27) Repinskaya I. B., Shakirov M. M., Koltunov K. Yu., Koptyug V. A., *J. Org. Chem. USSR*, **24**, 1719–1727 (1988).

28) Repinskaya I. B., Koltunov K. Yu., Shakirov M. M., Koptyug V. A., *J. Org. Chem. USSR*, **28**, 785–793 (1992).

29) Ostashevskaya L. A., Koltunov K. Yu., Repinskaya I. B., *Russ. J. Org. Chem.*, **36**, 1474–1477 (2000).

30) Koltunov K. Yu., Sobolev V. I., RU Patent 2356883 (2009).

31) Koltunov K. Yu., *Tetrahedron Lett.*, **49**, 3891–3894 (2008).

32) Koltunov K. Yu., Prakash G. K. S., Rasul G., Olah G. A., *Tetrahedron*, **58**, 5423–5426 (2002).

33) Reactions of isomeric 1,3- and 1,4-naphthalenediols with *o*-dichlorobenzene were not studied taking into account their poor reactivity towards comparatively stronger nucleophiles, such as benzene and cyclohexane (see, please, refs. 22–24), whereas the reactivity of 2,6-naphthalenediol was expected to be similar to that of **6d** in analogy to reaction with benzene (ref. 31).

34) Shao L., Wang F., Malcolm S. C., Hewitt M. C., Bush L. R., Varney M. A., Campbell U. C., Engel S. R., Hardy L. W., Koch P., Ma J., Patent W.O., 2007/081542 (2007).

35) Koltunov K. Yu., Prakash G. K. S., Rasul G., Olah G. A., *J. Org. Chem.*, **67**, 4330–4336 (2002).

36) Koptyug V. A., Andreeva T. P., Mamatyuk V. I., *J. Org. Chem. USSR*, **6**, 1859–1864 (1970).

37) Olah G. A., Prakash G. K. S., Sommer J., Molnar A., "Superacid Chemistry," 2nd ed., Wiley, 2009.

38) Smith G. P., Dworkin A. S., Pagni R. M., Zingg S. P., *J. Am. Chem. Soc.*, **111**, 525–530 (1989).

39) Smith G. P., Dworkin A. S., Pagni R. M., Zingg S. P., *J. Am. Chem. Soc.*, **111**, 5075–5077 (1989).

40) Koltunov K. Yu., Prakash G. K. S., Rasul G., Olah G. A., *J. Org. Chem.*, **72**, 7394–7397 (2007).

41) Koltunov K. Yu., Walspurger S., Sommer J., *Chem. Commun.* (Camb.), **15**, 1754–1755 (2004).

42) Koltunov K. Yu., Prakash G. K. S., Rasul G., Olah G. A., *Heterocycles*, **62**, 757–772 (2004).

43) Kamshii L. P., Author's Abstract of Thesis for Candidate of Chemical Sciences, Novosibirsk, 1976.

44) Kamshii L. P., Mamatyuk V. I., Koptyug V. A., *Zh. Org. Khim.*, **10**, 2194–2199 (1974).

45) Welch W. M. Jr., Harbert C. A., Koe B. K., Kraska A. R., U.S. Patent 4556676 (1985).