THE ALKALOIDAL CONSTITUENTS OF GELSEMIUM SEMPERVIRENS

With an Additional Paper

FISSION AND MOLECULAR REARRANGEMENT AS ALTERNATE MODES OF REACTION.

T H E S I S

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PREFACE

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C O N T E N T S.

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INTRODUCTION.

The North American shrub Gelsemium sempervirens, Aiton, (Loganiaceae) is commonly known as yellow jasmine, and grows in rich moist soils along the sea coast from Virginia to the south of Florida.

Attention seems first to have been called to the medicinal value of the rhizome and roots of this plant by Procter in 1852[1], and for about the last 70 years several of the pharmacopoeias, under the title of "Gelsemium", have recognised an extract of the dried rhizome and roots of gelsemium sempervirens.

The first investigation of the constituents of the root seems to have been conducted by Wormley[2] who isolated an impure amorphous alkaloidal fraction which he called gelsemine. It was shown by Wormley that gelsemine was accompanied in the plant by an acidic substance which he called "gelseminic acid".

Wormley's observations were confirmed by Sonnenschein[3] who proposed the formula ($C_{11}H_{19}NO_2$) for gelsemine, and for the hydrochloride, the formula $(C_{11}H_{19}NO_2)_2.HCl$. Robbins[4] in the same year confirmed Sonnenschein's formula for gelsemine.

Gelsemine was first obtained crystalline by Gerrard[5] and the formula $C_{24}H_{28}N_2O_4$ was proposed by him for it.

Thompson[6], who ascribed to gelsemine the formula $C_{54}H_{69}O_{12}N_4$, showed that it was accompanied in the plant by a second alkaloid which he obtained in an amorphous condition, and which he designated as "gelseminine". He describes gelseminine as a dark brown resinous mass giving only amorphous salts.

Both gelsemine and gelseminine were examined by Cushny[7] who proposed the formulae $C_{49}H_{63}O_{14}N_5$ and $C_{42}H_{47}O_{14}N_3$ respectively for the two bases.

Spiegel[8] suggested the formula $C_{22}H_{26}O_3N_2$ for the crystalline base (gelsemine), and recorded that he isolated two nitrogenous bases by fusing gelsemine methiodide with potash. He also recorded the isolation of two products on oxidising gelsemine with potassium permanganate.

Goeldner[9] confirmed Spiegel's formula for gelsemine and obtained his crystalline base melting at 160°. Goeldner repeated Spiegel's potash fusion of gelsemine methiodide and recorded the isolation of four different substances under varying conditions. He also reported the isolation of a permanganate oxidation product.

In 1910 the constituents of the root were examined by Moore[10] who isolated gelsemine and obtained it in the pure condition from acetone, melting point 178°. He found it to be optically active. He showed that gelsemine is $C_{20}H_{22}O_2N_2$, and that it crystallises with one molecule of solvent. The monohydrochloride of the base was prepared. Moore also isolated a brown amorphous alkaloidal product corresponding to the "gelseminine" of Thompson and Cushny, but was unable to obtain any crystalline derivatives. Among other products, he also isolated another amorphous alkaloid and a phytosterol. He proved, too, the identity of Wormley's gelseminic acid with scopoletin(7-hydroxy-6-methoxy coumarin).

In the following year Moore published an account of some of the reactions of gelsemine[11]. He was unable to obtain any oxidation products from gelsemine owing to the ease with which the alkaloid broke down when acted upon with oxidising agents. He found, however, that the base was stable to reducing agents, and that it remained intact on boiling with alkali hydroxides and with sodium ethoxide.

On boiling gelsemine with concentrated hydrochloric acid for some hours, Moore recorded that three new bases were produced. The chief product of this reaction was

an amorphous substance possessing the formula $C_{20}H_{24}O_3N_2$, which corresponds, therefore, with gelsemine, to which the elements of one molecule of water have been added. This base was called apogelsemine and several of its derivatives were prepared in the crystalline state.

The other two bases accompanying apogelsemine were found to be $C_{20}H_{23}O_2N_2Cl$, and $C_{20}H_{24}O_3N_2$, the latter being a hydrolytic product of the former. Both these bases were obtained crystalline, and were designated as chloro-isoapogelsemine and isoapogelsemine respectively. Only small yields of the last two substances were obtained as a result of this reaction.

Moore reports the preparation of monoacetyl derivatives of gelsemine and chloroisoapogelsemine, and diacetyl derivatives of apogelsemine and isoapogelsemine. These four bases were all found to be mono acidic bases.

On treatment of gelsemine methiodide with potash solution at 220°, and gelsemine methohydroxide with water at the same temperature, an anomalous change was found to take place, inasmuch as the expected gelsemethine was not formed, gelsemine being regenerated with elimination of methyl alcohol. Apogelsemine methyl hydroxide was found to behave in an analogous manner, apogelsemine being the only product of the reaction.

When chloroisoapogelsemine was treated with diethylaniline, it was found that the elements of hydrogen chloride were eliminated, with formation of either an isomer of gelsemine, or a mixture of such an isomer with gelsemine itself. Bromoisoapogelsemine has also been prepared by Moore by the action of hydrobromic acid on gelsemine.

Moore also reported that gelsemine contains neither methoxyl nor ethoxyl groups.

Another alkaloid, probably identical with Thompson's gelseminine, was isolated from the root of Gelsemium sempervirens by Sayre[12, 13, 14], and called by him sempervirine. Sayre isolated the alkaloid as the insoluble nitrate, of melting point 280°, and described the free base as crystallising from chloroform in reddish brown needles, and from alcohol in short thick needles. These were reported to fuse together at 220°, not melting, however, when heated to 280°. Solutions of the salts of sempervirine were found to respond to the usual alkaloidal precipitants.

After removal of sempervirine and gelsemine from the extract, Sayre isolated two amorphous alkaloids which he called gelsemidine and gelsemoidine. Neither of these two alkaloids were found to give crystalline derivatives.

In 1931 T.Q. Chou[15] published an account of an investigation of the constituents of Gelsemium sempervirens.

He confirmed Moore's formula of $C_{20}H_{22}O_2N_2$ for gelsemine and reported the isolation of a highly coloured weak base, very similar to Sayre's sempervirine in general chemical behaviour, but differing somewhat in melting point. He called this alkaloid sempervine.

Sempervine was described as crystallising from chloroform in blood red prismatic needles of melting point 223°, and from alcohol in red orthorhombic crystals of melting point 254°. Both gave rise to the same nitrate of melting point 282°d. Chou observed that sempervine was unstable to heat, crystallisation necessarily being carried out with rapidity, owing to prolonged heating on the water bath promoting resinification. The salts, however, were found to be quite stable.

Chou also reported the isolation of a new optically active alkaloid which he called gelsemicine. He allocated the formula $C_{20}H_{25}O_4N_2$ (sic) to gelsemicine, and recorded the melting point as 171°, the base being crystallised from acetone. Gelsemicine was found to be easily coloured on exposure to the air. The preparation of the monohydrochloride is reported.

Chou also described the isolation of an amorphous alkaloid, giving only amorphous salts.

In 1933 Hasenfratz[16] investigated the alkaloid sempervirine. He assigned to this highly coloured alkaloid the formula $C_{19}H_{16}N_2 + H_2O$, the molecule of water being lost at 100°. He recorded the melting point as 258-260° and noted an intense blue-violet fluorescence in very dilute alcoholic solutions.

In chloroform solution sempervirine was found to be optically inactive, as also was an aqueous solution of its hydrochloride.

Hasenfratz described the hydrochloride, nitrate, picrate and chloroplatinate of sempervirine, in all of which sempervirine acted as a monoacidic base. He recorded that the insoluble nitrate of sempervirine was precipitated by nitric acid from a 1/20000 aqueous solution of sempervirine hydrochloride.

In 1940 T.T. Chu and T.Q. Chou[17] published an account of the catalytic hydrogenation of gelsemine. Using Adams's platinum catalyst in presence of hydrogen, they found that two atoms of hydrogen were absorbed with the formation of a crystalline dihydrogelsemine. They recorded that dihydrogelsemine was unaltered on boiling with concentrated hydrochloric acid or with fuming hydriodic acid.

They also recorded that gelsemine, on treatment with

zinc and hydrochloric acid in presence of platinum or palladium chloride gave an isomer of gelsemine - isogelsemine - differing from gelsemine in melting point and specific rotatory power, and also a small amount of a substance to which they ascribed the formula $C_{18}H_{22}O_4N$ (sic).

Chou and Chu during this year have reported on the bromination and nitration of gelsemine[34]. They found that with bromine at a low temperature gelsemine gave a compound $C_{20}H_{22}O_2N_2Br_2$. They called this compound dibromogelsemine. When treated with acid or alkali, it was found to lose the elements of hydrogen bromide with ease, giving $C_{20}H_{21}O_2N_2Br$.

These investigators found that a low temperature nitration of gelsemine gave only an amorphous product, but with dihydrogelsemine under similar conditions they claim to have isolated a dinitrogelsemine (sic) of formula $C_{20}H_{22}O_6N_4$. This so-called dinitrogelsemine is reported to take up 12 atoms of hydrogen on catalytic reduction.

Considering the presence of a double bond in gelsemine and the formula assigned to the above "dibromogelsemine", gelsemine dibromide would seem to be the correct name for this compound.

It seems rather remarkable that a nitration of dihydrogelsemine should give a dinitrogelsemine of formula

$C_{20}H_{22}O_6N_4$. The reasonable presumption, however, would seem to be that this compound is a dinitrodihydrogelsemine, on account of the allocated formula and the absorption of only 12 atoms of hydrogen on catalytic hydrogenation.

From the varied collection of formulae which have been proposed for gelsemine at different times, it is obvious that a large number of the investigators have been working with alkaloidal fractions of doubtful purity, and consequently some of the results must be interpreted with a great deal of suspicion. It would seem, however, that the gelsemine isolated by Moore[10] was a pure substance, and that the physical constants recorded by him may be regarded as criteria of purity.

It will be seen that the alkaloid named sempervine by Chou approaches very closely in properties that named sempervirine by Sayre. The absence of analytical data for sempervine and sempervirine makes it impossible to arrive at any definite conclusion concerning the existence of both these alkaloids as separate entities. It seems, however, reasonable to presume that there is in fact only one such alkaloid, and that any slight differences in properties observed have been due to impure products.

In 1927 Hahn[18] speculated on the relationships of the alkaloids corynanthine, "gelseminine", and quebrachine, all of the formula $C_{21}H_{26}O_3N_2$, with the

Yohimbine alkaloids. On account of the confusion that has arisen in the literature as to the nomenclature of the two bases isolated from Gelsemium sempervirens, it is rather difficult to be certain about the identity of Hahn's "gelseminine" of formula $C_{21}H_{26}O_3N_2$.

In English literature, the crystalline base has been referred to as gelsemine, and the amorphous product as gelseminine (now called sempervirine), whilst most of the German investigators, for example Spiegel and Goeldner, have used these names in the opposite sense. In this paper the English nomenclature has been adhered to.

As, however, the formula $C_{21}H_{26}O_3N_2$ does not seem to have been previously proposed for either gelsemine or gelseminine, we must presume, in the absence of any analytical data in Hahn's publication in support of this formula, a mistake on the part of this investigator for gelsemine.

COLOUR REACTIONS.

Gelsemine dissolves in sulphuric acid giving a colourless solution, which, on the addition of a crystal of potassium dichromate, becomes red, then violet and then green. Strychnine and curarine give similar characteristic reactions with sulphuric acid and potassium dichromate.

Sempervirine, according to Chou[15], dissolves in sulphuric acid to give a reddish brown solution, becoming dirty green on adding a crystal of potassium dichromate.

On account of the botanical relationship, similar empirical formula, and strychnine-like action, one might assume some constitutive analogies between gelsemine and the strychnos group of alkaloids.

DERIVATIVES OF GELSEMINE.

COMPOUND	FORMULA	M.P.	$[\alpha]_D$	REF.
Gelsemine	$C_{20}H_{22}O_2N_2$	178°	+15.9°($CHCl_3$)	Moore[10]
	confirmed.	do.	+10° (do.)	Chou[15]
	-	do.	+17.7°(do.)	SFM
Hydrochloride	B.HCl	about 300°	+2.6°(water)	Moore[10]
	-	333°d*	-	SFM
Methiodide	B.$CH_3I.H_2O$ and B.CH_3I	-	+8.9°(water)	Moore[11]
	-	286°	-	Goeldner[9]
	-	From 286°d to 301°d	+5.95° (do.)	SFM
Hydrobromide	B.HBr	325°d*	-	SFM
Methobromide	B.CH_3Br	313° - 314°d	-	SFM

* Dependent on rate of heating. Figure given is for rapid heating.

DERIVATIVES OF SEMPERVIRINE.

COMPOUND	FORMULA	M.P.	$[\alpha]_D$	REF.
Sempervirine	-	223°($CHCl_3$)	-	Chou[15]
		254°(C_2H_5OH)		
	$C_{19}H_{16}N_2 \cdot H_2O$	258-260°(do.)	±0°	Hasenfratz[16]
Nitrate	-	282°d.	-	Chou[15]
	$B.HNO_3 \cdot 2H_2O$	-	-	Hasenfratz[16]
Hydrochloride	$B.HCl.2H_2O$	-	±0°	Hasenfratz[16]
	-	above 300°	-	Chou[15]
Methiodide	$B.CH_3I$	348°d.	-	SFM
Picrate	$B.C_6H_2(OH)(NO_2)_3$	-	-	Hasenfratz[16]
	confirmed	268°d.	-	SFM

SUMMARY AND DISCUSSION.

ISOLATION OF THE ALKALOIDS.

The starting material for this investigation consisted of 22.5 kilograms of the dry powdered root of Gelsemium sempervirens, Aiton, and the object of the work was the isolation of the alkaloidal constituents of the root, followed by their chemical investigation.

On account of the fact that sempervirine is unstable to heat, and is resinified to a large extent in boiling alcohol, it was decided, after some preliminary experiments, to carry out an extraction first of all with cold rectified spirit, followed by an extraction with boiling alcohol.

It was decided also to use the method of separation devised by Sayre[14] for the isolation of gelsemine, sempervirine, and the amorphous alkaloids, and also to attempt the isolation of gelsemicine from the gelsemine mother liquors as described by Chou[15], with certain small modifications in each case.

This was done and the yields of gelsemine and sempervirine were found to be very much larger than those recorded by Sayre, particularly in the case of the latter. This was due, presumably, to the employment of a cold alcoholic

extraction. The yield of gelsemine obtained was 0.13% compared with 0.07% recorded by Sayre[14] and that of sempervirine (as nitrate) was 0.084% compared with 0.026% reported by Sayre.

A small quantity of an amorphous alkaloid, not previously reported, was found in the gelsemine fraction, but could not be obtained crystalline.

This alkaloid was found to be very slightly soluble in water and alcohol on long heating. The melting point of this amorphous alkaloid is 324°d. An amorphous picrate was formed from water but could not be crystallised. On evaporating this alkaloid to dryness with hydrochloric acid a crystalline hydrochloride was formed, melting above 340°, but owing to the extreme solubility of this hydrochloride and the small amount available, it was not found possible to prepare a sufficient quantity of the pure material for analysis determinations.

From the fraction of the amorphous alkaloids called gelsemoidine by Sayre, there has been isolated a crystalline methiodide not previously reported. Analysis figures for this methiodide indicate a formula of either $C_{20}H_{24}O_3N_2.CH_3I$ or $C_{20}H_{22}O_3N_2.CH_3I$. The melting point of this methiodide suggests its identity with apogelsemine methiodide $C_{20}H_{24}O_3N_2.CH_3I$ (melting points 296-297°d. and 295°d. respectively), but the determination of its specific

rotation would seem to discount this view.

The value Moore[11] has found for the specific rotation of apogelsemine methiodide is $[\alpha]_D$ +12.4°. An attempt was made to repeat, as far as possible, the conditions employed by Moore for apogelsemine methiodide, for the determination of the specific rotation of "gelsemoidine" methiodide. This has, however, been found impossible, the new methiodide being less soluble in water than apogelsemine methiodide has been recorded to be. A saturated solution was used for the determination and a value of $[\alpha]_D^{20}$ +3.9° was found.

