Synthetic Studies of Dictamnine, an Alkaloid of Skimmia Repens, Nakai
I. The Synthesis of Dictamnal

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(Received April 15, 1956)

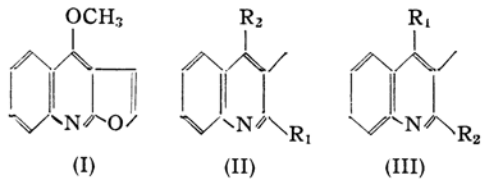
The structure of dictamnine, an alkaloid of Skimmia repens, Nakai, was determined by Asahina to be 4-methoxy-[2,3-b]-furoquinoline (I)[1]. Since then some other alkaloids (kokusagine, etc.) have been isolated and shown to be of furoquinoline type by analogous methods to that used by Asahina[2]. Recently some experiments assuring these structures were reported[3], but in none has it been possible to show definitely the existence of the furan nucleus.

Synthetic studies of dictamnine were carried out by Asahina[4] and by Grundon[3b], but they could only obtain pseudodictamnine, an isomer of dictamnine. As an approach to the synthesis of dictamnine, we attempted to obtain quinolines, in which positions 2 and 4 are substituted by groups different from each other. Although we have not yet been able to finish the synthesis of dictamnine itself, dictamnal, which is a degradative product of dictamnine, was first synthesized and its structure was ascertained.

Starting from nor-dictamnal, we obtained a series of compounds (Fig. 1). As to these compounds, it was ambiguous whether the compounds obtained were of the type II or III.

This problem was solved spectroscopically, as shown below.

When nor-dictamnal (IV) was refluxed with phosphorus oxychloride, tetrachloro derivative V was obtained, accompanied by a small amount of trichloro derivative VI and a basic compound (m.p. 260°) whose structure has not been ascertained yet. The tetrachloro derivative (V) was unexpectedly stable, being unable to react with conc. sulfuric acid, aniline, phenylhydrazine, and alkali, but gave the trichloro derivative (VI) when refluxed in acetic acid. The trichloro derivative (VI) gave acetal VII by a reaction with sodium methoxide in methanol. Treatment of this acetal (VII) with 10% hydrochloric acid afforded aldehyde VIII quantitatively. This aldehyde (VIII) gave methoxy derivative IX when refluxed with sodium methoxide in methanol. This product (IX) has properties very close to those of dictamnal[1], the degradative product of dictamnine. Namely, it melts at 260°, is not easily soluble in most organic solvents, gives a phenylhydrazone of m.p. 228°, and gradually dissolves in aqueous alkali to a yellow solution. But we are not in possession of the natural dictamnal to compare it with. Tetrachloro derivative V gave acetal X by a reaction with sodium



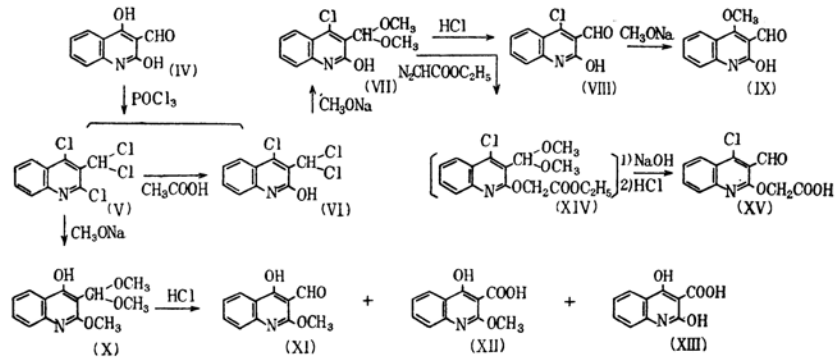


Fig. 1

1) T. Asahina, Y. Ohta and M. Inubuse, *Ber.*, **63**, 2045 (1930).

2) Y. Asahina and M. Inubuse, *Ber.*, **63**, 2052 (1930); R.J. Gell et al., *Austral. J. Chem.*, **8**, 422 (1955).

