UDC 581.19 : 582.763

59. **Takuo Okuda** : Coriamyrtin. VIII.[*2] Hydrogenation of Coriamyrtin.[*3]

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Coriamyrtin structure which has the same carbon skeleton as picrotoxinin[1] including an isopropenyl group was presented by Kariyone and Okuda[2] in a previous paper of this series, mainly on the basis of the structure of coriaria-lactone,[3] the aromatic derivative obtained from coriamyrtin by heating it with hydriodic acid in the presence of red phosphorus. Transfer of the double bond of the isopropenyl group attached to the six-membered carbon ring in coriamyrtin to one of the double bonds in the aromatic ring in coriaria-lactone by aromatization was presumed. The formation of coriaria-lactone from coriamyrtin is a reaction analogous to the aromatization of picrotoxinin to picrotic acid and is one of the most characteristic reactions of the coriamyrtin and picrotoxinin series of compounds.[2] In order to obtain further evidence on the structure of coriamyrtin, preparation of another aromatic derivative which may indicate some other features of the bondings in coriamyrtin was attempted. However, the attempts of dehydrogenation carried out with manganese dioxide along with sulfuric acid, sulfur, selenium, and also with palladium-charcoal were all unsuccessful. From picrotoxinin, another aromatic derivative, picrotonol has been prepared by Angelico[4] and also by Horrmann, *et al.*[5] by reaction with dilute mineral acid. Picrotonol has also been prepared by Mercer and Robertson[6] under milder conditions from "picrotonol precursor" which is derived from picrotoxinin by hydrogenation in the presence of palladium-charcoal catalyst. These aromatic derivatives of picrotoxinin retain most of carbon and oxygen features of picrotoxinin and have been an important basis for elucidating picrotoxinin structure.[1] Later, the "picrotonol precursor" was isolated by Slater[7] and was found to be an isomer of picrotoxinin. The isomer was named neopicrotoxinin and the isomerization was presumed to include transformation of the isopropenyl group of picrotoxinin to an isopropylidene group under the conditions of hydrogenation. This presumption was confirmed by ozonolysis of neopicrotoxinin.[7,8] It is understandable that the double bond of the isopropylidene group in neopicrotoxinin readily transfers into the six-membered carbon ring to form the aromatic ring of picrotonol. Since it is very likely that the isopropenyl group of coriamyrtin behaves analogous to the isopropenyl group of picrotoxinin on aromatization with hydriodic acid because the lactone of dimethylphthalide type in coriaria-lactone is identical with that in picrotic acid, readier formation of an aromatic derivative from coriamyrtin may also be expected if the isopropenyl group of coriamyrtin is transformed to isopropylidene group before aromatization.

Attempt to prepare an aromatization product of coriamyrtin, besides coriaria-lactone by heating coriamyrtin with dilute mineral acid, did not produce any pure product other

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[*2] Part Ⅶ : Yakugaku Zasshi, **73**, 930 (1953).

[*3] This paper constitutes Part XV of a series entitled "Studies on the Components of *Coriaria japonica* A. Gray." Part XIV : This Bulletin, **9**, 178 (1961).

1) H. Conroy : J. Am. Chem. Soc., **73**, 1889 (1951); **74**, 491, 3046 (1952).
2) T. Kariyone, T. Okuda : Yakugaku Zasshi, **73**, 930 (1952).
3) *Idem* : *Ibid.*, **73**, 928 (1952).
4) F. Angelico : Gazz. chim. ital., **39**, i 299 (1909); **40**, i 391 (1910); **41**, ii 337 (1911).
5) P. Horrmann, M. Hagendorn : Arch. Pharm., **259**, 7 (1921); P. Horrmann, F. Bishof : *Ibid.*, **259**, 165 (1921).
6) D. Mercer, A. Robertson : J. Chem. Soc., **1936**, 288.
7) S. N. Slater : *Ibid.*, **1949**, 806.
8) J. S. E. Holker, *et al.* : *Ibid.*, **1958**, 2987.

than isocoriamyrtin, although various concentrations of the acid were used under various conditions. By column chromatography on aluminum oxide, only isocoriamyrtin was obtained in crystalline state. Ultraviolet and infrared spectra of each fraction of each product were examined and no absorption considered to be that of aromatic compound was detected.

