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REGIOSELECTIVE AMINOMETHYLATIONS OF BICYCLIC PHENOLS

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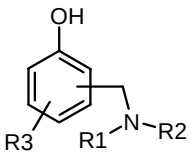
Abstract - The regioselectivity in the aminomethylations (the Mannich reaction) of bicyclic phenols has been studied. Highly regioselective Mannich reactions enable easy synthetic access to novel bicyclic dialkylaminomethylphenols under very mild reaction conditions.

INTRODUCTION

Dialkylaminomethylphenols (**1**) are an important class of compounds in the area of pharmaceuticals. Examples are the antimalarial Amodiaquin[1] and the selective δ-opioid receptor agonists BW373U86[2] and SL-3111[3] having therapeutic potential as analgesics.

It is clear that the regioselective synthesis of dialkylaminomethylphenols (**1**) is an important goal in organic synthesis.



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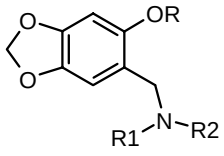
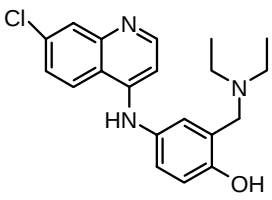
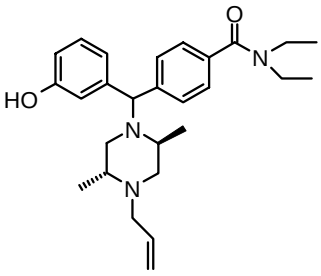


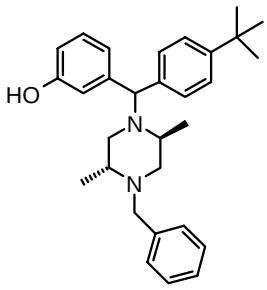
2a (R = H)
2b (R = alkyl)



Amodiaquin



BW373U86



SL-3111

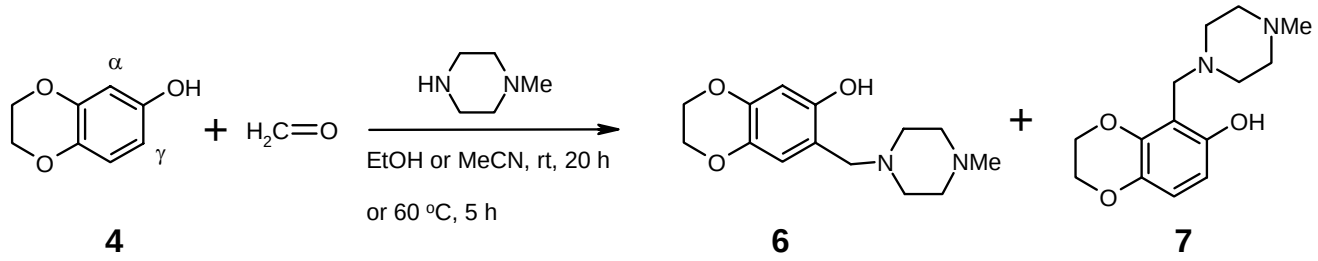
We have successfully used bicyclic dialkylaminomethylphenols (**2a**), which contain an annelated methylenedioxy ring, as synthetic precursors for anti-ischaemic compounds (**2b**)[4,5]. The bicyclic dialkylaminomethylphenols (**2a**) can efficiently be prepared from the corresponding bicyclic phenols in one step *via* a highly regioselective Mannich reaction.

In the course of a study aimed at novel anti-ischaemic compounds, it was needed to broaden the scope of our investigations to other bicyclic phenols. These are depicted in Table 1.

The regioselectivities of their Mannich reactions are discussed in detail.

