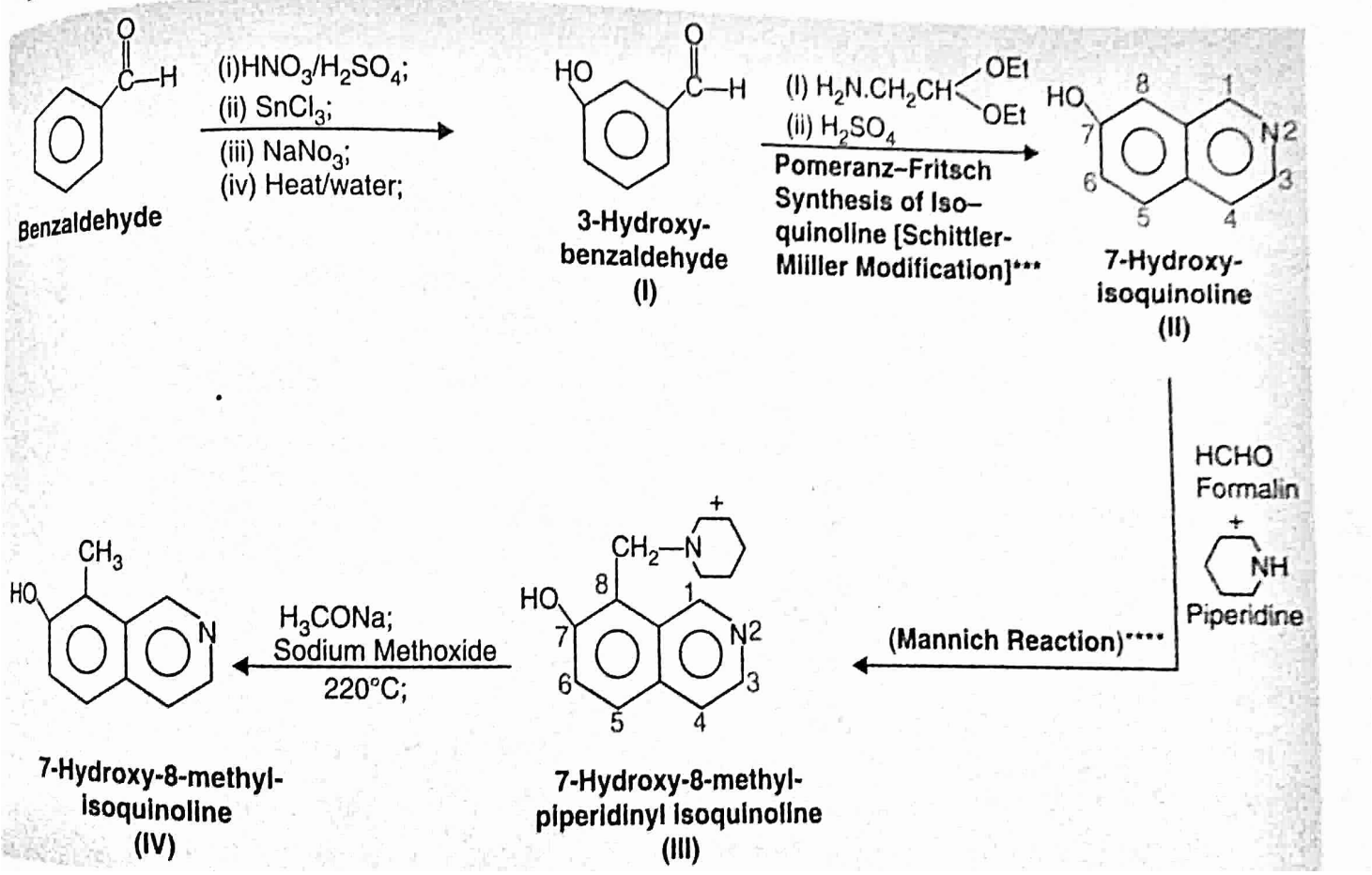
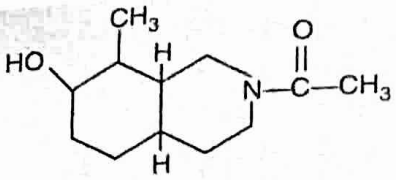
Quinine designates the age-old, famous, wonderful, and extremely effective **'antimalarial drug'** obtained from the bark of *Cinchona callisaya* Wedd. It has the following **chemical structure.**

9. **Synthesis :** Ultimately, the structure of **'quinine'** is further confirmed by its **total synthesis** reported by Muhtadi *et al.* (1983)*; Woodward and Doering (1944)**. In fact, these dedicated researchers carried out the **total synthesis,** starting from *ab initio* up to the **racemic mixture of 'quinotoxine';** and from this point onward Rabe continued the synthesis till its completion.