Further attempt to obtain aromatized derivative from coriamyrtin was started with preparation of a "precursor" of aromatized derivative which may be analogus to the "picrotonol precursor," and the "precursor" was subsequently heated with dilute mineral acid as in the preparation of picrotonol from neopicrotoxinin. Preparation of the "precursor" was attempted by hydrogenation of coriamyrtin over palladium-charcoal catalyst in ethanol and impure product was then heated with dilute sulfuric acid as in the preparation of picrotonol from picrotoxinin. This attempt failed like the attempt for direct aromatization of coriamyrtin by heating with hydrochloric acid, but coriamyrtin seems to have been isomerized during the hydrogenation.

When coriamyrtin was hydrogenated in ethanolic solution over palladium-charcoal catalyst, about one-half molar equivalent of hydrogen was absorbed during 40∼100 minutes and then initial rapid uptake of hydrogen ceased. On removal of the catalyst and the solvent, impure crystals were obtained. The product is difficultly purified by recrystallization, but formed a bromo derivative, $C_{15}H_{17}O_5Br$, m.p. 248°(decomp.). The new bromo derivative is considered to be an isomer of bromocoriamyrtin and was named β-bromocoriamyrtin. Bromocoriamyrtin which has been prepared by direct bromination of coriamyrtin is now called α-bromocoriamyrtin. When the hydrogenation product was heated with dilute sulfuric acid, ether-soluble product gave a dinitrophenylhydrazone, $C_{21}H_{22}O_8N_4$, m.p. 261∼263°, which is an isomer of dinitrophenylhydrazone of isocoriamyrtin. This means the formation of another isomer of coriamyrtin by hydrolysis of the hydrogenation product of coriamyrtin.

When hydrogenation of coriamyrtin over palladium-charcoal catalyst was continued for 4 hours, a crude product with the melting point varying from 180° to 190° was obtained. By bromination, this product formed another bromo derivative, $C_{15}H_{17}O_5Br$, m.p. 203°, which is also an isomer of bromocoriamyrtin, and was named γ-bromocoriamyrtin.

After hydrolysis, this hydrogenation product formed a dinitrophenylhydrazone which was found to be identical with the dinitrophenylhydrazone obtained from the product of hydrolysis after 40∼120 minutes' hydrogenation.

When hydrogenation was carried out with a solution of palladium chloride in hydro-

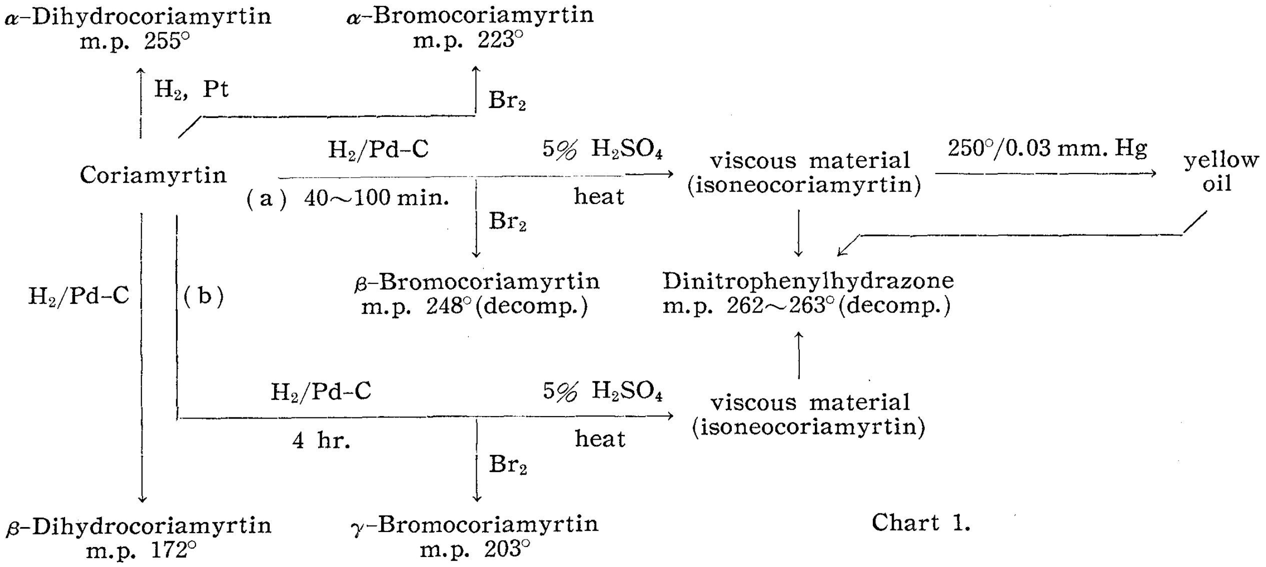
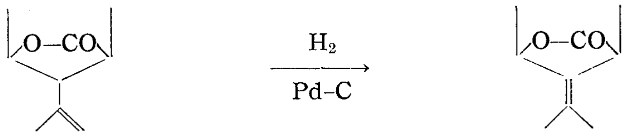


