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5,6-Dimethylbenz[c]acridines, functionalized in the 7-position by the carboxy, carbomethoxy, carboxamido, *N*-ethylcarboxamido, acetyl, cyano, chloro, methoxy or amino group are reported for the first time. Also various related 5,5-dimethyl-5,6-dihydrobenz[c]acridines including the 7-carbomethoxy, 6-hydroxy-7-carboxy, 6-bromo-7-carbomethoxy, 6-methoxy-7-carboxy, 6-methoxy-7-carbomethoxy, and 6-hydroxy-7-*N*-ethylcarboxamido derivatives which serve as precursors to the completely aromatized 5,6-dimethylbenz[c]acridines are also reported for the first time.

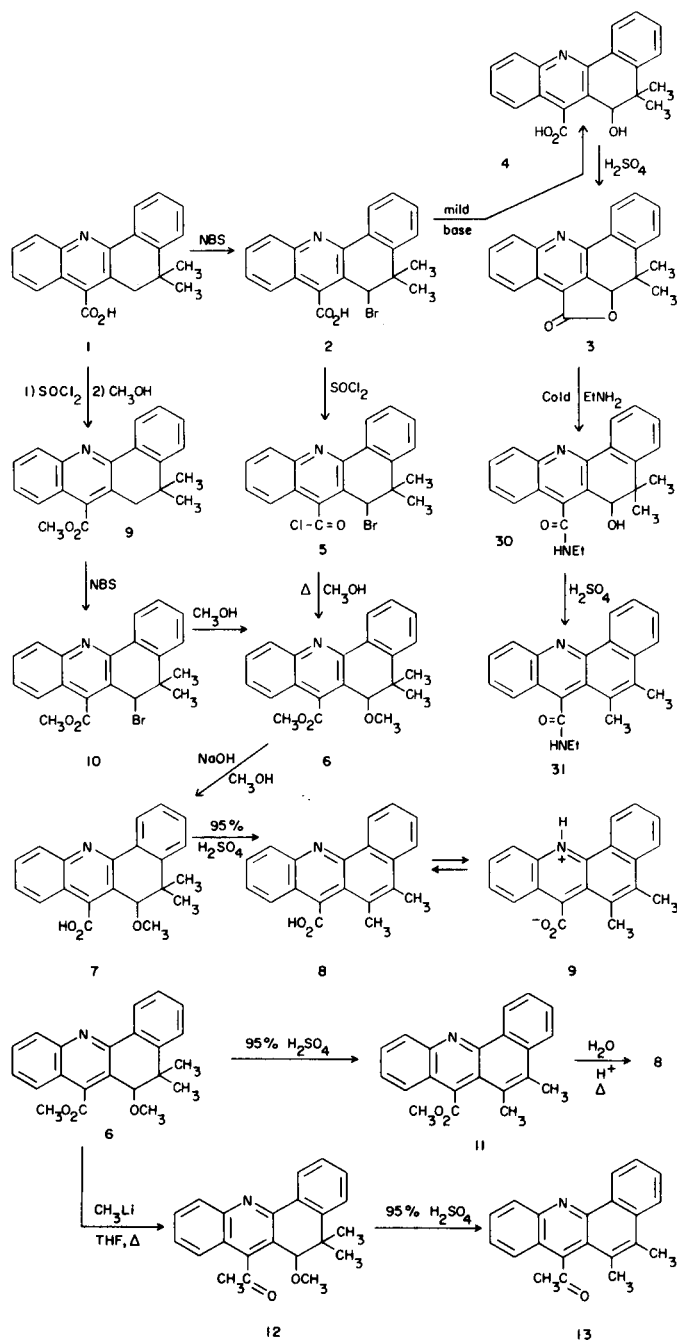
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### Results and Discussion.

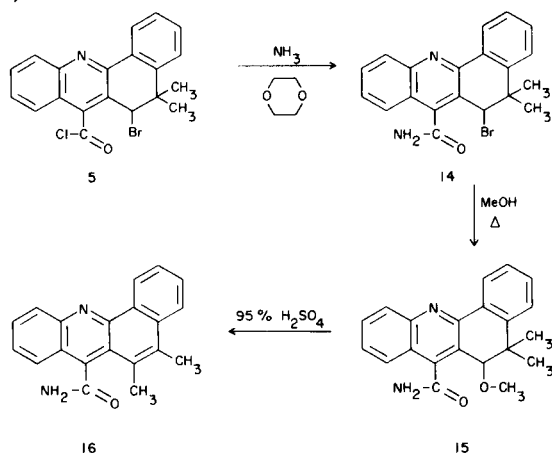
As an extension of our continuing program (1) concerned with the synthesis of new benz[c]acridines of potential biological interest as carcinogens, carcinostatic agents and as anti-parasitical agents, a wide variety of 5,6-dimethyl-7-substituted-benz[c]acridines have been obtained.

