Polynuclear Heterocycles. VI. The Reaction of 2,3-Dichloro-1,4-naphthoquinone with Aromatic Amines[1]

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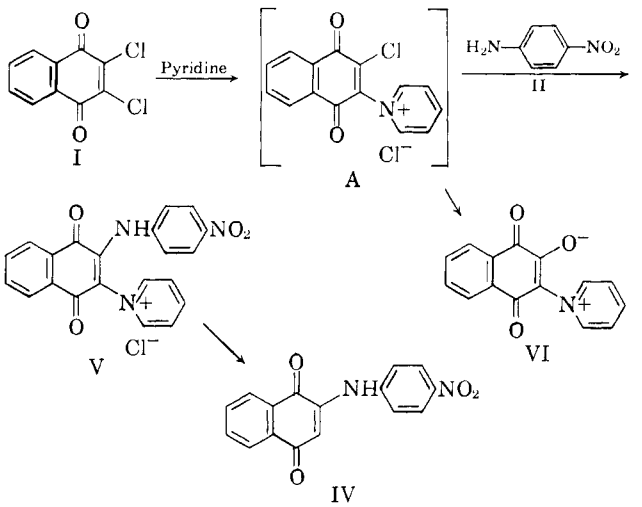
2,3-Dichloro-1,4-naphthoquinone (I) and *p*-nitroaniline react in the presence of pyridine to give 2-(*p*-nitroanilino)-1,4-naphthoquinone. Under similar conditions, *o*-phenylenediamine, *o*-aminophenol, 2-aminopyridine, and *o*-aminobenzenethiol react with I to give angular heterocyclic compounds. A common reaction path is suggested.

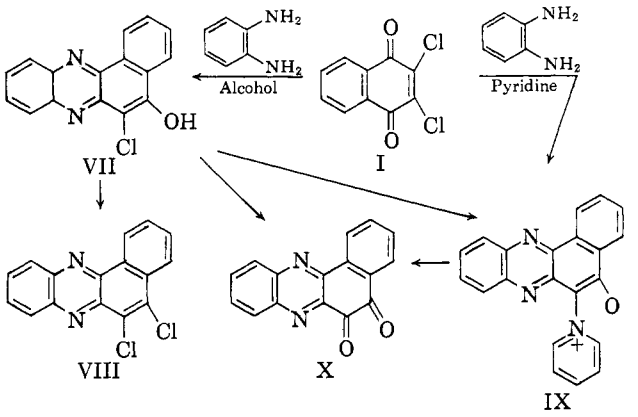
The addition of amines to 2,3-dichloro-1,4-naphthoquinone (I) is subject to electronic and steric effects as noted in a previous communication.[2] Plagemann[3] has reported that I and *p*-nitroaniline (II) react in alcohol to give 2-chloro-3-(4-nitroanilino)-1,4-naphthoquinone (III). We were unable to duplicate these results. We found that more vigorous conditions led to the formation of 2-(4-nitroanilino)-1,4-naphthoquinone (IV).[2] This unusual reaction in which a chlorine atom is replaced by a hydrogen atom seemed worth further investigation.

It has now been found that I and II react in 1,2,3-trichloropropane in the presence of one equivalent of pyridine to give 2-(4-nitroanilino)-1,4-naphthoquinone-3-pyridinium chloride (V) which, on treatment with aqueous sodium carbonate, gave IV, which has been prepared previously by Baltzer[4] from 2-hydroxy-1,4-naphthoquinone and II. If three or more equivalents of pyridine are used, IV is obtained directly.



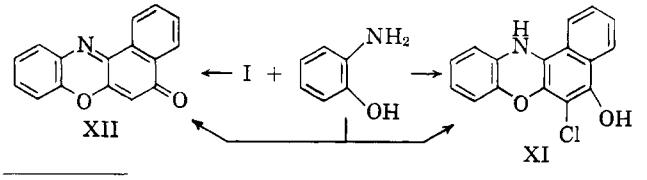
Presumably, the pyridine reacts with I to give the quaternary salt A which undergoes reaction with II because of the enhanced reactivity of the nuclear chlorine due to the pyridinium ion. As a test of this assumption, equivalent quantities of pyridine and I in trichloropropane were heated until the adduct A was formed. Attempts to recrystallize this product from water or ethanol gave 1,4-dioxo-3-pyridinium-2-naphthoxide (VI).[5] Therefore, II was added to A *in situ* and heating was continued for a further hour to give V. The mechanism for the conversion of V → IV is still being investigated.

