ON THE CHEMICAL CONSTITUTION OF MANGOSTIN. I.

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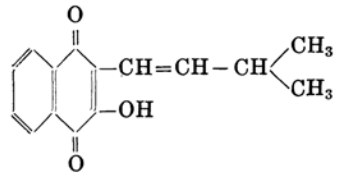
In the previous studies on mangostin, a yellow colouring matter extracted from the fruit-rind of *Garcinia mangostana*, many molecular formulas and various melting points were given to mangostin. W. Schmid,[1] P.R. Liechti,[2] Nijdam[3] and J. Dekker[4] presented $C_{40}H_{44}O_{10}$ (m.p. 190°C.), $C_{20}H_{22}O_5$ (m.p. 173°C.), $C_{23}H_{24}O_6$ (m.p. 176.5°C.) and $C_{16}H_{16}O_4$ (m.p. 176.5–177°C.) respectively. According to the results of the recent research reported by Dekker (loc. cit.) mangostin has one methoxyl and one hydroxyl groups in a molecule. In support of this fact he has shown that the methoxyl content of mangostin is about 8% (calculated value for $C_{15}H_{13}O_3 \cdot OCH_3$ is 11.4%) and that the methylation of mangostin gives a methylmangostin, which produces an acethyl-methylmangostin on acethylation. He also perceived smells resembling those of amyl alcohol and valerianic acid on alkali-fusion of mangostin, and has come to the conclusion that mangostin may probably be a methoxyl derivative of lapachol which has the annexed formula.



The present author re-examined the experiments carried out by the above mentioned investigators, especially by Dekker, and discovered some other new constituents and properties of mangostin, those of which are intended for a communication. It has, however, to be noted here that the experiments descrived in this paper had been made in 1927, when the publication of them was suspended by some reason, and that they are now communicated without any corrections to the author's opinion of that time, in spite of the fact that striking progress has lately been made in the investigations of mangostin.

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(1) Schmid, *Ann. Chem. Pharm.* **93** (1855), 83.
(2) Liechti, *Arch. Pharm.*, **229** (1891), 426.
(3) *Rec. Trav. Chim. Pays-Bas*, **35** (1916), 346.
(4) Dekker, *Rec. Trav. Chim. Pays-Bas*, **43** (1924), 727.

Mangostin, which the author extracted from the fruit-rind of *Garcinia mangostana* with ethyl alcohol and purified by recrystallisation from benzene and then from dilute ethyl alcohol, is a yellow leaflet crystal, which gives a dark green coloration with ferric chloride in dilute alcoholic solution and melts at 176.5–177°C. The results of the elementary analyses and the molecular weight determinations of mangostin correspond to the formula $C_{20}H_{22}O_5$, but the results of the determinations of methoxyl group give an appreciably lower value (OCH_3=7.50%) than the calculated value (OCH_3= 9.07%) for $C_{19}H_{19}O_4 \cdot OCH_3$.

On methylation with dimethylsulphate and potassium hydroxide in methyl alcoholic solution mangostin gives two kinds of methyl derivatives, both of which are not soluble in dilute alkalies and give the same coloration as that of mangostin with ferric chloride, and also the results of the elementary analyses and the molecular weight determinations of the derivatives correspond almost equally to a monomethyl-mangostin, $C_{19}H_{18}O_3$ $(OCH_3)_2$. But one is a yellowish-white needle crystal (m.p. 120.5–121°C., OCH_3=ca. 14%), which corresponds to the methylmangostin (m.p. 122.5–123°C., OCH_3=ca. 17%) prepared by Dekker, while the other (X) is a pale yellow leaflet crystal (m.p. 171–171.5°C., OCH_3=10.8%). The compound X seems to be an intermediate product of methylmangostin, since the methoxyl content of the former, as will be seen, lies between those of the latter and mangostin and also the compound X converts into the methylmangostin by further methylation with dimethylsulphate and potassium hydroxide.

An acethyl-methylmangostin prepared by acethylation of the methylmangostin with acetic anhydride and sodium acetate crystallises from benzene into white needles (m.p. 191–191.5°C.) and gives no coloration with ferric chloride in alcoholic solution. It corresponds to the acethyl-methylmangostin (m.p. 196°C.) prepared by Dekker, but the results of the analyses and the acethyl determinations correspond to the formula $C_{20}H_{20}O_4(OCH_3)COCH_3$.

Although the acethylation and the benzoylation of mangostin were tried under various conditions and many attempts were made on the separations of reaction products, it was difficult to fractionate the reaction products into pure components. It was, however, accomplished to isolate a compound which corresponds nearly to diacethyl-mangostin.

