Oxidative decomposition of 3-*p*-nitrophenylquinolizidine (XVI)—To a solution of 70 mg. of (XVI) in methanol, methyl iodide was added and warmed, whereby its methiodide was obtained. Recrystallized from ethanol as colorless plates, m.p. 237~239° (decomp.). *Anal.* Calcd. for $C_{15}H_{20}O_2N_2 \cdot CH_3I$: C, 47.7; H, 5.7. Found: C, 47.0; H, 5.3. A solution of 70 mg. of the methiodide was thoroughly mixed with freshly prepared silver oxide, filtered, and washed consecutively with water and alcohol. The filtrate and washings were combined and warmed on a boiling water bath for about 2 hours, allowing the alcohol to distill out. When cool, the mixture was salted out, and the oily substance that separated out was taken up in ether. The ether residue was suspended in water, and saturated potassium permanganate solution was dropped in, while warming on a water bath, until the color of the permanganate persisted. After decolorizing the permanganate with the addition of a small amount of methanol, the mixture was filtered, washed well with water, and the combined filtrate and washings was again filtered. The filtrate thereby obtained was evaporated on a water bath and acidification of the residual liquid separated 20 mg. of crude crystals. Purification by sublimation yielded colorless plates of m.p. 233~236°, which failed to give any depression of the melting point on admixture with authentic specimen (Kahlbaum preparation) of *p*-nitrobenzoic acid, m.p. 234~237°.

Summary

3-Phenyl- (II) and 3-*p*-acetaminophenylquinolizidine (III) were prepared by the following procedures. Condensation of 2-vinylpyridine and ethyl phenylacetate gave ethyl α-phenyl-γ-pyridylbutyrate (VII) whose reduction and cyclization yielded 3-phenyl-4-ketoquinolizidine (X). Reduction of (X) with lithium aluminum hydride or electrolytically, gave two different forms of 3-phenylquinolizidine (II) giving picrates of m.p. 152~153° and of m.p. 180~181°, from which the presence of stereoisomers was assumed. Nitration of (II) with sulfuric and nitric acids, followed by acetylation gave 3-*p*-acetaminophenylquinolizidine (III).

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28. Tatsuo Kariyone* and Takao Matsuno**: Studies on the Constituents of Orange Oil. I. On the Structure of Auraptene.

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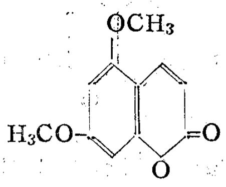
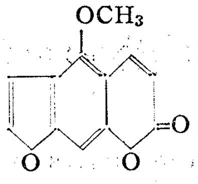
*and Kyoto College of Pharmacy***)

The oil of Citrus genera contains a minute quantity of coumarin derivatives, such as citraptene (I) in lemon oil and bergaptene (II) in bergamot oil, besides over 95% of *d*-limonene.



(I)



(II)

Komastu and Tanaka[1] first isolated, in 1930, a crystalline compound melting at 68° from the oil of *Citrus aurantium Natsudaidai* and named it auraptene. They considered it to be 7-hydroxycoumarin heptyl ether (III) without synthetic confirmation.

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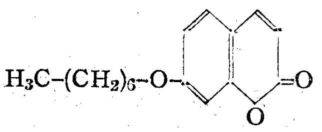
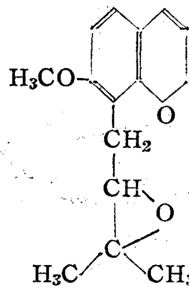
[1] S. Komatsu, *et al*: J. Chem. Soc. Japan, **51**, 478 (1930).
[2] H. Böhme, G. Pietsch: Arch. Pharm., **276**, 482 (1938); Ber., **72**, 773 (1939); *ibid.*, **72**, 780 (1939).

Böhme and Pietsch[2], in 1938, used the name auraptene for another coumarin derivative (m.p. 91°) isolated from the oil of sweet and bitter oranges. They assumed formula (IV) for it.



(III)



(IV)

In order to avoid confusion, Dodge[3] suggested retaining the name auraptene for the compound described by Komatsu, and to name the substance isolated by Böhme meranzin.