Chart 1.

chloric acid and charcoal added with water to an alcoholic solution of coriamyrtin for 5 hours, about one molar equivalent of hydrogen was absorbed to form a new dihydro derivative of coriamyrtin, m.p. 172°, which is now called β-dihydrocoriamyrtin. Dihydrocoriamyrtin which has been derived by hydrogenation with platinum catalyst is now called α-dihydrocoriamyrtin. Infrared spectrum of β-dihydrocoriamyrtin indicated complete disappearance of the double bond which is present in coriamyrtin at 6.10 μ. Results of hydrogenation, bromination, and hydrolysis are shown in Chart 1.

The ultraviolet absorption spectrum of the crude hydrogenation product, which gives β-bromocoriamyrtin on bromination, showed absorption peak at 215 mμ (log ε 4.14, in H_2O) which is characteristic of a tetrasubstituted double bond[9] like that in the spectrum of neopicrotoxinin.[10] This absorption indicates that the isomerization of coriamyrtin including transformation of isopropenyl group (I) to isopropylidene group (II), as in the isomerization of picrotoxinin to neopicrotoxinin[7,8] took place by hydrogenation over palladium-charcoal catalyst. The slowing down of the hydrogenation speed can be explained by the transformation of the double bond in coriamyrtin to a tetrasubstituted double bond. Although the isomer of coriamyrtin corresponding to neopicrotoxinin has not been isolated as a pure product in the present series of experiments, formation of an isomer of coriamyrtin which may be called neocoriamyrtin can be concluded by the results of bromination and hydrolysis, and also from ultraviolet spectrum of the hydrogenation products. The relation of the isomer produced by the hydrolysis of the hydrogenation product to "neocoriamyrtin" is considered to be analogous to that of isocoriamyrtin to coriamyrtin. The hydrolysis product may be called isoneocoriamyrtin.



(I) (II)

Experimental[*4]

Palladium Catalyst——$PdCl_2$ (0,05 g.) was dissolved in 0.2 cc. of conc. HCl and, with 3 cc. of H_2O, was added to 0.2 g. of charcoal which had been heated in a crucible over a direct flame and cooled in a desiccator. The mixture was reduced with H_2 until absorption of H_2 stopped (in 1 hr.) and the Pd-C catalyst was collected by filtration. Fresh catalyst was prepared for each hydrogenation experiment and was used immediately.

Hydrogenation of Coriamyrtin——a) A solution of coriamyrtin (0.5 g.) in 150 cc. of EtOH was shaken with 0.2 g. of Pd-C catalyst at atmospheric pressure in H_2. When the first relatively rapid absorption of H_2 had ceased (40～100 min., about one-half of the calculated amount of H_2 for one double bond in coriamyrtin had been absorbed), the hydrogenation was interrupted, the catalyst was filtered off, the solution was neutralized with Na_2CO_3, and the solvent was evaporated *in vacuo* on a water bath. The residue was dissolved in Et_2O and the solution was dried over Na_2SO_4. Et_2O was removed by distillation to give colorless crystals, m.p. varying from 180° to 190° (with previous shrinking). When mixed with coriamyrtin, the product melted at 200～205° (with previous shrinking).

b) A solution of coriamyrtin (0.5 g.) in 150 cc. of EtOH was shaken with 0.25 g. of Pd-C catalyst at atmospheric pressure in H_2. Absorption of H_2 reached about 2/3 of the calculated amount for one double bond in coriamyrtin in 4 hr. The product was treated in the same way as in the hydrogenation (a) to give colorless crystalline mass, m.p. 160～170°. On admixture with coriamyrtin, the product mostly melted at 160°, completely at 185°.

β-Bromocoriamyrtin——The product of the hydrogenation (a) (100 mg.) was dissolved in 10 cc. of

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[*4] All melting points are uncorrected.

[9] P. Bladon, H. B. Henbest, G. W. Wood : Chem. & Ind. (London), **1951**, 866; T. G. Halsall : *Ibid.*, **1951**, 867.

[10] R. B. Johnes, *et al.* : J. Chem. Soc., **1956**, 4715.

50% EtOH with heating on a boiling water bath and excess of Br_2 was added. When cooled, the reaction mixture deposited a white precipitate which was collected and recrystallized four times from EtOH to colorless needles, m.p. 248°(decomp.).