It seemed to us that an ideal starting point for the synthesis of the unknown 7-carboxy-5,6-dimethylbenz[c]acridine (**8**) would be known (5) lactone **3** or its precursor 7-carboxy-6-hydroxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (**4**), obtained by treating the known (3) 6-bromo analogue **2** with mild base. However the lactone **3** proved to be stable to sulfuric acid and the hydroxy acid **4** was converted to it by this reagent. Thus, a compound which would not undergo lactone formation was needed. The introduction of a 6-methoxyfunction, presumably, would solve this problem and also allow for rearrangement to occur. The method used to obtain the methoxy acid **7** was to convert the bromo acid **2** to its acid chloride **5**, which was easily done employing thionyl chloride. When **5** was refluxed with methanol the ester-ether **6** was readily obtained. The ester-ether **6** was also prepared from the readily available (2) 7-carboxy-5,5-dimethylbenz[c]acridine (**1**) *via* the carbomethoxy derivative **9** and then the bromo ester **10**. Compound **6** as well as compound **5** can be regarded as key intermediates. The ester-ether **6** was hydrolyzed with base to afford the methoxyacid **7**, which upon aromatization with 95% sulfuric acid afforded the bright red zwitterionic 7-carboxy-5,6-dimethylbenz[c]acridine **8**. The red color of **8** is presumably due to the charge distribution in the crystal as shown in **9**.

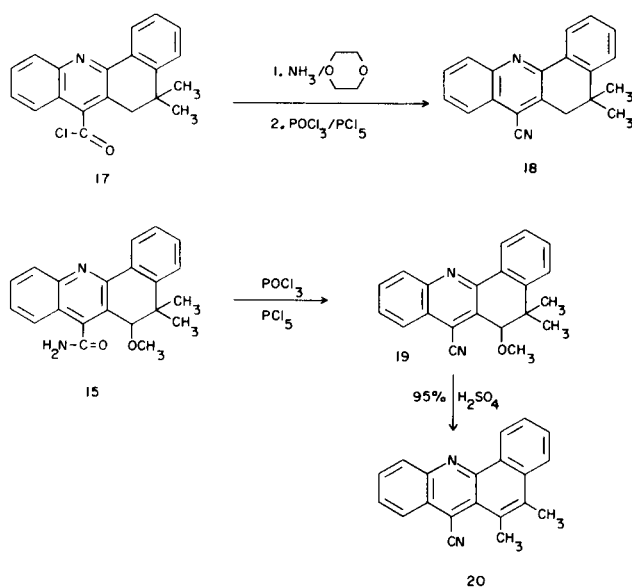
When the ester-ether **6** was treated with 95% sulfuric acid, at room temperature, a good yield of 7-carbomethoxy-5,6-dimethylbenz[c]acridine (**11**) was obtained, which was readily hydrolyzed to **8** on refluxing with hydrochloric acid. Compound **6** was also treated with methyl lithium in tetrahydrofuran at reflux temperature, to produce the 7-acetyl intermediate **12**, which was converted to the aromatic 7-acetyl-5,6-dimethylbenz[c]acridine (**13**).



The other key intermediate **5**, was also of interest, for when a solution of **5** in dry dioxane was treated with ammonia gas only the acid chloride group reacted to afford 6-bromo-7-carboxamido-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (**14**). In a facile manner, the bromine atom of **14** underwent replacement with hot methanol to give the amido-ether **15**, which was easily aromatized under usual conditions to afford 7-amido-5,6-dimethylbenz[*c*]acridine (**16**).

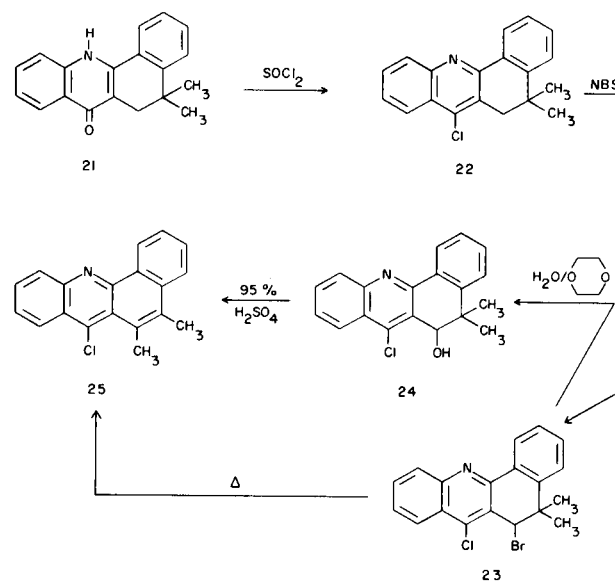


We also wished to synthesize the 7-cyano derivative **20**, but we were uncertain as to the cyano group's ability to withstand the sulfuric acid treatment necessary to aromatize the cyano ether **19**. In order to test the behavior of the cyano group under acidic conditions, 7-cyano-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (**18**) was prepared by treating the acid chloride **17** with ammonia in dry dioxane to form the amido intermediate, which was dehydrated with a mixture of phosphorus pentachloride and phosphorus oxychloride to afford **18**. When this cyano compound was treated in the usual manner necessary to



aromatize the other 6-methoxy benz[*c*]acridines (**6,7,12,15**), that is at room temperature with 95% sulfuric acid for up to one hour, no hydrolysis of the cyano group was observed. Thus it was subsequently found that **19**, which was obtained by dehydration of **15**, could be smoothly converted to 7-cyano-5,6-dimethylbenz[*c*]acridine (**20**).

