from ether gave pure *O*-methylcoccinine, m.p. 122–126°; $[\alpha]^{25}_{589}$ − 131°, $[\alpha]^{25}_{436}$ −342° (*c* 0.36).

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.45; H, 6.81; N, 4.45.

(b) *From epiisohaemanthamine:* A solution of 200 mg. of epiisohaemanthamine (XIV, R = H) in benzene was added to a dispersion of 250 mg. of potassium and finally was treated with 150 mg. of methyl *p*-toluenesulfonate, as in the *O*-methylation of isohaemanthamine. A 150-mg. yield of crude product was chromatographed on alumina with ethyl acetate, producing 75 mg. of crystalline *O*-methylcoccinine which was sublimed at 150° (5 μ) and recrystallized from a small amount of ether, m.p. 122–123° alone or on admixture with *O*-methylcoccinine derived from the *O*-methylation of coccinine. The infrared spectra (potassium bromide) of the two compounds also were identical. Subsequent elution with 20% methanol in ethyl acetate produced a trace of recovered epiisohaemanthamine.

O-Methyl-α-isocrinamine (XII, OCH_3 instead of OH). (a) *From crinamine:* A solution of 120 mg. of crinamine in 10 ml. of pyridine was treated with 0.20 ml. of methanesulfonyl chloride and finally with sodium methoxide in methanol under the conditions used in the conversion of haemanthamine to manthine. Chromatography of the crude reaction product on alumina with ethyl acetate produced 13 mg. (11%) of crystals, m.p. 171–172° (unchanged on crystallization from ethyl acetate). A mixture melting point with authentic *O*-methyl-α-isocrinamine prepared below was not depressed, and the infrared spectra (potassium bromide) were identical.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; OCH_3, 19.68. Found: C, 68.61; H, 6.43; OCH_3, 19.55.

(b) *From α-isocrinamine:* A benzene solution of 150 mg. of α-isocrinamine was combined with 180 mg. of potassium dispersed in benzene and 110 mg. of methyl *p*-toluenesulfonate under the conditions employed in the conversion of isohaemanthamine to manthine. A yield of 57 mg. of crude product possessing the correct infrared spectrum was obtained, but after chromatography on alumina this was reduced to 28 mg. (18%) of crystalline product, m.p. 171–172° alone or on admixture with that obtained above.

O-Methyl-β-isocrinamine (XVI, OCH_3 instead of OH). Methylation of 115 mg. of β-isocrinamine (XVI) by the method described previously gave 58 mg. of crude product. Chromatography on aluminum oxide and elution with 50% ethyl acetate in benzene gave 20 mg. of the methyl ether which was crystallized from ether, 15 mg., m.p. 155–156°; $[\alpha]^{24}_{589}$ −70°, $[\alpha]^{24}_{436}$ −203° (*c* 0.26).

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; 2 OCH_3, 19.68. Found: C, 68.67; H, 6.91; OCH_3, 19.83.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Naturally Occurring Oxygen Heterocyclics. VII.[1] The Structure of Mammein.[2,3]

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Degradation experiments are reported which demonstrate that mammein, an insecticidal principle of *Mammea americana* L., is 4-*n*-propyl-5,7-dihydroxy-6-isopentenyl-8-isovalerylcoumarin (I).

In an earlier paper[5] there was reported the characterization of some of the functional groups of mammein, a crystalline insecticidal principle which had been isolated earlier from *Mammea americana* L. by Morris and Pagan.[6] Its empirical formula was established[5] as $C_{22}H_{28}O_5$ and of the five oxygen atoms, two were shown to be present as phenolic hydroxyl groups, two form part of a lactone system (possibly in a coumarin) and the remaining one was assumed to exist as a carbonyl function on the basis of infrared evidence. Furthermore, the presence of an isopentenyl system, $(CH_3)_2C{=}CHC$, was demonstrated by ozonization and hydrogenation experiments.

The initial characterization studies[5] indicated that mammein was very sensitive towards alkali. Under mild conditions, mammein was isomerized irreversibly to isomammein, while more severe conditions resulted in rupture of the molecule. The present paper is concerned with a detailed examination of the behavior of mammein and some of its transformation products towards alkaline reagents and this has led to the complete elucidation of the structure of mammein. For the sake of simplicity, the subsequent discussion will be presented in terms of the expression I for mammein.

Hydrogenation[5] of mammein (I) results in the facile uptake of one equivalent of hydrogen with the formation of dihydromammein (II), whose ultraviolet absorption spectrum was very similar to that of the parent (I), thus showing that the double bond was not conjugated with the main chromophoric system. When dihydromammein (II) was heated with 5% aqueous alkali and the steam volatile constituents collected, there was isolated up to 88% of methyl *n*-propyl ketone (IV) and 93% of volatile acid. Esterification and

(1) Paper VI. R. A. Finnegan and C. Djerassi, *Tetrahedron Letters*, **No. 13**, 11 (1959).

(2) For preliminary communication see C. Djerassi, E. J. Eisenbraun, R. A. Finnegan, and B. Gilbert, *Tetrahedron Letters*, **No. 1**, 10 (1959).

