## THE SYNTHESES OF SOME FLUORENE DERIVATIVES

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### HIROKAZU MORITA

### A THESIS

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#### INTRODUCTION

The chemistry of fluorene in recent years has attracted considerable attention since it has been found that its derivatives possess important physiological properties such as their effects upon plant growth (58), estrogenic activity (28), as well as local anaesthetic and antispasmodic action (53). Of greater interest however is the carcinogenic activity of certain fluorene derivatives, for example, 2-acetylamino fluorene (52). These discoveries have initiated an investigation into the synthesis of other fluorene derivatives for possible carcinogenic activity as well as for other physiological and biological properties.

This thesis describes in part, an investigation which was undertaken primarily in the hope of synthesizing some fluorene derivatives of certain physiologically active compounds, namely, the barbituric acids. If successful it was hoped that the biological effects of these new compounds would be determined at a later date with the facilities and assistance of the Manitoba Medical College.

In order to investigate a general method of preparing certain fluorene derivatives, attempts have been made to determine the suitability of the Reformatsky Reaction and the Friedel-Craft Reaction. The former has been shown to be a convenient method for preparing many Q-hydroxy esters and its corresponding esters and acids, usually in fair yields, from ketones and  $\alpha$ -halogen esters. The Friedel-Crafts synthesis was undertaken with the object of determining a more readily applicable technique for the preparation of the 9-carboxylic esters of fluorene from biphenyl.

#### LITERATURE SURVERY

I. THE CHEMISTRY OF FLUORENE AND FLUORENONE

In 1867 Marcellin Bertholet (10) isolated a white fluorescent hydrocarbon melting at 113°C. from the 300-310° boiling fraction of crude anthracene. Because of its fluorescence he called it "Fluorene". Its structure has been determined from the investigations of Barbier (8), Fittig and Ostermayer (24), and is indicated in the synthesis of the compound from dichloromethane and biphenyl (1).



-Fluorene represented structurally by (I),



-possesses an activated methylene group at the 9 position located near two pairs ofdoubly linked carbon atoms. This activity has been explained by Thiele's theory of the ethylenic bond and also by the electronic theory of Goss and Ingold (29) and is evident by its formation of a sodium derivative with metallic sodium and with sodamide.

The synthesis of fluorene derivatives has been accomplished by direct substitution in the molecule itself or indirectly through some intermediate. Direct nuclear substitution in the benzene rings seem to follow a definite rule. Chlorine, bromine, nitricand sulphuricacids react in the 2 position and further subtitutions lead to the 2, 7 compounds. This special reactivity of the 2,7 positions is ascribed as being due to the superior directive properties of the phenyl group (41).

It is interesting to note that substituents in the 2 position greatly activate the methylene group in the 9 position as reported by Schiessler and Eldred (59). Pinck (45) has postulated that this increased activity may account for the carcinogenic activity of certain 2 substituted fluorenes.

Fluorenone (II), the oxidation product of fluorene,



is a common starting point for the preparation of 9 substituted fluorenes. Its preparation has been the object of study for many investigators. The simplest among the many diversified methods is the oxidation of fluorene by sodium dichromate in acetic acid (33). The advantage of this method lies in the fact that technical fluorene (98%) can be used, the impurities having little effect on the final yield.

With potassium permangante solution as the oxidizing agent the yield is reported to be mostly quantitative (17). Fluorenone of the highest purity is said to result from the conversion ofdiphenic acid (III), the reaction being rapid and quantitative (33).



Selenium oxide has also been used to oxidize fluorene to fluorenone (67).

In chemical behaviour fluorenone is similar to the aromatic ketones such as benzophenone, the carbonyl group being situated between two aromatic nuclei. Thus fluorenone forms oximes and hydrazones.

This bright yellow crystalline fluorenone is converted to the green solid thiofluorenone (IV) by treatment with hydrochloricacid and hydrogen sulphide (13).



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With a substituent in the 2 position fluorene is readily converted to its corresponding compound of fluorenone even by air (53), or by such mild oxidizing agents as potassium hypochlorite (59).

The reduction of fluorenone yields a secondary alcohol, fluorenol or 9-hydroxyfluorene (V). This reduc-



tion has been carried out with zinc dust and potassium hydroxide solution or ammonia (71). Aluminum amalgam in alcohol is a satisfactory reducing agent giving good yields (14). Bachman (6) has reported a 99% yield using sodium amalgam in absolute alcohol together with a mixture of anhydrous ether and benzene as the solvent. The reduction according to this procedure is not affected by the hydrogen liberated but proceeds through some intermediate compounds. An excess of sodium is used in the reduction with sodium since it has been found that with a theoretical amount of sodium a high yield of fluorenopinacol (VI) is formed (6).



Ferrier (22) obtained a quantitative yield of fluorenol by hydrogenating fluorenone with aluminum secondary butyl oxide. A smaller yield results when reduction is carried out with a powdered nickel on kieselguhr catalyst and hydrogen (36).

Fluorenol is readily converted into its corresponding fluorenyl halogens by means of such halogenating agents as phosphorus pentachloride (71) to give 9-chlorofluorene (VII).



Thionyl chloride (35) has been found to be a very efficient reagent for the preparation of this compound. An almost quantitative yield has been obtained by Hurd and Mold (36) by allowing fluorenol to react with concentrated hydrochloric acid.

Hurd and Mold applying the same procedure with a 41% hydrobromic acid reagent obtained a 66% yield of 9-bromo-

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fluorene. A better yield has resulted by the action of hydrogen bromide in glacial acetic acid (38). The product resulting from this procedure required no recrystallization. A shorter method is that of Bachman and Sheehan (7) which gave good yields with acetylbromide.

When N-bromosuccinimide was used as a brominating agent of fluorenol a 47% yield resulted (26). However a much better yield has been reported when this reagent was used with fluorene dissolved in carbon tetrachloride (73).

Sampey and Reid (57) have accomplished a photobromination of fluorene in carbon tetrachloride under a strong mercury arc or in direct sunlight. 60-64% yields of 9-bromofluorene were obtained. Sampey and King (56) following the study of this photobromination have discovered that the presence of iddine greatly affects the bromination and some of their tests showed that none of the bromine had entered the side chain.

Photobromination of fluorene to give 9,9-dibromofluorene (VIII),

+ C - Br + Br

has been undertaken by Sampey and Childress (55) through

the addition of assecond mole of bromine under strong irradiation. They report that this compound caused a severe dermatitis which spread over large areas of the body. The corresponding 9,9-dichloro compound is prepared by the action of phosphorus pentachloride on fluorenone (48).

Pinck and Hilbert (47) have reported an anamolous reaction between ammonia and 9-chlorofluorene. These reagents did not yield the expected 9-amino derivative even though the reaction was carried outwith liquid ammonia in a sealed tube. This confirms the earlier results ofCourtot and Peticolas (18). This peculiarity is attributed to the influence of the labile nature of the hydrogen in the 9 position because when this hydrogen is replaced by a relatively large group as the phenyl or the naphthyl group the halogen compound reacts normally with ammonia. Thus 9-chloro-9-phenylfluorene reacts with ammonia to give 9-amino-9-phenylfluorene (IX).

