QUATERNARY SALT FORMATION OF CINNOLINES

by

REES KENNETH POWELL

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF ARTS

in the department
of
CHEMISTRY

We accept this thesis as conforming to the standard required from candidates for the degree of MASTER OF ARTS.

Members of the Department of Chemistry.

THE UNIVERSITY OF BRITISH COLUMBIA

April, 1951

ABSTRACT

QUATERNARY SALT FORMATION OF

CINNOLINE

This study was initially undertaken with a view to preparing quaternary salts of cinnoline simulating the structure of the alkaloid papaverine. This would be possible by the synthesis of two compounds, viz., 6,7-dimethoxycinnoline and 3,4-dimethoxybenzyl-chloride. Some difficulty has been encountered in the synthesis of the former and from experimental evidence now at hand the latter can be considered to be unstable.

Some new examples of quaternary salts of 4-methycinnoline are reported but in general isolation of salts from 4-methycinnoline and benzyl-halides has been found impractical due to their hygroscopic properties.

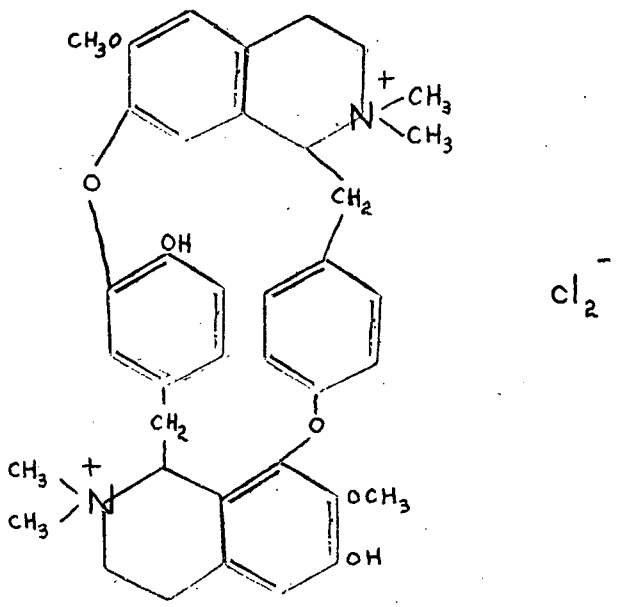
ACKNOWLEDGEMENTS

The author gratefully acknowledges; the willing and able assistance of Mr. G.G.S. Dutton who has during the course of the investigation been a most helpful advisor; also The National Research Council for material assistance in the form of a bursary. Valuable aid was provided by H.M. Erlendson, B. Garvie, and G. Kilgour who prepared some of the compounds used in this investigation.

CONTENTS

INTRODUCTION

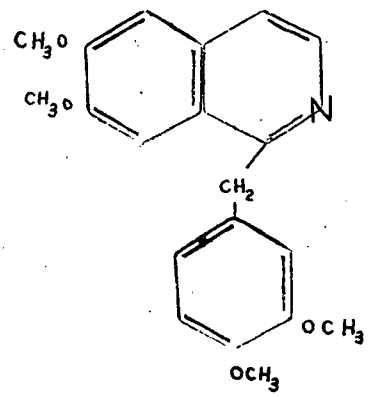
The quest for new and improved molecules possessing varying degrees of pharmacological activity dates back to antiquity. The plant alkaloids have been the greatest storehouse of active compounds, however, due to the great strides in organic synthesis in more recent times, an ever increasing number of active synthetic compounds is being reported. King[41] has recently put forth a plausible structure for d-tubocurarine cholride (A) a quaternary salt having curariform activity and in part responsible for the arrow poisons of the South American Indians.



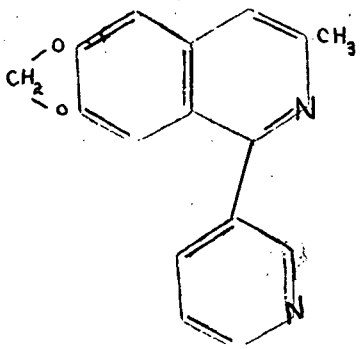
(A)

I

Greig[42] in his account of curariform activity lists in tabular form 58 pages of quaternary ammonium salts, the majority of which have curariform activity. The clinical use of papaverine, (B) and its substitute 6,7-methylenedioxy-1-α-pyridyl-3-methyl isoquinoline, (C) clearly demonstrates the activity of the isoquinoline nucleus.



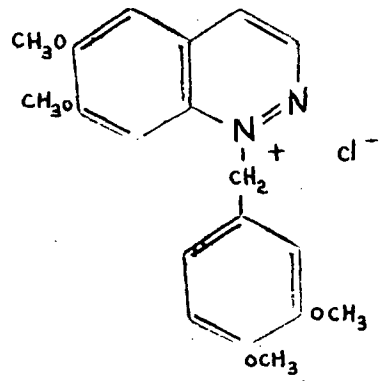
(B)



(C)

Papaverine itself in small doses produces light sleep which does not become deeper as the dose is increased. Larger doses produce reflex irritability and some tetanising action may ensue. In modern clinical medicine it is used for its paralysing action of the smooth muscle of the intestines and blood vessels. Greig[42] has shown that the benzyl group is frequently associated with paralyzing action. In pyridinium, strychninium, coniinium and brucinium salts the N-benzyl derivatives have the greatest curare actions whereas 1-benzylisoquinolines have relaxing actions.

In view of the coincidence between activity of quaternary salts and the benzyl group, the synthesis of a model compound containing the isoquinoline like structure, with a benzyl group attached to a quaternary nitrogen and having a constitution simulating papaverine was attempted, (D).



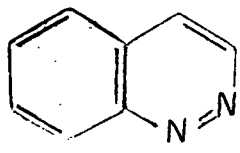
(D)

The only reference in the literature to quaternary salt formation in the cinnoline series is by Simpson[20] who obtained the methyl and ethyl iodides of some cinnoline derivatives, but did not make any reference to possible activity. Leonard[16] in his account of the chemistry of cinnolines reports no suggested use for cinnolines as medicinals.

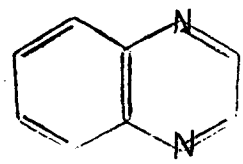
Although the compound (D) has not been prepared an explanation of the difficulties involved in the synthesis of such structures is set out, and a number of new cinnoline salts are reported.

THEORETICAL I

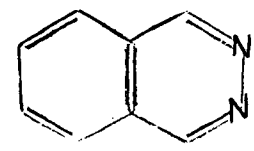
Cinnoline is a hetrocyclic binuclear base having the same numbering as quinoline and containing two vicinal nitrogen atoms. It is the least well known of the four isomeric structures.



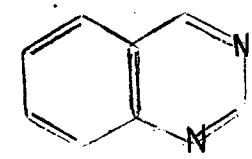
Cinnoline



Quinoxaline



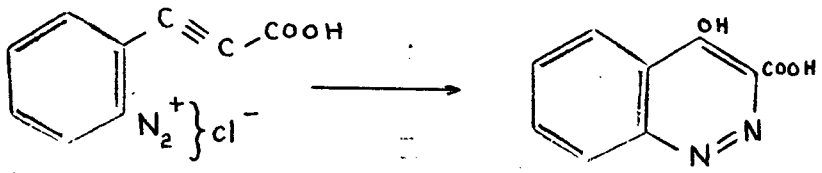
Phthalazine



Quinazoline

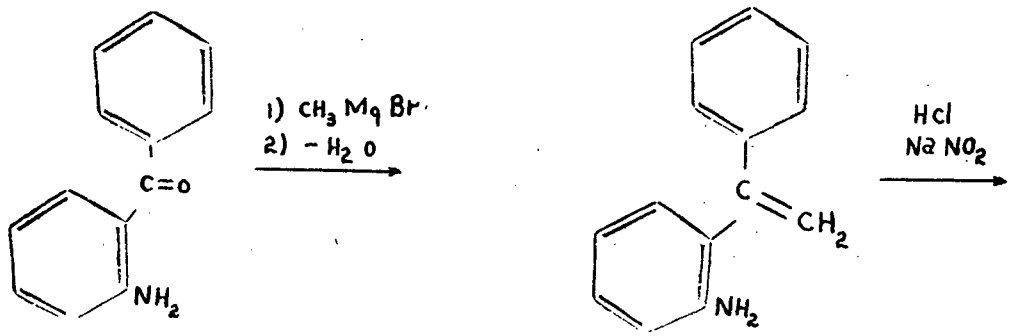
The discovery of cinnoline dates back to 1883 when von Richter[1] claimed to have obtained a derivative of the di-nitrogen base. The compound or its derivatives received little attention until 1945 when Simpson attempted to prepare compounds containing the cinnoline nucleus having antimalarial activity. The discouraging factor in cinnoline chemistry has doubtless been the lack of a convenient method of preparation in contrast to the more readily accessible isomeric compounds.