(3) Financial assistance by the National Science Foundation (grant No. G2162) and the National Heart Institute (grant No. H-2574) of the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged.

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(5) C. Djerassi, E. J. Eisenbraun, B. Gilbert, A. J. Lemin, S. P. Marfey, and M. P. Morris, *J. Am. Chem. Soc.*, **80**, 3686 (1958).

(6) M. P. Morris and C. Pagan, *J. Am. Chem. Soc.*, **75**, 1489 (1953).

vapor phase chromatography showed that this acid consisted largely of isovaleric acid, contaminated by some *n*-butyric acid (VI), and this conclusion was verified by the preparation and identification of their respective anilides. Since Kuhn-Roth oxidation[5] of mammein (I) had demonstrated the presence of three C-methyl groups, it is evident that *n*-butyric acid and methyl *n*-propyl ketone arise from the same part of the mammein molecule. The nonvolatile portion of this alkaline steam distillation furnished a crystalline phenol of the empirical formula $C_{11}H_{16}O_3$, which was identified as isopentylphloroglucinol (III).[7]

The three cleavage products isopentylphloroglucinol (III), methyl *n* propyl ketone (IV), and isovaleric acid (V), account for twenty-one out of the twenty-two carbon atoms of mammein and together with the earlier reported[5] ultraviolet and infrared spectral data suggest strongly that mammein is a substituted coumarin derivative. This supposition could be confirmed as follows:

A careful study of the rate of liberation of the volatile constituents during the alkaline treatment of mammein (I) demonstrated that isovaleric acid (V) was formed much more rapidly than methyl *n*-propyl ketone (IV). The alkali cleavage reaction was, therefore, repeated with II, except that the time was reduced to one hour. Acidification and direct crystallization afforded in poor yield a high melting (m.p. 237–239°) fluorescent phenol of the composition $C_{17}H_{22}O_4$, which could be methylated with dimethyl sulfate and potassium carbonate in acetone solution to the corresponding fluorescent dimethyl ether $C_{19}H_{26}O_4$. It should be noted that the phenol $C_{17}H_{22}O_4$ and isovaleric acid account for all carbon and oxygen atoms of the starting material, dihydromammein (II).

The ultraviolet absorption spectrum of the derived dimethyl ether $C_{19}H_{26}O_4$ was identical with that[8] of 5,7-dimethoxycoumarin and since longer alkaline treatment (*vide supra*) led to isopentylphloroglucinol (III) and methyl *n*-propyl ketone (IV), consideration of the possible cleavage mechanism leaves only 4-*n*-propyl-5,7-dimethoxy-6-isopentylcoumarin or 4-*n*-propyl-5,7-dimethoxy-8-isopentylcoumarin (VIII) as plausible structural alternatives for the fluorescent dimethyl ether $C_{19}H_{26}O_4$. The choice was settled by synthesis[9] of both isomers and the demonstration that 4-*n*-propyl-5,7-dihydroxy-8-isopentylcoumarin (VII) and its dimethyl ether (VIII) were identical with the degradation products of dihydromammein (II).

A parallel reaction sequence was then conducted with mammein (I) itself, except that the intermediate phenol IX was not isolated but methylated directly to the highly fluorescent 4-*n*-propyl-5,7-dimethoxy-8-isopentenylcoumarin (X), which was then hydrogenated to the above described 4-*n*-propyl-5,7-dihydroxy-8-isopentylcoumarin (VIII). The ultraviolet absorption spectra of VIII and X were identical in neutral or basic media, thus excluding the possibility that the double bond of X could be in conjugation with the aromatic ring. The actual location of the double bond in the 8-isopentenyl coumarin X was confirmed by ozonization, which furnished acetone as the 2,4-dinitrophenylhydrazone, uncontaminated by the corresponding derivative of formaldehyde.

