Tetrahedron Vol. 24, pp 5871 to 5879 Pergamon Press 1968 Printed in Great Britain

THE STRUCTURE OF FUKINONE, A CONSTITUENT OF *PETASITES JAPONICUS* MAXIM[1]

K. NAYA, I. TAKAGI, Y. KAWAGUCHI and Y. ASADA
Faculty of Science, Kwansei Gakuin University, Nishinomiya, Japan

Y. HIROSE and N. SHINODA
The Institute of Food Chemistry, Osaka, Japan

(*Received in Japan* 2 *March* 1968; *Received in the UK for publication* 2 *May* 1968)

Abstract—Fukinone (I), a new sesquiterpene ketone, was isolated from *Petasites japonicus* Maxim. Its structure and absolute configuration were established by the interconversion from isopetasol (V), a sesquiterpene of known absolute configuration, to dihydrofukinone (II).

Petasites japonicus Maxim. (Japanese name, "Fuki"), grows wild almost all over Japan, and is often cultivated as a leafy vegetable.

This paper reports the isolation and stereochemistry of a new sesquiterpene ketone, named fukinone, from the methanolic extract of the flower stalks of a cultivated variety "Aichiwasebuki" grown in Osaka prefecture:

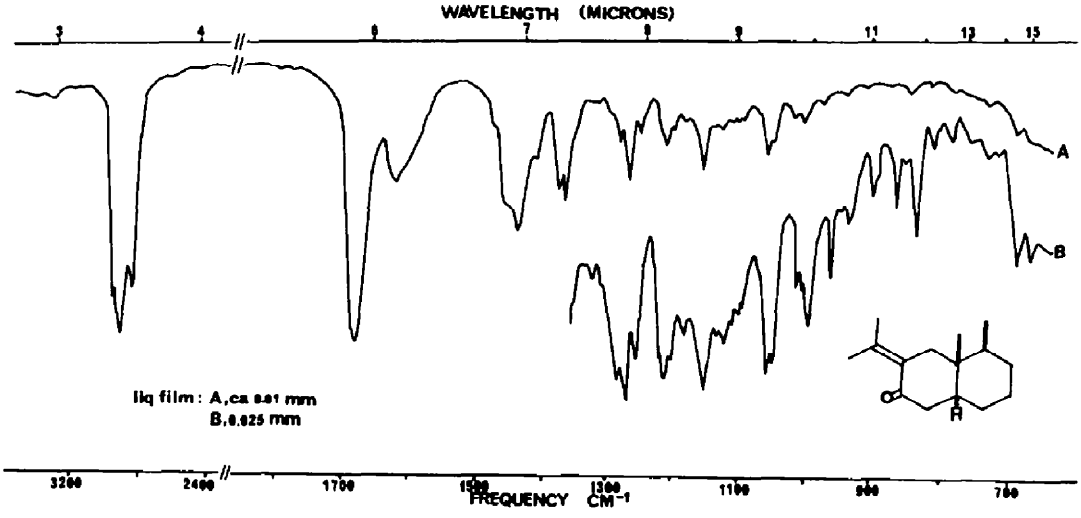


FIG. 1

Fukinone (I), $C_{15}H_{24}O$, b.p. 97°/0·8 mm; $[\alpha]_D^{24}$ +67·8° a colorless oil with a fragrant smell, was obtained from the methanolic extract by vacuum distillation and chromatography over silica gel. Its IR spectrum (Fig. 1) shows bands at 1685 and 1625

cm^{-1}, and in the UV a maximum due to an α,β-unsaturated carbonyl system[2] confirmed[3] by the formation of a semicarbazone, m.p. 201–202°, and a 2,4-dinitrophenylhydrazone, m.p. 151–152°. The NMR spectrum of fukinone (Fig. 2) exhibits two singlets at 1·78* and 1·90 for two methyls on a double bond, a singlet at 0·95 for an angular Me group and a doublet (3H, $J = 6$) at 0·84 for a secondary Me group.

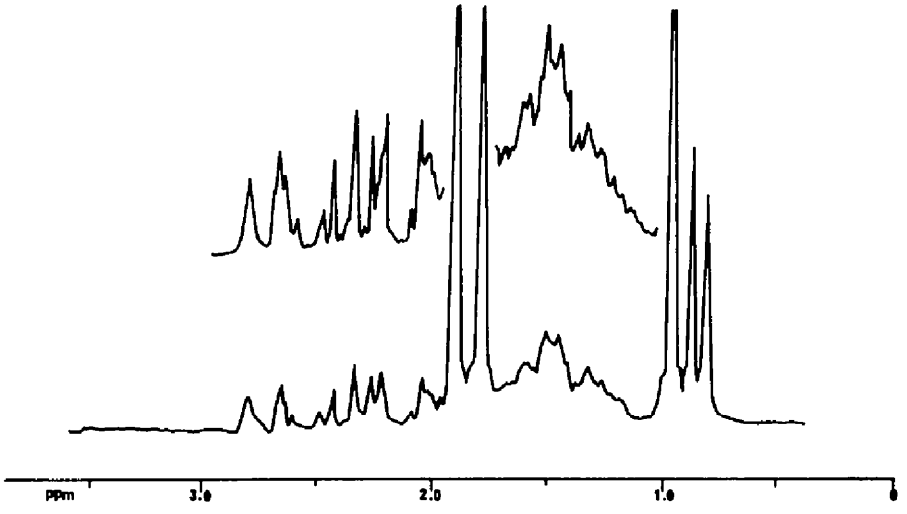


FIG. 2

From the above data, the fukinone molecule was assumed to be a bicyclic sesquiterpene having an α,β-unsaturated carbonyl system consisting of an isopropylidene group conjugated with a ketone.

