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TERPENOIDS—II

THE CHEMICAL CONVERSION OF ENMEIN INTO (—)-KAURANE—THE ABSOLUTE CONFIGURATION OF ENMEIN[1,2]

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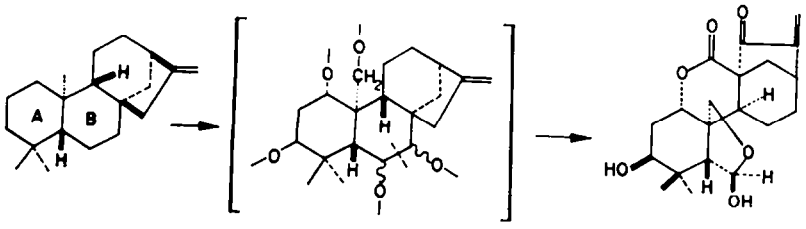
Abstract—The acyloin condensation of the lactone ester (III) which was derived from enmein, a diterpenoid bitter principle from *Isodon trichocarpus* Kudo, afforded several products, the main compound of which was shown to have structure XLII. The latter was converted into (−)-kaurane (LII) through a series of reactions. On the basis of the result, the absolute configuration II of enmein was positively established by a chemical evidence.

SINCE three research groups[3–5] isolated enmein, a diterpenoid bitter principle, from the leaves of *Isodon trichocarpus* Kudo (Japanese name: "Kurobana-hikiokoshi"; Labiatae) in 1958, many Japanese workers[3–9] have investigated its constitution Recently, the co-operation[10] of these schools on chemical research and a X-ray crystallographic study by another group[11] led to a clarification of the complicated structure II of enmein. However, the positive chemical evidence by which one can completely rule out the antipodal formula of II has never been available.

Enmein may be biogenetically regarded as a product derived from a diterpene hydrocarbon, (−)-kaurene (I), by the oxidative cleavage of ring B as shown:



I II

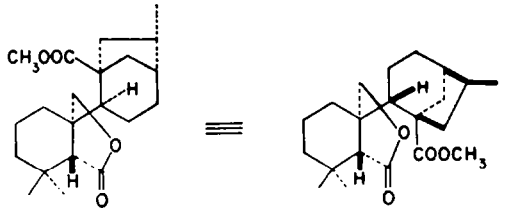
Chart I

Therefore, the conversion of enmein into (−)-kaurane[12] (α-dihydrokaurene), whose

[1] The investigation which forms the subject of this paper was first outlined in part in preliminary communication: *Chem. Pharm. Bull. Tokyo* **13**, 1023 (1965). (Terpenoids—I).
[2] From the Ph.D. Thesis of T. F., Kyoto University (1965).
[3] T. Ikeda and S. Kanatomo, *Yakugaku Zasshi* **78**, 1128 (1958).
[4] M. Takahashi, T. Fujita and Y. Koyama, *Yakugaku Zasshi* **78**, 699 (1958).
[5] K. Naya, *Nippon Kagaku Zasshi* **79**, 885 (1958).
[6] M. Takahashi, T. Fujita and Y. Koyama, *Yakugaku Zasshi* **80**, 594, 696 (1960).
[7] T. Ikeda, T. Kosuge and S. Kanatomo, *Yakugaku Zasshi* **78**, 947 (1958).
[8] S. Kanatomo, *Chem. Pharm. Bull. Tokyo* **6**, 680 (1958).
[9] S. Kanatomo, *Yakugaku Zasshi* **81**, 1049, 1437 (1961).
[10] [a] 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 and K. Adachi, *Tetrahedron Letters* 1243 (1964);
[b] T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, H. Irie, A. Numata, T. Fujita and T. Suzuki, *Tetrahedron* **22**, 1659 (1966).
[11] Y. Iitaka and M. Natsume, *Tetrahedron Letters* 1257 (1964).

absolute configuration has been established,[18] without any changes of the stereochemistry on the asymmetric centers would supply a chemical evidence on the absolute configuration of enmein. Moreover, this chemical interconversion would constitute a chemical recyclization of the biosynthetically cleaved ring B. These interests prompted us to do the present work.

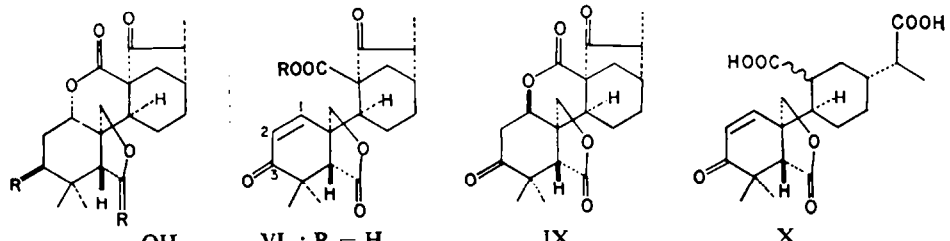
As a key reaction of the sequences, the acyloin condensation was chosen, and a compound III which has no oxygen function except useful lactone and ester was adopted as the material for the reaction.



III

Chart 2

Bisdehydrodihydroenmein (V), which has been prepared by chromic acid oxidation of dihydroenmein (IV), on hydrolysis[14] gave VI,[14] IX[10] and X.[10] The methyl ester VII of the acid VI on hydrogenation gave diketolactone ester (VIII). As the Wolff-Kishner and its modified reactions on VIII were unsuccessful, we treated the latter



IV : R = OH, H
V : R = O

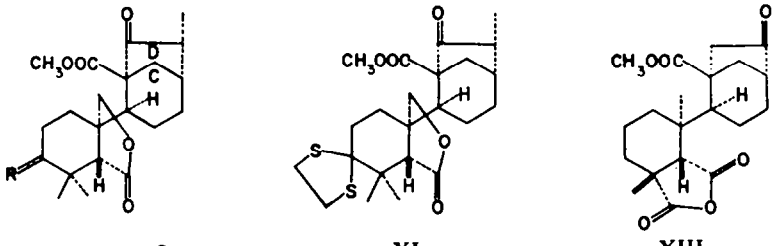
VI : R = H
VII : R = CH_3

IX

X

Chart 3

with ethanedithiol and borontrifluoride and desulfurized the resulting thioketal with



VIII : R = O
XII : R = H_2

XI

XIII

Chart 4

[13] L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis and P. S. Rutledge, *J. Chem. Soc.* 1851 (1962).

[13a] L. H. Briggs, B. F. Cain, R. C. Cambie B. R. Davis, P. S. Rutledge and J. K. Wilmshurst, *J. Chem. Soc.* 1345 (1963);

[13b] B. E. Cross, R. H. B. Galt and J. R. Hanson, *Ibid.* 2944 (1963).

[14] T. Kubota, T. Matsuura, T. Tsutsui and K. Naya, *Nippon Kagaku Zasshi* **84**, 353 (1963).

Raney nickel. The product formed in the first step corresponded to monothioketal formula $C_{23}H_{32}O_5S_2$ and was assigned C-3 thioketal structure (XI) from IR and NMR spectral investigations. Desulfurization afforded a compound XII, $C_{21}H_{30}O_5$, the IR spectrum of which showed the carbonyl absorptions of γ-lactone (1765 cm^{-1}), cyclopentanone (1744 cm^{-1}), and ester (1711 cm^{-1}). The ORD curve of compound XII showed a negative Cotton effect of the opposite sign to fujenoic acid derivative XIII.[15] The fact indicated that the stereochemistry between rings C and D in XII was same with that in dihydroenmein[6](IV) and that cleavage of δ-lactone ring had no effect on the ORD curve.

A raise in temperature or an extension of reaction time at room temperature in the thioketalization of diketolactone ester (VIII) yielded a product, $C_{26}H_{36}O_4S_4$, the IR spectrum of which showed the presence of γ-lactone (1765 cm^{-1}) and ester (1725 cm^{-1}), but no cyclopentanone. Its NMR spectrum gave a new methyl signal on a double bond at δ 1·70 ppm, instead of a methyl signal at δ 1·10 ppm (doublet) which appeared in that of XI, and also a new ethylene protons singlet of an additional thioketal at δ 3·30 ppm. These facts certified another thioketalization and a cyclopentanone ring cleavage accompanied by the simultaneous formation of a double bond, and led to structure XIV. Compound XIV on desulfurization with Raney nickel yielded a lactone ester (XV), $C_{21}H_{34}O_4$. Its NMR spectrum showed C-methyl signals at δ 0·79, 0·88, 0·96 and 1·19 ppm, two of which were regarded as a duplication of a couple of doublets and assigned to an isopropyl group. The compound XV was obtained also by thioketalization of XII followed by desulfurization. The mechanism[16] of the formations of XIV and XV was considered as follows:

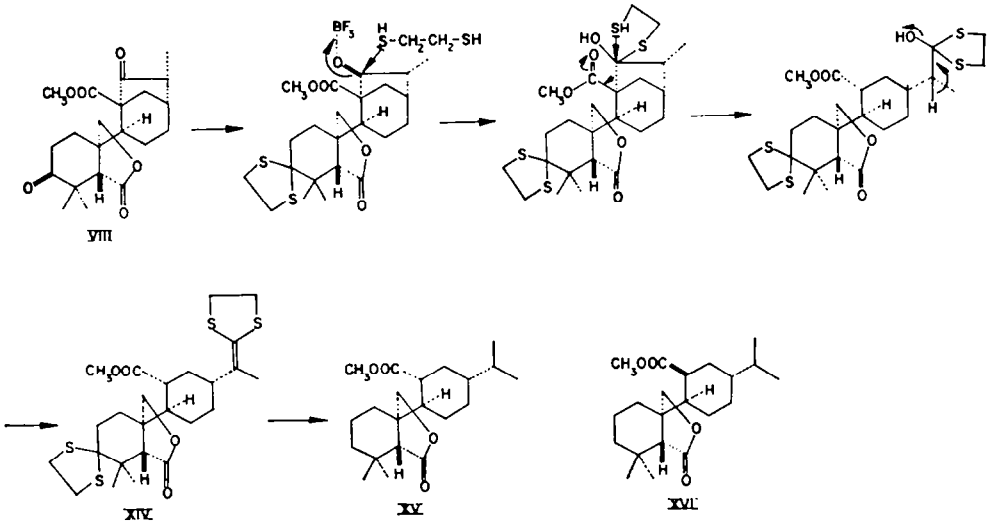


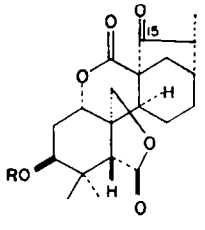
Chart 5

As a minor product, ester XVI, a stereoisomer of XV, was isolated. Considering from the above reaction mechanism, an enolization step of the carbomethoxyl group at C-8 intervenes in the process. So, the compound which has a more stable equatorial carbomethoxyl group to ring C should be produced predominantly. The treatment of

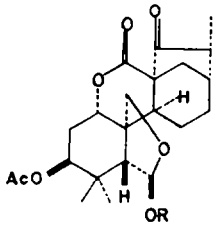
[15] B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 5052 (1963).
[16] R. Stevenson and L. F. Fieser, *J. Amer. Chem. Soc.* **78**, 1409 (1956).