Continuing interest in the chemistry of benzophenazines[2] led us to the examination of the condensation of I with *o*-phenylenediamine in the presence of pyridine. It is known that these components in alcohol give 6-chloro-5-hydroxybenzo[*a*]phenazine (VII).[6,7] The latter compound was converted by means of phosphoryl chloride to the known 5,6-dichlorobenzo[*a*]phenazine (VIII)[7] as a further confirmation for the structure of VII. With pyridine as a solvent, *o*-phenylenediamine and I gave 6-pyridinium benzo[*a*]phenazine 5-oxide (IX) which, on oxidation, gave the known 5,6-benzo[*a*]-phenazinequinone (X).[8] Reaction of VII with pyridine also gave IX. It is therefore probably an intermediate in the formation of IX.



Three other bifunctional amines were examined with the intention of determining the generality of the above reaction.

The reaction of *o*-aminophenol with I in alcohol gave the expected 6-chloro-5-hydroxybenzo[*a*]phenoxazine (XI); but if pyridine is used as a solvent, the product is the known 5-oxobenzo[*a*]phenoxazine (XII).[9] This replacement of a chlorine atom by a hydrogen atom under such mild conditions is noteworthy and will be discussed later.



(1) Contribution no. 2309 from the Kodak Research Laboratories.

(2) J. A. VanAllan, G. A. Reynolds, and R. E. Adel, *J. Org. Chem.*, **27**, 2873 (1962).

(3) A. Plagemann, *Ber.*, **15**, 484 (1882).

(4) C. Baltzer, *ibid.*, **14**, 1899 (1881).

(5) F. Ullmann and M. Ettisch, *ibid.*, **54**, 259 (1921).

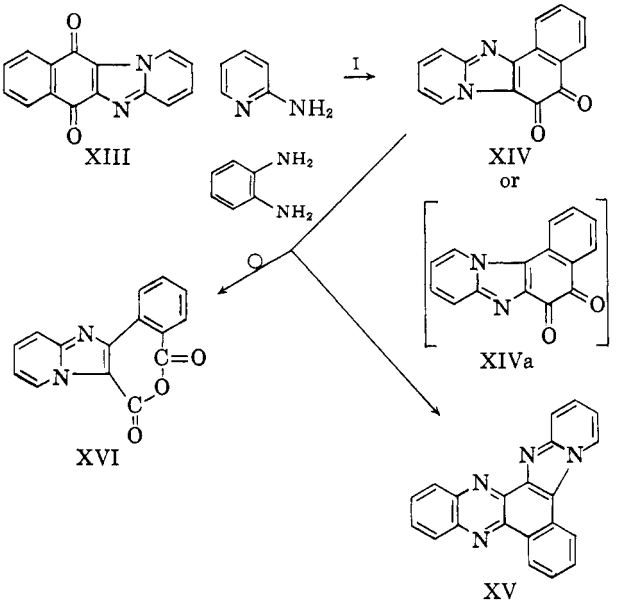
(6) Th. Zincke and M. Schmidt, *Ann.*, **286**, 27 (1895).

(7) G. M. Badger and R. Pettit, *J. Chem. Soc.*, 1877 (1952), prefer the ketonic tautomer, but the infrared spectrum of VII has adsorption in the 3.2-μ to 3.4-μ region characteristic of a hydrogen-bonded hydroxyl group and no absorption in the carbonyl region.

(8) O. Fischer and E. Schindler, *Ber.*, **39**, 2238 (1906).

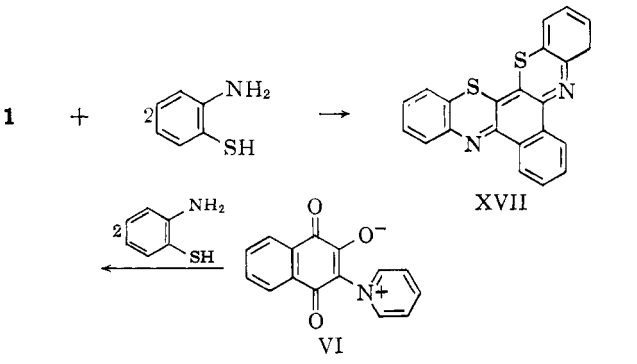
(9) F. Kehrmann, *ibid.*, **23**, 2446 (1890).

