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65. Tatsuo Ohta, Yo Mori, Chiaki Noda, and Toru Aoki : Furoquinolines. XX.*1 Alkaloids of the Leaves of *Ruta graveolens* L. and Synthesis of Dihydrokokusaginine.

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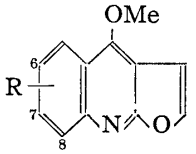
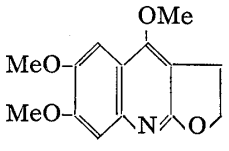
In Part XIII[1] of this series, the isolation of kokusaginine (I) and skimmianine (II) from the pericarps of *Ruta graveolens* L. was described. In the present series of work examinations were made on the basic constituents present in the leaves, and (I) and (II) were obtained in 0.01% yield, along with bergapten.

Like dictamnine and skimmianine,[2] hydrogenation of (I) over palladium oxide gave 2,3-dihydrokokusaginine (III), m.p. 173° (picrate, m.p. 229°). The structure of (I) was determined by permanganate oxidation[3] and by way of hydrogenolysis[4] as 4,6,7-trimethoxyfuro[2,3-*b*]quinoline. Although the linear structure for (I) was established[5] by the properties of the hydrogenolytic product of acronidine, a derivative of (I), direct evidence has not been brought about as yet. Therefore, the synthesis of (III) was carried out as will be described below.

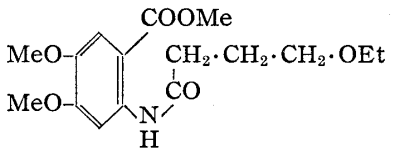
Condensation of methyl 6-aminoveratrate with 4-ethoxybutyric acid gave methyl 6-(4-ethoxybutyramido)veratrate (IV), m.p. 64~65°, which was cyclized to 6,7-dimethoxy-3-(2-ethoxyethyl)-4-hydroxycarbostyril (V), m.p. 206~208° (4-O-acetate (VI), m.p. 240~242°; 2,4-dichloro derivative (VII), m.p. 138~139°) by treatment with metallic sodium in boiling



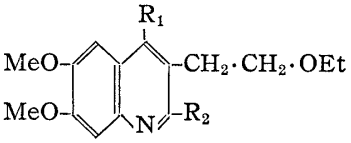
(I) R=6,7-MeO
(II) R=7,8-MeO



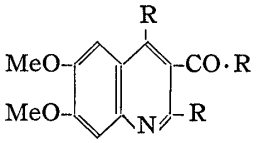
(III)



(IV)



(V) $R_1=R_2=OH$ (VI) $R_1=OAc$, $R_2=OH$
(VII) $R_1=R_2=Cl$ (VIII) $R_1=MeO$, $R_2=OH$



(IX) R=OH
(X) R=MeO

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*1 Part XIX. T. Ohta, Y. Mori, M. Hosoya : Tokyo Yakka Daigaku Kenkyû Nempô, **9**, 240(1959).
*2 Kashiwagi 4-chome, Shinjuku-ku, Tokyo (太田達男, 森　陽, 野田千秋, 青木　透).
1) T. Ohta, T. Miyazaki : Yakugaku Zasshi, **78**, 538(1958).
2) T. Ohta, *et al.* : *Ibid.*, **74**, 708(1954).
3) F. A. L. Anet, *et al.* : Austral. J. Sci. Research, **A5**, 412(1952).
4) M. Terasaka, K. Narahashi, T. Ohta : Yakugaku Zasshi, **75**, 1040(1955).
5) cf. J. R. Price : Fortschr. Chem. org. Naturstoffe, **13**, 324(1956).

xylene. Methylation of (V) with diazomethane[6],*1 furnished 4,6,7-trimethoxy-3-(2-ethoxyethyl)carbostyril (VIII), m.p. 180~181°. It is of interest to note that methylation of (V) occurs mainly in the 4-position, whereas norkokusagininic acid (IX) is attacked in both 2- and 4-positions,[7] giving methyl 2,4,6,7-tetramethoxyquinoline-3-carboxylate (X). Heating of (VIII) with polyphosphoric acid[8],*1 yielded 4,6,7-trimethoxy-2,3-dihydrofuro[2,3-*b*]quinoline (III), m.p. 173°, which was quite identical with 2,3-dihydrokokusaginine prepared from the natural alkaloid. The ultraviolet spectral curve of (III) resembled those of 4-methyl-2,3-dihydrofuro[2,3-*b*]quinoline[8] and 2,3-dihydrodictamnine (Fig. 1). These evidences established that kokusaginine had a linear tricyclic structure.