The various steps involved in the **total synthesis** of **'quinine'** are as stated under :

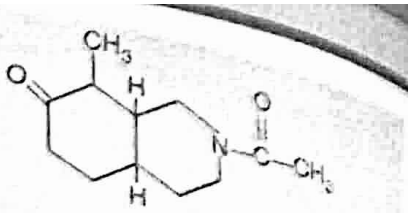


(I)[$(CH_3CO)_2O$];
Acetic Anlodride
(Ii)H_2-Rarey Ni;
(Reduction)



N-Acetyl-7-hydroxy-8=methyl-1,2,3,4,5,6,7,8-actahydro isoquinoline (V)

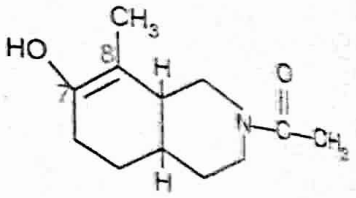
(I) CrO_3/CH_3COOH;
(Oxidation)
(ii) H_2-Raney Ni;
(Reduction)



N-Acetyl-7-keto-8-methyl-1,2,3,4,5,6,7,8-octahydro isoquinoline (VI) (keto-Form)

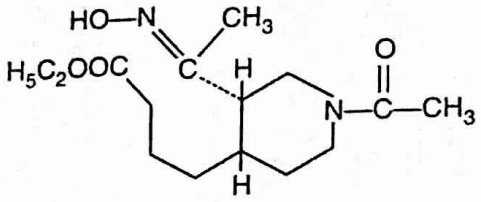
*Both '*keto*' and '*enol*-forms are duly separated by their crystalline hydrates

'*keto-enol*-tautomerism



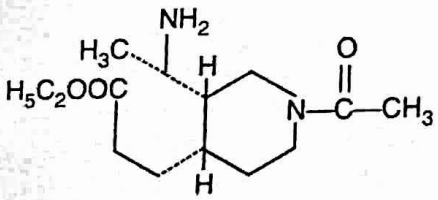
(VI A) ('*enol*-Form)

(I) H_5C_2-NO_2'
Ethyl Nitrite
(ii) H_5C_2-ONa
Sodium ethoxide
(Freshly prepared)

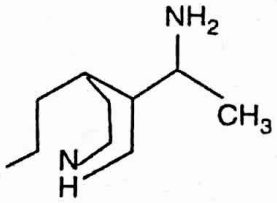


Homomeroquinene derivative (VII) (Redrawn)

H_2-Pt'
(Reduction)

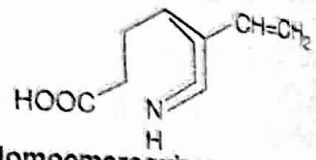


Or

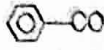


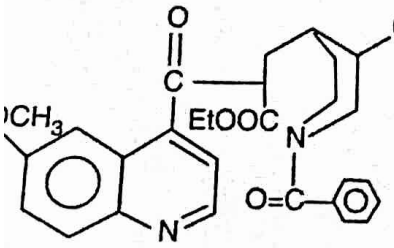
An Intermediate (VIII)

(I) CH_3I/K_2CO_3'
Methyl Iodide
(ii) KOH;Δ;



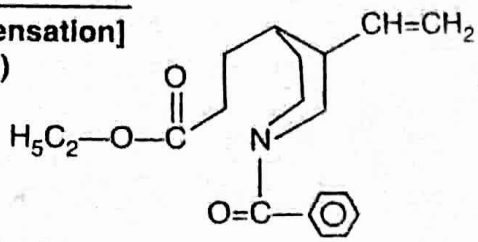
***cis*- (+)-Homoemeroquinene (IX)**

(I)C_2H_5OH/HCl;
(Ii) 
Benzoyl chloride



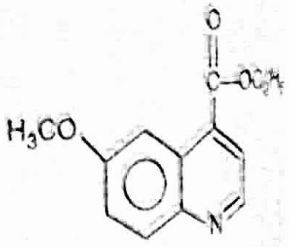
(A β-*keto*-Ester) (XII)

C_2H_5-ONa;
Sodium ethoxide
[Claisen Condensation] with (X)

