Masanobu Terasaka, Tatsuo Ohta, and Kazuko Narahashi: Alkaloids of the Root-bark of *Orixa japonica* Thunb. V*. On the Structure of Kokusagine.

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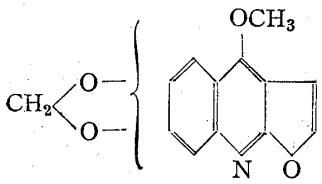
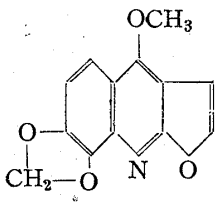
In the course of these studies, kokusagine, $C_{13}H_9O_4N$, was assumed to be methylenedioxydictamnine[1] (I), since it contains one methoxyl and one methylenedioxy group and it is converted by methyl iodide at 100° into isokokusagine, and further proof is the fact that the absorption spectra of kokusagine and dictamnine or skimmianine are almost identical.

We have isolated kokusagine, m.p. 196° (picrate, m.p. 171~172°), along with orixine[2], m.p. 152.5°, and skimmianine, m.p. 178°, from the methanolic extract of the lateral root of *Orixa japonica* Thunb., and following experiments were carried out to ascertain the position of the methylenedioxy group in kokusagine.

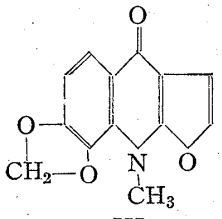
When a pure alcoholic solution of kokusagine was submitted to catalytic hydrogenation with platinum oxide as a catalyst, at room temperature and under ordinary pressure, almost two moles of hydrogen was absorbed and a compound, $C_{13}H_{13}O_4N$, which formed prisms, m.p. 169°, was obtained. Similar to the hydrogenation of dictamnine and skimmianine, it seems to have undergone the cleavage of its furan ring and to have formed methylenedioxy-4-methoxy-3-ethylcarbostyril[3]. When this compound was boiled with hydriodic acid, both demethylation and cleavage of the methylenedioxy group occurred and a phenolic base, m.p. 241~242°, was obtained. After the method of Oberlin[4], especially by following the method of Ozawa and his collaborators[5], the above hydrogenated compound was treated with aluminum chloride in nitrobenzene solution and then boiled with conc. hydrochloric acid, by which a phenolic base, m.p. 238~242°, was also obtained. With acetic anhydride and pyridine it gave a triacetate, m.p. 258°. These two bases and their acetates showed no depression of the melting point when admixed with 4,7,8-trihydroxy-3-ethylcarbostyril[6], m.p. 243~244°, and its acetate, m.p. 264°, respectively, which were derived from hydrogenated skimmianine. The structure of kokusagine, therefore, should be 7,8-methylenedioxydictamnine (II), and that of isotkokusagine, 7,8-methylenedioxyisodictamnine (III).



(I)



(II)



(III)

We wish to express our thanks to Mr. Zensaku Fujinaga, Director of the Fujinaga Pharmaceutical Company, for the extraction of the root.

* Part VI: J. Pharm. Soc. Japan, 62, 304 (1942).

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1) Terasaka: J. Pharm. Soc. Japan, 53, 1046 (1933).
2) *Ibid.*, 51, 707 (1931).
3) Ohta: *Ibid.*, 73, 63 (1953).
4) Oberlin: Arch. Pharm., 265, 256 (1927).
5) Ozawa, Kawanishi, Fujii: J. Pharm. Soc. Japan, 71, 1183 (1951).
6) Ohta, Miyazaki: This Bulletin, 1, 184 (1953).

Experimental

Extraction of Kokusagine—The lateral roots isolated from main roots were cut into small pieces, extracted with 96% methanol for 4~5 hours, and filtered while hot, the extraction being repeated twice. The filtrate was evaporated to a small volume and the viscous extract was warmed with 2% sulfuric acid. The clear reddish brown solution freed from resinous substances was made alkaline by the addition of ammonia, then shaken several times with ether. The ethereal soultion was washed first with a dil. potassium hydroxide solution, then with water, and dried. On evaporating there remained crystalline raw alkaloids, which formed, first from chloroform and ether, then from alcohol, colorless long needles, m.p. 196°; picrate, m.p. 171~172°. There was no depression of the melting point when mixed with authentic kokusagine and kokusagine picrate, respectively.

From the mother liquor of kokusagine, skimmianine, m.p. 178°, and orixine, m.p. 152.5°, were isolated by the same procedure as reported before.

Catalytic Reduction of Kokusagine (Formation of 7,8-Methylenedioxy-4-methoxy-3-ethylcarbostyril)—Hydrogenation was carried out with kokusagine (1.5 g.) in absolute alcoholic solution with platinum oxide as a catalyst. Almost 2 moles of hydrogen was absorbed quite smoothly, the violet fluorescence disappearing gradually. The solvent was removed under a reduced pressure by distillation and the residue was recrystallized from dilute alcohol. Colorless needles or prisms, m.p. 169°. Yield, 1.35 g. *Anal.* Calcd. for $C_{13}H_{13}O_4N$: C, 63.17; H, 5.26; N, 5.66. Found: C, 63.52; H, 4.94; N, 5.73.

Demethylation of the Reduction Product of Kokusagine and Cleavage of Methylenedioxy Group—i) One g. of the reduction product was dissolved in 10 cc. of conc. hydriodic acid (d=1.7) and two drops of acetic anhydride were placed in the Zeisel apparatus for methoxyl determination and boiled in a glycerol bath. After 1.5 hours, the cooled reaction mixture was made weak acid with bicarbonate and the crystals that separated were collected, washed with water, and crystallized from 10% alcohol. Slightly yellow needles, m.p. 241~242°. It gave green coloration with ferric chloride in an alcoholic solution. When mixed with authentic 2,4,7,8-tetrahydroxy-3-ethylquinoline, there was no depression of the melting point.

ii) To the solution of 1.1 g. of aluminum chloride and 10 cc. of nitrobenzene was added gradually 0.5 g. of the reduction product. The mixture soon became warm and before long went into solution. It was allowed to react for 2 hours. Then the solution was warmed at 45~50° for 30 minutes and, after adding 10 cc. of conc. hydrochloric acid, was heated under reflux for one hour. To the cold solution was added 10 cc. of conc. hydrochloric acid, the separated precipitate was washed first with water, then with alcohol, and recrystallized. Slightly yellow needles, m.p. 238~242°. Yield, 0.35 g. They showed no depression of the melting point when mixed with the above substance.

Acetylation of 2,4,7,8-Tetrahydroxy-3-ethylquinoline—To 80 mg. of 2,4,7,8-tetrahydroxy-3-ethylquinoline were added 2 cc. of acetic anhydride and 2 drops of pyridine and the mixture was heated on a boiling water bath for 1.5 hours. After decomposition of the excess acetic anhydride with ice-water, the acetate was recrystallized from alcohol to colorless needles, m.p. 257~258°. It gave no coloration with ferric chloride. When mixed with triacetate of 2,4,7,8-tetrahydroxy-3-ethylquinoline from skimmianine, there was no depression of the melting point.

(Received April 30, 1954)