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ISOLATION AND SYNTHESIS OF SOME COUMARIN COMPONENTS OF *MESUA FERREA* SEED OIL

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Abstract—Two different samples of *Mesua ferrea* seed oil yielded mammeigin and mesual as the main phenolic components. The synthesis of mammeisin and mammeigin has been carried out and also the conversion of mesual into mesuagin.

Mesua ferrea (Guttiferae) is a large tree common in Assam forests and the mountain regions of the west coast of India. It is very rich in oil (about 80%) but the oil is considered to be of poor quality because of the presence of polyphenols and volatile components of objectionable odour which seem to consist largely of carbonyl compounds.¹ The polyphenols consist of a number of hydroxy 4-phenyl coumarins which have been classed as neoflavanoids. The earliest to be isolated was mesuol² (I) and its correct constitution was established by Chakraborty and Das.³ The presence of mammeisin⁴ (II) has been reported in a sample of the seed oil obtained from Mysore State. More recently, mesuagin⁵ (III), a recent addition to the group of 4-phenyl coumarins and mammeigin (IV) have been found in a sample of the Assam seed oil. In this communication we wish to record our findings using different samples of Assam seed oil and also on some synthetic studies on related 4-phenyl coumarins.

A convenient method for isolating the phenolics present in the oil is by shaking the oil with methanol, concentrating the methanol extract and chromatographing it over a column of silica gel. By employing this procedure we have isolated mammeigin (IV) as the sole 4-phenyl coumarin from one sample of the Assam seed oil, though the presence of mammeigin (IV) and mesuagin⁵ (III) has been reported from another sample obtained from the same area. A further different sample of the oil examined by us when subjected to similar treatment yielded mesuol (I). The above method is more economical and less laborious. Mammeigin isolated from the *Mesua ferrea* oil has been found to be identical in all respects with a sample kindly supplied by Prof. R. A. Finnegan. The methyl ether of mammeigin (V) has been prepared as a useful derivative.

The study of the methods of synthesis of C_5 -substituted polyphenols has been in progress in this laboratory. As part of this programme the synthesis of mammeigin (IV) has now been carried out. The key intermediate in this synthesis is 4-phenyl-5,7-dihydroxy-6-isovaleryl coumarin (VI) which has been prepared by subjecting phloro-isovalerophenone obtained by the method of Kenny *et al.*⁶ to Pechmann condensation with benzoyl acetic ester. This

¹ K. R. BALA, S. NEELAKANTAN and T. R. SESHADRI, Current Sci. 37, 421 (1968).

² P. DUTTA, N. C. DEB and P. K. BOSE, J. Indian Chem. Soc. 17, 277 (1940).

³ D. P. CHAKRABORTY and B. C. DAS, Tetrahedron Letters 5727 (1966).

⁴ M. SUBRAMANYAM RAJU and N. V. SUBBA RAO, Indian J. Chem. 7, 1278 (1969).

⁵ D. P. CHAKRABORTY and D. CHATTERJI, J. Org. Chem. 34, 3784 (1969).

⁶ T. S. KENNY, A. ROBERTSON and S. W. GEORGE, J. Chem. Soc. 1601 (1939).

condensation has been recently carried out by Crombie *et al.*⁷ who obtained the 6-acyl coumarin (VI) as the sparingly soluble fraction that comes out of the reaction mixture, where as the 8-isomer (VII) was obtained from the mother liquor. In our experiment the 6-isomer (VI) has been obtained in markedly higher yield. An attempt to prepare the 7-propargyl ether of (VI) using 2-chloro-2-methyl-but-3-yne and cyclizing it to get mammeigin (IV) was not successful. Probably the presence of more than one reactive hydroxyl causes difficulty. Alternatively mammeigin (IV) has been synthesized using mammeisin (II) as an intermediate. In this connection 4-phenyl-5,7-dihydroxy-6-isovaleryl coumarin (VI) was subjected to prenylation with 2-methyl but-3-ene-2-ol in the presence of BF₃-etherate and the prenylated compound was found to be identical with a natural sample of mammeisin (II).





