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Directive Effects in the Bromination of Bicyclic Phenols

Relevance for the Mills-Nixon Effect*

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Bromination of 3,4-dimethylphenol and of some other related bicyclic phenols (*3*–*8*) has been studied. It was shown that most annulated non-aromatic rings favour bromination in the ar-β positions, with the exception of six-membered annulated rings which facilitate substitution in the ar-α position of the molecule (Scheme 1). It has further been shown that the oxygen-heterocyclic ring of 6-chromanol has a greater directing influence than the alicyclic annulated ring in 6-tetralol.

The results also indicate that large annulated rings, *viz.* seven-membered or larger, have a directing influence on substitution.

The reactivity of reduced benzocycloalkenes towards electrophilic reagents has attracted considerable attention. Much of this work has been inspired by the classical paper by Mills and Nixon,[1] where they report that 5-indanol (*3*) is substituted preferentially in position 6, *i.e.* in the β-position to the non-aromatic ring (ar-β), and that 6-tetralol (*4*) is similarly substituted in the ar-α position. This preference for reaction at only one of the two positions *ortho* to the hydroxyl group is known as the Mills-Nixon effect.

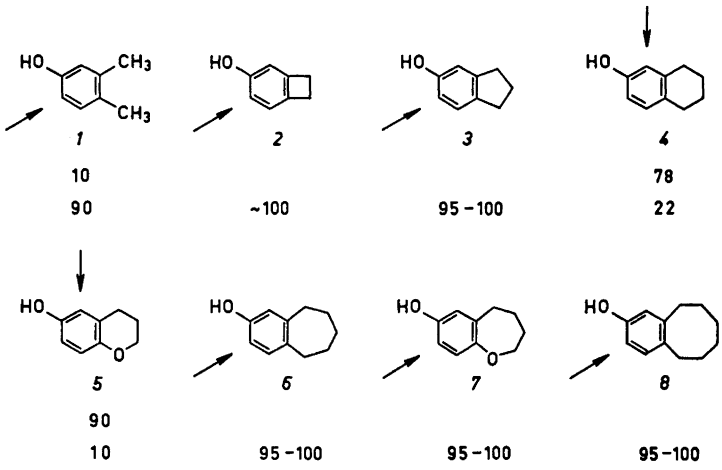
Much of the work in this field has been carried out with unsubstituted indane and tetralin, and its purpose has been the confirmation or invalidation of the Mills-Nixon effect. Extensive reviews covering the nearly work have been written by Bertier and Pullman [2] and by Badger.[3]

Electrophilic substitution reactions in unsubstituted indane and tetralin show only very moderate differences in reactivity between the ar-α and ar-β positions. [2,3] Investigations by Vaughan *et al.* [4,5] even indicate that the ar-β-carbons are the most reactive positions in both indane and tetralin. However, Bassindale *et al.*[6] have recently demonstrated in a kinetic study of the protodesilylation of *o*-xylene, indane, and tetralin that these compounds react as could be predicted according to the Mills-Nixon effect.

* Part V of The Directing Effect of Annulated Rings in Aromatic Systems. Part IV: Nilsson, J. L. G. and Selander, H. *Acta Chem. Scand.* **24** (1970) 2885.

The original work by Mills and Nixon [1] on substitution of 5-indanol (*3*) and 6-tetralol (*4*) as well as subsequent studies on these and similar bicyclic phenols [7–10] demonstrate that electrophilic substitutions occur predominantly at only one of the two positions *ortho* to the hydroxyl group. These observations may be interpreted as an enhancement of the inherent directing effect of the annulated ring due to the hydroxyl group. 5-Indanol (*3*) and 6-tetralol (*4*) and other similar ar-β substituted bicyclic compounds should therefore be more suited for qualitative studies of the directing effect of annulated rings than their unsubstituted analogues.