It has been reported that *o*-aminopyridine reacts with I to give the linear 5,11b-diazabenzo[*b*]fluorene-6,11-dione (XIII)[10]. This behavior is anomalous when compared with the behavior of *o*-phenylenediamine and *o*-aminophenol, both of which give angular cyclization products. It has now been found that I condenses with *o*-aminopyridine in ethoxyethanol to give 6b,11-diazabenzo[*a*]fluorene-5,6-dione (XIV) [or 7,11a-diazabenzo[*a*]fluorene-5,6-dione (XIVa)]; both isomers are possible but structure XIV is preferred, for reasons to be discussed. Since XIV reacts with *o*-phenylenediamine to give the phenazine derivative XV, there is little doubt that XIV has an *ortho*-quinone group from which it follows that cyclization has taken place to give the angular XIV, rather than the linear heterocycle, XIII.



Oxidation of XIV with sodium peroxide gave the anhydride XVI. This reaction is diagnostic of *o*-diketones[11] and substantiates the *o*-quinoid structure of XIV.

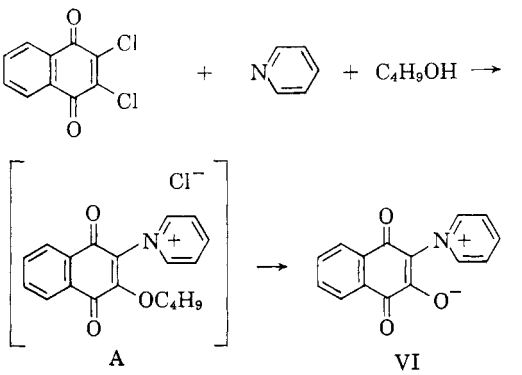
The condensation of *o*-aminobenzenethiol with I is exceptional in that, under the many reaction conditions employed, the sole product is 5,16-dithia-5,10-diazanaphtho[2,3*a*]benzo[*c*]anthracene(XVII). The driving force of this reaction must be very high, because even the enol betaine VI reacts with *o*-aminobenzenethiol to give XVII. A substance of this latter structure



is described by Fries and Ochwat.[12] It was obtained by the reduction of 2,3-bis(*o*-nitrophenylthio)-1,4-naphthoquinone, but its properties are quite different from those of the one obtained by us; *i.e.*, its melting point is given as above 350°, whereas ours melted sharply at 291°. This discrepancy has not been resolved.

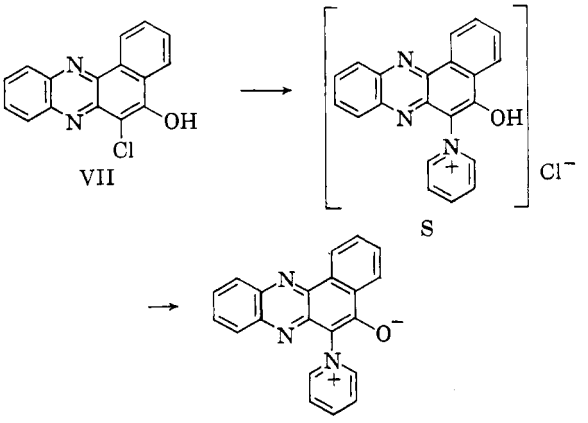
In summary, it has been found that I reacts with (a) *o*-phenylenediamine to give a cyclization product (IX) in which the chlorine atom is replaced by a pyridine residue; (b) *o*-aminophenol to give a cyclization product (XII) in which a chlorine atom is replaced by hydrogen; (c) *o*-aminopyridine to give a cyclization product (XIV) in which the chlorine atom is replaced by an oxygen atom; and (d) *o*-aminobenzenethiol to give a cyclization product (XVII) in which the chlorine atom is replaced by a sulfide linkage.

It occurred to us that, despite the diversity in the nature of the reaction products obtained by condensing I with various isoelectric bifunctional amines, there might be a common path for these reactions. To this end, I and two equivalents of pyridine were heated in anhydrous butanol. A vigorous reaction ensued, with the elimination of butyl chloride and the formation of VI in quantitative yield. This result is compatible with the assumption that an intermediate of type A is formed which subsequently loses butyl chloride to give VI.



