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THE DIRECTING EFFECT OF ANNELATED RINGS IN AROMATIC SYSTEMS—XI

BROMINATION OF BICYCLIC PHENOLS WITH HETEROCYCLIC ANNELATED RINGS*

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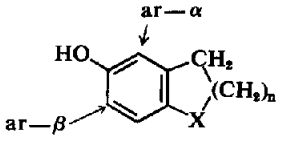
Abstract—Bicyclic phenols of type 1 with annelated rings containing a N or an O heteroatom (X = N or O) as well as the ring opened analogs have been brominated and the product distribution determined. The results indicate that while most annelated rings have a directing effect to the ar-β position of the molecule, a 6-membered annelated ring is an exception and it facilitates substitution in the ar-α position.

Bromination studies[1] of bicyclic phenols (1; X = CH_2; n = 0–4) have revealed, that most annelated nonaromatic rings have a directing effect to the ar-β position of the molecule with exception of a 6-membered annelated ring (1; X = CH_2; n = 2) which facilitates substitution in the ar-α position.



1

From the bromination of 1,2,3,4-tetrahydro-1-methyl-6-quinolinol hydrochloride (1; X =  , n = 2), however, only the ar-β brominated compound 7-bromo-1,2,3,4-tetrahydro-1-methyl-6-quinolinol could be isolated.[2] Considerable amounts of oxidation products were formed in this reaction but the result may still indicate that the non-aromatic ring of this 6-quinolinol derivative with a positively charged nitrogen, has a directing effect to the ar-β position and not to the ar-α position like the 6-membered rings of 6-tetralol (1; X = CH_2; n = 2). To study more extensively this phenomenon we decided to brominate phenols with heterocyclic annelated rings. The compounds chosen and the product distribution in the bromination reaction are shown in Scheme 1. We have previously observed that *p*-aminophenols only form oxidation products

*Part X: See Ref 2.

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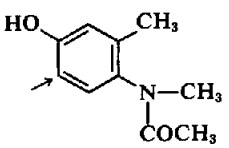
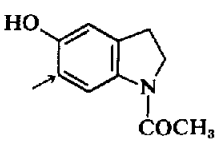


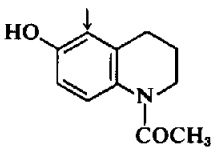
2

% ar-α 60
% ar-β 40



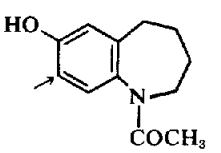
3

0
100



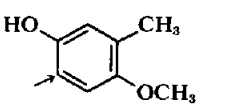
4

100
0



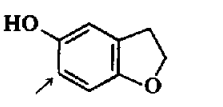
5

0
100



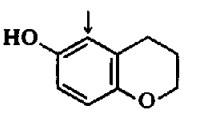
6

% ar-α 0
% ar-β 100



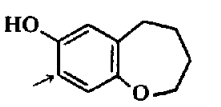
7

0
100



8

90
10



9

0
100

SCHEME 1. Product distribution in the bromination reaction.

upon bromination.[2] The corresponding N-acetyl derivatives was therefore used in this study.

The compounds **2–9** were prepared in a straight forward manner as described in the Experimental. Compound **2** has three Me groups, which in the NMR spectrum give rise to three separate singlets at $\delta = 2{\cdot}96$, 2·03 and 1·60 ppm, respectively. To elucidate the chemical shifts of these Me groups, 4-(N-methyl-d_3-acetamido)-3-methylphenol was prepared and its NMR spectrum recorded. This spectrum has no peak at $\delta = 1{\cdot}60$ ppm thus establishing the shift of the acetyl protons. The peaks due to the $\rangle NCH_3$ and the $ArCH_3$ groups could be assigned at 2·96 and 2·03 ppm, respectively, by comparison of the spectrum of **2** with that of 4-(N-methylacetamido)-phenol.[3]

Bromination reactions and results. The phenols **2–9** were brominated in CCl_4 solution using one equivalent of bromine as described.[1] The sites of bromination in the phenols are indicated by the arrows in Scheme 1. Bromination of 4-(N-methylacetamido)-3-methylphenol (**2**) (the ring opened analog) gave a mixture of two monobromo derivatives with very similar polarity. The compounds were identified as 4-(N-methylacetamido)-2-bromo-3-methylphenol (**10**) and 4-(N-methylacetamido)-6-bromo-3-methylphenol (**11**) by NMR and mass spectrometry. The two aromatic protons of **10** gave rise to an AB-pattern separated from the two singlets due to the aromatic protons of **11**. The NMR spectrum also revealed that **10** and **11** were formed in a ratio (ar-α/ar-β substitution) of 3 : 2. Compound **2** is thus brominated more easily in the ar-α than in the ar-β position in contrast to the result of the bromination of 3,4-dimethylphenol[1] which gave an ar-α/ar-β-ratio of 1 : 9. Bromination of 1-acetyl-5-indolinol (**3**) and of 1-acetyl-7-hydroxy-1H-2,3,4,5-tetrahydro-1-benzazepin (**5**) occurred entirely in the ar-β position while 1-acetyl-1,2,3,4-tetrahydro-6-quinolinol (**4**) was brominated only in position 5 (ar-α). This specificity for reaction at only one of the two possible positions *ortho* to the OH groups was demonstrated by GLC, TLC and NMR of the crude reaction mixtures.