In order to ascertain if annulated rings larger than six-membered ones exert a directing effect in aromatic systems, and to relate this effect to that of smaller rings, we have determined the product distribution from the bromination of the phenols *1* and *3-8* in Scheme 1. The mechanism of this reaction has been determined by Yeddanapalli and Gnanapragasam.[11]



Scheme 1. Bromination of 3,4-dimethylphenol and related phenols.

The two heterocyclic phenols *5* and *7* were included to get a comparison between the effects of carbocyclic and oxygen-heterocyclic non-aromatic rings. The benzocyclobutenol *2* was not studied here, mainly because this bicyclic system is known to give only ar-β substitution [12–14] (as indicated by the arrow in formula 2, Scheme 1), and also because the four-membered ring may easily open to give unexpected by-products.[15] 3,4-Dimethylphenol can be considered as an open analogue of the compounds with a carbocyclic annulated ring. Bromination of this compound has been investigated by other workers,[16] but the product distribution has not previously been determined.

BROMINATION REACTIONS AND RESULTS

The brominations were carried out in carbon tetrachloride solution at 0°, using one equivalent of bromine, and the products were isolated by preparative

TLC. By this technique and by GLC, the monobrominated products from *1*, *4* and *5* were separated into the two isomeric bromophenols, and their relative amounts were determined. The monobrominated products from *3*, *6*, *7*, and *8* appeared to be homogeneous on the thin layer plates thus indicating that only one of the two isomeric bromophenols had been formed. However, using the independently synthesized 4-bromo-5-indanol and 6-bromo-5-indanol, we found that mixtures of these phenols could not be separated by TLC or GLC although several solvent systems and gas chromatography columns were tested. It turned out that the relative amounts of the two compounds in a mixture could be determined by NMR spectroscopy, since their spectra show significant differences. In the spectrum of 4-bromo-5-indanol the two aromatic protons show an AB-pattern centered at $\delta = 6.92$ ppm (peaks at 7.11, 6.98, 6.86, and 6.73 ppm), while the two corresponding protons in 6-bromo-5-indanol appear as two singlets at $\delta = 7.22$ and 6.85 ppm. An NMR-spectrum of a mixture of the two compounds can thus be used to determine the relative amounts of the compounds. We estimate that 5 % of 4-bromo-5-indanol in 6-bromo-5-indanol can be detected by this technique. We also assume that the aromatic protons in the two possible mono-bromo derivatives of *6*, *7*, and *8* would give rise to similar patterns as those of the bromoindanols, hence the same technique was used to study the product distribution of these compounds. The results of the reactions are summarized in Scheme 1, and the physical data of the bromophenols formed are collected in Table 1.

3,4-Dimethylphenol was brominated in both the 2- and the 6-positions. The ratio of the 2-bromo- to the 6-bromophenol (ar-α/ar-β) was determined by TLC and GLC to 1/9. The steric hindrance of position 2 and the presence of a methyl group *para* to position 6 are the apparent reasons for the higher reactivity of the ar-β position.

The mono-bromo derivatives of 5-indanol (*3*) and of the phenols with large annulated rings (*6* – *8*) could not be separated by TLC and GLC, and the reaction mixtures were therefore analyzed by NMR spectroscopy as described above. The aromatic protons in all the bromo derivatives from these phenols appear in the spectra as two singlets (Table 1), thus indicating ar-β substitution. The spectra show no signals that would indicate an ar-α substitution. The products also have sharp melting points. We therefore conclude that bromination has occurred to at least 95 % in the ar-β positions of these phenols, as indicated by the arrows in Scheme 1.

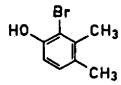
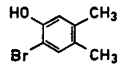
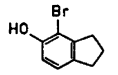
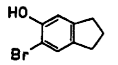
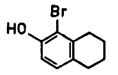
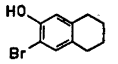
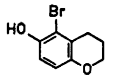
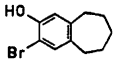
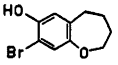
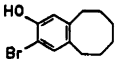
Phenols with six-membered annulated rings are brominated preferentially in the ar-α positions, in contrast to all the other bicyclic phenols in Scheme 1. The ratio ar-α/ar-β is approximately 4/1 in tetralol (*4*), where the non-aromatic ring is alicyclic, and 9/1 in chromanol, which has an oxygen-heterocyclic ring. The two mono-bromo derivatives of *4* and *5* were isolated by TLC and their structure determined by their characteristic spectral data.

