Dehydrogenation of Optically Active V (R = NO₂).—The total residue from the first of the irradiation experiments, containing optically active V (R = NO₂), was taken up in 25 cc. of acetic acid, cooled to 15° and treated dropwise over a period of 20 minutes with a solution of 1.25 g. of potassium dichromate and 2 cc. of sulfuric acid in 15 cc. of water. The temperature was maintained below 15° for an additional hour and 15 minutes and then allowed to rise to room temperature. After 8 hours at room temperature, the solvents were removed by lyophilization at −80°, the residue treated with water, made basic with sodium carbonate, extracted with benzene and the extract dried over magnesium sulfate. The solvent was evaporated and the residue examined polarimetrically. No rotation was observed, α_D +0.001 ± 0.005° (l = 1 dcm., 2.65 in ethanol).

Aromatic Cyclodehydration. XXIX.[1] 7-Methyl- and 7-Phenylbenzo[a]quinolizinium Salts

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By cyclodehydration of N-acetonyl- and N-phenacyl-α-phenylpyridinium salts the first fully aromatic benzoquinolizinium salts have been prepared. The structure of 7-methylbenzo[a]quinolizinium bromide has been demonstrated by its oxidation to phthalic acid.

Frequently overlooked in discussions of aromatic systems are what might be called the cationoid aromatics. These interesting compounds owe their aromaticity to the existence of a hetero atom in a higher valence state. Simple and familiar examples of such systems are the pyrillium (I, X = O) and thiapyrillium (I, X = S) salts in which a CH of the benzene ring is replaced by an oxonium or sulfonium linkage. The simplest aromatic system in-

corporating the ammonium nitrogen is the quinolizinium ion II. Despite the large amount of research done in the field of heterocyclic chemistry, compounds containing this aromatic structure have received little attention. When the present work was undertaken only a few compounds were believed or known to contain the quinolizinium nucleus.[3] The even smaller groups of wholly aromatic quinolizinium salts (all rings aromatic[3a,b,c,f]) consisted of a few complex compounds which, with the exception of the tetracarbomethoxy quinolizinium derivatives[3b] of Diels and Alder, were tetracyclic in nature.

It was felt that the much needed knowledge of the chemistry and pharmacology of the aromatic quinolizinium salts must come from a study of derivatives simpler and more readily available than those previously reported. For this reason the present synthesis of the first aromatic benzologs of the quinolizinium ion was undertaken.

When this work was substantially complete Boekelheide and Gall[4] published a new and convenient synthesis for 3,4-dihydroquinolizinium[5] iodide and showed that it could be dehydrogenated to quinolizinium iodide (II) in yields up to 15%.[6]

It was hoped that we might be able to apply the methods of aromatic cyclodehydration to the synthesis of some benzoquinolizinium salts. As has been pointed out earlier,[7] these methods obviate the necessity for dehydrogenation and are well suited for the synthesis of compounds which are not resistant to high temperatures.

The starting material for our synthesis was the easily prepared α-phenylpyridine[8] which did not quaternize satisfactorily with α-chloroacetone or α-bromoacetone, but at room temperature with freshly prepared α-iodoacetone afforded the expected salt (III, R = CH₃; X = I) in 85–90% yield.

It was anticipated that the cyclization of the new salt might prove much more difficult than had been observed in the case of the carbocyclic analog[9] since the positive charge on the nitrogen atom would strongly deactivate the phenyl nucleus. Actual cyclization experiments with the new iodide (III, R = CH₃, X = I) were very unsatisfactory, the

(1) For the previous communication of this series see This Journal, **76**, 4140 (1954).

(2) Public Health Service Research Fellow of the National Institutes of Health (1952–1954).

(3) (a) W. Schneider and K. Schroeter, Ber., **53B**, 1459 (1920); (b) O. Diels and K. Alder, Ann., **505**, 103 (1933); (c) S. Sugasawa and K. Kakemi, Ber., **71B**, 1860 (1938); (d) R. B. Woodward and B. Witkop, This Journal, **71**, 379 (1949); (e) R. B. Woodward and W. M. McLamore, ibid., **71**, 379 (1949); (f) R. Schwyzer, Helv. Chim. Acta, **35**, 867 (1952).

(4) V. Boekelheide and W. G. Gall, This Journal, **76**, 1832 (1954).

(5) According to the nomenclature employed by Boekelheide and Gall structure II is to be referred to as the dehydroquinolizinium ion. We feel that this usage violates established custom in the naming of aromatic nuclei, and throughout the present paper have employed the terminology of Chemical Abstracts, which designates II as the quinolizinium ion (C. A., **46**, 13667 (1952)).

