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.

DETROIT, MICH.

[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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was the earlier reported[4] isopentylphloroglucinol (VIII), which can be prepared by Friedel-Crafts acylation of phloroglucinol with isovaleryl chloride followed by Clemmensen reduction. Repeated Friedel-Crafts acylation proceeded in poorer yield (22%) to furnish isopentylisovalerylphloroglucinol (IX),[5] which was the required substrate for Pechmann condensation[6] with ethyl butyroacetate (X). In spite of extensive experimentation, the optimum conditions (acetic acid containing some sulfuric acid, six days, room temperature) provided only about 1% of a coumarin, which appeared[7] to be identical with dihydromammein (II). In view of the very poor yield in this condensation, it was felt that the synthesis of some of the other degradation products of mammein was required. The intermediate isopentylisovalerylphloroglucinol (IX) was of additional utility, as Clemmensen reduction provided the hitherto undescribed diisopentylphloroglucinol (XI), which was characterized as the crystalline triacetate XII. The identical substance has been obtained earlier[1] from mammein (I) and thus afforded the first direct evidence that both the isopentenyl and the isovaleryl substituents of mammein are attached to the aromatic ring.

In contrast to the difficulty encountered in the Pechmann condensation of isopentylisovalerylphloroglucinol (IX), which can almost certainly be attributed to steric hindrance, similar condensation of isovalerylphloroglucinol (VII) with ethyl butyroacetate (X) proceeded readily to provide 4-*n*-propyl-5,7-dihydroxy-6-isovalerylcoumarin (XIII), which was characterized further as the dimethyl ether XIV. Clemmensen reduction of the phenol XIII led to 4-*n*-propyl-5,7-dihydroxy-6-isopentylcoumarin (V) and thence by methylation to the dimethyl ether VI. Both V and VI were completely identical with the corresponding products from the sulfuric acid-catalyzed deacylation[1] of dihydromammein.

Theoretically, the Pechmann condensation of isovalerylphloroglucinol (VII) and ethyl butyroacetate (X) can proceed in two directions to give the 6-isovaleryl- (XIII) and/or the 8-isovaleryl- (XV) 4-*n*-propyl-5,7-dihydroxycoumarin. Actually, structure XIII can be assigned safely to the reaction product on the following grounds: (a) Just as in the isomerization of mammein (I) to isomammein (II), chelation between the ketonic function of the isovaleryl substituent and the adjacent phenolic group would favor cyclization with the *p*-hydroxyl group; (b) steric factors, which are known[6] to play an important role in the Pechmann reaction (see also condensation of IX and X), will also favor ring closure with the *p*-hydroxyl group; (c) the unambiguous synthesis (described below) of 4-*n*-propyl-5,7-dimethoxy-8-isopentylcoumarin (IV) which would have been identical with the methylated Clemmensen reduction product of the 8-isovaleryl isomer XV.

In an attempt to force the Pechmann condensation in the alternate direction (*viz.* VII → XV), isovalerylphloroglucinol (VII) was methylated with dimethyl sulfate in acetone solution in the presence of potassium carbonate to afford a crystalline dimethyl ether. Steric considerations[8] require that the free phenolic group is located *ortho* to the isovaleryl moiety and that the dimethyl ether is 2-hydroxy-4,6-dimethoxyisovalerophenone (XVI). Pechmann condensation of XVI with ethyl butyroacetate (X) in the above described manner (acetic acid containing concentrated sulfuric acid) did not proceed in the expected direction (to give the dimethyl ether of XV) but rather resulted in the formation of some phloroglucinol monomethyl ether[9] and most importantly, 4-*n*-propyl-5,7-dimethoxycoumarin (XVIII). The structure of this coumarin was established independently by Pechmann condensation of phloroglucinol with ethyl butyroacetate (X) to 4-*n*-propyl-5,7-dihydroxycoumarin (XVII)[10] followed by methylation to the dimethyl ether XVIII. This afforded the first clue to the ease of deacylation in the 5,7-dihydroxycoumarin series[11] and was used[1] to good advantage in the deacylation of dihydromammein (II) to 4-*n*-propyl-5,7-dihydroxy-6-isopentylcoumarin (V). When the condensation of 2-hydroxy-4,6-dimethoxyisovalerophenone (XVI) and ethyl butyroacetate (X) was conducted in aqueous sulfuric acid (rather than acetic acid–concentrated

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

(5) W. Riedl, *Ber.*, **85**, 692 (1952), prepared this substance by an alternate procedure.

