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Approved by:

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Joseph W. Sawicki

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A COMPARISON OF ACENAPHTHENONE WITH DESOXYBENZOIN IN BASE CATALYZED REACTIONS

A dissertation submitted to the

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by

RICHARD FLEMON NEBLETT

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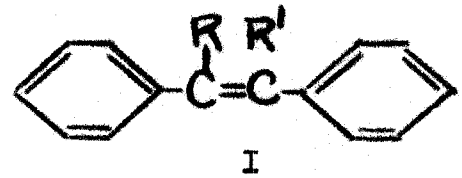
INTRODUCTION

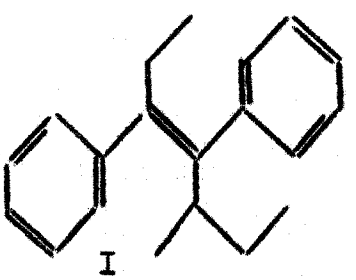
A study of the chemistry of cancer will reveal that this malignancy can be caused by a wide variety of chemical agents. Similarly the compounds which have shown some promise in inhibiting the growth of cancer are also quite varied in structure. Among the compounds which have received attention, either as inhibitors or promoters of this growth, are those derived from the 1,2-diphenylethane structure. The various modifications of this nucleus have led to compounds which may be classified more specifically as alpha-, alpha'-dialkyl stilbenes, 1,2-diphenylethylamines, alpha-dialkylaminodesoxybenzoins, and alpha-dialkylaminomethyl-desoxybenzoins. Reduction of the carbonyl group of the desoxybenzoins has also led to compounds of physiological interest. Despite the fact that the publication of the results of experiments with test animals has been delayed in the case of some of these compounds, the preparation and evaluation of closely analogous compounds should be of interest.

A series of derivatives of stilbene (I, R = R' = H)

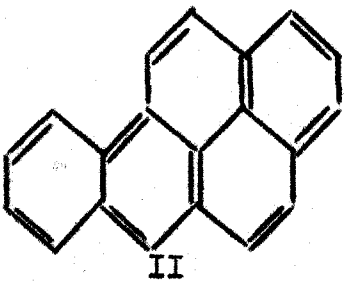


I

has been prepared (1) for testing as possible carcinogenic agents. The carcinogenic activity of one member of the series (I, R = ethyl, R' = sec-butyl) has been reported (2,3).



I

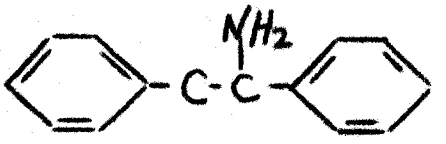


II

After each of two groups of twenty five mice had been painted twice weekly with a 0.3% solution of the compound in benzene, one tumor was developed in one of the surviving members of each group. Seve n of the first group survived after twelve months; thirteen of the second group (albinos) survived after fifteen months treatment. Both tumors were malignant and when portions of that from the albino were transplanted to ten other mice, five of the latte r developed identical tumors after a two months period. One explanation proposed for the carcinogenic activity of this compound is its close similarity to benzpyrene (II) which is well known to be a very active carcinogen.

The structures of some of the compounds which have been synthesized in the search for tumor inhibiting agents are shown on the next page. Compounds III, IV, VII, and VIII are reported to show some inhibiting effect on the growth of tumors (4,5). Although the syntheses of compounds V and IX have appeared (6,7), results of tests with these

compounds are as yet unpublished. Compounds of structure VI are reported to show no activity against tumors (8).



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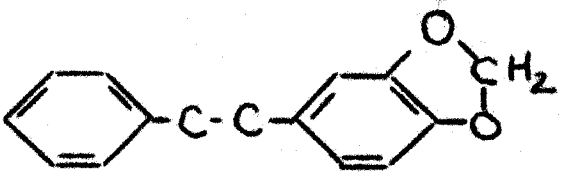
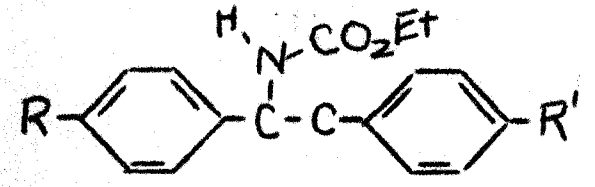
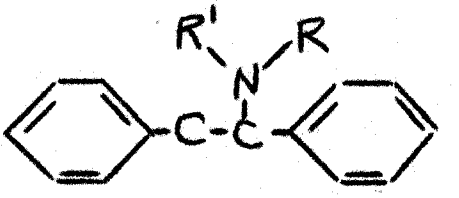


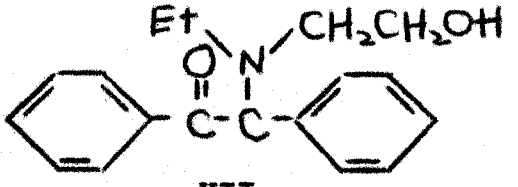
IV



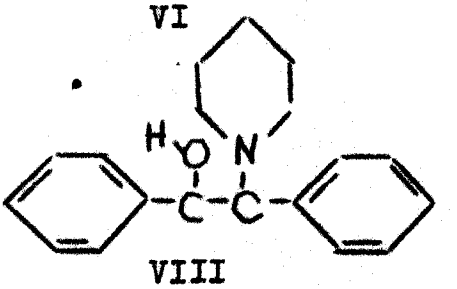
V



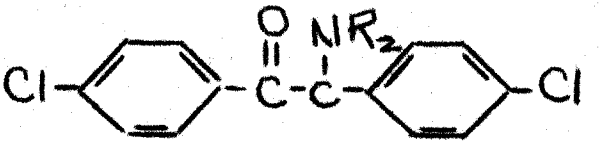
VI



VII

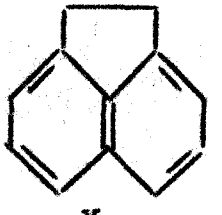


VIII



IX

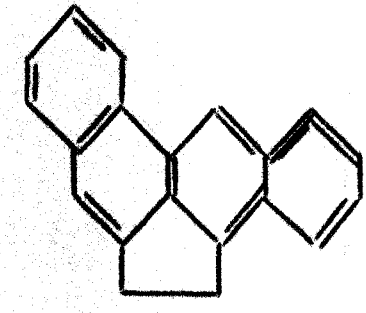
The hydrocarbon, acenaphthene (X), bears a strong structural similarity to 1,2-diphenylethane in that both ends of the aliphatic chain are substituted by an aromatic



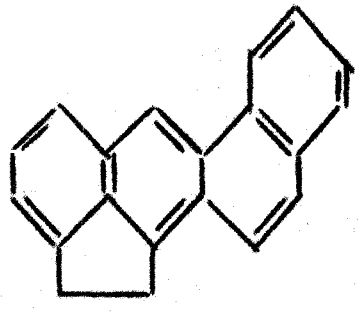
X

nucleus. Because of this similarity, this hydrocarbon might well prove to be an appropriate starting point for the synthesis of compounds analogous to those of carcinogenic interest in the 1,2-diphenylethane series. However, before such a program is begun, it would be pertinent to examine the effect, if any, which acenaphthene has on the production of cancer.

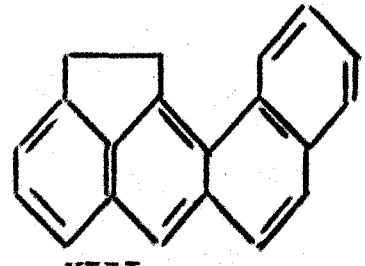
Acenaphthene itself apparently is incapable of producing cancer (9); in fact some experimenters have found that it inhibits slightly the growth of tumors (10) or produces irregular results in their growth (11). However, the acenaphthene nucleus is present in several carcinogenic polynuclear hydrocarbons, e.g. XI, XII, XIII (12,13).



XI



XII

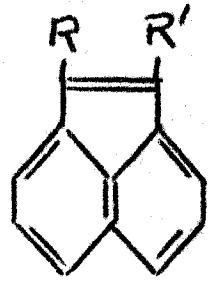


XIII

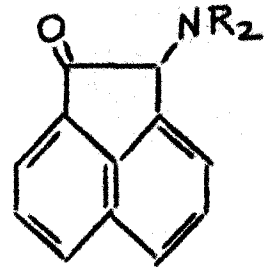
The effect of acenaphthene on plant life is well documented (14-21). It induces polyploidism, i.e., causes the chromosome number to be a multiple of that of the untreated cell. This action is described as being similar to the production of cancer in animals (14). Thus it might be concluded that if acenaphthene itself is non-carcino-

genic, some of its derivatives may be active carcinogens, while others may be able to inhibit the growth of tumors.

We therefore believe that a series of compounds of the structures XIV-XVII would be of interest in the chemistry of cancer. The potential carcinogens are represented by XIV where R may be the same or different from R' since there are contrasting opinions (22,23) concerning the influence of symmetry on carcinogenic activity. Compounds XV and XVI are also of interest in the chemistry of local anesthetics.



