THE SYNTHESIS OF 10-(4-HYDROXYMETHYLPHENYL)-1,2-BENZANTHRACENE

By

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TO MARGARET

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The author wishes to express his sincere appreciation to those who have helped make this investigation possible. The author also wishes to express his special appreciation to Dr. Frank A. Vingiello, his Research Advisor.

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INTRODUCTION

INTRODUCTION

In 1875 Volkmann, a surgeon, recognized the connection between skin tumours and an occupation in the tar industry (1). After this conclusion many research workers attempted to produce cancer upon the skin of experimental animals but were unsuccessful.

The first successful production of cancer in an experimental animal by coal tar, an extrinsic agent, was accomplish--ed in 1918 by Yamagiwa and Ichikawa (2). After this accomplishment, the next logical step was the determination of the active material in coal tar. This was materially aided by the discovery that (3):

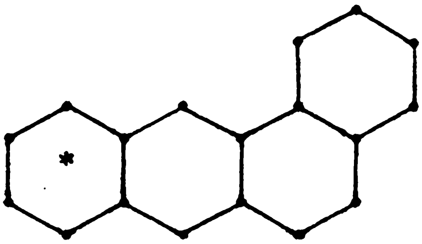
(1) The activity resided in high boiling nitrogen free fractions.

(2) A characteristic fluorescent spectrum was always associated with fractions with carcinogenic activity.

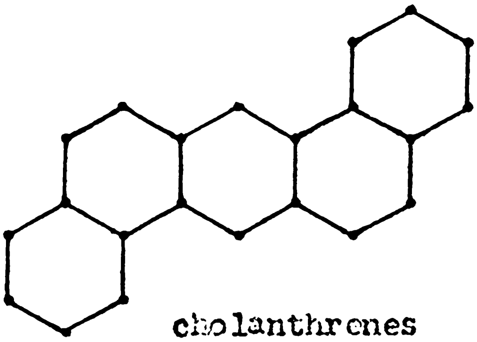
(3) Many compounds with similar properties could be prepared in the laboratory.

The group of polycylic aromatic hydrocarbons with the above characteristics which were synthesized and tested were:

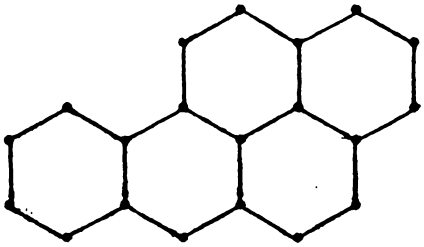
1,2-benzanthracenes



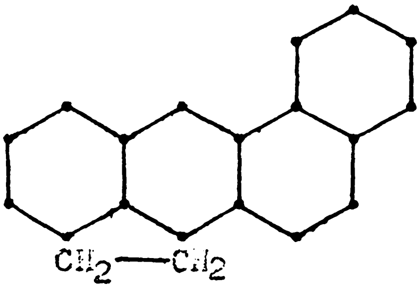
1,2,5,6-dibenzanthracenes



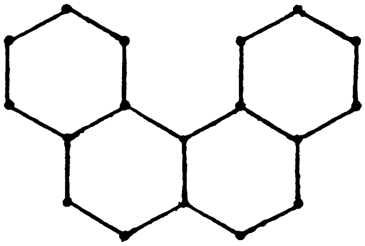
3,4-benzpyrenes



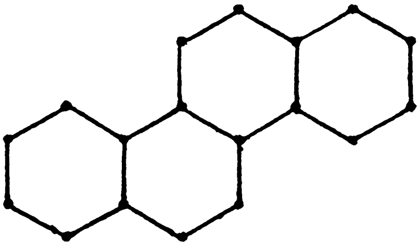
cholanthrenes



3,4-benzphenanthrenes



chrysenes



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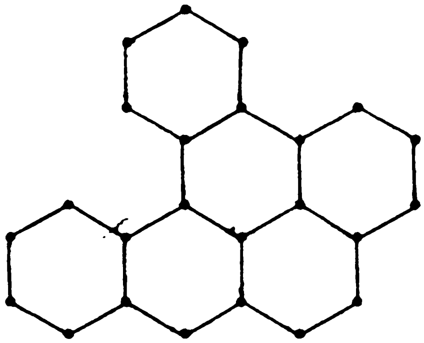
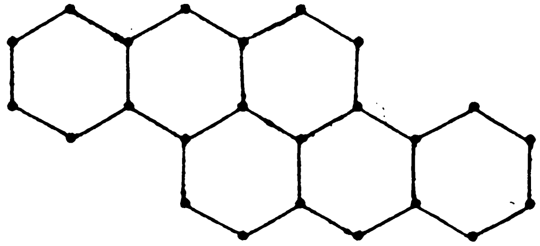
* All ring structures are aromatic, unless otherwise stated.

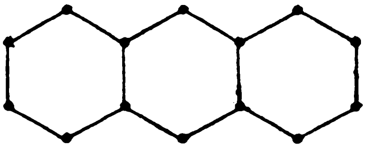
1,2,3,4-dibenzpyrenes



3,4,8,9-dibenzpyrenes



anthracenes



Many of these polycylic aromatic hydrocarbons and/or their derivatives were found to produce carcinomata in experimental animals.

During the past thirty years a vast amount of data has been collected on the chemistry of these particular polycylic aromatic hydrocarbons. Two notable experiments which gave rise to tremendous amounts of work in the benzanthracene series were:

(1) The conversion of desoxycholic acid, a natural product, to 20-methylcholanthrene, a carcinogenic compound, by Wieland and Dane (4).

(2) The discovery by Cook that the most potent carcinogens were the 1,2-benzanthracenes with a carbon substituent at either the 5,9 or 10 positions (5,6).

With these experiments in mind, research chemists attacked the problem of synthesizing related compounds in the 1,2-benzanthracene series in hope that the structural features of carcinogenic compounds would be discovered. A knowledge of the structural features of carcinogenic compounds would perhaps enable an explanation of the mechanics of carcinogenesis as produced by chemical agents. Due to the complexity of the problem progress has been very slow.

With this in mind Vingiello and Borkovec prepared the 9- and 10-phenyl, 9-and 10-monomethylphenyl, and 9-and 10-dimethylphenyl benzanthracenes using Bradsher's hydrobromic acid-acetic acid cyclization method, a modification of the Bradsher method or Borkovec's alumina method (7,8,9,10,11). These compounds were tested and 10-phenyl-1,2-benzanthracene was found to be carcinolytic (48).

This important discovery coupled with the recent work performed by R.K. Stevens made it imperative that 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene, presumably a more soluble derivative of 10-phenyl-1,2-benzanthracene, be synthesized and tested.

The purpose of this investigation was to synthesize 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene, and to briefly study one of the alternate synthetic routes to 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene.

HISTORICAL

HISTORICAL

A. Synthesis of 10-substituted 1,2-benzanthracenes

A survey of the literature through 1956 reveals that there are four synthetic routes which have been utilized to produce 10-substituted 1,2-benzanthracenes in respectable quantities. They are in reverse chronological order:

(1) Base catalyzed cyclization reaction of o-(α-naphthylmethyl)-benzoic acid with an alkyl or aryl lithium compound (12,13) . See Chart I.

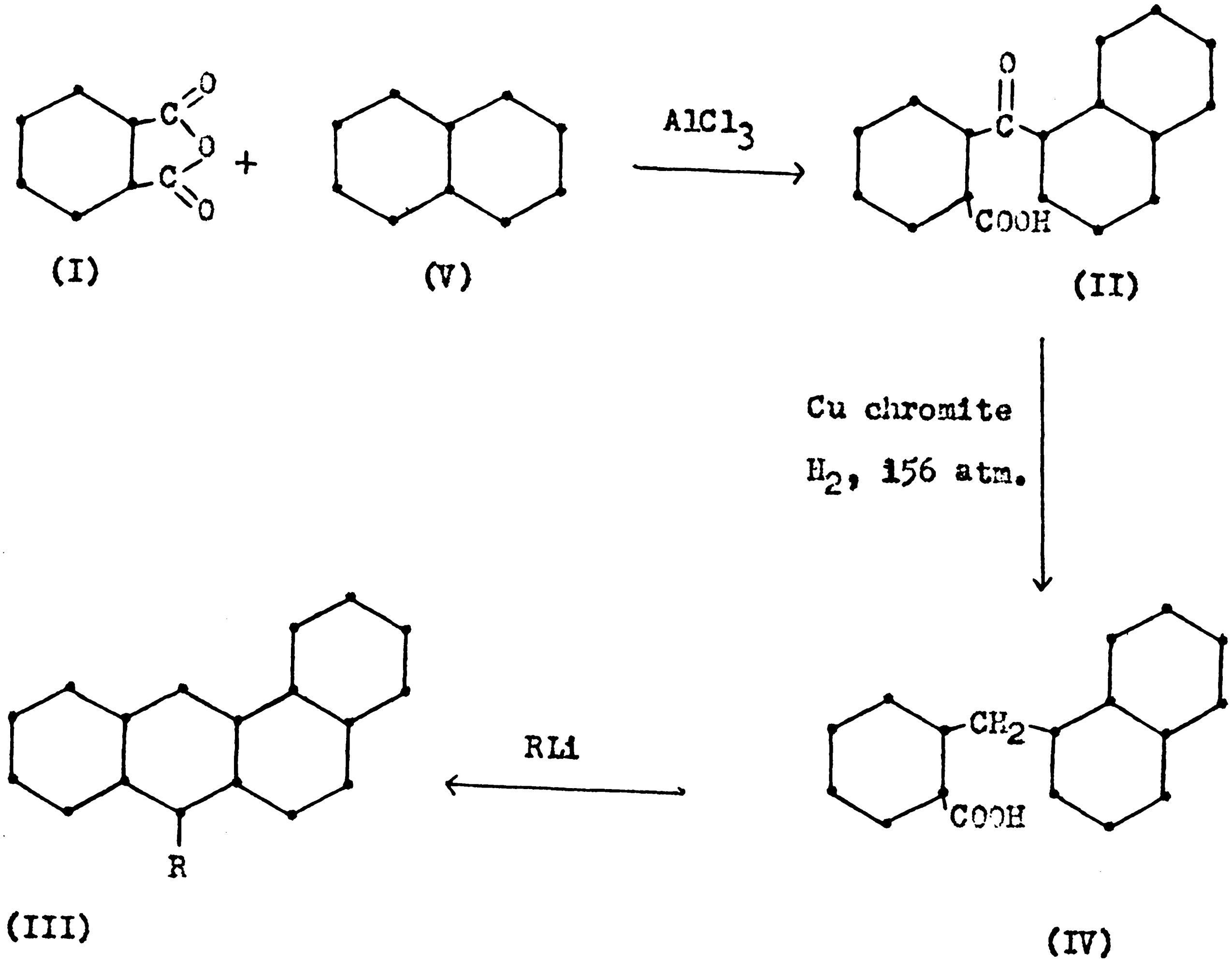
(2) Cyclization reaction of o-(α-naphthylmethyl) substituted benzophenones with hydrobromic acid and acetic acid or other media (8,10,11,14). See Chart II.

(3) Reaction of alkyl Grignard reagents with 2-(benzoyl)-α-naphthoic acid and subsequent reduction and cyclization (15). See Chart III.

(4) Reaction of alkyl Grignard reagents with 10-benzanthrone and subsequent dehydration (16, 17, 18). See Chart IV.

