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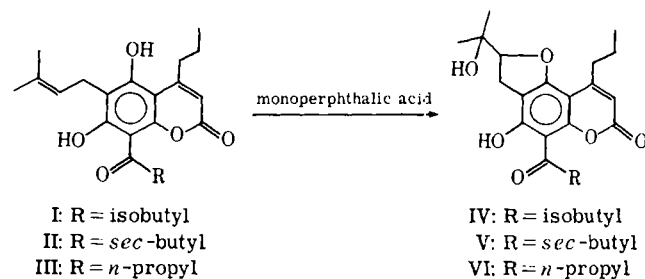
Constituents of *Mammea americana* L. IX: Oxidation of Mammein and Mammeisin

R. A. FINNEGAN[▲] and K. E. MERKEL

Abstract □ Cyclomammein, a putative mamey seed oil constituent, which has been obtained from mammein by treatment with peracids, was also produced upon air oxidation of the latter. In addition, two other air oxidation products of mammein were characterized. Both of these were also isolated by chromatography of the crude mammein mixture and, in common with cyclomammein, may be artifacts. One of these, designated M-9, $C_{22}H_{28}O_6$, m.p. 217–219°, is a linearly fused chromano coumarin; the other, L-2, $C_{22}H_{28}O_7$, m.p. 181–182°, contains a novel cyclic peroxide grouping and can be converted to cyclomammein by catalytic hydrogenation. The structures of these compounds were assigned on the basis of NMR and mass spectral measurements. The oxidation of mammein and mammeisin with dichlorodicyanobenzoquinone was also carried out. This leads to the corresponding chromeno coumarins: in the latter case, the product proved, as expected, to be identical with another mamey oil constituent, mammeigin. Finally, treatment of mammeisin with peracid leads to the derived dihydrofurano coumarin.

Keyphrases □ *Mammea americana* L.—oxidation of mammein and mammeisin □ Mammein and mammeisin—oxidation, isolation, and characterization of cyclomammein, chromeno and dihydrofurano coumarins □ Cyclomammein formation—oxidation of mammein □ Coumarins, chromeno and dihydrofurano formation—oxidation of mammein and mammeisin □ Oxidation of mammein and mammeisin— isolation and characterization of products □ NMR spectroscopy—identification, mammein and mammeisin oxidation products □ Mass spectroscopy—identification, mammein and mammeisin oxidation products

The preceding article (1) reported on the occurrence of a new series of *Mammea* coumarins (IV, V, and VI), which are related to mammein (I), neomammein (II), and normammein (III) in that the isopentenyl substituent at C-6 in the latter three molecules has undergone oxidative cyclization with the C-5 hydroxyl group to produce the hydroxyisopropyl dihydrofurano moiety



Scheme I

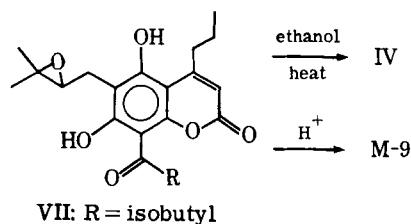
which is present in the former three, named cyclomammein (IV), cycloneomammein (V), and cyclonorammein (VI). The peracid oxidation of I, II, and III provided a convenient partial synthesis of IV, V, and VI, as illustrated in Scheme I. This article discusses the details of further studies on the oxidation of mammein (I) and mammeisin (XX).

DISCUSSION

Peracid Oxidation of Mammein: Mammein Epoxide and Compound M-9—While the reaction illustrated in Scheme I proceeded cleanly in good yield, treatment of I¹ with *m*-chloroperbenzoic acid for 5 hr. at 0° provided IV in only 29% yield. However, in addition to IV, there was isolated a second substance, isomeric with IV, in 14% yield. This new product proved to be identical with a compound called M-9, isolated several years ago² from mammein

¹ In the reactions described in this paper, the mammein (I) used as starting material was accompanied by small amounts of its difficultly separable congeners, II and III. Accordingly, the products are similarly "contaminated." The properties of the mammein mixture (I, with II and III) are discussed in Reference 1.

² R. A. Finnegan, unpublished experiments, 1959.