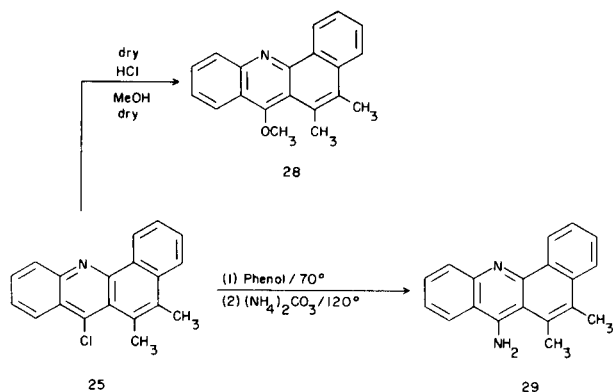
We were also interested in the synthetic routes to other 7-substituted-5,6-dimethylbenz[*c*]acridines. Of particular interest was the synthesis of 7-chloro-5,6-dimethylbenz[*c*]acridine (**25**). This compound had been synthesized previously by Nielsen and Cromwell (5), and found to possess a high degree of photodynamic toxicity (4). A simpler route, which more easily affords **25** was to chlorinate the acridone **21** with thionylchloride to yield **22** (5). NBS bromination of **22** using the heat of a sun lamp, gave a high yield of 6-bromo-7-chloro-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (**23**). Acidic hydrolysis, in dioxane, of **23** gave the chloro-alcohol **24** which underwent an acid catalyzed "α-elimination", and Wagner-Meerwein type rearrangement utilizing 95% sulfuric acid to give **25**. It was important, in the latter step, to add **24** slowly to the acid and at room temperature. Previous work has indicated that hot aqueous acidic solutions readily hydrolyze the chlorine atom in the meso position of benz[*c*]acridine.



The preparation of the 7-methoxy **28** and 7-amino **29** compounds were also of interest. 7-Methoxy-5,6-dimethylbenz[*c*]acridine (**28**) was prepared in excellent yield by treatment of the 7-chloro derivative **25** with dry hydrogen chloride and anhydrous methanol.

The 7-amino-5,6-dimethylbenz[*c*]acridine (**2a**) was desired for biological testing as an anti-tumor agent. The non-methylated 7-aminobenz[*c*]acridine (**6**) has been

reported to show antitumor action against the Furth rat leukemia (7). The amino derivative **29** was obtained by a procedure which was analogous to the method used by Albert and coworkers (6) to prepare 7-aminobenz[c]acridine from the 7-chloro derivative. Thus the dimethyl analogue **25** was found to react with phenol and then ammonium carbonate to produce the desired amino derivative **29**. The known (5) chloro derivative **25** was also made by still another method which involved the pyrolysis of bromo-chloro derivative **23**.



The lactone **30** underwent ring opening with ethylamine to produce the amido alcohol **31** which was readily aromatized to the *N*-ethylamide of 7-carboxy-5,6-dimethylbenz[c]acridine (**31**).

## EXPERIMENTAL

### 7-Carboxy-6-hydroxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (**4**).

Aqueous sodium hydroxide (20 ml., 10%) was added to a solution of the bromo acid **2** (12.5 g., 32.7 mmoles) in dioxane (100 ml.). The mixture was heated at reflux for 48 hours. The solution was evaporated to dryness to afford a gum. This gum was triturated with dilute aqueous hydrochloric acid. It slowly dissolved and precipitated a yellow solid. This solid was washed with water and dried. It was purified by dissolution in base, decolorization, and acidification. In this manner a pure sample of the hydroxy acid was obtained as a pale yellow powder (9 g., 86%, m.p. 223-226°); nmr (DMSO/TMS):  $\delta$  1.07 (s, 3H, CH<sub>3</sub>),  $\delta$  1.50 (s, 3H, CH<sub>3</sub>),  $\delta$  4.75 (s, 1H, H-6),  $\delta$  7.3-8.0 (m, 6H, arom),  $\delta$  8.18 (m, 1H, H-11),  $\delta$  8.58 (m, 1H, H-1).

*Anal.* Calcd. for C<sub>20</sub>H<sub>17</sub>NO<sub>3</sub>: C, 75.21; H, 5.37; N, 4.39. Found: C, 75.48; H, 5.27; N, 4.31.

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

A sample of the hydroxy acid **4** (1 g., 3.1 mmoles) was dissolved in sulfuric acid (95%, 40 ml.). After several hours the solution was poured onto ice and neutralized with a sodium bicarbonate solution. The resulting mixture was extracted with chloroform (3 x 200 ml). The chloroform extracts were dried and evaporated to afford the crude lactone. One recrystallization from aqueous acetone gave pure white crystals (0.8 g., 86%, m.p. 230-231°, lit (5) m.p. 230-231°); nmr (deuteriochloroform-TMS):  $\delta$  0.73 (s, 3H, CH<sub>3</sub>),  $\delta$  1.80 (s, 3H, CH<sub>3</sub>),  $\delta$  5.46 (s, 1H, H-6),  $\delta$  7.20-8.00 (m, 5H, arom),  $\delta$  8.20-8.90 (m, 3H, H-8, 11 and 1).

