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215. Takuo Okuda and Takashi Yoshida*1 : Coriamyrtin. X.*2 Structures of Coriamyrtin and Derivatives produced on the Reactions in Acid and Alkali.*3

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The structure (Ⅲ) is assigned to coriamyrtin on the basis of the formation of apocoriamyrtin (Ⅳ), dihydrocoriamyrtinpentaol (X), isohydrocoriamyrtin (Ⅻ), and other derivatives, and also of the spectral evidences.

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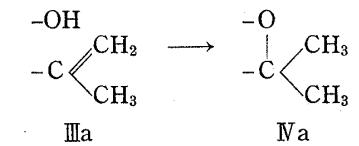
The chemical evidences of the carbon skeleton of coriamyrtin, $C_{15}H_{18}O_5$, the main toxic principle of *Coriaria japonica* A. GRAY, was first provided by the determination of the structure of coriarialactone (I) which is obtained by aromatization of coriamyrtin.[1] On the basis of this structure of the aromatization product, structure (Ⅱ) was proposed to be the most plausible one for coriamyrtin.[2] The presence of a hemiacetal group in Ⅱ was presumed mainly by the result of the isomerization of coriamyrtin and dihydrocoriamyrtin in acid to produce aldehydic isomers, isocoriamyrtin, $C_{15}H_{18}O_5$, and isohydrocoriamyrtin, $C_{15}H_{20}O_5$. The present authors have accumulated evidences to show the complete structure of coriamyrtin to be (Ⅲ).

The nuclear magnetic resonance (NMR) spectrum*4 (in pyridine) of coriamyrtin (Fig. 1) shows signals assignable to the isopropenyl group (8.05 and 5.03τ), the angular methyl group (8.52τ), and the methylene group (8.06~8.26τ, m). The signals at 5.28τ(m), and at 6.61τ (d, J=4 c/s) are attributable to the protons at C_3 and C_5. The isopropenyl signals are substituted in dihydrocoriamyrtin by doublets at 8.91τ (J=6 c/s) and 9.12τ (J=6 c/s) of the isopropyl group. These NMR signals are in accord with the skeleton of coriamyrtin shown by Ⅱ. However, there are two AB quartets in coriamyrtin at 6.92 and 6.69τ (J=4 c/s) and at 6.44 and 5.94τ (J=3 c/s), which are assignable to 2,2-disubstituted epoxide and to 1,2-disubstituted epoxide, respectively, taking the chemical evidences shown later into account.

The location of the hydroxyl group in coriamyrtin is presumed to be at C_6 by the ether formaton between C_6 and C_8 : When coriamyrtin was treated with concentrated hydrochloric acid for a few minutes at room temperature, a new isomer of coriamyrtin, $C_{15}H_{18}O_5$, m.p. 248°, which is named apocoriamyrtin (Ⅳ) was obtained. Disappearance of the double bond and the hydroxyl group is indicated by the infrared (IR) and the NMR spectra and also by the negative response to the bromine water test. The NMR spectrum (in pyridine) shows three methyl signals at 8.66, 8.61 and 8.49τ, while the signals of the isopropenyl group are absent. Two of these three methyl signals are assignable to the methyl groups in the partial structure (Ⅳa) which could be produced by the ring closure between the isopropenyl and the hydroxyl group as shown by Ⅲa→Ⅳa. No reaction occurred when either



Ⅲa Ⅳa

*1 Sakyo-ku, Kyoto (奥田拓男, 吉田隆志).

*2 Part Ⅸ : This Bulletin, **9**, 404 (1961).

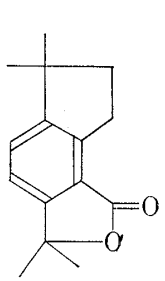
*3 This paper constitutes Part XVI of a series entitled "Studies on the Components of *Coriaria japonica* A. GRAY." A preliminary report of this work has been published : Tetrahedron Letters, **1964**, 439.

*4 NMR spectra were determined on a Varian Associates recording spectrometer (A-60) at 60 Mc. Chemical shifts were recorded in τ values, using tetramethylsilane as the internal reference.

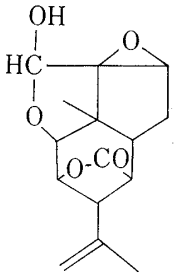
1) T. Kariyone, T. Okuda : Yakugaku Zasshi, **73**, 928 (1953).

2) *Idem* : *Ibid.*, **73**, 930 (1953).

dihydrocoriamyrtin or α-bromocoriamyrtin[3] was treated with hydriodic acid in agreement with this assumption. Apocoriamyrtin was also obtained by an analogous treatment of coriamyrtin with concentrated hydrochloric acid, or by treating coriamyrtin with hot dilute sulfuric acid. Although isocoriamyrtin has been known to be produced by the latter treatment,[4] it is likely that apocoriamyrtin is formed as the main product at the initial stage of the reaction, because the yield of Ⅳ on this treatment increased when the reaction was terminated in a shorter time. The formation of apocoriamyrtin under these reaction conditions would be a proof of spatially nearby location of the hydroxyl group to the isopropenyl group in coriamyrtin.



I



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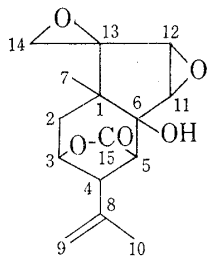

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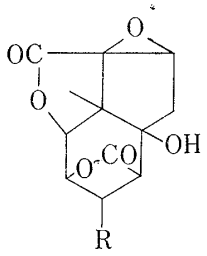
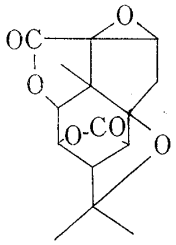
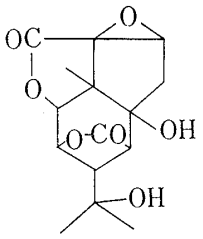


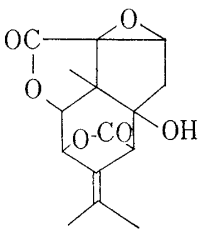
V : R= $CH_2=C(CH_3)-$
XXIII : R= $(CH_3)_2CH-$



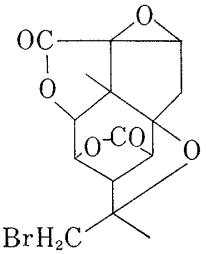
VI



VII



VIII



IX

When picrotoxinin (Ⅴ)[5] was treated with concentrated hydrochloric acid analogously, the ring closure took place to produce an isomer, $C_{15}H_{16}O_6$, m.p. 324° (decomp.), which was identified with anhydropicrotin (Ⅵ) which had been obtained by dehydration of picrotin (Ⅶ), and has been considered to possess an ether linkage between C_6 and C_8.[6] The treatment of picrotoxinin with concentrated hydriodic acid was found to give mixtures of anhydropicrotin and another isomer of picrotoxinin, which is regarded as being neopicrotoxinin (Ⅷ).[7] The increase of the latter product and the decrease of the former product were observed on the prolonged treatment.