We obtained auraptene, m.p. 68°, from the residue of orange oil manufactured by the essential oil industry. Analysis and molecular weight determination agreed with the formlua $C_{19}H_{20}O_3$, instead of $C_{16}H_{20}O_3$, which was given by Komatsu and Tanaka.

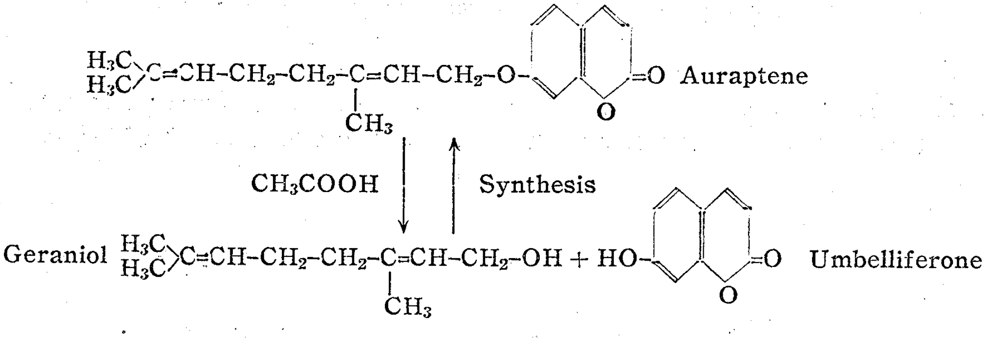
We synthesized 7-hydroxycoumarin heptyl ether, m.p. 38~40°, and proved it to be quite different from natural auraptene.

On decomposing auraptene by heating with hydriodic acid, previous workers[1,4] had obtained umbelliferone but failed to catch the alcoholic moiety.

On heating auraptene with glacial acetic acid, we obtained geraniol as well as umbelliferone, the former being contained as an acetate in the reaction product. Geranyl acetate was saponified with alkali and geraniol was identified as its diphenyl carbamate, melting at 82~83°. When decomposition is carried out completely in room temperature with a small amount of sulfuric acid added to acetic acid, geraniol is not obtained, owing to polymerization.

As the result of above reaction, auraptene is considered to be umbelliferone-7-geranyl ether instead of heptyl ether as considered by Komatsu and Tanaka.

We synthesized umbelliferone-7-geranyl ether by reacting geranyl chloride with umbelliferone in alkaline medium and proved it to be identical with the natural auraptene.



The authors wish to express their apprectiation to the San-ei Chemical Company, Osaka, for supplying them the crude orange oil used in this investigation.

Experimental

Isolation of auraptene—Crude oil obtained by expression of fresh peel of *Citrus aurantium Natsudaidai* is distilled *in vacuo* until the distillate becomes about 80% of crude oil, which is sold as orange oil. The distillation residue of dark brown, sticky semi-liquid, was dissolved in a small amount of ethanol, and allowed to stand at room temperature. In a few days, yellowish needle crystals separated out, which were successively recrystallized from ethanol, ether, petroleum

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3) Dodge: Am. Perfumer, 41, 31 (1940).

4) D. Nomura: J. Japan. Chem., 4, 561 (1950).

ether, and ethanol, to colorless prisms, m.p. 68°. *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.50; H, 7.38; Mol. Wt., 298. Found: C, 76.43; H, 7.42; Mol. Wt. (Rast), 308.

Synthesis of umbelliferone heptyl ether—To the alcoholic solution of 2.9 g. of potassium hydroxide and 8.1 g. of umbelliferone, 11 g. of heptyl bromide was added and the mixture was heated on a water bath for 6 hours, until the reaction mixture became neutral and the fluorescence disappeared. The solvent was distilled off, the residue was poured into water, and extracted with ether. The ethereal solution was washed with 5% sodium hydroxide solution to remove unchanged umbelliferone. The ether was distilled off and the residue was recrystallized from 50% alcohol and then from petroleum ether. Yield, 3.5 g. (m.p. 38~40°). *Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.84; H, 7.69: Mol. Wt., 260. Found: C, 74.00; H, 7.77: Mol. Wt. (Titration), 265.

