CHAPTER II

HISTORICAL

1. The occurrence of chemical compounds in *Micromelum*

1.1 *Micromelum integerrimum* (Buch.-Ham.) M.Roem.

Plant part	Chemical compound	Reference
stem and leaf	Micromelin Scopoletin	Cassady *et al.*, 1979.

1.2 *Micromelum minutum* Seem. (*M. pubescens* Blume)

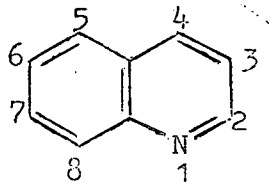
Plant part	Chemical compound	Reference
leaf	Micromelin (Micromelumin)	Lamberton *et al.*, 1967; Chatterjee *et al.*, 1968.
	Micropubescin	Chatterjee *et al.*, 1968.
	Microminutin	Ruangrungsi, interview 1980.
	Unknown Alkaloid(s)	Sastri, 1962; Lamberton *et al.*, 1967.

Plant part	Chemical compound	Reference
Stem and leaf	Hentriacontane Hentriacontanol β-Sitosterol	Bhakuni *et al.*, 1971.
	6-(2,3-Dihydroxy-3-methyl-butyl)-7-methoxy coumarin	Joshi *et al.*, 1975.
unknown	Osthol	Price, 1963.

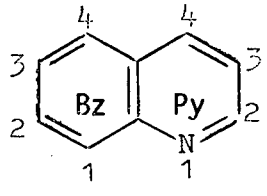
2. Chemical nature and classification of isoprenoid quinolone alkaloids

A large number of natural essentially non-terpenoid compounds contain isoprene units. Such compounds belong to diverse molecular types. The majority are components of higher plants, a few, however, are mould metabolic products. Among those of the rutaceous plants, isoprenoid quinoline type is an interesting one.

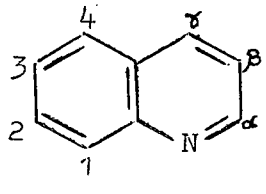
The quinoline ring system is theoretically obtained by fusing a benzene ring on to that of pyridine. The numbering system now universally adopted for the quinoline nucleus is shown in formula (1). However, in the older literature other schemes have been used to denote the position of substituents as shown in (2) and (3) (Elderfield, 1952).



(1)



(2)



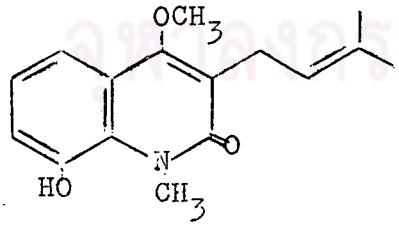
(3)

Most of the naturally occurring quinolones have been found to be derivatives of 2,4-dihydroxyquinoline. The chemical constitution of these compounds has been determined by the usually chemical analytic and synthetic processes, supplemented by spectroscopic evidence which has proved invaluable in distinguishing between 2- and 4-quinolone structures (Campbell, 1976; Price and Willis, 1959; McCorkindale, 1961; Goodwin and Horning, 1959).

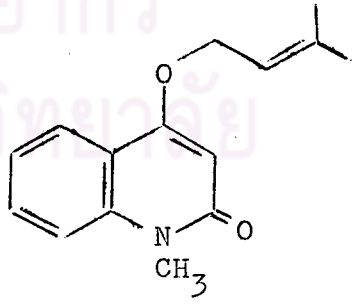
As furanoquinolines and pyranoquinolines have derived from isoprenoid intermediates (Collins and Grundon, 1969; Bowman *et al.*, 1973), the isoprenoid quinolone alkaloids may be classified by means of their main skeletons into 3 types:

2.1 Simple prenyl quinolone alkaloids

An isoprenoid side chain often attacks at the C-3 position of the quinolone nucleus (Geissman and Crout, 1969). Glycosolone (Das and Chowdhury, 1978) is one representative example of this type. Occasionally O-prenylation like ravenine (Paul and Bose, 1968) is also occurred.



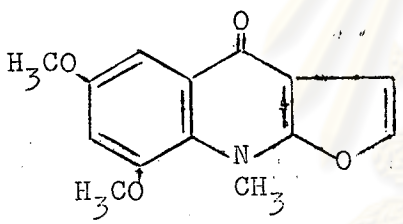
Glycosolone



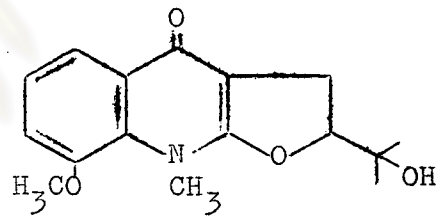
Ravenine

2.2 Furanoquinolone alkaloids

All the naturally occurring tricyclic furanoquinolones are linear. The aromatic ring is frequently substituted with a methoxy group at one or more positions. In some cases, the 2-position of the furan ring (usually dihydro) are variously substituted by alkyl or hydroxyalkyl side chain (Pakrashi and Bhattacharyya, 1965). For example, isomaculosidine (Gellert *et al.*, 1973; Storer and Young, 1973) and hydroxylunine (Goodwin *et al.*, 1959b; Szendrei *et al.*, 1973) are simple and hydroxyalkyl substituted furanoquinolones, respectively.



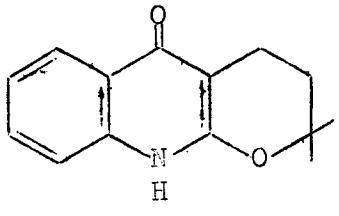
Isomaculosidine



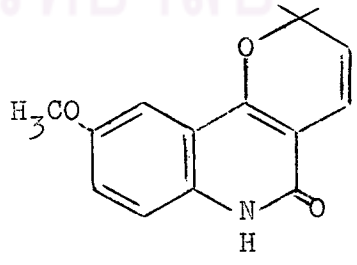
Hydroxylunine

2.3 Pyranoquinolone alkaloids

Both linear and angular pyranoquinolones like khaplofoline (Fakhrutdinova *et al.*, 1963) and haplamine (Akhmedzhanova *et al.*, 1974), respectively, are found in nature.