RESULTS AND DISCUSSION

The Mannich reaction[6] of phenols[7] is a synthetic method of wide application in organic synthesis. The Mannich reaction of sesamol (**3**) with a secondary amine and aqueous formaldehyde (37 wt. % solution) has been described earlier and proceeds smoothly in either ethanol or acetonitrile, to afford the benzylamines (**2a**) in high yields as the sole reaction products[4,8], in a slightly exothermic reaction. Unexpectedly, we found that the Mannich reaction of 6-hydroxy-1,4-benzodioxane (**4**) (exemplified by the reaction with 1-methylpiperazine as the amine) showed the slow formation[9] of a mixture of the two regioisomers (**6**) and (**7**) in a molar ratio of 62 : 38 (Scheme 1). Apparently, this ring enlargement, from a five membered ring in **3** to a six membered ring in **4** has a profound effect on both the reactivity and the regioselectivity in this aminomethylation. In order to try to influence the regioselectivity by variation of the solvent, this particular Mannich reaction (Scheme 1) was also carried out in organic solvents of different polarity (ether, ethyl acetate, THF, DMF, acetonitrile, and ethanol). It was anticipated that in the positively charged transition state of this electrophilic aromatic substitution reaction the polarity of the applied solvent might influence its regiochemical outcome. However, all these reactions afforded similar product mixtures of **6** and **7.** Apparently, the impact of the solvent polarity in this reaction is small.



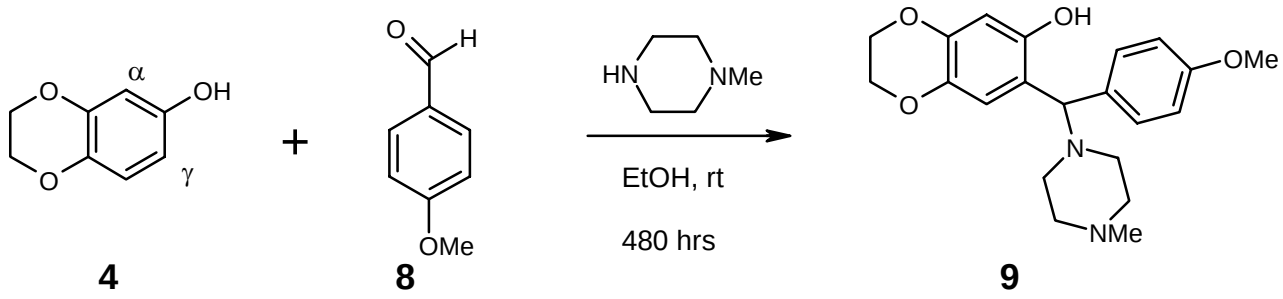
4 **6** **7**

Scheme 1

In order to study the effect of polar, acidic solvents[10] on the regiochemical outcome of this Mannich reaction acetic acid and TFA were applied. Acetic acid caused a significant acceleration of the reaction rate, in combination with slightly favouring γ-attack. As the reaction in pure TFA gave only decomposition products, a solution (2-4 molar equivalents) in ethanol was applied. This combination gave a slightly higher yield (about 70%) as well as a further increased selectivity in favour of the product (**6**) (molar ratio of **6** : **7** = 80 : 20 %, determined by ^{1}H-NMR integration).

From these results it can be concluded that polar, acidic solvents have an accelerating effect on the rate of this Mannich reaction, but at the same time remain a minor determinant for its regiochemical outcome.

As it has been described in the literature that steric hindrance is an important factor which affects the reaction rate in the Mannich reaction[6] of phenols[7] we attempted to react **4** with the more bulky *p*-methoxybenzaldehyde (**8**) in the Mannich reaction with 1-methylpiperazine. This variation of the applied aldehyde indeed has a profound regiochemical effect as it gave the slow formation of compound (**9**) as the sole reaction product (Scheme 2). These findings are in line with the regioselectivity of the same reaction[11] with sesamol (**3**). However, it should be notified that this particular reaction in the case of sesamol also proceeds much faster[11].
Therefore, it can be concluded that in the Mannich reaction of **4** with 1-methylpiperazine and *p*-methoxybenzaldehyde, the addition *via* α-attack is blocked by the increased steric hindrance of the more bulky aldehyde, whereas the formation (albeit more slowly) of compound (**9**) *via* γ-attack at the aromatic nucleus still occurs.