XV with sodium methoxide followed by methylation with diazomethane recovered the starting material and the same treatments with XVI isomerized it to XV. Thus, the carbomethoxyl group of XV was established to be equatorial to ring C.[17]

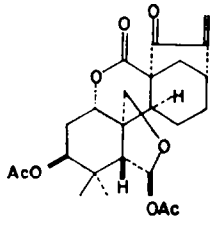
As the conversion of diketolactone ester VIII to the desired III resulted in failure as described above, attention was turned to an attempt for the first reduction of the carbonyl group at C-15 to methylene. Hemiacetal in enmein on treatment with ethanedithiol and borontrifluoride easily forms thioacetal, desulfurization of which affords a five-membered ring ether,[10] and it is necessary to keep a hydroxyl or an acetoxyl group on C-3 in order to hydrolyze the δ-lactone in enmein. Considering these experiences together, the known dehydrodihydroenmein (XVII)[10b] and its 3-acetate (XVIII)[10b] were regarded as the most suitable materials for the reduction of the carbonyl group at C-15 to methylene, and they were prepared by the following steps. Dihydroenmein (IV) on acetylation gave dihydroenmein diacetate (XIX),[4] which was also derived from enmein diacetate (XX) by hydrogenation. The partial hydrolysis of XIX with oxalic acid gave dihydroenmein-3-acetate (XXI),[10] which on chromic acid oxidation yielded dehydrodihydroenmein-3-acetate (XVIII).[10] The latter was also yielded from dihydroenmein diacetate (XIX) by direct partial oxidation with chromic acid in aqueous acetic acid. Acetate XVIII on hydrolysis with an equivalent methanolic potassium hydroxide solution gave dehydrodihydroenmein (XVII), which was also obtained from dihydroenmein (IV) by partial oxidation with an equivalent chromic acid.



XVII : R = H
XVIII : R = Ac



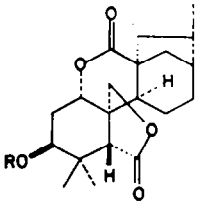
XIX : R = Ac
XXI : R = H



XX

Chart 6

The thioketalizations of dehydrodihydroenmein (XVII) and its 3-acetate (XVIII) at about 30 to 40° were effected. From acetate XVIII, an amorphous thioketal which was free from cyclopentanone carbonyl function was formed. Desulfurization with Raney nickel afforded a crystalline product, $C_{22}H_{30}O_6$, which gave a negative Legal's test. Spectral investigations expectedly allowed an assignment of dehydrodeoxodihydroenmein-3-acetate (XXIII) to the product. From dehydrodihydroenmein (XVII) a crystalline substance XXII, $C_{20}H_{28}O_5$, was yielded. Compound



XXII : R = H
XXIII : R = Ac

Chart 7

[17] The conversion of the compound XV into antipodal abietane is in progress in our laboratory.

XXIII on hydrolysis with N methanolic potassium hydroxide gave XXII, while the latter on acetylation gave the former.

In the foregoing reduction of ketone XVIII to XXIII, a couple of by-products were recognised. The TLC[18] of the crude products showed four spots. The substance of a largest R_f (0·65) proved to be the desired product XXIII, while that of a smallest R_f (0·20) was starting material (XVIII). Column chromatography of the crude products on silica gel could easily isolate a third substance of R_f 0·35 as crystals corresponding to $C_{22}H_{30}O_7$, in addition to the above two. Spectral evidences showed the presence of a γ-lactone, a δ-lactone, an acetate function and a hydroxyl group in the molecule. Acetylation gave a crystalline diacetate, $C_{24}H_{32}O_8$, which was identified with dehydrotetrahydroenmein-3,15-diacetate (XXVI)[10]. The latter has been prepared by sodium borohydride reduction of ketone XVIII and subsequent acetylation. Thus, the substance of R_f 0·35 proved to be dehydrotetrahydroenmein-3-acetate (XXV).

Another by-product of R_f 0·55 could not be isolated as a pure form. The NMR spectrum of the mixture with XXIII, however, gave a doublet (J = 2 c/s) of a methyl function on a double bond at δ 1·78 ppm. The mixture on catalytic hydrogenation gave XXIII as a sole product. Thus, the compound of R_f 0·55 could be reasonably assigned structure XXIV. The mechanism[16] for the formation of XXIV and XXV may be depicted as shown:

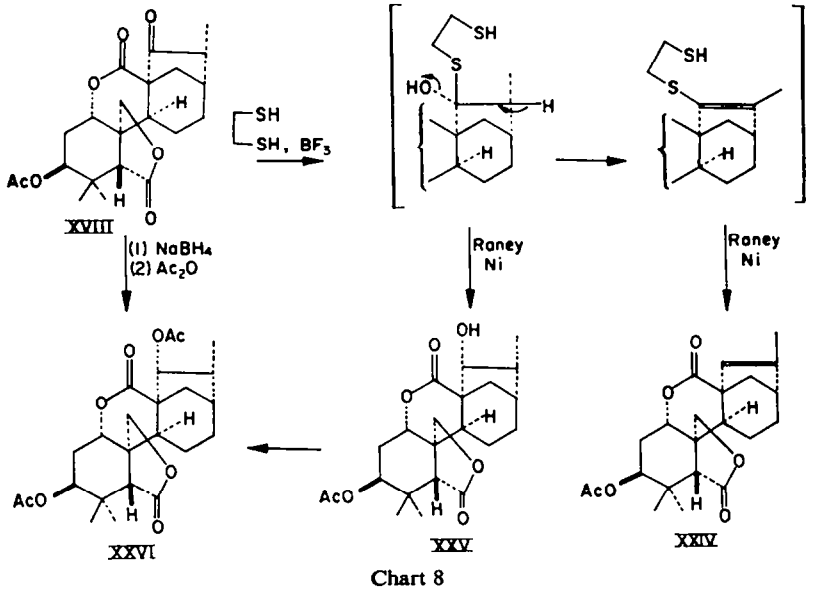


Chart 8

The following steps which led to III consisted of ring opening of the δ-lactone and subsequent removing of the oxygen function at C-3. Dehydrodeoxodihydroenmein (XXII) on chromic acid oxidation gave 3-keto compound XXVII, which on hydrolysis with $\frac{1}{100}$N KOH afforded an amorphous acid (A) and a crystalline acid (B), $C_{20}H_{26}O_5$. Spectral investigations on acids and their esters proved that acid A had a carboxyl group, a γ-lactone (IR: 1770 cm^{-1}) and a conjugated cyclohexenone in the molecule, while acid B contained a carboxyl group, a δ-lactone (IR: 1730 cm^{-1}) and a conjugated

[18] See Experimental.

cyclohexenone. Considering from the reaction process and these evidences, structures XXVIII and XXIX were assigned to acids A and B, respectively. The transformations of acid B on hydrolysis with $\frac{1}{100}$N KOH to acid A and of the methyl ester (XXXI) of acid B on recrystallization from methanol to that (XXX) of acid A established the isomeric relationship between these acids.

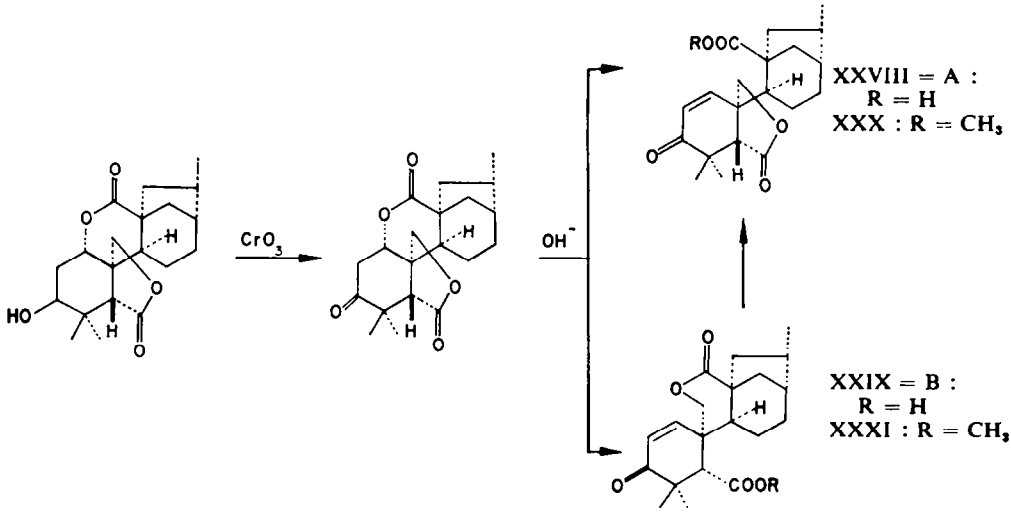


Chart 9

The catalytic hydrogenations of XXX and XXXI gave dihydroderivatives XXXII and XXXIII. The unsaturated ketone XXX on a further hydrogenation followed by acetylation gave 3-acetate XXXIV. A thioketalization of XXXII and subsequent desulfurization gave a crystalline compound, $C_{21}H_{32}O_4$, which gave a negative Legal's test. According to reduction of the ketone, IR absorption at 1715 cm^{-1} decreased its intensity when compared with that of XXXII. In NMR spectra, the product had singlet signals which could be assigned to the *gem* methyl groups on C-4 at δ 0·95 and 1·18 ppm, while the ketone XXXII had them at δ 1·31 and 1·21 ppm. The foregoing observation indicative of a diamagnetic shift of methyl proton signal at δ 1·31 ppm due to disappearance of the anisotropic effect of the carbonyl group gave an

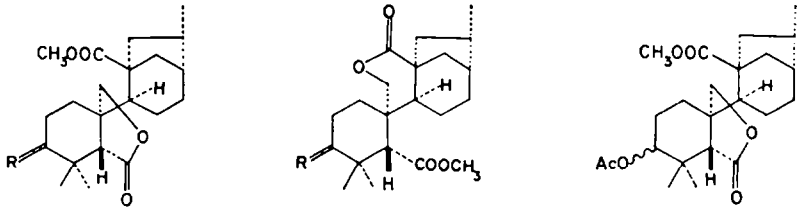
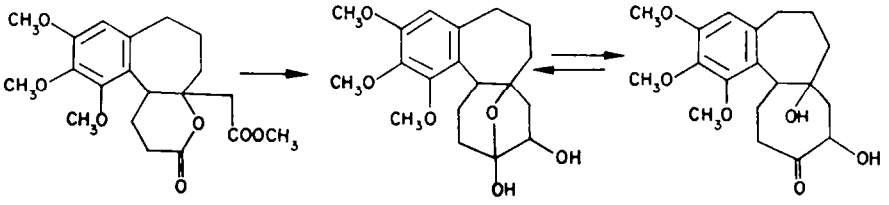


Chart 10

[19] For the reviews of acyloin condensation, see S. M. McElvain, *Organic Reactions* **4**, 256 (1948); and K. T. Finley, *Chem. Revs.* **64**, 573 (1964).

additional evidence for the successful reduction. Thus, the desired material III for the key acyloin reaction was prepared. The similar treatment of an isomer XXXIII gave a six-membered lactone ester XXXV.

