A STUDY OF SOME OF THE REACTIONS INVOLVED IN THE SYNTHESIS OF THE 1 4 BENZODIAZEPINES.

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SUPERVISOR: Mr. JOHN O . OGETO.

THIS IS A PAPER SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF THE BACHELOR OF PHARMACY OF THE UNIVERSITY OF NAIROBI.

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FOREWORD

"Cogito, ergo sum". This is perhaps the appropriate statement to start with, as work has been done.

For helping me carry out my project, I wish to record my gratitude to my supervisor Mr JOHN. O . OGETO for providing me with invaluable assistance as well as guidance in drawing up, performing and discussing the work.

I would also like to thank the Technical Staff of the department of Pharmacy for providing very useful pratical hints and suggestions.

My thanks also go to Beatrice for typing the original manuscript and those who in one way or other provided, the motivation to work.

MIYAWA; JOHN
MAY 1984

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ABSTRACT

The initial aim of this work was to synthesise both Diazepam (7 chloro- I,3 dihydro- I methyl- 5 phenyl 2H I4 benzodiazepin-2-one) and Oxazepam (7 chloro- I,3 dihydro- 3 hydroxy- 5 phenyl- 2H I4 benzo-diazepin-2-one)

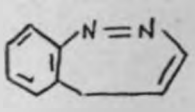
However due to the failure to obtain, in good time, commercial supplies of the intermediate 2- amino- 5 chloro- benzophenone (2 amino- 5 chlorophenyl- phenyl methanone) it was not possible to synthesise the benzodiazepine nucleus.

Hence this work mainly covers the synthesise of the 2 amino- 5 chloro benzophenone intermediate employing those chemicals that were available.

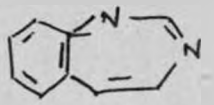
INTRODUCTION

The benzodiazepines are bicyclic,heterocyclic compounds having a benzene nucleus,fused to a seven membered ring containing two nitrogen atoms.

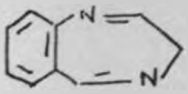
There are six classes of benzodiazepines whose synthesis and reaction differ considerably.



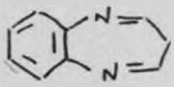
5H I2 Benzodiazepines



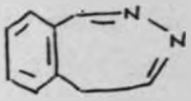
IH I3 Benzodiazepines



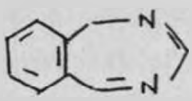
3H I4 Benzodiazepines



3H I5 Benzodiazepines



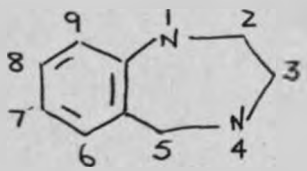
5H 23 Benzodiazepines



IH 24 Benzodiazepines

Only members of the I4 benzodiazepine class have shown sufficient pharmacologic activity to be useful clinically.

The benzodiazepines are numbered as shown below.



Starting at the position adjacent to the carbcyclic ring regardless of the position of the nitrogen atoms.

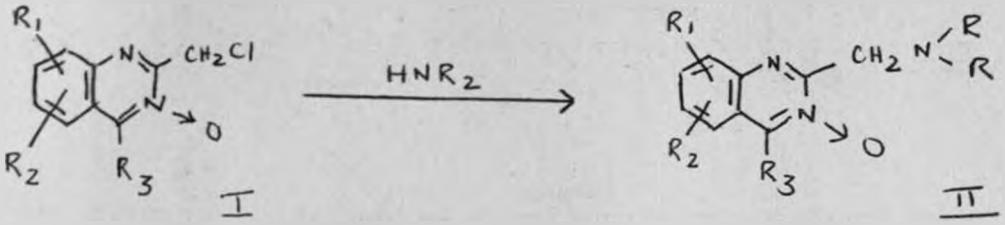
The term benzodiazepine implies a maximum degree of unsaturation i,e 3 double bonds in the seven membered ring

The position of the odd hydrogen atom even if occupied by another mono- or di- valent substituent is indicated by the term IH, 2H , 3H, etc.

LITERATURE REVIEW:

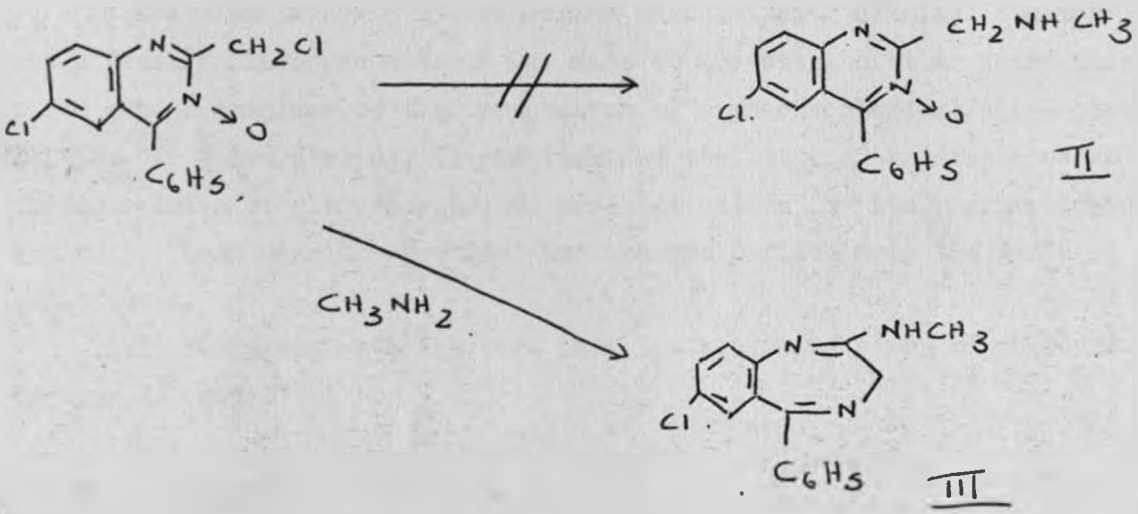
HISTORY

The benzodiazepines were introduced clinically in 1960 as a novel structural class of anti-anxiety agents. In a study aimed at developing new central nervous system (CNS) structures Sternbach[I] et al synthesised a number of quinazoline N oxides represented by the general formula I and transformed them by treatment with various amines . Secondary amines gave the expected substituition products of type II.

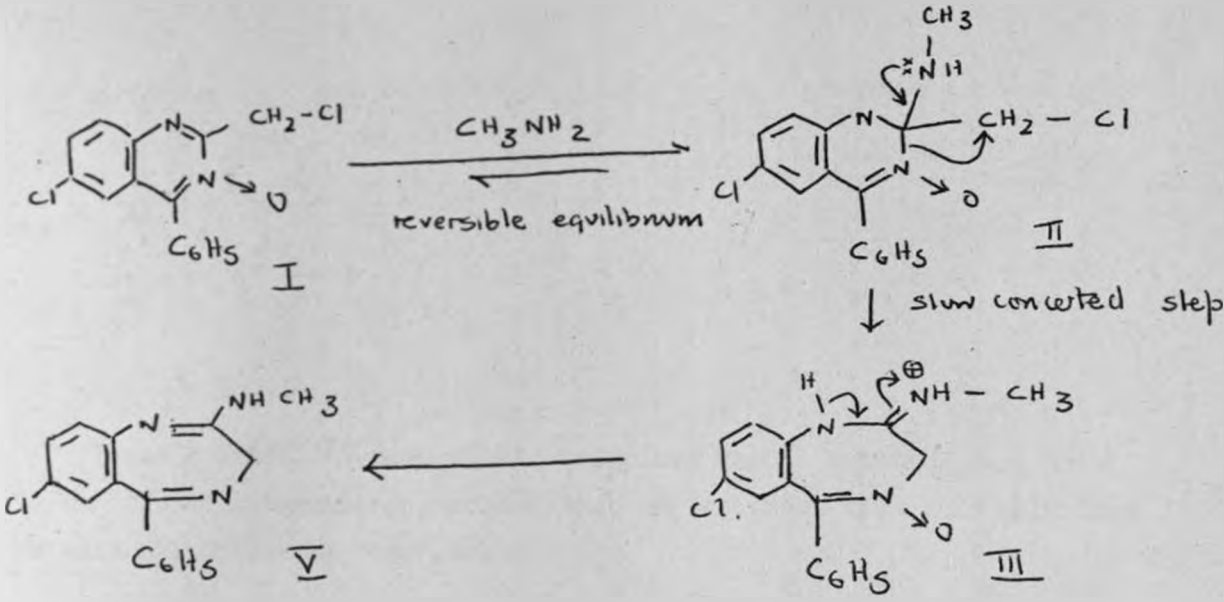


The reaction occurred with ease yielding products that crystallised well but these had poor pharmacologic activity.

The results were however quite different with primary amines. When a primary amine or ammonia was used in the reaction with compounds of type I. The first product of this type was obtained on treatment of the quinazoline derivative III with methylamine The physical and chemical properties of thisproduct indicated that it was not a substituted quinazol ine 3 oxide of formula III ~~containing~~ , but had the structural formula III containing a novel 7 membered heterocyclic ring.



The formation of the compound was postulated to occur by the following mechanism reaction sequence.



The methylamine instead ~~of~~ attacking the quinazoline N oxide molecule in the 2 position.

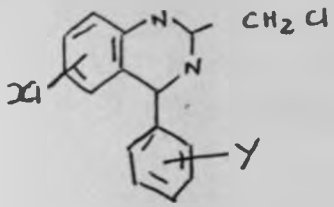
The methylamine did not replace the reactive chlorine atom as might be expected but attacked the quinazoline N oxide in the position 2 causing the formation of an intermediate of type II which is ultimately transformed via III into the I4 benzodiazepine derivative V

The I4 benzodiazepine derivative V (Chlordiazepoxide) was in the course of general screening shown to have anticonvulsant and sedative properties. A thorough study of its pharmacology and after completion of the toxicological studies and clinical investigation, the efforts culminated in its introduction in I960 under the tradename LIBRIUM.

As the water soluble hydrochloride used in thier clinical studies was extremely bitter,an attempt was made to investigate other forms that could lend themselves to the preparation of a pharmacologically acceptable elixir. In these studies, it was realised that some of the features so characteristic of chlordiazepoxide were not needed for its pharmacological activity. These were the N oxide function and particularly the basic substituent.

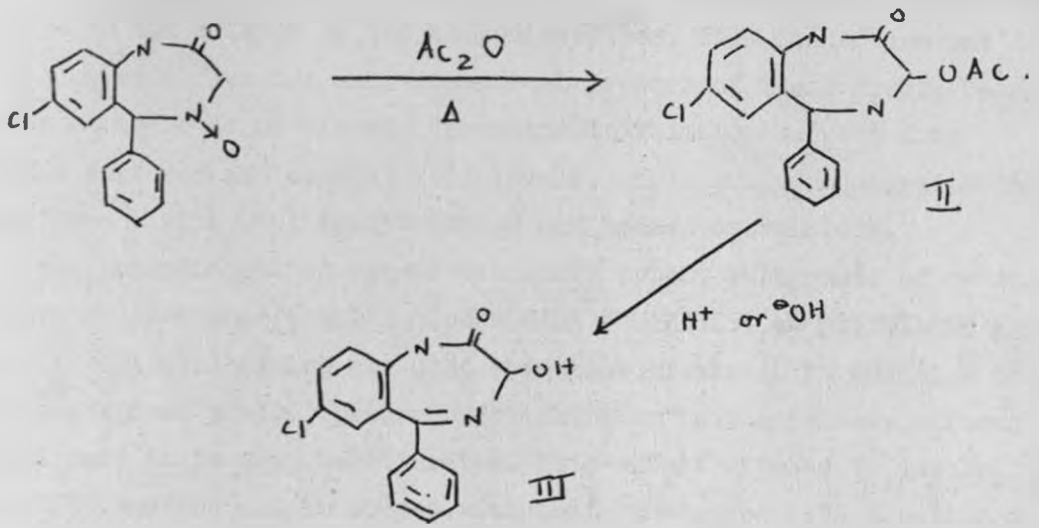
Their subsequent studies were into the intensive study of compounds of type III and IV

The N oxides of the type III were most readily accesible by treatment with alkali of 2 chloro-methyl- quinazoline N oxides of the type I.