(6) S. Sethna and R. Phadke, *Org. Reactions*, 1 (1953).

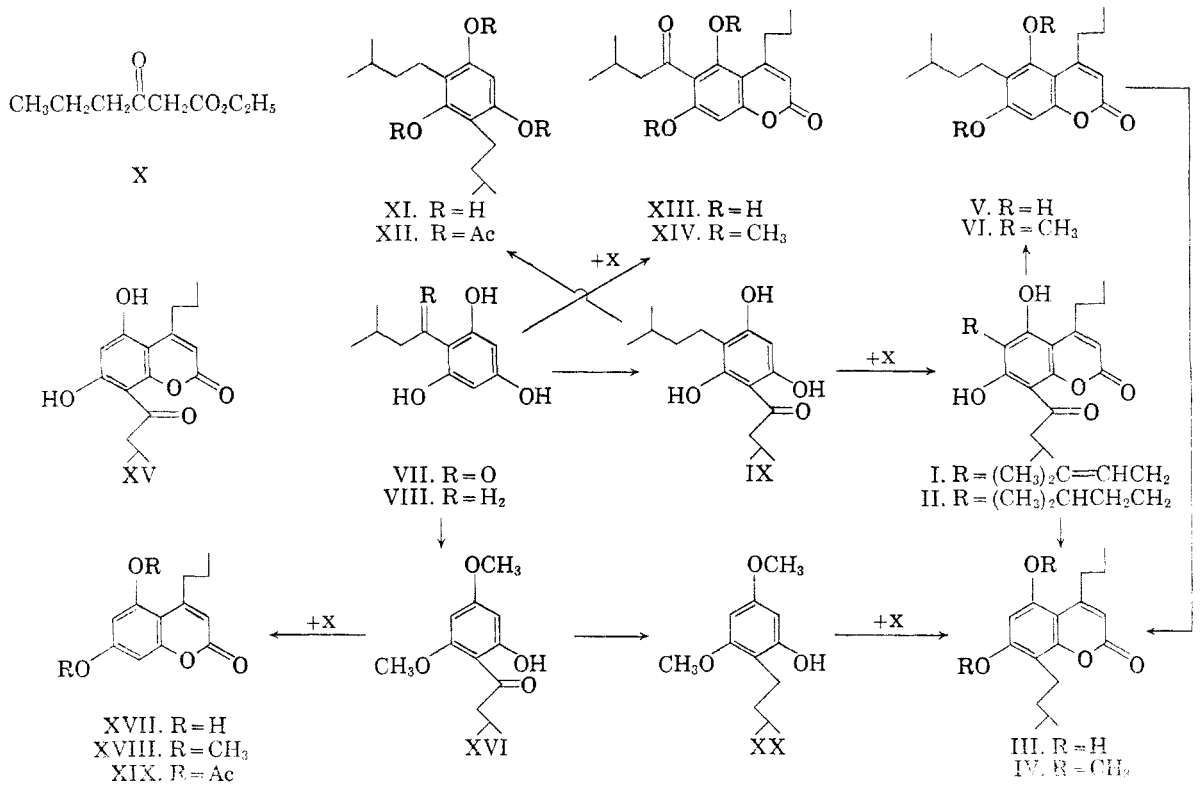
(7) There existed a minor divergence in melting point, but the infrared spectra as well as the x-ray powder diagrams were identical.

(8) The *ortho* hydroxyl group is not methylated, as it is strongly hydrogen bonded to the carbonyl group as demonstrated by the infrared carbonyl absorption at 6.14 μ and the hydroxyl absorption near 3.7 μ. This hydroxyl function is only very weakly acidic and is usually characterized by a purplish-brown ferric chloride reaction. An example of resistance to such methylation with diazomethane is recorded by A. Sonn [*Ber.*, 61, 2300 (1928)] and with methyl iodide (in the presence of potassium carbonate) by F. H. Curd and A. Robertson [*J. Chem. Soc.*, 437 (1933)], who established the structure of their product and also commented upon the ferric chloride test. In the present investigation we employed dimethyl sulfate in order to avoid nuclear methylation [see W. Baker and R. Robinson, *J. Chem. Soc.*, 3115 (1928)].

