298. *New Metabolites of* Gibberella fujikuroi. *Part VII.*[1] *The Preparation of Some Ring-*B *Nor-derivatives*

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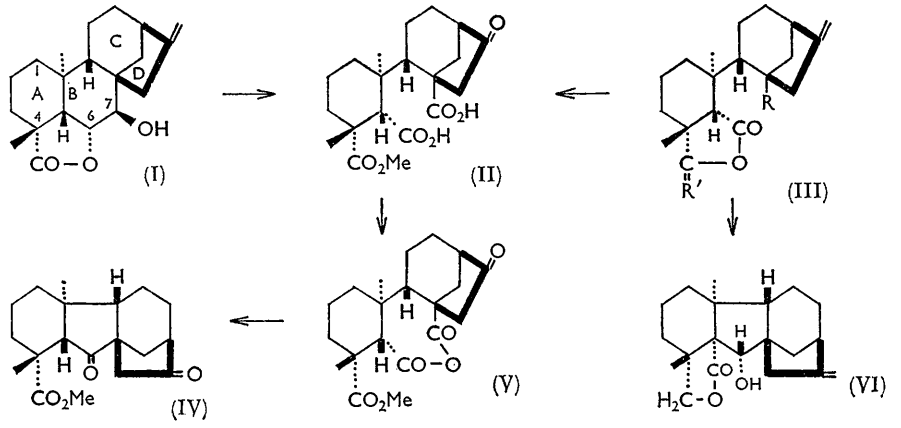
The partial synthesis of some gibbane derivatives, involving the ring closure of degradation products of fujenal and the rearrangement of the toluene-*p*-sulphonate of 7α-hydroxykaurenolide, is described.

Considerable attention has been directed[2] to the biological activity of compounds possessing the gibbane skeleton. 7-Hydroxykaurenolide[3] (I) occurs along with gibberellic acid as a diterpenoid metabolite of the fungus *Gibberella fujikuroi* ACC 917. Furthermore it belongs to the same enantiomorphic series whilst the parent hydrocarbon, (—)-kaurene, has been shown[3,4] to be converted *in vivo* into gibberellic acid. In this Paper the conversion of fujenal[5] (III; R = CHO, R′ = O) and 7-hydroxykaurenolide into compounds with the gibbane skeleton will be described. Two successful methods of ring contraction have been explored involving (i) the cyclisation of ring-B seco-derivatives, and (ii) rearrangement of ring-B.

The dicarboxylic acid (II) can be obtained in three stages from 7-hydroxykaurenolide[3] and in four stages from fujenal.[5] On refluxing with acetic anhydride it formed the internal 6,7-anhydride (V) (no acetoxyl), $\nu_{max.}$ 1794, 1742, and 1717 cm.$^{-1}$. The anhydride was hydrolysed to the parent acid with aqueous methanolic sodium hydroxide whilst on

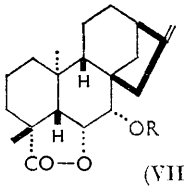


pyrolysis at 280° it evolved carbon dioxide to give a diketone which, from its infrared spectrum [$\nu_{max.}$ 1753, 1741 (cyclopentanones), and 1729 (ester) cm.$^{-1}$], must have the gibbane structure (IV). However, attempts to obtain confirmation of this by dehydrogenation to a fluorene were unsuccessful. Pyrolysis of the barium salt of the dicarboxylic acid gave intractable material showing infrared absorption characteristic of a five-membered anhydride whilst pyrolysis of the free dicarboxylic acid at 210° led to the formation of fujenoic acid 17-norketone.[5]

An alternative route to the gibbane skeleton involved reduction of fujenal with lithium aluminium hydride to form the hydroxy-lactone (III; R = CH_2·OH,R′ = H_2).[5] On one occasion the corresponding dihydroxy-acid was isolated from this reduction. The

[1] Part VI, Hanson, *J.*, 1963, 5061.
[2] Brian, Grove, and MacMillan, *Progr. Chem. Org. Nat. Prod.*, 1960, **18**, 350; Grove, *Quart. Rev.*, 1961, **16**, 56.
[3] Cross, Galt, and Hanson, *J.*, 1963, 2944.
[4] Cross, Galt, and Hanson, *J.*, 1964, 295.
[5] Cross, Galt, and Hanson, *J.*, 1963, 5052.