I

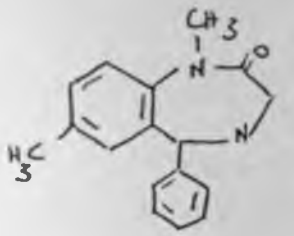
These N oxides in general did not prove useful but they were noted to undergo an interesting rearrangement on treatment with acid chlorides or acid anhydrides as shown below.



This transformation (POLONOVSKY rearrangement) results in the ~~trans~~ formation of the 3 acetoxy derivative II.

The hydroxy derivative III which resembles chlordiazepoxide in its activity was introduced in 1965 . It bore the generic name oxazepam and is marketed under the trade names SERAX, ADUMBRA and PRAXITEN.
The simple benzodiazepines without N oxide oxygen however were ~~not~~ pharmacologically more interesting than their N oxides I or their rearrangement products III , and were therefore more intensively studied. The search for alternative synthesis of this relatively simple compounds resulted in the various routes leading with good yields, to the desired products.

One of the first benzodiazepines which showed a very high biological activity and an interesting pharmacological profile is the methyl derivative. It was synthesised in 1959 and after the appropriate toxicological andclinical studies was marketed under the tradename VALIUM, Its generic name being Diazepam.



Diazepam

Pharmacology
6

The benzodiazepines have like the barbiturates, anticonvulsant, sedative and hypnotic effects. In addition the benzodiazepines possess the ability to reduce anxiety and aggression. They have a lower addictive potential than the barbiturates but have become common drugs of abuse.

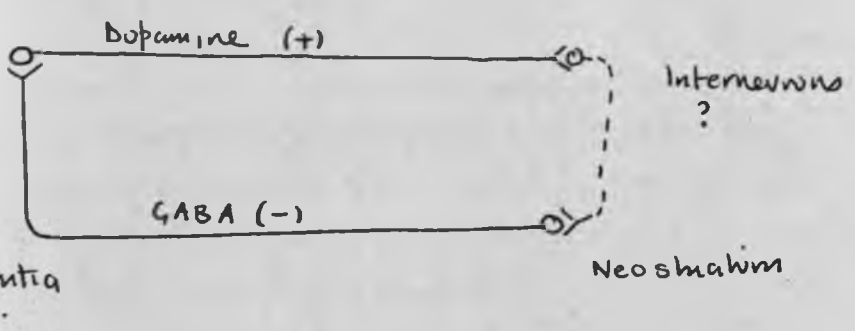
Current evidence suggests that GABAergic systems have an important role ~~in~~ in the effects of the benzodiazepines. This connection was initially made from the anti-convulsant propertyof these drugs. Despite the fact that there is no claerly demonstrable relation between drug induced seizures and central GABA levels, ample evidence suggests that interference with GABA transimissipn can induce convulsions.

The benzodiazepines are particularly potent antagonsts of seizures induced by isoniazid (which blocks GABA SYNTHESIS), ~~an~~ picrotoxin and pentylenetetrazol (which are GABA recephor blockers). In addition the benzodiazepines prolong presynaptic inhibition in the primary afferent spinal card as do the barbiturates. This effect appears to involve GABAERGIC neurons and in accord with that conclusion, GABA blocking agent prevents this action of the benzodiazepines.

With GABA acting as an inhibitory transmitter in the dopaminergic nigrostriatal pathway, facilitation of GABA ~~rena~~ transmission should produce a decrease in dopamine turn over - as schematically illustrated

This model has been supported by evidence that bicuculline reduces the inhibitory effect of chlordiazepoxide on striatal dopamine turn over - a similar mechanism may be proposed for noradrenaline and 5 hydroxy-try ptamine .

A



Schematic representation of possible GABA involvement in the dopaminergic nigrostriatal pathway.

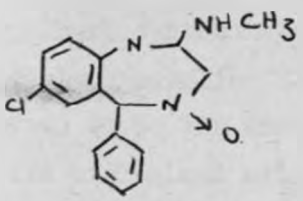
Although, the precise neurochemical mechanisms are far from clear there is same evidence that the anti-anxiety effects of benzodiazepines may involve serotonergic systems. This conclusion is born from; firstly p- chlorophenyl- alanine an inhibitor of 5HT synthesis also alters the suppressive effects of chlordiazepoxide in animal models of anxiety while the presumed 5 HT antagonists Methysergide and cinanserin both reduce anxiety in these models and add to the effects of benzodiazepi and secondly the benzodiazepines reduce the turnover of 5 HT in some brain regions with a total change in content.

These studies suggest that at least in part the antianxiety effects may result from the reduction of serotonergic activity.

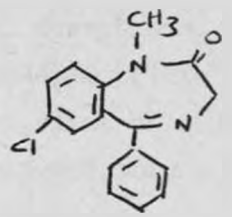
~~NB; It has been postulated that the reduction in the pre-inent effects~~

NB; It has been postulated that 5HT is involved in the punishment system and that reduction in the activity of that system diminishes the anxiety of potentially harmful situations.

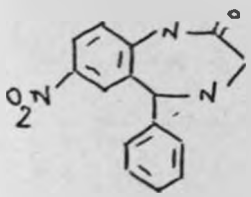
Metabolism



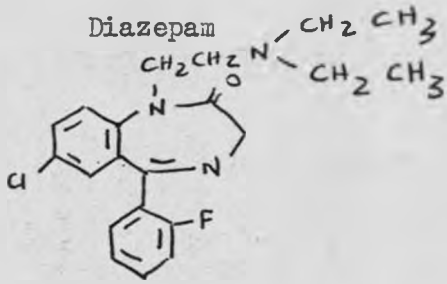
Chlordiazepoxide



Diazepam



Nitrazepam



Flurazepam

Those with alkyl function at position I undergo N de-alkylation resulting in compounds which retain biologic activity.

Those with aliphatic N also undergo N de-alkylation at those position

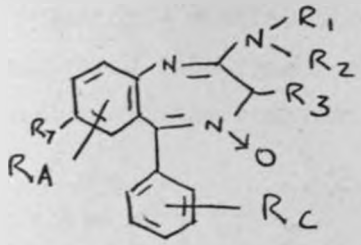
The benzodiazepines without a carbonyl group at position 2often obtai one by undergoing oxidation at position 2 to form an analogous lactam.

The lactams are readily hydroxylated at position 3 and subsequent glucuronidation at this position leads to rapid urinary excretion of these metabolites.

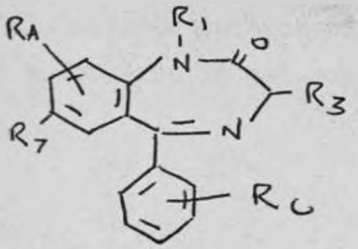
Many of the above reactions involve liver microsomal enzymes and changes in the activity of this enzymatic system do alter the rate of benzodiazepine metabolism. However the benzodiazepines per se do NOT induce the microsomal enzyme oxidising system.

Structure activity relationships.

We limit ourselves to the most intensively studied structures of the benzodiazepine (I4 benzodiazepine) derivatives types I and II.



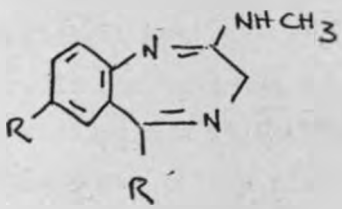
TYPE I



TYPE II

Compounds of type I (2 amino 3H I 4 benzodiazepine- 4 -oxides)

This group includes chlordiazepoxide which because of its valuable psychotropic properties has gained ~~board~~ broad clinical acceptance. Compound of this type were synthesized by treatment of the appropriately substituted 2 chloromethyl quinazoline N oxide with a primary amine chlordiazepoxide was determined to be the most potent of this group and only a few derivative approach its biological activity



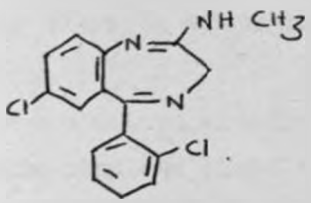
~~Structural~~ Structural changes in the methyl ammino substituent revealed that replacement of the methyl group by hydrogen reduced over-all potency to same extent while on the other hand the exchange of hydrogen for methyl did not alter the activity of the parent compounds.

The acetyl derivative of chlorodiazepoxide ~~retianed~~ retained original potency and similarly conversion of the weakly active butylamino- homolog to the corresponding acetyl derivative did not alter the biological properties.

Lengthening or branching of the substituent on the exocyclic nitrogen in position 2 as well as introduction of a heavier substituent invariably produced less active compounds.

Substitution in position 3 of the ring B had an unfavaourable effect on pharmacological activity replacement of the chlorine in position 7 of ring A by hydrogen or methyl group lowered overall activity while the effect of a bromo or a nitro group in that position was less pronounced. The trifluoro methyl compound essentially maintained muscle relaxant and taming effects of the parent compound but showed stronger anti-convulsant properties.

Multiple substitution in ring A as well as introduction of a substituent into ring C generally ~~carried~~ caused a decrease in potency with the exception of the compound below.



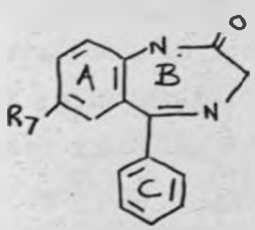
Bearing a chlorine in the 2' position of the C ring which retained most of its activity.

Replacement of ring C by hydrogen, methyl, cyclohexyl or ~~homocyclic~~ heterocyclic groups greatly reduced the biological effects.

Generally while many derivatives of chlordiazepoxide approach the overall biological activity of chlordiazepoxide none has proved to be superior. However, it can be noted that

- Increasing the size the substituent in position 2 lowers the potency.
- Replacement of the phenyl group in position 5 by other substituents results in decreased activity.

Compounds of type II (I3 dihychro 2H I4 benzodiazepin-2- ones)



This group includes diazepam, oxazepam and nitrazepam which all achieved clinical importance.

SUBSTITUENT IN RING A

Various compounds bearing a variety of substituents in various positions in ring A can be synthesized from the appropriately substituted aminobenzophenon Changes in ring A were found to influence singinficantly the activity,

An electron withdrawing substituent in position 7 had the most pronounced enhancing effect on the activity. The stronger the electron withdrawal the greater the potency.

i.e CF_3 > NO_2 > CN > Br > CI > F > H

Electron releasing groups had the opposite effect however, this rule is not without exception as compound bearing the electron releasing mercapho group in position 7 have substantial activity.

Substantial activity was also displayed by the methyl derivative but an increase in size of the methyl substituent caused a decisive fall in potency. Corresponding sulfoxides and sulfones in which the substituent has strong electron withdrawing properties showed a significant decrease in activity.

A large electron withdrawing group in the 7 position e.g (phenyl) resulted in complete lless of acrivity.

Single substitution in other postion of ring A had an unfavourable effect.

Substitution in ring C

Compound bearing substituents in position 7 which imparted maximum activity were used in most cases and both the nature and position of the s substituent in ring C were varied.

Substituent in 2' position gave the most significant results. Halogens generally increased the overall activity but other substituents into the 2' position usually resulted in a decrease in activity. This effect was mainly influenced by the size of the substituent and did not depend on its electroinductive properties.

Any substituent in the 3' or 4' position had an unfavourable effect.

The presence of two in more substituents in ring C resulted in almost complete less of activity.

Substituents in ring B

The substituent in position I has pronounced effects on molecular activity and is easily manipulated from the chemical point of view.

Compounds which had activating substituents in position 7 and also in the 2' position were the subject of investigation. Introduction of a methyl group into position I caused in most an increase in potency

Compounds with the electron releasing dimethyl amino group on a trifloromethyl or nitro group in position 7 had remarkable effects.

Introduction of an acetamido group into position 1 in the 7 cjloro-series considerably reduced the muscle relaxant and taming properties whereas the anti-Convulsant effects remains unaffected.