Catalytic hydrogenation of fukinone with Pd-C gave dihydrofukinone (II), $C_{15}H_{26}O$, b.p. 118°/3 mm, $[\alpha]_D^{22}$ +45·1° which shows an IR band at 1710 cm^{-1} corresponding to a saturated 6-membered ring ketone, and yielded a semicarbazone, m.p. 200·5–201·5° and a 2,4-dinitrophenylhydrazone, m.p. 171–172°. On catalytic hydrogenation to dihydrofukinone, the vinyl Me signals (1·78 and 1·90) in the NMR spectrum shifted upfield to 0·83 (d., $J = 6·5$, 3H) and 0·85 (d., $J = 6·5$, 3H) respectively, thereby indicating an isopropyl group.

The presence of an isopropylidene group[4] conjugated with a ketone was confirmed by alkaline hydrolysis which afforded acetone and desisopropylidenefukinone (III), m.p. 26–29°, b.p. 72–76°/4 mm, by a retroaldol reaction.

The rotary dispersion curves[5] of fukinone, dihydrofukinone and desisopropylidenefukinone (Fig. 3) are characteristic of A/B *cis*-fused 3-keto steroids although many sesquiterpenoids isolated from *Petasites* species are of the *cis*-decalin type,[4, 6, 7] that is, have an eremophilane skeleton. As we also isolated isopetasin (IV), the angelate of isopetasol (V) from wild strains of the plant and since the absolute configuration

* All chemical shifts are reported in ppm as δ values.

of isopetasol has been established,[6,8,9] tentative formulas I and II were suggested for fukinone and dihydrofukinone.

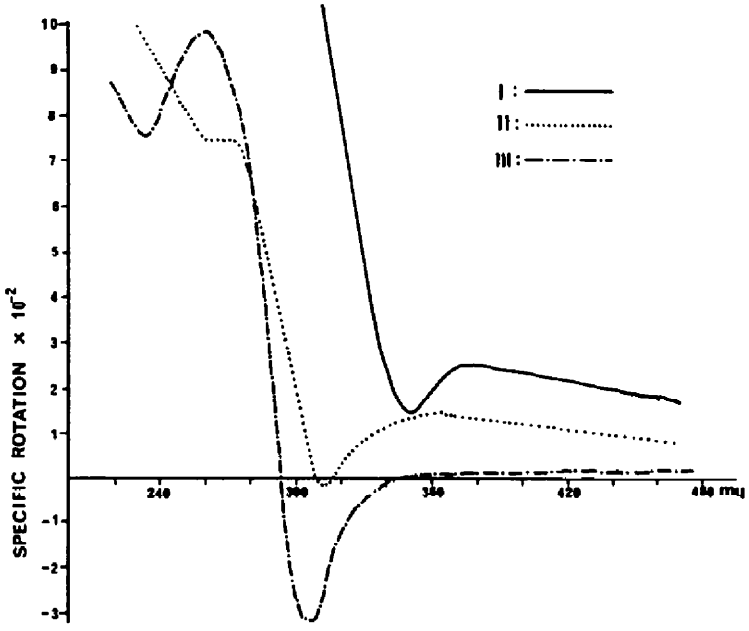


FIG. 3

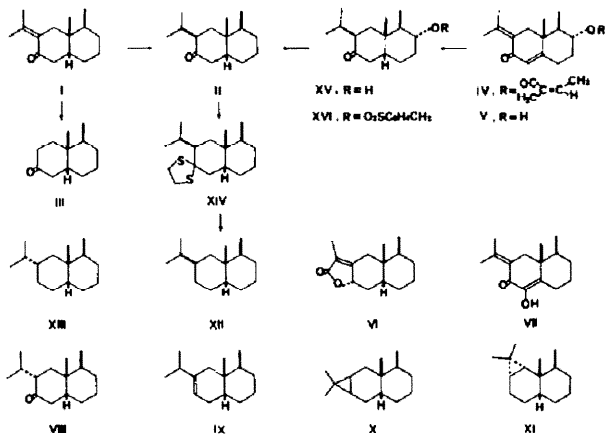
The physical properties of dihydrofukinone, its 2,4-dinitrophenylhydrazone and semicarbazone, closely resemble those of the base-stable ketone, (7β)-eremophilan-8-one[10,11] (II) and the corresponding derivatives derived from eremophilenolide[10,12] (VI) and hydroxyeremophilone[13] (VII) although the original base-labile isomer, (7α)-eremophilan-8-one[10,11] (VIII) could not be found in the hydrogenation products of fukinone.

The final confirmation of the constitution and absolute configuration of fukinone and its derivatives was obtained by the following reaction sequences.

Wolff–Kishner reduction of fukinone yielded two hydrocarbons, (IX and X). The former (IX) afforded a saturated hydrocarbon, which shows an IR spectrum on the whole identical with the one[14] published previously although IX proved to be a mixture of two hydrocarbons, (XII and XIII). Compound X shows NMR signals of two protons in the region of 0·45, indicating the presence of a cyclopropane ring, whereas it shows a MS pattern fundamentally different from that of ferulane (XI).[15] These facts elucidated the skeleton and the position of both the carbonyl group and the double bond of fukinone.

In addition dihydrofukinone (II) was converted into a crystalline ethylene thioketal (XIV), $C_{17}H_{30}S_2$, m.p. 73·5–74·5°, which on desulfurization with Raney nickel afforded a hydrocarbon, $C_{15}H_{28}$, $[\alpha]_D^{30}$ +17·3°, identical with the known eremophilane (XII) by the comparison of IR spectra.[14,16].

