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THE SYNTHESIS OF RISHITIN[1]

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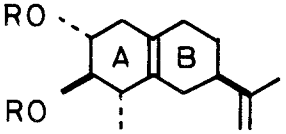
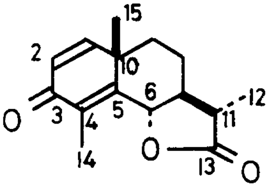
The titled compound, rishitin (1), is a representative member of a group of sesquiterpenes qualified as phytoalexins from diseased potatoes,[2] and the structure[3] and configurations[3,4] have been established well and characterized by an eudesmane skeleton with a double bond intervending between the two rings as well as three asymmetric centers in the A ring. We describe herein the regio- and stereo-selective synthesis of rishitin (1) from santonin (2), a totally synthesized sesquiterpenes.[5]



1 R = H
1a R = Ac



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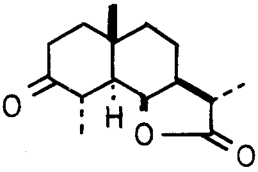

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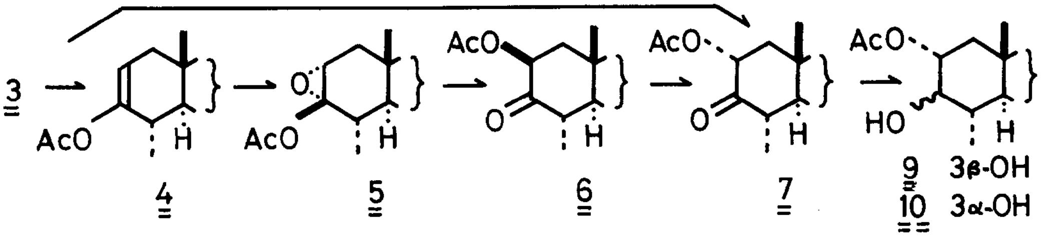
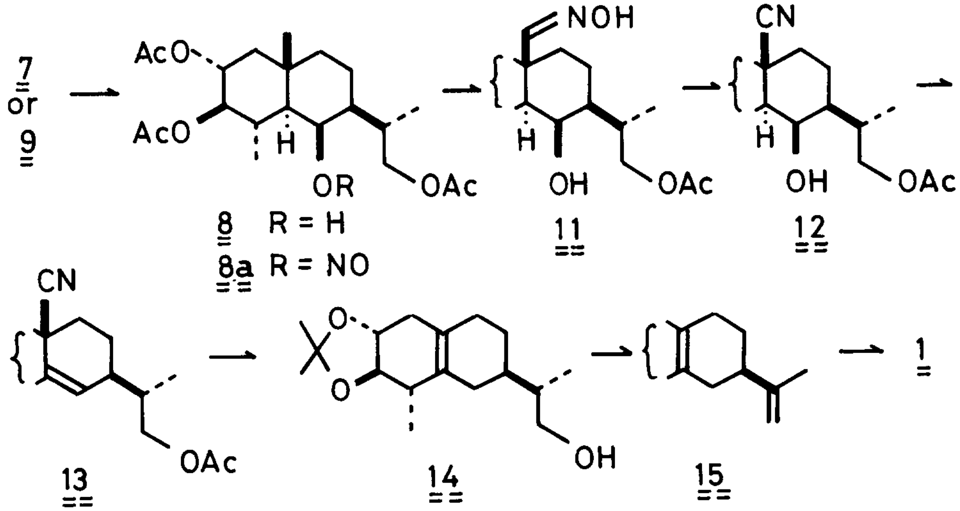
(-)-α-Santonin (2) was converted into 3-oxo-5,6α(H),4,11β(H)-eudesman-6,13-olide (3) by a known two-step process,[6] which on treatment with isopropenyl acetate and acid (reflux, 1 hr)[7] gave the corresponding enol acetate (4), mp 140-141°; Mass, m/e 292 (M^+) and 250 (base); IR,[8] ν_{max} 1773, 1755, and 1682 cm^{-1}; NMR,[8] δ 2.17 (3H, s, $OCOCH_3$) and 5.28 (1H, do t J = 5.5, 2.5, and 2.5 Hz, H at C_2), in 99% yield. Oxidation of 4 with perbenzoic acid ($CHCl_3$, 0°, 24 hr) produced 2α,3α-epoxy-3β-acetate (5), mp 156-156.5°; Mass, m/e 308 (M^+) and 266 (base); IR, ν_{max} 1771 and 1750 cm^{-1}; NMR, δ 2.10 (3H, s, $OCOCH_3$) and 3.45 (1H, d J = 5 Hz, H at C_2), in 91% yield, which was rearranged by heating at 170° (5 min) to 3-oxo-2β-acetate (6), mp 128-129°; Mass, m/e 308 (M^+) and 266 (base); IR, ν_{max} 1782 and 1737 cm^{-1}, and then epimerized with acid (HBr in AcOH, room temp, 17 hr)[9] to give 3-oxo-2α-acetate (7), mp 202-203°; Mass, m/e 308 (M^+) and 266 (base); IR, ν_{max} 1779, 1747, and 1718 cm^{-1}, in 70% yield from 5. The configurations of the acetoxy group at C_2 in these oxo-acetates (6 and 7) were defined clearly on the basis of the signal patterns due to the C_2-proton: 6, δ 5.35 (1H, do d J = 9 and 6 Hz); 7, δ 5.45 (1H, do d J = 13 and 7 Hz).[10] While compound 7 could be prepared by one-step oxidation of 3-ketone (3) [$Pb(OAc)_4$ in AcOH containing BF_3 and iso-C_3H_7OH, room temp, 24 hr][11] but in low yield (41%) along with 6 (9%), the over-all yield of 7 increased to 73%, when the aforementioned four-step reactions (3 → 7) were carried out without isolation of the intermediates (4, 5, and 6).



