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The Structure and Synthesis of Rishitinol. A Sesquiterpene Alcohol from Diseased Potato Tubers[1)]

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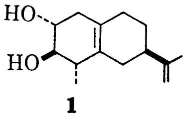
The structure and configuration of rishitinol (**2**), isolated from tuber tissues of white potatoes (*Solanum tuberlosum*×*S. demissum*) infected by an incompatible race of *Phytophtora infestans*, were deduced from spectral and chemical data and confirmed by the synthesis of its recemate. 5,8-Dimethyl-1-tetralone-3-carboxylic acid (**13**) prepared from 2,5-dimethylbenzyl chloride was esterified, reduced, and then dehydrated to the dihydronaphthalene derivative (**20**), which was converted into the oxyisopropyl derivative (**21**). The hydroboration of **21** followed by hydrogen peroxide oxidation afforded a multi-component mixture, from which *dl*-rishitinol (**25**=*dl*-**2**) was isolated along with isomeric glycols (**22**—**24**).

A few years ago we reported on the isolation[2)] and structure elucidation[3)] of an antifungal norsesquiterpene alcohol, rishitin (**1**), from tuber tissues of white potatoes (*Solanum tuberlosum*×*S. demissum*) infected by an incompatible race of *Phytophtora infestans*. Since the isolation of rishitin qualified as "phytoalexin," efforts have been made to isolate the alcohol and its closely related compounds from diseased plants of various species of the *Solanum* family in search of its biological significance as well as the biogenetic route.[4–8)] Recently we isolated a new sesquiterpene alcohol (**2**), designated as rishitinol, from the diseased white potato tubers and reported on the structure as well as the total synthesis of its racemic form.[9)] The details of the studies are given in this paper.



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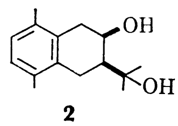

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[1)] Part VII of "Studies on the Phytoalexins"; Part VI, ref. 9.

[2)] K. Tomiyama, T. Sakuma, N. Ishizaka, N. Sato, N. Katsui, M. Takasugi, and T. Masamune, *Phytopathology*, **58**, 115 (1968).

[3)] a) N. Katsui, A. Murai, M. Takasugi, K. Imaizumi, T. Masamune, and K. Tomiyama, *Chem. Commun.*, **1968**, 43. b) For the absolute configurations of C_2, C_3, and C_4 of rishitin, see; N. Harada, and K. Nakanishi, *J. Amer. Chem. Soc.*, **91**, 3989 (1969); S. T. K. Bukhari and R. D. Guthrie, *J. Chem. Soc.*, *C*, **1969**, 1073.

[4)] a) N. Sato, K. Tomiyama, N. Katsui, and T. Masamune, *Ann. Phytopathol. Soc. Japan*, **34**, 140 (1968). b) N. Sato, K. Tomiyama, N. Katsui, and T. Masamune, *Nippon Shokubutsu Byori Gakkaiho*, **34**, 344 (1969). c) N. Ishizaka, K. Tomiyama, N. Katsui, A. Murai, and T. Masamune, *Plant and Cell Physiology*, **10**, 183 (1969).

[5)] J. L. Varns, J. Kuc, and E. B. Williams, *Phytopathology*, **61**, 174 (1971); J. L. Varns and J. Kuc, *ibid.*, **61**, 178 (1971).

[6)] G. Van den Ende, *Phytopath.*, *Z.* **64**, 68 (1969).

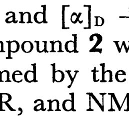
[7)] O.L. Ozeretskovskaya, N.I. Vasyukova, and L.V. Metlitsky, *Dokl. Acad. Sci.*, **5**, 189 (1969); L. V. Metlitsky, Yu. T. Djakov, O. L. Ozeretskovskaya, L. A. Yurganova, L. I. Chalova, and N. I. Vasyukova, *Izvestiya Acad. Nauk CCCD*, **3**, 399 (1971); N. I. Vasyukova, O. L. Ozeretskovskaya, and L. V. Metlitsky, *Pract. Biochem. Microbiol.*, **6**, 431 (1970); L. I. Chalova, N. I. Vasyukova, O. L. Ozeretskovskaya, and L. V. Metlitsky, *ibid.*, **7**, 55 (1971).

[8)] A. Stoessl, C. H. Unwin, and E. W. B. Ward, *Phytopath. Z.*, in the press.

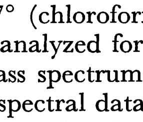
[9)] N. Katsui, A. Mastunaga, K. Imaizumi, and T. Masamune, *Tetrahedron Lett.*, **1971**, 83.

The sesquiterpene alcohol **2** was isolated as follows. The tuber slices of diseased white potatoes (8.5 kg) were treated by the reported procedure[2] to yield "the hexane-soluble fraction" (24.5 g). This on column chromatography over silicic acid afforded two relevant fractions, one (10.5 g) eluted with hexane containing the compound in question and the other eluted with hexane-acetone (92: 8) being more polar and rishitin-rich. The former was chromatographed over silicic acid and celite, and the resulting ether eluate, after removal of acidic substances, was rechromatographed over alumina. A rishitinol-rich fraction (180 mg) eluted with ether-methanol was further purified by thin layer chromatography (tlc) on silica gel and recrystallized to yield rishitinol **2** (50 mg), mp 128—129°C and $[\alpha]_D$ +47° (chloroform), in pure state.