For comparison purposes the specific rotation of gelsemine methiodide was determined, and found to differ slightly from Moore's value. The value found was $[\alpha]_D^{18}$ +6.0°, compared with that of $[\alpha]_D$ +8.9° recorded by Moore[10].

These results for gelsemine methiodide are in much closer agreement than those for "gelsemoidine" methiodide and apogelsemine methiodide, and it seems possible that the methiodide isolated from the gelsemoidine fraction is not, in fact, identical with apogelsemine methiodide. This possibility is, to a certain extent, enhanced by the fact that neither Sayre nor the present author were able to obtain "gelsemoidine" hydrochloride in the crystalline state, whereas apogelsemine hydrochloride is a crystalline

substance.

No attempt was made to prepare apogelsemine methiodide for comparison purposes as, for the isolation of pure apogelsemine, a relatively large expenditure of gelsemine would have been involved.

The attempted isolation of gelsemicine was not successful, this fraction consisting of a dark brown tarry material which contained some gelsemine.

GELSEMINE.

CHARACTERISATION.

Gelsemine, isolated from the extraction, was found to agree in melting point with that recorded by Moore[10]. As previous investigators have found different values for the specific rotation of gelsemine, it was thought advisable to check this reading. The value found was $[\alpha]_D^{20^\circ}+17.8^\circ$, compared with $[\alpha]_D+15.9^\circ$, and $[\alpha]_D+10^\circ$ recorded by Moore[10] and Chou[15] respectively.

The specific rotation of gelsemine methiodide was also found to differ slightly from the previously recorded result, $[\alpha]_D+6.0^\circ$ being found compared with $[\alpha]_D+8.9^\circ$ reported by Moore[11] (see page 16).

Gelsemine hydrobromide and gelsemine methobromide have been prepared and analysis results of these found to confirm Moore's formula for gelsemine.

Gelsemine has been found to give a deep pink colouration with a solution of p-dimethylamino benzaldehyde.

FUNCTIONAL GROUPS.

An $N\text{-}CH_3$ determination on gelsemine resulted in a value in agreement with that calculated for two $N\text{-}CH_3$ groups.

Gelsemine was subjected to catalytic reduction with a palladium catalyst at the ordinary temperature. It was

found that the volume of hydrogen absorbed corresponded to the reduction of one ethylenic double bond. The dihydrogelsemine formed was isolated in the crystalline state and its hydrochloride and methiodide prepared. The formula of this base was confirmed by analyses on the free base, hydrochloride and methiodide.

Dihydrogelsemine was found by Zerewitinoff estimation to contain one active hydrogen atom.

This preparation of dihydrogelsemine has since been published and confirmed by Chou[17].

Both gelsemine and dihydrogelsemine were found to be unchanged by the action of the Grignard reagent, the starting products being recovered in each case. Attempts at oxime formation of gelsemine have also been unsuccessful. It thus seems improbable that gelsemine contains a ketonic group.

On attempting to repeat Moore's preparation of acetyl gelsemine and on attempting to prepare benzoyl gelsemine, it has been found on all occasions that gelsemine was recovered unchanged from the reaction mixture.

No indications of the presence of a phenolic hydroxyl group in gelsemine have been noted, gelsemine having been found to be insoluble in aqueous caustic soda solution.

After the preparation of dihydrogelsemine, it seemed relevant to discover how this base would react with concentrated hydrochloric acid and to note if the change occurring with gelsemine would also take place with dihydrogelsemine. On subjecting dihydrogelsemine to prolonged boiling with concentrated hydrochloric acid, however, only the starting product was found to be recovered.

OXIDATION.

Moore[11] has recorded his inability to isolate any definite oxidation products from gelsemine owing to the ease with which the alkaloid broke down when acted on with oxidising agents.

An oxidation of gelsemine was carried out with potassium permanganate in acetone solution. It was found that at 0°C oxidation did not readily take place, but that it proceeded slowly at the ordinary temperature. From the reaction product a gum was obtained, from which neither crystals nor crystalline derivatives could be isolated.

As a result of a permanganate oxidation of dihydrogelsemine, a small amount of a brown gummy substance was isolated but could not be obtained crystalline. This substance was found to give a crystalline methiodide which, however, could only be recrystallised once if enough were

to be left for analysis. From the analysis figures for this methiodide, it seemed probable that no increase in the oxygen content of the molecule had taken place, and considering that the melting point was low, it was very probable that the product was, in fact, a somewhat impure specimen of dihydrogelsemine methiodide. For this reason the oxidation was not repeated on a larger scale.

An oxidation of gelsemine was carried out with hydrogen peroxide in the presence of osmium tetroxide at the ordinary temperature[19]. A yellow amorphous substance was isolated from this oxidation, but could not be obtained crystalline. On the assumption that this compound was an amine oxide, it was reduced with zinc and hydrochloric acid. A colourless amorphous solid was isolated from the reduction but could not be obtained crystalline either as the free base or as the hydrochloride or methiodide.

Dihydrogelsemine was oxidised with boiling dilute nitric acid, rapid colour changes being observed to take place in the solution during the oxidation. A colourless amorphous solid was isolated from the reaction mixture, but it could not be obtained in the crystalline state, nor could it be induced to yield crystalline derivatives.

REDUCTION.

Gelsemine has been found to give dihydrogelsemine on catalytic reduction with a palladium catalyst (see page 18).

Dihydrogelsemine was treated with boiling hydriodic acid and red phosphorus for a considerable period, dihydrogelsemine, however, being recovered unchanged from the reaction mixture. This observation has been confirmed by Chou[17].

Gelsemine also has been treated with boiling hydriodic acid and red phosphorus and found to yield an amorphous base. The hydrochloride and methiodide of this base were found to be amorphous, but a crystalline hydriodide was prepared. Analysis determinations on this hydriodide are in agreement with the calculated values for the formula $C_{20}H_{23}O_2N_2I.HI$, and it seems possible that this compound may be iodoisoapogelsemine - i.e., the iodine analogue of chloroisoapogelsemine.

To check this, a small quantity of the substance was hydrolysed by boiling with aqueous alcoholic potassium formate. Crystalline isoapogelsemine was not obtained, probably owing to the small amount of material available, but a crystalline methiodide was isolated from the reaction mixture, and this was found to melt at the temperature

recorded by Moore[11] for isoapogelsemine methiodide.

Iodoisoapogelsemine was subjected to reduction with zinc and acetic acid. From this reaction was isolated a base agreeing in melting point with dihydrogelsemine, and giving no depression in melting point on admixture with authentic dihydrogelsemine. This base formed a methiodide, agreeing in melting point with dihydrogelsemine methiodide, and giving analysis figures in agreement with those calculated for dihydrogelsemine methiodide.

Moore[11] has recorded that on removal of the elements of hydrogen chloride from chloroisoapogelsemine with diethylaniline, a base isomeric with gelsemine was produced. By the action of diethylaniline on iodoisoapogelsemine a large amount of tarry matter was produced, but from this was isolated a small quantity of a base agreeing in melting point with the product isolated by Moore. Analysis figures did not, however, agree, within experimental error, with those calculated for an isomer of gelsemine. This was probably due to the small quantity of material available and the consequent difficulty of obtaining absolute purity. As the yield from this reaction was very low and as the preparation of this compound in sufficient quantity for further reactions would have necessitated a relatively large expenditure of gelsemine, no repeat experiment was carried

out in order to check the analysis figures.

GENERAL REACTIONS.

Dihydrogelsemine methiodide was treated with sodium amalgam in boiling water solution. It was found that no free base was produced as a result of this reaction but that a solid product was obtained on acidification of the reaction mixture. The substance was found to be insoluble in all the usual organic solvents being soluble, however, in caustic soda solution. This substance could not be purified and therefore no analyses have been carried out on it. It did not respond to the usual tests for ionic mercury, and from its behaviour it seemed likely to be some mercurial derivative of the alkaloid.

It was thought possible that if a grouping such as -CO-N< were present in gelsemine, although opening on alkaline treatment, it might have escaped notice owing to ease of ring closure on further acid treatment.

With the object of confirming or refuting this idea, gelsemine was treated with an excess of piperidine at 230° for five hours. It was found that only gelsemine was recovered from this treatment.

As this reagent was very mild for this purpose, it was thought that baryta might be more suitable and accordingly, gelsemine was treated with baryta solution at 150°.

It was found, however, that most of the gelsemine was recovered from the reaction mixture by extraction. Had gelsemine contained the grouping -CO-N< , one would have expected the barium salt of the acid -COOH NH< to have been formed. In case reaction had proceeded partially this way, the residue from the extract was benzoylated, but no relevant products were isolated.

With the object of obtaining an oxygen free base or some simpler substance which might be identified, a dehydrogenation of gelsemine was attempted with selenium. A base was produced as a result of this reaction, but could not be isolated in the crystalline state. The crystalline methiodide of this base was obtained and analysed. Analysis figures for this methiodide are not conclusive and indicate either a loss of carbon or a gain of the elements of water. The methiodide is, however, definitely not gelsemine methiodide.

Considering the conditions employed, no attempt has been made to explain the formation of this product, and as reaction did not proceed smoothly on lines capable of elucidating the structural skeleton of gelsemine, further work with this reagent was abandoned.

The action of cyanogen bromide on gelsemine has

been studied, but although reaction took place with facility, the course of the reaction still remains rather obscure. The reaction was carried out in a mixture of ether and benzene, two products being isolated. A salt product was precipitated, while the other remained in solution.

The insoluble product, while probably being contaminated with some impurity, consisted mainly of gelsemine hydrobromide.

Some difficulty has been experienced with analyses of the soluble product. This substance crystallised readily from alcohol and no difficulty was experienced in crystallising it to constant melting point, which is 216°. On analysis, however, inconsistent results were obtained and no evidence as to the formula is available.

Considering the production of gelsemine hydrobromide during the reaction, one would anticipate a product consisting of gelsemine in which either one or two -CN groups replace hydrogen. The analysis figures indicate a gain of either one or two nitrogen atoms, but are not conclusive.

On hydrolysis of this compound with alcoholic potash, a compound was produced which, unfortunately, could not be crystallised. This compound gave with methyl iodide a crystalline methiodide. Analysis figures for

this methiodide are again unsatisfactory, but it is seen that the nitrogen content has probably dropped to two atoms in the molecule.

THE APO-ISOAPO CHANGE.

Moore[11] in 1911 recorded an interesting change undergone by gelsemine on refluxing with concentrated hydrochloric acid. Three new bases were isolated from the reaction mixture, the chief product being apogelsemine, $C_{20}H_{24}O_3N_2$, which corresponds therefore with gelsemine, to which the elements of one molecule of water have been added. The other two bases accompanying apogelsemine were isoapogelsemine, $C_{20}H_{24}O_3N_2$, and chloroisoapogelsemine, $C_{20}H_{23}O_2N_2Cl$, the former being a hydrolytic product of the latter.

Gelsemine and chloroisoapogelsemine were found to give monoacetyl derivatives, apogelsemine and isoapogelsemine giving diacetyl derivatives.

Two possible explanations of this conversion were considered as being the most feasible. The first of these consisted of the addition of a molecule of water (or hydrogen chloride) to an ethylenic double bond:

$$>C = C< \longrightarrow \begin{cases} >C(OH).CH< & \text{(apo)} \\ >CH.C(OH)< & \text{(isoapo)} \\ >CH.CCl< & \text{(chloroisoapo)} \end{cases}$$

The second tenative explanation considered was that in which the following grouping was functional:-

$-\overset{|}{\underset{|}{C}}-O-CH_2-CH=CH-$, i.e., a substituted allyl ether.

This view is enhanced by the consideration of the botanical and pharmacological relationships of gelsemine to strychnine.

By the action of concentrated hydrochloric acid, this grouping might be expected to undergo such a change that the following modifications could be isolated:-

1). $-\overset{|}{\underset{|}{C}}-OH + HO-CH_2-CH=CH-$ (apo)

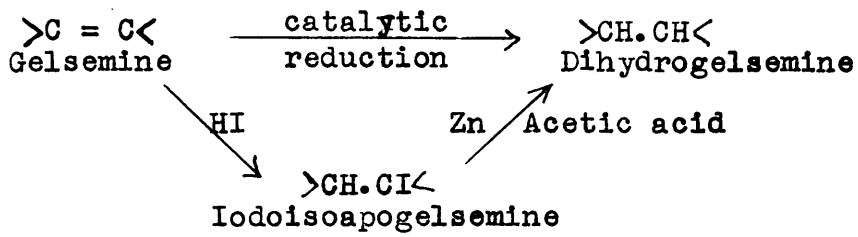
2). $-\overset{|}{\underset{|}{C}}-OH + CH_2=CH-\underset{OH}{\underset{|}{CH}}-$ (isoapo)

3). $-\overset{|}{\underset{|}{C}}-OH + CH_2=CH-\underset{Cl}{\underset{|}{CH}}-$ (chloroisoapo)

Bearing in mind, however, that Moore obtained monoacetyl derivatives of gelsemine and chloroisoapogelsemine, and diacetyl derivatives of apogelsemine and isoapogelsemine, it must be assumed <u>either</u> that the group $-\overset{|}{\underset{|}{C}}-OH$ is tertiary alcoholic, <u>or</u> that this group is capable of tautomerising to the group $>C=O$, as, on addition of a molecule of water to gelsemine, only one new active hydrogen atom (from the point of view of acetylation) has been developed in apogelsemine and isoapogelsemine, and none at all in chloroisoapogelsemine.

The presence of a double bond in gelsemine was demonstrated (see page 18), and the dihydrogelsemine formed was found to be unattacked by boiling hydrochloric acid (page 20) and boiling hydriodic acid (page 22). These facts, therefore, disposed of the second of the above tentative suggestions, as it seemed very improbable that a substituted normal propyl ether would be unattacked by boiling hydriodic acid.

Gelsemine itself was found to react with hydriodic acid to give iodoisoapogelsemine and this compound was found to be reduced by zinc and acetic acid to dihydrogelsemine (page 22). It thus seems that the first theory postulated is correct, reaction having proceeded as follows:-



GENERAL DISCUSSION.

The fact that dihydrogelsemine is unchanged by the action of boiling hydriodic acid and red phosphorus (page 22) raises the problem of the state of combination of the oxygen atoms in gelsemine.

Moore[11] has described the preparation of a mono-acetyl derivative of gelsemine. This is most likely to have arisen from an active hydrogen atom attached to an oxygen or a nitrogen atom. If formation of the acetyl derivative takes place at a hydroxyl group, this hydroxyl group (in dihydrogelsemine) is untouched by boiling hydriodic acid, thus suggesting a phenolic group.

No indications, however, have been noted suggesting the presence of a phenolic hydroxyl group, gelsemine having been found to be insoluble in aqueous caustic soda solution (page 19).

Attempts at oxime formation have been unsuccessful, and the Grignard reagent has failed to react with gelsemine and dihydrogelsemine (page 19).

Moore[11] has recorded the absence of methoxyl and ethoxyl groups and unsuccessful experiments have been conducted, designed to reveal the presence of a $>CO.N<$ group, if present, in gelsemine (page 24).

No definite conclusions have therefore been arrived at concerning the state of combination of the oxygen atoms in gelsemine.

Considering the above facts, it would seem as if formation of the acetyl derivative takes place at an

$>$NH group. An N-methyl determination on gelsemine has shown that two N-methyl groups are present in the molecule (page 18). If one were present as a $-NHCH_3$ group, it is feasible to predict that it would participate in salt formation. Now the methiodide of gelsemine has been shown by Moore[11] to regenerate gelsemine with caustic potash at 200°. If a $-NHCH_3$ grouping had participated in methiodide formation, an N-methyl gelsemine would have been produced by this treatment.

The acetyl derivative, however, may conceivably have arisen from a molecule containing a basic $-N(CH_3)_2$ group and a non- or feebly-basic $>$NH group. Unfortunately, the reaction of cyanogen bromide on gelsemine has not thrown any light on the state of combination of the nitrogen atoms in gelsemine, and no conclusions have been drawn on this question.