DISCUSSION OF THE RESULTS

The results of this investigation allow some conclusions to be drawn.

A non-aromatic annulated ring of a bicyclic aromatic compound exerts a directing influence on electrophilic substitution in the aromatic nucleus.

Table 1. Physical data for the bromophenols prepared.

Compound	Formula	M.p. °C	NMR δ-values [a]				Mass-spectrum M^+
			OH	Aromatic	Benzylic	Aliphatic	
	C_8H_9BrO	*b*	5.48	6.87 [c] (q,2)	*d*	—	
	C_8H_9BrO	77–79	5.15	7.12 (s,1) 6.73 (s,1)	*e*	—	
	C_9H_9BrO	73–74	5.34	6.92 [f] (q,2)	3.2–2.7 (t,4)	2.4–1.8 (m,2)	
	C_9H_9BrO	36–37	5.37	7.22 (s,1) 6.85 (s,1)	3.10–2.6 (t,4)	2.4–1.8 (m,2)	
	$C_{10}H_{11}BrO$	75–76	5.63	6.85 [g] (q,2)	2.8–2.4 (m,4)	1.9–1.5 (m,4)	
	$C_{10}H_{11}BrO$	45–47		7.22 (s,1) 6.79 (s,1)	2.8–2.5 (m,4)	1.9–1.5 (m,4)	
	$C_9H_9BrO_2$	117–118	5.20	6.78 [h] (q,2)	2.9–2.6 (t,2)	2.3–1.9 [i] (m,2)	230 (95 %) [j] 228 (100 %)
	$C_{11}H_{13}BrO$	54–55	5.30	6.76 (s,1) 7.16 (s,1)	2.9–2.5 (m,4)	2.0–1.4 (m,6)	239 (100 %) 241 (96 %)
	$C_{10}H_{11}BrO_2$	85–88		6.75 (s,1) 7.08 (s,1)	2.9–2.5 (m,4)	2.2–1.5 [k] (m,4)	242 (85 %) 244 (83 %)
	$C_{12}H_{15}BrO$	67–68	5.30	6.78 (s,1) 7.18 (s,1)	2.9–2.5 (m,4)	2.0–1.2 (m,8)	254 (100 %) 256 (97 %)

[a] Sample in $CDCl_3$-solution.
[b] B.p. 100°/10 mm. Liquid at room temp.
[c] AB-pattern; peaks at δ=7.05, 6.92, 6.82 and 6.68 ppm.
[d] Aromatic methyl groups at δ=2.35 (s,3) and 2.25 (s,3) ppm.
[e] Aromatic methyl groups at δ=2.15 (s,6) ppm.
[f] AB-pattern; peaks at δ=7.10, 6.97, 6.87 and 6.73 ppm.
[g] AB-pattern; peaks at δ=7.00, 6.88, 6.82 and 6.70 ppm.
[h] AB-pattern; peaks at δ=6.96, 6.79, 6.77 and 6.60 ppm.
[i] Multiplet at 4.3–3.9 ppm (2H) due to Ar–O–CH_2.
[j] 7-Bromo-6-chromanol (2 mg isolated) had the same molecular ion.
[k] Multiplet at 4.2–3.3 ppm (2H) due to Ar–O–CH_2–.

