Aromatic Cyclodehydration. LIII.[1] 6a-Azonianaphthacenequinones

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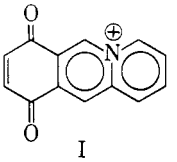
The reaction of 1,4-dimethoxy-2-(bromomethyl)naphthalene with picolinaldoxime or 2-benzoylpyridine, followed by cyclization with concomitant ether-cleavage and oxidation, has afforded 6a-azonianaphthacenequinones. These are the first compounds known to contain both a quinone and a quinolizinium nucleus.

The synthesis of a number of quinolizinium benzologs or azonia[3] polycyclic aromatic hydrocarbons has been reported,[4] but to date none of the related quinones has been described.

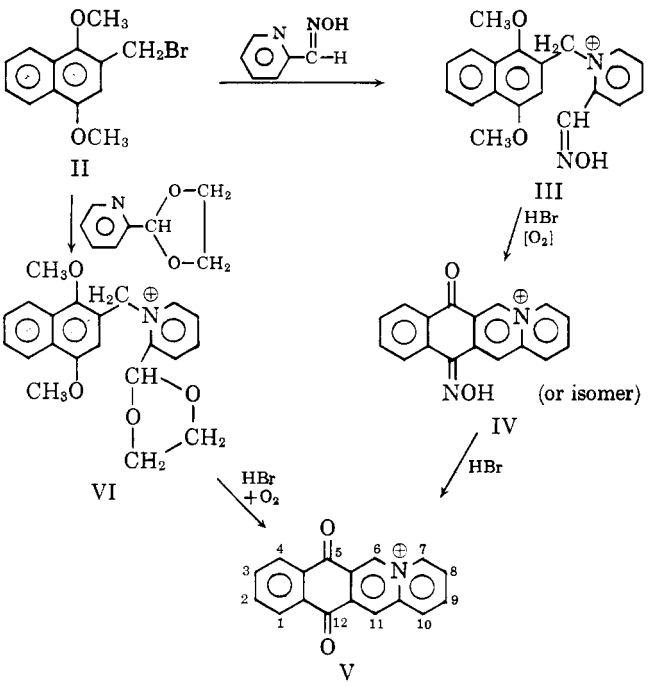
It seems unlikely that the quinolizinium ion could yield a stable *para* quinone since such a compound would be an acylammonium salt capable of reacting with a hydroxylic solvent. The simplest possible *para* quinone of the series would be 8a-azonia-1,4-anthraquinone (I) or its angular isomers.



I

We wish to report the synthesis of a benzolog of I. The reaction of 2-bromomethyl-1,4-dimethoxynaphthalene (II), with picolinaldoxime, afforded a 99% yield of the quaternary salt III. Cyclization, ether-cleavage, and oxidation of III were carried out by heating it for twenty-four hours in 48% hydrobromic acid, affording a small quantity (15%) of an insoluble product. This product had the composition expected for a monooxime (IV) of 6a-azonianaphthacenequinone. When the monooxime (IV) was boiled for forty-eight hours with a mixture of glacial acetic and 48% hydrobromic acid, a small quantity of 6a-azonianaphthacenequinone (V) was obtained. The quinone V could be obtained more directly by the use of 2-(1,3-dioxolan-2-yl)pyridine,[5] *via* the quaternary salt VI in an over-all yield of 63%. If air was bubbled through the cyclization mixture, a 70% yield of the quinone was obtained at the end of seven hours. A comparable experiment without bubbling in air afforded only an intractable gum.

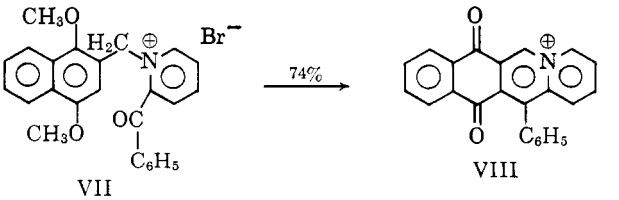
The infrared absorption spectrum of the quinone monooxime (IV) and the quinone (V) afforded some evidence as to the correctness of the formulation of V. Anthraquinone monooxime has a strong absorption band at 5.98 μ while anthraquinone has one at 5.93 μ[6]



II III IV V VI

(a 0.05-μ difference). The 6a-azonianaphthacenequinone monooxime (IV) has an absorption at 5.94 μ (0.04 μ lower than anthraquinone monooxime), but the quinone obtained upon hydrolysis, has an absorption at 5.89 μ (again a 0.05-μ difference). The oximido group appears more likely to be at position 12 (IV) rather than at position 5 for mechanistic reasons.[7] The formation of the oxime is most likely a true rearrangement, for when the quinone (V) was heated in hydrobromic acid with one mole of hydroxylamine hydrochloride, under the conditions of the cyclization, no oxime was obtained, and the quinone was recovered.