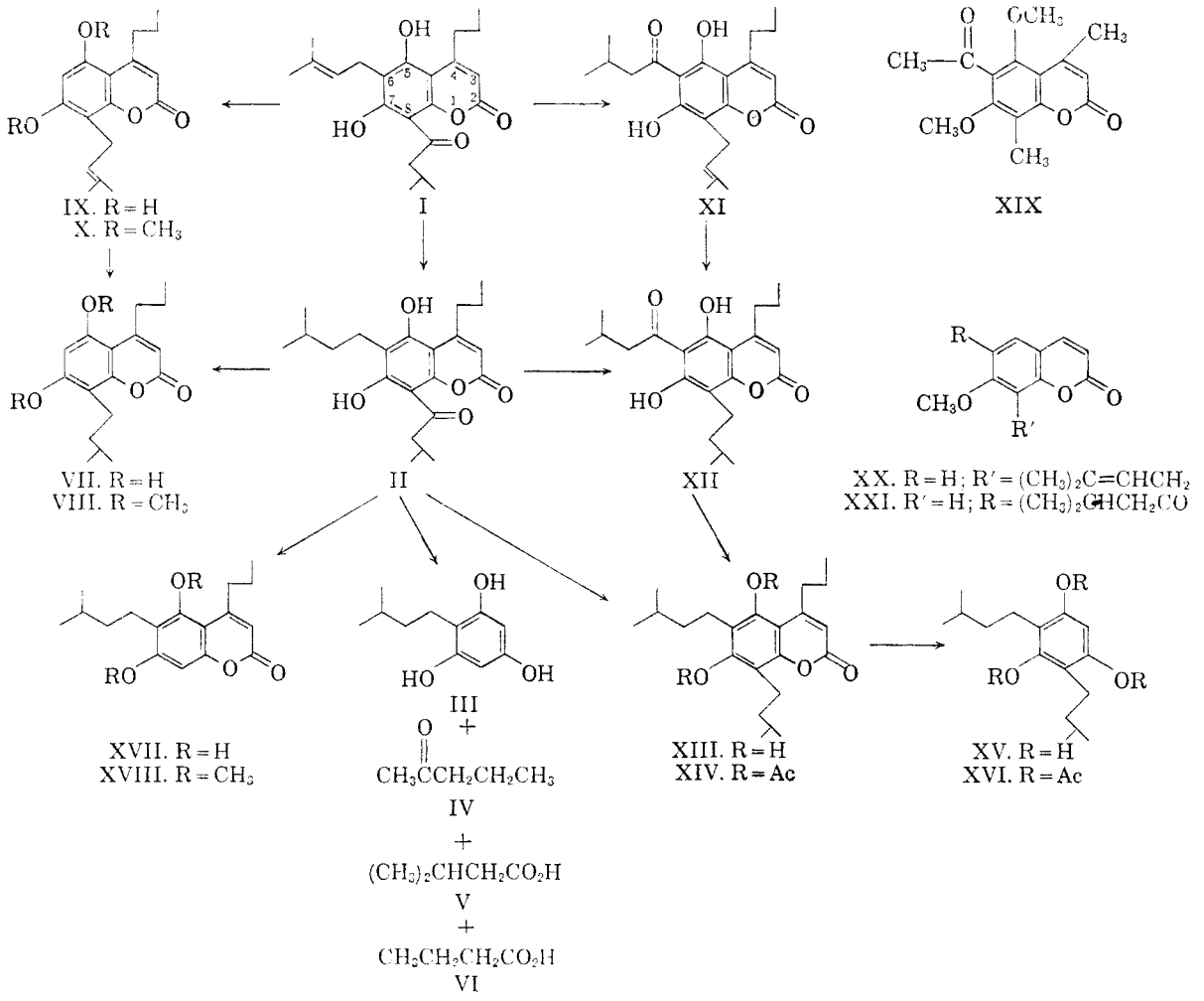
The conversion of mammein (I) and dihydromammein (II) into 4-*n*-propyl-5,7-dimethoxy-8-isopentylcoumarin (VIII) and the liberation of isovaleric acid (V) during the alkali cleavage reaction can now be summarized in terms of the expression 4-*n*-propyl-5,7-dihydroxy-x-isopentenyl-isovalerylcoumarin, the remaining uncertainty being the location of the isopentenyl and isovaleryl fragments. The fact that the isopentenyl or isopentyl groups are located at C-8 of the degradation products VIII and X, does not necessarily mean that this also applies to mammein (I) or dihydromammein (II), since the alkaline reaction conditions involved opening of the coumarin to the coumarinic acid, and subsequent ring closure upon acidification could then have proceeded in two alternate directions (VII or XVII). As far as the point of attachment of the isovaleryl substituent is concerned, this could be either in the remaining unsubstituted position of the phenolic ring or at C-3. The following evidence was adduced in order to settle this last point:

In our first paper[5] on this subject, we reported that exposure of mammein (I) to methanolic potassium hydroxide at room temperature followed by acidification led to a yellow isomer, isomammein (XI). Hydrogenation of isomammein (XI) furnished isodihydromammein (XII), which could also be obtained from dihydromammein (II) by mild treatment with base. The simplest interpretation of these changes is that isomammein (XI) and isodihydromammein (XII) represent the products of alternate ring closure of the coumarinic acids formed during the alkaline treatment of mammein (I) and dihydromammein (II). This could now be established unambiguously by the observation that Clemmensen reduction of either dihydromammein (II) or isodihydromammein (XII) led to the same oily phenol (XIII), which was characterized as the crystalline diacetate (XIV). When the latter was heated with 20% aqueous sodium hydroxide solution, there was isolated methyl *n*-propyl ketone (IV) as well as diisopentylphloroglucinol (XV),[9] which was identified as the crystalline triacetate XVI. The isolation of diisopentylphloroglucinol (XV) establishes the structure of the Clemmensen

(7) T. S. Kenny, A. Robertson, and S. W. George, *J. Chem. Soc.*, 1601 (1939).

(8) H. Böhme and T. Severin, *Arch. Pharm.*, 290, 486 (1957).

(9) R. A. Finnegan, B. Gilbert, E. J. Eisenbraun, and C. Djerassi, *J. Org. Chem.*, accompanying paper.



reduction product as 4-*n*-propyl-5,7-dihydroxy-6,8-di-isopentylcoumarin (XIII) and thus shows that both the isopentenyl and the isovaleryl groups of mammein must be located in the phenolic ring.