Hydride reduction of 3-ketone (7) (LAH in THF, reflux, 24 hr) followed by acetylation (Ac_2O and Py, room temp, 13 hr) afforded triacetate (8), mp 95.5-96.5°; Mass, m/e 338 (M^+ - AcOH) and 219 (base); IR, ν_{max} 3535, 1733, 1241, 1050, 1033, and 1027 cm^{-1}; NMR, δ 1.99 and 2.08 (3H and 6H, each s, $3OCOCH_3$), 3.89 and 4.21 (each 1H, do d J = 11, 6 and 11, 5 Hz, 2H at C_{13}), 4.08 (1H, br s W_H = 6.5 Hz, H at C_6), 4.70 (1H, t J = 10 Hz, H at C_3), and 5.11 (1H, do do d J = 11.5, 10, and 5 Hz, H at C_2), in 65% yield. In order to confirm the configuration at C_3 in 8, compound 7 was reduced with sodium borohydride (MeOH, 0°, 14 min) to give an almost 1:1 mixture of 3β- (41%) and 3α-alcohols (48%) (9 and 10), mp 249-249.5° and 190-191°, whose C_3-proton signals elucidated the respective configurations at C_3: 9, δ 3.13 (1H, t J = 9 Hz); 10, δ 3.91 (1H, br s W_H = 6.5 Hz). Hydride reduction of the former (9) (LAH) and subsequent acetylation also produced the relevant triacetate (8) in 72% yield, which was converted (NOCl in Py, -20° ∿ -30°) quantitatively into the 6β-nitrite (8a), mp 103.5-105.5°; IR, ν_{max} 1748, 1653, 1643, and 768 cm^{-1}; NMR, δ 5.94 (1H, br s W_H = 5 Hz, H at C_6).

Irradiation of the nitrite (8a) by a 200-W high pressure Hanovia lamp (C_6H_6, room temp, 2 hr)[12] followed by reflux in a 1:1 mixture of tetrahydrofuran and isopropyl alcohol (1 hr) produced a three-component mixture, from which 15-oxime (11), amorphous; Mass, m/e 410 (M^+ - OH) and 350 (base); IR ($CHCl_3$), ν_{max} 3235, 3135, and 1739 cm^{-1}; NMR, δ 2.00 and 2.07 (3H and 6H, each s, $3OCOCH_3$), 6.56 (1H, d J = 9 Hz, OH at C_6), 7.18 (1H, s, CH=N), and 10.45 (1H, s, N-OH), was isolated in 78% yield. This 15-oxime (11) underwent dehydration ($POCl_3$ in Py, room temp, 3 days) to give 6β-hydroxy-10-nitrile (12), mp 174.5-175.5°; Mass, m/e 409 (M^+) and 350 (base); IR, ν_{max} 3530, 2230, 1739, and 1728 cm^{-1}; NMR, δ 1.79 (1H?, s, OH), and Δ^5-10-nitrile (13), mp 103.5-105.5°; Mass, m/e 331

(M$^+$ - AcOH); IR, ν_{max} 2225 and 1745 cm^{-1}; NMR, δ 5.58 (1H, br s W_H = 5 Hz, H at C_6), in 65 and 4% yields, respectively. The latter (13) was also obtained by treatment of the former (12) with mesyl chloride (Py, room temp, 46 hr) and then with collidine under reflux (3 hr) in 78% yield.



