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# *The transformation of nitrogen-containing analogues of 2-naphthol*

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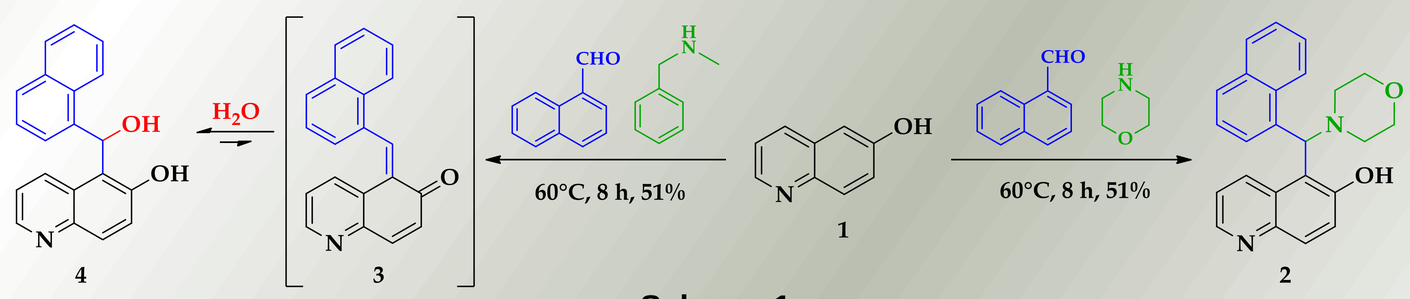
## Introduction

C-C bond formation can be a challenging issue in organic chemistry, but in the modified Mannich reaction it takes place relatively easily. In this widely used reaction, three components participate in the reaction: an aldehyde, an amine and an electron-rich aromatic compound (mainly 1- or 2-naphthol). Nitrogen-containing analogues (quinolinoles and isoquinolinoles) might be applied in this reaction, and the application is desired because of their wide-ranging biological activity; for instance, 6-hydroxyquinoline is a potential anti-hepatitis B virus agent, while 3-hydroxyisoquinoline is cytotoxic and metalloproteinase inhibitor [1].

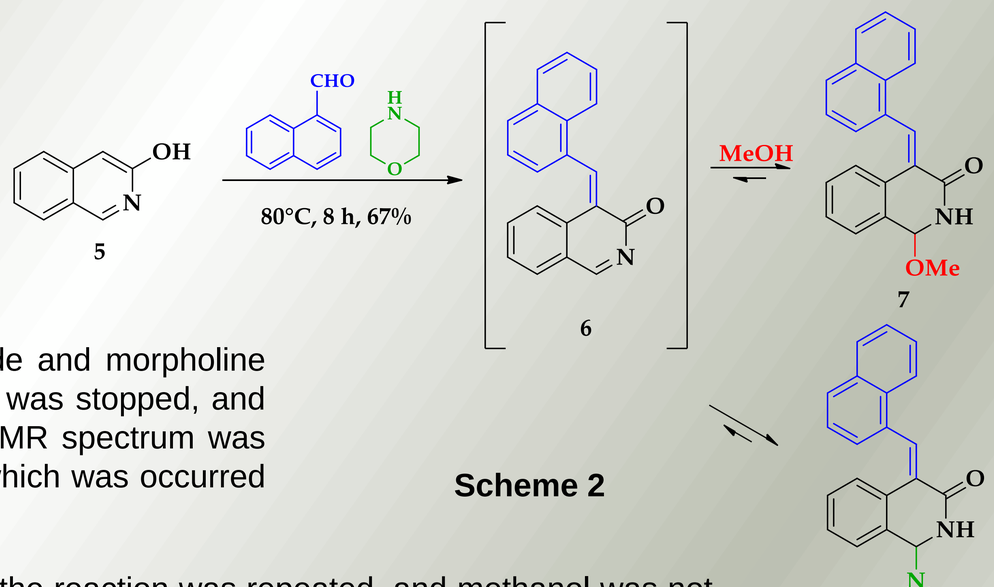
## Results and Discussion




**Scheme 1**

Our first attempt was the transformation of 6-hydroxyquinoline (**1**) as a 2-naphthol analogue. 6-hydroxyquinoline, 1-naphthaldehyde, and morpholine were reacted under neat conditions (**Scheme 1**). The reaction was monitored with thin layer chromatography (TLC), and after 8 hours a single spot of the product was observed. The $^1$H-NMR spectrum supported the structure of compound **2**.

In our previous work [2], *N*-benzylmethylamine was tested in the presence of 2-naphthol and some aromatic aldehydes. According to these findings, the reactivity of *N*-benzylmethylamine differed from other amines, hence it was desired to test it with 6-hydroxyquinoline. The reaction was performed under neat condition, and the temperature (60°C) was maintained by classical heating. The isolated product was the diol **4**, which means that *ortho*-quinone methide (*o*QM) **3** was stabilized via the addition of a water molecule.




