Microanalytical Laboratory to whom we are grateful. We are indebted to Miss Evelyn Schuber for preparation of 4,4′-dichloro-2,2′-dinitrodiphenyl disulfide. We wish to thank B. L. Lemke and Co., Inc., Lodi, N. J., for a generous sample of 2,2′-dinitrodiphenyl disulfide. Finally, we wish to acknowledge our debt to Mr. Morris Freifelder and Mr. George Stone for carrying out the catalytic hydrogenations described herein.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Benzacridines. III.[1] Synthesis and Chemistry of 6,6-Dimethyl-6,11-dihydrobenz[b]-acridine and Derivatives[2]

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6,6-Dimethyl-6,11-dihydrobenz[b]acridine (III) was synthesized in two ways starting with 1,1-dimethyl-2-tetralone *via* (a) 1,1-dimethyl-3-(*o*-nitrobenzal)-2-tetralone (I) by a reductive ring closure and (b) *via* 6,6-dimethyl-12-carboxy-6,11-dihydrobenz[b]acridine (II) by decarboxylation. The 11-morpholino- (V), 11-ethoxy- (VI) and 11-methoxy- (VII) derivatives of III were obtained from the very reactive 11-bromo-(IV) derivative of III. The 11-keto derivative VIII was obtained by the direct oxidation of III and by a hydrolytic oxidation of the 11-bromo-derivative IV. The expected tertiary carbinol X resulted from the reaction of VIII with methylmagnesium iodide. The ultraviolet spectra of III and its derivatives showed some interesting features and were useful in confirming these structures. These are the first syntheses of 6,11-dihydrobenz[b]acridines.

The benz[a]acridines and benz[c]acridines have been extensively studied, particularly in terms of the biological activity of their derivatives.[3] The linear benz[b]acridines, lacking the "K-region" to which the carcinogenic properties of the (a) and (c) series have been ascribed,[3,4] have received much less attention. The relatively limited synthetic approaches and reactions of the (b) series have been reviewed.[5] The Pfitzinger–Borsche reaction[6] has been used extensively for the synthesis of benz[c]-acridine derivatives.[1,3,5,7] Using isatin and *cis*-β-decalone, Buu-Hoi and co-workers obtained a mixture of the carboxyoctahydrobenz[b]- and benz-[a]acridines.[8]

In connection with a general program involving the synthesis of polycyclic nitrogen heterocyclic compounds for testing as carcinogenic and anti-tumor agents, it was of interest to investigate the two methods used in the synthesis of 5,5-dimethyl-5,6-dihydrobenz(c)acridines[1,7] from 4,4-dimethyl-1-tetralone, for the preparation of 6,6-dimethyl-6,11-dihydrobenz(b)acridine(III) from the isomeric and available 1,1-dimethyl-2-tetralone.[9]

An application of a method of precedent[8] for the synthesis of III consisted of the condensation of 1,1-dimethyl-2-tetralone[9] with isatin in aqueous alcoholic potassium hydroxide to give 6,6-dimethyl-12-carboxy-6,11-dihydrobenz(b)acridine (II), followed by thermal decarboxylation. The alternative method, superior in terms of yield, consisted of condensation of 1,1-dimethyl-2-tetralone with *o*-nitrobenzaldehyde in acetic–sulfuric acid mixture[1,7] to give 1,1-dimethyl-3-(*o*-nitrobenzal)-2-tetralone (I), followed by an iron–acetic acid reduction of the nitro group and an *in situ* ring closure of the amine (A) to form III.

The intermediate amine A underwent ring closure, possibly for steric reasons, much more readily than did the corresponding 2-(*o*-aminobenzal)-4,4-dimethyl-1-tetralones in forming the 5,5-dimethyl-5,6-dihydrobenz(c)acridines.[1,7] Catalytic hydrogenation of I produced only very small amounts of III and most of the starting material was recovered.

Since the preparation of 11-substituted derivatives of III was one objective of this investigation, the reactivity of the methylene group of this dihydrobenz(b)acridine was of primary interest. The recent successful preparation of 5,5-dimethyl-6-bromo-5,6-dihydrobenz(c)acridines[1,7] using N-bromosuccinimide suggested that III might be converted to the corresponding bromo derivative IV. The reaction of III with N-bromosuccinimide proceeded with great rapidity in the presence of benzoyl peroxide, but all attempts to isolate IV led to decomposition or reaction with the recrystallizing solvents. Consequently, solutions of IV were prepared and its further rapid reaction with alcohols and amines carried out without isolating the bromo intermediate.

