417. *The Synthesis of Dictamnine and γ-Fagarine.*

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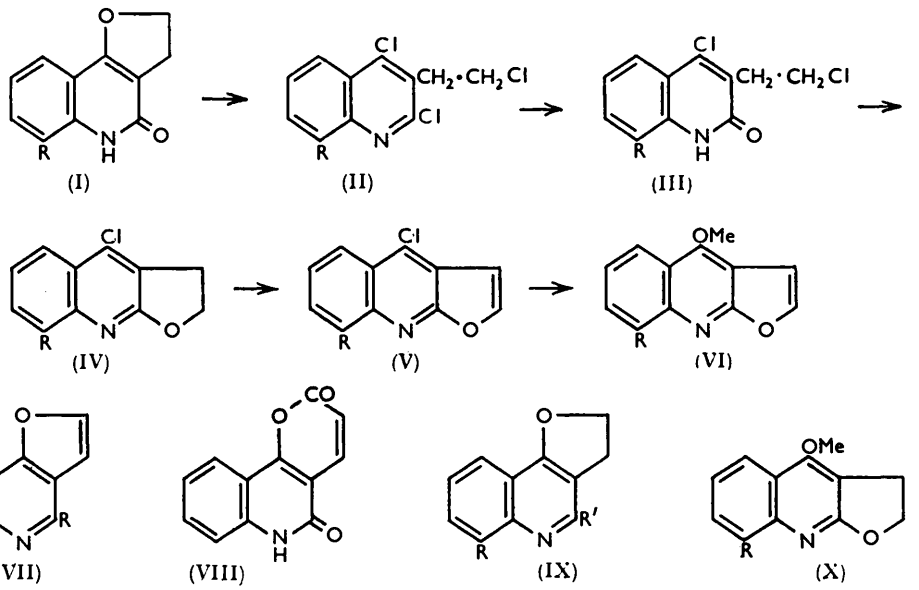
The alkaloids dictamnine (VI; R = H) and γ-fagarine (VI; R = OMe) have been synthesised from the angular dihydrofuranoquinolones (I; R = H, OMe). The structures of the intermediates have been confirmed by ultraviolet and infrared spectroscopy and by conversion into authentic furano-(2′ : 3′-2 : 3)quinoline.

THE furanoquinoline alkaloids are generally regarded as derivatives of furano(2′ : 3′-2 : 3)quinoline. Only in dictamnine (VI; R = H) has the presence of this system been established unequivocally,[1,2,3,4] but there is strong evidence[3,4,5] for an analogous constitution for skimmianine (XVI; R = OMe). Other alkaloids have been studied less intensively: thus, the degradation[6] of γ-fagarine to 2 : 4-dihydroxy-8-methoxyquinoline does not distinguish between the structures (VI; R = OMe) and (VII; R = OMe) for the alkaloid.

The linear structures for dictamnine and γ-fagarine have now been established by a synthesis[7] indicated in the reaction scheme (I—VI).*



We have shown[2] that reaction of aniline or *o*-anisidine with ethyl (2-ethoxyethyl)-malonate gives exclusively the angular dihydrofuranoquinolones (I; R = H and OMe), probably *via* 2 : 4-dihydroxyquinolines. Ring closure involving a 4-hydroxy-group is

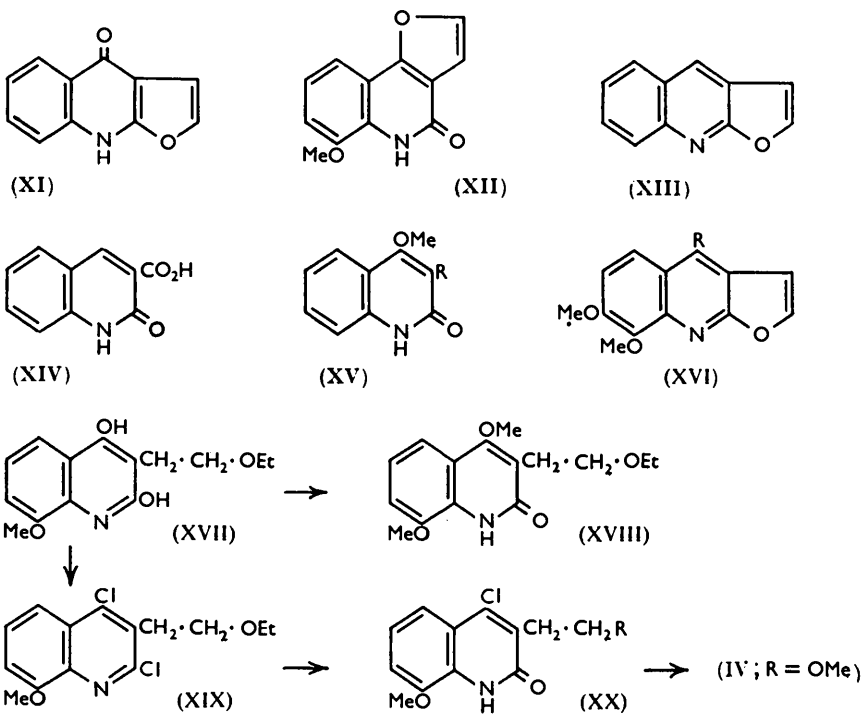
* *Added, March 15th*, 1957.—A synthesis of dictamnine was reported briefly by Sato and Ohta (*J. Chem. Soc. Japan*, 1956, **77**, 1630). We thank Dr. T. Sato for informing us of this work. Unpublished syntheses of furano(2′ : 3′-2 : 3)quinoline by King, Latham, and Partridge, and of dihydrodictamnine by Cook and Haynes are mentioned by Price (*Fortschr. Chem. org. Naturstoffe*, 1956, **13**, 320).

