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STRUCTURE OF CORIAMYRTIN

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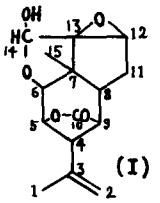
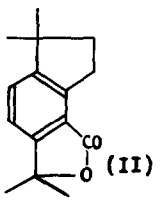
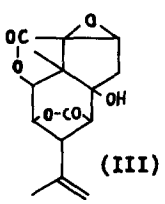
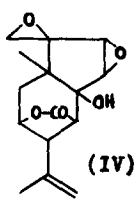
The structure of coriamyrtin, $C_{15}H_{18}O_6$, the main toxic principle of Coriaria japonica, was proposed in 1953 to be (I)[1] based on the structure of coriarialactone (II) obtained by aromatisation of coriamyrtin and also on a comparison of the properties of coriamyrtin with those of picrotoxinin (III)[2]. The presence of a hemiacetal group in (I) was presumed mainly from the formation of an aldehyde group in isocoriamyrtin, $C_{15}H_{18}O_6$, which is obtained by heating coriamyrtin in dilute sulphuric acid. Recent experiments, however, indicate a modified structure (IV) for coriamyrtin.



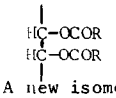






When the hydrogenated derivative, dihydrocoriamyrtin was heated in sodium carbonate solution, a neutral crystalline product, $C_{15}H_{24}O_7$, m.p. 212-214° was obtained. Unlike isocoriamyrtin, this product does not yield the 2,4-dinitrophenylhydrazone nor does it reduce Fehling solution. The presence of the lactone and remarkable increase of hydroxyl absorption are observed in the I.R. spectrum. A triacetate, $C_{21}H_{30}O_{10}$, m.p. 174° (N.M.R. in $CDCl_3$,

[1] T. Kariyone and T. Okuda, J. Pharm. Soc. Japan 73, 930 (1953).
[2] H. Conroy, J. Amer. Chem. Soc. 73, 1889 (1951).

7.83τ, 7.97τ)[+] was formed on acetylation with acetic anhydride in pyridine. The infrared spectrum (ν_{max}^{Nujol} 3430, 1768, 1740 cm^{-1}) of the triacetate shows the presence of a free hydroxyl group in addition to the γ-lactone and the acetyl groups. The increase of four hydrogens and two oxygens in the alkaline hydrolysis product is considered to be due to cleavage of two isolated ether linkages in dihydrocoriamyrtin to form four hydroxyl groups including one tertiary hydroxyl group. Accordingly, the formation of an aldehyde group on isomerisation must be attributed to some other structure than acetal or hemiacetal in coriamyrtin. Two signals at 4.63τ (d, J=5 cps) and 5.32τ (d, J=5 cps) in the N.M.R. of the triacetate may be assigned to  which can be located at C-11∼C-12 or C-5∼C-6.

A new isomer of coriamyrtin, apocoriamyrtin, $C_{15}H_{18}O_6$, m.p. 248° was obtained by dissolving coriamyrtin in concentrated hydriodic acid and then diluting the solution with water. Disappearance of the double bond and the hydroxyl group is indicated by infrared and N.M.R. spectra and by chemical analyses. The N.M.R. spectrum also shows two singlets of methyl groups at 8.49τ and 8.60τ besides the signal of an angular methyl group at 8.86τ (in $CHCl_3$) which seems to correspond to a signal at 8.68τ in coriamyrtin, and the signals of isopropenyl group in coriamyrtin (in $CHCl_3$) at 8.06τ and 5.03τ disappear in apocoriamyrtin, indicating a new ether linkage was formed between C-3 and C-8 by the isomerisation. The same isomer was obtained dissolving coriamyrtin in concentrated hydrochloric acid. In an analogous way picrotoxinin afforded an isomer, $C_{15}H_{18}O_6$, m.p. 324°, which was identified with anhydropicrotin which had been obtained by dehydration of picrotin[3] and has been considered to possess an ether linkage between C-3 and C-8[4]. Debromination of bromocoriamyrtin, $C_{15}H_{17}O_6Br$, was performed in an analogous way to that of bromopicrotoxinin[5] with zinc and ammonium chloride to afford coriamyrtin. Acetylation of coriamyrtin and dihydrocoriamyrtin with acetic anhydride in pyridine resulted in recovery

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[3] P. Horrmann, Ber. 43, 1903 (1910).