SCHEME 1



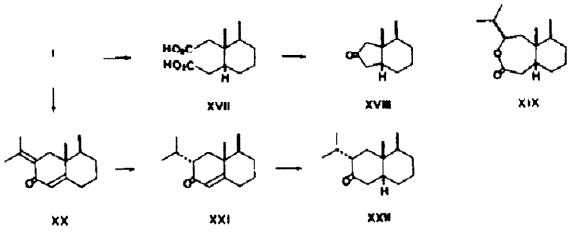
Conversion of isopetasol (V) *of known absolute configuration to dihydrofukinone.* Isopetasol (V)[4] was hydrogenated with Pd-C to provide tetrahydroisopetasol (XV), $C_{15}H_{26}O_2$, m.p. 103–104°, $[\alpha]_D^{22}$ +39·2°, which was ascertained to be a *cis*-2-decalone type by the expected negative Cotton effect. The tosylate of the decalone (XVI) was reduced with LAH to yield an alcohol which was treated with Jones' reagent to yield a ketone. This ketone was identified as dihydrofukinone (II) by GLC analysis and comparison of IR spectra, and by mixed m.p. determination of both the semicarbazone and 2,4-dinitrophenylhydrazone. Thus, the structure of fukinone and dihydrofukinone can be assigned as in stereoformulas I and II.

In addition to the above study, as further work for the structural determination of fukinone and dihydrifukinone, the following reactions were examined.

Ozonolysis of fukinone gave in good yield acetone and dicarboxylic acid (XVII), $C_{12}H_{20}O_4$, m.p. 187·5–188°. This was followed by esterification with ethereal diazomethane, Dieckmann condensation with sodium in toluene, and hydrolysis with hydrochloric acid in acetic acid to yield a 5-membered ketone (XVIII), $C_{11}H_{18}O$, as an oil.

Dihydrofukinone (II) was subjected to Baeyer–Villiger oxidation which provided a 7-membered lactone (XIX), m.p. 90–90·5°.

SCHEME 2



In addition, it was of interest to convert the *cis*-fused fukinone to the corresponding *trans*-fused isomer for the purpose of comparison. Dehydrogenation of fukinone with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[17] afforded dehydrofukinone (XX), $C_{15}H_{22}O$, b.p. 116–120°/3 mm. This was submitted to reduction[18] with lithium in liquid ammonia twice successively, providing a mixture of a saturated alcohol and a ketone (XXII) as the predominant products via 5,10-dimethyl-3-isopropyl-$\Delta^{1(9)}$-2-octalone (XXI).[11] The mixture was re-oxidized with Jones' reagent to *trans*-5,10-dimethyl-3α-isopropyldecalone-2 (XXII) $C_{15}H_{26}O$, $[\alpha]_D^{24}$ −17·4°, which exhibits a positive Cotton effect, typical of A/B *trans*-fused 3-keto steroids.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Mass spectra were measured with a Hitachi RMU-6 mass spectrometer; ion source temp 250°, chamber voltage 80 V and evaporation temp 150°. IR spectra were recorded with a JASCO DS-402G spectrophotometer and UV spectra were obtained with a Cary Model 14 spectrophotometer. RD curves were measured with a JASCO spectropolarimeter Model ORD-5. NMR spectra were determined with a Japan Electron Optics JNM-4H-100 spectrometer, using TMS as an internal standard ($\delta = 0$) and $CDCl_3$ as solvent. Analytical and preparative GLC were performed with a Shimadzu GC-1C apparatus on stainless steel column (3 mm × 3 m), using ethylene glycol adipate. TLC were run on silica gel (Merck Kieselgel G). Microanalyses were carried out in the microanalytical section of Shinogi Research Laboratory, Shionogi & Co. Ltd.

Isolation of fukinone (I). The dried flower stalks of *Petasites japonicus* Maxim. (10 Kg) were extracted with MeOH at room temp for 2 weeks. The extract was concentrated *in vacuo* to remove the solvent. The residue was dissolved in benzene, washed with sat $NaHCO_3$aq, then with water, dried over Na_2SO_4 and evaporated *in vacuo* leaving a dark brown oil (200 g). This oil was fractionated by vacuum distillation into a pale yellow oil, as the main fraction, b.p. 70–72°/2 × 10^{-3} mm (39 g). The distillate was chromatographed on Merck silica gel (750 g). Elution with pet. ether–ether (50:1) afforded almost pure fukinone. The pure (GLC) fukinone, a colorless oil, was obtained from the semicarbazone by steam distillation with a sat oxalic acid aq and after redistillation, b.p. 97 /0·8 mm, d_4^{20} 0·9955, n_D^{20} 1·5172; MS: M^+ ion *m/e* 220, base peak *m/e* 109; IR ν_{max}^{film} 1685, 1625 cm^{-1}; λ_{max}^{EtOH} 251 mμ (ε 6800), $[\alpha]_D^{24}$ +67·5 (*c*, 1·03 MeOH), $[\alpha]_D^{24}$ +67·8 (neat), RD in MeOH (*c*, 0·08): $[\alpha]_{440}$ +180°, $[\alpha]_{375}$ +255°, $[\alpha]_{346}$ +196°, $[\alpha]_{325}$ +570°, $[\alpha]_{295}$ +1900°; NMR: 1·90 (s, 3H, Me C=C), 1·78 (s, 3H, Me C=C), 0·95 (s, 3H, Me C), 0·84 (d, J = 6, Me CH). (Found: C, 81·66; H, 10·97. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%).

