

Synthesis and Characterization of Acetaminophen (paracetamol)[®] from Acetanilide by Diazotization Reaction and Comparing with Crude.



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ABSTRACT

This study describes the synthesis of acetaminophen is quite easy by new method via diazotization reaction. The prepared compound that is initiated from acetanilide as the first step of the reaction followed by nitration reaction of acetanilide to form p-nitroacetanilide , reduction of the final product to form p-aminoacetanilide, and creating a diazonium salt that is then reacted with solution of (10%,2.5M) sodium hydroxide . The prepared product was matched with the crude of paracetamol and the bands of FT.IR spectra of the product also was matched with FT.IR characterization of paracetamol tablets and the melting point too. The product which was carried out successfully by new path was very largely familiar in the chemical processes .The final produced yield 70 % as possible.

Introduction:

Acetaminophen (N-acetyl-P- Aminophenol) or Paracetamol, IUPAC Systematic Name 4-Hydroxy acetanilide , $C_8H_9NO_2$,AP) is a long-established substance being one of the most extensively employed drugs in the world ⁽¹⁾. Mild to moderate pain as well as for for treatment of headache and to reduce pyrexia ⁽²⁾. The painkilling properties of paracetamol were discovered by accident when a similar molecule (acetanilide) was added to a patient's prescription about 100 years ago, but since acetanilide was toxic in moderate doses⁽³⁾ . It is a valuable non-steroidal anti-inflammatory drug that is widely used for the management of pain and fever, in a variety of patients including children, the elderly and those with osteoarthritis. It is primary metabolic pathways involving the liver oxidation. ^(4,5) Some evidence suggests that ingestion of paracetamol in early life may cause asthma, eczema, and allergic rhinitis in some children . ⁽⁶⁻¹¹⁾

Exposure to paracetamol may increase respiratory oxidative stress by depleting glutathione in the lungs, thereby enhancing air way inflammation and broncho constriction ⁽¹²⁾.

Experimental:

Instrumentation :

FT-IR NICOLETIR-100- Infrared Spectrophometer was used to record the spectra using KBr disc as diffuse reflectance, Melting points were determined by an electric heated block apparatus (Gallen Kamp.).

Materials :

Conc. Hydrochloric acid was supplied by Fluka , ethanol absolute ,sodium hydroxide , acetanilide,acetic acid, sulfuric acid, nitric acid ,zinc , di ethyl ether ,di potassium carbonate , sodium nitrite , propanone , were supplied by BDH ,Tablets of paracetamol by SDI (samara drugs industrial) Iraq pharma ,The crude paracetamol was supplied by Furat company in iraq that imports from china .

General Procedures ⁽¹³⁾ :All reagents and solvents were used as obtained from commercial sources without further purification. .

FT.IR spectra of solids were obtained in KBr diffuse reflectance mode at Chemistry Depr. Coll. Of Education For Women , ANBAR UNIV.

p-Nitroacetanilide(2)⁽¹⁴⁾: Acetanilide (6 g, 44.4 mmole) was added to glacial acetic acid (10 mL) in a 50 mL Erlenmeyer flask while stirring, conc. sulfuric acid (10 mL) was poured into the solution until the acetanilide had dissolved. The flask was placed into an ice-salt bath and cooled to 5°C.

A solution of concentrated nitric acid (4 mL) and concentrated sulfuric acid (2.6 mL) was prepared.

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While stirring the acetanilide solution, the nitric/sulfuric solution was added drop wise at a rate such that the temperature did not rise over 20°C. the mixture was allowed to stand at room temp for 20 minutes. The reaction mixture was poured into cold water (50 mL) and ice (30 g) and the solid that formed was collected by vacuum filtration. The solid was washed three times by cold water (30mL) for research . The solid was recrystallized from ethanol, producing a pale yellow solid (3.3 g, 55% yield; mp 210-213°C, 215-217°C ⁽¹⁵⁾). A small amount was saved for analysis (IR and mp).

p-aminoacetanilide(3) ⁽¹⁴⁾: p-amino acetanilide (2g) was added to a 25 mL round bottom flask. While stirring , concentrated hydrochloric acid (5 mL) was slowly added. Zinc powder was added and all the contain was removed to beaker contain ice –salt as bath with stirring while all the portions was (20 mL) ,the reaction mixture was warmed in water bath for (10 mint) until dissolved all the mixture . A solution (24% ,6M) of sodium hydroxide was slowly added .Approximately (20-30 mL) to that was formed .The mixture separated by extraction from alkaloid compound . A small amount of potassium carbonate was added .

