

Benzacridines VI. (1a). Functional Derivatives of 5,6-Dimethylbenz[*c*]acridine (1b)

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5,5-Dimethyl-5,6-dihydrobenz[*c*]acridone has been synthesized by three different routes: a, from a condensation of anthranilic acid with 4,4-dimethyl-1-tetralone; b, by a catalytic hydrogenation of 2-(*o*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide followed by an acid catalyzed cleavage of the oxide ring and closure of the nitrogen heterocyclic ring; c, a multi-step process starting with 7-carboxy-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine. Several new functional derivatives of both 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine and of 5,6-dimethylbenz[*c*]acridine were also produced for biological study by others.

The first paper in this series (2) described a new pathway for the synthesis of benz[*c*]acridines substituted in the 5- and 6-positions of the ring structure. These locations involve the carbon atoms of the "K-region" of the ring system and additional substitutions in other positions of the structure of 5,6-dimethylbenz[*c*]acridine were undertaken to allow for further studies of chemical carcinogenesis and carcinostasis (3) with these polycyclic heterocyclic compounds.

## RESULTS AND DISCUSSION

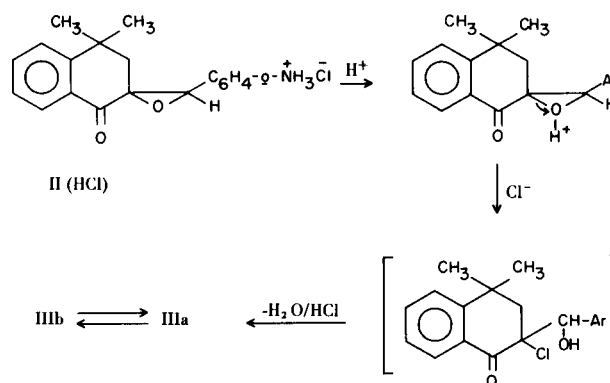
5,5-Dimethyl-5,6-dihydrobenz[*c*]acridone (III).

Three independent reaction schemes leading to 5,5-dimethyl-5,6-dihydrobenz[*c*]acridone (III) have been devised (see Chart A). This compound served as the starting material for the synthesis of several other 7-substituted-5,5-dimethyl-5,6-dihydrobenz[*c*]acridines (see Chart B) and the derived 7-substituted-5,6-dimethylbenz[*c*]acridines (see Charts C and D).

The most straightforward method for the preparation of the acridone (III) desired as a starting material for the preparation of other benz[*c*]acridines, is an adaptation of the method used by Reed (4) for the preparation of benz[*c*]acridone by the thermal condensation of anthranilic acid with  $\alpha$ -tetralone. Using 4,4-dimethyl-1-tetralone in place of  $\alpha$ -tetralone, a 50% yield of III resulted.

The acridone (III) was also obtained in an overall yield of 76% from the available (5) 2-(*o*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide (I) by catalytic hydrogenation followed by an acid catalyzed three-ring cleavage of the epoxide ring and closure of the six-ring nitrogen heterocyclic system. The intermediate 2-(*o*-aminobenzal)-4,4-

dimethyl-1-tetralone oxide (II) was somewhat unstable and the overall yield of III was improved by hydrogenating I in benzene solution and then proceeding directly to the acid-catalyzed cyclization without isolating II. Cyclization was facilitated by the azeotropic distillation of the mixture to remove water. Although the mechanisms for this series of changes are not at hand, the epoxy-ring in the intermediate II (as its hydrochloride) would be expected to open in the direction indicated between the oxygen atom and the carbon atom *alpha* to the carbonyl group as was previously found to be the case with 2-(*p*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide (6).



A third route, originally developed to confirm the structure of III as obtained from II, started with the known 7-carboxy-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (IV) (2) and produced several intermediates which also were of interest for biological study. In the reaction sequence (see Chart A) IV was converted to the acid chloride (V)

