conveniently, and in the presence of dilute sodium hydroxide the observed first-order rate constants fall as the reaction progresses. Acidimetric titration showed that the base concentration decreases during the reaction, presumably due to the autoxidation of small amounts of aldehyde to acid. The reaction was therefore studied in buffer solutions. In a typical run the reaction was started by adding 0.25 ml. of 0.0716 *M* 1,4-diazabicyclo-[2.2.2]octane–0.0445 *M* 1,4-diazabicyclo[2.2.2]octane perchlorate and 0.50 ml. of a 0.0794 *M* isobutyraldol solution, that was 0.0016 *M* in acid, by syringe to an n.m.r. tube under nitrogen. The tube was kept at 35 ± 0.1° and at recorded times the areas of the τ 8.85 peak of isobutyraldehyde and the 8.93 peak of isobutyraldol were measured. Using a relationship of the form of eq. 6 and a second relationship based on the concentrations of isobutyraldol known to be present in the original reaction solution the concentrations of aldol and isobutyraldehyde may be calculated. The results of this calculation are shown in Table II

TABLE II

BASE-CATALYZED DEALDOLIZATION OF ISOBUTYRALDOL IN WATER AT 35°[a]

Time, sec.	$A_{8.85}$[b]	$A_{8.93}$[c]	[Aldol]
0			0.0529
4,110	1.752	13.44	0.0451
5,200	3.40	17.64	0.0422
5,460	3.29	13.97	0.0407
7,740	4.25	10.92	0.0349
9,720	4.99	11.61	0.0338
11,520	6.14	10.34	0.0296
13,440	6.51	9.50	0.0278
14,610	7.95	11.50	0.0277

[a] $[C_6H_{12}N_2]$ = 0.0228 *M*, $[C_6H_{12}N_2H^+]$ = 0.0159 *M*. [b] Area of the τ 8.85 peak. [c] Area of the τ 8.93 peak.

and a plot of log ($[HAAH]_0/[HAAH]$) *vs.* time is shown in Figure 1.

The hydroxide ion concentrations in the various runs were calculated from the buffer ratio and the ionization constant of the buffer base at the appropriate ionic strength (calculated by the method described explicitly for trimethylamine in the preceding section).

The Acidity of Isobutyraldehyde Hydrate.—Two solutions of isobutyraldehyde were prepared simultaneously, with the total concentration of aldehyde (hydrate plus free aldehyde) being 0.107 *M* in each. One solution was 0.0964 *M* in sodium hydroxide and the other contained no added base. The absorbances (measured immediately) of the two solutions at 2850 Å. were 1.385 and 1.465, respectively, at 25°. From these observations the following *K* value may be calculated.

$$K = \frac{[Me_2CHCHOHO^-][H_2O]}{[Me_2CHCH(OH)_2][OH^-]} = 93$$

Acknowledgment.—We wish to acknowledge our indebtedness to the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, for Research Grant AM 06829-01 MCB in support of this investigation and to the National Science Foundation for grants that permitted the purchase of the n.m.r. spectrometer and aided in the purchase of the ultraviolet–visible spectrophotometer, whose purchase was also made possible by a generous grant from the Charles F. Kettering Foundation. We also wish to thank Eastman Chemical Products, Inc., for the gift of the isobutyraldehyde used in this investigation.

Further Studies of Mechanisms of Chlorinolysis of Sulfur–Carbon Bonds. The Mechanism of Abnormal Chlorinolysis and Desulfonylation of Sulfonyl Chlorides. III[1]

HAROLD KWART AND R. WILLIAM BODY

Department of Chemistry, University of Delaware, Newark, Delaware

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The incidence of the abnormal mechanism of chlorinolysis of sulfur–carbon bonds is apparently restricted to sulfides possessing the structural feature RS–(C=C)$_n$–C=N–. The factors involved in the competition of normal and abnormal reactions are examined in this context. The possibility that the abnormal course proceeds by a nucleophilic addition–elimination mechanism of the type encountered usually in aromatic and heteroaromatic systems has been evaluated. The effect of medium composition on the relative occurrence of the competing reaction mechanisms in particular cases has been explored. The inference that might be drawn from these results is that N-chlorination may create special facilitation for a nucleophilic displacement mechanism in the abnormal reaction. This has been examined by tracer experiments and discredited. Further consideration of the product distribution in experiments with 4-alkylthio-7-chloroquinoline substrates and the factors determining the stabilities of related sulfonyl chlorides suggest that an SNi mechanism can account for all the known characteristics of both the abnormal chlorinolysis reaction and the catalyzed decomposition of the sulfonyl chlorides.

An earlier article from these laboratories[2] has discussed the chlorinolysis of 4-benzylthio-7-chloroquinoline (I) and some of its derivatives. The principal cleavages products were reconciled with the intervention of a carbonium ion. However, 14% of the products arose from an alternative course which most certainly was not of carbonium ion character. It has been suggested[3,4] that benzylsulfonyl chloride (III) was formed by an SN2 displacement of the sulfenyl chloride from the 4-position by chloride ion. These available, competitive reaction paths are summarized in Scheme I.

The exclusive preference of chlorinolysis to occur *via* the normal SN1 path in most substrates is well documented.[2,5] However, in certain cases the displacement reaction path (SN2?), which we shall hereafter call *abnormal*, does manifest itself as a competing path.

(1) (a) Part of the data discussed here is taken from the Ph.D. dissertation of R. W. Body submitted in partial fulfillment of the requirements at the University of Delaware, June 1963. (b) Part of this paper has been presented before the American Association for the Advancement of Sciences Symposium on Recent Advances in Organic Chemistry, Philadelphia, Pa., Dec. 1962.

(2) Paper II: H. Kwart and L. J. Miller, *J. Am. Chem. Soc.*, **80**, 884 (1958).

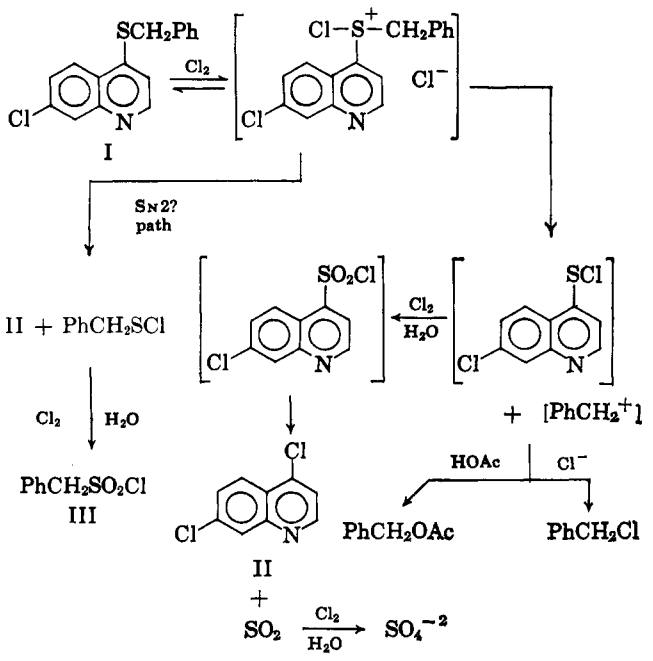
(3) R. H. Baker, R. M. Dodson, and B. Riegel, *ibid.*, **68**, 2636 (1946).

