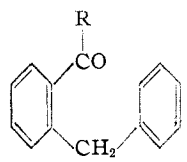
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

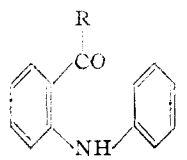
The Mechanism of Cyclization Reactions

BY ERNST BERLINER

Following the observation of E. Bergmann[1] that the acetal of *o*-benzylbenzaldehyde (I) yields a certain amount of anthracene when hydrolyzed with hydrochloric acid in acetone, Bradsher[2] worked out a convenient method of synthesizing 9-substituted anthracenes and 1,2-benzanthracenes in excellent yield by refluxing ketones of the type II with 34% hydrobromic acid and acetic acid. The synthesis of naphthalene by the cyclization of β-styrylaldehyde is considered by Bradsher[3] the simplest cyclodehydration reac-



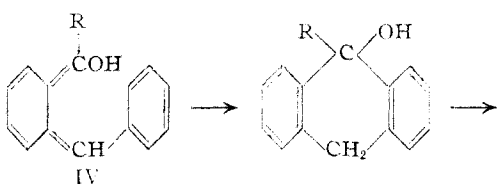
I R = hydrogen
II R = alkyl or phenyl



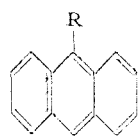
III R = alkyl or phenyl

tion of this type and similar to the formation of β-phenylnaphthalene from two molecules of phenylacetaldehyde observed by Zincke.[4]

A reaction analogous to the above hydrocarbon synthesis has been known in the acridine series for a long time and a number of acridines have been prepared[5] from the corresponding aldehydes or phenylketones (III) (in one case a methyl ketone). As far as the mechanism of the hydrocarbon synthesis is concerned, Bergmann suggested a similarity to the Elbs pyrolysis assuming enolization as the first step. Bradsher[6] pointed out

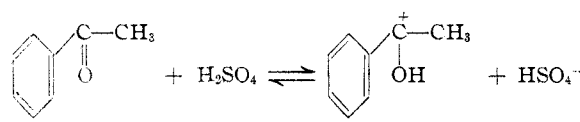


IV



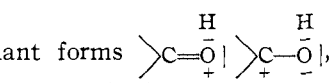
that the reaction is more like a Friedel–Crafts condensation than an Elbs pyrolysis, and proposed enolization as the first step followed by cyclization and subsequent loss of water.

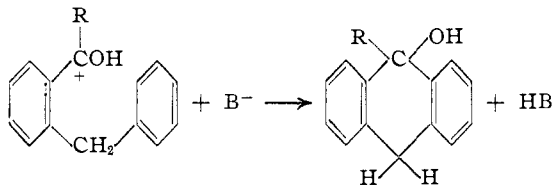
The following alternate explanation is based upon the behavior of carbonyl compounds in strongly acidic media and upon the concept of cyclodehydration as essentially an internal aromatic substitution. It is believed that the neutral enol (IV), even if it were formed by an acid-catalyzed enolization of the type proposed, would hardly undergo cyclization. It is now generally believed that ionic fragments play an important role as reaction intermediates, even in cases where the initial and final products are non-ionic in character and where the concentration of the ions is not great enough to be detected.[7] Thus in most aromatic substitution reactions, a positive fragment attacks a position of high electron density in the benzene ring, which loses a proton to the acid residue (base), after the intermediate complex is formed.[8] In order to satisfy these requirements, a mechanism is proposed on the basis of an addition of a proton to the carbonyl oxygen followed by an electrophilic substitution reaction. Addition compounds of the carbonyl group with acids and salts have long been known,[9] but their nature was not clearly understood until the work of Hantzsch, and later Hammett[10] showed that the solubility of carbonyl compounds in sulfuric acid depends on salt formation, as illustrated for the case of acetophenone



A proton is transferred from the acid to the carbonyl group and the conjugate acid of the ketone is positively charged. The first step in the cyclization reaction thus may be the formation of the conjugate acid (V), which is a hybrid of the