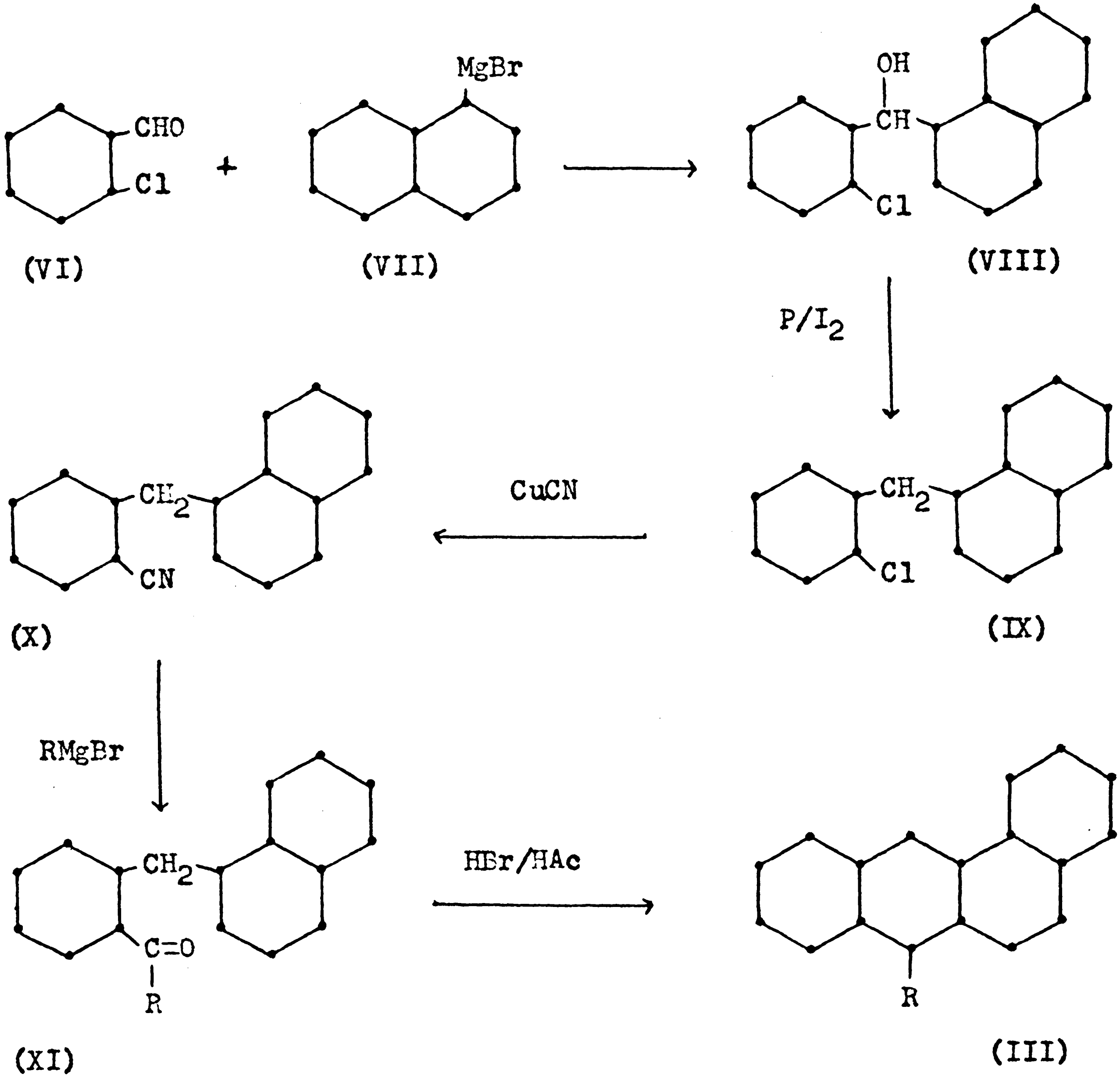
The above synthetic route which has been investigated most extensively, and often leads to a higher yield of final product, is the cyclization reaction of ketones with hydrobromic acid and acetic acid. Historically this reaction was

CHART I



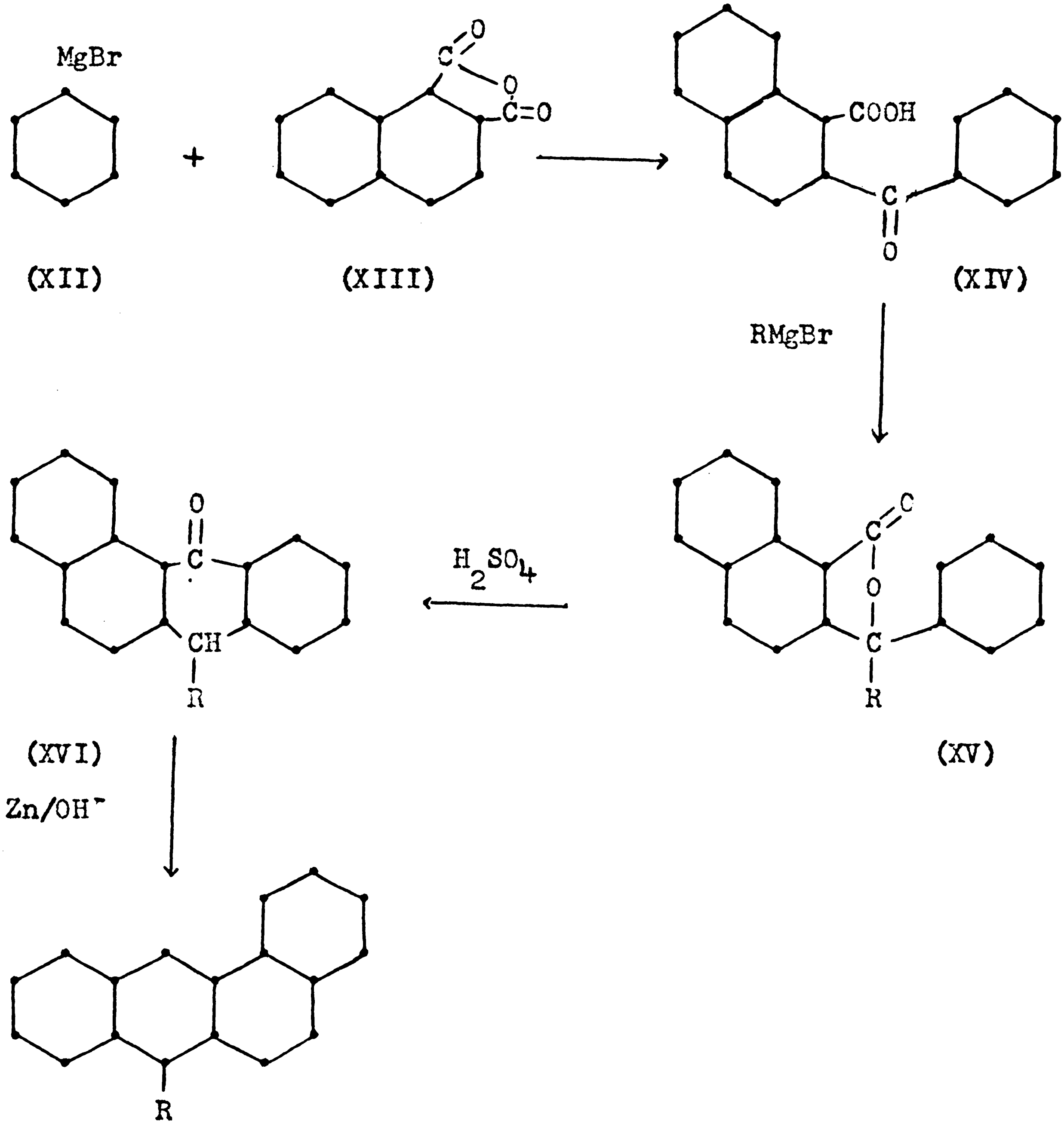
R is an alkyl or aryl group

CHART II



R is an alkyl or aryl group

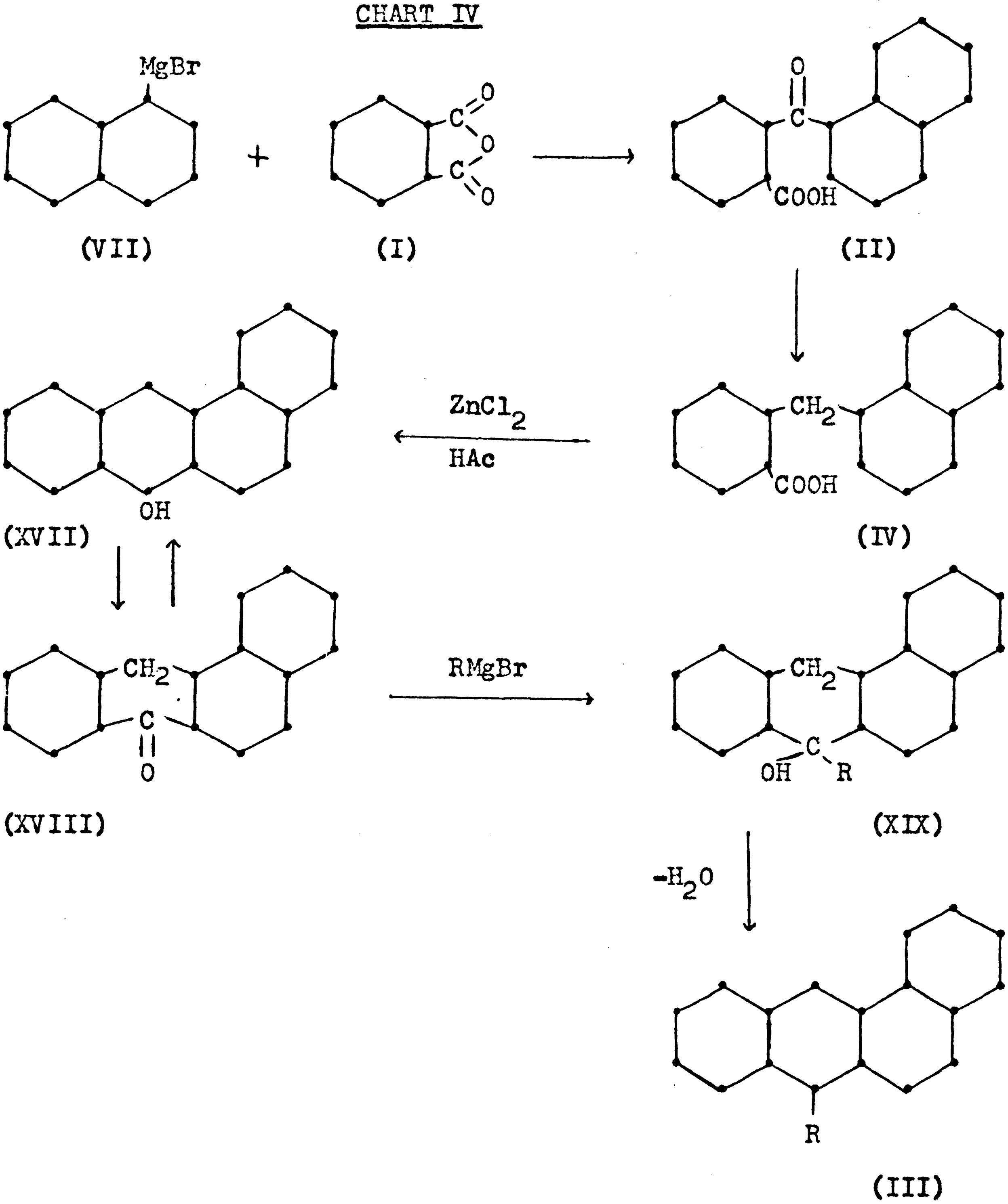
CHART III



(III)

R is an alkyl group

CHART IV



R is an alkyl group

performed by Bergmann in 1939 (19). In an attempt to hydrolyze the Grignard reagent complex formed between ethyl orthoformate and o-bromodiphenylmethane, Bergmann obtained large quantities of anthracene. Soon thereafter Bradsher made use of this valuable information to synthesize 9-methyl, 9-ethyl, and 9-phenyl anthracene from the respective ketones (20). Extension of this method for the preparation of 10-alkyl and aryl substituted 1,2-benzanthracenes soon followed (8, 10, 11, 21).

R. K. Stevens, in his Masters Thesis, reports the preparation of various 4-substituted 10-phenyl 1,2-benzanthracenes by cyclization of the respective ketones (14, 22). The compounds of that nature which were prepared are:

(1) 10-(4'-bromophenyl)-1,2-benzanthracene
(2) 10-(4'-chlorophenyl)-1,2-benzanthracene
(3) 10-(4'-cyanophenyl)-1,2-benzanthracene
(4) 10-(4'-carboxyphenyl)-1,2-benzanthracene
(5) 10-(4'-methoxyphenyl)-1,2-benzanthracene
(6) 10-(4'-hydroxyphenyl)-1,2-benzanthracene

B. Synthesis of primary alcohols from paraformaldehyde and Grignard reagents.

Grignard reagents add to formaldehyde in the following manner (23):

$$\text{(1)}\quad HCHO + RMgX \longrightarrow RCH_2OMgX$$

$$(2)\quad R\,CH_2\,O\,Mg\,X + H_2O \longrightarrow R\,CH_2\,OH + Mg(OH)X$$

Upon hydrolysis of the complex a primary alcohol is obtained. Moderate yields of the primary alcohol have been obtained. Zeigler reported 61% and 70% of the primary alcohol respectively with 4-Br $C_6\,H_4$ MgBr and $C_6\,H_5$ MgBr (24, 25). This reaction has also been employed with phenanthrene derivatives. Bachmann reported 50% of the carbinol from 9-phenanthrylmagnesium bromide (26).

C. Synthesis of primary alcohols from carboxylic acids by reduction with lithium aluminum hydride.

The use of lithium aluminum hydride has become a legend since the first report of its use as a reducing agent before the symposium on hydrides and related compounds at the Chicago Meeting of the American Chemical Society in 1946. The reason for its extensive use is mainly due to its high specificity, avoidance of condensations, side reactions and cleavage.