The methylmangostin seems to be an unsaturated compound, since it easily absorbs bromine in chloroform solution. A brominated methylmangostin prepared by the action of an equimolecular quantity of bromine on the methylmangostin in dry benzene solution is a deep yellow crystalline substance (decomp.p. 160°C.) and has a composition which corresponds almost nearly to a tribromo-methylmangostin. It is, however, so unstable

to water and light that the instability renders the purification of the bromo compound a matter of difficulty, namely, the tribromo-methylmangostin converts instantaneously on contact with water into a reddish-purple viscous matter which on exposure to light passes gradually into a yellow crystalline substance. Consequently it must be recrystallised from dry benzene and kept from moisture and light.

Considering the molecular formula of mangostin as $C_{20}H_{22}O_5=C_{19}H_{17}O_2(OH)_2\text{-}OCH_3$ from the above experimental results (notwithstanding the low methoxyl content which corresponds rather to $C_{24}H_{26}O_6$ than to $C_{20}H_{22}O_5$), the combined states of two atoms of oxygen are still unknown. To make clear it the author attempted to cause for mangostin the characteristic reactions of flavonol and also to prove the presence of some carbonyl groups in the molecule of mangostin by preparation of oxime and reduced acethylation of mangostin. He failed, however, to give any positive results.

When mangostin is subjected to alkali-fusion many decomposition products are formed. A vapour distilled from the melt during the fusion has an odour resembling that of amyl alcohol, as shown by Dekker, and condences on cooling to a minute quantity of yellow oil. From the melt six compounds can be isolated, of which oxalic, acetic, isovalerianic acids and phloroglucinol have been identified, while the other two compounds remain undetermined. One of the two unknown compounds, however, is a sparingly water-soluble acid which crystallises from water into yellowish-white microscopic needles (m.p. 373°C.) and the other is a water-insoluble yellow phenolic substance (m.p. 212°C.), which bears resemblance to mangostin in its chemical properties, namely, it gives a dark green coloration with ferric chloride and produces on alkali-fusion isovalerianic acid, phloroglucinol, and a vapour resembling amyl alcohol. This phenolic substance, however, differs from mangostin in crystalline form, melting point and composition, having the formula $C_{16}H_{16}O_5$. By the alkali-fusion of mangostin the present author obtained no benzoic acid reported by J. R. Hill[1].

Summary.

Judging from the above experimental results mangostin has the molecular formula $C_{20}H_{22}O_5$ and contains one methoxyl and two hydroxyl groups. It seems to be an unsaturated compound. The formations of isovalerianic acid and the oily matter resembling amyl alcohol by the alkali-fusion of mangostin suggest the presence of a branched side chain in the molecule of mangostin, and the isolation of phloroglucinol from the melt restricts the

(1) Hill, *J. Chem. Soc.*, **107** (1915), 595.

relative positions of methoxyl group, hydroxyl groups and oxygen atoms in the molecule of mangostin.

Although the author has failed to give any positive results in the researches for the characteristic reactions of flavonol and for the presence of carbonyl group in the molecule of mangostin, he has come to the conclusion that the chemical constitution of mangostin as a methoxyl derivative of lapachol is obviously untenable, since it is impossible to yield phloroglucinol from the derivative.

Experimental Part.

Mangostin. The dry powdered fruit-rinds of *Garcinia mangostana* were extracted with alcohol, and from the extracts alcohol was distilled off. The residues were extracted with hot water to remove a reddish-brown viscous matter and after drying were recrystallised from benzene. The yield of the crude mangostin was about 4.3% of the dry rind. The raw product was recrystallised repeatedly from benzene and 60% alcohol. The pure mangostin crystallised from dilute alcohol into yellow plates and melted at 176.5–177°C.

Anal. Subst. = 0.1605; CO_2 = 0.4105; H_2O = 0.0926 gr. Found: C = 69.75; H = 6.46%.

Mol. weight, measured cryoscopically in nitrobenzene, and after Rast. Subst. = 0.0756; nitrobenzene = 14.2390 gr.; f.p. depress. = 0.110°C. Found: mol. weight = 338. Subst. = 0.00135; camphor = 0.01168 gr.; m.p. depress. = 13.5°C. Found: mol. weight = 343.

Methoxyl, measured after Zeizel. Subst. = 0.00442; AgI = 0.00251 gr. Found: OCH_3 = 7.50%.

Calc. for $C_{19}H_{19}O_4 \cdot OCH_3$: C = 70.17; H = 6.43; OCH_3 = 9.07%; mol. weight = 342, and for $C_{23}H_{23}O_5 \cdot OCH_3$: C = 70.22; H = 6.39; OCH_3 = 7.55%; mol. weight = 410.

It was insoluble in water, petroleum ether, carbon tetrachloride and carbon bisulphide, but soluble easily in ether, alcohol, acetone, chloroform, nitrobenzene and acetic acid. It was also soluble in dilute alkalies and gave a dark green coloration with ferric chloride in alcoholic solution.

