A THESIS

PRESENTED TO THE FACULTY OF ARTS AND SCIENCES

OF

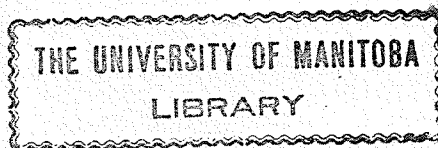THE UNIVERSITY OF MANITOBA

FOR THE

DEGREE OF MASTER OF SCIENCES.

by

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January 1924.   Canton, China.

"   ATTEMPTS AT THE SYNTHESIS OF CERTAIN

PYRIDINE AND QUINOLINE DERIVATIVES ALLIED TO SOME

DECOMPOSITION PRODUCTS OF THE

CINCHONA ALKALOIDS.   "

" ATTEMPTS AT THE SYNTHESIS OF CERTAIN PYRIDINE AND

QUINOLINE COMPOUNDS ALLIED TO THE DECOMPOSITION

PRODUCTS OF THE CINCHONA ALKALOIDS. "

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The work of Paul Rabe and his collaborators.

"   "   " A. Kauffman " "   "

"   "   " P. Karrer " "   "

"   "   " L. Ruzicka " "   "

c. with β-piperidyl propionic acid.

PART TWO.

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e. from triacetonamine.

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INTRODUCTION.

Recent advances in the realm of science ushered into the chemical world a new subject, that of synthetical chemistry, whose scope today is all-embracing, and as a result all substances, both organic and inorganic, are subject to its search. Alkaloidal chemistry forms no small part of organic chemistry and on account of its connexion, not only with the chemical world, but also with the medical profession, it came under special investigation so that today we have several synthetical alkaloids, while many others of greater complexity are still awaiting their synthesis, which should not be long in coming.

Quinine is one of those alkaloids and, being of great importance in medicine on accounts of its anti-febrile characteristics, attracted much attention, and much work has already been done in an attempt to synthesize this substance. The object of these researches may generally be divided into two;

a. _scientific_, as the synthesis of quinine is necessary to prove the structural formula of this substance.

b. _commercial_, since it is desirable to find some economical synthetical substance with similar physiological properties, but not possessing some of its objectionable qualities, e.g. its bitter taste, etc.

The synthetical work may generally be divided into the following three groups;

a. the synthesis of quininic acid.

b. the synthesis of 'the second half'

c. The synthesis of quinine-like compounds.

Quinine decomposes into two parts, the quinoline nucleus occuring in the form of quininic acid or its derivatives, and the 'second half' occuring in the form of meroquinine.

The first substance, quinic (or quininic acid) has been successfully synthesized, but a simpler method than the present method is more desirable. The chief problem now, however, is the synthesis of meroquinine, which no one has as yet been able to accomplish, and which today stands as the great barrier to the successful attainment of the above-mentioned aims. In the third division, however, many compounds have been obtained which are somewhat allied to quinine, but the main product itself has not yet been synthesized.

The present paper is an account of some work done with the object of preparing some substances that may be related to meroquinine or other decomposition products of quinine. The first series of attempts were made with the object of preparing some substances that may be in some way related to the decomposition products belonging to the second half. It was our purpose to use as an intermediate product, the $\alpha\gamma$-nitrile of acetoacetic ester having the formula

$$
\begin{array}{c}
\text{COOR} \\
\text{CH} \\
\text{HC}\diagup\quad\diagdown\text{CH.COOR} \\
\text{HC}\qquad\quad\text{CN}
\end{array}
$$
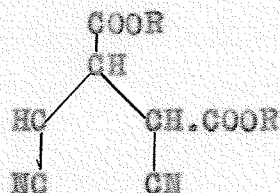
Subsequent attempts were directed at the preparation of certain derivatives allied to the decomposition products of quinine, belonging to the quinoline nucleus. Among these we

had tried to prepare 4-substituted pyridine or quinoline compounds which are in general quite difficult to prepare. The last attempt was at the preparation of nitro-acridine by the following methods;

    a. by the use of o-nitro-diphenylamine.

    b. by the condensation of aniline, o-nitro-phenol and formic acid.

The products yielded by these two reactions were found to differ in their chemical behaviour, through certain physical properties seemed to be similar. The conclusion arrived at was that the reaction with b. did not yield the nitro-acridine, but some other substance.

The final completion of the various problems was prevented by my appointment to my present position, where I have no opportunity to carry on work on account of the lack of an adequately equipped laboratory and the great difficulty in obtaining the required organic reagents.

I wish here to express my sincere gratitude and thanks to Dr. H. F. Armes, Professor of organic chemistry in the University of Manitoba, for his valuable advice and suggestions during the course of the year that I spent in his laboratory carrying out the above experiments.

Union Middle School

Pa-ti   Canton,
   CHINA.

                                _____

                                    Peter Mar

                                    January, 1924.

PART ONE.

THE RECENT WORK ON THE CHEMISTRY OF QUININE .
....

a. Recent Developments In the Study Of The Constitution of

The Cinchona Alkaloids.

b. General Formula and Rabe's Nomenclature.

c. Work on the Synthesis of Quinine and its Allied Substances.

....

i. Recent Developments In The Study Of The Constitution Of
The Cinchona Alkaloids.

. . . . .

1. Koenig's Formula.

The immense literature on the subject of the constitution
of quinine and cinchonine furnishes many interesting accounts
in which the structural formula of these substances underwent
many radical changes due to the various newly-discovered pro-
perties brought forth from time to time by the various inves-
tigators. Perhaps the first modern account of the chemical his-
tory was embodied in the dissertation of Wilhelm Koenig (1)
"Ueber das Merochinen und Ueber die Constitution der China-
alkaloide", in which he summarized the work done up to that time
(1906). He showed by a summary of the results that the two
formulae most probable were those of von Miller and Rhode and
his own (Chart I-Formulae I and II). Both formulae, however, did
not adequately explain in detail the chemical behaviour of the
alkaloids. Since that time, however, the following formulae;
viz: III-VI, have also been proposed by various investigators
as we shall read in the later pages.

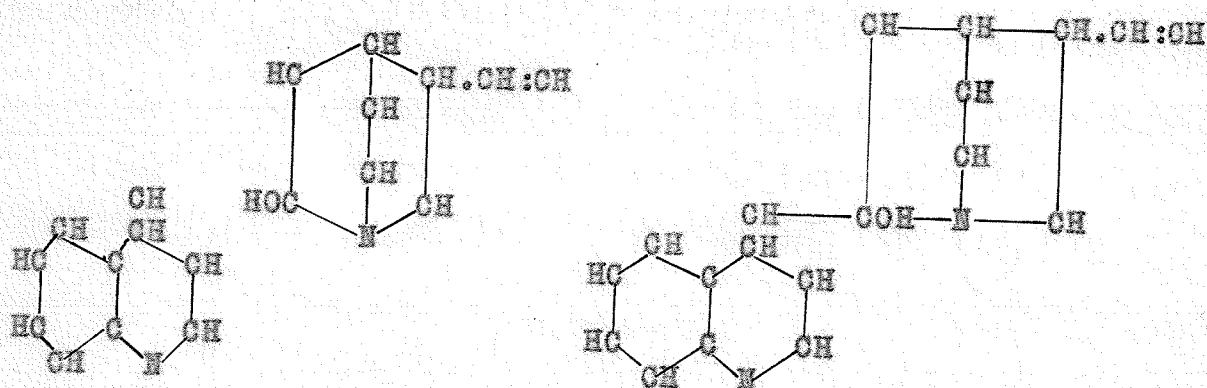
1. Koenigs. Ann. 347, pp. 143-232. (1906).
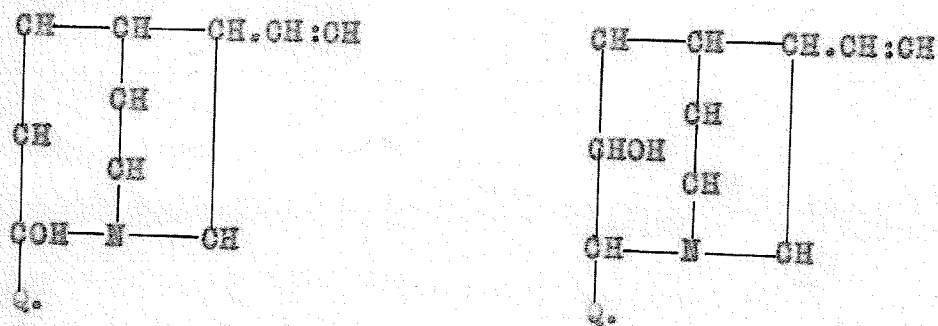
Chart One.

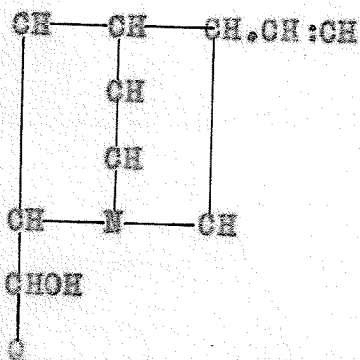## Constitutional Formulae Proposed By Investigators For Cinchonine.
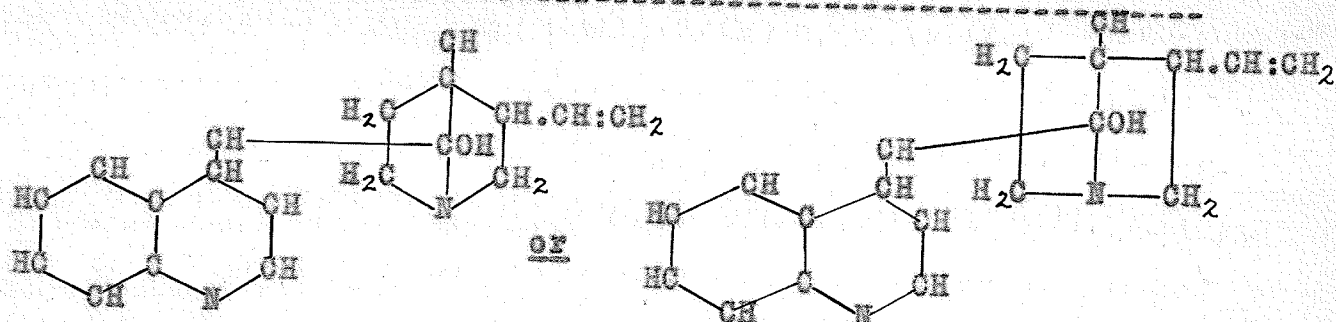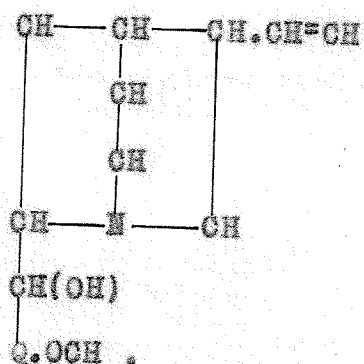

Formula I - von Miller and Rhode.

Formula II. Koenigs'
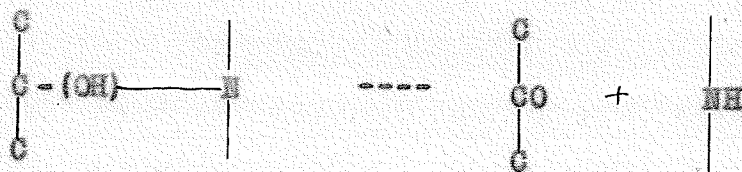
Formula III

Formula IV.

Formula V.

Formula VI Quinine.

Soon after Koenigs' paper was published Paul Rabe and his
collaborators, who for several years had been carrying out a
series of investigations on the cinchona alkaloids, directed
their attention to this phase of the constitution. Koenigs, in
his paper, proved the superiority of his formula over that of
Miller and Rhode, but there was one outstanding weakness, and that
was with regards to the oximes of the 'toxines'

Rabe's first paper on this subject was published a few
months (2) after Koenigs' in which the author reviewed briefly
the former works and showed that from the conversion of cincho-
nine into the imino-ketone, cinchotoxine, the following changes
must have been effected:

$$
\begin{array}{ccc}
\mathrm{C} & & \mathrm{C} \\
| & & | \\
\mathrm{C-(OH)} \quad\quad \mathrm{N} \quad\quad ---- \quad\quad \mathrm{CO} \;+\; \mathrm{NH} \\
| & & | \\
\mathrm{C} & & \mathrm{C}
\end{array}
$$

showing thereby that the C atom is directly linked on one hand
to the N atom of the second group, and on the other hand to the
(OH) group, (Formulae II and III). The two structures possible
are, first, as in Koenigs' formula, where the CO group in cincho-
toxine lies between two methylene groups giving his formula
for cinchonine, formula II; while the second possibility is where
the CO group is taken as being adjacent to the quinoline nucleus
giving the formula III.

Koenigs' formula (II) is further capable of explaining the
decomposition of cinchene into lepidine and meroquinine which

----

2. Rabe and Ritter - Ann. 350, 180-203 (1906).

he accomplished in 1900 (3) as shown in Equation I.

This reaction was taken to show the presence of 20 atoms
in the connecting side chain, with the N-atom adjacent to it, in
both cinchonine and cinchene. Koenigs explained this on the
supposition that cinchonine on hydrolysis loses two hydrogen
atoms yielding cinchene which may be represented thus:

$$Q . CH = C \begin{array}{ccc} CH & CH & CH.CH:CH \\ & CH & \\ & CH & \\ N & & CH \end{array}$$
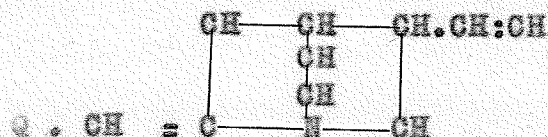
However, this formula does not explain to good advantage
the chemical behaviour of the oximes of cinchotoxine, only one
of which having been obtained, viz; mono-iso-nitroso-cinchotoxine
(4). This compound, together with its methyl and ethyl derivative,
yielded by Beckmann's reaction, cinchoninic acid and a base, to-
gether with a derivative of meroquinine and its nitrile (5) as
follows:

Iso-nitroso-Cinchotoxine	N-methyl Derivative	N-ethyl Derivative.
Cinchoninic acid + γ-amino-quinoline. + Meroquinine + Meroquinine nitrile	Cinchoninic acid + γ-amino quinoline. + Meroquinine + N-methyl mero-quinine nitrile	Cinchoninic acid. + γ-amino-quinoline. + Meroquinine + N-ethyl mero-quinine nitrile.

In the case of N-methyl-iso-nitroso-cinchotoxine the re-

3. J. prakt. Ch. 61,1. (1900)
4. Miller and Rhode, B. 28,1059 (1895).
5. Koenigs, B. 27, 900 (1894) and B. 30, 1332 (1897).
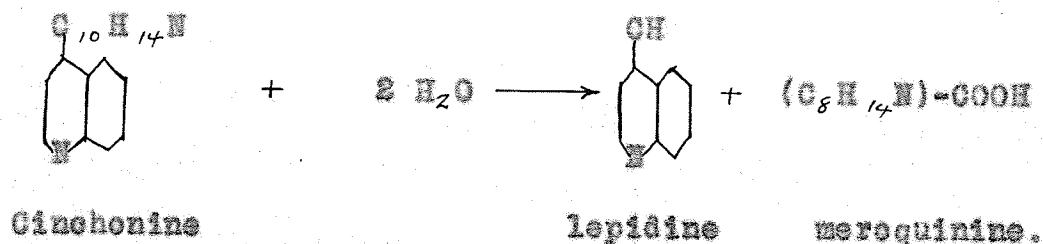
Equation I. <u>Decomposition of Cinchona.</u>

$C_{10}H_{14}N$ (structure) $+$ $2 H_2O$ $\longrightarrow$ OH (structure) $+$ $(C_8H_{14}N)\text{-}COOH$

Cinchonine   lepidine   meroquinine.

Chart II. <u>Decomposition of N-methyl</u>
<u>Iso-nitroso-cinchotoxine.</u>

COOH (structure)

NH (structure)

$\longleftarrow$ $CH_2 \cdot C_7H_{12}N$ / CH_2 / CO (structure) $\longrightarrow$

CH_2 — CH_2 / H_3CH $CH \cdot CH_2 \cdot CH_2NH_2$ / H_2C — $CH \cdot CH{:}CH$

CH_2 — CH_2 / H_3CH $CH \cdot CH_2CH_2COOH$ / H_2C — $CH \cdot CH{:}CH_2$
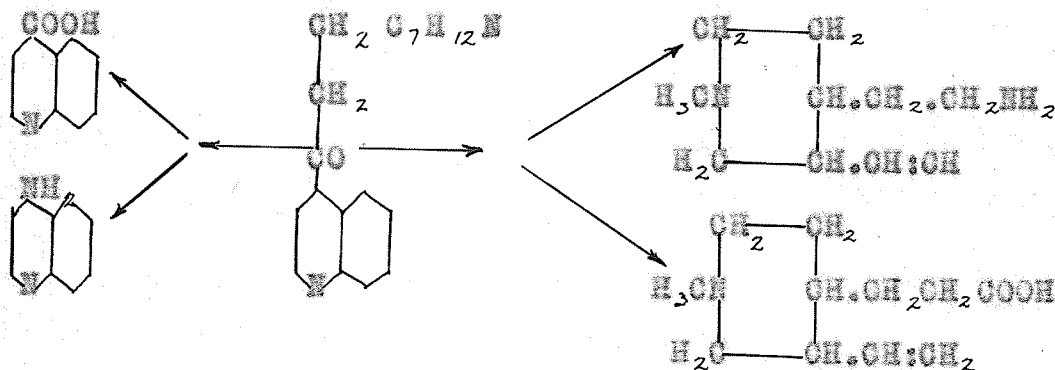
Chart III. <u>Behaviour of the "Toxine" Bases.</u>

	Koenige' formula	Rabe's formula
Formula	$Q.CH_2.CO.CH_2.C_7H_{12}N$	$Q.CO.CH_2.CH_2.C_7H_{12}N.$
Oximes	$\overset{NOH}{Q.CH_2.C.CH_2.C_8H_{14}N}$	$\overset{NOH}{Q.\overset{\shortparallel}{C}}.CH_2.CH_2.C_8H_{14}N$
Expect either	$Q.CH_2.NH \neq \|{-}CO.CH_2.C_8H_{14}N$	$Q.NH{-}\|{-}CO.CH_2.CH_2.C_8H_{14}N$
or	$Q.CH_2.CO{-}\|{-}NH.CH_2.C_8H_{14}N$	$Q.CH_2.CO{-}\|{-}NH.CH_2.CH_2.C_8H_{14}N.$
	<u>Beckmann's Reaction.</u>	
Expect	$Q.CH.NH_2 + COOH.CH_2.Q.$	$Q.CH_2NH_2 + COOH.CH_2C_8H_{14}N.$
or	$Q.NH_2 + COOH.CH_2.CH_2.C_8H_{14}N$	$QCOOH + NH_2CH_2CH_2C_8H_{14}N.$

action was represented by the chart II.

With mono-iso-nitroso-cinchotoxine we obtain meroquinine and meroquinine nitrile instead of the N-methyl derivative. This reaction was compared with a former one where o-benzil-monoxime yielded on treatment with PCl_5 , benzoyl benzimide chloride and benzonitrile, both of which can yield on further decomposition benzoic acid (6). This reaction may be represented thus;

$$
\begin{array}{ccccc}
\overset{\displaystyle NOH}{\|} & & \overset{\displaystyle N - CO - C_6H_5}{\|} & & \overset{\displaystyle N}{\|} \quad CO-C_6H_5 \\
C_6H_5-C - CO - C_6H_5 & \longrightarrow & C_6H_5C.Cl & ---- & C_6H_5C \quad + \quad Cl
\end{array}
$$

o-benzil monoxime   benzoyl benzimide Cl.
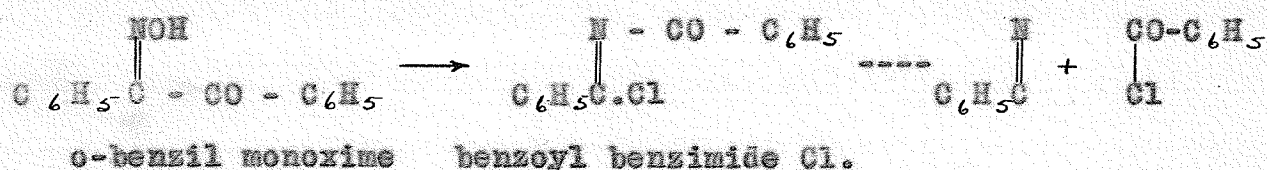
This reaction will, when applied to the cinchona bases, show that the C(OH) group is not attached to another methylene group and then to the quinoline nucleus, but is directly adjacent to it and, therefore Rabe favored formula III. This formula does not, however, explain the formation of cinchene as well as that of Koenigs and Rabe therefore proposed the assumption that in the transformation, there is a rearrangement of linkages.

The proposal of this formula turned Koenigs' attention to this phase of the subject, and soon in conjunction with Bernhart and Ibele (7) confirmed Rabe's formula for cinchotoxine, by a study of the behaviour of the oxime of N-methyl cinchotoxine, with Beckmann's reaction. According to theory the substances of the two proposed constitutions should behave as given in the chart III.

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5. Koenigs, B. 27, 900 (1894) and B. 30, 1332 (1897)
6. Ann. 274, 4 (1893) ; 296, 280 (1897) and B. 27, 306 (1894).
7. Koenigs. B. 648-652 (1907).

Chart IV. Cinchonine--Cinchotoxine.

$$
\begin{array}{cccc}
CH_2 & CH & CH.CH:CH_2 \\
& CH_2 & \\
& CH_2 & \\
CH & N & CH_2 \\
CHOH & & \\
Q. & &
\end{array}
\qquad
\begin{array}{cccc}
CH_2 & CH & CH.CH:CH_2 \\
& CH_2 & \\
& CH_2 & \\
CHOH-NH & CH_2 \\
CHOH & & \\
Q. & &
\end{array}
$$

$$
\begin{array}{cccc}
CH_2 & CH & CH.CH:CH_2 \\
& CH_2 & \\
& CH_2 & \\
CH_2 & NH & CH_2 \\
COH & & \\
Q & &
\end{array}
\qquad
\begin{array}{cccc}
CH_2 & CH & CH.CH:CH_2 \\
& CH_2 & \\
& CH_2 & \\
CH_2 & NH & CH_2 \\
CO & & \\
Q & &
\end{array}
$$
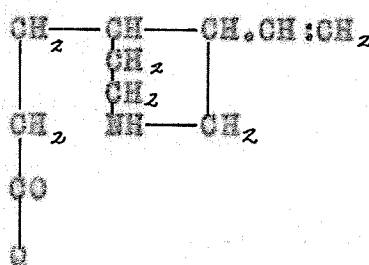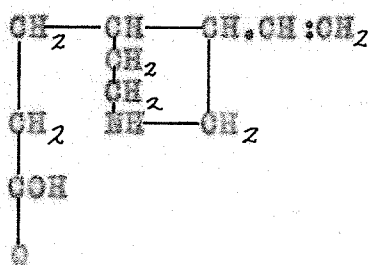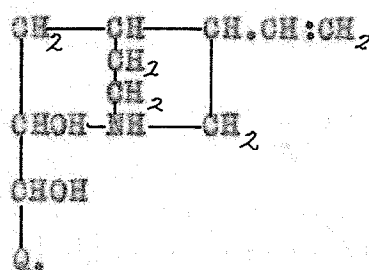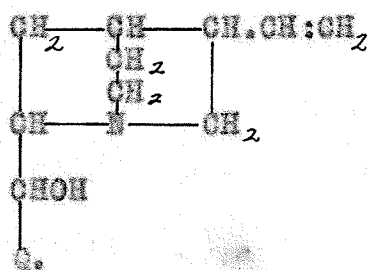
Explanation of the Change from Cinchonine to Cinchotoxine

Proposed by Rhode and Antonas.

