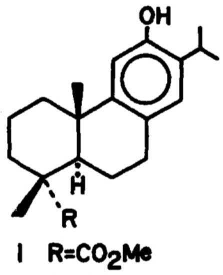
CHEMISTRY LETTERS, pp. 1311-1314, 1976. Published by the Chemical Society of Japan

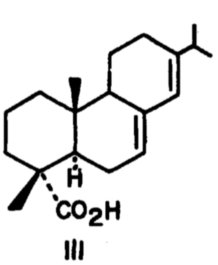
SYNTHESIS OF TAXOQUINONE, 7α-ACETOXYROYLEANONE, DEHYDROROYLEANONE, HORMINONE, 7-OXOROYLEANONE, AND INUROYLEANOL

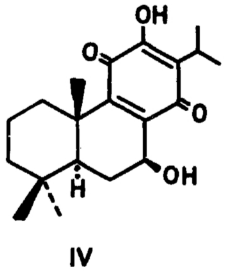
Takashi MATSUMOTO and Shogo HARADA
Department of Chemistry, Faculty of Science, Hiroshima University
Higashisenda-machi, Hiroshima 730

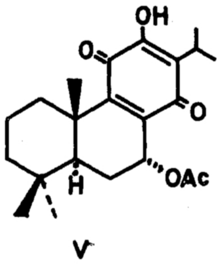
Oxidation of ferruginol (II) with benzoyl peroxide gave 12-benzoyloxy-11-hydroxyabieta-8,11,13-triene (X) which was converted into taxoquinone (IV), 7α-acetoxyroyleanone (V), dehydroroyleanone (VI), horminone (VII), 7-oxoroyleanone (VIII), and inuroyleanol (IX).

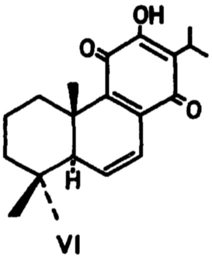
In our previous communication,1) it has been reported on the successful oxidation of C-11 position in methyl 12-hydroxyabieta-8,11,13-trien-18-oate (I)2) with benzoyl peroxide. As an extension of the work, we further attempted the conversion of ferruginol (II) prepared3) from (-)-abietic acid (III) via I, into naturally-occurring tricyclic diterpenes possessing an oxygen-function at C-11 position. Since (-)-abietic acid has been synthesized, any conversion starting from II can be regarded as a formal total synthesis. This communication4) will describe the synthesis of taxoquinone (IV),5,6) 7α-acetoxyroyleanone (V),7,8) dehydroroyleanone (VI),5,7,9,10)

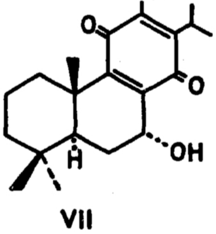

I R=CO$_2$Me
II R=Me

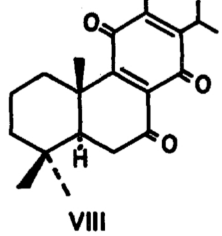

III

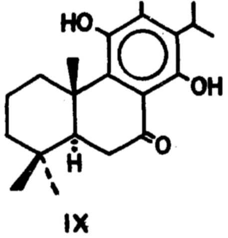

IV


V


VI

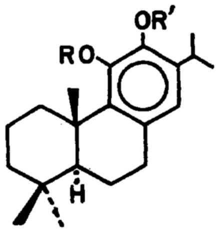

VII


VIII

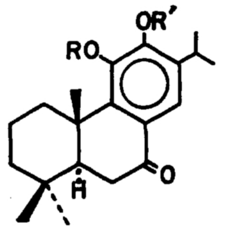

IX

horminone (VII),[5,11] 7-oxoroyleanone (VIII),[5,8] and inuroyleanol (IX).[8]