Replacment of phenyl group in position 5 generally caused a significant decrease in potency only the pyridyl derivatives displayed remarkable activity. The Tetrahydro derivatives of the 1 4 benzodiazepinones are generally less active than thier unsaturated precursors. Two thiones obtained from corresponding 1 4 benzodiazepin-2-ones by treatment with phosphorous pentasulfide are considerably less active than the corresponding 2 carbonyl derivatives.

The 14 benzodiazepinones of type II are the most potent of all 1 4 benzodiazepines studied. Only a few other general rules retained their validity concerning the two types of 1,4 benzodiazepines discussed. They can be sumarised as follows;

1) Electron withdrawing substituents in position 7 had a positive effect on the potency.

2) Hydrogenation of the double bond in the 4 5 position caused a significant decrease in activity.

3) Aphenyl group in positoin 5 conferred highest activity.

4) Substituents larger than methyl group in position 1 or 3 had an unfavourable effect on activity.

CLINICAL APPLICATION OF THE BENZODIAZEPINES.

As hypnotics, the benzodiazepines are effective hypnotics influencing sleep in several ways.

I) Shortening the period required to attain sufficient depth of sleep.

II) Increasing the total duration of sleep.

III)Reducing the frequency of interruption of sleep.

IV) Improving the subjectively experienced quality of sleep- the amount of REM sleep is hardly influenced and minimal REM rebound occurs on withdrawal.

The benzodiazepine derivatives Flurazepam and Nitrazepam find exlusive use as hypnotics in treating all kinds of sleep disorders as difficulty in getting to sleep, restless sleeping and early awakening. In this respect, the benzodiazepines are more useful than barbiturates as

I) They are of lower toxicity.

II) They hardly suppress REM sleep and have a much lower REM rebound on withdrawal.

iii) They are less quikly addictive.

As anti-convulsants in status epilepticus, diazepam IV is very effective.

As muscle relaxant, the benzodiazepines can be used in conditions of increased muscle tonus whether of myogenic or central origin.

As anxiolytics the benzodiazepines can be used to reduce acute tentions e.g Before operation diazepam iv is useful. The preoperative administration of benzodiazepine has a dual advantage. By calming the anxious patient smaller doses of anesthetic would be required.

The benzodiazepines are also useful in post-operative agitation and restlessness as a means of mamging alcohol abstinence. The benzodiazepines and more specifically chlorodiazeporide and diazepam are useful in the treatment of delirium tremens and its prevention after acute withdrawal of alcohol.Other withdrawal symptoms e.g anxiety,motor unrest and somatic manifestations as nausea and emesis also commonly show a favourable response to the benzodiazepines.

In psychiatric use the benzodiazepines like all psychotropic drugs require individualised doses. The optimal dose of a given compoundcan vary in different patients by as much as factor $10_{\frac{1}{2}}$ the reason is unclear.

The basis for these invidualised doses include:

i) Nature of the syndrome

ii) Characterstics of patients personality

iii) Setting in which the compound is given

iv) Patient - therapist expectations

v) Complex of pharmacokinetic factors, which is perhaps the most important.

The effects of the benzodiazepines becomes apparent after one or a few days

The benzodiazepines have only slight side effects and are of low toxcity.

These side effects that have been reported include:

i) Fatigue possibly due to hypotonia

ii) Diminished ability to concentrate.

SYNTHETIC ROUTES:

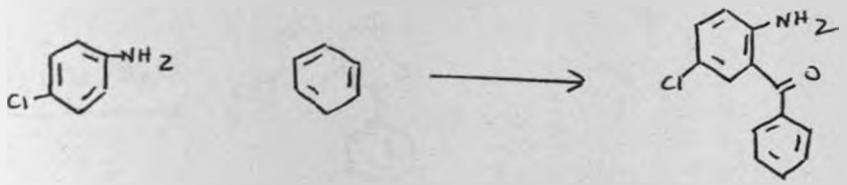
a) Synthesis of 2 amino 5 chloro benzophenone.

Synthesis from anilines.

The synthesis of 2 aminobenzophenones from anilines are the most straight forward of all the methods and usually require the least number of reaction steps to accomplish.

This generally involves a Friedel-craft acylation of an aniline. This acylation would normally result in para substitution to the amine group. If the para position is already substituted the group will be introduced ortho- to the amine group. Where the para- substituent is Chlorine or Bromine it can be removed by hydrgenolysis, to give the unsubstituted 2 aminobenzophenone.

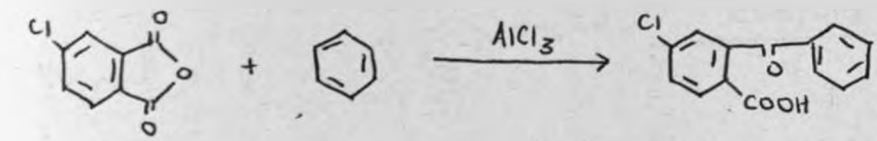
The conditions required for the Friedel craft reaction are quite vigorous and certain substituents (e.g OCH_3) are too labile for this procedure.

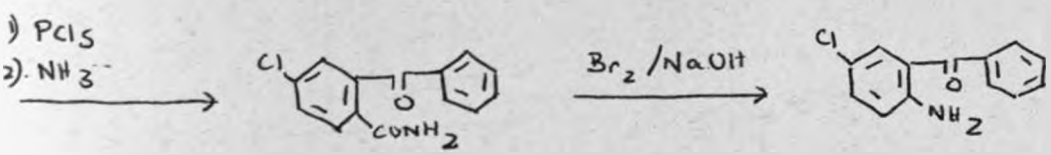


NB; removal of the 4 chloro substituent may be done by the following route. - reduction using $H_2 PdCl_2$ with KOAc.

Synthesis from 2 benzoyl / benzoic acids

The synthesis of 2 amino 5 chloro benzophenones by this method involves a Hoffman rearrangement of an amide as shown below.





This procedure is limited by the availability of the substituted phthalic anhydride as starting material and by the regio-selectivity of the Friedel craft acylation.

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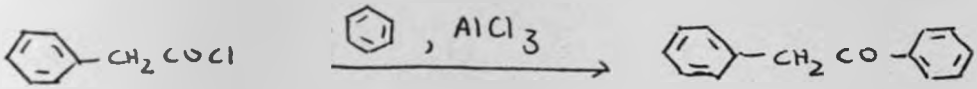
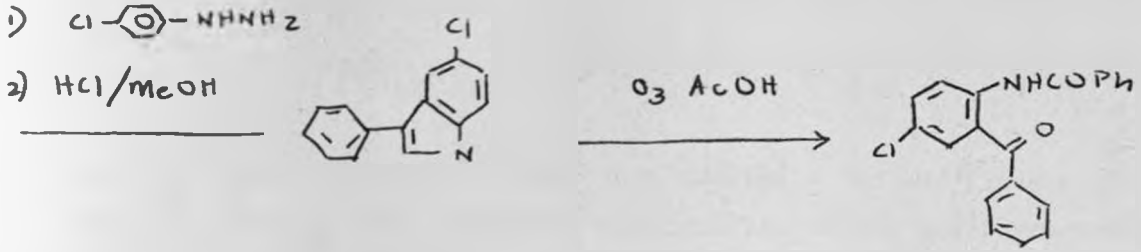
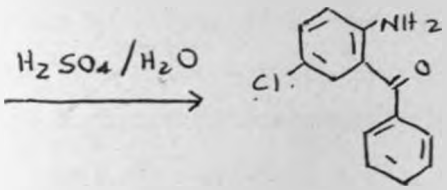
Synthesis from 3 aryl-indoles.

Starting with phenyl acetyl chloride.

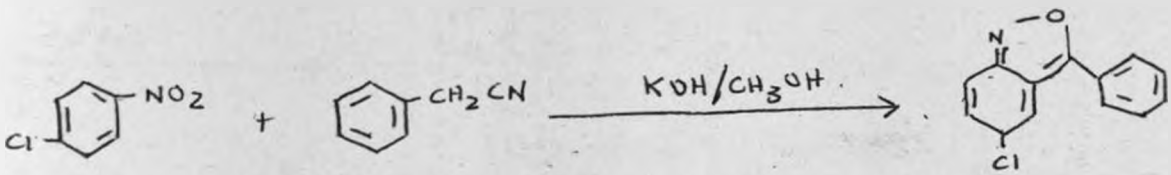


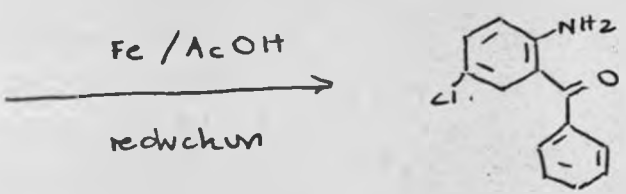




Synthesis from benzo-isoxazoles.

The 2 amino 5 chlorobenzophenone is obtained by chemical reduction of 2 I benz-isoxazoles (anthranils)



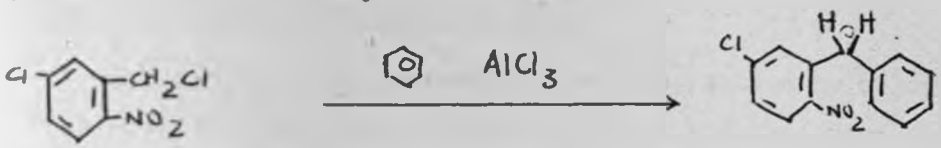


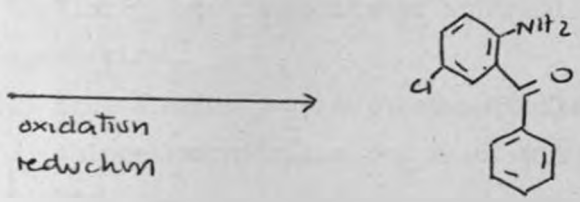
Synthesis from nitro-aryl substrates

This involves the Friedel craft reaction between a nitro-aryl substrate and benzene. The intermediate nitrobenzophenone is then reduced.

i) 5 chloro 2 nitrobenzyl Chloride

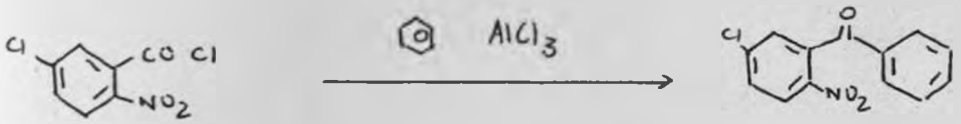
i) 5 chloro 2 nitro benzyl chloride.

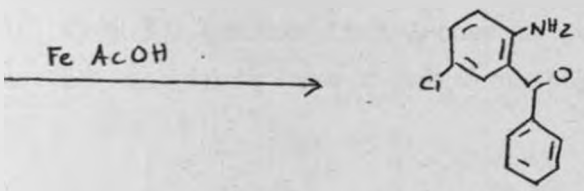




NB; The nitrobenzyl chloride is not a good substrate for the Friedelcraft reaction- probably due to detrimental complexation of the nitro group with the catalyst. However, if the 5 chloro 2 nitro- phenyl methane is obtained it can be converted to the benzophenone by use of an oxidising agent e.g $KMnO_4$ The nitro - group may then be reduced chemically.

ii)· 5 chloro nitro-benzoyl chloride.





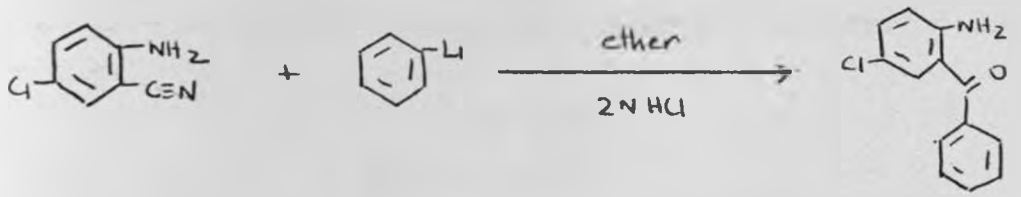
It may be possible to use 5 chloro 2 nitro benzoic acid, but this would most probably require activation of the acid group to permit Friedel-Craft acylation.