The bromination of coriamyrtin has been reported to produce α-bromocoriamyrtin, $C_{15}H_{17}O_5Br$,[3] which lacks the double bond and the hydroxyl group. The NMR spectrum (in $CDCl_3$) of α-bromocoriamyrtin now examined shows signals of two methyl groups on the tertiary carbon at 8.67 and 8.40τ, and an AB quartet which is assignable to the protons of the bromomethyl group at 6.51τ (J=11 c/s) and 6.26τ (J=11 c/s) supporting

3) T. Okuda : This Bulletin, **9**, 379 (1961).
4) T. Kariyone, T. Sato : Yakugaku Zasshi, **50**, 106 (1930).
5) H. Conroy : J. Am. Chem. Soc., **73**, 1889 (1951).
6) J.S.E. Holker, A. Robertson, J.H. Taylor with (in part) K.U. Holker and W.R.N. Williamson : J. Chem. Soc., **1958**, 2987.
7) S.N. Slater : *Ibid.*, **1949**, 806.

the partial structure of α-bromocoriamyrtin presumed previously.[2] The debromination of α-bromocoriamyrtin has been carried out with zinc and ammonium chloride to regenerate coriamyrtin. The bromination of coriamyrtin is thus shown to be analogous to the bromination of picrotoxinin to β-bromopicrotoxinin (IX).[8] Further investigations on the hydroxyl group in coriamyrtin provided additional data which are in accord with the location of the hydroxyl group at C_6: Attempted oxydation of dihydrocoriamyrtin with chromic acid, and acetylation of coriamyrtin and dihydrocoriamyrtin with acetic anhydride in pyridine resulted in recovery of the starting material, while the acetylation of dihydrocoriamyrtin in the presence of ferric chloride, carried out in an analogous way to the acetylation of tertiary hydroxyl group in dihydropicrotoxinin,[9] produced an amorphous acetate which shows the acetyl peak at 7.95τ (3H, s) in the NMR spectrum (in $CHCl_3$).

The ether formation on both the isomerization and bromination, and other properties of the hydroxyl group, coupled with the stereochemical consideration indicate that the hydroxyl group in coriamyrtin is located at C_6, and that the hydroxyl group and the isopropenyl group are located within bonding distance on the same side of the cyclohexane ring as found in picrotoxinin.[9]

A chemical evidence which shows the presence of two oxides in coriamyrtin has been obtained by the alkaline hydrolysis: Dihydrocoriamyrtin was treated with 10% sodium carbonate to produce a water soluble neutral compound, $C_{15}H_{24}O_7$, m.p. 212~214°, which is named dihydrocoriamyrtinpentaol (X). This product did not give the 2,4-dinitrophenylhydrazone nor did it reduce Fehling solution. The presence of the lactone and marked strengthening of the hydroxyl absorption are observed in the IR spectrum (in KBr) at 1767 (shoulder), 1740, and 3460 cm^{-1}. The product X gave a triacetate (XI), $C_{21}H_{30}O_{10}$, m.p. 174~175°, whose NMR spectrum (in pyridine) shows the presence of three acetyl groups by the signals at 8.13τ, 8.08τ, and 7.91τ, while the IR spectrum (in KBr) of this acetate shows the absorption band of hydroxyl group (3540 cm^{-1}) in addition to the lactone (1770 cm^{-1}) and the acetyl (1743 and 1250 cm^{-1}) absorptions. Since three of five oxygens in coriamyrtin are accounted for a lactone and a hydroxyl group, and other two are for oxides, the properties of the hydrolysis product indicate that the hydrolysis occurred at the two ethers, and that each of the two ether oxygens should be separated by more than one carbon in coriamyrtin. This observation coupled with the NMR spectrum of coriamyrtin which lacks the proton attributable to an acetal indicates the absence of either acetal or hemiacetal group in coriamyrtin.

More information concerning the ether linkages in coriamyrtin has been supplied by the inspection of isohydrocoriamyrtin (XII). The NMR spectrum of XII (Fig. 1) exhibits an aldehydic proton at 0.40τ (s) and an olefinic proton at 3.35τ (d, J=3 c/s), while the two AB quartets which were present in dihydrocoriamyrtin (in pyridine, 6.92 and 6.71τ, J=4 c/s, and 6.43 and 5.94τ, J=3 c/s) are absent. The signals attributable to the angular methyl

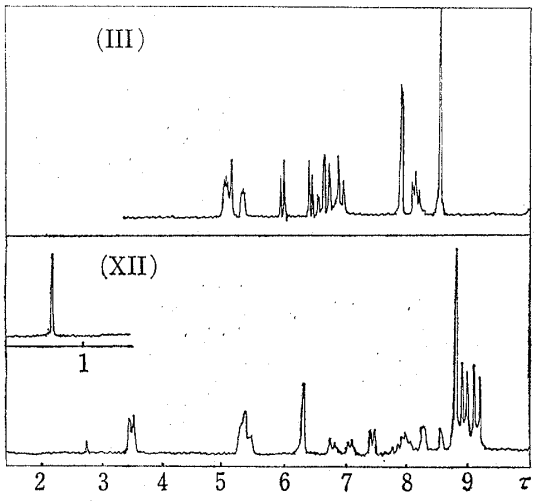
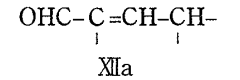


Fig. 1. Nuclear Magnetic Resonance Spectra of Coriamyrtin (III) (in pyridine) and Isohydrocoriamyrtin (XII) (in $CDCl_3$)