Bromination of 4-methoxy-3-methylphenol (**6**) gave a solid product which according to TLC and GLC was only one compound. The NMR spectrum of the crude product (Experimental), indicated an ar-β bromination. To determine if any ar-α bromination had occurred, the crude monobromophenol was methylated using dimethyl sulphate. As reference compounds 2-bromo-3-methylhydroquinone dimethylether and 2-bromo-5-methylhydroquinone dimethylether were available.[4] These ethers can easily be separated using GLC or TLC. We found that the only product formed after methylation of the above crude bromophenol was 2-bromo-5-methylhydroquinone dimethylether demonstrating that **6** is brominated exclusively in the ar-β position as indicated by the arrow in Scheme 1.

Bromination of 2,3-dihydro-5-benzofuranol (**7**) gave exclusively 6-bromo-2,3-dihydro-5-benzofuranol as shown by GLC-comparison of the silylated crude reaction product with the silylated 4-bromo- and 6-bromo-2,3-dihydro-5-benzofuranol.[4] This shows that **7** is brominated only in the ar-β position as the arrow indicates. In a previous paper[1] we have reported that 6-chromanol (**8**) is brominated to 90% in the ar-α position and that 7-hydroxyhomochroman (**9**) under these conditions is substituted only in the ar-β position.

The results indicate that only the 6-membered annelated ring is ar-α directing while other N- or O-heterocyclic annelated rings are ar-β directing. This is analogous to what was observed for phenols with alicyclic annelated rings.[1]

EXPERIMENTAL

General comments. M.p.s were determined with calibrated Anschütz thermometers in an electrically heated metal block. IR spectra were measured with a Perkin-Elmer 237 spectrophotometer, and NMR spectra were measured in CD_3SOCD_3 or $CDCl_3$ solns with a Varian Associates A 60 instrument. Chemical shifts are expressed in ppm relative to TMS ($\delta_{TMS} = 0{\cdot}00$ ppm). Mass spectra were obtained using an LKB 9000 instrument at 70 eV. Gas chromatography was performed using a Varian Aerograph 1700 instrument with a $6' \times \frac{1}{8}''$ internal diameter glass column filled with 3% J × R on Gas chrom Q, 100–200 mesh. TLC was performed as previously described.[5] Compounds **3**,[6] **6**,[7] **7**,[4] **8**[8] and **9**[1] were prepared following literature procedures. The phenols were brominated at 0° in CCl_4 soln and the products were isolated using preparative TLC as previously described.[1] The structure of each compound was assigned on the basis of their physical and spectral data.

4-(N-*Methylacetamido*)-3-*methylphenol* (**2**). 4-Amino-3-methylphenol[2] was N-methylated as described for 4-methylaminophenol[9] and the product directly N-acetylated as described below for 1-acetyl-1,2,3,4-tetrahydro-6-quinolinol. The overall yield after recrystallization from MeOH was 27%; m.p. 228–231°. (Found: C, 66·9; H, 7·11; N, 7·69. Calc. for $C_{10}H_{13}NO_2$: C, 67·0; H, 7·31; N, 7·82%); ν_{max} (KBr) 3160 cm^{-1} broad (OH), 1640 cm^{-1} (C=O); NMR (in CD_3SOCD_3-soln): $\delta = 7{\cdot}0$–$6{\cdot}3$ ppm (m, 3H, ArH); 2·96 ppm (s, 3H, $\rangle NCH_3$); 2·03 ppm (s, 3H, $ArCH_3$); 1·60 ppm (s, 3H, $—COCH_3$); MS: prominent peaks at *m/e* (rel. int. %) 180(12), 179(73) M^+, 165(5), 164(11), 138(9), 137(100), 136(75), 134(12), 122(56), 108(20), 107(19), 77(40), 66(19), 56(93) and 43(77).

4-(N-*Methyl*-d_3-*acetamido*)-3-*methylphenol* was prepared as described above using d_6-acetic anhydride, m.p. 228–231° (from MeOH); NMR (in CD_3SOCD_3 soln): $\delta = 7{\cdot}0 - 6{\cdot}3$ ppm (m, 3H, ArH); 2·96 ppm (s, 3H, $\rangle NCH_3$); 2·03 ppm (s, 3H, $ArCH_3$).

