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Chemistry and Pharmacology of Diterpenoids of *Siegesbeckia pubescens**

Koo Dong Han, Jae Hoon Kim and Sea Jong Oh

Natural Products Research Institute, Seoul National University, Seoul 110

"Hi-cheom", Korean name of *Siegesbeckia pubescens* MAKINO, which is grown abundantly not only in Korea, but also in other Asian countries, has long been used quite much in Korea from olden times, as folk medicine for the treatment of hypertension and inflammation. Its medicinal values were described in the famous "Pen-Tsao-Kang-mu" and in the other several description[1] indicating us that "Hi-chem" possesses antihypertensive and antiphlogistic effect.

In recent, there appeared several reports on the ingredients of *Siegesbeckia* species. The first one was reported in 1931 by Wehmer[2] who separated a bitter principle from *Siegesbeckia orientalis*, naming it darutin, but its chemical structure was not known. In 1960, Annie Diara[3] separated a glucoside with pimarane skeleton from *Siegesbeckia orientalis*, named it darutoside, and elucidated its chemical structure.

In our laboratory, extraction of the plant, "Hi-cheom", with methanol and then extensive fractionation has yielded five diterpenes (compound A, B, C, D and F) wich are shown in the Table I.

As shown in Table I, among these five kinds of diterpenoids, two components (A and C) were diterpene (A) or diterpene glucoside (C) with pimarane skeleton and other three components (B, D and F) with kaurane skeleton.

We found that compound B has remarkable antihypertensive activity by the animal test. In addition to this activity, we also found that the diterpene B has remarkable antiinflammatory action by the preliminary albumin coagulation test and rat-paw edema test. Two other diterpene D and F were proved also to have antiinflammatory activity.

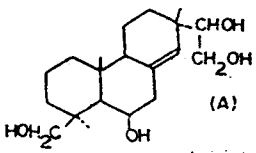
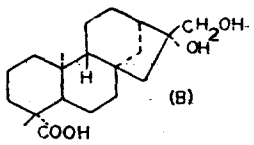
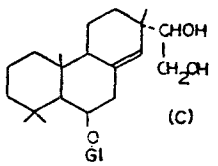
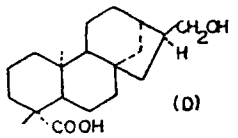
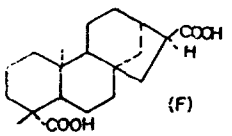
In contrast with these results, diterpenes with pimarane skeleton (A and C) were proved not to have such activities as antiinflammation and antihypertension.

These diterpenes will be described here.

Compound A[4]—Dried crushed plant was extracted with cold methanol. The extract was dissolved in 10% NaOH solution and extracted with butyl alcohol. Benzene was added to the

* Presented on Oct. 5, 1974 at the symposium on "Triterpenoids" organized by Natural Products Research Institute, Seoul National University.

Table I—Compounds isolated from *Siegesbeckia pubescens* MAKINO

Compound	Formula	Mp	$[\alpha]_D$
 (A)	$C_{20}H_{34}O_4$	192~3°	-22°
 (B)	$C_{20}H_{32}O_4$	260~2°	-88°
 (C)	$C_{26}H_{44}O_8 \cdot H_2O$	225 ~6°	-48°
 (D)	$C_{20}H_{32}O_3$	207.5°	-105.8°
 (F)	$C_{20}H_{30}O_4$	258~60°	-133.25°

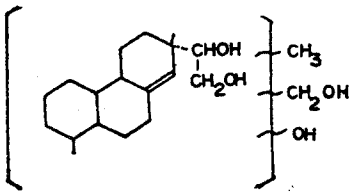
separated butyl alcohol fraction and on standing over night the butanol solution deposited a crystalline solid, which was filtered off. Recrystallization of the crude crystals from boiling water gave needles of compound A (**I**), $C_{20}H_{34}O_4$, mp 192~193° (ethyl alcohol), $[\alpha]_D$= −22° (c, 1.0 in dioxane), IR $\nu_{max}cm^{-1}$; 3325 (OH), 1654 (double bond), NMR (C_5D_5N) δ; 1.26 (3H, s, CH_3), 1.14 (3H, s, CH_3), 0.80 (3H, s, CH_3), 5.15 (1H, bs, $-C-CH=C-CH_2-$); MS (*m/e*) 338 (M^+), 320 ($M^+ - H_2O$), 289, 277, 259, 241.

Acethylation with acetic anhydride in pyridine at room temperature afforded a tetraacetate (**II**), $C_{28}H_{42}O_8$, IR $\nu_{max}cm^{-1}$; 1725, 1660, 1250, while treatment with acetone and anhydrous $CuSO_4$ at room temperature yielded a monoacetonide (**III**), $C_{23}H_{38}O_4$, mp 164~165°, $[\alpha]_D$= −44° (c, 1.0 in $CHCl_3$)*.

* Optical rotations were measured in chloroform solution unless otherwise stated.

Oxidation of I with HIO_4 in methanol gave formaldehyde and the aldehyde (IV), $C_{19}H_{30}O_3$, mp 127~129°, $[\alpha]_D=-118°$, IR $\nu_{max}cm^{-1}$; 3400 (OH), 2700 (CHO), 1718 (CHO), 1660 (double bond), NMR ($CDCl_3$) δ; 1.04 s, 0.70 s, (CH_3), 3.69 d, 3.34 d (J=11 c/s, $C_{18}-H_2$), 5.22 bs ($C_{14}-H$), 9.0 (CHO).

Spectral features of compound A and its derivatives II, III and IV, together with isolation of pimanthrene (V) by selenium dehydrogenation, suggest for it partial structure.



Partial structure of compound A.

In accord with this, oxidation of monoacetonide (III) with Sarett reagent gave a ketoaldehyde acetonide (VI), $C_{23}H_{34}O_4$, mp 116~117°, $[\alpha]_D=-46°$, IR $\nu_{max}cm^{-1}$; 1720 (C=0), 1658 (double bond). Its NMR spectrum (Table II) shows, among other, two lines at 3.06 δ and at 2.83 δ (J=13.7 c/s, 1H, part A of an AB system) which can be attributed to one proton of a methylenic group both allylic and adjacent to a carbonyl function. This fact locates the secondary hydroxyl function at C_6.