By use of 2-benzoylpyridine with 2-bromomethyl-1,4-dimethoxynaphthalene (II) 11-phenyl-6a-azonianaphthacenequinone VIII was synthesized in an over-all yield of 44% *via* the quaternary salt (VII).



VII VIII

The 6a-azonianaphthacenequinones (V and VIII) were yellow salts which gave a blue (in the case of V) or green (in the case of VIII) solution is distilled water

(1) For the preceding communication of this series, see C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83 (1963).

(2) This research was supported by a research grant NSF-G6215 of the National Science Foundation.

(3) The 1957 report of the IUPAC Nomenclature Committee, *J. Am. Chem. Soc.*, **82**, 5545, 5572 (1960), suggests the designation *azonia* as the quaternary nitrogen counterpart of the trivalent nitrogen *aza*. In this system of nomenclature, the quinolizinium ion would become 4a-azonianaphthalene.

(4) *E.g.*, (a) C. K. Bradsher and L. E. Beavers, *ibid.*, **78**, 2459 (1956); (b) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958); (c) C. K. Bradsher and T. W. G. Solomons, *J. Am. Chem. Soc.*, **82**, 1808 (1960).

(5) A recent paper (ref. 1) has described the use of 2-(1,3-dioxolan-2-yl)-pyridine in the synthesis of the acridizinium ion.

(6) The accepted value for the carbonyl absorption of anthraquinone is 5.95 μ (M. S. Flett, *J. Chem. Soc.*, 1441 (1948). We have used the value 5.93 μ, observed on our instrument, for purposes of comparison with other observed values.

(7) If as the evidence indicates, the transfer of hydroxylamine from carbon 11 is intramolecular, it appears more likely that it will be made to neighboring carbon 12 of the quinone, rather than the more distant carbon 5.

and in common polar organic solvents such as methanol, ethanol, acetonitrile, and acetone.

The formation of the blue and green colors was reversed by the addition of acid, and acidified solutions were found to be most effective in recrystallizing samples. When an acidified solution of V in distilled water was back titrated with standard base, the color change occurred at a pH of about 3.1. These observations suggest that even in distilled water the quinone salts are partially hydrolyzed to a highly colored pseudobase. It would be predicted that the adjacent quinone nucleus would make the carbon at position 6 more positive than the comparable (6) position of the acridizinium nucleus, and that the quinone salts would be in equilibrium with significant concentrations of the pseudobase at a pH lower than that required for pseudobase formation in the acridizinium system.

It may be seen from the ultraviolet absorption spectra in Table I that there is only a small difference between the spectra of the acidified (yellow), and the neutral (blue) solution of 6a-azonianaphthacenequinone (V) and only an insignificant difference in the case of the phenyl analog (VIII). The neutral (blue) solution of V, when exposed to diffuse daylight for only five days, changes to yellow-brown and the absorption spectrum is greatly altered. The change does not occur in the dark, and can be prevented by acidification of the solution.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA (AND LOG EXTINCTION COEFFICIENTS) OF 6a-AZONIANAPHTHACENEQUINONE SALTS

Compound	Acidified (*ca.* 10^{-3} *M* H^+)	Neutral: Freshly prepared	Neutral: After exposure
V	237 (4.45)	247 (4.47)	228 (4.67)
(Bromide)	248*[a] (4.37)	322* (3.86)	243* (4.67)
	312* (3.81)	357* (4.11)	
	358* (4.12)	372* (4.13)	
	372 (4.15)		
VIII	253 (4.55)	253 (4.54)	
(Perchlorate)	363* (4.14)	363* (4.13)	
	377 (4.16)	377 (4.15)	

[a] An asterisk indicates a shoulder.

Experimental

All analyses were by Dr. Ing. A. Schoeller, Mikroanalytisches Laboratorium, Kronach, West Germany. Melting points were determined using a Laboratory Devices Mel-Temp block and are uncorrected. Infrared spectra were measured in potassium bromide pellets using the Perkin-Elmer Model 21 spectrophotometer. The ultraviolet absorption spectra were recorded using a Cary Model 14 recording spectrophotometer with methanol as the solvent. Wave lengths are recorded in millimicrons and shoulders are indicated by an asterisk (*).