XIV



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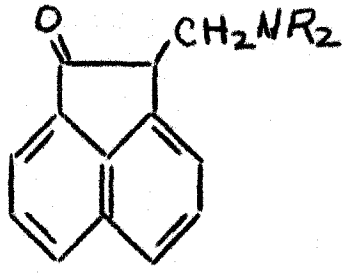
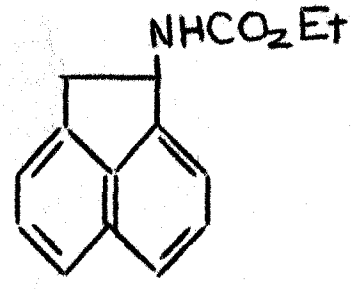


XVI



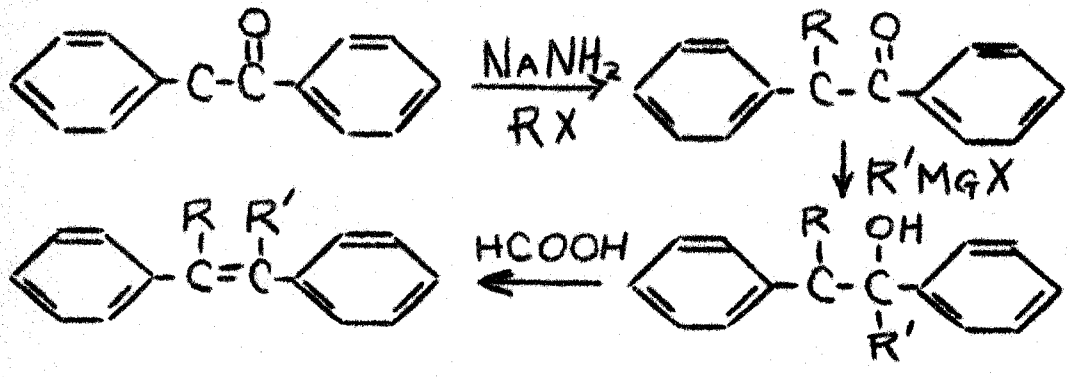
XVII

PROCEDURE AND DISCUSSION

In the introduction we have shown that several types of compounds derived from acenaphthene may be of possible interest in the chemistry of cancer. In an attempt to outline possible modes of preparation of these compounds, we have first examined the methods through which the analogous compounds derived from 1,2-diphenylethane were prepared. From such an examination and from a search of the literature on the chemistry of acenaphthene, we have tried to determine the applicability of previous syntheses to the ones we now propose.

The preparation of the potential carcinogens, the alpha, alpha'-dialkylstilbenes, was accomplished by the series of reactions shown in Flow Sheet I (1).

Flow Sheet I

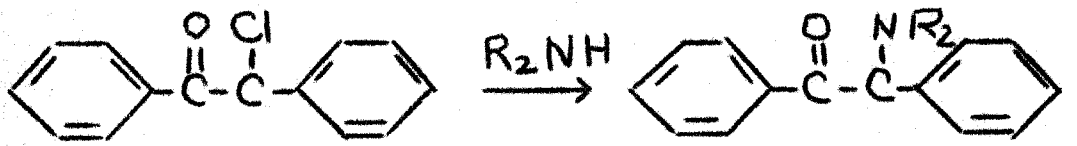


The various potential anti-carcinogens were prepared as outlined on Flow Sheets II-IV.

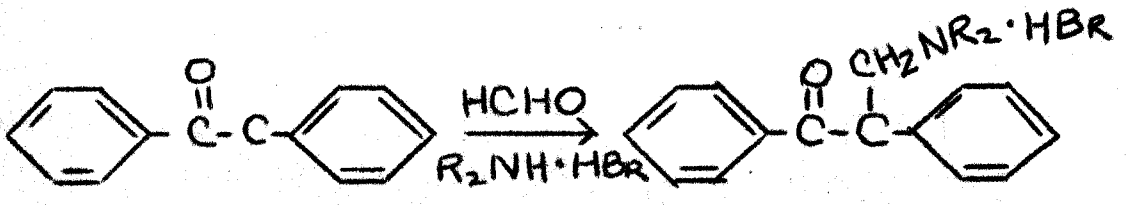
It may be seen from these flow sheets that in order

to conduct an analogous series of preparations with acenaphthene, the intermediates needed are acenaphthenone, an alpha-haloacenaphthenone, and 1-aminoacenaphthene (I-III).

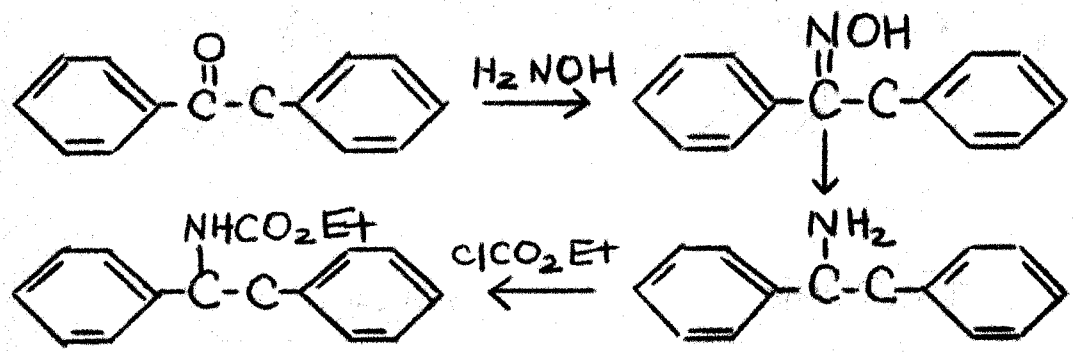
Flow Sheet II (5)

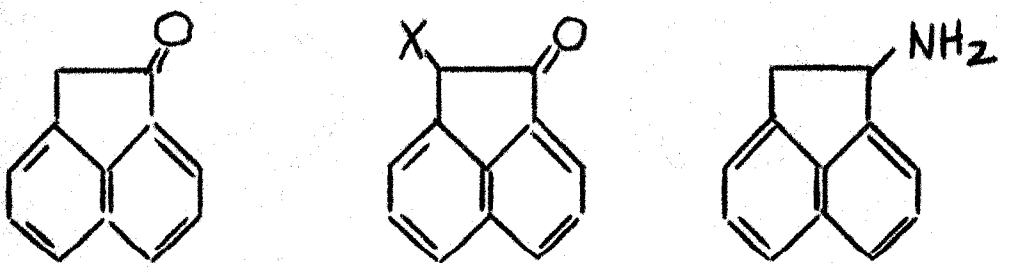


Flow Sheet III (5)



Flow Sheet IV (6)





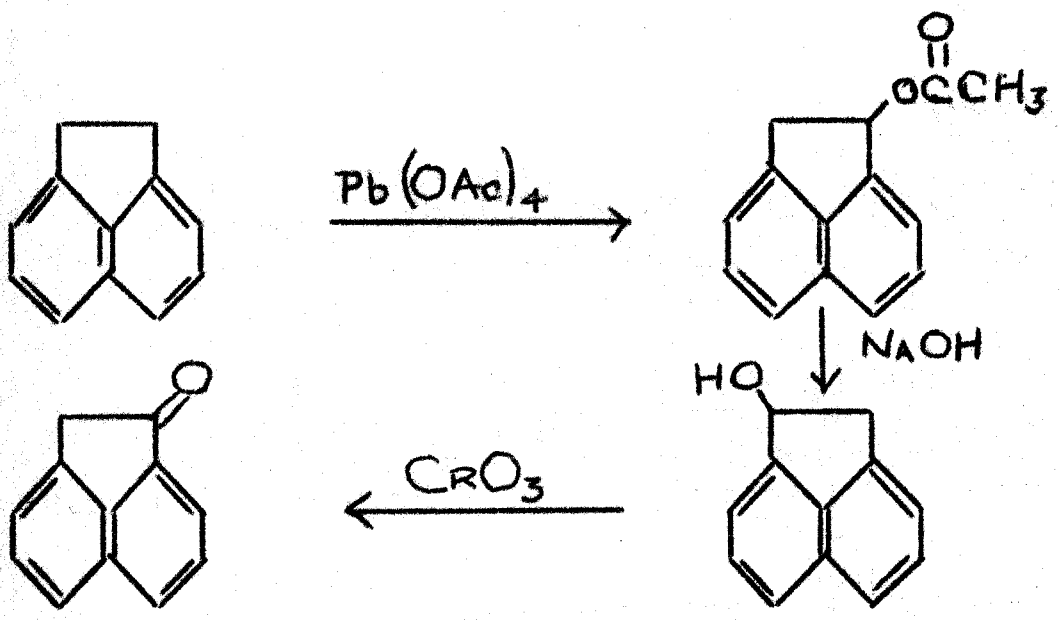
I II III

The chemistry of acenaphthene has been reviewed through 1936 in Elsevier's Encyclopedia of Organic Chemistry,