By way of comparison of the reactivity of IV, 9-bromofluorene reacts with dimethylamine in dilute alcohol at 80° with no competition from the solvent.[10] Bromide IV is apparently rapidly hydrolyzed in carbon tetrachloride solution on contact with water to produce the alcohol IX which in turn is rapidly oxidized in air to the keto acridine VIII.

(1) For paper II see, V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, **24**, 1077 (1959).

(2) Presented in part at 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

(3) For an excellent review entitled, "The Relation between Carcinogenic Activity and the Physical and Chemical Properties of Angular Benzacridines," see A. Lacassagne, N. P. Buu-Hoi, R. Daudel and F. Zajdela, "Advances in Cancer Research," Academic Press, Inc., New York, N. Y., 1956, Vol. IV, pp. 316–369.

(4) See C. A. Coulson, "Advances in Cancer Research," Academic Press, Inc., New York, N. Y., 1953, Vol. I, pp. 1–56.

(5) (a) A. Albert, "The Acridines," Edward Arnold and Co., London, 1951; (b) R. M. Acheson, "Acridines," Interscience Publishers, Inc., New York, N. Y., 1956; (c) C. F. H. Allen, "Six Membered Heterocyclic Nitrogen Compounds with Four Condensed Rings," Interscience Publishers, Inc., New York, N. Y., 1951.

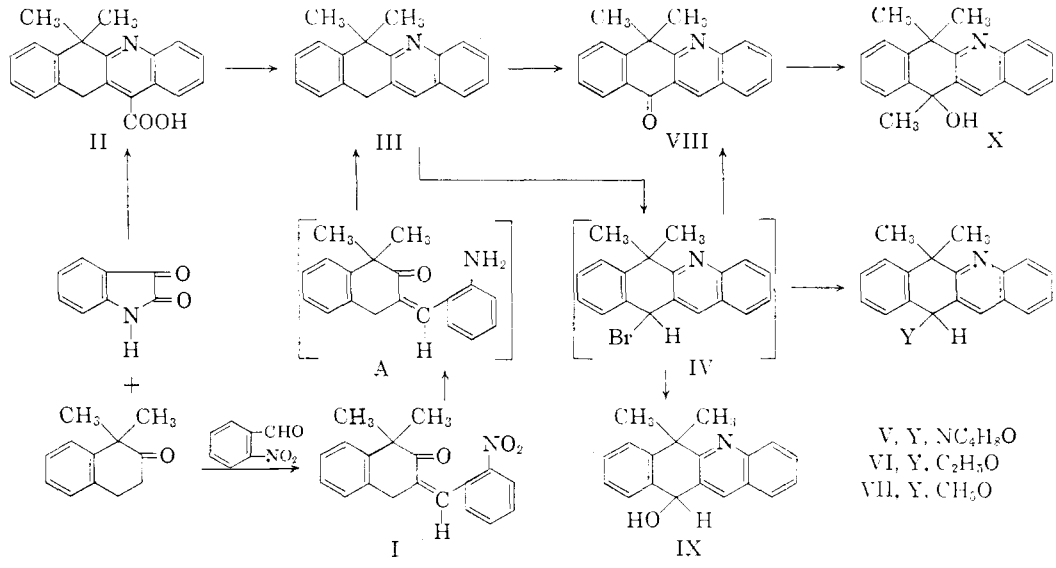
(6) J. von Braun and P. Wolff, *Ber.*, **55**, 3675 (1922).

(7) V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, **23**, 789 (1958).

(8) Ng. Ph. Buu-Hoi, P. Jacquignon and D. Lavit, *J. Chem. Soc.*, 2593 (1956).

(9) (a) M. D. Soffer, *et al.*, THIS JOURNAL, **72**, 3704 (1950); (b) N. H. Cromwell and R. D. Campbell, *J. Org. Chem.*, **22**, 520 (1957).

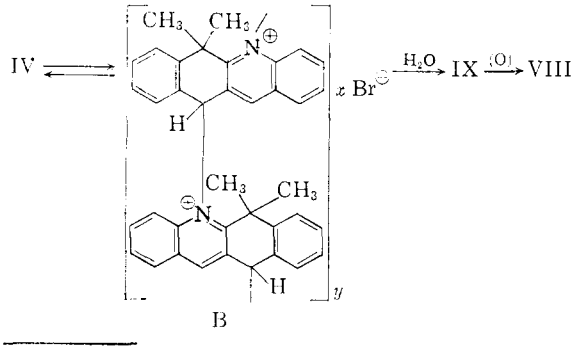
(10) C. K. Ingold and J. Jessop, *J. Chem. Soc.*, 2357 (1929).