### 6-Bromo-7-carbonylchloride-5,5-dimethyl-5,6-dihydrobenz[c]acridine (**5**).

A mixture of the bromo acid **2** (6 g., 15.7 mmoles) and thionyl chloride (5 ml.) was heated at reflux in anhydrous benzene (150 ml.) until 1 hour after the acid dissolved. The benzene was removed under reduced

pressure to afford a pale yellow oil. A cold (-20°) methanol-ether solution (1:2, 75 ml.) was added to the oil and stirred until a solution resulted. This solution was filtered and the ether removed under pressure without heating. The white crystals which precipitated from the methanol solution were collected, washed with cold methanol, and dried to afford the product (4.95 g., 85%, m.p. 140-142°); nmr (deuteriochloroform/TMS):  $\delta$  1.20 (s, 3H, CH<sub>3</sub>),  $\delta$  1.75 (s, 3H, CH<sub>3</sub>),  $\delta$  5.37 (s, 1H, H-6),  $\delta$  7.33-7.90 (m, 6H, arom),  $\delta$  8.23 (m, 1H, H-11),  $\delta$  8.67 (m, 1H, H-1).

*Anal.* Calcd. for C<sub>20</sub>H<sub>15</sub>BrClNO: C, 59.94; H, 3.77; N, 3.50. Found: C, 59.72; H, 3.71; N, 3.62.

### 7-Carbomethoxy-6-methoxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (**6**).

A solution of the bromo acid chloride **5** (4.95 g., 12.7 mmoles) in anhydrous methanol (125 ml.) was heated at reflux for 4.8 hours. The yellow solution was concentrated to a small volume (25 ml.). An aqueous solution of potassium carbonate (0.5 g., in 5 ml.) was added to the solution to neutralize the acid formed in the reaction. The solution was diluted to 125 ml. with water to precipitate the crude product. The solid was removed by filtration and dried affording the ester ether **6** (4.04 g., 94%, 146-148°). A portion of this material was recrystallized from aqueous ethanol to afford pure material (m.p. 148-150°); nmr (deuteriochloroform/TMS):  $\delta$  1.29 (s, 3H, CH<sub>3</sub>),  $\delta$  1.58 (s, 3H, CH<sub>3</sub>),  $\delta$  3.23 (s, 3H, OCH<sub>3</sub>),  $\delta$  4.10 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>),  $\delta$  4.23 (s, 1H, H-6),  $\delta$  7.35-7.90 (m, 3H, arom),  $\delta$  8.25 (m, 1H, H-11),  $\delta$  8.68 (m, 1H, H-1).

*Anal.* Calcd. for C<sub>22</sub>H<sub>21</sub>NO<sub>3</sub>: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.15; H, 6.15; N, 4.08.

### 7-Carboxy-6-methoxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (**7**).

A solution of the ester-ether **6** (4 g., 11.9 mmoles) in methanol (50 ml.) containing sodium hydroxide (0.7 g., 17.5 mmoles) was heated at reflux for 3 days. The methanol solution was evaporated to dryness and the residue dissolved in water (70 ml.). The aqueous solution was extracted with methylene chloride (3 x 50 ml.) to remove an impurity, heated at reduced pressure to remove traces of methylene chloride, charcoaled, filtered through a celite pad and acidified to pH ~5 with dilute hydrochloric acid. The white solid that precipitated was filtered, washed with water and dried to afford the product (3.6 g., 99%, m.p. 158-160°); nmr (DTFAA/TMS):  $\delta$  1.30 (s, 3H, CH<sub>3</sub>),  $\delta$  1.73 (s, 3H, CH<sub>3</sub>),  $\delta$  3.60 (s, 3H, OCH<sub>3</sub>),  $\delta$  4.80 (s, 1H, H-6),  $\delta$  7.6-8.5 (m, 8H, arom).

*Anal.* Calcd. for C<sub>21</sub>H<sub>19</sub>NO<sub>3</sub>: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.90; H, 5.81; N, 4.24.

### 7-Carbomethoxy-5,6-dimethylbenz[c]acridine (**11**).

A sample of the ester-ether **6** (400 mg., 1.1 mmoles) was dissolved in sulfuric acid (95%, 5 ml.) with shaking. After 20 minutes the reaction was quenched by pouring the mixture into water (100 ml.). All dehydration reactions were best monitored by tlc. A drop of the reaction mixture was worked up and examined by tlc (silica gel, benzene) to determine the extent of the reaction. Prolonged reaction times resulted in a decreased yield. The aqueous mixture from above was extracted with methylene chloride (3 x 50 ml). The extracts were dried and evaporated to give a yellow oil. This oil was dissolved in absolute alcohol and the resulting solution was decolorized. The ethanol solution was concentrated (10 ml.) and water was added. Crystallization of the product occurred upon cooling (260 mg., 71%, m.p. 148-149°). A similar reaction on 2.3 g. of starting material (55 ml., 95% sulfuric acid) gave a 62% yield; nmr (deuteriochloroform/TMS):  $\delta$  2.57 (s, 6H, CH<sub>3</sub>),  $\delta$  4.08 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>),  $\delta$  7.45-8.00 (m, 6H, arom),  $\delta$  8.30 (m, 1H, H-11),  $\delta$  9.50 (m, 1H, H-1).

*Anal.* Calcd. for C<sub>21</sub>H<sub>17</sub>NO<sub>2</sub>: C, 79.98; H, 5.44; N, 4.44. Found: C, 79.68; H, 5.39; N, 4.48.