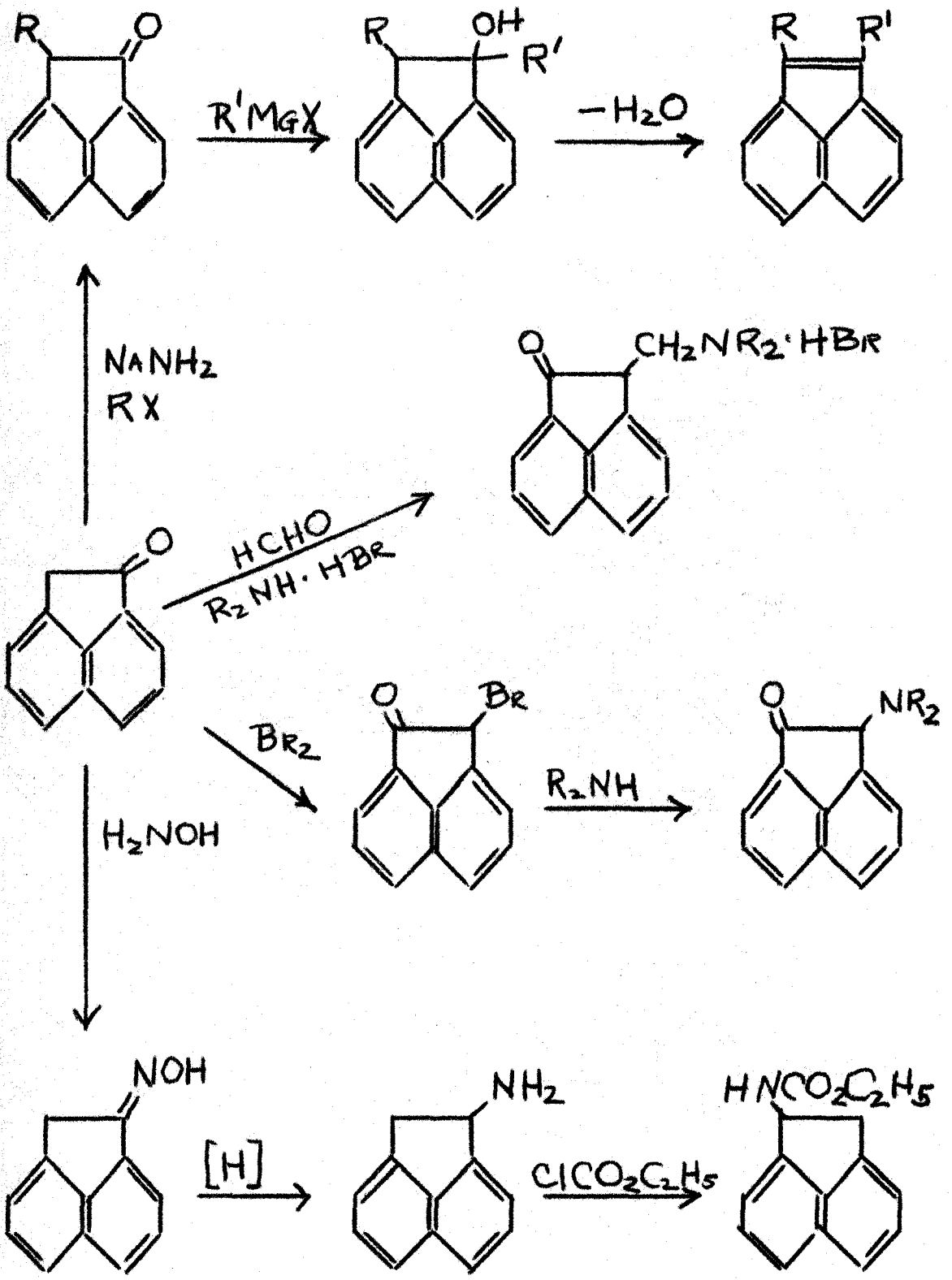
Volume 13. Chemical Abstracts was consulted for work subsequent to that reviewed in Elsevier.

Each of the compounds I-III has been described previously in the literature. Acenaphthenone (I) has been prepared by Fieser and Cason (24,25) as shown on Flow Sheet V. Although 2-chloroacenaphthenone has not been

Flow Sheet V



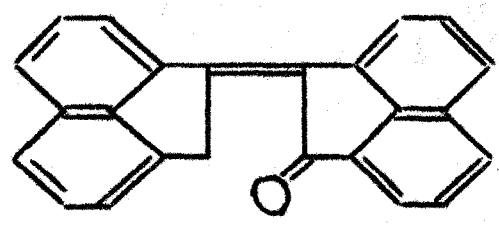
described in the literature, the 2-bromo derivative was prepared by Graebe (26) from equal molar amounts of bromine and acenaphthenone in carbon disulfide. 1-Aminoacenaphthene has been prepared (27), although in only moderate yield, by reduction of the oxime of acenaphthenone. Thus we have available each of the intermediates necessary to perform the desired series of reactions. These reactions are outlined in the flow sheet on the following page.



The literature on the chemistry of acenaphthene gave little additional insight on the probability of the proposed courses of reaction. No alkylation of acenaphthenone has been recorded. The Grignard reaction has been performed on acenaphthenone (24, 27, 28) and on 2-phenylacenaphthenone (prepared by cyclization procedures)(29,30)(31). Each of the workers on the Grignard reaction reported a very facile dehydration to the olefin. Neither the preparation of the urethane, the reaction of 2-bromoacenaphthenone with amines, nor the Mannich reaction with acenaphthenone have been reported. However, acenaphthenone has been reported to condense with formaldehyde to give 2-hydroxymethylacenaphthenone (32).

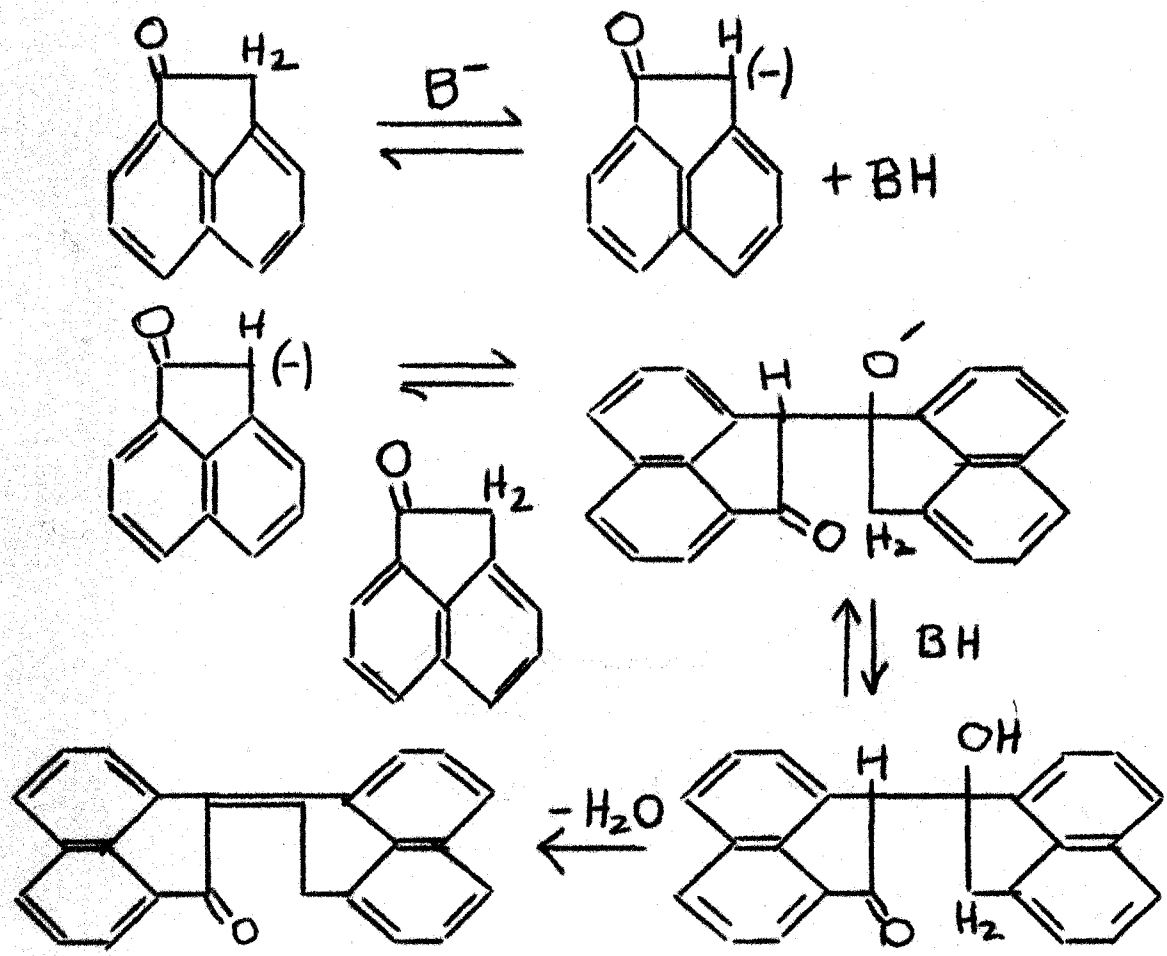
Attempted Preparation of Dialkylacenaphthylenes

Our attempts to alkylate acenaphthenone have met with failure due to the ease with which acenaphthenone condenses with itself in the presence of base to form biacenone (26). After the failure of the alkylation