This type of elimination reaction has been reported[3] previously in the 1,4-diazaphenanthrene series.

In an analogous manner, VII reacts with pyridine to give the unstable salt, S, which loses the elements of hydrochloric acid to give IX.



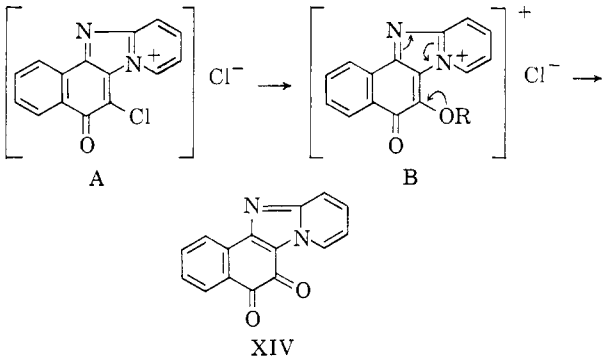
(10) P. Truitt, J. E. Cooper, III, and F. M. Wood, Jr., *J. Am. Chem. Soc.*, **79**, 5709 (1957).

(11) G. A. Reynolds, "Encyclopedia of Chemical Technology," Interscience Publishers, Inc., New York, N. Y., 1952, p. 136.

(12) K. Fries and P. Ochwat, *Ber.*, **56B**, 1292 (1923).

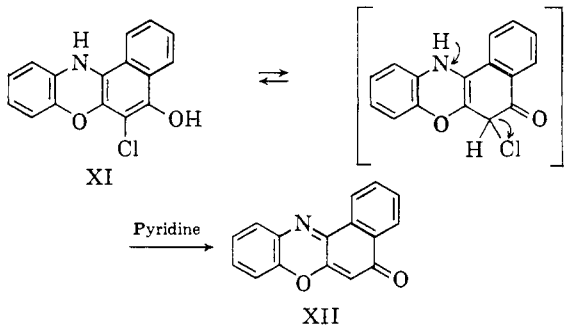
(13) O. N. Witt and C. Schmidt, *ibid.*, **25**, 1013, 2003 (1892).

Essentially the same mechanism operates in the formation of XIV.[14] That is, the chlorine atom in the initial cyclization product A is replaced by an alkoxy group which loses alkyl halide to give the enol betaine B, but the electronic configuration of B is favorable, as indicated, for the formation of XIV.



A B XIV

The mechanism for the replacement of the chlorine atom of XI by a hydrogen atom can be postulated as follows:



XI XII

It is possible that the chlorine atom is replaced by pyridinium in an intermediate step, but this is not essential to the mechanism.

Finally, the formation of XVII appears to occur *via* a Michael addition, the mercaptide ion adding twice to the quinone system, with the elimination of hydrogen chloride and subsequent ring closure through the amino groups. Pyridine is not necessary but it greatly facilitates this reaction.

The ultraviolet absorption data for compounds IV, V, VII, VIII, IX, X, XII, XV, and XVII are collected in Table I. The absorption maxima and extinction coefficient ($\epsilon \times 10^{-3}$) are recorded. The solvent is dimethylformamide.

TABLE I
ULTRAVIOLET ABSORPTION DATA

No.	λ_1, mμ	λ_2, mμ	λ_3, mμ
IV	270(15.2)	342(11.0)	444(6.5)
V	258(21.6)	310(13.5)	425(5.5)
VII	305(22.5)	380(6.0)	548(6.25)
VIII	298(34.0)	368(8.8)	382(13.3)
			408(12.0)
IX	275(22.8)	312(26.4)	482(10.5)
		344(10.5)	
X	302(21.2)	...	600(0.7)
XII	295(6.7)	358(9.5)	442(9.5)
XV	275(37.5)	330(16.0)	374(4.0)
	288(39.0)		442(7.2)
XVII	270(28.0)	360(11.0)	538(8.5)

(14) The ring nitrogen of 2-aminopyridine is known to quaternize in preference to the amino group. [See Reindel and Rosendahl, *ibid.*, **59**, 1064 (1926).] For this reason, it is assumed that 2,3-dichloronaphthoquinone reacts initially with the ring nitrogen, with the consequent formation of XIV rather than XIVa.