(9) H. Weidel and J. Pollak, *Monatsh.*, 21, 22 (1900).

(10) N. G. Kotwani, S. M. Sethna, and G. D. Advani, *Proc. Indian Acad. Sci.*, 15A, 441 (1942) report this condensation, but their constants of the 5,7-dihydroxy (XVII), 5,7-dimethoxy (XVIII), and 5,7-diacetoxy (XIX) 4-*n*-propylcoumarins are completely different from ours. We can offer no obvious explanation for this discrepancy.

(11) Several instances of deacylation accompanying the Pechmann condensation of acylresorcinols and α-naphthols are recorded in the literature (ref. 6, pp. 42, 45, 54), but no yields have been reported.



sulfuric acid), deacylation was accompanied by demethylation and 4-*n*-propyl-5,7-dihydroxycoumarin (XVII) was obtained directly.

As Pechmann condensation of 2-hydroxy-4,6-dimethoxyisovalerophenone (XVI) with retention of the acyl substituent failed, the substance was first subjected to Clemmensen reduction and the resulting 2-isopentyl-3,5-dimethoxyphenol (XX) was then condensed with ethyl butyroacetate (X) in acetic acid solution in the presence of concentrated sulfuric acid. The resulting, highly fluorescent 4-*n*-propyl-5,7-dimethoxy-8-isopentylcoumarin (IV) was completely identical with the methylated *base*-catalyzed deacylation product[1] of dihydromammein (II). As there can be no question about the orientation of the isopentyl group of synthetic IV, the *acid*-catalyzed deacylation product of dihydromammein must be V, thus fixing the location of the isopentyl substituent and hence establishing the complete structure of mammein (I).

It is pertinent to note that while the 8-isopentyl derivatives (III, IV) are fluorescent, this does not apply to the 6-isomers (V, VI) and thus affords a ready means of differentiation in chromatographic separations. In order to see whether the 6- and 8-substituted isomers are interconvertible *via* the common coumarinic acid, 4-*n*-propyl-5,7-dihydroxy-6-isopentylcoumarin (V) was kept at room temperature overnight with methanolic potassium hydroxide and then acidified. A combination of crystallization and chromatography, coupled with the striking fluorescence of the 8-isopentyl coumarin III, readily resulted in the separation of both III and V from the reaction medium.

EXPERIMENTAL[12]

Isopentylisovalerylphloroglucinol (IX). Anhydrous aluminum chloride (6.0 g.) was dissolved with swirling in a solution of 7.5 g. of isopentylphloroglucinol (VIII)[4] in 60 cc. of nitrobenzene. The mixture was cooled in an ice-salt bath and isovaleryl chloride (4.5 cc.) was added over a period of 10 min. The mixture was kept in the refrigerator for three days, then poured into ice (100 g.) and 2*N* hydrochloric acid and extracted with ether. After washing with water, 5% sodium bicarbonate and again water, the ether was removed and the residual solution was then submitted to steam distillation until all the nitrobenzene had been distilled. The hot aqueous solution was decanted from the orange residue and on cooling deposited 40 mg. of isopentylisovalerylphloroglucinol as yellow needles. The major portion was obtained by extracting the residue with hexane and then benzene, yielding a total of 2.4 g. (22%). Sublimation at 130–145°/0.02 mm. and recrystallization from benzene raised the m.p. to 168–170.5°; lit.,[5] m.p. 169–170°; $\lambda_{max}^{C_2H_5OH}$ 294, 335 (shoulder) mμ, log ε 4.17, 3.43, $\lambda_{min}^{C_2H_5OH}$ 252 mμ, log ε 3.07; $\lambda_{max}^{C_2H_5OH-NaOH}$ 327 mμ, log ε 4.28, $\lambda_{min}^{C_2H_5OH-NaOH}$ 272 mμ, log ε 3.25.[13]

Diisopentylphloroglucinol triacetate (XII). A solution of 1.0 g. of isopentylisovalerylphloroglucinol (IX) in 25 cc. of methanol was reduced with 16.0 g. of amalgamated zinc and 32 cc. of hydrochloric acid. The zinc and acid were added in small equivalent portions while the mixture was stirred and heated under reflux for 30 hr. Mercury was removed by decantation before the addition of each successive portion. At the end of the reaction, the mixture no longer exhibited an intense ultraviolet absorption peak at 294 mμ,

(12) 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.

