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*Short Communication*

# Modification of some organic compounds of pharmaceutical interest

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**In this article, the modification of the chemical structure of acetaminophen and ibuprofen is described. The esterification, acetaylation and hydrolysis products of acetaminophen and the nitration product of ibuprofen were prepared. The newly synthesized compounds were characterized by IR, $^{1}$H NMR and mass spectral analysis. The synthesized products will be tested and evaluated as antimicrobial agents.**

**Key words:** Acetaminophen, ibuprofen, drug, modification.

## INTRODUCTION

New drugs are constantly required to combat drug resistance. They are also required for the improvement in the treatment of existing disease. In addition, drugs are needed for the treatment of newly identified diseases and the production of safer drugs by the reduction or removal of adverse side effect (Thomas, 2003).

The most fruitful basis for the discovery of a new drug is to start with an old drug. This has been the most common and reliable route to new products. The existing drugs may need to be improved, for example, to get a better dosage form, to improve drug absorption or duration or, to increase potency to reduce the daily dosage (Gan et al., 2009; King, 1995).

The objective of this work was to try and synthesis new drugs from already existing ones by modifying the functional groups or by adding functional groups to leading compounds. In this article the modifications of acetaminophen and ibuprofen are presented.

## METHODS

### Extraction of the active ingredients

This method was used for the isolation of the active ingredients of acetaminophen and ibuprofen. Several tablets were crushed after removing the coat from coated tablets. The powdered material was transferred to a centrifuge tube with a tight fitting cap. Then 60 ml of methanol was added, the tube was capped and mixture was shaken thoroughly. The un-dissolved portion of the powder was allowed to settle in the centrifuge tube for 7 min. The liquid phase was transferred into another centrifuge tubes using a Pasteur pipette. A second portion of 60 ml of methanol was added to the undissolved powder in the original centrifuge tube. The shaking process was repeated as described previously. After the solid had settled, the liquid phase was transferred to the centrifuge tube containing the first extract.

The tube containing the combined extracts was centrifuged for 5 min. The supernatant liquid was carefully transferred into a small beaker. Column chromatography using alumina was conducted after which the solvent was evaporated in a water bath at 50°C. A gentle stream of dry air was directed into the beaker containing the liquid. After complete evaporation, the beaker was placed in an ice bath for 15 min. Crystallization of the product was induced by scratching the walls of the beaker. Vacuum filtration then followed after which the crystals were allowed to dry for 10 min. The melting point was determined (Pavia et al., 2005).

### Acetaminophen

$^{1}$H NMR spectrum (MeOD), δ, ppm: 5.8d (2H), 5.2 d (2H), 3.3 br. s (1H), 1.8 m (1H), 0.5 d (3H). IR spectrum (MeOD), v, $Cm^{-1}$: 3325, 3116, 2488, 1650, 1508, 1438, 1371, 1232, 678. $^{13}$C NMR spectrum (MeOD), $\delta_C$, ppm: 169, 153, 128, 120, 112, 20.

### Ibuprofen

$^{1}$H NMR spectrum ($CDCl_3$), δ, ppm: 7.3 d (2H), 7.1 d (2H), 3.7 q

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(1H), 2.4 d (3H), 1.8 m (1H), 1.5 d (2H), 0.9 d (6H). IR spectrum ($CDCl_3$), v, $Cm^{-1}$: 3450, 1718, 1558.
$^{13}C$ NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 180, 140, 137, 129, 127, 45, 44.9, 30, 22, 18.

**Modification of the drugs**

***Acetaminophen***

**Esterification:** Initially, 1.5 g of acetaminophen was placed in 100-mL round-bottom flask with 7-ml of acetic acid. The mixture was swirled until most of the solid had dissolved. 1-ml of concentrated sulfuric acid was added to the flask and the flask was swirled immediately. The mixture heated under reflux for 75 min. The mixture was occasionally stirred during the heating period. After heating, the mixture was allowed to cool to room temperature.

The reaction mixture was transferred to a separatory funnel. The reaction flask was rinsed with 15 ml of methylene chloride then transferred and added to the separatory funnel. The lower methylene chloride layer containing the product was drained into a small beaker. The remaining layer was extracted with second portion of methylene chloride and this was combined with the first extraction.

The combined methylene chloride layer was extracted with 25-ml water. The lower organic layer was drained into a beaker and the aqueous layer was discarded. The organic layer was returned to the separating funnel and was extracted twice with 15-ml of 5% aqueous sodium bicarbonate.

The crude ester was transferred to a clean conical flask and anhydrous sodium sulfate weighing 2.0 g was added. The flask was corked, swirled and allowed to stand for 15 min. The dry ester was then transferred to a clean flask.

**Acetylation:** A drying tube containing anhydrous calcium chloride was fitted into 25 ml round-bottom flask. 2.0 g of acetaminophen was placed in the round-bottomed flask with 8-ml of acetic anhydride. The flask was swirled to mix the reagents. 1.0 ml of 85% phosphoric acid was slowly added to the flask. The drying tube was placed on the flask and the reaction mixture was thoroughly mixed. The flask was placed in a bath of boiling water for 10 min with occasional swirling.

