# The Condensation Product of Monomethylammonium 6-Aminosalicylate with Acetone[1], [*]

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In previous papers it has been demonstrated that the 8-quinolinecarboxylic acid derivative was obtained by the reaction between the ammonium salt of 6-amionsalicylic acid (II) and β-diketone at room temperature,[2] and that the reaction of ammonium salt of II with ethyl acetoacetate gave 4,7-dihydroxy-2-methyl-8-quinolinecarboxylic acid as a major product.[3]

While the reaction of ammonium or ethylammonium 6-aminosalicylate with acetone has been demonstrated to give a compound I (R=H or $C_2H_5$),[4,5] the reaction of methylammonium 6-aminosalicylate with acetone has not yet been

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[1] K. Yamada, Presented at the 15th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1962.

[*] Part III in the series of Condensation of Aminosalicylic Acid Salts.

[2] K. Yamada, *Sci. Paper of the Inst. Pys. & Chem. Res.*, **56**, 101 (1962).

[3] K. Yamada, ibid., **56**, 109 (1962).

[4] K. Yamada and S. Seki, *J. Chem. Soc. Japan, Pure Chem. Soc.* (*Nippon Kagaku Zasshi*), **82**, 1368 (1961).

[5] K. Tamura, N. Sugiyama, S. Seki, K. Taya and K. Yamada, ibid., **80**, 662 (1959).

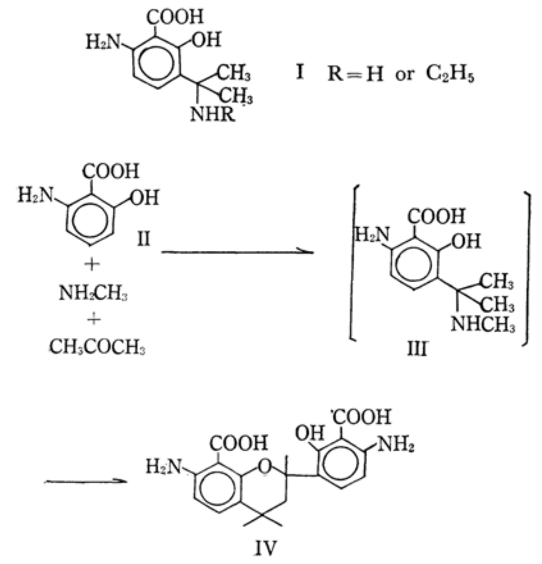

Fig. 1

studied. If the latter reaction proceeds as does the former, the III substance may be expected. Actually, however, the reaction product has not proved to be III.

Monomethylammonium 6-aminosalicylate was dissolved in acetone, and the solution was allowed to stand at room temperature. From this solution a solid was obtained. By purification with petroleum ether - ether, IV was obtained. IV could not be recrystallized from any solvents unless ether was added. IV was, however, readily susceptible to air-oxidation. The fact that flavan derivatives give a crystalline complex with ether is well-known.6) This fact, plus the analogy of the reaction of ammonium or ethylammonium 6-amionsalicylate with acetone, suggests that this compound is a flavan derivative such as IV.

The structure of IV was established as follows. It showed positive ferric chloride and Ehrlich-Herter tests. In addition, it was soluble in a sodium bicarbonate solution. The ultraviolet absorption spectrum of IV in ethanol had two absorption maxima, at 285 and 312 m$\mu$, which indicates no radical change from the ultraviolet spectrum of I. The infrared absorption spectrum in the KBr disk contained an amino band (3350 cm$^{-1}$), a hydroxyl band (3500—3200 cm$^{-1}$), a carbonyl band (1695 cm$^{-1}$) and a C–H out-of-plane deformation vibration band of the benzene ring (with two adjacent hydrogen atoms) (820 cm$^{-1}$). Its p$K_a'$ values were 3.9 (COOH) and 7.2 (COOH) in 55% methanol.7) By treatment with pyridine-acetyl chloride, it afforded a diacetyl derivative, the infrared absorption spectrum of which contained a $\nu$C=O (acetamido) band (1665 cm$^{-1}$). Therefore, it was presumed that the condensation product has no conjugated system except benzene, and that it has one hydroxyl, two amino and two carboxyl groups.

