NATURALLY OCCURRING OXYGEN HETEROCYCLICS V. [1]

MAMMEIN

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RECENT papers have been concerned with the isolation [2] and characterization [3] of mammein, a crystalline insecticidal constituent of the seeds of Mammea americana L. We should now like to record certain observations which lead to the assignment of structure I to this substance. Mammein represents the first naturally occurring coumarin [4] with a n-propyl substituent at C-4 and it is also interesting to note that a number of synthetic coumarins have been shown to exhibit insecticidal activity.[5]

Dihydromammein (II), in which the isopropylidene double bond [3] of mammein (I) has been reduced, upon heating with 5% aqueous alkali led to

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[1] Paper IV: D. Herbst, W. B. Mors, O.R. Gottlieb and C. Djerassi, J. Amer. Chem. Soc. 81, in press (1959).

[2] M. P. Morris and C. Pagan, J. Amer. Chem. Soc. 75, 1489 (1953).

[3] C. Djerassi, E. J. Eisenbraun, B. Gilbert, A. J. Lemin, S. P. Marfey and M. P. Morris, J. Amer. Chem. Soc. 80, 3686 (1958).

[4] For pertinent reviews see: F. M. Dean in L. Zechmeister's, Progress in the Chemistry of Organic Natural Products Vol. IX, pp. 225-291. Springer, Vienna (1952); L. Reppel, Pharmazie 9, 278 (1954); W. Karrer, Konstitution und Vorkommen der organischen Pflanzenstoffe, pp. 532-562 Birkhäuser, Basel (1958).

[5] P. Lauger, H. Martin and P. Müller, Helv. Chim. Acta 27, 892 (1944).

methyl n-propyl ketone,[6] isovaleric acid and isovalerylphloroglucinol (V).[7] These three cleavage products account for 21 out of the 22 carbon atoms of mammein and, together with the earlier reported [3] spectral results, suggest strongly that mammein is a substituted coumarin. Methylation of the residual material, after removal of the above cleavage products, furnished a crystalline, fluorescent dimethyl ether, m.p. 109-109.5°, of the composition $C_{19}H_{26}O_4$, whose ultraviolet absorption spectrum was virtually superimposable upon that [8] of 5,7-dimethoxycoumarin. The structure (XII) of this crucial degradation product was established by the following synthetic sequence:

Pechmann condensation of isovaleroylphloroglucinol (VII)[7] with ethyl butyroacetate (VIII) furnished 4-n-propyl-5, 7-dihydroxy-6-isovaleroylcoumarin (IX) [9] (m.p. 228-229°; found: C, 67.30; H, 7.32; O, 26.23. $C_{17}H_{20}O_5$ requires C, 67.09; H, 6.62; O, 26.29), which was transformed by Clemmensen reduction into 4-n-propyl-5,7-dihydroxy-6-isovalerylcoumarin (X) (m.p. 183.5-186°; found: C, 66.45; H, 7.98. $C_{17}H_{22}O_4 \cdot H_2O$ requires C, 66.21; H, 7.85.) Methylation with dimethyl sulfate and potassium carbonate provided the non-fluorescent 4-n-propyl-5, 7-dimethoxy-6-isovalerylcoumarin (XI) (m.p. 51-53°; found: C, 71.52;

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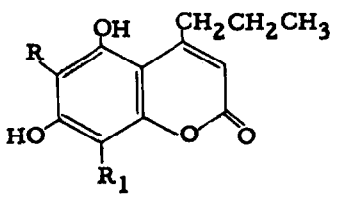
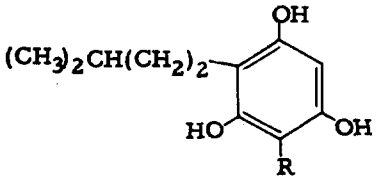
[6] This substance was first isolated in this laboratory by Dr. S.P. Marfey.

[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).

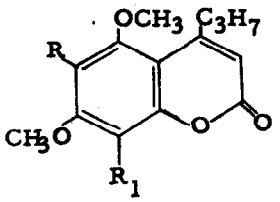
[9] We believe that ring closure in the direction of IX (rather than yielding the isomeric 8-isovaleroyl coumarin) is favored by steric considerations as well as by hydrogen bonding between the carbonyl group and the two ortho-hydroxyl groups.