### 7-Carboxy-5,6-dimethylbenz[c]acridine (**8**).

A solution of the aromatic ester **11** (2.8 g., 9.1 mmoles) in hydrochloric acid (50 ml. 6*M*) was heated at reflux for 24 hours. The mixture was transferred to an evaporating dish and evaporated to dryness on a steam bath. The residue was taken up in dilute potassium hydroxide and the resulting yellow solution was extracted with methylene chloride (3 x 100 ml.) to remove traces of starting material. The aqueous solution was placed under reduced pressure to remove traces of methylene chloride. The

solution was filtered and acidified to pH ~ 5. The red precipitate was collected washed well with water and air-dried. Purification could be effected by dissolving in dry dioxane, filtration, concentration of the dioxane and addition of either dry pentane or dry pet ether. The red material melted at 226-230°. The yellow material from the dioxane recrystallization melted at 210°; nmr (DTFAA/TMS):  $\delta$  2.82 (s, 3H, CH<sub>3</sub>),  $\delta$  2.97 (s, 3H, CH<sub>3</sub>),  $\delta$  6.8-8.6 (m, 8H, arom).

Anal. Calcd. for C<sub>30</sub>H<sub>15</sub>NO<sub>2</sub>: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.97; H, 4.99; N, 4.61.

This acid decarboxylates on heating with a free flame to produce 5,6-dimethylbenz[c]acridine. It also reacts with thionyl chloride in benzene followed by methanol to produce compound 11.

Acid 8 was also obtained in 80% yield when the methoxy acid 7 was dissolved in 95% sulfuric acid and after 20 minutes the reaction quenched by pouring the reaction mixture into cold water, m.p. 210°.

#### 7-Acetyl-6-methoxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (12).

Excess methyl lithium was added to a solution of the ester-ether 6 (2 g., 5.9 mmoles) in dry THF (25 ml.). After stirring for 15 minutes at room temperature the solution was warmed briefly on a steam bath. This period of heating was followed by the addition of methanol (10 ml.) and evaporation to dryness. The residue was taken up in aqueous methanol (66%, 60 ml.), decolorized and filtered over celite. The methanol was removed under reduced pressure. The brown crystals which formed were removed by filtration to afford the product in a crude form (1.68 g., 89%, m.p. 143-149°). After two recrystallizations from absolute ethanol with decolorization, there was obtained light tan crystals of the pure product (1.02 g., 54%, m.p. 154-155°); nmr (deuteriochloroform/TMS):  $\delta$  1.28 (s, 3H, CH<sub>3</sub>),  $\delta$  1.40 (s, 3H, CH<sub>3</sub>),  $\delta$  2.65 (s, 3H, COCH<sub>3</sub>),  $\delta$  3.33 (s, 3H, OCH<sub>3</sub>),  $\delta$  4.23 (s, 1H, H-6),  $\delta$  7.33-7.85 (m, 6H, arom),  $\delta$  8.17 (m, 1H, H-11),  $\delta$  8.58 (m, 1H, H-1).

Anal. Calcd. for C<sub>22</sub>H<sub>21</sub>NO<sub>2</sub>: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.94; H, 5.99; N, 4.17.

#### 7-Acetyl-5,6-dimethylbenz[c]acridine (13).

A sample of the acetyl ether 12 (0.9 g., 2.7 mmoles) was dissolved in sulfuric acid (95%, 25 ml.). After 45 minutes the reaction was quenched by pouring the mixture over ice. The mixture was neutralized with a sodium hydroxide solution and extracted with chloroform (3 x 200 ml.). The chloroform extracts were dried and evaporated to give a brown solid. After two recrystallizations from aqueous ethanol a pure sample was obtained as shiny brown plates (0.43 g., 53%, m.p. 158-159°); nmr (deuteriochloroform/TMS):  $\delta$  2.60 (s, 3H, CH<sub>3</sub>),  $\delta$  2.67 (s, 3H, COCH<sub>3</sub>),  $\delta$  7.40-8.45 (m, 7H, arom),  $\delta$  9.53 (m, 1H, H-1).

Anal. Calcd. for C<sub>21</sub>H<sub>17</sub>NO: C, 84.25; H, 5.73; N, 4.68. Found: C, 84.04; H, 5.77; N, 4.51.

#### 6-Bromo-7-carboxamido-5,5-dimethyl-5,6-dihydrobenz[c]acridine (14).

A sample of the bromo acid chloride 5 (2 g., 5 mmoles) was dissolved in dry dioxane (30 ml.), and warmed. Ammonia gas was bubbled into this hot solution. After 15 minutes the flow of ammonia was stopped, the reaction mixture filtered through a sintered glass funnel to remove ammonium chloride and evaporated to afford the product (1.5 g., 79%, m.p. 311°). The solid was dissolved in acetone (100 ml.) at room temperature and filtered to remove some solid material. The acetone solution was diluted to 500 ml. with cold water. The crystals which formed were dried under vacuum; nmr (DTFAA/TMS):  $\delta$  1.33 (s, 3H, CH<sub>3</sub>),  $\delta$  1.88 (s, 3H, CH<sub>3</sub>),  $\delta$  5.58 (s, 1H, H-6),  $\delta$  7.6-8.6 (m, 8H, arom).

Anal. Calcd. for C<sub>20</sub>H<sub>17</sub>BrN<sub>2</sub>O: C, 63.00; H, 4.50; N, 7.35. Found: C, 62.72; H, 4.51; N, 7.21.