Khaplofoline

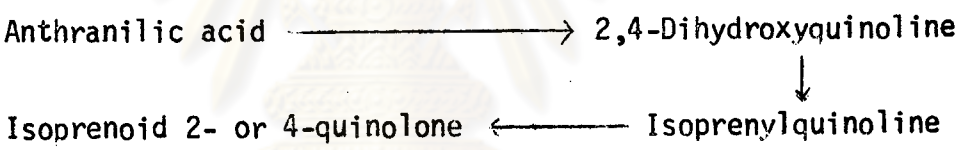


Haplamine

3. Biogenesis of isoprenoid quinolone alkaloids

The quinoline nucleus is found in a variety of naturally occurring compounds. Studies of the biosynthesis of these compounds indicate the existence of several pathways leading to this ring system. It has generally been considered that the quinoline alkaloids of the Rutaceae, together with the acridine and quinazoline alkaloids which often occur alongside them, are all derived from an "anthranilic acid" (Openshaw, 1967; Monkovic *et al.*, 1967; Finlayson and Prager, 1978).

The biosynthesis of isoprenoid quinolone base involves a successive process comprising:



3.1 Formation of anthranilic acid

Anthranilic acid may be formed from chorismic acid by the pathway described in Fig. 1, p.11, as well as from the amino acid tryptophan (Luckner, 1972).

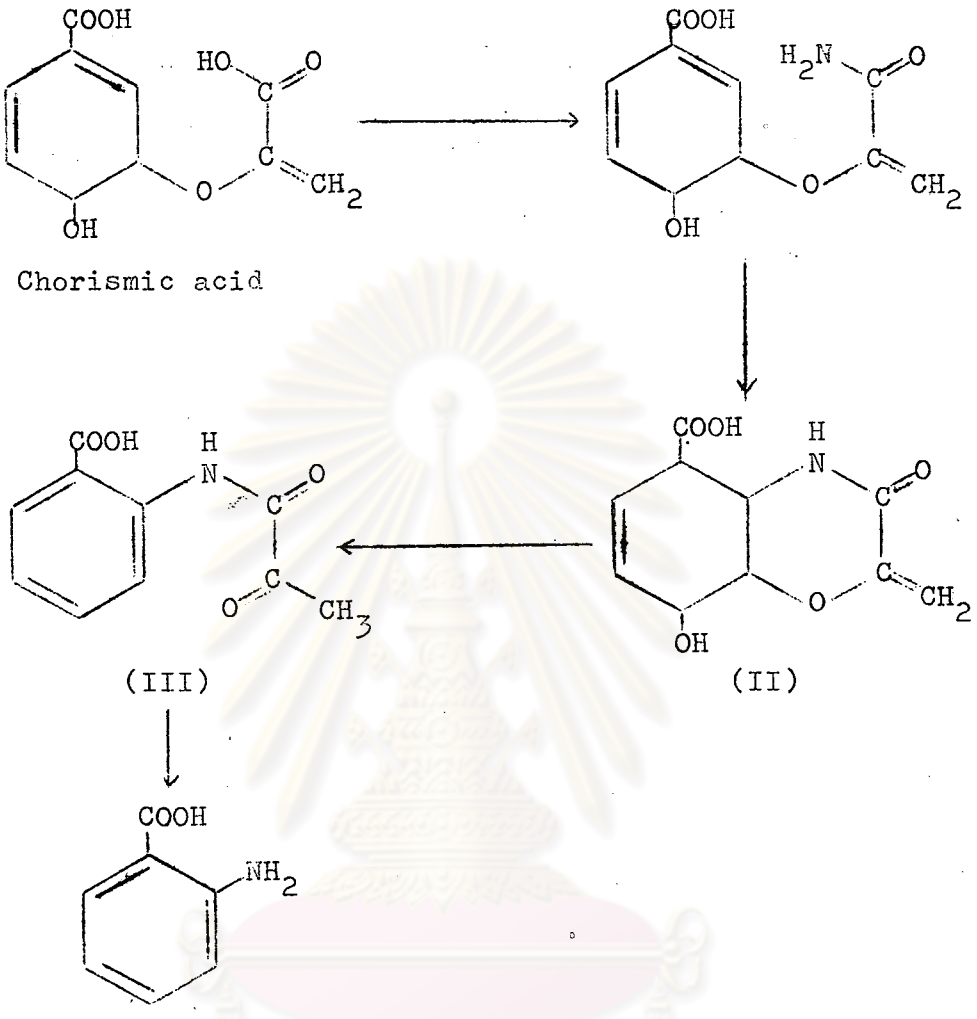


Figure 1. Possible mechanism of formation of anthranilic acid from chorismic acid.

Chorismic acid may be converted to *o*- and *p*-amino or hydroxybenzoic acids after elimination of the pyruvate group. For formation of anthranilic acid, the first step is probably the conversion of chorismic acid to the amide I, the amino group of which then is linked to the carbocyclic ring (compound II). Opening of the heterocyclic ring forms substance III. It may be considered to be amide of pyruvic acid

and may be decomposed hydrolytically to pyruvic acid and anthranilic acid (Luckner, 1972).

Anthranilic acid can arise by biochemical degradation of tryptophan. Its benzene nucleus, carboxyl group and amino group arise, in this degradative process from the phenyl ring, C(3) and the nitrogen atom of the indole nucleus tryptophan, respectively (Spenser, 1970).

3.2 Formation of 2,4-dihydroxyquinoline from anthranilic acid

2,4-Dihydroxyquinoline can plausibly be considered to arise by condensation of an anthranilic acid derivative (possibly the coenzyme A ester) with acetyl or malonyl coenzyme A, followed by cyclisation. The reaction is illustrated in Fig. 2 (Geissman and Crout, 1969).

