[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Benzacridines. I. Synthesis and Reactions of 5,6-Dihydrobenz[c]acridines

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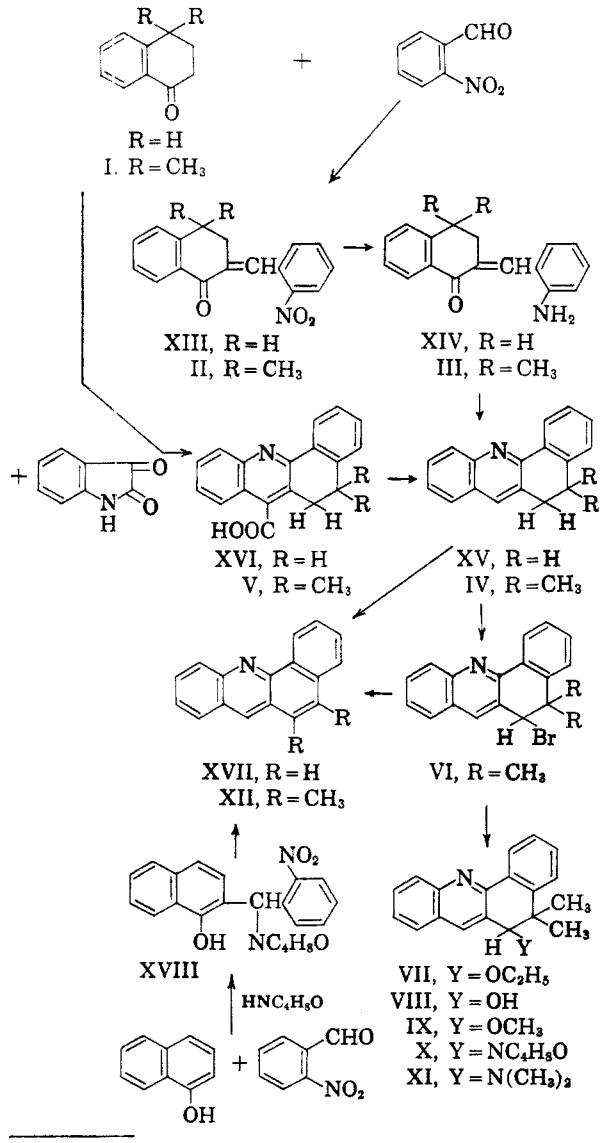
A convenient synthesis has been developed to prepare a number of substituted dihydrobenz[c]acridines and benz[c]-acridines. 5,6-Dimethylbenz[c]acridine was obtained through a Wagner-Meerwein rearrangement brought about by an "α-elimination" of hydrogen bromide from 6-bromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine. The ultraviolet absorption spectra of these new compounds are reported and compared.

During the course of a general program involving the synthesis of potential carcinogenic and antitumor agents, a new method of synthesis of benz[c]acridines has been developed, which has led to the hitherto unknown 5,6-dimethylbenz[c]acridine (XII). This compound is of particular interest in view of the fact that methyl groups are substituted on both carbon atoms of the so-called "K-region," which has been postulated to be a factor in the carcinogenic activity of the benz[c]acridines and condensed polynuclear hydrocarbons.[2]



The starting ketone I, 4,4-dimethyl-1-tetralone, was prepared using a revision of the procedure employed by Campbell and Cromwell.[3] It was found that condensation of the substituted tetralone I with *o*-nitrobenzaldehyde could be accomplished in a 94% yield in glacial acetic acid with sulfuric acid as the catalyst. Previous condensations of this type have been carried out under basic conditions,[4–6] or in 80% sulfuric acid.[7] The most satisfactory means found to reduce the nitroketone II to 4,4-dimethyl-2-(*o*-aminobenzal)-1-tetralone (III) was with iron and acetic acid. Catalytic reduction with Raney nickel gave in only one instance a trace of the cyclized compound IV. The aminoketone III was cyclized to 5,5-dimethyl-5,6-dihydrobenz[c]-acridine (IV) with extreme ease, as has been reported for the corresponding 2-(*o*-aminobenzal)-indanones leading to indenoquinolines.[8] This ready cyclization is reflected by the nearly identical ultraviolet spectra found for III and IV. It was shown that ultraviolet light brings about this ring closure of 2-(*o*-aminobenzal)-1-tetralones to 5,6-dihydrobenz[c]acridines.