A detailed study of the reduction of acids with lithium aluminum hydride has not been undertaken but a moderate amount of work has been accomplished in this field. The reaction which is performed in diethyl ether, tetrahydrofuran or bis (β-ethoxyethyl) ether can be represented by the following equation (27):

$$4\,R\,COOH + 3\,Li\,AlH_4 \longrightarrow (RCH_2O)_4\,LiAl + 2\,LiAlO_2 + 4H_2$$

The complex which forms is then hydrolyzed to the carbinol by dilute acid. The yields of the carbinol from various acids are reported by Nystrom and Brown and are given below (28):

Acid	Alcohol	% Yield
Stearic Acid	Octadecanol-1	91
Furoic Acid	Furfuryl Alcohol	85
Phenylacetic Acid	β-Phenylethanol	92
Benzoic Acid	Benzyl Alcohol	81
o-Chlorobenzoic Acid	o-Chlorobenzyl Alcohol	97

Also of interest in this problem was the effect of lithium aluminum hydride on polynuclear aromatic hydrocarbons. Sampey and Cox have reported that attempts to reduce naphthalene and anthracene in ether or dioxane were unsuccessful (29). Although reduction of the polynuclear aromatic hydrocarbons may not be possible cleavage of these compounds may occur. The cleavage of 9-benzoyl-anthracene to benzyl alcohol and anthracene in tetrahydrofuran has been reported (30).

DISCUSSION OF RESULTS

DISCUSSION OF RESULTS

A. Preparation of Synthetic Intermediates.

The preparation of 10-(4'-bromophenyl)-1,2-benzanthracene was carried out in essentially the same manner as Stevens (14, 22). See Chart V. The yields obtained are given in the table below:

Reaction	Yield (%)		
	I	II (31)	III (22)
Aldehyde (VI) to Carbinol (VIII)	76	95	75
Carbinol (VIII) to Methylene (IX)	45	60	54
Methylene (IX) to Nitrile (X)	71	69	72
Nitrile (X) to Ketone (XXIV)	71	72	50
Ketone (XXIV) to Hydrocarbon (XXV)	87	92	94

The overall yield of 10-substituted phenyl 1,2-benzanthracenes by this method is comparable to the yield obtained by Bradsher's base catalyzed synthesis of similar compounds.

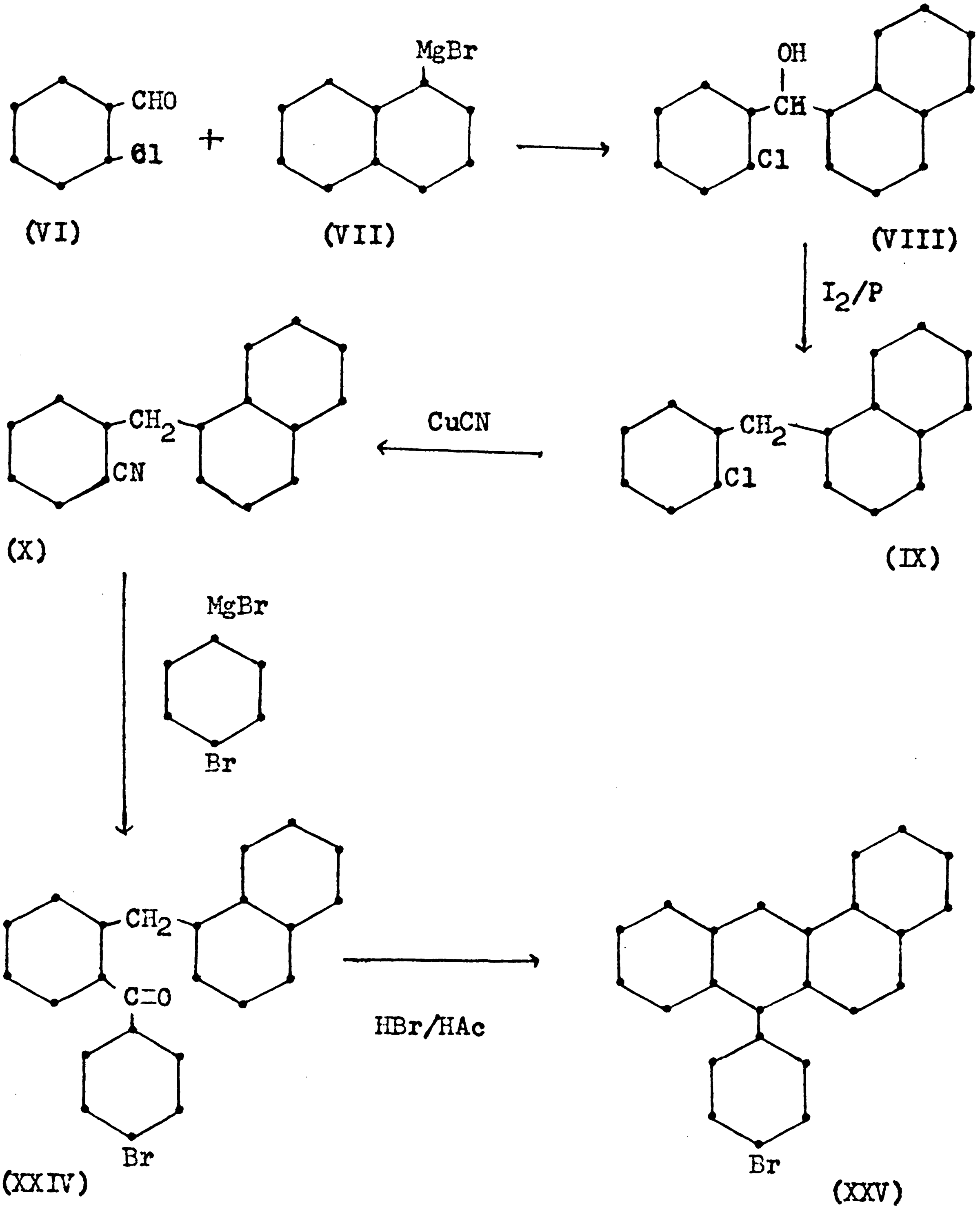
Even though the above route was a satisfactory route, an alternate route was investigated because of several factors:

(1) Inconvenience of reducing large quantities of 2-chlorophenyl-1-naphthylcarbinol with phosphorus and iodine.

(2) Private communication from Sih-Quan Quo that Grignard reagents could be condensed with *o*-chlorobenzylchloride (32).

(3) Recent report of Bradsher and Webster that lithium-

CHART V


CHO
Cl
MgBr
OH
CH
Cl
(VI)
(VII)
(VIII)
I2/P
CH2
CN
CuCN
CH2
Cl
(X)
(IX)
MgBr
Br
CH2
C=O
Br
HBr/HAc
Br
(XXIV)
(XXV)

aryl compounds react with *o*-(α-naphthylmethyl)-benzoic acid to form benzanthracenes (12, 13).

(4) Report of Ramsden, et al, that Grignard reagents could be prepared from chloro compounds in tetrahydrofuran by "entrainment" (33).

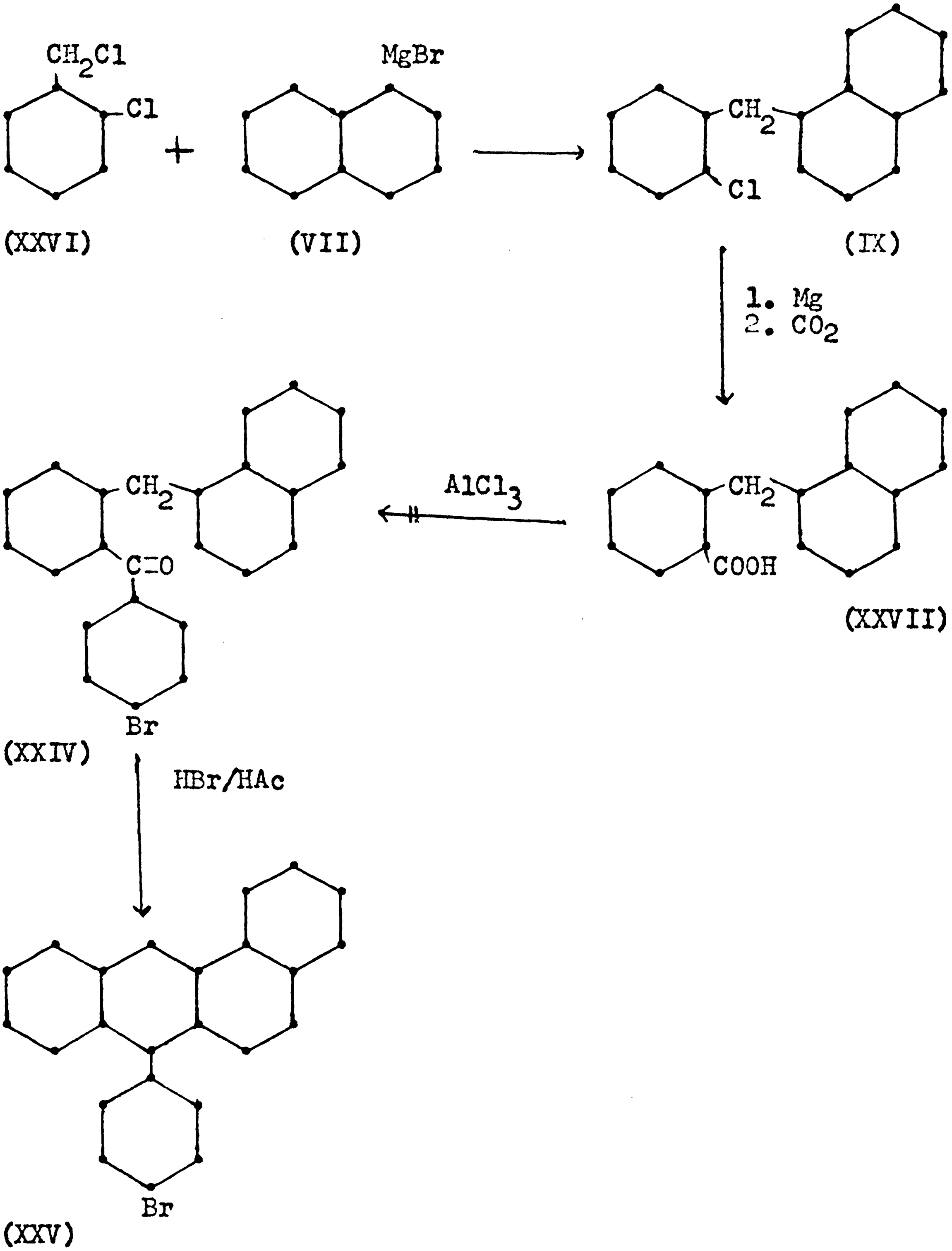
(5) Reports that show that benzoic acid can be reacted with bromobenzene in the presence of aluminum chloride (34).

This alternate route is schematically illustrated in Chart VI.

The reaction of *o*-chlorobenzychloride with the Grignard reagent of α-bromonaphthalene was performed as directed by Si-Gwan Quo, except iodine was used as an initiator for the Grignard reaction. The mixture was worked up and distilled and a yield of 65% was obtained. After allowing to stand for several days the liquid began to solidify. The melting point of the solid material was very near that of α,α'dinaphthyl. The liquid was decanted off and assuming that none of the α,α'-dinaphthyl dissolved in the *o*-chlorophenylnaphthylmethane the corrected yield was 26%. The failure of this reaction to give yields consistent with that observed by others may have been due to the formation of free radicals by the iodine. Traces of iodine have been known to promote side reactions in Grignard reactions. (23).

The second step in the synthetic scheme as indicated in Chart VI was performed in a manner as reported by Ramsden, et al (33). Using tetrahydrofuran and other cyclic ethers

CHART VI


CH$_2$Cl
Cl
+
MgBr
(XXVI)
(VII)
CH$_2$
Cl
(IX)
1. Mg
2. CO$_2$
CH$_2$
COOH
(XXVII)
AlCl$_3$
CH$_2$
C=O
Br
(XXIV)
HBr/HAc
Br
(XXV)

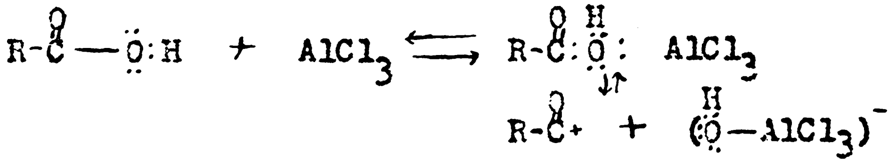
they have prepared the following chloro Grignard reagents in the indicated yields:

Reactant	Yield (%)
Chlorobenzene	95
p-Chlorotoulene	93
p-Methoxychlorobenzene	77
p-Chloro N,N' dimethylaniline	88
4-Chlorodiphenyl	22.6
α-Chloronaphthalene	40

As was expected the Grignard reagent was prepared from o-chlorophenyl-1-naphthylmethane with the use of tetrahydrofuran "entrainment", and long reflux periods. The resulting Grignard reagent was carbonated with dry ice and yields of 42% of the corresponding acid were obtained. This reaction is significant because it will perhaps enable the preparation of ketones without the synthesis of o-bromophenyl-1-naphthylmethane from o-bromotoulene and α-bromonaphthalene which is a time consuming process.