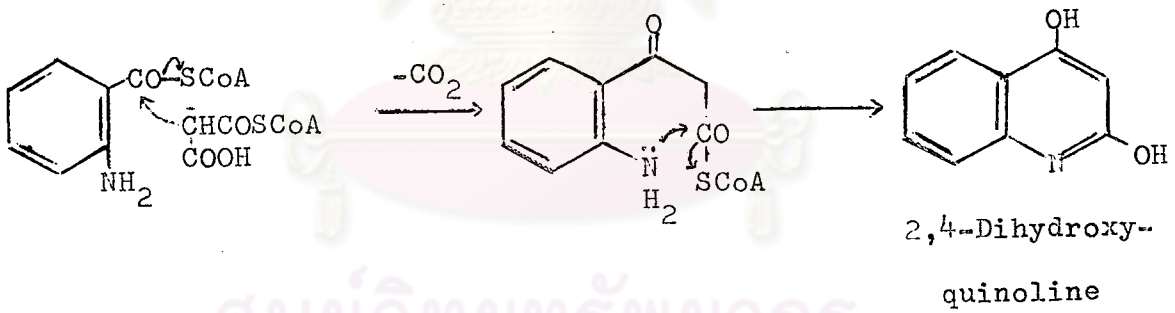
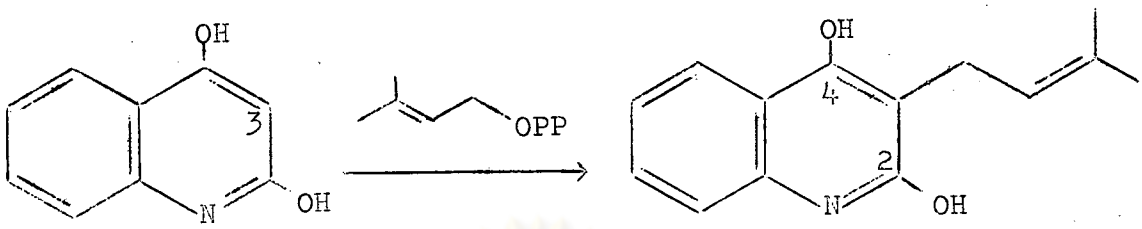


Figure 2. Formation of 2,4-dihydroxyquinoline.

3.3 Formation of isoprenylquinoline from 2,4-dihydroxyquinoline

Position C-3 in the 2,4-dihydroxyquinoline intermediate is obviously highly nucleophilic and therefore subject to ready prenylation. A possible route involves the introduction of a prenyl group, probably dimethylallyl pyrophosphate, into C-3 of the 2,4-dihydroxyquinoline to

form isoprenylquinoline as shown in Fig. 3 (Geissman and Crout, 1969).



2,4-Dihydroxyquinoline Isoprenylquinoline

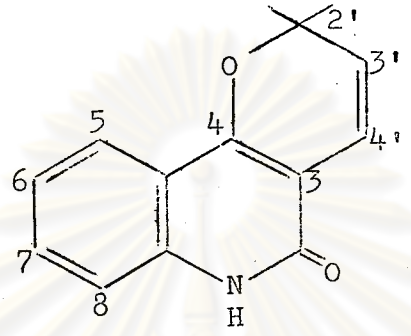
Figure 3. Formation of isoprenylquinoline

The isoprenylquinoline and its derivatives have been shown to be efficient precursors of isoprenoid quinolone alkaloids (Collins and Grundon, 1969; Geissman and Crout, 1969; Bowman *et al.*, 1973). The subsequent secondary modification steps typically include the aromatic ring substitution, hydroxylation of the side chain and oxidative cyclisation leading to an isoprenoid 2- or 4-quinolone compound, of which mechanism is individually specific.

4. Chemical nature of flindersine

The alkaloid flindersine was first isolated from the wood of *Flindersia australis* R. Br. (Rutaceae) in 1914 (Matthes and Schreiber, 1915), but it was probably incompletely purified; it was assigned the formula $C_{23}H_{26}O_7N_2$. In a recent reinvestigation of this tree, an alkaloid having very similar properties has been isolated; as it was apparently identical with the earlier base, the name flindersine has been retained, but the formula has been corrected to $C_{14}H_{13}O_2N$ (Brown *et al.*, 1954; Openshaw, 1960).

The structure and numbering system of flindersine [2',2'-dimethyl-α-pyrano-(5',6'-3,4)-2-quinolone] is shown below (Bowen and Lewis, 1978):



Flindersine was found to have a weakly alkaline reaction, to be optically inactive, and to be insoluble in water, sparingly soluble in light petroleum, but soluble in chloroform, ethyl alcohol, benzene, glacial acetic acid, hydrochloric acid, sulphuric acid, caustic alkali, glycerol, paraffin and fatty oils. Positive tests were given with the usual alkaloidal reagents and an orange colour with ferric chloride reagent (Brown *et al.*, 1954).

5. Biogenesis of flindersine

Like other isoprenoid quinolone alkaloids, the biosynthesis of flindersine reasonably occurred from a 3-isoprenylquinoline. Such a compound then cyclised to form the pyran via 2,2-dimethyl-chromene pathways. Two possible hypotheses were suggested (Bowman *et al.*, 1973).

5.1 Quinone methide route

The mechanism was initiated by oxidation of the 3-isoprenyl-quinolone anion (IV), followed by loss of a proton, giving rise to the

quinone methide intermediate (V) which then cyclised to form flindersine as shown in Fig. 4 (Ollis and Sutherland, 1961; Turner, 1964).

