7-Hydroxyindolizidine (Epimer A).—7-Ketoindolizidine (5.0 g.) in 25 ml. of 95% ethanol was hydrogenated over 0.5 g. of 5% ruthenium-on-carbon catalyst. After a 30-min. induction period, the theoretical quantity of hydrogen was rapidly absorbed. Removal of catalyst and solvent gave 4.84 g. of a mixture of epimeric amino alcohols (A–B) in a ratio of 45:55 (g.l.c.). This mixture was dissolved in petroleum ether (b.p. 30–60°) and separated by chromatography on neutral alumina (600 g., Woelm activity grade IV). Ether was used as the eluent. The first 1.36 g. of amino alcohol emerging from the column was pure A with succeeding fractions containing increasing amounts of B. Epimer A gave m.p. 99–100°.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71. Found: C, 68.1; H, 10.7.

The **picrate of A** was prepared in ether. Upon recrystallization from ether–methanol it gave m.p. 193° dec.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.44; H, 4.90. Found: C, 45.4; H, 4.9.

7-Hydroxyindolizidine (Epimer B).—7-Ketoindolizidine (2.0 g.) was reduced with potassium–ethanol in benzene according to a previously reported procedure.[12] The crude reduction mixture gave an A–B ratio of 4:96 (g.l.c.) with a small amount (about 3%) of an unknown higher boiling material. Vacuum distillation gave 1.3 g. of product, which upon sitting at 3° formed a white solid, m.p. 47–49.5°. Two recrystallizations from petroleum ether did not change this melting point. G.l.c. analysis revealed the product to contain only epimers A and B in a ratio of 4:96, respectively.

The picrate of B was prepared in ether and recrystallized (ethyl acetate–ether) to give m.p. 164–166°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.44; H, 4.90. Found: C, 45.4; H, 5.0.

8-Hydroxyindolizidine (Epimer A).—8-Ketoindolizidine (5.0 g.) was dissolved in absolute ethanol and reduced over 0.5 g. of 5% ruthenium-on-carbon catalyst. After a theoretical absorption of hydrogen, both catalyst and solvent were removed, leaving a crude reduction mixture of 85:15 A–B ratio (g.l.c.). Vacuum distillation gave an estimated 3.5 g. in four cuts of comparable size. Cut 1 contained >99.5% pure epimer A, a mobile liquid, b.p. 66–67° (3.8 mm.), $n^{25}D$ 1.4931. Cut 2 contained A of >98% epimeric purity (g.l.c.).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71. Found: C, 68.1; H, 10.8.

The **picrate of A** was prepared in ether and gave m.p. 145–146° (ethyl acetate–ether).

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.44; H, 4.90; N, 15.13. Found: C, 45.7; H, 5.0; N, 15.0.

8-Hydroxyindolizidine (Epimer B).—8-Ketoindolizidine (5.0 g.) in 25 ml. of absolute ethanol was reduced over 0.7 g. of 10% palladium-on-carbon catalyst. Removal of solvent and catalyst gave a crude reduction mixture with a 29:71 A–B ratio.[24] Vacuum distillation separated the mixture into four cuts, total of 3.4 g., of which cuts 3 (1.37 g.) and 4 (0.52 g.) contained B in 95 and 98% epimeric purities, respectively. Epimer B (cut 4) was a viscous liquid, b.p. 85° (3 mm.), $n^{25}D$ 1.5039.

The **picrate of B** was prepared in ether and gave m.p. 174–176° (lit.[3] 175–176°, isolated from what is now known to have been about a 23:77 A–B mixture) which was unchanged by further recrystallizations from ethyl acetate.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.44; H, 4.90. Found: C, 45.2; H, 4.6.

(24) The discrepancy between this A–B ratio and that given in Table II is likely due to the difference in catalyst–substrate ratio. The stereochemistry of palladium-on-carbon reductions is known to be sensitive to this ratio. See R. L. Augustine, *J. Org. Chem.*, **28**, 152 (1963).

