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THE STRUCTURE AND SYNTHESIS OF RISHITINOL, A NEW SESQUITERPENE ALCOHOL FROM DISEASED POTATO TUBERS (1)

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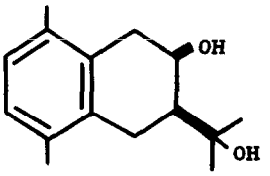
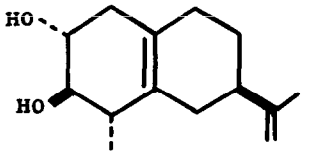
In a continuing study on rishitin (2), we have isolated a new sesquiterpene alcohol in 0.0001 % from tuber tissues of white potatoes (Solanum tuberlosum and S. demissum) infected by an incompatible race of phytophthora infestans. We describe herewith the structure of the alcohol, designated as rishitinol, as well as the total synthesis of its racemic form.



Rishitinol (I)



Rishitin

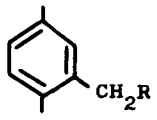
Rishitinol (I), m.p. 127-129°, $(\alpha)_D$ +47° ($CHCl_3$), was analyzed for $C_{15}H_{22}O_2$ (M^+ 234) (3) and resisted acetylation (Ac_2O-Py, room temp., 2 days) and oxidation with HIO_4 (room temp., 1 day). The UV, IR and NMR spectral data indicated that I contained the following structural units: tetra-substituted benzene (probably 1,4-dimethyl-2,3-dimethylene substituted benzene (4)) (λ_{max}^{EtOH} 263 mμ (ε 280); ν_{max}^{Nujol} 3070 and 1600 cm^{-1}; τ (60 MHz, $CDCl_3$) 7.81 and 7.75 (each 3H, s), ca. 7.1 (4H, br m) (6), and 3.10 (2H, s)); two tert. Me groups (τ 8.65 and 8.54 (each 3H, s)); one sec. OH group (ν 3300 cm^{-1}; τ ca. 7.1 (6)

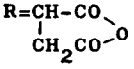
and 5.30 (1H, br s W_H = 7 Hz)); one tert. OH group (ν 3300 cm^{-1}; τ ca. 7.1 (6)). These facts suggested that rishitinol would be represented by (planar) structure I, which was confirmed by the synthesis described below.

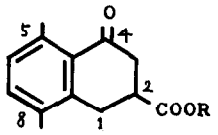
1,2,3,4-Tetrahydro-5,8-dimethyl-4-oxo-2-naphthoic acid (VII) was first prepared in a manner analogous to the synthetic procedure of the corresponding 5,8-demethyl derivative by Haworth et al. (7). Alkylation of ethyl sodioacetoacetate with 2,5-dimethylbenzyl chloride (II) (8) (reflux in EtOH, 6 hr) produced the 2,5-dimethylbenzyl derivative (III), b.p. 169-173° (5 mm Hg), which was again treated with Na in EtOH and then refluxed with ethyl cholroacetate (5.5 hr) to give acetylbenzylsuccinate (IV), b.p. 188-198° (5 mm Hg). Futher treatment of IV with alkali (2N NaOH) under reflux effected both hydrolysis and removal of the acetyl group to yield 2,5-dimethylbenzylsuccinic acid (V), m.p. > 240°, m/e 236, which on heating with Ac_2O formed the corresponding anhydride, m.p. 81-83°, ν_{max}^{Nujol} 1865 and 1785 cm^{-1}, in 24% yield from II. Friedel-Crafts cyclization of VI ($AlCl_3$ in $C_6H_5NO_2$, room temp., overnight) led to formation of a 2:1 mixture (70% yield) of β-naphthoic acid (VII), m.p. 135-137° (λ_{max}^{EtOH} 305 and 254 mμ (ε 2100 and 11,000, respectively); ν_{max}^{Nujol} 3200, 1735 and 1665 cm^{-1}; τ 7.70 and 7.40 (each 3H, s, two arom. Me), ca. 7.0 (5H, m, C$\underline{H}_2$ and C$\underline{H}$), 2.96 and 2.78 (each 1H, ABq J = 9 Hz, arom. $\underline{H}$), and -0.80 (1H, s, COO$\underline{H}$)) and its isomeric acid (VIII) containing hydrindanone skeleton, m.p. 113-115° (ν_{max}^{Nujol} 3150, 1705 and 1695 cm^{-1}; τ -1.04 (1H, s, COO$\underline{H}$)), which were separated by fractional recrystallizations. Apparently the formation of VIII, as compared with Haworth's result (no isolation of VIII') (7), would be caused by steric hindrance of one of the aromatic Me groups (9). β-Naphthoic acid VII was then converted (HCl, reflux in EtOH, 5 hr) into the corresponding ethyl ester (IX), m.p. 74-76° (ν_{max}^{Nujol} 1735 and 1670 cm^{-1}; τ 8.76 (3H, t J = 7 Hz, $COOCH_2C\underline{H}_3$) and 5.85 (2H, q J = 7 Hz, $COOC\underline{H}_2CH_3$)), in 70% yield.