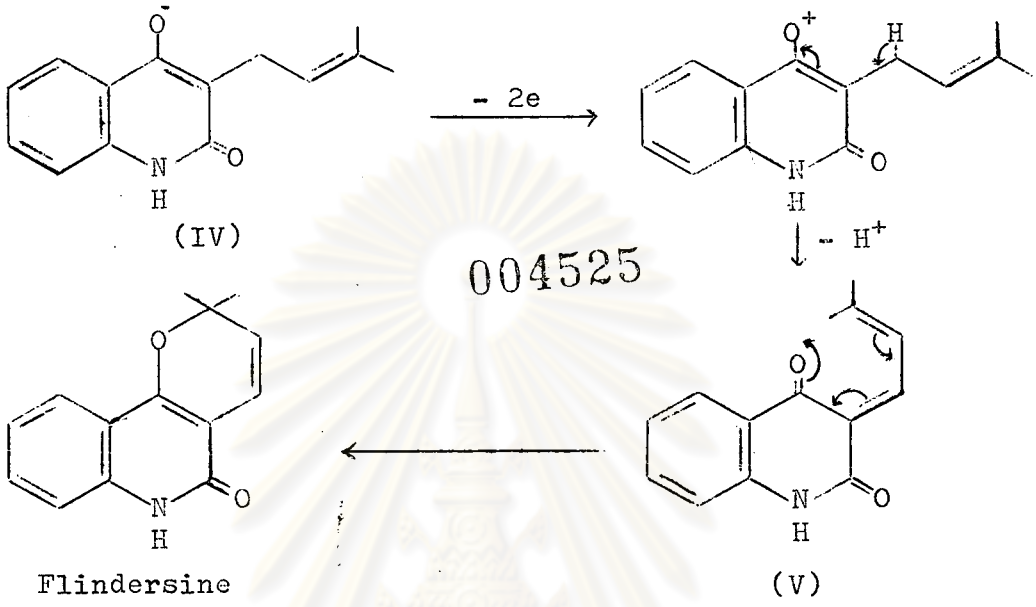


Figure 4. Formation of flindersine via a quinone methide route.

5.2 Allylic carbonium ion route

It was suggested that the C_5 units of isoprenoid compounds might have their origin based on mevalonic acid (Aneja *et al.*, 1958). The evolution of the alkaloid flindersine from such a precursor possibly summarised in Fig. 5. p 16.

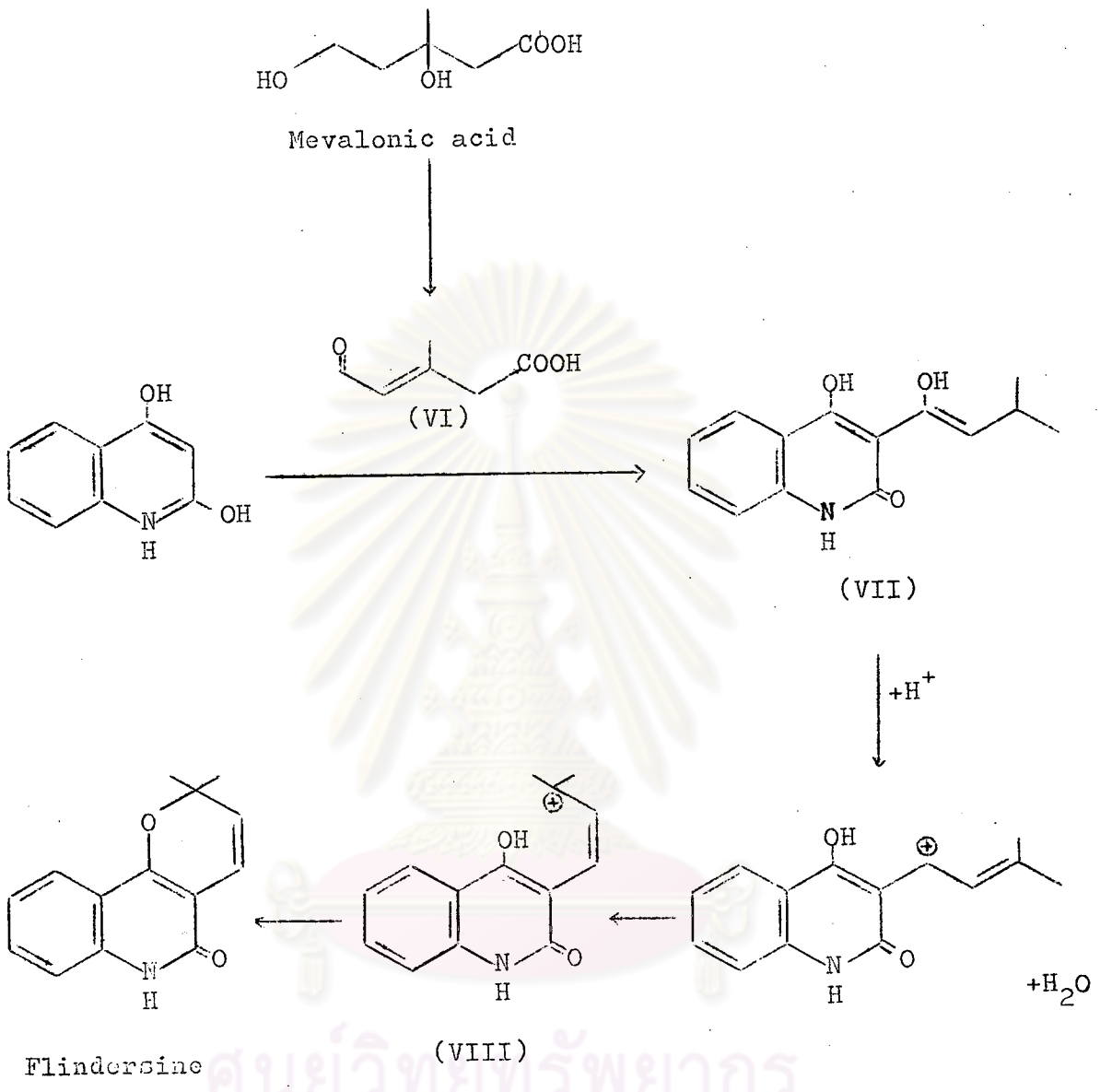
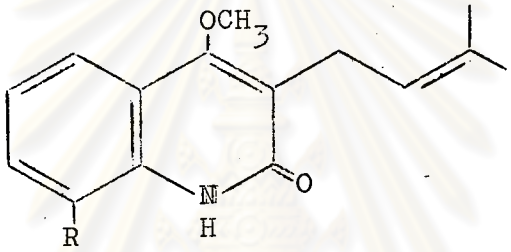


Figure 5. Formation of flindersine via an allylic carbonium ion route.