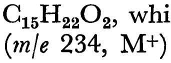
Compound **2** was analyzed for $C_{15}H_{22}O_2$, which was confirmed by the mass spectrum (*m/e* 234, M^+). The UV, IR, and NMR spectral data revealed the presence of the following structural units: one tetra-substituted benzene with two vicinal hydrogens [λ_{max} 263 mμ (ε 280); ν_{max} 3070, 1600, 810, and 804 cm^{-1}; τ 7.81 and 7.75 (each 3H, singlet), and 3.10 (2H, singlet)]; two *tertiary* methyl groups (τ 8.65 and 8.54 (each 3H, singlet)]; *secondary* and *tertiary* hydroxy groups [ν_{max} 3300 cm^{-1}; τ 7.25 (2H, broad singlet, disappeared on addition of deuterium oxide) and 5.30 (1H, broad singlet W_H=7 Hz)]. Compound **2** resisted acetylation under the usual conditions and oxidation with periodic acid. All the results together with the co-existence of rishitin in the same plant suggest that rishitinol would be represented either by (planar) structure **2a**, **2b**, or **2c**. Since these structures are regarded to be of hydroxyoccidol, we first intended to prepare *dl*-occidiol[10] (**3**) in anticipation of the effectiveness of the NMR spectrum of **3** for structural determination and the availability of the synthetic intermediates of **3** for the preparation of **2b**.



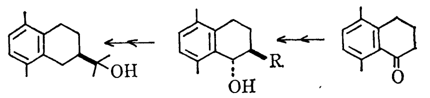
2a



2b



2c



3 **5** R=$COOC_2H_5$ **4**
6 R=$C(OH)(CH_3)_2$

The synthesis of *dl*-occidol was carried out by a slight modification of the procedure by Hirose and Nakatsuka,[10a)] starting with *p*-xylene and succinic anhydride *via* tetralone (**4**)[11] and oxyester (**5**). The resulting *dl*-occidol exhibited two six-proton singlets due to the gem-dimethyl and aromatic methyl protons, as shown in Table 1 in which the chemical shifts of relevant protons are summarized. In view of the large difference (0.11 ppm) in the chemical shift between two gem-dimethyl groups of **2**, this spectral pattern (*cf.*, Table 1) indicated that another hydroxyl group of **2** would hinder the presumed free rotation of the oxyisopropyl group and probably be located at one of the adjacent carbons. The possibility of structure **2c** would therefore be excluded. The synthetic intermediate **5** was then treated with methyl magnesium iodide to give glycol **6**. The relative configuration of the hydroxyl and oxyisopropyl groups in **6** was tentatively assigned to *trans*, because, in the NMR spectra of **5** and **6**, the proton on carbon bearing the hydroxyl group appeared as a doublet at τ 4.78 and 4.75 with coupling constants of 7 and 5 Hz, respectively. Glycol **6**, while it possessed the same molecular formula as **2**, differed definitely from **2**. On the basis of the large deshielding effect (0.24 ppm) caused by the hydroxyl group at the carbon adjacent to the benzene ring on the aromatic methyl protons, it was inferred that rishitinol would be formulated most favorably as **2a**.

As a synthetic approach to **2a**, 5,8-dimethyl-2-tetralone (**7**) was first prepared, starting from the corresponding 1-tetralone (**4**) and using a method analogous to that of the conversion of 1-tetralone into 2-tetralone.[12] However, the attempted formylation of **7** with methyl formate and sodium methoxide failed, forming a multi-component mixture. The one-step synthesis[13] of 5,8-dimethyl-2-tetralone-3-carboxylate was next undertaken but also failed; treatment of 2,5-dimethylphenylacetyl chloride with ethyl acrylate in the presence of aluminum chloride resulted in the formation of an intractable tarry material.

The synthesis of rishitinol was finally achieved as follows. 5,8-Dimethyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic acid (**13**) was first prepared in a manner analogous to the synthetic procedure of the corresponding 5,8-demethyl derivative by Haworth *et al.*[14] Alkylation of ethyl sodioacetoacetate with 2,5-dimethylbenzyl chloride[15] (**8**) produced the 2,5-dimethylbenzyl derivative (**9**), which was again treated with sodium in ethanol and then refluxed with ethyl chloroacetate to give acetylbenzylsuccinate (**10**) in 34% yield from **8**. In accordance with the structure **10**, the NMR spectrum exhibited signals due to an acetyl and two carbethoxy methyl protons. Further treatment of **10** with 2N sodium hydroxide under reflux effected both hydrolysis and removal of the acetyl group to yield 2,5-dimethylbenzylsuccinic acid (**11**) which on heating with acetic anhydride formed the corresponding anhydride (**12**) in 68% yield from **10**. The structure was supported by the IR absorption bands due to an acid anhydride group. The Friedel-Crafts cyclization of **12** led to the formation of a 2: 1 mixture of 5,8-dimethyl-1-tetralone-3-carboxylic acid (**13**) and its isomeric acid (**14**) containing a hydrindanone skeleton in 70% yield. They were separated by fractional recrystallization. While **13** showed an absorption maximum due to the carbonyl

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[10] a) Y. Hirose and T. Nakatsuka, *Bull. Agr. Chem. Soc. Jap.*, **23**, 143 (1959). b) M. Nakazaki, This Bulletin, **35**, 1387 (1962).

[11] Bold and dotted lines described in some structural formulas except **1**, **2**, and **3** refer to only relative configurations.

[12] F. Straus and A. Rohrbacker, *Ber.*, **54**, 40 (1921).

[13] *Cf.*, J. H. Burckhalper and J. R. Campbell, *J. Org. Chem.*, **26**, 4232 (1961); A. Rosowsky, J. Battaglia, K. K. N. Chen, and E. J. Modest, *ibid.*, **33**, 4288 (1968).

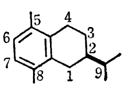
[14] R. Haworth, B. Jones, and M. Way, *J. Chem. Soc.*, **1943**, 10.