To date six main methods for the preparation of cinnolines have been quoted. The method of von Richter involves the cyclization of diazotised o-aminophenylpropiolic acids, (1).

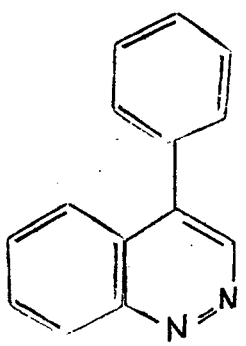


(1)

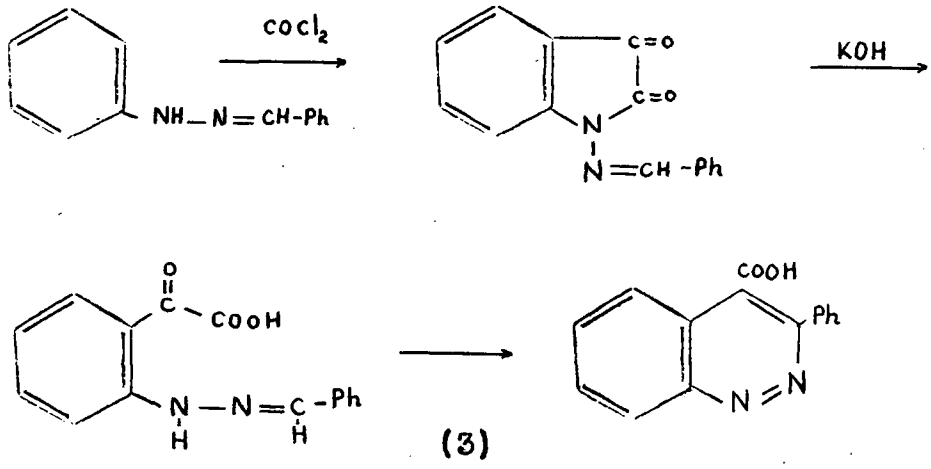
A somewhat easier route to the cinnoline ring system was explored by Stoermer and Fincke [2] using a reaction discovered by Widman[3] involving the cyclization of diazotised o-aminoarylethylenes to produce the corresponding 4-arylcinnolines. The requisite di-arylethylenes being obtained from the appropriate diarylketones and Grignard reagent, followed by dehydration of the resulting carbinols. (2).



(2)

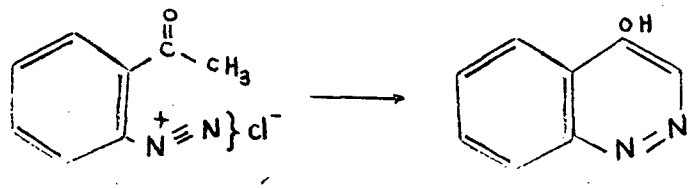


Stolle and Becker[4] in an attempt to prepare N-amino-isatin synthesized 3-phenylcinnoline-4-carboxylic acid by the folling series of reactions. (3)



(3)

In 1941 Borsche and Herbert[5] discovered the acetophenone synthesis of 4-hydroxycinnoline by diazotisation of o-aminoacetophenone. (4) In 1942 Pfannstill and

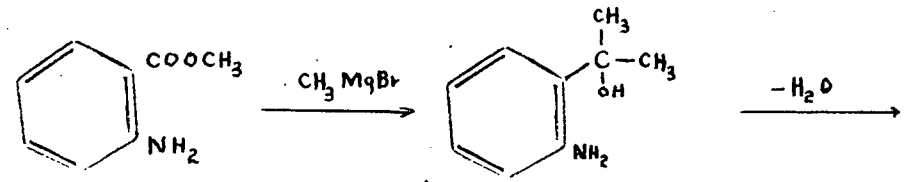


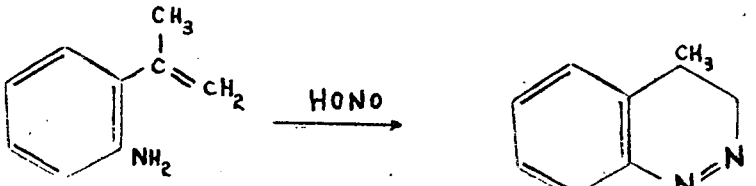
(4)

Janecke[6] obtained highly substituted cinnolines by dehydration of an o-carboxyphenylhydrazine, but their yields obtained were very porr. It is well to state here that in all examples mentioned, except in the case of von Richter, the formation of the cinnoline

was incidental to the main purpose of the investigation. In 1947 Jacobs et al.[7] and Simpson[8] obtained 4-methylcinnoline by the Widman-Stoermer reaction.

They started from readily accessible methyl-anthranilate and by treatment with methylmagnesium bromide and dehydration, followed by diazotisation and cyclization of the resulting o-iso propenylaniline obtained 4-methylcinnoline in overall yield of 70%.(5).





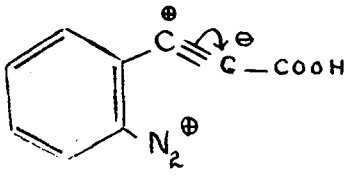
(5)

This was the first synthesis of a cinnoline where the ring was free from functional groups thereby opening the way for a study of the basic properties of the cinnoline nucleus.

Of the six methods available for the preparation of the cinnoline nucleus, Simpson[9] has shown that they all proceed by the same mechanism. He has found that cinnoline formation is dependent on a highly positive diazonium kation and at the same time,

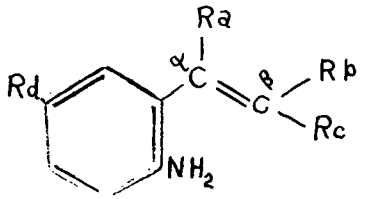
on the availability of electrons at the β-carbon atom of the ortho substituted chain.

Consideration of the mechanism of the Richter reaction shows that the carboxyl of the o-aminopropriolic acid, (6), has a relatively negative β-carbon atom and, at the same time, the inductive effect of the carboxyl group on the ring increases the positive charge on the diazonium kation and so cinnoline formation is favoured.



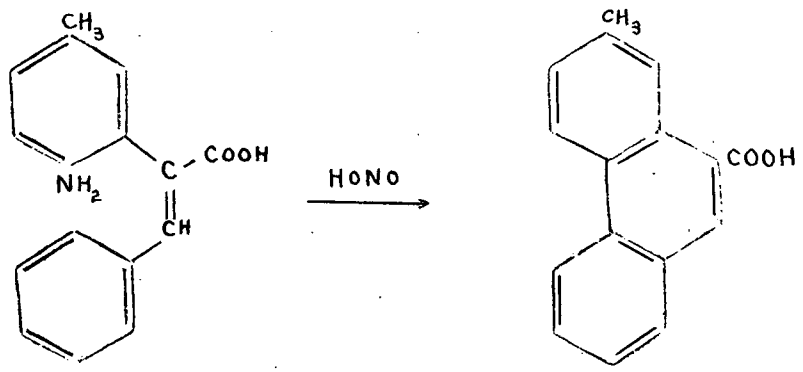
(6)

In order to elucidate the mechanism of the Widman-Stoermer reaction Simpson[10] studied the influence of substituents Ra and Rb, (7), with respect to the ease with which o-aminoarylethylenes ring closed to give cinnolines. Stoermer and Gaus[11] discovered that o-aminocinnamic acid, (7), Ra = H, Rb = COOH, does not yield a cinnoline. Considerably more evidence is available to show that when Rb is negative cinnoline formation is inhibited. In the Pschorr reaction, (7), Ra = H, Rb = Ph, Rc = COOH,



(7)

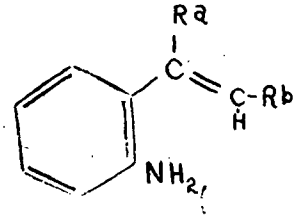
Rd = H, diazotisation leads to phenanthrene-9-carboxylic acid. In any such reaction where both Ra, and Rb ≠ H, cinnoline formation is impossible owing to the absence of the necessary hydrogen on the β-carbon. However in compounds of the type, (7), Ra = COOH, Rb = H, Rc = Ph, Rd = methyl, This hydrogen is available and now the Pschorr and Widman-Stoermer reactions are both possible. Mayer and Balle[12] have shown that diazotisation of this latter ethylene yields 2-methylphenanthrene-10-carboxylic acid, (8).