2-Bromomethyl-1,4-dimethoxynaphthalene (II).—A suspension of 1,4-dimethoxynaphthalene (13 g.) and paraformaldehyde (2.5 g.) in a mixture of glacial acetic acid (30 ml.) and carbon tetrachloride (200 ml.) was saturated with hydrogen bromide at room temperature. The reaction was considered complete when complete solution occurred. The carbon tetrachloride was removed under reduced pressure (aspirator) and water was added to the residue. The mixture was extracted thoroughly with benzene. The benzene extracts were washed with water and then with sodium bicarbonate solution. The dried (magnesium sulfate) benzene solution was concentrated (steam bath) and the residue crystallized from hexane yielding 16.6 g. (86%) of a yellow solid, m.p. 96.5–98.5°. The analytical sample crystallized from hexane as yellow needles, m.p. 98–99.5°.

Anal. Calcd. for $C_{13}H_{13}BrO_2$: C, 55.53; H, 4.66; Br, 28.43. Found: C, 55.70; H, 4.50; Br, 28.87.

1-(1,4-Dimethoxy-2-naphthylmethyl)-2-oximidomethylpyridinium (III) Bromide.—A solution containing 7.6 g. of 2-bromomethyl-1,4-dimethoxynaphthalene and 3.7 g. of picolinaldoxime in 20 ml. of dimethylformamide was allowed to stand for 24 hr. at room temperature. The yellow product was collected and washed with ethyl acetate, yield 10.7 g. (99%), m.p. 179–180°. Recrystallization of the salt from water afforded short pale yellow needles, m.p. 176–176.5°.

Anal. Calcd. for $C_{19}H_{19}BrN_2O_3$: C, 56.58; H, 4.75; N, 6.95. Found: C, 56.78; H, 4.93; N, 7.38.

The **perchlorate** was prepared from an aqueous solution of the bromide as yellow needles, m.p. 165.5–166°.

Anal. Calcd. for $C_{19}H_{19}ClN_2O_7$: C, 53.97; H, 4.53; N, 6.63. Found: C, 54.09; H, 4.75; N, 6.80.

The chloride was prepared by a quaternization reaction using 2-chloromethyl-1,4-dimethoxynaphthalene[8] in the quaternization reaction (19 days, 58% crude yield). The analytical sample formed yellow needles from ethanol, m.p. 188–189°.

Anal. Calcd. for $C_{19}H_{19}ClN_2O_3$: C, 63.59; H, 5.34; N, 7.81. Found: C, 63.72; H, 5.45; N, 7.91.

6a-Azonianaphthacenequinone Monooxime (IV) Bromide.—A suspension of 1.8 g. of the quaternary bromide (III) in 48% hydrobromic acid was heated for 24 hr. on the steam bath. The mixture was cooled and the brown precipitate collected, 0.25 g. (15%), m.p. >350°. No pure product could be isolated from the filtrate. Recrystallization of the brown precipitate from methanol yielded short red needles, m.p. >350°.

Anal. Calcd. for $C_{17}H_{11}BrN_2O_2$: C, 57.48; H, 3.12; N, 7.89. Found: C, 57.66; H, 3.22; N, 7.75.

The infrared spectrum of this compound contained a band in the carbonyl region at 5.94 μ, and a strong band in the C=N region (6.08–6.19 μ).

The **perchlorate** crystallized from methanol as red needles, m.p. >350°.

Anal. Calcd. for $C_{17}H_{11}ClN_2O_6$: C, 54.48; H, 2.96; N, 7.47. Found: C, 54.52; H, 2.99; N, 7.37.

1-(1,4-Dimethoxy-2-naphthylmethyl)-2-(1,3-dioxolan-2-yl)-pyridinium (VI) Bromide.—A solution of 10 g. of 2-bromomethyl-1,4-dimethoxynaphthalene and 6 g. of 2-(1,3-dioxolan-2-yl)-pyridine[5] in 25 ml. of dimethylformamide was allowed to stand at room temperature for 24 hr. The gummy precipitate, formed when ethyl acetate was added, solidified on vigorous stirring, yield 14 g. (90%), m.p. 143.5–145°. This material crystallized from methanol–ethyl acetate as colorless needles, m.p. 146.5–147°.

Anal. Calcd. for $C_{21}H_{22}BrNO_4$: C, 58.34; H, 5.13; N, 3.24. Found: C, 58.34; H, 5.09; N, 3.45.