Mammein and isomammein can now be represented only by structures I and XI. On mechanistic grounds, the 6-isopentenyl-8-isovalerylcoumarin I must be preferred for mammein, since in the resulting coumarinic acid hydrogen bonding[10] between the carbonyl group of the 8-isovaleryl substituent and the newly formed C-1 hydroxyl group would represent the driving force for the alternate ring closure leading to isomammein (XI). Furthermore, the ultraviolet absorption spectra of dihydroisomammein dimethyl ether[5] ($\lambda_{max}^{C_2H_5OH}$ 246, 297 mμ, log ϵ 4.08, 4.12; $\lambda_{min}^{C_2H_5OH}$ 238, 269 mμ, log ϵ 4.06, 3.90) and synthetic 4,8-dimethyl-5,7-dimethoxy-6-acetylcoumarin (XIX)[11] ($\lambda_{max}^{C_2H_5OH}$ 250, 296 mμ, log ϵ 4.11, 4.18; $\lambda_{min}^{C_2H_5OH}$ 235, 268.5 mμ, log ϵ 4.01, 4.01) are remarkably similar and differ significantly from that of dihydromammein dimethyl ether[5] ($\lambda_{max}^{C_2H_5OH}$ 295 mμ, log ϵ 4.09; $\lambda_{min}^{C_2H_5OH}$ 259.5 mμ, log ϵ 3.76).

The above assignment of structure I to mammein implies that during the alkaline cleavage of dihydromammein (II) to the fluorescent 4-*n*-propyl-5,7-dihydroxy-8-isopentylcoumarin (VII), ring closure of the intermediate coumarinic acid had occurred in the alternate direction and that consequently, the isopentyl group of the degradation product (VII) does not occupy the same position as in the parent dihydromammein (II). In connection with synthetic studies[9] in the coumarin series, it was observed that 75% sulfuric acid represents an excellent deacylating agent without causing any rearrangement, since the reaction proceeds with the intact coumarin skeleton rather than through the opened coumarinic acid. When these deacylating conditions were applied to dihydromammein (II), there was isolated in high yield a phenol and thence by methylation its dimethyl ether. Neither substance was fluorescent, in contrast to VII and VIII, but the substances were nevertheless isomeric. That the phenol represents the nonrearranged cleavage product 4-*n*-propyl-

(10) A similar observation has been made with 8-nitrocoumarins: M. Crawford and J. W. Rasburn, *J. Chem. Soc.*, 2155 (1956); R. M. Naik and V. M. Thakor, *J. Org. Chem.*, 22, 1240 (1957).

(11) F. M. Dean, E. Evans, and A. Robertson, *J. Chem. Soc.*, 4565 (1954). We are indebted to Dr. Dean (University of Liverpool) for this specimen.

5,7-dihydroxy-6-isopentylcoumarin (XVII) was demonstrated conclusively by its synthesis[9] and that of its dimethyl ether (XVIII), thus completing the rigorous structure proof of mammein (I) and *ipso facto* of isomammein (XI).

Mammein assumes an interesting position among the many naturally occurring coumarins.[12] It is the only one possessing a propyl substituent and is a member of the rare class of 4-substituted coumarins, the only other examples being some 4-phenyl[1,13,14] and 4-hydroxy[12] coumarins. While coumarins with isopentenyl[12] (*e.g.*, osthol (XX)[15]) or isovaleryl (geijerin (XXI)[16]) moieties are known, mammein represents the first naturally occurring one in which both groups can be found, a type of substitution pattern reminiscent of some of the hop constituents (humulone, lupulone).[17]

Biogenetically, mammein (I) seems unexceptional and its structure is completely consistent with the acetate hypothesis.[18] As far as the substance's insecticidal activity[6] is concerned, it is noteworthy that a number of synthetic coumarins have been shown[19] to possess such activity.

EXPERIMENTAL[20]

Alkali cleavage of mammein (I). (*a*) *Preliminary experiments.* Mammein was heated under reflux with 5% aqueous potassium hydroxide and the distillate collected in acidified 2,4-dinitrophenylhydrazine solution, the precipitated 2,4-dinitrophenylhydrazone of methyl *n*-propyl ketone (IV) being weighed at intervals. At the same time, aliquots of the alkaline solution were removed, acidified with phosphoric acid, steam distilled, and the total volatile acids determined by titration. The results are summarized as follows:

Time, hr.	% Yield of Methyl *n*-Propyl Ketone 2,4-DNP	% Yield of One Equivalent of Volatile Acid
0.75	4	27
2.0	23	74
14.0	87	93
20.0	89	100

(*b*) *Identification of volatile components.* A 1.134-g. sample of mammein (I) in 100 cc. of 5% aqueous potassium hydroxide was steam distilled for 20 hr. into a solution of 1.0 g. of 2,4-dinitrophenylhydrazine in 20 cc. of sulfuric acid and 80 cc. of water. The precipitate was collected, washed with water, dried, dissolved in benzene and filtered through a column of Fisher activated alumina. Evaporation of the benzene eluate afforded 0.71 g. (88%) of the orange colored 2,4-dinitrophenylhydrazone of methyl *n*-propyl ketone, m.p. 135–143°.[21] Recrystallization from ethanol raised the m.p. to 144.5–146°, undepressed upon admixture with an authentic specimen. Identity was confirmed further by comparison of the infrared spectra and by paper chromatography with cyclohexane on formamide-impregnated paper.