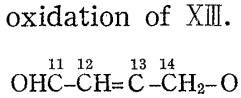
8) H. Conroy: J. Am. Chem. Soc., **74**, 491 (1952).
9) *Idem*: *Ibid.*, **79**, 5550 (1957).

group (8.77τ, s) which appear along with the methyl protons of the isopropyl group (9.11τ, d, J=6 c/s, and 8.91τ, d, J=6 c/s), and a proton which is assignable to C_5-H (7.35τ, d, J=3.5 c/s) indicate that these parts in dihydrocoriamyrtin has been retained on the formation of isohydrocoriamyrtin. The UV spectrum, λ_{max}^{EtOH} 232 mμ (log ε 3.96), and the IR spectrum, ν_{max}^{KBr} cm^{-1}: 1690 and 1615, coupled with the NMR spectum, show the presence of an aldehyde group conjugated with a trisubstituted double bond. Absence of α-hydrogen, and presence of a γ-hydrogen, as shown by the partial structure (XIIIa) are also indicated. Besides the aldehydic carbonyl band, two peaks of the carbonyl band are shown at 1768 and 1744 cm^{-1} in the IR spectrum measured in KBr disk. It might be necessary to confirm whether the latter peak is due to a ketone since XII has been reported to react with two moles of α-methylphenylhydrazine to give a derivative, $C_{29}H_{34}O_3N_4$.[10] However, the following experiments indicate that no other carbonyl group than those of aldehyde and lactone is present in XII. By sodium borohydride reduction of XII, a dihydro-derivative, $C_{15}H_{22}O_5$, m.p. 182~183°, which is named tetrahydrocoriamyrtin (XIII), has been produced. The reduction of the aldehyde to the primary hydroxyl group is shown by the IR and NMR (in pyridine, 5.40τ, diffused singlet, $-CH_2OH$) spectra. Tetrahydrocoriamyrtin gave a diacetate (XIV), $C_{19}H_{26}O_7$, m.p. 113~114°, whose NMR spectrum (in $CHCl_3$) exhibits the proton of $-OCH_2-$ at 5.35τ, a proton assignable to C_{11}-H at 4.58τ, and the acetyl protons at 7.92τ (6H). The IR spectrum (in Nujol) shows a hydroxyl band at 3330 cm^{-1}. An isopropylidene derivative (XV), $C_{18}H_{26}O_5$, m.p. 109~110°, which shows the presence of a hydroxyl group by the IR band at 3425 cm^{-1} (in $CHCl_3$) was also produced from XIII. It is indicated by these observations of the derivatives that three hydroxyl groups are present in XIII, and accordingly that there are two hydroxyl groups in XII. Isohydrocoriamyrtin-2,4-dinitrophenylhydrazone (XVI) also yielded an isopropylidene derivative (XVII), $C_{24}H_{28}O_8N_4$, m.p. 272° (decomp.). The possibility that an additional carbonyl group is present in XII is thus excluded. Tetrahydrocoriamyrtin consumed one-mole equivalent of periodate, indicating that two hydroxyl groups are vicinal to each other. Accordingly, a hydroxyl group should be located adjacent to C_6-OH in XII.



XIIIa

On the periodate oxidation of XIII, the product (XVIII), $C_{15}H_{20}O_5$, m.p. 202~203° (decomp.), whose IR spectrum shows absorptions of α,β-unsaturated aldehyde at 2830, 1660, and 1615 cm^{-1} was isolated. It is suggested by the UV absorption, λ_{max}^{EtOH} mμ (log ε): 250 (4.01) that the conjugated double bond might be exocyclic. The NMR spectrum shows an aldehydic proton at -0.20τ (d, J=6.5 c/s), and an olefinic proton at 4.12τ (q, J_1=6.5 c/s, J_2=2 c/s). The oxidation product XVIII gave the 2,4-dinitrophenylhydrazone, $C_{21}H_{24}O_8N_4$, m.p. 236° (decomp.), UV λ_{max}^{EtOH} mμ (log ε): 382 (4.32). The IR spectrum of XVIII shows absence of the ketone which is expected to be produced by the periodate oxidation of XIII. Accordingly, the formation of a hemiketal in XVIII is presumable. The analysis of the spin-spin coupling of C_{11}-H~C_{12}-H and C_{12}-H~C_{14}-H in XVIII was made with the aid of nuclear magnetic double resonance as shown in Table I. These results are consistent with the partial structure (XVIIIa).