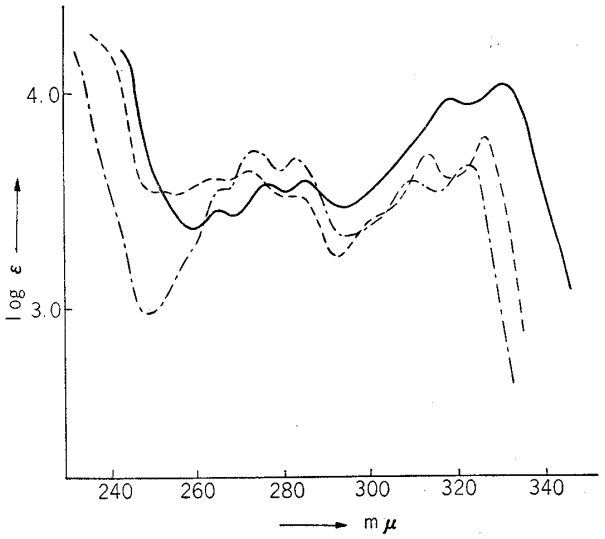

Fig. 1.
Molecular Extinction Curves (in EtOH)
——— Dihydrokokusaginine
— — — 4-Methyl-2,3-dihydrofuro-[2,3-*b*]quinoline
—·—· Dihydrodictamnine

Experimental

All m.p.s are not corrected

Isolation of the Alkaloids from the Leaves of *Ruta graveolens*—The leaves of *Ruta graveolens* were collected in early September of 1958 in the Medicinal Plant Garden attached to this College. Approximately 1 kg. of the air-dried leaves was soaked in 18 L. of MeOH for at least 5 days. After the extract was removed, the leaves were extracted 3 more times in a similar manner. The deep green extract was concentrated *in vacuo* and the residual syrup was treated repeatedly with 3% HCl (total, 1.7 L.) until no precipitation occurred with the Mayer reagent. The combined acid solution was neutralized with 20% NaOH to pH 2.4. The adherent gummy matter that separated out was removed by filtration, the filtrate was made alkaline with NH_4OH, and this was shaken thoroughly with $CHCl_3$. The $CHCl_3$ layer was separated, dried, filtered, and the filtrate was evaporated to dryness. The residue obtained was chromatographed on Al_2O_3 (3×20 cm.) in dehyd. benzene solution (50 cc.). The effluent liquor showing a violet fluorescence under ultraviolet light was evaporated. The residue was recrystallized from EtOH to white prisms, m.p. and mixed m.p. (with kokusaginine) 168~169°. Yield, 0.1 g.

On the other hand, the pale yellow chromatogram exhibiting a faint blue fluorescence under ultraviolet light was eluted with EtOH, by which yellowish crystals, m.p. 122~129°, were obtained. Since these crystals gave two spots (Rf 0.74 and 0.58 in 30% AcOH by volume) on paper partition chromatogram, they were rechromatographed on Al_2O_3. From the light yellow chromatogram, skimmianine was obtained by elution with EtOH. Yield, 0.1 g. It crystallized from EtOH to pale yellow prisms, m.p. 176.5°. Evaporation of the effluent liquor afforded bergapten, m.p. 187~188° (colorless needles from benzene). Yield, 0.5 g. Both substances thus obtained were confirmed by mixed fusion tests with authentic specimens.

Hydrogenation of Kokusaginine—An EtOH solution of kokusaginine (0.15 g.) was submitted to catalytic hydrogenation with PdO catalyst at ordinary pressure and temperature. The hydrogenated

6) cf. M. F. Grundon, N. J. McCorkindale : J. Chem. Soc., **1957**, 2177.
7) R. C. F. Brown : Austral. J. Chem., 8, 121(1955).
8) cf. T. Ohta, Y. Mori, S. Mihashi : Chem. & Ind. (London), **1959**, 1160.

product (m.p. 169~170°, after one crystallization from dil. EtOH) was chromatographed on Al_2O_3 in benzene solution. It recrystallized from a mixture of benzene and light petroleum (1:1) to colorless prisms, m.p. 173°. Yield, 34 mg. Its infrared spectrum was identical with that of the specimen of synthetic (III) described below. Picrate : Yellow prisms, m.p. 229° (from EtOH). *Anal.* Calcd. for $C_{14}H_{15}O_4N \cdot C_6H_3O_7N_3$ (picrate) : N, 11.42. Found : N, 11.06.