A water that soluble compounds was removed ,the organic layer was vaporated by vaccium , producing aplate browin solid (1.4 g ,70% yelid , A small amount was saved for analysis (IR and mp).

Acetaminophen(5) : A solution of concentrated hydrochloric acid (1 mL) and water (10 mL) was placed in a 50 mL Erlenmeyer flask. The solution was stirred while p-nitro acetanilide (2 g) was added. The mixture was cooled to 5°C in an ice bath. While stirring, a solution of sodium nitrite (0.5 g) in water (2 mL) was slowly added. The temperature was kept under 10°C. A solution of (10%,2.5M) sodium hydroxide (10 mL) was prepared and cooled to a temperature of 10°C and poured into the mixture with the diazonium salt to produce a phenol. The red white precipitate that formed was vacuum filtered and washed with water, producing a red white solid (70% yield; mp 166 -168°C).

Extraction and purification of paracetamol from tablets to use for comparing as a crude :

Two paracetamol tablets had been broken and was warmed with acetone (10mL) in small conical flask by placing the flask in warm 50°C water ,the undesolved

material was removed by using filter paper and funnel ,the propanone was allowed to be evaporated , the product crude paracetamol was white solid ⁽¹⁶⁾.

The amterial was purified by recrystallization from water by heating about (10 mL) of water to dissolve and any insoluble material was filtrated of glass wool in warm glass funnel ,the filtrate was cooled and dried the pure paracetamol washed by ether with filtered and dried in an oven.

Results and Discussion:

Acetanilide (mp 113.5-114°C) was nitrated to p-nitroacetanilide (mp 210-213°C, 215-217°C) ⁽¹⁷⁾ in 55% yield employing conc. nitric acid, glacial acetic acid , conc. sulfuric acid and an ice bath. The IR for acetanilide matched the spectra found in Aldrich Library of IR Spectra ^(20,21) with bands at: 3295-3000 cm^{-1} for a 2° amide or a NH stretch; 2000-1700 cm^{-1} for a monosubstituted benzene ring; 1664 cm^{-1} for C=O stretch (ketone); there are multiple peaks c. 1500 cm^{-1} that signify —C=C stretch (aromatic ring), N-O stretch, C-N amide; peak at 750 cm^{-1} that signifies N-H group bend (amides), monosubstituted benzene.

p-aminoacetanilide ⁽²¹⁾. The IR of p-aminoacetanilide (fig-1) matched the spectra found in the Aldrich Library of IR Spectra with bands at: 3400-3000 cm^{-1} signifying both and N-H stretch (2° amide), C-H stretch (aromatic); 1682 cm^{-1} C=O stretch (ketone); 1598, 1503 cm^{-1} C=C stretch (aromatic); 1567 cm^{-1} N-H bond (2° amide; C-N stretch (amide); 866-751 cm^{-1} N-H oop bend (amide); 851 cm^{-1} para disubstituted.

The group on p- aminoacetanilide was removed to form p-nitroacetanilide (mp 146.5-147°C, 147°C) in 70% yield using conc. Hydrochloric acid, (24%) 6M sodium hydroxide and zinc powder by ether. The IR for p-nitroacetanilide matched the spectra found in Aldrich Library of IR Spectra with bands at: 3482, 3361, 3228 cm^{-1} for N-H stretch (amine); 3100 cm^{-1} for C-H stretch (aromatic); 1632, 1594, 1476, 1452 cm^{-1} for C=C stretch (aromatic); 1500, 1400 cm^{-1} for N-O stretch; 1302 cm^{-1} for C-N amine (aromatic); 842 cm^{-1} N-H oop bend; c. 850 cm^{-1} for C-H group bend (para disubstituted).

The diazonium salt ⁽²¹⁾ of p-hydroxy acetanilide was formed by employing sodium nitrite and diluted conc. Hydrochloric acid (5mL) of 10% 2.5 M of sodium hydroxide was added to the diazonium salt by way of a substitution reaction . A solution of the

diazonium salt was warmed up kindly and gas was loosed to synthesis a phenols or can be substituted by OH group.