Treatment of the allyl nitrile (13) with sodium in refluxing toluene containing ethanol^{13} and then with acetone over silica gel (Wakogel Q-23) effected removal of the cyano group with concomitant migration of the double bond to give $\Delta^{5(10)}$-2,3-diol acetonide (14), oil; Mass, m/e 280 (M$^+$); IR (CCl$_4$), ν_{max} 3390, 1380, 1371, 1229, 1152, and 1089 cm^{-1}; NMR, δ 0.94 and 1.14 (each 3H, d J = 6.5 Hz, 12- and 14-CH$_3$), and 1.46 [6H, s, (CH$_3$)$_2$CO$_2$], in 75% yield from 13. The olefinic alcohol (14) was treated successively with tosyl chloride (Py, room temp, 20 hr), sodium iodide (acetone, reflux, 22 hr) and 5% potassium hydroxide (MeOH, reflux, 2.5 hr) to give diolefin (15), oil; Mass, m/e 262 (M$^+$) and 131 (base); IR (neat), ν_{max} 3080, 1643, 1378, 1370, 1229, 1100, 1083, 1042, and 888 cm^{-1}; NMR, δ 1.14 (3H, d J = 6.5 Hz, 14-CH$_3$), 1.44 [6H, s, (CH$_3$)$_2$CO$_2$], 1.72 (3H, s, 12-CH$_3$), 3.20 (1H, t J = 9 Hz, H at C$_3$), 3.58 (1H, do t J = 7, 9, and 9 Hz, H at C$_2$), and 4.64 and 4.74 (each 1H, br s W_H = 4 Hz, 13-CH$_2$), in 65% yield from 14. Acid hydrolysis of the acetonide (15) (0.5% H$_3$PO$_4$ in EtOH, reflux, 1 hr) afforded glycol, mp 58-60° and $[\alpha]_D$ -30.4° (EtOH); Mass, m/e 222 (M$^+$); IR (CCl$_4$), ν_{max} 3370, 3080, 1642, 1075, 1039, 1017, and 890 cm^{-1}; NMR, δ 1.14 (3H, d J = 6.5 Hz, 14-CH$_3$), 1.75 (3H, s, 12-CH$_3$), 3.18 (1H, t J = 9 Hz, H at C$_3$), 3.63 (1H, do t J = 7, 9, and 9 Hz, H at C$_2$), and 4.62 and 4.71 (each 1H, br s W_H = 4 Hz, 13-CH$_2$), in 78% yield, which was identical with natural rishitin^{3,14} (1) in all respects. The identity was reconfirmed by direct comparison of the respective diacetates: synthetic, mp 66-68° and $[\alpha]_D$ -14.1° (EtOH); Mass, m/e 246

(M^+ - AcOH); IR (CCl_4), ν_{max} 3070, 1749, 1642, 1242, 1225, 1030, and 890 cm^{-1}; NMR, δ 1.06 (3H, d J = 6.5 Hz, 14-C$\underline{H}_3$), 1.75 (3H, s, 12-C$\underline{H}_3$), 2.03 and 2.08 (each 3H, s, 2OCOC$\underline{H}_3$), and 4.64 and 4.74 (each 1H, br s W_H = 4 Hz, 13-C$\underline{H}_2$); natural[3,14] (**1a**). The over-all yield of rishitin (**1**) amounted to 7.1% from compound **3** and 2.7% from santonin (**2**).

References and Footnotes

1) Part II of "Synthetic Studies of Rishitin and Related Compounds." The following reference can be considered as Part I of this series. N. Katsui, A. Matsunaga, K. Imaizumi, T. Masamune, and K. Tomiyama, *Tetrahedron Lett.*, 83 (1971); *Bull. Chem. Soc. Japan*, **45**, 2871 (1972).
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3) N. Katsui, A. Murai, M. Takasugi, K. Imaizumi, T. Masamune, and K. Tomiyama, *ibid.*, 43 (1968).
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7) Cf., K. Kato, Y. Hirata, and S. Yamamura, *Tetrahedron*, **27**, 5987 (1971).
8) The IR and NMR spectra were measured in Nujol and deuterochloroform, unless otherwise stated. The abbreviations "s, d, t, br, and do" in the NMR spectra denote "singlet, doublet, triplet, broad, and double," respectively.
9) Cf., K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).
10) Cf., K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).
11) Cf., H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc.*, 4472 (1961).
12) Cf., D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, **83**, 4076 (1961).
13) Cf., R. Gardi, C. Pedrali, and A. Ercoli, *Gazz. Chim. Ital.*, **93**, 525 (1963); *Chem. Abs.*, **59**, 8825e (1963).
14) The optical rotations, $[\alpha]_D$, of natural rishitin (**1**) and its diacetate (**1a**) should be revised to -35.1° and -14.1° (EtOH), respectively.