[15] H. Stephen, W. F. Short, and G. Gladding, *ibid.*, **117**, 510 (1920).

TABLE 1. THE NMR SPECTRA OF OCCIDOL **3** AND ITS DERIVATIVES

Compound	Δ	Substitutents in formula **28** OH	Chemical Shift (τ) Methyl protons[a)] at C$_5$	C$_8$	C$_9$		Protons[a)] at C$_6$ and C$_7$
3	/	C$_9$	7.80	7.80	8.70	8.70	3.10
29[b)]	Δ^1	C$_9$	7.78	7.70	8.58	8.58	3.14
21	Δ^3	C$_9$	7.77	7.80	8.80	8.80	3.20
6	/	C$_9$ and C$_1$ (α)	7.80	7.56	8.69	8.50	3.02
22	/	C$_9$ and C$_4$ (α)	7.60	7.82	8.72	8.75	3.05
24	/	C$_9$ and C$_3$ (α)	7.84	7.84	8.65	8.65	3.10
2	/	C$_9$ and C$_3$ (β)	7.75	7.81	8.65	8.54	3.10
30[b)]	/	C$_1$ (α) and C$_2$ (α)	7.79	7.57	9.09[c)]	8.99[c)]	3.02

a) Singlet b) For preparation, see Experimental c) Doublet



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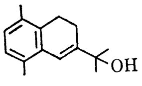

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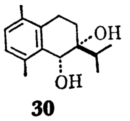

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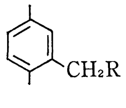
group in a six-membered ring, **14** showed one due to the group in a five-membered ring. The UV and NMR spectra of both compounds also supported the assigned structures. In view of the fact that Haworth's cyclization with the demethyl derivative of **12** resulted in the isolation of only 1-tetralone-3-carboxylic acid,[14)] it would be noticeable that compound **14** was formed in a considerable yield. Apparently the present result would be derived from large steric hindrance against the six-membered ring rather than the five-membered[16)] caused by one of the aromatic methyl groups. Tetralone **13** was then converted with hydrogen chloride in ethanol into the corresponding ethyl ester (**15**) in 70% yield.



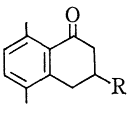
8 R=Cl

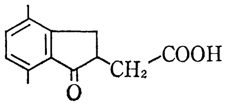
9 R=CH(COCH$_3$) COOC$_2$H$_5$

10 R=C(COCH$_3$)(COOC$_2$H$_5$) CH$_2$COOC$_2$H$_5$

11 R=CH(COOH) CH$_2$COOH

12 R=$\begin{array}{l}\text{CH—CO}\diagdown \\ | \qquad\quad \text{O} \\ \text{CH}_2\text{—CO}\diagup\end{array}$



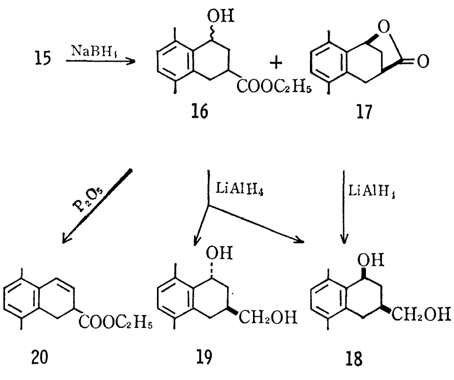


13 R=COOH **14**

15 R=COOC$_2$H$_5$

The reduction of the ketoester **15** with sodium borohydride in ethanol produced a mixture of hydroxy esters (**16**) and γ-lactone (**17**), which were isolated by column chromatography in 61 and 30% yields, respectively. Hydroxy esters (**16**) gave only one spot on tlc. However, on treatment with lithium aluminum hydride **16** formed a 1 : 1 mixture of two glycols, which were separated by preparative tlc to give a glycol (**18**), mp 125—127°C, and a glycol (**19**), mp 111—113°C, in 35 and 35% yields, respectively. The relative configuration of the hydroxyl and the carbethoxyl groups of these glycols was made by the formation of the *cis*-glycol **18** on reduction of the γ-lactone **17** with the *cis*-configuration at the carbons in question. **16** was thus, subjected to dehydration with phosphorus pentoxide. The reaction proceeded smoothly to give dihydronaphthalene derivate (**20**) in 70% yeild.

As a final step of the synthesis, an attempted hydration of dihydronaphthalenes by hydroboration followed by hydrogen peroxide oxidation[17)] gave no fruitful result. Ester **20** was then converted into the oxyisopropyl derivative (**21**) in 53% yield by treatment with methylmagnesium iodide. Compound **21** showed the UV spectrum in good accord with the structure and also displayed an NMR spectrum resembling closely that of occidol **3** except for signals due to olefinic protons.



Hydroboration of the olefin **21** folowed by oxidation with hydrogen peroxide afforded a multi-component mixture, which was separated roughly into three fractions by column chromatography over silica gel. The least mobile fraction obtained in 27% yield showed two spots on tlc. However, on purification by preparative

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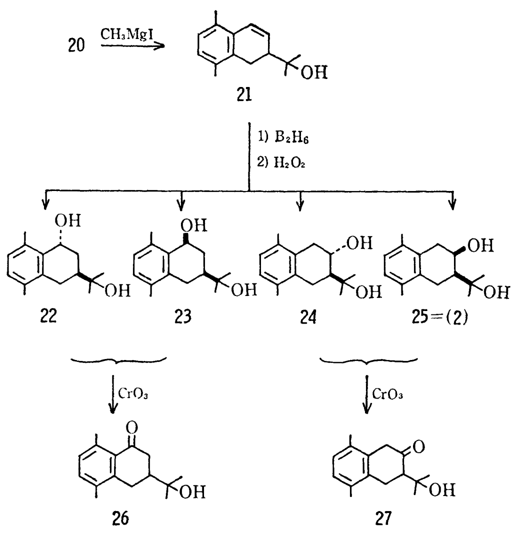
[16)] *Cf.*, R. T. Arnold and P. N. Craig, *J. Amer. Chem. Soc.*, **72**, 2728 (1950), and their previous papers.

