BENZ(C)ACRIDINES
FROM 4,4-DIMETHYL-1-TETRALONE

by

LAWRENCE ARTHUR NIELSEN

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TITLE

BENZ(C)ACRIDINES FROM 4,4-DIMETHYL-1-TETRALONE

BY

Lawrence Arthur Nielsen

APPROVED	DATE
Norman H. Cromwell, Chairman	July 11, 1962
Gordon A. Gallup	"
Robert B. Johnston	"
Thomas L. Tompson	"
Donald M. Pace	"

SUPERVISORY COMMITTEE

GRADUATE COLLEGE UNIVERSITY OF NEBRASKA

I would like to express my sincere appreciation to Dr. N. H. Cromwell for the suggestion of this research problem and for his insight and patience demonstrated during its completion.

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INTRODUCTION

A. Nomenclature.

Nomenclature in the benzacridine series has been made confusing by the use of several systems. A brief scanning of the literature reveals the names 1,2-naphthacridine,[1] 2,1-naphthacridine,[2] 1,2-benzacridine,[3] 3,4-benzacridine,[4] 5,6-benzacridine[5] and benz(c)acridine for the same ring system (Chart I). The problem is briefly mentioned by Albert[6] and extensively discussed by Acheson.[7]

The nomenclature and numbering used in this thesis (see Chart I) is that currently used by Chemical Abstracts and illustrated in the Ring Index[8] (ring system no. 5148). Where reference is made to work in which other systems are used, the compounds cited have been renamed to conform to this system.

B. Literature Survey.

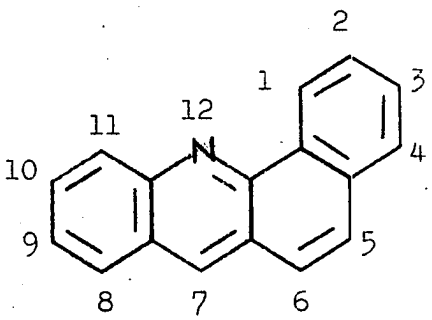
With the discovery of the acridine ring system in 1870, Graebe[9,10] initiated a fascinating new area of heterocyclic research.

Work on the benz(c)acridine series began in the early 1900's with the synthesis of the parent benz(c)acridine[11] from the thermal reaction of 2-tolyl-1-naphthylamine and lead dioxide, and that of benz(c)acridone[2] from the reaction of N-(1-naphthyl)anthranilic acid and phosphorus pentoxide. Tetrophan[1] was synthesized in 1922, and in the ensuing ten years many of its 5,6-dihydro derivatives[5,12,13,14] and homologues[12,15] were characterized.

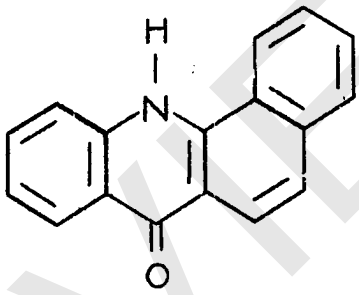
Benz(a)- and benz(c)acridines have been isolated from coal tar pitch.[16] Although several acridine alkaloids[7] have been isolated, no other source of naturally occurring benzacridines has been discovered.

CHART I

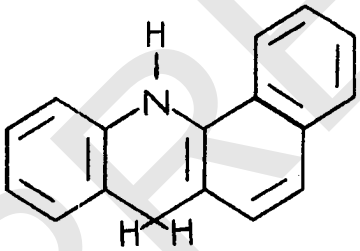
Nomenclature of the Benz(c)acridines



Benz(c)acridine

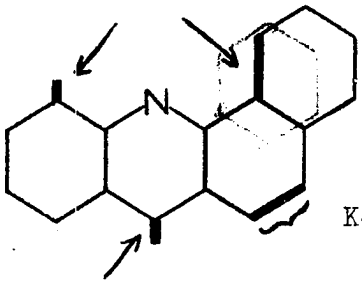


Benz(c)acridone



Benz(c)acridan

Peri-positions



Meso-position

K-region
or
Meso-
phenanthrenic
region

The books by Albert[6] and Acheson[7] offer comprehensive coverage of the acridine field up to 1950 and 1954, respectively. A detailed work treating only the benzacridines is not available and probably not yet warranted.

