400 mg. (40%) and melted at 260–265°. Several crystallizations of crude product from acetone–Skellysolve B gave an analytical sample, m.p. 263–265°, λ_{max} 252.5 mμ (ε 12,100), $[\alpha]_D$ +161° (dioxane).

Anal. Calcd. for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 68.20; H, 7.27.

Oxidation of Seleno-1-dehydrotestosterone with Hydrogen Peroxide to (VIIIa).—To 300 mg. of seleno-1-dehydrotestosterone in 3 ml. of acetic acid was added 0.5 ml. of 30% aqueous hydrogen peroxide. The solution was kept at room temperature for 20 minutes and then diluted with 50 ml. of water. Upon cooling at 5° overnight, colorless needles appeared. The mixture was filtered and the product was washed with cold water, and dried; weight 200 mg., m.p. 174–178°, λ_{max} 252 mμ (ε 10,600), $[\alpha]_D$ −62.5° ($CHCl_3$), pK_a 5.5 (equivalent weight 407).

Anal. Calcd. for $C_{19}H_{26}O_4Se$: C, 57.43; H, 6.60. Found: C, 57.14; H, 6.77.

CHICAGO 90, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

The Structure of Mangostin[1]

BY PETER YATES AND GEORGE H. STOUT[2]

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Mangostin is shown to be 1,3,6-trihydroxy-7-methoxy-2,8-di-(3-methyl-2-butenyl)-xanthone (X).

Mangostin is the yellow coloring matter obtained from various parts of the mangosteen tree (*Garcinia mangostana, Guttiferae*). It was isolated first by Schmid in 1855 from the fruit hulls[3]; it has subsequently been obtained from the bark and dried sap.[4] The last is by far the richest source, yielding 30–50% of mangostin. It was early claimed that mangosteen hulls surpass cinchona bark as a febrifuge and they and the bark also have been used in the treatment of dysentery,[5] but there have been no reports on the pharmacological properties of mangostin itself.

Mangostin is a bright yellow, optically inactive, phenolic, crystalline material, m.p. 182–183°. Although a number of workers have investigated its chemistry,[3,4,6–13] there has been continuing disagreement over its empirical formula and molecular weight, leading in turn to a range of proposed molecular formulas. The most recently advocated formula, $C_{23}H_{24}O_6$, was advanced by Murakami[12] as a result of analyses of derivatives of mangostin containing additional elements. On this basis, Murakami concluded from his own and earlier work that mangostin had the following functional groups: two double bonds susceptible to hydrogenation, one methoxyl group, and three hydroxyl groups, two of which readily could be methylated and a third which could be acetylated, but methylated only with great difficulty. In addition, Dragendorff[4] had observed that mangostin and dimethylmangostin form complexes with boron pyroacetate ("boroacetic anhydride")[14] and deduced that it must contain a carbonyl function in a β-relationship to the unreactive hydroxyl group.

The first significant degradative work was carried out by Dragendorff[4,10] who found that isovaleric acid and an amyl alcohol were obtained on fusion of mangostin with potassium hydroxide. He also observed that oxidation of mangostin or dimethylmangostin gave α-hydroxyisobutyric acid, while oxidation of tetrahydromangostin with chromic acid gave isocaproic acid. Ozonolysis of dimethylmangostin yielded acetone peroxide and a major fragment which he formulated as $C_{15}H_{14}O_6$ or $C_{22}H_{20}O_9$. Subsequently, Yamashiro[11] repeated the basic fusion of mangostin and obtained acetic acid, oxalic acid, isovaleric acid, phloroglucinol and a yellow, phenolic compound, which on renewed basic fusion gave phloroglucinol and isovaleric acid. Shortly thereafter, Murakami[12] investigated the cleavage of mangostin in ethanolic potassium hydroxide at 170–180°; he isolated isoamyl alcohol, a 3,5-dihydroxy-2-methoxyisopentenylbenzene (I) and 2-methyl-2-hepten-6-ol (II). In the light of his isolation of I, he reformulated Yamashiro's phenol as a $C_{19}H_{18}O_6$ compound and assigned to it the structure III. On the basis of this assignment, the isolation of II, and other observations, he proposed the structure IV for mangostin.[15]

It appeared to us that the evidence available did not justify the formulation of mangostin as IV and that, indeed, there were substantial grounds for doubting the correctness of this structure. Thus: (i) the yellow color, and more generally, the ultraviolet spectrum[4] of mangostin were inconsistent with IV; (ii) the question of the molecular formula of

(1) In part, from the Ph.D. Thesis of George H. Stout, Harvard University, 1956; a preliminary account of part of this work has appeared previously: P. Yates and G. H. Stout, *Chemistry & Industry*, 1392 (1956).

(2) National Science Pre-doctoral Fellow, 1954–1955; General Electric Rice Fellow, 1955–1956.

(3) W. Schmid, *Ann.*, **93**, 83 (1855).

(4) O. Dragendorff, *ibid.*, **482**, 280 (1930).

(5) P. Kuo-Hao, *Arch. Schiffs- und Tropen Hygiene*, **40**, 440 (1936); J. M. Dalziel, "The Useful Plants of Tropical West Africa," Crown Agents for Overseas Governments and Administrations, London, 1937, p. 92.

(6) P. R. Liechti, *Arch. Pharm.*, **229**, 426 (1891).

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

(8) A. L. van Scherpenberg, *Rec. trav. chim.*, **35**, 361 (1915).

(9) J. Dekker, *ibid.*, **43**, 727 (1924).

(10) O. Dragendorff, *Ann.*, **487**, 62 (1931).

(11) S. Yamashiro, *Bull. Chem. Soc. Japan*, **7**, 1 (1932).

(12) M. Murakami, *Proc. Imp. Acad. (Tokyo)*, **7**, 254, 311 (1931); *Ann.*, **496**, 122 (1932); *J. Chem. Soc. Japan*, **53**, 150, 162 (1932).

(13) A. Tschirch and E. Stock, "Die Harze," Borntraeger Verlag, Berlin, 3rd ed., Vol. II, 1936, p. 1562.

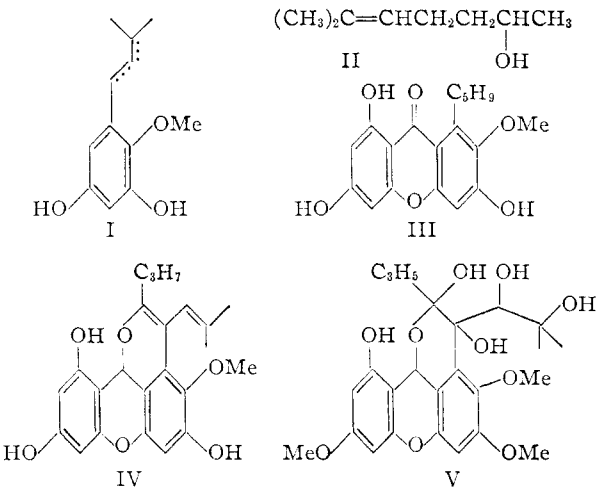
(14) O. Dimroth and T. Faust, *Ber.*, **54**, 3020 (1921); O. Dimroth, *Ann.*, **446**, 97 (1926).

(15) A structure based on a C_{24}-formulation for mangostin which is referred to in two subsequent discussions[16,17] appears to result from a misreading of Murakami's proposal and to have no basis in fact.

(16) F. Mayer and A. H. Cook, "The Chemistry of Natural Coloring Matters," Reinhold Publ. Corp., New York, N. Y., 1943, p. 249.

(17) R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955, p. 45.

mangostin could not yet be considered to have been settled decisively, in that a series of earlier analyses by Dragendorff[10] indicated a consistently higher carbon content for mangostin and its derivatives than that required by the formula $C_{23}H_{24}O_6$; further, Murakami's own analytical results were not without ambiguity (*vide infra*); (iii) although Murakami had established the structure of I and appeared to be on firm ground in attributing a structure of type III to Yamashiro's phenol, the orientation of all the substituents on the xanthone nucleus was not rigorously defined; (iv) the nature of the side



chain was ill-established: first, it was incomplete in respect to the C_3H_7 group; second, it was difficult to discern a rational scheme to explain the formation of II by basic degradation; third, the failure to isolate any acid higher than isocaproic acid by oxidation of tetrahydromangostin was surprising; fourth, it failed to lead to an acceptable formulation for the ozonolysis product obtained by Dragendorff[10]; (v) there existed severe difficulties in formulating and explaining the properties of certain other reaction products of mangostin in terms of IV, *e.g.*, the product from the oxidation of dimethyl mangostin with potassium permanganate, to which Murakami assigned the structure V.