**Scheme 2**

Our next step was the examination of the reactivity of 3-hydroxyisoquinoline (**5**). 1-Naphthaldehyde and morpholine were applied in modified Mannich reaction (**Scheme 2**). After 8 hours of reaction time, the reaction was stopped, and the mixture was purified by column chromatography (ethyl-acetate:methanol 20:1). When the $^1$H-NMR spectrum was examined, the incorporation of a methanol molecule to the isoquinoline scaffold was observed (**7**), which was occurred through the intermedier *o*QM **6** by a nucleophilic attack to the position 1.

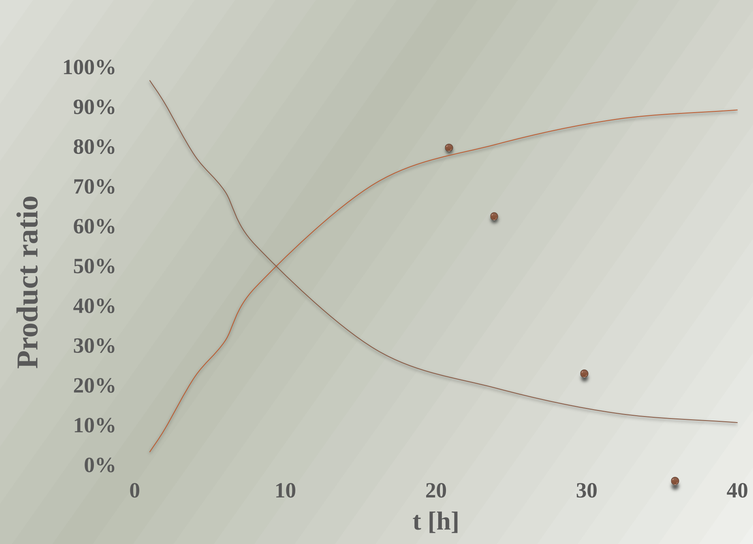



**Figure 1**

To avoid the formation of **7**, the reaction was repeated, and methanol was not used in any step. In this case, the stabilization of the *o*QM did not take place via the attack of a methanol molecule, but the attack of morpholine, resulting **8B** (**Scheme 2**).

The reaction was also monitored by $^1$H-NMR spectra. We analysed the product ratios (**Figure 1**), and concluded that there is another intermedier/product (**9**). The ratios were estimated according to the characteristic signs of **8B** and **9**. The ratio of **9** was almost 100% at the beginning of the reaction, while **8B** was near to 0, but during the reaction, the percentage of **9** was decreased and the **8A** simultaneously increased.