Hydrolysis of the Product of the Hydrogenation——a) The product of the hydrogenation (a) (200 mg.) was added to 10 cc. of 5% H_2SO_4 and the mixture was refluxed gently. The crystals dissolved in 10 min. After refluxing for 20 hr., the reaction mixture was cooled, neutralized with $NaHCO_3$, and extracted with Et_2O. Et_2O solution, after drying over Na_2SO_4 and removing the solvent by distillation, gave pale brown viscous material. The product formed a yellow dinitrophenylhydrazone from EtOH solution and recrystallized from EtOH, m.p. 261~263°(decomp.). *Anal.* Calcd. for $C_{21}H_{22}O_8N_4$: C, 55.02; H, 4.84; N, 12.22. Found : C, 55.55; H, 5.10; N, 12.03.

The crude product from the hydrogenation (a)(300 mg.) was distilled at 0.03 mm. Hg with bath temperature of 250°. A small amount of viscous material obtained as the distillate formed a dinitrophenylhydrazone which melted at 260~262° after repeated recrystallization from EtOH. When mixed with the dinitrophenylhydrazone prepared from the above crude product, no melting point depression was observed.

b) The crude product was treated with 5% H_2SO_4 in the same way as that of the hydrogenation (a) to give viscous material which formed a dinitrophenylhydrazone, m.p. 260~262°. The dinitrophenylhydrazone showed no melting point depression on admixture with the dinitrophenylhydrazone obtained in the above-mentioned experiment.

γ-Bromocoriamyrtin——Bromination of the product of the hydrogenation (b) was carried out in the same way as the bromination of the product of the hydrogenation (a). After repeated recrystallization of the product from EtOH, colorless needles, m.p. 203°, were obtained. Mixed melting point was depressed with bromocoriamyrtin. When mixed with β-bromocoriamyrtin, it started to shrink at 180°, melted at 230°. *Anal.* Calcd. for $C_{15}H_{17}O_5Br$: C, 50.42; H, 4.76. Found : C, 50.63; H, 4.83.

β-Dihydrocoriamyrtin——A solution of 0.05 g. of $PdCl_2$ in 0.3 cc. of conc. HCl was added, with 0.3 g. of charcoal and 5 cc. of distilled water, to a solution of 0.5 g. of coriamyrtin in 150 cc. of EtOH. The mixture was shaken at atmospheric pressure in H_2 for 5 hr. The catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was dissolved in Et_2O and the solution was dried over Na_2SO_4. The solvent was removed by distillation to give almost colorless viscous material which formed colorless pillars, m.p. 172°, by repeated recrystallization from EtOH. Melting point was depressed on admixture with coriamyrtin and α-dihydrocoriamyrtin. The compound does not react with Br_2 solution in H_2O. *Anal.* Calcd. for $C_{15}H_{20}O_5$: C, 64.28; H, 7.11. Found : C, 14.54; H, 6.92.

Chromatography of the Hydrolysis Product from Coriamyrtin——Finely powdered coriamyrtin (1 g.) was added to 400 cc. of 5% H_2SO_4 and the mixture was heated in a boiling water bath for 8 hr. After cool, the solution was extracted seven times with Et_2O. Combined Et_2O solution was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and Et_2O was evaporated to give pale yellow viscous residue. The residue was dissolved in 10 cc. of dehyd. $CHCl_3$ and the solution was poured through a column of Al_2O_3 (0.7 cm. × 20 cm.). Elution was carried out with $CHCl_3$ and 25-cc. portions of the eluate were collected. The solvent was evaporated from each fraction. Colorless crystals were obtained from the 4th, 5th, and 6th fractions. Recrystallization from hydr. EtOH gave pillars, m.p. 224°. Yield, 0.2 g. It strongly reduces the Fehling solution and $AgNO_3$ solution in dil. NH_4OH with mild heating. *Anal.* Calcd. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.50. Found : C, 64.71; H, 6.65,

The author wishes to express his sincere thanks to Dr. Tatsuo Kariyone, Chief of National Institute for Hygienic Sciences, and Prof. Koiti Kimura of this University for their guidance and encouragements. The author is indebted to Miss Ikuko Uchida of this Faculty for infrared spectra and the members of Microanalytical Center of this Faculty for microanalysis.