By treatment with *p*-toluenesulfonyl chloride in pyridine, the monoacetonide (III) is converted into a mixture of a monotoluene-*p*-sulfonate (VII), $C_{30}H_{44}O_6S$, a ditoluene-*p*-sulfonate (VIII), $C_{37}H_{50}O_8S_2$, and a cyclic ether (IX), $C_{23}H_{36}O_3$, which was resolved by chromatography on silica gel. In the NMR spectrum of IX the tertiary oxymethylene signals appear as an AB system centered at 3.90 δ and 3.23 δ (J=8 c/s). this coupling constant idicates the presence of a five membered heterocyclic ring[5], thus suggesting the tertiary hydroxymethyl group in compound A is at C_4 or at C_{10}.

Since the chemical shifts of the methyl groups of compound A and its derivatives (Table II) are in accordance with those of diterpenoids with a pimarane skeleton, assuming a chair conformation for ring B in order to explain the shielding effect[6] on C_{20}, the tertiary hydro-

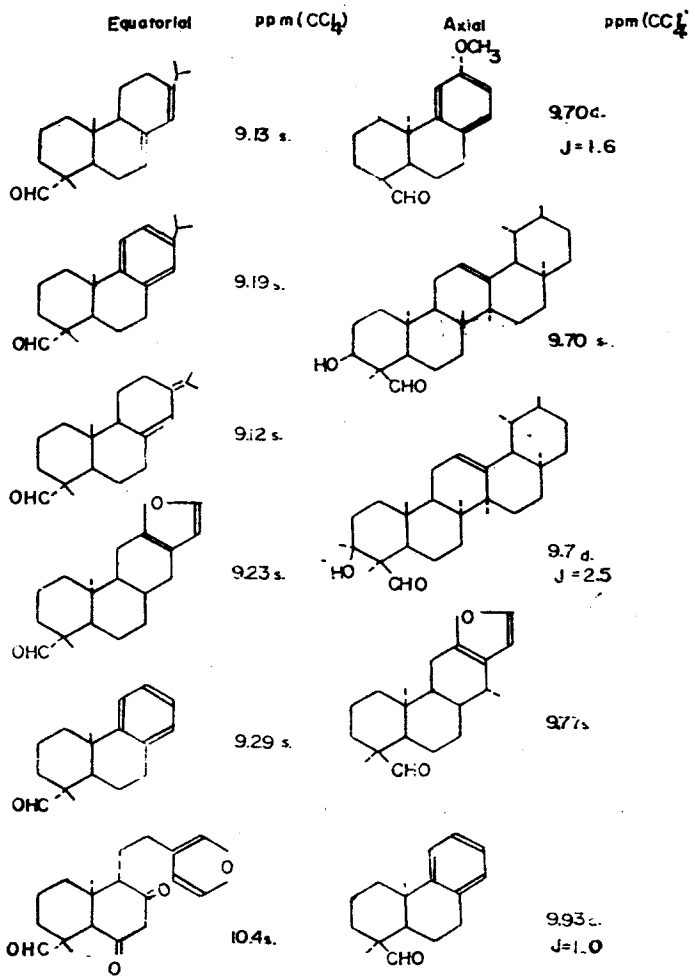
Table II—Chemical shifts of the derivatives of compound A (δ values in $CDCl_3$).

Compound	C_{13}	C_{10}	C_4	$C_{(18)}-H_2$		$C_{(14)}-H$
II	0.95 s	0.91 s	1.04 s	4.10 d	3.94d(J=10.8)	5.15 bs
III	0.92 s	0.78 s	1.04 s	3.73 d	3.34 d(J=12)	5.08 bs
IV	1.04 s	0.70 s	1.07 s	3.69 d	3.34 d(J=11)	5.22 bs
VI	0.93 s	0.68 s	1.24 s	-CHO	9.7 s	5.22 bs
IX	0.95 s	0.88 s	1.00 s	3.90 d	3.23 d(J=8)	5.04 bs
XI	1.16 s	0.51 s	1.31 s	—	—	5.45 bs
XIII	0.93 s	1.01 s	1.04 s	?	3.34 d(J=11)	5.12 bs

xymethyl group should be at C_4.

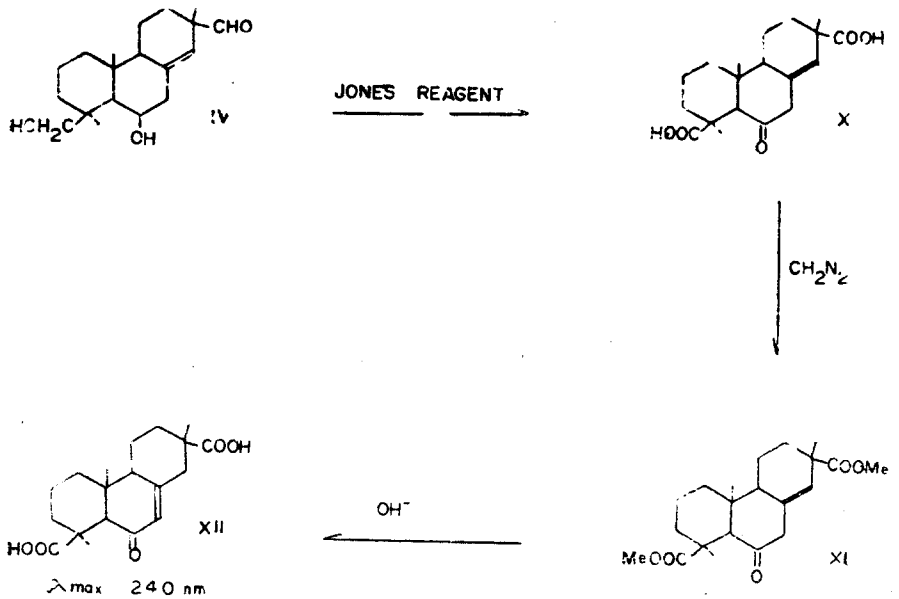
The assignment of configuration at C_4 rests upon the chemical shift and multiplicity of the aldehydic proton of **VI** (singlet at 9.7 δ).