Chart V.

$$
\begin{array}{cccc}
CH_2 & CH & CH.CH:CH_2 \\
& CH_2 & \\
& CH_2 & \\
HOOC & N & CH_2 \\
\end{array}
\qquad
\begin{array}{cccc}
CH & CH & CH.CH:CH \\
& CH & \\
& CH & \\
HON=C & N & OH \\
\end{array}
$$

meroquinine $\qquad\qquad$ β-vinyl-quinuclidineoxime.

$$
\begin{array}{cccc}
CH_2 & CH & CH.CH:CH_2 \\
& CH_2 & \\
& CH_2 & \\
CH & N & CH_2 \\
CO & & \\
Q & &
\end{array}
\qquad
\begin{array}{cccc}
CH_2 & CH & CH.CH:CH_2 \\
& CH_2 & \\
& CH_2 & \\
CH & N & CH_2 \\
CH(OH) & & \\
Q & &
\end{array}
$$
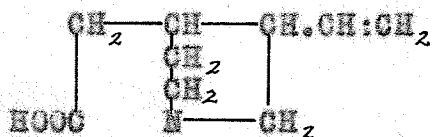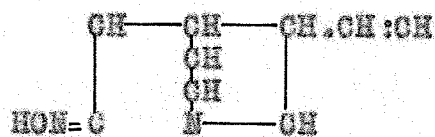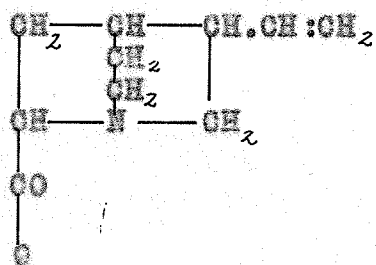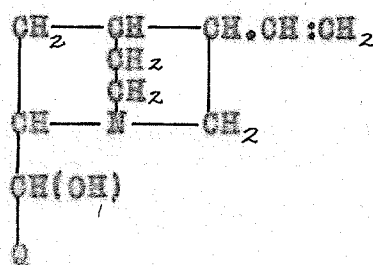
Cinchoninone $\qquad\qquad$ Cinchonine.

Rabe's Proof of the Proposed Formula (V) for Cinchonine.

This reaction was carried out and a yield of 6% cinchoninic acid and 43% of 4-amino-quinoline was obtained. Later work showed that besides these two products there were present also 4-amino-ethyl-methyl-3-vinyl-piperidine, or N-methyl-homo-meroquinine nitrile and N-methyl-homomeroquinine (8). Therefore, Koenigs acknowledge Rabe's formula for cinchotoxine, but showed a preference for formula V, which had been proposed several years previous by the latter investigator, this formula having instead of the carbonyl group, a secondary alcoholic grouping in its stead.

Formula V was then supported by the work of Rhoade and Antonaz (9), who studied the action of sodium ethoxide and amyl nitrite on cinchotoxine, in absolute alcohol, and in nitrobenzene and absolute alcohol, a better yield being obtained in the latter case. A sodium derivative was yielded by the reaction, which was not decomposed by treatment with carbonic acid. In this reaction the nitrite acted as an oxidising agent, cinchoninicacid and a group of products from the other half of the molecule was the result, but among all these no trace of meroquinine can be detected (10). This fact proved that the group $CH_2.CO.CH_2$ is absent, the carbonyl group being directly linked to the quinoline nucleus as shown in chart IV.

At the same time Rabe (11) obtained an intermediate oxidation product cinchoninone by oxidising the alkaloid with chromic acid in sulfuric acid or glacial acetic acid. This substance has

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8. B.40 , 2873-2882 (1907).

9.

10. B. 40, 2329-2338 (1907).

11. Rabe- B. 40, 3655 (1907).

the formula $C_{19}H_{20}N_2O$. It differs from cinchonine by 2 carbon atoms, and has the properties of a base, a phenol and a ketone. On oxidation it yielded cinchoninic acid and meroquinine, and also exhibits keto-enol tautomerism, yielding both an oxime and an ortho-benzoyl derivative (12).

Amyl nitrite decomposes the base producing cinchoninic acid and an oxime $C_9H_{13}N=N.OH$, a reaction similar to the formation of di-acetyl monoxime from ethyl-methyl aceto-acetate (13) thus;

$$CH_3CO.CH(CH_3).COOR \longrightarrow CH_3.CO.C(NOH).CH_3$$

as compared with
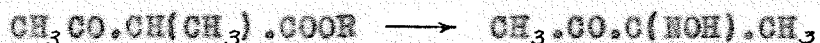
$$C_{19}H_{20}N_2O + HONO \longrightarrow C_9H_6N.COOH + C_9H_{13}N.NOH$$

Knowing, therefore, the formula for meroquinine, he showed that the oxime must be α-oximido-β-vinyl-quinuclidine, so that cinchoninone must have the formula VI, and the behaviour of this substance thus pointing to the existence of a secondary alcoholic grouping, giving for cinchonine the formula V, so the reaction was represented as in chart V.

Still further evidence as to the probability of this structure was furnished by the analogy with the behaviour of certain other alkaloids. The rearrangement of the alkaloids to their 'toxines' was taken by Rabe to be analagous to the transformation of narcotin into narceine, of hydrastine to hydrastein and of oxy-codeine into keto-di-hydro-methyl-morphimethine (14).

The transformation of narcotine into the keto-base takes place

12. Rabe and Bucholz, B. 41,62 (1908).
13. Meyer and Zublick, B. 11,322. (1878).
14. Rabe and Ackermann B. 40, 2013 (1907).

according to Roser and Freund and Frankfurter (15) by heating
the methyl iodide with alkali which produces nornarceine. This
is similar to the change from cinchonine methiodide into methyl-
cinchotoxine, as in both cases a ring was opened attended by the
disappearance of the alcoholic hydroxyl group with the simult-
aneous formation of the ketone group, this change, in the case of
narcotin, taking place with the hydrolytic cleavage of the lactone
ring.

A second analogy was taken from the formation of cinchotoxine
from cinchonine by heating with dilute acetic acid. Narcotine
heated with dilute acetic acid for 72 hours at 105-110 yields
also the keto-base attended by another by-product (16). This
change was represented thus (17)

Narcotine————————Gnoscopine————————Nornarceine
                                    ————————Cotarnine and Meconine.
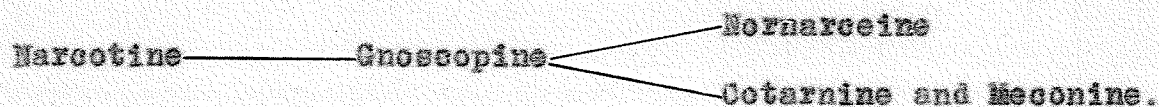
Gnoscopine was shown to be an isomer of narcotine and on
treatment with acetic acid, as above, yielded the above decompos-
ition products. Nornarceine will not be further attacked by acetic
acid and therefore similar in conduct to cinchotoxine.

From these two observations, viz:
a. the decomposition of the methiodides of the alkaloids into the
keton base, and
b. The change to the keto-base being accomplished thru the action

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15. Roser, Ann. 247, 167 (1888).
    Freund and Frankfurter, Ann. 277, 57 (1893).
16. Miller and Rhode, Ber. 27, 1187-1279 . (1894) 28,1056 (1895)
17. Smith. Pharm. J.trans. (3) 9, 82. (1878).

of dilute acetic acid, cinchonine yielding cinchotoxine, and narcotine yielding nornarceine.

The conclusion arrived at was that there exists in both alkaloids the group N.CH.CH(OH).

When cinchoninone was identified Rabe again employed this method to the ketone, showing the analogy between this substance and tropinone and codeinone, thus further strengthening his own formula.

Hence, of the five formulae, the one that is universally accepted today is formula V. The mass of evidence supports it, since it answers to the best advantage not only the chemical properties formerly known, but practically all the properties recently discovered, viz:

(i) the transformation cinchonine into cinchene

(ii) the hydrolysis of cinchene into lepidine and meroquinine

(iii) the decomposition of iso-nitroso-cinchotoxine into cinchoninic acid and meroquinine nitrile.

(iv) the formation of cinchotoxine and cinchoninone, which are analagous to the change in many alkaloids containing certain groups in common.

The Structure of Quinine.

The bulk of the work reviewed in the former pages has been done with cinchonine and from it the constitution of quinine was developed. Quinine differs from the former alkaloid by the residue of one methoxyl group ($-CH_3O$), and its decomposition products and derivatives form two parallel series differing from each other by the same amount, thus:
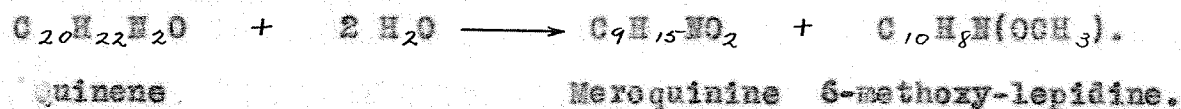
	Cinchonine products	Quinine products.
Oxidation	Cinchotenine $C_{18}H_{20}N_2O_3$	Quitenine $C_{19}H_{22}N_2O_4$
and	Cinchoninic acid $C_{10}H_7NO_2$	Quininic acid $C_{11}H_9NO_3$
with PCl.	Cinchene $C_{19}H_{20}N_2$	Quinene $C_{20}H_{22}N_2O$
Isomers	Cinchonicine $C_{19}H_{22}N_2O$	Quinicine $C_{20}H_{24}N_2O_2$
Oxidation	Cinchoninone $C_{19}H_{20}N_2O$	Quininone $C_{20}H_{22}N_2O_2$

With these and other evidences it was shown that quinine is mono-methoxy cinchonine.

The decomposition products are similar to those of cinchonine, the part involving the 'second half' being identical in both cases, while the quinoline products are p-methoxy derivatives of the products obtained with cinchonine. Since quinine yields quininic acid instead of cinchoninic acid, as is the case of cinchonine, and since quinic acid is p-methoxy-cinchoninic acid, the methoxy group must be situated in the 6-position of the quinoline nucleus.

Further evidences of this last fact is furnished by the hydrolysis of cinchene and quinene, for when heated with phos-

phorus at 175°C the following reactions took place:

$$C_{19}H_{20}N_2 \quad + \quad 2\,H_2O \longrightarrow \quad C_9H_{15}NO_2 \quad + \quad C_{10}H_9N$$

Cinchene   Meroquinine   Lepidine.

$$C_{20}H_{22}N_2O \quad + \quad 2\,H_2O \longrightarrow \quad C_9H_{15}NO_2 \quad + \quad C_{10}H_8N(OCH_3).$$

quinene   Meroquinine   6-methoxy-lepidine.

This again shows that the methoxy group is in the 6-position, and thus we may conclude that quinine is 6-methoxy cinchonine.

Work the later decomposition products of these alkaloids similar proofs were derived, and therefore today, reasoning from the formula universally accepted for cinchonine, i.e. formula V, we obtain for quinine the formula;
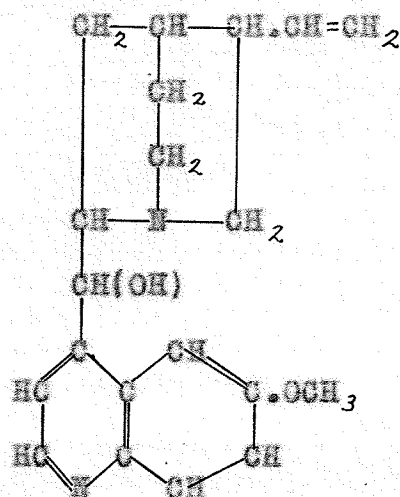
c. Work On The Synthesis Of Quinine and Its Allied Substances.

The problem of the Synthesis of Quinine may be roughly
divided into three parts, viz:

(a) the synthesis of the quinoline nucleus, i.e. quinic
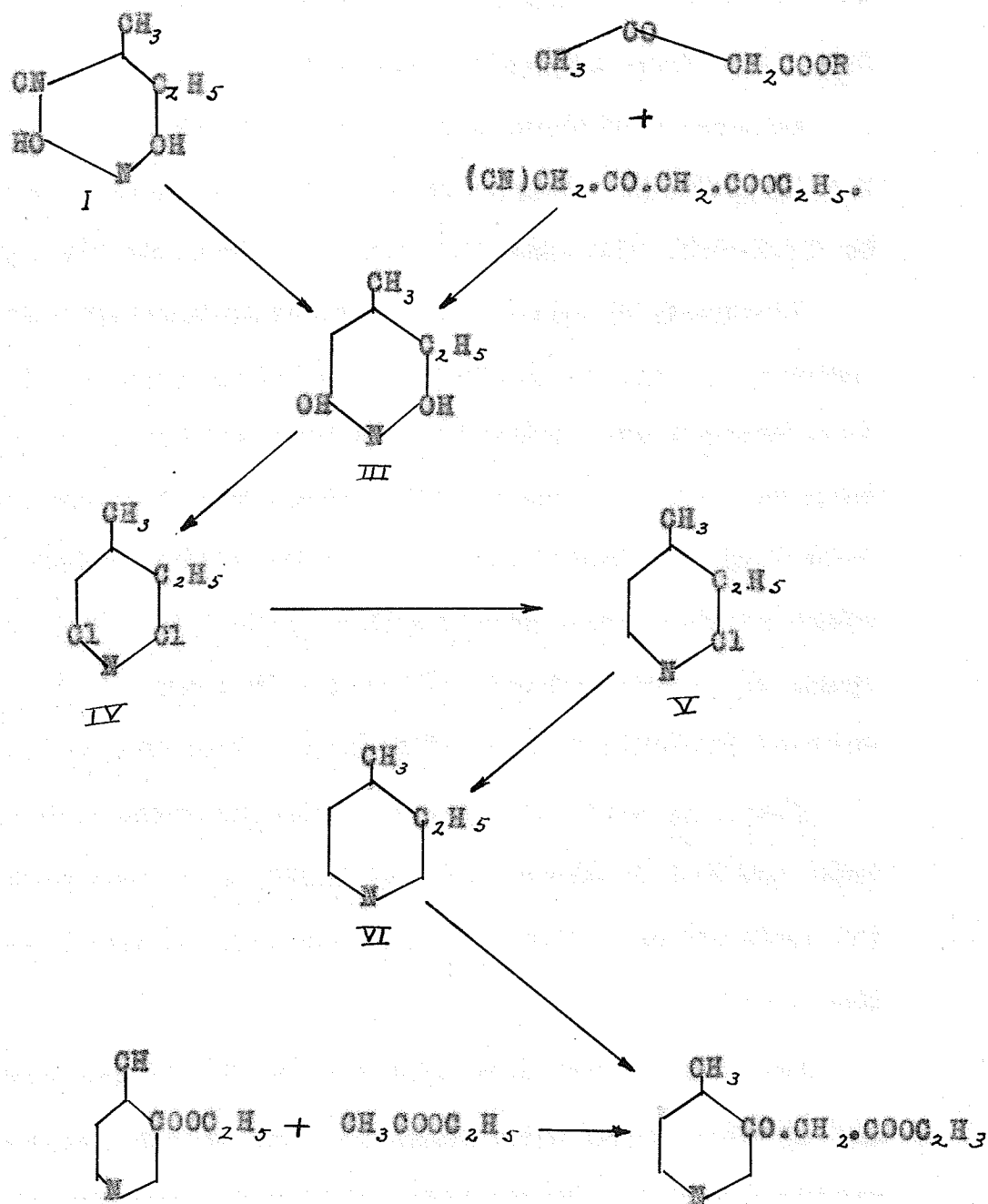acid.

(b) the synthesis of the 'second half' i.e. compounds with
the quinuclidine ring, and laso homo-meroquinine and N-methyl-
homo-cincholoipone.

(c) the condensation of the above two halves into the
quinine-like bodies.

On the first division, that of the synthesis of quinic acid
together with their allied compounds, much work has already been
accomplished, mainly through the work of Kauffmann and his co-
workers during the years 1911-1915. The quinuclidine ring and
many allied compounds have been synthesized, but the compounds
meroquinine and N-methyl-cincholoipone have not yet been totally
built up by any investigator. As to the condensations of the two
halves, the recent work of investigators yielded interesting
quinolyl ketones, many of which differ from the original alkaloids
by a small margin. However, with all this work, a complete syn-
thesis from simple organic compounds has not yet been accomplished,
what has been accomplished being allied derivatives, or else pro-
ducts obtained by reactions employing decomposition products
of the cinchona alkaloids.

Synthesis of β/collidine.

I

$CH_3-CO-CH_2COOR$

$+$

$(CH)CH_2.CO.CH_2.COOC_2H_5.$

III

IV

V

VI

CH_3 ... $COOC_2H_5 + CH_3COOC_2H_5 \longrightarrow$ ... $CO.CH_2.COOC_2H_3$

1. The Synthesis of The Second Half and Its Derivatives.

....

a. The Synthesis of β-collidine.

β- collidine, $C_8H_{11}N$, or 4-methyl-3-ethyl pyridine (VI)
was recently synthesized by Leopold Ruzicka (18) and Paul
Rabe (19) from different reactions.

Ruzicka's synthesis was accomplished thru the product of
2-6-di-hydroxy-β-collidine (III) a substance formerly synthesized
by Guareschi (20) and later by Rogerson and Thorpe (21).

Guareschi's synthesis was accomplished by heating γ-cyano-β
-methyl-α-ethyl glutaconimide (I) or 5-cyano-2, 6-dihydroxy-
4-methyl-3-ethyl pyridine with hydrobromic acid, from which 2-6
hydroxy-β- collidine was produced. The same substance was ob-
tained by the condensation of ethyl-aceto-acetate (VII) and
ethyl-cyano-ethyl-aceto-acetate, with the aid of sodium, the
cyano glutaconic ester (IX) being then obtained, subsequent hyd-
rolysis yielding the β-collidine. (Rogerson and Thorpe's synthesis).

Starting with this product Ruzicka transformed it first
into the 2-6 dichloro (IV) compound, and then into the mono-chloro
(V) derivative, elimination of the remaining chloro group yielded
the β-collidine.

Rabe uses ethyl homo-nicotinate (X) as his starting point,
and by condensing with ethyl acetate in the presence of sodium

18. Ruzicka, Helv.chem.acta. 2,358-348 (1919).
19. Rabe and Jantzen, B. 54,925-929 (1921).
20. Guareschi, Estr.Mem.Reale.Accad.Sci.Torino. ii. 46.
21. Rogerson and Thorpe, J.C.S. 87, 1685 (1905)

ethoxide and benzene obtained a β-ketonic ester, which on hydrolysis by concentrated hydrochloric acid in alcoholic solution gave 3-acetyl-4-methyl-pyridine. This hydrazone when heated with powdered caustic potash yielded the desired compound.
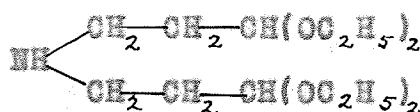
b. The Synthesis of Cincholoiponic Acid.
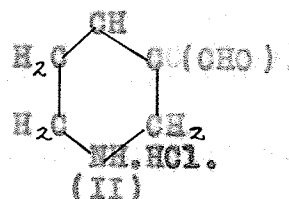.............................

This synthesis was first accomplished by A. Wohl and M.S. Losanitch (22). Imino-di-propionacetal (I) on treatment with hydrochloric acid passes into Δ^3-p - ptetra-hydro-pyridine aldehyde (II) the hydrochloride of its aldoxime reacting with thionyl chloride yielding 4-chloro-piperidine-3-nitrile chlorhydrate (III). On elimination of hydrochloric acid Δ-3-tetra-hydro-pyridine nitrile (IV) resulted, condensation of this with sodio-malonic ester and subsequent hydrolysis gave two products 4-pipecoline-3-ω-dicarboxylic acid (V) representing the two possible cincholoiponic acids.

β-imino-di-propaldehyde tetra-methyl-acetal was prepared by heating under pressure for 6 hours at 118-120°C β-chloropropaldehyde diethylacetal with a saturated solution of ammonia in alcohol. Cold concentrated hydrochloric acid closes the ring giving the aldehyde. This was then converted into the aldoxime, then into the hydrochloride, and then subjected to the action of thionyl chloride, the product then being transformed into 3-cyano-Δ^3-tetra-hydro-pyridine nitrile by the action of caustic soda. Claisen's condensation with ethyl malonate yields a product which on heating with barium hydroxide gave α-racemic - 3-carboxyl-amido-4-piperidyl acetic acid hydrochloride, the rac-

---
22. Wohl and Losanitch, B. 40.4698-4711 (1907)

Synthesis of Cincholoiponic Acid.

NR
CH₂—CH₂—CH(OC₂H₅)₂
CH₂—CH₂—CH(OC₂H₅)₂

$$NR \begin{matrix} CH_2-CH_2-CH(OC_2H_5)_2 \\ CH_2-CH_2-CH(OC_2H_5)_2 \end{matrix}$$

(I)

H₂C—CH
H₂C—CH₂
NH.HCl.
CH(CHO))

(II)

CH₂—CHCl.
CH₂—CH.CN
CH₂—CH₂
NH.Cl

(III)

CH₂—CH
CH₂—CH₂
NH
C(CN)

(IV)

CH₂—CH.CH₂.COOH
CH₂—CH(COOH)
CH₂—CH₂
NH.HCl.

(V)

CH₂—CH.CH₂.COOH
CH₂—CH(COOH)
CH₂—CH₂
NH.

