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"DIMETHYLMANGOSTIN HYDROCHLORIDE"

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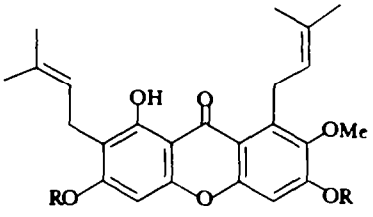
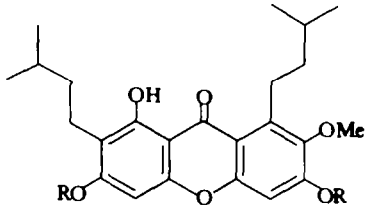
Abstract—The structure of "dimethylmangostin hydrochloride", a product from the treatment of dimethylmangostin (II) with boiling hydrochloric acid in acetic acid, has been shown to be XVIII. A second product, dimethyl-1-isonormangostin (IV), has been isolated from the reaction mixture. The mode of formation of these products has been elucidated by the isolation of the intermediate products, 3',3"-dichlorotetrahydrodimethylmangostin (VIII) and 3'-chlorodihydrodimethylisomangostin (IX), and by ultraviolet spectroscopic studies.

MANGOSTIN, the coloring matter of the fruit hulls, bark and dried latex of *Garcinia mangostana*, has been shown to have the structure I.[3] The determination of this structure permitted the assignment of structures to many of the known transformation products of mangostin. There remained, however, several products to which structures could not be assigned unambiguously. We now describe the elucidation of the structures of three of these compounds, first obtained by Murakami:[4] "dimethylmangostin hydrochloride", a product from the treatment of dimethylmangostin (II) with hydrochloric acid in boiling acetic acid; "dimethylmangostin ethylate", the product from the treatment of dimethylmangostin hydrochloride with base; and the product from the treatment of "dimethylmangostin ethylate" with methylmagnesium iodide.



I, R = H
II, R = Me



III, R = H
VI, R = Me

Dimethylmangostin hydrochloride is a bright yellow, water-soluble, ether-insoluble compound. The reported elemental analytical data are consistent with a formulation involving the addition of hydrogen chloride to dimethylmangostin, but do not reveal whether loss of a CH_2 group occurs (i.e. demethylation of a OMe

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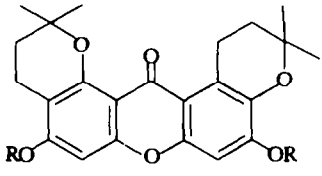
[3] P. Yates and G. H. Stout, *J. Am. Chem. Soc.* **80**, 1691 (1958).

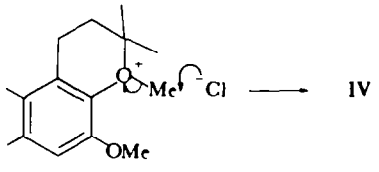
[4] M. Murakami, *Proc. Imp. Acad. Tokyo* **7**, 311 (1931); *Liebigs Ann.* **496**, 122 (1932); *J. Chem. Soc. Japan* **53**, 150, 162 (1932).

group); this ambiguity arises in part because of the isolation of crystalline dimethylmangostin hydrochloride only as solvates with water and/or hydrogen chloride. It is not a simple xanthylium salt, as is tetrahydronormangostin hydrobromide, formed by treatment of tetrahydromangostin (III) with hydrogen bromide in boiling acetic acid,[4] since it is resistant to catalytic hydrogenation, indicating that both of the side-chain double bonds undergo change during the reaction.[4] Further, dimethylmangostin hydrochloride does not regenerate dimethylmangostin on treatment with base, but is converted by aqueous potassium hydroxide to "dimethylmangostin ethylate",[5] which is also resistant to hydrogenation and is reconverted to dimethylmangostin hydrochloride by brief warming with concentrated hydrochloric acid.[4]

Dimethylmangostin hydrochloride was prepared in 56% yield by the procedure of Murakami;[4] a second product was isolated in 16% yield by chromatography of the ether-soluble material obtained from the trituration of the total crude reaction product with ether. The latter was identified as compound IV, previously obtained by methylation of compound V,[6] formed by treatment of mangostin with hydriodic acid and iodine.[3] The acid-catalyzed ring closure involving the *peri* OH group and the adjacent isopentenyl side chain at C2 is unexceptional, the formation of the second dihydropyran ring involves demethylation of the OMe group at C7. Since tetrahydrodimethylmangostin (VI) is reported to be resistant to demethylation by hydrochloric acid,[4] the demethylation of dimethylmangostin probably proceeds *via* the species VII; the low nucleophilicity of the chloride ion then being compensated by the strategic location of the Lewis acid formed by protonation of the side chain double bond. Dimethylmangostin hydrochloride is not an intermediate in the formation of IV since further treatment of dimethylmangostin hydrochloride with hydrochloric acid in boiling acetic acid effected no change. Also, further treatment of IV under these reaction conditions failed to convert it to dimethylmangostin hydrochloride.



IV, R = Me
V, R = H

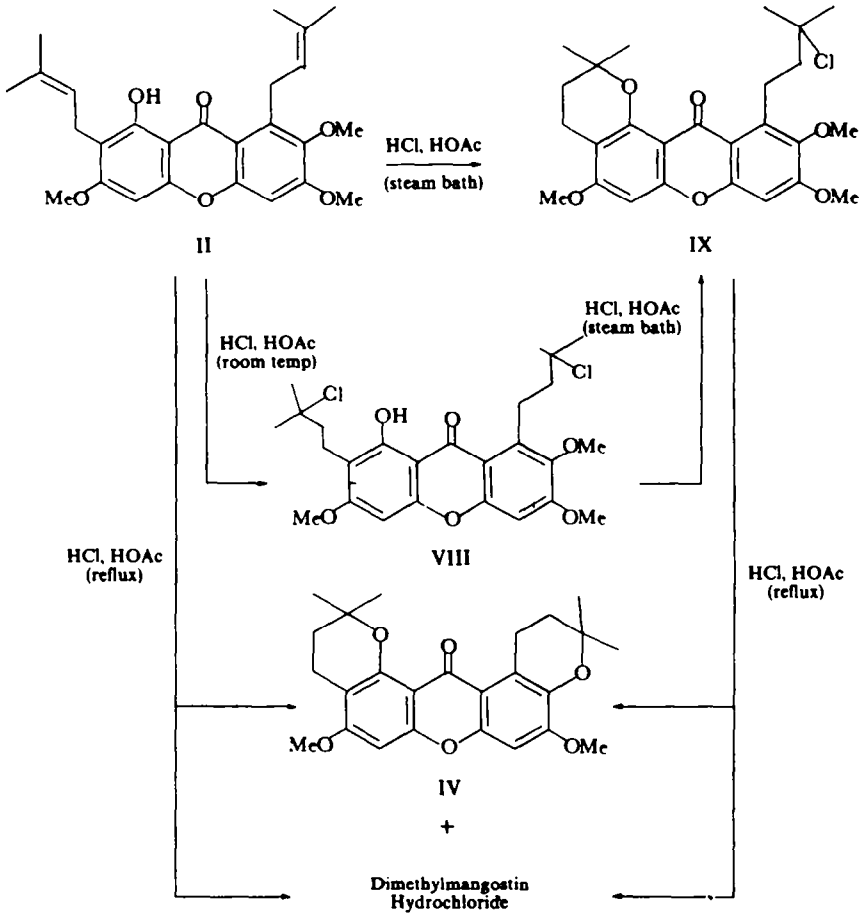


VII

The determination of the structure of dimethylmangostin hydrochloride was approached by an investigation of the reaction between dimethylmangostin (II) and hydrochloric acid under milder conditions and the reaction of dimethylmangostin hydrochloride with base. Treatment of II with hydrochloric acid in acetic acid at room temperature gave a pale yellow compound, $C_{26}H_{32}O_6Cl_2$. The IR spectrum of this product showed it to be a xanthone rather than a xanthylium salt. This

[5] This compound was recrystallized from ethanol by Murakami[4] and, since he believed that it possessed two carbon atoms more than dimethylmangostin, he termed it an "ethylate".