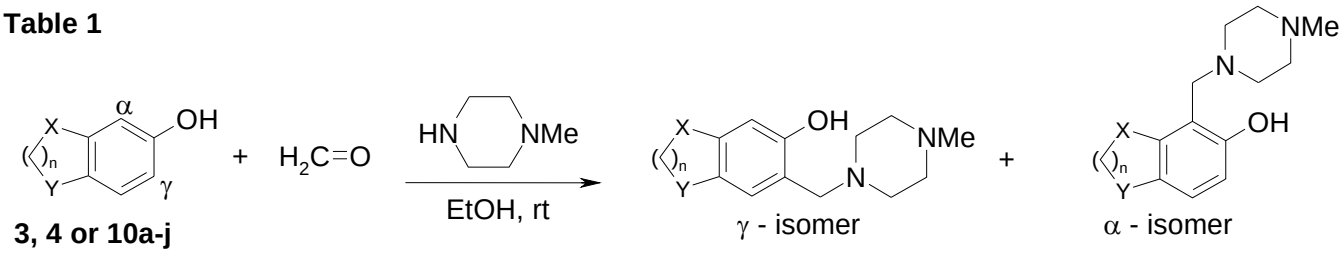
4 **8** **9**

Scheme 2

The profound effects of the change in ring size between the bicyclic phenols (**3**) to (**4**) on both the reactivity and the orientation in their Mannich reactions prompted the investigation of other - structurally more diverse - bicyclic phenols in this particular reaction. Therefore, a number of bicyclic phenols[12] (**10a**-**l**) and the structurally closely related 3,4-dimethoxyphenol (**10m**) were subjected to the Mannich reaction under very mild reaction conditions[13]. The resulting product ratios (γ – vs. α -attack, respectively) as well as the chemical yields are depicted in Table 1.

The differences between the regiochemical outcome of the phenols (**3**, **10b**, **10d**, and **10f**) with their fused five membered rings in comparison to those having fused six membered rings (**4**, **10c**, **10e**, and **10g**), can be rationalized by invoking the so-called Mills-Nixon effect[14]. Mills and Nixon found that some bicyclic fused benzenes, containing a saturated six membered ring, exhibit a different orientation (mainly *via* α-attack) in their electrophilic aromatic brominations, as compared to both their five membered and seven membered ring analogues (which were reported to react mainly *via* γ-attack.

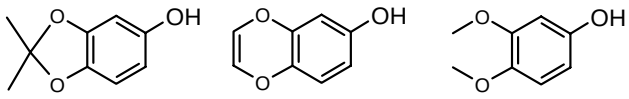
Table 1



3, 4 or 10a-j

Phenol[12]	**n**	**X**	**Y**	**Yield**[13, 14] **(%)**	**Regioisomer Ratio**[*)] **(%)**	
					γ–position	**α–position**
3	1	O	O	76	100	0
4	2	O	O	50	62	38
10a	3	O	O	44	67	33
10b	1	O	CH_2	56	100	0
10c	2	O	CH_2	35	21	79
10d	1	CH_2	O	61	100	0
10e	2	CH_2	O	37	21	79
10f	1	CH_2	CH_2	47	77	23
10g	2	CH_2	CH_2	51	34	66
10h	1	O	C=O	27	0	100
10i	2	O	C=O	57	0	100
10j	2	C=O	O	59	0	100
10k				70	100	0
10l				63	100	0
10m				64	100	0

*) Molar product ratios were determined *via* ^{1}H-NMR integration of the aromatic signals.