Reduction of IX with $NaBH_4$ in EtOH afforded a mixture of hydroxy ester (X) (10), oil (ν_{max}^{Nujol} 3300 and 1730 cm^{-1}; τ 8.03 (1H, s, O$\underline{H}$) and 5.05 (1H, t J = 3 Hz, C$\underline{H}$(OH)) and γ-lactone (XI), m.p. 129-131° (ν_{max}^{Nujol} 1765 cm^{-1}; τ 4.30 (1H, d J = 6 Hz, C$\underline{H}$OCO)), which were isolated in 61 and 30% yields, respectively. Dehydration of X with P_2O_5 in C_6H_6 proceeded smoothly to give styrene (XII),

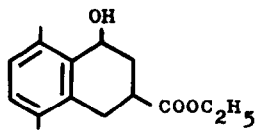
oil, λ_{max}^{EtOH} 260 mμ (ε 8000), which on treatment with CH_3MgI (room temp., overnight) produced the oxyisopropyl derivative (XIII), m.p. 46-48° (λ_{max}^{EtOH} 260 mμ (ε 11,000); ν_{max}^{Nujol} 3360 cm^{-1}; τ 8.80 (6H, s, two tert. Me), 4.01 (1H, dd J = 10 and 4 Hz, olefinic H at C_3), and 3.37 (1H, dd J = 10 and 2 Hz, olefinic H at C_4)), in 37% yield from X. Hydroboration of XIII followed by oxidation with H_2O_2 resulted in formation of a multi-component mixture, which was roughly separated by column chromatography (SiO_2) into the starting olefin XIII (30%),



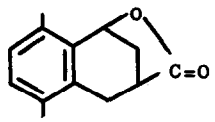
II R=Cl, III R=$CH(COCH_3)(COOC_2H_5)$
IV R=$C(COCH_3)(COOC_2H_5)(CH_2COOC_2H_5)$
V R=$CH(COOH)(CH_2COOH)$, VI R= 



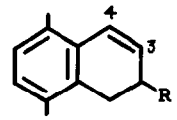
VII R=H, IX R=C_2H_5



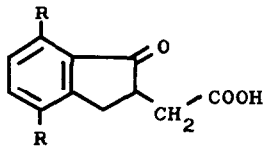
X



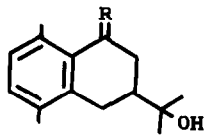
XI



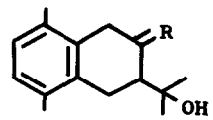
XII R=$COOC_2H_5$
XIII R=$C(OH)(CH_3)_2$



