

The Directing Effect of Annulated Rings in Aromatic Systems

I. Oxidative Coupling of Indanols and Tetrahydronaphthols. Relevance for the Mills-Nixon Effect

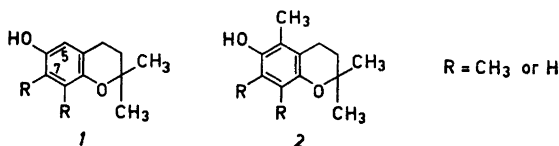
J. LARS G. NILSSON, HANS SELANDER, HANS SIEVERTSSON
and INGER SKANBERG

Department of Organic Chemistry, Faculty of Pharmacy, Box 6804, S-113 86 Stockholm, Sweden

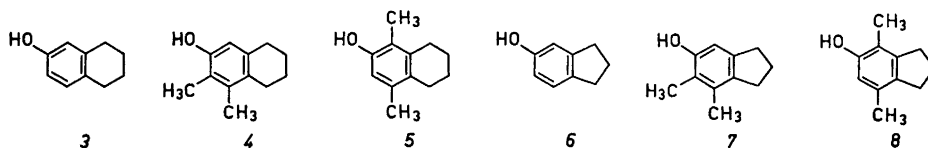
The oxidation of unsubstituted and methyl substituted 5-indanols and 6-tetralols has been studied using alkaline ferricyanide as oxidizing agent. The purpose of the investigation was to determine the influence of an annulated non-aromatic ring on the coupling reaction, *i.e.* to study the Mills-Nixon effect in the oxidative coupling of phenols.

Under the conditions used, no preference for coupling at one of the two possible positions *ortho* to the hydroxyl group was observed. This indicates that an alicyclic five- or six-membered annulated ring has no directing effect, or only a very weak one, on the oxidative coupling. This is in contrast to the behavior of 6-chromanols where the annulated ring exerts a very strong directing effect to the 5-position of the molecule.

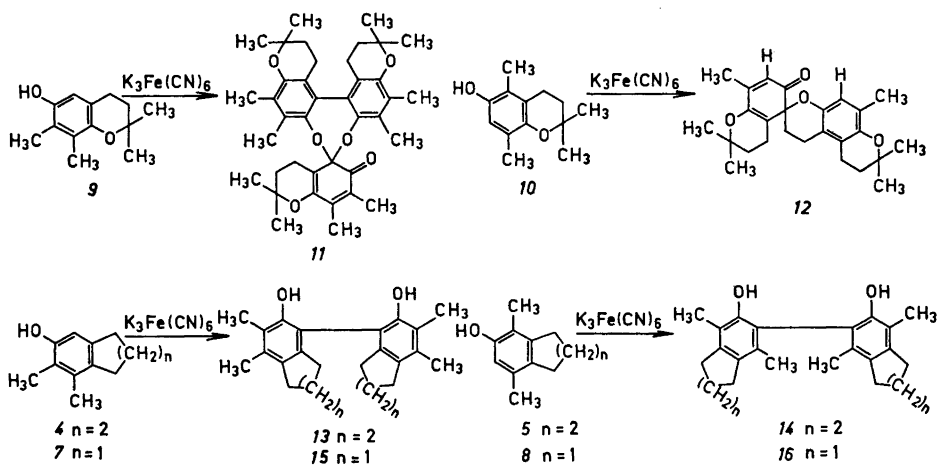
The influence of annulated rings on various reactions of aromatic compounds was brought to our attention during the work on tocopherol (vitamin E) chemistry that has occupied us for some time. During this work, which has recently been reviewed,¹ we observed that the heterocyclic ring in the chromanols of type 1 and 2 exerted a strong directing effect to the 5-position in both electrophilic and oxidative coupling reactions.