[1] Asahina, Ohta, and Inubuse, *Ber.*, 1930, **63**, 2045.
[2] Grundon, McCorkindale, and (in part) Rodger, *J.*, 1955, 4284.
[3] Brown, Hobbs, Hughes, and Ritchie, *Austral. J. Chem.*, 1954, **7**, 348.
[4] Ohta and Mori, *Ann. Reports Tokyo Coll. Pharm.*, 1955, **5**, 48.
[5] Asahina and Inubuse, *Ber.*, 1930, **63**, 2052.
[6] Berinzaghi, Maruzabal, Labriola, and Deulofeu, *J. Org. Chem.*, 1945, **10**, 181.
[7] Cf. Grundon and McCorkindale, *Chem. and Ind.*, 1956, 1091.

also involved in the formation [8] of the pyronoquinolone (VIII) from 2 : 4-dihydroxyquinoline and malic acid, and in the synthesis of flindersine.[8] Thus, linear furanoquinolines are unlikely to result directly from dihydroxyquinoline derivatives. We expected that 4-chloro-2-quinolones would be more useful intermediates.

The dihydrofuranoquinolone (I; R = H) with phosphorus oxychloride gave 2 : 4-dichloro-3-2′-chloroethylquinoline (II; R = H),[2] now obtained in higher yield (59%) by modifying the reaction conditions. A by-product, $C_{11}H_8ONCl$, was isolated with properties expected for the angular dihydrofuranoquinoline (IX; R = H, R′ = Cl). The trichloro-compound (II; R = H) is conveniently prepared from aniline and ethyl (2-ethoxyethyl)malonate without purification of the intermediate dihydrofuranoquinolone. Treatment of the dihydrofuranoquinolone (I; R = OMe) with phosphorus oxychloride afforded the trichloro-derivative (II; R = OMe) and the chlorodihydrofuranoquinoline (IX; R = OMe, R′ = Cl).

The successful preparation [9] of 4 : 7-dichloro-1 : 2-dihydro-2-oxoquinoline by acid hydrolysis of 2 : 4 : 7-trichloroquinoline led us to examine this reaction as a general method for preparing 4-chloro-2-hydroxyquinolines. 2 : 4-Dichloro-3-ethoxycarbonylquinoline was hydrolysed to 4-chloro-3-ethoxycarbonyl-1 : 2-dihydro-2-oxoquinoline (by M. N.

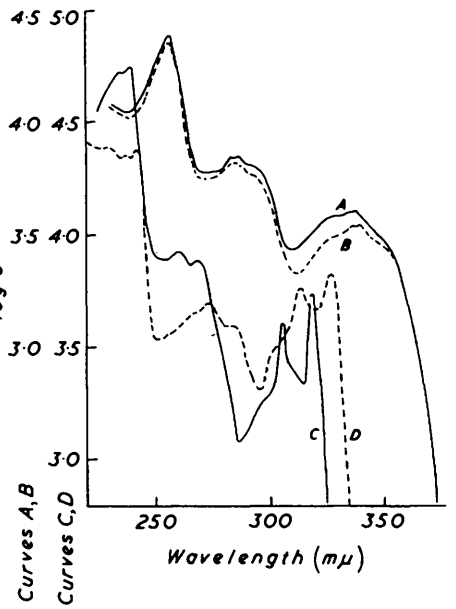


Rodger), and by the same method the two trichloro-compounds (II; R = H) and (II; R = OMe) furnished, in good yield, the dichloro-derivatives (III; R = H) and (III; R = OMe). The three products had the properties of 2-quinolones, namely, insolubility in dilute aqueous alkali, infrared maxima at 1654—1650 cm.$^{-1}$ (NH·CO in a 2-quinolone), and intense ultraviolet absorption at 2720—2870 Å.

Chromatography of the chloroquinolone (III; R = H) on alkaline alumina afforded the linear dihydrofuranoquinoline (IV; R = H) (40%), and this ring closure was effected

[8] Brown, Hughes, and Ritchie, *Austral. J. Chem.*, 1956, **9**, 279.
[9] Rowlett and Lutz, *J. Amer. Chem. Soc.*, 1946, **68**, 1290.

almost quantitatively with silver oxide in aqueous ethanol. 4-Chloro-4′ : 5′-dihydro-8-methoxyfurano(2′ : 3′-2 : 3)quinoline (IV; R = OMe) was prepared in the same way from the corresponding dichloro-compound (III; R = OMe). Reaction with sodium methoxide furnished the methoxydihydrofuranoquinolines (X; R = H and OMe). The properties of the former compound correspond to those recorded [10] for dihydrodictamnine, prepared by reduction of the alkaloid. Dehydrogenation of the chlorodihydrofuranoquinoline (IV; R = OMe) with palladium–charcoal gave the chlorofuranoquinoline (V; R = OMe) in small amount, whereas reaction with *N*-bromosuccinimide and treatment of the crude intermediate with diethylaniline gave a high yield of this compound. The products from these reactions had identical infrared spectra, but that obtained by the bromination-dehydrobromination technique did not give satisfactory analyses, possibly because of the presence of an impurity containing aromatic bromine. Application of the same reaction to 4-chloro-4′ : 5′-dihydrofurano(2′ : 3′-2 : 3)quinoline (IV; R = H) gave the corresponding furanoquinoline (V; R = H) and similar difficulties were encountered in the purification of the product. Reaction with sodium methoxide afforded the methoxyfuranoquinoline



Ultraviolet-light absorption in ethanol of the by-product from the reaction of 4-chloro-8-methoxyfurano(2′ : 3′-2 : 3)quinoline with sodium methoxide (A), 4-chloro-3-2′-ethoxyethyl-1 : 2-dihydro-8-methoxy-2-oxoquinoline (B), 2-methoxyfurano(3′ : 2′-3 : 4)quinoline (C), and 4-chloro-4′ : 5′-dihydrofurano(2′ : 3′-2 : 3)quinoline (D).

