Notes

UDC 547.98.02

Noboru Kutani : The Chemical Structure of Aceritannin (Acertannin). I. Determination of the Location of Two Galloyl Groups in Aceritannin.[*1]

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Perkin and Uyeda[1)] first reported the isolation from the leaves of *Acer Ginnala* Maxim.[*3] of a crystalline tannin named acertannin,[*4] $C_{20}H_{20}O_{13} \cdot 2H_2O$, m.p. 164~166°, $[\alpha]^{15}_{D}$ +20.55° (Me_2CO). This furnished octaacetate, m.p. 154~155°, and was cleaved on hydrolysis into two moles of gallic acid and one mole of aceritol, a monoanhydrohexitol, $C_6H_{12}O_5$, m.p. 142~143°, $[\alpha]^{19}_{D}$ +39° (1%, in H_2O) (tetraacetate, m.p. 74~75°), presumed to be formulated as 1,4-anhydro-D-mannitol (I).

The formation of two moles of tri-O-methylgallic acid after hydrolysis of methylated aceritannin, which could not be induced to crystallize, led the previous workers to formulate aceritannin as one of the isomeric di-O-galloyl-1,4-anhydro-D-mannitols.

Later, however, aceritol was proved[2)] to be identical with polygalitol, $C_6H_{12}O_5$, m.p. 142~143°, $[\alpha]^{19}_{D}$ +42.86° (c=1.0, H_2O), a naturally occurring monoanhydro-D-hexitol, which has been proved, after years of controversy,[5)] to be formulated as 1,5-anhydro-D-glucitol (II) through studies of unequivocal degradation and total synthesis.[3~5)]

Now it follows that aceritannin might well be formulated as one of the six possible isomers, i.e., 2,6- (III), 3,6- (IV), 4,6- (V), 2,3- (VI), 2,4- (VII), and 3,4-di-O-galloyl-1,5-anhydro-D-glucitol (VIII).

In order to select the unequivocal one from among these isomers for aceritannin, detailed experiments have now been carried out and whose description and discussion of the result are presented in this paper.

As reported,[1,2)] aceritannin was cleaved on hydrolysis into two moles of gallic acid and one mole of polygalitol.

Differing, however, from the description of Perkin and Uyeda, aceritannin was methylated with either diazomethane or methyl iodide, and fused with potassium carbonate in dehyd. acetone to yield crystalline hexamethyl ether, $C_{20}H_{14}O_7(OCH_3)_6$, m.p. 172~173°, $[\alpha]^{29}_{D}$ +24° (Me_2CO), which furnished diacetate, $C_{20}H_{12}O_5(OCH_3)_8 \cdot (OSO_2C_6H_4 \cdot CH_3(p))$, m.p. 85°, indicative of the presence of six phenolic and two alcoholic hydroxyl groups in aceritannin.

[*1] Reported briefly in J. Kumamoto Women's Univ., **3**, 57(1951) (C. A., **49**, 187(1955)). A part of this work was carried out during World War II at the Laboratory of the Phytochemical Department, Institute of Pharmacognosy, University of Seoul, Korea.

[*2] Ōemachi, Kumamoto (九谷 昇).

1) A. G. Perkin, Yoshisuke Uyeda : J. Chem. Soc., **1922**, 66.

[*3] Japanese name : Chôsen-karakogi-kaede. A deciduous tree of Aceraceae, and a native of Korean Peninsula, Southern Manchuria, and Eastern Siberia.

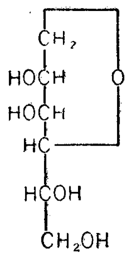
[*4] According to the customary nomenclature of natural products, the name aceritannin will be used hereafter instead of acertannin.

2) W. Freudenberg, E. F. Rogers : J. Am. Chem. Soc., **59**, 1602(1937).

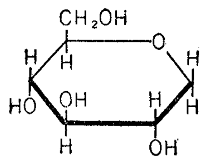
3) (a) N. K. Richtmyer, C. S. Hudson : *Ibid.*, **65**, 64(1943); (b) R. C. Hockett, M. Conley : *Ibid.*, **66**, 464(1944).