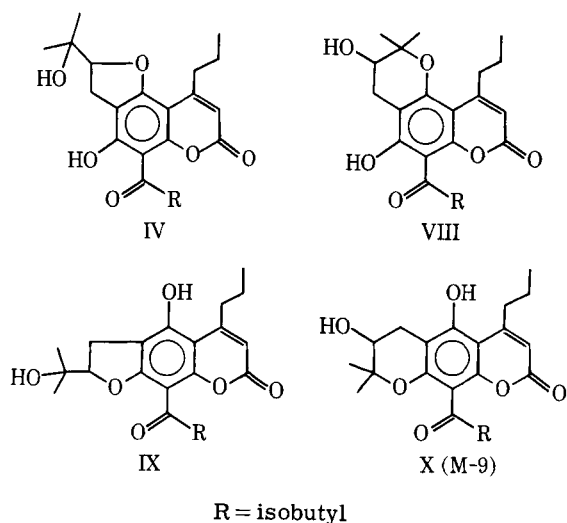


Scheme II

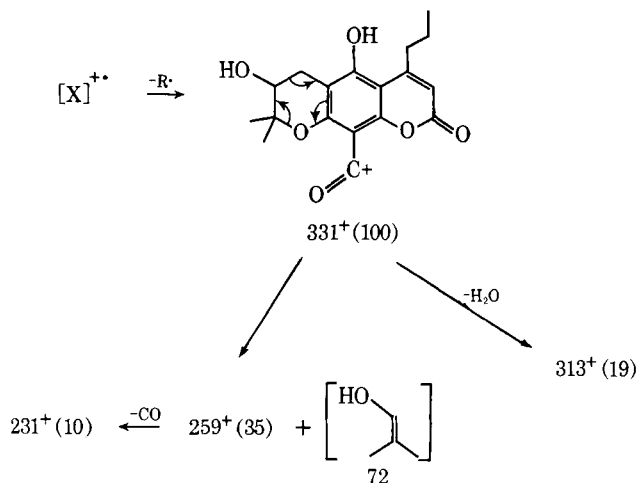
mother liquors and which has since been reisolated. When I was treated with *m*-chloroperbenzoic acid at room temperature, but for only 1 hr., it was possible to isolate the intermediate mammein epoxide (VII), a substance that had eluded us during earlier epoxidation studies (1). Its structure followed from its mode of formation and microanalytical and spectral data, as well as from its chemical reactivity which was quite pronounced. Indeed, simple heating in ethanol during attempts at recrystallization resulted in its quantitative conversion into cyclomammein (IV)¹, while treatment of VII with dilute mineral acid provided mainly M-9 (Scheme II).

Possible structures for M-9, which could be simply derived from the epoxide VII by alternative modes of interaction of the oxide group with the phenolic hydroxyl groups, are illustrated in Scheme III. Structure IV was naturally ruled out since it had been already assigned to cyclomammein. Among the remaining possibilities, the NMR and mass spectral data required the choice of Structure X for M-9. The absence of a hydrogen-bonded hydroxyl group was evident from the lack of absorption at low field (-1 to -5τ) typical of such a function. The hydroxyl line appeared at $+4.65\tau$, indicative of a nonchelated hydroxyl, which was sufficient evidence upon which to rule out the angularly fused Structure VIII. Consistent with this was the fact that the compound failed to give a positive reaction with ferric chloride. The remaining choice between IX and X, the linearly fused isomers, was governed again by reference to the NMR spectrum which showed a triplet ($J = 6.5$ Hz.) at 6.23τ ($>CHOH$) which is compatible only with Structure X.

The mass spectrum of X was generally similar to that of IV; however, certain differences were apparent which supported the assignment of X. The base peak in the spectrum of X, as well as in IV (1) and the other *Mammea* coumarins (2), arises from the loss of R from the acyl substituent. The ion thereby resulting from X, m/e 331, may then give rise to m/e 313 by the loss of water, and to m/e 259 by the loss of 72 mass units as indicated by the arrows in Scheme IV. The relative abundance of these latter two peaks weighs heavily in favor of the chroman Structure X rather than the dihydrofuran Structure IX. Although they are present in the spectrum of IV, their relative abundances are only 2 and 10%, respectively. Furthermore, the ion at m/e 59, which occurs in the spectrum of IV with a relative abundance of 9% and which was taken in support of the hydroxy-isopropyl dihydrofuran structure (1) [i.e., $(CH_3)_2C^+OH$], is present in the spectrum of X only to the extent of 2%. As expected¹, the



Scheme III



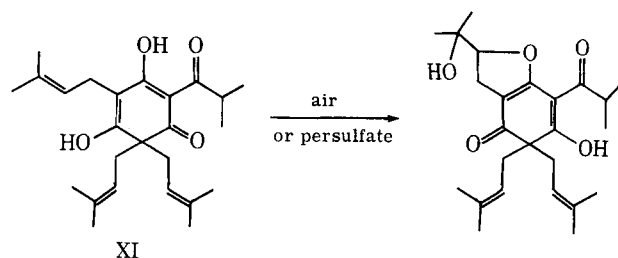
Scheme IV

spectrum also showed an ion at m/e 374, indicative of the presence of the nor-compound, X, with R = *n*-propyl.

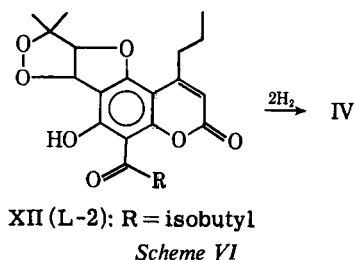
Air Oxidation of Mammein (I): Compound L-2—After a chloroform solution of mammein¹ stood for 5 days in a loosely stoppered flask, several new substances could be detected by TLC. After 20 days, a crystalline precipitate appeared which was identified as M-9 (X); after 75 days, simple filtration gave a 5.4% yield of M-9 (m.p. $217-219^\circ$) of the highest quality so far encountered. Examination of the filtrate (TLC) showed the presence of additional M-9, cyclomammein (IV), and a substance called L-2 which was originally isolated by Crombie *et al.* (3). Four other substances were detected but not identified. The air oxidation of I to IV has a close precedent (4) in the air oxidation of colupulone (XI), as illustrated in Scheme V.