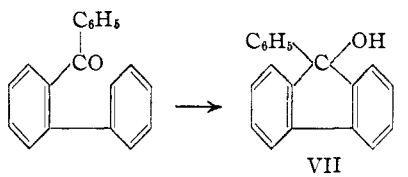
(1) E. Bergmann, *J. Org. Chem.*, **4**, 1 (1939).
(2) Bradsher, THIS JOURNAL, **62**, 486, 1077 (1940).
(3) Bradsher, *ibid.*, **64**, 1007 (1942).
(4) Zincke and Breuer, *Ann.*, **226**, 23 (1884); **240**, 137 (1887); Carter and van Loon, THIS JOURNAL, **60**, 1077 (1938).
(5) Ullmann and Ernst, *Ber.*, **39**, 298 (1906); Ullmann and Broide, *ibid.*, **39**, 356 (1906); Mayer and Stein, *ibid.*, **50**, 1306 (1917); Jensen and Rehwisch, THIS JOURNAL, **50**, 1144 (1928).
(6) References 2 and 3 and Abstracts from the 103rd meeting of The American Chemical Society, Memphis, Tenn., April, 1942.
(7) Whitmore, THIS JOURNAL, **54**, 3274 (1932); Meerwein and van Emster, *Ber.*, **55**, 2500 (1922); Arndt and Eistert, *ibid.*, **69**, 2381 (1936); Hammett, THIS JOURNAL, **59**, 1063 (1937).
(8) For general references: Ingold, *Chem. Rev.*, **15**, 225 (1934); Price, *ibid.*, **29**, 37 (1941).
(9) Houben, "Methoden der organischen Chemie," Georg Thieme, Leipzig, 1930, Vol. 3, page 470 ff.
(10) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 54 ff.

two resonant forms  , the positive charge being distributed between the oxygen and carbon atoms. The ring closure is an electrophilic attack by the carbon atom on the opposite ortho position forming the dihydroanthranol (VI), which readily suffers dehydration.



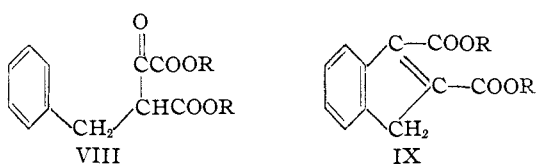
V VI

This mechanism does not require enolization as the first step and no active hydrogen is necessary. This concept is substantiated by the present observation that a similar cyclization can be accomplished with a compound which has no hydrogen available for enolization. When 2-phenylbenzophenone[11] was treated according to the procedure of Bradsher a mixture was obtained from which 9-phenylfluorenol and its acetate were isolated. Furthermore, when the same ketone was treated with sulfuric acid and acetic anhydride, a substance was obtained identical with a polymer of 9-phenylfluorenol obtained by treating the carbinol (VII) with the same reagents.[12] A reaction



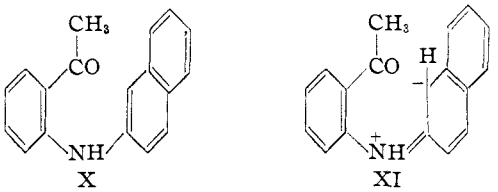
VII

very similar to the one considered was discovered by Bougault,[13] who found that the ester of the keto acid (VIII) undergoes ring closure under the



VIII IX

influence of sulfuric acid to give the indene dicarboxylic ester IX. The reaction was studied by Auwers and Moeller[14] and has proved useful in synthesis.[15] Auwers and Moeller regarded the enol form of the ketone as reaction intermediate, but here again the neutral enol, although it certainly could be present in this case, is not likely to enter into the substitution reaction for reasons given above. The first step in the proposed mechanism is the same as in the mechanism for acid-catalyzed enolization.[16] After the positively charged conjugate acid is formed, the ketone which is about to enolize, attacks the ring before the neutral enol is formed, and while it still carries the positive charge.



X XI

The cyclization proceeds with greater ease in the acridine series. If the secondary amine (X) is dissolved in glacial acetic acid and a few drops of concentrated sulfuric acid are added the reaction is completed after short heating, whereas much longer periods are necessary in the case of the hydrocarbons. The amino group (X) is much stronger ortho-directing than the methylene group, and an equivalent structure (XI) can be written with a true negative charge in the ortho position.[17]

The cyclization reaction has been utilized further for the synthesis of three higher benzologs of 9-methylacridine, namely, the 1,2-benz-, 3,4-benz- and 1,2,3,4-dibenz- derivatives. Since dibenzacridines have been shown to possess carcinogenic properties it seemed of interest to test these meso-substituted derivatives for comparison with the potent isolog 9-methyl-1,2-benzanthracene.