3) (a) T. Ohta and Y. Mori, *Pharm. Bull.* **3**, 396 (1955). (b) M.F. Grundon, et al., *J. Chem. Soc.*, 1955, 4284.

4) Y. Asahina and M. Inubuse, *Ber.*, **65**, 61 (1932).

methoxide in methanol. It was dissolved in dilute hydrochloric acid and, on neutralization with sodium hydroxide, gave a precipitate of aldehyde XI (m.p. 80°), an isomer of dictamnal. Some amounts of white crystals were obtained from the filtrate on standing for a long time. On fractional recrystallization from dilute methanol, two amphoteric substances were obtained (m.p. 110°, and m.p. 172–3°). These seem to be XII and XIII, respectively, but the melting point of XII is not identical with the reported one (225°)[1,*].

Ewing et al.[5] reported on the influence of the position of the substituent upon the spectra of monohydroxyquinolines. From their data one can say as a whole that hydroxyquinolines of α-naphthol type (4-, 5- and 8-) have only one maximum over 250 mμ (about 320 mμ) while β-naphthol types (2-, 3-, 6- and 7-) have two maxima in the same region (275 mμ and 330 mμ). Of these quinolines, 2- and 4-hydroxyquinolines can take keto-forms as well as phenol-forms. In practice the spectra of these two are unaffected in 1/100 N alkali, contrary to the practice of all the other derivatives. When the concentration of the alkali increases to 10%, the spectrum of 2-hydroxyquinoline shifts, while that of the 4-isomer is not affected even in the concentration of 50%. This fact shows that both of them exist as the keto-forms but the 2-isomer takes the phenol-form in alkali more easily than the 4-isomer. By making the solutions alkaline, all the curves of hydroxyquinolines of α-naphthol type shift, but, in case of β-type, it is characteristic that the short-wavelength absorption maximum flattens.

Keeping these data in mind we measured the ultraviolet spectra of the above mentioned compounds (VI–IX) (Figs. 2–5). The spectra of all these compounds are very similar to those of hydroxyquinolines of β-naphthol type, especially to that of 2-hydroxyquinoline. (Although the spectrum of dictamnal deviates a little from the others, it shows at least the same inclination.) It is to be noted here that the substituents at position 3 do not affect the spectra and the acidity of these quinolines is so strong as to cause the flattening of the short-wavelength absorption maxima even in the alkali concentration of 1/100 N and as not to be affected in acid concentration of 1/100 N. From these facts it can be concluded that all these compounds (VI–IX) are 2-hydroxyquinoline derivatives.

Contrary to the spectroscopic behaviors of the above mentioned compounds (VI–IX), the spectra of X and XI (Figs. 6 and 7) are not like those of β-naphthol types. They are affected in acid but not in alkali. Moreover, the spectra of both compounds are very different from each other in either neutral or alkaline solution, while they are similar in acid solution. It can be supposed from these facts that these compounds are 4-hydroxy derivatives and exist as the keto-

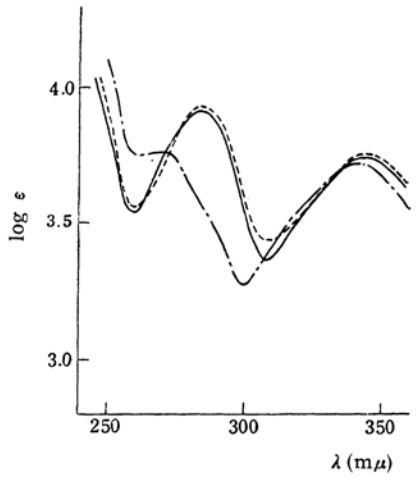


Fig. 2. 2-Hydroxy-3-dichloromethyl-4-chloroquinoline (VI).
—— neutral
····· acid
—·— alkali