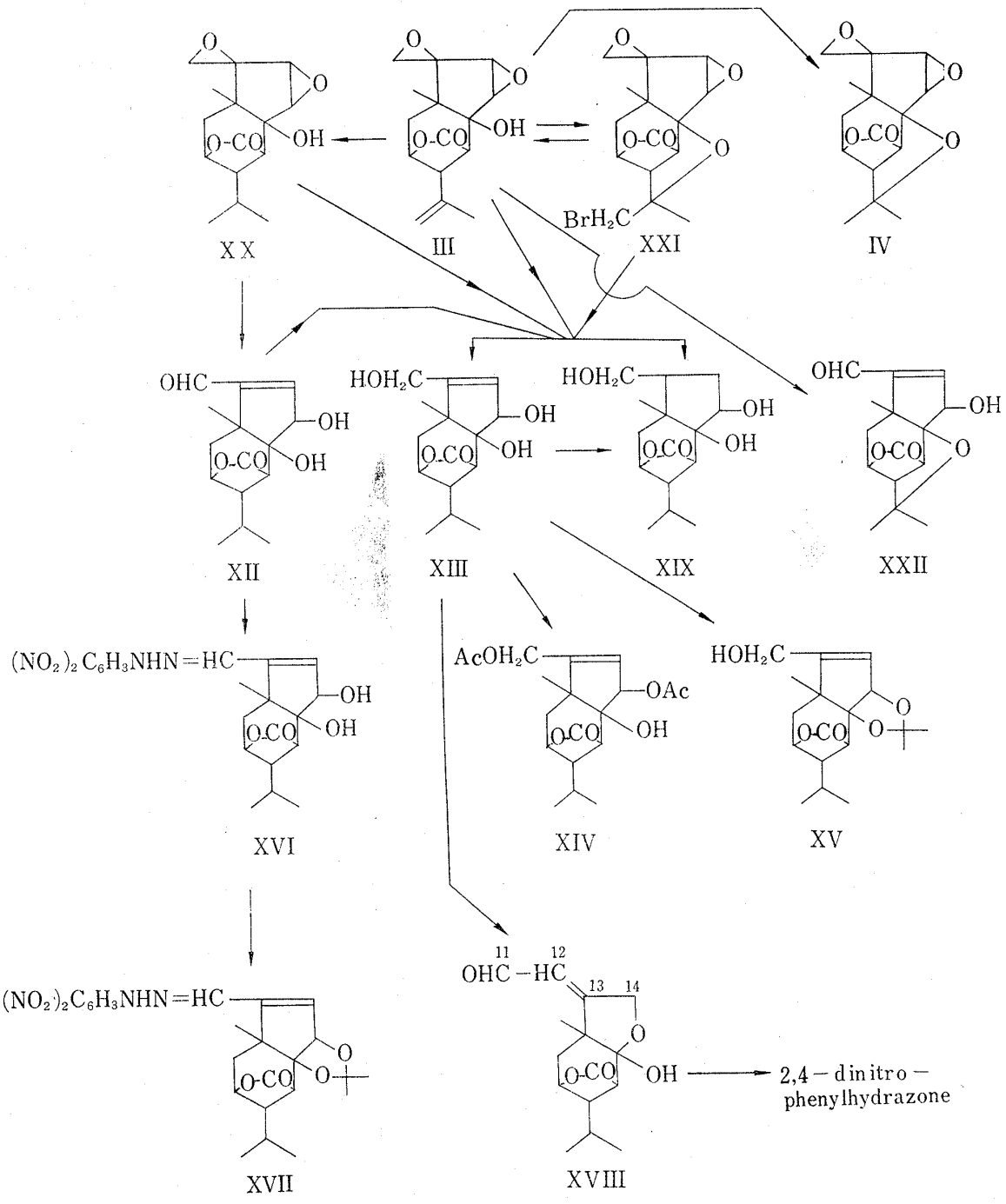


XVIIIa

Catalytic hydrogenation of isohydrocoriamyrtin was formerly reported to yield hexahydrocoriamyrtin, $C_{15}H_{24}O_5$, m.p. 199~200°.[11] This product has been found by thin-layer chromatography to be composed of two constituents, and these have been isolated by elution chromatography through an alumina column. One constituent, $C_{15}H_{22}O_5$, m.p. 183~184°, whose IR and NMR spectra show the presence of a double bond, has

10) T. Kariyone, K. Kashiwagi: Yakugaku Zasshi, **54**, 9 (1934).
11) T. Kariyone, N. Kawano: *Ibid.* **71**, 924 (1951).

been found to be identical with tetrahydrocoriamyrtin in all respects. Another constituent (XIX), $C_{15}H_{24}O_5$, m.p. 165~166°, has been shown by the IR and NMR spectra to be saturated. The structural correlation of XIX to XIII has been proved by catalytic hydrogenation of the latter. Up to about half a mole equivalent of hydrogen was slowly absorbed, and then no more uptake of hydrogen was observed. The product was identified with "hexahydrocoriamyrtin," and then was fractionated by chromatography on alumina into two constituents which were identified as XIII and XIX, respectively. This result indicates that XIX is the saturated derivative of XIII. Although the IR spectrum of XIX in Nujol shows the carbonyl absorption at 1740 cm^{-1}, it is attributable to the γ-lactone on the basis of the above result. When equal amounts of XIII and XIX were dissolved together in ethanol, and then the solvent was distilled, the residue was



found to be identical with "hexahydrocoriamyrtin." These results, combined with the fact that the melting point of "hexahydrocoriamyrtin" is higher than either one of the constituents indicate that "hexahydrocoriamyrtin" could be a molecular compound composed by 1:1 ratio of XIII and XIX. "Hexahydrocoriamyrtin" was also obtained when coriamyrtin, dihydrocoriamyrtin, or α-bromocoriamyrtin were treated with Raney nickel in boiling ethanol, although it happened sometimes in these experiments that the product was composed mostly of tetrahydrocoriamyrtin. The formation of "hexahydrocoriamyrtin" by both procedures shown above and the hydrogenation of XII, in addition to the spectral evidences would be indicative of retention of the carbon skeleton of coriamyrtin in XII.

It is now considered that the only part in the molecule of XII where the partial structure XIIa can be present is $C_{11}\sim C_{14}$ with the aldehyde group located at C_{14}. Since one hydroxyl group in XII has been shown to be located adjacent to C_6-OH, the former will be at C_{11}. The structure of isohydrocoriamyrtin thus expressed by XII is consitent with all data shown above. It is observed in the NMR spectrum of XII (in $CDCl_3$) that one of the methylene protons shows a large downfield shift to 6.89τ (double doublet, J_1 =15 c/s, J_2=4 c/s), while another proton of the methylene group is shown at 8.38τ as a single doublet (J=15 c/s). The downfield shift of one proton will be attributable to the presence of the carbonyl group at C_{14}. The secondary splitting of this lower signal will be due to the spin-spin coupling with C_3-H.

The location of the methylene group at C_2 and the couplings within each set of the AB quartets in dihydrocoriamyrtin have been confirmed by the spin-spin decoupling technic. This technic was also applied to apocoriamyrtin to prove the coupling of the

