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ESTABLISHMENT OF THE STRUCTURAL CORRELATION BETWEEN CORIAMYRTIN AND TUTIN

Takuo Okuda and Takashi Yoshida
Faculty of Pharmaceutical Sciences, Kyoto University
Sakyo-ku, Kyoto, Japan

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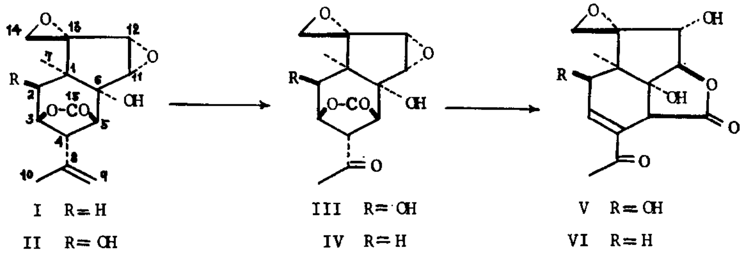
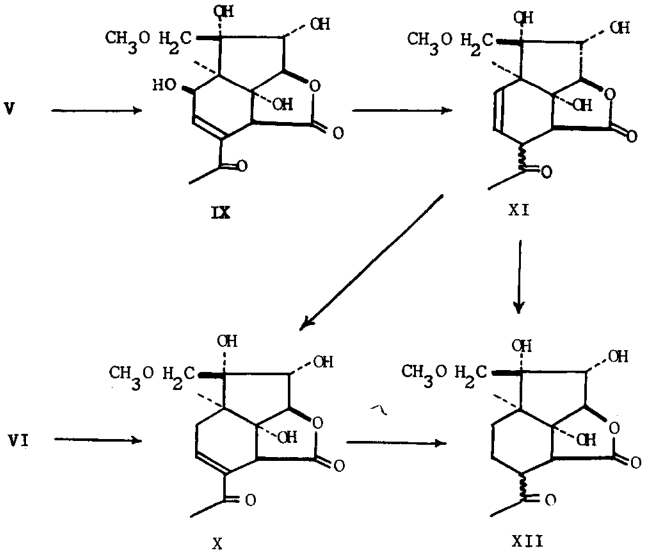
The difference between the structure of coriamyrtin I which was elucidated on the basis of the chemical evidences,1) and the structure of tutin II which was proposed by the X-ray crystallography of α-bromoisotutin and α-bromoisotutinone,2) is at C_2 where the former has no substituent while the latter has a secondary hydroxyl group. This structural correlation has now been established by the identification of the conversion products from coriamyrtin and tutin by reactions involving elimination of the C_2-hydroxyl group of tutin. The absolute configuration of coriamyrtin has also been determined by this experiment since the absolute configuration of tutin was already proved to be represented by II.3)

Initial attempts to convert either tutin, dihydrotutin, or α-bromotutin, to coriamyrtin, dihydrocoriamyrtin, or bromocoriamyrtin directly by removing the C_2-hydroxyl group, or by reducing the C_2-ketone which is produced by oxidation of the C_2-hydroxyl group were unsuccessful. The 2-position in tutin and derivatives, particularly the C_2-ketone, seems sterically hindered and the presence of two epoxides made the desired conversion complicated.