In view of these considerations we embarked upon a further study of the chemistry of mangostin which has led us to propose a new formula and structure.[18]

Formula.—The wide variation in the results of molecular weight determinations by early workers using various cryoscopic and ebullioscopic methods led Murakami to prepare and analyze derivatives of mangostin containing sulfur, chlorine and bromine. Although these results confirm the higher molecular weight values and are therefore compatible with the formula $C_{23}H_{24}O_6$, they do not serve to distinguish unambiguously between this formula and $C_{24}H_{26}O_6$. We therefore have had resort to an X-ray determination of the molecular weight, probably the most accurate and reliable means of arriving at the molecular weight of a nicely crystalline organic compound.[19] Tetrahydrodimethylmangostin, prepared by catalytic hydrogenation of dimethylmangostin, crystallized in monoclinic needles of moderate size and was used for the determination. The resulting value of 453 ± 12 provided a powerful argument in favor of $C_{24}H_{26}O_6$ (mol. wt. of tetrahydrodimethyl derivative 442) rather than $C_{23}H_{24}O_6$ (mol. wt. of tetrahydrodimethyl derivative 428). Furthermore, although not decisive in themselves, our own elemental analyses on mangostin and its derivatives favored the former formulation, as had those of Dragendorff. Finally, as will appear in the sequel, our degradative studies corroborate the formula $C_{24}H_{26}O_6$.

Nucleus.—The arguments of Murakami regarding the presence of a xanthone nucleus in Yamashiro's phenol appeared sound, and on this basis it seemed not unlikely that mangostin itself had a xanthone nucleus. That this was indeed the case was shown by comparison of the ultraviolet spectra of mangostin and its derivatives with those of a number of synthetic polyhydroxyxanthone derivatives; their close similarity is apparent from Table I. In addition, mangostin, its derivatives, and the model polyhydroxyxanthones all show a strong band in their infrared spectra at 6.05–6.10 μ; this band may be assigned to the stretching vibration of the xanthone carbonyl group.[20] Thus both the infrared and ultraviolet spectral data are in full accord with the presence of a polyhydroxyxanthone nucleus in mangostin and are incompatible with a structure such as IV with an ether bridge at C9.

Of the three structures, III, VI and VII, for Yamashiro's phenol which are compatible with the degradative evidence, both VI and VII contain two hydroxyl groups *peri* to the carbonyl. Murakami argued that since this compound contained only one hydroxyl group resistant to methylation, its structure could therefore be neither VI nor VII, and must be III. However, this argument is of dubious value since in the case of the known 1,8-dihydroxyxanthone derivatives, desmethylswertianol (VIII)[21] and ravenelin (IX),[22] the methylation of one *peri* hydroxyl group is accomplished much more readily than methylation of both. We consider that a sounder basis for choice of the orientation as in III is a comparison of the ultraviolet spectra of xanthones containing only one *peri* hydroxyl group with those of 1,8-dihydroxyxanthone and IX (Table I). The introduction of a second *peri* hydroxyl group brings about both a bathochromic and hypochromic shift of the two longer wave length bands.[23] Since mangostin and its derivatives do not show these shifts in their spectra, it may be concluded that they do not possess two *peri* hydroxyl groups and that the orientation of the substituents must be as in III,

(18) Dragendorff alone among previous investigators has reported the isolation of two isomeric compounds, α- and β-mangostin.[4] The α-mangostin corresponded in properties to the mangostin of other workers and of the present investigation. The β-mangostin was isolated in a yield of about 4% of that of the α-mangostin and was obtained only from *sun-dried* latex. Extraction of fresh latex gave no β-mangostin and thus it may be considered to be an artifact.[10]

(19) *Cf.* J. M. Robertson in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, eds., Academic Press, New York, N. Y., 1955, p. 468.

(20) *Cf.* E. D. Bergmann and S. Pinchas, *J. chim. phys.*, **49**, 537 (1952).

(21) Y. Asahina, J. Asano and Y. Ueno, *Bull. Chem. Soc. Japan*, **17**, 104 (1942).

(22) H. Raistrick, R. Robinson and D. E. White, *Biochem. J.*, **30**, 1303 (1936).

(23) *Cf.* R. C. Shah, A. B. Kulkarni and S. R. Dalal, *J. Sci. Ind. Res. (India)*, **13B**, 175 (1954).

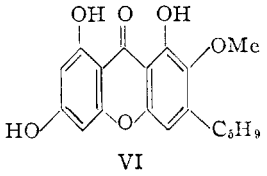
TABLE I

ULTRAVIOLET SPECTRA OF MANGOSTIN AND ITS DERIVATIVES AND OF HYDROXYXANTHONE DERIVATIVES

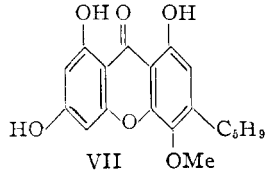
Compound	λ_{max}^{EtOH}, mμ (log ε)			
Mangostin	243(4.54)	259(4.44)	318(4.38)	351(3.86)
Dimethylmangostin	245(4.50)	262(4.53)	314(4.36)	350(3.81)
Tetrahydrodimethylmangostin	244(4.45)	261(4.48)	312(4.34)	351(3.78)
1,6-Dihydroxyxanthone[a]	247(4.3)	263(4.0)	305(4.1)	355(3.8)
1-Hydroxy-3,7-dimethoxyxanthone[b]	239(4.5)	261(4.7)	311(4.2)	.....
1,3,6-Trihydroxyxanthone	237(4.56)	251(4.40)	313(4.35)	337(4.09)
1-Hydroxy-3,6-dimethoxyxanthone	238(4.52)	251(4.41)	307(4.33)	337(4.01)
1,3,7-Trihydroxy-6-methoxyxanthone	239(4.34)	256(4.50)	310(4.15)	362(3.99)
1-Hydroxy-3,6,7-trimethoxyxanthone	238(4.37)	256(4.59)	309(4.23)	356(4.09)
1,8-Dihydroxyxanthone[a]	229(3.75)	252(3.90)	334(3.30)	380(2.90)
Ravenelin (IX)[a]	231(4.0)	263(4.25)	343(3.8)	>400(~3.2)

[a] R. P. Mull and F. F. Nord, *Arch. Biochem.*, **4**, 419 (1944). [b] L. Canonica and F. Pelizzoni, *Gazz. chim. ital.*, **85**, 1007. (1955).

which is thus firmly established as the structure of Yamashiro's phenol.



VI



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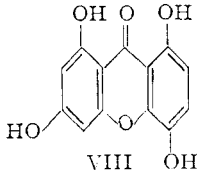
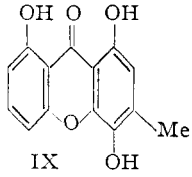


VIII



IX

Nature of the Side Chains.—With fourteen carbon atoms assigned to a methoxyxanthone nucleus, ten remain for incorporation into one or more side chains, in which must be located two double bonds. That these double bonds are not conjugated with each other nor with the nucleus is shown by the essential identity of the ultraviolet spectra of dimethylmangostin and tetrahydrodimethylmangostin (*cf.* Table I), since it would be anticipated that reduction of part of such a conjugated system would be accompanied by an hypsochromic shift.[24]

Although isolation of a methylheptenol from basic degradation led Murakami to the conclusion that all the extranuclear carbon atoms of mangostin, apart from the methoxyl group, were in a single side chain, neither he nor Dragendorff were able to isolate any fragment larger than isocaproic acid by oxidative degradation of tetrahydromangostin. We have reinvestigated this crucial experiment. Tetrahydromangostin, obtained by catalytic hydrogenation of mangostin,[4,12] was treated with ozone, then with acid potassium permanganate. The resulting fatty acid was analyzed quantitatively by the partition chromatography procedure of Moyle, Baldwin and Scarisbrick.[25] The analysis showed the presence of 1.06 molar equivalents of a caproic acid, the absence of higher fatty acids, and the formation of only a trace of a valeric acid. Oxidation of a larger sample of tetrahydromangostin, distillation of the volatile acid fraction and conversion of the entire distillate *via* the acid chloride to the amide gave, after a single crystallization, pure isocaproamide. Thus the formation of isocaproic acid as essentially the only fatty acid, resulting from oxidation of tetrahydromangostin was confirmed. Further, since it was found that treatment of authentic isocaproic acid under the conditions used for the oxidation of tetrahydromangostin gave only a 61% recovery, the quantitative results demonstrated that there must be *two* groups present in tetrahydromangostin capable of giving rise to isocaproic acid. Thus the extranuclear carbon atoms, apart from the methoxyl group, must be attached to the nucleus in the form of two isoamyl side chains. Conversely, the requirement of ten carbon atoms in these side chains confirms the correctness of the C_{24}-formulation for mangostin. The presence of two isoamyl side chains requires that four C–CH_3 groups be present in mangostin. That such was the case was confirmed by a study of the nuclear magnetic resonance spectrum of dimethylmangostin. Quantitative counts on a number of spectra showed the ratio of the areas of the C–CH_3 and O–CH_3 peaks to be 1.33–1.40; since three methoxyl groups are known to be present, this corroborates the presence of four C–CH_3 groups.