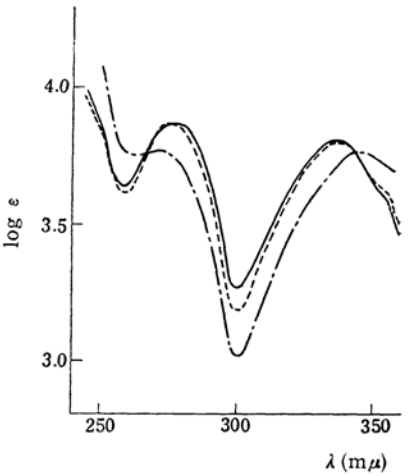


Fig. 3. 2-Hydroxy-3-dimethoxymethyl-4-chloroquinoline (VII).
—— neutral
····· acid
—·— alkali

* R.F.C. Brown reported that this value was not correct: *Austral. J. Chem.*, 7, 384 (1954).

5) G.W. Ewing and E.A. Steck, *J. Am. Chem. Soc.*, 68, 2181 (1946); ibid, 71, 238 (1949). cf. B. Witkop et al., *J. Am. Chem. Soc.*, 73, 2641 (1951).

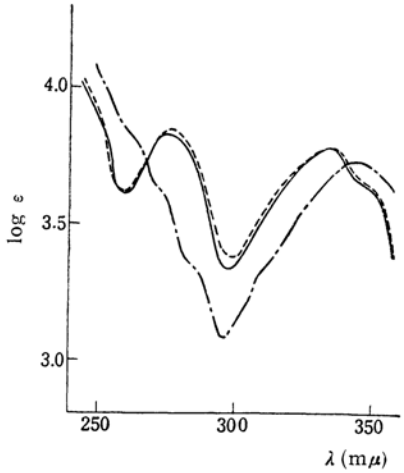


Fig. 4. 2-Hydroxy-3-formyl-4-chloroquinoline (VIII).
—— neutral ····· acid –·– alkali

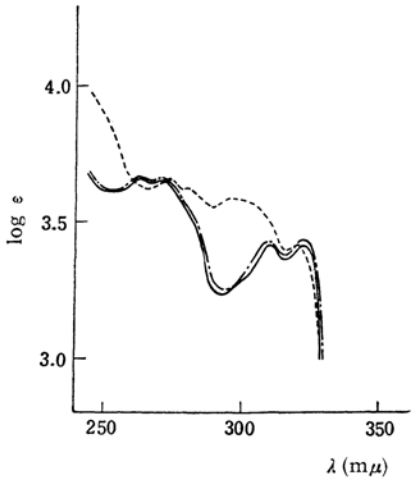


Fig. 6. 2-Methoxy-3-dimethoxymethyl-4-hydroxyquinoline (X).
—— neutral ····· acid —·— alkali

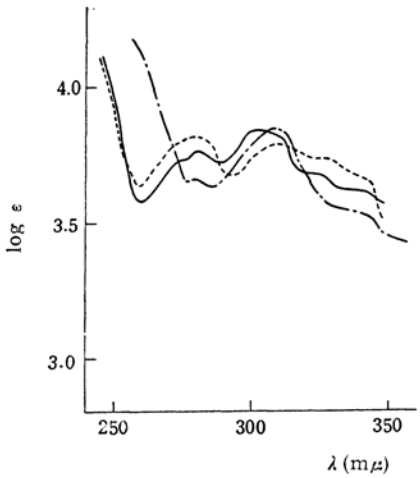


Fig. 5. 2-Hydroxy-3-formyl-4-methoxyquinoline (IX).
—— neutral ····· acid –·– alkali

