Polynuclear Heterocycles. VIII. N-(2-Arylamino-1,4-dioxynaphthyl-3)pyridinium Salts

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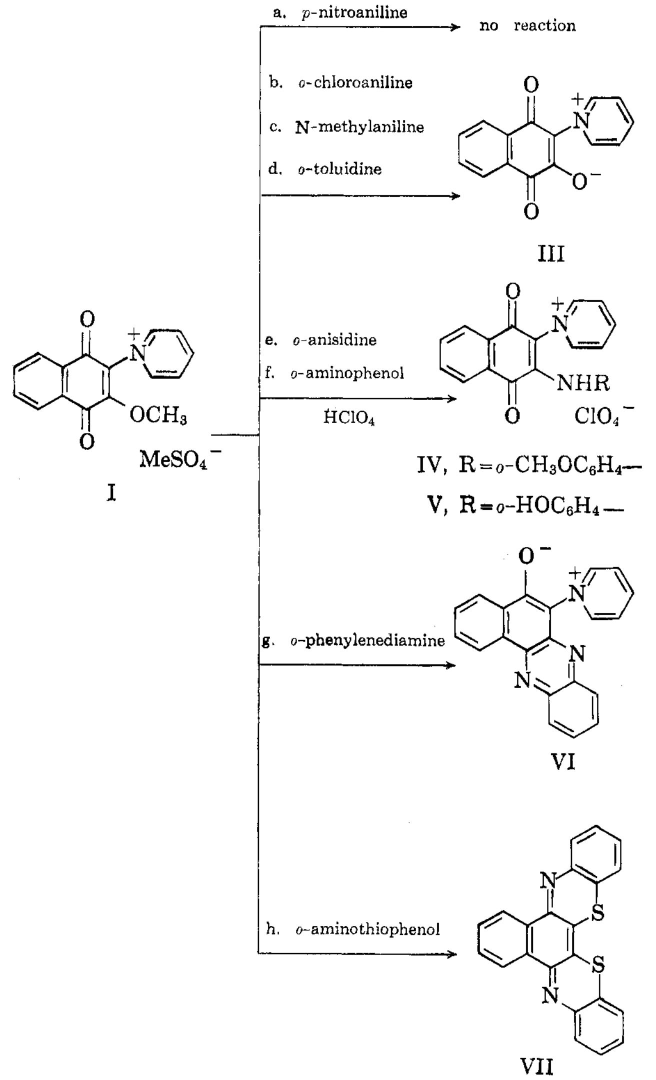
The reactivities of N-(1,4-dioxo-2-methoxynaphthyl-3)pyridinium salts and 2,3-dichloro-1,4-naphthoquinone with aromatic amines are compared. The methoxy group of the pyridinium salt is not replaced by sterically hindered or weakly basic amines. A method is described for overcoming this difficulty.

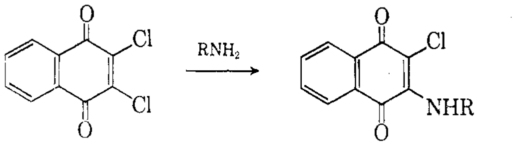
In the preceding paper of this series[1] it was reported that the methoxy group of N-(1,4-dioxo-2-methoxynaphthyl-3)pyridinium methosulfate[2] (I) was displaced readily by aniline. The investigation of this reaction has been extended here to include anilino derivatives that contain substituents which affect the basicity or the steric nature of the amino group. A comparison was made of the reaction of these amines with I, with 2,3-dichloro-1,4-naphthoquinone (II), and with II in the presence of pyridine.

The results which were obtained from the reaction of I with various amines are summarized in accompanying reaction scheme. It is evident from the results with amines (a, b, c and d) that electronic and steric effects can prevent the replacement of the methoxy group of I by an amine. The formation of the enol-betaine (III)[3] from the reaction of I and the hindered amines (b, c, and d) is the result of cleavage of the methoxy group between the oxygen atom and the methyl group rather than the oxygen atom and the naphthoquinone nucleus. This was demonstrated by isolating methylated amines from the reaction mixture as well as III. In examples employing b, c, or d, a mixture of methylated amines was obtained which could not be separated. However, when a tertiary amine such as pyridine was used, N-methylpyridinium methosulfate was isolated in good yield.