It was thought that a hydrolysis of acetyl gelsemine should be attempted in order to examine the possibility of the formation of the acetyl derivative having taken place at a carbon atom, but on attempting to repeat Moore's preparation of acetyl gelsemine and on attempting to prepare benzoyl gelsemine, on all occasions gelsemine has been recovered unchanged.

SEMPERVIRINE.

The instability of the alkaloid sempervirine limits to a certain extent the type of reaction which may be carried out upon it. For this reason, it is necessary that any reaction to be carried out on the free base be carried out at the ordinary temperature. As the salts of sempervirine are, however, much more stable than the free base, a higher temperature range is available for any reaction carried out on a salt or in acid medium.

Crystallisation in this field is a technique that has been attended with a certain amount of difficulty. T.Q. Chou[15] has recorded that the crystallisation of sempervirine must be carried out with rapidity to prevent resinification. Similar types of problems have been encountered in a few other cases. For instance, it has been found that sempervirine methiodide prepared in alcoholic solution was always obtained amorphous. All attempts to crystallise this amorphous methiodide were unsuccessful. If, however, a chloroformic solution was employed for the preparation, crystalline sempervirine methiodide was obtained, but in some cases recrystallisation from aqueous alcohol resulted in an amorphous product, and in others, a crystalline product.

CHARACTERISATION.

Sempervirine, obtained from the nitrate, was found to agree in melting point with the figure published by Hasenfratz[16].

Sempervirine methiodide has been prepared and analysis figures have been found to agree with the formula assigned to sempervirine by Hasenfratz. Analyses of sempervirine picrate have also confirmed this formula.

REDUCTION.

On subjecting sempervirine to catalytic hydrogenation, with palladium as catalyst, it was found that an amount of hydrogen was absorbed approximately equivalent to that required for the reduction of three ethylenic double bonds. It was found that this reduction discharged the red colour of the solution, a colourless solution with only a very faint blue fluorescence being obtained. It was, however, not found possible to isolate the reduction product in the crystalline state owing to its rapid resinification in the air. Attempts to prepare a crystalline hydrochloride and methiodide were also unsuccessful, resins being obtained in both cases.

The product of electrolytic reduction was again not isolated owing to its instability in air.

Sempervirine was also subjected to prolonged boiling with hydriodic acid and red phosphorus, but was found to be recovered unchanged from this treatment.

OXIDATION.

Some oxidation experiments have been conducted on sempervirine but have been attended with little success. From an oxidation with potassium permanganate, only a tarry material was isolated from the reaction mixture.

An attempted oxidation with dilute nitric acid resulted in the formation of a dark red amorphous mono nitrosempervirine. The salts prepared from this compound were also found to be amorphous.

Chromic acid was also used as an oxidising agent for sempervirine. In the first attempt some of the sempervirine was precipitated as an insoluble chromate and was recovered unchanged at the end of the reaction. There was, however, isolated from this reaction a small quantity of a methiodide, differing considerably from sempervirine methiodide in melting point.

This compound does seem to be different from sempervirine methiodide on account of the following considerations:-

(a). There is a big difference in melting points. These are, of course, decomposition points but the measurements were made under the same conditions.

(b). The chloroform solution of the free base, from which the methiodide was prepared, was colourless, whereas a chloroform solution of sempervirine is coloured red-brown.

From the small quantity of this material available analysis results for carbon, hydrogen and nitrogen only were obtained. As insufficient material was available for an iodine determination, the probable percentage of iodine was calculated from the nitrogen determination, on the basis of one iodine atom to two nitrogen atoms. From these tentative figures, it was found that the percentages for carbon, hydrogen, nitrogen and iodine (calculated from nitrogen) gave on addition almost exactly 100.

It would thus seem that there is no oxygen in the molecule and that this compound has arisen from sempervirine on oxidation by loss of carbon atoms only, and with no gain of oxygen. Owing to the incomplete nature of the analysis results, it has not been possible to assign a formula to this methiodide, but it does seem certain that it contains fewer carbon atoms than sempervirine.

Two repeat experiments were carried out with larger quantities of sempervirine under conditions slightly

modified in order to prevent the precipitation of the insoluble chromate. In one case, a crystalline methiodide was obtained and found to agree with the first specimen in melting point. There was, however, in this case insufficient material for any analysis. In the second repeat, such a small amount of material was obtained that it could not even be identified. Owing to the limited amount of sempervirine available, it was decided not to pursue this oxidation any further at present.

An oxidation of sempervirine was carried out with hydrogen peroxide in presence of osmium tetroxide[19]. Reaction was found to take place and a brown amorphous solid was obtained. This substance, however, could not be obtained crystalline. On the assumption that it was an amine oxide, it was subjected to reduction with zinc dust and hydrochloric acid. The reduction product was also found to be amorphous and could not be obtained crystalline either as the free base or in the form of derivatives.

GENERAL REACTIONS.

An attempt was made to carry out a Hofmann degradation on sempervirine methiodide, but the product obtained from this reaction again could not be obtained crystalline.

As a result of the action of cyanogen bromide on

sempervirine in chloroform solution, it was found that a soluble and an insoluble product were produced. The soluble product was found to be amorphous, forming an amorphous hydrochloride and methiodide.

The insoluble product, on purification, was found to consist of yellow needles. This substance seemed to be the hydrobromide of a base, but on analysis consistent, but indecisive, figures were obtained. On preparing a picrate from the free base derived from this hydrobromide its properties were found to agree with those of sempervirine picrate. The hydrobromide gave analysis figures, however, inconsistent with those calculated for sempervirine hydrobromide, so it would seem that the product of this reaction is a mixture of the hydrobromide of sempervirine with that of another base.

It was not found possible to separate the components of this mixture by crystallisation. A crystalline methiodide (or mixture of methiodides) was prepared from this substance, but it was not found possible to recrystallise it.

EXPERIMENTAL.

ISOLATION OF THE ALKALOIDS.

The following preliminary experiments were carried out before the complete extraction was commenced. One kilogram of the dried powdered root was extracted at the ordinary temperature with 4 litres of rectified spirits, by shaking in two Winchester quart bottles for about 24 hours. The extract was filtered and tested for alkaloid with potassium mercuric iodide. Alkaloid was shown to be present.

The residue from this extraction was now extracted by boiling with 4 litres of rectified spirits for 6 hours. On filtering this extract and testing for alkaloid the test was again found to be positive.

The residue from this hot extract was now extracted with 4 litres of boiling rectified spirits containing 10% by volume of concentrated hydrochloric acid. On testing this extract for alkaloid, the result was found to be negative.

It was therefore decided to extract the powdered root firstly with cold spirit and then with boiling spirit, and to use the method of isolation described by Sayre and Watson[14], with certain modifications.

The starting material consisted of 22.5 kilograms of dried powdered root and the cold alcoholic extraction was carried out as follows:-

Using 500 gram lots of the powdered root and 2 litres of rectified spirits in a Winchester quart bottle, the extraction was carried out by agitation in an electric shaker for 15-20 hours. After filtration and washing of the residue with a little spirit, the extract was concentrated under a pressure of about 80 mm. and a bath temperature of 40-50°, to a light syrup.

After adding ammonium hydroxide in excess to this light syrup, it was extracted with a large excess of chloroform (5 times) until the extract was free from alkaloid. The chloroform extract was now concentrated under reduced pressure and the concentrate extracted with 0.5% hydrochloric acid until all the alkaloid had been removed. At this stage there was a considerable separation of tarry material.

This solution of alkaloid hydrochlorides was now treated with a saturated solution of sodium nitrate (1 volume sodium nitrate solution to 20 volumes of acid extract). This resulted in the immediate formation of a light yellow amorphous precipitate of sempervirine nitrate. This was filtered off and purified as follows:-

The precipitate was dried in a vacuum. It was then dissolved in hot water and reprecipitated with a saturated solution of sodium nitrate. The precipitate was filtered off and the process repeated twice. It was then crystallised from absolute alcohol, about 13.5 grams of pure sempervirine nitrate, melting point 282°d., being obtained.

The solution obtained from the filtration of the sempervirine nitrate (crude) was about 30 litres in bulk. To reduce the bulk of this solution, Sayre added some alkali and concentrated. As, however, there were present in this solution some hydrochloric acid and nitrate ions, this process was regarded as rather risky and the bulk was reduced by making alkaline with ammonium hydroxide and extracting with chloroform. The chloroform extract was concentrated to about one thirtieth of its bulk and extracted with hydrochloric acid solution (1 part concentrated hydrochloric acid to 4 parts of water), until free from alkaloid, giving a solution of alkaloid hydrochlorides.

This solution was extracted with chloroform to remove any gelseminic acid. The solution of alkaloid hydrochlorides was now made alkaline with ammonium hydroxide and extracted first of all with ether (3 times) and then with chloroform (3 times).

1). <u>Ether extract.</u> The ether was removed from the

ether extract by distillation, a dark red gummy material being obtained. This gum was dissolved in boiling acetone and the solution filtered, a small amount of residue being obtained. The residue was a colourless amorphous material and amounted to about 200 milligrams.

From the filtrate, on cooling, gelsemine crystallised in long colourless needles. On recrystallisation from hot acetone, pure gelsemine was obtained of melting point 178°. The yield of pure gelsemine was about 20 grams.

The colourless amorphous substance obtained above was very difficultly soluble in water and alcohol and could not be obtained crystalline. It was found to melt at 324°d. and to contain about 7% of nitrogen. In water solution with picric acid in water, an amorphous picrate was deposited, but it could not be obtained crystalline.

On evaporating the alkaloid to dryness with concentrated hydrochloric acid, a hydrochloride was formed. This hydrochloride was found to crystallise from absolute alcohol as colourless needles melting above 340°. Unfortunately, owing to the extreme solubility of the hydrochloride in alcohol and water, it could not be crystallised again, doping with ether bringing it down in the amorphous state. As it had only been crystallised once, it was not regarded as being pure enough for analysis, and no analyses

were carried out upon it.

2). Chloroform extract. The chloroform was removed from the chloroform extract by distillation under reduced pressure, a colourless amorphous solid being left. This solid was dissolved in a small quantity of absolute alcohol and the solution saturated with dry hydrogen chloride. On addition of dry ether to this solution, a light brown amorphous precipitate was obtained.

This precipitate of hydrochlorides was filtered off, the residue being found to darken in the air and to be somewhat deliquescent. The residue was washed with a little chloroform, when all but a small amount of gummy residue dissolved. These two fractions (the chloroform soluble part and the residue) agree with Sayre's observations[14] and were named by this worker Gelsemidine (the chloroform insoluble hydrochloride) and Gelsemoidine (the chloroform soluble hydrochloride).

Some of the chloroform solution was washed with a little water, and picric acid in water solution was added to the washings. An amorphous picrate of indefinite melting point was obtained, but could not be crystallised.

The free base was obtained from the chloroform solution of "gelsemoidine" hydrochloride by shaking with

ammonium hydroxide. On removing the chloroform, a dark brown solid was obtained with a smell reminiscent of acetamide. This compound could not be obtained crystalline and it seemed to be easily resinified on exposure to the air.

On adding methyl iodide to the chloroform solution containing the free base, dark brown crystals were deposited on standing. On recrystallising these from absolute alcohol containing a few drops of water (5 times), the pure substance was obtained as colourless prisms, m.p. 296-297°d.

The analysis figures obtained for this methiodide are shown compared with those calculated for $C_{21}H_{27}N_2O_3I$ (A) and $C_{21}H_{25}N_2O_3I$ (B).

	Found.			Calculated.	
	(i)	(ii)	(iii)	(A)	(B)
C	52.54%	52.60%	52.54%	52.28%	52.50%
H	5.49%	5.56%	5.54%	5.60%	5.21%
N	5.90%			5.81%	5.83%
I	26.61%			26.35%	26.46%

(i) Dried at the ordinary temperature.

(ii) Dried at 120° for one hour.

(iii) Dried at 120° for ten hours.

The value for the specific rotation of this

methiodide is shown compared with the value recorded by Moore for apogelsemine methiodide.

0.2044 gms. of the methiodide, made up to 20 ccs. with water, were found to give α_D +0.08° in a 2 dcm. tube at 20°C. This gives $[\alpha]_D^{20}$ +3.9°. The solution used for this determination was a saturated solution at 20°C. Compare Moore's determination for apogelsemine methiodide - $C_{21}H_{27}N_2O_3I$ - m.p. 295° d.(11)

0.2670 gms. made up to 20 ccs. with water gave α_D +0°20' in a 2 dcm. tube, whence $[\alpha]_D$ +12.4°.

For comparison purposes the specific rotation of gelsemine methiodide was taken and it is shown compared with that published by Moore(11).

0.1856 gms. of gelsemine methiodide (dried at 120°), made up to 20 ccs. with water, were found to give α_D +0.11° in a 2 dcm. tube at 18°C, whence $[\alpha]_D^{18°}$ +6.0°. The solution used for this determination was a saturated solution at 18°C. Compare Moore's determination for gelsemine methiodide (dried at 120°).

0.2050 gms. made up to 20 ccs. with water gave α_D +0°11' in a 2 dcm. tube, whence $[\alpha]_D$ +8.9°.

From this cold extraction there was obtained about 20 grams of gelsemine, 13.7 grams of sempervirine nitrate,

a small quantity of an amorphous base in the gelsemine fraction and about one and a half grams of a crystalline methiodide from the fraction of the amorphous alkaloids called gelsemoidine by Sayre.

The residue of root from the cold alcoholic extract was now extracted with boiling rectified spirit, in lots of two kilos with 8 litres of spirit. The extract was concentrated to a light syrup and the concentrate treated in exactly the same way as in the cold extract, with the exception of the operation designed to reduce the bulk of the solution after the filtration of sempervirine nitrate. This operation was omitted. Although the bulk was of somewhat similar dimensions to that of the cold extract, it was thought that the advantages obtained by the reduction in bulk were not in proportion to the labour involved.

During the extractions in this separation rather more tarry matter was deposited than in the cold alcoholic extract separations.

From this extract about 5 grams of sempervirine nitrate were isolated and about 9 grams of gelsemine. Only a very small amount of the amorphous alkaloid accompanying gelsemine in the cold extract was found in the hot extraction.

Total yields:-

gelsemine	...	about 29 grams,
sempervirine nitrate		about 19 grams.

From the gelsemine mother-liquors an attempt was made to isolate the alkaloid gelsemicine described by T.Q. Chou[15].

The acetone mother-liquors were warmed slightly under reduced pressure to remove the acetone and the residue was dissolved in absolute alcohol. Some hydrobromic acid solution was added and then some more alcohol. On being allowed to stand for a few days a colourless solid was deposited, shown by Chou to be gelsemine hydrobromide. This was filtered off.

Chou then evaporated the filtrate to dryness over a water bath. This proceeding was, however, regarded as being rather risky, so a small amount of water was added to the solution, which was then made alkaline, and the resultant mixture extracted with chloroform. The chloroform was removed from this extract under reduced pressure and attempts made to crystallise the dark-brown resinous residue from acetone. No crystals could be obtained. On charcoaling the solution the brown colour was not removed, neither were any crystals obtained.

On adding methyl iodide to the acetone solution, small non-crystalline colourless warty lumps were deposited on standing. On filtering off and crystallising from very slightly aqueous alcohol and ether, colourless needles

were obtained, m.p. 293-294°.

Analysis figures found are shown compared with those calculated for $C_{20}H_{22}O_2N_2 \cdot CH_3I$.

	Found.	Calculated.
C	54.50%	54.51%
H	5.51%	5.36%
N	6.2%	6.01%.

Gelsemine methiodide has been found to melt at temperatures between 286°d. (as listed by Goeldner[9]). and 295°d. With large crystals the melting point has been found to be 301-302°d. Considering the fact that this methiodide was obtained from the gelsemine mother liquors, it seems very probable that it is gelsemine methiodide.

No gelsemicine has therefore been isolated from the extract.

GELSEMINE.

CHARACTERISATION.

SPECIFIC ROTATION OF GELSEMINE.

0.1013 gms. of gelsemine (dried at 120°) made up to 5 ccs. with chloroform gave α_D +0.36° at 20° in a 1 dcm. tube, whence $[\alpha]_D^{20}$ +17.8°. The concentration of gelsemine in chloroform differs only slightly from that used by Moore[10] for his result of $[\alpha]_D$ +15.9°.

