The Chemistry on Diterpenoids in 1968

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I. INTRODUCTION

The author has published a series of the reviews.¹⁻⁴ This review deals with an outline of the chemical works on diterpenoids in 1968.

The classification consists of podocarpane, labdane, clerodane, pimarane, isopimarane, abietane, totarane, cassane, kaurane, gibberellane, atisane, aconane, beyerane, taxane, and the others, in accordance with a proposal** for a systematic nomenclature subscribed to by most workers in this area.⁵

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** The IUPAC Commission on the Nomenclature of Organic Chemistry has discussed these proposals and considered that they are as a whole in accordance with the general principles of the nomenclature of organic chemistry.
H. PODOCARPANE DERIVATIVES

Methyl rac-deisopropyldehydroabietate (3) was derived from 1 via 2 by Spencer et al. The synthesis was developed to that of podocarpic acid, that is, methyl rac-podocarpate (6) was synthesized from 4 via 5. Methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (7) was converted into 8. The corresponding acid chloride 9 was subjected to Friedel-Crafts cyclization to yield D-homosteroid 10. Lactone 11 was formed by Reformatsky reaction of 13-succinyl derivative. The rearrangement of C-12 O-allyl ether gave normal C-13 allyl ether.

*3 Represented as one enantiomer.
phenol 12 and coumaran 13. Peracid oxidation of 7 gave the expected quinone 14 and hydroxy dienone 15. Unsaturated ketone 16 on photolysis in methanol gave only the corresponding saturated ketone 17.8

Compound 18 was prepared from 19 in a fair yield, but attempted cyclization of compounds possessing a 1'-substituted-2'-carboxyethyl side chain at C-13 was unsuccessful. The C-17 ketone 20 was obtained in low yield from the 13-acrylyl compound 21.9 The conversion of O-methylpodocarpic acid (22) into 12-methoxy-19-norpodocarpa-8,11,13-trien-4-amine (23) was investigated.10 A variety

\[\text{(22)}: R=\text{COOCH}_3 \]
\[\text{(23)}: R=\text{NH}_2, \text{NH}_3, \text{NH}_4^+ \]
\[\text{(24)}: R=\text{COOCH}_3 \]
\[\text{(25)}: R=\text{H} \]
\[\text{(26)}: R=\text{Br} \]
\[\text{(27)}: R=\text{Et} \]
\[\text{(28)}: R=\text{P} \]
\[\text{(29)}: R=\text{COOCH}_3 \]
\[\text{(30)}: R=\text{COEt} \]
\[\text{(31)}: R=\text{H} \]
\[\text{(32)}: R=\text{Br} \]
\[\text{(33)}: R=\text{Et} \]
\[\text{(34)}: R=\text{P} \]
\[\text{(35)}: R=\text{COOCH}_3 \]
\[\text{(36)}: R=\text{COEt} \]
of derivatives of podocarpic acid (24), for instance, 25–30, gave their corresponding 7-oxo-compounds, 31–36 in moderate to good yield by a brief treatment with bromine in ether, preferably containing a free-radical initiator such as benzoyl peroxide, followed by hydrolysis.\(^\text{11}\)

10-Cyano-12-hydroxy-7-oxo-20-norpodocarpa-5, 8, 11, 13-tetraene (37), a model for tricyclic C-aromatic diterpenoids, was synthesized.\(^\text{12}\)

\[
\text{(37)} \quad \text{(38)} \quad \text{(39)} \quad \text{(40)} \quad \text{(41)}
\]

Stipanovic and Turner\(^\text{13}\) attempted to synthesize 41 from 38 via 39 and 40, but the reaction of diazoacetic ester on 39 was unsuccessful and 40 was not obtained. They examined the same reaction using more simple models.

A stereoselective synthesis of rac-desoxypodocarpic acid (as 42) and rac-13-methoxydesoxypodocarpic acid (as 43a) was reported by Ireland and Giarrusso.\(^\text{14a}\) Methyl 13-hydroxydesopropyldehydroabietate (43b) was synthesized by an Indian group.\(^\text{14b}\) The stereochemistry of 6-bromo-7-oxo derivative 44 was established by X-ray analysis. Bromination of sugiyl methyl ether was examined.\(^\text{15}\) Conformational analysis of 6-bromo-7-oxopodocarpic acid derivatives was tried by application of the Nuclear Overhauser Effect.\(^\text{16}\) Okamoto et al.\(^\text{17}\) published a

\[
\text{(42)} \quad \text{(43a)}: R^1=\text{Me}, R^2=\text{H}, R^3=\text{COOH} \\
\text{(43b)}: R^1=R^2=\text{H}, R^3=\text{COOCH}_3
\]

new method for angular formylation using Reimer-Tiemann's reaction. They prepared 47 via 46 starting from 45.

III. LABDANE DERIVATIVES

14, 15, 16-Trisnor-labd-8(17)-ene-6α, 13-diol (48) was subjected to cyclization
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in the presence of p-toluenesulfonic acid to give 6α- and 6β-hydroxy-8,13-oxido-14,15,16-trisnorlabdane (49a, b), which were dehydrated to yield a same unsaturated product 50.187 19-Oxo-labd-8(17)-en-15-ol (51) (imbricatal), from the oleoresin of *Araucaria imbricata*, was converted into 17-nor-8-oxy-labdan-15-oic acid (52) by Bruns.19 Thus, the S-configuration at C-13 in imbricatadiol (53), imbricatal (51=54), imbricatal-15-acetate (55), imbricatic acid (56), and imbricatic acid-15-acetate (57) was proved.

