NEW PROCEDURE FOR OBTAINING INDOMETHACIN

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A new procedure has been developed for the synthesis of indomethacin by the Fischer reaction, based on the acylation of sodium 2-(4-methoxyphenyl)-1-hydrazosulfonate with 4-chlorobenzoyl chloride and subsequent interaction with levulinic acid in the presence of formic acid.

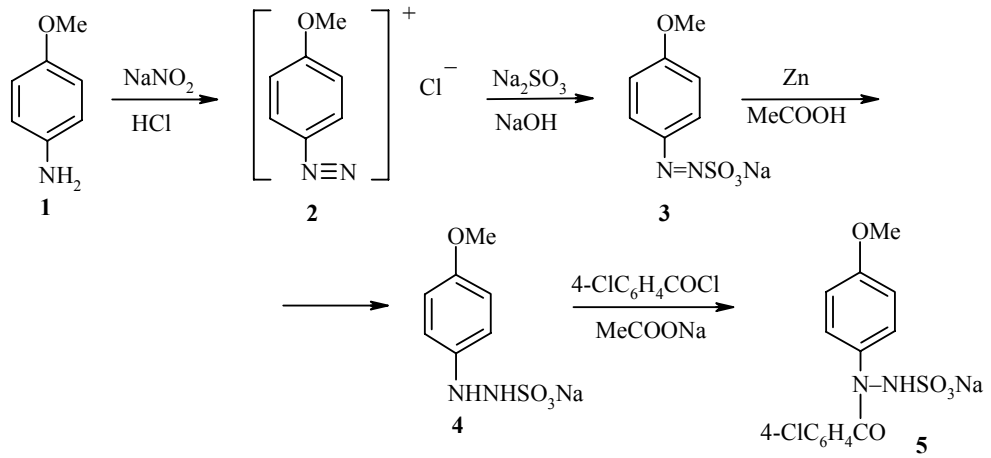
Keywords: indomethacin, catalysis with sodium hydrogen sulfate, Fischer reaction.

Indomethacin belongs to the derivatives of 2-(1H-indolyl-3)acetic acid and is one of the most active nonsteroidal anti-inflammatory preparations [1].

Many of the known methods of synthesizing indomethacin contain a large number of steps, occasionally under fairly complex conditions, and assume, for example, the use of alkali metal hydrides or sodium at the stage of introducing a 4-chlorobenzoyl group into the indole ring [2].

Following an analysis of the literature we chose the variant including acylation of sodium 2-(4-methoxyphenyl)-1-hydrazosulfonate [3]. This procedure appeared optimal to us for the number of stages and the yield of product.

We used 4-methoxyaniline (**1**) as starting material, which was diazotized with the formation of 4-methoxybenzenediazonium chloride (**2**) with conversion of the latter into sodium 4-methoxybenzenediazosulfonate (**3**). The latter was reduced with zinc dust with the formation of sodium 2-(4-methoxyphenyl)-1-hydrazosulfonate (**4**). Acylation of sulfonate **4** with 4-chlorobenzoyl chloride led to the formation of sodium 2-(4-chlorobenzoyl)-2-(4-methoxyphenyl)-1-hydrazosulfonate (**5**).



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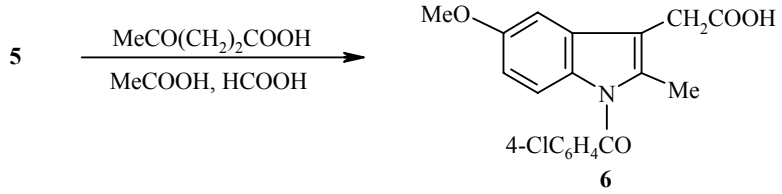
The distinguishing feature of the procedure developed by us is the use of formic acid at the indolization stage. On indolization of hydrazine **5** into indomethacin **6** it was necessary to select an acid catalyst which would remove the sulfonate protection from the nitrogen atom with subsequent formation of a hydrazone on reaction with levulinic acid, and would catalyze the Fischer reaction without deacylating the 4-chlorobenzoyl group. The use of mineral acids (sulfuric, HCl, orthophosphoric) in this reaction led to the formation of a mixture of indomethacin and deacylated indomethacin. We discovered that on using formic acid as catalyst, hydrazine **5** reacts with levulinic acid with the formation of indomethacin **6** without deacylation.