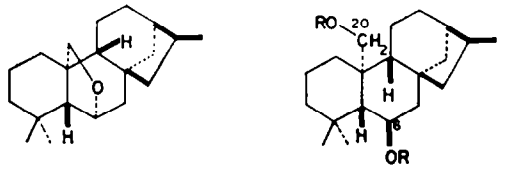
Acyloin condensation[19] has been useful for preparing of the alicyclic compounds. Sheehan *et al.*[20] and Adams *et al.*[21] synthesized the rings A,[20a] C[20c] and D[20a,b,c,21] of steroids under nitrogen with sodium in liquid ammonia. These reactions were acyloin condensations with diesters. In the total synthesis of colchicine van Tamelen *et al.*[22] carried out a reaction with lactone ester XXXVI using Sheehan's method to convert it to an acyloin product XXXVII.



XXXVI XXXVII

Chart 11

Now, we carried out acyloin condensation of III with sodium in liquid ammonia according to van Tamelen's method as described in detail in the experimental section. The neutral fraction from the reaction product gave six spots on TLC. Repeated column chromatographies on silica gel and alumina isolated a crystalline by-product. The substance has largest R_f value on TLC and corresponded to $C_{20}H_{32}O$ by mass analysis. The IR and NMR spectral analyses led to an ether structure XXXVIII and a chemical evidence that this substance was identical with the ether which was produced from kaurane-6β,20-diol (XXXIX) by treatment with *p*-toluenesulfonyl chloride supported the structure.



XXXVIII XXXIX : R = H
XL : R = Ac

Chart 12

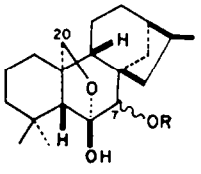
[20] [a] J. C. Sheehan, R. C. Coderre, L. A. Cohen and R. C. O'Neill, *J. Amer. Chem. Soc.* **74**, 6155 (1952);
[b] J. C. Sheehan, R. A. Coderre and P. A. Cruickshank, *Ibid.* **75**, 6231 (1953);
[c] J. C. Sheehan, W. F. Erman and P. A. Cruickshank, *Ibid.* **79**, 147 (1957);
[d] J. C. Sheehan and W. F. Erman, *Ibid.* **79**, 6050 (1957).

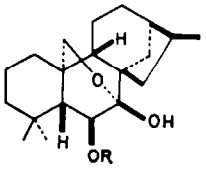
[21] W. J. Adams, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 297 (1956).

[22] E. E. van Tamelen, T. A. Spencer, Jr., D. S. Allen, Jr. and R. L. Orvis, *Tetrahedron* **14**, 8 (1961).

The product which gave second largest R_f value on TLC was yielded rather abundantly in a suitable condition. Column chromatography on silica gel was effective also for isolation of this product, $C_{20}H_{34}O_2$. The compound had two hydroxyl groups (IR and NMR spectra), but no carbonyl function (IR spectrum). The analysis of NMR spectra of the diol and its diacetate led to an assignment of the structure of kaurane-6β,20-diol (XXXIX). In the NMR spectrum of the diol XXXIX, the methylene protons on C-20 appeared as a singlet at δ 4·02 ppm and a proton on C-6 as a multiplet at δ 3·60–4·20 ppm. In diacetate XL, the methylene protons on C-20 appeared as AB type at δ 4·45 ppm which showed a reasonable paramagnetic shift explaining a primary alcohol at C-20, and a proton on C-6 as an octet at δ 5·27 ppm, which gave a reasonable explanation for a secondary alcohol at C-6. The coupling constant values of the octet (J = 5, 9·5 and 11 c/s) enabled the assignment of equatorial bond to the hydroxyl group at C-6.

A minor crystalline product (alcohol A) which gave the third high R_f value was isolated also by column chromatography on silica gel. It afforded analytical results in agreement with the empirical formula $C_{20}H_{32}O_3$. The substance which gave the fourth spot was found only in a very small amount, and its R_f value was so close to the fifth spot, that the isolation was impossible. The main product (alcohol B) which appeared as the fifth spot on TLC was usually obtained in the yield of 10–20% as crystals. Analysis afforded results which support a $C_{20}H_{32}O_3$ formula. The following data led to the structure assignments of XLI and XLII to alcohols A and B, respectively.





XLI = Alcohol A : R = H XLII = Alcohol B : R = H
XLIII = Acetate A : R = Ac XLIV = Acetate B : R = Ac

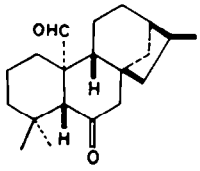
Chart 13

Both of them on acetylation gave monoacetates, acetate A XLIII and acetate B XLIV, which were shown to have another hydroxyl group by spectral evidence. The comparison of NMR spectrum of alcohol with that of acetate gave significant informations in each case. A singlet signal of one proton at δ 3·30 ppm in alcohol A, which was assigned to the proton on C-7, caused a paramagnetic shift on acetylation to move to δ 4·69 ppm in acetate A, while a doublet signal of one proton at δ 4·17 ppm in alcohol B, which was assigned to the proton on C-6, moved similarly to δ 5·01 ppm in acetate B. The methylene proton signal of C-20 appeared as a singlet at δ 3·89 ppm in alcohol A, while it appeared as a AB type at δ 4·01 ppm in alcohol B. Acetylation gave no paramagnetic shift on these signals.

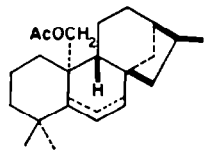
Thus, alcohols A and B were shown to be the normal acyloin products and to have hemiketal structures. The stereochemistry of the hydroxyl group at C-7 in XLI has not been clarified chemically or spectrometrically. The stereochemistry of the hydroxyl group at C-6 in XLII was reasonably estimated from NMR spectrum: the coupling constant (J = 4 c/s) of the doublet signal of the proton on C-6 in XLII and

that (4·5 c/s) in acetate XLIV coincided with the value[23] calculated from the dihedral angle (120°) between H on C-6 and H on C-5 in a boat form. The remaining sixth product could not be characterized because of the scarcity of the material, but it could be a triol, considering from the R_f value.

Kaurane-6,20-diol (XXXIX) on oxidation with chromic acid-pyridine complex easily gave a keto aldehyde XLV, but subsequent Wolff-Kishner reduction was unsuccessful: the small scale preliminary tests with the keto aldehyde XLV of the methods of Djerassi *et al.*[24] and of Nagata *et al.*[25] gave a mixture of many kinds of undesired products, provided that only a small peak, the retention time of which was



XLV



XLVI

Chart 14

identical with that of (−)-kaurane, appeared in the gaschromatography of the hydrocarbons from the reaction product in the latter case, but its isolation was impossible. Test of Barton's modification[26] which was useful for the hindered ketone also gave a similar result. Moreover, an attempt to make use of Mexican's method[27] was also in vain.

These facts led to a conclusion that direct Wolff-Kishner reduction of carbonyl group at C-6 was impossible, as in the case of zeorin,[28] a 6-keto triterpene.

An attempted pyrolysis of diacetate XL to introduce a double bond as in XLVI was unsuccessful, but a further investigation would be worthy, if enough amount were available.

Now, we gave up the route from diol XXXIX and chose hemiketal alcohol XLII as a material to (−)-kaurane. An isomer XLI was regarded as a less suitable material, because it was equivalent with undesired 6-keto compound. The Wolff-Kishner reaction with α-ketol has often given an unsaturated product as shown in several examples.[21,29,30] These facts led us to expect the formation of unsaturated alcohol XLVII from hemiketal alcohol XLII through the Wolff-Kishner reaction. The material was heated with 98·5% hydrazine prepared by Kusama's method[31] and anhydrous ethanol in a sealed tube at 170–180°, then sodium ethoxide was added and heated again to decompose the hydrazone. The reaction gave the expected kaur-6-en-20-ol

[23] [a] H. Conroy, *Advances in Organic Chemistry* Vol. II; p. 311. Interscience, New York, N.Y. (1960); [b] N. S. Bhacca and D. H. Williams, *Application of NMR Spectroscopy in Organic Chemistry, Illustration from the Steroid Field* p. 50. Holden-Day (1964).

[24] H. Vorbrueggen and C. Djerassi, *J. Amer. Chem. Soc.* **84**, 2990 (1960).

[25] W. Nagata and H. Itazaki, *Chem. & Ind.* 1194 (1964).

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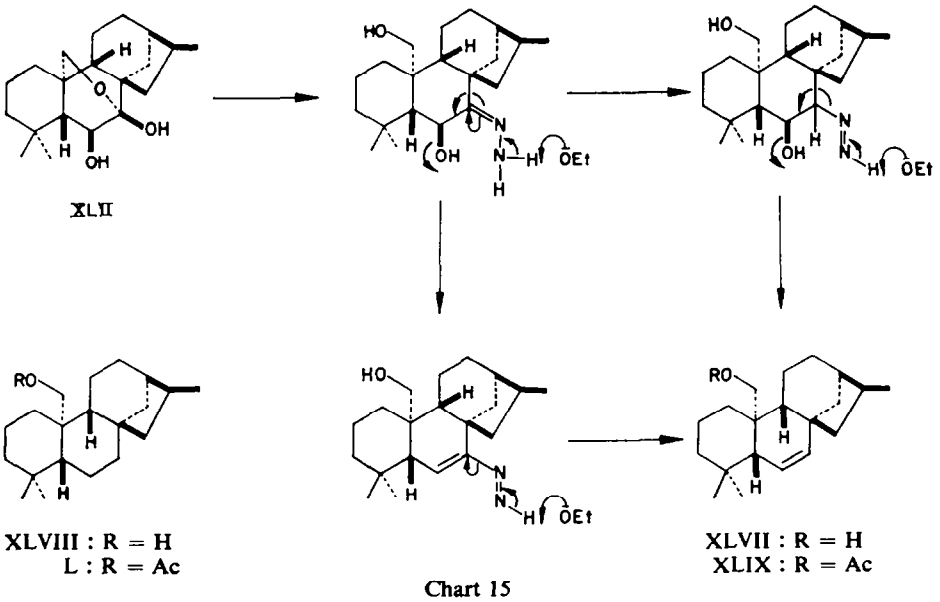
(XLVII) as prisms having m.p. 61–62°. The IR and NMR spectra reasonably supported the structure. The reaction mechanism[32] will be depicted as follows:



XLII

XLVIII : R = H
L : R = Ac

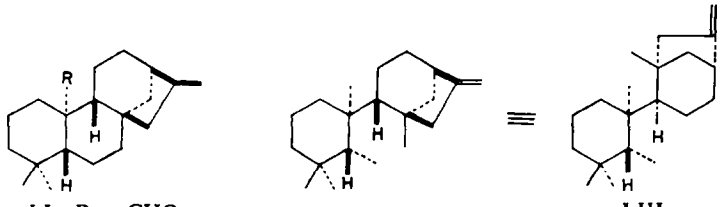
XLVII : R = H
XLIX : R = Ac

Chart 15

Kaur-6-en-20-ol (XLVII) and its acetate (XLIX) on catalytic hydrogenation gave kauran-20-ol (XLVIII) and acetate (L), respectively. The latter on hydrolysis yielded the former.