From *Juniperus phoenicea*, 12-hydroxylabd-8(17)-en-19-oic acid (58) was isolated.20 Mangoni and Adinolfi21,22 established the stereochemistry of marrubiin, especially that of C-9 hydroxy group, as shown in formula 59. The structures of compounds X and Y, two labdane diterpenoids isolated together with marrubiin from *Leonotis leonurus*, were elucidated as shown in formulas 60 and 61, respectively.23 In the absence of pyridine dehydration of marrubiin with phosphorus trichloride appears to yield exclusively the Δ⁴⁰⁻olefin whereas in its presence the Δ³⁻isomer predominates.24 From *Marrubium vulgare*, marrubenol (62) and the hemiacetal 63 were isolated besides marrubiin.24 A partial synthesis of marrubiin from compound 64 was carried out.25 From *Marrubium incanum* a new diterpenoid 65,26 whose physical properties correspond with those described by L. A. Salei et al.,27 was isolated. A full paper on the structure 66 of ozic
acid isolated from the wood of *Daniellia ogea* was published. The corresponding alcohol, ozol (67) was also isolated. From the wood of *D. oliveri* danielllic acid (68) was isolated. Chromic acid oxidation of sclareol was investigated and isolation of at least seven compounds was effected by chromatography of the methylated products. No pimarane derivatives were obtained.

From oleoresin of black kauri *cis* (69) and *trans*-communie acid (70), abietic acid, neoabietic acid, agathic acid (71), methyl agathate, and a new aldehydic carboxylic acid, agathalic acid (72) were isolated. The latter was reduced to agatholic acid (73) by sodium borohydride. From the dry leaves of *Aphana-mixis polystachya* aphanamixol (74) was isolated. Eperuic acid (75), its trans-isomer, ent-7,13-labdadien-15-oic acid (76), 8(17),13-labdadien-15-oic acid (77), and the enantiomer (named "copalic acid") of 77 were isolated from *Oxystigma oxyphyllum*.

The structure 78 was proposed for neoandrographolide, a diterpene glucoside from *Andrographis paniculata*. Dehydration investigation of sclarealdehyde (80), a product from chromic acid oxidation of sclareol (79) was reported. The chromic acid oxidation product of sclareol, which was a mixture containing sclarealdehyde (80), was subjected to lithium aluminum hydride or sodium borohydride reduction. From the reaction mixture, diol 81 was isolated as acetate. Two new isoambreinolides, 82 and its 8-epimer 83, were synthesized and characteriz-
Ruzicka and Janot\textsuperscript{37} treated sclareol (79) with β-naphthalenesulfonic acid at 190° and got a hydrocarbon C\textsubscript{20}H\textsubscript{32}, to which they assigned structure 84. Carman and Dennis\textsuperscript{83} reinvestigated the reaction and got a hydrocarbon C\textsubscript{20}H\textsubscript{30}, to which they assigned structure 85. They provided a rearrangement mechanism for the product formation. Manool (86) and agathadiol (87) cyclize in formic acid to the 13-epimeric pimara-8,15-dienes and 14α-hydroxybeyerane derivatives. The mechanistic and biosynthetic implications of these results and the nuclear magnetic resonance spectra of relevant tricyclic and tetracyclic diterpenes were discussed.\textsuperscript{39} Manool (86), 13-epimanool, and the allylic primary alcohols 88\textsubscript{a} and 88\textsubscript{b} were subjected to acid-promoted dehydration (AcOH-H\textsubscript{2}O-H\textsubscript{2}SO\textsubscript{4} (83:10:7) at 50°). The four labdadienols gave product mixtures of essentially similar composition which varies with time. Their in vitro conversion into pimara- and rosa-dienes was discussed.\textsuperscript{40} A new diterpene triol was isolated from Goodenia ramelii, and structure 89 was assigned to it.\textsuperscript{41} Extracts of the leaves of Psiadia altissima contained diterpenoid glycosides, the major aglycone of which is probably 90.\textsuperscript{81}\textsuperscript{b}

IV. CLERODANE DERIVATIVES

A bitter principle was isolated from the roots of Solidago altissima and named solidagonic acid, whose structure 91 was elucidated by Kotake et al.\textsuperscript{45} From
the roots of *Solidago serotina* furan-containing clerodane derivatives were isolated and structures 92 to 96 were tentatively assigned to them.\(^\text{43a}\) The absolute configuration 97 was assigned to (—)-hardwickiic acid.\(^\text{44a}\) Kolavelool (101) and methyl hardwickiate (98) were derived from kolavenol (99) and its acetate (100), respectively.\(^\text{44b}\) Constitution and configuration of diosbulbin -A, -B, and -C were elucidated as 102, 103 and 104 by chemical and physical methods. They were isolated from Dioscoreaceous plants.\(^\text{45}\) The full paper of the assignment of structure 105 to crotonin, a norditerpene from *Croton lucidus*, was published.\(^\text{46}\)