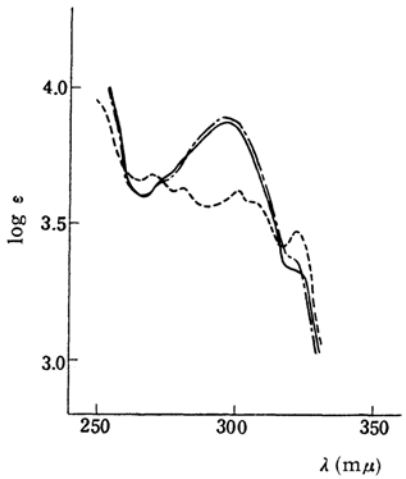
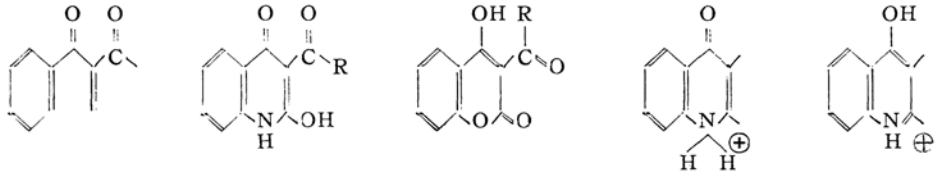


Fig. 7. 2-Methoxy-3-formyl-4-hydroxyquinoline (XI).
—— neutral ····· acid —·— alkali

forms. The extinct absorption maximum of XI at 297 mμ (log ε, 3.9) is supposed to be caused by the partial structure like XVI. Indeed, the other compounds having such structures (3-acyl-2,4-dihydroxyquinoline, XVII, and 3-acyl-4-hydroxycoumarin, XVIII) show strong absorption in the same region[6]. Acetal X lacking this structure, therefore, exhibits a very different spectrum. But, in acid solution, that is in protonated state, the enol-form (XX) is supposed to be more stable than the keto-form (XIX); so that the influence of the substituent at position 3 disappears and the spectra of X and XI become similar. Indeed, both the spectra in



(XVI) (XVII) (XVIII) (XIX) (XX)

6) K. Tomita, *J. Pharm. Soc. Japan.* **71**, 1100 (1951).

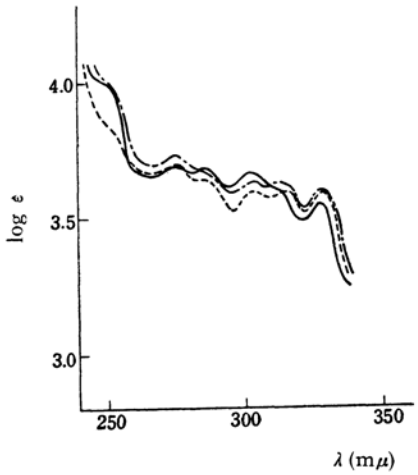


Fig. 8. 3-Formyl-4-chloroquinolyl-2-glycolic acid (XV).
—— neutral ····· acid –·– alkali

acid solution are very similar to that of XV (Fig. 8), which can take only an enol-form like XX.

In order to synthesize dictamnine, we tried to get a compound of the type XV. The previously mentioned acetal (VII) is fairly acidic and, when a sodium methoxide solution was added to its methanol solution, a sodium salt was obtained. From the aqueous solution of this sodium salt a precipitate, supposedly a silver salt, was obtained by the addition of aqueous silver nitrate. Its purification, however, was difficult. It was soluble in toluene and seemed to have reacted with ethyl bromoacetate, but the substance obtained from the reaction mixture was only the starting acetal (VII). The sodium salt, moreover, did not react with ethylene oxide. The acetal (VII) did not react with ethyl diazoacetate even at 160°, but it did at 110° in the presence of copper powder to give an oil which was supposed to be XIV[7]. This was directly hydrolysed by aqueous alkali and acidification with hydrochloric acid gave XV. The cyclization to make furan nucleus is being carried out at present.

Experimental

Absorption Spectra.—All spectra were measured with Beckman Quartz Spectrophotometer, Model DU.

Solvents.—(a) Neutral: Commercial methanol was once distilled. (b) Acid and alkaline: One cubic centimeter of tenth normal aqueous solutions of reagent grade hydrochloric acid (f=1.27) and sodium hydroxide (f=0.941) were diluted with methanol to 10 cc.