Methylmangostin. A solution of 10 gr. of mangostin in 300 c.c. of methyl alcohol was shaken with 50 gr. of dimethyl sulphate and then with an excess of 50% potassium hydroxide solution, separating out methylmangostin as a pale yellow crystalline substance. The methylmangostin was filtered after a short standing and washed with water and recrystallised from ethyl alcohol. It crystallised into pale yellow needles from alcohol and melted at 120.5–121°C. The yield was about 7 gr.

Anal. Subst. = 0.1334; CO_2 = 0.3470; H_2O = 0.0831 gr. Found: C = 70.94; H = 6.81%.

Methoxyl, measured after Zeizel. Subst. = 0.00443; AgI = 0.00474 gr. Found: OCH_3 = 14.13%.

Calc. for $C_{19}H_{18}O_3(OCH_3)_2$: C = 70.80; H = 6.74; OCH_3 = 17.42% and for $C_{23}H_{22}O_4(OCH_3)$: C = 70.75; H = 6.60; OCH_3 = 14.60%.

It was insoluble in water and sparingly soluble in cold alcohol, but very soluble in ether, acetone, benzene and ligroine. It gave a dark green coloration with ferric chloride in alcoholic solution.

The methyl alcoholic solution filtered from methylmangostin was evaporated and acidifield with dilute hydrochloric acid, separating out a yellow mass. The separated mass was filtered and recrystallised from ethyl alcohol, crystallising in pale yellow plates which melted at 171–171.5°C. The yield was about 2 gr.

Anal. Subst. = 0.1346; CO_2 = 0.3493; H_2O = 0.0806 gr. Found: C = 70.77; H = 6.70%.

Mol. weight, measured after Rast. Subst. = 0.00088; camphor = 0.00903 gr. m.p. depress. = 11.0. Found: mol. weight = 354.

Methoxyl, measured after Zeizel. Subst. = 0.00435; AgI = 0.00358 gr. Found: OCH_3 = 10.86%.

Calc. for $C_{19}H_{18}O_3(OCH_3)_2$: C = 70.80; H = 6.74; OCH_3 = 17.42%; mol. weight = 356.

This compound (X) gave the same coloration as those of methylmangostin and mangostin with ferric chloride, but it was generally less soluble in the ordinary organic solvents than the last two compounds, i.e. sparingly soluble in ether, benzene, chloroform and acetic acid in the cold state. It was also insoluble in dilute alkalies and lowered its melting point exceedingly when mixed with mangostin.

The yield of methylmangostin in proportion to that of the compound X increased with the quantity of dimethyl sulphate employed, and indeed the compound X was converted into methylmangostin on further methylation with dimethyl sulphate and potassium hydroxide.

Acethyl-methylmangostin. Two gr. of methylmangostin was mixed with 4 gr. of anhydrous sodium acetate and 20 gr. of acetic anhydride and heated for 2 hours. On cooling the reaction mixture acethyl-methylmangostin separated out as a white mass, which was filtered and washed with hot water and recrystallised from benzene, yielding white needle crystals; m.p. 191–191.5°C. The yield was about 2 gr.

Anal. Subst. = 0.1371; CO_2 = 0.3512; H_2O = 0.0831 gr. Found: C = 69.86; H = 6.78%. Acethyl. Subst. = 0.5000 gr. equivalent KOH (0.0729N.) = 16.3 c. c. Found: $COCH_3$ = 10.20%. Calc. for $C_{21}H_{23}O_5{\cdot}COCH_3$: C = 69.30; H = 6.60; $COCH_3$ = 10.79%.

It was insoluble in cold dilute alkalies and gave no coloration with ferric chloride in alcoholic solution.

Acethylation and Benzoylation of Mangostin. Four gr. of mangostin was mixed with 20 gr. of anhydrous sodium acetate and 60 c.c. of acetic anhydride and warmed at 40–50°C for 3 days keeping from moisture. The reaction products were extracted with ether and the ethereal solution was shaken with a solution of sodium bicarbonate to remove the acetic anhydride and then the ether was distilled off, leaving a yellow crystalline mass. The yield was about 5 gr. The raw product was fractionally recrystallised from methyl alcohol, yielding two kinds of crystals, namely, plate (m.p. 107–108°C.) and needle (m.p. 115–118°C.) crystals. The latter which was still impure was analysed.

Acethyl. Subst. = 0.5003 gr. equivalent KOH (0.0518 N.) = 41.3 c.c.
Found : $COCH_3 = 18.39\%$. Calc. for $C_{20}H_{20}O_5(COCH_3)$: $COCH_3 = 20.09\%$.

