and XV seems to be 4-en-3-one compound from its ultraviolet spectrum. The nuclear magnetic resonance spectra were also measured and given in Table II.

TABLE II.

Compound	Solvent	Signal (τ)			
		18-CH_3	19-CH_3	21-CH_3	
I	pyridine	9.25	8.45	8.57	
I+I′	〃	9.20	8.34	8.48	5.60 (d, C-6 H) 4.25 (s, broad)
V+XIII	〃	9.15	8.40		5.97 (q, C-6 H) 4.25 (s)

These data also support the presence of Δ^5 in I′. Since sarcostin has been isolated from the same plant, biogenetic analogy would favor Δ^5-structure. Above evidences suggest the probable structure of I for tomentogenin (5α-dihydroutendin) and I′ for dehydrotomentogenin (utendin). Prof. Reichstein established the structure of utendin mainly on the basis of structural relation to digoxigenin.*1

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Selective Oxidation of the C_1- or C_{12}-Methyl Group in Antipodal Deoxypodocarpic Acid Type Compounds*1~*3

Selective oxidation of the C_1- or C_{12}-methyl group of the antipodal deoxypodocarpic acid type compounds, which was derived from abietic acid (I), would be a stimulating problem, for these oxidized compounds could be regarded as potential intermediates for syntheses of many kinds of natural diterpenoids. Now we like to report the syntheses of these oxidized compounds shown as XIX and XX.

The ester (III)[1], derived from abietic acid (I), was readily hydrogenated including hydrogenolysis (Pd-C, EtOAc, H_2SO_4) to 10β-acetoxy ester (V), NMR (τ)*4 : 8.73 (C_1-CH_3),

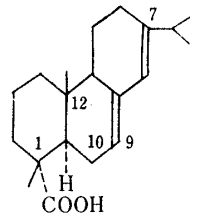
*1 This communication will be published in detail as Diterpenoids V. Part IV : Sci. Papers Inst. Phys. Chem. Res., 58, 15 (1964).

*2 This work was presented at the International Symposium on the Chemistry of Natural Products held at Kyoto, Japan, on April 16, 1964. (Symposium Abstracts, p. 41-2)

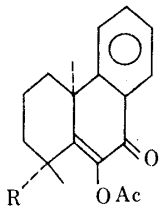
*3 All analytical values were in good agreement with the molecular formula shown. All melting points (except m. m. p.) were measured on the Kofler block and were uncorrected. All NMR spectra were measured at 60 Mc. (Varian Model A-60) in $CDCl_3$ *vs.* Me_4Si as internal reference. (Authors thank to Dr. K. Takeda and Dr. K. Tori, Shionogi & Co., Ltd., Osaka, for the NMR measurements and also to Dr. Y. Kawazoe, National Cancer Center, Tokyo, for his discussion on them.

*4 All assignments of the chemical shifts for methyl group of these compounds in this communication will be discussed in detail in our future report.

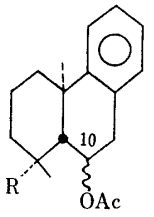
1) A. Tahara, O. Hoshino, Y. Hamazaki : This Bulletin, **11**, 1328 (1963).



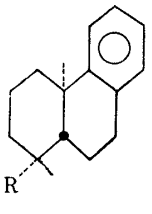
abietic acid(I)



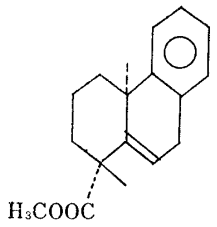
II : R=CN
III : R=COOCH$_3$



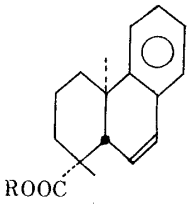
IV : R=CN *5,2)
(C_{10}–OAc; α)
V : R=COOCH$_3$
(C_{10}–OAc; β)



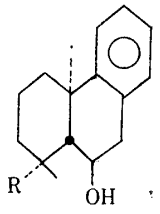
VI : R=CN
VII : R=COOCH$_3$
VIII : R=COOH