An Approach to the Synthesis of 8a-Azoniaacridine Salts[1]

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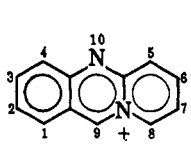
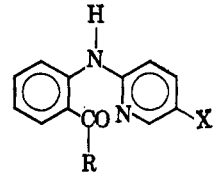
The addition of excess phenyl- or methyllithium to 2-(2-carboxyanilino)pyridine yields not the expected ketones, but instead tertiary alcohols which may be cyclodehydrated to 6,11-dihydro-11-azaacridizinium derivatives. 2′-Aminoacetophenone and, to a more limited extent, -benzophenone undergo condensation with 2-bromopyridines and 2-chloroquinolines. With one exception, the new condensation products appear to be the pseudo-bases of 8a-azoniaacridine derivatives.

Although the 1-azaquinolizinium ion is known,[2] neither of its fully aromatic linear benzologs has been reported. The present communication describes experiments directed toward the synthesis of one of these, the 8a-azoniaacridine[3] (or pyrido[2,1-*b*]quinazolin-10-ium) system (I).

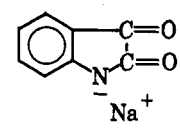


I

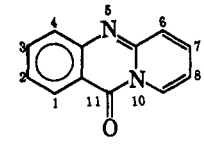


II

The best approach to the new aromatic system (I) appeared to be the synthesis and cyclization of a 2-anilinopyridine (II) with an acyl, aroyl, or formyl group at the *ortho* position of the phenyl ring. The sodio derivative (III) of isatin, which can be alkylated[4] with methyl iodide, could not be made to react with 2-bromopyridine. Likewise the attempt to prepare an anilinopyridine from 2-aminobenzonitrile by reaction with 2-bromopyridine failed under basic or neutral (sealed tube) conditions. The condensation of ethyl anthranilate (or the free acid) with 2-chloro- or 2-bromopyridine is known to yield 11H-pyrido[2,1-*b*]-quinazolin-11-one (IV), and alkaline hydrolysis of IV, followed by acidification, is known to yield 2-(2-carboxyanilino)pyridine (II, R = OH, X = H).[5] It was found that treatment of the acid II with excess



III



IV

(1) This research project was supported by U. S. Public Health Research Grants (H-2170) from the National Heart Institute and (CA-05509) from the National Cancer Institute.

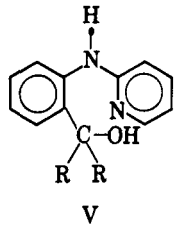
(2) A. N. Nesmeyanov, M. I. Rybinskaya, and N. K. Belskii, *Dokl. Akad. Nauk SSSR*, **113**, 343 (1957); *Chem. Abstr.*, **51**, 14712 (1957).

(3) Nomenclature as recommended by Commission on the Nomenclature of Organic Chemistry of the International Union of Pure and Applied Chemistry (IUPAC 1957 Rules); *J. Am. Chem. Soc.*, **82**, 5545, 5572 (1960).

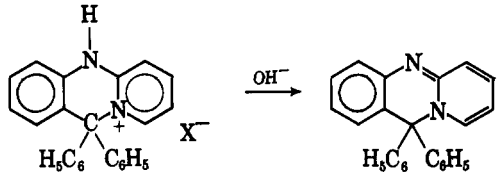
(4) G. Heller, *Ber.*, **40**, 1294 (1907).

(5) S. Carboni, *Atti Soc. toscana sci. nat. Pisa, Proc. Verbali Mem.*, **62A**, 261 (1955); *Chem. Abstr.*, **50**, 16767 (1956).

(3–5 mole equiv.) methyl- or phenyllithium gave not the expected ketone II,[6] but the tertiary carbinol V. The same carbinols (V) were obtained (in better yield) when 11H-pyrido[2,1-*b*]quinazolin-11-one (IV) was



V

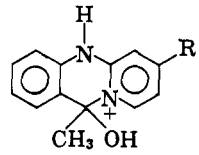


VI VII

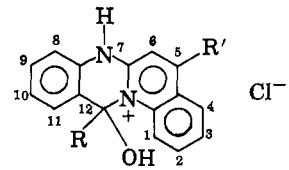
treated with excess Grignard or organolithium reagent. Cyclization of the diphenyl carbinol V (R = C_6H_5) with acids afforded what are believed to be 9,9-diphenyl-,9,10-dihydro-8a-azoniaacridine salts (VI) and the action of alkali on the salts gave what is probably 11,11-diphenyl-11H-pyrido[2,1-*b*]quinazoline (VII).