**V. Pimarane and Isopimarane Derivatives**

8,15-Isopimaradien-18-oic acid (106) was isolated as methyl ester from balsam of *Pinus peuce*.\(^\text{47}\) From the acidic fraction of the extract of *Juniperus phoenicea* a new hydroxyacid diterpene was isolated and characterized as 6α-hydroxysandaracopimaric acid (107).\(^\text{48}\) The structures of virescenol A and B, metabolites of *Oospora virescens*, were elucidated as shown in formulas 108 and 109, respectively.\(^\text{49}\) They readily undergo an acid-catalyzed isomerization to afford isovirescenol A and B, which have \(\Delta^7\) instead of \(\Delta^8\). Isolation and constitution of oblongifoliol, a new diterpene of *Croton oblongifolium*, was reported. Its structure was
shown to be ent-3β, 19-dihydroxypimara-8(14), 15-diene (110). Sandaracopimaric acid (111) was synthesized starting from testosterone acetate via 14 steps. As catalytic dehydrogenation product of sandaracopimaric acid (111), compound 112 had been obtained. Now, this optically active compound was synthesized from R-(−)-methylethylsuccinic acid (mono methyl ester) and 5-methylnaphthylmagnesium bromide. Isolation and structure of a new diterpene lactone from *Trichothecium roseum* was published. The substance was formulated as 6β-hydroxyrosenonolactone (113) on the basis of chemical and spectroscopic evidence.

Circular dichroism data on lactones possessing the same skeleton were discussed. Biosynthesis of rosenonolactone was studied. Geranylgeraniol was incorporated in rosenonolactone (114). In the course of biosynthesis the hydride shift from C-9 to C-8 should be involved. This proposal was proved to be correct by feeding of doubly-labelled 4R-[4H : 2-14C] mevalonic acid lactone. Deoxorosenonolactone was incorporated into rosenonolactone (114) and rosololactone (115).

Manool (86) was treated with formic acid in chloroform to give three pimarane and isopimarane derivatives and a beyerane derivative. From the products sandaracopimaraadiene (116), isopimaraadiene (117), and rimuene (118) were derived chemically. The similar experiments on cyclization of manool were reported.

A new acid was isolated from *Beyeria brevifolia*, and its structure was eluci-
VI. ABIETANE AND TOTARANE DERIVATIVES

Monohydroboration-oxidation of abietic acid and methyl abietate with both diborane and t-2, 3-dimethylbutylborane led to preferential attack on the 7, 8-double bond to give 7-hydroxy-8(14)-enes, e.g., 120. Dihydroboration-oxidation with these reagents yielded mainly 7β,14β-dihydroxy derivatives, e.g., 121, with smaller amounts of the 7α,14α-dihydroxy-compounds and a third 7, 14-diol of unknown stereochemistry. Abietic acid in absolute ethanol was irradiated for 96 hours with 2537A light in the absence of oxygen and then esterified with diazomethane. Chromatography of the crude product on silica gel gave 122a and 122b. The formation of 122a involves the bicyclobutane intermediate 123. Treatment of methyl abietate with tetrachloro-o-benzoquinone in xylene gave a solid adduct, to which structure 124 was assigned on the basis of spectroscopic investigation. Diels-Alder adducts of citraconic anhydride and methyl resinate were investigated. An adduct 125 was converted into the epoxide, which was subjected to acidic methanolysis to give 126. The latter was transformed into dilactone 127. Oxidation of 126 with di-2-phenyl-1,2-oxazoline (DPO) gave 128, followed by treatment of 128 with hydrobromic acid to produce 129.
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dation of methyl abietate by monoperphthalic acid was investigated. Methyl 12-acetyldehydroabietate was subjected to potassium borohydride reduction to give two kinds of alcohols, which were regarded as rotational isomers between two large substituents at C-11 and C-12. Similarly, lithium aluminum hydride reduction of the same material yielded two kinds of diols.

Treatment of the diazomethyl ketone 129, derived from dehydroabietic acid (128), with a suspension of silver oxide in methanol afforded methyl homodehydroabietate (130) (55%), a liquid ketone 131 (20%), and a ketone 132 (22%). Methyl 12-ω-bromoacetyldihydroabietate was heated with thiourea in EtOH to yield methyl 12-(2-amino-5-thiazolyl)-dehydroabietate. Methyl 12-(α-bromopropionyl)-dehydroabietate was treated with thiourea to afford methyl 12-(2-amino-4-methyl-5-thiazolyl)-dehydroabietate.

Incubation of methyl dehydroabietate (methyl ester of 128) with Corticium sasakii yielded methyl 3β-hydroxydehydroabietate (133) and methyl 3β,7β-dihydroxydehydroabietate (134). Both of 3β-hydroxy 133 and 7β-hydroxy-derivative 135 on incubation with C. sasakii gave diol 134. Incubation of methyl 7-oxodehydroabietate (136) afforded methyl 3β,6β-dihydroxy-7-oxodehydroabietate (138) via 3β-intermediate 137. Hydroxylation appears to occur first in the C-3 β position, then in the C-6 β or C-7 β position of the dehydroabietanes. Oxygenation of dehydroabietanes at C-3, C-6, or C-7 by this fungal oxidase is analogous to the position of oxygenation of dehydroabietanes obtained from Juniperus trees. Degradation of dehydroabietic acid by bacteria (Flavobacterium resinovoros) to 3-oxo-19-nor-dehydroabietane (139) and the proposed pathway were reported. Methyl dehydroabietate was subjected to microbial degradation by Arthrobacter sp. isolated from lodgepole pine to give dehydroabietic acid, methyl 3-oxodehydroabietate, and compound 140 (as methyl ester).