Another cyclodehydration reaction, where ionic fragments appear to be the intermediates, is the formation of 9-phenylfluorenes from triarylcarbinols.[18,19] The reaction proceeds with surprising ease and is accompanied by a remarkable color change. Thus when the carbinol (XII) is

(11) Schlenk and Bergmann, *Ann.*, **464**, 34 (1928).

(12) Kliegl, *Ber.*, **38**, 290 (1905); **43**, 2490 (1910).

(13) Bougault, *Compt. rend.*, **159**, 745 (1915).

(14) Auwers and Moeller, *J. prakt. Chem.*, [2] **109**, 124 (1925).

(15) Fieser and Hershberg, THIS JOURNAL, **57**, 1851 (1935), **58**, 2314 (1936); Ruzicka, *Helv. Chim. Acta*, **16**, 833 (1933); Cook and co-workers, *J. Chem. Soc.*, 667, 1319 (1935).

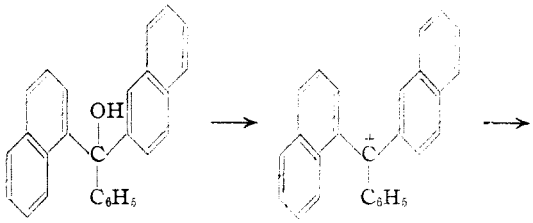
(16) Pederson, *J. Phys. Chem.*, **37**, 751 (1933); **38**, 581 (1934); Reitz, *Z. physik. Chem.*, **A179**, 119 (1937); Cohen and Urey, THIS JOURNAL, **60**, 679 (1938).

(17) The secondary amino group in this medium apparently is not basic enough to form the meta-directing ammonium ion. If, however, only sulfuric acid is used, heating to a higher temperature and for a longer time becomes necessary.

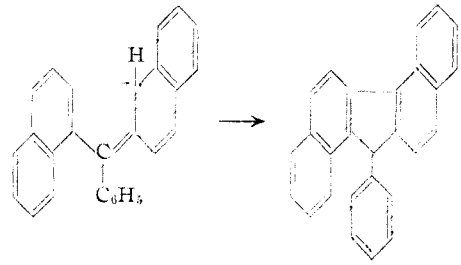
(18) Kliegl, *Ber.*, **38**, 287 (1905); Ullmann, *ibid.*, **38**, 2216, 2219 (1905); Tschitschibabin, *J. prakt. Chem.*, **84**, 760 (1911); **88**, [2] 514 (1913); **90**, [2] 168 (1914).

(19) Bachmann and Kloetzel, *J. Org. Chem.*, **2**, 356 (1937); Schoepfle, THIS JOURNAL, **44**, 192 (1922).

dissolved in acetic acid and heated to the boiling point, the solution is but slightly colored. If a few drops of hydrochloric acid are added at the boiling point a deep green color appears for a few seconds, water is given off as the green color disappears, and a reddish-brown color results. The reaction is over and another drop of hydrochloric acid does not produce any further color change. The fluorene, XV, crystallizes from the cooled solution and the whole reaction resembles those with inorganic ions. The carbinol itself dissolves in sulfuric acid with the same green color. In all observed cases the transient color was identical with the color of the carbinol in sulfuric acid. It is generally accepted that the color which is obtained when triarylcarbinols are dissolved in sulfuric acid, or when they are treated with different inorganic salts, is due to the color of the positive carbonium ion. Therefore, it seems justifiable to assume that the first step in the cyclodehydration is the formation of the carbonium ion (XIII).



XII XIII



XIV XV

The positive charge is distributed on the ortho and para postions, accounting for the stability of these ions. If the charge moves to the nearest ortho position, an equivalent structure (XIV) is obtained which allows substitution on the opposite ring. This is followed by aromatization. If the initial step consists in the formation of the carbonium ion and not in the loss of water, any electrophilic reagent other than strong mineral acids should bring about the cyclization. This was confirmed by dissolving the carbinol (XII) in an inert solvent and adding different salts which are known to effect ionization of the triarylcarbinols. In each case a complex precipitated immediately which had the color of the carbinol in sulfuric acid, and the fluorene was obtained after decomposition with water. This explains why it is so difficult to prepare stable salts or the chlorides of the higher benzologs of triphenylcarbinol.[18,19] Two fluorene derivatives, 1,2,5,6- and 1,2,7,8-dibenz-9-phenylfluorene were synthesized by the above reaction. The intermediate carbinols were prepared by the Grignard action of a naphthyl halide and a naphthyl phenyl ketone. The possibility of reaction in the phenyl instead of the naphthyl group to form the 9-naphthyl-benzfluorene is less likely because of the relative inertness of the phenyl group. Furthermore, Schoepfle[19] and Ullmann[18] prepared similar compounds by the dehydration of the carbinols, as well as by the action of phenylmagnesium bromide on the corresponding fluorenones and obtained identical compounds. It can be assumed, therefore, that the above compounds have the structure assigned to them.