(VI)

CH₃
C₂H₅
N

+

Cl
Cl—C—Cl
CHO

→

CH₂.CHOH.CCl₃
CH—C—C.C₂H₃
CH—CH
N

(I)

→

CH=CH.COOH
C—C.C₂H₅
CH—CH
N

(II)

→

CH₂.CH₂.COOH
CH₂—CH
CH₂—CH.C₂H₅
CH₂—CH₂
NH
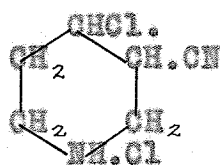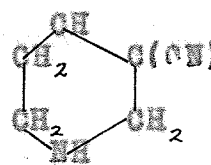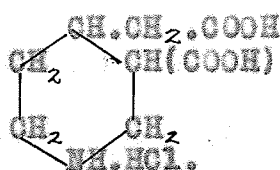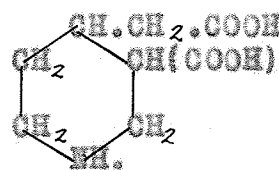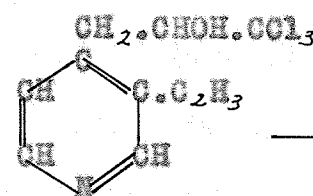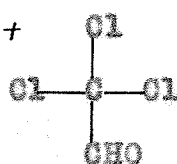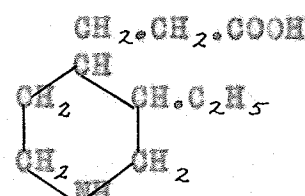
(III)

Synthesis of Homo-cincholoipone.

emic cincholoiponic acid being formed from this by hydrolysis.

If instead of subjecting the acid to the treatment of barium hydroxide before hydrolysis, the hydrolysed compound will then be found to be the β-racemic cincholoiponic acid.

The racemic acid must then be resolved into its optically active components, which was accomplished by Wohl and Maag (23) thru the brucine salts. It was found that the cincholoiponic acid of the decomposition products of the alkaloids was identical in its properties to the dextro-form of the β-racemic acid.

c. Synthesis of Homo-cincholoipone.

. . . .

The synthesis of this substance is of importance in that it is a step towards the synthesis of the main decomposition product of the 'second half,' meroquinine. It differs from the latter in that instead of the vinyl group in the 3-position, it has the ethyl group.

This synthesis was recently accomplished by Koenigs and Ottman (24), who condensed β-collidine with chloral in the presence of zinc chloride yielding chloral collidine (I) or 3-ethyl-4-β-hydroxy-$\gamma\gamma\gamma$-trichloro-N propyl pyridine. Hydrolysis with absolute alcoholic potash yielded β-3-ethyl-4-pyridine acrylic acid (II), which on reduction with sodium in hot amyl alcohol gave the corresponding piperidyl compounds, homo-cincholoipone (III)

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24. Koenigs and Ottman B. 54, (1343-1350) (1921).

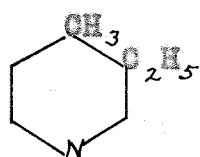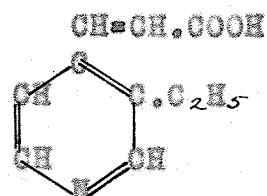# Synthesis of Quinuclidine.
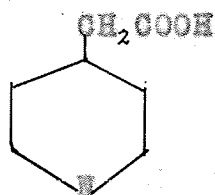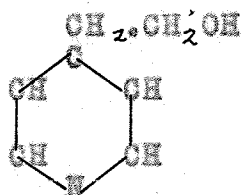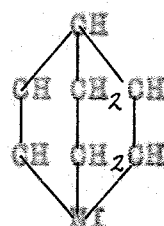
(I)   (II)   (III)
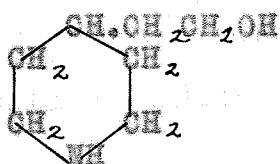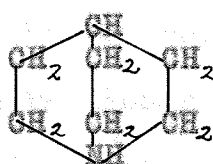
(IV)   (V)

Synthesis of Ethyl-Quinuclidine.
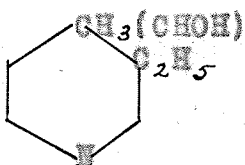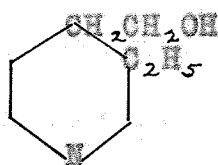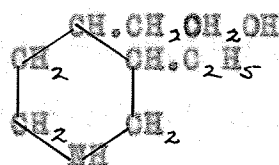
(VI)   (VII)   (VIII)
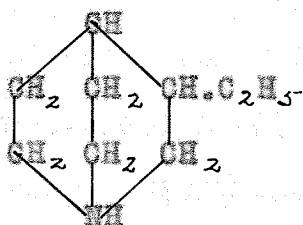
(IX)

d. The Synthesis of quinuclidine.

. . . .

The bicyclic ring which Koenigs took as the basis of the 'second half' of the cinchonine formula was first synthesized by Karl Loeffler and Fritz Steitzel in 1909 (25) while working out the analogy between the α and the γ-picolyl substances. Koenigs has shown that γ-picoline condenses with 3 molecules of formaldehyde into a tri-methylol derivative (26), while the α-derivative yields by the same method α-picolyl-alkine, and the authors therefore endeavored to obtain γ-picolyl alkine by calculating the amount of formaldehyde so that only one molecule will enter into combination.

γ-picoline was mixed with 20% formaldehyde and heated for 20 hours at 135-140°, the resulting substances being the mono-methylol derivative γ-picolyl alkine (4 -hydroxy-ethyl pyridine) (II). This, on warming with 70% hydriodic acid and red phosphorus, was transformed into the pyridonium iodide (III).

If the alkine be reduced by Ladenburg's method, the piperidine derivative γ-pipecolyl alkine (IV) is produced from which quinuclidine hydriodide (V) is obtained.

Koenigs, several years previous (26), obtained 3-ethyl-pyridyl ethanol by heating methyl-ethylpyridine (VI) in an alcoholic solution of formaldehyde for 36 hours. This substance was reduced to the piperidyl compound (VII) and then by sodium and alcohol changed into ethyl-quinuclidine. (IX)

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25. Loeffler and Steitzel B.42,124-132 (1909)

26. Koenigs, B. 35,1349-1557 (1902)

The Synthesis of Quinine-like Substances.

From Cincholoipone.

$C_2H_5 \cdot CH$ — CH — CH_2
CH_2 CH_2
CH_2 CH_2
CH_2 — N $COOR$
    CO
    C_6H_5

(I)   + CH_3O ... $COOR$ ... N   or $COOR$ ... N

$C_2H_5 \cdot CH$ — CH — CH_2
      CH_2 CH_2 — CO ... OCH_3
      CH_2 $COOR$ N
CH_2 — N
    $CO \cdot C_6H_5$

(II)

$C_2H_5 \cdot CH$ — CH — CH_2
      CH_2 CH_2 — CO
      CH_2 $COOR$ N
CH_2 — N
    $CO \cdot C_6H_5$

(V)

$C_2H_5 \cdot CH$ — CH — CH_2
      CH_2 CH_2
      CH_2 CO ... OCH_3
CH_2 — NH N

(III)

$C_2H_5 \cdot CH$ — CH — CH_2
      CH_2
      CH_2
CH_2 — NH CO N

(VI)

$C_2H_5 \cdot CH$ — CH — CH_2
      CH_2
      CH_2
CH_2 — N — CH_2 — CO ... OCH_3
            N

(IV)

$C_2H_5 \cdot CH$ — CH — CH_2
      CH_2
      CH_2
CH_2 — N — CH_2 — CO
            N
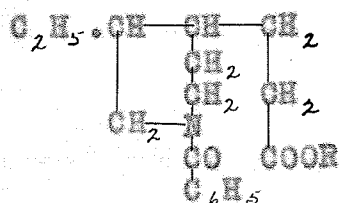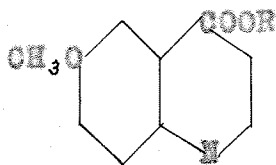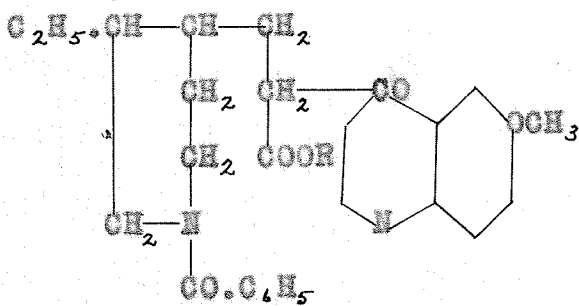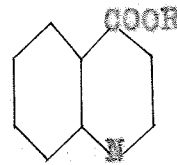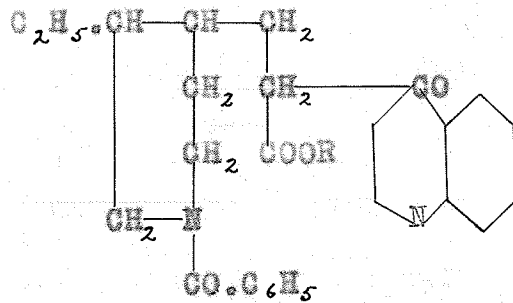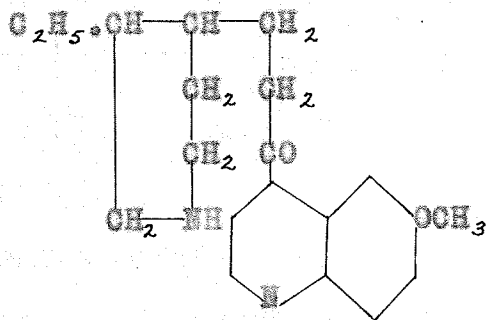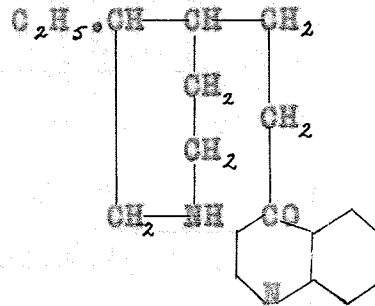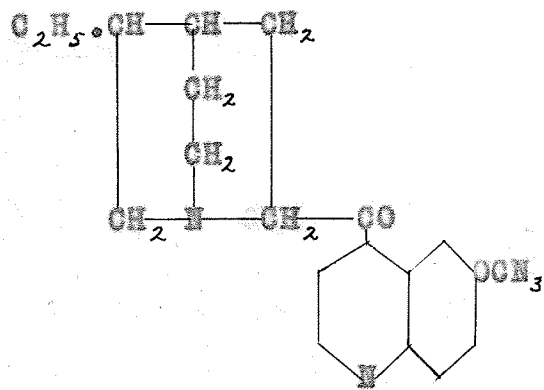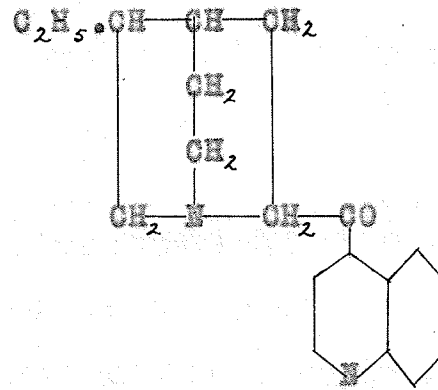
(VII)

2. The Synthesis of The Quinine Like Derivatives

a. From the Quinine Decomposition Products.

....

Cincholoipone.

This substance was produced by the decomposition of certain derivatives of the cinchona alkaloids. It is obtained as a decomposition product of the oxime of quinotoxine (27) and also by the method of Kauffmann and Brunschweiler (28) by boiling di-hydro-cinchonine hydrochloride with sodium acetate and 50% acetic acid from which they obtained cinchotoxine, this substance was then transformed into the benzoyl derivative, the methosulfate prepared, and on oxidation the N-benzoyl homocincholoipone was obtained.

This substance was converted into its ethyl ester, hydrolysed to ethyl homocincholoiponate (I) and by Claisen's reaction in benzol solution was condensed with ethyl cinchonate or ethyl quinate into a β-ketonic ester (II and V), further hydrolysis eliminates the carb-ethoxyl and benzoyl giving di-hydro-cinchotoxine (VI) or di-hydro-quinicine (VII). The toxine bases can then be converted into the ketone and thru that to the di-hydro-cinchonine (VII) and dihydroquinine (IV), by the method described in the next paragraph.

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27. B.40,648 (1907) and B.40,2013 (1907).

28. Kauffmann and Brunschweiler B. 49,2299-2310 (1916)

29. B. 51. 1360-1365 (1918)

30. B. 52, 1842-1850 (1919)

Synthesis with the Toxines.

$$CH_2=CH.OH \quad CH \quad CH_2$$
$$CH_2$$
$$CH_2$$
$$CH_2 \quad NH \quad CH_2$$
$$C_9H_6N.CO$$

(I)

$$CH_2=CH.CH \quad CH \quad CH_2$$
$$CH_2$$
$$CH_2$$
$$CH_2 \quad NBr \quad CH_2$$
$$C_9H_6N.CO$$

(II)

$$CH_2=CH.CH \quad CH \quad CH_2$$
$$CH_2$$
$$CH_2$$
$$CH_2 \quad N \quad CH_2$$
$$C_9H_6N.CO$$

(III)

$$CH_2=CH.CH \quad CH \quad CH_2$$
$$CH_2$$
$$CH_2$$
$$CH_2 \quad N \quad CH_2$$
$$CH(OH)$$
$$C_9H_6N.$$

(IV)

Commanducci's Work.

$$CH_2 \quad CH \quad CH.CH=CH_2$$
$$CH_2 \quad CH_2$$
$$CH_2 \quad CH_2$$
$$CO \quad NH \quad CH_2$$

$$CH_2 \quad CH \quad CH.CH=CH_2$$
$$CH_2 \quad CH_2$$
$$CH_2 \quad CH_2$$
$$P.COH \quad NH \quad CH_2$$
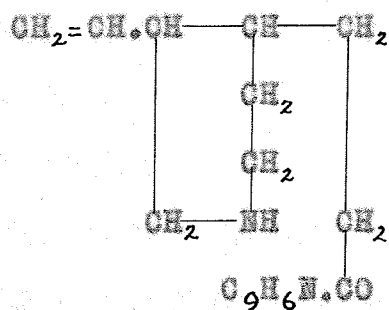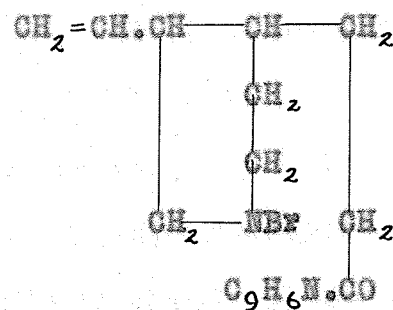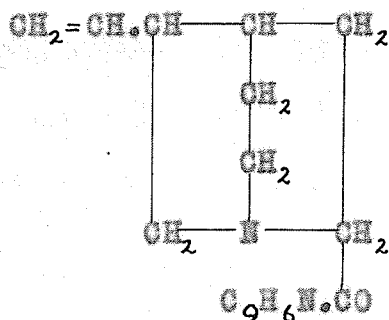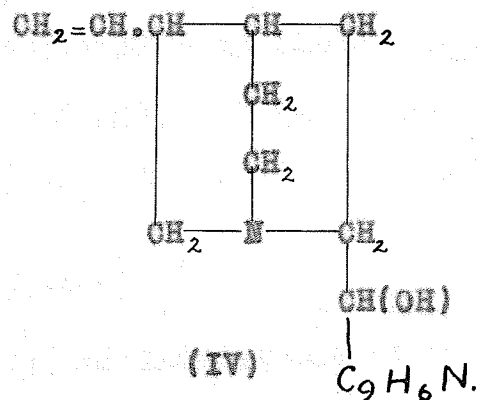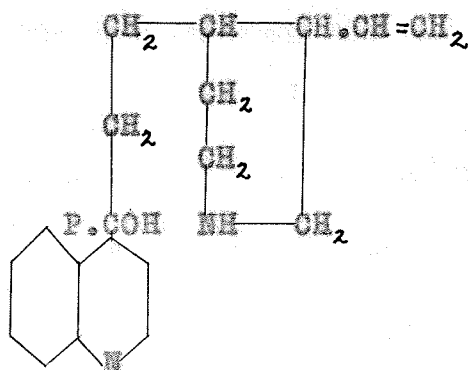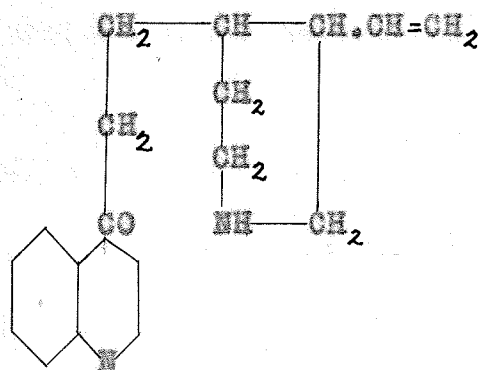
from the 'toxines'.

From the result of the work on the substances cinchotoxine and cinchoninene Rabe was able to accomplish the partial synthesis of cinchonine (31) and quinine (32). The toxine (I) was treated with hypobromous acid (Sodium hypobromite in hydrochloric acid solution) yielding the N-bromo-derivative (II) subsequent removal of the hydrogen bromide from the molecule thru the action of sodium ethylate in hot alcoholic solution yields cinchoninone (III). Reduction with sodium and alcohol produced cinchonine identical with the original substance. If, instead of using cinchotoxine, quinotoxine be used, quinine is obtained as the product.

Commanducci's Work.

Exio Commanducci in 1909 and 1910, in proving the constitution of cinchotoxine, prepared a series of secondary alcohols derived from these ketones. These he named cinchotoxols. Cinchotoxine acted on by Grignard's reagent yielded a complex compound which, on treatment of water, yielded ethyl cinchotoxol, $C \ H \ N \ Et. \ (OH)$ from which a chloro compound was produced by the action of PCl or $POCl$.

By using different reagents differing derivatives were also obtained, e.g. the phenyl and β-naphthol derivatives.

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31. Rabe B.44,2088-2091 (1911)

32. Rabe and Hindler B.51,466-467 (1918)

33. Rend. Accad.Sci.Fis.Mat.Napoli (iii) 15, 32-43 (1909)

The Work Of Adolf Kauffmann and His Collaborators.

Kauffmann's first paper appeared soon after that of Rabe, in which he also set forth his attempts at the synthesis of quinoline derivatives with the group -CH(OH)CH.N in the 4 position (41). In connexion with Peyer (42) they have managed to elongate the 4-side chain thru the 4-cyan-quinoline by the use of Grignard's reaction, subsequent treatment with water and ammonia yielding ketones, thus from quinic acid (I) and methyl magnesium iodide the substance methyl -methoxy quinolyl-4-ketone (II) was produced.

Rabe's paper 'Synthetiche Vorversuche' (43) contained an account of 4-quinolyl benzyl ketone (III) obtained from the ester. The authors now, by employing quinonitrile (I), obtained the substance methyl (6-methoxy-4-quinolyl) ketone (II) and from 6-ethoxy-4-cyan-quinoline (IV) the corresponding 6-ethoxy derivative.

Reduced in acetic acid solution with zinc dust these ketones yielded carbinols, thus methyl (6-methoxy- -quinolyl) ketone (V) gave a good yield of methyl (6-methoxy-4-quinolyl-carbinol (VI) The oximes of these compounds can be reduced with zinc chloride and hydrochloric acid, yielding an amino-alcohol.

The alkyl-oxy-4-quinolyl-ketones obtained with methyl or a methylene group attached to the carbonyl group, reacts with halogens giving derivatives which condenses with amines, and then can be reduced to compounds allied to quinine, e.g.

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41. Kauffmann, Peyer and Kunkler B.45,3090 (1912)
42.
43. Rabe,Humius,Pasternack,etc. B. 45,2163 (1912)

6-ethoxy-4-quinolyl-methyl-ketone (VII)

bromine in HBr.

Hydrobromide of 6-ethoxy-4-quinolyl-bromo-methyl-ketone. (VIII)

piperidine (IX)

6-ethoxy-4-quinolyl-piperidine-methyl-ketone (X)

palladium and hydrogen reduction

6-ethoxy-4-piperidino- - hydroxy ethyl quinoline (XI).

The Work of P. Karrer.

The 4-quinolyl ketones obtained by Kauffmann and Rabe and their co-workers differ from the true formula of quinine in many respects. Karrer (44) states:-

"Das l- Chinolyl-2-amino-ethanol und seine Substitutionsprodukte, welche die neiden Forscher synthetisch gewonnen haben, werden von ihnen chemisch als nahe Verwasdte des Chinine aufgefasst.

Meines Erachtens ist diese Auffassung nur bedingt haltbar. Sie haftet zu sehr am schematischen Formelbild und beruecksichtigt manche Eigenheit der Chinistruktur zu wenig. In Chinin ist die sekundare Alkohol-gruppe tragende C-atom auf beiden Seiten mit C-atomen verknupt die Ringen angehoren (Chinolin und Piperidin resp. Chinuclidin ring) in den Chinolyl-amino-athanolen tragt dagegen das gleiche C-atom auf der Seite eine offene fette Kette und keinen basischen Ring." (cf. opposite page for formulae)

---

44. P. Karrer - B. 50,1499 (1917).

Karrer's Quinolyl-ketones.