The oxidation of the saturated alcohol XLVIII with chromic acid-pyridine complex[24] under nitrogen afforded a corresponding aldehyde LI. The heating of a mixture of aldehyde and 98·5% hydrazine in anhydrous ethanol, which was sealed in a tube, for 42 hours at 170–180°, subsequent decomposition of the resulting hydrazone by heating for two days with added potassium hydroxide, and column chromatography of the reaction products on alumina followed by recrystallization gave needles of a hydrocarbon, m.p. 87·5–88·5°, $[\alpha]_D^{22}$ −28·7°.

The compound was identified with (−)-kaurane[33] (LII) by mixed m.p. test, IR



LI : R = CHO
LII : R = CH

LIII

Chart 16

[32] [a] D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.* 3045 (1954);
[b] T. D. Perrine and L. F. Small, *J. Org. Chem.* **17**, 1540 (1952).

[33] Prof. L. H. Briggs, Auckland University, kindly supplied the samples of (−)-kaurane and (−)-epikaurane.

spectra, gaschromatography, mass spectra and ORD curves comparisons. Thus, the conversion of enmein into (−)-kaurane was accomplished.[34]

Because the absolute configuration of (−)-kaurane has been established[13] as described above, the present interconversion means a positive evidence for the absolute stereochemistry LIII of the carbon skeleton of enmein. Moreover, the evidences for the axial conformation for the hydroxyl group at C-3, the equatorial conformation for the bond between C-1 and oxygen and *cis* orientation of the hydroxyl group on C-6 of hemiacetal and the hydrogen on C-5 have been presented.[10] Hence, the present work establishes the absolute configuration of enmein and dihydroenmein which has been found together in the same plant source to be shown as formulas II and IV, respectively.

EXPERIMENTAL

All m.ps were determined by a micro m.p. apparatus (yanagimoto) and were uncorrected. Unless otherwise stated, UV spectra were recorded in EtOH on a Hitachi model EPS-3 spectrophotometer, IR spectra in $CHCl_3$ on a Hitachi model EPI-S2 spectrophotometer and NMR spectra in $CDCl_3$ with TMS as an internal standard on a Varian A-60 spectrometer.

Extracts were dried over Na_2SO_4.

Mallinckrodt silicic acid was used for column chromatography. TLC plates were coated with Nakarai Silica Gel No. 1 or Silicagel G acc. to Stahl, Merck.

Isolation of enmein (II) *from* Isodon trichocarpus. Dried leaves (1 kg) collected in Ishikawa prefecture was extracted with MeOH under reflux. Concentration of the extract gave a precipitate which was washed with MeOH and with Et_2O. Crystallization from MeOH gave II (5 g) as needles, m.p. 297–299° (dec), $[\alpha]_D^{19}$ −131·3° (*c*, 1·0; pyridine), UV λ_{max}: 233 mμ (log ε 3·85), IR ν_{max}^{Nujol}: 3460; 1755; 1710; 1640 cm^{-1}, NMR $\delta_{ppm}^{Pyridine}$: 1·04 (3H, singlet); 1·32 (3H, singlet); 3·84 (1H, broad quartet); 4·48 (2H, AB type, J = 9 c/s); 5·30 (1H, doublet, J ≃ 1 c/s); 5·43 (1H, quartet, J = 7 and 11 c/s); 5·90 (1H, singlet); 5·98 (1H, doublet, J ≃ 1 c/s). (Found: C, 66·11; H, 7·38. Calc. for $C_{20}H_{26}O_6$: C, 66·28; H, 7·23%.)

Dihydroenmein (IV). A solution of II (1·5 g) in MeOH (150 ml) was hydrogenated in the presence of Adams' catalyst. H_2 (96 ml) was absorbed within 1 hr. The usual treatment of the filtrate gave IV (1·3 g) as needles, m.p. 274–276° (dec), $[\alpha]_D^{20}$ −123·5° (c, 0·33; EtOH), UV λ_{max}: 295 mμ (ε 39), IR ν_{max}^{Nujol}: 3460; 1755; 1710 cm^{-1}. (Found: C, 66·15; H, 8·03. Calc. for $C_{20}H_{28}O_6$: C, 65·91; H, 7·74%.) Dihydroenmein gave a positive Legal's test.

Bisdehydrodihydroenmein (V). A solution of CrO_3 (3 g) in AcOH (20 ml) was added over a period of 30 min to a solution of dihydroenmein (5 g) in AcOH (300 ml) and then stirred for 3 hr. Destruction of excess oxidant with MeOH, evaporation *in vacuo* and dilution with water gave a crystalline precipitate (4·35 g) which was recrystallized from MeOH to yield V as fine crystals, m.p. 218–220° (dec), UV λ_{max}: 290 mμ (ε 70), IR ν_{max}^{Nujol}: 1779; 1760; 1728; 1716 cm^{-1}, NMR $\delta_{ppm}^{Pyridine}$: 1·03 (3H, doublet); 1·38 (3H, singlet); 1·42 (3H, singlet); 2·82 (1H, singlet); 2·98 (1H, doublet of doublets, J = 6 and 14 c/s); 3·55 (1H, doublet of doublets, J = 11 and 14 c/s); 4·73 (2H, AB type, J = 10 c/s); 5·22 (1H, doublet of doublets, J = 6 and 11 c/s). (Found: C, 66·59; H, 6·79. Calc. for $C_{20}H_{24}O_6$: C, 66·65; H, 6·71%.)

Hydrolysis of Bisdehydrodihydroenmein (V) *Dihydroenmeinenonoic acid* (VI), *bisdehydrodihydroenmein-C-1-epimer* (IX) *and unsaturated ketodiacid* (X)

(i) Compound V (6 g; 0·0168 mole) in $\frac{1}{100}$N KOH (1680 ml) was refluxed for 12 hr. After cooling and acidification with HCl, the solution was extracted with AcOEt. The organic layer, after extraction with 5% Na_2CO_3aq, washing with water and drying, was evaporated to recover the starting material (50 mg). The above 5% Na_2CO_3 extract, combined with washings, was acidified with HCl and extracted with AcOEt. The organic layer was washed with water, dried and evaporated. Addition of MeOH to the syrupy residue yielded crystalline IX which was recrystallized from MeOH (180 mg),

[34] Okamoto *et al.* published a successful conversion of enmein into (−)-kaurane independently. Their route was found to be almost the same with ours except the steps of reduction of carbonyl group at C-15: K. Shudo, M. Natsume and T. Okamoto, *Chem. Pharm. Bull. Tokyo* **13**, 1019 (1965).

m.p. 208–210°, IR ν_{max}^{KBr}: 1770; 1750; 1719 cm^{-1}, NMR $\delta_{ppm}^{Pyridine}$: 1·08 (3H, doublet, J = 7 c/s); 1·38 (3H, singlet); 1·45 (3H, singlet); 2·89 (1H, doublet of doublets, J = 3·7 and 15·5 c/s); 3·60 (1H, doublet of doublets, J = 2·5 and 15·5 c/s); 4·71 (2H, AB type, J = 10 c/s); 5·23 (1H, doublet of doublets, 2·5 and 3·7 c/s). (Found: C, 66·90; H, 6·97. Calc. for $C_{30}H_{44}O_6$: C, 66·65; H, 6·71%.) Concentration of the filtrate from IX afforded VI (3·8 g) which was recrystallized from MeOH to give needles, m.p. 240–241° (dec), IR ν_{max}^{KBr}: 3100; 1781; 1750; 1712; 1663 cm^{-1}. (Found: C, 66·74; H, 6·87. Calc. for $C_{30}H_{44}O_6$: C, 66·65; H, 6·71%.) The methyl ester (VII) prepared by the reaction with diazomethane in MeOH had m.p. 249°, UV λ_{max}: 224 mμ (ε 9900), IR ν_{max}^{KBr}: 1772; 1749; 1727; 1690 cm^{-1}. (Found: C, 67·63; H, 7.27. Calc. for $C_{31}H_{46}O_6$: C, 67·36; H, 7·00%.)

(ii) Compound V (4·272 g) in $\frac{1}{15}$N KOH (133 ml) was refluxed for 12 hr and the acidic fraction was treated as usual to give the unsaturated X, m.p. 299–302° (dec), UV λ_{max}: 228 mμ (ε 7200), IR ν_{max}^{KBr}: 3400 (broad); 2650 (shoulder); 1765; 1700; 1677 cm^{-1}.

The acid X was often produced also in the case of (i) as a by-product.

The methyl ester had m.p. 154–155°, UV λ_{max}: 226 mμ (ε 8300), IR ν_{max}^{KBr}: 1771; 1729; 1683 cm^{-1}. (Found: C, 64·89; H, 7·42. Calc. for $C_{32}H_{50}O_7$: C, 65·01; H, 7·44%.)

Diketo lactone ester (20-*hydroxy*-6,7-*secokaurane*-3,15-*dione*-6,7-*dioic acid* 7-*methyl ester* 6 → 20-*lactone*) (VIII)

A solution of VII (800 mg) in MeOH (200 ml) was hydrogenated in the presence of 10% Pd-C (1 g) at 15°; H_2 (60 ml) was absorbed rapidly. The catalyst was filtered off and washed with $CHCl_3$–MeOH. The filtrate, combined with washings, was evaporated *in vacuo*. The residue gave a solid which crystallized from MeOH to give needles of VIII (750 mg), m.p. 221–222°, $[\alpha]_D^{24}$ −92·1° (*c*, 0.64; $CHCl_3$), IR ν_{max}: 1758; 1712 cm^{-1}, NMR δ_{ppm}: 1·13 (3H, doublet, J = 7 c/s); 1·19 (3H, singlet); 1·31 (3H, singlet); 3·71 (3H, singlet); 4·77 (2H, AB type, J = 10 c/s). (Found: C, 67·26; H, 7·62. Calc. for $C_{31}H_{38}O_6$: C, 67·00; H, 7·50%.)