10k **10l** **10m**

This phenomenon was initially explained by assuming that the ring fused to the aromatic system affects either the bond angles at the common link or the bond length thereof, thereby affecting the stability of the various possible transition states for substitution[15]. As these differences in bond angles or lengths could not be detected neither experimentally nor by several kinds of calculations, this explanation is very unlikely to account for the orientation results. The amount of (hyper)conjugation of the orbitals at the common link was postulated to rationalize the observed modes of orientation[16]. It was rationalised by Behan *et al*.[16] that the rate of reaction at the α–position for different conjugative effects will not vary so much as the rates of reaction at their γ–position. The results in Table 1 reveal a different orientation (exclusively γ-orientation) in the Mannich reaction of the bicyclic phenols (**3**, **10b**, and **10d**) (all

containing a fused five membered ring) in comparison to those having fused six membered rings, *viz*. **4**, **10c**, **10e**, and **10g** (both α– and γ–orientation). The regiochemical outcome of the seven membered ring analogue (**10a**) resembles that of its six membered ring analogue (**4**).
The orientation (predominantly γ, but also some α) in the case of the indan derivative (**10f**) is less pronounced as compared with the results of **3**, **10b**, and **10d**, respectively. The observed orientation is in agreement with the observed regiochemistry in the bromination of indanes[17].

It was found that the rates of reaction in the five membered ring analogs in which X=O (**3** and **10b**) are considerably higher than those in which X = CH_2 (**10d** and **10f**). These rate differences may be explained by the stronger mesomeric electron donating power of this oxygen atom in the intermediate σ-complex, in comparison to the hyperconjugative effect of the CH_2 group. The lower reactivity of **10h** in which X=O seems to contradict the foregoing statement, but can be rationalised by invoking the inductive electron withdrawing effect from the adjacent carbonyl group (*via* the methylene group in the annelated ring) on this oxygen atom. This is confirmed by electron density calculations (MOPAC, AM1) which indeed reveal a somewhat lower electron density at the ring oxygen atom in **10h** as compared to **10i**[18]**.**

The lack of high regioselectivities in the Mannich reaction of the phenols (**4**, **10a**, **10c**, and **10e-g**) prompted to test also the bicyclics (**10h-j**). As these latter compounds contain a strongly electron withdrawing carbonyl substituent in the annelated ring, we anticipated a profound effect on the regiochemical outcome. As a matter of fact, the benzofuranone (**10h**) and both chromanones (**10l**) and (**10j**) react exclusively at their α–position. Apparently, the size of the annelated ring is not the regiochemistry denominator for these compounds. The observed α–orientation can be rationalised by the theory of Dewar[19], which states that 1,2,4-trisubstituted benzenes, wherein an electron withdrawing and an electron donating substituent are ortho to each other and which have an electron donating substituent at their 4-position, will mainly yield the 1,2,3,4-monosubstition product. This phenomenon[19] has been ascribed to the conjugation between the adjacent 1- and 2-substituent which tend to increase the bond order of the annular bond and thereby direct substitution to the 3-position.
Intriguingly, the orientation in the case of 6-hydroxy-benzodioxin (**10l**) is not in line with its benzodioxane derivative (**4**)**,** but instead resembles that of sesamol (**3**). This may be ascribed to either the electron rich nature of the olefinic bond in the attached ring, which may give a strong charge stabilisation of the intermediate cationic σ-complex, or by the decrease of strain, as compared with its benzodioxane congener (**4**).

3,4-Dimethoxyphenol (**10m**) can be regarded as the monocyclic counterpart of the bicyclics (**3**) and (**4**). As in **10m** the fused ring is absent, the possibility of additional strain by the fused ring attachment in the intermediate cationic σ-complex, is absent too. The regiochemical outcome[17] of the Mannich reaction in **10m** resembles the orientation of 5-hydroxy-1,3-benzodioxole (**3**).

Also, compound (**10k**) (the dimethyl congener of **3)** shows the same regioselectivity as compared with **3**.

The rate of reaction in the Mannich reactions of both **3** and **10k** is higher in comparison to **10m**. It may be concluded that apparently the conjugative electron donating effect of the methylenedioxy moieties in both **3** and **10k**, and the minor opposing effect of ring strain, gives an optimal charge stabilisation of their intermediate σ-complexes, thereby resulting in a fast and regiospecific Mannich reaction.

CONCLUSIONS

Two types of highly regioselective Mannich reactions on bicyclic phenols are highlighted, thereby enabling easy synthetic access to pure dialkylaminomethylphenols (**1**) as pharmaceutically relevant building blocks.