(VI; R = H), identical with dictamnine. The chlorofuranoquinoline (V; R = H) was hydrolysed by acid to the 4-quinolone (XI), identical with a sample of nordictamnine obtained from the alkaloid. The chlorofuranoquinoline (V; R = OMe) was converted by sodium methoxide into the methoxy-derivative (VI; R = OMe), indistinguishable from γ-fagarine. Analyses for a by-product of this reaction agreed best with the formula $C_{11}H_8ONCl(OMe)_2,\frac{1}{2}H_2O$. As the ultraviolet spectrum is almost identical with that of the 2-quinolone (XX; R = OEt) (see Figure), we suggest provisionally that the compound is the chloroquinolone (XX; R = OMe). The infrared absorption at 1631 cm.$^{-1}$ is slightly lower than that shown by most 2-quinolones, but the band has the shape and very high intensity characteristic of 2-quinolone absorption. The by-product may arise by attack of OMe^- on the furan ring, with subsequent reduction.

Infrared and ultraviolet spectra are valuable for distinguishing 2- from 4-quinolones.[11] Our results (Table 1) support the generalisation that 2-quinolones show ultraviolet absorption at 2700—2850 Å (ε 6300—9000) absent in 4-quinolones, and that the long-wavelength

[10] Cook and Haynes, *Austral. J. Chem.*, 1954, **7**, 273.
[11] For discussion and refs. see ref. 2 and Mason, *Chem. Soc. Special Publ. No.* 3, 1955, p. 139.

band is more intense in 4-quinolones. Further, strong amide-carbonyl infrared absorption occurs at 1660—1640 cm.$^{-1}$ in 2-quinolones whereas 4-quinolones show weaker maxima at lower frequencies (1620—1630 cm.$^{-1}$). It appears that 2-methoxyquinolines or dihydrofurano(2′ : 3′-2 : 3)quinolines show in their spectra (Nos. 1—7 of Table 2, and Figure) some of the characteristics of 2-quinolones. Furano(2′ : 3′-2 : 3)quinolines show normal behaviour (see, for example, Nos. 8—11 of Table 2).

The structures of the intermediates (IV—VI, and X) are also supported by non-identity with the angular isomers of established structure.[2] In order to complete the series, the furanoquinolone (XII) [2] was converted through the chloro-derivative (VII; R = Cl) into 2 : 8-dimethoxyfurano(3′ : 2′-3 : 4)quinoline (VIII; R = OMe), an isomer of γ-fagarine.

TABLE 1. *Infrared absorption bands* (KBr *disc*) *and ultraviolet absorption* (*in ethanol*) *of* 2- *and* 4-*quinolones.*

		Main ultraviolet absorption maxima					
No.	Substance	λ	ε	λ	ε	λ	ε
1	3-Carboxy-2-quinolone	228	42,700	289	10,000	348	5,500
2	(III; R = H)	228	35,500	272	8,100	330	7,400
3	(III; R = OMe)	257	27,500	287	7,200	340	3,500
4	4-Chloro-3-ethoxycarbonyl-2-quinolone	228	28,200	275	7,700	335	6,200
5	(XX; R = OEt)	256	21,900	285	6,500	338	3,400
6	(XVIII)	252	22,900	278	6,900	326	3,300
7	3-Carboxy-4-quinolone	245	18,600	—	—	308	12,300
8	(XI)	245	44,700	—	—	329	14,800
	Nor-γ-fagarine [12]	242	47,900	—	—	329	11,300
	iso-γ-Fagarine [12]	246	43,400	—	—	336	12,200
	Norskimmianine [12]	253	40,600	—	—	326	9,400
	*iso*Skimmianine [12]	258	45,800	—	—	331	11,400
	*iso*Kokusaginine [13]	252	50,300	—	—	327 342	10,000 10,000

	Infrared maxima (cm.$^{-1}$).				
No.	2-Quinolone amide I	No.	2-Quinolone amide I	No.	4-Quinolone amide I
1	1651	4	1648	7	1620
2	1650	5	1641	8	1625
3	1650	6	1644		

TABLE 2. *Infrared absorption* (KBr *disc*) *in the region* 1700—1630 *cm.*$^{-1}$ *and ultraviolet absorption* (*in ethanol*) *of quinolines with an ether function in the* 2-*position.*

			Main ultraviolet absorption maxima					
No.	Substance	Infrared *	λ	ε	λ	ε	λ	ε
1	(X; R = H)	1631	228	46,800	270	7,600	317	4,900
2	(X; R = OMe)	1635	247	38,900	278	6,600	322	2,500
3	(IV; R = H)	1645	242	24,000	274	4,900	327	6,600
4	(IV; R = OMe)	1642	254	38,900	289	4,000	325	3,300
5	(IX; R = H, R′ = OMe)	1641	230	38,000	276	5,400	314	1,900
6	2-Methoxyfurano(3′ : 2′-3 : 4)-quinoline	1637	239	56,200	261	8,300	317	5,400
7	(VII; R = OMe)	1642	246	49,000	—	—	308	1,200
8	(VI; R = H)	—	235	58,900	—	—	312	8,700
9	(VI; R = OMe)	—	242	60,300	—	—	308	6,600
10	(V; R = H)	—	240	64,500	—	—	312	1,230
11	(V; R = OMe)	—	250	47,900	—	—	322	8,100
12	(XIII)	—	234	50,300	—	—	306	1,100

* All the infrared peaks are of medium intensity.

The angular chlorodihydrofuranoquinoline (IX; R = H, R′ = Cl) with sodium methoxide furnished the corresponding methoxy-compound (IX; R = H, R′ = OMe), an isomer of dihydrodictamnine.