The residual alkaline solution was acidified with phosphoric acid, steam distilled, and the volatile acids were titrated indicating the formation of nearly 1 equivalent of acid. The alkaline titration solution was acidified to *p*H 2 with hydrochloric acid, saturated with sodium chloride, and extracted with ether. Most of the ether was removed cautiously by distillation through a Podbielniak column, an ethereal solution of diazoethane was added and after a few minutes, the excess solvent was removed and the residual ethyl ester was subjected to vapor phase chromatography on a silicone–stearic acid substrate supported on Celite, indicating the presence of ethyl isovalerate and ethyl butyrate in a ratio of about 7:1. Confirmation of these conclusions was obtained by actually recovering some of the pure esters from the chromatogram and identifying them by infrared spectroscopy as well as by converting them into their respective anilides which were compared by mixture melting point and X-ray diffraction.[22]

(*c*) *Isolation of 4-n-propyl-5,7-dimethoxy-8-isopentenylcoumarin* (X).[21] A solution of 1.0 g. of mammein in 50 cc. of 5% aqueous sodium hydroxide solution was heated under reflux for 3 hr., extracted with ether (negligible residue), acidified and re-extracted with ether to furnish 0.89 g. of oily acidic material. This contained the required phenol IX, which was not purified but transformed directly into its dimethyl ether X by heating 0.57 g. under reflux for 5 hr. with 25 cc. of dry acetone, 0.56 cc. of dimethyl sulfate and 1.62 g. of anhydrous potassium carbonate. Dilution with water and extraction with ether furnished a highly fluorescent semisolid which was chromatographed on 30 g. of Merck acid-washed alumina. The product was eluted with benzene, the course of the chromatogram being followed conveniently by the fluorescence of the solution; yield, 0.22 g., m.p. 127–129°. Further recrystallization from hexane raised the m.p. to 130–132°, no color with ferric chloride, λ_{max}^{KBr} 5.81 (s), 6.15 (m), and 6.21 (s) μ; $\lambda_{max}^{C_2H_5OH}$ 262, 323 mμ, log ϵ 4.05, 4.17, $\lambda_{min}^{C_2H_5OH}$ 244, 273 mμ, log ϵ 3.89, 3.37; $\lambda_{max}^{C_2H_5OH\text{-}KOH}$ 227, 262, 323 mμ, log ϵ 3.96, 3.97, 4.10, $\lambda_{min}^{C_2H_5OH\text{-}KOH}$ 244, 273 mμ, log ϵ 3.74, 3.07.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65; 2 OCH_3, 19.62. Found: C, 71.93; H, 7.83; OCH_3, 20.43.

When 50 mg. of the dimethyl ether X was heated under reflux with 25 cc. of 10% sodium hydroxide and 5 cc. of ethanol, dilution with water and extraction left no residue. Acidification with hydrochloric acid, extraction with ether, drying and evaporation provided 47 mg. of colorless crystals (fluorescent in ethanolic solution), which exhibited m.p. 130–131.5° after one recrystallization from hexane and whose infrared spectrum was identical with that of the starting material.

(12) For summaries see: F. M. Dean in L. Zechmeister's *Progress in the Chemistry of Organic Natural Products*, Springer, Vienna, 1952, Vol. IX, pp. 225–91; L. Reppel, *Pharmazie*, 9, 278 (1954); W. Karrer *Konstitution und Vorkommen der Organischen Pflanzenstoffe*, Birkhäuser, Basel, 1958, pp. 532–62.

(13) J. Polonsky, *Bull. Soc. Chim. France*, 929 (1958) and earlier papers; A. Ormancey-Potier, A. Buzas, and E. Lederer, *Bull. Soc. Chim. France*, 577 (1951).

(14) V. K. Ahluwalia and T. R. Seshadri, *J. Chem. Soc.*, 970 (1957).

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

(16) F. N. Lahey and D. J. Wluka, *Australian J. Chem.*, **8**, 125 (1955).

(17) C. H. Hassall in J. W. Cook's *Progress in Organic Chemistry*, Butterworths, London, 1958, Vol. 4, Chap. 4.

(18) A. J. Birch in L. Zechmeister's *Progress in the Chemistry of Organic Natural Products*, Springer, Vienna, 1957, Vol. XIV, pp. 186–216.

(19) P. Läuger, H. Martin, and P. Müller, *Helv. Chim. Acta*, **27**, 892 (1944).

(20) All melting points were determined on the Kofler block. We are indebted to Miss B. Bach for the infrared spectra and to Dr. A. Bernhardt, Mülheim, Germany, for the microanalyses.

(21) This experiment was first performed by Dr. S. P. Marfey in this laboratory.

(22) We are indebted to Dr. R. T. Rapala of Eli Lilly and Co. for arranging for these measurements.