The steric limitations of the reaction are overcome if the *ortho* substituent sufficiently increases the basicity of the aniline derivative, as shown by the reaction of e and f with I to yield compounds IV and V. The difunctional amines (g and h) introduce the additional factor that the primary reaction products undergo cyclization to yield VI and VII.[3] It should be noted that the methoxy group of I is displaced by a mercapto group in the case of compound h. The additional driving force for the reaction of these difunctional amines is very pronounced since the reaction is essentially complete in minutes, compared to hours required for the reaction of aniline or e and f.

The amines (a → f) were treated with 2,3-dichloro-1,4-naphthoquinone (II) in alcohol solution, and it was found that a, b, and c gave no reaction, whereas d, e, and f yielded compounds VIII,[4] IX[5] and X. The reaction of II with g and h has been shown[3] to yield 6-chloro-5-hydroxybenzo[*a*]phenazine (XI) and VII, respectively. These results show that the reactivities of I and II are similar with amines in alcoholic solution.



II

VIII, R = o-$CH_3C_6H_4$–
IX, R = o-$CH_3OC_6H_4$–
X, R = o-HOC_6H_4–

However, amines a → e reacted with II in the presence of two equivalents of pyridine in 1,2,3-trichloropropane solution to yield XII,[3] XIII, XIV, XV-and IV.

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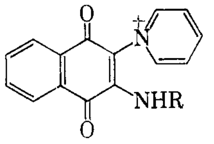
[1] J. A. VanAllan and G. A. Reynolds, *J. Org. Chem.*, **28**, 1022 (1963).

[2] In the preparation of I (see ref. 1), sulfuric acid in the dimethyl sulfate leads to the formation of N-(1,4-dioxo-2-hydroxynaphthyl-3)-pyridinium methosulfate rather than I. The hydroxy quaternary salt reverts to the enol-betaine on treatment with water or basic materials.

[3] J. A. VanAllan and G. A. Reynolds, *J. Org. Chem.*, **28**, 1019 (1963).

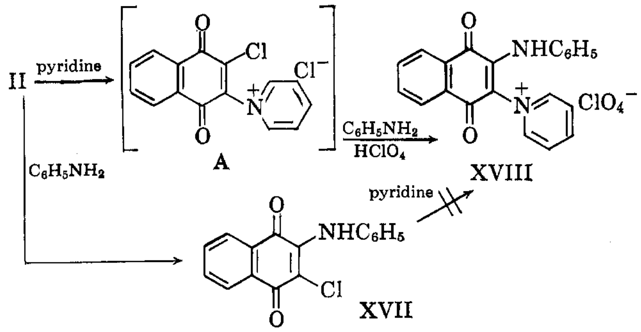
[4] A. Plagemann, *Ber.*, **15**, 484 (1882).

[5] Ng. Ph. Bui Hoi, *Bull. soc. chim. France*, **11**, 578 (1944).

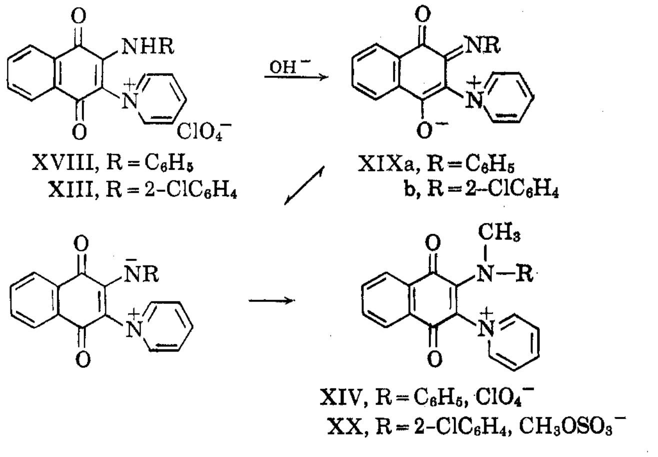


Cl^- (or ClO_4^-)
XII, R = p-$NO_2C_6H_4$—
XIII, R = o-ClC_6H_4—
XIV, R = $\underset{CH_3}{C_6H_5N}$—
XV, R = o-$CH_3C_6H_4$—