(4) D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 38 (1951).

(5) H. Kwart and R. K. Miller, *J. Am. Chem. Soc.*, **78**, 5678 (1956).

SCHEME I

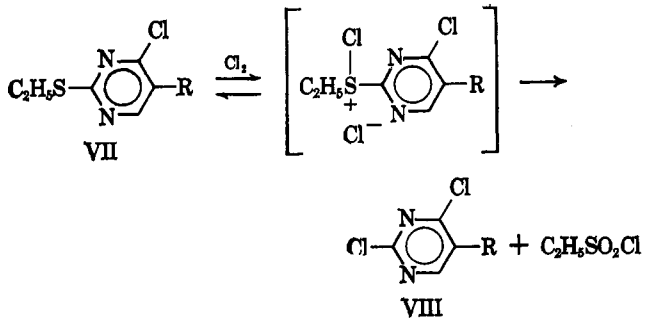
AVAILABLE PATHS OF CHLORINOLYSIS OF I



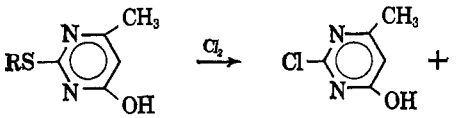
Results

Cases of Abnormal Chlorinolysis.—From examination of all the well-characterized instances of sulfide chlorinolysis in the literature and the sum total of our studies of this subject in the laboratory to date we can deduce the following generalization: the abnormal reaction only occurs where the sulfur is bonded by one of its valences to an unsaturated center conjugated with an imino nitrogen, as in R–S–(C=C)$_n$–C=N– (where n may be zero). When this structural requirement is met, the extent of *normal* chlorinolysis taking place correlates with that portion of the total product in which the imino nitrogen moiety remains associated with the sulfur only long enough to undergo loss of the sulfur as SO_4^{-2} and giving rise to a residue possessing a carbon–chlorine bond.

A typical example is the chlorinolysis of the pyrimidine sulfide VII, reported by Johnson and co-workers[6,7] to yield VIII and ethanesulfonyl chloride and interpreted to proceed *via* attack by chloride ion, as shown below.



Apparently the normal reaction path, which would have formed ethyl chloride and ethanol, was not detected by these authors. In the analogous case of the chlorinolysis in acetic acid medium (containing a reaction equivalent of water) of 2-ethylthio-4-methyl-6-oxypyrimidine (IX), we have confirmed Sprague and Johnson's observations[6] with VII. Only ethanesulfonyl chloride and a nearly quantitative yield of the easily isolated 2-chloropyrimidine (XI) were found. Cleavage of IX by only the abnormal path is readily understood since the alternative (normal) route is suppressed, involving, as it does, the intervention of an unlikely *ethyl cation.*[2] This conclusion is also supported by the results of chlorinolysis of the corresponding 2-benzylthiopyrimidine X. The sulfate



IX, R = ethyl
X, R = benzyl

100% $EtSO_2Cl$ (from IX)
49% $C_6H_5CH_2Cl$ + 16% $C_6H_5CH_2OAc$ + 56.2% SO_4^{-2} (from X)

ion presumably was formed from an equivalent amount of the 2-pyrimidinesulfonyl chloride which decomposed in the medium with evolution of SO_2. Where a relatively stable carbonium ion is possible, as in X, the abnormal reaction occurs to an extent no greater than 25%.

Rounding out these observations is the chlorinolysis of 4,6-dichloro-2-phenylthio-1,3,5-triazine which was chlorinolyzed in the same way to yield nearly 73% of benzenesulfonyl chloride. About 61% of cyanuric chloride was recovered, but no other products were obtained. This also agrees with the conclusion that where only an unstable phenyl cation can be formed normal cleavage does not occur and the abnormal cleavage characteristic of sulfides attached at the 2-position of the pyrimidine ring takes place, apparently exclusively. Diphenyl sulfide, however, which can neither afford a normal SN1 pathway for chlorinolysis nor fulfill the structural requirements (cited earlier) for the abnormal pathway, *shows no chlorinolytic reactivity.*

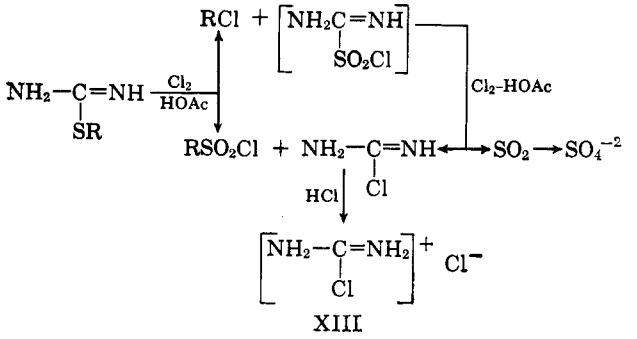
Experiments directed toward a more quantitative examination were based on the prior chlorinolysis studies of Johnson and co-workers[7–10] with S-alkylisothiouronium salts. These workers suggested this as a convenient way to prepare alkylsulfonyl chlorides in good yields. However, in their studies high yields were obtained only in the case of primary alkyl sulfides, the yields declined in the instance of secondary alkyl, and tertiary alkyl sulfides did not produce sulfonyl chlorides. In the last case the reaction seemingly proceeded well, but all of the original sulfide sulfur appeared as sulfate ion in the product. The other product isolated in all cases was alleged[8–10] to be cyanamide dihydrochloride (by analysis). However, the same analytical data would fit chloroformamidine hydrochloride (XIII) and would thereby be consistent with the abnormal chlorinolysis scheme (see Table I).

The competition of the normal and abnormal reaction courses in S-alkylisothiouronium substrates can be seen in the results listed for several *para*-sub-

(6) J. M. Sprague and T. B. Johnson, *J. Am. Chem. Soc.*, **57**, 2252 (1935).
(7) T. B. Johnson, *Proc. Natl. Acad. Sci. U. S.*, **25**, 448 (1939).
(8) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **58**, 1348 (1936).
(9) T. B. Johnson and J. M. Sprague, *ibid.*, **59**, 1837, 2439 (1937).
(10) T. B. Johnson and J. M. Sprague, *ibid.*, **61**, 176 (1939).