Compound L-2, m.p. $181-182^\circ$, was also isolated from the chromatography of the crude mammein mixture (I, II, and III) and has the formula $C_{22}H_{26}O_7$, indicating the highest oxidation level of any *Mammea* coumarin so far encountered. Its NMR spectrum showed that the substituents at C-3, C-4, and C-8¹ were intact, as was the hydroxyl at C-7 (-4.4τ and positive ferric chloride test). The additional signals, which must arise from the remnants of the C-6 substituent, consisted of a singlet at 8.56τ (6H, the two methyl groups) and an AB quartet, one half centered at 3.92τ (1H, $J = 6$ Hz.) and the other at 4.53τ (1H, $J = 6$ Hz.). This quartet was first considered to arise from a pair of vinyl hydrogens attached to a chromene ring; however, the chemical shifts and the coupling constants corresponded very poorly with expectations based on numerous literature models. An important clue to the structure of L-2 was discovered when it was observed that catalytic reduction produced, *inter alia*, cyclomammein (IV); this fact, along with the spectral and analytical data, is most easily accommodated by Structure XII containing the unusual cyclic peroxide moiety (Scheme VI).

The AB quartet, then, is due to absorption by the hydrogens located at the ring junctures, and it is assumed that this juncture is *cis* in view of the great difficulty normally encountered in the formation of *trans*-fused five-membered rings. The presence of a peroxide unit in the molecule was verified by the observation of a positive test with potassium iodide in acetic acid. (This test was negative for IV and VII.) Compound L-2 shows an abnormally high carbonyl frequency in the IR (1754 cm^{-1} compared with 1715 cm^{-1} for IV).



Scheme V



The reason for this effect is not clear, although it may be in some way related to the increased strain in the molecule stemming from the presence of the additional five-membered ring.

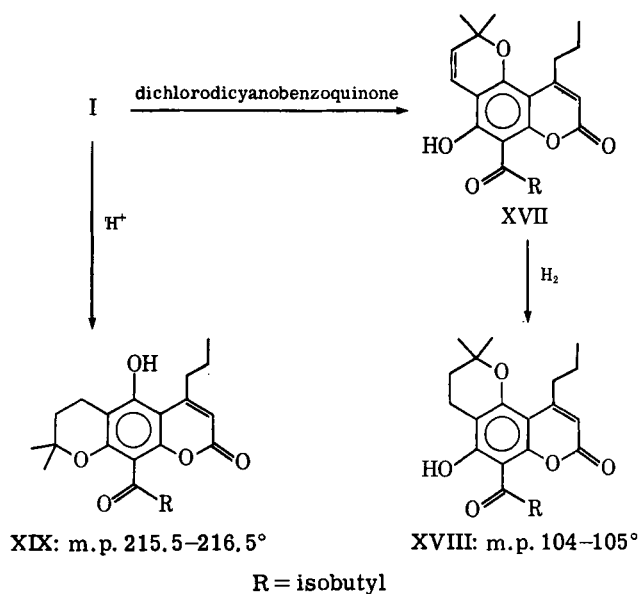
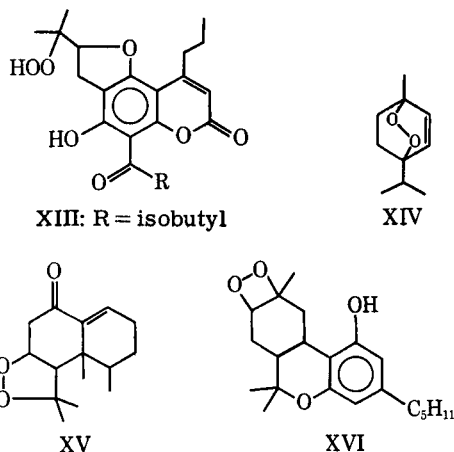
The mass spectrum of L-2 differs markedly from that of the other *Mammea* coumarins in which the base peak uniformly arises by the loss of R· from the acyl substituent. To be sure, this process occurs with L-2 to give the ion m/e 345; however, the abundance of this ion is only 14% of the base peak which is at m/e 43. The fragmentation of L-2 appears to be dominated, perhaps not surprisingly, by the presence of the peroxide ring. A hypothetical scheme which rationalizes the formation of many of the major ions was presented by Merkel (5).

In addition to L-2, Crombie *et al.* (3) also isolated the related hydroperoxide XIII (Compound L). Aside from ascaridole (XIV), the authors are aware of only one other cyclic peroxide isolated from plant sources: the terpene nardosinone (XV) reported by Rücker (6). An interesting four-membered peroxide (XVI) has been isolated from the mixture obtained in the pyridine-catalyzed reaction of olivetol with citral (7).

Dichlorodicyanobenzoquinone Oxidation of Mammein—Following the procedure used by Dudley and Chiang (8) for the oxidation of isolapachol, mammein¹ was converted into the corresponding chromene derivative XVII and then, by reduction, to the chroman XVIII (Scheme VII). That the cyclization occurred in the direction involving the C-5 hydroxyl as shown, rather than the C-7 hydroxyl, was evident from the NMR spectrum which showed a signal at τ 4.43 for the chelated hydroxyl group. The formation of the chromene ring was clearly indicated by the vinyl hydrogen absorption which appeared as an *AB* quartet with the expected chemical shifts (3.28 τ , 1H, J = 10 Hz.; 4.42 τ , 1H, J = 10 Hz.). Compound XVII was recently synthesized by Games and Haskins (9).

It is interesting that the acid-catalyzed cyclization of mammein, in contrast to the oxidative cyclizations, occurs to give the linear derivative XIX, whose structure was deduced from its analytical and spectral properties as well as the fact that it was clearly different from its isomer XVIII (*cf.*, the reactions of epoxide VII).