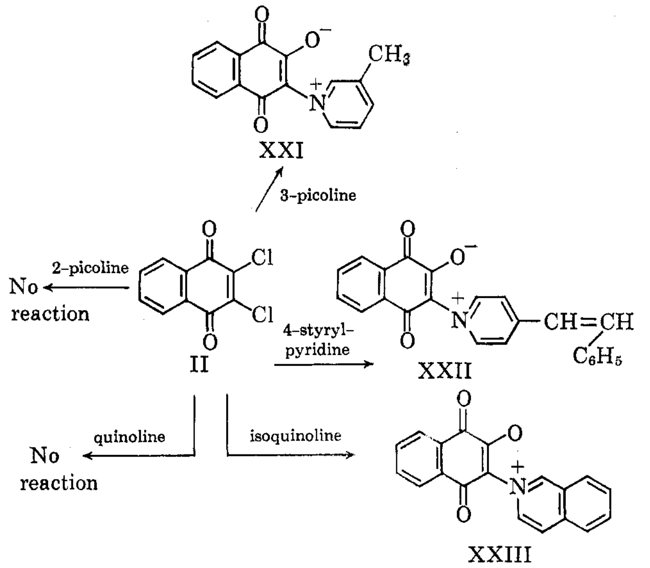
The amine f yielded 5-oxobenzo[*a*]phenoxazine (XVI),[3] g gave VI, and h gave VII.[3] The addition of amines to II under these conditions probably involves the intermediate A rather than XVII, since XVII has been prepared[4] and does not react with pyridine. Attempts were made to prepare intermediate A by the reaction of II with pyridine, but the product isolated was III. The reactivity of the proposed intermediate A with nucleophilic reagents is great enough to overcome the weakly basic properties of amine a and the steric hindrance of b, c, and d. The formation of III from A is probably due to hydrolysis by atmospheric moisture.



It has been reported[3] that N-[1,4-dioxo-2-(4-nitroanilino)naphthyl-3]pyridinium chloride (XII), on treatment with base, gave 2-(4-nitroanilino)-1,4-naphthoquinone. This unexpected result led us to examine the behavior of N-(2-anilino-1,4-dioxonaphthyl-3)pyridinium perchlorate (XVIII) and N-[2-(2-chloroanilino)-1,4-dioxonaphthyl-3]pyridinium perchlorate (XIII) with base. These compounds reacted in the expected manner to give enol-betaine (XIXa and XIXb) which, on methylation, yielded XIV and XX. Compound XIV was also prepared by the reaction of II and N-methylaniline in the presence of pyridine. Since both XIII and XVIII react with base to give enol-betaines; the behavior of 1,4-dioxo-2-(4-nitroanilino)naphthyl-3-pyridinium chloride, XII, toward bases appears to be anomalous.



The effect of pyridine on the reaction of 2,3-dichloro-1,4-naphthoquinone (II) with arylamines was investigated by replacing the pyridine by 2-, 3-, and 4-picoline, quinoline, isoquinoline and 4-styrylpyridine. The reactions were carried out: (1) by heating an alcohol