CHART A

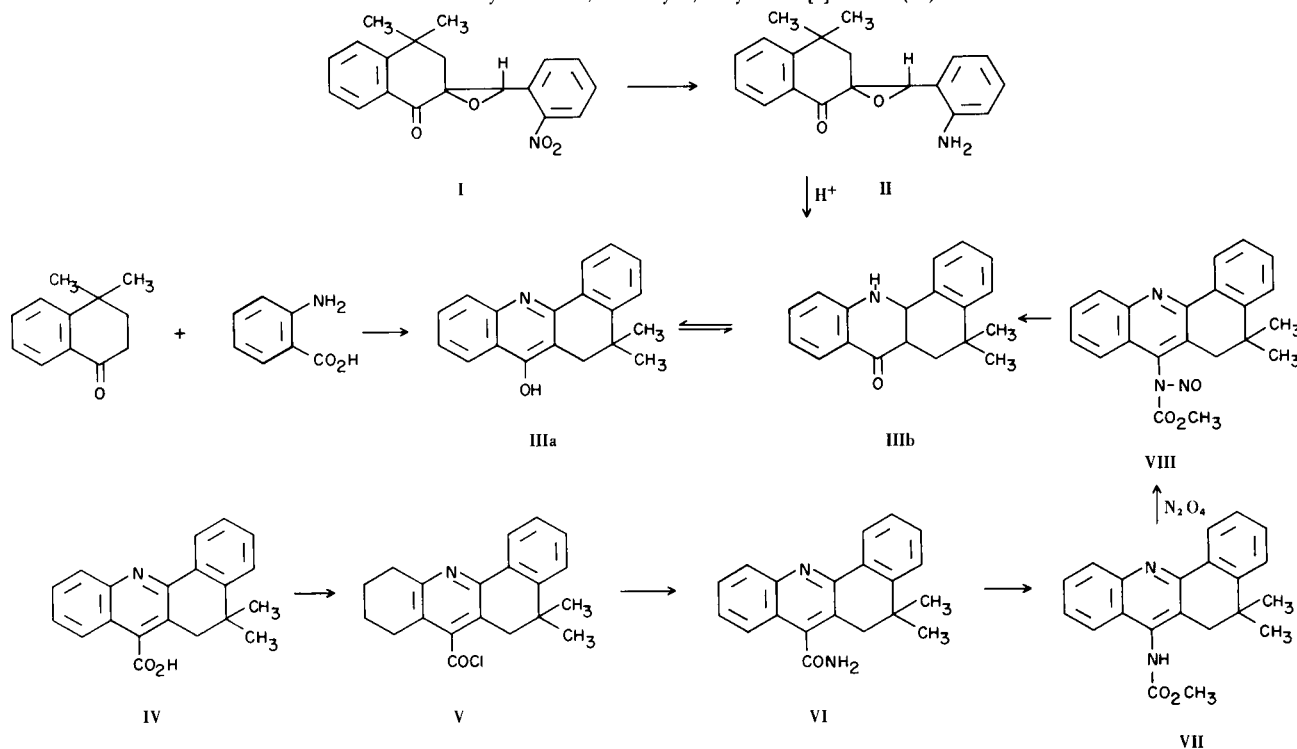
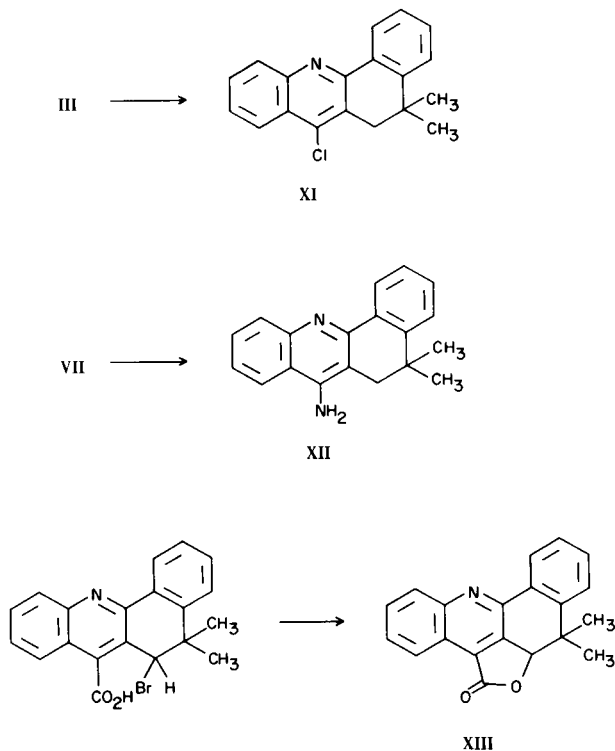
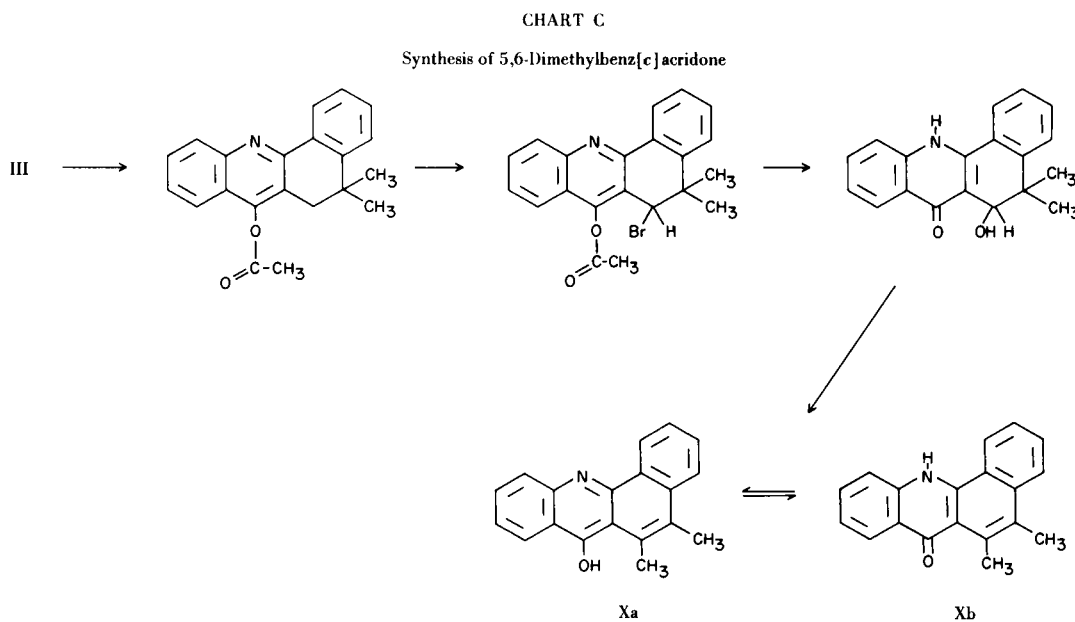
Methods of Synthesis of 5,5-Dimethyl-5,6-dihydrobenz[*c*]acridone (III)

CHART B

Synthesis of 7-Substituted 5,5-Dimethyl-5,6-dihydrobenz[*c*]acridines

which in turn gave a good yield of 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine-7-carboxamide (VI) by reaction with ammonia. Amide VI reacted normally under Hofmann reaction conditions in methanol to give methyl 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine-7-carbamate (VII). *N*-Nitrosation of VII to give *N*-nitroso methyl 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine-7-carbamate (VIII) was performed by slightly modifying the conditions of White (7). Base-catalyzed hydrolysis of VIII, presumably to give the diazonium salt (8), followed by acid hydrolysis gave a fair yield of III. Ultraviolet and infrared spectra, as well as elemental analysis, were used to confirm structural assignments of compounds V-VIII. Melting point, mixture melting points and conversion to the acetate IX were used to demonstrate that the same compound III resulted from the three above described reaction schemes. A single strong carbonyl peak in the infrared spectrum of IX at  $1775\text{ cm}^{-1}$  demonstrated that the compound obtained was the ester and not an amide. Ultraviolet and infrared spectral studies with III imply that it has the acridone structure (IIIb) (9). Other 7-Substituted 5,5-Dimethyl-5,6-dihydrobenz[*c*]acridines.

The reaction sequences to produce several of these compounds are outlined in Chart B. Reaction of III with either thionyl chloride or phosphorous oxychloride gave

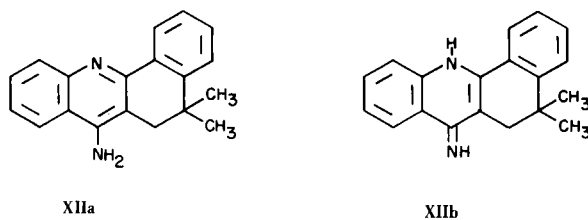


5,5-dimethyl-7-chloro-5,6-dihydrobenz[*c*]acridine (XI) in good yield. However, XI proved to be of little value as an intermediate due to its extreme stability. It could not be hydrolyzed back to III and the chloro group was not replaceable by phenoxy, methoxy or *sec*-amino groups.