SYNTHESIS FROM ANTHRANILIC ACIDS.

Anthranilic acids are available from Isatins by oxidation with alkaline hydrogen peroxide. The synthesis of Isatins has been reviewed[13] and an additional procedure for the preparation of Isatins containing electron withdrawing substituents has been reported by Grausmann et al.[6,7] Similarly, most substituted anthranilic acid derivatives can be synthesised.

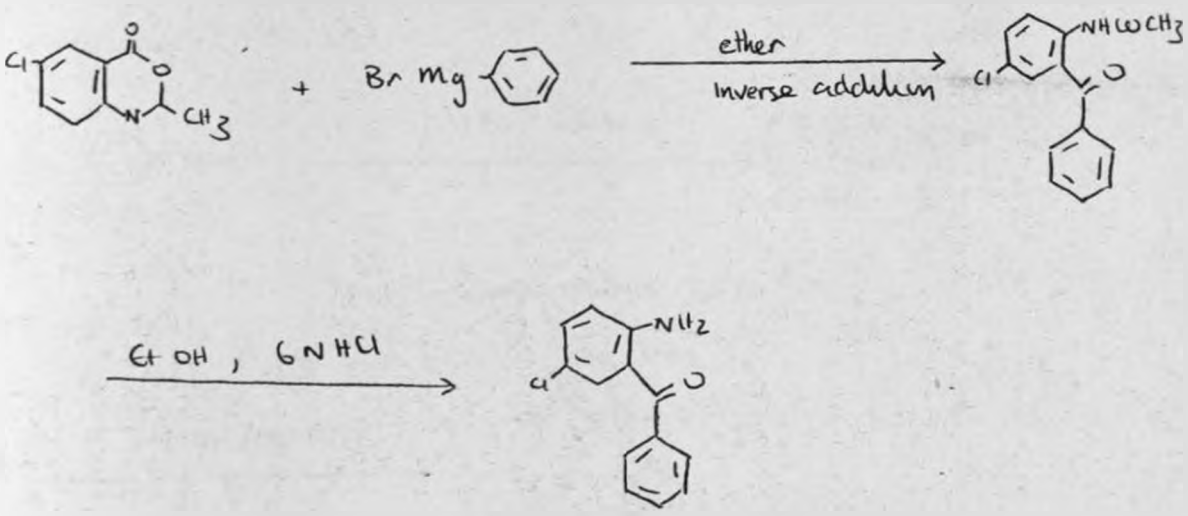
1) from 2 amino 5 chloro-benzonitrile.

2 amino-benzonitriles can react with Aryl Grignard reagents or organo-lithium reagents to give 2 aminobenzophenones.



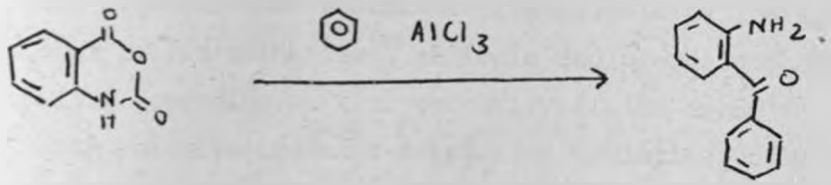
The drawback is the availability of 2 aminobenzonitriles for use as starting materials.

II) from 3 1 benzoxazines-4-ones prepared from anthranilic acids and acetic anhydride have a Grignard reagent inversely added onto them.

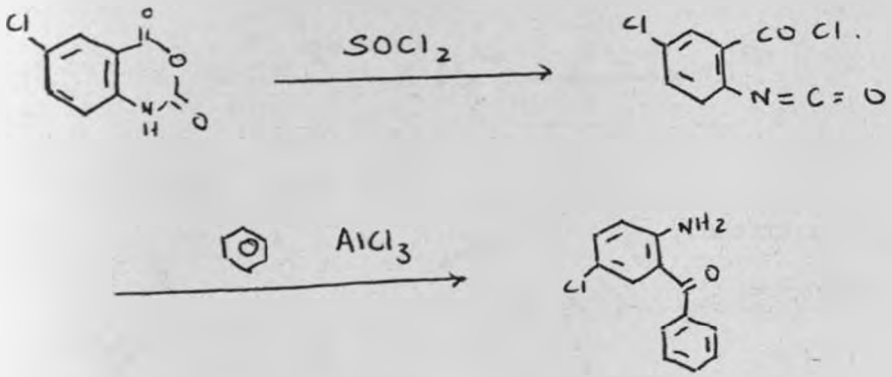


iii) from isatoic anhydrides.

Using an isatoic anhydride derivative as the acylating agent for the Friedel craft reaction , 2 amino-benzophenone has been synthesised.

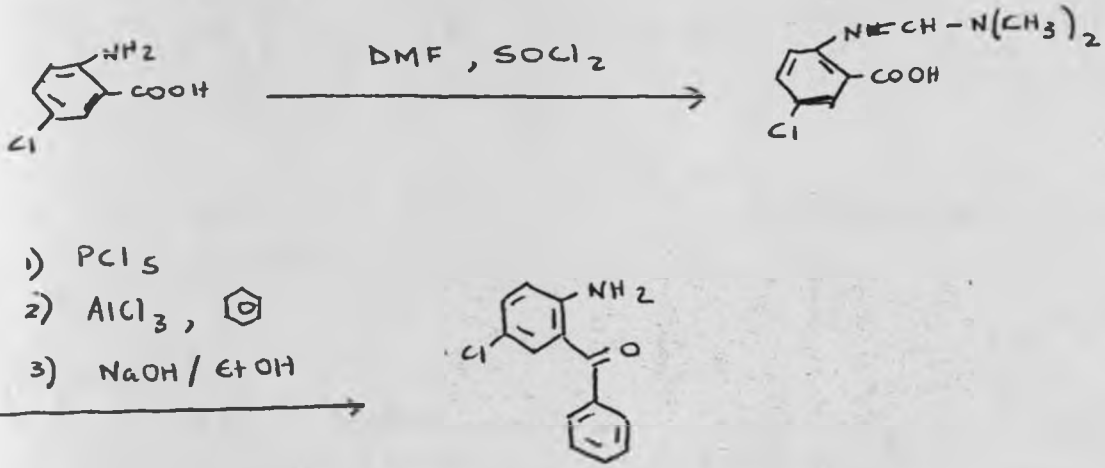


The method has been modified by first converting the isatoic anhydride to a 2 iso-cyanobenzoyl chloride which is then undergoes a friedel craft reaction.



iv) from formamidine.

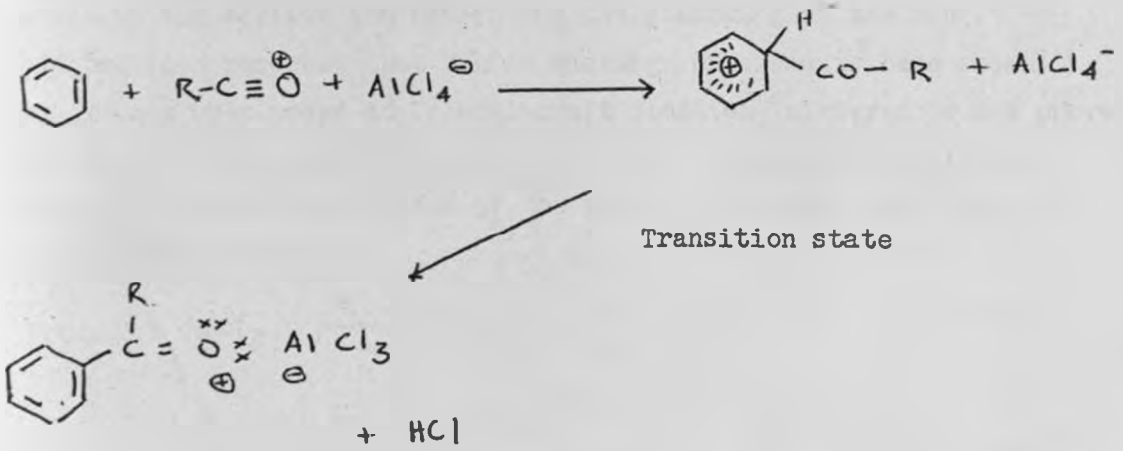
The amino group in, ~~postulated~~ 5 chloro anthranilic acid is first protected by forming an amidine with dimethyl formamidine. Then after forming an acid chloride in-situ it is able to undergo a Friedel-craft reaction.



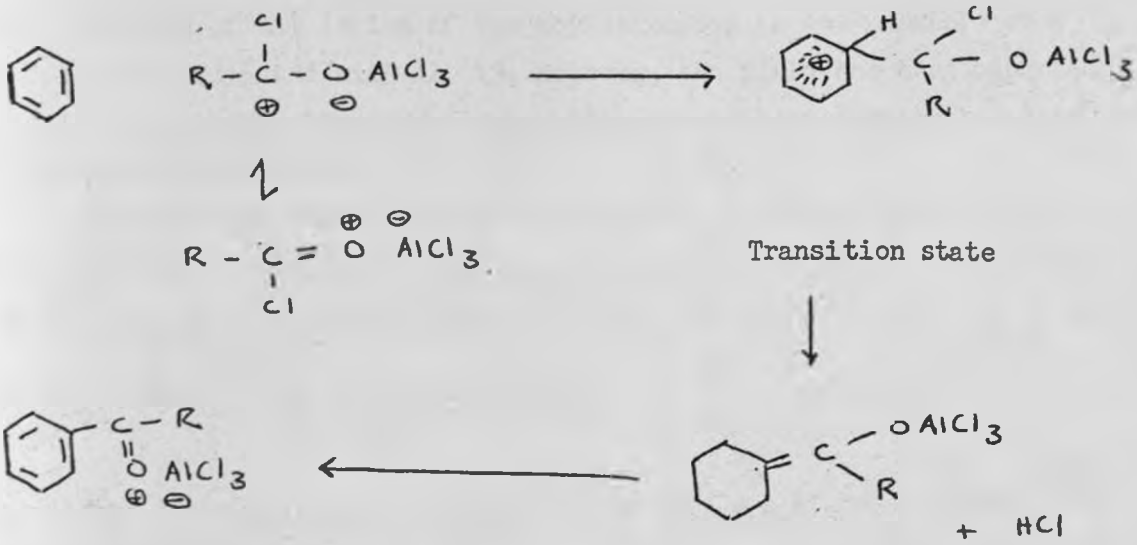
The methods described thus far involve, in most cases some kind of Friedel craft reaction. The electrophile either being generated from the N containing aromatic or in other cases from an appropriate benzoic acid derivative.

The Friedel_craft reactions (i.e acylations) are believed to occur by either of two mechanisms,[10] an ionic and/or nucleophilic substituition mechanism, depending on the reactivity of the aromatic substrate.

With reactive aromatic substrates acylation would occur by both processes simultaneously. ~~t~~ THe acylation of less activated hydrocarbons e.g toluene would proceed to a large extent by a~~s~~ substituition mechanism:= and in the case of benzene exclusively so.
i.e aryl cations are sufficiently reactive to account for the rapid acylation of unreactive compounds.
Ionic mechanism;



Stable intermediate
Substitution mechanism;



Normal Friedel-craft acylation reaction with aromatic substrates of wide range of reactivities, probably proceed by this type of substitution mechanism. The ionic mechanism only becoming important under special circumstances.

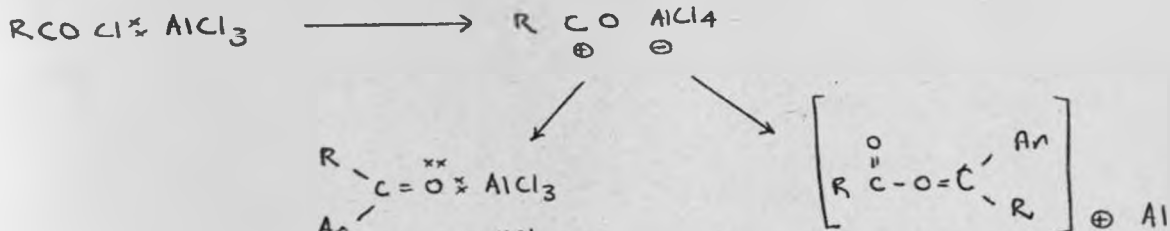
- When a sterically hindered acyl halide is used.
- When a sterically hindered position is being substituted.