4) (a) N. K. Richtmyer, C. J. Carr, C. S. Hudson : *Ibid.*, **65**, 1477(1943); (b) R. K. Ness, H. G. Fletcher, Jr., C. S. Hudson : *Ibid.*, **72**, 7(1950).

5) See the reviews : (a) H. G. Fletcher, Jr., N. K. Richtmyer : "Applications in the Carbohydrate Field of Reductive Desulfurization with Raney Nickel," Advances in Carbohydrate Chem., **5**, 1 (1950); (b) L. F. Wiggins : "Anhydrides of Pentitols and Hexitols," *ibid.*, **5**, 191(1950).



(I)



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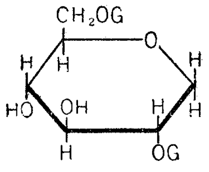

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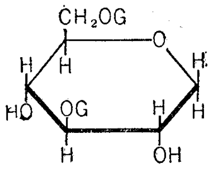

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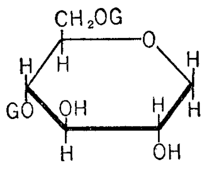

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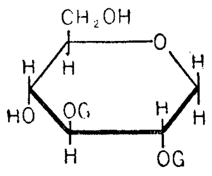

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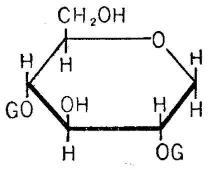

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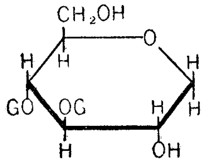

(VIII)

G = galloyl group

Hydrolysis of this hexamethyl ether afforded two moles of tri-O-methylgallic acid and one mole of polygalitol, indicative of the fact that two moles of gallic acid are esterified, independently of each other, with any two of the four alcoholic hydoxyl groups in one mole of polygalitol, to form one mole of aceritannin.

Furthermore, evidences have now been presented for the location of two galloyl groups in aceritannin through the negative results of (a) periodate oxidation of hexa-O-methylaceritannin, (b) Oldham-Rutherford[6] test for di-O-tosyl-hexa-O-methylaceritannin, and (c) tritylation of hexa-O-methylaceritannin, indicating the absence in aceritannin of adjacent carbon atoms carrying hydroxyl groups and a free, primary alcoholic hydroxyl group.

The foregoing evidences rule out (III), (V), (VI), (VII), and (VIII) because of the presence in each of them of either a *trans*-glycol grouping or a free, primary alcoholic hydroxyl group.

Now it follows from the foregoing that aceritannin should be formulated as 3,6-di-O-galloyl-1,5-anhydro-D-glucitol (III), in which both a *trans*-glycol grouping and a free, primary alcoholic hydroxyl group are lacking.

Further work on the elucidation of the chemical structure of aceritannin through

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[6] W. H. Oldham, J. K. Rutherford : J. Am. Chem. Soc., **54**, 366(1932).

unequivocal total synthesis is now under way and a detailed account of its result will be reported in due course of time.

After this work was completed, attention was drawn to the paper published by Powers and Cataline[7] on the isolation from the the bark of *Acer spicatum* L. of a crystalline tannin provisionally named Acer spicatum tannin, $C_{20}H_{20}O_{13} \cdot 2H_2O$, m.p. 165~166°, $[\alpha]_D^{27}$ +17.5° (Me_2CO), which upon hydrolysis furnished two moles of gallic acid and one mole of polygalitol. There can be little doubt that Acer spicatum tannin might well be identical with aceritannin because of striking agreement in characteristic properties between the two tannins.

Experimental[*5]

Isolation of Aceritannin—i) The isolation procedure of Perkin and Uyeda[1] was modified as follows: The fresh leaves of *Acer Ginnala* MAXIM.[*6] were air-dried and extracted with 10 times its weight of boiling water for 3 hr. The dark brown filtrate was concentrated to a small volume *in vacuo* and the concentrate was allowed to stand to precipitate crude tannin as yellowish brown paste. Yield, ca. 12%.