(8)

The non-formation of cinnoline in these cases is attributable either to the aryl residue on the β-carbon or the carboxyl on the α-carbon or to both. Further Sachs and Hilpert[13] have shown that 2-aminostilbenes in which both α- and β-ethylenic carbon atoms carry hydrogens decompose on diazotisation. However, Ruggli and Staub[14] have shown these were trans derivatives and if the cis forms are used phenanthrene can be obtained in 80% yield. Ruggli and Dinger[15]

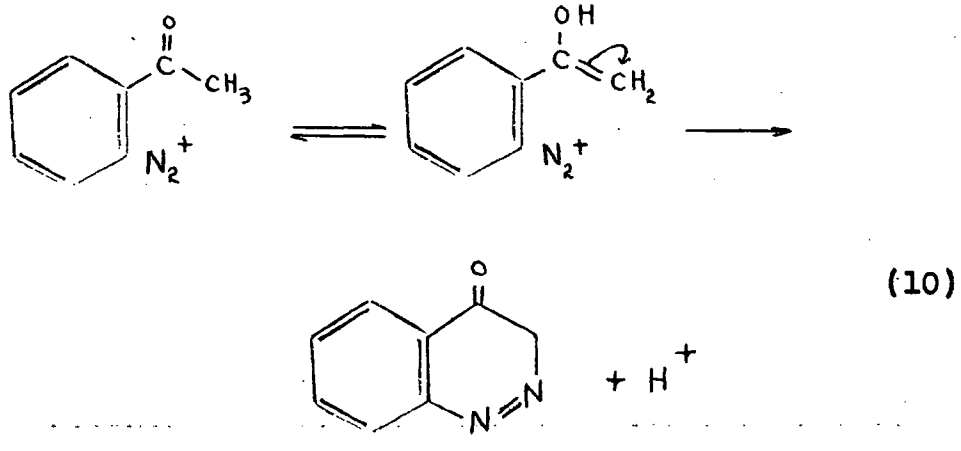
have diazotised other cis- and trans-stilbenes and have inno case isolated any nitrogen containing compounds. We must therefore conclude that cinnoline formation is inhibited when, (9), Rb= aryl or other negative group and , Ra= H, or COOH.



(9)

This is in agreement with Simpson's suggested mechanism, viz, that the β-carbon atom must be relatively negative.

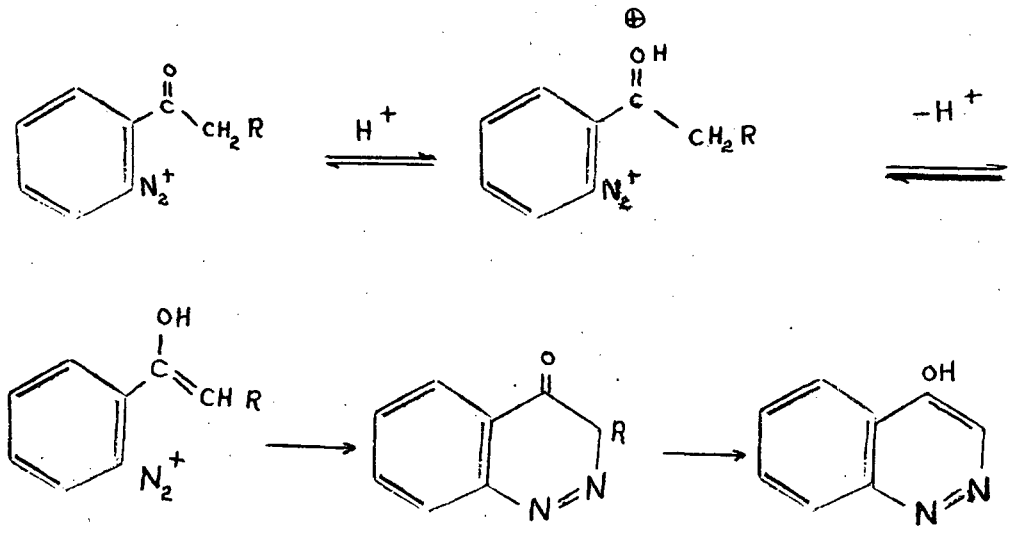
The mechanism of the 4-hydroxycinnoline synthesis, discovered accidently by Borsche and Herbert, (footnote) and so aptly used by Simpson and co workers, has further supported Simpson's theory of cinnoline formation. During the diazotisation of o-aminoacetophenones, enolization of the ketone must occur at some stage in order that cyclization may take place, (10).



(10)

footnote: They were carrying out the Sandmeyer reaction to obtain o-Br-acetophenone.

Leonard[16] has suggested that the reaction may involve an intramolecular coupling of the diazonium kation with an enolate anion, this would be akin to the coupling reaction of diazonium salts with phenoxide ions to form azo dyes. This mechanism is highly untenable as cinnoline cyclization takes place in concentrated acid whereas diazonium coupling takes place in basic solution. Further Hodgson and Marsden[17] have stated that in the coupling reaction of diazomium salts under alkaline conditions the reactive species is not the simple diazonium ion. Watson[18] sets out the accepted mechanism for acid-catalysed enolization of a carbonyl group and Simpson[19] has interpreted the mechanism of cinnoline formation by the following series of transformations, (11).



(11)

He has found that the yield of cinnoline from a given diazotised o-aminoacetophenone is a competition reaction of the diazonium kation for the negative β-carbon atom or the reaction of the diazonium kation to form a hydroxyl group. In keeping with this theory he has found a high yield of cinnoline using high acid concentration and low temperature. Simpson has also studied the formation of cinnoline when groups that will vary the basicity of the amino group are present in the ring of the o-aminoacetophenone. Electron attractive groups para to the amino group will produce a relatively weaker base. On diazotisation these weak bases will produce a relatively more positive diazonium kation, and an expected higher yield of the corresponding cinnoline. Included is a table compiled from Simpson's separate papers which clearly bears out this theory.

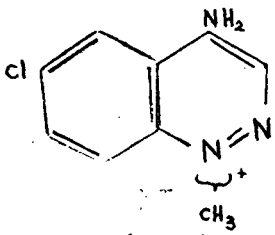
Cinnoline	Conditions	Yield
4-OH	75% H_2SO_4 and HAc, 10-90°	10%
"	3.5N HCl, room temp.	43%
"	conc. HCl, 50-60°	70%
7-Cl-4-OH	5N HCl,	30%
"	3.5N H_2SO_4, 28 days @ 20° then 70-80° for 1 hour	81%
"	conc HCl	90%
4-OH-3-methyl	2N HCl, room temp.	18%
"	conc HCl,	83%
6-Cl-4-OH-7-methyl	5N HCl, 70-80°	90%
	2N HCl, 70-80°	30% and 45% of Phenol

From the foregoing considerations we conclude that the ease of formation and the yields of cinnoline depend on two factors, the availability of electrons on the β-carbon atom and the weakness of the amino group of the ortho-amino compound.

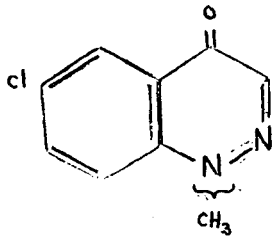
THEORETICAL II

Simpson[20] has shown that the basic center of 4-methylcinnolines is at N_1. He attempted to produce quaternary salts of 4-methylcinnoline and by a study of their decomposition reactions determine the position of attachment of the quaternary group thereby locating the center of basic character of the compound.

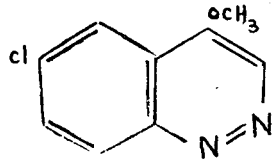
The methiodide obtained from 6-chloro-4-amino-cinnoline, (11), on treatment with hot alkali proved to be 6-chloro-1-methyl-4-cinnoline, (12), identified as the same product obtained by treatment of 6-chloro-4-hydroxycinnoline with methyl sulphate. Whereas treatment of 4,6-dichlorocinnoline with sodium methoxide yielded the isomeric 6-chloro-4-methoxycinnoline, (13).