[6] This was previously named isodemethylmangostin;[3] we now suggest it be named 1-isonormangostin; the related compound[3] in which one of the pyran rings has been formed at the oxygen atom attached to C3 rather than C1 then becomes 3-isonormangostin.



spectrum also showed the presence of a free OH group at C1, both by virtue of the "funnel-shape"[3] of the C–H stretching band, due to superimposition on the broad chelated OH band, and the absence of a band at 6·17–6·20 μ (a band in the 6·15–6·20-μ region has previously been found to be characteristic of 1-hydroxyxanthones in which the OH group is alkylated or acylated;[3] in the case of mangostin derivatives this range can now be narrowed somewhat: see Table 1). The UV spectrum also demonstrated the presence of a free C1 hydroxyl group since all compounds in the dimethylmangostin series of known structure which retain the xanthone nucleus and a free C1 OH group have the three longest wave-length maxima in their UV spectra at 260–262, 309–318, and 345–366 mμ, and are yellow, while the spectra of those compounds in which the C1 OH group has been etherified by closure of the adjacent isopentenyl side chain have these maxima at 255–258, 301–302, and 337–350 mμ, and are colorless (Table 2). Consequently, the compound, $C_{26}H_{32}O_6Cl_2$, is formulated as the simple adduct, 3′,3″-dichlorotetrahydrodimethylmangostin (VIII).

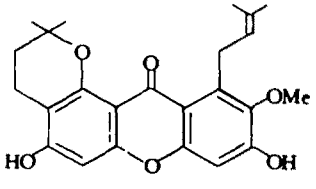
When either VIII or dimethylmangostin (II) was treated with concentrated hydrochloric acid in acetic acid on the steam bath for 1·3 hr, a colorless compound, $C_{26}H_{31}O_6Cl$, was formed. Its IR and UV spectra showed it to be a xanthone lacking

a free C1 OH group and it is formulated as 3'-chlorodihydrodimethylisomangostin (IX).[7] Treatment of IX with hydrochloric acid in boiling acetic acid gave a mixture of dimethylmangostin hydrochloride and IV, indicating that it is an intermediate in the formation of both of these products from dimethylmangostin.

The assignment of structure IX was confirmed in the following ways. Treatment of IX with silver perchlorate in formic acid led rapidly to the precipitation of silver chloride and the formation of a mixture of formate ester and alcohol which after saponification yielded 3'-hydroxydihydrodimethylisomangostin (X), which was obtained earlier[3] by treatment of dimethylmangostin with warm formic acid followed by saponification. The parent compound of this series, dimethylisomangostin (XI) was formed by treatment of dimethylmangostin with *p*-toluenesulfonic acid in glacial acetic acid on the steam bath; when aqueous acetic acid was used as the reaction medium, a mixture of X and XI was formed. Closure of one isopentenyl side chain at the C1 OH group in XI was established by its IR and UV spectra (Tables 1 and 2), and retention of the other isopentenyl side chain was shown by the fact that it is converted on hydrogenation to a dihydro compound, formulated as XII, with essentially the same UV spectrum, and that on ozonolysis it formed an unconjugated aldehyde (3·68, 5·80 μ), formulated as XIII. Treatment of XI with hot aqueous formic acid followed by saponification gave X. Treatment with hydrochloric acid in acetic acid in the cold afforded IX.

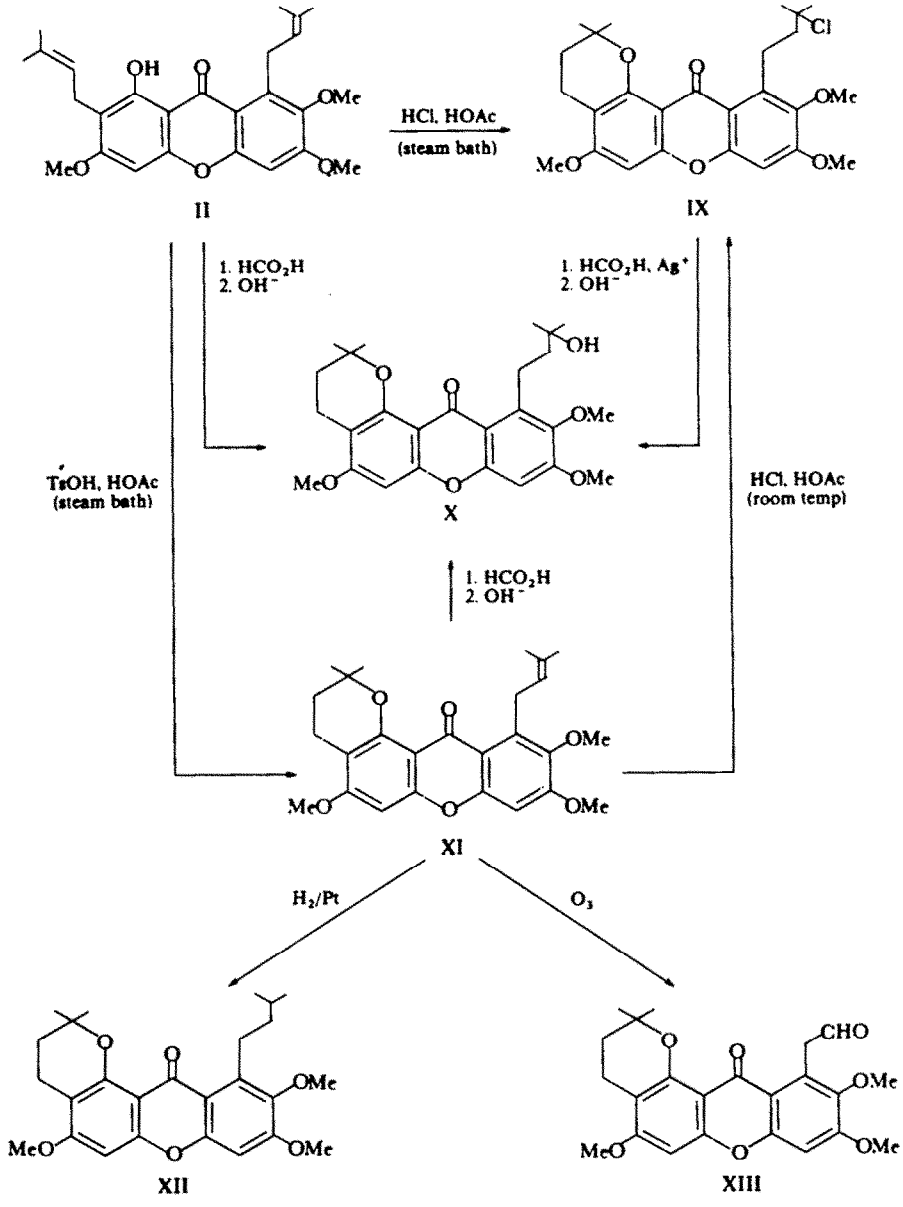
The product formed on treatment of dimethylmangostin hydrochloride with base ("dimethylmangostin ethylate"[5]) was found to have the formula $C_{26}H_{32}O_7$: i.e. it is isomeric with compound X. Its IR and UV spectra (Tables 1 and 2) established that it is a member of the isomangostin series; the presence of a OH group was indicated by its IR spectrum (2·99 μ). Oxidation with chromic anhydride in acetic acid gave a product, $C_{26}H_{30}O_7$, with an essentially unchanged UV spectrum, but with a new band (5·85 μ) in its IR spectrum, characteristic of a saturated ketonic group. The oxidation product can hence be formulated as 2'-oxodihydrodimethylisomangostin (XIV), and the parent OH compound as 2'-hydroxydihydrodimethylisomangostin (XV). These assignments were confirmed by the demonstration that treatment of XV with isopropylmagnesium bromide gave a product, $C_{29}H_{40}O_7$, formulated as XVI, identical to that obtained on treatment of the aldehyde XIII with an excess of isopropylmagnesium bromide.[8] In contrast to the product obtained by the action of isopropylmagnesium bromide on XV, that formed by methylmagnesium iodide shows no OH band in its IR spectrum. Its composition is in accord with its formulation