The condensation of o-(α-naphthylmethyl)-benzoic acid with bromobenzene which was the next reaction in the sequence failed to produce a ketone or a cyclized hydrocarbon. The acid, o-(α-naphthylmethyl)-benzoic acid was recovered contaminated with a yellow impurity, which probably was benzanthrone.

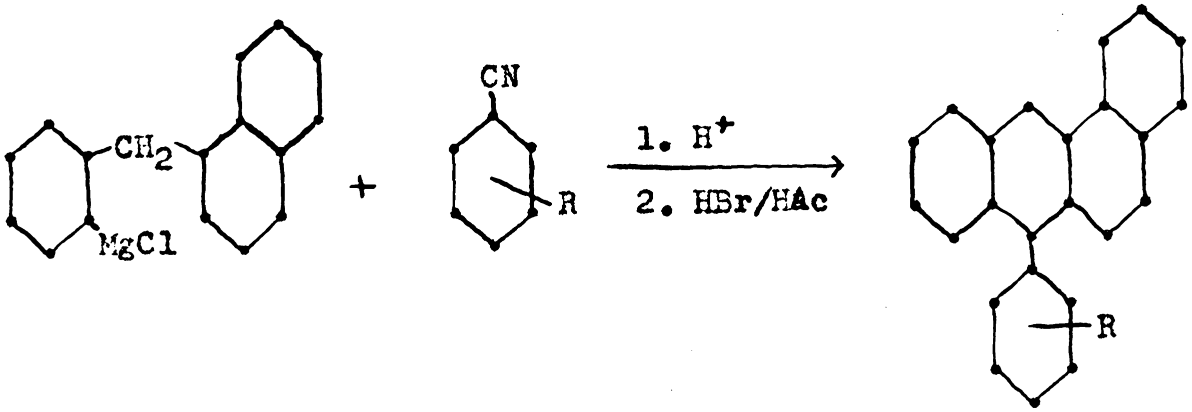
The Friedel-Crafts reaction mechanism for the addition of acids to hydrocarbons has been postulated to proceed by the formation of a carbonium ion (35,43):



$$R-\overset{O}{\overset{\|}{C}}-\ddot{\underset{\cdot\cdot}{O}}:H + AlCl_3 \rightleftharpoons R-\overset{O}{\overset{\|}{C}}:\overset{H}{\ddot{O}}: \ AlCl_3$$
$$\updownarrow$$
$$R-\overset{O}{\overset{\|}{C}}^{+} + (\overset{H}{\underset{\cdot\cdot}{\ddot{O}}}-AlCl_3)^{-}$$

The failure of the reaction of *o*-(*α*-naphthylmethyl)-benzoic acid with bromobenzene under the conditions employed may have been due to the failure to form carbonium ions. Stronger conditions probably would lead to large quantities of benzanthrone instead of the keto acid.

Even though the acylation step in the sequence failed, the *o*-(*α*-naphthylmethyl)-benzoic acid which was prepared from *o*-chlorobenzylchloride could be utilized as an intermediate in the base catalyzed condensation type of preparation of 10-phenyl-1,2-benzanthracene. Also, as was stated previously, the Grignard reagent of 2-chlorophenyl-1-naphthylmethane could be utilized in the preparation of ketones which could be cyclized to 10-substituted phenyl 1,2-benzanthracene.



This reaction is especially noteworthy because:

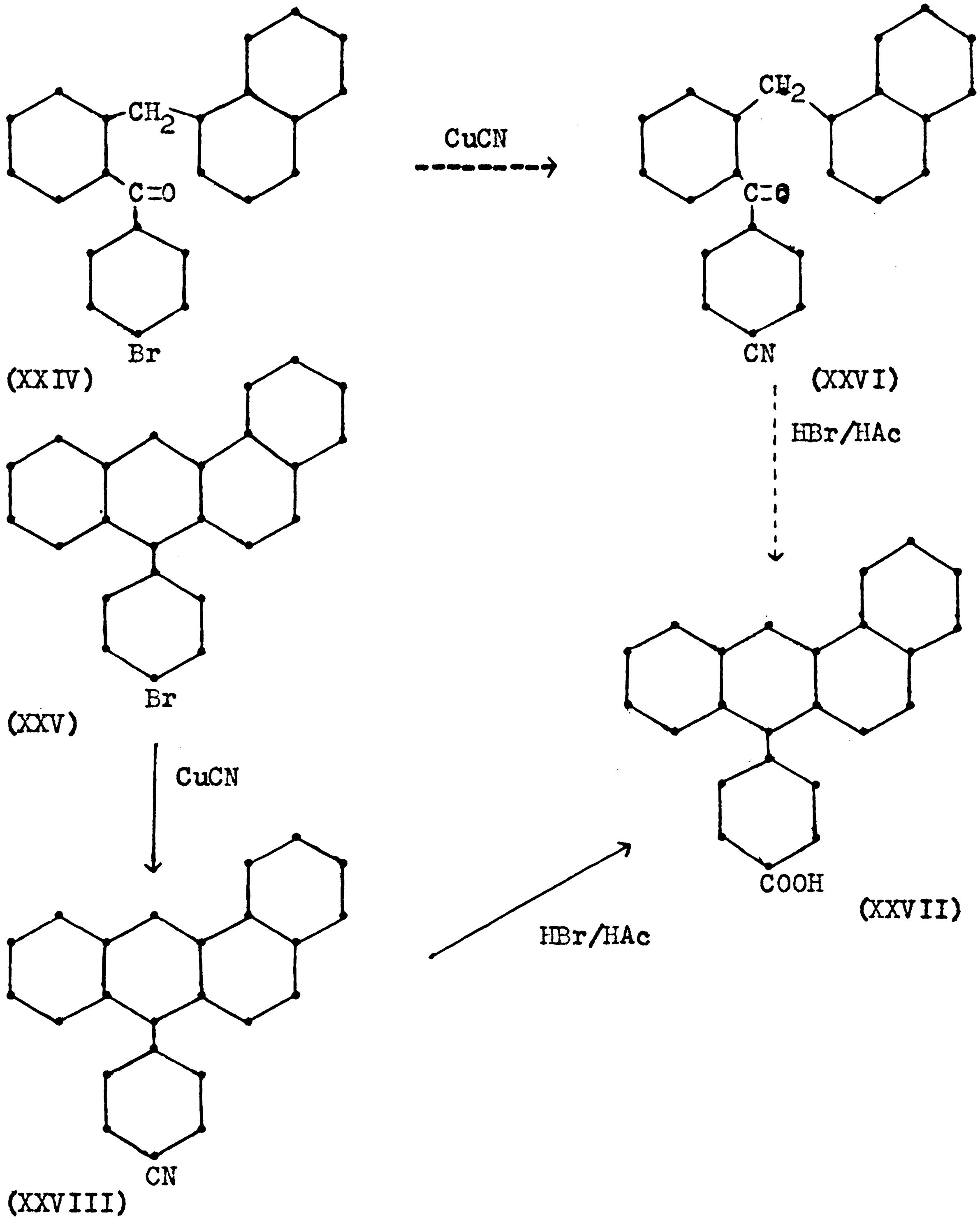
(1) This type of synthesis has been employed by Schlechter in his synthesis of the 9-pyridylanthracenes (36).

(2) A modified type of Rosenmund-von Braun reaction using dimethylformamide as a solvent has given 90% yield of cyano compounds from halo compounds (37).

(3) Report that good yields of substituted cyano compounds can be obtained from substituted benzoic acids by heating with a high boiling nitrile (38).

The preparation of 10-(4'-carboxyphenyl)-1,2-benzanthracene was performed exactly as Stevens had reported (14,22) and also by an alternate method which gave poor yields of the acid. In Chart VII the synthetic route of Stevens is indicated by the broken line arrow while the alternate route is indicated by a solid line arrow. The step in the alternate route which was responsible for the low yields of the acid was the Rosenmund-von Braun conversion of 10-(4'-bromophenyl)-1,2-benzanthracene to 10-(4'-cyanophenyl)-1,2-benzanthracene. Since this type of conversion in the benzanthracene series has been successfully performed in good yields by Newman (39), it would be expected that a favorable change in the experimental conditions could produce an increase in the yield if the failure to react was due to size of the molecule.

CHART VII


CH$_2$
C=O
Br
(XXIV)
CuCN
CH$_2$
C=O
CN
(XXVI)
HBr/HAc
Br
(XXV)
CuCN
COOH
(XXVII)
HBr/HAc
CN
(XXVIII)

B. Attempted Synthesis of 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene from 10-(4'-bromophenyl)-1,2-benzanthracene

Various hydroxymethylphenyl alcohols have been prepared from the Grignard reagent of a bromo compound and formaldehyde (24, 25). The procedure for this preparation is relatively simple provided the Grignard reagent of the halophenyl compound can be made. Carr in his B.S. Thesis (31) was unable to prepare the Grignard reagent of 10-(4'-bromophenyl)-1,2-benzanthracene. The following experiments were performed and gave negligible yields of the desired product:

(1) 10-(4'-bromophenyl)-1,2-benzanthracene (0.026 moles), magnesium (0.026 moles), and 1 g. of methyl iodide in 300 ml. of dry ether was refluxed for one hour. The reaction began but died away.

(2) Same as (1) above, except 200 ml. of dry ether was employed and one-half the quantity of magnesium and 10-(4'-bromophenyl)-1,2-benzanthracene. The reaction began but died away.

(3) 10-(4'-bromophenyl)-1,2-benzanthracene (0.013 moles), magnesium (0.013 moles), and methyl iodide in 200 ml. of ether and 100 ml. of benzene was refluxed for 50 hours. The magnesium did not react.

(4) 10-(4'-bromophenyl)-1,2-benzanthracene (0.013 moles), magnesium activated with iodine (0.013 moles) in 300 ml. of ether was refluxed for 50 hours.

The magnesium did not react. Kunkel in his B.S. Thesis (40) also was unable to prepare the Grignard reagent of 10-(4'-bromophenyl)-1,2-benzanthracene. The following experiments were performed and gave negligible yields of the desired product:

(1) Attempted preparation of the Grignard reagent of 10-(4'-bromophenyl)-1,2-benzanthracene using diethyl ether as a solvent.

(2) Attempted preparation of the Grignard reagent of 10-(4'-bromophenyl)-1,2-benzanthracene using tetrahydrofuran as a solvent.

At the present time the Grignard reagent of 10-(4'-bromophenyl)-1,2-benzanthracene has not been prepared. The following experiments were performed with extremely pure 10-(4'-bromophenyl)-1,2-benzanthracene:

(1) The use of iodine-activated magnesium and butyl bromide as initiator in diethyl ether gave little if any Grignard reagent after eight hours reflux as indicated by subsequent carbonation.

(2) The above was repeated. There was no Grignard reagent after six hours reflux as indicated by addition of water and recovery of 10-(4'-bromophenyl)-1,2-benzanthracene.

(3) Use of methyl iodide as initiator and tetrahydrofuran as a solvent yielded little if any Grignard reagent after one hour reflux as determined by attack upon the magnesium.

The inactivity of 10-(4'-bromophenyl)-1,2-benzanthracene was amazing since the compound could be considered as a para substituted bromobenzene, and there could be little resonance interaction between the benzene and the benzanthracene rings.

The literature was searched for other bromo compounds which could not be converted into the corresponding Grignard reagent. These compounds are listed below:

(1) 4-bromododecane (41)
(2) 2-bromoflourene (42)
(3) 3-bromoacenapthene (42)
(4) 2-bromoacenapthene (42)
(5) 2-p-bromophenyldioxolane (43)

In most of these compounds the inactivity of the bromine could be attributed to resonance interaction with the aromatic ring.

Another search was made to discover compounds similar to 10-(4'-bromophenyl)-1,2-benzanthracene for which Grignard reagents had been prepared. The following were discovered:

(1) p-bromodiphenyl (44)
(2) 9-(4'-bromophenyl)-10-(4''-bromophenyl)-anthracene (45)

In the cases of the above halides no particular difficulty was encountered in preparing the Grignard reagents.