7) J. Maas et al., *Rec. trav. chim.*, **74**, 175 (1955).

2,4-Dichloro-3-dichloromethylquinoline (V).—Fifteen grams of nor-dictamnal (IV)[4] was refluxed with 110 cc. of phosphorus oxychloride for ninety minutes. The brown solution was gradually poured into crushed ice with constant stirring. After standing overnight, the separated crystals were collected. Yield 20 g. They were washed with 15% hydrochloric acid and the insoluble matter was recrystallized from dilute methanol. White needles, m.p. 125.5–6°. Yield 13 g.

Anal. Found: C, 42.25; H, 2.05; N, 5.31. Calcd. for $C_{10}H_5NCl_4$: C, 42.70; H, 1.78; N, 4.98%. From the mother liquor, a small amount of trichloro derivative VI was obtained (see below).

2-Hydroxy-3-dichloromethyl-4-chloroquinoline (VI).—Tetrachloro derivative V (5.5 g.) was refluxed with 30 cc. of glacial acetic acid for ninety minutes. Hydrogen chloride was soon evolved and crystals began to separate in one hour. After cooling the precipitate was collected and washed with acetic acid. It was fairly pure and used for the succeeding reactions without purification. Yield 3 g. The sample for analysis was obtained by recrystallization from glacial acetic acid. White needles, m.p. 253°.

Anal. Found: C, 46.31; H, 2.60; N, 6.02. Calcd. for $C_{10}H_5NOCl_3$: C, 45.63; H, 2.28; N, 5.34%.

2-Hydroxy-3-dimethoxymethyl-4-chloroquinoline (VII).—Four grams of crude substance VI was suspended in 40 cc. of methanol and 50 cc. of a sodium methylate solution, containing 1.5 g. of sodium, was added. The solid dissolved immediatety to give a yellow solution, but soon after, a white solid was deposited. After being refluxed for ninety minutes, the solid was collected, washed with methanol, and dissolved in hot water. After the insoluble matter was filtered off, aqueous ammonium chloride was added to the yellow filtrate to precipitate a white crystalline substance. It was fairly pure and used for succeeding reactions without purification. m.p. 163°. Yield 2 g. The sample for analysis was obtained by recrystallization from dilute methanol. m.p. 164–5°

Anal. Found: C, 56.11; H, 4.95; N, 5.23. Calcd. for $C_{12}H_{12}NO_3Cl$: C, 56.69; H, 4.74; N, 5.53%.

Sodium Salt of 2-Hydroxy-3-dimethoxymethyl-4-chloroquinoline.—To a hot solution of 1 g. of VII in 50 cc. of methanol, 40 cc. of a sodium methylate solution, containing 1.2 g. of sodium, was added. On cooling, white needles were obtained. m.p. over 250°. Yield 0.85 g. The substance was dissolved in hot water and on adding aqueous ammonium chloride, VII was recovered.

Anal. Found: N, 4.90, Calcd. for $C_{12}H_{11}NO_3ClNa$: N, 5.07%.

3-Formyl-4-chloroquinol-2-yl-glycolic Acid (XV).—Two grams of acetal VII was intimately mixed with 0.4 g. of copper powder, and 1 g. of ethyl diazoacetate was dropwise added during a period of forty-five minutes at 110–120°, with continuous stirring. The reaction mixture was kept at 130° for an additional fifteen minutes and cooled. To the brown paste a small amount of ether was added, and the unchanged starting material and

copper powder were filtered off and washed with ether. The filtrate and washings were combined and ether was evaporated. The residual oil was heated with 40 cc. of 10% aqueous sodium hydroxide at about 50° to complete solution. Acidification of the solution with hydrochloric acid gave a yellow oil which soon solidified. Recrystallization from benzene gave XV in light yellow needles melting at 162°.