(11a)

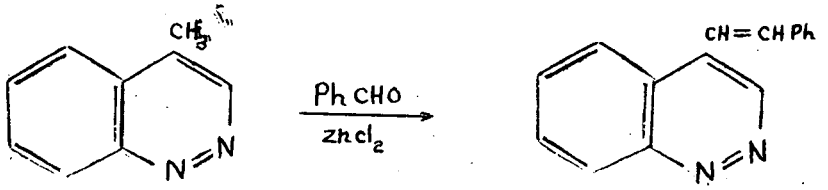


(12)

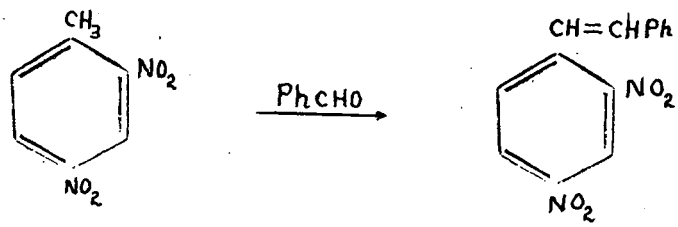


(13)

The position of quaternary salt formation in 6-chloro-4-aminocinnoline is thus established at N_1. Further the condensation of 4-methylcinnoline ethiodide with p-dimethylaminobenzaldehyde[21] to produce dyes shows enhanced activity of the 4 position due to the basic character of N_1. Jacobs et al.[22] we able to condense 4-methylcinnoline with benzaldehyde in the presence of zinc chloride, (14), a reaction akin to the condensation of benzaldehyde with 2,4-dinitrotoluene, (15).



(14)



(15)

These facts point to N_1 as the basic center of 4-substituted cinnolines, this being the position of highest electron density.

Because the author was interested in the formation of quaternary salts of cinnoline, a consideration of the factors affecting quaternary salt formation in general was undertaken.

Menschutkin[23] studied the reaction of triethy-

amine with alkyl-halides in acetone at 100°. He found the reaction to be bimolecular and his relative velocity cofficients are given in the following table.

methyl	1140.0
ethyl	10.0
n-propyl	1.93
n-butyl	1.38
n-heptyl	1.08
n-octyl	1.0

Long[24] has measured the rates of interaction of cyclic teriary bases with organic halides to form quaternary salts. His results were of the same order as Menschutkin's. Thomas[25] studied the effects of various alkyl groups and some nuclear substituents on the reactivities of tertiary aromatic bases with organohalides, however, as was the mode of the day, he explained any variations in reactivity of substituted bases or halides by steric hindrances.

A modern theory of reaction mechanism and reactivity of various substituted bases and halides is now at hand. It has been often said that the elements lying between helium and neon cannot expand their valence shell beyond and octet. All efforts to obtain derivatives of 5-covalent nitrogen have been unsuccessful. Schlenk and Hotlz[26] prepared compounds containing

5 hydrocarbon groups ie, tetramethylammonium benzyl, however they found them to behave as ionized salts $(CH_3)_4N:^+ R^-$. Attempts to obtain compounds with 5 simple alkyl groups by the interaction of quaternary ammonium halides with metal alkyls were unsuccessful[27]. Further in no case was the alkyl group derived from the metal found enter the valence shell of the nitrogen atom. It must be assumed then that the nitrogen atom with its 5 valence electrons can coordinate 3 alkyl groups; each donating an electron; and then will share its pair of electrons with any electron seeking reagent, but it will not coordinate more than 4 groups directly in its valence shell.

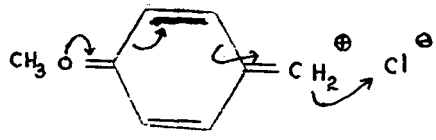
Baker[28] has make an exhaustive study of the factors affecting quaternary salt formation. He has shown the reaction of substituted benzyl-halides with pyridine to form salts proceeds by two steps, a), the anionisation of the halogen and, b), coordination of the nitrgen atom with its electron pair to the now electron deficient methylene system. We see then that in salt formation the electron pair of the nitrogen accepts the free aryl residue only after anionisation has taken place. It is therefore clear that nuclear substituents in the halide which enhance accession of electrons to side chain, ie, CH_3, OCH_3, will enhance salt formation and vice versa. Hence anionisation of the halogen is the main factor

in determining relative reactivities of benzyl-halides in reactions with pyridine.

Alteration of the halogen atom for any given benzyl nucleus introduces a striking anomaly. Since the velocity of the reaction is determined mainly by the ability for anionisation of the halogen it would be expected to increase in the order of electron affinity $I < Br < Cl$. However the experimental order for quaternary salt formation is found to be the reverse $Cl < Br < I$. This suggests a consideration as to whether the ease of separation of the halogen atom as a negative ion is necessarily the same as the order of anionic stabilities of the halide ions.

Considering again nuclear substituents, Baker[29] found that p-methoxybenzyl-halides formed pyridinium salts so fast the velocity could not be measured. He suggests that the resonance effect of the p-methoxy group is strong enough to produce an "ionized salt" from of the halide, (16). We see then in this case anionisation, the rate determing step in the reaction, has occurred even before the pyridine is present.

Footnote.

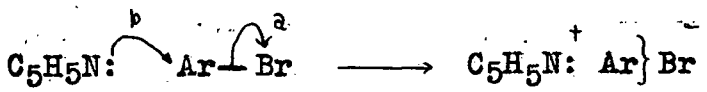


(16)

footnote. See under discussion.

As a further consideration in salt formation mechanism Baker[30] has shown that activation energies for the reaction of benzyl-bromide with pyridine are almost identical with those of α-picoline. If basic strength is a measure of electron availability then as α-picoline is ten times as strong a base as pyridine, electron availability can have little effect on quaternary salt formation.

In summary Baker has shown that the reaction between benzyl-halides and tertiary bases is bimolecular and involves simultaneous addition and dissociation denoted by the electron cycle, (17). Although the



(17)

energy of activation is unaffected by substituent groups in the aryl nucleus the velocity of the reaction is altered. Electron accession increases reaction velocity up to a point but on the other hand electron recession decreases the velocity. Greater recession from the side-chain than that produced by para-nitro in the nucleus, alters the mechanism and greatly increases the velocity. It is to be considered that the electron cycle above is to be completed before salt formation will occur, however, initiation of this cycle can occur by the incipient anionisation of the halogen, (a above), or the electrostriction of the tertiary base, (b above). Baker has

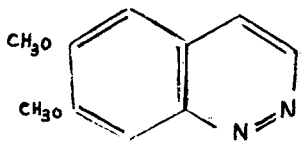
found that the critical point where the probability for initiation of the reaction by methods (a) and (b) is equal is at para-nitrobenzyl-halide. We can therfore say that all groups in the nucleus that repel electrons and all attracting groups down to para-nitro react by method (a) and all more powerful electron attracting groups react by method (b).

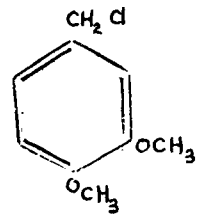
Such a view also accomodated the experimental effect of solvent on salt formation. The greater the ionizing power off the solvent the more pronounced will be the effect of substituent groups in the halide nucleus in enhancing or retarding the anionisation of the halide ion. Baker[31] showed that the retarding influence of a paranitro substituent is clearly existent in 90% ethanol but is absent in dry acetone. in the face of such results it seems difficult to any longer assume that in non ionizing solvents, the general inductive polar effect of substituents in the halide nucleus is concerned with the polarizability or polarization of the carbon-halogen bond.

The author would like to point out that Baker measured his rates of reaction by titration of the halide ion with siliver nitrate. He therefore made the assumption that the rate of salt formation was a true function of the concentration of ionic halide present in solution. The author has found that some of these quaternary salts do not behave as ionized salts.