[7] We introduce the name isomangostin for i.



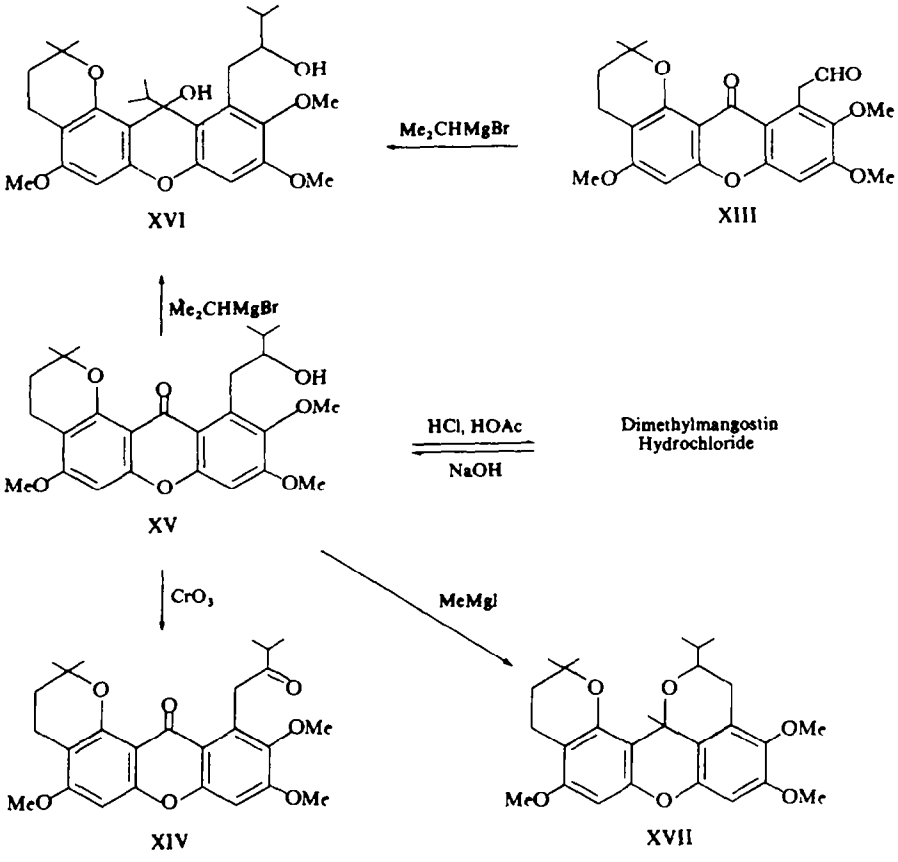
i

[8] This product does not melt sharply; this may be due either to its being a mixture of diastereoisomers or to thermal, dehydration below the melting point.



as the dehydrated adduct, XVII. The failure of XVI to undergo analogous facile dehydration is presumably due to steric interactions involving the isopropyl group at C9.

It has already been noted that XV can be reconverted to dimethylmangostin hydrochloride by treatment with hydrochloric acid. The ease with which these two compounds can be interconverted under very mild conditions was demonstrated by UV spectroscopy. A dilute solution of dimethylmangostin hydrochloride in 95%



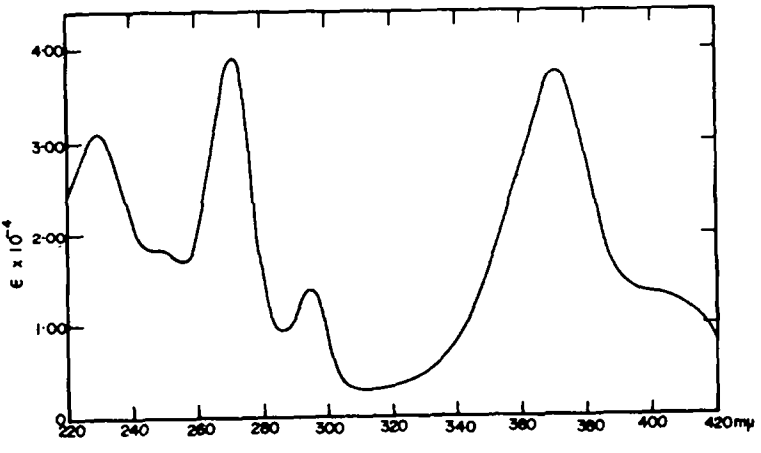


FIG. 1. UV spectrum of dimethylmangostin hydrochloride in aqueous ethanol.

TABLE 1. IR BANDS IN THE 6·0–6·3-μ REGION OF MANGOSTIN AND ITS DERIVATIVES

	$\lambda_{max}^{CCl_4}$ (μ)		
Mangostin (I)	6·09		6·21
Dimethylmangostin (II)	6·08		6·26
Tetrahydrodimethylmangostin (VI)	6·08		6·25
Dimethylmangostin dialdehyde	6·06		6·24
2',2''-Dioxo-3',3''-dihydroxytetrahydrodimethylmangostin	6·07		6·23
3-Isonormangostin	6·08		6·23
Methyl-3-isonormangostin	6·07		6·23
3,3''-Dichlorotetrahydrodimethylmangostin (VIII)	6·08		6·26
Dimethylmangostin acetate	6·06	6·17	6·25
Dimethyl-1-isonormangostin (IV)	6·06	6·19	6·25
1-Isonormangostin (V)	6·10	6·19	6·25
3'-Chlorodihydrodimethylisomangostin (IX)	6·04	6·20	6·26
3'-Hydroxydihydrodimethylisomangostin (X)	6·04	6·18	6·25
3'-Formoxydihydrodimethylisomangostin	6·04	6·20	6·26
Dimethylisomangostin (XI)	6·02	6·19	6·26
Dihydrodimethylisomangostin (XII)	6·04	6·21	6·27
Dimethylisomangostin aldehyde (XIII)	6·07	6·20	6·27
2'-Oxodihydrodimethylisomangostin (XIV)	6·07	6·20	6·26
2'-Hydroxydihydrodimethylisomangostin (XV)	6·09	6·19	6·25

Spectra were obtained in the present work or taken from Ref. 3.