The yield (70 % ,mp.166-168°C) was collected after crystallization, FT.IR for the product(Acetaminophen) as the spectra in (fig 2) with bands 3325 cm^{-1} for (O-H group); 3413 cm^{-1} for C-N amide; 1662 cm^{-1} C=O stretch(ketone); 1552 cm^{-1} C=C stretch (aromatic); 850 cm^{-1} for C-H group bend (para disubstituted).

FT.IR of (Acetaminophen) spectra matched the spectra of that was extracted from paracetamol as medicine (mp.170°C) Relative molecular mass: 151.17) and the crude paractamol from furat company (mp.170 °C) , that can be show in the table(1).

The spectra results obtained besides the melting points are in a good accordance with that reported by the other authors .This enhance the validity of our new path for the synthesis of paracetamol .The spectra show in Figures (2,3,4). .

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Table(1) :FT.IR spectra bands of the Prepared compounds.

No.	Functional group	Prepared compound. cm^{-1}	Crude Medicine. cm^{-1}	Extracted Medicine. cm^{-1}
1	(C=C) aromatic	1508	1563	1508
2	C-H aromatic	3069	3025	3069
3	(N-H) Amide	3413	3325	3324
4	(C=O) ketone	1662	1654	1654
5	C-CH ₃	2926	2793	2881
6	O-H	3295	3163	3163

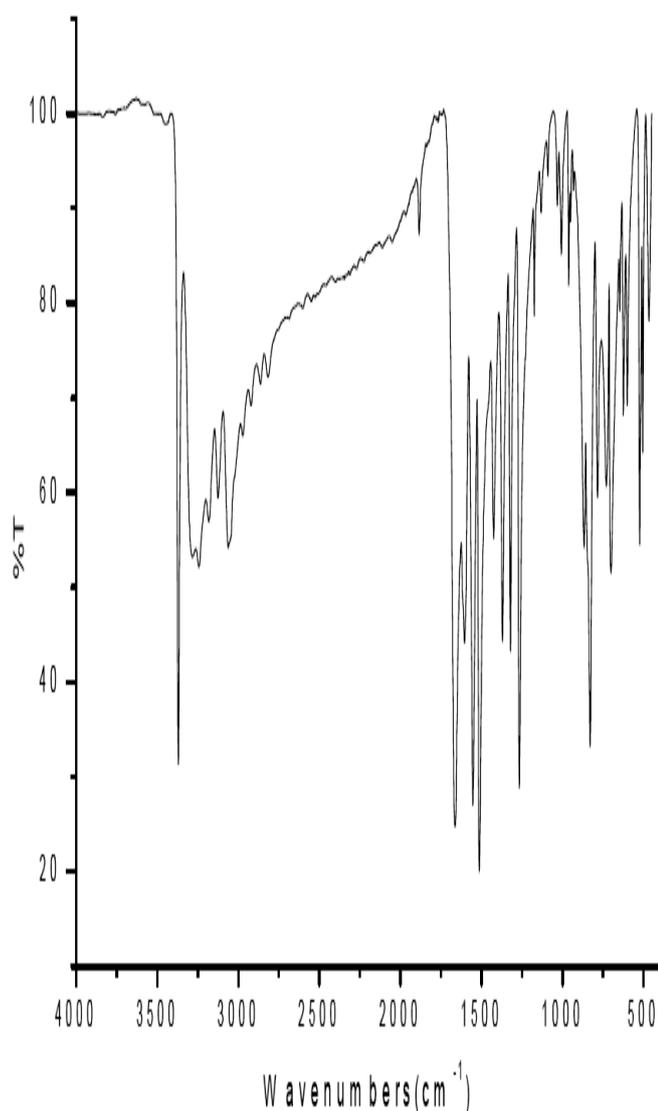


Figure (1) : IR spectra of p-aminoacetanilide(22)