An investigation on the resins of several Callitris species (Cupressaceae) led
to isolation of callitrisic acid (141), a new diterpenoid.\(^{68}\) The \textit{rac}-callitrisic acid was synthesized from an intermediate 142.\(^{59a, b}\) \textit{rac}-Carnosol dimethyl ether (as 143) and \textit{rac}-carnosic acid dimethyl ether (as 144) were synthesized.\(^{70}\) \(\beta\)-Ketosulfoxide was effectively used for condensation in the synthesis as shown in Chart 1.

\begin{center}
\textbf{Chart 1}
\end{center}

Two novel diterpenoid quinone methides, taxodione (145) and taxodone (146), were isolated from \textit{Taxodium distichum}. Each showed significant inhibitory activity against the Walker carcinosarcoma 256 in rats, at 40 and 25 mg/kg, respectively.\(^{71}\) Novel ring openings in methyl levopimarate (147) were investigated at 200° in the presence of catalytic amount of KOH. The products were found to be 148, 149, and cis isomer of 149.\(^{72}\) From dried red roots of \textit{Salvia miltiorrhiza}, two novel pigments, hydroxytanshinone (150) and methyl tanshinonate (151) were isolated.\(^{73}\) Total syntheses of tanshinone-I (152), -II (153), and cryptotanshinone (154) were published by two groups.\(^{74a, b}\) Another short-step syntheses were also reported.\(^{75}\) A stereoselective formation of a tricyclic system and the total synthesis of \textit{rac}-fichtelit (as 155) was reported by Johnson et al.\(^{76}\) The outline is shown in Chart 2.
Deamination of 18-nor-4-amino-abieta-8, 11, 13-triene was investigated.\textsuperscript{77} Oxidative degradation of methyl neoabieta (156) and methyl levopimarate (147) yielded 157 and 158, respectively, both of which can be used as good intermediates for synthesis of diterpenoids.\textsuperscript{78}
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6α-Bromo-7-oxototaryl acetate (159) was treated with NaHCO₃ in DMSO to give α, β-unsaturated ketones (d₅) (60 %) and a secditerpenoid 160 (5 %). The high yield (80 %) of 160 was achieved when 6α-bromo-7-oxototarol (161) was used.⁷⁹ A nuclear magnetic resonance study of hindered rotation in biphenyls was carried out using podototarin diacetate (162) and podototarin dimethyl ether (163).⁸⁰ The structure 164 was assigned to inumakilactone A, a bitter bisnorditerpenoid, isolated from the wood of Podocarpus macrophyllus.⁸¹ Structures of nagilactone, A (165), B (166), C (167), and D (168), novel nor- and bisnor diterpenoids isolated from Podocarpus Nagi, were elucidated.⁸²

VII. CASSANE DERIVATIVES

Three new alkaloids were isolated from the bark of Erythrophleum guineense syn. E. suaveolens. Chemical and spectroscopic data provided evidence for the structure of two of them, cassamidine (169) and coumidine (170), and strongly suggested that the third alkaloid, erythrosuamine is represented by 171.⁸³ From the seeds of Caesalpinia bonducuella, α-, β-, and γ-caesalpin were isolated.⁸⁴

VIII. KAURANE AND BEYERANE DERIVATIVES

Foliage from Cryptomeria japonica was analyzed for diterpenoid hydrocarbons by Overton et al.⁸⁵ Samples grown from some seed sources furnished ent-kaurene ((-)-kaurene) as the sole product of this type, whilst those from other sources yielded only phyllocladene. These observations were found to be seasonally independent and it was concluded that C. japonica exists in two chemically distinct forms. Combined gas chromatography-mass spectrometry was effectively applied to quantitative analysis of mixtures of diterpene-hydrocarbons.⁸⁶ ent-17-Nor-16β-tosyloxykaurane (172) was heated at reflux with HOAc in the presence of NaOAc to give a mixture of acetates (ca. 90 % yield), from which, after treatment with LiAlH₄ alcohol 173 was isolated in 5 % yield. The latter was convert-
ed into \textit{ent}-phyllolodan (174) via oxidation followed by Wittig reaction. Similarly, alcohol 175 was isolated from the above mixture in 25\% yield. The same treatment of the alcohol yielded atisirene (176). \textit{ent}-17-Noratisan-13-one (178) was prepared from \textit{ent}-kaurene via the ketol (177). Neotasisiene (179) was derived from 178 by Wittig reaction. Structures were established for three new diterpenes, \textit{ent}-kaurene-3β, 16, 17, 19-tetraol (180), \textit{ent}-kaureane-3β, 16, 19-triol (181) and \textit{ent}-kaurene-3β, 16, 17-triol (182), which were obtained from \textit{Beyeria latifolia}. \textit{ent}-12α, 17-Dihydroxy-16β-kauran-19-oic acid was isolated as methyl ester 183 from \textit{Beyeria leschenaultii}. Four known kauranes were also isolated. Isolated of the known kauranes and beyeranes from \textit{Beyeria brevifolia} was reported. A succinate 184 was isolated from \textit{Goodenia strophiolata} accompanied by the known diol. The same diterpenoid was also isolated from \textit{G. ramelii}. From \textit{corols} of \textit{Sideritis sicula}, two new diterpenes, sideridiol and siderol were isolated. Structures 185 and 186 were assigned to them. The absolute configuration was established by correlation with \textit{ent}-isokaurene. Further investigation led to isolation of third diterpene, sideroxol, whose structure was elucidated as shown in formula 187. On the basis of chemical and spectroscopic evidence, structure 188 was assigned to grandifloric acid extracted from the resin of \textit{Espeletia grandiflora}. Similar diterpenoids 189 and 190 were isolated together with 188.
The structure 191 was assigned to xylopic acid, a new diterpenic acid isolated from *Xylopia aethiopica*.94* ent-16β-hydroxykauran-19-ol (192) and ent-16β-hydroxykauran-19-oic acid (193) were isolated among other metabolites from a large-scale fermentation of *Fusarium moniliforme*.96* Recently the bitter principles of the *Isodon* species have been shown to be kauranoid diterpenes. Induced amongst these are a number of compounds of which enmein (194) is the best known, where ring B of the kaurene skeleton has been cleaved. Fujenal (195) from *Gibberella fujikuroi* represents another example of this series. Cleavage between C-6 and C-7 permits rotation about the 9-10 bond. Molecular models suggest that this rotation is probably hindered and it was of interest to distinguish between the two possible rotamers of fujenal (195 and 196). The investigation by Hanson and White97* gave an evidence for the prevalence of the rotamer 195 in the ground state of fujenal. The transformation of steviol (197) into ent-6β, 7α, 13-trihydroxykauren-16-en-19, 6β-olide (198) by *Gibberella fujikuroi* was reported by the same authors.98* Doubly-labelled 4R-(4³H and 2-¹⁴C)-mevalonic acid lactone was fed to *Gibberella fujikuroi*. 7,18-Dihydroxy-kaurenolide and gibberellic acid were isolated. Whereas the kaurenolide retained all the tritium of the parent mevalonate, the gibberellic acid had lost one tritium atom. From this result and degradation experiment the following conclusions could be drawn. i) The C-9-hydrogen atom of the tetracyclic diterpenes remains throughout the cyclization stages including the formation of ring D, and a 4(9)β-pimaradiene is excluded at this stage. ii) During the elimination of a C-20 substituent and the formation of the lactone ring of the gibberellins a 4(10)β or 4(15)α olefin is precluded, because both the 9 and 5-tritiums are retained. iii) Cyclization of a geranylgeranylpentanoylphosphate derived from 4R-(4³H)-mevalonic acid lactone would be expected to produce an axial tritium atom at position 3 in a kaurenoid precursor. Since this atom is retained in gibberellic acid, inversion must have taken place at this center on hydroxylation.99* 