A number of variables can be manipulated in Friedel-craft reactions these include, the catalyst, solvent, acylating agent and substrate.

Friedel-craft reactions (acylations) require somewhat more than stoichiometric amounts of electrophilic catalysts and many poor yields have been ascribed to insufficient amounts of catalyst. One of the factors necessitating the higher than stoichiometric amounts of the catalyst is the likely inhibition of the reaction by the product. The product may inhibit the reaction in one of the two ways;

- Tie up the catalyst preventing ionisation of the acylating agent.
- Tie up the acylium ion preventing its attacking of the ring.

It has been reported that halide exchange experiments[8] have shown that ketones when added to Friedel-craft reaction, mixtures do not prevent ionisation of the acyl halide hence, in the presence of substantial amounts of catalyst the action of the acylum ion rather than that of the catalyst is blocked.



NB: Inhibition of the action of the acylation ion is not possible when Ar COR is co-ordinated with Al Cl3. However, the yield has been reported to fall off rapidly, when more than optimum amounts of catalyst is used in the acylation reaction.

A number of Lewis acid catalyst can be used in Friedel-craft acylations. These Lewis acid catalysts include,

$Al Br_3$ $Cb Cl_5$ $Ti Cl_4$ $Zr Cl_4$ $Fe Br_3$ $Sb Br_3$ $Be Cl_2$ $P_2 O_5$

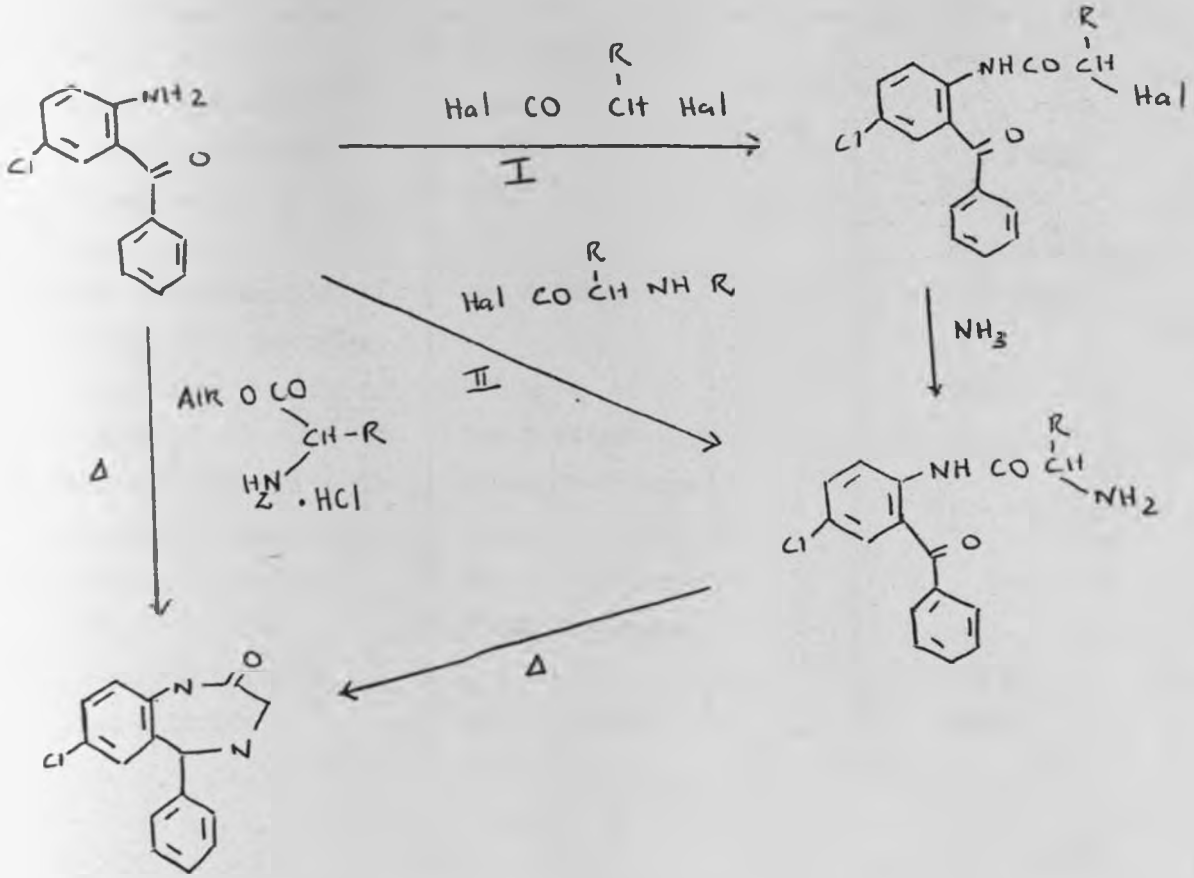
$Mb Cl_5$ WCl_6 Zn H_2SO_4 $Zn Cl_2$ $Cu Cl_2$ and $Hg Cl_2$.

The latter three give good yields, without the use of a solvent, at elevated temperatures.

Aluminium chloride is the cheapest and most efficient, its purity is however important as it influences the yield of the product. Water is believed to have an activating influence on aluminium halides. This has been explained by the formation of hydrates of the type (Al X3 OH) H which can act as powerful sources of protons. Such acids would be expected to behave in a similar manner as other proton acids that can act as catalyst.

Synthesis of I4 benzodiazepin-2-ones

Starting with the 2 amino benzophenones there are several synthetic routes for the synthesis of the I4 benzodiazepin -2-ones. The principal and most frequently used synthetic routes are:



~~This~~ These reaction routes involve nucleophilic substitution reaction ~~me~~ mechanisms in which the lone pairs of electrons on the nitrogen atoms attack the electro-deficient carbon atoms of the carbonyl moieties.

The first route is more versatile facilitating better yields ~70 -80 % despite the involvement of several steps in the reaction sequence.

The third route facilitates the synthesis of benzodiazepinones with substituents at position 3 since many ~~and~~ α amino acids bearing additional substituents ~~at~~ on the α carbon are commercially available.

Other routes of synthesis of the 7 membered ring often involve the use of intermediates possessing a protected or potential glycine moiety

CHEMICALS AND REAGENTS

CHEMICAL	SUPPLIER	GRADE
Benzoic acid	May & Baker	Lab; reag:
Benzoyl chloride	Merck	
4 Chloro-aniline	B D H	Lab; reag:
Chloroform	B D H	Analar
Diethyl ether	May & Baker	Analytical reag:
Dimethyl-formamide	May & Baker	Lab; reag:
2 4 Dinitro- phenyl-hydrazine	B D H	Analar
Glycerol	May & Baker	Lab; reag:
Ortho-phosphoric acid	Howse Mc George	
Phosphorous pentoxide	Merck	
Potassium hydroxide	Howse Mc George	
Sodium chloride	Howse Mc George	
Stannous chloride	B D H	Analar
Zinc chloride	May & Baker	Analar

REAGENTS

I) 2 4 Dinitro- phenyl hydrazine (4°/0)

About 4g of 2 4 Dinitro- phenyl hydrazine was weighed out and dissolved in 100mls of N N Dimethyl formamide to obtain an approximately 4 % solution of 2 4 Dinitro- phenyl hydrazine in N N Dimethyl-formamide.

2) Polyphosphoric acid

The polyphosphoric acid was prepared by stirring a mixture of 8 parts by weight of phosphorous pentoxide and 5 parts by volume of 90 % ortho-phosphoric acid at 85°C for 30 min. Thisgave the resulting product of 82-85% P_2O_5 content, consisting of 35 % tri-polyphosphoric acid the remainder being phosphoric acid and other polyphosphoric acids.

EQUIPMENT

I) Pye unicam Ultra Violet spectrophotometer Model SP 800A

2) Perkin Elmer Infra red spectrophotometer Model 727B

3) Mettler H35A Analytical balance

4) Gallenkamp melting point apparatus

THIN LAYER CHROMATOGRAPHIC STUDY OF THE CRUDE PRODUCT

The single development ascending thin layer chromatographic technique was employed using Kieselgel GF_{254} as adsorbent.

Preliminary studies were carried out on microscope slides to select a suitable solvent system. Various solvent systems were tried which included Benzene-methanol (I7:3) Chloroform-ether (3:I) No seperation was effected but a suitable R_f value (0.5) was obtained with Benzene-Methanol (I7-3) mixture as mobile phase.

Further TLC investigation was carried out on larger plates for each crude reaction product. The layers were prepared by spreading a slurry of 30g Kieselgel GF_{254} in 60 mls of water with a Desaga spreader, to a thickness of 250 μm. After drying at room temperature, the plates were activated by drying in an oven at II0°C for I hour. The mobile solvent system was placed into a developing chamber of size 2Ix6x2I cm lined with filter paper. The tank was allowed to equilibrate for at least an hour.

AN approximately 0.5 $^{w}/_{o}$ v solution of the crude product in ether was used for spotting. visualisation was performed using ultra violet light followed by spraying with a 2 4 Dinitro-phenylhydrazine solution in methanol. The plates were allowed to stand for 2-3 min until the spots developed maximum color intensity.

The HR_f values for the spots were obtained and calculated.

NB; pure 2 amino- 5 chloro- benzophenone was not available for reference.

EXPERIMENTAL WORK:

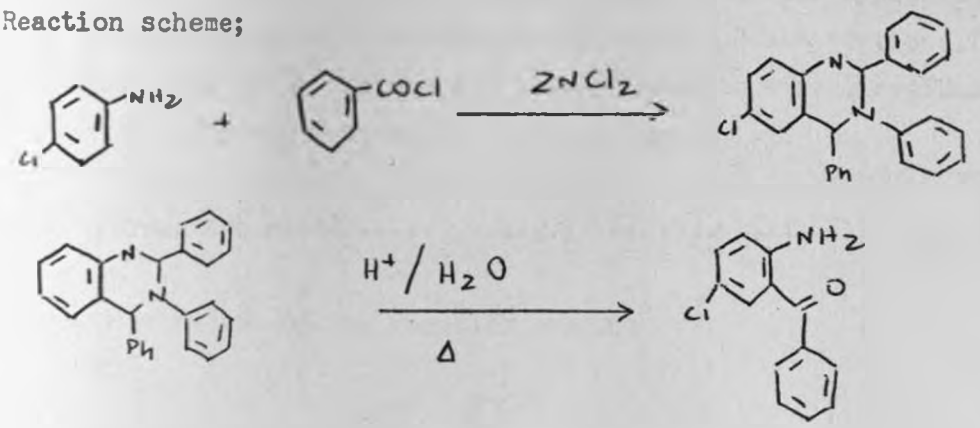
SYNTHESIS OF 2 AMINO- 5CHLORO- BENZOPHENONE

METHOD I: Zinc chloride method.

Reactants 4 Chloro- aniline, Benzoyl chloride.

Catalyst Zinc chloride

Reaction scheme;



0.I724 moles (20 mls) of Benzoyl chloride in a 500ml flask was heated in a glycerol bath saturated with sodium chloride. To the 0.I724 moles of benzoyl chloride heated to I20°C was added in portions with stirring 0.05644 moles 7.2g of 4 chloro-aniline. The mixture was then heated to I80°C and 0.0675I moles (9.2g) of $ZnCl_2$ was added. The temperature of the reaction mixture was gradually increased to 220°C, during which the reaction mixture assumed a dark purple color, and kept there until HCl evolution had ceased. - This took about 45min.

The reaction mixture was then allowed to cool to I25°C, afterwhich 20mls of water was cautiously added ,the reaction mixture swirled and heated to reflux. The hot water layer was decanted and the procedure repeated once.