7-Carboxy-5,5-dimethyl-6-bromo-5,6-dihydrobenz[*c*]acridine, prepared by the published method (10) was readily hydrolyzed in basic solution to give, upon acidification, the lactone (XIII) of 7-carboxy-5,5-dimethyl-6-hydroxy-5,6-dihydrobenz[*c*]acridine. The infrared spectrum showed a strong lactone carbonyl peak at  $1776\text{ cm}^{-1}$  and the absence of a hydroxyl peak. The ultraviolet spectrum showed a definite deviation from that of the normal 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine. The main peak at  $270\text{ m}\mu$  showed a shoulder, and the pattern in the  $300$  to  $360\text{ m}\mu$  range consisted of a shoulder at  $334\text{ m}\mu$ , a peak at  $346\text{ m}\mu$  and a smaller peak at  $360\text{ m}\mu$ . The normal pattern in this latter range consisted of two peaks at about  $302$  and  $316\text{ m}\mu$  with a shallow minimum between them and two peaks of slightly higher extinction coefficients at about  $332$  and  $346\text{ m}\mu$  with a deeper minimum between them.

The synthesis of 5,5-dimethyl-7-amino-5,6-dihydrobenz[*c*]acridine (XII) was successfully accomplished by the hydrolysis of VII. An attempt to synthesize XII from XI using ammonium carbonate in phenol (11) yielded only starting material (XI). Compound XII resisted basic hydrolysis and diazotization. Mild diazotization conditions yielded only starting XII, while stronger conditions gave an intractable dark brown material.

The amino structure (XIIa) rather than the imino form (XIIb) was selected on the basis of spectral analysis. The



ultraviolet spectrum curve showed some deviation from that of the normal shape of 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine. The main chromophore at  $270\text{ m}\mu$  is a broader peak with a shoulder on the high rather than the low wave-length side; the extinction coefficient is almost great enough to call the peak bifurcated. Also the fine structure of the  $300$  to  $350\text{ m}\mu$  area has degenerated to a broad peak at  $325\text{ m}\mu$  with shoulders at  $314$ ,  $346$  and  $362\text{ m}\mu$ . Mason (12) points out that there is steric hindrance to conjugation between the exocyclic nitrogen atom and the aromatic nucleus in the case of *meso*- and *peri*-amines. This could explain the minor deviations from the expected pattern in the electronic spectrum of XIIa.

Mason further points out that the infrared study of the tautomerism of *N*-heteroaromatic amines is not limited in this way since the vibrational spectra of individual N-H groups are compared. The infrared spectrum of XII shows asymmetric and symmetric N-H stretching vibration

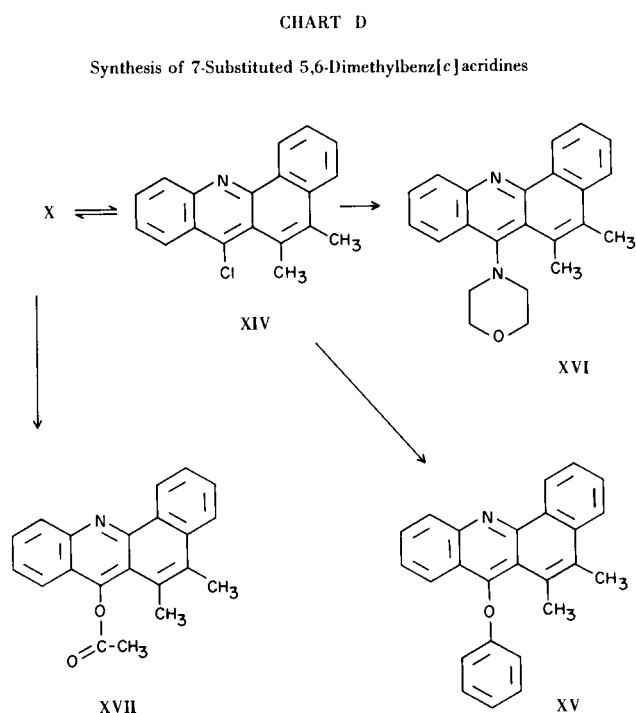
bands at  $3520\text{ cm}^{-1}$  and  $3440\text{ cm}^{-1}$ , respectively, in chloroform and at  $3510\text{ cm}^{-1}$  and  $3430\text{ cm}^{-1}$ , respectively, in carbon tetrachloride. In both media the intensities of the symmetrical bands are higher than those of the asymmetrical bands. Mason's study indicates that *N*-heteroaromatic amines in the amino form exhibit asymmetric and symmetric N-H stretching vibration bands at about  $3500\text{ cm}^{-1}$  and  $3400\text{ cm}^{-1}$ , respectively, in carbon tetrachloride and that the intensity of the latter is greater. *N*-Heteroaromatic imines included in his study show either a single N-H stretching vibration band of low intensity at about  $3300\text{--}3400\text{ cm}^{-1}$  when the *N*-hetero atom is substituted, or a strong band at  $3448\text{ cm}^{-1}$  and a weak one at  $3298\text{ cm}^{-1}$  in the case of 12-aminobenz[*b*]acridine (Chemical Abstracts nomenclature) in which case the *N*-hetero atom is unsubstituted. A strong band at  $1628\text{ cm}^{-1}$ , attributed to N-H deformation, is also exhibited by XII.

#### 5,6-Dimethylbenz[*c*]acridone (X).

The *N*-bromosuccinimide (NBS) bromination of III was not a smooth reaction and thus the desired 6-bromo derivative could not be obtained in amounts necessary for the conversion to X. Although the ester (IX) was found to readily undergo allylic bromination with NBS, the resulting crude 6-bromo derivative gave only a small yield of X on thermal dehydrobromination-rearrangement. It had previously been found (13) that 5,5-dimethyl-6-hydroxy-5,6-dihydrobenz[*c*]acridine (2) would not undergo a dehydration-rearrangement under normal Wagner-Meerwein conditions, *i.e.*, warming with glacial acetic acid containing 20% sulfuric acid. It has now been found that this dehydration-rearrangement to produce 5,6-dimethylbenz[*c*]acridine is readily accomplished with concentrated sulfuric acid at room temperature or on warming in polyphosphoric acid. The crude 5,5-dimethyl-6-hydroxy-7-acetoxy-5,6-dihydrobenz[*c*]acridine obtained from the hydrolysis of the corresponding crude 6-bromo derivative was dehydrated-rearranged to give an overall 91% yield (based on IX) of the acridone X on heating with PPA (Chart C). Infrared and ultraviolet spectral studies of X suggest that it exists essentially in the acridone form (Xb) (9).

#### Other 7-Substituted-5,6-dimethylbenz[*c*]acridines.

Reaction sequences used to produce several such derivatives are outlined in Chart D. Acetylation of X was more difficult than for III and produced the 7-acetoxy-5,6-dimethylbenz[*c*]acridine (XVII) in only 55% yield. Ultraviolet and infrared spectra were consistent with the ester structure. Phosphorus oxychloride readily converted the acridone (X) into 7-chloro-5,6-dimethylbenz[*c*]acridine (XIV). This compound was stable to base but readily



underwent acid-catalyzed hydrolysis to reproduce X. The chloride (XIV) reacted with phenol to give 5,6-dimethyl-7-phenoxybenz[*c*]acridine (XV) in fair yield at  $120^\circ$  but this compound was of little use as an intermediate to prepare the desired 7-amino derivatives and only low yields resulted. 5,6-Dimethyl-7-morpholinobenz[*c*]acridine (XVI) was obtained in fair yield by heating the chloride (XIV) to a high temperature with morpholine.