TABLE I

CHLORINOLYSIS OF S-ALKYLISOTHIOURONIUM SALTS IN ACETIC ACID MEDIUM



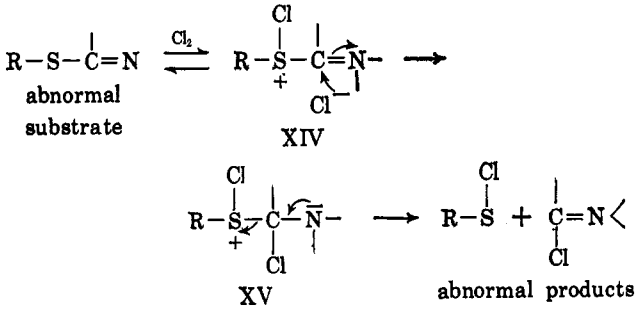
XIII

R	SO_4^{-2}, %[a]	RSO_2Cl, %[b]	Estimated % of abnormal reaction
Benzyl	44.1	39.5	47
p-Methylbenzyl	99.3	0	0
p-Nitrobenzyl	0	90.5	100

[a] Normal product. [b] Abnormal product.

stituted benzyl cases. The anticipated influence of various *para* substituents on the stability of the corresponding benzyl cation appears to correlate well with the occurrence of the normal reaction path in the mechanistic competition. Thus the cation-stabilizing *p*-methyl group directs the reaction *completely* normal; the *p*-nitro group, having precisely the opposite effect on the benzyl cation stability, displaces the reaction course exclusively toward the abnormality identified with the structural feature RS–C=N–.

Evaluation of a Possible Nucleophilic Displacement Mechanism for the Abnormal Reaction.—Such a mechanism has been proposed earlier by Tarbell and Harnish[4] to account for the abnormal products. This might be understood as a nucleophilic addition–elimination at the unsaturated carbon in the pertinent structure of the chlorosulfonium ion XIV. For example, in the typical abnormally reacting substrate XII, attack by chloride could result in the adduct XV, followed by loss of RSCl in accord with the usual pattern of such mechanisms.



This mechanism possesses many attractive features at first glance, including the highly suggestive fact that analogs with different leaving groups on the heterocyclic ring (or other conjugated imine systems) suffer such addition–elimination displacements with great facility. Several suitable chlorinolysis substrates which possessed structural features that made possible the evaluation of this course of the abnormal reaction were therefore selected for study. For example, benzyl 2,4-dinitrophenyl sulfide is a substrate which can undergo both the normal course of chlorinolysis proceeding through the benzyl cation, as well as a possible competing abnormal course in which nucleophilic addition–elimination (displacement) at the sulfur-bonded carbon of the 2,4-dinitrophenyl ring is well accommodated.[11] The extent to which 2,4-dinitrochlorobenzene is formed can be taken to represent the competition afforded by an abnormal path developing *via* such a displacement mechanism.

In carrying out the above experiment, nearly 86% of the total (theoretical yield based on an entirely normal course) of benzyl chloride and acetate was recovered. No benzylsulfonyl chloride could be identified. While only 58% of pure 2,4-dinitrobenzenesulfonyl chloride was recovered, no evidence was obtained that indicated the formation of any other nitro-containing product. Evidently, a structurally fostered nucleophilic addition–elimination does *not* take place in this compound in competition with the normal formation of benzyl cation.

We then turned to chlorinolysis of substrates in which the normal carbonium ion mechanism may be strongly or even completely suppressed, while the opportunities for the displacement mechanism are enhanced by the presence of a favorable structural feature. In three cases possessing these characteristics in varying degree, the results were entirely the same: phenyl 2,4-dinitrophenyl sulfide, phenyl 2,4,6-trinitrophenyl sulfide, and ethyl 2,4-dinitrophenyl sulfide yielded *no* chlorinolysis cleavage products; 92–100% of the starting materials were recovered.

For comparison and emphasis we also report the results in Table II demonstrating the ease with which chlorinolysis can be effected in substrates conceded to facilitate a carbonium ion reaction course. It is thus clear that the abnormal chlorinolysis of sulfides does *not* take place *via* a mechanism which can be said to resemble the usual nucleophilic addition–elimination mechanism.

TABLE II

VARIOUS REFERENCE CHLORINOLYSIS RESULTS IN AQUEOUS ACETIC ACID

R–S–R′	$R'SO_2Cl$, %	ROAc + RCl, %	SO_4^{-2}, %	RSO_2Cl, %
i-C_3H_7–S–C_6H_5	76	75.4	0	0
t-C_4H_9–S–C_6H_5	60.5	38	0	0
$C_6H_5CH_2$–S–$C_6H_3(NO_2)_2$	58	86	0	0
$C_6H_5CH_2$–S–$CH_2C_6H_4$-*p*-NO_2	90.5	83.1	0	0

The Effect of Medium on the Extent of Abnormal Reaction.—The experiments in this category were undertaken on the premise of a mechanism involving ionic intermediates. Since all of the substrates studied to date which evidence any of the abnormal pattern possess a basic –C=N– grouping, and, in view of the acid nature of the usual medium (HOAc) of chlorinolysis, experiments were devised to inquire into the possible role of acid.

To assess the extent to which the unshared pair on nitrogen in the typical quinoline substrate (I) had

(11) See for a full discussion and references supporting this premise J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 398 ff.

TABLE III

CHLORINOLYSIS OF 4-THIOQUINOLINE SUBSTRATES IN MEDIA OF VARYING ACIDITY

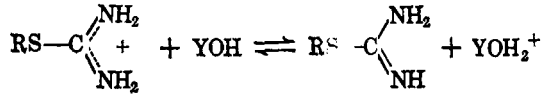
Reaction Medium	Products, % of theoretical total recovered			Approx. %	
	RSO_2Cl	ROAc + RCl	SO_4^{-2}	Normal reaction	Abnormal reaction
		4-Benzylthio-7-chloroquinoline			
HOAc–$HClO_4$ (1 equiv.)	0	85	100	100	0
HOAc[a]	14	47	86	86	14
HOAc–NaOAc (pH = 4)	23.6	44	55	70	30
t-BuOH–KOH	41.0	...	11.8	22	78
		4-Phenylthio-7-chloroquinoline			
HOAc	69	0	0	0	100
HOAc–$HClO_4$ (1 equiv.)	0	0	0	0	0

[a] Reference 2.

been coordinated in an acid medium, the method of McCurdy and Galt[12] was employed. The ultraviolet spectrum of I was taken in the presence of varying amounts of perchloric acid and the absorbance at the 350-mμ maximum was carefully estimated. A plot of perchloric acid concentration (% stoichiometric) *vs.* absorbance gave a straight line which showed a maximum in absorbance with exactly equimolar amounts of perchloric acid and sulfide, indicating that the base had been completely protonated.