[17)] G. Zweifel and H. C. Brown, "Organic Reactions," Vol. 13, John Wiley & Sons, Inc., London and New York (1963), p. 27.

tlc followed by recrystallization, it afforded only one 1-hydroxytetralin derivate (**22**) in 18% yield. However, the Jones oxidation[18] of both the pure alcohol **22** and the residue left on isolation of **22** produced the same 1-tetralone derivative (**26**) indicating the presence of an epimeric alcohol (**23**). The relative configurations of **22** and **23** were assigned to *trans* and *cis* on the basis of the appearance of the proton at C_1 of **22** as a triplet with J of 3 Hz at τ 5.10, since it is not probable that both the hydroxyl and oxyisopropyl groups would assume axial conformations. The middle fraction obtained in 26% yield was subjected to acetylation. The product was separated by preparative tlc to give monoacetate (**24a**) and the unreacted glycol (**25**) in 10 and 6% yields, respectively. **24a** on hydrolysis with alkali readily afforded glycol (**24**). As expected, both glycols **24** and **25** were oxidized with the Jones reagent to yield the same 2-tetralone derivative (**27**). The NMR spectra of these alcohols, consistent with the structures, made it possible to assign *trans* and *cis* configurations to the glycols **24** and **25**, respectively; the proton at C_2 of **24** appeared as a multiplet with W_H of 25 Hz centered at τ 6.50, while that of **25** as a broad singlet with W_H of 7 Hz at τ 5.24.



Compound **25** has now been identified as a racemate of rishitinol by comparison of the UV, IR, NMR, and mass spectra as well as tlc. In view of the absolute configuration of rishitin[3] and occidol,[10b] rishitinol would also possesses the β-oriented oxyisopropyl group. Hence rishitinol is represented most favorably by structure **2**.

Experimental

The melting points were measured in open capillaries and uncorrected. The optical rotations, UV and IR spectra were taken in chloroform, 99% ethanol and Nujol, respectively, unless otherwise stated. The NMR spectra were recorded in deuterochloroform at 60 and/or 100 MHz, tetramethylsilane being used as an internal standard. The following abbreviations were used in the NMR spectra. "s singlet, d doublet, t triplet, q quartet, b broad, and m multiplet." Thin layer chromatography (tlc) was carried out over silica gel of Merck G, and column chromatography over silica gel of Mallinckrodt A.R. 100 mesh or alumina of Merck Active I, neutral.

Isolation of Rishitinol (2). Tuber slices of the R_1 cultivar Rishiri (White potato, *Solanum tuberosum* × *S. demissum*) (60 kg), inoculated with an incompatible race of *Phytophthora infestans* (Mont.) d By, were dried (8.5 kg), homogenized, extracted, and separated in the same manner as that reported previously.[1] The resulting "hexane-soluble fraction"[1] (24.5 g) contained rishitin (**1**) and rishitinol (**2**). This fraction was chromatographed over silica gel (150 g) and celite (70 g), using hexane and hexane–acetone as eluents and separated roughly into two parts, one (10.5 g) eluted with hexane and the other eluted with hexane–acetone (92:8) and rishitin-rich (tlc). The former, less polar, was then rechromatographed over silica gel (100 g) and celite (30 g), using hexane, benzene, chloroform, ether, and ether–methanol as eluents. The yellow oil (5.9 g) obtained from the ether eluates was dissolved again in ether and shaken with 5% aqueous sodium carbonate to remove acidic components. The remaining ether solution was washed with water, dried, and evaporated to leave a neutral substance (3.1 g). This was again chromatographed over alumina (60 g), using hexane, hexane–benzene, benzene, benzene–ether, ether, and ether–methanol as eluents. The eluate from ether–methanol (99:1) gave a crystalline material (180 mg) on trituration with hexane, which showed a single spot on tlc (R_f=0.63, chloroform–ether, 1:1) and was collected by filtration. This was recrystallized twice from hexane to give pure rishitinol (**2**) (50 mg), mp 128—129°C, $[\alpha]_D$ +47°; mass, *m/e* 234 (M^+); IR, ν_{max} 3070, 1600, 810, and 804 cm^{-1}; UV. λ_{max} 263 mμ (ε 280); NMR, τ 8.65, 8.54, 7.81 and 7.75 (each 3H, s), 8.25 (1H, m), 7.25 (2H, br s, disappeared on addition of deuterium oxide), 7.05 (4H, m), 5.30 (1H, br s W_H= 7 Hz,) and 3.10 (2H, s).

Found: C, 76.88; H, 9.46%. Calcd for $C_{15}H_{22}O_2$: C, 76.37; H, 9.51%.

Rishitinol **2** was treated with acetic anhydride (0.3 m*l*) and pyridine (0.2 m*l*) at room temperature for 2 days. After the usual work-up, the starting material was recovered unchanged.

A solution of **2** (10 mg) in ethanol (10 m*l*) was added to a solution of sodium metaperiodate (15.6 mg) in water (18 m*l*) and acetic acid (2 m*l*), and the mixture was then diluted to 30 m*l* with water and allowed to stand at room temperature. A part (5 m*l*) of the solution was taken out three times at intervals of a day and titrated with a 0.0115 N sodium thiosulfate solution after addition of 2 m*l* of 0.1 N potassium iodide; 0.32, 0.29 and 0.25 moles of the metaperiodate were consumed in each run.