In 1930, Mills and Nixon² reported that certain electrophilic substitution reactions of 5-indanol and of 5,6,7,8-tetrahydro-2-naphthol* occurred at only one of the two formally equal positions *ortho* to the hydroxyl group. This phenomenon has later been referred to as the "Mills-Nixon effect". A similar selectivity has been found in electrophilic substitution reactions³⁻⁵ and oxidative coupling⁶ of chromanols related to tocopherols. We were able to show that this directing effect was due to the annulated heterocyclic non-aromatic ring of the chromanol.⁶ To study the effect of other annulated rings we have now oxidized the phenols 3-8 which are chromanol analogues having an alicyclic instead of a heterocyclic non-aromatic ring. Our object was to determine if the annulated rings in these phenols also exert a directing effect in oxidative coupling reactions, *i.e.* show a Mills-Nixon effect.



Indanols and tetralols with three different substitution patterns were chosen for the investigation. We first studied compounds in which both positions *ortho* to the hydroxyl group are unsubstituted (3 and 6) since the



Scheme 1

Scheme 1. Oxidation products of chromanols, indanols and tetralols with analogous substitution pattern in the aromatic rings.

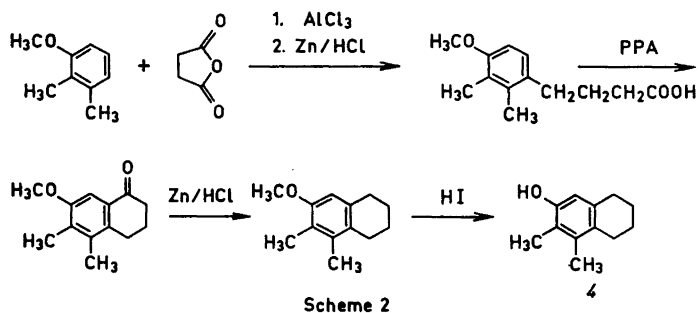
* This nomenclature is in accord with that used by *Chemical Abstracts*. In the following discussion this compound will be referred to as 6-tetralol (*cf.* Ref. 3). Analogous designations are used for the methyl substituted tetrahydro-2-naphthols studied here.

structure of the coupling product of these phenols could reveal a preference for reaction at only one of the two possible *ortho* positions.

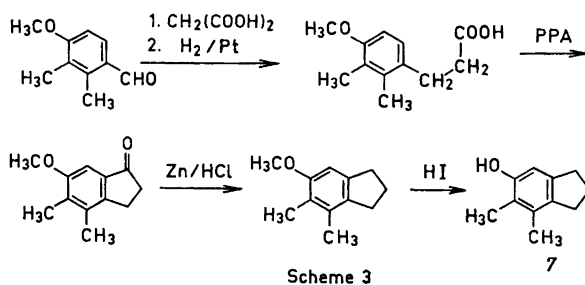
We also studied the oxidation of the two dimethyl-6-tetralols (4 and 5) and the corresponding dimethyl-5-indanols (7 and 8). When the corresponding chromanols 9 and 10⁷ were oxidized with alkaline ferricyanide, coupling occurred only at the 5-position, but two entirely different types of oxidation products were formed.⁸ As shown in Scheme 1, oxidation of 9 gave rise to a spiroketal-trimer 11 while compound 10 formed the spiro dimer 12 under the same conditions. We therefore wanted to determine if similar compounds were formed from phenols having a 5- or a 6-membered alicyclic annulated ring instead of the heterocyclic ring in the chromanols.

SYNTHETIC PROCEDURES

The tetralols 4 and 5, previously described in the literature, were synthesized more conveniently by the method indicated in Scheme 2 for the preparation of 7,8-dimethyl-6-tetralol (4).



The dimethyl-5-indanols 7 and 8 were prepared as shown for 6,7-dimethyl-5-indanol (7) in Scheme 3.

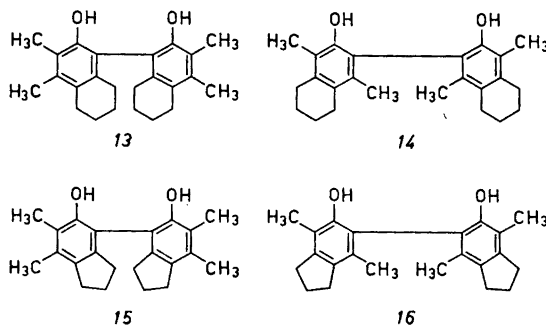


OXIDATION PROCEDURES AND RESULTS

As oxidizing agent we used alkaline ferricyanide, which has been previously extensively used to study tocopherol oxidation.^{1,7} The oxidations were carried out in two-phase systems as previously described,^{8,9} using an aqueous alkaline solution of potassium ferricyanide which was rapidly stirred with an ethereal solution of the phenol. After appropriate reaction times, the products were isolated by preparative TLC.