Table I. Nuclear Magnetic Double Resonance Data

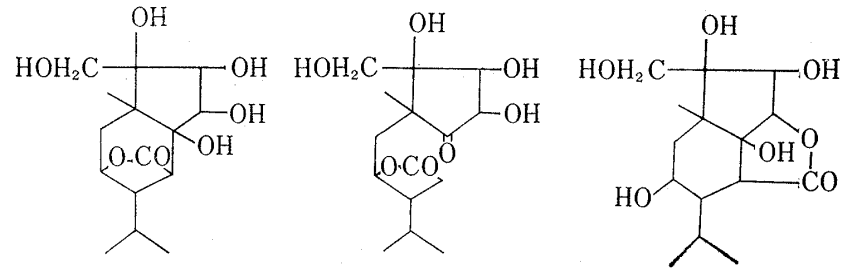
Compound solvent	Irradiated proton (τ)	Observed proton (τ)	Multiplicity change
(XVIII)	12-H 4.14	11-H −0.20	d ⟶ s
$CDCl_3$		14-H 5.33	d ⟶ s
	11-H −0.20	12-H 4.14	q ⟶ ds
	14-H 5.33	12-H 4.14	q ⟶ d
(XX)	2-H 8.33	3-H 5.32	m ⟶ d
pyridine	14-H 6.93	14-H 6.72	d ⟶ s
	11-H 6.43 (or 12-H)	12-H 5.94 (or 11-H)	d ⟶ s
(IV)	3-H 5.23	4-H 6.98	*a*)
pyridine	4-H 6.98	5-H 6.51	dd ⟶ ds
	14-H 6.95	14-H 6.73	d ⟶ s
	11-H 6.41 (or 12-H)	12-H 6.03 (or 11-H)	d ⟶ s

s: singlet d: doublet q: quartet ds: diffused singlet dd: diffused doublet
a) One of the peaks centered in the quartet was markedly sharpened.

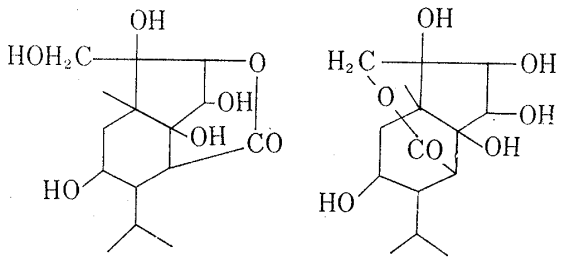
AB quartets (Table I). Since the structure of isohydrocoriamyrtin XII indicates that two oxides in coriamyrtin are bound with four carbons at $C_{11}\sim C_{14}$, and that one oxide would be the terminal epoxide at $C_{13}\sim C_{14}$, which is shown as the AB quartet at the higher field in the NMR spectrum of coriamyrtin, another AB quartet at lower field will be assigned to the epoxide at $C_{11}\sim C_{12}$. This location of the latter epoxide is also supported by the NMR spectra (in pyridine) of dihydrocoriamyrtinpentaol which shows an AB quartet at 5.17τ (J=6 c/s) and 4.76τ (J=6 c/s), and of the triacetate XI which shows downfield shift of the AB quartet to 4.69τ (J=6 c/s) and 4.12τ (J=6 c/s). The structure

of dihydrocoriamyrtin thus elucidated to be (XX) is compatible with both the acid catalyzed isomerization to XII, and the alkaline hydrolysis to the pentaol X. Accordingly, the structure of coriamyrtin is expressed by the formula III. Apocoriamyrtin and α-bromocoriamyrtin would then have the structure (IV) and (XXI), respectively, although alternative isomeric structures of XXI which will be discussed in a subsequent paper can not be disregarded at present. The structure of isocoriamyrtin is shown by XXII based on the indications of the NMR spectrum (in $CDCl_3$) which shows three singlets of methyl protons at 8.58, 8.55 and 8.42τ, and the absence of the isopropenyl group to indicate the ether formation at $C_6 \sim C_8$, and also signals at 0.32τ (s), 3.19τ (d, J=3 c/s), and 5.32τ (d, J=3 c/s), which show that the partial structure XIIa will be present in isocoriamyrtin.

The structure of dihydrocoriamyrtinpentaol could be shown by (Xa) if no other reaction than the hydrolysis of the two epoxides in XX occurred during the formation of X. The possibility that the retroaldol cleavage took place at $C_5 \sim C_6$ to produce the



Xa Xb Xc



Xd Xe

cyclopentanone (Xb) in an analogous way to the retroaldol cleavage of dihydropicrotoxinin[12] is excluded since the IR spectrum of the potassium salt, which was obtained by further hydrolysis of X shows no carbonyl absorption besides new peaks at 1570 cm^{-1} and 1400 cm^{-1}. However, structure (Xc) which could be produced by the opening of the lactone during the hydrolysis followed by relactonization with C_{11}-OH is also assignable to the pentaol, while structures (Xd) and (Xe), which could be formed if the relactonization occurred with C_{12}-OH or C_{14}-OH, are incompatible with the lactone carbonyl absorption of the triacetate XI.

The stereochemistry of coriamyrtin and problems of its derivatives will be discussed in the subsequent papers.

Experimental*5

Apocoriamyrtin (IV)——a) To finely ground crystals of coriamyrtin (III) (100 mg.), conc. HI (1 ml., sp.

*5 Melting points are uncorrected. Specific rotations were recorded with a Rex Photoelectric Polarimeter. Neutral alumina (Woelm), and silica gel G acc. to Stahl (E. Merck) were used for elution chromatography and thin-layer chromatography, respectively.

12) M. Sutter, E. Schlittler : Helv. Chim. Acta, **32**, 1855, 1860 (1949).

gr. 1.7) was added. Complete dissolution was effected immediately. Water (5 ml.) was added 3 min. later, and after standing 4 hr., crystals were filtered. The filtrate was extracted with ether, and the organic phase was washed with $Na_2S_2O_3$ and water successively. After drying over Na_2SO_4, the solvent was distilled to give an additional crop of crystals. Total yield: 70 mg. Recrystallization from EtOH afforded colorless needles, m.p. 248°. *Anal.* Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.58; H, 6.35. $NMR^{pyridine}_{max}(\tau)$: 8.66(s), 8.61(s), 8.49(s) ($(CH_3)_2C$–O–, CH_3–$\overset{|}{C}$–); 8.36(d), 8.22(diffused doublet) (–CH_2–); AB q, 6.95, 6.73(J=4 c/s) (terminal epoxide); ABq, 6.41, 6.03 (J=3 c/s) (C_{11}–C_{12} epoxide).