Compound IV was also prepared *via* the Pfitzinger-Borsche reaction,[9] by condensing the ketone-I with isatin to give 7-carboxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (V), which on thermal decarboxylation resulted in the dihydrobenzacridine IV. Of the two routes to compound IV, the series involving condensation with *o*-nitrobenzalde-

(1) To whom correspondence concerning this article should be addressed.

(2) For an excellent discussion of the theoretical significance of the "K-region" and its relationship to carcinogenicity in benzacridines, see C. A. Coulson, *Advances in Cancer Research*, Academic Press, Inc., New York, N. Y., 1953, Vol. I, pp. 1–56.

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(6) A. Hassner, N. H. Cromwell, and S. J. Davis, *J. Am. Chem. Soc.*, **79**, 230 (1957).

(7) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 893 (1958).

(8) S. Ruhemann and S. I. Levy, *J. Chem. Soc.*, **103**, 551 (1913).

(9) J. von Braun and P. Wolff, *Ber.*, **55**, 3675 (1922).

hyde and ring closure of III gave higher yields and cleaner products than the method involving the Pfitzinger-Borsche reaction.

When compound IV was treated with *N*-bromosuccinimide, the 6-bromo derivative (VI) was obtained in 82% yield. This proved to be an especially versatile reagent, in view of the high order of reactivity of the bromine group. Compound VI was converted to the 6-ethoxy- and 6-methoxy-derivatives (VII and IX) by treatment with ethanol and methanol, respectively, and to the 6-hydroxy-derivative VIII by treatment with sodium hydroxide.[10] In a like manner, the bromo compound was readily converted to the 6-morpholino- and 6-dimethylamino-derivatives, X and XI.

Perhaps the most interesting reaction carried out with the bromo compound was its conversion to 5,6-dimethylbenz[*c*]acridine (XII). When the bromo compound was heated to 160°, the light yellow molten mass turned to a bright red solid. This solid proved to be the hydrobromide salt of the benz[*c*]acridine XII resulting from a combination of an "α-elimination" of hydrogen bromide and a Wagner-type rearrangement of a 5-methyl group to the 6-position. Studies are currently being made to determine the mechanism of this rearrangement, as well as to find other means of bringing it about.

The two routes described above for IV were also used to synthesize the unsubstituted parent 5,6-dihydrobenz[*c*]acridine (XV) for purposes of comparison. α-Tetralone was condensed with *o*-nitrobenzaldehyde to yield 2-(*o*-nitrobenzal)-1-tetralone (XIII), which was then reduced to 2-(*o*-aminobenzal)-1-tetralone (XIV). Compound XIV was readily cyclized with hydrochloric acid or ultraviolet light (see Table I) to 5,6-dihydrobenz[*c*]-acridine (XV), which was also prepared by the method of von Braun and Wolff.[9] Aromatization of XV by heating with lead oxide produced benz[*c*]-acridine (XVII).[9]

Benz[*c*]acridine was also obtained by another route, though in a very small yield. A Mannich condensation of α-naphthol, morpholine, and *o*-nitrobenzaldehyde resulted in 2-(*N*-α-morpholino-*o*-nitrobenzyl)-1-naphthol (XVIII). Reduction of XVIII with iron and acetic acid gave benz[*c*]-acridine (XVII). The mechanism by which this transformation proceeds is not known at present.