The 2,4-dinitrophenylhydrazone was prepared by Brady's method and crystallized from EtOH as deep red needles, m.p. 151–152°, λ_{max}^{EtOH} 374 mμ (ε 25,600). (Found: C, 62·89; H, 7·31; N, 13·90. $C_{21}H_{28}N_4O_4$ requires: C, 62·98; H, 7·05; N, 13·99%).

The semicarbazone was prepared by the NaOAc method and recrystallized from EtOH as fine prisms; m.p. 201–202°, λ_{max}^{EtOH} 253 mμ (ε 11,670). (Found: C, 69·20; H, 9·83; N, 14·99. $C_{16}H_{27}N_3O$ requires: C, 69·27; H, 9·81; N, 15·15%).

Dihydrofukinone (II). Fukinone (I; 5 g) in EtOH (13·5 ml) was hydrogenated at room temp and atm press in the presence of 10% Pd–C catalyst (700 mg). The product was chromatographed over silica gel (100 g), and elution with pet. ether–ether (50:1) afforded dihydrofukinone (II). The pure (GLC) ketone was obtained from the semicarbazone as in the case of I, as a colorless oil: b.p. 118–120° (bath temp)/3 mm, d_4^{20} 0·9626, n_D^{20} 1·4901; MS: M^+ ion *m/e* 222, base peak *m/e* 110; IR: ν_{max}^{film} 1710 cm^{-1}; $[\alpha]_D^{22}$ +45·1 (*c*, 4·375, $CHCl_3$); RD in MeOH (*c*, 0·098): $[\alpha]_{450}$ +81·6°, $[\alpha]_{350}$ +142·8°, $[\alpha]_{312}$ −15·3°, $[\alpha]_{270}$ +744·9°, $[\alpha]_{261}$ +740·8°, $[\alpha]_{230}$ +1000°; NMR: 0·93 (s, 3H), 0·85 (d, J = 6·5, 3H), 0·83 (*d*, J = 6·5, 3H), 0·88 (*d*, J = 7, 3H). (Found: C, 80·91; H, 11·74. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

The yellow 2,4-dinitrophenylhydrazone recrystallized from EtOH as needles, m.p. 171–172°. (Found: C, 62·89; H, 7·54; N, 14·05. $C_{21}H_{30}N_4O_4$ requires: C, 62·66; H, 7·51; N, 13·92%).

The semicarbazone recrystallized from MeOH aq as fine prisms, m.p. 200·5–201·5°. (Found: C, 68·70; H, 10·62; N, 15·14. $C_{16}H_{29}N_3O$ requires: C, 68·77; H, 10·46; N, 15·04%).

Desisopropylidenefukinone (III). A soln of I (1.2 g), KOH (2·1 g), EtOH (25 ml) and water (30 ml) was refluxed in a current of N_2 for 20 hr. The volatile vapors were collected in a cold water trap. The volatile portion gave acetone 2,4-dinitrophenylhydrazone, m.p. 124·5–125·5°, undepressed by an authentic sample. (Found: C, 45·55; H, 4·53; N, 23·14. Calc. for $C_9H_{10}N_4O_4$: C, 45·38; H, 4·23; N, 23·52%).

The solvent was removed *in vacuo* and the residue extracted with ether and dried over Na_2SO_4. The ether extract was evaporated leaving an oil (848 mg) which was distilled at 72–76°/4 mm and solidified on cooling, m.p. 26–29°; MS: M^+ ion *m/e* 180, base peak *m/e* 109; IR: ν_{max}^{film} 1720 cm^{-1}; $[\alpha]_D^{33}$ +20·66° (*c*, 1·065, EtOH); RD in MeOH (*c*, 0·1): $[\alpha]_{450}$ +32°, $[\alpha]_{347}$ 0°, $[\alpha]_{306}$ −320°, $[\alpha]_{293}$ 0°, $[\alpha]_{262}$ +990°, $[\alpha]_{235}$ +750°. (Found: C, 79·60; H, 11·27. $C_{12}H_{20}O$ requires: C, 79·94; H, 11·18%).

The 2,4-dinitrophenylhydrazone crystallized from EtOH aq as orange needles, m.p. 121–122°. (Found: C, 59·69; H, 6·84; N, 15·44. $C_{18}H_{24}N_4O_4$ requires: C, 59·98; H, 6·71; N, 15·55%).

The semicarbazone crystallized from EtOH as fine prisms, m.p. 214–215°. (Found: C, 65·53; H, 9·85; N, 17·21. $C_{13}H_{23}N_3O$ requires: C, 65·78; H, 9·77; N, 17·71%).

Isolation of isopetasin (IV). The dried flower stalks of wild *Petasites japonicus* Maxim. (34 kg) were extracted with MeOH. The extract was taken up in benzene. Distillation of the washed and dried benzene extract left a dark viscous oil (2·4 kg). The residual oil was chromatographed on Merck neutral alumina and then silica gel. Elution with benzene gave IV (38 g) which was crystallized from MeOH aq as colorless needles, m.p. 100–100·5°, $[\alpha]_D^{24}$ +29·7° (*c*, 1·092, $CHCl_3$); IR: ν^{KBr} 1695, 1660, 1635 cm^{-1}; λ_{max}^{EtOH} 239 mμ (ε 7000), 277 mμ (ε 3710); NMR: 6·05 (q, *J* = 7·5, 1H, a vinyl proton of angelate), 5·63 (s, 1H, CH═C), 4·84 (m, 1H, CH—O—), 1·85–2·05 (4 × Me—C═C), 1·06 (s, 3H), 1·00 (d, *J* = 6·5, 3H). (Found: C, 75·90; H, 9·05. Calc. for $C_{20}H_{28}O_3$: C, 75·91; H, 8·92%).