H<sub>4</sub> C - NH<sub>3</sub> H<sub>4</sub> - C<sub>6</sub>H<sub>5</sub> ( IX )

Fluorenol and the halogen derivatives which have been mentioned thus far can be made from asingle fluorene derivative. This versatile reagent is 9-diazofluorene (X) and is obtained by the oxidation of fluorenone hydrazone (65).



Hydrolysis of this product gives 9-fluorenol.



With hydrogen chloride a good yield of 9-chlorofluorene is obtained. Reaction with thionyl chloride gives 9,9-dichlorofluorene.

 $\begin{array}{cccc} C_{c}H_{4} & N \\ I & C & H \\ C_{c}H_{4} & N \end{array} \xrightarrow{Soci_{2}} & I & C & H \\ C_{c}H_{4} & N & C_{c}H_{c} & C_{i} \\ \end{array}$ 

Bromine in carbon bisulphide reacts to give 9,9-

Recently (48) 9,9-difluorofluorene has been prepared from 9,9-dichlorofluorene and hydrogen fluoride in the presence of mercuric chloride. The product is somewhat unstable.

The 9-bromo and 9-chlorofluorenes are useful reagents

for the synthesis of many 9-substituted derivatives. Bachmann and Sheehan (7) have condensed 9-bromofluorene with malonic ester, followed by hydrolysis and decarboxylation to give a good yield of 9-fluorene acetic acid (XI).

 $\begin{array}{cccc} C_{6}H_{4} & H_{2} \\ C_{6}H_{4} & C_{6}H_{4} \\ C_{6}H_{4} & C_{6}H_{4} \\ \end{array} \xrightarrow{H_{2}} C_{6}H_{4} & C_{6}H_{4} \\ \end{array} \xrightarrow{H_{2}} C_{6}H_{4} & H_{2}O \end{array}$  $C_6H_4$  CH-CH<sub>2</sub>CO<sub>2</sub>H  $\leftarrow$  heat  $C_6H_4$  CH-CH(CO<sub>2</sub>H)<sub>2</sub>  $C_6H_4$  (XII)

This acid has been prepared by heating a monohalogen ester and fluorene at a relatively high temperature (74).

 $C_{6}H_{4} \ CH_{2} + B_{7}CH_{2}CO_{2}Et \longrightarrow C_{6}H_{4} \ CH-CH_{2}CO_{2}Et$ 

The melting point of this acid appears to vary according to the procedure used. The malonic ester synthesis gave a melting point of  $131.5-132.5^{\circ}$ C. whereas Sieglitz and Jassoy (63) reported the temperature to be  $137^{\circ}$ C. Schlenk and Bergmann (60) have reported two melting points for an  $\measuredangle$ - and a &-form, the temperatures being  $222^{\circ}$  and  $232^{\circ}$  respectively. Existence of isomeric fluorene derivatives has

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been claimed by many investigators.

The lower homologue of 9-fluorene acetic acid, namely fluorene-9-carboxylic acid (XII), has been prepared in a variety of ways. It has been prepared directly by the reaction of 9-sodiofluorene and carbon dioxide (60) or from 9-fluorenylmagnesium bromide (XI) and carbon dioxide (66).

Г H CHCO2MgBr CHMOBr. HO HCOH

Vorlander (70) prepared the acid directly from benzilic acid as follows:



Previously Delacre (20) had applied the Friedel-Crafts reaction on ethyltrichloroacetate and benzene.

The well known hydroxy derivative of fluorene-9-carboxylic acid is 9-hydroxyfluorene-9-carboxylic acid usually

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called diphenylene glycolic acid (XVI). It is readily prepared by heating phenanthraquinone (XV) with sodium hydroxide solution (22). The phenanthraquinone undergoes a benzilic rearrangement similar to an open chanin *d*-diketone.

(XYI) (XV)

This d-hydroxy acid readily oxidizes to fluorenone.

The use of the Grignard derivative of fluorene has been investigated by Tucker and Whalley (62) who have prepared 9-fluorenylmagnesium bromide. Grignard and Courtot (71) prepared this reagent by heating fluorene with ethyl magnesium bromide in a solvent. It behaves like other normal Grignard reagents.

C2H5M9Br CHM9Br + C2H6

Miller and Bachman (37) investigating the use of 9chlorofluorene for synthetic purposes could not duplicate the results of Courtot in preparing this Grignard reagent. Tucker and Whalley however obtained fair yield of fluorenylmagnesium bromideby using an excess of ethyl magnesium bromide with fluorene.

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It hasbbeen found that the Grignard reagent of 9bromo-9-phenyl fluorene (XVII) forms in a subtle manner. If the reactants are in a mole per mole ratio the Grignard reagent (XVIII) is formed normally (4).

(XVII) (XNIII)

If however only 0.5 gram atom of magnesium reacts a free radical 9-phenyl fluoryl (XIX) is said to be present.

(XIX)

This free radical then can take on an additional half mole of magnesium to form the normal compound.

Although the reactions and the properties of 9 substituted fluorenes are diversified and in many cases from the chemical point of view unusual, the attention of many chemists in recent years has been directed towards the study of those derivatives having substituents in the benzene rings and especially to those compounds possessing biological action. The syntheses of these compounds have added much to the knowledge of the structure of fluorene.

As mentioned before direct substitution generally

occurs at the 2,7 and 9 positions. To obtain substituents in the other positions recourse to indirect methods is necessary. The conversion of phenanthraquinone derivatives to fluorenes and fluorenones have been investigated with sometthoroughness. However the use of appropriate intermediates for the syntheses of fluorene compounds has recently received encouraging impetus through the expanded knowledge of biphenyl chemistry.

It will be recalled that P. Adams obtainedfluorene itself from dichloromethane andbiphenyl. The syntheses of new biphenyl derivatives has led to the successful preparation of fluorenone and fluorene derivatives with substituents in the 3, 4, and 6 positions.

Pure 4-methylfluorene (XXI) has been obtained from 2,2' dimethyl biphenyl (XX) with a palladium charcoal catalyst (44).

heat -CH

According to this procedure derivatives of fluorene may be prepared by the catalytic cyclodehydrogenation of 2-methyl biphenyl derivatives.

Lôngo and Pirona (40) have made a study of the syn-

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thesis of fluorene compounds from biphenyl derivatives and in particular the influence of the positions of substituting groups on the formation of fluorene structures. They were able to prepare 1-methylfluorene and 1,6-dimethylfluorne (XXII) through the synthesis of some new biphenyls.