(13) For relevant ultraviolet data on acylmethylphloroglucinols see R. A. Morton and Z. Sawires, *J. Chem. Soc.*, 1052 (1950); T. W. Campbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **73**, 2708 (1951).

but showed a weaker maximum at 278 mμ. The methanol was removed *in vacuo* and the product was extracted with ether, washed, dried, and evaporated yielding 0.69 g. of crude diisopentylphloroglucinol (XI).

A portion (0.38 g.) of the phenol was acetylated with 5 cc. of pyridine and 1 cc. of acetic anhydride by keeping at room temperature for 24 hr. and then heating on the steam bath for 5 hr. The crude crystalline triacetate weighed 0.25 g. and after recrystallization from hexane it exhibited m.p. 104.5–105°, $\lambda_{max}^{CHCl_3}$ 5.63 (s), 6.16 (w), 6.24 (w) μ, $\lambda_{max}^{C_2H_5OH}$ 267 mμ, log ε 2.55, $\lambda_{min}^{C_2H_5OH}$ 250 mμ, log ε 2.31.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.34; 3 acetyl, 32.73. Found: C, 67.44; H, 8.44; O, 24.08; acetyl, 31.61.

Pechmann condensation of isopentylisovalerylphloroglucinol (IX) *with ethyl butyroacetate* (X). Isopentylisovalerylphloroglucinol (IX) (0.5 g.) was dissolved in 10 cc. of acetic acid and 0.32 cc. of ethyl butyroacetate (X)[14] was added followed by 0.33 cc. of concd. sulfuric acid. The mixture was allowed to stand in a stoppered flask at room temperature for 6 days, when a sample no longer exhibited the ultraviolet absorption spectrum of the β-keto ester ($\lambda_{max}^{C_2H_5OH-NaOH}$ 275 mμ, log ε 4.5), and was then poured into 40 cc. of water. Extraction with ether, washing with sodium bicarbonate, water, drying, and evaporation yielded 0.54 g. of a red semicrystalline mass which was chromatographed on 20 g. of Merck acid-washed alumina. Elution with benzene, trituration with hexane, and finally repeated recrystallization from hexane afforded 7.5 mg. of nearly colorless crystals, m.p. 133–134.5°, undepressed upon admixture with dihydromammein (II).[15] The infrared spectra and x-ray diffraction patterns[16] were identical. Upon standing for several weeks, the melting point of the synthetic coumarin had risen spontaneously to 136–138°, but we were never able to obtain such a high melting point with natural dihydromammein. Further elution of the column with mixtures of benzene and ether led to 0.27 g. of recovered isopentylisovalerylphloroglucinol (IX).

4-n-Propyl-5,7-dihydroxy-6-isovalerylcoumarin (XIII). Isovalerylphloroglucinol (VII)[4] (2.02 g.) and ethyl butyroacetate (X)[14] (1.75 g.) were dissolved in 40 cc. of acetic acid, 1.33 cc. of concd. sulfuric acid was added with swirling, and the mixture was kept at room temperature for 48 hr., at which time it was filled with colorless needles. These were filtered (1.14 g., m.p. 154–190°) and the filtrate was left standing for an additional 4 days whereupon further material separated (0.41 g., m.p. 184–205°). Purification was best accomplished by partition chromatography on 80 g. of silicic acid and 30 g. of Celite using benzene-ethyl acetate (1:1) saturated with formamide,[17] the substance traveling with the solvent front. The recovery of material with m.p. 212–229° was approximately 50%. The analytical sample crystallized as colorless needles from benzene and isopropyl alcohol, m.p. 228–229°, $\lambda_{max}^{CHCl_3}$ 3.07, 5.80, 6.07, 6.13 μ, $\lambda_{max}^{C_2H_5OH-HCl}$ 281, 323 mμ, log ε 4.36, 4.04, $\lambda_{min}^{C_2H_5OH-HCl}$ 244.5, 308 mμ, log ε 3.46, 3.96; $\lambda_{max}^{C_2H_5OH-NaOH}$ 235, 297, 400 mμ, log ε 4.17, 4.19, 4.08, $\lambda_{min}^{C_2H_5OH-NaOH}$ 228, 262, 329 mμ, log ε 4.16, 3.79, 3.75.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.10; H, 6.62; O, 26.29. Found: C, 67.30; H, 7.02; O, 26.23.