This effect is dependent on the size of the annulated ring. While most rings favour ar-β substitution, a six-membered annulated ring facilitates substitution in the ar-α position of the molecule (Scheme 1). Comparison of our results with previously reported data indicate that the directing effect is enhanced by the presence of an electron donating ar-β substituent in the aromatic ring. A possible explanation of this has been discussed by Vaughan *et al.*[4] and by Bassindale *et al.*[6]

Comparing aromatic compounds with different six-membered annulated rings, it is apparent that the oxygen-heterocyclic ring in chromanol (*5*) has a stronger directing effect than the alicyclic ring in tetralol (*4*). Since the steric hindrance of position 5 in *4* and *5* is likely to be very similar, the stronger directing effect observed in *5* is apparently an inherent property of the heterocyclic ring. A similar difference between chromanol and tetralol derivatives has previously been observed in oxidative coupling of such phenols.[17] No difference in reactivity was observed in the bromination of *6* and *7*.

Large annulated rings seem to have a directing influence on substitution. No ar-α products were detected in the reaction mixture from the bromination of *6*, *7*, and *8*, while 10 % of ar-α substituted 3,4-dimethylphenol was isolated. Since position 2 in this phenol presumably is more sterically hindered[10] than the ar-α positions of *6*, *7*, and *8*, the results seem to indicate a directing influence by large annulated rings (seven-membered or larger) on the substitution reaction. Since large rings are attached to benzene without any strain,[18,19] the directing effect is probably exerted in the transition state and not when the molecule is in the ground state. This has been suggested by Vaughan *et al.*[4] in their work on the substitution of indane, and also by Bassindale *et al.*[6] in their report on protodesilylation of the same compounds. The directing effect by large annulated rings is under further investigation, using other experimental techniques.

EXPERIMENTAL

General comments. Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. Infrared spectra were measured with a Perkin-Elmer 237 spectrophotometer, and nuclear magnetic resonance spectra were measured in $CDCl_3$ solutions with a Varian Associates A 60 instrument. Chemical shifts are expressed in ppm relative to tetramethylsilane ($\delta_{TMS} = 0.00$ ppm). Mass spectra were obtained using an LKB 9000 instrument at 70 eV. Thin layer chromatography was performed as previously described.[9] Gas chromatography was performed using a Varian Aerograph 2100 instrument with a 6′ × 1/8″ internal diameter glass column filled with 3 % J × R on GasChrom Q, 100 – 200 mesh. A number of other columns were also used, as indicated above.

3,4-Dimethylphenol (*1*), 5-indanol (*3*), and 6-tetralol (*4*) were commercially available. 6-Chromanol[20] (*5*), 6,7,8,9-tetrahydro-2-hydroxy-5H-benzocycloheptene[21] (*6*), and 5,6,7,8,9,10-hexahydro-2-hydroxybenzocyclooctene[21] (8) were prepared following the literature procedures.

Synthesis of 2,3,4,5-tetrahydro-7-hydroxy-1-benzoxepin (*7*) (7-hydroxyhomochroman)

2,3,4,5-Tetrahydro-1-benzoxepin. 2,3,4,5-Tetrahydro-5-oxo-1-benzoxepin[22] (35 g; 0.22 mol) in toluene (100 ml) was added to amalgamated zinc (100 g), concentrated HCl (175 ml) and water (75 ml), and the mixture was stirred and refluxed overnight. After

cooling, the liquid layer was decanted from residual zinc, the toluene layer was separated and the aqueous layer extracted with ether. The combined organic extracts were washed with water, with saturated $NaHCO_3$-solution, dried (Na_2SO_4) and evaporated. The oily residue was distilled to yield 20 g (61 %) of tetrahydrobenzoxepin, b.p. 104 – 106°/19 mm. The compound has previously been prepared by another route,[23] reported b.p. 102°/18 mm. The NMR-spectrum of the compound was in agreement with that reported by Schweizer *et al.*[24]

2,3,4,5-Tetrahydro-7-nitro-1-benzoxepin. 2,3,4,5-Tetrahydro-1-benzoxepin (18 g; 0.12 mol) was slowly added with stirring to 60 % nitric acid (100 ml) while the temperature was kept below 5° by external cooling. When the addition was complete, the mixture was kept at room temperature for 20 min and then poured into 500 ml of ice water. It was then extracted with ether, the extract was washed with water, with saturated $NaHCO_3$-solution, dried (Na_2SO_4) and evaporated. The residue was distilled affording 13 g (56 %) of the nitrobenzoxepin, b.p. 142 – 145°/1 mm. (Found: C 62.4; H 5.81; N 7.22. Calc. for $C_{10}H_{11}NO_3$: C 62.2; H 5.74; N 7.25.)