Oxidation of 6-tetralol (3) and 5-indanol (6) gave almost exclusively oligomeric material. Attempts were made to carry out the reaction in very dilute solutions or with less than one equivalent of potassium ferricyanide, but only the unreacted phenol and oligomeric material could be isolated. Molecular weight determinations indicated pentamers but the structures were not further elucidated.

Oxidation of 7,8-dimethyl-6-tetralol (4) [alicyclic analogue of γ -tocopherol model compound (9) ⁷] with one equivalent of alkaline ferricyanide gave as the major product (43 % yield) a white crystalline compound, m.p. 172–176°, isolated by preparative TLC. Molecular weight determination indicated a dimer. (When excess of the oxidizing agent (3 equivalents) was used, the yield of the dimer was approximately the same. The corresponding indanol 7 (below) gave under these conditions an oligomer.) The IR-spectrum shows an OH-stretching band at 3500 cm^{-1} and the UV-spectrum has λ_{max} (hexane) = 280 (sh) and 287 nm. The NMR-spectrum, which has no peaks ascribable to



aromatic protons, shows a singlet at τ 5.52 (2H) representing two OH-groups. Benzylic protons (8H) appear as a multiplet centered at τ 7.40 (7.20–7.60), aromatic methyl groups give rise to a singlet (12 H) at τ 7.82 and aliphatic ring protons (8H) appear as a multiplet at τ 8.10–8.50. These data are consistent with the formulation of the compound as the biphenyl type 13 formed by C–C coupling at the 5-positions of the molecules. Besides this dimer, a number of other products were formed in low yield, none of which was a spiroketal trimer corresponding to 11. The structures of these byproducts were not studied in detail.

Oxidation of 5,8-dimethyl-6-tetralol (5) [alicyclic analogue of the β -tocopherol model compound (10) ⁷] also gave a dimer in 40 % yield, identified as

compound *14* by its spectral data, presented in Table 1. Three equivalents of the oxidizing agent afforded the same yield of product.

Treatment of 6,7-dimethyl-5-indanol (*7*) with three equivalents of alkaline ferricyanide gave an oligomeric compound (approx. 70 % yield). Molecular weight determination indicated a pentamer. In addition to this, a phenolic compound (IR-stretching band at 3500 cm^{-1}) was isolated in 3 % yield. The same phenol was obtained in 38 % yield when one equivalent of the oxidizing agent was used. The molecular weight indicated a dimer and the UV-spectrum shows λ_{max} (hexane) at 288 nm. The NMR-spectrum which has no peaks ascribable to aromatic proton, shows a broad peak at τ 5.25 (2 H) representing two OH-groups, the benzylic protons, aromatic methyl groups, and aliphatic ring protons together form a multiplet (24 H) at τ 7.0–8.2. A sharp signal representing about 12 H at τ 7.80 in this multiplet is apparently due to aromatic methyl groups. These data are consistent with structure *15* for this dimer.

4,7-Dimethyl-5-indanol (*8*) also gave mainly oligomeric material when oxidized with three equivalents of potassium ferricyanide. Molecular weight determination indicated an octamer. When one equivalent of the oxidizing agent was used, a phenolic compound identified as the biphenyl dimer *16* was isolated in 42 % yield. The structure determination is based on the molecular weight and the spectral data presented in Table 1.

DISCUSSION OF THE RESULTS

Homolytic oxidation of monohydric phenols forms dimers, trimers, or polymers as the most important reaction products. This reaction occurs *via* radical coupling *ortho* and *para* to the hydroxyl group. Benzylic coupling can occur when all the *ortho* and *para* positions are substituted. Oxidative coupling of chromanols was found to be an exception to this general rule.¹ As indicated above very little polymeric material was formed, and a strong preference for coupling at only one (the 5-position) of the two possible *ortho* positions was evident.