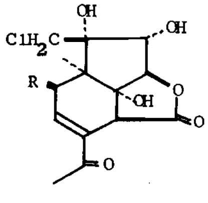
The C_2-hydroxyl group of tutin has finally been eliminated after making it an allylic alcohol as follows: By the ozonolysis of tutin, a norketone III, $C_{14}H_{16}O_7$, m.p. 215° (decomp.)[λ_{max}^{MeOH} 270mμ(logε 1.48), ν_{max} 1750 and 1700 cm^{-1}, 4) N.M.R.5) (in pyridine), 7.51τ(-$COCH_3$)] was obtained. Comparison of the N.M.R. signals of the angular methyl and the epoxide protons of III [8.10τ(C_1-CH_3), AB quartets at 5.24τ and 6.93τ(J=6 c.p.s., C_{14}-H) and at 5.86τ and 6.45τ (J=3 c.p.s., C_{11}-H and C_{12}-H)] with those of tutin3) indicates retention of the steric correlation between epoxides and C_2-hydroxyl group of tutin. The ozonolysis of coriamyrtin yielded the corresponding norketone IV $C_{14}H_{16}O_6$, m.p. 179° (decomp.)[λ_{max}^{MeOH} 270mμ(logε 1.45), ν_{max}1775 and 1709 cm^{-1}, N.M.R.(in pyridine), 7.54τ(-$COCH_3$)]. Tutinnorketone III was isomerized in the presence of a trace of sodium methoxide in methanol to tutinisonorketone V, $C_{14}H_{16}O_7$, m.p. 224° (decomp.)[λ_{max}^{EtOH} 232mμ(logε 3.99) and 320mμ(logε 1.71), ν_{max} 1753 and 1665 cm^{-1}, N.M.R.(in pyridine-d_5), 6.89τ(s., 2H, C_{14}-H), AB quartet at 4.54τ and 4.40τ(J=3 c.p.s., C_{11}-H and C_{12}-H), 5.33τ(d., J=6 c.p.s., C_2-H) and 2.47τ(d., J=6 c.p.s., C_3-H)]. Analogously, coriamyrtinnorketone IV was isomerized to coriamyrtinisonorketone VI, $C_{14}H_{16}O_6$, m.p. 153°(decomp.) [λ_{max}^{EtOH} 232mμ(logε 3.93) and 314mμ(logε 1.65), ν_{max}1750, 1668 and 1638 (medium) cm^{-1}, N.M.R.(in pyridine-d_5), AB quartets at 7.10τ and 7.02τ(J=5 c.p.s., 2H, C_{14}-H) and at 5.05τ and 4.63τ(J=4 c.p.s., C_{11}-H and C_{12}-H), and a vinyl proton at





2.6-2.9τ(C_3-H)]. It is deduced that a double bond, which is conjugated with the C_8-ketone, has been produced at C_3-C_4 in V and VI with the cleavage of the C-O bonding at C_3 of III and IV, and that the C_{11}-C_{12} epoxide has been opened. These two steps of the transformation from both coriamyrtin and tutin are thus found similar in the main part to the reactions which derive α- and β-picrotoxinone from picrotoxinin.6) The infrared absorption of the lactone carbonyl of coriamyrtinisonorketone in chloroform (1775 cm^{-1}) and the comparison of the lactone carbonyl absorptions of V and VI in mineral oil with the δ-lactone absorption of β-picrotoxinone (1740 cm^{-1}) indicate that the lactones in V and VI are γ-lactones and accordingly bridged C_5 and C_{11} in both of V and VI.

The transfer of the lactone group which had been protecting the two epoxides in I, II, III and IV to C_5-C_{11} should lower the stability of the terminal epoxides in V and VI since they are no longer protected from the rear attack. Indeed, the terminal epoxides in V and VI were found to be cleaved readily by dilute hydrochloric acid in acetic acid or water with formation of chlorohydrins, VII, $C_{14}H_{17}O_7Cl$, m.p. 213°(decomp.)[λ_{max}^{MeOH} 232mμ(log ε 3.84), N.M.R.(in DMSO-d_6), AB quartet at 6.02τ and 6.24τ(J=12 c.p.s., 2H, C_{14}-H) and 2.60τ (d., J=6 c.p.s., C_3-H)], and VIII, $C_{14}H_{17}O_6Cl$, m.p. 172-173° [λ_{max}^{MeOH} 231mμ(log ε 3.92), N.M.R. (in DMSO-d_6), 6.23τ(s., 2H, C_{14}-H) and 2.68τ(q., C_3-H)]. The N.M.R. spectra of these products measured in dimethylsulfoxide indicate the presence of two secondary and two tertiary hydroxyl groups in VII, and a secondary and two tertiary hydroxyl groups in VIII showing that the chlorine has substituted at C_{14} of both compounds. These chlorohydrins were obtained in high yields



VII R= OH
VIII R= H

even when hydrogenation of V and VI was done over palladium-charcoal catalyst in acetic acid in the presence of hydrochloric acid. No absorption of hydrogen was observed during this reaction, and the products were fairly resistant to further hydrogenation over platinum catalyst.