The reaction was considered to undergo initial oxidation of the primary alcoholic group of the mevalonic acid to aldehyde and dehydration to produce a double bond, giving rise to the aldehyde-acid (VI). Reaction of the aldehyde spearhead of (VI) with an activated C-3 position of the 2,4-dihydroxyquinoline and decarboxylation would lead to

the formation of (VII) (Aneja *et al.*, 1958). The proposed allylic carbonium ion intermediate (VIII) was brought about by protonation of (VII) and elimination of a water molecule. The final step was the intermediate ring closure, causing to flindersine formation (Whalley, 1961).

The allylic carbonium ion pathway was said to be alternative. This suggestion was confirmed by attempting to prepare linear pyranoquinolines, hence, the 4-methoxy-2-quinolones (a and b) were treated with



4-Methoxy-2-quinolone

a, R = H; b, R = OCH_3

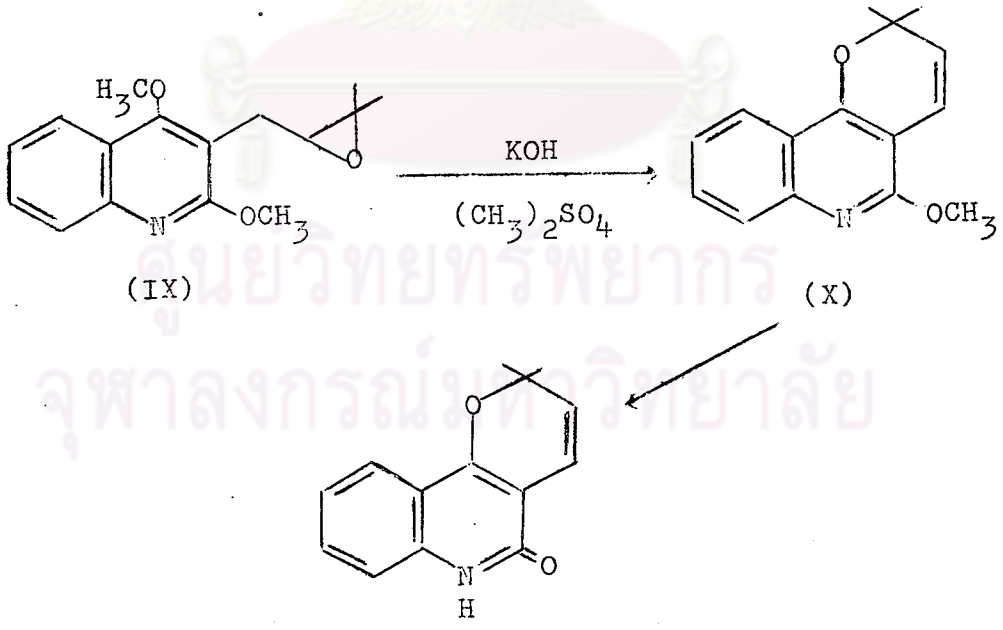
2,3-dichloro-5,6-dicyanobenzoquinolone (DDQ) but no reaction was observed. A possible explanation for this unexpected result was that formation of a quinone methide from a 2-quinolone would involve disruption of the benzenoid system. Thus, the *in vitro* evidence rationalised the occurrence of angular rather than linear pyranoquinoline alkaloids, and supported the quinone methide theory of biosynthesis; the alternative allylic carbonium ion intermediate (VIII) should provide no barrier to the formation of linear compounds after protection of the 4-hydroxy group (Bowman *et al.*, 1973).

6. Chemical synthesis of flindersine

Several methods were proposed for the synthesis of flindersine (Brown *et al.*, 1956; Piozzi *et al.*, 1969; Bowman *et al.*, 1970; Huffman and Hsu, 1972; Bowman *et al.*, 1973). The base-catalysed rearrangement of an isoprenyl epoxide reaction is one outstanding because it has provided good yield and implied biosynthetic significance (Bowman *et al.*, 1973).

6.1 Preparative process

Treatment of the dimethoxyquinoline epoxide (IX) with aqueous potassium hydroxide in dimethylsulphoxide at 100°C gave a pyranoquinoline (X) (77%). The pyran was further demethylated with hydrobromic acid to give flindersine (81%) (Fig. 6) (Bowman *et al.*, 1973).



Flindersine

Figure 6. Chemical synthesis of flindersine

6.2 Mechanism of the reaction

By using deuteriated solvents and following the reaction of the epoxide (IX) by NMR spectroscopy, indicated that the pyranoquinoline (X) was formed from the epoxide (IX) via the allylic alcohol (XI) and (XII); the suggested mechanism was shown in Fig. 7 (Bowman *et al.*, 1973).