2,3,4,5-Tetrahydro-7-amino-1-benzoxepin. An ethanolic solution of the above nitro compound (11 g; 0.057 mol) was hydrogenated over Raney-Ni W-2 at room temperature in a Parr apparatus with an initial pressure of 3 kg/cm² until the theoretical amount of hydrogen had been consumed. The catalyst was filtered off, most of the ethanol was evaporated *in vacuo*, and the residue was dissolved in ether. HCl-gas was then introduced to precipitate the amine hydrochloride, which was recrystallized from ethanol-ether to yield 7.2 g (63 %) of the pure compound, m.p. 215 – 220° (dec.). (Found: C 59.7; H 7.39; N 6.85. Calc. for $C_{10}H_{13}NO \cdot HCl$: C 60.2; H 7.07; N 7.02.)

2,3,4,5-Tetrahydro-7-hydroxy-1-benzoxepin (7). The above amine hydrochloride (7 g; 0.035 mol) was dissolved in phosphoric acid (150 ml; 1.5 mol), and sodium nitrite (3.1 g; 0.045 mol) in water (25 ml) was slowly added at 0°. The solution was then kept at that temperature for 2 h, 2.5 g of urea was added to decompose excess of nitrite, and the mixture was heated to 90° for 30 min to convert the diazonium salt to phenol. After cooling, the phenol was extracted into ether, the extract dried (Na_2SO_4) and evaporated. The brown residue was placed on a column of silica gel (100 g) which was eluted with portions of ether/light petroleum of increasing polarity. The phenol was eluted with 500 ml of ether/light petroleum (3:10), affording 2.4 g (42 %) of a white compound, m.p. 83 – 84° (from ligroine). (Found: C 72.8; H 7.01. Calc. for $C_{10}H_{12}O_2$: C 73.1; H 7.37.) ν_{max} (KBr) = 3400 cm^{-1} (OH). NMR: δ = 6.80 – 5.80 ppm (m,3H,Ar*H*); 5.15 ppm (broad, 1H,O*H*); 3.90 – 3.65 ppm (t,2H,Ar – O – C*H*₂ –); 2.70 – 2.40 ppm (m,2H,Ar – C*H*₂ –), and 2.10 – 2.40 ppm (m,4H,aliphatic ring protons). MS: *m/e* 164 (100 %, M^+), 136 (13 %), 135 (15 %), 134 (17 %), 123 (54 %), 122 (26 %), 121 (20 %), 107 (48 %), 94 (91 %), 91 (20 %), 79 (39 %), 77 (59 %), 67 (30 %), 66 (48 %), and 65 (43 %).

Bromination reaction

The appropriate phenol (1 mM) was dissolved in CCl_4 (25 ml), containing 2 % diethyl-ether. (The ether addition was necessary to bring some of the phenols into solution.) The solution was cooled to 0°, and 1 mmol of bromine in CCl_4 (1 ml) was added all at once, and the solution kept at 0° until the bromine colour had disappeared. The solvent was evaporated *in vacuo* and the residue subjected to preparative TLC in ether/light petroleum 1:10. The plates were generally developed three consecutive times in this solvent and the edges of the plates were sprayed with Gibbs' reagent.[25] The bands were removed separately from the plates, eluted with ether, and the solvent evaporated under a stream of nitrogen. The yields of monobrominated products, thus determined, was 90 – 100 %. The structure of each compound was assigned on the basis of its melting point and characteristic spectral data (Table 1). The amount of each bromophenol was determined by weighing the isolated pure compound, and the relative amounts of the two bromophenols were also determined by GLC. The mixtures of mono-bromo derivative of *3* and of *6 – 8* were isolated by TLC and analyzed by NMR as described above.

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