Analyses of product distribution obtained on chlorinolysis of I in media of varying degrees of acidity are listed in Table III. Apparently when the unshared electrons on the nitrogen are fully coordinated (in the form of the conjugate acid, quinolinium ion) no abnormal cleavage occurs *regardless of whether the second sulfide substituent permits the normal carbonium ion reaction course.*

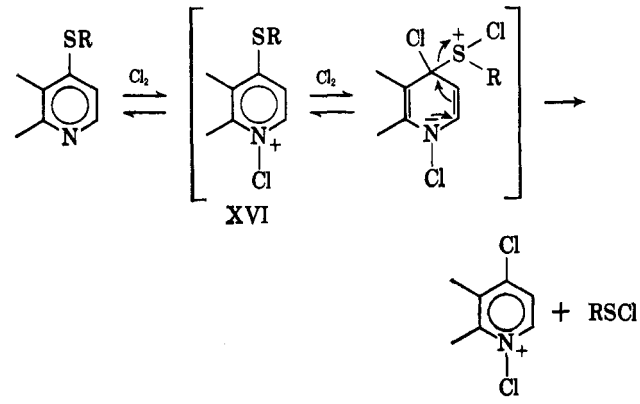
A rather dramatic effect of medium change on the direction of cleavage results when pure water rather than acetic acid is used in the chlorinolysis of S-benzylisothiouronium salts. In acetic acid (see Table I) about 47% of the reaction takes the abnormal course. In pure water, however, *ca.* 100% of the reaction is abnormal and little if any SO_4^{-2} can be detected in the product mixture. These medium effects are readily interpreted on the basis of the availability of the free nitrogen base in the equilibrium with its conjugate acid. In the basic solvent (YOH = water) some



free base exists in the equilibrium, and, as inferred from the studies above with quinoline substrates, it is only the free base which can promote the abnormal reaction course. In the acid solvent (YOH = acetic acid) considerably less of the free isothiourea base is available and the *normal* reaction competes in product determination.

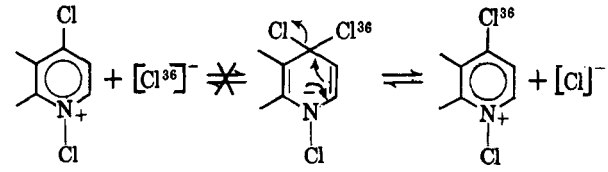
Discussion

A reasonable explanation for the increased abnormal cleavage with decreasing hydrion concentration involves coordination of the available unshared pairs on the nitrogen in RS–(C=C)$_n$–C=N– by halogen as the critical feature of the abnormal mechanism. This led us to consider the possibility (outlined below) that an electron-deficient species (XVI) may be formed in solution which could strongly facilitate the nucleophilic addition–elimination mechanism even though this process fails to occur in even the most reactive nonheterocyclic models we devised to test the possibility (see above). A proposal for this effect is shown below.



XVI

A tracer study was designed to ascertain whether the above proposed N-chlorination of the quinoline could indeed provide *extraordinary activation* of the 4-position for a nucleophilic addition–elimination mechanism of this nature. A solution of 4,7-dichloroquinoline in acetic acid was treated for 30 min. (many half-lives of the chlorinolysis reaction) with a solution of ^{36}Cl anion previously equilibrated in acetic acid with elementary chlorine. A second sample was permitted to react for 16 hr. under the same conditions. On quenching both samples, the 4,7-dichloroquinoline was isolated and purified of any ionic contaminants. Neither product exhibited more than 0.5% of the expected activity based on equilibration of the ^{36}Cl in solution acording to the following relationship (probed by this experiment).



These results verify that the degree of nucleophilic displacement facilitation expected from N-chlorination of the quinoline in order to account for the abnormal cleavage reaction *cannot* be realized. However, N-chlorination is an essential step in the abnormal process, and in the next section we consider evidence and arguments which allow for this event in a more likely mechanistic sequence.

(12) W. H. McCurdy, Jr., and J. Galt, *Anal. Chem.*, **30**, 940 (1958).

Several reports have cited the instability of ordinary sulfonyl chlorides at high temperatures and/or in the presence of powerful electrophilic reagents.[13-16] The most recent of these,[16] presenting a thorough kinetic study of the various influences affecting the course of decomposition of RCl and SO_2, has concluded that an ionic process is operating. It would appear that any factor or additive that would tend to create positive charge at the sulfone sulfur center will accelerate the expulsion of SO_2. In the sulfonyl chloride intermediates encountered in our studies which possessed the structure $-N{=}C-(C{=}C)_n-SO_2Cl$, the tendency to undergo this desulfonylation reaction is extraordinarily enhanced.

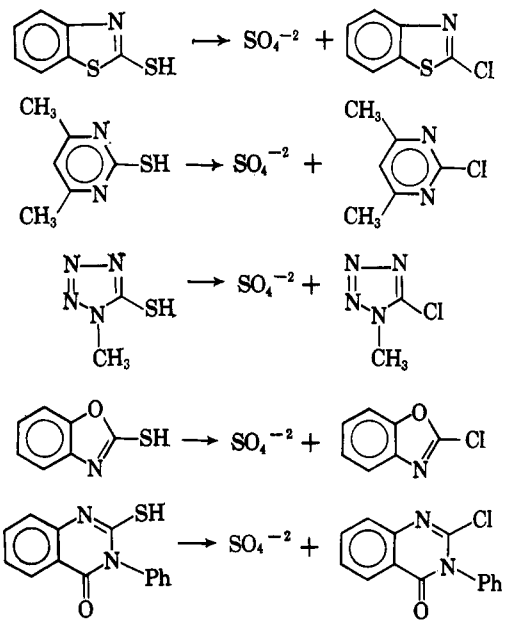
At this point it is profitable to recall the earlier observation[4] that 4-quinolinesulfonyl chloride, generated in the presence of chlorine, suffers expulsion of SO_2 with formation of 4-chloroquinoline. This result was rationalized[2] as typical of an SNi mechanism. However, it now appears that only certain chlorosulfonated positions of the quinoline nucleus are susceptible to this mode of decomposition. Thus, the isolation of a 67% yield of 4,7-dichloro-6-quinolinesulfonyl chloride on chlorinolysis[3] of 6-benzylthio-4,7-dichloroquinoline suggests that an SNi decomposition is not as greatly facilitated for the 6- as it is for the 4-chlorosulfonyl group.