The C_5 unit has thus been introduced into a preformed 4-phenyl coumarin nucleus and in the compound under consideration the only vacant position where the C_5 unit can be attached is the 8-position. Therefore this constitutes an unambiguous synthesis of mammeisin (II) and confirms its constitution.

The next step was the oxidative cyclization of mammeisin (II) using DDQ. Treatment of mammeisin (II) with molar quantities of DDQ at room temperature gave mammeigin (IV) in almost quantitative yields. Mesuol (I) was then subjected to similar oxidative cyclization and the cyclized compound was found to have the properties reported for mesuagin⁵ (III). It was however observed that larger quantites of DDQ than the molar proportion or heat treatment in these conversions resulted in very poor yields. This facile conversion of mammeisin (II) and mesuol (I) to the corresponding chromeno compounds provides an explanation of their co-existence in nature.

EXPERIMENTAL

All m.ps are uncorrected. U.v. spectra were taken on a manual Hilger spectrophotometer in 95% EtOH; log ϵ values are given in brackets. I.r. spectra were recorded in KBr on a Perkin-Elmer infracord. Light petroleum had b.p. 60-80°. TLC was done on silica gel supplied by the National Chemical Laboratory, Poona. Unless otherwise stated the solvent system used for TLC was benzene (BDH).

Isolation of Mammeigin (IV) and Mesuol (I)

Mesua ferrea seed kernel powder (800 g) collected during 1967 was extracted with light petroleum in a soxhlet for 48 hr and the extract concentrated under reduced pressure to yield oil (616 g). The oil (150 g) was

⁷ L. CROMBIE, D. E. GAMES and A. MCCORMICK, J. Chem. Soc. (c) 2553 (1967).

shaken with MeOH (400 ml) in a bottle for 6 hr and left overnight for the emulsion to break. MeOH was separated and the process repeated $\times 3$. MeOH from the combined extract was removed under reduced pressure. The residue was distilled with benzene (250 ml $\times 3$) to remove moisture. The extract thus obtained was treated with excess of light petroleum and left overnight when a sticky brown mass separated. It was an inseparable mixture and was not investigated. The clear solution was decanted, concentrated to a small volume and passed through a column of silica gel. The column was eluted successively with light petroleum, benzene and MeOH. Benzene and MeOH eluates did not yield any crystalline compound. Light petroleum eluate when rechromatographed over a column of silica gel yielded a compound which crystallized from MeOH as fine yellow needles, yield 490 mg, m.p. 144–146°, M⁺ 404. (Found: C, 74·7; H, 6·2; C₂₅H₂₄O₅ requires C, 74·2; H, 5·9%). The compound gave green ferric reaction. These properties suggested the compound was mammeigin and the identity was confirmed by comparison with a sample of mammeigin provided by Prof. R. A. Finnegan.

Subsequent Et_2O and acetone extracts of seed kernel residue did not yield any crystalline compound. The EtOH extract yielded a white crystalline substance which gave Molisch's test, m.p. 183–184°, $[a]_D + 66°$. These properties agreed with those of sucrose and the identity was confirmed by comparison with an authentic sample.

An earlier sample of oil, collected during 1965 when subjected to similar treatment yielded mesuol which was identical with a sample of mesuol sent by Dr. D. P. Chakraborty.

Methyl Ether of Mammeigin (V)

Mammeigin (60 mg) was refluxed with Me_2SO_4 (0.2 ml) and K_2CO_3 (1 g) in acetone (10 ml) for 5 hr. The product crystallized from light petroleum as colourless cubes, m.p. 126–129°. (Found: C, 75.3; H, 6.7; --OCH₃ 13.8; $C_{26}H_{26}O_5$ requires C, 75.0; H, 6.7; --OCH₃ 14.0%.)