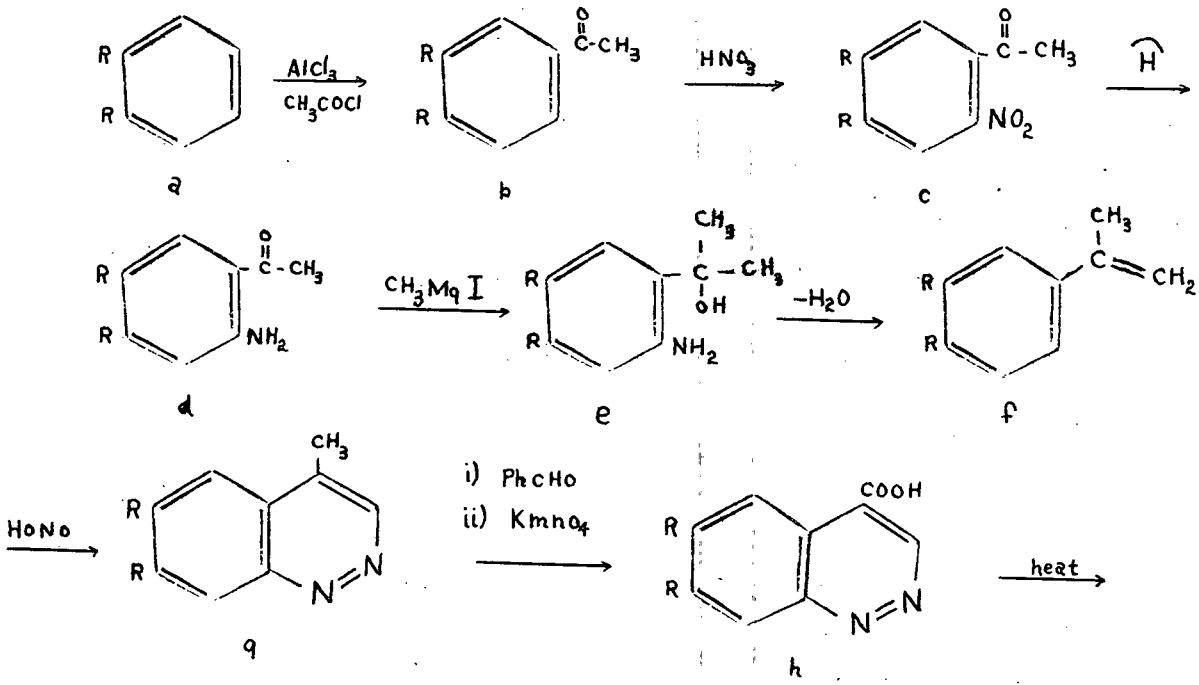
DISCUSSION.

In order to synthesize the quaternary salt which is the analogue of papaverine two products, 6,7,-dimethoxycinnoline and 3,4-dimethoxybenzylchloride are required.



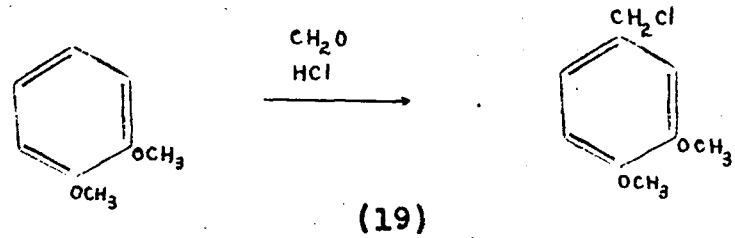


Neither of these compounds are reported in the literature and so an attempted synthesis of these two compounds was undertaken. (18) and (19).



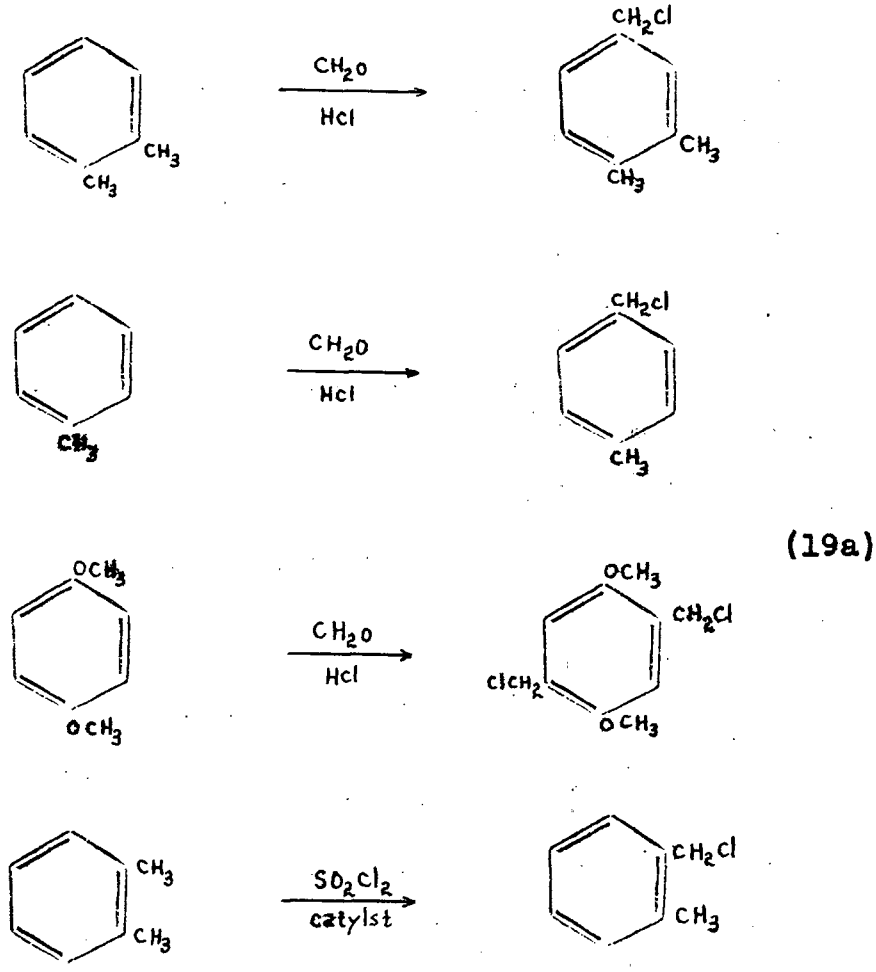
(18)

17



(19)

Erlendson[32] has studied the Blanc reaction and side chain chlorination using sulphuryl chloride. Although he did not obtain 3,4-dimethoxybenzyl chloride by either of the above methods he did obtain the following alkyl substituted benzyl chlorides. (19a).



(19a)

From the theoretical considerations already presented, page 7, it is seen that the 2-iso propenyl-4,5-dimethoxyaniline, (18f), will produce a weakly positive diazonium kation and an expected lower yield of cinnoline than the corresponding unsubstituted derivative. Simpson has obtained the ketone, (18d), and has converted it to the corresponding 4-OH-6,7-dimethoxycinnoline. No reference has been made to the reaction of this ketone by the method proposed by the author. The ketone has been obtained but reduction of the nitro group to the amine has consistently given poor yields and difficuly has been encountered in the reaction of this ketone with CH_3MgI

For considerations regarding the formation of substituted benzylchorides the reader is referred to H.M. Earlenson[32]. He has in conjunction with the author prepared a number of mono- and di-substituted benzyl-halides. In general the reactivity of the halide increases with Baker's theory of substituent groups in the nucleus, page (13). Para-methoxy-benzyl-chloride was found to be so reactive that it decomposed even on distillation at reduced pressure. The chloromethylation of hydroquinonedimethylether proceeded to the disubstituted product, and the three xylyl chlorides converted to the corresponding iodides with sodium iodide were stable only a few days. From this experimental evidence it would seem that 3,4-dimethoxybenzyl-halides are difficult to obtain and unstable.

If Bakers theory of quaternary salt formation is correct, (page 15), then, 6,7-dimethoxycinnoline and 3,4-dimethoxybenzyl chloride would be expected to readily form a salt, ie, N_1 of the cinnoline is a relatively strong base due to the electron releasing groups in the nucleus. The anionisation of the chloride of the 3,4-dimethoxybenzyl chloride is made more facile by electron accession in the side chain due to the electron releasing para-methoxyl group.