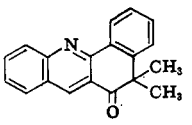
Discussion of ultraviolet spectra. The ultraviolet spectra of the dihydrobenz[*c*]acridines and benz-[*c*]acridines are given in Table I. The spectra of the unsubstituted and substituted dihydrobenzacridines are seen to be quite identical, differing only slightly in both wave length and ϵ_{max}. The only notable exception is 6-bromo-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (VI), which has only a single high intensity absorption band in 220–330 mμ range of the spectrum and a different longer wave length fine structure than is found for the other dihydrobenzacridines.

TABLE I

SUMMARY OF ULTRAVIOLET SPECTRA OF BENZACRIDINE DERIVATIVES

Compound	No.	Ultraviolet Max.[a] λ mμ	ε × 10⁻³
2-(*o*-Aminobenzal)-1-tetralone	XIV[b,c]	213	34.0
		(220)	29.0
		(258)	28.6
		265	35.4
		300	7.76
		315	8.48
		330	11.6
		345	13.1
4,4-Dimethyl-2-(*o*-aminobenzal)-1-tetralone	III[d,e]	212	36.1
		(214)	35.2
		(223)	27.3
		(258)	28.2
		265	34.9
		315	8.04
		329	10.2
		344	11.5
Benz[*c*]acridine	XVII[f]	(214)	24.8
		224	37.9
		(267)	47.6
		274	66.5
		285	56.4
		347	6.32
		363	8.12
		382	8.18
5,6-Dimethylbenz[*c*]acridine	XII[g]	221	34.8
		(270)	46.5
		278	53.9
		292	47.6
		323	5.00
		338	5.97
		351	6.10
		369	7.05
		387	7.10
5,6-Dihydrobenz[*c*]acridine	XV[b]	214	35.7
		(220)	30.3
		(258)	31.1
		265	38.5
		287	8.34
		300	8.00
		315	8.70
		330	12.2
		344	14.0
7-Carboxy-	XVI[b]	214	31.1
		(266)	21.2
		(260)	26.2
		226	33.1
		316	7.24
		331	9.80
		345	11.2
5,5-Dimethyl-	IV[b]	213	35.5
		(220)	29.3
		(259)	29.4
		265	36.9

(10) The structure of the hydroxy compound VIII is shown by the fact that it is readily oxidized to the corresponding ketone, m.p. 89–90° in 80% yield with CrO_3



in 80% acetic acid. This ketone shows an infrared carbonyl band at 1685 cm.$^{-1}$ and its analysis agrees with the following structure. The chemistry of this compound will be discussed in a forthcoming publication.

TABLE I (*Continued*)

Compound	No.	Ultraviolet Max.[a] λ mμ	ε × 10⁻³
		300	8.30
		315	9.00
		330	12.4
		345	14.2
		257[d]	30.0
		265	37.8
		299	9.02
		314	8.72
		329	11.9
		344	14.0
7-Carboxy-5,5-dimethyl-	V[b]	214	34.4
		(226)	23.7
		(260)	29.9
		267	36.0
		317	8.10
		331	10.1
		345	12.3
5,5-Dimethyl-6-ethoxy-	VII[h]	214	36.4
		(220)	32.2
		(260)	28.8
		267	34.0
		299	8.96
		314	8.56
		329	11.2
		343	12.7
5,5-Dimethyl-6-methoxy-	IX[b]	213	41.9
		(215)	40.5
		(224)	30.5
		(260)	30.0
		267	35.4
		298	9.20
		313	8.84
		328	11.4
		343	12.8
5,5-Dimethyl-6-hydroxy-	VIII[d]	212	38.7
		215	38.9
		(226)	30.6
		(259)	32.3
		266	36.0
		313	9.20
		328	11.0
		343	12.6
5,5-Dimethyl-6-(*N*-morpholino)-	X[d]	(223)	25.6
		(260)	31.4
		266	34.3
		316	9.30
		330	10.3
		346	11.5
5,5-Dimethyl-6-dimethylamino-	XI[d]	212	43.7
		215	44.0
		(225)	30.0
		(260)	33.1
		267	38.6
		315	9.08
		330	11.1
		345	11.6
6-Bromo-5,5-dimethyl-	VI[d]	266	38.5
		334	7.40
		(340)	7.00
		349	7.29