In order to confirm the location of the double bond in the isopentenyl moiety, ozone was passed for 17 min. through a solution of 125 mg. of X in 10 cc. of glacial acetic acid. After stirring with 1.0 g. of ferrous sulfate and 15 cc. of water for 20 min., steam was passed through the solution and the distillate was collected in a solution of 1.0 g. of 2,4-dinitrophenylhydrazine, 80 cc. of water, and 20 cc. of concd. sulfuric acid. The yellow precipitate of acetone 2,4-dinitrophenylhydrazone was washed and dried; yield, 40 mg., m.p. 115–122°. Chromatography on a column of 6.0 g. of kieselguhr and 18.0 g. bentonite[23] and elution with benzene containing 0.5% methanol afforded pure acetone 2,4-dinitrophenylhydrazone, m.p. 125–126°. No trace of formaldehyde 2,4-dinitrophenylhydrazone was encountered, which according to model experiments could have been detected readily in a mixture with acetone 2,4-dinitrophenylhydrazone.

Hydrogenation of 4-n-propyl-5,7-dimethoxy-8-isopentenylcoumarin (X). A solution of 141 mg. of X in 25 cc. of absolute methanol was hydrogenated with 20 mg. of pre-reduced platinum oxide catalyst until no more hydrogen was taken up (4 hr.). Filtration of the catalyst and evaporation of the solvent *in vacuo* yielded a crystalline solid (m.p. 92–105°) which was chromatographed on 12 g. of Alcoa alumina (grade F-20). Elution with 1:1 ether-benzene provided colorless crystals, m.p. 109–110° (after recrystallization from hexane), which were strongly fluorescent in ethanol solution; λ_{max}^{KBr} 5.82 (s), 6.15 (m), 6.21 (s) μ; $\lambda_{max}^{C_2H_5OH}$ 262, 323 mμ, log ϵ 3.96, 4.06, $\lambda_{max}^{C_2H_5OH}$ 243, 272 mμ, log ϵ 3.73, 3.23; $\lambda_{max}^{C_2H_5OH\text{-}KOH}$ 227, 262, 323 mμ, log ϵ 3.71, 3.84, 4.02, $\lambda_{min}^{C_2H_5OH\text{-}KOH}$ 243, 273 mμ. The substance proved to be identical with specimens of 4-*n*-propyl-5,7-dimethoxy-8-isopentylcoumarin (VIII) prepared from dihydromammein (*vide infra*) or by synthesis.[9]

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; O, 20.10. Found: C, 71.31; H, 8.36; O, 20.41.

Alkali cleavage of dihydromammein (II). (*a*) *Isolation of volatile components and of isopentylphloroglucinol* (III). Steam was passed for 3 hr. through a solution of 2.17 g. of dihydromammein (II) in 72 cc. of 5% aqueous potassium hydroxide solution, the distillate being collected in a dilute sulfuric acid solution of 2,4-dinitrophenylhydrazine and the *methyl n-propyl ketone 2,4-dinitrophenylhydrazone* (0.73 g., m.p. 133–140°; m.p. 146–147° after purification) was filtered. The residue from the steam distillation was cooled, saturated with Dry Ice until the solution was neutral, and a pale green precipitate (220 mg.) was filtered, which was combined with an additional 160 mg. obtained by extraction with chloroform. The volatile acids were identified by vapor phase chromatography of their ethyl esters as ethyl isovalerate and ethyl butyrate.

The crude solid was recrystallized from chloroform-hexane and then sublimed at 120° and 0.02 mm., yielding white crystals, m.p. 124–126°, which were identified by mixture melting point determination and comparisons of the infrared spectra and X-ray diffraction patterns[22] with authentic *isopentylphloroglucinol* (III).[7] In a second experiment where no attempt was made to isolate the volatile acids, over 60% of the phenol could be obtained. $\lambda_{max}^{C_2H_5OH}$ 237, 271, 276, 279 mμ, log ϵ 3.46, 2.99, 2.97, 2.93, $\lambda_{min}^{C_2H_5OH}$ 251 mμ, log ϵ 2.57.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.33; H, 8.22; O, 24.46. Found: C, 67.67; H, 8.39; O, 24.19.

(*b*) *Isolation of 4-n-propyl-5,7-dihydroxy-8-isopentylcoumarin* (VII). Dihydromammein (310 mg.) in 10 cc. of 5% aqueous potassium hydroxide was heated under reflux for 1 hr. in an atmosphere of nitrogen and then poured into ice and hydrochloric acid. Extraction with ether, washing, drying, and evaporation afforded 271 mg. of brown oil, possessing an odor of isovaleric acid. Digestion of this oil with benzene afforded 39 mg. of a tan colored solid, m.p. 220–233°, which fluoresced strongly in ethanol solution. Recrystallization from chloroform-methanol raised the m.p. to 237–239°, undepressed upon admixture with a synthetic specimen[9] of 4-*n*-propyl-5,7-dihydroxy-8-isopentylcoumarin (VII). The infrared and ultraviolet spectra of the two samples were identical.

Anal. Calcd. for $C_{17}H_{22}O_4 \cdot H_2O$: C, 66.21; H, 7.85. Found: C, 65.53; H, 7.28.