Monothioketal (20-*hydroxy*-6,7-*secokaurane*-3,15-*dione*-6,7-*dioic acid* 7-*methyl ester* 6 → 20 *lactone* 3-*ethylenethioketal*) (XI) *and dithioketal* (20-*hydroxy*-6,7-*secoenantioabiet*-15-*ene*-3,16-*dione*-6,7-*dioic acid* 7-*methyl ester* 6 → 20-*lactone* 3,16-*diethylenethioketal*) (XIV)

A mixture of VIII (634 mg), ethanedithiol (3 ml) and BF_3-etherate (6 ml) was allowed to stand at room temp for 2 days. The reaction mixture was poured onto ice water containing Na_2CO_3, and the alkaline mixture extracted with $CHCl_3$. The extract was washed with water, dried and evaporated *in vacuo* and the residue (983 mg) was chromatographed on silica gel (12 g). The elution with $CHCl_3$ gave main groups of fraction I and fraction II. The early fraction (I: 273 mg) was crystallized from acetone to give a *dithioketal* (XIV) as needles (30 mg), m.p. 264–266·5°, IR ν_{max}: 1765; 1725 cm^{-1}, NMR δ_{ppm}: 1·20 (3H, singlet); 1·48 (3H, singlet); 1·70 (3H, singlet;) 2·68 (1H, singlet); 3·25 (4H, multiplet); 3·30 (4H, singlet); 3·67 (3H, singlet); 3·96 (2H, singlet). (Found: C, 56·81; H, 7·04. $C_{35}H_{54}O_4S_4$ requires: C, 56·81; H, 6·87%.) The fraction II (482 mg) was crystallized from hexane–$CHCl_3$ to give a *monothioketal* (XI) as needles (400 mg), m.p. 220°, IR ν_{max}^{Nujol}: 1755; 1711 cm^{-1}, NMR δ_{ppm}: 1·10 (3H, doublet, J = 6 c/s); 1·19 (3H, singlet); 1·56 (3H, singlet); 3·28 (4H, multiplet); 3·78 (3H, singlet); 3·99 (2H, singlet). (Found: C, 61·28; H, 7·21. $C_{33}H_{52}O_5S_2$ requires: C, 61·05; H, 7·13%.)

Mono keto lactone ester (20-*hydroxy*-6,7-*secokauran*-15-*one*-6,7-*dioic acid* 7-*methyl ester* 6 → 20-*lactone*) (XII)

A mixture of XI (840 mg) and Raney Ni W-2 (10 g),which was prepared in the usual manner,[35] in EtOH (300 ml) was refluxed for 8 hr. After cooling, the mixutre was filtered and the recovered catalyst was washed 5 times with hot EtOH (100 ml each). The filtrate, combined with washings, on evaporation *in vacuo* gave a crystalline residue (411 mg) which was chromatographed on silica gel (8 g). Elution with $CHCl_3$ gave *a keto lactone ester* XII (340 mg) which crystallized from MeOH and hexane–$CHCl_3$ as needles, m.p. 132–134°, $[\alpha]_D^{24}$ −18·8° (*c*, 0·64; $CHCl_3$), IR ν_{max}^{Nujol}: 1765; 1744; 1711 cm^{-1}, NMR δ_{ppm}: 0·98 (3H, singlet); 1·10 (3H, doublet, J = 7 c/s); 1·18 (3H, singlet); 2·13 (1H, singlet); 3·78 (3H, singlet); 4·97 (2H, singlet). (Found: C, 69·88; H, 8·51. $C_{31}H_{50}O_5$ requires: C, 69·58; H, 8·34%.)

[35] R. Mozingo, *Organic Syntheses* Coll. Vol. III; p. 181. Wiley, New York (1955).

ORD of compound XII *in methanol* (*c*, 0·21), 22°. $[\varphi]_{700}$ +32·4, $[\varphi]_{592}$ ±0, $[\varphi]_{335}^{trough}$ −2500, $[\varphi]_{328}^{Peak}$ +3680, $[\varphi]_{356}^{trough}$ +3070, $[\varphi]_{350}^{Peak}$ +3210, $[\varphi]_{335}$ +2560.

Lactone ester (*20-hydroxy-6,7-secoenantioabietane-6,7-dioic acid 7-methyl ester 6 → 20-lactone*) (XV) *and its C-8-epimer* (XVI)

(i) A mixture of XIV (300 mg) and Raney Ni W-2 (6 g) in EtOH (300 ml) was refluxed for 8 hr, and the reaction product was chromatographed on silica gel (5 g). The fraction which was eluted by $CHCl_3$ gave *the lactone ester* XV as needles (200 mg), m.p. 106·5–107·5°, IR ν_{max}: 1770 (shoulder); 1768; 1728 cm^{-1}, NMR δ_{ppm}: 0·84 (6H, doublet, J = 6 c/s); 0.96 (3H, singlet); 1·19 (3H, singlet); 2·32 (1H, singlet); 3·68 (3H, singlet); 3·92 (2H, singlet). (Found: C, 71·67; H, 9·88. $C_{31}H_{34}O_4$ requires: C, 71·96; H, 9·78%.) The filtrate from XV was rechromatographed on silica gel. The early fraction which was eluted with $CHCl_3$ gave *the* C-8 *epimeric lactone ester* (XVI) which crystallized from MeOH as needles (10 mg), m.p. 84–85°, IR ν_{max}^{KBr}: 1757; 1735 cm^{-1}, NMR δ_{ppm}: 0·84 (6H, doublet, J = 5 c/s); 1·08 (3H, singlet); 1·16 (3H, singlet); 2·22 (1H, singlet); 3·00 (1H, broad); 3·63 (3H, singlet); 4·04 (2H, AB type, J = 9·5 c/s). (Found: C, 71·70; H, 10·66. $C_{31}H_{34}O_4$ requires: C, 71·96; H, 9·78%.) The C-8 epimeric XVI (150 mg) was refluxed in 5% MeONa–MeOH (20 ml) for 35 min and allowed to stand overnight. The acidic fraction was treated with CH_2N_2 to yield a methyl ester which was identical with XV. (Mixed m.p. and IR spectra comparison.)

(ii) A mixture of XII (300 mg), ethanedithiol (3 ml) and BF_3-etherate (5 ml) was allowed to stand. After 2 days at room temp, the mixture was agitated for a week at 30–40°. On cooling, the mixture was poured into Na_2CO_3aq in which ice had been added and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated *in vacuo*. The residue was dissolved in EtOH (300 ml) and Raney Ni W-2 (6 g) was added. The mixture was treated in the manner described above to give crystals, m.p. 106·5°, which was identified with XV by mixed m.p. and IR spectra comparison.

Enmein diacetate (XX)

A solution of II (0·5 g) in Ac_2O (3 ml)–pyridine (5 ml) was heated on a water bath for 3 hr. Evaporation *in vacuo* and crystallization of the residue from MeOH gave XX (300 mg) which had m.p. 223–225° (dec), $[\alpha]_D^{19}$ −76·2° (*c*, 1·7; $CHCl_3$), IR ν_{max}^{Nujol}: 1755; 1720 cm^{-1}. (Found: C, 64·30; H, 7·04. Calc. for $C_{34}H_{30}O_8$: C, 64·56; H, 6·77%.)

Dihydroenmein diacetate (XIX)

A solution of XX (0·5 g) in AcOH (100 ml) was hydrogenated in the presence of Adams' catalyst yielding XIX as prisms (300 mg), m.p. 235–236° (dec), $[\alpha]_D^{19}$ −84·0° (*c*, 1·2; $CHCl_3$), IR ν_{max}^{Nujol}: 1760; 1725 cm^{-1}. (Found: C, 64·18; H, 7·45. Calc. for $C_{34}H_{32}O_8$: C, 64·27; H, 7·19%.) The compound was prepared also by the reaction of dihydroenmein with Ac_2O-pyridine.

Dihydroenmein-3-acetate (XXI)

A mixture of XIX (1·112 g) in water (57 ml) was refluxed with oxalic acid (330 mg) for 3 hr yielding XXI (0·725 g), m.p. 244–245°, $[\alpha]_D^{24}$ −111° (*c*, 0·66; $CHCl_3$), IR ν_{max}^{Nujol}: 3545; 1755; 1713 cm^{-1}. (Found: C, 65·29; H, 7·61. Calc. for $C_{32}H_{30}O_7$: C, 65·01; H, 7·44%.)

Dehydrodihydroenmein-3-acetate (XVIII)

(i) A solution of XXI (710 mg) in AcOH (30 ml) was treated with CrO_3 (300 mg) for 3 hr. Destruction of excess oxidant with MeOH and condensation *in vacuo* gave crystals which were chromatographed on silica gel (20 g). The XVIII eluted with $CHCl_3$ crystallized from MeOH as needles (600 mg), m.p. 275–280°, $[\alpha]_D^{24}$ −58·7° (*c*, 0·61; $CHCl_3$), IR ν_{max}: 1760; 1727 cm^{-1}. (Found: C, 65·63; H, 7·13. Calc. for $C_{32}H_{28}O_7$: C, 65·35; H, 6·98%.)

(ii) To XIX (20 g) in AcOH (500 ml) and water (50 ml) was added under stirring a solution of CrO_3 (12 g) in AcOH (80 ml) and water (20 ml) over a period of 1 hr. The mixture was stirred at room temp for 3 hr and left overnight after addition of MeOH. Evaporation *in vacuo* and dilution with water yielded crystalline XVIII (16·3 g), m.p. 274–280°, which was identified with a sample of the product from (i). (Mixed m.p. and IR spectra comparison.)

Dehydrodihydroenmein (XVII)

(i) *Hydrolysis of dehydrodihydroenmein-3- acetate* (XVIII). Compound XVIII (1·0 g) in MeOH (400 ml) was hydrolyzed with 1N KOH (8·75 ml) and water (40 ml) under reflux for 3 hr. The solution was condensed *in vacuo* to afford crystals (519 mg). To the filtrate was added water to give a second crop of crystals. Combined product was recrystallized from MeOH to give XVII as prisms (264 mg), m.p. 239°, IR ν_{max}^{Nujol}: 3500; 1773; 1755; 1710 cm^{-1}, NMR $\delta_{ppm}^{Pyridine}$: 1·02 (3H, doublet, J = 7 c/s); 1·11 (3H, singlet); 1·40 (3H, singlet); 2·85 (1H, singlet); 4·90 (1H, broad); 4·47 (2H, AB type, J = 10 c/s); 5·29 (1H, doublet of doublets, J = 7 and 11 c/s). (Found: C, 66·05; H, 7·21. Calc. for $C_{30}H_{36}O_6$: C, 66·28; H, 7·23%.)