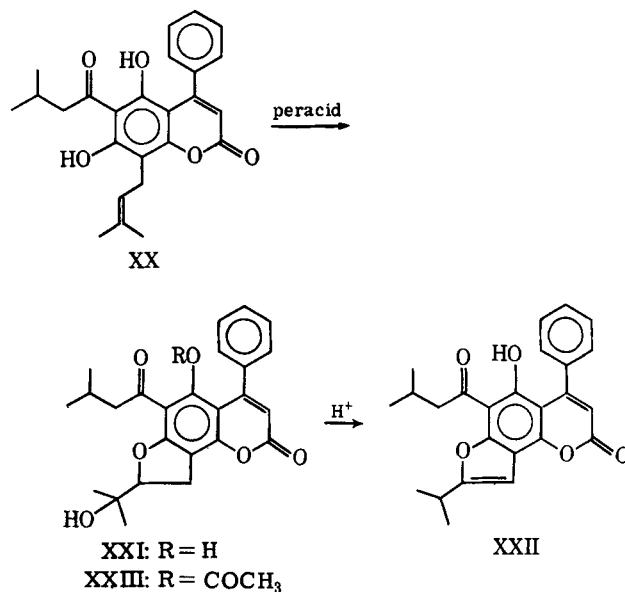
Peracid and Dichlorodicyanobenzoquinone Oxidations of Mammeisin (XX)—Reaction of mammeisin (XX) (10) with peracid led to the dihydrofurano coumarin, cyclomammeisin (XXI). This structure (Scheme VIII), rather than the corresponding chroman, was clear from its NMR spectrum. An anomalous feature of this spectrum, however, was the fact that the methylene hydrogens next to the C-6 carbonyl group appeared, under high resolution, as an eight-line *ABX* pattern, indicating the magnetic nonequivalence of the two protons. It is not clear how this arises, although it may be



due to restricted rotation and crowding of the acyl substituent, probably brought about by an unusually strong hydrogen bond with the C-5 hydroxyl. This strong hydrogen bond may, in turn, be the result of a buttressing effect of the 4-phenyl group. This second-order coupling is absent in the spectrum of the (phenolic) acetate derivative (XXIII), which does show an exceptionally high field resonance (8.70 τ) for the acetate methyl, no doubt a shielding effect of the proximate phenyl substituent.

The mass spectrum of XXI differs from its relatives bearing a 4-*n*-propyl group in that the parent ion peak is also the base peak, indicating the stabilizing influence of the phenyl group. Major fragmentation pathways include the loss of acetone from the parent to give m/e 364 (37%), which is supported by a metastable peak at m/e 314.5. In common with other *Mammea* coumarins, the loss of the isobutyl radical from the acyl substituent is also important. Other fragmentation pathways parallel those reported for columbianetin (11) and marmesin (12). The abundant ion at m/e 59 (48%) has already been noted as being diagnostic for the hydroxyisopropyl dihydrofurano moiety in these compounds.

The acid-catalyzed dehydration and rearrangement of XXI to XXII has ample precedent (13). Also, it is perhaps not surprising that cyclomammeisin (XXI) has been found, along with its 6 α -methylbutyryl isomer, to be present in mamey seed oil (14).



Scheme VIII

Finally, the reaction of mammeisin (XX) with dichlorodicyanobenzoquinone provided easy access to the chromeno coumarin, mammeisin (XXIV), a mamey seed constituent whose structure was determined previously in this laboratory (Scheme IX) (15).

Mammein Oxidation Products as Artifacts—It is impossible to give a definite answer to whether the mammein oxidation products are artifacts. The isolation work in this laboratory was carried out with mamey seed oil that had been stored for a long time. Indeed, IV, X, and XII were obtained by rechromatography of a preisolated, but crude, *Mammea* mixture of I, II, and III; it has been noted that X was originally isolated from mammein mother liquors. Furthermore, we were informed by Dr. D. E. Games³ that Compounds IV, XII, and XIII could not be detected in fresh extracts in Crombie's laboratory. This negative evidence, along with the facile conversion of I to IV, X, and XII by simple exposure to air as reported here, makes it probable that these products are artifacts. It has not yet been determined whether or not these oxidations are light catalyzed, although similar photooxygenations of isopentenyl side chains, both sensitized and unsensitized, have been reported (16–18).

Since a number of natural products contain the dihydrofurano or chromano moieties present in IV and X, it is possible that some of these are also the result of oxidative transformations which occur during isolation, rather than being true plant metabolites.