Characterization of IX was limited to observation of the infrared spectrum of a mixture in which it is assumed to be a major constituent. This spectrum exhibited no band in the carbonyl region but showed absorption at 3300 cm.$^{-1}$ ascribable to OH and/or NH only on the assumption of a considerable degree of hydrogen bonding.

The analogous 9-bromo-10,10-diphenyl-9,10-dihydroanthracene appeared to require boiling in aqueous acetic acid for hydrolysis to the 9-hydroxy derivative and refluxing alcoholic potassium hydroxide solution for alcoholysis.[11] Morpholine substitution of the isomeric 5,5-dimethyl-6-bromo-5,6-dihydrobenz(c)acridine[7] required heating the reactants in the absence of solvent.

Many of the characteristics of the 11-bromo-derivative IV, including the presence of an orange-colored insoluble oil in its reaction mixture, are conveniently explained by the hypothesis that it exists in equilibrium with a polymeric quaternary benzacridinium salt (B). The behavior of the solutions of the bromo derivative IV bears a qualitative resemblance to the heterocyclic quaternary ammonium fluorenyls described by Krohnke.[12] Like IV, fluorenylquinolinium bromide does not crystallize but precipitates an orange oil from a nonpolar solvent mixture. Also like IV, it yields the ketone, fluorenone, upon treatment with cold aqueous solvent.



(11) C. Lieberman and S. Lindenbaum, *Ber.*, **38**, 1799 (1903).
(12) F. Krohnke, *ibid.*, **83**, 253 (1950).

Among the several non-hydrolytic solvents (including chloroform) tried, only acetonitrile was able to dissolve the orange colored oil (B) formed in the reaction mixtures of IV.

In order that sufficient quantities of the interesting new keto acridine VIII could be obtained for further studies,[13] its preparation by direct oxidation of III was undertaken. Chromic acid oxidation of III to VIII gave yields superior to those obtained in the oxidation of fluorene to fluorenone,[14] and failed to oxidize the *gem*-dimethyl carbon, as in the case of the analogous hydrocarbon, 10,10-dimethyl-9,10-dihydroanthracene.[15] Use of the mild conditions of Jacobson[16] may have permitted the specificity. A cleaner oxidation of III to give IV in higher yield was accomplished by the action of nitric acid catalyzed by lead acetate, a reagent used by Rivkin[17] for the oxidation of diphenylmethane to benzophenone in 80–90% yield. The lead salt was found, by its erroneous omission in one experiment with III, to be essential to a reasonable rate of reaction. Presumably, lead oxide is formed in solution and may be the actual oxidizing agent.

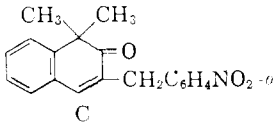
The 11-ketobenz(b)acridine VIII formed an oxime only with considerable difficulty but reacted readily with methylmagnesium iodide to produce the product X which analysis and spectra studies clearly indicate is the carbinol.

Several attempts to effect a transannular rearrangement–elimination reaction of derivatives of 6,6-dimethyl-6,11-dihydrobenz(b)acridine (III) to a fully aromatic benz(b)acridine derivative failed to produce any material with the expected spectral[18,19] or melting point characteristics of these compounds.[5b,c] Attempts included treatment of the proposed 11-hydroxy derivative IX with methanolic hydrogen chloride and sodium hydroxide,

(13) In a following article further investigation with VIII will be reported.
(14) E. H. Huntress, E. B. Hershberg and I. S. Cliff, THIS JOURNAL, **53**, 2720 (1931).
(15) F. Hallgarten, *Ber.*, **21**, 2508 (1888).
(16) R. P. Jacobson, THIS JOURNAL, **73**, 3463 (1951).
(17) S. M. Rivkin, *J. Applied Chem.* (*U.S.S.R.*), **11**, 83 (1938).
(18) R. M. Acheson and C. W. Jefford, *J. Chem. Soc.*, 2676 (1956).
(19) A. Pacault, *Bull. soc. chim. France*, 1270 (1950).

thermal decomposition (190° at 12 mm.) of the bromide IV, and treatment of the bromide IV with silver nitrate in acetonitrile.