The water insoluble blackish-purple mass that remained in the flask was dissolved in a mixture of IOmls Glacial acetic acid, I3mls conc; H_2SO_4 and 7mls distilled water. The solution was then refluxed for I7hrs then allowed to cool.

The cooled reaction mixture was poured into a large amount of water (I00mls at approx; 0°C) The solution was then filtered through a sintered glass filter. The filtrate was extracted with two 40mls portions of ether seperating it from the acid insoluble 4 chloroaniline formed from II. The ether extracts were washed with an excess of alkali to remove benzoic acid then combined and reduced to a small volume using the rotatory flask evaporator The ethereal extracts was transferred to a conical flask and covered with a perforated aluminium foil and allowed to evaporate to dryness at room temperature i,e approx 20°C

A yellow residue was obtained which was heavily contaminated with dark colored matter. It could not be further purified by recrystallisation from

In an effort to extract the expected reaction product from this residue an acidic solution of the residue was made in 70mls HCl and filtered through Whatman paper grade 3 into a seperatiry funnel. The solution was then made distinctly alkaline to litmus paper, using potassium hydroxide pellets and an ether extraction performed using three 30mls portions.The ether portions were then combined and concentrsted to a small volume then stored overnight to produce a yellow-brown residue.

Weight of reaction product.....00.6278g

Percentage yield..... 4.8 %

Charecterisation of the reaction product

TE

TEST	OBSERVATION	INFERENCE
Appearance	Yellowish-brown	-
Solubility in water	Does not dissolve	Compound has low polarity.
Melting point	Melts in temperature range I02- I06°c	Compound is not pure.
2 4 Dinitro- phenyl hydrazine test	Yellow prepcipitate is formed	Confirms the prescence of a carbonyl group.

The ultra-vilet and Infra-red spectra of the crude reaction product were obtained.

Interpretatinn of the spectra

Ultra-violet spectrum

This obtained for the ethanolic solution.

From the U.V spectrum, the R band at 387 nm ($n-\pi^*$ transition)provides evidence of the existence of the carbonyl C=O group chromophore. This peak disappears IN the acidic ethanolic solution as aresult of electron localisation as shown overleaf.

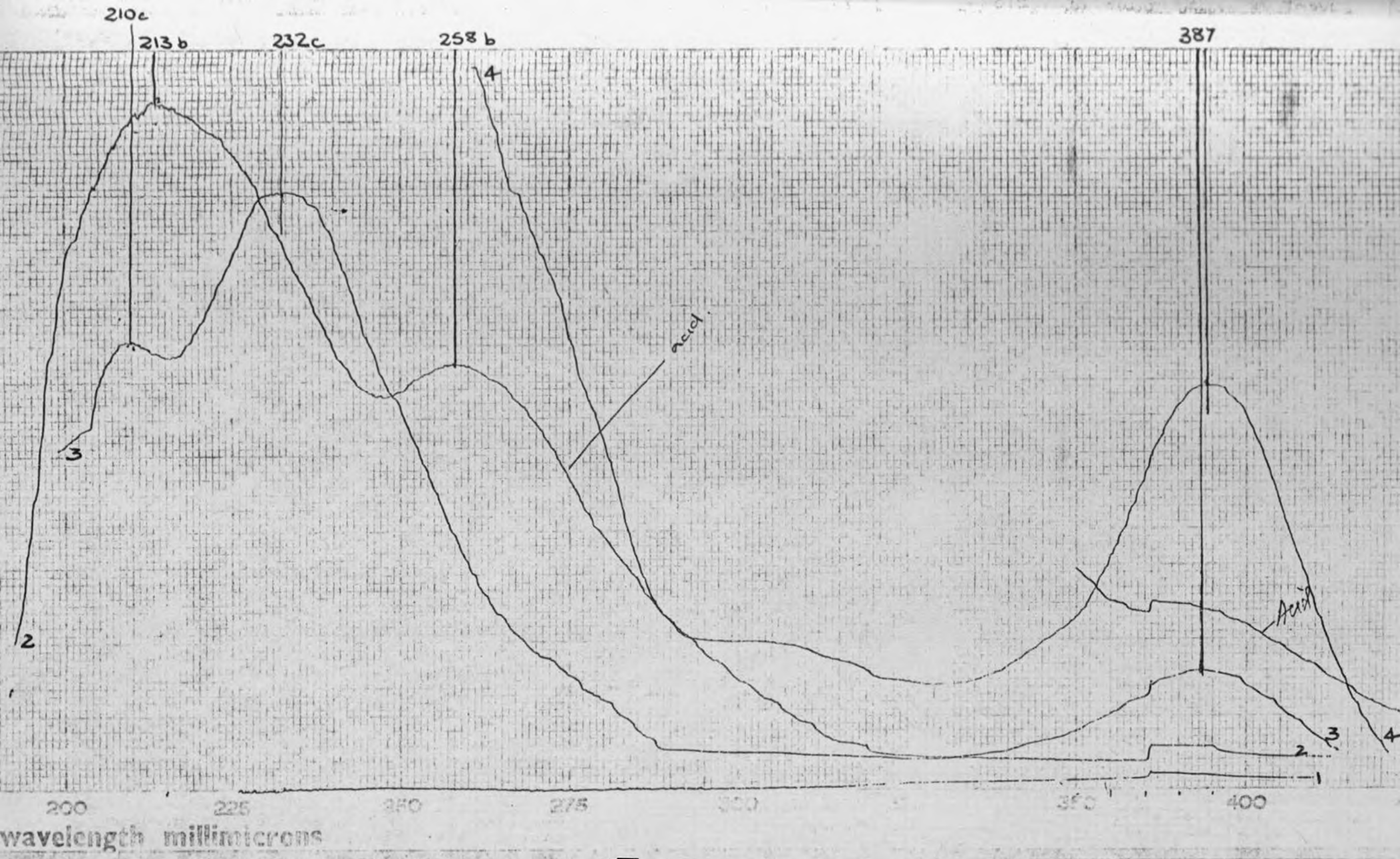
The K band (π-π^* transitions) CAn attributed to the conjugated enone system. It undergoes a typical Bathochromic shift to a longrer wavelenth as the solvent polarity is increased by acidification. This bathochromic shift presumably results from a reduction in the energy level of the x excited state accompanying dipole-dipole interaction and hydrogen bonding.

Infra-red spectrum

This was obtained in Chloroform as the use of Potassium bromide disks persistently produced poor spectra.

From the I.R spectra the peak at I640cm^{-I} can be assigned to C-O stretching vibration of the carbonyl group. This peak provides evidence of acylation of the 4 chloro-aniline.

Assignment of the other peaks is made difficult due to the poor spectrum obtained. However the N-H stretching and C-H stretching vibrations occur at 3400 cm and 3000 cm respectively. The N-H deformation vibration peak at I630 cm has most probably been masked by the carbonyl C-O stretching peak at I640 cm. However the peak at I200 cm due to C-N stretching vibration is indicative of an aryl amine. (Ar-NH_2)


210c
213 b
232c
258 b
387
4
3
2
Acid
Acid
3
4
2
1
200
225
250
275
300
350
400
wavelength millimicrons

PHASE CHLOROFORM

REMARKS

HI ENERGY ☐ CAL. ☐

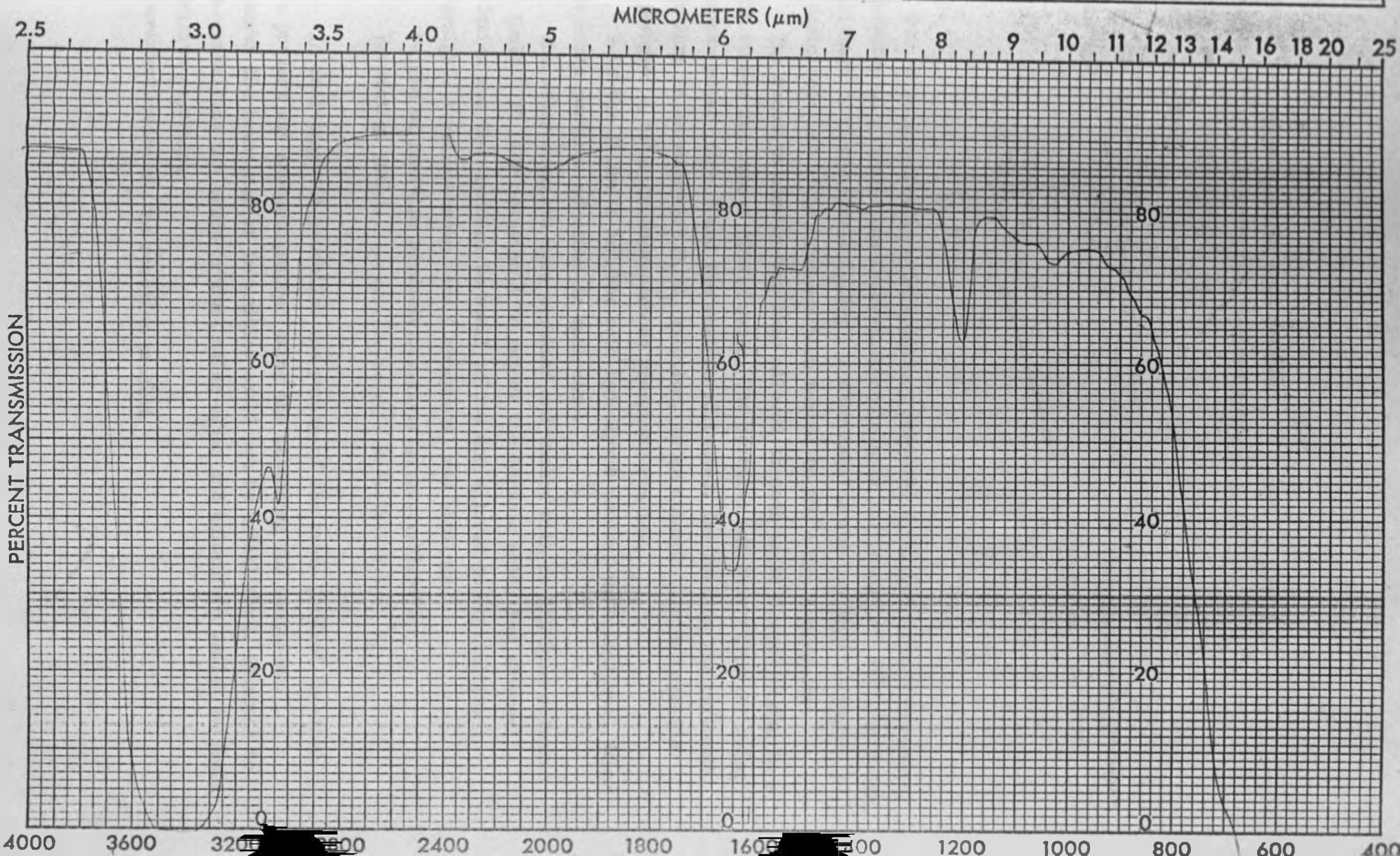
RESOLUTION ☐

OPERATOR THURANIRA DATE 9/12/83

SAMPLE BENZOPHENONE

$ZnCl_2$ method

ORIGIN

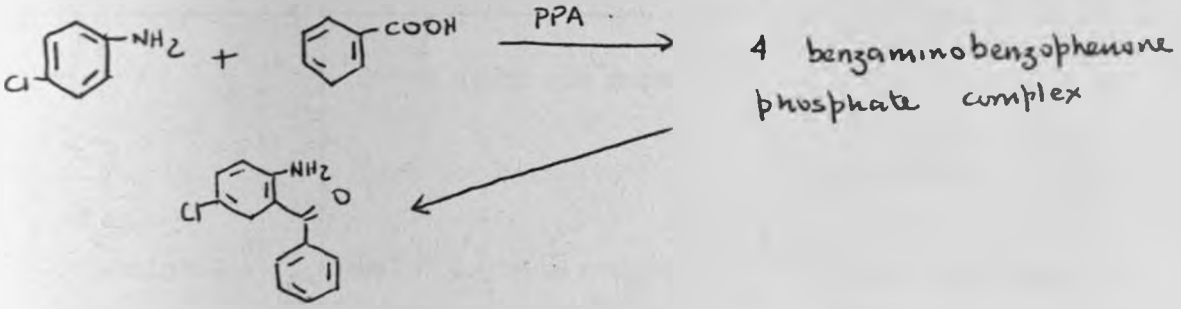


METHOD 2: Polyphosphoric acid method.