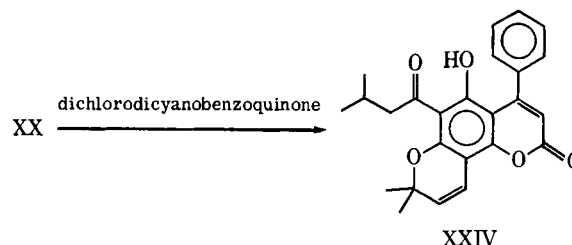
EXPERIMENTAL⁴

Mammein Epoxide (VII)—A solution of *m*-chloroperbenzoic acid (1.48 g., 8.5 mmoles) in methylene chloride (10 ml.) was added dropwise to a stirred solution of mammein¹ (2.00 g., 5.35 mmoles) in methylene chloride (15 ml.). The reaction mixture was stirred for 1 hr. at room temperature. The insoluble *m*-chlorobenzoic acid was separated by filtration and washed with methylene chloride. The combined methylene chloride solutions were washed with saturated aqueous sodium bicarbonate solution (6 × 20 ml.), water (4 × 20 ml.), and saturated aqueous sodium chloride solution (2 × 20 ml.); they were then dried with anhydrous magnesium sulfate and evaporated to dryness. The solid residue was recrystallized from ether-hexane to give a white crystalline solid, m.p. 124–125°, 1.68 g., 80.5% yield. Three further recrystallizations from ether-hexane furnished the analytical sample of VII, m.p. 125–126°; $\nu_{\text{max}}^{\text{KBr}}$: 2950, 1730, 1721 (sh), 1631 (sh), 1597, 1399, and 1198 cm^{-1} ; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N HCl}}$: 225, 235 (sh), and 300 nm.; log ϵ : 4.37, 4.21, and 4.43; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N NaOH}}$: 242, 235 (sh), and 375 nm.; log ϵ : 4.39, 3.80, and 4.31; NMR (CDCl_3 , tetramethylsilane): τ —5.0 (1H, s), 0.73 (1H, s), 3.92 (1H, s), and 6.0–9.2 (25H, m). Consistent with the structure assigned to VII is the lack of signals between 4 and 6 τ . A definite assignment of signals for the α -proton of the epoxide ring and the adjacent benzylic protons was not possible due to the complexity of the spectrum. The signals for the methyl protons in the starting material (8.15 and 8.20 τ) are shifted upfield in the product to 8.40 (3H, s) and 8.58 τ (3H, s). A further difference is observed for the absorption of the phenolic hydroxyl proton at C-5. In the starting mammein it appears at 3.15 τ , while in VII it is shifted down to 0.73 τ . This shift may be an indication of hydrogen bonding of this proton to the epoxide oxygen.

Anal.—Calc. for $\text{C}_{22}\text{H}_{28}\text{O}_6$: C, 68.02; H, 7.27. Found: C, 68.11; H, 7.34.

Attempted recrystallization of VII from hot ethanol resulted in the quantitative formation of cyclomammein (IV), as judged by mixed melting point and spectral comparisons.

Compound M-9 (X) by Chromatography of Mammein¹ Mixture—In the previous article (1) the isolation of the crude mammein mixture (I, II, and III) from mamey oil and its additional purification by further chromatography was described. In a similar way, mammein (9 g.) was chromatographed through a column of acid-washed alumina (Merck, deactivated with 3% water). This particular column was eluted over several months with hexane, benzene, chloroform, and mixtures of these for a total of 70 fractions. The majority of the residues were crystalline; as has been described (1), the separation of I, II, and III, as well as the formation of IV, V, VI, X, and XII could be followed by TLC. The residue from Fraction 29 (1:1 benzene-chloroform) was triturated with chloroform to



Scheme IX

furnish a white solid, m.p. 213–217°, 27 mg. The spectral properties of this compound were indistinguishable from those of compound M-9, m.p. 207–211°, isolated previously² from mammein mother liquors; $\nu_{\text{max}}^{\text{KBr}}$: 3367 (broad), 2959, 1701, 1592, 1563, 1391, 1190, 1138, and 1122 cm^{-1} ; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N HCl}}$: 223, 258, and 319 nm.; log ϵ : 4.36, 3.80, and 4.24; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N NaOH}}$: 258, 328, and 388 nm.; log ϵ : 4.15, 4.31, and 3.94; NMR (dimethyl sulfoxide-*d*₆, tetramethylsilane): τ . 4.07 (1H, s), 4.65 (1H, broad singlet), 6.23 (1H, t, J = 6.5 Hz.), 6.9–7.6 (6–7H, m), 8.10–8.65 (4–5H, m), 8.70 (3H, s), 8.78 (3H, s), and 8.88–9.20 (9H, m).

Anal.—Calc. for $\text{C}_{22}\text{H}_{28}\text{O}_6$: C, 68.02; H, 7.27. Found: C, 68.03; H, 7.27.

Compound L-2 (XII) by Chromatography of Mammein¹ Mixture—The preceding article (1) described the chromatographic separation of 10.71 g. of the mammein mixture, which led to the isolation of cyclomammein (IV)¹. In that experiment the fractions (80–113) (benzene to 4:1 benzene-chloroform) preceding those from which IV was obtained contained 1.75 g. of a new substance identified as L-2, a compound first isolated by Crombie *et al.* (3). Recrystallization of the crude residues from benzene-hexane gave 0.75 g. of tan needles, m.p. 160–178°. This material was further purified by charcoal treatment (chloroform solution) and subsequent recrystallization from ethanol to give fine white needles, m.p. 175–177°. Three additional recrystallizations from ethanol furnished the analytical sample, m.p. 181–182°; $\nu_{\text{max}}^{\text{KBr}}$: 2959, 2924, 2865, 1754, 1634, 1616 (sh), 1605, 1466, 1427, 1395, 1351, 1233, 1203, 1176, 1151, 1135, 1120, 911, and 817 cm^{-1} ; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N HCl}}$: 221, 290, and 310 (sh) nm.; log ϵ : 4.42, 4.35, and 4.21; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N NaOH}}$: 235, 280 (sh), and 370 nm.; log ϵ : 4.36, 3.79, and 4.29; NMR (CDCl_3 , tetramethylsilane): τ —4.43 and —4.39 (1H, two singlets), 3.92 (1H, d, J = 6 Hz.), 3.99 (1H, s), 4.53 (1H, d, J = 6 Hz.), 6.7–7.3 (3–4H, m), 8.0–8.6 (4H, m), 8.56 (6H, s), and 8.6–9.1 (7–8H, m).