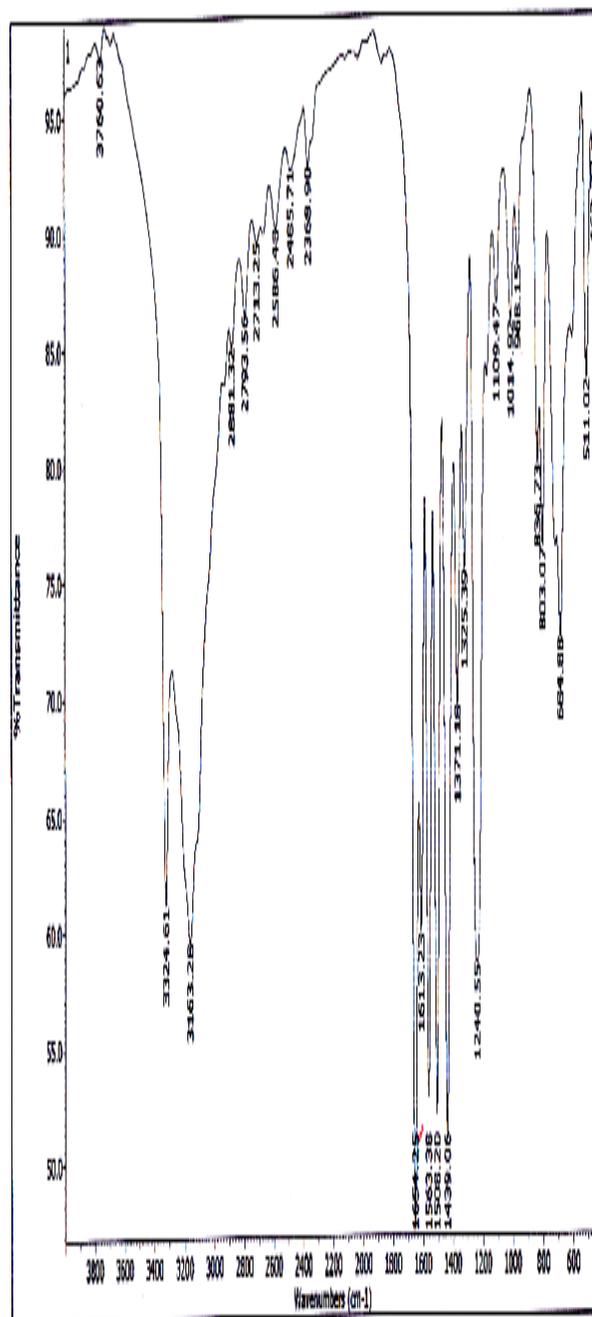


Figure (2) : FT.IR spectra of crude Acetaminophen.

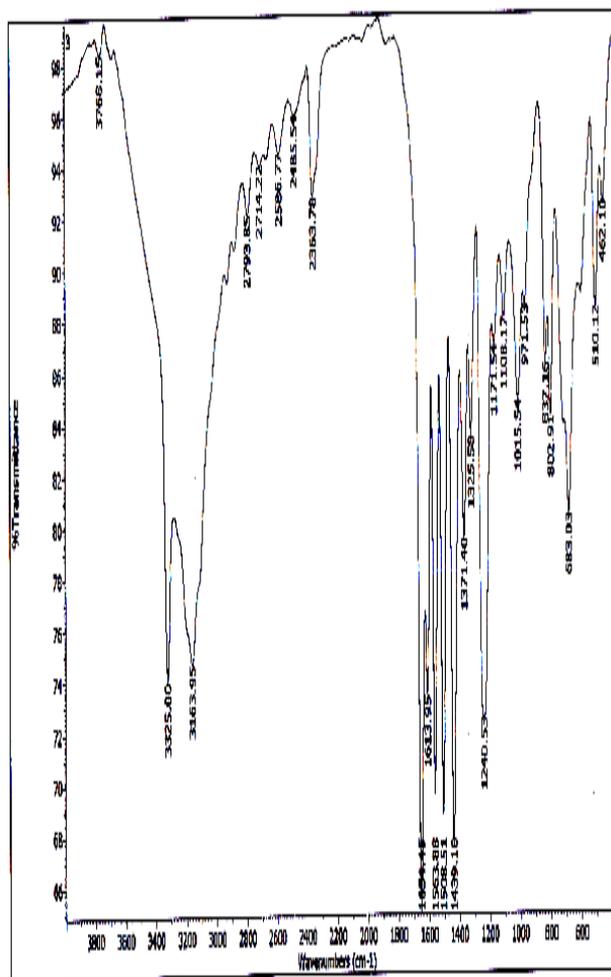


Figure (3) : FT-IR spectra of extracted Acetaminophen.