TABLE 2. UV MAXIMA OF DIMETHYLMANGOSTIN AND ITS DERIVATIVES

	λ_{max}^{EtOH} (mμ)			
Dimethylmangostin (II)	245	262	318	351
Tetrahydrodimethylmangostin (VI)	244	261	312	351
Dimethylmangostin dialdehyde	244	261	314	345
2',2''-Dioxo-3',3''-dihydroxytetrahydro-dimethylmangostin	244	260	309	352
Methyl-3-isonormangostin	242·5	261·5	317	366
3',3''-Dichlorotetrahydrodimethylmangostin (VIII)	243	261	314·5	349
Dimethyl-1-isonormangostin (IV)	245 (sh)	258	301	350
3'-Chlorodihydrodimethylisomangostin (IX)	244·5	254·5	302	335
3'-Hydroxydihydrodimethylisomangostin (X)	245	255	302	337
3'-Formoxydihydrodimethylisomangostin	245	255	302	337
Dimethylisomangostin (XI)	245	255	302	336
Dihydrodimethylisomangostin (XII)	244·5	255·5	302	335
Dimethylisomangostin aldehyde (XIII)	244·5	256	304·5	340
2'-Oxodihydrodimethylisomangostin (XIV)	245	255·5	302·5	338
2'-Hydroxydihydrodimethylisomangostin (XV)	243	255	305	340 (sh)

Spectra were obtained in the present work or taken from Ref. 3.

ethanol when treated with a slight excess of aqueous sodium hydroxide was decolorized immediately. The UV spectrum of the solution (Fig. 2, Curve 2), which was recorded immediately, was completely different from that of the original solution (Fig. 1). The UV spectrum of the solution slowly underwent a further change over a period of about 40 min (Fig. 2) and finally became identical to that of XV (Fig. 2, Curve 5); an isosbestic point was observed for the spectra recorded after addition of base. Addition of an excess of hydrochloric acid to this basic solution had only a slight immediate effect on its spectrum; slow changes occurred over a period of several hours (Fig. 3), however, and the spectrum was finally identical to that of dimethylmangostin hydrochloride (Fig. 3, Curve 9); five isosbestic points were observed in the case of these spectra. When hydrochloric acid was added only 30 sec after basification of a solution of dimethylmangostin hydrochloride, the UV spectrum of the resulting solution immediately became identical to that of dimethylmangostin hydrochloride.

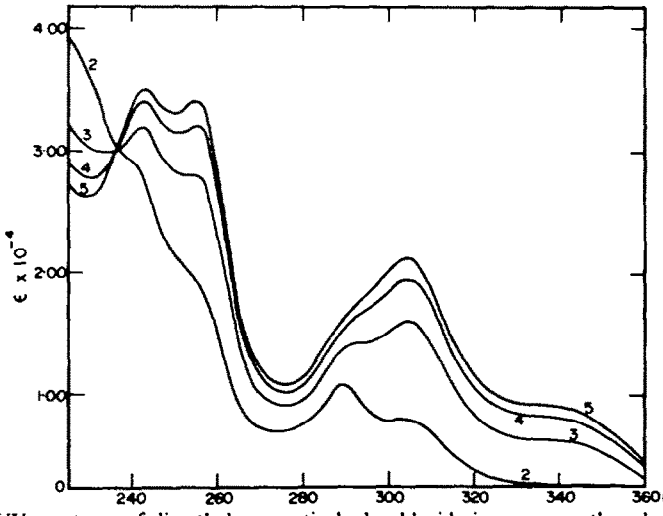


FIG. 2. UV spectrum of dimethylmangostin hydrochloride in aqueous ethanol after basification with aqueous sodium hydroxide, recorded immediately (Curve 2) and thereafter at ca. 7 min intervals (Curves 3–5).

These data find complete interpretation in terms of structure XVIII for dimethylmangostin hydrochloride.[9,10] Treatment with aqueous base would be expected to give XIX in a fast reaction, which could be rapidly reversed by immediate addition of hydrochloric acid. On standing in the basic solution XIX could slowly undergo base-catalyzed opening of the cyclic hemiketal to give XV. Acidification of the basic solution of XV with hydrochloric acid could reverse these reactions by slow, acid-catalyzed closure to XIX followed by rapid conversion to XVIII. On this basis, the isosbestic point of Fig. 2 corresponds to mixtures of the two species XV and XIX.

[9] This structure is in accord with our elemental analytical data, if dimethylmangostin hydrochloride is formulated as the solvate $C_{26}H_{31}O_6Cl \cdot CH_3CO_2H \cdot H_2O$.

[10] The related seven-membered ring structure, XXIII, is excluded since it would give X instead of XV on treatment with base. Further, the nuclear magnetic resonance spectrum of dimethylmangostin hydrochloride shows the presence of a hydrogen atom on the carbon atom to which the carbonyl oxygen atom of mangostin becomes attached (multiplet at δ^1= 4·5 ppm).

while the isosbestic points of Fig. 3 correspond to mixtures of XV and XVIII. The postulation of XIX as a rapidly formed intermediate in the conversion of XVIII to XV is supported by two pieces of evidence. First, the UV spectrum of the solution of dimethylmangostin hydrochloride immediately after basification is very similar to the spectra of the xanthydrol derivatives XVI and XVII. Second, treatment of a solution of dimethylmangostin hydrochloride in methanol with methanolic sodium methoxide gives a solution whose UV spectrum is similar to that obtained immediately after treatment of ethanolic dimethylmangostin hydrochloride with aqueous base; however, in the case of sodium methoxide, no change occurred in the spectrum of the solution upon standing. This is in accord with the expectation that in the latter case the ketal XX would be formed but would not undergo further reaction.