Since the double bonds of mangostin are not in conjugation, one double bond must be located in each side chain. Their position was determined by a re-examination of the ozonolysis product from dimethylmangostin, first prepared by Dragendorff.[10] Acetone peroxide was obtained, as previously reported, together with a product similar in properties to the material to which Dragendorff assigned the formula $C_{15}H_{14}O_6$ or $C_{22}H_{20}O_9$; to this product we now assign the formula $C_{20}H_{18}O_8$. Its infrared spectrum showed bands in the 6–6.4 μ region similar to those of mangostin and its derivatives, confirming the retention of the xanthone nucleus; in addition, it showed a weak band at 3.69 μ and a very sharp, strong band at 5.81 μ, together characteristic of the presence of a saturated aldehydic group. Quantitative measurements of the intensity of the aldehyde carbonyl stretching band gave a relative molar intensity[26] of 29, as compared with 11.3 for

(24) *Cf.*, for example, M. L. Wolfrom, W. D. Harris, G. F. Johnson, J. E. Mahan, S. M. Moffett and B. Wildi, THIS JOURNAL, **68**, 406 (1946).

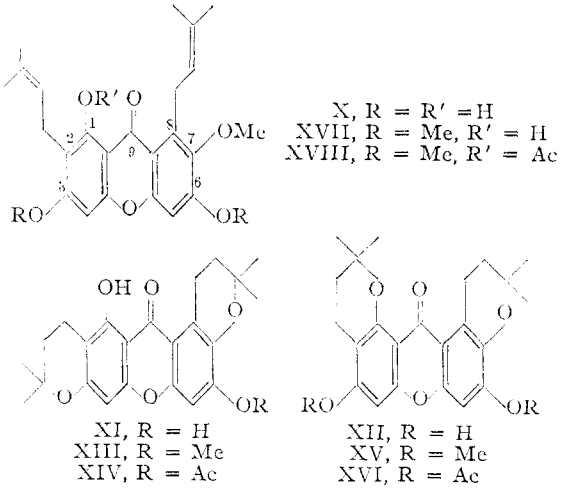
(25) V. Moyle, E. Baldwin and R. Scarisbrick, *Biochem. J.*, **43**, 308 (1948).

(26) In arbitrary units; the measurements were made by replacement in a cell of unknown thickness.

phenylacetaldehyde (band at 5.80 μ), suggesting the presence of two aldehyde groups in the molecule. Confirmation of this fact and also of the newly assigned formula was obtained by the ready preparation of a bis-semicarbazone, $C_{22}H_{24}N_6O_8$.[27] The nuclear magnetic resonance spectrum of the ozonolysis product showed that all of the C–CH_3 groups of dimethylmangostin were lost on ozonolysis. The loss of four C–CH_3 groups when six carbon atoms are removed with the formation of a dialdehyde is only possible if both side chains end in isopropylidene groups. The results of the ozonolysis, therefore, confirm the presence of two isopentenyl side chains in mangostin and show that the double bonds must be in the β,γ-position with respect to the nucleus.

Position of the Side Chains.—One of the side chains must be located at C8 in order to explain the formation of III on basic fusion. We now develop arguments which place the second side chain at C2.

Hill reported that the demethylation of mangostin with hydriodic acid proceeded smoothly to give a demethylmangostin which on remethylation did not give dimethylmangostin and which gave a monoacetyl derivative. We have confirmed Hill's observations and assign the formula $C_{23}H_{24}O_6$ to demethylmangostin; we have found also that methylation of demethylmangostin with dimethyl sulfate and base gave a monomethyl derivative, isomeric with mangostin, which resisted further methylation. If, on the other hand, the demethylation is carried out in hydriodic acid in the presence of iodine, a dark red crystalline product is obtained which, after recrystallization from methanol, analyzes approximately as $C_{23}H_{24}O_6I_2 \cdot 2CH_3OH$. This readily can be converted by treatment with sodium bisulfite or by solution in chloroform and extraction of iodine with aqueous potassium iodide into isodemethylmangostin, $C_{23}H_{24}O_6 \cdot C_2H_5OH$ (from ethanol). Acetylation of isodemethylmangostin gave a diacetate, $C_{27}H_{28}O_8$, while methylation gave a dimethyl derivative, $C_{25}H_{28}O_6$. These two isomeric demethyl compounds must arise from alternate modes of cyclization of the isopentenyl side chains onto adjacent hydroxyl groups under the influence of the strongly acidic media; such cyclizations are known among compounds having isoprenoid side chains.[24,28] The side chain at C8 possesses only one adjacent potential hydroxyl function, and can therefore cyclize in one fashion alone. Hence the second side chain must be located in such a way as to provide the possibility of cyclization in two directions. The only position which provides two *ortho* hydroxyl groups is C2. Consequently mangostin must have the structure X, leading by demethylation and cyclization to demethylmangostin (XI) or isodemethylmangostin (XII). This assignment of the structures of the demethyl compounds is clearly consonant with the formation of a monomethyl derivative XIII and a monoacetate XIV from demethylmangostin and a dimethyl derivative XV and a diacetate XVI from isodemethylmangostin.



X, R = R' = H
XVII, R = Me, R' = H
XVIII, R = Me, R' = Ac

XI, R = H
XIII, R = Me
XIV, R = Ac

XII, R = H
XV, R = Me
XVI, R = Ac

Confirmation of this relationship between XI and XII was obtained in several ways. In the nuclear magnetic resonance spectrum of dimethylmangostin and other compounds with very strongly hydrogen-bonded hydroxyl groups, the peak due to the hydrogen participating in the strong hydrogen bond is shifted very far in the unshielded direction, and consequently is distinguished very readily from the bands due to all other hydrogens in the molecule. Methyldemethylmangostin shows such a peak, as anticipated on the basis of structure XIII, but dimethylisodemethylmangostin (XV) does not. Also although the *peri*-hydroxyl group does not give rise to a well-defined O–H stretching band in the infrared, it shows as a broad, weak base to the C–H stretching band, extending usually from 3.2 to 4.0 μ or higher.[29] This characteristic "funnel-shaped" C–H band appears in demethylmangostin and its methyl ether, but is absent in isodemethylmangostin and its derivatives. The iso series showed a further effect in the infrared which appears to be of general diagnostic value in distinguishing 1-hydroxyxanthones from their ethers or esters. For all of the 1-hydroxyxanthones investigated including mangostin (X), dimethylmangostin (XVII), and a number of model compounds, the infrared spectra showed two major bands in the 6.0–6.3 μ region; one of these, at 6.06–6.09 μ, corresponded to carbonyl absorption,[30] while the other at 6.20–6.27 μ, may be assigned to the aromatic nucleus.[30] In eight cases, however, in which the 1-hydroxyl group was etherified or esterified a third major band appeared in this region, at 6.13–6.20 μ (Table II). This band was of almost exactly the same intensity as the band at 6.20–6.27 μ; both of these bands are very sharp and although separated by only 0.05–0.08 μ are easily resolved in carbon tetrachloride solution.[31]

Finally, compounds of the iso series were found to be relatively strong oxonium bases, giving yellow-

(27) Dragendorff prepared an oxime from the ozonolysis product which he initially formulated as a monoöxime[10]; later, however, he considered it best formulated as a dioxime: see reference 13, p. 1582.

(28) S. Wawzonek in "Heterocyclic Compounds," Vol. II, R. C. Elderfield, ed., John Wiley and Sons, New York, N. Y., 1951, p. 393 *et seq.*

(29) V. C. Farmer, N. F. Hayes and R. H. Thomson, *J. Chem. Soc.*, 3600 (1956).

(30) R. N. Jones and C. Sandorfy in "Chemical Applications of Spectroscopy," W. West, ed., Interscience Publishers, Inc., New York, N. Y., 1956, pp. 394 *et seq.*

(31) The sole exception observed was in the case of isodemethylmangostin diacetate, which showed a single peak at 6.23 μ, perhaps due to fortuitous overlap.

TABLE II

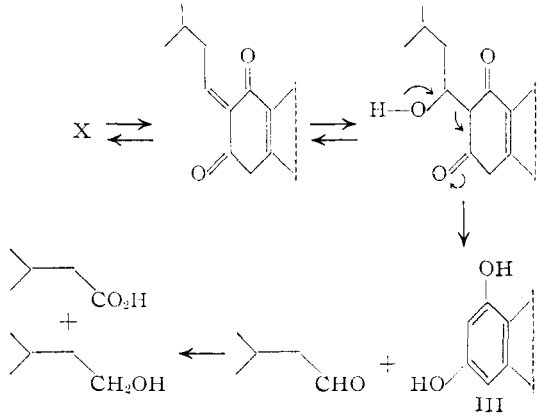
INFRARED BANDS IN THE 6.0–6.3 μ REGION OF 1-ALKOXY- OR 1-ACYLOXYXANTHONE DERIVATIVES

Compound	$\lambda_{max}^{CCl_4}$, μ		
Isodemethylmangostin (XII)	6.10	6.19	6.25
Dimethylisodemethylmangostin (XV)	6.06	6.19	6.25
Dimethylmangostin acetate (XVIII)	6.06	6.17	6.25
1-Acetoxyxanthone	5.99	6.15	6.20
1-Methoxyxanthone	6.03	6.20	6.27
1-Acetoxy-3,6-dimethoxyxanthone	6.02	6.13	6.20
Formoxydihydrodimethylmangostin (XXI)[a]	6.04	6.20	6.26
Hydroxydihydrodimethylmangostin (XXII)[a]	6.05	6.18	6.25