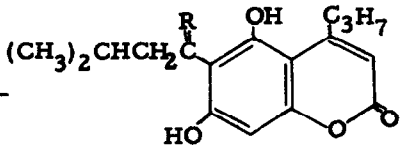




I R=$(CH_3)_2C{=}CHCH_2$; R_1=$(CH_3)_2CHCH_2CO$
II R=$(CH_3)_2CHCH_2CH_2$; R_1=$(CH_3)_2CHCH_2CO$
III R=$(CH_3)_2CHCH_2CO$; R_1=$(CH_3)_2C{=}CHCH_2$
IV R=R_1=$(CH_3)_2CHCH_2CH_2$; OH=$OCOCH_3$

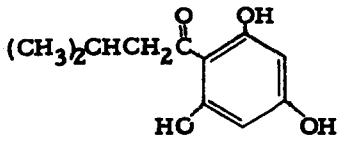
V R=H
VI R=$(CH_3)_2CHCH_2CH_2$





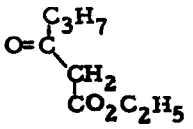
XI R=$(CH_3)_2CHCH_2CH_2$; R_1=H
XII R=H; R_1=$(CH_3)_2CHCH_2CH_2$

IX R=O
X R=H_2



VII

+



VIII

H, 8.05; O, 19.91; OCH_3, 20.08. $C_{19}H_{26}O_4$ requires C, 71.67; H, 8.23; O, 20.40; 2 OCH_3, 19.49), while alkaline opening of X followed by acidification and methylation with dimethyl sulfate afforded XI as well as the fluorescent isomer 4-n-propyl-5, 7-dimethoxy-8-isovalerylcoumarin (XII) (m.p. 109-110°). The latter proved to be identical with the alkali cleavage product $C_{19}H_{26}O_4$ (Found: C, 71.59; H, 8.35; O, 29.41; OCH_3, 19.93) of dihydromammein (II), thus establishing the presence of a coumarin skeleton and the nature of the substituents at positions 4,5 and 7 of mammein. The identification of the cleavage product with the synthetic 4-n-propyl-5, 7-dimethoxy-8-isovalerylcoumarin (XII) does not necessarily imply that the isovaleryl group in dihydromammein (II) was also situated in the same position, since the coumarinic acid generated in the alkaline cleavage reaction could have cyclized in two directions as was found to be the case with synthetic X.

In order to demonstrate that both the isovaleroyl and the isopentenyl groups of mammein (I) were located in the aromatic ring, dihydromammein (II) was subjected to Clemmensen reduction followed by acetylation and the resulting 4-n-propyl-5, 7-diacetoxy-6, 8-di-isovalerylcoumarin (IV) m.p. 103-107°; found: C, 70.59; H, 8.10; O, 21.51. $C_{26}H_{36}O_6$ requires C, 70.24; H, 8.16; O, 21.59) was heated with alkali. Acetylation of the phenolic component of this cleavage led to the triacetate of di-isovalerylphloroglucinol (VI), which was synthesized by Clemmensen reduction of isovaleryl-isovaleroylphloroglucinol [10] followed by acetylation (m.p. 104.5-105°; found: C, 67.44; H, 8.44; O, 24.08; CH_3CO, 31.61. $C_{22}H_{34}O_6$ requires C, 66.98; H, 8.69; O, 24.34; 3 CH_3CO, 32.73).

The above reactions require that mammein be represented either by

[10] W. Riedl, Ber. 85, 692 (1952).

structure I or III. We have already reported [3] that treatment of mammein at room temperature with base followed by acidification furnished a yellow isomer, isomammein, which is clearly the product arising from alternate ring closure of the intermediate coumarinic acid. For mechanistic reasons[11] (hydrogen bonding of the hydroxyl groups ortho to the isovaleroyl group in the coumarinic acid favoring ring closure in the alternate direction) and because of the similarity of the ultraviolet absorption spectra of isomammein dimethyl ether [3] and 4,8-dimethyl-5, 7-dimethoxy-6-acetyl-coumarin,[12] we assign structure III to isomammein, from which it follows that mammein is 4-n-propyl-5, 7-dihydroxy-6-isopentenyl-8-isovaleroyl-coumarin (I).

Work on other constituents of Mammea americana L. is in progress.[13]

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[11] M. Crawford and J. W. Rasburn, J. Chem. Soc. 2155 (1956); R. M. Naik and V. M. Thakor, J. Org. Chem. 22, 1240 (1957).

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

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