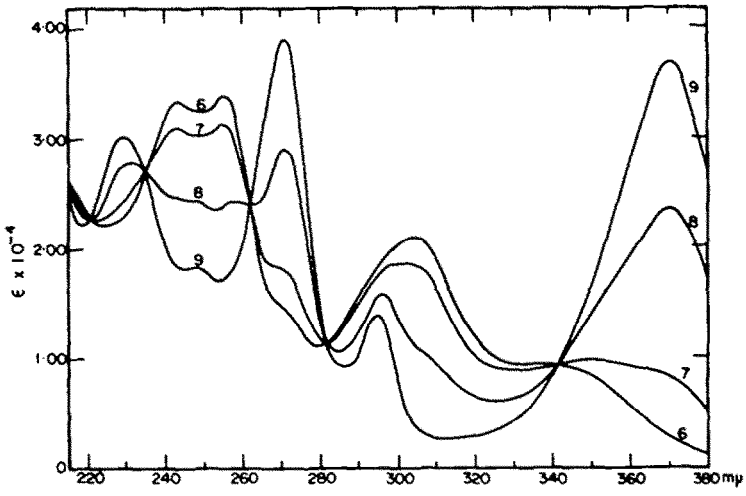
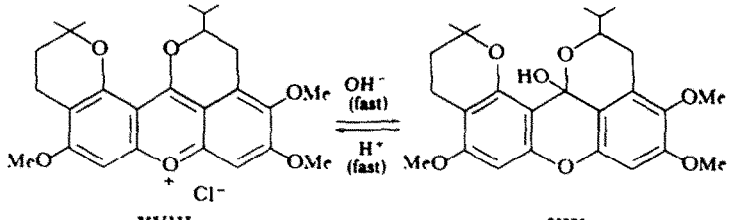
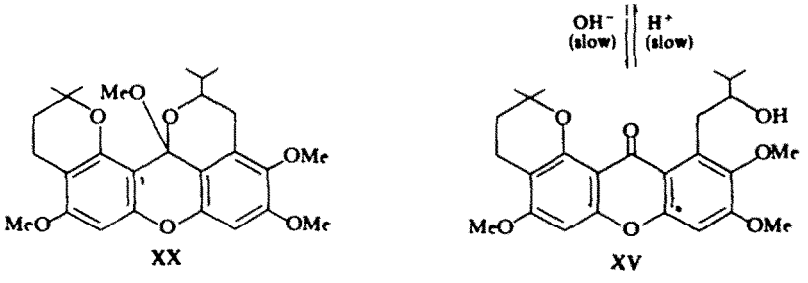


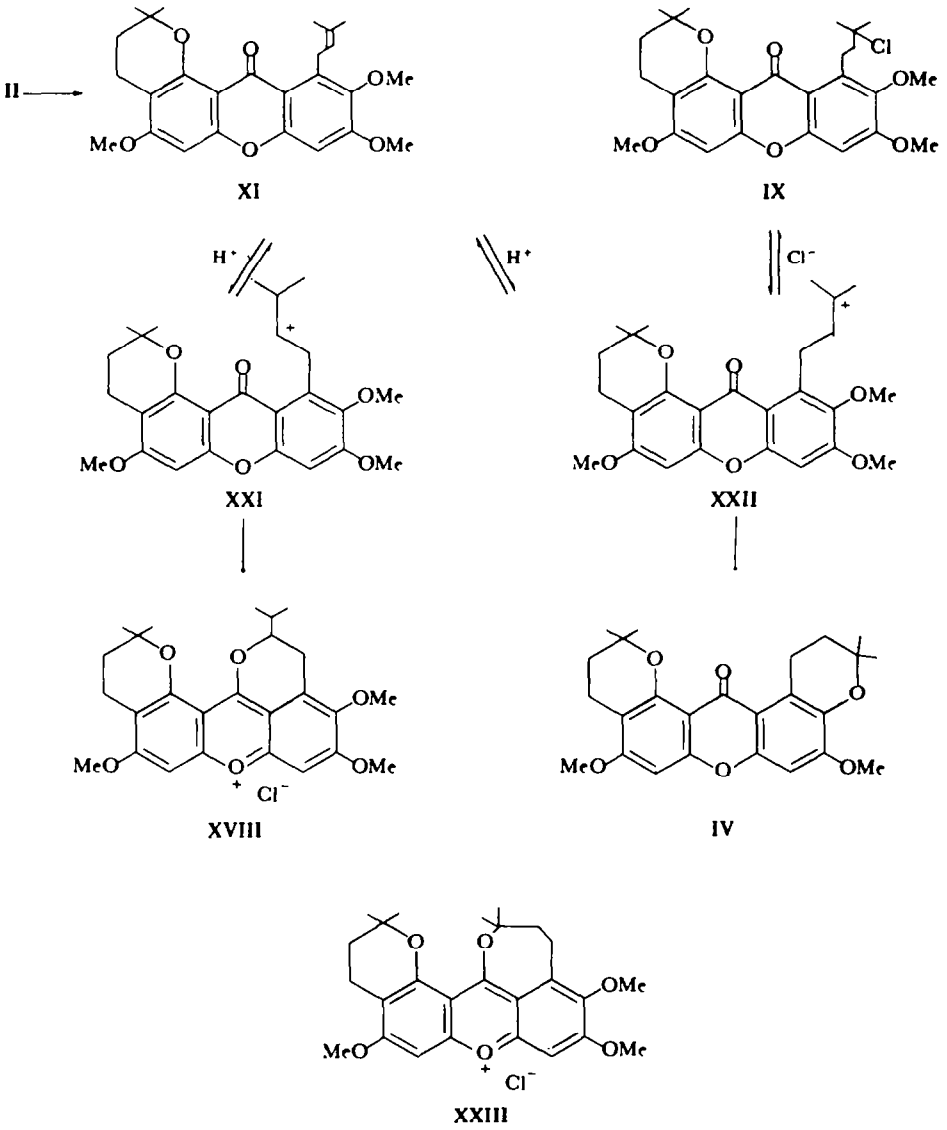
FIG. 3. UV spectrum of dimethylmangostin hydrochloride in aqueous ethanol after basification followed by acidification after 0·5 min, recorded immediately (Curve 6) and thereafter at intervals to 250 min (Curve 9).



XVIII XIX



XX XV



The structure XVIII proposed for dimethylmangostin hydrochloride not only accounts for the transformations discussed above but also permits the rational interpretation of its formation from dimethylmangostin and its relationship to the products discussed earlier in terms of the type of reaction scheme above. The closure of the side chain at C2 is undoubtedly faster than either of the other two cyclizations, as shown by the isolation of IX and XI under milder reaction conditions. The subsequent closure of the other side chain may proceed *via* the two discrete carbonium ions XXI and XXII, *via* variants of these arising by concerted attack of the oxygen atom involved in the cyclization, or *via* a single bridged species formed by protonation

of the double bond of XI. The fact that XVIII, the product of anti-Markownikoff addition to the double bond, predominates can be ascribed to the relative slowness of the demethylation step in the sequence XXII ⇌ VII → IV. Both product-forming steps must be irreversible since neither product can be converted to the other under the conditions of the original reaction.

EXPERIMENTAL

M.ps were taken on a Fisher–Johns block and are uncorrected.

Dimethylmangostin hydrochloride (XVIII) *and dimethyl-1-isonormangostin* (IV) *from dimethylmangostin* (II)

Compound II[3] (5 g) was heated under reflux for 4·5 hr in a mixture of glacial AcOH (50 ml) and conc HCl (25 ml). The reaction mixture was concentrated to a very small volume on the steam bath under vacuum, and the yellow-brown residue was thoroughly triturated with ether to give solid, crude dimethylmangostin hydrochloride (3·8 g, 56%). The hydrochloride was recrystallized by soln in a very small amount of glacial AcOH and careful addition of ether over several hr. An analytical sample was obtained as bright yellow needles, dec. ca. 145°, $\lambda_{max}^{CHCl_3}$ 2·98, 6·13, 6·26 μ, λ_{max}^{EtOH} 229 mμ (log ε 4·50), 247 mμ (sh, log ε 4·27), 271·5 mμ (log ε 4·59), 295 mμ (log ε 4·15), 371 mμ (log ε 4·58), 400 mμ (sh, log ε 4·12). (Found: C, 60·62; H, 6·93; Cl, 6·17. $C_{26}H_{31}O_6Cl \cdot CH_3CO_2H \cdot H_2O$ requires: C, 60·81; H, 6·74; Cl, 6·41%).