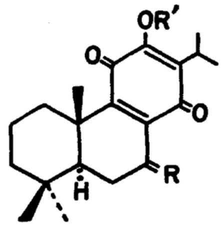
Oxidation[3] of II with benzoyl peroxide in chloroform (r.t., 4 hr) afforded 12-benzoyloxy-11-hydroxyabieta-8,11,13-triene (X: 44%) which gave a positive Gibb's test,[12] suggesting the presence of an aromatic proton para to a phenolic hydroxyl group; mp 132.5-133°C, $[\alpha]_D$ +81.2°, IR: 3575, 3350, 1740 cm^{-1}, NMR: 0.97 (s, $-\overset{|}{C}(CH_3)_2$), 1.17 and 1.19 (each d and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.33 (s, $C_{10}-CH_3$), 5.17 (s, -OH), 6.50 (s, C_{14}-H), 7.4-8.3 (m, $-C_6H_5$). Methylation of X in refluxing methyl ethyl ketone with methyl iodide in the presence of potassium carbonate (8 hr) afforded two monomethyl ethers, XI (38%, mp 183.5-184.5°C) and XII (60%, mp 125-126°C). Reductive cleavage of benzoyl group in XI was carried out with lithium aluminum hydride in refluxing ether (2 hr) and the resulting phenol (XIII, 80%, mp 94-94.5°C) showed a positive Gibb's test. Oxidation of XI with chromic anhydride in acetic acid (r.t., 22 hr) gave a 7-oxo compound (XIV, 54%), mp 197-198°C, $[\alpha]_D$ +68.9°, IR: 1739, 1676 cm^{-1}, which on alkaline hydrolysis gave cryptojaponol (XV, mp 205-206.5°C).[13] Thus, the structure of XI was assigned as 11-benzoyloxy-12-methoxyabieta-8,11,13-triene. Subsequently, XII was hydrolyzed with aqueous sodium hydroxide in refluxing methanol (1 hr) to give the corresponding phenol (XVI, 80%, mp 114.5-115°C) which, in contrast with XIII, gave a negative Gibb's test. XII was also subjected to oxidation with chromic anhydride in acetic acid (r.t., 24 hr) to give a benzoyloxy p-benzoquinone (XVII, 27%, mp 196-197°C) which on alkaline hydrolysis gave royleanone (XVIII, mp 181.5-183°C),[7] and a 7-oxo compound (XIX, 44%), mp 163-163.5°C, $[\alpha]_D$ +38°, IR: 1740, 1678 cm^{-1}, NMR: 0.99 (s, $-\overset{|}{C}(CH_3)_2$), 1.22 and 1.27 (each d and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.40 (s, $C_{10}-CH_3$), 3.70 (s, $-OCH_3$), 7.3-8.4 (m, $-C_6H_5$), 7.76 (s, C_{14}-H). The above results suggested the structure of XII to be 12-benzoyloxy-11-methoxyabieta-8,11,13-triene. Reduction of XIX with sodium borohydride in methanol (0°C, 3 hr) followed by acetylation of the resulting alcoholic product with acetic anhydride in pyridine (r.t., 22 hr) gave a mixture of 7β-acetoxy-12-benzoyloxy-11-methoxyabieta-8,11,13-triene (XX, 75%) and its 7α-acetoxy isomer (XXI, 15%), mp 176-177°C, $[\alpha]_D$ +75.2°. The stereochemistry of the acetoxyl groups was established on the basis of the presence of C-7 proton signals with half-height width of 12 Hz at δ 5.90 for XX and 5 Hz at δ 5.86 ppm for XXI in their NMR spectra. This reaction procedure leading to the 7-acetoxy compounds is suitable for the synthesis of taxoquinone (IV) possessing a 7β-hydroxyl group. However, in order to obtain 7α-acetoxyroyleanone (V) and horminone (VII) it is necessary to prepare XXI predominantly. For this purpose, the



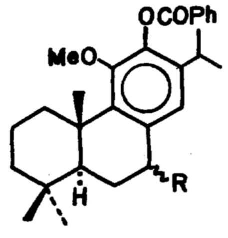
X R=H, R'=COPh
XI R=COPh, R'=Me
XII R=Me, R'=COPh
XIII R=H, R'=Me
XVI R=Me, R'=H