Methylation of auraptene—1.5 g. of auraptene was dissolved in 54 cc. of 10% sodium hydroxide solution, with stirring and warming on a water bath. A considerable amount of insolube yellow oil was observed on the surface of the yellow solution. After cooling, 12 cc. of dimethyl sulfate was added through a dropping funnel in 3 portions. Finally, 10 cc. of 10% sodium hydroxide was added, and the mixture was heated on a water bath for about 30 min. The reaction mixture was cooled, acidified, and extracted with ether. The ethereal extract was extracted with 3% sodium carbonate solution, and the aqueous layer was neutralized with dil. hydrochloric acid. The resulting brown oily substance was treated with hydrated ethyl acetate and petroleum ether, and the orange, viscous crystalline substance was obtained. Recrystallization from hydrated ethanol gave 0.3 g. of crystalline substance, m.p. 57~58°. *Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.9. Found: C, 72.65; H, 8.0. 0.9 g. of unchanged auraptene was recovered from the ethereal extract.

Methylation of synthetic umbelliferone heptyl ether—1.5 g. of the material was methylated by the same way as described above. Recrystallization from petroleum ether gave 0.7 g. of large rhombic compact crystals, m.p. 67°. *Anal.* Calcd for $C_{17}H_{24}O_4$: C, 69.86; H, 8.21. Found: C, 69.67; H, 8.56.

Alkaline fusion of auraptene—To the fused mixture of about 1 cc. of water and 10 g. of potassium hydroxide, 1 g. of the material was added and fused at 210~220° for 75 min. After cooling, the mixture was dissolved in water and acidified with conc. sulfuric acid. The tarry substance that separated was extracted with ether. After the removal of ether and vacuum distillation, white needles, m.p. 108°, were obtained. Yield, 0.14 g. It was proved to be resorcinol.

Decomposition of auraptene with acetic acid—5 g. of auraptene was dissolved in 10 cc. of glacial acetic acid and heated in an oil bath at 138~144° for 10 hours. On cooling, white crystals separated out, which were recrystallized from ethanol, and proved to be umbelliferone (A), m.p. 232°. Yield, 2 g. To 0.13 g. of this substance (A), 10 g. of acetic anhydride and one drop of conc. sulfuric acid were added and the mixture was allowed to stand overnight. The reaction mixture was poured into 300 cc. of ice-water with stirring, and the white crystals that precipitated were recrystallized from 50% ethanol to 0.15 g. of a product which melted at 141~142°. Mixed fusion with an authentic sample of umbelliferone acetate did not show any depression of the melting point.

The filtrate was neutrallized with soda and extracted with ether. After washing and drying, the ether was distilled off. The viscous residue was distilled under a diminished pressure. The fraction which boiled out at 100~110°/5 mm. was collected. Yield, 0.6 g. *Anal.* Calcd. for $CH_3COOC_{10}H_{17}$: C, 73.46; H, 10.20. Found: C, 73.72; H, 10.08.

0.6 g. of this fraction was saponified with 5% methanolic potassium hydroxide solution and 0.4 g. of alcoholic substance with aromatic odor was obtained. A mixture of 0.3 g. of the liquid dissolved in 0.5 g. of dry pyridine and 0.42 g. of diphenyl carbamide chloride[5] was heated for 2 hours on a boiling water bath and steam-distilled. The colored residue was recrystallized from ethanol, to colorless needles, m.p. 82~83°. The mixed fusion with an authentic specimen of geranyl diphenyl urethane showed no depression. *Anal.* Calcd. for $C_{23}H_{27}O_2N$: C, 79.08; H, 7.73: N, 4.01. Found: C, 79.30; H, 7.57; N, 3.93.

Two g. of auraptene was dissolved in 20 cc. of glacial acetic acid containing 4 drops of conc. sulfuric acid and allowed to stand overnight at room temperature. The white needles (A), m.p. 232°, that were obtained proved to be umbelliferone. Yield, 0.7 g. The crystals were acetylated with conc. sulfuric acid and acetic anhydride. The mixed m.p. with an authentic sample of umbelliferone acetate did not show any depression.