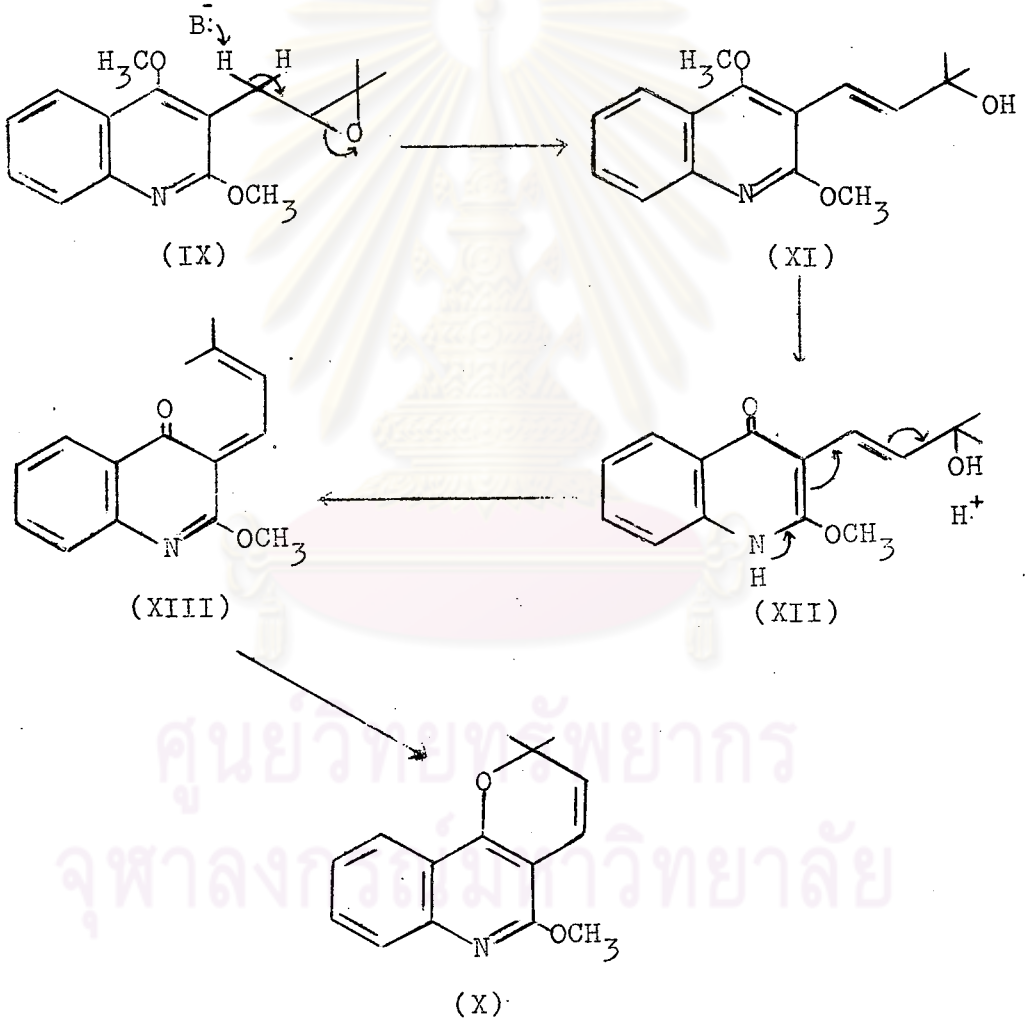


Figure 7. Suggested mechanism of the synthetic reaction.

Base-catalysed rearrangements of epoxides to allylic alcohol [e.g. (IX)→(XI)] have been discussed previously (Cope and Heeren, 1965; Rickborn and Thummel, 1969), and *trans*-olefins were found to be the preferred products, as in this case. It was suggested that when the solution was neutralised, dehydration of the alcohol (XII) and subsequent cyclisation occurred through quinone methide (XIII) (Bowman *et al.*, 1973).

An alternative mechanism for decomposition of the allylic alcohol (XII), as shown in Fig. 8 p. 21 , involved dehydration to the diene (XIV) followed by isomerisation of the *trans*-double bond [(XIV) → (XV)], and finally by cyclisation (Bowman *et al.*, 1973). This mechanism seemed less likely than the quinone methide route, since the formation of pyranoquinoline (X) from allylic alcohol (XII) occurred at ambient temperature in slightly acidic medium, whereas the isomerisation of dienes [e.g. (XIV)→(XV)] usually required more vigorous condition (Schweizer *et al.*, 1966).