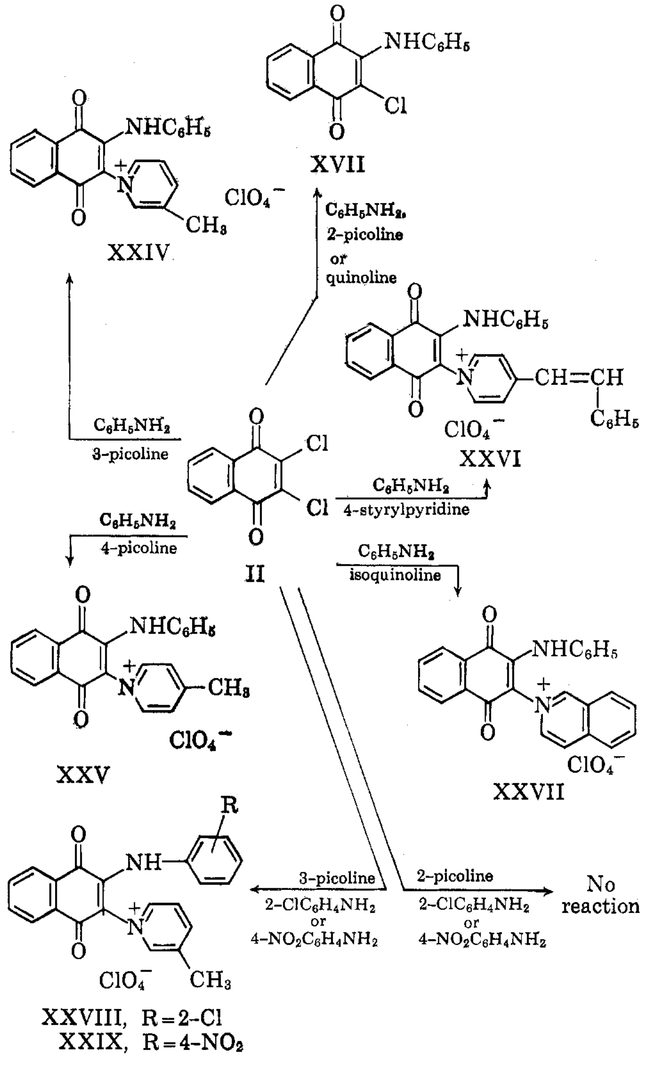


Table I

Ultraviolet Absorption Data

	λ_1 (ϵ)[a]	λ_2 (ϵ)	λ_3 (ϵ)	Solvent
VI	275 (22.8)	312 (26.4)	482 (10.5)	Dimethylformamide
VII	270 (28.0)	360 (11.0)	538 (8.5)	Acetonitrile
XII	258 (21.6)	310 (13.5)	425 (5.5)	Water
XVI	295 (6.7)	358 (9.5)	442 (9.5)	Dimethylformamide
XXVII	293 (37.0)	~338 (8.5)		Dimethylformamide

[a] Extinction coefficients are reported as $\epsilon \times 10^{-3}$.

solution of 2,3-dichloro-1,4-naphthoquinone (II) with the substituted pyridine derivatives, quinoline, and isoquinoline; (2) by heating a mixture of II, the heterocyclic bases, and aniline, 2-chloroaniline or 4-nitroaniline in 1,2,3-trichloropropane. The results of these reactions are summarized (p. 2684, col. 2).

The steric effect of an α substituent in the pyridinium moiety is evident since quinoline and 2-picoline did not react with II, while 3-picoline, 4-styrylpyridine, and isoquinoline gave the enol-betaines, XXI, XXII, and XXIII, respectively. Aniline reacted with II in the presence of 3- and 4-picoline, 4-styrylpyridine, and isoquinoline to yield the anilino quaternary salts XXIV, XXV, XXVI, and XXVII, respectively. Under the same conditions, α-picoline and quinoline acted only as acid binders and the resulting product was XVII. No reaction occurred between 2-chloroaniline or 4-nitroaniline and II in the presence of 2-picoline, but with 3-picoline the respective pyridinium salts, XXVIII and XXIX , were obtained. The reactions of II with 4-picoline and II with 4-picoline and either *o*-chloroaniline or *p*-nitroaniline yielded unidentifiable products. It is probable that the active methyl group of the picolinium ring has entered into the reactions. These results are consistent with the assumption that an intermediate of type A is common to all these reactions.

The ultraviolet absorption data of representative compounds are collected in Table I.

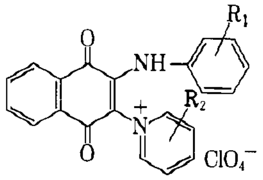
Experimental

The following general methods illustrate the procedures used in the preparation of arylaminonaphthylpyridinium salts. The analytical data are collected in Table II.

Method A.—A mixture of 0.01 *M* quantities of N-(1,4-dioxo-2-methoxynaphthyl-3)pyridinium methosulfate (I) and a substituted aniline in 50 ml. of methanol was heated on the steam bath for 2 hr. The reaction mixture was poured into water and 2 ml. of 70% perchloric acid was added. The product was collected by filtration. Crystallization of the product from a suitable solvent gave the pure arylaminonaphthylpyridinium salt in a yield of 70 to 80%.