1-*Acetyl*-1,2,3,4-*tetrahydro*-6-*quinolinol* (**4**). A soln of 1,2,3,4-tetrahydro-6-quinolinol hydrochloride[10] (1·5 g; 8·1

mmole) in MeOH (15 ml) was neutralized using 1 M NaOH. Ac_2O (0·82 g; 8·1 mmole) was added to the stirred soln and after 3 hr at 20° the solvent was removed *in vacuo*, the residue suspended in water (10 ml), the mixture acidified with 5 M HCl and extracted with chloroform (3 × 5 ml). The organic extracts were dried (Na_2SO_4) and the chloroform was evaporated *in vacuo*. The residue was recrystallized from EtOAc to yield 1·4 g (90%) of 1-acetyl-1,2,3,4-tetrahydro-6-quinolinol m.p. 170–172°. (Found: C, 69·3; H, 6·75; N, 7·20. Calc. for $C_{11}H_{13}NO_2$: C, 69·1; H, 6·85; N, 7·33%); ν_{max} (KBr) = 3100 cm^{-1} (OH), 1620 cm^{-1} (>C=O); NMR (in $CDCl_3$-soln): δ = 6·9–6·4 ppm (m, 3H, ArH); 3·70 ppm (t, 2H, >NCH_2—, J = 6·5 cs); 2·57 ppm (t, 2H, $ArCH_2$—, J = 6·5 c/s); 2·16 ppm (s, 3H, —$COCH_3$); 2·2–1·6 ppm (m, 2H, $ArCH_2C_2CH_2$—). MS: Prominent peaks at *m/e* (rel. int. %): 191 (6, M^+), 150(11), 149(100), 148(75), 147(13), 146(13), 134(18), 133(15) and 43(27).

7-Hydroxy-1H-2,3,4,5-tetrahydro-1-benzazepin hydrochloride. A mixture of 7-metoxy-1H-2,3,4,5-tetrahydro-1-benzazepin hydrochloride[11] (6·0 g, 0·02 mmole) and colourless hydroiodic acid (48 g, 57%) was gently boiled for 5 min. Excess acid was then distilled off *in vacuo*. The residue was dissolved in 60 ml water, neutralized with 10% $NaHCO_3$aq and extracted with ether (6 × 40 ml). The combined organic extract was dried (Na_2SO_4) and dry HCl was introduced to precipitate the hydrochloride of 7-hydroxy-1H-2,3,4,5-tetrahydro-1-benzazepin (yield 3·3 g; 60%) m.p. 213–214° from EtOH. (Found: C, 60·0; H, 7·02; N, 7·12. Calc. for $C_{10}H_{13}NO{\cdot}HCl$: C, 60·2; H, 7·07; N, 7·02%); ν_{max} (KBr): 3280 cm^{-1} (OH), 2700 cm^{-1} (>$\overset{\oplus}{N}$—H); NMR (in CD_3SOCD_3-soln): δ = 7·5–6·3 ppm (m, 3H, ArH); 3·4–2·5 ppm (m, 4H, $ArCH_2$— and >$\overset{\oplus}{N}CH_2$—); 2·2–1·3 ppm (m, 4H, aliphatic ring protons); MS: Prominent peaks at *m/e* (rel. int.%) 164(14), 163(100, M^+—HCl), 162(43), 148(23), 147(5), 146(7), 135(25) and 134(61).

1-Acetyl-7-hydroxy-1H-2,3,4,5-tetrahydro-1-benzazepin (**5**) was prepared from the above tetrahydrobenzazepin in 83% yield as described above for **4**, m.p. 183–185° (from EtOAc). (Found: C, 70·0; H, 7·16; N, 6·90. Calc. for $C_{12}H_{15}NO_2$: C, 70·2; H, 7·37; N, 6·83%); ν_{max} (KBr): 3200 cm^{-1} (OH), 1610 cm^{-1} (>C=O); NMR (in CD_3SOCD_3-soln): δ = 7·1–6·3 ppm (m, 3H, ArH); 4·5–4·1 ppm (m, 2H, >N—CH_2—); 2·7–2·3 ppm (m, 2H, $ArCH_2$—); 1·9–1·4 ppm (m, 4H, aliphatic ring protons); 1·68 ppm (s, 3H, —$COCH_3$); MS: Prominent peaks at *m/e* (rel. int. %) 206(15), 205(100, M^+), 164(20), 163(100), 162(60), 148(25), 147(45), 146(30), 135(25), 134(40) and 133(10).