(I)   (II)   (III)   (IV)

(V)   (VI)   (VII)

(VIII)   (IX)

(X)   (XI)
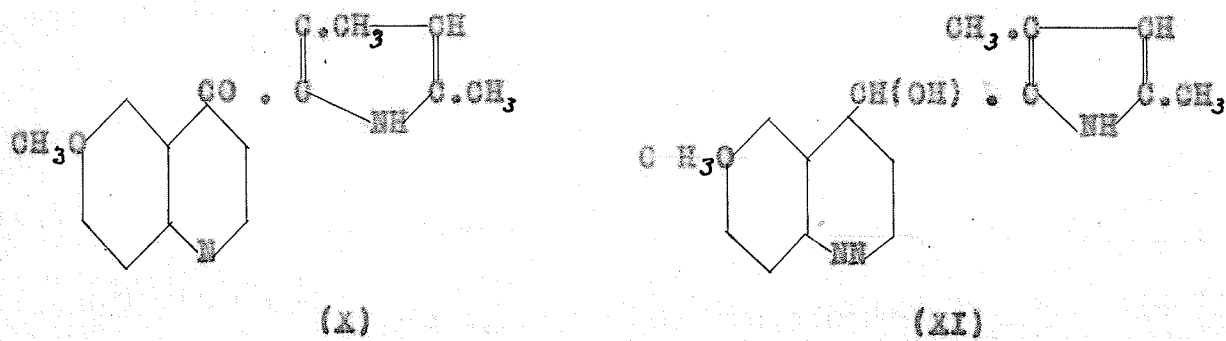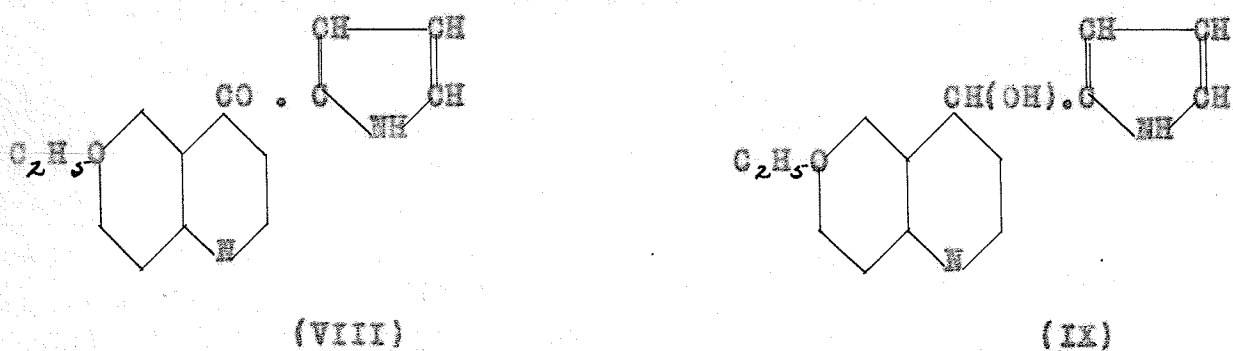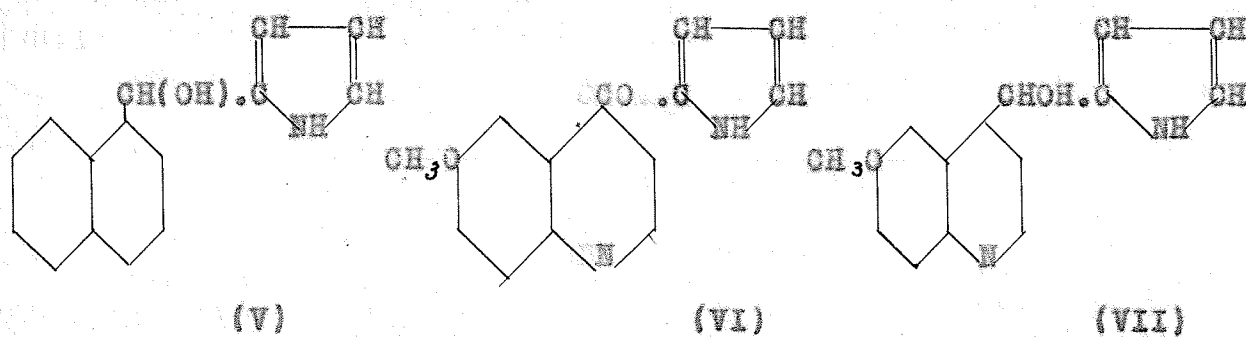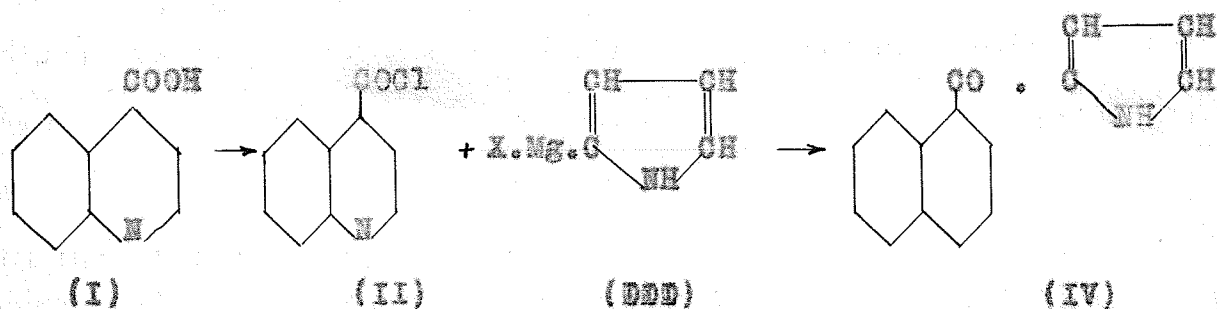
He therefore endeavored to overcome this defect by preparing some products that were more closely allied to the original formula. This was accomplished by the action of Grignard's reagent on 4-quinoline carboxylic acid chlorides or its substitution products, thus;

Quinoline 4-carboxylic acid (cinchoninic acid) (I)

+ thionyl chloride and heat

Quinoline 4-carboxylic acid chloride chlorhydrate (II)

+ pyrryl magnesium iodide (III) in benzol

4- quinolyl-2-pyrryl ketone (IV)

+ acetic acid, and reduction by HCl + Zn.

4-quinolyl-2-pyrryl-carbinol (V)

In the same way there was obtained the following;

4-p-methoxy-quinolyl-2-pyrryl-ketone and carbinol (VI & VII)

4-p-methoxy-quinolyl-2-pyrryl-ketone and carbinol (VIII & IX)

4-p-methoxy-quinolyl-2-(3.5-dimethyl pyrrol ketone and

carbinol (X & XI)

The Work Of Leopold Ruzicka.

Still closer were the compounds prepared by Ruzicka (45) related to those of Karrer, when he announced his results with what he terms mono-cyclic cinchona alkaloids. Quinoline carboxylic esters were condensed (46) with methyl-2-piperidone, etc., the product of which was then by hydrolysis with hydrochloric acid trans-

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45. Helv,chim.acta 4, 482-285.

46. Helv,chim.acta 4, 486-505.

(I)   (II)   (III)   (IV)

(V)   (VI)   (VII)

(VIII)   (IX)   (X)

(XI)   (XII)
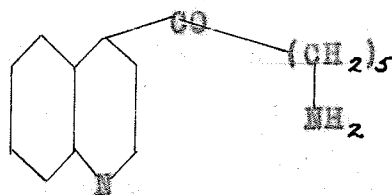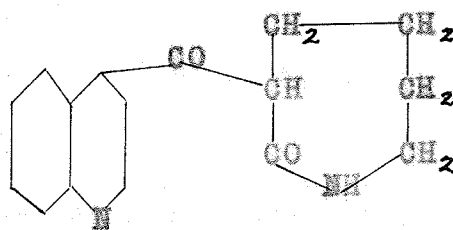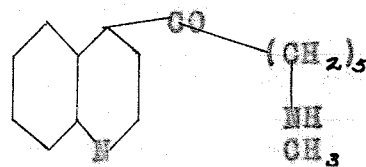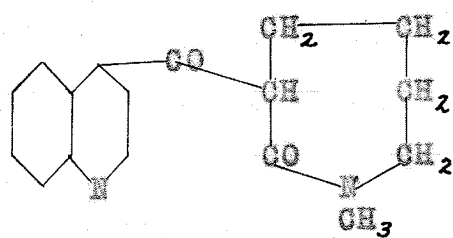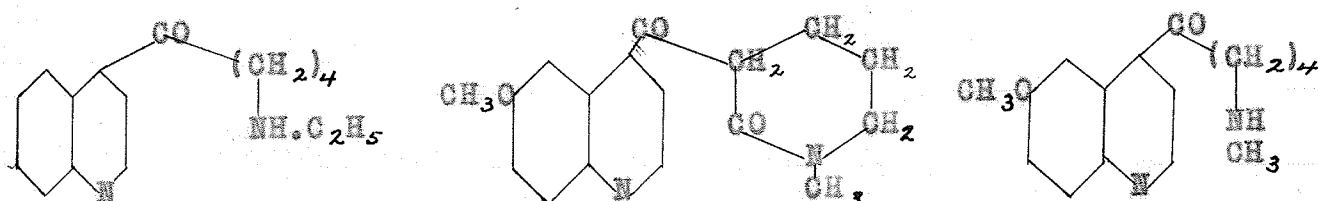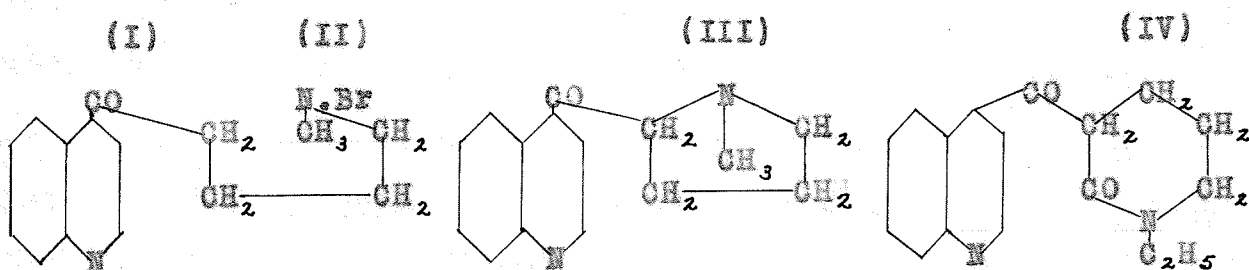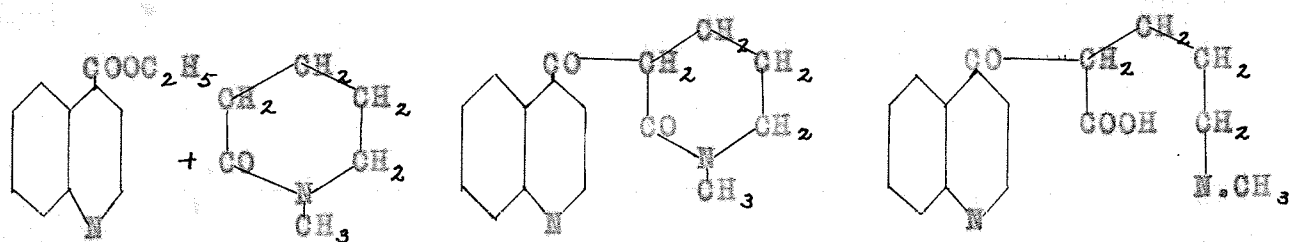
(XIII)   (XIV)

formed into aliphatic quina-toxines. These substances were then transformed into the monocyclic quinaketones thru the loss of hydrogen bromide from the bromides of the toxines.

Ethyl cinchonate (I) condenses with N-methyl- -piperidone (II) into 4-quinolyl-3-N-methyl-2-piperidonyl ketone (III) by the use of sodium ethoxide, hydrolysis of which yields the quinatoxine 4-quinolyl-methyl-amino-butyl-ketone (IV). Bromine in a 40% HBr solution produces the di-hydrobromide (V) treatment with excess of ice-cold alcoholic caustic soda transforms this derivative into the quinaketone 4-quinolyl 2-N-methyl-pyrrolidyl ketone (VI).

By employing various reagents he obtained the following:
4-quinolyl-3-N-piperidonyl ketone (VII)
4-quinolyl- -ethyl amino-butyl ketone (VIII)
6-methoxy-4-quinolyl-3-N-methyl-2-piperidonyl ketone (IX) hydro-
lysing to 4-methyl-6-quinolyl- -methyl amino-butyl ketone (X)
Cinchoninic ester condenses with

(a) -methyl-amino-hexoic lactam yielding 4-quinolyl-3-2-keto-hexamethylene-1-methyl-imino-ketone (XI) hydrolysing into 4-quinolyl-methyl-amino-amyl-ketone (XII)

(b) cyclo-hexanone-iso-oxime yielding 4-quinolyl (3-keto-hexamethylene-1-imino ketone) (XIII) which on hydrolysis yield 4-quinolyl (-amino-amyl ketone) (XIV).

The products thus obtained are more closely allied to the cinchona alkaloids than those prepared by Karrer, having the connecting C-atom in the nulcear position, with the 'second half' made up of a piperidyl ring, which forms the basis of the quinuclidine ring in the original formula.

$$CH_3 \quad + \quad Cl\text{-}\underset{CHO}{\overset{Cl}{C}}\text{-}Cl$$

(I) (II)

(III)

(IV)

(V)

A. Preparation of β-piperidyl-propionic acid.

(VI)

(VII)

(VIII)

(IX)

(X)

(XI)

(XII)

(XIII)

(XIV)
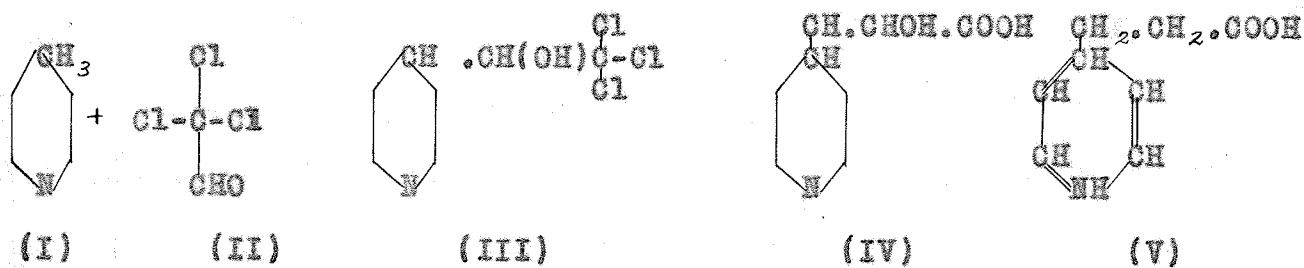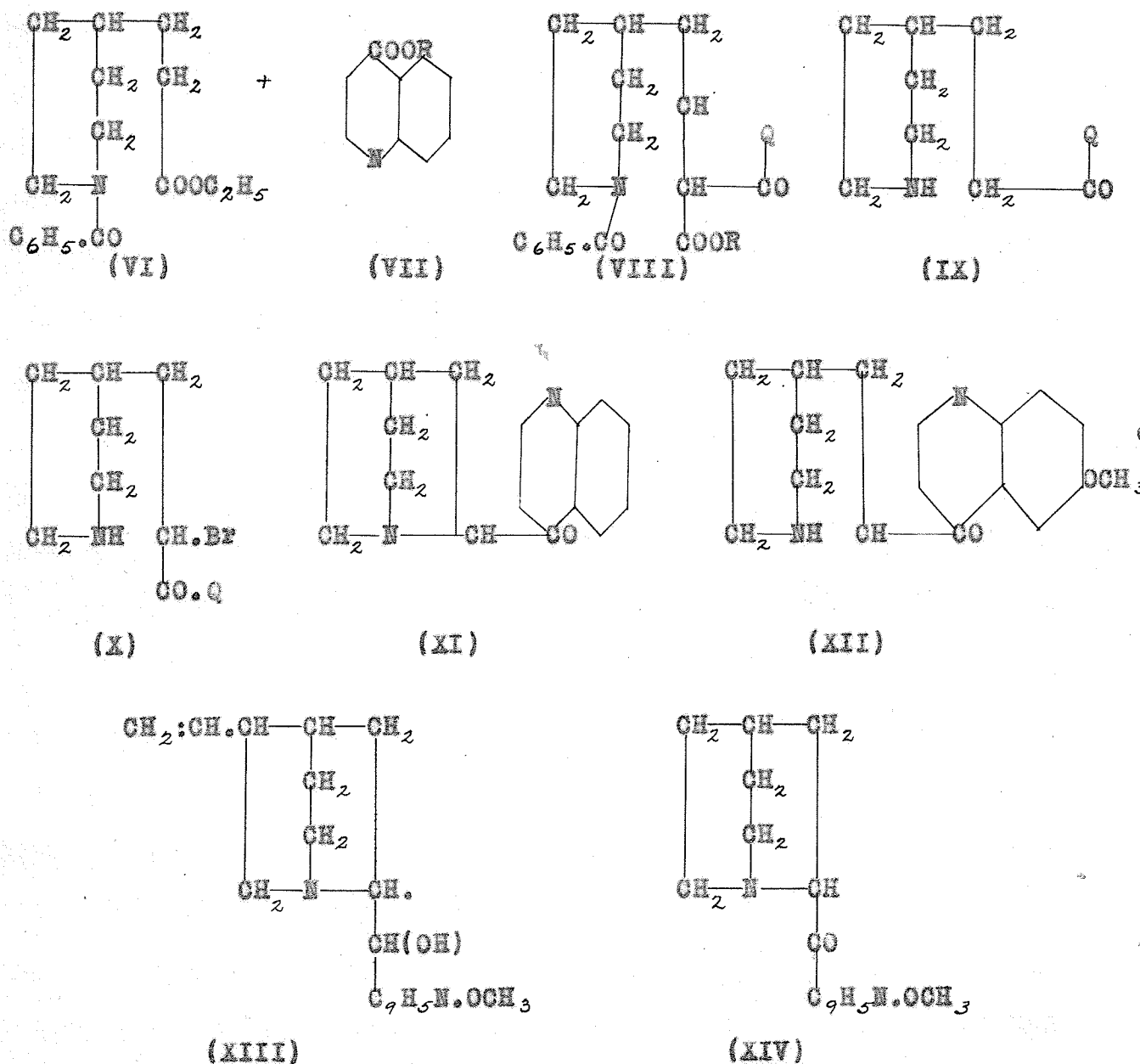
B. Preparation of Rabe's quinine-like Bases.

c. With β-piperidyl-propionic acid.

With β-piperidyl-propionic acid as the starting point, and

using it as the basis of the quinuclidine nucleus, some compounds

very closely allied to quinine were synthesized by Paul Rabe (48).

The starting product, β-piperidyl propionic acid, was synthesized

by the same worker (47), but condensing 4-methyl-pyridine (I) with

chloral (II) in the presence of zinc chloride obtaining 4-chloral

picoline (III) treatment with ice-cold potash yielding β-pyridyl

acrylic acid (IV) subsequent reduction by sodium yields the acid.

On benzoylation, the product was then condensed with cinchon-

inic ester (VII) in benzol solution thru the agency of sodium

ethoxide, the β-ketonic ester (VIII) thus obtained was then de-

prived of its ethyl and benzoyl groups, yielding the amino-

ketone (4-piperidyl-ethyl)-4-quinolyl ketone (IX) or according

to Rabe's nomenclature (49) Rubatoxanon. This substance was sug-

gested as the parent substance of the cinchona alkaloids. Bromination

of this substance and subsequent hydrolysis yields the product

Rubanon (XI).

Using quinic acid β-piperidyl-4-ethyl-6-methoxy-quinolyl-4-

ketone (XII) or 6-methoxy Rubatoxanon resulted, which yielded 6-

methoxy-rubanon or quinuclidyl-8-6-methoxy quinolyl-4-ketone (XIV).

The similarity between this substance and quinine (XIII) may be

seen by a comparison of the formulae, the only difficulty now be-

ing the unsaturated side chain in the quinuclidine nucleus, and

quinine may be synthesized.

47. Rabe und Kindler B. 52,1842 (1919)
48. Rabe und Wagner   B. 55. 532 (1922)
49. Rabe .B. 55, 522 (1922)

PART II.

" ATTEMPTS AT THE SYNTHESIS OF CERTAIN COMPOUNDS
ALLIED TO THE DECOMPOSITION PRODUCTS OF THE CINCHONA ALKALOIDS

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1. Attempts at the synthesis of Compounds allied to Meroquinine

2. Attempt at the preparation of a 4- substituted pyridine
    Compound.

3. Attempt at the Synthesis of a 4-quinoline compound

4. Attempts at the Preparation of Nitro-acridine.

5. Summary.

"   Attempts At The Synthesis Of Certain Pyridine

And Quinoline Derivatives Allied To The

Decomposition Products Of The Cinchona Alkaloids."

- -

The following pages contain a summary of some of the work

that was done with the object of synthesizing some compounds that

would be allied in constitution to some decomposition products

of the cinchona alkaloids. As stated above, these compounds are

divided into the two classes, viz:

(a) The compounds related to the "second half" or its decom-

position products.

(b) The compounds related to the quinoline bases, being dec-

omposition products of that nucleus in that alkaloid.

A short summary of the synthetic work already done by var-

ious investigators is given in the preceding section. The quin-

oline nuclei, namely; quininic or cinchoninic acids have already

been synthesized, these compounds were fairly difficult to obtain,

and the methods of synthesis now known are long and tedious with

unsatisfactory yields, and therefore a much shorter method is much

desired.

As to the derivatives of the "second half" the chemist has

still to prepare these substances. Meroquinine or its derivatives

have not as yet been totally synthesized, though several of its de-

composition products, e.g. cincholoiponic acid, cinchomeronic acid,

homo-cincholoipone, etc., have already been prepared. Even meroquinine

itself will not be the final product desired, since the side chain in the 4-position is free instead of being attached to the nitrogen atom. The closer allied substance must be a quinuclidine derivative, a substance allied to the β-piperidyl propionic acid recently prepared by Paul Rabe. Though the difficulties seem many it may not be long before we shall see this synthesis completed, and the desired object attained. At present the synthesis of meroquinine is of theoretical importance, it being necessary to synthesize this substance in order to settle the perplexing question connected with the constitutional formula of the cinchona alkaloids.

In view of the importance of this work it was the object of the authors to make some attempts at the preparation of some derivative of meroquinine, some compound that may be related to either meroquinine itself or to the β-piperidyl propionic acid, and also attempts at the preparation of 4-pyridine or 4-quinoline compounds which may be of importance to the synthetic problem of quininic and cinchoninic acids.

1. Attempts At The Synthesis Of Compounds Allied To

MEROQUININE.

Meroquinine, the decomposition product of quinine, and its allied alkaloids, has the formula $C_9H_{15}NO_2$. Its constitutional formula has been the subject of much study and the formula generally accepted is

                         CH$_2$COOH
                         CH
            H$_2$C   CH.CH=CH$_2$
            H$_2$C   CH$_2$
                         NH
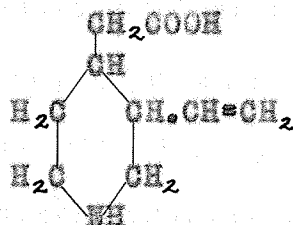
The requirements of this molecule are;

1. a piperidine ring

2. a propyl group in the 4-position and

3. a vinyl group in the 3-position.

The difficulties in such a synthesis are the preparations of 4-substituted pyridines or quinolines, and also that of a substance with an unsaturated side chain, in a reduced pyridine ring.

The method proposed for this preparation was to obtain in the first place a di-cyano derivative of the formula

        CH$_2$——CO——CH$_2$——COOR
        | |
        CN   CN

                (I)
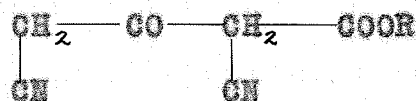
in which the α and the γ positions are occupied by CH$_2$CN groups with the ketone group in the β position. The object is to obtain from this compound a di-amino compound (II) on reduction, so that on heating a closed ring (III) may be obtained thru the elimination of a molecule of ammonia. The purpose of the ketone group in the β position is to furnish a point at which the

propyl group may be added on by Grignard's synthesis, with the required reagent, this reaction to be accomplished either before or after the reduction of the nitrile, according to the stability of the compound. The substance thus obtained will have either one of the formulae IV or V. A method may be found by which the ester group may be transformed into an unsaturated chain yielding the meroquinine derivative (VI). With this substance if prepared, attempts can be made to close the 4-side chain with the formation of the bicyclic ring (VII) required by the quinuclidine formula (VIII).

It was proposed to prepare the above nitrile (I) by one or more of the following ways:

a. From aceto-acetic ester, to obtain the di-cyan-aceto-acetate by the conversion of the di-bromo derivative into the corresponding nitrile.

b. From dichlorhydrin, to endeavor to prepare the corresponding nitrile.

c. From the condensation of cyanacetyl chloride and cyanacetic acid.

It may also be possible to synthesize the di-amine (II) by a condensation of two molecules of β-alanine.