[a] *Vide infra.*

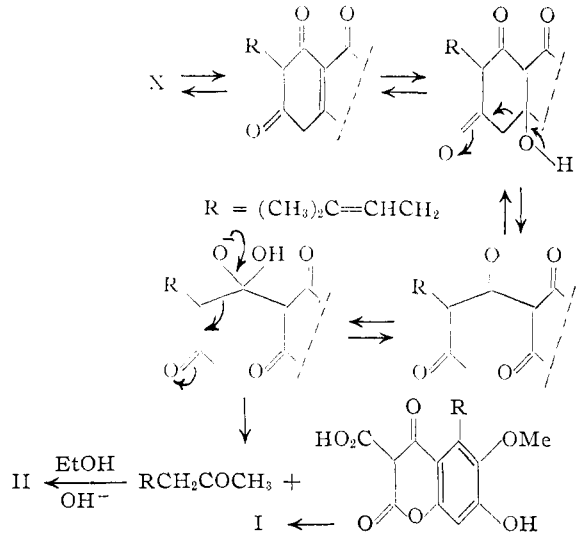
green fluorescent colors when shaken in benzene with aqueous perchloric acid and frequently precipitating crystalline perchlorates under these conditions. On the other hand, this phenomenon was not observed with mangostin and its derivatives containing a free hydroxyl group at C1. These observations are in full accord with the known relative basicities of 1-methoxyxanthones and the corresponding 1-hydroxy compounds.[32] Presumably the iodine-containing intermediate in the formation of isodemethylmangostin has an oxonium salt type structure, since its infrared spectrum resembles in many respects that of the perchlorate of isodemethylmangostin; however, its full structure has not been elucidated.

Degradative Pathways.—We return now to some aspects of the basic degradation of mangostin which require reinterpretation in terms of the newly proposed structure X. The formation of isoamyl alcohol and isovaleric acid on basic fusion of phenols containing isoprenoid side chains is well known[33] and can be envisioned as occurring in the present case by the following type of pathway, involving shift of the double bond, hydration and reverse aldol cleavage and then by conversion of isovaleraldehyde to the corresponding alcohol and acid by a Cannizzaro reaction



Such a route also explains the formation of Yamashiro's phenol III; unlike the side chain at C2, that at C8 has no free hydroxyl group in the *ortho* or *para* position which would permit the reverse aldol elimination; it therefore survives in III. The formation of isovaleric acid on further basic fusion of III may be attributed to demethylation of the latter to an intermediate with a free hydroxyl group in a position *ortho* to the side chain, which is then eliminated.

The isolation of the methylheptenol II on treatment of mangostin with ethanolic potassium hydroxide, which at first directed attention to the formulation of mangostin with a single side chain, may be explained in terms of an alternative degradative route involving rupture of the potential phloroglucinol ring by hydration and reverse aldol cleavage, and then by cleavage of the resulting β-diketone to give a methylheptenone, derived from both side chain and ring, which is reduced to II under the influence of ethanolic base.[34] The fragment remaining after the loss of methylheptenone could serve readily as the source of I.



Other Products from Mangostin.—Murakami has reported that the action of potassium permanganate in acetone on dimethylmangostin yields a polyhydroxy compound to which he assigned structure V. Repetition of this work has shown that the product is best formulated as $C_{26}H_{30}O_{10}$. This product is resistant to hydrogenation. Its infrared spectrum shows bands at 2.92 and 5.85 μ in addition to those attributable to the xanthone nucleus, indicating the introduction of one or more hydroxyl and saturated ketonic groups; its ultraviolet spectrum is very similar to that of dimethylmangostin, indicating that no change has occurred in the nucleus. Although the oxidation product is itself resistant to cleavage by periodic acid or lead tetraacetate, on reduction with sodium borohydride it yields a crystalline mixture of alcohols (broad band at 2.90 μ, no carbonyl band at 5.85 μ) which is cleaved smoothly by periodic acid to give the dialdehyde XIX obtained by the ozonolysis of dimethylmangostin. We therefore assign the bis-α-ketol structure XX to the original oxidation product. The formation of α-ketols as primary products from oxidation of ethylenic compounds with potassium permanganate in neutral or weakly basic media has ample precedent.[35] In the present case, further

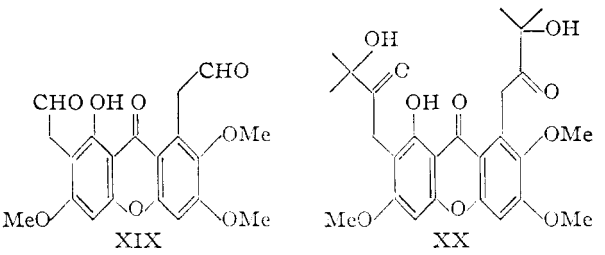
(32) K. C. Roberts, L. A. Wiles and B. A. S. Kent, *J. Chem. Soc.*, 1792 (1932).

(33) *Cf.*, for example, M. L. Wolfrom and J. Mahan, THIS JOURNAL, **64**, 308 (1942).

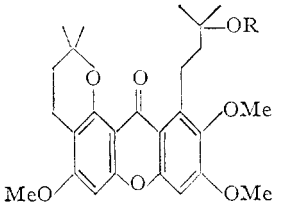
(34) The yield of II is low: *ca.* 5%.[12]

(35) G. King, *J. Chem. Soc.*, 1788 (1936); J. E. Coleman, C. Ricciuti and D. Swern, THIS JOURNAL, **78**, 5342 (1956).

oxidation of XX was minimized because of its insolubility in the reaction medium. It may be surmized that the formation of α-hydroxyisobutyric acid by the oxidation of mangostin itself with potassium permanganate proceeds *via* such ketol formation.

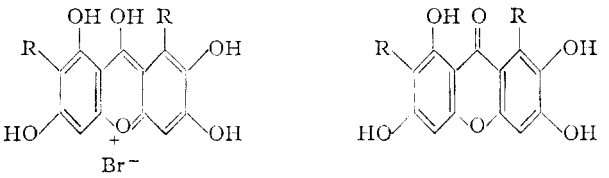


In the course of attempts to oxidize dimethylmangostin with performic acid a product was isolated whose composition, $C_{27}H_{32}O_8$, corresponded to the addition of the elements of formic acid. It was shown subsequently that the same product could be obtained by the action of formic acid on dimethylmangostin. This product is assigned the structure XXI for the following reasons. Its infrared spectrum showed a band at 5.80 μ and also revealed the lack of a free hydroxyl group at C1 in that the C–H stretching band was not "funnel-shaped" and the 6.0–6.3 μ region showed the presence of three major bands (*vide supra*). The formoxy compound XXI was hydrolyzed very readily to the corresponding hydroxy compound XXII. The infrared spectrum of this product showed a sharp hydroxyl band at 2.87 μ, lacked the carbonyl at 5.80 μ, and exhibited the features, present in XXI, which have been found to be characteristic of the iso series. In addition, both XXI and XXII were found to have the basic properties shown by other members of that series. The formulation XXI for the formoxylation product accounts for the failure of a second molecule of formic acid to add and is in accord with the known ability of formic acid to effect cyclizations of this type.[36] Its formation further corroborates the placement of one side chain adjacent to the hydroxyl at C1.



XXI, R = CHO
XXII, R = H

Murakami has reported the formation of tetrahydronormangostin hydrobromide by the action of hydrobromic acid on tetrahydromangostin; on treatment with water this was converted to tetrahydronormangostin, which gave tetrahydrodimethylmangostin on methylation.[12] These products are readily accommodated on the basis of formula X for mangostin. The hydrobromide may be formulated as XXIII, resulting from demethylation and oxonium salt formation[37]; hydrolysis would give XXIV, which, unlike the demethyl derivatives previously discussed, is a simple normangostin derivative, since cyclic ether formation is no longer possible when the side chains have been reduced. However, dimethylmangostin hydrochloride obtained by Murakami by the action of hydrochloric acid on dimethylmangostin[12] cannot be a simple normangostin derivative since it is resistant to hydrogenation and its structure is being investigated further.



XXIII R = $(CH_3)_2CHCH_2CH_2$ XXIV

Structural Relations.—The present study has shown that mangostin is a member of the relatively small group of naturally occurring xanthones. As has been pointed out by Robinson,[17] these all contain one ring with the phloroglucinol or resorcinol type of oxygen substitution; mangostin thus conforms to this general pattern. It may be noted further that mangostin, like almost all other naturally occurring xanthones with three oxygen functions attached to the second ring, possesses the hydroxyquinol type of substitution in that ring. Apparently the only other naturally occurring xanthone reported to have an isoprenoid side chain is jacareubin with a dimethylpyran ring.[38] On the other hand, a considerable number of natural products are known in which isoprenoid side chains are attached to other types of aromatic nuclei, *e.g.*, chlorophorin[39] (stilbene); rottlerin[40] (cinnamoylresorcinol); rotenone,[41] toxicarol[42] (isoflavanones); osthol,[43] ostruthin[44] (coumarins). However, mangostin is exceptional in having two such side chains and joins the osage orange pigments osajin and pomiferin in this rare category.[24] It would seem idle to speculate at this time on the biogenetic stage at which the side chains are introduced.