The **perchlorate** was recrystallized from methanol–ethyl acetate, m.p. 149–149.5°.

Anal. Calcd. for $C_{21}H_{22}ClNO_8$: C, 55.81; H, 4.91; N, 3.10. Found: C, 56.10; H, 4.75; N, 3.15.

6a-Azonianaphthacenequinone (V) Bromide. (A) By Cyclization of Quaternary Salt (VI).—A mixture of 4 g. of crude 1-(1,4-dimethoxy-2-naphthylmethyl)-2-(1,3-dioxolan-2-yl)pyridine (VI) with 40 ml. of 48% hydrobromic acid was heated on the steam bath for 7 hr., while air was passed through. The solution was diluted with 100 ml. of water and cooled, affording 2.2 g. (70%) of a yellow solid, m.p. above 350°. Recrystallized from water containing a trace of hydrobromic acid, the product was obtained as yellow needles, m.p. above 350°, infrared absorption at 5.89 μ (carbonyl region).

(B) By Hydrolysis of the Monooxime (IV) Bromide.—A small sample of the monooxime (IV) bromide was refluxed for 48 hr. in a mixture of acetic and 48% hydrobromic acids. A part of the material appeared to dissolve. The unchanged monooxime was removed by filtration, and the filtrate was concentrated affording a yellow compound, m.p. >350°, which was identical in infrared spectrum with the material obtained by method A.

Anal. Calcd. for $C_{17}H_{10}BrNO_2$: C, 60.02; H, 2.96; N, 4.12. Found: C, 59.75; H, 3.26; N, 4.40.

Neutral solutions of 6a-azonianaphthacenequinone salts in distilled water or common organic solvents such as methanol, ethanol, acetonitrile, and acetone were blue. The color of the solution turned to yellow upon acidification with mineral acid.

(8) B. R. Baker and G. H. Carlson, *J. Am. Chem. Soc.*, **64**, 2657 (1942).

By dissolving a sample of the quinone in hydrochloric acid and titrating with sodium hydroxide it was determined that the pH of the color change was about 3.07.

A sample of 6a-azonianaphthacenequinone bromide was heated for 24 hr. on the steam bath with an equimolar amount of hydroxylamine hydrochloride in 48% hydrobromic acid (cyclizing conditions). No insoluble material was formed, and only starting material could be recovered from the solution.

The **perchlorate** of 6a-azonianaphthacenequinone (V) crystallized from water as yellow needles, m.p. 331.5–332°.

Anal. Calcd. for $C_{17}H_{10}ClNO_6$: C, 56.76; H, 2.80; N, 3.91. Found: C, 56.87; H, 2.91; N, 4.07.

1-(1,4-Dimethoxy-2-naphthylmethyl)-2-benzoylpyridinium Bromide (VII).—A solution of 4 g. of 2-(bromomethyl)-1,4-dimethoxynaphthalene and 3.1 g. of 2-benzoylpyridine in 10 ml. of dimethylformamide was allowed to stand at room temperature for 4 days. The addition of ether precipitated 3.9 g. (60%) of a yellow solid, m.p. 132–133°. The analytical sample crystallized from methanol–ethyl acetate as yellow needles, m.p. 132–133°.

Anal. Calcd. for $C_{25}H_{22}BrNO_3$: C, 64.66; H, 4.78; N, 3.02. Found: C, 64.44; H, 4.69; N, 3.39.

11-Phenyl-6a-azonianaphthacenequinone (VIII) Bromide.—A mixture containing 1.5 g. of the 2-benzoylpyridinium salt (VII) and 15 ml. of 48% hydrobromic acid was heated for 16 hr. on the steam bath. The acid was removed under reduced pressure, and the yellow residue recrystallized from methanol–ethyl acetate, yield 0.99 g. (74%), m.p. above 350°. The analytical sample formed yellow plates, m.p. >350°, and a strong absorption at 5.87 μ (carbonyl region).

Anal. Calcd. for $C_{23}H_{14}BrNO_2 \cdot {}^1/_2\ H_2O$: C, 64.95; H, 3.56; N, 3.29. Found: C, 64.84; H, 3.48; N, 3.54.

This compound formed green solutions in distilled water and in the common polar organic solvents. The green color was turned to yellow by the addition of mineral acid.

The **perchlorate** crystallized from methanol as yellow plates, m.p. 332–334°.