Many chemists feel that the Grignard reagent of 10-(4'-bromophenyl)-1,2-benzanthracene can be made (47). However, the inactivity of the 10-(4'-bromophenyl)-1,2-benzanthracene could prevent the formation of a Grignard reagent by a normal technique. Often a difficult Grignard reagent has been prepared by employing a new solvent, special type of magnesium, special "entrainment" procedure, or a Grignard catalyst. A good example of this was in the development of the technique for the preparation of chloro Grignard reagents in tetrahydrofuran and other cyclic ethers (33).

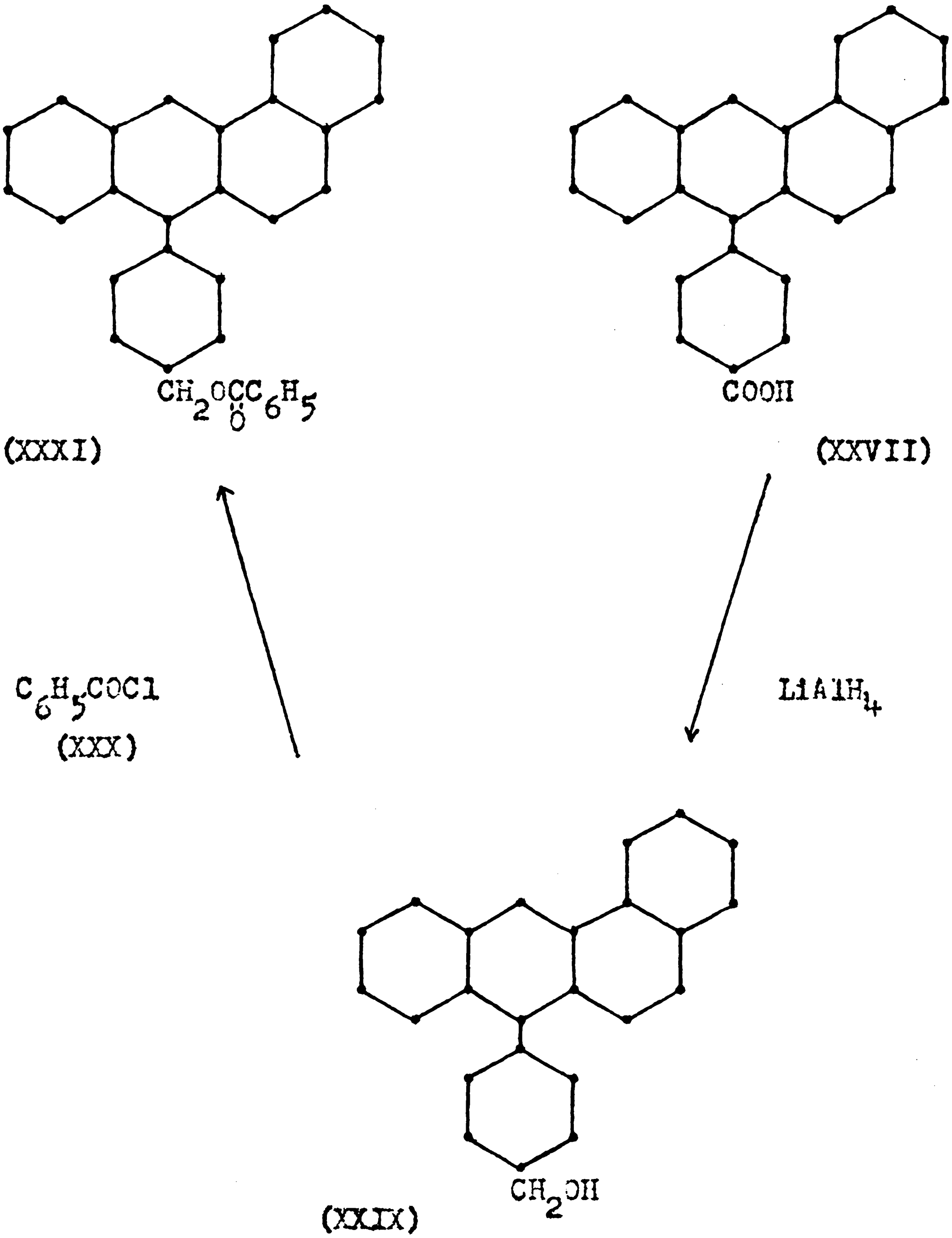
Often however, as in this problem, the desired compound is available by other synthetic routes so the preparation of the Grignard reagent was abandoned.

C. Preparation of 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene

Since the discovery of lithium aluminum hydride by Finholt, Bond and Schlesinger in 1947, many novel applications of lithium aluminum hydride have been reported. One of these is the reduction of carboxylic acids to alcohols in diethyl ether or tetrahydrofuran. The reduction is straight forward yielding little or no by-products.

Using the reduction of an ether-soluble compound as a guide (50) the reduction of 10-(4'-carboxyphenyl)-1,2-benzanthracene to 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene was performed in tetrahydrofuran. The 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene was produced in 92% yield.

CHART VIII



(XXXI)

(XXVII)

$LiAlH_4$

C_6H_5COCl
(XXX)

(XXIX)

The reduction of the acid in tetrahydrofuran yielded also a red material which was probably due to the cleavage of tetrahydrofuran. This material was difficult to separate from the alcohol. Only after passing through alumina was this separation accomplished. By employing milder conditions only a small amount of the red material was obtained. This smaller quantity was removed by animal charcoal.

Because of the limited solubility of 10-(4'-carboxyphenyl)-1,2-benzanthracene in diethyl ether a slurry technique was employed in the lithium aluminum hydride reduction in ether. This gave a rather low yield of the alcohol. Increased heating time would probably increase this considerably.

The solubility characteristics of 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene were:

Solvent	Solubility
(1) Isoamyl alcohol	Moderately soluble
(2) Ethyl alcohol (95%)	Very soluble
(3) Benzene	Moderately soluble
(4) Ligroin	Slightly soluble
(5) Tetrahydrofuran	Very soluble

The proof of structure of the compound prepared by the reduction of 10-(4'-carboxyphenyl)-1,2-benzanthracene (See Chart VII) was based upon the following:

(1) Elementary analysis

(2) Synthesis

(3) Ultraviolet spectra *

(4) Infrared spectra *

(5) Elementary analysis of a representative derivative

Difficulty was experienced in getting the elementary analysis of 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene within the range of that expected to be given by experimental error. Contamination of the analytical sample with a small amount of 10-(4'-carboxyphenyl)-1,2-benzanthracene, which is not very soluble in dilute sodium hydroxide, or with water could be the cause of the slightly low percentage of carbon. The infrared spectrum of the alcohol would lead one to believe that the impurity was not 10-(4'carboxyphenyl)-1,2-benzanthracene because there was no appreciable carbonyl peak at 5.9 microns.

The proof of the structure of the compound from the reduction of 10-(4'-carboxyphenyl)-1,2-benzanthracene is also based upon the synthesis of the alcohol from o-chlorobenzaldehyde and 1-bromonaphthalene through a series of reactions which have been demonstrated to give 10-phenyl-1,2-benzanthracenes and are reliable and free from rearrangements. Also Stevens has demonstrated that 10-(4'-carboxyphenyl)-1,2-benzanthracene was obtained in the cyclization of 2-(1-naphthyl-

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* The instrument employed and the experimental conditions for the infrared and ultraviolet spectra are given at the end of the experimental and with the respective curves in the appendix.

methyl)-4'-cyanobenzophenone. The infrared spectrum of 10-(4'-carboxyphenyl)-1,2-benzanthracene confirms this:

(1) A sharp carboxyl peak at 5.9 microns.

(2) 1,4-disubstitution in benzene indicated by a weak peak at 6.2 microns and a strong peak at 12.2 microns.

(3) Benzanthracene nucleus indicated by peaks at 6.7, 11.3 and 13.4 microns.

The ultraviolet spectra of the compound thought to be 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene and 10-phenyl-1,2-benzanthracene had the maxima of absorption indicated in the appendix. This demonstrates that the compound prepared by the reduction of 10-(4'-carboxyphenyl)-1,2-benzanthracene was a benzanthracene.

The infrared spectrum of the compound prepared by the reduction of 10-(4'-carboxyphenyl)-1,2-benzanthracene had the following significant peaks:

(1) Primary alcohol vibrations at 9.8 and 2.9 microns (broad).

(2) 1,4-disubstitution in benzene at 12.2 microns.

(3) Benzanthracene vibrations at 6.7, 11.3 and 13.4 microns.

This information coupled with the ultraviolet spectrum and the chemical reactions of formation gives a firm basis for assigning to this compound the structure 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene (XXIX).

Also the benzoate of the alcohol (XXXI) was prepared. (See Chart VIII). The infrared spectrum of the compound formed from the benzoyl chloride and the alcohol had peaks at 5.8, 7.8 and 9.0 microns, which are characteristic of a benzoate.

The data discussed above is adequate proof that the compound synthesized by the reduction of 10-(4'-carboxyphenyl)-1,2-benzanthracene was 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene.

EXPERIMENTAL

EXPERIMENTAL [a,b,c]

2-chlorophenyl-1-naphthylcarbinol (VIII).

A Grignard reagent was prepared from 24.3 g. (1.0 mole) of magnesium turnings, 207 g. (1.0 mole) of the α-bromonaphthalene and 600 c.c. of dry diethyl ether. When the reaction was complete, 140 g. (1.0 mole) of o-chlorobenzaldehyde dissolved in 250 ml. of dry ether was added slowly. The resulting mixture, a cream yellow, was then stirred overnight. A warm bath was then placed under the flask and the mixture refluxed for 45 minutes. The water bath was replaced with an ice bath and the Grignard complex decomposed with 300 ml. of cold 20% ammonium chloride solution. The organic layer was decanted into a flask and reserved. The solid residue remaining in the flask was extracted once with 250 ml. of ether. The ether extraction and organic layer were combined and washed three times with water in a separatory funnel. The organic layer was then dried over $CaCl_2$ for 19 hours and then concentrated.

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[a] All melting points were obtained using a Fisher-Johns melting point apparatus and are uncorrected.

[b] All analyses were carried out by the Geller Microanalytical Laboratories, West Englewood, New Jersey.

[c] All temperatures are expressed in degrees centigrade.

The product was a yellow viscous oil; 200 g., 75% yield crude.

2-chlorophenyl-1-naphthylmethane (IX).

A mixture of 200 g. (0.75 mole) of 2-chlorophenyl-1-naphthylmethane, 1500 ml. of 90% acetic acid, 46 g. of red phosphorus and 46 g. of iodine was heated under reflux with stirring for 45 hours.

The hot solution was then filtered by pouring over glass wool to remove excess phosphorus . The filtrate was then mixed with 2-3 kg. of ice and 1100 ml. of ethyl ether was added. While stirring the resulting solution was neutralized with 20% sodium hydroxide. The etheral layer was separated, washed three times with dilute NaOH, once with water and dried overnight over $CaSO_4$. Concentration and vacuum distillation yielded a yellow oil, b.p. 165-170° (1 mm.) [Lit. (21) b.p. 189-192° (2 mm.)] yield 83 g. (43%).

Preparation of 2-chlorophenyl-1-naphthylmethane (IX).

A Grignard reagent was prepared from 0.12 g. (0.48 mole) of magnesium and 100 g. (0.48 mole) of 1-bromonaphthalene in 250 ml. of dry ether. Iodine was used as an initiator. When reaction was complete two-thirds of the ether was distilled off and 100 ml. of dry benzene was added. Then with stirring 77.3 g. (0.48 mole) of o-chlorobenzylchloride in

100 ml. of benzene is added slowly. The resulting mixture is refluxed four hours at approximately 75°. The complex is decomposed with 100 ml. of dilute hydrochloric acid and stirred overnight. The water and organic layer are separated. The organic layer is washed with water and dried over anhydrous calcium chloride. The dry solution is concentrated and crudely distilled at reduced pressure, yielding a yellow oil, b.p. 185-200° (2 mm.) [Lit. (21) b.p. 189-192° (2 mm.)] yield 80 g. (65%).

The yellow oil partially crystallized after standing at room temperature for two days. The solid material was filtered and washed with ethanol m.p. 148-152° [Lit. (51) $\underline{\alpha}$,$\underline{\alpha}$'-dinaphthyl m.p. 156°]. The filtrate was a yellow oil, yield 32 g. (26%) which did not crystallize on standing.