Synthesis of auraptene—Geranyl chloride was prepared from geraniol according to the procedure of Forster and Cardwell[6]. 0.3 g. of sodium was dissolved in 50 cc. of absolute alcohol, and to this 1.7 g. of geranyl chloride and 1.5 g. of umbelliferone were added. The mixture was heated under reflux for 8 hours. The reaction product was dissolved in ether, and the ethereal solution, after evaporation, separated pale brown needles, which recrystallized from alcohol, to m.p. 68°.

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5) A. Conduché: A. Ch., [8] 13, 71 (1908).
6) M. O Forster, D. Cardwell: J. Chem. Soc., 103, 1341 (1913).

Yield, 0.3 g. *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.51; H, 7.38. Found: C, 76.23; H, 7.24. Mixed melting point with natural auraptene did not show depression.

Summary

Auraptene, m.p. 68°, previously isolated by Komatsu and Tanaka from orange oil obtained by the expression of fresh peels of *Citrus aurantium Natsudaidai* (Japanese summer orange), corresponded to formula $C_{19}H_{22}O_3$ and was proved to be umbelliferone-7-geranyl ether, instead of heptyl ether, $C_{16}H_{20}O_3$, as considered by Komatsu and Tanaka. We have obtained umbelliferone and geraniol (identified as geranyl diphenyl urethane, m.p. 82~83°) by heating auraptene in acetic acid solution. Synthetic umbelliferone-7-geranyl ether was proved to be identical with auraptene.

(Received March 24, 1953)

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29. Kyosuke Tsuda, Nobuo Ikekawa, Hiroshi Mishima, Akira Iino, and Tomoo Morishige: Studies on the Coal Tar Bases. I. Synthesis of Tetramethylpyridine.

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It has hitherto been reported that all the polymethylpyridines except 3,4,5-trimethylpyridine and pentamethylpyridine exist in the coal tar bases. In many cases, the structures of these pyridines are presumed from that of pyridine-polycarboxylic acids derived by oxidation. However, the determination of the configuration of alkyl radicals of pyridine only by the properties of those polycarboxylic acids has proved inaccurate since the constants of alkylpyridines differ from those given in some references.

During studies on coal tar bases as described in the present paper, it became necessary to synthesize polymethylpyridines, the samples of which could be compared with those isolated from coal tar and an attempt was made to obtain polymethylpyridines.

Only one of the tetramethylpyridines has been synthesized. Oparina[1] obtained a series of methyl homologs of pyridine, by passing a mixture of methyl ethyl ketone, formaldehyde, and ammonia over heated alumina, from which 2,3,5,6,-tetramethylpyridine was isolated. For obtaining a pure sample, we found a better process of synthesis.

2,3,5,6,-Tetramethylpyridine. Recently, Karrer and Mainoni[2] prepared pentamethylpyridine from 3,5-dicarbethoxy-2,4,6,-trimethylpyridine and, by utilizing this principle, 2,3,5,6,-tetramethylpyridine was synthesized. 2,6-Dimethyl-3,5-dicarbethoxypyridine (I)[3], prepared by the Hantzsch cyclization using ammonia, acetoacetic ester, and formaldehyde, was reduced with lithium aluminum hydride to the dicarbinol (II), derived to the dichloride (III) by chlorination, and finally to 2,3,5,6,-tetramethylpyridine (IV) by catalytic reduction.

2,3,5,6-Tetramethylpyridine thereby obtained was a prismatic crystals, m.p. 76°, b.p. 198°, giving a picrate of m.p. 173.5°. These constants coincide with those in the literature. Chloroplatinate, yellow needles, m.p. 179°, mercuric chloride salt, colorless needles, m.p. 170°. This compound (IV) was found to be identical with the tetramethylpyridine, m.p. 76°, which was separated from a fraction of $b.p_{100}$ 130~132°, from coal tar bases

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[1] M. P. Oparina: Ber., **64**, 569 (1931); C. A., **44**, 1108 (1950).

[2] P. Karrer, S. Mainoni: Helv. Chim. Acta, **34**, 2151 (1951).

[3] A. Hantzsch: Ann., **215**, 1 (1882); Ber., **18**, 1744 (1885); F. Erglemann: Ann., **231**, 50 (1885); L. Claisen: *Ibid.*, **297**, 39 (1897).