1-alkoxy substituent in the alkylation described above is parallel to that of the 1-alkyl group reported by Leonard and Fujii.[9]

Further interest in the first alkylation stems from the conversion (57%) of I to 9-benzyladenine 1-oxide hydrobromide (Ⅷ), m.p. 240~243° (decomp.), by the reaction with two mole equivalents of benzyl bromide at an elevated temperature (120°) for 3 hrs. The free base of m.p. 285° (decomp.) obtained from Ⅷ was deoxygenated with hydrogen and Raney nickel to give (95% yield) 9-benzyladenine (Ⅶc), which was obtained also by heating the salt (Ⅷ) in N,N-dimethylacetamide[*3] under reflux for 1 hr.

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[*3] The recently proposed mechanism by E.C. Taylor and E.E. Garcia (J. Am. Chem. Soc., **86**, 4721 (1964)) for the deoxygenation of the 7-N-oxide group of 8-substituted theophyllines in DMF seems not to be applicable to our case.

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UDC 574.597.02.07

Conversion of Enmein to (−)-Kaurane. The Absolute Stereochemistry of Enmein

In the joint paper with several research groups,[1] we have reported the chemical structure of enmein, a diterpene bitter substance from *Isodon trichocarpus* Kudo, is to be formulated as I and this result was ascertained by our X-ray diffractio nstudy.[2] The absolute configuration of enmein has been proposed[1] on the basis of the optical rotatory dispersion data and the conformational analysis and hence enmein was biogenetically considered to be a diterpene homolog of (−)-kaurene. In the present communication, we wish to describe the transformation of enmein into (−)-kaurane (α-dihydro(−)-kaurene)[3,4] through multi-step chemical reactions, which confirms the absolute configuration of enmein with antipodal A/B stereochemistry to steroids.[*1]

Diketolactone methyl ester (Ⅲ), m.p. 212~212.5°, ν_{max}^{KBr} cm^{-1}: 1761, 1714 (*Anal.* Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50. Found: C, 67.27; H, 7.47), derived from dihydroenmein (Ⅱ) by a series of reactions mainly described by Kubota, *et al.*,[5] was treated with ethanedithiol at room temperature in the presence of boron trifluoride etherate

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[*1] The recent X-ray study using the anomalous dispersion method has also confirmed this absolute configuration. cf. Y. Iitaka, M. Natsume: Acta Cryst., in press.

1) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, M. Takahashi, H. Irie, A. Numata, T. Fujita, T. Okamoto, M. Natsume, Y. Kawazoe, K. Shudo, T. Ikeda, M. Tomoeda, S. Kanatomo, T. Kosuge, K. Adachi: Tetrahedron Letters, No. 20, 1243 (1964).
2) Y. Iitaka, M. Natsume: *Ibid.*, No. 20, 1257 (1964).
3) L.H. Briggs, R.W. Cawley: J. Chem. Soc., **1948**, 1888.
4) L.H. Briggs, B.F. Cain, R.C.C ambie, B.R. Davis, P.S. Rutledge, J.K. Wilmshurst: *Ibid.*, **1963**, 1345.
5) T. Kubota, T. Matsuura, T. Tsutsui, K. Naya: Nippon Kagaku Kaishi, **84**, 353 (1963).