Biacenone

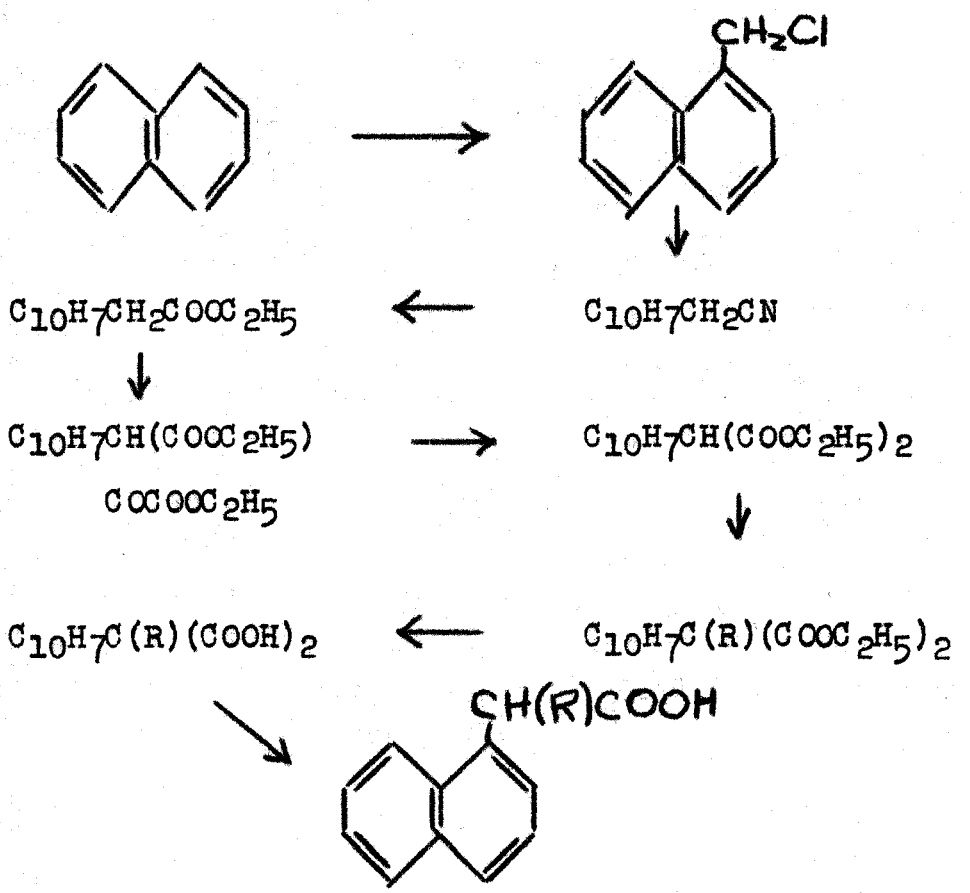
reaction using sodamide, we attempted the reaction using the sodium salt of t-amyl alcohol as the basic constituent. This reagent has been used with success in the alkylation of ketones which condense readily (33). Despite our use of this reagent, biacenone was isolated as the only product of this reaction. Therefore we have concluded that the rate of the condensation reaction is much faster than that in which the anion of the ketone is formed. The condensation reaction goes to completion since a molecule of water is lost irreversibly in the process.



In another approach to the alkylation reaction, we have tried to introduce a carbethoxy group in the desired position before the introduction of the alkyl group. In one procedure (34) the ethyl oxalyl group was introduced first by means of sodium ethoxide and diethyl oxalate; the ethyl oxalyl group was then converted to the carbethoxy group by pyrolysis. By this method we were able to prepare a reddish oil which was not isolated, but which on pyrolysis did not yield the alpha-carbethoxy ketone. An attempt by an established procedure (35) to add the carbethoxy group directly yielded only biacenone. The almost instantaneous formation of biacenone in this reaction, which is conducted in an excess of diethyl carbonate, illustrates the ease with which acenaphthenone condenses with itself. The formation of the dimer to some extent could be expected since it has been shown that carbethoxylation is a reversible reaction in the presence of sodium ethoxide (36) #.

In a work (Duthie and Plant; J. Chem. Soc. 1952, 1899) which appeared after the completion of our experiments in this direction, the authors reported results similar to ours. They isolated the first product after the introductio n of the ethyl oxalyl group and characterized it. In addition they found that formylation was unsuccessful and led only to biacenone.

The third approach to the synthesis of the alpha-alkyl acenaphthenones was the attempted cyclization of a group of alpha-(1-naphthyl)-alpha-alkylacetic acids (34). These acids were prepared by a somewhat long procedure shown on the following flow sheet.



There have been several cyclizations of 1-naphthylacetic acids reported in the literature (37,30,38,39) although the yields were only moderately good. A study (40) of the cyclization of 1-naphthylacetyl chloride in various solvents with aluminum chloride reported the highest yield

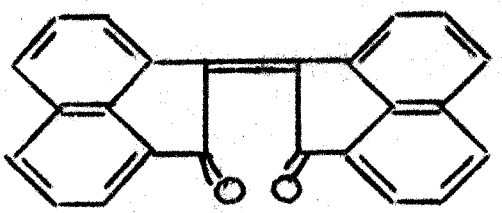
to be 40% in benzene or chlorobenzene. The difficulty in this cyclization may be attributed to the fact that the aliphatic bond resulting from this reaction, i.e. the 1,2-bond in the acenaphthene structure, is stretched considerably beyond the normal carbon-carbon bond distance to a length of 1.8 Angstrom units (41). A very recent work shows that the introduction of a second five-membered ring in the five-six positions of acenaphthene occurs only when the molecule is partially hydrogenated. (42).

We have attempted the cyclization of the 1-methyl- and the 1-ethyl-1-naphthylacetic acids without success. The procedures we used were those involving aluminum chloride thionyl chloride, anhydrous hydrogen fluoride, stannic chloride-thionyl chloride, and stannic chloride-phosphorus pentachloride. In those cases in which a solvent was used benzene was always selected. From each of the reactions only a small amount of base-insoluble material was isolated. It was usually obtained as an oil although it was sometimes caused to solidify. We were unable to obtain a positive ketone test with 2,4-dinitrophenylhydrazine, nor were any of these materials volatile in steam as is acenaphthenone. However, in view of the fact that other cyclizations have been recorded, we feel that further work along this line may be profitable.

Attempted Preparation of alpha-Amino Acenaphthenones

We have met with little success in our attempts to prepare a serie s of alpha-amino ketones from acenaphthenone. Successful large scale preparations of the intermediate, 2-bromoacenaphthenone, were made, although in diethyl ether rather than in carbon disulfide which was used in the first preparation of this compound (26). Desoxybenzoin has also been brominated in ether (43).

The reaction of 2-bromoacenaphthenone with secondary amines, with the possible exception of morpholine, leads almost exclusively to the formation of biacenedione, a dimer described earlier (26) as being formed by the action of alkali on 2-bromoacenaphthenone or by the partial oxidation of acenaphthenone. This reaction occurred in

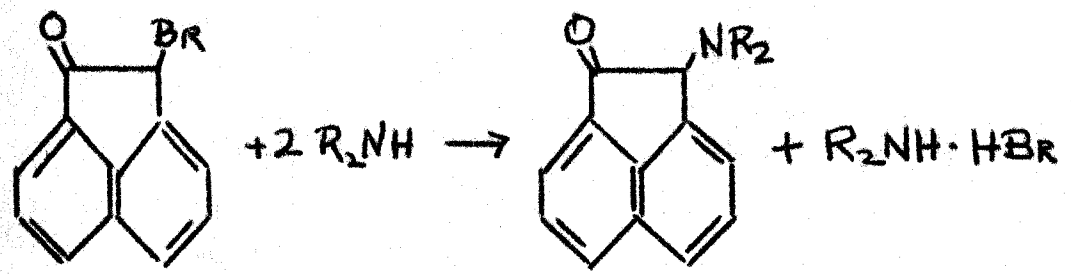


Biacenedione

toluene or acetone solution, in the cold or at reflux temperature, or in the absence of solvent other than excess amine. A similar reaction seems not to have been recorded with desyl chloride.

The formation of this dimer in the reaction mixture is particularly disadvantageous since it not only decreases

the amount of amino ketone formed, but also makes more difficult the isolation of that which is formed. Because two moles of amine are required for complete reaction in the following scheme, each mole of biacenedione formed leaves as a contaminant two unreacted moles of secondary amine. The separation of the salts of the amino ketone



and of the secondary amine is somewhat difficult since they exhibit similar solubilities. Analysis of the product of the reaction in which morpholine was used indicated that this product was a mixture of the two salts with that of the amino ketone predominating. It was not considered advisable to attempt an isolation of the amino ketones as free bases since the oxidation of alpha-amino ketones has been promoted in the presence of base (44).

The Mannich Reaction

The Mannich reaction has been reviewed by Blicke (45). The essential components are a compound containing a hydrogen of marked reactivity, formaldehyde, and an amine usually as the hydrochloride or hydrobromide. Ketones

containing a hydrogen on an alpha carbon are probably the most common source of the active hydrogen compound. Formaldehyde may be employed either as an aqueous solution or as paraformaldehyde. Many amines have been used in this reaction although there are several which are said not to react. Ethyl alcohol is the solvent used most commonly, although iso-amyl alcohol has been used when a higher reaction temperature was desired. The reaction results in the substitution of an aminomethyl group for the active hydrogen atom.

Desoxybenzoin has been shown to react with morpholine hydrobromide, paraformaldehyde, and ethanol to form alpha-phenyl, alpha-(N-morpholinylmethyl)-methyl phenyl ketone.

We have not as yet found the optimum conditions for the Mannich reaction with acenaphthenone. We have conducted a series of experiments in which we have varied the length of the reaction, the solvent, the amines and their salts, and the nature of the formaldehyde. These experiments are summarized in the experimental portion of this paper.

Often we were able to isolate only secondary amine salts as the ether-insoluble products of this reaction, i.e. the materials which should be either the Mannich product or unchanged secondary amine salt. In other cases this ether-insoluble material was not the starting material

but was an amorphous, resinous solid which was high-melting and which was very insoluble in the common solvents. When it was possible to obtain solution in the higher boiling solvents such as glacial acetic acid or dimethylformamide, the material seemed to decompose with the formation of intractable resins. The one encouraging feature in this series of reactions is that the melting points of the crude materials differed when different secondary amine salts were used. Therefore these materials are neither the hydroxymethyl compound formed by the addition to formaldehyde only, nor are they polymers of the olefin formed when Mannich products are pyrolyzed. It is for these reasons that we believe that further experiments on this reaction will lead to the preparation of Mannich products from acenaphthenone in a characterizable state.

