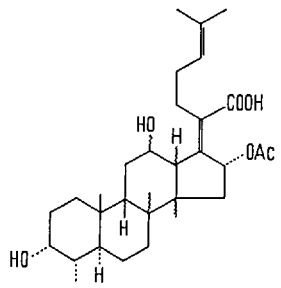
The Location of the Ring C Hydroxyl Group in Fusidic Acid

In a previous paper[1] structure I was proposed for the antibiotic fusidic acid. The localization of the axial hydroxyl group in ring C was based upon the formation of an ene-dione on base-catalyzed elimination of acetic acid



I

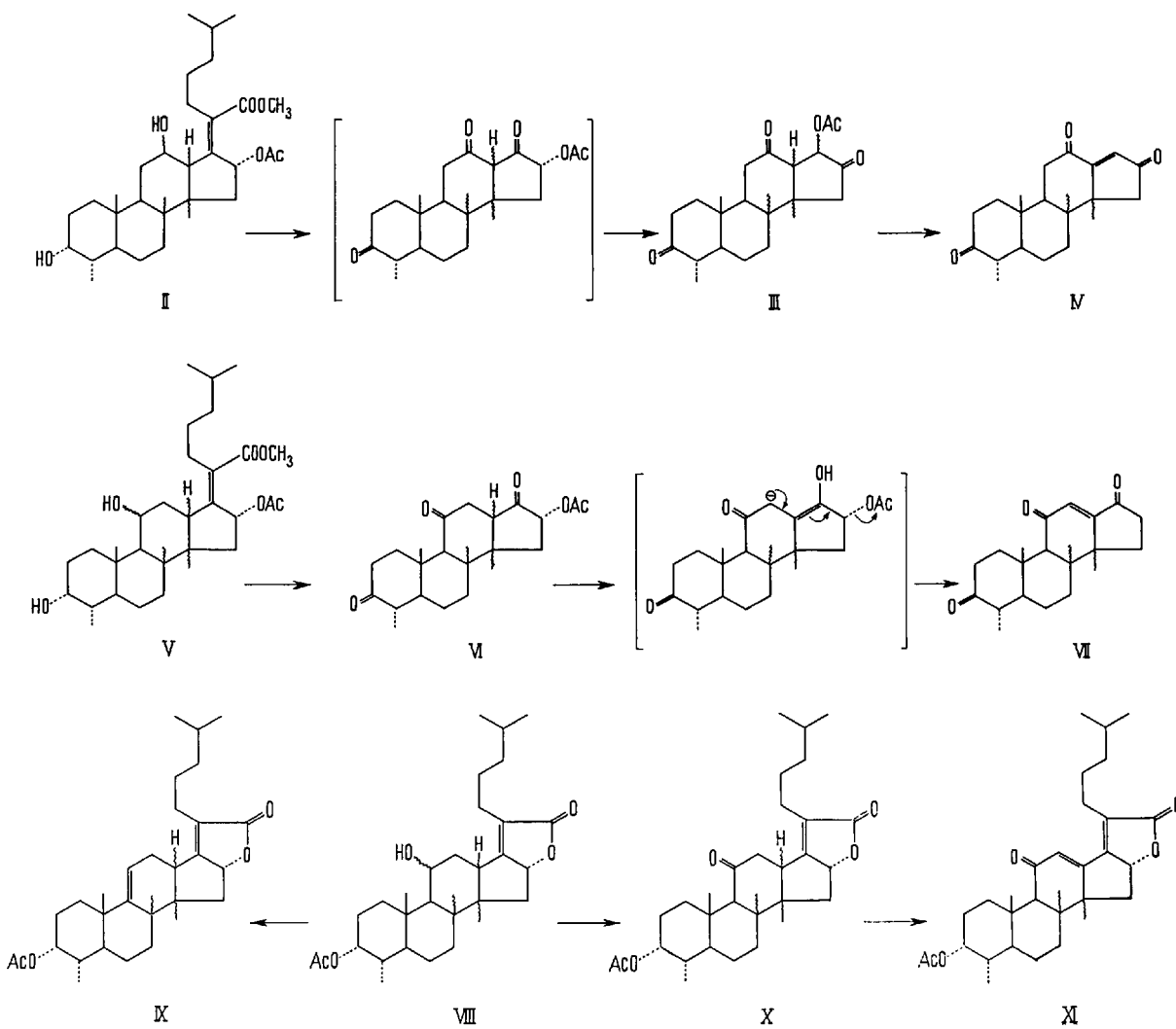
from a compound obtained on ozonolysis of dihydrofusidic acid methyl ester. It was supposed[1] that this sequence of reactions proceeded according to scheme II → IV. The formation of an ene-dione may, however, equally well be rationalized by assuming the presence of a hydroxyl group at C_{11} (scheme V → VII) and the following observations indicate that the latter interpretation is the correct one:

(i) It can be shown by the double irradiation technique[2] that in the NMR-spectrum[3] of dihydrofusidic acid methyl ester (V) there is no spin–spin interaction between the protons on the carbon atoms bearing hydroxyl groups (δ = 3.80 and 4.40) and the C_{18}-proton (δ = 3.02).

(ii) Dehydration of 16-deacetyldihydrofusidic acid lactone 3-acetate (VIII)[1] with thionylchloride/pyridine at −20°C gave a compound IX[4] containing only one olefinic proton (NMR-spectrum[5]: signal at δ = 5.50) and having the same chromophore as VIII.

