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SYNTHESIS OF 4, 5-DIHYDROXY-9, 10-DIOXOANTHRACENE-2-BENZYL CARBOXYLATE ESTER FROM RHEIN

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ABSTRACT

Rhein and several analogues thereof, are particularly important from commercial point of view and are known for their use in the treatment of degenerative diseases of the joints, for example osteoarthritis, osteoporosis and rheumatoid arthritis. Rhein occurs in nature in plant families such as *Cassia, Rheum* and *Rhamnus,* but in a very less concentration. Aloin, a natural substance isolated from various species of aloe, consist almost exclusively of barbaloin (10-β-glucopyranosyl-1, 8-dihydroxy-3-hydroxymethyl-anthracen-9-one). Barbaloin, the C-glycoside of aloe-emodin anthrone, localizes in the outer rind of the aloe vera leaf, has been reported to constitute upto 30% of aloe plants dried leaf exudate and proposed as a part of defense mechanism against herbivores. In this paper, an attempt has been made to prepare rhein from barbaloin via formation of aloe-emodin and its chemical modification using benzyl alcohol to prepare its benzyl carboxylate ester.

INTRODUCTION: Rhein (1, 8-dihydroxyanthraquinone - 3- carboxylic acid) [1] is a compound found in the free state and as a glucoside in *Rheum* species, senna leaves; and also in several other species of Cassia [2]. Rhein (**Fig. 1**) is currently a subject of interest because of its antifungal, antiviral, antitumor, antioxidant and antiangiogenic effect [3, 4, 5, 6].

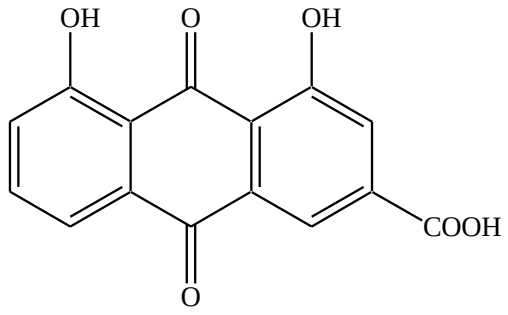


Fig 1. Rhein

It also serves as a starting compound for the synthesis of diacerein (1, 8-diacyl derivative of rhein) [7] (**Fig. 2**) which has anti-inflammatory effect and is useful in the treatment of osteoarthritis, characterized by a progressive destruction and erosion of cartilage.

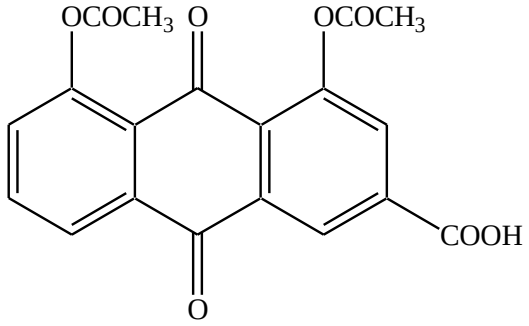


Fig 2. Diacerein

Recently, it has been found that these molecules might be used for the treatment of chronic inflammation, the prevention and the treatment of organ and tissue transplant rejection, the treatment or prevention of vascular diseases and in treating insulin resistance. According to the recent resurgence of interest of this significant class of molecules, the need of material for clinical trials and biochemical evaluations is therefore obvious [8]. Thus; an attempt has been made to synthesize rhein from barbaloin (**Fig. 3**) via aloe-emodin (**Fig. 4**) and its chemical modification using benzyl alcohol to prepare its benzyl carboxylate ester.

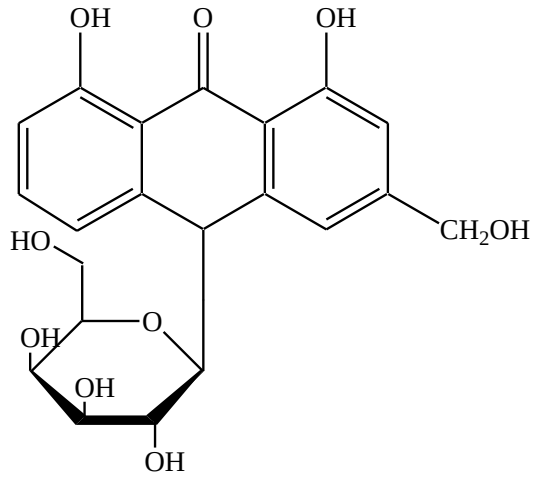


Fig 3. Barbaloin

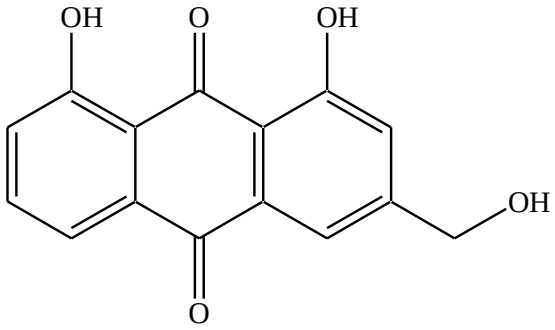


Fig.4. Aloe-emodin

MATERIAL & METHODS: All the chemicals were of analytical grade. Jasco V-530 UV/VIS sectrophotometer was used for analysis. IR spectra were taken as KBr pellets on Perkin-Elmer FTIR spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on a JEOL, FT NMR, JMM-MY 60 FT in DMSO-d_6. Mass spectra were recorded on Micromass, Q-TOF MS ES+.Aloin (72%) was procured from Yucca Enterprises.