In a study[7] of the NMR spectra of diterpenoids containing an aldehyde at C_4 and an axial proton C_3 it has been shown that equatorial aldehydic protons appear at 9.12~9.3 δ as singlets while axial aldehydic protons at 9.7~9.9 δ as doublets ($J<3$ c/s) (Scheme 1). The value of the chemical shift of the aldehydic proton in **VI** therefore can be explained through a downfield shift due to the carbonylic function at C_6. Since it resonates at 10.1~10.4 δ[8,9] in diterpenoids containing an axial aldehydic group at C_4 and a keto group at C_5, the aldehydic function in **VI** can be assumed equatorial.



Scheme 1—Different between chemical shifts of axial aldehyde and that of equatorial aldehyde.

Furthermore, aldehyde (**IV**) with Jones reagent in acetone gave a ketodiacid (**X**), $C_{19}H_{26}O_5$, which yields the corresponding dimethylester (**XI**), $C_{21}H_{30}O_5$, by treatment with diazomethane. Saponification of **XI** with aqueous 2.5N NaOH in ethylene glycolmonomethylether in 3 hr at 150°, standard conditions for C_4 equatorial carbomethoxyl groups, afforded an isomeric ketodiacid (**XII**) which exhibits an UV absorption maximum at 240nm (Scheme 2).



Scheme 2—Standard condition for C_4—COOMe(eq.).

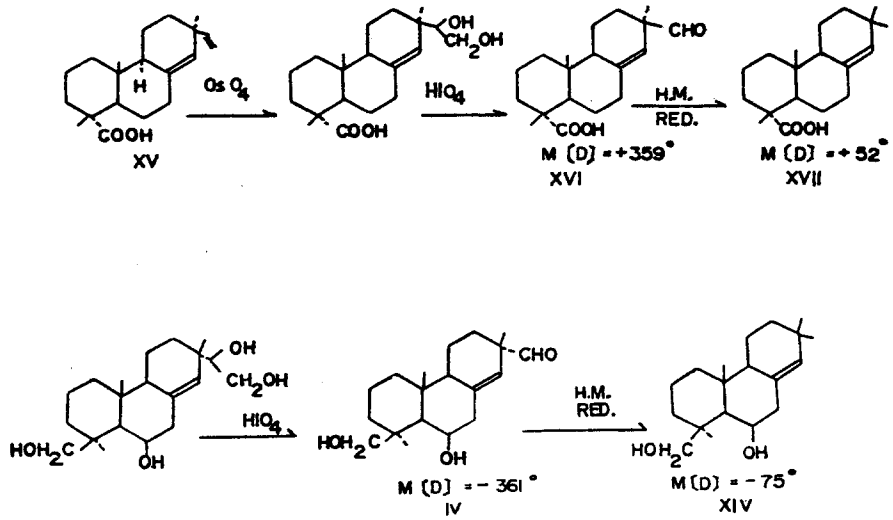
The configuraion at C_6 is provided by obtaining a C_6 epimeric monoacetonide (**XIII**), $C_{23}H_{38}O_4$, on $NaBH_4$ reduction of **VI** in aqueous tetrahydrofuran. This monoacetonide (**XIII**) is reconverted in **VI** by Sarett oxidation. The conclusion is, therefore, that the C_6 hydroxyl group in **XIII** must have the axial configuration[10] since the complex hydride reduction of **VI** is sterically controlled by the 1, 3-axial substituents in C_4 and in C_{10}.

The stereoconfiguration at C_{13} was established to be β-orientation (same as in darutigenol [11]) by comparing the difference (ΔRM −286, Table III) of molecular rotation M[D] between the hydroxy aldehyde (**IV**) and the nor-alcohol (**XIV**) both derived from compound A with

Table III—Molar rotatory power of compound A and pimaric acid.

Compound	Derivatives	M[D]	ΔRM
Compd. A	Hydroxy-aldehyde (IV)	−361	−286
	Nor-alcohol (XIV)	−75	—
Pimaric acid	Aldehyde acid (XVI)	+359	+307
	Nor-acid (XVII)	+52	—

that (ΔRM +307, Table III) between the aldehyde acid (**VI**) and the nor-acid (**XVII**) both derived from pimaric acid of which the configuration at C_{13} was already known as the α-orientation (Scheme 3).



Scheme 3—Syntheses of **XVI**, **XVII**, **IV** and **XIV**.

The shielding effect on the tertiary methyl group at C_{10} in the derivative of compound A having a carbonyl function at C_{13} suggests a cis relation between these two centers.

Therefore it is suggested that the compound A has its methyl group at C_{10} in the α-orientation.