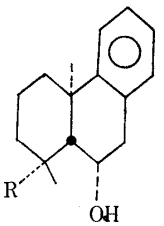
IX



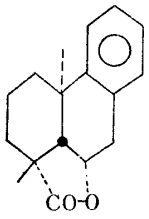
X : R=CH$_3$
XI : R=H



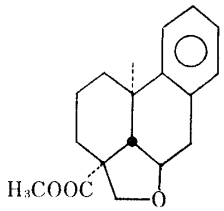
XII : R=COOH
XIII : R=COOCH$_3$
XIV : R=CH$_2$OH



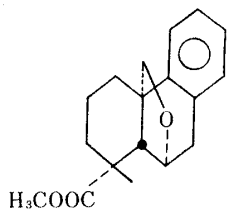
XV : R=COOH
XVI : R=COOCH$_3$
XVII : R=CH$_2$OH



XVIII



XIX



XX

8.98 (C_{12}–CH_3) and the authentic methyl deoxypodocarpate enantiomer (VII),[2] NMR (τ) (standard) : 8.73 (C_1–CH_3), 8.97 (C_{12}–CH_3) under the same condition as Wenkert and coworkers firstly reported[2] (nitril (II) ⟶ α-acetoxy nitril IV*5+VI).

Pyrolysis (290~300°) and deacetic acid reaction (AcOH, H_2SO_4, 80°) of V gave conjugated double bond ester (X), $C_{18}H_{22}O_2$, m.p. 79°, UV λ_{max}^{EtOH} mμ (ε) : 264 (8600), NMR (τ) : 3.57 (singlet, 2H, C_6H_5–C(H)=C(H)–C(H)–), 7.60 (singlet, 1H, C_6H_5–C(H)=C(H)–C(H)–), GC*6 and unconjugated double bond ester (IX), $C_{18}H_{22}O_2$, m.p. 121°, UV λ_{max}^{EtOH} mμ (ε) : 273 (600), 267 (670), 260 580), NMR (τ) : 4.02 (triplet, 1H, >C(H)–C(H)–C_6H_5), 6.49 (doublet, 2H, >C(H)–CH_2–C_5H_6), GC, in ratio of 1:3 and 3:1 respectively.

Since both the unsaturated compounds (IX and X) were catalytically hydrogenated to the same authentic compound (VII) (antipodal *trans* A/B ring fusion) and IX could not be isomerized to X under the pyrolysis and the deacetic acid condition, X is directly

*5 The hydrogenation (Pd-C, EtOAc, H_2SO_4) of III have sufficient posssibility to give β C_{10}-OAc and β C_{11}-H of V (for instance, in consideration of 1,4 addition mechanism of H_2 to –C=C–C=O system).

2) E. Wenkert, *et al.* : J. Am. Chem. Soc., **80**, 211 (1958); **82**, 3229 (1960); Can. J. Chem., **41**, 1924 (1963).

produced from V without the isomerisation and V should have the skeleton of methyl deoxypodocarpate enantiomer.

Alkaline hydrolysis (KOH, ENG,*6 180~200°) of V yielded 10-hydroxy acid (XII) having two kinds of crystalline forms, $C_{17}H_{22}O_3$, m.p. 157~158°, IR ν_{max}^{KBr} cm^{-1} : 3580, 3400, 1725, 1695, NMR (τ) : 8.44 (C_1-CH_3), 8.88 (C_{12}-CH_3) and $C_{17}H_{22}O_3 \cdot \frac{1}{2}H_2O$, m.p. 156~158° (once melted at about 80°), IR ν_{max}^{KBr} cm^{-1} : 3420, 3360, 1660. In order to prove that the C_{10}-O configuration had not altered during the above condition of alkaline hydrolysis (V→XII), its 10-hydroxy ester (XIII), $C_{18}H_{24}O_3$, m.p. 79~80°, IR $\nu_{max}^{CCl_4}$ cm^{-1} *7 : 3618, 1732; 3549, 1713 (intramolecular hydrogen bond by the diluted method), NMR (τ) : 8.51 (C_1-CH_3, −13.2 c.p.s. shift from that of the standard VII; C_{10}-OH is nearly located to C_1-CH_3 [3]), 8.98 (C_{12}-CH_3), GC, methylated from XII by the usual method, gave back to V by the treatment with acetyl chloride and pyridine.