Anal.—Calc. for $\text{C}_{22}\text{H}_{26}\text{O}_7$: C, 65.66; H, 6.51. Found: C, 66.20; H, 6.73; M^+ 402.

This compound gave a positive ferric chloride test and liberated iodine from a solution of potassium iodide in acetic acid, characteristic of peroxides (19). Thus, a small sample (1–3 mg.) of L-2 was dissolved in glacial acetic acid (0.3 ml.) under a carbon dioxide atmosphere. Addition of solid potassium iodide (3–6 mg.) led to simultaneous liberation of iodine. This test was negative with IV and VII, which were tested under the same conditions.

Catalytic Reduction of Compound L-2—Compound L-2, m.p. 168–172°, 0.197 g., was stirred in a 1:8 mixture of ethanol-ethyl acetate (40 ml.) with 10% palladium-on-carbon (0.05 g.) in a hydrogen atmosphere at 25°. After 2 hr., 1.34 molar equivalents of hydrogen were taken up. Filtration of the mixture and evaporation of the solvent afforded a slightly brown semisolid (0.225 g.). Crystallization of this material from benzene-hexane gave a colorless solid (0.090 g.), m.p. 130–134°. TLC of this material gave a weak spot with an identical R_f value to that of IV and a stronger spot of lower R_f value. Concentration of the mother liquor gave another crystalline material, m.p. 118–125° (0.045 g., 25%), which was identified by IR, NMR, and TLC comparisons as cyclomammein (IV).

In two additional attempts to carry out the reduction described above, mixtures of higher melting solids (*e.g.*, 148–157, 159–164, and 140–155°), all having nearly identical IR spectra and giving negative peroxide tests, were obtained but were not characterized. Further reduction gave material, m.p. 100–130°, which showed five spots on TLC of lower mobility than that of IV. It appears that overreduction takes place, but it is not known why the initial reduction of L-2 to give IV could not be reproduced, at least in two attempts.

Air Oxidation of Mammein—A sample of mammein, which showed by TLC only the three spots for I, II, and III, m.p. 123–129°

³ D. E. Games, private communication, 1966.

⁴ See Footnote 6 in Reference 1.

(2.000 g.), was dissolved in chloroform (20 ml.) and allowed to stand in contact with air at room temperature. After 5 days, TLC showed additional spots of lower mobility than that of the starting material. After 20 days, the separation of a crystalline white solid began to take place. After 75 days, this solid was separated by filtration, washed with chloroform, and dried to give 0.109 g. (5.4%) of fine white needles, m.p. 217–219°. This product was identified by spectral and TLC comparisons as Compound M-9 (X). TLC analysis of the chloroform filtrate showed a total of eight components, of which four were identified as starting material, Compound L-2¹ (XII), cyclomammein (IV)¹, and Compound M-9¹ by comparison with authentic samples applied on the same plate.

Compound M-9 from Peracid Oxidation of Mammein—*m*-Chloroperbenzoic acid (0.750 g., 3.7 mmoles) was added in one portion to an ice-cooled, stirred solution of mammein¹ (1.00 g., 2.7 mmoles) in chloroform (20 ml.). The mixture was stirred for 5 hr. at 0°, after which time TLC analysis indicated that the starting material was consumed. The solution was diluted with chloroform (30 ml.) and then washed with saturated aqueous sodium bicarbonate solution (8 × 20 ml.), water (4 × 20 ml.), and saturated sodium chloride solution (2 × 25 ml.); it was dried with anhydrous magnesium sulfate. Evaporation of the solvent afforded a yellow solid which was then triturated with benzene. The insoluble material was separated by filtration to give 0.143 g. of a white crystalline solid, m.p. 190–195° (14%). One recrystallization from aqueous ethanol raised the melting point to 201–203°. This product was homogeneous by TLC, and its spectral data (IR, UV, and NMR) were indistinguishable from those of Compound M-9 (X).

From the benzene filtrate was isolated, in 29% yield, the compound cyclomammein (IV)¹, as shown by TLC and spectral comparisons.

Oxidation of Mammein with Dichlorodicyanobenzoquinone: Chromene XVII—A solution of mammein¹ (1.000 g., 2.69 mmoles) in benzene (10 ml.) was added in one portion to a stirred solution of 2,3-dichloro-5,6-dicyanobenzoquinone (0.714 g., 3.15 mmoles) in benzene (10 ml.). The reaction mixture was stirred for 24 hr. at room temperature and filtered, and the collected solid (the hydroquinone) was washed thoroughly with benzene. The combined benzene solutions were evaporated to dryness, and the resulting dark-brown oil was redissolved in benzene (1.0 ml.) and applied to a column of neutral alumina (Woelm, activity grade II). Elution with benzene (375 ml. total) and evaporation of the eluent gave 331 mg. yellow oil; further elution with benzene-chloroform mixtures provided only negligible amounts of oily residues. The oily product was dissolved in hexane (3 ml.), and the solution was filtered and cooled to –15°. The crystalline material obtained was separated and washed with cold hexane, m.p. 70–89°, 0.177 g. (18% yield). Several recrystallizations from cold hexane provided the analytical sample of XVII, m.p. 89–91°; $\nu_{\text{max}}^{\text{KBr}}$: 2959, 1748, 1642, 1616, 1580, 1410, 1393, 1198, 1179, 1149, 1130, and 1111 cm^{-1} ; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N HCl}}$: 221, 274, and 300 nm.; log ϵ : 4.28, 4.26, and 4.37; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N NaOH}}$: 242, 280 (sh), and 380 nm.; log ϵ : 4.32 and 4.27; NMR (CDCl_3 , tetramethylsilane): τ –4.43 (1H, s), 3.28 (1H, d, J = 10 Hz.), 4.00 (1H, s), 4.42 (1H, d, J = 10 Hz.), 6.88 (2H, d, J = 6.5 Hz.), 7.09 (2H, t, J = 8 Hz.), 8.0–8.6 (3H, m), 8.47 (6H, s), and 8.65–9.18 (9H, m).