SPECIFIC ROTATION OF GELSEMINE METHIODIDE.

See page 44.

PREPARATION OF GELSEMINE HYDROBROMIDE.

A solution of hydrobromic acid was added to gelsemine in alcoholic solution. Colourless prisms were deposited and filtered off. This substance was recrystallised from boiling aqueous alcohol and a melting point of 325°d. recorded. This melting point was found to vary somewhat with the rate of heating employed during the determination, and the figure recorded is for rapid heating.

Analysis:

	Found.	Calculated.
C	59.67%	59.55%
H	5.87%	5.70%.

PREPARATION OF GELSEMINE METHOBROMIDE.

Methyl bromide (from potassium bromide and methyl sulphate) was passed through a solution of gelsemine in ether, a colourless solid being deposited. This substance was recrystallised from absolute alcohol and obtained as colourless needles of melting point 313-314°.

Analysis:

	Found	Calculated
C	60.41%	60.43%
H	6.08%	5.99%.

EHRLICH'S REAGENT.

An alcoholic solution of gelsemine was found to give a deep pink colouration with a solution of p-dimethylaminobenzaldehyde in dilute hydrochloric acid.

FUNCTIONAL GROUPS.

N-CH_3 DETERMINATION.

The following result was obtained with gelsemine on examination for N-CH_3 groupings:-

4.520 mg. gelsemine gave 6.650 mg. silver iodide, being equivalent to 18.2% N-CH_3. Two N-CH_3 groups require 18.00%.

DIHYDROGELSEMINE.

0.4680 grams of gelsemine free from solvent of crystallisation, dissolved in absolute alcohol, and 0.1041 grams of palladium chloride dissolved in water, were mixed and shaken with hydrogen in a catalytic hydrogenation apparatus at the ordinary temperature and very slightly raised pressure. In about one hour no more hydrogen was being absorbed. The volume of hydrogen absorbed, calculated at NTP was 44.2 ccs. The volume calculated for the reduction of one double bond is 45.7 ccs.

The palladium was filtered off and the solution made alkaline with ammonium hydroxide. It was extracted with chloroform, the chloroform removed and the residue crystallised from acetone. Dihydrogelsemine was obtained as colourless needles, and on further crystallisation was obtained pure, melting point 220-221°. Dihydrogelsemine has also been obtained as colourless prisms of the same melting point. Chou[17] gives the melting point as 224-225°.

Analysis figures are shown compared with those calculated for $C_{20}H_{24}O_2N_2$.

	Found	Calculated
C	74.09%	74.07%
H	7.27%	7.41%

Zerewitinoff determination.

6.538 mg. dihydrogelsemine gave 0.60 ccs. methane at 749 mm. and 14°, which is equivalent to 0.32% active hydrogen. This corresponds to one active hydrogen (calc. 0.31%).

DIHYDROGELSEMINE METHIODIDE.

On addition of methyl iodide to a solution of dihydrogelsemine in acetone, the crystalline methiodide was deposited on standing. It was filtered off and recrystallised from alcohol and ether, being obtained as colourless needles of melting point 300 - 301°d. Chou[17] records the melting point as 301 - 302°d. Analysis figures are shown compared with those calculated for $C_{20}H_{24}O_2N_2 \cdot CH_3I$.

	Found	Calculated.
C	54.10%	54.09%
H	5.85%	5.79%
N	5.99%	5.79%
I	27.14%	27.27%.

ACTION OF HYDROCHLORIC ACID ON DIHYDROGELSEMINE.

Dihydrogelsemine (400 mg.) was boiled for three hours with 15 ccs. of concentrated hydrochloric acid. The solution was evaporated to dryness under reduced

pressure and then evaporated to dryness three times with absolute alcohol. The colourless solid obtained was recrystallised three times from absolute alcohol and the pure substance obtained as colourless needles, melting point 328°d. The analysis figures for material dried at the ordinary temperature are shown compared with those calculated for $C_{20}H_{24}O_2N_2 \cdot HCl \cdot H_2O$.

	Found	Calculated.
C	63.33%	63.5%
H	7.37%	7.15%
N	7.66%	7.4%
Cl	9.4%	9.13%.

This compound was shown to be dihydrogelsemine hydrochloride. Chou records a melting point of 318-320°d. for this compound.

Some of this hydrochloride was dissolved in water and ammonium hydroxide added. The free base formed was extracted with chloroform and the chloroform removed. On crystallising from acetone, colourless needles were obtained melting point 220°, and mixed melting point with dihydrogelsemine 220°. On adding methyl iodide to the acetone mother liquor, a crystalline methiodide was obtained which, on recrystallisation from alcohol and

ether, gave colourless needles melting point 299-300°d. (dihydrogelsemine methiodide - melting point 300-301°d.).

ACTION OF A GRIGNARD REAGENT ON GELSEMINE.

Butyl magnesium bromide was prepared in ether from 1.1 gms. of butyl bromide. Pure gelsemine (330 mg.) was added gradually to this reagent in ether solution, resulting in the formation of some colourless precipitate. The mixture was refluxed for a few hours and then poured into a saturated solution of ammonium chloride.

A colourless precipitate was obtained and filtered off. On recrystallising from aqueous alcohol, colourless needles were obtained of melting point 332°d (gelsemine hydrochloride, m.p. 333°d. (see page 54)). An aqueous solution of this substance was made alkaline with ammonium hydroxide, and extracted with ether. After drying, the ether was removed from the extract, and the residue crystallised from acetone. The product was obtained as colourless needles and was shown to be gelsemine by melting point and mixed melting point determinations.

ACTION OF A GRIGNARD REAGENT ON DIHYDROGELSEMINE.

Methyl magnesium iodide was prepared in dry ether from 200 mg. of magnesium. A solution of about 300 mg. of dihydrogelsemine in dry ether was added to the Grignard

reagent. A slight colourless precipitate began to form, and on boiling, this precipitate increased in bulk. After boiling for about two hours the ether was distilled off, and a saturated solution of ammonium chloride added. This solution was now extracted with chloroform and the chloroform removed from the extract. The residue was found on crystallising from acetone to give the melting point of the starting material (220°) and to give no depression in melting point on admixture with the starting material. The hydrochloride was prepared by evaporating to dryness with hydrochloric acid and crystallising from absolute alcohol. The melting point obtained - 327° - agrees with that for dihydrogelsemine hydrochloride. The methiodide was also prepared with methyl iodide and an acetone solution of the free base. On recrystallisation from alcohol and ether, the melting point of the product was found to agree with that found for dihydrogelsemine methiodide - 300°d.

ATTEMPTED PREPARATION OF A GELSEMINE OXIME.

Gelsemine (100 mg.) was refluxed in pyridine solution for a few hours with about 10 mg. of hydroxylamine hydrochloride. A white precipitate was formed and was filtered off. On crystallisation from aqueous alcohol it was found to melt at 333°d. A nitrogen

determination resulted in a value of 7.63%. The calculated value for gelsemine hydrochloride is 7.79%. This substance was shown to be gelsemine hydrochloride by conversion to gelsemine, m.p. 178°. The melting point of 333° is about 30° higher than that recorded by Moore[10], but this is presumably due to the rapidity of the rate of heating employed during the determination. On preparing gelsemine hydrochloride directly from gelsemine, the same melting point was found.

The attempt was repeated with the same quantities in water solution containing sodium acetate and sufficient alcohol to complete solution. The mixture was refluxed for about three hours. From this reaction, however, gelsemine was again recovered unchanged.

ATTEMPTS TO PREPARE ACETYL GELSEMINE.

An attempt was made to prepare acetylgelsemine by the method described by Moore[11]. The product could not be crystallised from methyl alcohol, but colourless needles were obtained from acetone. They were found to melt at 106° with resolidification at about 120°, and a final melting at 176°. On drying this substance further in air, it was found to melt at 178°, no depression being recorded on admixture with gelsemine.

An attempt was also made by the action of acetic anhydride and sodium acetate on gelsemine under reflux for six hours. The reaction mixture was poured into water, neutralised with sodium carbonate, and extracted with ether. From this extract there was isolated only gelsemine on crystallisation from acetone.

ATTEMPT TO PREPARE BENZOYL GELSEMINE.

Gelsemine (300 mg.) in chloroform solution was shaken with benzoyl chloride and caustic soda solution until the smell of benzoyl chloride had disappeared. The chloroform was removed from the chloroform layer, gelsemine only being isolated from the residue on crystallisation from acetone.

SOLUBILITY OF GELSEMINE IN CAUSTIC SODA SOLUTION.

About 20 mg. of gelsemine were warmed with 3 ccs. of water. On boiling, some of the gelsemine went into solution. About 300 mg. of solid caustic soda were added, and the solution boiled. No further solution was seen to take place. The solution was filtered and a stream of carbon dioxide passed through it. A little sodium bicarbonate was precipitated but on adding a drop or two of water, this redissolved. No gelsemine separated from this solution.

OXIDATION.

OXIDATION OF GELSEMINE WITH PERMANGANATE.

Gelsemine (400 mg.) was dissolved in pure acetone and the solution cooled in ice. 440 mg. of finely powdered potassium permanganate (equivalent to four atoms of oxygen) were added very gradually to the stirred solution. Although Moore[11] states that gelsemine is very readily oxidised by potassium permanganate, it was found, at the beginning of the operation, that oxidation did not readily take place at this temperature and so the reaction was allowed to proceed at room temperature.

After completion of the addition of the above amount of permanganate, it was found that reaction only proceeded very slowly with a further addition. This oxidation took about 30 hours to complete.

The precipitated manganese dioxide was filtered off and the acetone removed from the filtrate at the ordinary temperature. A light brown gum was obtained as residue, but could not be induced to yield crystals. No crystalline substances could be obtained on treatment of the gum with alcoholic hydrogen chloride or with methyl iodide.

OXIDATION OF DIHYDROGELSEMINE WITH POTASSIUM PERMANGANATE.

Dihydrogelsemine (300 mg.) was dissolved in pure acetone and 0.3-0.4 gms. of potassium permanganate in

acetone solution (6-8 atoms of oxygen) added gradually with gentle heating. After 3 hours the manganese dioxide was filtered off and the acetone removed. A brown gummy product was obtained in rather small quantity, but could not be crystallised. Methyl iodide was added to the acetone solution of this gum, some crystals being deposited on standing. These crystals were colourless needles and melted indefinitely about 240°. On recrystallising the melting point was raised to 260°, but owing to the small quantity obtained they were not further recrystallised.

This experiment was not repeated on a larger scale owing to the fact that on an analysis for carbon, hydrogen and nitrogen being carried out on these crystals of rather doubtful purity, it seemed probable that there had been no increase in the oxygen content of the molecule, and that the product was in fact a rather impure specimen of dihydrogelsemine methiodide.

OXIDATION OF GELSEMINE WITH HYDROGEN PEROXIDE.

Gelsemine (200 mg.) in tert. butyl alcohol was added to a dry tert. butyl alcoholic solution of hydrogen peroxide containing a small quantity of osmium tetroxide.

The solution was allowed to stand overnight at about 17°, a yellow amorphous substance being deposited from the solution. This substance was filtered off and attempts made to crystallise it. These were unsuccessful.

On the assumption that this compound was an amine oxide, it was submitted to reduction with zinc and hydrochloric acid. The substance was taken up in a dilute hydrochloric acid alcohol mixture, and an excess of zinc dust added gradually. The resulting solution was made alkaline with caustic soda and extracted with chloroform. The chloroform was removed and attempts made to crystallise the residue. These were unsuccessful, a colourless amorphous solid only being obtained.

The hydrochloride was obtained by passing dry hydrogen chloride into an alcoholic solution of the free base and adding ether. On attempting to crystallise it, it could only be obtained as a colourless amorphous solid. Attempts to prepare a crystalline methiodide were also unsuccessful, an amorphous product always being obtained.

NITRIC ACID OXIDATION OF DIHYDROGELSEMINE.

Dihydrogelsemine (150 mg.) was dissolved in 8 ccs. of 25% nitric acid and the solution refluxed for 4 hours. On commencement of heating, a bright green colour was produced, this being rapidly followed by changes to dark

green, black, violet, wine and finally pale pink. After the reaction was completed, the nitric acid was distilled off under reduced pressure. A solid remained, but could not be obtained in the crystalline state. On the presumption that the product was the nitrate of a base, its aqueous solution was made alkaline with sodium carbonate and extracted with chloroform. On evaporating off the chloroform, an amorphous solid was left, which again could not be crystallised. This substance was dissolved in hydrochloric acid and evaporated to dryness. Attempts to crystallise the product were unsuccessful.

On adding methyl iodide to an acetone solution of the free base, a thick black oil was deposited. This oil was dissolved in boiling absolute alcohol, charcoaled and allowed to cool. A colourless amorphous solid was deposited, but could not be obtained crystalline.

R E D U C T I O N.

ACTION OF HYDRIODIC ACID ON DIHYDROGELSEMINE.

Dihydrogelsemine (120 mg.) was refluxed with 10 ccs. of hydriodic acid (S.G. 1.7) and red phosphorus for 21 hours. When cool, water was added to the reaction mixture and the residual red phosphorus filtered off. The filtrate was made alkaline and extracted with chloroform. On

removal of the chloroform and crystallisation from acetone, colourless needles were obtained, melting point 219-220°. Mixed melting point with dihydrogelsemine was 219-220°. With methyl iodide a methiodide was obtained from the acetone mother liquor and on recrystallisation from alcohol and ether colourless needles were obtained, melting point 299-300°d. (dihydrogelsemine methiodide, melting point 300-301°d.).

REDUCTION OF GELSEMINE WITH HYDRIODIC ACID.

Gelsemine (150 mg.) was refluxed with 12 ccs. of hydriodic acid (S.G. 1.7) and red phosphorus for 30 hours. The reaction mixture was diluted with water and the residual red phosphorus filtered off. The acid solution was then neutralised with sodium carbonate and extracted with chloroform. The chloroform was distilled off and attempts made to obtain the resulting residue crystalline. This was not found to be possible.

Methyl iodide was added to an acetone solution of this substance, a colourless amorphous precipitate being obtained. This methiodide could not be obtained crystalline.

The free base was taken up in as small a quantity of boiling absolute alcohol as possible and ½ cc. of

hydriodic acid solution (S.G. 1.7) added. This resulted in the immediate formation of light brown crystals. The crystals were filtered off and dissolved in a boiling aqueous alcohol mixture. The solution was charcoaled and on cooling deposited the pure hydriodide as colourless needles of melting point 298°d.

Analysis figures are shown compared with those calculated for $C_{20}H_{23}O_2N_2I \cdot HI$.

	Found	Calculated.
C	41.83%	41.52%
H	3.98%	4.15%
N	4.85%	4.84%

HYDROLYSIS OF IODOISOAPOGELSEMINE.

A small quantity of iodoisoapogelsemine was refluxed with aqueous alcoholic potassium formate for about 6 hours. The solution was made alkaline and extracted with ether. The ether extract was dried with sodium sulphate and the ether distilled off, but attempts to crystallise the residue were unsuccessful.

This residue was dissolved in chloroform and methyl iodide was added. On addition of a little ether, a crystalline methiodide was deposited. This methiodide was recrystallised from aqueous alcohol/ether and obtained

as colourless plates of melting point 266°d. Moore records isoapogelsemine methiodide as crystallising in glistening plates, melting and decomposing at 266°(11).

REDUCTION OF IODOISOAPOGELSEMINE.

Iodoisoapogelsemine hydriodide (200 mgs.) was dissolved in boiling glacial acetic acid, and 1 gm. of zinc filings added. The mixture was boiled for a few hours. On cooling, the reaction mixture was treated with caustic soda solution until it was alkaline and then extracted with ether. The ether extract was dried over sodium sulphate and the ether distilled off. The residue was taken up in boiling acetone, light brown prisms being deposited after standing for a few days. On recrystallisation from acetone (twice), colourless needles were obtained, being found to melt at 219-220°, and giving no depression on admixture with dihydrogelsemine.