The theoretical methods proposed for the preparation of the initial compounds are dealt with in their respective sections, the main theoretical process may be recorded as follows:

$$
\begin{array}{ccc}
& \overset{CO}{\underset{\substack{CH_2 \\ | \\ CN}}{\quad}} \overset{CH.COOR}{\underset{\substack{| \\ CN}}{\quad}} & \longrightarrow \quad \overset{CH_2.COOR}{\underset{\substack{C(OH) \\ CH_2 \quad CH.COOR \\ | \qquad | \\ CN \qquad CN}}{\quad}}
\end{array}
$$

(I)   (IV)

$$
\overset{CO}{\underset{\substack{CH_2 \quad CH.COOR \\ | \qquad | \\ CH_2 \quad CH_2 \\ | \qquad | \\ NH \qquad NH}}{\quad}} \longrightarrow \overset{CH.COOR}{\underset{\substack{C(OH) \\ CH_2 \quad CH.COOR \\ | \qquad | \\ CH_2 \quad CH_2 \\ | \qquad | \\ NH \qquad NH}}{\quad}}
$$

(II)   (V)

(III)

CH_2 CO $CH.COOR$
CH_2 CH_2
NH

(VI)

$CH.COOR$
CH
CH_2 $CH.COOR$
CH_2 CH_2
NH

(VII)

CH
CH_2 CH_2 $CH.COOR$
CH_2 CH_2 CH_2
NH

$CH.COOH$
CH
CH_2 $CH.CH=CH_2$
CH_2 CH_2
NH

Meroquinine.

CH
CH_2 CH_2 CH_2
CH_2 CH_2 CH_2
NH

Quinuclidine.   (VIII)
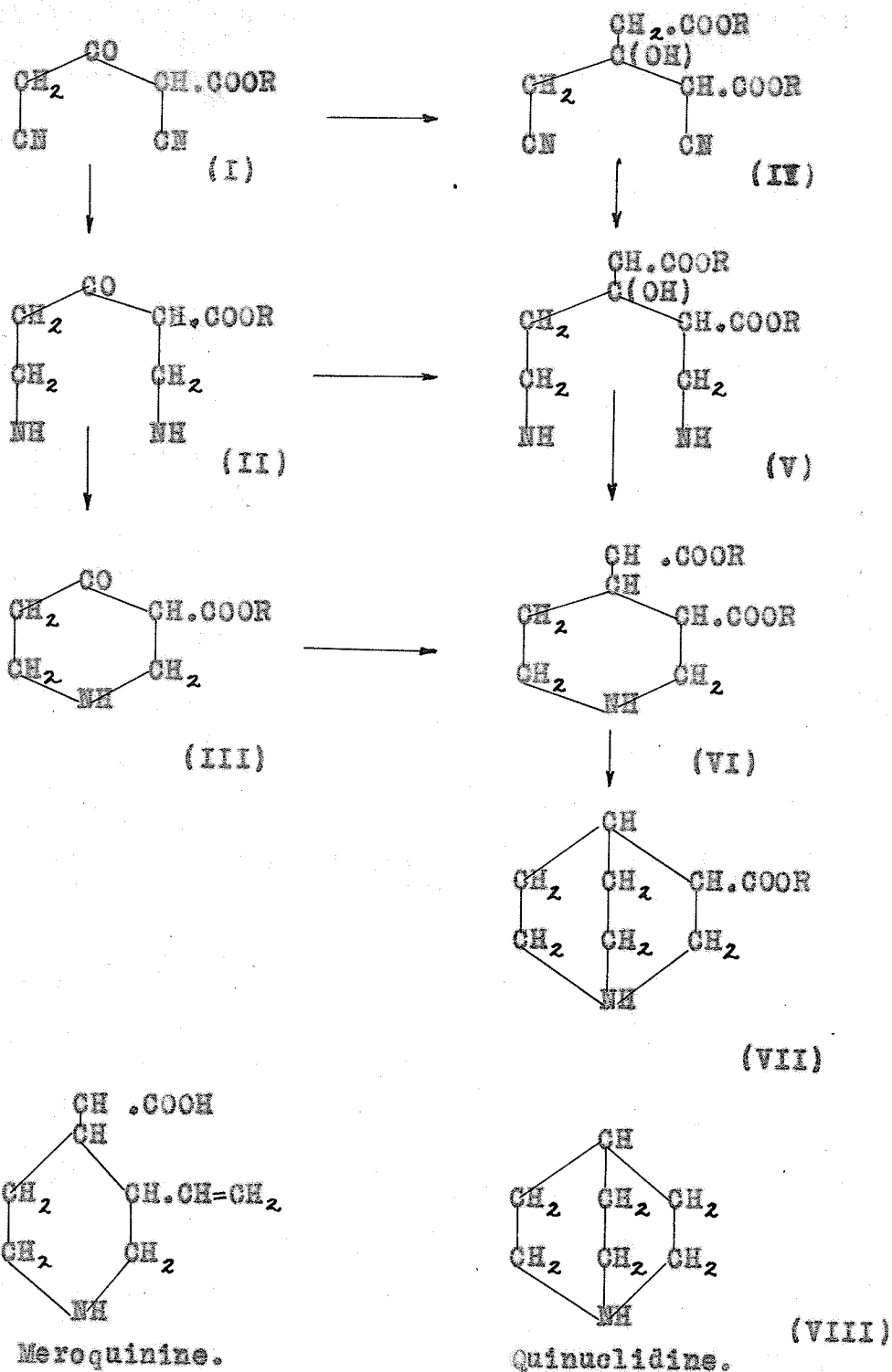
Theoretical methods proposed for the Preparation of Compounds
Allied in Constitution to MEROQUININE.

With aceto-acetic ester (I) as a starting point, it was pro-
posed to prepare a substance allied to meroquinine by the pre-
paration of $\alpha\gamma$-di-cyan-ethyl-aceto-acetate (IV) from this point
to proceed as proposed in the preceding pages.

It was found that to prepare the di-cyano-compound (IV), it
may be done thru the method of Bernary (50) thru chloracetyl
cyanacetic acid. However, we attempted to prepare the substance
thru the di-bromo compound, $\alpha\gamma$-di-bromo-ethyl aceto-acetate (III).
In order to prepare this halide, however, it is necessary to pre-
pare first the gamma-mono-brom derivative (II) so that the whole
process of the preparation of the nitrile may be represented thus;

$$
\begin{array}{c}
\text{CO} \\
\diagup \quad \diagdown \\
CH_3 \qquad CH_2COOC_2H_5
\end{array}
\qquad \text{(I)}
$$

$$
\begin{array}{c}
\text{CO} \\
\diagup \quad \diagdown \\
CH_2 \qquad CH_2 \cdot COOC_2H_5 \\
| \\
Br
\end{array}
\qquad \text{(II)}
$$

$$
\begin{array}{c}
\text{CO} \\
\diagup \quad \diagdown \\
CH_2 \qquad CH \cdot COOC_2H_5 \cdot \\
| \qquad\qquad | \\
Br \qquad\qquad Br
\end{array}
\qquad \text{(III)}
$$

$$
\begin{array}{c}
\text{CO} \\
\diagup \quad \diagdown \\
CH_2 \qquad CH \cdot COOC_2H_5 \cdot \\
| \qquad\qquad | \\
CN \qquad\qquad CN
\end{array}
\qquad \text{(IV)}
$$

----

50. Erich Bernary, B.41,2403-2404 (1908).
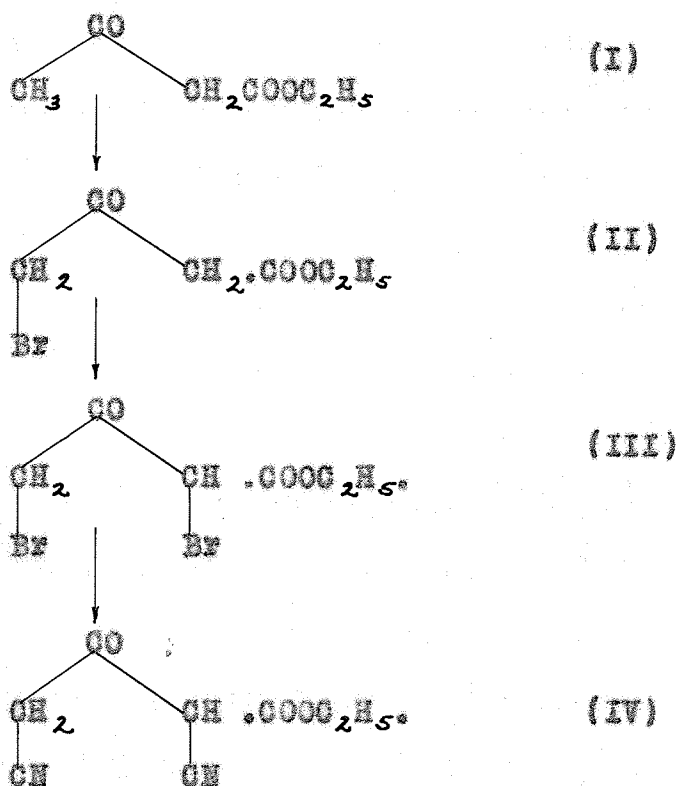
The main reactions may be stated thus:

Ethyl-aceto-acetate (I) may be converted into the gamma bromo compound (II) further bromination yielding the $\alpha\gamma$ -di-brom aceto-acetic ester (III). On reacting with potassium cyanide (KCN) the di-cyano compound may be obtained (IV) subsequent manipulation to follow as in Chart I.

Of the substances above mentioned the mono-brom and di-brom compounds have been prepared by the direct bromination of ethyl aceto-acetate in carbon disulfide solution. The di-cyano derivative has also been prepared as stated above, but no mention of its preparation, or any attempts at its preparation thru the di-bromo-compound, can be found in the references available.

Ethyl-γ-bromo-aceto acetate was prepared, according to Beilstein (51), by Conrad Schmidt in 1896 (52). Aceto-acetic ester was dissolved in 1-2 volumes of carbon disulfide and brominated, in a freezing solution, left overnight, and the next day, the brominated layer washed, dried and distilled, the carbon disulfide being first distilled off, further purification was attained by distillation in vacuo.

A slight modification of this method was given by Prof. Lee Irvin Smith (private communication) which yielded better re-sults. Both the halogen and the acet-acetic ester were first dissolved in carbon disulfide before bromination, the resulting reaction being thus less vigorous and attended by less evolution of heat. Fuller details for the purification of the compound was

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51. Beilstein, Handbuch, Supplement, Band I,239.

52. Conrad Schmidt, B. 29,1045. (1896).

also given. (This perhaps may be due to the fact that the original papers were inaccessible in the library).

From this derivative in carbon disulfide solution further bromination yields the di-brom compound which should crystallize in white needles. M.P. 45 - 49°. (53)

Prof. Smith's preparation necessitates the purification of the compound thru the copper derivative, and then reconversion into the di-bromo-aceto-acetic ester.

The di-cyano compound prepared by Bernary (50) was obtained from chloracetyl cyanoacetic ethyl ester (III) by the action of potassium cyanide (KCN). The former ester was prepared by the interaction of cyanacetic ester (I) with chloracetyl chloride (II) in ethereal solution thru the agency of the sodium derivative of the former compound.

"10 gms. of the resulting substance chloracetyl cyano-aceto-acetic ester was dissolved in a solution of 10 gm.s of KCN in 50 cc. of water, and the resulting mixture carefully warmed in the water bath till it began to color, when the warming was stopped and the substance allowed to react. The heat of reaction was allowed to reach 50-60° C. and then the whole was kept at that temperature for 1/4 of an hour. The resulting red solution was then acidified, the cyano-derivative precipitating in crystalline form, with a yield of about 6 gms. This was then dissolved in a little ethyl acetate filtered from the dark red reaction product, extracting the substance from solution with ether, from which it crystallizes in colorless

----

53. Epprecht. A. 278,85. (1894)

crystals M.P. 87-89° C. "

   Instead of using the above substance, chloracetyl cyano-aceto-acetic ester, in which we have in the γ-position a chloro group, and in the α-position a cyano group, we proposed to use the di-bromo compound, having in both these positions a bromo group, from which the nitrile may be prepared.

   Bernary's Synthesis of $\alpha\gamma$-dicyan-ethyl aceto-acetate.

$$CH_2—CO—\boxed{Cl \quad \underset{+}{ } \quad H}CH.COOR \quad \longrightarrow \quad CH_2—CO—CH.COOR$$

(II)   (I)   (III)

$$CH_2—CO—CH.COOR$$

(IV)
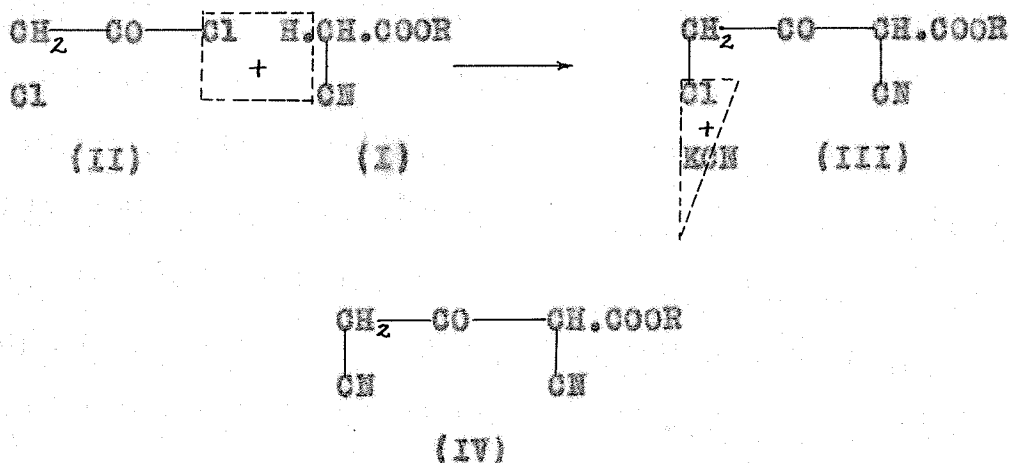
EXPERIMENTAL

Ethyl-γ-mono-brom-aceto-acetate, $CH_2.CO.CH_2.COOC_2H_5$.
$Br.$

Preparations	A	B	C
Ethyl aceto-acetate	100 gms.	50 gms.	100 gms.
Carbon disulfide	150 cc.	75 cc.	150 gms.
Bromine	123 gms.	61.5 gms.	123 gms.

The aceto-acetic ester was first dissolved in 1-2 volumes of carbon disulfide and then placed in an ice-salt freezing mixture, and the bromine added to it in small quantities, vigorous ebullition took place with the evolution of dense fumes of hydrobromic acid. When the whole amount has been added the mixture is left to react until bromination is complete, which usually takes about 12-15 hours, usually overnight. When no more fumes were evolved by the mixture the resulting substances, a dark brown heavy layer, was separated and washed with water, the ester layer separated, collected and then dried in a conical flask over calcium chloride. As much as possible of the carbon disulfide was then distilled off on the water bath, a dark red viscous liquid being left behind.

Preparation A was used in an attempt at the preparation of the di-bromo compound. Preparation B and C were subjected to distillation in order to purify the ester, the boiling point of which is 125°C at 10 mm. pressure. However, in both cases the pure substance was not obtained. In the case of B, before the correct boiling point was reached, the substance started to decompose into a tarry mass, while was reddish vapor, together with a light yellow

liquid distilled over. In the case of C the following fractions
were obtained;

(1) 15 -40 mm. B.P. up to 100°C. a colorless liquid, mostly
carbon disulfide.

(2) 15-40 mm. B.P. 100-125°C, a pale yellowish liquid, which
turned dark on exposure to air. Yield about 5 gms.

(3) 30 mm. The substance decomposed and fumes passed over into
the receiver and trap bottle.

Fluctuations in temperature with decomposition of the products
took place as soon as the mixture was heated to certain temperature,
in this case, before a temperature of 120° was reached.

Some months later the communication of Prof. Smith came to
hand, and better results were obtained from following his directions.
Preparation A.

Acetoacetic ester	10 grammes.
dissolved in Carbon disulfide	10 cc.
Bromine	12 grammes
dissolved in carbon disulfide	40 cc.

The ester was brominated in the cold by gradually adding the
bromine solution to the ester solution. Ebullition took place at
each addition, accompanied by evolution of hydrobromic acid gas. The
product was washed twice with water, dried over calcium chloride and
the solvent then distilled off. The red oil that remained was
then subjected to vacuo distillation, the fraction passing over
at 120-150°C under 30 mm. pressure, was retained as the - mono-brom
ester. This product comes over, in vacuo as a yellow liquid
which gradually attained a deeper color; on release of pressure,

this liquid turned red, and on longer standing attained a dark red color. The major part of this substance distilled over at 127-150° under 30 mm. pressure, a small quantity also was produced by heating up to 150° Over 150° , however, the substance started to decompose into the tarry mass and vapors obtained in the previous set of experiments.

Preparation B.

Ethyl aceto-acetate	39 gms.
dissolved in carbon disulfide	25 cc.
Bromine	48 gms.
dissolved in carbon disulfide	150 cc.

The process described was followed, the reactions also proceeded smoothly, the yield of the reaction product being 55 gms. (somewhat below Prof. Smith's result, which was 61 gms.) This product was then purified in several portions, the following was noted:

The substance was divided into 5 parts and distilled in vacue separately and under different conditions in order to ascertain the best conditions for purification.

Portion a. 10 grams was distilled as directed in the above instructions, the portion distilling over at 125-150° under 30 mm. pressure, the main portion distilling over at 130-132° C. Decomposition began at 152°C and the remaining portion decomposed into a charred mass. Yield about 5 grammes.

Portion b. 10 grammes was distilled at 12-10 mm. pressure, the distillare being collected at 120° C. At about 123°C after about 1 gram of the distillate has been collected, the substance

started to decompose, and the heating was therefore stopped. Further heating after the substance had cooled to about 100°C resulted in all cases, in decomposition at 120°C. The remaining mixture in the flask was found to consist of the liquid ester with some tarry matter. This tarry matter was separated from the liquid and then subjected to further distillation, but the decomposition again took place as soon as a temperature of 120° was reached, so that this portion was spoilt for further purification. Even though the pressure was lowered, i.e. at 30 mm., no product was obtained, but a continual decomposition.

Portion c. 12 grammes, was placed in the flask in which decomposition took place and distilled. This was done immediately after the above experiment, the distillation flask having been washed with distilled water, but a little tarry matter still adhered to the bottom of the flask. As before, decomposition again took place at about 125°C under 30 mm. pressure.

Portion d. The remainder of the substance was placed in a clean flask and distilled at 125-150° under 30 mm. pressure. The purification proceeded smoothly as in the first portion (a).

From these few experiments it was able to determine the best conditions for the purification of this ester. The yield obtained was about 25 grams of the purified substance. It is a reddish liquid, which turned into a dark red on further standing in contact with air. It is a fairly heavy and oily liquid possessing a very disagreeable odor, irritating to the delicate membranes of the eyes, especially when heated. It is hardly soluble in water, but soluble in alcohol and ether.

α - y - ethyl di-brom-aceto-acetate.

$Br.CH_2.CO.CH(Br).COOC_2H_5.$

The crude product obtained in preparation A according to
Beilstein's method was further brominated by dissolving in 25 g
of carbon disulfide, and again brominated with a further molecule
of bromine (123) grams.) The resulting mixture was a dark red oil,
darker in color than the mono-brom ester, more heavy and viscous.
It retained still its obnoxious odorand would not crystallize
even after standing for several months. (Epprecht described this
substance as crystallizing in white needles)

The products obtained in preparations B and C were rendered
useless by the above attempts at purification, and therefore no
substance was available for this experiment.

The product obtained from the method of Prof. Smith was next
employed, the method he used being also recommended. About 20 gms.
of the mono-ester was dissolved in 20 cc of carbon disulfide was
gradually added, shaking the flask at the same time. This was then
left for bromination to complete itself. The product was then
washed in a solution of sodium carbonate (3%), then with water 3
times and then with distilled water, in order to remove the solvent.

The resulting substance was a dark red oil similar to that
obtained in former experiments, weighing 21 gms. The liquid was
then dissolved in ether and shaken up with a saturated solution of
copper acetate when a green precipitate was obtained. This was
filtered at the suction pump washed with alcohol and then dried. This

is the copper salt of the compound. This salt suspended in ether
and dilute hydrochloric acid added, which decomposed the compound.
The etheral layer was then separated from the acid aequeous layer,
washed several times with water, and finally dried with calcium
chloride and then distilled off. The residue should be pure
$\alpha\gamma$ ethyl-di-brom-aceto-acetic ester.

The first experiment was tried with about 2 grams of the
salt, but the resulting substance was of negligible quantity,
appearing in the bottom of the basin as a few drops of colorless
oil, which evaporated on standing for a few days.

The next experiment was tried with 10 gms of the salt, but
due to some mistake in the manipulation no yield was obtained.

The same was tried with the remainder of the compound, but
the experiment was not finished in time before my departure.

$\alpha\gamma$ - di-cyan-ethyl aceto-acetate.

$$CH_2-CO-CH-COOC_2H_5$$
$$\quad | \qquad\quad |$$
$$\quad CN \qquad CN$$
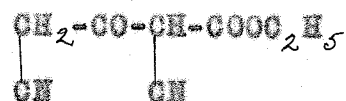
A portion of the crude ester obtained in the above experi-
ment was used, 20 grams of it being added to 32 grams of potassium
cyanide dissolved in 100 cc. of water. Coloration of the mixture
took place immediately with a slight evolution of heat. The sol-
ution turned successively from the reddish color to a brown, dark
brown and then into a black mixture, accompanied by a deposition
of tarry matter. The heat evolved, however, was not sufficient to
raise the temperature to the required amount, and therefore it was
warmed in the water bath and the solution carefully kept at 50-60°C,

till no more heat was evolved. When the temperature began to lower the flask was placed in a water bath at 55°C for 15 minutes. The reaction mixture was then cooled and dilute sulfuric acid added, effervesence took place accompanied by heating of the solution. The acidified solution was then filtered. An error was introduced here in that it was attempted to extract the nitrile from the solution instead of from the tarry matter, which was thrown away before the error was discovered.

This was repeated and this time using half the above mentioned quantities, proceeding exactly as described above until the part after the acidification, when the tarry matter and residue was filtered off and dissolved in ethyl acetate, and this solution precipitated with ether, a flocculent precipitate resulting from this precipitation. This was filtered off and then dissolved in a little ether, and then the solvent was distilled off.

A negative result was obtained, a minute quantity of reddish tar being left behind as a residue.

Preparation of this nitrile was attempted by direct combination of the di-brom compound with KCN, in which 10 gms. of the crude ester was dissolved in 20 cc. of ethyl alcohol, and to this was added 8 gms. of KCN. No reaction took place in the cold. The mixture was therefore refluxed in the fume chamber for 1 hour, the resulting substance being only a black tarry decomposition product, which on extraction with ether yielded no result. Smaller quantities were tried varying the time of refluxing, and the character of the solvent, but the result is the same all thru, decomposition taking place in all cases.