The biological study of selected examples of the new compounds reported here has been undertaken by others and is being reported elsewhere (14).

#### EXPERIMENTAL (15)

##### A. Preparation of 5,5-Dimethyl-5,6-dihydrobenz[*c*]acridone (III).

##### 1. Via 2-(*o*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide (I).

##### a. 2-(*o*-Aminobenzal)-4,4-dimethyl-1-tetralone oxide (II).

The free base was prepared by adding 50 ml. of benzene and 0.2 of platinum oxide, pre-reduced in a quantitative, atmospheric pressure hydrogenation apparatus, to 5.00 g. (0.0155 mole) of 2-(*o*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide (I) (5) in 100 ml. of benzene. Hydrogen uptake after 3 hours was 95% of theoretical. The precipitate, formed during hydrogenation, was dissolved in cold benzene and the solution was filtered. The addition of petroleum ether, b.p.  $30\text{--}60^\circ$ , gave 2.98 g. (66%) of white needles, m.p.  $154\text{--}155^\circ$ . Recrystallization from ether gave white needles, m.p.  $147\text{--}151^\circ$ ; U.V.  $\lambda_{\text{max}}$  247, (259), 300 m $\mu$  ( $\epsilon$ , 16,900, 15,200, 5,130); (potassium bromide)  $\nu(\text{NH})$ 3480/14, 3380/20, 3258/10;  $\nu(\text{C=O})$ 1680/43,  $\nu(\text{Ar})$ (1643)/38, 1635/40, (1612)/32, 1608/36, (chloroform-lithium fluoride)  $\nu(\text{NH})$ 3470/24, 3390/30,

$\nu(\text{C}=\text{O})$ 1686/78,  $\nu(\text{Ar})$ 1612/51, 1599/50; (chloroform)  $\nu(\text{NH})$ 3475/25, 3395/27,  $\nu(\text{C}=\text{O})$ 1685/81,  $\nu(\text{Ar})$ (1627)/65, 1619/67, 1607/71.

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{19}\text{NO}_2$ : C, 77.79; H, 6.53; N, 4.77. Found: C, 77.49; H, 6.77; N, 4.97.

The hydrochloride of II was prepared by bubbling anhydrous hydrogen chloride into a filtered solution of 0.64 g. of II in 600 ml. of dry ether, giving 0.71 g. (98.7%) of a white, powdery solid, m.p. 131-132° (dec.). Attempts at purification were unsuccessful; U.V.  $\lambda$  max 246, (259), 301  $m\mu$  ( $\epsilon$ , 16,400, 14,600, 4,720); (potassium bromide)  $\nu(\text{NH})$ 3425/8,  $\nu(\text{C}=\text{O})$ 1687/36,  $\nu(\text{Ar})$ 1604/22.

#### b. Cyclization of II.

A solution of 1.46 g. (0.005 mole) of II in 20 ml. of concentrated hydrochloric acid was heated 30 minutes on a steam bath, cooled and neutralized with dilute sodium hydroxide. The resulting solid was recrystallized from methanol-water to give 0.88 g. (64.3%) of white needles, m.p. 269.5-272.5°; U.V.  $\lambda$  max 265, 273, (305), 317, (335), 349, 363  $m\mu$  ( $\epsilon$ , 29,900, 33,400, 7,400, 11,200, 8,000, 10,800, 8,500);  $\lambda$  max (95% ethanol) (215), 265, 273, (307), 317, (337), 350, 365,  $m\mu$  ( $\epsilon$ , 22,100, 31,100, 34,400, 7,800, 11,800, 8,240, 11,300, 8,960); (potassium bromide-lithium fluoride prism)  $\nu(\text{NH})$ 3420/9, 3260/30,  $\nu(\text{C}=\text{O})$ 1624/58,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$  1607/51, 1567/53; chloroform-lithium fluoride prism)  $\nu(\text{NH})$ 3425/25,  $\nu(\text{C}=\text{O})$ 1624/51,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$ 1602/43, 1567/37; (chloroform)  $\nu(\text{OH})$ 3670/14, 3430/26,  $\nu(\text{C}=\text{O})$ 1630/64,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$ 1610/67, 1570/80; (methylene chloride)  $\nu(\text{OH})$ 3665/22, 3539/10,  $\nu(\text{NH})$ 3430/18,  $\nu(\text{C}=\text{O})$ 1632/71,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$ 1613/75, 1580/75, 1574/76, 1538/62.

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{17}\text{NO}$ : C, 82.88; H, 6.22; N, 5.09. Found: C, 82.97; H, 6.65; N, 5.09.

#### c. Reduction of I Followed by Cyclization.

A solution of 2.0 g. (0.006 mole) of I in 50 ml. of benzene was added to 0.1 g. of pre-reduced platinum oxide in 30 ml. of benzene in a quantitative hydrogenation apparatus. Hydrogen uptake was stoichiometric after 45 minutes. Dry hydrogen chloride was bubbled into the reaction mixture forming a viscous yellow oil insoluble in benzene. About three-fourths of the benzene was removed on a steam bath to effect cyclization. After cooling, the residual benzene was removed by filtration and the solid was washed with benzene. The solid product was dissolved in methanol and the catalyst was removed by filtration. The methanolic solution was neutralized with 5% sodium bicarbonate, and the product precipitated upon the addition of water. Crystallization from methanol-water gave 1.29 g. (76%) of III.

#### 2. Via 7-Carboxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (IV).

##### a. 5,5-Dimethyl-5,6-dihydrobenz[c]acridine-7-carbonyl chloride (V).

To 9.6 g. (0.032 mole) of 5,5-dimethyl-7-carboxy-5,6-dihydrobenz[c]acridine (IV) (2) in 100 ml. of benzene was added 5 ml. of thionyl chloride. The mixture was heated at reflux for 1.5 hours, about one-half hour beyond the time at which solution was effected. The solvent and excess thionyl chloride were evaporated and the residue was redissolved in benzene. The solution was decolorized with Norite A and most of the benzene was evaporated. The addition of hexane gave 8.59 g. (84.2%) of slightly yellow crystals, m.p. 135-136°, U.V.  $\lambda$  max 214, (225), (260), 268, 302, 318, 333, 347  $m\mu$  ( $\epsilon$ , 43,800, 26,320, 26,880, 34,580, 7,040, 7,460, 10,650, 12,570); (carbon tetrachloride)  $\nu(\text{C}=\text{O})$ 1787/84.