<u>2-(1-naphthylmethyl)-benzonitrile (X).</u>

A mixture of 83 g. (0.32 mole) of 2-chlorophenyl-1-naphthylmethane, 48 g. (0.54 mole) of cuprous cyanide, 25 ml. of dry pyridine and a small crystal of copper sulfate was placed in a 250 ml. round bottom flask. The mixture was heated in a metal bath, and the pyridine allowed to escape gradually through the tall condenser while the temperature of the bath was maintained at 250-260° for 21 hours. The resulting mixture after setting for two days was crudely distilled under reduced pressure using a von Braun distilling head. The yellow oil was dissolved in ether and transferred to an Erlenmeyer flask. Evaporation in vacuo of the ether gave a crude yield of 30 g. (36%). The oil was dissolved in 95% ethanol and crystallized, m.p. 58-60° [Lit. (21) m.p. 59-60°] .

2-(1-naphthylmethyl)-benzoic acid (IV).

One gram (0.042 mole) of magnesium, 2.9 g.(0.02 mole) of methyl iodide and 50 ml. of dry tetrahydrofuran was added to a three-necked flask equipped with stirrer, reflux condenser and dropping funnel. After the reaction had become vigorous 5.2 g. (0.02 mole) of 2-chlorophenyl-1-naphthylmethane dissolved in 180 ml. of dry tetrahydrofuran was added. The resulting mixture is then refluxed for 24 hours. The warm solution is poured over an excess of crushed solid carbon dioxide and stirred vigorously. The resulting complex was decomposed with ice and dilute hydrochloric acid. The organic layer was decanted. The water layer was extracted twice with diethyl ether and added to the organic layer. The organic layer was extracted with dilute sodium hydroxide and acidified. After the tetrahydrofuran was evaporated in vacuo at room temperature, a white oily solid formed, 2.6 g. (43%). Recrystallization from 95% ethanol gave a white solid which melted at 143-146°. [Lit. (48) m.p. 146-147°].

2-(1-naphthylmethyl)-4'-bromobenzophenone (XXIV).

A Grignard reagent was prepared from 108.2 g. (0.42 mole) of 1,4-dibromobenzene and 10.8 g. (0.45 mole) of magnesium turnings in 500 ml. of dry ether. A solution of 40 g. (0.16 mole) of 2-(1-naphthylmethyl)-benzonitrile dissolved in 200 ml. of dry benzene was added dropwise to the reaction flask as the ether was slowly distilling away. Distillation of the solvent was discontinued when reflux temperature was 75°. The mixture was then heated with stirring under reflux for 18 hours.

The mixture was then decomposed with 75 ml. of 20% ammonium chloride solution and the brown organic layer decanted from the solid residue. The residue was extracted several times with benzene and the extract combined with the organic layer. The combined extracts were washed three times with water and 100 ml. of dilute hydrochloric acid was added. After a large portion of the benzene had been distilled off, 400 ml. of 10% sulfuric acid and 800 ml. of toluene was added and the mixture heated under reflux in nitrogen atmosphere for 48 hours. The toluene layer was separated from the acid layer, washed twice with water, twice with dilute sodium bicarbonate and once again with water and dried over anhydrous magnesium sulfate. The dried solution was concentrated and vacuum distilled. A slightly yellow viscous oil, b.p. 260-295° (1.5 mm.) [Lit. (14) 270-280° (2 mm.)], yield 24.5 g. (39%). The oil was dissolved in ethanol and white crystals were isolated, m.p. 105-107° [Lit. (14) m.p. 106-107°] .

2-(1-naphthylmethyl)-4'-cyanobenzophenone (XXVI).

A mixture of 30.2 g. (0.075 mole) of 2-(1-naphthylmethyl)-4'-bromobenzophenone, 10.1 g. (0.11 mole) of cuprous cyanide, 25 ml. of dry pyridine and a crystal of anhydrous cupric sulfate were heated at 180° for three hours in a 100 ml. round bottom flask in a metal bath. The temperature was then raised to 210-220° and maintained at that temperature for 22 hours. The resulting mixture was crudely distilled under reduced pressure. The distillate was dissolved in ethanol and concentrated light yellow crystals were obtained, yield 6.1 g. (24%), m.p. 117-118° [Lit. (14) m.p. 117-118°] .

10-(4'-bromophenyl)-1,2-benzanthracene (XXV).

A mixture of 12 g. (0.03 mole) of 2-(1-naphthylmethyl)-4'-bromobenzophenone, 100 ml. of glacial acetic acid and 50 ml. of 48% hydrobromic acid were placed in a 500 ml. round bottom flask and heated under reflux for 24 hours. Upon cooling the benzanthracene layer in the bottom of the flask hardened. The acid filtered off and the solid dissolved in benzene. The solution was concentrated and ethyl alcohol added induce crystallization, yield 10.0 g. (87%) m.p. 161-163°. [Lit. (14), 163-163.5°] .

Attempted preparation of 10-(4'-bromophenyl)-1,2-benzanthracene (XXV).

To a 100 ml. round bottom flask containing 25 ml. of bromobenzene and 2 g. (0.008 mole) of 2-(α-naphthylmethyl)-benzoic acid is added slowly 1.8 g. (0.014 mole) of anhydrous aluminum chloride. The mixture is then heated on steam bath for two to three hours. The mixture is then poured on ice and 1:1 hydrochloric acid , benzene and ether are added and the organic layer separated and dried over anhydrous calcium chloride. Vacuum distillation gave only 20 ml. of a low boiling material and a residue in the pot. The residue was dissolved in 95% ethanol and crystallized. A light yellow solid was obtained which had the following properties:

(1) m.p. 140-145°.

(2) Soluble in concentrated sodium hydroxide.

(3) Ultraviolet spectrum did not resemble the benzanthracene spectrum.

Attempted preparations of the Grignard reagent 10-(4'-bromophenyl)-1,2-benzanthracene.

A. Two grams (0.083 mole) of magnesium and five large crystals of iodine were placed in a round bottom flask fitted with a reflux condenser and drying tube. The flask was heated until the iodine bagan to sublime and then allowed to set overnight.

Five drops of *n*-butyl bromide dissolved in 50 ml. of ether were added. After the reaction was proceeding vigorously 1.5 g. (0.005 mole) of 10-(4'-bromophenyl)-1,2-benzanthracene dissolved in 75 ml. of dry ether was added. For two hours the reaction proceeded without any additional heat. Then the reaction mixture was refluxed for eight hours.

The Grignard reagent was then poured onto an excess of crushed solid carbon dioxide. The Grignard complex was then decomposed with dilute hydrochloric acid. Extraction with sodium hydroxide and then acidification yielded no precipitate.

B. In a dry three-neck flask equipped with stirrer, reflux condenser and dropping funnel was placed 0.2 g. (0.0083 mole) of magnesium turnings, three large crystals of iodine and 10 ml. of dry ether. This mixture was refluxed and stirred for six hours.

One drop of *n*-butyl bromide and 1 g. (0.002 mole) of 10-(4'-bromophenyl)-1,2-benzanthracene dissolved in 50 ml. of ether was added. The mixture was then refluxed for four hours.

Water was added slowly. The water and ether solutions were separated and the ether layer was evaporated almost to dryness *in vacuo*. Filtration gave a yellow material (0.8 g.). Recrystallization from ethanol gave whitish-yellow crystals, m.p. 161-164°.

C. Into a flask equipped with stirrer, reflux condenser, and dropping funnel was placed 1 g. (0.002 mole) of 10-(4'-bromophenyl)-1,2-benzanthracene, 30 ml. of Eastman white label tetrahydrofuran, 0.1 g. (0.004 mole) of magnesium and one drop of methyl iodide and a crystal of iodine. The mixture was then refluxed 11 hours and the magnesium examined. No attack upon the magnesium had occurred.

10-(4'-cyanophenyl)-1,2-benzanthracene (XXVIII).

A mixture of 5 g. (0.013 mole) of 10-(4'-bromophenyl)-1,2-benzanthracene, and 2.4 g. (0.027 mole) of cuprous cyanide was dissolved in 8 ml. of dry pyridine in a 100 ml. round bottom flask. A crystal of cupric sulfate was added and the mixture heated for 24 hours at 210-270° in a metal bath. The material was extracted from the flask with hot benzene, charcoaled and recrystallized from ethanol. White crystals were obtained, m.p. 196-198°, yield 0.8 g. (19%) [Lit. (14) m.p. 197-198°] .

10-(4'-carboxyphenyl)-1,2-benzanthracene (XXVII).

A mixture of 6.0 g. (0.017 mole) of 2-(1-naphthylmethyl)-4'-cyanobenzophenone, 75 ml. of glacial acetic acid and 40 ml. of 48% hydrobromic acid was heated under reflux for 18 hours, and then allowed to stand for 48 hours. Filtering the resultant mixture yielded 2.0 g. of the acid. The filtrate was treated with 25 ml. of cold water and filtered again. The 0.5 g. of acid obtained was combined with the above 2.0 g. The 2.5 g. of acid (43%) dissolved in 95% ethanol. Off-white crystals were obtained, m.p. 295-300°. [Lit.(14) m.p. 298-300°] .

10-(4'-carboxyphenyl)-1,2-benzanthracene (XXVII).

A mixture of 2.8 g. (0.009 mole) of 10-(4'-cyanophenyl)-1,2-benzanthracene, 15 ml. of 48% hydrobromic acid and 25 ml. of glacial acetic acid was heated under reflux for 24 hours. The mixture was cooled and filtered. The off-white sand crystals were washed once with water and recrystallized from ethanol, yielding 1.6 g. (52%) of a white micro crystals, m.p. 297-300° . [Lit. (14) m.p. 298-300°] .

Preparation of 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene (XXIX).

A. Into a three-necked flask equipped with stirrer, reflux condenser and dropping funnel was placed a mixture of 0.15 g. (0.040 mole) of lithium aluminum hydride and 100 ml. of dry tetrahydrofuran. The stirrer was started and 1.3 g. (0.004 mole) of 10-(4'-carboxyphenyl)-1,2-benzanthracene dissolved in 50 ml. of tetrahydrofuran was added. The resulting mixture was heated gently for two hours *. The mixture was then cooled and 25 ml. of water was added cautiously to destroy excess lithium aluminum hydride. Then an iced solution of 10 ml. of concentrated sulfuric acid in 150 ml. of water was added. Fifty ml. of ethyl ether was added and the organic layer separated. The water layer was extracted with ether and the extraction was combined with the organic layer. The organic layer was washed with dilute hydrochloric acid, sodium bicarbonate solution and then finally with water. The organic layer was dried overnight over anhydrous magnesium sulfate. The solution was treated with carbon black and then concentrated. Light pink crystals were obtained, 1.2 g. (92%) m.p. 160-170°.

The pink crystals were placed on top of a five inch column of alumina and eluted with petroleum ether and ethanol. Concentration and chilling gave off-white wax-like crystals, m.p. 174-176°. Recrystallization from isoamyl alcohol gave off-white crystals melting at 178-179°. The analytical sample

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* A lavender color develops after about 15 minutes of heating.

was recrystallized from ligroin to give white, waxy, feather-like crystals, m.p. 178-179°.

		C	H
Anal.	Calculated for $C_{25}H_{18}O$:	89.79	5.43
	Found :	88.82	5.38

B. A slurry of 0.5 g. (0.015 mole) of lithium aluminum hydride, 3.3 g. (0.0095 mole) of 10-(4'-carboxyphenyl)-1,2-benzanthracene and 75 ml. of diethyl ether was refluxed three hours with stirring. Excess lithium aluminum hydride was decomposed cautiously with water. The product was then worked up as in A above. Concentration of the resulting solution gave 0.9 g. (23.4%) of the alcohol. Dissolving the alcohol and treating with animal charcoal gave white crystals, m.p. 177-179°.

Preparation of 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene benzoate (XXXI).

In a 50 ml. Erlenmeyer flask was placed 0.3 g. (0.009 mole) of 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene and an excess of benzoyl chloride. The resulting solution was boiled for 15 minutes over a low flame. The hot solution was poured into 25 ml. of cold water and allowed to solidify. The solid was extracted with warm saturated sodium bicarbonate solution. The resulting solid was recrystallized from benzene-ethanol (50-50) to give a yellowish-orange solid which melted at 159-162°. Repeated recrystallization from the above solvent gave yellow crystals, m.p. 160-161°.

Experimental conditions for ultraviolet and infrared spectra.

The ultraviolet spectrum of 10-(4-hydroxymethylphenyl)-1,2-benzanthracene was obtained using a Perkin-Elmer Spectracord (Model 3000, 1 cm., quartz cells). The concentration, the solvent, the slit width, and the scanning time are given on the curve in the appendix.