Anal. Calcd. for $C_{23}H_{14}ClNO_6$: C, 63.38; H, 3.23; N, 3.21. Found: C, 63.11; H, 3.24; N, 3.38.

The Reaction of 3-Acyl-4-hydroxycoumarins with Ammonium Salts[1]

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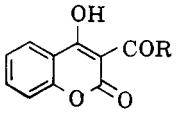
Ammonium acetate or amines in acetic acid react readily with 3-acetyl- or 3-benzoyl-4-hydroxycoumarin to form amino or imino substitution products. By using H_2O^{18} it was shown that the substitution took place in the 3α-position of the 3-acylcoumarin.

The reaction of 3-acyl-4-hydroxycoumarins with ammonium salts represents an interesting extension of the well established[3] reaction of β-diketone systems with amines.



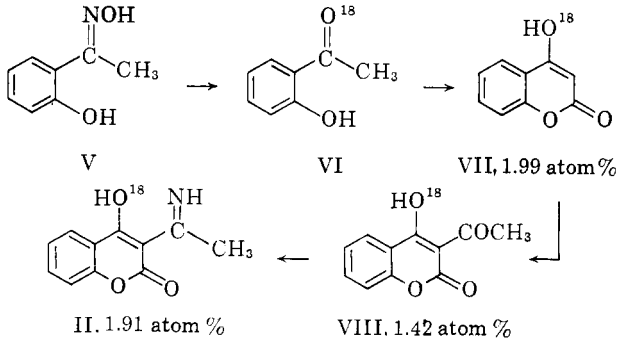
Ia. R = CH_3
Ib. R = C_6H_5

In our initial experiments ammonium acetate, the acylcoumarin, and ethyl cyanoacetate were refluxed in benzene in an attempted Knoevenagel condensation. 3-Acetyl- (Ia) and 3-benzoyl-4-hydroxycoumarin (Ib) yielded the corresponding amino or imino compounds II and III. It is of interest to note that Iguchi and Hisatune[4] assigned structure II to a product obtained by treatment of Ia with ammonia. No supporting evidence was given.

When 3-carbethoxy-4-hydroxycoumarin, 4-hydroxycoumarin, and dibenzoylmethane were treated with ammonium acetate in benzene, no imino compounds were formed. When ethylamine, isopropylamine, aniline, or ethanolamine reacted with equimolar quantities of acetic acid and Ib, good yields of the corresponding amino or imino compounds were obtained. Diethylamine and piperidine under the same conditions gave only the salts of Ib.

The nitrogen function could enter Ia and Ib either at the 2-, 4-, or 3α-position. Substitution at the 2-position was considered least likely since aniline[5] and morpholine[6] substitute in position 4 of 4-hydroxycoumarin (IV). If ammonium acetate reacted with Ia labeled with O^{18} in position 4, the position of the nitrogen substitution could be shown by the retention or loss of the O^{18}. Scheme A shows the approach used. Hydrolysis of *o*-hydroxyacetophenone oxime (V) in acidified H_2O^{18} formed *o*-hydroxyacetophenone-C=O^{18} (VI). This was condensed with diethyl carbonate to form 4-hydroxy-O^{18}-coumarin (VII). 3-Acetyl-4-hydroxy-O^{18}-coumarin (VIII) was obtained by the reaction of VII with acetyl chloride in pyridine. It was found that VIII (1.42 atom % excess) and ammonium acetate yielded II (1.91 atom % excess). The calculated value was 1.89 atom % excess for II if the nitrogen entered the 3α-position.

Both Davis and Hurd[7] and Dudek and Holm[8] have assigned specific structures to the β-diketone derivatives they investigated; we feel that the analogy between the



SCHEME A

(1) Published with the approval of the director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation. This work is from the Ph.D. theses of Robert A. Kloss, 1956, and C. Wiener, 1960, done under the supervision of Professor Karl Paul Link.

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(3) N. H. Cromwell, *Chem. Rev.*, **38**, 83 (1946).

(4) S. Iguchi and K. Hisatune, *J. Pharm. Soc. Japan*, **77**, 98 (1957).

(5) R. Anschütz, *Ann.*, **367**, 204 (1909).

(6) O. P. Spaulding, H. S. Mosher, and F. C. Whitmore, *J. Am. Chem. Soc.*, **72**, 5338 (1950).

(7) R. B. Davis and P. Hurd, *ibid.*, **77**, 3284 (1955).

(8) G. O. Dudek and R. M. Holm, *ibid.*, **84**, 2691 (1962).