Synthesis of Model Xanthones.—Of the hydroxyxanthone derivatives used for spectral comparison, four were previously unknown. Two of these, 1-hydroxy-3,6-dimethoxyxanthone and 1-acetoxy-3,6-dimethoxyxanthone were prepared from the known 1,3,6-trihydroxyxanthone. 1,3,7-Trihydroxy-6-methoxyxanthone was prepared by the condensation of phloroglucinol and 2,5-dihydroxy-4-methoxybenzoic acid in the presence of zinc chloride–phosphorus oxychloride[45]; it was converted to 1-hydroxy-3,6,7-trimethoxyxanthone

(36) L. Claisen, F. Kremers, F. Roth and E. Tietze, *Ann.*, **442**, 210 (1925).

(37) *Cf.* the formation from xanthone of a hydrobromide which is readily decomposed by water; M. Gomberg and L. H. Cone, *ibid.*, **376**, 183 (1910).

(38) F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.*, 3932 (1953).

(39) F. E. King and M. F. Grundon, *ibid.*, 3348 (1949); 3547 (1950).

(40) A. McGookin, A. B. Percival and A. Robertson, *ibid.*, 309 (1938); H. H. Brockmann and K. Maier, *Ann.*, **535**, 149 (1938).

(41) F. B. LaForge, H. L. Haller and L. E. Smith, *Chem. Revs.*, **12**, 181 (1933).

(42) S. W. George and A. Robertson, *J. Chem. Soc.*, 1535 (1937).

(43) E. Späth and O. Pesta, *Ber.*, **66**, 754 (1933).

(44) E. Späth and K. Klager, *ibid.*, **67**, 859 (1934).

(45) P. K. Grover, G. D. Shah and R. C. Shah, *J. Chem. Soc.*, 3982 (1955).

by methylation with methyl iodide and potassium carbonate.

Experimental[46]

Isolation of Mangostin. (i) **From Fruit Hulls.**—In a typical run the finely powdered mangosteen hulls[47] (193 g.) were extracted with benzene in a Soxhlet apparatus for 30 hours. The extract was concentrated to about 50 ml., and on standing it gave 2.25 g. of crude mangostin, m.p. 169–172°. Ligroin was added to the mother liquor and on further standing it gave an additional 2.67 g. of crude product; total yield, 2.55%. Several repetitions of this process gave very variable yields, ranging from 1.4 to 3.8%: the m.p. of the crude material was usually in the range 164–172°. Extraction with ethanol did not improve the yield. (ii) **From bark.**—In one run the powdered tree bark[47] (253 g.) gave by the same procedure 5.45 g. of crude mangostin (2.2%). (iii) **From dried latex.**—The dried latex[47] (10 g.) was refluxed briefly with benzene and filtered. The filtrate was cooled and concentrated to 40 ml.; deposition was induced by scratching, yielding 3.0 g. of crude mangostin, m.p. 170–173°. In a subsequent experiment, the latex (69.6 g.) was extracted in a Soxhlet apparatus with benzene (250 ml.) for 36 hours: there was obtained from the extract on standing, in two crops, 36.4 g. (52%) of crude mangostin.

Purification of Mangostin (X).—Crude mangostin (0.50 g.) in ether–benzene (1:3; 8 ml.) was chromatographed on a column of Woelm acid alumina (Grade III, 5.5 g.) packed in benzene; continued elution with ether–benzene (1:3; 20 ml.) yielded mangostin as a yellow powder, m.p. 176.5–179.5° (0.34 g.). The resulting product dissolved in ether–benzene (1:4) was passed through another column of similar alumina to give a bright yellow product, m.p. 180.5–182.5°; this yielded after two crystallizations from benzene an analytical sample, m.p. 181.6–182.6°; infrared spectrum (CCl_4): 2.85, 2.93, 6.08, 6.14 (shoulder), 6.20 and 6.32 μ; ultraviolet spectrum, see Table I.

Anal. Calcd. for $C_{24}H_{26}O_6$: C, 70.23; H, 6.39. Found: C, 69.99, 70.16; H, 6.30, 6.56.

Dimethylmangostin (XVII).—Crude mangostin (6.0 g.) was chromatographed on alumina (20 g.) as above and this partially purified material was dissolved in methanol (40 ml.) and treated with dimethyl sulfate (15 ml.), then with 50% aqueous potassium hydroxide in small amounts until the solution remained basic. After dilution with water the precipitate was filtered, washed with water, and dried. The crude product was treated with carbon tetrachloride; the solution was filtered from undissolved inorganic salts and evaporated to give 5.0 g. of crude dimethylmangostin, m.p. 110–116°. A solution of 1.15 g. of this material in benzene–petroleum ether (1:1) was passed through a column of Woelm "neutral" alumina (Grade III, 3.5 g.). The column was washed with the same solvent (30 ml.) to give 0.97 g. of purified material, m.p. 119–121°, which on crystallization from ethanol gave 0.85 g. of light yellow fluffy needles, m.p. 121.5–122.5°. Two further recrystallizations from ethanol, one from acetic acid, and four more from ethanol yielded an analytical sample, m.p. 123.3–123.8°; infrared spectrum (CCl_4): 6.07, 6.25 and 6.29 (shoulder) μ; ultraviolet spectrum, see Table I; NMR spectrum (CCl_4): 740 (chelated hydroxyl), 1115 (methoxyl) and 1205 (=C-methyl) cycles[48]; the ratio of the areas of the 1205 and 1115 peaks in a number of spectra varied from 1.33 to 1.40.

Anal. Calcd. for $C_{26}H_{30}O_6$: C, 71.21; H, 6.90. Found: C, 70.98, 71.00; H, 6.65, 6.81.

Tetrahydrodimethylmangostin.—Dimethylmangostin (0.0241 g.) in acetic acid (2 ml.) was hydrogenated over prereduced Adams platinum oxide catalyst in a micro-hydrogenation apparatus: 2.06 molar equivalents of hydrogen were absorbed. The solution was filtered and the solvent evaporated to give yellow crystals, m.p. 89–96°. Several recrystallizations from ethanol gave stout, yellow needles, m.p. 105–107°, infrared spectrum (CCl_4), 6.09 and 6.27 μ; ultraviolet spectrum, see Table I. Rotation and Weissenberg photographs were taken using Cu_α radiation on single crystals rotated about the axis of elongation. Constants determined for the unit cell were $a = 10.03 \pm 0.075$ Å., $b = 9.33 \pm 0.05$ Å., $c = 16.24 \pm 0.12$ A. The density of the crystals was determined by loss of weight in water as 1.208 ± 0.024 g./cm.^{3}.

Anal. Calcd. for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74; mol. wt., 442. Found: C, 70.69; H, 7.70; mol. wt. (X-ray), 453 ± 12.

Acetyldimethylmangostin (XVIII).—Crude dimethylmangostin (0.308 g.) was heated overnight on the steam-bath with acetic anhydride (5.5 ml.) and pyridine (0.3 ml.). Water was added and the heating was continued for 30 minutes. The solution was cooled and the crude product was filtered and crystallized from ethanol to give 0.197 g. of acetate. This was further purified by recrystallization from benzene–ligroin yielding fine, white, matted needles, m.p. 193–194.5° (reported[4] m.p. 193–194°); infrared spectrum (CCl_4): 5.63, 6.06, 6.17 and 6.25 μ; ultraviolet spectrum (EtOH): 245.5 mμ (log ϵ 4.65), 272 mμ (shoulder, log ϵ 4.10), 304.5 mμ (log ϵ 4.38), 334 mμ (inflection, log ϵ 3.96).

Quantitative Oxidation of Tetrahydromangostin.—Mangostin (0.150 g.) was hydrogenated in acetic acid over prereduced Adams catalyst; 2.00 molar equivalents of hydrogen was absorbed. The solution was diluted with ethyl acetate, filtered and the acetic acid washed out with water and dilute aqueous sodium bicarbonate. The ethyl acetate solution was dried, cooled in Dry Ice–acetone, and treated with ozonized oxygen for 0.5 hour. Excess ozone was removed by a stream of nitrogen. The solution was warmed to 0° and then shaken with a dilute solution of potassium permanganate in dilute sulfuric acid; the ethyl acetate layer was extracted with aqueous sodium bicarbonate. This process of alternate oxidation with acid potassium permanganate and extraction with aqueous sodium bicarbonate was repeated three times. The combined aqueous washings and extracts were acidified and treated with dilute aqueous potassium permanganate until manganese dioxide began to precipitate. The mixture was cleared with sodium bisulfite, saturated with sodium chloride, and extracted repeatedly with ether. The ethereal extract was dried, evaporated to very small volume, and made up to exactly 10.00 ml. with a 1% v./v. solution of butanol in chloroform.