When IV was refluxed in 10% hydrochloric acid, V was obtained. Its infrared absorption spectrum contained bands of amino and hydroxyl groups (3350 cm$^{-1}$), and a C–H out-of-plane deformation vibration of the benzene ring (with one and two adjacent hydrogen atoms) (840 cm$^{-1}$), but the carbonyl band had disappeared. The Ferric chloride and Ehrlich-Herter tests were positive. Therefore, it was found to be a decarboxylated amino-hydroxyl compound. V was easily oxidized by air and changed to a sticky substance.

The diazotization of the amino-hydroxy compound V, followed by the Sandmeyer reaction,8) resulted in the formation of the dichloro compound (VI). VI was then catalytically reduced with palladium black to a halogen-free compound (VII). The infrared absorption spectrum of VII showed a hydroxyl band (3300 cm$^{-1}$) and a C–H out-of-plane deformation band (with four adjacent hydrogen atoms) (750 cm$^{-1}$). The molecular weight of VII was 260 (by Rast method). Therefore, the compound IV is probably a dimer of 3-isopropenyl-6-aminosalicylic acid. The $\lambda_{max}$ value (282 m$\mu$) of VII in ethanol was shifted to 290 m$\mu$ in a 0.5 N sodium hydroxide solution. Since hindered or partially-hindered phenols usually show a bathochromic shift of 10—20 m$\mu$ in a 0.5 N alkaline solution,9,10) the structure VII with a hindered hydroxyl group is sufficient to explain the 8 m$\mu$ shift. The NMR spectrum in carbon tetrachloride had a sharp singlet at 8.67 $\tau$ (6 : methyl protons of *gem*-dimethyl groups),11,12) a singlet at 8.45 $\tau$ (3: methyl protons) and a singlet at 5.01 $\tau$ (hydroxyl proton), as well as complex multiplets at 8.2—8.4 $\tau$ (2: aliphatic protons) and 2.8—3.2 $\tau$ (8: aromatic protons).13) Thus, the NMR data are consistent with the structure of 2′-hydroxy-2,4,4-trimethylflavan. The behavior of forming crystalline adducts with ether was characteristic of flavans.14,15) The methylation of

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6) K. Fries, *Ber.*, **41**, 371 (1908).

7) H. C. Brown, "Determination of Organic Structures by Physical Methods," Academic Press, New York (1955), p. 567.

8) T. Sandmeyer, *Ber.*, **17**, 1633 (1884).

9) N. D. Coggeshall and A. S. Glessner, *J. Am. Chem. Soc.*, **71**, 3150 (1949).

10) H. Hart, J. L. Corbin, C. R. Wagner and C. Y. Wu, ibid., **85**, 3269 (1963).

11) H. Hart, J. L. Corbin, C. R. Wagner and C. Y. Wu, ibid., **85**, 3270 (1963).

12) T. F. Wood, W. M. Easter, M. S. Carpenter and J. A. Angiolini, *J. Org. Chem.*, **28**, 2248 (1963).

13) J. A. Pople, "High-resolution Nuclear Magnetic Resonance," McGrow-Hill, New York (1959); E. J. Corey, E. M. Philbin and T. S. Wheeler, *Tetrahedron letters*, **1961**, 429.

14) W. Baker, R. F. Curtis and J. F. W. McOmie, *J. Chem. Soc.*, **1951**, 76; W. E. Noland, C. G. Richards, H. S. Desai and M. R. Venkiteswaran, *J. Org. Chem.*, **26**, 4254 (1961).

15) Many solvents are known to form the same adduct compounds with flavans. Since all such solvents are proton acceptors, salt formation or hydrogen bonding involving the 2′-hydroxyl group or ring oxygen may play a part in the formation of the 1 : 1 type adducts (over 40 examples are now known).