Discussion of Absorption Spectra.—The assignment of the exocyclic α,β-unsaturated ketone structure to I, rather than the endocyclic structure C, is based primarily on the dissimilarity of its absorption spectra to those of 1,1-dimethyl-2-keto-

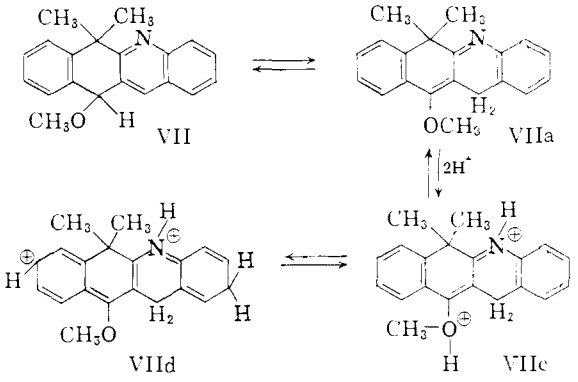


C

1,2-dihydronaphthalene and its derivatives.[20] The spectra of the analogous *o*-nitrobenzalacetone appears not to have been reported. The ultraviolet spectrum of I showed a strong band at 254.5 mμ and weaker absorption at 310–320 mμ in the nitrostyrene and cinnamoyl area (280–320 mμ) of the spectrum.[21] The infrared carbonyl frequency at 1691 cm.$^{-1}$ was in the area to be expected for an analog of benzalacetone[20] but not for that of a derivative of 1,1-dimethyl-2-keto-1,2-dihydronaphthalene.[20]

The effectiveness of the dihydro ring in electronically isolating the aromatic systems in these new 6,11-dihydrobenz(b)acridines II, III, V, VI, VII and X, is evident from the similarity of their ultraviolet spectra to that of quinoline.[22] With the exception of 6,11-dihydroxydihydrobenz(b)acridine[23] for which the structure is uncertain[5c] and products of Diels–Alder reactions with benz(b)acridine[18] and benz(g)quinoline,[24] these 6,11-dihydrobenz(b)acridines are the first compounds of this type to be prepared. Apparently the parent 6,11-dihydrobenz(b)acridine is unknown. An interplaner angle of about 140° would be expected to be formed between the benzene and the quinoline nuclei, about the 6,11-axis of these compounds II, III, V, VI, VII and X, which would effectively prevent orbital overlap in the excited state and electron delocalization such as is evident in some non-cyclic diaryl methylene systems.[25] The ultraviolet spectra studies indicate the effect to be equivalent to the bridgehead substitution resulting from the Diels–Alder reaction at the 6,11-positions in benz(b)acridine.[18]

Attempts to rearrange the 11-methoxy derivative VII to an enol ether VIIa failed. With methanolic hydrogen chloride, the ultraviolet spectrum showed no evidence of the existence of VIIa in the solution. In 100% sulfuric acid, however, the ether VII appears to be capable of more profound structural changes, as evidenced by the ultraviolet spectrum in this medium. The strong absorption at 460 mμ is accompanied by changes in the 200–300 mμ range of the spectrum where absorption typical of quinoline[22] is considerably suppressed. These facts indicate that the structure VII has been altered, and

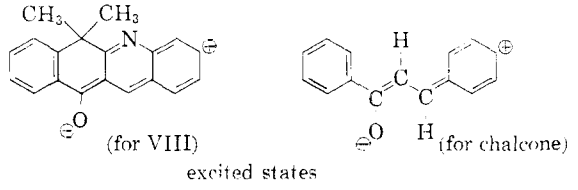


VII VIIa VIId VIIc

it is suggested that in this medium VII may exist as a dipolar ion such as VIIc ⇄ VIId. The dipolar ion VIId could give strong absorption at 460 mμ. That the structural change is reversible is demonstrated by reversion of the spectrum to one related to the acid salts of quinoline[22] (or III) on dilution of the sulfuric acid to 77%. It is evident from the sulfuric acid spectral study of III that the same type of structural change may occur in the absence of the ether group, as might be expected, but to a much lesser extent. These spectra in 100% sulfuric acid are noteworthy in that they alone show distinction between 11-substituents in 6,6-dimethyl-6,11-dihydrobenz(b)acridines.

Considerable study of the infrared spectra of the dihydrobenzacridines in comparison with the quinoline spectra on file in this Laboratory did not result in the unequivocal assignment of any band which might be of use for identification.

The introduction of a trigonal carbon atom at position 11 in the dihydrobenz(b)acridine III in forming the 11-ketodihydrobenz(b)acridine VIII flattens the model of the molecule. This provides for facile cross-conjugation of the carbonyl group with the benzene and quinoline nuclei. The infrared spectrum of VIII showed a carbonyl band at 1665 cm.$^{-1}$ and a strong ultraviolet band at 314 mμ which may be compared with the cinnamoyl band in chalcone.[21]



(for VIII) (for chalcone)

excited states

The bands at 221 and 269 mμ for VIII are probably due to electronic transitions involving the quinoline system.

Acknowledgment.—This investigation was supported in part by grant CY 2931 from the National Cancer Institute, U. S. Public Health Services.