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{16}\text{ClNO}$ : C, 74.64; H, 5.01; N, 4.35. Found: C, 74.90; H, 5.09; N, 4.07.

##### b. 5,5-Dimethyl-5,6-dihydrobenz[c]acridine-7-carboxamide (VI).

After addition with stirring of 4.43 g. (0.014 mole) of V in 25 ml. of dioxane to 15 ml. of concentrated aqueous ammonia in 25 ml. of dioxane, the solution was heated on a steam bath for 30 minutes. After evaporation of the solvent, the residue was thoroughly washed with water and crystallized, after charcoaling, from methanol-water to give 3.6 g. (86.2%) of white needles, m.p. 182-183°; U.V.  $\lambda$  max 214, 225, (259), 267, 302, 316, 332, 346  $m\mu$  ( $\epsilon$ , 34,200, 15,600, 20,400, 32,200, 5,500, 5,800, 7,900, 9,100); (potassium bromide)  $\nu(\text{NH})$ 3455/32, 3110/36,  $\nu(\text{C}=\text{O})$  1673/77,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$ 1594/41, 1510/22, 1492/29; (methylene chloride)  $\nu(\text{NH})$ 3510/30, 3400/35,  $\nu(\text{C}=\text{O})$ 1688/84,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$ 1592/60, 1562/11, 1509/25; (chloroform)  $\nu(\text{NH})$ 3510, 3400/35,  $\nu(\text{C}=\text{O})$ 1682/82,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$ 1590/59, 1560/12.

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}$ : C, 79.44; H, 6.00; N, 9.27. Found: C, 79.92; H, 6.22; N, 9.22.

##### c. Methyl 5,5-Dimethyl-5,6-dihydrobenz[c]acridine-7-carbamate (VII).

A solution of 0.35 g. (0.015 g.-atom) of sodium in 25 ml. of methanol was added to 2.3 g. (0.0076 mole) of VI dissolved in 25 ml. of methanol. To this was added rapidly with stirring 1.21 g. (0.0076 mole) of bromine in 25 ml. of methanol. After standing at room temperature for several minutes, the reaction mixture was heated on a steam bath for 20 minutes, cooled and made just acid to litmus with acetic acid. The solvent was evaporated and the residue was washed with water and dried to give 2.2 g. (87%) of a white solid, m.p. 186-191°. From ethyl acetate-pentane were obtained white crystals, m.p. 188-191°; U.V.  $\lambda$  max 213, 228, (260), 268, 302, 316, 330, 345  $m\mu$  ( $\epsilon$ , 35,600, 24,900, 31,000, 40,300, 9,500, 10,200, 12,300, 13,700); (potassium bromide)  $\nu(\text{NH})$ 3315/29,  $\nu(\text{C}=\text{O})$ 1710/64,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$ 1603/25, 1581/10, 1528/56.

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_2$ : C, 75.88; H, 6.07; N, 8.43. Found: C, 75.96; H, 6.01; N, 8.71.

##### d. Methyl N-Nitroso-5,5-dimethyl-5,6-dihydrobenz[c]acridine-7-carbamate (VIII).

A slight modification of the procedure of White (7) was used. Nitrogen dioxide was bubbled into methylene chloride at 0° for several minutes and titrated iodometrically. A two-fold excess (10 ml.) of this solution in 25 ml. of methylene chloride was cooled to about -60° in a dry ice-acetone bath; 1.0 g. of sodium acetate was added and the mixture was placed in an ice-water bath. A solution of 1.34 g. (0.004 mole) of VII in 10 ml. of methylene chloride was added with stirring. After standing at room temperature for 30 minutes, the reaction mixture was washed with 5% sodium bicarbonate, twice with water and dried over anhydrous sodium sulfate. After evaporation of solvent at room temperature, the yellow oil was recrystallized from methanol-water to give 1.1 g. (76%) of yellow plates, m.p. 138-140° (dec.), softens at 136°; U.V.  $\lambda$  max 215, (225), (262), 269, 304, 320, 335, 349  $m\mu$  ( $\epsilon$ , 46,100, 29,600, 3,800, 37,300, 8,300, 8,600, 12,300, 13,700); (carbon tetrachloride)  $\nu(\text{C}=\text{O})$ 1769/74,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$ 1617-1625/16, 1605/30,  $\nu(\text{N}=\text{O})$ 1510/37; (methylene chloride)  $\nu(\text{C}=\text{O})$  1767/75,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$ 1624/16,  $\nu(\text{N}=\text{O})$ 1550/34, 1505/39; (chloroform)  $\nu(\text{C}=\text{O})$ 1765/83,  $\nu(\text{C}=\text{C}$  and  $\text{C}=\text{N})$ 1624/23, 1609/40,  $\nu(\text{N}=\text{O})$ 1557/41, 1503/33.

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_3$ : C, 69.79; H, 5.30; N, 11.63. Found: C, 69.68; H, 5.61; N, 11.71.

##### e. Base-Catalyzed Hydrolysis of VIII.

Upon addition of a solution of 0.3 g. of potassium hydroxide

in 10 ml. of isopropyl alcohol to a suspension of 0.35 g. (0.0097 mole) of VIII in 10 ml. of isopropyl alcohol, complete solution was effected at room temperature with a color change from light yellow to orange. The solution was immediately poured with rapid stirring into about 150 ml. of hot 3 *N* sulfuric acid giving gas evolution. After heating for 15 minutes on a steam bath, the reaction mixture was cooled and brought to about pH 4 with 6 *N* sodium hydroxide. The layers which formed were separated and the alcoholic layer evaporated. The residue, after evaporation of the isopropyl alcohol, was washed with ethyl acetate and crystallized from methanol-water to give 0.15 g. (55%) of III, identified by m.p., mixture m.p. and (as described below) acetylation.

### 3. *Via* Condensation of 4,4-Dimethyl-1-tetralone and Anthranilic Acid.

Following the procedure of Reed (4), 6.25 g. (0.036 mole) of 4,4-dimethyl-1-tetralone and 5.0 g. (0.037 mole) of anthranilic acid were heated together up to 120° over about one hour and then heated at 220° for 30 minutes. After cooling, benzene was added to the reaction mixture to give a clear, red solution. Seeding with authentic III initiated crystallization to give 5.0 g. (50%) of III, identified *via* m.p., mixture m.p. and acetylation.