A chromatographic column was prepared after the procedure of Moyle.[25] Silicic acid (Mallinckrodt, 100 mesh, 10 g.) was ground with 2 *M* phosphate buffer, *p*H 8.4 (6 ml.) and then slurried with 50 ml. of a 1% v./v. solution of butanol in chloroform which had been shaken with 2 *M* hydrogen dipotassium phosphate solution and filtered (this solvent is referred to hereafter as 1% butanol). The slurry was poured into an 18-mm. bore chromatographic column and allowed to settle as the solvent ran out: a further 25 ml. of 1% butanol was passed through the column before use. The following collection and estimation procedure was used: 10-ml. fractions were collected, diluted with 10 ml. of methanol and treated with 4 drops of 0.04% cresol red; a stream of nitrogen was blown through the solutions to remove carbon dioxide and they were titrated immediately with 0.0108 *N* aqueous sodium hydroxide. Blanks run using this procedure gave a titer of 0.05–0.06 ml. An aliquot (3 ml.) of the above solution of acids from the oxidation was pipetted onto the column and washed in with a few milliliters of 1% butanol. When the sample had been absorbed, the column was eluted with the same solvent. The first five fractions gave a total titer of only 0.30 ml. of 0.0108 *N* base (corrected for blank titers) indicating the absence of significant amounts of high molecular weight acids. Fractions 6–22 contained the C_6-acid peak[25] and gave a total titer of 10.76 ml. (corrected for blank titers), *i.e.*, 0.116 mmole of a C_6-acid or 1.06 moles per mole of mangostin. Subsequent elution with a solution of 10% butanol in chloroform gave fractions with a total titer of 0.34 ml. (corrected) only, showing that not more than 0.03 mole of C_5-acid per mole of mangostin is present.

The C_6-acid was identified as isocaproic acid by oxidation of a larger sample of tetrahydromangostin, distillation of the volatile acid product in a molecular still and preparation of the amide *via* the acid chloride. After one crystallization from ether–cyclohexane the amide had m.p. 121–122°, undepressed by admixture with authentic isocaproamide. Authentic isocaproic acid was found to be eluted in the same fractions.

(46) Melting points are uncorrected.

(47) Obtained from S. B. Penick and Co., New York; we thank Mr. Giles St. Clair for his coöperation in the obtaining of this material.

(48) On an arbitrary scale in which the aromatic and methyl proton resonance peaks of toluene are assigned values of 1000 and 1197 cycles, respectively.

A sample of authentic isocaproic acid was subjected to the same oxidation and estimation procedure used for tetrahydromangostin: a recovery of 61% was obtained.

Ozonolysis of Dimethylmangostin. Formation of XIX.—Dimethylmangostin (5.0 g.), dissolved in dichloromethane (50 ml.), was cooled in Dry Ice–acetone and treated with ozone until no further ozone was absorbed (45 minutes). Excess potassium iodide in 80% methanol was added to the cold solution and, after standing a few minutes, the solution was poured into cold water and treated with dilute sulfuric acid and sufficient sodium bisulfite to react with all of the iodine. The dichloromethane solution was washed with water, dried and freed of solvent. The residue was treated with carbon disulfide and the yellow solid filtered and washed with carbon disulfide to remove iodoform to give 2.6 g. (59%) of the crude dialdehyde, m.p. 180–190° dec. Several recrystallizations from methyl ethyl ketone and from acetic acid gave a pale yellow crystalline powder, m.p. 192–194° dec.; infrared spectrum ($CHCl_3$): 3.69(w), 5.81, 6.06, 6.24 and 6.33 μ; quantitative measurements of the relative intensities of the carbonyl bands of the dialdehyde and of phenylacetaldehyde (b.p. 88–89° (18.5 mm.), $n^{19.5}D$ 1.5265, infrared band at 5.80 μ) were made on standard solutions in the same cell using the same spectrophotometer schedule and gave relative molar extinction coefficients[26] of 29 and 11.3, respectively; ultraviolet spectrum (EtOH): 244 mμ (log ϵ 4.48), 261 mμ (log ϵ 4.49), 314 mμ (log ϵ 4.35), 345 mμ (log ϵ 3.88).

Anal. Calcd. for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70. Found: C, 61.86, 61.63; H, 4.63, 4.72.

The bis-semicarbazone was prepared from the dialdehyde (0.100 g.) by slurrying it in pyridine (1.5 ml.) and treating with a solution of sodium acetate (0.100 g.) and semicarbazide hydrochloride (0.100 g.) in water (1.5 ml.). The dialdehyde dissolved and the solution was heated on the steam-bath for 10 minutes, diluted with water, cooled, and filtered to give 0.119 g. of sandy, yellow powder which decomposed slowly above 235° without melting. It was purified by triturating with boiling ethanol–ethyl acetate and then with hot pyridine: the decomposition point was unaffected; infrared spectrum (Nujol): 5.96, 6.07 and 6.25 μ.

Anal. Calcd. for $C_{22}H_{24}O_8N_6$: C, 52.80; H, 4.83; N, 16.79. Found: C, 52.54, 52.71; H, 5.11, 5.24; N, 16.76, 16.52.

Demethylmangostin (XI).—Mangostin (1.20 g.) was refluxed for 13 hours with 47% hydriodic acid (13 ml.) which contained no free iodine. The solution was cooled and the solid filtered, washed with water, and dried to give 1.12 g. of crude product, m.p. 170–180°. Several crystallizations from ethanol–water and from cyclohexane gave yellow needles, m.p. 186–190°; infrared spectrum ($CHCl_3$): 2.87, 6.08 and 6.23 μ.

Anal. Calcd. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.73; H, 6.34.

Methyldemethylmangostin (XIII).—Demethylmangostin (0.500 g.) was dissolved in methanol and methylated with methyl sulfate (5 ml.) and concentrated aqueous potassium hydroxide, added dropwise until the solution remained strongly basic. The yellow crystalline precipitate was filtered and recrystallized from ethanol–chloroform to give 0.200 g. of methyl ether, m.p. 217–218°. Two recrystallizations from ethanol–dichloromethane gave matted, yellow needles, m.p. 218.5–219.2°; infrared spectrum (CCl_4): 6.07, 6.23 and 6.32 μ; ultraviolet spectrum (EtOH): 242.5 mμ (log ϵ 4.42), 261.5 mμ (log ϵ 4.59), 317 mμ (log ϵ 4.36), 366 mμ (log ϵ 3.99); NMR spectrum (CCl_4): chelated hydroxyl peak in similar position to that of dimethylmangostin.

Anal. Calcd. for $C_{24}H_{26}O_6$: C, 70.23; H, 6.39; OMe, 7.56. Found: C, 70.01; H, 6.27; OMe, 7.12.

Isodemethylmangostin (XII).—Mangostin (2.0 g.) was refluxed for 10.5 hours with constant boiling hydriodic acid (20 ml.) which contained free iodine. The mixture was cooled and the solid filtered, washed with water and carbon tetrachloride and crystallized from methanol to give 1.38 g. of brick-red crystalline powder. A sample recrystallized from methanol gave dark red needles which decomposed above 175°; infrared spectrum (Nujol): 6.13, 6.25, 6.35 (shoulder), 6.56 μ.

Anal. Calcd. for $C_{23}H_{24}O_6I_2 \cdot 2CH_3OH$: C, 42.04; H, 4.47; I, 35.54. Found: C, 43.20; H, 4.39; I, 34.87, 35.17.

The once-crystallized product (0.500 g.) was dissolved in warm ethanol and treated with aqueous sodium bisulfite until the original dark red color was converted to a bright yellow. Water and sodium chloride were added and the solution was extracted with dichloromethane. The extract was dried, diluted with cyclohexane and concentrated until crystallization began. Cooling and filtration gave 0.268 g. of yellow crystals, m.p. 245–247° dec. Several recrystallizations from benzene–methanol and then from ethanol–water gave isodemethylmangostin as very pale yellow needles, m.p. 258.5–260° dec.; infrared spectrum ($CHCl_3$): 2.89, 3.12, 6.10, 6.19, 6.25 μ; ultraviolet spectrum (EtOH): 245 mμ (shoulder, log ϵ 4.46), 255 mμ (log ϵ 4.52), 307 mμ (log ϵ 4.29), 352 mμ (log ϵ 3.99).

Anal. Calcd. for $C_{23}H_{24}O_6 \cdot C_2H_5OH$: C, 67.85; H, 6.83. Found: C, 67.91; H, 6.94.

The same product was obtained by treating the iodine-containing material in chloroform solution with aqueous potassium iodide. The chloroform solution changed from deep red to bright yellow and gave on evaporation isodemethylmangostin; the aqueous extract contained free iodine as vouchsafed by its color and by a positive starch test, which was destroyed with aqueous sodium thiosulfate.

Dimethylisodemethylmangostin (XV).—Isodemethylmangostin (0.100 g.) was dissolved in methanol and treated with methyl sulfate (2 ml.). Concentrated aqueous potassium hydroxide was added dropwise until the solution remained strongly basic. Addition of water gave a precipitate of 0.070 g. of fine, near-white needles, m.p. 205–210°. Repeated recrystallization from ethanol–water and from cyclohexane–dichloromethane gave white needles, m.p. 213.9–215.2°; infrared spectrum (CCl_4): 6.06, 6.19, 6.25 μ; ultraviolet spectrum (EtOH): 245 mμ (shoulder, log ϵ 4.46), 258 mμ (log ϵ 4.58), 301 mμ (log ϵ 4.27), 350 mμ (log ϵ 3.99); NMR spectrum (CCl_4): no peak below 1000 cycles.[48]

Anal. Calcd. for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65; 2 OMe, 14.61. Found: C, 70.61; H, 6.73; OMe, 10.99, 11.45.