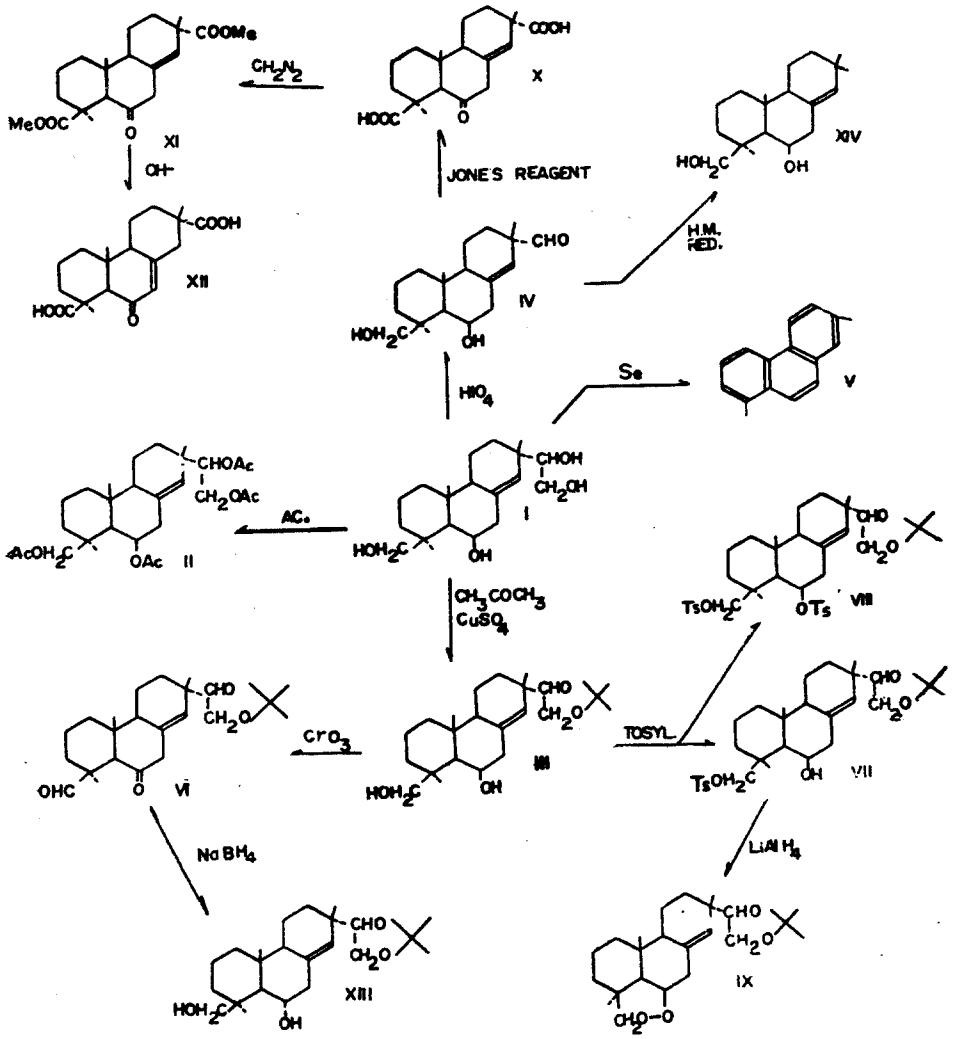
Derivatives of compound A are listed in Scheme 4.

Compound C[12,13]—Dried plant was extracted with cold methanol. The extract was repeatedly extracted with Et_2O and then butanol. The butanol extract was dissolved in water and the solution saturated with NaOH was added to it. On standing over night, a considerable quantity of crystalline solid was precipitated.

Crystallization of the crude crystals from hot water and alumina column chromatography of the crystals gave needles of the compound C (**I**), $C_{26}H_{44}O_8 \cdot H_2O$, mp 225~6°, $[\alpha]_D$=−48° (c=1.0, MeOH), IR $\nu_{max}cm^{-1}$; 3330 (OH), 1650 (double bond), NMR (CD_3OD) δ; 5.2 (1H, bs, −C−CH=C−CH_2−), 0.83 (3H, s, −C−CH_3), 1.05 (3H, s, −CH_3).

Acethylation of **I** with acetic anhydride and pyridine at room temperature afforded a hexaacetate (**II**) $C_{38}H_{56}O_{14}$, mp 128°, $[\alpha]_D$=−43.2° (c, 1.0, MeOH), IR $\nu_{max}cm^{-1}$; 1735, 1240 (ester), NMR (CD_3OD) δ; 5.3 (1H, bs, −C−CH=C−CH_2−), 2.03~2.07 (−O−CO−CH_3), 0.83 (3H, s, −CH_3), 1.03 (3H, s, −CH_3).

Hydrolysis of **I** with beta-glucosidase in aqueous solution at 36° for 60 hrs gave 1 mole of glucose (glucoosazone, mp 208°) and an aglucone (**III**), $C_{20}H_{34}O_3$, mp 163°, $[\alpha]_D$=−10°

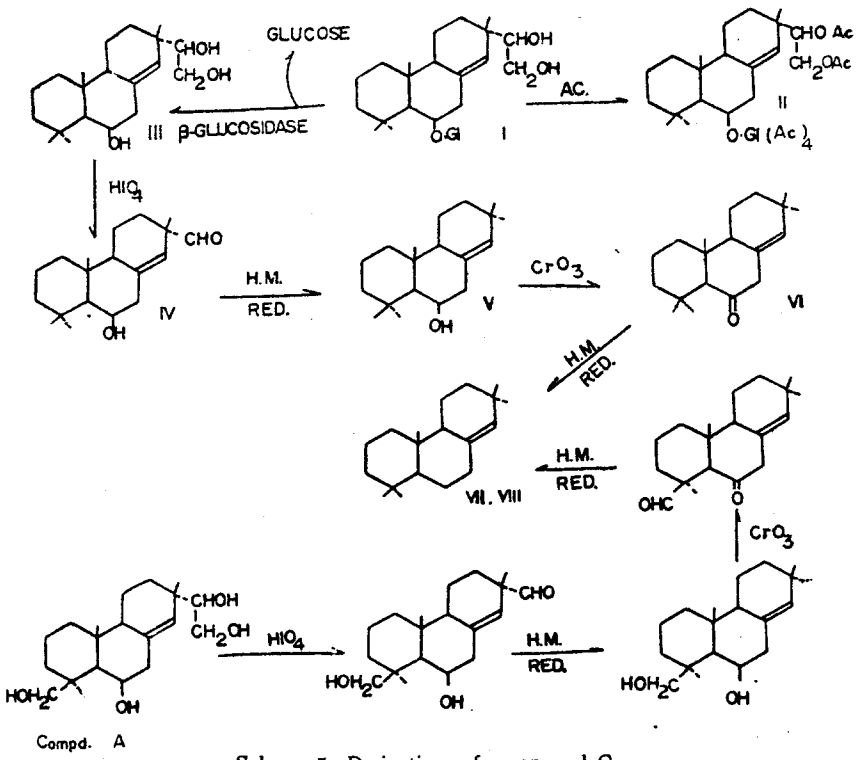


Scheme 4—Derivatives of compound A.