hydroxy-lactone, on oxidation with chromium trioxide, gave the aldehyde (III; R = CHO, R′ = H_2),[5] which, on refluxing with 0·5N-methanolic sodium hydroxide, underwent an internal aldol condensation to form a hydroxy-γ-lactone, $C_{20}H_{28}O_3$. Since microhydrogenation of this revealed only one double bond, present [from the infrared ($\nu_{max.}$ 3065, 1650, and 875 cm.$^{-1}$) and nuclear magnetic resonance (τ = 5·15) spectra] as a terminal methylene group, the lactone was tetracarbocyclic. Although the hydroxyl group was not acetylated with acetic anhydride in pyridine, oxidation of the hydroxy-lactone with chromium trioxide gave a keto-lactone ($\nu_{max.}$ 1745, 1720, 1650, and 875 cm.$^{-1}$), which, as a β-keto-lactone, was decarboxylated on pyrolysis. The gibbane structure (VI) for the condensation product is consistent with its n.m.r. spectrum which showed a one-proton singlet at τ = 5·98 and a two-proton double doublet at τ = 5·8 and 6·3, J = 9 c./sec., assigned to the >C(OH)*H* and >C·CH_2O· protons, respectively. Reduction of the keto-lactone with sodium borohydride regenerated the parent hydroxy-lactone. Attack of the reagent from the less-hindered β-face of the molecule leads to the α-configuration for the hydroxyl group, as in (VI).



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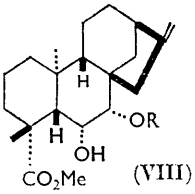

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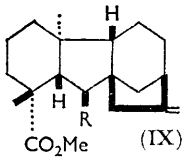

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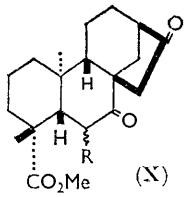

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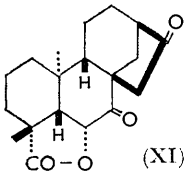

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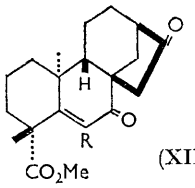

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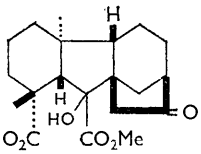

(XIII)

The solvolysis of 11α-acetoxy-12-methanesulphonylrockogenin has been shown[6] to lead to the extrusion of a carbon atom with the formation of a ring-C noraldehyde. However, the kaurenolides possess a diaxial diol system, whereas rearrangement requires the elimination of an equatorial group. Indeed, it is possible that the kaurenolides retain the perhydrophenanthrene skeleton, since the ring-B substituents are unfavourably oriented for ring contraction. The equatorial 7-alcohols were readily available through reduction of the 7-oxo-kaurenolides with sodium borohydride and these, on alkaline hydrolysis and methylation, gave, *inter alia*, the corresponding 6α(*ax*),7α(*eq*)-diols.[3] On treatment with toluene-*p*-sulphonyl chloride in pyridine, methyl 6α,7α-dihydroxykaur-16-en-19-oate[3] gave only a monotoluene-*p*-sulphonate (VIII; R = SO_2·C_6H_4Me) in which the free hydroxyl is shown in the sequel to be at the 6-position. This compound was recovered largely unchanged after treatment with refluxing 10% methanolic potassium hydroxide, sodium methoxide, and potassium t-butoxide. However, treatment of the monotoluene-*p*-sulphonate of 7α-hydroxykaurenolide (VII; R = SO_2·C_6H_4Me) with refluxing 10% methanolic potassium hydroxide gave, after methylation of the crude product, a 10—15% yield of a B-noraldehyde (IX; R = CHO). The major product from this reaction was the toluene-*p*-sulphonate (VIII; R = SO_2·C_6H_4Me) thus implying that the free hydroxyl group was at the 6-position. Presumably hydrolysis of the lactone ring provided some anchimeric assistance for the elimination of the 7-toluene-*p*-sulphonate with concomitant migration of the 5→6 bond. Under the same conditions, hydrolysis of the 7(*ax*)-toluene-*p*-sulphonate gave mainly intractable material from which the 6α,7β-diol was isolated.

[6] Wendler, Hirschmann, Slates, and Walker, *J. Amer. Chem. Soc.*, 1955, **77**, 1632.