VIII R=CH_3
VIII' R=H



XIVa R=ax-OH, H
XIVb R=eq-OH, H
XVII R=O



XVa R=ax-OH, H(cis)
XVb R=eq-OH, H(trans)
XVIb R=eq-OAc, H(trans)
XVIII R=O

α-hydroxy- (XIV 27%) and β-hydroxy-tetralin derivatives (XV, 26%). While only one α-hydroxytetralin (XIVa), m.p. 142-143° (ν_{max}^{Nujol} 3400 cm^{-1}; τ 5.10 (1H, t J = 3 Hz, CH(OH)) could be isolated in pure state in 18% yield by repeated recrystallizations, XIVa and its mother liquor afforded the same α-tetralone derivative (XVII), ν_{max}^{film} 3420 and 1665 cm^{-1}, in good yields, indicating the formation of an epimeric alcohol (XIVb). On the other hand, the latter XV was submitted to acetylation (Ac_2O-Py, room temp.) followed by separation on TLC

plates to give an unacetylated glycol (XVa), m.p. 127-129° (ν_{max}^{Nujol} 3400, 1460, 1380, 1040, and 815 cm^{-1}; τ 8.65 and 8.54 (each 3H, s, two tert. Me), 7.82 and 7.75 (each 3H, s, arom. Me), 5.24 (1H, br s W_H = 7 Hz, C<u>H</u>(ax-OH)), and 3.05 (2H, s, arom. <u>H</u>)) and monoacetate (XVIb), oil (ν_{max}^{film} 3360 and 1730 cm^{-1}, τ 7.91 (3H, s, OCOC<u>H</u>$_3$) and ca. 4.8 (1H, m W_H = 25 Hz, C<u>H</u>(OCOCH$_3$))), in 6 and 9% yields, respectively, which on hydrolysis formed a glycol (XVb), m.p. 127-128° (ν_{max}^{Nujol} 3300 cm^{-1}; τ ca. 6.5 (1H, br m W_H = 25 Hz, C<u>H</u>(eq-OH)). As expected, XVa and XVb were oxidized with Jones reagent to yield the same β-tetralone derivative (XVIII), oil, ν_{max} 3400 and 1705 cm^{-1}.

Compound XVa has now been identified to be a racemic form of rishitinol by comparison of the spectra (UV, IR, NMR and mass) as well as TLC. In view of the absolute configuration of rishitin (2) and occidol (11), it would be certain that rishitinol also possesses the β-oriented oxyisopropyl group. Since both the hydroxyl and oxyisopropyl groups would improbably assume axial conformations, compound I is represented most favorably by structure I.

<u>Acknowledgement</u> --- The authors are indebted to Mr. N. Sato, Hokkaido Agricultural Experiment Station, for preparation of raw material.

<u>Footnotes and References</u>

(1) Part VI of "Studies on the Phytoalexins;" Part V, N. Ishizaka, K. Tomiyama, N. Katsui, A. Murai, and T. Masamune, <u>Plant & Cell Physiol.</u> <u>10</u>, 183 (1969).

(2) N. Katsui, A. Murai, M. Takasugi, K. Imaizumi, T. Masamune, and K. Tomiyama, <u>Chem. Comm.</u> 43 (1968).

(3) Satisfactory analyses, UV, IR and NMR spectra were obtained for all new compounds described here.

(4) The NMR spectrum of I resembled closely, except absorption at τ 5.30, that of <u>dl</u>-occidol (5).

(5) Y. Hirose and T. Nakatsuka, <u>Bull. Agr. Chem. Soc. Japan</u> <u>23</u>, 143 (1959).

(6) The absorption near τ 7.1 proved to overlap with that due to <u>two</u> OH protons by addition of D_2O.

(7) R. Haworth, B. Jones and M. Way, <u>J. Chem. Soc.</u> 10 (1943).

(8) H. Spephen, W. F. Short and G. Gladding, <u>Ibid.</u> <u>117</u>, 510 (1920).

(9) Cf. R. T. Arnold and P. N. Craig, <u>J. Am. Chem. Soc.</u> <u>72</u>, 2728 (1950), and their previous papers.

(10) The configuration of X will be discussed in a full paper.

(11) M. Nakazaki, <u>Bull. Chem. Soc. Japan</u> <u>35</u>, 1387 (1962).