With methyl iodide, a solution of this base in acetone was found to give a crystalline methiodide. On recrystallisation from aqueous alcohol and ether, the pure methiodide was isolated as colourless needles of melting point 301-302°d. Compare dihydrogelsemine methiodide - m.p. 300-301°d.

Analysis figures for this methiodide, after drying

at 120°, are shown compared with those calculated for $C_{20}H_{24}O_2N_2.CH_3I$.

	Found.	Calculated.
C	54.00%	54.09%
H	5.63%	5.79%
N	6.07%	6.05%.

ACTION OF DIETHYLANILINE ON IODOISOAPOGELSEMINE.

About 400 mg. of iodoisoapogelsemine were refluxed with 15 ccs. of diethylaniline for a few hours. A black tarry solid was deposited during the reaction. Sodium carbonate solution was added to the reaction mixture, and the whole steam distilled to remove diethylaniline. The solution remaining contained some tarry matter. This solution was extracted with ether and the extract dried over sodium sulphate. The ether was removed from the extract and the residue dissolved in boiling acetone. This solution was charcoaled, and after standing for a few days, light brown crystals were deposited. These were recrystallised twice from acetone, colourless prisms of melting point 106-108° being obtained.

Analysis figures for this compound, after drying at 70°, are shown compared with those calculated for $C_{20}H_{22}O_2N_2$:

	Found	Calculated.
C	72.09%	74.53%
H	7.08%	6.83%
N	8.55%	8.7%.

Moore[11] recorded that by the action of diethylaniline on chloroisoapogelsemine, a base of melting point 105-108° was obtained, being an isomer of gelsemine. The above compound is probably identical with the substance described by Moore, but the quantity available did not permit of its further purification. The very low yield obtained by the above preparation discouraged a repeat experiment for the purpose of checking the analysis figures.

GENERAL REACTIONS.

REDUCTION OF DIHYDROGELSEMINE METHIODIDE WITH SODIUM AMALGAM.

Dihydrogelsemine methiodide (300 mg.) was dissolved in 5 ccs. of hot water and heated on a boiling water bath. 10-12 gms. of 3% sodium amalgam were added and the mixture heated for 6-7 hours on the water bath. When the mixture was cool, it was extracted with chloroform and the chloroform removed from the extract. Nothing was obtained from this extract on evaporating off the chloroform.

The residual alkaline solution was acidified and on standing a brown solid was deposited. Owing to the insolubility of this substance in all the usual solvents, it was not found possible to crystallise it. It was, however, soluble in caustic soda solution and was precipitated from it on acidification. By this process the substance was neither purified nor obtained in the crystalline state, so no analyses were carried out on it. This compound did not respond to the usual tests for ionic mercury, and from its behaviour it would seem to be some mercurial derivative of the alkaloid.

ACTION OF PIPERIDINE ON GELSEMINE.

Gelsemine (200 mg.) was boiled for 12 hours with 10-15 ccs. of piperidine. The piperidine was distilled off on the water bath under reduced pressure and the residue crystallised from acetone. Colourless needles were obtained of melting point 178°. A mixed melting point with gelsemine was also found to be 178°.

This action was repeated in a Carius tube at a temperature of 230-240° for five hours. In this case the starting product was again found to be recovered unchanged.

ACTION OF BARYTA ON GELSEMINE.

Gelsemine (300 mg.), barium hydroxide (1.5 gm.) and 10 ccs. of water were heated in a Carius tube at 150° for five hours. On opening the tube the reaction mixture was extracted with ether. The ether was distilled off from the extract and the residue crystallised from acetone, colourless needles being obtained of melting point 178°. A mixed melting point determination with gelsemine showed no depression. On preparing the methiodide from the ether extract with methyl iodide it was found to melt at 294°d.

The residual solution from the ether extract was shaken with benzoyl chloride until the smell of the latter was no longer present. A precipitate was formed at this stage and was filtered off. This was found to be benzoic acid. The filtrate was now agitated with silver oxide for a considerable period to remove all halide ions in the solution. The excess of silver oxide and the silver halide was filtered off, and a stream of carbon dioxide passed through the solution to remove barium. The precipitate of barium carbonate was filtered off and residual solution evaporated to dryness. A very small amount of a colourless solid remained as residue, but this was found to be barium benzoate.

ACTION OF SELENIUM ON GELSEMINE.

Gelsemine (500 mg.) was heated with four atoms of selenium (250 mg.) in an atmosphere of nitrogen at 230° for 18 hours. Colourless crystals sublimed up the tube, and probably consisted of selenium dioxide. When the mixture was cool it was extracted first of all with ether. The ether was removed from the extract and attempts made to crystallise the residue from acetone. No crystals could be obtained. On addition of methyl iodide to the acetone solution, a coarse granular precipitate was obtained. This precipitate was filtered off and after charcoaling its solution in aqueous alcohol, colourless needles were obtained by the addition of ether. The crystals were found to melt at 285°d. The quantity of material obtained was too small for analysis, but this may possibly have been gelsemine methiodide.

The residue from the ether extract was extracted with chloroform and the chloroform removed from the extract. The resultant residue was found to be insoluble in acetone. Attempts were made to obtain this compound crystalline, but it could only be isolated in the amorphous state. The methiodide was prepared by boiling an alcohol/chloroform solution with methyl iodide. The resultant dark brown solution was charcoaled and ether added. Almost colourless crystals were obtained melting about 270°d.

This material could not be recrystallised from alcohol or aqueous alcohol, and it was found that on cautiously adding ether to a hot aqueous alcoholic solution, an amorphous precipitate was always obtained even after seeding with some of the crystals. Eventually crystals were obtained by doping the aqueous alcoholic solution rapidly with ether, causing the precipitation of the amorphous substance and allowing to stand. On standing overnight the precipitate became crystalline.

Analysis figures for this substance, dried at 120°, are shown compared with those calculated for (I) $C_{20}H_{24}O_3N_2.CH_3I$ and (II) $C_{20}H_{22}O_2N_2.CH_3I$.

	Found		Calculated.	
	(A)	(B)	(I)	(II)
C	52.61%	52.70%	52.28%	54.51%
H	5.76%	5.55%	5.6%	5.36%
N	6.47%	7.14%	5.81%	6.01%
I	25.92%		26.35%	27.25%.

From the analysis figures of this methiodide and the fact that the free base was insoluble in acetone, it is obvious that the product does not consist of gelsemine methiodide. The analysis figures would seem to indicate either a gain of the elements of water or loss of carbon.

The product of this reaction is, however, of little interest from the point of view of the structural considerations of the gelsemine molecule, and this matter has therefore not been pursued further.

ACTION OF CYANOGEN BROMIDE ON GELSEMINE.

On account of unsatisfactory analysis figures for the products of this reaction, the reaction has been carried out four times under slightly varying conditions with a view to obtaining pure products. The method recorded here is that found to give the largest yield of the product of melting point 216°.

Gelsemine (1 gm.) was dissolved in dry ether and benzene, and a slight excess of a dry freshly prepared ethereal solution of cyanogen bromide added. Care was taken that moisture had no access to the reaction mixture, and it was refluxed for 6 hours. After refluxing for a short period, a colourless precipitate was formed. When the reaction was complete, this precipitate was filtered off.

This residue was crystallised from aqueous alcohol (four times) and obtained as colourless needles or prisms of melting point 326°d. Analyses were carried out on different batches of this material, two of which are shown

compared with figures calculated for gelsemine hydrobromide - $C_{20}H_{22}O_2N_2.HBr$.

	Found.		Calculated.
	(I)	(II)	
C	59.56%	59.65%	59.55%
H	5.93%	6.01%	5.70%
N	7.48%	7.43%	6.94%.

Prepared gelsemine hydrobromide has been found to melt at 325°d.

A quantity of this material was dissolved in water and the solution made alkaline with ammonium hydroxide. This was extracted with ether and the ether extract dried with sodium sulphate. The ether was removed from the extract and the residue taken up in boiling acetone. From this acetone solution, on seeding with a crystal of gelsemine, colourless needles were deposited. On recrystallisation from boiling acetone, these were found to melt at 178° and to give no depression on admixture with pure gelsemine.

Some difficulty was encountered in obtaining crystalline gelsemine from this fraction and in two experiments it was not accomplished until the material had been warmed with an aqueous alcoholic solution of caustic soda. This rather points to the presence of impurity in this

fraction. In the above experiment, however, the quantity of gelsemine isolated indicated that the major portion of this fraction consisted of gelsemine hydrobromide.

The filtrate from the crude gelsemine hydrobromide was now warmed on the water bath to remove solvent and any excess cyanogen bromide. The residue was taken up in boiling absolute alcohol, about half a gram of crystalline substance being deposited on cooling. This substance was easily soluble in alcohol and was crystallised to constant melting point from it (four times). It was obtained as lustrous plates or prisms of melting point 216°.

Analysis figures obtained for this compound were neither consistent nor in agreement with any one formula. Four sets of found analysis figures are shown compared with those calculated for $C_{20}H_{21}O_2N_2.CN$.

	Found.				Calculated.
	(I)	(II)	(III)	(IV)	
C	-	70.85%	71.68%	71.82%	72.62%
H	-	5.59%	5.49%	5.58%	6.05%
N	12.28%	13.16%	13.86%	14.06%	12.10%

It would thus seem that although the melting point was constant, a pure product was not obtained. No crystalline derivative of this substance could be prepared

for a check on the analyses.

On refluxing with methyl iodide in benzene solution only the starting product was recovered, identified by melting point and mixed melting point.

With dry hydrogen chloride in ether solution, an amorphous hydrochloride was obtained, but this substance could not be obtained crystalline.

HYDROLYSIS OF THE COMPOUND OF MELTING POINT 216°.

An alcoholic solution of the compound of melting point 216° (300 mg.) was refluxed with 500 mg. of caustic potash for 6 hours. When the reaction was complete, the solution was diluted and extracted with ether. The ether extract was dried and the ether removed. The residue was taken up in boiling acetone, but could not be induced to yield crystals. No success was attained on utilising other solvents.

On addition of methyl iodide to an acetone solution of the hydrolytic product, a crystalline methiodide was deposited on standing. This was recrystallised from aqueous alcohol/ether and obtained as colourless crystals of melting point 297-298°d.

Analysis figures for this methiodide are shown compared with those calculated for (A) $C_{19}H_{22}O_2N_2.CH_3I$

and (B) $C_{20}H_{22}O_2N_2.CH_3I$.

	Found.	Calculated.	
		(A)	(B)
C	53.10%	53.09%	54.51%
H	5.75%	5.53%	5.36%
N	6.70%	6.19%	6.01%
I	27.70%	28.12%	27.25%

S E M P E R V I R I N E.

CHARACTERISATION.

PREPARATION OF SEMPERVIRINE.

On account of the fact that sempervirine is somewhat unstable and is resinified to a fair extent on boiling with alcohol or chloroform, the following method has been found most suitable for its preparation from the nitrate.

Sempervirine nitrate was dissolved in as small a quantity as possible of a boiling 1:1 alcohol/water mixture. While still hot, a slight excess of ammonium hydroxide solution was added, care being taken that no precipitate was allowed to form. On cooling, crystalline sempervirine was deposited and filtered off. This can be purified further, if necessary, by careful crystallisation from boiling alcohol.

SEMPERVIRINE METHIODIDE.

On adding methyl iodide to a solution of sempervirine in chloroform, buff coloured plates of the methiodide were deposited on standing. This methiodide was found to be difficultly soluble in boiling alcohol and in boiling water. It was, however, obtained as light brown

crystals from a boiling alcohol-water mixture. Its melting point was found to be 348°d.

Analysis figures are shown compared with those calculated for $C_{19}H_{16}N_2 \cdot CH_3I$.

	Found.	Calculated.
C	57.86%	57.97%
H	4.86%	4.59%
N	6.80%	6.76%.

PREPARATION OF SEMPERVIRINE PICRATE.

On addition of picric acid in absolute alcohol solution to a chloroform solution of sempervirine, a yellow amorphous precipitate was obtained. This was filtered off and crystallised from alcohol. The melting point was found to be 268°d. Analysis figures are shown compared with those calculated for $C_{19}H_{16}N_2 \cdot C_6H_3N_3O_7$.

	Found.	Calculated.
C	59.75%	59.88%
H	3.94%	3.79%.

This picrate has been prepared by Hasenfratz[16] but no melting point was recorded by him.

REDUCTION.

CATALYTIC HYDROGENATION OF SEMPERVIRINE.

0.6108 grams of sempervirine dissolved in alcohol,

and 0.0894 grams of palladium chloride in water, were shaken in a catalytic hydrogenation apparatus with hydrogen at the ordinary temperature and at very slightly raised pressure until absorption ceased. After about five hours 154 ccs. of hydrogen at 753 mm. and 23°C. had been absorbed. This is equivalent to 2.8 double bonds.

The solution containing the reduction product had lost its original red colour, and was now colourless, with a faint suspicion of a blue fluorescence.

After filtering off the palladium, the solution was made alkaline with ammonium hydroxide and extracted with chloroform. On removal of the chloroform a resin was obtained which darkened in the air and from which no crystals could be obtained. Neither a crystalline hydrochloride nor methiodide could be obtained.

In a repeat experiment, after filtration of the palladium, the solution was acidified with hydrochloric acid and evaporated to dryness. On attempting to crystallise the residue from absolute alcohol some colourless crystals were obtained together with some resinous matter. On exposure to the air the crystals resinified, and no further crystalline products could be isolated.

ELECTROLYTIC REDUCTION OF SEMPERVIRINE.

The cell for this reduction consisted of a 100 cc. beaker with a cylindrical lead cathode of area 75 sq.cm., containing a porous pot in which the anode consisted of a strip of lead 4 mm./ 1.5 cm./ 5 cm..

The cell was filled with 20% sulphuric acid, the cathode connected to the positive, the anode connected to the negative and a current of $2\frac{1}{2}$ - 4 amps passed for three hours.

The cell was now filled with 60% sulphuric acid and a current of $2\frac{1}{2}$ amps passed for 4 - 5 hours in the reverse direction.

Sempervirine was dissolved in alcohol containing 20% of sulphuric acid and the solution placed in the cathode chamber. A 20% solution of sulphuric acid was placed in the anode chamber and a current of $2\frac{1}{2}$ - 5 amps passed for 24 hours with external cooling.

The acid solution was now made alkaline, resulting in the precipitation of a colourless amorphous solid. On filtering off this solid it darkened and resinified in the air. No crystals were obtained from it, nor could any crystalline derivatives be isolated.

ACTION OF HYDRIODIC ACID ON SEMPERVIRINE.

200 mg. of sempervirine were refluxed with 10 ccs. of hydriodic acid (S.G. 1.7) and red phosphorus for 30 hours. When the reaction mixture was cool, it was diluted with water, causing the precipitation of a small quantity of a colourless amorphous solid. This, together with the residual red phosphorus, was filtered off.

On adding sodium carbonate to the filtrate, some colourless material was precipitated before neutralisation had occurred. This was filtered off and the filtrate made alkaline. No more material was deposited from this alkaline solution and nothing was obtained from a chloroform extract. The residue from the above filtration was dissolved in boiling absolute alcohol and allowed to crystallise. Colourless needles were obtained of melting point 333-335°d. Analysis figures found are shown compared with those calculated for sempervirine hydriodide - $C_{19}H_{16}N_2.HI$.

	Found.	Calculated.
C	57.08%	57.00%
H	4.06%	4.25%.

On extracting the colourless solid from the red phosphorus residue, this was found to be the same compound.

The colourless solid was dissolved in hot alcohol

and a few drops of caustic soda solution added. On standing brown crystals were deposited of melting point 259-260°. A mixed melting point determination with sempervirine did not show any depression.

O X I D A T I O N.

PERMANGANATE OXIDATION OF SEMPERVIRINE.

About 250 mg. of sempervirine were dissolved in pure dry acetone. Owing to the low solubility of sempervirine in acetone, the bulk of this solution was about 300 ccs.. Finely powdered potassium permanganate was added gradually with stirring to this solution until an amount equivalent to 12 atoms of oxygen had been used. After stirring for a while the solution was refluxed for an hour. A few ccs. of water were added and the manganese dioxide filtered off. The acetone was removed from the filtrate, a dark brown material being obtained from which no crystals could be isolated. On evaporating some of this material to dryness with dilute hydrochloric acid and extracting the residue with absolute alcohol, only a dark brown resinous material was obtained, from which no crystals could be isolated.