[4] J. S. E. Holker, A. Robertson, J. H. Taylor with (in part) K. U. Holker and W. R. N. Williamson, J. Chem. Soc. 2987 (1958).

[5] P. Horrmann, Ber. 45, 2090 (1912).

[+] Nuclear magnetic resonance spectra were determined on a Varian Associates recording spectrometer (A-60) at 60 Mc. with tetramethylsilane internal reference standard (τ=10.00).

of starting material while acetylation of dihydrocoriamyrtin with acetic anhydride in the presence of ferric chloride, like the acetylation of dihydropicrotoxinin[6,7] afforded an amorphous acetate (N.M.R. in $CHCl_3$, 7.95τ). These results suggest the presence of a tertiary hydroxyl group at C-8 and also that the spacial configurations of the cyclohexane ring and the hydroxyl, isopropenyl and γ-lactone groups are identical with those in picrotoxinin[7].

In addition to the chemical evidence previously reported[1], the spectra of isohydrocoriamyrtin, $\lambda_{max}^{H_2O}$ 232mμ(log ε 3.97), ν_{max}^{KBr} 1688 cm^{-1}, N.M.R. (in $CHCl_3$), 0.40τ(s), 3.35τ(d, J=3 cps) indicate the presence of

in this compound. The N.M.R. spectrum also indicates the presence of the angular methyl group at 8.77τ. This suggests that no cleavage of carbon-carbon bonding took place between C-7 and adjacent carbons during the isomerisation of dihydrocoriamyrtin to isohydrocoriamyrtin. The only part of the molecule of isohydrocoriamyrtin where the structure shown above can be present is in the cyclopentane ring with the aldehyde group located at C-14. Isohydrocoriamyrtin gives 2,4-dinitrophenylhydrazone, $C_{21}H_{24}N_4O_8$, m.p. 268°(decompn.), and is hydrogenated to afford hexahydrocoriamyrtin, $C_{15}H_{24}O_6$[8], m.p. 198-199°, which yields diacetate, $C_{19}H_{28}O_7$, m.p. 103-104°. The infrared spectrum of the diacetate (in Nujol, 3455 cm^{-1}) shows the presence of a free hydroxyl group. With sodium borohydride isohydrocoriamyrtin was reduced to a crystalline product, $C_{15}H_{28}O_6$, m.p. 170°, which yielded a diacetate, $C_{19}H_{28}O_7$, m.p. 113-114°, I.R. (in Nujol), 3330 cm^{-1}(OH), N.M.R. (in $CHCl_3$), 7.92τ and an isopropyridene derivative, $C_{18}H_{28}O_6$, m.p. 109-110°, I.R. (in $CHCl_3$), 3425, 1770, 1380, 1340 cm^{-1}, N.M.R. (in pyridine), 8.43τ, 8.53τ, and also consumed one mole equivalent of periodate. Isohydrocoriamyrtin-2,4-dinitrophenylhydrazone also yielded an isopropyridene derivative, $C_{24}H_{28}N_4O_8$, m.p. 272°(decompn.), $\nu_{max}^{CHCl_3}$ 3270 cm^{-1}(NH), N.M.R. (in $CHCl_3$), 8.51τ, 8.53τ. These results indicate that a secondary alcohol is located at C-11 of isohydrocoriamyrtin and its derivatives, and accordingly that the structure of isohydrocoriamyrtin is (V). From

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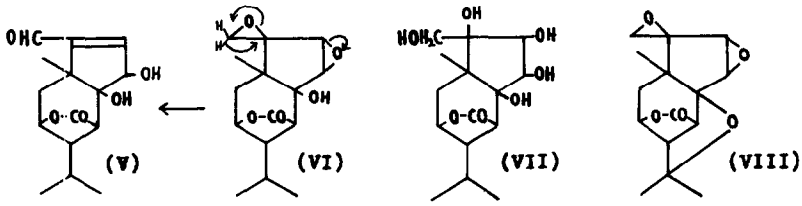
[6] J. C. Benstead, H. V. Brewerton, J. R. Fletcher, M. Martin-Smith, S. N. Slater, and A. T. Wilson, J. Chem. Soc. 1042 (1952).