[a] Ultraviolet determinations were made at about 25° using a Cary recording spectrophotometer, model 11 MS. [b] 5.0×10^{-5} molar concentration in 95% ethanol. [c] This compound was converted to compound XV during the determination. [d] 5.0×10^{-5} molar concentration in isooctane. [e] This compound was converted to compound IV during the determination. [f] 2.5×10^{-5} molar concentration in 95% ethanol. [g] 2.5×10^{-5} molar concentration in isooctane. [h] 4.25×10^{-5} molar concentration in 95% ethanol.

The differences between the spectra of the completely aromatic benz[*c*]acridines and the dihydrobenzacridines are quite apparent, however. The maxima for the benz[*c*]acridines (XII and XVII) have generally higher extinction coefficients, and there are two peaks of high intensity absorption and a shoulder in the 250–300 mμ region, while the dihydrobenzacridines have only one high intensity band with a shoulder in the same region. The fine structure for the dihydrobenzacridines is found in the region of 280–350 mμ, while the corresponding absorption bands for the benz[*c*]acridines are found in the 320–390 mμ region.

EXPERIMENTAL

4,4-Dimethyl-1-tetralone (I). Compound I was synthesized by the procedure of Campbell and Cromwell[3] with two simplifying modifications.

4-Methyl-4-phenylpentanothiomorpholide,[3] 246 g. (0.89 mole), was refluxed with 1.5 l. of concentrated hydrochloric acid for 48 hr. The mixture was cooled and extracted with one liter of benzene. The benzene layer was extracted twice with the theoretical amount of 25% sodium hydroxide solution. The alkaline solution was acidified with sulfuric acid and the aqueous mixture was then extracted with benzene. The benzene extract was washed with water and dried over magnesium sulfate, and the benzene was removed under reduced pressure. The crude 4-methyl-4-phenylpentanoic acid was distilled at 140–141° (0.8 mm.), giving 163.7 g. (96% yield) of pure acid.

The acid was then directly converted to ketone I. Polyphosphoric acid, 500 g., was placed in an 800 ml. beaker and heated to 90° on a steam bath. 4-Methyl-4-phenylpentanoic acid, 172 g. (0.9 mole), was heated separately to 65°. The polyphosphoric acid was removed from the steam bath, the warm 4-methyl-4-phenylpentanoic acid added in one lot, and the mixture stirred for 3 min. The mixture was then placed on the steam bath, an additional 300 g. of polyphosphoric acid was added, and the mixture stirred for 25 min., while maintaining the temperature at 90°. After cooling it was poured into ice water with stirring. When the brown, viscous oily precipitate had changed completely to a light yellow color, it was extracted with three portions of ether. The ether extract was washed successively with 300 ml. of water, two 200 ml. portions of 5% sodium hydroxide solution, 300 ml. of water, 200 ml. of 3% aqueous acetic acid, and 100 ml. of water. The ether layer was dried over magnesium sulfate and the ether evaporated. Distillation at 125–131°[3] (2 mm.) gave 136.9 g. (88% yield) of ketone I.

4,4-Dimethyl-2-(o-nitrobenzal)-1-tetralone (II).[11] To a solution of 25 g. (0.167 mole) of *o*-nitrobenzaldehyde and 29 g. (0.167 mole) of I in 170 ml. of glacial acetic acid was added 35 ml. of 95% sulfuric acid. The mixture was allowed to stand at room temperature for three days, after which time the crystals were collected by filtration. Recrystallization from glacial acetic acid resulted in 48 g. (94% yield) of 4,4-dimethyl-2-(*o*-nitrobenzal)-1-tetralone, m.p. 188–189°.