ACTION OF DILUTE NITRIC ACID ON SEMPERVIRINE.

Sempervirine nitrate (100 mg.) was refluxed for

20 hours with 10 ccs. of 25% nitric acid. Most of the sempervirine nitrate dissolved on heating at first, but very soon a bulky yellow amorphous precipitate was obtained.

When the reaction mixture was cool, this precipitate was filtered off. It was found to be very slightly soluble in alcohol, water and acetone, but could not be obtained crystalline.

Some of this substance was dissolved in a large bulk of boiling water, and sodium carbonate solution added. On extracting with chloroform a crimson solution of the free base was obtained. The chloroform was removed from the extract and attempts made to crystallise the residue. It was not found to be possible to obtain this substance crystalline, but the amorphous dark red substance was found to separate fairly well in small particles from a boiling alcoholic solution on cooling. This substance was taken up in hot alcohol, allowed to precipitate on cooling and filtered. After repeating this 5 times, a nitrogen estimation was carried out on this purified amorphous dark red substance, and was found to agree with that calculated for a mononitrosempervirine.

N found - 13.87%; calculated for $C_{19}H_{15}N_2NO_2$ - 13.25%.

The hydrochloride and methiodide of this base were both prepared, but could only be obtained in the amorphous state.

OXIDATION OF SEMPERVIRINE WITH CHROMIC ACID.

A solution of 200 mg. of sempervirine in acetic acid was warmed slightly on the water bath, and a solution of chromic anhydride in slightly aqueous acetic acid added gradually. An amount of chromic acid equivalent to 4 atoms of oxygen was used.

A green colour was developed and a yellow amorphous precipitate was formed. After warming for 1½-2 hours on the water bath the yellow precipitate was filtered off. Attempts were made to crystallise this substance, but were unsuccessful. The melting point of the amorphous material was above 330°, and it was probably sempervirine chromate. On warming with alcoholic ammonia solution and extracting with chloroform, sempervirine was shown to be present, (A) by formation of the methiodide, melting point 348°d. from a portion of the chloroform extract with methyl iodide, and (B) by isolation of a small quantity of sempervirine which did not depress the melting point of authentic material.

The acetic acid filtrate from above was placed in an evacuated desiccator over sticks of caustic potash. After a few days, all the acetic acid was removed and a green coloured glass was left. Water was added to this,

the whole dissolving on gentle warming. Ammonium hydroxide was then added and the solution extracted with chloroform. The chloroform extract was colourless and on addition of methyl iodide to this, buff coloured crystals were deposited. These were filtered off and recrystallised from slightly aqueous alcohol/ether, being obtained as light brown needles of melting point 313-314°d. Unfortunately there was only sufficient material for carbon, hydrogen and nitrogen analyses, the results of which are shown below:

	Found	Calculated for $C_{16}H_{14}N_2 \cdot CH_3I$	Calculated for $C_{19}H_{16}N_2 \cdot CH_3I$
C	54.19%	54.25%	57.97%
H	4.98%	4.52%	4.59%
N	7.42%	7.44%	6.76%
I	33.66% (calculated from N)		
	100.25		

This experiment was repeated twice, under slightly modified conditions, so that precipitation of the sempervirine chromate did not take place.

In the first repeat the chromic acid solution was added very gradually to the stirred solution of sempervirine heated to 90°C. An amount of chromic acid equivalent

to 12 atoms of oxygen was used and stirring was continued for about 20 hours. The method of isolation used was the same as above, but in spite of the fact that 500 mg. of sempervirine were used, only a very small amount of an amorphous material was obtained on adding methyl iodide to the chloroform extract. On crystallising this from slightly aqueous alcohol/ether, there was obtained only sufficient crystalline material for a melting point. This was found to be the same as in the original experiment.

In the second repeat, 500 mg. of sempervirine were again used. The oxidation was carried out at the ordinary temperature, the chromic acid solution being added very slowly to prevent the precipitation of the insoluble chromate. Stirring was continued for 4 days. On using the method of isolation described above, a very small amount of crystalline methiodide was obtained from the chloroform solution. In this case, however, the amount was insufficient even for an ordinary melting point determination.

In the above two repeat experiments the aqueous solution (from which the chloroform extract was obtained) was examined for any acidic oxidation products, but without success.

OXIDATION OF SEMPERVIRINE WITH HYDROGEN PEROXIDE.

By adding a solution of hydrogen peroxide (100 vols.) to tert. butyl alcohol and repeatedly drying with sodium sulphate, a dry solution of hydrogen peroxide in tert. butyl alcohol was obtained. A few milligrams of osmium tetroxide in tert. butyl alcohol were added to this solution, and then sempervirine in tert. butyl alcohol. This mixture was allowed to stand at room temperature overnight, a brown amorphous material being deposited. This solid was filtered off, but all attempts to obtain it crystalline were unsuccessful.

On the assumption that this substance would be an amine oxide, a solution of it in aqueous alcohol was reduced with zinc dust and dilute hydrochloric acid. After reaction had ceased, the solution was made alkaline with caustic soda and extracted with chloroform. The chloroform was allowed to evaporate at the ordinary temperature, a light brown solid being left. This solid could not be obtained crystalline, nor could any crystalline derivatives be prepared from it.

GENERAL REACTIONS.

ACTION OF ALKALI ON SEMPERVIRINE METHIODIDE.

Sempervirine methiodide (800 mg.), was heated in a

Carius tube with caustic potash solution (5 gm. KOH in 20 cc. water) to a temperature of 195° for 4 hours. After opening the tube the reaction mixture was acidified with concentrated hydrochloric acid and filtered. Apart from some silica, there was as residue some dark brown glassy material. Attempts to obtain this glass crystalline were unsuccessful, as also were attempts to prepare any crystalline derivatives from it.

The acid filtrate was made alkaline with sodium carbonate and the solution extracted with chloroform. On removal of the chloroform a colourless solid residue was left. In spite of repeated attempts at crystallisation this substance could only be isolated in the amorphous state. The hydrochloride and methiodide were also amorphous.

ACTION OF CYANOGEN BROMIDE ON SEMPERVIRINE.

Sempervirine (300 mg.) in chloroform solution was warmed with an excess of an ether solution of cyanogen bromide for 6 hours. A dark brown precipitate was deposited and filtered off.

The solvent was removed from the filtrate, a reddish brown solid being left. This solid, which contained some resinous matter, could not be obtained crystalline, nor

could a crystalline hydrochloride or methiodide be prepared from it, both the latter being amorphous.

The residue from the filtration was dissolved in boiling absolute alcohol and charcoaled. On cooling, bright yellow needles were deposited. These were recrystallised four times from absolute alcohol and found to melt at 325°d.

The results of analysis do not agree, within experimental error, for a pure compound derived from sempervirine. The found results from this and a repeat experiment are, however, shown against those calculated for (1) sempervirine hydrobromide and (2) $C_{17}H_{18}N_2 \cdot HBr$, for comparison purposes.

	Found.		Calculated.	
	(I)	(II)	(1)	(2)
C	61.03%	60.89%	64.59%	61.63%
H	5.27%	5.37%	4.81%	5.74%
N	8.26%	8.15%	7.93%	8.46%.

This hydrobromide probably contained a certain amount of sempervirine hydrobromide. On adding ammonium hydroxide to an aqueous alcoholic solution of this substance, the colour of the solution deepened and a yellow amorphous precipitate separated out. This was extracted with chloroform and the chloroform removed. The residue

obtained was dark brown and could not be crystallised.

On adding an alcoholic solution of picric acid to a portion of the chloroform extract, a yellow amorphous picrate was deposited. This was crystallised from absolute alcohol, deep orange prisms of melting point 267°d. being obtained. The melting point of this substance was not depressed on admixture with authentic sempervirine picrate. Analysis results also point to the identity of this substance with sempervirine picrate.

	Found.	Calculated.
C	59.22%	59.88%
H	3.98%	3.79%
N	13.81%	13.97% for $C_{19}H_{16}N_2 \cdot C_6H_3N_3O_7$.

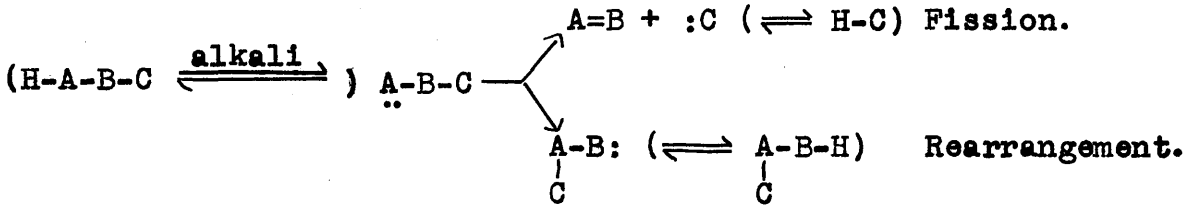
On adding methyl iodide to a chloroform solution of the free base, light brown crystals were deposited from the solution. This methiodide was found to be very difficultly soluble in boiling water, alcohol, or alcohol/water mixture, and when once in solution it could not be induced to crystallise again. Consequently, no purification of this substance could be undertaken.

FISSION AND MOLECULAR REARRANGEMENT AS ALTERNATE MODES OF REACTION.

FISSION AND MOLECULAR REARRANGEMENT AS ALTERNATE MODES OF REACTION.

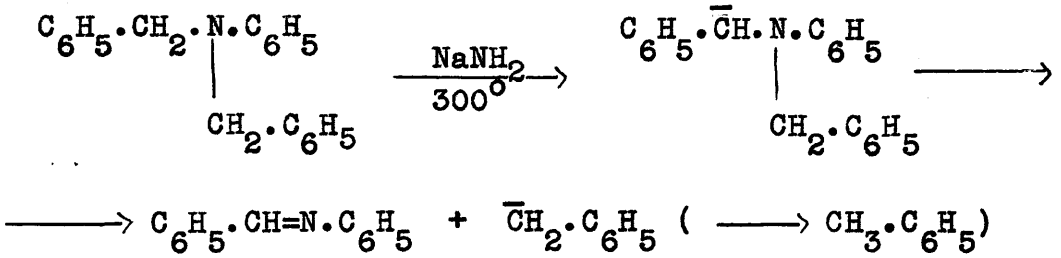
INTRODUCTION.

A very general representation of the reactions being studied can be shown as follows:-



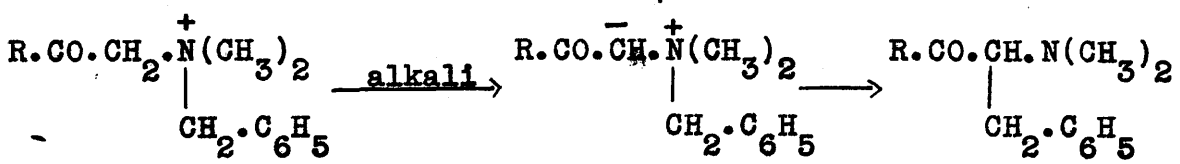
The processes shown in brackets may or may not be involved in any given case. Examples of these cases are given by the following two reactions:-

Fission:



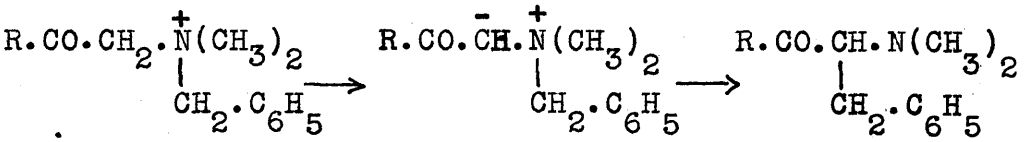
(Reference: unpublished communication from Dr. T.S.Stevens).

Rearrangement:



These reactions involve changes in the value of the covalency of the atoms concerned. Both in the fissions and the rearrangements the covalency of A increases by one unit, and in very many cases this is a change from a highly unstable to an intrinsically stable condition of that atom. We may then consider that the tendency to this change furnishes the main driving force for the reaction, which will proceed the more readily the less stable :A happens to be.

For example, the following rearrangement can be effected under such conditions that the first stage is rapid and complete and the rate of the whole process



I II III

determined by the second stage. Then it is found that the reaction is retarded by the presence in R of substituents calculated to increase the acidity of the reactive hydrogen in I, i.e., to increase the stability of $-\bar{C}H-$ in II.

To take an extreme case, the rearrangement of amine oxides requires a much higher temperature than that for phenacyl ammonium salts.

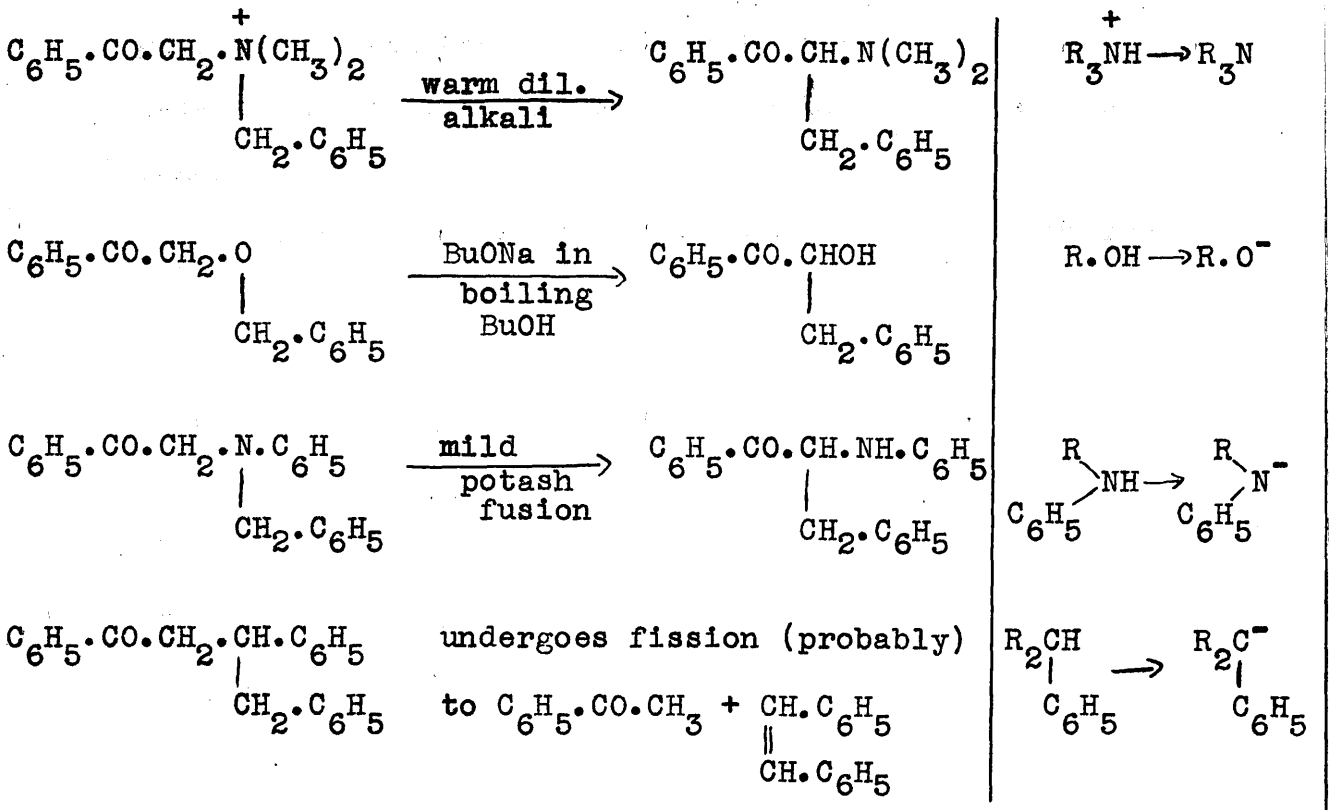
Again, when the stability of A in its lower state of covalency is exceedingly small, we are forced to begin with H-A-B-C and may have to use very drastic conditions to extract the hydrogen at all. As far as our limited knowledge goes, the groups fluorenyl and H-C(CN)(C_6H_5)- should behave rather like phenacyl.