An approach to the synthesis of II, more direct than any of the foregoing, would be the direct condensation of bromopyridine with an *o*-aminophenyl ketone. Attempts to condense 2′-aminoacetophenone with 2-bromopyridine under neutral or basic conditions[7,8] failed; final success was achieved by condensation in dilute aqueous hydrochloric acid.[9] Only in the case in which 2-bromo-5-nitropyridine was used as the halide was the product a ketone (II, R = CH_3, X = NO_2). In the other two cases, when 2-bromopyridine or 2-bromo-4-methylpyridine was used, the product (in low yield) was a salt which gave no evidence of a carbonyl group in the infrared absorption spectrum. While it was expected that the two new salts (isolated as bromides) would be 9-methyl-8a-azoniaacridine bromide and 6,9-dimethyl-8a-azoniaacridine bromide, the elemental analyses showed the presence of at least 1 additional mole of water, and the ultraviolet absorption spectra did not resemble that of acridizinium bromide.[10]

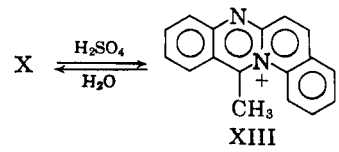
Better yields of similar salts were obtained when 2-chloroquinoline or 2-chloro-4-methylquinoline was used with 2′-acetophenone or 2-aminobenzophenone. On the basis of the classical work of Albert[11] on the covalent hydration of quinazolines, and of experiments to be cited, it is proposed that the new salts are 9-methyl-9-hydroxy-9,10-dihydro-8a-azoniaacridine salts (VIII and IX) and 11-substituted 12-hydroxy-7,12-dihydro-12a-azoniabenz[*a*]acridine salts (X–XII). Evidence for this formulation was found in the behavior of X in concentrated sulfuric acid. A solution of X in methanol gave a relatively simple ultraviolet absorption



VIII, R = H
IX, R = CH_3



X, R = CH_3; R′ = H
XI, R = C_6H_5; R′ = H
XII, R = C_6H_5; R′ = CH_3



XIII

spectrum with maxima at 245, 272, and 372 mμ. In concentrated sulfuric acid, a greatly altered and more complex spectrum was recorded with maxima at 224, 307, 332, and 364 mμ and with additional points of inflection at 242, 251, 275, and 450 mμ. The spectrum in concentrated sulfuric acid is more nearly what one would expect for an azonia[3] analog (XIII) of benz[*a*]acridine (or benz[*a*]anthracene[12]). The change in spectrum was reversed on dilution of the acid mixture, and at roughly 50% sulfuric acid–50% water (by volume) the absorption spectrum had become virtually the same as that recorded in methanol.

Similar results were obtained with n.m.r. measurements. A sample of X in trifluoroacetic acid (tetramethylsilane as external standard) showed a singlet at τ 7.27 (three protons) assigned to the methyl group, a broad singlet at −2.38 (one proton) assigned to the NH proton, and another singlet at −0.86 tentatively assigned to the OH proton. The aromatic region showed a complex absorption centered at approximately τ 2. In concentrated sulfuric acid, using the same external standard, the methyl singlet occurred at τ 5.34 (thus strongly deshielded), whereas the peaks assigned to OH and NH disappeared. The aromatic absorption appeared to be centered at about τ 1. In a solution consisting of approximately 1:1 sulfuric acid–water (by volume) the methyl group appears at τ 6.9, the aromatic protons again appear to be centered at about 2, and a broad band at −2.72 may be due to the proton on NH, but this is uncertain.

On the basis of the foregoing evidence, it appears likely that the acid-catalyzed condensation of 2-halopyridines and quinolines with *o*-aminophenyl ketones in dilute acid affords pseudo-bases (VIII–XII). These pseudo-bases undergo dehydration in concentrated sulfuric acid to afford azoniaacridine salts, but, on dilution of the acid, covalent hydration occurs causing reversion to the pseudo-bases.

