## Synthetic Studies of Dictamnine, an Alkaloid of Skimmia repens, Nakai. II. The Synthesis of Dictamnine

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As an approach to the synthesis of dictamnine (I), some experiments were reported in our previous paper<sup>1)</sup>. Recently the synthesis of dictamnine was reported by Tuppy et al.<sup>2)</sup>, but its details have not yet been known. In this communication we describe the synthesis of dictamnine accomplished independently in our laboratory.

As previously reported, we synthesized the aldehyde II, and tried to cyclize it to the furoquinoline derivative III. Numerous attempts, however, to effect the cyclization of II to III were unsuccessful.





In their study of synthesizing dictamnine, Grundon et al. obtained 2,4-dichloro-3-(2chloroethyl)-quinoline (IV)<sup>3)</sup>. In our previous paper we reported that only the 2-chlorine atom of the 2,4-dichloroquinoline



<sup>1)</sup> T. Sato and M. Ohta, This Bulletin, 29, 817 (1956).

H. Tuppy, et al., Angew. Chem., 68, 388 (1956).
M. F. Grundon, et al., J. Chem. Soc., 1955, 4284.



maximum  $(275 \text{ m}\mu)$  of 2-hydroxyquinoline derivatives flattens generally in alkaline solution, but the spectrum of V in alkaline solution becomes identical with that of VII (Fig. 2) owing to cyclization, and the



characteristics described above could not be observed. The different spectroscopic characteristics of VII from those of the 2-hydroxyquinoline derivatives exclude the possibility that VII might be the vinyl derivative such as VIII. When VII was heated with hydrogen bromide, the bromo derivative VI was obtained, whose spectroscopic characteristics were very similar to those of the chloro derivative V.

Though it was difficult to separate V and VII, VII was obtained readily in pure state when the crude product was treated with methanolic sodium hydroxide. The methoxy derivative IX was obtained from the chloro derivative VII by treatment with sodium methylate at 100°. Our methoxy derivative melted at 92° (sintering at 82-3°), and gave the picrate having a m.p. of 187°, while the m.p's of the specimens from a natural source are  $96-7^{\circ}$  and  $183^{\circ}$ , respectively<sup>4)</sup>.



The dehydrogenation of the dihydrofuroquinoline derivatives VII and IX to the corresponding furoquinoline derivatives was not effected by palladium-charcoal in boiling diphenyl ether.

In order to obtain the bromo derivative X, we treated the chloro derivative VII with bromine, but the substance thus obtained was the perbromide having an empirical formula of  $C_{11}H_8NOClBr$ .

The desired bromo derivative X was obtained when the chlorodihydrofuroquinoline derivative VII was refluxed with N-bromosuccinimide in carbon tetrachloride in the presence of a small amount of benzoyl peroxide, and the solvent was removed under a reduced pressure though the position of the bromine atom was When carbon tetrachloride uncertain. was not removed, another substance decomposing at 92° was obtained. Although its structure has not yet been determined, it gave the bromo derivative X when treated with pyridine. The methoxydihydrofuroquinoline derivative IX gave no well-defined product with N-bromosuccinimide. The desired dictamnine (I) was obtained by the reaction of the bromo derivative X with sodium methylate in a sealed tube at  $100^{\circ}$ .

The synthetic dictamnine was shown to be identical with the natural specimen by their melting points, mixed melting points and melting points of their picrates.

## Experimental

Absorption spectra.—All spectra were determined in the same way as reported in our previous paper.

2,4-Dichloro-3-(2-chloroethyl)-quinoline

(IV).—It was prepared by the Grundon's method<sup>3</sup>) with slight modifications. Methyl cellosolve was used as a starting material instead of cellosolve;

4) T. Ohta, et al., J. Pharm. Soc. Japan, 74, 708(1954).

p-toluenesulfonyl chloride instead of benzenesulfonyl chloride was used for preparing the malonic acid derivative; and the amount of diphenyl ether in the condensation of aniline with the malonic acid derivative was minimized. Namely, 40 g. of diethyl (2-methoxyethyl)-malonate and 12 g. of aniline were refluxed in 60 g. of diphenyl ether for three hours. Thus, on cooling the reaction mixture, fairly pure 4-hydroxy-2,3dihydrofuro[3,2-c]quinoline, m.p. 275° (decomp.), was obtained. Yield 19 g. The crude product was treated with phosphorus oxychloride and the trichloro derivative IV thus obtained was used without purification in the next step.

2-Hydroxy-3-(2-chloroethyl)-4-chloroquinoline (V).—A solution of 17 g. of the trichloro derivative IV in 100 cc. of glacial acetic acid was heated under a reflux for three hours, after which about 200 cc. of water was added. The product was collected, and washed with water, m.p. 130—170°. Yield 15 g. Repeated recrystallization from dilute methanol or dilute acetic acid raised the m.p. to 190°.

Anal. Found: C, 54.62; H, 3.94; N, 5.47. Calcd. for  $C_{11}H_9NOCl_2$ : C, 54.55; H, 3.72; N, 5.78 %.

## 4-Chloro-2,3-dihydrofuro[2,3-b]quinoline

(VII).—In the other recrystallization process of the crude product described above, the cyclized derivative VII, m.p. 113°, was obtained instead of the open-chain derivative V.