The literature confirms that only the 6-quinolinesulfonyl chloride has been isolated under these reaction conditions.[3] The 5-, 6-, 7-, and 8-quinolinesulfonyl chlorides have been prepared by the conventional method of treating the sulfonic acid with PCl_5.[17-20] There are no reports that either 2-, 4-, 5-, or 7-quinolinesulfonyl chlorides have been prepared by a method involving chlorinolysis.

References may be found[21,22] which demonstrate that both 2- and 4-mercaptopyridines and related derivatives[23] are converted to the corresponding sulfonyl chlorides by chlorine. These reactions could be carried out successfully only in concentrated HCl near 0° or lower temperatures. It was noted that, at room temperature, 2- or 4-pyridinesulfonyl chlorides decomposed to SO_2 and the respective chloropyridines. Isolation of the pure sulfonyl chlorides could not be accomplished in any case; only a sulfonamide product could be obtained by treating the (crude) cold reaction mixture with ammonia. This same procedure has also been applied[24] to prepare the similarly unstable sulfonyl chloride derived from 4-mercaptopyridine 1-oxide. In an earlier attempt[25] these same workers were unable to prepare the sulfonyl chloride from the 1-oxide of 4-pyridinesulfonic acid and PCl_5. The only product observed was 4-chloropyridine 1-oxide. They have interpreted their results on the assumption of a sulfonyl chloride intermediate in this transformation.

An examination of all the quinoline and pyridine cases indicates that the only readily isolated sulfonyl chlorides (*via* chlorinolysis) possess a *meta* orientation of the functional group with respect to the nitrogen.

Additional cases to be found which are completely consistent with this orientation factor in the desulfonylation mechanism are the following from the data of Roblin and Clapp (a sulfonyl chloride intermediate is assumed).[26] Some of the entries have been known as far back as 1899.[27]

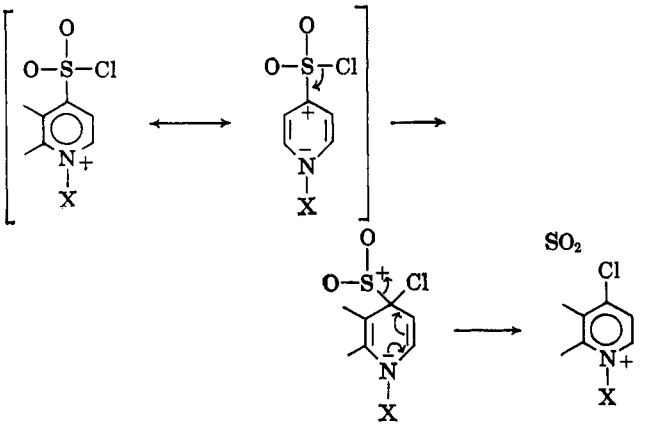


The generality emerges, then, that (apparently) imino-conjugated chlorosulfonyl derivatives of the structure $-N{=}C-(C{=}C)_n-SO_2Cl$ are unstable under certain very definite conditions and rearrange to produce SO_2 ($\rightarrow SO_4^{-2}$) and the corresponding chloro derivative. It has been shown earlier in this article that desulfonylation occurred in the protonated (by $HClO_4$) quinoline case. The fact that both the 5- and 7-quinolinesulfonyl chlorides can be prepared in stable form by treatment of the sulfonic acid with PCl_5 (where excess acid is undoubtedly present) suggests however that protonation *can afford some protection against a very rapid desulfonylation reaction effected by chlorinating agents.* This is to say, in the absence of protonation the desulfonylation of quinolinesulfonyl chlorides[17-20] by chlorinating agents appears to occur much more readily. Furthermore, under the same (PCl_5) circumstances, the 1-oxides of 4-pyridinesulfonic acid produced only 4-chloropyridine 1-oxide (and presumably SO_2). The major difference here, clearly, is the oxygen bonded to nitrogen, which is known[28] to impart some positive character to the heterocyclic nitrogen.

These earlier observations, as well as our own, can be rationalized by considering the following argument.

(13) H. Limpricht, *Ber.*, **6**, 534 (1873).
(14) J. Boeseken and H. W. van Ockenburg, *Rec. trav. chim.*, **33**, 320 (1914).
(15) W. E. Truce and C. W. Vriesen, *J. Am. Chem. Soc.*, **75**, 5033 (1953).
(16) A. Reiche and E. Naumann, *J. prakt. Chem.*, **9**, 108 (1959).
(17) A. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959).
(18) R. Ponci and F. Gialdi, *Farmaco* (Pavia), *Ed. Sci.*, **9**, 459 (1954); *Chem. Abstr.*, **49**, 11657*b* (1955).
(19) A. Claus and W. Schmeisser, *J. prakt. Chem.*, [2] **40**, 447 (1889).
(20) G. Buchmann and E. Schalinatus, *ibid.*, [4] **16**, 152 (1962).
(21) A. M. Comrie and J. B. Stenlake, *J. Chem. Soc.*, 3514 (1958).
(22) Z. Talik and E. Plazek, *Acta Polon. Pharm.*, **12**, 5 (1955); *Chem. Abstr.*, **51**, 17911*c* (1957).
(23) W. T. Caldwell and E. C. Kornfeld, *J. Am. Chem. Soc.*, **64**, 1695 (1942).
(24) J. Angulo and A. M. Muncio, *Anales real soc. espan. fis. quim.* (Madrid), **56B**, 395 (1960).
(25) J. Angulo and A. M. Muncio, *ibid.*, **55B**, 527 (1959).
(26) R. O. Roblin and J. W. Clapp, *J. Am. Chem. Soc.*, **72**, 4890 (1950).
(27) H. N. McCoy, *ibid.*, **21**, 111 (1899).
(28) H. H. Jaffé, *ibid.*, **76**, 3527 (1954).

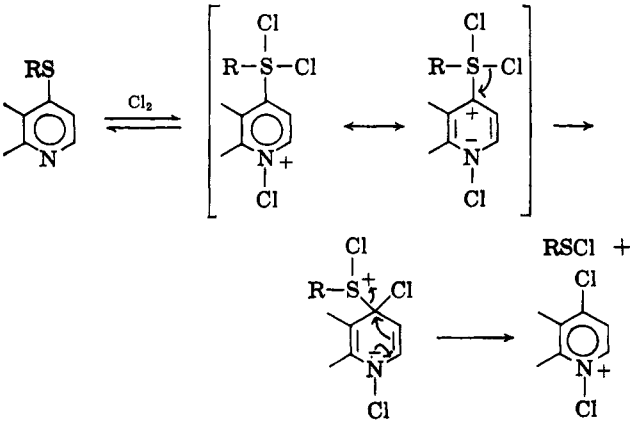
The imino-conjugated chlorosulfonyl group is not of itself unstable, but develops instability when the imino nitrogen acquires a threshold magnitude of positive character such as results from protonation of a pyridine nucleus or conversion to a 1-oxide structure. A similar degree of positive character is conferred on the imino nitrogen in the chlorinolysis reaction through coordination of the unshared electron pair by the powerfully electrophilic halogen. Such positive character residing on the conjugated imino nitrogen may be visualized as the driving force for SO_2 expulsion in an SNi process (see below where X = Cl^+, H^+, or $-\underline{O}$).