The total synthesis of rac-kaur-16-en-19-oic acid (as 199), rac-monogynol (as 200) and some oxygenated kauranes, chemically and biologically interesting tetracyclic diterpenes, was accomplished by Mori and Matsui100* as shown in Chart 3. Preparation of some lactones of podocarpane and kaurane series from tricyclic or tetracyclic resin and analogs was described by the same authors.101* A tetrahydrofurano-hydrophenanthrene derivative was synthesized in the synthetic studies on cafestol.102* ent-19-Nor-16β-kaurane (201) and ent-19-nor-kaurane (202)
were prepared from *ent*-16β-kaurane-3β, 17, 19-triol (203) and *ent*-16-kaurene-3β, 19-
diol (204) through unambiguous route, and the products were proved to be identi-
cal with the samples derived from atractyligenin (205). The stereochemistry, 
especially that of C-9, of atractylanic acid (206), which was derived from 
tractyligenin, was confirmed by a partial synthesis from 7, 18-dihydroxykaurenol-
lide (207). A full paper on the synthesis of (−)-6-methyl-7-oxo-bicyclo [3, 2,
1) octane (208), the antipodal substance of a pyrolysis product of bisdehydrodihydroenmein (209), was published by Uyco et al.\textsuperscript{105} On the basis of spectral data and biogenetic considerations the structure 210 had been deduced by Fujita et al.\textsuperscript{101} for trichodonin isolated from \textit{Isodon trichocarpus}. Kubota and Kubo\textsuperscript{407} isolated the same compound from \textit{I. japonicus} and confirmed unambiguously this structural assignment by correlating trichodonin with isodonal (211) which is also present in \textit{I. japonicus}. They also isolated a new diterpenoid epinodosin (212), which is the C-11 epimer of the known nodosin. The full papers which deal with the structure and absolute configuration of nodosin (213)\textsuperscript{109} and isodocarpin (214)\textsuperscript{109} were published by Fujita et al. Four possible epimeric alcohols 215–218
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were partially synthesized, and the interesting epimerizations of 215 to 216 and of 217 to 218 were discussed. A review on the diterpenoids of "Enmeiso" was published in Japanese. Another review about the chemistry on diterpenoids of *Isodon* species was published in English by Fujita. The carbon skeleton 219 was deduced for vakognavine, an alkaloid of *Aconitum palatum*. A new simple synthesis of veatchine from 220 was reported by Wiesner *et al.*

The compound 220 was converted into 221, which was treated with sodium ethoxide in refluxing ethanol to give 222. The latter was transformed through a series of reactions into 223, which had been converted into veatchine. A conjugated ketone 224 was synthesized, then the compound was transformed into 225.