Anal. Found: C, 63.92; H, 4.09; N, 7.10. Calcd. for  $C_{11}H_8NOC1$ : C, 64.08; H, 3.88; N, 6.79%.

VII was more conveniently obtained as follows: A mixture of 15 g. of the crude product melting at 130—170°, resulting from the reaction of the trichloro derivative IV with glacial acetic acid, and 100 cc. of methanol solution containing 5 g. of sodium hydroxide was heated under a reflux for two hours, and then about 200 cc. of water was added. The dihydrofuroquinoline derivative VII thus obtained was sufficiently pure for the next step, m.p. 111°. Yield 8 g.

2-Hydroxy-3-(2-bromoethyl)-4-chloroquinoline (VI).—To a solution of 0.1 g. of the dihydrofuroquinoline derivative VII in 1.5 cc. of glacial acetic acid was added 1 cc. of 48% aqueous hydrobromic acid solution and heated under a reflux for fifteen minutes. On adding water, white needles were obtained. Recrystallization from dilute acetic acid gave an analytical sample, m.p.  $190^{\circ}$ .

Anal. Found: C, 46.10; H, 3.44; N, 5.26. Calcd. for  $C_{11}H_9NOBrCl$ : C, 45.99; H, 3.14; N, 4.88 %.

4-Methoxy-2,3-dihydrofuro[2,3-b]quinoline (IX).—To a solution of 0.4 g. of the chloro derivative VII in 3 cc. of methanol, 5 cc. of sodium methylate solution containing 0.15 g. of sodium, was added and heated in a sealed tube at  $100^{\circ}$ for three hours. After being set aside overnight the sodium chloride was filtered off and the filtrate was concentrated to about 3 cc. under a reduced pressure. On addition of water, white crystals were obtained. Recrystallization from dilute methanol afforded white needles, m.p.  $92^{\circ}$  (sintering at  $82 - 3^{\circ}$ ).

Anal. Found: C, 70.32; H, 5.67; N, 7.14. Calcd. for  $C_{12}H_{11}NO_2$ : C, 71.64; H, 5.47; N, 6.96 %.

The picrate was prepared in ether and was recrystallized from methanol, m.p.  $187^{\circ}$ .

Anal. Found: N, 13.12. Calcd. for  $C_{18}H_{14}N_4O_9$ : N, 13.02 %.

4-Chloro-2,3-dihydrofuro[2,3-b]quinoline

**perbromide.**—To a solution of 0.3 g. of VII in 10 cc. of carbon tetrachloride was added 0.23 g. of bromine dissolved in 1 cc. of carbon tetrachloride within twenty minutes with stirring at room temperature. After being stirred for one additional hour, the yellow crystals were collected and reprecipitated from methanol solution with water at room temperature, m.p.  $122^{\circ}$  (decomp.).

Anal. Found: C, 46.69; H, 3.17; N, 5.09. Calcd. for  $C_{11}H_8NOClBr$ : C, 46.15; H, 2.80; N, 4.89%.

2- or 3-bromo-4-chloro-2,3-dihydrofuro[2,3b]quinoline (X).—A mixture of 1 g. of dihydrofuroquinoline derivative VII, 1 g. of N-bromosuccinimide and 0.1 g. of benzoyl peroxide in 50 cc. of carbon tetrachloride was heated under a reflux for forty-five minutes. After the succinimide was filtered off, the solution was concentrated to about 15 cc. On cooling, the bromo derivative X was obtained, m.p.  $120^{\circ}$ .

Anal. Found: C, 46.08; H, 2.78; N, 5.26. Calcd. for  $C_{11}H_7NOClBr$ : C, 46.31; H, 2.46; N, 4.91 %.

When carbon tetrachloride was not removed, a substance decomposing at  $92^{\circ}$  was obtained. When its pyridine solution was diluted with water, the bromo derivative X crystallized in white needles, but its further recrystallization from pyridine-water was unsuccessful. Recrystallization of the substance decomposing at  $92^{\circ}$ or of the bromo derivative X from dilute methanol gave a substance with a m.p. of  $113^{\circ}$ , whose structure could not be determined.

**Dictamnine** (I).—To a solution of 0.15 g. of the bromo derivative X in 2 cc. of methanol was added 2.5 cc. of sodium methylate solution containing 0.075 g. of sodium. The mixture was heated in a sealed tube at 100° for two hours and allowed to stand overnight. After the inorganic salts were filtered off and methanol was partly evaporated, water was added. The dictamnine thus obtained was fairly pure, melting at  $130-1^{\circ}$ , (natural product; m.p.  $132-3^{\circ})^{5}$ ; a mixed melting point with natural dictamnine was  $130-1^{\circ}$ .

Anal. Found. C, 72.11; H, 4.72; N, 7.14. Calcd. for  $C_{12}H_9NO_2$ : C, 72.35; H, 4.55; N, 7.03%.

The melting point of its picrate obtained in the same way as described in the literature<sup>5)</sup> also coincided with that from natural source (m.p.  $163^{\circ}$ ).

<sup>5)</sup> Y. Asahina, T. Ohta and M. Inubuse, Ber., 63, 2045 (1930).

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