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.34; H, 5.48; N, 4.53.

4,4-Dimethyl-2-(o-aminobenzal)-1-tetralone (III). Compound II, 48 g. (0.156 mole), was dissolved with heating in 800 ml. of glacial acetic acid and 80 ml. of water. While heating the mixture on a steam bath, a total of 20 g. of reduced iron powder was added in small portions, with occasional shaking. The solution was heated for 15 min. after the

(11) This compound was first prepared in this laboratory by Mr. Ronald Bambury, M.S. Thesis, University of Nebraska, 1958.

evolution of hydrogen had ceased and was then poured into 1.5 l. of ice water with rapid stirring. To the aqueous mixture was added 1.8 l. of 33% potassium hydroxide, and the mixture allowed to stand overnight. The solid material was collected by filtration, washed with water, and dried. The solid was extracted thoroughly with absolute ethanol. The alcoholic extract was evaporated to 500 ml. volume, water was added, and the solution cooled. Bright yellow crystals of 4,4-dimethyl-2-(*o*-aminobenzal)-1-tetralone precipitated from solution, wt., 36 g.; m.p., 135–137° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 81.98; H, 6.78; N, 5.12.

Treatment of III with picric acid produced the picrate of 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine, m.p. 202–203° (see below).

5,5-Dimethyl-5,6-dihydrobenz[c]acridine (IV). Ketone III was dissolved in 95% ethanol, 50 ml. of concentrated hydrochloric acid was added, and the solution evaporated to dryness on a steam bath. The residue was redissolved in 95% ethanol and treated with charcoal. After filtration, the bright yellow solution was neutralized with 5% sodium bicarbonate solution. Water was added and the mixture was cooled. The precipitated solid was collected by filtration and recrystallized, with charcoal treatment, from aqueous acetone. White needles of IV, m.p. 112–113°, were obtained. The over-all yield from the nitroketone II was 33.6 g. (83%).

Anal. Calcd. for $C_{19}H_{17}N$: C, 88.00; H, 6.60; N, 5.40. Found: C, 87.92; H, 6.69; N, 5.30.

The picrate of IV was prepared by adding a solution of IV in 95% ethanol to a saturated solution of picric acid in ethanol, and cooling. The picrate melted at 202–203°.

Anal. Calcd. for $C_{25}H_{20}N_4O_7$: C, 61.47; H, 4.13. Found: C, 61.64; H, 4.22.

Compound IV was also obtained by ring closure of the aminobenzal ketone III by irradiation with ultraviolet light. A solution of 0.2 g. of compound III in one liter of 95% ethanol was irradiated for 30 hr. with a Hanovia Utility Model Quartz Lamp, 115 volts, 60 cycles, 4.6 amps. The solution gradually turned colorless and fluorescence became evident. The solution was concentrated to a volume of 25 ml. under vacuum and charcoaled. Upon the addition of water and cooling, colorless crystals of IV precipitated from solution.

7-Carboxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (V). Compound V was prepared by the Pfitzinger-Borsche reaction, using the procedure of von Braun.[9] A solution of 6 g. (0.034 mole) of ketone I, 5.05 g. (0.034 mole) of isatin, 6.5 g. of potassium hydroxide, 10 ml. of methanol, and 6.5 ml. of water was refluxed for 8 hr. The basic solution was diluted with water and extracted with ether. The alkaline solution was acidified to methyl orange with hydrochloric acid. Recrystallization from dioxane (charcoal) gave 6.5 g. (63% yield) of V, m.p. 256.5–257°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 5.12. Found: C, 78.76; H, 5.51; N, 5.12.