Table II

Pyridinium Salts



	R_1	R_2	Emp. form.	M.p., °C.	% Calcd. C	H	Cl	N	% Found C	H	Cl	N	Solvent of crystallization	Method of prepn.
IV	2-OCH$_3$	H	$C_{22}H_{17}ClN_2O_7$	285	58.0	3.6		6.0	57.8	3.8		6.0	CH$_3$CN	A
V	2-OH	H	$C_{21}H_{15}ClN_2O_7$	235	57.1	3.4		6.3	57.0	3.8		6.2	CH$_3$CN-ether	A
XIII	2-Cl	H	$C_{21}H_{14}Cl_2N_2O_6$	275	54.8	3.0		6.1	54.6	3.1		6.0	CH$_3$CN	B
XV	2-CH$_3$	H	$C_{22}H_{17}ClN_2O_6$	251	60.0	3.9		6.4	59.9	4.1		6.2	C$_2$H$_5$OH	B
XVIII	H	H	$C_{21}H_{15}ClN_2O_6$	298	59.1	3.5	8.3	6.6	58.8	3.7	8.5	6.4	CH$_3$CN	B
XIV[a]	H	H	$C_{22}H_{17}ClN_2O_6$	230	60.0	3.9		6.4	59.9	4.0		6.4	CH$_3$CN-CH$_3$OH	B and C
XX[b,d]	2-Cl	H	$C_{23}H_{19}ClN_2O_6S$	270	56.7	3.9		5.8	56.6	3.9		5.7	CH$_3$OH	C
XXIV	H	3-CH$_3$	$C_{22}H_{17}ClN_2O_6$	230	60.0	3.9		6.4	59.8	4.0		6.6	CH$_3$CN-ether	B
XXV	H	4-CH$_3$	$C_{22}H_{17}ClN_2O_6$	294	60.0	3.9		6.4	59.7	3.7		6.3	water	B
XXVI	H	4-CH=CHC$_6$H$_5$	$C_{29}H_{21}ClN_2O_6$	243	65.8	4.0	6.7	5.3	66.1	4.1	6.7	5.1	Acetic acid	B
XXVII	H	3,4-Benzo	$C_{25}H_{17}ClN_2O_6$	389	63.1	3.6	7.5	5.9	63.0	3.2	7.6	6.0	DMF[c]-C$_2$H$_5$OH	B
XXVIII	2-Cl	3-CH$_3$	$C_{22}H_{16}Cl_2N_2O_6$	242	55.6	3.4	14.9	5.9	55.2	3.6	15.0	6.1	CH$_3$CN-ether	B
XXIX	4-NO$_2$	3-CH$_3$	$C_{22}H_{16}ClN_3O_8$	295	54.4	3.3	7.3	8.6	54.6	3.5	7.4	8.9	CH$_3$CN-ether	B

[a] N-Methyl derivative of XVIII. [b] N-Methyl derivative of XIII. [c] Dimethylformamide. [d] Isolated as the methosulfate.

Method B.—A mixture of 0.02 *M* of 2,3-dichloro-1,4-naphthoquinone (II), 0.04 *M* of heterocyclic tertiary amine, 0.02 *M* of substituted aniline and 20 ml. of 1,2,3-trichloropropane was heated on the steam bath for 2 hr. In cases where the product separated on cooling, it was isolated by filtration, taken up in a minimum amount of warm methanol and 2 ml. of 70% perchloric acid was added. If the product did not separate on cooling, the solvent was removed at reduced pressure, the residue was taken up in a minimum amount of warm methanol and perchloric acid was added. The perchlorate salts were isolated by filtration and crystallized from a suitable solvent to give the pure product in 75–80% yield.

Method C. N-[1,4-Dioxo-2-(N-methylanilino)naphthyl-3]pyridinium Perchlorate (XIV).—Equal quantities by weight of 1-oxo-2-phenylimino-3-pyridinium-4-naphthoxide (XIXa) and dimethyl sulfate were heated on the steam bath for 2 hr. An equal volume of methanol was added, followed by 2 ml. of 70% perchloric acid. On cooling, glistening black crystals separated which were collected by filtration. Crystallization from acetonitrile–methanol gave the pure product in a yield of 84%.

N-[2-(2-Chloro-N-methylanilino)-1,4-dioxonaphthyl-3]pyridinium perchlorate (XX) was prepared in a similar manner.

2-Chloro-3-(2-hydroxyanilino)-1,4-naphthoquinone (X).—A mixture of 11.3 g. (0.05 *M*) of 2,3-dichloro-1,4-naphthoquinone (II), 10.8 g. (0.1 *M*) of *o*-aminophenol, and 100 ml. of methanol was refluxed on the steam bath for 2 hr. The mixture was diluted with 400 ml. of water and the product was isolated by filtration, and dried; yield, 14 g.; m.p. 195° (from chlorobenzene).