Although there has been no extensive spectral study of the benz(c)acridines, the works of Katritzky,[17] Mason[18,19,20] and the Russian school[21,22] have added significantly to factual as well as theoretical knowledge in the field.

Workers currently active in the benz(c)acridine field include Buu-Hoi,[23] Elslager,[24,25,26] Tanasescu[27] and Cromwell.[28,29,30]

C. Synthesis of Benz(c)acridines.

1. General.

The methods of synthesis of the benz(c)acridine ring system are logical extensions of the general methods of the acridine series as discussed by Albert[6] and Acheson[7] and outlined by Bell.[31] Especially useful have been a) Bernthsen's Reaction, b) the Pfitzinger-Borsche Reaction and c) cyclization of N-arylanthranilic acids, as exemplified in Chart II. Two interesting and potentially useful synthetic procedures, both yielding a benz(c)acridone-type system, have not been discussed in the above references. These are the method of Tanasescu[27] and Reed's[32,33] extension of the method discovered by Tiedtke.[34] Finally, the synthetic route developed by Cromwell with Bell[27,28] and Adelfang,[29] especially pertinent to the work presented in this thesis, deserves some discussion.

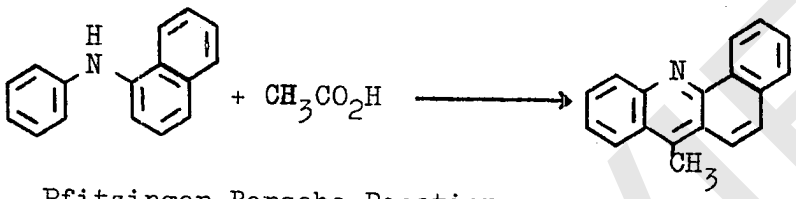
2. Tanasescu's Procedure.

Tanasescu and co-workers recently reported the synthesis of benz(c)acridone by the reaction of o-nitrobenzaldehyde and naphthalene in the presence of polyphosphoric acid. About 1/3 of the product isolated was naphthyl-5-