Anal.—Calc. for $\text{C}_{22}\text{H}_{26}\text{O}_5$: C, 71.33; H, 7.08. Found: C, 71.12; H, 7.02.

Catalytic Reduction of XVII: Chroman XVIII—A solution of the chromene XVII¹ (0.153 g, 0.41 mmole) in ethanol (15 ml.) and 5% palladium-on-carbon (75 mg.) was stirred in a hydrogen atmosphere at 25°. After 1 hr., 1.2 molar equivalents of hydrogen had been taken up and the mixture was filtered, the catalyst being washed with hot ethanol. The filtrate and washings were combined and evaporated to dryness to yield 0.130 g. (84%) yellow oil, which was crystallized from hexane to give pale-yellow crystals of XVIII, m.p. 93–97° (61 mg., 40%). Three additional recrystallizations from aqueous ethanol afforded the analytical sample, m.p. 104–105°; $\nu_{\text{max}}^{\text{KBr}}$: 2941, 1739, 1613, 1590, 1565, 1425, 1404, 1374, 1302, 1294, 1205, 1160, and 1121 cm^{-1} ; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N HCl}}$: 222, 297, and 316 nm.; log ϵ : 4.42, 4.39, and 4.24; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N NaOH}}$: 240 and 384 nm.; log ϵ : 4.40 and 4.29.

Anal.—Calc. for $\text{C}_{22}\text{H}_{28}\text{O}_5$: C, 70.95; H, 7.58. Found: C, 70.66; H, 7.88.

Acid-Catalyzed Cyclization of Mammein: Chroman XIX—Concentrated sulfuric acid (0.2 ml.) was added dropwise to a stirred solution of mammein¹ (817 mg., 2.2 mmoles) in glacial acetic acid

(15 ml.). The reaction mixture was kept for 3 hr. at room temperature; then a white precipitate was separated by filtration, washed with glacial acetic acid (10 ml.) and water (20 ml.), and dried. Recrystallization of this product from aqueous ethanol furnished white needles, m.p. 205–208°, 296 mg. (37%). From the filtrate there was obtained an additional 199 mg. (16%) of less pure XIX, m.p. 184–187°. Four recrystallizations of the higher melting first crop from aqueous ethanol gave white needles, m.p. 215.5–216.5°; $\nu_{\text{max}}^{\text{KBr}}$: 3333, 2950, 1704, 1600, 1393, 1178, 1170, 1144, and 1114 cm^{-1} ; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N HCl}}$: 227, 261, and 325 nm.; log ϵ : 4.35, 3.75, and 4.22; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N NaOH}}$: 260, 328, and 390 nm.; log ϵ : 4.13, 4.30, and 3.89; NMR (dimethyl sulfoxide- d_6 , tetramethylsilane): τ 4.04 (1H, s), 6.83–7.50 (8H, m), 7.75–8.50 (6H, m), 8.69 (6H, s), and 8.80–9.13 (13H, m).

Anal.—Calc. for $\text{C}_{22}\text{H}_{28}\text{O}_5$: C, 70.95; H, 7.58. Found: C, 71.22; H, 7.42.

Preparation of Cyclomammeisin (XXI) by Peracid Oxidation of Mammein (XX)—A solution of mammein (2.065 g., 5.07 mmoles) in chloroform (20 ml.) was added dropwise to a freshly prepared ice-cooled solution of monoperphthalic acid (2.4 g., 13.2 mmoles) in ether (16 ml.). The reaction mixture was stirred for 14 hr. at 0° and then kept for 48 hr. at –15°. Insoluble phthalic acid was separated by filtration and washed with chloroform (2 × 10 ml.). The filtrate and the chloroform solutions were combined and then washed with water (2 × 20 ml.), saturated aqueous sodium bicarbonate solution (5 × 20 ml.), water (2 × 20 ml.), and saturated aqueous sodium chloride solution (2 × 20 ml.); they were then dried with anhydrous magnesium sulfate. Evaporation of the solvent and crystallization of the resulting residue from ether-hexane gave a yellow crystalline solid, m.p. 130–135°, 1.209 g. Concentration of the mother liquor with simultaneous addition of hexane gave a second crop of less pure material, m.p. 125–135°, 0.188 g. The residue from these mother liquors was chromatographed through a column of neutral alumina (5 g., Woelm, activity grade II). An additional amount of crystalline product (0.337 g.), m.p. 141–143°, was obtained from the benzene-hexane and benzene eluates. The yield of XXI, based on the total amount of crystalline material (1.734 g.) obtained, was 83.5%. Several recrystallizations from ether-hexane raised the melting point to 148–150°; $\nu_{\text{max}}^{\text{KBr}}$: 3509, 3003, 1727, 1639, 1595, 1443, 1395, 1232, 1149, 1111, and 768 cm^{-1} ; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N HCl}}$: 232, 282, and 351 nm.; log ϵ : 4.14, 4.40, and 4.03; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N NaOH}}$: 242 (sh), 282 (sh), 318, and 432 nm.; log ϵ : 4.30, 4.14, 4.13, and 4.01; NMR (CDCl_3 , tetramethylsilane): τ –4.92 (1H, s), 2.69 (5H, m), 4.28 (1H, s), 5.07 (1H, t, J = 9 Hz.), 6.68 (2H, d, J = 9 Hz.), 6.89 (1H, s), 7.07 (2H, m), 7.5–8.2 (1H, m, J = 6.5 Hz.), 8.51 (3H, s), 8.68 (3H, s), and 9.02 (6H, d, J = 6.5 Hz.). The compound gave a green color with ferric chloride.