Dichlorhydrin, the intermediate product in the preparation of epichlorhydrin, furnishes us with another possible source of the nitrile. This substance is produced by the action of hydrochloric acid gas on glycerol. In this reaction the two secondary alcoholic groupings are replaced by two chlorine groups, thus giving $\alpha\alpha$-dichlorhydrin, as follows:

$$
\begin{array}{l}
CH_2OH \\
CHOH \quad + \quad HCL \quad ----- \quad
\begin{array}{l}
CH_2Cl \\
CHOH \quad + \quad H_2O \\
CH_2Cl
\end{array} \\
CH_2OH
\end{array}
$$

    glycerol   dichlorhydrin.
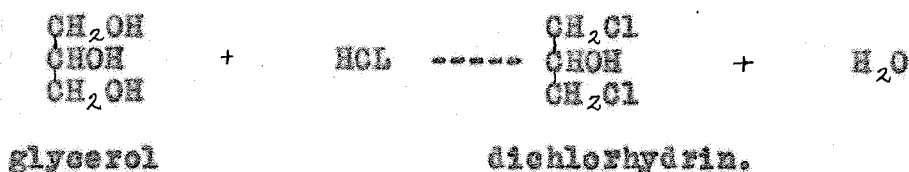
In this formula the difference between this and the nitrile is that the nitrile has, instead of the two chloro-group, the two cyano-groups. It may be possible to substitute two nitrile groups at these above mentioned positions, and therefore a few experiments were conducted with this end in view. Should it be possible to obtain the nitrile, subsequent manipulation may be carried out as in the former outlines. No preparation of dicyanhydrin can be found in the literature available, and therefore it was endeavored to carry out a reaction somewhat as follows:

$$
\begin{array}{l}
CH_2Cl \\
CHOH \quad + \quad 2KCN \quad ----- \quad
\begin{array}{l}
CH_2CN \\
CHOH \quad + \quad 2KCl. \\
CH_2CN
\end{array} \\
CH_2Cl
\end{array}
$$

    dichlorhydrin   dicyanhydrin.
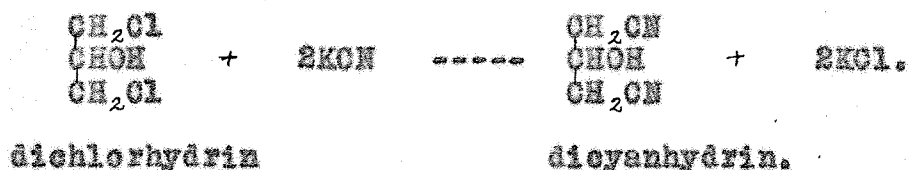
The general method for the preparation of this substance is that of Reboul (54) which is given in Cohen's (55) text. The glycerol was first dehydrated, mixed with an equal volume of glacial acetic acid, and then hydrochloric acid gas passed in till saturation was effected.

55.Reboul. Annalen,Supl. 1,221 (1861)

The resulting mixture was then distilled, and dichlorhydrin passes over at 160-210°.

A modification of the process was recently advanced (56) in which it was shown that the dichlorhydrin obtained in the above manner contained besides the substance itself some polyglycerides and other impurities, and so the author described a process for the preparation of pure dichlorhydrin.

Dehydration of the glycerol was carried on for two hours, and then only 6% glacial acetic acid used. There is also a slight modification in the apparatus in that instead of using a large flask a distilling flask was used, and the saturation of the liquid may then be seen by the gas issuing from the side tube. Then instead of distilling under atmospheric pressure the purification was carried out under 15 mm pressure at 70-110°C. This portion, together with the recovered dichlorhydrin from the initial fraction, was again distilled at 167-179°C. the yield being 87% of theory.

This product was then changed into epichlorhydrin by means of caustic soda, and then by careful manipulation hydrochloric acid was added to the mixture, the dichlorhydrin extracted with ether and dried over sodium sulfate (anhydrous). Distillation of the solvent and distillation under atmospheric pressure gives a yield of 60% being obtained. This process gives pure dichlorhydrin, but the yield is much less than the preceding method, and where the crude ester suffices, it is not as desirable as the former.

---

55. J.B. Cohen "Practical Organic Chemistry." Preparation 32, p.111.

56. Hill & Fische Journ. Am. Chem. Soc. 44,2583 (1922)

Dichlorhydrin.

$CH_2Cl.CHOH.CH_2Cl.$

Rebouls method was first employed in which 500 grams of gly-
cerol was dehydrated by heating on a sandbath until the thermom-
eter immersed in it registered 175°C. The dehydrated substance
weighing 455 gms. was added to 375 gms. of glacial acetic acid.
Into this mixture, contained in a round-bottomed flask, was passed
dried hydrochloric acid gas, until no more absorption would take
place, and then the whole was heated for an hour or so on the
water bath. After leaving it for 24 hours, gas was again passed
thru the mixture until it was saturated, and the resulting mixture
was then divided into two portions and distilled separately. The
yield obtained was very unsatisfactory, the fraction coming over
at 160-210° being only 25 cc. and the residual protion forming the
bulk of the preparation. The second portion yielded a little more
and the total yield of this preparation was only about 100 gms.
Cooling ans further heating of the mixture gave no additional yield.

Later on towards the end of the session the second method was
discovered, and an attempt was made to prepare the pure substance
for use. According to directions glycerol was dehydrated for 2
hours at 160° and the dehydrated substance (100 gms) together with
6 gms of glacial acetic acid was placed in a distillation flask
fitted with a side tube, and the mixture heated to 100° C while
hydrochloric acid gas was passed thru into the mixture. This add-
ition of gas was continued for 6 hours until the absorption of gas

was complete. The product was then distilled under reduced pressure (15 mm) and the following fractions collected:

(1) 30-70° C consisting of aequeous HCl, containing a little dichlorhydrin which may have distilled over with the HCl. The product in this portion was neutralized with sodium carbonate solution, thus precipitating the dichlorhydrin, which was dissolved in the acid. The precipitated substance was added to the following portion:

(2) collected from 80-110° C containing a mixture of the isomers of dichlorhydrin.

(3) above 120° C the distillate consists of a small amount of dichlorhydrin, together with a residue of polylycerides.

The yields obtained were 10, 50 and 5 grams for the respective portions. The total yield obtained for this reaction was 54 grams. Lack of time prevented the completion of this preparation, and so the crude product was utilized in the following experiments:

Di - cyan-hydrin.

$CH_2CN.CHOH.CH_2CN.$

To 10 grams of dichlorhydrin was added a solution of 5 gms of KCN dissolved in 50 cc. of water. No heat of reaction was observed and apparently there was no change in the cold. On heating, however, the mixture turned brown and decomposition took place. No product could be extracted from the resulting mixture.

A similar quantity was taken, and treated this time in a water bath, heating for some time, but litte or no change in coloration was observed.

Instead of water, a mixture of 50 cc. methyl alcohol, and an equal amount of water was employed, with similar results, no change taking place until on heating over a naked flame when decomposition took place, accompanied by effervesence in the vicinity of the drops of dichlorhydrin.

" The Use of Cyanacetic Esters. "   (Discussion)

In the preceding pages mention was made of Bernary's syn-
thesis of the di-cyano compound which we attempted to prepare.
The starting point of his synthesis was the compound chloracetyl
cyano-aceto-acetic ester, $ClCH_2.CO.CH(CN)COOC_2H_5$.   The di-cyano
derivative was obtained from this compound by substitution, by
which the halide atom was replaced by the nitrile group. This
intermediate substance differs from the nitrile in the one atom
the chlorine atom, and was prepared by the condensation of cyan-
acetic ester, and chloracetyl chloride, thru the sodium derivative
of the former compound. (cf. constitutional formulae of Bernary's
synthesis in the preceding pages)

Seeing that the chlorine atom of the intermediate product
was derived from the use of chlor-acetyl chloride, it may be
possible that instead of using the chloride, to use the nitrile
by which means the di-cyano compound may be prepared. We may
represent this reaction thus:

Theoretical Consideration of The Synthesis.
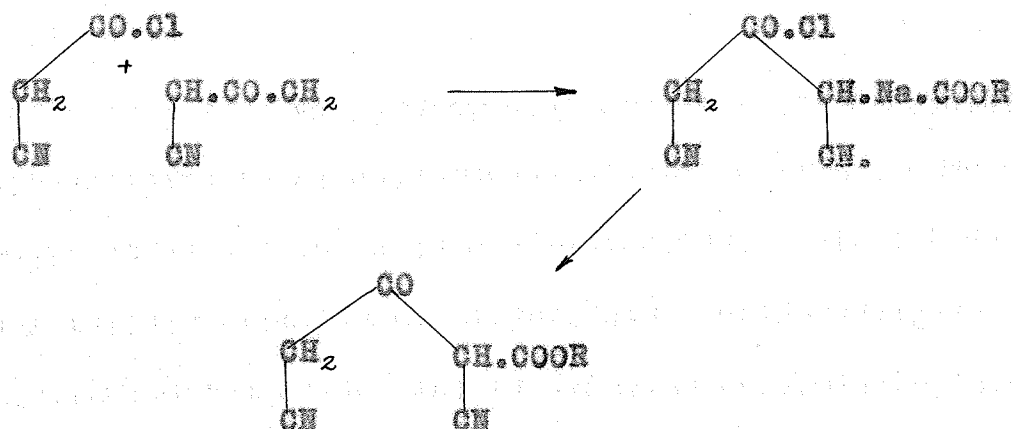
" Attempts at the Synthesis by Condensation of β-Alanine."

Instead of preparing the di-amino compound from the nitrile
as proposed in the former pages, it may be possible to prepare this
di-amino compound, which we intended to obtain from the reduction
of the nitrile, without first preparing the latter compound. It may
perhaps be possible thru the agency of aceto-acetic ester conden-
sation on β-alanine (IV), the resulting condensation product may
have the formula (V), which is our objective.

β-alanine, or β amido-propionic acid has been prepared by
Hoogewerff and van Dorp (57) and later on by Lengfeld and Stieglitz
(58) from succinimide (II). The method of Hoogewerff and van Dorp
was to treat succinimide (obtained by the distillation of ammonium
succinate (I) with an alkaline solution of potassium hypobromite
the resulting solution being potassium β-propionate (IV). This
salt must now be transformed into the acid by interaction with
hydrochloric acid, after which it is treated with silver sulfate,
the silver precipitated with hydrogen sulfide, and purification
finally attained thru the barium salt. This method, however, is
tedious and the following method, that of Lengfeld and Stieglitz,
is the more desirable. The succinimide (I) was first converted
into brom-succinimide (VI) thru the action of bromine, the imide
being dissolved in ice cold aequeous solution of sodium hydroxide.
On boiling this with sodium methoxide in methyl alcoholic solution

(57) Hoogewerff and van Dorp - Rev. Trav. Chem. 10,4-12 (1891)

(58) Lengfeld and Stieglitz - Am. Chem.J. 15. 215-222 and

Am. Chem. J. 15. 504-518.

methylic-metho-carbonyl β-amido-propionate (VII) was produced which was later changed into the hydrochloride (VIII) and finally into the acid itself (IV).

Aceto-acetic ester condensation of two molecules of this substance may yield as a product the amine desired (V) as follows:

$$
\begin{array}{c}
\text{COOR} \\
\text{CH}_2 \quad \text{CH}_2\text{COOR} \\
\text{CH}_2 \quad \text{CH}_2 \\
\text{NH}_2 \quad \text{NH}_2
\end{array}
\quad + \quad \longrightarrow \quad
\begin{array}{c}
\text{CO} \\
\text{CH}_2 \quad \text{CH:COOR} \\
\text{CH}_2 \quad \text{CH}_2 \\
\text{NH}_2 \quad \text{NH}_2 \\
\text{(V)}
\end{array}
$$

Preparation of β-alanine.

$$
\begin{array}{l}
\text{CH}_2\text{COONH} \\
\text{CH}_2\text{COONH}
\end{array}
\quad \text{(I)}
$$

$$
\downarrow
$$

$$
\begin{array}{l}
\text{CH CO} \\
\quad\quad\quad \text{NH} \\
\text{CH}_2\text{CO}
\end{array}
\quad \text{(II)} \quad \longrightarrow \quad
\begin{array}{l}
\text{CH}_2\text{CO} \\
\quad\quad\quad \text{NBr} \\
\text{CH}_2\text{CO}
\end{array}
\quad \text{(VI)}
$$

$$
\downarrow \qquad\qquad\qquad\qquad\qquad\qquad \downarrow
$$

$$
\begin{array}{l}
\text{CH}_2\text{COOK} \\
\text{CH}_2 \\
\text{NH}_2
\end{array}
\quad \text{(III)} \qquad\qquad\qquad
\begin{array}{l}
\text{CH}_2\text{COOCH}_2\text{H}_5 \\
\text{CH}_2\text{COOCH}_2\text{H}_5
\end{array}
\quad \text{(VII)}
$$

$$
\downarrow \qquad\qquad\qquad\qquad\qquad\qquad \downarrow
$$

$$
\begin{array}{l}
\text{CH}_2\text{COOR} \\
\text{CH}_2 \\
\text{NH}_2
\end{array}
\quad \text{(IV)} \qquad\qquad\qquad
\begin{array}{l}
\text{CH}_2\text{COOH} \\
\text{CH}_2\text{NH}_2\cdot\text{HCl}
\end{array}
\quad \text{(VIII)}
$$

$$
\downarrow
$$

$$
\begin{array}{l}
\text{CH.COOH} \\
\text{CH}_2\text{NH}_2
\end{array}
\quad \text{(IX)}
$$
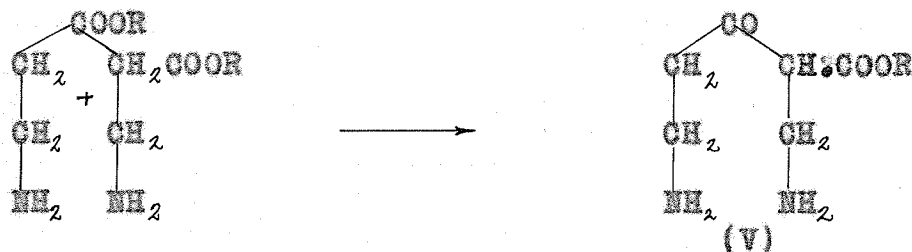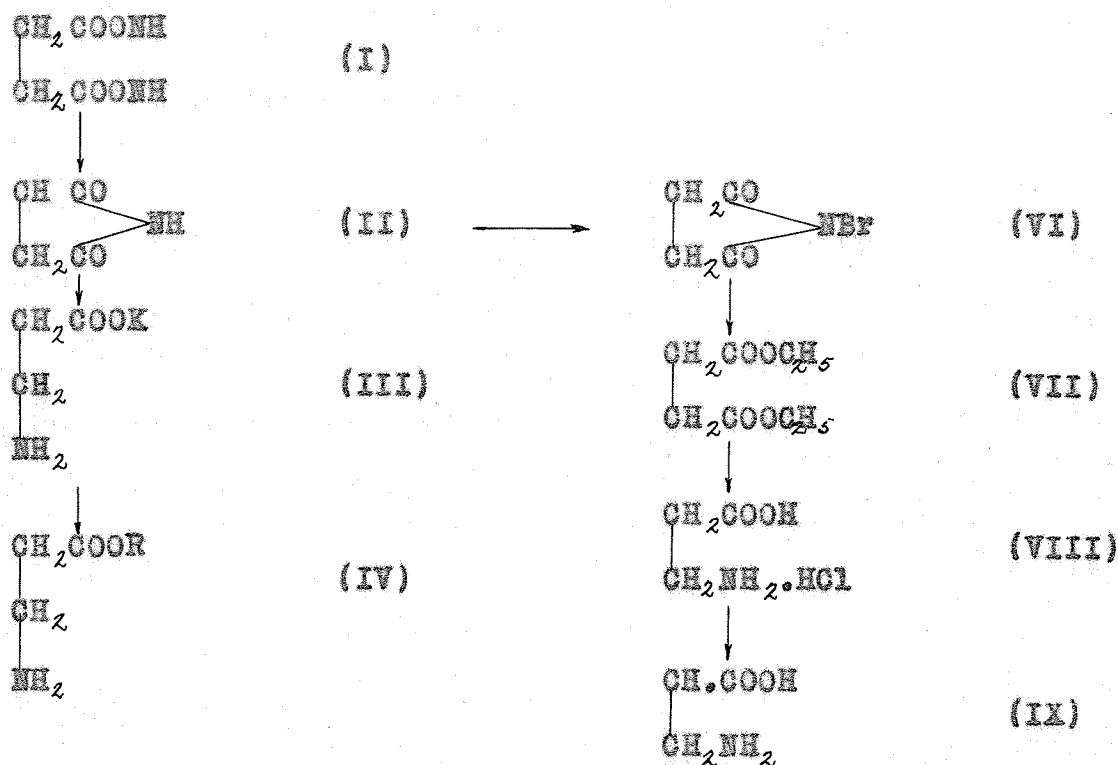
The original papers were not contained in the volumes of the library, and so the following attempts were made with whatever instructions we could glean from the pages of the Abstracts of this paper (59)

EXPERIMENTAL.

150 gms. of ammonium succinate was distilled, yielding 122.5 gms. of succinimide (B.P. 260-289.5°)

100 gms. of the imide was dissolved in an ice cold solution of 40 gms sodium hydroxide, in 250 cc of water. To this was added slowly and with stirring 160 gms. of bromine, a semi-liquid mass separates out, which became solid as the mixture cooled. The product was left over-night to react, and next morning was filtered by suction, pressed on a porous plate and dried.

Bromo-succinimide is a yellow amorphous powder as obtained by the above method, M.P. 172-177°. It was also obtained from hot benzene as colorless tetragonal crystals. The yield of the above preparation was 163 gms.

β - amino-propionic acid.

$NH_2.CH_2.CH_2.COOH.$

30 grams of bromo-succinimide was dissolved in 50 cc. of methyl alcohol, together with 20 gms of sodium methoxide in methyl alchoholic solution. The mixture was heated over a water bath to boiling for a period of about two hours. The resulting solution was then distilled to separate the solvent, and the residue dissolved in water, cooled, extracted by means of ether, and neutralized with hydrochloric acid. The thereal solution was separated, filtered and evaporated. No yield was obtained.

Repetition of this preparation gave no result.

" Condensation of Pyridine and Carbon Tetra-chloride."

------------------------o-o-o------------------------------

Phenol (I) condenses with chloroform, in the presence of sod-
ium hydroxide, with the formation of ortho-hydroxy-benzaldehyde or
salicyl-aldehyde, and p-hydroxy-benzaldehyde (IV). This reaction is
regarded as having passed thru the intermediate stage (II) before
change into the final product (III) or (IV).

The 4-substituted pyridines are allied to p-hydroxy-benzalde-
hyde in that they are both 4-substituted compounds of a simple ar-
omatic ring, but differ only in that the former are derived from the
pyridine ring, while the latter is derived from the benzene nucleus.
However, these two nuclei behave similarly in many reactions, and it
was therefore attempted to prepare the pyridine compounds by a sim-
ilar reaction, using, instead of chloroform, carbon tetra-chloride, and,
instead of phenol, the base pyridine. Should this method be success-
ful it would be a fairly easy method for preparing the 4-substituted
pyridines, which have been prepared only thru complicated reactions.
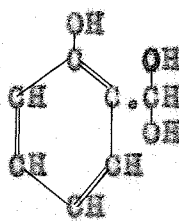The above reactions may be represented as follows:
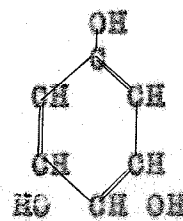
a. Condensation of Phenol and Chloroform.
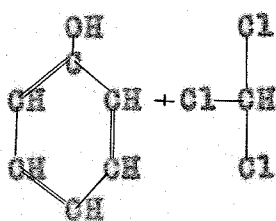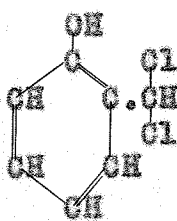
(I)   (II)   (III)   (IV)

b. Theoretical Condensation of Pyridine and Carbon-tetrachlorid
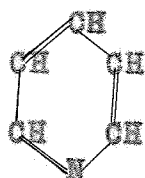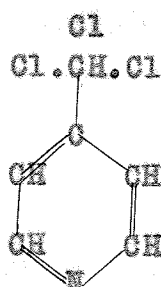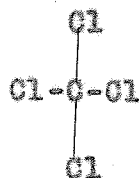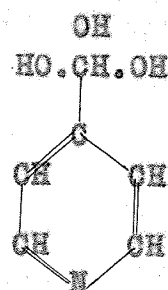
(V)　　　　　　　　　　　(VI)　　　　　　(VII)

EXPERIMENTAL.

Following the plan of the Salicyl-aldehyde preparation the condensation was attempted as follows.

Materials　Carbon Tetrachloride　　　　　　80 grams.

　　　　　　Pyridine　　　　　　　　　　　40　　"

　　　　　　Alcoholic Potash　　　　　　　20% solution.

　　　containing ordinary alcohol 560 gms. and potash 112 gms.

Apparatus　A large flask (F), 2-litres, and round bottomed, was connected to the condenser (C) by means of an adapter (A). Thru the cork of (F) passes also a dropping funnel (D). The flask was placed in the water bath (B) for heating purposes.

Procedure　The alcoholic potash was made and mixed with the pyridine in the large 2-liter flask. This mixture was then placed on a large water bath, and warmed gently. The carbon tetrachloride was poured into the dropping funnel and allowed to drop slowly upon the warmed mixture. Reaction took place with the darkening of the mixture. The whole was then heated for three hours at the boiling point of the solution, after which a black tarry mass appeared at the bottom of the flask. Bumping may be avoided by using pieces of a porous plate.

50 cc. of distilled water was added, and the mixture subjected to steam distillation until all traces of carbon tetra-chloride and pyridine had disappeared from the distillate. The tarry matter was then filtered thru a wet filter and the filtrate, which was of a dark brown color, was neutralized with 4% acetic acid, addition of which caused a change in the color to a lighter shade. The resulting solution was employed in the following experiments:

a. Attempts at Decolorization.

(1) A portion of the solution was shaken up with ether in an attempt to extract the color from the solution. This was unsuccessful.

(2) The original solution, un-neutralized, was shaken up with ether, no color was extracted.

(In the above cases a brown precipitate settled out on standing.)

(3) The solution was boiled with charcoal and filtered. A clear yellowish solution was obtained.

(4) The original un-neutralized solution was boiled with charcoal and filtered. No change in the color of the solution resulted.

In these two cases no precipitate was obtained.

Result - No color could be extracted with ether, but a brown precipitate obtained, boiling with charcoal does not change the color, but the filtered solution gave no precipitate. In the first two cases, therefore, the precipitate must have been in suspension in the solution.

b. Attempts at The Preparation of Metallic Salts

If these compounds are 4-substituted compounds, metallic salts should be obtained, especially the copper salt, which is characteristic of this series of substances.

(i) Using the neutralized Solution.