The acid (XII) could be lactonized by heating with 10% hydrochloric acid to give XVIII, $C_{17}H_{20}O_2$, m.p. 174~176°, IR : ν_{max}^{KBr} 1758 cm^{-1}, GC, which was not returned back to XII, but to new isomeric acid (XV), $C_{17}H_{22}O_3$, m.p. 165~167° (depressed m. m. p. with XII), IR ν_{max}^{KBr} cm^{-1} : 3210, 1675, NMR (τ) : 8.72 (C_1-CH_3), 8.63 (C_{12}-CH_3), by alkaline hydrolysis (KOH, H_2O-MeOH, 80~100°). The lactone (XVIII) was readily hydrogenated (Pd-C, AcOH, H_2SO_4) to the authentic deoxypodocarpic acid enantiomer (VIII). The new hydroxy acid (XV) was easily lactonized again to the original lactone (XVIII) and was also methylated to the corresponding hydroxy ester (XVI), $C_{18}H_{24}O_3$, m.p. 144~147°, IR $\nu_{max}^{CCl_4}$ cm^{-1} *7 : 3485, 1715 (intramolecular hydrogen bond by the diluted method), NMR (τ) : 8.70 (C_1-CH_3), 8.63 (C_{12}-CH_3, −20.4 c.p.s. shift from the standard VII; C_{10}-OH is nearly located to C_{12}-CH_3 [3]), GC.

The isomeric methyl esters (XIII and XVI) were dehydrated by methanesulfonyl chloride to give the unsaturated esters (IX, X) and the lactone (XVIII) in ratio of 3:3:2 and 1:1:2 respectively and no isomerisation of IX to X was occurred under this condition. These facts show XIII, XVI and their derivatives have the common skeleton of deoxypodocarpic acid enantiomer. XIII and XVI also were reduced by $LiAlH_4$ to the corresponding alcohols (XIV), $C_{17}H_{24}O_2$, m.p. 163~164.5°, IR ν_{max}^{KBr} cm^{-1} : 3310, NMR (τ) : 8.71 (6H, C_1-CH_3 and C_{12}-CH_3) and (XVII), $C_{17}H_{24}O_2$, m.p. 176~177.5°, IR ν_{max}^{KBr} cm^{-1} : 3310, NMR (τ) : 8.90 (C_1-CH_3), 8.45 (C_{12}-CH_3) respectively.

Some obvious differences between above the two systems (XIII and XVI) were shown as following: i) Although both the esters (XIII and XVI) were hydrolized by alkaline treatment (KOH-MeOH, reflux) to the respective original acids (XII and XV), the more drastic alkaline treatment (KOH, ENG, 200°) of XVI and XVIII afforded conjugated double bond acid (XI), $C_{17}H_{20}O_2$, m.p. 145~148°, UV λ_{max}^{EtOH} mμ : 265, which was methylated to the ester (X), while the isomeric ester (XIII) only gave the hydroxy acid (XII). Isomerisaton including hydrolysis of the unconjugated ester (IX) to the conjugated acid (XI) was occured under the drastic alkaline treatment. ii) In a treatment of both the esters (XIII and XVI) on alumina, the former was only recovered, but the latter was quantitatively converted to the lactone (XVIII). iii) In thermal treatment (ENG, 200°) XIII was only recovered, while XVI was converted to a mixture consisting of XVIII, X and IX in ratio of 8:4:1.