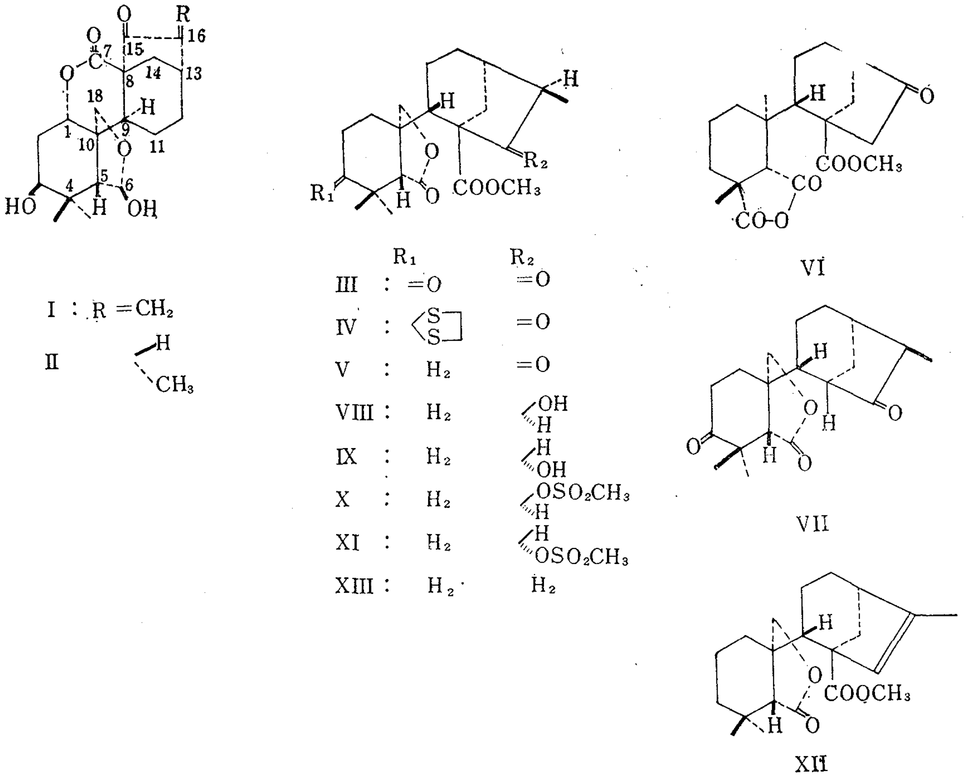

Chart 1.

and desulfurization of the resulting monothioketal (IV), m.p. 211～213° (*Anal.* Calcd. for $C_{23}H_{32}O_5S_2$: C, 61.03; H, 7.13. Found : C, 61.42; H, 7.03) was effected over Raney nickel (W-4) to furnish monoketolactone ester (V), m.p. 126～128°, $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1775, 1755, 1720 (*Anal.* Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found : C, 69.47; H, 8.05). Optical rotatory dispersion curve of V was almost antipodal with respect to that of fujenoic acid derivative (VI).[6] Since the five-membered ring ketone of V resisted to further thioketal formation, contrary to the case of VII,[1] removal of the ketone function was accomplished as follows.

Reduction of V with sodium borohydride and subsequent chromatography over silica-gel resulted in the formation of two epimeric alcohols, *i.e.* VIII, m.p. 133.5～134°, $\nu_{\text{xɐɯ}}^{\text{KBr}}$ cm^{-1} : 3580, 1775, 1720 (*Anal.* Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found : C, 69.49; H, 8.91) and IX, m.p. 154～154.5°, $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3570, 1770, 1736 (*Anal.* Found : C, 69.51; H, 8.83), each of which was converted with methanesulfonyl chloride in pyridine to their methanesulfonates, X, m.p. 170.5～171°, $\text{NMR}^{\text{CDCl}_3}\ \tau$: 6.91 (s, $C\underline{H}_3SO_2O$-), 6.28 (s, $C\underline{H}_3OOC$-), 6.11 (s, $-C\underline{H}_2-O-CO-$), 5.04 (d, J=10.5 c.p.s., $\rangle C\underline{H}-OMs$) (*Anal.* Calcd. for $C_{22}H_{34}O_7S$: C, 59.71; H, 7.75. Found : C, 59.59; H, 7.65) and XI, m.p. 150.5～151° (decomp.), $\text{NMR}^{\text{CDCl}_3}\ \tau$: 7.09 (s), 6.32 (s), 6.10 (s), 5.53 (d, J=3.7 c.p.s.) (*Anal.* Found : C, 59.29; H, 7.78). Elimination of methanesulfonic acid from XI was observed when its pyridine solution was refluxed briefly, whereas X required reflux in 2-methyl-5-ethylpyridine. In either case was obtained an unsaturated compound (XII), m.p. 124～126°, $\text{NMR}^{\text{CDCl}_3}\ \tau$: 9.18 (s), 8.85 (s, *gem.* di-$C\underline{H}_3$), 8.32 (s, $-CH=C-C\underline{H}_3$), 6.34 (s, $-COOC\underline{H}_3$), 6.22 (s, $-C\underline{H}_2-O-CO-$), 4.17 (br, $-C\underline{H}=C-CH_3$) (*Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found : C. 72.47; H, 8.79), which was hydrogenated over platinum oxide in acetic acid to give XIII, m.p. 117～118°, $\nu_{\text{max}}^{\text{CS}_2}$ cm^{-1} : 1779, 1730, $\text{NMR}^{\text{CDCl}_3}\ \tau$: 6.42 (s, $-COOC\underline{H}_3$), 6.22 (s, $-C\underline{H}_2-O-CO-$) (*Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found : C, 72.62, 72.75, 72.26; H, 9.09,

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6) B.E. Cross, R.H.B. Galt, J.R. Hanson : J. Chem. Soc., **1963**, 5052.