Thermal decarboxylation of acid V. Compound V, 7.6 g. (0.025 mole), was melted in a small Erlenmeyer flask, and the molten material was maintained at 260° until the evolution of carbon dioxide had ceased (about 2 hr.). After cooling, the residue was triturated with 10% potassium hydroxide and the alkaline mixture was extracted with ether. The ether layer was washed with water and the ether was evaporated. Recrystallization of the solid from ethanol gave 6.1 g. (94% yield) of IV, m.p. 112–113°, identical with that prepared by ring closure of the aminoketone III.

6-Bromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine (VI). To a solution of 19.7 g. (0.076 mole) of IV in 250 ml. of carbon tetrachloride was added 13.5 g. (0.076 mole) of *N*-bromosuccinimide and 0.25 g. of benzoyl peroxide. The mixture was refluxed for 3 hr., after which time the heavy NBS had changed completely to the light succinimide. The mixture was cooled and filtered, and extracted first with 200 ml. of 5% sodium bicarbonate solution and then washed with two 150-ml. portions of water. After drying the carbon tetrachloride layer over magnesium sulfate, the solvent was removed under reduced pressure. The solid residue was dissolved in acetone *at room temperature*, treated with charcoal, and reprecipitated by the addition of water. The fine white needles were dried immediately in a vacuum desiccator, resulting in 21 g. (82% yield) of VI, m.p. 145–147°.

Anal. Calcd. for $C_{19}H_{16}NBr$: C, 67.49; H, 4.74; Br, 23.63. Found: C, 67.40; H, 4.87; Br, 23.76.

5,5-Dimethyl-6-ethoxy-5,6-dihydrobenz[c]acridine (VII). A solution of 0.85 g. of the bromo compound VI in 20 ml. of absolute ethanol was heated on a steam bath for 1 hour. After charcoal treatment, the solution was neutralized with 5% sodium bicarbonate solution, water was added, and the solution was cooled. The crude product was collected by filtration and recrystallized from ethanol to give 0.70 g. (92% yield) of VII in the form of white needles, m.p. 96–97°.

Anal. Calcd. for $C_{21}H_{21}NO$: C, 82.94; H, 7.08; N, 4.61. Found: C, 83.14; H, 6.98; N, 4.61.

The picrate was prepared in the usual manner and melted at 197–198° (with decomposition).

Anal. Calcd. for $C_{27}H_{24}N_4O_8$: C, 60.90; H, 4.54. Found: C, 60.71; H, 4.76.

5,5-Dimethyl-6-hydroxy-5,6-dihydrobenz[c]acridine (VIII). To a solution of 2 g. of the bromo compound VI in 25 ml. of dioxane was added 10 ml. of 10% sodium hydroxide solution. The solution was heated for 1 hr. on a steam bath. The solvent was evaporated and the residue dissolved in aqueous ethanol. The ethanolic solution was neutralized with dilute hydrochloric acid, treated with charcoal, and cooled. Large, white needles formed which melted at 155–157°. Another recrystallization from ethanol gave 1.25 g. (77% yield) of the hydroxy compound, m.p. 159–160°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.98; H, 6.22; N, 5.09. Found: C, 83.21; H, 6.57; N, 5.02.

A picrate of VIII softened at about 215°, but did not melt up to 250°.

5,5-Dimethyl-6-methoxy-5,6-dihydrobenz[c]acridine (IX). A solution of 1 g. of the bromo compound VI in 20 ml. of methanol was refluxed for 3 hr. Neutralization of the solution with 5% sodium bicarbonate solution, followed by recrystallization from aqueous methanol, gave 0.8 g. (94% yield) of colorless crystals of IX, m.p. 152.5–154°.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.25; H, 6.76; N, 4.89.