The wide applicability of this method has been further demonstrated by the preparation of 3-nitrofluorenone (XXIV) from 5-nitro-2-biphenyl carboxylic acid (XXIII) and concentrated sulphuric acid, the biphenyl derivatives being obtained by a new synthesis (49).



The use of biphenyl chemistry and direct nuclear substitution have been applied in the synthesis of 2-acetylamino fluorene (XXVI) from 2-iodo-biphenyl (XXV) with radioactive carbon 14 in the 9 position of the molecule (51).

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Miller and Bachman (43) have given a review of the methods used for the preparation of substituted fluorenones. These methods are discussed under five types. They are:

- (1) Direct substitution to give 2,7 derivatives.
- (2) Elimination of hydrogen bromide from substituted obenzophenones.



(3)

The arrangement of phenanthraquinone derivatives.

-17-



-18-

(4)

The dehydration of o-carboxydiphenyl derivatives.



(5)

Coupling of diazotized o-aminobenzophenone derivatives.



They have applied these general methods for the preparation of 3- and 4-bromofluorenones.

A critical review of fluorene chemistry reveals how little is known of its reactions and above all its structure. Although the fluorene molecule is generally believed to be indicated by (I),



there are evidences which indicate that this picture does not convey the true molecular structure.

Lothrop (41) has located the double bonds in fluorene by a method which is usually applied to aromatic hydrocarbons and he has shown that the fluorene molecule has the benzenoid rather than the naphthoid rings. Moreover it is suggested that the double bonds have no fixed position.

Bergmann and Berlin (9) have confirmed Lothrop's results and have found that in fluorenone as well as fluorene the double bonds are not stationary. They have based their conclusion partially by the fact that 2-acetoxyfluorenone and 2-acetoxyfluorene (XXVII) on the Fries rearrangement give 1-acetyl-2-hydroxy derivatives (XXVIII).



Hence fluorene, like benzene, is not to be represented exclusively by a single structure such as (I).

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The spatial configuration of the fluorene molecule is still a matter of dispute. From timeto time many workers have reported widely different melting points and properties for the apparently same derivative and these have been assumed to be isomers. Two theories exist regarding the structure of fluorene. One is the uniplanar structure of Pinck and Hilbert (46) and the other is that of Cook and Iball (15) who proposed that the planes of the **six-membered** rings are inclined at an angle of 20° to the plane of the five-membered ring. According to the latter theory there would exist not only isomers of monosubstituted fluorene compounds but also isomers of such compounds as (XXIX).



These isomers are possible since substitution at the 9 carbon atom can produce isomers depending on whether the substituent is cis or trans to the inclined six-membered rings. All efforts to resolve these isomers have failed making the possibility of resolving non-planar compounds remote.

However recently Ray and Kreiser (51) have succeeded in resolving 9-hydroxyfluorene-2-carboxylic acid (XXX) and methyl 9-aminofluorene-2-carboxylate (XXXI) into their

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isomeric forms. The former was accomplished using strychnine.

(xxx)

CH.

(XXXI)

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### II. EXTENSIONS OF THE REFORMATSKY REACTION.

\$-hydroxy esters have been prepared by the condensation of an d-halogen ester and an aldehyde or a ketone in the presence of zinc. This is the well known Reformatsky reaction (54). The orginal reaction was carried out with acetone and ethylchloroacetate.

H,O CH3 C OH C CH, CO, Et

(XXXII)

The product an  $\beta$ -hydroxy ester is  $\beta$ -hydroxyisovaleric ester (XXXII).

Occasionally the final product is not the hydroxy ester but the corresponding unsaturated one. This has been found to be the case with fluorenone and ethylbromacetate (63).

CO + Br CH2CO2EL HO C= CHC 0 Et

(XXXIV)

Using benzene as the solvent the isolated product was fluorenylidene acrylic ester (XXXIV).

With some ketones the yields in these reactions are relatively poor because of side reactions. Hussey and Newman (37) have made a study of the yields of the Reformatsky products and they reported a three to four fold increase in the products by using a three fold excess of bromester and a large excess of zinc.

The Reformatsky reaction is not only a method for preparing -hydroxy esters and the corresponding unsaturated esters and acids but also is a convenient procedure for lengthening the carbon chain. The versatility of this reaction is fully discussed in "Organic Reactions" Volume I, Chapter I, by R. L. Shriner.

Although this reaction has been generally carried out

with  $\checkmark$ -halogen esters, synthesis involving other halogen esters have been reported. Haberland and Heinrich (31) have extended the reaction to \$-halogen esters. They condensed 6-methoxytetralone (XXXV) and ethyl 𝔅-bromopropionate using finely divided magnesium. Toluene was used as the solvent. The final product after hydrolysis and reduction was 𝔅-(6-methoxy-3,4-dihydro-1-naphthyl) propionic acid (XXXVI).



Recently \$-(2-methylcyclohex-l-enyl) butyric acid (XXXVIII) has been synthesized by condensing 2-methyl cyclohexanone (XXXVII) with methyl \$-bromocrotonate and amalgamated zinc (16).

BrCH2CH=CH -CH\_CH=CHCO\_CH\_ (XXXVII) (xxxvm)

The use of **3**-bromocrotonic ester was previously accomplished by Ziegler, Schylmann and Winkelman (75) who used benzaldehyde as the carbonyl compound.

The use of d-halogen esters of dibasic acids has been

attempted by Gilbert (27) who used several ketones and ethyl bromomalonate. In all of their attempted reactions the desired product was not obtained. For example, benzophenone and ethyl bromomalonate did not give the corresponding hydroxy ester (XXXIX), the only products isolated being the unchanged ketone and the halogen ester.

 $C_{e}H_{5} \subset O + BrCH(CO_{2}Et)_{2} \xrightarrow{Zn} C_{e}H_{5} \subset OH(CO_{2}Et)_{2}$ (XXXIX)

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SUBSTITUTED BARBITURIC ACIDS

III.

The derivatives of barbituric acid or malonyl urea (XL),



have found extensive use as hypnotics and were introduced into therapeutic use by Fischer and von Mering.

No satisfactory theory has been proposed for the relationship between physiological activity and chemical constitution. Nor is the mechanism of the action of the barbituric acid series known. The activity of the different homologous substituents in the barbituric acid series has been discussed in several literature references (61).

The method of Fischer and Dilthey (23) is generally employed for the preparation of these acids. The procedure involves a condensation between an alkyl halide and malonic ester with sodium ethylate as the condensing agent. The resulting alkyl malonic ester (usually a high boiling oil) is then condensed with urea to give the des-

-26-



A second alkyl group may then be introduced by repeating the malonic ester condensation or as in some cases if the two alkyl groups are the same only one operation is necessary. The final product is a 5,5-dialkyl barbituric acid (XLII).



Many variations of these acids are possible through changes of R<sub>1</sub> and R<sub>2</sub> substituents and investigations in this field have been undertaken to determine combinations of different substituents which would afford a better therapeutic action and clinical advantages than do the products now in use.