(6) The paper of Boekelheide and Gall (ref. 4) also revealed that Beaman and Woodward had prepared quinolizinium salts in very poor yield.

(7) C. K. Bradsher and A. K. Schneider, This Journal, **60**, 2960 (1938); C. K. Bradsher, Chem. Revs., **38**, 447 (1945).
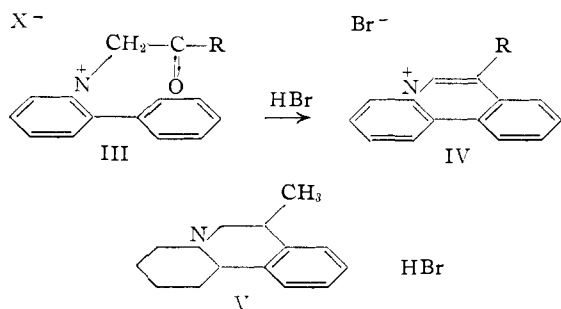
(8) J. C. W. Evans and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 517.

(9) C. K. Bradsher and W. J. Jackson, This Journal, **76**, 734 (1954).

iodide ion being oxidized to free iodine and intractable materials produced. It was found necessary to convert the iodide salt to the chloride (III, X = Cl), which was done by the action of a silver chloride suspension. The new chloride was not crystalline, but when dissolved in 48% hydrobromic acid and the solution refluxed for 51 hours the desired 7-methylbenzo[a]quinolizinium bromide (IV, R = CH₃) was obtained in 75% yield. Since the product was extremely water soluble it had to be isolated by vacuum evaporation of the acid solution followed by recrystallization of the salt from an ether–alcohol mixture. The new bromide (IV, R = CH₃) appeared to be solvated, but the corresponding picrate had the expected composition.

Hydrogenation of the benzoquinolizinium bromide (IV, R = CH₃) in the presence of Adams catalyst resulted in the uptake of exactly 4 moles of hydrogen yielding what is believed to be the hydrobromide V of the heptahydrobenzoquinolizinium derivative.

Oxidation of IV (R = CH₃) yielded a small quantity of phthalic acid, indicating the correctness of our formulation, while the ultraviolet absorption spectra of the uncyclized (III) and cyclized (IV) iodides (Fig. 1) make it clear that the cyclization reaction has resulted in an increase in molecular extinction coefficient and a shift toward longer wave lengths. These effects would be predicted for a transition from a restricted biphenyl type of structure to a planar polycyclic aromatic one.
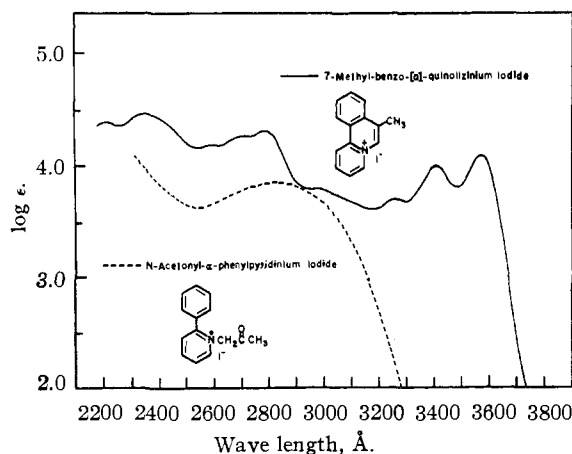

Fig. 1.—Ultraviolet absorption spectra of: (—), 7-methyl-benzo[a]quinolizinium iodide; (----), N-acetonyl-α-phenyl-pyridinium iodide

In contrast to bromoacetone, phenacyl bromide quaternizes satisfactorily with α-phenylpyridine at room temperature affording a 60–75% yield of the expected salt (III, R = C₆H₅, X = Br). As would be expected from the comparison of cyclization rates of phenyl and methyl ketones[10] the cyclization rate of the phenacyl salt (III, R = C₆H₅) is much slower than its acetonyl counterpart (R = CH₃) a total reflux period of fourteen days being required to obtain a 42% yield of the benzoquinolizinium salt (IV, R = C₆H₅). Figure 2 shows the ultraviolet absorption spectra of the 7-phenylbenzo[a]-quinolizinium bromide (IV, R = C₆H₅) and the ketone (III, R = C₆H₅) from which it was formed. Both curves show relationship to those obtained from the methyl analogs (Fig. 1).