Experimental

1,1-Dimethyl-3-(*o*-nitrobenzal)-2-tetralone (I).—To a solution of 22.0 g. (0.145 mole) of *o*-nitrobenzaldehyde in 60 ml. of 10% sulfuric acid–90% acetic acid, 23.08 g. (0.132 mole) of 1,1-dimethyl-2-tetralone[9] was added dropwise with stirring at 12°. After standing for two days at room temperature 27.4 g. (67.2%) of the crude product was collected by filtration. The filtrate deposited 4.51 g. (11%) additional product after standing for three weeks. Recrystallization of

(20) R. D. Campbell and N. H. Cromwell, THIS JOURNAL, **79**, 3456 (1957).

(21) W. B. Black and R. E. Lutz, *ibid.*, **77**, 5134 (1955).

(22) C. W. Ewing and E. A. Steck, *ibid.*, **68**, 2181 (1946).

(23) W. St. Lesnianski, *Ber.*, **51**, 695 (1918).

(24) A. Etienne, *Ann. chim.*, **12** [11], 1 (1946).

(25) See W. O. Ferrier and J. Iball, *Chemistry & Industry*, 1296 (1954), for a discussion of the structure of the related 9,10-dihydroanthracene.

the crude solid gave 30.3 g. (74.5% yield) of yellow needles, m.p. 158.5–160°, of I; λ_{max}^{26} 254.5, 310–320 (sh.) mμ (ε 15,600, 4,000); $\gamma_{C=O}$,[27] 1691/70, (1681/53 in Nujol); $\gamma_{C=C}$, 1612/38 (1612/33 in Nujol); γ_{Ar}, 1602/54 (1597/48 in Nujol).

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.57; H, 5.76; N, 4.89.

6,6-Dimethyl-12-carboxy-6,11-dihydrobenz(b)acridine (II).—A solution of 20 g. (0.115 mole) of 1,1-dimethyl-2-tetralone, 17.18 g. (0.121 mole) of isatin and 20 g. of potassium hydroxide in 20 ml. of water and 100 ml. of 95% ethanol was refluxed for 24 hours. Most of the alcohol was removed from the reaction mixture by distillation, 450 ml. of water added and the basic solution extracted several times with ether. The basic water layer was saturated with carbon dioxide and the precipitated crude product, 21.1 g. (61% yield), removed and recrystallized twice after charcoal treatment, from dioxane to give 12.38 g. (35% yield) of the pure amino acid II, m.p. 239° dec.; λ_{max} 220, 230, 273, 306, 318 mμ (ε × 10^{-3}, 34.0, 42.8, 5.2, 5.0, 5.2); γ_{COOH}, 1645/42; $\gamma_{C=C,\ Ar,\ C=N}$ 1613/58, 1603/61, 1573/39 (all in Nujol).

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 78.60; H, 5.73; N, 4.75.

6,6-Dimethyl-6,11-dihydrobenz(b)acridine (III). a. Decarboxylation of II.—A 1.0-g. (0.0033 mole) sample of II and 5 mg. of copper powder were heated in a 5-ml. distilling flask in an oil-bath at 245–250° until carbon dioxide evolution ceased. From the residual material 0.710 g. (79% yield) of pure III was obtained, m.p. 95.5–97°, recrystallized from ethanol; λ_{max} 220, 231, (235), 273, 292, 298, 305, 318 mμ (ε × 10^{-3}, 39.5, 45.1, 41.3, 4.8, 3.4, 3.2, 4.5, 5.9); λ_{max} in 0.1 *N* HCl–95% C_2H_5OH, (241), 243, 323 mμ (ε × 10^{-3}, 47.0, 52.5, 10.6); λ_{max} in aq. 77% H_2SO_4, 244, 324 mμ (ε × 10^{-3}, 53.0, 13.0); λ_{max} in 100% H_2SO_4, 241, 246, 324, 460 mμ (ε × 10^{-3}, 54.0, 55.5, 11.1, 5.8); γ, 1623/60, 1607/58 (1616/19, 1601/23 in Nujol).

Anal. Calcd. for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 88.41; H, 6.56; N, 5.28.

b. Reduction of I.—To a vigorously stirred, boiling solution of 20.0 g. (0.653 mole) of I in 180 ml. of acetic acid, 4 ml. of water, then 7.4 g. (0.121 mole) of electrolytic iron were added slowly. The hot suspension was filtered and the filtrate poured into a cold solution of 350 g. of potassium hydroxide in 850 ml. of water. After standing for 12 hours Celite was added and the mixture filtered. The Celite mat was washed with water and the product extracted from it with ethanol. Charcoal treatment and recrystallization of the crude product gave 12.3 g. (72.5% yield) of pure III as yellow colored prisms, m.p. 95–97°, identical with the product produced by method a.