5,5-Dimethyl-6-(N-morpholino)-5,6-dihydrobenz[c]acridine (X). A solution of 3 g. (0.0089 mole) of the bromo compound VI and 15 ml. of morpholine was refluxed for 24 hr. The solution was then cooled, poured into water with stirring, and the solid collected by filtration. The crude product was dissolved in ethanol, treated with charcoal, and reprecipitated by adding water and cooling. Recrystallization from ethanol gave 2.6 g. (85% yield) of 5,5-dimethyl-6-(N-morpholino)-5,6-dihydrobenz[c]acridine, m.p. 159–161°.

Anal. Calcd. for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.28; H, 6.85; N, 8.07.

5,5-Dimethyl-6-dimethylamino-5,6-dihydrobenz[c]acridine (XI). Five grams of the bromo compound VI and 15 ml. of anhydrous dimethylamine were heated at 100° in a sealed tube for 8 hr. The tube was then cooled, opened, and the contents poured into ice water. The aqueous mixture was extracted with 75 ml. of benzene. The benzene layer was washed repeatedly with water until the water extract was neutral. The benzene solution was dried and evaporated and the residual material recrystallized from ethanol to give colorless crystals of the dimethylamino compound XI, m.p. 93–95°, yield 3.0 g. (67%).

Anal. Calcd. for $C_{21}H_{22}N_2$: C, 83.40; H, 7.34; N, 9.26. Found: C, 83.55; H, 7.13; N, 9.13.

5,6-Dimethylbenz[c]acridine (XII). Two grams of the bromo compound VI was heated in a small Erlenmeyer flask in an oil bath. The bromo compound melted to a light yellow liquid, and changed to a bright red solid at about

160°. Heating was continued for 10 min. at 170°. The red-brown residue was dissolved in warm, aqueous dioxane and the solution neutralized with 5% sodium bicarbonate solution. Upon cooling, a solid precipitated and was collected by filtration. The solid was dissolved in acetone, treated with charcoal, and reprecipitated by the addition of water. Another recrystallization from acetone gave 1.1 g. (72% yield) of XII in the form of fine, light yellow needles, m.p. 162–163°.

Anal. Calcd. for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.94; H, 5.86; N, 5.26.

The picrate was prepared in the usual manner and melted with decomposition at 253–254°.

Anal. Calcd. for $C_{25}H_{18}N_4O_7$: C, 61.73; H, 3.73. Found: C, 61.51; H, 3.79.

2-(o-Nitrobenzal)-1-tetralone (XIII).[7] *o*-Nitrobenzaldehyde, 15 g. (0.1 mole), was dissolved in 150 ml. of glacial acetic acid and 30 g. of 95% sulfuric acid was added with cooling. α-Tetralone, 14.6 g. (0.1 mole), was added to this solution with stirring. The reaction mixture was allowed to stand at room temperature for 72 hr., after which time the crude product was collected by filtration. Recrystallization from glacial acetic acid (charcoal) gave 20.9 g. (75% yield) of 2-(*o*-nitrobenzal)-1-tetralone, m.p. 121–122°.[7]

2-(o-Aminobenzal)-1-tetralone (XIV). The nitroketone XIII, 5.8 g. (0.02 mole), was dissolved in a solution of 40 ml. of glacial acetic acid and 20 ml. of water. The solution was heated on a steam bath to 70°, and 2.5 g. of iron powder added in small portions. Heating was continued for 45 min. with occasional shaking. The solution was then poured over 200 g. of ice and water. One hundred fifty ml. of 33% potassium hydroxide solution was added, and the mixture allowed to stand overnight.

The solid material was filtered off and extracted with 200 ml. of absolute ethanol. The addition of water precipitated bright, yellow-orange crystals of 2-(*o*-aminobenzal)-1-tetralone, m.p. 123–124°; yield 3.3 g. (64%).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.85; H, 5.98; N, 5.97.