A 22-mg. sample of this phenol in 2.5 cc. of anhydrous acetone was heated under reflux for 13 hr. with 0.2 g. of anhydrous potassium carbonate and 3 drops of dimethyl sulfate. After adding an additional 1 cc. of acetone, 0.2 g. of potassium carbonate, and 3 drops of dimethyl sulfate, the mixture was heated for 11 hr., then cooled and filtered. Evaporation of the filtrate yielded a brownish solid, which after recrystallization from hexane gave colorless crystals (fluorescent in ethanol solution); yield, 9.5 mg., m.p. 108–109.5°, undepressed when mixed with either synthetic[9] or mammein-derived (*vide supra*) *4-n-propyl-5,7-dimethoxy-8-isopentylcoumarin* (VIII). Identity was also established by infrared comparison.

Alternatively, the dimethyl ether VIII could be obtained directly by heating under reflux for 3 hr. a solution of 260 mg. of dihydromammein (II) in 25 cc. of 5% sodium hydroxide solution and methylating the resulting crude acidic fraction (203 mg.) with dimethyl sulfate and potassium carbonate in acetone solution. Chromatography provided 68 mg. of the dimethyl ether, m.p. 104–106°, raised to 109.5–110.5° upon recrystallization from hexane.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; 2 OCH_3, 19.60. Found: C, 71.59; H, 8.35; OCH_3, 19.93.

Acid-catalyzed deacylation of dihydromammein (II) *to 4-n-propyl-5,7-dihydroxy-6-isopentylcoumarin* (XVII). Dihydromammein (310 mg.) was stirred with 3 cc. of 75% aqueous sulfuric acid for 70 hr. at room temperature and the yellow slurry was then poured unto ice water, filtered, and washed with water. The aqueous filtrate possessed an odor strongly reminiscent of isovaleric acid. The solid was dissolved in ether, and dried thoroughly with anhydrous sodium sulfate, filtered, and concentrated. Addition of hexane afforded white needles (190 mg.) of 4-*n*-propyl-5,7-dihydroxy-6-isopentylcoumarin (XVII) with m.p. 183–186.5°, unchanged upon mixing with a synthetic specimen.[9] The infrared spectra of both samples were identical and they did not exhibit any fluorescence in ethanol solution.

Methylation in acetone solution with dimethyl sulfate–potassium carbonate (24 hr.) followed by chromatography and recrystallization from aqueous methanol led to *4-n-propyl-5,7-dimethoxy-6-isopentylcoumarin* (XVIII), m.p. 52–54°, undepressed on admixture with an authentic[9] specimen.

4-n-Propyl-5,7-diacetoxy-6,8-di-isopentylcoumarin (XIV). (*a*) *From dihydromammein* (II). Mossy zinc (2.7 g.) was mixed with 2.4 cc. of water and treated with a solution of 0.14 cc. of concd. hydrochloric acid, 0.27 g. of mercuric chloride, and 1.8 cc. of water. After stirring vigorously for 2 hr., the reaction mixture was washed four times with water, once with methanol, and dihydromammein (1.37 g.) dissolved in 35 cc. of methanol was then added along with 3 cc. of concd. hydrochloric acid. The stirred reaction mixture was heated to reflux and after 40 min. an additional 2.5 cc. of concd. hydrochloric acid was introduced. The reaction was allowed to proceed for a total of 2.25 hr. before the mixture was cooled. The solution was decanted from the residual zinc, partially evaporated, diluted with water, and extracted with ether. The ether extracts were washed with 5% sodium bicarbonate, then with water, and the aqueous extracts were extracted with ether. The combined organic layers were dried and evaporated to yield 1.28 g. of 4-*n*-propyl-5,7-dihydroxy-6,8-di-isopentylcoumarin (XIII) as a brownish resin, which resisted all attempts at crystallization even after repeated chromatography; $\lambda_{max}^{CHCl_3}$ 2.78, 3.00, 5.86 (s), 6.20 (s), 6.32 (m) μ; $\lambda_{max}^{C_2H_5OH}$ 261, 329 mμ, log ϵ 3.77, 3.99, $\lambda_{min}^{C_2H_5OH}$ 248, 275 mμ, log ϵ 3.64, 3.11.

(23) J. A. Elvidge and M. Whalley, *Chem. & Ind.* (*London*), **1955**, 589.

A portion (550 mg.) of the phenol was dissolved in 20 cc. of pyridine and 5 cc. of acetic anhydride, left at room temperature for 24 hr., and then heated on the steam bath for 7 hr. before dilution with water and extraction with ether. The ether extracts were washed several times with dilute sulfuric acid, then water, dried, and evaporated. The resulting semicrystalline diacetate XIV was recrystallized four times from hexane whereupon it exhibited m.p. 104–107° (420 mg.).

Anal. Calcd. for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16; O, 21.59. Found: C, 70.59; H, 8.10; O, 21.51.