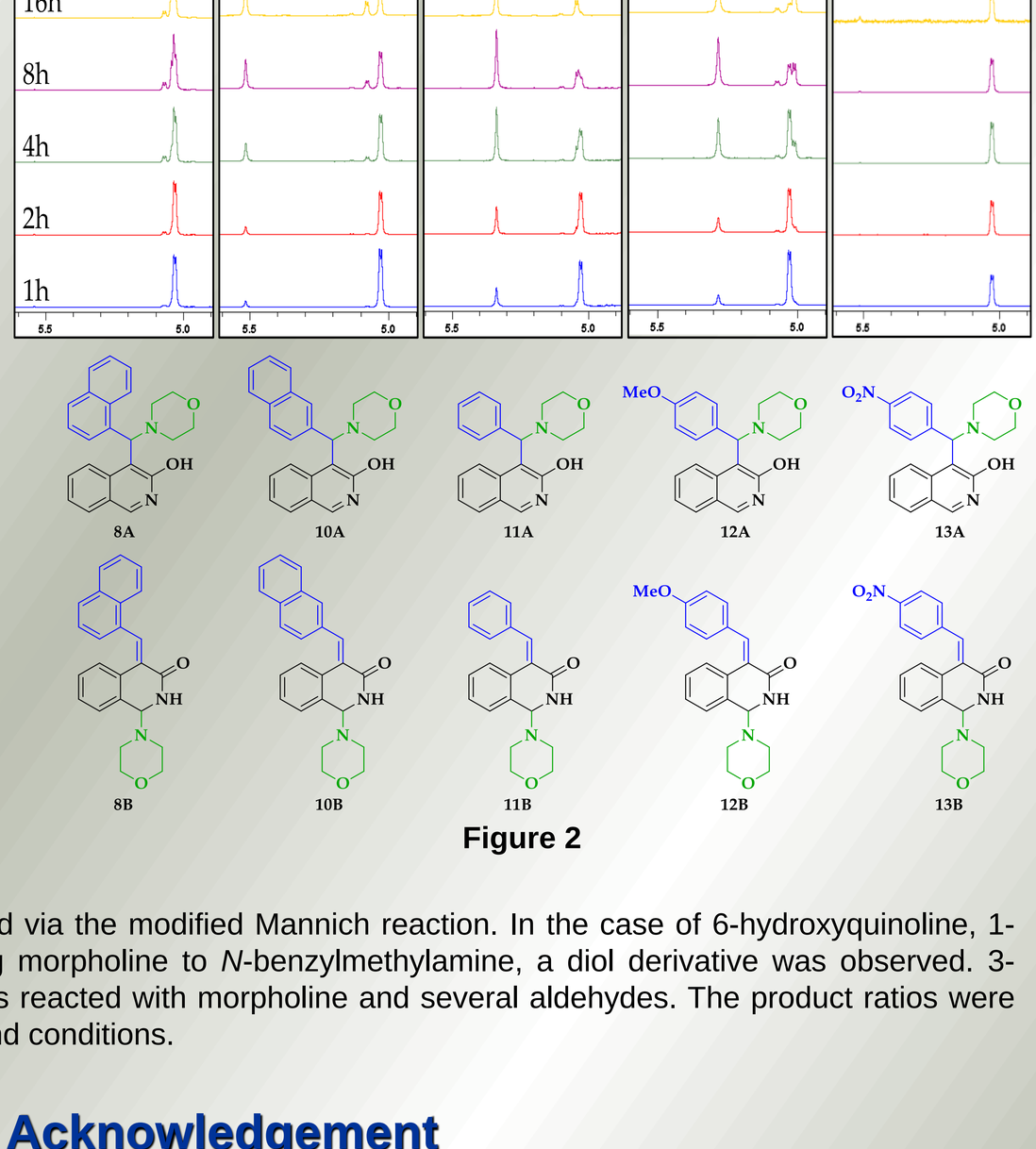
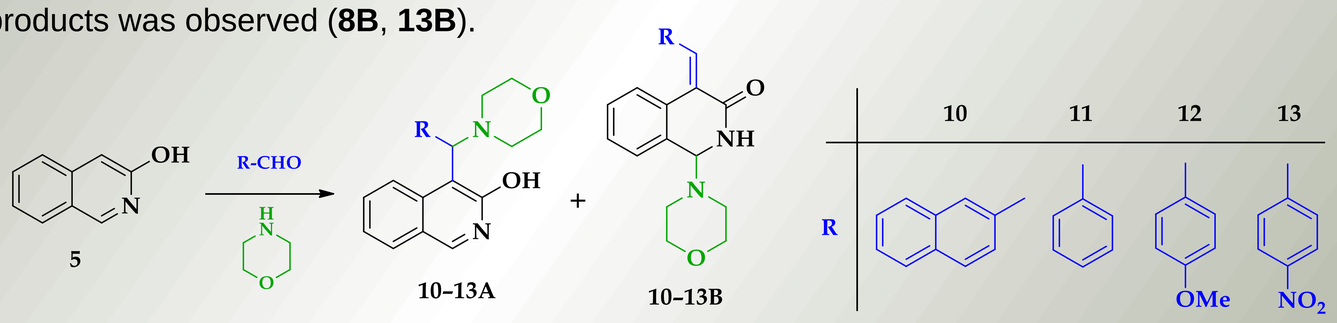



**Figure 2**

Subsequently, a systematic test was performed to reveal the influence of the aldehydes on the product ratios. 2-Naphthaldehyde, benzaldehyde, *p*-methoxy- and *p*-nitrobenzaldehyde were tested, resulting **10A,B–13A,B** (**Scheme 3**). The mixtures were sampled in five appointments: at 1, 2, 4, 8 and 16 hours reaction time (**Figure 2**). In the case of **10–12** the classical Mannich products (**10A–12A**) and also the 1-substituted products (**10B–12B**) were observed. The presence of **8A** and **13A** was not detected, only the presence of 1-substituted products was observed (**8B**, **13B**).




**Scheme 3**

## Conclusion

The syntheses of new 6-hydroxyquinoline and 3-hydroxyisoquinoline derivatives were achieved via the modified Mannich reaction. In the case of 6-hydroxyquinoline, 1-naphthaldehyde and morpholine, the classical Mannich product was isolated, while changing morpholine to *N*-benzylmethylamine, a diol derivative was observed. 3-Hydroxyisoquinoline showed unexpected reactivity, and resulted diverse structures when it was reacted with morpholine and several aldehydes. The product ratios were monitored; however, further examinations need to be performed to determine the exact ratios and conditions.

## References

[1] Bunker, A. M.; Sliskovic, D. R. US6974822B2, **2005**.
[2] Szatmári, I.; Barta, P.; Csámpai, A.; Fülöp, F. *Tetrahedron* **2017**, *73*, 4790.

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