Treatment of XIV with picric acid produced the picrate of 5,6-dihydrobenz[*c*]acridine, m.p. 206°.[9]

5,6-Dihydrobenz[c]acridine (XV). Ring closure of XIV was effected by evaporating a hydrogen chloride containing 95% alcoholic solution of 3.3 g. of the aminoketone to dryness on a steam bath. The hydrochloride product was redissolved in aqueous ethanol, treated with charcoal, and neutralized with 5% sodium bicarbonate solution. Water was added, the solution cooled, and the precipitate collected by filtration. Recrystallization from ethanol gave 2.6 g. (85% yield) of 5,6-dihydrobenz[*c*]acridine, m.p. 65° (lit. 60°).[9] The over-all yield from the nitroketone XIII was 54%.

Compound XV was also prepared using the procedure of von Braun and Wolff.[9] Decarboxylation of "Tetrophan" (XVI) (see below) gave an 88% yield of XV. The crude product melted at 59–60°, but treatment of an alcoholic solution of the hydrochloride salt with charcoal, neutralization with Na_2CO_3 and recrystallization from alcohol gave colorless crystals, m.p. 65°, identical with the product obtained by ring closure of the amino ketone XIV.

7-Carboxy-5,6-dihydrobenz[c]acridine, "Tetrophan" (XVI). The Pfitzinger-Borsche reaction was used to prepare "Tetrophan," employing the procedure of von Braun.[9] Dioxane was found to be a more satisfactory solvent for recrystallization of the crude acid. A yield of 83% of XVI was obtained, m.p. 250° (lit. 252°).[9]

2-(α-N-Morpholino-o-nitrobenzyl)-1-naphthol (XVIII).[12] A solution of 19.3 g. (0.134 mole) of α-naphthol, 20 g. (0.134 mole) of *o*-nitrobenzaldehyde, and 12.7 g. (0.148 mole) of morpholine in 17 ml. of ethanol was allowed to stand for 24 hr. under nitrogen. After adding a small amount of ethanol, the mixture was cooled and the crude product crystallized from solution. Recrystallization from ethanol gave 25 g. (52% yield) of compound XVIII in the form of bright yellow crystals, m.p. 128–129.5°.

Anal. Calcd. for $C_{21}H_{21}N_2O_4$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.10; H, 5.60; N, 7.50.

Benz[c]acridine (XVI). *A.* The procedure of von Braun[9] was used to dehydrogenate XV to benz[*c*]acridine. A 60% yield of light yellow needles of the fully aromatic compound was obtained, melting at 107–108° (lit. 108°).

The picrate salt was prepared in the usual manner, m.p. 249° (lit. 226–229°).[9]

Anal. Calcd. for $C_{23}H_{14}N_4O_7$: C, 60.27; H, 3.08; N, 12.22. Found: C, 60.16; H, 3.16; N, 12.84.

B. Compound XVIII, 5.5 g. (0.015 mole), was added to a solution of 35 ml. of glacial acetic acid and 15 ml. of water. The mixture was warmed to 70° on a steam bath, and 1.9 g. of reduced iron powder added in small portions. After the addition of iron was complete, the reaction mixture was heated an additional 30 min. on the steam bath. The mixture was poured over 200 g. of ice and water, 100 ml. of 33% potassium hydroxide solution was added and allowed to stand overnight. The solid precipitate was collected by filtration and extracted with 200 ml. of hot, absolute ethanol. The alcohol solution was evaporated to dryness on the steam bath, and the residue extracted with 1:1 hydrochloric acid. The acidic solution was charcoaled and then neutralized with dilute sodium carbonate solution. Recrystallization of the resulting solid from ethanol gave a 10% yield of benz[*c*]acridine in the form of light yellow needles which melted at 107.5–108°. A mixed melting point determination with authentic benz[*c*]acridine showed the two compounds to be identical.

The picrate was prepared in the usual manner, m.p. 249°. A mixed melting point determination with authentic benz[*c*]acridine picrate, from *A* above, showed the two picrates to be identical.

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(12) This compound was first prepared in this laboratory by Dr. A. Hassner, Ph.D. Thesis, University of Nebraska, 1956.