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Drug Design 2020: The potential use anacardic acid in the synthesis of the 1, 4-Dihydroxy anthraquinone- Lydia Kisula- Rhodes University

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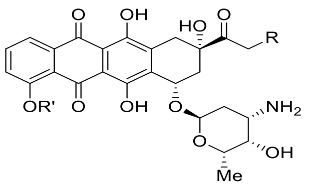
Anthraquinone moiety is an important constituent of the largest group numerous naturally occurring quinones (Roy et.al 2016). Anthraquinones have long been used as an active ingredient in most of the traditional Chinese herb medicine (Tatyana 2009 and Chu et.al 2012). Due to their broad diversity and numerous applications both in the pharmaceutical industry and dye industry these compounds have raised interest in chemists.

Anthraquinones are most famous in cancer chemo-therapy for example anthracyclines such as doxorubicin and daunomycin (fig 1) are used for treatment of various human cancers (Zhao et.al 2015).



1: R = H, R' = Me Adriamycin (Doxorubicin)

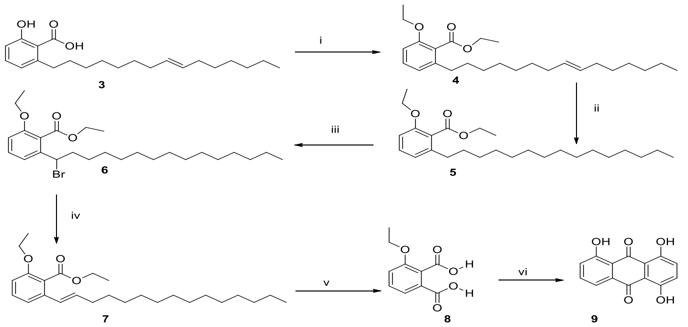
2: R = OH, R' = Me Daunorubicin

Figure 1: The anthracycline anticancer drugs Adriamycin (1) and daunorubicin (2)

The presence of the 1,4-dihydroxyanthraquinone is the predominant feature of the anthracyclines. This feature has caused in recent days, the 1,4-dihydroxyantharquinone to be employed as a synthon for the construction of other compounds with improved anticancer efficacy (Liu et. al 2019 and Zhao et.al 2013).

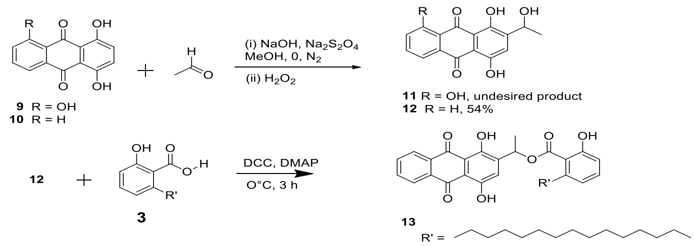
On the other hand the cashew nut shells are the agro-wastes from the cashew industry. The liquid obtained after extraction of the shells is called the cashew nut shell liquid (CNSL) and is source of unsaturated long-chain phenols that are of many industrial applications (Rodrigues et.al 2006).

One among the components of CNSL is anacardic acid 3, this report gives the synthetic conversion of anacardic acid to 1,4,5-trihydroxy anthraquinone (Scheme 1). This is the first report for the 1,4,5-trihydroxyanthraquinone 9 to be synthesized from the agro-waste cashew nutshells



Scheme 1: synthetic convesion of anacardic acid 3 to 1,4,5-trihydroxy anthraquinone 9
(i) Diethylsulphate, DMS, K_2CO_3 ACN 24 h, 90° C, (ii) Pd/C 24 h Methanol, (iii) NBS, BPO,CCl_4, 3 h 90° C
(iv) DBU, 5 h Toluene 110°C (v) $FeCl_3.6H_2O$, aq. 70% TBHP, 36 h NaOH, H_2O, 80 ° C
(vi) NaCl/$AlCl_3$, 180-220 ° C,1½ h

Subjecting compound **9** to Marschalk reaction could not give the desired product. However quinizarin **10** from commercial source reacted well with acetaldehyde. Considering the useful biological activities of anthraquinones and anacardic acid the study was further extended to synthesize esters of 2-substituted 1,4-dihydroxy-9,10-anthraquinones



Scheme 2: Synthesis of 2-substituted 1,4 -dihydroxyanthraquinone ester

This dissertation reports on the synthetic efforts towards (S)-1,6-dihydroxy-7-(1- hydroxyethyl)anthracene-9,10-dione (3), an anthraquinone which is analogous to a naturally occurring (S)-1,2,6-trihydroxy-7-(1- hydroxyethyl) anthracene-9,10-dione (4), from simple and readily available anacardic acid (5). The main goal was to prepare the substituted phthalic anhydride namely 4-methoxyisobenzofuran-1,3-dione (6) from anacardic acid (5) and subsequently couple this phthalic anhydride with the benzene derivative (s)-2-(1- hydroxyethyl)phenol (7) to obtain the targeted anthraquinone 3. Anacardic acid, the major phenolic constituent of natural cashew nut shell liquid was isolated as a stable salt of calcium and used as starting material in the synthesis. Subjecting this through a series of reactions gave the desired 3-methoxyphthalic anhydride 6. The benzene derivative, 2-acetylphenol (8), which is the immediate synthetic precursor of 7, was prepared from phenol. Subsequently, Friedel-Crafts Acylation (FCA) was employed in coupling 6 and 8 to get anthraquinone 7-acetyl1,6dihydroxyanthracene-9,10-dione

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(50), which is very advanced precursor of targeted anthraquinone 3. However, the face reaction gave the anthraquinone 2-acetyl-1,8- dihydroxyanthracene-9,10-dione (51) which was obtained in small quantity and moderate purity and thus hindered its complete structural assignment as well as its further information. During the synthesis, the progress of the reaction was monitored by TLC whereas column chromatography was used in the purification of most of the synthesized compounds. Both 1H- and 13C-NMR techniques were used in the confirmation of the chemical structure of the synthesized compounds.

CONCLUSIONS:

The depletion of fossil fuels as sources of fine chemicals for various applications calls for search for alternative renewable sources. Nature is abounding with materials which when appropriately manipulated can serve as renewable supplies of fine chemicals. One such material is Cashew Nut Shell Liquid (CNSL) from the cashew plant Anacardium occidentale which is grown along the coast of Tanzania for its kernels, cashew nuts. Cashew Nut Shell Liquid is rich in phenolic compounds with unsaturated C15 side chain meta substituents (Akinhanmi and Atasie 2008). Both the phenolic, alkene and carboxylic acid functional groups present in these natural lipids renders components of CNSL amenable to transformations into a variety of materials and fine chemicals.

The authors has reported on the utilization of cardanol components and anacardic acid of nCNSL in the synthesis of dyes, a detergent, a kairomone component and other useful chemicals. The chemistry reported in this paper has demonstrated once again the versatility of cashew nut shell liquid as a renewable natural resource for synthesis of fine and industrial chemicals. Accordingly, further synthetic work on the use of cardol and cardanol, the other major components of Cashew Nut Shell Liquid, as starting material for synthesis of fine chemicals and natural products is in progress and shall be reported in due course