(iii) Chromium (VI) oxide oxidation of VIII to the corresponding ketone X, followed by selenium dioxide dehydrogenation in tert. butanol-acetic acid (99:1) afforded an

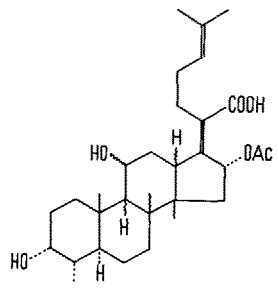
[1] W. O. Godtfredsen and S. Vangedal, Tetrahedron *18*, 1029 (1962).
[2] R. Freeman and D. Whiffen, Mol. phys. *4*, 321 (1961).
[3] Measured with a Varian HR-60 spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in δ-values.
[4] The physical data for the compounds VIII–XI are given in the Table. All compounds gave satisfactory microanalyses and the IR-spectra are consistent with the given structures.
[5] Measured with a Varian A-60 spectrometer in $CDCl_3$ solution.



α,β-unsaturated ketone, the UV-spectrum of which indicates an extended conjugation consistent with formula XI. A compound with a similar chromophore was obtained on analogous treatment of the 16-θ-acetyl methyl ester corresponding to X.

A more direct proof for the presence of a hydroxyl group at C_{11} based upon ozonolysis of a 16-unsubstituted derivative of fusidic acid will be published in a forthcoming paper.

The arguments for the absence of a methyl group at C_9 previously set forth[1] are no longer valid in view of the new location of the hydroxyl group. However, the presence of a hydrogen atom at C_9 can now be deduced from the formation of the Δ^{9-11} compound IX as well as from the previously reported[1] experiments on the base catalyzed epimerization of derivatives of fusidic acid containing a carbonyl group in ring C. Fusidic acid is consequently believed to be represented by formula XII.



XII

Compound		M.p.	UV-spectrum (EtOH) λ max (mμ)	ε	$[\alpha]^D(CHCl_3)$
VIII	$C_{31}H_{48}O_5$	183–184°	223	14000	+ 44°
IX	$C_{31}H_{46}O_4$	143–144°	221	15500	+ 26°
X	$C_{31}H_{46}O_5$	153–154°	222	13800	+113°
XI	$C_{31}H_{44}O_5$	188–189°	280	17500	−358°

Zusammenfassung. Durch Herstellung der zwei Verbindungen IX und XI wurde erwiesen, dass die Hydroxylgruppe im Ring C der Fusidinsäure an C_{11} haften muss. Daraus sowie aus früheren Experimenten[1] lässt sich für die Fusidinsäure die revidierte Konstitutionsformel XII ableiten.

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A Group of Fatty Acids with 'Tetramethylene Interruption' in the Double Bond System[1]

Lipids from leaves and nuts of the tree *Ginkgo biloba* contain several C_{20} and C_{18} acids with double bonds in a 1,7 position relative to each other. In analogy to methylene-interrupted double bonds, they may be called 'tetramethylene-interrupted'. The group of isomers represents about 10% of the fatty acids in Ginkgo and includes nearly all the C_{20} acids. Oleic, linoleic and linolenic acids represent the greater part of the C_{18} acids; however, the isomers are present in the C_{18} series too, while they have not been found with the C_{16} chain length.

DAVIDOFF and KORN[2] found *cis,cis*-5,11-octadecadienoic acid as a major lipid constituent of the slime mold *Dictyostelium discoideum*, and BAGBY *et al.*[3] have reported *cis, cis*-5,13-docosadienoic acid from seed oil of the tree *Limmanthes douglasii*. Because several acids with such an unusual system of double bonds were detected in Ginkgo, a detailed examination of their structure and biosynthesis has been undertaken. As a first step in this direction, we report here the composition and identification of the fatty acids of *Ginkgo biloba*.

The methyl esters were fractionated by liquid–liquid chromatography[4] and gas–liquid chromatography[5,6], and the individual esters or mixtures of isomers were identified by ozonization procedures before and after alkaline isomerization. One of the structure determinations is outlined as an example. A methyl ester had been tentatively identified as an eicosatrienoate according to LLC and GLC retentions. Ozonization-reduction[7] of this ester gave a C_5 aldehyde-ester and a C_6 aldehyde which were identified by GLC. Thereby, the position of the extreme double bonds at carbons 5 and 14 were demonstrated. The fragments between these double bonds were identified by ozonization-oxidation[8]. After esterification of the resulting acids, GLC showed dimethyl adipate and glutarate in equivalent amounts. Malonate was also detected. These results locate the internal double bond at either position 8 or 11.

The exact location of this double bond can be established by alkaline isomerization and subsequent ozonization. It was shown that linoleic acid, after alkaline isomerization under standard conditions[9], yielded by ozonization-reduction C_6 and C_7 aldehydes and C_9 and C_{10} aldehyde-esters in equivalent amounts. Oleic acid remained unchanged under the isomerization conditions. Therefore, conjugation of double bonds interrupted with one methylene group proceeds equally from both sides of the unsaturated system, while an isolated double bond is

[1] This work has been supported by a research grant from the National Institutes of Health (USPHS AM-05165) and by the Hormel Foundation.

[2] F. DAVIDOFF and E. KORN, Biochem. Biophys. Res. Comm. *9*, 44, 54 (1962).

[3] M. O. BAGBY, C. R. SMITH, T. K. MIWA, R. L. LOHMAR, and I. A. WOLFF, J. Org. Chem. *26*, 1261 (1961).

[4] H. SCHLENK and J. GELLERMAN, J. Amer. Oil Chemists' Society *38*, 555 (1961).

[5] H. SCHLENK, J. GELLERMAN, and D. SAND, Anal. Chem. *34*, 1529 (1962).

[6] H. SCHLENK and D. SAND, Anal. Chem. *34*, 1676 (1962).

[7] H. SCHLENK et al., to be published.

[8] E. KLENK and W. BONGARD, Hoppe-Seyler's Z. *290*, 181 (1952).

[9] R. HOLMAN and H. HAYES, Anal. Chem. *30*, 1422 (1958).