XIV R=COPh, R'=Me
XV R=H, R'=Me
XIX R=Me, R'=COPh



XVII $R=H_2$, R'=COPh
XVIII $R=H_2$, R'=H
XXII R=α-H, β-OAc, R'=COPh
XXIII R=α-H, β-OH, R'=Me
XXIV R=α-OAc, β-H, R'=COPh
XXV R=O, R'=Me



XX R=β-OAc
XXI R=α-OAc

direct acetoxylation on C-7 position in XII was attempted and the ratio of XX and XXI could be improved by treatment with lead tetraacetate in refluxing acetic acid (N_2 atmosphere, 40 min) in 57% yield (ca. 1:2 ratio). Oxidation of XX in acetic acid with chromic anhydride (r.t., 24 hr) afforded 7β-acetoxy-12-benzoyloxy-11,14-dioxoabieta-8,12-diene (XXII, 37%), mp 155-160°C, $[\alpha]_D$ +30°, IR: 1737, 1663 cm^{-1}. Hydrolysis of XXII with aqueous sodium hydroxide in methanol (reflux, 30 min) followed by treatment with dilute hydrochloric acid (reflux, 5 min) gave taxoquinone (IV, 68%),$^{14)}$ mp 206-207°C, $[\alpha]_D$ +344°, IR: 3548, 3378, 1671, 1647, 1623, 1597 cm^{-1}, NMR ($CDCl_3$): 0.93 (s, $-\dot{C}(CH_3)_2$), 1.22 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.35 (s, $C_{10}-CH_3$), 3.84 (d, J=2 Hz, C_7-OH), 4.84 (m, $W_{1/2}$=20 Hz, C_7-H), 7.33 (s, $C_{12}-OH$), Mass: m/e 332 (M^+). According to the methods of Eugster et al.,$^{5)}$ the product IV was converted into its methyl ether (XXIII), dehydroroyleanone (VI),$^{14)}$ mp 166-167°C, $[\alpha]_D$ -609°, IR: 3363, 1665, 1635, 1610 cm^{-1}, NMR ($CDCl_3$): 0.98, 1.02, and 1.04 (each s, $-\dot{C}(CH_3)_2$ and $C_{10}-CH_3$), 1.22 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.14 (t, J=3 Hz, C_5-H), 6.45 (dd, J=3 and 10 Hz, C_6-H), 6.81 (dd, J=3 and 10 Hz, C_7-H), 7.32 (s, $C_{12}-OH$), and 7-oxoroyleanone (VIII),$^{15)}$ mp 202-203°C, IR: 3400, 1695, 1663, 1645, 1575 cm^{-1}, NMR ($CDCl_3$): 0.93 and 0.96 (each s, $-\dot{C}(CH_3)_2$), 1.22 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.36 (s, $C_{10}-CH_3$), 6.98 (s, -OH). Similarly, XXI was also oxidized with chromic anhydride in acetic acid (r.t., 20 hr) to afford 7α-acetoxy-12-benzoyloxy-11,14-dioxoabieta-8,12-diene (XXIV, 23%), mp 261-262°C, $[\alpha]_D$ +42°, IR: 1738, 1664 cm^{-1}. This was then subjected to partial hydrolysis with sodium hydrogencarbonate in refluxing aqueous methanol (1 hr) to give 7α-acetoxyroyleanone (V, 97%),$^{14)}$ mp 212-214°C, $[\alpha]_D$ -7°, IR: 3390, 1736, 1671, 1642, 1608 cm^{-1}, NMR ($CDCl_3$): 0.89 (s, $-\dot{C}(CH_3)_2$), 1.19 and 1.22 (each d and J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.24 (s, $C_{10}-CH_3$), 2.02 (s, $-OCOCH_3$), 5.94 (m, $W_{1/2}$=6 Hz, C_7-H), 7.13 (s, $C_{12}-OH$). Alkaline hydrolysis of XXIV followed by treatment with dilute hydrochloric acid afforded horminone (VII, 81%),$^{14)}$ mp 176-178°C, $[\alpha]_D$ -120°, IR: 3570, 3380, 1671, 1647, 1627, 1601 cm^{-1}, NMR ($CDCl_3$): 0.91 and 0.99 (each s, $-\dot{C}(CH_3)_2$), 1.22 (s, $C_{10}-CH_3$), 1.22 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.05 (s, C_7-OH), 4.75 (m, $W_{1/2}$=9 Hz, C_7-H), 7.27 (s, C_{12}-OH). Finally, XXIII was oxidized with chromic anhydride-pyridine complex (r.t., 48 hr) to give the corresponding 7-oxo compound (XXV, 22%),[8] mp 90-92°C, which on reduction with sodium sulfite in acetic acid (95°C, 2 min) gave inuroyleanol (IX, 70%),[15] mp 185-186°C, $[\alpha]_D$ +106°, IR: 3520, 1620 cm^{-1}, NMR ($CDCl_3$): 0.96 (s, $-C(CH_3)_2$), 1.37 (s, $C_{10}-CH_3$), 1.39 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 3.80 (s, $-OCH_3$), 5.72 (s, C_{11}-OH), 13.30 (s, C_{14}-OH).