Acknowledgment.—I wish to express my sincere thanks to Professor L. F. Fieser, Harvard University, under whom I have the privilege to work and without whose generous help and kind interest this work would not have been accomplished. I also thank Mrs. L. F. Fieser for her help in preparing the manuscript.

Experimental[20]

***o*-(α-Naphthyl)-aminoacetophenone.**—A mixture of 2.4 g. of *o*-aminoacetophenone,[21] 4 g. of α-bromonaphthalene, 5 g. of potassium carbonate and 0.3 g. of copper powder was heated in refluxing nitrobenzene (50 cc.) in an all glass apparatus. The solution became dark and carbon dioxide was evolved. After three hours the reaction mixture was steam-distilled to remove the solvent and excess reagents, and the residue was taken up in ether–benzene, and dried with sodium sulfate. After evaporation, a brown oil remained which could be used for cyclization without further purification. The oil crystallized upon the addition of alcohol and 3.9 g. was obtained as small yellow prisms after several recrystallizations from alcohol and a little benzene, m. p. 96.4–97.2°.

Anal.[22] Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.78. Found: C, 83.00; H, 5.65.

9-Methyl-3,4-benzacridine.—Three grams of the above oil was dissolved in 25 cc. of glacial acetic acid, 3 cc. of concentrated sulfuric acid was added, and the flask was placed on the steam-bath. The yellow sulfate of the acridine precipitated immediately and was filtered after ten minutes' heating. It was suspended in water, and the base (2.5 g.) which precipitated on addition of concentrated ammonia, was filtered and dried. It formed yellow needles from alcohol, m. p. 111.6–112.2°.

(20) All melting points are corrected.

(21) Clar, *Arch. Pharm.*, **14**, 240 (1902).

(22) Microanalyses by Miss F. Werble.

Anal. Calcd. for $C_{18}H_{13}N$: C, 88.86; H, 5.38. Found: C, 88.91; H, 5.33.

The **picrate** (fine yellow needles) is sparingly soluble in the common solvents. Higher boiling solvents (toluene, dioxane) dissolve it, but with decomposition. The picrates of the other acridines show the same properties. It was crystallized from acetone; m. p. 251–255° (dec.).

Anal. Calcd. for $C_{24}H_{16}N_4O_7$: N, 11.86. Found: N, 11.83.

o-(β-Naphthyl)-aminoacetophenone (X) was prepared in the same way as the other isomer from 3.1 g. of *o*-aminoacetophenone, 5.2 g. of β-bromonaphthalene, 6 g. of potassium carbonate and 0.3 g. of copper powder in 50 cc. of boiling nitrobenzene. The remaining oil was distilled at 6 mm. and 195–196°. In an attempt to prepare the picrate, a precipitate was formed after short boiling with picric acid which proved to be the picrate of the cyclized product.

Anal. Calcd. for $C_{18}H_{15}NO$: N, 5.36. Found: N, 5.4.

9-Methyl-1,2-benzacridine.—Four grams of the oil was heated on the steam-bath in 25 cc. of glacial acetic acid and 4 cc. of concentrated sulfuric acid. After fifteen minutes it was poured on ice and filtered. The filtrate was treated with ammonia and the acridine which precipitated (3.7 g.) was dried and recrystallized repeatedly from benzene–ligroin. It forms yellow, shining plates, m. p. 145–145.2°.

Anal. Calcd. for $C_{18}H_{13}N$: C, 88.86; H, 5.38. Found: C, 88.87; H, 5.1.

The **picrate** forms small yellow needles from acetone, m. p. 245–248° (dec.).

Anal. Calcd. for $C_{17}H_{16}N_4O_7$: N, 11.86. Found: N, 11.56.

9-Methyl-1,2,3,4-dibenzacridine.—A mixture of *o*-aminoacetophenone (1.5 g.), 9-bromophenanthrene (3 g.), potassium carbonate (4 g.) and copper powder (0.3 g.) was heated in 40 cc. of nitrobenzene as described for the other isomers. The remaining oil was taken up in glacial acetic acid (20 cc.) and after the addition of 3 cc. of concentrated sulfuric acid heated for twenty-five minutes on the steam-bath. Part of the sulfate precipitated and was filtered off and treated with ammonia. This was combined with the precipitate obtained after adding ammonia to the filtrate, and crystallized from a little alcohol and benzene, as straw-like needles (3 g.), m. p. 121.4–122.4°.