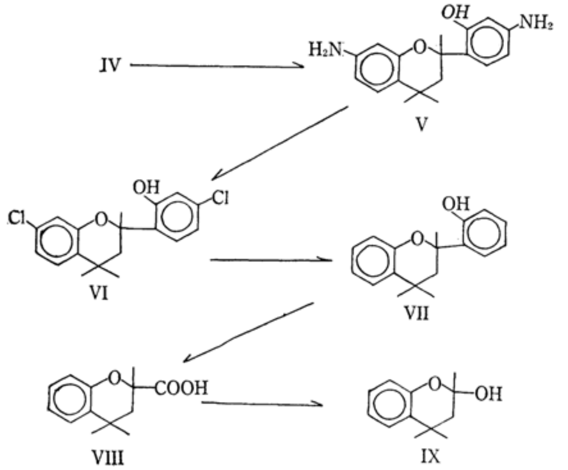

Fig. 2

VII with diazomethane gave a monomethoxy compound. Its infrared absorption spectrum did not show a hydroxyl band.

Compound VII was oxidized with potassium permanganate to an acid VIII. If the structure of VII is hydroxyflavan, the oxidized compound VIII should be chromancarboxylic acid. Its infrared absorption spectrum showed the group frequencies which characterize an acid carbonyl group, and a C–H out-of-plane deformation vibration of the benzene ring (with four adjacent hydrogen atoms). The ultraviolet absorption maxima in ethanol appeared at 226.5, 274.5 and 281.5 m$\mu$. The melting point of VIII coincided well with that of the literature.[16]

The decarboxylation of the acid VIII by the usual method was very difficult. When, however, a mixture of VIII and copper chromite in quinoline was heated, the compound $C_{12}H_{16}O_2$ (IX) was formed by the loss of carbon monoxide. The melting point and infrared absorption spectrum of this compound were identical with those of 2-hydroxy-2,4,4-trimethylchroman. The loss of carbon monoxide by heating in quinoline with copper chromite is frequently observed in this type of compound.[14] These degradation reactions and physical properties are consistent with the structure of IV, 7, 4′-diamino-2′-hydroxy-2, 4, 4-trimethylflavan-8, 3′-dicarboxylic acid.

It is known that the flavan derivative is obtained by the reduction of naturally-occurring flavon derivatives or by the cyclization of allyl ethers. The reaction of methylammonium 6-aminosalicylate with acetone presents another new method of preparing the flavan derivative.

The mechanism of the condensation reaction of monomethylammonium 6-aminosalicylate with acetone is considered to be following. Much as in

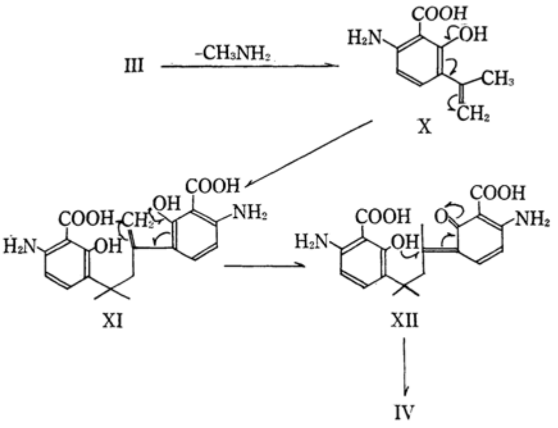

Fig. 3

the reaction of ammonium 6-aminosalicylate with acetone, it is probable that at the first stage 6-aminosalicylate produces an unstable intermediate III. III can readily lose its methylamino on account of its hyperconjugation by methyl group to give the 3-isopropenyl derivative X, which, in turn, can dimerize by means of proton transfer and electron rearrangement. The ready dimerization of 3-isopropenyl salicylic acid[5] and its derivatives would support this mechanism. The dimer XI (enol form), is probably in keto-enol equilibrium with the reactive form, XII, containing the more highly-substituted (and the more sterically-hindered) double bond. The process of cyclization is shown in Fig. 3. This is supported by the fact that the dimerization of the vinyl compound is promoted by an acid catalyst.