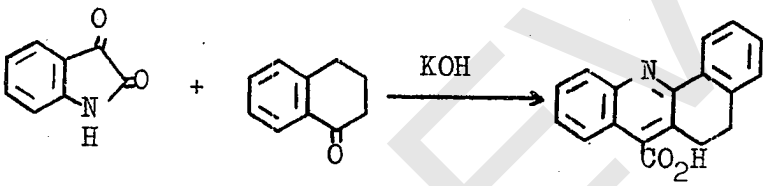
CHART II

Synthesis of Benz(c)acridine Ring Systems

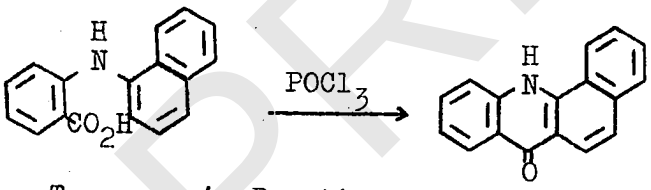
A. Bernthsen's Reaction



B. Pfitzinger-Borsche Reaction



C. Cyclization of N-Arylanthranilic Acids



D. Tanasescu's Reaction

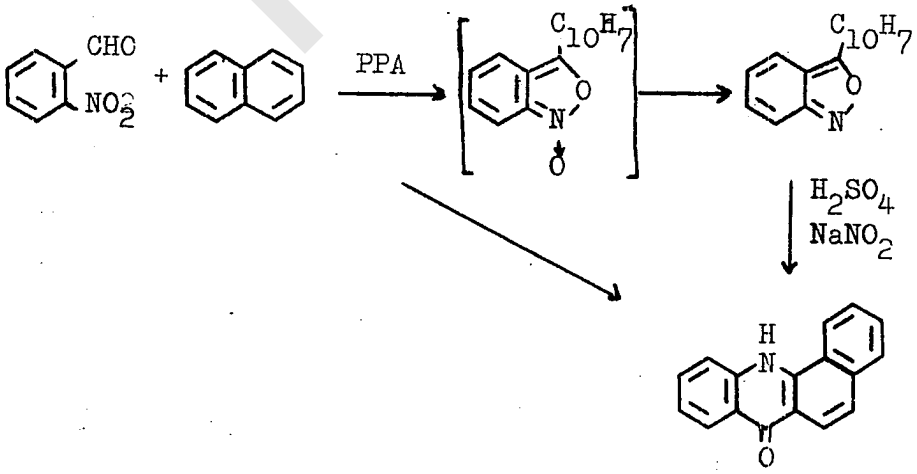
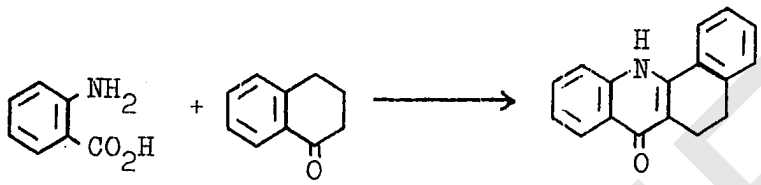
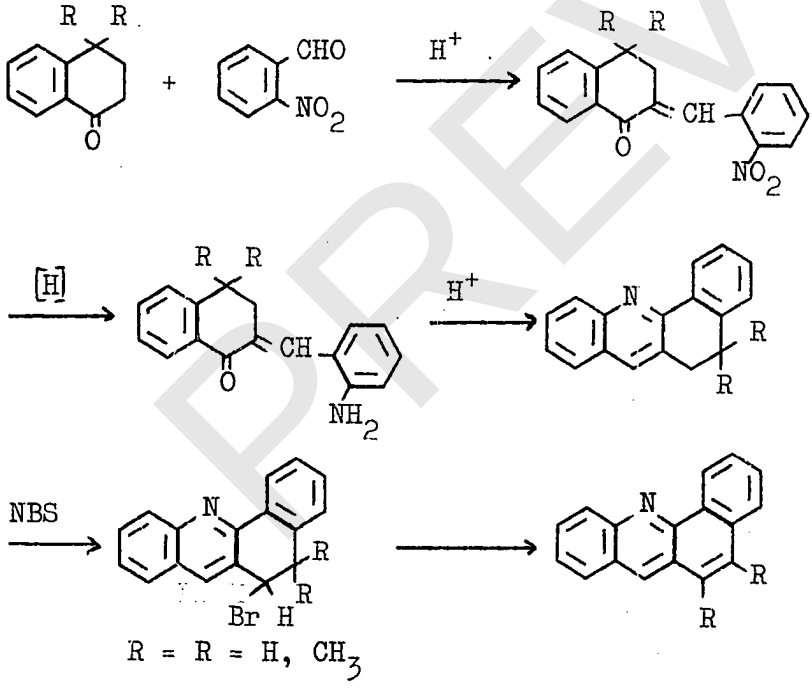


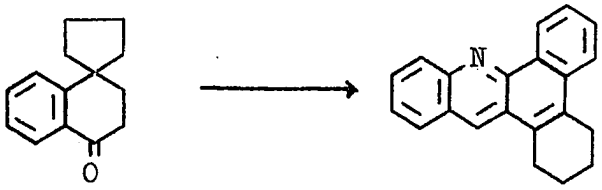
CHART II (continued)

E. Method of Reed and Tiedtke



F. Method of Cromwell





benzo(c)isoxazole, which could be converted to benz(c)-acridone by treatment with sulfuric acid and sodium nitrite; the remaining 2/3 was benz(c)acridone. The postulated reaction path is shown in Chart II.