Anal. Calcd. for $C_{22}H_{15}N$: C, 90.07; H, 5.1. Found: C, 90.05; H, 4.9.

The picrate forms yellow needles from acetone; m. p. 206–208° (dec.).

Anal. Calcd. for $C_{18}H_{18}N_4O_7$: N, 10.72. Found: N, 10.44.

β-Benzoylnaphthalene.—A Grignard solution prepared from 18 g. of bromobenzene and 2.8 g. of magnesium turnings was treated with 12 g. of β-naphthonitrile in absolute ether; a crystalline precipitate separated after short boiling. Refluxing and stirring was maintained for five hours, after which time the mixture was decomposed with ammonium chloride solution. The ether layer was evaporated and the remainder refluxed with 50 cc. of water, 16 cc. of acetone, and 25 cc. of concentrated hydrochloric acid. After three hours the cooled solution was extracted with ether and the ketimide hydrochloride, which was not hydrolyzed, was treated once more with acid to which 30 cc. of benzene was added. The combined organic layers were dried and the solvents evaporated. The remaining solid was crystallized from alcohol: (15 g., 82.5%), m. p. 81–82°.[23]

α,β-Dinaphthylphenylcarbinol (**XII**).—A Grignard solution was prepared from 8 g. of α-bromonaphthalene and 0.94 g. of magnesium turnings in absolute ether. About 0.5 cc. of α-bromonaphthalene was added at the end of the reaction to take care of the unreacted magnesium. Eight grams of β-benzoylnaphthalene was added over a period of twenty-five minutes, and stirring and refluxing was maintained for two hours after which the complex was decomposed with ice-cold 25% ammonium chloride solution. The organic layer was separated, dried over sodium sulfate and the oil remaining after evaporation crystallized readily upon the addition of ether–ligroin (9 g., 72%). The carbinol crystallizes with benzene or alcohol when in contact with these solvents. The addition products are very stable and melt between 195–205° with loss of solvent. The carbinol was recrystallized from ether–ligroin as small white prisms; m. p. 168–169°. It dissolves in concentrated sulfuric acid with a dark green color and appears red in transmitted light.

Anal. Calcd. for $C_{17}H_{20}O$: C, 89.97; H, 5.59. Found: C, 90.09; H, 5.84.

1,2,5,6-Dibenz-9-phenylfluorene (**XV**).—Four grams of the crude carbinol was dissolved in 15 cc. of glacial acetic acid, heated to the boiling point and a few drops of hydrochloric acid added. The solution turned green and then reddish. An oil separated which solidified on cooling. It was crystallized repeatedly from acetic acid and forms white needles, m. p. 219–219.5°. It is soluble in ether, warm benzene, hot acetic acid, sparingly soluble in alcohol and ligroin.

Anal. Calcd. for $C_{27}H_{18}$: C, 94.7; H, 5.3. Found: C, 94.67; H, 5.3.

The following experiments were carried out with 100 mg. of the carbinol. It was dissolved in benzene (5 cc.) and a spatula full of aluminum chloride, aluminum bromide, iodine, phosphorus pentachloride, or a few drops of stannic chloride was added. In each case the green complex separated immediately. The mixture was heated for about five minutes on a steam-bath, and then decomposed with water until it had all dissolved. The fluorene was isolated from the benzene layer. No fluorene was obtained by heating the carbinol in refluxing xylene or acetonitrile.

β,β-Dinaphthylphenylcarbinol was prepared in the same way as the other isomer from 9 g. of β-bromonaphthalene and 1.1 g. of magnesium to which 9 g. of β-benzoylnaphthalene was added in ether and benzene. The reaction mixture was worked up as usual and a quantity of small white needles (2 g.) separated from the ether–benzene solution after drying and concentrating. A further quantity (3 g.) was obtained on concentrating the solution but about half of the carbinol remained in an oily condition and crystallized only very slowly in the ice chest. Recrystallized from benzene–ether (very little soluble in

(23) Kollarits and Merz, *Ber.*, **6**, 543 (1873), give 82°.

ether) it melts at 216.5–217.5°. A dilute solution of the compound in concentrated sulfuric acid looks green when viewed through a thin layer, but red in more concentrated solutions.

