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68. **Shoji Shibata,**[*1] **Motoko Nakahara,**[*2] **and Norio Aimi**[*1] : Studies on the Constituents of Japanese and Chinese Crude Drugs. IX.[*3] Paeoniflorin, A Glucoside of Chinese Paeony Root. (2).[*3]

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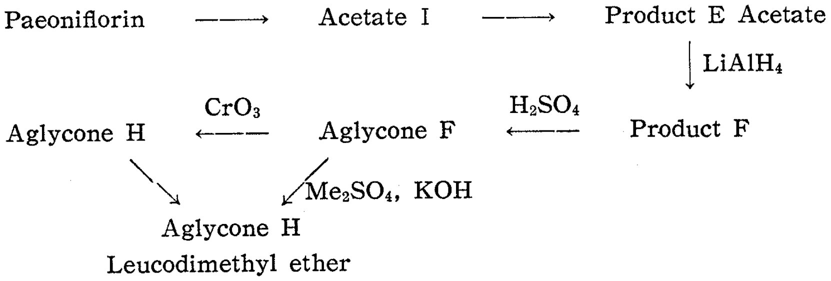
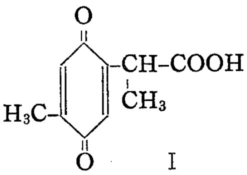
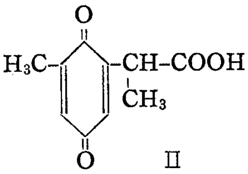
As described in the preceding paper,[1] all the efforts to obtain the aglycone of paeoniflorin either by acid or enzyme have failed. The hydrolysis of product F afforded glucose and aglycone F which, however, was not obtained in a pure crystalline form being converted into a resinous substance during the process of recrystallization.

On oxidation with chromic acid, the aglycone F yielded a yellow crystalline quinonic substance, m.p. 132° named aglycone H. The aglycone H was formulated as $C_{10}H_{10}O_4$, which furnished a leucodimethyl ether, $C_{12}H_{16}O_4$, m.p. 113~114°, on reduction followed by methylation. The leucodimethyl ether of aglycone H was also afforded directly by the methylation of aglycone F.

The chemical and physical evidences led to the conclusion that the aglycone H would be represented as in the formula I or II, and the leucodimethyl ether as III or IV.




I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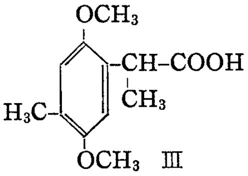
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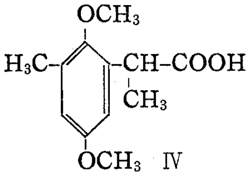
IV

It should be noted that the aglycone H retains all the carbon atoms of the assumed desbenzoyl aglycone of paeoniflorin. The establishment of the structure of aglycone H and its leucodimethyl ether, which would provide a significant evidence for the structure of paeoniflorin has been pursued synthetically.

2′,5′-Dimethoxy-4′-methylacetophenone (VI) was oxidized to yield an α-ketocarboxylic acid (VII).

After esterification of the α-ketocarboxylic acid (VII), methylmagnesium iodide was reacted with the ester to afford methyl 2-(2,5-dimethoxy-4-methylphenyl)lactate (IX) which was then hydrolyzed and dehydrated to form XI by heating in glacial acetic acid.

The final step of the synthesis was completed by the catalytic hydrogenation of the compound XI to yield 2-(2,5-dimethoxy-4-methylphenyl)propionic acid (XII), m.p. 113°.

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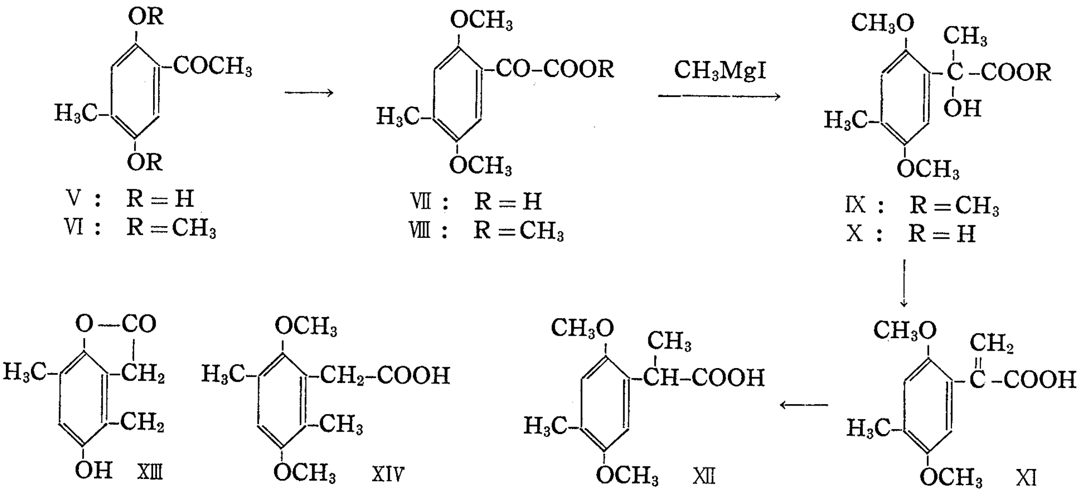
[*3] Part VIII and (1) : This Bulletin, **11**, 372 (1963).