## Experimental

**4′, 7-Diamino-2′-hydroxy-2, 4, 4-trimethylflavan-3′, 8-dicarboxylic Acid (IV).**—A solution of methylammonium salt of 6-aminosalicylic acid,[17] which had been obtained from 10 g. of II, as has been described before,[2] in 50 ml. of dry acetone was allowed to stand at room temperature for one week. During this time, crystals were gradually separated. These crystals were then collected and dissolved in a 1 N sodium hydroxide solution. After neutralization with dilute hydrochloric acid, the solution was extracted with ether. The ether solution was dried with anhydrous sodium sulfate, and the ether was removed. The residue was recrystallized from petroleum ether with a small amount of ether. Pale yellow fine needles, m. p. 97°C (decomp.) were obtained. Yield, 3 g.

Found: C, 62.4; H, 6.98; N, 5.98. Calcd. for $C_{20}H_{22}O_6N_2 \cdot (C_2H_5)_2O$: C, 62.6; H, 7.01; N, 6.08%.

It was very sensitive to oxygen. Even in the crystalline state, it soon changed from colorless to red. A ferric chloride test was positive (dark red). Ehrlich-Herter and sodium nitroprusside tests were positive. UV: $\lambda_{max}^{EtOH}$ 265, 330 m$\mu$. IR: 3500—3200, 3350, 1695

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[16] W. Baker and J. C. McGowan, *J. Chem. Soc.*, **1952**, 1781; **1938**, 347.

[17] K. Yamada, K. Taya and S. Seki, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **83**, 107 (1962).

820 cm$^{-1}$.18) p$K_a'$: 3.9 (COOH) and 7.2 (COOH) in 55% methanol.19) IV gave a diacetyl derivative with pyridine-acetyl chloride. IR: 1665 cm$^{-1}$ (acetamido carbonyl).

**4′, 7-Diamino-2′-hydroxy-2, 4, 4-trimethylflavan (V).**—A suspension of 1.3 g. of IV in 20 ml. of 10% hydrochloric acid was refluxed for 5 hr. Carbon dioxide thus evolved vigorously. The neutralization of the resulting solution with a dilute sodium hydroxide solution separated precipitates, which were then recrystallized from petroleum ether-ether. Pale yellow needles, m. p. 177—180°C (decomp.), were obtained. Yield, 0.8 g.

Found: C, 70.6; H, 8.59; N, 7.30. Calcd. for $C_{18}H_{22}O_2N_2\cdot(C_2H_5)_2O$: C, 71.0; H, 8.74; N, 7.41%.

Ferric chloride and Ehrlich-Herter tests were positive. UV: $\lambda_{max}^{EtOH}$ 235, 325 m$\mu$. IR: 3350, 840 cm$^{-1}$.

**4′, 7-Dichloro-2′-hydroxy-2, 4, 4-trimethylflavan (VI).**—To a solution of 2 g. of V in a mixture of 15 ml. of concentrated hydrochloric acid and 15 ml. of water was dropped a solution of 0.6 g. of sodium nitrite in 2 ml. of water at 0—5°C with shaking. To the reaction mixture was then added a cuprous chloride solution, prepared from 9 g. of copper sulfate. After it had been kept at 60°C for 5 min., this solution was cooled in an ice bath. The precipitates were collected and recrystallized from light petroleum. Rhombic crystals, m. p. 135°C, were obtained. Yield, 1.1 g.

Found: C, 64.1; H, 5.3; Cl, 20.8. Calcd. for $C_{18}H_{18}O_2Cl_2$: C, 64.1; H, 5.3; Cl, 21.1%.

IR: 3380, 850 cm$^{-1}$. A ferric chloride test was positive.