#### B. Synthesis of 5,6-Dimethylbenz[*c*]acridino (X).

##### 1. 5,5-Dimethyl-7-acetoxy-5,6-dihydrobenz[*c*]acridine (IX).

A solution of 5.93 g. (0.0216 mole) of III and 5 ml. of acetic anhydride in 50 ml. of pyridine and 5 ml. of *N,N*-dimethylformamide was heated at reflux for 2 hours. After cooling to room temperature, the reaction mixture was poured into 200 ml. of ice-water. The resulting oil solidified to give, after recrystallization from methanol-water, 6.18 g. (90.3%) of a white crystalline product. Recrystallization from *n*-hexane gave white needles, m.p. 115.5-116.5°; U.V.  $\lambda$  max 225, (258), 265, 299, 312, 327, 343  $\mu$  ( $\epsilon$ , 27,700, 31,900, 39,900, 10,400, 10,400, 11,900, 13,400); (potassium bromide)  $\nu$ (C=O)1762/76,  $\nu$ (C=C and C=N)1629/26, 1614/23, 1605/29, 1581/11, 1562/17, 1507/39 (carbon tetrachloride),  $\nu$ (C=O)1775/85,  $\nu$ (C=C and C=N)1628/53, 1603/44.

*Anal.* Calcd. for  $C_{21}H_{19}NO_2$ : C, 79.47; H, 6.03; N, 4.41. Found: C, 79.70; H, 6.24; N, 4.41.

##### 2. 5,6-Dimethylbenz[*c*]acridone (X).

A suspension of 2.0 g. (0.011 mole) of *N*-bromosuccinimide in a solution of 3.46 g. (0.011 mole) of IX in 100 ml. of carbon tetrachloride was heated at reflux for 2 hours. A total of 0.1 g. of benzoyl peroxide was added during the reflux period. The cooled reaction mixture was filtered and the filtrate was washed with 5% sodium bicarbonate, water, and dried over anhydrous sodium sulfate. The solvent was evaporated on a rotary film evaporator at room temperature. The residual solid was dissolved in 40 ml. of dioxane, and 15 ml. of 10% sodium hydroxide were added. After heating on a steam bath for one hour, the cooled reaction mixture was partially neutralized with 6 *N* hydrochloric acid and evaporated to dryness. The residue was thoroughly washed with water, dissolved in methanol and neutralized to pH 7. The addition of water precipitated a white solid which was collected by filtration and dried. This material was dissolved in 150 g. of polyphosphoric acid (PPA) at 140° and heated at that temperature for 2 hours. The reaction mixture was cooled and poured into 200 ml. of ice water to give 2.72 g. (91.3%) of a yellow solid and recrystallized from acetone, m.p. 279.5-281.5°; U.V.  $\lambda$  max 207, 213, 233, 259, (275), 284, (298), 311, 324, 343, (373), 389  $\mu$  ( $\epsilon$ , 36,200, 34,400, 27,800, 27,800, 32,400, 45,400, 12,000, 11,000, 7,000, 9,200, 4,800, 7,200); (potassium bromide)

$\nu$ (NH)3320/15,  $\nu$ (C=O)1633/58,  $\nu$ (C=C and C=N)1611/48, 1598/45, 1581/55, 1570/61, 1536/63; (methylene chloride)  $\nu$ (OH)3665/12, 3583/5,  $\nu$ (NH)3450/7,  $\nu$ (C=O)1633/43,  $\nu$ (C=C and C=N)1618/45, 1599/36, 1538/30; (chloroform)  $\nu$ (NH)3460/9,  $\nu$ (C=O)1630/47,  $\nu$ (C=C and C=N)1615/49, 1593/42.

*Anal.* Calcd. for  $C_{19}H_{15}NO$ : C, 83.49; H, 5.53; N, 5.13. Found: C, 83.10; H, 5.67; N, 5.46.

#### C. Synthesis of Some 7-Substituted 5,5-Dimethyl-5,6-dihydrobenz[*c*]acridines.

##### 1. 5,5-Dimethyl-7-chloro-5,6-dihydrobenz[*c*]acridine (XI).

###### a. From III and Phosphorus Oxychloride.

A solution of 0.75 g. (0.0027 mole) of III in 10 ml. of phosphorus oxychloride and one drop of concentrated sulfuric acid was refluxed 2.5 hours and the excess phosphorus oxychloride was distilled off under aspirator pressure at 125°. The residual yellow oil was allowed to cool and a mixture of ice and concentrated ammonia was added. The aqueous phase was extracted with chloroform and the combined chloroform extracts were washed with 0.5% aqueous ammonia, then with water and dried over anhydrous sodium sulfate. The chloroform was evaporated and the slightly yellow solid crystallized from ethyl acetate to give 0.61 g. (76%) of white needles, m.p. 148-149°; U.V.  $\lambda$  max 229, (261), 268, 303, 317, 331, 346  $\mu$  ( $\epsilon$ , 26,900, 32,900, 42,100, 9,900, 10,000, 11,800, 13,200); (isooctane)  $\lambda$  max 228, 260, 268, (290), 302, 315, 329, 344  $\mu$  ( $\epsilon$ , 27,200, 37,400, 45,800, 10,400, 10,900, 10,300, 11,500, 13,200); (potassium bromide)  $\nu$ (C=C and C=N)1587/16, 1578/15; (chloroform)  $\nu$ (C=C and C=N)1593/52, 1578/38.

*Anal.* Calcd. for  $C_{19}H_{16}ClN$ : C, 77.67; H, 5.49; N, 4.77; Cl, 12.07. Found: C, 77.29; H, 5.35; N, 4.85; Cl, 12.51.

###### b. From III and Thionyl Chloride.

A solution of 1.0 g. (0.0036 mole) of III in 100 ml. of benzene and 10 ml. of thionyl chloride was heated at reflux for 3 hours. The benzene and excess thionyl chloride was removed on a rotary film evaporator. The residue was crystallized from *n*-hexane, after charcoaling, to give 0.83 g. (78%) of white crystals, m.p. 147-148°; mixed m.p. with authentic XI, 147-148°.

The attempted hydrolysis of XI was performed by heating a solution of 14 mg. of XI in 4 ml. of 7% hydrochloric acid at reflux for one hour. The solution was cooled and neutralized with sodium carbonate solution. The precipitate which formed was collected by filtration and recrystallized from methanol-water to give 12 mg. of white crystals, m.p. 147-149°; mixed m.p. with authentic XI, 147-149°. A solution of 12 mg. of XI in 2 ml. of concentrated hydrochloric acid which was heated under reflux for 1.5 hours gave only starting material.

The attempted reaction of XI with ammonium carbonate in phenol was performed by following the procedure of Albert and Ritchie (11). Compound XI, 0.67 g. (0.002 mole), was dissolved in phenol at ca. 70°, and 0.5 g. (0.01 equivalent) of ammonium carbonate was added with stirring. The reaction mixture was heated at 100° for 15 minutes and then at 120° for 1.5 hours with the occasional addition of a total of 0.2 g. of additional ammonium carbonate. Only starting material was recovered.