Anal. Calcd. for $C_{27}H_{20}O$: C, 89.97; H, 5.59. Found: C, 90.17; H, 5.52.

1,2,7,8-Dibenz-9-phenylfluorene.—The cyclization was carried out on the oil. Three grams in 30 cc. of glacial acetic acid and 3 cc. of hydrochloric acid were refluxed for twenty minutes. An oil and a solid separated, which were filtered off and extracted with boiling acetic acid without further drying. This removed an unidentified by-product which, when not removed, made the purification of the fluorene very difficult. The white compound which was obtained after cooling the solution was recrystallized several times by suspending it in hot ligroin and adding just enough benzene to bring it into solution, small white needles arranged in rosets resulted; m. p. 148.5–149.5°.

Anal. Calcd. for $C_{27}H_{18}$: C, 94.7; H, 5.3. Found: C, 94.6; H, 5.15.

α,α-Dinaphthylphenylcarbinol.—This compound was first made by Elbs[24] from benzoic ester and α-bromonaphthalene and later by Schoepfle who used toluene to improve the yield. We prepared it by the above general method using 11 g. of bromonaphthalene, 1.3 g. of magnesium and 11 g. of α-benzoylnaphthalene[25] (64% yield). In order to obtain crystals, the ether solution was concentrated to a small volume and ligroin was added until no more of the light oil separated. The supernatant layer which contained the by-products was disregarded. The carbinol crystallized in the desiccator after a few cc. of benzene was added, m. p. 169–170°.

3,4,5,6-Dibenz-9-phenylfluorene was prepared as above, the transient color is purple; m. p. 275° (as given by Schoepfle).

Cyclization of 2-Phenylbenzophenone, 1.—One gram of 2-phenylbenzophenone was dissolved in 10 cc. of glacial acetic acid and 10 cc. of 34% hydrobromic acid was added at the boiling point. Five more cc. of acetic acid was added to keep all in solution. After twenty-four hours a yellow oil separated and boiling was continued for two more days. The oil solidified on cooling and crystallized on rubbing. The crude product softened between 105–107° and melted between 150–160°. It was extracted with hot ether and the ether soluble product recrystallized three times from acetic acid. Twenty mg. of white needles was obtained, m. p. 169–171°. Kliegl[26] gives 169–169.5° for 9-phenylfluorenol acetate.

The compound apparently contained some of the polymerization product which is difficult to remove. The combined mother liquors were boiled with sodium acetate in acetic acid to hydrolyze the acetate still present and a white compound, m. p. 106–107°, precipitated on pouring on ice[26] (given for 9-phenylfluorenol 107–108°). This crude product was reduced with zinc, hydrochloric acid and acetic acid and the obtained hydrocarbon (about 50 mg.) recrystallized once from alcohol in which it is soluble with a distinct blue fluorescence, m. p. 142.8–144.6° (lit. 145–146°[27]); mixed m. p. 142.4–144.4.

2. Five hundred mg. of the ketone was dissolved in 10 cc. of acetic anhydride and heated on the steam-bath. One cc. of concentrated sulfuric acid was added. The yellow compound which separated melted over the wide range of 260–300° and had the properties of the polymer of 9-phenylfluorenol. It was dissolved in chloroform and reprecipitated with alcohol, as suggested by Kliegl.[26] It darkens at about 250° and melts between 300–330°. The cyclization of the ketone with hydrobromic acid is of no preparative value for making the carbinol because the polymer is always formed along with it. This makes the yield low and the carbinol hard to purify.

Summary

9-Methyl-1,2-benzacridine, 9-methyl-3,4-benzacridine, 9-methyl-1,2,3,4-dibenzacridine as well as 9-phenyl-1,2,5,6-dibenzfluorene and 9-phenyl 1,2,7,8-dibenzfluorene were synthesized by cyclizing the corresponding methyl ketones or dinaphthylphenylcarbinols, respectively. A mechanism for the cyclodehydration reaction is suggested which involves as the first step the formation of a positively charged fragment followed by an electrophilic aromatic substitution reaction.

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(24) Elbs, *J. prakt. Chem.*, **35**, 506 (1887).

(25) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., second edition, 1911, p. 192.

(26) Kliegl, *Ber.*, **38**, 290 (1905).

(27) Ullmann and Wurstemburger, *ibid.*, **37**, 74 (1904).