The aldehyde (IX; R = CHO) showed absorption in the infrared at 2738 cm.$^{-1}$ (aldehyde C–H) and 1730 and 1712 (ester and aldehyde) cm.$^{-1}$. It was oxidised to a gibbane monocarboxylic acid (IX; R = CO_2H). Examination of molecular models, together with the mode of preparation, suggested that the carboxyl group existed in the more stable β-configuration typical of the gibberellins.

The elimination of a 6-substituent by a Favorski reaction was explored since tracer studies have shown that, in the biosynthesis of gibberellic acid, the 7-carbon atom is extruded.[7] Bromination of the 7,16-diketone (X; R = H) gave a monobromo-compound (X; R = Br). However, treatment with sodium in methanol showed that debromination and dehydrobromination were occurring in preference to ring contraction. Attempts to prepare the αβ-unsaturated ketone (XII; R = H) were unrewarding. Treatment of the bromo-ketone with lithium chloride in dimethylformamide afforded the diketo-lactone (XI). With lithium iodide and lithium carbonate, the starting material was recovered; more prolonged treatment gave a mixture, the major component of which was the diketoester (X; R = H) separated from traces of the αβ-unsaturated ketone by chromatography and crystallisation. The diketo-lactone (XI) was also isolated.

The benzillic acid rearrangement has been successful in ring-B contraction of diterpenes.[9] However, prolonged treatment of the diosphenol (XII; R = OH) [3] with strong alkali, followed by methylation, produced the diester (XIII) in only low yield.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are corrected. Extracts were dried over sodium sulphate. Light petroleum refers to the fraction, b. p. 60—80°. Grade II Wöelm acid alumina and silica gel (Hopkin and Williams Ltd.) were used for chromatography. Unless otherwise stated, infrared spectra were determined as Nujol mulls. Nuclear magnetic resonance spectra were determined in chloroform with tetramethylsilane as an internal standard on a Varian A 60 instrument.

16-Oxo-6,7-seco-17-norkauran-6,7,19-trioic acid 19-methyl ester (II) [3] was prepared by the oxidation of either 7,16-dioxo-6,7-seco-17-norkauran-6,19-dioic acid 19-methyl ester 6→7-lactol form or methyl 6α,7β-dihydroxy-16-oxo-17-norkauran-19-oate in acetone solution with 8N-chromium trioxide in sulphuric acid.[8]

Anhydride Formation from the Acid (II).—The dicarboxylic acid (II) (80 mg.) in acetic anhydride (5 ml.) was heated under reflux for 5 hr. The excess of reagent was then removed *in vacuo* leaving a gum which crystallised from acetone–light petroleum as plates of 16-*oxo*-6,7-*seco*-17-*norkauran*-6,7,19-*trioic acid* 6,7-*anhydride* 19-*methyl ester* (V) (40 mg.), m. p. 195—198° (Found: C, 65·9; H, 7·4; OMe, 8·9%; no acetyl. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2; OMe, 8·6%), $\nu_{max.}$ (in $CHBr_3$) 1794 and 1742 (7-ring anhydride and cyclopentanone), 1717 (ester) cm.$^{-1}$, $\nu_{max.}$ 1775, 1748, and 1728 cm.$^{-1}$.

Hydrolysis of the Anhydride.—The anhydride (30 mg.) in methanol (5 ml.) was treated with 0·5N-sodium hydroxide solution (4 ml.) for 16 hr. at 0°. The solution was poured into dilute hydrochloric acid (30 ml.) and extracted with ethyl acetate. The extract was washed with water and dried. The solvent was evaporated to give a gum which slowly crystallised from acetone–light petroleum giving the dicarboxylic acid (10 mg.) (II), m. p. 172° reset and remelt 204—206°, identified by its infrared spectrum.

Pyrolysis of the 6,7-*Anhydride* (V).—The anhydride (45 mg.) was heated in a Pyrex tube under nitrogen for 16 hr. at 350° during which time carbon dioxide (baryta trap) was evolved. The distillate was chromatographed on silica gel (10 × 1 cm.). Elution with 10% of ethyl acetate in light petroleum gave *methyl* 1β,4aα-*dimethyl*-8,10-*dioxogibbane*-1α-*carboxylate* (IV) (15 mg.) which crystallised from acetone–light petroleum as plates, m. p. 150—152° (Found; C, 71·6; H, 8·3. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2%), $\nu_{max.}$ 1753 and 1741 (cyclopentanones), 1729 (ester) cm.$^{-1}$, (in CCl_4) 1753, 1742, and 1725 cm.$^{-1}$. Attempts to dehydrogenate this compound (50 mg.) with selenium were unsuccessful.