9.34, 9.20). The same compound (XIII) was also obtained when either X or XI was catalytically reduced over Raney nickel (W-4) under high pressure (70~140 atm.) at the elevated temperature (60~140°).

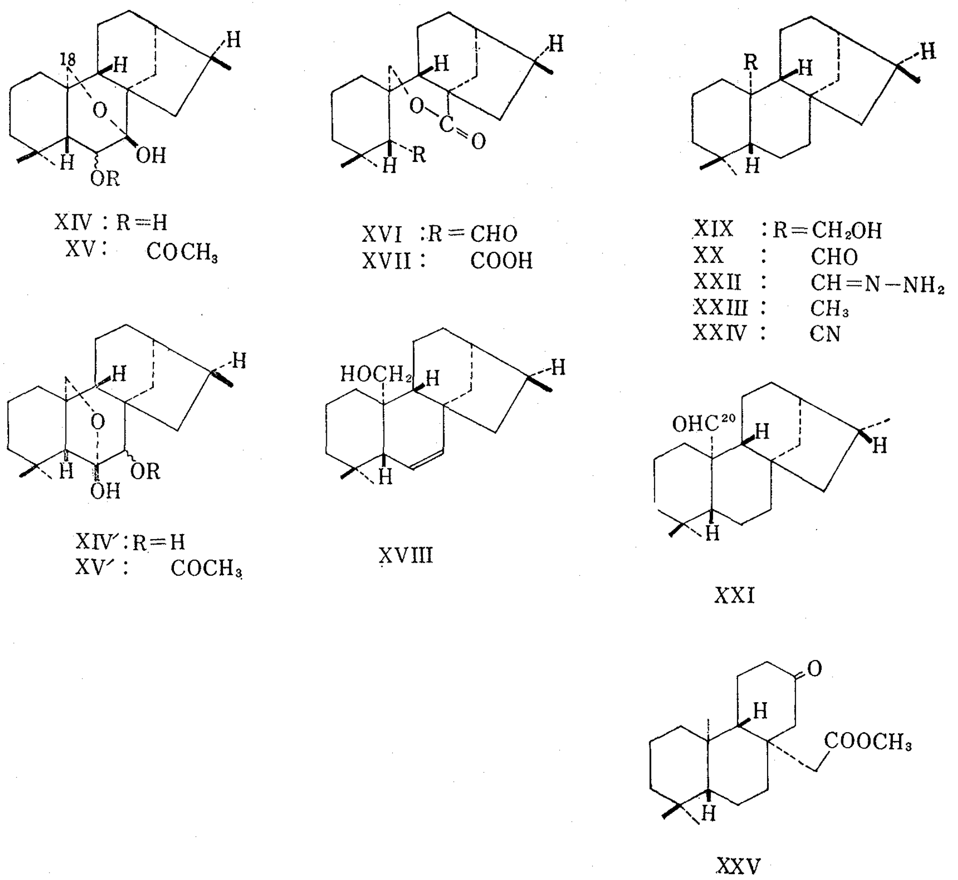

Chart 2.

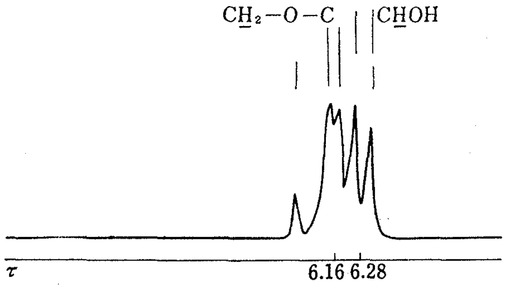

Fig. 1.

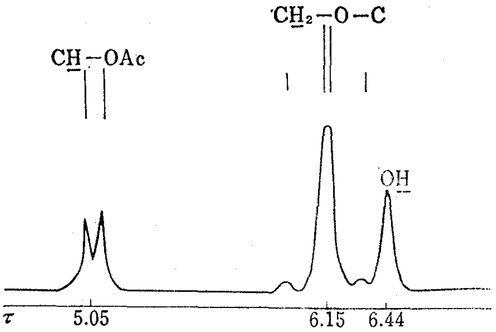

Fig. 2.