#### 7-Carboxamido-6-methoxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (15).

A mixture of the amido bromide 14 (2.3 g., 6 mmoles), anhydrous potassium carbonate (1 g.) and anhydrous methanol (100 ml.) was heated to reflux and held at reflux for 18 hours. After this period of heating the carbonate had dissolved and some potassium bromide had precipitated. Water (25 ml.) was added and the solution was heated under reduced pressure to remove the methanol. The crystals which precipitated from the aqueous solution were removed by filtration, dried, and recrystallized

from aqueous ethanol to afford the product (1.7 g., 86%, m.p. 211-213°); nmr (deuteriochloroform/TMS):  $\delta$  1.63 (s, 3H, CH<sub>3</sub>),  $\delta$  1.87 (s, 3H, CH<sub>3</sub>),  $\delta$  3.18 (s, 3H, OCH<sub>3</sub>),  $\delta$  4.32 (s, 1H, H-6),  $\delta$  6.17 and 6.50 (broad singlets, 2H, CONH<sub>2</sub>),  $\delta$  7.3-8.0 (m, 6H, arom),  $\delta$  8.17 (m, 1H, H-11),  $\delta$  8.67 (m, 1H, H-1).

Anal. Calcd. for C<sub>21</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>: C, 76.11; H, 5.78; N, 8.46. Found: C, 76.21; H, 6.08; N, 8.50.

#### 7-Carboxamido-5,6-dimethylbenz[c]acridine (16).

A sample of the amide ether 15 (1.5 g., 5 mmoles) was dissolved in sulfuric acid (15 ml., 95%) with shaking. After standing for 25 minutes the reaction was hydrolyzed by pouring the mixture into ice and water (1,000 ml.). The pH was adjusted to around 8 with sodium hydroxide solution (50%). The mixture of water and yellow solid was continuously extracted with chloroform for 96 hours. The chloroform solution and the yellow solid it contained were dissolved in absolute ethanol (2,000 ml.) at reflux and filtered. The filtrate was concentrated to 500 ml. and cooled. The yellow solid was removed by filtration and dried. This material was dissolved in dioxane (20 ml.), filtered and treated with petroleum ether (39-41°, 30 ml.) to precipitate the product (0.6 g., 40%, m.p. 286-287°); nmr (DTFAA/TMS):  $\delta$  2.83 (s, 3H, CH<sub>3</sub>),  $\delta$  3.03 (s, 3H, CH<sub>3</sub>),  $\delta$  7.8-8.8 (m, 7H, arom),  $\delta$  9.07 (m, 1H, H-8).

Anal. Calcd. for C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O: C, 79.97; H, 5.37; N, 9.33. Found: C, 80.19; H, 5.66; N, 9.09.

#### 7-Cyano-5,5-dimethyl-5,6-dihydrobenz[c]acridine (18).

Phosphorus oxychloride (5 ml.) was added to a mixture of 7-amido-5,5-dimethyl-5,6-dihydrobenz[c]acridine (5) (1 g., 3.3 mmoles) and phosphorus pentachloride (0.65 g., 3.1 mmoles). The resulting mixture was heated at reflux for 1 hour. The dark solution was poured over ice and stirred until a yellow precipitate formed. The mixture was extracted with ether (3 x 100 ml.). The ether extracts were combined and washed with a sodium bicarbonate solution, water and saturated sodium chloride solution. The ether solution was dried over anhydrous potassium carbonate, filtered and evaporated to dryness. One recrystallization from aqueous ethanol gave the pure product (0.5 g., 53%, m.p. 180-182°); nmr (deuteriochloroform/TMS):  $\delta$  1.35 (s, 6H, CH<sub>3</sub>),  $\delta$  3.23 (s, 2H, H-6),  $\delta$  7.38-7.90 (m, 5H, arom),  $\delta$  8.13 (m, 2H, H-8 and 11),  $\delta$  8.62 (m, 1H, H-1).

Anal. Calcd. for C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.42; H, 5.43; N, 9.62.

#### 7-Cyano-6-methoxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (19).

A mixture of the carboxamido ether 15 (3 g., 9 mmoles) and phosphorus pentachloride (2 g., 9.6 mmoles) was treated with phosphorus oxychloride (10 ml.). The workup, as described above, afforded an oil which crystallized upon the addition of absolute alcohol. A recrystallization from aqueous alcohol gave the product as white crystals (2 g., 71%, m.p. 213-214°); nmr (deuteriochloroform/TMS):  $\delta$  1.07 (s, 3H, CH<sub>3</sub>),  $\delta$  1.70 (s, 3H, CH<sub>3</sub>),  $\delta$  3.35 (s, 3H, OCH<sub>3</sub>),  $\delta$  4.52 (s, 1H, H-6),  $\delta$  7.3-7.9 (m, 5H, arom),  $\delta$  8.25 (m, 2H, H-8 and 11),  $\delta$  8.67 (m, 1H, H-1).

Anal. Calcd. for C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.17; H, 5.80; N, 8.90.

#### 7-Cyano-5,6-dimethylbenz[c]acridine (20).

A sample of the cyano ether 19 (2 g., 6.4 mmoles) was dissolved in concentrated sulfuric acid (40 ml., 95%). After stirring for 3 hours the reaction was quenched by pouring over ice. The resulting mixture was neutralized with a sodium hydroxide solution (10%). Water was added to dissolve the sodium sulfate which precipitated and the mixture was filtered to remove the yellow product. The dried product was dissolved in hot dioxane (100 ml.) and the resulting solution was decolorized, filtered, and concentrated to 25 ml. Petroleum ether was added to this solution to precipitate yellow needles of product (1.2 g., 67%, m.p. 253-255°); nmr (DTFFA/TMS):  $\delta$  2.93 (s, 3H, CH<sub>3</sub>),  $\delta$  3.33 (s, 3H, CH<sub>3</sub>),  $\delta$  8.05-9.30 (m, 8H, arom).