The crude aceritannin was dissolved in warm EtOH and the insoluble matter was filtered off. The filtrate was concentrated *in vacuo* to a small volume and kept in a refrigerator overnight. The separated crystalline paste was collected and washed with a small amount of EtOH. Recrystallization from boiling water gave pure aceritannin as colorless micro-needles, m.p. 164~166° (reported[1] m.p. 164~166°). *Anal.* Calcd. for $C_{20}H_{20}O_{13} \cdot 2H_2O$: C, 47.27; H, 4.65. Found (in material dried at room temp. *in vacuo*): C, 47.27; H, 4.15. $[\alpha]_D^{12}$ +20° (0.1%, in Me_2CO); $[\alpha]_D^{12}$ +20° (0.1%, in EtOH) (reported[1] $[\alpha]_D^{15}$ +20.55° (Me_2CO)). UV λ_{max} mμ (log ε): 222(4.58), 279(4.26); λ_{min} 243 mμ (log ε 3.70). IR ν_{max}^{Nujol} cm^{-1}: 3460, 3236(OH); 1669(-CO-O-); 1605, 1531 (aromatic ring); 862, 837(1,2,3,5-tetrasubstituted aromatic ring).

ii) The air-dried, fresh leaves[*7] of *Acer aidzuense* NAKAI[*8] were worked up in the same manner as above and gave pure crystalline tannin, which melted at 164~166°, either alone or on admixture with aceritannin.

Acetylation of Aceritannin: Formation of Octa-O-acetylaceritannin (3,6-Bis-O-(tri-O-acetylgalloyl)-2,4-di-O-acetyl-1,5-anhydro-D-glucitol)—One g. of aceritannin was acetylated with 10 cc. of Ac_2O and a few drops of conc. H_2SO_4, and the acetate was recrystallized from MeOH as ball-like masses of colorless micro-needles, melting at 154~155° (reported[1] m.p. 154~155°). *Anal.* Calcd. for $C_{20}H_{12}O_5(OCOCH_3)_8$: C, 53.73; H, 4.48. Found: C, 53.42; H, 4.27. $[\alpha]_D^{12}$ +60° (0.05%, in EtOH); $[\alpha]_D^{12}$ +60° (0.2%, in Me_2CO). UV λ_{max} mμ (log ε): 210(3.56), 280(2.90); λ_{min} 260 mμ (log ε 2.68). IR ν_{max}^{Nujol} cm^{-1}: 1779, 1748 (CH_3CO-O-); 1712 (-CO-O-); 1605 (aromatic ring); 848, 765 (1,2,3,5-tetrasubstituted aromatic ring). Its EtOH solution gave no coloration with $FeCl_3$.

Hydrolysis of Aceritannin: Formation of Gallic Acid and Polygalitol (Aceritol)—Hydrolysis of aceritannin was carried out in the same manner as reported by Perkin and Uyeda.[1] Hydrolysis of 3.0496 g. of aceritannin afforded 1.9597 g. of anhydrous gallic acid (64.23%), which corresponded to 2 moles (67.44%) obtainable from 1 mole of aceritannin dihydrate, $C_{20}H_{20}O_{13} \cdot 2H_2O$.

The crude gallic acid from the acid hydrolysate was recrystallized from boiling water (charcoal) as almost colorless needles, which decomposed over 220° with effervescence and darkening. *Anal.* Calcd. for $C_7H_6O_5 \cdot H_2O$: C, 44.68; H, 4.26. Found: C, 44.71; H, 4.64. UV λ_{max} mμ (log ε): 222(4.27), 273(4.00); λ_{min} 240 mμ (log ε 3.23). IR ν_{max}^{Nujol} cm^{-1}: 3427(OH); 1675(-CO-O-); 1580, 1502(aromatic ring); 858, 762 (1,2,3,5-tetrasubstituted aromatic ring).

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[7] J. L. Powers, E. H. Cataline: J. Am. Pharm. Assoc., Sci. Ed., **30**, 209(1941).