Diacetylisodemethylmangostin (XVI).—Isodemethylmangostin (0.130 g.) was refluxed overnight with acetic anhydride (4 ml.) and pyridine (1 ml.). The solution was cooled, poured into cold water, and the resulting brownish crystalline mass was filtered and crystallized from cyclohexane to give 0.136 g. of white needles, m.p. 222–226°. One recrystallization from ethanol–water and two from cyclohexane gave white needles, m.p. 232.6–234°; infrared spectrum (CCl_4): 5.63, 6.03, 6.23 μ; ultraviolet spectrum (EtOH): 248 mμ (log ϵ 4.54), 260 mμ (log ϵ 4.56), 287 mμ (log ϵ 4.07), 360 mμ (log ϵ 3.92).

Anal. Calcd. for $C_{27}H_{28}O_8$: C, 67.49; H, 5.87; 2 CH_3CO, 17.91. Found: C, 67.69; H, 6.28; CH_3CO, 18.41.

A sample of the diacetate when hydrolyzed with sodium hydroxide in aqueous ethanol gave back isodemethylmangostin.

Tests for Basicity toward Perchloric Acid.—Samples were dissolved in benzene; a few drops of water were added followed by a mixture of 70% perchloric acid in benzene–ether. Formation of a perchlorate was indicated by the appearance of a distinct yellow-green fluorescent color. The following compounds gave a positive test: isodemethylmangostin,[49] dimethylisodemethylmangostin,[49] formoxydihydrodimethylmangostin, hydroxydihydrodimethylmangostin. The following compounds gave a negative test: mangostin, dimethylmangostin, demethylmangostin, methyldimethylmangostin.

Oxidation of Dimethylmangostin with Potassium Permanganate. Formation of XX.—Dimethylmangostin (1.0 g.) was dissolved in acetone (20 ml.) and treated with potassium permanganate (2.5 g.) in acetone–water (1:1, 40 ml.) over a period of 25 minutes. After the mixture had stood for 14 hours the permanganate color had been discharged. The manganese dioxide was filtered together with a colorless crystalline product. The deposit was suspended in dilute sulfuric acid and treated with sodium bisulfite until all the manganese dioxide had dissolved. The crystalline residue

(49) In these cases, a crystalline perchlorate was deposited; infrared spectrum (Nujol) of isodemethylmangostin perchlorate: 6.12 6.23, 6.36, 6.52 μ.

was filtered, washed and dried to give 0.211 g. of fine, pale yellow needles, m.p. 227–229°. Concentration of the original aqueous acetone filtrate yielded a further 0.081 g. of material, m.p. *ca.* 219°. Several recrystallizations from ethanol–acetone and from ethanol–chloroform gave pale yellow needles, m.p. 231–232°; infrared spectrum ($CHCl_3$): 2.92, 5.85, 6.07, 6.23, 6.33 μ; ultraviolet spectrum (EtOH): 244 mμ (log ϵ 4.52), 260 mμ (log ϵ 4.53), 309 mμ (log ϵ 4.39), 352 mμ (log ϵ 3.90).

Anal. Calcd. for $C_{26}H_{30}O_{10}$: C, 62.14; H, 6.02. Found: C, 62.37, 61.87; H, 6.38, 6.05.

Attempted hydrogenation of XX in acetic acid over Adams catalyst led to no absorption of hydrogen and the starting material was recovered unchanged. Attempted reaction with periodic acid in aqueous dioxane, lead tetraacetate in acetic acid, or sodium bismuthate with 85% phosphoric acid in acetone–dichloromethane–ethanol failed to effect cleavage of XX.

Oxidative Cleavage of Reduced XX. Formation of XIX.—A solution of XX (0.135 g.) in hot ethanol was treated with aqueous sodium borohydride in excess. The solution was boiled for 20 minutes, cooled and allowed to stand for 1 hour. It was then poured into water, neutralized to *p*H 6 with dilute hydrochloric acid, and extracted with ethyl acetate. Evaporation of the extract gave a pale yellow foam which on crystallization from benzene yielded 0.099 g. of yellow crystals, m.p. 135–165°; infrared spectrum (CCl_4): 2.9, 6.12, 6.24 μ (no band 5–6 μ).

The reduced material was dissolved in ethanol–ethyl acetate, and an aqueous solution of periodic acid (0.125 g.) was added to the solution. After standing for 24 hours in the dark the solution was poured into water and extracted with dichloromethane. Removal of the solvent from the extract and crystallization of the residue from methyl ethyl ketone gave a yellow crystalline powder, m.p. 192–194° dec., undepressed by admixture with XIX, obtained by ozonolysis of dimethylmangostin. The identity of the two products was confirmed by comparison of their infrared spectra, which were superimposable.

Reaction of Dimethylmangostin with Formic Acid. Formation of Formoxydihydrodimethylmangostin (XXI) and Hydroxydihydrodimethylmangostin (XXII).—The following procedure was carried out in the presence of hydrogen peroxide. It was later found, however, that this was not necessary for the success of the reaction.

A solution of dimethylmangostin (1.07 g.) in warm formic acid (98%) was cooled and hydrogen peroxide (30%, 0.86 ml.) was added. After standing 2.5 hours the mixture was poured into water, made strongly basic with potassium hydroxide, cooled, and extracted with ether. Evaporation of the extracts gave an oil which solidified on trituration with methanol. Crystallization from ethanol–water gave 0.436 g. of crystalline formoxydihydrodimethylmangostin, m.p. 148–150°. Several recrystallizations from benzene–ligroin and ethanol–water gave pure XXI as white needles, m.p. 154–155°; infrared spectrum (CCl_4): 5.80, 6.04, 6.20, 6.26 μ; ultraviolet spectrum (EtOH): 245 mμ (log ϵ 4.54), 255 mμ (log ϵ 4.54), 302 mμ (log ϵ 4.33), 337 mμ (log ϵ 3.97).

Anal. Calcd. for $C_{27}H_{32}O_8$: C, 66.92; H, 6.66. Found: C, 67.28, 67.56; H, 6.88, 6.77.

The mother liquors from the first crystallization were treated with aqueous potassium hydroxide. After 1.5 hours the solution was poured into water; the resulting white flocculent precipitate was filtered, dried and crystallized from benzene–ligroin to give 0.146 g. of hydroxydihydrodimethylmangostin. Repeated recrystallizations from benzene–ligroin give a pure product, m.p. 205–206°; infrared spectrum (CCl_4): 2.87 (sharp), 6.05, 6.18, 6.25 μ.

Anal. Calcd. for $C_{26}H_{32}O_7$: C, 68.40; H, 7.07. Found: C, 68.13, 68.26; H, 7.16, 7.23.

The relationship between these two products was confirmed by the formation of XXII on treatment of pure XXI with dilute aqueous ethanolic potassium hydroxide at room temperature for one hour.

1-Hydroxy-3,6-dimethoxyxanthone.—1,3,6-Trihydroxyxanthone (0.103 g.), prepared from phloroglucinol and β-resorcylic acid by the general method of Grover, Shah and Shah,[45] was dissolved in acetone and treated with potassium carbonate (0.120 g.) and methyl iodide (0.146 g.). The mixture was refluxed overnight. The solution was decanted and freed of solvent and the residue taken up in dichloromethane–water. The organic layer was washed with dilute aqueous potassium hydroxide, dried and evaporated to give 0.080 g. of crude product, m.p. 175–180°. A sample recrystallized from ethanol and from benzene–cyclohexane gave very pale yellow, matted needles, m.p. 179.2–179.8°; infrared spectrum ($CHCl_3$): 6.05, 6.22, 6.36 μ; ultraviolet spectrum, see Table I.

Anal. Calcd. for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.38; H, 4.57.

1-Acetoxy-3,6-dimethoxyxanthone.—1-Hydroxy-3,6-dimethoxyxanthone (0.116 g.) was added to acetic anhydride (3 ml.) and pyridine (1 ml.) and the mixture was heated on the steam-bath overnight. Ethanol (0.5 ml.) was added and heating continued for 30 minutes. The solution was poured into water and the mixture was extracted with dichloromethane. The extract was washed with water, dried, and concentrated to give 0.096 g. of white crystalline product, m.p. 175.2–176°. A sample recrystallized from ethanol–water and from benzene–cyclohexane had m.p. 177.4–178.2°; infrared spectrum ($CHCl_3$): 5.62, 6.02, 6.13, 6.20 and 6.40 μ.