Almost no work has been reported on quaternary salt formation in the cinnoline series[20]. While the attempted synthesis of 6,7-dimethoxycinnoline and 3,4-dimethoxybenzyl chloride was being undertaken the author made a study of salt formation of the readily available 4-methylcinnoline and some of the more common organic-halides. The results of this investigation are summarized in the table, (20), and shows for the majority of aryl-halides used for reaction with 4-methylcinnoline, comparatively few salts were isolated in a crystalline condition. Baker[28] studied the rates of reaction of benzyl-halides with pyridine in dry acetone. In order to prevent errors in his results from hydrolysis of the unused benzyl-halides due to the presence of moisture in the solvent he used the hygroscopic properties of the quaternary salts to dry the acetone before use. He

Table (20)

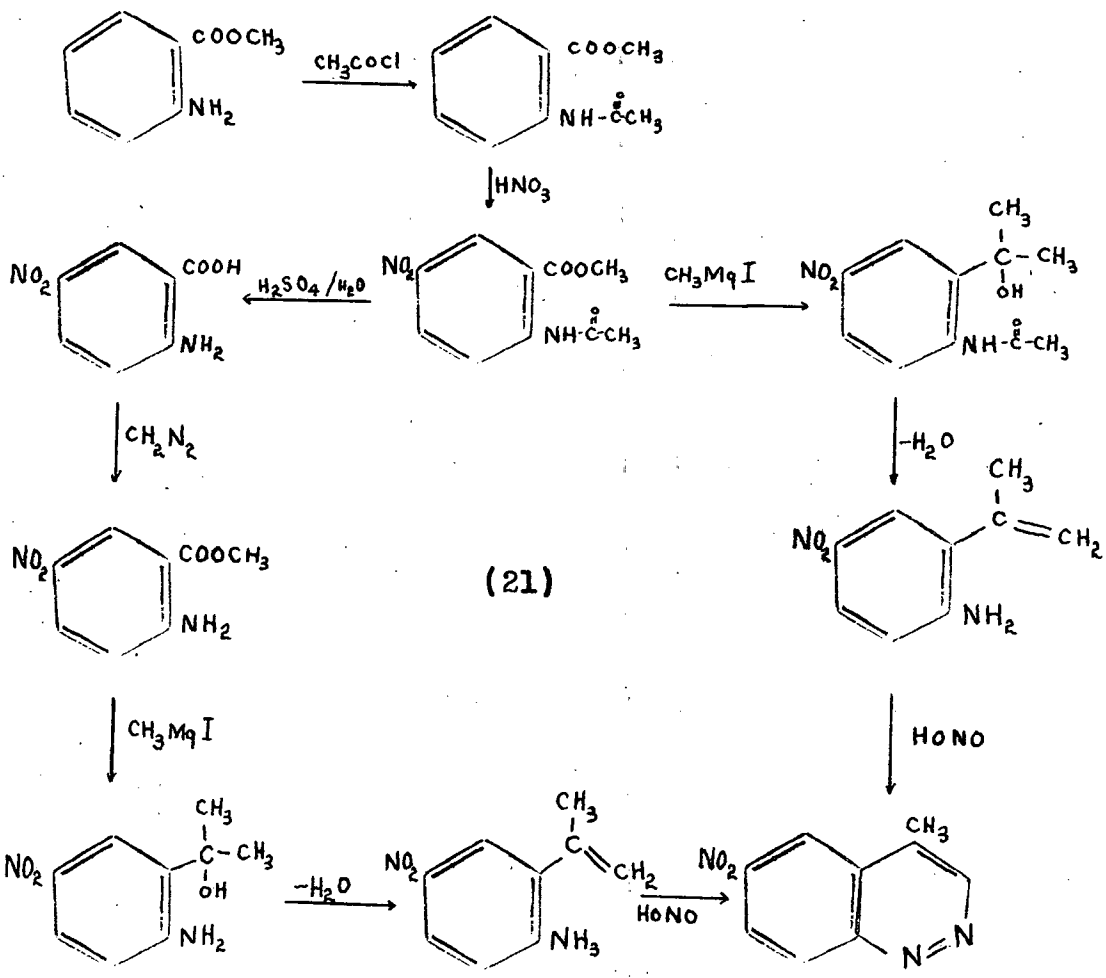
base	halide	color change	
Quinoline	CH_3I	clear-yellow	1
"	C_2H_5I	clear-pale yellow	2
"	benzylchloride	clear-red	3
"	benzylbromide	clear-cream	4
"	benzyliodide	clear-yellow	5
"	p-NO_2-benzylbromide	clear-red	6
2,6-dimethyl-	CH_3I	yellow white	7
quinoline	C_2H_5I	yellow-red	8
"	benzylchloride	no reaction	9
4-methyl-	CH_3I	yellow-orange	10
cinnoline	C_2H_5I	yellow-red	11
"	n-C_4H_9Br	yellow-green	12
"	benzylchloride	yellow-green	13
"	benzylbromide	yellow-brown	14
"	benzyliodide	yellow-red	15
"	3-Me-benzylchloride	no reaction	16
"	2-Me-benzylchloride	yellow-blue	17
"	4-Me-benzylchloride	no reaction	18
"	2-OH-4-NO_2-benzylchloride	yellow-green	19
"	3,4-diMe-benzylchloride	yellow-green	20
"	2,4-diMe-benzylchloride	yellow-blue	21
"	1,4-diMe-benzylchloride	yellow-blue	22
"	O-Cl-benzylchloride	yellow-dark specks	23
"	p-Cl-benzylchloride	yellow-dark specks	24
"	2,4-diCl-benzylchloride	yellow-blue	25
"	3,4-diCl-benzylchloride	no reaction	26
"	p-NO_2-benzylbromide	yellow-pink-white	27

	time	form of salt	mp.°C.	remarks
1	½ hour	fine yellow needles	135	reported 133
2	8 days	fine yellow prisms	145d	" 158
3	reflux 24 hours	coarse red prisms	113	" 65 & 170
4	"	coarse cream prisms	192.5d	
5	"	coarse yellow needles	156	reported 135
6	"	red prisms	198	turns yellow at mp.
7	3 days	yellow white needles	240	reported 237
8	10 days			
9	10 days			
10	½ hour	orange needles	196d	reported 169
11	4 hours	red needles	154	" 154
12	8 days	green solid		hygroscopic
13	90 days	green oil		
14	18 hours	yellow needles		hygroscopic
15	3 hours	yellow red needles		"
16	8 days			
17	8 days	clear blue prisms		hygroscopic
18	10 days			
19	30 seconds	green prisms	76	
20	8 days	green oil		
21	8 days	blue prisms		hygroscopic
22	4 days	clear blue prisms	under 50	"
23	8 days	dark scales		decomposition
24	8 days	blue green prisms		hygroscopic
25	8 days	clear prisms	91	
26	8 days			
27	3 hours	fine green needles	202	

did not isolate any of the salts but merely titrated the halide ion at various times with aqueous silver nitrate.

The author believes that certain of the salts described in the table are so hygroscopic that their isolation as crystalline compounds is not feasible. Further it is considered that salt formation has occurred in all cases due to the separation of a hydrated oil from the original homogeneous solution. That this is so is seen in the formation of yellow needle like crystals from a solution of 4-methylcinnoline and benzyl-iodide in dry ether in a sealed ampoule. These crystals liquify to a green oil on exposure to the atmosphere. As further evidence that salt formation has occurred the author presents the following experimental evidence. The precipitation of silver halides on addition of aqueous silver nitrate to etheral solutions of the oils takes place at a velocity far exceeding the rate of hydrolysis of the free organic-halides. This would indicate the presence of an ionized halide ion. The addition of aqueous alkali to both isolated crystalline salts and hydrated oils results in the formation of blue dyes indicative of quaternary ammonium hydroxides,[43].

It has already been stated, page (13), Baker studied the rates of reaction of benzyl-halides with electron repelling groups in the nucleus of the basic constituent. In order to examine the effect of electron attracting substituents an attempted synthesis of 6-nitro-4-methylcinnoline was undertaken by way of the following reactions, (21). This synthesis was not completed as it was felt that if salts of 4-methyl-cinnoline could not be isolated, there is no reason to expect the less reactive 6-nitro-4-methylcinnoline would form salts capable of isolation and analysis.



o-isopropene-aniline

A solution of 50g. of methylanthranilate in 500cc. of ether was added during stirring over $\frac{3}{4}$ hour to CH_3MgI. (made from Mg. 40g., CH_3I 240g. ether 750cc., 4 moles of Grignard are required for each mole of ester used.). The temperature was maintained below 0°C. during the addition and the yellow suspension was then heated under reflux for 5 hours. The mixture was cooled and poured into NH_4Cl and ice and ether layer allowed to separate. The water layer was further extracted with fresh ether and the combined extracts dried over anhydrous $MgSO_4$ and the solvent removed by distillation. 48g. of the oily carbinol was recovered. Acetylation with cold Ac2O gave a solid derivative after $\frac{1}{2}$ hour. recrystallization from benzene-ligroin gave needles, mp. 146° , Simpson, mp. 146-147°.