[7] Birch, Rickards, Smith, Harris, and Whalley, *Tetrahedron*, 1959, **7**, 241.
[8] Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457.
[9] Grove and Riley, *J.*, 1961, 1105.

Pyrolysis of the Dicarboxylic Acid (II).—The dicarboxylic acid (50 mg.) was heated in a Pyrex tube under nitrogen at 205° for 2 hr. The organic material (gum; 47 mg.) was recovered with ethyl acetate and crystallised from acetone–light petroleum (charcoal) as prisms, m. p. 248—250° (decomp.), identical with fujenoic acid norketone.[5]

On one occasion fujenoic acid norketone (50 mg.) was heated in a Pyrex tube at 285° under nitrogen for 3 hr. and the effluent gases passed through a solution of barium hydroxide. When the temperature reached 270°, carbon dioxide (0·8 mol.) was evolved. The residue was recovered with ethyl acetate and chromatographed on silica gel. Elution with 10% of ethyl acetate in light petroleum gave a compound (20 mg.) which crystallised from acetone–light petroleum as needles (m. p. 133°), $\nu_{max.}$ (in $CHBr_3$) 1851, 1780 (5-ring anhydride), and 1759 (cyclopentanone) cm.$^{-1}$.

The lactone (III; R = CHO, R′ = H_2) was prepared [5] by the reduction of fujenal with lithium aluminium hydride in refluxing ether followed by oxidation in acetone solution with the 8N-chromium trioxide reagent.[8] On one occasion 7,19-*dihydroxy*-6,7-*seco*-(−)-*kaur*-16-*en*-6-*oic acid*, m. p. 155—157° (Found: C, 71·4; H, 9·7. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·6%), $\nu_{max.}$ 3250, 2570, 1675 (br.), 1650, 880 cm.$^{-1}$, τ = 8·86, 8·69 (−C(CH$_3$)−), 6·8, 5·85 (doublets; J 11 c./sec.) 6·30, 6·03 (doublets; J 8·5 c./sec.) (−CH_2OH), 5·25 (C=CH_2), was isolated from this reduction.

Action of Alkali on the Lactone (III, R; CHO, R′ = H_2).—The lactone (390 mg.) in methanol (5 ml.) was heated under reflux with aqueous 1·5N-sodium hydroxide solution (40 ml.) for 5·5 hr. The solution was cooled and the precipitate which separated (119 mg.) was filtered off. Crystallisation from acetone–light petroleum gave 10α-*hydroxy*-1α-*hydroxymethyl*-1β,4aα-*dimethyl*-8-*methyl-enegibbane*-10a-*carboxylic acid* 10a→1α-*lactone* (VI) as needles, m. p. 164—165° (Found: C, 75·9; H, 8·8. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%), $\nu_{max.}$ 3453, 3065, 1754 (γ-lactone), 1650, and 875 (C=CH_2) cm.$^{-1}$, τ = 8·95 (−C(CH$_3$)−), 8·78 (−C(CH$_3$)−), 8·6—8·52 (ring protons), 7·85 and 7·7 (allylic protons), 6·3 and 5·8, J 9 c./sec. (lactone protons), 5·98 (10-proton), and 5·15 (C=CH_2).

The alkaline filtrate was acidified and the organic material recovered with ether. The solvent was washed, dried, and evaporated to give a gum which was methylated with diazomethane and chromatographed on alumina. Elution with 25% of ethyl acetate in light petroleum gave the starting material (110 mg.).

The hydroxy-lactone was recovered after treatment with pyridine and acetic anhydride for 18 hr.

Oxidation of the Hydroxy-lactone (VI).—The hydroxy-lactone (175 mg.) in acetone (10 ml.) was treated with the 8N-chromium trioxide reagent (0·13 ml.) for 2 hr. Methanol was added and the solution concentrated; it was then diluted with water and extracted with ethyl acetate. The extract, after washing first with sodium hydrogen carbonate solution and then with water, was dried and evaporated to give a gum which was chromatographed on alumina. Elution with 10% ethyl acetate in light petroleum gave the corresponding keto-lactone (95 mg.) which crystallised from aqueous methanol as needles, m. p. 142—143° (Found: C, 76·25; H, 8·6. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·3%), $\nu_{max.}$ 1745, 1650, and 875 cm.$^{-1}$, τ = 8·88, 8·64 (C−CH_3), 6·25, 6·00 (doublets; J 8 c./sec., −CH_2O−), and 5·1 (C=CH_2).