(ii) *Oxidation of dihydroenmein* (IV). To a solution of IV (1·0 g) in AcOH (100 ml) and water (10 ml) was added dropwise under stirring CrO_3 (210 mg, 1 equivalent: 200 mg) in AcOH (2·5 ml) and water (2·5 ml) over a period of 30 min at 5–10° and the mixture was allowed to stand overnight. Evaporation of the solvent, after destruction of excess oxidant with MeOH, gave a gum which was crystallized from MeOH to give XVII (437 mg) as prisms, which was identical with the authentic sample.

Acetylation of dehydrodihydroenmein

A solution of dehydrodihydroenmein (100 mg) in pyridine (2 ml) was treated with Ac_2O (6 ml) for 4 hr on a water bath, yielding XVIII (108 mg), m.p. 276–278°, which was identified with the authentic sample.

Dehydrodeoxodihydroenmein-3-acetate (XXIII) *and dehydrotetrahydroenmein-3-acetate* (XXV)

A suspension of XVIII (500 mg) in ethanedithiol (3 ml) was stirred with BF_3-etherate (2 ml) at 30–40° for 24 hr, during which time the starting material was dissolved. After further addition of ethanedithiol (3 ml) and BF_3-etherate (3 ml) and standing at 30–40° for 3 days, the reaction mixture was poured into ice-cold Na_2CO_3aq. Extraction with $CHCl_3$, drying and evaporation gave a residue (870 mg) which was refluxed in EtOH (300 ml) with Raney Ni W-2 (10 g) for 8 hr. The desulfurized material showed 4 spots on TLC ($CHCl_3$:Me_2CO = 98:2): R_f 0·65 (compound-*a*); 0·55 (compound-*b*); 0·35 (compound-*c*); 0·20 (compound-*d*). The crude product was chromatographed on silica gel (6 g). From the early fractions eluted with $CHCl_3$ the compound-*a* was obtained. The latter crystallize from MeOH in needles (200 mg) of *dehydrodeoxodihydroenmein-3-acetate* (XXIII), m.p. 206–209°, $[\alpha]_D^{24}$ −21·6° (*c*, 0·6; $CHCl_3$), IR ν_{max}: 1773; 1735 cm^{-1}, IR ν_{max}^{KBr}: 1770; 1725 cm^{-1}, NMR δ_{ppm}: 1·00 (3H, doublet, J = 6·5 c/s); 1·11 (3H, singlet); 1·15 (3H, singlet); 2·12 (3H, singlet); 2·53 (1H, singlet); 4·08 (2H, AB type, J = 10 c/s); 4·74 (1H, doublet of doublets, J = 7 and 11·5 c/s); 4·96 (1H, doublet of doublets, J = 2 and 3·5 c/s). (Found: C, 67·68; H, 7·99. $C_{32}H_{50}O_6$ requires: C, 67·67; H, 7·74%.) The substance showed a negative Legal's test.

The middle fractions eluted with $CHCl_3$ gave a mixture (10 mg) of compound-*a* and compound-*b*, and the isolation of each compound by chromatography or recrystallization was difficult. The NMR spectrum of the mixture showed a doublet at δ 1·00 ppm (J = 7 c/s) (tertiary Me protons), singlets at δ 1·12 and 1·15 ppm (quaternary Me protons), a doublet at δ 1·78 ppm (J ≃ 2 c/s) (vinylic Me protons) and a doublet at δ 5·71 ppm (broad) (vinylic proton). The IR spectrum of the mixture was essentially identical with that of XXIII. Hydrogenation of the above mixture (10 mg) in the presence of Adams' catalyst afforded crystals, m.p. 205–208°, (9 mg) which showed no signals at δ 1·78 ppm (vinylic Me) and δ 5·71 ppm (vinylic proton) on NMR spectrum and proved to be identical with XXIII. (Mixed m.p., IR spectra, TLC.)

The last fractions, combined with the mother liquor of the above products, were chromatographed again on silica gel (2 g) under elution with $CHCl_3$ to give the compound-*c* (25 mg) and the compound-*d* (20 mg). The compound-*c* was identical with the starting material XVIII. The compound-*d* was recrystallized from MeOH to give *dehydrotetrahydroenmein-3-acetate* (XXV), m.p. 225–227°, IR ν_{max}: 3550; 1768; 1725 cm^{-1}, NMR δ_{ppm}: 0·90 (3H, doublet, J = 7 c/s); 1·12 (3H, singlet); 1·17 (3H, singlet); 2·13 (3H, singlet); 2·60 (1H, singlet); 4·20 (2H, singlet); 4·76 (1H, doublet of doublets, J = 7 and 11 c/s); 5·00 (2H, multiplet). (Found: C, 65·31; H, 7·55. $C_{32}H_{50}O_7$ requires: C, 65·01; H, 7·44%.) Compound XXV (10 mg) was dissolved in pyridine (0·5 ml) and Ac_2O (0·5 ml) was added. The mixture was allowed to stand overnight at room temp and heated for 3 hr on a water bath yielding after recrystallization of the product from MeOH XXVI (7 mg), m.p. 273–274°, which proved to be identical with a sample derived from dehydrotetrahydroenmein as described below.

Dehydrotetrahydroenmein-3,15-diacetate (XXVI)

To XVII (3 g) in EtOH (300 ml) was added dropwise under stirring $NaBH_4$ (3 g) in EtOH (100 ml). The mixture was warmed at 70° for 1 hr and left overnight at room temp yielding dehydrotetrahydroenmein (1·74 g), m.p. 247–248°. A solution of dehydrotetrahydroenmein (50 mg) in pyridine (1 ml) was treated with Ac_2O (1 ml) and allowed to stand overnight. After subsequent heating for 3 hr on a water bath, the resulting product was recrystallized from MeOH to give XXVI (35 mg), m.p. 273°, IR ν_{max}^{KBr}: 1778; 1750; 1727 cm^{-1}, NMR δ_{ppm}: 0·80 (3H, doublet); 1·18 (3H, singlet); 1·19 (3H, singlet); 2·09 (3H, singlet); 2·13 (3H, singlet); 2·60 (1H, singlet); 4·24 (2H, AB type, J = 10 c/s); 4·78 (1H, doublet of doublets, J = 6 and 11 c/s); 5·02 (1H, doublet of doublets, J = 2·5 and 3·5 c/s); 5·78 (1H, doublet, J = 10 c/s). (Found: C, 64·55; H, 7·43. Calc. for $C_{34}H_{32}O_8$: C, 64·27; H, 7·19%.) This diacetate was identical with the diacetate obtained in the aforegoing experiment. (Mixed m.p., IR spectra and TLC.)

Dehydrodeoxodihydroenmein (XXII)

(i) *Hydrolysis of dehydrodeoxodihydroenmein-3-acetate* (XXIIII). A solution of XXIII (2·786 g) in MeOH (230 ml) was refluxed with 1N NaOH (7·5 ml) for 2 hr. Neutralization with $\frac{1}{10}N$ H_2SO_4, evaporation of the solvent and dilution with water gave a crystalline precipitate (2·19 g) which was recrystallized from MeOH to yield *dehydrodeoxodihydroenmein* (XXII) as needles, m.p. 236–239°, $[\alpha]_D^{24}$ −51·4° (*c*, 0·60; $CHCl_3$), IR ν_{max}: 3600; 3450; 1766; 1723 cm^{-1}, NMR δ_{ppm}: 1·00 (3H, doublet, J = 5 c/s); 1·03 (3H, singlet); 1·26 (3H, singlet); 2·57 (1H, singlet); 4·05 (2H, AB type, J = 10 c/s); 3·80 (1H, multiplet); 4·97 (1H, doublet of doublets, J = 7 and 11 c/s). (Found: C, 68·98; H, 7·89. $C_{30}H_{36}O_6$ requires: C, 68·94; H, 8·10%.)

(ii) *Thioketalization and desulfurization of dehydrodihydroenmein* (XVII). A mixture of XVII (171 mg), ethanedithiol (1·5 ml) and BF_3-etherate (0·5 ml) was treated at 30–40° under stirring for 3 days. The mixture was poured into ice cold Na_2CO_3aq and extracted with $CHCl_3$. The residue obtained by evaporation of $CHCl_3$ was chromatographed on silica gel (5 g). The fractions eluted with $CHCl_3$ gave XXII, identical with the foregoing sample. (Mixed m.p. and IR spectra.)

Dehydrodeoxodihydroenmeinone (XXVII)

Compound XXII (2·19 g) in AcOH (50 ml) was treated with CrO_3 (1 g) at room temp for 3 hr. Excess oxidant was destroyed with MeOH and the mixture was evaporated *in vacuo*. Water was added to the residue and the mixture was extracted with $CHCl_3$. The extract was washed with Na_2CO_3aq, dried and evaporated. The resulting residue was chromatographed on silica gel (20 g) under elution with $CHCl_3$. The main fractions were combined and crystallized from MeOH to give *dehydrodeoxodihydroenmeinone* (XXVII; 750 mg), m.p. 196–200°, IR ν_{max}: 1773; 1740; 1721 cm^{-1}, NMR δ_{ppm}: 1·00 (3H, doublet, J = 6 c/s); 1·28 (6H, singlet); 2·56 (1H, singlet); 3·00 (1H, multiplet); 4·30 (2H, AB type, J = 10 c/s); 4·89 (1H, doublet of doublets, J = 7 and 11 c/s). (Found: C, 69·63; H, 7·38. $C_{30}H_{36}O_6$ requires: C, 69·34; H, 7·59%.)

Hydrolysis of Dehydrodeoxodihydroenmeinone (XXVII)

Acid A (*20-hydroxy-6,7-secokaur-1-en-3-one 6,7-dioic acid 6 → 20 lactone*) (XXVIII) *and acid B* (*7 → 20 lactone isomer*) (XXIX)

Compound XXVII (1·35 g) was refluxed in $\frac{1}{10}N$ KOH (450 ml) for 5 hr. The solution was acidified with dil. HCl and extracted with AcOEt. The organic layer was extracted with 10% Na_2CO_3aq. The alkaline extract was acidified and again extracted with AcOEt. The extract was washed with water, dried and evaporated. The residue crystallized from MeOH as needles (267 mg) of *acid B* (XXIX), m.p. 267–269°, UV λ_{max}: 224 mμ (ε 10800), IR ν_{max}^{KBr}: 3400; 1730; 1660 cm^{-1}. (Found: C, 69·21; H, 7·68. $C_{30}H_{36}O_6$ requires: C, 69·34; H, 7·57%.) The filtrate from acid B was concentrated to give *acid A* (XXVIII) as gum (968 mg), IR ν_{max}^{KBr}: 3200; 1770; 1720; 1680 cm^{-1}.

Acid B (XXIX; 20 mg) was refluxed in $\frac{1}{10}N$ KOH (7 ml) for 4 hr. The solution was treated in the usual manner to give acid A (XXVIII; 16 mg) from the acidic fraction. The identification was done by the comparison of IR spectra. The methyl ester was also identified with the methyl ester XXX of acid A which will be described below. (Mixed m.p. and IR spectrum.)