Reactants 4 Chloro-aniline, Benzoic acid.

Catalyst Polyphosphoric acid

Reaction scheme;



To a polyphosphoric acid solution, prepared by mixing I20g Phosphorous pentoxide with 75mls Conc Ortho-phosphoric acid and heated at 85°C for 30min, a mixture of 0.075253mole (9.60g) 4 chloroanilne and 0.076I£mole (9.30g) benzoic acid was added. The was then heated to 200°c in a sandbath.

The reaction mixture was then allowed to cool to 80°C then poured in a thin stream into about 300mls water. The solution was then filteredo using Whatman paper grade 3 and the residue collected. The residue was refluxed for 2hrs in an ethanolic H_2SO_4 solution, in an attempt to hydrolyse the 4 ~~phospho~~ 4 benzaminobenzophenone phosphate complex.

Both the filtrate and the acid hydrolysis product were extracted using two 80mls portions of ether in each case.

The ether extracts were combined and washed with an alkaline solution (80mls $^{N}/_{IO}$ KOH solution) to remove the benzoic acid, The ethereal solution was then reduced to small volume and allowed to crystallise overnight. A yellow-brown mass (amorphous) was obtained

Weight of reaction product.....0I.5694g

Percentage yield..... 9.0 $^{o}/_{o}$

In an attempt to establish the purity of the crude product obtained the product was chromatographed using the ascending TLC technique. However the prescence of impurities could not be established. Attempts to re-crystallize the crude product using ether and chloroform failed to yield definite crystals.

Charecterisation of the reaction product

Characterisation of the reaction product

TEST	OBSERVATION	INFERENCE
Appearance	Brown amorphous mass	-
Solubility in water	Does not dissolve	Compound has low polarity
Melting point	Melts in temperature range IOI - I06°C	Compound is relatively unpure
2 4 D initro- phenyl HYdrazine test	A yellow precipitate Is formed	Confirms the prescence of a carbonyl group

The ~~ultra- violet and~~ Infra-red spectra of the crude reaction product were obtained.

Interpretation of the Infra-red spectrum

The broad peak at 3000cm can be assigned to $-NH_3$ stretching frequencies. The primary amine salt was probably isolated from the acidic reaction mixture. The broad peak combines the NH asymmetric, NH symmetric and the CH stretching v vibrational peaks.

The NH deformation peaks I600cm and the NH_3 rocking frequency near 800cm are not easily discernible.

The peak at I690cm can be assigned to C-O stretching of the carbonyl group whose prescence is confirmed by the 24 Dinitro-phenyl hydrazine test.

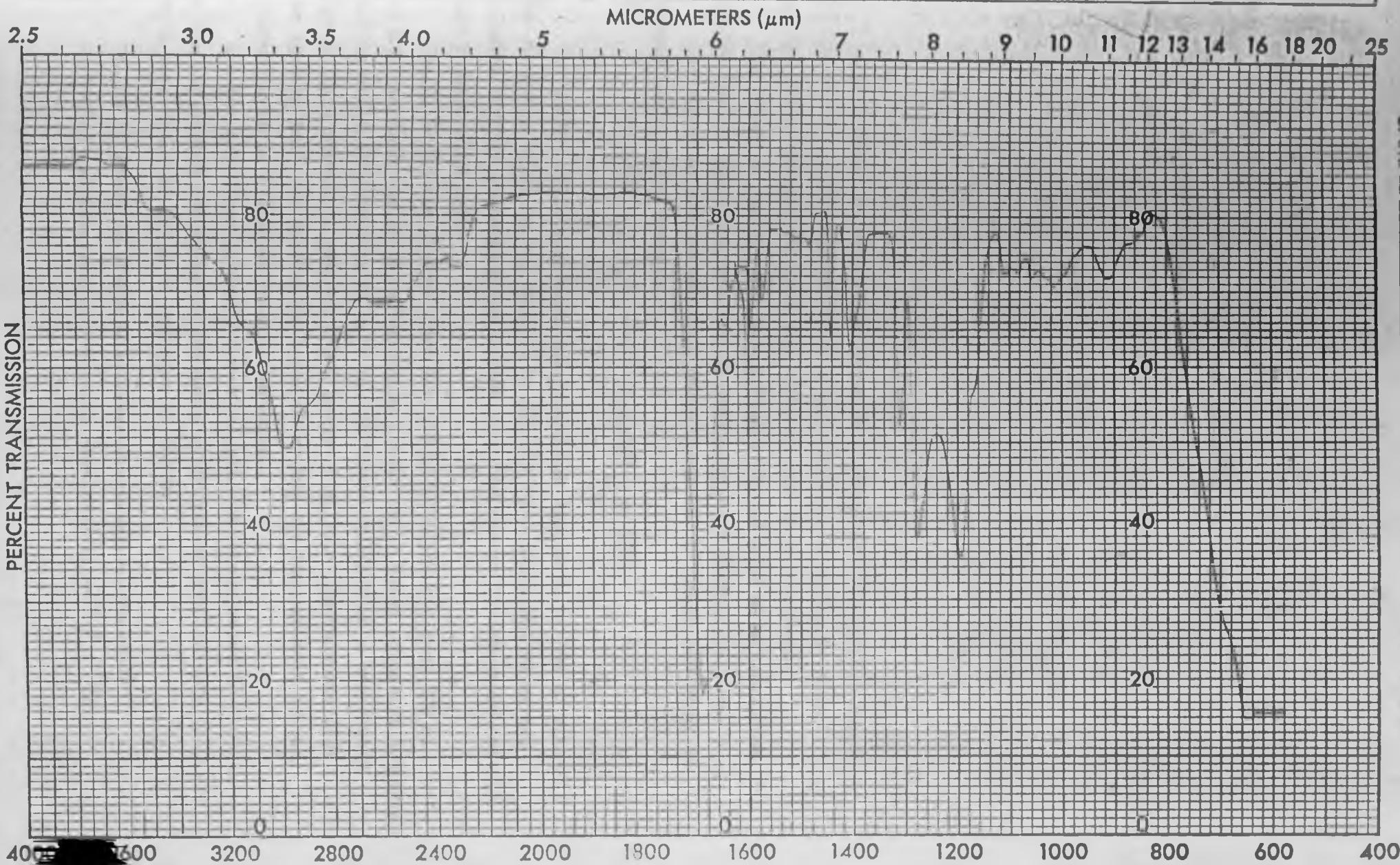
PHASE CHLOROFORM

RESOLUTION ☐

REMARKS

OPERATOR [illegible] DATE 24/11/83

ORIGIN Product PPA method



SAMPLE

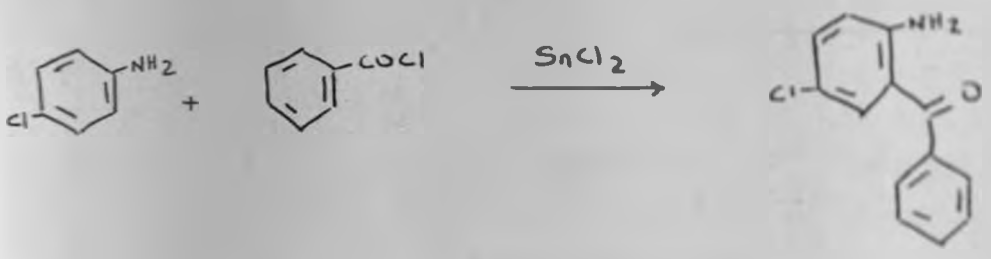
SPECTRUM NO. PPA/4/3

METHOD 3: Stannous Chloride method.

Reactants 4 Chloro-aniline, Benzoyl chloride

Catalyst Stannous chloride

Reaction scheme;



To a mixture of 15.0900g (0.0669mole) Stannous chloride and 4.0164g (0.0315mole) 4 chloroaniline in a 250ml round-bottomed flask, 20ml (0.1724 mole) benzoyl chloride was added in two 10 ml portions.

The reaction mixture was then refloxed at 150°C in an oil bath for an hour during which the reaction mixture assumed a yellowish-brown hue.

The reaction mixture was then poured into 100 ml distilled water to destroy the benzoyl chloride.

viz $C_6H_5COCl + H_2O \longrightarrow C_6H_5COOH + HCl$

The yellow solid mass that was formed was dissolved in 100 ml ethanol. The ethanolic solution was diluted to 500 mls with distilled water and fillered through sintered glass filter No. 4 to remore the stannous chloride that precipitated out.

The filtrate was divided into two 250 ml portions and each 250 ml portion was made distinitly alkaline to litmus paper using potassium hydroxide pallels while in contact with a 70 ml. Chlroroform layer in a seperatory funnel. This served to extract the 2 amino- 5 chloro- benzophenone from the agueous into the chloroform layer retaining the benzoic acid in the aqueous layer as its water soluble benzoate.

The two choroform extracts were combined and concentrated to a small volume and stored for hours in the dark. After yellow cystals were obtained which were noted to daken on exposure to light.

Weight of reaction product.....00.7507g

Percentage yield.....18.3 %

Charecterisation of the reaction product

TEST	OBSERVATION	INFERENCE
Appearance	Yellowish-brown	-
Solubility in Water	Does not dissolve	Compound has low polarity.
Melting point	Melts in temperature range II0- II3° C	Compound is not pure.
2 4 Dinitro - phenyl hydrazine test	Yellow prepcipitate is formed	Confirms the presence of a carbonyl group.

The Infra-red spectrum of the crude reaction product was obtained.

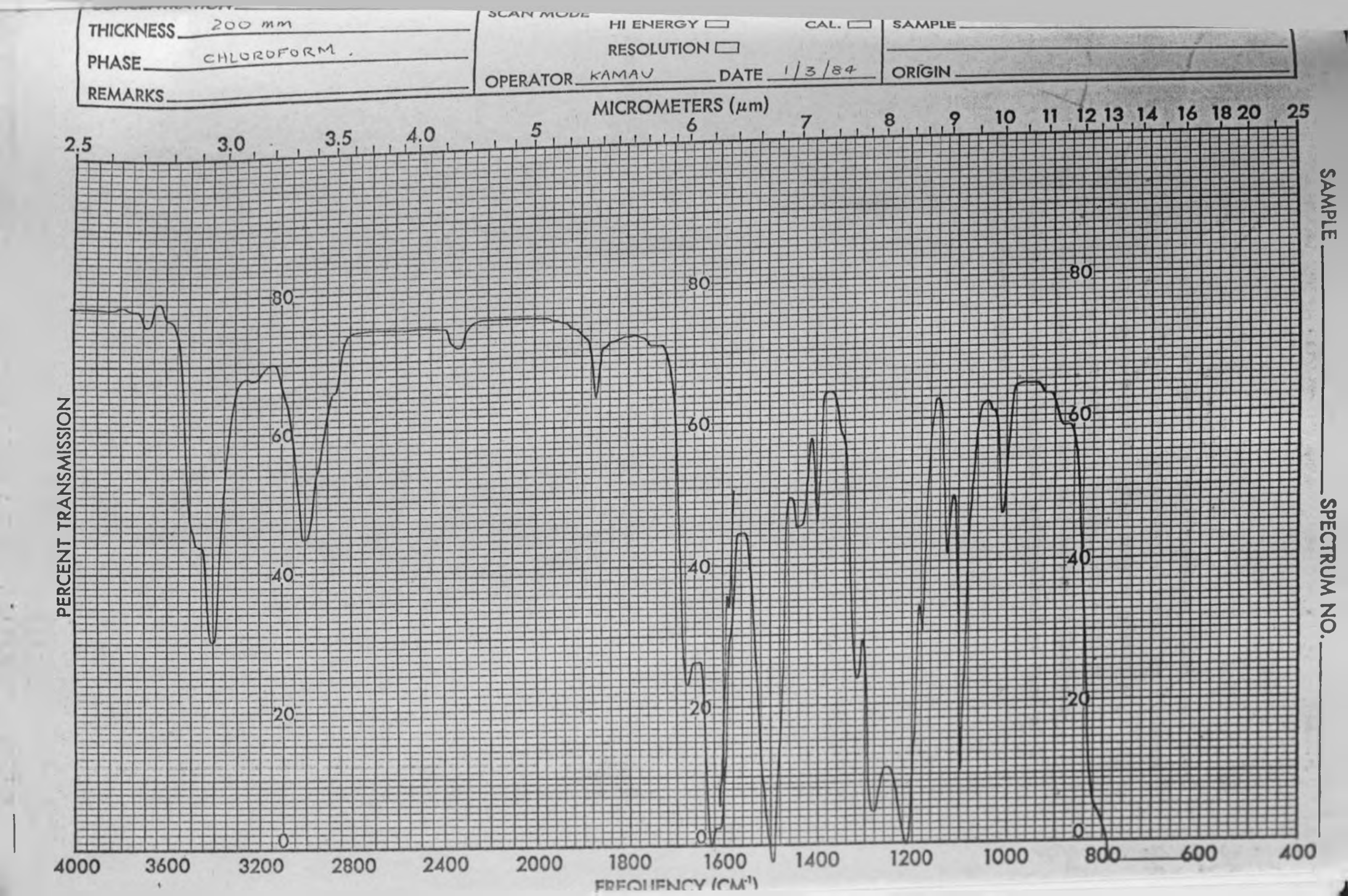
Interpretation of the Infra-red spectrum.