2,5-Dihydroxy-4-methoxybenzoic Acid.—A solution of 2-hydroxy-4-methoxybenzoic acid (15.7 g.)[50] in 10% aqueous sodium hydroxide (150 ml.) was treated dropwise with stirring over the course of several hours with potassium persulfate (25.2 g.) in water (450 ml.).[51] The mixture was then allowed to stand overnight, acidified to *p*H 3 and extracted with ether. The aqueous layer was made strongly acidic and heated on the steam-bath for 40 minutes. The mixture was cooled and extracted with ether. The extract was evaporated to give 4.6 g. of crude product, m.p. 180–185° dec. A sample recrystallized several times from water with charcoal treatment had m.p. 199–200° dec. (recorded m.p. 201° dec. for this compound, prepared by an alternative route).[52]

1,3,7-Trihydroxy-6-methoxyxanthone.—Crude 2,5-dihydroxy-4-methoxybenzoic acid (1.0 g.) was dried for 18 hours at 110° and mixed with anhydrous phloroglucinol (1.1 g.), powdered fused zinc chloride (4.0 g.) and phosphorus oxychloride (13 ml.).[45] The mixture was heated at 70° for 2 hours and poured into ice-water. The resulting dark red precipitate was filtered and slurried with dilute aqueous sodium bicarbonate. The slurry was centrifuged and the solid was slurried with water and re-centrifuged. The washed material was treated with acetone. The acetone solution was filtered and concentrated to give 0.170 g. of pale pink powder, m.p. 301° dec.; a second crop of 0.119 g. of darker material, m.p. 290–295° dec., also was obtained. The combined crude products were sublimed at 2×10^{-5} mm. and 210° (bath temperature) to give a yellow powder, m.p. 313° dec. A sample was crystallized from ethanol–water giving long, yellow, matted needles, m.p. 309–310° dec.; infrared spectrum (Nujol): 3.06, 6.07, 6.21, 6.36 μ; ultraviolet spectrum, see Table I.

Anal. Calcd. for $C_{14}H_{10}O_6$: C, 61.32; H, 3.68. Found: C, 61.18; H, 3.79.

1-Hydroxy-3,6,7-trimethoxyxanthone.—1,3,7-Trihydroxy-6-methoxyxanthone (0.200 g.), potassium carbonate (0.200 g.) and methyl iodide (0.300 g.) were refluxed in acetone for 4 hours. The solution was filtered and freed of solvent, and the residue was taken up in dichloromethane–water. The organic layer was washed with dilute aqueous potassium hydroxide and evaporated to give 0.055 g. of crude product, m.p. 215°. Sublimation at 165° (bath temperature) and 2×10^{-5} mm. followed by crystallization from ethanol gave a yellow, crystalline powder, m.p. 219.5–221°; infrared spectrum ($CHCl_3$): 6.07, 6.24, 6.34 μ; ultraviolet spectrum, see Table I.

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.71; H, 4.64.

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(50) St. v. Kostanecki and J. Tambor, *Ber.*, **28**, 2302 (1895).

(51) *Cf.* W. Baker and N. C. Brown, *J. Chem. Soc.*, 2303 (1948).

(52) S. Rajagopalan, T. R. Seshadri and S. Varadarajan, *Proc. Indian Acad. Sci.*, **30A**, 265 (1949).

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The Relative Stability of Bridged Hydrocarbons. Norbornene and Nortricyclene[1]

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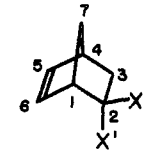
Nortricyclene (II), a compound containing a three-membered ring, was found to be more stable than the olefinic isomer norbornene (I). Equilibration of both pure materials at the temperature of reflux by means of a silica–alumina catalyst gave mixtures with identical composition, 23% I and 77% II. There was no evidence for the formation of isomers other than I and II in the reaction. The earlier methods of preparation of norbornene, involving dehydration or dehydrohalogenation of norbornyl derivatives, are shown to have led instead to mixtures containing nortricyclene (II) as the major component. The same acid catalyst did not isomerize norbornadiene (IV). Norbornane (III) was almost entirely unaffected by prolonged heating with aluminum chloride and aluminum bromide. The theoretical implications of these results are discussed.

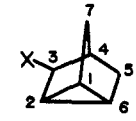
The heat of isomerization of cyclopropane to propene has been estimated to be −7.86 kcal. per mole.[2] Three-membered rings, when present in more complicated molecules, generally are unstable relative to olefinic isomers with the same sequence of carbon atoms; conversion usually can be accomplished by heat or by suitable catalysts.[3a,3b]

Among the most interesting of these cyclopropane–olefin transformations are those involving homoallylic rearrangement.[3b,6,9,11,12] When, in such rearrangements, interconversion between the cyclic and acyclic forms is possible, it is often observed that the formation of cyclopropyl derivatives is favored in reactions governed by kinetic control, while conditions permitting thermodynamic control of the reaction course lead to production of olefinic products. However, it has been pointed out by Roberts,[11] that certain transformations in the bicyclo[2.2.1]heptane ring system furnish exceptions to this generalization. Thus, in reactions presumably involving free radical, anionic and cationic intermediates, derivatives of nortricyclene (II) predominated over those related to norbornene (I) to a considerable extent.

Many additional examples are now available to lend support to this initial conclusion. For instance, the solvolysis of 5-norbornen-2-*endo*- and *exo*-yl (dehydronorbornyl) (Ia and Ib) and 3-nortricyclyl (IIa) derivatives,[11,13] as well as the nitrous acid deamination of 5-norbornene-2-*endo*-yl amine (Ia, X′ = NH_2),[13,14] gave mixtures of Ib and IIa consisting chiefly (83–96%) of nortricyclenic products (IIa). Furthermore, several groups of workers[15–17] have studied the addition of one mole of various reagents to norbornadiene (IV) under a variety of experimental conditions. In strong acid-catalyzed carboxylic acid media, *e.g.*, acetic acid–toluenesulfonic acid[16] and formic acid–boron trifluoride,[15] which would be expected to give largely thermodynamic control of the product ratios, only 10–15% of olefinic esters (Ib, X = OAc or OOCH) were present in the product. It appears, therefore, in these instances, that derivatives containing a cyclopropane ring are favored at equilibrium. However, there has been no successful attempt to ascertain the exact position of such equilibria. Such a study appeared to be particularly desirable



I, X = X′ = H
Ia, X = H
Ib, X′ = H



II, X = H
IIa, X ≠ H

(1) Paper I of a series on Bridged Ring Systems.

(2) J. W. Knowlton and F. D. Rossini, *J. Research Natl. Bur. Standards*, **43**, 113 (1949). The value for the free energy of isomerization does not appear to be available.

(3) (a) *Cf.*, for example, the isomerization of cyclopropane[4,5] and of simple substituted cyclopropanes,[4,6,7] rearrangements in the *thujane* and *carane* series,[8] and the conversion of 3,5-cyclosteroids into cholestene derivatives.[9,10] A discussion, extremely pertinent to points raised in the present paper, has been presented by Roberts and co-workers.[11] (b) A comprehensive review of the chemistry of small ring compounds is available; E. Vogel, *Fortschr. Chem. Forsch.*, **3**, 430 (1955).

(4) G. Egloff, G. Hulla and V. I. Komarewsky, "Isomerization of Pure Hydrocarbons," Reinhold Publishing Corp., New York, N. Y., 1942.

(5) R. H. Lindquist and G. K. Rollefson, *J. Chem. Phys.*, **24**, 725 (1956); J. R. McNesby and A. S. Gordon, *ibid.*, **25**, 582 (1956).

(6) J. D. Roberts and R. H. Mazur, THIS JOURNAL, **73**, 2509, 3542 (1951).

(7) R. Criegee and A. Rimmelin, *Ber.*, **90**, 414 (1957).

(8) J. Simonsen and L. N. Owen, "The Terpenes," Vol. II, Cambridge University Press, Cambridge, 1949.

(9) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Third Ed., Reinhold Publishing Corp., New York, N. Y., 1949, pp. 256 ff.; E. M. Kosower and S. Winstein, THIS JOURNAL, **78**, 4347, 4354 (1956).

(10) For an additional steroid example, see A. R. H. Cole, *J. Chem. Soc.*, 3810 (1954), and references therein cited.

(11) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett and R. Armstrong, THIS JOURNAL, **72**, 3116 (1950); *cf.* also J. D. Roberts, W. Bennett and R. Armstrong, *ibid.*, **72**, 3329 (1950); J. D. Roberts and W. Bennett, *ibid.*, **76**, 4623 (1954); S. Winstein, H. M. Walborsky and K. Schreiber, *ibid.*, **72**, 5795 (1950).

(12) For a discussion with leading references, see M. Simonetta and S. Winstein, *ibid.*, **76**, 18 (1954).

(13) J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *ibid.*, **77**, 3034 (1955).

(14) W. E. Parham, W. T. Hunter and R. Hanson, *ibid.*, **73**, 5068 (1951).

(15) L. Schmerling, J. P. Luvisi and R. W. Welch, *ibid.*, **78**, 2819 (1956).

(16) S. Winstein and M. Shatavsky, *Chemistry & Industry*, 16 (1956); THIS JOURNAL, **78**, 592 (1956).

(17) S. J. Cristol and G. D. Brindell, Abstracts of Papers, Cincinnati Meeting, Am. Chem. Soc., March, 1955, p. 35N.