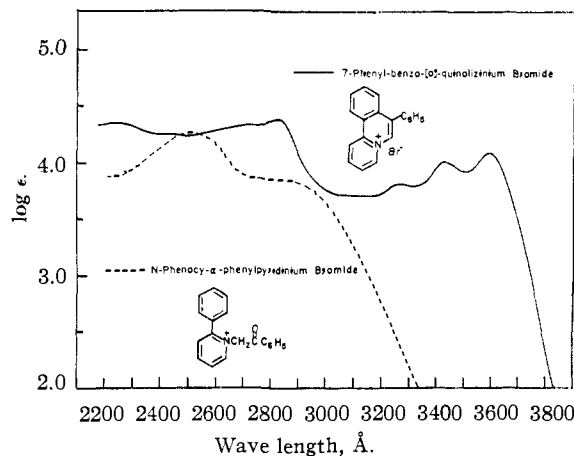Fig. 2. Ultraviolet absorption spectra of: (—), 7-phenyl-benzo[a]quinolizinium bromide; (----), N - phenacyl - α - phenylpyridinium bromide.

Experimental[11]

N-Acetonyl-α-phenylpyridinium Iodide (III, R = CH₃, X = I).—Seven and one-half grams of freshly-prepared iodoacetone[12] was dissolved in 5 g. of α-phenylpyridine.[8] The mixture became perceptibly warmer and darker in color. At the end of two weeks the dark solid mass was thoroughly crushed and then washed with peroxide-free ether.[13] The resulting solid was dissolved in 25 ml. of absolute ethanol and ether was added to the point of incipient cloudiness. After the first crop of crystals had been collected further additions of ether were carried out until finally only oil precipitated. The combined solid fractions were then dissolved in 25 ml. of hot water treated with acid-washed[14] Norite, filtered and concentrated under vacuum at 80° until a thick gum remained. This residue was crystallized from ethanol–ether as tan flakes, m.p. 162–163°; yield 9.6 g. (88%). Further recrystallizations gave a product, m.p. 163–164°.

The picrate formed yellow plates, m.p. 143.5–144.2° (with previous softening).

Anal.[15] Calcd. for C₂₀H₁₆O₈N₄: C, 54.57; H, 3.66. Found: C, 54.50; H, 3.70.

7-Methyl-benzo[a]quinolizinium Bromide (IV, R = CH₃).—A solution prepared from 2.46 g. of N-acetonyl-α-phenylpyridinium iodide (III, R = CH₃, X = I) in 10 ml. of distilled water containing two drops of concentrated hydrochloric acid was placed in a 100-ml. round-bottomed flask

(10) C. K. Bradsher and F. A. Vingiello, *ibid.*, **71**, 1434 (1949).

(11) All melting points are uncorrected.

(12) R. Scholl and G. Matthaiopoulos, *Ber.*, **29**, 1558 (1896).

(13) Unpurified ether contained sufficient peroxide to oxidize the iodide ion to free iodine.

(14) Unwashed Norite apparently contained traces of a basic substance which converted some of the product to a highly-colored impurity.

(15) All analyses are by Micro Tech Laboratories, Skokie, Illinois.

and freshly prepared and thoroughly washed silver chloride (from 3 g. of silver nitrate) was added by use of 50 ml. of distilled water. The resulting suspension was mechanically stirred for two hours then filtered. The silver halide mixture was washed thoroughly with hot water and the washings combined with the filtrate. The almost colorless combined filtrates were concentrated *in vacuo* at 80°, and the residue was transferred to an all-glass apparatus by use of 15 ml. of 48% hydrobromic acid. The acid solution was heated without the reflux condenser until the temperature of the distillate reached 125°. The mixture was refluxed for 51 hours and then concentrated *in vacuo* at 80° until essentially all of the hydrobromic acid was removed. The dark sticky residue was dissolved in 20 ml. of water, decolorized with Norite, filtered and again concentrated *in vacuo*. The residue was dissolved in absolute alcohol and once more evaporated to dryness yielding a crystalline solid. The solid was purified by dissolving it in absolute alcohol and precipitating it by the careful addition of ether. The tan solid was collected and washed with a 1:1 ether–alcohol mixture and dried in a vacuum desiccator; yield 1.53 g. (76%), m.p. 281–283° dec. (previous sintering at 270°). Once more recrystallized in approximately the same manner, but filtered through acid-washed Norite and Supercel, the product was obtained as tiny, light cream colored needles, m.p. 283° dec., yield 1.51 g. (75%).

The iodide prepared from an aqueous solution saturated with potassium iodide was recrystallized from alcohol–ether as tiny tan flakes, m.p. 267–268° dec.