By the treatment with methanol in the presence of perchloric acid, V produced a methoxyl derivative IX, $C_{15}H_{20}O_8$ m.p. 246°(decomp.)[ν_{max}1760 and 1668 cm^{-1}, N.M.R.(in DMSO-d_6), 6.70τ(-OCH_3), AB quartet at 6.32τ and 6.59τ(J=10 c.p.s., 2H, C_{14}-H), and 2.61τ(d., J=6 c.p.s., C_3-H)], and VI gave the corresponding methoxyl derivative X, $C_{15}H_{20}O_7$, m.p. 164-165°; $[\alpha]_D^{30}$=+31.3°(c=1.06 in MeOH)[ν_{max}1750, 1660 and 1635(medium) cm^{-1}, N.M.R.(in DMSO-d_6), 6.72τ(-OCH_3), 6.63τ(s., 2H, C_{14}-H), and 2.70τ(q., C_3-H)]. The N.M.R. spectra of these methoxyl derivatives in dimethylsulfoxide indicate presence of two secondary and two tertiary hydroxyl groups in IX, and a secondary and two tertiary hydroxyl groups in X showing that the methoxyl group has been introduced at C_{14} of these compounds.

The methoxide IX was then treated with zinc dust in refluxing acetic acid to give the product XI, $C_{15}H_{20}O_7$, m.p. 183-185°[λ_{max}^{MeOH}283mμ(logε 1.96), ν_{max}1765, 1707 and 1640(shoulder) cm^{-1}, N.M.R.(in DMSO-d_6), 2H at 3.7-4.2τ]. The N.M.R. spectra measured in dimethylsulfoxide shows the presence of a secondary and two tertiary hydroxyl groups. It is considered that the elimination of C_2-hydroxyl group accompanied by the shift of the double bond to C_2-C_3 occurred during this reaction.
Upon hydrogenation over palladium-charcoal catalyst in methanol, this compound absorbed one mole equivalent of hydrogen to give

the saturated product XII, $C_{15}H_{22}O_7$, m.p. 141-143°, $[\alpha]^{25}_D$+65.7° (c=0.205 in MeOH), ν_{max} 1778 and 1705 cm^{-1}. The O.R.D. spectrum of XII showed a positive rotation maximum at 300mμ($[\Phi]^{25}$+4,155°, c=0.3365 in MeOH), and the compound gave a yellow 2,4-dinitrophenylhydrazone, $C_{21}H_{26}N_4O_{10}$, m.p. 236°(decomp.). The saturated product was also obtained from X as crystalls, m.p. 143-145°, $[\alpha]^{30}_D$+62.7°(c=0.407 in MeOH), either by hydrogenation over palladium-charcoal catalyst after absorbing one mole equivalent of hydrogen, or by zinc dust reduction in acetic acid, and the identification with the product XII from XI was done by mixed melting point, and by infrared and O.R.D. spectra.

In addition to the identification of the hydrogenation products thus obtained from X and XI, direct transformation of XI to X was performed by refluxing XI with potassium acetate in ethanol, and the product, m.p. 161-163°, $[\alpha]^{29}_D$+34.5° (c=0.289 in MeOH) was identified with X by mixed melting point and infrared spectra.

The identity of the configuration at C_4 in the original compounds is not proved by this conversion alone. However, the C_4 configuration has already been established by the ether formation between C_6 and C_8 by various reactions such as bromination,[1,7] action of hydrochloric acid and hydriodic acid,[1] and lead tetraacetate oxidation.[8] Accordingly, these identifications of the conversion products from coriamyrtin and tutin establish their correlation as indicated above, and show the absolute configuration of coriamyrtin to be I.

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