Methyl ester of acid A (*20-hydroxy-6,7-secokaur-1-en-3-one-6,7-dioic acid 7-methyl ester* 6 → 20 *lactone*) (XXX)

Methylation of XXVIII (950 mg) with CH_2N_2 in MeOH, chromatography on silica gel with $CHCl_3$ and crystallization from MeOH gave *the methyl ester* XXX as prisms (912 mg), m.p. 146–148°, UV λ_{max}: 233 mμ (ε 9500), IR ν_{max}: 1770; 1723; 1682 cm^{-1}, NMR δ_{ppm}: 1·00 (3H, doublet, J = 6 c/s); 1·19 (3H, singlet); 1·38 (3H, singlet); 3·01 (1H, singlet); 3·66 (3H, singlet); 4·15 (2H, AB type, J = 10 c/s); 6·17 (1H, doublet, J = 10 c/s); 6·98 (1H, doublet, J = 10 c/s). (Found: C, 69·87; H, 7·96. $C_{31}H_{38}O_5$ requires: C, 69·79; H, 7·83%.)

Methyl ester of acid B (*20-hydroxy-6,7-secokaur-1-en-3-one-6,7-dioic acid 6-methyl ester* 7 → 20-*lactone*) (XXXI)

The methyl ester XXXI was prepared from acid B (250 mg) by the reaction with CH_2N_2 to afford gum (249 mg), UV λ_{max}: 224 mμ (ε 9490), IR ν_{max}: 1725; 1680 cm^{-1}, NMR δ_{ppm}: 1·01 (3H, doublet, J = 7 c/s); 1·14 (3H, singlet); 1·36 (3H, singlet); 2·81 (1H, singlet); 3·72 (3H, singlet); 4·58 (2H, AB type, J = 12 c/s); 6·09 (1H, doublet, J = 11 c/s); 6·76 (1H, doublet, J = 11 c/s). The gum was crystallized from MeOH, but it isomerized to XXX which was identified by mixed m.p. and IR spectrum.

Hydrogenation of ester XXX.

20-hydroxy-6,7-secokauran-3-one-6,7-dioic acid 7-methyl ester 6 → 20-*lactone* (XXXII). Unsaturated ester XXX (877 mg) in MeOH was hydrogenated in the presence of 10% Pd–C to give *a saturated ester* XXXII (852 mg) as gum, IR ν_{max}: 1770; 1715 cm^{-1}, NMR δ_{ppm}: 1·02 (3H, doublet, J = 6 c/s); 1·21 (3H, singlet); 1·31 (3H, singlet); 2·56 (1H, singlet); 3·68 (3H, singlet); 4·25 (2H, AB type, J = 11 c/s).

3-*Acetoxy-20-hydroxy-6,7-secokaurane-6,7-dioic acid 7-methyl ester* 6 → 20-*lactone* (XXXIV). The XXX (50 mg) in MeOH (5 ml) was hydrogenated in the presence of Adams' catalyst (10 mg). Evaporation of the solvent gave a gum which was acetylated with Ac_2O (1 ml)–pyridine (1 ml). The treatment in the usual manner and purification by chromatography on silica gel gave crystals which recrystallized from MeOH to yield *the acetate* XXXIV as needles (25 mg), m.p. 175–177°, IR ν_{max}: 1770; 1725 cm^{-1}, NMR δ_{ppm}: 0·91 (3H, singlet); 1·10 (3H, doublet, J = 6 c/s); 1·18 (3H, singlet); 2·09 (3H, singlet); 2·63 (1H, singlet); 3·70 (3H, singlet); 4·63 (2H, AB type, J = 11 c/s); 4·57 (1H, broad). (Found: C, 68·17; H, 8·57. $C_{32}H_{34}O_6$ requires: C, 67·95; H, 8·43%.)

Hydrogenation of ester XXXI

20-hydroxy-6,7-secokauran-3-one-6,7-dioic acid 6-methyl ester 7 → 20-*lactone* (XXXIII). The ester XXXI (50 mg) was hydrogenated in MeOH (10 ml) in the presence of 10% Pd–C (50 mg). The product was chromatographed on silica gel to give a gum which proved to be saturated: IR ν_{max}: 1715 cm^{-1}.

20-Hydroxy-6,7-secokaurane-6,7-dioic acid 7-methyl ester 6 → 20-*lactone* (III).

Ethanedithiol (1 ml) and BF_3-etherate (0·5 ml) were added to XXXII (810 mg). The solution colored to yellow. After standing for 15 min at room temp no spot of the starting material was shown on TLC. After standing for an additional 15 min, the mixture was poured into ice-cold Na_2CO_3aq. Extraction with $CHCl_3$ followed by the treatment of the extract in the usual manner gave an amorphous thioketal, which was desulfurized with Raney Ni W-2 (9·0 g) in EtOH (300 ml) under reflux for 8 hr. The filtrate from the catalyst, combined with washings of Ni, was evaporated to give a residue (615 mg) which was chromatographed on silica gel (15 g) with elution by $CHCl_3$ to yield *the lactone ester* III. Recrystallization from hexane–$CHCl_3$ gave needles (230 mg), m.p. 149–155°, IR ν_{max}: 1760; 1715 cm^{-1}, NMR δ_{ppm}: 0·95 (3H, singlet); 1·00 (3H, doublet, J = 6 c/s); 1·18 (3H, singlet); 3·68 (3H, singlet); 3·91 (2H, singlet). (Found: C, 72·08; H, 9·23. $C_{31}H_{32}O_4$ requires: C, 72·38; H, 9·26%.) Compound III gave a negative Legal's test.

20-Hydroxy-6,7-secokaurane-6,7-dioic acid 6-methyl ester 7 → 20-*lactone* (XXXV).

The thioketal prepared from XXXIII (50 mg) by the reaction of ethanedithiol (1 ml)–BF_3 etherate (0·5 ml) was desulfurized in EtOH (100 ml) with Raney Ni W-2 (2 g). Chromatography on silica gel and crystallization from hexane–$CHCl_3$ gave *the lactone ester* (XXXV) as needles (15 mg), m.p. 161–162°, IR ν_{max}: 1715 cm^{-1}.

Acyloin condensation of lactone ester III

The III (1·5 g) was dried over P_2O_5 *in vacuo* at room temp for 3 days. The material was dissolved in anhydrous Et_2O (50 ml) and put in a dropping funnel. The apparatus consisted of a 0·5 l. three-necked flask equipped with a dropping funnel in the center neck, gas inlet tube for N_2 and ammonia in one side neck and a dry ice condenser in another neck. The top of the condenser was open to the atmosphere through a large drying tube containing KOH pellets and silica gel. A stream of purified and dried N_2 was passed through the running of the reaction. Anhydrous Et_2O (100 ml) and anhydrous NH_3 (125 ml) were introduced into the flask. While the mixture was vigorously stirred with magnetic stirrer, Na (750 mg), freshly cut, was added quickly through the ammonia inlet, which was stoppered after the Na addition. Then the ethereal solution of III was dropwise added over a period of 2 hr. The characteristic blue–black color of Na in liquid NH_3 persisted until after completion of the addition of the lactone ester. After addition of MeOH (5 ml)–Et_2O (50 ml) to remove the excess Na, ammonia was allowed to evaporate. The reamining mixture was acidified with 5% HCl and Et_2O layer was separated. The aqueous layer was thoroughly extracted with Et_2O. The combined Et_2O extracts were then washed with Na_2CO_3aq, dried and evaporated to yield a residue (1·2 g). TLC of the residue showed spots of R_f 0·90, 0·65, 0·50, 0·47, 0·45 and 0·10 when developed with $CHCl_3$–Me_2CO (90:10). The product was column-chromatographed on silica gel (25 g) with elution by $CHCl_3$ and 55 fractions of each 5 ml were separated.

6α,20-*Epoxy-kaurane* (XXXVIII). Fraction numbers 6–17 were rechromatographed on silica gel with elution by $CHCl_3$ and again on neutral alumina (activity III) with benzene. The main fractions were combined and the solvent was evaporated to give a residue, which was crystallized from acetonitril to afford XXXVIII (R_f 0·90) as needles (5 mg), m.p. 130–131°, IR ν_{max}: 1045 cm^{-1}, NMR δ_{ppm}: 0·89 (3H, singlet); 0·97 (3H, singlet); 1·00 (3H, doublet, J = 5 c/s); 3·81 (2H, AB type, J = 9 c/s); 4·23 (1H, multiplet). (Mol. wt. Found: 274 in mass spectrum. $C_{20}H_{34}O$ requires: 274.)

Kaurane-6β,20-diol (XXXIX). The filtrate from XXXVIII and the fractions of Nos 18–26 were combined and rechromatographed on silica gel (20 g) with $CHCl_3$. The evaporated main fractions were crystallized from MeOH to give *diol* XXXIX (R_f 0·65) as needles (100 mg), m.p. 152–154°, IR ν_{max}^{KBr}: 3300; 1028 cm^{-1}, NMR δ_{ppm}: 1·00 (3H, doublet, J = 5 c/s); 1·06 (3H, singlet); 1·15 (3H, singlet); 3·90 (1H, multiplet); 4·02 (2H, singlet). (Found: C, 78·50; H, 11·08. $C_{20}H_{34}O_2$ requires: C, 78·38; H, 11·18%.) *The diacetate* XL, prepared by the reaction with Ac_2O–pyridine at room temp for 24 hr, had m.p. 92–94°, IR ν_{max}: 1725 cm^{-1}, NMR δ_{ppm}: 0·92 (3H, singlet); 1·00 (3H, doublet, J = 6 c/s); 1·06 (3H, singlet); 2·04 (3H, singlet); 2·10 (3H, singlet); 4·45 (2H, AB type, J = 12 c/s); 5·27 (1H, octet, J = 5, 9·5 and 11 c/s). (Found: C, 73·22; H, 9·63. $C_{24}H_{38}O_4$ requires: C, 74·19; H, 9·34%.)

6α,20-*Epoxy-kaurane-6β,7ξ-diol* (XLI). The filtrate from XXXIX and the fractions of Nos 27–35 were combined and chromatographed on silica gel (20 g) with $CHCl_3$. The early fractions were evaporated and crystallized from MeOH to give *alcohol A* XLI (R_f 0·50; 15 mg), m.p. 185–187°, IR ν_{max}: 3600; 3350 cm^{-1}, NMR δ_{ppm}: 0·95 (3H, doublet, J = 6·5 c/s); 1·09 (3H, singlet); 1·28 (3H, singlet); 3·30 (1H, singlet); 3·89 (2H, singlet). (Found: C, 74·61; H, 10·36. $C_{20}H_{32}O_3$ requires: C, 74·96; H, 10·06%.) *The acetate A* XLIII, prepared by the reaction with Ac_2O–pyridine at room temp for 24 hr had m.p. 167–168°, IR ν_{max}: 3500; 1720 cm^{-1}, NMR δ_{ppm}: 0·96 (3H, doublet, J = 7 c/s); 1·07 (3H, singlet); 1·27 (3H, singlet); 2·09 (3H, singlet); 3·99 (2H, AB type, J = 9 c/s); 4·69 (1H, singlet). (Mol. wt. Found: 362 in Mass spectrum. $C_{22}H_{34}O_3$ requires: 362.)