The dark red 2,4-dinitrophenylhydrazone crystallized from EtOH, m.p. 188–189°. (Found: C, 62·91; H, 6·73; N, 11·05. Calc. for $C_{26}H_{32}N_4O_6$: C, 62·89; H, 6·50; N, 11·28%).

Isopetasol (V). A soln of IV (1 g), KOH (800 mg), EtOH (15 ml) and water (5 ml) was allowed to stand at room temp for 3 days. The dark red colored soln was neutralized to pH 8–9 with dil H_2SO_4 and concentrated *in vacuo*. The residual oil was taken up in ether, washed with water and dried over Na_2SO_4. The extract was evaporated to leave a neutral oil (750 mg) which partly crystallized. Chromatography on silica gel (20 g) and elution with benzene–EtOAc (15:1) afforded a fraction (520 mg) which was recrystallized from pet. ether as colorless needles, m.p. 124–125°, undepressed upon admixture with V, m.p. 124–125° of known structure and absolute configuration.[8,9] The IR spectra of both compounds were fully superimposable: $[\alpha]_D^{33}$ +135° (*c*, 1·015, $CHCl_3$); MS: M^+ ion *m/e* 234; IR: ν^{KBr} 3500, 1655, 1623, 1613 cm^{-1}; λ_{max}^{EtOH} 246 mμ (ε 5770), 277 mμ (ε 3480); NMR: 5·80 (s, 1H, CH═C), 3·63 (m, 1H, CH—OH), 2·08 (s, 3H, Me—C═C), 1·85 (s, 3H, Me—C═C), 1·15 (d, *J* = 6·2, 3H, Me—CH), 0·98 (s, 3H, Me—C). (Found: C, 76·65; H, 9·52. Calc. for $C_{15}H_{22}O_2$: C, 76·88; H, 9·46%).

The residual aq layer was acidified with dil H_2SO_4 and extracted continuously with ether for 25 hr. The dried ethereal extract was evaporated to afford a semi-solid residue (200 mg). The crude acidic material (177 mg) was neutralized to phenolphthalein with 0·1N NaOH aq, and refluxed with *p*-phenylphenacyl bromide (385 mg) in EtOH (3 ml) for 3 hr. The resulting product (163 mg) was chromatographed on silica gel (10 g) and elution with benzene–pet. ether (2:3) gave a fraction which was crystallized from EtOH aq to furnish *p*-phenylphenacyl angelate as colorless leaflets, m.p. 89·5–90·5°. (Found: C, 77·84; H, 5·95. Calc. for $C_{19}H_{18}O_3$: C, 77·53; H, 6·16%). This analytical sample showed no m.p. depression on admixture with an authentic sample of *p*-phenylphenacyl ester of angelic acid.

Wolff–Kishner reduction of fukinone (I). A mixture of KOH (5 g) and fukinone semicarbazone (1·2 g) was heated in a round-bottomed flask equipped with a downward condenser. The reaction was very rapid and after heating for about 10 min, the mixture was diluted with water and extracted with ether. The distillate was also extracted with ether and both extracts were combined, washed, dried and evaporated. The residue (600 mg) consisted mainly of two hydrocarbons, which were chromatographed on silica gel and elution with n-hexane to yield X (150 mg), an unresolved mixture (200 mg) and another hydrocarbon (IX; 200 mg). The hydrocarbon IX (150 mg) was hydrogenated in glacial AcOH with PtO_2. When H_2 absorption ceased, the mixture was diluted with water and extracted with ether. The extract was washed, dried and evaporated to afford a mixture of two saturated hydrocarbons, which were separable neither by adsorption chromatography nor by GLC.

For trial, dihydrofukinone (II) was subjected to Wolff–Kishner reduction to yield a mixture of two hydrocarbons, which was identical with that obtained from IX.

(7β)-*Eremophilane* (XII)

(a) *Dihydrofukinone thioketal* (XIV). To a mixture of II (800 mg) and ethane dithiol (1 ml), BF_3–etherate (1 ml) was added dropwise with ice cooling and stirring. The mixture was allowed to stand at room temp for 1 hr, diluted with MeOH (2 ml) and concentrated under reduced press (65°/30 mm). The resulting solid was removed by filtration, washed with water and dried *in vacuo* to give crystalline XIV (940 mg).

Crystallization from MeOH furnished colorless crystals, m.p. 73·5–74·5°. (Found: C, 68·35; H, 10·20; S, 21·69. $C_{17}H_{30}S_2$ requires: C, 68·39; H, 10·13; S, 21, 48%).

(b) *Desulfurization of the thioketal* (XIV). The thioketal XIV (910 mg) was heated under reflux with Raney Ni (10 g) in abs EtOH (60 ml) for 14 hr. The Raney Ni was filtered off and washed with hot EtOH. The combined filtrates were evaporated *in vacuo* to give a colorless oil (550 mg) which was purified by GLC affording pure XII, $[\alpha]_D^{30}$ +17·3° (neat), d_4^{20} 0·8955, n_D^{20} 1·4839; MS: M^+ ion *m/e* 208, base peak *m/e* 165. (Found: C, 86·66; H, 13·45. Calc. for $C_{15}H_{28}$: C, 86·46; H, 13·54%).