Experimental

The 2,3-dichloro-1,4-naphthoquinone (I) and the *p*-nitroaniline (II) used in the following experiments were Eastman Grade Chemicals.

2-(4-Nitroanilino-1,4-naphthoquinone (IV) and 2-(4-Nitroanilino)-1,4-naphthoquinone-3-pyridinium Chloride (V).—A suspension of 5.6 g. of I and 3.85 g. of II in 50 ml. of 1,2,3-trichloropropane was heated until solution was complete and then 3 ml. of pyridine was added. Heating was continued for 2 hr. After cooling, the product was collected by filtration and crystallized from water to give 6.5 g. of V, m.p. 272°.

Anal. Calcd. for $C_{21}H_{14}O_4N_3Cl$: C, 62.0; H, 3.4; N, 10.1. Found: C, 62.2; H, 3.3; N, 10.0.

A solution of 3.0 g. of V in water was made alkaline with sodium carbonate. The precipitate was collected and crystallized from trichlorobenzene to give 2.1 g. of IV, m.p. 339°. The infrared spectrum of IV was identical with an authentic sample of 2-(4-nitroanilino)-1,4-naphthoquinone.[4]

1,4-Dioxo-3-pyridinium-2-naphthoxide (VI).—A suspension of 11.3 g. (0.05 mole) of I in 50 ml. of butanol containing 8 ml. of pyridine was brought to reflux. A vigorous reaction ensued and, after 10–15 min., the reaction mixture solidified. The precipitate was collected by filtration to give 11 g. of VI, m.p. 305°. The mixture melting point and infrared spectrum of this compound were identical with those of the compound prepared by the method of Ullmann and Ettisch.[5] The carbonyl absorption at 5.98 μ is typical of 1,4-naphthoquinones.

In one experiment, the reaction flask was equipped with a fractionating column and still head and the volatile components (b.p. 75–100°) were collected. Refractionation yielded 3.1 g. of butyl chloride, b.p. 78°, which was identical with an authentic sample.

6-Chloro-5-hydroxybenzo[*a*]phenazine (VII).—A suspension of 11.3 g. of I and 5.4 g. of *o*-phenylenediamine in 100 ml. of ethanol was heated on the steam bath for 4 hr. The bronze-colored crystalline solid was collected, slurried in hot acetic acid, filtered, and dried to give 12 g. of VII,[6,7] m.p. 268°.

5,6-Dichlorobenzo[*a*]phenazine (VIII).—A suspension of 5 g. of VII in 15 ml. of phosphoryl chloride was heated to 80° and 4 g. of phosphorus pentachloride added. This solution was heated for 2 hr., cooled, and the precipitate collected on a sintered-glass funnel. The crystals so obtained were extracted with hot acetonitrile and crystallized from chlorobenzene to give 3.1 g. of VIII, m.p. 201° (lit.,[7] m.p. 202°).

Anal. Calcd. for $C_{16}H_8N_2Cl_2$: C, 64.4; H, 2.7; N, 9.4. Found: C, 64.3; H, 2.7; N, 9.2.

6-Pyridinium Benzo[*a*]phenazine 5-Oxide (IX).—A mixture of 9.0 g. (0.04 mole) of I and 4 g. of *o*-phenylenediamine in 100 ml. of pyridine was heated on the steam bath for 1 hr. The orange solid was collected and crystallized from pyridine to give 7.44 g. (85% yield) of IX, m.p. 323°. The infrared spectrum showed no absorption in the carbonyl region.

Anal. Calcd. for $C_{21}H_{13}N_3O$: C, 78.1; H, 4.0; N, 13.0. Found: C, 78.1; H, 4.4; N, 12.7.

5,6-Benzo[*a*]phenazinequinone (X).—A suspension of 5.0 g. of IX in 50 ml. of acetic acid containing 5 ml. of nitric acid (d = 1.42) and 3 ml. of water was heated on the steam bath for 1 hr. The bright yellow precipitate was filtered off and crystallized from trichlorobenzene to give 2.8 g. of X, m.p. 265° (lit.,[9] m.p. 265°); carbonyl absorption at 5.96 μ.