Preparation of Ethyl N-(1-Acenaphthenyl)-carbamate

The preparation of the urethane from 1-aminoacenaphthene and ethyl chlorocarbonate occasioned little difficulty. The amine was prepared according to a published procedure (27) by reduction of the oxime of acenaphthenone. Since the free amine is rather difficult to obtain pure, a solution was prepared by neutralizing an aqueous solution of the amine hydrochloride with sodium hydroxide and then

extracting the amine with ether. The ethereal solution was dried over sodium sulfate. Addition of equal molar amounts of pyridine and ethyl chlorocarbonate to the cold solution caused the precipitation of pyridine hydrochloride. After filtration the urethane was isolated by evaporating the solvent. The urethane was recrystallized from ethanol.

Other Reactions

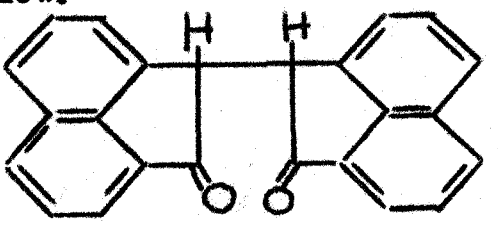
An attempt to apply the Voigt reaction to the unknown 2-hydroxyacenaphthenone led us to develop another procedure for the preparation of 2-acetoxyacenaphthenone, a compound which has been described by Criegee and Klonk (46) who prepared it by the action of lead tetraacetate on acenaphthenone. The yield in this reaction was rather low (18%). The action of lead tetraacetate on ketones has been described by Waters (47) as a rapid, but not very specific, reaction. In an attempt to improve the yield of this product, we applied the method which Barnes and Tulane (48) used on desyl bromide. They treated the alpha-bromo ketone with potassium acetate in glacial acetic acid to obtain benzoin acetate in nearly quantitative yield. Although our yield (55%) is not so good as that obtained with desyl bromide, it nevertheless represents an improvement over the previous method. The chief factor which diminishes the yield is the formation of biacenedione, formed previously

by the action of other bases on 2-bromoacenaphthenone.

The basic hydrolysis of 2-acetoxyacenaphthenone to 2-hydroxyacenaphthenone proved to be more difficult than was expected. Criegee and Klonk (46) have described the formation of molecular complexes of one molecule of an alpha-hydroxy ketone and one molecule of an alpha-diketone when the ester of the alpha-hydroxy ketone is hydrolyzed with base, the alpha-hydroxy ketone being susceptible to oxidation by molecular oxygen under alkaline conditions (44). This reaction apparently occurs in the hydrolysis of 2-acetoxyacenaphthenone since we were able to isolate the alpha-diketone, acenaphthenequinone, from the reaction mixture. Hydrolysis of the acetoxy ketone in acidic media led to tar formation.

When the basic hydrolysis was conducted in the presence of sodium hydrosulfite, a colorless, crystalline precipitate was obtained by recrystallization of the hydrolysis product from glacial acetic acid. Its analysis, however, did not agree with that calculated for 2-hydroxy-acenaphthenone but rather gave an empirical formula of $C_{12}H_{7}O$. Its high melting point (265°, uncorr.) suggested that the molecular formula might be $C_{24}H_{14}O_2$. This is the formula of the sodium hydrosulfite reduction product of biacenedione, 2,2'-biacenaphthenyl-1,1'-dione (49) which has a corrected melting point of 258° and is also colorless and may be recrystallized from glacial acetic acid. Our

hydrolysis product was therefore assigned the structure as shown below.



2,2'-Biacenaphthenyl-1,1'-dione

Since we had not prepared 2-hydroxyacenaphthenone, We could not attempt the Voigt reaction under the conditions described by Lutz et.al. (5). They have also used an alternate method (50) in which the alpha-hydroxy ketone and the primary amine are heated together in benzene and the water formed in the reaction is removed by azeotropic distillation. We have applied the latter reaction to 2-acetoxyacenaphthenone, using two moles of benzylamine so that the ester could be cleaved in the same reaction and perhaps eliminate the necessity of isolating the alpha-hydroxy ketone. Slightly more than the theoretical amount of water was collected in this experiment, indicating that there was also some reaction at the ketone function; the latter reaction has been shown to occur when aromatic amines are used. Analysis of the product of our reaction indicated it to be a mixture of approximately 50% of the aminoketone and 50% of benzylamine (as hydrochlorides).

Comparison of the Reactions of Desoxybenzoin and of Acenaphthenone

The following summary, compiled from the literature and from our experience, lists the similarities and the differences in the reactions of desoxybenzoin and acenaphthenone and their derivatives in a group of reactions pertinent to this research problem.

A. Reactions whose results show the similarities of the two compounds

1. Bromination. The bromination of the alpha position of both compounds proceeds smoothly in ether solution.

2. Conversion of the alpha-bromo ketone to the alpha-acetoxy ketone. Both ketones may be converted to the alpha-acetoxy ketone by potassium acetate in glacial acetic acid solution although with acenaphthenone the yield is lower because of the formation of biacenedione.

3. Dehydration of the alcohols derived through the Grignard reaction. The tertiary alcohols resulting from a Grignard reaction with desoxybenzoin or with acenaphthenone are easily dehydrated to olefins when a hydrogen atom is available on an adjacent carbon atom.

4. Preparation of a urethane from 1-amino-acenaphthene and from 1,2-diphenylethylamine. Both of the

amines react smoothly with ethyl chloroformate to form a urethane.

B. Reactions in which acenaphthenone differs from desoxybenzoin.

1. Alkylation. Although desoxybenzoin has been alkylated after the formation of a sodium salt with sodium amide, the use of this and other basic reagents with acenaphthenone leads almost entirely to the formation of biacenone.

2. Mannich reaction. Although desoxybenzoin undergoes the Mannich reaction with formaldehyde and secondary amine salts, acenaphthenone under a wide variety of conditions either fails to react at all or else gives very insoluble, resinous products.

3. Conversion of an alpha-halo ketone to an alpha-amino ketone. Alpha-chlorodesoxybenzoin has been reacted with a variety of secondary amines to form alpha-amino ketones. With alpha-bromoacenaphthenone, however, reaction with amines leads almost exclusively to the formation of biacenedione.

4. Hydrolysis of the alpha-acetoxy ketone. The hydrolysis of benzoin acetate is said to proceed almost quantitatively. With alpha-acetoxy acenaphthenone oxidation to acenaphthenequinone occurs under the conditions which were successful with benzoin acetate. With alkali and sodium hydrosulfite the reduction product of biacenedione

was isolated.

5. Voigt reaction. The reaction of benzoin and a primary amine in the presence of phosphorus pentoxide to form an alpha-amino ketone proceeds in moderate yield. The reaction also occurs when a solution of the reactants is azeotropically distilled. When a variation of the latter reaction was tried with 2-acetoxyacenaphthenone, the product obtained indicated that the reaction occurred to a lesser extent than with benzoin.

EXPERIMENTAL

A. Attempted preparation of 2-dialkylaminoacenaphthenone hydrochloride

1. Acenaphthene was secured from the Reilly Tar and Chemical Company and was used without further purification.

2. Acenaphthenol acetate was prepared according to Cason (25).

3. Acenaphthenol was prepared according to Cason (25).

4. Acenaphthenone was prepared according to Fieser and Cason (24).

5. 2-Bromoacenaphthenone (26) was prepared in the following manner:

To a suspension of 33.6 g. (0.2 moles) of acenaphthenone in 250 ml. of dry ether at room temperature was added in a slow, steady stream a solution of 33.6 g. (0.21 moles) of bromine in 25 ml. of dry ether. The suspension was stirred vigorously throughout the addition and external cooling was sometimes needed to control the vigor of the reaction. The acenaphthenone dissolved almost immediately with the formation of a nearly colorless solution. Precipitation of 2-bromoacenaphthenone began a few minutes after the addition of bromine was complete. the mixture was stirred for one hour at room temperature and then one hour at 0°. The product was collected by

suction filtration, washed with a little cold, dry ether, and dried in air. This material was used for subsequent preparations. The average yield was 70%. A sample recrystallized from ligroin (b.p. 90°-120°) melted at 112°. From the mother liquors could be recovered about ten grams of a less pure material which was always converted to 2-acetoxyacenaphthenone without purification.