(c, 1.0, MeOH), IR $\nu_{max}cm^{-1}$; 3450 (OH), 1650 (double bond), NMR (CD_3OD) δ; 5.18 (1H, bs, C−CH=C−CH_2−), 0.83 (3H, s, C−CH_3).

Oxidation of **III** with sodium metaperiodate in ethylalcohol solution gave formaldehyde together with nor-aldehyde (**IV**), $C_{19}H_{30}O_2$, mp 114~5°, $[\alpha]_D$=−77.1° (c, 1.0, EtOH), IR $\nu_{max}cm^{-1}$; 3360, 2720 (CHO), 1730 (CHO), NMR (CD_3OD) δ; 5.2 (1H, bs, C−CH=C−CH_2−), 0.88 (3H, s, −CH_3), 1.0 (3H, s, −CH_3), 9.25 (1H, s, −CHO)

Reduction of the nor-aldehyde (**IV**) by Huang-Minlon method gave a mono-nor-alcohol (6β-hydroxy-nor-darutene) (V), $C_{19}H_{32}O$; mp 137.5°, $[\alpha]_D$=−40° IR $\nu_{max}cm^{-1}$; 3200 (OH),



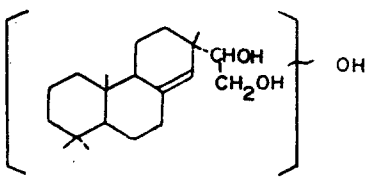
Scheme 5—Derivatives of compound C.

NMR ($CDCl_3$) δ; 5.2 (1H, bs, C_{14}—H), 0.8 (s, CH_3), 0.92 (s, CH_3), 1.0 (s, CH_3).

Oxidation of mono-nor-alcohol (V) with Sarett reagent gave 6-keto-nor-darutene (VI), $C_{19}H_{30}O$; mp 97~8°, IR $\nu_{max}cm^{-1}$; 1695 (C=O), NMR ($CDCl_3$) δ; 0.95 s, 0.97 s, 1.0 s, 1.08 s, ($-CH_3$), 5.27 (bs, C_{14}—H), 2.89 d, 2.66 d (J=12.75 c/s, 1H, part A of an AB system).

Reduction of the ketone (VI) by Huang-Minlon method gave a nor-darutene (VII), $C_{19}H_{32}$, mp 42°, $[\alpha]_D$=−28°, identical with authentic hydrocarbon (nor-darutene) (VIII), $C_{19}H_{32}$, mp 42°, $[\alpha]_D$=−28.72°, derived from compound A (Scheme 5).

Spectral feature of compound (I), its aglucone (III) and derivatives (II) and (IV), together with isolation of pimanthrene by selenium dehydrogenation and synthesis of nor-darutene



Partial structure of aglucone (III).

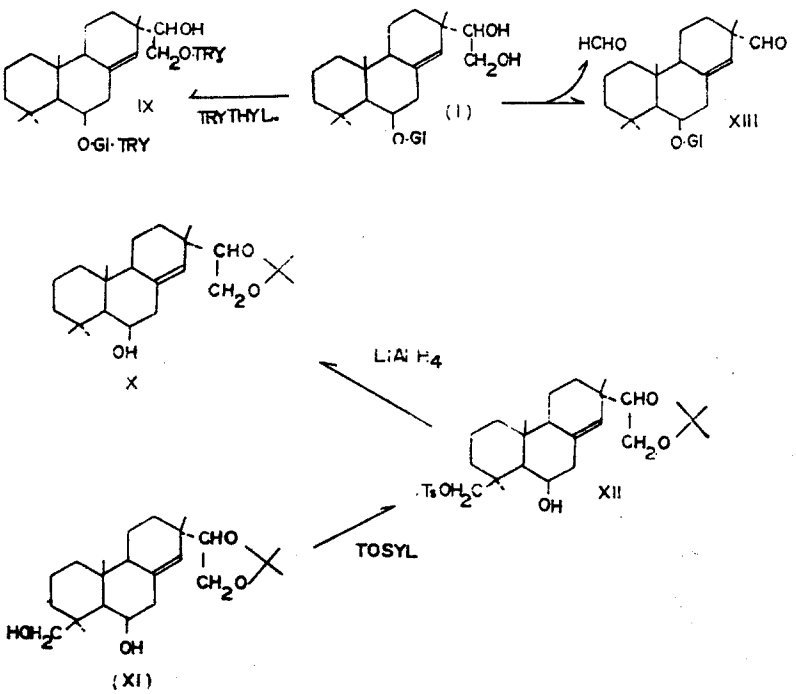
(**VII**), suggest for aglucone (**III**) partial structure.

In the NMR spectrum two lines at 2.87 τ and 2.66 τ (J=12.75 c/s, 1H, part A of an AB system) can be attributed to one proton of a methylenic group both allylic and adjacent to a carbonyl function, moreover the aglucone acetonide (**X**) was identical with authentic sample prepared from the compound A, **XI** in which the secondary hydroxyl function was established to be located at C_6 (Scheme 6). These facts indicate that the secondary hydroxyl function is at C_6.

Trithylation of **I** with triphenylchloromethane and pyridine at room temperature for 8 days affords ditrithylether (**IX**), $C_{64}H_{72}O_8$, mp 115~6°, $[\alpha]_D$=−91.85°. Oxidation of **I** with sodium metaperiodate in ethylalcohol solution gave formaldehyde (**XI**) together with nor-aldehyde (**XIII**) (Scheme 6).

These facts (formation of formaldehyde and ditrithylether) indicate that the glucose moiety is combined with the C_6 hydroxyl group of the aglucone.

Compound B[14]—Dried crushed plant collected near the Seoul, Korea, was extracted with cold ether. The extract was repeatedly washed with 8% $NaHCO_3$ and extracted with 5% NaOH. The solution was washed out with a small volume of ether and when acidified with 10% HCl, a precipitate of a acid was formed.