-27-

ired substituted acid (XLI).

Although, in general, the substituents are introduced into the malonic ester before it is condensed with urea to form the substituted acid, many of the complex barbiturates have been synthesized from the monosubstituted acids and even from barbituric acid itself. This is possible because the second substituent enters the 5-carbon atom more readily than the first. For example, the alkyl allyl barbituric acids have been made by dissolving the monoalkyl barbituric acid in sodium hydroxide solution and the allyl bromide added gradually (69). In fact this procedure was originally used by Fischer and Dilthey (23) who obtained diethylbarbituric acid (Veronal) from ethylbarbituric acid and ethyl iodide.

This modified procedure has an advantage over the classical method in view of the fact that yields of substituted malonic esters are occasionally low. This fact in addition to the low yields obtained in the urea condensation prompted Cox and Houston (19) to prepare the 5monosubstituted barbituric acid directly from barbituric acid itself. They obtained good yields of 5-acetonyl barbituric acid (XLIII) by condensing barbituric acid with chloroacetone using sodium acetate as the condensing agent.

-28-

CONH CONH  $co + cich_{2}coch_{3} \longrightarrow ch_{3}coch_{2}coch_{3}$ (XLIII)

Copper sulphate (12) in place of sodium acetate has been used as a condensing agent for the preparation of 5,5allyl fufurylbarbituric acid. It appears therefore that these modifications have a much wider application than at first realized.

#### DISSCUSSION OF RESULTS

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#### I. THE REFORMATSKY REACTIONS WITH FLUORENONE

The condensation of aldehydes and ketones with  $\checkmark$ halogen esters in the presence of zinc, namely the Reformatsky reaction, is one of the most useful reaction in organic syntheses. It is useful not only for the preparation of hydroxy and unsaturated esters but in particular for the preparation of longchain ketones and aldehydes (2).

The application of the Reformatsky reaction for the preparation of 9-substituted fluorenes has not appeared in the literature and since only a few 9-fluorenyl ketones are known it was considered of interest to initiate an investigation into the synthesis of these compounds by determining the nature and yields of the Reformatsky prod-. ucts with fluorenone.

One general method of preparing ketones may be indicated schematically as follow:

 $R \xrightarrow{C=0} + CH_2CO_2Et \xrightarrow{Zn} \xrightarrow{R} \xrightarrow{OH} \xrightarrow{C} CH_2CO_2Et$ Br



# A. <u>SYNTHESIS OF FLUORENYLIDENE ACRYLIC ESTER (XLIV) AND</u> ETHYL & (9-HYDROXYFLUORENYL) PROPIONATE (XLV).

The present work was undertaken in order to determine whether the hydroxy ester or its corresponding unsaturated ester could be obtained in sufficient yields to warrant it use for further synthetic purposes as outlined above. The reactions were carried outwith ethylbromoacetate and ethyl **d**-bromopropionate.



-32-

 $H_{4}^{\prime} = H_{3}CHCO_{2}Et \xrightarrow{Zn} CH_{4}^{\prime}C_$ OH CHCOLET (XLV)

Fluorenone was prepared by the method Huntress, Herschberg and Cliff (33) with the added modification whereby less acetic acid was used to improve the yield. The yield may also be slightly improved by gently distilling off part of the solvent.

In the first attempted reaction with fluorenone and ethylbromoacetate the results of Sieglitz and Jassoy (63) were confirmed and it has been found that a better yield is obtained by using a mixture of toluene and benzene together with a excess of the zinc and the ester. For twenty grams of fluorenone it was found advisable to use a larger amount of the zinc than is described in the literature. The procedure in the literature was repeated giving a yield of 71% of the pure product whereas with an excess of zinc a yield of 82% was obtained. It has been found that with ethylbromoacetate and ethyl -bromopropionate the yields of the unsaturated ester and the hydroxy ester derivatives respectively were comparatively good. The main difficulty encountered in these reactions occurred during the recrystallization of the crude product. Long standing in the cold was necessary before crystallization was complete.

B. <u>REFORMATSKY REACTION WITH ETHYL</u> B-BROMOPROPIONATE.

Although the Reformatsky reaction is generally carried out with J-halogen esters an attempt was made to extend this condensation with a S-halogen ester. The literature records only one instance (27) where this extension has been successful. In this present work the attempted condensation was that of fluorenone and ethyl S-bromopropionate.

 $C_{G}H_{4} = CO + CH_{1}CH_{2}CO_{2}Et \xrightarrow{Zn} = C_{G}H_{4} = OH$   $C_{G}H_{4} = C + CH_{1}CH_{2}CO_{2}Et \xrightarrow{Zn} = C_{G}H_{4} = C + CH_{2}CH_{2}CO_{2}Et$ 

This reaction was first attempted with zinc turnings as well as magnesium turnings without success. The reaction was then repeated with a zinc couple and a benzenetoluene mixture as the solvent whence a faint reaction was observed. The final product obtained was a colourless crystalline solid melting at 258-259°C. and only slightly soluble in most organic solvents.

Analysis of the isolated substance gave C, 82.57% and H, 6.47%, whereas the theoretical percentages based on the hydroxy ester are C, 76.54% and H, 6.43% and that of the corresponding unsaturated ester C, 81.78% and H, 6.11%.

Since combustion analysis indicated the product to be the unsaturated ester rather ban the hydroxy ester further identification was attempted. Sodium fusion analysis indicated the absence of any halogen whereas tests with acid permanganate solution as well as with bromine water did not give the characteristic reactions for unsaturation.

However Borsche and Nieman (11) have prepared the free acid by an indirect method and have reported the melting point of the unsaturated acid as 202-203°C. if recrystallized from hot benzene. To confirm the presence of the unsaturated ester saponification of the ester to the free acid was attempted using 30% potassium hydroxide solution. The compound isolated gave a melting point of 243-245°C. recrystallized from hot benzene. Combustion analysis gave C. 78.21% and H. 6.24%. Qualitative analysis with acid permanganate and bromine solution gave no indication of unsaturation and with sodium bicarbonate solution a negative test for the free acid group was obtained. The presence of any active ketonic group or enol group could not be detected.

Before further identification and analysis of the ester and the hydrolysis product can be carried out a comprehensive study of the possible side reactions in this condensation would be necessary. Moreover it would appear from the result of this particular case that the main product obtained was not the normal Reformatsky product but a product of some undetermined side reaction involving bothe the ketone and the halogen ester. The possibility of halogen esters which have been found in other Reformatsky reactions can be, at least in this instance, be ruled out since qualitative tests did not show the presence of any halogen. Other possibilities include complex self-condensations of the bromo-ester to give non-halogenated *d*-keto esters which have been reported by Hussey and Newman (37).

Identification of the original product as well as the compound obtained from the saponification would require a more detailed analysis and with the time available was beyond the scope of the investigation. However in view of the uncertain nature of the results obtained twould seem profitable to investigate the Reformatsky reaction of eethyl  $\beta$ -bromopropionate with several otheractive ketones in order to determine the nature of the products.