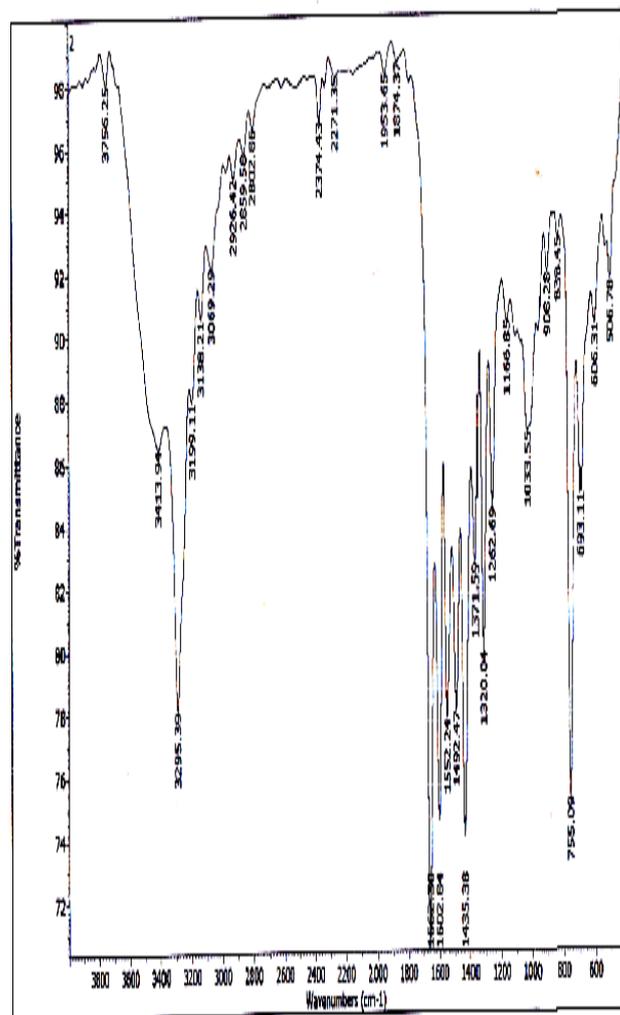
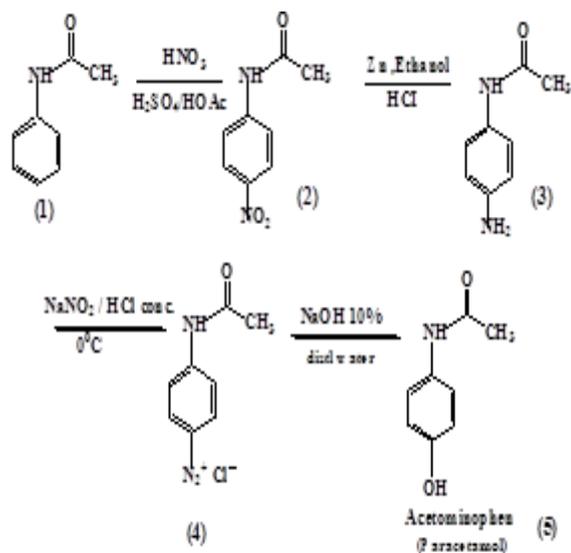


Figure (4) : FT-IR spectra of prepared Acetaminophen .



تحضير وتشخيص مركب اسيتومينوفين (الباراسيتامول)® من الاسيتنلايد بتفاعل الديليزة ومقارنته مع الأصل

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الخلاصة :

في هذا البحث تم تحضير مركب الاسيتومينوفين بطريقة جديدة وسهلة وغير مكلفة وذلك بتفاعل الديليزة , وقد تم تحضير المركب ابتداء من الاسيتنلايد كخطوة اولى للتفاعل , حيث تمت نيترة المركب لتكوين بارا نايترو استنلايد ثم اختزاله الى بارا امينواستنلايد ثم تحضير الدايزونيوم ثم عومل بمحلول (10% , M 2.5) هيدروكسيد الصوديوم بالتعويض النيوكلوفيلي للحصول على المقابل , تم فحص بعض الخصائص الفيزيائية مثل نقاط الانصهار للمركب وكذلك التشخيص الطيفي بالأشعة تحت الحمراء وقد جاءت النتائج مطابقة مع مركب الاسيتومينوفين القياسي إلى حد كبير (95%) تقريبا وكانت نسبة المنتج أكثر من 70 % تقريبا .