Ethyl 1-Hydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthoate (5). A solution of methyl 5,8-dimethyl-1-oxo-1,2,3,4-tetrahydro-2-naphthoate[10a] (10 g), mp 75—76°C, in ethanol (45 m*l*) was treated with a solution of sodium borohydride (2.2 g) in ethanol (75 m*l*) in the same manner as that of Hirose and Nakatsuka.[10a] The resulting oily product showed two spots and chromatographed over silica gel (120 g) and celite (40 g), using benzene, benzene–chloroform, and chloroform as eluents. Fractions eluted with benzene–chloroform gave a crude sample of **5** (3.7 g), which on trituration with hexane yielded a crystalline material, showing a single spot. Fractions eluted with chloroform afforded a brown oil (3.8 g), which was a mixture of **5** and, probably, its carbomethoxy

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[18] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, **1953**, 2548.

homologue[19] (checked by tlc). The above crystalline substance was recrystallized from hexane for analysis to give **5** (2.1 g), mp 65—66°C; mass, *m/e* 248 (M^+); IR, ν_{max} 3360 and 1720 cm^{-1}; NMR, τ 8.68 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 7.80 and 7.56 (each 3H, s, $C\underline{H}_3$ at C_5 and C_8), 5.75 (2H, q, $J=7$ Hz, $COOC\underline{H}_2CH_3$), 4.79 (1H, br s, $\underline{H}$ at C_1) and 3.03 (2H, s, $\underline{H}$ at C_6 and C_7).

Found: C, 72.48; H, 8.24%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

2-(1-Hydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthyl)propan-2-ol (6). A solution of the hydroxy ester **5** (200 mg) in dry ether (10 m*l*) was added to the Grignard solution prepared from magnesium (75 mg) and methyl iodide (450 mg) in dry ether (7 m*l*) at room temperature. After being left at the same temperature for 20 hr, the mixture was treated with a saturated ammonium chloride solution (20 m*l*) and extracted with ether. Evaporation of ether gave a brown residue (150 mg) which was separated into two portions by preparative tlc (solvent, ether). The more mobile portion (80 mg) was identified as the unreacted ester (**5**) by tlc and the mixed melting point method. The less mobile one, showing a single spot, was extracted with acetone–methanol from the plates and gave **6** (60 mg) which resisted crystallization and further purification. However, its NMR spectrum was in good accord with the structure; τ 8.69 and 8.50 (each 3H, s, $(C\underline{H}_3)_2COH$), 7.80 and 7.56 (each 3H, s, $C\underline{H}_3$ at C_5 and C_8), 4.75 (1H, d, $J=5$ Hz, $\underline{H}$ at C_1) and 3.02 (2H, s, *H* at C_6 and C_7).

dl-*Occidol (3).* Compound **19** (954 mg), dissolved in a 2 : 1 mixture (40 m*l*) of ethanol and acetic acid was hydrogenated over Adams platinum (500 mg as $PtO_2 \cdot H_2O$) at room temperature for 1 hr, when almost one mole of hydrogen was absorbed. The reaction was further continued for 7 hr. After removal of the catalyst and the solvent, the residue was dissolved in ether. The ethereal solution was washed with a sodium carbonate solution and water, dried, and evaporated to leave a crystalline material (800 mg), which was recrystallized from hexane to give **3**, mp 102—103°C; UV, λ_{max} 266 mμ (ε 200); NMR, 8.70 (6H, s), 7.80 (6H, s) and 3.10 (2H, s).

Found: C, 82.43; H, 9.97%. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

2,5-Dimethylbenzyl Chloride (8). A mixture of *p*-xylene (500 m*l*), paraformaldehyde (32 g), and zinc chloride (40 g) was heated at 70°C for 15 min and then cooled to 50°C. Dry hydrogen chloride was passed into the mixture for 30 min at 50—60°C. After the whole mixture was washed with water, 5% sodium bicarbonate, and water successively, the xylene solution was separated, dried and distilled to give compound **8** (71 g), bp 88—90°C/5 mmHg (lit,[14]) bp 105°C/15 mmHg).

Ethyl Aceto-2,5-dimethylbenzylacetate (9). The chloride **8** (140 g) was added slowly to an ethanol solution of ethyl sodioacetoacetate preparaed from sodium (20.8 g), ethanol (250 ml), and ethyl acetoacetate (234 g). The mixture was then refluxed for 6 hr, when sodium chloride precpitated was removed by filtration. The filtrate was concentrated and distilled *in vacuo* to yield a pale yellow oil (**9**) (167.4 g), bp 169—173°C/5 mmHg; IR, ν_{max} 1735 and 1720 cm^{-1}.

Ethyl α-Aceto-α-2,5-dimethylbenzylsuccinate (10). Compound **9** (167 g) was treated with sodium (15.4 g) dissolved in ethanol (200 m*l*), and mixed with ethyl chloroacetate (87.4 g). The whole mixture was worked up in the same manner as mentioned above. The product (**10**), oil, bp 185—198°C/5 mm Hg, showed spectra consistent with the assigned structure; IR, ν_{max} 1735 and 1705 cm^{-1}; NMR, τ 8.80 and 8.83 (each 3H, t, $J=8$ Hz, $COOCH_2C\underline{H}_3$), 7.77 (9H, s, CH_3CO and aromatic CH_3), and 5.90 and 5.93 (each 2H, q, $J=8$ Hz, $COOC\underline{H}_2CH_3$).