(1) with lead acetate - a brown flocculent precipitate obtained

(2)   " copper   "   - "   " "   "   "   "

(3)   " calcium "   - "   "   "   "   "

(4)   " acetic acid - "   "   "   "   "

(5)   " mercuric chloride "   "   "   "

together with a heavy white crystalline precipitate
on standing.

(ii) Using solution (a 3)

This solution has been boiled with charcoal and filtered.

(1) with lead acetate - no result.

(2) with copper acetate - no result.

(3) with calcium acetate - no result.

(4) with acetic acid - no precipitate.

(5) with mercuric chloride - a slight brown precipitate, with heavy
shining plates on standing.

(iii) Concentration.

A portion of the neutralized solution was concentrated by
heating over a water bath for some time. The brown precipitate
separated out at first, followed by a crystalline substance. When
the solution had boiled down to 1/4 its original volume it was
allowed to cool and the mixture filtered, a dark brownish black
solution being obtained. The following reactions were tried:

(1) with lead acetate - no precipitate - on standing overnight a

                              slight brown precipitate appeared.

(2) with copper acetate - same as above.

(3) with copper acetate - same result.

(4) with acetic acid - slight cloudiness and precipitation overnight.

(5) with mercuric chloride - heavy brown precipitate.

(iv) Experiments with salt obtained in iii.

The salt which separated out in the above concentration was dissolved in water, a dark brown solution being obtained.

(1) The solution on standing gave a brown precipitate.

(2) The solution added to copper acetate also gave a dark brown precipitate.

(3) The solution was allowed to stand for one hour and then the precipitate filtered off and shaken with copper acetate - also the same dark brown precipitate.

R E S U L T S .

It will be seen, therefore, from the above list of experiments that the condensation does not produce a 4-substituted compound which separates out in the process described for the purification of 4-hydroxy benzaldehyde. The reaction took place in a similar way, in both cases the color change was observed on the addition of the chloro-compound. The steam distillation removes the excess of both these reaction products, the only difference is that instead of a red resinous substance settling out we have a black tarry mass. The similar results given in the first series of experiments cause the suspicion that the precipitate was not totally filtered.

and, therefore, the filtrate was again carefully subjected to suction filtration, the resulting mixture yielded, however, the same brown flocculent precipitate.

The precipitation of the brown flocculent substance, in all these experiments, appeared identical in all cases, it corresponds and agrees with each other in its physical properties. That it is a colloidal substance may be gathered from the fact that it passes thru filter paper, while the filtered solution gave the appearance of a true solution, yet on addition of the various reagents a brown precipitate settles out in every case, except when it has been boiled with charcoal and filtered, when all the suspended matter would have adhered to the charcoal, and thus the filtrate gave no precipitate on addition of the above reagents.

The precipitate obtained is insoluble in ether and common organic solvents, and may be taken therefore as the tarry matter separating out during the reaction.

Therefore, since no substance could be obtained from the re- action product that gave any indication of being a 4-substituted compound, and since all 4-substituted pyridines yield characteristic salts easily on being shaken up with copper acetate, therefore, we may conclude that the experiment was a failure in attempting to prepare the 4-substituted pyridines thru the condensation of car- bon tetrachloride and pyridine.

" Attempts with Triacetonamine "

Triacetonamine, C H NO, or 2-2-6-6-tetra-methyl-hexa-hydro-
4-piperidone, has the constitutional formula

$$(CH_3)_2 C \quad \underset{NH}{\overset{CO}{\underset{CH_2 \quad CH_2}{\bigcirc}}} \quad C(CH_3)_2$$
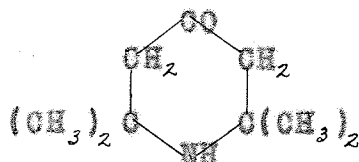
This substance furnishes another possible starting point for
the preparation of a 4-substituted compound, allied to meroquinine.
If a propyl group can be added to the 4-position, which may be
brought about by Grignard's synthesis with the required reagent,
then this compound differs from meroquinine only in that it has
not the vinyl group in the 3-position, and also in the possession
of the dimethyl groups in the 2 and 6 positions.

This substance has been used in the preparation of many pip-
eridyl derivatives, and therefore it was attempted to prepare a
substance allied to meroquinine from this product. It may be first
subjected to Grignard's synthesis, producing thereby a substance
of the formula (II) and then on elimination of the methyl groups,
it will yield the substance (III) a 4-substituted piperidine deri-
vative thus

$$(CH_3)_2 C \quad \underset{NH}{\overset{CO}{\underset{CH_2 \quad CH_2}{\bigcirc}}} \quad C(CH_3)_2$$

(I)

$$(CH_3)_2 C \quad \underset{NH}{\overset{CH.COOR \atop OH}{\underset{CH_2 \quad CH_2}{\bigcirc}}} \quad C(CH_3)_2$$

(II)

$$\underset{NH}{\overset{CH.COOR \atop CH}{\underset{CH_2 \quad CH_2}{\overset{CH_2 \quad CH_2}{\bigcirc}}}}$$

(III)
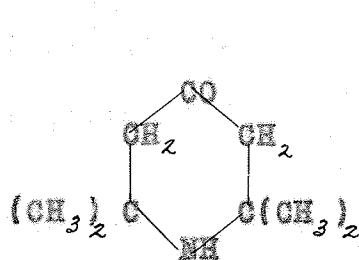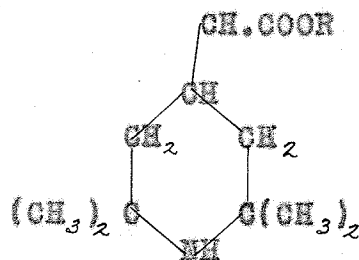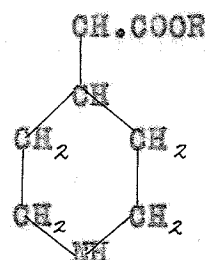
Triacetonamine was prepared by Heintz (60) thru the condensation of a molecule of diacetonamine, with acetone, with the agency of ammonia. The methods of purification were also determined by the same author. Later investigators also succeeded in preparing the substance from other sources, viz; from mesityl oxide, (61) phorone (62) by Guareschi's reaction (63) etc. However, the original method seems to be the best one.

The original method was to prepare in the first place diacetonamine by leaving acetone, which has been saturated with ammonia, for two or three weeks, adding then to this solution of oxalic acid, thus giving the oxalate, which can then be extracted by the use of hot alcohol (64). From this product triacetonamine was obtained by prolonged boiling with acetone, the base to be later extracted by crystallization of the oxalate (65). These methods are, however, tedious, it takes a long time to complete and it yields poor results.

In a recent publication (64 a) a modified method for the preparation of diacetonamine was published, which gave fairly good results. Together with acetone was placed some calcium chloride, and the ammonia then introduced. The absorption of ammonia was considerably faster, and accompanied by some heat which, therefore, necessitates the use of a reflux condenser in order to prevent the loss of

60. Heintz.-Chem. Centr. 1874. 372.

61. Guareschi -

62.   J.C. Abst. 1875

63.   B. 1899 - 32,2244

64. Sokoloff and Latschinoff - B. 7,1384.
   a. A.E. Everest (J.C.S. trans..) 115.1.588 (1924)

aceton. The mixture was then left,instead of three to four weeks
as in the original preparation, it was necessary to lay it aside for
8-10 days, when the reaction is practically complete. By that time
the ammonia absorbed by the calcium chloride has been gradually
liberated,and the water,liberated by the reaction,dissolves the
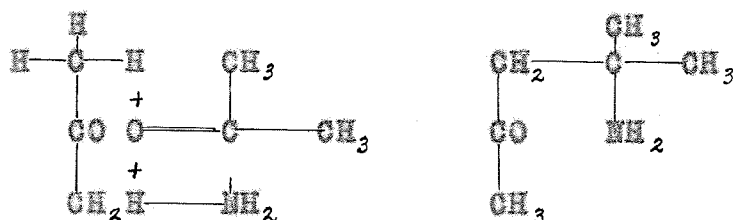
Acetone + ammonia = Diacetonamine.

calcium chloride, giving an aequeous layer with the amine layer
on top. This, therefore, is of great advantage in the separation
since the amine layer can thus be obtained free from the aequeous
product of the reaction. The alcohol needed in the subsequent
extraction also does not need to be of such high percentage, and
the yield is much better than the original method. A comparison
of the two methods may be seen from the following table,
where (a) represents the method using calcium chloride and (b) the
original method.

	(a)	(b)
Acetone taken	1045 gms.	2100 gms.
" recovered	45 "	1100 gms.
" used	1000 gms.	1000 gms.
Alcohol used	3 liters of rectified spirits	2½ liters absolute.
Time of keeping	8-10 days	24-28 days
Number of saturations	1	4
Yield	725 gms.	440 gms.

Triacetonamine was prepared from diacetonamine by condensation with a further molecule of acetone. The acetone was dried over calcium chloride, and then mixed with the diacetonamine and boiled for some time. Triacetonamine forms, and can be obtained thru the oxalate

$$CH_2 \begin{array}{c} CH_3 \\ | \\ C-CH_3 \\ | \\ NH \\ | \\ H \end{array} \quad + \; O = C \begin{array}{c} CH_3 \\ CH_3 \end{array} \qquad \begin{array}{c} CH_3 \\ | \\ CH_2-C-CH_3 \\ CO \quad NH \\ CH_2-C-CH_3 \\ | \\ CH_3 \end{array}$$
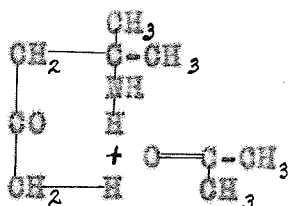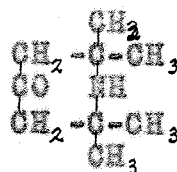
Diacetonamine + acetone   Triacetonamine.

EXPERIMENTAL

Apparatus

A. Ammonia Generator.

A 1-liter round-bottomed flask fitted with a two-holed cork, thru which passes the safety tube and the delivery tube. This is partly filled with ammonia and placed in a water bath.

B. Drying Towers.

3 drying towers filled (a) with calcium oxide in lumps, (b) similarly filled, and (c) with sticks of caustic soda.

C. Reaction Chamber.

A large 2-liter round bottomed flask fitted with a two-holed rubber stopper, one used for the gas inlet and the other attached to an adapter, which in turn is connected to a reflux condenser. The second hole is connected with the former end of the apparatus.

Procedure.

Ammonia water was placed in the generator and heated, the gas given off being then led to the drying towers, the two sections being joined by rubber connexions to a T-tube which acts as a safety valve.

In a large 2-liter flask was placed 500 gms of acetone, previously dried over calcium chloride, together with 100 gms of calcium chloride. By connecting the apparatus up as shown in the diagram dried ammonia was passed into the acetone until a weight of 700 gms. was obtained. The large flask was then disconnected and left to stand, with occasional shakings for 7-8 days, at which time the mixture has separated into two layers, this separation starting at the first day or so, and as the reaction proceeded the calcium chloride became more and more liquid, while the upper layer gradually passed from a pale yellow to a red color. After 10 days the two layers were separated as far as possible by decantation. A further quantity being obtained by ether extraction of the aequeous solution.

The upper layer, containing di-acetonamine and smelling strongly of ammonia was then connected with a suction pump and air dried by passing thru concentrated sulfuric acid in drying towers was drawn thru the mixture till no smell of ammonia could be detected.

An equal amount of acetone, (500 grams) previously dried was added and the whole boiled on a water bath for two days, when a dark red solution was obtained. This was cooled and an amount of ordinary alcohol in which was dissolved 200 grams of oxalic acid was added

Triacetonamine oxalate precipitated out with evolution of heat as a light brown precipitate, and this was filtered off in the Buchner funnel, after the solution has been acidified. The filtrate was retained. These crystals were then dissolved in a little water and evaporated on a water bath to a small bulk and much crystals separated out, finally filtering by suction, the filtrate also retained.

The crystals were again dissolved in water, the insoluble salt filtered, and caustic potash added until alkaline. This solution was then extracted with ether and on evaporation of the solvent triacetonamine crystallizes out, the first few extractions being colored with the red substance, but the later extractions were not dyed. These crystals were then purified as far as possible by fractional crystallizations and drying between blotting paper. Resulting crystals were still tinged by the red dye, and not absolutely colorless.

R E S U L T S.

	I	II	III
Acetone	500 gms	500 gms	500 gms
Calcium Chloride	200 gms	100 gms	150 gms.
Time of keeping	10 days	12 days	11 days
Addition of acetone	500 gms	400 gms	350 gms.
Time of boiling	24 hours	18 hours	36 hours
Oxalic acid	200 gms	200 gms	110 gms.
Alcohol (ordinary)	700 cc.	400 cc.	400 cc.
Solution (diaceton)		487 gms.	310 gms.
Yield	50 gms.	40 gms.	60 gms.

NOTES.

I. Saturations with ammonia. Nov. 9 ----- ammonia added 60 gms.

                                " 10 ----- " " 110 gms.

    Error - amount of calcium chloride added should have been only

                   100 gms.

II. Required quantities employed.

On the first saturation only 60 gms of ammonia could be added and no more. The next day, after letting it stand overnight, still no more addition could take place, and therefore 40 gms. of calcium chloride was again added, and this time absorption would not take place again. The yield obtained from this preparation was very unsatisfactory, hard to purify and contains much coloring matter. The initial extract being nearly black in color. The crystals obtained when dissolved in ether yielded, besides the ordinary yellow ethereal solution of triacetonamine, a sticky red oily layer, which appeared in the bottom of the vessel. It crystallizes in arborescent clumps, quite distinct in properties from the tri-acetonamine.

III. On account of the small yield of preparation II a large amount of calcium chloride was employed with the intention of passing in just the required amount of ammonia. However, absorption was so rapid that the required amount 100 grms. was easily passed, and when the whole was weighed it was found to have absorbed 132 grams of the gas. The time required for this absorption was only 5½ hours as compared with the 18 hours in case I.

Experiments with Triacetonamine.

The triacetonamine obtained above was impure, and contained as
an impurity some reddish coloring substance. It was therefore at-
tempted to prepare the benzoyl derivative in order to see whether
it were possible to attain purification thru that compound, and also
using the benzoyl group to protect the amino group during the sub-
sequent reactions. However, this substance, being both a ketone and
an amine, this benzoylation may take place with either one of the
two groups, and therefore it will be necessary also to ascertain
in which position the reaction has taken place.

Schotten-Baumann's reaction is the usual method by which ben-
zoyl derivatives are prepared, this method being to add the reagent
to the base, and make alkaline with caustic soda solution, heat gently
until the smell of benzoyl chloride disappears, and the benzoylated
compound separates out as an oil or a solid. This method giving
negative results, variations of this was employed to no effect, a
summary of the experiments already performed being given below.

I. Triacetonamine and benzoyl chloride Gently Heated.

a. Benzoyl chloride was added to twice the amount of triaceton-
amine, and gently heated, the crystals gradually melted giving a semi-
viscuous brownish melt. Strong caustic soda solution was added, the
mass instantly changed to a white solid, and when the smell of the
chloride has disappeared the solid was pressed out on a porous plate
and dried, the crystals obtained melting at 160 C, and also soluble in
water.

b. A weak solution of the above NaOH was used, with a similar
result, the product being soluble in alkalies.

c. The reaction mixture was cooled in a tap suddenly, the resulting substance being the same as those obtained above.

d. Instead of NaOH, a solution of sodium carbonate was employed with similar results.

Benzoylation evidently did not take place, as the solid obtained was soluble in alkalies, and having a melting point of 160 it may be benzoic acid.

II. Triacetonamine and Benzoyl Chloride In The Cold.

a. The base on addition to the reagent gradually dissolved, with slight evolution of heat and gas. The crystals pass from the solid thru the semi-viscuous stage to a yellowish liquid. A solution of NaOH (1:1) was added, and the liquid mass instantly changed to a yellowish mass with much evolution of heat. The solid was then washed with alkaline water, pressed out on a porous plate and dried. The substance in this case did not melt even up to the temperature of 220-250 C. and also soluble in alkalies.

b. Instead of a 1:1 solution of NaOH, a 1:4 solution was employed, in which case the reaction was not so rapid, an oil was seen to separate out, but this disappeared if shaken up in the alkaline water, giving a yellow solution. The solution on extraction with ether, and evaporation of the solvent yielded a solid melting at 24-57.

c. The solution was 1:8 in this experiment, the oil obtained crystallized, and after purifying gave a melting point of 56.

d. Cooling suddenly under the tap, gave smaller crystals settling down, the crystals melting at 24-39.

In these cases the reaction was attempted without heating the mixture, and though heating seemed to have occurred in every experiment the resulting substance gave the melting points of the original base.

III. The Reaction Mixture Refluxed.

a. The reaction mixture in this case was neutralized and then refluxed, at the beginning of which dense fumes were given off, and later on, as the temperature reached a higher point, colorless plates of the base was seen to be deposited on the sides of the cooler parts of the containing flask, leaving a brownish solid in the bottom. On addition of NaOH this solid turned into an oily substance, further addition of water dissolving the product, while the solution on extraction with ether yielded a solid with the melting point of the base

b. Longer heating was done in this experiment, the result being the same as the above.

c. The mixture was heated strongly in this case, the substance melted and started to boil. It was then taken off and poured into alkaline waters when a solution smelling of benzaldehyde was obtained.

Thus by refluxing the material, still no change seemed to have taken place, the resulting products gave the melting points and reactions of Triacetonamine.

Attempts At The Condensation
Of Triacetonamine.

Reformatsky's Reaction.

Not being able to attain the benzoylation of the base, we then attempted to accomplish Reformatsky's reaction upon this product, and accordingly the following experiments were made.

A. With acetoacetic acid.

a. 2 gm of Triacetonamine was dissolved in 15 cc. of dried ether and to this was added 3 cc of ethyl mono-chloracetic ester and some zinc turnings. No reaction took place in the cold, and on heating the mixture in the water bath boiling took place, the liquid evaporated and the solid left was a mixture of triacetonamine, the ester and the zinc turnings.

b. Reaction was tried with benzene as a solvent, with also a negative result.

c. The metal was changed using zinc dust as the metal, and later using magnesium powder, also with a negative result.

B. With iodo-propionic ester.

a. With zinc turnings, no reaction took place in the cold, on boiling for a while the resulting product on separation gave again the original substances.

b. Zinc dust and also magnesium powder was employed, later experiments using benzene as a solvent, and all yielded no result.

As this substance sublimes at a fairly low temperature it was tried to purify the substance by sublimation, but the yield was small, and the amount obtained was not enough for experimentation.

It was also found that former investigators have proved this substance to be a mono-hydrate, this fact perhaps being the cause of the failure of the above experiments. Therefore it was attempted to dehydrate the substance. It has been dehydrated according to Beilstein by the use of dried ether, and the process was attempted. However, the yields obtained were still hydrated giving melting points between that of the hydrate and the anhydrous substance. It was necessary to leave the work at this point.

Reactions with Ethyl Cinnamate.

Compounds of quinoline with the 4-position substituted by another group, form the basis of the quinoline nucleus of the cinchona alkaloids, the decomposition of quinine and cinchonine yielding quinic and cinchonic acids respectively. These two substances have been synthesized by various investigators during the last few years, an account of which is given in a recent paper "Ueber der Synthese der Chininsaure" by Halberkann (67) and a later notice by Kauffmann (68).

The two main methods are those done by the above authors, Halberkann's method was to condense p-anisidin (I) with mesoxalic acid (II), obtaining thereby p-methoxy-di-oxindol carbonic ethyl ester (III) treatment with potash giving rise to p-methoxy isatin. (IV). This substance was subsequently condensed with pyrotartaric acid yielding methoxy-6-quinoline di carboxylic acid (V), elimination of carbon dioxide forming quinic acid (VI).

Kauffmann's preparation was attained thru Skraup's synthesis using p-anisidin (I) and glycerine, from which was obtained p-methoxy-quinoline (VIII), the nitrile (IX) was then prepared, subsequent conversion into the methyl ester with the alimination of carbon dioxide forming quinic acid.

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67. Halberkann - B. 55, p. 614 (1922)

68. Kauffmann - B. 55, p.614 (1922)

Ethyl Cinnamate.

(XI)

(XIII)

(XIV)

(XII)

(XVII)

(XV)

(XVIII)

(XVI)

$$NaHC \begin{matrix} COOR \\ COOR \end{matrix} \longrightarrow$$

(XIX)

(XX)

$+ \; NaOH \longrightarrow$

(XXII)

(XXII)

(XXIII)

(XXIV)
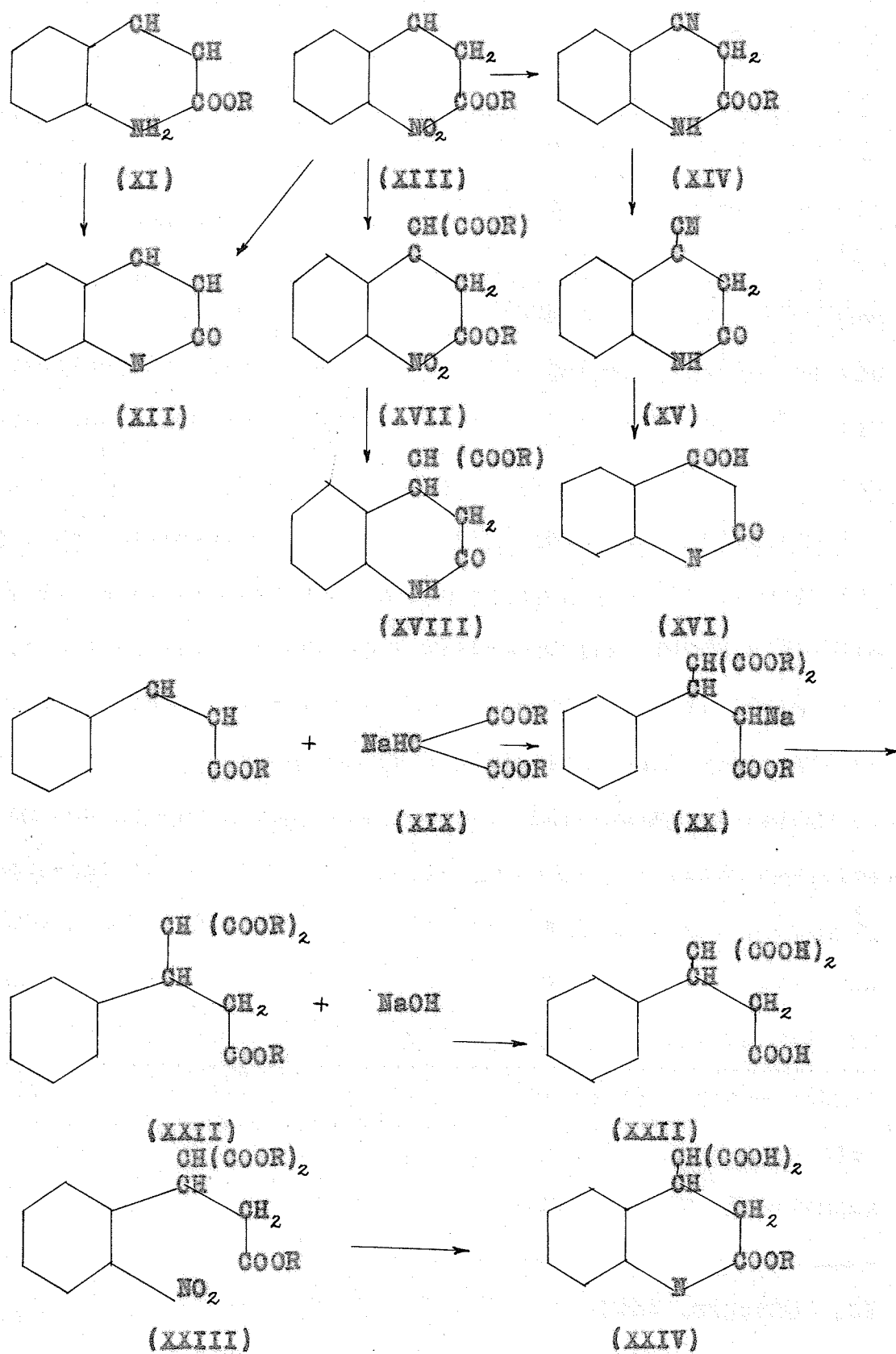
Ortho-amido-cinnamic ester (XI) on heating gives rise to the anhydride (XII) carbostyril, the lactime formula of which is γ-oxy-quinoline. This same substance could be obtained by the reduction of ortho-nitro-cinnamic ester (XIII) with ammonium sulfide (69). Therefore, it was proposed to utilize this reaction, in preparing a cinchoninic acid derivative, by the preparation first of o-nitro-cinnamic acid or its ester, substitute in the β-position of its side chain a nitrile group as in XIV or by Grignard's synthesis with the required reagent prepare a derivative allied to XVII. The nitrile can be reduced, giving the closed ring, as in carbostyril, and also the carboxyl group in the γ-position, thus giving a 4-substituted quinoline derivative, di-hydro-carbostyril γ-carboxylic acid or α-oxy-$\beta\gamma$-dihydro-cinchoninic acid (XVI). Other groups may be substituted at this position, and thus by using different reagents different groups may be substituted at that position, and the substances similar to those prepared by the former workers, as given in the preceding pages, can be synthesized.