Tetrahydroisopetasol (XV). A soln V (2 g) in EtOH (20 ml) was hydrogenated at room temp in the presence of 10% Pd–C (370 mg). H_2 uptake (2 moles) ceased after 9 hr. The catalyst was filtered off and the solvent was evaporated *in vacuo* to afford a viscous oil in quantitative yield which exhibited a negative RD Cotton effect. The viscous oil (2 g) was heated under reflux under N_2 in MeOH (10 ml) soln with a catalytic amount of Na. The MeOH was removed *in vacuo* and the residue extracted with ether. The product (1·9 g) was crystallized from pet. ether to afford XV as colorless leaflets, m.p. 103–104°, IR: ν_{max}^{KBr} 3460, 1700 cm^{-1}; $[\alpha]_D^{22}$ +39·2° (*c*, 2·50, MeOH), RD in MeOH (*c* 0·11): $[\alpha]_{589}$ +45°, $[\alpha]_{350}$ +100°, $[\alpha]_{293}$ +290°, $[\alpha]_{268}$ +135°, $[\alpha]_{225}$ +527°; NMR: 3·58 (m, 1H, CH—OH), 0·95 and 1·05 (*d*, *J* = 7, 6H, Me_2CH), 0·97 (s, 3H, Me—C), 0·88 (d, *J* = 7, Me—CH). (Found: C, 75·83; H, 10·89. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

The 2,4-dinitrophenylhydrazone crystallized from EtOH aq as yellow needles, m.p. 168–170°. (Found: C, 60·25; H, 7·17; N, 13·54. $C_{21}H_{30}N_4O_5$ requires: C, 60·27; H, 7·23; N, 13·39%).

The semicarbazone crystallized from MeOH aq as fine needles, m.p. 188–190°. (Found: C, 65·36; H, 10·04; N, 14·27. $C_{16}H_{29}N_3O_2$ requires: C, 65·05; H, 9·90; N, 14·23%).

Conversion from tetrahydroisopetasol (XV) *to dihydrofukinone* (II). To a soln of XV (810 mg) in dry pyridine (7 ml), *p*-toluenesulfonyl chloride (1·85 g) was added at 0° and left at room temp for 3 days. The reaction mixture was poured into ice-water (30 ml) with stirring to yield a colorless ppt. The resulting XVI (1·35 g) in dry ether (30 ml) was added to a well-stirred suspension of LAH (300 mg) in dry ether (20 ml) and stirred under reflux for 24 hr. The excess hydride was decomposed with moist ether followed by water and dil HCl aq. The aqueous layer was extracted with ether and the combined ethereal extract washed with dil $NaHCO_3$ aq and water. The dried extract was evaporated to afford a monol as a colorless solid (810 mg).

To a soln of the monol (810 mg) in acetone (60 ml), a soln of $Na_2Cr_2O_7$ (225 mg) in AcOH (10 ml), conc. H_2SO_4 (17 ml) and water (70 ml) was added dropwise with stirring at 0° over 1 hr. After the excess reagent was decomposed with MeOH, the solvent was removed *in vacuo*, and the product (800 mg) was taken up in ether, washed with dil NaOH aq and water, dried over Na_2SO_4. The solvent was removed to yield an oily ketone (803 mg) which was chromatographed over silica gel (25 g) and elution with pet. ether–ether(100:1) affording II (321 mg). The ketone (291 mg) was converted to the semicarbazone, m.p. 198–199° after recrystallization from EtOH as fine prisms. The free ketone (78 mg) was obtained from the semicarbazone (160 mg) by steam distillation with a saturated oxalic acid aq and distilled at 143–145° (bath temp)/6·5 mm. Identity of this ketone and dihydrofukinone was established by mixed m.p. determination of both semicarbazones, GLC analysis, comparison of IR and MS spectra. This ketone exhibited the following spectra, IR: ν_{max}^{film} 1710 cm^{-1}; MS: M^+ ion *m/e* 222, base peak *m/e* 110: RD in MeOH (*c*, 0·1): $[\alpha]_{450}$ +90°, $[\alpha]_{350}$ +120°, $[\alpha]_{350}$ +120°, $[\alpha]_{312}$ +22°, $[\alpha]_{270}$ +650°, $[\alpha]_{230}$ +970°.

Ozonolysis of fukinone (I). Fukinone I (2·17 g) in $CHCl_3$ (40 ml) was ozonized at ice temp for 2 hr. The solvent was removed *in vacuo* and the residue heated with water (15 ml) in a current of N_2 for 4 hr on a water bath. The volatile vapors were collected in an ethanolic soln of 2,4-dinitrophenylhydrazine sulfate. The yellow ppt was filtered off and recrystallized from MeOH to give acetone 2,4-dinitrophenylhydrazone as yellow needles, m.p. 125–126°, undepressed upon admixture with an authentic sample. (Found: C, 45·29; H, 4·51; N, 23·55. Calc. for $C_9H_{10}N_4O_4$: C, 45·38; H, 4·23; N, 23·52%).

The non-volatile residue was made alkaline with $NaHCO_3$ aq and extracted with ether. The aqueous layer was acidified with dil HCl aq and left in a refrigerator overnight. The resulting ppt (1·54 g) was collected and crystallized from EtOAc–pet. ether to furnish XVII (1·4 g) as colorless prisms, m.p. 187·5–188°; $[\alpha]_D^{23}$ +51·5° (*c*, 0·99, MeOH); Neutral equiv. = 226 (as dicarboxylic acid); (Found: C, 63·42; H, 9·00. $C_{12}H_{20}O_4$ requires: C, 63·13; H, 8·83%).