The flask was then removed from the boiling water and the content poured over a 10 g of ice in 100-mL beaker. 5 ml of 6 M sodium hydroxide was used to partially neutralize the mixture. Sodium hydroxide was slowly added until the pH was between 7 to 8. Then the mixture was allowed to cool to room temperature and the product was collected by vacuum filtration. Air was pulled through the product for 15 min to dry (Carrathers and Coldham, 2004).

**Ibuprofen**

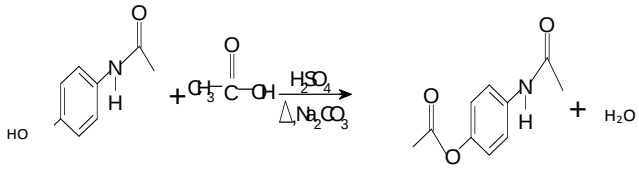
***Nitration***

In a 100-mL beaker, 3-ml of concentrated sulfuric acid was added and cooled to 0℃. 1 g of Ibuprofen was added to th e beaker. The mixture was cooled to -5℃ using an ice salt bath. A mixture of 2 mL concentrated sulfuric acid and 2 mL concentrated nitric acid were slowly added. The mixture was stirred continuously during the addition of the acid and the temperature was maintained below 15℃. The mixture was removed from the ice bath and allowed to warm to room temperature and was left to stand for 15 min. After this period the mixture was poured over 25 g of crushed ice from ionized water in a 100-mL beaker. When the ice had melted the mixture was isolated using vacuum filtration. The product was washed with two 12-mL portion of cold distilled water.

## RESULTS

### Acetaminophen

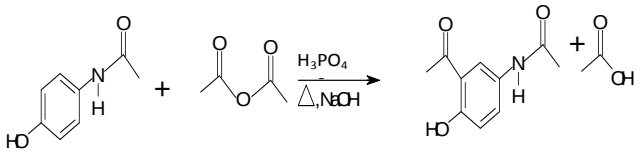
***Esterification***



Acetaminophen

**Equation 1:** The esterification reaction of acetaminophen with acetic acid.
$^1H$ NMR spectrum (MeOD), δ, ppm: 5.8d (2H), 5.2 d (2H), 3.3 S (1H), 1.8 m (1H), 0.5 d (3H). IR spectrum (MeOD), v, $Cm^{-1}$: 3325, 3165, 2488, 1654, 1562, 1508, 1438, 1371, 1323, 804, 511. $^{13}C$ NMR spectrum (MeOD), $\delta_C$, ppm: 168, 153, 128, 121, 113, 21.

***Acetylation***

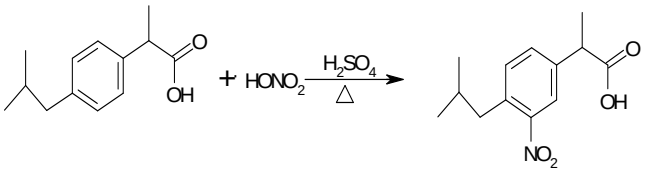


Acetaminophen

**Equation 2:** The acetylation reaction of acetaminophen with acetic anhydride.
$^1H$ NMR spectrum (MeOD), δ, ppm: 7.5d (2H), 7.1 d (1H), 3 br. s (1H), 1.8 m (1H), 2.3 s (6H). IR spectrum (MeOD), v, $Cm^{-1}$: 3365, 3139, 1745, 1689, 1508, 1542, 1502, 1363, 1236, 118, 925, 810, 700. $^{13}C$ NMR spectrum (Acetone),$\delta_C$, ppm: 168, 147, 138, 122, 119, 23.

### Ibuprofen

***Nitration***



**Equation 3:** The Nitration reaction of ibuprofen.
$^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 7.8 m (3H), 3.8 q (1H), 2.8 d (3H), 1.8 m (1H), 1.5 d (2H), 0.9 d (6H). IR spectrum ($CDCl_3$), v, $Cm^{-1}$: 3960, 1705, 1533, 1352. $^{13}C$

NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 180, 152, 149, 138, 132, 131, 123, 44, 41, 34, 30, 22, 18.

## DISCUSSION

In the esterification reaction of acetaminophen with acetic acid, it was observed from the IR analysis that the hydroxyl group signal in acetaminophen is not shown and there is additional carbonyl group signal in the spectrum, which suggests the formation of the desired ester.

In the acetylation reaction of acetaminophen with acetic anhydride, the IR analysis showed an additional signal for a carbonyl group. The $^1H$ NMR spectrum showed additional three aliphatic hydrogens.

In the Nitration reaction of ibuprofen, the $^1H$ NMR spectrum showed three aromatic hydrogens instead of four aromatic hydrogens in the parent compound which suggest the formation of the anticipated product.

## Conclusions

It is expected that the resulting new compounds will show different pharmaceutical effects from that of the parent compounds. Biological activities of the new compounds will be the subject of a separate communication once available.

## ACKNOWLEDGEMENT

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