The picrate formed yellow needles from acetone, m.p. 230–230.5°.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.88; H, 3.34. Found: C, 57.06; H, 3.52.

11b-H-7-Methyl-1,2,3,4,6,7-hexahydrobenzo[a]quinolizine Hydrobromide (V).—One gram of pure 7-methylbenzo[a]quinolizinium bromide (IV, R = CH₃) was dissolved in 25 ml. of absolute alcohol, 0.100 g. of Adams catalyst was added and the mixture hydrogenated at room temperature and atmospheric pressure until absorption of hydrogen ceased. The total absorption was 100% of the theoretical assuming four moles of hydrogen to be absorbed.

The catalyst was filtered off, the solution concentrated *in vacuo* and the hydrobromide recrystallized from alcohol–ether as a white solid, m.p. 195–198°; yield 0.62 g. (60%). After two recrystallizations from alcohol–ether the product was obtained as small colorless needles, m.p. 199°.

Anal. Calcd. for $C_{14}H_{20}NBr$: Br, 28.32. Found (by titration): Br, 28.50.

Oxidation of 7-Methyl-benzo[a]quinolizinium Bromide (IV, R = CH₃).—A pure sample of the bromide (IV, R = CH₃, 289 mg.) was dissolved in 10 ml. of water and the mixture heated to 83°. The solution was mechanically stirred while a total of 15 ml. of hot potassium permanganate solution (prepared from 3.27 g. of potassium permanganate and 50 ml. of water) was added as rapidly as the solution was decolorized. Two milliliters of a 25% solution of sodium hydroxide was then added[16] and the remaining per-

manganate together with 4 ml. of sodium hydroxide was added over a period of four hours. The solution was heated with stirring for 36 hours at which time decolorization had occurred. The hot solution was acidified with dilute sulfuric acid, and the manganese dioxide filtered off. The filtrate was concentrated to 50 ml. and extracted with ether in a continuous extractor. The first fraction was removed after six hours and yielded nothing except an unidentified oil. Extraction was continued for 16 hours with a second portion of ether. Evaporation of this second fraction yielded 88 mg. of a semi-solid which when triturated with cold chloroform afforded a white residue (50 mg.), m.p. 185–190°. Repeated sublimation yielded slender glistening colorless needles, m.p. 131°, which did not depress the melting point of a pure sample of phthalic anhydride and gave the characteristic fluorescein test.[17]

N-Phenacyl-α-phenylpyridinium Bromide (III, R = C₆H₅, X = Br).—Three grams of phenacyl bromide and 2 g. of α-phenylpyridine were warmed until melted and then intimately mixed. At the end of nine days a solid crystalline mass had formed. This solid was triturated with pure ether, and crystallized from alcohol–ether yielding 3.11 g. (68%) of the quaternary salt, m.p. 167.5–170°. A carefully recrystallized sample melted at 168–170°.

The perchlorate formed by addition of perchloric acid to an aqueous solution of the bromide formed colorless needles from methylene chloride–ether, m.p. 140.2–140.5°.

Anal. Calcd. for $C_{19}H_{16}NO_5Cl$: C, 61.05; H, 4.32. Found: C, 60.94; H, 4.34.

7-Phenylbenzo[a]quinolizinium Bromide (IV, R = C₆H₅).—One gram of N-phenacyl-α-phenylpyridinium bromide (III, R = C₆H₅, X = Br) was placed in an all-glass apparatus with 4 ml. of 48% hydrobromic acid and refluxed for 14 days. At the end of this period the dark solution was concentrated *in vacuo* at 80° until essentially all of the hydrobromic acid had been removed. The residue was dissolved in water and the solution treated with Norite, filtered and again concentrated *in vacuo*. The resulting glass was dissolved in absolute alcohol and again evaporated to dryness. The gummy product was crystallized from absolute alcohol–ether as colorless needles, m.p. 272–274°; yield 0.4 g. (42%). A recrystallized sample melted at 276–277°.

The perchlorate was obtained from methylene chloride as tiny white needles, m.p. 190–192°.

The picrate formed yellow needles from absolute alcohol, m.p. 197.5–198.2°.

Anal. Calcd. for $C_{25}H_{16}N_4O_7$: C, 61.98; H, 3.33. Found: C, 62.13; H, 3.27.

Ultraviolet absorption spectra were determined in 95% ethanol solution with a Beckman model DU quartz spectrophotometer using 1-cm. silica cells.

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(16) It was found that earlier introduction of sodium hydroxide led to the formation of a water-insoluble gum which did not oxidize satisfactorily.

(17) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 148.