The ethereal extract from the trituration of the total reaction product was washed with water and K_2CO_3aq, dried over $MgSO_4$, and evaporated to a glass. This was dissolved in a 10% soln of benzene in pet. ether and chromatographed on Merck alumina (50 g; 40 mm column). Elution with a 10% soln of ether in benzene (300 ml) and recrystallization from benzene–pet. ether gave dimethyl-1-isonormangostin (0·60 g, 12·5%), m.p. 215·3–216·5°; IR and UV spectra identical with those of the methylation product of 1-isonormangostin (isodemethylmangostin);[3,6] a mixed m.p. showed no depression.

Heating of dimethyl-1-isonormangostin in a refluxing mixture of glacial AcOH and conc HCl for 12 hr failed to effect significant change, as shown by the IR spectrum of the residue obtained by evaporation of the reaction soln under reduced press. Similar treatment of dimethylmangostin hydrochloride for 36 hr also was without effect.

3′,3″-*Dichlorotetrahydrodimethylmangostin* (VIII)

Compound II (500 mg) was dissolved in glacial AcOH (40 ml) and conc HCl (5·0 ml) was added. After 24 hr the crystalline deposit of VIII (470 mg, 81%) was filtered, and washed with 40% glacial AcOH in pet. ether and then with pet. ether. Recrystallization from cyclohexane–pet. ether afforded an analytical sample as very fine, light yellow needles, m.p. 156·5–157·5°, $\lambda_{max}^{CCl_4}$ 6·08, 6·26 μ, λ_{max}^{EtOH} 243·5 mμ (log ε 4·45), 261 mμ (log ε 4·49), 314·5 mμ (log ε 4·36), 349 mμ (log ε 3·81). (Found: C, 61·39; H, 6·16; Cl, 13·78. $C_{26}H_{32}O_6Cl_2$ requires: C, 61·06; H, 6·31; Cl, 13·86%).

3′-*Chlorodihydrodimethylisomangostin* (IX)

(i) *From dimethylisomangostin* (XI). Compound XI (100 mg) was dissolved in glacial AcOH (8 ml), conc HCl (1 ml) was added and the soln was allowed to stand at room temp for 24 hr. It was then poured into a mixture of ether and water. The ethereal layer was washed with water and K_2CO_3aq, dried over $MgSO_4$, and evaporated to give an almost colorless glass (105 mg, 97%). Crystallization from cyclohexane–pet. ether gave 80 mg (74%) of colorless crystals, m.p. 158·5–160° dec. An analytical sample prepared by recrystallization from the same solvent pair had m.p. 161·5–163° dec, $\lambda_{max}^{CCl_4}$ 6·04, 6·20, 6·26 μ, λ_{max}^{EtOH} 244·5 mμ (log ε 4·56), 254·5 mμ (log ε 4·56), 302 mμ (log ε 4·36), 335 mμ (log ε 3·97). (Found: C, 65·77; H, 6·57; Cl, 7·24. $C_{26}H_{31}O_6Cl$ requires: C, 65·74; H, 6·58; Cl, 7·47%).

(ii) *From dimethylmangostin* (II). Compound II (250 mg) was dissolved with heating in glacial AcOH (10 ml) and conc HCl (2·5 ml) was added. A little more AcOH was added to restore homogeneity. The soln was heated for 1·3 hr on the steam bath, poured into cold water, and extracted with ether. The ethereal extract was washed several times with water and finally with K_2CO_3. After being dried over $MgSO_4$, it was evaporated to give a glass (140 mg, 52%) which on trituration with pet. ether gave solid material having IR and UV spectra identical with those of the product formed by method (i).

(iii) *From* 3′,3″-*dichlorotetrahydrodimethylmangostin* (VIII). Compound VIII (150 mg) was dissolved in glacial AcOH (20 ml) and conc HCl (2·5 ml) was added. The mixture was heated on the steam bath for 1·3 hr, and worked up as in method (ii) to give a glass (120 mg, 93%). Crystallization from

cyclohexane–pet. ether afforded a product, m.p. 158·5–159·5° dec, having IR and UV spectra identical with those of material formed by method (i).

Conversion of 3'-chlorodihydrodimethylisomangostin (IX) *to 3'-hydroxydihydromethylisomangostin* (X).

Compound IX was dissolved in a little 88% formic acid and an excess of a formic acid soln of silver perchlorate was added. AgCl precipitated almost immediately. The entire reaction mixture was treated with a mixture of ether and water. The ethereal layer was washed several times with water and finally with $NaHCO_3$ aq, dried over $MgSO_4$, and evaporated to give a residue whose IR spectrum indicated it to be a mixture of 3'-formoxydihydrodimethylisomangostin and X.[3] It was heated under reflux with methanolic KOH aq for a few min, and the soln was allowed to stand for 2 hr. The soln was then extracted with ether, and the ethereal extract was washed with water, dried over $MgSO_4$, and evaporated. Recrystallization of the residue from benzene–pet. ether gave a product, m.p. 204–205°, undepressed on admixture with X;[3] the IR spectra of the two samples were identical.

Dimethylisomangostin (XI)

(i) Compound II (500 mg) was dissolved in glacial AcOH (40 ml), *p*-toluenesulfonic acid (1 g) was added, and the soln was heated on the steam bath for 0·5 hr. It was poured into cold water (ca. 250 ml), and the resulting yellow suspension was extracted with ether. The ethereal soln was extracted several times with water and finally with K_2CO_3 aq, dried over $MgSO_4$, and evaporated to give a yellow oil (510 mg), which was taken up in benzene and chromatographed on Merck alumina (25 g; 20 mm column). Compound XI (405 mg) was eluted by 10 ml of a 25% soln of ether in benzene, and was recrystallized from cyclohexane–pet. ether. An analytical sample was obtained as clusters of fine, white needles,, m.p. 129·5–130·2°, $\lambda_{max}^{CCl_4}$ 6·02, 6·19, 6·26μ, λ_{max}^{EtOH} 245 mμ (log ε 4·54), 255 mμ (log ε 4·54), 302 mμ (log ε 4·34), 336 mμ (log ε 3·94). (Found: C, 70·97; H, 6·98. $C_{26}H_{30}O_6$ requires: C, 71·21; H, 6·90%).

(ii) Compound II (1·0 g) was dissolved in glacial AcOH (80 ml) and a soln of *p*-toluenesulfonic acid (2·0 g) in water (10 ml) was added. The mixture was heated on the steam bath for 1 hr, poured into water, and extracted with ether. The ethereal extract was washed several times with water and finally with K_2CO_3 aq, dried over $MgSO_4$, and evaporated to give a yellow, oily, partially crystalline product (1·06 g). This was dissolved in benzene (30 ml) and adsorbed onto Merck alumina (25 g; 20 mm column). XI (370 mg, 37%) was eluted with benzene (100 ml) and a 25% soln of ether in benzene (200 ml). A second fraction (670 mg, 64%) was eluted with a 2% soln of MeOH in ether. After one recrystallization, this material melted at 201–203° and showed no depression of m.p. on admixture with X.