In the rearrangement, the covalency of B is diminished by one unit while that of C remains unaltered. It is legitimate to compare the two following types of covalency change:-

$$:A\text{-}B\text{-}C \longrightarrow C\text{-}A\text{-}B:$$

$$C\text{-}A\text{-}B\text{-}H \longrightarrow C\text{-}A\text{-}B: + H^{+}$$

in a series of cases and to take the acidity of C-A-B-H as a measure of the tendency of B to suffer a diminution of covalency, as in the rearrangement - provided we keep A and C constant while varying B, and that the relative tendencies of coordinatively unsaturated Bs to increase their covalency are, to a sufficient degree of approximation, independent of the nature of the partner with which they are to combine.



at a very high temperature.

(Reference: Unpublished communication from Dr. T.S. Stevens). Ease of migration is seen to decrease with diminishing acidity of C-A-B-H.

In the case of fission, the covalency of C is diminished by unity, while that of B remains unaltered. Here, then, we may expect facility of fission to increase with acidity of H-C.

In a similar way we may seek to correlate the relative tendencies to fission or rearrangement in any

given case with the relative stabilities of :C and C-A-B: and so with the relative acidities of H-C and C-A-B-H.

The available data indicate that fission is much more facile intrinsically than rearrangement, i.e., that rearrangement takes place only if :C is much less stable than C-A-B: . Consider the series:-

$C_6H_5.CO.\bar{C}H.\overset{+}{N}(CH_3)_2.CH_2.C_6H_5$ Rearrangement[20].

*$C_6H_5.CO.\bar{C}H.O.CH_2.C_6H_5$ Rearrangement.

$C_6H_5.\bar{C}H.O.CH_2.C_6H_5$ Rearrangement and fission[21].

*$C_6H_5.CO.\bar{C}H.N(C_6H_5)CH_2.C_6H_5$ Rearrangement.

$C_6H_5.\bar{C}H.N(C_6H_5)CH_2.C_6H_5$ Fission.

$C_6H_5.\bar{C}H.N(CH_3)CH_2.C_6H_5$ Fission.

The second, fourth, fifth and sixth examples are unpublished communications from Dr. T.S. Stevens.

Here H-C is always toluene, and rearrangement gives place to fission as C-A-B-H changes from definitely

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*Not examined for fission.

acid $R.\overset{+}{N}H(CH_3)_2$ through R.OH to $R.NH(CH_3)$. Fission predominates, however, long before the acidity of C-A-B-H has fallen to that of toluene.

In general we may assume that the nature of C will have but little effect on the acidity of C-A-B-H and so it would seem that the simplest systematic line of attack on this potentially enormous field would be to study series of compounds in which either A-B is constant and C varies or C is constant and A-B varies, noting the point in each series at which fission gives place to rearrangement.

From practical considerations, A is limited to some such radicle as fluorenyl, phenacyl or desyl and the readily available variants of group B in descending order of theoretical tendency to favour rearrangement are $-\overset{+}{N}(Alk)Ar.-$, $-\overset{+}{N}(Alk)_2-$, -O-, -N.Ar-, -N.Alk -.

GENERAL OUTLINE OF RESULTS.

The series of compounds chosen for study all contained the 9-fluorenyl radicle as group A, and the benzyl group as group C. Group B was chosen to consist of -N(Alk)Ar- , $-N(Alk)_2-$, -O- , -NAr- , -NAlk- . The compounds chosen were:-

1). Methylphenylbenzyl-9-fluorenyl ammonium halide.

2). Dimethylbenzyl-9-fluorenyl ammonium halide.

3). Benzyl-9-fluorenyl ether.

4). Benzyl-9-fluorenyl aniline.

5). Benzyl-9-fluorenyl methylamine.

According to theoretical considerations, rearrangement should give place to fission on passing from 1) to 5). The aim of this work was to examine these compounds, under suitable alkaline conditions, for rearrangement and fission, noting at what point in the series fission superseded rearrangement.

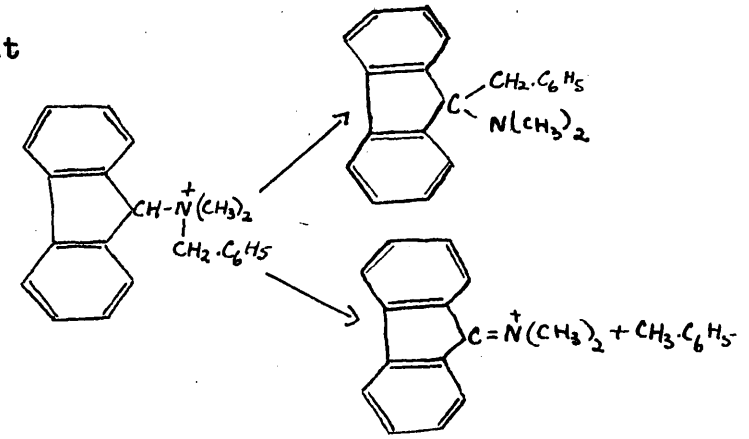
It was, however, not found possible to prepare methylphenylbenzyl-9-fluorenyl ammonium halide by the usual methods. The remaining compounds and some derivatives were prepared and examined under varying alkaline conditions.

It was found that dimethylbenzyl-9-fluorenyl ammonium bromide reacted in warm dilute caustic soda

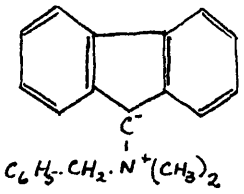
solution. Reaction could take place in either, or both, of two ways:-

1). Rearrangement

2). Fission

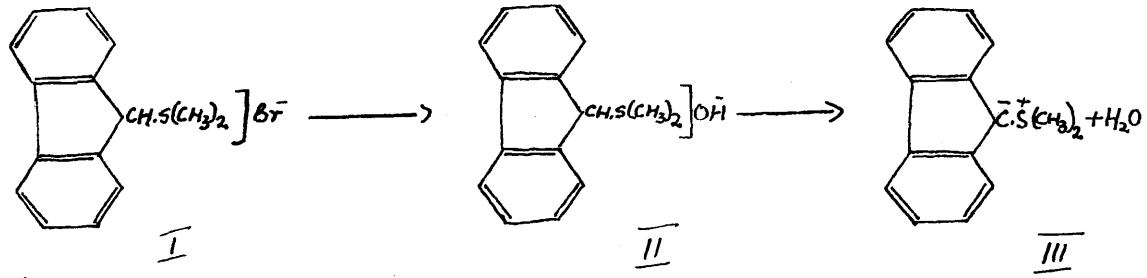


Toluene and dimethylamine as products of fission were tested for, but not found. An 80% yield of pure rearrangement product was obtained. The picrate, methiodide, and methopicrate of this compound were prepared for reference. During the reaction, a red intermediate oil was formed, and separated from the solution. This rather suggests the presence of



but attempts made to isolate this interesting compound were unsuccessful.

Compare Ingold and Jessop[22], who, by the action of caustic soda solution on I, obtained III.

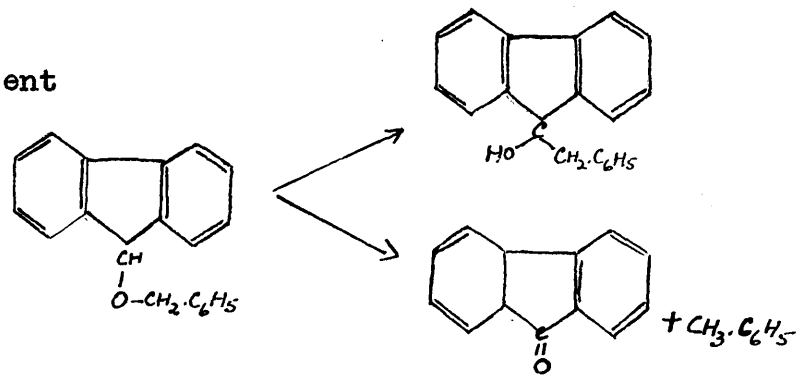


Attempts have been made to synthesise this rearrangement product, but have not been attended with any success. The compound was shown to be a tertiary amine by the formation of a methiodide. It was also shown to be a derivative of 9-benzyl fluorene, by reduction of the methiodide of the rearrangement product to 9-benzyl fluorene with sodium amalgam.

Benzyl 9-fluorenyl ether was prepared, and by the action of dry sodium ethoxide at 100°, 9-fluorenol only was obtained. Now in the case of this ether, if either rearrangement or fission are to take place, reaction will occur as follows:-

1). Rearrangement

2). Fission



With boiling butyl alcoholic sodium n. butoxide, however, the rearrangement product, 9-benzyl-9-fluorenol, was obtained, agreeing in melting point with the literature value[23].

Toluene as a product of fission was tested for, but

was not found. The rearrangement product was compared, and found to be identical, with a synthetic specimen.

Benzyl-9-fluorenyl aniline was treated with the following alkaline reagents:-

1). Dry sodium ethoxide at 150-200°,

2). Solid caustic soda at 290-310°,

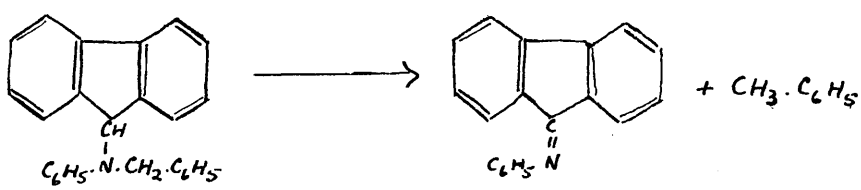
3). Sodamide at 200°,

4). Lithium methyl at 100°, 150°, 200° and 240°,

5). Lithium phenyl at 110° and 130°,

6). Metallic potassium in decalin.

By the action of caustic soda at 300°, some indications were obtained that fission had taken place, but are not regarded as satisfactory on account of the small quantities obtained, and indications that decomposition in other directions had also taken place. This compound on fission should give rise to fluorenone anil and toluene:



Evidence for fission consisted of the isolation of a small quantity of toluene, and its characterisation as 2:4-dinitrotoluene. Also a small quantity of aniline was detected as its 246 tribromo derivative at the stage where it might be expected as a hydrolytic product of fluorenone anil. Benzyl aniline was also isolated.

Failure to isolate either fluorenone or fluorenone anil, led to the decision to use a more reactive reagent which would possibly cause reaction to take place at a lower temperature. The use of lithium phenyl and lithium methyl did not, however, produce any further evidence, nor did any of the other reagents used.

Benzyl-9-fluorenyl methylamine was also treated with lithium phenyl and lithium methyl without success. The use of solid caustic soda at 295° resulted in the formation of a considerable quantity of difluorenyl, but no compounds indicative of fission or rearrangement were isolated.

The last two compounds seemed to undergo gross decomposition at a lower temperature than that at which they would react to give fission or rearrangement products.

EXPERIMENTAL.

9-Bromo fluorene, as an essential starting product for all the required compounds was prepared from fluorene. Fluorene was oxidised to fluorenone[24]. The fluorenone obtained was now reduced to fluorenol[25] and 9-bromo fluorene prepared from this by the action of dry hydrogen bromide[26].

DIMETHYLBENZYL-9-FLUORENYLAMMONIUM BROMIDE.

By the action of 9-bromo fluorene (5 gm.) in benzene on benzyldimethylamine (2.8 gm.) in benzene in the cold, colourless plates of dimethylbenzyl-9-fluorenyl-ammonium bromide were deposited on standing. This product was recrystallised from boiling absolute alcohol, and the melting point of the pure product was found to be 165-166°. On analysis the percentage Br was found to be 20.7 compared with 21.0% for the calculated value.

With picric acid in alcoholic solution, this substance deposited a picrate. On recrystallisation from absolute alcohol, light yellow needles were obtained of melting point 182-183°. Analysis: percentage nitrogen found - 10.85; calculated - 10.60.

METHYLPHENYLBENZYL-9-FLUORENYLAMMONIUM HALIDE.

Benzyl methyl aniline was prepared[33] and warmed

with a molecular equivalent of 9-bromo fluorene for an hour or two in benzene solution. The reaction mixture was allowed to stand for two months, but no material was deposited from the solution.

METHYL-9-FLUORENYL ANILINE was prepared by warming 5 gms. 9-bromofluorene (1 mol.) with 4.5 gms. methyl aniline (2 mols.) on a water bath for two hours. The reaction mixture was diluted with benzene, allowed to stand for a few hours, and the precipitated hydrobromide filtered off. Some of the benzene was distilled off and methyl alcohol added. Crystals were deposited from this solution, filtered off, and recrystallised from benzene and methyl alcohol. Fine colourless silky needles were obtained, melting point 102-103°. A mixed melting point with 9-bromofluorene (m.p. 104°) was found to be 75°. The nitrogen percentage found for this compound is shown compared with the calculated value. Found, 5.28%; calc. 5.17%.

A solution of methyl 9-fluorenyl aniline in benzene was added to an acetone solution of benzyl iodide and allowed to stand. After standing for about a month no crystals were deposited from the solution. Some of the acetone was removed under reduced pressure, and a little

nitromethane was added. Crystals were deposited, but they were found to consist of difluorenyl, melting point 237-238°. For the use of nitromethane compare Ingold and Jessop[22], who have used this solvent with success for the preparation of salts which could not be prepared in other solvents.

BENZYL-9-FLUORENYL ETHER.

To 1 gm. of silver nitrate in 5 ccs. of benzyl alcohol (dissolves on heating) was added 1 gm. of 9-bromofluorene in warm benzene. An immediate precipitate of silver bromide was obtained. Some methyl alcohol was added and the mixture was filtered. The filtrate was washed with water and then steam distilled to remove benzyl alcohol, benzaldehyde and solvent. The residue was extracted with ether, dried with sodium sulphate and the ether removed. The product was crystallised from methyl alcohol, being obtained as colourless silky needles of melting point 68-69°. Analysis figures are shown compared with the calculated values.

Found: C, 87.85%; calc. C, 87.91%,
H, 6.29%; H, 6.23%.

This method was used for the preparation of this ether because the usual methods for ether preparation

have been found to be unsuccessful (unpublished communication from Dr. T.S. Stevens), and is similar to that employed by Kliegl, Wünsch, and Weigele[27] for the preparation of 9-fluorenyl ethyl ether.

BENZYL-9-FLUORENYL ANILINE.

4.5 gms. of 9-bromofluorene (1 mol.) were refluxed in benzene solution with 7 gms. of benzyl aniline (2 mols.) for two hours. The solution was diluted with benzene, allowed to stand for a short while, and the precipitated hydrobromide filtered off. After removal of some of the benzene, crystals were obtained by the addition of a little methyl alcohol. They were recrystallised from benzene and methyl alcohol and obtained as colourless fine needles of melting point 144°. Found: N = 4.24%, $C_{26}H_{21}N$ requires N = 4.04%.

BENZYL-9-FLUORENYL METHYLAMINE.

Benzyl methylamine was prepared by condensing benzaldehyde and methylamine in ether solution and reducing the product with sodium amalgam[28].

Equal weights of benzyl methylamine and 9-bromo fluorene were allowed to react, a certain amount of heat being developed. Benzene was added, and after standing for a while, the benzylmethylamine hydrobromide was

filtered off. Some of the benzene was removed, and on the addition of methyl alcohol the product crystallised out. The substance was recrystallised from benzene and methyl alcohol and was obtained as colourless needles of melting point 87-88°. Analysis - nitrogen found 5.24%, calculated 4.91%.

A picrate was prepared from picric acid in ether, and benzyl-9-fluorenyl methylamine in benzene. The crystals deposited were recrystallised from absolute alcohol and were obtained pure as yellow stout prisms of melting point 163-164°. A nitrogen determination gave 10.85%, which is in agreement with the calculated value of 10.91%.

ACTION OF ALKALI ON DIMETHYLBENZYL-9-FLUORENYLAMMONIUM BROMIDE.