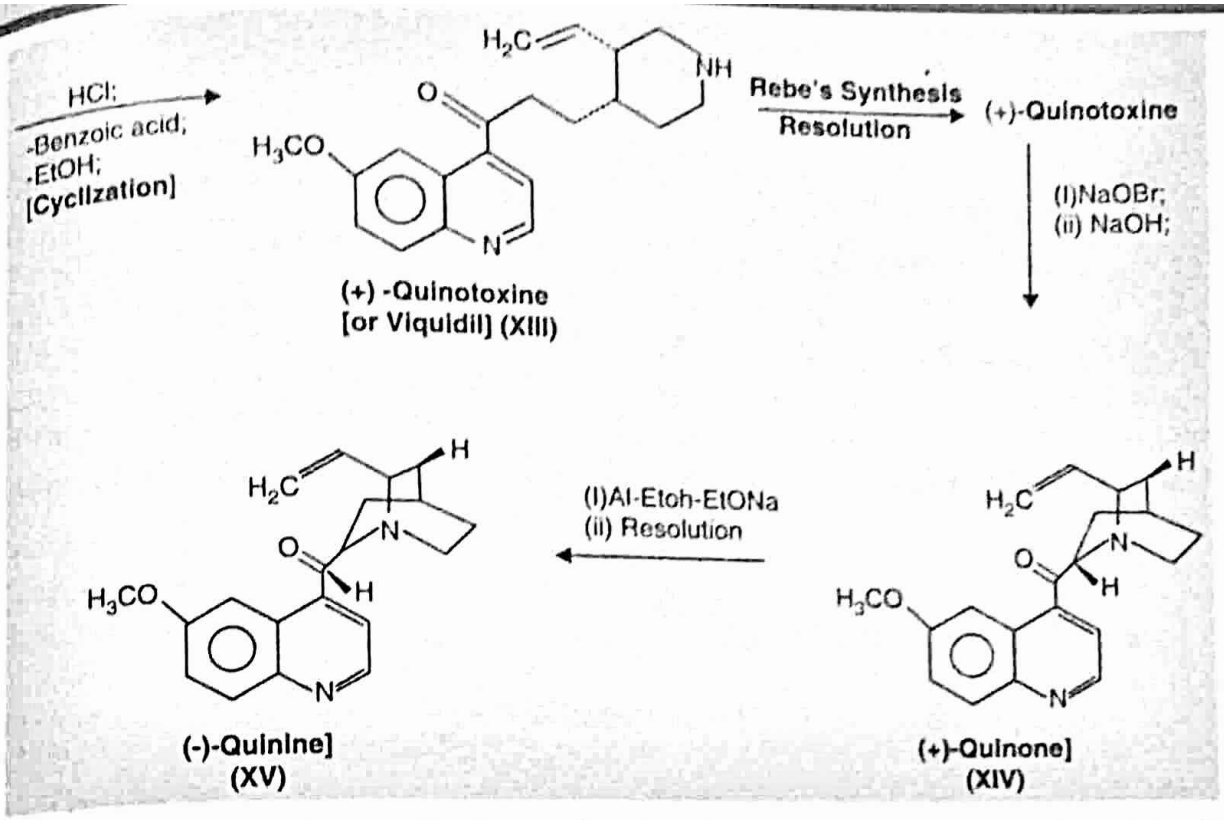


N-Benzoylated ethyl ester of homomero quinene (XI)

+



Ethyl quininate (X)



Explanations : The various cardinal steps involved in the **'total synthesis'** of ***'quinine'*** by *three* researchers : **Muhtadi, Woodward,** and **Rabe** are explicitly enumerated as under ;

(1) **Benzaldehyde** when nitrated–reduced–diazotized–hydrolyzed yields **3–hydroxy benzaldehyde (I),** which upon **Pomeranz–Fritsch** synthesis using diethoxy ethyl amine and H_2SO_4 produces **7–hydroxy isoquinoline (II).**

(2) The resulting product on **Mannich Reaction** using *formalin* and *piperidine* yields **7–hydroxy–8–methyl piperidinyl isoquinoline (III),** which on treatment with freshly prepared **sodium methoxide at 220° C** produces **7–hydroxy–8–methyl–isoquinoline (IV).**

(3) The **product (IV)** when treated *first* with **acetic anhydride** and *secondly* with **Raney-Ni** (*i.e.*, **reduction**) yields **N–acetyl–7–hydroxy 8–methyl–1,2,3,4,5,6,7,8–octahydro–isoquinoline (V).**

(4) The resulting **product (V)** *first* with **oxidation** with **chromium–6–oxide,** and **reduction** with **Raney–Ni** yields **N–acetyl–7–*keto*–8–methyl–1,2,3,4,5,6,7,8–octahydro isoquinoline (VI).**

(5) The ***keto*–form of product (VI)** undergoes ***'keto-enol'*–tantomerism** to produce the corresponding **'enol' form (VI A).**

(6) The resulting **product (VIA)** when treated *first* with **ethyl nitrite** and *secondly* with **sodium ethoxide** gives rise to the formation of **homomeroquinene derivative (VII)** due to the cleavage between **C–7** and **C–8,** which on subsequent *reduction* with **H_2–Pt** yields an **intermediate (VIII).**

(7) The ***redrawn* intermediate (VIII)** on *first* reaction with **methyl iodide** and **K_2CO_3,** and *secondly* with KOH and boiling produces ***cis*–(±)–*homomeroquinene (IX),*** which upon treatment with **EtOH/HCl** and **benzoyl chloride** yields *two* distinct *products* of reaction **ethyl quinindate (O)** and **N–benzoylated ethyl ester of homomeroquinene (XI).**

(8) The **product (X)** undergoes **Claisen Condensation** with **sodium ethoxide** to yield a **β–keto ester (XII),** which on treatment with HCl undergoes **cyclization** to produce the racemic mixture of **quinotoxine (XIII)**, also known as **'viquidil'.**

(9) **Rabe's Synthesis** *i.e.*, resolution of **product (XIII)** gives **(+)–quinotoxine,** which upon treatment with **NaOBr** and **NaOH** yields **(+)–quinone (XIV).**

(10) The resulting **product (XIV)** on reaction with **Al/EtOH/EtONa** and subsequent resolution produces **(–)–quinine (XV).**