2,5-Dimethylbenzylsuccinic Acid (11). A suspension of the succinate **10** (261 g) in 2 N sodium hydroxide (1.2 *l*) was refluxed for 26 hr and poured onto a mixture of ice and hydrochloric acid. The resulting precipitates were collected, washed with water, and recrystallized from methanol to afford **11** (138 g); mass, *m/e* 236 (M^+); IR, ν_{max} 3300 and 1705 cm^{-1}. It turned gradually brown and then dark brown at 160—170°C, but did not melt below 240°C.

2,5-Dimethylbenzylsuccinic Anhydride (12). The acid **11** (80.5 g) was refluxed with acetic anhydride (161 g) for 30 min. The reaction mixture was worked up as usual and crude crystalline anhydride was recrystallized from carbon tetrachloride to afford **12** (69 g) mp 80—83°C; IR; ν_{max} 1865 and 1785 cm^{-1}.

5,8-Dimethyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid(13) and 4,7-Dimethyl-1-indanone-2-acetic Acid (14). The anhydride **12** (7.4 g) was added slowly under stirring to aluminum chloride (10 g) suspended in nitrobenzene (35 m*l*) under cooling by an ice-bath. The cold mixture was stirred at the temperature for 1 hr and at room temperature overnight, and poured onto a mixture of ice and hydrochloric acid. The aqueous mixture was then subjected to steam distillation to remove nitrobenzene, and extracted with chloroform. On removal of the solvent the chloroform solution afforded a reddish residue (5.5 g), which was purified by column chromatography on silica gel (150 g) and celite (15 g). Fractions eluted with benzene–acetone (1 : 1—1 : 4) gave a crystalline mass, which was recrystallized from benzene to give **13** (4.9 g), fine needles, mp 127—131°C. This was recrystallized from the same solvent for analysis to give **13** (2.8 g), plates, mp 135—137°C; UV, λ_{max} 254 (log ε 4.07) and 305 mμ (log ε 3.34); IR, ν_{max} 3280, 1705, and 1665 cm^{-1}; NMR, τ 7.70 and 7.40 (each 3H, $C\underline{H}_3$ at C_5 and C_8), 7.00 (5H, m), 2.96 and 2.78 (each 1H, d, $J=9$ Hz, $\underline{H}$ at C_6 and C_7) and -0.80 (1H, s, $COO\underline{H}$).

Found: C, 71.71; H, 6.39%. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%.

The mother liquors obtained on the above recrystallizations were combined and evaporated to leave a crystalline residue, which was recrystallized repeatedly from benzene to give **14** (1.1 g), mp 113—115°C; IR, ν_{max} 3150, 1705, and 1695 cm^{-1}; NMR, τ 7.70 and 7.40 (each 3H, s), *ca.* 7.0 (5H, m), 2.96 and 2.81 (each 1H, d, $J=10$ Hz) and -1.04 (1H, s).

Ethyl 5,8-Dimethyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoate (15). The naphthoic acid **13** (20.5 g) was esterified with 5% ethanolic hydrogen chloride under reflux for 5 hr and gave a crystalline ester, which was recrystallized from hexane to yield **15** (16.2 g), mp 74—76°C; IR ν_{max} 1735 and 1670 cm^{-1}; NMR, τ 8.76 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 5.85 (2H, q $J=7$ Hz, $COOC\underline{H}_2CH_3$), 7.71 and 7.41 (each 3H, s), *ca.* 7.0 (5H, m), and 2.98 and 2.86 (each 1H, AB q, $J=10$ Hz).

Ethyl 4-Hydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthoate (16) and 5,8-Dimethyl-1,2,3,4-tetrahydro-2,4-naphthalenecarbolactone (17). A solution of the naphtoate **15** (8 g), in ethanol (155 m*l*) was reduced with sodium borohydride (1.8 g) in ethanol (50 m*l*) under cooling in an ice-bath for 3 hr. The product consisted of two components (tlc), which were separated by column chromatography over silica gel (200 g), using benzene, benzene–ether and ether as eluents; one was eluted from benzene–chloroform (19 : 1—1 : 5) and the other

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[19] This substance, which had been reported to be methyl ester,[10a)] was apparently a mixture of the methyl ester and ethyl ester **5**, since the result of elemental analysis did not agree with the calculated value for $C_{14}H_{18}O_3$.

from benzene–chloroform (1:6—1:1). The former was recrystallized from benzene to give lactone **17**, (2.4 g), mp 129—131°C; IR, ν_{max} 1765 cm^{-1}; NMR, τ 7.84 and 7.62 (each 3H, s), 4.30 (1H, d, J=6 Hz) and 3.00 (2H, s).

The latter was obtained as colorless oil which showed a single spot but proved to be a mixture of two C_4-epimers formulated as (planar) structure **16** from the NMR spectral data; τ 8.76 and 8.71 (total 3H, t, J=8 Hz, $COOCH_2C\underline{H}_3$) 7.80 and 7.60 (each 3H, s, $C\underline{H}_3$ at C_5 and C_8), 5.89 and 5.78 (total 2 H, q, J=8 Hz, $COOC\underline{H}_2CH_3$), and 3.03 (2H, s, $\underline{H}$ at C_6 and C_7).