Scheme 6—Synthesis of **X** from **XI**.

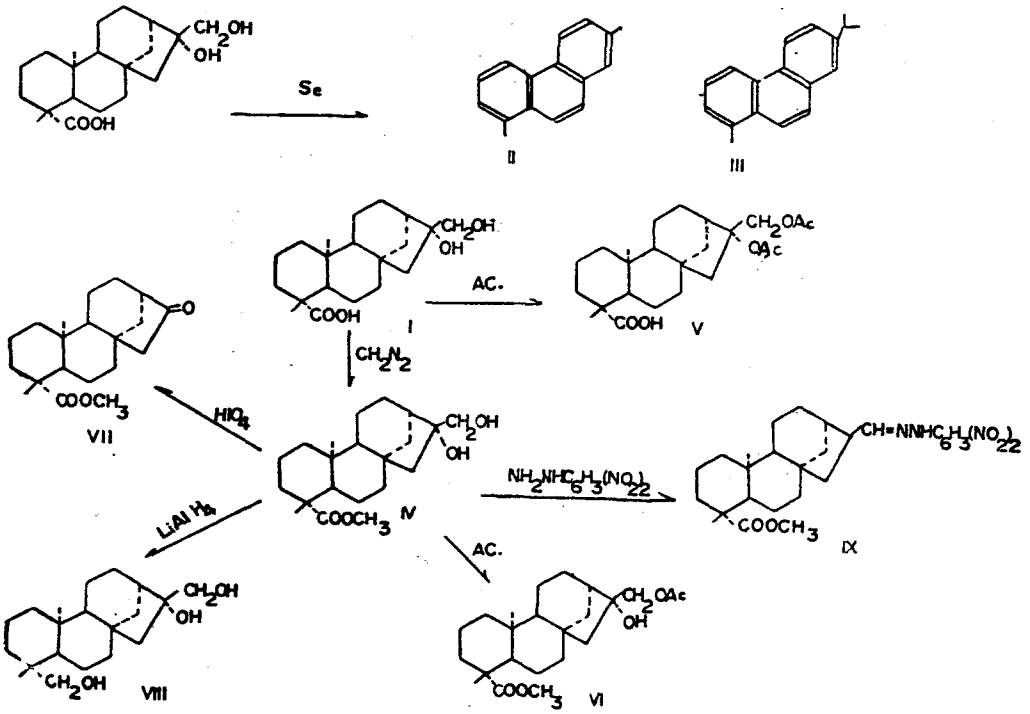
Crystallization of the precipitate from methanol—ethylacetate mixture gave a prism of compound B (I) $C_{20}H_{32}O_4$, mp 260~2°, MS (*m/e*); 336 (M^+), 318, 305, 287, 259, 241, $[\alpha]_D$= −88°, IR $\nu_{max}cm^{-1}$; 3470 (OH), 1700 (COOH), NMR δ; 8.7, 8.55 (CH_3).

Pimanthrene (**II**) and retene (**III**) was obtained by selenium dehydrogenation of the compound B methylester(**IV**), $C_{21}H_{34}O_4$, mp 153~4°, IR $\nu_{max}cm^{-1}$; 3620 (OH), 3570 (OH), 1730 ($COOCH_3$), NMR δ; 6.36(s, CO_2Me), 6.3 (s, $-CH_2OH$), which was prepared by the methylation with diazomethane, was undepressed by admixture with an authentic sample (which was given by professor P.R. Jefferies).

Compound B methylester easily formed a monoacetate (**VI**), $C_{23}H_{36}O_5$, mp 121~2°, NMR τ; 5.27 (q, J=12.4 c/s, $-CH_2-OAc$) was obtained. Periodic acid oxidation of the methylester gave nor-ketoester (**VII**) $C_{20}H_{30}O_3$, mp 142~3°, IR $\nu_{max}cm^{-1}$; 1740, 1725 ($-CO-O-CH_3$). The IR spectral absorption of ketoester at 1740 cm^{-1} indicates the presence of a five membered ketone ring.

The triol (**VIII**), $C_{20}H_{34}O_3$, mp 222~223° was obtained by reduction of methylester with lithium aluminium hydride.

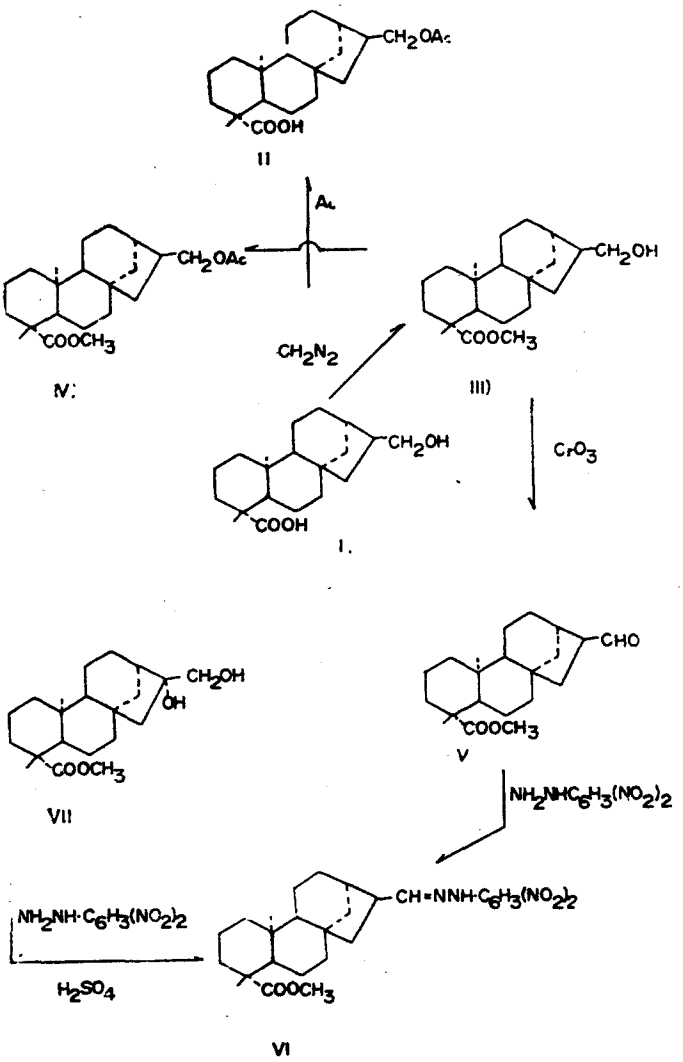
Pinacolic rearrangement of the methylester gave the aldehyde which was identified as its 2, 4-dinitrophenylhydrazone (**IX**), $C_{27}H_{36}O_6N_4$, mp 183~5° by comparison with an authentic sample (Scheme 7). Formation of the nor-ketoester and the results of pinacolic rearrangement