Anal. Found: C, 54.23; H, 3.56; N, 5.65; Cl, 13.0. Calcd. for $C_{12}H_8NO_4Cl$: C, 54.13; H, 3.01; N, 5.26; Cl, 13.4%.

2-Hydroxy-3-formyl-4-chloroquinoline(VIII).—Acetal VII was suspended in a small amount of 10% aqueous hydrochloric acid and warmed for ten minutes. The insoluble matter was collected and recrystallized from methanol. Yellow needles, m.p. 268°.

Anal. Found: C, 57.95; H, 3.14; N, 6.92. Calcd. for $C_{10}H_6NO_2Cl$: C, 57.69; H, 2.89; N, 6.75%.

2-Hydroxy-3-formyl-4-chloroquinoline Phenylhydrazone.—Aldehyde VIII and phenylhydrazine were heated in methanol for thirty minutes. On cooling, the yellow needles were recrystallized from methanol, m.p. 233°.

Anal. Found: N, 13.92. Calcd. for $C_{13}H_{12}N_3OCl$: N, 14.09%.

2-Hydroxy-3-formyl-4-methoxyquinoline (dictamnal) (IX).—Two grams of aldehyde VIII were refluxed with 9 cc. of methanol and 9 cc. of a sodium methylate solution, containing 0.27 g. of sodium, for two hours. During this period the form of crystals changed. The light yellow solid was collected and washed with water. It was recrystallized from a large amount of methanol. White needles, m.p. 260°.

Anal. Found: C, 64.62; H, 4.56; N, 7.17. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89%.

2-Hydroxy-3-formyl-4-methoxyquinoline Phenylhydrazone.—Aldehyde IX and phenylhydrazine were heated in methanol. Addition of water gave yellow needles. They were recrystallized from methanol, m.p. 228°.

Anal. Found: N, 14.28. Calcd. for $C_{17}H_{15}N_3O_2$: N, 14.33%.

2-Methoxy-3-dimethoxymethyl-4-hydroxyquinoline (X).—The tetrachloro derivative (V) (4.3 g.) and 60 cc. of a sodium methylate solution, containing 1.8 g. of sodium, were refluxed for ninety minutes. After standing overnight the solid was filtered off. The filtrate was concentrated in vacuo to about 40 cc., and water was added. The separated oil was taken up in ether, and the ethereal solution was evaporated. The residual oil soon solidified. A small amount of the solid was recrystallized from dilute methanol for analysis. White needles, m.p. 62–4°.

Anal. Found: C, 62.37; H, 6.27; N, 5.44. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62%.

2-Methoxy-3-formyl-4-hydroxyquinoline (XI).—The crude acetal (X) was suspended in water and 18% aqueous hydrochloric acid was gradually added until all the solid was dissolved. The solution was warmed for some time and made alkaline with aqueous caustic soda. Repeated recrystallizations of the separated solid (A) from dilute methanol gave XI in white needles melting at 82–3°.

Anal. Found: C, 65.43; H, 4.81; N, 6.88. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89%.

2-Methoxy-4-hydroxyquinoline-3-carboxylic Acid (XII).—The alkaline mother liquor, from which the solid (A) was removed in the above process, gave some amounts of crystals on standing for a few days. They were dissolved in water and the solution was neutralized with aqueous hydrochloric acid. An amphoteric substance was obtained. Recrystallization from dilute methanol gave XII in white needles melting at 110°. Soluble in aqueous sodium bicarbonate.

Anal. Found: C, 60.10; H, 4.02; N, 6.83. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4 14; N, 6.39%.

2,4-Dihydroxyquinoline-3-carboxylic Acid (XIII).—From the mother liquor in the above recrystallization process, white needles were obtained by adding water. Recrystallization from dilute methanol gave XIII in white needles melting at 172–3°. Soluble in aqueous sodium bicarbonate.

Anal. Found: C, 58.26; H, 3.30; N, 6.85. Calcd. for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.83%.

The authors are indebted to Mr. A. Kondo for the microanalyses.

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