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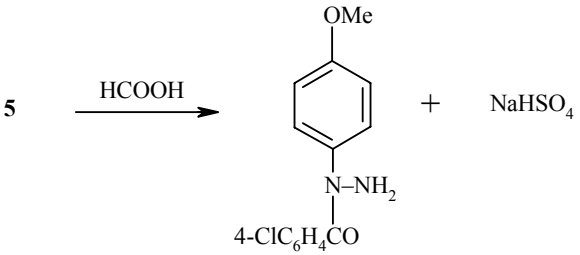

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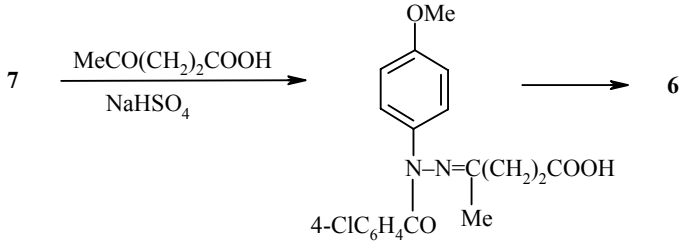
We propose that under the action of formic acid removal of the sulfonate group occurs with the formation of sodium hydrogen sulfate, which acts as an acid catalyst at the indolization stage, and proceeds without isolating the intermediate hydrazone **8**.



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It was shown experimentally that hydrazone **8** is not converted into indomethacin (**6**) on heating in formic acid in the absence of $NaHSO_4$.

EXPERIMENTAL

4-Methoxybenzenediazonium Chloride (2). A solution of sodium nitrite (12.3 g, 0.18 mol) in water (28 ml) was added with vigorous stirring to a cooled (-5°C) mixture of 4-methoxyaniline (**1**) (20 g, 0.16 mol), water (20 ml), and conc. HCl (45.6 ml) at such a rate that the temperature did not exceed 0°C. The mixture was stirred at the same temperature a further 30 min and a test sample was taken at the end of the diazotization reaction. The obtained solution of diazonium salt was used immediately to obtain sodium 4-methoxybenzenediazosulfonate.

Sodium 4-Methoxybenzenediazosulfonate (3). The reaction mixture after the diazotization reaction was poured in one batch into a solution of sodium sulfite (25.2 g, 0.2 mol) and NaOH (6.5 g, 0.16 mol) in water (150 ml) at 5°C, and stirred for 30 min. The resulting solid was filtered off, washed with 2-propanol (2 × 50 ml), and dried at room temperature. Yield 38 g. The compound obtained was used in the following stage without further purification to obtain sodium 2-(4-methoxyphenyl)-1-hydrazosulfonate (**4**).

Sodium 2-(4-Methoxyphenyl)-1-hydrazosulfonate (4). Sodium 2-(4-methoxyphenyl)-1-diazosulfonate (**3**) (38 g, 0.18 mol) was added with stirring to a solution of acetic acid (38 ml) in water (100 ml), and zinc dust (10.4 g, 0.16 mol) was added in portions with vigorous stirring to the resulting suspension. The mixture was stirred at room temperature for 4 h. The reaction mixture was cooled to 5°C, the solid was filtered off, and dried in a vacuum desiccator over $CaCl_2$ to constant weight. Yield 28 g (75%).

Sodium 2-(4-Chlorobenzoyl)-2-(4-methoxyphenyl)-1-hydrazosulfonate (5). A mixture of sodium 2-(4-methoxyphenyl)-1-hydrazosulfonate (**4**) (24.8 g, 0.1 mol), sodium acetate (10 g, 0.12 mol), glacial acetic acid (200 ml), and *p*-chlorobenzoyl chloride (15.4 ml, 0.12 mol) was stirred for 6 h. The solid was filtered off, and washed in turn with absolute ethanol (50 ml) and water (50 ml). The obtained compound was dried in a vacuum desiccator over $CaCl_2$ to constant weight. Yield 32.7 g (88%).

2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic Acid (Indomethacin) (6). A mixture of thoroughly powdered sodium 2-(4-chlorobenzoyl)-2-(4-methoxyphenyl)-1-hydrazosulfonate (**5**) (4.6 g, 0.012 mol), levulinic acid (1.5 g, 0.013 mol), acetic acid (35 ml), and formic acid (10 ml) was heated to boiling and maintained at this temperature for 6 h. The reaction mixture was cooled, poured into water (100 ml), and left for 12 h at room temperature. The solid was filtered off, washed with water (50 ml), and recrystallized from 50% aqueous alcohol (10 ml per g of crude substance). Yield 3.16 g (66%); mp 153-154°C. According to [2] mp 153-154°C.

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