Reduction of the Keto-lactone.—The keto-lactone (50 mg.) in methanol (5 ml.) was treated with sodium borohydride (50 mg.) for 5 hr. The solution was acidified with dilute hydrochloric acid and the needles which formed (29 mg.) were collected and recrystallised from aqueous methanol to give the hydroxy-lactone (VI), m. p. 164°, identified by its infrared spectrum.

The Toluene-p-*sulphonate of* 7α-*Hydroxykaurenolide* (VII).—This was prepared by treatment of the corresponding alcohol [3] with toluene-*p*-sulphonyl chloride in dry pyridine at room temperature for 72 hr. The 7α-*toluene*-p-*sulphonate* (VII; R = SO_2·C_6H_4Me) of 6α,7α-dihydroxykaur-16-en-19-oic acid 19→6α-lactone crystallised from acetone–light petroleum as needles, m. p. 160—161° (Found: C, 69·2; H, 7·5. $C_{27}H_{34}O_5S$ requires C, 68·9; H, 7·3%), $\nu_{max.}$ 1771 (γ-lactone), 1667 (double bond), 1598 (ar.), and 893 (C=CH_2) cm.$^{-1}$.

The 7α-*toluene*-p-*sulphonate* (VIII; R = SO_2·C_6H_4Me) of methyl 6α,7α-dihydroxykaur-16-en-19-oate [3] crystallised from acetone–light petroleum as needles, m. p. 190—192° (Found: C, 67·2; H, 7·4. $C_{28}H_{36}O_6S$ requires C, 67·2; H, 7·25%), $\nu_{max.}$ 3410, 1695, 1654, 1590, and 890 cm.$^{-1}$.

Ring-contraction Reactions.—(*a*) The toluene-*p*-sulphonate of (VII) was recovered after

heating under reflux with 10% methanolic potassium hydroxide solution (4·5 hr.), methanolic sodium methoxide (3 hr.), and potassium-t-butoxide in t-butanol–benzene (4 hr.) followed by methylation and chromatography.

(*b*) The 7α-toluene-*p*-sulphonate of 6α,7α-dihydroxykaur-16-en-19-oic acid 19→6α-lactone (210 mg.), potassium hydroxide (3 g.), and methanol (30 ml.) were heated under reflux for 4·5 hr. The solution was concentrated under reduced pressure, diluted with water, acidified, and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated to give a neutral gum (150 mg.) which was chromatographed on alumina. Elution with light petroleum gave *methyl* 10β-*formyl*-1β,4aα-*dimethyl*-8-*methylenegibbane*-1α-*carboxylate* (IX) (22 mg.) which crystallised from light petroleum as needles, m. p. 68—70° (Found: C, 76·1; H, 9·45. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·15%), $\nu_{max.}$ 2738 (aldehydic C–H), 1730, 1712 (ester and aldehyde), 3073, 1655, and 880 (C=CH_2) cm.$^{-1}$.

Further elution with 10—20% of ethyl acetate in light petroleum gave the monotoluene-*p*-sulphonate of methyl 6α,7α-dihydroxykaur-16-en-19-oate (61 mg.) as needles, m. p. 189—190°, identified by its infrared spectrum. In subsequent experiments the total (acidic and neutral) fractions were methylated with diazomethane prior to chromatography, thus giving slightly higher yields.

Oxidation of the Aldehyde (IX).—The aldehyde (71 mg.) in acetone (5 ml.) was treated with the 8N-chromium trioxide reagent [8] (0·25 ml.) at room temperature for 2 hr. Methanol was added, and the solution concentrated, diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to give a gum which was chromatographed on silica gel (12 × 1 cm.). Elution with 15—20% of ethyl acetate in light petroleum gave 1α-*methoxycarbonyl*-1β,4aα-*dimethyl*-8-*methylenegibbane*-10β-*carboxylic acid* (22 mg.) which crystallised from acetone–light petroleum as needles, m. p. 196—198° (Found: C, 72·8; H, 8·7. $C_{21}H_{30}O_4$ requires C, 73·2; H, 8·8%), $\nu_{max.}$ 2623 (carboxyl OH), 1724 (ester), 1697 (carboxyl), 1655, 1622, and 891 (C=CH_2) cm.$^{-1}$.