In order to construct the B ring of kaurene structure, we could find that the acyloin condensation was most satisfactory and the B ring formation was achieved by using dispersed sodium in boiling toluene-xylene-tetrahydrofuran mixture. Main product (XIV), m.p. 215~216°, was obtained after chromatographic purification in 15~40% yield and possessed an empirical formula of $C_{20}H_{32}O_3$ (*Anal.* Calcd. : C, 74.96; H, 10.06. Found : C, 74.88; H, 10.11). The product behaved as an α-ketol and this character was clearly detected by coloration with triphenyltetrazolium chloride in diluted alkali; however, no carbonyl function was observed in its infrared absorption spectrum. On acetylation with acetic anhydride in pyridine, XIV produced a monoacetyl derivative

(XV), m.p. 176~178°, ν_{max}^{Nujol} cm^{-1} : 3580, 1728 (*Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found : C, 72.92; H, 9,37), which still exhibited the presence of a hydroxyl group in the infrared and nuclear magnetic resonance spectra. Therefore, the hydroxyl group, which remained unacetylated, could be considered to be that of a hemiketal function and the structure (XIV) or (XIV′) was eventually postulated for the condensation product. Evidence for the structure (XIV) rather than XIV′ was gained in two ways. (i) In the nuclear magnetic resonance spectrum of XIV, the proton signals at the 6.0~6.4 τ region (Fig. 1) were interpreted as combination of an AB type quartet originated from methylene protons at C-18 and a doublet of one proton attributable to the hydrogen at the carbon atom bearing the secondary hydroxyl, which was neighbored by a methine group, and furthermore, the nuclear magnetic resonance spectrum of the acetate (XV) was consistent well with the structure (XV) (Fig. 2). (ii) The product (XIV) consumed one molar equivalent of periodate to form the compound (XVI) having both aldehyde and δ-lactone functions, $\nu_{max}^{Cap.}$ cm^{-1} : 1720~1730, NMR^{CDCl_3} τ : 7.84 (d, J=5 c.p.s., $\rangle C\underline{H}-CHO$), 5.31 (q, $-C\underline{H}_2-O-CO-$), 0.11 (d, J=5 c.p.s., $\rangle CH-C\underline{H}O$), which was characterized by the facile formation of a carboxylic acid (XVII), m.p. 200~203°, ν_{max}^{KBr} cm^{-1} : 1730, 1683 (*Anal.* Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found : C, 71.88; H, 8.81) with chromium trioxide in acetic acid. The same carboxylic acid was readily obtained when XIII was hydrolyzed with alkali, followed by relactonization, and thus the structure of the acyloin condensation product was rigorously established.

Removal of the masked α-ketol system was successful by Huang-Minlon reduction of XIV and the resulting unsaturated compound (XVIII), m.p. 56.5~62°, $[\alpha]_D^{34.5}$ +55° (c=0.54, $CHCl_3$), NMR^{CDCl_3} τ : 6.24 (s, $-C\underline{H}_2OH$), 4.59 (m, $-CH-C\underline{H}=C\underline{H}-$) (*Anal.* Calcd. for $C_{20}H_{32}O \cdot 1/2\,H_2O$: C, 80.75; H, 11.18. Found : C, 81.39, 81.57; H, 11.40, 11.45) was hydrogenated on platinum oxide in acetic acid to afford the carbinol (XIX), m.p. 81~81.5°, $[\alpha]_D^{34}$ −20° (c=0.61, $CHCl_3$) (*Anal.* Calcd. for $C_{20}H_{34}O$: C, 82.69 ; H, 11.80. Found : C, 82.58 ; H, 11.52), which was oxidized with chromium trioxide-pyridine complex to the aldehyde (XX), m.p. 105~108°, $[\alpha]_D^{32}$ −98° (c=0.11, CH_3OH), ν_{max}^{KBr} : 1699 cm^{-1} (*Anal.* Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found : C, 83.06; H, 11.10). Optical rotatory dispersion curve of XX (negative Cotton effect) was almost identical with that of epikaur-20-al (XXI).7) Although the aldehyde group of XX was extremely sterically hindered, XX could be converted to its hydrazone (XXII), m.p. 82.5~84° (*Anal.* Calcd. fof $C_{20}H_{34}N_2$: N, 9.26. Found : N, 9.43) by applying the Nagata's procedure8) in good yield, Alkaline degradation of XXII was accomplished by selecting the reaction condition to be heating the hydrazone in diethylene glycol with a big excess of potassium hydroxide and a few drops of anhydrous hydrazine in a sealed tube at 230~240° (bath temperature) for fifteen hours. A crystalline hydrocarbon $[\alpha]_D^{25}$ −32.5° (c=2.1, $CHCl_3$) thus obtained in maximum 60% yield melted at 86.5~87° and its elemental analysis fit the expected empirical formula for (−)-kaurane[*2] (*Anal.* Calcd. for $C_{20}H_{34}$: C, 87.51; H, 12.49. Found : C, 87.84; H, 12.29). Identity of this hydrocarbon with (−)-kaurane (XXIII) was performed by admixture, comparisons of infrared absorption spectra and nuclear magnetic resonance spectra and the mixed vapor phase chromatography using three different