6. The preparation of the 2-dialkylaminoacenaphthenone hydrochlorides was attempted via the following procedures:

Procedure A. To a solution of 12.35 g. (0.050 moles) of 2-bromoacenaphthenone dissolved in 150 ml. of dry toluene at room temperature was added 0.10 moles of amine. The solution became dark and precipitated a mixture of the secondary amine hydrobromide and biacenedione. The reaction mixtures were permitted to stand for two hours and were then diluted with 50 ml. of dry ether. The solid products were collected by suction filtration. Acidification of the filtrate with an ethereal solution of hydrogen chloride precipitated the soluble basic products of the reaction. These were collected by suction filtration and recrystallized from a 50% mixture of glacial acetic acid and iso-propyl ether. Biacenedione, which is water insoluble, was isolated from its mixture with amine hydrobromide precipitated from the original reaction mixture by dissolving the amine hydrobromide in hot water. The

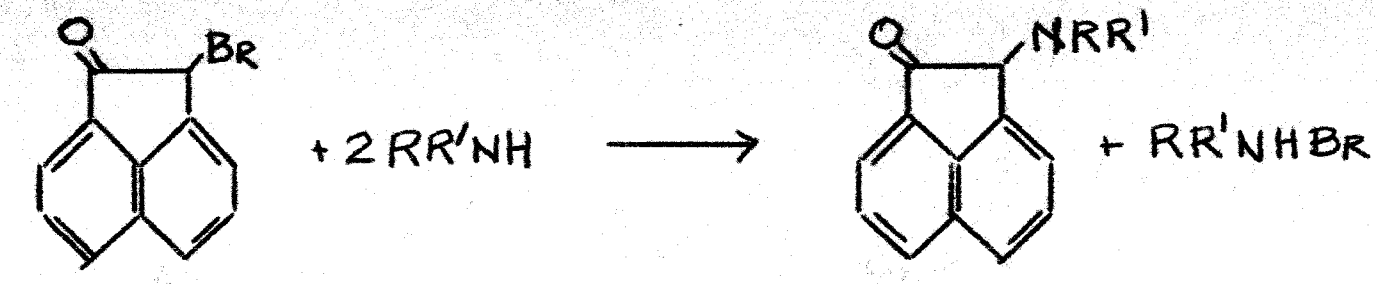
results of this series of reactions are summarized in Table I.

Procedure B. This procedure is patterned after that of Lutz et. al. (5). The results of this series of reactions are summarized in Table II.

To 6.18 g. (0.025 moles) of 2-bromoacenaphthenone contained in a 50 ml. Erlenmeyer flask were added 0.075 moles of secondary amine at room temperature except as indicated in the table. After standing from one to three hours, the mixtures were triturated with ether and then with water. The ether layers were washed with water after filtration from the biacenedione formed in the reaction. The ether extracts were dried over sodium sulfate, filtered, and acidified with an ethereal solution of hydrogen chloride. The solid products were recrystallized by dissolving them in hot ethanol, clarifying the solution with charcoal, filtering, and precipitating with dry iso-propyl ether.

Procedure C. To a solution of 12.35 g. (0.050 moles) of 2-bromoacenaphthenone in 200 ml. of dry, boiling acetone was added dropwise 0.10 moles of secondary amine in 25 ml. of acetone. After one half hour the solution was concentrated to 50 ml. and 100 ml. of iso-propyl ether was added. After the solution had cooled, the precipitated amine hydrobromide and biacenedione were collected by suction filtration. The filtrate was treated with dry hydrogen chloride and the precipitate was collected. In

Table I



R R'NH				(3)	
structure	wt. used	(1)	(2)	weight	m.p. °C
diethylamine	7.31 g.	12.85 g.	5.65 g.	4.90 g.	230-2
piperidine	8.52 g.	10.6 g.	2.3 g.	9.0 g.	241-2 (4)
morpholine	8.71 g.	7.95 g.	trace	12.55 g.	193-4 (4)
dimethylamine	5.0 g.(5)	8.65 g.	1.70 g.	2.1 g.	270 (4)
dicyclohexylamine	18.1 g.	11.3 g.	trace	14.3 g.	334 (4)
diethanolamine	10.5 g.	oil	6.5 g.	---	---

(1) weight of solid precipitated from reaction solution

(2) weight of biacenedione isolated

(3) solids precipitated from reaction solution with dry hydrogen chloride

(4) recrystallized from glacial acetic acid and iso-propyl ether

(5) 13.7 g. of 2-bromoacenaphthenone used

Table II

amine	wt. of amine used	wt. biacene-dione found	aminoketone hydrochloride Wt.	aminoketone hydrochloride m.p. °C	remarks
piperidine	6.38 g.	4.65 g.	0.14 g.	241-245	(1)
morpholine	6.53 g.	4.27 g.	0.56 g.	200 d.	(1)
diethylamine	5.48 g.	3.6 g.	-----	225-227	(1,2)
diethanolamine	7.9 g.	4.85 g.	oil	-----	(3)
ethyl ethanolamine	6.68 g.	4.45 g.	oil	-------	(6)
phenyl ethanolamine	10.3 g.	----	oil	-----	(4)
dicyclohexylamine	13.6 g.	-----	4.33 g.	± 310	(5)

(1) Mixture became very warm; cooling necessary

(2) Explosive when confined

(3) Warmed on the steam plate for a few minutes

(4) no biacenedione isolated

(5) Mixture solidified and was difficult to dissolve

(6) Ethyl ethanolamine courtesy the Carbide and Carbon Chemicals Company

those cases when the precipitate was oily, it was digested with 100 ml. of dry ethanol to induce crystallization. The mother liquors were concentrated to obtain additional product. The total solids obtained after the hydrogen chloride treatment were recrystallized by dissolving them in ethanol, clarifying the hot solutions with charcoal, filtering, and adding iso-propyl ether to the filtrate until precipitation began. The results of this series of reactions are summarized in Table III.

Table IV summarizes the analytical data on the products of the reactions described above.

B. Mannich reactions

The following paragraphs describe the general procedures followed in our attempts to perform the Mannich reaction with acenaphthenone. Table V should be consulted for the details of the reactions, i. e., the reactants, their proportions, the solvent, the time of reaction, and the melting points of the materials isolated.

Procedure A. A mixture of acenaphthenone, formaldehyde, and secondary amine salt was dissolved in the solvent and then refluxed for the desired period. Mineral acid was added when paraformaldehyde was used in order to aid in the depolymerization of this reagent. A gummy precipitate was often visible in the reaction mixture. After the reaction had proceeded for the desired length of time, the

Table III

Amine	wt. of amine used	wt amine hydrobromide formed	aminoketone-hydrochloride wt.	aminoketone-hydrochloride m.p.	m.p. amine· HCl
piperidine	8.5 g.	8.05 g.	3.15 (3)	215-217 (2) 238 (3)	237 d.
diethylamine	8.75 g.	8.75 g.	-------	-------	228-9
dicyclohexylamine	18.1 g.	13.85 g.	11.0 (2)	325-330 (2) 334 (3)	300-315
ethyl ethanolamine	8.9 g,	9.0 g.	0.80 (3)	208-213 (2) 241-3 (3)	170
morpholine	8.7 g.	8.25 g.	10.75 (2)	192-194 (2) 195-6 (3)	175
dimethylamine	5.0 g. (1)	4.90 g.	-------	--------	170-171
diethanolamine	10.5 g.	oil	------	-------	-----

(1) 9.35 g. 2-bromoacenaphthenone and 150 ml. of acetone used

(2) crude

(3) recrystallized

Table IV

Analytical Data - Preparation of Amino Ketone Hydrochlorides

Amine	Procedure	m.p. amino-ketone hydro-chloride (1)	m.p. amine hydrochlo-ride (2)		Analyses (%) Calculated for (1)	(2)	Found
Piperidine	A	241-2	237 d.	C	77.3	49.5	48.94
				H	6.82	9.88	9.96
				N	5.30	11.5	11.35
Morpholine	A, C	195-6	175	C	72.2	38.9	65.73
				H	6.02	8.1	5.90
				N	5.26	11.3	4.72
Dicyclohexylamine	C	334	300-15	C	75.0	66.0	65.74
				H	7.81	11.0	11.24
				N	3.65	6.42	6.41
Dimethylamine	A	270	170-1	C	67.7	29.4	72.72
				H	5.65	9.8	3.86
				N	5.65	17.2	0.0
Ethyl ethanolamine	C	241-3	170	C	65.8	38.3	85.11
				H	6.16	9.55	4.34
				N	4.79	11.2	0.0

mixtures were diluted with acetone or ether, washed with a small amount of water to remove unchanged secondary amine salts, and then recrystallization of the gummy products was attempted. These products were nearly insoluble in alcohol and the use of higher-boiling solvents such as glacial acetic acid or dimethylformamide led to increased gum formation. Melting points of the resulting products were taken and recorded if a definite range was observed. Some of the materials exhibited some solubility in chloroform, but dilution of these solutions with alcohol, acetone, or ether failed to give a crystalline product.

Procedure B. A mixture of 0.050 moles of acenaphthenone, 0.10 moles of paraformaldehyde, and 0.050 moles of secondary amine hydrobromide was refluxed with 2½ ml. of concentrated hydrobromic acid in 50 ml. of absolute ethanol. After four hours reflux one gram of paraformaldehyde was added and this addition was repeated after eight hours reflux. The mixtures were refluxed for a total of 21-24 hours and then were diluted with 200 ml. of hot acetone. Only the reaction with dicyclohexylamine hydrobromide gave an appreciable amount of precipitate on cooling. This precipitate proved to be unreacted dicyclohexylamine hydrobromide. After filtration from any precipitate which had formed on cooling, the solutions were concentrated and diluted with ether. This caused the precipitation of oils in most cases. These oils were

crystallized by dissolving them in glacial acetic acid, concentrating these solutions until the temperature of the distillate was 115° or higher, and then diluting the residue with iso-propyl ether. A comparison of their melting points indicated that these precipitates were largely unreacted secondary amine hydrobromides.