Acknowledgment. The authors are grateful to Arakawa Rinsan Kogyo Co., Ltd. for generous gift of rosin. Thanks are also due to Professor S. Morris Kupchan, University of Virginia, to Professor C. H. Eugster, Zürich University, and to Professor O. E. Edwards, National Research Council, Ottawa, for their kind supply of the natural samples and spectral copies.

REFERENCES

1) T. Matsumoto, Y. Ohsuga, and K. Fukui, Chem. Lett., 1974, 297.
2) R. C. Cambie and R. A. Franich, Aust. J. Chem., 24, 117 (1971).
3) The details will be report elsewhere.
4) IR spectra were taken in $CHCl_3$ and NMR in CCl_4 unless otherwise specified. Their chemical shifts are presented in terms of δ values. Optical rotations were measured in $CHCl_3$ on a Yanaco OR-50D.
5) M. Hensch, P. Rüedi, and C. H. Eugster, Helv. Chim. Acta, 58, 1921 (1975).
6) S. M. Kupchan, A. Karim, and C. Marcks, J. Amer. Chem. Soc., 90, 5923 (1968); J. Org. Chem., 34, 3912 (1969).
7) O. E. Edwards, G. Feniak, and M. Los, Can. J. Chem., 40, 1540 (1962).
8) S. V. Bhat, B. S. Kalyanaraman, H. Kohl, N. J. de Souza, and H.-W. Fehlhaber, Tetrahedron, 31, 1001 (1975).
9) J. H. Gough and M. D. Sutherland, Aust. J. Chem., 19, 329 (1966).
10) C. H. Eugster, Palette, 1968, 25; Chem. Abstr., 69, 54262e (1968).
11) M.-M. Janot and P. Potier, Ann. Pharm. France, 22, 387 (1964).
12) F. E. King, T. J. King, and L. C. Manning, J. Chem. Soc., 1957, 563.
13) T. Kondo, M. Suda, and M. Teshima, Yakugaku Zasshi, 82, 1252 (1962).
14) The synthetic IV, V, VI, and VII were respectively shown to be identical with natural taxoquinone (mp 212-214°C, $[\alpha]_D$ +340°),[6] 7α-acetoxyroyleanone (mp 212-214.5°C, $[\alpha]_D$ -14°),[7] dehydroroyleanone (mp 166-168.5°C, $[\alpha]_D$ -620°),[7] and horminone (mp 178-180°C, $[\alpha]_D$ -130°)[11] by mixed mp and spectral comparisons (IR and NMR).
15) The IR and NMR spectra of the synthetic VIII and IX were identical with those published[8] for 7-oxoroyleanone (mp 204-205°C) and inuroyleanol (mp 185-187°C, $[\alpha]_D$ +113.9°), respectively.

(Received September 22, 1976)