[1] S. Shibata, M. Nakahara : *Ibid.*, **11**, 372 (1962).



The product XII was established to be identical with the aglycone H leucodimethyl ether, m.p. 113～114°, by a mixed fusion.

During the process of the synthetical study of aglycone H leucodimethyl ether, 2,5-dimethoxy-3,6-dimethylphenylacetic acid (XIV) was synthesized as a reference compound from 4,7-dimethyl-5-hydroxy-2(3*H*)benzofuranone (XIII)[2] by the action of dimethyl sulfate and alkali.

Experimental

2′,5′-Dihydroxy-4′-methylacetophenone (V)[3]——A mixture of 2-methylhydroquinone diacetate (33 g.) and anhydr. $AlCl_3$ (66 g.) was poured gradually into a flask preparatively heated at 125～130° in an oil bath. The temperature was maintained at 120° for 15 min. After cooling the reaction mixture was pulverized and added into ice-water (400 cc.) and conc. HCl (30 cc.). The brownish precipitates formed were filtered and dissolved in benzene, from which colorless needles were obtained on evaporation.

The product, 2′-hydroxy-5′-acetoxy-4′-methylacetophenone, recrystallized from MeOH gave m.p. 108°, IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1760 (phenolic acetate), 1630 (aryl acetyl). *Anal.* Calcd. for $C_{11}H_{12}O_9$: C, 63.45; H, 5.81. Found : C, 63.74; H, 5.69.

The monoacetate was hydrolyzed with a mixture of conc. HCl in MeOH (1:4) (200 cc.) at room temperature. After 1 hr. standing, the mixture was poured into ice-water and the precipitates formed were filtered. 2′,5′-Dihydroxy-4′-methylacetophenone (V) thus obtained was recrystallized from benzene to give yellowish green leaflets, m.p. 146°, yield, 7.0 g.

2′,5′-Dimethoxy-4′-methylacetophenone (VI)[4]——The above compound V (6.0 g.) was refluxed for 7 hr. with Me_2SO_4 (14 cc.), anhydr. K_2CO_3 (24 g.) in Me_2CO (100 cc.). The methylated product formed yellow needles, m.p. 76°, yield, 3.5 g.

(2,5-Dimethoxy-4-methylphenyl)glyoxylic Acid (VII)——A solution of $KMnO_4$ (7.0 g.) and KOH (2.6 g.) dissolved in H_2O (140 cc.) was dropped into a solution of the compound VI (3.5 g.) in pyridine (23 cc.) under ice-cooling and vigorous stirring. After 7 hr. the reaction mixture was treated as usual to obtain a yellow acidic compound, which was recrystallized from benzene to form golden yellow needles, m.p. 170°, yield, 2.0 g. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 2800～2300, 1740 (COOH), 1675 (C=O). *Anal.* Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found : C, 58.74; H, 5.32.

Methyl (2,5-Dimethoxy-4-methylphenyl)glyoxylate (VIII)——The above keto-carboxylic acid VII (2.5 g.) was dissolved in abs. MeOH (50 cc.) and saturated with dried HCl gas under cooling. After standing overnight MeOH was evaporated to leave yellow needles, which were recrystallized from MeOH to give m.p. 112.5°, yield, 2.0 g. IR $\nu_{\max}^{CS_2}$ cm^{-1} : 1750 ($COOCH_3$), 1670 (C=O). *Anal.* Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found : C, 60.22; H, 5.93.

Methyl 2-(2,5-Dimethoxy-4-methylphenyl)lactate (IX)——A Grignard reagent (1.6 mol. equiv.) prepared from MeI (680 mg.) and Mg. (120 mg.) in abs. Et_2O (50 cc.) was dropped into a solution of the above

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2) L.I. Smith, J. Nichols : J. Am. Chem. Soc., **65**, 1739 (1943).

3) J.L.R. Williams : J. Org. Chem., **22**, 772 (1957).