*cis-1-Hydroxy-3-hydroxymethylene-5,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**18**) and its Isomer (**19**).* To a solution of the hydroxy ester (**16**, 176 mg) in dry ether (20 m*l*) was added slowly an ether solution (5 m*l*) of lithium aluminum hydride (50 mg) under stirring at room temperature. After being left for 20 hr, the reaction mixture was worked up as usual to leave an amorphous product (143 mg) showing two spots on tlc. This was subjected to preparative tlc (ether) to give two crystalline glycols. The less polar glycol was recrystallized from hexane containing methanol to give the *cis* isomer (**18**, 51 mg), mp 125—127°C, and the more polar the *trans* isomer (**19**, 52 mg), mp 111—113°C (from ether). The *cis* isomer was also obtained in 70% yield from lactone **17** under the same conditions as above.

The *cis* glycol (**18**, 54 mg) was acetylated with acetic anhydride–pyridine (1:1, 1.2 m*l*) at room temperature for 24 hr. The reaction mixture was worked up as usual and gave the diacetate (41 mg), oil, showing a single spot on tlc; IR, ν_{max} 1730, 1240, and 810 cm^{-1}; NMR, τ 7.97 and 7.94 (each 3H, s, $OCOC\underline{H}_3$), 7.79 (6H, s, $C\underline{H}_3$ at C_5 and C_6), 5.88 (2H, d, J=7.5 Hz, $C\underline{H}_2OCOCH_3$), 3.99 (1H, double t, J=5, 5 and 0.5 Hz, $\underline{H}$ at C_1), and 3.02 (2H, s, $\underline{H}$ at C_6 and C_7).

The diacetate of *trans* isomer **19** was also obtained in 54% yield, oil; IR, ν_{max} 1727, 1240 and 810 cm^{-1}; NMR, τ 7.95 and 7.93 (each 3H, s), 7.79 (6H, s), 5.86 (2H, d, J=5 Hz), 3.88 (1H, t, J=3 Hz) and 2.95 (2H, s).

*Ethyl 5,8-Dimethyl-1,2-dihydro-2-naphthoate (**20**).* An epimeric mixture of the hydroxynaphthoates (**16**, 10.4 g) dissolved in dry benzene (25 m*l*) was dehydrated with phosphorus pentoxide (7.5 g) suspended in dry benzene (17 m*l*) in the manner described before. The reaction mixture was worked up as usual and purified by chromatography over silica gel (250 g) and celite (50 g) to give dihydronaphthoate **20** (6.8 g), oil, showing a single spot; IR ν_{max} 1735 cm^{-1}; UV, λ_{max} 260 mμ (log ε 3.90).

*2-(5,8-Dimethyl-1,2-dihydro-2-naphthyl)propan-2-ol (**21**).* A solution of the naphthoate (**20**, 2.9 g) in dry ether (15 m*l*) was subjected to the Grignard reaction by the same procedure as that for conversion of **5**, using the reagent prepared from magnesium (1.2 g) in ether (10 m*l*) and methyl iodide (9.0 g) in ether (20 m*l*). The reaction gave a crude alcohol (2.2 g) which was chromatographed over alumina (80 g). The eluate from benzene-chloroform (3:2—5:7) gave crystalline material on trituration with benzene. The crystals were recrystallized from benzene to yield **21** (1.6 g), needles, mp 46—48°C; UV, λ_{max} 260 mμ (log ε 4.04); IR, ν_{max} 3360 cm^{-1}; NMR, τ 8.80 (6H, s, $(C\underline{H}_3)_2COH$), 7.80 and 7.77 (each 3H, s), 4.01 (1H, double d, J=10 and 4 Hz, $\underline{H}$ at C_3), 3.37 (1H, double d, J=10 and 2 Hz, $\underline{H}$ at C_4) and 3.20 (2H, s).

*Hydroboration of Compound **21**.* Into a stirred solution of the alcohol **21** (1.45 g) in dry tetrahydrofuran (35 m*l*) was passed diborane, prepared from sodium borohydride (1.0 g) dissolved in diglyme (5 m*l*) and boron trifluoride etherate (6 m*l*) dissolved in diglyme (4 m*l*), for 1 hr at room temperature under nitrogen. The mixture was then diluted with water and made alkaline with 3 N sodium hydroxide (5 m*l*). To the alkaline solution was added dropwise 30% hydrogen peroxide (6.5 m*l*), and the whole mixture was stirred at 35—50°C for 1 hr and then extracted with ether. The ether solution was washed with a saturated sodium chloride solution, dried, and evaporated to give a multi-component (1.35 g) which was separated into three fractions by chromatography over alumina (38 g). The most mobile fraction eluted with benzene-chloroform (4:1—3:2) gave the unreacted alcohol **21** (0.45 g). The niddle fraction eluted with benzene-chloroform (1:1) afforded a colorless oil (0.4 g), consisting meinly of two components and the least mobile eluted with benzene-chloroform (2:3) did a two other components mixture (0.43 g).

*2-(trans-1-Hydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-3-naphthyl) propan-2-ol (**22**) and its cis-1-Hydroxy Isomer (**23**).* The least mobile fraction was further purified by preparative tlc using ether. A component showing a slightly smaller R_f value than that of rishitinol (**2**) was extracted with acetone-methanol. Removal of the solvent gave an amorphous substance which crystallized partially on trituration with benzene. The crystalline mass (**22**, 270 mg) was recrystallized from the same solvent and melted at 142—143°C; NMR, τ 8.72 and 8.75 (each 3H, s), 7.82 and 7.60 (each 3H, s), 5.10 (1H, t, J=3 Hz) and 3.05 (2H, s). The mother liquors obtained on removal of **22** were evaporated *in vacuo* to leave an amorphous residue (68 mg) showing almost the same IR spectrum as **22**. Examination of the residue by tlc indicated the presence of **22** and another component, the latter not being isolated in pure state even through its acetyl derivative. However, the component proved to be compound **23**, an epimer at C_4 of **22**, since both pure **22** and crude **23** on oxidation with the Jones' reagent afforded the same 1-tetralone derivative **26**, oil, in the same yield (70%); IR, ν_{max} 3420 and 1665 cm^{-1}.