Manool and agathadiol cyclize in formic acid to 14α-hydroxybeyereane derivatives 226 and 227 besides pimarane derivatives. Three new diterpenes, which were correlated with beyerol and were shown to be modified *ent*-beyer-15-enes 228, 229, and 230, were yielded from a variety of *Beyeria leschenaultii*. The structure and stereochemistry of *ent*-hibaene (231), erythroxylool A (232), erythroxylool B (233), and erythroxydiol A (234) were assigned on the basis of spectroscopic properties and chemical reactions. Erythroxydiol A (234) was

*See also section III.*
converted into erythroxylos A (232), and erythroxylos A (monogynol) (232) and B (233) were converted into \textit{ent}-hibaene (231). Two norditerpenoid tertiary alcohols, 235 and 236, and three diterpenoid epoxides, 237, 238, and 239, were isolated from \textit{Erythroxylon monogynum}. Compound 241, a potential intermediate for synthesis of gibberellins, was derived from 240 through a route shown in Chart 4 by Mori, Matsui \textit{et al.}\cite{119} The biogenetic-like rearrangements of isosteviol de-

drivatives 242 and 243 were carried out to give several products, among which methyl trachyloban-19-oate (244) was found from the reaction of 242 (as its sodium salt) in 10\% ethylene glycol diethylcarbitol at 180-190\degree.\cite{120} Stereochem-

istry of grayanotoxin I was investigated more in detail and the stereochemical structure 245 with the 246 (not 247) type hydroazulene was presented.\cite{121}
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**IX. GIBBERELLANE DERIVATIVES**

Gibberellic acid $16\,S,\,17$-epoxide (248) and its acetate (249) were converted by Wagner-Meerwein's rearrangement into hydroxymethyl derivatives 250 and 251, respectively. *Allo*-gibberic acid $16\,S,\,17$-epoxide (252) was rearranged to 253. *Gibberellin* $A_{16}$, a new metabolite of *Gibberella fujikuroi*, was isolated as the methyl ester, and the structure (254) was elucidated. An intermediate (as 255) for synthesis of gibberellins was synthesized as racemic compound. Fragmentation patterns of gibberellin $A_4$ methyl ester (256) and its 3-keto-1-13-

hydroxy-16, 17-dihydro analog (257) as well as mass spectra of some $J'$- and $J''$-unsaturated compounds of gibberellin series were investigated. Gibberellin derivatives unsaturated in the ring A gave different mass spectra, depending on the position of the double bond. This is useful for the determination of the position of double bond. 1,2-Dicarbomethoxy-7-methyindene (258) was synthesized. Its Diels-Alder reaction with butadiene yielded tetrahydrofluorene derivative 259. The double bond isomers of 1,2-dicarbomethoxy-6-methoxyindene, 260 and 261,
and another pair of 1, 2-dicarbomethoxyindene, 262 and 263, were synthesized. In each case, the less highly substituted double bond isomer 260 or 262 is the more stable. However, derivatives of each of these indenes reacted with 1, 3-butadiene to give the Diels-Alder adduct (264 and 265) derived from the more highly substituted double-bond isomer.127

None of 7-hydroxykaurenolide (266), its related triol (267) and 7α-hydroxykaurenolide (268) was incorporated into gibberellic acid by Gibberella fujikuroi, but 7-hydroxykaurenolide (266) was converted into 7, 18-dihydroxykaurenolide (269) in high yield. Incorporation of alcohol 270 into gibberellic acid was much higher than that of diene 271.128 Seven 14C-labelled compounds, including gibberel-

lins A₁₂, A₁₃ and A₁₄, were prepared and tested as precursors in the biosynthesis of gibberellic acid by Gibberella fujikuroi. It was suggested by Cross et al.124 that gibberellic acid is biosynthesized from ent-kaurene ((−)-kaurene) through 272 and gibberellin A₁₄ (274) or the corresponding 7-aldehyde 273. Gibberellin A₁₃ (275) was not thought to be a precursor of gibberellic acid. The biosynthetic pathway suggested by them is shown in Chart 5. Although several kaurene derivatives, 276, 277 and 278 having the 16-methylene group, undergo ring contraction to gibberellanes, e.g. 279, with base, those having a 16-keto-group, 280 and 281 do not. The fact was considered to be due to a long-range effect associated with the 16-keto-group.129 Methyl 3-dehydrogibberellate (282) was treated with zinc in acetic acid and then with aqueous sodium bicarbonate to give a reductive delactonized product 283.130 The presence of three water-soluble
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Chart 5

gibberellins was confirmed in immature seeds of morning glory (Pharbitis nil). The structure of the main component was elucidated as 3-O-β-glucosyl-gibberellin A₃ (284). A short review about isolation of new gibberellins from higher plants and their biological activity was published. It is concerned with Bamboo gibberellin, Pharbitis gibberellin, gibberellin A₃ glucoside (284), and Canavalia gibberellins I and II. A new gibberellin, tentatively called Lupinus gibberellin I, was isolated from young yellow lupin seeds (Lupinus luteus). It was shown
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to have structure (285).\(^{133}\)

A new nomenclature of gibberellins was proposed.\(^{134}\) According to this, Lupinus gibberellin-I, Bamboo gibberellin, Pharbitis gibberellin, Canavalia gibberellin-I and -II were named gibberellins \(A_{19}, A_{21}, A_{29}, A_{21}, A_{22}\), respectively. A review on the isolation techniques of plant growth substances was published, in which purification of bamboo gibberellin by counter-current distribution and isolation of gibberellins \(A_{1}\) and \(A_{3}\) by partition chromatography were described.\(^{135}\) Gibberellin \(A_{23}\), that is, gibberellin \(A_{4}\) glucoside (284) was isolated from immature seeds of Lupinus luteus.\(^{136}\) Investigations of gibberellins in Phaseolus multiflorus by combined gas chromatography-mass spectrometry have been carried out by MacMillan et al. They\(^{137}\) reported the detection of gibberellin \(A_{20}\) (Pharbitis gibberellin) (286) in extracts of young seed of the plant and some observations on the structures of compounds \(a\) and \(b\), previously isolated from seeds of \(P.\) multiflorus\) by Jones.\(^{138}\) The investigation provided strong support for the structure 287, originally suggested for compound \(b\) by Jones.