Oxidation of 2,2,7,8-tetramethyl-6-chromanol (*9*), model compound of γ -tocopherol, gave the spiroketal trimer *11* in good yield by C–C and C–O coupling at the 5-position. Similar oxidation of the corresponding tetralol *4* or indanol *7*, both with the same aromatic methyl substitution pattern as *9*, gave the simple dimers *13* and *15*, respectively, formed by C–C coupling.

Oxidation of the β -tocopherol model *10* gave the spiro dimer *12* by benzylic type coupling involving the 5-methyl group. Similar oxidation of the corresponding tetralol *5* or indanol *8*, both alicyclic analogues of the β -tocopherol model *10*, gave the simple dimers *14* and *16*, respectively, formed by C–C coupling at the 7-positions of the molecules. No reaction products formed by coupling *via* the 5-methyl groups were detected.

The results obtained here indicate that the strong directing effect seen in 6-chromanols in both electrophilic substitution and oxidative coupling is less pronounced or not present in coupling reactions of bicyclic phenols with alicyclic annulated rings. It appears that the ring oxygen in the chromanols is the cause of the unusual coupling reactions that these compounds undergo,

Table 1. Physical constants for oxidation products of the studied indanols and tetralols.

Compound	Formula	Yield %	M.p. °C	Mol. Wt. Found/ Calc.	UV λ_{max} (hexane) (nm)	IR KBr disc cm^{-1}	NMR. τ -values ^a			
							OH	Benzylic	Aromatic methyl groups	Aliphatic ring protons
13	$\text{C}_{24}\text{H}_{30}\text{O}_2$	43	172—176	372/350	287 280 (sh)	3500	5.52 (s,2)	7.20—7.60 (m,8)	7.82 (s,12)	8.10—8.50 (m,8)
14	$\text{C}_{24}\text{H}_{30}\text{O}_2$	40	223—226	372/350	285 277 (sh)	3500	5.45 (s,2)	7.10—7.60 (m,8)	7.90 (s,6) 8.20 (s,6)	8.10—8.40 (m,8)
15	$\text{C}_{22}\text{H}_{28}\text{O}_2$	38	172—173	338/322	288	3500	5.25 (s,2)	b	7.80 b (12H)	b
16	$\text{C}_{22}\text{H}_{28}\text{O}_2$	42	227—230	347/322	286	3500	5.38 (s,2)	6.90—7.35 (m,8)	7.85 c 8.15	c

^a Sample in CDCl_3 -solution.^b Benzylic protons, aromatic methyl groups and aliphatic ring protons form together a multiplet at τ 7.0—8.2. See text.^c Multiplet due to the aliphatic ring protons overlap with one of the singlets of the aromatic methyl groups. Aromatic methyl groups and aliphatic ring protons integrate to 16 H.

by influencing both the type of product formed and also the preference for reaction at only one of the two *ortho* positions.

The yields of the dimers 13–16 (see Table 1) indicate that coupling can take place at either the 5- or the 7-position regardless of whether the annulated alicyclic ring is five or six membered. According to the findings of Mills and Nixon,² electrophilic substitution of these phenols occurs at the 5-position of 6-tetralol (3) and at the 6-position of 5-indanol (6). Such effects do not seem to be as strong in oxidative coupling of these phenols as for the chromanols. It is also noteworthy that microsomal hydroxylation of 6-tetralol yields 6,7-dihydroxytetralin and that 5,6-dihydroxytetralin was not found as a metabolite.¹⁰ Studies of the directing effect of other annulated rings are in progress.

EXPERIMENTAL

General comments. Infrared spectra were measured on a Perkin-Elmer 237 spectrophotometer, and ultraviolet absorptions were measured on a Bausch & Lomb Spectronic 505 spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian Associates A 60 instrument, using CDCl₃-solutions. The chemical shifts are expressed in τ units relative to tetramethylsilane. Molecular weights were determined with a Hitachi Perkin-Elmer model 115 Molecular Weight Apparatus using benzene as solvent. Thin layer chromatography was performed using silica gel G plates of 0.3 mm (analytical) and 1 mm (preparative) thickness. The plates were activated by heating at 130° for 1.5 h and were stored in a dry cabinet until used. 6-Tetralol and 5-indanol were commercially available.