*2-(trans-2-Hydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-3-naphthyl)-propan-2-ol (**24**) and its cis-2-Hydroxy Isomer **25**=dl **2**).* The foregoing middle fraction, obtained from hydroboration products of **21**, was oxidized with the Jones' reagent to give 2-tetralone devative (**27**) (IR, ν_{max} 1705 cm^{-1}) as a single product, indicating the components to be 2-hydroxy tetralin derivatives. They were separated by acetylation; treatment of the fraction (390 mg) with acetic anhydride–pyridine (1:1, 4 m*l*) at room temperature for 24 hr afforded an oily mixture (353 mg). This was purified by preparative tlc using chloroform–ether (1:1) to yield an unacetylated, crude crystalline substance (90 mg), mp 127—129°C, and an oily acetate (**29a**, 180 mg); IR, ν_{max} 3360 and 1730 cm^{-1}; NMR, τ 8.75 (6H, s), 7.91 (3H, s, $OCOC\underline{H}_3$), 7.84 and 7.80 (each 3H, s), *ca.* 7.0 (6H, m), 4.80 (1H, m, W_H=25 Hz, $C\underline{H}OAc$) and 3.15 (2H, s). Hydrolysis of the acetate (**24a**) in refluxing 1 N methanolic potassium hydroxide afforded a glycol, which was crystallized from hexane to give compound **24** (39 mg), mp 127—128°C; IR, ν_{max} 3300 cm^{-1}; NMR, τ 8.65 (6H, s), 7.84 (6H, s), *ca.* 6.5 (1H, br m, W_H=25 Hz, $C\underline{H}OH$) and 3.10 (2H, s); R_f=0.60 (chloroform–ether, 1:1) and 0.32 (chloroform–ether, 4:1).

The crude crystalline glycol was recrystallized from hexane to afford compound **25** (25 mg), mp 127—129°C; mass, *m/e* 234 (M$^+$); UV, λ_{max} 265 mμ (ε 300); NMR, τ 8.65 and 8.54 (each 3H, s), 7.82 and 7.75 (each 3H, s), 5.30 (1H, br s, W_H=7 Hz) and 3.05 (2H, s); R_f=0.63 (chloroform–ether, 1:1) and 0.28 (chloroform–ether, 4:1). The compound was confirmed to be a racemic form of rishitinol (**2**) in all respects (NMR, IR, UV, and mass spectra and tlc).

*2-(5,8-Dimethyl-3,4-dihydro-2-naphthyl)propan-2-ol (**29**).* To a cooled and suspended mixture of phosphorus pentoxide

(1.6 g) in dry benzene (6 m*l*) was added a solution of compound **5** (3.7 g) in dry benzene (18 m*l*) under stirring, and the mixture was stirred at 0°C for 5 hr. The cold mixture was then poured into water and extracted with ether. After being washed with water and dried, the ether solution was evaporated to leave a crystalline material which, on recrystallization from ethanol, yielded ethyl 5,8-dimethyl-3,4-dihydro-2-naphthoate (3 g), mp 53—54°C; IR, ν_{max} 1695 and 1620 cm^{-1}; NMR, τ 8.64 (3H, t, J=7 Hz), 7.73 and 7.62 (each 3H, s), 5.74 (2H, q, J=7 Hz), 3.06 (2H, s) and 2.28 (1H, s).

Found: C, 78.05; H, 7.68%. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88%.

The naphthoate (2.3 g) was subjected to the Grignard reaction under the same conditions as for compound **6**. The reaction mixture was worked up as usual and gave an oily product (2.2 g), which was chromatographed over alumina (45 g) using hexane and benzene as eluents. Fractions eluted with benzene afforded a colorless oil (**29**) (2.0 g), showing a single spot; IR, ν_{max} 3360 cm^{-1}; NMR, τ 8.58 (6H, s), 7.78 and 7.70 (each 3H, s) and 3.33 (1H, s).

Found: C, 83.22; H, 9.42%. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32%.

*2-(1,2-Dihydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthyl)-propane (***30***).* *dl*-Occidol (**3**, 105 mg) was heated with 90% formic acid (1 g) on a water-bath for 1 hr, and the mixture was cooled and diluted with ether. The ether solution was washed with 5% sodium carbonate and water, dried, and evaporated to give an oily product. While this dehydratd product showed a single spot on tlc, it was found to consist of a few unsaturated compounds by examination of the NMR spectrum. This was therefore used for the subsequent reaction without further purification. Osmium tetroxide (80 mg) was added to a solution of oil (52 mg) in dry ether (3 m*l*) and pyridine (0.08 m*l*) under stirring at room temperatute. The mixture immediately turned dark violet and dark brown osmate esters deposited after 5 min. After being left for 2 days, the whole mixturs was evaporated under reduced pressure and the residual osmate ester was decomposed by reflux with a mixture of sodium sulfite (600 mg) and 50% aqueous ethanol (100 m*l*) for 2 hr. After filtration of black precipitates deposited, the filtrate was diluted with water and extracted with ether. Evaporation of the dried extract followed by trituration of the residue with hexane afforded a crystalline product, which was recrystallized from the same solvent to give pure **30** (18 mg), mp 85—86°C; NMR, τ 9.09 (3H, d, J=7 Hz), 8.09 (3H, J=7 Hz), 7.79 and 7.57 (each 3H, s), 5.25 (1H, br s, W_H=6 Hz) and 3.02 (2H, s).

Found: C, 76.63; H, 9.44%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.

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