C. Attempted preparation of substituted acenaphthylenes

1. Attempts to alkylate acenaphthenone

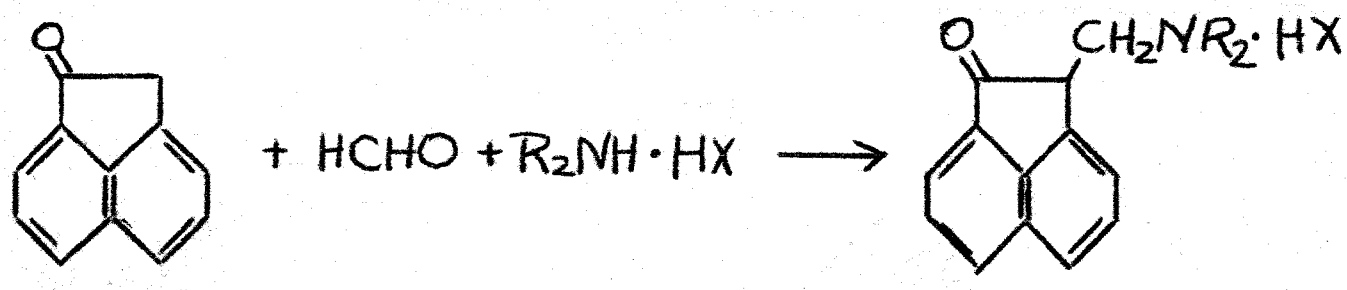
The following paragraphs describe our attempts to alkylate acenaphthenone. The references are to typical procedures after which our experiments are patterned.

(a). (51) A mixture of 3.36 g. (0.02 moles) of acenaphthenone and 0.80 g. (0.0205 moles) of sodium amide in 25 ml. of dry benzene was refluxed until the evolution of ammonia had nearly ceased. During this period the solution turned dark red in color and later deposited a reddish solid. The reaction was interrupted after four hours, water was added, the solid was collected and recrystallized from toluene. It crystallized in yellow needles which melted at 262° and was identified as biacenaphthenone (26).

(b). (33) To a solution of 3.36 g. (0.02 moles) of acenaphthenone and 1.57 ml. (0.02 moles) of ethyl bromide in 50 ml. of benzene was added 0.02 moles

Table V

Mannich Reactions with Acenaphthenone



Procedure A.

Amine	HX	Solvent	Molar ratio to Acenaphthenone HCHO	Molar ratio to Acenaphthenone $R_2NH \cdot HX$	Time (hrs.)	Product m.p. °C	Notes
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Dimethylamine	HCl	EtOH	2	1	2	-----	
"	"	i-AmOH	2	1	4	-----	
"	"	"	2	1	23	-----	
"	"	EtOH	2	1	23	-----	
"	"	"	2	1	1	255-6	
"	"	none	2	1	1	120, 276-9	at 150°
"	"	EtOH	2	1	24	170-2 188-210	
"	"	i-AmOH	2	1	2	200-215	

Table V (continued)

Mannich Reactions with Acenaphthenone

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Dime thylamine	HCl	EtOH	2	1	1	-----	
Piperidine	"	"	2	1	2	-----	
"	"	"	2	1	6½	249	
"	"	"	2	1	48	-----	at room temp.
"	"	"	2	1	2	278-9	
"	"	"	2	1	24	175-240	
"	"	HOH	1	1	48	235-245 -----	
"	"	i-AmOH	2	1	2	235-265	
"	"	"	2	1	24	250-265	
"	HBr	EtOH	2	1	2½	262-263	
"	---	HOAc	2	1	3	------	
"	---	EtOH	2	1	8½	-----	
"	---	"	2	1	48	-----	aqueous HCHO at room temp.
Dicyclohexylamine	HCl	EtOH	2	1	2¼	336	
"	"	i-AmOH i-AmOH	2	1	3¼	330	

Table V (continued)

Mannich Reactions with Acenaphthenone

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Ammonia	HCl	EtOH, HOH	2	1	2	-----	
Diethylamine	HCl	EtOH	2	1	2¼	225-260	
"	"	"	2	1	8	205-225	
"	"	i-AmOH	2	1	2	243-253	
"	"	HOAc	2	1	½	240-244	
Morpholine	"	EtOH	2	1	1	255-	
"	"	"	2	1	24	237-238	
"	"	"	1	1	2½	238-240 225-260	(pptd.)
"	"	"	1	1	2½	175-267 -255	(by dil'n.)
"	"	"	1	1	½	175 180-264	recryst'd.
"	"	MeOH	1.1	1	2¼	267-269	
"	"	i-AmOH	2	1	2	244-247	
"	"	EtOH, HOH	2	1	2	-----	aqueous HCHO
"	"	EtOH	1/5	1/5	2 3/4	252	
"	"	none	1/5	1/5	3	249-252	recryst'd.

Table V (continued)

Mannich Reactions with Acenaphthenone

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Morpholine	HOAc	EtOH	1	1	4	oil	
Procedure B.							
Morpholine	HBr	EtOH	3 1/3	1	4	214-220	
Dicyclohexylamine	"	"	3 1/3	1	24	325-330	
Morpholine	"	"	3 1/3	1	24	166	
Piperidine	"	"	3 1/3	1	21	240-242	
Dimethylamine	"	"	3 1/3	1	24	------	
Diethylamine	"	"	3 1/3	1	22	157-175	

of the sodium salt of t-amyl alcohol in toluene (52). The cold solution turned a brilliant red. It was refluxed for five hours and then neutralized with dilute hydrochloric acid. The organic layer was separated and dried over sodium sulfate. Evaporation of this solution gave biacenone. The use of ethyl iodide in this procedure gave the same results.

(c). To a suspension of 0.80 g. of sodium amide in dry ether at 0° was added, over a period of two hours, an ethereal solution of 3.36 g. (0.02 moles) of acenaphthenone. No color developed during this addition. When the solution was warmed to room temperature, it became deep red in color. Then 3.12 g. (0.02 moles) of ethyl iodide was added and the mixture was stirred at 0° for two hours. After stirring the mixture from 12 to 14 hours and allowing the temperature to rise to that of the room, we then refluxed it for one hour. The mixture was hydrolyzed with dilute hydrochloric acid and filtered from a yellow precipitate. This solid, after recrystallization from chloroform, melted at 262° and was identified as biacenone.

(d). To a toluene solution of 2.2 g. (0.025 moles) of the sodium salt of t-amyl alcohol was added dropwise, over a two hours period, a solution of 3.36 g. (0.02 moles) of acenaphthenone in benzene. After the addition of 6.24 g. (0.04 moles) of ethyl iodide, the solution

was refluxed for one hour. After the usual acidification, extraction, and drying, biacenene was the only product isolated.

(e). The use of sodium ethoxide for the basic component in the reaction yielded biacenone as the only isolable product.

2. Attempts to carbethoxylate acenaphthenone

(a). (34) To a solution of sodium ethoxide prepared from 2.3 g. (0.10 moles) of sodium in 50 ml. of ethanol was 15 g. (0.13 moles) of diethyl oxalate and 16.8 g. (0.10 moles) of acenaphthenone. A yellow solid precipitated almost immediately. The mixture was heated to reflux and then the heat was removed. After cooling, the mixture was hydrolyzed with dilute sulfuric acid. A heavy, reddish oil was extracted with ether and the extracts were dried over sodium sulfate. After removal of the solvent, four grams of powdered glass were added and the residue was heated at 175° for one hour under a pressure of 15 mm. of mercury. The residue was then distilled under a pressure of 3 mm. with the bath temperature gradually being raised to 300°. A small amount of yellowish solid was collected and recrystallized from aqueous ethanol. It melted at 121° and did not depress the melting point when mixed with an authentic sample of acenaphthenone.

(b). (35,36) Dry sodium ethoxide was prepared by dissolving 2.4 g. (0.105 moles) of sodium in

40 ml. of dry ethanol and then removing the solvent under reduced pressure. A solution of 16.8 g. (0.10 moles) of acenaphthenone in 84 ml. of diethyl carbonate was added. The mixture became very viscous and stirring was stopped. The mixture was treated with ice water and hydrochloric acid. After extraction with benzene, drying of the extracts over sodium sulfate, and removal of the solvent, a yellow solid remained. After recrystallization from chloroform the solid was identified as biacenone, m.p. 262°.

3. Attempted cyclization of alkylated 1-naphthylacetic acids

The required acetic acids were prepared by the method described by Blicke and Feldkamp (34).

Procedure 1. This procedure is essentially that of Bachmann and Sheehan (37). An acid chloride was prepared by dissolving 10 g. (0.0466 moles) of alpha-(1-naphthyl)-butyric acid in 30 ml. of dry ether and 10 ml. of redistilled thionyl chloride. Five drops of pyridine were added and the mixture was permitted to stand at room temperature for one half hour. The solvent was removed at reduced pressure, 15 ml. of dry benzene were added, and this was also removed under reduced pressure. The residue was extracted with 250 ml. of dry benzene and the solution was cooled to 0°. Fifteen grams of aluminum chloride were added and the mixture was permitted to stand for one hour at room temperature as the solution darkened and hydrogen

chloride was evolved. The suspension was hydrolyzed with ice and concentrated hydrochloric acid. The benzene solution was dried over sodium sulfate after being washed with ammonia and water. After removal of the solvent, the residual oil did not crystallize.

When this preparation was repeated, the oil was induced to crystallize by trituration with petroleum ether. After recrystallization from ligroin, it weighed one gram and melted at 115-116° but failed to give a positive test with 2,4-dinitrophenylhydrazine.

Two trials of this procedure with alpha-(1-naphthyl)-propionic acid did not yield a crystalline product. When the oils were steam distilled and nine liters of distillate were collected, concentration of the ethereal extracts of this distillate gave a small amount of solid which melted at 145°. This solid did not give a positive test with 2,4-dinitrophenylhydrazine.