Anal. Calcd. for $C_{16}H_{10}ClNO_3$: C, 64.6; H, 3.4; Cl, 11.8; N, 4.7. Found: C, 64.9; H, 3.8; Cl, 11.7; N, 4.4.

1-Oxo-2-phenylimino-3-pyridinium-4-naphthoxide (XIXa).—To a suspension of 3 g. of N-(2-anilino-1,4-dioxonaphthyl-3)pyridinium perchloroate (XVIII) in 150 ml. of hot water was added 10 ml. of a saturated sodium carbonate solution. The mixture was stirred for 3 hr. while it cooled to room temperature. The product was isolated by filtration, m.p. 298°.

Anal. Calcd. for $C_{21}H_{14}N_2O_2$: C, 77.3; H, 4.3; N, 8.6. Found: C, 76.9; H, 4.2; N, 8.2.

2-(2-Chlorophenylimino)-1-oxo-3-pyridinium-4-naphthoxide (XIXb) was prepared in the same manner; m.p. 195° (from toluene).

Anal. Calcd. for $C_{21}H_{13}ClN_2O_2$: C, 69.8; H, 3.6; N, 7.8. Found: C, 69.4; H, 3.8; N, 7.6.

1,4-Dioxo-3-(3-methylpyridinium)-2-naphthoxide (XXI).—A mixture of 22.7 g. (0.1 *M*) of 2,3-dichloro-1,4-naphthoquinone (II), 18.6 g. (0.2 *M*) of 3-picoline, and 250 ml. of 2-ethoxyethanol was refluxed for 2 hr. and after cooling, the product was isolated by filtration, and crystallized from water to give 26 g. of XXI, m.p. 260°.

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.5; H, 4.1; N, 5.3. Found: C, 72.2; H, 4.4; N, 5.4.

Other naphthoxides prepared in this manner were the following.

1,4-Dioxo-3-(4-styrylpyridinium)-2-naphthoxide (XXII), m.p. 370° (from dimethylformamide); yield, 85%.

Anal. Calcd. for $C_{23}H_{15}NO_3$: C, 78.2; H, 4.3; N, 4.0. Found: C, 78.5; H, 4.5; N, 4.0.

1,4-Dioxo-3-isoquinolinium-2-naphthoxide (XXIII), m.p. 330° (from pyridine); yield, 74%.

Anal. Calcd. for $C_{19}H_{11}NO_3$: C, 75.9; H, 3.6; N, 4.6. Found: C, 76.3; H, 3.7; N, 4.7.

2-Anilino-3-chloro-1,4-naphthoquinone (XVII).—This compound has been prepared in a number of ways[6]. We prefer the following method. A mixture of 2,3-dichloro-1,4-naphthoquinone (22.7 g.) (0.1 *M*), 12 ml. (0.13 *M*) of aniline, and 20 ml. of 2-picoline (0.2 *M*) in 100 ml. of 1,2,3-trichloropropane was heated at 95–100° for 3 hr. After cooling, the product, which had separated, was collected by filtration, washed with methanol, and dried; yield, 25 g. (89%); m.p. 210°.

N-(1,4-Dioxo-2-hydroxynaphthyl-3)pyridinium Perchlorate.[2]—A suspension of 5 g. of III in 20 ml. of dimethyl sulfate which contained about 3% of sulfuric acid was heated on the steam bath for 2 hr. or until solution occurred. Methanol (50 ml.) was added, followed by 3 ml. of 70% perchloric acid. The product separated and was collected by filtration, washed with acetone, and dried, yield, 4.7 g.; m.p. 295°.

Anal. Calcd. for $C_{15}H_{10}ClNO_7$: C, 51.2; H, 2.8; N, 3.9; Cl, 10.1. Found: C, 51.3; H, 2.4; N, 4.1; Cl, 10.4.

Alternatively, 5 g. of III was dissolved in 200 ml. of hot 10% hydrochloric acid. The solution was filtered from a small amount of insoluble material and treated with 3 ml. of 70% perchloric acid in 10 ml. of water. The product, which separated immediately, was collected, washed with water, and dried; yield, 5.2 g.; m.p. 295°. The infrared absorption curve was identical with that of the product obtained from dimethyl sulfate and sulfuric acid.