Catalytic hydrogenation with Raney nickel of 2.5 g. of I in ethyl acetate produced only 21 mg. of III after shaking under three atmospheres of hydrogen for 8 hours; 1.51 g. (72%) of the starting material I was recovered.

With platinum oxide under the same conditions 1.00 g. of I produced 0.286 g. of III, m.p. 94–97°, and 0.323 g. of an unidentified material, m.p. 136–139°, after three hours of hydrogenation.

6,6-Dimethyl-11-bromo-6,11-dihydrobenz(b)acridine (IV).—A suspension of 1.29 g. (0.005 mole) of III, 0.89 g. (0.005 mole) of N-bromosuccinimide and about 50 mg. of benzoyl peroxide in 20 ml. of carbon tetrachloride was heated gently under a reflux condenser with a Bunsen flame until reaction became vigorous. As the reaction subsided heat was reapplied and this process repeated until nearly all of the N.B.S. had disappeared and the solution had just started to darken in color. The reaction mixture was filtered free of succinimide and the filtrate used immediately in the subsequent reactions of IV, which it appeared to contain in quantities up to 74% based on yields of products of which it is assumed to be the precursor. When carbon tetrachloride solutions of IV were allowed to stand for short periods of time an orange colored insoluble oil precipitated.

(26) Ultraviolet spectra were determined with a Cary model 11-MS recording spectrophotometer using 5 × 10^{-5} *M* 95% ethanol solutions unless otherwise indicated.

(27) Infrared spectra were determined with a Perkin–Elmer model 21 double-beam instrument using sodium chloride optics and matched 1.0-mm. sodium chloride cells and 12 mg./ml. CCl_4 solutions unless otherwise indicated; band frequencies are recorded as cm.$^{-1}$/% abs.

6,6-Dimethyl-11-morpholino-6,11-dihydrobenz(b)acridine (V).—To the carbon tetrachloride solution of the product IV from the reaction of 1.29 g. (0.005 mole) of III, 2.5 ml. (0.016 mole) of morpholine was added at room temperature. The morpholine hydrobromide, which precipitated immediately, was removed and the solution washed with water, dried and concentrated to produce 1.15 g. (67% yield) of V as colorless crystals after recrystallization from ethanol, m.p. 151–153°; λ_{max} 233, 264, 271, 303, 318 mμ (ε × 10^{-3}, 44.3, 4.6, 4.5, 4.0, 4.5); $\gamma_{C=C,\ C=N,Ar.}$ 1623/60, 1608/54.

Anal. Calcd. for $C_{25}H_{24}N_2O$: C, 80.20; H, 7.02, N, 8.13. Found: C, 80.14; H, 6.96; N, 8.51.

6,6-Dimethyl-11-ethoxy-6,11-dihydrobenz(b)acridine(VI).—The carbon tetrachloride was removed from a solution of IV resulting from the reaction of 1.29 g. (0.005 mole) of III and replaced with 20 ml. of freshly prepared abs. ethanol. The reaction mixture was refluxed for 30 minutes, 0.5 g. of anhyd. sodium carbonate added and refluxing was continued for an additional hour. The solution was filtered, concentrated and cooled to produce 1.17 g. (74% yield) of VI; colorless crystals, recrystallized from ethanol, m.p. 107–109°; λ_{max} 234, 267–274, 305, 318 mμ (ε × 10^{-3}, 50.0, 5.0, 4.3, 5.0).

Anal. Calcd. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98. Found: C, 83.59; H, 7.09.

6,6-Dimethyl-11-methoxy-6,11-dihydrobenz(b)acridine (VII).—The methoxy derivative VII was prepared in manner analogous to that described above for VI, giving a 51% yield of colorless crystals after recrystallization from methanol, m.p. 94–95.5°; λ_{max} 231, 236, 274, 305, 318 mμ (ε × 10^{-3}, 50.0, 50.0, 5.0, 4.3, 5.0); λ_{max} in aq. 77% H_2SO_4, 241, 244, 324 mμ (ε × 10^{-3}, 55.0, 61.0, 12.0); λ_{max} in 100% H_2SO_4, 236, 303, 320, 460 mμ (ε × 10^{-3}, 22.0, 18.0, 7.5, 34.0).

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62. Found: C, 83.12; H, 6.88.