The attempted synthesis of 5,5-dimethyl-7-methoxy-5,6-dihydrobenz[*c*]acridine was performed by heating a solution of 0.83 g. (0.0028 mole) of XI in methanolic sodium methoxide, prepared from 0.2 g. (0.01 g.-atom) of sodium dissolved in 75 ml. of methanol, under reflux for 8 hours. Again only starting material was recovered.

2. 5,5-Dimethyl-7-amino-5,6-dihydrobenz[*c*]acridine (XII).

To a solution of 2.26 g. (0.007 mole) of VII in 100 ml. of methanol was added 50 ml. of 4% potassium hydroxide. The solution was heated under reflux for 7 hours, cooled and acidified with 6 *N* hydrochloric acid. After refluxing several minutes, the solution was made just basic to litmus and the solvent was evaporated. The resulting white solid was thoroughly washed with water and recrystallized from methanol-water to give 1.27 g. (67%) of a white solid, m.p. 140-145°. After recrystallization from 2-propanol, the m.p. increased to 146.5-147.5°; U.V.  $\lambda$  max (222), 270, (276), (314), 325, (346), 362,  $m\mu$  ( $\epsilon$ , 19,000, 37,400, 36,200, 9,300, 10,100, 7,100, 4,400); (potassium bromide)  $\nu(\text{NH})$ 3460/6, 3370/21,  $\nu(\text{NH deformation})$ 1624/54, 1612/57,  $\nu(\text{C=C and C=N})$ 1578/40, 1556/30, 1504/53; (carbon tetrachloride)  $\nu(\text{NH})$ 3510/24, 3430/34,  $\nu(\text{NH def.})$ 1628/93,  $\nu(\text{C=C and C=N})$ 1592/60, 1508/76; (chloroform)  $\nu(\text{NH})$ 3510/17, 3440/27,  $\nu(\text{NH def.})$ 1628/84,  $\nu(\text{C=C and C=N})$ 1587/51, 1505/47.

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{18}\text{N}_2$ : C, 83.17; H, 6.61; N, 10.21. Found: C, 83.18; H, 6.70; N, 10.36.

## a. Attempted Hydrolysis of XII.

A 0.3 g. sample of XII in 50 ml. of 6 *N* hydrochloric acid was heated at reflux for 4 hours. The reaction mixture was cooled and the solid was removed by filtration and shown to be XII.

## b. Attempted Diazotiation of XII.

Using mild conditions a solution of 0.24 g. (0.00087 mole) of XII in 25 ml. of methanol was acidified with 3 ml. of 6 *N* hydrochloric acid, and 0.07 g. (0.001 mole) of sodium nitrite was added with stirring. The reaction mixture was then poured into an excess of hot 3 *N* sulfuric acid and heated on a steam bath 15 minutes. After cooling, the solution was neutralized with dilute sodium hydroxide giving a white precipitate which was found to be XII.

Using strong conditions, a solution of 0.5 g. (0.0072 mole) of sodium nitrite in 5 ml. of concentrated sulfuric acid at 15° was added 0.31 g. (0.0011 mole) of XII. The solution was added to 10 ml. of glacial acetic acid and stirred for one hour. The reaction mixture was then poured into 25 ml. of 3 *N* sulfuric acid and heated on a steam bath for one hour, then cooled and neutralized to give only a very small amount of dark brown material which could not be crystallized.

3. Lactone (XIII) of 7-Carboxy-5,5-dimethyl-6-hydroxy-5,6-dihydrobenz[*c*]acridine.

A solution of 0.51 g. (0.0013 mole) of 7-carboxy-5,5-dimethyl-6-bromo-5,6-dihydrobenz[*c*]acridine, prepared according to Cromwell and Bell (13), was dissolved in 10 ml. of dioxane and 5 ml. of 6 *N* sodium hydroxide and heated on a steam bath for one hour. After cooling, the reaction mixture was neutralized to pH 3-4 with 6 *N* hydrochloric acid and poured into ca. 100 ml. of water. The yellow precipitate was collected by filtration, washed and dried. Crystallization from acetone-water, with acidification to pH 4, gave 0.3 g. (75%) of white needles, m.p. 230.5-231°; U.V.  $\lambda$  max 212, (226), 270, (334), 346, 360  $m\mu$  ( $\epsilon$ , 54,500, 33,000, 37,800, 12,200, 16,250, 12,500); (potassium bromide)  $\nu(\text{C=O})$ 1776/84,  $\nu(\text{C=C and C=N})$ 1653/30, 1618/16, 1606/14, 1528/36; (carbon tetrachloride)  $\nu(\text{C=O})$ 1779/94,  $\nu(\text{C=C and C=N})$ 1653/43, 1620/11, 1609/11; (methylene chloride)  $\nu(\text{C=O})$ 1775/87, (1765)/82,  $\nu(\text{C=C and C=N})$ 1656/40, 1621/11, 1610/14, 1530/39; (chloroform)  $\nu(\text{C=O})$ 1774/87, (1763)/84,  $\nu(\text{C=C and C=N})$ 1654/41, 1621/10, 1610/11.

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{15}\text{NO}_2$ : C, 79.71; H, 5.01; N, 4.65.

Found: C, 79.54; H, 5.11; N, 4.91.

D. Synthesis of Various 7-Substituted 5,6-Dimethylbenz[*c*]acridines.1. 5,6-Dimethyl-7-chlorobenz[*c*]acridine (XIV).

A solution of 1.0 g. (0.0037 mole) of X in 15 ml. of phosphorus oxychloride was heated at reflux for one hour, cooled and poured into 200 ml. of concentrated ammonia and 200 g. of ice. The mixture was stirred several minutes and then extracted with chloroform. The combined extracts were washed, dried over anhydrous sodium sulfate and evaporated to give a yellow solid. Crystallization, with charcoaling, from ethyl acetate gave 0.65 g. (61%) of yellow needles, m.p. 147.5-149°; U.V.  $\lambda$  max 224, 238, (279), 285, 298, (334), 349, 364, 379, 398  $m\mu$  ( $\epsilon$ , 36,800, 29,400, 46,500, 50,600, 49,900, 3,800, 5,300, 5,800, 6,000, 5,200; (isooctane)  $\lambda$  max 224, 240) (278), 287, 299, 333, 348, 362, 378, 397  $m\mu$  ( $\epsilon$ , 37,200, 29,600, 44,400, 51,600, 51,200, 4,600, 6,200, 7,000, 7,200, 6,200); (carbon tetrachloride)  $\nu(\text{C=C and C=N})$ 1622/24, 1610-1510/29, 1498/65.