Scheme 7—Derivatives of compound B.

indicate that a glycolic hydroxy group exist in the side chain. With these results obtained by the above experiments and observations, compound B was identified as 16, 17-dihyroxy-16β-(−)-kauran-19-oic acid, already isolated by P.R. Jefferies[15] from *Beyeria* species.

Compound D[16]—The filtrate, obtained by filtration of precipitate of the compound B as shown above was recovered with 5% of HCl into ether. The ether extract was chromatographed on silica gel. Elution with $CHCl_3$—MeOH (9 : 1) mixture gave needles of compound D (I), $C_{20}H_{32}O_3$, mp 207.5°, $[\alpha]_D$=−105.8°, IR $\nu_{max}cm^{-1}$; 3440 (OH), 1700 (COOH),



Scheme 8—Derivatives of compound D (I).

NMR δ; 8.75 (s, C_4-CH_3), 9.05 (s, $C_{10}-CH_3$).

Acetate (**II**), $C_{22}H_{34}O_4$, mp 170°, IR $\nu_{max}cm^{-1}$; 1745, 1695 (ester carbonyl), 1236 (acetoxy) and methylester acetate (**IV**), $C_{23}H_{36}O_4$, mp 105°, IR $\nu_{max}cm^{-1}$; 1738 (ester), 1236 (acetoxy) were prepared by acethylation of compound D or methylester with acetic anhydride and anhydrous sodium acetate, respectively.

Methylester (**III**), $C_{21}H_{34}O_3$, mp 113.5° was prepared by methylation of compound D with diazomethane. Methylester-2, 4-dinitrophenylhydrazone (**VI**), mp 183~4° was prepared by the usual way from aldehyde (**V**) obtained by Sarett oxidation of the methyl ester (**III**). Melting point of this phenylhydrazone was undepressed by admixture with an authentic sample prepared from the compound B with pinacolic rearrangement (Scheme 8). The chemical shifts (singlet) at 8.75 τ and 9.05 τ were observed, respectively.

According to NMR studies about kaurane derivatives by Tiers[17], in —COOH group is substituted at C_4 axially, the chemical shift of CH_3 proton at C_4 and C_{10} shows 8.76 τ and 9.06 ~9.07 τ, respectively as shown in the Table IV.

Based upon these NMR data observed and the results of the Tiers NMR studies on the kaurane derivatives (Table IV), it was established that the —COOH groups is located at C_4.

With these results obtained by the above experiments and observations, compound D was identified as 17-hydroxy-16β-(−)-kauran-19-oic acid (**I**).

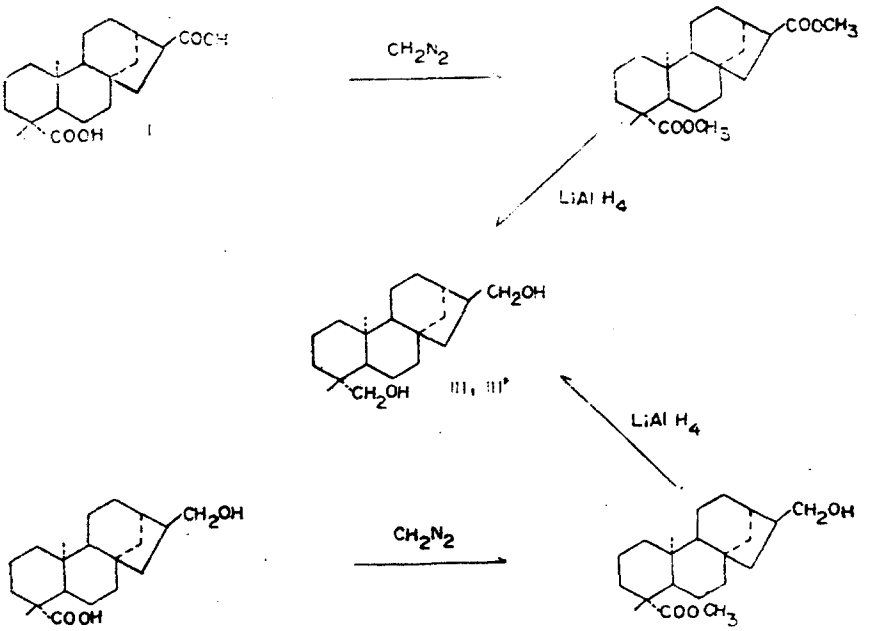
Compound F[18]—The soluble fraction in 5% of NaOH solution was acidified with 5% of HCl and resulting precipitate was filtered. $CHCl_3$ was added into the filtrate and the resulting precipitate were chromatographed on silicagel. Elution with $CHCl_3$—MeOH mixture (8 : 1) gave needles of compound F(**I**), $C_{20}H_{30}O_4$, mp 258~260°, MS (*m/e*), 334 (M^+), $[\alpha]_D$=−133.25°, IR ν_{max}^{KBr} cm^{-1}; 2650, 1701, 1245 (−COOH), NMR δ; 8.77, 9.05.

Dimethylester (**II**), $C_{22}H_{34}O_4$, mp 110°, $[\alpha]_D$=−96.8°, was obtained by usual way. 16β-(−)-Kauran-17, 19-diol (**III**), $C_{20}H_{34}O_2$, mp 179°, $[\alpha]_D$=−49.1°, was prepared by reduction of the methylester (**II**) with $LiAlH_4$.