Dihydrodimethylisomangostin (XII)

Compound XI (250 mg) in glacial AcOH was hydrogenated over Pt at room temp. for 45 min. The soln was filtered and poured into water, and the resulting suspension was extracted with ether. The ethereal extract was washed with water and K_2CO_3 aq, dried over $MgSO_4$ and evaporated to a glass (238 mg, 95%). This was dissolved in benzene and chromatographed on Merck alumina (5 g; 10 mm column). XII (230 mg, 92%) was eluted with 3:1 ether–benzene (50 ml). An analytical sample was prepared by recrystallization from cyclohexane–pet. ether and had m.p. 131–133°, $\lambda_{max}^{CCl_4}$ 6·04, 6·21, 6·27μ λ_{max}^{EtOH} 244·5 mμ (log ε 4·54), 255·5 mμ (log ε 4·54), 302 mμ (log ε 4·34), 335 mμ (log ε 3·94). (Found: C, 71·28; H, 7·39. $C_{26}H_{32}O_6$ requires: C 70·89; H, 7·32%).

Ozonolysis of dimethylisomangostin (XI)

Formation of XIII. Compound XI (506 mg) was dissolved in MeOH (19 ml) and AcOEt (2 ml). The soln was cooled to −80° and ozonized O_2 was passed through the soln until damp starch–KI test paper held over the surface of the soln was suddenly darkened. The soln was allowed to stand for 10 min at −80°, and then excess NaI in 80% MeOH was added, and the soln was poured into water. The resulting mixture was extracted with 2:1 ether AcOEt; the brownish extract was washed with water, a very small volume of acidified $NaHSO_3$ aq (sufficient to change the color from brown to yellow), K_2CO_3 aq (which decolorized the soln), and again with water. The extract was dried over $MgSO_4$ and concentrated to a volume of 2 ml. Ether (1 ml) was added followed by pet. ether (10 ml) in small portions. This resulted in the formation of a mass of light yellow crystals (266 mg, 56%). A colorless analytical sample was prepared by recrystallization from AcOEt–ether and had m.p. 177–181° dec, $\lambda_{max}^{CCl_4}$ 3·68, 5·80, 6·07, 6·20, 6·27 μ, λ_{max}^{EtOH} 244·5 mμ (log ε 4·50), 256 mμ (log ε 4·50), 304·5 mμ (log ε 4·29), 340 mμ (log ε 4·07). (Found: C, 66·80; H, 5·74. $C_{23}H_{24}O_7$ requires: C, 66·98; H, 5·87%).

Conversion of dimethylisomangostin (XI) *to 3'-hydroxydihydrodimethylisomangostin* (X)

Compound XI (100 mg) was dissolved in 88% formic acid (1 ml) and the yellow soln was heated on the steam bath for 0·5 hr. NaOH (2 g) in MeOH was added, and the colorless mixture which contained a flocculent white ppt (presumably potassium formate) was heated under reflux for 2 hr. It was then poured into water and extracted with ether. The ethereal extract was washed with water and K_2CO_3 aq, dried over $MgSO_4$, and evaporated to give a highly crystalline residue (108 mg). This was taken up in benzene and chromatographed on Merck alumina (5 g; 10 mm column). Starting material (19 mg) was eluted with ether (50 ml) and 3'-hydroxydihydromethylisomangostin (77 mg, 92% based on non-recovered XI) was eluted with 4% MeOH in ether (50 ml). Recrystallization from benzene–pet. ether gave a product, m.p. 201·8–203·8°, this was shown to be X by a mixed m.p. determination and IR and UV spectral comparison.

Conversion of 3'-chlorodihydrodimethylisomangostin (IX) *to dimethylmangostin hydrochloride* (XVIII)

Compound IX (35 mg) was heated at 130° for 4·5 hr in a mixture of glacial AcOH (3 ml) and conc HCl (1·5 ml). The reaction mixture was evaporated to a very small volume and after thorough trituration of the residue with ether, crude XVIII was collected by filtration. After one crystallization from AcOH–ether, the IR spectrum of the product (15 mg) was identical with that of XVIII. Evaporation of the ethereal extract from the trituration gave a small residue whose IR spectrum was similar to that of IV.

Treatment of dimethylmangostin hydrochloride (XVIII) *with base*

Formation of 2'-hydroxydihydrodimethylisomangostin (XV). (i) Crude XVIII (2·56 h) was treated with 5% $NaHCO_3$ aq (250 ml) in a separatory funnel. Ether (50 ml) was added, and the red suspension was shaken occasionally during 5 days. The 2 layers were then separated; the aqueous portion was washed with ether, and the combined ethereal soln was dried over $MgSO_4$ and evaporated. The residue was dissolved in benzene and adsorbed onto Merck alumina (40 g; 10 mm column). The column was washed with a 50% soln of benzene in pet. ether (360 ml) to remove any IV which might have contaminated the crude XVIII, and the product was eluted with benzene (400 ml), ether (100 ml) and 3% MeOH in ether (100 ml). The six 100-ml fractions thus obtained were evaporated and triturated with pet. ether to give a total of 1·21 g (60%) of XV. This was crystallized from cyclohexane–pet. ether to give a colorless product. The compound was obtained both as needles, m.p. 126·5–128·5°, and as prisms, m.p. 156·4–157·7°. These gave identical IR and UV spectra in soln, and could be interconverted by cross-seeding of their soln; $\lambda_{max}^{CCl_4}$ 2·99, 6·09, 6·19, 6·25 μ, λ_{max}^{EtOH} 243 mμ (log ε 4·54), 256 mμ (log ε 4·54), 305 mμ (log ε 4·34), 340 mμ (infl; log ε 4·00). (Found: C, 68·38; H, 7·16. $C_{26}H_{32}O_7$ requires: C, 68·40; H, 7·07%).

(ii) Compound XVIII (1 g) was dissolved in 95% EtOH (333·3 ml). 5% NaOH aq (38 drops) was added and a 0·40 ml aliquot of the red reaction mixture was removed. It was diluted to 50 ml with 95% EtOH and its UV spectrum was recorded immediately and thereafter at approximately 7 min intervals. After 30 min, the spectrum was identical to that of XV. The reaction mixture was then concentrated to 50 ml by evaporation under reduced press and was poured into water. The mixture was extracted with ether; the ethereal extract was washed with 5% HCl aq (2 ml), K_2CO_3 aq, and water, and was dried over $MgSO_4$. Evaporation of the solvent under reduced press gave an oil which was chromatographed on Merck alumin (20 g; 20 mm column). Elution with 1:1 benzene–ether gave XV. After one recrystallization from cyclohexane–pet. ether, the yield was 562 mg (75%).

Heating of a soln of 2'hydroxydihydrodimethylmangostin in glacial AcOH and conc HCl reconverted it to XVIII.