A sample (0.27 g.) of the coumarin XIII was dissolved in 10 cc. of dry acetone, 0.2 cc. of dimethyl sulfate and 1.0 g. of anhydrous potassium carbonate were added, and after heating under reflux for 1.5 hr. an additional 0.07 cc. of dimethyl sulfate and 0.5 g. of potassium carbonate were added. Refluxing was continued for a total of 24 hr., the cooled solution was filtered and the acetone evaporated to give 0.36 g. of crystalline residue. Recrystallization from hexane afforded colorless plates and needles (0.20 g.) of *4-n-propyl-5,7-dimethoxy-6-isovalerylcoumarin* (XIV), m.p. 90–91.5°, $\lambda_{max}^{CHCl_3}$ 5.81, 5.86, 6.23 μ, $\lambda_{max}^{C_2H_5OH}$ 245 (shoulder), 319 mμ, log ε 3.87, 4.01, $\lambda_{min}^{C_2H_5OH}$ 272 mμ, log ε 3.58.

Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28; O, 24.07; 2 OCH_3, 18.66. Found: C, 68.54; H, 7.75; O, 23.42; OCH_3, 19.31.

4-n-Propyl-5,7-dihydroxy-6-isopentylcoumarin (V). Zinc dust (3.0 g.) was stirred with 2.4 cc. of water and amalgamated by the addition of a solution of 0.3 g. of mercuric chloride in 0.15 cc. of hydrochloric acid and 1.8 cc. of water. After stirring for 2 hr., the zinc was washed with water and a solution of 1.6 g. of 4-*n*-propyl-5,7-dihydroxy-6-isovalerylcoumarin (XIII) in 45 cc. of hot methanol was added, followed by 6.0 cc. of concd. hydrochloric acid. The mixture was heated under reflux with stirring for 1 hr., then decanted, concentrated *in vacuo*, diluted with water, and extracted with ether. The ether extracts were washed with 5% sodium bicarbonate, water, dried, and evaporated to give 1.63 g. of resin which on trituration with hexane-ether (10:1) led to 1.34 g. of crystals, m.p. 167–182°. One recrystallization from benzene-ethanol afforded 0.63 g. of product of m.p. 181.5–184.5°. The analytical sample was obtained as light buff colored crystals after repeated recrystallization from ether-heptane (Norit) and dilute isopropanol; m.p. 183.5–186°, λ_{max}^{KBr} 2.80, 2.98, 3.14 (doublet), 5.97, 6.22, 6.37 μ, $\lambda_{max}^{C_2H_5OH}$ 248 (shoulder), 258, 329 mμ, log ε 3.80, 3.76, 4.20, $\lambda_{min}^{C_2H_5OH}$ 254.5, 269 mμ, log ε 3.74, 3.07; $\lambda_{max}^{C_2H_5OH-NaOH}$ 279.5, 383 mμ, log ε 3.94, 4.12, $\lambda_{min}^{C_2H_5OH-NaOH}$ 269.5, 302 mμ, log ε 3.88, 2.94. The coumarin did not fluoresce in ethanol solution.

Anal. Calcd. for $C_{17}H_{22}O_4 \cdot H_2O$: C, 66.21; H, 7.85. Found: C, 66.45; H, 7.98.