#### C. REFORMATSKY REACTION WITH BROMOMALONIC ESTER.

The condensation between ketones and bromomalonic ester has been previously attempted without success (27). In view of the reactivity of fluorenone it seemed profitable to attempt the reaction with fluorenone with a view to preparing the hydroxy ester (XLVI).



Although a vigorous reaction was observed the desired product could not be isolated. The final product, a viscous heavy liquid, distilled over an indefinite range of temperature under reduced pressure. The only distillate which could be identified was fluorenone boilingat 220-226°C./20 mm. and melting at 82-83°C. However it is of interest to note that of the original 20 grams of the ketone used only 6.2 grams were recovered. The residual product since impure was not subjected to any further rigorous analysis.

The fact than an appreciable amount of the ketone used

was not recovered indicates that a side reaction involving fluorenone and probably induced by the presence of a zinc complex as taking place. This has been observed with dertain ketones (2).

## II. <u>ATTEMPTED RRIEDEL-CRAFTS SYNTHESIS OF FLUORENE-9,9-</u> DICARBOXYLIC ESTER (XLVII).

The literature affords only two examples where biphenyl compounds have been converted to fluorene derivatives by the Friedel-Crafts reaction. P. Adam (1) obtained fluorene itself from dichloromethane and biphenyl. Dutt (21) appears to be the first investigator to apply successfully Adam's method. The mechanism of the reaction in both cases has not been reported.

Since the literature records no example of the synthesis of 9-fluorene esters by Adam's method an attempt was made to prepare fluorene-9,9-dicarboxylic ester (XLVII) from biphenyl and ethyl dibromomalonate.

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Ethyl dibromomalonate was prepared by the direct bromination of malonic ester using two moles of bromine with red phosphorus as a catalyst. It is customary to prepare the dibromo ester from the intermediate monobromo compound but the procedure adopted gave the dibromo product in good yields.

In the attempted Friedel-Crafts synthesis aluminum chloride in excess of the two moles required were used for every mole of biphenyl. The reactions carried out with several modifications did not appear to be spontaneous and therefore the reactants were refluxed with stirring. A vigorous evolution of Hydrogen bromide occurred during the initial refluxing period and upon the usual treatment of the dark brown aluminum complex intermediate the desired ester was not isolated.

This isolation was first attempted by fractional distillation under reduced pressure. The distillated collected all boiled over indefinite temperature ranges giving dark red liquids which failed to solidify. Analysis of the distillates indicated the presence of some unchanged dibromomalonate as well as other undetermined halogen compounds. The heavy residue was dissolved in a minimum amount of absolute alcohol and left in the cold for several days. The precipitate obtained was identified as unreacted biphenyl, m.p. 66-68°. Fluorene-9,9-dicarboxylic ester has been reported to melt at 99.5° (11).

Although only a cursory investigation of this reaction was possible it appears that a more detailed study would be in order in view of the fact that this Friedel-Crafts synthesis if successful would be capable of various extensions into other dihalogen esters such as dichloroacetic, dichlorosuccinic etc, and this constitutes an entirely new approach for the preparation of fluorene acids.

#### III. THE SYNTHESIS OF FLUORENYLBARBITURIC ACIDS.

The classical method of Fischer and Dilthey (23) was used whereby monofluorenyl malonic ester was condensed with urea in the presence of sodium ethylate as the condensing agent. The steps involved in the synthesis may be indicated schematically as follows:

[H]

CHBr + CH (COLET) NaOEt CH(CO2Et) CO(NH2)2

- The reduction of fluorenone to fluorenol was accomplished with aluminum amalgam according to the method of Cohen (14). Conversion of the alcohol to the halide was carried out by a solution of 48% hydrogen bromide in glacial acetic acid giving 9-bromofluorene. This bromination has an advantage in the fact that the product which separates during the reaction requires no recrystallization. The corresponding chloro-compound was obtained in good yields using thionyl choride. However since the bromo product was more readily prepared it was used in the remainder of this investigation.

The success of the condensation between 9-bromofluorene and malonic ester using sodium ethylate as the condensing agent was found to depend upon the nature of the absolute alcohol used. Ordinary absolute alcohol (99%) was treated

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further with magnesium turnings and a little iodine and this super-dry alcohol was used immediately. The resulting monofluorenyl malonic ester was collected over a 5° range under reduced pressure since it was found that at temperatures slightly above this range traces of a yellow halogen product distilled over. The disubstituted malonic esters were prepared with similar procedures although they gave poor yields. Attempts to prepare difluorenyl malonic ester were unsuccessful.

The urea condensations of monofluorenyl and ethyl fluorenyl malonic esters both gave colourless crystalline solids melting at 232-2340 and 240-243° respectively. The presence of nitrogen was confirmed in both compounds but time was not available for a quantitative determinagion.

In view of the low yields in the urea condensation an attempt was made to synthesize the monofluorenyl barbituric acid by condensing barbituric acid itself with 9-bromofluorene in the presence of sodium acetate. Barbituric acid was prepared by the method described by A. I. Vogel (79) and also by condensing malonic acid and urea in the presence of acetic anhydride.

As a possible extension of the latter method condensation between malonic ester and urea with acetic anhydride was attempted. The reaction was first carried out at 120-

-41-

125° but the isolated product was monoacetyl urea melting at 217-218°. This reaction between urea and acetic anhydride has previously been reported by Hugershoff (32) and also by Kohmann (39). The temperature was then lowered to 90-95° using a trace of concentrated sulphuric acid as a catalyst whence a very small amount of barbituric acid m.p.  $242-244^{\circ}$  was obtained. The use of sodium ethylate as the condensing agent gave the best results.

#### EXPERIMENTAL

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#### I. OXIDATION OF FLUORENE TO FLUORENONE.

In a three-litre round bottom flask equipped with a 500 ml. dropping funnel and a long condenser (reflux) were placed technical fluorene (200 grams) and technical glacial acetic acid (250 ml.) and the mixture heated to boiling. Through the droppingfunnel a warm solution of sodium dichromate (590 grams) in glacial acetic acid (650 ml.) and water (200 ml.) was added slowly so that the boiling was uninterrupted and no permanent precipitate appeared. When this addition was complete the solution was refluxed for at least three and one-half hours whence upon cooling the liquid, it was poured into three litres of ice-water mixture and then allowed to stand for two hours.

The resulting yellow precipitate was filtered through a fine cloth and washed first with water containing a little sulphuric acid and then several times with water and air dried. The air dried crude product was distilled under reduced pressure from a 500 ml. Claisen flask containing some glass wool to prevent bumping. The temperature of distillation was disregarded since subsequent recrystallization removed the residual impurities. Distillation was discontinued when the distillate acquired an orange tinge. The yellow product was cooled and dissolved in a minimum amount of benzene and precipitated by slowly adding twice its volume of petroleum ether. On standing bright long yellow crystals of fluorenone separated. These were filtered and the mother liquor concentrated to give addit-ional product. Yield, 143 grams melting at 82-83°C.