(*b*) *From isodihydromammein* (XII). The Clemmensen reduction of 178 mg. of isodihydromammein (XII) was performed as described above for dihydromammein (II) and the crude phenol was acetylated with pyridine–acetic anhydride to afford after one recrystallization from hexane 34 mg. of 4-*n*-propyl-5,7-diacetoxy-6,8-diisopentylcoumarin (XIV), m.p. 100–103°. A second recrystallization raised the m.p. to 103–105°, alone or admixed with the diacetate prepared from dihydromammein (II). The infrared spectra of the two samples were identical.

Alkali cleavage of 4-n-propyl-5,7-diacetoxy-6,8-di-isopentylcoumarin (XIV). Nitrogen was bubbled through 35 cc. of 20% aqueous sodium hydroxide solution for 15 min. prior to the addition of 420 mg. of the diacetate XIV. The solid dissolved upon heating to give a pale yellow solution. Heating under reflux was continued for 4 days, the condenser was then adjusted downward, and the mixture was distilled (with periodic replacement of water) for 2 days into a sulfuric acid solution of 2,4-dinitrophenylhydrazine yielding (after filtration through alumina) 166 mg. of methyl *n*-propyl ketone 2,4-dinitrophenylhydrazone.

The residue from the distillation was treated with Dry Ice and extracted with ethyl acetate. The extracts were dried and evaporated to give 99 mg. of diisopentylphloroglucinol (XV) as a brown resin; $\lambda_{max}^{C_2H_5OH}$ 266–268 mμ, log ε 3.65, $\lambda_{min}^{C_2H_5OH}$ 246 mμ, log ε 3.55. The phenol was dissolved in 5 cc. of pyridine and 1.5 cc. of acetic anhydride and heated on the steam bath for 36 hr. in a current of nitrogen. After working up in the usual manner, there was obtained 98 mg. of resin which was chromatographed on 3 g. of Merck acid-washed alumina. From the 4:1 benzene-hexane eluate there was obtained 16 mg. of crystals, m.p. 84.5–92° after one recrystallization from hexane. Infrared examination of the later fractions of the chromatogram indicated incompletely acetylated material and these fractions were combined and reacetylated for 67 hr. on the steam bath yielding an additional 13 mg. of crystals, m.p. 88–90.5° (after recrystallization from hexane). Combination of the two fractions and repeated recrystallization did not raise the m.p. above 91–94°, while the synthetic specimen[9] of *diisopentylphloroglucinol triacetate* (XVI) exhibited m.p. 104.5–105°. Nevertheless, the triacetate appears to be largely XVI, possibly contaminated by a slight impurity, since the mixture melting point was not depressed and the ultraviolet and infrared absorption spectra were identical.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 67.36; H, 8.71.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Naturally Occurring Oxygen Heterocyclics. VIII.[1] Synthesis of Some Coumarins Related to Mammein[2]

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The Pechmann condensation of a number of substituted phloroglucinols with ethyl butyroacetate (X) is reported and the structures of the condensation products established. Condensation of isovalerylphloroglucinol (VII) with X led to 4-*n*-propyl-5,7-dihydroxy-6-isovalerylcoumarin (XIII) rather than the 8-isovaleryl isomer (XV). Clemmensen reduction of XIII afforded 4-*n*-propyl-5,7-dihydroxy-6-isopentylcoumarin (V), identical with a degradation product of dihydromammein (II). Pechmann condensation of 2-hydroxy-4,6-dimethoxyisovalerophenone (XVI) with ethyl butyroacetate (X) gave 4-*n*-propyl-5,7-dimethoxycoumarin (XVIII), which was synthesized from phloroglucinol. Attention is called to the ease of acid-catalyzed deacylation of such coumarins, which may be of significant advantage in the degradation of naturally occurring acyldihydroxycoumarins, as the possibility of rearrangement (*e.g.*, II → III) in base-promoted deacylations is eliminated. Clemmensen reduction of 2-hydroxy-4,6-dimethoxyisovalerophenone (XVI) to 2-isopentyl-3,5-dimethoxyphenol (XX) followed by Pechmann condensation with ethyl butyroacetate (X) furnished 4-*n*-propyl-5,7-dimethoxy-8-isopentylcoumarin (IV), another degradation product of dihydromammein (II).

In the preceding article[1] there was reported degradative evidence that mammein, an insecticidal principle from *Mammea americana* L., is correctly represented as 4-*n*-propyl-5,7-dihydroxy-6-isopentenyl-8-isovalerylcoumarin (I). The substitution pattern, notably in the aromatic ring, was based principally upon the structures of two transformation products, namely 4-*n*-propyl-5,7-dihydroxy-8-isopentylcoumarin (III)—produced by base-promoted deacylation with rearrangement of dihydromammein (II) (*via* alternate ring closure of its coumarinic acid)— and 4-*n*-propyl-5,7-dihydroxy-6-isopentylcoumarin (V), which is formed in the acid-catalyzed deacylation of II. Their constitution rests upon comparison with authentic samples, whose synthesis together with other ancillary observations is reported herewith.

The first synthetic attempt in this series was actually the most ambitious one, namely the preparation of dihydromammein (II). The starting material

(1) Paper VII, C. Djerassi, E. J. Eisenbraun, R. A. Finnegan, and B. Gilbert, *J. Org. Chem.*, accompanying paper.

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