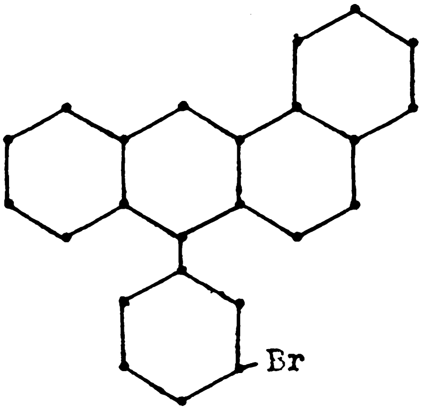
The infrared spectra of the benzanthracenes were obtained using a Beckmann IR-5. The potassium bromide discs were prepared by the following method:

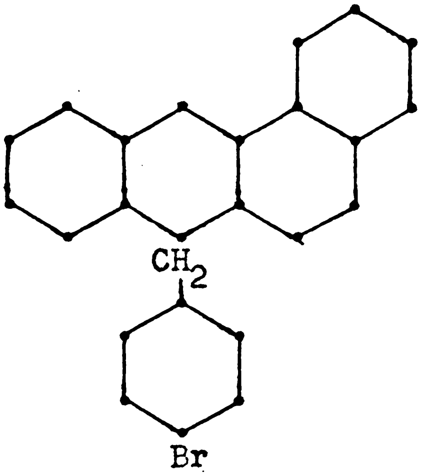
A weighed sample of the benzanthracene was combined with the appropriate weight of infrared grade potassium bromide. The mixture was shaken 55 seconds by a motor driven shaker. Then the mixture was pressed into a disc using a hydraulic press. (20,000 lbs./in.^{2})

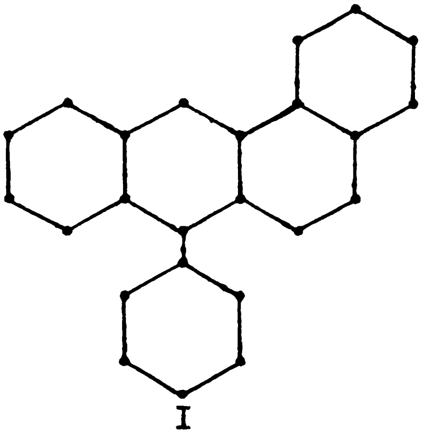
SUGGESTIONS FOR FUTURE INVESTIGATION

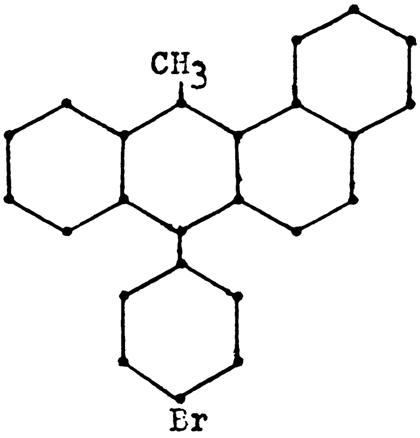
A substantial reason for the inactivity of the bromine in 10-(4'-bromophenyl)-1,2-benzanthracene cannot be advanced without further investigation into the chemical properties of 10-substituted phenyl 1,2-benzanthracenes. This would entail performing two complementary studies:

(1) Preparation and reaction of magnesium upon compounds of which the following are examples:

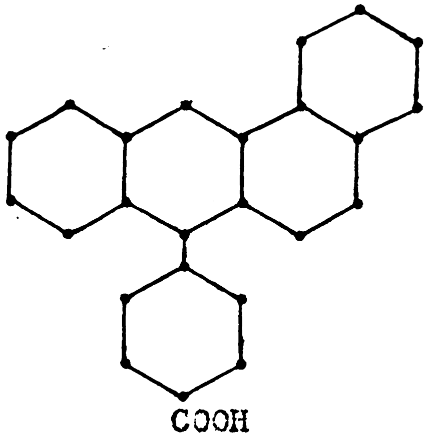


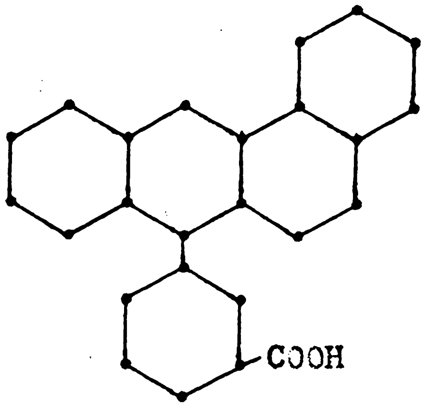


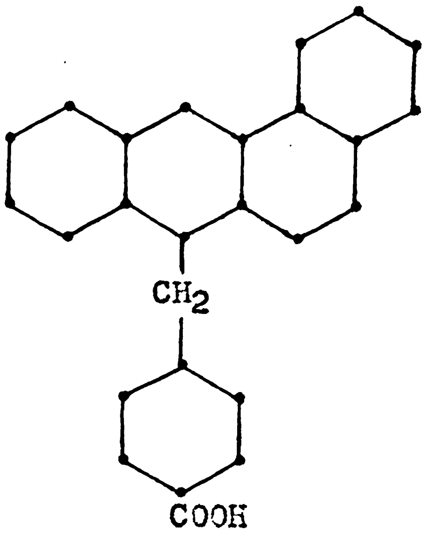




(2) Preparation and measurement of the ionization constants of the following compounds:







SUMMARY

SUMMARY

A. The alcohol, 10-(4'-hydroxymethylphenyl)-1,2-benzanthracene, was prepared by the reduction of 10-(4'-carboxyphenyl)- 1,2-benzanthracene. The structure of the alcohol was proven by:

(1) Ultraviolet spectra
(2) Infrared spectra
(3) Elementary analysis
(4) Preparation of the benzoate

B. The preparation of the Grignard reagent of 10-(4'-bromophenyl)-1,2-benzanthracene was unsuccessful. An explanation of this anomaly was not discovered.

C. The Grignard reagent of 2-(1-naphthylmethyl)-chlorobenzene was prepared by the use of tetrahydrofuran and "entrainment" with methyl iodide.

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LITERATURE CITED

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VITA

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APPENDIX

ABSORPTION MAXIMA OF SEVERAL 10 SUBSTITUTED BENZANTHRACENES

(Wavelength in mu)

10-phenyl-1,2-benzanthracene (8)	10-(4'-methylphenyl)-1,2-benzanthracene (8)
222	222
260	259
271	271
281	281
292	292
322	321
336	336
352	350
365	366

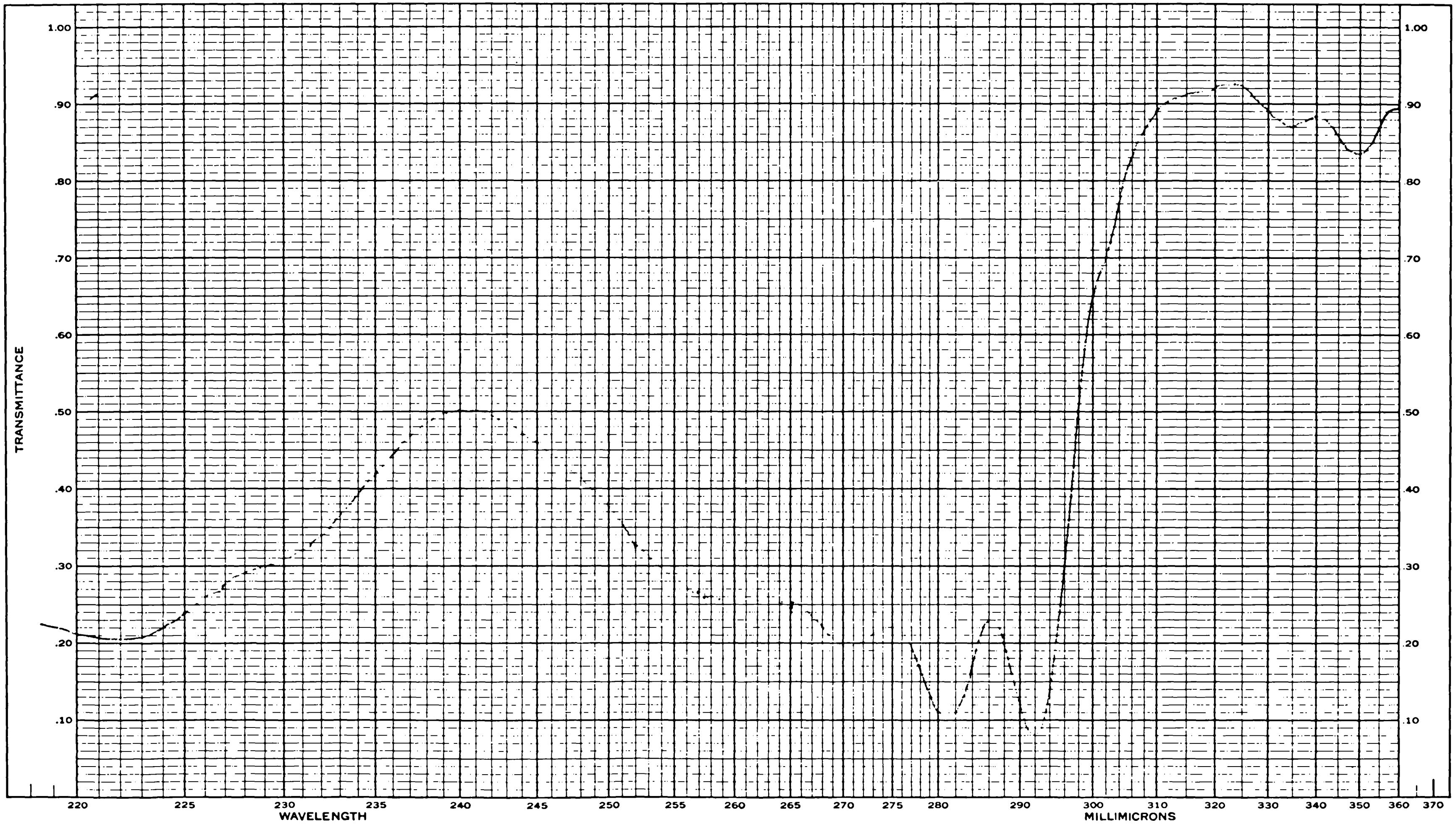
10-(4'-carboxyphenyl)-1,2-benzanthracene (22)	10-(4'-hydroxymethylphenyl)-1,2-benzanthracene
224	222
230	232
257	257
270	270.5
284	281
292	292
330	334
345	349

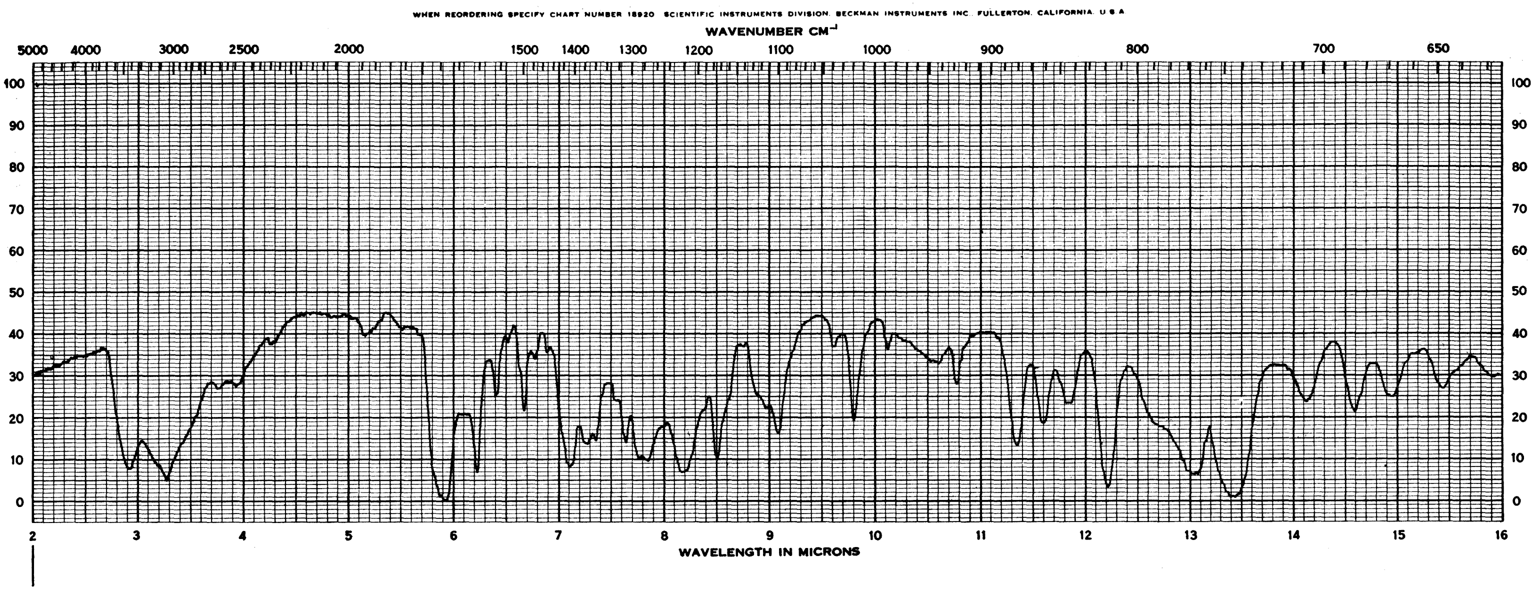
SAMPLE 10 - (4' - hydroxymethylphenyl) - 1, 2 benzanthracene
SOLVENT 95% ethanol
CONC. 10 mg./l
CELL Quartz

SPECTRACORD
WARREN ELECTRONICS INC.