Preparation of 5,6,7,8-tetrahydro-3,4-dimethyl-2-naphthol (4)

3-(4-Methoxy-2,3-dimethylbenzoyl)propionic acid. This compound was prepared in quantitative yield from 2,3-dimethylanisole and succinic anhydride using the procedure described by Fieser and Hershberg.¹¹ The crude product had m.p. 169–171° and after crystallization it melted 173–174°. (Lit.¹² 174°).

4-(4-Methoxy-2,3-dimethylphenyl)butyric acid. The method for Clemmensen reduction described by Martin¹³ was used with some modifications. The above acid (50 g; 0.21 mole), amalgamated zinc (100 g; 1.5 mole), concentrated HCl (175 ml), water (75 ml), and toluene (100 ml) were stirred under reflux for 1.5 h. A further 100 ml of concentrated HCl was added and the mixture was refluxed and stirred overnight. While still hot it was decanted from residual zinc and then cooled, when the organic acid precipitated. It was extracted into ether, and the water layer was extracted once more with ether. The organic extracts were dried (Na₂SO₄) and the ether was evaporated. When the residual toluene solution was left overnight at 0°, 36 g (77 %) of the desired compound crystallized, m.p. 119–120° (Lit.¹² 119–120°).

1-Keto-7-methoxy-5,6-dimethyl-1,2,3,4-tetrahydronaphthalene. A mixture of the above butyric acid (10 g) and polyphosphoric acid¹⁴ (100 g) was rapidly stirred at 60° for 15 min. The red viscous solution was then poured into crushed ice (200 g) and stirred until all the ice had melted. The white precipitate was extracted into ether which was washed with water (2 × 50 ml), with saturated NaHCO₃-solution (50 ml), again with water, dried (Na₂SO₄) and evaporated. This yielded 8.3 g (90 %) of the ketone, m.p. 76–78° (Lit.¹² 78–79°).

7-Methoxy-5,6-dimethyl-1,2,3,4-tetrahydronaphthalene was prepared by Clemmensen reduction of the above ketone using the method described by Martin.¹³ The crude product (75 % yield) melted 57–63° (Lit.¹² 65°) and was used in the next step without further purification.

5,6,7,8-Tetrahydro-3,4-dimethyl-2-naphthol (4). A mixture of the above ether (5 g), acetic acid (25 ml), and hydroiodic acid (8.3 g; 57 %) was gently refluxed for 2 h. After

cooling, it was diluted with water and extracted with ether. The ether extract was washed with water (5 × 50 ml), with saturated NaHCO₃-solution (50 ml), with Na₂S₂O₃-solution, dried (Na₂SO₄) and evaporated. The crystalline residue (4.4 g; 95 %) melted at 95–105°. After sublimation and crystallization from light petroleum/ether it melted at 114–115° (Lit.¹² 114–115°), λ_{\max} (hexane) 278, 283 and 287 nm; ν_{\max} (KBr) 3350 cm⁻¹ (OH). NMR: singlet at τ 3.67 (1 H, ArH), multiplet at τ 7.15–7.60 (4 H, ArCH₂-), singlet at τ 7.86 (6 H, ArCH₃) and multiplet at τ 8.0–8.40 (4 H, aliphatic ring protons).

Preparation of 5,6,7,8-tetrahydro-1,4-dimethyl-2-naphthol (5)

This phenol was prepared as described for 4. It has previously been prepared by Fieser and Lothrop¹⁵ using a different route. The overall yield obtained here from 2,5-dimethylanisol was 27 %, m.p. 104–105° (Lit.¹⁵ 104–105°). λ_{\max} (hexane) 276, 282 and 286 nm. ν_{\max} (KBr) 3350 cm⁻¹ (OH). NMR: singlet at τ 3.59 (1 H, ArH), multiplet at τ 7.30–7.70 (4 H, ArCH₂-) singlets at τ 7.90 and 7.94 (altogether 6 H, ArCH₃) and multiplet at τ 8.15–8.45 (4 H, aliphatic ring protons).