Methyl 6-(4-Ethoxybutyramido)veratrate (IV)—A mixture of methyl 6-aminoveratrate (12 g.) and 4-ethoxybutyric acid (7.5 g.) was refluxed for 20 hr. in an oil bath of 200~210°. After cool, the whole was acidified with 2*N* HCl and extracted with ether. The ether layer was washed with $NaHCO_3$ solution, dried, and evaporated. The residue was crystallized from light petroleum to colorless needles, m.p. 64~65°. Yield, 8.1 g. *Anal.* Calcd. for $C_{10}H_{23}O_6N$: C, 59.06; H, 7.13; N, 4.31. Found: C, 58.84; H, 7.05; N, 4.56.

6,7-Dimethoxy-3-(2-ethoxyethyl)-4-hydroxycarbostyril (V)—Preparation of (V) was carried out after the manner of 4-hydroxycarbostyril synthesis described in Part I of this series.[9] From the $NaHCO_3$-insoluble portion, the expected 6,7-dimethoxy-3-(2-ethoxyethyl)-4-hydroxycarbostyril was obtained by refluxing 11.5 g. of (IV) with Na (0.9 g.) for 3 hr. in xylene (60 cc.) instead of toluene. Colorless needles (from MeOH), m.p. 206~208°. Yield, 1.7 g. *Anal.* Calcd. for $C_{15}H_{11}O_5N$: C, 61.42; H, 6.53; N, 4.78. Found : C, 61.67; H, 6.81; N, 4.97.

The $NaHCO_3$-solution was acidified with HCl and the precipitate was crystallized from MeOH to colorless silky needles, m.p. 143~145° (0.9 g.), which was identified with 6-(4-ethoxybutyramido)-veratric acid, m.p. 143~145°, prepared from (IV) by hydrolysis with 10% MeOH-KOH. *Anal.* Calcd. for $C_{15}H_{21}O_5N$: C, 57.86; H, 6.80; N, 4.50. Found : C, 57.54; H, 6.96; N, 4.79.

4-O-Acetate (VI) of (V)—Prepared from 0.4 g. of (V), Ac_2O (6.0 cc.), and pyridine (1 drop) by boiling for 1 hr. Colorless silky needles (from MeOH), m.p. 240~242°. It is easily hydrolyzed to (V) when warmed with 10% NaOH solution. *Anal.* Calcd. for $C_{17}H_{21}O_6N$: C, 60.88; H, 6.31; N, 4.18. Found : C, 60.62; H, 6.37; N, 4.48.

2,4-Dichloro-6,7-dimethoxy-3-(2-ethoxyethyl)quinoline (VII)—Prepared from 1.18 g. of (V) by heating with $POCl_3$ (11.8 cc.) for 2 hr. Colorless needles (from EtOH), m.p. 138~139°. *Anal.* Calcd. for $C_{15}H_{17}O_3NCl_2$: C, 54.56; H, 5.16; N, 4.24. Found : C, 54.78; H, 5.51; N, 4.14.

4,6,7-Trimethoxy-3-(2-ethoxyethyl)carbostyril (VIII)—To 0.5 g. of (V) suspended in ether, an excess of CH_2N_2 was added and methylated. The compound insoluble in 1% NaOH was collected and recrystallized from EtOH to colorless prisms, m.p. 180~181°. Yield, 0.11 g. *Anal.* Calcd. for $C_{16}H_{21}O_5N$: C, 62.52; H, 6.88; N, 4.56. Found : C, 62.09; H, 6.52; N, 4.38.

4,6,7-Trimethoxy-2,3-dihydrofuro[2,3-*b*]quinoline—To 0.12 g. of (VIII), 3.0 g. of polyphosphoric acid was added and heated for 2 hr. at 120~130°. The mixture was poured into ice-water and made alkaline with NaOH. The precipitate thereby obtained was crystallized from a mixture of benzene and light petroleum (1:1) to colorless prisms, m.p. 173°. *Anal.* Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 5.36. Found : C, 64.74; H, 5.86; N, 5.14.

Picrate : Yellow prisms, m.p. 229°. The melting points of synthetic (III) and its picrate were not lowered when respectively mixed with the specimens derived from the natural alkaloid.

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Summary

The leaves of *Ruta graveolens* L. contained skimmianine and kokusaginine. The latter was hydrogenated to give 2,3-dihydrokokusaginine, which was identical with 4,6,7-trimethoxy-2,3-dihydrofuro[2,3-*b*]quinoline prepared from 4,6,7-trimethoxy-3-(2-ethoxyethyl)carbostyril by cyclization with polyphosphoric acid.

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9) T. Ohta : Yakugaku Zasshi, **73**, 63(1953).