7α,20-*Epoxy-kaurane-6β,7β-diol* (XLII). The following fractions on usual treatment yielded *alcohol B* XLII (R_f 0·45) (170 mg), which was recrystallized from $CHCl_3$–Me_2CO and was shown to have m.p. 219°, IR ν_{max}^{KBr}: 3550; 3375 cm^{-1}, NMR $\delta_{ppm}^{Pyridine}$: 0·95 (3H, doublet, J = 6·5 c/s); 1·02 (3H, singlet); 1·07 (3H, singlet); 4·01 (2H, AB type, J = 11 c/s); 4·17 (1H, doublet, J = 4 c/s). (Found: C, 75·02; H, 10·02. $C_{20}H_{32}O_3$ requires: C, 74·96; H, 10·06%.) *The acetate B* XLIV, prepared by the reaction with Ac_2O in pyridine at room temp for 24 hr, had m.p. 174–177°, IR ν_{max}: 3550; 1730 cm^{-1}, NMR δ_{ppm}: 0·83 (3H, singlet); 0·95 (3H, doublet, J = 6·5 c/s); 1·10 (3H, singlet); 2·07 (3H, singlet); 3·87 (2H, AB type, J = 9 c/s); 5·01 (1H, doublet, J = 4·5 c/s). (Found: C, 72·60; H, 9·67. $C_{24}H_{36}O_4$ requires: C, 72·89; H, 9·45%.)

Kauran-6-on-20-al (XLV). Kauranediol XXXIX (3 mg) in pyridine (0·3 ml) was added to a slurry of CrO_3 (3 mg) in pyridine (0·3 ml) over a period of 4 hr and then stirred overnight, all operations being conducted in a current of N_2. The mixture, dilluted with water, was extracted with ether and washed with Na_2CO_3aq. The crude product obtained from the usual treatment of the ethereal extract

was chromatographed on neutral alumina (activity III) (100 mg) with benzene to give *the keto aldehyde* XLV, m.p. 87–116°, IR ν_{max}: 2750; 1710 cm^{-1}, NMR δ_{ppm}: 10·00 (1H, singlet).

The conversion of diol XXXIX *to ether* XXXVIII

Compound XXXIX (11 mg) in pyridine (1·1 ml) was allowed to stand with *p*-toluenesulfonyl chloride (68 mg) at room temp for 24 hr and after heating at 50° for 5 hr on a water bath, the reaction mixture was left at room temp for additional 5 days in order to complete the reaction. Water was added cautiously and the product was extracted with Et_2O. Evaporation of the washed and dried ethereal extract yielded a gum, which was chromatographed on neutral alumina (activity III) with benzene to give XXXVIII (4 mg), m.p. 130–131°, identical with the sample described above.

Attempted Wolff-Kishner reactions on keto aldehyde XLV.

(i) *Nagata's method.* A mixture of XLV (10 mg), 98·5% $NH_2{\cdot}NH_2$ (425 mg) and $NH_2{\cdot}NH_2{\cdot}2HCl$ (76 mg) was heated in triethylene glycol (745 mg) at 140° for 12 hr. Then, KOH pellets (400 mg) were added and the mixture was again heated raising the temp gradually to 220° during 3 hr. After additional heating at 220–230° for 3 hr and cooling, water (5 ml) was added. The treatment of the ethereal extract gave an amorphous residue (10 mg), which was column-chromatographed on neutral alumina (500 mg). The gas chromatography[86] of a hexane eluate, which had R_f 0·90 on TLC on silica gel developed with $CHCl_3$, showed that it consisted of about ten kinds of hydrocarbons. The retention time of a second largest peak was identical with that of (−)-kaurane (13·8 min). Another hexane eluate having R_f 0·88 on TLC proved to be a mixture of two components, which gave their retention times, 19·7 and 21·3 min, on gas chromatogram.

(ii) *Djerassi's method.* A mixture of XLV (1·7 mg) and 98·5% $NH_2{\cdot}NH_2$ (0·6 ml) was heated in triethylene glycol (3 ml) at 140° for 20 hr. The KOH pellets (80 mg) was added and the temp was gradually raised to 220° over a period of 5 hr. After the heating at 220° was kept for 24 hr, the treatment of the reaction mixture gave an oil (1 mg) which had R_f 0·88 on TLC. The latter proved to be a mixture of two components the retention times of which were found to be 19·7 and 21·3 min on gas chromatogram just as in the case of (i).

(iii) *Barton's method.* Diethylene glycol (0·4 ml), fresh distilled with added Na, and 98·5% $NH_2{\cdot}NH_2$ (0·08 ml) were heated to reflux at 180°. On cooling, XLV (2 mg) was added and the mixture was refluxed for 24 hr at 210°. The fraction eluted by hexane proved to be a mixture which contained the aforegoing substances having the retention times of 19·7 and 21·3 min.

(iv) *Mexican method.* A mixture of XLV (7 mg), $NH_2{\cdot}OH{\cdot}HCl$ (10 mg) and anhydrous AcONa (10 mg) was refluxed in EtOH (1 ml) for 14 hr. Concentration of the reaction mixture, extraction of water-added mixture with AcOEt and treatment of the extract gave a mono-oxime, m.p. 247°, IR ν_{max}: 1710 cm^{-1}. The latter (3 mg), 98·5% $NH_2{\cdot}NH_2$ (0·6 ml) and Na (5 mg) was mixed in diethylene glycol (0·75 ml). The mixture was heated in a sealed tube at 200° for 2 hr. The treatment of the product gave just a same result as in the case of (iii).

Pyrolysis of diacetate XL

The XL (48 mg) was sealed in a glass tube *in vacuo* and heated at 295–305° for 40 min. Extraction with Et_2O, washing with $NaHCO_3$aq and evaporation of the solvent gave a gum, the gas chromatography[86] of which showed many peaks of hydrocarbons.

Kaur-6-en-20-ol (XLVII)

A mixture of XLII (20 mg) and 98·5% $NH_2{\cdot}NH_2$ (0·2 ml) in EtOH (0·2 ml) was heated in a sealed tube at 170–180° for 20 hr. On cooling, Na (30 mg) and EtOH (0·4 ml) were added and again heated in a sealed tube at 180° for 2 days. The ethereal extract was washed with dil. HCl and with water, dried and evaporated to give a residue (15 mg), which was chromatographed on neutral alumina (activity I; 200 mg). The hexane eluate (0·6 mg) and benzene eluate (6 mg) were combined and recrystallized from MeOH to give *an unsaturated alcohol* XLVII, m.p. 61–62°, IR ν_{max}: 3650; 3550; 1650 cm^{-1}, NMR δ_{ppm}: 0·91 (6H, singlet); 1·01 (3H, doublet, J = 6 c/s); 3·87 (2H, singlet); 5·41

[86] Gas chromatogram was recorded with Hitachi Model F 6 equipped with Golay-type capillary column (45 m) coated with SE-30 and hydrogen flame ionization detector. Separation was operated at 190° with N_2 gas pressure of 0·5 kg/cm^2.

(1H, doublet of doublets, J = 10 and 2·5 c/s); 5·64 (1H, doublet of doublets, J = 10 and 1 c/s). (Found: C, 78·72; H, 10·94. $C_{20}H_{32}O \cdot H_2O$ requires: C, 78·38; H, 11·18%.) Acetylation gave an amorphous *acetate* XLIX, NMR δ_{ppm}: 2·10 (3H, singlet).

Kauran-20-*ol* (XLVIII)

Kaurenol XLVII (50 mg) was dissolved in MeOH (5 ml) and hydrogenated in the presence of Adams' catalyst. The crude product was recrystallized from MeCN to give *kauranol* XLVIII as needles, m.p. 78–79°, IR ν_{max}: 3640; 3475 cm^{-1}, NMR δ_{ppm}: 0·86 (3H, singlet); 0·92 (3H, doublet, J = 6 c/s); 1·08 (3H, singlet); 4·11 (2H, singlet). *Kauranol acetate* (L), prepared from XLIX by hydrogenation in MeOH in the presence of Adams' catalyst, was amorphous and showed IR ν_{max}: 1725 cm^{-1} and NMR δ_{ppm}: 0·88 (3H, singlet); 0·91 (3H, doublet, J = 6 c/s); 1·08 (3H, singlet); 2·08 (3H, singlet). Hydrolysis of L (6 mg) under reflux with 1N KOH in EtOH (1 ml) for 5 hr gave XLVIII (4 mg).

Kauran-20-*al* (LI)

A solution of XLVIII (46·1 mg) in pyridine (5 ml) was dropwise added over a period of 4 hr to a slurry of CrO_3 (46 mg) in pyridine (5 ml) under stirring in the N_2 atm. After standing overnight, ethereal extract gave a crude product (39 mg), which was chromatographed on neutral alumina (3·0 g). The hexane eluate gave prisms, which recrystallized from MeOH to yield pure *kauranal* LI (12·3 mg), m.p. 96–98°, IR ν_{max}: 2750; 1700 cm^{-1}.

(−)-*Kaurane* (LII)

While a mixture of LI (12·3 mg), 98·5% $NH_2 \cdot NH_2$ (1·8 ml) and ethylene glycol (10 ml) was heated in a sealed tube at 170–180° for 30 hr, no clear solution was prepared. Then, EtOH (4·5 ml) was added and the mixture was heated again in a sealed tube at 180° for 42 hr. On cooling, the contents were put into a round-bottomed flask (50 ml). The KOH pellets (440 mg) were added and the mixture was heated at 100° to evaporate EtOH. Subsequently, the heating at 220° was kept for 2 days. On cooling, the reaction mixture was extracted with Et_2O and the extract gave a crude product, which was column chromatographed on acidic alumina (activity I; 3 g). The hexane eluate gave crystals, which recrystallized from MeCN to afford needles (2 mg), m.p. 87·5–88·5°, $[\alpha]_D^{23}$ −28·7° (*c*, 0·25; MeOH). (Mol. wt. Found: 274 in Mass spectrum. Calc. for $C_{20}H_{34}$: 274). Identity with (−)-kaurane was established by mixture m.p. determination, IR and Mass spectra comparisons, ORD (negative plain curve) and gas chromatography (see footnotes 36, provided that separation was operated at 170° with N_2 gas pressure of 1·5 kg/cm^2; retention time: 10·2 min).

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