The quaternary salt (5 gms.) was dissolved in a small quantity of water and boiled in a distilling flask with 100 ccs. of a 10% caustic soda solution. The distillate was led into and absorbed in dilute hydrochloric acid in order that products of fission might be isolated. These products would be toluene and dimethylamine. When the solution in the flask became warm, a rich red oil was seen to separate. This soon lost its red colour and was deposited as a light brown gum on the surface of the flask. After the distillation was complete, the residue in the

flask was extracted with ether. The extract was dried with sodium sulphate and the ether distilled off. The residue was crystallised from boiling methyl alcohol, colourless stout prisms being obtained of melting point 98-99°. The yield of pure product obtained was 80%.

The distillate from the reaction was extracted with petroleum ether 60-80°, the extract then being treated with a nitrating mixture. From this, no dinitrotoluene was isolated. The distillate, residual from this extract, was now evaporated to dryness. As no residue of dimethylamine hydrochloride was obtained here, and no toluene was found to be present, the indications are that fission did not take place.

The only product of the reaction was that melting at 98-99°. On analysis, 5.0% of nitrogen was found. The value calculated for the rearrangement product - $C_{22}H_{21}N$ - is 4.7%.

9-BENZYL-9-DIMETHYLAMINO FLUORENE PICRATE.

On addition of an ether solution of picric acid to a solution of the rearrangement product also in ether, the picrate was deposited. On recrystallisation from absolute alcohol, light yellow needles of melting point 214-215° were obtained. On analysis, 10.7% of nitrogen was found. That calculated for $C_{22}H_{21}N.C_6H_3O_7N_3$ is 10.6%.

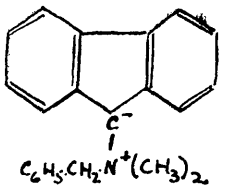
9-BENZYL-9-DIMETHYLAMINO FLUORENE METHIODIDE.

The methiodide was prepared from the rearrangement product by the addition of methyl iodide to a benzene solution of the substance. The deposited crystals were recrystallised from absolute alcohol, the pure methiodide being isolated as small colourless prisms of melting point 165-166°. On analysis the found value for nitrogen was 3.28%, that calculated for $C_{22}H_{21}N.CH_3I$ being 3.17%.

9-BENZYL-9-DIMETHYLAMINO FLUORENE METHOPICRATE.

This compound was prepared from the methiodide and picric acid in absolute alcohol. On recrystallising from alcohol, yellow plates of melting point 145-146° were obtained. On analysis this compound gave 10.36% of nitrogen, the calculated value for $C_{22}H_{21}N.C_7H_5O_7N_3$ being 10.33%.

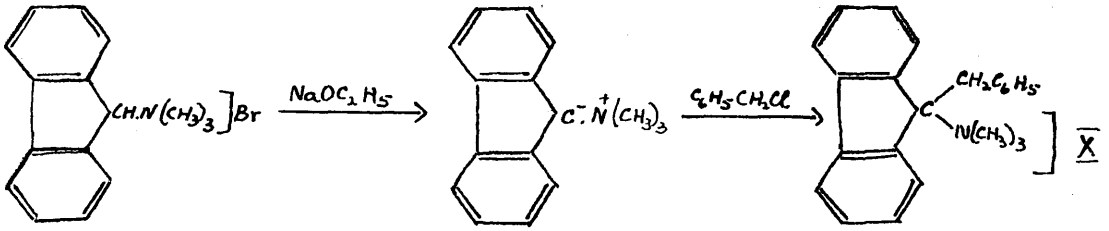
In repeat experiments attempts were made to isolate the red intermediate oil produced in the rearrangement and which was presumed to be



Extraction with various solvents of this oil at the time of its formation always resulted in the fading of the colour and the isolation of the rearrangement product.

ATTEMPTED SYNTHESES OF THE REARRANGEMENT PRODUCT.

1). As the methopicrate of the rearrangement product.

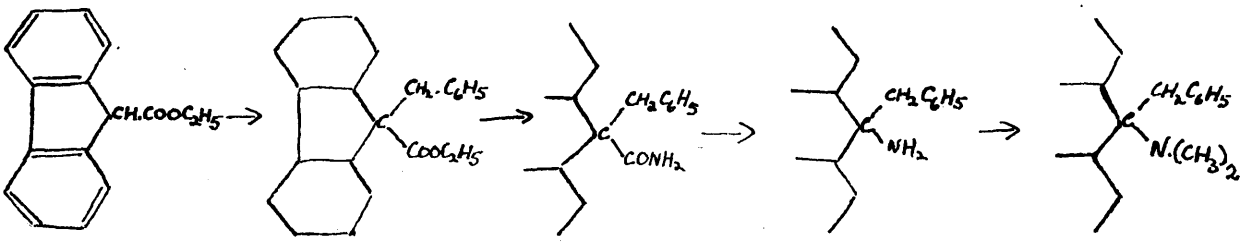


Trimethyl-9-fluorenylammonium bromide was prepared by the action of 9-bromofluorene on an ether solution of trimethylamine. Colourless needles were obtained of melting point 191-192°d. The picrate was prepared in and crystallised from alcohol, melting point 165-166°. The literature melting points are 189-190°d. and 175° respectively[29]. The melting point of the picrate could not be raised to the literature value on recrystallisation, but analysis points to the authenticity of the specimen. (Found N = 12.69%, calc. N = 12.4%).

Trimethyl-9-fluorenylammonium bromide (1.5 gm.) in alcohol was refluxed for a short period with a solution of sodium ethoxide from 0.11 gm. of sodium. Benzyl chloride (1 gm.) was added and the mixture refluxed for one and a half hours. The sodium halide was filtered off. On treatment of the solution with picric acid, a picrate was obtained of melting point 164 - 165°. The

recrystallised picrate was found to give a melting point, and mixed melting point with trimethyl-9-fluorenylammonium picrate, of 165-166°, so that the starting material only was recovered.

2). Synthesis according to the scheme



(a). The potassium derivative of 9-carbethoxy fluorene was prepared and from this 9-benzyl-9-carbethoxy fluorene was obtained[30].

(b). For the preparation of the amide from this, 6 gms. of 9-benzyl-9-carbethoxy fluorene were heated with alcoholic ammonia in a sealed tube at 150° for five hours. The product was found to consist of a mixture of the starting product and another substance. The mixture was separated by dissolving in benzene and adding petroleum ether 60-80° to the warm solution. On cooling, colourless crystals were obtained and on recrystallising from alcohol, the melting point was found to be 131°. This compound was found to contain no nitrogen, and was shown to be 9-benzyl fluorene. The other component of the

mixture remaining in the petroleum ether solution was found to be the starting product. This synthesis had therefore to be abandoned.

REDUCTION OF THE METHIODIDE OF THE REARRANGEMENT PRODUCT.

520 mg. of the methiodide of the rearrangement product were dissolved in about 10 ccs. of an aqueous alcoholic mixture. 10 gms. of a 3% sodium amalgam were added, and the mixture kept boiling for four hours. When cool, water was added and the solution extracted with ether. The ether extract was dried with sodium sulphate and the ether removed. The residue was dissolved in boiling alcohol, colourless needles being deposited on cooling. The substance was recrystallised from absolute alcohol, a melting point and mixed melting point with 9-benzyl fluorene of 131° being obtained.

ACTION OF ALKALI ON BENZYL-9-FLUORENYL ETHER.

Benzyl-9-fluorenyl ether (800 mg.) was heated with solid sodium ethoxide (prepared from 1 gm. of sodium) to 100°. After addition of water the solution was extracted with ether. The ether extract was dried and the ether distilled off. The residue was crystallised from benzene and petroleum ether, colourless crystals being obtained of melting point 150-151°. This product was shown by mixed melting point determination with authentic material to be 9-fluorenol.

Benzyl-9-fluorenyl ether (1 gm.) was refluxed with n. butyl alcoholic sodium n. butoxide (from 1 gm. of sodium) for two and a half hours. Ether was added to the reaction mixture and the ether layer washed many times with water. The ether layer was then dried and the ether removed. The residue was crystallised from benzene and petroleum ether and obtained as colourless prisms of melting point 129°. This melting point is about 10° low for the rearrangement product[23], and it was found that it could not be raised by recrystallisation. The substance was therefore refluxed in absolute alcohol solution with potassium ethoxide to oxidise any fluorenol present to fluorenone[31]. This was seen to take place by the production of a dark orange colour in the solution. After an hour's reflux the solution was diluted with water and extracted with ether. The ether extract was dried with sodium sulphate and the ether removed. The residue was crystallised twice from benzene and obtained pure, melting point 137°. A mixed melting point determination with authentic 9-benzyl-9-fluorenol did not show any depression. The rearrangement product was obtained in 70% yield.

9-Benzyl-9-fluorenol was prepared, for comparison,

by the action of benzyl magnesium chloride on fluorenone.

A repeat experiment was carried out in which toluene as a product of fission was tested for. After the alkaline treatment, the butyl alcoholic solution was extracted with petroleum ether 60-80°. On washing the butyl alcohol out of this extract with water, the 9-benzyl-9-fluorenol separated out from the petroleum ether and was filtered off. The filtrate was distilled and then heated with a nitrating mixture, but no dinitrotoluene was obtained.

ACTION OF ALKALI ON BENZYL-9-FLUORENYL ANILINE.

(a). Benzyl-9-fluorenyl aniline (1 gm.) was heated with solid sodium ethoxide to 180-200° for two hours. Arrangements were made to collect any volatile substance distilling off. No toluene, however, as a product of fission was isolated. After the addition of water to the reaction mixture, it was extracted with ether. The extract was dried and the ether distilled off. On crystallising the residue from boiling methyl alcohol, colourless crystals were obtained of melting point 143-144°. A mixed melting point determination with the starting product did not give any depression.

(b). Benzyl-9-fluorenyl aniline (1 gm.) was heated with sodamide to 200°. A very small amount of liquid distilled over and was collected. Charring of the residue was seen to take place. The liquid was taken up in a few ccs. of petroleum ether 60-80° and warmed with a nitrating mixture. The petroleum ether was distilled off, water added, and the residue extracted with benzene. The benzene was distilled off and the residue crystallised from aqueous methyl alcohol. A small quantity of almost colourless needles was obtained. This substance was shown to be 2.4.dinitrotoluene by melting point and mixed melting point determinations, the latter with authentic material. Water was added to the reaction mixture, which was then treated in the same way as the reaction mixture in the next experiment - (c). No further evidence for fission could be obtained. A small quantity of difluorenyl, melting point 237-238°, was, however, isolated.

(c). Benzyl-9-fluorenyl aniline (1 gm.) was heated with solid caustic soda to 290-310° for two hours. One drop of liquid distilled over and was collected. This was taken up in a few ccs. of petroleum ether 60-80° and, as in the last experiment, was shown to be toluene by nitration to the 2.4.dinitro derivative. Water was added to the reaction mixture, which was then extracted

with ether. If fission had taken place, fluorenone anil should have been found at this stage. On removing the ether from this extract, no crystals could be obtained from the residue. This residue was therefore refluxed for a short period with concentrated hydrochloric acid, so that if any fluorenone anil were present it would be converted to fluorenone and aniline.

The acid solution was extracted with petroleum ether, and the solvent removed from the extract. The residue could not be crystallised so it was taken up in a little methyl alcohol and a solution of 2.4.dinitrophenylhydrazine added. This was warmed on the water bath for a few minutes, a red brown non-crystalline solid separating. This solid could not be obtained crystalline. It was high melting (280-281°) and did not depress the melting point of authentic fluorenone 2.4.dinitrophenylhydrazone. It could not, however, be shown to be fluorenone 2.4.dinitrophenylhydrazone owing to the small quantity of it obtained, and its amorphism.

The above acid solution was made alkaline with caustic soda and the solution steam distilled. From the steam distillate, by extraction with ether and addition to this extract of a small quantity of bromine, there was

isolated a small amount of tribromoaniline. This indicated that some fluorenone anil may have been present at the previous stage, mixed, probably, with more complex material. From the steam distillate, before ether extraction, there was also isolated mechanically a small quantity of benzyl aniline. This has no place in the scheme for fission and indicates that decomposition seemed to be taking place at the temperature employed.

(d). Lithium methyl was prepared in dry ether from lithium (0.76 gm.) and methyl iodide according to the method described by Gilman[32]. Benzyl-9-fluorenyl aniline (1 gm.) in ether was added to the lithium methyl solution and the ether distilled off. The temperature was then raised to 100° and maintained for half an hour. When cool, water was added and the solution was extracted with ether. The ether extract was dried and the ether removed. On crystallising the residue from boiling methyl alcohol, only the starting product was obtained, proof being given by a mixed melting point determination.

(e). Benzyl-9-fluorenyl aniline was treated again with lithium methyl, the temperature this time being raised to 150°. From the reaction mixture, the starting product only was isolated.

(f). On repeating this experiment at 200°, again only the starting product was obtained.

(g). The reaction was again repeated, the mixture this time being heated to 240°. Considerable charring took place, and nothing was isolated from the tar produced.

(h). Lithium phenyl was prepared in a similar manner to lithium methyl, from lithium and bromo benzene[32]. Benzyl-9-fluorenyl aniline was added in ether to the ether solution of lithium phenyl, a deep red colour being produced. The ether was distilled off and the mixture heated to 130°. A tar was produced, from which no relevant products could be isolated. Diphenyl (as a decomposition product of lithium phenyl) was isolated on steam distillation.

(i). On repeating this experiment at 110°, the same result was obtained.

(j). Benzyl-9-fluorenyl aniline was treated with a molecular quantity of metallic potassium in boiling decalin for four hours. A tar was obtained from which no crystalline products could be isolated.

ACTION OF ALKALI ON BENZYL-9-FLUORENYL METHYLAMINE.

An ether solution of benzyl-9-fluorenyl methylamine was added to an ether solution of lithium methyl and the ether distilled off. The mixture was heated to 100°. Water was added to the reaction mixture and the

solution extracted with ether. The ether extract was dried with sodium sulphate and the ether removed. On crystallising the residue from methyl alcohol, the starting product was shown to be the only product by a mixed melting point determination.

This experiment was repeated, the heating being continued to about 200°. Water was added to the reaction mixture, which was then extracted with ether. The extract was dried and the ether removed. A dark brown amorphous solid was obtained from which no crystals could be isolated. This solid was boiled for a short period with concentrated hydrochloric acid, and extracted with carbon tetrachloride. This extract, on removal of solvent, gave rise to a dark brown tar from which no crystalline product could be isolated. On treatment of a methyl alcoholic solution of this tar with 2.4.dinitrophenylhydrazine, no indications of the presence of fluorenone were obtained. The examination of the above acid solution for basic products - in particular for methylamine hydrochloride - was unsuccessful.

Benzyl-9-fluorenyl methylamine was treated with lithium phenyl and the temperature raised to 210°. Water was added to the reaction mixture, which was then treated in exactly the same way as the reaction mixture in the

last experiment. An amorphous material was obtained also in this experiment, and no crystalline products were isolated.

Benzyl-9-fluorenyl methylamine (1 gm.) was treated with solid caustic soda (2 gms.) at 295° for two hours. Arrangements were made to collect any toluene distilling over, but none was obtained. When the reaction mixture was cool, water was added, and it was extracted with ether. The extract was dried and the ether removed. On taking up the residue in boiling benzene and adding methyl alcohol, crystals were deposited. On recrystallisation from the same solvent, colourless needles of melting point 239° were obtained. These were shown to be difluorenyl by a mixed melting point determination.

Attempts were made to isolate any other products from the mother liquors of the first difluorenyl crystallisation. These, however, could only be induced to yield a brown tar. To test for the presence of fluorenylidene methylamine as a product of fission in this tar, it was refluxed with hydrochloric acid for a short period. The mixture was then extracted with petroleum ether and the solvent removed from the extract. The residue, which consisted of a small amount of a brown tarry material, was

dissolved in methyl alcohol and a solution of 2.4.dinitrophenylhydrazine added, to test for the presence of fluorenone as a hydrolytic product of fluorenylidene methylamine. Nothing was obtained by this treatment indicative of the presence of fluorenone. The residual acid solution was tested for any basic products, but without success.

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