[*5] The microanalyses and optical measurements were carried out through the courtesy of Dr. A. Watanabe of Research Laboratories, Takeda Pharmaceutical Industries, Ltd., the ultraviolet absorptions were measured in MeOH with a Shimadzu Model QB-50 spectrophotometer, and the infrared absorptions were measured in Nujol with a Perkin-Elmer Model 21 spectrophotometer provided with NaCl prism, through the courtesy of Messrs. H. Kozuma and K. Kawasaki of Technical Department of Minamata Factory, Shin-Nippon Chisso Hiryo Co., Minamata, Kumamoto-ken.

[*6] Collected in the summer of 1941 in the vicinity of Kaeson, Korea.

[*7] Collected in the summer of 1947 in Kurohiji, Kuma-gun, Kumamoto-ken, under the kind guidance of Mr. K. Mayebara.

[*8] Japanese name: Karakogi-kaede.

The acid was acetylated with Ac_2O and a few drops of conc. H_2SO_4 and the acetate was recrystallized from boiling water to colorless needles, melting at 170°, either alone or on admixture with tri-O-acetylgallic acid. *Anal.* Calcd. for $C_7H_3O_2(OCOCH_3)_3$: C, 52.70; H, 4.05. Found : C, 53.05; H, 4.05. UV λ_{max} mμ (log ε) : 213 (3.13), 270 (2.32); λ_{mi} 255~260 mμ (log ε 2.26). IR ν_{max}^{Nujol} cm^{-1}: 1793, 1789 (CH_3CO-O-); 1605, 1499 (aromatic ring); 868, 854 (1,2,3,5-tetrasubstituted aromatic ring).

The acid mother liquor freed of gallic acid was worked up in the same manner as reported by Perkin and Uyeda,1) and the solid produced was recrystallized from MeOH to colorless needles, m.p. 142~143°, either alone or on admixture with polygalitol.[*9] *Anal.* Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.31. Found : C, 43.68; H, 7.15. $[\alpha]_D$ +43° (1%, in H_2O) (reported2) +42.86° (c=1.0, H_2O)). IR ν_{max}^{Nujol} cm^{-1} : 3289, 3205~3155 (OH); 913, 873. Its pattern was found to be superimposable with that of polygalitol[*9] and distinguished from that of styracitol (1,5-anhydro-D-mannitol).

Acetylation of this substance with Ac_2O and fused NaOAc afforded the acetate, which was recrystallized from a mixture of benzene and petr. ether to colorless needles, m.p. 75°, either alone or on admixture with tetra-O-acetylpolygalitol prepared by acetylation of polygalitol.[*9] *Anal.* Calcd. for $C_6H_8O(OCOCH_3)_4$: C, 50.60; H, 6.02. Found : C, 50.45; H, 6.20. $[\alpha]_D^{27}$ +39.6° (EtOH).[*10] IR ν_{max}^{Nujol} 1739 cm^{-1} (CH_3CO-O-). Its pattern agreed with that of tetra-O-acetylpolygalitol.

Methylation of Aceritannin : Formation of Hexa-O-methylaceritannin (3,6-Bis-O-(tri-O-methylgalloyl)-1,5-anhydro-D-glucitol)—a) To ice-cooled solution of 3 g. of aceritannin in 300 cc. of Me_2CO an excess of an ethereal solution of diazomethane was added. A reaction occurred immediately and after a while, there began to separate a solid, which, on being left in a refrigerator overnight, solidified to a crystalline paste. The solid was collected and recrystallized from MeOH to colorless micro-needles, m.p. 172~173°. Concentration of the mother liquor afforded a further crop of the same product. *Anal.* Calcd. for $C_{20}H_{14}O_7(OCH_3)_6$: C, 56.52; H, 5.80; OCH_3, 33.70. Found : C, 56.57, 56.34; H, 6.01, 5.93; OCH_3, 32.88, 32.85. $[\alpha]_D^{29}$ +24° (Me_2CO). UV λ_{max} mμ (log ε) : 216 (4.55), 266 (4.13); λ_{min} 235 mμ (log ε 3.55). IR ν_{max}^{Nujol} cm^{-1} : 3448, 3279, 3175 (OH); 1706 (-CO-O-); 1582, 1499 (aromatic ring); 853, 761, 751 (1,2,3,5-tetrasubstituted aromatic ring). It is sparingly soluble in MeOH, EtOH, and Me_2CO, and insoluble in Et_2O. Its MeOH solution gave no coloration with $FeCl_3$.