Rhein was prepared semi synthetically by two steps (**Fig. 5)**:

A) Conversion of barbaloin to aloe-emodin

B) Oxidation of aloe-emodin to rhein

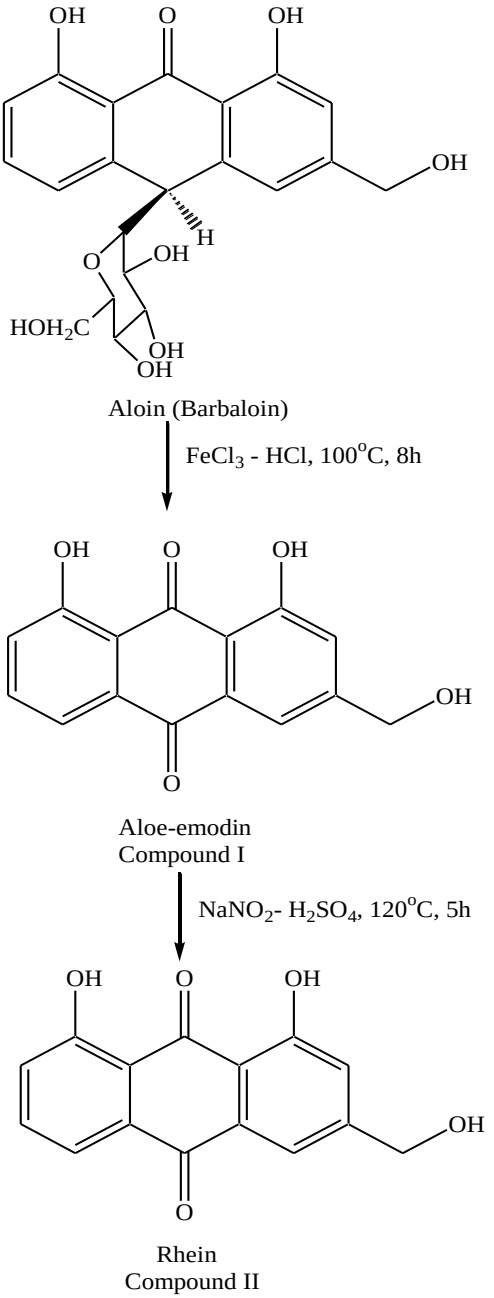


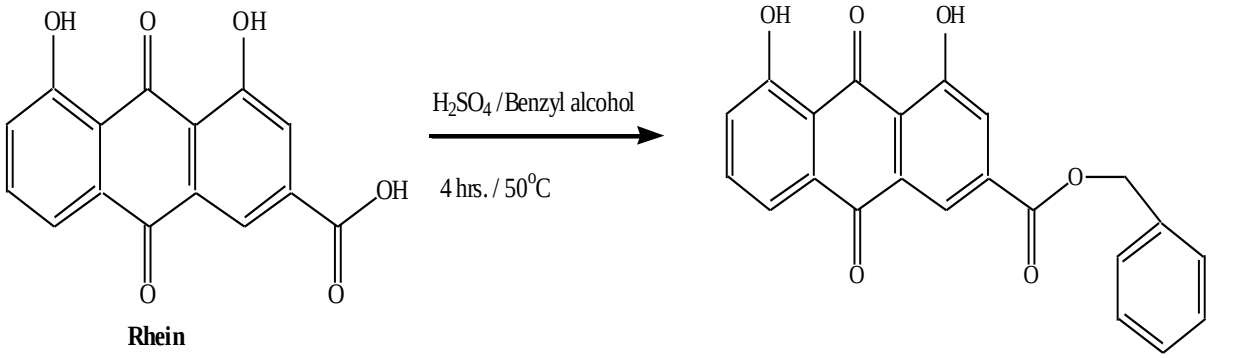
FIG. 5: SEMISYNTHETIC PREPARATION OF RHEIN

Step 1: Oxidative hydrolysis of barbaloin to aloe-emodin: Oxidative hydrolysis of barbaloin was carried out using ferric chloride and hydrochloric acid. About 10 g of barbaloin (about 72% pure) was added to an acidic solution comprising of a mixture of 250 ml of concentrated hydrochloric acid with 750 ml of water. 500 ml of a 20 % aqueous solution of ferric chloride solution was added to the above acidic solution and the resulting mixture was transferred to a round bottom flask. Toluene, about 300 ml of was added to the above solution and the biphasic mixture refluxed for 8 h at 100 $\pm$ 10˚C. At the end of 8 h the reaction mixture was allowed to cool to about 90˚C and the organic layer was separated, collected and kept overnight at 8 $\pm$ 2˚C to yield crystals of aloe-emodin (Compound I).