Melting point of the diol was undepressed by admixture with the authentic sample (**III**) prepared by reduction of the compound D methylester with $LiAlH_4$ (Scheme 9). And also the IR spectra of both are coincidental.

Table IV—Chemical shifts of methyl groups in kaurane derivatives (τ values in $CDCl_3$).

Axial C_4 group	C_4-CH_3	$C_{10}-CH_3$
CH_3	9.15, 9.19	8.99~9.00
CH_2OH	9.04~9.05	9.01
CH_2OAc	9.06	8.96~8.98
CHO	9.01	9.14
COOMe	8.83	9.18~9.19
COOH	8.76~8.77	9.06~9.07
CH_2OTs	9.10~9.11	9.14~9.18
Sample	8.75	9.05



Scheme 9—Derivatives of compound F(I).

In the NMR spectra, the chemical shifts at 8.77 δ and 9.66 δ was observed, respectively. The chemical shifts indicate the location of —COOH group at C_4 as in the case of compound D.

With these results, the compound F was identified as 16β-(—)-kauran-17, 19-diacid (I).

In order to examine the effect of the compound B on blood pressure of renal hypertensive rats, the following method was used. In order to make artificial hypertension, we selected 12 rats weighing 90~115g, and applied the figure of eight ligature method to the left kidney of each rat, and two weeks later, the other side kidney was ectomized. Ten weeks later 6 animals were given 50mg of the compound per kilogram body weight per day by oral administration for 10 days and 6 animals were given 50 mg of water alone as a control group. Blood pressures were measured under light ether anesthesia and body weights were recorded. Their results are shown in the Fig. 1. As shown in the Fig. 1, the rats received the compound showed decreased blood pressure. The mean maximal decrease was 23 mmHg during 10 days of administration.

And also, in order to test the effect of this compound B on antiinflammation, the following two methods were used. One is protein heat coagulation method as preliminary test and the other is rat-paw edema test.

In the case of heat coagulation test, in a small glass tube, 2.7 ml of 0.1% albumin solution and 0.3 ml of sample solution were added and warmed exactly 3 minutes at 67° in water bath. After cooling, the turbidity was determined by colorimetric method. The rate of inhi-

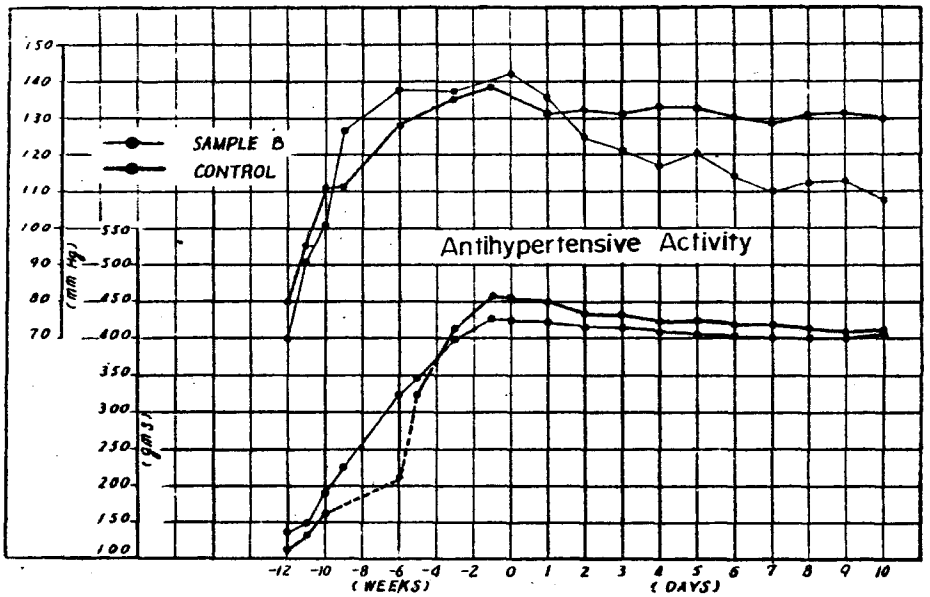


Fig. 1—Antihypertensive effects of compound B. The drug was administered on O day.

Table V—Inhibitory effecs of compound B and D on heat coagulation of bovine serum albumin.

Drug	Turbidity on the conc. (Mole) of			Inhibition(%) on the conc (Mole) of		
	1×10^{-4}	3×10^{-4}	1×10^{-3}	1×10^{-4}	3×10^{-4}	1×10^{-3}
Control	0.52	—	0.70	—	—	—
Compound B	0.27	—	0.30	48.0	—	57.1
p-Methoxycinnamic acid	0.48	—	0.42	7.5	—	40.0
Control	0.66	1.43	—	—	—	—
Compound D	0.45	0.77	—	31.8	46.2	—

Table VI—Inhibitory effects of compound B on rat-paw edema.

Phlogistic agent	Mean volume of edema (ml)		Inhibition %	P value
	Control	Exp.		
10% yeast-saline	0.972	0.806	17.1	$P<0.001$
35% formalin-saline	0.603	0.372	38.3	$P<0.01$
10% egg white-saline	0.587	0.273	53.5	$P<0.01$

bition was measured from the turbidity. The antiinflammatory activity of compound D was tested by the same method as mentioned above.

The results are shown in the Table V. As shown in the Table V, heat coagulation of albumin was remarkably inhibited by compound B compared with other antiphlogistic agent such as *p*-methoxycinnamic acid.

The remarkable antiinflammatory activity of compound B by rat-paw edema test was shown in the Table VI.

Rat-paw edema test was undertaken as follows. After 1 hour of oral administration of 300 mg of compound B per kg body weight of rats, yeast-saline, formaline-saline or egg-white-saline as a phlogistic agent was injected into the plantar surface of the paw of each rat. And then the mean volume of edema paw surface was measured, and antiinflammatory activity was estimated from the mean value of the volume compared with that of the control.

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