Bromination of the Diketone (X; R = H).—Methyl 7,16-dioxo-17-norkauran-19-oate [3] (104 mg.) in chloroform (4 ml.) was treated with a solution of bromine (1·25 g. in 25 ml.) (4 ml.) in acetic acid at room temperature for 2 hr. The solution was diluted with chloroform, and washed successively with aqueous sodium metabisulphite, sodium hydrogen carbonate solution, and water; it was then dried and evaporated to give a crystalline residue. Recrystallisation from acetone–light petroleum gave *methyl* 6ξ-*bromo*-7,16-*dioxo*-17-*norkauran*-19-*oate* (69 mg.), m. p. 158—160° (Found: C, 55·65; H, 6·4. $C_{20}H_{27}O_4Br,H_2O$ requires C, 55·9; H, 6·3%), $\nu_{max.}$ 1747 and 1713 cm.$^{-1}$.

Attempted Favorski Reaction with the Bromo-ketone (X; R = Br).—Methyl 6-bromo-7,16-dioxo-(−)-17-norkauran-19-oate (50 mg.) was heated for 4 hr. under reflux with a solution of sodium methoxide (from 150 mg. sodium) in dry methanol (7 ml.). The solution was diluted with water, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. After the extract had been washed with sodium hydrogen carbonate solution and then with water, it was dried and evaporated to give a gum which was chromatographed on alumina (10 × 1 cm.). Elution with 20% of ethyl acetate in light petroleum gave crystals (15 mg.), m. p. 101—104°, $\nu_{max.}$ 1745—1705br, 1670m, and 1645w cm.$^{-1}$. This compound was shown by repeated crystallisation to be a mixture consisting mainly of the diketoester (X; R = H), m. p. 129—131°, identified by infrared spectrum.

Attempted Dehydrobromination of the Bromo-ketone (X; R = Br).—(i) A mixture of the bromo-ketone (46 mg.), dried lithium chloride (100 mg.) and dimethylformamide (10 ml.) was refluxed for 2 hr. and poured into water (100 ml.). Recovery with ethyl acetate gave the diketo-lactone (XI; 34 mg.).

(ii) A mixture of the bromo-ketone (72 mg.), dried lithium iodide (150 mg.), lithium carbonate (150 mg.), and dimethylformamide (3 ml.) was refluxed for 2 hr. The starting material (65 mg.) was recovered.

(iii) The time of reflux was extended to 3·5 hr. Recovery in ethyl acetate yielded a gum (47 mg.) which was chromatographed on alumina. Elution with 20% of ethyl acetate in light petroleum gave a crystalline mixture (24 mg.), m. p. 112—118°, identical (infrared spectrum) to the product obtained from the attempted Favorski reaction above. Elution with 40% ethyl acetate gave the diketo-lactone (10 mg.).

Treatment of the Diosphenol (XII; R = OH) *with Strong Alkali*.—A solution of potassium hydroxide (4 g.) in water (10 ml.) was added to the diosphenol (XII; R = OH; 0·4 g.) in

ethanol (10 ml.) and the mixture refluxed for 6 hr. Water (25 ml.) was added and the ethanol was removed *in vacuo*. The solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The products were separated into acid and neutral portions with sodium hydrogen carbonate solution. The acids (319 mg.) were chromatographed on silica and eluted with increasing concentrations of ethyl acetate in light petroleum. Only intractable material (194 mg.) was eluted. The column contents were then extracted with sodium hydrogen carbonate and, after acidification, were recovered in ethyl acetate. This gave a gum (78 mg.), which was methylated and chromatographed on alumina (ethyl acetate–light petroleum). Elution with 20% ethyl acetate yielded 1β,4aα-*dimethyl*-10ξ-*hydroxy*-8-*oxogibbane*-1α,10ξ-*dicarboxylic acid dimethyl ester* (XIII; 28 mg.) which was recrystallised from acetone–light petroleum, m. p. 139—142° (Found: C, 66·7; H, 8·0. $C_{21}H_{30}O_6$ requires C, 66·6; H, 8·0%), $\nu_{max.}$ 3348, 1939, 1734, and 1690 cm.$^{-1}$.

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