The bicyclic phenols (**3, 10b**, **10d**, **10k**, and **10l**), which contain electron donating alkyl groups or oxygen atoms in their fused ring, were shown to react regiospecifically *via* γ-attack.

The bicyclic phenols (**10h-j**)**,** which contain both an electron withdrawing carbonyl group and an electron donating substituent in their fused ring, were shown to react regiospecifically *via* α-attack. The observed regioselectivity (γ-attack *versus* α-attack) in the Mannich reaction of the exemplified bicyclic phenols (**3**, **4**, and **10**), strongly depends on both the composition and size of the fused ring (the possible directing effect of occurring ring strain, in combination with the extent of charge stabilisation in their intermediate cationic σ-complexes).

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9. The Mannich reaction is irreversible, as both purified **6** and **7** were not interconverted under the applied reaction conditions of the Mannich reaction.
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13. The progress of the reaction was monitored by TLC. In some cases, a small amount of starting phenol was still present at work-up. The yields refer to the isolated γ- and α-regioisomer mixtures.
14. Mannich reaction of sesamol (**3**) - To a stirred solution of **3** (5.00 gram, 0.0362 mol) and N-methylpiperazine (3.63 g, 0.0362 mol) in EtOH (25 mL) was slowly added formaldehyde (29.4 g, 37 % aqueous solution which contains 0.0362 mol formaldehyde). The resulting solution was stirred for 4 h at rt and evaporated *in vacuo* to afford a yellow solid (9.0 g). Recrystallisation from EtOAc gave the γ–isomer *5-hydroxy-6-[(4-methyl-1-piperazinyl)methyl]-1,3-benzodioxole* (6.9 g, 76 %). mp 95-97 ^{o}C (white powder). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 2.40-2.80 (m, 9H), 3.60 (s, 2H), 5.86 (s, 2H), 6.40 (s, 1H), 6.46 (s, 1H). EIMS *m/z*: (rel. int.) 250 (M^+, 15), 150 (32), 100 (39), 58 (100). HRMS *m/z*: calcd for $C_{13}H_{18}N_2O_3$: 250.1317. Found: 250.1337.
The Mannich reaction of *6-hydroxy-1,4-benzodioxane* (**4**) was carried out according to the above procedure described for **3**, but as the reaction proceeded more slowly, the required reaction time for completion was 20 h. The reaction yielded an oil which consisted of **6** and **7** in a molar ratio of 62 : 38, respectively, according to ^{1}H-NMR integration (*Cf*. Table 1). *6-hydroxy-7-[(4-methyl-1-piperazinyl)methyl]-1,4-benzodioxane* (**6**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 2.40-2.90 (m, 9H), 3.60 (s, 2H), 4.15-4.23 (m, 4H), 6.36 (s, 1H), 6.49 (s, 1H). *6-hydroxy-5-[(4-methyl-1-piperazinyl)methyl]-1,4-benzodioxane* (**7**): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.40-2.90 (m, 9H), 3.75 (s, 2H), 4.15-4.23 (m, 4H), 6.32 (d, J=8 Hz, 1H), 6.67 (d, J=8 Hz, 1H).
The Mannich reaction of *2,2-dimethyl-5-hydroxy-1,3-benzodioxole* (**10k**) (14.7 g, 0.0886 mol) was carried out according to the above procedure for **3**, to afford the γ–isomer *2,2-dimethyl-5-hydroxy-6-[(4-methyl-1-piperazinyl) methyl]-1,3-benzodioxole* in 70 % yield, after recrystallisation from petroleum ether. mp 99-101 ^{o}C (colorless plates). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.63 (s, 6H), 2.30 (s, 3H), 2.40-2.80 (m, 9H), 3.58 (s, 2H), 6.31 (s, 1H), 6.35 (s, 1H). EIMS *m/z*: (rel. int.) 278 (M^+, 35), 178 (96), 138 (65), 58 (100). HRMS *m/z*: calcd for $C_{15}H_{22}N_2O_3$: 278.1630. Found: 278.1634.
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