Acetylation of this substance in the usual manner afforded the acetate, which was recrystallized from MeOH to colorless needles, m.p. 155°. *Anal.* Calcd. for $C_{20}H_{12}O_5(OCH_3)_6(OCOCH_3)_2$: C, 56.60; H, 5.66; OCH_3, 29.26. Found : C, 56.41; H, 5.57; OCH_3, 29.41. $[\alpha]_D$ +108° (MeOH). UV λ_{max} mμ (log ε) : 222 (4.52), 268 (4.41); λ_{min} 235 mμ (log ε 3.63). IR ν_{max}^{Nujol} cm^{-1} : 1736 (CH_3CO-O-), 1704 (-CO-O-), 1577, 1502 (aromatic ring), 761 (1,2,3,5-tetrasubstituted aromatic ring).

b) Twenty-five g. of aceritannin was methylated in Me_2CO with 40 cc. of MeI and 20 g. of fused K_2CO_3, and the product was recrystallized from MeOH to colorless micro-needles, m.p. 172~173°, either alone or on admixture with hexa-O-methylaceritannin obtained as above.

In one experiment, 11 g. of aceritannin was methylated in 150 cc. of dehyd. MeOH with sufficient amount of MeI and fused K_2CO_3, and the product was recrystallized from dil. EtOH to colorless needles, m.p. 85°, either alone or on admixture with methyl tri-O-methylgallate. *Anal.* Calcd. for $C_6H_2(OCH_3)_3COOCH_3$: C, 58.41; H, 6.19; OCH_3, 54.87. Found : C, 58.36; H, 6.26; OCH_3, 54.11. UV λ_{max} mμ (log ε) : 215 (4.79), 264 (4.33); λ_{min} 235 mμ (log ε 3.60). IR ν_{max}^{Nujol} cm^{-1} : 1776~1761, 1706 (-CO-O-); 1580, 1504 (aromatic ring); 864, 767, 760 (1,2,3,5-tetrasubstituted aromatic ring).

Hydrolysis of this substance afforded a product, which recrystallized from boiling water as colorless needles, m.p. 169~170°, either alone or on admixture with tri-O-methylgallic acid.

Hydrolysis of Hexa-O-methylaceritannin : Formation of Tri-O-methylgallic Acid and Polygalitol—To a solution of 1.3 g. of hexa-O-methylaceritannin in 10 cc. of MeOH, 6.5 cc. of *N* NaOH solution was added and the mixture was allowed to stand at room temp. for 48 hr. After being heated on a water bath for 5 min., the reaction mixture was acidified with dil. H_2SO_4 and thoroughly shaken with Et_2O. Removal of Et_2O afforded a solid, which was recrystallized from boiling water to colorless needles, m.p. 169~170°, either alone or on admixture with tri-O-methylgallic acid. Yield, 0.7382 g. (56.78%). Yield, 0.9985 g. (76.81%). *Anal.* Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.66. Found: C, 56.34; H, 6.06. UV λ_{max} mμ (log ε) : 210 (3.82), 263 (3.40); λ_{min} 235 mμ (log ε 3.60). IR ν_{max}^{Nujol} cm^{-1}: 1675 (-CO-O-); 1575, 1502 (aromatic ring); 857, 761 (1,2,3,5-tetrasubstituted aromatic ring).