From the Infra-red spectrum obtained seven clear peaks are discernible. The first occurring at 3400 cm almost masks a peak occuring at 3475 cm . The two peaks can be assigned to the primary amine group, the peak at 3475 cm being due to symmetric NH stretching mode and the peak at 3400 cm being due to symmetric NH stretching mode. That the peaks are related to each other is evident from fact that they obey the relation drawn up by bellamy and williams[3]

i.e $v_{sym} = \dfrac{v_{sym} - 345.53}{0.876}$

$$v_{asym} = \frac{3400 - 345.53}{0.876} \qquad 3486.8$$

The strong peak at I630 cm can be assigned to NH_2 deformation vibrational mode and the peak at I280 cm due to C-N stretching of the aromatic anine. These peaks indicate the presence of a primary aromatic amine.


THICKNESS 200 mm
PHASE CHLOROFORM
REMARKS
SCAN MODE
HI ENERGY
CAL.
RESOLUTION
OPERATOR KAMAU
DATE 1/3/84
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5
3.0
3.5
4.0
5
6
7
8
9
10
11
12
13
14
16
18
20
25
PERCENT TRANSMISSION
80
60
40
20
0
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
FREQUENCY (CM-1)
SAMPLE
SPECTRUM NO.

The peak at I680 cm may be assigned to C=O stretching vibrational mode suggesting the presence of a new group formed on acylation of the 4 chloro amine. The substitution pattenn into the aromatic ring is possibly asymmetic by virtue of the peaks occuring in region I225 - 950 cm

The CH str vibrational mode at 3000 cm only serves to indicate aromaticity just as the weak the CH overtone and combination band of CH out of plane bending absorption at I870 cm

DISCUSSION

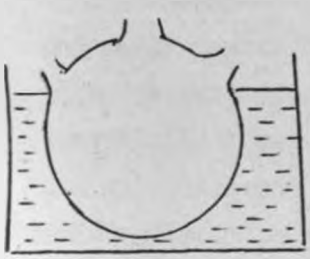
Friedel craft acylations provide the most obvious means of synthesizing 2 amino-5 chloro-benzophenone and indeed numerous benzophenone. Of the catalysts investigated $FeCl_3$ causeed a violent reaction forming dirty brown mass from which nothing meaningful was isolated. Cupric chloride ($CuCl_2$) on the other hand failed to provide a product despite refloxing for an hour.

However, $ZNCl_2$, polyphosphoric acid and stannors chloride facilitated reaction between 4 chloroanitine and benzoyl chloride/benzoic acid. In all three cases elevated temperatures were required for the reactions to proceed. Achieving and maintaing the respective temperatures was rather unsatisfactory due to lack of the appropiriate facilities. This was particularly so where temperatures required were in excess of $180^{\circ}C$. In the friedel craft reaction employing $ZNCL_2$ as catalyst the reaction temperature of $220^{\circ}C$ was attained by employed a glycerol bath saturated with sodium chloride. This solution boils at $220^{\circ}C$.

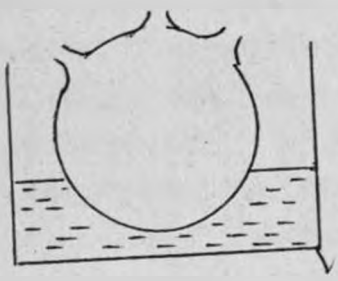
The use of the glycerol bath had several disadvantages firstly the attainament of the reaction temperature requires a protracted heating period under stable ambient condition ,

- achieved by employing the fume cupboard.
- secondly the reaction temperature was also the boiling point of the glycerol solution saturated with sodium chloride as a result vapouration of glycerol from the bath and its recondensation above the apparatus often messed up the experimental area. Hence when employing polyphosphoric acid as the catalyst an alternative means of achieving the elevated temperature was sought . In this case a sand bath was employed - the principle being that sand baths can be used to achieve elevated temperatures and as the reaction mixture was found to boil at this temperature a satisfactory arrangement would provide for the achievement and maintainance of $220^{\circ}C$ for the required period.

The two round bottomed flask could be immersed in the sand bath to varying degrees the extremes of which are illustrated below.



I



II

Arrangement II was more suitable as it did not result in charring of the reaction mixture as often as it did in arrangemnt I. As the sandbath was able to acumulate and retain heat. The heat supply was periodically reduced after attaining the reaction temperature.

The reaction employing stannows chloride SnCIz as catalyst was able to pro proceed at lower temperatures which was achieved by the use of an oil bath.

The reaction conditions employed to synthesize 2 amino 5 chloro benzophenone by employing zinc chloride as catalyst was evidently harsh. As it resulted in formation of the purple addition product which sternbach et al proposed be hydrolysed over a I7 h period. The hydrolytic ~~milieu nuclear~~ employed experimentally (H^+/H_2O) failed to significantly hydrolyse this purple addition product - the latter was observed to dissolve in hot acidic solution and precipitate out as fine particles on cooling. The particles contaminate the crude product obtained and could not be filtered through sintered glass filters.

However, yellow cystalline material contaminated/speckled with the purple particulate matters was eventually obtained by ether extraction. The only evidence that acylation had actually occurred were the peak at I640 cm on the IR spectrum of the crude product and formation of a yellow 2 4 dinitrophenyl-hydrazone precipitate when the crude product was shaken with a 4% W/v 2 4 dinitrophenylhydrazine solution.

A lower reaction temperature would perhaps have been more suitable the optimal temperature being at which the zinc chloride is able to catalyse the acylation with a minimum of side reactions.

Polyphosphoric acid at 200°C as catalyst provided less drastic conditions however, it was noted that if the reaction vessel (round bottomed flask) was nearly wholly immersed in the sand bath the reaction vessel contents were easily charred. But at 200°C the reaction proceeded with the formation of a brown reaction mixture which staskun attributes to a presumed 4 benzomino benzophenone phosphate complex.

The ethereal extracts of this reaction mixture formed yellowish brown amorphous crystals when allowed to crystallise. Re-crystallisation using ether or chloroform failed to produce yellow crystals. Proof of acylation was obtained from the IR spectrum of the crude product - the peak at 1680 cm due to a carbonyl (C=O) group of the benzophenone. The fact that the ether extraction was performed on the acidic reaction mixture gives credence to the differences in the IR spectra obtained.

For the crude product obtained here by the use of stannous chloride as catalyst as the ether extraction was from acidic solution the N-H str vibrational and CH stretching vibrational peaks of the primary amine have been found to give the broad NH stretching peak for NH_3 centrered at 3000cm rotably the C-N str peak at I200cm was not allowed through the NH deformation vibrational peaks fail to appear.

e.g at I500cm

Again the test for presence of carbonyl group employing 2 4 dinitropheny-hydrazine gave a positive result.

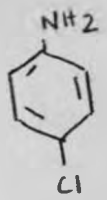
ie yellow precipitate of hydrazine was formed confirming the presence of a new group.

The synthetic route employing stannous chloride as catalyst was most conveinent as the reaction conditions could be achieved and maintained satisfactorily. The synthetic route also provided the highest yield when compared to those involving the use of polyphosphoric acid on zinc chloride as catalysts respectively.

The methods employed to synthesize 2 amino 5 chloro benzophenone are not the most satisfactory is evident from Walsh's review[15] of 2 amino 5 chloro-benzophenone synthesis. This reasoning is based on several reasons.

Firstly, the most appropriate cataylst for the fredel craft acylation of 4 chloroaniline by benzoyl chloride is aluminium III chloride. Aluminium chloride is a part from being cheapest is the most efficient, its purity is important as this is believed to influence the yield of the product R. YD kulkani reports that (BI $CI_3.2H_2O$) Bismuth trichloride dihydrate as catalyst at 90-I40^{o}C for I5-20 minutes with a crystal of iodine to further accelerate.The reaction has been found to be useful. The whole variety of friedel craft reaction catalysts would have to be assessed to determine which are more suitable catalysts.

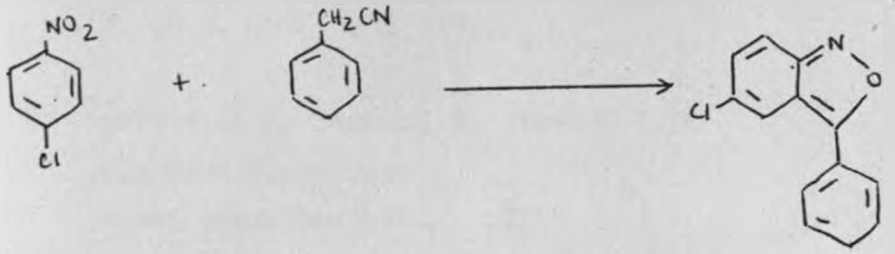
Secondly this type of acylation of 4 chloro amiline may not be preferable because of the two substituents; the amino group and the chloro group both ortho para directors. But the chloro group is deactivating as opposed to the activating influence of the amino group R. No evidence obtained as yet indicates the relative activating/ deactivating influences of either the amino or the chloro group respectively. However, it is suggested that the activating influence of the amino group greatly exceeds the deactivating influence of the chloro group leaving steric factors to determine the site ~~of acylation~~ and extent of acylation



NH_2 ortho para director activating

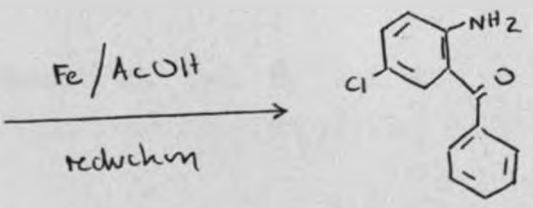
Cl ortho para director deactivating

In most of the methods reviewed by Walsh the acylating agent in most cases in an aniline derivative which acylates/ alkylates a benzone ring as optioned to benzoyl chloride / benzoic acide serving as acylating agent. This obviates the steric factors. Hindering acylation of the position ortho to the amino group and indeed by employing the route involving the synthesis form 2 I benzisoxazoles (anthranils) sharma et al[9] have obtained an overall yield of 55%. They employ a two step method outlined as follows.



3 phenyl 5 chloro anthranil.

yield 93%



yield 60%

This reaction route evidently does NOT involve a direct friedel craft reaction however, note that the P chloro nitrobenzene (a 4 chloroaniline derivative) is attacked by a nucleophite ie nucleophitic benzyl cyanide. c.f. Friedel craft acylations - elctrophitic attack of 4 chloroaniline by acylium ion generated from either benzoic acid/ benzoyl chloride.

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