Although each of the X groups may impart a positive charge when bonded to the imino nitrogen, there is a decided difference in the magnitude. In an ammonium ion, as is well known, the positive charge of the ion resides almost entirely on the hydrogen. In the N-oxide, the nitrogen is only fractionally positive.[28] It may be anticipated, however, in the case of coordination by Cl^+ that the nitrogen would develop a much fuller extent of positive character. The observation that 4-pyridinesulfonyl chloride can be prepared by chlorination (in the cold) in concentrated HCl solution but not in acetic acid solution, where the imino nitrogen is only incompletely protonated, is a good case in point. When this sulfonyl chloride is not protected by complete protonation (*via* an excess of strong acid) against conversion to the chloroimmonium ion, massive instability to desulfonylation is the result. Yet this mechanism, which derives its driving force from the electron deficiency on nitrogen, cannot be mobilized at low temperatures through the (conjugate acid) ammonium ion.

A Possible SNi Mechanism of Abnormal Chlorinolysis.—The similarity of structural requirements for the abnormal cleavage of sulfides and the SNi decomposition of specific sulfonyl chlorides and the implication of halogen as an electrophilic catalyst coordinating the unshared electrons on the imino nitrogen in both reactions are, to say the least, very suggestive. Thus, an attractive, common explanation of the role of chlorine in both may be seen in the following parallel SNi mechanism.

There is, however, one striking difference. The attachment of Cl^+ appears to be the only means by which the abnormal chlorinolysis will occur. We will recall that no abnormal cleavage occurs when 4-benzylthio-7-chloroquinoline is chlorinolyzed in the presence of a sufficient amount of $HClO_4$ to convert it



to its conjugate ammonium ion. Furthermore, the chlorinolysis of the corresponding pyridine 1-oxide proceeds *only* through the normal route; no benzylsulfonyl chloride is detected, only benzyl chloride, benzyl acetate, and SO_4^{-2}. Clearly, then, a threshold degree of positive charge on the imino-conjugated nitrogen is required to bring about the SNi rearrangement of the tetracovalent sulfur dichloride intermediate. Much less positive character on this nitrogen, however, will accommodate the needs of the analogous SNi rearrangement in the corresponding sulfonyl chlorides.

A second question arises in connection with the (proposed) tetracovalent sulfur dichloride intermediate in the abnormal chlorinolysis mechanism. An experiment was devised to subject this mechanistic possibility to a critical test. The rationale of this experiment is based on two sets of prior observations: (1) the *t*-butyl and benzyl sulfides experience the normal course of chlorinolysis with approximately the same ease,[29] and (2) a *t*-butyl group creates great steric difficulties and tends to inhibit the formation of a tetracovalent state of a sulfur atom to which it is bonded. This is in keeping with the consistent failure to form *t*-butylsulfonyl chloride under any reaction circumstances,[30] and the frequent reports by Douglass and co-workers[31,32] of their inability to prepare *t*-$BuSCl_3$ while the ethyl and isopropyl homologs are formed readily. This is to say that a tetracovalent sulfur cannot be sterically accommodated in a bond to the *t*-butyl group; some obvious cases to the contrary are the formation of *t*-butyl sulfones by H_2O_2 oxidation of the sulfides.[33] However, there is abundant evidence indicating *kinetic* reluctance of *t*-butylsulfenyl derivatives to achieve a tetracovalent state of the sulfur.[34]

We can therefore anticipate that a 4-*t*-butylthio-7-chloroquinoline (XVII) would have great difficulty forming the (tetracovalent) sulfur dichloride intermediate postulated above to lie astride the path of abnormal chlorinolysis. On the other hand, the for-

(29) This matter is to be discussed fully in a forthcoming article on our kinetic studies of the chlorinolysis reaction. It would appear that appropriate substrates for the normal chlorinolysis undergo reaction at rates possessing a very small range of activation free energies.

(30) Unpublished results of P. S. Strilko from these laboratories.

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(33) C. R. Strauss, H. G. Guay, and H. J. Harwood, *J. Org. Chem.*, **29**, 1945 (1964).

(34) Private communication of unpublished work of Professor A. Fava, July 1962.

mation of the *t*-butyl substituted chlorosulfonium chloride, which must occur as a precurser step if any chlorinolysis is to be realized, apparently experiences no such prohibition. In line with earlier mechanistic proposals and interpretations[35] of the course of α-chlorination of methyl *t*-butyl sulfoxides, a *t*-butyl chlorosulfonium ion is supported by all evidence as a reaction intermediate.

These expectations are completely fulfilled. No abnormal product can be observed on chlorinolysis of XVII: 98% of the normal product (SO_4^{-2}) can be recovered under conditions which give 14–72% of abnormal product with the benzyl homolog.

Experimental

All melting point and boiling point data recorded below are uncorrected.

Materials.—The following sulfides were prepared by literature procedures: 4-benzylthio-7-chloroquinoline, m.p. 141° (lit.[3] m.p. 140–141°); ethyl 2,4-dinitrophenyl sulfide, m.p. 114° (lit.[36] m.p. 115°); phenyl 2,4-dinitrophenyl sulfide, m.p. 120–121° (lit.[36] m.p. 121°); benzyl 2,4-dinitrophenyl sulfide, m.p. 130–131° (lit.[36] m.p. 130°); *p*-nitrobenzylbenzyl sulfide, m.p. 56–57° (lit.[37] m.p. 56°); 2-benzylthio-4-methyl-6-oxypyrimidine, m.p. 174–176° (lit.[38] m.p. 176–178°); 2-ethylthio-4-methyl-6-oxypyrimidine, m.p. 143° (lit.[39] m.p. 144–145°); isopropyl phenyl sulfide, b.p. 56° (1 mm.) [lit.[40] b.p. 207° (750 mm.)]; *t*-butyl phenyl sulfide, b.p. 65° (3 mm.) [lit.[40] b.p. 73° (5 mm.)]; S-*p*-nitrobenzylthiouronium chloride, m.p. 220° (lit.[41] m.p. 223°); and 4-benzylthiopyridine 1-oxide, m.p. 61° (lit.[42] m.p. 61–62°).