The tertiary alcohol was then dehydrated in a Dean and Stark tube with the aid of 250cc. of dry toluene and a small crystal of iodine. The theoretical amount of water was obtained in 4 hours. The toluene was removed under reduced pressure and the residue distilled using a mirror jacketed Vigreux column, bp. of the olefin 84°/4mm. Jacobs et al.[7] bp. 83.5 - 87.5 /1-2mm. yield 35g. 79% of the theoretical was recovered.

4-methylcinnoline

30g. of the olefin was dissolved in a solution of 60cc. of conc. HCl in 200cc. of water. The solution was cooled to 5° and thesuspension obtained was diazotised with 20% $NaNO_2$ until a positive test was immediately obtained with starch-iodide paprer. The clear dark green solution was diluted to 400cc. and warmed during ½ hour to 50° on a water bath and held at that temperature till the coupling reaction with alkaline β-naphthol became negative. At this stage the reaction mixture had changed color to a deep red. The system was connected to a gas burette to determine the amount of deamination occuring in the reaction; 200cc. of gas were collected which is a neligible amount. The solution was made basic with aqueous NaOH and extracted with ether in a continuous extractor for 3 days. The ether extracts were dried and evaporation of the ether yielded yellow green crystals. A sample recrystallized from hexane gave mp. 72 - 73°. Jacobs et al. mp. 72.5 - 74°. Distillation of the ether residue under reduced pressure yielded 24g. of a grey green solid, bp. 133° /4mm. Jacobs et al bp. 135-137° / 3mm. Recrystallization from hexane gave grey-yellow needles mp. 74°. Nitrogen calc. 19.4%. found 18.9%. Yield from methylanthranilate used was 50% of the theoretical.

Acetoveratrone

62g. of acetyl chloride was added to 100g. of vertrole in 260cc. of carbon disulphide in a 1 liter conical flask cooled to below - 10°. 100g. of powdered $AlCl_3$ (practical grade), was added in small portions with constant shaking. As the reaction proceeded the magenta colored complex settled out in round rough stones and hydrogen chloride was evolved. After all the $AlCl_3$ had been added to reaction mixture was heated under reflux to 50° on a water bath for ¾ hour. The resulting clear layer of CS_2 was decanted and the addition of crushed ice decomposed the complex giving a brown oily layer and a collodial $Al(OH)_3$ layer. The whole was filtered through sintered glass using a filter aid and the oily layer separated. The water layer was extracted with $CHCl_3$ and the extracts added to the oil whereupon emulsification of the oil took place. On drying over $MgSO_4$ and evaporation of the solvent the residue was distilled under reduced pressure. Yield 83g. of clear oil bp. 127-130° / 1mm. 63% of the theoretical. The oil crystallized on standing to a white solid, mp. 50 °. Koepfli and Perkin[33], bp. 160-162° /10mm.,
Oxime mp. 137.5 - 138°

6-nitroacetoveratrone [34]

54g. of powdered of liquid acetoveratrone was added in small portions to a mechanically stirred mixture of HNO_3 (88cc. d 1.42) and conc. H_2SO_4 (80cc.) the temperature maintained between -5° and -3° during the addition. The nitroketone usually but not always began to crystallize after the last of the ketone had been added. The mixture was stirred at the reaction temperature for a further ½ hour and the mass was then poured into water. The nitro-compound was worked up in the usual way and recrystallized from ethanol. 51g. of long golden needles mp. 132-134°. Simpson,[34] mp. 133-135°. Yield 75% of the theoretical.

6-aminoacetoveratrone.

a. 5g. of 6-nitroacetoveratrone in acetic acid (40cc.) was heated on a steam bath with iron powder 7.5g. added in small portions during 1 hour with frequent shaking. Addition of 10cc. portions of water were made at the start of the reaction and after ¾ hour. After a total of 1½ hours the mixture was diluted with 50% sodium acetate till cloudy and extracted with $CHCl_3$ till extracts were no longer colored. The extracts were dried with K_2CO_3 and the solvent removed on a steam bath, the residue was taken up in dilute HCl, treated with Darco and precipitated with dilute NaOH. 3g. of yellow crystal-

line material were obtained. A sample recrtstallized from ether gave yellow brown needles mp. 100-104°. Simpson[34] mp. 103-105°.

b. Reduction of 6-nitroacetoveratrone with an Adam's machine using Raney nickel catalyst was attempted with varying pressures and temperatures, however no good yields were obtained and in all cases the product was contaminated with dark material which could only be removed by distillation.

c. Reduction of the nitro compound was attempted using the method of West[35] by iron powder in HCl and methanol. However reduction was incomplete by this method.

Note; all the aminoacetoveratrone obtained in several runs was distilled under greatly reduced pressure when a total of 20g. of yellow crystalline solid was obtained, bp. 150° /0.1mm.

(2-amino-4,5-dimethoxy-phenyl)-dimethyl-carbinol.

(19.5g. .1 mole) of 6-aminoacetoveratrone in 100cc. of toluene was added during stirring to CH_3MgI (.31 moles) made from Mg. and CH_3I in ether. The temperature was maintained at 0° during the addition and a yellow green suspension was obtained. A further 200cc. of toluene was added and the mixture

warmed and the ether removed by distillation. When all of the ether had been driven off the mixture was refluxed for 2 hours, cooled and poured into ice and NH_4Cl. The toluene layer was separated and the water layer made neutral with sodium acetate, and extracted with $CHCl_3$. The toluene and $CHCl_3$ layers were separately evaporated and the residue from both taken up in dil. HCl, filtered through Darco and on making basic with dil. NaOH. 3g. of a white solid was obtained.

The difficulty in this reaction is the slight solubility of the amino-ketone in solvents suitable for the Grignard reaction.

N-acetyl-methyl anthranilate

1 mole of methyl anthranilate was added to 1.1 moles of acetic anhydride and warmed to just below the boiling point for 1 hour. The mixture was then cooled and poured into dilute sodium acetate and the white crystalline solid recrystallized from ethanol. 180g. of recrystallized material mp100° was obtained. yield 93% of the theoretical.

5-nitro-N-acetyl-methyl anthranilate

Nitration of N-acetyl-methyl anthranilate was carried out using the method of Vogel[36]. The crude nitro-compound was recrystallized from ethanol, mp. 162°.

Note: It was hoped to carry out a Grignard reaction with this nitro compound as the table (21) shows. However the nitro compound is insoluble in Grignard reaction solvents and so it was decided to hydrolize the nitro compound to the corresponding amino-acid and esterfy and then to try the Grignard reaction on the more soluble amino ester.

5-nitro- anthranilic acid.

The hydrolysis of the amide (5-nitro-N-acetyl-methyl anthranilate) was carried out in 70% $H2SO_4$ using the method of Vogel[37]. Difficulty was encountered in recovering the amino acid from the 70% H_2SO_4. The best method was to dilute the acid solution with an equal volume of water and on cooling in an ice bath a yellow sludge settled out. This sludge was collected on a sintered glass funnel using a filter aid, and was dissolved from the filter cake using boiling ethanol. Evaporation of some of the solvent gave fine yellow needles mp. 265°, Reported [38] 280° (263°)

Quaternary Salts

All salts were make by mixing equal molar quantities of base and halide in dry ether and allowed to stand at room temp. till salt formation had occurred. When possible they were recrystallized from ether containing a little ethanol. Note: In most cases refluxing to increase the rate of reaction lead to decomposition.

Benzyl chloride

B.D.H. benzyl chloride was distilled under reduced pressure and the fraction boiling at 46.5° / 7mm. was collected.

Benzyl bromide

2 moles of bromine was added through a dropping funnel to 2.1 moles of boiling toluene irradiated with a 150 watt lamp. After addition of the bromine was complete (1 hour) the mixture was refluxed till the evolution of HBr had ceased. The mixture was then distilled and after a forerun of toluene the benzyl bromide was collected bp. 195-205°. Schramm[39] 198°. and 127°/80mm. Redistillation through a short column gave 220g. of clear liquid bp. 68° / 5mm. Yield of pure product 65% of the theoretical.