Mori, Matsui, Sumiki, et al.\(^{139,140}\) converted rac-epigibberic acid (as 288), which had been synthesized by themselves, into 290 via an important intermediate 289. Since the ketone 290 had been converted into gibberellin C (291) by them,\(^{141}\) this completed total synthesis of rac-gibberellin C. Gibberellin C had been transformed into gibberellin \(A_{4}\)\(^{142}\) which had been converted into gibberellins \(A_{3}\)\(^{143}\) and \(A_{9}\).\(^{144}\) Conversion of gibberellin \(A_{9}\) into \(A_{10}\) had also been reported.\(^{145}\) Thus, the foregoing work constituted the formal total synthesis of rac-gibberellins \(A_{3}, A_{4}, A_{9}\) and \(A_{10}\). The same group\(^{146}\) reported the synthetic sequence for the conversion of compound 292 into 293. Gibberellin \(A_{24}\) (294), a new aldehydic
gibberellin was isolated from *Gibberella fujikuroi*. Circular dichroism of some C19 gibberellins and their methyl esters, and some other related compounds at wave length of 200~300 m$\mu$ was investigated and the application of the lactone chromophore to their structural and stereochemical elucidation was described. The synthesis of perhydrofluorenone derivative 295 was reported by Kitahara et al. The outline of the route is shown in Chart 6.

Cross and Stewart reported that addition of the labelled ent-pimara-8(14), 15-diene (296) to a fermentation of *Gibberella fujikuroi*, and isolation of the metabolites produced, gave labelled methyl gibberellate (incorporation 0.05 %) and labelled 7-hydroxykaurenolide. Hanson and White proved by feeding [2-3H$_2$, 2-14C] mevalonic acid lactone to *Gibberella fujikuroi* that ent-pimara-8(14), 15-diene (296) is a precursor for ent-kaurene, 7-hydroxykaurenolide, and 7, 18-

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dihydroxykaurenolide. They also prepared labelled ent-pimara-8(14), 15-diene (296) (14C and 3H), and carried out feeding experiments to *Gibberella fujikuroi*. Its very low incorporation (0.02 %) to gibberellic acid was observed. Decarboxylation of C20 gibberellin to C19 gibberellin was discussed on the basis of multiple labelled mevalonate experimental results. Subsequently, Cross and Stewart revised their foregoing report. They described that pimaradiene and pimaradienol are not incorporated into gibberellic acid, on the basis of the degradation experiments.
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X. ATISANE DERIVATIVES

The tentative structure 297 previously proposed for an alkaloid isolated from Delphinium cardinale was confirmed. The alkaloid is identical with hetisine, which was first obtained as the transformation product of hetisine and later isolated from D. denudatum. Ten alkaloids were isolated from Spiraea japonica and the structure 298 of spiradine A was elucidated by X-ray analysis. The structures 299 and 300, were assigned to spiradine B and C, respectively, based on the chemical correlation with A. Subsequently, spiradine D isolated from the same plant source proved to be represented as 301. The plane structures, 302 and 303, were proposed for spiradines F and G, respectively. A key intermediate 304 in the synthesis of atidine (305) and ajaconine (306) was prepared.

The synthesis of methyl 13, 16-cycloatisan-18-oate (methyl anti-trachylobanate) (307) from methyl levopimarate was reported by Herz et al. The compound 308 which was derived from the starting material via Diels-Alder reaction was converted into 309 by the mesylation, and the latter was transformed into the final product as shown in the Chart 7.
XI. ACONANE DERIVATIVES

On the basis of mass spectrometry, the NMR data of acetylbenzoyl derivative, and the NMR data of the product prepared from pyrolysis of diacetyl derivative, the formula 310 was proposed for talatizamine.\(^{160}\) The structure of jesaconitine isolated from *Aconitum* species was elucidated as 311, on the basis of the NMR data of the alkaloid and its pyrolysis products. The pyrolysis was carried out in an NMR tube, and continuously monitored by NMR spectroscopy to provide evidence for the elimination product. This method of pyrolysis constituted a rapid and convenient way of establishing the presence of certain C-8 ester groups in these diterpene alkaloids using small amounts of material.\(^{161}\)

XII. TAXANE DERIVATIVES

A constituent of the heartwood of *Taxus cuspidata* was isolated and named taxusin.\(^{162}\) Hydrolysis of taxusin gave tetraol 312, which had been isolated from *T. baccata* by English workers.\(^{163}\) The application of Mills’ rule gave same conclusion on the absolute configuration of C-13 hydroxy group. Taxusin corresponds to tetraacetate of 312.\(^{162}\)