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[*2] Physical data of (−)-kaurane has been reported to be m.p. 84~85°, $[\alpha]_D$ −32°,4) and m.p. 85~87°, $[\alpha]_D^{26}$ −33° (c=0.5, $CHCl_3$). B.E. Cross, R.H.B. Galt, J.R. Hanson : J. Chem. Soc., **1963**, 2956. cf. (−)-epikaurane, m.p. 54~56°, $[\alpha]_D^{21}$ −67° (c=1.0, $CHCl_3$).4)

[*3] 1% QF-1, 1% DC 440, and 1% Versamid on DMDS-treated Chromosorb W.

[*4] The authors are much grateful to Dr. R.H.B. Galt, I.C.I., England, for supplying us the authentic specimen of (−)-kaurene.

7) H. Vorbruegen, C. Djerassi : J. Am. Chem. Soc., 84, 2990 (1962).

8) W. Nagata, H. Itazaki : Chem. & Ind. (London), **1964**, 1194. Thanks are due to Dr. W. Nagata, Shionogi & Co., Ltd. for informing us the reaction condition.

columns*[3] with the authentic XXIII, derived from (−)-kaurene.*[4] The formation of a cyano compound (XXIV), m.p. 103~104°, $\nu_{\max}^{\text{KBr}}$: 2220 cm^{-1} (*Anal.* Calcd. for $C_{20}H_{31}N$: C, 84.14; H, 10.95; N, 4.91. Found: C, 83.87; H, 10.90; N, 4.72) was observed in 20~40% yield during the drastic alkali degradation of XXII.

Since (−)-kaurene has been inter-related to phyllocladene[9] through XXV and correlated to podocarpic acid by way of garryfoline[7] and atisine,[10~12] the present work has established the absolute configuration of enmein. As the backbone stereochemistry of the compound (XIV) was determined beyond doubt, conversion of enmein to the diterpene alkaloids is in progress.

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11) D. Dvornik, O.E. Edwards: Chem. & Ind. (London), **1958**, 623; *Idem*: Can. J. Chem., **42**, 137 (1964).
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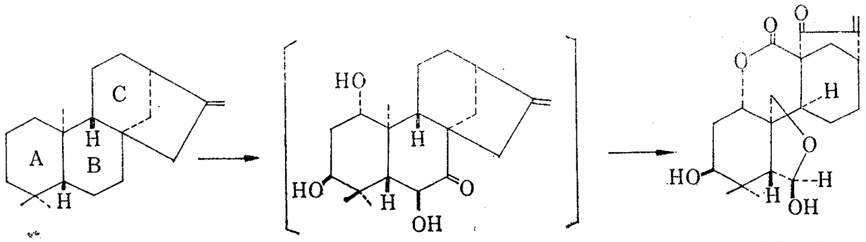
[Chem. Pharm. Bull. 13(8)1023~1027(1965)]

UDC 547.597.02.07

The Absolute Configuration of Enmein Transformation of Enmein into (−)-Kaurane

Recently, it was shown by chemical methods[1] and X-ray analysis[2] that the structure and stereochemistry of enmein, a bitter principle of *Isodon trichocarpus* Kudo could be represented as shown in formula (I). Its absolute configuration was also proposed on the basis of optical rotatory dispersion data and conformational analysis, but no chemical evidence on it has been provided.

It may be assumed that enmein is biogenetically derived from (−)-kaurene by oxidative cleavage of its B ring followed by recyclization, as shown in Chart 1.



(−)-kaurene

I

Chart 1.

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1) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, M. Takahashi, H. Irie, A. Numata, T. Fujita, T. Okamoto, M. Natsume, Y. Kawazoe, K. Sudo, T. Ikeda, M. Tomoeda, S. Kanatomo, T. Kosuge, K. Adachi: Tetrahedron Letters, No. 20, 1243 (1964).
2) Y. Iitaka, M. Natsume: *Ibid.*, No. 20, 1257 (1964).