Methylation of a sample of this coumarin was effected as described above with dimethyl sulfate in acetone solution in the presence of freshly roasted potassium carbonate. The crude 4-*n*-propyl-5,7-dimethoxy-6-isopentylcoumarin (VI) was chromatographed on Merck acid-washed alumina and eluted with 1:1 hexane-benzene. Recrystallization from aqueous methanol provided the analytical sample with m.p. 51–53°, $\lambda_{max}^{CHCl_3}$ 5.83, 6.23, 6.44 μ, $\lambda_{max}^{C_2H_5OH}$ 226, 244 (shoulder), 253.5, 327 mμ, log ε 4.21, 3.71, 3.47, 4.10, $\lambda_{min}^{C_2H_5OH}$ 220.5, 251.5, 263 mμ, log ε 4.20, 3.46, 2.84. The substance exhibited no fluorescence in ethanol solution.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23; O, 20.10; 2 OCH_3, 19.49. Found: C, 71.52; H, 8.05; O, 19.91; OCH_3, 20.08.

Base-catalyzed isomerization of 4-n-propyl-5,7-dihydroxy-6-isopentylcoumarin (V). *Isolation of 4-n-propyl-5,7-dihydroxy-8-isopentylcoumarin* (III). 4-*n*-Propyl-5,7-dihydroxy-6-isopentylcoumarin (V) (194 mg.) and 373 mg. of potassium hydroxide were dissolved in 6.8 cc. of methanol and the dark colored reaction mixture was allowed to stand at room temperature for 22 hr. before dilution with water, acidification, and extraction with ether. The yellow ether extracts after drying and evaporation afforded 176 mg. of yellowish oil. Digestion with hexane-chloroform produced 47 mg. of nearly white crystals, m.p. 225–235°, which

(14) This ester was prepared by the following the directions of F. B. LaForge, N. Green, and W. A. Gersdorff, *J. Am. Chem. Soc.*, **70**, 3707 (1948) [see also S. B. Soloway and F. B. LaForge, *J. Am. Chem. Soc.*, **69**, 2677 (1947)] for ethyl 3-oxo-6-octenoate. A similar procedure was employed by M. Jackman, M. Klenk, B. Fishburn, B. F. Tullar, and S. Archer, *J. Am. Chem. Soc.*, **70**, 2884 (1948), but they used less than the necessary two moles of sodium hydride for maximum yields. Purification of the β-keto ester was effected through its copper salt [M. Montagne, *Bull. Soc. Chim. France*, 63 (1946)] according to the method of J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1220 (1944).

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

(16) Courtesy of Dr. R. T. Rapala, Eli Lilly and Co., Indianapolis, Ind.

(17) For details see D. Lavie and D. Willner, *J. Am. Chem. Soc.*, **80**, 710 (1958).

fluoresced strongly in ethanol solution. Recrystallization from chloroform-methanol raised the m.p. to 240–241°, undepressed upon admixture of 4-*n*-propyl-5,7-dihydroxy-8-isopentylcoumarin (III) derived[1] from dihydromammein (II); λ_{max}^{KBr} 3.08, 6.02, 6.25, 6.38 μ, $\lambda_{max}^{C_2H_5OH}$ 258 (shoulder), 264.5, 326 mμ, log ϵ 3.96, 4.03, 4.09, $\lambda_{min}^{C_2H_5OH}$ 244, 276 mμ, log ϵ 3.60, 3.09; $\lambda_{max}^{C_2H_5OH-NaOH}$ 284, 374 (shoulder), 403 mμ, log ϵ 4.13, 4.00, 4.05, $\lambda_{min}^{C_2H_5OH-NaOH}$ 267, 307 mμ, log ϵ 3.92, 3.25.

From the mother liquors, there was isolated 25 mg. of nonfluorescent granular crystals, m.p. 169–185°, which after recrystallization from aqueous methanol exhibited m.p. 183.5–186° and was identical with the starting material V. Chromatography of the combined mother liquors (117 mg.) afforded an additional 18 mg. of V and 37 mg. of III.