Ethyl cinnamate (X) also condenses with sodium malonate (XIX) with the formation of phenyl-glutaric acid (XXII) the intermediate stages are represented as being of the formula represented by XX and XXI. This also suggested the possibility of obtaining a derivative of the formula XXIII by using, instead of ethyl cinnamate, o-nitro-ethyl cinnamate, which substance may then be reduced to a substance having the formula XXIV. These are the objects of the experiments with ethyl cinnamic ester.

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69. Chiozza, 1852.

In order to obtain the raw products of this synthesis it is necessary to prepare first the ester of cinnamic acid, then from that by nitration to prepare the o-nitro-compound, subsequent manipulation to be conducted as proposed.

The method for preparing the ester is the method of Fisher and Speyer, which gave better results than the ordinary esterificatio. The nitration of this product, however, is more difficult a proposition, several methods having been recorded. The ordinary method (70) is to nitrate the acid itself, and separate it by means of alcohol, or to esterify the product of this nitration, and then separate by mean of ether. Ethyl cinnamate and fuming nitric acid may also be used, separation being attained by pouring immediately into cold water, and separating with alcohol. A more involved method was proposed by Muller (71) by which cinnamic acid is added to nitric acid of S.G. 1.48, mixing the pasty mass so obtained with 10 volumes of iced water, washing the residue, and drying on porous plate. It is then esterified with alcohol heating in a closed condenser with a rapid stream of hydrogen, the mass dissolving giving a yellow liquid, and from this the o-ester may be prepared.

Stuart (72) gave fuller instructions for its preparation, the ethyl cinnamate was dropped into fuming nitric acid, cooled with ice and immediately after reaction has finished, to pour into water, and the ester extracted by means of alcohol. Evaporation of the solvent yields the o-nitro cinnamic ester.

70. Watt's Chemical Dictionary pp. 189 vol. ii.

71. Muller - Ann. 212, 122-149.

72. Chas. M. Stuart - J.C.S. Trans. 43,408 (1883)

RESULT.

Ethyl Cinnamate.

$$C_6H_5.CH=CH.COOC_2H_5.$$
----

1. 100 gms of cinnamic acid was subjected to esterification by the
usual method of boiling for some time with sulfuric acid. The yield
was about 50 grams. B.P. 269-270°C.

2. 50 grams cinnamic acid was esterified by the Fisher and Speyer's
method, a better yield being obtained this time.

The above two preparations gave a yield of about 90 grams boil-
ing at 266-267°C.

Ethyl ortho-nitro-cinnamic ester.

$$C_6H_5 \underset{NO_2}{\overset{CH=CH.COOC_2H_5.}{<}}$$
----
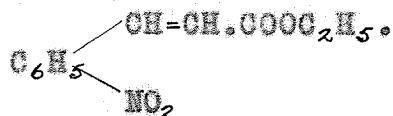
1.   100 grams of ethyl cinnamate was dropped by means of a
dropping funnel into fuming nitric acid colled with ice. The re-
sulting solution was at once poured into ice water, washed, and instead
of a solid, an oily mass was obtained, which was reddish in color. On
washing with alcohol a small amount of white crystals were obtained,
while the filtrate assumed a red color, and the alcohol after evapor-
ation left a red, viscous oil.

2.   Ethyl cinnamate 10 grams was dropped from a funnel into a
mixture of 12 cc. of concentrated nitric acid (S.P. 1.42) and
concentrated sulfuric acid 12 cc. which had previously been cooled
in ice. The contents of the flask was well shaken during the re-
action, fumes of nitrous acid were evolved and vigorous action took
place. When all the ester had been added the whole was immediately

poured into ice water, a semi-solid mass being obtained. The product was then separated dissolved in cold alcohol, a solid gray substance being obtained on filtration. The filtrate, however, yielded no solid on evaporation, but remained as a reddish oil even after long standing.

This method was repeated, care being taken that the temperature does not rise above the freezing point of water, and this time a slight amount of solid was obtained from the filtrate, but when dried it gave a melting point of 124 and, therefore, is not the o-ester, but more likely the p-ester, which has entered into solution.

III. Later on, Stuart's paper was found, and experiments employing his method were made, with better results, but still unable to obtain the o-ester in pure form.

5 grams of ethyl cinnamate was dropped into fuming nitric acid at 0° C thru a dropping funnel, care being taken that the temperature should not rise over $2-3^\circ$C, care being taken that sulfuric acid is avoided. Immediately after all the ester has been added the whole mixture was thrown into ice water, a yellowish curdy precipitate was obtained, which was collected on a filter, and washed carefully with ice cold alcohol. The yellow color of the precipitate changed to white and the filtrate assumed a reddish tinge. The alcohol was evaporated off and the residue cooled and thrown into a beaker of cold water, an emulsion was obtained and an oily substance settled at the bottom. On standing overnight this mass crystalized, and was then collected and dried between blotting papers. Yield 1.6 g. M.P. $44-46^\circ$C and then $138-140^\circ$C, and therefore may be said to be

a mixture of the ortho- and para esters, their melting points being 37-40° and 135 C.

Later experiments were tried with similar results, each preparation yielding a reddish colored oil which would not crystallize on standing even for about six weeks. Portions were placed in the vacuum dessicator to see if it would crystallize, but it did not do so after standing for about a month.

As it was quite late in the session that the above experiments were made, and as a series of attempts at the preparation of the pure solid ortho-ester was unsuccessful, attention was directed to other phases of the subject and this part neglected so that the later experiments were not accomplished, only the above having been done.

CH₃COOH appears as CH_3COOH

(I)   (II)   (III)

(IV)   (V)

H.COOH → $H.COOH$

(VI)   (VII)

HCHO
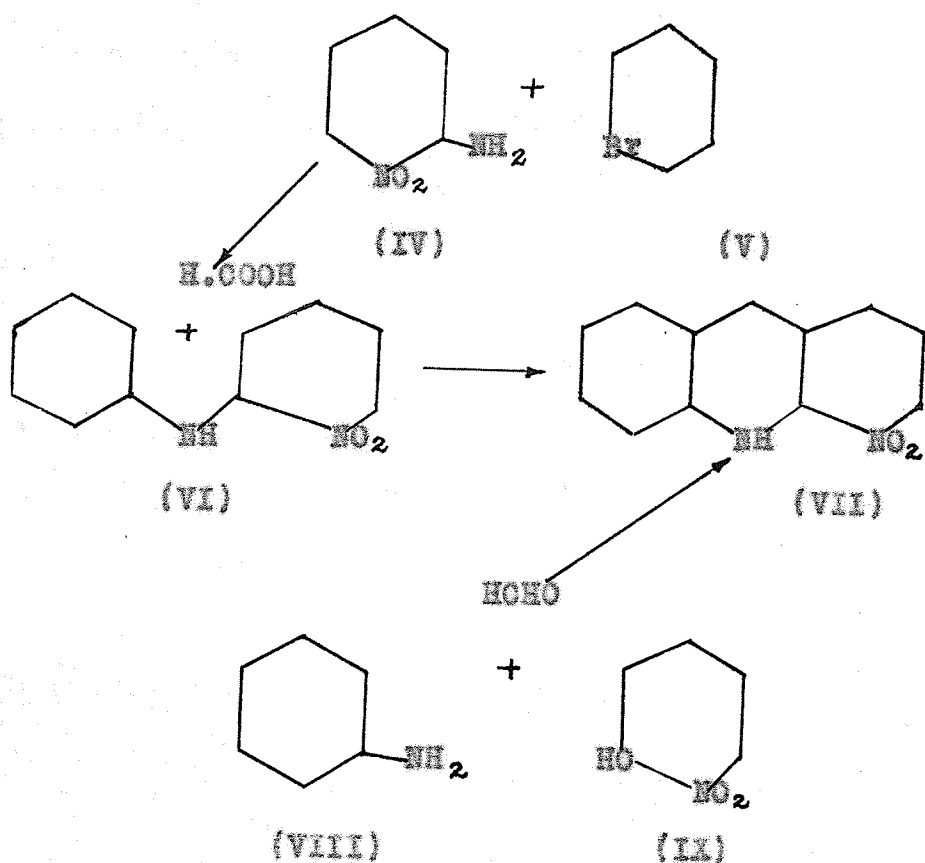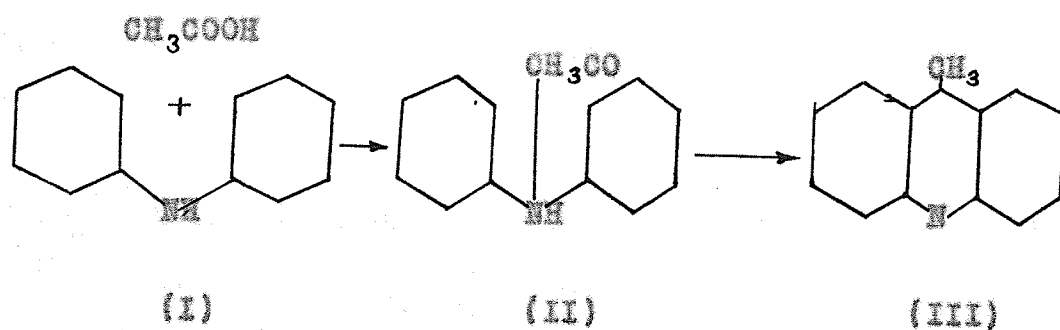
(VIII)   (IX)

" Attempts At The Preparation of Nitro-Acridine "

Formulae I-III - Bernthsen's synthesis

Formulae IV-VII - Proposed synthesis of Nitro acridine from Ortho-nitro-diphenylamine and formic acid.

Formulae VIII-IX - Proposed synthesis of from aniline, ortho-nitro-phenol, and formalin.

" Attempts At The Synthesis of Nitro-acridine. "

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from o-nitro-diphenyl-amine.

9-methyl acridine (III) was synthesized by Bernthsen (73) by the condensation of di-phenylamine (I) with glacial acetic acid, in the presence of zinc chloride, yielding by this reaction N-acetyl-diphenyl-amine (II), the dehydration of which forms the acridine ring, with the methyl group in the 9-position.

It was attempted to accomplish a similar synthesis by the use of ortho-nitro-diphenylamine (VI) yielding thereby a derivative of nitro-acridine (VII) using formic acid and formaldehyde, in order to obtain this acridine derivative.

At the same time another preparation was conducted in order to attempt the synthesis of the same compound by the condensation of o-nitro phenol, aniline, and formic acid.

Bernthsen's synthesis was employed in the following preparation, with crude o-nitro-diphenylamine which was prepared by Goldberg's method (74) by the condensation of o-nitro-aniline (IV) and bromobenzene (V) in the presence of methyl iodide, and this was then condensed as demanded by the acridine synthesis.

RESULTS.

The first two or three condensations failed on account of insufficient care in regulating the temperature of the reaction

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73. Bernthsen   Ann. 224,34 (1884).

74. Goldberg,   Ber. 40,4541. (1907).

The products in all these cases was a porous, light, frothy material which on cooling solidified, and yielded a black charred powder.

An experiment conducted on a small scale, with slow and careful heating yielded better results and accordingly, the later experiments were made with greater care. The results were as follows:

1. O-nitro-diphenylamine   10 grams

   Formic acid   15 cc.

   Zinc chloride   18 gms.

The nitro-diphenylamine was added to the formic acid, in a small round-bottomed flask (50cc) and the zinc chloride introduced. The solution, which was initially of a reddish color, gradually deepened in color, the mixture around the zinc chloride assuming first a red color, which later spread thru the whole mass, finally causing a change in color from dark red to purple, and then to black. Evolution of heat was noticed around the sticks of zinc chloride, and on allowing to stand for a few moments the mixture may be seen to separate into layers, a creamy colored layer on top of a dark brown oily portion. This was then placed into a water bath and heated at the boiling point of water for one hour, the vapors being allowed to escape. After this period, the mixture became homogeneous and a strong smell of acetic acid began to be evolved. The substance was then transferred to the oil bath, heated at about 60 and very carefully raised to 100 degrees, and there allowed to remain for about half an hour, subsequently raising the temperature slowly to about 190°C, this procedure taking at least two hours.

Should the rise be too abrupt, the mixture will suddenly froth

up at about 175-180°C and a black charred mass obtained, but if
sufficient control of the temperature was taken, the mixture will
remain in a liquid form even up to 200°C, boiling gently all the
time. After heating for some time, the melt turned black in color,
and tarry substances began to separate out on the sides of the
flask. During the heating acetic vapor was evolved.

After being kept at 190° for about 10-14 hours the substance
was removed from the bath, and allowed to cool down to about 100°.
At the same time equal volumes of sulfuric acid and water was
mixed, giving thereby a hot mixture of 50% sulfuric acid. The cool
melt was then poured into a large round bottomed flask, (250 cc.)
and the hot acid poured into ~~mixtge~~ it until all was in solution.
The small flask in which some of the resinous matter still remained
was then washed with hot acid, the resinous matter in both filtered
off, and extracted finally with hot, very dilute sulfuric acid
the extracts were then mixed and allowed to cool.

Animal charcoal was then added to the solution, and then was
filtered off at the suction pump, the resulting solution being a
greenish fluorescent solution. The solution was then precipitated
with ammonia, a floculent precipitate being at first obtained, while
the material that separated out later was more solid in character.
This mixture was allowed to stand overnight, and then filtered by
suction on the next day, the solid being retained as the substance
desired. The filtrate was inadvertently left aside for a few days
when a whitish solid separated out from the solution. This was
later collected and found to have the properties identical with the

main product, but the yield was not large enough to justify the manipulation.

The yield was then washed thoroughly with ammoniacal water, transferred to a porous plate, and left to dry, the product being of a brownish color, mostly amorphous, powdered and here and there seemed to show a crystalline tendency. Yield obtained was 17.9 g.

This preparation was repeated, the yield being a little larger and of a darker color than the former. The same quantities of substances were used of the various materials, but the yield was different. As far as can be ascertained there was no difference in the reaction, nor were there any differences in the manipulation of the substances.

"The Condensation of Aniline, O-nitro-phenol, and Formic Acid."

No reference to such a reaction can be found in the literature available, and so experiments were tried to affect the above condensation hoping to prepare in this way nitro-acridine. The reaction may be stated as being accomplished thus; the hydroxyl group condenses with the amino-group of the aniline, this yielding the substance VI, further condensation with formic acid, closes the ring with the formation of nitro-acridine (VII).

EXPERIMENTAL.

9.3 gms. aniline

13.9 gms. of o-nitro-phenol

20 cc. of formalin.

The o-nitro-phenol was added to formalin and 100 cc. of water. No reaction took place. The phenol did not dissolve, hydrochloric acid was added to acidify the mixture. Aniline in hydrochloric acid solution was then added, a slow and gradual deepening in the color took place, with the evolution of a slight amount of heat. This was then placed in the water bath, refluxed for about half an hour. After a little while a flesh colored substance was produced, which later turned into a curdy mass, and finally became a reddish mass, with a red colored solution in the holes of the mass.

The substance while hot was instantly poured into a flask and well shaken up, with a soda solution, and was then left to cool. The mixture, when filtered from the soda solution of the phenol, was thoroughly washed with water until the filtrate gave no precipitate on acidification. The solid remaining was left on the porous plate to dry.

Different quantities of the different substances were used
and the following results obtained:

	I.	II.	III.
Aniline	9.3 gms.	9.3 gms.	18.6 gms.
Phenol	13.9 "	13.9 "	13.9 "
Formalin	20 cc.	40 cc.	20 cc.
Yields	15.5 gms.	17.4 gms.	32.1 gms.

In the first case, the required theoretical amounts were
used, in the second case the amount of formalin was doubled,
while in the third case the amount of aniline was doubled. The
above yield will show that the last gave the best yield.

There is a little difference in the color of the various
products, being in the case of I light yellow in color, in case
II a little darker, and in the last condensation dark yellow.

They are all amorphous powders, and when dry are very light.
It is not soluble in any solvent, tests having been tried with
many substances. It was found to be slightly soluble, but e.g.
in alcohol, methyl alcohol, ethylaceto-tate, ether and chloroform,
we found that it left a trace of their presence on evaporation of
their solvents. They are insoluble in amyl alcohol, benzene,
aniline, benzoic acid, pyridine, acetone, ligroin, carbon tetra-
chlorid and carbon disulfide.

The melting point of this substance cannot be determined,
though several attempts were made. This property seemed to show it
to be a mixture, as the melting points obtained were very indefinite.

SUMMARY.

The work presented in the above pages may be briefly summarized here. Many different methods have been proposed for the preparation of compounds allied to the various derivatives of the decomposition products of cinchona alkaloids. Several methods have been tried, and the investigation closed, but many others were unfinished due on one hand to the limited references available, and on the other hand, to the fact that it was necessary for me to leave before the experiments were concluded, in order to fulfill my present appointment.

1. Attempts with Aceto-Acetic Ester.

A. γ -mono-brom-aceto-acetic ester.

a. The ester was prepared, and the best method was that of the Professor Smith.

b. Purification was attained by heating under reduced pressure of 30 mm. instead of 10 mm. as recommended by Epprecht.

c. In purification of the substance it is necessary to avoid over-heating, and the temperature must be raised slowly and carefully.

d. Never endeavor to purify material in which traces of former decomposition products are present. Distillation flasks in which decomposition has taken place must be absolutely clean before used for the next distillation.

B. $\alpha\gamma$ -di-brom-aceto-acetic ester.

a. Though the pure substance was not obtained, the directions given by Professor Smith gave the best results.

b. Purification is hard to accomplish, Professor Smith states

"I have made the ester several times, but it is exceedingly difficult to purify. It is a white crystalline product which melts at 45-49°, but the highest melting point I was ever able to obtain was 59° and this in only on experiment. In all cases an oil remained which would not solidify even in ice and hydrochloric acid."

C. αy - dicyan-aceto-acetic ester.

a. The proposed method of preparing this substance from the di-brom ester was unsuccessful in the attempts with the crude halide.

The pure halide may yield different results, but this was not attempted on account of the difficulty in obtaining the pure di-brom ester.

2. <u>Attempts with Di-Chlorhydrin.</u>"

Attempts to prepare the dicyanhydrin from dichlorhydrin was unsuccessful, no reaction taking place under ordinary temperatures and decomposition taking place at higher temperatures. No compound could be extracted from the reaction product.

3.   A proposed method for the procedure with cyanacetic acid was given.

4.   Attempts to prepare the di-amine product by the condensation of β-alanine was unsuccessful, due to the inability to obtain the raw product (β-alanine) itself. The reason for the failure of the initial preparation may be due to lack of references on this subject, or substance.

5. Condensation of Carbon tetrachloride and Pyridine.

a. Experiments were made to ascertain whether these substances will condense after the method of the preparation of salicylaldehyde and p-hydroxy-benzaldehyde. The para-compound was the one desired. The two substances evidently reacted, but on following the methods for purification no definite compound could be isolated from the reaction product.

b. A colloidal substance was found, however, on addition of certain solutions, or on standing, but this was identical with the resinous product of the reaction.

c. This attempt can be said to be unsuccessful, for attempts to prepare the copper salt of the products were unsuccessful, and the copper salts are characteristic of the para substituted pyridines.

6. Experiments with Triacetonamine.

a. A method for the preparation of triacetonamine from the crude diacetonamine was given.

b. Diacetonamine can be prepared, employing certain modifications which gives better results than the usual method found in former references.

c. Purification was fairly difficult with the product obtained, the coloring matter being quite hard to rid of.

Benzoylation would not take place with the product obtained (the hydrate), experiments with the anhydrous product have not been completed.

d. Attempts at the use of Grignard's synthesis on the hydrate gave no product, while with the anhydrous substance, a similar result was obtained.

e. Further manipulation was prevented by the lack of material

6. Experiments with Ethyl Cinnamate.

a. In this preparation great care must be made in order to keep the temperature well below -2° C during nitration.

b. Stuart's method is the best method for this preparation, fuming nitric acid and ethyl cinnamate being employed.

c. Pure o-nitro-cinnamic ester was not obtained, due to the difficulty in the purification. Indication of its presence can be seen in that the product melted partly at the M.P. of the desired compound.

d. Further experimentation was impossible on account of the lack of references, and also because no pure ester was isolated.

7. Attempts at the Preparation of Nitro-Acridine.

a. From o-nitro diphenylamine and formic acid.

A yellow condensation product was obtained by this reaction.

Complete investigation of the properties was not made on account of the lack of time.

b. From Aniline, O-nitro-phenol and formalin.

A condensation product obtained which is similar in many respects to the above substance.

Double the required amount of aniline gave the greatest yield.

Analysis of the product gave varying results, tending to indicate that the product is a mixture of substances.

Investigation of the properties also unfinished on account of the lack of time.

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