The following sulfides were synthesized in the same manner as the corresponding compound above and were characterized (before being studied further): 4-phenylthio-7-chloroquinoline, m.p. 87–88° (*Anal.* Calcd. for $C_{15}H_{10}ClNS$: C, 66.35; H, 3.68. Found: C, 66.34; H, 3.72.); 4-*t*-butylthio-7-chloroquinoline, m.p. 69–70° (*Anal.* Calcd. for $C_{13}H_{14}ClNS$: C, 62.03; H, 5.57; Cl, 14.12. Found: C, 61.43; H, 5.79; Cl, 14.25.); and S-*p*-methylbenzylthiouronium chloride, m.p. 164–165° (*Anal.* Calcd. for $C_9H_{13}ClN_2S$: C, 49.88; H, 6.00. Found: C, 50.06; H, 6.31.).

S-Benzylthiouronium chloride was purchased from Distillation Products Industries and 4,6-dichloro-2-phenylthio-1,3,5-triazine was a gift of Dr. H. Koopman, N. V. Philips-Duphar, Weeps, Holland.

Chlorinolysis Reactions.—The general procedure used was that of Kwart and Miller.[2] A material balance was not sought in all reactions.

Chlorinolysis of 4-Benzylthio-7-chloroquinoline. A. In Acetic Acid–Perchloric Acid.—A mixture of 20.0 g. of sulfide dissolved in 100 ml. of glacial acetic acid containing 6.0 ml. of water and 7.5 ml. of 70% perchloric acid was chlorinolyzed. The products isolated were 5.59 g. (27.1%) of 4,7-dichloroquinoline hydroperchlorate, m.p. 230° (melting point and infrared spectrum identical with those of the compound prepared by treating 4,7-dichloroquinoline with perchloric acid); 4.21 g. (47.6%) of benzyl chloride, b.p. 178.8° (lit.[43] b.p. 179°), identified by its β-naphthyl ether,[43] m.p. 100–101°; 3.92 g. (37.4%) of benzyl acetate, b.p. 215° (lit.[43] b.p. 216°), which gave a positive hydroxamic acid test[43] for esters; 10.46 g. (75.4%) of 4,7-dichloroquinoline, m.p. 86–87° (lit.[44] m.p. 86°); and 84.9% sulfate ion.

B. In Acetic Acid–Sodium Acetate.—The sulfide (9.85 g.) was dissolved in a solution of 25.4 g. of sodium acetate trihydrate in 60 ml. of glacial acetic acid containing 2.5 ml. of water.

After chlorinolysis the products isolated were 23.6% benzylsulfonylchloride, m.p. 92–93° (lit.[43] m.p. 92°), which yielded an anilide, m.p. 102–103° (lit.[43] m.p. 102°); 22.3% benzyl chloride; 21.7% benzyl acetate; 19.2% 4.7-dichloroquinoline; and 55.7% sulfate ion.

C. In *t*-Butyl Alcohol–Potassium Hydroxide.—The sulfide (15.95 g.) was suspended in 100 ml. of *t*-butyl alcohol to which 0.314 g. of potassium hydroxide and 5.0 ml. of water had been added.

After chlorinolysis the products isolated were 41.0% benzylsulfonyl chloride and 11.8% sulfate ion.

Chlorinolysis of 4-Phenylthio-7-chloroquinoline. A. In Acetic Acid.—A quantity (10 g.) of the sulfide was chlorinolyzed in 60 ml. of glacial acetic acid containing 4.0 ml. of water. The products identified were 51.7% 4,7-dichloroquinoline; 19.4% 4,7-dichloroquinoline hydrochloride, sublimed 130–150° (*Anal.* Calcd. for $C_9H_6Cl_3N$: C, 46.05; H, 2.56; Cl, 45.41. Found: C, 46.11; H, 2.59; Cl, 45.70.); and 68.7% benzenesulfonyl chloride, b.p. 66–67° (1 mm.) [lit.[45] b.p. 65.9 (1 mm.)], which yielded a sulfonamide, m.p. 153–154° (lit.[43] m.p. 153°); no sulfate ion was detected.

B. In Acetic Acid–Perchloric Acid.—No cleavage products were detected. More than 95% of the material was recovered unchanged upon work-up.

Chlorinolysis of 4-*t*-Butylthio-7-chloroquinoline.—The sulfide (10 g.) was chlorinolyzed in 100 ml. of glacial acetic acid containing 3.0 ml. of water. After the reaction, complete examination of the aqueous phase showed 96.7% of the original sulfur to be present as sulfate ion.

Chlorinolysis of Benzyl 2,4-Dinitrophenyl Sulfide.—The sulfide (10.0 g.) was suspended in 80 ml. of glacial acetic acid to which 2.5 ml. of water had been added. After chlorinolysis, the products identified were 67.8% benzyl chloride, 18.1% benzyl acetate, and 58.1% 2,4-dinitrobenzenesulfonyl chloride, m.p. 94° (lit.[46] m.p. 95°), which yielded an amide, m.p. 153–154° (lit.[46] m.p. 156–157°).

Chlorinolysis of 4-Benzylthiopyridine 1-Oxide.—The sulfide (10.8 g.) was chlorinolyzed in 75 ml. of glacial acetic acid containing 3.6 ml. of water and the following products were identified: 58.6% benzyl chloride, 18.7% benzyl acetate, and 15.5% sulfate ion.

Chlorinolysis of Isopropyl Phenyl Sulfide.—The sulfide (8.44 g.) was chlorinolyzed in 100 ml. of glacial acetic acid containing 4.0 ml. of water. The products isolated were 76.0% benzenesulfonyl chloride and 4.5 g. of a material, b.p. 119–123°, which gave an infrared spectrum corresponding to an aliphatic chloro compound. Data for the latter compound compares favorably with that reported for 2-chloro-4-methylpentane [lit.[47] b.p. 111–112° (733 mm.)].

Chlorinolysis of *t*-Butyl Phenyl Sulfide.—The sulfide (20.0 g.) was chlorinolyzed in 100 ml. of glacial acetic acid containing 5.4 ml. of water. The products isolated were 37.9% *t*-butyl acetate, b.p. 95° (lit.[48] b.p. 98°), identified as an ester by infrared, and 60.5% benzenesulfonyl chloride.

Chlorinolysis of 2-Ethylthio-4-methyl-6-oxypyrimidine.—The sulfide (12.0 g.) was chlorinolyzed in 100 ml. of water to yield 38.4% ethanesulfonyl chloride, b.p. 64° (14 mm.) (lit.[43] b.p. 70° (20 mm.)], and 96% 2-chloro-4-methyl-6-oxypyrimidine hydrochloride, m.p. 260° (lit.[49] m.p. 270°). No sulfate ion was detected.