4-Phenyl-5.7-dihydroxy-6-isovaleryl Coumarin (VI)

To a mixture of phloro-isovalerophenone⁶ (1 g) and benzoyl acetic ester (1 g) in glacial HOAc (15 ml) was added conc. H_2SO_4 (0.6 ml). The solution which was initially yellow acquired a deep yellow colour. It was kept at room temp. for 3 days when almost colourless needles separated. The crystals were filtered, washed with light petroleum and then with H_2O and dried (0.5 g). It crystallized from MeOH as long colourless needles, single spot on TLC, $R_f 0.75$ (benzene-ethyl acetate, 50:15), m.p. 242-244° (lit⁷ m.p. 244-245°). It gave brownish green ferric reaction. (Found: C, 70.8; H, 5.6; $C_{20}H_{18}O_5$ requires C, 71.0; H, 5.3%.)

Mammeisin (II)

The above ketone (150 mg) was dissolved in dry dioxan (10 ml) and freshly distilled BF₃-etherate (0.5 ml) was added. The solution which was pale yellow initially acquired a deep yellow colour. To this was added 2-methyl-but-3-ene-2-ol (0.05 ml) and the solution was stirred for nearly 90 min at 50°. Excess ether was added to the mixture and the solution washed with water (10 ml \times 3) to remove dioxan. The Et₂O layer was dried (Na₂SO₄) and concentrated to a small volume when the unreacted ketone crystallized out first. The mother liquor on careful fractional evaporation yielded a yellow crystalline compound (25 mg) which was repeatedly crystallized from a mixture of benzene-light petroleum yielding pale yellow stout rectangular prisms which started sintering at 92° and melted completely at 112° (lit.⁷ m.p. 83-84°; lit.⁸ m.p. 98-109°). The compound gave brownish green Fe³⁺ reaction. Natural sample of mammeisin after purification and crystallization showed the same behaviour on heating. The synthetic sample was found to be identical with the natural sample in all respects (R_{f_2} mixed m.p. and i.r.).

Mammelgin (IV)

To a solution of mammeisin (25 mg) in dry benzene (3 ml) was added DDQ (1 mole). The deep orange solution was kept shaking for 2 hr at room temp. (28°). A buff coloured solid separated. After leaving overnight, the mixture was filtered to remove the solid, the clear solution concentrated to a small volume and then passed through a column of silica gel. The column was eluted with a mixture of benzene-light petroleum (1:3). The yellow coloured band which started moving first was eluted. The eluate (TLC single spot) was evaporated to dryness; the residue crystallized from methanol as yellow needles m.p. 144–145° alone or on admixture with a natural sample of mammeigin, λ_{max} synthetic and natural 233, 286 and 348–50 m μ (4·40, 4·49, 3·78), R_f identical and superimposable i.r. The conversion was almost quantitative. Both mammeisin and mammeigin have the same TLC R_f . But these can be distinguished when sprayed with alcoholic FeCl₃. Mammeisin produces brownish green colour and mammeigin a characteristic emerald green.

Mesuagin (III)

Mesuol (25 mg) in dry benzene (3 ml) was treated with DDQ (1 mole) and the reaction product worked up exactly as described in the conversion of mammeisin to mammeigin. The compound isolated from the

⁸ R. A. FINNEGAN, M. P. MORRIS and C. DJERASSI, J. Org. Chem. 26, 1180 (1961).

reaction mixture crystallized from light petroleum as yellow stout rectangular prisms, m.p. $151-153^{\circ}$ (lit.⁵ m.p. $152-153^{\circ}$) λ_{max} 233, 286 and 348-350 m μ (4·44, 4·53, 3·82), [lit.⁵ values 235, 285-286 and 362 m μ (4·31, 4·40, 3·79)]. A natural sample of mesuagin was not available for direct comparison. The i.r. spectrum of the synthetic sample compared well with the i.r. spectrum of mesuagin kindly supplied by Dr. D. P. Chakraborty. Here again, mesuol was found to give brownish green ferric reaction and mesuagin emerald green ferric reaction.

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