Anal.—Calc. for $\text{C}_{23}\text{H}_{26}\text{O}_6$: C, 71.07; H, 6.20. Found: C, 70.34; H, 6.07. Two additional microanalyses gave even lower values for carbon.

Acetylation of XXI: Acetate XXIII—A solution of cyclomammeisin (XXI) (0.200 g., 0.475 mmole) in pyridine (1.5 ml.) and acetic anhydride (1.5 ml.) was stirred for 24 hr. at room temperature. The reaction mixture was poured into water (50 ml.), and the white precipitate was separated by filtration, washed with water (5 × 50 ml.), and dried. Recrystallization from chloroform-hexane gave a white crystalline solid, m.p. 142–144°, 0.173 g. (78% yield). Four recrystallizations from chloroform-hexane gave an analytical sample of XXIII, m.p. 145–146°; $\nu_{\text{max}}^{\text{KBr}}$: 3534, 3003, 1748, 1701, 1618, 1433, 1370, 1232, 1205, 1188, 1149, 1121, 1099, 1032, 861, and 698 cm^{-1} ; NMR (CDCl_3 , tetramethylsilane): τ 2.57 (5H, m), 3.95 (1H, s), 5.06 (1H, t, J = 9 Hz.), 6.50 (1H, s), 6.58 (2H, d, J = 9 Hz.), 7.21 (2H, d, J = 6.5 Hz.), 7.5–8.2 (1H, m, J = 6.5 Hz.), 8.62 (3H, s), 8.70 (6H, s), and 9.10 (6H, d, J = 6.5 Hz.). The compound gave a negative ferric chloride test.

Anal.—Calc. for $\text{C}_{27}\text{H}_{28}\text{O}_7$: C, 69.81; H, 6.08. Found: C, 69.55; H, 6.10.

Dehydration of XXI: Benzofuran XXII—Cyclomammeisin (XXI), (0.200 g., 0.475 mmole) was dissolved in glacial acetic acid (5 ml.), and concentrated sulfuric acid (0.1 ml.) was added to the vigorously stirred solution. The reaction mixture was kept for 72 hr. at 70° and was then allowed to cool to room temperature. A yellow crystalline solid was separated by filtration, washed with glacial acetic acid and water, and then dried. Fine yellow needles of XXII were thus obtained, m.p. 176–179°, 63 mg., 32% yield. Dropwise addition of water to the filtrate furnished another crop of less pure XXII, m.p. 150–163°, 90 mg. (47%). Four recrystallizations of the first

crop from ethanol raised the melting point to 187–188°; $\nu_{\text{max}}^{\text{KBr}}$: 3472, 2985, 1751, 1631, 1605, 1473, 1372, 1170, 1125, 855, and 768 cm^{-1} ; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N HCl}}$: 242, 295, and 370 nm.; log ϵ : 4.34, 4.58, and 3.73; $\lambda_{\text{max}}^{95\% \text{ ethanol}-0.01 \text{ N NaOH}}$: 267, 339, and 442 nm.; log ϵ : 4.41, 4.13, and 3.68; NMR (CDCl_3 , tetramethylsilane): τ –4.55 (1H, s), 2.57 (5H, s), 3.23 (1H, s), 3.88 (1H, s), 6.6–7.1 (1H, m, J = 6.5 Hz.), 8.58 (6H, d, J = 6.5 Hz.), and 8.94 (6H, d, J = 6.5 Hz.). This product gave a green color with ferric chloride.

Anal.—Calc. for $\text{C}_{25}\text{H}_{24}\text{O}_5$: C, 74.24; H, 5.98. Found: C, 73.81; H, 6.25.

Conversion of Mammeisin (XX) to Mammeigin (XXIV) by Treatment with Dichlorodicyanobenzoquinone—A solution of mammeisin (XX) (0.500 g., 1.24 mmoles) in benzene (5 ml.) was added in one portion to a stirred solution of 2,3-dichloro-5,6-dicyanobenzoquinone (0.332 g., 1.46 mmoles) in benzene (5 ml.). The reaction mixture was stirred for 13 hr. at room temperature and filtered, and the collected solid was washed thoroughly with benzene. The combined benzene solutions were evaporated to dryness, and the resulting dark-brown oil was chromatographed through 10 g. neutral alumina (Woelm, activity grade II). Elution with benzene (120 ml.) and evaporation of the solvent gave a yellow solid (0.208 g., 41.7%, m.p. 136–142°. Recrystallization from ether–hexane gave XXIV, m.p. 146–147° [lit. (15) m.p. 144–146°]. Comparison of this product with an authentic sample of XXIV (15), by IR, UV, and NMR spectroscopy as well as by TLC and mixed melting-point determinations, showed them to be identical. A similar oxidation of XX was reported recently (20).

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