The chlorofuranoquinoline (V; R = H) with hydrazine hydrate gave the hydrazino-derivative which, without purification, was converted by aqueous copper sulphate into furano(2′ : 3′-2 : 3)quinoline (XIII). Permanganate oxidation of this compound to

3-carboxy-2-quinolone (XIV) demonstrates conclusively the linear structure of the precursors.

Our experience with synthetic furanoquinolines suggests alternative methods of determining the structure of furanoquinoline alkaloids. A study of the properties of the nor- and *iso*-derivatives provides the best preliminary indication of the structures of the alkaloids. For example, the 4-quinolone nature of nor-γ-fagarine is clearly suggested by its ultraviolet spectrum,[12] and by its solubility in aqueous alkali.[12] Published data [12, 13] (Table 1) indicate analogous constitutions for the requisite derivatives of skimmianine and kokusaginine. The established methods of degradation require oxidation [1, 5, 6] to a quinoline acid (XV; R = CO_2H, for dictamnine) or hydrogenation [14] to a 3-ethylquinoline (XV; R = Et, for dictamnine). These have been synthesised from the corresponding 2 : 4-dihydroxyquinolines and diazomethane,[2, 3, 4] but the selective methylation of the 4-hydroxy-group is based only on analogy with 2 : 4-dihydroxyquinoline. Further, this reaction is not applicable [15] to all 2 : 4-dihydroxyquinolines, and additional evidence is desirable to complete the proof of structure. In the case of dictamnine this was provided [2] by conversion of ethyl dictamnate (XV; R = CO_2Et) to 3-carboxy-2-chloro-4-methoxyquinoline of established constitution. A more satisfactory procedure might involve oxidation of the unsubstituted furanoquinolines prepared from the chlorofuranoquinolines by the method described above and used previously for the angular isomers. The chlorofuranoquinolines are likely to be readily available from the hydrolysis products of the alkaloids and, indeed, we have shown that nordictamnine with phosphorus oxychloride gives an excellent yield of the chlorofuranoquinoline (V; R = H). The alkaloid skimmianine (XVI; R = OMe) is converted [16] directly into the hydrazino-derivative (XVI; R = $NH{\cdot}NH_2$) and use of this process would shorten the proposed reaction sequence.

Our earlier attempts [2] to synthesise γ-fagarine employed 3-2′-ethoxyethyl-2 : 4-dihydroxy-8-methoxyquinoline (XVII). An improved preparation is described in the Experimental section. Reaction with diazomethane gave 3-2′-ethoxyethyl-1 : 2-dihydro-4 : 8-dimethoxy-2-oxoquinoline (XVIII), a constitution confirmed by its infrared and ultraviolet spectra (Table 1).

Ring closure to a linear furanoquinoline did not occur, the quinolone being recovered after prolonged heating in diphenyl ether or with polyphosphoric acid. The dihydroxyquinoline (XVII) was converted quantitatively into the corresponding dichloro-compound (XIX), hydrolysed by hydrochloric acid to a monochloro-quinoline having the characteristic properties (Table 1) of a 2-quinolone of structure (XX; R = OEt). This compound in boiling diphenyl ether afforded the chlorodihydrofuranoquinoline (IV; R = OMe). This constitutes an alternative synthesis of γ-fagarine, but the yield of the chlorodihydrofuranoquinoline, based on *o*-anisidine, compares unfavourably with that obtained in the previous preparation.

Experimental

2 : 4-Dichloro-3-2′-chloroethylquinoline (II; R = H).—(*a*) 1 : 2 : 4′ : 5′-Tetrahydro-2-oxofurano(3′ : 2′-3 : 4)quinoline (7·91 g.) and phosphorus oxychloride (50 c.c.) were heated under reflux for 3½ hr., the phosphorus oxychloride was removed and water added. The precipitate (9·4 g.), dissolved in 1 : 1 benzene–light petroleum (b. p. 60—80°), was chromatographed on alumina. Elution with the same solvent gave 2 : 4-dichloro-3-2′-chloroethylquinoline (6·74 g., 59%), m. p. 99—100°, crystallising from ethanol in colourless needles, m. p. 110—112°. Further elution with the same solvent gave *2-chloro-4′ : 5′-dihydrofurano(3′ : 2′-3 : 4)quinoline* (0·73 g., 8%), separating from ethanol in colourless prisms, m. p. 162—163° (Found : C, 64·2; H, 4·2; N, 7·3; Cl, 17·8. $C_{11}H_8ONCl$ requires C, 64·2; H, 3·9; N, 6·8; Cl, 17·2%).

[12] Deulofeu and Bassi, *Anal. Asoc. quím. argentina*, 1952, **40**, 249.
[13] Lamberton and Price, *Austral. J. Sci. Res.*, 1953, **6**, 69.
[14] Ohta, *J. Pharm. Soc. Japan*, 1953, **73**, 63.
[15] Brown, *Austral. J. Chem.*, 1955, **8**, 121.
[16] Ohta, Miyazaki, and Mori, *Ann. Reports Tokyo Coll. Pharm.*, 1954, **4**, 7.

(*b*) Crude 1 : 2 : 4′ : 5′-tetrahydro-2-oxofurano(3′ : 2′-3 : 4)quinoline [prepared from aniline (29·2 g.)] was refluxed with phosphorus oxychloride (400 c.c.) for 3½ hr., the excess of phosphorus oxychloride was removed, and the residue shaken with chloroform and water. The chloroform layer was separated, dried, and evaporated, and the residue was extracted with boiling light petroleum (b. p. 40—60°) (300 c.c.). Concentration of the light petroleum solution afforded the trichloro-compound as colourless needles (16·87 g.), which began to soften at 100° and melted at 108—111°, suitable for subsequent reaction. The petroleum-insoluble material, dissolved in benzene, was chromatographed on alumina. Elution with benzene gave a further quantity of the trichloro-compound (9·77 g.; total yield 26·3 g., 32% based on aniline). Further elution of the column gave a white solid, m. p. 152—156° alone or mixed with 2-chloro-4′ : 5′-dihydrofurano(3′ : 2′-3 : 4)quinoline obtained as in (*a*).