When the solution of (Ⅲ) (200 mg.) in conc. HI (2 ml.) was left to stand for 2hr., and then treated in analogous way as above, 66 mg. of crude crystals were obtained. After recrystallization from EtOH, the product was identified with (Ⅳ) obtained above.

b) A suspension of finely ground crystals of coriamyrtin (0.5 g.) in conc. HCl (5 ml.) was vigorously stirred for 1 hr., and then 2.5 ml. of conc. HCl was added. Stirring was continued for an additional 2 hr. A small amount of insoluble material was filtered, and water (20 ml.) was added to the filtrate. The diluted filtrate was extracted with ether, and the dried extract was evaporated to give a viscous residue which was dissolved in a small amount of boiling EtOH. The solution was concentrated to yield colorless crystals which were collected (90 mg.), and recrystallized from EtOH to give colorless needles, m.p. 249~250°. Identification with the product obtained in a) was done by mixed fusion and IR spectra.

c) To finely ground coriamyrtin (1g.), 1% H_2SO_4 (350 ml.) was added, and the suspension was heated on a boiling water-bath. The crystals were dissolved within 1 hr., and the solution was neutralized with NaOH, concentrated to 50 ml. *in vacuo*, and extracted with ether. The extract was dried over $MgSO_4$, and was distilled to give an oily residue which deposited colorless crystals on standing. The crystals were collected (0.1 g.), and recrystallized from EtOH to give pure crystals of (Ⅳ). The oily filtrate was chromatographed on an alumina column (1×25 cm.) using $CHCl_3$ as eluant to give *iso*-coriamyrtin (XXⅡ).

Anhydropicrotin (VI) and Neopicrotoxinin (VIII)——a) To finely ground picrotoxinin (V) (200 mg.), conc. HI (1.2 ml.) was added. With vigorous stirring, complete dissolution was effected in a few minutes. Water (5 ml.) was added 10 min. later, and the diluted solution was left to stand for 1 hr. to complete deposition of crystals which were collected by filtration (130 mg.). Recrystallization from EtOH afforded colorless crystals of (Ⅵ), m.p. 324° (decomp.), which were identified by mixed fusion and IR spectra with anhydropicrotin obtained from picrotin.[6] *Anal.* Calcd. for $C_{15}H_{16}O_6$: C, 61.60; H, 5.50. Found: C, 61.66; H, 5.59.

The mother liquor was extracted with ether, and the organic layer was washed with $Na_2S_2O_3$ solution and then with water. The dried extract was evaporated to give a crystalline residue which was recrystallized from acetone–petroleum benzine to give colorless crystals of (Ⅷ), m.p. 210~213° (26 mg.). *Anal.* Calcd. for $C_{15}H_{16}O_6$: C, 61.60; H, 5.50. Found: C, 61.48; H, 5.73. $NMR^{pyridine}_{max}(\tau)$: 8.56(s), 8.23(s), 8.20(s) ($(CH_3)_2C$=, CH_3–$\overset{|}{C}$–); 7.65(d, J=14 c/s), 6.86(q, J_1=14 c/s, J_2=3 c/s) (–CH_2– at C_{11}); 6.37(s, C_5–H); 5.86(d, J=3 c/s, C_{12}–H); 5.16(d, J=4 c/s, C_2–H); 4.22(d, J=4 c/s, C_3–H).

The treatment of picrotoxinin (1.0 g.) with conc. HI (5 ml.) for 2 hr. yielded 220 mg. of precipitate which on recrystallization from EtOH gave 160 mg. of (Ⅵ). By extraction of the mother liquor with ether, 300 mg. of crude crystals were obtained, and were recrystallized from EtOH–ether to give pure crystals of (Ⅷ).

b) Finely ground picrotoxinin (0.50 g.) was stirred vigorously with conc. HCl (15 ml.). The effected solution deposited crystalline precipitate whose amount increased slowly. The precipitate was filtered 1.5 hr. later. The filtrate was allowed to stand for 2 hr., water (20 ml.) was added, and then left to stand overnight to produce white precipitate which was filtered and combined with the first crop. Recrystallization from EtOH afforded colorless crystals, m.p. 324° (decomp.), which were identified with (Ⅵ) by mixed fusion and IR comparison.

Bromination of Coriamyrtin and Debromination of α-Bromocoriamyrtin——Bromine was added to the solution of coriamyrtin (1.0 g.) in hot water (500 ml.) until the bromine color persisted. After cooling, the precipitate was filtered, and recrystallized from EtOH to give colorless crystals of (XXⅠ), m.p. 220° (0.75 g.). *Anal.* Calcd. for $C_{15}H_{17}O_5Br$: C, 50.43; H, 4.76. Found: C, 50.25; H, 4.91. $NMR^{CDCl_3}_{max}(\tau)$: 8.67(s), 8.40 (s) (CH_3); AB q, 7.17, 6.95(J=4 c/s, epoxide); AB q, 6.71, 6.32(J=3 c/s, epoxide); AB q, 6.51, 6.26(J=11 c/s, –CH_2Br).

α-Bromocoriamyrtin (XXⅠ) (1.0 g.) was suspended in boiling EtOH (20 ml.), and 20% NH_4Cl solution in water (1.5 ml.) was added. Zinc powder (0.5 g.) was added in small portions to the boiling mixture. The equal amount of NH_4Cl solution was added 30 min. later, and zinc powder (0.5 g.) was added again in small portions. After boiling for one additional hour, the solid was filtered. Recrystallization from EtOH provided needles, m.p. 226° (0.5 g.), which were identified with coriamyrtin.

Dihydrocoriamyrtinpentaol (X)——A suspension of finely powdered coriamyrtin (1.0 g.) in 10% Na_2CO_3 (170 ml.) was stirred in N_2 atmosphere at 80° for 45 min. The resulting solution was cooled, and stirred with Amberlite IR-120(H-form, 200 ml.). The resin was filtered and the filtrate was evaporated *in vacuo* to give yellow oily residue which was crystallized from EtOH–EtOAc. Recrystallization from the same solvent mix-

ture provided colorless prisms of (X), m.p. 212~214° (262 mg.). *Anal.* Calcd. for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.99; H, 7.67. $[\alpha]_D^{20}$ +19° (c=0.9, H_2O). IRν_{max}^{KBr} cm^{-1}: 3460, 1767(shoulder), 1740.