Anal. Calcd. for C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>: C, 85.08; H, 5.00; N, 9.93. Found: C, 84.86; H, 4.94; N, 9.97.

#### 6-Bromo-7-chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine (23).

*N*-Bromosuccinimide (3.44 g., 19.3 mmoles) was added to a hot carbon tetrachloride solution (150 ml.) of 7-chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine (**22**) (5) (4.0 g., 13.7 mmoles). The mixture was heated to reflux by the heat generated from a 500 watt sun lamp. The reaction was complete in 15 minutes as evidenced by the conversion of NBS to succinimide. The mixture was chilled and filtered to remove the succinimide and unreacted NBS. The filtrate was evaporated to a yellow oil which could be recrystallized from hexane with charcoal to afford the pure product (4.65, 91%, m.p. 151-152°); nmr (deuteriochloroform/TMS):  $\delta$  1.18 (s, 3H, CH<sub>3</sub>),  $\delta$  1.80 (s, 3H, CH<sub>3</sub>),  $\delta$  5.78 (s, 1H, H-6),  $\delta$  7.40-8.00 (m, 5H, arom),  $\delta$  8.22 (m, 2H, H-8 and H),  $\delta$  8.73 (m, 1H, H-1).

*Anal.* Calcd. for C<sub>19</sub>H<sub>15</sub>BrClN: C, 61.23; H, 4.06; N, 3.76. Found: C, 61.02; H, 3.81; N, 4.02.

#### 7-Chloro-6-hydroxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (**24**).

The bromo chloro compound **23** (4 g., 10.8 mmoles) was dissolved in dioxane (50 ml.). To this solution water was added until a faint turbidity existed and more dioxane was added until the solution became clear. Hydrobromic acid in acetic acid (32%, 1 ml.) was added and the solution was stirred for 36 hours at reflux. A solution of potassium carbonate was added to the reaction mixture to neutralize the acetic and hydrobromic acid. The reaction mixture was evaporated to dryness, dissolved in methanol and diluted with water. The methanol was then removed under reduced pressure. The white solid was collected, washed with water, and recrystallized from ethanol to afford the product (3.09 g., 95%, m.p. 212-214°); nmr (deuteriochloroform/TMS):  $\delta$  1.02 (s, 3H, CH<sub>3</sub>),  $\delta$  1.70 (s, 3H, CH<sub>3</sub>),  $\delta$  2.18 (s (broad); 1H, OH),  $\delta$  5.12 (s, 1H, H-6),  $\delta$  7.20-8.32 (m, 5H, arom),  $\delta$  8.13 (m, 2H, H-8 and 11),  $\delta$  8.54 (m, 1H, H-1).

*Anal.* Calcd. for C<sub>19</sub>H<sub>16</sub>ClNO: C, 73.66; H, 5.21; N, 4.52. Found: C, 73.71; H, 5.03; N, 4.49.

#### 7-Chloro-5,6-dimethylbenz[c]acridine (**25**).

Alcohol **24** (3 g., 9.7 mmoles) was powdered and added in portions to sulfuric acid (95%, 50 ml.). The course of the reaction was monitored by tlc and when completed (30 minutes - 1 hour) the acid solution was poured over crushed ice and carefully neutralized with sodium bicarbonate. The chloro compound will hydrolyze in hot acidic aqueous solution. The basic mixture was extracted with ether (300 ml.) and chloroform (5 x 200 ml.). The organic layers were combined, dried and evaporated to afford the crude chloro compound **25**. One recrystallization from ethanol afforded yellow needles of product (2.3 g., 82%, m.p. 148-149°, lit. m.p. 148-149° (5)).

#### 7-Methoxy-5,6-dimethylbenz[c]acridine (**28**).

Hydrogen chloride gas was bubbled into a solution of the chloro compound **25** (1 g., 3.4 mmoles) in anhydrous methanol. After 5 minutes the addition of gas was stopped and the flask was stoppered and set aside for 30 minutes. The methanol solution was concentrated to a small volume and an aqueous potassium carbonate solution was added until a clear solution was obtained. As the methanol was removed from the solution under reduced pressure, the product crystallized from solution. One recrystallization from aqueous ethanol gave the pure product (0.96 g., 98%, m.p. 94-95°); nmr (deuteriochloroform/TMS):  $\delta$  2.53 (s, 3H, CH<sub>3</sub>),  $\delta$  2.83 (s, 3H, CH<sub>3</sub>),  $\delta$  3.85 (s, 3H, OCH<sub>3</sub>),  $\delta$  7.38-8.05 (m, 5H, arom),  $\delta$  8.25 (m, 2H, H-8 and 11),  $\delta$  9.55 (m, 1H, H-1).

*Anal.* Calcd. for C<sub>20</sub>H<sub>17</sub>NO: C, 83.59; H, 5.96; N, 4.87. Found: C, 83.27; H, 5.93; N, 4.97.