SERIAL NO.
SLIT 2
SCANNING TIME 4
DATE March 20, 1958

U.V. 3991





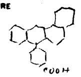
SPECTRUM NO. ______

DATE March 24, 1959

SAMPLE 10 - (4' - carboxyphenyl)
1, 2 - benzanthracene.

SOURCE CIL

STRUCTURE



PATH ______ mm

SOLVENT ______

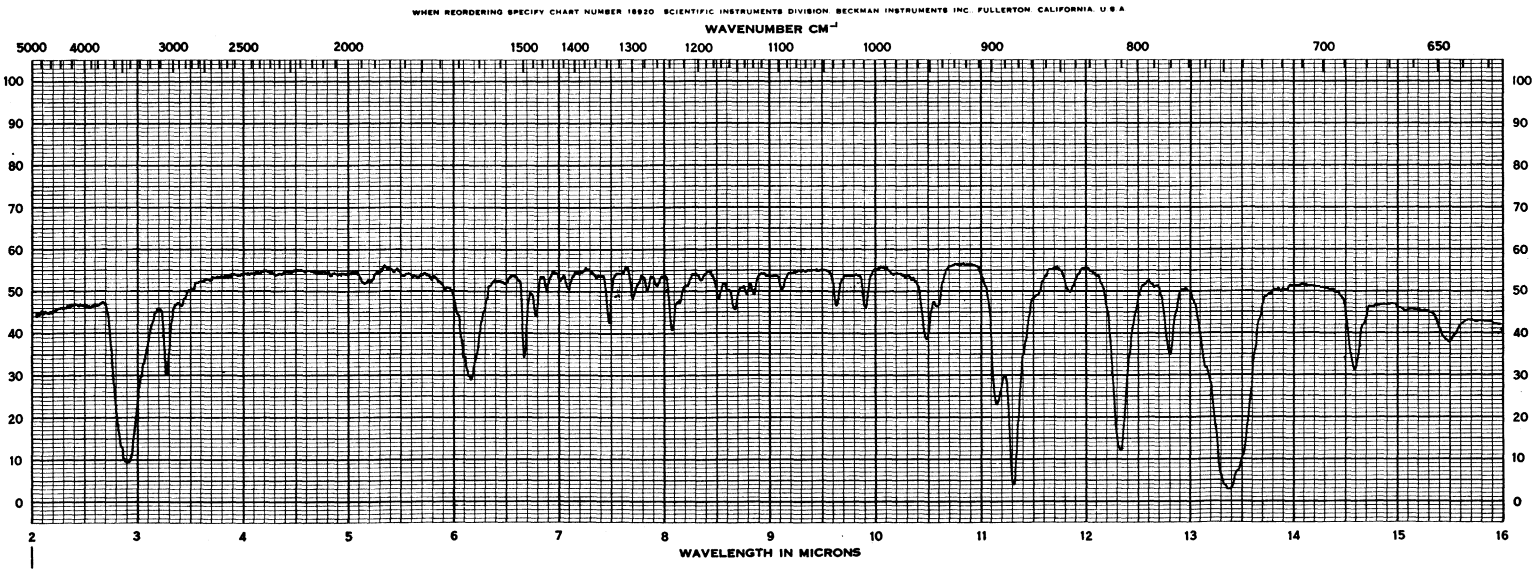
CONCENTRATION 0.45% in KBr

PHASE Solid

COMMENTS ______

ANALYST ______

Beckman
INFRARED
SPECTROPHOTOMETER



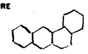
SPECTRUM NO. ______

DATE April 14, 1959

SAMPLE 1, 2 - benzanthracene

SOURCE CIL

STRUCTURE



PATH ______ mm

SOLVENT ______

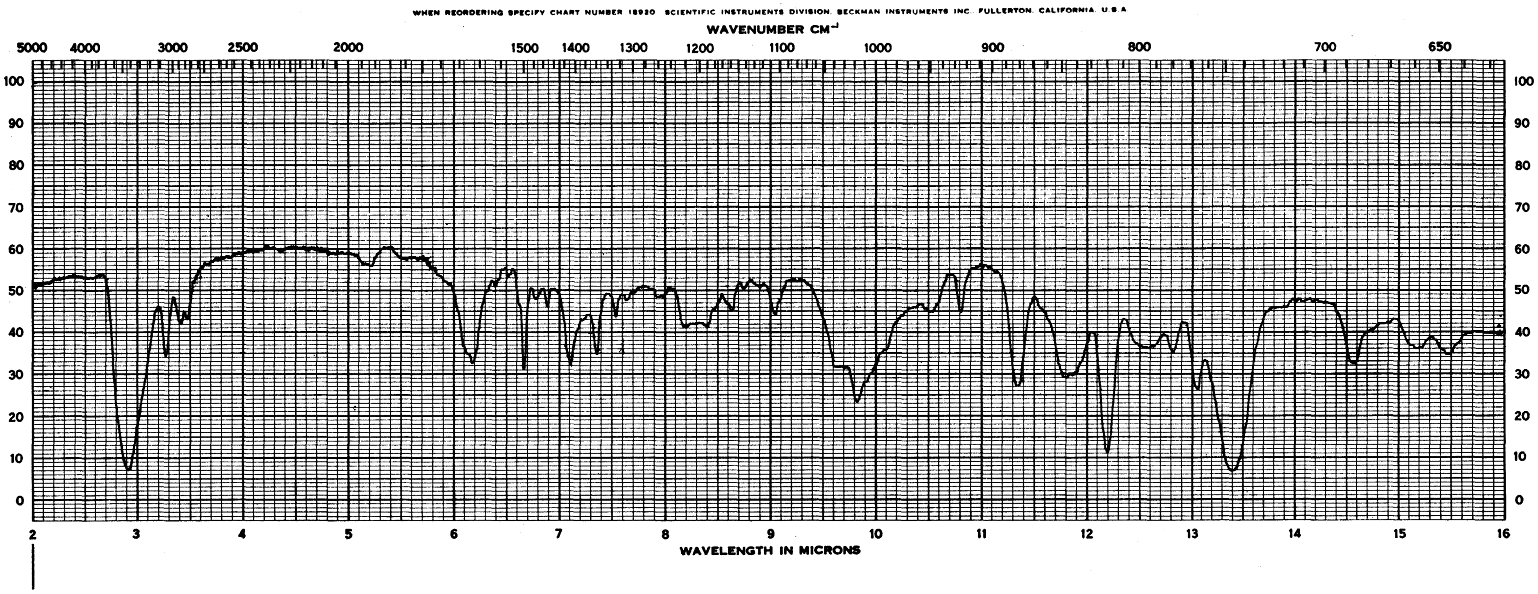
CONCENTRATION 0.33% in KBr

PHASE Solid

COMMENTS ______

ANALYST ______

Beckman
INFRARED
SPECTROPHOTOMETER



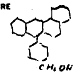
SPECTRUM NO. ______

DATE March 10, 1959

SAMPLE 10 - (4' - hydroxy methylphenyl) - 1, 2 - benzanthracene

SOURCE CIL

STRUCTURE



PATH ______ mm

SOLVENT ______

CONCENTRATION 0.39% in KBr

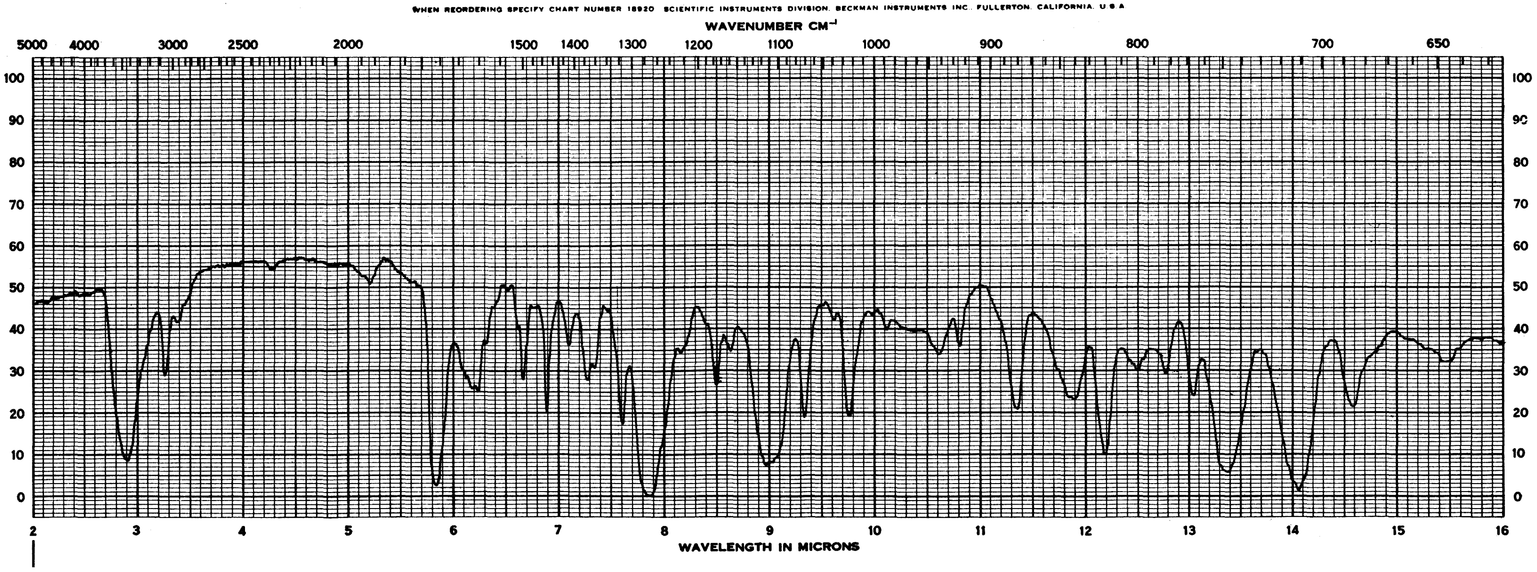
PHASE Solid

COMMENTS ______

ANALYST ______

Beckman

INFRARED SPECTROPHOTOMETER



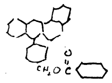
SPECTRUM NO. ______

DATE March 24, 1959

SAMPLE Benzoate of 10 - (4' - hydroxymethylphenyl) 1, 2 - benzanthracene

SOURCE CIL

STRUCTURE



PATH ______ mm

SOLVENT ______

CONCENTRATION .51% in KBr

PHASE Solid

COMMENTS ______

ANALYST ______

Beckman

INFRARED SPECTROPHOTOMETER

THE SYNTHESIS OF 10-(4-HYDROXYMETHYLPHENYL)-1,2-BENZANTHRACENE

The alcohol, 10-(4-hydroxymethylphenyl)-1,2-benzanthracene, a more soluble derivative of 10-phenyl-1,2-benzanthracene, a physiologically active compound, was prepared by the reduction of 10-(4-carboxyphenyl)-1,2-benzanthracene with lithium aluminum hydride.

The structure of the alcohol, 10-(4-hydroxymethylphenyl)-1,2-benzanthracene, was proven by:

1. ultraviolet spectra
2. infrared spectra
3. elementary analysis
4. preparation of a derivative.

In an attempt to prepare the alcohol by the classical method of allowing paraformaldehyde to react with a Grignard reagent difficulty was experienced. The Grignard reagent of 10-(4-bromophenyl)-1,2-benzanthracene could not be prepared using the normal Grignard technique,"entrainment", and iodine-activated magnesium. An explanation of this anomaly was not discovered.

In an attempt to synthesize 10-(4-carboxyphenyl)-1,2-benzanthracene by an alternate method the Grignard reagent of 2-(1-naphthylmethyl)-chlorobenzene was prepared by the use of tetrahydrofuran as a solvent and "entrainment" with methyl iodide.