#### II. REFORMATSKY REACTIONS WITH FLUORENONE.

#### A. SYNTHESIS OF FLUORENYLIDENE ACRYLIC ESTER.

In a 500 ml. three necked flask provided with a stirrer, dropping funnel and a reflux condenser was placed freshly cleaned dry zinc turnings (12 grams) and a solution of fluorenone (20 grams) in dry benzene (40 ml.) and toluene (30 ml.). A crystal of iodine was added to this solution and through the dropping funnel ethylbromoacetate (28 grams) was added dropwise and on warming the flask momens tarily a vigorous reaction set in. The stirrer was set in motion and the halogen ester added slowly to maintain gentle refluxing.

After all of the ester has been added the resulting dark brown mixture was refluxed for two hours on a water bath, thesstirring being uninterrupted. Then the mixture was treated with cold dilute sulphuric acid, the aqueous layer separated and the benzene-toluene layer washed several times with water then dried over anhydrous sodium sulphate

When dry, the solvent was removed by distillation and the residue, a very viscous brown liquid, was dissolved in absolute alcohol and left in the refrigerator for several days whence yellow crystals of the product separated. These were recrystallized from absolute alcohol giving bright fluffy crystals melting at 74-75°C. Yield, 23 grams (82%).

### B. SYNTHESIS OF ETHYL d- (9-HYDROXYFLUORENYL) PROPIONATE.

Fluorenone (20 grams), ethyl *d*-bromopropionate (28 grams), freshly cleaned zinc turnings (15 grams), and dry benzene (80 ml.) were used as before. After the initial vigorous reaction subsided the mixture was refluxed for The residue after distillation of the solvent two hours. was a very viscous orange-yellow liquid which failed to solidify even after standing for one week. The heavy oil was dissolved in absolute alcohol and after six days stand-These ing in the cold pale yellow crystals separated. were recrystallized from absolute alcohol givingwwhite crystals melting at 81-82°C. Yield, 23 grams (75%). Analysis: Calculated as C<sub>18</sub>H<sub>18</sub>O<sub>3</sub>: C, 76.59% H,6.38% . C. 75.22% H.6.14%. Found:

C. THE REFORMATSKY REACTION WITH ETHYL G-BROMOPROPIONATE.

This reaction was first attempted with pure zinc turnings used in the previous reactions and also with Grignard magnesium turnings but in both cases after repeated trials no reaction was detected. The condensation was then attempted by means of a zinc couple. This couple was prepared by gently heating a small amount of solid mercuric chloride and freshly cleaned zinc turnings in an Erlenmeyer flask so that the mercuric chloride sublimed on the surface of the metal. The couple was stored in dry toluene ready for use.

Fluorenone (20 grams), ethyl  $\beta$ -bromopropionate (34 grams), zinc couple (15 grams), and dry toluene (70 ml.) were used according to preceding procedures. A very faint initial reaction was observed. The reaction mixture was refluxed for six hours, cooled, then hydrolyzed with cold dilute acetic acid when colourless crystals separated out. These were filtered, washed with cold benzene. Yield, 3.4 grams m.p. 256-258°C.

The benzene washings were combined with the main toluene solution and the aqueous layer separated. This aqueous layer washed with benzene and the benzene solution combined with the main portion and dried over anhydrous sodium sulphate. After removal of the solvents additional products appeared.

The product was recrystallized from a large volume of boiling benzene giving colourless crystals melting at 258-259°. Yield, 6.9 grams.

#### ANALYSIS OF THE PRODUCT

- (a) Sodium fusion analysis gave no indication of halogens present.
- (b) Negative unsaturation tests were obtained with acid permanganate solution and with bromine water.
- (c) Attempts to detect any active ketonic group by means of phenylhydrazine addition products failed.
- (d) Attempts to detect the presence of free enol groups with cold ferric chloride solution failed.
- (e) The product obtained was difficultyly soluble in ether, benzene, chloroform, acetone, alshohol, carbon tetrachloride and petroleum ether at room temperature but soluble in 1,4-dioxane.

Combustion analysis of the ester recrystallized from boiling benzene gave:

Found: C, 82.57% H, 6.47%. Calculated as hydroxy ester  $C_{18}H_{18}O_3$ : C, 76.59% H, 6.38%. Calculated as unsaturated ester  $C_{18}H_{16}O_2$ : C, 81.78% H, 6.11%.

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Saponification of this product to the free acid was attempted with 30% potassium hydroxide solution and 1,4-dioxane as the solvent. Hydrolysis with sulphuric acid gave a white solid melting at 243-246°C. recrystallized repeatedly from hot benzene. Analysis of this product gave identical results as the original product and tests with sodium bicarbonate solution to detect the free acid group showed negative results. Combustion analysis gave the following results: C, 78.21% H, 6.24%.

Because of the limited time available further efforts to analyze these products were abandoned but it is hoped that a more detailed investigation on this reaction will be made in the future.

#### D. THE REFORMATSKY REACTION WITH BROMOMALONIC ESTER

Bromomalonic ester (20 grams), fluorenone (10 grams), dry benzene (50 ml.) and zinc turnings (6 grams) were treated as in the previous Reformatsky syntheses. A vigorous reaction was observed, cooling being necessary and giving a dark brown liquid. After hydrolysis and removal of the solvents attempts were made to isolate any possible products by fractional distillation under reduced pressure but the distillates obtained were all coloured and boiled over at an indefinite range of temperature. At 220-

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225°/20 mm. fluorenone distilled over and this was dissolved in benzene and reprecipitated with petroleum ether. Yield, 6.2 grams. M.p. 83-84°C.

Il grams of liquid boiling at 152-194°/20 mm. were also collected. Efforts to separate this fraction into its components by further fractional distillation were fruitless and the distillates collected over this range all showed the presence of halogen.

It appears that the previous results obtained with this bromoester apply equally well to fluorenone. However it should be noted that less than half of the ketone used was recovered.

#### III. ATTEMPTED SYNTHESIS OF FLUORENE-9,9-DICARBOXYLIC ESTER.

Synthesis of fluorene-9,9-dicarboxylic ester was attempted using dibromomalonic ester and biphenyl with an excess of anhydrous aluminum chloride.

#### A. SYNTHESIS OF DIBROMOMALONIC ESTER.

In a 500 ml. two necked flask fitted with a reflux condenser and a separatory funnel with a fine tip were placed ethyl malonate (80 grams, 0.5 mole), carbon tetrachloride (100 ml.), and red phosphorus (0.9 grams). In the separatory funnel freshly dried bromine (165 grams, 1.02 moles) was placed and ten mls. of bromine run in with intermittent shaking. Witha slight initial warming a vigorous reaction took place whence the rest of the bromine was added gradually so that gentle refluxing was maintained. When this addition wascompleted the mixture was refluxed until hydrogen bromide was no longer evolved. The mixture was cooled, washed four times with 50 ml. portions of 5% sodium carbonate solution and finally with water, then dried over anhydrous sodium sulphate. Distillation under reduced pressure gave 132 grams of colourless liquid, b.p. 169-171<sup>0</sup>/33 mm. Yield based on malonic ester, 83%.

