PREPARATION OF PARACETAMOL FROM PHENOL I

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ABSTRACT

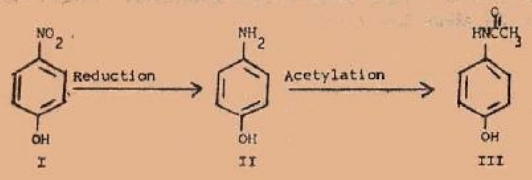
Paracetamol is one of the most heavily prescribed and purchased analgesics in Nigeria. However, a fortune of foreign exchange is lost by the country annually from its importation because the basic raw materials are not locally available. Now in the wake of petrochemical production within the country, about 30,000 metric tonnes of phenol are to be produced yearly by the Kaduna Plant. It will therefore be proper to start testing the feasibility of synthesising this drug from such basic molecules, with a view to establishing optimum reaction conditions for large scale manufacturing.

The synthesis of the drug via a three-staged reaction procedure starting from phenol is hereby reported. Thin layer chromatography, UV and IR spectroscopies were used in this pilot study, to prove the purity of the product obtained. Although the synthesis can be accomplished within a 24 hour period under laboratory conditions, the yield of paracetamol was found to be poor at 8% based on the amount of phenol used and 38% based on the p-nitrophenol intermediate. However, it was observed that improvement on the paracetamol yield could be investigated by applying further experimental controls on the nitration and isolation steps of the reaction route being reported.

INTRODUCTION

Paracetamol (III) is a drug which is familiar to most Nigerians. It is highly prescribed by physicians and heavily purchased as an over the counter drug for the alleviation of minor body pains headache and pyrexia. These are particularly common ailments in Nigeria, due to the hot weather and the manual nature of most of our day-to-day undertakings. Manufacturing business in paracetamol is therefore highly rewarding as evidenced by the many brand names that are today available in Nigerian market.[1] These include; Panadol®, Panamol®, Panatac®, Pentax®, and Anagol®.

Despite the numerous brand names however, a fortune of foreign exchange is annually expended on the importation of the drug both by the government and the manufacturers. This is because the basic raw materials needed for its snythesis are not locally available. A literature review of the various methods[2–5] of synthesis revealed the following typical reaction sequence.



In this sequence, either of the precursoer p-nitrophenol I or the intermediate p-aminophenol II can be regarded as a basic raw material, none of which has been available in Nigeria. Now in the wake of petrochemical avolution within the country, the produetion of up to 30,000 metric tonnes of phenol has been indicated to begin in the phase 3 of the NNPC petrochemical programme.[6] Phenol is base material for many industries and a feedstock for many end-use products. Booking for these few tons has therefore started in earnest. But it also has many basic pharmaceutical uses, including its being used in a one-step reaction to obtain precursor I in the synthesis of III. The feasibility of obtaining paracetamol starting from phenol was therefore undertaken and investigated with a view to laying proper groundwork for its local production in the coming era of petrochemicals in Nigeria.

EXPERIMENTAL

All solvents and acids were of laboratory grade and were used without re-distillation. The phenol and acetic anhydride (BDH, England) were also used without re-purification. The paracetamol product was characterised using TLC in methanol: ammonia (100: 1.5) mobile phase, UV (Pye-Unicam SP8-100UV/VIS) and IR (Pye Unicam SP3–300 IR) spectroscopies. The detection of spots on the TLC plates after chromatographic development was by viewing under UV lamp at 254nm. The melting point was determined on a Gallenkamp melting point apparatus.

p–Nitrophenol

Into a two-necked flask containing 80ml water was added 0.5 mole of concentrated sulphuric acid cautiously. The flask was cooled to about 10°C by placing inside an ice-water bath. Then 0.35 mole of sodium nitrate was dissolved in the acid solution. At this stage, 0.20 mole of phenol was melted with 4 ml water and the solution was added dropwise into the mixture in the flask at such a rate that the temperature did not exceed 20°C. After all of the phenol had been added, the mixture was allowed to stand for 1 h with frequent shaking. The solution was then poured into a separating funnel and left until the mother liquor clearly separated from the oily nitro products. After running off the mother liquor the oily residue was washed repeatedly with water in order to remove all traces of the acid in the mixture. The oil was then arranged for distillation to remove the low-boiling o-nitrophenol product. After no more o-nitrophenol residue was boiled with about 1g activated charcoal, and filtered. This was repeate i one more time before obtaining a creamy white shining crystals of the required p-nitrophenol which were filtered and dried between filter papers.

p-Aminophenol

In a condender – carrying flask containing all of the p-nitrophenol product synthesised above and 0.005 mole tin dust, was added very cautiously 0.09 mole concentrated hydrochloric acid. The reaction mixture was then placed in a water bath maintained at 80°C for 2 h with constant shaking the solid nitrophenol soon disappeared to give a dark solution containing the p-aminophenol which was used directly without isolation.

aracetamol

The pH of the solution above containing the p-aminophe-ol was adjusted to 6.5 with concentration ammonia. Then 1.02 mole of acetic anhydride was added and the mixture ncubated at 80°C in a water bath for 3 h, after which it was llowed to stand at ambient temperatures overnight.