N-Methylpyridinium Perchlorate.—A solution of 2 g. of I and 10 ml. of pyridine was heated on the steam bath for 0.5 hr. An orange solid separated which was collected by filtration and identified as III. The filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 10 ml. of hot water, a little insoluble material was filtered off, and the filtrate again evaporated to dryness. The residue was taken up in 5 ml. of methanol and 0.5 ml. of 70% perchloric acid was added. On chilling, a solid separated as white needles; yield, 0.8 g.; m.p. 129–130°.

Anal. Calcd. for $C_6H_8ClNO_4$: C, 37.3; H, 4.1; N, 7.3. Found: C, 37.1; H, 4.1; N, 7.3.

The infrared spectrum of this material was identical with that of an authentic sample of N-methylpyridinium perchlorate.

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(6) "Encyclopedia of Organic Chemistry," Vol. 12B, Elsevier Publishing Co., Amsterdam, 1952, p. 2987.

Heterocyclic Vinyl Sulfides. XX. The Reaction of Cyclic Sulfoxides with Acetic Anhydride[1]

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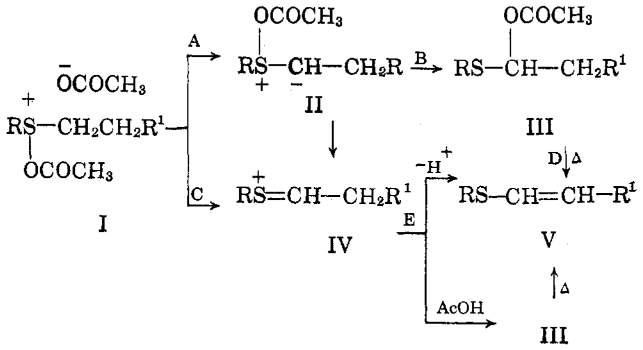
The reactions of 1,4-dithiane 1-oxide and 1,4-dithiane 1,4-dioxide with hot acetic anhydride have been examined, and the structures of the principal products have been established. Evidence has been obtained supporting carbonium ion intermediates in the Pummerer reaction.

The decomposition of sulfoxides in hot acetic anhydride, a reaction analogous to that originally reported by Pummerer,[2] has been shown to be an attractive preparative route[3] to certain α,β-unsaturated sulfides. While the details of the mechanism of this reaction were unknown, the related pathways outlined in the accompanying equations have been implied or suggested.[2-4] Step B could involve an intramolecular rearrangement of II, or a substitution–elimination process involving acetate ion. The formation of ethers,[4a] when related reactions of sulfoxides are carried out in the presence of alcohols, suggest either the substitution–elimination process at step B, or the presence of the intermediate IV. That the olefin V can be formed by thermal decomposition of III has been established.[3b]



The purpose of this study was to determine whether this reaction could be extended successfully to heterocyclic compounds containing more than one sulfur atom, and to determine whether such a study would furnish additional information related to the mechanism of the process.

Preliminary studies were made using 1,4-dithiane 1-oxide (VI). The reaction proceeded smoothly at steam bath temperature, and 1,4-dithiene (VII) was obtained in 53% yield.

Of greater interest was the reaction of 1,4-dithiane 1,4-dioxide (VIII), and for this study the *trans* isomer[5]

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(1) This work was supported by the Office of Ordnance Research, U. S. Army, contract no. DA-ORD-31-124-61-G13.

(2) R. Pummerer, *Ber.*, **43**, 1401 (1910).

(3) (a) L. Horner and P. Kaiser, *Ann.*, **626**, 19 (1959); (b) W. E. Parham and R. Koncos, *J. Am. Chem. Soc.*, **83**, 4034 (1961).

(4) (a) E. F. Schroeder and R. M. Dodson, *ibid.*, **84**, 1904 (1962); (b) W. R. Sorenson, *J. Org. Chem.*, **24**, 978 (1959); (c) D. Walker and J. Leib, *Can. J. Chem.*, **40**, 1242 (1962); (d) W. J. Kenney, J. A. Walsh, and D. A. Davenport, *J. Am. Chem. Soc.*, **83**, 4019 (1961), contains additional references to related reactions.

(5) (a) E. V. Bell and G. M. Bennett, *J. Chem. Soc.*, 1798, (1927); (b) H. M. M. Shearer, *ibid.*, 1394 (1959); (c) P. B. D. DeLaMare, D. J. Millen, J. G. Tillett, and D. Watson, *ibid.*, 1619 (1963).