solvent, was unsuccessful, because no foaming was observed during the heating and no product was obtained after removing the unreacted reagents.

In contrast, by the treatment of the two esters in equimolar quantities in boiling xylene there remained a small amount of substance after recovering the unreacted reagents. This residue boiled at 167–172° (4–5 mm.), readily solidified and recrystallized from alcohol to colorless fine needles, m.p., 143–145°. The m.p., mix. m.p., and elementary analyses showed that it was quite identical with the acetyl derivative obtained by the previous two reactions and, in return, these facts established that they were all *N*-methyl-3-acetyl-4-hydroxyquinolones-(2). *Anal.* Calcd. for $C_{12}H_{11}O_3N$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.07; H, 5.13; N, 6.23.

Similarly, from ethyl *N*-ethylanthranilate and ethyl acetoacetate was derived *N*-ethyl-3-acetyl-4-hydroxyquinolone-(2), b.p., 144–154° (3 mm.) and m.p., 116–117° (from alcohol). *Anal.* Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.49; H, 5.85; N, 6.63.

Summary

1) 3-Acyl-2,4-dihydroxyquinolines were synthesized by the Friedel-Crafts reaction of 2,4-dihydroxyquinoline, and similarly, *N*-alkyl-3-acyl-4-hydroxyquinolones-(2) by the same procedure of *N*-alkyl-4-hydroxyquinolone-(2). Some of them were also prepared by the cyclization method to confirm the chemical structures of the products obtained by the Friedel-Crafts reaction.

2) 3-Acetyl and 3-benzoyl derivatives of both 2,4-dihydroxyquinoline and *N*-alkyl-4-hydroxyquinolone-(2) were also derived from their acetates and benzoates by the Fries rearrangement.

3) 3-Formyl derivatives were prepared by the Reimer-Tiemann reaction.

4) The ultraviolet absorption spectra of these synthetic compounds and of the related substances were examined for the identification of their chemical structures.

5) Most of these acylated compounds were found to be less active against *Staph. aureus in vitro* than 3-acyl-4-hydroxycoumarins.

6) *N*-Methyl-3-acyl-4-hydroxyquinolones-(2) were found to have a slight tendency to increase their antimicrobial activities with the elongation of their carbonyl side-chains.

(Received June 14, 1951)

325. Tutou Aihara: On the Principles of *Xanthoxylum piperitum* DC. IV. The Structure of Sanshoamide.

(Pharmaceutical Institute, Medical Faculty, University of Tokyo*)

In the first paper¹⁾ of this study, the late Prof. M. Asano and the author reported a new crystalline substance melting at 110–111° occurring in the fresh unripe fruits of *Xanthoxylum piperitum* DC., and named it sanshoamide. In connection with studies on sanshoöls^{2,3)} some efforts were made thereafter to determine the chemical structure of sanshoamide.

This substance was obtained from the non-volatile fraction of the ethereal extract of the fresh fruits collected in the early summer.

* Bunkyo-ku, Tokyo. (相原 傳)

1) M. Asano and T. Aihara: This Journal, **69**, 79 (1949).

2) T. Aihara: Ibid., **70**, 43 (1950).

3) T. Aihara: Ibid., **70**, 47 (1950).

In connection with chemical structures, it is interesting to note that a biogenetical relationship exists between the contents of sanshoamide and sanshoöls. The content of sanshoamide in the fruit decreases during the ripening period and, in contrast, that of sanshoöls gradually increases. It may be possible to suppose, therefore, that sanshoamide having a hydroxyl in the basic portion of the molecule would be a precursor of the sanshoöls.

The author wishes to thank Prof. Shoji Shibata for his kind advices and is indebted to Miss R. Ota and Mr. B. Kurihara of the Institute for Infectious Diseases, and to Miss. S. Yamamoto and Mr. H. Tani of this department, for the analyses.

Experimental

Isolation of sanshoamide—The unripe fresh fruits of *Xanthoxylum piperitum* DC. collected in the early summer were digested with ether, three times, at a room temperature. The solvent was distilled off and the residue was steam distilled to remove the essential oils. The ethereal solution of the residue was dried over anhydrous sodium sulfate and the filtrate was shaken vigorously with magnesia for 2 hrs. Then the solvent was removed and the residue was extracted with methanol at a room temperature and methanol was distilled off under a reduced pressure leaving a dark green residue possessing a strong pungent taste. On treatment with boiling 50% methanol, a sparingly soluble oily substance (crude sanshoöl) separated which was removed by decantation and a crystalline substance was obtained from the soluble portion on cooling. The latter was recrystallized from benzene to colorless needles, m.p. 110–111°, and named sanshoamide. (Yield: 0.066% of the fresh fruits).

Sanshoamide is readily soluble in most of the organic solvents, readily discolors bromine and permanganate solutions, is very unstable when exposed to air, resulting in the depression of its melting point of 10° or more within a few hours. It is somewhat stable in the ethereal solution for a short period of time but the degeneration cannot completely be prevented. *Anal.* Calcd. for $C_{16}H_{25}O_2N$; C, 73.00; H, 9.50; N, 5.32. Found: C, 72.84; H, 9.02; N, 5.37.

Octahydrosanshoamide—0.740 g. of sanshoamide was catalytically hydrogenated with Pd-C as a catalyst, absorbing four moles of hydrogen (Calcd.: 252 cc. Found: 268 cc.) during 1 hr. The product was recrystallized from petroleum ether to colorless needles, m.p. 56–57°, which is readily soluble in conc. H_2SO_4 or conc. HCl, giving a colorless solution. *Anal.* Calcd. for $C_{16}H_{33}O_2N$; C, 70.84; H, 12.18; N, 5.16. Found: C, 70.58; H, 12.18; N, 4.90, 5.11.