XIII. THE OTHERS

Johnson\(^{164}\) published a review on nonenzymic biogenetic-like olefinic cyclizations. The ORD curves of many diterpenecarboxylic acids and related compounds were taken and examined by English workers.\(^{165}\) Discussions on preferred conformations of carboxylic acids and carboxyl sector rule were described. The NMR investigation on forty four kinds of diterpene alkaloids and related compounds was published.\(^{166}\) On the basis of the NMR data of C-4 methyl group in a series of atisine and veatchine, the conformation of ring E was discussed. The relationship between the chemical shift of C-4 methyl protons and nitrogen
atom was also discussed. The conformation of the primary hydroxy group at C-18 or C-19 in many diterpenoids was discussed on the basis of the chemical shift of C-4 methyl protons' signal in the NMR spectra. Similarly, the conformation of C-4 axial and equatorial carboxylic acids, esters, and aldehydes in diterpenoids was discussed on the basis of NMR data of C-10 methyl group. The NMR spectra and conformations of some lactones of octa- and decahydro-8-hydroxy-naphthoic acids were discussed, on relation to synthesis of diterpenoid acids. A ten-step stereoselective synthesis of racemic andrographolide lactone (as 313), which had been obtained previously in optically active form by degradation of triaceteylandrographolide, was published.

Turner et al. published procedures for the synthesis of tetracyclic intermediates—e.g., 314 and 315—incorporating the bridged nitrogen-containing ring common to many of the diterpene alkaloids.

Wiesner et al. carried out a stereoselective synthesis of pentacyclic intermediate 316 during the synthesis in the series of diterpene alkaloids. Stereoselective synthesis of racemic tricyclic dicarboxylic acid (as 317), a synthetic model for the N-acetyl-dicarboxylic acid 318, was reported by Pelletier et al. Stereo-selective synthesis of racemic perhydrophenanthrene derivative (as 319) was reported by Dutta et al. Spectral properties of Schiff bases of retinal were investigated. 1-(Retinylideneamino)-2-propanol (320) and its 11-cis isomer were prepared by condensing retinal with 1-amino-2-propanol in dry acetonitrile, and
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\( \lambda_{max} \) in non polar solvent was discussed.\(^{173}\) Thunbergol, a new macrocyclic diterpene alcohol, was isolated from the oleoresin of *Pseudotsuga menziesii*, and structure 321 was assigned to this.\(^{174}\) A new diterpene, incensole-oxide (322), was isolated from the resin produced by *Boswellia carteri*. Chemical and physicochemical data showing the position of the oxirane ring supported the structure.\(^{175}\) The new diterpenes, isocembrene (323) and isocembrol, were isolated from oleo-

![Image of chemical structures](image)

resin of *Pinus sibirica*.\(^{176}\) The plane structure of the latter is identical with 321. The antibacterial marine diterpene eunicin was isolated from *Eunicea mammosa* and characterized,\(^{177}\) and structure 324 was assigned to it. The assignment was fully substantiated by the X-ray crystallographic study of its iodoacetate.\(^{178}\) From the petroleum ether extract of dried *Eunicella strica*, a new diterpenoid, eunicellin was isolated. The structure 325 was presented on the basis of chemical evidence and an X-ray analysis of dibromide.\(^{179}\) The molecular structure of ryanodol p-bromo benzyl ether was elucidated as 326 on the basis of X-ray analysis.\(^{180}\) The structure was identical with that proposed by Wiesner et al.\(^{181}\) except that the configuration of the carbon atom carrying the isopropyl group in the five-membered ring is reversed. An article, which represents the English version of the second part of a lecture on the structure of ryanodine (327) delivered by Wiesner\(^{182}\) in 1967, in the auditorium of the Institute for Org. Chem. and Biochemistry, Czechoslovak Academy of Sciences, was published. Ryanodol was treated with excess periodate and then alkali to give a C\(_{19}\) compound, whose structure 328 was proposed on the basis of the several reactions.\(^{183}\) The structure 329 was proposed for a C\(_{19}\) acid obtained together with the foregoing ketone in the periodate oxidation of ryanodol.\(^{184}\)

Hecker *et al.* published a series of the reports on the chemistry of phorbol. They were concerned with polybenzoate and polyacetate of phorbol and phorbol-3-ol, functional derivatives of allyl-group of phorbol,\(^{185}\) ether derivatives of

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phorbol, the α, β-unsaturated tertiary 1, 2-ketogroup in phorbol, and the oxidation of phorbol with leadtetraacetate. Another report on the chemistry and structure of phorbol was published by Crombie et al. The structure and absolute configuration have been established by the X-ray analysis of its bromine-containing derivative.

Characterization of the oxygen substituents of fusicoccin (fusicoccin A), C_{38}H_{38}O_{13}, a highly phytotoxic metabolite of Fusicoccum amygdali, led to a partial structure. Crystallographic studies of two mercuribromide derivatives prepared from fusicoccin and its deacetylaglycone resulted in the presentation of the structure and relative stereochemistry for deacetyl aglycone. On the basis of chemical works and X-ray data, Barton et al. presented the complete structure including absolute configuration. These results were completely identical with those of the independent work on fusicoccin A by Ballio and his colleagues. They carried out an X-ray determination of the structure of the iodobenzenesulfonate of fusicoccin with supporting chemistry.

d-Malabaricol (334) was converted into d-ambreinolide (335). A biosynthetic study with viridin (336), an active antifungal metabolic product of Gliocladium virens, led to a conclusion that the metabolite is biosynthesized from mevalonic acid lactone by way of farnesyl pyrophosphate, squalene epoxide, and lanosterol, and excluded the possibility that the compound might be derived from mevalonic acid via geranylgeranyl pyrophosphate and a tricyclic diterpenoid (cassane type skeleton). The biosynthesis of pleuromutilin, a metabolite from Pleurotus mutilus, was described by Arigoni.
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