2 : 4-*Dichloro*-3-2′-*chloroethyl*-8-*methoxyquinoline* (II; R = OMe).—1 : 2 : 4′ : 5′-Tetrahydro-8-methoxy-2-oxofurano(3′ : 2′-3 : 4)quinoline (7·38 g.) and phosphorus oxychloride were refluxed for 3½ hr., the excess of reagent was removed, and the residue treated with water to give a brown solid (7·5 g.), m. p. 90—92°, which was extracted (Soxhlet) with light petroleum (b. p. 40—60°), leaving a residue (A). On concentration of the extract, the *trichloro*-derivative separated as a pale yellow solid (5·72 g., 58%), m. p. 107—109°. It crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 108—109° (Found: C, 49·9; H, 3·6; N, 4·9; Cl, 35·9. $C_{12}H_{10}ONCl_3$ requires C, 49·6; H, 3·5; N, 4·8; Cl, 36·6%).

The residue (A) (0·82 g., 10%), m. p. 145—158°, consisted of 2-*chloro*-4′ : 5′-*dihydro*-8-*methoxyfurano*(3′ : 2′-3 : 4)*quinoline* and crystallised from ethanol in colourless needles, m. p. 162° (Found: C, 59·1; H, 4·5; Cl, 15·0. $C_{12}H_{10}O_2NCl,\frac{1}{2}H_2O$ requires C, 58·9; H, 4·5; Cl, 14·5%).

4-*Chloro*-3-*ethoxycarbonyl*-1 : 2-*dihydro*-2-*oxoquinoline* (with M. N. Rodger).—2 : 4-Dichloro-3-ethoxycarbonylquinoline (4·0 g.) was heated in 6N-hydrochloric acid (112 c.c.) and dioxan (100 c.c.) for 2 hr. Addition of water (1 l.) precipitated the *quinolone*, crystallising from ethyl acetate in needles (1·63 g., 44%), m. p. 202—203° (Found: C, 57·1; H, 3·8; N, 5·7. $C_{12}H_{10}O_3NCl$ requires C, 57·3; H, 4·0; N, 5·6%), insoluble in aqueous alkali, and giving no colour with ferric chloride.

4-*Chloro*-3-2′-*chloroethyl*-1 : 2-*dihydro*-2-*oxoquinoline* (III; R = H).—(*a*) 2 : 4-Dichloro-3-2′-chloroethylquinoline (1 g.), 6N-hydrochloric acid (28 c.c.), and dioxan (22 c.c.) were refluxed for 3 hr. and kept at room temperature for 12 hr. The precipitate (0·45 g.), m. p. 169—175°, was extracted with boiling aqueous methanol, and the insoluble residue (0·04 g.) removed. The *quinolone* separated from the solution in needles (0·26 g., 29%), m. p. 169—175° raised to 174—175° by crystallisation from methanol (Found: C, 54·7; H, 3·8; Cl, 29·0. $C_{11}H_9ONCl_2$ requires C, 54·6; H, 3·7; Cl, 29·3%). The compound, when heated above its m. p., resolidified in needles, m. p. >300°. It was insoluble in aqueous alkali, and gave only a faint yellow colour with ferric chloride in ethanol.

(*b*) The trichloro-compound was hydrolysed as described above except that heating was discontinued after 1 hr. 10 min. After 12 hr. at room temperature the quinolone was obtained as needles (0·43 g., 47%), m. p. and mixed m. p. 171—177°. Dilution of the acid solution with an equal volume of water precipitated 2 : 4-dichloro-3-2′-chloroethylquinoline (0·15 g.), m. p. and mixed m. p. 109—111°.

4-*Chloro*-3-2′-*chloroethyl*-1 : 2-*dihydro*-8-*methoxy*-2-*oxoquinoline* (III; R = OMe).—Hydrolysis of 2 : 4-dichloro-3-2′-chloroethyl-8-methoxyquinoline (2·82 g.) with 6N-hydrochloric acid (79 c.c.) and dioxan (62 c.c.) as in (*a*) above gave the *chloroquinolone* in colourless needles (1·6 g., 57%), m. p. 190—193°, unchanged by crystallisation from methanol (Found: C, 53·1; H, 4·0; N, 5·3; Cl, 26·0. $C_{12}H_{11}O_2NCl_2$ requires C, 53·0; H, 4·1; N, 5·1; Cl, 26·1%), insoluble in dilute aqueous alkali, and giving no colour with ferric chloride.

4-*Chloro*-4′ : 5′-*dihydrofurano*(2′ : 3′-2 : 3)*quinoline* (IV; R = H).—(*a*) 4-Chloro-3-2′-chloroethyl-1 : 2-dihydro-2-oxoquinoline (1·94 g.) in ethanol (130 c.c.) and water (90 c.c.) was refluxed for 3 hr. with silver oxide (from silver nitrate, 6 g.). The filtered solution was concentrated to remove ethanol and extracted with chloroform. Evaporation of the chloroform gave the *dihydrofuranoquinoline* (1·59 g., 97%), m. p. 105—111°, suitable for subsequent reactions. Purification by chromatography on alumina, elution with benzene, evaporation, and crystallisation from aqueous ethanol gave rods, m. p. 115—116° (Found: C, 64·6; H, 4·0. $C_{11}H_8ONCl$ requires C, 64·2; H, 3·8%).

(*b*) A solution of the chloroquinolone (0·19 g.) in benzene was chromatographed over alumina.

Elution with benzene gave the dihydrofuranoquinoline (0·073 g., 45%), m. p. and mixed m. p. 110—112°.