In order to prepare the aimed compounds, both the isomeric methyl ester (XIII and XVI) were oxidized with lead tetraacetate and iodine under ultraviolet illumination[4] to

*6 Abbreviation, GC, showed the compound was checked its purity by liquid gas chromatography (Author thank to Dr. N. Ikekawa, this Institute, Tokyo, for his advice on them) and abbreviation, ENG, showed ethylene glycol.

*7 These values were measured by Perkin Elmer 112G infrared spectrometer (Grating, single beam system).

3) Y. Kawazoe, *et al.* : This Bulletin, **10**, 338 (1962).
4) Ch. Meystre, *et al.* : Experientia, **17**, 475 (1961).

give the corresponding ethers (XIX), $C_{18}H_{22}O_3$, m.p. 161~163°, IR ν_{max}^{KBr} cm^{-1} : 1710, NMR (τ) : 8.96 (C_{12}-CH_3), shifted signal (C_1-CH_3) of XIII was disappeared, GC, and XX, $C_{18}H_{22}O_3$, m.p. 128~129°, IR ν_{max}^{KBr} cm^{-1} : 1715, NMR (τ) : 8.74 (C_1-CH_3), shifted signal (C_{12}-CH_3) of XVI was disappeared, GC, in good yield.

On the base of the above mentioned results, possible configuration at C_{10} of both the systems (XIII, XVI and their derivatves) could be discussed.

Since C_{10}-OH of the ester (XVI) having methyl deoxypodocarpate enantiomer skeleton is nearly located to the C_{12}-methyl group and also is combined with the C_{12}-methyl group to give the ether (XX), the configuration at C_{10} of XVI and its derivatves have only one possibility (α C_{10}-OH in half chair B-ring, now regardless of conformation of A-ring). On the other way, C_{10}-OH of the isomeric ester (XIII) having the same skeleton as XVI is, in contrast, nealy located to the C_1-methyl group and is combined with the C_1-methyl group to give the corresponding ether (XIX), so C_{10}-OH configuration of XIII and its derivatives could be considered as β-configuration in half chair B-ring.[*5,*8] In other words, stereochemical relationship of both the systems (XIII nnd XVI) is configurational isomer at C_{10}-OH and isomerisation of the configuration at C_{10} ($\beta \rightarrow \alpha$) must be occurred during the lactonization of XII.[*9]

Anyhow, the selective oxidation of the C_1- and C_{12}-methyl group of these type componds is accomplished. Now, using these compounds, syntheses of some diterpenoids and studies on stereochemical problems of XIII and XVI system are still in progress.

The authors are indebted to Prof. Emeritus E. Ochiai, Tokyo University, for his valuable advice and encouragement.

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*8 Other possibility on C_{10}-OH configuration (it is α C_{10}-OH in half boat B-ring and thus, stereochemical relationship of both the systems (XIII and XVI) is conformational isomer at B-ring) will be cancelled firmly in our future report.

*9 Authors thank to Dr. W. Nagata, Shiongi & Co., Ltd., Osaka for discussion on stereochemistry of the isomeric compounds.

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The Occurrence of (ω-1)-Hydroxylation as the Major Metabolism of Alkylaryl Ethers in Rabbits

In studies on the metabolic fate of a wide variety of alkylaryl ethers by a number of workers, it has been elaborated that the ethers can be cleaved oxidatively to phenols and aldehydes by the enzyme systems locating in liver microsomes and requiring both reduced nicotinamide-adenine dinucleotide phosphate (NADPH) and oxygen.[1] This O-dealkylation has been known as a sole metabolic pathway of alkylaryl ethers (Chart 1).

$$Ar\text{-}O\text{-}CH_2\text{-}R \xrightarrow[NADPH,\ O_2]{\text{liver microsomes}} \left[\begin{array}{c} OH \\ | \\ Ar\text{-}O\text{-}CH\text{-}R \end{array}\right] \longrightarrow Ar\text{-}OH + RCHO$$

Chart 1.

1) R. T. Williams : "Detoxication Mechanisms," 2nd ed., p. 324. Chapman & Hall, London (1959).