Dihydrocoriamyrtinpentaol-triacetate (XI)——Finely powdered dihydrocoriamyrtinpentaol (95 mg.) in the mixture of Ac_2O (2 ml.) and pyridine (2 ml.) was allowed to stand at room temperature overnight. The resulting solution was poured into ice water, the white crystalline mass was collected, and washed with ice water. Colorless needles of XI, m.p. 174~175° (80 mg.) were obtained on recrystallization from aqueous EtOH. *Anal.* Calcd. for $C_{21}H_{30}O_{10}$: C, 56.99; H, 6.83. Found: C, 57.30; H, 7.07. $[\alpha]_D^{15}$ +72.4° (c=0.44, $CHCl_3$). IRν_{max}^{KBr} cm^{-1}: 3540(OH); 1770(γ-lactone); 1743, 1250(acetyl). $\nu_{max}^{CHCl_3}$ cm^{-1}: broad band, peaks at 1772, 1753, 1742. NMR$_{max}^{pyridine}(\tau)$: 8.92 (d, J=6 c/s, 6H, $(CH_3)_2$ CH–); 8.32 (CH_3–$\overset{|}{C}$–);8.13, 8.08, 7.91(AcO×3); 5.62 (s, $-CH_2O-$); ABq, 4.69, 4.12$\left(\text{J=6 c/s.-}\overset{|}{C}\text{-CH-CH-}\overset{|}{C}\text{-}\right)$; 4.05(m, >C<u>H</u>–OAc).

Hydrolysis of Dihydrocoriamyrtinpentaol (X)——A solution of (X) (5 mg.) in methanolic 0.5*N* KOH (0.08 ml.) was refluxed in a boiling water-bath for 30 min. After cooling, the solvent was removed by lyophilization to provide white solid potassium salt. IRν_{max}^{KBr} cm^{-1}: 1570, 1400 ($-COO^-$).

Isohydrocoriamyrtin (XII)——A suspension of finely ground dihydrocoriamyrtin (XX) (2 g.) in 1.5% H_2SO_4 (700 ml.) was heated in a boiling water-bath for 15 hr. The resultant solution was neutralized with NaOH and concentrated *in vacuo* to 300 ml., and extracted with ether. The dried extract was evaporated to provide an oily residue which was crystallized from EtOH-H_2O. Recrystallization from the same solvent mixture afforded prisms, m.p. 148~149° (990 mg.). *Anal.* Calcd. for $C_{15}H_{20}O_5$: C, 64.29; H, 7.14. Found: C, 64.36; H, 7.18. $[\alpha]_D^{15}$+64.9° (c=0.49, $CHCl_3$). UVλ_{max}^{EtOH} mμ(log ε): 232(3.96). IRν_{max}^{KBr} cm^{-1}: 3420(OH); 1768, 1744 (γ-lactone); 1690, 1615(α,β-unsaturated aldehyde).

Tetrahydrocoriamyrtin (XIII)——A solution of $NaBH_4$ (25 mg.) in MeOH (5 ml.) was added in portions to a solution of (XII) (154 mg.) in MeOH (15 ml.). After standing 24 hr. at room temperature, the mixture was acidified with AcOH, and evaporated *in vacuo*. The residue was taken up with water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4, and evaporated to yield a crystalline residue. Recrystallization from MeOH afforded colorless needles, m.p. 182~183° (105 mg.). *Anal.* Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.74; H, 8.09. $[\alpha]_D^{25}$+108.7° (c=0.6, dioxane). IRν_{max}^{KBr} cm^{-1}: 3400, 3270(OH); 1765(γ-lactone), 1650 (double bond). NMR$_{max}^{pyridine}(\tau)$: 5.40(diffused singlet, $-CH_2OH$); 3.72(m, C_{12}–H).

Diacetyltetrahydrocoriamyrtin (XIV)——Tetrahydrocoriamyrtin (50 mg.) was acetylated with Ac_2O (0.3 ml.) and pyridine (0.3 ml.). The acetate was recrystallized from ligroin to afford prisms, m.p. 113~114° (25 mg.). *Anal.* Calcd. for $C_{19}H_{26}O_7$: C, 62.25; H, 7.15. Found: C, 62.30; H, 7.16. $[\alpha]_D^{25}$+208.7° (c=0.62, dioxane). IRν_{max}^{Nujol} cm^{-1}: 3330(OH); 1740, 1245, 1220(AcO). NMR$_{max}^{CHCl_3}(\tau)$: 7.92(s, AcO×2); 5.35(diffused singlet, $-CH_2OAc$); 4.58(diffused doublet, C_{11}–H).

Isopropylidenetetrahydroncoriamyrtin (XV)——A solution of tetrahydrocoriamyrtin (50 mg.) in acetone containing a drop of conc. H_2SO_4 was stirred with anhydrous $CuSO_4$ (40 mg.) for 5 days at room temperature, and then refluxed for 20 hr. Filtered solution was neutralized with Na_2CO_3, and evaporated *in vacuo* to yield an oily residue which was chromatographed on a column of alumina (1.5×10 cm.). The acetonide was eluted by $CHCl_3$, and was recrystallized from petr. benzine to give colorless needles, m.p. 109~110°. *Anal.* Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.08; H, 8.35. IR$\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 1770, 1620, 1380, 1340. NMR$_{max}^{pyridine}(\tau)$: 8.63(s), 8.53(s), 8.43(s) $\left(CH_3\text{-}\overset{|}{C}\text{-}, (CH_3)_2C\langle^{O-}_{O-}\right)$.

Isohydrocoriamyrtin-2,4-dinitrophenylhydrazone-acetonide (XVII)——A solution of isohydrocoriamyrtin-2,4-dinitrophenylhydrazone (50 mg.) in acetone (20 ml.) containing a drop of conc. H_2SO_4 was stirred with anhydrous $CuSO_4$ for 2 days. The solution was neutralized with Na_2CO_3, and filtered. The solvent was removed from the filtrate, and the crystalline residue was recrystallized from acetone-EtOH to give yellow needles, m.p. 272° (decomp.) (42 mg.). *Anal.* Calcd. for $C_{24}H_{28}O_8N_4$: C, 57.59 H, 5.64. Found: C, 57.42; H, 5.59. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3270(NH); 1766(γ-lactone); 1340(CH_3). NMR$_{max}^{CHCl_3}(\tau)$: 8.54(s), 8.51(s), 8.47(s) $\left((CH_3)_2C\langle^{O-}_{O-}, CH_3\text{-}\overset{|}{C}\text{-}\right)$.