4-Chloro-4′ : 5′-dihydro-8-methoxyfurano(2′ : 3′-2 : 3)quinoline (IV; R = OMe).—(a) *From 4-chloro-3-2′-chloroethyl-1 : 2-dihydro-8-methoxy-2-oxoquinoline.* As above (silver oxide), the chloroquinolone (0·5 g.) was converted into the *dihydrofuranoquinoline* (0·41 g., 95%), separating from ethanol in needles, m. p. 186—188° (Found : C, 61·7; H, 4·6; Cl, 14·5. $C_{12}H_{10}O_2NCl$ requires C, 61·2; H, 4·3; Cl, 15·0%).

(b) *From 4-chloro-3-2′-ethoxyethyl-1 : 2-dihydro-8-methoxy-2-oxoquinoline* (see below). A solution of the chloroquinolone (1 g.) in diphenyl ether (25 c.c.) was heated under reflux for 4 hr. Addition of light petroleum (b. p. 40—60°) yielded starting material (0·33 g.), m. p. and mixed m. p. 156—160°. The light petroleum–diphenyl ether solution was concentrated to small bulk, and the diphenyl ether removed by steam-distillation. The residue separated from ethanol in needles (0·28 g.), m. p. 146—149°, but repeated crystallisation from ethanol effected no further purification. The crude material in benzene was chromatographed on acid-washed alumina. Elution with benzene gave the furanoquinoline (0·16 g., 19%), m. p. and mixed m. p. 186—188°. Elution of the column with chloroform gave a further quantity (0·07 g.) of the chloroquinolone (total recovery, 0·40 g., 40%).

4′ : 5′-Dihydro-4-methoxyfurano(2′ : 3′-2 : 3)quinoline (X; R = H).—4-Chloro-4′ : 5′-dihydrofurano(2′ : 3′-2 : 3)quinoline (0·5 g.) in a methanol solution of sodium methoxide [from sodium (0·5 g.) and methanol (10 c.c.)] was heated under reflux for 4 hr. The methanol was removed, water added, the mixture extracted with chloroform, and the chloroform evaporated. The residue, in benzene, was chromatographed on alumina. Elution with benzene gave the *dihydromethoxyfuranoquinoline* (0·31 g., 63%), m. p. 102—105°. The analytical sample crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 104—105° (lit.,[10] m. p. 103—104°) (Found : C, 71·5; H, 5·5; N, 6·9; OMe, 14·9. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5; N, 7·0; 1OMe, 15·4%).

4′ : 5′-Dihydro-4 : 8-dimethoxyfurano(2′ : 3′-2 : 3)quinoline (X; R = OMe).—By the method described in the previous experiment 4-chloro-4′ : 5′-dihydro-8-methoxyfurano(2′ : 3′-2 : 3)-quinoline was converted into the crude *dimethoxydihydrofuranoquinoline*, crystallising from aqueous ethanol in needles (0·12 g., 61%), m. p. 163—168°. After chromatography in benzene on alumina, a sample had m. p. 168—170° (Found : C, 67·9; H, 6·1; N, 5·7. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7; N, 6·1%).

4-Chlorofurano(2′ : 3′-2 : 3)quinoline (V; R = H).—(a) *From 4-chloro-4′ : 5′-dihydrofurano-(2′ : 3′-2 : 3)quinoline.* The dihydrofuranoquinoline (3 g.), *N*-bromosuccinimide (3·2 g.), a trace of benzoyl peroxide, and carbon tetrachloride (100 c.c.) were heated under reflux for 2 hr. The mixture, at room temperature, was filtered and the solution was evaporated under reduced pressure. The residue was refluxed with diethylaniline (30 c.c.) for 3 hr., added to 3N-hydrochloric acid (250 c.c.), and extracted with ether. Evaporation of the ether yielded an orange solid (2·36 g.), m. p. 105—110°, which was chromatographed in benzene on alumina. Elution with benzene afforded the furanoquinoline (2·05 g., 59%), m. p. 105—113°, crystallising from methanol in colourless rods, m. p. 112—114° (Found : C, 62·4; H, 3·3; Cl, 17·1%). The analytical data were unsatisfactory, but the product was shown to be identical with an authentic sample prepared as in (b) below by a mixed m. p. determination and by infrared spectra.

(b) *From nordictamnine* (see below).—Nordictamnine (0·056 g.) and phosphorus oxychloride (1 c.c.) were heated under reflux for 1 hr. and the excess of reagent was removed under reduced pressure. Addition of water gave the *chlorofuranoquinoline* (0·051 g., 83%), m. p. 111—115°, separating from methanol (charcoal) in colourless needles, m. p. 114—116° (Found : C, 65·2; H, 3·0. $C_{11}H_6ONCl$ requires C, 64·9; H, 3·0%).

4-Chloro-8-methoxyfurano(2′ : 3′-2 : 3)quinoline (V; R = OMe).—(*a*) A solution of 4-chloro-4′ : 5′-dihydro-8-methoxyfurano(2′ : 3′-2 : 3)quinoline (1 g.) in diphenyl ether (10 c.c.) was refluxed for 13 hr. in the presence of 10% palladium–charcoal (0·75 g.). Light petroleum (b. p. 40—60°) was added to the cooled, filtered reaction mixture, the solution was decanted from a small quantity of yellow gum, and the light petroleum removed by evaporation and the diphenyl ether by steam-distillation. A yellow gum was obtained from the aqueous mixture with ether and chromatographed in benzene on alumina. Elution of the first yellow band with benzene gave the required *chlorofuranoquinoline* (0·05 g., 5%), m. p. 170—179°, separating from ethanol in pale yellow prisms, m. p. 178—180° (Found : C, 61·6; H, 3·6. $C_{12}H_8O_2NCl$ requires C, 61·7; H, 3·5%). Further elution with benzene gave unchanged dihydrofuranoquinoline (0·04 g.),

m. p. and mixed m. p. 175—177°. Elution with benzene–chloroform (4 : 1) furnished 1 : 2 : 4′ : 5′-tetrahydro-8-methoxy-2-oxofurano(3′ : 2′-3 : 4)quinoline (0·009 g.), m. p. and mixed m. p. 202—206°.