6,6-Dimethyl-11-keto-6,11-dihydrobenz(b)acridine (VIII). a. Oxidation of III with Nitric Acid and Lead Acetate.—A mixture of 5.0 g. (0.0194 mole) of III, 25 mg. of lead acetate, 11 ml. of water and 3.8 ml. of dioxane was refluxed with stirring while 8 ml. of concd. nitric acid was added at such a rate as to redissolve a precipitate which formed. After 7 hours of reflux evolution of the nitric oxide fumes had ceased. Cooling the solution precipitated 6.5 g. (93% yield) of the crude hydronitrate salt of VIII, m.p. 187–192° dec. Treatment of a slurry of the salt in chloroform with 10% sodium carbonate solution produced 4.33 g. (82% yield) of the free base VIII, which after recrystallization from acetone gave 4.15 g. (80% yield) of pure VIII as colorless crystals, m.p. 135–136°; λ_{max}221, 269, 314 mμ (ε × 10^{-3}, 33.4, 23.8, 17.4); $\gamma_{C=O}$, 1665/98 (1652/80 Nujol); $\gamma_{C=C\ or\ C=N}$, 1620/46 (1624/60 Nujol); γ_{Ar}, 1604/47, 1593/55, 1562/21 (1604/66, 1597/66, 1540/33 Nujol).

Anal. Calcd. for $C_{20}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13. Found: C, 83.97; H, 5.72; N, 5.29.

b. Oxidation of III with Chromic Acid.—To a refluxing solution of 1.29 g. (0.005 mole) of III in 13 ml. of acetic acid, a solution of 2.0 g. of chromic anhydride in 7 ml. of 80% acetic acid in water was added dropwise. After the presence of insoluble material in the reaction mixture became evident, the addition was discontinued. The reaction mixture was warmed for 30 minutes over steam, the insoluble material removed by filtration and the filtrate poured into water to precipitate 0.985 g. (70% yield) of the crude ketone VIII, m.p. 132–137°. Charcoal treatment and recrystallization from acetone gave 0.786 g. (56% yield) of pure VIII, m.p. 135–136°.

c. Hydrolysis and Oxidation of IV.—A solution of 1.5 g. of solids, obtained from evaporation of the carbon tetrachloride from a reaction mixture to produce IV, in 50 ml. of 75% aq. acetic acid was boiled for 15 minutes, evaporated under vacuum to about 10 ml., neutralized with aq. sodium hydroxide and extracted with benzene. After drying and evaporation of the benzene solution and recrystallization of the residue, 0.976 g. of pure VIII, m.p. 135–137°, resulted.

Attempts to produce **6,6-dimethyl-11-hydroxy-6,11-dihydrobenz(b)acridine (IX)** by hydrolysis of IV in nitrogen saturated aqueous dioxane gave colorless crystalline material, m.p. 135–140°, which when mixed with VIII gave a melting range of 120–125°, and strong infrared bands in Nujol at 3300, 1635 and 1597 cm.$^{-1}$ but none between 1700 and 1636 cm.$^{-1}$. This material, which is probably mainly

the hydroxy compound IX, oxidized on standing in the air to the ketone VIII.

6,6,11-Trimethyl-11-hydroxy-6,11-dihydrobenz(b)acridine (X).—A 1.0-g. (0.00356 mole) portion of VIII was extracted from the thimble of a Soxhlet apparatus into a 12 ml. of ether solution of methylmagnesium iodide made from 1.02 g. (0.0072 mole) of methyl iodide. The red colored complex was decomposed with a saturated ammonium chloride solution. From the ether solution 0.954 g. (91% yield) of crude tertiary carbinol X, m.p. 151–155°, resulted; recrystallized from petroleum ether, m.p. 156–158°; λ_{max} 231, 273, 294, 300, 307, 313, 321 mμ ($\epsilon \times 10^{-3}$, 48.6, 4.3, 3.9, 3.9, 4.9, 4.0, 6.3); γ_{OH}, 3606/31, $\gamma_{C=C \text{ and/or } C=N}$, 1625/28, 1600/30.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.30; H, 6.55; N, 4.92.

6,6-Dimethyl-11-oximino-6,11-dihydrobenz(b)acridine (XI) was not obtained by the usual methods for preparing oximes. A solution of 0.698 g. (0.01 mole) of hydroxylamine hydrochloride and 2.37 g. of dry pyridine in 10 ml. of freshly prepared abs. ethanol was mixed with a solution of 1.0 g. (0.0036 mole) of VIII in 30 ml. of abs. ethanol and refluxed for 5 days during which time the alcohol and water were allowed to distil off slowly being replaced from time to time with fresh abs. ethanol. A 68% yield, 0.818 g., of crude oxime, m.p. 219–224°, was isolated; recrystallization from ethanol gave colorless flakes, m.p. 222–224°, λ_{max} 244.5 mμ (ϵ 40,800).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.10; H, 5.58; N, 9.81.