6-Chloro-5-hydroxybenzo[*a*]phenoxazine (XI).—A mixture of 11.0 g. of I and 11 g. of *o*-aminophenol in 100 ml. of ethanol was heated at 95–100° for 3 hr. After cooling, the product was collected by filtration and crystallized from aqueous ethanol to give 6.8 g. of XI, m.p. 220°. The infrared spectrum has absorption in the 3–4-μ region and no absorption in the carbonyl region.

Anal. Calcd. for $C_{16}H_{10}NO_2Cl$: C, 67.8; H, 3.5; N, 5.0; Cl, 12.4. Found: C, 67.5; H, 3.8; N, 5.4; Cl, 12.2.

5-Oxobenzo[*a*]phenoxazine (XII).—The preceding experiment was repeated but using 100 ml. of pyridine in place of the ethanol. The brown solid so obtained was crystallized from ethanol to give 4.2 g. of XII, m.p. 190°, identical in every respect with the compound prepared by the method of Kehrmann.[9] Alternatively a mixture of 11.3 g. of I, 5.5 g. of *o*-aminophenol in 150 ml. of methanol containing 6 g. of potassium hydroxide was refluxed

for 3 hr. After cooling, 7.0 g. of XII, m.p. 189°, was obtained. A mixture of 3 g. of XI and 20 ml. of pyridine, heated on the steam bath for 1 hr., gave 2.8 g. of XII. The carbonyl absorption for XII occurred at 5.95 μ.

6b,11-Diazabenzo[*a*]fluorene-5,6-dione (XIV).—A mixture of 22.7 g. of I, 19 g. of *o*-aminopyridine in 100 ml. of ethoxyethanol was refluxed for 5 hr. To this was added 200 ml. of ethanol and the precipitate collected to give 26 g. of XIV, m.p. 298° (lit.,[10] m.p. 306°); carbonyl absorption at 5.97 μ.

Anal. Calcd. for $C_{15}H_8O_2N_2$: C, 72.6; H, 3.2; N, 11.3. Found: C, 72.6; H, 3.6; N, 11.1.

4a,9,14,15-Tetrazabenzo[*c*]indeno[2,1-*a*]anthracene (XV).—A mixture of 2.5 g. of XIV and 1.5 g. of *o*-phenylenediamine in 25 ml. of acetic acid was refluxed for 3 hr. The bright yellow precipitate which separated was collected and crystallized from trichlorobenzene to give 2.3 g. of XV, m.p. 285°, and no absorption in the carbonyl region of the infrared.

Anal. Calcd. for $C_{21}H_{12}N_4$: C, 78.8; H, 3.8; N, 17.5. Found: C, 78.6; H, 3.9; N, 17.4.

3-Phenyl-1,3a-diazaindene-2,2′-dicarboxylic Anhydride (XVI).—A suspension of 3.0 g. of XIV in 100 ml. of ethanol was treated with 5 ml. of 30% hydrogen peroxide, followed by 5 ml. of 50% sodium peroxide. After the mixture had been stirred at 25–30° for 1 hr., it was heated to 50° and 25 ml. of water and 5 ml. more of hydrogen peroxide were added. When solution was complete (10 min.), the solution was treated with Norit, filtered, and acidified with acetic acid. The white precipitate was crystallized from water to give 1.7 g. of white crystals of XVI, m.p. 195°. The anhydride absorption occurs at 5.48 and 5.72 μ.

Anal. Calcd. for $C_{15}H_8O_3N_2$: C, 68.3; H, 3.0; N, 10.6. Found: C, 68.6; H, 3.4; N, 10.6.

15,16-Dithia-5,10-diazanaphtho[2,3-*a*]benzo[*c*]anthracene (XVII).—Pyridine (50 ml.) containing 2.5 g. of VI and 3.0 ml. of *o*-aminobenzenethiol was heated to reflux for 2 hr., an equal volume of methanol was added, and the mixture chilled to give 2.5 g. of XVII, m.p. 291° (from dichlorobenzene), with no absorption in the NH or carbonyl region of the infrared spectrum.

Anal. Calcd. for $C_{22}H_{12}N_2S_2$: C, 71.5; H, 3.2; N, 7.6. Found: C, 71.5; H, 3.2; N, 7.3.

Other solvents, such as ethanol, ethoxyethanol, toluene, or dimethylformamide, gave XVII, but the yield was lower than in the example employing pyridine. A mixture of 3 g. of the enol betaine VI and 4 ml. of *o*-aminobenzenethiol refluxed for 2 hr. gave 3.2 g. of XVII.