(*b*) 4-Chloro-4′ : 5′-dihydro-8-methoxyfurano(2′ : 3′-2 : 3)quinoline (1 g.) was brominated-dehydrobrominated by the method applied above to 4-chloro-4′ : 5′-dihydrofurano(2′ : 3′-2 : 3)-quinoline. A solution of the crude product in benzene–light petroleum (20 : 1) was chromatographed on alumina. Elution with the same solvent gave the furanoquinoline (0·71 g., 72%), m. p. 163—171°, which crystallised from ethanol in colourless needles, m. p. 169—172° (mixed m. p. and infrared spectra).

Dictamnine (VI; R = H).—4-Chlorofurano(2′ : 3′-2 : 3)quinoline (0·11 g.) in methanolic sodium methoxide [from sodium (0·11 g.) and methanol (2·5 c.c.)] was refluxed for 3 hr. The methanol was evaporated, water added, and the mixture extracted with chloroform. Evaporation of the chloroform gave a yellow solid (0·11 g.) which was purified by chromatography on alumina. Elution with benzene gave *dictamnine* in colourless needles (0·036 g., 33%), m. p. 129—131°, raised by crystallisation from light petroleum (b. p. 60—80°) to 132° alone or mixed with an authentic sample (Found : C, 72·6; H, 4·6. $C_{12}H_9O_2N$ requires C, 72·4; H, 4·6%). The ultraviolet spectra [$\lambda_{max.}$ 308 (log ε 3·88), 312 (log ε 3·86), 328 mμ (log ε 3·82)] of the natural and the synthetic alkaloid were identical, and the infrared spectra were indistinguishable.

Nordictamnine (XI).—4-Chlorofurano(2′ : 3′-2 : 3)quinoline (1 g.) in 10N-hydrochloric acid (5 c.c.) and ethanol (20 c.c.) was heated under reflux for 10 hr., the ethanol removed, and the solution was made alkaline with 2N-aqueous sodium hydroxide and extracted with chloroform. The aqueous solution was acidified and the yellow precipitate (0·4 g.), m. p. 218—223°, sublimed at 190—195° (bath)/0·1 mm.

Nordictamnine was obtained as a white sublimate (0·24 g., 26%), m. p. 235—240°, shown to be identical with a sample obtained from the natural alkaloid by a mixed m. p. and by the infrared spectra.

γ-Fagarine (VI; R = OMe).— 4-Chloro-8-methoxyfurano(2′ : 3′-2 : 3)quinoline (0·13 g.) in methanolic sodium methoxide [from sodium (0·13 g.) and methanol (3 c.c.)] was heated under reflux for 2 hr. After removal of methanol and addition of water, the mixture was extracted with chloroform. Evaporation of the chloroform and washing the residue with ether furnished a *substance* (0·044 g., 30%) separating from ethanol in colourless plates, m. p. 195—199° (Found : C, 56·0; H, 5·2; Cl, 11·7; OMe, 23·6. $C_{13}H_{14}O_3NCl,\frac{1}{2}H_2O$ requires C, 56·4; H, 5·5; Cl, 12·8; 2OMe, 22·4%), insoluble in aqueous sodium hydroxide and giving no colour with ferric chloride.

Evaporation of the ether washings gave a yellow gum which was chromatographed in benzene on alumina. Elution with benzene–chloroform (4 : 1) gave *γ-fagarine* (0·025 g., 20%), m. p. 127—141°, crystallising from light petroleum (b. p. 60—80°) in pale yellow prisms, m. p. 138—140° alone or mixed with the natural alkaloid (Found : C, 68·1; H, 4·9. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8%). The ultraviolet spectrum [$\lambda_{max.}$ 308 (log ε 3·87), 323 (log ε 3·85), 334 mμ (log ε 3·79)] was identical with that of an authentic sample, as was also the infrared spectrum.

The *picrate*, prepared in ether, separated from ethanol in yellow plates, m. p. 172—173° (lit.,[17] m. p. 176°) (Found : C, 49·8; H, 3·1; N, 12·5. $C_{19}H_{14}O_{10}N_4$ requires C, 49·8; H, 3·1; N, 12·2%).

4′ : 5′-Dihydro-2-methoxyfurano(3′ : 2′-3 : 4)quinoline (IX; R = H, R′ = OMe).—2-Chloro-4′ : 5′-dihydrofurano(3′ : 2′-3 : 4)quinoline (0·17 g.) in methanol was refluxed with sodium methoxide [from sodium (0·17 g.)] for 2 hr. After evaporation, water was added and the mixture extracted with ether. Evaporation of the ether gave the *dihydromethoxyfurano-quinoline* as a colourless oil which crystallised in needles (0·12 g., 67%), m. p. 77—81°, and separated from light petroleum (b. p. 40—60°) in colourless plates, m. p. 81—82° (Found : C, 71·9; H, 5·3; OMe, 15·2. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5; 1OMe, 15·4%).

2-Chloro-8-methoxyfurano(3′ : 2′-3 : 4)quinoline (VII; R = Cl).—A solution of 1 : 2-dihydro-8-methoxy-2-oxofurano(3′ : 2′-3 : 4)quinoline (0·08 g.) in phosphorus oxychloride was refluxed for 1 hr., the excess of reagent removed, and water added. The precipitate of the *chlorofurano-quinoline* (0·059 g., 68%) crystallised from ethanol (charcoal) in colourless needles, m. p. 133—134° (Found : C, 61·9; H, 3·4. $C_{12}H_8O_2NCl$ requires C, 61·7; H, 3·5%).