4-(N-methylacetamido)-2-bromo-3-methylphenol (**10**) *and 4-(N-methylacetamido-6-bromo-3-methylphenol* (**11**). Bromination of **2** gave a mixture of these two compounds isolated in 67% yield and in a ratio of 3:2 as shown by NMR (5% of the starting material remained unchanged); MS: *m/e* (rel. int. %) 259(21) and 257(24) (M^+); NMR (compound **10**) (in CD_3SOCD_3-soln): δ = 2·91 ppm (s, 3H, >N—CH_3); 2·14 ppm (s, 3H, Ar—CH_3) and 1·56 ppm (s, 3H, —$COCH_3$). The two aromatic protons give rise to an AB pattern centered at 6·84 ppm, δ_A = 6·94 ppm, δ_B = 6·74 ppm, J_{AB} = 9 c/s; NMR (compound **11**) (in CD_3SOCD_3-soln): 7·24 and 6·75 ppm (s, 1H each, Ar—H); 2·91 ppm (s, 3H, >NCH_3); 1·98 ppm (s, 3H, $ArCH_3$) and 1·56 ppm (s, 3H, —$COCH_3$).

4-(N-methylacetamido)-2,6-dibromo-3-methylphenol (**12**). This compound was isolated in 4% yield as a by-product in the bromination of **2**, m.p. 191–194°; MS: *m/e* (rel. int. %) 337(17), 335(34), 333(19) (M^+).

1-Acetyl-6-bromo-5-indolinol (**13**). This compound was isolated in 35% yield (38% of the starting material remained) as the only product when **3** was brominated, m.p. 214–216° (from EtOAc). (Found: C, 46·9; H, 3·88; N, 5·35. Calc. for $C_{10}H_{10}BrNO_2$: C, 46·9; H, 3·94; N, 5·47%); MS: *m/e* (rel. int. %) 257(43), 255(44) (M^+); NMR (in CD_3SOCD_3-soln): δ = 7·95 and 6·65 ppm (s, 1H each, ArH); 3·95 ppm (t, 2H, J = 8 c/s, >N—CH_2—); 2·95 ppm (t, 2H, J = 8 c/s, $ArCH_2$—); 2·05 ppm (s, 3H, —$COCH_3$).

1-Acetyl-5-bromo-1,2,3,4-tetrahydro-6-quinolinol (**14**). The title compound was obtained in 72% yield (14% of the starting material remained unchanged) as the only product from the bromination of **4**, m.p. 193–195° (from EtOH). (Found: C, 48·7; H, 4·52; N, 5·33. Calc. for $C_{11}H_{12}BrNO_2$: C, 48·9; H, 4·48; N, 5·19%); MS: *m/e* (rel. int. %) 271(37), 269(40) (M^+); NMR (in CD_3SOCD_3-soln): 3·55 ppm (t, 2H, J = 6 c/s, >NCH_2—); 2·65 ppm (t, 2H, J = 7 c/s, $ArCH_2$—); 2·2–1·6 ppm (m, 2H, aliphatic ring protons). The two aromatic protons give rise to an AB pattern centered at 6·91 ppm, δ_A = 7·12 ppm, δ_B = 6·70 ppm, J_{AB} = 9 c/s.

1-Acetyl-8-bromo-7-hydroxy-1H-2,3,4,5-tetrahydro-1-benzazepin (**15**). This compound was obtained in 71% yield in the bromination of **5**. No 6-bromo derivative could be detected by TLC or in the NMR spectrum, m.p. 222–224° from EtOAc. (Found: C, 50·5; H, 4·83; N, 4·83. Calc. for $C_{12}H_{14}BrNO_2$: C, 50·4; H, 4·97; N, 4·93%); MS: *m/e* (rel. int. %) 285(72), 283(77) (M^+); NMR (in CD_3SOCD_3-soln): δ = 7·28 and 6·75 ppm (s, 1H each, ArH); 4·5–4·1 ppm (m, 2H, >NCH_2—); 2·7–2·3 ppm (m, 2H, $ArCH_2$—); 1·72 ppm (s, 3H, —$COCH_3$); 1·9–1·4 ppm (m, 4H, aliphatic ring protons).

2-Bromo-4-methoxy-5-methylphenol (**16**). This compound was formed as the only product when **6** was brominated, m.p. 77–79° (from light petroleum); MS: prominent peaks at *m/e* (rel. int. %) 218(85), 216(93) (M^+), 203(100), 201(94), 121(10) and 94(21); NMR (in $CDCl_3$-soln): δ = 6·65 ppm (s, 1H) and 6·60 ppm (q, 1H, J ~ 0·5 c/s), both signals due to aromatic protons. The quartet is probably due to allylic coupling to the aromatic Me groups; δ = 4·83 ppm (s, 1H, OH); 3·62 ppm (s, 3H, —OCH_3); 2·08 ppm (s, 3H, $ArCH_3$).

2-Bromo-5-methylhydroquinone dimethylether. Compound **16** was methylated using dimethyl sulphate in

methanolic KOH.[12] The diether was quantitatively formed and identified by chromatographic and spectral comparisons with an authentic sample.[4]

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