#### 7-Amino-5,6-dimethylbenz[c]acridine (**29**).

Using a procedure analogous to that of Albert for the preparation of 7-aminobenz[c]acridine (**6**), a 0.18 g. (0.0007 mole) sample of **25** was dissolved in 0.85 g. of freshly distilled phenol at 70°. Subsequently 0.1 g. of finely powdered ammonium carbonate was added during two minutes of stirring. The temperature was raised to 120° and maintained for one-half hour. The dark red solution was rapidly poured into 100 ml. of sodium hydroxide solution and allowed to stand until a light brown precipitate had formed. The precipitate was collected, washed with water and dissolved in 1*N* acetic acid. The amine was then reprecipitated on

the addition of excess sodium hydroxide solution and recrystallized from toluene to give 0.14 (85% yield) of yellow plates, m.p. 210°; ir (chloroform):  $\nu$  = 3530 cm<sup>-1</sup> (w NH as), 3440 cm<sup>-1</sup> (m NHS), 1630 cm<sup>-1</sup> (s, NH in plane bending), 2980 cm<sup>-1</sup> (br CH unsat), 1380 cm<sup>-1</sup> (m CH<sub>3</sub> bending), 1430 cm<sup>-1</sup> (m, CH<sub>3</sub> as bending), 1550, 1500 cm<sup>-1</sup> (s, C=C); nmr (deuteriochloroform/TMS):  $\delta$  = 2.50, 2.70 m (three protons each (methyl)), 7.20-10.00 m, 8 protons (aromatic); ms: M<sup>+</sup> 272-18, M<sup>+</sup> -NH<sub>2</sub> 257.15.

*Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>: C, 83.82; H, 5.88; N, 10.30. Found: C, 83.72; H, 6.03; N, 10.22.

#### Pyrolysis of 6-Bromo-7-chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine, **23** to Produce **25**.

A 0.54 g. (0.0015 mole) sample of 6-bromo-7-chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine (**23**) was heated in a constant temperature oil bath for ten minutes at 219°. The resulting red solid was thoroughly triturated with hot aqueous ethanol. After cooling, the ethanolic solution was filtered and dilute aqueous potassium carbonate solution was added to precipitate the yellow product. The precipitate was collected and recrystallization from aqueous acetone gave 0.27 g. (61%) of light yellow needles identified as 7-chloro-5,6-dimethylbenz[c]acridine (**25**). The melting point with authentic **25** confirmed the product to be **25**, m.p. 148-149°; nmr (deuteriochloroform/TMS):  $\delta$  2.65 (m, 3 protons),  $\delta$  2.93 (m, 3 protons, methyl groups),  $\delta$  7.58-8.65 (m, 7 protons, 9.00 m, 1 proton, aromatic).

#### 6-Hydroxy-7-*N*-ethylcarboxamido-5,5-dimethyl-5,6-dihydrobenz[c]acridine (**30**).

A sample of the lactone **3** (1.0 g., 3.32 mmoles) was added to cold ethyl amine (10 ml. -10°). The mixture was stored in the refrigerator and after 1 hour the lactone had dissolved. Ether (80 ml.) was added to the solution and the resulting mixture was filtered. The filtrate was heated to boiling and petroleum ether (10 ml. at 41-46°) was added. As the ethyl ether evaporated white crystals of product precipitated. These were collected and recrystallized from ether-petroleum ether to afford the pure product (0.9 g., 78%, m.p. 188-190°); nmr (deuteriochloroform):  $\delta$  0.93 (s, 3H, CH<sub>3</sub>),  $\delta$  1.55 (s, 3H, CH<sub>3</sub>),  $\delta$  1.12 (t, 3H, CH<sub>3</sub>, J = 7.0 cps),  $\delta$  3.17 (broad s, 1H, OH),  $\delta$  3.37 (q, 2H, CH<sub>2</sub>, J = cps),  $\delta$  4.45 (s, 1H, H-6),  $\delta$  6.62 (broad s, 1H, NH),  $\delta$  7.35-7.85 (m, 6H, arom),  $\delta$  8.07 (m, 1H, H-11),  $\delta$  8.37 (m, 1H, H-1).

*Anal.* Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.12; H, 6.34; N, 8.12.

#### 7-*N*-Ethylcarboxamido-5,6-dimethylbenz[c]acridine (**31**).

A sample of the amide alcohol **30** (1 g., 2.9 mmoles) was dissolved in sulfuric acid (95%, 20 ml.). After stirring at room temperature two hours the acid solution was poured over a mixture of crushed ice and aqueous sodium hydroxide (10%). The resulting mixture was continuously extracted with chloroform for 8 hours. The organic extracts were dried and evaporated to give the crude yellow product (0.7 g., 74%). A pure sample m.p. 285-286° could be obtained by recrystallization from alcohol or dioxane-petroleum ether as described above for the 7-carboxamido compound **16**; nmr (DTFAA):  $\delta$  1.50 (t, 3H, CH<sub>3</sub>, J = 7.0 cps),  $\delta$  2.77 (s, 3H, CH<sub>3</sub>),  $\delta$  2.92 (s, 3H, CH<sub>3</sub>),  $\delta$  3.88 (q, 2H, CH<sub>2</sub>, J = 7.0 cps),  $\delta$  7.8-8.8 (m, 7H, arom),  $\delta$  9.03 (m, 1H, arom).

*Anal.* Calcd. for C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.19; H, 6.05; N, 8.63.

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