Oxidation of 2'-hydroxydihydrodimethylisomangostin (XV)

Formation of 2'-oxodihydrodimethylisomangostin (XIV). Crude XV (610 mg) was dissolved in glacial AcOH (ca. 10 ml) and the soln was cooled in an ice bath. A soln of CrO_3 (100 mg) in water (9 drops) and AcOH (20 drops) was added. The dark soln was kept in an ice bath, which melted and warmed to room temp in 3 hr. The reaction mixture was then poured into water and extracted with ether. The ethereal extract was washed with water and K_2CO_3 aq, dried over $MgSO_4$, and evaporated. The residue was taken up in benzene and chromatographed on Merck alumina (20 g; 20 mm column). The product was eluted with a soln of 10% ether in benzene (160 ml), this eluate was evaporated to a glass, which was crystallized from cyclohexane–pet. ether to give XIV (100 mg, 16·5%). An analytical sample was obtained by recrystallization from the same solvent pair as colorless rhombs, m.p. 187·9–188·9°. The compound also crystallized as plates which underwent a change of form at 145–150° and melted at 188°; $\lambda_{max}^{CCl_4}$ 5·85, 6·07, 6·20, 6·26 μ, λ_{max}^{EtOH} 245 mμ (log ε 4·52), 255·5 mμ (log ε 4·52), 302·5 mμ (log ε 4·33), 338 mμ (log ε 3·99). (Found: C, 68·66; H, 6·71. $C_{26}H_{30}O_7$ requires: C, 68·70; H, 6·65%).

Formation of XVI

(i) *From 2'-hydroxydihydrodimethylisomangostin* (XV). Compound XV (200 mg) was dissolved in benzene (5 ml) and ether (3 ml), and the soln was treated with 10 ml of a soln of the Grignard reagent formed from Mg (1·2 g), isopropyl bromide (2·2 ml), and ether (48 ml). A light grey suspension was formed which redissolved after approximately 3 min. After a few more mins, a little more of the Grignard reagent was added and, when no change was observed, 30% NH_4Cl aq (10 ml) was slowly added, followed by 5% HCl aq (3 ml). The mixture was extracted with ether; the ethereal extract was washed with K_2CO_3 eq, dried over $MgSO_4$, and evaporated to an oil (219 mg, 97%). Trituration with pet. ether gave a solid material which was recrystallized from cyclohexane–pet. ether. The m.p. of this compound was not sharp; the analytical sample softened ca. 160° and melted between 180 and 190°; $\lambda_{max}^{CCl_4}$ 2·90, 6·16, 6·23, 6·34 μ, λ_{max}^{EtOH} 214 mμ (log ε 4·72), 248 mμ (infl; log ε 4·08), 290 mμ (log ε 3·63). (Found: C, 69·79; H, 7·90. $C_{29}H_{40}O_7$ requires: C, 69·57; H, 7·96%).

(ii) *From* XIII. Dimethylisomangostin aldehyde (XIII; 260 mg) was dissolved in benzene (5 ml) and ether (3 ml), and the soln was treated with 10 ml of a soln of i-PrMgBr formed from Mg (1·2 g), i-PrBr (2·2 ml), and ether (48 ml). A yellow suspension was formed which quickly redissolved. After the reaction mixture had been allowed to stand for 2 hr, excess NH_4Cl aq was cautiously added, followed by 5% HCl aq. The mixture was extracted with ether; the ethereal extract was washed with K_2CO_3 aq and water, dried over $MgSO_4$, and evaporated to give a light brown oil (305 mg, 92%). Trituration with pet. ether gave solid material which was recrystallized from cyclohexane–pet. ether. The IR and UV spectra of the product were identical with those of the product obtained by route (i). The melting behaviour of the two products was the same and a mixed m.p. showed no depression.

Reaction of 2'-hydroxydihydrodimethylisomangostin (XV) *with methylmethylmagnesium iodide*

Formation of XVII. Compound XV (300 mg) was dissolved in benzene (5 ml) and ether (5 ml), and the soln was treated with 10 ml of a soln of MeMgI formed from Mg (1·2 g), MeI (5 ml), and ether (45 ml). A yellow-grey suspension was formed. After 4 days, water was added dropwise, followed by NH_4Cl aq and 5% HCl aq. The mixture was extracted with ether; the ethereal extract was washed with K_2CO_3 aq and water, and was treated with Norit and dried over $MgSO_4$. Evaporation of the solvent left a light yellow residue (350 mg). Trituration with pet ether gave solid material which was recrystallized from MeOH. An analytical sample had m.p. 152–153·8°; $\lambda_{max}^{CCl_4}$ 6·16, 6·24, 6·33 μ, λ_{max}^{EtOH} 250 mμ (infl; log ε 4·03), 290 mμ (log ε 3·66). (Found: C, 71·23; H, 7·47. $C_{27}H_{32}O_6$ requires: C, 71·34; H, 7·54%).

Interconversion of dimethylmangostin hydrochloride (XVIII) *and 2'-hydroxydihydrodimethylisomangostin* (XV)

Spectrophotometric study. (i) Compound XVIII (0·60 mg) was dissolved in 95% EtOH (25·0 ml) to give a yellow soln. A 5 ml aliquot was taken, water (2 drops) was added, and the UV spectrum of the soln was recorded (Fig. 1); the spectrum was that of XVIII. A second aliquot was taken and water (1 drop) and 2·5% NaOH aq (1 drop) were added. The soln was decolorized instantly and its UV spectrum was recorded immediately (Fig. 2, Curve 2) and thereafter at approximately 7 min intervals (Fig. 2, Curves 3–5). After 23 min, the spectrum (Fig. 2, Curve 5) was identical with that of XV. An isosbestic point involving Curves 2–5 was observed at 237 mμ (log ε 4·48). A third aliquot was taken, and 2·5% NaOH aq (1 drop) was added, the soln becoming colourless. After 0·5 min 5% HCl aq (1 drop) was added, whereupon the soln again became yellow. Its UV spectrum was then recorded and was found to be identical to that of XVIII (Fig. 1). A fourth aliquot was taken, and 5% NaOH aq (1 drop) was added. After 35 min its UV spectrum was recorded and it was found to be identical with Curve 5 of Fig. 2. One drop of 5% HCl aq was then then added, and the UV spectrum was recorded immediately (Fig. 3, Curve 6) and thereafter at intervals (Fig. 3, Curves 7–9) until a spectrum, recorded after 250 min (Fig. 3, Curve 9), was identical to that of XVIII. Isosbestic points involving Curves 6–9 were observed at 221 mμ (log ε 4·35), 235 mμ (log ε 4·42), 262 mμ (log ε 4·37), 282 mμ (log ε 4·05), and 343 mμ (log ε 3·98).

(ii) A soln of XVIII (1·20 mg) was prepared in MeOH (50·0 ml, dried with Mg). A 5 ml aliquot was taken and its UV spectrum was recorded; the spectrum was identical to that of XVIII (Fig. 1). One drop of an approximately 2% soln of MeONa in anhyd MeOH was added, decolorizing the yellow soln; the UV spectrum, which was recorded immediately, was similar to Curve 2 of Fig. 2. The spectrum was recorded again after 7 min and after 21 min and found to be unchanged.