Experimental[13]

All analyses were carried out by Dr. Ing. A. Schoeller, Kronach, Germany. The melting points were taken in capillaries using a Mel-Temp apparatus and are corrected. The ultraviolet absorption spectra for which log extinction coefficients are reported were measured in 95% ethanol using a Cary Model 14 spectrophotometer. All other ultraviolet data was obtained using a Perkin-Elmer Model 202 spectrophotometer. With both instru-

(6) *Cf.* M. S. Newman and J. Mangham, *J. Am. Chem. Soc.*, **71**, 3342 (1949); M. S. Newman and T. S. Bye, *ibid.*, **74**, 905 (1952).
(7) T. D. Perrine and L. J. Sargent, *J. Org. Chem.*, **14**, 583 (1949).
(8) H. Jensen and F. Rethwisch, *J. Am. Chem. Soc.*, **50**, 1114 (1928).
(9) *Cf.* C. K. Banks, *ibid.*, **66**, 1127 (1944).
(10) C. K. Bradsher and L. E. Beavers, *ibid.*, **77**, 4812 (1955).
(11) *E.g.*, A. Albert, R. Goldacre, and J. N. Phillips, *J. Chem. Soc.*, 2240 (1948); A. Albert, D. J. Brown, and H. Wood, *ibid.*, 2066 (1956); A. Albert, W. Armarego, and E. Spinner, *ibid.*, 2689 (1961).
(12) G. M. Badger, R. S. Pearce, and R. Pettit, *ibid.*, 3199 (1951).
(13) The authors are indebted to Dr. Elmer F. Litzinger, Jr., who repeated some of the preparative work described.

ments 1-cm. quartz cells were used. The n.m.r. data was obtained using Varian A-60 spectrometer.

Diphenyl[2-(2-pyridylamino)phenyl]carbinol (V, R = C_6H_5).—A solution of 2.14 g. (0.01 mole) of 2-(2-carboxyanilino)pyridine (II, R = OH, X = H)[5] was stirred in dry tetrahydrofuran in an atmosphere of dry nitrogen while an excess of phenyllithium (0.03–0.05 mole) in ether was added dropwise during 1 hr. The mixture was allowed to stand an additional hour and was decomposed with ice–water. The ethereal layer was separated, dried, and concentrated, and the product crystallized from ethyl acetate as colorless microneedles, 1.5 g. (43%), m.p. 210–211°.

Anal. Calcd. for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72. Found: C, 81.56; H, 5.80.

The same product was obtained (66% yield) by reaction of an excess of phenyllithium with 11H-pyrido[2,1-*b*]quinazolin-11-one (IV).

Dimethyl[2-(2-pyridylamino)phenyl]carbinol (V, R = CH_3).—The dimethylcarbinol V, R = CH_3, was prepared from the acid in essentially the same way (47% yield) using an excess of methyllithium. The carbinol formed colorless rhombs, m.p. 132–134°, from ethyl acetate.

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.52; H, 6.83; N, 12.42.

The same product (47% yield) was obtained by action of excess methyllithium on 11H-pyrido[2,1-*b*]quinazolin-11-one (IV).

9,9-Diphenyl-9,10-dihydro-8a-azoniaacridine Chloride (VI, X = Cl).—The diphenylcarbinol V, R = C_6H_5 (1 g.), was heated on a steam bath for 30 min. with 10 ml. of 2 *N* hydrochloric acid. The original colorless suspension turned bright yellow. The salt was collected, washed, dried, and recrystallized from acetic acid as small yellow prisms, m.p. 323–324°, yield quantitative.

Anal. Calcd. for $C_{24}H_{19}ClN_2$: C, 77.72; H, 5.16. Found: C, 77.45; H, 5.27.

The bromide VI, X = Br, was prepared similarly except that 48% hydrobromic acid was used. It formed yellow needles, m.p. 356–358°, from ethanol.

Anal. Calcd. for $C_{24}H_{19}BrN_2$: C, 69.40; H, 4.61; N, 6.75. Found: C, 69.36; H, 4.84; N, 7.14.

11,11-Diphenylpyrido[2,1-*b*]quinazoline (VII).—The base (VII), obtained by action of alkali on VI, X = Br, crystallized from ethyl acetate as bright yellow prisms, m.p. 221.5–223.5°.

Anal. Calcd. for $C_{24}H_{18}N_2$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.31; H, 5.48; N, 8.59.

General Procedure for the Condensation of Amino Ketones with 2-Bromopyridines or 2-Chloroquinolines.—2-Aminobenzophenone or 2′-aminoacetophenone (0.01 mole) and the halopyridine or -quinoline (0.012 mole) were added to 100 ml. of water containing 1 ml. of either concentrated hydrochloric or 48% hydrobromic acid. Where necessary in order to achieve homogeneity, ethanol (up to 20 ml.) was added to the reaction mixture.