Chlorinolysis of 2-Benzylthio-4-methyl-6-oxypyrimidine.—The sulfide (16.0 g.) was chlorinolyzed in 100 ml. of glacial acetic acid containing 5.0 ml. of water to yield 49.1% benzyl chloride, 16.0% benzyl acetate, 18.6% benzylsulfonyl chloride, 28.0% 2-chloro-4-methyl-6-oxypyrimidine, and 56.2% sulfate ion.

Chlorinolysis of 4,6-Dichloro-2-phenylthio-1,3,5-triazine.—A solution of 3.77 g. of sulfide in 100 ml. of glacial acetic acid containing 1.0 ml. of water was chlorinolyzed to yield 72.6%

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(49) M. M. Endicott and T. B. Johnson, *ibid.*, **63**, 1286 (1941).

benzenesulfonyl chloride and 60.6% cyanuric chloride, m.p. 142° (lit.[45] m.p. 145°).

Chlorinolysis of S-Benzylthiouronium Chloride. A. In Acetic Acid.—A quantity (5.0 g.) was chlorinolyzed to yield 39.5% benzylsulfonyl chloride and 44.1% sulfate ion.

B. In Water.—A quantity (5.0 g.) was chlorinolyzed to yield 93.2% benzylsulfonyl chloride. No sulfate ion was detected.

Chlorinolysis of S-*p*-Methylbenzylthiouronium Chloride.—The sulfide (6.6 g.) was chlorinolyzed in 50 ml. of glacial acetic acid containing 4.0 ml. of water to yield 99.3% sulfate ion.

Chlorinolysis of S-*p*-Nitrobenzylthiouronium Chloride.—A solution containing 5.0 g. of sulfide in 50 ml. of glacial acetic acid containing 2.0 ml. of water was chlorinolyzed to yield 90.5% *p*-nitrobenzylsulfonyl chloride, m.p. 92° (lit.[50] m.p. 90°). No sulfate ion was detected.

Chlorinolysis of Benzyl *p*-Nitrobenzyl Sulfide.—The sulfide (15.0 g.) dissolved in 50 ml. of glacial acetic acid containing 12.0 ml. of water was chlorinolyzed to yield 90.5% *p*-nitrobenzylsulfonyl chloride, 45.7% benzyl chloride, and 37.4% benzyl acetate.

Radioactive Interchange of $^{36}Cl^-$ with 4,7-Dichloroquinoline.—The $^{36}Cl^-$ was procured from the Oak Ridge National Laboratory as an aqueous HCl solution with the following analysis: 145.6 mg./ml. of chloride, 4.1 *N* acid, 0.05 ± 10% mc./ml., and specific activity of 0.343 mc./g.

A solution (22 ml.) of 4,7-dichloroquinoline (0.0084 g./ml.) in 1:1 acetic acid–water was placed in a flask and 100 λ of the isotope solution was added. This was stirred at room temperature for 5 min. and then 2.0 ml. of this solution was withdrawn, neutralized with aqueous sodium hydroxide, and diluted to 5.0 ml. with water; 0.17 ml. of this solution was withdrawn, dried, and counted to give 3644 c.p.m.

The remainder of the original solution was allowed to stir for 30 min. and then 10.0 ml. was withdrawn and neutralized. The precipitated solid was filtered, dried, weighed, and counted; weight 59.1 mg., count 43 c.p.m.

A quantity of 1.0 ml. of 0.040 *M* chlorine in glacial acetic acid was added to the remaining 10 ml. and the solution was stirred for 30 min. The entire solution was neutralized and the precipitated solid was filtered, dried, weighed, and counted; weight 37.9 mg., count 1150 c.p.m.

A second experiment was made in which 10.0 ml. of the 4,7-dichloroquinoline solution, 50 λ of the isotope solution, and 1.0 ml. of the chlorine solution were mixed and allowed to stand for 16 hr. This was worked up as before to yield 61.5 mg.; count 1640 c.p.m.

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The Formation of N,N'-Dihydroxyethylenebisamides from Glyoxal and Selected Amides

SIDNEY L. VAIL, CLIFFORD M. MORAN, AND ROBERT H. BARKER

Southern Regional Research Laboratory[1] *and Department of Chemistry, Tulane University, New Orleans, Louisiana*

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The addition of carboxylic acid amides and carbamates to glyoxal to form N,N'-dihydroxyethylenebisamides (I) is favored by basic conditions. In general, linear derivatives of I are formed by the addition of unsubstituted amides, such as acetamide, benzamide, or isopropyl carbamate, to glyoxal. However, the addition of formamide to glyoxal produced a low yield of N,N'-dihydroxyethylenebisformamide, the major reaction product being 1,4-diformyl-2,3,5,6-tetrahydroxypiperazine. Formation of linear derivatives of I has also been extended to include the N-substituted amides, N-methylformamide and 2-pyrrolidone. N,N'-Methylenebis(methyl carbamate) was added to glyoxal to form 1,3-dicarbomethoxy-4,5-dihydroxyimidazolidine. Attempts to form a dihydroxydiazetidine were unsuccessful. The formation of some methyl ethers and the acetates of I is reported.

Based on extensive studies of the addition reactions of amides to formaldehyde,[2] it has been proposed that under alkaline conditions the amido nitrogen may attack an aldehyde carbonyl as a nucleophile to produce I. On examination of eq. 1 and 2, it is evident that

$$>NH + OH^- \rightleftharpoons >N^- + H_2O \qquad (1)$$

$$>N^- + \underset{H}{\overset{O}{\overset{\|}{C}}} + H_2O \rightleftharpoons >N-\underset{H}{\overset{OH}{C}}- + OH^- \qquad (2)$$

I

electronic factors which increase the electron density on the amido nitrogen should reduce the deprotonation of the amide and inhibit the addition to glyoxal.[3]

The base-catalyzed additions of acetamide and methyl and ethyl carbamate to glyoxal have been reported[4] to form linear N,N'-dihydroxyethylenebisamides (II). However, of the examples provided in these patents,[4] apparently only one compound was purified to the extent that it was accurately characterized (Table I). It has been possible to extend this base-catalyzed reaction to produce compounds of the general structure II from formamide, acrylamide, isopropyl carbamate, benzamide, N-methylformamide, and 2-pyrrolidone. Formamide, acrylamide, benzamide, and 2-pyrrolidone reacted readily, whereas N-methylformamide and isopropyl carbamate were slower.

$$2RCONHR' + (CHO)_2 \rightleftharpoons \begin{matrix} O \\ \| \\ RC-NR'-CH-OH \\ \quad\quad\quad | \\ RC-NR'-CH-OH \\ \| \\ O \end{matrix} \qquad (3)$$

IIa, R = CH_3; R' = H
b, R = OCH_3; R' = H
c, R = OC_2H_5; R' = H

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. The mention of trade names and firms does not imply their endorsement by the Department of Agriculture over similar products or firms not mentioned.

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