Oxidation of Tetrahydrocoriamyrtin (XIII) with Sodium Metaperiodate——A solution of 0.25*M* $NaIO_4$ (2 ml.) was added to a solution of (XIII) (77 mg.) in aqueous EtOH (40%, 3 ml.). After standing at room temperature for 24 hr., crystals were collected. Recrystallization from benzene afforded colorless needles of (XVIII), m.p. 202~203° (decomp.) (50 mg.). The filtrate was neutralized with $NaHCO_3$, concentrated *in vacuo* to 3 ml., and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over $MgSO_4$, and evaporated to yield an additional crop of (XVIII), m.p. 202~203° (decomp.) (12 mg.). *Anal.* Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.56; H, 7.20. UVλ_{max}^{EtOH} mμ(log ε): 250(4.01). IRν_{max}^{KBr} cm^{-1}: 3300(OH); 2830, 1660, 1615(α,β-unsaturated aldehyde); 1768(γ-lactone). NMR$_{max}^{CDCl_3}(\tau)$: 9.07(d, J=6 c/s), 8.9(d, J=6 c/s) (iso-Pr.); 8.48(s, $CH_3\text{-}\overset{|}{C}\text{-}$), 5.3(d, J=2 c/s, $-CH_2O-$); 4.12(q, J_1=6.5 c/s, J_2=2 c/s), –0.20(d, J=6.5 c/s, $-\overset{|}{C}$=CH–CHO).

The 2,4-dinitrophenylhydrazone was obtained by adding a solution of the reagent in aqueous EtOH containing sulfuric acid to the ethanolic solution of (XVIII). Recrystallization from EtOH yielded orange needles, m.p. 236° (decomp.). *Anal.* Calcd. for $C_{21}H_{24}O_8N_4$: C, 54.78; H, 5.25; N, 12.17. Found : C, 54.85; H, 5.32; N, 12.07. UV λ_{max}^{EtOH} mμ(log ε) : 382(4.32). IR ν_{max}^{KBr} cm^{-1} : 3450, 3250(OH, NH); 1741(1784 cm^{-1} when measured in $CHCl_3$, γ-lactone).

Hexahydrocoriamyrtin——a) Isohydrocoriamyrtin (XII) (200 mg.) was hydrogenated over previously reduced PtO_2 (20 mg.) in EtOH to absorb 1.87 mole equivalent of H_2 during 4 hr. The catalyst was filtered, washed with EtOH, and the filtrate combined with the washing was evaporated *in vacuo*. The residue was recrystallized from aqueous EtOH to provide colorless prisms, m.p. 200~201° (100 mg.). *Anal.* Calcd. for $C_{30}H_{46}O_{10}$: C, 63.58; H, 8.18. Found : C, 63.41; H, 8.40. IR ν_{max}^{Nujol} cm^{-1} : 3410, 1770, 1220, 1190, 1170, 1125, 1060, 1030, 920. This product showed two spots on the thin-layer chromatography when developed with EtOAc–petr. benzine (9:1) using I_2 as the coloring indicator.

b) A solution of coriamyrtin (500 mg.) in EtOH (100 ml.) was refluxed with Raney nickel W-2[13] (5 g.) for 7 hr. The catalyst was filtered, washed with EtOH, and the filtrate combined with the washing was evaporated to yield an oily residue which was crystallized from petr. benzine. Recrystallization from EtOH–petr. benzine afforded colorless needles, m.p. 200~201°, which were identified with the product of a) by mixed fusion and IR comparison (100 mg.).

c) A solution of dihydrocoriamyrtin (XX) (900 mg.) in EtOH (250 ml.) was refluxed with Raney nickel W-2 (9 g.) for 7 hr. After filtration of the catalyst and distillation of the solvent, the product was crystallized from petr. benzine and then recrystallized from EtOH–petr. benzine to provide colorless needles, m.p. 199~200°, which were identified with the product of a) and b) (220 mg.).

d) α-Bromocoriamyrtin (300 mg.) was treated with Raney nickel W-2 (5 g.) for 8 hr. in an analogous way as described above, and the product was recrystallized from acetone–petr. benzine to provide crystals which were identified with the product of a)~c).

Isolation of (XIII) and (XIX) from "Hexahydrocoriamyrtin"——"Hexahydrocoriamyrtin" (130 mg.) was dissolved in warm acetone, and the solution was poured on an alumina column (1.5×25 cm.). Initial eluant was EtOAc–petr. benzine (9:1), and the ratio of EtOAc was gradually increased. Fractions eluted with EtOAc–petr. benzine (95:5) provided crystals which were recrystallized from acetone–petr. benzine to afford colorless prisms of (XIX), m.p. 165~166° (42 mg.). *Anal.* Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found : C, 63.18; H, 8.48. IR ν_{max}^{Nujol} cm^{-1} : 3400, 3300(OH); 1740(lactone). NMR $_{max}^{pyridine}(\tau)$: 7.20(d, J=4 c/s, C_5–H), 5.93(m, C_{14}–H×2), 5.34(m, C_3–H).

The fraction eluted with EtOAc–petr. benzine (98:2) yielded crystals which were recrystallized from $CHCl_3$–hexane to afford colorless crystals, m.p. 175~176° (35 mg.). This product was identified with tetrahydrocoriamyrtin (XIII) by mixed fusion and IR comparison.

"Hexahydrocoriamyrtin" from (XIII) and (XIX)——Tetrahydrocoriamyrtin (4 mg.) and the saturated product (XIX) (4 mg.) were dissolved in warm EtOH (0.5 ml.), and the solvent was removed to give a residue which was recrystallized from petr. benzine to afford crystals, m.p. 199~200°. This product was identified with "hexahydrocoriamyrtin" by mixed melting point and IR spectra.

Hydrogenation of Tetrahydrocoriamyrtin (XIII)——Tetrahydrocoriamyrtin (55 mg.) was hydrogenated over previously reduced PtO_2 (10 mg.) in AcOH (15 ml.) to absorb *ca.* half a mole equivalent of hydrogen within 4.5 hr. The filtered solution was evaporated *in vacuo*, and the residue was recrystallized from acetone–petr. benzine to yield crystals, m.p. 198~199° (36 mg). This product was identified with "hexahydrocoriamyrtin" by IR comparison and mixed fusion. Chromatographic separation carried out as above provided (XIII) and (XIX).

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13) R. Mozingo : "Organic Syntheses," **21**, 15 (1941).