Benzyl iodide

To 100g. of sodium iodide in 500g. of acetone was added 63g. of redistilled benzyl chloride. The solution was refluxed for 4 hours, cooled and the precipitate of sodium chloride filtered off. The acetone was removed and the benzyl iodide distilled under reduced pressure bp. 82° / 7mm. The distillate was shaken with a small portion of mercury to remove traces of iodine and then redistilled, bp. 83° / 7mm. Heilbron[40] 93° /10 mm.

SUPPLEMENT

In an investigation being carried out by Mr. G.G.S. Dutton it was required to synthesize all the o- and p-hydroxy-n-alkyl-phenols with alkyl groups containing from 1 to 7 carbons. This supplement represents a portion of the experimental work done by the author during the period in which the main thesis was being prepared.

Acid Chlorides

The acid chlorides of all acids used to make esters were made in the following way.

1 mole of the acid was added slowly through a dropping funnel to 1.1 moles of redistilled thionyl chlroide cooled to 0°C. The reaction mixture was shaken periodicaly and when all of the acid had been added the mixture was warmed till the evolution of HCl was complete and then heated under reflux for 1 hour. The mixture was then distilled and the forerun of thionyl chloride collected and then the crude acid chloride. Redistillation through a short column gave acid chloride of a purity suitable for use. Yields range 70-90%.

Phenyl esters

Phenyl esters were prepared in the following manner.

1. mole of the acid chloride was poured in a thin stream onto 1.1 moles of phenol. The mixture was heated until the evolution of hydrogen chloride was complete and the ester distilled. If a large boiling range was observed the ester was redistilled through a short column. Yields ranged 80-90%.

p-hydroxyacetophenone

To 272g. of phenylacetate in 1140cc. of purified nitrobenzene in a flask cooled to below 20°C. was added 400g. of powdered $AlCl_3$ (practical grade) with shaking. The temperature was maintained below 20°C. during the addition and the resulting brown suspension allowed to stand overnight at room temperature. The solution was then warmed on a water bath to 50°C. for 1 hour, cooled and poured into ice and HCl. The nitrobenzene was removed by steam distillation and the residue crystallized from the water on cooling. Yield of crude product 200g. The product was found difficult to purify without loss of material. Distillation under reduced pressure gave a pink oil b.p. 155-160°C /2mm. which solidified on standing. Treatment of the crude product with NaOH, charcoal and a filter aid, followed by acidification yielded yellow crystals, m.p. 106-107°C. m.p. of the pure compound 109°C. In 4 runs the yields varied from 50-60%.

o-and p-hydroxyacetophenone.

120g. of phenylacetate was added in small portions to 180g. of $AlCl_3$ (practical grade) which had been preheated to 70°C. The evolution of HCl was very rapid and the temperature of the mixture rose to about 130°C. Heat was applied to maintain the temperature at 140°C. for ¾ hour. The reaction mixture was cooled somewhat and a mixture of 500cc. of conc. HCl in 500cc. of water was added in portions to the flask. A violent reaction followed and the dark complex gave way to a red oil.# The oil was separated and washed with 50% HCl and with warm water. The water layer and washings were cooled and extracted with two 100cc. portions of ether. The ether extracts were added to the oil and the ether and water removed at the pump. Distillation of the residual oil gave 34g. 28%, of clear oil bp. 77-80°C. /1mm. and 50g. 50%, of a pink solid bp. 155-160°C. / 1mm.

#. It would be more profitable to hydrolyze lower members of the series with ice and HCl due to the rate of hydrolysis.

O- and p-hydroxybutyrlphenone

100g. (.6 moles) of the ester was added in small portions to 119g. (.8 moles) of $AlCl_3$ which had been preheated to 70°. The evolution of HCl was rapid and the temperature of the mixture rose to about 135°. Heat was applied to maintain the temperature at 140° for ¾ hour. The reaction mixture was cooled to 30° and a mixture of 300cc. of conc. HCl and 450cc. of warm water was added in portions to the reaction mixture. The yellow grey complex dissolved and gave way to a bright red oil. The mixture was again cooled to 30° and the oil separated, washed with 50% HCl and with warm water. The wet oil was distilled and after removal of the water 32g. 32% of clear oil, bp. 105° /2mm., and 40g. 40% pf a white solid, bp 160-173° /2mm. were obtained.

o- and p-hydroxy-n-valerophenone

89g. of ester at 70° was added in a thin stream to 90g. of $AlCl_3$ (practical grade) preheated to 50° and the temperature rose to 140°. The mixture was then heated to 150°-160° for ¾ hour and then cooled to 40°. 250cc. of conc. HCl in 250g. of water was poured onto the orange mass. The mixture was warmed until the complex decomposed and while still hot the brown oil was separated, washed with warm 50% HCl and then with warm water. The wet oil on

distillation yieled 39g. 44%, of the ortho isomer bp. 125° / 3mm. and 40g. 45%, of the para isomer bp. 185-190° /2.5mm. The para isomer crystallized on standing.

o- and p-hydroxy iso valerophenone

178g. (1 mole) of the ester and 195g. (1.3 moles) of $AlCl_3$ was treated in the same manner as for n-valerophenones. Distillation under reduced pressure yielded 63cc. 34%, of the ortho isomer bp. 101-103° / 1mm. and 50cc. 41% of the para isomer bp. 160-168° / 1 mm.

Note: This work is still under way and the constants for the derivatives has not been completed although 2,4-dinitrophenylhydrazines, semicarbazones and hydantoins of all the compounds listed have been made.

BIBLIOGRAPHY

1. von Richter, (Ber. 16 677 (1883)).
2. Stoermer and Fincke, (Ber. 42 3115 (1909)).
3. Widman, (Ber. 16 677 (1883)).
4. Stolle and Becker, (Ber. 57 1123 (1924)).
5. Borsche and Herbert, (Ann. 546 293 (1941)).
6. Pfannstill and Janecke, (Ber. 75 1096 (1942)).
7. Jacobs et al., (J.A.C.S. 68 1310 (1947)).
8. Simpson, (J.S.C. 1947 809).
9. Simpson, (J.C.S. 1942 and subq.).
10. Simpson, (J.C.S. 1943 447-9).
11. Stoermer and Gaus, (Ber. 45 3104 (1912)).
12. Mayer and Balle, (Ann. 403 167 1914)).
13. Sachs and Hilpert, (Ber. 39 899 (1906)).
14. Ruggli and Staub, (helv. chim. Acta. 20 37).
15. Ruggle and Dinger, (Helv. chim. Acta. 24 173).
16. Leonard, (Chem. Rev. 37 269 (1945)).
17. Hodgson and Marsden, (J.S.C. 1945 207).
18. Watson, (Modern theories of Org. Chem. p, 169).
19. Simpson, (J.C.S. 1948 1172).
20. Simpson, (J.C.S. 1947 1652 and pref.).
21. Simpson, (J.C.S. 1947 1652).
22. Jacobs et al., (J.A.C.S. 68 1310 (1947)).
23. Menschutkin, (Zeit. physikal chem. 5 589 (1890)).
24. Long, (J.C.S. 1911 2164).

25. Thomas, (J.C.S. 1913 594).

26. Schlenk and Holtz, (Ber., 49 603 (1916)).

27. Marvel et al., (J.A.C.S. 48 2689 (1926)).

28. Baker, (J.C.S. 1931 2416), and subq.

29. Baker, (J.C.S. 1931 2416).

30. Baker, (J.C.S. 1939 519).

31. Baker, (J.C.S. 1939 519).

32. Erlendson, (Unpublished).

33. Koepfli and Perkin, (J.C.S. 1928 2989).

34. Simpson, (J.C.S. 1946 96).

35. West R.W., (J.C.S. 1925 494).

36. Vogel, (Practical Organic Chem., page 558.).

37. Vogel, (Practical Organic Chem., page 558.).

38. Heilbron, (Dictionary of Org, Compds., III 91.)

39. Schramm, (Ber., 18 608 (1885)).

40. Heilbron, (Dictionary of Org. Compds., I 247).

41. King, (J.C.S. 1935 138; 1948 265).

42. Greig, (Chem. Rev. 42 285 (1947)).

43. Walls, (J.C.S. 1944 and Subq.).