Catalytic hydrogenation of the oxime XI with Raney nickel in ethanol at 45 lb./in.^{2} for 10 hours produced an oil from which no solid product was isolated.

LINCOLN, NEBR.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Alkaloids from *Apocynaceae*. III.[1] Alkaloids of *Tabernaemontana* and *Ervatamia*. The Structure of Coronaridine, A New Alkaloid Related to Ibogamine[2]

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Six representative species of the genera *Ervatamia* and *Tabernaemontana* were investigated. The alkaloids ibogamine (Id), voacangine (Ia) and voacamine, common to the genera *Tabernanthe* and *Voacanga*, were isolated. In addition to these, four other alkaloids are described: olivacine (alkaloid "205"), dregamine, tabernaemontanine and coronaridine (Ic). The latter is shown by saponification and decarboxylation to be carbomethoxyibogamine (Id). Dregamine and tabernaemontanine are examples of 2-acylindole alkaloids.

In pursuing the study of different members of the family *Apocynaceae*, we became interested in botanical relatives of the African hardwood *Tabernanthe iboga* Baill.[1] This plant is a source of numerous alkaloids which have been studied by pharmacologists as potential stimulants.[4] The structures of these alkaloids have been elucidated by Taylor.[5]

Another genus closely related botanically to *Tabernanthe* is *Voacanga*.[6] The major alkaloid of *Voacanga africana*, voacangine (Ia), and that of *Tabernanthe iboga*, ibogaine (Ib), differ only in that the former contains an additional carbomethoxy function. The close relationship of these two alkaloids has been demonstrated by the conversion of voacangine to ibogaine.[7] While these two compounds are quite similar chemically, their pharmacology is different[8] in that voacagine lacks the stimulant properties of ibogaine.

Tabernanthe and *Voacanga* are close botanical relatives, being found in the same faimily: (*Apocynaceae*), subfamily (*Plumeroideae*) and tribe (*Tabernaemontanoideae*).[6]

In view of the structural correlations found among the constituents of these genera, it was of interest to investigate other members of the same tribe in the hope of finding biogenetically related alkaloids. Such alkaloids were present.[9]

The tribe *Tabernaemontanoideae* contains, according to Pichon,[10] twenty closely related genera. The largest of these are the genera *Tabernaemontana* with 140 species and *Ervatamia* with 92–96 species.[11] Of the remaining eighteen genera, eight are monotypic, and the rest range from two to twenty species.

We have chosen to investigate the two larger genera because of their broad distribution and availability. The following species were examined: *Ervatamia coronaria*, *E. divaricata*, *Tabernaemontana undulata*, *T. psychotrifolia*, *T. oppositifolia* and *T. australis*.

Ervatamia coronaria, syn. *Tabernaemontana coronaria*. This plant, an 8–10 foot tree, is cultivated throughout India both for the ornamental value of its fragrant white blossoms and as a medicinal. The leaves, bark and flowers of the plant are used in the Ayurvedic system for different ailments as a soothing agent.

(1) Alkaloids from Apocyanaceae, II, Norbert Neuss, *J. Org. Chem.*, **24**, 2047 (1959).

(2) Presented in part before the Organic Division of the 139th National Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

(3) On leave from the University of Illinois as a trainee in the summer employment program, 1958, of Eli Lilly and Co., Indianapolis, Ind.

(4) J. A. Schneider, *Ann. N. Y. Acad. Sci.*, **66**, Art. 3 (1957), March 14, and references cited therein.

(5) W. I. Taylor, THIS JOURNAL, **79**, 3298 (1957).

(6) K. Schumann, in A. Engler and K. Pranti, "Die naturlichen Pflanzenfamilien," Vol. 4, part 2, 1895, p. 109.

(7) F. Percheron, Alain Le Hir, R. Goutarel and M. W. Janot, *Compt. rend. acad. sci.*, **245**, 1141 (1957).

(8) R. C. Rathbun, Lilly Research Laboratories Pharmacology Division, private communication.

(9) After the presentation of these results, Walls, Collera and Sandoval reported the isolation, from the genus *Stemmadenia*, of the new alkaloids (+)-quebrachamine, isovocangine, stemmadenine, as well as the known alkaloids voacangine, voacamine, tabernanthine and ibogamine. These alkaloids are characteristic constituents of the genus *Voacanga*. The presence of these alkaloids in *Stemmadenia sp.* indicates the relationship of this genus to those of *Tabernanthe*, *Voacanga* and *Tabernaemontana* (*Tetrahedron*, **2**, 173 (1958)).

(10) M. Pichon, *Mem. Mus. Nat. Paris*, **24**, 111 (1948), *et seq.*

(11) In some species these genera are synonymous.