[7] H. Conroy, J. Amer. Chem. Soc. 74, 491 (1952); 79, 5550 (1957).

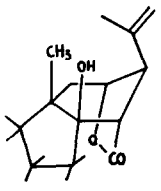
[8] T. Kariyone and N. Kawano, J. Pharm. Soc. Japan 71, 924 (1951).



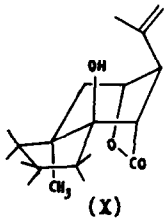
the structure of isohydrocoriamyrtin, the two ether linkages in dihydrocoriamyrtin are considered to be on the cyclopentane ring and at C-14. The ether which formed the aldehyde in isohydrocoriamyrtin is most adequately considered to be an epoxide at C-13~C-14, and the other ether, which must be attributed to the group to give the double bond and the secondary hydroxyl group on isomerisation to isohydrocoriamyrtin, is necessarily also an epoxide at C-11~C-12. The structure of dihydrocoriamyrtin thus expressed by (VI) is satisfactory to explain both acid and alkaline hydrolysis as (VI)⟶(V) and (VI)⟶(VII). Accordingly the structure of coriamyrtin is expressed by (IV). Apocoriamyrtin would then have the structure shown by (VIII). Concerning the structure of the alakline hydrolysis product, possibilities of cleavage of the lactone followed by relactonisation from C-10~C-5 to C-10~C-11 or retroaldol reaction at C-8 to produce an inactive ketone on the cyclopentane ring were also considered. However, the hydrolysis product yielded a monoisopropyridene derivative which consumed one mole equivalent of periodate to indicate that the structures which have the γ-lactone at C-10~C-11 must be excluded. The infrared spectrum of the potassium salt of the further alkaline hydrolysis product of the original hydrolysis product shows complete disappearance of absorptions in the range of 1700-1800 cm^{-1} suggesting the absence of a ketone group in the compound.

Two stereoisomers, cis- (IX) and trans- (X), are possible at C-7 and C-8 in coriamyrtin, but the former is favoured because of the marked distortion of the cyclopentane ring in the latter. Four diastereoisomers can be assigned for each of them when conformations of the two epoxides are considered. Among them, (XI) will be the most probable for the

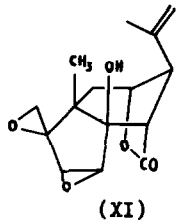
configuration of coriamyrtin since only in this configuration is the γ-lactone located close behind the two epoxides and thus protects them from rearward attack, giving the unusual stability to these epoxides as in derivatives of picrotoxinin[7,8]. The stability of the epoxides in coriamyrtin seems comparable with that of the epoxide in picrotoxinin although any derivative which corresponds to β-bromopicrotoxininic acid[9] which has higher stability is not obtainable from coriamyrtin because it has no oxygen linked with C-6 to form δ-lactone besides being different in the relative location of the lactone and the epoxides with picrotoxinin. The structure of tutin which is a sub-constituent in Coriaria japonica and the main toxic principle in Coriaria species grown in New Zealand has recently been elucidated to be (XIII) or its mirror image as the result of X-ray crystalography.[10,11] The structure (XIII) has been considered preferable for the absolute configuration of tutin because of the analogy to the absolute configuration of picrotoxinin (XII).[12] Concerning the absolute configuration of coriamyrtin, two alternative configurations, (XI) and its mirror image may be considered. Among them (XI) is favoured by the analogy to picrotoxinin. The relationship between (XI) and (XIII) is in accordance with our previous presumption[13] that tutin is hydroxycoriamyrtin.



(IX)



(X)



(XI)

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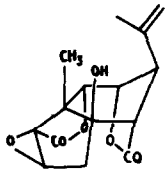
10 B. M. Craven, Nature 1193 (1963).

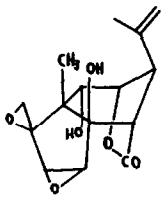
11 M. F. Mackay and A. McL. Mathieson, Tetrahedron Letters 1399 (1963).

12 B. M. Craven, Tetrahedron Letters 21 (1960).

13 T. Okuda, Pharm. Bull. (Tokyo) 3, 185 (1954).



(XII)



(XIII)