2-Hydroxy-4,6-dimethoxyisovalerophenone (XVI). Isovalerylphloroglucinol (VII)[4] (2.1 g.) was dissolved in 50 cc. of dry acetone and treated with 1.87 cc. of dimethyl sulfate and 3.0 g. of freshly roasted potassium carbonate. The mixture was heated under reflux for 6 hr., then filtered, and the solvent evaporated. The resulting oil was chromatographed on 50 g. of Merck acid–washed alumina and eluted with hexane and hexane-benzene (1:1), giving 2.3 g. of crystalline solid. Two recrystallizations from hexane (cooling in Dry Ice) afforded material with m.p. 46–49°, which was used for the subsequent step, while the analytical sample was recrystallized several times until a constant m.p. of 50–50.5° was reached; purple-brown color with ethanolic ferric chloride solution, $\lambda_{max}^{CHCl_3}$ 2.82 (w), 3.6–3.85 (w), 6.14, 6.27 μ, $\lambda_{max}^{C_2H_5OH}$ 298 mμ, log ϵ 4.11, $\lambda_{min}^{C_2H_5OH}$ 245 mμ, log ϵ 2.59, $\lambda_{max}^{C_2H_5OH-NaOH}$ 238, 286, 335 mμ, log ϵ 4.00, 3.65, 3.47, $\lambda_{min}^{C_2H_5OH-NaOH}$ 263, 310 mμ, log ϵ 3.26, 3.37.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61; O, 26.86; 2 OCH_3, 26.05. Found: C, 65.45; H, 7.76; O, 26.44; OCH_3, 26.13.

2-Isopentyl-3,5-dimethoxyphenol (XX). 2-Hydroxy-4,6-dimethoxyisovalerophenone (XVI) (2.9 g., m.p. 46–49°) in 30 cc. of methanol was added to amalgamated zinc (prepared by shaking for 20 min. 4.0 g. of mossy zinc with a solution consisting of 5 cc. of water, 0.5 cc. of concd. hydrochloric acid, and 0.25 g. of mercuric chloride, followed by decantation and washing). Hydrochloric acid (1.5 cc.) was added and the mixture was heated under reflux for 5 hr. When processed in the usual manner, infrared inspection of the crude total product indicated that it still contained a large amount of starting material and the entire lot was redissolved in 25 cc. of methanol and 2.5 cc. of hydrochloric acid and heated under reflux with 8 g. of amalgamated zinc, hydrochloric acid (0.5 cc.) being added after 3, 15, 23, 28, and 40 hr. The resulting oil crystallized immediately upon scratching and its infrared spectrum was virtually identical with that of its analytical sample. Five recrystallizations from hexane (once with Norit) afforded 360 mg. of colorless needles, m.p. 55.5–56.5° and from the mother liquors 600 mg. of lower melting (51–54.5°) crystals. A specimen of the higher melting fraction was dried at 25°/0.05 mm. for 12 hr., whereupon it exhibited m.p. 56–57°.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.49; H, 8.83.

4-n-Propyl-5,7-dimethoxy-8-isopentylcoumarin (IV). 2-Isopentyl-3,5-dimethoxyphenol (XX) (330 mg.) and ethyl butyroacetate (X) (0.4 cc.) were dissolved in 5 cc. of acetic acid and 0.3 cc. of concd. sulfuric acid; the dark red solution was allowed to stand at room temperature for 72 hr. before diluting with water and filtering. Two recrystallizations from hexane afforded 253 mg. of the coumarin IV (highly fluorescent in ethanol solution), m.p. 108.5–109.5°. Mixture melting point determination and ultraviolet as well as infrared spectral comparison demonstrated complete identity with samples derived from mammein,[1] dihydromammein, or a specimen obtained by methylation of the above described 4-*n*-propyl-5,7-dihydroxy-8-isopentylcoumarin (III) isolated from the alkaline isomerization of the synthetic 4-*n*-propyl-5,7-dihydroxy-6-isopentylcoumarin (V).