The reaction solution was maintained at reflux temperature until a small sample, upon diazotization and treatment with alkaline 2-naphthol, showed that nearly all of the amino ketone had reacted, the usual interval being 6–24 hr. The acidic solution was concentrated under vacuum and the residue was recrystallized. The results are given briefly below.

9-Methyl-9-hydroxy-9,10-dihydro-8a-azoniaacridine (VIII) bromide was prepared by refluxing 2′-aminoacetophenone and 2-bromopyridine for 18 hr. yielding, from ethanol–ethyl acetate, 5–40% of yellow prisms: m.p. 177–179°; λ_{max} 258 mμ (log ε 4.16), 288 (3.42), 298 (3.43), and 349 (3.86).

Anal. Calcd. for $C_{13}H_{13}BrN_2O \cdot 0.5H_2O$: C, 51.90; H, 4.03; N, 9.34. Found: C, 51.77; H, 4.50; N, 9.23.

The **perchlorate** formed yellow plates from ethanol, m.p. 215.5–217.5°.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_5$: C, 49.93; H, 4.19; N, 8.96. Found: C, 50.09; H, 4.41; N, 9.12.

6,9-Dimethyl-9-hydroxy-9,10-dihydro-8a-azoniaacridine (IX) bromide was prepared by refluxing 2′-aminoacetophenone and 2-bromo-4-methylpyridine for 17 hr. (20 ml. of ethanol added): yield 21% of yellow prisms from ethanol–ethyl acetate, m.p. 217.5–219.5°.

Anal. Calcd. for $C_{14}H_{15}BrN_2O$: C, 54.73; H, 4.92; N, 9.12. Found: C, 54.30; H, 4.73; N, 9.24.

12-Methyl-12-hydroxy-7,12-dihydro-12a-azoniabenz[*a*]acridine chloride (X) was prepared from 2′-aminoacetophenone and 2-chloroquinoline by refluxing for 17 hr.: yield 86% of yellow prisms, m.p. 175–177°, from ethanol–ethyl acetate; λ_{max} 245 mμ (log ε 4.80), 272 (4.71), and 372 (4.62).

Anal. Calcd. for $C_{17}H_{15}ClN_2O \cdot 0.25H_2O$: C, 67.32; H, 5.15; N, 9.24. Found: C, 67.33; H, 5.02; N, 9.23.

12-Phenyl-12-hydroxy-7,12-dihydro-12a-azoniabenz[*a*]acridine chloride (XI) was prepared by refluxing 2′-aminobenzophenone and 2-chloroquinoline for 24 hr. (10 ml. of ethanol added). The yield from ethanol–ethyl acetate–petroleum ether (b.p. 30–60°) was 70% of pale yellow microneedles: m.p. 158.5–168.5°; λ_{max} 205 mμ (log ε 4.74), 254 (4.58), and 348 (4.06).

Anal. Calcd. for $C_{22}H_{17}ClN_2O \cdot 0.5H_2O$: C, 71.45; H, 4.90; N, 7.58. Found: C, 71.94; H, 5.04; N, 7.49.

5-Methyl-12-phenyl-12-hydroxy-7,12-dihydro-12a-azoniabenz[*a*]acridine chloride (XII) was prepared from 2-aminobenzophenone and 2-chloro-4-methylquinoline by refluxing for 24 hr. (20 ml. of ethanol added). The product consisted of colorless microneedles, m.p. 199.5–201.5°, from methanol–ethyl acetate (85% yield).

Anal. Calcd. for $C_{23}H_{19}ClN_2O \cdot 0.5H_2O$: C, 71.96; H, 5.25; N, 7.29. Found: C, 71.54; H, 5.53; N, 7.08.

***o*-(5-Nitro-2-pyridylamino)acetophenone (II, R = CH_3, X = NO_2).**—When 2′-aminoacetophenone was allowed to react with 2-bromo-5-nitropyridine in acidified boiling water for 6 hr. as described above, the product (74% yield), crystallized from acetic acid as yellow prisms, m.p. 187.5–189.5°, showed a characteristic absorption at 1665 cm.$^{-1}$ in the carbonyl region of the infrared, and was not a salt: λ_{max} 206 mμ (log ε 4.19), 238 (4.39), 262 (inflection point) (3.86), and 387 (4.46).

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.31. Found: C, 60.79; H, 4.13.

In concentrated sulfuric acid the ultraviolet absorption spectrum was greatly altered with a new maximum at about 260 mμ and absorption further into the visible region.