**2′-Hydroxy-2, 4, 4-trimethylflavan (VII).**—A solution of 0.5 g. of dichloro-flavan (VI) in 10 ml. of methanol was reduced with hydrogen at an atmospheric pressure of 10 in the presence of 0.5 g. of palladium black and 0.3 g. of powdered anhydrous sodium acetate for 8 hr. To the filtered solution water was then added until all the precipitates had been separated. The recrystallization of the precipitates from petroleum ether gave prisms, m. p. 99°C. Yield, 0.25 g.

Found: C, 80.1; H, 7.6; mol. wt. (Rast), 260. Calcd. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5%; mol. wt. 268.

A ferric chloride test was positive. IR: 330, 750 cm$^{-1}$.

This compound was characterised as the -$OCOCH_3$ derivative; hexagonal prisms; m. p. 96°C.

Found: C, 81.8; H, 7.3. Calcd. for $C_{20}H_{22}O_2$: C, 81.6; H, 7.53%.

UV: $\lambda_{max}^{EtOH}$ 230, 282 m$\mu$.

**2, 4, 4-Trimethylchroman-2-carboxylic Acid (VIII).**—A solution of 1 g. of VII in 10 ml. of acetone was oxidized by the rapid addition of potassium permanganate in 300 ml. of acetone. The mixture boiled spontaneously, and the oxidation reaction was completed in 5 min. After the acetone had been removed, 50 ml. of water, 13 g. of sodium pyrosulfite and 13 ml. of 2 N hydrochloric acid were added to the residue. Sulfur dioxide was then passed in until the mixture became colorless. The mixture was extracted with ether. The ether solution was washed with water and extracted with four 5 ml. portions of a saturated sodium bicarbonate solution. The aqueous layer was washed with 10 ml. of ether and then acidified with hydrochloric acid. Pale yellow solid precipitates were collected at 0°C. Recrystallization from benzene gave an acid, VIII; 0.15 g.; rhombs; m. p. 172°C. UV: $\lambda_{max}^{EtOH}$ 226.5, 274.5, 281.5 m$\mu$. IR: 1695, 758 cm$^{-1}$. p$K_a'$: 4.6 (COOH) in 62% methanol. The structures of VIII and its methyl derivative were confirmed by their melting point infrared and ultraviolet absorption spectra.

**The Reaction of 2, 4, 4-Trimethylchroman-2-carboxylic Acid with Copper Chromite-Quinoline.**—A mixture of 0.3 g. of the acid VIII, 0.5 ml. of freshly-distilled quinoline, and 0.5 g. of copper chromite were refluxed for 20 min. The cooled mixture was then poured into 15 ml. of concentrated hydrochloric acid. After the mixture had been heated on a boiling water-bath for 15 min., 20 ml. of water was added. The solid precipitates which separated were filtered off through sand and washed with 30 ml. of ether. The aqueous layer was then extracted with three 10 ml. portions of ether. After the substance had been shaken with 10 ml. of a saturated sodium bicarbonate solution, the ether was removed. The oily residue, which soon solidified, was recrystallized from petroleum ether. Prisms, m. p. 90°C, were obtained. The melting point of IX was the same as that of the literature.16)

Found: C, 75.5; H, 8.6. Calcd. for $C_{12}H_{16}O_2$: C, 75.0; H, 8.3%. UV: $\lambda_{max}^{EtOH}$ 274, 279 m$\mu$. IR: 3440, 750 cm$^{-1}$.

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18) The IR absorption spectra were recorded with a Nihon Bunko Model DS 301 and Hitachi Model S-2 spectrophotometers. The UV absorption spectra were recorded with a Hitachi Model EPS-2 spectrophotometer; a pair of 1 cm. quartz cell was used. The NMR spectra were measured with a Nihon-denshi type NMR spectrometer equipped with a 60 Mc.

19) All p$Ka'$ measurements were carried out at 25±1°C with a Radiometer (Copenhagen) type SBR-2/SBU-1/TTT-1/TTA-2 titration equipment.