A mixture of octahydrosanshoamide (0.5 g.), acetyl chloride (10 g.) and anhydrous sodium acetate (0.5 g.) was gently boiled for 1 hr. The mixture was poured into ice water, made alkaline and extracted with ether. It is recrystallized from a small amount of petroleum ether to colorless needles, m.p. 46–48° (micro-m.p.). *Anal.* Calcd. for $C_{18}H_{35}O_3N$; N, 4.47. Found: N, 4.55.

Hydrolysis of octahydro-sanshoamide—A mixture of 1 g. of octahydrosanshoamide and 20 cc. of dil. HCl (1:1) was heated on a steam bath for 2 hrs. The reaction product was extracted with ether from which a waxy crystalline substance was obtained. Recrystallized from dil. alcohol to colorless plates, m.p. 43°, showing no depression of melting point by a mixed fusion with *n*-lauric acid. The amide of the acid was proved to be identical with *n*-lauric amide (m.p. 99°) by a mixed fusion.

The aqueous solution separated from ethereal layer was evaporated to dryness and dried in a vacuum desiccator leaving a very hygroscopic crystalline amine hydrochloride.

Picrate: Golden yellow plates, m.p. 89-90° (micro-m.p.), from dil. ethanol.

Benzoate: Prepared by the Schotten-Baumann method; recrystallizing from ligroin, the product forms colorless needles, m.p. 107-108° (softening from 103°). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.39; H, 7.77; N, 7.25. Found: C, 68.07; H, 7.83; N, 7.47.

It was proved by a mixed fusion to be identical with synthetic *N*-benzoate of 2-hydroxy-isobutylamine-1, m.p. 107-108°.

Oxidation of octahydrosanshoamide: 3 g. of octahydro-sanshoamide was dissolved in 20 cc. of conc. H_2SO_4 , and diluted with water to 200 cc. To this solution, 7 g. of finely powdered $KMnO_4$ was gradually added under vigorous stirring at a room temperature. After a complete discoloration of the permanganate solution, the precipitates were filtered off, the filtrate was made alkaline and steam-distilled. 100 cc. of the distillate was acidified with dil. H_2SO_4 and again steam distilled. A solution of *p*-nitrophenylhydrazine (0.2 g.) in acetic acid (5 cc.) was added to the first run (30 cc.) of the distillate, when yellow needles, m.p. 149°, separated out. By a mixed fusion, it was proved to be identical with acetone-*p*-nitrophenylhydrazone. *Anal.* Calcd. for $C_9H_{11}O_2N_3$: N, 21.76. Found: N, 21.50.

The solution remaining in the flask was made alkaline and steam distilled. Ammonia was proved in the distillate as its benzoate, m.p. 125°.

Synthesis of 2-hydroxy-isobutylamine-1: Under vigorous stirring, 2.8 g. of hydrochloride of glycooll ethyl ester was gradually added to an ice-cooled ethereal solution (50 cc.) of Grignard's reagent prepared from Mg (2.4 g.) and CH_3I (14.2 g.). After 30 minutes, the reaction mixture was heated on a steam bath for half an hour, then continuously extracted with ether.

After removal of ether, a basic oily product was obtained, which gave a benzoate, m.p. 107-108°, identical with the amine benzoate, m.p. 108°, obtained from hydrosanshoamide by hydrolysis. *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.39; H, 7.77; N, 7.25. Found: C, 68.15; H, 7.91; N, 7.01.

Synthesis of octahydrosanshoamide (*N*-2'-hydroxy-isobutyl-*n*-lauric amide-1): Ethereal solution of the synthetic 2-hydroxy-isobutylamine-1 was mixed with *n*-lauric chloride under ice-cooling. After half an hour, the solution was successively washed with alkali, HCl and water. The solvent was removed by distillation and the residue was recrystallized from petroleum ether to colorless needles, m.p. 56-57°, which was proved by a mixed fusion to be identical with octahydrosanshoamide. *Anal.* Calcd. for $C_{16}H_{33}O_2N$: C, 70.84; H, 12.18; N, 5.16. Found: C, 71.06; H, 12.18; N, 5.46.

Oxidation of sanshoamide—A suspension of 2.8 g. sanshoamide in water of 45-50° was stirred and 24 g. of $KMnO_4$ was added gradually, keeping this temperature. Manganese dioxide was removed from the reaction mixture and steam-distilled. Addition of acetic acid solution of *p*-nitrophenylhydrazine to 20 cc. of the distillate precipitated yellow needles, m.p. 149°, of acetone-*p*-nitrophenylhydrazone.

The residual solution was acidified and again steam-distilled. Acetic acid was confirmed as its *p*-bromophenacyl bromide, m.p. 86°, from the distillate. Succinic acid, m.p. 185°, was proved from the residue.

Summary

The structure of sanshoamide, a principle of the unripe fruits of *Xanthoxylum piperitum* DC. was studied and the formula was represented as *N*-2'-hydroxy-2,4,8,10-dodecatetraeneamide-1'.

(Received June 18, 1951)

326. Hiroshi Mitsuhashi: Crystallographic Study of Crude Drug Components. III.

On the Configuration of Santonin and Its Derivatives. (1).

(Pharmaceutical Institute, Medical Faculty, University of Tokyo*)

Considered from the structural formula of santonin possessing four asymmetric carbon atoms in its molecule, 16 stereo-isomeric forms are theoretically possible. However,

* Bunkyo-ku, Tokyo. (三橋 博)