The residue obtained by evaporating the mother liquor freed of tri-O-methylgallic acid was extracted with MeOH. Concentration of the MeOH solution deposited a solid, which was recrystallized from MeOH to colorless needles, m.p. 142~143°, either alone or on admixture with polygalitol.[*9]

[*9] The original specimen isolated by J. Shinoda, S. Sato, and D. Sato (Ber., **65**, 1219 (1932)) from the root of *Polygala tenuifolia* WILLDENOW and furnished through the courtesy of Dr. J. Shinoda. This substance has now been found to have $[\alpha]_D^{27}$ +42° (1%, in H_2O) instead of $[\alpha]_D^{16}$ +47.81° (H_2O), the value recorded by J. Shinoda, *et al.* (*loc. cit.*).

[*10] Independently of this work, N. K. Richtmyer and C. S. Hudson3a) found $[\alpha]_D^{20}$ +38.90° (c=2, $CHCl_3$) for this substance.

Methylation of Octa-O-acetylaceritannin—A solution of 8 g. of octa-O-acetylaceritannin in 24 cc. of MeOH was methylated according to the method of West and Holden[8] with 12 cc. of Me_2SO_4 in 18 cc. of CCl_4 and 6.4 g. of NaOH solution (50%). The product obtained was recrystallized from MeOH to colorless needles, m.p. 85°, either alone or on admixture with methyl tri-O-methylgallate. Attempts to isolate tetra-O-methylpolygalitol from the reaction mixture were unsuccessful.

Oxidation of Hexa-O-methylaceritannin with Periodate—Oxidation of hexa-O-methylaceritannin with KIO_4 was repeated under a variety of experimental conditions. Even after a long standing at room temp., consumption of the oxidant was not recognized in each case, giving complete recovery of the original substance.

Tosylation of Hexa-O-methylaceritannin : Formation of Di-O-tosyl-hexa-O-methylaceritannin (3,6-Bis-O-(tri-O-methylgalloyl)-2,4-di-O-tosyl-1,5-anhydro-D-glucitol)—One hundred mg. of hexa-O-methylaceritannin in 1 cc. of anhyd. pyridine was tosylated with 83.6 mg. of tosyl chloride and the product was recrystallized from Me_2CO as colorless needles, m.p. 85°(decomp.). *Anal.* Calcd. for $C_{40}H_{44}O_{17}S_2$: C, 55.81; H, 5.12. Found : C, 55.76; H, 5.23.

In accordance with the method of Oldham and Rutherford,[6] a mixture of 15 mg. of this substance and 20 mg. of NaI was dissolved in 0.5 cc. of anhyd. Me_2CO and heated in a sealed tube at 100° in a boiling water bath for 2 hr., and the resulting solution was allowed to cool to room temperature. Even after a long standing, flaky precipitate of sodium *p*-toluenesulfonate was not recognized in the solution, indicating the absence of a free, primary alcoholic hydroxyl group in aceritannin.

Treatment of Hexa-O-methylaceritannin with Trityl Chloride and Pyridine—Attempts to tritylate hexa-O-methylaceritannin according to the method of Helferich[9] were unsuccessful and this indicated the absence of a free, primary alcoholic hydroxyl group in aceritannin.

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Summary

Examinations were made on the chemical structure of aceritannin (acertannin), an oligogalloylated, crystalline tannin, $C_{20}H_{20}O_{13}\cdot 2H_2O$, m.p. 164~166°, $[\alpha]^{12}_{D}$ +20° (Me_2CO and EtOH, each), which was first isolated by Perkin and Uyeda from the leaves of *Acer Ginnala* MAXIM. It has now been proved that aceritannin should be formulated as 3,6-di-O-galloyl-1,5-anhydro-D-glucitol, i.e., no other than 1-deoxy derivative of 3,6-di-O-galloyl-D-glucopyranose, a compound first isolated by Freudenberg (Ber., **52**, 1238 (1919)) as one of the partial hydrolysis products of chebulinic acid, and later, unequivocally synthesized by Schmidt and Schach (Ann., 571, 29(1951)).

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8) E. S. West, F. Holden : J. Am. Chem. Soc., **56**, 930(1934).
9) B. Helferich : Ann., **442**, 1(1924); Ber., **58**, 872(1925).