2 : 8-Dimethoxyfurano(3′ : 2′-3 : 4)quinoline (VII; R = OMe).—Reaction of 2-chloro-8-methoxyfurano(3′ : 2′-3 : 4)quinoline (0·2 g.) with sodium methoxide gave the *dimethoxy-derivative* in pale yellow needles (0·197 g., 98%), m. p. 162—163°, unaffected by crystallisation

[17] Deulofeu, Labriola, and de Langhe, *J. Amer. Chem. Soc.*, 1942, **64**, 2326.

from light petroleum (b. p. 60—80°) (Found : C, 68·4; H, 4·8; N, 6·1. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8; N, 6·1%).

Furano(2′ : 3′-2 : 3)*quinoline* (XIII).—A mixture of 4-chlorofurano(2′ : 3′-2 : 3)quinoline (0·98 g.), 90% hydrazine hydrate (2 c.c.), and ethanol (6 c.c.) was heated under reflux for 3 hr. Complete evaporation gave a yellow solid, m. p. 225—235° (decomp.), which was refluxed with 10% aqueous copper sulphate (30 c.c.) for 1 hr. The solution was made strongly alkaline with aqueous sodium hydroxide and extracted with ether. Evaporation of the ether gave the *furanoquinoline* (0·192 g., 23%), crystallising from light petroleum (b. p. 40—60°) in colourless needles, m. p. 76—77° (Found : C, 78·2; H, 3·9; N, 8·1. $C_{11}H_7ON$ requires C, 78·1; H, 4·2; N, 8·3%).

Potassium Permanganate Oxidation of Furano(2′ : 3′-2 : 3)*quinoline.*—A solution of potassium permanganate (0·6 g.) in acetone (28 c.c.) was added during 1½ hr. to furano(2′ : 3′-2 : 3)-quinoline (0·2 g.) in acetone (10 c.c.). After the addition of water, the solution was clarified with sulphur dioxide, and the acetone removed by evaporation. 3-Carboxy-2-hydroxyquinoline slowly crystallised as a yellow solid (0·06 g., 27%), separating from ethanol in pale yellow needles, m. p. 300—312° (Found : C, 63·3; H, 3·4. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7%). The product was identical (mixed m. p. and ultraviolet and infrared spectra) with a sample (m. p. 300—312°) prepared by Friedlander and Goering's method.[18]

3-2′-*Ethoxyethyl*-2 : 4-*dihydroxy*-8-*methoxyquinoline* (XVII).—The crude product (31·7 g.) was obtained from *o*-anisidine (28·9 g.) as described previously. A chloroform solution was shaken with several portions of 2N-aqueous sodium hydroxide, dried, and evaporated, to give 1 : 2 : 4′ : 5′-tetrahydro-8-methoxy-2-oxofurano(3′ : 2′-3 : 4)quinoline, separating from ethanol in prisms (3·79 g., 7%), m. p. and mixed m. p. 218—220°. The alkaline washings were acidified and extracted with chloroform. Evaporation of the chloroform solution gave the dihydroxy-compound in pale brown prisms (23·8 g., 39%), m. p. and mixed m. p. 123—130°, sufficiently pure for use in subsequent reactions.

3-2′-*Ethoxyethyl*-1 : 2-*dihydro*-4 : 8-*dimethoxy*-2-*oxoquinoline* (XVIII).—3-2′-Ethoxyethyl-2 : 4-dihydroxy-8-methoxyquinoline (2·2 g.), suspended in ether (200 c.c.) containing a few drops of methanol, was treated with excess of ethereal diazomethane. After 12 hr. at room temperature, the solvent was evaporated and the residue dissolved in ether (50 c.c.). When the solution was concentrated to 25 c.c. the *dimethoxyquinoline* was deposited as colourless plates (1·0 g.), m. p. 119—120°, and a further quantity (0·32 g.), m. p. 115—118°, was obtained by concentration of the ether solution (total 1·32 g., 57%). Crystallisation from aqueous methanol gave plates, m. p. 122—123° (Found : C, 65·0; H, 6·6. $C_{15}H_{19}O_4N$ requires C, 65·0; H, 6·9%).

2 : 4-*Dichloro*-3-2′-*ethoxyethyl*-8-*methoxyquinoline* (XIX).—3-2′-Ethoxyethyl-2 : 4-dihydroxy-8-methoxyquinoline (20 g.) and phosphorus oxychloride (200 c.c.) were refluxed for 1 hr. and the excess of reagent removed. Addition of water gave the *dichloro-compound* (22·14 g., 99%), separating from aqueous ethanol in needles, m. p. 73—74° (Found : C, 56·0; H, 4·9; Cl, 23·8. $C_{14}H_{15}O_2NCl_2$ requires C, 56·0; H, 5·0; Cl, 23·6%).

4-*Chloro*-3-2′-*ethoxyethyl*-1 : 2-*dihydro*-8-*methoxy*-2-*oxoquinoline* (XX; R = OEt).—The above dichloro-compound (1·16 g.), 6N-hydrochloric acid (28 c.c.), and dioxan (20 c.c.) were heated under reflux for 2½ hr. and kept at room temperature for 12 hr. The crystalline precipitate (0·7 g., 65%), m. p. 159—160°, of the *chloroquinolone* was purified by chromatography on alumina. Elution with chloroform, evaporation, and crystallisation from ethanol gave needles, m. p. 162—163° (Found : C, 59·8; H, 5·6; N, 5·4; Cl, 12·3. $C_{15}H_{16}O_3NCl$ requires C, 59·7; H, 5·7; N, 5·0; Cl, 12·6%).

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[18] Friedlander and Goering, *Ber.*, 1884, **17**, 459.