3. Method of Reed and Tiedtke.

Tiedtke discovered in 1909 the thermal condensation of anthranilic acid and cyclohexanone to give a tetrahydroacridone. Reed demonstrated the utility and a degree of specificity of the reaction by the preparation of various methyl- and dimethyltetrahydroacridones, N-methyltetrahydroacridone from N-methylanthranilic acid, and the 2-methylderivatives (no 4-methyl) from 3-methylcyclohexanone. He extended the reaction to the benz(c)acridones by using tetralones in place of cyclohexanones.

4. Synthetic Route of Cromwell.

As shown in Chart II, this method consists of condensation of a tetralone and o-nitrobenzaldehyde, reduction of the nitro group and cyclization to give a 5,6-dihydrobenz(c)acridine. The previously unknown 5,5-dimethyl-5,6-dihydrobenz(c)acridine was obtained when 4,4-dimethyl-1-tetralone was used. The 9-, 10-, and 11-chloro derivatives were prepared by the use of the suitably substituted o-nitrobenzaldehyde.

Bromine could be substituted in the 6-position (methylene group) by reaction with N-bromosuccinimide. Replacement of the bromine by a variety of amines, alcohols and hydroxyl gave a series of the 6-substituted derivatives.

The preparation of 5,6-dimethylbenz(c)acridine was accomplished by the thermal "α-dehydrobromination" rearrangement of 5,5-dimethyl-6-bromo-5,6-dihydrobenz(c)-acridine. The generality of this Wagner-type elimination-rearrangement has been demonstrated by the preparation of

5,6,7,8-tetrahydrobenz(a,c)acridine starting from 4,4-tetramethylene-1-tetralone.

D. Properties of Benz(c)acridines.

1. Chemical.

Like the methods of synthesis, the chemical properties of the benz(c)acridines are generally analogous to those of the corresponding acridines. Little is known of the electrophilic substitution properties.

Nucleophilic substitution at the 7-position (meso-position) of benz(c)acridine should be rather facile, by analogy with acridine,[35] although this has apparently not been studied. The oxygen function of benz(c)acridones is readily replaced by halogen, which is then reactive to hydrolysis or replacement by, e.g., amines.[26,36]

Benz(c)acridine has recently been found to undergo free radical substitution.[37] Reaction with benzyl radicals gave a 64% yield of 7-benzylbenz(c)acridine.

The enhanced reactivity of the 5- and 6-positions is illustrated by the reaction of osmium tetroxide with 7,9-dimethylbenz(c)acridine[38] to give 7,9-dimethyl-5,6-dihydroxy-5,6-dihydrobenz(c)acridine.

2. Physical.

The benz(c)acridines are high-melting yellow solids, somewhat insoluble in most common organic solvents. The benz(c)acridones, much higher-melting and less soluble than the corresponding acridines, are crystallized with difficulty from such solvents as pyridine or dioxane. Dilute solutions of these compounds fluoresce strongly from blue-violet to green.

3. Physiological.

The physiological activity of the benz(c)acridines varies considerably with only small changes in structure.

Tetrophan was found to exert a strychnine-like action[39] while the 5,5-dimethyl derivative showed a curious myotonic activity in rats and cats.[40]

Carcinogenic activity of varying degrees has been reported[41,42,43] for a number of alkyl- and polyalkyl-benz(c)acridines. Some carcinogenic activity has been observed in the case of 5,6-dimethylbenz(c)acridine[44] while the 9- and 10-chloro derivatives have shown slight anti-tumor activity.[45]

The correlation between carcinogenic activity and electron density at the K-region (meso-phenanthrenic region) has been discussed.[46]

STATEMENT OF PROBLEM

The problem studied in this thesis consists essentially of two main parts. The first of these deals, broadly, with a study of the 7-substituted derivatives of 5,5-dimethyl-5,6-dihydrobenz(c)acridine and of 5,6-dimethylbenz(c)acridine.

The second is concerned with an investigation of the Grignard reactions of 5,5-dimethyl-6-keto-5,6-dihydrobenz(c)acridine.