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#### B. ATTEMPTED FRIEDEL-CRAFTS SYNTHESIS.

A mixture of biphenyl (7.7 grams, .05 moles), dibromomalonate (15.9 grams, .05 moles), and anhydrous aluminum chloride (14.7 grams, .10 mole plus 10% excess ), with dry carbon bisulphide (30 ml.) were refluxed for eight hours in a 500 ml. two necked flask fitted with a mechanical stirrer and a reflux condenser with a hydrogen bromide trap. After the evolution of hydrogen bromide ceased, the solvent was distilled off and the resulting pasty aluminum intermediate poured slowly over a mixture of cracked ice and hydrochloric acid. The aqueous mixture was extracted twice with 30 m. portions of benzene and washed twice with water, once with 10% sodium hydroxide and twice more with water until the final water washings were colourless. The final benzene extract was dried over anhydrous calcium chloride and the benzene distilled off. The residue was heated to 120%/35 mm. whence a dark red liquid distilled over. Distillation was continued up to 175%/35 mm. since no sharp boiling point ranges were obtained. Yield obtained Brom 120-175%/35 mm., 6.2 grams.

Distillation was discontinued at 200°C. The residue was cooled and digested in a minimum amount of hot absolute alcohol and filtered. From the filtrate 3.6 grams of biphenyl melting at 66-68°C. were isolated. The insoluble product when heated on a nickel spatula left a residue containing aluminum compounds.

A cursory analysis indicated that the fraction distilling at 120-175°/35 mm. contained unchanged dibromomalonate in addition to other halogen compounds but no fluorene-9,9-dicarboxylic ester was isolated.

In the second attempt the mixture of biphenyl, anhydrous aluminum chloride (.10 mole plus 25% excess ) and carbon bisulphide was heated to the boiling point of the solvent and by means of an addition tube a solution of dibromomalonic ester in carbon bisulphide (20 ml.) was added slowly through the course of two hours after which the mix-

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ture was refluxed for eight hours. This modification gave almost identical results obtained before except that only 2.9 grams of biphenyl were isolated.

Use of 50% excess of aluminum chloride appeared to alter the reaction very little except that a larger amount (8.2 grams) of the fraction boiling at 120-175°/35 mm. was obtained. Analysis of this fraction indicated the presence of some unchanged dibromomalonic ester plus other unknown halogen containing compounds. Attempts to determine the components of these halogen compounds by means of fractional distillation failed since no sharp boiling point ranges were obtained.

Three trials were made in each of the three reactions but in all of the nine attempts no fluorene-9,9-dicarboxylic ester could be isolated.

#### IV. SYNTHESIS OF FLUORENYL BARBITURIC ACIDS.

#### A. REDUCTION OF FLUORENONE TO FLUORENOL.

To a solution of fluorenone (20 grams) in 80% ethyl alcohol (220 ml.) freshly prepared aluminum amalgam was added. The latter was prepared as follows: Freshly cleaned alimunum turnings (40 grams) were stirred in a 5% mercuric chloride solution for a few minutes and then washed quickly with cold water followed by alcohol. The amalgam thus prepared was used immediately.

The addition of the amalgam to the alcoholic solution gave a vigorous reaction. When this reaction subsided the mixture was refluxed for two hours. After cooling, the grey insoluble mass was filtered and washed several times with 95% alcohol and the filtrate distilled until all of the solvent was removed leaving **z** white solid residue. The residue was dissolved in ether and then precipitated with petroleum ether **giving woo**ly crystals. Yield, 17.1 grams (85%), m.p. 156-157.5<sup>o</sup>C.

When 20 mesh aluminum metal (55 grams) were used in place of the metal turnings 16.7 grams (80% yield) of fluorenol were obtained.

#### B. <u>SYNTHESIS OF 9-BROMOFLUORENE</u>.

Fluorenol (17 grams) was dissolved in glacial acetic acid (180 ml.), the solution being kept at 60°C. To this warm solution 48% hydrobromic acid (40 grams) were added with stirring. The resulting solution was kept at 60° for one hour with intermittent shakingand left at room temperature overnight whence colourless crystals separated. The mother liquor was decanted off and to it an equal volume of cold water added giving additional crystals. The combined products were washed several times with alcohol and dried. Recrystallization was unnecessary. Yield, 16.8 grams (74%), m.p. 103-104°C.

Neither the use of hydrobromic acid in excess of 40 grams nor higher temperatures of reaction increased the yield.

#### C. SYNTHESIS OF MONOFLUORENYL MALONIC ESTER.

A solution of 9-bromofluorene (18 grams) in dry benzene (100 ml.) was added gradually to a chilled solution of sodiomalonic ester prepared from malonic ester (26.8 grams), absolute alcohol (99.8%, 110ml.) and sodium metal ( 2.9 grams). The entire operation was carried out in an atmosphere of nitrogen. When the addition was complete the mixture was refluxed on a water bath for three hours after which the alcohol and benzene were slowly distilled off and the residue was cooled, treated with cold water and the oily layer washed with water, then extracted with ether and dried over anhydrous calsium chloride.

Fractional distillation gave a pale yellow liquid boiling at 142-145°/14 mm. Yield, 16.8 grams, (70.5%).

Analysis:	Found:	С,	75-34%	н,	5.81%.
	Calculated: (as C <sub>20</sub> H <sub>20</sub> O <sub>4</sub> )	C,	75.00%	н,	6.03%.

In order to prepare the difluorenyl malonicester the above procedure was repeated using twice the amount of 9bromofluorene (36 grams) and sodium (5.8 grams). Only the monofluorenyl ester (13.2 grams) distilling at 125-130°/5.6 mm. was collected and identified.

#### D. SYNTHESIS OF ALKYLFLUORENYL MALONIC ESTER.

Ethylfluorenyl malonic ester and n-butyl malonic ester were synthesized as in the preceding procedure using the alkyl substituted malonic ester, ethyl malonic ester (18.8 grams) and n-butyl malonic ester (21.6 grams) respectively with sodium (2.3 grams), 9-bromofluorene (24.5 grams), absolute alcohol (99.8%, 50 ml.) and dry benzene (90 ml.). The products obtained were:

(1) Ethylfluorenyl malonic ester, b.p. 152-157<sup>0</sup>/13 mm. Yield, 16.2 grams (46.0%). Analysis С, 75.41% Н, 6.56%.