A soln of the dimethyl ester prepared from dicarboxylic acid (1·39 g) with ethereal diazomethane in dry toluene (7 ml) was added dropwise to a suspension of Na (125 mg) powder in dry toluene (10 ml) at 100–105° over 1·5 hr. After cooling, the unchanged Na was decomposed with a small amount of EtOH and the mixture acidified with dil HCl aq. The organic layer was separated, washed with $NaHCO_3$ aq and water, dried over Na_2SO_4 and evaporated *in vacuo*. The resulting keto ester (1 g) in AcOH (5 ml) and conc HCl aq

(5 ml) was refluxed for 2 hr. After neutralization with dil NaOH aq, the mixture was extracted with ether, dried over Na_2SO_4 and concentrated to afford a yellow oil (600 mg). Chromatography over silica gel (20 g) and elution with benzene afforded XVIII (530 mg) as a colorless oil, b.p. 105–110° (bath temp)/3 mm, MS: M^+ ion *m/e* 166, base peak *m/e* 109; ν_{max}^{film} 1745 cm^{-1}; NMR: 2·04 (q, J_{AB} = 17·5, 2H), 1·01 (s, 3H), 0·81 (d, J = 6·5, 3H); $[\alpha]_D^{23}$ −126° (*c*, 1·03, MeOH), RD in MeOH (*c*, 0·106): $[\alpha]_{589}$ −141°, $[\alpha]_{312}$ −4620°, $[\alpha]_{274}$ +5100°, $[\alpha]_{230}$ +3010°. (Found: C, 79·28; H, 10·94. $C_{11}H_{18}O$ requires: C, 79·46; H, 10·92%).

The 2,4-dinitrophenylhydrazone crystallized from EtOH as orange yellow needles, m.p. 141–142·5°. (Found: C, 59·08; H, 6·48; N, 16·20. $C_{17}H_{22}N_4O_4$ requires: C, 58·94; H, 6·40; N, 16·18%). The semicarbazone recrystallized from EtOH as colorless leaflets, m.p. 209·5–210°. (Found: C, 64·66; H, 9·38; N, 18·80. $C_{12}H_{21}N_3O$ requires: C, 64·54; H, 9·48; N, 18·82%).

Baeyer–Villiger oxidation of dihydrofukinone (II). A soln of II (300 mg) in $CHCl_3$ (1 ml) was added dropwise at 0° to a soln of perbenzoic acid (377 mg) in $CHCl_3$ (5·5 ml) containing a catalytic amount of conc H_2SO_4 and the mixture allowed to stand in a refrigerator for 22 hr. The mixture was extracted with ether. The ether extract was washed $NaHCO_3$ aq, sat $FeSO_4$ aq and water, dried over Na_2SO_4 and the solvent evaporated to afford a solid (566 mg). The residual solid was chromatographed over silica gel (20 g) and eluted with pet. ether to furnish XIX (102 mg) which was recrystallized from MeOH aq as colorless leaflets, m.p. 90–90·5°, $[\alpha]_D^{16}$ +37° (*c*, 1·0, EtOH); MS: M^+ ion *m/e* 238, base peak *m/e* 195; IR: ν^{Nujol} 1710, 1280 cm^{-1}; NMR: 4·21 (q, J = 5, 7; 1H), 3·22 (t, J = 11·9, 1H), 0·98 (d, J = 7·5, 3H), 0·97 (d, J = 7·5, 3H), 0·92 (s, 3H), 0·81 (d, J = 7·5, 3H). (Found: C, 75·52; H, 11·04. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

Preparation of trans-5,10-*dimethyl*-3α-*isopropyldecalone*-2 (XXII)

(a) *Dehydrogenation of fukinone* (I) *with DDQ* (2,3-*dichloro*-5,6-*dicyano*-*p*-*benzoquinone*). Anhyd HCl was bubbled with stirring for 5 sec into a soln of I (1 g) and DDQ (1·15 g) in dry dioxan (15 ml). Soon crystals separated and TLC analysis showed that the dehydrogenation was almost completed in 30 min. After filtration and concentration of the soln, the residual oil was diluted with ether, washed with 1% NaOH aq and water, and dried over Na_2SO_4. The solvent was evaporated to leave an oil (804 mg). The product was chromatographed on silica gel (20 g) and eluted with pet. ether–ether (50:1) to give XX (700 mg) as a pale yellow oil, b.p. 116–120°/3 mm; IR: ν_{max}^{film} 1662, 1627 cm^{-1}; λ_{max}^{EtOH} 278 mμ (ε 8830), 248 mμ (ε 11,230).

(b) *Reduction of dehydrofukinone* (XX) *with lithium-liq. ammonia*. A soln of XX (700 mg) in dry THF (8 ml) was added dropwise over a period of 8 min into a stirred soln of Li (550 mg) in dry liq. NH_3 (80 ml). After stirring for an additional 4 min, NH_4Cl (5 g) was added and the ammonia was allowed to evaporate. The residue was diluted with water (40 ml) and the mixture was extracted with ether. The washed and dried extract was concentrated to afford a yellow oil (680 mg). The main product proved to be XXI by GLC analysis and the physical properties. The pure XXI was obtained by GLC as a colorless oil, MS: M^+ ion *m/e* 220, base peak *m/e* 178; IR: ν_{max}^{film} 1670, 1662 cm^{-1}; λ_{max}^{EtOH} 237 mμ (ε 14,000); $[\alpha]_D^{15}$ +134° (*c*, 0·99, $CHCl_3$); RD in MeOH (*c*, 0·1): $[\alpha]_{589}$ +140°, $[\alpha]_{450}$ +260°, $[\alpha]_{393}$ +350°, $[\alpha]_{354}$ 0°, $[\alpha]_{347}$ −110°, $[\alpha]_{340}$ 0°, $[\alpha]_{328}$ +800°. (Found: C, 81·99; H, 10·93. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%).

The 2,4-dinitrophenylhydrazone crystallized from EtOH as red needles, m.p. 169·5–170·5°, λ_{max}^{EtOH} 377 mμ ε 28,750). (Found: C, 63·31; H, 7·04; N, 13·76. $C_{21}H_{28}N_4O_4$ requires: C, 62·98; H, 7·05; N, 13·99%).