Preparation of 6,7-dimethyl-5-indanol (7)

4-Methoxy-2,3-dimethylcinnamic acid was prepared from 4-methoxy-2,3-dimethylbenzaldehyde¹⁶ and malonic acid in 90 % yield as described for 3,4,5-trimethoxycinnamic acid,¹⁷ m.p. 225–227° (from ethanol). (Found: C 70.0; H 6.83. Calc. for C₁₂H₁₄O₃: C 69.9; H 6.86). ν_{\max} (KBr) 1665 cm⁻¹ (C=O), 1610 cm⁻¹ (C=C).

3-(4-Methoxy-2,3-dimethylphenyl)propionic acid. The cinnamic acid above (20 g; 0.097 mole) in ethanol (150 ml) was hydrogenated in a Parr apparatus using platinum as catalyst and an initial pressure of 3 kg/cm². After the theoretical amount of hydrogen had been consumed the mixture was filtered through Celite, the solvent was removed *in vacuo* and the residue was recrystallized from ligroin to yield 17.5 g (87 %) of the acid, m.p. 124–126°. (Found: C 69.4; H 7.41. Calc. for C₁₂H₁₆O₃: C 69.2; H 7.74). ν_{\max} (KBr) 1700 cm⁻¹ (C=O).

6-Methoxy-4,5-dimethylindanone was prepared from the propionic acid using the method described above for 7-methoxy-5,6-dimethyltetralinon. The crude indanone (96 % yield) was used in the next step without purification. A small sample was crystallized from ligroin for analysis, m.p. 144–145.5°. (Found: C 75.7; H 7.15. Calc. for C₁₂H₁₄O₂: C 75.8; H 7.43). ν_{\max} (KBr) 1685 cm⁻¹ (C=O).

5-Methoxy-6,7-dimethylindane was prepared by Clemmensen reduction of the indanone using the method described by Martin.¹³ The compound was purified by distillation, b.p. 100–102° (2.5 mm), m.p. 37.5–39°. (Found: C 81.6; H 9.22. Calc. for C₁₂H₁₆O: C 81.8; H 9.17). ν_{\max} (KBr) 2630 cm⁻¹ (OCH₃), no C=O absorption.

6,7-Dimethyl-5-indanol (7) was prepared by cleavage of the above ether using hydriodic acid as described for 4. The phenol was obtained in 72 % yield, m.p. 126–128° (from light petroleum). (Found: C 81.0; H 8.70. Calc. for C₁₁H₁₄O: C 81.4; H 8.70). λ_{\max} (hexane) 283 nm. ν_{\max} (KBr) 3300 cm⁻¹ (OH). NMR: singlet at τ 3.50 (1 H, ArH), multiplet at τ 7.0–7.4 (4 H, ArCH₂-) and multiplet at τ 7.75–8.10 (8 H, ArCH₃ and aliphatic ring protons). A sharp peak in the latter multiplet (approx. 6 H) at τ 7.85 is apparently due to the aromatic methyl groups.

Preparation of 4,7-dimethyl-5-indanol (8)

This phenol was prepared as described for 7. The compound has previously been prepared by Fieser and Lothrop¹⁵ using a different route. The overall yield in our synthesis from 4-methoxy-2,5-dimethylbenzaldehyde was 25 %, m.p. 110–112° (from light petroleum). (Lit.¹⁵ 111–112°) λ_{\max} (hexane) 283 nm. ν_{\max} (KBr) 3300 cm⁻¹ (OH). NMR: singlet at τ 3.60 (1 H, ArH), multiplet at τ 7.0–7.4 (4 H, ArCH₂-), and multiplet at

τ 7.65–8.15 (8 H, ArCH₃ and aliphatic ring protons). Two sharp peaks in the latter multiplet (together approx. 6 H) at τ 7.85 and 7.88 are apparently due to the aromatic methyl groups.

Oxidative procedures

The oxidations were carried out as previously described for the oxidation of the β -model compound 10,⁸ using ether as the organic solvent. The products were isolated by preparative TLC using ether/light petroleum mixtures as solvent and recrystallized from light petroleum. The structure of each compound described is assigned on the basis of molecular weight determinations and its characteristic spectral properties (Table 1).

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