4) R. Royer, P. Demerseman, A. Cheutin, E. Allegrini, R. Michelet : Bull. soc. chim. France, **1957**, 1385.

compound VIII (750 mg.) under ice-cooling for 3 hr., when yellow orange mass appeared. The yellow orange substance dissapeared and brownish resinous precipitates formed when further 6 mole equiv. MeMgI solution was added. The mixture was stirred for 30 min. under cooling, and for another 30 min. at a room temperature. Then the mixture was refluxed on a water bath for another 30 min. The faint red syrupy product which was separated by usual treatment was washed with hexane to obtain a solid material. On recrystallization from hexane, it formed colorless plates, m.p. 109°, yield, 300 mg. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3600 (OH), 1750 ($COOCH_3$). *Anal.* Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.56; H, 7.10.

2-(2,5-Dimethoxy-4-methylphenyl)acrylic Acid (XI)——The compound IX (100 mg.) was refluxed in 5% methanolic KOH for 3 hr. From the reaction mixture a syrupy acid portion was separated by the usual method, which was then dissolved in glacial AcOH (15 cc.) and refluxed for 3 hr. The solvent was removed *in vacuo*, and the residue was treated with H_2O to form white amorphous substance, which was recrystallized from $CHCl_3$ and hexane to give colorless needles, m.p. 164°, yield, 20 mg. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3000~2500, 1700 (COOH), 1627 (double bond). *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.80; H, 6.54.

2-(2,5-Dimethoxy-4-methylphenyl)propionic Acid (XII)——The compound XI dissolved in MeOH (20 cc.) was reduced catalytically using Pd-C (20%, 50 mg.) as a catalyst. The product formed colorless prisms, m.p. 113°, yield, 15 mg. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3000~2500, 1710 (COOH); 860 (benzene ring). *Anal.* Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.05; H, 7.22.

The compound XII was proved to be identical with aglycone H leucodimethyl ether (=aglycone F methyl ether) by a mixed fusion and the comparison of their IR spectra.

(2,5-Dimethyl-3,6-dimethoxyphenyl)acetic Acid (XIV)——A mixture of 4,7-dimethyl-5-hydroxy-2-(3*H*)benzofuranone (XIII), Me_2SO_4 (5 cc.) and MeOH (10 cc.) was boiled, and added with KOH (5 g.) in MeOH (25 cc.). The mixture was refluxed for 1 hr. and extracted with Et_2O after acidification to separate XIV which was recrystallized from hexane to form crystals, m.p. 137°, yield, 85 mg. NMR spectrum was measured in CCl_4 at 60 Mc. using Varian Associates PD 60 apparatus (Fig. 1). *Anal.* Calcd. for $C_{12}H_{16}O_4$: C, 64.29; H, 7.14. Found: C, 64.52; H, 7.26.

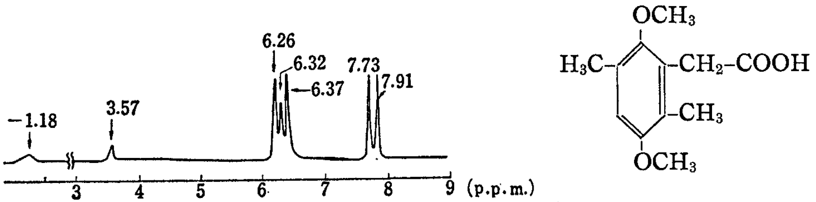

Fig. 1.

τ: 7.91, 7.73 (aromatic $C\underline{H}_3$);
τ: 6.37, 6.26 ($OC\underline{H}_3$);
τ: 6.32 $-C\underline{H}_2-$;
τ: 3.57 (aromatic proton);
τ: −1.18 ($COO\underline{H}$).

(3,6-Dimethyl-*p*-benzoquinone-2-acetic) Acid (XV)——On oxidation of the compound XIII (100 mg.) with CrO_3 (100 mg.) in 0.7*N* H_2SO_4 610 cc. at room temperature for 2 hr., a quinone XV was yielded as yellow needles, m.p. 143.5~144°, yield, 35 mg.

The authors are grateful to Mr. Y. Kawazoe of this Faculty for measurement of the nuclear magnetic resonance spectra. The infrared and ultrarviolet spectral measurements and microanalysis were carried out by the members of microanalytical laboratories of this Faculty and the Research Institute for Applied Microbiology of this University to whom the authors' thanks are due.

Summary

2-(2,5-Dimethoxy-4-methylphenyl)propionic acid (XII) was synthesized and proved to be identical with aglycone H leucodimethyl ether which was derived from paeoniflorin, a glucoside of Chinese Paeony root.

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