About 100ml water was then poured into the reaction nixture and the solution heated with 1g charcoal for about min and filtered. This operation was repeated once more efore the decolourised filtrate was concentrated to low olume for white paracetamol crystals to be obtained. The rystals were filtered and washed with minimum amount of ce-cold water. The crystals were dried between filter paper.

RESULTS AND DISCUSSION

The results of the TLC showed single spots for both the eference and synthesised paracetamol with identical R_f alue of 0.82.

The melting point determination gave an uncorrected ange of 165 – 167°C (cf 168 – 172°C).[5]

Figure 1 shows the UV scan of both the reference and ynthesised paracetamol in 0.01M NaOH. Identical spectro-hotometric behaviour was observed with peak absorbances t 258nm.

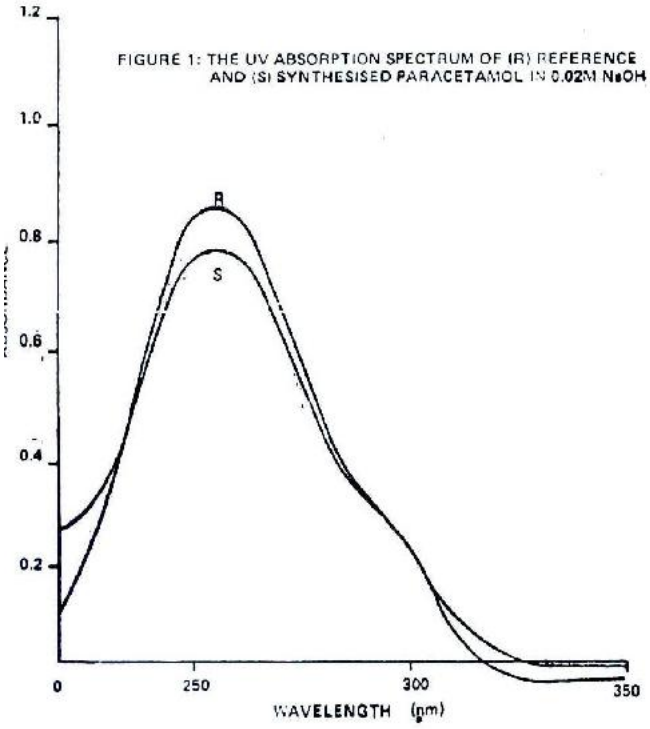


FIGURE 1: THE UV ABSORPTION SPECTRUM OF (R) REFERENCE AND (S) SYNTHESISED PARACETAMOL IN 0.02M NaOH

The IR scan of both samples showed that the relevant absorption bands are identical at 3400 – 3000cm^{-1} (s) due to the H-bonding vibrations of the phenolic OH, 167cm^{-1} (s) due to the C = 0 shetching vibration, 1600cm^{-1} (s), 1570cm^{-1} (s) and 1520cm^{-1} (s) all due to the aromatic vibrations of the phenyl ring in paracetamol.

Economics

Although the synthesis of paracetamol can be accomplished within a 24 hour period, the yield of the paracetamol was found to be 8% based on the phenol precursor and 38% based on p-nitrophenol intermediate. This yield is obviously very low especially for industrial applications. However this present work is merely investigatory and subsequently, improvement on some of the reaction steps shall be attempted in order to get optimum paracetamol yield. Two such steps are identifiable,

(i) Nitration of phenol. This gives both o and p-nitrophenol products, with the o-product usually in higher yield. The yield of the p-product which is required could be increased to a major proportion probably by hindering sterically the approach of the NO_2^+ electrophile to the o-position. This could be acheived by staring with acetylated phenol. The carboxy group on the phenolic oxygen would be expected to reduce the general o/p directability of the oxygen and also electronically and sterically hinder the o-position; such that the reaction will have to take place at the farthest point away (p-position) from the directin goxygen.

(ii) Isolation of paracetamol. As dark-brown coloured paracetamol is usually obtained more than two steps of boiliding with decoloruing charcoal were normally required before white crystals of paracetamol could be obtained. Unavoidably, the charcoal often adsorbs some of the products away from solution during these decolourisation stages. Isolation by extraction with chloroform or ether was tried initially, but brownish crude products were also obtained. Perhaps a combination of extraction and crystallation would suffice for obtaining pure paracetamol in good yield.

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