Calculated: C, 75.00% H, 6.82%. (as  $C_{22}H_{24}O_{4}$ )

n-Butylfluorenyl malonic ester, b.p. 169-175°/14 mm. (2)

Yield, 13.9 grams (36.8%).

Found:

Analysis:

Found:	с,	76 <b>.18%</b> T	н,	7.05%.
Calculated : (as $C_{24}H_{28}O_4$ )	С,	75•79%	н,	7•37%•

#### THE FLUORENYLBARBITURIC ACIDS. Ε.

MONOFLUORENYLBARBITURIC ACID (1)

A mixture of sodium (1.15 grams) dissolved in ab-(a)solute alcohol (99.8%, 60 ml.) with fluorenyl malonic ester (8.1 grams) and dry urea (1.5 grams) was heated at 105-110°C. for eight hours. The alcohol was then slowly distilled off, the residue dissolved in water and made acid to Congo red with hydrochloricacid. Colourless crystals melting at 232-234°C. were obtained. Yield, 2.9 grams.

(b) SYNTHESIS OF BRBITURIC ACID WITH ACETIC ANHYDRIDE

In a 500 ml. flask provided with a reflux condenser and an addition tube, urea (30 grams ) was dissolved in glacial acetic acid (120 ml.) followed by malonicester (40 grams). The mixture was heated to 90-95°C. and through the addition tube freshly redistilled acetic anhydride (125 ml.) was gradually added over a period of 65 minutes with frequent shaking.

When addition was completed the temperature was maintained at 9-95° for about twelve hours. The mixture was cooled and the resulting precipitate filtered, washed with cold water, dissolved in dilute cold sodium hydroxide solution, and made acid to Congo red with hydrochloric acid, then filtered. After leaving the filtrate in the cold for several hours barbituric acid precipitated. Yield, 5.9 grams (18.5%), m.p.  $2+3-2+5^{\circ}C$ .

If the temperature was raided to 120-125°, no barbituric acid was isolated but 27.5 grams of monoacetyl urea melting at 217-219°C. were isolated.

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## (c) SYNTHESIS OF MONOFLUORENYLBARBITURIC ACID WITH SODIUM ACETATE

To a boiling solution of barbituricaacid (3.2 grams) in water (30 ml.) contained in a 250 ml. two necked flask provided with a reflux condenser; a hot solution of 9bromofluorene (6.1 grams) and sodium acetate (2.7 grams) in 90% alcohol (165 ml.) was slowly added over a period of two hours, the alcoholic solution being always kept warm as the 9-bromofluorene precipitated at room temperature.

When addition was complete the mixture was refluxed for three hours, then 50 ml. of the liquid distilled off and upon cooling the reaction product precipitated out. These were filtered and dissolved in cold sodium hydroxide solution and filtered again. The product was reprecipitated by making the filtrate acid with hydrochloric acid. The precipitate was recrystallized from 40% alcohol giving colourless crystals melting at 233-236°C. Yield, 1.6 grams.

A mixed melting point of this product with that obtained in procedure (a) above gave no depression. Qualitative analysis showed the presence of nitrogen but no halogen. Timed did not permit a quantitative nitrogen determination of the products obtained.

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#### (2) ATTEMPTED SYNTHESIS OF ALKYLFLUORENYLBARBITURIC

#### ACID

#### (a) ETHYLFLUORENYLBARBITURIC ACID

A mixture of ethylfluorenyl malonic ester (17.6 grams), dry urea (4.5 grams), and sodium (2.3 grams) in absolute alcohol (20 ml.) was heated at 90-95°C. for eight hours and treated as in the previous experiments. Colourless crystals were obtained as the final product. Yield, 2.7 grams, m.p. 239-242°C.

Sodium fusion analysis of this product gave positive nitrogen test but time did not permit a quantitative determination.

When the above procedure was repeated with the heating continued for two days, 2.3 grams of colourless crystals melting at 240-243°C. were obtained. This product gave a positive nitrogen test and mixed melting point determinations with the product obtained in (a) gave 237-240°C.

## (b) n-BUTYLFLUORENYLBARBITURIC ACID

(i) n-Butylfluorenyl malonic ester (19.0 grams, .05 mole),
dry urea (4.5 grams, .75 mole), sodium (2.3 grams, .05
mole) in absolute alcohol (25 ml.) were heated in a 250

ml. flask fitted with reflux condenser and calcium chloride drying tube by means of an oil bath kept at 95°C. The mixture was heated for ten hours and then the alcohol slowly distilled off over the course of two hours. The contents of the flask were cooled, dissolved in cold water, filtered, and made acidic to Congo red with concentrated hydrochloric acid and left in the refrigerator for two days. The solution was slightly yellow. Crytals, **pale yellow** in colour were obtained, Yield, 0.8 grams melting at 245-247.5°C. Concentrating the mother liquor gave only a trace of additional product. Recrystallization from 40% alcohol gave crystals melting at 244-247°C. Sodium fusion of this product gave a positive nitrogen test.

(ii) Heating the same reactants in (i) on an oil bath at 98°C. for two days gave (after recrystallization from 40% alcohol) colourless crystals melting at 245-247°C. Yield, 1.3 grams.

(iii) To a mixture of urea (4.5 grams) and n-butyl fluorenyl malonic ester (19.0 grams) dissolved in absolute alcohol (20 ml.) freshly distilled contained in a two necked flask fitted with an addition tube and reflux condenser, a solution of sodium (2.3 grams) in dry alcohol (20 ml.) was slowly added through the addition tube, the reactants beingheated by an oil bath kepted at 90°. This required three hours and when completed the mixture was heated at 85° for an additional eight hours. Then the alcohol was slowly distilled off for two hours and the mixture cooled and treated as before. The final product after recrystallization from 40% alcohol gave colourless crystals melting at 245-247.5°C. Yield, 1.8 grams.

Analysis of the product gave a positive nitrogen test. Mixed melting point with the product obtained in procedure (ii) above gave 241-244.5°C.

Time did not permit a quantitative determination of nitrogen for the products obtained in the above experiments.

#### SUMMMARY

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- The synthesis of fluorenylidene acrylic ester (m.p. 74-75°) and ethyl *≺*-(9-hydroxyfluorenyl) propionate (m.p. 81-82°) by means of the Reformatsky reaction with fluorenone is described.
- The extension of the Reformatsky reaction to bromomalonic ester and ethyl β-bromopropionate with fluorenone has been attempted.
- 3. The preparation of fluorene-9,9-dicarboxylic ester from dibromomalonic ester and biphenyl in the presence of anhydrous aluminum chloride has been attempted without success.
- 4. The syntheses and isolation of fluorenyl malonic ester (b.p. 125-130°/5.6 mm.), ethylfluorenyl malonic ester (b.p. 152-157°/13 mm.), and butylfluorenyl malonic ester (b.p. 169-175°/14 mm.) are given. The condensation of these new substituted malonic esters with urea in the presence of sodium ethylate is also outlined.

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