Mangostin was also acethylated with the addition of zinc powder, obtaining none other than the above mentioned reaction products.

Benzoylation was also carried out by the action of benzoyl chloride on mangostin in alkaline solution, but the reaction products were so complex as to render their isolations a matter of difficulty.

Tribromo-methylmangostin. In a solution of 1 gr. of methylmangostin in 10 gr. of dry benzene an equimolecular quantity of bromine was added drop by drop, precipitating a yellow crystalline substance. The precipitates were filtered and recrystallised from dry benzene, forming the aggregates of deep yellow irregular leaflet crystals. The yield was about 1 gr. It decomposed at about 160°C. When this yellow compound had come in contact with water, it converted instantaneously into a reddish-purple viscous matter, which on exposure to light changed gradually again into a yellow crystalline substance.

Anal. Subst. = 0.2041 ; AgBr = 0.1880 gr. Found : Br = 39.22%. Calc. for $C_{21}H_{23}O_5 \cdot Br_3$: Br = 40.34%.

Alkali-fusion of Mangostin. A mixture of 300 gr. of potassium hydroxide and 50 gr. of water was heated to about 170°C. and 30 gr. of mangostin was gradually added to the fusion mixture under constant stirring. A vapour evolved from the melt during the fusion process was condenced to a yellow oil, which had an odour resembling that of amyl alcohol. When mangostin had been dissolved homogeneously, the melt was cooled and pulverized quickly and dissolved in an ice cold dilute sulphuric acid, leaving a dark brown viscous matter. The aqueous solution was filtered from the

insoluble viscous matter and subjected to steam distillation. Volatile acids were separated from the distillates and fractionated by distillation into two parts. One of the fractions boiled at 117–119°C.; yield ca. 4 gr. It was converted into an anilide by heating with aniline. The anilide melted at 114°C. and was identified with acetanilide. The other fraction boiled at 177–180°C.; yield ca. 4 gr. It was neutralized with ammonium carbonate and heated to 230°C. in a sealed tube, yielding an amide which melted at 135°C. and was identified with isovaleramide.

The aqueous solution from which the volatile acids had been distilled off was extracted with ether. The ethereal solution was washed with a solution of sodium bicarbonate and distilled down to dryness, and the phenolic residue was recrystallised from water, yielding white plate crystals; yield ca. 1.2 gr. It melted at 215°C. in the anhydrous state.

Crystalline water. Air dried subst. = 0.1450; after drying at 120° = 0.1126 gr. Found: H_2O = 22.34%. Calc. for $C_6H_6O_3 \cdot 2H_2O$: H_2O = 22.22%.

Anal. Subst. = 0.1676; CO_2 = 0.3586; H_2O = 0.0747 gr. Found: C = 58.36; H = 5.00%. Calc. for $C_6H_6O_3$: C = 58.43; H = 4.92%.

It produced no precipitates with lead acetate in an aqueous solution and gave bluish-violet coloration with potassium hydroxide and hydrogen peroxide. Phloroglucinol-test with pine tree and concentrated hydrochloric acid was positive and also no depressions in the melting point of the phenolic product were observed when it was mixed with phloroglucinol.

The aqueous solution from which the phenolic part was extracted was concentrated and extracted again with ether, isolating only oxalic acid; yield ca. 1.5 gr.

The dark brown viscous matter separated from the acidic solution of the melt was dried and recrystallised from benzene, forming yellow needle crystals. The yield was about 18 gr. It resembled closely to mangostin in its chemical properties, namely, solubilities in organic solvents, coloration with ferric chloride, and the productions of isovalerianic acid, phloroglucinol, and of a vapour resembling amyl alcohol on alkali-fusion. It, however, melted at 212°C. and lowered its melting point remarkably when mixed with mangostin.

Anal. Subst. = 0.1792; CO_2 = 0.4358; H_2O = 0.0863 gr. Found: C = 66.33; H = 5.40%.

Mol. weight, measured after Rast. Subst. = 0.00056; camphor = 0.00556 gr.; m.p. depress. = 14. Found: mol. weight = 288.

The benzene mother liquor was evaporated and extracted repeatedly with hot water, separating out pale yellow microscopic needle crystals on cooling. It melted at 373°C. The yield was 0.06 gr.

Anal. Subst. = 0.1506 ; CO_2 = 0.3328 ; H_2O = 0.0459 gr. Found : C = 60.27 ; H = 3.41%.

It was insoluble in chloroform and petroleum ether, but very soluble in ethyl alcohol, ether and acetic acid. It was acidic in alcoholic solution and dissolved in dilute alkalies, giving a strong fluorescence.

The last two compounds obtained from the brown viscous matter remain undetermined.

In conclusion, the author wishes to express his hearty thanks to Prof. Riko Majima for his kind guidance in this research.

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