The semicarbazone was prepared by heating with semicarbazide HCl–pyridine for 4·5 hr and crystallized from EtOH as prisms, m.p. 217–218·5° (dec). (Found: C, 69·59; H, 9·85; N, 15·14. $C_{16}H_{27}N_3O$ requires: 69·27; H, 9·81; N, 15·15%).

The above oil (670 mg) in dry dioxan (6 ml) was directly reduced again with Li (550 mg) in liquid NH_3 (100 ml) as described above. The resulting oil (620 mg) showed two main spots on TLC (pet. ether–ether, 10:1) and and OH absorption in its IR spectrum.

(c) *Oxidation with* CrO_3. A soln of CrO_3 (202 mg) in water (5 ml) and conc H_2SO_4 (1 ml) was added dropwise to the above oil (620 mg) in acetone (10 ml) over a period of 20 min in a current of N_2 and under ice-cooling. After standing for 40 min at room temp, the mixture was diluted with water, extracted with ether, washed with water and dried. Evaporation of the solvent gave a yellow oil (590 mg) which was chromatographed on silica gel (9 g) and elution with pet. ether–ether (40:1) afforded XXII (400 mg). The pure sample was obtained by GLC, d_4^{20} 0·9563; n_D^{20} 1·4883; MS: M^+ ion *m/e* 222, base peak *m/e* 110; IR: ν_{max}^{film} 1710 cm^{-1}; $[\alpha]_D^{24}$ −17·4° (*c*, 3·90, $CHCl_3$), RD in MeOH (*c*, 0·097): $[\alpha]_{350}$ +61°, $[\alpha]_{314}$ +472°, $[\alpha]_{300}$ 0°, $[\alpha]_{274}$ −1040°, $[\alpha]_{250}$ −915°, $[\alpha]_{225}$ −1400°; NMR: 0·99 0·78 (4 × Me) (Found: C, 81·14; H, 11·86. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

The yellow 2,4-dinitrophenylhydrazone recrystallized from EtOH as needles, m.p. 170·5–171·5°. The

mixed m.p. with the 2,4-dinitrophenylhydrazone of II exhibited a marked depression (m.p. 151–153). (Found: C, 62·59; H, 7·46; N, 13·77. $C_{21}H_{30}N_4O_4$ requires: C, 62·66; H, 7·51; N, 13·92%).

The semicarbazone recrystallized from EtOH as colorless prisms, m.p. 194–196°. The mixed m.p. with the semicarbazone of II showed a marked depression (m.p. 183·5–185·5°). (Found: C, 68·85: H, 10·53; N, 15·00. $C_{16}H_{29}N_3O$ requires: C, 68·77; H, 10·46; N, 15·04%).

Acknowledgement—We are deeply indebted to Dr. Carl Djerassi (University of Stanford) for a generous supply of isopetasol and to Dr. A. Marsili (Istituto di Chimica Farmaceutica e Tossicologica dell' Universita) for a gift of ferluanc. We wish to thank Dr. H. Ishii for the IR spectrum of eremophilane.

REFERENCES

[1] This work was supported in part by a grant from the ministry of Education of Japan.
[2] A. I. Scott, *Interpretation of the Ultraviolet Spectra of Natural Products* p. 57 Pergamon Press, London (1964).
[3] A. E. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy*, p. 121. Edward Arnold, London (1957).
[4] D. Herbst and C. Djerassi, *J. Am. Chem. Soc.* **82**, 4337 (1960).
[5] C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*. McGraw-Hill, New York (1960).
[6] A. Stoll, R. Morf, A Rheiner and J. Renz, *Experientia* **12**, 360 (1956); A. Aebi, T. Waaler and J. Buchi, *Pharm. Weekblad* **93**, 397 (1958).
[7] L. Novotný, Ch. Tabacikova-Wlotzka, V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.* **29**, 1922 (1946); L. Novotný, V. Herout and F. Šorm, *Ibid.* **29**, 2182 (1964); J. Hochmannova, V. Herout and F. Šorm, *Ibid.* **29**, 2369 (1964).
[8] A. Aebi and C. Djerassi, *Helv. Chim. Acta* **42**, 1785 (1959).
[9] C. Djerassi, R. Mauli and L. H. Zalkow, *J. Am. Chem. Soc.* **81**, 3424 (1959).
[10] L. Novotný, J. Jizba, V. Herout, F. Šorm, L. H. Zalkow, S. Hu and C. Djerassi, *Tetrahedron* **19**, 1101 (1963).
[11] L. H. Zalkow, A. M. Shaligram, S. Hu and C. Djerassi, *Ibid.* **22**, 337 (1966).
[12] L. Novotný, V. Herout and F. Šorm, *Tetrahedron Letters* 697 (1961); *Coll. Czech. Chem. Comm.* **27**, 1400 (1962).
[13] L. H. Zalkow, F. X. Markley and C. Djerassi, *J. Am. Chem. Soc.* **82**, 6354 (1960).
[14] M. Horák, O. Motl, J. Pliva and F. Šorm, "*Terpenspektren* II, SI 18", Akademie Verlag, Berlin (1963).
[15] S. Carboni, A. Da Settimo, V. Malaguzzi, A Marsili and P. L. Pacini, *Tetrahedron Letters* 3017 (1965).
[16] H. Ishii, T. Tozyo and M. Minato, *J. Chem. Soc.* 1545 (1966).
[17] H. J. Ringold and A. Turner, *Chem. & Ind.* 211 (1962).
[18] G. Stork and S. D. Darling, *J. Am. Chem. Soc.* **82**, 1512 (1960)