4-n-Propyl-5,7-dihydroxycoumarin (XVII). (*a*) *By Pechmann condensation*[10] *of phloroglucinol with ethyl butyroacetate* (X). A mixture of 2.0 g. of phloroglucinol, 2.0 g. of ethyl butyroacetate (X),[14] and 20 cc. of cold 75% aqueous sulfuric acid was stirred at room temperature for 1.5 hr., at which time the mixture became homogeneous. Shortly thereafter, a yellow precipitate formed and, after stirring for 3 hr., the mixture was poured onto ice and the yellow solid (m.p. 184–230°) filtered. Three recrystallizations from aqueous ethanol afforded 1.40 g. of very light tan needles, m.p. 227–233°, while the analytical sample exhibited m.p. 230–234°, λ_{max}^{KBr} 3.12, 6.04, 6.17, 6.38 μ.

Anal. Calcd. for $C_{12}H_{12}O_4 \cdot H_2O$: C, 60.50; H, 5.92. Found: C, 60.92; H, 5.79.

(*b*) *By Pechmann condensation of 2-hydroxy-4,6-dimethoxyisovalerophenone* (XVI) *with ethyl butyroacetate* (X). The Pechmann condensation of 2.0 g. of 2-hydroxy-4,6-dimethoxyisovalerophenone (XVI) was conducted exactly as described under (a) with phloroglucinol except that the reaction time was extended to 4 days. The once recrystallized (methanol-chloroform) solid showed m.p. 219–232°, while recrystallization from aqueous ethanol afforded tan needles, m.p. 224–233°, which proved to be identical by mixture melting point determination and infrared comparison with the above described sample of 4-*n*-propyl-5,7-dihydroxycoumarin (XVII).

4-n-Propyl-5,7-dimethoxycoumarin (XVIII). (*a*) *By methylation of 4-n-propyl-5,7-dihydroxycoumarin* (XVII). A mixture of 0.5 g. of 4-*n*-propyl-5,7-dihydroxycoumarin (XVII), 20 cc. of dry acetone, 2.0 g. of anhydrous potassium carbonate, and 0.5 cc. of dimethylsulfate was heated under reflux for 1 hr. (note reduced reaction time as compared with 6- or 8-isopentyl derivatives), filtered, and the filtrate evaporated. The yellow crystalline solid was recrystallized three times from chloroform-hexane to produce 246 mg. of colorless crystals of the dimethyl ether XVIII,[10] m.p. 113.5–115°, which was identical (mixture melting point, infrared spectrum) with the sample described below.

(*b*) *By Pechmann condensation of 2-hydroxy-4,6-dimethoxyisovalerophenone* (XVI) *with ethyl butyroacetate* (X). To a solution of 5.20 g. of 2-hydroxy-4,6-dimethoxyisovalerophenone (XVI) and 4.01 g. of ethyl butyroacetate (X) in 80 cc. of glacial acetic acid was added 5.0 cc. of concd. sulfuric acid. The mixture was kept at room temperature for 6.5 days, then heated on the steam bath for 7.5 hr. before pouring onto ice water. The product was isolated by means of ethyl acetate and the crude tarry material (5.0 g.) was dissolved in ether and filtered through Merck acid–washed alumina. The dark amber resin obtained after evaporation of the ether solution was then chromatographed on 100 g. of Merck acid–washed alumina. The early 1:1 hexane-benzene eluates yielded an oil which crystallized on cooling; three recrystallizations from hexane gave 10 mg. of phloroglucinol monomethyl ether,[9] m.p. 78–79°. From the benzene-hexane eluates (3:2; 9:1) there was obtained 1.2 g. of colorless solid, m.p. 90–110° (fluorescent in ethanol solution), which was recrystallized twice from chloroform-hexane to yield shiny needles, m.p. 114–115°, $\lambda_{max}^{CS_2}$ 5.76, 6.20 μ (doublet), $\lambda_{max}^{CHCl_3}$ 5.86, 6.23 μ (doublet).

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50; O, 25.78; 2 OCH_3, 25.60. Found: C, 67.64; H, 6.58; O, 25.47; OCH_3, 24.70.

4-n-Propyl-5,7-diacetoxycoumarin (XIX).[10] Acetylation of XVII with acetic anhydride and pyridine (12 hr., room temperature) and recrystallization from ether-hexane provided colorless needles, m.p. 105–107°, $\lambda_{max}^{CHCl_3}$ 5.64, 5.79, 6.18, 8.35 μ.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.86; H, 5.22.

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