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{14}\text{ClN}$ : C, 78.21; H, 4.84; N, 4.80; Cl, 12.15. Found: C, 78.16; H, 4.86; N, 4.88; Cl, 12.09.

## a. Hydrolysis of XIV.

The addition of 25 ml. of 6 *N* hydrochloric acid to 0.10 g. (0.0006 mole) of XIV effected an immediate color change from yellow to orange. Upon heating, the solid dissolved. The solution was heated at reflux for 30 minutes, giving rise to the formation of a precipitate. The reaction mixture was cooled, poured into 100 ml. of water and neutralized to litmus with 6 *N* sodium hydroxide. The solid was collected and crystallized from methanol-water to give 0.16 g. (90%) of yellow needles, m.p. 278.5-280.5°; mixture m.p. with authentic X, 278.5-281°.

b. Attempted Synthesis of 5,6-Dimethyl-7-methoxy-benz[*c*]acridine.

A mixture of 0.31 g. (0.001 mole) of XIV in 30 ml. of methanol and 0.05 g. of sodium (0.002 g.-atom) in 10 ml. of methanol was heated at reflux for 10 hours without effecting complete solution. Only starting material was recovered.

2. 5,6-Dimethyl-7-phenoxybenz[*c*]acridine (XV).

A mixture of 0.48 g. (0.0016 mole) of XIV and 3 g. of phenol was heated at 120° for one hour. After cooling, the reaction mixture was poured into an excess of 3 *N* sodium hydroxide giving a yellow precipitate. Crystallization from benzene-hexane gave 0.3 g. (52%) of yellow needles, m.p. 195.5-196.5°; U.V.  $\lambda$  max 222, (234), (276), 284, 297, 328, 342, 357, 373, 393  $m\mu$  ( $\epsilon$ , 50,500, 31,600, 47,100, 51,800, 55,000, 5,130, 6,630, 6,600, 5,900, 5,130); (potassium bromide)  $\nu(\text{C=C and C=N})$ 1617/8, 1592/21, 1562/27, 1493/36.

*Anal.* Calcd. for  $\text{C}_{25}\text{H}_{19}\text{NO}$ : C, 85.93; H, 5.48; N, 4.01. Found: C, 86.03; H, 5.49; N, 4.17.

3. 5,6-Dimethyl-7-morpholinobenz[*c*]acridine (XVI).

## a. Sealed Tube Method.

A mixture of 0.58 g. (0.0021 mole) of XIV and 0.4 g. (0.0046 mole) of morpholine was heated in a sealed tube at 200° for 14 hours. After cooling, the tube was opened, ethyl acetate was added and morpholine hydrochloride was removed by filtration. The ethyl acetate solution was treated with charcoal and the solvent was evaporated. Methanol was added to the remaining oil, precipitating a solid. Crystallization from hexane gave 0.30 g. (44%) of yellow plates, m.p. 146-147.5°; U.V.  $\lambda$  max 226, (266),

274, (290), 300, (312), 346, 362, 381, 398  $m\mu$  ( $\epsilon$ , 35,200, 29,500, 32,800, 34,500, 44,300, 24,800, 4,250, 5,500, 7,000, 7,250); (potassium bromide)  $\nu(C=C$  and  $C=N)$ 1623/6, 1610/8, 1565/16, 1543/22, 1503/35.

*Anal.* Calcd. for  $C_{23}H_{22}N_2O$ : C, 80.67; H, 6.48; N, 8.18. Found: C, 81.08; H, 6.43; N, 8.40.

b. Phenol Method.

A solution of 0.34 g. (0.0012 mole) of XIV in 1.0 g. of phenol was heated at  $100^\circ$  for 30 minutes and then at  $120^\circ$  for 30 minutes. To this was added 5 ml. of morpholine, and heating was continued at  $150^\circ$  for 1.5 hours. After cooling, the reaction mixture was poured into an excess of 3 *N* sodium hydroxide, precipitating a yellow solid. This was washed, dried, and dissolved in benzene. The benzene solution was chromatographed through an alumina column. Two yellow bands separated. The first, after evaporation of solvent gave yellow platelets which were recrystallized from methanol, m.p.  $132-139^\circ$ . This material was shown by spectral studies to be impure XVI.

4. 5,6-Dimethyl-7-acetoxybenz[c]acridine (XVII).

A solution of 0.47 g. (0.0017 mole) of X in 5 ml. of dimethylformamide, 15 ml. of pyridine and 3 ml. of acetic anhydride was refluxed for 3.5 hours. After cooling, the reaction mixture was poured into ice water, giving a yellow solid, which was crystallized from benzene-hexane to give 0.3 g. (55%) of yellow needles, m.p.  $206-210^\circ$  (vac.); U.V.  $\lambda$  max 223, (232), (273), 282, 295, 326, 342, 356, 373, 392  $m\mu$  ( $\epsilon$ , 37,500, 29,800, 45,000, 49,300, 49,300, 5,000, 6,400, 5,900, 5,500, 4,800); (methylene chloride)  $\nu(C=O)$ 1770/69,  $\nu(C=C$  and  $C=N)$ 1624/17, 1610/10, 1600/10, 1568/40, 1495/40; (chloroform)  $\nu(C=O)$ 1770/71,  $\nu(C=C$  and  $C=N)$ 1626/19, 1612/10, 1602/11, 1571/41, 1498/32.

*Anal.* Calcd. for  $C_{21}H_{17}NO_2$ : C, 79.98; H, 5.43. Found: C, 80.27; H, 5.65.

E. 5,6-Dimethylbenz[c]acridine from 5,5-Dimethyl-6-hydroxy-5,6-dihydrobenz[c]acridine.

1. With Sulfuric Acid.

A sample (0.81 g., 0.0029 mole) of the 6-hydroxy compound was dissolved in 11 g. of concentrated sulfuric acid with noticeable warming. After standing at room temperature for 10 minutes, the orange solution was diluted with water and neutralized with 3 *N* sodium hydroxide to give a yellow solid which was collected by filtration, washed and dried. Crystallization from benzene gave 0.73 g. (96.5%) of yellow needles, m.p.  $161-162^\circ$ ; mixture m.p. with authentic 5,6-dimethylbenz[c]acridine,  $161-162.5^\circ$  (2)

2. With Polyphosphoric Acid.

A solution of 1.84 g. (0.0067 mole) of the 6-hydroxy compound in about 75 g. of PPA was heated at  $95^\circ$  for 45 minutes. The cooled reaction mixture was poured into water and the resulting mixture was neutralized with 3 *N* sodium hydroxide. The precipitate which formed was collected, washed, dried and crystallized from benzene to give 1.24 g. (72%) of yellow needles, m.p.  $161-163^\circ$ ; mixture m.p. with authentic 5,6-dimethylbenz[c]acridine,  $161-163^\circ$ .

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