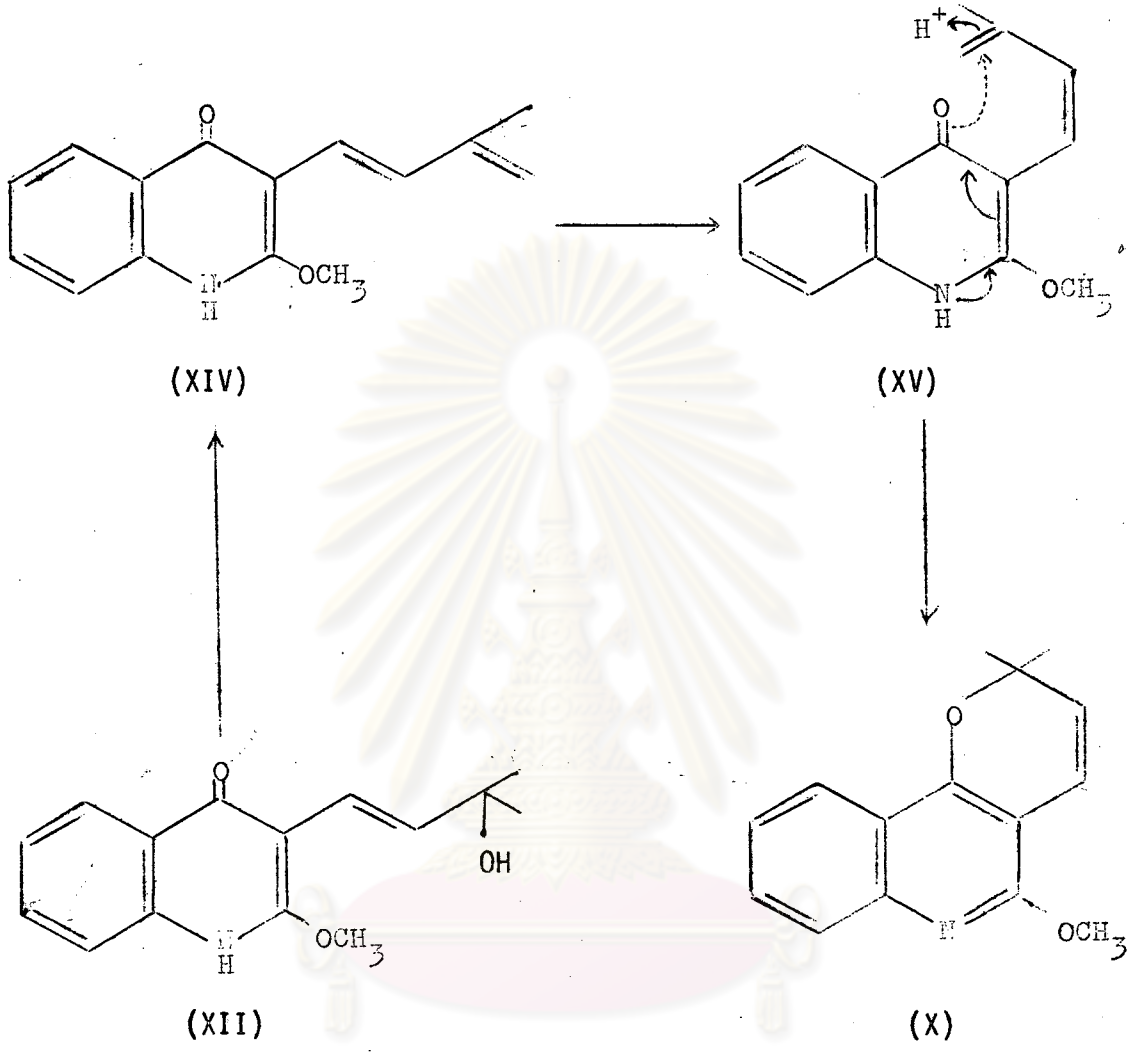


Figure 8. An alternative mechanism of the synthetic reaction.

7. Isoprenoid quinolone alkaloid bearing plants

Acrophyllidine

- *Acronychia haplophylla* (F. Muell.) Engl. (Rutaceae)

(Lahey and McCamish, 1968; Lahey *et al.*, 1969)

Acrophylline

-*Acronychia haplophylla* (F. Muell.) Engl. (Rutaceae)

(Lahey and McCamish, 1968; Lahey *et al.*, 1969)

Atanine

- *Pavenia spectabilis* Engl. (Rutaceae)

(Paul and Bose, 1968)

- *Fagara zanthoxyloides* Lam. (Rutaceae)

(Eshiet and Taylor, 1966; Eshiet and Taylor, 1968)

Balfourodine

- *Balfourodendron riedelianum* Engl. (Rutaceae)

(Rapoport and Holden, 1959; Rapoport and Holden, 1960)

- *Ptelea trifoliata* L. ssp. *pallida* (Greene) V.L. Bailey var. *confinis* (Greene) V.L. Bailey (Rutaceae)

(Szendrei *et al.*, 1973)

Balfourolone

- *Balfourodendron riedelianum* Engl. (Rutaceae)

(Rapoport and Holden, 1959; Rapoport and Holden, 1960)

3-Dimethylallyl-4-dimethylallyloxy-2-quinolone

- *Haplophyllum tuberculatum* (Rutaceae)

(Lavie *et al.*, 1968)

Edulinine

- *Casimiroa edulis* Llave *et* Lex. (Rutaceae)
  (Iriarte *et al.*, 1956; Toube *et al.*, 1967)
- *Eriostemon trachyphyllus* F. Muell. (Rutaceae)
  (Lassak and Pinhey, 1969)
- *Citrus macroptera* Montr. (Rutaceae)
  (Johns *et al.*, 1970)

(-)-Edulinine

- *Fagara mayu* (Bert. ex Hook. *et* Arn.) Engl.
  (syn. *Zanthoxylum mayu* Bert.) (Rutaceae)
  (Torres and Cassels, 1978)

O^4 Ethyl Analog of Balfourolone

- *Balfourodendron riedelianum* Engl. (Rutaceae)
  (Rapoport and Holden, 1961)

Flindersine

- *Flindersia australis* R. Br. (Rutaceae)
  (Matthes and Schreiber, 1915; Brown *et al.*, 1954)
- *Haplophyllum tuberculatum* (Rutaceae)
  (Lavie *et al.*, 1968)
- *Geijera parviflora* Lindl. (Rutaceae)
  (Dreyer and Lee, 1972)
- *Atalantia roxburghiana* Hook f. (Rutaceae)
  (Bowen and Lewis, 1978)

Folifine

- *Haplophyllum foliosum* Vved. (Rutaceae)
  (Faizutdinova *et al.*, 1967)

Foliosidine

- *Haplophyllum foliosum* Vved. (Rutaceae)

  (Eskairov *et al.*, 1959; Razzakova *et al.*, 1972)

- *Haplophyllum perforatum* Kar. *et* Ker. (Rutaceae)

  (Razzakova *et al.*, 1977)

Foliosidine acetonide

- *Haplophyllum foliosum* Vved. (Rutaceae)

  (Tel' nov. *et al.*, 1971)

Glycosolone

- *Glycosmis pentaphylla* (Retz) DC (Rutaceae)

  (Das and Chowdhury, 1978)

Haplamine

- *Haplophyllum perforatum* Kar. *et* Ker. (Rutaceae)

  (Akhmedzhanova *et al.*, 1974)

Hydroxylunacridine

- *Lunasia amara* Blanco (Rutaceae)

  (Goodwin *et al.*, 1959a; Goodwin *et al.*, 1959b)

Hydroxylunacrine

- *Lunasia amara* Blanco (Rutaceae)

  (Goodwin *et al.*, 1959b)

Hydroxylunidine

- *Lunasia amara* Blanco (Rutaceae)

  (Goodwin *et al.*, 1959b)

Hydroxylunidonine

- *Ptelea trifoliata* L. (Rutaceae)

  (Reisch *et al.*, 1975b)

Hydroxylunine

- *Lunasia amara* Blanco (Rutaceae)

  (Goodwin *et al.*, 1959b)

- *Ptelea trifoliata* L. ssp. *pallida* (Greene) V.L. Bailey var. *confinis* (Greene) V.L. Bailey (Rutaceae)

  (Szendrei *et al.*, 1973)

Ifflaiamine

- *Flindersia ifflaiana* F. Muell. (Rutaceae)

  (Bosson *et al.*, 1963)

Isobalfourodine

- *Balfourodendron riedelianum* Engl. (Rutaceae)

  (Rapoport and Holden, 1960)

Isodictamnine

- *Dictamnus albus* L.