Step II: Oxidation of aloe-emodin to rhein: In this procedure the aloe-emodin which was prepared from barbaloin is first subjected to oxidation. Sodium nitrite 1.275 g was dissolved in 7 ml of sulphuric acid; the solution was heated to about 120°C. Aloe-emodin, 0.5 g of was added in parts to this mixture over a period of 30 min. The reaction mixture was kept at this temperature for 5 h.

At the end of 5 h the reaction mixture was poured into ice to get orange brown precipitate (containing a mixture of rhein and the starting material aloe-emodin). The precipitate so formed was filtered and dried to obtain crude rhein. This was then dissolved in sodium carbonate solution pH below 9.5 and extracted with organic solvent. The unreacted aloe-emodin present gets extracted into the organic solvent (Toluene). Rhein is again regenerated from sodium bicarbonate solution using hydrochloric acid. The precipitate is then filtered, washed, dried and recrystallized from methanol to obtain rhein (Compound II).

Esterification of rhein with benzyl alcohol (Fig.6): Rhein (0.300 g) was dissolved in methanol (10 ml) and benzyl alcohol (1 mol) was added to it. Sulphuric acid (0.5 mol) was added as a catalyst. The reaction was stirred for 4 hours at 50 ^{0}C. Further purification was carried out using column chromatography with Petroleum ether: Ethyl acetate (80:20) as mobile phase.Orange colored compound was obtained (Compound III).



Rhein

4,5-dihydroxy-9, 10-dioxoanthracene-2-benzyl carboxylate ester

Compound III

FIG. 6: ESTERIFICATION OF RHEIN WITH BENZYL ALCOHOL

RESULTS AND DISCUSSION: The compounds (both final and intermediate) were subjected to spectral analysis to confirm their molecular structures apart from comparative records of their m.p. / b.p., while the progress of the reaction was monitored by TLC. The characteristic absorption bands (IR and NMR) of the compounds as shown are well in conformity with these given in literature and these confirmed the molecular structures of the target compound. Some important peaks of IR and NMR peaks of synthesized compound are given below.

Aloe-emodin (I): Orange crystals (total yield 49.01 %); R_f 0.36 [Petroleum ether: ethyl acetate (7:3)] ; Melting point 221-222^{o}C. λ_{max} (MeOH) 291, 428. IR Spectra (KBr, ν_{max}, cm^{-1}): 1633.7 (Aromatic C=C), 1651.6 (Ketone), 3432.2 (OH), cm$^{-1.}$ ^{1}H-NMR (DMSO-d_6) – δ 11.93 (2H), 7.8-7.3 (5H), 5.61 (1H) , 4.62(2H). $(M)^+$ at m/z - 271 (Ionization mode TOF MS ES+).

Rhein (II): Yellow solid (total yield 55.48 %); R_f 0.4[ethyl acetate: methanol: water (100:13.5:10)]; Melting point 320-322ºC. λ_{max} (MeOH) 256, 332, 430. IR Spectra (KBr, ν_{max}, cm^{-1}): 1695 (carbonyl), 1629 (carboxyl), 3063 (-OH).^{1}H-NMR (DMSO-d_6) – δ 12.1(2H), 7.2-8.5 (5H), 13.5 (1H). $(M)^+$ at m/z- 285 (Ionization mode TOF MS ES+).

4, 5-dihydroxy-9, 10-dioxoanthracene-2-benzyl carboxylate ester (III): Orange solid; R_f 0.40 [petroleum ether: ethyl acetate (7:3)]; 149-151 ^{0}C. λ_{max} (MeOH) 436. IR spectra (KBr, ν_{max}, cm^{-1}) : 1605.1(Aromatic C=C), 1664 (Ketone), 1722(C=O),2729 (-CH), 3434 (OH) cm^{-1}.^{1}H-NMR (DMSO-d_6) – δ 11.89 (S, 2OH), 8.11 (S, 2H), δ 7.80-7.22 (d, 3H), 7.51-7.41 (m, 5H), δ 5.40(S, 2H). $(M)^+$ at (-CH_2) m/z- 373 (Ionization mode TOF MS ES+).

CONCLUSION: Hence an attempt has been made to synthesize rhein via aloe-emodin and a new benzyl carboxylate ester derivative of rhein using benzyl alcohol; however this compound needs to be evaluated for its efficacy.

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