Procedure 2. Ten grams (0.05 moles) of alpha-(1-naphthyl)-propionic acid were dissolved in 100 g. (5.0 moles) of anhydrous hydrogen fluoride. After the hydrogen fluoride had evaporated, the residual solid was extracted with sodium hydroxide solution to leave only a very small amount of alkali-insoluble material. Recrystallized from benzene and ligroin, this solid melted at 137-138°.

Procedure 3. To the acid chloride from 10 grams (0.05 moles) of alpha-(1-naphthyl)-propionic acid, prepared as before with thionyl chloride, was added 150 ml. of benzene and then two equivalents (26 g.) of stannic chloride dissolved in 50 ml. of benzene. Reaction was allowed to occur during 15 minutes at 0°. After hydrolysis with ice and hydrochloric acid, the organic layer was washed with water, sodium carbonate solution, with water again, and then was dried over sodium sulfate. After evaporation of the solvent, the tarry residue could not be crystallized.

When the acid chloride was prepared using phosphorus pentachloride and then treated with stannic chloride (53), the oil obtained after the usual isolation procedure could not be crystallized. Most of the starting material was obtained from the alkaline extract.

Steam distillation of the combined preparations in this procedure gave only a trace of solid material.

D. Preparation of ethyl N-(1-acenaphthenyl)-carbamate

To a dry ethereal solution of 1-aminoacenaphthene isolated from an aqueous solution of 12 g. (0.053 moles) of 1-aminoacenaphthene hydrochloride made basic with sodium hydroxide were added 4.6 g. (0.053 moles) of dry pyridine and 6.31 g. (0.053 moles) of redistilled ethyl chloroformate. There was an immediate precipitation of

pyridine hydrochloride. The mixture was allowed to stand at room temperature for one hour. The pyridine hydrochloride was collected by suction filtration, washed with ether, and the combined ethereal solutions were evaporated to dryness on the steam plate. The solid from the evaporation was recrystallized from ethanol in the form of colorless needles which melted at 161°. Concentration of the mother liquors yielded an additional quantity of material. The total yield was 3.4 g. (31%).

Analysis. Calculated for $C_{15}H_{15}ON$: C, 74.6; H, 6.22; N, 5.80.

Found: C, 74.02; H, 6.19; N, 5.79.

E. Other Preparations

1. 2-Acetoxyacenaphthenone (4) was prepared in a manner similar to the preparation of benzoin acetate by Barnes and Tulane (48). A solution of 60 g. (0.243 moles) of 2-bromoacenaphthenone in 300 ml. of glacial acetic acid was refluxed with 65 g. (0.66 moles) of freshly fused potassium acetate for thirty minutes. The solution was cooled and poured into a large volume of water. The mixture was extracted with benzene. An orange solid which was not readily soluble in cold benzene was separated from the water layer and identified as biacenedione, m.p. 295°(26). The benzene extracts were dried over sodium sulfate, the solvent was removed, and the residue was distilled under

vacuum. Trituration of the heavy, viscous distillate with petroleum ether, b.p. 30-60°, induced crystallization to a nearly colorless solid. Recrystallization of this solid from methanol gave colorless crystals which melted at 94-95° #. The yield of recrystallized product was 30 g. (55%).

In one preparation of 2-acetoxyacenaphthenone by this method, recrystallization of the distilled product from ligroin gave as the first precipitate a brilliant red compound of undetermined structure. It was recrystallized from glacial acetic acid in the form of brilliant red needles which melted at 248-249°. When treated with alcoholic potassium hydroxide and then neutralized with hydrochloric acid, an alcoholic solution of the red compound gave an orange compound which melted at 237-238° after recrystallization from glacial acetic acid and water. The red compound decolorized dilute permanganate and also decolorized a solution of bromine in chloroform.

Analysis of red compound: C,88.86; H,4.37.

2. The preparation of 2-hydroxyacenaphthenone was attempted by alkaline hydrolysis of 2-acetoxyacenaphthenone. To a solution of 5.65 g. (0.025 moles) of 2-acetoxyacenaphthenone in 50 ml. of methanol was added 1.50 g. of

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Criegee and Klonk (46) reported a melting point of 71-72°.

sodium hydroxide in 10 ml. of water. The mixture was refluxed for one hour and then poured into water. The greenish solid was collected, dried, and recrystallized from glacial acetic acid. It was yellow in color, melted at 241°, and was identified as acenaphthenequinone when it did not depress the melting point of an authentic sample (54).

When the hydrolysis was conducted with one gram of sodium hydrosulfite in addition to the sodium hydroxide, the solid isolated was colorless, and after recrystallization from ethyl acetate and then from aqueous acetic acid, it melted at 264-265°. Its analysis was that of 2,2'-biacenaphthenyl-1,1'-dione (49).

Analysis. Calculated for 2-hydroxyacenaphthenone ($C_{12}H_8O_2$): C,78.3; H,4.35.

Calculated for 2,2'-biacenaphthenyl-1,1'-dione ($C_{24}H_{14}O_2$): C,86.2; H,4.19.

Found: C,85.8; H,4.43.

3. Formation of 2-benzylaminoacenaphthenone hydrochloride. To a solution of 11.3 g. (0.050 moles) of 2-acetoxyacenaphthenone in 100 ml. of dry benzene (the solution was dried by azeotropic distillation) was added 11 ml. (0.10 moles) of benzylamine. The mixture became very dark on refluxing and the water formed in the reaction was collected in a Stark and Dean trap. Slightly less than

one ml. of water was collected. After refluxing for 1½ hours the reaction had apparently ceased. The solution was filtered and acidified with hydrogen chloride in dry ether. The precipitate was collected by filtration and recrystallized from glacial acetic acid and ether in the form of light yellow needles which melted at 218° after several such recrystallizations.

Analysis. Calculated for 2-benzylaminoacenaphthenone hydrochloride ($C_{19}H_{16}ONCl$): C,73.5; H,5.16; N,4.51.

Calculated for benzylamine hydrochloride ($C_7H_{10}NCl$): C,58.3; H,6.94; N,9.72.

Found: C,65.17; H,6.08; N,7.47

4. Attempted preparation of N-(2-keto-1-acenaphthenyl)-pyridinium iodide. A mixture of 8.4 g. (0.050 moles) of acenaphthenone and 12.7 g. (0.10 moles) of iodine were dissolved in 15 ml. of pyridine. The mixture became warm on standing and soon solidified. After one hour the mixture was washed with ether to remove the excess pyridine and then with water to dissolve the pyridinium iodide formed. Evaporation of the aqueous washings gave 11.0 grams of the monohydrate of pyridinium iodide (approximately theoretical yield). A portion of the residue from the washings was recrystallized from ethanol and iso-propyl ether in the form of brownish needles which melted at 170-171° and which apparently decomposed on standing.

A stoppered vial of the recrystallized material smelled strongly of pyridine after three weeks standing. The material was not submitted for analysis.

SUMMARY AND SUGGESTIONS FOR FURTHER RESEARCH

A. Procedures for the preparation of the following compounds have been improved:

1. 2-Bromoacenaphthenone
2. 2-Acetoxyacenaphthenone.

B. The preparation of ethyl N-(1-acenaphthenyl)-carbamate has been accomplished.

C. Acenaphthenone has been shown not to yield Mannich reaction products under a wide range of conditions and reactants.

D. The reaction of 2-bromoacenaphthenone with secondary amines has been shown to yield biacenedione almost to the exclusion of the formation of other products.

E. The preparation of 2-alkyl acenaphthenones has been attempted by the following methods:

1. A variety of alkylation procedures
2. The introduction of a carbethoxy group in the 2-position as an intermediate step
3. Cyclization of naphthylacetic acids under several different conditions.

This study has shown that acenaphthenone may be dimerized to biacenone by reaction with several different basic reagents.

F. The results obtained in this study suggest the following as suitable subjects for further research:

1. Further study should bemade on the Mannich reaction with acenaphthenone, particularly with respect to the order of addition of the reagents.

2. In view of the previous, although limited, success obtained by others in the cyclization of naphthylacetic acids, further work should be attempted with the higher homologues of this acid in order to define more clearly the effects of structure upon this cyclization.

ADDENDUM

The results of tests performed at the Sloan-Kettering Institute for Cancer Research are summarized below.

Toxicity Assay

Injection medium: ½% Carboxy methyl Cellulose in Isotonic Saline

Volume injected per 20 gram: 0.5 ml.

Strain: Banks male

Dose: 500 mg./kg.

Compound	Mortality	weight change on third day
Ethyl N-(1-acenaphthenyl)-carbamate	0/5	± 1
2-Morpholinoacenaphthenone hydrochloride (1)	0/5	± 2.0

(1) Impaired locomotion followed by slight tonic behavior; slight clonic movement of limbs, dyspnea

Sarcoma 180 In Vivo Inhibition

(data on following page)

Sarcoma 180 In Vivo Inhibition

Compound	In vivo test (1)		
	Result	wt. change, grams (3)	Deaths
2- Morpholinoacenaphthenone hydrochloride	(2)	-1.0/3.0	2
Ethyl N-(1-acenaphthenyl)-carbamate	(2)	1.5/3.0	1

(1) 500 mg./kg. injected per mouse per day for seven days

(2) tumors in the treated animals have grown as well as the controls or have on the average grown to 3/4 the diameters of the control tumors

(3) The numerator indicates the average weight changes in the five test animals, and the denominator indicates the average weight change in the control group.

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