  (syn. *D. angustifolius* Sweet) (Rutaceae)

  (Gellert *et al.*, 1973; Akhmedzhanova *et al.*, 1978)

- *Dictamnus caucasicus* Hort. (Rutaceae)

  (Asatiani *et al.*, 1972)

Isomaculosidine

- *Dictamnus albus* L. (Rutaceae)

  (Gellert *et al.*, 1973; Storer and Young, 1973)

3-Isopentenyl-4-methoxy-7,8-methelenedioxy-2-quinolone

- *Ptelea trifoliata* L. (Rutaceae)

  (Dreyer, 1969)

Isoptelefoline

- *Ptelea trifoliata* L.

  (Reisch *et al.*, 1970a)

Kaplofoline

- *Haplophyllum foliosum* Vved. (Rutaceae)

  (Fakhrutdinova *et al.*, 1963)

Lunacridine

- *Lunasia amara* Blanco (Rutaceae)

  (Goodwin *et al.*, 1959b)

Lunacrine

- *Lunasia amara* Blanco (Rutaceae)

  (Goodwin *et al.*,1959b; Goodwin and Horning, 1959)

- *Lunasia quercifolia* (Warb.) Lauterb. et K. Schum.

  (Rutaceae)

  (Johnstone *et al.*, 1958)

Lunasia II (Identical with Lunacrinol)

- *Lunasia amara* Blanco (Rutaceae)

  (Goodwin *et al.*, 1959b; Beyerman and Rooda, 1960)

Lunidine

- *Lunasia amara* Blanco var. *reparda* (Lauterb. et K. Schum.) Lauterb.

  (Rutaceae)

  (Ruegger and Stauffacher, 1963)

- *Ptelea trifoliata* L.

  (Reisch *et al.*, 1975b)

Lunidonine

- *Lunasia amara* Blanco var. *reparda* (Lauterb. et K. Schum.) Lauterb.

  (Rutaceae)

  (Ruegger and Stauffacher, 1963)

Lunine

- *Lunasia quercifolia* (Warb.) Lauterb. *et* K. Schum. (Rutaceae)
  (Johnstone *et al.*, 1958)
- *Lunasia amara* Blanco (Rutaceae)
  (Goodwin *et al.*, 1959b)

N-Methylflindersine

- *Spathelia sorbifolia* (L.) Fawc. & Rendle (Rutaceae)
  (Adams *et al.*, 1973)
- *Ptelea trifoliata* L. (Rutaceae)
  (Reisch *et al.*, 1975a)

6-Methoxyisodictamnine

- *Dictamnus caucasicus* Hort. (Rutaceae)
  (Asatiani *et al.*, 1972)

Nor-orixine

- *Orixa japonica* Thunb. (Rutaceae)
  (Terasaka *et al.*, 1960)

Oricine

- *Oricia suaveolens* (Engl.) Verdoon (Rutaceae)
  (Abe and Taylor, 1971)

Pholiosidine

- *Haplophyllum foliosum* Vved. (Rutaceae)
  (Pastukhova *et al.*, 1965)

Preskimmianine

- *Dictamnus albus* L.
  (syn.*D.angustifolius* Sweet) (Rutaceae)
  (Storer and Young, 1973; Akhmedzhanova *et al.*, 1978)

Ptelecortine

- *Ptelea trifoliata* L. (Rutaceae)

  (Reisch *et al.*,1972)

Ptelefolidine

- *Ptelea trifoliata* L. (Rutaceae)

  (Reisch *et al.*, 1970a; Korosi *et al.*, 1975)

Ptelefolidine methylether

- *Ptelea trifoliata* L. (Rutaceae)

  (Reisch *et al.*, 1970a; Korosi *et al.*, 1975)

Ptelefoline

- *Ptelea trifoliata* L. (Rutaceae)

  (Reisch *et al.*, 1970a; Reisch *et al.*, 1970b)

Ptelefoline methylether

- *Ptelea trifoliata* L. (Rutaceae)

  (Reisch *et al.*,1972)

Ptelefructine

- *Ptelea trifoliata* L. (Rutaceae)

  (Reisch *et al.*,1970a)

Pteleoline

- *Ptelea trifoliata* L. (Rutaceae)

  (Reisch *et al.*,1972)

Ravenine

- *Ravenia spectabilis* Engl. (Rutaceae)

  (Paul and Bose, 1968)

Ravenoline

- *Ravenia spectabilis* Engl.(Rutaceae)

  (Paul and Bose, 1968)

Ribalinidine

- *Balfourodendron riedelianum* Engl. (Rutaceae)
  (Corral *et al.*, 1968)

Ribalinine

- *Balfourodendron riedelianum* Engl. (Rutaceae)
  (Corral and Orazi, 1967)
- *Fagara mayu* (Bert. ex Hook.et Arn.) Engl.
  (syn. *Zanthoxylum mayu* Bert.) (Rutaceae)
  (Torres and Cassels, 1978)

Spectabiline

- *Lemonia spectabilis* Lind.
  (syn.*Ravenia spectabilis* Engl.) (Rutaceae)
  (Talapatra *et al.*, 1969)

2,3,4,9-Tetrahydro-2,2,3,9-tetramethyl-4-oxo-furano(2,3-b)quinoline

- *Flindersia ifflaiana* F. Muell. (Rutaceae)
  (Chamberlain and Grundon, 1971)

4,6,8-Trimethoxy-3-(3',3'-dimethylallyl-N-methyl-2-quinolone

- *Ptelea trifoliata* L. (Rutaceae)
  (Reisch *et al.*, 1975a)