Polynuclear Heterocycles. VII. The Properties of Azacarbons Containing the Enol Betaine Structure[1]

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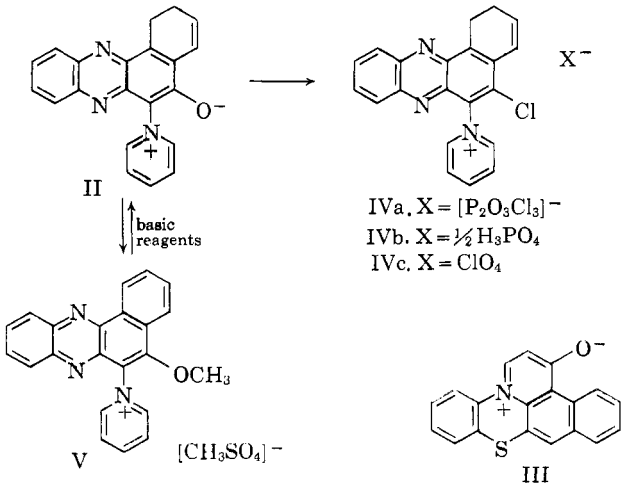
The properties of 1*H*-benzo[*b*]pyrido[1,2,3-*mn*]phenothiazin-1-one (III) and quinolizone (XV), both of which appear to exist in highly polarized form, are compared with the enol betaines, 6-pyridiniumbenzo[*a*]phenazine 5-oxide (II), 1,4-dioxo-3-pyridinium 2-naphthoxide (VIII).

Initial studies dealing with the reaction of 2,3-dichloronaphtho-1,4-quinone (I) with *o*-phenylenediamine showed that these components react in the presence of pyridine to give 6-pyridiniumbenzo[*a*]phenazine 5-oxide (II).[2] The formal analogy of II to 1*H*-benzo[*b*]pyrido[1,2,3-*mn*]phenothiazin-1-one (III)[3] with respect to charge separation prompted us to compare the chemistry of these compounds. To this end, II was treated with phosphorus oxychloride to give the 5-chlorobenzo[*a*]phenazine pyridinium salt (IVa) which was successively converted to the phosphate salt (IVb) and to the perchlorate (IVc). Dimethyl sulfate reacts with II to give 5-methoxybenzo[*a*]phenazine-6-pyridinium methosulfate (V). The reaction of II with phosphorus oxychloride and dimethyl sulfate is therefore analogous to the corresponding reactions of III.[4]



Treatment of V with alcoholic piperidine, pyridine, sodium acetate, and potassium hydroxide gave the enol betaine II in over 90% yield. It has not been established whether the methoxy group is displaced by the base or the cleavage occurs between the oxygen atom and the methyl group. Attempts to replace the chlorine atom of IVc with piperidine resulted in the formation of 6-amino-5-chlorobenzo[*a*]phenazine (VI). The formation of an acetyl derivative (VIa) confirms the presence of an amino group and the infrared spectrum of VI shows that the amino group is primary. Oxidation of VI to benzo[*a*]phenazine-5,6-quinone (VII) demonstrates that VI still retains the benzo[*a*]-phenazine structure, *i.e.*, no rearrangement has occurred. The formation of VI from IVc is consistent with the concept that the initial reaction is the formation of the pseudo base A which undergoes subsequent ring opening to B which is then hydrolyzed to VI. This reaction has its counterpart in the hydrolysis of 2,4-dinitrobenzene pyridinium chloride to 2,4-dinitroaniline.[5]

We next turned our attention to the behavior of 1,4-dioxo-3-pyridinium 2-naphthoxide (VIII) which has an enol betaine structure similar to II. This material was recovered unchanged after three hours' boiling in phosphoryl chloride. If more vigorous conditions

(1) Contribution no. 2310 from the Kodak Research Laboratories.

(2) Part VI, J. A. VanAllan and G. A. Reynolds, *J. Org. Chem.*, **28**, 1019 (1963).

(3) J. A. VanAllan, G. A. Reynolds, and R. E. Adel, *ibid.*, **27**, 1659 (1962).

(4) Part V, G. A. Reynolds and J. A. VanAllan, *ibid.* **28**, 527 (1963).

(5) "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 426.