Summary

Hydrogenation of coriamyrtin with palladium catalysts resulted in formation of impure products which gave two new isomers of bromocoriamyrtin, β-bromocoriamyrtin, m.p. 248° (decomp.), and γ-bromocoriamyrtin, m.p. 203°, depending on the condition of the hydrogenation. Bromocoriamyrtin formerly obtained is now called α-bromocoriamyrtin. On hydrolysis with dilute sulfuric acid, the crude products from both hydrogenation gave the same dinitrophenylhydrazone which is an isomer of the dinitrophenylhydrazone of isocoriamyrtin. Hydrogenation with palladium catalyst under a stronger condition resulted in formation of an isomer of dihydrocoriamyrtin, m.p. 172°. From these results, forma-

tion of an isomer, which will be called neocoriamyrtin, by the hydrogenation of coriamyrtin with palladium catalyst was presumed. Neocoriamyrtin is considered to possess an isopropylidene group formed by transformation of the isopropenyl group in coriamyrtin. Unlike neopicrotoxinin, which gives aromatic picrotonol when heated in dilute mineral acid under mild conditions, the crude product which is presumed to contain neocoriamyrtin gave no aromatic derivative when heated in dilute mineral acid under various conditions. It was confirmed by chromatography and ultraviolet spectra that direct action of dilute mineral acid on coriamyrtin also gave no aromatic derivative.

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60. Ken'ichi Takeda, Hiroshi Ōsaka, and Norihide Maezono : On Steroidal Sapogenins. II.[1] Synthesis of Some 7-Oxygenated 5β,25D-Spirostanes.

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At the beginning of studies on the structure of metagenin,[2] 5β,25D-spirostane-2β,3β,11α-triol (XIV), a new steroidal sapogenin isolated from *Metanarthecium luteo-viride* Maxim., a possibility for the position 7 for the third of the three hydroxyl groups of metagenin was not excluded. Therefore, attempt was made to synthesize 5β,25D-spirostan-7α-ol (Xa), -7β-ol (XIIa), and -7-one (XI) from the known steroidal sapogenin.

7-Oxygenated 5β-steroids are well known in the cholic acid series, but no example is found in the 5β-spirostane series. In the 5β-cholestane series, Henbest, *et al.*[3] mentioned a formation of 7α-methoxy-5β-cholestan-3-one by catalytic hydrogenation of 7α-methoxycholest-4-en-3-one and the present authors reported[4] the synthesis of some 7-oxygenated 5β-cholestanes by hydrogenation of 7α-(tetrahydro-2′-pyranyloxy)cholest-4-en-3-one. In the present work, this method was applied to 7α-hydroxydiosgenin acetate[5] (IIa) to obtain 7-oxygenated 5β,25D-spirostanes.

7α-(Tetrahydro-2′-pyranyloxy)diosgenin acetate (IIb), obtained from 7α-hydroxydiosgenin acetate (IIa) by treatment with dihydropyran and phosphoryl chloride, was converted to 4-en-3-one (III) by saponification of the acetoxyl group to 3-ol (IIc), followed by Oppenauer oxidation. The intermediates (IIb), (IIc), and (III), did not crystallize, their formulae being assumed from infrared spectra (see Experimental). The 4-en-3-one (III), containing 4,6-dien-3-one (IV) as a by-product according to its infrared spectrum, was hydrogenated over platinum oxide in methanol solution to a saturated ketone (Va) and the latter was cleavaged to C_7-alcohol (Vb) with hydrochloric acid. The crude reaction product was purified on alumina to afford three products; substances of m.p. 191°(A) and of m.p. 210°(B) as a by-product, and substance of m.p. 240°(C) as a main product.

Substance (A) was determined as 3,3-dimethoxy-5β,25D-spirostane (VI) from its analy-

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[*1] Imafuku, Amagasaki, Hyogo-ken (武田健一, 大坂　弘, 前園憲英).

[1] A paper entitled "The Isomers of 25D-,5β-Spirostane-2,3-diol" by K. Takeda, T. Okanishi, A. Shimaoka (This Bulletin, **7**, 942 (1959)) is designated as Part I of this series.

[2] *a*) K. Takeda, K. Hamamoto : Tetrahedron Letters, **3**, 1 (1960); *b*) K. Hamamoto : This Bulletin, **9**, 32 (1961).

[3] H. B. Henbest, E. R. H. Jones : J. Chem. Soc., **1948**, 1798.

[4] K. Takeda, H. Osaka, K. Horiki : Yakugaku Zasshi, **81**, 325 (1961).

[5] H. J. Ringold, G. Rosenkranz, C. Djerassi : J. Am. Chem. Soc., **74**, 3318 (1952).